The automated flow synthesis of fluorine containing organic compounds

by

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DECLARATION

I, Chantal Scholtz declare that the thesis/dissertation, which I hereby submit for the degree PhD Chemistry at the University of Pretoria, is my own work and has not previously been submitted by me for a degree at this or any other tertiary institution.

Signature :...   **Date :**....................................

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" To a synthetic chemist, the complex molecules of nature are as beautiful as any of her creations. The perception of that beauty depends on the understanding of chemical structures and their transformations, and, as with a treasured work of art, deepens as the subject is studied, perhaps even to a level approaching romance. It is no wonder that the synthetic chemist of today is filled with joy by the discovery of a new naturally occurring structure and the appearance of yet another challenge to synthesise.[1]*"* *E.J. Corey*

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[1] Corey, E.J. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 455.

SUMMARY

Organofluorine chemistry has a rich history, spanning as far back as the 16th century to current times where it is frequently used in the pharmaceutical industry. The incorporation of fluorine within a molecule has the ability to modify the pharmacokinetic as well as pharmacodynamic properties of that compound. This means that the presence of fluorine can have a profound impact on the nature and functioning of a drug. As a result of these properties of fluorine it has been incorporated in many successful drugs such as Prozac, Lipitor, celecoxib and numerous anti-cancer agents. However, the incorporation of fluorine is not always straight forward, which has resulted in the development of a number of different fluorinating agents and fluorinating processes.

Flow chemistry is the newest addition to this ever-evolving field, allowing for more efficient syntheses with substantially improved safety profiles and yields. Flow chemistry is a novel technology which can be used for the economical manufacture of fine chemicals, and more specifically, active pharmaceutical ingredients (API's) in an environment where economies of scale are often not realized. Flow chemistry is defined as the "use of continuous plug flow reactors as opposed to conventional batch reactors" for the synthesis of fine chemical intermediates and API's.

As a result of flow chemistry being a relatively new field, its use for fluorination and the synthesis of fluorinated drugs has not yet been extensively explored. This study focusses on the conversion of traditional batch synthesis to continuous flow processes for 5-fluorocytosine (marketed as the drug Flucytosine), hexafluorobuta-1,3-diene, aryl diazonium tetrafluoroborate salts, aryl hydrazines and celecoxib (marketed as the drug Celebrex) in an effort to develop processes which would be more industrially viable or at the very least, expand the scope of technology available to organofluorine chemists.

LIST OF ABBREVIATIONS

ACN - acetonitrile

API - active pharmaceutical ingredient

ATP - adenosine triphosphate

BER - borohydride exchange resin

BPR - back pressure regulator

COX - cyclooxygenase

CTT - 2-chloro-1,1,2-trifluorotriethylamine

DAST - diethylaminosulfur trifluoride

DFI - 2,2-difluoro-1,3-dimethylimidazolidine

DMF - *N,N*-dimethylformamide

DMSO - dimethyl sulfoxide

DTBP - di-*tert*-butyl peroxide

3-EAN - 3-ethoxyacrylonitrile

ETFA - ethyl trifluoroacetate

EWG - electron withdrawing group

5-FC - 5-fluorocytosine

FFM - falling film microreactor

h - hours

HFBD - hexafluorobuta-1,3-diene

HFC-134a - 1,1,1,2-tetrafluoroethane

HT PTFE - high temperature polytetrafluoroethylene

IPA	-	isopropanol / isopropyl alcohol
IPN	-	isopentyl nitrite
LDA	-	lithium diisopropylamide
4-MAP	-	4-methylacetophenone
MBC	-	micro bubble column
MFSDA	-	methyl fluorosulfonyl difluoroacetate
NFSI	-	*N*-fluorobenzenesulfonimide
NMR	-	nuclear magnetic resonance
NSAIDs	-	non-steroidal anti-inflammatory drugs
PET	-	positron emission tomography
PGs	-	prostaglandins
psi	-	pound-force per square inch, 1 psi = 0.068 atm
PTFE	-	polytetrafluoroethylene
R_f	-	retention factor
RT	-	room temperature
SDF	-	selective direct fluorination
TBAF	-	tetrabutylammonium fluoride
TLC	-	thin layer chromatography
THF	-	tetrahydrofuran
$TMSCF_3$	-	trifluoromethyltrimethylsilane
XRF	-	X-ray fluorescence

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Introduction

1. Fluorine in Organic Chemistry

1.1. KEYWORDS

Fluorine, organofluorine, fluorination, fluorinated drugs, flow chemistry, fluorinating agents.

1.2. ABSTRACT

Fluorine has a rich history, spanning as far back as the 16th century in which mineral fluorides were first recognized, up to current times where it is frequently used in the pharmaceutical industry. The incorporation of fluorine within a molecule has the ability to modify the pharmacokinetic as well as physiochemical properties of that compound. This means that the presence of fluorine can have a profound impact on the nature and functioning of a drug. As a result of these properties of fluorine it has been incorporated in many successful drugs such as Prozac, Lipitor, Celebrex (celecoxib) and numerous anti-cancer agents. However, the incorporation of fluorine is not always simple, which has resulted in the development of a number of different fluorinating agents and fluorinating processes. Flow chemistry is the newest addition to this ever-evolving field, allowing for more efficient syntheses with substantially improved safety profiles and yields.

1.3. THE HISTORY OF FLUORINE

The known history of fluorine dates back as far as the 16th century during which time mineral fluorides were first recognized,[1] and by the 17th century the mineral fluorite fluorspar was being combined with sulfuric acid to obtain an unknown acid for the purposes of glass etching.[1] The unknown acid was finally characterized by Scheele in 1771 and named hydrofluoric acid.[1] This resulted in the realization that hydrofluoric acid contained an element that was still unknown at the time and this element happened to be fluorine.[1] Elemental fluorine was first isolated by

Moissan in 1886 by means of electrolysis of a mixture of hydrogen fluoride and potassium hydrogen difluoride, which earned him a Nobel prize in 1906.[1-5]

Ten years later, in 1896 the Belgian chemist Swarts heated methyl iodoacetate with silver fluoride to obtain methyl fluoroacetate, a synthesis which is often viewed as being the start of modern organofluorine chemistry, a field which took long to develop due to the difficulties and hazards involved with handling highly reactive and corrosive fluorine-based reagents.[1,6-7]

In 1922 Swarts followed his synthesis of methyl iodoacetate with the synthesis of trifluoroacetic acid, further laying the foundation for organofluorine chemistry.[6] Thereafter, 1926 saw the synthesis of carbon tetrafluoride and this was followed in 1927 by the Schiemann method of aromatic fluorination.[1] Shortly thereafter, in the 1930's Midgley and Henne successfully synthesized chemically and thermally stable fluorocarbons which were used as lubricants and the now infamous refrigerants.[6]

The major drive towards developing the field of fluorine chemistry came during World War II (1939 – 1945) as a result of the "Manhattan project", in which the isotopes of uranium hexafluoride needed to be fractionated.[8] This required compounds resistant to uranium hexafluoride vapours, and resulted in the preparation of a series of perfluoro-organic compounds, and so, catalytic perfluorination was developed.[8] It was also during World War II when research into the biological effects of incorporating fluorine into organic molecules began, by groups in England (Saunders and co-workers) and Germany (Schrader).[6] However, the real drive to study the pharmacology and toxicology of fluorine came later in 1943 when Marais showed that monofluoroacetate was responsible for the toxicity of the South African plant *Dichapetalum cymosum*.[6]

The 1950's was all about the chemistry of functional derivatives of fluorine including anaesthetics and fluorinated elastomers,[5,7] while the 1960's saw the development of selective fluorination methods and rapid growth in the fields of perfluoroaromatic chemistry and the use of fluorinated compounds in the pharmaceutical industry.[5,7] At this stage, synthetic methodology was still limited to the use of hydrogen fluoride or elemental fluorine, which required the use of specialized equipment to effect fluorine substitution.[5] It wasn't until the 1980's, after the introduction of diethylaminosulfur trifluoride (DAST), which is a more stable and easily handled reagent that fluorine gained more popularity, as evidenced by the noticeable increase in the number of registered fluorinated pharmaceuticals from that period onwards.[5]

It was in a 1947 paper, after the war had ended, that McBee foresaw and discussed the potential future of fluorine in organic chemistry.[9] He made predictions about the uses for fluorine which over the last 70 years or so have gradually materialized and in some instances gone far beyond what he envisioned.[9] Since then, fluorine has found use in various polyfluoro compounds,[6] aerosol propellants,[6] fire extinguishers,[6] fire proofing,[9] anaesthetics,[6] polymers,[6] refrigerants,[9] insulators,[9] dyes,[9] lubricants,[9] sealants,[1] non-stick coatings,[1] fluoroplastics e.g. PTFE,[1] agri-chemicals[9] and 20-25% of pharmaceuticals[10] to mention a few uses. The history of fluorine is short in comparison to that of the more well-known elements such as carbon and oxygen, but the future prospects in the field of fluorine chemistry are exciting.

1.4. WHAT MAKES FLUORINE SPECIAL FOR USE IN MEDICINAL COMPOUNDS

Fluorine, the 9th element on the periodic table, has special properties that makes it interesting for medicinal chemistry, as its incorporation within drugs can result in the modulation of the steric, electronic and lipophilic properties, which in turn affects the pharmacokinetic and pharmacodynamic properties of the drug.[11] The small size and large electronegativity of fluorine has a profound influence on many aspects,[12] which are examined in more detail below.

1.4.1. **Mimic effect**

In terms of size, fluorine is a small atom with a van der Waals radius of 1.47 Å, which is only slightly larger in size than hydrogen (1.20 Å) and slightly smaller than oxygen (1.57 Å), with the C-F bond length (1.41 Å) being only slightly longer than the C-H bond length (1.09 Å).[3,13] As a result of the similarity in size, replacing a hydrogen by fluorine within a molecule does not noticeably affect the overall size of the molecule.[6] Indeed it can be seen in solid state X-ray structures that hydrogen and fluorine often interchange which is suggestive of a close isosteric relationship.[13] This implies that replacing a hydrogen with fluorine does not have a large steric impact and that binding to target proteins is not affected, making fluorine an excellent mimic for hydrogen.[12,13]

This form of electronic modulation is known as bioisosteric substitution and it is a meaningful strategy when looking for a moiety which is able to reinforce interactions between drugs and their receptors, without drastically altering the overall geometry of the molecule.[7,11] The enzymes within a living organism are unable to distinguish sterically between non-fluorinated molecules and the analogous fluorinated ones, resulting in the fluorinated molecules being assimilated into the metabolic cycles in the same way as the non-fluorinated molecules would have been.[1] A number of examples can be found in the literature which demonstrate this ability of enzyme macromolecular recognition sites to recognize and bind fluorinated analogues of their natural substrates, with the highly toxic fluoroacetic acid in the tricarboxylic acid cycle often being referenced in this context.[14-16]

1.4.2. **Block effect and metabolic stability**

The most stable single bond in organic chemistry is the C-F bond (~485 kJ.mol^{-1}) versus the C-H bond (~425 kJ.mol^{-1}) and this is as a result of the effective overlapping of the 2s and 2p orbitals of fluorine with the matching orbitals of carbon.[10,17] Increasing fluorine substitution results in further increases in the bond strength with reported values of 531 kJ.mol^{-1} for terminal CF_3 groups.[17] Neighbouring C-C single bonds are also strengthened while allylic C=C double bonds are made weaker by the presence of fluorine substituents.[3] Fluorocarbons are thus chemically and thermally stable as well as being biologically inert and having improved stability towards oxidation.[1,7,17]

Metabolic stability or resistance to oxidation is one of the most important factors affecting the bioavailability of compounds and is a persistent challenge for many drug discovery programs.[10,12,18] Drugs are frequently metabolically oxidized by the group of cytochrome P450 monooxygenase liver enzymes which limits their bioavailability.[10,18] One strategy which is primarily used to counter this problem is to use a fluorine substituent to block the metabolically labile site or block adjacent or distal sites as the C-F bond is stronger and more resistant to oxidative attack by the cytochrome P450 enzymes, resulting in an increased half-life for the drug.[3,11,12,14,18]

In aromatic ring systems the site of metabolic oxygen incorporation can be blocked by fluorine substitution and result in a reduction in the rate of oxidation.[5] This could be due to one of three main effects: steric hindrance preventing the oxidizing enzyme accessing the site, lower nucleophilicity of the aromatic ring due to inductive effects or as a result of the intermediate carbocation being resonance destablilized.[5] Aliphatic oxidation is seen as the abstraction of a hydrogen atom to obtain a radical moiety followed by oxidation to obtain an alcohol.[5] Fluorine substitution of the labile hydrogen atom can thus have a profound influence on the rate of metabolism.[5] Systems prone to oxidation such as olefins, heterocyclic and electron rich phenyl rings can thus have their metabolic stabilities improved by incorporation of a fluorine or fluorine containing substituent.[19]

Reductive processes can also be blocked with fluorine serving as an isostere for carbonyl moieties.[19] However, the blocking strategy only works in situations where the fluorine substitution does not negatively affect binding to the target protein or generate toxic metabolites.[5,12]

1.4.3. **Effect on lipophilicity**

Lipophilic modulation is an important strategy, particularly when it comes to drug absorption or translocation across the lipid bilayers, as this affects the bioavailability of the drug.[7,11] Orally administered drugs are absorbed and distributed by one of two routes: active transport which requires energy input in the form of ATP and passive transport which does not require energy and is the most common form of absorption. However, passive transport relies on cell membrane permeability which implies that the drug needs to be lipophilic enough to enter the lipid core but not get captured.[10]

In order for drugs to have a good binding affinity to target proteins, substituents which are strongly lipophilic are required, but this often comes at the expense of solubility.[12,18] This means that a balance is required between the overall minimum polarity (hydrophilicity) and lipophilicity.[3,18] The presence of C-F bonds on an aryl ring, next to a functional group containing a heteroatom, or next to a π-system noticeably increases the lipophilicity of a molecule, with the CF_3 group being one of the most lipophilic groups available.[6,10,15] The CF_3 group is strongly electron withdrawing in nature, which noticeably lowers the electron density of neighbouring polar functional groups and decreases the basicity of amine and hydroxyl groups.[5,16] This results in a reduction in the ability of these polar groups to form hydrogen bonds to water, decreasing the hydrophilicity.[16] This through-bond σ-inductive effect of the CF_3 substituent is so strong that it can have an effect up to three carbons away.[16]

Statistical analysis indicates that the inclusion of a single fluorine substituent could on average increase the lipophilicity by about 0.17 units, although this is biased by the large number of aromatic compounds which contain hydrogen to fluorine substitutions.[5] On the other hand, the fluorination of aliphatic compounds often results in a decrease in the lipophilicity of the compound,[5,15,16] although this phenomenon has not been as extensively investigated when compared to aromatic systems.

1.4.4. **Inductive effects and the influence on pK_a**

Fluorine is the most electronegative element (4.0, Pauling), far exceeding the value of hydrogen (2.2, Pauling), with the C-F bond exhibiting a strong dipole moment that is able to interact with other dipoles.[10,12] This results in a large electronic effect, which can have mechanistic implications due to changes in electron distribution as well as changes in the dipole moments or pK_a values for a molecule.[6,12,13] The presence of strongly basic groups in a drug can have a limiting effect on the bioavailability of that drug.[12,18] This implies that changes in pK_a can have a major effect on the pharmacokinetic as well as binding properties.[10,18]

The incorporation of fluorine close to an acidic or basic group can increase the acidity or reduce the basicity respectively, depending on the position of the fluorine substitution, ultimately resulting in improved membrane permeability.[12,18] The effect on pK_a is additive with each fluorine substituent added decreasing the pK_a to a similar extent.[15,19] Typically the pK_a of acetic acid is 4.76 while the corresponding α-fluorinated analogues have pK_a's of 2.59 (CH_2FCOOH), 1.24 (CHF_2COOH) and 0.23 (CF_3COOH).[18] Conversely the pK_a of protonated ethylamine is 10.7 while its β-fluorinated analogues have pk_a's of 8.97 ($CH_2FCH_2NH_2$), 7.52 ($CHF_2CH_2NH_2$) and 5.7 ($CF_3CH_2NH_2$).[3,18]

In the case of anilines, quinolines, pyridines and piperidine rings, the incorporation of fluorine reduces the basicity of the nitrogen centre resulting in increased oral bioavailability.[3,15] Amine basicity is also noticeably reduced by the introduction of a fluorine due to the σ-inductive effect, resulting in an increased ratio of neutral to protonated molecules.[3,16] In contrast, the acidity of the N-H bond in sulfonamide (RSO_2NH_2) is increased by the introduction of a fluorine substituent, improving deprotonation.[3,16] The acidity of carboxylic acids, alcohols, phenols and heterocycles is also increased with adjacent fluorine substitution.[15,16]

For aliphatic systems the effect of fluorine substitution on pK_a diminishes with increased distance from the functional group being modulated, although fluorine substituents as far as five bonds away can still have a minor impact.[5,19] In cyclic systems the effect of fluorine substitution on pK_a is dependent on whether the fluorine is orientated axially or equatorially.[5] In basic systems equatorial substitution generally lowers the pK_a to a greater extent due to the alignment of the ring C-C σ orbital with the low-lying C-F σ^* orbital (Figure 1.1), resulting in electron density shifting away from the basic group and reducing its basicity.[5,19] Axial substitution has a smaller effect as the protonated base is stabilized by means of a charge-dipole interaction with the axially orientated fluorine (Figure 1.1), and for this reason in these systems axial orientation is preferred over equatorial.[5]

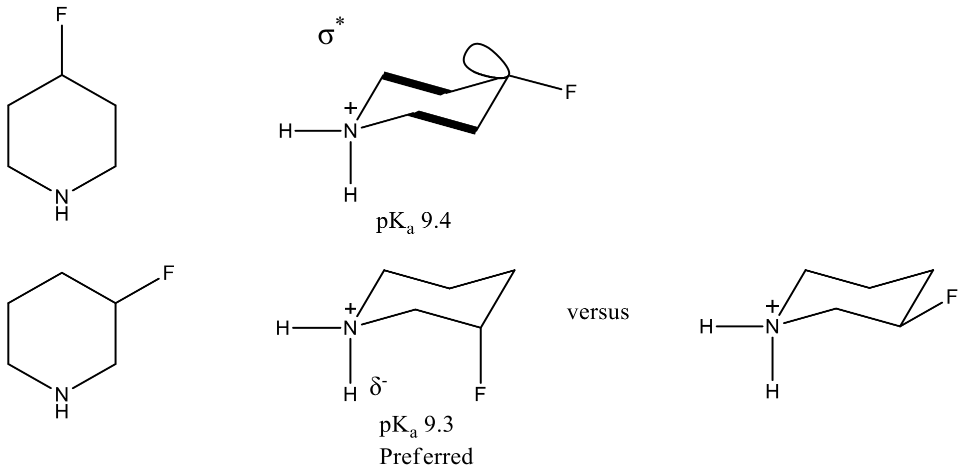


Figure 1.1: Effect of equatorial versus axial orientation on pK_a.[5]

1.4.5. **Conformational effects**

Even though fluorine has a slightly larger van der Waals radius than hydrogen, experimental evidence indicates that substituting a single hydrogen with fluorine results in only minor steric and geometric changes when compared to the analogous hydrocarbon.[13] The replacement of CH_2 with CF_2, however, has a much larger effect while the CH_3 and the CF_3 groups are not similar at all, resulting in more noticeable changes.[10,13]

Based on the van der Waals hemispheres the CF_3 group is 2-3 times larger than the CH_3 group and it has been suggested that the CF_3 group is closer in molar size to an isopropyl group.[13,16] This, however, is a point of dispute as many argue that the CF_3 group is in actual fact closer in size to an ethyl group and that the isopropyl group is larger.[3,10] Despite the similarity in size the molecular shapes of the CF_3 and ethyl groups are very different and this can have a large impact on molecular conformation.[3,10]

The average volumes of the CH_2 and CH_3 groups are estimated to be 27 Å and 54 Å respectively, compared to the CF_2 and CF_3 groups at 38 Å and 92 Å, respectively.[17] This means that incorporation of a CF_3 group could have a profound effect on the molecular conformation.[18]

The highly polarized C-F bond is easily able to accept electrons from vicinal electron-donating orbitals by means of its vacant $\sigma^*_{C\text{-}F}$ orbital (hyperconjugation), but the electron occupied $\sigma_{C\text{-}F}$ orbital is unwilling to donate electrons.[5,16,19] There is also reduced bonding electron pair repulsion between the C-F and neighbouring bonds due to the high electronegativity of fluorine.[5] Thus, compounds containing fluorine are more likely to adopt a *gauche* instead of an *anti*-conformation as a result of strong electronic modification, even though the *anti*-conformation is expected based on steric and electrostatic predictions.[10,16,19] This *gauche* phenomenon is explained by considering the additional stabilization which is obtained from the crucial donation of electrons from the adjacent $\sigma_{C\text{-}H}$ orbital to the lower lying vacant $\sigma^{*}_{C\text{-}F}$ orbitals.[10,16,19] The preference for the *gauche* conformation can also be attributed to the presence of charge-dipole interactions discussed previously under inductive effects (Figure 1.1).[5,19]

The almost ionic nature of the C-F bond also results in a large dipole moment which can affect the conformation of organofluorine compounds by means of dipole-dipole interactions.[5,19] For example, in the α-fluoroamides, the amide and the C-F bond orientate in an antiperiplanar conformation which allows the amide and C-F dipoles to oppose each other.[5] The effect of fluorine substitution on overall conformation is therefore often difficult to predict as a result of the large number of factors that play an influencing role, making this is an ongoing area of research.

1.4.6. **Binding interactions and affinity**

Substituting fluorine for hydrogen is frequently used to increase the binding affinity of a compound.[12,13,18] As a result, the incorporation of fluorine into a compound can have a substantial effect on the binding affinity and selectivity of protein-ligand complexes.[12,18] These binding interactions could be by means of a direct interaction between the protein and fluorine or indirect as a result of fluorine's ability to modulate the polarity of other functional groups which interact with the protein.[12,18] It has been found that in many instances, the incorporation of a fluorine substituent results in a minor improvement in the binding affinity as a result of the improved lipophilicity.[5,18]

Considering the electronegativity of fluorine, one would expect C-F to exhibit similar behaviour to C-N and C-O units and therefore be a good hydrogen bond acceptor.[3] This is however, not the case and fluorine is deemed to be a poor hydrogen bond acceptor and is thus not as suitable for replacing groups such as oxygen, which are good hydrogen acceptors.[3,5,13]

The topic of whether covalently bound fluorine is able to participate in hydrogen bonding within protein-ligand complexes is one of huge debate, but evidence from crystal structures suggests that the interactions between C-F and protein-ligand complexes are more likely to be via multiple weak polar interactions, and not hydrogen bonds.[5,10,16,18]

It has been determined that the fluorine substituents present on ligands favour orientation towards electropositive regions within the receptor sites.[3] Peptide bonds within particularly hydrophobic regions of proteins have been found to generate a favourable fluorophilic environment, allowing for multipolar interactions such as $C\text{-}F\cdots C{=}O$, $C\text{-}F\cdots H\text{-}C_\alpha$ and $C\text{-}F\cdots H\text{-}N$ as well as interactions with the positively charged guanidinium side chain of arginine and the amide side chains of glutamine and asparagine.[3] Fluorine is able to intramolecularly or intermolecularly share three sets of lone pair electrons with atoms that are electron deficient, which also promotes multiple interactions.[16] Should the opposite effect be required and the binding affinity needs to be reduced, a fluorine substituent introduced into an electronegative region will achieve this result.[3]

1.5. FLUORINATED DRUGS

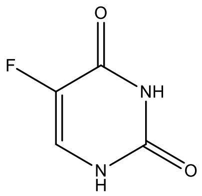
The first fluorinated drug was developed in 1957, but up until the 1970's the use of fluorine in medicinal chemistry was rare due to the synthetic challenges involved.[3,12,18] Since then, a large number of organofluorine drugs have been prepared, with approximately 20-25% of all registered pharmaceuticals incorporating at least one fluorine atom.[11,18,20] The significance of fluorine in medicinal chemistry is frequently acknowledged and as such fluorinated drugs have been designed to work as phosphodiesterase inhibitors, serotonin reuptake inhibitors, target various kinases, atherosclerosis treatments, antibacterial and antiparasitic agents, anti-cancer agents as well as for radiolabeling to mention a few.[11,12,14]

For an orally administered drug to be successful it must first be absorbed through the intestines and enter the bloodstream.[7,10] Thereafter, it needs to be transported across a series of phospholipid membranes in order to reach the target site.[7,10] Once at the target site the drug needs to bind and provide the anticipated effect followed by metabolism at an acceptable rate without the production of toxic metabolites.[7,10] It is well known that fluorine substitution can have a profound effect on the previously mentioned processes as well as drug potency, selectivity and bioavailability.[5] The presence of fluorine in drugs can act on binding in one of two ways: it can alter the dipole moment or it can be cleaved from the bound drug followed by covalent binding in a process known as suicide inhibition.[7]

1.5.1. **Anti-cancer agents**

Cancer remains one of the biggest medical problems facing modern society and the quest for more effective anti-cancer agents is an ongoing one, despite the many successes.[20] Fluorine has played a prominent role in this field, with many anti-cancer agents containing at least one fluorine atom.[14]

5-Fluorouracil (5-FU, **1**), synthesized in 1957,[10,20] is a cytotoxic agent used in cancer chemotherapy that works as a potent anti-metabolite which binds irreversibly through a suicide inhibition mechanism to the thymidylate synthase enzyme after *in-situ activation*.[6,18] Other fluorinated inhibitors of thymidylate synthase include 5-fluoro-2'-deoxyuridine (**2**) as well as some prodrug derivatives.[20] Skin cancers, and a range of solid tumours have been treated using 5-FU (**1**), but this comes with a risk of severe neurotoxic and cardiotoxic side effects due to the absence of selectivity for the tumour cells.[10,20] In an effort to improve the safety profile a number of 5-FU prodrugs such as galocitabine (**3**), capecitabine (**4**), furtulon (**5**), camofur (**6**), ftorafur (**7**) and emitefur (**8**) have been developed (Figure 1.2).[20]



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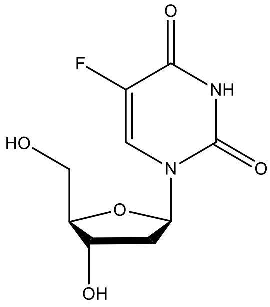

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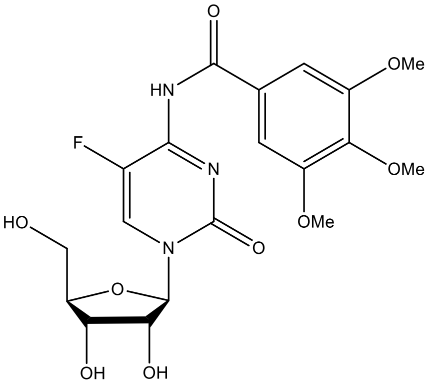

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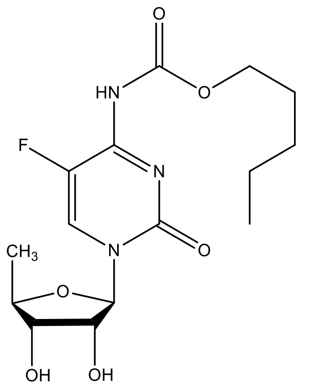

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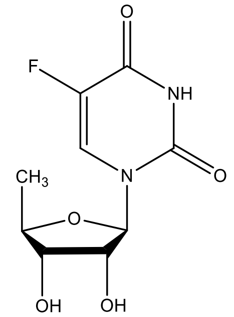

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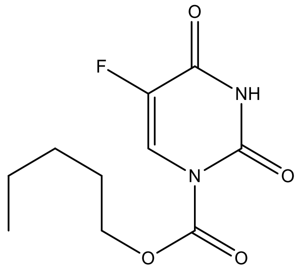

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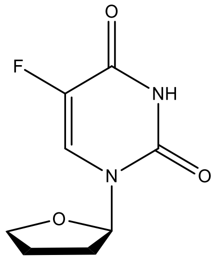

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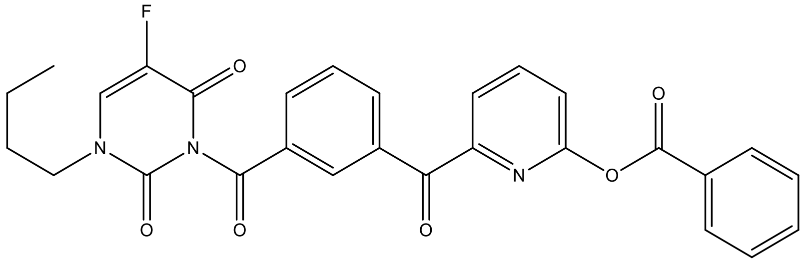

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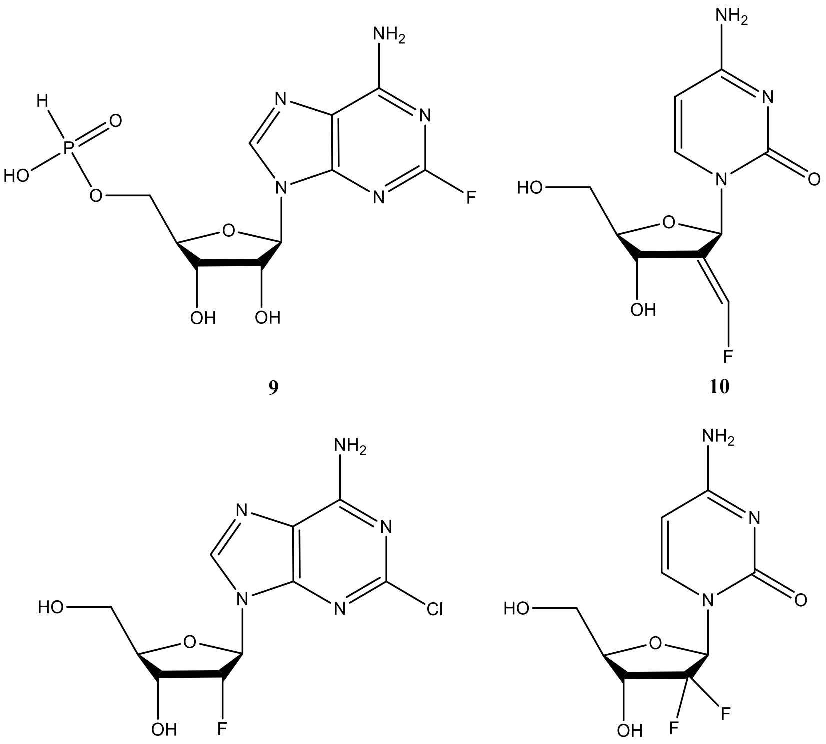
Figure 1.2: Fluorinated anti-cancer drugs.

Fludarabine (**9**), tezacitabine (**10**) and clofarabine (**11**) which are all fluorinated adenosine anti-metabolites work as DNA polymerase inhibitors which have shown effectivity against chronic lymphocytic leukemia (Figure 1.3).[20,21] Incorporation of fluorine into these drugs improved their metabolic stability.[21] Gemcitabine (**12**), an inhibitor of ribonucleotide reductase and DNA synthesis is used for the treatment of pancreatic cancer and non-small cell lung cancer (Figure 1.3).[20,21] Unfortunately, **12** suffers from a narrow therapeutic index as it is fairly toxic and it is readily deaminated by deoxycytidine deaminase to an inactive uracil derivative, which shortens the half-life of the drug.[20]



9 **10** **11** **12**

Figure 1.3: Fluorinated DNA enzyme inhibitors.

Fulvestrant (**13**), a steroidal anti-estrogen which does not exhibit agonist effects is used for the treatment of hormone-sensitive advanced breast cancer in postmenopausal women in cases of progression after prior anti-estrogen therapy (Figure 1.4).[10,20,21] It is a competitive inhibitor, competing with estradiol for the estrogen receptors with a corresponding reduction in tumour cell proliferation.[10] For the treatment of prostate cancer, flutamide (**14**), hydroxyflutamide (**15**), nilutamide (**16**) and later casodex (**17**) were developed which are able to block the pharmacological effects of testosterone (Figure 1.4).[20] Dutasteride (**18**) was introduced for the treatment of benign prostatic hyperplasia and works by inhibiting both type 1 and type 2 5α-reductases, the enzymes responsible for converting testosterone into dihydrotestosterone (Figure 1.4).[21]

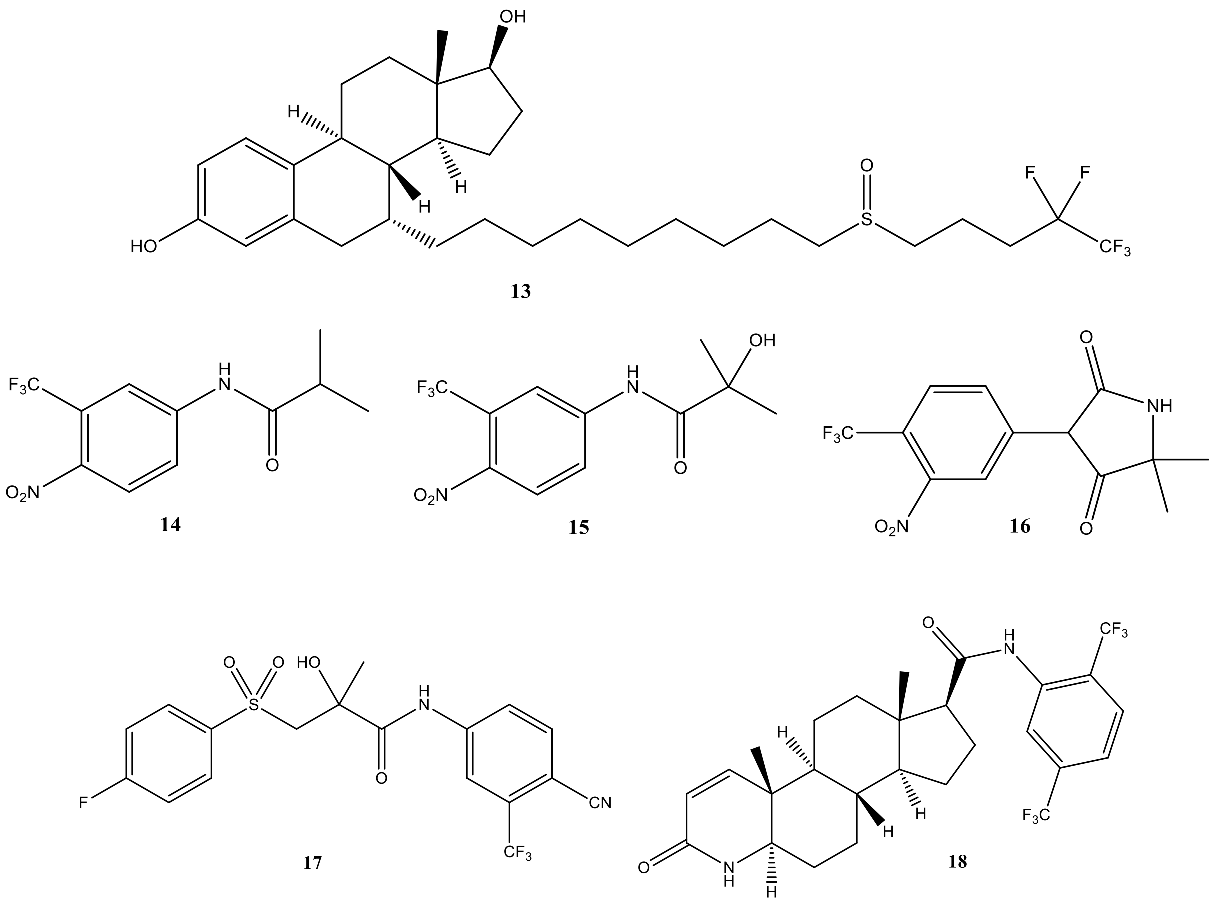
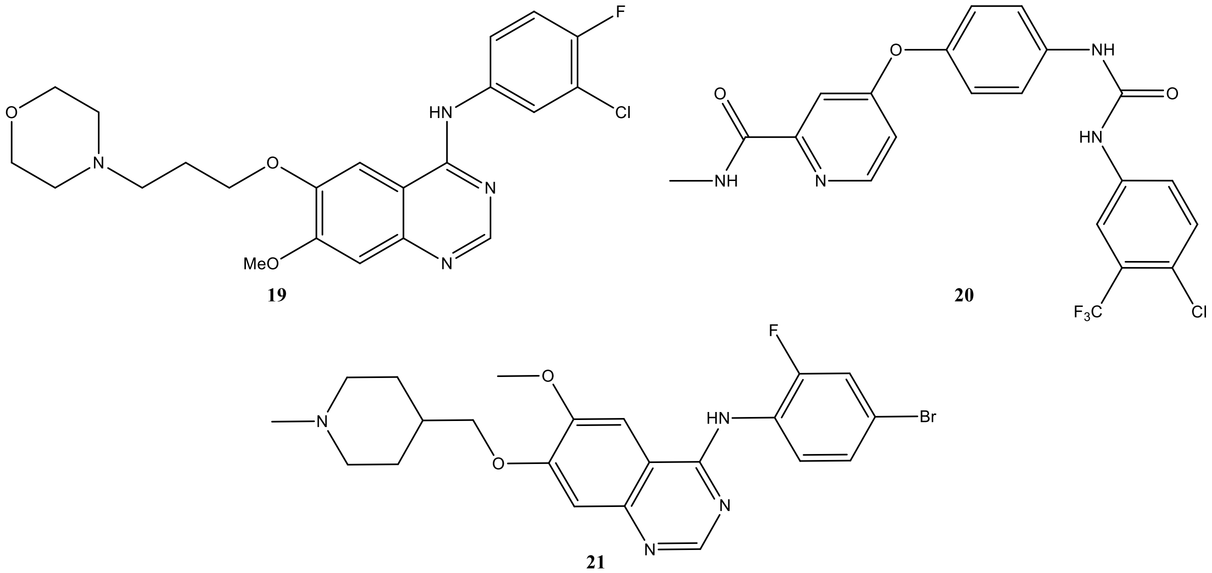


Figure 1.4: Fluorinated drugs for the treatment of breast and prostate cancers.

Almost every phase of cell function is regulated by protein kinases, which are responsible for mediating signal transduction pathways.[20] As such, the development of inhibitors that target protein kinases is an important field of research in the quest for new therapies, which has so far met with some success with the approval of drugs like gefitinib (**19**), sorafenib (**20**) and vandetanib (**21**) (Figure 1.5).[20] In the search for alternative protein kinase inhibitors a large number of the compounds proposed contain fluorinated groups since fluorine has been shown to have a notable therapeutic impact.[20]



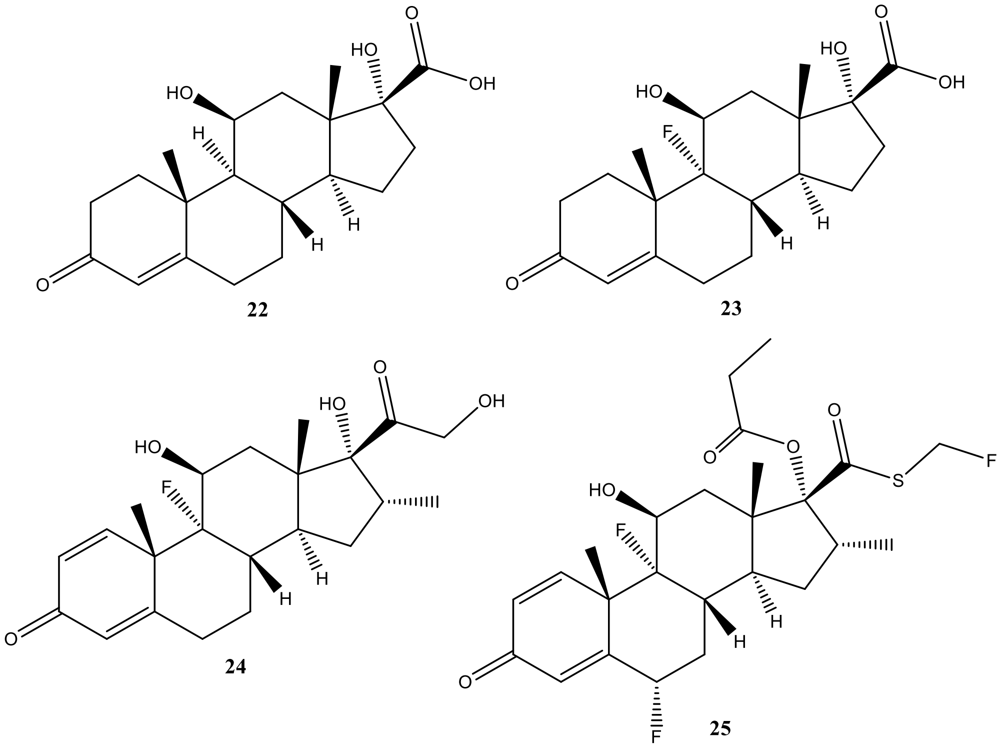
19 **20** **21**

Figure 1.5: Fluorinated protein kinase inhibitors.

1.5.2. **Anti-inflammatories**

A large number of anti-inflammatories are available on the market consisting of the steroidal and non-steroidal types, which can be further classified depending on their modes of action and inhibitory properties. Many of these anti-inflammatories contain at least one fluorine atom in their structure.[20]

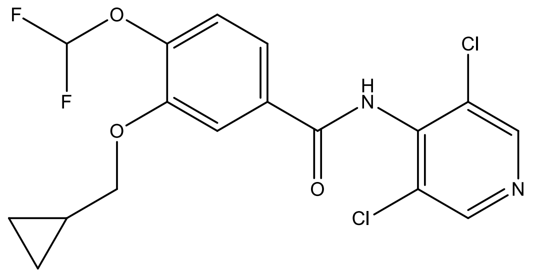
The first commercially successful group of drugs in which a C-F bond was introduced to obtain a useful modification of biological activity was the fluorinated corticosteroids.[7] Derived from cortisol (**22**), the 9-α-fluoro analogue (**23**) was designed to inhibit inflammatory processes (Figure 1.6).[6,12] The incorporation of fluorine in the structure, resulted in an increase in the acidity of the position 11 hydroxyl group which inhibited unwanted oxidation and improved binding affinity.[16] Glucocorticoid derivates such as dexamethasone (**24**) and fluticasone propionate (**25**) have also been developed (Figure 1.6).[5] The fluorine substituents in **25** were incorporated in order to increase potency as well as increase the rate of clearance from the body in order to reduce systemic side effects.[5]



22 23 24 25

Figure 1.6: Fluorinated corticosteroids and glucocorticoids.

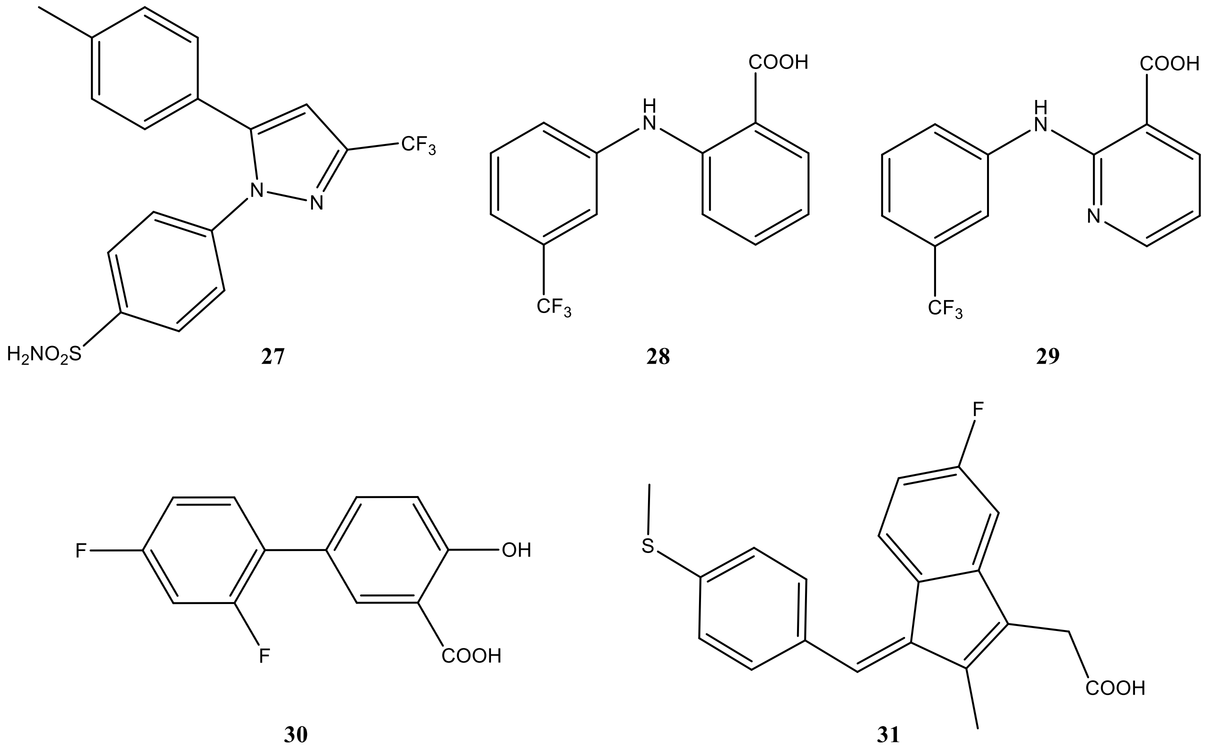
Roflumilast (**26**) was developed as an orally administrable selective inhibitor of the phosphodiesterase-4 (PDE4) enzyme and acts as an anti-inflammatory agent (Figure 1.7).[11] It is effective for the treatment of diseases affecting the lungs such as chronic obstructive pulmonary disease (COPD), asthma, pulmonary hypersensitivity and adult respiratory distress syndrome (ARDS).[11]



26

Figure 1.7: The PDE4 inhibitor roflumilast.

When it comes to anti-inflammatories, the non-steroidal anti-inflammatory drugs (NSAIDs) are a well-known class containing many examples. One of the most interesting drugs in this class is celecoxib (**27**), a selective cyclooxygenase-2 (COX-2) inhibitor, which demonstrates the huge effect that fluorine substitution can have on metabolic stability (Figure 1.8).[12,18] The original lead compound contained a fluorine substituent on the one phenyl ring and exhibited a very high metabolic stability with an unacceptably long biological half-life.[12,18] The fluorine substituent was thus removed and replaced with the more metabolically labile methyl group to obtain celecoxib (**27**), which had a more acceptable biological half-life.[12,18] Other anti-inflammatories which fall into the NSAID group are flufenamic acid (**28**), niflumic acid (**29**), diflunisal (**30**) and sulindac sulfide (**31**) (Figure 1.8).[20]



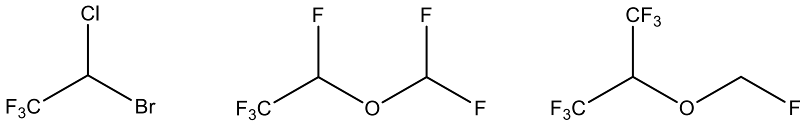
27 **28** **29**

30 **31**

Figure 1.8: Fluorinated NSAIDs.

1.5.3. **Anaesthetics**

Up until 1956, diethyl ether and chloroethane were the most commonly used anaesthetics, despite the risks associated with their use.[7] Halothane (**32**) was the first volatile anaesthetic containing fluorine to be widely used due to its improved safety profile (Figure 1.9).[7] Since then, a number of fluorinated alternatives such as desflurane (**33**) and sevoflurane (**34**) have become commercially available in which the metabolic stability as well as recovery times have been improved (Figure 1.9).[7]



32 **33** **34**

Figure 1.9: Fluorinated anaesthetics.

1.5.4. **Atherosclerosis**

One of the predominant causes of mortality in the modern world is coronary heart disease as a result of the thickening of the arterial walls due to the presence of high levels of low-density lipoprotein cholesterol (LDL-C) in the blood.[11] This condition often leads to strokes or myocardial infarctions, which in many instances can leave an individual disabled or be fatal.[11] A number of fluorinated drugs have been developed in an effort to combat the causes of the disease.

Among the first generation drugs for treating atherosclerosis was Fluvastatin (**35**), an inhibitor of the HMG CoA reductase enzyme which is responsible for high levels of LDL-C.[11] This was followed by the development of second generation drugs such as atorvastatin (Lipitor, **36**) cerivastatin (**37**), rosuvastatin (**38**) and pitavastatin (**39**) which were more efficient inhibitors of HMG CoA reductase due to the presence of a crucial 4-fluorophenyl substitution (Figure

1.10).[11,14,15] These drugs were termed "superstatins" as they exhibited improved metabolic stability with increased potency and a lower risk of drug-drug interactions.[14] However, the use of cerivastatin (**37**) resulted in adverse effects on muscles and was ultimately withdrawn from the market in 2001.[11]

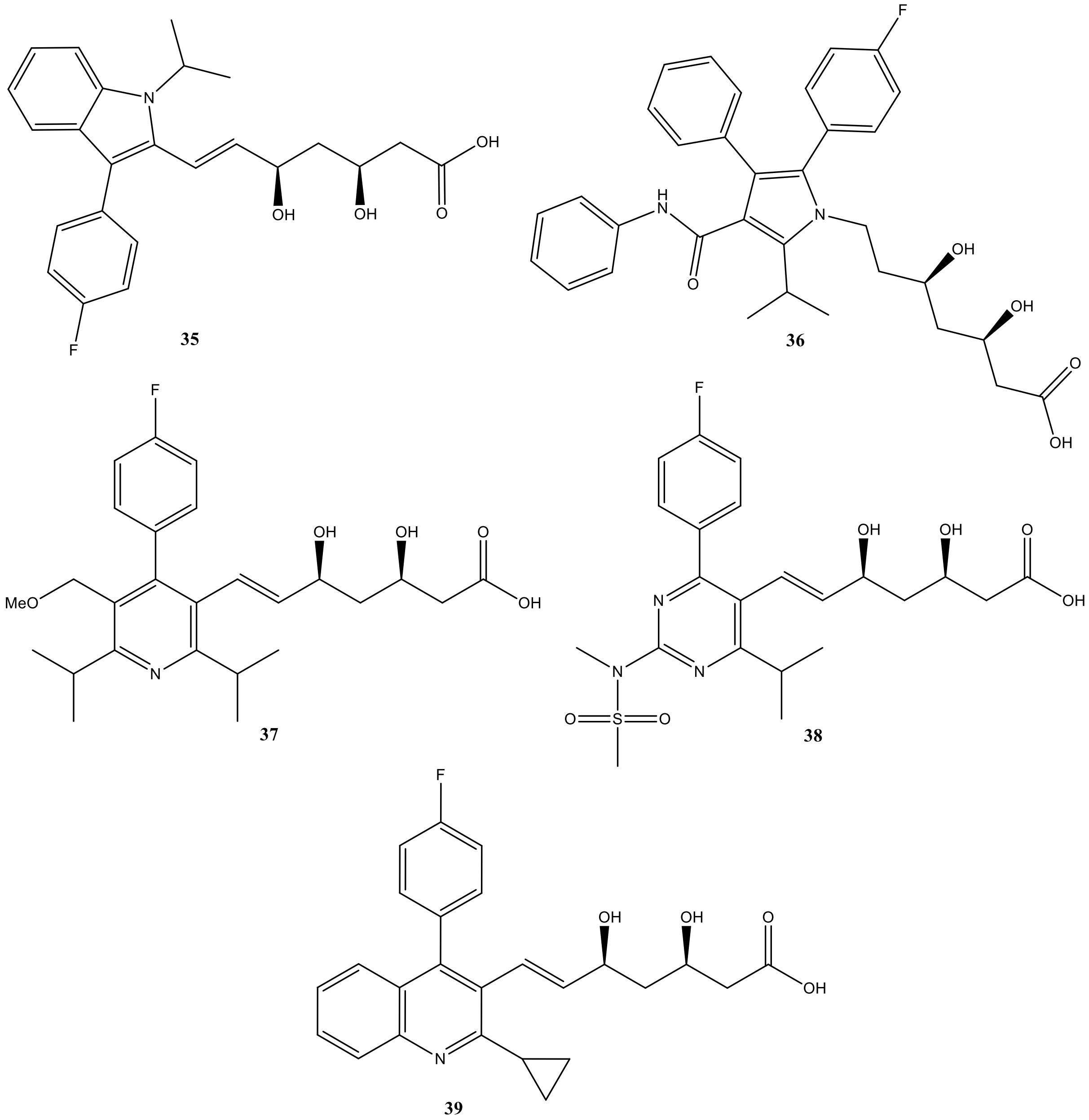


Figure 1.10: Fluorinated statin type drugs for the treatment of atherosclerosis.

Another route to combatting atherosclerosis involves inhibiting the cholesterol absorption process.[11,14] The gall bladder is responsible for the excretion of cholesterol into the intestines for re-absorption into the blood, and ezetimibe (**40**) is able to block this process (Figure 1.11).[11] The original lead compound was metabolically unstable due to the presence of a methoxy group thus, fluorine atom substituents were used to block the two metabolically labile sites.[14,18] The one fluorine atom replaced the labile methoxy group while the other prevents the oxidation of the phenyl ring to phenol, ultimately resulting in the highly potent ezetimibe (**40**).[12,18]

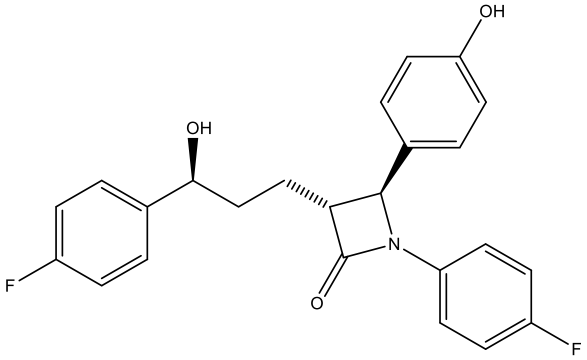


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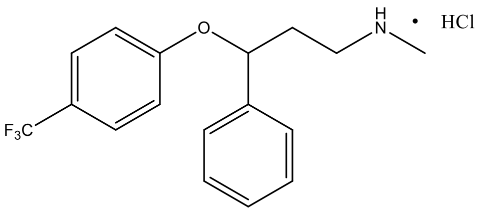
Figure 1.11: The fluorinated cholesterol absorption inhibitor ezetimibe.

1.5.5. **Psychiatric drugs**

One class of psychiatric drugs are mood stabilizers, which generally target the serotonin reuptake process in the brain, resulting in higher levels of serotonin and improved mood.[11,14] One of the best known examples of this class is the drug Prozac (fluoxetine hydrochloride, **41**), which was approved by the FDA in 1987 (Figure 1.12).[11,14] It is prescribed for the treatment of depression, bulimia and obsessive compulsive disorder.[10] The fluorine substituent in Prozac was introduced in order to increase the potency as well as the selectivity of the drug.[10,14] Other approved drugs which also target the serotonin reuptake process include fluvoxamine (**42**), paroxetine (**43**), citalopram (**44**) and escitalopram (**45**) (Figure 1.12).[14] These drugs are typically prescribed for the treatment of depression.[14]



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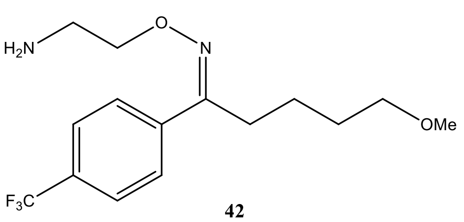

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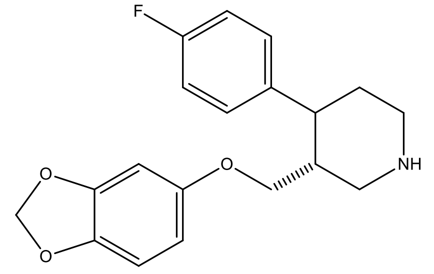

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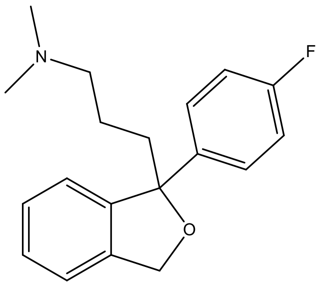

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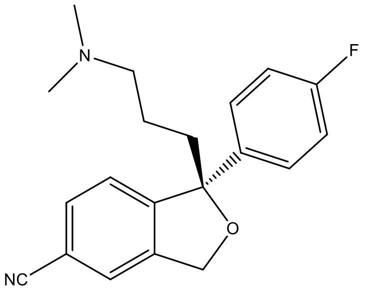

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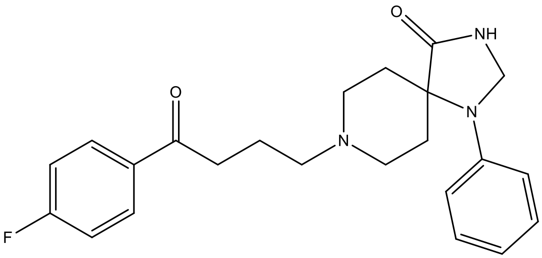
Figure 1.12: Fluorinated drugs affecting the serotonin reuptake process in the brain.

Another class of psychiatric drugs are the antipsychotics, which typically target various points in the dopaminergic pathway for the treatment of schizophrenia.[14] The first fluorinated antipsychotic drugs were spiroperidol (**46**) and haloperidol (**47**) and it was determined that the 4-fluorobenzoyl group was crucial for potency (Figure 1.13).[14] The second generation antipsychotic risperidone (**48**) works on multiple facets as it targets the serotonergic and adrenergic pathways as well as the dopaminergic one (Figure 1.13).[14]



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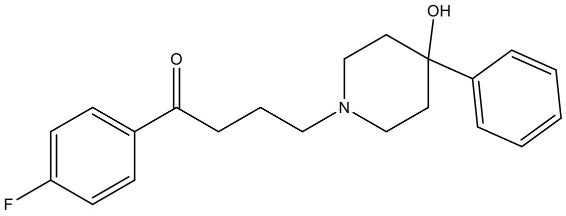

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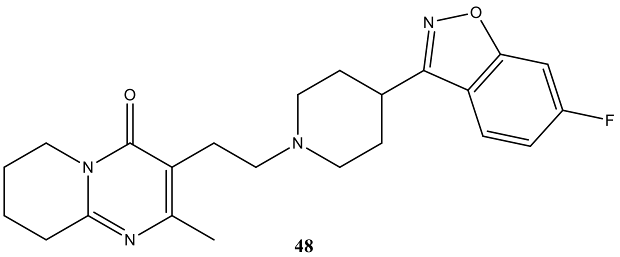

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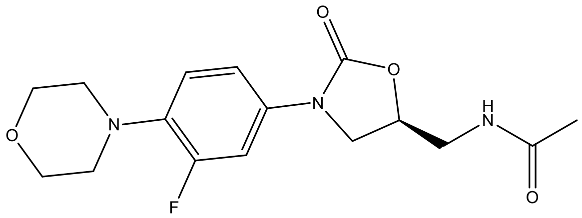
Figure 1.13: Fluorinated antipsychotics.

1.5.6. **Antibacterial agents**

When it comes to treating infections caused by drug resistant gram-positive bacteria, linezolid (**49**) has become one of the antibiotics of choice (Figure 1.14).[11,14] Linezolid (**49**) is an oxazolidinone that was specifically designed to target the early downstream stages of ribosomal protein synthesis, rather than the later RNA or DNA stages.[11] The incorporation of a fluorine substituent in the structure resulted in substantial improvements in the rate of oral absorption and near total bioavailability profiles, which is what makes this drug so successful.[11]



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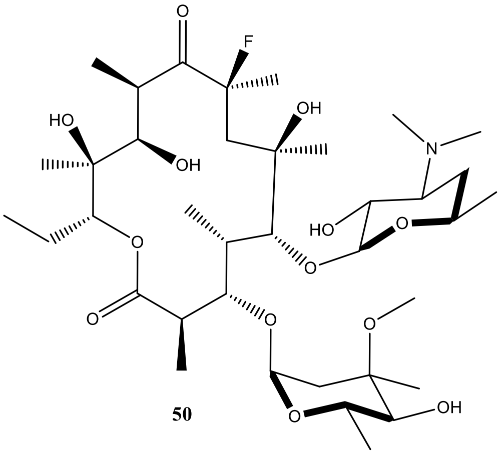

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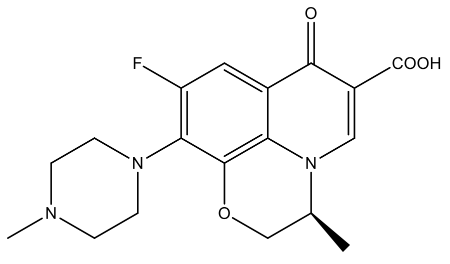
Figure 1.14: Fluorinated ribosomal inhibitors.

In flurithromycin (**50**), a fluorinated derivative of erythromycin, a fluorine atom was incorporated into the structure in order to improve metabolic stability, as well as bioavailability when compared to its parent compound (Figure 1.14).[10,21] Flurithromycin (**50**), works by inhibiting bacterial 50S ribosomal subunit assembly.[14]



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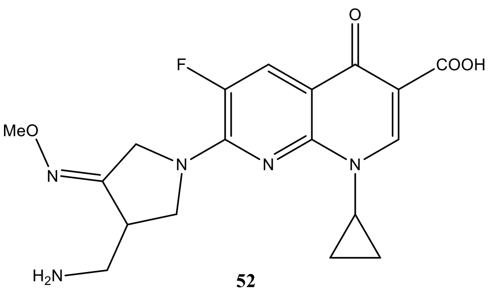

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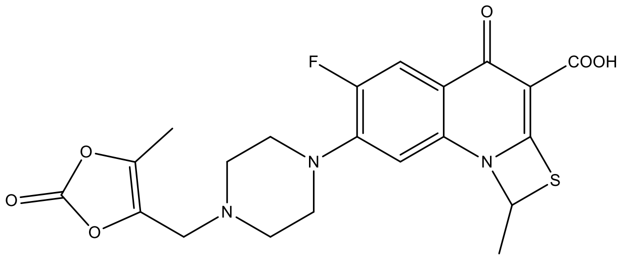

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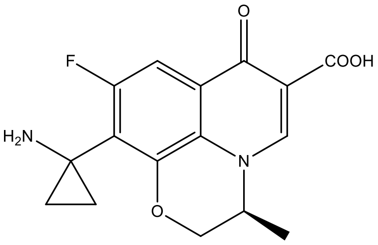

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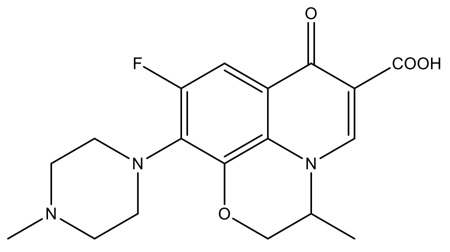

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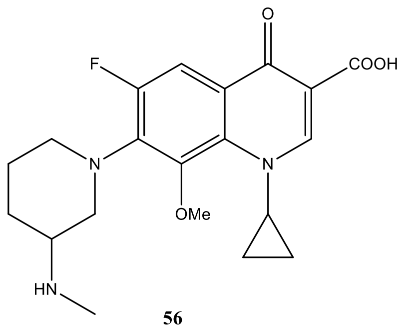

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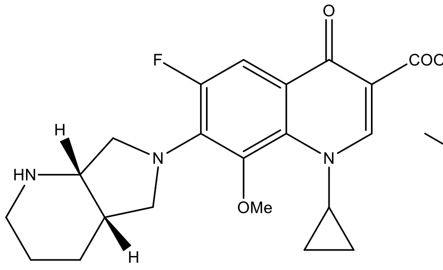

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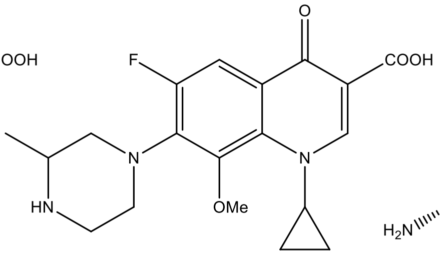

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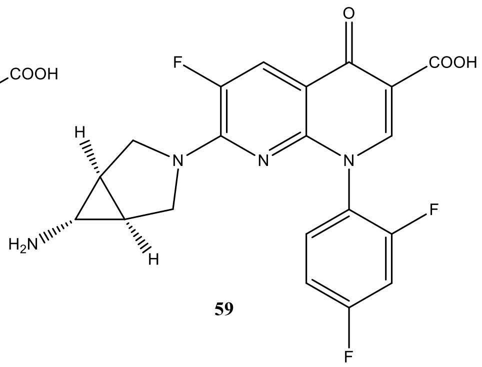

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Figure 1.15: Fluoroquinolone type drugs.

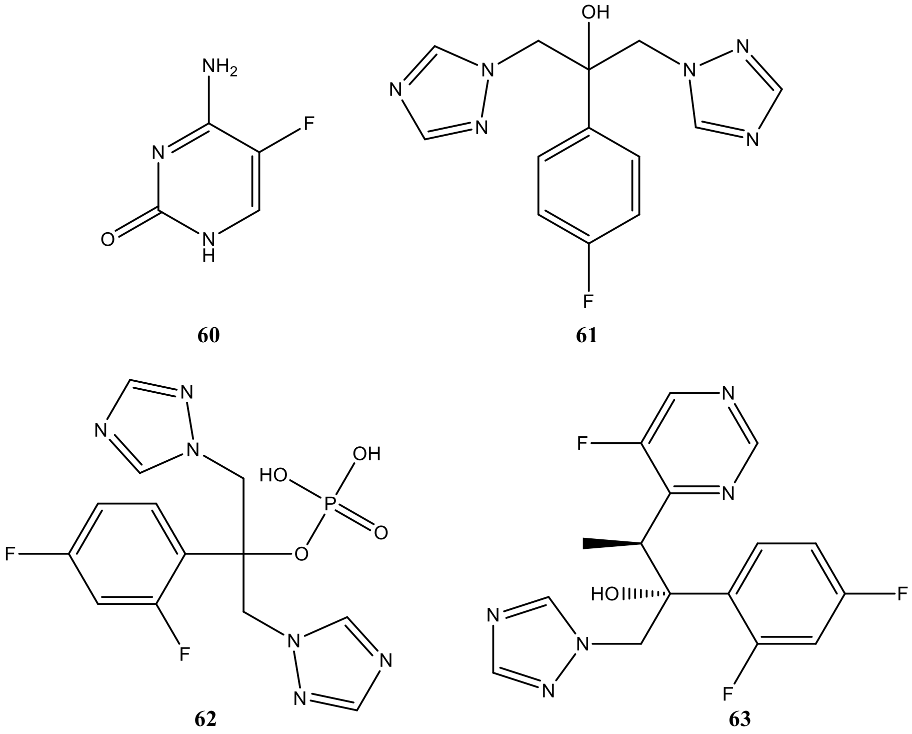
In the case of the fluoroquinolones, it was determined that the presence of a fluorine in the 6-position resulted in a 100-fold improvement in the minimum inhibitory concentration, as well as improved cell penetration.[12,14] A number of drugs were successfully marketed and the list includes levofloxacin (**51**), gemifloxacin (**52**), prulifloxacin (**53**), pazufloxacin (**54**), ofloxacin

(**55**), balofloxacin (**56**), moxifloxacin (**57**), gatifloxacin (**58**) and trovafloxacin (**59**).[14] These drugs work by inhibiting DNA gyrase or topoisomerase IV or both (Figure 1.15).[14]

1.5.7. **Antifungal agents**

Sterol C-14 demethylase is an enzyme required in the biosynthesis of ergosterol which is a constituent of fungal cell walls.[21] 5-Fluorocytosine (Flucytosine, **60**) is an effective inhibitor of sterol C-14 demethylase, making **60** a valuable antifungal agent (Figure 1.16).[21]

In 1988, fluconazole (**61**) was licensed for the treatment of serious systemic fungal infections (Figure 1.16).[14] It is also used to treat vaginal yeast infections.[22] This was followed by the development of the prodrug fosfluconazole (**62**) which was more water soluble and became available in 2004 (Figure 1.16).[14] Another drug in this class is voriconazole (**63**), which exhibits even higher activity than **61** (Figure 1.16).[14] The incorporation of fluorine in these drugs resulted in improved oral bioavailability as well as metabolic stability.[5]



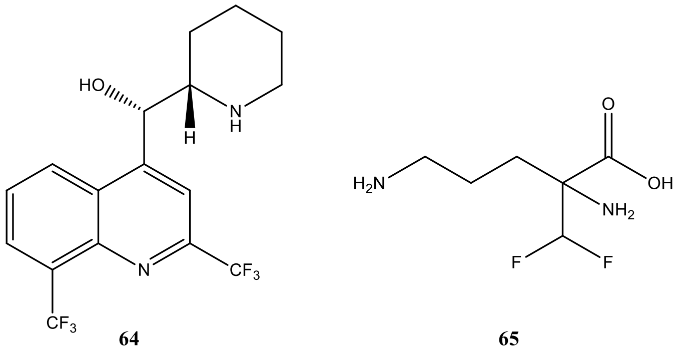
60 **61** **62** **63**

Figure 1.16: Fluorinated antifungal agents.

1.5.8. **Antiparasitic agents**

Parasites remain one of the major challenges in medicine, particularly in third world countries, with the global prevalence continuing to increase for drug sensitive as well as drug resistant forms.[11] With increasing global temperatures due to global warming, malaria is predicted to become a major burden to the health care system, especially since an effective vaccine is yet to be developed.[11]

Mefloquine (Larium, **64**) which has been in use since the mid 1980’s, is the classic antimalarial and can be found on the World Health Organization’s list of essential medicines (Figure 1.17).[11,23] However, mefloquine (**64**) has started encountering an increase in drug resistance so the search for effective alternatives has become a focal point for numerous industrial and academic research groups.[11]



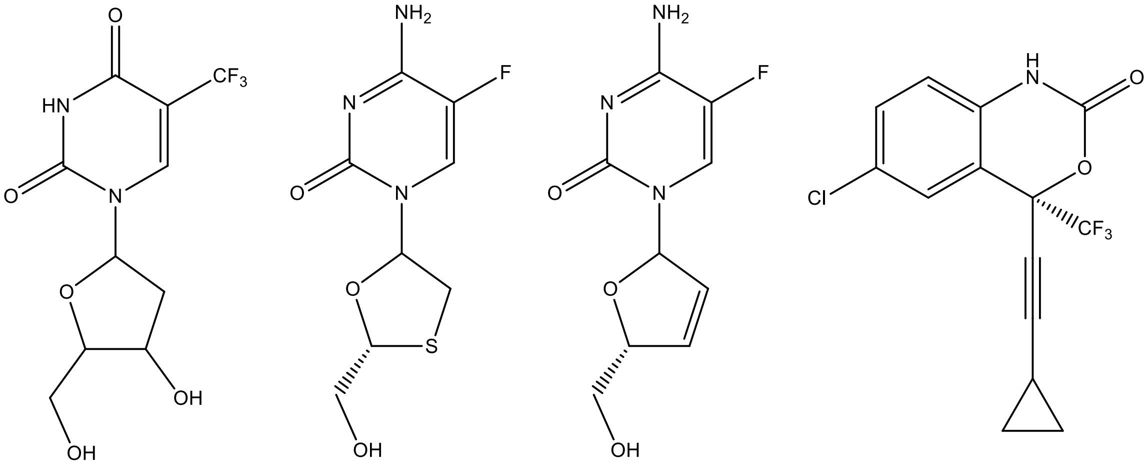
64 **65**

Figure 1.17: Fluorinated antiparasitic agents.

The drug eflornithine (**65**) was specifically designed to inhibit the enzyme ornithine decarboxylase and is used to treat African sleeping sickness caused by the parasite *Trypanosoma gambiense* (Figure 1.17).[11,21]

1.5.9. **Antiviral agents**

An antiviral drug acting as a mechanism based inactivator resulting in irreversible inhibition of thymidylate synthase is trifluridine (**66**) (Figure 1.18).[10,21] It is typically prescribed for the topical treatment of herpes simplex virus infection in the eyes.[10,21]



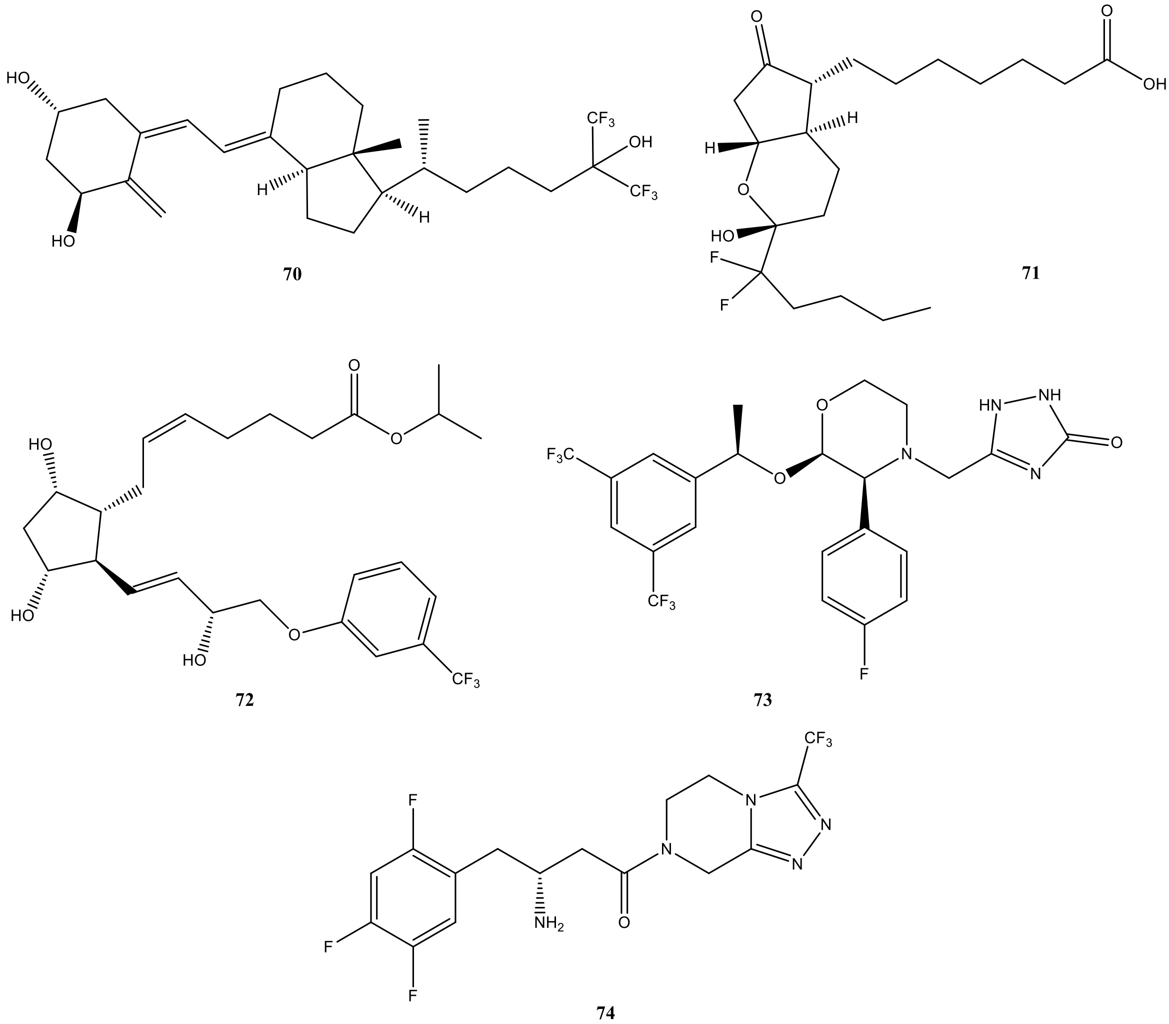
66 **67** **68** **69**

Figure 1.18: Fluorinated antiviral agents.

Emtricitabine (**67**) and elvucitabine (**68**) are nucleoside derivatives of flucytosine (**60**) which work as nucleoside reverse transcriptase inhibitors.[21] Emtricitabine (**67**), is specifically used in the treatment of HIV infection and is also prescribed for the treatment of hepatitis B, while **68** is still in clinical trials for the treatment of HIV and hepatitis B.[21] A non-nucleoside based inhibitor of the reverse transcriptase enzyme is efavirenz (**69**) and it is also used to treat HIV.[10] The trifluoromethyl group in **69** was shown to lower the pK_a of the cyclic carbamate and this was crucial for the potency of the drug.[10]

1.5.10. **Miscellaneous drugs**

Fluorinated drugs can even be found in the treatment of bone diseases, chronic constipation, ocular disorders, nausea and diabetes.[15,21] For bone diseases such as hypocalcemia, osteomalacia and rickets, the hypercalcemiant falecalcitriol (**70**) is prescribed (Figure 1.19), while for chronic constipation conditions lubiprostone (**71**) was developed (Figure 1.19).[21] The prodrug travoprost (**72**) is used for the topical treatment of glaucoma and intra-ocular hypertension (Figure 1.19).[21]



70 **71** **72** **73** **74**

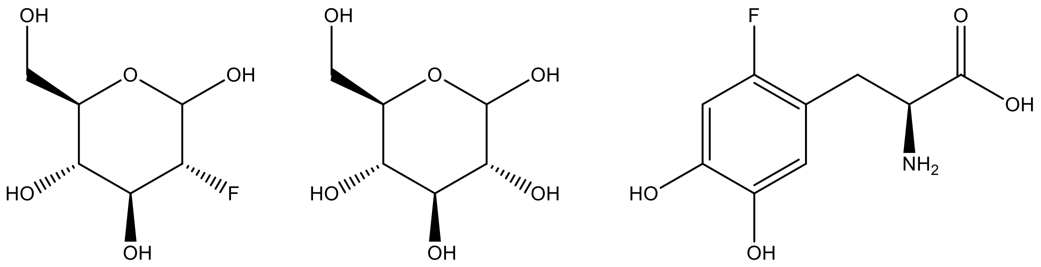
Figure 1.19: Fluorinated drugs for the treatment of bone disease, constipation, nausea, ocular disorders and diabetes.

Aprepitant (**73**) is prescribed for the treatment of nausea and vomiting induced by chemotherapy (Figure 1.19).[15] It is a neurokinin-1 (NK-1) receptor antagonist and it was the first of its kind.[5] The original lead compound suffered from poor metabolic stability which was improved by fluorination of the phenyl group, while it has been found that the bistrifluoromethylphenyl moiety is important for penetration into the central nervous system.[15] Type 2 diabetes is treated with sitagliptin (**74**), the first marketed dipeptidyl peptidase-4 (DPP-4) inhibitor.[5,15] The original lead compound suffered from low potency and poor oral bioavailability which was improved by incorporation of a fluorophenyl substituent.[5,15]

1.5.11. **Radiolabeling and Positron Emission Tomography (PET)**

Positron emission tomography (PET) has become an important tool for diagnostic imaging as it allows for real time, non-invasive *in vivo* imaging.[11,12] Radionuclides frequently used are ^{15}O (half-life = 2 min), ^{13}N (half-life = 10 min) and ^{11}C (half-life = 20 min).[10] Fluorine-18 on the other hand has a half-life of 110 minutes and also decays by means of positron emission which can be easily detected.[7,12] This makes fluorine an ideal radionuclide due to the fact that it has a longer half-life, which allows for easier synthesis and longer imaging times.[10]

One of the most commonly used radiopharmaceuticals for PET is 2-fluorodeoxyglucose (**75**), a fluorinated analogue of glucose (**76**), which is transported into cells followed by phosphorylation, resulting in further metabolism being inhibited (Figure 1.20).[7,10,12] This traps the radiolabeled molecule inside the cell and results in the ability to directly measure the rate of glucose metabolism.[7,12] The radiopharmaceutical, ^{18}F-DOPA (**77**) has been used to study the biodistribution and metabolism of DOPA, an important brain neurotransmitter.[7,12] ^{18}F substitution is becoming a valuable tool as PET is able to provide important information with regards to drug delivery and turnover within tissues and this is made easier by the ever increasing number of fluorinated drugs available on the market.[10]



75 **76** **77**

Figure 1.20: Fluorinated radiolabeled ligands for PET.

1.6. FLUORINATION REAGENTS

Alexander Borodin is often credited with the synthesis of the first organofluorine compound, which he reported in 1862.[1] He performed the first nucleophilic halogen exchange reaction in which he converted benzoyl chloride into benzoyl fluoride using potassium bifluoride.[1] However, the real first synthesis of an organofluorine compound occurred much earlier with Dumus and co-workers reporting the preparation of methyl fluoride from dimethyl sulfate in 1835.[1,15] The first aryl C-F bond to be prepared was by Schmitt and co-workers in 1870 by means of diazofluorination using HF (aq.) with heating.[1]

As mentioned previously, elemental fluorine was first isolated by Moissan in 1886 and shortly thereafter, he described the reactions between organic compounds and fluorine as “spontaneous and catastrophic”, resulting in the production of clouds of HF and soot as it is a dangerous oxidizing agent.[2,6] Due to the extreme reactivity of fluorine, its use in laboratory fluorinations remained limited with the ability to perform direct fluorinations only beginning from the 1930’s onwards, once it was realized that successful fluorination depended on the effective dissipation of heat.[2,3]

In nature very few compounds exist that contain a C-F bond which means that many of the organofluorine compounds required, need to be synthetically prepared and this has led to the development of many different fluorinating agents through the years.[24,25] The scope and effectiveness of synthetic methodology for the incorporation of fluorine has expanded notably since the 1960's.[22] However, the more widespread use of fluorination only began around 1970, upon the introduction of selective fluorinating agents, which were safe to handle and did not require the use of specialized equipment.[3,15]

Generally speaking there are three different approaches to fluorination which is dependent on whether fluorine cations, fluorine anions or fluorinated synthons are used.[8,15] In the preparation of perfluoro compounds fluorine atoms are typically used, but these conditions are usually too reactive for specific fluorination.[8] Specific fluorinations were thus, more frequently carried out under nucleophilic conditions until the development of electrophilic fluorine reagents broadened the reaction spectrum.[8]

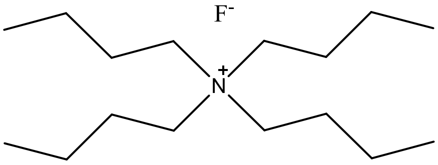
Selective direct fluorination (SDF) is defined as the replacement of one or two hydrogen atoms under conditions which promote nucleophilic attack of the substrate on the electrophilic fluorine, while at the same time curbing the competitive free radical processes.[24] These prerequisites limit the choice of reaction solvent to the use of aprotic solvents having high dielectric constants (e.g. acetonitrile) or strong protonic acids (e.g. sulfuric acid) which are able to increase fluorine's susceptibility to nucleophilic attack by encouraging the polarization of the fluorine molecule.[24] These solvents are also able to accept the fluoride counter ion that is formed in the transition state.[24] SDF reactions have been successfully performed on aromatic, heterocyclic and aliphatic systems, while addition to carbon-carbon double bonds typically proceeds via *syn* addition.[24]

1.6.1. **Sources of nucleophilic fluorine**

Nucleophilic fluorination is the process in which a fluorine anion is transferred to an electron poor centre.[4] A wide range of nucleophilic fluorinating reagents which are used to form C-F bonds are available and the list includes 2,2-difluoro-1,3-dimethylimidazolidine (DFI), diethylaminosulfur trifluoride (DAST), bis(2-methoxyethyl) aminosulfur trifluoride (Deoxofluor), hydrogen fluoride, metal fluorides and sulfur tetrafluoride to mention a few.[3,6,15]

One of the most widely used fluorinating reagents is hydrogen fluoride as it is readily available and affordable.[6] The major drawback to its use is its volatility and extreme corrosiveness, which requires the use of specialized reaction conditions and vessels.[4,6] Olah improved the utility of HF in 1973 by the introduction of pyridinium poly(hydrogen fluoride), which is now known as Olah's reagent.[4,6] It has an estimated composition of 70% HF and 30% pyridine in the form of a stable liquid, which does not lose HF below 50°C.[4,6] The introduction of this reagent allowed for the exploration of a range of new applications.[6]

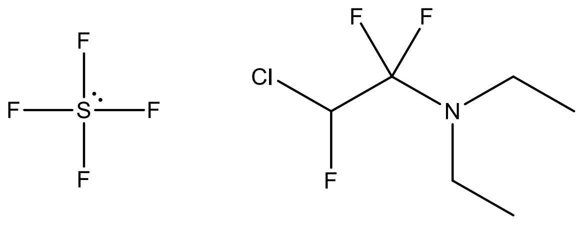
Nucleophilic halogen exchange using potassium fluoride was reported by Gottlieb in 1936,[1] which introduced another popular source of nucleophilic fluorine in the form of the inorganic fluorides (e.g. silver fluoride).[6] They are typically cheap and readily available, but require the use of anhydrous polar solvents in order to obtain acceptable concentrations of dissolved fluoride for reaction.[6] The presence of water in the reaction negatively impacts the nucleophilicity of fluoride as it is strongly solvated in protic solvents.[4,6] In more recent times tetrabutylammonium fluoride (TBAF, **78**) has become a popular alternative instead of the metal fluorides as the large cations reduce ion pairing in aprotic solvents due to delocalization of the positive charge (Figure 1.21).[4,15]



78

Figure 1.21: Structure of TBAF.

Dupont introduced sulfur tetrafluoride (**79**) in 1960 and it was often used in combination with catalytic HF (liquid) or Lewis acids in order to reduce required reaction temperatures and times (Figure 1.22).[6] However, SF_4 (**79**) suffered from the disadvantages of being extremely toxic (similar to phosgene) and having high volatility, requiring the use of specialized reaction vessels.[6] Reaction yields were also typically poor.[6]

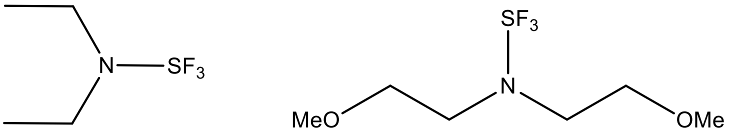


79 **80**

Figure 1.22: Structures of sulfur tetrafluoride (**79**) and CTT (**80**).

2-Chloro-1,1,2-trifluorotriethylamine (CTT, **80**) was first prepared in 1959 and can be considered as the forerunner of DAST (Figure 1.22).[6] It was easier to handle than SF_4 (**79**), but was extremely hygroscopic and could not be stored long at room temperature.[6] It was however, tolerant of a range of functional groups and was thus successfully used for the fluorination of sensitive alcohols.[6]

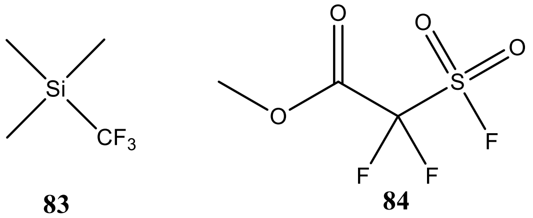
Since the introduction of diethylaminosulfur trifluoride (DAST, **81**), which was first prepared by Middleton in 1975, SF_4 is no longer used (Figure 1.23).[4,6] DAST (**81**) has a substantially improved safety profile as it can be stored at room temperature in plastic bottles and is easy to handle.[6] DAST (**81**) is used for the conversion of alcohols and carbonyl compounds to their respective fluoro derivatives and is more tolerant of a wider range of reaction conditions (solvents, temperature) while giving improved yields.[6,15,26] The introduction of DAST (**81**) was the start of a new era in fluorine chemistry and since its introduction numerous syntheses of organofluorine compounds have been reported.[6] DAST (**81**) does, however, suffer from the disadvantages in that it is hygroscopic, volatile and cannot be used at temperatures above 90°C, at which it disproportionates into SF_4 and $(Et_2N)_2SF_2$ which is also explosive.[27] Deoxofluor (**82**), prepared in the late 1990's, addresses the issue of thermal stability (Figure 1.23).[4]



81 **82**

Figure 1.23: Structures of the nucleophilic fluorinating agents DAST (**81**) and deoxofluor (**82**).

Trifluoromethyltrimethylsilane ($TMSCF_3$, **83**), also known as the Ruppert-Prakash reagent was synthesized in 1984 and is a source of nucleophilic trifluoromethyl anions, which are able to react with carbonyl compounds resulting in the formation of C-CF_3 bonds (Figure 1.24).[4,15] Another source of CF_3^- anions is methyl fluorosulfonyl difluoroacetate (MFSDA, **84**) (Figure 1.24).[15]



83 **84**

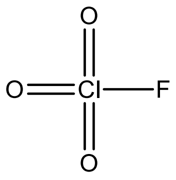
Figure 1.24: Reagents for trifluoromethylation.

1.6.2. **Sources of electrophilic fluorine**

Electrophilic fluorination is the process in which a F^+ cation is transferred to an electron rich centre.[4] F^+ cations, however, do not exist independently and thus sources of F^+ needed to be developed.[4] Many electrophilic fluorinating reagents typically contain an N-F or O-F moiety in their structure, which is able to transfer electropositive fluorine to the carbanions formed from carbonyl compounds.[15]A wide range of electrophilic fluorinating reagents which are used to form C-F bonds are available and the list includes tamed fluorine (diluted with nitrogen gas), perchloryl fluoride, hypofluorites, xenon difluoride, Selectfluor® and *N*-fluorobenzenesulfonimide (NFSI) to mention a few.[3,8]

Replacing a hydrogen atom bonded to an sp^2 or sp^3 carbon is the most direct method to introduce a fluorine atom into an organic molecule, but this requires an electrophilic fluorinating agent.[24,27] The most reactive, as well as most affordable source of electrophilic fluorine is fluorine gas.[1,24] Reactions between fluorine and organic compounds have been described as exceptionally fast, extremely exothermic and very often explosive as well as being toxic and having no selectivity, all of which make working with elemental fluorine a daunting task.[4,27] Since the 1960's, however, tamed fluorine is commercially available in the form of cylinders as a mixture diluted with nitrogen, which moderates its reactivity and improves its safety profile as it substantially reduces the risk of explosion.[1,24] Unfortunately, the use of fluorine gas still requires the use of specialized reaction equipment, which precludes its use for many research laboratories.[27]

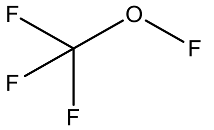
The first reagent to be identified as a source of electrophilic fluorine was perchloryl fluoride (**85**), which readily gave fluoro derivatives after reaction with the anions of weak acids (Figure 1.25).[4,8] Even though **85** is affordable, it suffers from the disadvantage that it is only able to react non-selectively with strongly nucleophilic centres and produces chloric acid as a by-product, which is highly explosive in organic admixtures.[6,8] The hazards associated with the use of **85** can be reduced by dilution with nitrogen gas and slow bubbling conditions.[6]



85

Figure 1.25: Structure of perchloryl fluoride.

The hypofluorites, having the general formula R_F–O–F in which R_F is a fully fluorinated carbon radical were described by Barton in 1968.[6,8] The hypofluorites are able to react with electron rich systems to obtain fluorinated derivatives in good yields.[8] The difference is that the hypofluorites don't need as strong a nucleophilic centre as **85**, are much easier to work with and have a substantially reduced risk of explosion.[8] The simplest member of this class is trifluoromethyl hypofluorite (CF_3OF, **86**), which is a toxic gas, while acetyl hypofluorite (**87**) has become the more popular alternative (Figure 1.26).[6,8]



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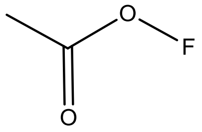


87

Figure 1.26: The electrophilic hypofluorite reagents.

Xenon difluoride (XeF_2), a commercially available crystalline white solid is one of the easiest fluorinating agents to use, however, it is extremely expensive and this has limited its use in synthesis.[4,6] It has been shown to react with alkenes to yield *vic*-difluorides, but it is susceptible to re-arrangement reactions which also limits its utility.[6]

The N-F class of electrophilic fluorination reagents has broadened substantially and includes *N*-fluoropyridinium triflate salts (**88**), *N*-alkyl-*N*-fluorosulfonamides (**89**), *N*-

fluorobenzenesulfonimide (NFSI, **90**), Selectfluor® (**91**) and its derivatives (Figure 1.27).[4] The advantages of the N-F reagents are many and include their stability and easy handling.[4] The propensity for electrophilic fluorination increases with a decrease in the electron density of the N^+-F site, which can be modulated by changing the ring substituents, allowing for the tuning of selectivity and reactivity in these reagents.[4]

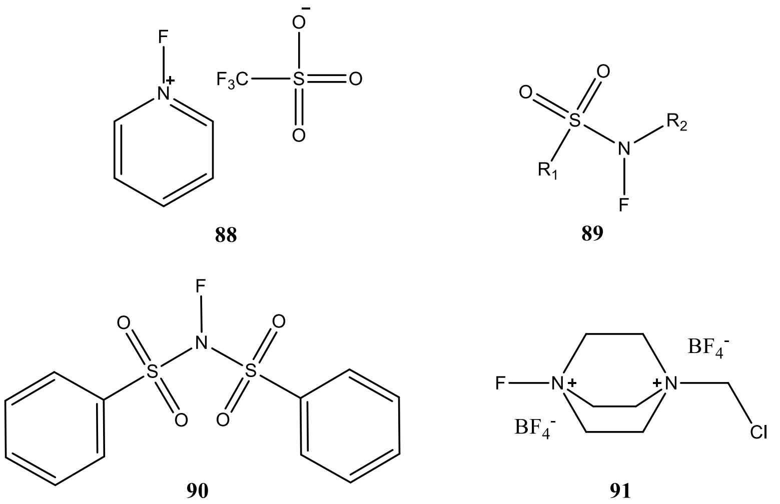


Figure 1.27: N-F fluorinating reagents.

Selectfluor® (**91**), a popular, commercially available electrophilic fluorinating agent, is a crystalline solid that is stable up to 100 °C that can be used in a range of solvents, with acetonitrile being preferred.[26] It is also easy to handle, and non-toxic.[19] This reagent has been used extensively, particularly for the synthesis of fluorinated heterocycles in excellent yields.[15]

In addition to developing tunable *N*-fluoropyridinium triflate salts (**88**) for electrophilic fluorination, the group of Umemoto and co-workers also developed the corresponding electrophilic trifluoromethylation reagents.[4] These reagents are able to transfer a CF_3 group to enolates, carbanions, enol ethers and various electron rich moieties.[4]

Thanks to the synthetic developments in the field of fluorination, it is now possible to synthesise fluorinated analogues of nucleosides, amino acids, sugars and lipids amongst other important drugs.[22] Synthetic methods for the enantioselective introduction of fluorine are in the early stages of development and as such, the development of fluorinating reagents is an area of research which continues to grow and evolve.[4]

1.7. FLUORINATIONS UTILISING FLOW CHEMISTRY

Flow chemistry is a novel technology which can be used for the economical manufacture of fine chemicals, and particularly active pharmaceutical ingredients (API's) in an environment where economies of scale are not usually realized. Flow chemistry is defined as the "use of continuous plug flow reactors as opposed to conventional batch reactors"[28,29] for the synthesis of fine chemical intermediates and API's.

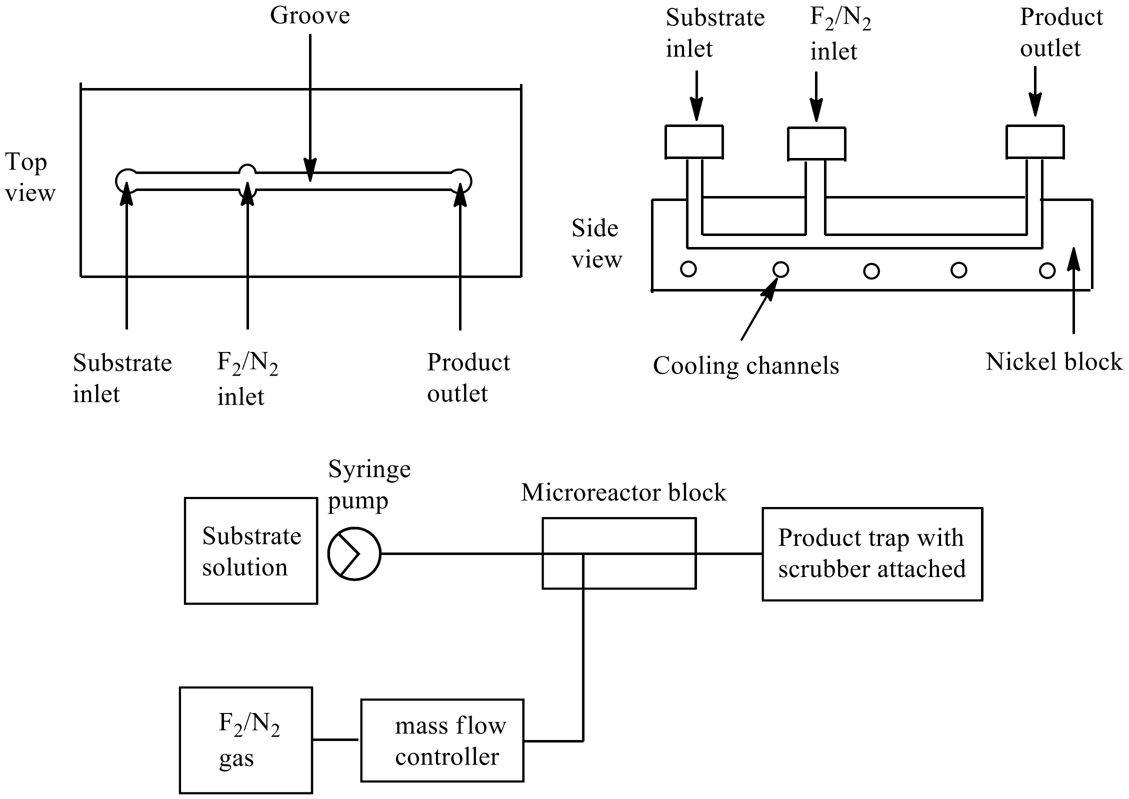
Chemical reactions are run in continuous flow streams which means that reagents are continuously pumped into the reactor while the products are continuously pumped out.[29,30] This implies that only a small amount of material is reacting at any given moment in time, which is the main contributing factor to the improved safety profile of the technology.[29,30] The speedy removal of products from the reactor also limits decomposition of sensitive substrates often leading to improved purities and yields.[29,30]

Flow chemistry makes use of immobilized reagents, scavengers and catch and release techniques in order to facilitate in-line work-up, purification and optimization.[30,31] Traditional glassware is replaced with cartridges and columns that can be pre-packed with various solid supported reagents, or by reaction microchips and coils which allow for the controlled mixing of reagents along with excellent control of reaction temperature, pressure and reaction time.[30,31] Homogenous processes typically occur within tubular or microchip reactors, while heterogenous processes occur within fixed bed reactors packed with the solid or polymer supported reagents or catalysts.[28-33]

Some of the advantages of flow chemistry in comparison to traditional batch chemistry include higher specificity, higher yields, higher throughput with smaller reactor volumes, lower production costs, improved mixing and scale-up, excellent mass and heat transfer as well as improved use of solvents and chemicals to mention a few.[28-33] Despite the many advantages of flow chemistry, no technology is perfect and some of the disadvantages include the high cost of the equipment, dispersion of reagents and products through the system, the use of highly corrosive reagents such as aqueous hydrochloric acid which are often not well tolerated as well as the problem of precipitates, which lead to reactor blockages and thus need to be avoided.[28,29,33] This can have a major influence on time, as methods need to be found to circumvent some of these situations.[28,29,33]

Typically, organofluorine synthesis is faced with many challenges such as poor stability of reagents, difficulties associated with handling of these reagents, stringent equipment requirements and the limited range of reagents that are currently available.[27] The syntheses also often suffer from poor selectivity and the presence of unstable intermediates.[27] The use of flow chemistry has provided a viable solution to many of these challenges, particularly when it comes to the safe handling of reagents and dealing with unstable intermediates.[27] The use of flow chemistry for fluorination results in small volumes of fluorine being in contact with reagents, more efficient mixing, better heat exchange and thus temperature control, improved gas/liquid interfaces and a substantially improved safety profile.[34]

The first flow synthesis incorporating fluorine was reported in 1999 by Chambers and Spink.[35,36] They designed a microreactor which they manufactured from a block of nickel in which they cut a groove to serve as the microreactor, followed by sealing with a block of polychlorotrifluoroethene (Scheme 1.1).[35,36] The reactants and solvents were then injected by means of a syringe and syringe pump while the fluorine/nitrogen mixture was introduced from a cylinder by means of a mass-flow controller.[35,36] Using this setup they performed several selective fluorinations on gram scale to obtain aromatic sulfur pentafluorides from aromatic disulfides as well as fluorinated β-dicarbonyls with excellent efficiencies while obtaining a through-put of 0.5-5.0 mL.h^{-1}.[35,36]



Scheme 1.1: Initial microreactor designed by Chambers and Spink shown at the top with the flow scheme shown below.[35,36]

The original microreactor of Chambers and Spink only contained a single channel and in order to prove scalability they manufactured a three channel microreactor using the same design as shown in Scheme 1.1.[35,36] This design was, however, not practical for further scale up as each channel required its own separate feed system, resulting in a very large number of joints and fittings.[37] The reactor was thus re-designed to incorporate reservoirs in a base block which fed into a plate that contained 3, 9 or 30 channels.[37] The channels were once again sealed with a sheet of polychlorotrifluoroethene and all the plates were screwed together tightly to complete the reactor.[37] This reactor was then used to demonstrate the direct fluorination of diesters,[37] malonate esters,[37] ethyl acetoacetate,[34] 1,3-ketoesters,[38] 1,3-diketones,[38] 1,3- and 1,4-disubstituted aromatics[39] using flow conditions to obtain good yields in shorter reaction times using flow rates of 0.43 – 1.27 mmol.h^{-1}.channel^{-1}.

In 2000, Jähnisch and co-workers reported the direct fluorination of toluene using elemental fluorine by means of two different reactors: a falling film microreactor (FFM) and a micro bubble column (MBC).[40] The FFM was a vertically orientated device in which a thin film of liquid (around 10 μm thick) was fed through openings at flow rates of 11.1-19.6 mL.h^{-1} into a plate containing a number of reaction channels and allowed to run down the surface under the force of gravity (Figure 1.28).[40] This allowed for a large contact area between the liquid and dilute fluorine gas which was passed over the surface of the liquid.[40]

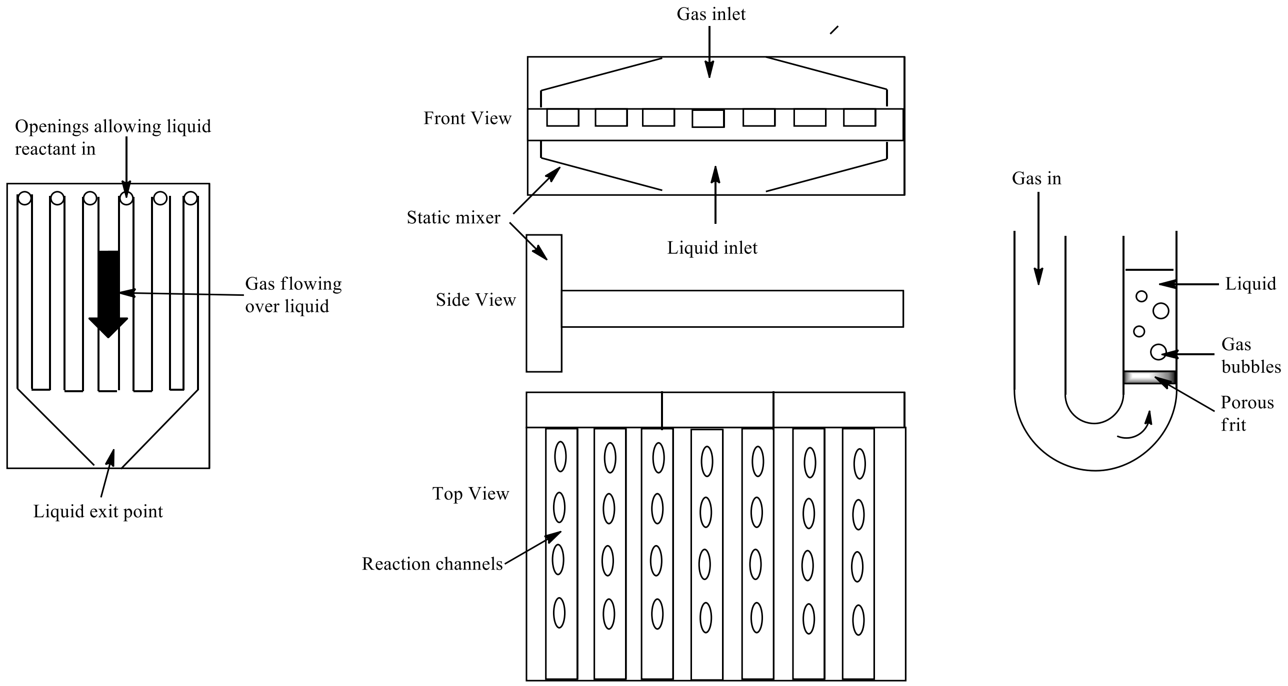
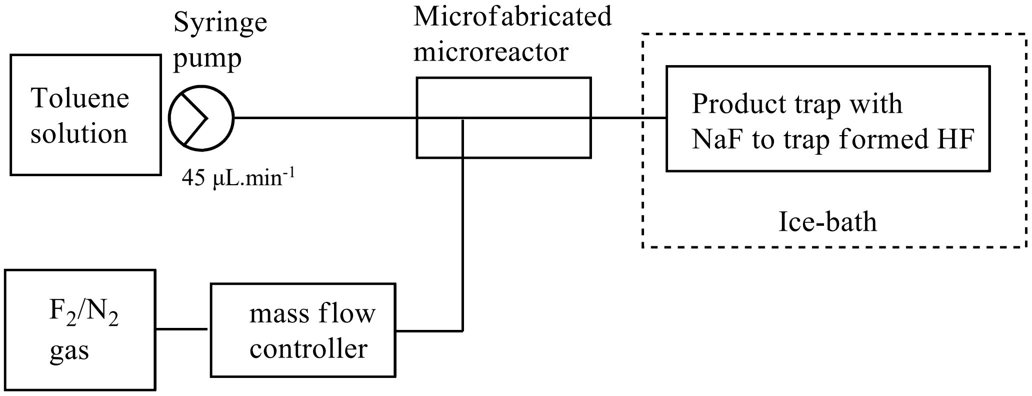


Figure 1.28: Falling film microreactor (left), microbubble column (middle) and laboratory bubble column of Jähnisch and co-workers.[40]

The MBC consisted of an initial static mixing unit followed by a reaction unit containing channels (Figure 1.28).[40] Within the MBC, alternating plugs of liquid (flow rate of 13 mL.h^{-1}) and gas (flow rate of 12-50 mL.min^{-1}) were obtained where the liquid plugs were around 110-700 μm thick between the gas bubbles but only around 10 μm thick between the walls of the channel and the gas bubble, which notably increased the surface area for reaction.[40] The FFM and MBC exhibited an increase in selectivity and conversion when compared to the traditional benchtop method which consisted of a tube fitted with a porous frit allowing the gas to be dispersed into the liquid (Figure 1.28).[40]

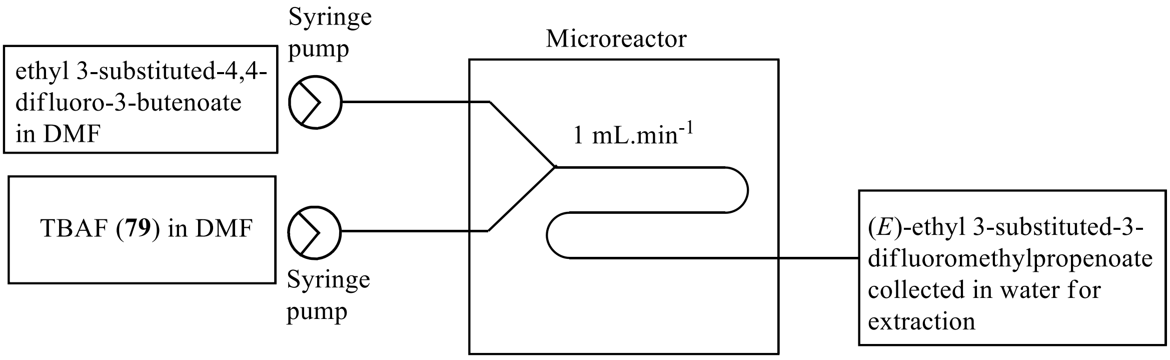
This was followed by de Mas and co-workers, who in 2003, built a microfabricated microreactor chip by means of silicon processing and metal deposition techniques.[41] They used pyrex and silicon as the structural materials coated with a thin film of nickel and silicon oxide to provide corrosion protection.[41] The reactor chip was then mounted between a stainless steel base and plexiglass viewing plate securely screwed together, using gaskets to effectively seal the unit. Their reactor allowed for the safe and efficient direct mono-fluorination of toluene in good yield with acceptable selectivity at a rate of 2 mg.h^{-1} (Scheme 1.2).[41]



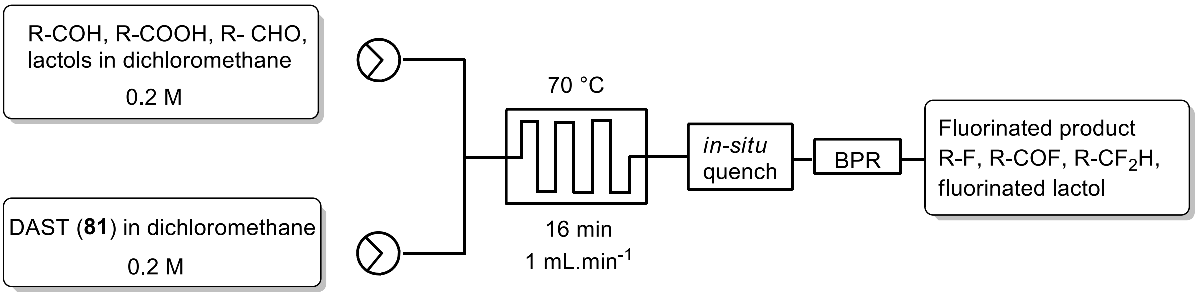
Scheme 1.2: Flow scheme used by de Mas and co-workers for the direct fluorination of toluene.[41]

In 2004, the group of Turnbull also developed their own microreactor to use with elemental fluorine, drawing inspiration from the design of Chambers and Spink.[2] The idea behind their design was to have something that could quickly and easily be stripped down for cleaning and re-assembled, thus they went with a “sandwich” system.[2] A stainless steel body was therefore machined that could hold three PTFE plates and contained appropriate inlet and outlet ports.[2] The first PTFE plate featured the liquid and gas inlets as well as the product outlet in the form of three holes drilled into the plate.[2] The second PTFE plate had the reaction channel cut through it, while the third plated served as a closing plate.[2] This was capped off with a larger steel plate which was screwed into place to apply the necessary pressure to seal the system.[2] They then proceeded to test their reactor using the direct fluorination of anisole, nitrobenzene and toluene in acetonitrile as model reactions. They pumped the solutions (50-100 mg.mL^{-1}) at a flow rate of 1.0 mL.h^{-1} and the fluorine at a gas flow rate of 10 mL.min^{-1} with all the reactions exhibiting mono-fluorination to some extent.[2] They also performed fluorination of a β-diketone for the purposes of comparison.[2]

Kitazume and co-workers[42] in 2005 reported the stereoselective synthesis of terminal difluoromethylated alkenes to (*E*)-difluoromethylated alkenes in high stereoselectivities (>99:<1) by means of a proton migration in the presence of TBAF (**79**) in DMF using a microreactor (Scheme 1.3).[42] In their work they found that control of the reaction temperature was critical for control of the *E/Z* ratio, with the use of a microreactor leading to superior temperature control when compared to batch reactions.[42]



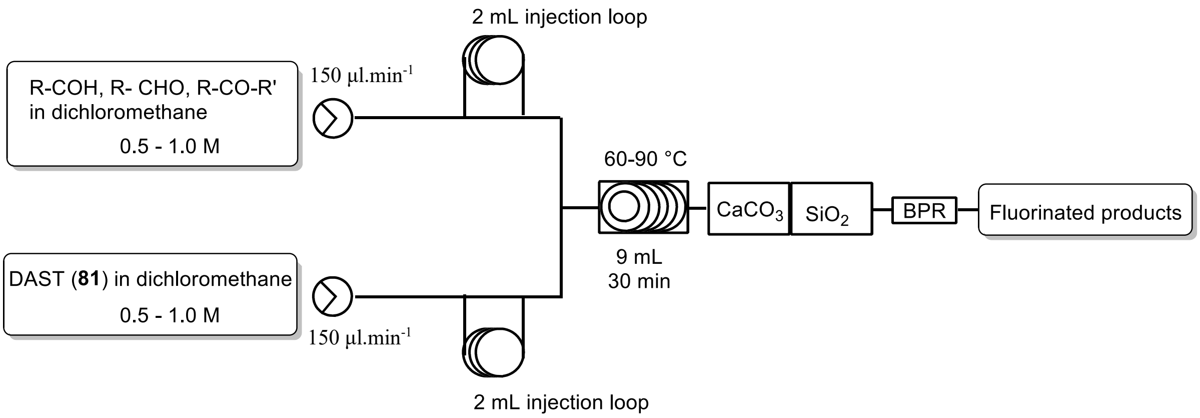
Scheme 1.3: Flow scheme for the stereoselective synthesis of (*E*)-difluoromethylated alkenes used by Kitazume and co-workers.[42]



Scheme 1.4: Flow synthesis for the deoxyfluorination of lactols, alcohols, carboxylic acids and aldehydes developed by Seeberger.[43]

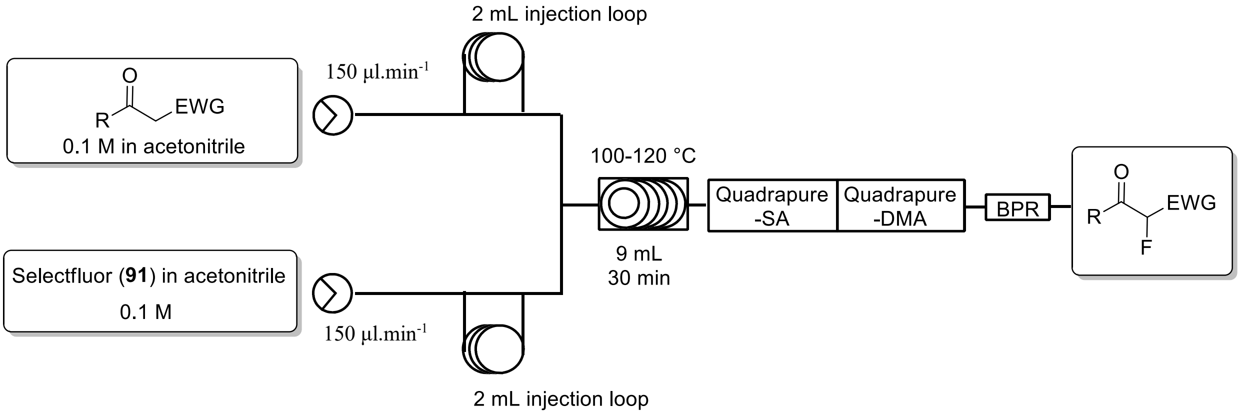
The first reports of flow synthesis using DAST (**81**) for the conversion of alcohols and carbonyl compounds to the analogous fluoro derivatives appeared in 2008, with both the groups of Seeberger[43] and Ley[44] publishing their results. Seeberger and co-workers developed a general method for the deoxyfluorination of lactols, alcohols, carboxylic acids and aldehydes (Scheme 1.4). The solutions of the starting material and DAST (**81**) in dichloromethane were injected into a Syrris FRX microreactor (16 cm^3) followed by heating to a temperature of 70 °C for a reaction time of 16 minutes at a flow rate of 1 $mL.min^{-1}$.[43] This was followed by the *in-situ* quenching of the formed HF and excess DAST (**81**) followed by collection of the crude fluorinated product.[43] The incorporation of a back pressure regulator (BPR) allowed for super heating of the dichloromethane without the risk of gassing out.[43] Manual extraction followed by column chromatography provided the purified products in good to excellent yields.[43]

The group of Ley focused on the conversion of alcohols, aldehydes and ketones, obtaining similar results to Seeberger.[44] In their work, Ley and co-workers made use of the R2+/R4 reactor which is available from Vapourtec.[44] Their reaction setup made use of sample loops (2 mL) for the injection of the reagents (0.5 M, 1 mmol scale) followed by mixing in a T-piece.[44] The flow stream then passed through a coil reactor (9 mL) heated to 60-90 °C and passage through an Omnifit® glass column packed with calcium carbonate and silica gel (Scheme 1.5).[44] This arrangement prevented the corrosive DAST (**81**) from coming into contact with metal components as well as allowed for *in-situ* quenching and purification.[44] The output of the reactor was collected and the solvent evaporated to obtain the fluorinated products in good yields without the requirement of further work-up or purification protocols, making this method arguably more effective than that of Seeberger.[44]

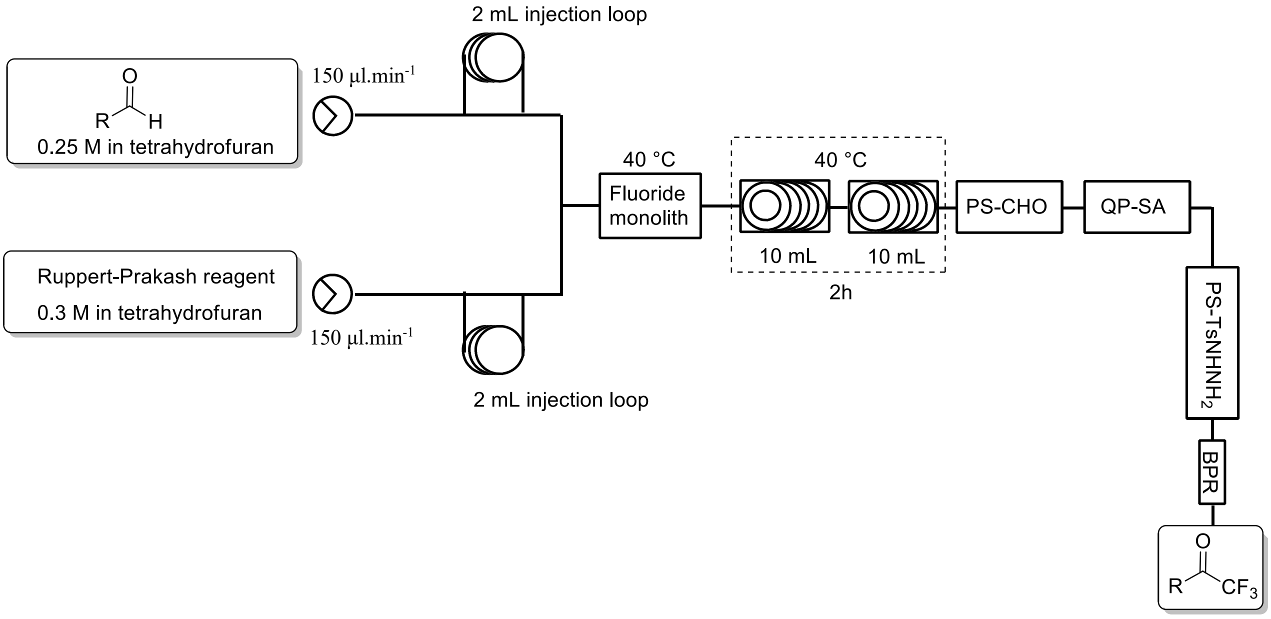


Scheme 1.5: Continuous flow setup for DAST (**81**) fluorination used by Ley and co-workers.[44]

During the course of their research they also noted that many sensitive functional groups remained intact during the process.[26,44] Ley and co-workers proceeded to follow this work with an improved procedure incorporating an in-line infrared detector between the Omnifit® column and the BPR as a tool for direct analysis of product formation allowing for more rapid process optimization.[45] Continuing their work on fluorinations, using similar reactor setups to that shown in Scheme 1.5, they then developed flow syntheses in which they used Selectfluor® (**91**) to fluorinate activated carbonyls and olefins (Scheme 1.6) as well as used the Ruppert-Prakash reagent on aldehydes to generate the trifluoromethylated addition products (Scheme 1.7).[26]

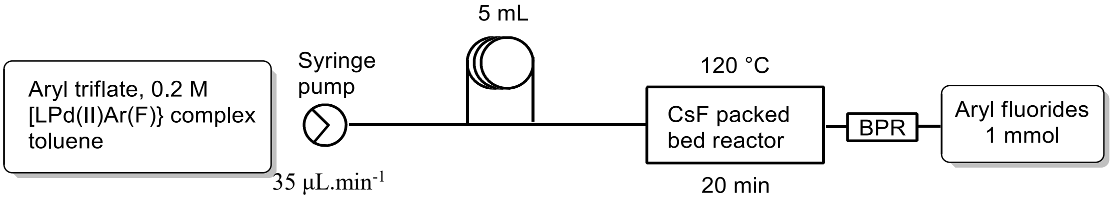


Scheme 1.6: Continuous flow setup for Selectfluor® (**91**) fluorination.[26]



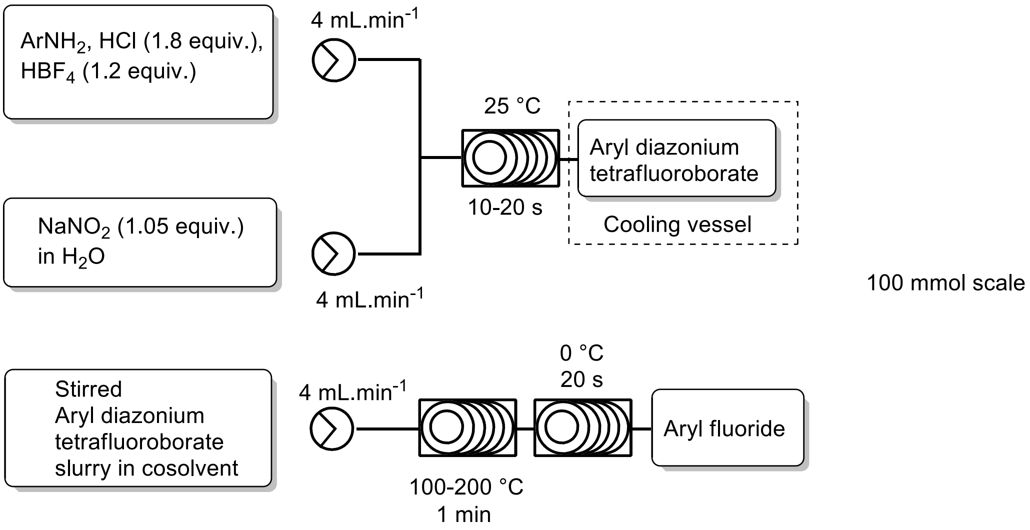
Scheme 1.7: Continuous flow setup for the Ruppert-Prakash trifluoromethylation.[26]

The group of Buchwald developed a flow process for the reductive elimination of aryl fluorides by means of a palladium catalyzed conversion of aryl triflates with cesium fluoride (Scheme 1.8).[27,46] The catalyst used was a [LPd(II)Ar(F)] complex where L was the biaryl monophosphine ligand *t*BuBrettPhos, while the cesium fluoride was packed into a packed-bed reactor which they developed in-house.[46,47] The use of flow chemistry allowed for a substantial reduction in reaction time as well as required the use of less catalyst and less cesium fluoride when compared to the corresponding batch reaction.[46,47]



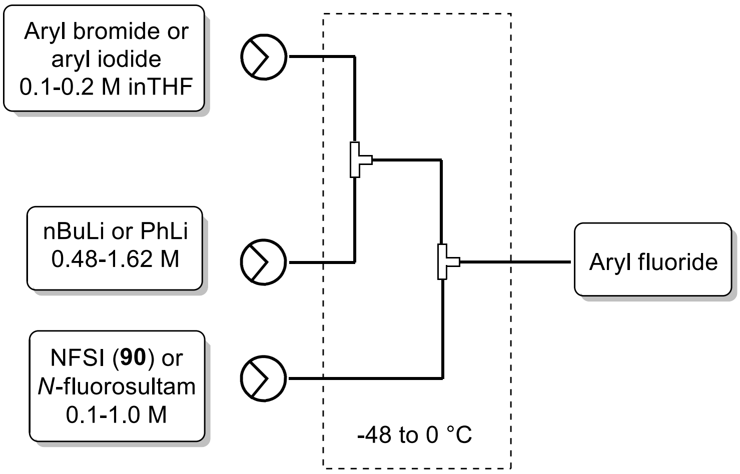
Scheme 1.8: Reductive elimination of aryl fluorides under flow conditions.[27,46,47]

A flow process for the synthesis of aryl fluorides by means of the Balz-Schiemann reaction was reported by Yu and co-workers in which they formed a diazonium tetrafluoroborate salt in one process followed by the controlled thermal decomposition in a second process (Scheme 1.9).[48] The first process resulted in the formation of the diazonium tetrafluoroborate which was crystallized out followed by manual filtration and drying.[48] The diazonium tetrafluoroborate was then suspended in the required cosolvent system and pumped through a heated coil to initiate thermal decomposition to the corresponding aryl fluoride.[48] In their process they battled with solubility problems, but managed to obtain improved yields when compared to the batch process.[48]



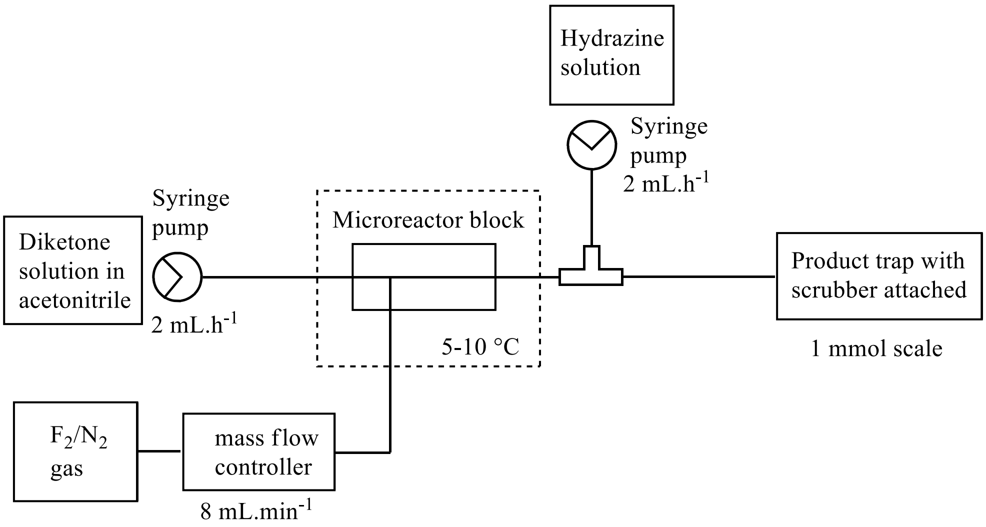
Scheme 1.9: Two stage flow process for the Balz-Schiemann reaction.[48]

Following an alternative route, Nagaki and co-workers opted for the reaction of aryl organolithium reagents with electrophilic fluorinating agents under flow conditions for the synthesis of functionalized aryl fluorides in acceptable yields (Scheme 1.10).[49] They took advantage of the short residence times that can be achieved using flow microreactors as it enabled them to make use of highly unstable aryl lithium compounds.[49] Their system made use of two T-piece mixers for reagent mixing followed by a short reaction path before collection of the product.[49]



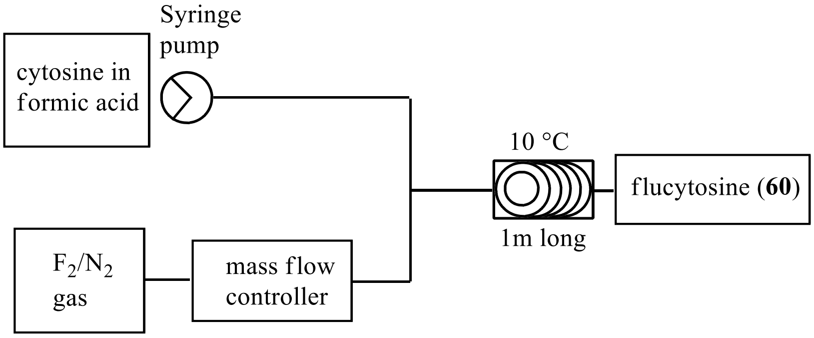
Scheme 1.10: Flow synthesis of aryl fluorides using organolithium reagents.[49]

Breen and co-workers reported the continuous flow synthesis of 4-fluoropyrazole derivatives by means of a direct fluorination of diketones (1 mmol scale), followed by a cyclization reaction with a hydrazine derivative in a two-step telescoped process.[50] This was the first report of a gas/liquid-liquid/liquid process incorporating fluorination.[50] Their process involved reaction between dilute fluorine gas and a solution of the diketone within the nickel metal reactor developed by Chambers and Spink discussed earlier, followed by reaction with a solution of hydrazine by means of a T-piece (Scheme 1.11).[50] The output of the reactor was collected in a vessel which contained water for the effective quenching of any excess HF formed and which was also connected to a soda-lime scrubber.[50] Manual extraction followed by column chromatography provided the pure product in good yields.[50]



Scheme 1.11: Gas/liquid-liquid/liquid flow synthesis of 4-fluoropyrazole derivatives.[50]

In 2017, the one step flow synthesis of flucytosine (**60**) was reported by Harsanyi and co-workers in which they used 10% fluorine in nitrogen to fluorinate cytosine using formic acid as the solvent, obtaining a yield of 63% after trituration and filtration, which was almost double that obtained using traditional batch processes (38%).[51] For their flow synthesis they opted for the use of a narrow-bore stainless steel tube to serve as the reaction vessel using a mass flow controller to control the rate of fluorine addition and a syringe pump for the addition of the cytosine solution (Scheme 1.12).[51] As proof of concept they performed the reaction on pilot scale resulting in the isolation of 58 g.h^{-1} flucytosine (**60**) after work-up.



Scheme 1.12: The flow synthesis of flucytosine (**60**) of Harsanyi and co-workers.[51]

The flow synthesis of multiple radiolabeled imaging probes has also been reported, with Lee and co-workers using a microreactor to prepare 2-deoxy-2-[^{18}F]fluoro-D-glucose in high radiochemical yield and purity.[52] The group of Steel also opted for the preparation of 2-deoxy-2-[^{18}F]fluoro-D-glucose as a model compound obtaining a yield of 40% with a total reaction time of 10 minutes.[53] Numerous groups have since reported the flow synthesis of 2-deoxy-2-[^{18}F]fluoro-D-glucose, [^{18}F]fallypride and [^{18}F]annexin using various different flow reactors and techniques.[27,54]

1.8. CONCLUSION

Fluorine is typically introduced to effectively modulate various pharmacokinetic and physiochemical properties and as such the synthesis of fluorinated compounds has become an integral part of many drug research programs, which has led to numerous highly successful drugs.[12,18] The use of fluorine in medicinal chemistry has provided strong motivation for the development of more efficient synthetic methodology, however, the introduction of fluorine into a molecule is not always simple and can add substantially to the cost of a project.[19,26] Thus, the development of fluorination methods which are safe, effective, affordable and efficient as well as suitable for industrial scale remains an ongoing challenge.[25,36] Great strides have been made as many fluorinating agents have been developed, some of which have enjoyed more success than others.[36] Advances in flow chemistry have made it possible to safely and efficiently perform selective fluorination as well as perfluorination reactions at both laboratory and industrial scale, although much work still remains to be done in advancing the utility of flow chemistry when it comes to organofluorine chemistry.[24] Further improvements in synthetic methodology could result in an increase in the number of fluorinated drugs available on the market as well as make many of the currently available fluorinated drugs more affordable, such as flucytosine (**60**), which is on the World Health Organization's list of essential drugs, but is prohibitively expensive, especially for poorer third world countries which have the greatest need.[5,51]

As a result of flow chemistry being a relatively new field, its use for fluorination and the synthesis of fluorinated drugs has not yet been extensively explored. This study focusses on the conversion of traditional batch synthesis to continuous flow processes for the following selection of compounds:

- 5-Fluorocytosine (marketed as the drug Flucytosine, **60**), which is an important antifungal agent.
- Hexafluorobuta-1,3-diene, which is an industrially important dry-etch reagent.
- Aryl diazonium tetrafluoroborate salts, which are important intermediates in many syntheses.
- Aryl hydrazines, which are required for the synthesis of many drugs including pyrazoles such as Celecoxib (**27**).
- Celecoxib (marketed as the drug Celebrex, **27**), which is an important anti-inflammatory drug.

The syntheses will be examined in terms of feasibility for translation to flow chemistry, with each synthesis being optimized under batch and flow conditions to allow for fair comparison between the two methods. The flow processes developed should ideally be industrially viable or at the very least, expand the scope of technology available to organofluorine chemists.

1.9. REFERENCES

(1) Okazoe, T. *Proc. Jpn. Acad., Ser. B*, **2009**, *85*, 276.

(2) Turnbull, M.D.; Carter, N.B.; Dennison, S.; Deacon, J.; Holley, R. *Chimia*, **2004**, *58*, 159.

(3) Müller, K.; Faeh, C.; Diederich, F. *Science*, **2007**, *317*, 1881.

(4) Kirk, K.L. *Org. Process Res. Dev.*, **2008**, *12*, 305.

(5) Swallow, S. Fluorine in Medicinal Chemistry, Chapter 2 in Progress in Medicinal Chemistry, Volume 54, Elsevier, **2015**, pp 65 – 133.

(6) Mann, J. *Chem. Soc. Rev.*, **1987**, *16*, 381.

(7) Chambers, R.D. General Discussion of Organic Fluorine Chemistry, Chapter 1 in Fluorine in Organic Chemistry, Blackwell Publishing Ltd, Oxford, UK, **2004**, pp 1 – 9.

(8) Barton, D.H.R. *Pure Appl. Chem.*, **1970**, *21*, 285.

(9) McBee, E.T. *Indust. & Eng. Chem.*, **1947**, *39*, 2.

(10) Purser, S.; Moore, P.R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.*, **2008**, *37*, 320.

(11) Ismail, F.M.D. *J. Fluorine Chem.*, **2002**, *118*, 27.

(12) Shah, P.; Westwell, A.D. *J. Enzyme Inhib. Med. Chem.*, **2007**, *22*, 527.

(13) O’Hagan, D.; Rzepa, H.S. *Chem. Commun.*, **1997**, 645.

(14) Kirk, K.L. *J. Fluorine Chem.*, **2006**, *127*, 1013.

(15) Hagmann, W.K. *J. Med. Chem.*, **2008**, *51*, 4359.

(16) Yamazaki, T.; Taguchi, T.; Ojima. Unique Properties of Fluorine and Their Relevance to Medicinal Chemistry and Chemical Biology. Chapter 1 in Fluorine in Medicinal Chemistry and Chemical Biology, Ojima, I. (ed.), Blackwell Publishing Ltd, Oxford, UK, **2009**, pp 3 – 46.

(17) Krafft, M.P. *Adv. Drug Deliv. Rev.*, **2001**, *47*, 209.

(18) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem*, **2004**, *5*, 637.

(19) Gillis, E.P.; Eastman, K.J.; Hill, M.D.; Donnelly, D.J.; Meanwell, N.A. *J. Med. Chem.*, **2015**, *58*, 8315.

(20) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.*, **2006**, *127*, 303.

(21) Bégué, J.-P.; Bonnet-Delpon, D. *J. Fluorine Chem.*, **2006**, *127*, 992.

(22) Gerig, J.T. Fluorine NMR, **2001**, pp 1 – 3.

(23) Croft, A.M. *J. R. Soc. Med.*, **2007**, *100*, 170.

(24) Sandford, G. *J. Fluorine Chem.*, **2007**, *128*, 90.

(25) Breen, J.R.; Sandford, G.; Yufit, D.S.; Howard, J.A.K.; Fray, J.; Patel, B. *Beilstein J. Org. Chem.*, **2011**, *7*, 1048.

(26) Baumann, M.; Baxendale, I.R.; Martin, L.J.; Ley, S.V. *Tetrahedron*, **2009**, *65*, 6611.

(27) Amii, H.; Nagaki, A.; Yoshida, J.-I. *Beilstein J. Org. Chem.*, **2013**, *9*, 2793.

(28) Ley, S.V.; Baxendale, I.R. *Nat. Rev.*, **2002**, *1*, 573.

(29) Baxendale, I.R.; Ley, S.V. Solid Supported Reagents in Multi-Step Flow Synthesis. New Avenues to Efficient Chemical Synthesis: Emerging Technologies. Ernst Schering Foundation Symposium Proceedings 2006-3, Eds P.H. Seeberger, T. Blume, Springer-Verlag: Berlin, Heidelburg, **2007**, Chapter 3, pp 151-185.

(30) Pastre, J.C.; Browne, D.L.; Ley, S.V. *Chem. Soc. Rev.*, **2013**, *42*, 8849.

(31) Baxendale, I.R.; Deeley, J.; Griffiths-Jones, C.M.; Ley, S.V.; Saaby, S. and Tranmer, G.K. *Chem. Commun.*, **2006**, 2566.

(32) Ley, S.V. and Baxendale, I.R. *The Chemical Record*, **2002**, *2*, 377.

(33) Wegner, J.; Ceylan, S.; Kirschning, A. *Chem. Commun.*, **2011**, *47*, 4583.

(34) Chambers, R.D.; Fox, M.A.; Holling, D.; Nakano, T.; Okazoe, T.; Sandford, G. *Lab Chip*, **2005**, *5*, 191.

(35) Chambers, R.D.; Spink, R.C.H. *Chem. Commun.*, **1999**, 883.

(36) Chambers, R.D.; Holling, D.; Spink, R.C.H.; Sandford, G. *Lab Chip*, **2001**, *1*, 132.

(37) Chambers, R.D.; Fox, M.A.; Holling, D.; Nakano, T.; Okazoe, T.; Sandford, G. *Chem. Eng. Technol.*, **2005**, *28*, 344.

(38) Chambers, R.D.; Fox, M.A.; Sandford, G. *Lab Chip*, **2005**, *5*, 1132.

(39) Chambers, R.D.; Fox, M.A.; Sandford, G.; Trmcic, J.; Goeta, A. *J. Fluorine Chem.*, **2007**, *128*, 29.

(40) Jähnisch, K.; Baerns, M.; Hessel, V.; Ehrfeld, W.; Haverkamp, V.; Löwe, H.; Wille, Ch.; Guber, A. *J. Fluorine Chem.*, **2000**, *105*, 117.

(41) de Mas, N.; Günther, A.; Schmidt, M.A.; Jensen, K.F. *Ind. Eng. Chem. Res.*, **2003**, *42*, 698.

(42) Kitazume, T.; Kawai, K.; Nihei, T.; Miyake, N. *J. Fluorine Chem.*, **2005**, *126*, 59.

(43) Gustafsson, T.; Gilmour, R.; Seeberger, P.H. *Chem. Commun.*, **2008**, 3022.

(44) Baumann, M.; Baxendale, I.R.; Ley, S.V. *Synlett*, **2008**, *14*, 2111.

(45) Carter, C.F.; Lange, H.; Ley, S.V.; Baxendale, I.R.; Wittkamp, B.; Goode, J.G.; Gaunt, N.L. *Org. Process Res. Dev.*, **2010**, *14*, 393.

(46) Watson, D.A.; Su, M.; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S.L. *Science*, **2009**, *325*, 1661.

(47) Noël, T.; Maimone, T.J.; Buchwald, S.L. *Angew. Chem. Int. Ed.*, **2011**, *50*, 8900.

(48) Yu, Z.-Q.; Lv, Y.-W.; Yu, C.-M.; Su, W.-K. *Tetrahedron Lett.*, **2013**, *54*, 1261.

(49) Nagaki, A.; Uesugi, Y.; Kim, H.; Yoshida, J.-I. *Chem. Asian J.*, **2013**, *8*, 705.

(50) Breen, J.R.; Sandford, G.; Yufit, D.S.; Howard, J.A.K.; Fray, J.; Patel, B. *Beilstein J. Org. Chem.*, **2011**, *7*, 1048.

(51) Harsanyi, A.; Conte, A.; Pichon, L.; \rabion, A.; Grenier, S.; Sandford, G. *Org. Process Res. Dev.*, **2017**, *21*, 273.

(52) Lee, C.-C.; Sui, G.; Elizarov, A.; Shu, C.J.; Shin, Y.-S.; Dooley, A.N.; Huang, J.; Daridon, A.; Wyatt, P.; Stout, D.; Kolb, H.C.; Witte, O.N.; Satyamurthy, N.; Heath, J.R.; Phelps, M.E.; Quake, S.R.; Tseng, H.-R. *Science*, **2005**, *310*, 1793.

(53) Steel, C.J.; O'Brien, A.T.; Luthra, S.K.; Brady, F. *J. Label. Compd Radiopharm.*, **2007**, *50*, 308.

(54) (a) Elizarov, A.M.; van Dam, R.M.; Shin, Y.S.; Kolb, H.C.; Padgett, H.C.; Stout, D.; Shu, J.; Huang, J.; Daridon, A.; Heath, J.R. *J. Nucl. Med.*, **2010**, *51*, 282. (b) Gillies, J.M.; Prenant, C.; Chimon, G.N.; Smethurst, G.J.; Dekker, B.A.; Zweit, J. *Appl. Radiat. Isot.* **2006**, *64*, 333. (c) Gillies, J.M.; Prenant, C.; Chimon, G.N.; Smethurst, G.J.; Perrie, W.; Hamblett, I.; Dekker, B.A.; Zweit, J. *Appl. Radiat. Isot.* **2006**, *64*, 325. (d) Lu, S.; Giamis, A.M.; Pike, V.W. *Curr. Radiopharm.*, **2009**, *2*, 49. (e) Briard, E.; Zoghbi, S.S.; Siméon, F.G.; Imaizumi, M.; Gourley, J.P.; Shetty, H.U.; Lus, S.; Fujita, M.; Innis, R.B.; Pike, V.W. *J. Med. Chem.*, **2009**, *52*, 688. (f) Lu, S.-Y.; Watts, P.; Chin, F.T.; Hong, J.; Musachio, J.L.; Briard, E.; Pike, V.W. *Lab Chip*, **2004**, *4*, 523. (g) Pascali, G.; Mazzone, G.; Saccomanni, G.; Manera, C.; Salvadori, P.A. *Nucl. Med. Biol.*, **2010**, *37*, 547. (h) Pascali, G.; Nannavecchia, G.; Pitzianti, S.; Salvadori, P.A. *Nucl. Med. Biol.*, **2011**, *38*, 637. (i) Chun, J.-H.; Lu, S.; Lee, Y.-S.; Pike, V.W. *J. Org. Chem.*, **2010**, *75*, 3332. (j) Philippe, C.; Ungersboeck, J.; Schirmer, E.; Zdravkovic, M.; Nics, L.; Zeilinger, M.; Shanab, K.; Lanzenberger, R.; Karanikas, G.; Spreitzer,

H.; Viernstein, H.; Mitterhauser, M.; Wadsak, W. *Bioorg. Med. Chem.*, **2012**, *20*, 5936. (k) Keng, P.Y.; Chen, S.; Ding, H.; Sadeghi, S.; Shah, G.J.; Dooraghi, A.; Phelps, M.E.; Satyamurthy, N.; Chatziioannou, A.F.; Kim, C.-J.; van Dam, R.M. *Proc. Natl. Acad. Sci.*, **2012**, *109*, 690.

Chapter 2:

5-Fluorocytosine

2. Synthesis of 5-Fluorocytosine

2.1. KEYWORDS

5-Fluorocytosine, Selectfluor®, antifungal.

2.2. ABSTRACT

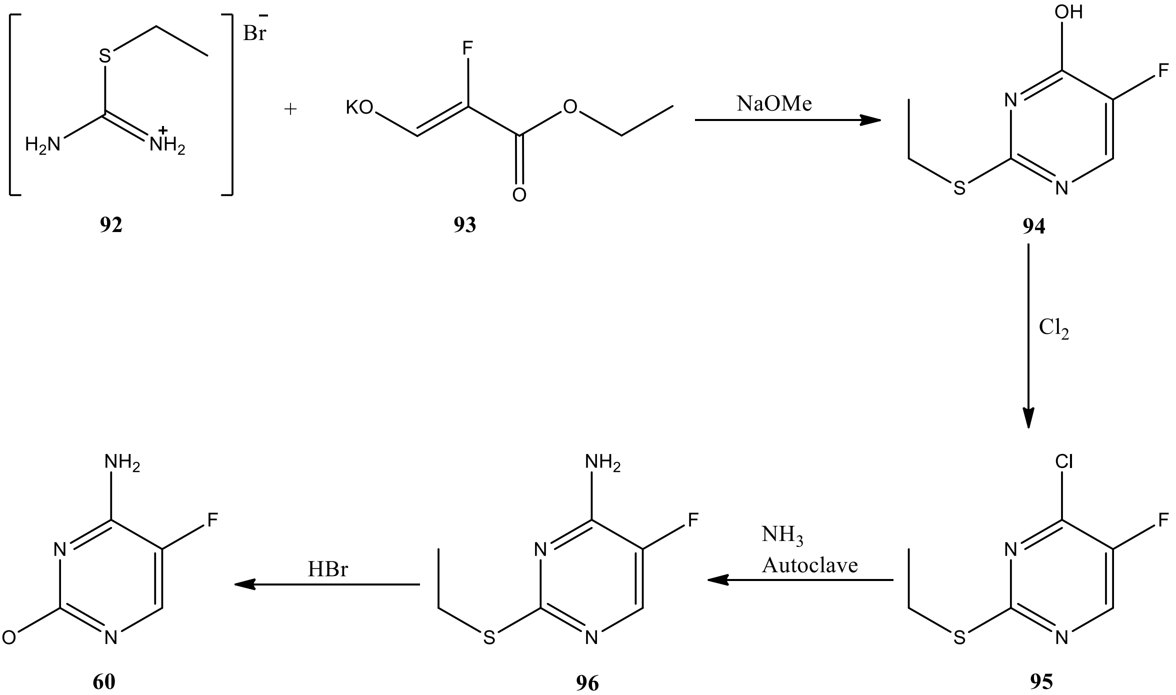
The efforts to develop a batch mode synthesis of 5-fluorocytosine (5-FC, **60**), an important antifungal and anti-cancer prodrug are reported. The batch mode synthesis of cytosine (**97**) was achieved by means of a condensation reaction between urea (**103**) and 3-ethoxyacrylonitrile (**104**) with improved work-up and purification (82%), followed by unsuccessful endeavors at electrophilic fluorination using Selectfluor® (**91**) to access 5-FC (**60**). The reactions were also critically examined for potential conversion to a continuous flow process, which could not be achieved due to the poor solubility of cytosine (**97**) in a wide range of solvents.

2.3. INTRODUCTION

5-Fluorocytosine (5-FC, **60**) is an important, high demand antifungal agent which is frequently used with azole type antifungals like fluconazole.[1] More recently it has found use in the therapeutic treatment of various types of cancer, particularly colorectal carcinomas. For this approach 5-FC (**60**) is used in conjunction with an *Escherichia coli* gene coding for the enzyme cytosine deaminase in an enzyme/prodrug anti-cancer combination.[1] Furthermore, 5-FC (**60**) is also an essential intermediate in the synthesis of another anticancer agent – capecitabine.[2]

5-FC (**60**) was first prepared by Duschinsky and co-workers[3] in 1957 starting from a pseudothiourea salt (**92**) and an α-fluoro-β-keto ester enolate (**93**) in the presence of base to obtain 2-(ethylthio)-5-fluoropyrimidin-4-ol (**94**). Compound **94** then underwent chlorination (**95**), followed by amination (**96**) and hydrolysis to obtain 5-FC (**60**) in a yield of 52% (Scheme 2.1).

Duschinsky and co-workers[4] later reported an alternative synthesis starting from 5-fluorouracil involving chlorination at the C-2 and C-4 positions of the pyrimidine ring, followed by amination of the C-4 position and hydrolysis of the C-2 position to obtain 5-FC (**60**) in a yield of 96%. Undheim and Gacek[5] also chose to start with 5-fluorouracil, but opted instead for thionation of the C-4 position, followed by chlorination of C-4 and finally amination of C-4 to insert the required amino functionality to obtain 5-FC (**60**) in a yield of 80%.



Scheme 2.1: First synthesis route of Duschinsky and co-workers to access 5-FC (**60**).[3]

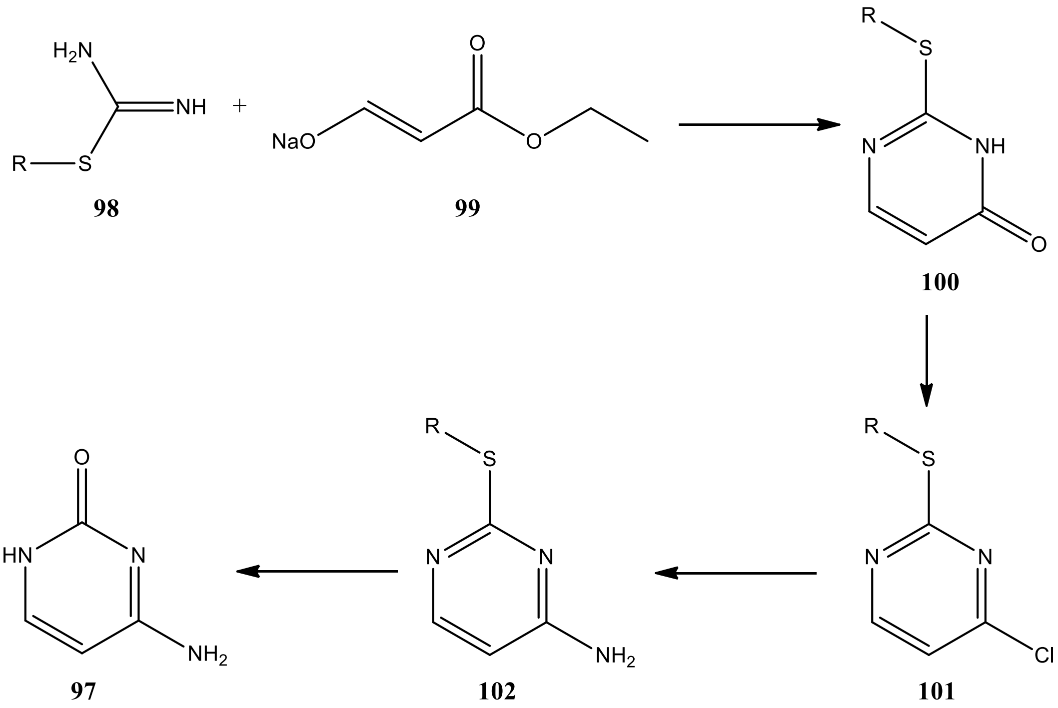
A much shorter route to 5-FC (**60**) involves the direct fluorination of cytosine. Robins and co-workers[6] used trifluoromethyl hypofluorite in trichlorofluoromethane to obtain 5-FC (**60**) in a yield of 85%, while Takahara[7] elected to use HF in combination with F_2 gas diluted with N_2 gas to obtain 5-fluorocytosine hydrofluoride in 89% yield. In their efforts to study the mechanism and stereochemistry of the fluorination reaction, Visser and co-workers[8] performed the fluorination of cytosine using gaseous acetyl hypofluorite and F_2 gas for comparative purposes, obtaining 5-FC (**60**) in yields of 7-29%.

In an alternative synthesis, Baasner and Klauke[9] started with 2,5-difluoro-4,6-dichloropyrimidine, which was hydrogenated to obtain 2,5-difluoro-4-chloropyrimidine followed by nucleophilic substitution to obtain 4-chloro-5-fluoro-2-hydroxypyrimidine and amination to obtain 5-FC (**60**) in a yield of 98%.

The first flow synthesis of 5-FC was reported by Harsanyi and co-workers[2,10] from cytosine using formic acid as the solvent and gaseous F_2 diluted with N_2 as the source of electrophilic fluorine. This was followed by a lengthy work-up procedure requiring more than 12 hours to obtain 5-FC (**60**) in 83% yield, compared to the batch reaction which only resulted in a yield of 38% using the same reagents.

Most of these syntheses either suffered from many steps, low yields or the use of difficult to handle reagents such as HF and F_2 gas. While the more direct syntheses also rely on the availability of relatively expensive cytosine (**97**), which is a biologically important pyrimidine compound that occurs naturally in nucleic acids.[11] An efficient and cost-effective synthesis of cytosine (**97**) would thus be beneficial towards the synthesis of 5-FC (**60**) and many other research projects.

The first synthesis of cytosine (**97**) was reported in 1903 by Wheeler and Johnson[11,12] starting from a pseudothiourea (**98**) and the sodium salt of ethyl formyl acetate (**99**) to obtain 2-mercapto-4-oxypyrimidine (**100**) (Scheme 2.2). This was followed by reaction with phosphorus pentachloride to obtain 2-mercapto-4-chloropyrimidine (**101**), which was subjected to amination (**102**) followed by hydrolysis to obtain cytosine (**97**).



Scheme 2.2: First synthesis route of Wheeler and Johnson to access cytosine (**97**).[11,12]

The synthesis of Wheeler and Johnson was disadvantaged by its use of difficult techniques and the evolution of methanethiol. This was circumvented by Hilbert and Johnson[11] via conversion of uracil to 2,4-dichloropyrimidine followed by amination to obtain 2-chloro-4-aminopyrimidine, which could then be hydrolyzed to cytosine (**97**) in a yield of 85%.

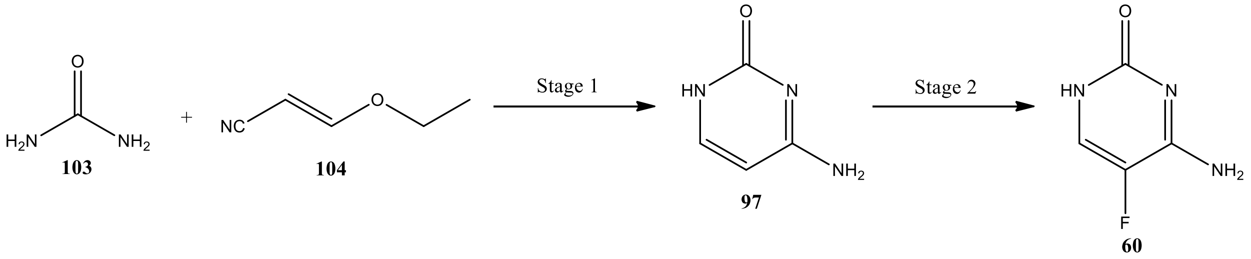
In an alternative synthesis, Hilbert and Jansen[13] opted to convert 2,4-dichloropyrimidine into 2,4-diethoxypyrimidine followed by preparation of the sodium salt thereof, which was treated with acetic acid and then aminated to obtain cytosine (**97**). The starting material of choice for Hitchings and co-workers[14] was dithiouracil which they subsequently selectively aminated at the C-4 position followed by formation of the corresponding carboxymethylthiopyrimidine and hydrolysis to obtain cytosine (**97**) in a yield of 83%. A major drawback of this synthesis was the tedious work-up procedures coupled with numerous recrystallizations.

The most popular and most widely tested route to access cytosine (**97**) involves reacting urea (**103**) with 3-ethoxyacrylonitrile (**104**) or other cyanoacetal in various solvents and under various reaction conditions resulting in reported yields of 43-78%,[15] the major disadvantage, being complicated and extensive work-up procedures involving numerous acid-base extractions, neutralizations and recrystallizations to access pure cytosine (**97**).[15]

To date, a short, high yielding batch synthesis for 5-FC (**60**) along with its continuous flow alternative, using reagents which are easy to handle and that are readily available has not been reported.

2.4. RESULTS AND DISCUSSION

The preferred synthetic route to access 5-fluorocytosine (**60**) (Scheme 2.3) involved a condensation reaction between urea (**103**) and 3-ethoxyacrylonitrile (**104**) to access cytosine (**97**) (Stage 1). This was be followed by electrophilic fluorination using Selectfluor® (**91**) to obtain 5-fluorocytosine (**60**) (Stage 2). Batch optimization was performed to investigate if there were any improvements to be made to the reported protocols and assess whether the reactions could be successfully translated to an automated flow process.



Scheme 2.3: Synthetic route to 5-fluorocytosine (**60**).

Batch optimization stage 1: Since the majority of published procedures[15] report reacting urea (**103**) with 3-ethoxyacrylonitrile (**104**) or other cyanoacetal, this route was deemed to be the simplest and most reliable to access cytosine (**97**) in good yields. It was determined that improvements to the first stage would benefit the overall synthesis, thus, the reaction was optimized in terms of solvent, temperature, duration and concentration. The work-up procedures were also carefully evaluated as this appeared to be the point at which the most product loss occurred. A solvent screen using low molecular weight protic solvents was initially performed, with the base source derived from the *in-situ* preparation of the corresponding sodium salts (Table 2.1).

Table 2.1: Solvent optimization using the method of Loquai and co-workers[15c]

	Solvent	**Temperature (°C)**	**Yield (%)**
1	MeOH	80	10
2	EtOH	80	15
3	^{i}PrOH	80	59
4	*t*-BuOH	90	28

Standard conditions:**103** (1.1 equiv.), **104** (1.0 equiv.), base (1.2 equiv.), 3 h.

The condensation reaction proceeded satisfactorily as monitored by TLC (thin layer chromatography), however, the isolated yields were disappointingly low. It was speculated that the poor yields obtained were a result of the work-up and purification protocols adapted from literature, which involved multiple concentrations to dryness (3-4 times), pH adjustments (1-2 times) and re-crystallizations (3-4 times) resulting in multiple stages at which product loss could occur.[14,15c] An improved and simplified work-up and purification protocol was developed which took advantage of the solubility/insolubility of cytosine in various solvents. The reaction mixture was diluted with EtOH, filtered through a silica plug and concentrated. The crude cytosine was dissolved in water followed by washing with an organic solvent. The aqueous layer was collected, concentrated to dryness and the residue obtained suspended in acetonitrile followed by vacuum filtration to afford cytosine (**97**) as a fine, light yellow solid. This avoided the use of pH adjustments and multiple re-crystallizations.

A set of temperature optimization reactions were performed using isopropanol in the range of 25-100 °C (Figure 2.1) and when coupled with the new work-up and purification protocol afforded an isolated yield of 72% for cytosine (**97**) at 90 °C, above which temperature the yield decreased substantially.

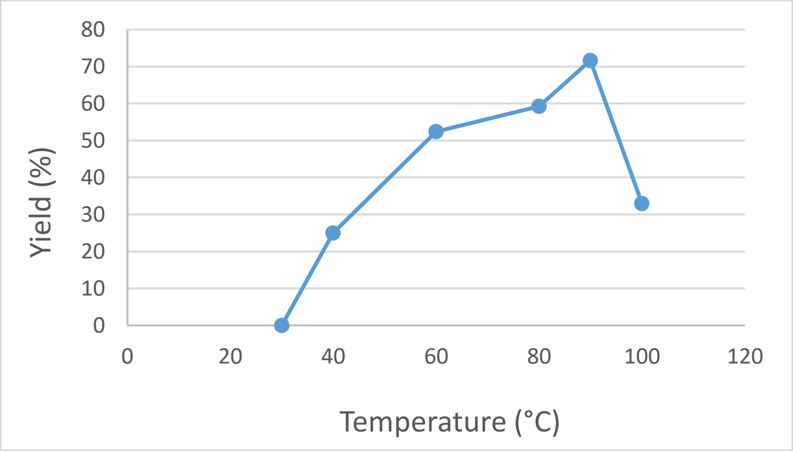


Figure 2.1: Study of the effect of reaction temperature on formation of **97**.

Standard conditions: **103** (1.3 equiv.), **104** (1.0 equiv.), sodium isopropoxide (1.2 equiv.), IPA, 3 h.

The effect of altering the limiting reagent from 3-ethoxyacrylonitrile (**104**) to urea (**103**) was then examined (Table 2.2) and even though the reactions in which urea (**103**) was the limiting reagent gave lower yields when using the initially devised work-up protocol (described above), it was determined that these reaction conditions would allow for further improvement and simplification of the reaction work-up. Due to the insolubility of cytosine (**97**) in isopropanol, the formed cytosine (**97**) could be collected by vacuum filtration without the need for tedious extractions and it was decided that further optimization would lead to improvements in the yield.

Table 2.2: Effect of altering the limiting reagent

Equiv. Urea (103)	**Equiv. 3-ethoxyacrylonitrile (104)**	**Equiv. Sodium isopropoxide**	**Temperature**	**Yield (%)**
1.3	1.0	1.2	80	59
1.0	1.1	1.0	80	46
1.3	1.0	1.2	90	72
1.0	1.1	1.0	90	56

Standard conditions: IPA, 3 h, extraction based work-up.

An evaluation of the reaction duration in isopropanol (Figure 2.2) showed a yield of 82 % for **97** obtained after 2 hours of reaction, thereafter at higher temperatures the isolated yield plateaued.

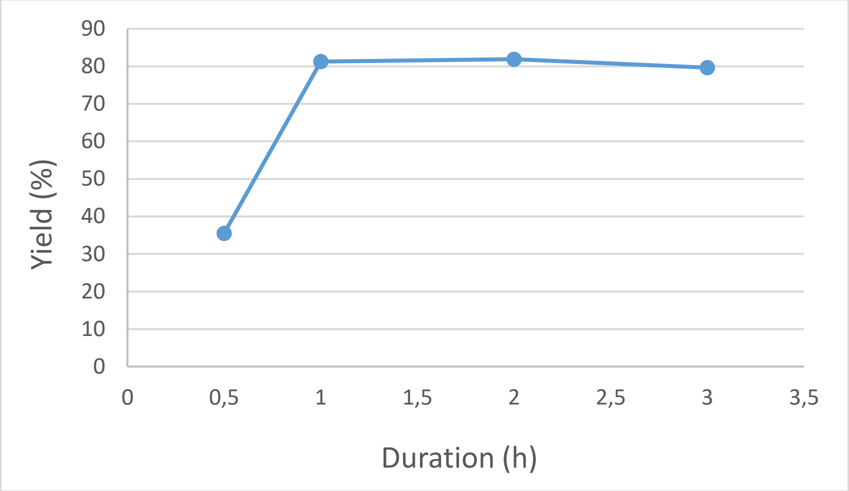


Figure 2.2: Study of the effect of reaction duration on formation of **97**.

Standard conditions: **103** (1.0 equiv.), **104** (1.1 equiv.), sodium isopropoxide (1.0 equiv.), IPA, 90 °C.

An assessment was then performed to determine the highest concentration that the reaction could be performed at relative to urea (**103**) (Table 2.3). This information also allowed the determination of the lowest concentration relative to urea (**103**) at which the reaction could be performed without reduced yields. This resulted in an optimal concentration of 1.63 M, with the isolated yield decreasing noticeably as the concentration decreased.

Table 2.3: Concentration optimization

Equiv. Urea (103)	Equiv. 3-ethoxyacrylonitrile (104)	Equiv. Sodium isopropoxide	[Urea] (M)	Yield (%)
1.0	1.1	1.0	1.12	40
1.0	1.1	1.0	1.34	75
1.0	1.1	1.0	1.63	82

Standard conditions: IPA, 1 h, 90 °C.

The final optimized batch conditions for the condensation involved a reaction time of 2 hours at 90 °C using 1.0 equiv. urea (**103**), 1.1 equiv. 3-ethoxyacrylonitrile (**104**) and 1.0 equiv. sodium isopropoxide in IPA at a concentration of 1.63 M relative to urea (**103**). This was followed by a work-up/purification involving vacuum filtration to obtain a yield of 82% of **97** which could be carried forward into stage 2.

Saladino and co-workers reported ^{1}H NMR spectral shifts of δ 7.35 (m, 1H, CH); 7.15 (br s, 1H, NH); 5.60 (m, 1H, CH) and 3.40 (br s, 2H, NH_2) using d_6-DMSO as solvent.[16a] Bio-Rad Laboratories on the other hand obtained ^{1}H NMR spectral shifts of δ 10.6 (br s, 1H); 7.3 (d, 1H); 7.1 (br s, 2H) and 5.6 (d, 1H) using d_6-DMSO as solvent (Figure 2.3).[16b] In the presence of D_2O, only the shifts at δ 7.3 and δ 5.6 remained detectable, with the absent shifts being assigned to the NH and NH_2 protons.[16c]

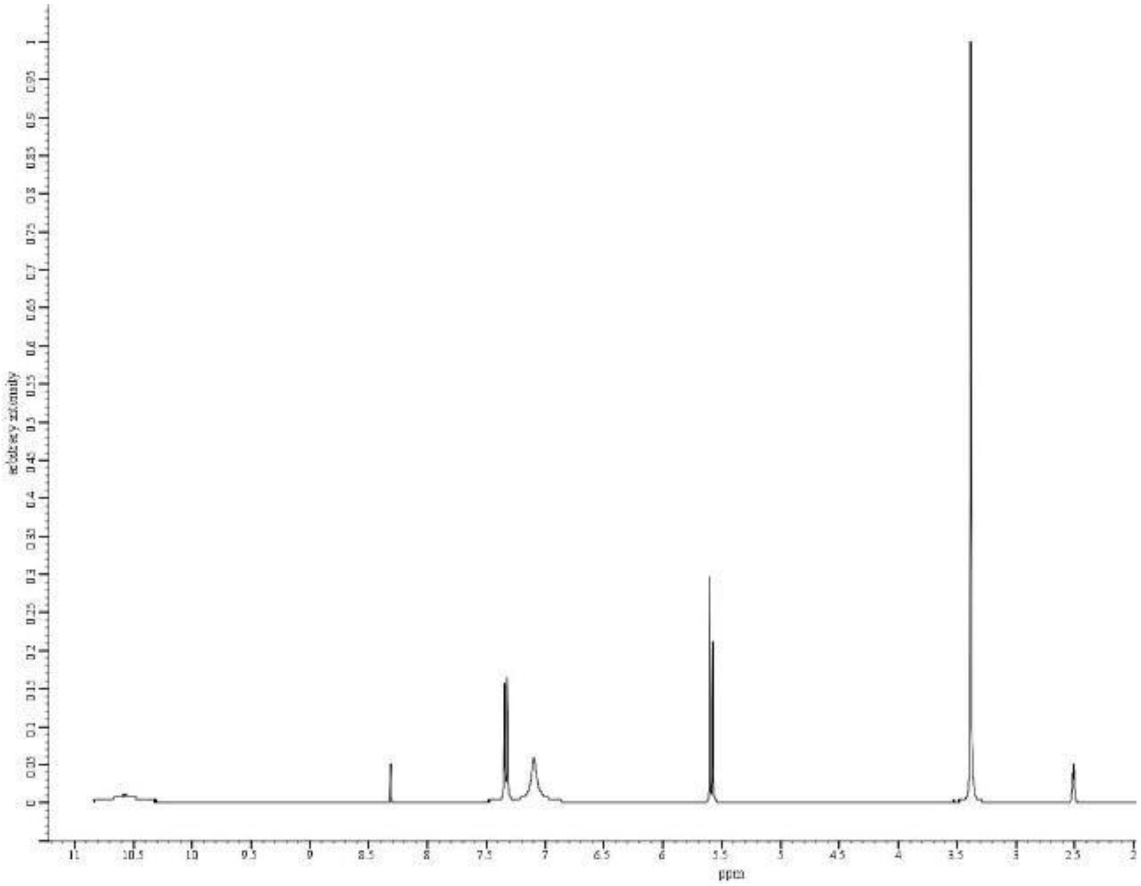


Figure 2.3: ^{1}H NMR spectrum of Bio-Rad Laboratories.[16b]

The experimental ^{1}H NMR spectrum (Figure 2.4) obtained exhibited shifts at δ 10.66 (s, 1H, NH); 7.34 (d, 1H, *J* 6.96, NC<u>H</u>CH); 7.15 (s, 2H, NH_2) and 5.60 (d, *J* 6.96, 1H, NCHC<u>H</u>), with the shifts at δ 10.66 and δ 7.15 disappearing in a D_2O exchange experiment, which indicated that these shifts belonged to the NH and NH_2 protons. These results correlate well with the data obtained by Bio-Rad Laboratories, which would indicate that the group of Saladino and co-workers potentially incorrectly assigned their spectrum possibly due to poor resolution, which is evidenced by the fact that they reported multiplets instead of well defined doublets for the ring proton shifts. They also appear to mistake residual water in their spectrum for the NH_2 shift – which may have led them to miss the shift at 10.6, which is difficult to detect due to the very broad nature of the peak.

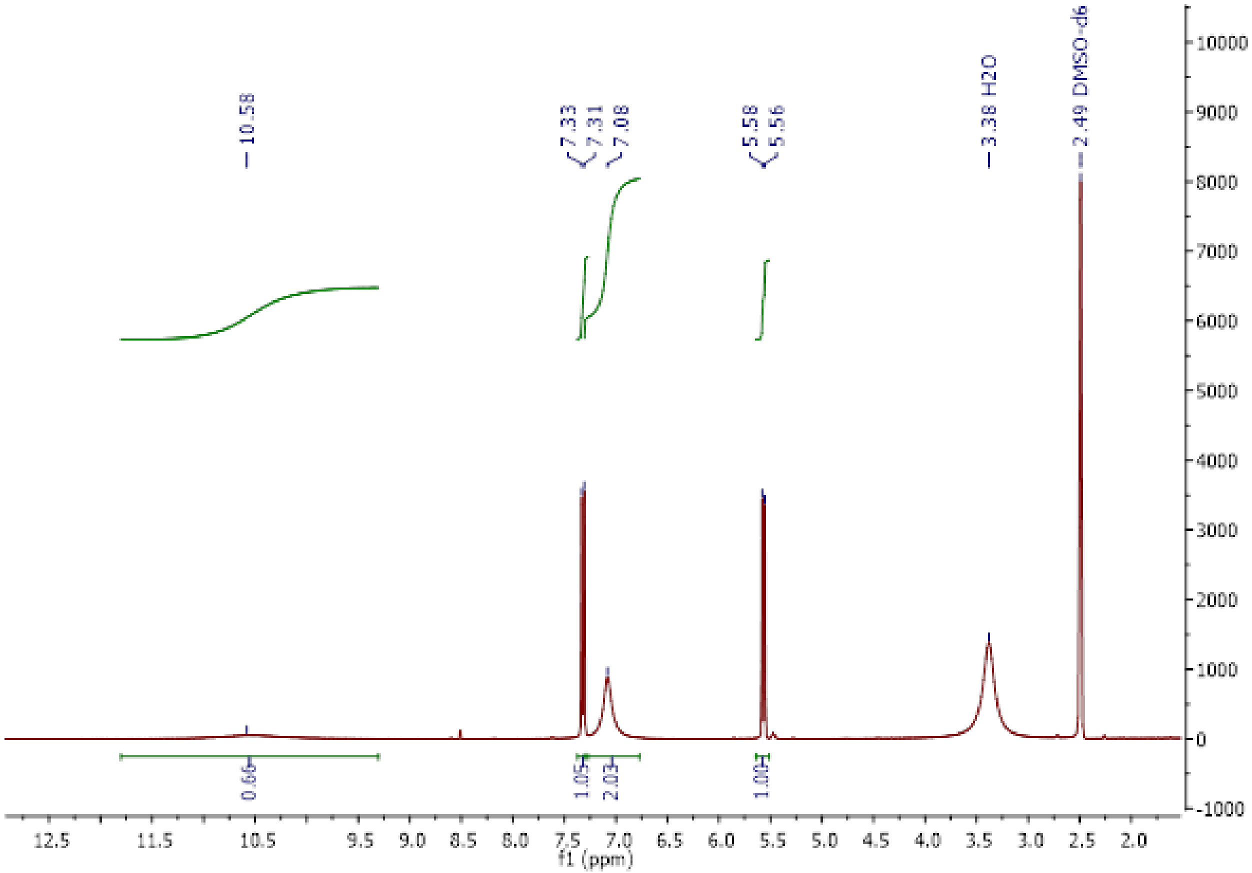


Figure 2.4: Experimental ^{1}H NMR spectrum of cytosine (**97**).

Batch optimization stage 2: The majority of published procedures report using trifluoromethyl hypofluorite[6a,b] or gaseous fluorine,[2,7,8,10] to effect the electrophilic fluorination of cytosine (**97**) resulting in reported yields of 7-85% for 5-fluorocytosine (**60**). Numerous reports can be found in which Selectfluor® (**91**) is successfully used as an electrophilic fluorinating agent,[17] however, no report could be found in which Selectflour® (**91**) has been used to synthesise 5-FC (**60**) from cytosine (**97**). A solvent screen was performed using the available literature procedures as reference.[17a,18] The choice of applicable solvents were severely limited by the range of solvents tolerated by Selectfluor® (**91**) and the poor solubility of cytosine (**97**) in most solvents (Table 2.4).

Table 2.4: Solvent optimization

	Solvent	**Temperature (°C)**	**Yield (%)**
1	Acetonitrile	Room for 2 hours	0
2	H_2O	90 for 70 hours Room for 2 weeks	0

Standard conditions: **97** (1.0 equiv.), Selectfluor® (**91**, 1.5 – 2.0 equiv.).

According to literature,[17] for reasons of solubility, the preferred solvent for electrophilic fluorinations involving Selectfluor® (**91**) is usually acetonitrile with the reaction proceeding rapidly at room temperature. It was speculated that the insolubility of cytosine (**97**) in acetonitrile is what resulted in the reaction failing to produce any of the desired product, thus the reaction was repeated using water as the solvent with heating. This also failed to produce the desired product. Looking at the pyrimidine ring it can be seen that the two nitrogen atoms within the ring exert a strong electron withdrawing effect. This results in an aromatic system which is electron poor and thus more susceptible to nucleophilic attack, specifically at the C-4 and C-6 positions. As a result of this electron arrangement within the pyrimidine ring the C-5 position is thus weakly susceptible to electrophilic attack.[19] This reasoning led to the proposition that the C-5 position of the pyrimidine ring of cytosine (**97**) is not activated/nucleophilic enough for the electrophilic fluorination to occur. Motorin and co-workers[19] report that the C-5 position of the pyrimidine ring undergoes electrophilic reaction only after the pyrimidine ring has been activated by nucleophilic addition at the C-6 position. This implies that a method to sufficiently activate the C-5 position before electrophilic fluorination would thus first need to be extensively investigated in order to obtain the desired 5-fluorocytosine (**60**).

Translation to continuous flow: In order for a reaction to be viable for translation to flow the reaction mixture needs to be homogenous, or make use of solid supported reagents when a heterogenous system is required. This implies that if there is evidence of precipitation or formation of thick suspensions or slurries under batch conditions then the reaction cannot easily be performed under flow conditions as this will result in severe blockages within the pumps and tubing of the reactor. During the batch optimization of stage 1, extensive precipitation of the product cytosine (**97**) was observed across the range of solvent systems tested. As a result of this it was decided that stage 1 could not be safely converted to a continuous flow process. Stage 2 shows potential for translation to a continuous flow process, but this would be heavily dependent on the reaction conditions required to activate the C-5 position sufficiently for reaction with Selectfluor® (**91**). Any sign of reagent solubility issues or precipitation would also complicate the translation of this stage to continuous flow. The poor solubility of cytosine (**97**) in most solvents is the major restricting factor for both stage 1 and stage 2 in terms of conversion from a traditional batch synthesis to a multistep continuous flow process. This makes finding a solvent which is conducive to the chemistry of both stages extremely difficult, potentially requiring a solvent swap between stages. Due to these factors the probability of developing a multistep continuous flow process for the synthesis of 5-fluorocytosine (**60**) starting from urea (**103**) and 3-ethoxyacrylonitrile (**104**) is substantially reduced.

2.5. CONCLUSION

In conclusion we have demonstrated an improved batch process for the synthesis of cytosine (**97**) in a yield of 82%, using reagents which are commercially available and safe to handle. A simplified work-up and purification protocol was also developed, which contributed significantly to the improved yields. The batch synthesis of 5-fluorocytosine (**60**) could not be achieved, probably due to the poor activity of the C-5 position of the pyrimidine ring of cytosine (**97**). The reactions were evaluated for potential translation to continuous flow, however, the multistep flow synthesis of 5-fluorocytosine (**60**) could not be achieved due to the poor solubility of cytosine (**97**) in a wide range of solvents as this would have resulted in severe blockages within the reactor unit, and because 5-fluorocytosine (**60**) could not be successfully accessed under batch conditions in the allocated time.

2.6. EXPERIMENTAL SECTION

All solvents and reagents were purchased from Sigma-Aldrich and used without further purification. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AVANCE-III 300 MHz spectrometer or a Bruker AVANCE-III 400 MHz spectrometer with the residual solvent peak as an internal reference (DMSO-d_6 = 2.49 and 39.5 ppm for ^{1}H and ^{13}C NMR spectra respectively). Chemical shifts, δ, are reported in parts per million (ppm), and splitting patterns are given as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m). Coupling constants, *J*, are expressed in hertz (Hz). Yields refer to isolated pure products unless stated otherwise.

General procedure for the preparation of cytosine (97)

A solution of sodium (0.11 g, 4.6 mmol, 1.0 equiv.) was dissolved in isopropanol (2.8 mL) followed by the addition of urea (**103**) (0.27 g, 4.6 mmol, 1.0 equiv.) and warming to 90 °C. Thereafter, 3-ethoxyacrylonitrile (**104**) (0.50 mL, 4.9 mmol, 1.1 equiv.) was added dropwise. The reaction mixture was stirred at 90 °C for 2 hours. The solid formed was collected by vacuum filtration and washed with isopropanol (2 x 4 mL) to obtain a pale yellow solid (0.41 g, 3.7 mmol, 82%). R_f = 0.26 (60 % EtOAc/MeOH). ^{1}H NMR (400 MHz d_6-DMSO) 10.66 (s, 1H, NH); 7.34 (d, 1H, *J* 6.96, NC$\underline{\text{H}}$CH); 7.15 (s, 2H, NH_2); 5.60 (d, *J* 6.96, 1H, NCHC$\underline{\text{H}}$). ^{13}C NMR (100 MHz d_6-DMSO) 165.71, 164.87, 151.96, 91.71.

Attempted preparation of 5-fluorocytosine (60)

A solution of cytosine (**97**) (0.17 g, 1.5 mmol, 1.0 equiv.) was dissolved in water (25 mL) followed by the addition of Selectfluor® (**91**) (1.10 g, 3.1 mmol, 2.0 equiv.) and reaction at 90 °C for 70 hours followed by room temperature for 2 weeks. Amberlite-IRA400 (1.11 g) and Amberlyst-15 (1.11 g) were added followed by reaction for 1 hour. The resins were removed by vacuum filtration and washed with water (2 x 10 mL). The filtrate was concentrated to obtain a pale yellow solid which was not the expected product by NMR spectroscopic analysis.

2.7. REFERENCES

(1) Vermes, A.; Guchelaar, H.-J.; Dankert, J. *J. Antimicrob. Chemother.*, **2000**, *46*, 171.

(2) Harsanyi, A.; Conte, A.; Pichon, L.; Rabion, A.; Grenier, S.; Sandford, G. *Org. Process Res. Dev.*, **2017**, *21*, 273.

(3) (a) Duschinsky, R.; Pleven, E.; *J. Am. Chem. Soc.*, **1957**, *79*, 4559 (b) Duschinsky, R.; Heidelberger, C. 5-Fluorocytosine and preparation thereof. Patent no: 2945038, Jul 1960.

(4) Duschinsky, R. Process and intermediates for deoxyfluorocytidine. Patent no: 3040026, Jun 1962.

(5) Undheim, K.; Gacek, M. *Acta Chem. Scand.*, **1969**, *23*, 294.

(6) (a) Robins, M.J.; Naik, S.R. *J.C.S. Chem. Comm.*, **1972**, 18. (b) Robins, M.J.; MacCoss, M.; Naik, S.R.; Ramani, G. *J. Am. Chem. Soc.*, **1976**, *98*, 7381.

(7) Takahara, T. Process for preparing 5-fluorocytosine salt. Patent no: 4473691, Sep 1984.

(8) Visser, G.W.M.; Boele, S.; v. Halteren, B.W.; Knops, G.H.J.N.; Herscheid, J.D.M.; Brinkman, G.A.; Hoekstra, A. *J. Org. Chem.*, **1986**, *51*, 1466.

(9) Baasner, B.; Klauke, E. Process for the preparation of 5-fluorocytosine. Patent no: 4703121, Oct 1987.

(10) Sandford, G.; Harsanyi, A. Process for producing fluorocytosine and fluorocytosine derivatives. Patent no: WO2016/030662 A1, Mar 2016.

(11) Hilbert, G.E.; Johnson, T.B. *J. Am. Chem. Soc.*, **1930**, *52*, 1152.

(12) Wheeler, H.L.; Johnson, T.B. *Am. Chem. J.*, **1903**, *29*, 492, 505.

(13) Hilbert, G.E.; Jansen, E.F. *J. Am. Chem. Soc.*, **1935**, *57*, 552.

(14) Hitchings, G.H.; Elion, G.B.; Falco, E.A.; Russell, P.B. *J. Biol. Chem.*, **1949**, *177*, 357.

(15) (a) Bendich, A.; Getler, H.; Brown, G.B. *J. Biol. Chem.*, **1949**, *177*, 565. (b) Tarsio, P.J.; Nicholl, L. *J. Org. Chem.*, **1957**, *22*, 192. (c) Loquai, H.; Peeters, H.; Vogt, W. Verfahren zur Herstellung von Cytosin. DE 3434142 A1, Mar 1986. (d) Hilgers, G.; Hess, J. Verbessertes Verfahren zum Fällen von Cytosin aus alkalischen Lösungen mit Schwefelsäure. DE 3829100 A1, Mar 1990. (e) von Itter, F.-A. Verfahren zur Herstellung von Cytosinen. DE 3906855 A1, Sep 1990.

(16) (a) Saladino, R.; Crestini, C.; Neri, V.; Ciciriello, F.; Costanzo, G.; Di Mauro, E. *ChemBioChem*, **2006**, *7*, 1707. (b) SciFinder; Chemical Abstracts Service: Columbus, OH; Proton-1 NMR spectrum; spectrum ID WHSP49650; RN 71-30-7; https://scifinder.cas.org; AIST: Integrated Spectral Database System of Organic Compounds. (Data were obtained from the National Institute of Advanced Industrial Science and Technology (Japan)). (c) SciFinder; Chemical Abstracts Service: Columbus, OH; Proton-1 NMR spectrum; spectrum ID HB_07550; RN 71-30-7; https://scifinder.cas.org; BIORAD: Copyright Bio-Rad Laboratories. All Rights Reserved.

(17) (a) Lal, G.S.; Pastore, W.; Pesaresi, R. *J. Org. Chem.*, **1995**, *60*, 7340. (b) Lal, G.S.; Pez, G.P.; Syvret, R.G. *Chem. Rev.*, **1996**, *96*, 1737. (c) Banks, R.E. *J. Fluorine Chem.*, **1998**, *87*, 1. (d) Singh, R.P.; Shreeve, J.M. *Acc. Chem. Res.*, **2004**, *37*, 31. (e) Nyffeler, P.T.; Durón, S.G.; Burkart, M.D.; Vincent, S.P.; Wong, C.-H. *Angew. Chem. Int. Ed.*, **2005**, *44*, 192.

(18) Radwan-Olszewska, K.; Palacios, F.; Kafarski, P. *J. Org. Chem.*, **2011**, *76*, 1170.

(19) Motorin, Y.; Seidu-Larry, S.; Helm, M. DNA and RNA Pyrimidine Nucleobase Alkylation at the Carbon – 5 Position, Chapter in DNA Methyltransferases - Role and Function, Advances in Experimental Medicine and Biology 945, Jeltsch, A.; Jurkowska, RZ. (eds.), Springer International Publishing, Switzerland, **2016**, pp 19 – 33.

Chapter 3:

Hexafluorobuta-1,3-diene

3. Solid Supported Synthesis of Hexafluorobuta-1,3-diene

3.1. KEYWORDS

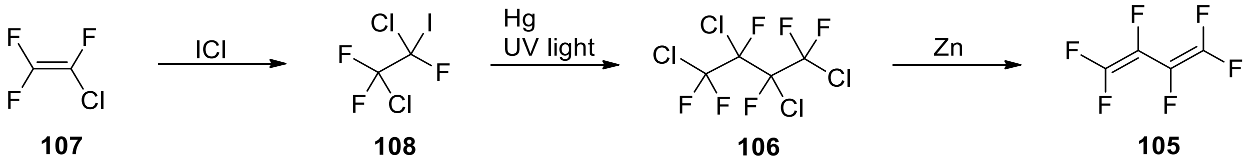
Hexafluorobuta-1,3-diene, solid supported $ZnCl_2$, HFC-134a, 1,1,1,2-tetrafluoroethane.

3.2. ABSTRACT

Efforts to develop an alternative conventional batch mode synthesis of hexafluorobuta-1,3-diene (HFBD, **105**), a dry-etch reagent of industrial importance, as well as endeavors to develop an automated flow chemistry route are reported. The batch mode synthesis of hexafluorobuta-1,3-diene (**105**) has been attempted by means of silica supported zinc(II) chloride with the aim of accessing the more stable silica-(1,2,2-trifluorovinyl)zinc chloride (**112**) moiety, while reducing the potential of the formation of the unwanted bis-(1,2,2-triflorovinyl)zinc (**111**) moiety. Despite multiple attempts, detectable quantities of HFBD (**105**) could not be isolated after either the batch or flow synthesis. The difficulties related to the batch mode synthesis as well as the translation to flow chemistry are discussed.

3.3. INTRODUCTION

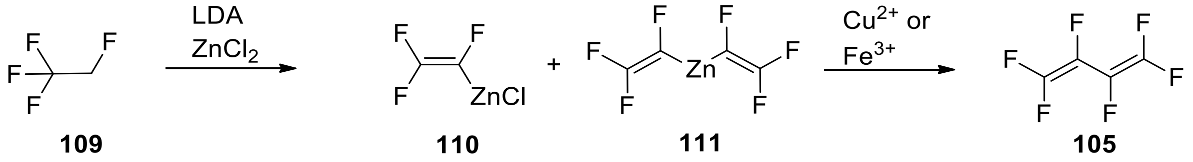
Hexafluorobuta-1,3-diene (HFBD, **105**) is an industrially valuable compound as it can be used as a termonomer in the formation of fluoroelastomers and polymers.[1] It is also used extensively as a dielectric dry-etching gas due to its negligible global warming potential and short atmospheric lifetime.[2,3] HFBD (**105**) was first prepared by Miller and co-workers[4] by means of a direct fluorination of 1,2-dichloro-1,2-difluoroethylene to obtain hexafluoro-1,2,3,4-tetrachlorobutane (**106**) followed by dechlorination to obtain HFBD (**105**). In addition to the low yields obtained, this synthesis also suffered from the disadvantages of using elemental fluorine as well as the formation of many side products, which made this route unsuitable for industrial application. Numerous alternative routes to access HFBD (**105**) were explored by Haszeldine[4-7] with the most notable one reacting chlorotrifluoroethylene (**107**) in the presence of iodine monochloride to obtain 1,2-dichloro-1,1,2-trifluoroiodoethane (**108**). Irradiation of **108** in the presence of mercury-initiated dimerization to obtain hexafluoro-1,2,3,4-tetrachlorobutane (**106**) was followed by dehalogenation in the presence of zinc to give HFBD (**105**) in yields of 92-98% (Scheme 3.1).[4a]



Scheme 3.1: Synthesis route of Haszeldine.[4a]

However, the use of mercury was a major drawback to this route leading to this approach being widely explored by multiple research groups, using alternative reagents to effect the various transformations in an effort to develop a more industrially applicable synthesis. To circumvent the mercury-initiated dimerization Tarrant and Lilyquist[8] used benzoyl peroxide at 100 °C to initiate the dimerization reaction, while Henne and Postelneck[9] opted for Zn in acetic acid. Dědek and Chvátel[10] elected to use UV light without the presence of mercury, but obtained only 34% of the required dimerized adduct. A larger number of research groups focused their attention on the final dehalogenation step with ethyl magnesium bromide in tetrahydrofuran being a popular alternative.[1,2,11]

Hedrick and co-workers[12] more recently developed an alternative route which started with the conversion of readily available iodotrifluoroethylene or 1,1,1,2-tetrafluoroethane (**109**) into trifluorovinylzinc bromide and trifluorovinylzinc chloride (**110**) respectively as well as the by-product **111**, followed by dimerization initiated by Cu^{2+} or Fe^{3+} salts to obtain HFBD (**105**) in yields of about 69% (Scheme 3.2). This route has been less extensively investigated and optimized by other research groups,[3,13] but shows potential as an industrially viable synthesis due to its use of readily available, cost effective starting materials and the simplicity of the reaction sequence.



Scheme 3.2: Synthesis route of Hedrick and co-workers.[9]

In an alternative approach using a different synthetic route, Tortelli and co-workers[14] start with the readily available trichloroethylene which undergoes fluorodimerization in the presence of F_2 carried in helium. The formed dimer was then dehydrochlorinated to obtain 1,2,3,4-tetrachloro-1,4-difluorobuta-1,3-diene, which was subsequently fluorinated to 1,2,3,4-tetrachloro-1,1,2,3,4,4-hexafluorobuta-1,3-diene. The final step was dechlorination over zinc to obtain HFBD (**105**) in a yield of around 95%.

In conjunction with our local industrial partner Pelchem we were tasked with developing an industrially viable process for the synthesis of HFBD (**105**) for potential local commercialization. Since to the best of our knowledge no synthesis of HFBD (**105**) making use of flow chemistry or solid supported reagents has been reported, we thought this would be a good avenue to pursue. Herein the efforts and difficulties of developing an alternative batch process for the synthesis of HFBD (**105**) are described and the difficulties related to the translation to flow chemistry are discussed. The applicability of flow synthesis when compared to the conventional batch process is also evaluated.

3.4. RESULTS AND DISCUSSION

The preferred synthetic route to access hexafluorobuta-1,3-diene (**105**) (Scheme 3.2) involved the use of lithium diisopropylamide (LDA) to initiate metalation of 1,1,1,2-tetrafluoroethane (HFC-134a, **109**) to form the (1,2,2-trifluorovinyl)lithium moiety followed immediately by transmetalation to obtain the more stable (1,2,2-trifluorovinyl)zinc(III) chloride (**110**) adduct. Fe^{3+} or Cu^{2+} initiated dimerization then results in the formation of hexafluorobuta-1,3-diene (**105**). Batch optimization was performed to assess the suitability of the reactions for flow translation as well as investigate if there were any improvements to be made to the reported protocols.

Batch optimization: Numerous papers have been published studying the synthesis and stability of the (1,2,2-trifluorovinyl)lithium moiety.[15] It is generally agreed that (1,2,2-trifluorovinyl)lithium is best prepared using a base such as *n*-butyllithium or lithium diisopropylamide in tetrahydrofuran (THF) or diethyl ether at -78 °C, with warmer reaction temperatures leading to rapid decomposition. The electrophilic trapping of the trifluorovinyl species has also been extensively studied and demonstrated *in situ* using a range of electrophiles, with $ZnCl_2$ leading to the much more thermally stable (1,2,2-trifluorovinyl)zinc(III) chloride (**110**) moiety and its corresponding dimer bis-(1,2,2-trifluorovinyl)zinc (**111**) in a ratio of approximately 90:10.[16,17] The addition of Fe^{3+} or Cu^{2+} salts followed by heating under a stream of nitrogen then results in the collection of the formed hexafluorobuta-1,3-diene (**105**) in a trap cooled to -78 °C.[3,12,13] It was decided that improved formation of (1,2,2-trifluorovinyl)zinc(III) chloride (**110**), with reduced formation of the bis compound (**111**) would be beneficial to the synthesis thus the reaction was optimized in terms of reagents used and order of addition.

It was decided that solid supported $ZnCl_2$ would benefit the synthesis as the steric bulk imparted by a solid support medium would potentially reduce the formation of bis compound **111** as well as make the reaction more amenable to translation to flow. Thus, the $ZnCl_2$ was supported on silica resulting in a $ZnCl_2$ loading of 13.5% by XRF analysis.[18] Iron(III) chloride and copper(II) acetate were then evaluated as sources of Fe^{3+} and Cu^{2+} ions respectively. It was found that $FeCl_3$ was far more soluble in THF than $Cu(CH_3COO)_2$, with $Cu(CH_3COO)_2$ requiring approximately 5 times more THF per mol than in the case of $FeCl_3$. All experiments were thus performed using $FeCl_3$ as the initiator of dimerization due to the small volume of tetrahydrofuran required to solubilize it. This also simplified the addition, and for reasons of concentration would also be more practical for flow conditions at a later stage.

Due to the starting reagent HFC-134a (**109**) having a boiling point of -26 °C and the required product HFBD (**105**) having a boiling point of 6-7 °C the reaction setup required careful consideration. A minimum of three necks was required on the reaction vessel, one to accommodate a dry-ice/acetone condenser incorporating a nitrogen inlet, one for the addition of the reagents and one for the removal of the formed product. The reagent inlet side needed to be interchangeable in order to accommodate a septum to allow for the injection of the LDA and a septum for holding the tube to bubble in the HFC-134a (**109**), followed by addition of the $FeCl_3$ in THF solution by means of a dropping funnel. The product outlet consisted of a tap connected by means of silicon tubing to a trap cooled to -78 °C, allowing for control of collection as the tap could be opened and closed as required during the different stages of the reaction.

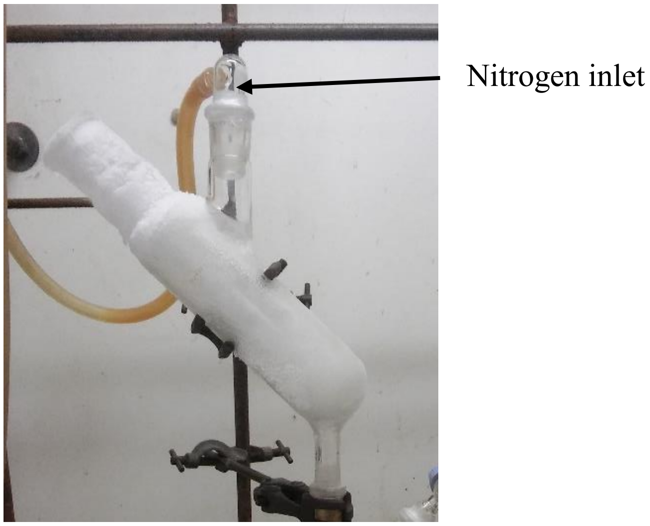


Figure 3.1: Close up photo of dry-ice/acetone condenser with nitrogen inlet.

Figure 3.2: Photo of batch experimental setup for synthesis of HFBD (**105**).

The temperature at which the HFC-134a (**109**) was added to the SiO_2-$ZnCl_2$ slurry was then carefully evaluated. Upon addition of the HFC-134a (**109**) at 10 °C according to literature procedures,[3] it was found that the HFC-134a (**109**) did not react sufficiently with the reaction mixture or escaped the reaction vessel before having sufficient time to react with the LDA and SiO_2-$ZnCl_2$, resulting in no detectable product by NMR spectroscopic analysis. The reaction mixture was then cooled to -30 °C, which is below the boiling point of HFC-134a (**109**) (boiling point -26 °C) in order to ensure that all of the HFC-134a (**109**) was available in solution and could not escape the reaction vessel. These conditions also failed to produce the desired product in any detectable quantities. It was then thought that the order of addition might be the influencing factor as the HFC-134a (**109**) first needs to be deprotonated by the LDA before transmetalation can occur, thus the LDA was first added to the SiO_2-$ZnCl_2$ slurry followed by addition of the HFC-134a (**109**), which also failed to produce the desired product.

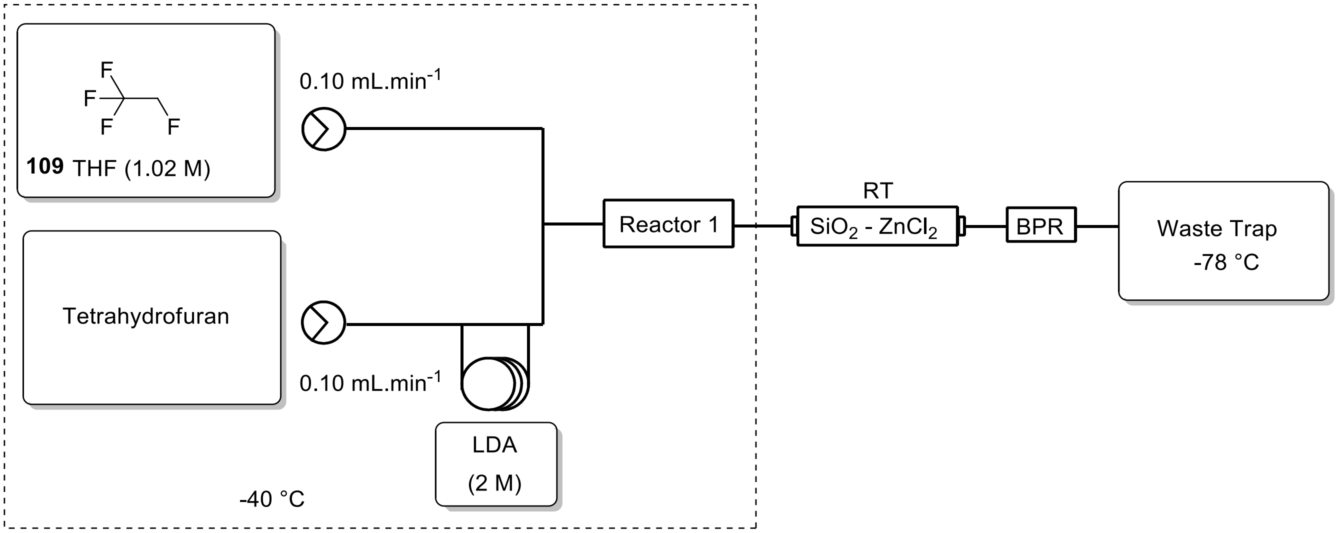
According to the literature procedure[3] the $ZnCl_2$ was used as the limiting reagent and thus the SiO_2-$ZnCl_2$ was also used as the limiting reagent in all of the above experiments. This may however have resulted in inefficient contact and mixing for reaction with the $ZnCl_2$ to occur under traditional batch conditions, thus the equivalents of the SiO_2-$ZnCl_2$ used in the reaction was increased to 1.6, while making the HFC-134a (**109**) the limiting reagent in an effort to obtain the desired product. This also failed to produce HFBD (**105**) in detectable quantities.

The traditional batch synthesis presented with many difficulties, particularly the requirement of specialized glassware and a reaction setup requiring numerous ground glass joints (Figures 3.1-3.2). Despite that every effort was made to effectively seal the joints against leaks, the possibility still existed that a lot of product loss could have occurred at these points. The silicon tubing (Figure 3.2) used for transfer of the crude HFBD (**105**) to the collection vessel could potentially have been permeable to this gas also resulting in loss of the product.

Another complication was the purification of the desired product from the large volumes of THF which also transferred over during the collection stage. Literature procedures[3] do not describe the purification procedures used and it is unlikely that only HFBD (**105**) would have been collected when using a nitrogen gas stream and a small vacuum to aid transfer, as is done in the literature. The distillation of HFBD (**105**) from THF thus also required specialized glassware with joints which could potentially leak. Various different distillation assemblies and conditions were investigated in an effort to isolate the desired product in large enough quantities to detect, without success.

Thus, for a true indication as to whether the SiO_2-$ZnCl_2$ is a suitable source of $ZnCl_2$ the correct apparatus would need to be available and it is conceivable that if the correct apparatus were to be used, having limited joints and a more efficient transfer system then HFBD (**105**) could potentially be successfully prepared under traditional batch conditions. It was thought that under flow conditions, the exposure of HFC-134a (**109**) and LDA to the SiO_2-$ZnCl_2$ would be easier to perform and control. Thus, it was decided to still pursue a flow synthesis, despite the lack of success under batch conditions.

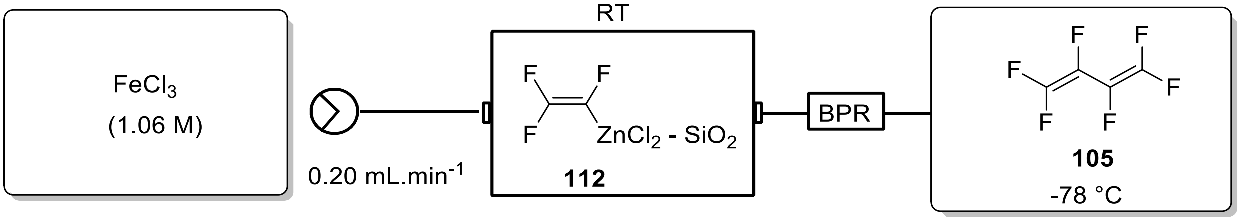
Stepwise flow optimization: All flow experiments were performed using the Uniqsis FlowSyn platform.[19] For the flow preparation of the silica supported (1,2,2-trifluorovinyl)zinc(III) chloride (**112**) the system was operated with two HPLC pumps, a reactor to allow mixing of reagents, an OmniFit® column (10 mm i.d. by 100 mm length) packed with the prepared silica-$ZnCl_2$ and a 100 psi back pressure regulator (BPR) fitted at the output flow stream. The reagent feedstock for pump A was HFC-134a (**109**, 1.02 M) in tetrahydrofuran and for pump B was LDA (1 M) pre-loaded in a 10 mL loop (Scheme 3.3).



Scheme 3.3: Equipment setup for the flow synthesis of silica supported (1,2,2-trifluorovinyl)zinc(III) chloride (**112**).

The delivery method for LDA and HFC-134a (**109**) was critically examined. It was decided that a pre-loaded loop feed would be the best delivery method for the LDA in order to minimize exposure to moisture and prevent potential blockage of the pump. For **109**, both stock bottle and pre-loaded loop delivery methods were examined, and it was found that loop delivery was best as the bottle feed resulted in gassing out of **109**. For the initial run the reactor of choice was the 2 mL mixing chip to allow for thorough mixing of the HFC-134a (**109**) and LDA in order to form the required (1,2,2-trifluorovinyl)lithium moiety. This setup proved to be inefficient as the mixing chip exhibited a leak which allowed moisture into the system resulting in the precipitation of the LDA. The mixing chip was then replaced with a T-piece mixer which resulted in successful reaction and formation of the required silica supported (1,2,2-trifluorovinyl)zinc(III) chloride (**112**) as observed by the colour of the column changing from white to yellow-brown. Further attempts to repeat the reaction failed due to leaks developing at the T-piece, allowing moisture into the system and causing the LDA to precipitate leading to blockage of the PTFE tubing.

For the flow preparation of hexafluorobuta-1,3-diene (**105**) the system was operated with one HPLC pump, an OmniFit® column (10 mm i.d. by 100 mm length) packed with the prepared silica supported (1,2,2-trifluorovinyl)zinc(III) chloride (**112**) and a 100 psi back pressure regulator (BPR) fitted at the output flow stream. The reagent feedstock for pump A was $FeCl_3$ (1.06 M) in tetrahydrofuran (Scheme 3.4).



Scheme 3.4: Equipment setup for the flow synthesis of HFBD (**105**).

Initially the reaction was performed with the column held at room temperature. However, this proved to be problematic as the reaction built up too much pressure due to the gassing out of **105** which resulted in the failure of the PTFE tubing connected to the column and loss of the volatile product. The reaction could not be repeated at 0 °C as the required silica supported (1,2,2-trifluorovinyl)zinc(III) chloride (**112**) could not be successfully re-prepared due to difficulties maintaining a dry, leak free system. Unfortunately, further efforts to mitigate the technical issues encountered were not performed, as a preliminary techno-economic analysis performed by our industrial partner, Pelchem, suggested that the market size and pricing was not conducive to further investment in the project. That being said, it was speculated that if the dimerization reaction was performed at 0 °C then HFBD (**105**) would be in its liquid state (boiling point 6-7 °C) and thus the chances of gassing out and high pressure building up would be substantially reduced, which would then lead to the successful preparation of **105** after distillation from tetrahydrofuran.

3.5. CONCLUSION

In conclusion we have demonstrated efforts to develop an alternative batch process for the synthesis of HFBD (**105**) using $ZnCl_2$ supported on silica, which failed to produce the desired product in detectable quantities. The multistep flow synthesis of HFBD (**105**) could not be achieved due to difficulties maintaining an inert, dry, leak free environment using our modular setup and it is envisioned that should a completely sealed, moisture free system be used then it is conceivable that the synthesis could be successfully achieved under flow conditions with greater ease and lower possibility of product loss when compared to traditional batch procedures. This would then lead to a rapid, effective synthesis process which could be of use industrially for the large-scale synthesis of HFBD (**105**).

3.6. EXPERIMENTAL SECTION

All solvents and reagents were purchased from Sigma-Aldrich and used without further purification. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AVANCE-III 300 MHz spectrometer or a Bruker AVANCE-III 400 MHz spectrometer with the residual solvent peak as an internal reference (DMSO-d_6 = 2.49 and 39.5 ppm for ^{1}H and ^{13}C NMR spectra respectively). Chemical shifts, δ, are reported in parts per million (ppm), and splitting patterns are given as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m). Coupling constants, *J*, are expressed in hertz (Hz). Yields refer to isolated pure products unless stated otherwise.

Preparation of activated silica[18]

Silica gel 60 (10.03 g) was suspended in a mixture of distilled water (50 mL) and aqueous hydrochloric acid (32%, 50 mL) followed by reflux overnight. The reaction mixture was allowed to cool to room temperature followed by collection of the silica by vacuum filtration and washing with excess water until the washings were neutral. The activated silica was dried and stored in an oven at 70 °C.

Preparation of solid supported $ZnCl_2$[18]

Zinc(II) chloride (1.52 g, 11 mmol) and activated silica (5.00 g) were suspended in dichloromethane (30 mL) followed by reflux overnight. The SiO_2-$ZnCl_2$ formed was collected by vacuum filtration and washed with dichloromethane (3 x 10 mL) followed by drying in an oven at 70°C. The SiO_2-$ZnCl_2$ was determined to be 13.5% $ZnCl_2$ by XRF analysis.

General batch procedure for the preparation of hexafluorobuta-1,3-diene (105)

Under a nitrogen atmosphere and using a dry-ice:acetone condenser, 1,1,1,2-tetrafluoroethane (**109**) (1.21 g, 11.9 mmol) was bubbled slowly into a slurry of SiO_2-$ZnCl_2$ (1.43 g, 10.5 mmol) in tetrahydrofuran (10 mL) cooled to -30 °C. Lithium diisopropylamide (2.0 M , 10.5 mL, 21.0 mmol) was added dropwise with the needle tip immersed in the reaction mixture to prevent decomposition of the formed vinyllithium, followed by stirring at room temperature for 1 hour. A solution of iron(III) chloride (1.79 g, 11.1 mmol) in minimum tetrahydrofuran was added dropwise to the reaction mixture at 0 °C. The reaction mixture was warmed gently while using nitrogen to blow the product over into a trap cooled to -78 °C. The crude mixture obtained was distilled at room temperature into a trap cooled to 0 °C to obtain a colourless liquid which was not the desired product **105,** as determined by NMR spectroscopic analysis.

Flow synthesis

General methods for the preparation of stock solutions

1,1,1,2-Tetrafluoroethane (HFC-134a, 109) in tetrahydrofuran

A stock solution of 1,1,1,2-tetrafluoroethane **109** was prepared by dissolving **109** (2.5 g, 24.5 mmol) in tetrahydrofuran (24 mL) cooled to -40 °C.

Iron(III) chloride in tetrahydrofuran

A stock solution of iron(III) chloride was prepared by dissolving iron(III) chloride (1.04 g, 6.4 mmol) in tetrahydrofuran (6 mL).

Lithium diisopropylamide

Lithium diisopropylamide (2.0 M) was used as purchased and was preloaded in a loop having a tetrahydrofuran plug before and after the loaded lithium diisopropylamide.

General procedure for the stepwise flow synthesis of silica-(1,2,2-trifluorovinyl)zinc(III) chloride (112)

The 1,1,1,2-tetrafluoroethane **(109)** stock solution (continuous feed) and the lithium diisopropylamide solution (4.5 mL, 2.0 M) were each pumped at a flow rate of 0.100 $mL.min^{-1}$ into a T-piece cooled to 0 °C and through an Omnifit® column (10 mm i.d. by 100 mm length) packed with SiO_2-$ZnCl_2$ (2.79 g, 2.8 mmol) held at room temperature. The output of the reactor was collected in a flask cooled to -78 °C until no further excess reagent was eluted.

General procedure for the stepwise flow synthesis of hexafluorobuta-1,3-diene (105)

The iron(III) chloride stock solution (3.8 mL) was pumped at a flow rate of 0.200 mL.min^{-1} through the Omnifit® column (10 mm i.d. by 100 mm length) loaded with silica-(1,2,2-trifluorovinyl)zinc(III) chloride (**112**) at room temperature. The output of the reactor was collected in a flask cooled to -78 °C until no further product was eluted.

3.7. REFERENCES

(1) (a) Bargigia, G; Tortelli, V; Tonelli, C. Process for the synthesis of hexafluorobutadiene and of higher perfluorinated dienes. European patent no: 0205892 A1, Dec 1986. (b) Zhu, J.; Chen, S.; Wang, B.; Zhang, X. *Int. J. Org. Chem.*, **2014**, *4*, 331.

(2) Miki, J; Yoshimi, H; Aoyama, H. Process for production of perfluoroalkadienes. European patent no: 1247791 A1, Oct 2002.

(3) Ramachandran, P.V.; Reddy, G.V. *J. Fluorine Chem.*, **2008**, *129*, 443.

(4) (a) Haszeldine, R.N. *J. Chem. Soc.*, **1952**, 4423. (b) Miller, W.T. Polyunsaturated fluoroolefins. Patent no: 2668182, Feb 1954.

(5) Haszeldine, R.N. *J. Chem. Soc.*, **1954**, 4026.

(6) Haszeldine, R.N. *J. Chem. Soc.*, **1955**, 3880.

(7) Haszeldine, R.N. Coupling of halogenated organic compounds. Patent no: 3046304, Jul 1962.

(8) Tarrant, P.; Lilyquist, M.R. *J. Am. Chem. Soc.*, **1955**, *77*, 3640.

(9) Henne, A.L.; Postelneck, W.M. *J. Am. Chem. Soc.*, **1955**, *77*, 2334.

(10) Dědek, V.; Chvátal, Z. *J. Fluorine Chem.*, **1986**, *31*, 363.

(11) (a) Bargigia, G.; Tortelli, V.; Tonelli, C. Process for the synthesis of hexafluorobutadiene and of higher perfluoroinated dienes. Patent no: 4654448. Mar 1987. (b) Bargigia, G.;

Tortelli, V.; Tonelli, C.; Modena, S. Process for the synthesis of perfluoroalkandienes. European patent no: 0270956. Jun 1986. (c) Bargigia, G.; Tortelli, V.; Tonelli, C.; Modena, S. Process for the synthesis of perfluoroalkandienes. Patent no: 5082981. Jan 1992. (d) Ji, H.-S.; Cho, O.-J.; Ryu, J.-G.; Ahn, Y.-H.; Kim, B.-S.; Kim, D.-H. Method of preparing perfluoroalkadiene. Patent no: 2008/0262195 A1. Oct 2008. (e) Ji, H.-S.; Cho, O.-J.; Ryu, J.-G.; Ahn, Y.-H.; Kim, B.-S.; Kim, D.-H. Method of preparing perfluoroalkadiene. Patent no: 7504547 B2. Mar 2009. (f) Miki, J.; Yoshimi, H.; Aoyama, H. Process for production of perfluoroalkadienes. Patent no: 2002/0193643 A1. Dec 2002. (g) Wlassics, I.; Tortelli, V. Dehalogenation process. European patent no: 1719750 A2. Nov 2006. (h) Wlassics, I.; Tortelli, V. *J. Fluorine Chem.*, **2008**, *129*, 359. (i) Ohno, H.; Ohi, T. Process for producing hexafluoro-1,3-butadiene. Patent no: 2009/0216053 A1. Aug 2009.

(12) Hedrick, V.; Brandstadter, S.; Boggs, J.; Cohn, M.; Ghojala, V.R.; Ramachandran, P.V. Chemical production processes and systems. International patent no: WO 2006/026400 A1. Mar 2006.

(13) Burton, D.J.; Hansen, S.W.; Morken, P.A.; MacNeil, K.J.; Davis, C.R.; Xue, L. *J. Fluorine Chem.*, **2008**, *129*, 435.

(14) (a) Tortelli, V.; Millefanti, S.; Carella, S. Process for the synthesis of perfluorobutadiene. International patent no: WO 2009/087067 A1. Jul 2009. (b) Tortelli, V.; Millefanti, S.; Carella, S. Process for the synthesis of perfluorobutadiene. Patent no: 2010/0280291 A1. Nov 2010. (c) Tortelli, V.; Millefanti, S.; Carella, S. Process for the synthesis of perfluorobutadiene. Patent no: 8536387 B2. Sep 2013.

(15) (a) Tarrant, P.; Johncock, P.; Savory, J. *J. Org. Chem.*, **1963**, *28*, 839. (b) Burdon, J.; Coe, P.L.; Haslock, I.B.; Powell, R.L. *Chem. Commun.*, **1996**, 49. (c) Banger, K.K.; Brisdon,

A.K.; Gupta, A. *Chem. Commun.*, **1997**, 139. (d) Burdon, J.; Coe, P.L.; Haslock, I.B.; Powell, R.L. *J. Fluorine Chem.*, **1997**, *85*, 151. (e) Coe, P.L. *J. Fluorine Chem.*, **1999**, *100*, 45. (f) Burdon, J.; Coe, P.L.; Haslock, I.B.; Powell, R.L. *J. Fluorine Chem.*, **1999**, *99*, 127.

(16) (a) Heinze, P.L.; Burton, D.J. *J. Fluorine Chem.*, **1986**, *31*, 115. (b) Hansen, S.W.; Spawn, T.D.; Burton, D.J. *J. Fluorine Chem.*, **1987**, *35*, 415. (c) Heinze, P.L.; Burton, D.J. *J. Org. Chem.*, **1988**, *53*, 2714. (d) Anilkumar, R.; Burton, D.J. *Tetrahedron Letters*, **2002**, *43*, 2731.

(17) Raghavanpillai, A.; Burton, D.J. *J. Org. Chem.*, **2004**, *69*, 7083.

(18) Gupta, R.; Gupta, M.; Paul, S.; Gupta, R. *Can. J. Chem.*, **2007**, *85*, 197.

(19) www.uniqsis.com

(20) Perrins, D.D.; Armarego, W.L.F. *Purification of laboratory chemicals*. 3rd Ed., Pergamon Press, Oxford, **1992**.

Chapter 4:

Aryl Diazonium Tetrafluoroborate Salts

4. Flow Synthesis of Aryl Diazonium Tetrafluoroborate Salts

4.1. KEYWORDS

Aryl diazonium tetrafluoroborate salt, diazotization, flow chemistry.

4.2. ABSTRACT

The comparison of an improved conventional batch mode synthesis of aryl diazonium tetrafluoroborate salts (**113**), which are important synthons in organic chemistry, with their flow chemistry alternative is reported. The continuous flow synthesis of aryl diazonium tetrafluoroborate salts (**113**) has been achieved by means of a diazotization reaction to access the unstable aryl diazonium chloride salts (**115**) followed by reaction with sodium tetrafluoroborate to obtain the corresponding aryl diazonium tetrafluoroborate salts (**113**). A batch synthesis procedure with improved work-up and purification (21-100% yields) is reported. The successful conversion from batch to continuous flow conditions allowed for improved yields (64-100%) with shortened reaction times (3 min vs 30 min) and an improved safety profile.

4.3. INTRODUCTION

The first diazonium salt was prepared by Peter Griess in 1858 when he synthesized diazonitrophenol.[1,2] The name "diazo" originates from the French "diazote" meaning dinitrogen[1] and since then aryl diazonium salts have become important synthons in organic synthesis due to the ease with which the diazonium group can be displaced by a wide range of nucleophiles.[3] The diazonium salts can be broadly classified either as “super” electrophiles, aryl cation precursors or aryl radical precursors depending on their role in a reaction.[2,4]

In the last 160 years the range of reactions involving diazonium salts has expanded from the development of the Sandmeyer reaction to obtain C-Cl, C-Br and C-CN bonds in 1884 and the Pschorr intramolecular substitution reaction for the synthesis of biaryltricyclics in 1896.[2] This was followed by the intermolecular Gomberg-Bachmann reaction in 1924 and shortly thereafter in 1927, the Balz-Schiemann reaction involving the thermal decomposition of diazonium tetrafluoroborates to obtain the difficult to access aryl C-F bond.[2] The Meerwein arylation followed in 1939 and 38 years later in 1977 Kikukawa and Matsuda laid the foundation for palladium catalyzed cross-coupling.[2] Since then developments in C-C, C-B, C-S and C-N bond formation with and without retention of N_2 can be found in the literature.[5] Table 4.1 shows the extensive range of reactions in which diazonium salts are utilized.

Table 4.1: Reactions of diazonium salts

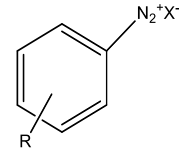
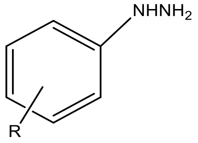
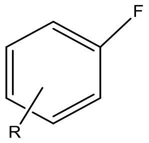
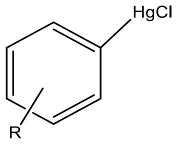
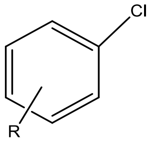
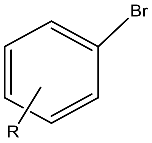
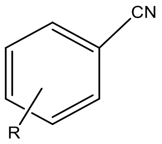
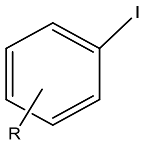
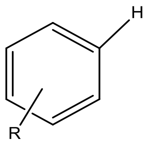
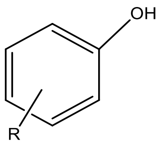
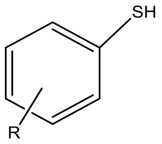
Diazonium Salt	Other Reagents	Product	Reference
 X = BF_4^-; Cl^- or other counter anion	$SnCl_2$, HCl Or Na_2SO_3		6, 7
	Balz-Schiemann reaction Heat or Cu (s)		5, 8-10
	$SnCl_2 + HgCl_2$		11
	Sandmeyer reaction CuCl		8, 10
	Sandmeyer reaction CuBr		8, 10
	Sandmeyer reaction CuCN		8
	KI or I_2		5, 8, 12
	H_3PO_2, H_2O		5, 8, 10
	Cu_2O, Cu^{2+}, H_2O Or H_2SO_4, H_2O		3, 4, 8, 13, 14
	NaSH		8

Table 4.1 continued: Reactions of diazonium salts

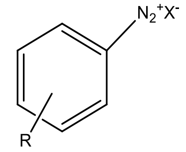
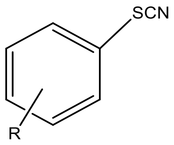
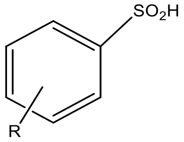
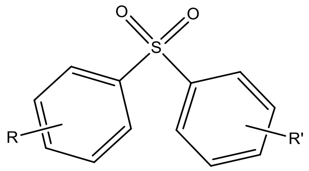
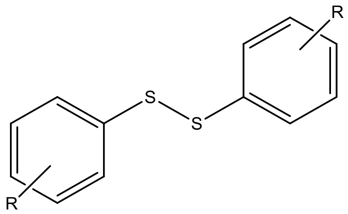
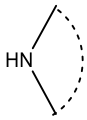
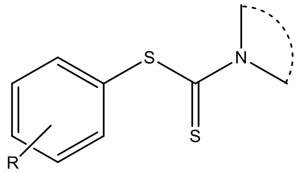
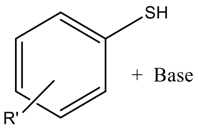
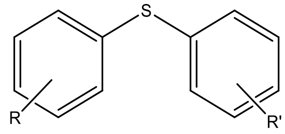
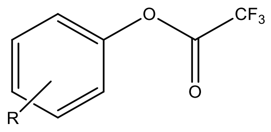
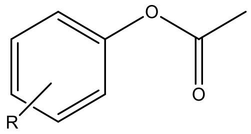
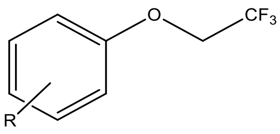
Diazonium Salt	Other Reagents	Product	Reference
 X = BF$_4^-$; Cl$^-$ or other counter anion	CuSCN		8
	SO$_2$, H$_2$, Pd/C		15
	SO$_2$, hydrazine, aryliodonium tetrafluoroborate		16
	CS$_2$, cathodic reduction		2, 17
	CS$_2$, H$_2$O, 		2, 18
			4, 5, 19
	Trifluoroacetic acid		3, 13
	Acetic anhydride Or acetic acid		3, 4, 20-22
	Trifluoroethanol		3, 23

Table 4.1 continued: Reactions of diazonium salts

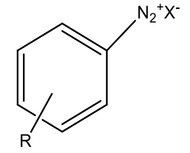
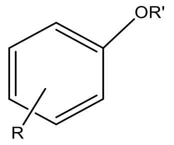
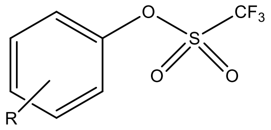
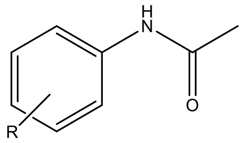
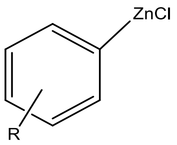
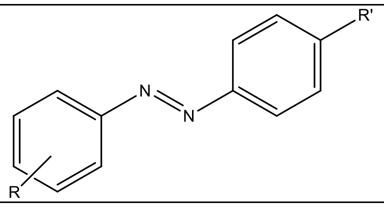
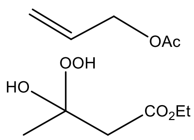
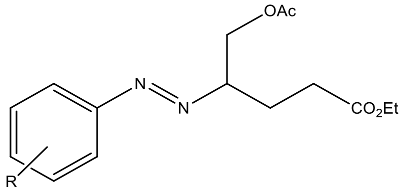
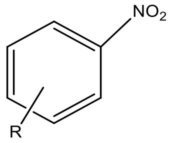
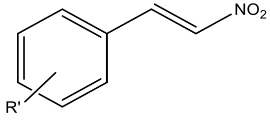
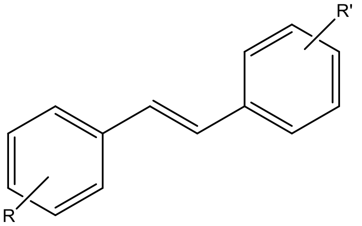
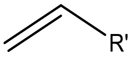
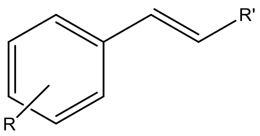
Diazonium Salt	Other Reagents	Product	Reference
 $X = BF_4^-$; Cl^- or other counter anion	R'OH		4
	CF_3SO_3H		4, 5, 24
	ACN, *hv*		25
			5, 26
	$FeSO_4$ 		2, 27
	$NaNO_2$, Cu^0		5
	Stilbene derivatives Eosin Y, green LED, 		28
	Heck-Matsuda reaction; Pd^0 		2, 3, 28 - 30

Table 4.1 continued: Reactions of diazonium salts

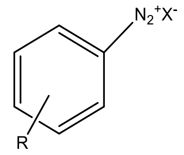
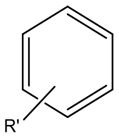
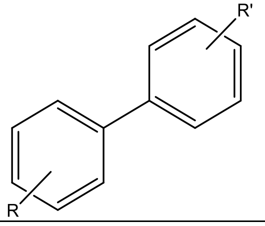
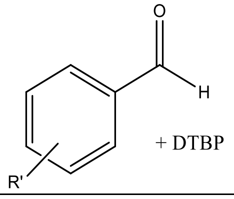
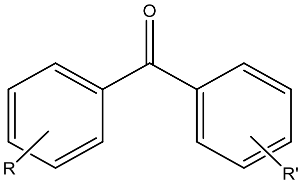
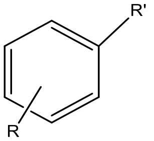
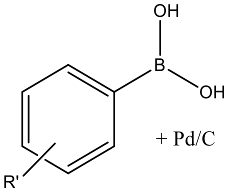
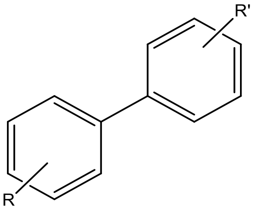
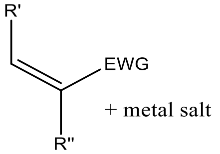
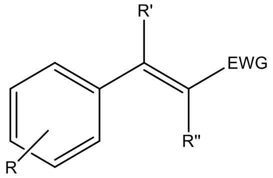
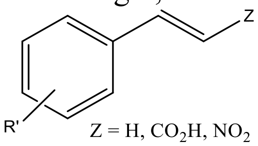
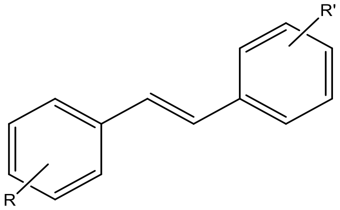
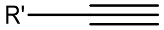
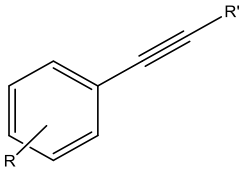
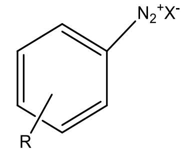
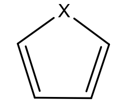
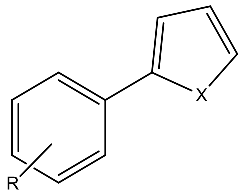
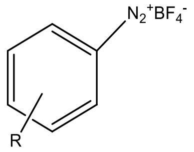
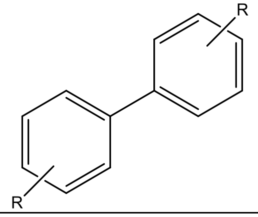
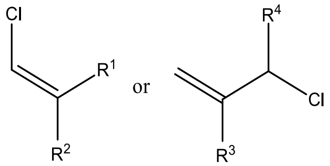
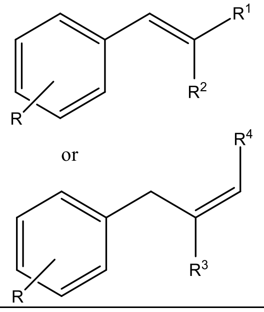
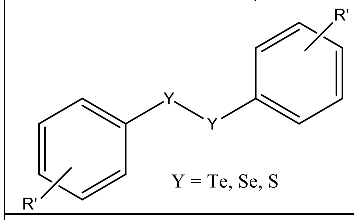
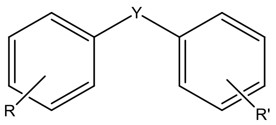
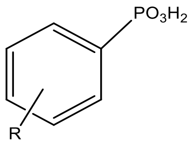
Diazonium Salt	Other Reagents	Product	Reference
 $X = BF_4^-$; Cl^- or other counter anion	Gomberg-Bachmann reaction  $+ HO^-$		8, 31
	 + DTBP		32
	Stille reaction R'-Sn(alkyl)$_3$, Pd^0, ligands		3, 33
	Suzuki-Miyaura reaction  + Pd/C		3, 34, 35
	Meerwein arylation reaction  + metal salt		5, 36
	$[Ru(bpy)_3]^{2+}$, blue light,  Z = H, CO_2H, NO_2		28
	Sonagashira cross-coupling reaction $PdCl_2$, 		2, 37, 38

Table 4.1 continued: Reactions of diazonium salts

Diazonium Salt	Other Reagents	Product	Reference
 $X = BF_4^-$; Cl^- or other counter anion	C-H arylation Eosin Y, LED light  X = O, S, NBoc		2, 39
	$FeCl_2$, 		2, 40
	Allylation & vinylation Fe^{2+},  R^1 = Cl, aryl; R^2 = H, Cl R^3 = H, Me, Cl, CO_2Et; R^4 = H, Me		41
	Zn, $(MeO)_2C=O$, microwave,  Y = Te, Se, S		5, 42
	PCl_3, CuBr catalyst, H_2O		5
	Functionalization of nanomaterials		1

The first report for the generation of a diazonium salt under flow conditions was that of de Mello and co-workers[43] in which they used a nanoscale monolithic chip design to prepare an aryl diazonium chloride followed by *in-situ* quenching to obtain azo dyes. The same group,[44] then demonstrated a microfluidic reactor where the aim of their research was to demonstrate that aryl diazonium chloride salts could be synthesized on-chip followed by their immediate *in-situ* chloro-dediazonation under safe and straightforward conditions to obtain conversions of 40-49% by GC analysis.[44]

The *in-situ* generation and use of aryl diazonium salts can be found in a variety of published flow syntheses where the diazonium cation is stabilized by $BF_3(OH)^-$,[45] $MeSO_3^-$,[46] acetate[47] and chloride[48] anions. In other flow syntheses the formation of a triazene moiety instead of a diazonium cation was favoured by completely avoiding the use of an acid.[49] In many instances, the syntheses suffered from solubility issues due to precipitation which needed to be circumvented, required large equivalents of acid and nitrite or required complex and highly specialized reactor setups in order to successfully achieve the desired end products. For a more detailed discussion Felpin and co-workers[50] published an extensive review covering the topic of diazonium salts in flow in 2015.

In terms of flow syntheses involving aryl diazonium tetrafluoroborates only two references could be found. Yu and co-workers[51] focused on the Balz-Schiemann reaction using sodium nitrite with a combination of hydrochloric and fluoroboric acid under aqueous conditions to form the aryl diazonium tetrafluoroborate salt *in-situ*, followed by fluoro-dediazonation to obtain aryl fluorides in good yields.[51] Even though their process was successful it suffers from the disadvantages of using dangerous acids, which also requires the use of Hastelloy steel components and a slurry forms which could potentially block the reactor. These factors make the process arguably unattractive for scale up and industrial purposes.

Baxendale and co-workers[52] explored the generation of aryl diazonium chloride species under aqueous, organic and solid phase conditions followed by an immediate ascorbic acid reduction to hydrazine derivatives. One example was done in which an aryl diazonium chloride was converted into the corresponding aryl diazonium tetrafluoroborate, however, this reaction was performed by collecting the bulk of the reactor output in a flask which contained a suspension of sodium tetrafluoroborate, and was not done as a continuous flow process.[52] While this process was successful for generating hydrazine derivatives in good yields under continuous flow conditions, it would be challenging to convert this to a large scale synthesis of aryl diazonium tetrafluoroborates as this would require extensive mixing of the slurry on a large scale to obtain complete conversion, which is not ideal for some of the more unstable diazonium tetrafluoroborate salts which have faster rates of decomposition. This method would also require devising a method to separate the unreacted sodium tetrafluoroborate from the aryl diazonium tetrafluoroborate salt on a large scale.

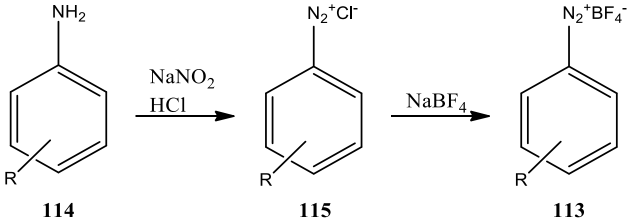
The majority of research available has focused mainly on the generation of aryl diazonium chloride salts with very little mention of the aryl diazonium tetrafluoroborate salts. The primary disadvantages of particularly the aryl diazonium chloride salts are that these salts are exceedingly difficult to isolate due to poor stabilities even at room temperature, as well as the tendency of the salts to react explosively.[1] The aryl diazonium tetrafluoroborate salts on the other hand are much more stable and can thus be isolated, if desired, at a substantially reduced risk of explosion.[4,5,34]

Only a few aryl diazonium tetrafluoroborate salts are available commercially,[1,2] thus a procedure to quickly, efficiently and safely prepare aryl diazonium tetrafluoroborate salts on a large scale for use in a wide range of syntheses would be of synthetic advantage. This is especially true if the synthesis designed is versatile enough to allow for easy diversion of the aryl diazonium tetrafluoroborate salts into various different synthetic pathways. This implies that the *in-situ* formation of the aryl diazonium chloride salt must not form precipitates or decompose before it can be converted into the aryl diazonium tetrafluoroborate salt, which must also preferably be completely soluble under the reaction conditions used in order for it to be available in a convenient form for any downstream flow reactions that may be required e.g. Heck-Matsuda, Suzuki-Miyaura, Balz-Schiemann reactions, etc.

To date, a short, high yielding batch synthesis for aryl diazonium tetrafluoroborate salts (**113**) along with a continuous flow alternative, which can be easily coupled with other downstream flow processes using reagents which are safe, easy to handle and that are readily available has not been reported.

4.4. RESULTS AND DISCUSSION

The preferred synthetic route to access aryl diazonium tetrafluoroborate salts (**113**) (Scheme 4.1) involved a diazotization reaction between an aryl amine (**114**), a nitrite source and an acid source to access the aryl diazonium chloride (**115**). This would immediately be followed by reaction with sodium tetrafluoroborate to obtain the aryl diazonium tetrafluoroborate salt (**113**). Batch optimization was performed to investigate if there were any improvements to be made to the reported protocols and assess whether the reactions could be successfully translated to an automated flow process.



R= any substituent
in the *o*-, *m*- or *p*- position

Scheme 4.1: Synthesis route to aryl diazonium tetrafluoroborate salts (**113**).

Batch optimization: The majority of published procedures report the diazotization of the aryl amine (**114**) using sodium nitrite and aqueous hydrochloric acid in water, followed by addition of a large excess of sodium tetrafluoroborate or fluoroboric acid resulting in the precipitation of the aryl diazonium tetrafluoroborate (**113**), which generally results in good yields depending on the position and type of substituents (R in Scheme 4.1) attached to the benzene ring.[5,8,9] Alternatively an alkyl nitrite can be used instead of sodium nitrite which allows the reaction to be conducted in an organic solvent,[5] thus isopentyl nitrite was selected as the nitrite source as it would allow for some flexibility when testing different solvents. It was decided that improvements in the solubilities of the aryl diazonium salts (**115** and **113**) would be beneficial to the flow synthesis at a later stage thus the reaction was optimized in terms of solvent, tetrafluoroborate delivery method, acid source and acid stoichiometry. The work-up procedures were also carefully evaluated as this appeared to be the stage in which the most product loss and decomposition occurred. A basic solvent screen using low molecular weight polar solvents was initially performed (Table 4.2). All batch optimizations were performed using aniline (**114a**, R = H) at a concentration of 0.66 M as a model system.

Table 4.2: Solvent optimization using literature procedures[8,13]

	Solvent	**Temperature (°C)**	**Yield (%)**
1	H_2O	0	20
2	1:1 EtOH/H_2O	0	48
3	DMF	0	19
4	None[a]	0	3
5	1:1 EtOH/DMF	0	20
6	ACN	0	61

[a]Minimum DMF used to dissolve $NaBF_4$ before addition

Standard conditions: aniline (**114a**) (1.0 equiv., 0.66 M), isopentyl nitrite (1.1 equiv.), HCl (32%, 5.1 equiv.), $NaBF_4$ (2.0 equiv.), 30 min.

The diazotization reaction to obtain benzenediazonium chloride (**115a**, R = H) generally proceeded satisfactorily as observed by noticeable colour changes or precipitation of the formed benzenediazonium chloride (**115a**, R = H). A solution of sodium tetrafluoroborate in minimum solvent was then added to affect the conversion to benzenediazonium tetrafluoroborate (**113a**). This reaction also appeared to generally work well as evidenced by further colour changes/precipitation, however, the isolated yields were in many instances disappointingly low. Many of the above reactions (Table 4.2) resulted in heterogenous reaction conditions and it was speculated that the poor yields obtained were a result of poor reaction between the soluble and insoluble components. This theory is supported by the reaction conducted in ACN, in which the benzenediazonium chloride (**115a**, R = H) and benzenediazonium tetrafluoroborate (**113a**) were both soluble and resulted in the best yield (61%).

An optimization was performed to determine the best sodium tetrafluoroborate delivery method using ACN (Table 4.3) and when the formed benzenediazonium chloride (**115a**, R = H) was pushed through a narrow column packed with sodium tetrafluoroborate a yield of 78% for benzenediazonium tetrafluoroborate (**113a**) was obtained. Other tetrafluoroborate delivery methods involving addition of $NaBF_4$ portion wise as a solid, as a solution or supported on silica resulted in significantly lower yields. In addition to the improved yields obtained through use of the column it was also noted that the sodium chloride by-product formed during the reaction remained trapped in the column, which allowed for simplification of the work-up procedure.

Table 4.3: Optimization of sodium tetrafluoroborate delivery method

	$NaBF_4$ source	**Addition method**	**Solvent**	**Yield (%)**
1	$NaBF_4$	Solution	DMF	19
2	SiO_2-$NaBF_4$	Solid	DMF	0
3	$NaBF_4$	Solid	ACN	61
4	$NaBF_4$	Column	ACN	78

Standard conditions: aniline (**114a**) (1.0 equiv., 0.66 M), isopentyl nitrite (1.1 equiv.), HCl (32%, 5.1 equiv.), $NaBF_4$ source (2.0 equiv.), ≥30 min, 0 °C.

The effect of altering the acid source for the reaction and thus the stabilizing counter anion was then examined (Table 4.4) and it was found that most acids resulted in diazotization of aniline (**114a**, R = H), but that the product of the diazotization failed to react with the sodium tetrafluoroborate to yield benzenediazonium tetrafluoroborate (**113a**). Only the acids containing the chloride counter anion showed formation of **113a**, with ethanolic hydrochloric acid (1.25 M) resulting in a quantitative yield. This indicated that completely anhydrous conditions favoured the formation of the desired benzenediazonium tetrafluoroborate (**113a**).

Table 4.4: Optimization of acid source

	Acid source	Solvent	Yield (%)
1[a]	HCl 32%	DMF	19
2[a]	Ambelyst-15 H^+	DMF	0
3	Acetic acid	ACN	0
4	Nitric acid	ACN	0
5	Tosic acid	ACN	0
6	HCl 32%	ACN	78
7	Ethanolic HCl 1.25 M	ACN	100

Standard conditions: aniline (**114a**) (1.0 equiv., 0.66 M), isopentyl nitrite (1.1 equiv.), acid (5.1 equiv.), $NaBF_4$ (2.0 equiv.) in column, ≥30 min, 0 °C.

[a] $NaBF_4$ was added as a solution in DMF to these experiments.

Finally, an assessment was performed to determine the lowest stoichiometric amount of acid that could be used (Table 4.5) without compromising the yield of the reaction.

Table 4.5: Optimization of acid stoichiometry

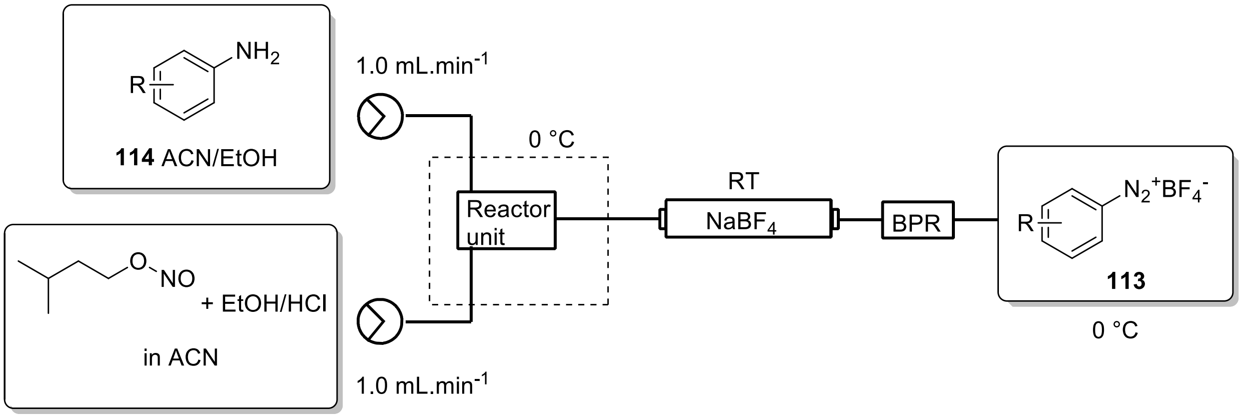
	Acid	Equivalents	Yield (%)
1	HCl 32%	5.1	78
2	HCl 32%	1.1	100
3	Ethanolic HCl 1.25M	1.1	100

Standard conditions: aniline (**114a**) (1.0 equiv., 0.66 M), isopentyl nitrite (1.1 equiv.), $NaBF_4$ (2.0 equiv.) in column, 15 min, 0 °C.

The lowest stoichiometric amount of acid that could be used without compromising the yield was found to be 1.1 equivalents relative to aniline (**114a**, R = H), with higher stoichiometric amounts of acid resulting in noticeably decreased yields. Decreasing the amount of acid to less than 1.0 equivalent relative to aniline (**114a**, R = H) was not considered feasible as this would have resulted in the in-sufficient *in-situ* generation of the required nitrous acid according to the reaction mechanism, which would have had a negative impact on the yield expected.

The final optimized batch conditions (performed on a 400 mg scale relevant to the product) for the diazotization reaction involved a reaction time of 15 minutes at 0 °C using 1.0 equiv. aniline (**114a**, R = H), 1.1 equiv. isopentyl nitrite, 1.1 equiv. ethanolic hydrochloric acid (1.25 M) in ACN at a concentration of 0.66 M relative to aniline (**114a**, R = H) which was allowed to pass through a narrow column packed with 2.0 equiv. sodium tetrafluoroborate. This was followed by a work-up/purification involving concentration to dryness, suspension in tetrahydrofuran and vacuum filtration to obtain a quantitative yield of **113a**.

Flow optimization: All flow experiments were performed using the Uniqsis FlowSyn SS platform.[53] For the optimization the system was operated with two HPLC pumps connected to either a 2 mL glass mixing chip, a PTFE T-piece mixer, a 2 mL HT PTFE coil or a combination of these reactors (Scheme 4.2) at 0 °C. Thereafter the flow path proceeded through a glass Omnifit® column (10 mm i.d. by 100 mm length) packed with sodium tetrafluoroborate (1.25 g, 2.0 equiv.) at room temperature prior to exiting through a 100 psi back pressure regulator (BPR). The reagent feedstock for pump A was an aryl amine in acetonitrile and for pump B was isopentyl nitrite and ethanolic HCl in acetonitrile. Aniline (**114a**, R = H) was once again used as a model compound during the optimization studies.



Scheme 4.2: Initial equipment setup for the flow synthesis of aryl diazonium tetrafluoroborate salts (**113**).

The 2 mL glass mixing chip was identified as the first reactor to evaluate for the diazotization reaction due to its excellent mixing abilities. An initial screen of concentration was performed to determine the highest concentration at which the reaction could be done without the formation of precipitates which could lead to the blockage of the reactor.

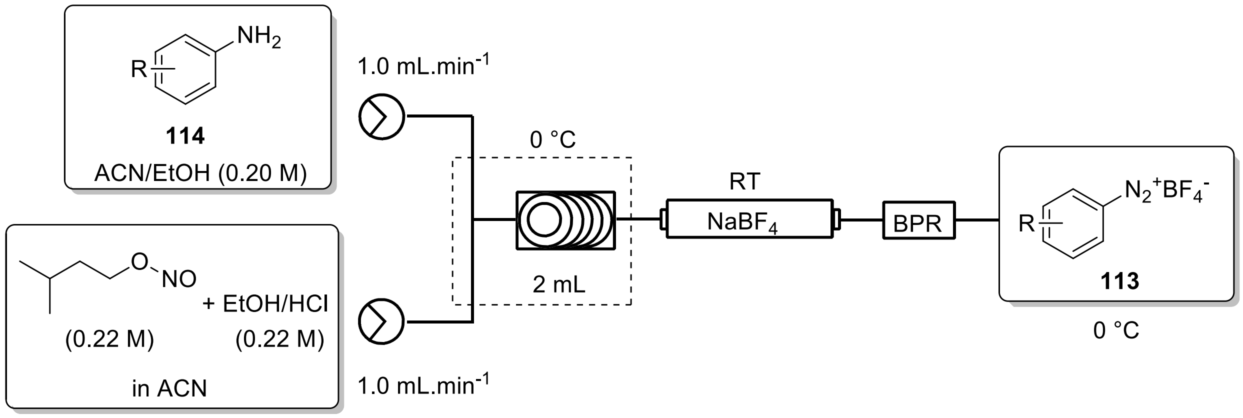
For the first run, a concentration of 1.0 M for aniline (**114a**, R = H) was selected. However, rapid precipitation within the mixing chip was observed which resulted in the reaction aborting due to blockage and over-pressurization. The concentration was subsequently reduced to 0.5 M for aniline (**114a**, R = H), which also resulted in precipitation within the mixing chip leading once again to blockage, over-pressurization and reaction abortion. The concentration was then reduced to 0.2 M for aniline (**114a**, R = H). This resulted in only a trace amount of precipitation within the mixing chip, which did not cause a blockage, did not cause the system to over-pressurize and thus did not cause the reaction to abort. This meant that the highest concentration relative to aniline (**114a**, R = H) at which the reactions remained homogeneous and at which the reactor was able to successfully complete the experimental run was 0.20 M with increasing concentrations resulting in aborted experiments due to blockages.

The presence of trace amounts of precipitate in the reaction was still a concern, thus, it was reasoned that the T-piece would be a more suitable reactor. It was thought that the build-up of precipitates would be less likely to accumulate within the T-piece, while the absence of the furrows (present in the mixing chip) would also reduce nucleation sites and therefore, hopefully eliminate the formation of precipitates. It was further speculated that the diazotization reaction was occurring very rapidly, with the time spent within the mixing chip being too much. The mixing chip was thus removed and replaced with the PTFE T-piece mixer. Using a concentration of 0.2 M for aniline (**114a**, R = H), no precipitation was observed and the experimental run was able to complete without any pressurization issues. Unfortunately, only a mixture of aniline (**114a**, R = H) and benzenediazonium chloride (**115a**, R = H) was obtained, with none of the desired product detectable. This implied that the mixing time using the T-piece mixer was insufficient to form the benzenediazonium chloride (**115a**, R = H) before its entry into the column packed with sodium tetrafluoroborate.

In order to increase the reaction time, the 2 mL HT PTFE coil was added into the system after the T-piece mixer, but before the column packed with sodium tetrafluoroborate. Once again using a concentration of 0.2 M for aniline (**114a**, R = H), no precipitation was observed and the experimental run was once again able to complete without any pressurization issues. Using this equipment setup, the desired benzenediazonium tetrafluoroborate (**113a**) was finally detected.

For further optimization studies the system was thus operated with two HPLC pumps connected via a PTFE T-piece mixer (Scheme 4.3, Figure 4.1) at 0 °C. Thereafter the flow path proceeded through the 2 mL HT PTFE coil at 0 °C and a glass Omnifit® column (10 mm i.d. by 100 mm length) packed with sodium tetrafluoroborate (1.25 g, 2.0 equiv.) at room temperature prior to exiting through a 100 psi back pressure regulator (BPR). The reagent feedstock for pump A was an aryl amine (0.20 M) in acetonitrile/ethanol and for pump B was isopentyl nitrite (0.22 M) and ethanolic HCl (0.22 M) in acetonitrile. Aniline (**114a**, R = H) was once again used as a model compound during the further optimization studies.

Figure 4.1: Photo of flow reactor setup for flow synthesis of aryl diazonium tetrafluoroborate salts (**113**).



Scheme 4.3: Final equipment setup for the flow synthesis of aryl diazonium tetrafluoroborate salts (**113**).

A subsequent screen of flow rates (Table 4.6) was performed which afforded a quantitative yield of **113a** with a total residence time of 2 minutes and 39 seconds, after a work-up/purification involving concentration to dryness, suspension in tetrahydrofuran and vacuum filtration. Performing the diazotization at room temperature by removing the coil from the ice-bath resulted in large amounts of decomposition and unwanted by-products.

Table 4.6: Optimization of flow rate for formation of **113a**

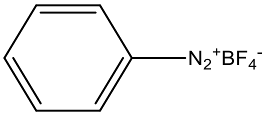
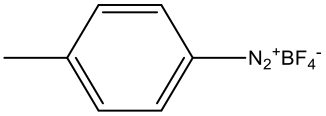
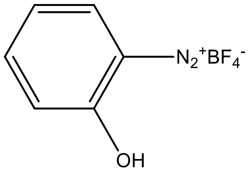
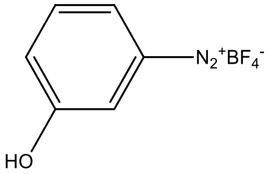
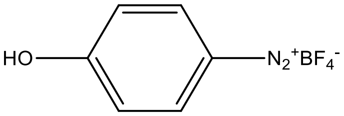
[a] Flow rate refers to the combined flow rates of both pumps set at a 1:1 ratio

Flow rate ($mL.min^{-1}$)[a]	Residence time coil (min)	Residence time column (min)	Yield (%)
1.0	2	3:30	46
1.5	1:20	2:20	100
2.0	1	1:39	100

Standard conditions: aniline (**114a**) (1.0 equiv.), isopentyl nitrite (1.1 equiv.), ethanolic HCl (1.1 equiv.), $NaBF_4$ (2.0 equiv.), 0 °C.

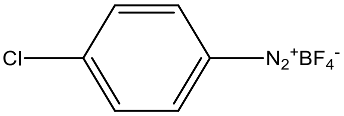
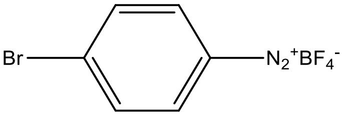
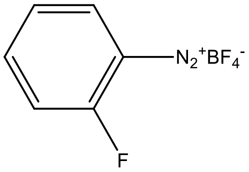
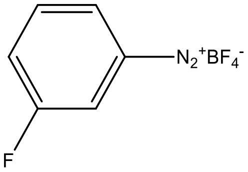
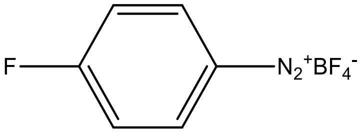
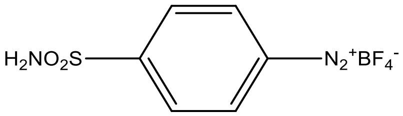
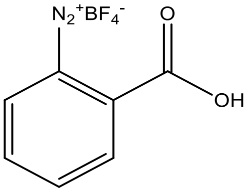
The optimized conditions (performed on a 400 mg scale relevant to the product) were then applied to the synthesis of a range of aryl diazonium tetrafluoroborate salts (**113**) (Table 4.7) from their respective aryl amines (**114**), requiring only minor adjustments to the solvent system or flow rates used in order to obtain good yields of all tested compounds. Once again it was noted that the sodium chloride formed as a by-product appeared to remain trapped in the column. This did not result in any fluctuations or spikes in the system pressure as the NaCl was forming at a rate equal to the consumption of the $NaBF_4$ and was thus simply taking the place of the $NaBF_4$ and not significantly altering the volume of the contents of the column.

Table 4.7: Aryl diazonium tetrafluoroborate salts synthesized

	Product	Solvent system	Flow rate ($mL.min^{-1}$)	Batch yield (%)	Flow yield (%)
113a		93% ACN/EtOH	2.0	100	100
113b		60% ACN/EtOH	2.0	40	85
113c		80% ACN/EtOH	2.0	31	64
113d		60% ACN/EtOH	2.0	77	100
113e		50% ACN/EtOH	1.5	21	100

Standard conditions: aryl amine (**114**) (1.0 equiv., 0.20 M), isopentyl nitrite (1.1 equiv., 0.22 M), ethanolic HCl (1.1 equiv., 0.22 M), $NaBF_4$ (2.0 equiv.), 0 °C.

Table 4.7 continued: Aryl diazonium tetrafluoroborate salts synthesized

	Product	Solvent system	Flow rate ($mL.min^{-1}$)	Batch yield (%)	Flow yield (%)
113f		76% ACN/EtOH	2.0	80	98
113g		76% ACN/EtOH	2.0	90	99
113h		76% ACN/EtOH	2.0	100	100
113i		76% ACN/EtOH	2.0	99	100
113j		93% ACN/EtOH	2.0	83	100
113k		60% ACN/EtOH	2.0	36	0
113l		60% ACN/EtOH	1.75	75	99

Standard conditions: aryl amine (**114**) (1.0 equiv., 0.20 M), isopentyl nitrite (1.1 equiv., 0.22 M), ethanolic HCl (1.1 equiv., 0.22 M), $NaBF_4$ (2.0 equiv.), 0 °C.

The continuous flow process afforded a range of aryl diazonium tetrafluoroborate salts (**113**) in good isolated yields of 64-100% with the exception of 4-sulfamoylbenzenediazonium tetrafluoroborate (**113k**), in which case the starting sulfanilamide (**114k)** could not be sufficiently solubilized for use in the flow reactor. NMR spectroscopic data obtained closely correlated with that available in the literature,[54] when literature NMR spectroscopic data was available. However, for many of the compounds literature NMR spectroscopic data was not available for comparison, making this the first report of its kind. A representative example highlighting the interpretation of the characterizing data is given below for the conversion of 4-bromoaniline (**114g**) to 4-bromobenzenediazonium tetrafluoroborate (**113g**).

In 4-bromoaniline (**114g**) the ^{1}H NMR spectrum has a distinctive peak at δ 5.21 ppm belonging to the NH_2 functional group (Figure 4.2). In the ^{1}H NMR spectrum of 4-bromobenzenediazonium tetrafluoroborate (**113g**) it can be clearly seen that this peak has disappeared which indicates that reaction has taken place at the nitrogen as expected (Figure 4.3). The aromatic protons have also shifted noticeably downfield (δ 8.56, d, J = 8.9 Hz, 2H and δ 8.24, d, J = 8.9 Hz, 2H) in 4-bromobenzenediazonium tetrafluoroborate (**113g**) when compared to 4-bromoaniline (**114g**, δ 7.12, d, J = 8.8 Hz, 2H and δ 6.53, d, J = 8.8 Hz, 2H)) which indicates that the aromatic protons are more deshielded in **113g** due to the diazonium group pulling electron density out of the aromatic ring. The group of Bonin and co-workers[57c] reported ^{1}H NMR spectroscopic shifts of δ 8.76 (d, J = 9.3 Hz, 2H) and δ 8.32 (d, J = 9.3 Hz, 2H) using acetone-d_6, which correlates fairly well when solvent differences are taken into account.

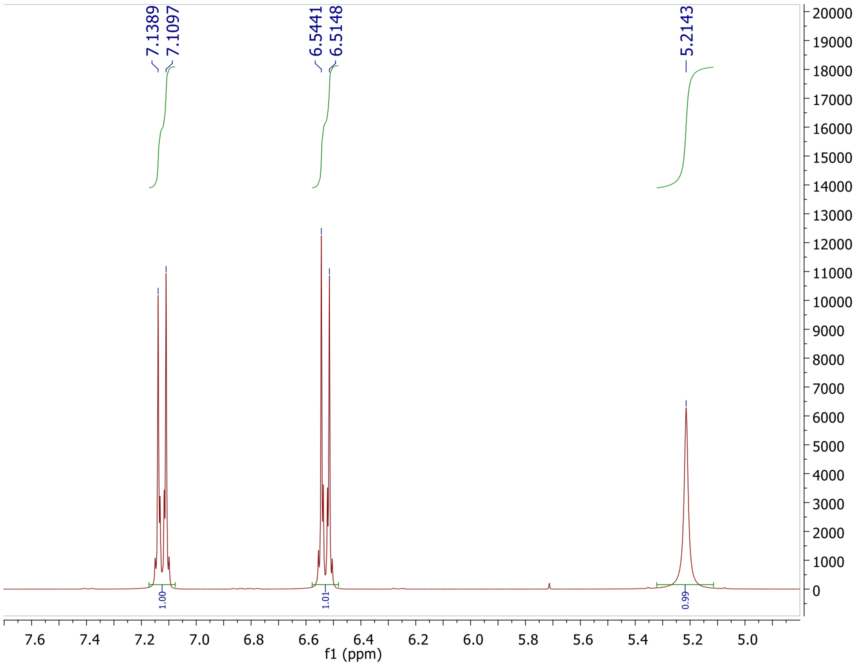


Figure 4.2: Experimental ^{1}H NMR spectrum of 4-bromoaniline (**114g**).

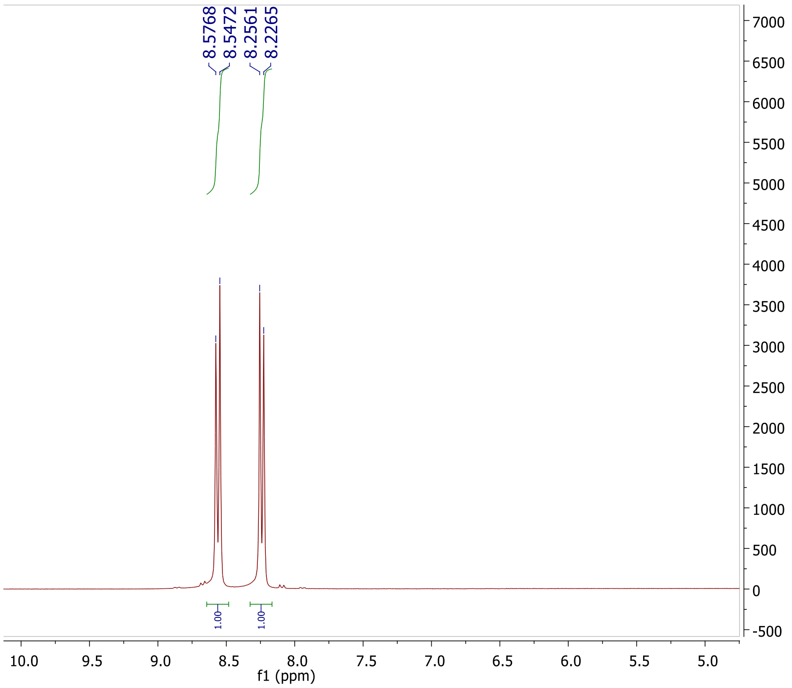


Figure 4.3: Experimental ^{1}H NMR spectrum of 4-bromobenzenediazonium tetrafluoroborate (**113g**).

The ^{13}C NMR spectrum provides a more accurate comparison as Bonin and co-workers[57c] elected to use d_6-DMSO, which matches the solvent choice for this work. They reported ^{13}C NMR spectroscopic shifts of δ 137.1, 135.0, 134.4 and 115.5 ppm respectively. Figure 4.4 shows that ^{13}C NMR spectroscopic shifts of δ 136.6, 134.6, 134.0 and 115.1 ppm were obtained, which correlates well with that obtained by Bonin and co-workers.[57c]

When comparing the ^{19}F NMR spectroscopic data, Bonin and co-workers[57c] reported a shift of δ -150.8 ppm for the fluorine atoms of the fluoroborate group. A shift of δ -148.2 ppm (Figure 4.5) was obtained in this work which also correlates well with that of Bonin and co-workers.

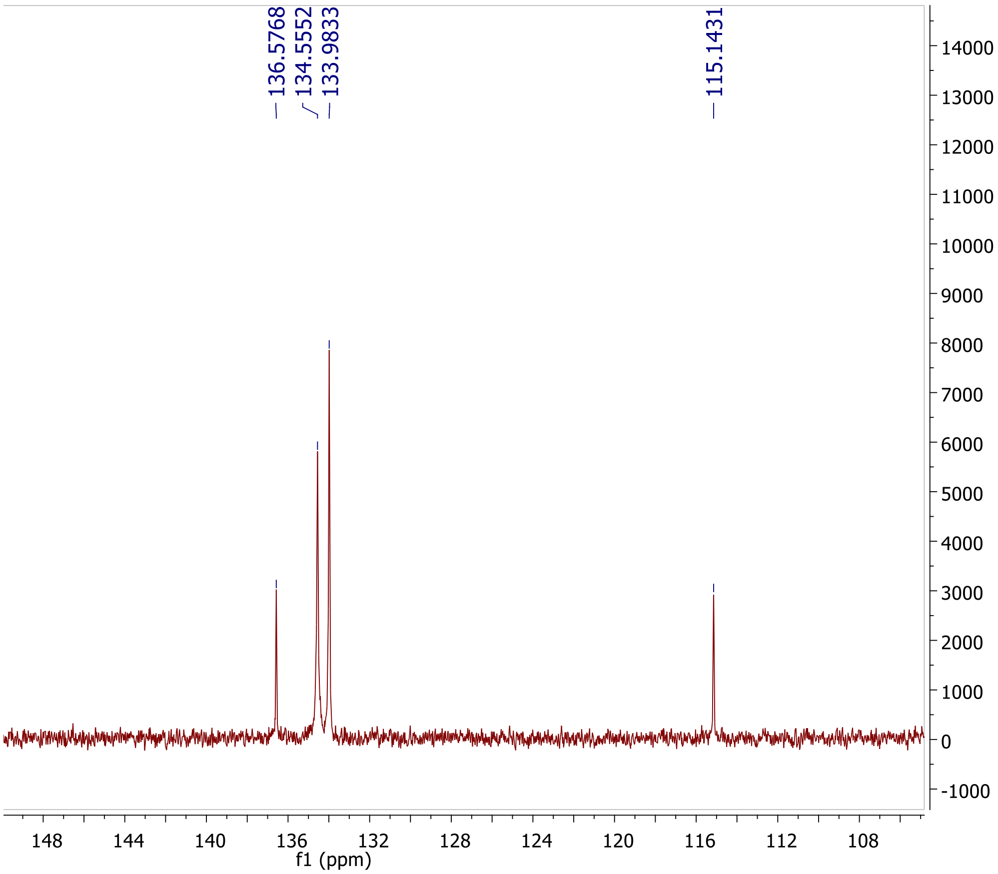


Figure 4.4: Experimental ^{13}C NMR spectrum of 4-bromobenzenediazonium tetrafluoroborate (**113g**).

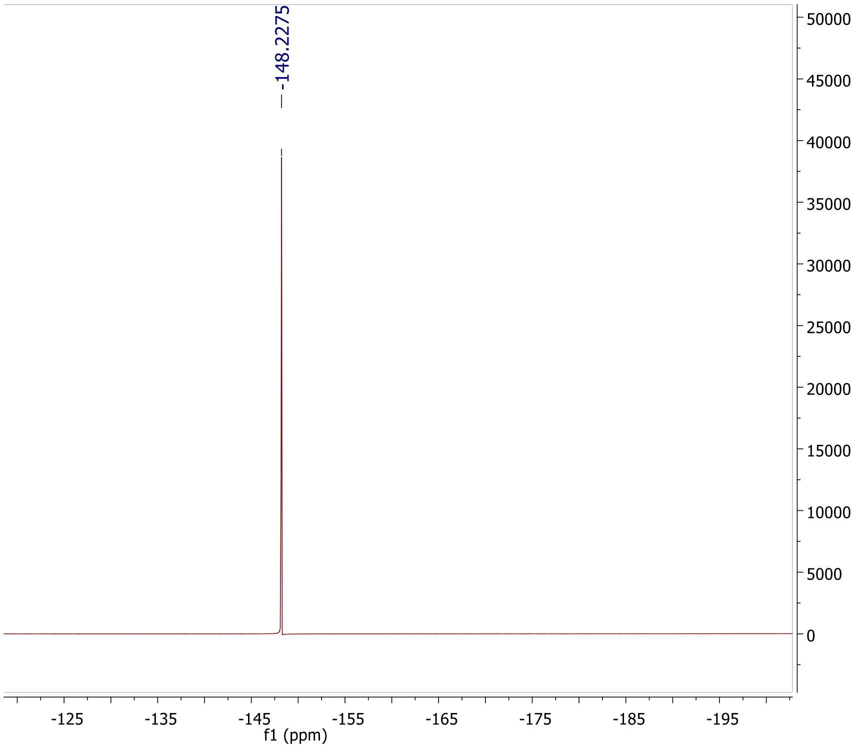


Figure 4.5: Experimental ^{19}F NMR spectrum of 4-bromobenzenediazonium tetrafluoroborate (**113g**).

The ^{1}H, ^{13}C and ^{19}F NMR spectroscopic data for all remaining compounds synthesized was analyzed in an analogous manner.

4.5. CONCLUSION

In conclusion an improved batch process and a high yielding continuous flow process for the synthesis of aryl diazonium tetrafluoroborate salts (**113**) has been demonstrated, the latter of which does not require the handling or isolation of the unstable aryl diazonium chloride (**115**) intermediate, has a greatly reduced residence time relative to existing batch processes (3 min vs 30+ min) and has a substantially improved safety profile. The continuous flow route thus shows significant advantages over the currently reported batch syntheses of aryl diazonium tetrafluoroborate salts (**113**). The approach could also conceivably be used for the rapid synthesis of aryl diazonium tetrafluoroborate salts (**113**) on a large scale, while also being suitable for coupling to further downstream flow reactions at a later stage as the now soluble aryl diazonium tetrafluoroborate salt (**113**) can be flowed over the many required solid-state catalysts or mixed with other solubilized reagent streams to effect the various transformations identified in Table 4.1. NMR spectroscopic and IR data has also been obtained for compounds which have not been previously characterized in the literature.

4.6. EXPERIMENTAL SECTION

All solvents and reagents were purchased from Sigma-Aldrich and used without further purification. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AVANCE-III 300 MHz spectrometer or a Bruker AVANCE-III 400 MHz spectrometer with the residual solvent peak as an internal reference (DMSO-d_6 = 2.49 and 39.5 ppm for ^{1}H and ^{13}C NMR spectra respectively). Chemical shifts, δ, are reported in parts per million (ppm), and splitting patterns are given as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m). Coupling constants, *J*, are expressed in hertz (Hz). Yields refer to isolated pure products unless stated otherwise.

General procedure for the batch preparation of aryl diazonium tetrafluoroborate salts (113)

A solution of aryl amine (**114**) (2 mmol, 1.0 equiv.) in acetonitrile (5 mL) was cooled to 0 °C followed by dropwise addition of ethanolic hydrochloric acid (2.2 mmol, 1.1 equiv.) and dropwise addition of isopentyl nitrite (2.2 mmol, 1.1 equiv.). The reaction mixture was pushed three times through a syringe packed with sodium tetrafluoroborate (4 mmol, 2.0 equiv.). The output of the syringe was collected in a flask cooled to 0 °C followed by concentration to dryness. The residue obtained was suspended in tetrahydrofuran and the solid product collected by vacuum filtration after washing with tetrahydrofuran.

Flow synthesis

General methods for the preparation of stock solutions

Aryl amine in acetonitrile

A stock solution of aryl amine (**114**) was prepared by dissolving the aryl amine (**114**) (2.0 mmol, 0.20 M) in the correct percentage ratio of acetonitrile/ethanol as can be found in Table 4.8.

Isopentyl nitrite / Ethanolic hydrochloric acid in acetonitrile

A stock solution of isopentyl nitrite and ethanolic hydrochloric acid was prepared by dissolving isopentyl nitrite (1.6 mL, 11.9 mmol, 0.22 M) and ethanolic hydrochloric acid (9.5 mL, 11.9 mmol, 0.22 M) in acetonitrile (54 mL).

General procedure for the stepwise flow synthesis of aryl diazonium tetrafluoroborate salts (113)

The aryl amine (11.0 mL) stock solution and the isopentyl nitrite/ethanolic hydrochloric acid (11.0 mL) stock solutions were both pumped at flow rates of 1 mL.min^{-1} through a T-piece mixer followed by a 2 mL HT PTFE coil cooled to 0 °C and a glass Omnifit® column (10 mm i.d. by 100 mm length) packed with sodium tetrafluoroborate (1.25 g, 11.4 mmol) at room temperature. The output of the reaction was collected in a flask cooled to 0 °C followed by concentration to dryness. The residue obtained was suspended in tetrahydrofuran and the solid product collected by vacuum filtration after washing with tetrahydrofuran.

Benzenediazonium tetrafluoroborate (113a)

Light pink solid (batch: 0.63 g, 3.3 mmol, 100%; flow: 0.42 g, 2.2 mmol, 100%). ^{1}H NMR (300 MHz d_6-DMSO) 8.64 (d, 2H, *J* 8.07, Ar-H); 8.24 (dd, 1H, J_1 7.28, J_2 7.28, Ar-H); 7.96 (dd, 2H, J_1 7.85, J_2 7.85, Ar-H). ^{13}C NMR (75 MHz d_6-DMSO) 140.92, 132.69, 131.29, 116.02. ^{19}F NMR (282 MHz, d_6-DMSO) -148.30. ν_{max} 3105, 2292, 1016, 754, 662 cm^{-1}.

4-Methylbenzenediazonium tetrafluoroborate (113b)

Light brown solid (batch: 0.16 g, 0.8 mmol, 40%; flow: 0.34 g, 1.7 mmol, 85%). ^{1}H NMR (300 MHz d_6-DMSO) 8.53 (d, 2H, *J* 8.46, Ar-H); 7.78 (d, 2H, *J* 8.37, Ar-H); 2.56 (s, 3H, CH_3). ^{13}C NMR (75 MHz d_6-DMSO) 154.02, 132.67, 131.81, 111.92, 22.35. ^{19}F NMR (282 MHz, d_6-DMSO) -148.26. ν_{max} 3111, 2286, 1581, 1011, 817, 723 cm^{-1}.

2-Hydroxybenzenediazonium tetrafluoroborate (113c)

Off-white solid (batch: 0.12 g, 0.6 mmol, 31%; flow: 0.26 g, 1.2 mmol, 64%). ^{1}H NMR (400 MHz d_6-DMSO) 7.60 (d, 1H, *J* 8.04, Ar-H); 7.42 (dd, 1H, J_1 7.86, J_2 7.86, Ar-H); 6.84 (s, 1H, OH); 6.59 (d, 1H, *J* 9.24, Ar-H); 6.37 (dd, 1H, J_1 7.48, J_2 7.48, Ar-H). ^{13}C NMR (75 MHz d_6-DMSO) 173.43, 139.91, 127.21, 121.68, 116.02, 91.35. ^{19}F NMR (282 MHz, d_6-DMSO) -148.57. ν_{max} 1306, 1010, 750, 608 cm^{-1}.

3-Hydroxybenzenediazonium tetrafluoroborate (113d)

Brown solid (batch: 0.32 g, 1.5 mmol, 77%; flow: 0.40 g, 1.9 mmol, 100%). ^{1}H NMR (300 MHz *d_6*-DMSO) 11.41 (s, 1H, OH); 8.09 (d, 1H, *J* 7.53, Ar-H); 7.94 (s, 1H, Ar-H); 7.74 (dd, 1H, J_1 7.25, J_2 7.25, Ar-H); 7.59 (d, 1H, *J* 6.12, Ar-H). ^{13}C NMR (75 MHz *d_6*-DMSO) Could not be obtained due to decomposition. ^{19}F NMR (282 MHz, *d_6*-DMSO) -148.45. ν_{max} 3199, 1411, 1306, 1011, 725 cm^{-1}.

4-Hydroxybenzenediazonium tetrafluoroborate (113e)

White solid (batch: 0.09 g, 0.4 mmol, 21%; flow: 0.40 g, 1.9 mmol, 100%). ^{1}H NMR (300 MHz *d_6*-DMSO) 8.29 (d, 2H, *J* 9.21, Ar-H); 6.96 (d, 2H, *J* 8.85, Ar-H). ^{13}C NMR (75 MHz *d_6*-DMSO) Could not be detected due to decomposition. ^{19}F NMR (282 MHz, *d_6*-DMSO) -148.49. ν_{max} 2113, 2082, 1827, 1305, 1012, 595 cm^{-1}.

4-Chlorobenzenediazonium tetrafluoroborate (113f)

White solid (batch: 0.33 g, 1.5 mmol, 80%; flow: 0.39 g, 1.7 mmol, 98%). ^{1}H NMR (300 MHz *d_6*-DMSO) 8.67 (d, 2H, *J* 8.91, Ar-H); 8.09 (d, 2H, *J* 8.91, Ar-H). ^{13}C NMR (75 MHz *d_6*-DMSO) 146.57, 134.42, 131.63, 114.72. ^{19}F NMR (282 MHz, *d_6*-DMSO) -148.26. ν_{max} 3108, 2289, 1313, 1290, 1024, 833, 771 cm^{-1}.

4-Bromobenzenediazonium tetrafluoroborate (113g)

White solid (batch: 0.37 g, 1.4 mmol, 90%; flow: 0.40 g, 1.5 mmol, 99%). ^{1}H NMR (300 MHz d_6-DMSO) 8.56 (d, 2H, J 8.88, Ar-H); 8.24 (d, 2H, J 8.88, Ar-H). ^{13}C NMR (75 MHz d_6-DMSO) 136.58, 134.56, 133.98, 115.14. ^{19}F NMR (282 MHz, d_6-DMSO) -148.23. ν_{max} 3097, 2282, 1291, 1029, 827, 759 cm^{-1}.

2-Fluorobenzenediazonium tetrafluoroborate (113h)

Light yellow solid (batch: 0.44 g, 2.1 mmol, 100%; flow: 0.40 g, 1.9 mmol, 100%). ^{1}H NMR (300 MHz d_6-DMSO) 8.73 (dd, 1H, J_1 6.63, J_2 6.63, Ar-H); 8.37 (dd, 1H, J_1 7.10, J_2 13.52, Ar-H); 7.99 (dd, 1H, J_1 9.18, J_2 9.18, Ar-H); 7.81 (dd, 1H, J_1 7.95, J_2 7.95, Ar-H). ^{13}C NMR (75 MHz d_6-DMSO) 160.36 (d, $J_{C\text{-F}}$ 273.20), 144.72 (d, $J_{C\text{-F}}$ 9.06), 133.44 (d, $J_{C\text{-F}}$ 3.77), 127.47, 118.71 (d, $J_{C\text{-F}}$ 15.85), 105.57 (d, $J_{C\text{-F}}$ 12.83). ^{19}F NMR (282 MHz, d_6-DMSO) -102.55 (F), -148.37 (BF_4^-). ν_{max} 3106, 2292, 1287, 1250, 1029, 830, 769 cm^{-1}.

3-Fluorobenzenediazonium tetrafluoroborate (113i)

White solid (batch: 0.43 g, 2.1 mmol, 99%; flow: 0.40 g, 1.9 mmol, 100%). ^{1}H NMR (300 MHz d_6-DMSO) 8.66 (d, 1H, J 7.59, Ar-H); 8.58 (d, 1H, J 8.28, Ar-H); 8.20 (dd, 1H, J_1 8.45, J_2 8.45, Ar-H); 8.00 – 8.08 (m, 1H, Ar-H). ^{13}C NMR (100 MHz d_6-DMSO) 160.61 (d, $J_{C\text{-F}}$ 252.58), 133.61 (d, $J_{C\text{-F}}$ 9.06), 129.88 (d, $J_{C\text{-F}}$ 3.02), 129.20 (d, $J_{C\text{-F}}$ 21.13), 119.54 (d, $J_{C\text{-F}}$ 30.19), 117.35 (d, $J_{C\text{-F}}$ 12.08). ^{19}F NMR (282 MHz, d_6-DMSO) -105.75 (F), -148.24 (BF_4^-). ν_{max} 3101, 2300, 1235, 1028, 874, 789, 651 cm^{-1}.

4-Fluorobenzenediazonium tetrafluoroborate (113j)

Light yellow solid (batch: 0.37 g, 1.7 mmol, 83%; flow: 0.40 g, 1.9 mmol, 100%). ^{1}H NMR (400 MHz *d$_6$*-DMSO) 8.77 – 8.82 (m, 2H, Ar-H); 7.84 – 7.90 (m, 2H, Ar-H). ^{13}C NMR (100 MHz *d$_6$*-DMSO) 168.47 (d, $J_{C\text{-F}}$ 267.68), 137.02 (d, $J_{C\text{-F}}$ 12.08), 119.42 (d, $J_{C\text{-F}}$ 25.16), 111.86 (d, $J_{C\text{-F}}$ 3.02). ^{19}F NMR (377 MHz, *d$_6$*-DMSO) -87.21 (F), -148.17 (BF_4^-). ν_{max} 3114, 2291, 1252, 1016, 843, 682 cm^{-1}.

4-Sulfamoylbenzenediazonium tetrafluoroborate (113k)

Pale yellow solid (batch: 0.15 g, 0.6 mmol, 36%). ^{1}H NMR (300 MHz *d$_6$*-DMSO) 8.85 (d, 2H, *J* 8.73, Ar-H); 8.32 (d, 2H, *J* 8.76, Ar-H); 8.05 (s, 2H, SO_2NH_2). ^{13}C NMR (75 MHz *d$_6$*-DMSO) 153.37, 134.05, 128.06, 119.46. ^{19}F NMR (282 MHz, *d$_6$*-DMSO) -148.25. ν_{max} 2079, 1663, 1306, 1011, 618 cm^{-1}.

2-Carboxybenzenediazonium tetrafluoroborate (113l)

White solid (batch: 0.31 g, 1.3 mmol, 75%; flow: 0.40 g, 1.7 mmol, 99%). ^{1}H NMR (400 MHz *d$_6$*-DMSO) 12.21 (s, br, 1H, OH); 7.71 (dd, 1H, J_1 8.04, J_2 1.46 Ar-H); 7.56 (dd, 1H, J_1 8.58, J_2 8.58, Ar-H); 7.12 (d, 1H, *J* 7.72, Ar-H); 7.10 (d, 1H, *J* 7.52, Ar-H). ^{13}C NMR (100 MHz *d$_6$*-DMSO) 172.33, 157.50, 135.29, 130.36, 129.77, 120.62, 116.96. ^{19}F NMR (377 MHz, *d$_6$*-DMSO) -148.33. ν_{max} 3099, 2281, 1728, 1047, 725, 635 cm^{-1}.

4.7. REFERENCES

(1) Mohamed, A.A.; Salmi, Z.; Dahoumane, S.A.; Mekki, A.; Carbonnier, B.; Chehimi, M.M. *Adv. Colloid Interface Sci.*, **2015**, *225*, 16.

(2) Mo, F.; Dong, G.; Zhang, Y.; Wang, J. *Org. Biomol. Chem.*, **2013**, *11*, 1582.

(3) Ram, R.N.; Singh, V. *J. Chem. Res.*, **2006**, 800.

(4) Shriver, J.A.; Flaherty, D.P.; Herr, C.C. *Jour. Iowa Acad. Sci.*, **2009**, *116*, 27.

(5) Maas, G.; Tanaka, M.; Sakakura, T. Benzenediazonium Tetrafluoroborate, Section in Encyclopedia of Reagents for Organic Synthesis 2nd Ed., book 1., Paquette, L.A.; Crich, D.; Fuchs, P.L.; Molander, G.A. (eds.), Wiley, **2009**, pp 436 – 441.

(6) Coleman, G.H. Organic Synthesis, Coll. Vol. 1, Conant, J.B.; Thompson, H.R. (eds.), **1941**, pp 442 – 444.

(7) Eichen Conn, R.S.; Douglas, A.W.; Karady, S.; Corley, E.G.; Lovell, A.V.; Shinkai, I. *J. Org. Chem.*, **1990**, *55*, 2908.

(8) Furniss, B.S.; Hannaford, A.J.; Smith, P.W.; Tatchell, A.R. Formation of diazonium salts and their uses in Vogel's Textbook of Practical Organic Chemistry 5th Ed., Pearson Prentice Hall, **1989**, pp 920 – 953.

(9) Hudlicky, M. Replacement of Nitrogen by Fluorine in Chemistry of Organic Fluorine Compounds 2nd Ed., Horwood, E.; Mellor, J. (eds.), Ellis Horwood and Prentice Hall, **1992**, pp 160 – 169.

(10) Solomons, T.W.G.; Fryhle, C.B. Replacement Reactions of Arendiazonium Salts in Organic Chemistry 8th Ed., Brennan, D.; Molloy, K. (eds.), John Wiley and Sons, Inc., **2004**, pp 966 – 972.

(11) Dunker, M.F.W.; Starkey, E.B.; Jenkins, G.L. *J. Am. Chem. Soc.*, **1936**, *58*, 2308.

(12) Citterio, A.; Arnoldi, A. *Synth. Commun.*, **1981**, *11*, 639.

(13) Horning, D.E.; Ross, D.A.; Muchowski, J.M. *Can. J. Chem.*, **1973**, *51*, 2347.

(14) Lewis, E.S. *J. Am. Chem. Soc.*, **1958**, *80*, 1371.

(15) Pelzer, G.; Keim, W. *J. Mol. Catal. A: Chem.*, **1999**, *139*, 235.

(16) Liu, X.; Li, W.; Zheng, D.; Fan, X.; Wu, J. *Tetrahedron*, **2015**, *71*, 3359.

(17) Barba, F.; Ranz, F.; Batanero, B. *Tetrahedron Lett.*, **2009**, *50*, 6798.

(18) Chatterjee, T.; Bhadra, S.; Ranu, B.C. *Green Chem.*, **2011**, *13*, 1837.

(19) Abeywickrema, A.N.; Beckwith, A.L.J. *J. Am. Chem. Soc.*, **1986**, *108*, 8227.

(20) Hodgson, H.H.; Foster, C.K. *J. Chem. Soc. Abs.*, **1942**, 747 (*Chem. Abs.*, **1943**, *37*, 8447.

(21) Haller, H.L.; Schaffer, P.S. *J. Am. Chem. Soc.*, **1933**, *55*, 4954.

(22) Burgstahler, A.W.; Abdel-Rahman, M.O.; Chien, P.-L. *Tetrahedron Lett.*, **1964**, *5*, 61.

(23) Canning, P.S.J.; McCrudden, K.; Maskill, H.; Sexton, B. *J. Chem. Soc. Perkin Trans. 2*, **1999**, 2735.

(24) Yoneda, N.; Fukuhara, T.; Mizokami, T.; Suzuki, A. *Chem. Lett.*, **1991**, 459.

(25) Milanesi, S.; Fagnoni, M.; Albini, A. *Chem. Commun.*, **2003**, *39*, 216.

(26) Curtin, D.Y.; Ursprung, J.A. *J. Org. Chem.*, **1956**, *21*, 1221.

(27) Blank, O.; Raschke, N.; Heinrich, M.R. *Tetrahedron Lett.*, **2010**, *51*, 1758.

(28) Zhang, N.; Quan, Z.-J.; Zhang, Z.; Da, Y.-X.; Wang, X.-C. *Chem. Commun.*, **2016**, *52*, 14234.

(29) Kikukawa, K.; Matsuda, T. *Chem. Lett.*, **1977**, 159.

(30) Beletskaya, I.P.; Cheprakow, A.V. *Chem. Rev.*, **2000**, *100*, 3009.

(31) Gomberg, M.; Bachmann, W.E. *J. Am. Chem. Soc.*, **1924**, *46*, 2339.

(32) Tripathi, S.; Singh, S.N.; Yadav, L.D.S. *Tetrahedron Lett.*, **2015**, *56*, 4211.

(33) Koza, D.J.; Nsiah, Y.A. *Bioorg. Med. Chem. Lett.*, **2002**, *12*, 2163.

(34) Colleville, A.P.; Horan, R.A.J.; Tomkinson, N.C.O. *Org. Process Res. Dev.*, **2014**, *18*, 1128.

(35) Willis, D.M.; Strongin, R.M. *Tetrahedron Lett.*, **2000**, *41*, 6271.

(36) Meerwein, H.; Buchner, E.; van Emsterk, K. *J. Prakt. Chem.*, **1939**, *152*, 237.

(37) Fabrizi, G.; Goggiamani, A.; Sferrazza, A.; Cacchi, S. *Angew. Chem. Int. Ed.*, **2010**, *49*, 4067.

(38) Panda, B.; Sarkar, T.K. *Chem. Commun.*, **2010**, *46*, 3131.

(39) Hari, D.P.; Schroll, P.; König, B. *J. Am. Chem. Soc.*, **2012**, *134*, 2958.

(40) Ding, Y.; Cheng, K.; Song, Q.; Song, Q. *Tetrahedron Lett.*, **2012**, *53*, 6269.

(41) Heinrich, M.R.; Blank, O.; Ullrich, D.; Kirschstein, M. *J. Org. Chem.*, **2007**, *72*, 9609.

(42) Kundu, D.; Ahammed, S.; Ranu, B.C. *Green Chem.*, **2012**, *14*, 2024.

(43) Wootton, R.C.R.; Fortt, R.; de Mello, J. *Lab Chip*, **2002**, *2*, 5.

(44) Fortt, R.; Wootton, R.C.R.; de Mello, A.J. *Org. Process Res. Dev.*, **2003**, *7*, 762.

(45) Li, B.; Widlicka, D.; Boucher, S.; Hayward, C.; Lucas, J.; Murray, J.C.; O'Neil, B.T.; Pfisterer, D.; Samp, L.; VanAlsten, J.; Xiang, Y.; Young, J. *Org. Process Res. Dev.*, **2012**, *16*, 2031.

(46) Oger, N.; Le Grognec, E.; Felpin, F.-X. *J. Org. Chem.*, **2014**, *79*, 8255.

(47) Ahmed-Omer, B.; Barrow, D.A.; Wirth, T. *Tetrahedron Lett.*, **2009**, *50*, 3352.

(48) (a) Chen, M.; Buchwald, S.L. *Angew. Chem. Int. Ed.*, **2013**, *52*, 4247. (b) Yu, Z.; Xie, X.; Dong, H.; Liu, J.; Su, W. *Org. Process Res. Dev.*, **2016**, *20*, 774.

(49) (a) Malet-Sanz, L.; Madrzak, J.; Holvey, R.S.; Underwood, T. *Tetrahedron Lett.*, **2009**, *50*, 7263. (b) Malet-Sanz, L.; Madrzak, J.; Ley, S.V.; Baxendale, I.R. *Org. Biomol. Chem.*, **2010**, *8*, 5324. (c) Jacq, J.; Pasau, P. *Chem. Eur. J.*, **2014**, *20*, 12223. (d) D'Attoma, J.; Camara, T.; Brun, P.L.; Robin, Y.; Bostyn, S.; Buron, F.; Routier, S. *Org. Process Res. Dev.*, **2017**, *21*, 44.

(50) Oger, N.; Le Grognec, E.; Felpin, F.-X. *Org. Chem. Front.*, **2015**, *2*, 590.

(51) Yu, Z.-Q.; Lv, Y.-W.; Yu, C.-M.; Su, W.-K. *Tetrahedron Lett.*, **2013**, *54*, 1261.

(52) Hu, T.; Baxendale, I.R.; Baumann, M. *Molecules*, **2016**, *21*, 918.

(53) www.uniqsis.com

(54) (a) Kizil, M.; Yilmaz, E.I.; Pirinççioğlu, N.; Aytekin, Ç. *Turk. J. Chem.*, **2003**, *27*, 539. (b) Tang, Z.Y.; Zhang, Y.; Wang, Y.; Wang, W. *Synlett*, **2010**, *5*, 804. (c) Bonin, H.; Delbrayelle, D.; Demonchaux, P.; Gras, E. *Chem. Commun.*, **2010**, *46*, 2677.

Chapter 5:

Aryl Hydrazines

5. The Synthesis of Aryl Hydrazines – Investigating the Conversion from Batch to Continuous Flow Conditions

5.1. KEYWORDS

Aryl hydrazines, reduction, borohydride exchange resin (BER), $SnCl_2$, Na_2SO_3.

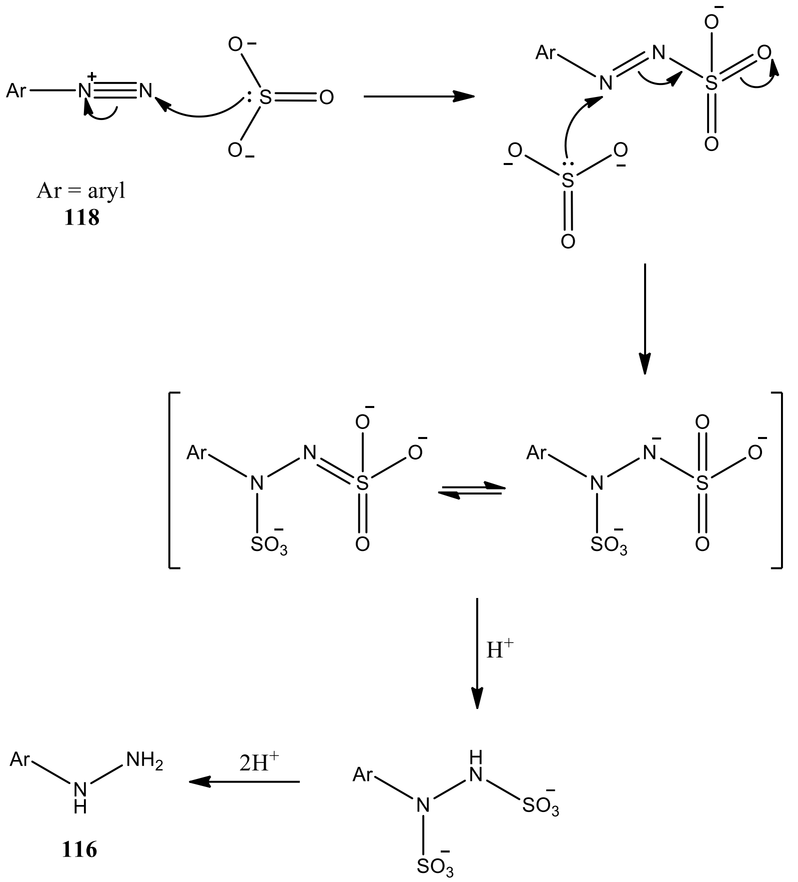
5.2. ABSTRACT

Aryl hydrazines (**116**) are important intermediates in organic chemistry required for the synthesis of various important heterocyclic compounds such as pyrazoles e.g. Celecoxib (**27**) (Chapter 6). The efforts to develop a simpler and more consistent batch mode synthesis of aryl hydrazines (**116**), which could be translated to a continuous flow process are reported. Various experimental conditions, reducing agents and modifications thereof are examined. All reactions tested were also critically evaluated for potential conversion to a universally applicable continuous flow process, which could not be successfully achieved using the reaction conditions tested due to various reasons which are discussed.

5.3. INTRODUCTION

Aryl hydrazines (**116**) are important intermediates in organic synthesis, particularly for the pharmaceutical industry as a number of hydrazine derivatives have demonstrated interesting biological activity.[1,2] The presence of hydrazine derivatives can also be noted in many prominent pesticides, amino acid precursors, dyestuffs, agrochemicals and drugs, while also serving as a key moiety in the synthesis of heterocycles[2,3] such as indoles,[4-7] β-lactams,[4] quinazolines,[4] indazoles,[5,7] aryl triazoles,[5] pyrazolones,[6] carbazoles,[7] triazines,[7] indazolones[7] and pyrazoles.[4-7] Aryl hydrazines (**116**) are of particular importance for combination with 1,2- or 1,3-difunctional adducts[3] for the synthesis of heterocycle and pyrazole derivatives such as Celecoxib (**27**), a medicinally important anti-inflammatory drug (Chapter 6). Aryl hydrazines (**116**) are also required for the preparation of diphenylcarbazones used as analytical reagents[8] and as antibacterial agents against *Mycobacterium tuberculosis*,[2,8] while some substituted hydrazines are required for the synthesis of azapeptides (peptidomimetics) for the treatment of HIV/AIDS, SARS and hepatitis.[2,3,9] Yet other hydrazine derivatives have been shown to be effective as a treatment for hypertension and Parkinson's disease.[2] More recently, hydrazine derivatives have shown potential as a new class of antifungal agents, specifically against *Candida* spp.[10] Aryl hydrazines (**116**) are also of general synthetic use allowing for access to aryl hydrazides[10] through acylation and aryl amines[11] through reduction. Hydrazine derivatives have also been found to occur naturally, although these are very scarce and to date only four hydrazine derivatives which are non-acylated have been reported, details for which can be found in a review written by Le Goff and Ouazzani.[12]

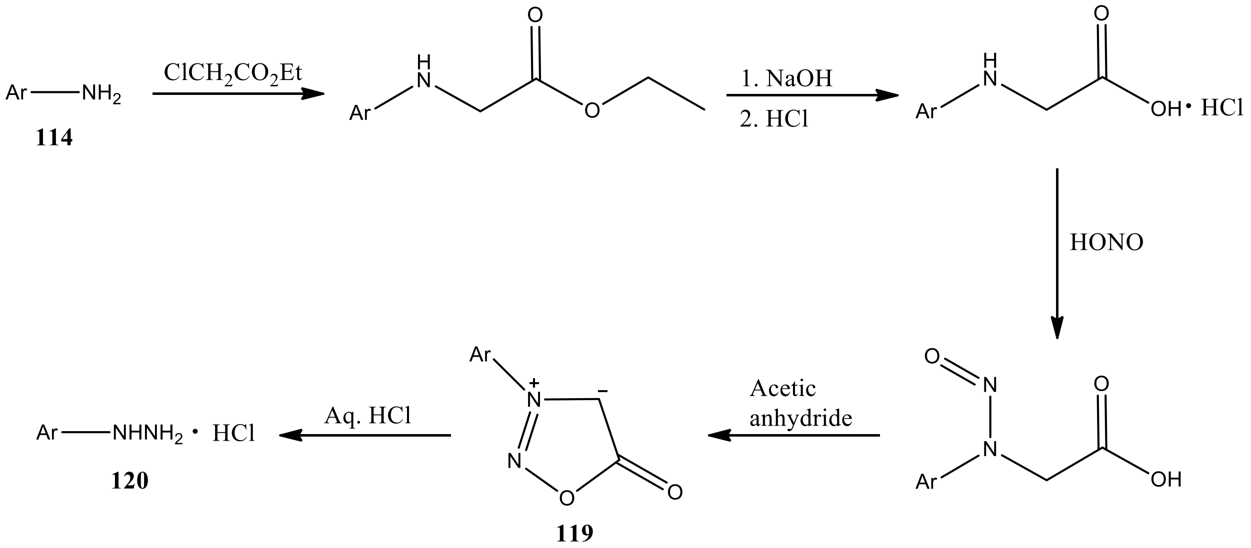
It was thanks to the work of Griess in 1858 on the synthesis of diazonium salts (see Chapter 4 for details and references) that Fischer was able to prepare the first aryl hydrazine – phenylhydrazine (**117**) in 1875 after directly reducing the diazonium salt of aniline using a sulfite salt.[3,13] Sulfite salts have remained a relevant choice as reductants in the literature due to their low toxicity and ready availability despite the requirement of a large excess of reagents (mechanism in Scheme 5.1) and the need for more complex work-up and purification protocols resulting in more inconsistent yields.[14,15]



Scheme 5.1: Mechanism for sulfite reduction of aryl diazonium salts (**118**) to aryl hydrazines (**116**).[15]

More frequently, the diazonium salt (**118**) has been reduced by tin(II) chloride in the presence of acid as this method has proven to be simpler, faster, more efficient, more consistent and is able to tolerate a wider range of substituents on the aromatic ring than the sulfite method.[11,16] The major disadvantages of this method is the extreme toxicity of tin(II) chloride, its expense, and the large amounts of toxic tin wastes that are generated, making this method unsuitable for the manufacture of pharmaceuticals.[7,17,18] The work-up protocol to obtain the free base (which is often unstable) instead of the hydrochloride salt is also a tedious process that requires treatment with excess base followed by extraction.[8a,19]

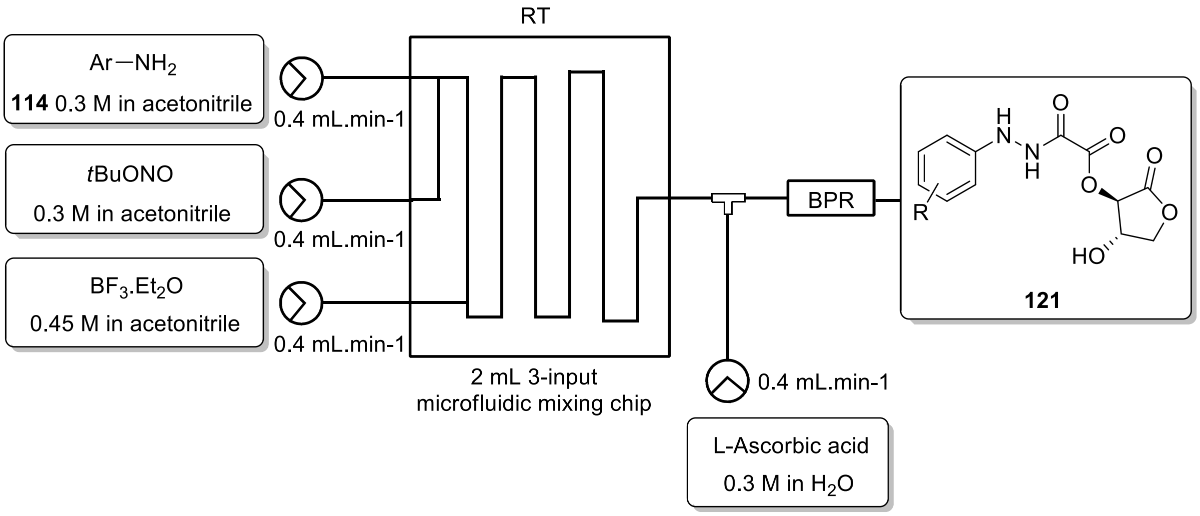
A number of research groups have explored a range of alternative reagents, with Chaikin and Brown[20] using sodium borohydride to reduce benzenediazonium chloride. They, however, obtained a mixture of benzene, aniline (**114a**) and phenylhydrazine (**117**), all in poor yields[20] while Bandgar and Thite[8a] opted to use borohydride exchange resin (BER) for the reduction of aryl diazonium tetrafluoroborate salts (**113**) to their corresponding aryl hydrazines (**116**) in yields of 60-91%. In another paper, the same group then reported the use of Zn-$NiCl_2•6H_2O$ as a reducing system to obtain yields of 70-90%.[8b] Hunsberger and co-workers[21] found that acid hydrolysis of sydnones (**119**) (Scheme 5.2) resulted in the formation of the corresponding aryl hydrazine hydrochlorides (**120**) and was a good method for obtaining hydrazines which could not be accessed using conventional methods.



Scheme 5.2: Synthesis of Hunsberger and co-workers.[21]

Demers and Klaubert[22] prepared aryl hydrazine hydrochlorides (**120**) by addition of aryl metallics (Grignard reagents) to azodicarboxylates followed by hydrolysis to obtain yields of 12-88%. In some instances, a metal catalyzed cross-coupling reaction between an aryl halide and hydrazine hydrate ($N_2H_4•H_2O$) are reported in which [{Pd(cinnamyl)Cl}$_2$] with a ligand and base,[5] CuI with K_3PO_4[7] or CuBr with a ligand, ketone additive, K_3PO_4 and a phase transfer catalyst[17] are utilized to obtain aryl hydrazines (**116**). More recently L-ascorbic acid has attracted the attention of various research groups as a mild, environmentally friendly reducing agent for the reduction of the diazonium salt to the corresponding aryl hydrazine (**116**),[18,19,23] with the group of Norris[18] reporting large-scale and pilot-plant operations. A number of reports can also be found for the synthesis of *N*-alkyl and *N*-aryl substituted hydrazines,[1-4,9,24] with a more detailed discussion covering the synthesis of hydrazines and substituted hydrazines to be found in Comprehensive Organic Functional Group Transformations II.[25]

The first flow synthesis to be reported was that of Ley and co-workers[23] in which they prepared an aryl hydrazine masked as an oxamide (**121**). Aryl diazonium tetrafluoroborate salts (**113**) were generated within a 2 mL microfluidic chip followed by quenching with L-ascorbic acid via a T-piece at the exit of the chip to obtain the oxamide intermediate (**121**) in 98% yield (Scheme 5.3).[23] The same group[26] then expanded on their previous work, opting to form the diazonium chloride salt followed by its reduction with L-ascorbic acid in the multistep flow synthesis of pyrazoles. The formed aryl hydrazines (**116**) were generated as the oxamide derivates and immediately used in the next reaction *in-situ*.[26] A similar approach was taken by Baxendale and co-workers,[27] although their study was primarily focused on the optimization of the flow synthesis of the diazonium salts.



Scheme 5.3: Flow synthesis of aryl hydrazines masked as oxamides (**121**).[23,26]

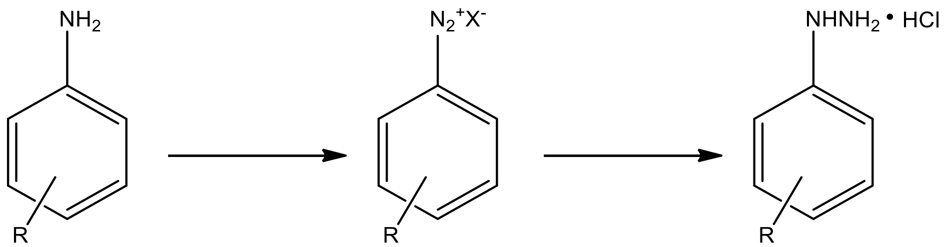
In their efforts to develop a flow process for the synthesis of pyrazoles, Li and co-workers[28] performed the diazotization reaction to obtain Aryl-$N_2^+BF_3OH^-$ under flow conditions, which required sonication in order to prevent blockage of the reactor. This was followed by batch reduction using tin(II) chloride, citing failed efforts to find an alternative reducing agent as the reason for proceeding with the undesirable tin(II) chloride.[28] In their flow synthesis of functionalized heterocycles Buchwald and co-workers[6] opted for a palladium catalyzed direct cross-coupling reaction between aryl chlorides and hydrazine under flow conditions followed by the *in-situ* trapping of the aryl hydrazine intermediates as the corresponding benzaldehyde hydrazones. Once again, sonication was required in order to prevent blockage of the reactor.[6]

A continuous flow synthesis of 2-ethylphenylhydrazine hydrochloride was reported by the group of Su and co-workers,[29] but they did not expand their methodology to the synthesis of other aryl hydrazines (**116**). In their experimental methodology, they react a 1.5 M solution of 2-ethylaniline in 3.0 equivalents of aqueous HCl with a 6.0 M aqueous solution of sodium nitrite to effect diazotization, followed by reduction with a 1.8 M aqueous solution of sodium sulfite.[29] The output of the reactor was collected in a heated toluene/hydrochloric acid solution followed by an extraction work-up protocol to obtain a reported yield of 94%.[29] Even though this synthesis was successful, it suffers from the disadvantages of solubility issues which forced the group to increase the inner diameter of all their reactors in order to avoid blockages and the system required the use of expensive Hastelloy components and coils throughout in order to prevent corrosion due to the presence of a very large excess of aqueous HCl, which arguably makes this method impractical and challenging for industrial purposes.

Many of the above-mentioned reactions either require expensive reagents and catalysts[7,17] specialized reaction conditions such as a glovebox[5,17] or Hastelloy components.[29] Other reactions need harsh conditions, require many steps to obtain the desired aryl hydrazine (**116**) or produce large amounts of toxic waste. A more efficient synthesis of aryl hydrazines (**116**) making use of easily accessible and affordable reagents that does not produce large amounts of waste would be highly beneficial to the pharmaceutical industry, especially for the preparation of indoles, pyrazoles and other important heterocycles.

5.4. RESULTS AND DISCUSSION

The preferred synthetic route to access aryl hydrazines (**116**) (Scheme 5.4) involved a diazotization reaction between an aryl amine (**114**), acid and a nitrite source to access the aryl diazonium salt (**113 or 115**) followed by reduction to obtain the aryl hydrazine hydrochloride (**120**). Batch optimization was performed to investigate if there were any improvements to be made to the reported protocols and assess whether the reactions could be successfully translated to an automated flow process.



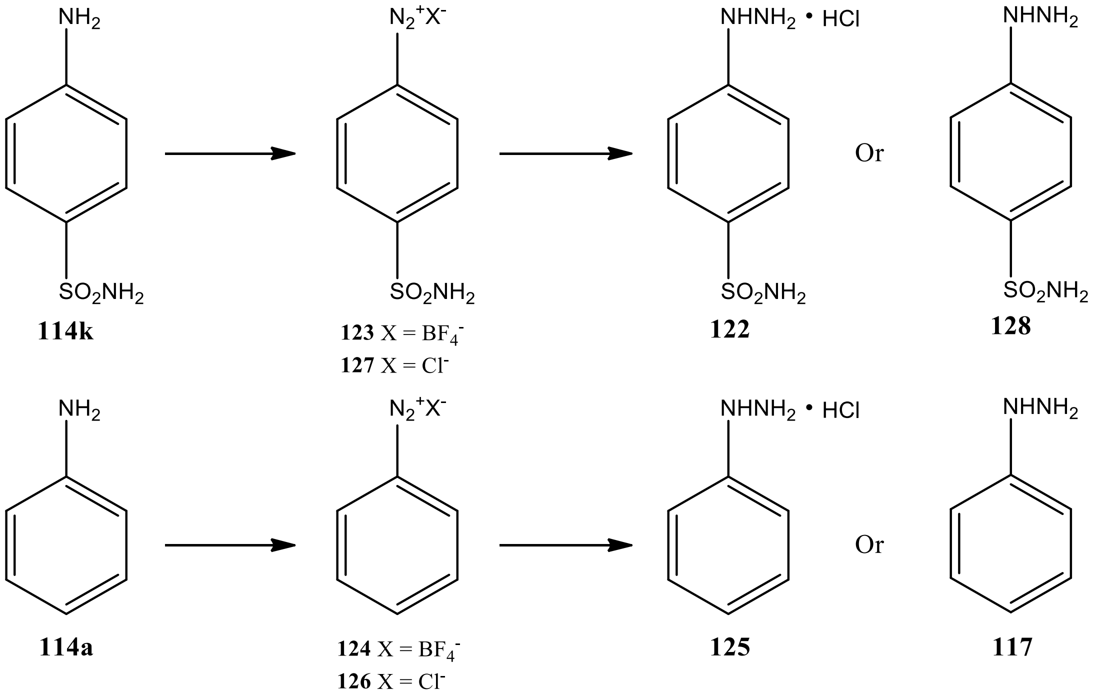
114

113 X = BF_4^-
115 X = Cl^-
or other counter anion

120

Scheme 5.4: Synthesis route to aryl hydrazine hydrochlorides (**120**).

Batch optimization: The majority of published procedures report reacting the aryl amine (**114**) with sodium nitrite and HCl under aqueous conditions for the diazotization reaction followed by reduction with $SnCl_2$[16] or Na_2SO_3[14] in HCl under aqueous conditions (Scheme 5.5). It was determined that improvements to the reduction reaction would benefit the overall synthesis. Since the diazotization reaction was extensively investigated and optimized in Chapter 4, emphasis could be placed on determining the best method for reduction with the aim of being able to perform the reduction under continuous flow conditions after coupling it to the already established diazotization flow process (Chapter 4). The reduction reaction was examined in terms of solvent, temperature, duration and reagents used with sulfanilamide (**114k**) and aniline (**114a**) serving as the model aryl amines. The work-up protocols were also carefully evaluated depending on the procedure and reagents used.



Scheme 5.5: Synthesis of model compounds.

Since the $SnCl_2$ reduction method consistently gave more reliable results in the literature this was deemed to be a good starting point. The procedure of Soliman[16c] was used to synthesise 4-sulfamidophenylhydrazine hydrochloride (**122**) in a yield of 83%. Even though the yield for the reaction is very good and the experimental procedure including work-up protocol is easy to perform, this method suffers from the drawbacks of using toxic tin and translation to a continuous flow process would be challenging due to the formation of precipitates and the need to use corrosive aqueous HCl. This reaction did however provide a standard against which all other reactions could be compared in terms of final yield, simplicity, toxicity and applicability for conversion to flow.

In an effort to make the $SnCl_2$ reduction more amenable to flow conditions the use of alternative acids was examined (Table 5.1). H_2SO_4 was used instead of aqueous HCl following the procedure of Soliman[16c] which resulted in very poor conversion. The use of Amberlyst® 15 H$^+$ and Amberlite® IR120 H$^+$ resins was also examined, with the only modification being that all the acid required was added to the diazotization reaction followed by direct addition of the solid $SnCl_2$ to the reaction.

Table 5.1: Effect of altering the acid

	Acid	Yield (%)
1	H_2SO_4	1
2	Amberlyst® 15 H$^+$	2
3	Amberlite® IR120 H$^+$	0

Standard conditions: Sulfanilamide (**114k**) (1.0 equiv.), acid (12.7 equiv.), $NaNO_2$ (1.0 equiv.), $SnCl_2$ (2.6 equiv.), H_2O (62.4 equiv.), overnight, 0 °C.

These results indicated that modifications to the $SnCl_2$ methodology were not well tolerated and would not easily lead to a synthesis which could be translated to a flow process. Since the aryl diazonium tetrafluoroborates salts (**113**) (Chapter 4) could be successfully prepared under batch and flow conditions in high yields, the reduction of these salts was examined more closely. The paper of Bandgar and Thite[8a] indicated that aryl diazonium tetrafluoroborate salts (**113**) could be quickly and efficiently reduced by borohydride exchange resin (BER). This appeared to be a very viable route for conversion to flow synthesis since the solubilized aryl diazonium tetrafluoroborate salts (**113**) synthesized in Chapter 4 could simply be pushed through a column packed with BER under flow conditions to effect reduction and obtain aryl hydrazines (**116**).

Using the procedure of Bandgar and Thite,[8a] sulfanilamide (**114k**) was diazotized followed by reduction with BER in MeOH. However, in our hands these reaction conditions failed to produce any detectable quantity of 4-sulfamidophenylhydrazine hydrochloride (**122**). It was speculated that the poor solubility of 4-sulfamidobenzenediazonium tetrafluoroborate (**123**) in MeOH resulted in poor interaction with the BER resulting in no noticeable product formation (Table 5.2), with only decomposition products being obtained. The MeOH was thus replaced with DMF in which **123** was completely soluble, which also failed to produce the expected 4-sulfamidophenylhydrazine hydrochloride (**122**) after extensive reaction time at 0 °C and reaction at room temperature overnight, also resulting in only decomposition products. The possibility was then considered that the batch of BER being used was no longer viable and so to eliminate this possibility the BER was replaced with sodium borohydride, which again resulted in no formation of the anticipated **122**. To rule out the possibility that **123** was decomposing before it could be reduced the reaction was performed at -20 °C, also resulting in no detectable product formation.

Table 5.2: BER reduction reactions using sulfanilamide (**114k**) as starting amine

	Reducing agent	Solvent	Temperature (°C)	Duration	Yield (%)
1	BER	MeOH	0	20 min	0
2	BER	DMF	0 → RT	Overnight	0
3	$NaBH_4$	DMF	0 → RT	20 min	0
4	BER	DMF	-20	20 min	0

Standard conditions: Sulfanilamide (**114k**) (1.0 equiv.), HCl (32%, 5.1 equiv.), $NaNO_2$ (1.0 equiv.), $NaBF_4$ (excess.), H_2O, 0 °C, 30 min for diazotization; reducing agent (1.5 equiv.).

Since the 4-sulfamidobenzenediazonium tetrafluoroborate (**123**) was being prepared under aqueous conditions in the above experiments (Table 5.2) the possibility existed that the salt was not completely dry resulting in residual water being present which could destroy the BER or sodium borohydride. The diazotization conditions were therefore altered to the anhydrous conditions developed in Chapter 4. Aniline (**114a**) was also used in place of sulfanilamide (**114k**) since the electron withdrawing effect of the sulfonamide functional group could be adversely influencing the reactivity.

For the initial experiment $NaBF_4$ was added directly to the formed benzenediazonium chloride followed by reaction for 30 minutes to obtain benzenediazonium tetrafluoroborate (**124**) *in-situ* followed by reaction with BER for a further 30 minutes, which resulted in no detectable phenylhydrazine hydrochloride (**125**) (Table 5.3). To ensure that rapid decomposition of **124** was not the problem $NaBF_4$ and BER were added simultaneously to the reaction mixture followed by reaction for 1 hour so that as **124** formed it could immediately be reduced. This also failed to produce any detectable product. It was then speculated that the *in-situ* formation of **124** was not efficient enough when compared to pushing the benzenediazonium chloride through a column packed with $NaBF_4$ as was done in Chapter 4. The formed benzenediazonium chloride was thus pushed through a column packed with $NaBF_4$ to obtain the benzenediazonium tetrafluoroborate salt (**124**), to which BER was added resulting in no formation of the desired phenylhydrazine hydrochloride **(125)**.

Table 5.3: BER reduction reactions using aniline (**114a**) as starting amine

	Reducing agent	Solvent	Duration (min)	Yield (%)
1	BER	ACN	30 & 30	0
2	BER	ACN	60	0
3	BER	ACN	30	0
4	BER	ACN/EtOH	30 & 30	0
5	BER	ACN/EtOH	60	0
6	BER	ACN/EtOH	30	0
7	$NaBH_4$	ACN/MeOH	30	0
8	$NaBH_4$	ACN/MeOH	30	0

Standard conditions: Aniline (**114a**) (1.0 equiv.), ethanolic HCl (1.1 equiv.), isopentyl nitrite (1.1 equiv.), $NaBF_4$ (2.0 equiv.), reducing agent (1.5 equiv.), 0 °C.

The aprotic nature of acetonitrile was then considered to potentially be a limiting factor in the reaction thus experiments 1 – 3 (Table 5.3), which were discussed above, were repeated using 88%

acetonitrile/ethanol as the solvent system (experiments 4 – 6, Table 5.3). The presence of a protic solvent made no difference to the reaction as none of the repeated reactions yielded the expected phenylhydrazine hydrochloride (**125**) in any detectable quantities. Once again to rule out the possibility that the batch of BER being used was not the problem, experiments 1 and 3 were repeated using sodium borohydride instead of BER with 88% acetonitrile/methanol as the solvent system (experiments 7 – 8, Table 5.3). The use of sodium borohydride instead of BER also failed to produce the desired product, which indicated that both sodium borohydride and its solid supported counterpart (BER) were unable to reduce the benzenediazonium tetrafluoroborate salt (**124**) under these reaction conditions.

It was then speculated that the presence of HCl in the reaction may be having a quenching effect on the BER thus the acid free procedure of de Mello and co-workers[30] was examined more closely. In their procedure they diazotize aryl amines (**114**) with isopentyl nitrite in DMF at 65 °C followed by reaction with $CuCl_2$ to obtain aryl chlorides. For this work it was proposed that the $CuCl_2$ could be replaced with $NaBF_4$ to obtain the aryl diazonium tetrafluoroborate salt (**113**) which could then be reduced using BER under acid free conditions. Aniline (**114a**) was thus reacted with isopentyl nitrite at 60-70 °C for 30 minutes to allow for diazotization to occur followed by cooling to 0 °C for the addition of $NaBF_4$ and reaction at this temperature for 1 hour. BER was then added and the reaction allowed to proceed overnight at room temperature after which none of the desired phenylhydrazine (**117**) could be detected (Table 5.4). It was then speculated that benzenediazonium tetrafluoroborate (**124**) might be too stable for the BER to reduce thus the experiment was repeated without the addition of $NaBF_4$ in the hope that the BER would be able to easily reduce the much more unstable benzenediazonium formed from the acid free diazotization of aniline (**114a**). This also failed to produce the expected product in any detectable quantities.

The high temperature of the reaction was then suspected to be the problem since it is well known that diazonium species are unstable at elevated temperatures thus the diazotization reaction was repeated at 0 °C. Reducing the temperature of the reaction also had no effect and none of the anticipated product was obtained. The reaction was then performed using sulfanilamide (**114k**) in DMF, which also failed to produce any of the desired product.

Table 5.4: Acid free reaction conditions

	Amine	$NaBF_4$ equiv.	Solvent	Temperature (°C)	Duration (h)	Yield (%)
1	Aniline	2.0	THF/MeOH	60 → 0 → RT	0.5; 1; 24	0
2	Aniline	0	THF/MeOH	60 → 0 → RT	0.5; 1; 24	0
3	Aniline	2.0	THF/MeOH	0 → RT	0.5; 1; 24	0
4	Sulfanilamide	2.0	DMF	0 → RT	0.5; 1; 24	0

Standard conditions: Amine (1.0 equiv.), isopentyl nitrite (2.4 equiv.), BER (1.5 equiv.). Stepwise addition of reagents allowing time for each stage to react before addition of next reagent.

A number of variations (±30) of the above reactions were performed making use of freshly prepared BER using literature procedures,[8a,31] regenerated BER, Celite-$NaBH_4$,[32] polymer supported tetrafluoroborate and SiO_2-$NaBF_4$,[33] which were all prepared as and when required. Various solvent systems were also tested in an effort to find a combination of reagents and conditions which would lead to the formation of the desired product. Unfortunately, none of the reactions produced the anticipated aryl hydrazine (**116**) in detectable quantities. Across the full range of experiments done (±30) no convincing evidence could be found that indicated the diazotization reaction occurs successfully under acid free conditions, which correlates well with the findings in Chapter 4 in which it was determined that the acid is necessary for the diazotization reaction to occur.

These experiments also indicated that BER and sodium borohydride could not successfully reduce the aryldiazonium tetrafluoroborate salts (**113**) in sufficiently detectable quantities and this is corroborated by the findings of Chaikin and Brown[20] who got a mixture of benzene, aniline (**114a**) and phenylhydrazine (**117**) amongst other products, all in poor yields. Attention was then turned to sulfur based reducing agents using the procedure of Robinson and Good[14b] as reference. They opted to use sodium bisulfite generated *in-situ* under acidic conditions to reduce benzenediazonium chloride (**126**) to phenylhydrazine hydrochloride (**125**). For this work the diazotization of sulfanilamide (**114k**) using sodium nitrite in 1 M HCl was successful, however a freshly prepared solution of $NaHSO_3$ followed by addition of concentrated HCl only produced the expected product **122** in a poor yield of 27% (Table 5.5). In a follow up experiment, the $NaHSO_3$ was replaced with $KHSO_3$, which failed to produce the desired product. The reaction and work-up protocol required was also very tedious which could explain the poor yield and these conditions were not amenable for translation to a continuous flow process thus alternative procedures were sought in the literature.

Table 5.5: Reactions based on the procedure of Robinson and Good[14b]

	Reducing agent	**Yield (%)**
1	$NaHSO_3$	27
2	$KHSO_3$	0

Standard conditions: Sulfanilamide (**114k**) (1.0 equiv.), HCl (1 M, 3.0 equiv.), $NaNO_2$ (1.0 equiv.), reducing agent (4.8 equiv.), HCl (32%, 10.1 equiv.), H_2O, overnight, 0 → 80 °C.

Na_2SO_3 is more frequently used in literature thus the procedure of Winum and co-workers[14e] was applied. In their procedure they diazotize benzenesulfonamides under aqueous conditions followed by addition of a solution of Na_2SO_3 and reaction at room temperature overnight for the reduction.

This procedure was applied to sulfanilamide (**114k**) (Table 5.6) but failed to produce the desired 4-sulfamidophenylhydrazine hydrochloride (**122**) after application of the complex and tedious work-up protocol involving many stages including concentration, suspension, filtration, re-dissolving, pH adjustment, extraction, concentration, re-suspension and acidification followed by a final filtration. The reaction was repeated two more times with modifications to the work-up protocol involving solvent changes, leaving out pH adjustments and cutting down on the number of stages in each case with the aim of limiting product loss, both of which failed to produce **122**. One reaction was done in which the HCl was replaced with H_2SO_4, which did not yield **122** in detectable quantities. It was then thought that the reaction temperature for the reduction step was too low thus the reaction was repeated at 60-70 °C, which did not provide the required **122** after applying the literature work-up protocol of Winum and co-workers.[14e] With the poor results obtained and the complexity of the work-up protocol this procedure would also not have been amenable for translation to a continuous flow process.

Table 5.6: Reactions based on the procedure of Winum and co-workers[14e]

	Acid	**Temperature (°C)**	**Work-up**	**Yield (%)**
1	HCl	RT	Winum	0
2	HCl	RT	Modified	0
3	HCl	RT	Modified	0
4	H_2SO_4	RT	Modified	0
5	HCl	60-70	Winum	0

Standard conditions: Sulfanilamide (**114k**) (1.0 equiv.), acid (90.0 equiv.), $NaNO_2$ (2.5 equiv.), Na_2SO_3 (4.0 equiv.), H_2O, overnight.

An alternative procedure by Zhao and co-workers[14d] was then examined which differed from that of Winum and co-workers[14e] in that the order of addition of the reagents was different, the reaction temperature was different and the work-up protocol was much simpler. For the first experiment (Table 5.7) the procedure of Zhao and co-workers,[14d] which included the alkalization step using 12% w/v sodium carbonate was repeated using aniline (**114a**) as the model compound, which resulted in the formation of phenylhydrazine hydrochloride (**125**) in a yield of 47%. Aiming to improve the yield and simplify the procedure the experiment was repeated without the alkalization step as this seemed unnecessary, which resulted in an improvement in the yield to 57%.

Table 5.7: Reactions based on the procedure of Zhao and co-workers[14d]

	Acid and equiv.	Nitrite source	Sulfite source and equiv.	Solvent	Temperature (°C)	Duration (h)	Yield (%)
1	HCl; 23.5	$NaNO_2$	Na_2SO_3; 11.0	H_2O	Reflux	3	47
2	HCl; 23.5	$NaNO_2$	Na_2SO_3; 11.0	H_2O	Reflux	3	57
3	HCl; 23.5	$NaNO_2$	Sulfite resin;* 11.0	H_2O	70	Overnight	0
4	HCl; 23.5	$NaNO_2$	Sulfite resin;ǂ 11.0	H_2O	70	Overnight	0
5	HCl; 23.5	$NaNO_2$	Sulfite resin;* 11.0	H_2O	Reflux	Overnight	0
6	HCl; 2.1 & Amberlyst-15; 23.5	$NaNO_2$	Na_2SO_3; 11.0	H_2O	Reflux	Weekend	0
7	HCl; 2.2	$NaNO_2$	Na_2SO_3; 2.0	H_2O	Reflux	3	0
8	Ethanolic HCl; 2.2	IPN	Na_2SO_3; 2.0	ACN	Reflux	3	0
9	Ethanolic HCl; 1.1 & HCl; 22.0	IPN	Na_2SO_3; 11.0	EtOH	Reflux	Overnight	0
10	Ethanolic HCl; 1.1 & HCl; 23.5	IPN	Na_2SO_3; 11.0	ACN & H_2O	80	3	20
11	Ethanolic HCl; 1.1 & HCl; 23.5	IPN	Na_2SO_3; 11.0	ACN & H_2O	90	Overnight	0

Standard conditions: Aniline (**114a**) (1.0 equiv.), nitrite source (1.1 equiv.), step 1 stir for 15 min at 0 °C, step 2 stir for 1 h at RT.

*Sulfite resin prepared by method 1. ǂ Sulfite resin prepared by method 2. IPN = isopentyl nitrite.

In reactions where yield = 0 %, only unidentified material was isolated.

The experimental protocol at this stage could not be directly translated to continuous flow conditions thus the use of solid supported sulfite was investigated. The solid supported sulfite required was prepared by two different methods – the first method involved stirring a solution of Na_2SO_3 with Amberlite IRA-400 resin at 75-85 °C overnight and the second involved repeatedly pushing a solution of Na_2SO_3 through a column packed with Amberlite IRA-400 resin. Both resins were then tested under identical reaction conditions (Table 5.7), but failed to reduce the phenyldiazonium chloride (**126**) to phenylhydrazine hydrochloride (**125**). Typically, the resin used is only stable up to a maximum temperature of about 70-80 °C and the temperature of 70 °C at which the reaction was conducted may have been too low for the reduction reaction to occur, thus the reaction was repeated at reflux to see what effect this would have. The resin appeared to have survived the higher reaction conditions although none of the desired **125** could be detected. Since the use of solid supported sulfite proved unsuccessful the use of Amberlyst® 15 H^+ as the acid source for the reduction was then investigated. Replacing HCl with an equimolar amount of Amberlyst® 15 H^+ also failed to produce **125** in detectable quantities.

In an effort to make the reaction more atom efficient as well as reduce the amount of highly corrosive aqueous HCl the total equivalents of aqueous HCl was reduced from 23.5 to 2.2 and the equivalents of Na_2SO_3 was reduced from 11.0 to 2.0. This however proved to be detrimental to the reaction resulting in no product formation, which correlated well to the requirements of the reaction mechanism for sulfite reduction (Scheme 5.1).

Anhydrous reaction conditions were then investigated using the diazotization protocol previously established in Chapter 4. A solution of aniline (**114a**) in acetonitrile was diazotized using isopentyl nitrite in the presence of ethanolic HCl followed by addition to a suspension of Na_2SO_3 in acetonitrile. This was followed by the usual 1 hour at room temperature and 3 hours of reflux which failed to produce detectable amounts of phenylhydrazine hydrochloride (**125**) (Table 5.7). The insolubility of Na_2SO_3 in acetonitrile was suspected to be the problem thus the reaction was repeated using ethanol. In the same experiment the equivalents of acid used was also adjusted with 1.1 equivalent of ethanolic HCl being used for the diazotization and 22.0 equivalents of aqueous HCl being used to help solubilize the Na_2SO_3 followed by reflux overnight, which also failed to produce the desired **125**. The use of an acetonitrile/water co-solvent system was then investigated in which acetonitrile was used for the diazotization reaction with ethanolic HCl and isopentyl nitrite, while water was used for the Na_2SO_3 and aqueous HCl reduction step. This resulted in the formation of phenylhydrazine hydrochloride (**125**) in 20% yield after reflux for 3 hours. In an effort to increase the yield the reaction was repeated and allowed to reflux overnight, but this had an adverse effect on the reaction with none of the desired product detected. This indicated that the product was not stable at high temperatures for extended periods of time. A more in-depth investigation into the optimum duration for the reaction was not performed since the reaction still exhibited precipitation issues which would not have been conducive towards translation to a continuous flow process which was the primary aim of the research. Another drawback of this method was the requirement of a large excess of aqueous HCl which is unsuitable for use with the continuous flow reactor due to its highly corrosive nature and a suitable replacement acid could not be identified.

5.5. CONCLUSION

In conclusion it has been demonstrated that sulfanilamide (**114k**) can be easily diazotized to form 4-sulfamidobenzenediazonium chloride (**127**) under acidic conditions, but that the reduction of this salt is best achieved using $SnCl_2$ in aqueous HCl to obtain 4-sulfamidophenylhydrazine hydrochloride (**122**) in a yield of 83%. Other reducing agents investigated in this work failed to produce the same results when applied to sulfanilamide (**114k**) and aniline (**114a**), which correlates with the experience of Li and co-workers.[28] All reactions that were done were evaluated for potential translation to continuous flow, however the multistep flow synthesis of aryl hydrazines (**116**) or aryl hydrazine hydrochlorides (**120**) could not be achieved due to the poor performance of the various reducing agents tested, solubility issues or the use of incompatible reagents. There are still a large number of reducing agents which have not yet been considered or tested for the reduction of aryl diazonium salts to aryl hydrazines, which could not be evaluated in the allocated time.

5.6. EXPERIMENTAL SECTION

All solvents and reagents were purchased from Sigma-Aldrich and used without further purification. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AVANCE-III 300 MHz spectrometer or a Bruker AVANCE-III 400 MHz spectrometer with the residual solvent peak as an internal reference (DMSO-d_6 = 2.49 and 39.5 ppm for ^{1}H and ^{13}C NMR spectra respectively). Chemical shifts, δ, are reported in parts per million (ppm), and splitting patterns are given as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m). Coupling constants, *J*, are expressed in hertz (Hz). Yields refer to isolated pure products unless stated otherwise.

Procedure for preparation of borohydride exchange resin (BER)[8a,31]

Amberlite IRA-400 (5.00 g) was suspended in distilled water (50 mL) followed by addition of a solution of sodium borohydride (0.95 g, 25.0 mmol) in distilled water (50 mL) and stirring at room temperature for 1 hour. The resin was collected by vacuum filtration and washed with distilled water (3 x 30 mL) followed by drying under vacuum at 65 °C for 2 hours. The resin was stored in an oven at 70 °C.

Procedure for re-generation of BER (2nd generation BER)

Spent resin (5.01 g) was suspended in distilled water (50 mL) followed by addition of a solution of sodium borohydride (9.52 g, 251.5 mmol) in distilled water (50 mL) and stirring at room temperature for 2.5 hours. The resin was collected by vacuum filtration and washed with distilled water (3 x 30 mL) followed by drying under vacuum at 65 °C for 2 hours. The resin was stored in an oven at 70 °C.

Procedure for preparation of Celite supported borohydride[32]

Celite (1.32 g) and sodium borohydride (1.33 g, 35.2 mmol) were ground together using a mortar and pestle.

Procedure for preparation of resin supported tetrafluoroborate (method 1)

Amberlite IRA-400 (19.9 g) was suspended in distilled water (80 mL) followed by addition of a solution of sodium tetrafluoroborate (11.04 g, 100.5 mmol) in distilled water (200 mL) and stirring at room temperature for 1 hour. The resin was collected by vacuum filtration and washed with distilled water (3 x 100 mL) followed by drying under vacuum at 65 °C for 2 hours. The resin was stored in an oven at 70 °C.

Procedure for preparation of resin supported tetrafluoroborate (method 2)

Amberlite IRA-400 (19.9 g) was suspended in dimethylformamide (45 mL) followed by addition of a solution of sodium tetrafluoroborate (2.498 g, 22.8 mmol) in dimethylformamide (45 mL) and stirring at room temperature for 2.5 hours. The resin was collected by vacuum filtration and washed with dimethylformamide (3 x 30 mL) followed by drying under vacuum at 65 °C overnight. The resin was stored in an oven at 70 °C.

Preparation of activated silica[33]

Silica gel 60 (10.03 g) was suspended in a mixture of distilled water (50 mL) and aqueous hydrochloric acid (32%, 50 mL) followed by reflux overnight. The reaction mixture was allowed to cool to room temperature followed by collection of the silica by vacuum filtration and washing with excess water until the washings were neutral. The activated silica was dried and stored in an oven at 70 °C.

Procedure for preparation of SiO_2-$NaBF_4$[33]

Sodium tetrafluoroborate (0.70 g, 6.4 mmol) and activated silica (2.53 g) were suspended in dichloromethane (16 mL) followed by reflux overnight. The SiO_2-$NaBF_4$ formed was collected by vacuum filtration and washed with dichloromethane (3 x 10 mL) followed by drying in an oven at 70°C.

Procedure for preparation of resin supported sulfite (method 1)

Amberlite IRA-400 (50 mL) was suspended in a solution of sodium sulfite (20.15 g, 159.9 mmol) in distilled water (100 mL) followed by stirring at 75-85 °C for 24 hours. The resin was collected by vacuum filtration and washed with distilled water (3 x 50 mL) followed by drying under vacuum at 65 °C for 2 hours. The resin was stored in an oven at 70 °C.

Procedure for preparation of resin supported sulfite (method 2)

A solution of sodium sulfite (20.15 g, 159.9 mmol) in distilled water (100 mL) was repeatedly run through a column packed with Amberlite IRA-400 (50 mL). The resin was collected by vacuum filtration and washed with distilled water (3 x 50 mL) followed by drying under vacuum at 65 °C for 2 hours. The resin was stored in an oven at 70 °C.

General batch preparation of 4-Sulfamidophenylhydrazine Hydrochloride (122) via $SnCl_2$ reduction[16c]

Sulfanilamide (**114k**) (5.01 g, 29.1 mmol, 1.0 equiv.) was cooled to 0 °C followed by the addition of ice (29.11 g, 1.6 mol, 55.5 equiv.) and aqueous hydrochloric acid (32 %, 14.5 mL, 0.2 mol, 5.1 equiv.). A solution of sodium nitrite (2.01 g, 29.1 mmol, 1.0 equiv.) in water (4.0 mL, 0.2 mol, 6.9 equiv.) was added in a dropwise fashion and the solution was allowed to stir until all the sulfanilamide had dissolved. This mixture was rapidly added to a pre-cooled 0 °C solution of tin(II) chloride (14.38 g, 75.8 mmol, 2.6 equiv.) in aqueous hydrochloric acid (32 %, 21.7 mL, 0.2 mol, 7.6 equiv.) with vigorous stirring. The reaction mixture was placed in the fridge at 0-4 °C overnight. The solid formed was collected by vacuum filtration followed by washing with cold ethanol (3 x 20 mL) to obtain 4-sulfamidophenylhydrazine hydrochloride as a pearlescent white solid (5.37 g, 24 mmol, 83%). $R_f = 0.16$ (20% hexane/EtOAc). ^{1}H NMR (400 MHz d_6-DMSO) 10.55 (s, 2H, $SO_2N\underline{H_2}$); 8.91 (s, 1H, $N\underline{H}NH_2$); 7.68 (d, 2H, *J* 8.00, Ar-H); 7.19 (s, 2H, $NHN\underline{H_2}$); 7.05 (d, 2H, *J* 8.00, Ar-H). ^{13}C NMR (100 MHz d_6-DMSO) 148.47, 136.11, 126.94, 113.36.

Attempted batch preparation of 4-Sulfamidophenylhydrazine (128) via BER reduction[8a]

Sulfanilamide (**114k**) (0.50 g, 2.9 mmol, 1.0 equiv.) was cooled to 0 °C followed by the addition of ice (2.95 g, 163.5 mmol, 55.5 equiv.) and aqueous hydrochloric acid (32 %, 1.5 mL, 14.8 mmol, 5.1 equiv.). A solution of sodium nitrite (0.20 g, 2.9 mmol, 1.0 equiv.) in water (0.4 mL, 20.0 mmol, 6.9 equiv.) was added in a dropwise fashion and the solution was allowed to stir until all the sulfanilamide had dissolved. A solution of sodium tetrafluoroborate (1.05 g, 9.5 mmol, excess) in water (1 mL) was added dropwise followed by warming to room temperature for 30 minutes. The formed solid was collected by vacuum filtration and washed with methanol (2 x 2 mL). The solid was suspended in methanol (5.5 mL) and cooled to 0 °C followed by addition of BER (0.98 g, 2.5 mmol) and stirring for 20 minutes. The resin was removed by vacuum filtration and washed with methanol (3 x 2 mL). The filtrate was collected and concentrated to dryness to obtain an unidentified material by NMR spectroscopic analysis..

Attempted batch preparation of Phenylhydrazine Hydrochloride (125) via BER reduction

A solution of aniline (**114a**) (0.4 mL, 3.8 mmol, 1.0 equiv.) in acetonitrile (5 mL) was cooled to 0 °C followed by the dropwise addition of ethanolic hydrochloric acid (3.4 mL, 4.3 mmol, 1.1 equiv.) and the dropwise addition of isopentyl nitrite (0.6 mL, 4.3 mmol, 1.1 equiv.). Sodium tetrafluoroborate (0.85 g, 7.7 mmol, 2.0 equiv.) was added followed by stirring at 0 °C for 30 minutes after which BER (2.31 g, 5.8 mmol, 1.5 equiv.) was added. After stirring a further 30 minutes at 0 °C the solids were removed by vacuum filtration and washed with acetonitrile (3 x 2 mL). The filtrate was acidified using aqueous hydrochloric acid (32%) and an unidentified solid which was not the expected product was collected by vacuum filtration after washing with acetonitrile (3 x 2 mL).

Attempted batch preparation of Phenylhydrazine (117) via BER reduction (acid free method)[30]

Isopentyl nitrite (1.1 mL, 8.2 mmol, 2.4 equiv.) was added dropwise to a solution of aniline (**114a**) (0.3 mL, 3.3 mmol, 1.0 equiv.) in tetrahydrofuran (10 mL) followed by heating at 60-70 °C for 30 minutes. The reaction was cooled to 0 °C and sodium tetrafluoroborate (0.73 g, 6.7 mmol, 2.0 equiv.) was added followed by stirring at 0 °C for 1 hour. Methanol (0.2 mL, 4.9 mmol, 1.1 equiv.) and BER (2.01 g, 5.0 mmol, 1.5 equiv.) were added and the reaction allowed to stir at room temperature overnight. TLC analysis of the reaction mixture indicated no product formation, which was confirmed by NMR spectroscopic analysis, which exhibited only unidentified material.

Attempted batch preparation of 4-Sulfamidophenylhydrazine Hydrochloride (122) via $NaHSO_3$ reduction[14b]

Sulfanilamide (**114k**) (0.45 g, 2.6 mmol, 1.0 equiv.) was dissolved in hydrochloric acid (1M, 7.8 mL, 7.8 mmol, 3.0 equiv.) followed by dilution with water (5.2 mL) and cooling to 0 °C. A solution of sodium nitrite (0.18 g, 2.7 mmol, 1.0 equiv.) in water (2.6 mL) was added dropwise followed by rapid addition of a solution of sodium bisulfite (1.31 g, 12.6 mmol, 4.8 equiv.) in water (7.8 mL). The reaction mixture was warmed to 80-85 °C for 2 hours followed by dropwise addition of aqueous hydrochloric acid (32%, 2.6 mL, 26.5 mmol, 10.1 equiv.). Heating at 80-85 °C was continued overnight with a stream of argon directed upon the surface. The solid residue obtained was suspended in acetonitrile and the solid collected by vacuum filtration after washing with acetonitrile (3 x 5 mL). The collected solid was dissolved in dimethylformamide followed by vacuum filtration to obtain the filtrate which was concentrated to dryness. A cream-brown solid collected by vacuum filtration after recrystallization from ethanol was not the desired product by NMR spectroscopic analysis, but an unidentified material.

Attempted batch preparation of 4-Sulfamidophenylhydrazine Hydrochloride (122) via Na_2SO_3 reduction (method 1)[14e]

Sulfanilamide (**114k**) (0.50 g, 2.9 mmol, 1.0 equiv.) was cooled to 0 °C followed by the addition of cold water (5.2 mL, 286.7 mmol, 95.6 equiv.) and aqueous hydrochloric acid (32 %, 25.7 mL, 261.7 mmol, 90.0 equiv.). A solution of sodium nitrite (0.50 g, 7.3 mmol, 2.5 equiv.) in water (1.5 mL) was added in a dropwise fashion and the solution was allowed to stir until all the sulfanilamide had dissolved. Sodium sulfite (1.48 g, 11.8 mmol, 4.0 equiv.) was added followed by stirring at room temperature overnight. The mixture was concentrated to dryness under vacuum and the residue obtained suspended in acetone (10 mL) followed by vacuum filtration. The collected solid was dissolved in a minimum amount of water and the pH adjusted to 7 using 10% sodium hydroxide. The solution was extracted with ethyl acetate (3 x 30 mL) and the organic phases were pooled, dried and concentrated. The dried residue was dissolved in a minimum of acetone followed by dropwise addition of aqueous hydrochloric acid (32%) resulting in the precipitation of a solid. The solid was collected by vacuum filtration and washed with acetone (3 x 5 mL) and was not the expected product after NMR spectroscopic analysis, but an unidentified material.

General batch preparation of Phenylhydrazine Hydrochloride (125) via Na_2SO_3 reduction (method 2)[14d]

Aqueous hydrochloric acid (32%, 2 mL, 20.4 mmol, 2.3 equiv.) was added dropwise to a solution of aniline (**114a**) (0.8 mL, 8.8 mmol, 1.0 equiv.) in water (10 mL) cooled to 0 °C followed by dropwise addition of a solution of sodium nitrite (0.68 g, 9.9 mmol, 1.1 equiv.) in minimum water and stirring for 15 min. The reaction mixture was then alkalized to pH 6 – 7 using a 12% w/v sodium carbonate solution. This reaction mixture was then added dropwise to a 0 °C pre-cooled solution of sodium sulfite (12.31 g, 97.7 mmol, 11.0 equiv.) in water (23 mL) followed by reaction at room temperature for 1 hour. Aqueous hydrochloric acid (32%, 18 mL, 183.4 mmol, 20.9 equiv.) was added dropwise followed by reflux for 3 hours after which the reaction was allowed to gradually cool to room temperature and then cooled to 0 °C for 15 minutes. The solid formed was collected by vacuum filtration followed by washing with cold water (3 x 5 mL) to obtain phenylhydrazine hydrochloride as a pink-brown solid (0.60 g, 4.2 mmol, 47%). ^{1}H NMR (400 MHz d_6-DMSO) 10.36 (s, 2H, $\mathrm{NHN\underline{H}_2}$); 8.35 (s, 1H, $\mathrm{N\underline{H}NH_2}$); 7.24 (dd, 2H, J_1 7.42, J_2 8.46, Ar-H); 7.00 (d, 2H, J 7.68, Ar-H); 6.90 (dd, 1H, J_1 7.34, J_2 7.34, Ar-H). ^{13}C NMR (100 MHz d_6-DMSO) 145.69, 128.91, 121.33, 114.53.

5.7. REFERENCES

(1) Harrak, Y.; Romero, M.; Constans, P.; Pujol, M.D. *Lett. Org. Chem.*, **2006**, *3*, 29.

(2) Bredihhin, A.; Groth, U.M.; Mäeorg, U. *Org. Lett.*, **2007**, *9*, 1097.

(3) Ragnarsson, U. *Chem. Soc. Rev.*, **2001**, *30*, 205.

(4) Lee, A.S.-Y.; Chung, C.-H.; Chu, S-F.; Chang, Y.-T. *J. Chin. Chem. Soc.*, **2009**, *56*, 202.

(5) Lundgren, R.J.; Stadiotto, M. *Angew. Chem. Int. Ed.*, **2010**, *49*, 8686.

(6) DeAngelis, A.; Wang, D.-H.; Buchwald, S.L. *Angew. Chem. Int. Ed.*, **2013**, *52*, 3434.

(7) Chen, J.; Zhang, Y.; Hao, W.; Zhang, R.; Yi, F. *Tetrahedron*, **2013**, *69*, 613.

(8) (a) Bandgar, B.P.; Thite, C.S. *Synth. Commun.*, **1997**, *27*, 635. (b) Bandgar, B.P.; Uppalla, L.S. *J. Chem. Research*, **1999**, 714.

(9) Ru, C.-H.; Guo, S.-H.; Pan, G.-F.; Zhu, X.-Q.; Gao, Y.-R.; Wang, Y.-Q. *Org. Lett.*, **2018**, *20*, 1910.

(10) Neumann, D.M.; Cammarata, A.; Backes, G.; Palmer, G.E.; Jursic, B.S. *Bioorg. Med. Chem.*, **2014**, *22*, 813.

(11) Zhang, Y.; Tang, Q.; Luo, M. *Org. Biomol. Chem.*, **2011**, *9*, 4977.

(12) Le Goff, G.; Ouazzani, J. *Bioorg. Med. Chem.*, **2014**, *22*, 6529.

(13) Fischer, E. *Ber. Dtsch. Chem. Ges.*, **1875**, *8*, 589.

(14) (a) Coleman, G.H. Phenylhydrazine in Organic Synthesis, Coll. Vol. 1, Conant, J.B.; Thompson, H.R. (eds.), **1941**, pp 442 – 444. (b) Robinson, J.R.; Good, N.E. *Can. J. Chem.*, **1957**, *35*, 1578. (c) Patel, V.R.; Desai, H.T. *J. Atoms and Molecules*, **2013**, *3*, 520. (d) Zhao, S.; Zhang, Y.; Zhou, H.; Xi, S.; Zou, B.; Bao, G.; Wang, L.; Wang, J.; Zeng, T.; Gong, P.; Zhai, X. *Eur. J. Med. Chem.*, **2016**, *120*, 37. (e) Winum, J.-Y.; Dogné, J.-M.; Casini, A.; de Leval, X.; Montero, J.-L.; Scozzafava, A.; Vullo, D.; Innocenti, A.; Supuran, C.T. *J. Med. Chem.*, **2005**, *48*, 2121.

(15) Norman, R.O.C.; Coxon, J.M. Reduction to aryl hydrazines in Principles of Organic Synthesis, 3rd ed., Blackie Academic & Professional, London, **1993**, pp 419-420.

(16) (a) Hunsberger, M.; Shaw, E.R.; Fugger, J.; Ketcham, R.; Lednicer, D. *J. Org. Chem.*, **1956**, *21*, 394. (b) Carlin, R.B.; Carlson, D.P. *J. Am. Chem. Soc.*, **1959**, *81*, 4673. (c) Soliman, R. *J. Med. Chem.*, **1979**, *22*, 321. (d) Demerson, C.A.; Humber, L.G. Process for preparing 1,8-diethyl-1,3,4,9-tetrahydropyrano(3,4-B)-indole-1-acetic acid, Etodolac. US 4585877, Apr 1986. (e) Harden, F.A.; Quinn, R.J.; Scammells, P.J. *J. Med. Chem.*, **1991**, *34*, 2892. (f) Jiang, L.-L.; Tan, Y.; Zhu, X.-L.; Wang, Z.-F.; Zuo, Y.; Chen, Q.; Xi, Z.; Yang, G.-F. *J. Agric. Food Chem.*, **2010**, *58*, 2643.

(17) Kurandina, D.V.; Eliseenkov, E.V.; Ilyin, P.V.; Boyarskiy, V.P. *Tetrahedron*, **2014**, *70*, 4043.

(18) Norris, T.; Bezze, C.; Franz, S.Z.; Stivanello, M. *Org. Process Res. Dev.*, **2009**, *13*, 354.

(19) Marinozzi, M.; Marcelli, G.; Carotti, A.; Natalini, B. *RSC Adv.*, **2014**, *4*, 7019.

(20) Chaikin, S.W.; Brown, W.G. *J. Am. Chem. Soc.*, **1949**, *71*, 122.

(21) Fugger, J.; Tien, J.M.; Hunsberger, I.M. *J. Am. Chem. Soc.*, **1955**, *77*, 1843.

(22) Demers, J.P.; Klaubert, D.H. *Tetrahedron Lett.*, **1987**, *28*, 4933.

(23) Browne, D.L.; Baxendale, I.R.; Ley, S.V. *Tetrahedron*, **2011**, *67*, 10296.

(24) (a) Wolter, M.; Klapars, A.; Buchwald, S.L. *Org. Lett.*, **2001**, *3*, 3803. (b) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Licandro, E.; Maiorana, S.; Perdicchia, D. *Org. Lett.*, **2005**, *7*, 1497. (c) Tšupova, S.; Mäeorg, U. *Org. Lett.*, **2013**, *15*, 3381.

(25) Chiara, J.L. Hydrazines and Related Functions, Section 2.15.8 in Comprehensive Organic Functional Group Transformations II, Vol. 2, Katritzky, A.R.; Taylor, R.J.K.; Ramsden, C. (eds.), Elsevier, Oxford, **2005**, pp 765 – 769.

(26) Poh, J.-S.; Browne, D.L.; Ley, S.V. *React. Chem. Eng.*, **2016**, *1*, 101.

(27) Hu, T.; Baxendale, I.R.; Baumann, M. *Molecules*, **2016**, *21*, 918.

(28) Li, B.; Widlicka, D.; Boucher, S.; Hayward, C.; Lucas, J.; Murray, J.C.; O'Neil, B.T.; Pfisterer, D.; Samp, L.; VanAlsten, J.; Xiang, Y.; Young, J. *Org. Process Res. Dev.*, **2012**, *16*, 2031.

(29) Yu, Z.; Tong, G.; Xie, X.; Zhou, P.; Lv, Y.; Su, W. *Org. Process Res. Dev.*, **2015**, *19*, 892.

(30) Fortt, R.; Wootton, R.C.R.; de Mello, A.J. *Org. Process Res. Dev.*, **2003**, *7*, 762.

(31) Goudgaon, N.M.; Wadgaonkar, P.P.; Kabalka, G.W. *Synth. Commun.*, **1989**, *19*, 805.

(32) Gilmore, K.; Vukelić, S.; McQuade, D.T.; Koksch, B.; Seeberger, P.H. *Org. Process Res. Dev.*, **2014**, *18*, 1771.

(33) Gupta, R.; Gupta, M.; Paul, S.; Gupta, R. *Can. J. Chem.*, **2007**, *85*, 197.

Chapter 6:

Celecoxib

6. Optimization of Batch and Automated Flow Syntheses of Celecoxib

6.1. KEYWORDS

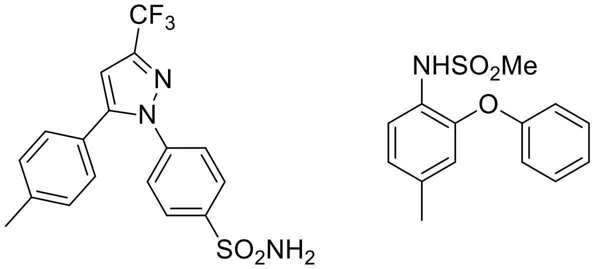
Continuous flow synthesis, celecoxib, pyrazole.

6.2. ABSTRACT

The comparison of an improved conventional batch mode synthesis of celecoxib (**27**), a nonsteroidal anti-inflammatory drug, with its flow chemistry alternative is reported. The stepwise and continuous flow synthesis of celecoxib (**27**) has been achieved by means of a Claisen condensation to access 4,4,4-trifluoro-1-(4-methyl-phenyl)-butane-1,3-dione (**132**) followed by a cyclo-condensation reaction with 4-sulfamidophenylhydrazine hydrochloride (**122**) to obtain the pyrazole moiety. A batch synthesis procedure with improved work-up and purification (90% yield) is reported. The successful conversion from batch to continuous flow conditions allowed for improved yields (>90%) with greatly shortened reaction times (20 h vs 1 h). This work is the subject of a provisional patent specification which has been filed.

6.3. INTRODUCTION

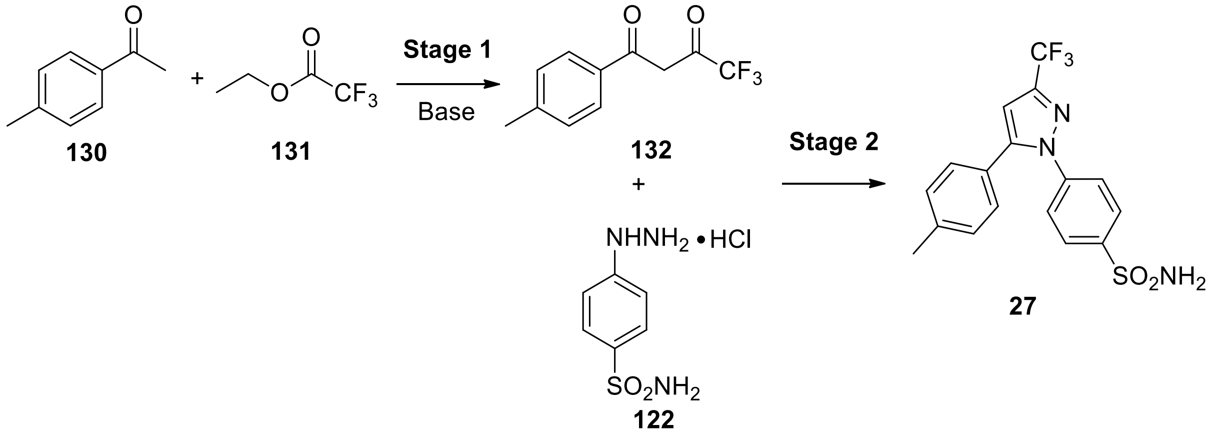
Celecoxib (**27**) is a nonsteroidal anti-inflammatory drug (NSAID) that is frequently used in the treatment of conditions such as arthritis and is often prescribed for acute pain.[1] It has also been shown to possess anti-cancer properties.[2-4] Typically NSAIDs work by inhibition of the cyclooxygenase (COX) enzymes,[5] which are involved in arachidonic acid metabolism leading to the synthesis of thromboxanes[6] and prostaglandins (PGs) – the major mediators of pain.[2,6] Conventional NSAIDs inhibit both COX-1 and COX-2, with COX-1 being inhibited to a greater extent, leading to undesirable side effects such as gastrointestinal bleeding and ulcers with long term use.[2,4,5] The selective inhibition of COX-2 results in anti-inflammatory effects without the undesirable gastrotoxic side effects.[3] Two major classes of compounds have been developed as selective COX-2 inhibitors; the “coxibs” of which celecoxib (**27**) is a classic example and the methanesulfonamide type compounds such as nimesulide (**129**) (Figure 6.1).[1,2,7]



27 **129**

Figure 6.1: Structures of celecoxib (**27**) and nimesulide (**129**).

Celecoxib (**27**) was first prepared by Penning and co-workers[8] by means of a Claisen condensation between 4-methylacetophenone (4-MAP, **130**) and ethyl trifluoroacetate (ETFA, **131**) in methanol to obtain dione (**132**) followed by a cyclo-condensation reaction with (4-sulfamoylphenyl)hydrazine hydrochloride (**122**) to obtain the 1,5-diarylpyrazole (**27**) in a yield of 46% (Scheme 6.1). The same group determined that using the hydrochloride salt of the hydrazine instead of the phenylhydrazine in the cyclo-condensation reaction resulted in the regioselective formation of the 1,5-diarylpyrazole, limiting the formation of the undesired 1,3-diarylpyrazole regioisomer. This approach is still used industrially,[9] however several optimizations primarily focusing on the use of more appropriate solvents for both the Claisen, the cyclo-condensation as well as improved work-up and product isolation have resulted in more acceptable yields in the range of 73-89%.[10-14] Several alternative approaches using different synthetic routes have been reported with yields in the range of 35-80%.[9,15-18]



Scheme 6.1: Claisen condensation and cyclo-condensation synthesis route for celecoxib (**27**).

Flow chemistry is a novel technology which makes use of immobilized reagents, scavengers and catch and release techniques in order to overcome some of the problems traditionally associated with conventional batch synthesis such as work-up, purification and optimization.[19] Traditional glassware is replaced with cartridges and columns that can be pre-packed with various solid supported reagents, or by reaction microchips and coils which allows for the controlled mixing of reagents along with excellent control of reaction temperature, pressure and reaction time.[19] To date several flow syntheses of pyrazoles have been reported[20-28] with the Ley group recently having reported a four-step flow synthesis of several pyrazoles including the first flow synthesis of celecoxib (**27**) in 48% yield via a metal-free amine-redox process.[27] Britton and Jameson[28] followed this with a modular flow based process to form the pyrazole core followed by a batch Ullmann coupling and batch deprotection to obtain celecoxib (**27**) in 71% yield.

Figure 6.2: Photo of flow reactor setup for continuous multistep flow synthesis of celecoxib (**27**).

Herein we describe an improved batch and continuous flow processes for the synthesis of celecoxib (**27**), which could potentially be modified to access a range of pyrazoles. We demonstrate an efficient Claisen condensation to obtain the required 1,3-dicarbonyl adduct followed by cyclo-condensation with the appropriate hydrazine hydrochloride across two steps and we evaluate the advantages of the flow synthesis when compared to the conventional batch processes.

6.4. RESULTS AND DISCUSSION

The preferred synthetic route to access celecoxib (**27**) (Scheme 6.1) involved a Claisen condensation between 4-methylacetophenone (**130**) and ethyl trifluoroacetate (**131**) to form the dione (**132**) (Stage 1). This was followed by a cyclo-condensation with 4-sulfamidophenylhydrazine hydrochloride (**122**) to obtain celecoxib (**27**) (Stage 2). Batch optimization was performed to both assess the suitability of the reactions for flow translation as well as investigate if there were any improvements to be made to the reported protocols.

Batch optimization stage 1: The majority of published procedures report heating 4-MAP (**130**) and ETFA (**131**) in the presence of a base at about 80 °C for a period of 10-20 hours resulting in yields ranging from 40% pure to 95% crude.[8,29] It was decided that a more consistent first stage would be beneficial to the overall synthesis thus the reaction was optimized in terms of solvent, temperature, duration and concentration. The work-up procedures were also critically evaluated as this appeared to be the phase in which the most product loss occurred. A basic solvent screen using low molecular weight protic solvents was initially performed, with the base source derived from the *in-situ* preparation of the corresponding sodium salts (Table 6.1).

Table 6.1: Solvent optimization using literature procedures[8,29c]

	Solvent	**Temperature (°C)**	**Yield (%)**
1	MeOH	80	15
2	EtOH	80	5
3	IPA[a]	80	-

[a] Reaction abandoned due to extensive time taken to form the sodium salt of *iso*-propanol.

Standard conditions: **130** (1.0 equiv.), **131** (1.1 equiv.), base (1.6 equiv.), 16 h.

The Claisen condensation proceeded satisfactorily as monitored by TLC (thin layer chromatography), however the isolated yields (Entries 1 and 2) were disappointingly low. It was speculated that the poor yields obtained were a result of the work-up and purification protocols adapted from literature.[8,29] An improved and simplified work-up and purification protocol was developed by simply removing the protic solvent *in vacuo* followed by trituration of the resulting solid residue in hexane. This afforded dione **132** as a fine, light brown solid which could be isolated by vacuum filtration.

A temperature optimization was performed using MeOH in the range of 25-90 °C (Figure 6.3) and when coupled with the new work-up and purification protocol afforded a quantitative yield for dione **132** in the range of 25-50 °C above which temperature the yield began to decrease.

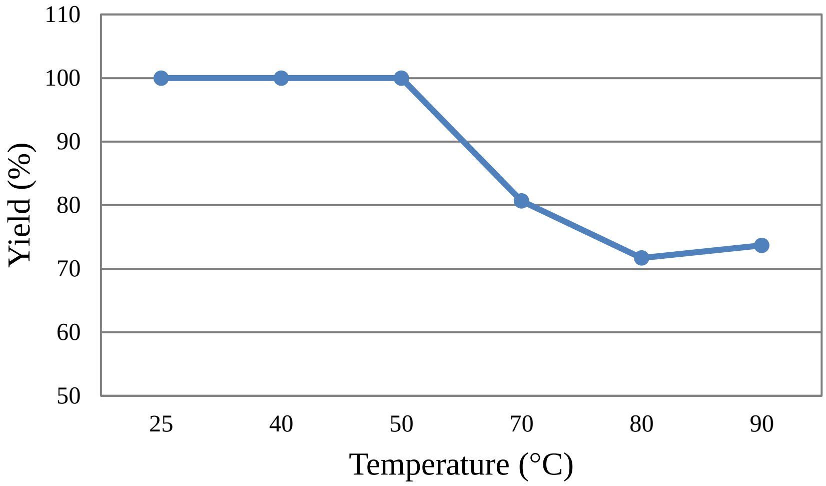


Figure 6.3: Study of the effect of reaction temperature on formation of dione (**132**).

Standard conditions: **130** (1.0 equiv.), **131** (1.1 equiv.), NaOMe (1.6 equiv.), MeOH, 16 h. For reactions above the boiling point of MeOH a sealed pressure tube was used.

When repeated with absolute ethanol at room temperature a lower yield of 83% was obtained although with a notable reduction in reaction time (17 h vs. 5.5 h). The improved rate of reaction and lower toxicity profile when compared to methanol prompted us to proceed with the batch optimization using absolute ethanol despite the slightly lower yield.

An assessment of the reaction time in ethanol (Figure 6.4) showed an almost quantitative yield (97 %) for **132** obtained after 3 hours of reaction with the isolated yields steadily decreasing as the reaction time increased.

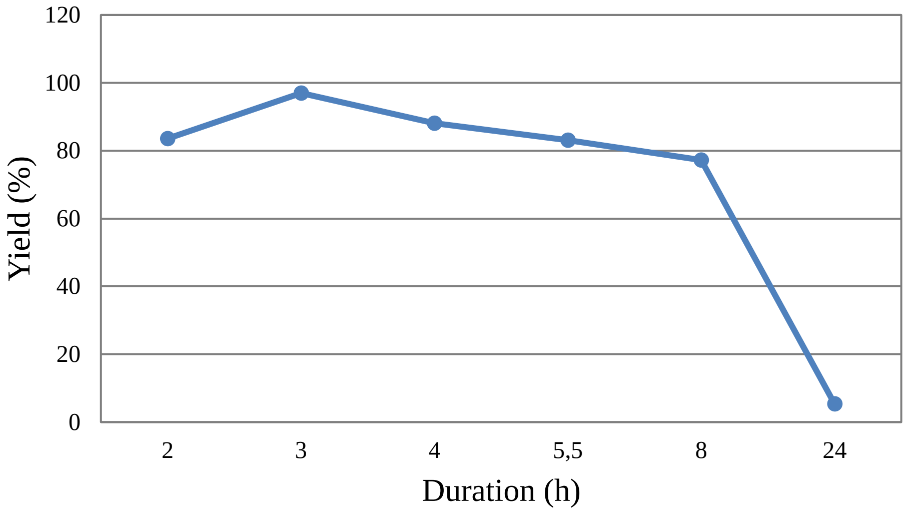


Figure 6.4: Study of the effect of reaction duration on formation of dione (**132**).

Standard conditions: **130** (1.0 equiv.), **131** (1.1 equiv.), NaOEt (1.6 equiv.), EtOH, RT.

Finally, in a lead up to translating the reaction to flow an assessment was performed to determine the highest concentration that the reaction could be performed at relative to 4-MAP (**130**), and the lowest stoichiometric amount of base that could be used (Table 6.2).

Table 6.2: Concentration and base stoichiometry optimization

Equiv. 4-MAP (130)	Equiv. ETFA (131)	Equiv. NaOEt	[4-MAP] (M)	Yield (%)
1.0	1.1	1.6	0.71	46
1.0	1.1	1.4	0.71	100
1.0	1.1	1.3	0.71	80
1.0	1.1	1.1	0.71	78
1.0	1.1	1.4	0.76	100
1.0	1.1	1.4	0.85	98
1.0	1.1	1.4	0.94	97

Standard conditions: EtOH, RT.

The lowest stoichiometric amount of base that could be used without compromising the yield was found to be 1.4 equivalents relative to 4-MAP (**130**). This information was then used to determine the highest concentration relative to 4-MAP (**130**) at which the reaction could be performed without reduced yields and loss of homogeneity, resulting in an optimal concentration of 0.76 M.

The final optimized batch conditions for the Claisen condensation involved a reaction time of 3 hours at room temperature using 1.0 equiv. 4-MAP (**130**), 1.1 equiv. ETFA (**131**) and 1.4 equiv. NaOEt in absolute EtOH at a concentration of 0.76 M relative to 4-MAP (**130**). This was followed by a work-up/purification involving concentration, trituration in hexane and vacuum filtration to obtain a quantitative yield of **132** which could be carried forward into stage 2.

Batch optimization stage 2: The majority of the current literature procedures available reflux **132** with **122** for extended periods of time (>20 h) in various solvents followed by a standard extractive work-up and crystallization resulting in reported yields ranging from 46-84%.[8,10-14] We again assessed the reaction in terms of solvent, temperature, duration and concentration. The work-up procedure was once again evaluated as this also appeared to be an area which could benefit from improvement. The solvents chosen were based on compatibility with the stage 1 Claisen condensation.

The most promising procedures reported made use of either ethanol or 50% ethyl acetate/water as a solvent system.[8,13] Unfortunately in our hands we were only able to obtain low yields of 8-12% when following the reported protocols. The yields obtained were a concern, especially since TLC analysis had indicated good reaction progression and it was again speculated that the extractive work-up and subsequent recrystallization was the problem. The solubility of celecoxib (**27**) was examined in various solvents and then compared to the solubility of **132** and **122** in the same solvents. Celecoxib (**27**) was found to be soluble in ethyl acetate while **132** and **122** were insoluble. As such the work-up was adjusted by simply removing the reaction solvent *in vacuo*, re-dissolving the resulting residue in ethyl acetate and removing the unreacted

132 and **122** by vacuum filtration. The filtrate was then concentrated *in vacuo* affording celecoxib (**27**) as a pure, fine, pale yellow solid. This method resulted in substantial improvement in the isolated yields (50-60%) of celecoxib (**27**). Since absolute ethanol matched the optimal solvent identified in stage 1 it was decided to continue with batch optimizations using the same solvent. A temperature optimization was performed in the range of 25-100 °C (Figure 6.5).

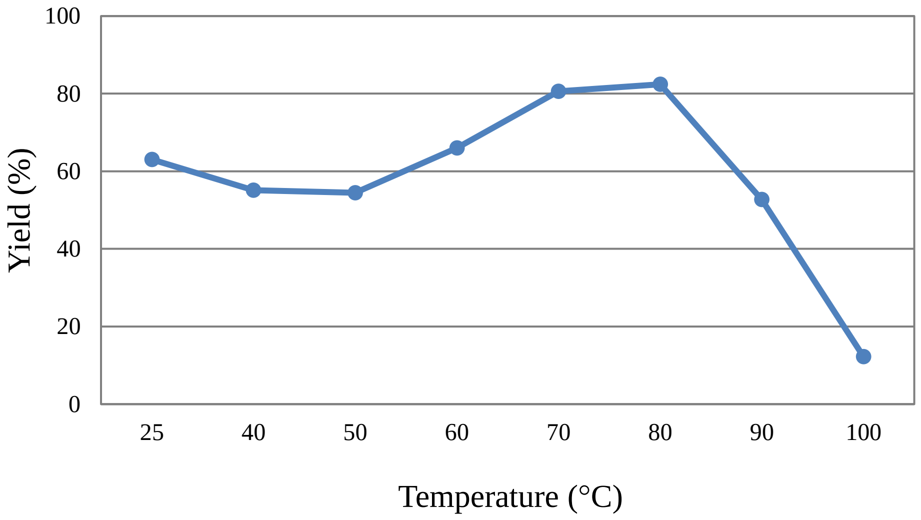


Figure 6.5: Study of the effect of reaction temperature on formation of celecoxib (**27**).

Standard conditions: **132** (1.1 equiv.), **122** (1.0 equiv.), EtOH, 17 h. For reactions above the boiling point of EtOH a sealed pressure tube was used.

The optimal temperature for the reaction was found to be between 70-80 °C with yields of 81-82% with a sharp decrease in the yields at higher temperatures with noticeable precipitation. Subsequent optimization of the reaction time afforded a yield of 90% after 17 h (Figure 6.6). Interestingly the yields also decreased sharply at longer reaction times suggesting possible loss of product due to decomposition with extended heating.

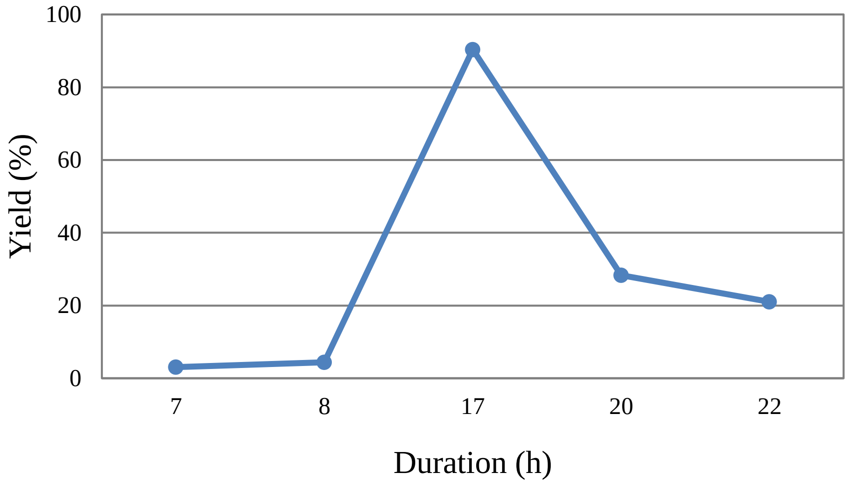


Figure 6.6: Study of the effect of reaction duration on formation of celecoxib (**27**).

Standard conditions: **132** (1.1 equiv.), **122** (1.0 equiv.), EtOH, 80 °C.

Finally, the highest concentration relative to dione **132** at which the cyclo-condensation could be performed without compromising the yield, while avoiding the formation of precipitates was 0.08 M with increasing concentrations resulting in lower yields (Figure 6.7).

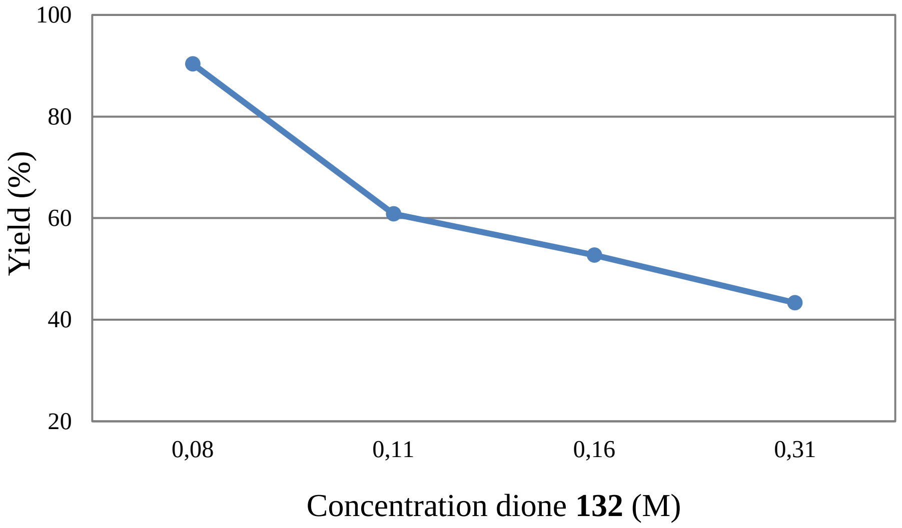
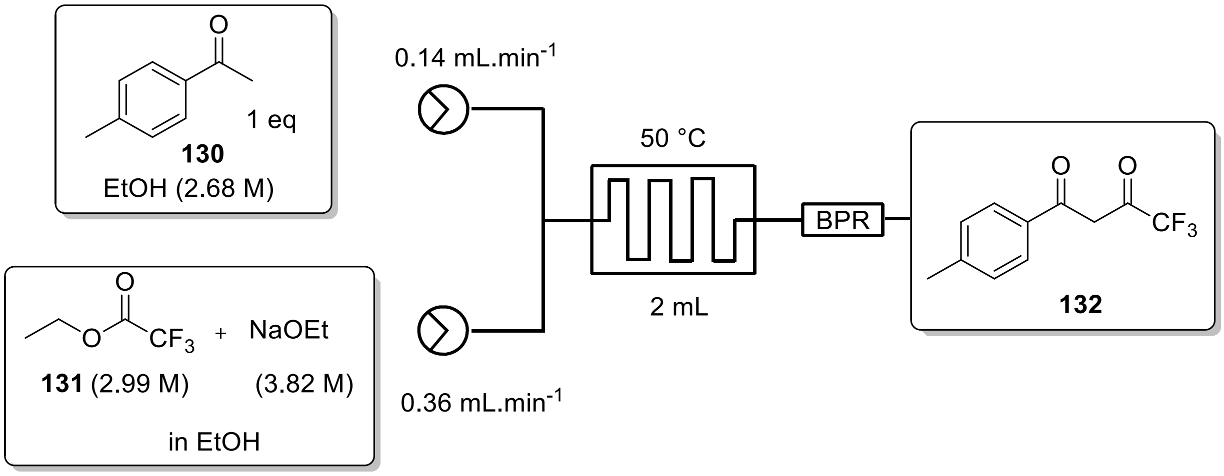


Figure 6.7: Study of the effect of concentration of **132** on formation of celecoxib (**27**).

Standard conditions: **122** (1.0 equiv.), EtOH, 17 h, 80 °C.

The optimum batch conditions for the cyclo-condensation reaction was 17 hours at 80 °C using 1.1 equiv. of **132** and 1.0 equiv. of **122**, at a concentration of 0.08 M in absolute ethanol relative to **132**. This was followed by a work-up involving concentration, suspension in ethyl acetate, vacuum filtration and concentration of the filtrate to obtain **27** in a yield of 90%.

Stepwise flow optimization stage 1: All flow experiments were performed using the Uniqsis FlowSyn platform.[30] For the stage 1 optimization the system was operated with two HPLC pumps, a 2 mL mixing chip and a 100 psi back pressure regulator (BPR) fitted at the output flow stream. The reagent feedstock for pump A was 4-MAP (**130**, 2.68 M) in absolute ethanol and for pump B was ETFA (**131**, 2.99 M) and sodium ethoxide (3.82 M) in absolute ethanol (Scheme 6.2).



Scheme 6.2: Equipment setup for the flow synthesis of dione (**132**).

An initial screen of flow rates was done at 50 °C (Table 6.3) which afforded a best isolated yield of 43% with a residence time of 4 minutes. A subsequent temperature screen in the range of 30 to 150 °C with the same residence time showed no further improvement in the yield (Figure 6.8). It was observed that reaction temperatures below 50 °C were inefficient with yields < 5%, as with the batch process route the isolated yields also decreased steadily with increasing temperature above 50 °C.

Table 6.3: Optimization of flow rate for formation of dione (**132**)

[a] Flow rate refers to the combined flow rates of both pumps set at a 1:1 ratio

Flow rate (mL.min^{-1})[a]	Residence time (min)	Yield (%)
0.25	8	35
0.50	4	43
1.00	2	29

Standard conditions: **130** (2.68 M), **131** (2.99 M), NaOEt (3.82 M), 50 °C.

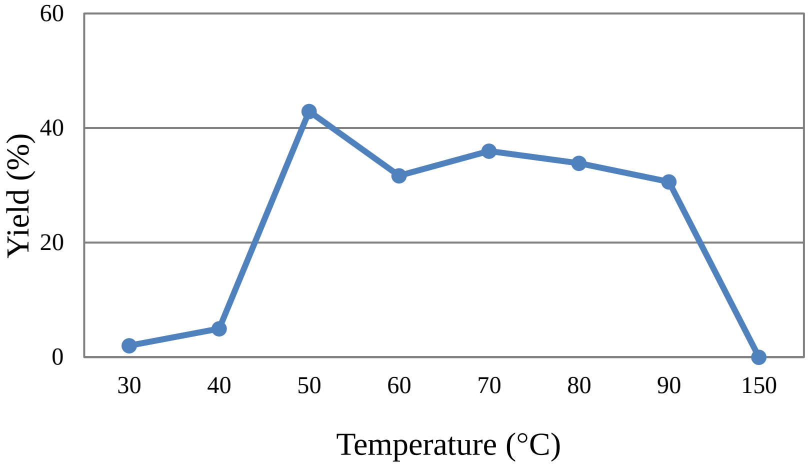


Figure 6.8: Study of the effect of reaction temperature on formation of dione (**132**).

Standard conditions: **130** (2.68 M), **131** (2.99 M), NaOEt (3.82 M), 0.50 mL.min^{-1}, pump ratio 1:1.

In an attempt to increase the reaction yield the stoichiometric ratio of ETFA/NaOEt relative to 4-MAP (**130**) was increased (Table 6.4) with the flow rate maintained at 0.50 mL.min^{-1} at 50 °C.

Table 6.4: Concentrations of solutions used in concentration screen

Reactor (A : B)	Solution A [4-MAP] (M)	Solution B [ETFA] (M)	Solution B [NaOEt] (M)	Yield (%)
1 : 1	2.68	2.99	3.82	43
1 : 1.5	2.68	4.49	5.73	83
1 : 2.5	2.68	7.48	9.55	93
1 : 3	2.68	8.97	11.46	89

Standard conditions: 2 mL mixing chip, standard solutions of **130** (2.68 M), **131** (2.99 M), NaOEt (3.82 M), 50 °C, 0.50 mL.min^{-1}.

A stoichiometric ratio of 2.5:1 ETFA/NaOEt:4-MAP corresponding to 2.8 and 3.5 equivalents of ETFA and NaOEt respectively showed complete conversion by TLC and afforded a 93% isolated yield of dione **132**.

In 4-methylacetophenone (**130**) the ^{1}H NMR spectrum has a peak at δ 2.47 ppm integrating for 3H belonging to the α-carbon (Figure 6.9). In the ^{1}H NMR spectrum of the dione (**132**) it can be clearly seen that this peak has shifted noticeably downfield to δ 5.92 ppm, which indicates that reaction has taken place at the α-carbon as expected (Figure 6.10). The integration value has also altered from 3 to 1, which is indicative of the enolate resonance structure of dione (**132**). The groups of Singh[2] and Ahlström[29a] reported ^{1}H NMR spectral shifts of δ 7.84 (d, *J* = 8.2 Hz, 2H); 7.30 (d, *J* = 8.0 Hz, 2H); 6.54 (s, 1H) and 2.43 (s, 3H) using $CDCl_3$, which correlates fairly well when solvent differences are taken into account.

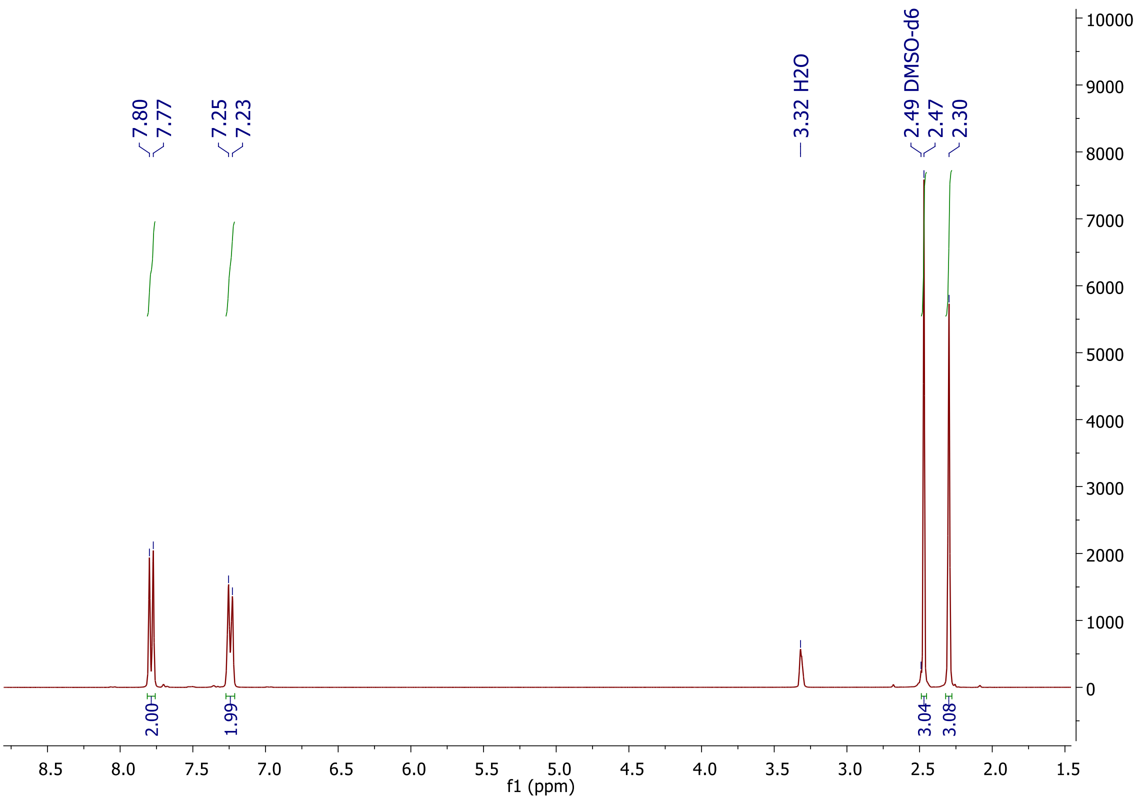


Figure 6.9: Experimental ^{1}H NMR spectrum of 4-methylacetophenone (**130**).

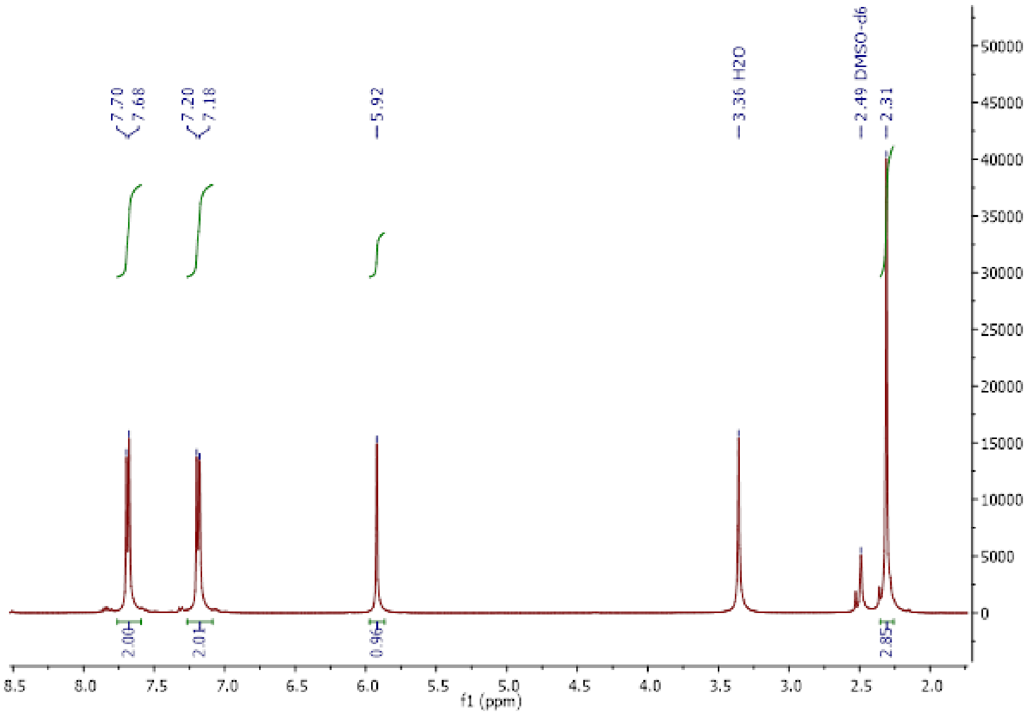
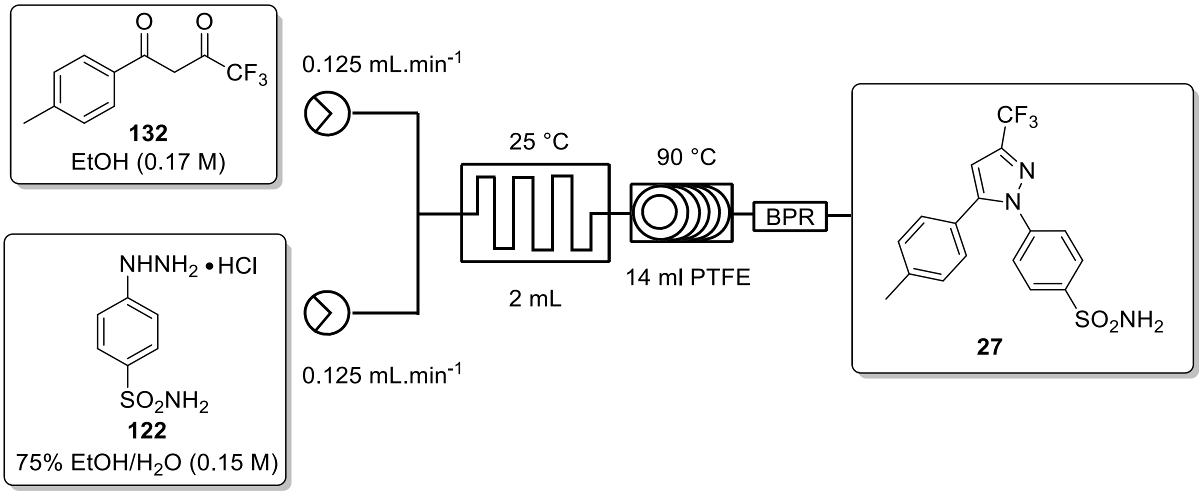


Figure 6.10: Experimental ^{1}H NMR spectrum of dione (**132**).

Stepwise flow optimization stage 2: The second stage reactor setup made use of two HPLC pumps, a 2 mL mixing chip, a 14 mL HT PTFE coil reactor and a back pressure regulator (BPR) fitted at the output flow stream (Scheme 6.3). It was found that a 2 mL mixing chip at RT was beneficial to improve mixing of the reagents before reaction in the heated coil reactor.



Scheme 6.3: Equipment setup for the flow synthesis of celecoxib (**27**).

As batch optimizations showed that temperature plays a crucial role in the formation of celecoxib (**27**) an initial temperature screen was performed in the range of 50-140 °C at a flow rate of 0.50 mL.min^{-1} (Figure 6.11). An isolated yield of 52-53% was obtained between 90 and 100 °C, once again as observed in the batch optimizations there is a dramatic decrease in isolated yield at higher temperatures.

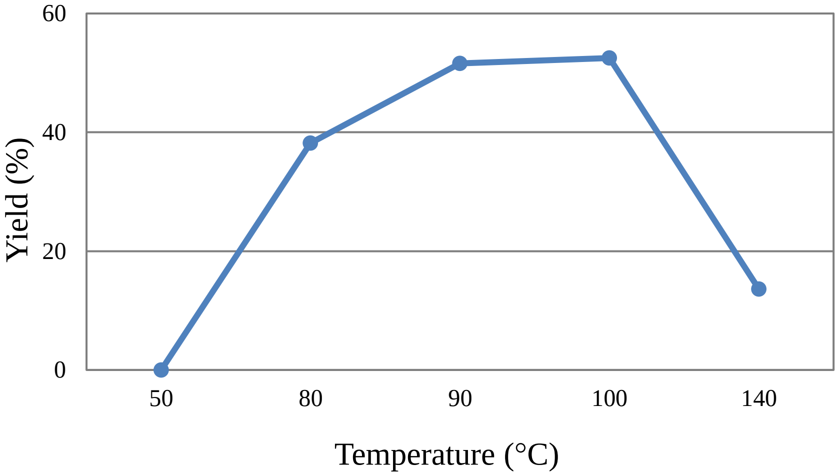


Figure 6.11: Study of the effect of reaction temperature on formation of celecoxib (**27**).

Standard conditions: **132** (0.17 M), **122** (0.15 M), EtOH, 0.50 mL.min^{-1}.

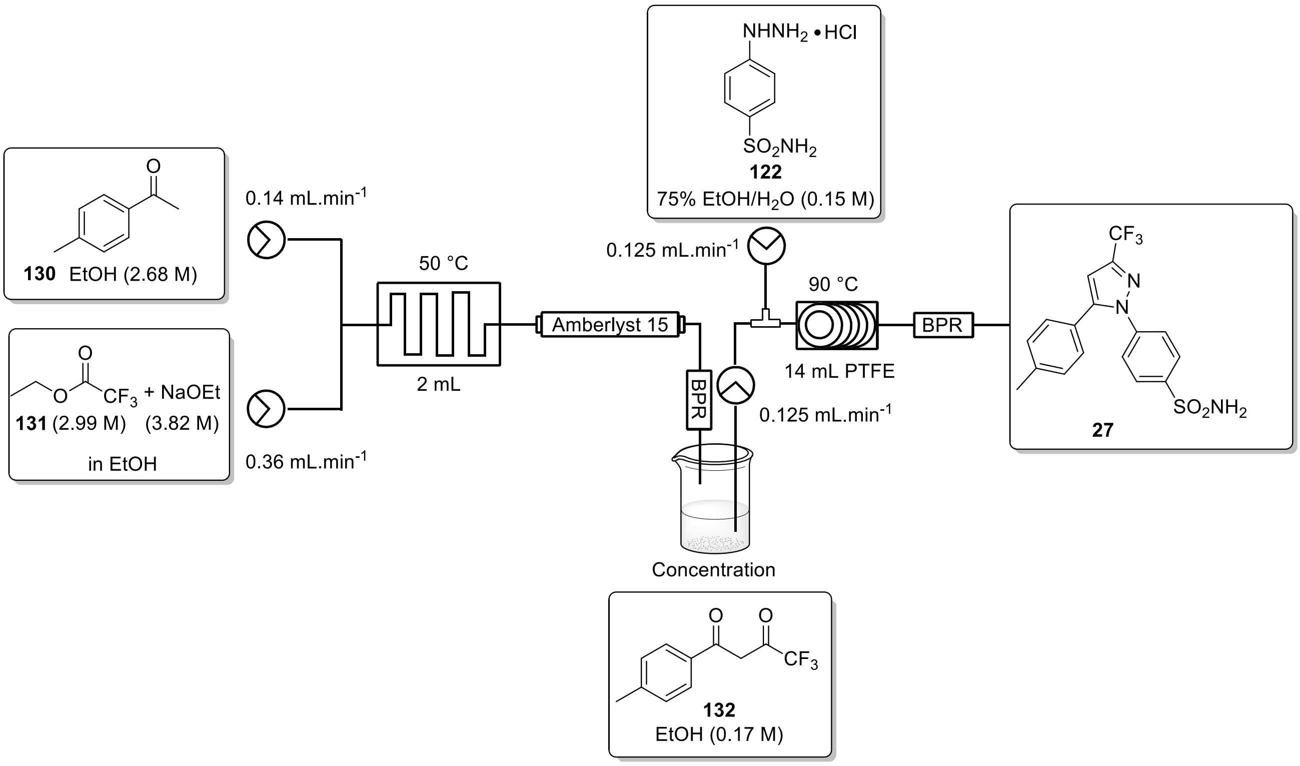
Optimization of residence time was performed at 90 °C (Table 6.5), affording a quantitative conversion of dione **132** to celecoxib (**27**) with a coil residence time of 56 min.

Table 6.5: Optimization of flow rate for formation of celecoxib (**27**)

Flow rate (mL.min^{-1})	**Residence time mixing chip (min)**	**Residence time HT PTFE coil (min)**	**Yield (%)**
0.20	10	70	88
0.25	8	56	100
0.50	4	28	58

Standard conditions: 2 mL mixing chip, 14 mL HT PTFE coil, standard solutions of **132** (0.17 M), **122** (0.15 M), 90 °C.

Multistep flow synthesis: For a multistep flow synthesis the individual flow steps needed to be combined. The reactor setup (Scheme 6.4) involved the reaction of 4-MAP (**130**) and ETFA (**131**) in the presence of sodium ethoxide in a 2 mL mixing chip at 50 °C, thereafter passage through an OmniFit® column (10 mm i.d. by 100 mm length) packed with Amberlyst-15 Hydrogen form (1.25 g) to neutralize the excess base after the Claisen condensation and a 100 psi back pressure regulator (BPR). An in-line concentration step heating the run-off at 80 °C was required to remove unreacted ETFA (bp 60-62 °C) after stage 1. Thereafter hydrazine **122** was introduced through a T-piece mixer and subsequent passage through a 14 mL PTFE coil reactor at 90 °C and finally a 100 psi back pressure regulator at the output flow stream.



Scheme 6.4: Equipment setup for continuous flow synthesis of celecoxib (**27**).

The coupled process afforded celecoxib (**27**) in an isolated yield of 90% after employing the work-up/purification developed during the batch optimization of stage 2. In order to test the robustness of the flow synthesis it was performed on a 10 g scale which was allowed to run overnight, also resulting in an isolated yield of 90%. It is envisioned that on industrial scale a LiquiSonic® sensor (or similar device) could be incorporated within the in-line concentration unit, allowing for online, real-time monitoring of the concentration of dione (**132**).[31] The in-line concentration unit would be equipped with an outlet port for the removal of excess ETFA (**131**) which would then be recycled, but it would also be equipped with an inlet port for EtOH linked to a programmed control unit, allowing for automation of the concentration process. Thus, in the event that too much EtOH is removed, EtOH could be added slowly until the required concentration is obtained.

In the dione (**132**) the ^{1}H NMR spectrum has a distinct peak at δ 5.92 ppm belonging to the enolate proton (Figure 6.10). In the ^{1}H NMR spectrum of celecoxib (**27**) it can be seen that this peak has shifted noticeably downfield to δ 7.18 ppm due to its becoming more deshielded as a result of the nitrogen atoms in the ring pulling the electron density (Figure 6.12). The group of Reddy and co-workers[13] reported ^{1}H NMR spectral shifts of δ 7.89 (d, J = 8.8 Hz, 2H); 7.55 (d, J = 8.8 Hz, 2H); 7.52 (s, NH_2); 7.22 (m, 4H); 7.17 (s, 1H) and 2.32 (s, 3H) using DMSO-d_6 which correlates exactly with the NMR spectral data obtained in this work.

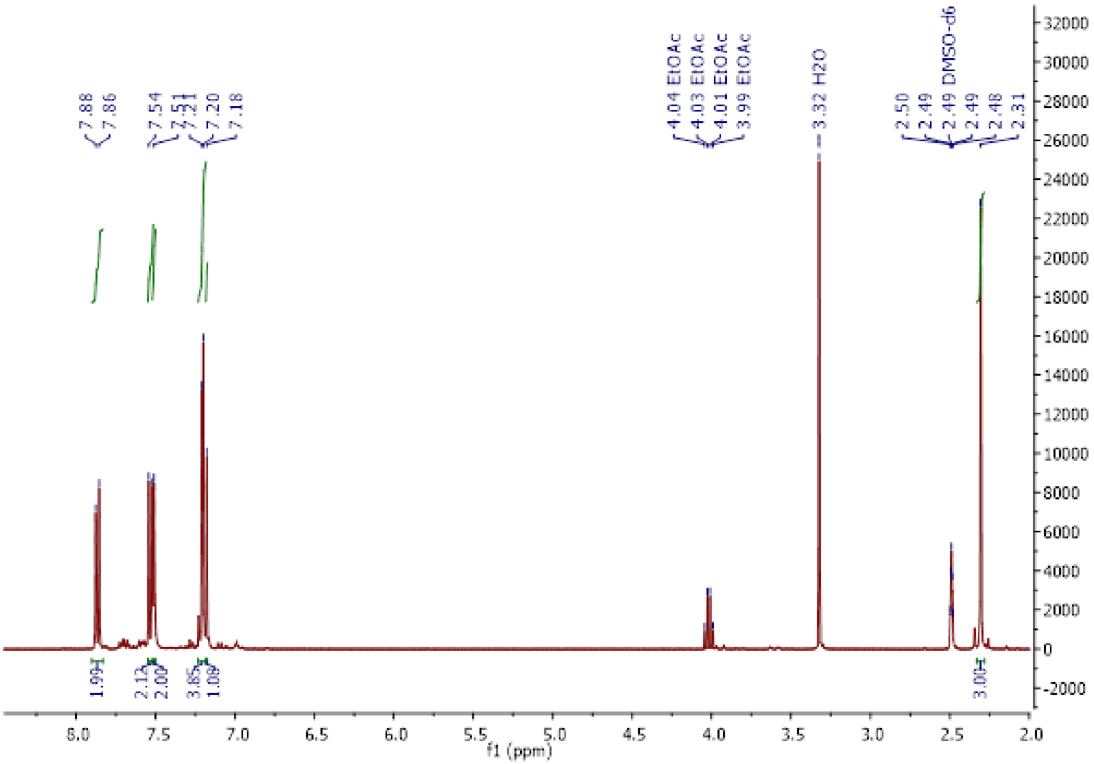


Figure 6.12: Experimental ^{1}H NMR spectrum of celecoxib (**27**).

6.5. CONCLUSION

In conclusion we have demonstrated both an improved batch process and a high yielding continuous flow process for the synthesis of celecoxib (**27**), the latter of which does not require the handling of intermediates, is conducted in a green solvent system and has a greatly reduced residence time relative to existing batch processes. The continuous flow route shows significant advantages over the currently reported batch syntheses of celecoxib (**27**) and the approach could also conceivably be used for the rapid synthesis of pyrazole analogues.

6.6. EXPERIMENTAL SECTION

All solvents and reagents were purchased from Sigma-Aldrich and used without further purification. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AVANCE-III 300 MHz spectrometer or a Bruker AVANCE-III 400 MHz spectrometer with the residual solvent peak as an internal reference (DMSO-d_6 = 2.49 and 39.5 ppm for ^{1}H and ^{13}C NMR spectra respectively). Chemical shifts, δ, are reported in parts per million (ppm), and splitting patterns are given as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m). Coupling constants, *J*, are expressed in hertz (Hz). Yields refer to isolated pure products unless stated otherwise.

Batch preparation of 4,4,4-Trifluoro-1-(4-methyl-phenyl)-butane-1,3-dione (132)

A solution of sodium (0.12 g, 5.2 mmol, 1.4 equiv.) was dissolved in absolute ethanol (3.9 mL) followed by the dropwise addition of ethyl trifluoroacetate (**131**) (0.5 mL, 4.1 mmol, 1.1 equiv.). Thereafter 4-methyl acetophenone (**130**) (0.50 mL, 3.8 mmol, 1.0 equiv.) in absolute ethanol (1.4 mL) was added dropwise over 15 minutes. The reaction mixture was stirred at room temperature for 3 hours. The mixture was concentrated *in vacuo* and the solid obtained suspended in hexane (15 mL) with vigorous stirring followed by vacuum filtration and washing with hexane (2 x 2 mL) to obtain a cream-brown solid (0.86 g, 3.7 mmol, 100%). R_f = 0.23 (25 % EtOAc/hexane). ^{1}H NMR (400 MHz d_6-DMSO) 7.69 (d, 2H, *J* 7.69, Ar-H); 7.19 (d, 2H, *J* 7.18, Ar-H); 5.92 (s, 1H, $\mathrm{CO\underline{CH_2}CO}$); 2.31 (s, 3H, $\mathrm{C\underline{H_3}}$). ^{13}C NMR (100 MHz d_6-DMSO) 185.62, 168.85 (q, $J_{C\text{-}F}$ 27.84), 139.89, 138.96, 128.70, 126.66, 119.43(q, $J_{C\text{-}F}$ 292.16), 86.84, 20.91. ^{19}F NMR (377 MHz, d_6-DMSO) -74.42.

Batch preparation of 4-Sulfamidophenylhydrazine Hydrochloride (122)[32]

Sulfanilamide (**114k**) (5.01 g, 29.1 mmol, 1.0 equiv.) was cooled to 0 °C followed by the addition of ice (29.11 g, 1.6 mol, 55.5 equiv.) and aqueous hydrochloric acid (32 %, 14.5 mL, 0.2 mol, 5.1 equiv.). A solution of sodium nitrite (2.01 g, 29.1 mmol, 1.0 equiv.) in water (4.0 mL, 0.2 mol, 6.9 equiv.) was added in a dropwise fashion and the solution was allowed to stir until all the sulfanilamide had dissolved. This mixture was rapidly added to a pre-cooled 0 °C solution of tin(II) chloride (14.38 g, 75.8 mmol, 2.6 equiv.) in aqueous hydrochloric acid (32 %, 21.7 mL, 0.2 mol, 7.6 equiv.) with vigorous stirring. The reaction mixture was placed in the fridge at 0-4 °C overnight. The solid formed was collected by vacuum filtration followed by washing with cold ethanol (3 x 20 mL) to obtain 4-sulfamidophenylhydrazine hydrochloride (**122**) as a pearlescent white solid (5.37 g, 24 mmol, 83%). *Rf* = 0.16 (20% hexane/EtOAc). ^{1}H NMR (400 MHz d_6-DMSO) 10.55 (s, 2H, $SO_2N\underline{H_2}$); 8.91 (s, 1H, $N\underline{H}NH_2$); 7.68 (d, 2H, *J* 8.00, Ar-H); 7.19 (s, 2H, $NHN\underline{H_2}$); 7.05 (d, 2H, *J* 8.00, Ar-H). ^{13}C NMR (100 MHz d_6-DMSO) 148.47, 136.11, 126.94, 113.36.

Batch preparation of Celecoxib (27)

4,4,4-Trifluoro-1-(4-methyl-phenyl)-butane-1,3-dione (**132**) (0.31 g, 1.3 mmol, 1.1 equiv.) was added to a solution of 4-sulfamidophenylhydrazine hydrochloride (**122**) (0.27 g, 1.2 mmol, 1.0 equiv.) in absolute ethanol (16.3 mL) followed by reaction at 80 °C for 17 hours. The mixture was concentrated *in vacuo* and the solid obtained suspended in ethyl acetate (30 mL) followed by vacuum filtration. The filtrate was concentrated to obtain celecoxib (**27**) as a pale yellow solid (0.41 g, 1.1 mmol, 90 %). R$_f$ = 0.33 (20 % methanol/dichloromethane). ^{1}H NMR (400 MHz d_6-DMSO) 7.87 (d, 2H, *J* 7.86, Ar-H); 7.53 (d, 2H, *J* 7.53, Ar-H); 7.51 (s, 2H, $N\underline{H_2}$); 7.21 – 7.19 (m, 4H, Ar-H); 7.18 (s, 1H, $C\underline{H}$); 2.31 (s, 3H, $C\underline{H_3}$). ^{13}C NMR (100 MHz d_6-DMSO) 145.27, 143.99, 142.17 (q, $J_{C\text{-}F}$ 37.90), 141.11, 139.11, 129.42, 128.78, 126.80, 126.00, 125.36, 121.30 (q, $J_{C\text{-}F}$ 269.02), 106.15, 20.79. ^{19}F NMR (377 MHz, d_6-DMSO) -60.86.

Flow synthesis

General methods for the preparation of stock solutions

4-Methyl acetophenone (130) in ethanol

A stock solution of 4-methyl acetophenone **130** was prepared by dissolving **130** (14.3 mL, 107 mmol) in absolute ethanol (40 mL).

Ethyl trifluoroacetate (131)/sodium ethoxide in ethanol

A stock solution of ethyl trifluoroacetate **131** and sodium ethoxide was prepared by dissolving sodium metal (4.39 g, 191 mmol) in absolute ethanol (50 mL) followed by the addition of **131** (17.8 mL, 150 mmol).

4-Sulfamidophenylhydrazine hydrochloride (122) in ethanol

A stock solution of 4-sulfamidophenylhydrazine hydrochloride **122** was prepared by dissolving **122** (1.32 g, 5.9 mmol) in 75 % ethanol/water (40 mL)

General procedure for the stepwise flow synthesis of 4,4,4-Trifluoro-1-(4-methyl-phenyl)-butane-1,3-dione (132)

The 4-methyl acetophenone **130** stock solution (1.48 mL) and the ethyl trifluoroacetate **131** /sodium ethoxide stock solution (3.70 mL) were pumped at flow rates of 0.14 mL.min^{-1} and 0.36 mL.min^{-1} respectively through a 2 mL glass mixing chip heated to 50 °C. The output of the reactor was collected until no further product was eluted and the solvent removed *in vacuo*. The solid obtained was suspended in hexane (15 mL) with vigorous stirring followed by vacuum filtration and washing with hexane (2 x 2 mL) to obtain a cream-brown solid (0.84 g, 3.7 mmol, 93%).

Stepwise flow synthesis of Celecoxib (27)

4,4,4-Trifluoro-1-(4-methyl-phenyl)-butane-1,3-dione **132** stock solution (7 mL) and 4-sulfamidophenylhydrazine hydrochloride **122** stock solution (7 mL) were each pumped at a flow rate of 0.125 mL.min^{-1} into a 2 mL glass mixing chip at room temperature and through a 14 mL PTFE coil heated to 90 °C. The output of the reactor was collected until no further product was eluted and the solvent removed *in vacuo*. The solid obtained was suspended in ethyl acetate (30 mL) followed by vacuum filtration. The filtrate was concentrated to obtain a pale yellow solid (0.393 g, 1.0 mmol, 99%). R_f = 0.33 (20% methanol/dichloromethane).

Multi-step flow synthesis of Celecoxib (27)

The 4-methyl acetophenone **130** (1.01 mL) stock solution and the ethyl trifluoroacetate **131**/sodium ethoxide (2.53 mL) stock solution were pumped at flow rates of 0.14 mL.min^{-1} and 0.36 mL.min^{-1} respectively through a 2 mL glass mixing chip heated to 50 °C followed by an Omnifit® column (10 mm i.d. by 100 mm length) packed with Amberlyst-15 resin hydrogen form (1.25 g, 5.9 mmol). The output (4,4,4-Trifluoro-1-(4-methyl-phenyl)-butane-1,3-dione **132**) of the reaction was collected in a beaker held at 80 °C with an air stream blowing over the surface to concentrate the solution down to 16.4 mL (0.16 M relative to **132**). The concentrated solution of **132** (15.0 mL) and the 4-sulfamidophenylhydrazine hydrochloride **122** stock solution (15.0 mL) were both pumped at flow rates of 0.125 mL.min^{-1} and mixed via a stainless steel T-piece followed by reaction in a 14 mL HT PTFE coil heated to 90 °C. The output of the reactor was collected until no further product was eluted and the solvent removed under vacuum. The solid obtained was suspended in ethyl acetate (30 mL) followed by vacuum filtration. The filtrate was concentrated *in vacuo* to obtain a pale yellow solid (0.76 g, 2.0 mmol, 90%).

6.7. REFERENCES

(1) Gaulier, S.M.; McKay, R. and Swain, N.A. *Tetrahedron Lett.*, **2011**, *52*, 6000.

(2) Singh, S.K.; Reddy, P.G.; Rao, K.S.; Lohray, B.B.; Misra, P.; Rajjak, S.A.; Rao, Y.K. and Venkateswarlu, A. *Bioorg. Med. Chem. Lett.*, **2004**, *14*, 499.

(3) Boschi, D.; Lazzarato, L.; Rolando, B.; Filieri, A.; Cena, C.; Di Stilo, A.; Fruttero, R. and Gasco, A. *Chem. Biodiversity.*, **2009**, *6*, 369.

(4) Desai, D.; Kaushal, N.; Gandhi, U.H.; Arner, R.J.; D'Souza, C.; Chen, G.; Vunta, H.; El-Bayoumy, K.; Amin, S. and Prabhu, K.S. *Chem.-Biol. Interact.*, **2010**, *188*, 446.

(5) Menozzi, G.; Merello, L.; Fossa, P.; Mosti, L.; Piana, A. and Mattioli, F. *Il Farmaco*, **2003**, *58*, 795.

(6) Kuge, Y.; Katada, Y.; Shimonaka, S.; Temma, T.; Kimura, H.; Kiyono, Y.; Yokota, C.; Minematsu, K.; Seki, K.; Tamaki, N.; Ohkura, K. and Saji, H. *Nucl. Med. Biol.*, **2006**, *33*, 21.

(7) Gao, M.; Wang, M.; Miller, K.D.; Hutchins, G.D. and Zheng, Q-H. *Appl. Radiat. Isot.*, **2009**, *67*, 2019.

(8) Penning, T.D.; Talley, J.J.; Bertenshaw, S.R.; Carter, J.S.; Collins, P.W.; Docter, S.; Graneto, M.J.; Lee, L.F.; Malecha, J.W.; Miyashiro, J.M.; Rogers, R.S.; Rogier, D.J.; Yu, S.S.; Anderson, G.D.; Burton, E.G.; Cogburn, J.N.; Gregory, S.A.; Koboldt, C.M.; Perkins, W.E.; Seibert, K.; Veenhuizen, A.W.; Zhang, Y.Y. and Isakson, P.C. *J. Med. Chem.*, **1997**, *40*, 1347.

(9) Oh, L.M. *Tetrahedron Lett.*, **2006**, *47*, 7943.

(10) (a) Zhi, B.; Newaz, M. Process for preparing 3-haloalkyl-1H-pyrazoles. Patent no: 5892053, Apr 1999. (b) Zhi, B.; Newaz, M. Process for preparing 3-haloalkyl-1H-pyrazoles. Patent no: 5910597, Jun 1999.

(11) O'Shea, P.; Tillyer, R.D.; Wang, X.; Clas, S-D. and Dalton, C. Synthesis of 4-[5-substituted or unsubstituted phenyl)-3-substituted-1H-pyrazol-1-yl]benzenesulfonamides. Patent no: 6150534, Nov 2000.

(12) Letendre, L.J.; McGhee, W.D.; Snoddy, C.; Klemm, G. and Gaud, H.T. Synthesis of diaryl pyrazoles. Patent no: 7141678 B2, Nov 2006.

(13) Reddy, A.R.; Sampath, A.; Goverdhan, G.; Yakambaram, B.; Mukkanti, K. and Reddy, P.P. *Org. Process Res. Dev.*, **2009**, *13*, 98.

(14) Ambati, V.R.R.; Garaga, S.; Mallela, S.P.S. and Meenakshisunderam, S. An improved process for the preparation of celecoxib. Patent no: WO 2010/095024 A2, Aug 2010.

(15) Beveridge, R.E.; Fernando, D. and Gerstenberger, B.S. *Tetrahedron Lett.*, **2010**, *51*, 5005.

(16) Reddy, R.; Ramana, V. and Bell, S.C. *Chem. Abstr.*, **2003**, *138*, 271677.

(17) Hu, J.; Chen, S.; Sun, Y.; Yang, J. and Rao, Y. *Org. Lett.*, **2012**, *14*, 5030.

(18) (a) Shang, Y.; Du, J. and Cui, H. *Org. Prep. Proced. Int.*, **2014**, *46*, 132. (b) Sano, K. and Hara, S. *Heterocycles*, **2010**, *80*, 349.

(19) (a) Baxendale, I.R.; Deeley, J.; Griffiths-Jones, C.M.; Ley, S.V.; Saaby, S. and Tranmer, G.K. *Chem. Commun.*, **2006**, 2566. (b) Ley, S.V. and Baxendale, I.R. *The Chemical Record*, **2002**, *2*, 377.

(20) Smith, C.J.; Iglesias-Sigüenza, F.J.; Baxendale, I.R. and Ley, S.V. *Org. Biomol. Chem.*, **2007**, *5*, 2758.

(21) (a) Baxendale, I.R.; Schou, S.C.; Sedelmeier, J. and Ley, S.V. *Chem. Eur. J.*, **2010**, *16*, 89. (b) Lange, H.; Carter, C.F.; Hopkin, M.D.; Burke, A.; Goode, J.G.; Baxendale, I.R. and Ley, S.V. *Chem. Sci.*, **2011**, *2*, 765.

(22) Breen, J.R.; Sandford, G.; Yufit, D.S.; Howard, J.A.k.; Fray, J. and Patel, B. *Beilstein J. Org. Chem.*, **2011**, *7*, 1048.

(23) Obermayer, D.; Glasnow, T.N. and Kapper, C.O. *J. Org. Chem.*, **2011**, *76*, 6657.

(24) Li, B.; Widlicka. D.; Boucher, S.; Hayward, C.; Lucas, J.; Murray, J.C.; O'Neil, B.T.; Pfisterer, D.; Samp, L.; VanAlsten, J.; Xiang, Y. and Young, J. *Org. Process Res. Dev.*, **2012**, *16*, 2031.

(25) DeAngelis, A.; Wang, D-H. and Buchwald, S.L. *Angew. Chem. Int. Ed.*, **2013**, *52*, 3434.

(26) Battilocchio, C.; Deadman, B.J.; Nikbin, N.; Kitching, M.O.; Baxendale, I.R. and Ley, S.V. *Chem. Eur. J.*, **2013**, *19*, 7917.

(27) Poh, J-S.; Browne, D.L. and Ley, S.V. *React. Chem. Eng.*, **2016**, *1*, 101.

(28) Britton, J.; Jamison, T.F. *Eur. J. Org. Chem.*, **2017**, *44*, 6566.

(29) (a) Ahlström, M.M.; Ridderström, M.; Zamora, I.; Luthman, K. *J. Med. Chem.*, **2007**, *50*, 4444. (b) Bűttner, S.; Riahi, A.; Hussain, I.; Yawer, M.A.; Lubbe, M.; Villinger, A.; Reinke, H.; Fischer, C. and Langer, P. *Tetrahedron*, **2009**, *65*, 2124. (c) Szabó, G.; Fischer, J.; Kis-Varga, A. and Gyires, K. *J. Med. Chem.*, **2008**, *51*, 142.

(30) www.uniqsis.com

(31) www.sensotech.com

(32) Soliman, R. *J. Med. Chem.*, **1979**, *22*, 321.

Chapter 7:

Conclusion & Future Work

7.1. KEYWORDS

Fluorine, organofluorine, 5-fluorocytosine, hexafluorobuta-1,3-diene, aryl diazonium tetrafluoroborate salts, aryl hydrazines, celecoxib, flow chemistry.

7.2. CONCLUDING REMARKS AND FUTURE WORK

Organofluorine chemistry has a rich history and an even more interesting future. Fluorine's ability to modulate the pharmacokinetic as well as physiochemical properties of drugs makes it an important tool for the pharmaceutical industry.[1] The incorporation of fluorine into a molecule can improve its metabolic stability, bioavailability and binding affinity, all factors which contribute to a drug's efficacy.[1]

The incorporation of fluorine into drugs has however, always been limited by the synthetic methodology and reagents available.[2-4] For a long time, elemental fluorine was too reactive and explosive for use, until it was tamed by dilution with nitrogen gas.[2,5] The introduction of safer and easier to handle nucleophilic as well as electrophilic fluorinating agents allowed for a notable increase in the use of fluorine in synthesis.[2,6]

Despite the synthetic challenges, fluorinated drugs still make up 20-25% of all registered pharmaceuticals, with fluorine being an integral component in many drug research and development programs.[2-4] Although traditional batch synthesis still dominates in academia and industry, continuous flow synthesis is a rapidly developing field which is quickly growing in popularity. The advantages of flow chemistry are many, with the improved safety profile being a particularly attractive point, especially when it comes to fluorination reactions.[7,8]

As a result of flow chemistry being a relatively new field, its use for fluorination and the synthesis of fluorinated drugs has not yet been extensively explored. There are numerous traditional batch methodologies as well as fluorinated drug syntheses which could potentially benefit from translation into flow-based processes. Translation to flow processes could increase the safety profiles, improve the yields and make the drugs more affordable.

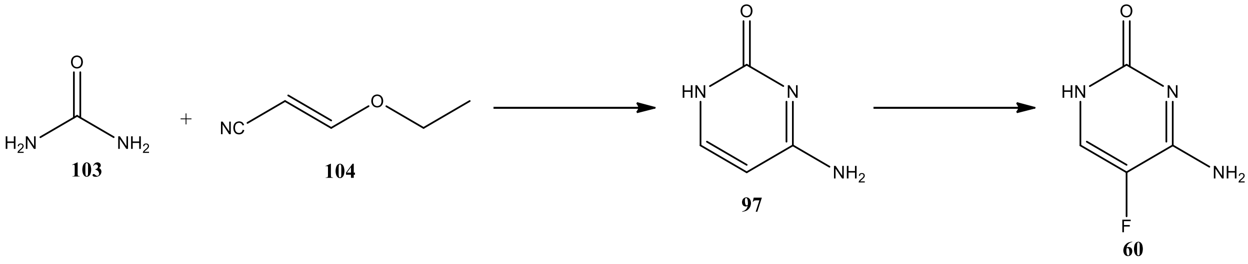
In this work the conversion of traditional batch synthesis to continuous flow processes was explored for 5-fluorocytosine (flucytosine, **60**), hexafluorobuta-1,3-diene (**105**), aryl diazonium tetrafluoroborate salts (**113**), aryl hydrazines (**116**) and celecoxib (**27**) in an effort to develop processes which would be more industrially viable or at the very least, expand the scope of technology available to organofluorine chemists. Each synthesis presented with different challenges, met with different levels of success and opened new research avenues which will be discussed in more detail below.

7.2.1. **Chapter 2: 5-Fluorocytosine (60)**

5-Fluorocytosine (**60**), marketed as the drug flucytosine is an important antifungal and anti-cancer prodrug.[9] It is on the World Health Organization's list of essential medicines, but it is extremely expensive and thus unaffordable for many of the poorer third world countries which need it the most.[10] Only one flow chemistry process has been reported for this critical drug so far, but it suffers from a lengthy and complicated work-up protocol.[10] A simple, successful flow synthesis of 5-fluorocytosine (**60**) could make this drug more affordable and thus more accessible to a large portion of the world population.

An improved batch process for the synthesis of cytosine (**97**) in a yield of 82% using reagents which are commercially available and safe to handle was demonstrated, but the batch synthesis of 5-fluorocytosine (**60**) could not be successfully achieved. The conversion of the traditional batch process to a continuous flow process was evaluated, but based on observations made during the batch process, a flow process wasn't deemed feasible.

The primary limiting factor to obtaining a successful flow synthesis of 5-fluorocytosine (**60**) was the poor solubility of cytosine (**97**) in a wide range of traditional solvents while the electrophilic fluorination using Selectfluor® (**91**) did not occur as anticipated. Literature indicated that the cytosine ring would first need to be activated by nucleophilic addition at the C-6 position.



Scheme 7.1: Synthesis route to 5-fluorocytosine (**60**).

Future work on this project would involve investigating the use of tubing having a wider inner diameter along with sonication or the use of peristaltic pumps for the condensation of urea (**103**) and 3-ethoxyacrylonitrile (**104**) to obtain cytosine (**97**). The wider inner diameter along with the sonication should help to keep the cytosine (**97**) which precipitates out, moving through the reactor, preventing blockage. The in-house development of an in-line triturator large enough to collect the formed cytosine (**97**) could also be explored. This would then allow for convenient solvent swap for the second step.

For the electrophilic fluorination of cytosine (**97**) to 5-fluorocytosine (**60**), the use of non-traditional solvents or co-solvent systems could be explored. In order to activate the ring sufficiently, nucleophilic addition at the C-6 position is required and this could be achieved by the addition of a base such as hydroxide or bisulfite.[11] This implies that water could be a good solvent to consider as it would solubilize the cytosine (**97**) as well as the base followed by reaction with Selectfluor® (**91**) in acetonitrile, which is miscible with water. These reaction conditions could then potentially be translated to flow. Alternatively, electrophilic fluorination reagents such as the *N*-fluoropyridinium triflate salts or NFSI (**90**) could be examined instead of Selectfluor® (**91**).

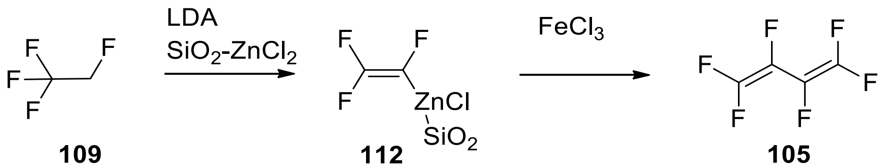
These modifications were not pursued further in this work due to time constraints.

7.2.2. **Chapter 3: Hexafluorobuta-1,3-diene (105)**

Hexafluorobuta-1,3-diene (HFBD, **105**) is an industrially valuable compound used in the production of fluoroelastomers, polymers and as a dielectric dry-etching gas.[12-14] A number of batch syntheses have been reported for its production, varying in difficulty and success, however, to date no continuous flow synthesis has been reported. In conjunction with our industrial partner we were tasked with developing an industrially viable process for the synthesis of HFBD (**105**) for potential local commercialization since South Africa has large reserves of fluorspar which are currently underutilized. A successful flow synthesis of HFBD (**105**) could thus have led to the development of a new industrial opportunity for South Africa.

Efforts to develop an alternative batch process making use of $ZnCl_2$ supported on silica are reported, but the desired HFBD (**105**) could not be isolated in detectable quantities. The conversion to a multistep continuous flow process could not be achieved due to difficulties experienced in maintaining a dry, inert and leak free environment using the modular setup available.

The primary limiting factor to obtaining a successful flow synthesis of HFBD (**105**) was the design of the reactor available, as it is designed to be modular in nature for easy modification. This meant that there were many joints in the system, increasing the probability of the presence of leaks.



Scheme 7.2: Synthesis route to hexafluorobuta-1,3-diene (**105**).

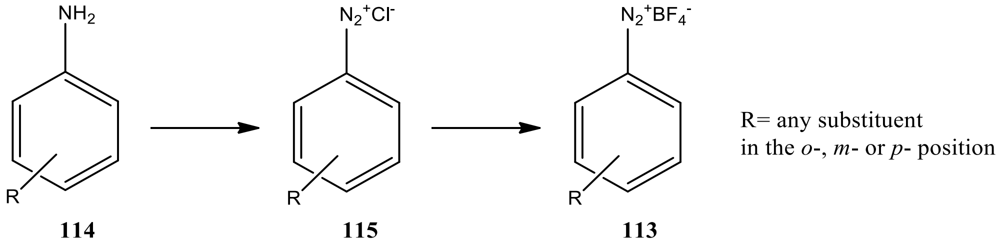
Future work on this project would involve investigating less modular systems or re-design of the reactor system in order to mitigate the technical issues encountered. The incorporation of an in-line analysis system such as head-space GCMS would be beneficial in monitoring the process as well as assist in identifying problems such as leaks. It is envisioned that should a completely sealed, moisture free system be used then it is conceivable that the synthesis could be successfully achieved under flow conditions with greater ease and lower possibility of product loss when compared to traditional batch procedures. This process could then also be investigated for the synthesis of other gaseous perfluoro compounds.

These modifications were not pursued further in this work as a preliminary techno-economics analysis performed by our industrial partner Pelchem suggested that even if the project were successful it would not be financially viable.

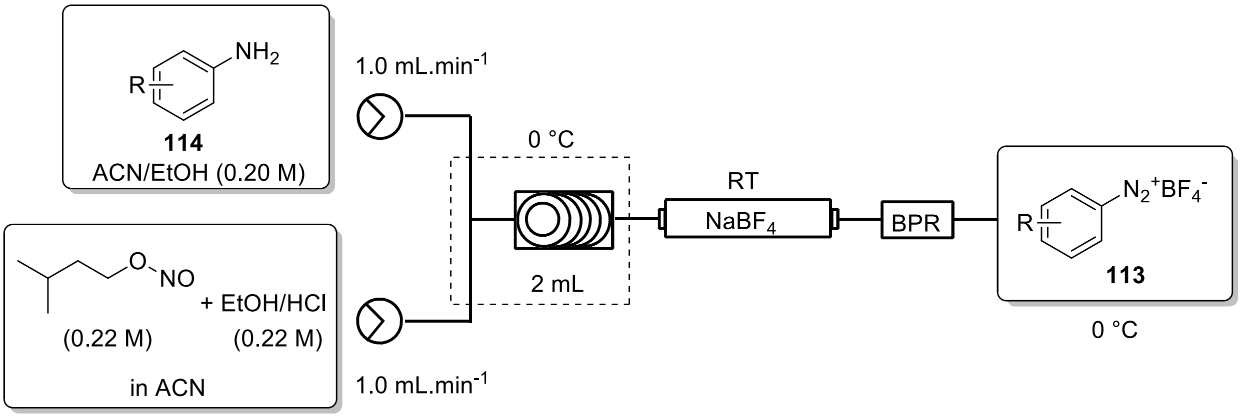
7.2.3. **Chapter 4: Aryl diazonium tetrafluoroborate salts (113)**

Aryl diazonium tetrafluoroborate salts (**113**) are important synthons in organic chemistry due to the ease with which the diazonium group can be displaced by a wide range of nucleophiles.[15] Only a few aryl diazonium tetrafluoroborate salts (**113**) are available commercially[16,17] thus a procedure to quickly, efficiently and safely prepare aryl diazonium tetrafluoroborate salts (**113**) on large scale for use in a wide range of syntheses would be of synthetic advantage. A number of batch syntheses have been reported, but these generally struggle with stability or poor yields, especially for some functional groups. To date a short, high yielding batch synthesis for aryl diazonium tetrafluoroborate salts (**113**) along with its continuous flow alternative has not been reported.

An improved batch process as well as a high yielding continuous flow process for the synthesis of aryl diazonium tetrafluoroborate salts (**113**) has been demonstrated. The flow process does not require the isolation or handling of the unstable diazonium chloride intermediate which improves the yield and safety profile of the reaction. This approach could be used for the rapid synthesis of aryl diazonium tetrafluoroborate salts (**113**) on large scale for coupling to further downstream reactions. NMR spectroscopic and IR data has also been obtained for compounds which have not been previously characterized in the literature.



Scheme 7.3: Synthesis route to aryl diazonium tetrafluoroborate salts (**113**).



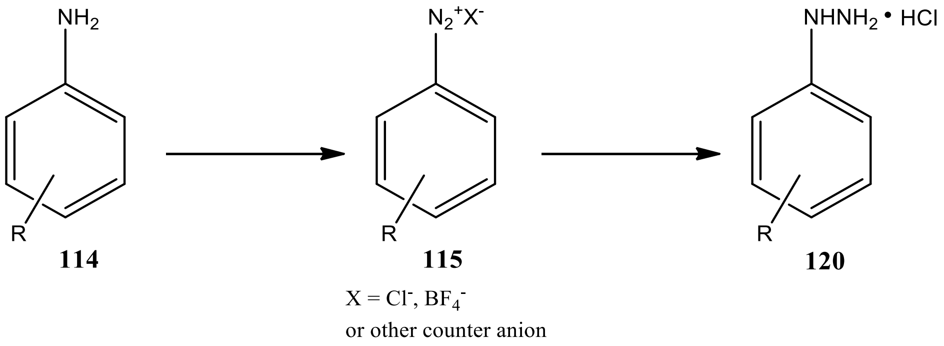
Scheme 7.4: Equipment setup for the flow synthesis of aryl diazonium tetrafluoroborate salts (**113**).

Future work on this project would involve elaborating the utility of this process by coupling it to further downstream reactions such as the Balz-Schiemann reaction, Sandmeyer reaction, reduction to aryl hydrazines and many other potential conversions to alternative functional groups. This would involve investigating and translating the currently available batch procedures to compatible flow conditions which ultimately would increase the capability and scope of flow chemistry as a larger range of reactions could then be quickly and efficiently performed.

7.2.4. **Chapter 5: Aryl hydrazines (116)**

Aryl hydrazines (**116**) are important intermediates in organic synthesis, specifically for the pharmaceutical industry where some hydrazines have exhibited interesting biological activities.[18,19] Hydrazine derivatives also form part of many pesticides, amino acid precursors, dyestuffs, agrochemicals and drugs, while also serving as a key moiety in the synthesis of heterocycles.[19,20] A more efficient synthesis of aryl hydrazines (**116**) making use of easily accessible and affordable reagents that does not produce large amounts of waste would be highly beneficial to the pharmaceutical industry, especially for the preparation of important heterocycles. A number of batch syntheses to obtain aryl hydrazines (**116**) are available but often make use of toxic reagents or suffer from poor yields. To date a generally applicable, high yielding continuous flow synthesis of aryl hydrazines using easily accessible, non-toxic reagents has not been reported.

In this work it has been demonstrated that aryl amines (**114**) are easily diazotized to the corresponding aryl diazonium chlorides (**115**) under acidic conditions, but that the reduction of this salt is not so straightforward. In an effort to obtain reaction conditions which were conducive to translation to flow a number of different reducing agents, solvents and reaction conditions were examined to obtain the aryl hydrazine (**116**) or corresponding aryl hydrazine hydrochloride (**120**), all without success. At this stage the best reducing agent still appears to be the toxic $SnCl_2$, which correlates with the findings of Li and co-workers.[21] The multistep flow synthesis of aryl hydrazines (**116**) could thus not be achieved in the allocated time.



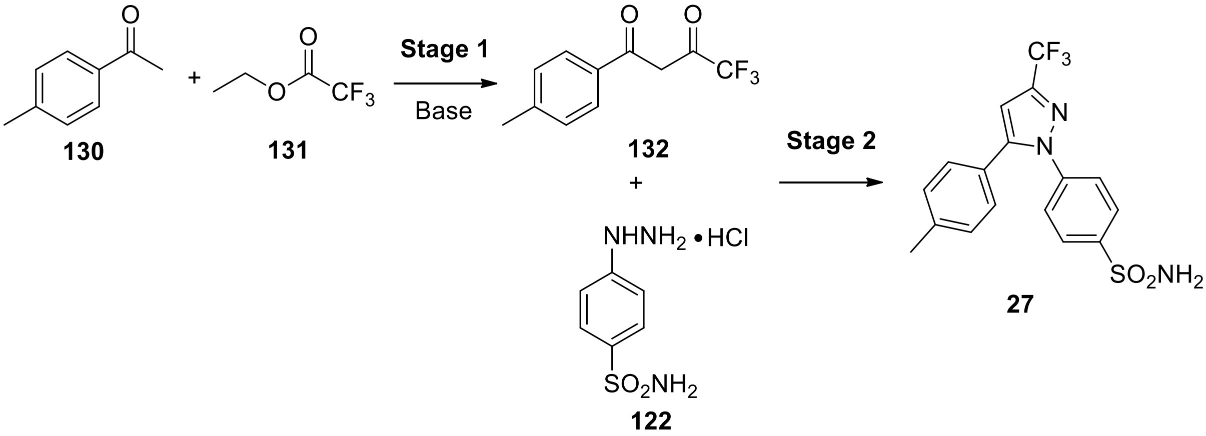
Scheme 7.5: Synthesis route to aryl hydrazine hydrochlorides (**120**).

Future work on this project would involve expanding the range of reducing agents to some of those which have not yet been explored such as cyanoborohydride supported on an anion exchange resin[22] or $Zn\text{-}NiCl_2{\bullet}6H_2O$.[23] There are still many different reducing agents available, some which may not yet have been considered as feasible under batch conditions for various reasons, but which may work well under flow conditions. The ultimate goal would be to find a set of homogenous or heterogenous conditions compatible with translation to flow, which would then make it possible to quickly and easily synthesise these valuable intermediates.

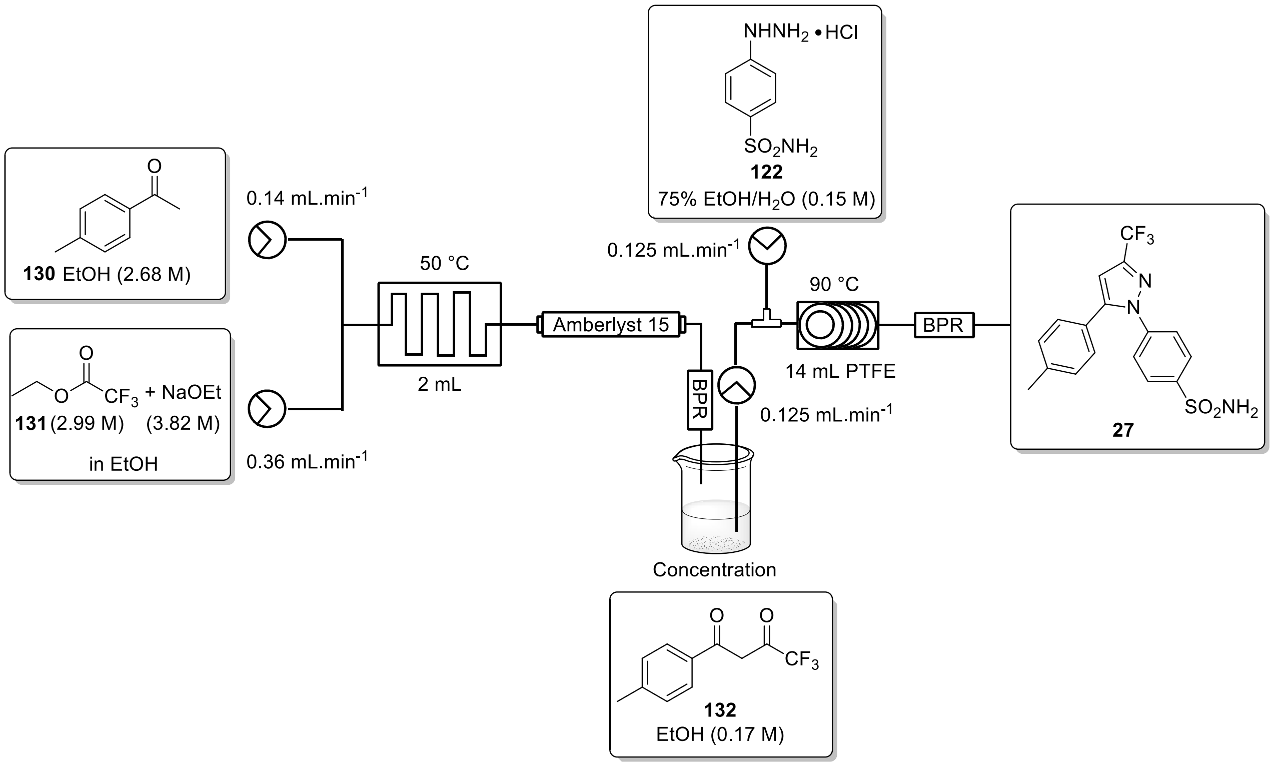
7.2.5. **Chapter 6: Celecoxib (27)**

Celecoxib (**27**) is a nonsteroidal anti-inflammatory drug (NSAID) that is regularly used in the treatment of conditions such as arthritis or the treatment of acute pain.[24] This drug does however suffer from the disadvantage that it is relatively expensive, making it inaccessible to many individuals and in South Africa its cost currently restricts its use to the private sector. Several flow syntheses of pyrazoles have been reported, including that of celecoxib (**27**). These processes were however, either not optimized for celecoxib (**27**) [25] or were not completely flow-based, requiring a traditional batch step to obtain **27**.[26] A straightforward, high yielding, multistep continuous flow synthesis of celecoxib (**27**), which could make this drug more affordable has not yet been reported.

An improved batch and a high yielding (90%) multistep continuous flow processes for the synthesis of celecoxib (**27**) is described. An efficient Claisen condensation to obtain the required 1,3-dicarbonyl adduct followed by cyclo-condensation with the appropriate hydrazine hydrochloride across two steps is demonstrated. The reaction conditions applied do not require the handling of intermediates, is conducted in a green solvent and has a substantially reduced reaction time when compared to the traditional batch processes. This work is the subject of a provisional patent specification which has been filed.



Scheme 7.6: Synthesis route to celecoxib (**27**).



Scheme 7.7: Equipment setup for continuous flow synthesis of celecoxib (**27**).

Future work for this project would involve investigating whether the developed reaction conditions could be applied to the synthesis of other important pyrazole moieties in high yields. This would involve combining a range of 1,3-diones with a range of aryl hydrazine hydrochlorides to generate the corresponding pyrazoles. Pyrazole moieties are key building blocks in many drug syntheses and having a more efficient synthesis could positively impact the cost of many pharmaceuticals. The development of an efficient flow synthesis of aryl hydrazines (**116**) and their corresponding hydrochlorides (**120**) would thus complement the flow synthesis of celecoxib (**27**) and other pyrazoles, making the entire process more competitive.

7.3. FINAL REMARKS

Compared to traditional batch chemistry, flow chemistry is still in its infancy and a lot of work still remains to be done when it comes to converting traditional batch syntheses and processes into continuous flow-based processes. With the knowledge gained from both the successes and the failures, this work has helped to contribute to the fields of orgaonfluorine chemistry as well as flow chemistry and its quest for more efficient, greener, quicker and safer protocols. The most notable contribution is the multistep continuous flow synthesis of celecoxib (**27**) which could potentially be used industrially to manufacture celecoxib (**27**) more efficiently and affordably, resulting in improved downstream access to this important drug to the general populous.

7.4. REFERENCES

(1) Ismail, F.M.D. *J. Fluorine Chem.*, **2002**, *118*, 27.

(2) Müller, K.; Faeh, C.; Diederich, F. *Science*, **2007**, *317*, 1881.

(3) Shah, P.; Westwell, A.D. *J. Enzyme Inhib. Med. Chem.*, **2007**, *22*, 527.

(4) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem*, **2004**, *5*, 637.

(5) Turnbull, M.D.; Carter, N.B.; Dennison, S.; Deacon, J.; Holley, R. *Chimia*, **2004**, *58*, 159.

(6) Hagmann, W.K. *J. Med. Chem.*, **2008**, *51*, 4359.

(7) Ley, S.V.; Baxendale, I.R. *Nat. Rev.*, **2002**, *1*, 573.

(8) Baxendale, I.R.; Ley, S.V. Solid Supported Reagents in Multi-Step Flow Synthesis. New Avenues to Efficient Chemical Synthesis: Emerging Technologies. Ernst Schering Foundation Symposium Proceedings 2006-3, Eds P.H. Seeberger, T. Blume, Springer-Verlag: Berlin, Heidelburg, **2007**, Chapter 3, pp 151-185.

(9) Vermes, A.; Guchelaar, H.-J.; Dankert, J. *J. Antimicrob. Chemother.*, **2000**, *46*, 171.

(10) Harsanyi, A.; Conte, A.; Pichon, L.; Rabion, A.; Grenier, S.; Sandford, G. *Org. Process Res. Dev.*, **2017**, *21*, 273.

(11) Motorin, Y.; Seidu-Larry, S.; Helm, M. DNA and RNA Pyrimidine Nucleobase Alkylation at the Carbon – 5 Position, Chapter in DNA Methyltransferases - Role and Function, Advances in Experimental Medicine and Biology 945, Jeltsch, A.; Jurkowska, RZ. (eds.), Springer International Publishing, Switzerland, **2016**, pp 19 – 33.

(12) (a) Bargigia, G; Tortelli, V; Tonelli, C. Process for the synthesis of hexafluorobutadiene and of higher perfluorinated dienes. European patent no: 0205892 A1, Dec 1986. (b) Zhu, J.; Chen, S.; Wang, B.; Zhang, X. Int. J. Org. Chem., 2014, 4, 331.

(13) Miki, J; Yoshimi, H; Aoyama, H. Process for production of perfluoroalkadienes. European patent no: 1247791 A1, Oct 2002.

(14) Ramachandran, P.V.; Reddy, G.V. J. Fluorine Chem., 2008, 129, 443.

(15) Ram, R.N.; Singh, V. *J. Chem. Res.*, **2006**, 800.

(16) Mohamed, A.A.; Salmi, Z.; Dahoumane, S.A.; Mekki, A.; Carbonnier, B.; Chehimi, M.M. Adv. Colloid Interface Sci., 2015, 225, 16.

(17) Mo, F.; Dong, G.; Zhang, Y.; Wang, J. Org. Biomol. Chem., 2013, 11, 1582.

(18) Harrak, Y.; Romero, M.; Constans, P.; Pujol, M.D. Lett. Org. Chem., 2006, 3, 29.

(19) Bredihhin, A.; Groth, U.M.; Mäeorg, U. Org. Lett., 2007, 9, 1097.

(20) Ragnarsson, U. Chem. Soc. Rev., 2001, 30, 205.

(21) Li, B.; Widlicka, D.; Boucher, S.; Hayward, C.; Lucas, J.; Murray, J.C.; O'Neil, B.T.; Pfisterer, D.; Samp, L.; VanAlsten, J.; Xiang, Y.; Young, J. Org. Process Res. Dev., 2012, 16, 2031.

(22) Hutchins, R.O.; Natale, N.R.; Taffer, I.M. *J.C.S. Chem. Comm.*, **1978**, 1088.

(23) Bandgar, B.P.; Uppalla, L.S. *J. Chem. Res.*, **1999**, 714.

(24) Gaulier, S.M.; McKay, R. and Swain, N.A. Tetrahedron Lett., 2011, 52, 6000.

(25) Poh, J-S.; Browne, D.L. and Ley, S.V. React. Chem. Eng., 2016, 1, 101.

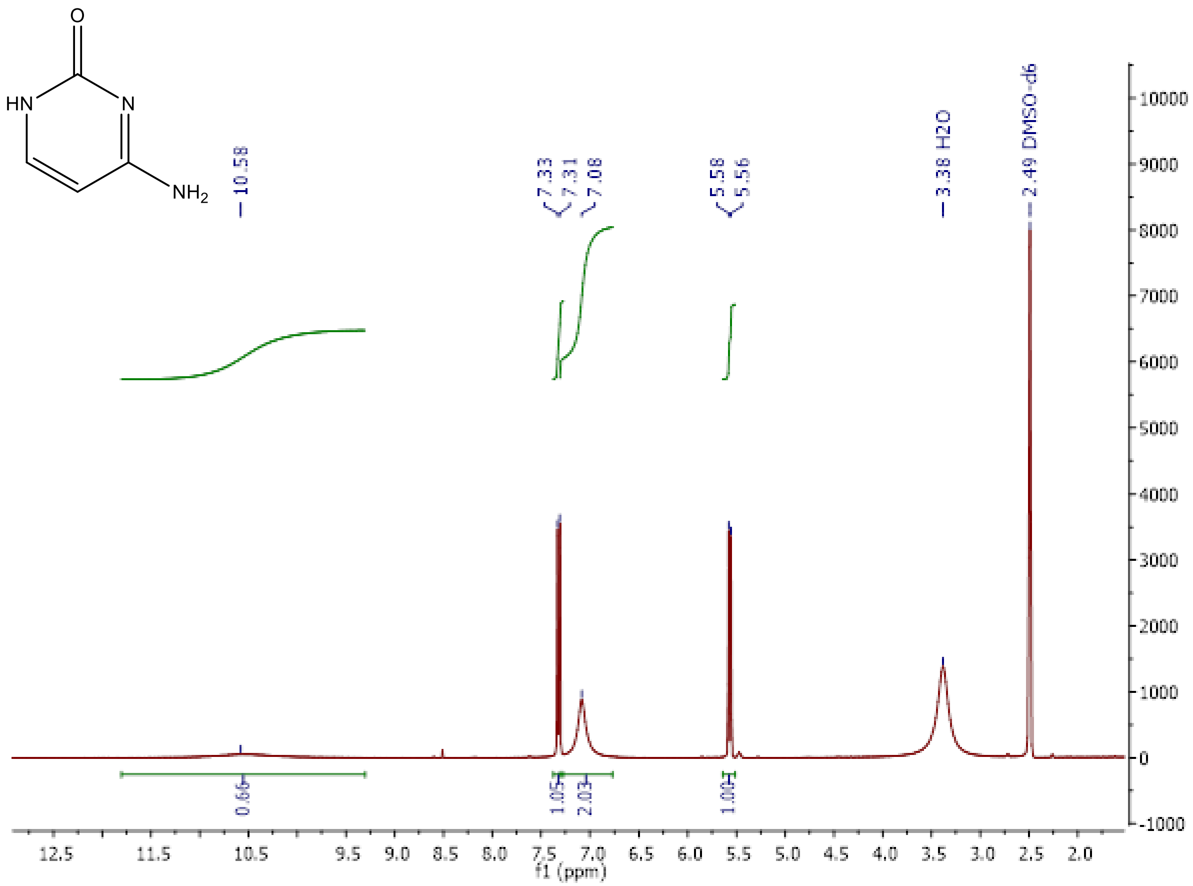
(26) Britton, J.; Jamison, T.F. Eur. J. Org. Chem., 2017, 44, 6566.

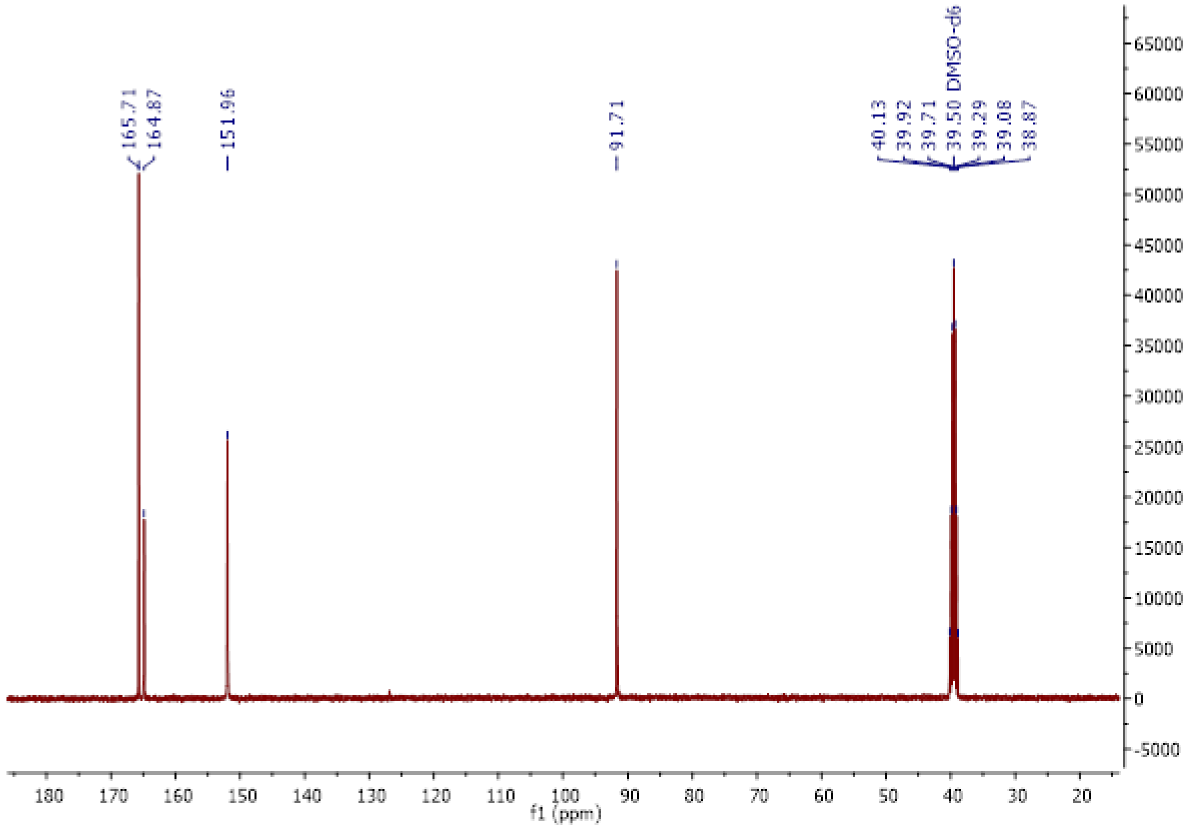
Chapter 8:

Appendix

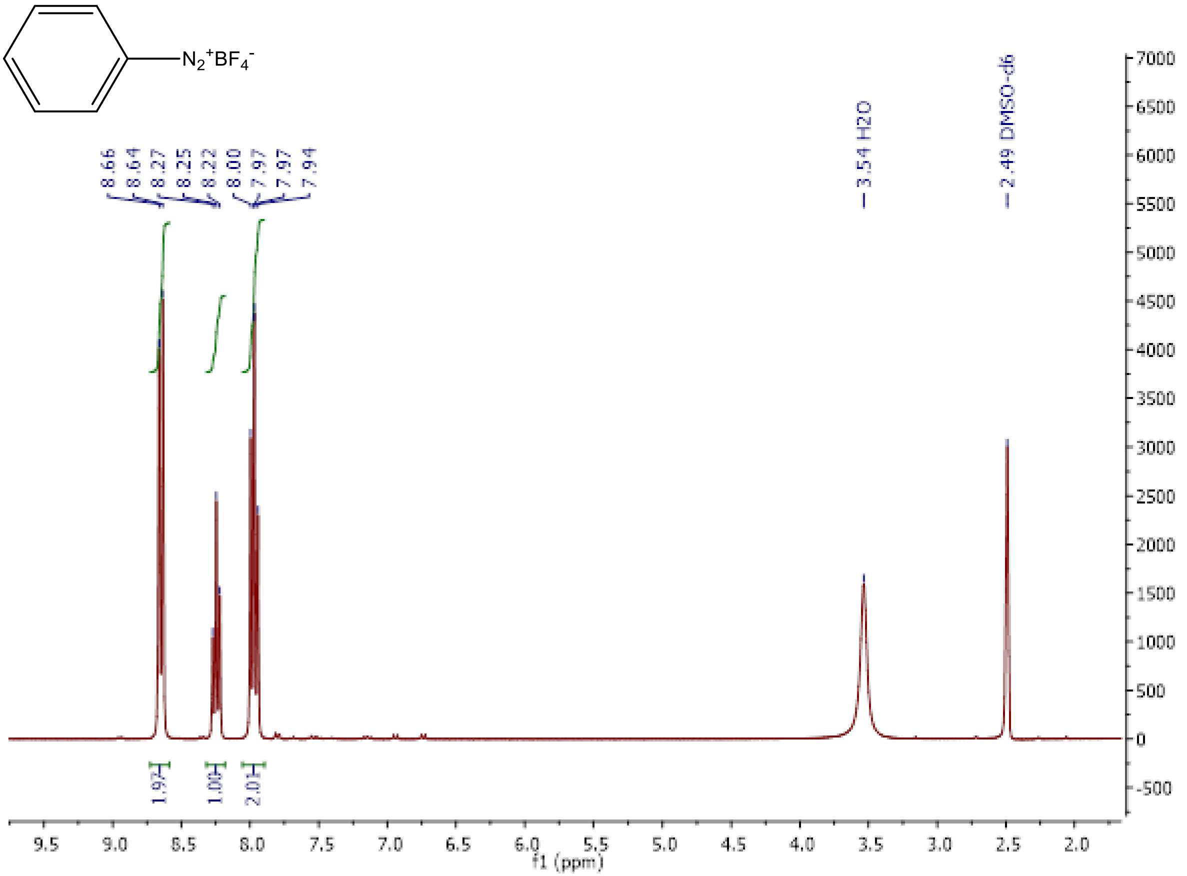
8.1. Selected ^{1}H, ^{13}C, and ^{19}F NMR spectra

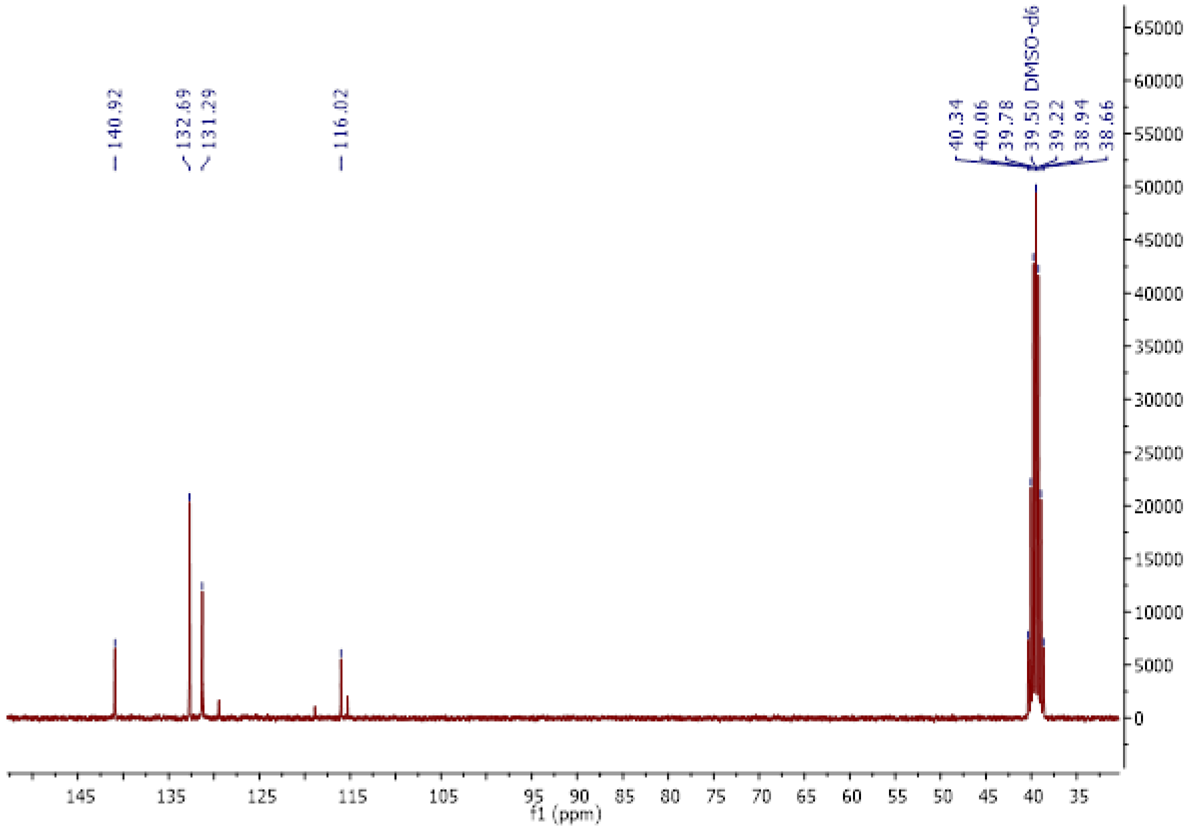
8.1.1. **Chapter 2:** Cytosine (**97**)

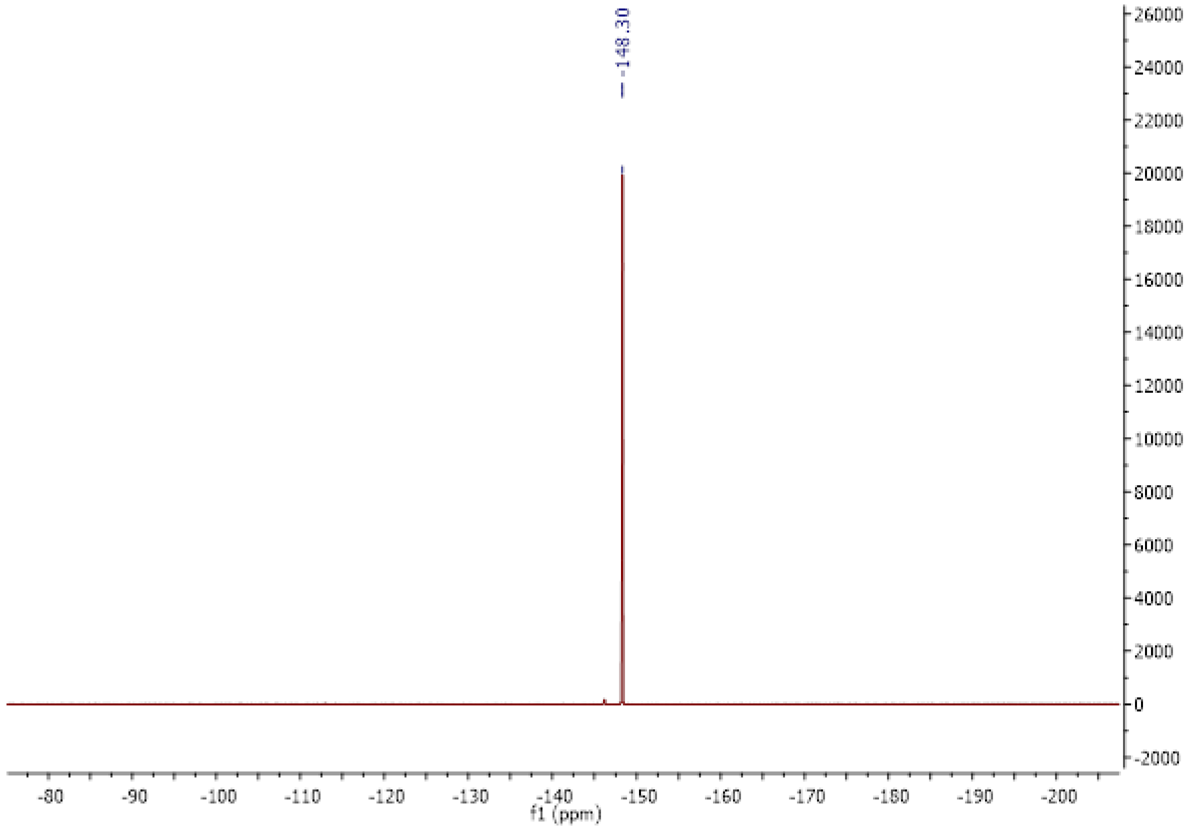




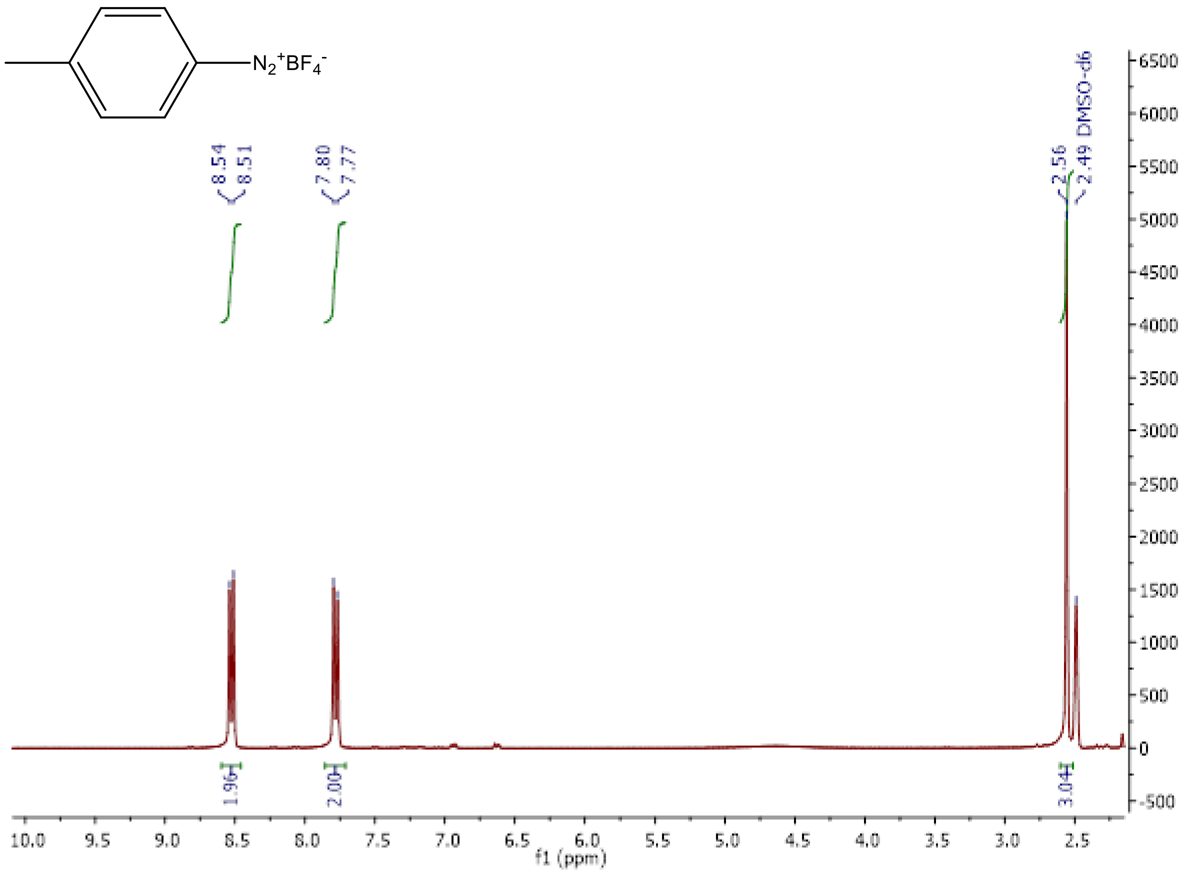
8.1.2. **Chapter 4:** Benzenediazonium tetrafluoroborate (**113a**)

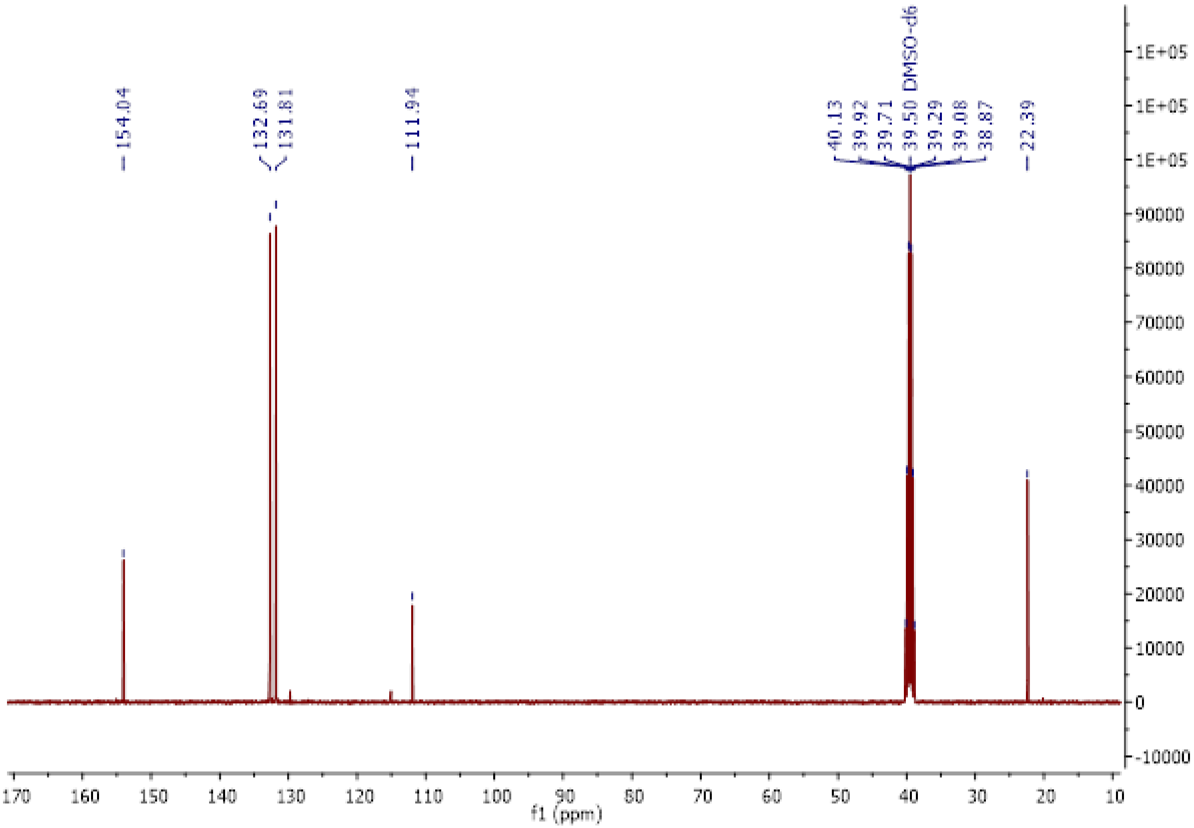






8.1.3. **Chapter 4:** 4-methylbenzenediazonium tetrafluoroborate (**113b**)

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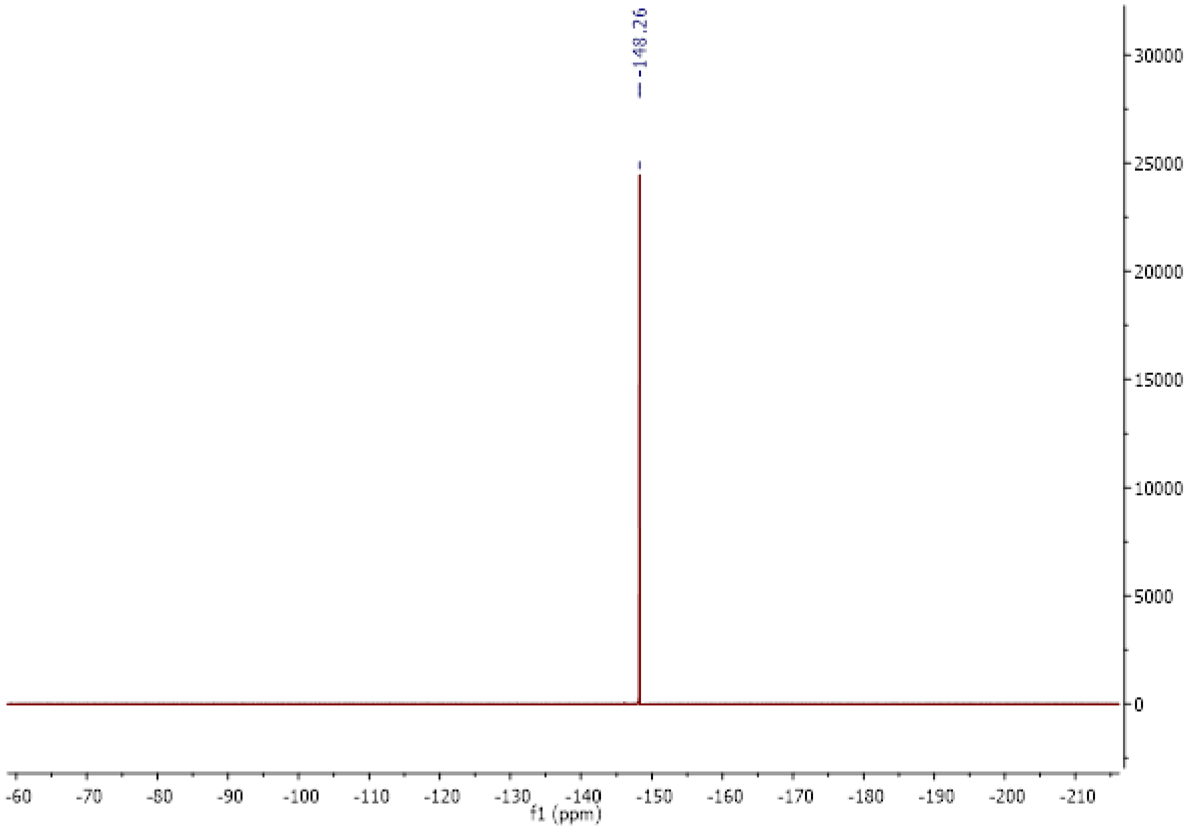
132.69
131.81
111.94
40.13
39.92
39.71
39.50 DMSO-d6
39.29
39.08
38.87
22.39
1E+05
1E+05
1E+05
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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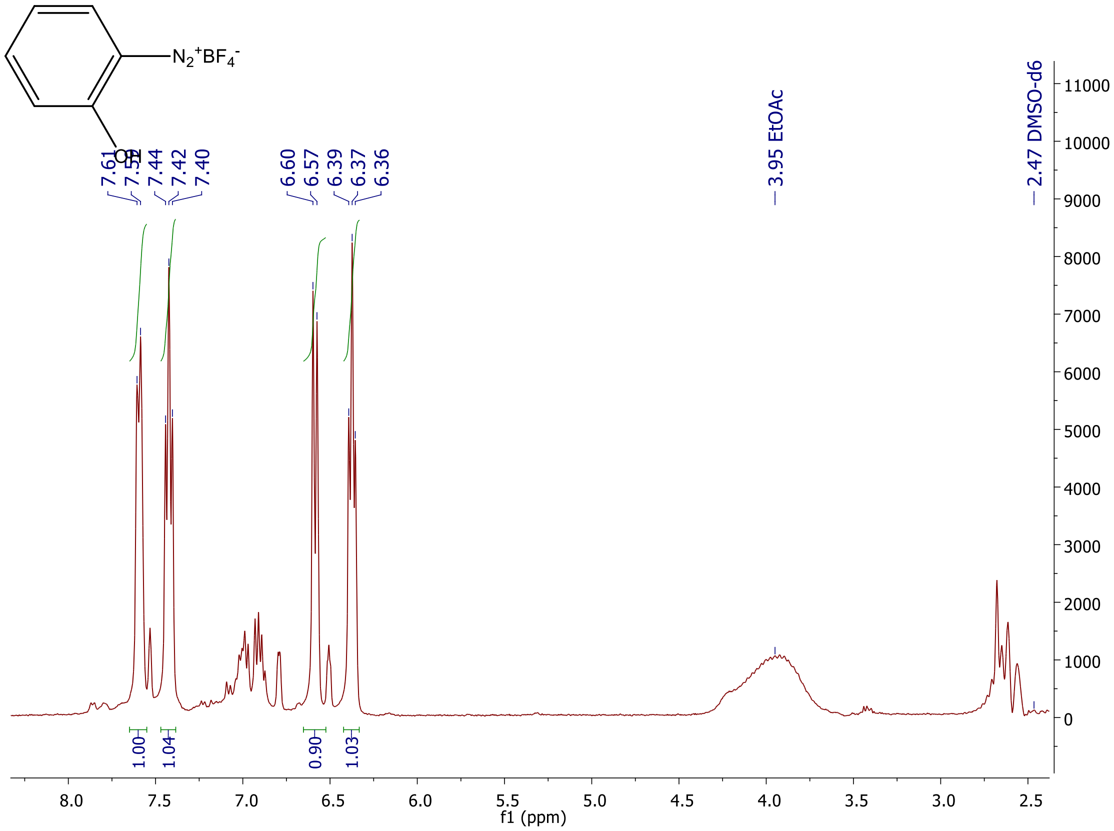
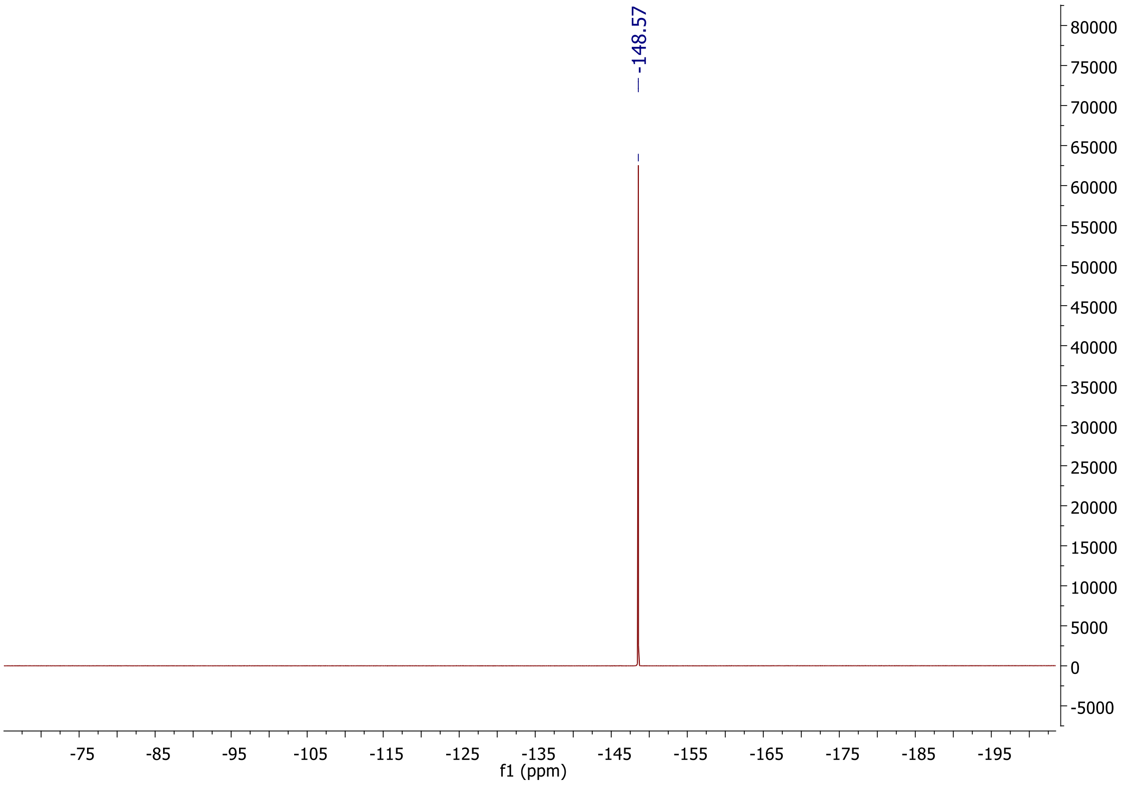
30000
25000
20000
15000
10000
5000
0
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

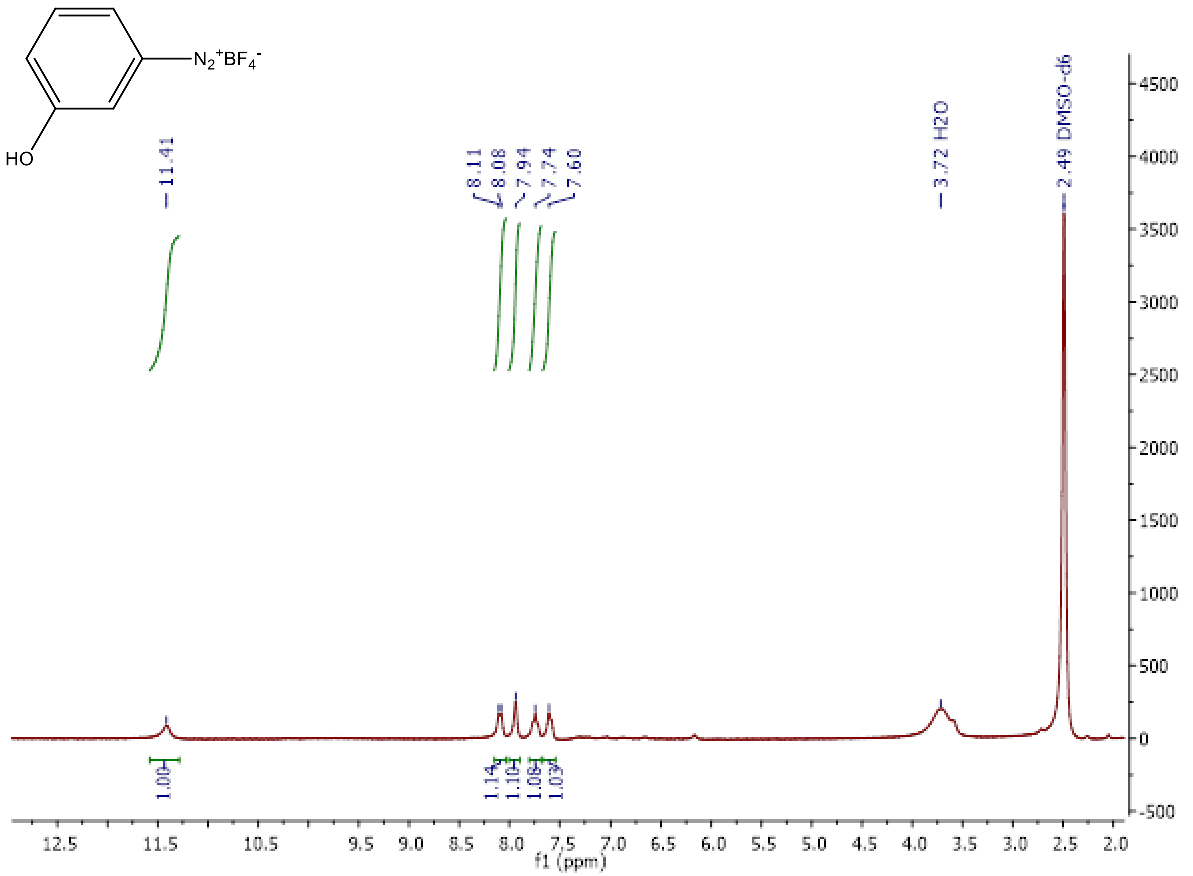
8.1.4. **Chapter 4:** 2-hydroxybenzenediazonium tetrafluoroborate (**113c**)

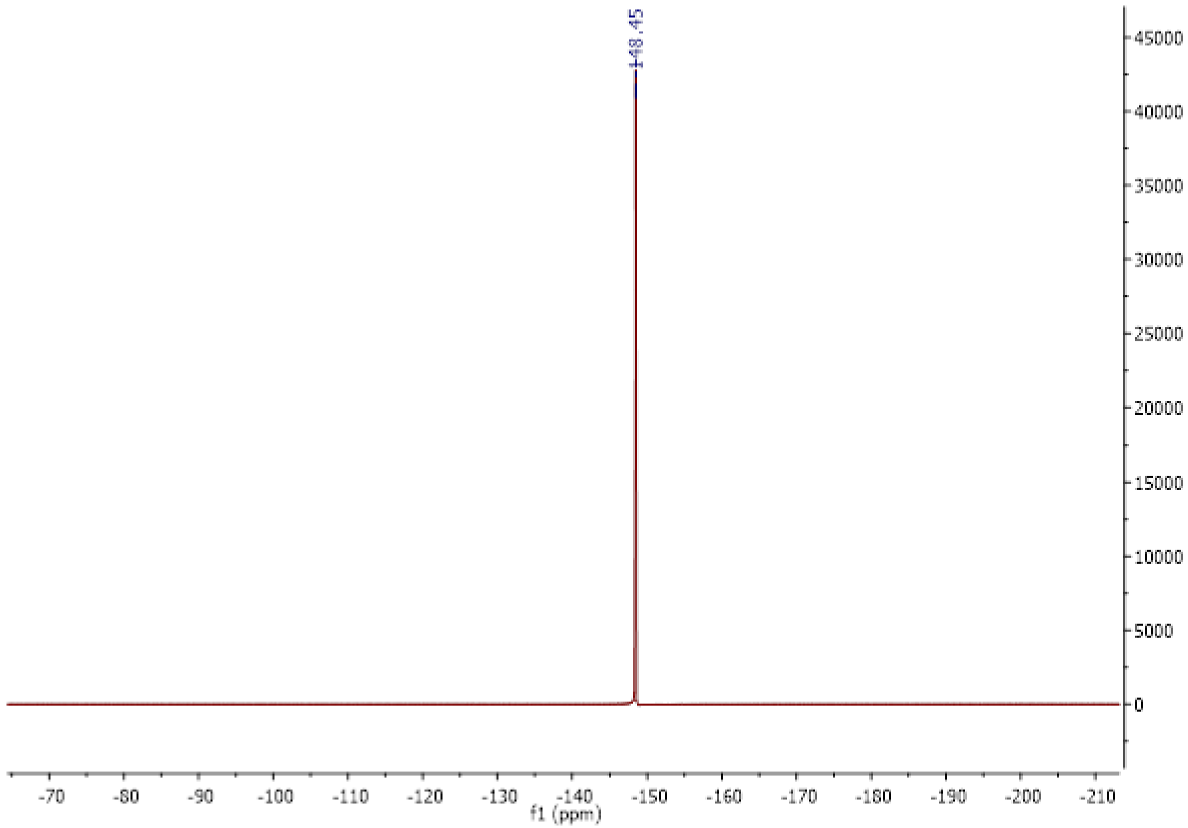




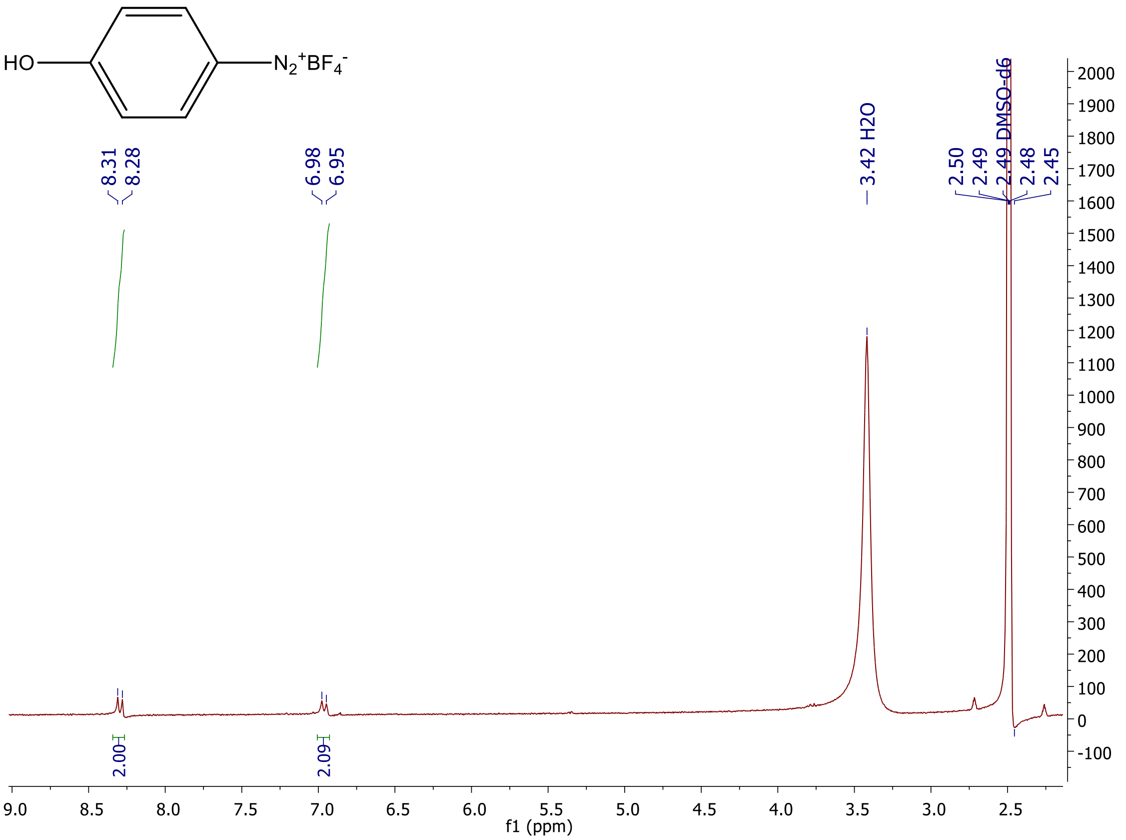
[*] Sample was poorly soluble in DMSO-d_6 and exhibited rapid decomposition in solution.

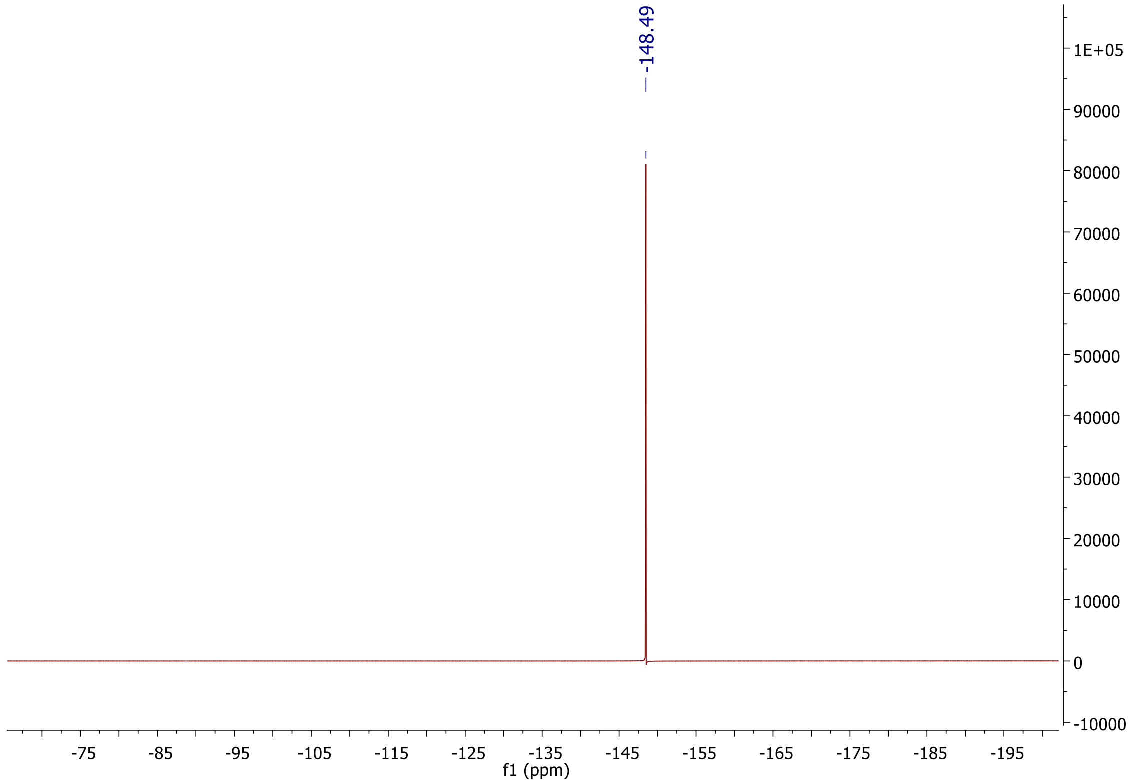
8.1.5. **Chapter 4:** 3-hydroxybenzenediazonium tetrafluoroborate (**113d**)





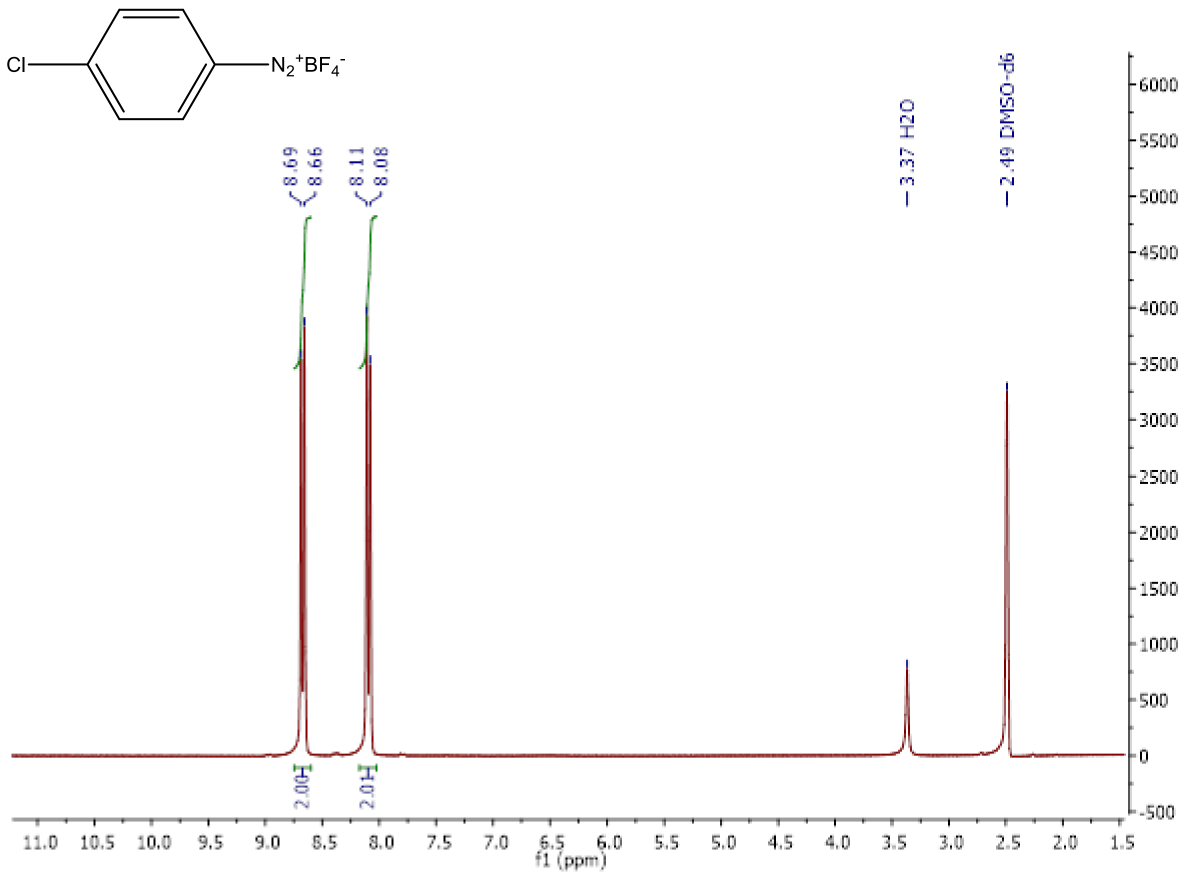
8.1.6. **Chapter 4:** 4-hydroxybenzenediazonium tetrafluoroborate (**113e**)

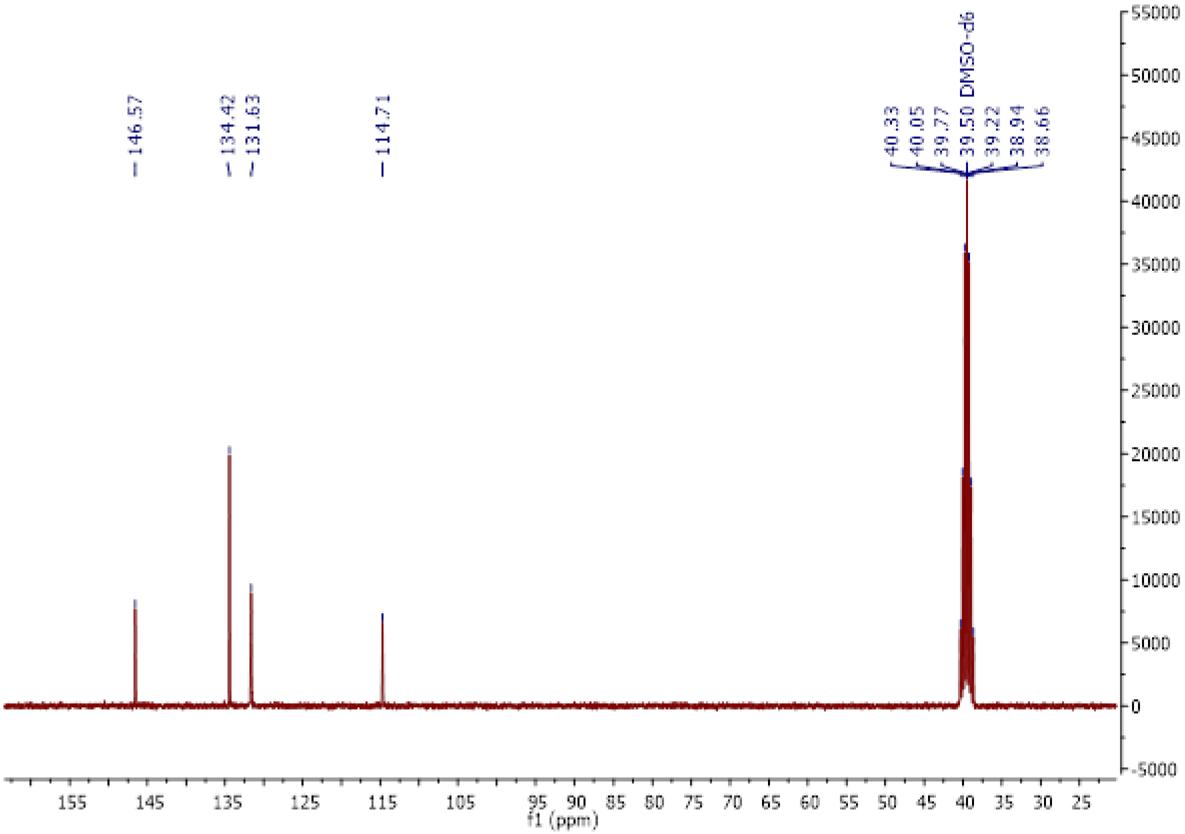


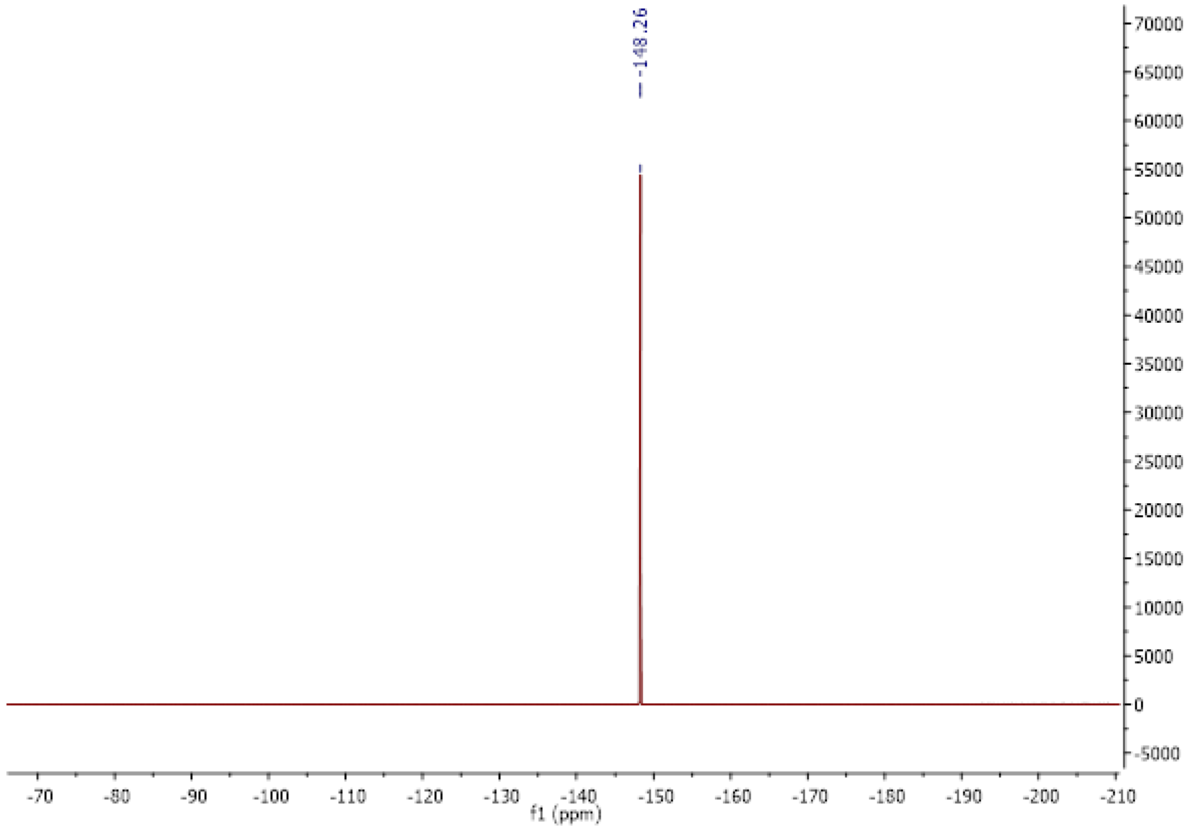


*Sample was poorly soluble in DMSO-d_6 and exhibited rapid decomposition in solution.

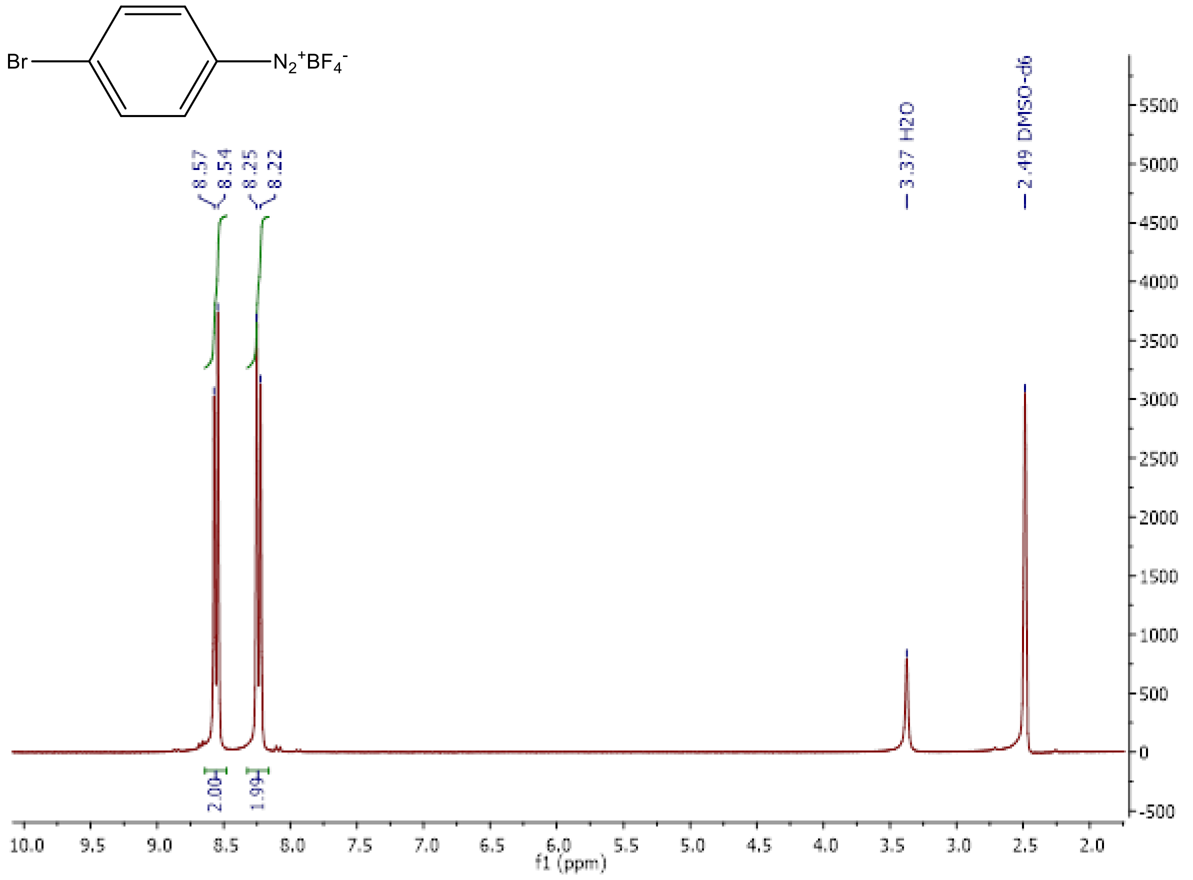
8.1.7. **Chapter 4:** 4-chlorobenzenediazonium tetrafluoroborate (**113f**)

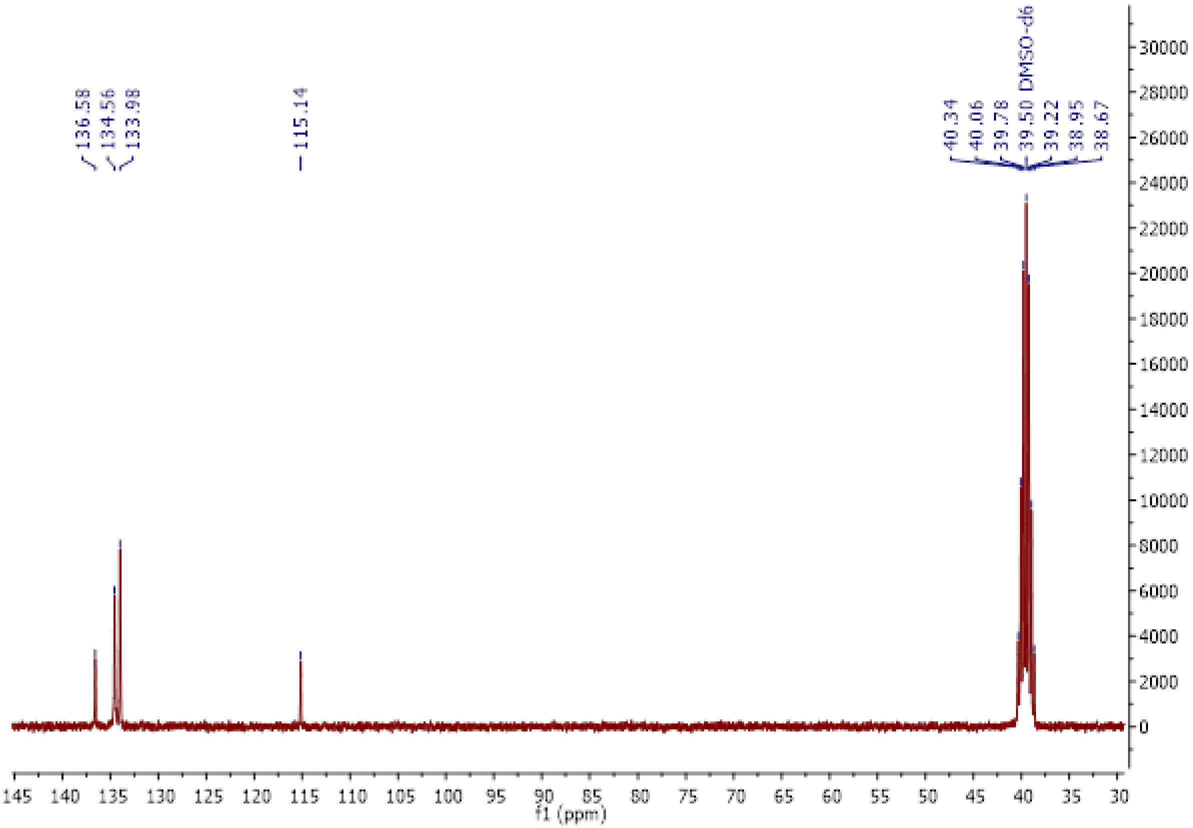






8.1.8. **Chapter 4:** 4-bromobenzenediazonium tetrafluoroborate (**113g**)

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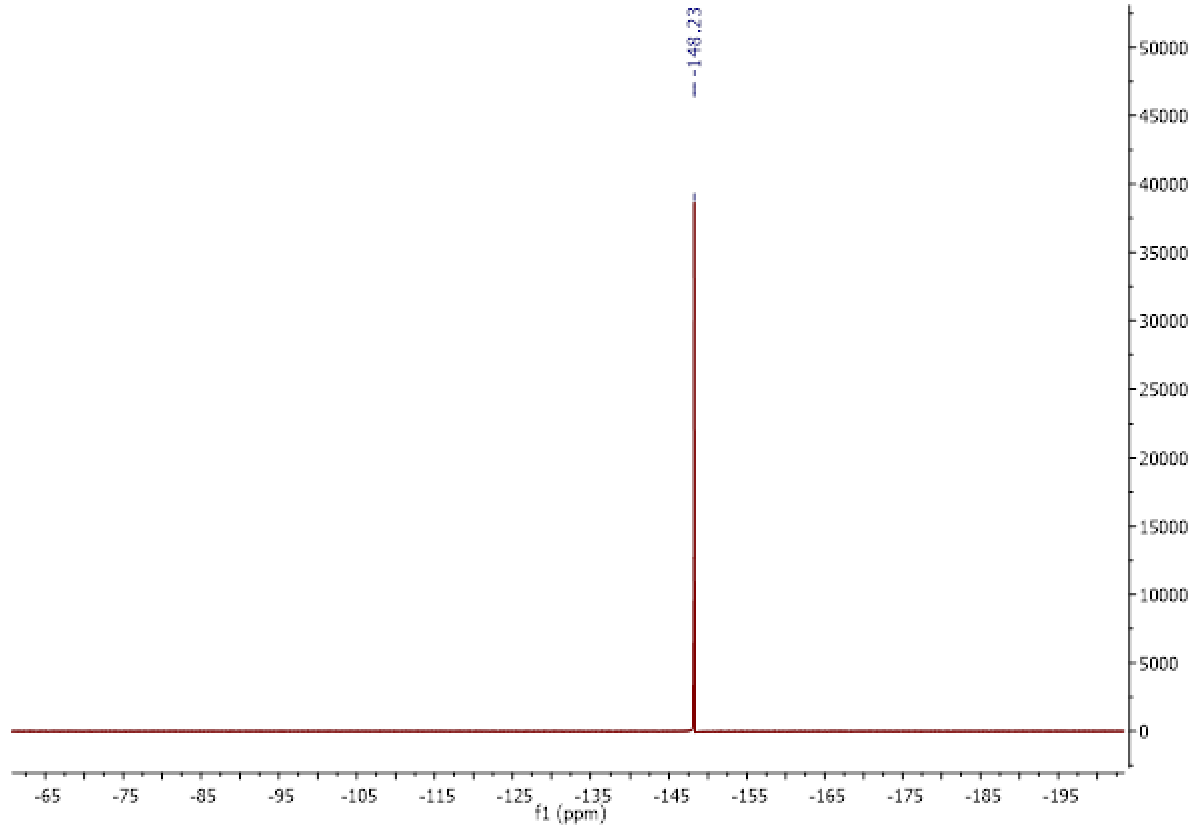
133.98
115.14
40.34
40.06
39.78
39.50 DMSO-d6
39.22
38.95
38.67
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30
f1 (ppm)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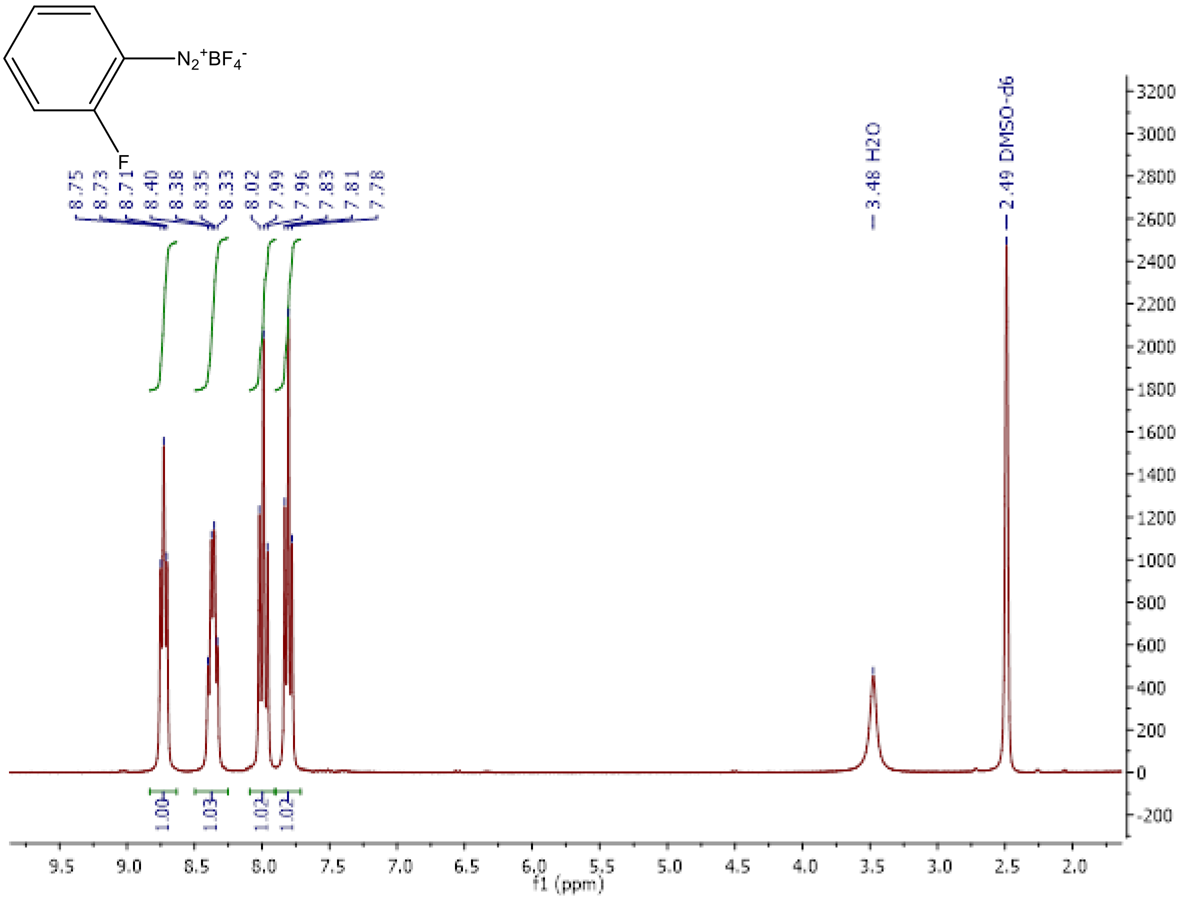
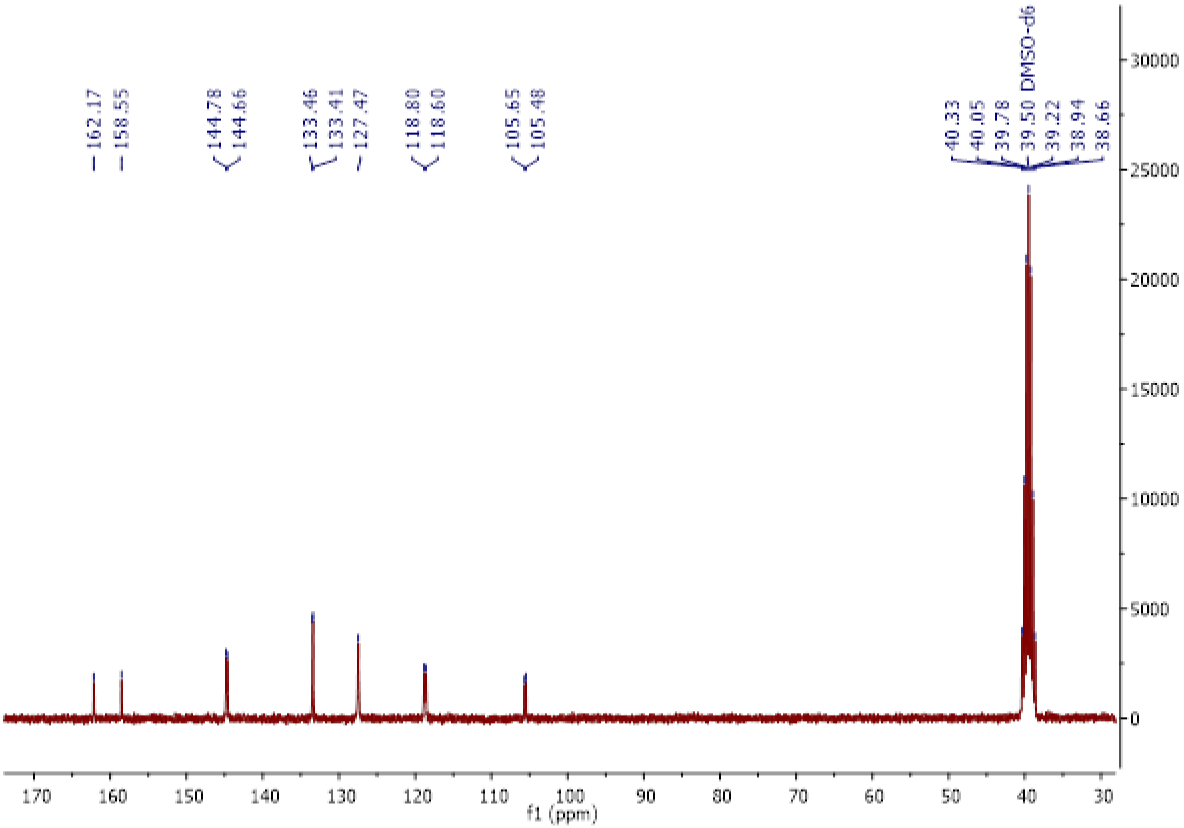
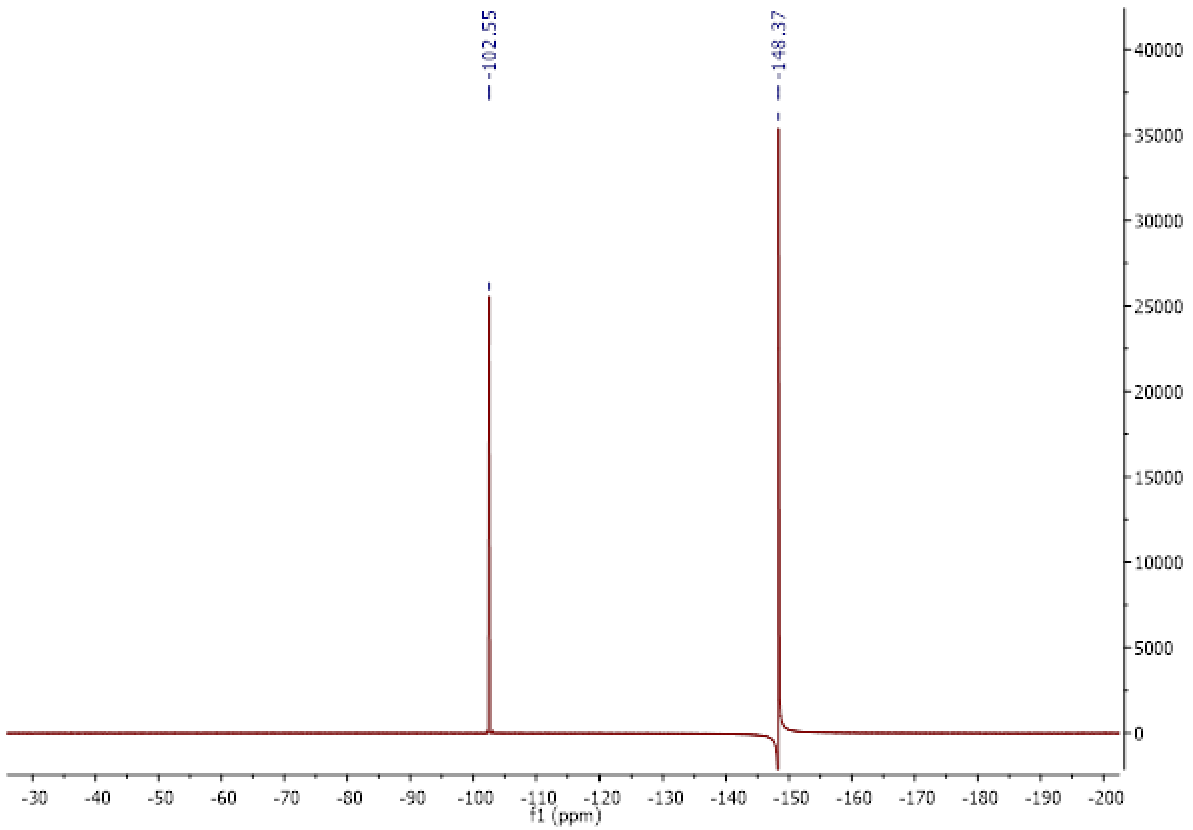
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-65 -75 -85 -95 -105 -115 -125 -135 -145 -155 -165 -175 -185 -195
f1 (ppm)

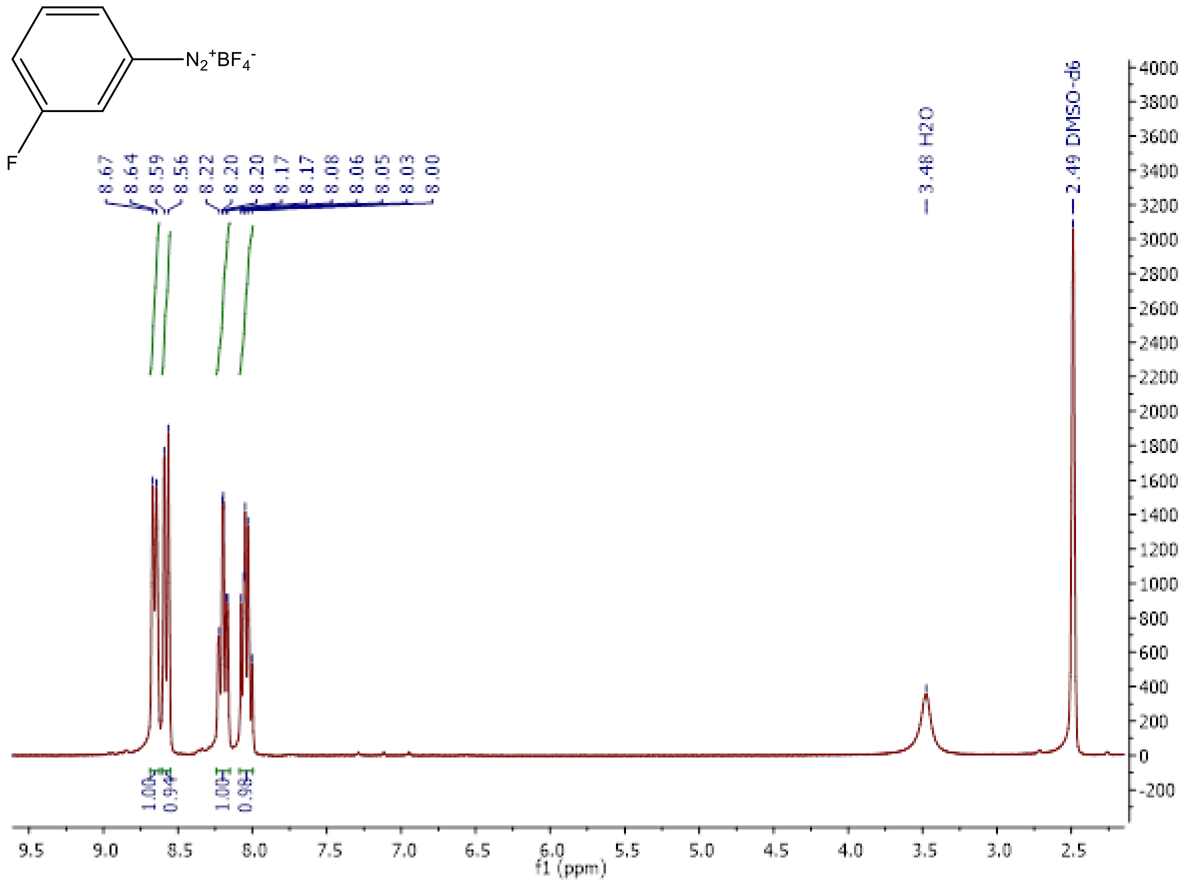
8.1.9. **Chapter 4:** 2-fluorobenzenediazonium tetrafluoroborate (**113h**)

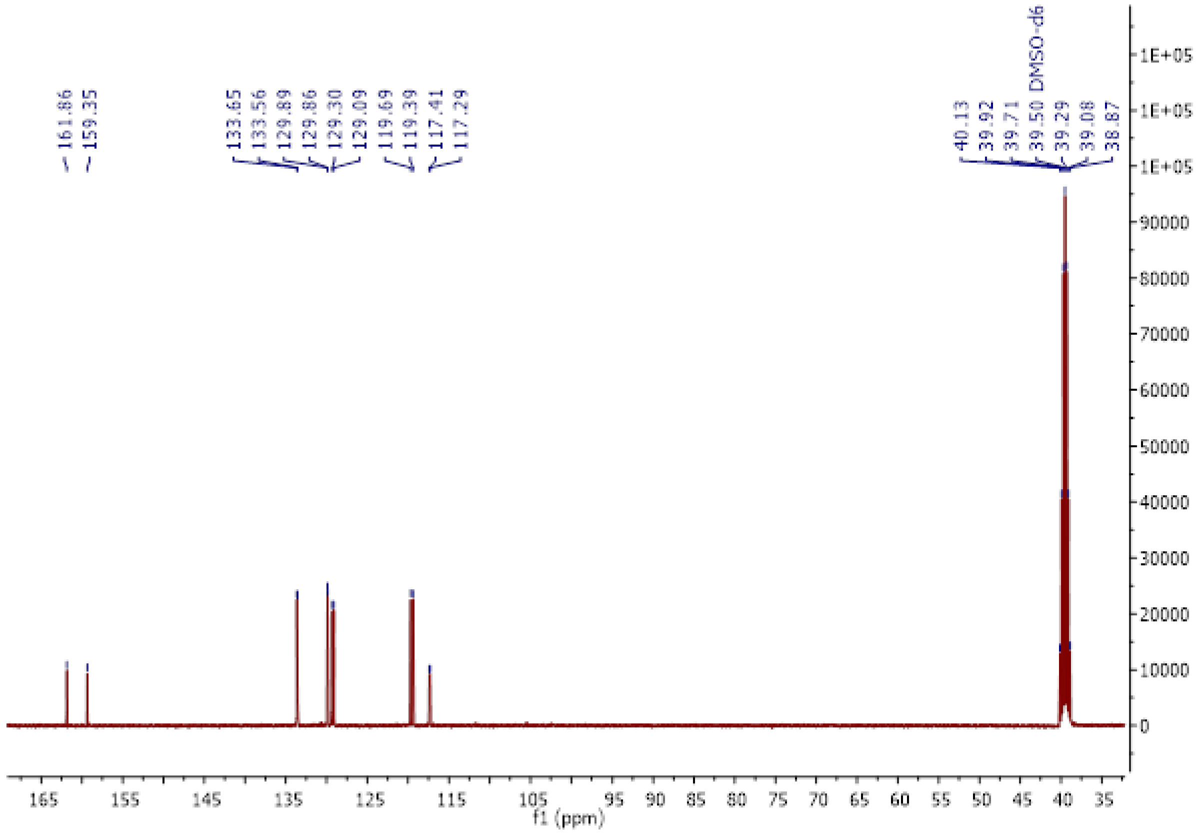






8.1.10. **Chapter 4:** 3-fluorobenzenediazonium tetrafluoroborate (**113i**)

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129.09
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119.39
117.41
117.29
40.13
39.92
39.71
39.50 DMSO-d6
39.29
39.08
38.87
1E+05
1E+05
1E+05
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80000
70000
60000
50000
40000
30000
20000
10000
0
165
155
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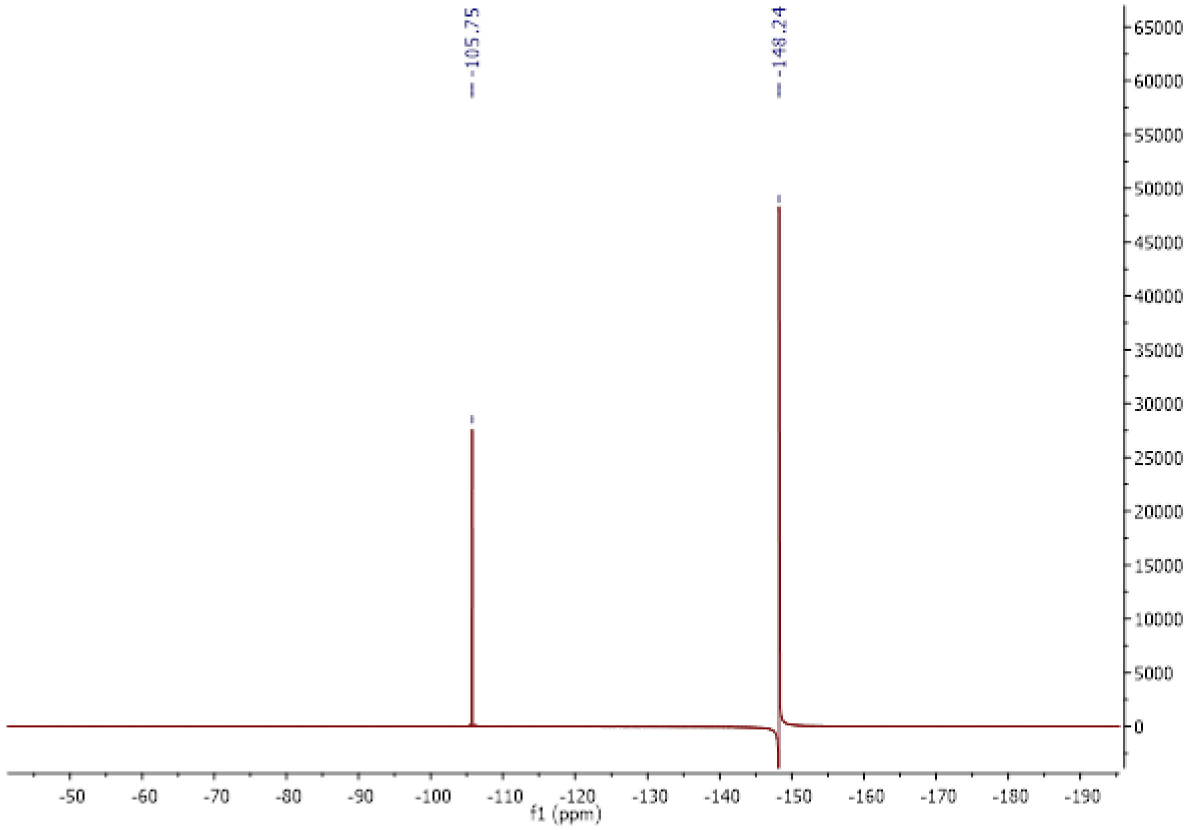
60
55
50
45
40
35
f1 (ppm)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-60
-70
-80
-90
-100
-110
-120
-130
-140
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-170
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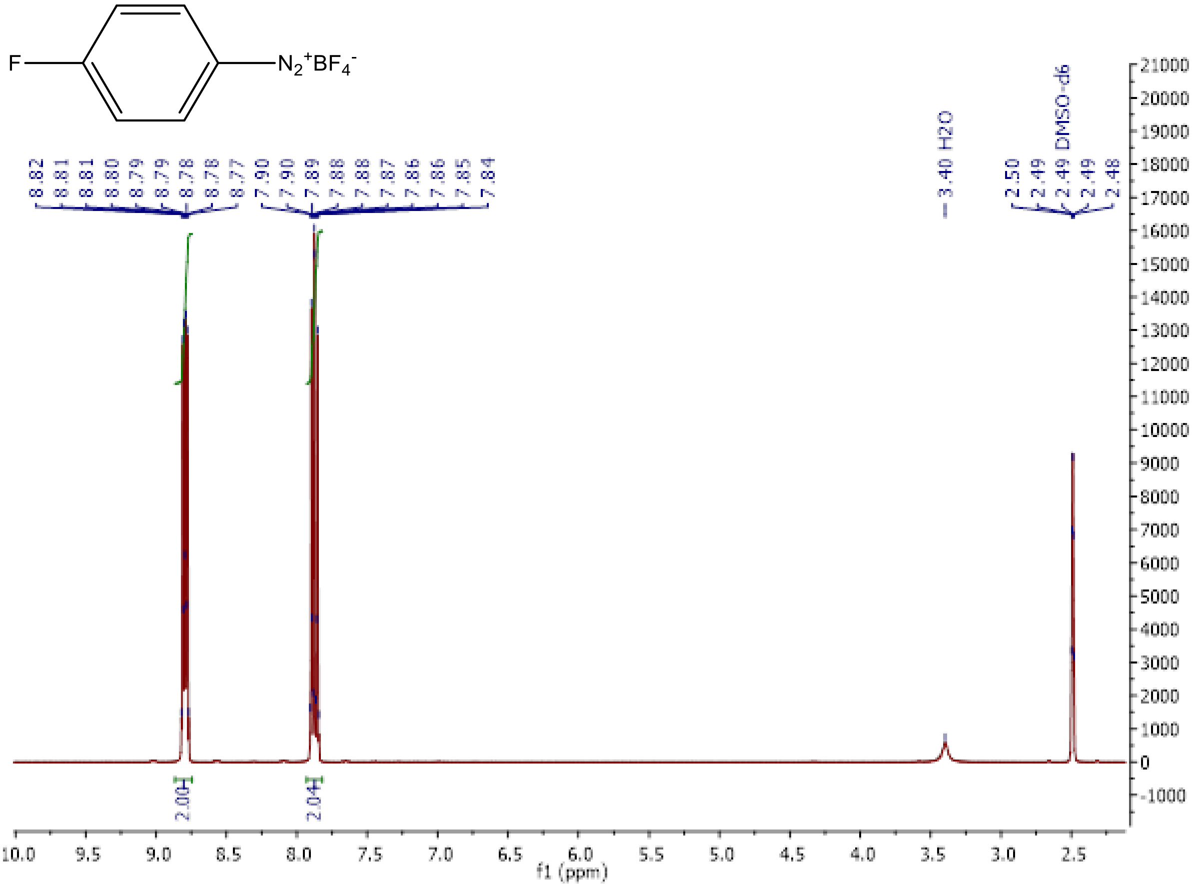
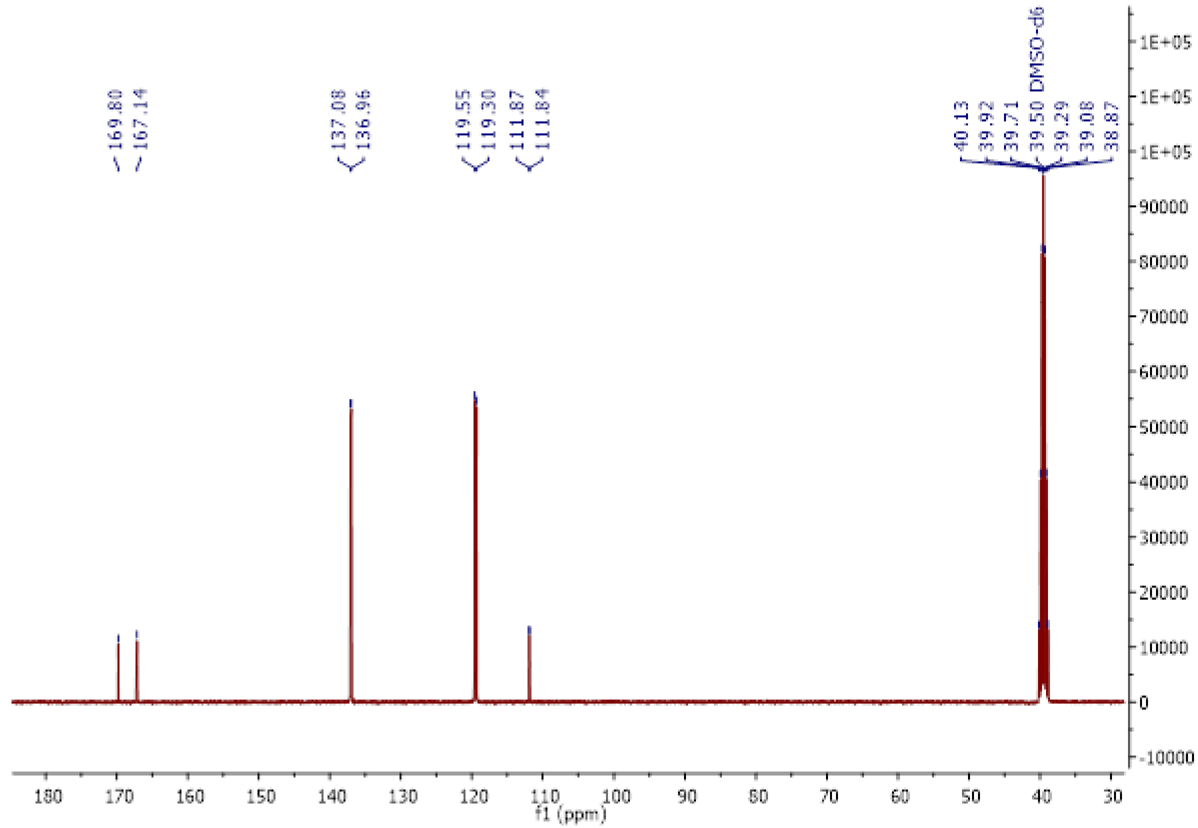
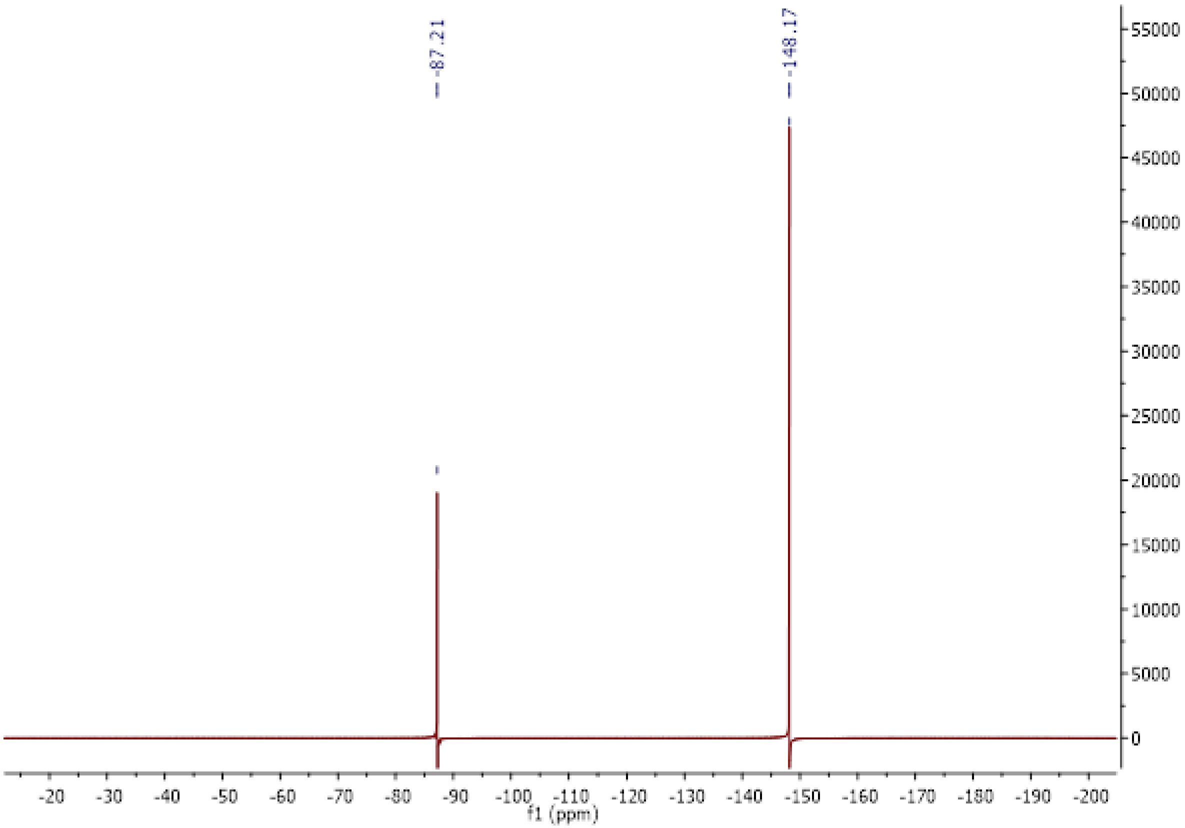
f1 (ppm)

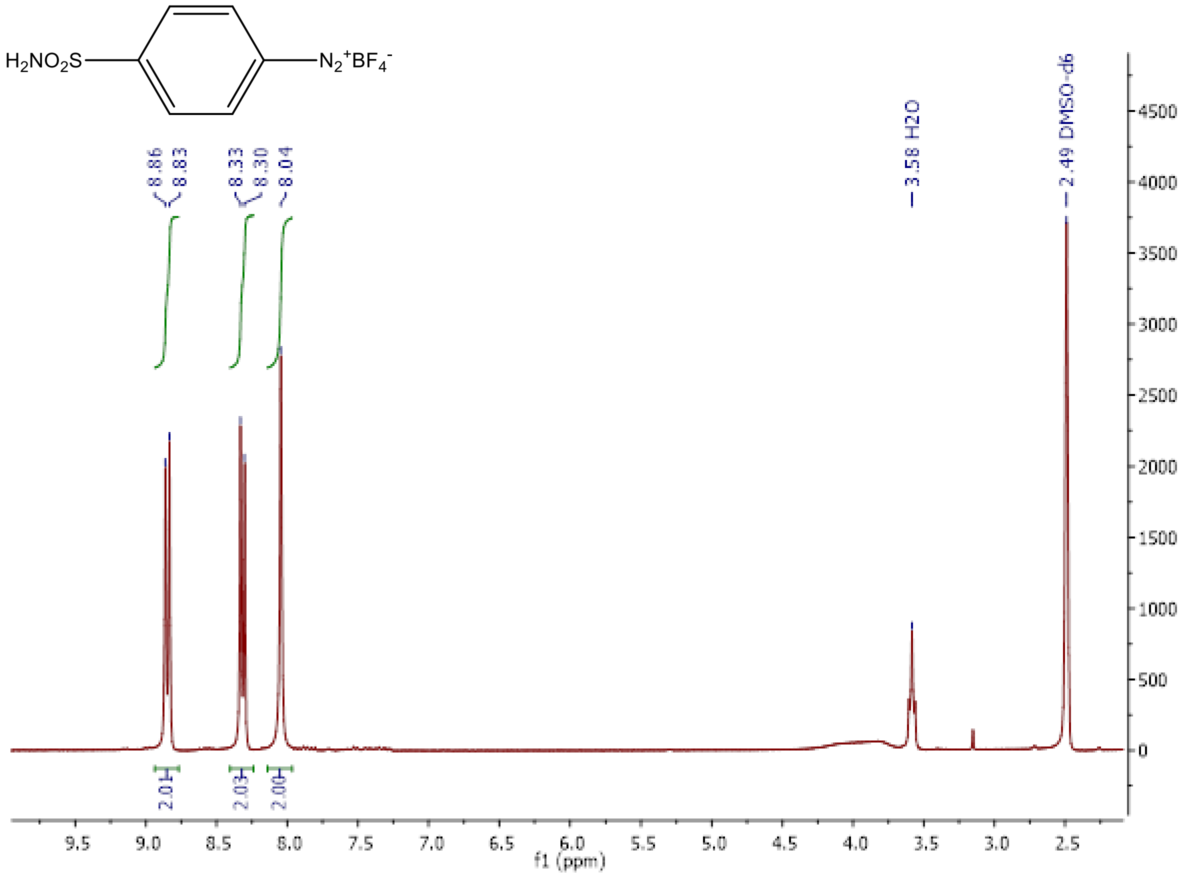
8.1.11. **Chapter 4:** 4-fluorobenzenediazonium tetrafluoroborate (**113j**)

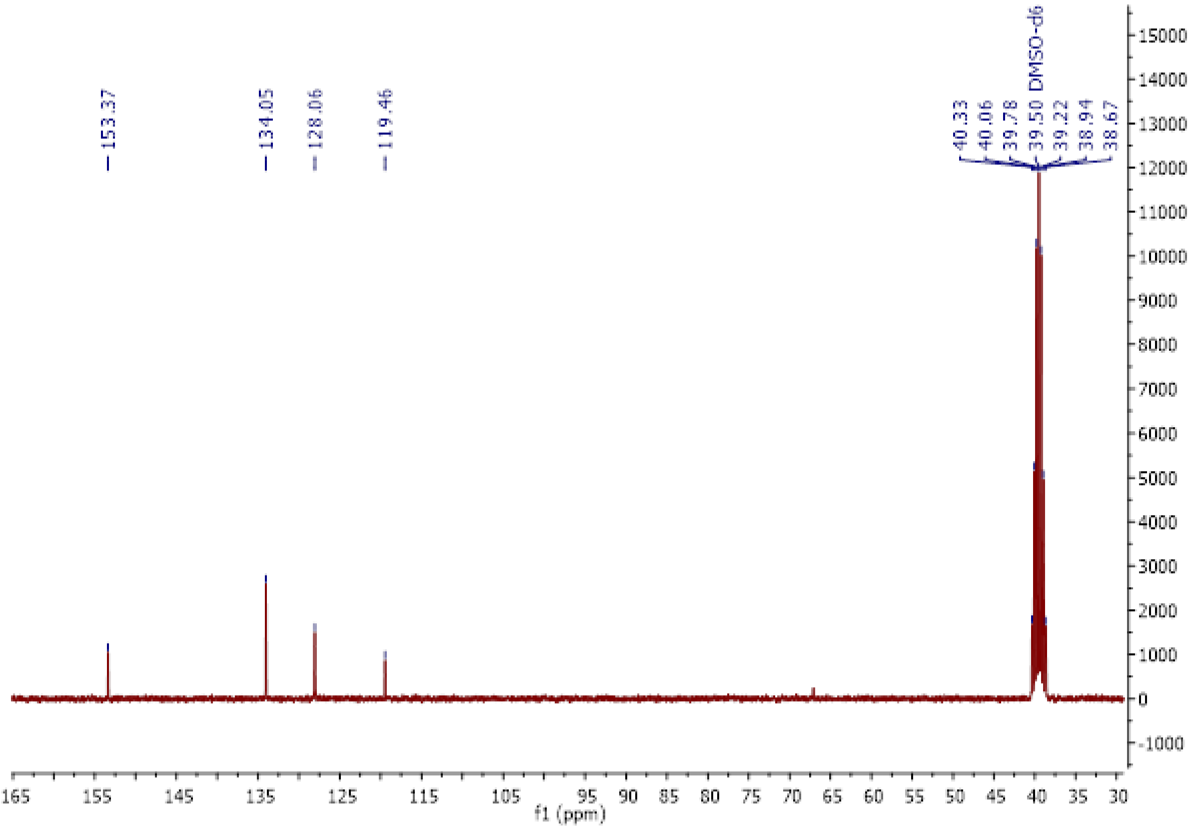






8.1.12. **Chapter 4:** 4-sulfamoylbenzenediazonium tetrafluoroborate (**113k**)

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38.94
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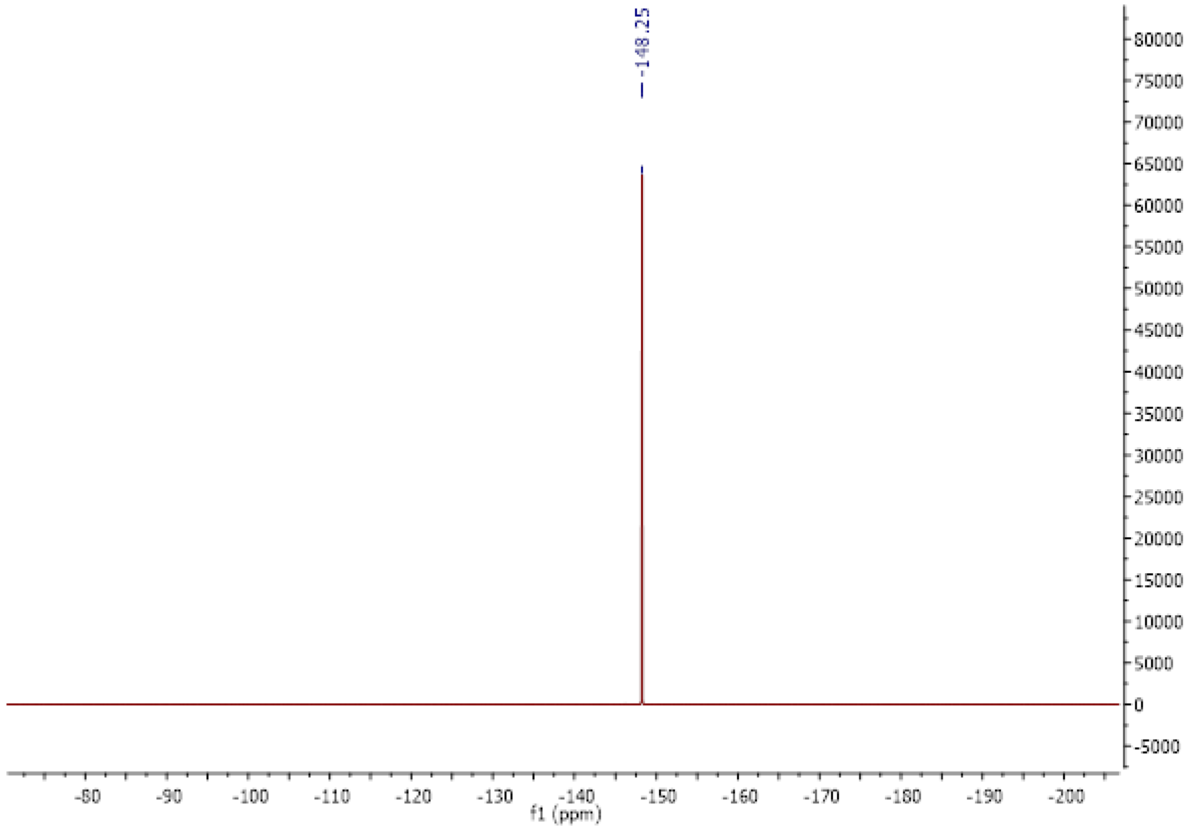
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
165
155
145
135
125
115
105
95
90
85
80
75
70
65
60
55
50
45
40
35
30
f1 (ppm)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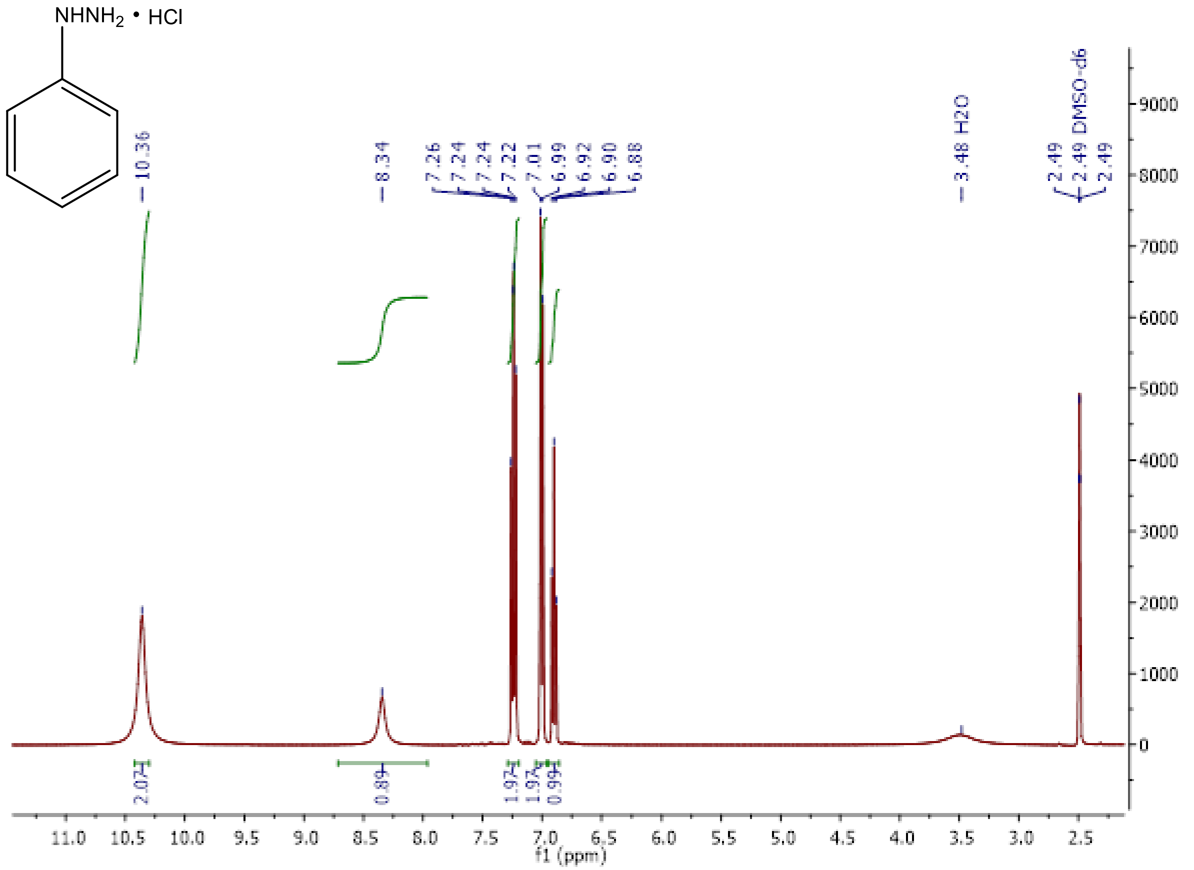
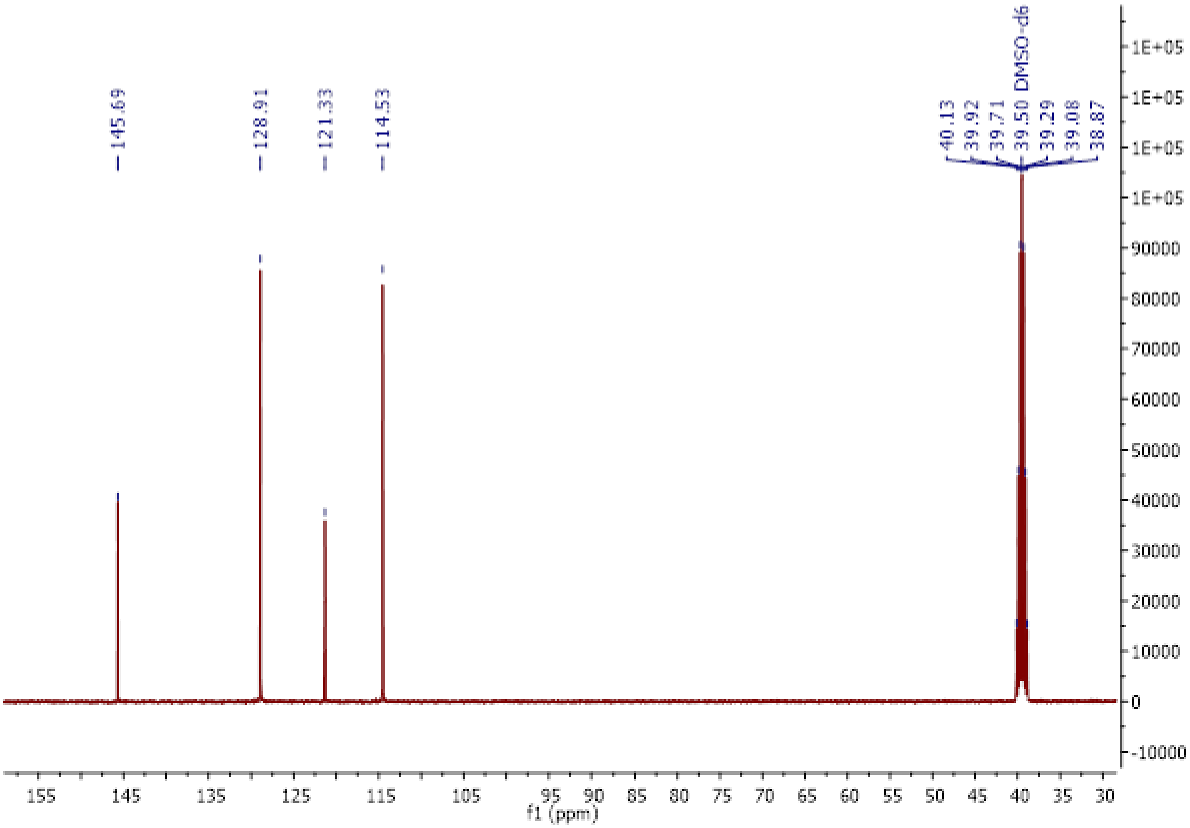
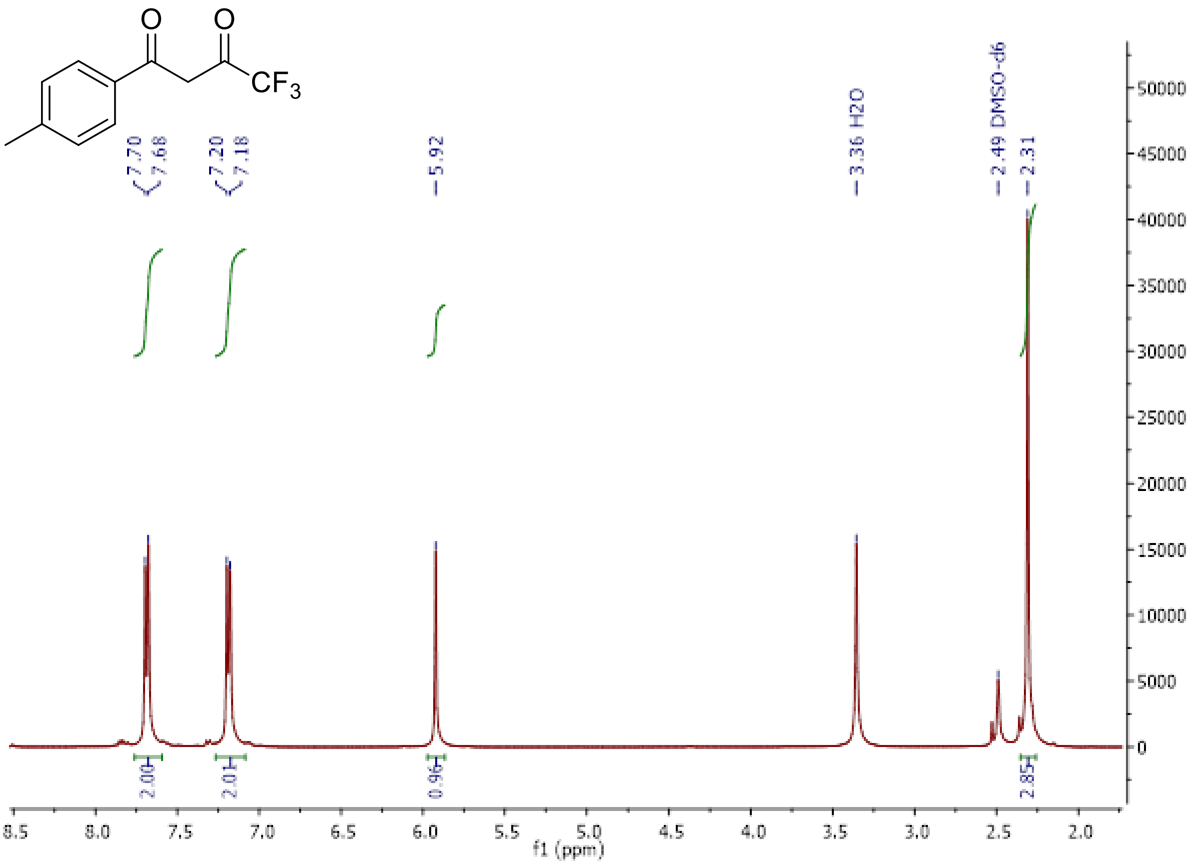
10000
5000
0
-5000
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

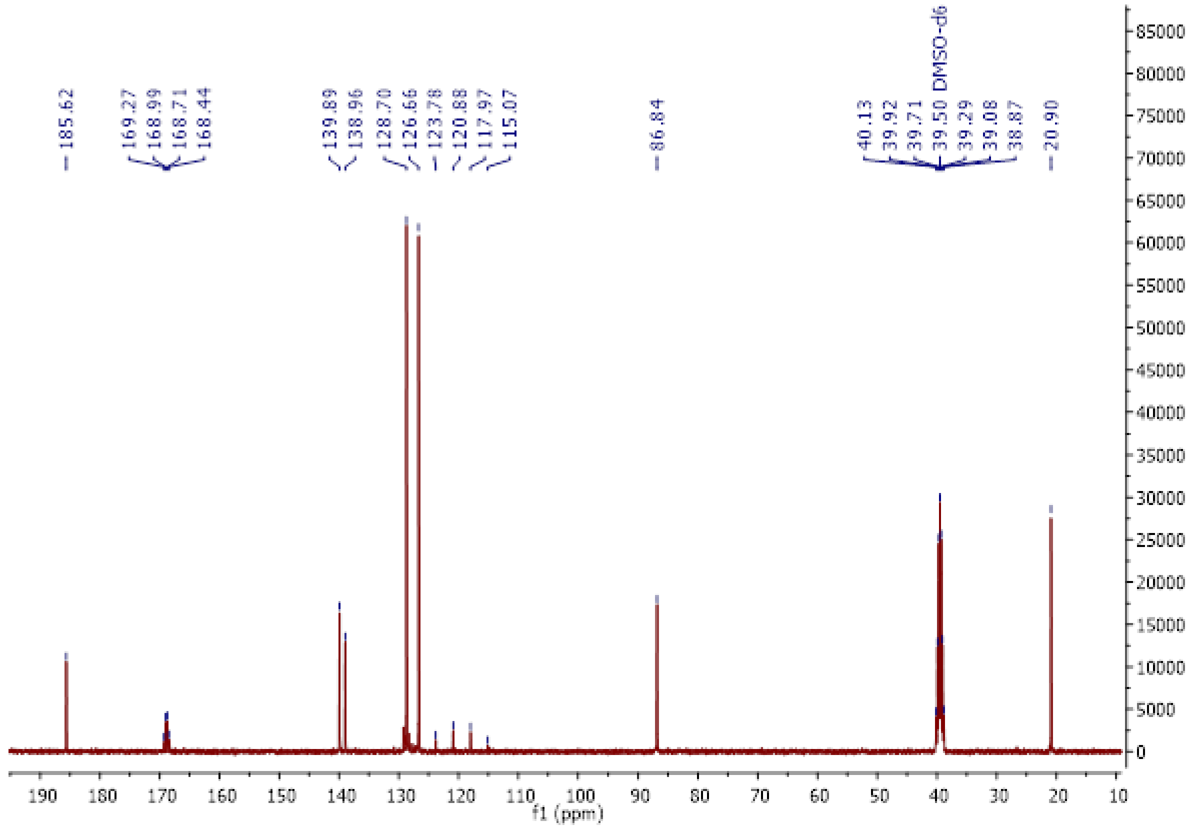
8.1.13. **Chapter 5:** Phenylhydrazine hydrochloride (**125**)

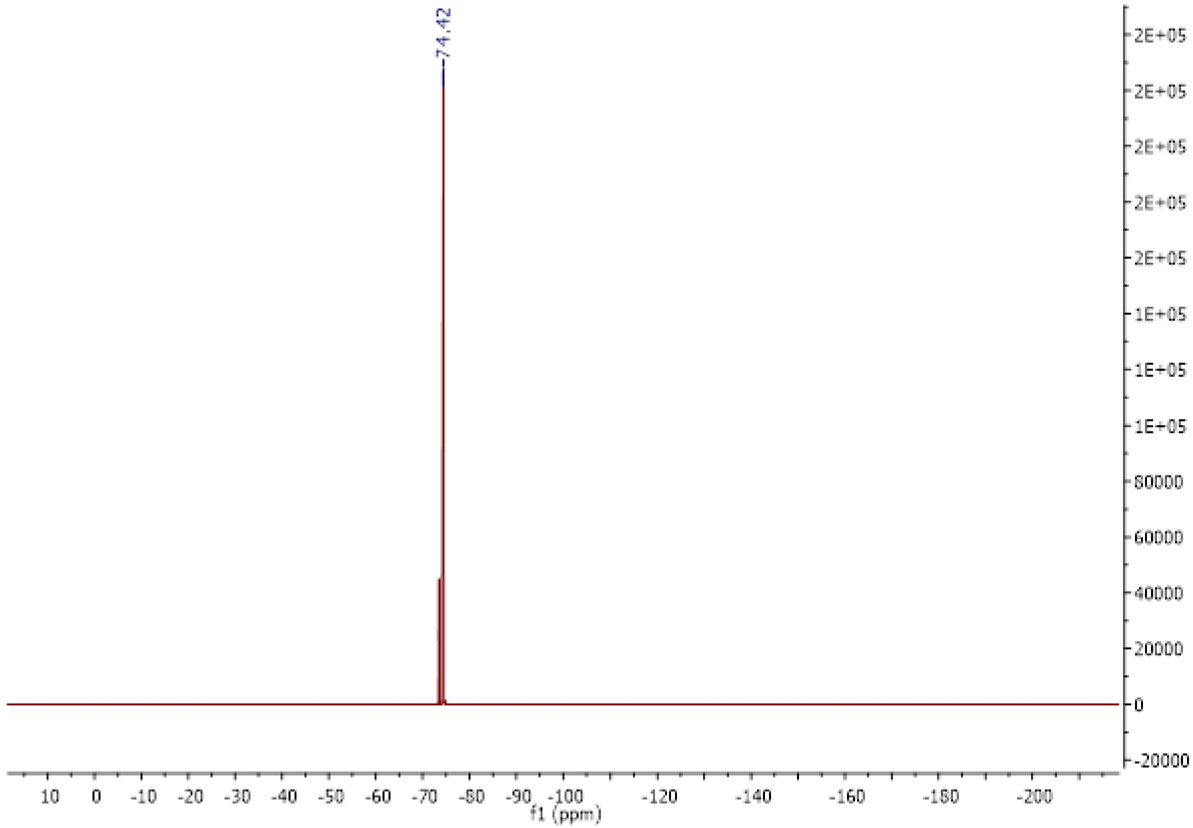




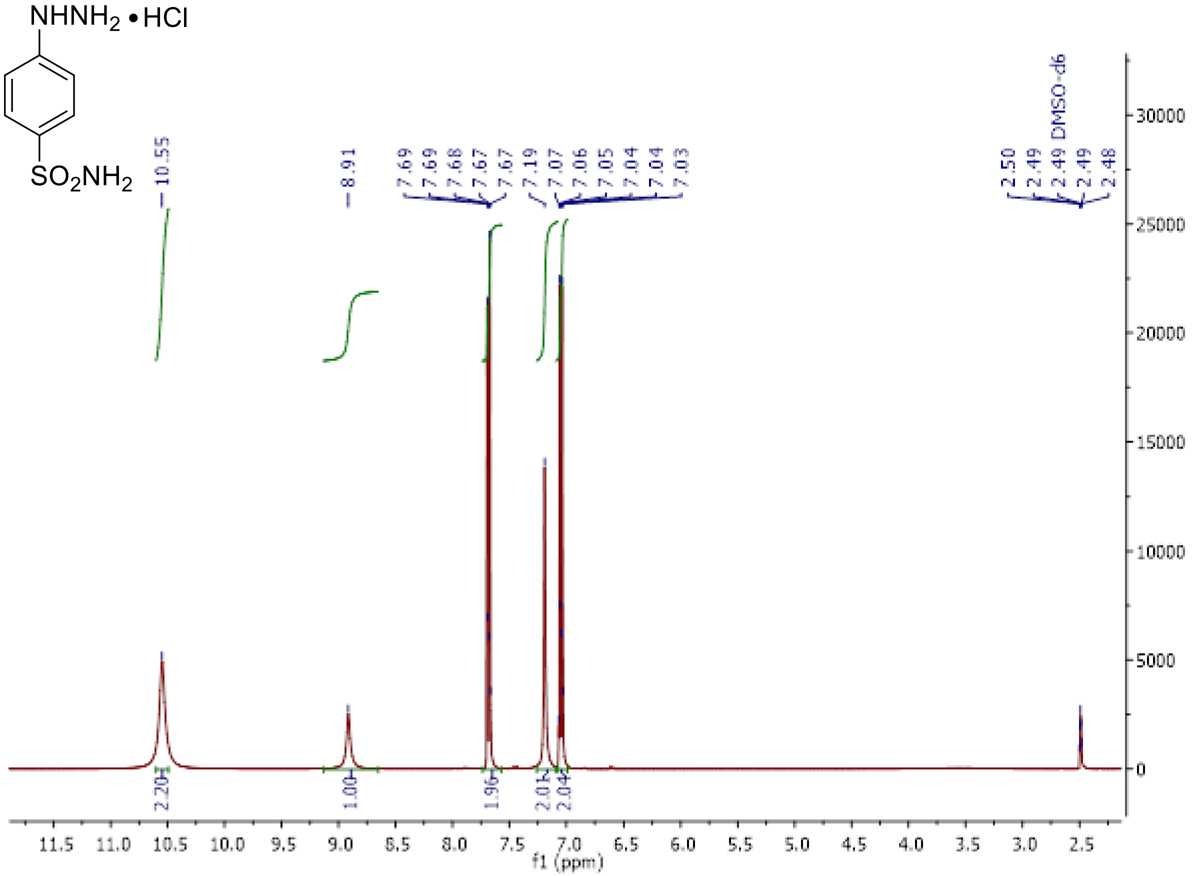
8.1.14. **Chapter 6:** 4,4,4-Trifluoro-1-(4-methyl-phenyl)-butane-1,3-dione (**132**)

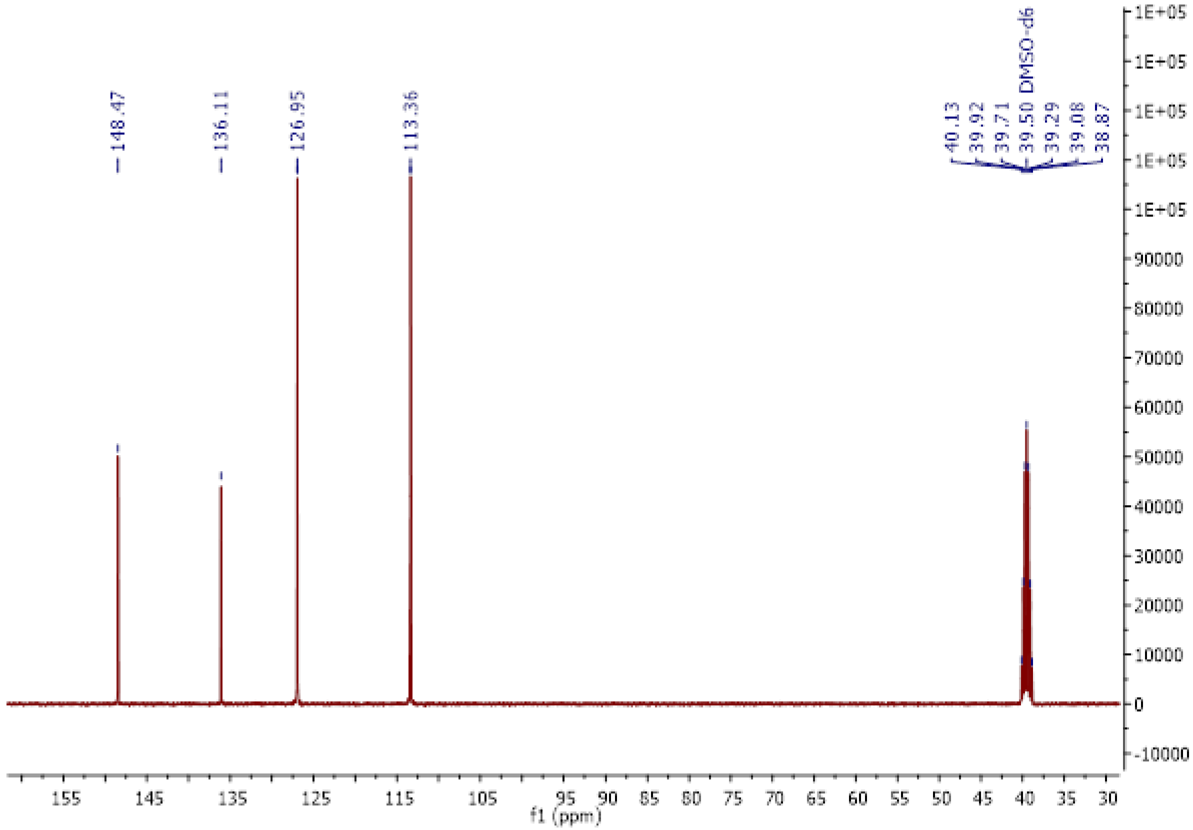




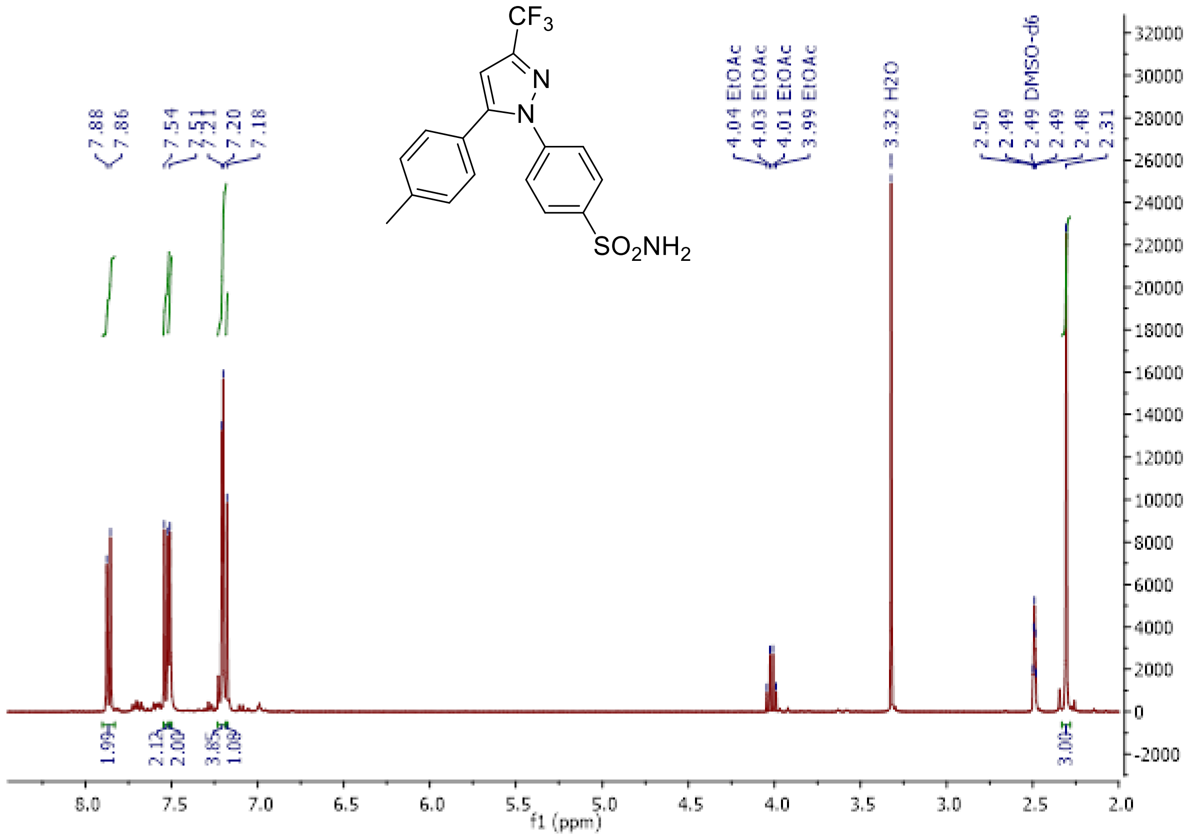


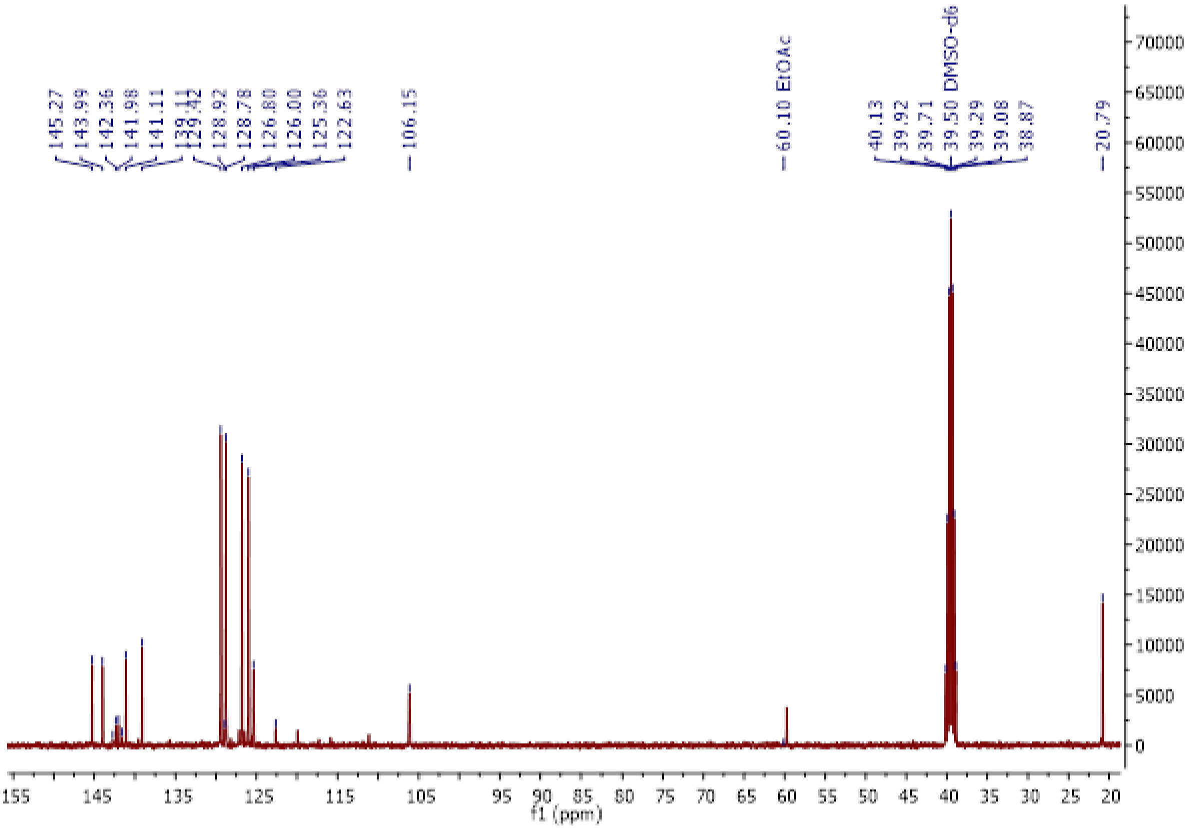
8.1.15. **Chapter 6:** 4-Sulfamidophenylhydrazine hydrochloride (**122**)





8.1.16. **Chapter 6:** Celecoxib (**27**)

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125.36
122.63
106.15
60.10 EtOAc
40.13
39.92
39.71
39.50 DMSO-d6
39.29
39.08
38.87
20.79
70000
65000
60000
55000
50000
45000
40000
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30000
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15000
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5000
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145
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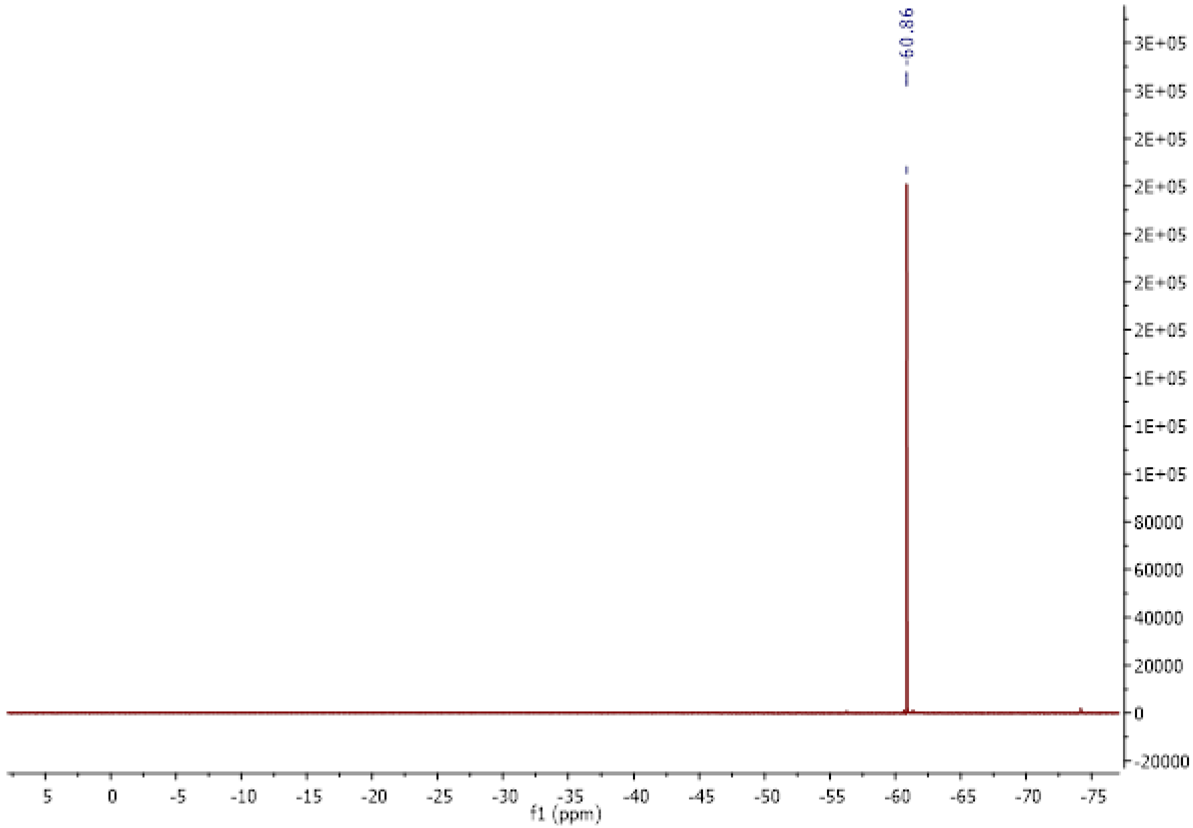
f1 (ppm)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f1 (ppm)

REPUBLIC OF SOUTH AFRICA
PATENT APPLICATION

COPY OF PROVISIONAL SPECIFICATION

Application No.	2017/06552
Filing Date	29 September 2017
Your Ref	
Our Ref	P78758ZP00
Name of Applicant(s)	UNIVERSITY OF PRETORIA
Name of Inventor(s)	RILEY, Darren SCHOLTZ, Chantal
Title of Invention	MANUFACTURE OF CELECOXIB
Completion Date	29 September 2018

The specification has been drafted and the patent application has been filed on the assumption that the invention is “new”. The fact that we have undertaken to file this application should NOT be interpreted as an indication or guarantee that a valid patent will be obtained for the invention.

If a patent based on this application is granted then its term will be 20 years commencing with the date of filing of the complete specification, subject to payment of renewal fees.

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REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978
PROVISIONAL SPECIFICATION
[Section 30(1) – Regulation 28]

OFFICIAL APPLICATION NO.

21	01	**2017/06552**

LODGING DATE

22	2017/09/29

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51	

FULL NAME(S) OF APPLICANT(S)

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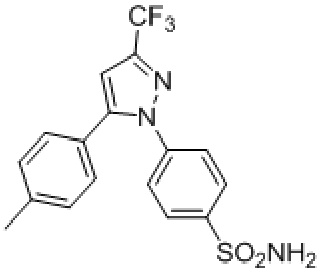
TITLE OF INVENTION

54	MANUFACTURE OF CELECOXIB

MANUFACTURE OF CELECOXIB

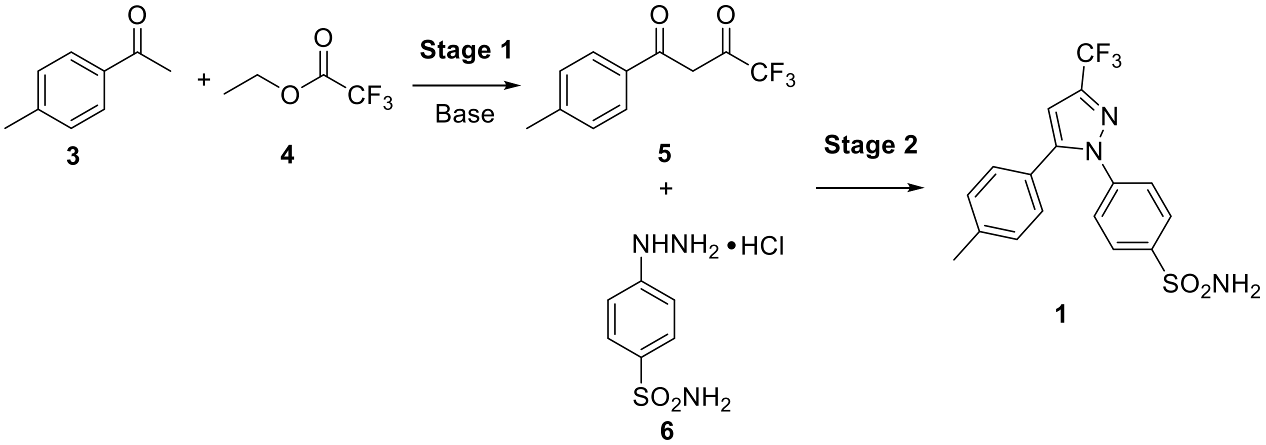
THIS INVENTION relates to the manufacture of celecoxib. In particular, the invention relates to a continuous process for the manufacture of celecoxib, and to celecoxib when produced by the process.

Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID) that is frequently used in the treatment of conditions such as arthritis and that is often prescribed for acute pain. It has also been shown to possess anti-cancer properties. The structure of celecoxib is shown below.



Typically NSAIDs work by inhibition of the cyclooxygenase (COX) enzymes, which are involved in arachidonic acid metabolism leading to the synthesis of thromboxanes and prostaglandins (PGs) – the major mediators of pain. Conventional NSAIDs inhibit both COX-1 and COX-2, with COX-1 being inhibited to a greater extent, leading to undesirable side effects such as gastrointestinal bleeding and ulcers with long term use. The selective inhibition of COX-2 results in anti-inflammatory effects without undesirable gastrotoxic side effects. Two major classes of compounds have been developed as selective COX-2 inhibitors; the “coxibs” of which celecoxib is a classic example and the methanesulfonamide type compounds such as nimesulide.

Celecoxib was first prepared by Penning and co-workers by means of a Claisen condensation between 4-methylacetophenone (4-MAP, **3**) and ethyl trifluoroacetate (EFTA, **4**) in methanol to obtain the dione (**5**) followed by a cyclo-condensation reaction with (4-Sulfamoylphenyl)hydrazine hydrochloride (**6**) to obtain the 1,5-diarylpyrazole (**1**), i.e. celecoxib, in a yield of 46% (Scheme 1).



Scheme 1: Claisen condensation and cyclo-condensation synthesis route for celecoxib (**1**)

The same group determined that using the hydrochloride salt of the hydrazine instead of the phenylhydrazine in the cyclo-condensation reaction resulted in the regioselective formation of the 1,5-diarylpyrazole, limiting the formation of the undesired 1,3-diarylpyrazole regioisomer. This approach is still used industrially, however several optimizations primarily focusing on the use of more appropriate solvents for both the Claisen condensation and the cyclo-condensation as well as improved work-up and product isolation have resulted in more acceptable yields reportedly in the range of 73–89%. Several alternative approaches using different synthetic routes have been reported with yields in the range of 35-80%.

Conventionally, celecoxib has been produced in relatively small amounts in batch processes, typically taking in excess of 24 hours. This has contributed to a retail price for celecoxib, in at least some countries such as South Africa, which is so high that it makes celecoxib unaffordable to the public health system. A continuous process for manufacturing celecoxib at an attractively high yield, in a significantly reduced time and in high quantities would be desirable. It would be even more desirable if such a continuous process could provide a product yield and quality that are better than that achieved by batch processes.

Several flow syntheses of pyrazoles have been reported (Smith, C.J.; Iglesias-Sigüenza, F.J.; Baxendale, I.R. and Ley, S.V. *Org. Biomol. Chem.*, **2007**, *5*, 2758, (a) Baxendale, I.R.; Schou, S.C.; Sedelmeier, J. and Ley, S.V. *Chem. Eur. J.*, **2010**, *16*, 89. (b) Lange, H.; Carter, C.F.; Hopkin, M.D.; Burke, A.; Goode, J.G.; Baxendale, I.R. and Ley, S.V. *Chem. Sci.*, **2011**, *2*, 765, Breen, J.R.; Sandford, G.; Yufit, D.S.; Howard, J.A.k.; Fray, J. and Patel, B. *Beilstein J. Org. Chem.*, **2011**, *7*, 1048, Obermayer, D.; Glasnow, T.N. and Kapper, C.O. *J. Org. Chem.*, **2011**, *76*, 6657, Li, B.; Widlicka. D.; Boucher, S.; Hayward, C.; Lucas, J.; Murray, J.C.; O'Neil, B.T.; Pfisterer, D.; Samp, L.; VanAlsten, J.; Xiang, Y. and Young, J. *Org. Process Res. Dev.*, **2012**, *16*, 2031, DeAngelis, A.; Wang, D-H. and Buchwald, S.L. *Angew. Chem. Int. Ed.*, **2013**, *52*, 3434, and Battilocchio, C.; Deadman, B.J.; Nikbin, N.; Kitching, M.O.; Baxendale, I.R. and Ley, S.V. *Chem. Eur. J.*, **2013**, *19*, 7917). The Ley group (Poh, J-S.; Browne, D.L. and Ley, S.V. *React. Chem. Eng.*, **2016**, *1*, 101) recently reported a four-step flow synthesis of several pyrazoles including the flow synthesis of celecoxib in 48% yield via a metal-free amine-redox process. According to the book *Green Chemistry in the Pharmaceutical Industry*, Peter J. Dunn, Andrew Wells and Michael T. Williams, John Wiley & Sons, February 2010, Pfizer also presented a continuous process to prepare celecoxib.

According to the invention, there is provided a continuous process for the manufacture of celecoxib, the process including

reacting a stream of a first solution and a stream of a second solution in a first reactor in the presence of a base at a first reaction temperature of between about 45°C and about 90°C and at a first reaction pressure, wherein the first solution is a solution of 4'-methylacetophenone in a first organic solvent and the second solution is a solution of ethyl trifluoroacetate in a second organic solvent, and wherein the first reaction pressure prevents boiling inside the first reactor;

continuously withdrawing a stream of a first reactor product from the first reactor, the first reactor product including a solution of 4,4,4-Trifluoro-1-(4-methylphenyl)butane-1,3-dione in the first organic solvent and the second organic solvent;

reacting a stream of the first reactor product and a stream of a third solution in a second reactor at a second reaction temperature of between about 80°C and about 110°C and at a second reaction pressure, wherein the third solution is a solution of (4-

Sulfamoylphenyl)hydrazine hydrochloride in a third organic solvent, and wherein the second reaction pressure prevents boiling inside the second reactor; and

continuously withdrawing a stream of a second reactor product from the second reactor, the second reactor product including a solution of celecoxib in organic solvent.

The first organic solvent and/or the second organic solvent and/or the third organic solvent may be a low molecular weight protic solvent.

The first organic solution may be selected from the group consisting of methanol, ethanol, isopropyl alcohol, butan-1-ol, pentan-1-ol, hexan-1-ol and mixtures of two or more of these.

Preferably, the first organic solvent is ethanol, more preferably absolute ethanol.

The second organic solvent may be selected from the group consisting of methanol, ethanol, isopropyl alcohol, butan-1-ol, pentan-1-ol, hexan-1-ol and mixtures of two or more of these.

Preferably, the second organic solvent is ethanol, more preferably absolute ethanol.

The third organic solvent may be selected from the group consisting of methanol, ethanol, isopropyl alcohol, butan-1-ol, pentan-1-ol, hexan-1-ol and mixtures of two or more of these.

Preferably, the third organic solvent is ethanol.

The third solution preferably also includes some water to improve the solubility, and hence the concentration, of the (4-Sulfamoylphenyl)hydrazine hydrochloride in the third solution. Thus, the third solution may include water in a concentration of at least about 20% by volume, preferably at least about 25% by volume, more preferably at least about 30% by volume.

Preferably, the first organic solvent and the second organic solvent and the third organic solvent are the same, e.g. ethanol.

The base may be selected from the group consisting of sodium ethoxide, sodium methoxide, sodium hydroxide, sodium isopropoxide, sodium tert-butoxide, potassium ethoxide, potassium methoxide, potassium isopropoxide, any low molecular weight sodium alkoxide and mixtures of two or more of these.

Preferable, the base is sodium ethoxide.

The second solution may include the base. Instead, the base may be fed as a further stream to the first reactor, e.g. as a solution in ethanol or methanol.

The first reaction temperature may be between about 45°C and about 80°C, preferably between about 45°C and about 70°C, more preferably between about 45°C and about 60°C, most preferably between about 45°C and about 55°C, e.g. about 50°C.

The second reaction temperature may be between about 80°C and about 100°C, preferably between about 85°C and about 100°C, more preferably between about 85°C and about 95°C, e.g. about 90°C.

The first reaction pressure may be between about 69 kPa(absolute) and about 3343 kPa(absolute), preferably between about 103 kPa(absolute) and about 1724 kPa(absolute), more preferably between about 207 kPa(absolute) and about 1240 kPa(absolute), e.g. about 690 kPa(absolute).

The second reaction pressure may be between about 69 kPa(absolute) and about 2068 kPa(absolute), preferably between about 103 kPa(absolute) and about 1724 kPa(absolute), more preferably between about 207 kPa(absolute) and about 690 kPa(absolute), e.g. about 310 kPa(absolute).

The base may be present in the first reactor in excess of a stoichiometric requirement, e.g. in an excess of at least about 200%, or at least about 250%, or at least about 300%, e.g. 350%. Hence, the first reactor product may include excess base.

The ethyl trifluoroacetate may be present in the first reactor in excess of a stoichiometric requirement, e.g. in an excess of at least about 150%, or at least about 200%, or at least about 250%, e.g. about 280%.

Advantageously, the first reactor product typically includes 4,4,4-Trifluoro-1-(4-methylphenyl)butane-1,3-dione in a yield of at least 90%, e.g. about 93%.

The process may include neutralising excess base in the first reactor product. Typically, the excess base is neutralised in the stream of the first reactor product withdrawn from the first reactor.

In one embodiment of the invention, the excess base is neutralised by addition of an acid, e.g. trifluoroacetic acid. As will be appreciated, the use of an acid may require more expensive materials of construction.

In another, possibly preferred embodiment of the invention, the excess base is neutralised by contacting the first reactor product with an acidic cation exchanger, preferably a strongly acidic cation exchanger such as Amberlyst® 15 hydrogen form. Typically, the first reaction product is contacted with the acidic cation exchanger by contacting the stream of the first reactor product with the acidic cation exchanger. As will be appreciated, in a continuous, industrial scale process, the cation exchanger will need to be regenerated or replaced from time to time.

The process may include increasing the concentration of 4,4,4-Trifluoro-1-(4-methylphenyl)butane-1,3-dione in the first reaction product, prior to reacting a stream of the first reaction product and a stream of the third solution. Advantageously, increasing the concentration of 4,4,4-Trifluoro-1-(4-methylphenyl)butane-1,3-dione in the first reaction product, prior to reacting a stream of the first reaction product and a stream of the third solution expedites the reaction of the first product and the third solution, thus advantageously reducing a required reactor residence time, potentially leading to a reduction in equipment size and hence capital and operating costs.

The concentration of 4,4,4-Trifluoro-1-(4-methylphenyl)butane-1,3-dione may be increased by removing some of the first organic solvent and the second organic solvent from the first reaction product, e.g. through flashing or through evaporation.

The process may include recycling the organic solvent removed from the first reaction product to form the first solution and/or the second solution and/or the third solution.

The first reactor may be a continuous reactor or flow reactor. Preferably, the first reactor is a plug flow reactor, e.g. a tubular reactor or pipe reactor.

The second reactor may be a continuous reactor or flow reactor. Preferably, the second reactor is a continuous stirred tank reactor or is in the form of a plurality of continuous stirred tank reactors arranged in series.

The first reactor may be operated to provide a residence time for reactor content of between about 1 minutes and about 10 minutes, preferably between about 2 minutes and about 8 minutes, more preferably between about 3 minutes and about 6 minutes, e.g. about 4 minutes.

The second reactor may be operated to provide a residence time for reactor content of between about 7 minutes and about 140 minutes, preferably between about 14 minutes and about 93 minutes, more preferably between about 28 minutes and about 70 minutes, e.g. about 56 minutes.

Care must be taken to ensure that the second reactor is not operated with a too long residence time or a too high temperature, to prevent decomposition of celecoxib.

The process may include recovering celecoxib from the second reactor product as a solid. Celecoxib may be recovered as a solid by removing solvent, e.g. by means of vacuum evaporation.

The process may include recycling the solvent removed from the second reactor product to form the first solution and/or the second solution and/or the third solution. As the solvent removed from the second reactor product is likely to include water, the solvent removed from the second reactor product is preferably recycled to form the third solution.

The process may include, in a purification stage, purifying the solid celecoxib by re-dissolving the solid celecoxib in an organic solvent, e.g. ethyl acetate, to provide a celecoxib solution. Solid celecoxib may be recovered from the celecoxib solution by subjecting the celecoxib solution to filtration to provide a filtrate, and concentrating the filtrate, e.g. *in vacuo*, to obtain solid celecoxib, which is typically a pale yellow solid.

The process may include recycling the organic solvent used to purify the celecoxib, to the purification stage, after removal thereof to provide the solid celecoxib.

In one embodiment of the invention, the process includes

reacting a stream of a first solution and a stream of a second solution in a first reactor in the presence of excess sodium ethoxide at a first reaction temperature of 50±5°C or 50±4°C or 50±3°C and at a first reaction pressure, wherein the first solution is a solution of 4'-methylacetophenone in absolute ethanol and the second solution is a solution of ethyl trifluoroacetate in absolute ethanol, and wherein the first reaction pressure prevents boiling inside the first reactor;

continuously withdrawing a stream of a first reactor product from the first reactor, the first reactor product including a solution of 4,4,4-Trifluoro-1-(4-methylphenyl)butane-1,3-dione in absolute ethanol;

neutralising excess sodium ethoxide in the first reactor product;

optionally, increasing the concentration of 4,4,4-Trifluoro-1-(4-methylphenyl)butane-1,3-dione in the first reaction product by removing solvent from the first reaction product;

reacting a stream of the first reactor product and a stream of a third solution in a second reactor at a second reaction temperature of about 90±5°C or 90±4°C or 90±3°C and at a second reaction pressure, wherein the third solution is a solution of (4-Sulfamoylphenyl)hydrazine hydrochloride in a solution of ethanol and water, and wherein the second reaction pressure prevents boiling inside the second reactor; and

continuously withdrawing a stream of a second reactor product from the second reactor, the second reactor product including a solution of celecoxib in ethanol and water.

The invention extends to celecoxib when produced by the process as hereinbefore described.

The invention will now be described by way of the following experimental optimisation study and the drawings.

In the drawings,

Figure 1 shows a schematic diagram of equipment setup for a first stage experimental optimisation for the flow synthesis of 4,4,4-Trifluoro-1-(4-methylphenyl)butane-1,3-dione;

Figure 2 shows a graph of yield of 4,4,4-Trifluoro-1-(4-methylphenyl)butane-1,3-dione as a function of reaction temperature;

Figure 3 shows a schematic diagram of equipment setup for a second stage experimental optimisation for the flow synthesis of celecoxib;

Figure 4 shows a graph of yield of celecoxib as a function of reaction temperature;

Figure 5 shows a schematic diagram of equipment setup for an optimised multi-step or multi-stage laboratory scale process for the flow synthesis of celecoxib; and

Figure 6 shows a schematic flow diagram of a continuous process in accordance with the invention for the manufacture of celecoxib on a commercial scale.

Experimental optimisation study

All flow experiments were performed using the Uniqsis FlowSyn platform (see www.uniqsis.com). All reagents were purchased from Sigma-Aldrich. ^{1}H and ^{13}C NMR data were recorded on a Bruker AVANCE-III 400 MHz spectrometer with the residual solvent peak as an internal reference (d_6-DMSO = 2.54 and 40.45 ppm for ^{1}H and ^{13}C NMR respectively).

A stock solution of 4’-methylacetophenone **3** was prepared by dissolving acetophenone (14.3 mL, 107 mmol) in absolute ethanol (40 mL).

A stock solution of ethyl trifluoroacetate **4** and sodium ethoxide was prepared by dissolving sodium metal (4.39 g, 191 mmol) in absolute ethanol (50 ml) followed by the addition of ethyl trifluoroacetate (17.8 mL, 150 mmol).

A stock solution of 4-Sulfonamide-phenylhydrazine hydrochloride, i.e. (4-Sulfamoylphenyl)hydrazine hydrochloride **6** was prepared by dissolving (4-Sulfamoylphenyl)hydrazine hydrochloride (1.32 g, 5.9 mmol) in 75 % ethanol/water (40 mL) .

Figure 1 shows a schematic diagram of equipment setup for a first stage optimisation, in a laboratory scale flow synthesis process for manufacturing celecoxib, for the flow synthesis of 4,4,4-Trifluoro-1-(4-methylphenyl)butane-1,3-dione. For the first stage optimisation the system was operated with two HPLC (high-performance liquid chromatography) pumps, a 2mL mixing chip and a 100 psi (689 kPa) back pressure regulator (BPR) fitted downstream of the mixing chip. The reagent feedstock for one of the pumps (hereinafter referred to as pump A) was a solution of 4’-methylacetophenone (**3**, 2.68 M) in absolute ethanol and the reagent feedstock for the other pump (hereinafter referred to as pump B) was a solution of ethyl trifluoroacetate (**4**, 2.99 M) and sodium ethoxide (3.82 M) in absolute ethanol.

A general procedure for the stepwise flow synthesis of 4,4,4-Trifluoro-1-(4-methyl-phenyl)-butane-1,3-dione (**5**) was as follows: The 4’-methylacetophenone **3** stock solution (1.48 mL) and the ethyl trifluoroacetate **4** /sodium ethoxide stock solution (3.70 mL) were pumped at flow rates of 0.14 mL.min^{-1} and 0.36 mL.min^{-1} respectively through the 2 mL glass mixing chip heated to 50°C. The output of the reactor was collected until no further product was eluted and the solvent removed *in vacuo*. The solid obtained was suspended in hexane (15 mL) with vigorous stirring followed by vacuum filtration and washing with hexane (2 x 2 mL) to obtain a cream coloured solid (0.84 g, 3.7 mmol, 93%).

An initial screen of flow rates was done at 50°C (Table 1) which afforded a best isolated yield of 43% with a residence time of 4 minutes. A subsequent temperature screen in the range of 30 to 150°C with the same residence time showed no further improvement in the yield (Figure 2). The standard conditions were as follows: **3** (2.68 M), **4** (2.99 M), NaOEt (3.82 M), 0.50 mL.min^{-1}, pump ratio 1:1. It was observed that reaction temperatures below 50°C were inefficient with yields < 5%, and the isolated yields also decreased steadily with increasing temperature above 50°C.

Table 1: Optimization of flow rate for formation of 4,4,4-Trifluoro-1-(4-methylphenyl)butane-1,3-dione

Flow rate (mL.min^{-1})[a]	**Residence time (min)**	**Yield (%)**
0.25	8	35
0.50	4	43
1.00	2	29

[a] Flow rate refers to the combined flow rates of both pumps A and B set at a 1:1 ratio

Standard conditions: **3** (2.68 M), **4** (2.99 M), NaOEt (3.82 M), 50 °C.

In an attempt to increase the reaction yield the stoichiometric ratio of ethyl trifluoroacetate (ETFA)/sodium ethoxide (NaOEt) relative to 4'-methylacetophenone (4-MAP) was increased (Table 2) with the flow rate maintained at 0.50 mL.min^{-1} at 50°C.

Table 2: Concentrations of solutions used in concentration screen

Reactor (pump A:pump B)	**Solution A**	**Solution B**		**Yield (%)**
	[4-MAP] (M)	**[ETFA] (M)**	**[NaOEt] (M)**	
1 : 1	2.68	2.99	3.82	43
1 : 1.5	2.68	4.49	5.73	83
1 : 2.5	2.68	7.48	9.55	93
1 : 3	2.68	8.97	11.46	89

Standard conditions: 2 mL mixing chip, standard solutions of **3** (2.68 M), **4** (2.99 M), NaOEt (3.82 M), 50°C, 0.50 mL.min^{-1}, new work-up.

A stoichiometric ratio of 2.5:1 ETFA/NaOEt:4-MAP corresponding to 2.8 and 3.5 equivalents of ETFA and NaOEt respectively showed complete conversion by thin layer chromatography and afforded a 93% isolated yield of 4,4,4-Trifluoro-1-(4-methylphenyl)butane-1,3-dione **5**.

Figure 3 shows a schematic diagram of equipment setup for a second stage optimisation for the laboratory scale flow synthesis of celecoxib. A second stage reactor setup made use of two HPLC pumps, a 2 mL mixing chip, a 14 mL HT PTFE (high temperature polytetrafluoroethylene) heated coil reactor and a back pressure regulator fitted downstream of the coil reactor. It was found that a 2 mL mixing chip at room temperature was beneficial to improve mixing of the reagents before reaction in the heated coil reactor.

(4-Sulfamoylphenyl)hydrazine hydrochloride (**6**) was prepared as follows: Sulfanilamide (5.01 g, 29.1 mmol, 1.0 eq) was cooled to 0°C followed by the addition of ice (29.11 g, 1.6 mol, 55.5 eq) and aqueous hydrochloric acid (32 %, 14.5 ml, 0.2 mol, 5.1 eq). A solution of sodium nitrite (2.01 g, 29.1 mmol, 1.0 eq) in water (4.0 ml, 0.2 mol, 6.9 eq) was added in a dropwise fashion and the solution was allowed to stir until all the sulfanilamide had dissolved. This mixture was rapidly added to a pre-cooled 0°C solution of tin (II) chloride (14.38 g, 75.8 mmol, 2.6 eq) in aqueous hydrochloric acid (32 %, 21.7 ml, 0.2 mol, 7.6 eq) with vigorous stirring. The reaction mixture was placed in a fridge at 0-4°C overnight. The solid formed was collected by vacuum filtration followed by washing with cold EtOH (3 x 20 ml) to obtain (4-Sulfamoylphenyl)hydrazine hydrochloride as a pearlescent white solid (5.37 g, 24 mmol, 83%). R_f = 0.16 (20% hexane/EtOAc). ^{1}H NMR (400 MHz d_6-DMSO) 10.60 (s, 2H, $SO_2N\underline{H_2}$); 8.96 (s, 1H, $N\underline{H}NH_2$); 7.74 (d, 2H, *J* 12.00, Ar-H); 7.24 (s, 2H, $NHN\underline{H_2}$); 7.11 (d, 2H, *J* 8.00, Ar-H). ^{13}C NMR (100 MHz d_6-DMSO) 149.41, 137.05, 127.89, 114.31.

4,4,4-Trifluoro-1-(4-methylphenyl)butane-1,3-dione (**5**) was prepared as follows: A solution of sodium (0.12 g, 5.2 mmol, 1.4 eq.) was dissolved in absolute ethanol (3.9 mL) followed by the dropwise addition of ethyl trifluoroacetate (**4**, 0.5 mL, 4.1 mmol, 1.1 eq.).

Thereafter 4′-methylacetophenone (**3**, 0.50 ml, 3.8 mmol, 1.0 eq) in absolute ethanol (1.4 ml) was added dropwise over 15 minutes. The reaction mixture was stirred at room temperature for 3 hours. The mixture was concentrated *in vacuo* and the solid obtained suspended in hexane (15 ml) with vigorous stirring followed by vacuum filtration and washing with hexane (2 x 2 ml) to obtain a cream coloured solid (0.86 g, 3.7mmol, 100%). R_f = 0.23 (25 % EtOAc/hexane). ^{1}H NMR (400 MHz d_6-DMSO) 7.69 (d, 2H, *J* 7.69, Ar-H); 7.19 (d, 2H, *J* 7.18, Ar-H); 5.92 (s, 1H, $COC\underline{H_2}CO$); 2.31 (s, 3H, $C\underline{H_3}$). ^{13}C NMR (100 MHz d_6-DMSO) 185.62, 169.27*, 168.99*, 168.71*, 168.44*, 139.89, 138.96, 128.70, 126.66, 123.78†, 120.88†, 117.98†, 115.07†, 86.84, 20.91. ^{19}F NMR (377 MHz, d_6-DMSO) -74.42. *†Signals exhibit splitting due to coupling with fluorine.

A general procedure for the stepwise laboratory scale flow synthesis of celecoxib was as follows: 4,4,4-Trifluoro-1-(4-methyl-phenyl)-butane-1,3-dione **5** stock solution (7 mL) and (4-Sulfamoylphenyl)hydrazine hydrochloride **6** stock solution (7 mL) were each pumped at a flow rate of 0.125 mL.min^{-1} into the 2 mL glass mixing chip at room temperature and through the 14 mL PTFE coil heated to 90°C. The output of the reactor was collected until no further product was eluted and the solvent removed *in vacuo*. The solid obtained was suspended in ethyl acetate (30 mL) followed by vacuum filtration. The filtrate was concentrated to obtain a pale yellow solid (0.393 g, 1.0 mmol, 99%). R_f = 0.33 (20% methanol/dichloromethane).

Batch optimizations showed that temperature plays a crucial role in the formation of celecoxib **1**. An initial temperature screen was thus performed in the range of 50-140°C at a flow rate of 0.50 mL.min^{-1} (Figure 4). Standard conditions were: 0.17 M **5**, 0.15 M **6**, EtOH, 0.50 mL.min^{-1}. An isolated yield of 52-53% was obtained between 90 and 100°C. There was a dramatic decrease in isolated yield at higher temperatures.

Optimization of residence time was performed at 90°C (Table 3), affording a quantitative conversion of 4,4,4-Trifluoro-1-(4-methylphenyl)butane-1,3-dione **5** to celecoxib **1** with a coil residence time of 56 minutes.

Table 3: Optimization of flow rate for formation of celecoxib

Flow rate (mL.min^{-1})	**Residence time mixing chip (min)**	**Residence time HT PTFE coil (min)**	**Yield (%)**
0.20	10	70	88
0.25	8	56	100
0.50	4	28	58

Standard conditions: 2 mL mixing chip, 14 mL HT PTFE coil, standard solutions of **5** (0.17 M), **6** (0.15 M), 90 °C.

Figure 5 shows a schematic diagram of equipment setup for a multi-step laboratory scale flow synthesis of celecoxib **1**. The process shown in Figure 5 involved the reaction of 4-MAP **3** and ETFA **4** in the presence of sodium ethoxide in a 2 mL mixing chip at 50°C, thereafter passage through an OmniFit® column packed with Amberlyst® 15 hydrogen form cation exchange resin to neutralize excess base after the Claisen condensation. Although not shown in Figure 5, a back pressure regulator was used downstream of the OmniFit® column. An in-line concentration step heating the run-off from the OmniFit® column, at 80°C, was used to remove unreacted ETFA (boiling point 60-62°C) from run-off. Thereafter hydrazine **6** was introduced through a T-piece mixer and subsequent passage through a 14 mL PTFE coil reactor at 90°C and finally through a 100 psi (689 kPa) back pressure regulator.

A general procedure for the laboratory scale multi-step flow synthesis of celecoxib **1** was as follows: The 4'-methylacetophenone **3** (1.48 mL) stock solution and the ethyl trifluoroacetate **4/**sodium ethoxide (3.70 ml) stock solution were pumped at flow rates of 0.14 mL.min^{-1} and 0.36 mL.min^{-1} respectively through the 2 mL glass mixing chip heated to 50°C followed by the Omnifit ® column packed with Amberlyst® 15 hydrogen form resin (1.25 g, 5.9 mmol). The output (4,4,4-Trifluoro-1-(4-methyl-phenyl)-butane-1,3-dione **5**) of the reaction was collected in a beaker held at 80°C with an air stream blowing over the surface to concentrate the solution down to 16.4 mL (0.17 M relative to **5**). The concentrated solution of **5** (15.0 mL) and the (4-Sulfamoylphenyl)hydrazine hydrochloride **6** stock solution (15.0 mL) were both pumped at flow rates of 0.125 mL.min^{-1} and mixed via a stainless steel T-piece followed by reaction in the 14 mL HT PTFE coil heated to 90°C. The output of the reactor was collected until no further product was eluted and the solvent removed under vacuum. The solid obtained was suspended in ethyl acetate (30 ml) followed by vacuum filtration. The filtrate was concentrated *in vacuo* to obtain a pale yellow solid (0.76 g, 2.0 mmol, 90%).

The coupled process shown in Figure 5 thus afforded celecoxib **1** in an isolated yield of 90% after employing a work-up/purification developed during earlier batch optimization of stage 2.

Referring to Figure 6 of the drawings, reference numeral 10 generally indicates a continuous process in accordance with invention for the manufacture of celecoxib. The process 10 includes a first reactor in the form of a pipe reactor 12 with a static inline mixer 14, a pair of parallel cation exchangers 16.1 and 16.2, a concentration stage 18, a second reactor in the form of a plurality of continuous stirred tank reactors 20.1, 20.2 and 20.3 arranged in series, a solvent recovery stage 22, a product purification stage 24 and a product recovery stage 26.

The pipe reactor 12 is provided with feed lines 28 and 30. A process line 32 leads from the pipe reactor 12 via the cation exchangers 16.1 and 16.2, the concentration stage 18, the continuous stirred tank reactors 20.1, 20.2 and 20.3, the solvent recovery stage 22 and the product purification stage 24 to the product recovery stage 26.

The concentration stage 18 is provided with an ethanol withdrawal line 34 and the continuous stirred tank reactor 20.1 is provided with a feed line 36. The solvent recovery stage 22 is provided with a solvent withdrawal line 38 and the product recovery stage 26 is provided with a product withdrawal line 40, a solvent recycle line 42 leading back to the product purification stage 24 and an impurities withdrawal line 44.

In order to produce celecoxib on a commercial in the continuous process 10, a solution of 4’-methylacetophenone in absolute ethanol is continuously fed (typically pumped from a feedstock tank, not shown) by means of the feed line 28 to the pipe reactor 12, and a solution of ethyl-trifluoroacetate and sodium ethoxide in absolute ethanol is continuously fed (typically pumped from a feedstock tank, not shown) to the pipe reactor 12 by means of the feed line 30. The solutions fed by means of the feed lines 28, 30 are intimately mixed by means of the static inline mixer 14 and pass through the pipe reactor 12 in plug flow fashion. The pipe reactor 12 is operated at a temperature of about 50°C and is typically heated externally, e.g. electrically or by means of a heat transfer fluid passed through a jacket (not shown) surrounding the pipe reactor 12.

The sodium ethoxide is fed in a stoichiometric excess of about 3.5 molar equivalents and the ethyl trifluoroacetate is fed in a stoichiometric excess of about 2.8 molar equivalents, relative to the 4’-methylacetophenone, per unit of time. Typically, the 4’-methylacetophenone is fed in a concentration of about 2.7 M. Feed rates are such that the pipe reactor 12 is operated in a plug flow mode with a residence time of about 4 minutes.

If desired, the pipe reactor 12 can be operated at a superatmospheric pressure by means of a pressure control valve (not shown) located between the cation exchangers 16.1, 16.2 and the concentration stage 18.

A solution of ethanol, excess sodium ethoxide, excess ethyl-trifluoroacetate and 4,4,4-Trifluoro-1-(4-methyl-phenyl)-butane-1,3-dione is continuously withdrawn from the pipe reactor 12 and fed by means of the process line 32 to one of the cation exchangers 16.1, 16.2. The cation exchangers 16.1, 16.2 contain a strongly acidic cation exchange resin such as Amberlyst® 15 hydrogen form. The strongly acidic cation exchange resin neutralises the excess sodium ethoxide, providing a neutralized first reactor product.

As will be appreciated, only one of the cation exchangers 16.1, 16.2 is typically in use, with the second cation exchanger 16.2, 16.1 being regenerated, in conventional fashion.

The neutralized first reactor product is transferred by means of the process line 32 to the concentration stage 18 where the concentration of the 4,4,4-Trifluoro-1-(4-methyl-phenyl)-butane-1,3-dione is increased by means of removal of ethanol. Typically, the ethanol is removed by means of evaporation, e.g. using an evaporative concentrator operating at a temperature of no more than about 80°C. The evaporated ethanol is withdrawn by means of the ethanol withdrawal line 34 and can be condensed and then re-used in the preparation of feedstock for the pipe reactor 12.

A concentrated first reactor product is withdrawn from the concentration stage 18 by means of the process line 32 and fed to the continuous stirred tank reactor 20.1, where it is mixed with a solution of (4- Sulfamoylphenyl)hydrazine hydrochloride in a mixture of ethanol and water, which is fed by means of the feed line 36 to the continuous stirred tank reactor 20.1. The volumetric ratio of ethanol to water is about 75:25. The 4,4,4-Trifluoro-1-(4-methyl-phenyl)-butane-1,3-dione is fed in a concentration of about 0.17 M and the (4-Sulfamoylphenyl)hydrazine hydrochloride is fed in a concentration of about 0.15 M. The feed rates of the solution of (4- Sulfamoylphenyl)hydrazine hydrochloride and the solution of 4,4,4-Trifluoro-1-(4-methyl-phenyl)-butane-1,3-dione are about the same and the 4,4,4-Trifluoro-1-(4-methyl-phenyl)-butane-1,3-dione is thus fed in a slight stoichiometric excess to the reactor 20.1.

The 4,4,4-Trifluoro-1-(4-methyl-phenyl)-butane-1,3-dione and the (4-Sulfamoylphenyl)hydrazine hydrochloride are reacted in the continuous stirred tank reactors 20.1, 20.2 and 20.3 at a temperature of about 90°C, for a period of about 1 hour, under a pressure of about 310 kPa, to form a second reactor product which includes celecoxib in solution. The second reactor product is withdrawn by means of the process line 32 from the reactor 20.3 and fed to the solvent recovery stage 22, where solvent, i.e. ethanol and water, is removed by means of vacuum evaporation and withdrawn by means of the solvent withdrawal line 38. The solvent withdrawn by means of the solvent withdrawal line 38 can be recycled and used in the preparation of a solution of (4- Sulfamoylphenyl)hydrazine hydrochloride for feeding by means of the feed line 36 to the continuous stirred tank reactor 20.1.

Solid celecoxib is transferred from the solvent recovery stage 22 to the product purification stage 24 by means of the process line 32. In the product purification stage 24, the solid celecoxib is re-dissolved in ethyl acetate fed by means of the solvent recycle line 42. A solution of celecoxib in ethyl acetate is then transferred by means of the process line 32 from the product purification stage 24 to the product recovery stage 26. In the product recovery stage 26, the solution of celecoxib in ethyl acetate is filtered, preferably under vacuum, providing a filtrate, from which the ethyl acetate is removed under vacuum, to provide a purified solid celecoxib which is removed by means of the product withdrawal line 40. Filter cake, which includes impurities separated from the ethyl acetate/celecoxib solution during filtration is removed by means of the impurities withdrawal line 44. Ethyl acetate is recycled by means of the solvent recycle line 42 to the product purification stage 24.

The invention, as illustrated, provides a high yielding (at least 90%) continuous flow process for the synthesis of celecoxib, which does not require the handling of intermediates, which is conducted in a green solvent system and which has a greatly reduced residence time (less than about 2 hours) relative to existing batch processes. The continuous flow route shows significant advantages over currently reported batch synthesis processes for celecoxib and the approach could also conceivably be used for the rapid synthesis of pyrazole analogues. The process of the invention, as illustrated, is directly scalable and promises a reduction of about 48% in cost of raw materials when benchmarked against best current batch process routes.

DATED THIS 29TH DAY OF SEPTEMBER 2017

ADAMS & ADAMS
APPLICANT'S PATENT ATTORNEYS

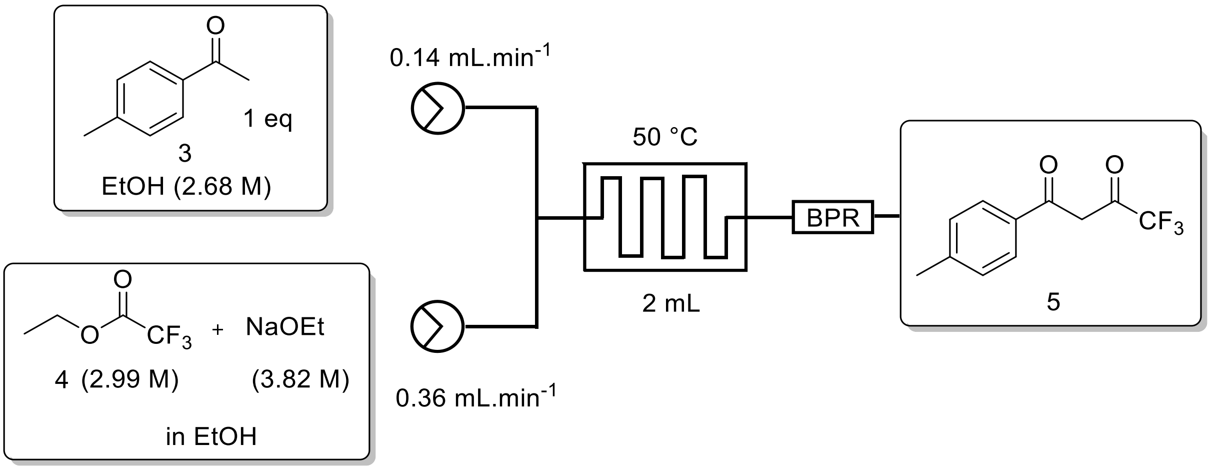


Figure 1

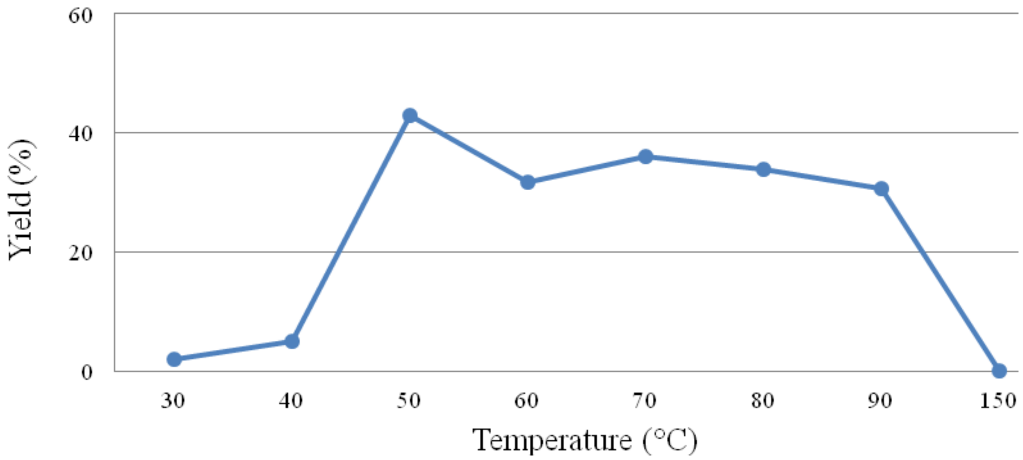


Figure 2

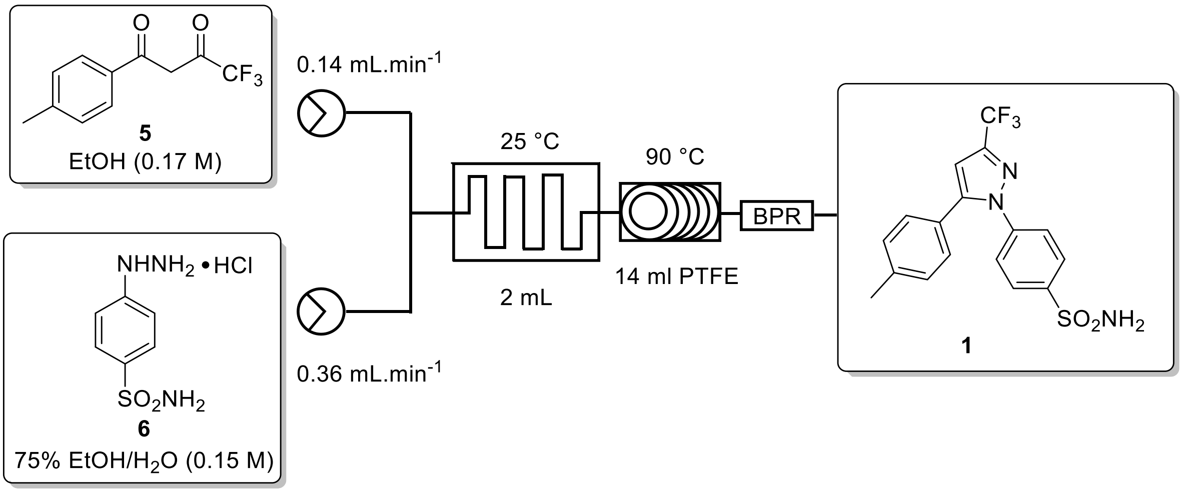


Figure 3

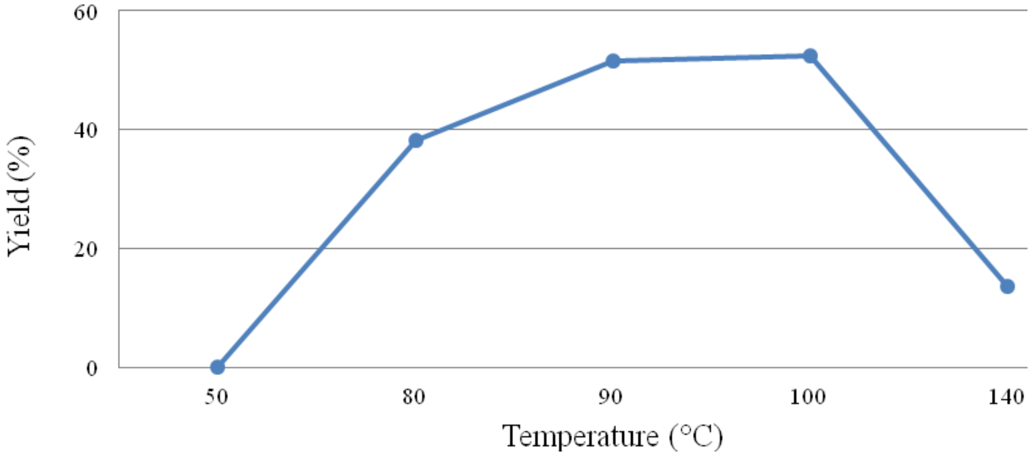


Figure 4

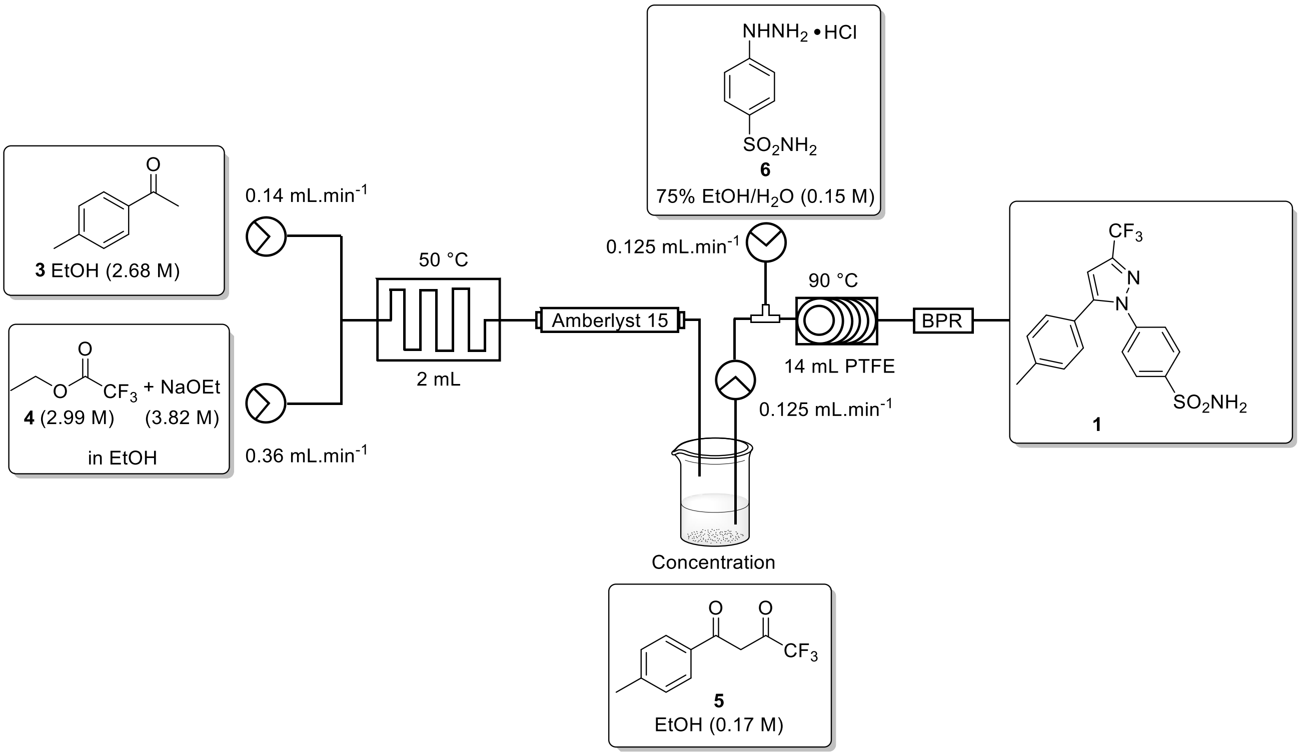

NHNH2 • HCl
SO2NH2
6
75% EtOH/H2O (0.15 M)
3 EtOH (2.68 M)
0.14 mL.min-1
50 °C
0.125 mL.min-1
90 °C
CF3
N
N
Amberlyst 15
BPR
O
CF3 + NaOEt
4 (2.99 M) (3.82 M)
in EtOH
0.36 mL.min-1
2 mL
14 mL PTFE
0.125 mL.min-1
SO2NH2
1
Concentration
CF3
5
EtOH (0.17 M)

Figure 5

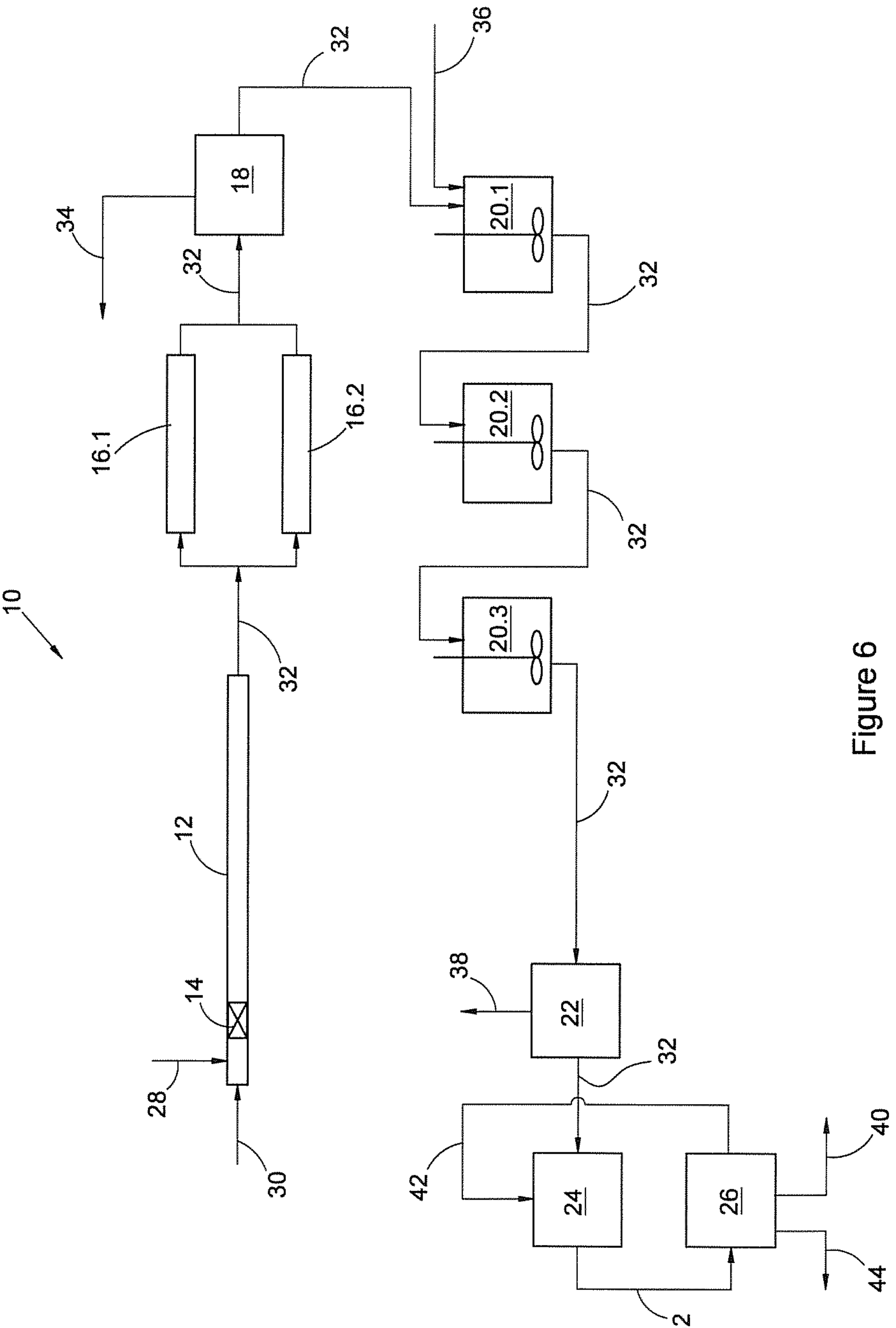

10
28
30
14
12
32
16.1
16.2
32
18
34
32
36
20.1
32
20.2
32
20.3
32
22
38
32
42
24
26
40
44
32

Figure 6

8.3. Draft aryl diazonium tetrafluoroborate paper

COMMUNICATION

Concise, rapid and high yielding flow synthesis of aryldiazonium tetrafluoroborates

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A concise, rapid and high yielding flow synthesis of aryl diazonium tetrafluoroborate salts is reported. The flow approach has been achieved by means of a diazotization reaction to access unstable aryl diazonium chloride salts followed by reaction with sodium tetrafluoroborate to afford the corresponding aryldiazonium tetrafluoroborate in yields of 64-100%.

Introduction

The synthesis of aryl diazonium salts were first reported by Griess in 1858,[1,2] since then they have become important synthons in organic synthesis due in part to the ease with which the diazonium group can be displaced by a wide range of nucleophiles.[3] In the last 160 years the range of reactions involving diazonium salts has expanded from the development of the Sandmeyer reaction to obtain C-Cl, C-Br and C-CN bonds in 1884 and the Pschorr intramolecular substitution reaction for the synthesis of biaryltricyclics in 1896.[2] This was followed by the intermolecular Gomberg-Bachmann reaction in 1924 and shortly thereafter in 1927, the Balz-Schiemann reaction involving the thermal decomposition of diazonium tetrafluoroborates to obtain the difficult to access aryl C-F bond.[2] The Meerwein arylation followed in 1939 and 38 years later in 1977 Kikukawa and Matsuda laid the foundation for palladium catalyzed cross-couplings.[2] Since then developments in C-C, C-B, C-S and C-N bond formation with and without retention of N_2 can be found in the literature.[4]

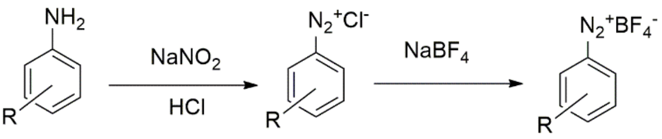
In 2002, de Mello and co-workers reported for the first time the generation of a diazonium salt under flow conditions in which they used a nanoscale monolithic chip to prepare an aryl diazonium chloride followed by *in-situ* quenching to obtain azo dyes.[5] The same group subsequently demonstrated a linked *in-situ* chloro-dediazonation.[6]

The *in-situ* generation and use of aryl diazonium salts has subsequently been reported in several flow syntheses,[7-10] as has the synthesis of related triazene moieties.[11] In many instances the syntheses suffered from solubility issues, required the use of large excesses of acid and nitrite, or required complex and specialized reactor setups. A detailed overview of which can be found in the 2015 review of Felpin and co-workers.[12]

To date, only two examples have been reported involving the synthesis and use of aryl diazonium tetrafluoroborates under flow conditions. In the first instance Yu and co-workers demonstrated a Balz-Schiemann reaction using sodium nitrite with a combination of hydrochloric and fluoroboric acid under aqueous conditions to form the aryl diazonium tetrafluoroborate salt *in-situ*, followed by fluoro-dediazonation to obtain aryl fluorides in good yields.[13] In the second instance Baxendale and co-workers explored the generation of aryl diazonium chloride species under aqueous, organic and solid phase conditions, followed by an ascorbic acid reduction to afford hydrazine derivatives.[14] In both instances the aryl tetrafluoroborates are prepared and consumed *in situ*, and to date a general flow-process for the preparation and isolation of pure aryldiazonium tetrafluoroborates has, to the best of our knowledge, not been described.

The most widely utilised approach to access aryl diazonium tetrafluoroborate salts (Scheme 1) involves the diazotization of an aryl amine in the presence of sodium nitrite and hydrochloric acid under aqueous conditions.[4,16,17] Thereafter, treatment with sodium tetrafluoroborate or fluoroboric acid, results in the precipitation of the desired aryldiazonium tetrafluoroborate salt.

In developing an approach that could be applied to a flow system, an initial batch-mode investigation/optimisation was



Scheme 1: General approach for the synthesis of aryl diazonium tetrafluorborate salts

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

undertaken to identify conditions that would afford homogeneous reaction mixtures. Initially, sodium nitrite was exchanged for isopentyl nitrite allowing the reactions to be performed in more solubilising organic solvents and several potential solvent systems were screened (Table 1).[4]

Under solvent free conditions, the conversion was very poor at only 3% (entry 1). The use of DMF, ethanol or water either alone or as mixtures afforded improvements in the yields, although these were still only poor to moderate at 19-48% at best (entries 2-5), however, when using acetonitrile, the yield improved to 61% (entry 6). In the latter case, the reagents, apart from sodium tetrafluoroborate appeared to be solubilised at a concentration of 0.66 M relative to aniline. The yield was further improved to 78% by initially performing the diazotisation step at 0 °C, followed by passing the reaction mixture through a column packed with sodium tetrafluoroborate (entry 7).

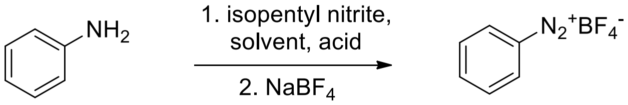
In an effort to minimise the amount of acid used, the reaction was then optimised in terms of the stoichiometric excess of the 32% hydrochloric acid used, and fortuitously, when decreasing the excess from 5.1 equivalents to 1.1 equivalents the yield improved to 100% (entry 8). Finally, to avoid the use of corrosive aqueous hydrochloric acid the process was repeated using ethanolic hydrochloric acid (1.25 M) affording quantitative isolated yields at both 5.1 and 1.1 equivalents acid (entries 9 and 10).

The final optimised process involved the diazotisation of aniline (0.66 M, 1.0 equiv.) with *iso*-pentyl nitrite (1.1 equiv.) and ethanolic hydrochloric acid (1.25 M, 1.1 equiv.) in acetonitrile at 0 °C (15 min reaction time), prior to passage across a column packed with sodium tetrafluoroborate to afford the desired sodium tetrafluoroborate (2.0 equiv.).

In order to convert the process to flow the general setup depicted in scheme 2 was developed using a Uniqsis FlowSyn SS reactor (figure 1). The setup involved the use of two HPLC pumps connected via a T-piece adaptor to a 2 mL PTFE coil reactor (both at 0 °C). The coil reactor was in turn connected in series to an Omnifit® column housing sodium tetrafluoroborate (at ambient temperature), followed by a back-pressure regulator fitted at the output flow stream.

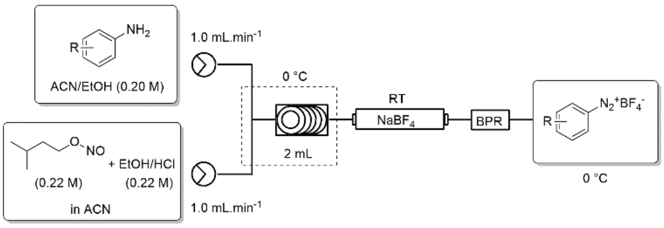
The process was initially envisaged with the diazotisation occurring in a cooled mixing chip followed by conversion to the corresponding tetrafluoroborate salt by passage through a column housing the insoluble sodium tetrafluoroborate. Unfortunately, although not apparent in batch-mode, when utilising a mixing chip there was a gradual build-up of precipitated diazonium hydrochloride salt in the chip which ultimately led to reactor fouling. In an attempt to overcome this issue, the reaction concentration was reduced from 0.66 M to 0.2 M, however, the problem persisted and not wanting to dilute the reaction mixture any further we exchanged the mixing chip for a T-piece mixer connected in series to a 2 mL PTFE coil reactor (id 1 mm), which we felt would be less likely to suffer from blockages. Utilising this set-up, reactor fouling was avoided and there was no visual evidence of the build-up of solids occurring inside the PTFE tubing. Thereafter, the process was optimised in terms of residence time, ultimately affording pure benzenediazonium tetrafluoroborate in quantitative yield with a residence time of 2 min 39 sec at a flow rate of 2 $mL.min^{-1}$. The scope of the reaction was then tested through the synthesis of a range of aryl diazonium tetrafluoroborate salts (Table 2) from their respective aryl amines, requiring only minor adjustments to the solvent system or flow rates used. The set-up afforded most of the desired tetrafluoroborate salts in isolated yields of 98-100% except for 4-methylbenzenediazonium tetrafluoroborate (85%) and 2-hydroxybenzenediazonium tetrafluoroborate (64%). In the case of 4-sulfamoylbenzenediazonium tetrafluoroborate the sulfanilamide

Table 1: Batch optimisation for the preparation of aryl tetrafluoroborates



Entry	Solvent	Acid		Yield (%)
		Source	Equiv.	
1	None[a]	32% HCl	5.1	3
2	DMF	32% HCl	5.1	19
3	H_2O	32% HCl	5.1	20
4	1:1 EtOH/DMF[a]	32% HCl	5.1	20
5	1:1 EtOH/H_2O	32% HCl	5.1	48
6	CH_3CN	32% HCl	5.1	61
7	CH_3CN[b]	32% HCl	5.1	78
8	CH_3CN[b]	32% HCl	1.1	100
9	CH_3CN[b]	1.25 M Ethanolic HCl	5.1	100
10	CH_3CN[b]	1.25 M Ethanolic HCl	1.1	100

Standard conditions: aniline (1.0 equiv., 0.66 M), isopentyl nitrite (1.1 equiv.), acid (5.1 or 1.1 eq.), $NaBF_4$ (2.0 equiv.), 30 min, 0 °C



Scheme 2: Schematic representation of our flow set-up for the conversion of anilines to aryldiazonium tetrafluoroborates.

Figure 1: Uniqsis FlowSyn SS reactor set-up for the synthesis of aryldiazonium tetrafluoroborates

starting reagent could not be sufficiently solubilized for use in the flow reactor (entry 11). In all cases apart from entry 11 the flow yields were equal to or better than the corresponding batch yields.

Conclusions

We have successfully developed a concise, rapid and high yielding flow method for the synthesis of aryldiazonium tetrafluoroborates, and to the best of our knowledge this is the first report of a flow system allowing the synthesis and isolation of aryldiazonium tetrafluoroborates. The flow approach notably affords comparable or improved yields when compared to existing batch approaches and furthermore under flow conditions no downstream processing/purification is required outside of solvent removal. Investigations into telescoping the described setup into reactions wherein the obtained tetrafluoroborates are further functionalised are ongoing in our laboratory.

Experimental section

All solvents and reagents were purchased from Sigma-Aldrich and used without further purification. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AVANCE-III 300 MHz spectrometer or a Bruker AVANCE-III 400 MHz spectrometer with the residual solvent peak as an internal reference (DMSO-d_6 = 2.49 and 39.5 ppm for ^{1}H and ^{13}C NMR respectively). Chemical shifts, δ, are reported in parts per million (ppm), and splitting patterns are given as singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m). Coupling constants, *J*, are expressed in hertz (Hz). Infrared spectra were run on a Bruker ALPHA platinum ATR spectrometer. The absorptions are reported on the wavenumber (cm^{-1}) scale, in the range of 400-4000 cm^{-1}. Yields refer to isolated pure products unless stated otherwise. Flow reactions were performed on a Uniqsis FlowSyn Stainless Steel reactor.

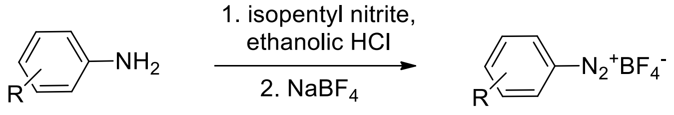
General protocol A - batch synthesis of aryl diazonium tetrafluoroborate salts

A solution of aryl amine (2 mmol, 1.0 equiv.) in acetonitrile (5 ml) was cooled to 0 °C. Ethanolic hydrochloric acid (2.2 mmol, 1.1 equiv.) was then added to the solution in a drop-wise fashion followed by the drop-wise addition of isopentyl nitrite (2.2 mmol, 1.1 equiv.). The reaction mixture was passed through a syringe packed with sodium tetrafluoroborate (4 mmol, 2.0 equiv.) three times and on the final pass the output of the syringe was collected in a flask cooled to 0 °C followed by concentration to dryness. The residue obtained was then suspended in tetrahydrofuran facilitating the precipitation of the pure aryldiazonium tetrafluoroborate salts which were then collected by vacuum filtration and washed with tetrahydrofuran.

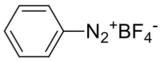
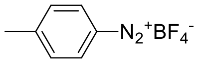
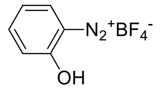
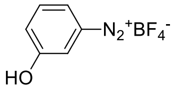
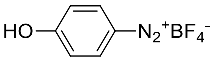
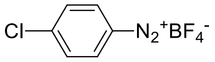
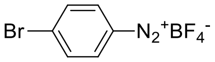
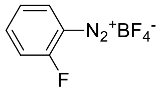
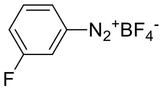
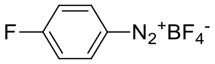
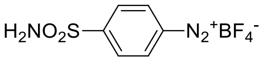
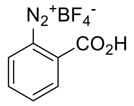
General protocol B - flow synthesis of aryl diazonium tetrafluoroborate salts

A solution of aryl amine (11.0 ml, 0.2 M in CH_3CN/EtOH see ratios in table 2) and a solution of isopentyl nitrite/ethanolic hydrochloric acid (1.6 mL/9.5 ml, 0.22 M in CH_3CN) were combined at a T-piece mixer (see table 2 for flow rates) cooled to 0˚C and reacted in a 2 mL HT PTFE coil also cooled to 0 ˚C. The combined stream was then passed through a glass Omnifit® column packed with sodium tetrafluoroborate (1.25 g, 11.4 mmol) at room temperature, followed by passage through a back-pressure regulator. The output stream was collected in a flask cooled to 0 °C and concentrated to dryness. The residue obtained was then suspended in tetrahydrofuran facilitating the precipitation of the pure aryldiazonium tetrafluoroborate salts which were then collected by vacuum filtration and washed with tetrahydrofuran.

Table 2: Reaction scope



1a-l 2a-l

Entry	Aniline	Product	Solvent system	Flow Rate (ml min^{-1})	Yield (%)	
					Batch	Flow
1	1a		93% CH_3CN/EtOH	2.0	100	100
2	1b		60% CH_3CN/EtOH	2.0	40	85
3	1c		80% CH_3CN/EtOH	2.0	31	64
4	1d		60% CH_3CN/EtOH	2.0	77	100
5	1e		50% CH_3CN/EtOH	1.5	21	100
6	1f		76% CH_3CN/EtOH	2.0	80	98
7	1g		76% CH_3CN/EtOH	2.0	90	99
8	1h		76% CH_3CN/EtOH	2.0	100	100
9	1i		76% CH_3CN/EtOH	2.0	99	100
10	1j		93% CH_3CN/EtOH	2.0	83	100
11	1k		60% CH_3CN/EtOH	2.0	36	0
12	1l		60% CH_3CN/EtOH	1.75	75	99

Standard conditions: Aryl amine (1.0 equiv., 0.20 M), isopentyl nitrite (1.1 equiv.), ethanolic hydrochloric acid (1.1 equiv.), $NaBF_4$ (2.0 equiv.).

Benzenediazonium tetrafluoroborate (2a). The titled compound was prepared following either protocol A or B affording a light pink solid (batch: 0.63 g, 3.3 mmol, 100%; flow: 0.42 g, 2.2 mmol, 100%). **^{1}H-NMR (300 MHz DMSO-d_6):** δ = 8.64 (d, 2H, *J* 8.07 Hz), 8.24 (dd, 1H, *J* 7.28 & 7.28 Hz), 7.96 (dd, 2H, *J* 7.85 & 7.85 Hz). **^{13}C-NMR (75 MHz DMSO-d_6)** δ = 140.92, 132.69, 131.29, 116.02. **^{19}F NMR (282 MHz, DMSO-d_6)** δ = -148.25, -148.30. **FT-IR neat ν (cm^{-1})** 3105, 2292, 1016, 754, 662. Data match those previously reported.

4-Methylbenzenediazonium tetrafluoroborate (2b). The titled compound was prepared following either protocol A or B affording a light brown solid (batch: 0.16 g, 0.8 mmol, 40%; flow: 0.34 g, 1.7 mmol, 85%). **^{1}H-NMR (300 MHz DMSO-d_6):** δ = 8.53 (d, 2H, *J* 8.46 Hz), 7.78 (d, 2H *J* 8.37), 2.56 (s, 3H). **^{13}C-NMR (75 MHz DMSO-d_6)** δ = 154.02, 132.67, 131.81, 111.92, 22.35. **^{19}F NMR (282 MHz, DMSO-d_6)** δ = -148.20, -148.26. **FT-IR neat ν (cm^{-1})** 3111, 2286, 1581, 1011, 817, 723. Data match those previously reported.

2-Hydroxybenzenediazonium tetrafluoroborate (2c). The titled compound was prepared following either protocol A or B affording an off-white solid (batch: 0.12 g, 0.6 mmol, 31%; flow: 0.26 g, 1.2 mmol, 64%). **^{1}H-NMR (300 MHz DMSO-d_6):** δ =7.60 (d, 1H, *J* 8.04 Hz), 7.42 (dd, 1H, *J* 7.86 & 7.86 Hz), 6.84 (s, 1H), 6.59 (d, 1H, *J* 9.24 Hz), 6.37 (dd, 1H, *J* 7.48 & 7.48). **^{13}C-NMR (75 MHz DMSO-d_6)** δ = 173.43, 139.91, 127.21, 121.68, 116.02, 91.35. **^{19}F NMR (282 MHz, DMSO-d_6)** δ = -148.51, -148.57. **FT-IR neat ν (cm^{-1})** 2280, 1306, 1010, 750, 608.

3-Hydroxybenzenediazonium tetrafluoroborate (2d). The titled compound was prepared following either protocol A or B affording a brown solid (batch: 0.32 g, 1.5 mmol, 77%; flow: 0.40 g, 1.9 mmol, 100%). **^{1}H-NMR (300 MHz DMSO-d_6):** δ = 11.41 (s, 1H), 8.09 (d, 1H, *J* 7.53), 7.94 (s, 1H), 7.74 (dd, 1H, *J* 7.25 & 7.25 Hz), 7.59 (d, 1H, *J* 6.12). **^{19}F NMR (282 MHz, DMSO-d_6)** δ = -148.40, -148.45. **FT-IR neat ν (cm^{-1})** 3199, 1411, 1306, 1011, 725.

4-Hydroxybenzenediazonium tetrafluoroborate (2e). The titled compound was prepared following either protocol A or B affording a white solid (batch: 0.09 g, 0.4 mmol, 21%; flow: 0.40 g, 1.9 mmol, 100%). **^{1}H-NMR (300 MHz DMSO-d_6):** δ = 8.29 (d, 2H, *J* 9.21 Hz), 6.96 (d, 2H, *J* 8.85 Hz). **^{19}F NMR (282 MHz, DMSO-d_6)** δ = -148.43, -148.49. **FT-IR neat ν (cm^{-1})** 2113, 2082, 1827, 1305, 1012, 595.

4-Chlorobenzenediazonium tetrafluoroborate (2f). The titled compound was prepared following either protocol A or B affording white solid (batch: 0.33 g, 1.5 mmol, 80%; flow: 0.39 g, 1.7 mmol, 98%). **^{1}H-NMR (300 MHz DMSO-d_6):** δ = 8.67 (d, 2H, *J* 8.91 Hz), 8.09 (d, 2H, *J* 8.91 Hz). **^{13}C-NMR (75 MHz DMSO-d_6):** δ = 146.57, 134.42, 131.63, 114.72. **^{19}F NMR (282 MHz, DMSO-d_6)** δ = -148.20, -148.26. **FT-IR neat ν (cm^{-1})** 3108, 2289, 1313, 1290, 1024, 833, 771.

4-Bromobenzenediazonium tetrafluoroborate (3g)

The titled compound was prepared following either protocol A or B affording a white solid (batch: 0.37 g, 1.4 mmol, 90%; flow: 0.40 g, 1.5 mmol, 99%). **^{1}H-NMR (300 MHz DMSO-d_6):** δ = 8.56 (d, 2H, *J* 8.88 Hz); 8.24 (d, 2H, *J* 8.88 Hz). **^{13}C-NMR (75 MHz DMSO-d_6):** δ = 136.58, 134.56, 133.98, 115.14. **^{19}F NMR (282 MHz, DMSO-d_6)** δ = -148.17, -148.23. **FT-IR neat ν (cm^{-1})** 3097, 2282, 1291, 1029, 827, 759. Data match those previously reported.

2-Fluorobenzenediazonium tetrafluoroborate (3h). The titled compound was prepared following either protocol A or B affording a light-yellow solid (batch: 0.44 g, 2.1 mmol, 100%; flow: 0.40 g, 1.9 mmol, 100%). **^{1}H-NMR (300 MHz DMSO-d_6):** δ = 8.73 (dd, 1H, *J* 6.63 & 6.63 Hz), 8.37 (dd, 1H, *J* 7.10 & 13.52 Hz), 7.99 (dd, 1H, *J* 9.18 & 9.18 Hz), 7.81 (dd, 1H, *J* 7.95 & 7.95 Hz). **^{13}C-NMR (75 MHz DMSO-d_6):** δ = 162.17, 158.55, 144.78, 144.66, 133.46, 133.41, 127.47, 118.81, 118.60, 105.65, 105.48. **^{19}F NMR (282 MHz, DMSO-d_6)** δ = -102.55, -148.31, -148.37. **FT-IR neat ν (cm^{-1})** 3106, 2292, 1287, 1250, 1029, 830, 769.

3-Fluorobenzenediazonium tetrafluoroborate (3i). The titled compound was prepared following either protocol A or B affording a white coloured solid (batch: 0.43 g, 2.1 mmol, 99%; flow: 0.40 g, 1.9 mmol, 100%). **^{1}H-NMR (300 MHz DMSO-d_6):** δ = 8.66 (d, 1H, *J* 7.59 Hz), 8.58 (d, 1H, *J* 8.28 Hz), 8.20 (dd, 1H, *J* 8.45 & 8.45 Hz), 8.00 – 8.08 (m, 1H). **^{13}C-NMR (75 MHz DMSO-d_6):** δ = 161.86, 159.35, 133.65, 133.56, 129.89, 129.86, 129.30, 129.09, 119.69, 119.39, 117.41, 117.29. **^{19}F NMR (282 MHz, DMSO-d_6)** δ = -105.75, -148.18, -148.24. **FT-IR neat ν (cm^{-1})** 3101, 2300, 1235, 1028, 874, 789, 651.

4-Fluorobenzenediazonium tetrafluoroborate (3j). The titled compound was prepared following either protocol A or B affording a light-yellow solid (batch: 0.37 g, 1.7 mmol, 83%; flow: 0.40 g, 1.9 mmol, 100%). **^{1}H-NMR (300 MHz DMSO-d_6):** δ = 8.77 – 8.82 (m, 2H), 7.84 – 7.90 (m, 2H). **^{13}C-NMR (75 MHz DMSO-d_6):** δ = 169.80, 167.14, 137.08, 136.96, 119.55, 119.30, 111.87, 111.84. **^{19}F NMR (282 MHz, DMSO-d_6)** δ = -87.21, -148.12, -148.17. **FT-IR neat ν (cm^{-1})** 3114, 2291, 1252, 1016, 843, 682. Data match those previously reported.

4-Sulfamoylbenzenediazonium tetrafluoroborate (3k). The titled compound was prepared following either protocol A affording a pale-yellow solid (batch: 0.15 g, 0.6 mmol, 36%). **^{1}H-NMR (300 MHz DMSO-d_6):** δ = 8.85 (d, 2H, *J* 8.73), 8.32 (d, 2H, *J* 8.76), 8.05 (s, 2H). **^{13}C-NMR (75 MHz DMSO-d_6):** δ = 153.37, 134.05, 128.06, 119.46. **^{19}F NMR (282 MHz, DMSO-d_6)** δ = -148.19, -148.25. **FT-IR neat ν (cm^{-1})** 2079, 1663, 1306, 1011, 618.

2-Carboxybenzenediazonium tetrafluoroborate (3l). The titled compound was prepared following either protocol A or B affording a white solid (batch: 0.31 g, 1.3 mmol, 75%; flow: 0.40 g, 1.7 mmol, 99%). **^{1}H-NMR (300 MHz DMSO-d_6):** δ = 12.21 (s, br, 1H), 7.71 (dd, 1H, *J* 8.04 & 1.46 Hz), 7.56 (dd, 1H, *J* 8.58 & 8.58 Hz), 7.12 (d, 1H, *J* 7.72 Hz), 7.10 (d, 1H, *J* 7.52). **^{13}C-NMR (75 MHz DMSO-d_6):** δ = 172.33, 157.50, 135.29, 130.36, 129.77, 120.62, 116.96. **^{19}F NMR (282 MHz, DMSO-d_6)** δ = -

148.27, -148.33. **FT-IR neat ν (cm^{-1})** 3099, 2281, 1728, 1047, 725, 635.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 A.A. Mohamed, Z. Salmi, S.A. Dahoumane, A. Mekki, B. Carbonnier and M.M. Chehimi, *Adv. Colloid Interface Sci.*, 2015, **225**, 16.

2 F. Mo, G. Dong, Y. Zhang and Wang, *J. Org. Biomol. Chem.*, 2013, **11**, 1582.

3 R.N. Ram and V. Singh, *J. Chem. Res.*, 2006, 800.

4 G. Maas, M. Tanaka and T. Sakakura, Benzenediazonium Tetrafluoroborate, Section in Encyclopaedia of Reagents for Organic Synthesis 2nd Ed., book 1., Paquette, L.A.; D. Crich, P.L. Fuchs and G.A. Molander(eds.), Wiley, 2009, 436 – 441.

5 R.C.R. Wootton, R. Fortt, and J. de Mello, *Lab Chip*, 2002, **2**, 5.

6 R. Fortt, R.C.R. Wootton and J de Mello, *Org. Process Res. Dev.*, 2003, **7**, 762.

7 B. Li, D. Widlicka, S. Boucher, C. Hayward, J. Lucas, J.C. Murray, B.T. O'Neil, D. Pfisterer, L. Samp, J. Van Alsten, Y. Xiang, and J. Young, *Org. Process Res. Dev.*, 2012, **16**, 2031.

8 N. Oger, E. Le Grognec and F.-X. Felpin, *J. Org. Chem.*, 2014, **79**, 8255.

9 B. Ahmed-Omer, D.A. Barrow and T. Wirth, *Tetrahedron Lett.*, 2009, **50**, 3352.

10 (a) M. Chen and S.L. Buchwald, *Angew. Chem. Int. Ed.*, 2013, **52**, 4247. (b) Z. Yu, X. Xie, H. Dong, J. Liu and W. Su, *Org. Process Res. Dev.*, 2016, **20**, 774.

11 (a) L. Malet-Sanz, J. Madrzak, R.S. Holvey and T. Underwood, *Tetrahedron Lett.*, 2009, **50**, 7263. (b) L. Malet-Sanz, J. Madrzak, S.V. Ley and I.R. Baxendale, *Org. Biomol. Chem.*, 2010, **8**, 5324. (c) J. Jacq and P. Pasau *Chem. Eur. J.*, 2014, **20**, 12223. (d) J. D'Attoma, T. Camara, P.L. Brun, Y. Robin, S. Bostyn, F. Buron, and S. Routier, *Org. Process Res. Dev.*, 2017, **21**, 44.

12 N. Oger, E. Le Grognec, and F.-X. Felpin, *Org. Chem. Front.*, 2015, **2**, 590.

13 Z.-Q. Yu, Y.-W. Lv, C.-M. Yu, and W.-K. Su, *Tetrahedron Lett.*, 2013, **54**, 1261.

14 T. Hu, I.R. Baxendale and M. Baumann, *Molecules*, 2016, **21**, 918.

15 A.P. Colleville, R.A.J. Horan and N.C.O. Tomkinson, *Org. Process Res. Dev.*, 2014, **18**, 1128.

16 B.S. Furniss, A.J. Hannaford, P.W. Smith and A.R. Tatchell, Formation of diazonium salts and their uses in Vogel's Textbook of Practical Organic Chemistry 5th Ed., Pearson Prentice Hall, 1989, 920 – 953.

17 M. Hudlicky, Replacement of Nitrogen by Fluorine in Chemistry of Organic Fluorine Compounds 2nd Ed., E. Horwood and J. Mellor (eds.), Ellis Horwood and Prentice Hall, 1992, 160 – 169.