Rapid formation of 2-lithio-1-(triphenylmethyl)imidazole and substitution reactions in flow

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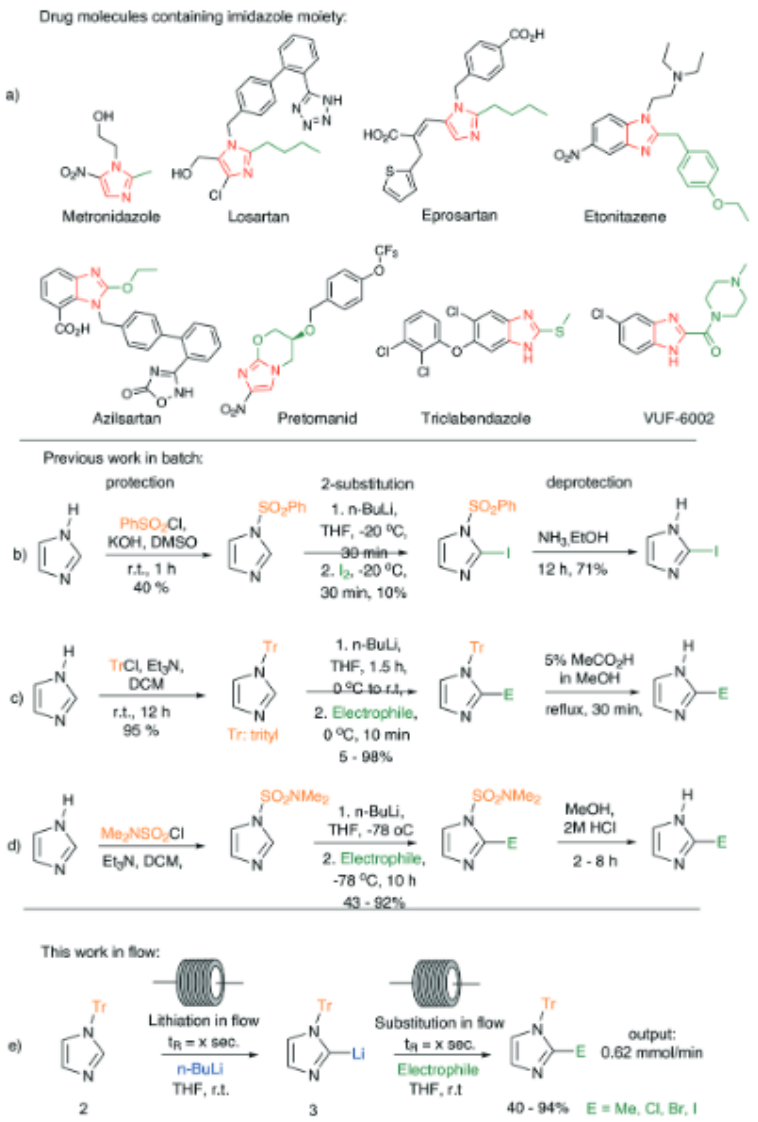
Abstract

The functionalisation of imidazoles is a necessary step in the formation of many active pharmaceutical intermediates. Herein, we report a flow chemistry approach for the rapid and efficient formation of 2-lithio-1-(triphenylmethyl)imidazole at ambient temperature and its reaction with a range of electrophiles, achieving modest to high yields (40–94%) in short reaction times (<1 min). The method is amenable to the scale-up of this highly reactive lithio-imidazole intermediate.

Imidazole, the eponymous five-membered N-heterocycle ring, is an industrially important and chemically versatile building block widely used for the development of pharmaceuticals, agrochemicals, carbene ligands and ionic liquids.[1–3] It is found in many naturally occurring compounds such as alkaloids, histamine, histidine and vitamin B12.[1–3] Imidazole is electron-rich, a feature that enables it to bind with various receptors and enzymes in biological systems via weak non-covalent interactions.[4,5] The broad spectrum of biological activities of

imidazoles has resulted in intensive medicinal chemistry programmes focused on developing imidazole pharmacophores. Consequently, imidazole structures are found in a wide range of drugs for the treatment of parasitic, fungal and bacterial infections, hypertension, inflammation and immune disorders.[4–7]

Imidazole is an unsaturated five-membered heterocyclic compound that is susceptible to a wide range of chemical transformations.[8] While the functionalisation of imidazole at the N-1, C-4 and C-5 positions has been extensively investigated fewer versatile protocols for C-2 functionalisation have been reported despite the high prevalence of C-2 modified drug molecules (Scheme 1a). Iodination was first demonstrated by Sundberg in 1977, using a phenylsulfonyl protecting group for N-1 (Scheme 1b).[9] Masking the N-1 proton permits strong bases, including organolithium reagents, to access the proton at the C-2 position. However, due to the instability of the sulfonyl group under lithiation conditions, the 2-iodo product can only be isolated in low yields ~10%. Later, Kirk reported that by protecting the N-1 position with a triphenylmethyl (trityl) group, C-2 can be reliably functionalised with a range of electrophiles (Scheme 1c).[10] Other protecting groups including *N*,*N*-dimethylsulfonyl (Scheme 1d), phenylmethyl, benzyloxy and tetrahydro-pyran-2-yl have also been reported, however, there is no clear advantage over the readily available trityl protecting group.[11–14] A small number of direct 2-functionalisation methods have also been reported, however, they lack chemical versatility or require more expensive reagents.[15,16]



Scheme 1 Drug molecules with variously functionalised imidazole groups (a) previously reported protection, substitution and deprotection routes used to derivatise the C-2 position of imidazole (b–d). Lithiation and substitution steps translated to flow (e).

Although organolithium reagents are highly effective for deprotonation, they are challenging to apply on a large scale. In addition to their inherent air and moisture sensitivity, deprotonation reactions with organolithium reagents are highly exothermic, and involve fast reaction kinetics. Consequently, they can be difficult to control in terms of mixing and heat management. The high flammability and low stability of lithiated intermediates coupled with the large quantities of organolithium precursors required on scale-up presents further safety challenges. Lithiations were categorised as “Type A” reactions by Roberge, whereby the

reaction is extremely fast, often takes place at the mixing zone and is rate limited by mixing.[17,18]

In the past decade, flow chemistry has attracted much interest for safely scaling-up organic reactions involving organometallic reagents such as organolithium and Grignard reagents.[19–26] The small dimensions (I.D. ~1 mm) of the reactor channels or tubes in flow systems result in large surface area-to-volume ratios that enhance heat exchange and mixing. This improved temperature control and efficient mixing can deliver higher reaction selectivity, reproducibility and improve process safety compared to conventional bulk reactors.[27,28] Translating organometallic reactions to flow presents key challenges, including the formation of metal salt precipitates that can result in reactor blockages. Such blockages can, however, be minimised by carefully controlling flow rates, reagent concentrations and process temperatures.[19,20]

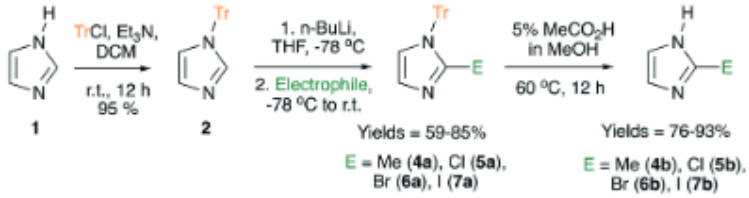
Herein, we report a two-step flow method to rapidly synthesise C-2 functionalised imidazoles *via* a lithiation step with *n*-butyllithium, followed by reaction with a range of electrophiles (Scheme 1e).

The model lithiation of the N-1 trityl protected imidazole using *n*-BuLi was initially optimised under batch conditions and reacted further with methyl iodide (Scheme 2). The batch method involved dropwise addition of *n*-BuLi (1.6 M in hexanes) to 1-tritylimidazole in THF at −78 °C, stirring for 0.5 hour followed by quenching with MeI. The reaction was warmed to room temperature and stirred for 12 hours to give 2-methyl-1-tritylimidazole (**4a**) in 85% isolated yield. Under similar conditions an improved yield of 2-chloro-1-tritylimidazole (**5a**) (61%) was achieved using trichloroisocyanuric acid (TCICA) compared to the previous literature reports ~50% that use *N*-chlorosuccinimide and *tert*-butyl-hypochlorite.[10,11] Reactions with *N*-bromosuccinimide (NBS) and iodine were also conducted, generating 2-bromo-1-tritylimidazole (**6a**) and 2-iodo-1-tritylimidazole (**7a**) respectively (Table 1). After deprotection in 5% acetic acid/methanol at 60 °C, the 2-functionalised imidazoles (**4–7b**) were consistently obtained with >76% isolated yields.

Table 1 Summary of batch 1-tritylimidazole lithiations and electrophilic quench reactions

Reagent	Ratio BuLi : E^+	BuLi/E^+ (h)	Conv.[a] (%)	Yield[b]	Yield[b]
MeI	1 : 1	0.5/12	100	 **(4a)**, 85%	 **(4b)**, 93%
TCICA	1 : 0.36	1/12	100	 **(5a)**, 61%	 **(5b)**, 88%
NBS	1 : 1	1/12	100	 **(6a)**, 58%	 **(6b)**, 76%
I_2	1.15 : 1	0.5/12	100	 **(7a)**, 65%	 **(7b)**, 79%

Batch reaction conditions: dropwise addition of *n*-BuLi (1.6 M in hexanes) to 1-tritylimidazole in THF (0.16 M) at −78 °C followed by reaction with electrophile and warming to RT followed by trityl deprotection with 5% acetic acid in methanol. [a] Conversion determined by NMR spectroscopy. [b] Isolated yield.



Scheme 2 Generation of 1-trityl-2-litho-imidazole and its derivatization with different electrophiles.

A preliminary flow set-up was constructed initially for the translation of the lithiation step of 1-tritylimidazole at ambient temperature followed by the electrophilic quenching step in batch (Fig. 1, set-up A). The reactor consisted of inlets for *n*-BuLi solution and 1-tritylimidazole solution in THF, a mixing-tee and short reactor coil. The solubility of 1-tritylimidazole was limited to common ethereal solvents typically used for lithiation reactions. THF was the preferred solvent for the reaction offering the highest solubility (~0.20 M) compared to either dimethoxyethane (~0.05 M) or dioxane (~0.13 M). A solution of 1-tritylimidazole was prepared as a 0.16 M solution in anhydrous THF, slightly lower than the solubility threshold to avoid precipitation within the reactor tubing. *n*-BuLi solution (1.6 M in hexane) was used and both inlets joined with a simple tee-piece of wider internal diameter (I.D. 2 mm) than the tubing, which is known to benefit mixing by enhancing turbulence at the inlet junction and also reduce clogging.[20,28,29] The reaction mixture was then passed through a reaction coil (FEP tubing, I.D. 1 mm, lengths 60–400 cm), collected in a vial containing a solution of methyl iodide in anhydrous THF under nitrogen and stirred for 5 min followed by addition of triethylamine to precipitate unreacted MeI. The mixture was filtered through a layer of celite and concentrated *in vacuo* for further analysis.

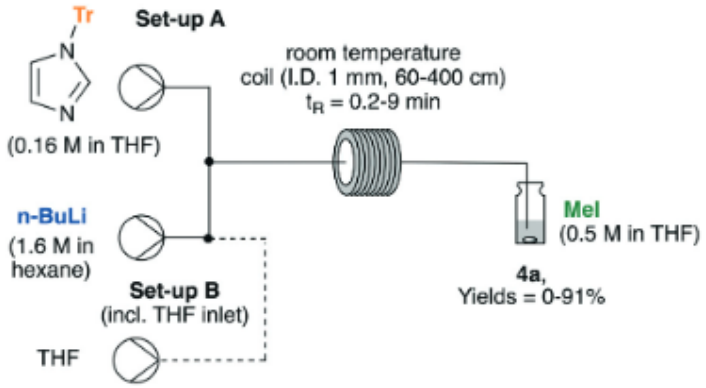


Fig. 1 Preliminary flow set-up for the optimisation reaction of *n*-BuLi with 1-tritylimidazole.

Table 2 Optimisation of 1-tritylimidazole lithiation in flow and reaction with MeI

Entry	Ratio BuLi : MeI	Flow rate[a] (mL min^{-1})	t_R (min)	Coil length (cm)	Coil volume (mL)	Set-up	Conv.[b]	Yield[b]
1	1 : 1	0.47	1.0	60	0.47	A	4%	0%
2	1 : 1	0.47	4.3	260	2.04	A	65%	54%
3	1 : 1	0.35	9.0	400	3.14	A	81%	53%
4	1 : 1	0.45	7.0	400	3.14	A	85%	62%
5	1 : 1	0.65	5.0	400	3.14	A	79%	62%
6	1 : 1	1.05	3.0	400	3.14	A	83%	68%
7	1 : 1	1.05	1.5	200	1.57	A	82%	75%
8	1.2 : 1.2	3.14	0.5	200	1.57	B	90%	88%
9	1.2 : 1.2	5.24	0.3	200	1.57	B	92%	91%
10	1.2 : 1.2	7.85	0.2	200	1.57	B	88%	87%

[a] Total flow rate. [b] Conversion and yield determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard and based on the quantity of 2. Note: conversions may be underestimated if quenching of 3 occurs due to traces of H^+/H_2O.

Preliminary testing of the flow set-up with a residence time of one min (60 cm, 0.47 mL reactor coil) and flow rate of 0.47 mL min^{-1}, resulted in no product formation, potentially indicating insufficient mixing of reagents. By extending the reaction coil from 60 cm to 260 cm (2.0 mL) and increasing the residence time to 4.33 min, a much-improved conversion of **2** and 54% yield of **4a** were achieved (Table 2). The reaction coil was further extended to 400 cm (3.1 mL) with residence times ranging from nine to three min (entries 3–6). While the longer reaction channel improved the conversion, varying the flow rate and hence the residence time did not significantly change the conversion. The conversion remained consistent, peaking at ~80%, whilst the yield of the reaction increased from 53% to 68% as the residence time decreased. The yield was further improved to 75% at the shorter residence time of 1.5 minutes by halving the length of the reaction coil (entry 7). This data suggests that a reaction coil length of ~200 cm and a short residence time of <2 min is optimal for this set-up. Results (Fig. S2, ESI†) show that extended residence times gave lower yields of **4a** while the conversion of 1-tritylimidazole (**2**) remained relatively consistent and therefore indicating increased levels of decomposition of **3** before MeI quenching can occur.

During these preliminary tests, occasional blockages occurred in the tee-piece joining the inlets of the *n*-BuLi and 1-tritylimidazole solutions; this was likely due to the low solubility of 1-tritylimidazole in hexane. An additional inlet containing THF was introduced into the *n*-BuLi stream to avoid this precipitation issue (Fig. 1, set-up B). As *n*-BuLi is unstable in THF at room temperature, the mixing channel was kept to a minimal length (50 cm). Since the previous test showed prolonged residence time led to increased decomposition, higher flow rates were used (3.14–7.85 mL min^{-1}). The stoichiometric ratio of *n*-BuLi was also increased slightly to 1.2. Under these new conditions, significantly improved yields of **4a** (87–91%) were achieved, likely due to combined factors of more efficient mixing, owing to increased turbulence at the higher flow rates, and lower levels of decomposition of **3** due to shorter residence times prior to quenching. No significant differences in conversions and yields were observed when the residence time increased from 0.2 to 0.5 min. The lithiation reaction conditions in entry 9, Table 2 were selected for further substrate scope investigations.

The flow set-up was modified further to include the in-line reaction of the electrophile (Fig. 2); the detailed flow rates are listed in Table S2, ESI.† The flow rates of the lithiation reaction

Table 3 The substrate scope of C-2 lithiation-substitution of imidazole with a range of electrophiles in flow. Lith. – lithiation step; Subs. – substitution step; Electro. equiv. – the equivalence of electrophile with respect to 1-tritylimidazole; prod. – product

Entry	Electrophile	Lith. t_R min	Subs. t_R min	Electro. equiv.	Prod.	Conv[a]	Yield[b]
1	MeI[c]	0.3	0.31	1.2	**4a**	98%	93%
2	C_2Cl_6	0.3	0.51	1.2	**5a**	100%	94%
3	$C_2Br_2Cl_4$	0.3	0.51	1.2	**6a**	100%	70%
4	I_2	0.3	0.31	1.2	**7a**	70%	65%
5	EtI[d]	0.25	1.02	1.8	**8**	90%	84%
6	BuI[d]	0.25	1.02	1.8	**9**	70%	58%
7	4-Methoxybenzyl iodide[e]	0.3	0.31	1.2	**10**	N.A.	56%
8	DMF	0.3	0.31	3.0	**11**	100%	88%
9	2-Octanone	0.3	0.61	1.2	**12**	69%	40%
10	$ClCO_2Et$[f]	0.3	0.61	1.2	**13**	100%	—
11	Diphenyl disulfide	0.3	0.61	1.2	**14**	100%	78%
12	TMSCl	0.3	0.31	1.2	**15**	—	N.R.
13	TIPSCl	0.3	0.61	1.2	**16**	—	N.R.

[a] Conversion and yield determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard and based on the quantity of **2**. Note: conversions may be underestimated if quenching of **3** occurs due to traces of H^+/H_2O. [b] Isolated yield. [c] Scaled-up to a 10-minute reaction. [d] Total flow rate = 4.62 mL min^{-1}. [e] Only di-substituted product isolated, NMR conversion not reported due to overlap on the spectrum. [f] Starting material decomposed, no expected product formed.

were generally maintained at the optimised conditions (entry 9, Table 2) and the electrophile solution was infused at 2.46 mL min^{-1} unless otherwise specified. The residence time and concentration of the electrophile solution were optimised according to the respective electrophiles. Running the sequential lithiation of **2** and in-line methylation using MeI resulted in comparably high yields of **4a** (93%) *vs.* the off-line MeI reaction (Table 3). This was scaled-up by operating the reaction for 10 minutes, resulting in the isolation of 1.85 g of **4a**. Chlorination and bromination of **3** were then attempted first using TCICA and NBS respectively, however, in-line addition of TCICA or NBS to a stream of **3** in flow resulted in precipitate formation, most likely lithium amide salts. The reactions were repeated using the alternative reagents hexachloroethane and 1,2-dibromotetrachloroethane as the sources of chloride and bromide cations.[30,31] No precipitates were observed during the reactions giving full conversions and high yields of 94% and 70% respectively. Iodination was effectively achieved using elemental iodine as electrophile and 65% of 1-trityl-2-iodoimidazole (**7a**) was isolated.

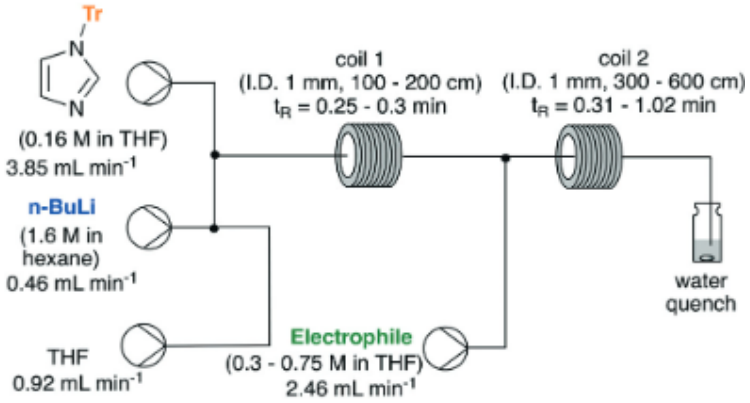


Fig. 2 Flow set-up for the generation of 2-lithio-1-tritylimidazole (**3**) and in-line reaction with various electrophiles.

Ethyl and *n*-butyl iodides were used as electrophiles to alkylate the 2-position of imidazole (entries 5 and 6). As the length of the alkyl chain increased the rate of reaction was found to decrease and longer residence times were required to improve the conversions and yields. Ethyl iodide required more than three times the residence time than reaction with MeI to produce a similar yield. Under the same conditions, the substitution with *n*-butyl iodide was incomplete with only 70% conversion and 58% isolated yield.

Reaction with a benzyl iodide (4-methoxybenzyl iodide) produced a di-substituted species 2-(1,2-bis(4-methoxyphenyl)ethyl)-1-tritylimidazole (**10**) with a 56% yield. After the first substitution, the allyl position was stabilised by two aromatic systems, potentially allowing the second lithiation to occur on this carbon and subsequently reacted with an additional benzyl iodide. 2-Formylation was successfully performed by using DMF as the electrophile *via* a Bouveault reaction, producing 1-trityl-2-imidazolecarboxaldehyde (**11**) in 88% yield. The scope of this reaction could be further expanded to produce ketones by using other amides including dimethylacetamide and dimethylpropanamide as the electrophile, as similar Bouveault reactions have been reported.[32–35] 1-Trityl-2-lithioimidazole also reduces aldehyde and ketone functionalities to secondary and tertiary alcohols *via* nucleophilic addition. This is demonstrated in reaction of **3** with 2-octanone as the electrophile to afford the tertiary alcohol, 2-(1-tritylimidazol-2-yl)octan-2-ol (**12**), in modest yield (40%).

The substitution of **3** proceeded reliably in flow with diphenyl disulfide giving full conversion and 78% yield of 2-(phenylthio)-1-tritylimidazole (**14**) under the standard flow conditions. Other disulfides including methyl disulfide have also been reported to undergo this reaction.[36]

Using ethyl chloroformate as an electrophile to introduce an ester group and generate ethyl 1-tritylimidazole-4-carboxylate (**13**) was previously demonstrated by Kirk.[10] Under flow conditions, infusion of the ethyl chloroformate solution resulted in the formation of a white precipitate, most likely LiCl, which gradually blocking the system. Disappointingly, none of the expected product was isolated from the reaction mixture obtained before the blockage and the starting materials were found to decompose. Similarly, no expected products were isolated from the reactions with trimethylsilyl chloride (TMSCl) and triisopropylsilyl chloride (TIPSCl). As silyl groups are unstable in even weakly acidic or alkaline conditions, the product could have been desilylated during quenching to yield the starting material.

In conclusion, a simple flow system has been used to firstly optimise the lithiation reaction of 1-tritlyimidazole in the C-2 position and then to screen the reactivity of a range of electrophiles. Whilst the flow system was demonstrated to effectively generate 1-trityl-2-lithioimidazole rapidly at ambient temperature, precipitation occurred that resulted in occasional blockages. This could be circumvented by in-line dilution of the *n*-BuLi stream with THF. The reaction of 1-trityl-2-lithioimidazole with a range of electrophiles displayed

varying yields depending on the nature of the electrophile, for example the more reactive MeI gave almost quantitative yields whereas *n*-butyl iodide gave a modest 58% yield. Other functionality could be introduced to the imidazole; chlorination and bromination reactions proved to be high yielding, and so to was reaction with DMF to generate an aldehyde group. The reaction is currently limited by the need to undertake the deprotection step in batch, however, we are currently exploring routes to translate this step to flow. This two-step process is fast, amenable to producing gram quantities of material and can be conveniently carried out at ambient temperature. The flow process represents a step towards to scaling-up the synthesis of a range of C-2 functionalised imidazoles.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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