Optimization and scale-up for commercialization of a novel synthesis of Triclosan

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By

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Abstract

The research described in this dissertation was undertaken with the aim of developing and commercializing a new product for DOW – Sentrachem Company. The optimization and scale-up, for the commercialization, of a novel synthesis of the broad-spectrum anti-bacterial, Triclosan, is described.

The product was synthesized in three reaction steps: The diphenyl ether, 5-chloro-(2,4-dichlorophenoxy)acetophenone, was synthesized via a copper(II) catalysed, Ullmann Ether Synthesis by coupling 2,4-dichlorophenol and 2,5-dichloroacetophenone. A Baeyer-Villiger Oxidation reaction with peroxymaleic acid yielded the ester, 2-acetoxy-2',4',4-trichlorodiphenyl ether. The ester was transesterified with methanol with an acid catalyst to yield the product, 2,4,4'-trichloro-2'-hydroxydiphenylether (Triclosan).

Optimization of a laboratory scale synthesis and a multi-kilogram scale-up is described. The process was successfully scaled-up and recommendations have been made to progress to a mini-production plant for a second phase scale-up.

Acknowledgements

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- Thank you to the 'Triclosan team':

Process development:	Dr Gert Lourens Vladimir Cukan Magrieta Snyman Linda van Sckalkwyk
Analytical laboratory:	Flip Mouton Les Cornish
Scale-up team:	Mohamed Moola Vladimir Cukan

- Thanks to DOW – Sentrachem for allowing me to use this information to write this dissertation.

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Chapter 1

Introduction

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1. List of abbreviations

DCM – Dichloromethane.

DCPCAP – 5-chloro-2-(2,4-dichlorophenoxy)acetophenone.

FTIR – Fourier transformed infrared spectrometer

GC – Gas chromatograph.

ICP – Inductively coupled plasma, atomic adsorption spectrometer.

NMR – Nuclear magnetic resonance spectrum or spectrograph.

TCS – Triclosan. 2,4,4'-Trichloro-2'-hydroxydiphenyl ether.

TCSE – Triclosan ester. 2-Acetoxy-2',4',4-trichlorodiphenyl ether.

2. Introduction

The laboratory optimization and scale-up of a novel three-step synthesis of the broad spectrum anti-microbial, Triclosan is described. An international patent has been applied for to protect the intellectual property rights of this synthesis in the name of Dr Gert Lourens who developed this synthesis. This new synthesis was developed into a commercially viable process for the commercial production of Triclosan.

This development work required a good knowledge of organic synthesis, analytical chemistry, physical chemistry, catalysis and the types and use of large-scale production equipment.

2.1. The product

Triclosan [2,4,4'-trichloro-2'-hydroxydiphenyl ether] is a topical anti-microbial that is used in the formulation of many antibacterial products. Surgical scrub soaps, deodorants, toothpaste, mouthwash and anti-septic wound dressings are but a few applications. The product is well suited for human use because it exhibits good skin compatibility, high stability and a high toxicological safety. It is active against most gram-positive and gram-negative bacteria as well as many fungi[1]. Triclosan was developed by Ciba-Geigy Corporation and is manufactured by them in quantities of thousands of tons per year. The product is sold by them under the trademark Irgasan DP-300.

2.2. Methodology

The laboratory synthesis was developed and optimized in order to establish the ideal reagents, minimum amounts of reagents, reaction conditions and methods of purification. The production equipment required for scale-up was identified based on the physical properties of the chemicals involved and the required handling procedures. Production costs were estimated and continually updated to ensure that

the process remained financially viable. Once the laboratory-scale synthesis was fully optimized and the large-scale equipment required had been identified, the process was scaled up.

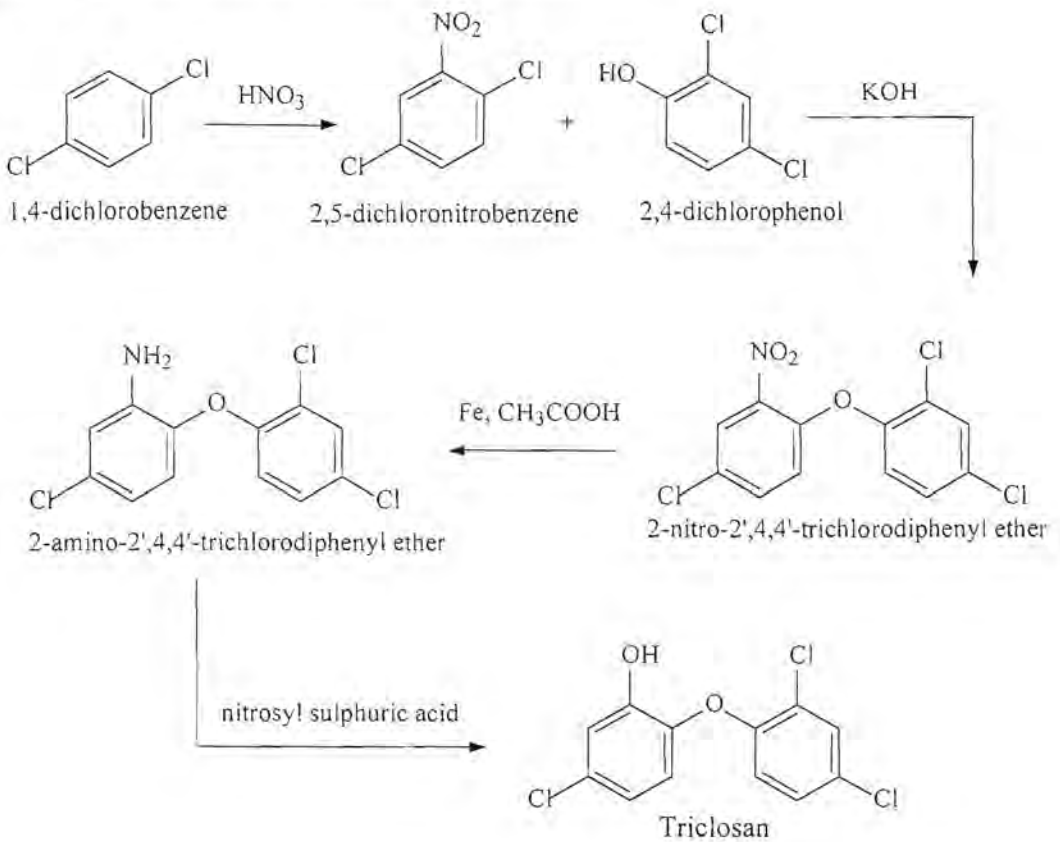
In developing this commercial process it was essential to scale-up the reaction to about a quarter of the size of an envisaged production batch. This was done in order to identify the exact equipment to be required for full-scale production and to further optimize reaction parameters to suit larger equipment. This reaction was scaled-up in a 250 litre reactor; the estimated batch size for a production plant was 1000 litres.

In order to compete in an existing market, a generic product must have an advantage over the original manufacturer's product. A lower production cost and/or a superior quality is usually required. Both were established by developing a sophisticated and shorter synthesis of this product. This synthesis and the process were developed and optimized to meet stringent purity specifications and to produce Triclosan in the most cost-effective manner that could be devised.

3. The existing synthesis route

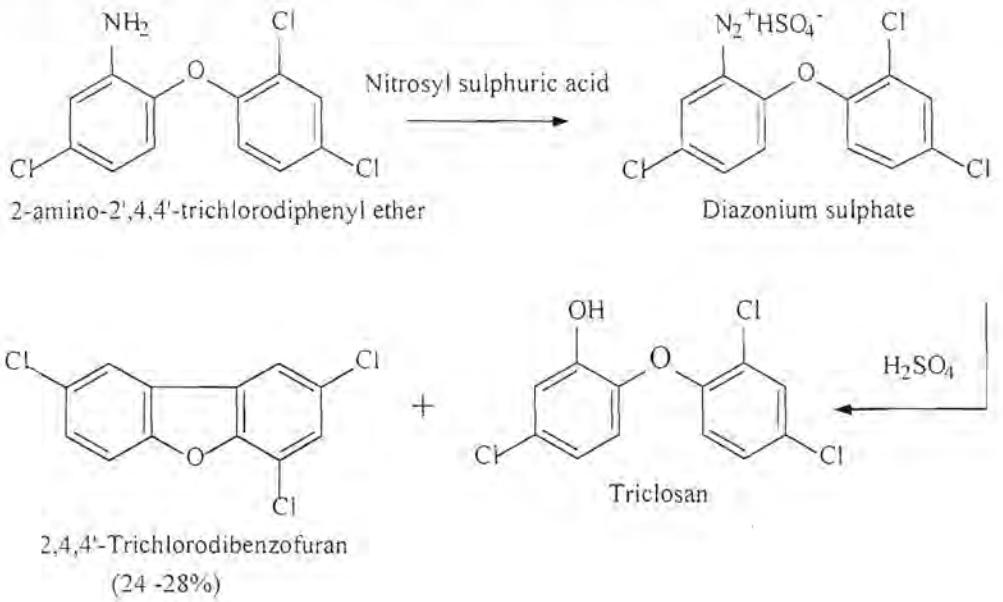
The original patent holder (now expired) and manufacturer of Triclosan is Ciba-Geigy. Their process described in the cited patents is as follows:

Diagram: The Ciba-Geigy route to Triclosan.



The last step of this process is the most crucial. In the procedures described [2,3], the analine was diazotized with nitrosyl sulphuric acid or sodium nitrite in sulphuric acid to form the diazonium sulphate. The latter was then decomposed with a mixture of 50 to 80% aqueous sulphuric acid in o-dichlorobenzene at 165°C. No yields were given but in later patents [4,5] describing methods of purification of this material, yields of 53 to 63% were claimed with the removal of the accompanying 24 to 28% trichlorodibenzofuran (See diagram).

Diagram: Last step of Ciba-Geigy Triclosan process



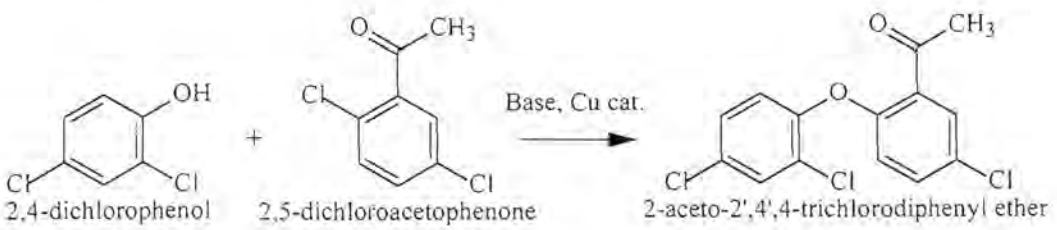
3.1. Downfall of the existing synthesis

The cited patents describe a purification process consisting of up to six extractions with trichloroethylene followed by distillation and crystallization from an aliphatic petroleum ether solvent (B.p. 130 to 138°C). The large volumes of solvents, sulphuric acid and dibenzofuran waste streams are expensive to dispose of, usually requiring incineration. At present there are no licensed chemical incinerators in South Africa. Dibenzofurans are also extremely toxic, and possibly carcinogenic having effects similar to chlorodioxins[6, 7]. From an environmental, health and safety point of view, the formation of these large amounts of dibenzofurans is highly undesirable.

4. The new process

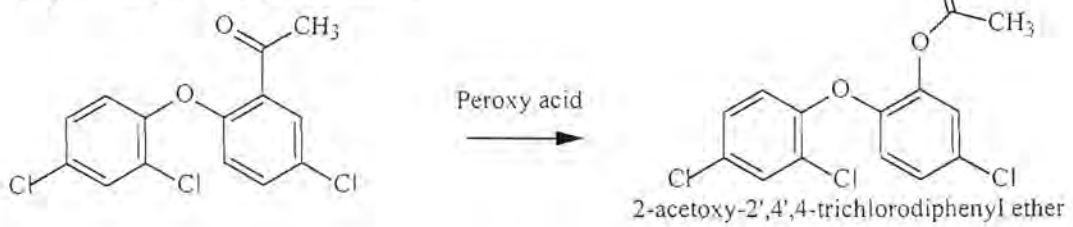
This synthesis consists of three reaction steps; each described in a separate chapter of this dissertation. The general reaction scheme is as follows:

Step 1: Ulmann ether synthesis



2,4-dichlorophenol + 2,5-dichloroacetophenone → 2-aceto-2',4',4-trichlorodiphenyl ether

Step 2: Baeyer-Villiger oxidation



2-acetoxy-2',4',4-trichlorodiphenyl ether

Step 3: Transesterification

4.1. Advantages of this process

The process described in this dissertation has an advantage over the existing process in that minimal amounts of chlorinated dioxins and no dibenzofurans were formed. Less purification steps were required and therefore a much lower volume of waste was generated. Low waste disposal costs and high yields gave this process a financial advantage over the Ciba-Geigy process.

The reagents, 2,4-dichlorophenol and maleic anhydride, are products of this company, DOW-Sentrachem. This value addition to basic chemicals made this process even more attractive for the company. Further advantages were gained when planning the location of production facility. The site identified for the production plant is situated next to the 2,4-dichlorophenol production plant, which will reduce the transportation costs of raw materials.

A large volume of aqueous sodium chloride waste will be piped to the chlor-alkali facility on the same site for use as process water. A waste stream of aqueous maleic acid will be transported by rail-tankers to another site for recycling to the reagent, maleic anhydride. All of these factors contributed to increasing the potential profit that could be made from the production of Triclosan, for the DOW - Sentrachem Company.

5. Literature references

[1] Ciba-Geigy circular 2507 E: Official drug registration.

[2] E. Model, J Bindler: US Patent 3, 506, 702 (1970)

[3] E. Model, J Bindler: US Patent 3, 624, 447 (1971)

[4] R,B Lund, G,W Brown: US Patent 4, 467, 117 (1984)

[5] R,B Lund: US Patent 4, 486, 610 (1984)

[6] F. D'Souza (Ed); Disaster Research In Practice: The Chemical Scythe, pp30-60.Plenum Press 1984

[7] E, H. Blair (Ed) Advances In Chemistry Series 120: Chlorodioxins - Origin and Fate. ACS 1973

Chapter 2

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1. Step 1: Ullmann Ether Synthesis

1.1. Introduction

The first step of this synthesis of Triclosan is the manufacture of a diphenyl ether via the Ullmann ether synthesis[1]. This reaction is a well-established method for the manufacture of diphenyl ethers. It involves heating aryl halides with potassium or sodium phenoxides in the presence of a copper catalyst. Copper catalysts that have been used are the copper(I) halides, copper(I) and copper(II) oxides, basic carbonates and carboxylates[2,3]. Solvents play a significant role in the Ullmann reaction in that they not only dissolve the reagents but also bring the copper salt catalyst into solution[4].

This reaction describes the copper catalyzed coupling of 2,4-dichlorophenol and 2,5-dichloroacetophenone to give the diphenyl ether, 2-aceto-2',4',4-trichlorodiphenyl ether, or to be more correct 5-chloro-2-(2,4-dichlorophenoxy)acetophenone. For ease of use the name was shortened to DCPCAP (from **di**chloro**p**henoxy -**c**hloro**a**ceto**p**henone). Sodium bicarbonate was used as a base and copper(II)chloride as catalyst. Toluene was used as the solvent and the reaction mixtures were dried during the reaction by azeotropic distillation at 120°C. Anhydrous conditions were required to prevent the copper catalyst from being extracted from the reaction mixture into an aqueous phase, making it unavailable for reaction and also to prevent by-product formation as described later.

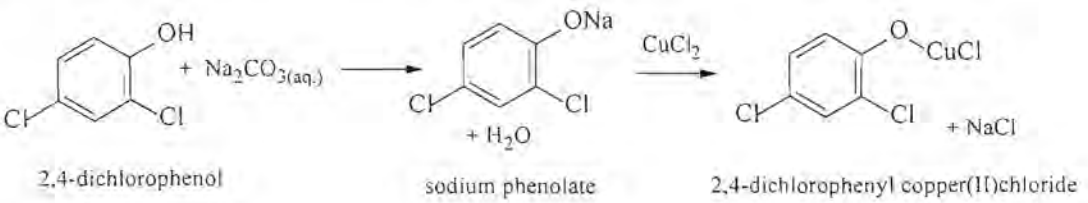
1.2. Reaction mechanism

Results obtained by others[4,5] have lead to the conclusion that the mechanism is most probably a nucleophilic aromatic substitution involving a carbon-halogen bond cleavage. They suggest a biphenyl copper species to be a common intermediate. During an acid base reaction, the phenolic proton of 2,4-dichlorophenol, reacts with sodium carbonate to form a sodium phenolate. This in turn reacts with the copper(II)chloride

catalyst to form chloro (2,4-dichlorophenoxy) copper(II) [Diagram 1.1]. The copper phenolate reacts with another sodium phenolate to form the suggested biphenyl copper intermediate shown in [Diagram 1.2]. The Cu-O bonds will in all probability be more ionic in character.

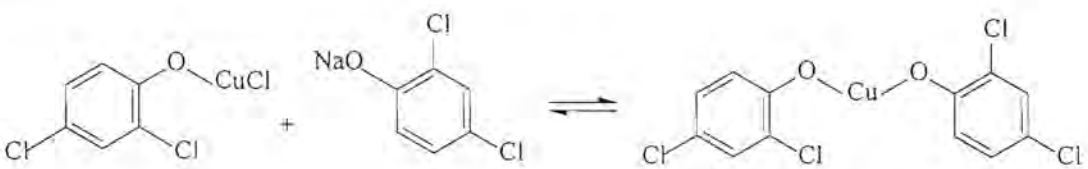
Diagram 1: Formation of the proposed copper(II)diphenolate intermediate.

1.1



2,4-dichlorophenol — sodium phenolate — 2,4-dichlorophenyl copper(II)chloride

1.2



bis(2,4-dichlorophenoxy) copper(II)

+ NaCl

The acetyl group of 2,5-dichloroacetophenone withdraws electrons from the benzene ring creating an activated aryl halide. On studying the resonance structures [Diagram 2] of the molecule, it can be seen that the carbon at the ortho position of resonance structure (2) becomes positively charged. The copper phenolate intermediate, shown in diagram 1.2, reacts with the acetophenone at this position to form the required diphenyl ether. This activation of the carbon atom ortho to the acetyl group was seen by analysis of the reaction products. No products of meta substitution were detected.

Diagram 2: Resonance structures of 2,5-dichloroacetophenone.

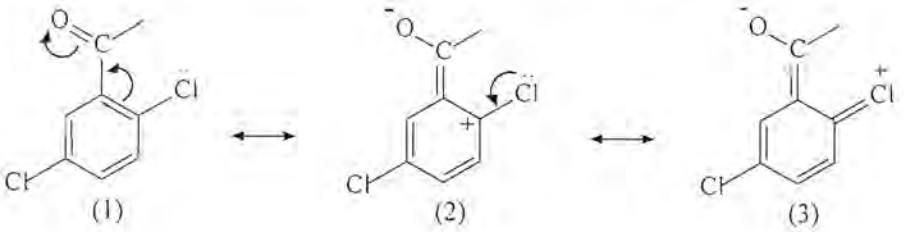
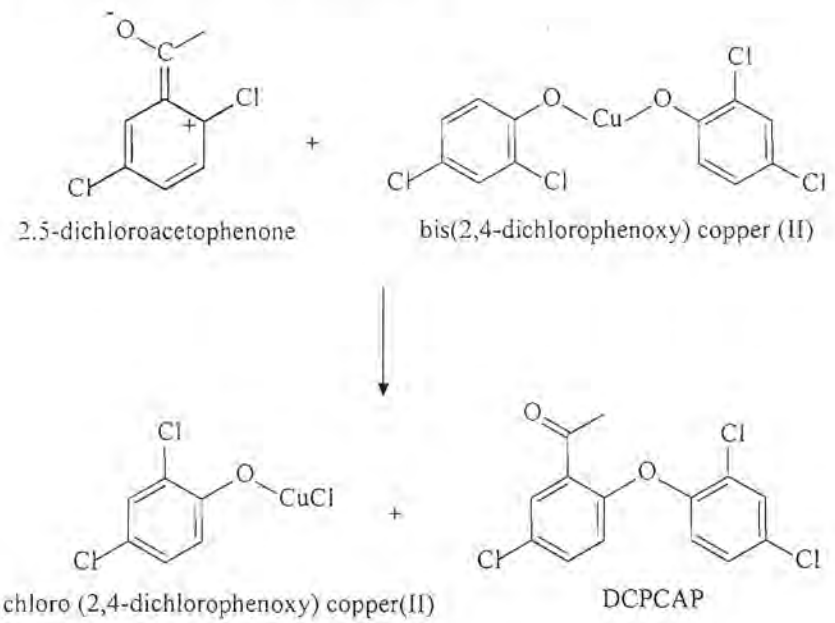


Diagram 3: Formation of the diphenyl ether



The mechanism will in all probability involve one electron transfers[4].

1.3. Optimization of reaction conditions

All variables in this reaction were optimized by my colleagues Vladimir Cukan and Magrieta Snyman and will therefor not be discussed here.

One large-scale experiment was conducted to obtain starting material for the second step of the synthesis of Triclosan. See experimental procedure 1, pp. 2-17.

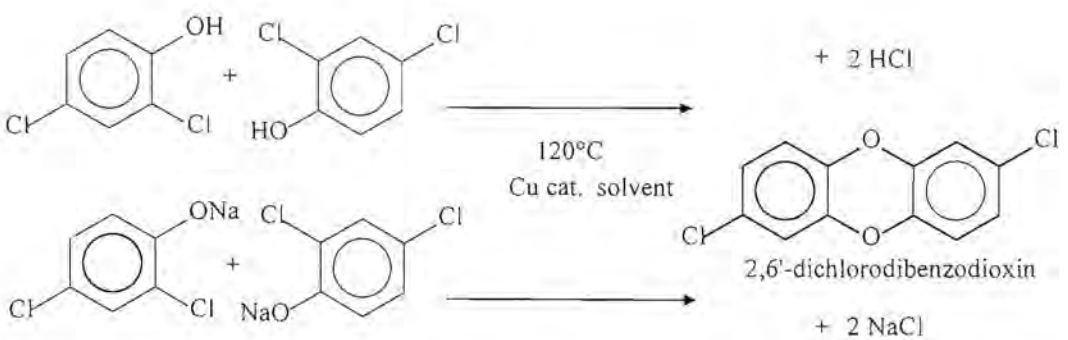
1.4. By-product formation

By-products formed in this reaction were identified (by my colleague Dr Christoff Bollmann) using GC-MS. The fragmentation mass spectra of the compounds were compared with the spectra of pure standards for identification. Samples of the reaction mixture were also spiked with standards and injected into a gas chromatograph to compare retention times for a secondary identification.

1.4.1. By-product 1: Chlorinated dibenzo-p-dioxins.

The by-products that have the most impact on this synthesis are chlorinated dibenzo-p-dioxins. Although they are formed in very small amounts, they are extremely toxic, carcinogenic and tetragenic[6], requiring very careful handling. Dioxins are formed by the condensation of phenols or halogenated alkali phenolates[7]. Copper and copper salts are also effective as condensation catalysts[8]. An excess of a strong base such as sodium hydroxide and temperatures from 160°C and higher, favour the formation of dioxins[7,8]. Although sodium carbonate is a weaker base and lower temperatures were used in this synthesis, some dibenzo-p-dioxins did form.

Diagram 4: Formation of dibenzodioxins by condensation of halogenated phenols or sodium phenolates.



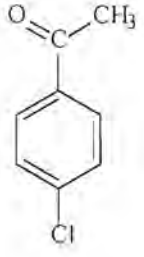
Kunzevich, A.D., Golovkov, V,F,. Rembovskii, V,R,: Russian Chemical Reviews. 65 (1) 28 (1996)

GC-MS spectra of concentrated mother liquor from the crystallization of DCPCAP showed molecules that were most probably the dichloro and monochloro dibenzo-p-dioxins (See appendix B-1 and B-2 pp. 2-25, 26). Dehalogenation of dioxins has been documented[7], suggesting a mechanism for the formation of the monochloro-dioxins found. The database on the mass spectrometer also matched the fragmentation patterns with those of the dioxins. It was decided to accept that these were in fact the dioxins rather than synthesize and handle such toxic compounds in any quantity.

1.4.2. By-product 2: 4-Chloroacetophenone

The major by-product found was 4-chloroacetophenone [Diagram 5]. The mechanism for the formation of this compound is uncertain but the presence of water, high temperature and a large amount of copper catalyst were found to increase the rate of its formation.

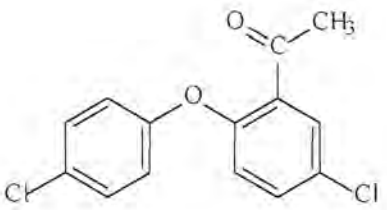
Diagram 5: Structure of 4-Chloroacetophenone



1.4.3. By-product 3: 5-chloro-2-(4-chlorophenoxy)acetophenone

This is a minor by-product that was found to originate from an, impurity 4-chlorophenol, found in the 2,4-dichlorophenol raw material. 4-Chlorophenol undergoes the Ullmann ether reaction with 2,5-dichloroacetophenone to form by-product 3.

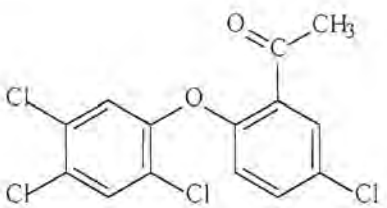
Diagram 6: Structure of 5-chloro-2-(4-chlorophenoxy)acetophenone



1.4.4. By-product 4: 5-Chloro-2-(2,4,5-trichlorophenoxy)acetophenone

This is also a minor impurity that was found to originate from an impurity in the dichlorophenol raw material. 2,4,5-trichlorophenol also couples with the acetophenone via the Ullmann Ether reaction to form by-product 4.

Diagram 7: Structure of 5-chloro-2-(2,4,5-trichlorophenoxy)acetophenone



1.5. Purification

The most time and cost effective method of purifying the diphenyl ether product (DCPCAP) was found to be crystallization from toluene. The DCPCAP crystals were filtered on a Buchner funnel and washed with a small quantity of cold toluene. The product cake was dried in airflow on the Buchner funnel.

2. Alternative copper catalysts - Solid catalyst systems.

2.1. Introduction

As already discussed the Ullmann ether synthesis requires a copper catalyst for the reaction to proceed. The process optimized by my colleagues uses copper(II)chloride as catalyst. In the reaction work up, sodium chloride and the copper catalyst are washed out of the reaction medium with acidified water. Since copper ions are phytotoxic and must be removed before the discharge of wastewater, this water containing copper is costly to dispose of. In an attempt to circumvent this, the use of solid copper catalysts was investigated. The advantage of solid catalysts is that they can be easily filtered off for disposal, reducing the cost of wastewater treatment. Recycling of the filtered catalyst could also reduce raw material costs.

Two different solid copper catalyst systems were tried, supported copper(II) and zero valent Raney-Copper catalyst.

2.1.1. Introduction to supported copper catalysts.

A supported catalyst is made by dispersing a catalytically active metal, in this case copper, on an inert support. Catalyst supports are porous, high surface area materials that supply a physically strong structure to hold catalytically active atoms or ions. The active species is spread on the surface of the support as a thin to mono-atomic layer or as small clusters of atoms. Catalysts made in this way have a catalytic surface area similar to the surface area of the support.

Supported catalysts made by ion exchange

Ion exchanged catalysts are made using supports which have ion exchangeable counter ions on their surface. Much like ion exchange resins, the support's counter ion is replaced (ion exchanged) with a catalytically active ion. In this case copper ions were the required catalyst.

Ion exchanged copper on Montmorillonite clay.

Montmorillonite is a naturally occurring zeolite clay, with a crystalline structure of more or less alternating silica and alumina groups arranged in flat sheets. Counter ions of many different ion exchangeable species are present on the support, magnesium being most predominant. Two catalysts were prepared using a literature procedure [9]. One by exchanging copper directly with the ions present on untreated clay and one by first acid washing the clay in hydrochloric acid to convert it to an acidic form before exchanging with copper.

Supported catalysts made by impregnation.

Impregnated catalysts are made by wetting a porous support with a solution containing catalytically active metal ions. The wet support is dried and baked (calcined) in an oven. The calcination process fixes the catalytic metal to the support surface via solid state reactions between the support's surface and the catalyst metal. At the high temperatures used when calcining, protons and hydroxides on the supports' surface are removed as water creating Lewis acid and base sites (dehydroxylation). The catalyst metal ions and counter ions react at these sites to become chemically bound to the surface.[10 and references therein]

The technique used here to impregnate the catalytic species on the catalyst support is called pore filling. The pore volume of the highly porous support was determined by dripping distilled water onto a dry, previously weighed sample while stirring with a glass rod. When the support appeared damp, but not wet and was no longer free flowing, the pores were assumed to be full of water. The volume of water per unit mass of support is called the pore volume. The impregnated catalysts used here were made by filling the pores of dry supports with a copper solution and drying them in an oven.

Impregnated copper on alumina

Active alumina is a highly porous Al_2O_3 structure consisting of aluminium bridged by oxygen atoms. Active alumina is made by calcining a dried aluminium hydroxide gel. The conversion of aluminium hydroxide in the dried gel to aluminium oxides and the removal of water creates a porous structure. A commercially available chromatographic grade gamma alumina with a surface area of $200m^2/g$ was used as the support. This was impregnated with copper to form the catalyst using experimental procedure 2, pp. 2-19.

Impregnated copper on silica-alumina

A porous, amorphous silica-alumina support was made using a procedure explained in experimental procedure 3 (pp. 2-19) and impregnated with copper to form the catalyst using experimental procedure 4 (pp. 2-19).

2.1.2. Raney copper catalyst

Raney metal catalysts were discovered and patented by Murray Raney in 1925. Raney copper is a porous, extremely active, zero valent copper catalyst. The high activity is due to its large surface area and it is markedly more active than finely divided copper. Raney copper is made by dissolving the aluminium out of a homogenous copper-aluminium alloy leaving a porous copper metal [11,12,13]. This catalyst was tested to determine the catalysis of zero valent copper in the Ullmann ether synthesis and was made using experimental procedure 5 (pp. 2-20).

2.1.3. Reactions with solid copper catalysts

The catalysts were tested for activity by stirring them in a reaction mixture, at the same conditions used for the optimized copper chloride catalyst process. Reaction monitoring was done by gas chromatography. For easy comparison between copper chloride and solid catalyst reactions, the amount of catalyst used was calculated to give the same mole ratios of copper. See experimental procedure 6 (pp. 2-20).

2.1.4. Results and discussion

Table of results for solid Cu catalysis

Catalyst	Mole equivalents Cu	% Conversion to DCPCAP*
$CuCl_2$ (for comparison)	0,03	75,2
Cu on Alumina	0,03	2,8
Cu on Silica/alumina	0,03	4,2
Raney copper	0,03	70,6
Raney copper	0,06	72,1

* % Conversion was the maximum conversion attained irrespective of reaction time.

2.1.5. Conclusion

The two supported copper catalysts gave very low yields of products and it was decided not to pursue these catalysts further. The Raney copper catalyst gave good yields and low by-product formation, however due to the cost of manufacturing and the difficulty in handling Raney copper in inert atmospheres in a production environment, it was decided not to pursue Raney copper catalysts further.

3. Alternative diphenyl ether synthesis using azo compounds.

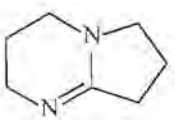
3.1. Introduction

Di- and tri-azo compounds have been found to facilitate the coupling of a phenol with an aryl halide via a bimolecular dehydrohalogenation reaction. Triazobicyclodecene (TBD) has been used to synthesize diphenyl ethers from various phenols and alkyl or aryl halides [14]. The hydrogen halide formed in the reaction being scavenged by TBD.

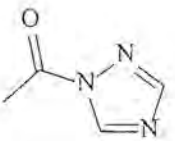
It was thought that if an azo compound could facilitate the formation of diphenyl ethers without the need for copper catalysis, then a polymer linked azo compound could be used. The polymer beads could easily be filtered out of solution, reactivated and recycled, in essence a solid phase combinatorial synthesis[14]. If successful, a catalyst of

this type would eliminate copper from the wastewater stream making disposal cheaper and lessening the environmental impact. Two azo salts were tested with the idea that if this reaction worked, a means of attaching the azo compound to a polymer bead would be found later. 1,5-Diazabicyclo- [4,3,0]non-5-ene (DBN) and acetyltriazole [Diagram 6] were tested. (See experimental section 7, pp. 2-21)

Diagram 6: Structures of DBN and acetyltriazole.



1,5-Diazabicyclo[4.3.0]non-5-ene
(DBN)

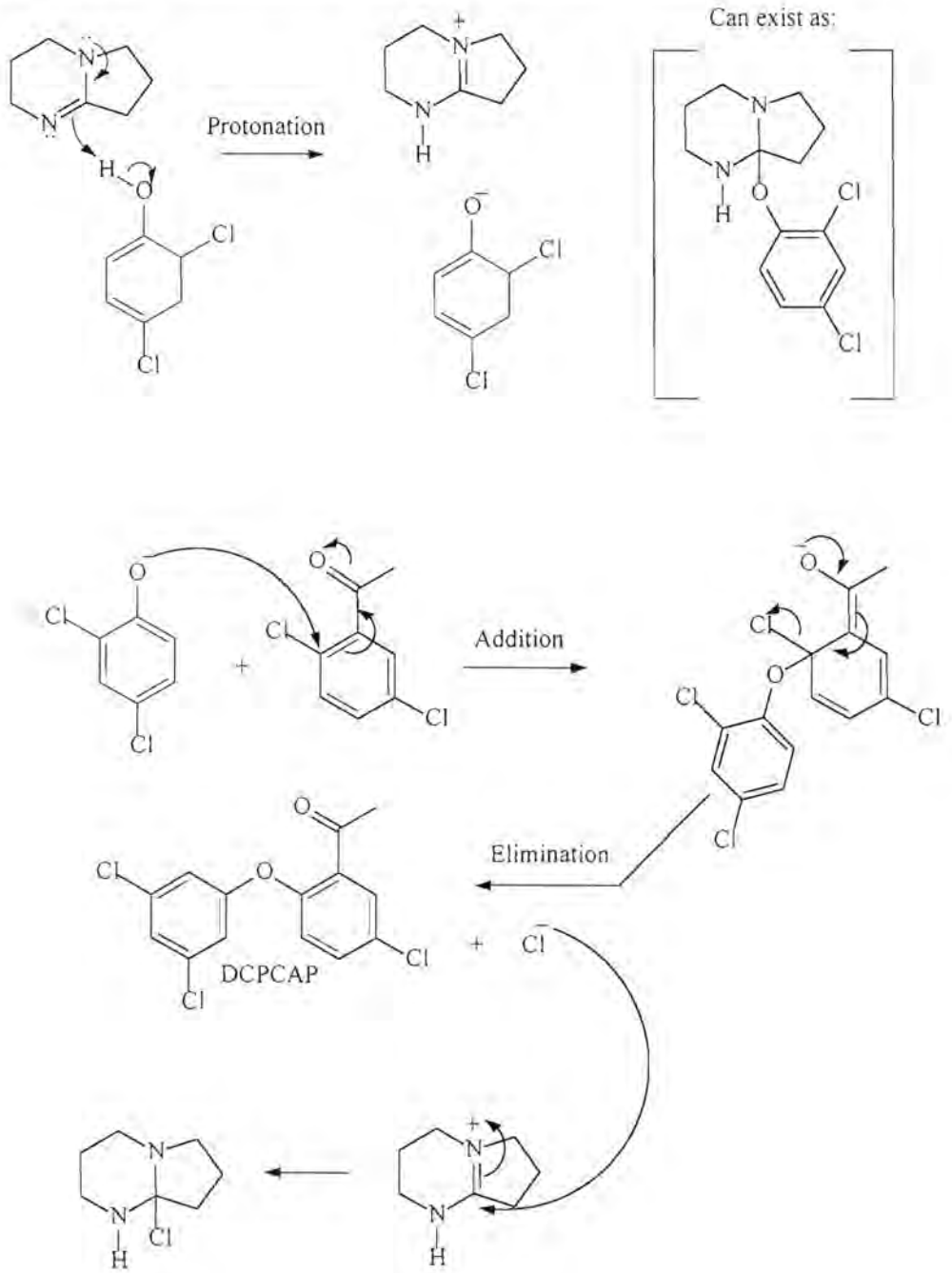


5-Acetyl-1,3,5-triazole

3.2. Diaryl ether formation with azo compounds.

It has been discovered from NMR and infrared studies [14] that a sterically hindered base will scavenge the hydrogen halides formed in this coupling reaction. DBN with its' high basicity, high steric hindrance and low nucleophilicity, was chosen to act as the halide scavenger. DBN will deprotonate the phenol, specifically 2,4-dichlorophenol and the species $DBNH^+/ArO^-$ will result. The phenoxide will then, via addition and elimination reactions generate the aryl ether DCPCAP. See diagram 8.

Diagram 8: Mechanism of azo mediated diphenyl ether synthesis



3.3. Results

Azo salt	Temperature °C	Time (h)	GC area % ether
(1) Acetyl triazole	40	3	0
(2) DBN	35	3	9
(3) DBN	60	18	29,8

Acetyl triazole did not facilitate the reaction while DBN gave a reaction but the reaction rate was too slow and it decomposed under the reaction conditions.

3.4. Conclusion

The azo mediated coupling of the phenol and aryl chloride did work to some extent. Optimization of the reaction conditions and the investigation of different di- and tri-azo compounds may lead to a viable synthesis. A management decision was taken to not persue the use of azo-compounds further due to the financial risks involved in using new technology in a production facility.

4. Experimental

4.1. Procedure 1: Ullmann ether coupling of 2,4-dichlorophenol and 2,5-dichloroacetophenone.

All the reagents shown in the table were loaded into a 10-litre glass reactor equipped with a Dean and Starke azeotropic reflux distillation apparatus, overhead stirrer and thermometer. The reactor was slowly heated in an oil bath to 120°C. The reaction was carried out under toluene reflux with azeotropic removal of water. Reaction monitoring was done on a gas chromatograph fitted with a DB-5 capillary column equipped with an injection splitter.

Raw materials:

#	Chemical	Mass (g)	% Purity	No. moles	equivalents
1	2,5-Dichloroacetophenone	1165.5	97.3	6	1
2	2,4-Dichlorophenol	1086.7	99.0	6.6	1.1
3	Sodium carbonate	453.7	91.1	3.9	1.3
4	$CuCl_2.2H_2O$	42	97.0	0.239	0.04
5	Toluene	600	99.8	-	-

The reaction was stopped after 17 hours when the concentration of the acetophenone was 2,5% on gas chromatograph area %. The reaction was cooled to 90°C, 800 g of toluene and 1800 ml of 3% HCl were added. This water wash was to remove sodium chloride and the copper catalyst; the acid was to facilitate a phase separation. The phases were separated and the organic phase was washed twice with 1 litre of distilled water to remove traces of acid, sodium chloride and copper. The organic phase was filtered to remove some suspended solids and the solvent was removed by distillation at 130°C. A vacuum of 4 millibar was applied and the temperature was increased to 170°C to distil off a light fraction containing unreacted starting materials and decomposition products. The product remaining in the bottom of the still was dissolved at 65°C in 1,56 litres of a solvent mixture of 65% heptane and 35% toluene. The product was crystallized by slowly cooling to 2°C with strong agitation. The crystals were vacuum filtered on a Buchner funnel and washed with a small quantity of cold toluene (-5°C).

A light brown, crystalline product 5-chloro-2-(2,4-dichlorophenoxy)acetophenone was obtained at a yield of 64,2% (based on dichloroacetophenone) and purity of 99,5%.

4.1.1. Analysis of recrystallized material

GC-MS: (See appendix B-3, pp. 2-27, for spectrum)
(Mass, [ion fragment] rel. intensity) : (314, $[M]^+$, 25); (299, $[M-CH_3]^+$, 20); (279, $[M\text{-}Cl]^+$, 3); (264, $[M-Cl, -CH^3]^+$, 22); (236, $[M\text{-}Cl, -COCH_3]^+$, 13); (153, $[M - C_6H_3Cl_2O]^+$, 100).

GC Spectrum: (See appendix A-1, pp. 2-23, for chromatogram)
Rt. = 6.422 minutes.

Melting point:
94,3 °C (No literature references found)

FTIR: (See appendix D-1, pp. 2-29, for spectrum)
ν (cm^{-1}), KBr
1261,88 (C-O stretch – ether)
1672,93 (C=O stretch - aryl alkyl ketone)

H-NMR (300 MHz) in $CDCl_3$: (See appendix C-1, pp. 2-28, for spectrum)

δ 7,786(1H, d, J= 2,7Hz, Ar-H),
δ 7,481(1H, d, J= 2,4Hz, Ar-H),
δ 7,327(1H, dd, J= 9,0Hz, J= 2,7Hz, Ar-H),
δ 7,237(1H, dd, J= 8,7Hz, J= 2,4Hz, Ar-H),
δ 6,939(1H, d, J= 8,7Hz, Ar-H),
δ 6,639(1H, d, J= 8,7Hz, Ar-H),
δ 2,649(3H, s, $C(O)CH_3$)

4.2. Procedure 2: Preparation of impregnated copper on alumina catalyst.

Copper chloride ($CuCl_2 2H_2O$, 6.34g, 0.037 moles) was dissolved in the pore volume (28,5 ml) of dry activated alumina (Kanto Chemicals, 50 g). The copper solution was dripped onto the alumina while stirring well with a glass rod. (Pore filling technique) The damp catalyst was stored in a constant humidity vessel and maintained at 35°C over-night to equilibrate. The catalyst was then dried at 40°C in a vacuum oven to a constant mass, then calcined in a muffle oven at 350° for three hours.

4.3. Procedure 3: Preparation of porous, amorphous silica-alumina.

Amorphous silica-alumina was made by precipitating an equimolar solution of aluminium and silica as a mixed hydroxide gel by the addition of 3 mole equivalents of sodium hydroxide. The gel was filtered on a Buchner funnel and washed repeatedly with deionised water until neutral. The gel was then dried at 120°C, calcined at 450°C in a muffle oven overnight and stored in a dessicator. The product was a white granular powder.

4.4. Procedure 4: Preparation of impregnated copper on amorphous silica-alumina catalyst.

The dry amorphous silica-alumina support was impregnated with copper using the pore filling technique. Copper(II)chloride, 5% by mass of the support, was dissolved in the pore volume of a weighed amount of dry support. This solution was dripped onto the dry support with stirring. The 'pore filled' support was stored in a constant humidity vessel overnight, at 35°C, to equilibrate and then dried to a constant mass at 50°C in a vacuum oven. The dry catalyst was calcined in a muffle oven at 350°C for three hours and stored in a dessicator.

4.5. Procedure 5: Preparation of Raney copper catalyst.

Raney copper was made by melting equal masses of copper and aluminium metal with an oxygen-acetylene welding torch. The flame was set rich in acetylene to provide a reducing atmosphere to prevent oxidation of the metals. The melt was well stirred by the gas flame to create a homogenous mixture. The melt was poured into cold water to quench and create a brittle product, which was easily crushed and sieved. The crushed alloy was leached with 4,2 mole equivalents of aqueous 30% sodium hydroxide. The sodium hydroxide leached the aluminium out of the alloy leaving a porous, high surface area copper. The Raney copper catalyst was stored in a 2% sodium hydroxide solution to protect it from air oxidation. The catalyst was washed with deionized water until pH neutral before use. The catalyst was tested for activity by washing with ethanol and drying on a filter paper. On contact with air, an extremely fast and exothermic air oxidation turned the catalyst red with heat indicating an active catalyst.

4.6. Procedure 6: Ullmann ether coupling using solid copper catalysts.

The same procedure as experimental procedure 1 was used but in place of copper chloride, the alternative catalysts were used as shown in the following tables:

4.6.1. Reagents:

#	Chemical	Mass (g)	% Purity	No. moles	Mole equivalents
1	2,5-Dichloroacetophenone	97.1	97.3	0.5	1
2	2,4-Dichlorophenol	90.56	99.0	0.55	1.1
3	Sodium carbonate	34.6	91.1	0.33	1.3
4	Toluene	47	99.8	-	-
5	catalyst	See table below.	-	-	-

Catalyst	Mass of catalyst (g)	% Cu on support	Mass of copper (g)
Cu on alumina	200	0,5	1
Cu on silica-alumina	142	0,7	1
Raney copper	1	98	1
Raney copper	2	98	2

4.7. Procedure 7: Diaryl ether formation using azo compounds.

2,4-Dichlorophenol and 2,5-dichloroacetophenone were dissolved in acetonitrile in a 3-necked round bottom glass flask equipped with a magnetic stirrer, a thermometer, a reflux condenser and a nitrogen supply. The azo salt was added while stirring the mixture and purging with nitrogen. The mass of reagents used is indicated in the table of reagents. The reactor was enclosed in aluminium foil to exclude light and warmed to 60°C in a water bath. Samples were periodically taken and the reaction was monitored by gas chromatography for the formation of DCPCAP.

4.7.1. Reagents:

Chemical	equivalents	moles	mass (g)	Temp. (°C)
2,4-dichlorophenol	1,2	0,029	4,69	-
2,5-dichloroacetophenone	1	0,024	4,54	-
Acetonitrile	-	-	6,00	-
(1) Acetyl triazole	1	0,025	2,78	40
(2) DBN	1	0,025	3.00	35
(3) DBN	2	0,050	5,96	60

Appendix A: Gas chromatography

Instrument:	Hewlett-Packard 6890 series GC Hewlett-Packard 3396 A integrator

Column:

Capillary column:	J&W Scientific DB-1
Length:	30m
ID:	0.53mm
Film thickness:	3µm
Carrier gas:	Helium

Temperature program:

Initial temp:	200°C
Initial time:	1.00min.
Ramp:	15°C/min
Final temp:	270°C
Hold time:	12min

Injection port:

Mode:	Split
Split ratio:	35:1
Splitter flow:	32 ml/min
Septum purge:	2.5 ml/min
Temperature:	270°C
Head pressure:	55kPa

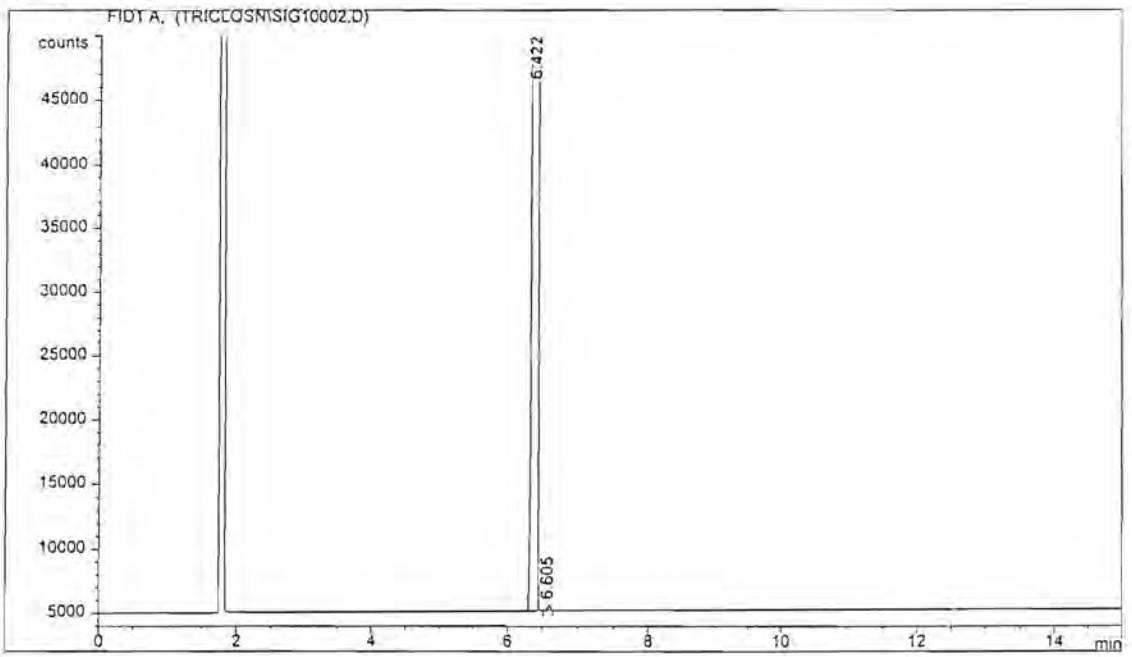
Detector:

Type:	FID
Temperature:	280°C

A-1: Gas chromatogram of DCPCAP

```
Sample Name      : DCPCAP                                    Vial :   1
Acq. Operator    : Les
                                                  Inj Volume : 1 µl
Acq. Method      : C:\HPCHEM\3\METHODS\TRICLOSN.M
```

Triclosan




```
=============================================================================
                          Area Percent Report
=============================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount         :      1.00000  [ng/5ul]   (not used in calc.)


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  counts*s    [counts]     %
----|-------|----|-------|----------|----------|--------|
   1   6.422 BB    0.0474 1.47374e6  4.25454e5  99.94180
   2   6.605 BB    0.0282  858.27777  471.37024  0.05820
```

Appendix B: GC-Mass spectroscopy

Instrument: Hewlett-Packard 6890 series GC-MS

GC parameters:

Column:

Capillary column:	(Silica) HP-1
Length:	30m
I.D:	0.2mm
Film thickness:	0.2µm
Outlet pressure:	Vacuum
Carrier gas:	Helium

Temperature program:

Initial temp:	50°C
Initial time:	1.00min
Ramp:	10°C/min
Final temp:	300°C
Final time:	14min.
Total flow:	32 ml/min

Injection port:

Temperature:	250°C
Pressure:	50kPa
Mode:	Split
Split ratio:	30:1
Split flow:	29 ml/min

Mass spectrograph parameters:

Ionization source:

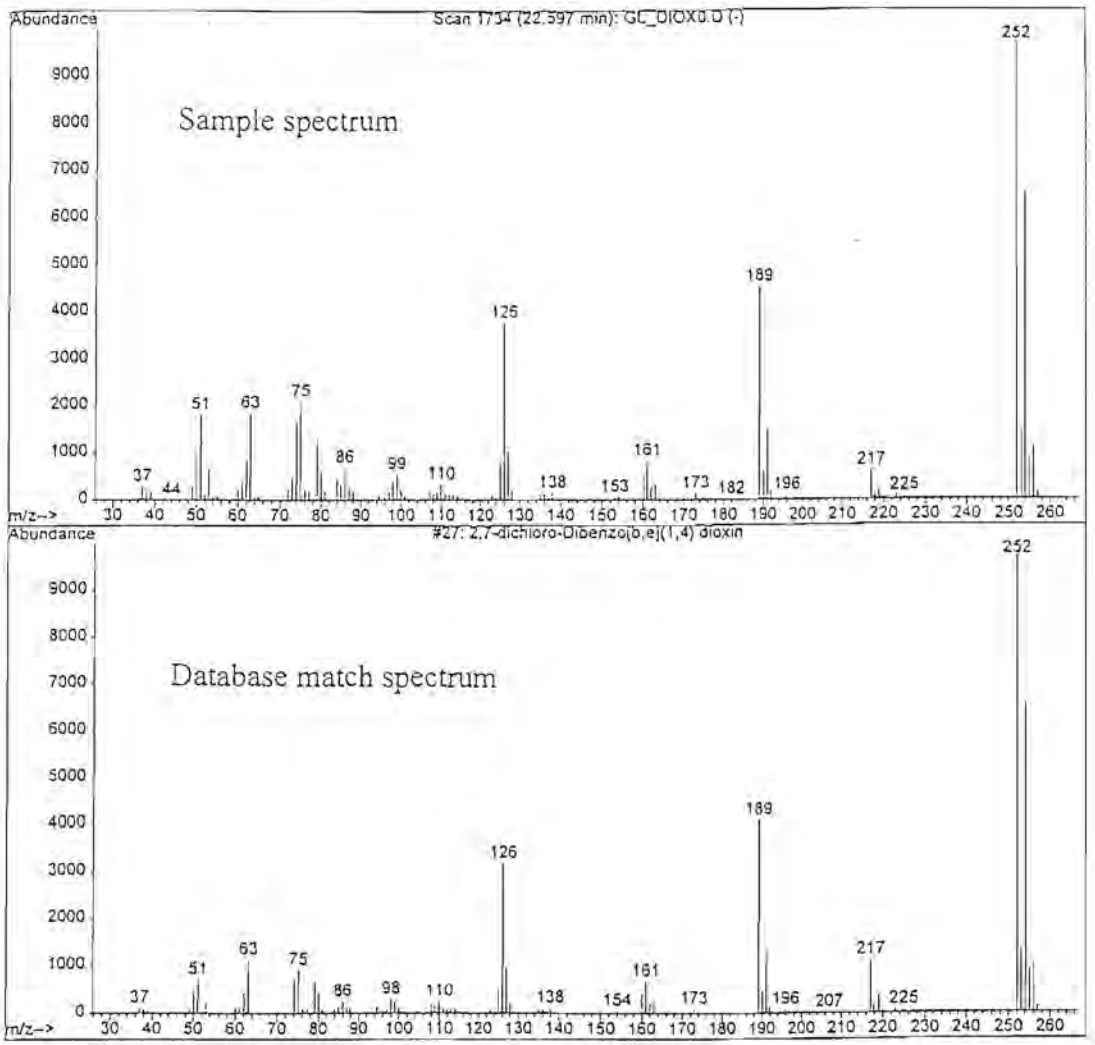
Mode:	Electron impact
Electron energy:	70 eV

Detector:

Type:	Quadropole positive ion mass selective detector with horn electron photo-multiplier.
System vacuum:	0.0015 kPa

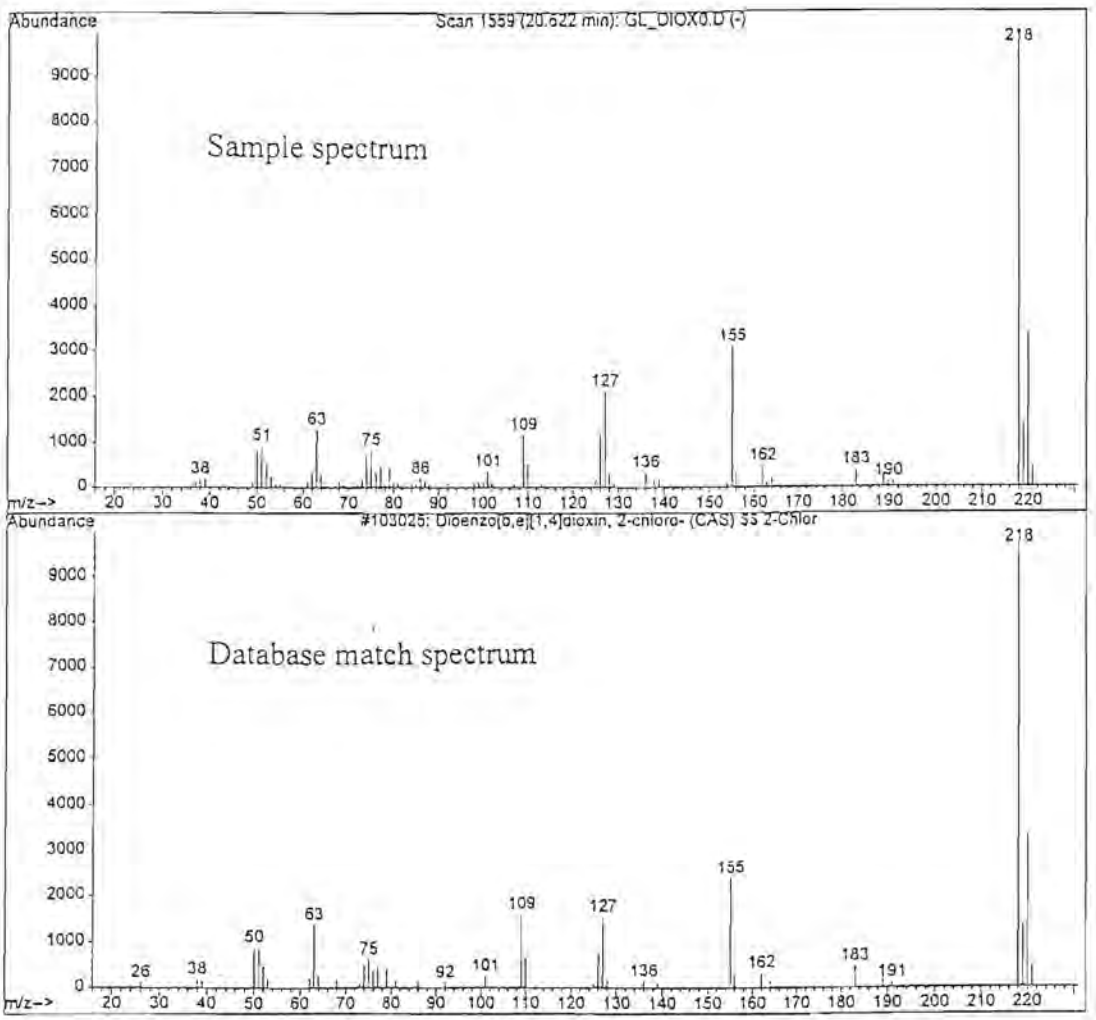
B-1: Mass spectrum of dichlorodibenzodioxin

```
Library Searched : C:\DATABASE\DG.L
Quality          : 94
ID               : 2,7-dichloro-Dibenzo[b,e](1,4) dioxin
```



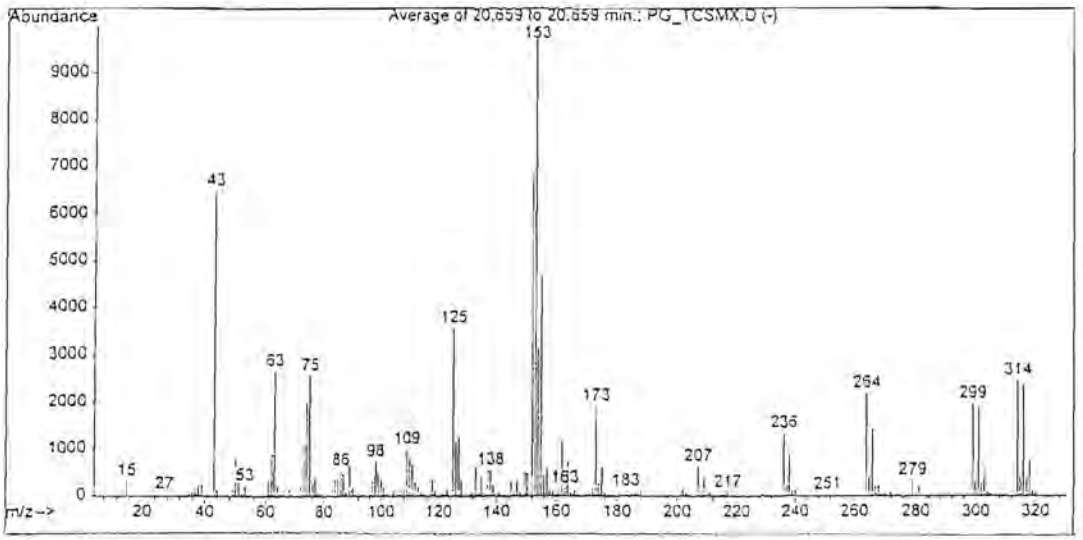
B-2: Mass spectrum of monochlorodibenzodioxin

```
Library Searched : C:\DATABASE\wiley275.L
Quality          : 96
ID               : Dibenzo[b,e][1,4]dioxin, 2-chloro- (CAS) $$ 2-Chlor
                   odibenzo-p-dioxin $$ Dibenzo-p-dioxin, 2-chloro- $$
                    2-Chlorodibenzo-para-dioxin
```



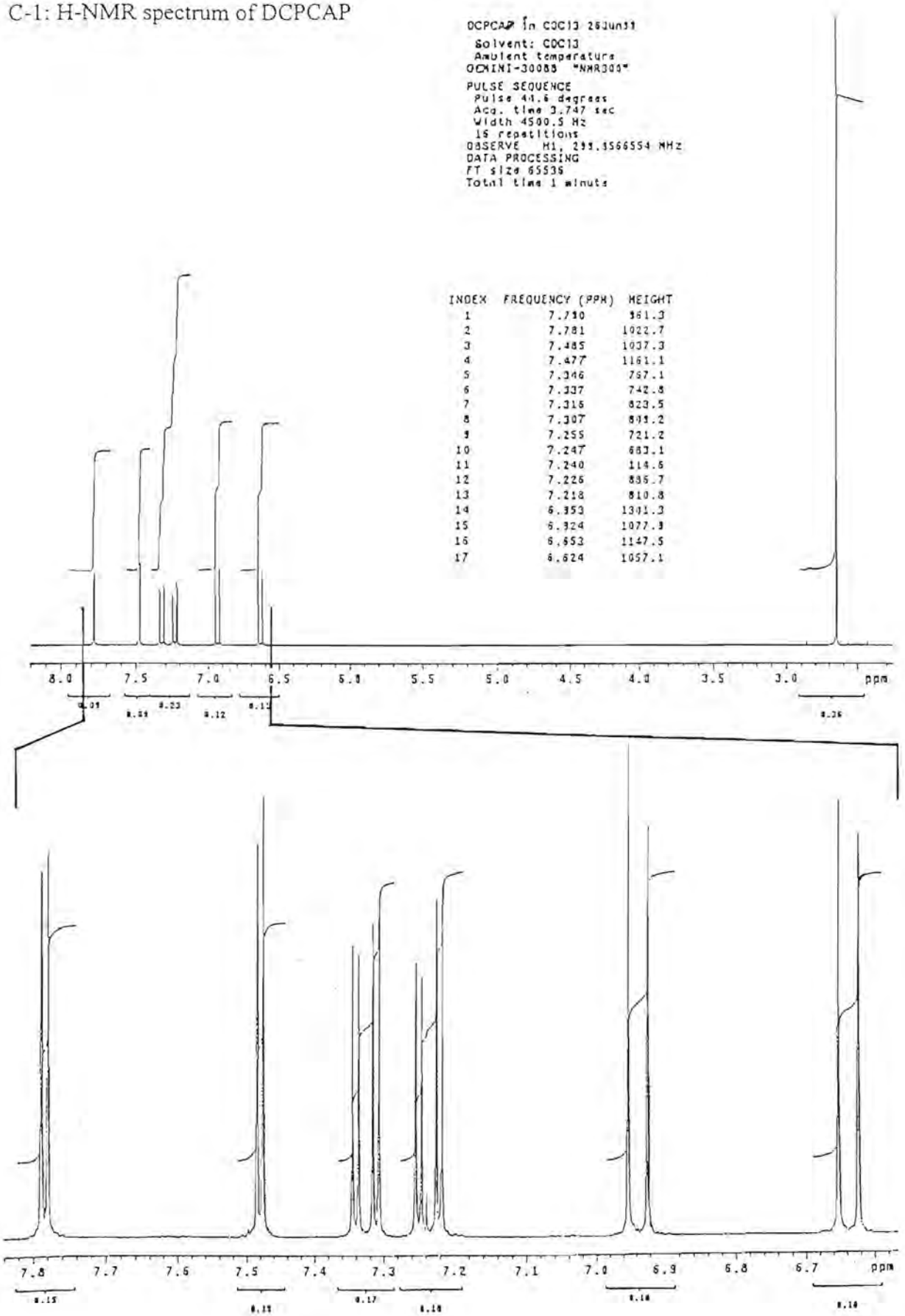
B-3: Mass spectrum of DCPCAP

```
Library Searched : C:\DATABASE\DG.L
Quality          : 99
ID               : DCPCAP (2,4,4'-Trichloro-2'-acetodiphenylether)
```



Appendix C: H-NMR spectra

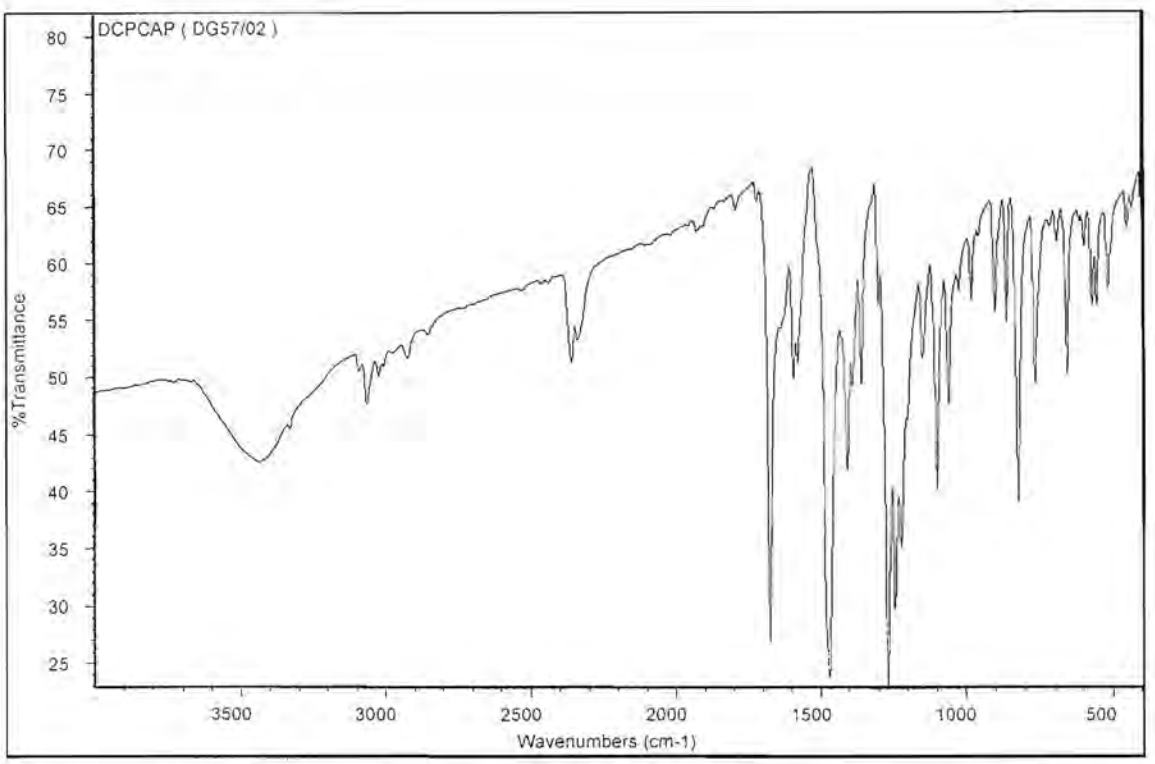
C-1: H-NMR spectrum of DCPCAP



Appendix D: FTIR spectra

Instrument: Nicolet Avatar 360 FT-IR

D-1: FTIR spectrum of DCPCAP (KBr disk)



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Chapter 3

Step 2: Baeyer-Villiger oxidation

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1. Introduction

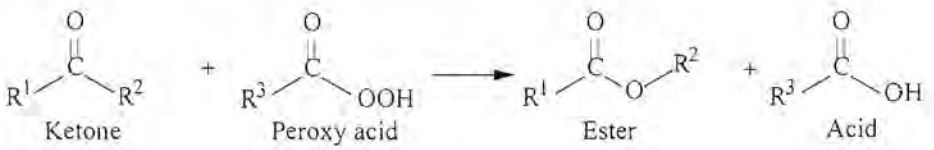
The second reaction step, in this synthesis of Triclosan, is the Baeyer-Villiger oxidation of the diphenylether, 2-acetyl-2',4',4-trichlorodiphenylether (DCPCAP), formed in the first step. The product of this reaction is the ester of the diphenylether, 2-acetoxy-2',4',4-trichlorodiphenylether. This product was given the common name Triclosan ester and abbreviated to TCSE for ease of use.

The Baeyer-Villiger oxidation of acyclic ketones to esters and cyclic ketones to lactones is well known and has been subjected to much study. The oxidation reagent is a peroxy acid. Baeyer and Villiger[1] [2] first demonstrated the reaction in 1899. They used peroxysulphuric acid (Caro's acid) to oxidize the ketones, camphor and tetrahydrocarvone to lactones. Numerous ketones have subsequently been oxidized to lactones and esters. It was soon discovered that organic peroxy acids worked as well if not better than the mineral peroxy acids. The organic peroxy acids are better suited where reagents can not tolerate strong mineral acids. They have almost entirely replaced mineral acids as oxidants in organic synthesis. Many different organic peroxy acids have been used successfully in Baeyer-Villiger reactions. The peroxy acids of acetic acid [3], triflouroacetic acid [4], benzoic acid [5], maleic acid [6], mono-sodium peroxyphthalic acid [7] have been most commonly used but there are many other peroxy acids that are also effective oxidants.

1.1. Mechanism of the Baeyer-Villiger reaction.

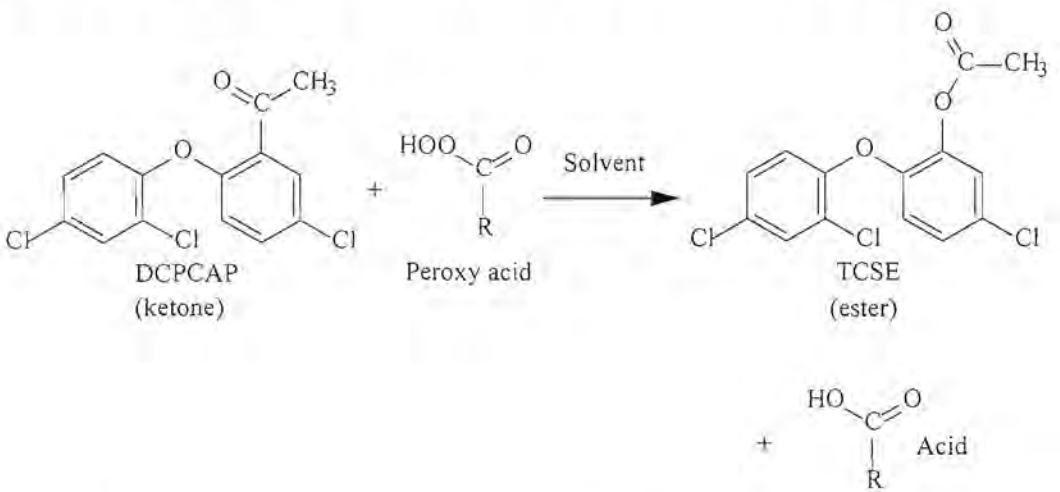
The overall reaction scheme for the oxidation of acyclic ketones can be represented as shown in diagram 1:

Diagram 1: General Baeyer-Villiger reaction scheme



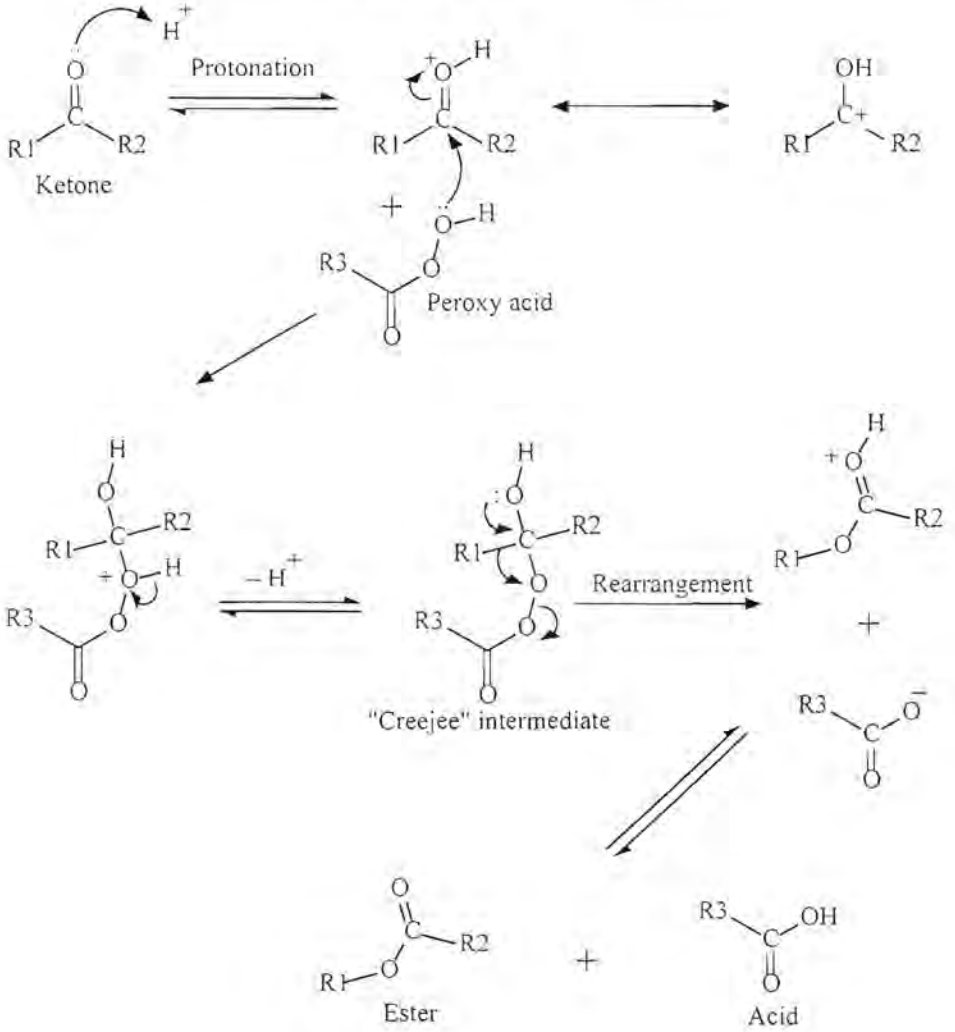
For this synthesis of Triclosan ester, the reaction scheme is represented in diagram 2:

Diagram 2: Baeyer-Villiger reaction scheme for the synthesis of TCSE



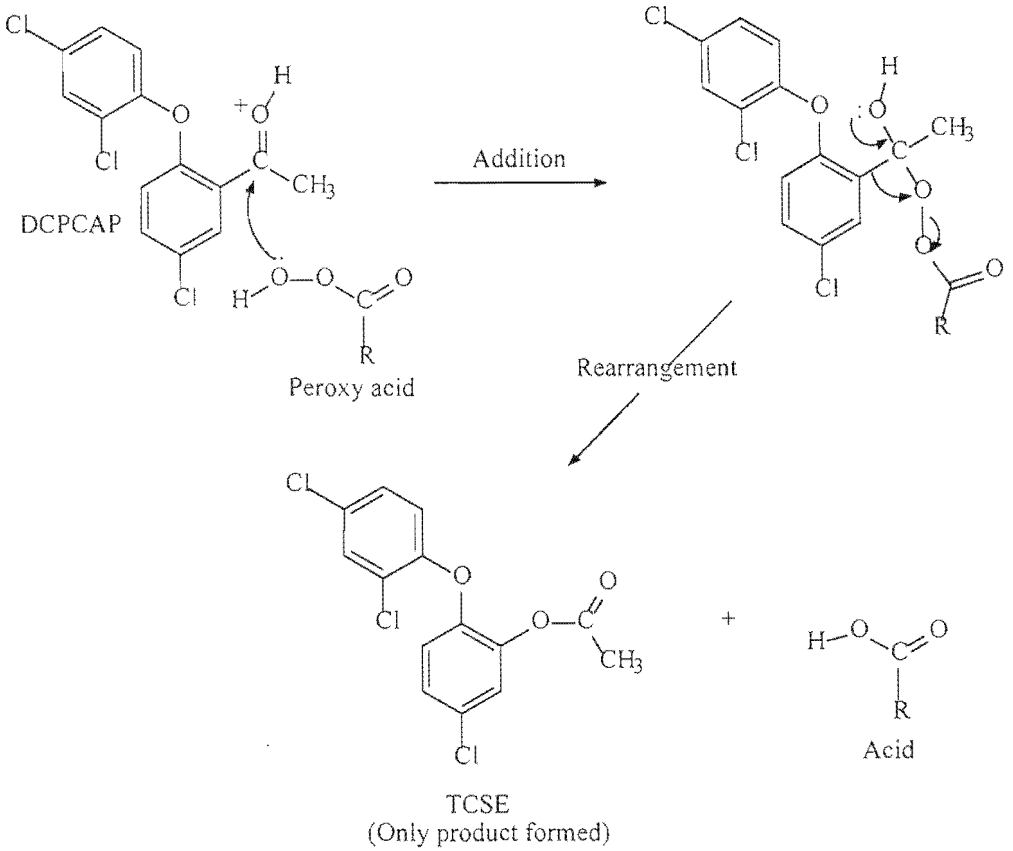
The mechanism originally proposed by Creejee[8], was confirmed by several elegant ^{18}O – isotopic studies [9 10 11]. These studies proved that an initial protonation of the carbonyl oxygen occurs followed by a nucleophilic addition of the peroxy acid to the formed carbocation (see diagram 3). Doering and Dorfmann[11] and Plesnicar[12] used the "Creejee" intermediate terminology, this must not be confused with the Creejee mechanism for ozonolysis shown in the literature[13].

Diagram 3: Mechanism of the Baeyer-Villiger oxidation.



The most stable, electron rich group then migrates to the electrophilic oxygen to give the ester and releases the acid [Diagram 4]. It has been shown [14] that the migrating group does so with complete retention of configuration. It has also been shown that no free electron deficient oxygen species or carbocation are formed during the rearrangement. The rearrangement probably occurs via a transition state and is acid catalyzed. In the case of the Baeyer-Villiger oxidation of DCPCAP, the diphenylether group migrates preferentially. Analysis of the reaction products has shown that no products were formed as a result of migration of the methyl group.

Diagram 4: Formation of the rearranged Triclosan ester.

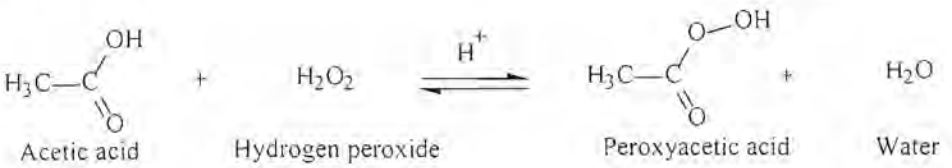


1.2. Organic peroxy acids

The active oxygen of hydrogen peroxide is not readily available for oxidation reactions with organic compounds. Organic acids and anhydrides however, are readily oxidized to peroxy acids by the action of hydrogen peroxide [10 11 15 and references]. The active oxygen of peroxy acids is an active oxidant for many organic compounds. Hydrogen peroxide is not soluble in many non-polar organic solvents which also reduces its' usefulness in organic synthesis. Peroxy acids are soluble, at least to a useful extent, in non-polar organic solvents.

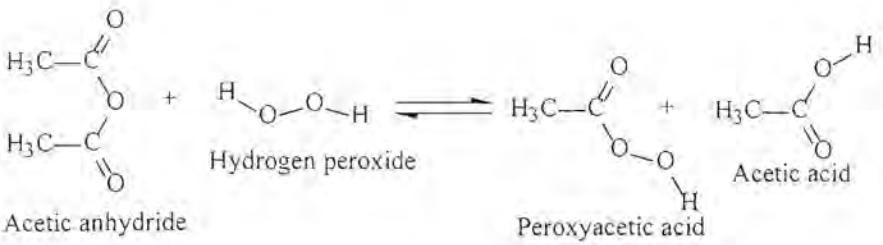
Peroxy acids can be made by the reaction of hydrogen peroxide with organic acids with the aid of a strong acid catalyst [Diagram 5]. The stronger acids, like triflouroacetic and formic acid, do not require an acid catalyst since they impart enough acidity to the solution to be self-catalyzed.

Diagram 5: The formation of peroxyacetic acid by oxidation of acetic acid



Another method of preparation is the reaction of anhydrides with hydrogen peroxide [Diagram 6]. This reaction reaches equilibrium quickly and does not require a strong acid catalyst.

Diagram 6: The formation of peroxyacetic acid by peroxide oxidation of acetic anhydride



For the Baeyer-Villiger reaction, the peroxy acid can be formed in-situ by adding hydrogen peroxide to a solution containing the substrate, acid catalyst and the acid or anhydride. This method is preferred since it is simpler and there will be no loss of active oxygen due to slow decomposition of the peroxy acid over extended storage times.

1.3. Pre-treatment of DCPCAP.

It was found in initial experiments that oxidation reactions using different batches of DCPCAP proceeded at different rates. Peroxides and peroxy acids are inherently unstable, and many metals are known to catalyze their decomposition [16 17]. The DCPCAP (2-acetyl-2',4',4-trichlorodiphenylether) from step one of this process was found to contain traces of metals and it was assumed that these metals caused the decomposition of the peroxy acids. The total residual peroxides at the end of these reactions also differed considerably, indicating different rates of peroxide decomposition.

Elemental analysis of different batches of DCPCAP showed varying concentrations of metals. Copper and iron were most predominant; both are active peroxide decomposition catalysts. By analyzing all possible sources of this metal contamination, the copper was found to be residue from the copper catalyst used in step one whilst iron and traces of other metals were found to be contaminants in the reagents 2,5-dichloroacetophenone and 2,4-dichlorophenol used in the first reaction step. No other source of metals was found.

Complexing agents are known to stabilize hydrogen peroxide solutions by complexing metal ions and preventing metal catalyzed decomposition. An oxidation reaction using a typical sample of DCPCAP was carried out with added EDTA to see if it would stabilize the peroxide - peroxy acid system. It was found that all of the peroxide species decomposed before the reaction was complete. To test if metal-EDTA complexes were responsible for peroxide decomposition, a dichloromethane solution of the same sample was extracted (shaken for 2 hours) with an aqueous EDTA solution. The peroxide species decomposed as before indicating that the metals were not present as cationic species but most likely zero valent metal particles.

To test this hypothesis, a sample of the same batch of DCPCAP was dissolved in dichloromethane and filtered through a thick pre-formed pad of filter-aid. The oxidation reaction of this sample proceeded smoothly to completion, analysis showed that 20% of the original peroxide remained after the reaction. This finding confirmed that the metals were indeed present as zero valent metals although of exceptionally small particle size. (The particles were not visible in the solution and did not settle on standing). Filtration of such small particles is inherently difficult to do on a large-scale production plant, therefore a hydrochloric acid extraction of a dichloromethane solution of DCPCAP was tested as a means of dissolving and removing these metals. (Experimental procedure 1, pp. 3-27)

After a dichloromethane solution of DCPCAP was extracted with an aqueous HCl solution, the time to complete the reaction as well as the amount of residual peroxides at the end of the reaction became constant. An ICP analysis of a typical sample of DCPCAP showed 87ppm of total metals and 1,3ppm of total metals after the acid

extraction procedure. This procedure was decided on since it would be easy to do in a production facility and it did not contribute much to the production costs.

1.4. Selection of solvent.

The solvent chosen for this reaction step had to comply with the usual criteria that are applied to solvents:

- Had to dissolve all of the reagents
- Not be reactive
- Readily available
- Relatively inexpensive.

Another very important factor that was considered was flammability. When peroxide is used in a reaction, especially at elevated temperatures, oxygen is released as the peroxide undergoes thermal decomposition. A solvent of low flammability can become a potential explosive in the oxygen-enriched atmosphere of a reactor headspace. Chlorinated solvents are the least flammable but tend to be toxic or carcinogenic. Dichloromethane is non-flammable in atmospheres of up to 30% oxygen and is not considered to be toxic or carcinogenic. It was found to be a good solvent for DCPCAP and the reaction product Triclosan ester. In initial experiments it was also found to be a good solvent for the reaction and complied with all of the selection criteria. It was decided that dichloromethane would be the solvent of choice for this reaction. Where liquid organic acids were used in the Baeyer-Villiger reaction, the acids themselves were tested as solvents. After completion of the experimental work it was found that the organic acids tested (formic and acetic acids) were not effective solvents for this reaction.

1.5. Selection of peroxy acid.

In choosing the peroxy acid for this reaction step, the following criteria were used:

- It had to be the most suitable oxidant for the reaction.
- It had to be readily available.
- Safe to use.
- Cost effective.
- Recovery or recycle of the organic acid was desirable.

Many different organic peroxy acids have been shown in the literature to be effective in the Baeyer-Villiger oxidation of carbonyl compounds to esters. Some organic peroxy acids are stable enough to be isolated and can be purchased as is, while others must be formed in-situ from the corresponding acid or anhydride and hydrogen peroxide.

It was decided that, if the peroxy acid were to be made in-situ, a 60% hydrogen peroxide solution would be used in all experiments. This decision was taken because it is commercially available and it is the strongest concentration that may be transported under the oxidant hazard label. Hydrogen peroxide of concentrations higher than 60% is classified by transport regulations as an explosive. The transportation and storage costs of chemicals classified as such are prohibitive and no local source of greater than 60% peroxide could be found.

Early experiments showed that when using non-polar solvents, the water present in the peroxy acid caused aqueous and organic phases to separate. Analysis of the two phases by titration with Ce^{4+} (peroxyacids) and thiosulphate (hydrogen peroxide) [26,27] showed that 75 to 80% of the peroxy acid and most of the free hydrogen peroxide remained in the aqueous phase. This caused the reaction rates to become excessively long. Homogenisation by high speed stirring and the use of isooctyl and tetraoctylammonium bromide phase transfer catalysts did not improve the reaction rate. Therefor it was concluded anhydrous peroxy acids had to be used when using non-polar organic solvents.

The peroxy acids that were studied for the oxidation of DCPCAP were:

- Peroxyformic acid
- Peroxyacetic acid
- Peroxymaleic acid
- Peroxyphthalic acid
- Mono-magnesium peroxyphthalic acid

Other peroxy acids like peroxytriflouroacetic and m-chloroperoxybenzoic were considered too expensive or not readily available enough for use in this synthesis.

2. Peroxyformic acid.

Peroxyformic acid is unstable and explosions of 45% peracid have been documented [18], therefor for safety reasons, it was decided to limit the concentration of the peracid to 12,5% in the reaction mixture. (Assuming 100% conversion of peroxide to peracid). Formic acid is a strong enough acid to self-catalyze the formation of the peroxy acid[19] as well as catalyzes the Baeyer-Villiger rearrangement.

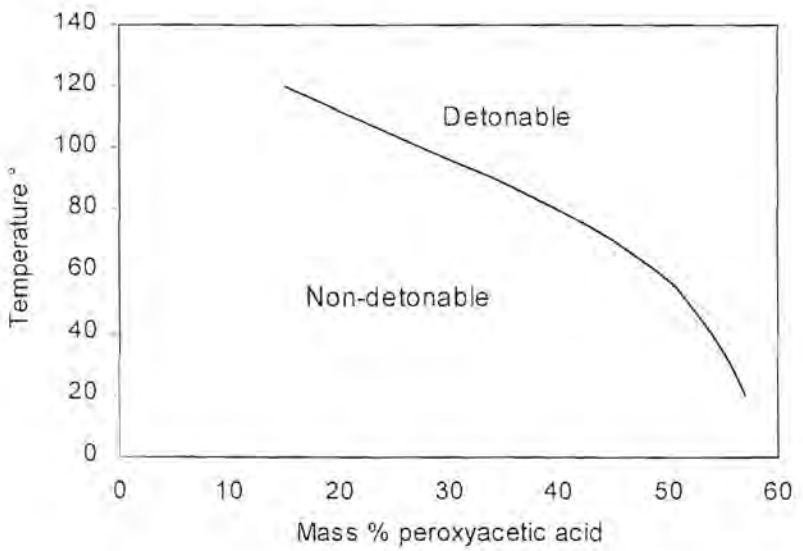
2.1. Oxidation of DCPCAP with peroxyformic acid

Peroxyformic acid is too unstable to be stored for any length of time and must be prepared directly before use. It was prepared in-situ by the oxidation of formic acid with hydrogen peroxide in the presence of DCPCAP (see experimental procedure 2, pp. 3-28). Formic acid also acted as the solvent in the reaction. At 30°C, very little of the starting material, DCPCAP. was dissolved and after 3 hours only 0,5% conversion was obtained. The reaction was then heated to 45°C to dissolve more DCPCAP. After a further three hours a conversion of 5,1% was achieved. At a temperature of 45°C, oxygen evolution was seen as the peracid decomposed. After six hours of reaction time, all of the peroxide species had decomposed. It was decided that peroxyformic acid was too unstable for use in this reaction.

3. Peroxyacetic acid

Peroxy acetic acid is a commonly used oxidant in the Baeyer-Villiger oxidation reaction with numerous publications for experimental detail [20] [21]. Peroxyacetic acid can become shock sensitive and detonate under certain conditions. Graph 1 [22] shows the boundaries between detonable and non-detonable regions for peroxyacetic acid in acetic acid in the temperature range of 20° to 120°C.

Graph 1: Detonable and non-detonable regions for peroxyacetic acid in acetic acid.



All experiments were designed so that the reaction mixtures were always well inside the non-detonable region.

It has been found [23] that acetic acid catalyzes the addition of the peracid to the carbonyl function of the ketone, but is not acidic enough to catalyze the rearrangement. A strong acid catalyst must be added for the reaction to proceed. This was found, in initial experiments to be true also for this synthesis. Peroxyacetic acid in anhydrous acetic acid gave slow reaction rates. Conversions of DCPCAP to Triclosan ester were in the order of 2% in 22 hours. The same reaction with added sulphuric acid achieved a conversion of 90% in 22 hours.

It was also found that added sulphuric acid catalyst facilitated the transesterification of the reaction product, Triclosan ester, to the final product, Triclosan (The reaction is explained in full in chapter 4). If this reaction could be made to work, this could be a convenient one-pot synthesis of Triclosan.

3.1. Formation of peroxyacetic acid

The formation of this peroxy acid was studied in order to decide whether to use anhydrous conditions with a non-polar solvent or hydrous conditions and a polar solvent. The use of hydrous conditions would mean that the peroxy acid could be made by the oxidation of acetic acid with hydrogen peroxide. This would be the method of choice since acetic acid recovered from the reaction could be recycled for subsequent batches. If an anhydrous system were required then the oxidant would have to be made from the anhydride. Recovered acetic acid would have to be disposed of since it cannot be dehydrated in a cost-effective manner.

3.1.1. Formation of peroxyacetic acid from acetic acid

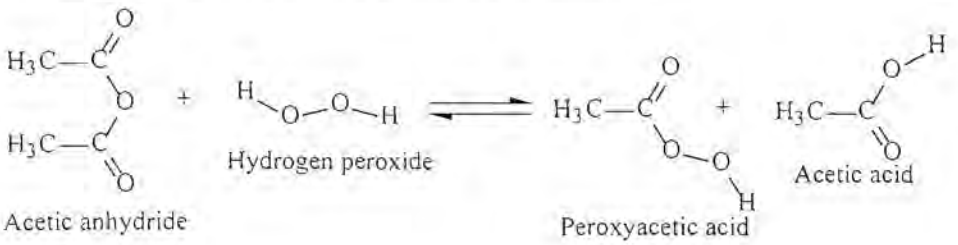
In the oxidation of acetic acid to peroxyacetic acid, with hydrogen peroxide, water in the hydrogen peroxide shifts the equilibrium away from the formation of the peroxy acid. Commercially available peroxyacetic acid is made from high strength hydrogen peroxide (around 90%) in order to obtain the highest concentrations of the peracid possible. Other methods use lower concentrations of hydrogen peroxide and remove water by azeotropic distillation.[24]. Small amounts of hydrogen peroxide also distil with water allowing for the possibility of a build up of highly concentrated and possibly explosive peroxide in the fractionating column. It was decided that the distillation of peroxides would be too dangerous to do in a multifunctional production area due to the danger of explosions.

Tests were done to see what concentration of peroxyacetic acid could be made from 60% hydrogen peroxide. See experimental procedure 3, pp. 3-28. The equilibrium concentration of the peroxy acid was found to be 5,3 %.

3.1.2. Formation of peroxyacetic acid from acetic anhydride

It was found that DCPCAP was not very soluble in acetic acid therefore it was decided to use dichloromethane as solvent and anhydrous peroxyacetic acid as the oxidant. Preliminary experiments suggested a reaction temperature of 40°C to be near optimum. Peroxyacetic acid was made in-situ by the oxidation of acetic anhydride with 60% hydrogen peroxide.

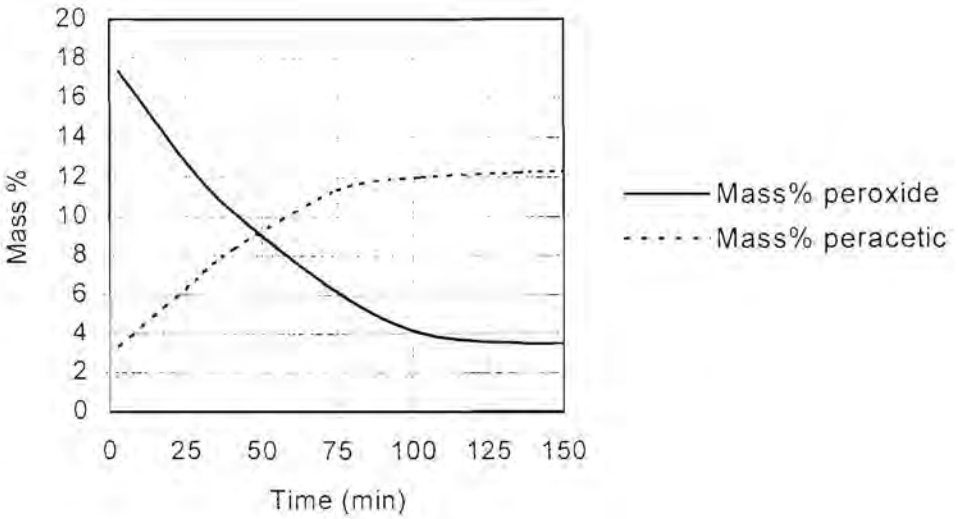
The overall reaction can be represented as follows:



Hydrogen peroxide, in the presence of an excess of acetic anhydride, can form the explosive diacetylperoxide. To prevent this, only enough acetic anhydride was added to react with the hydrogen peroxide and water present in the peroxide, forming an anhydrous reaction mixture.

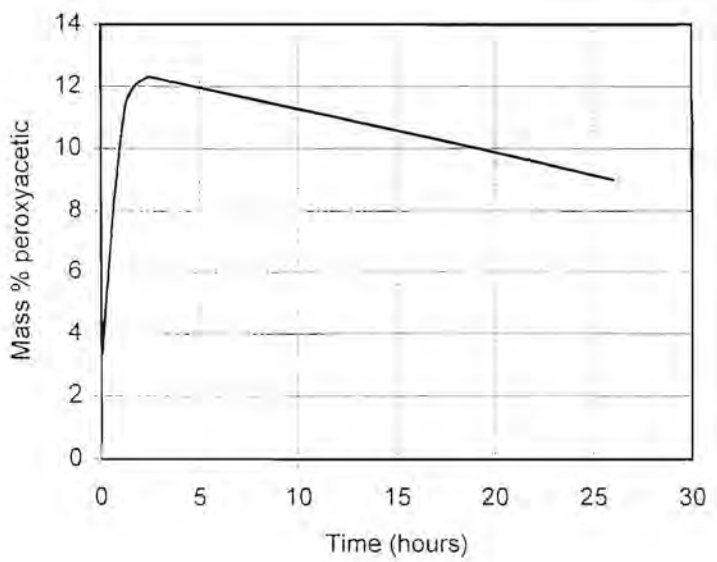
To aid in the understanding of the oxidation reaction rate, the rate of formation of peroxyacetic acid from the anhydride at 40°C was determined. Dichloromethane was added in the same ration as used in the oxidation reactions to limit concentration effects. (See experimental procedure 3, pp. 3-28) The results are represented in graph 2.

Graph 2: Rate of formation of peroxyacetic acid



The concentration of peroxyacetic acid reached a maximum after 2 hours. At equilibrium, the conversion of hydrogen peroxide to the peroxy acid was 92%. By extending the time scale, the thermal decomposition of the peracid at 40°C over time was also well illustrated. See graph 3.

Graph 3: Rate of formation and decomposition of peroxyacetic acid.



3.2. *Oxidation of DCPCAP with hydrous peroxyacetic acid.*

Peroxyacetic acid is commercially available, therefor its use in this reaction was investigated. A sample of this oxidant was analyzed and found to consist of: 36,5% peroxyacetic acid, 15% water, 1% sulphuric acid and the balance was acetic acid. This reagent could not be used with the solvent dichloromethane since the organic and aqueous phases separated and most of the peroxides were extracted into the aqueous layer. It was found that in a two-phase system, the oxidation reactions were prohibitively slow. Glacial acetic acid was used as a polar solvent for the reaction to prevent phase separation. The strong acid catalyst required for the reaction was already present in the peroxy acid but an additional 1,5 % (m/m) was added to ensure that there was sufficient catalyst present to eliminate any reaction rate limitations. A series of reactions were done to investigate the optimum temperature required for this reaction and if this reagent would be effective for this synthesis. (See experimental procedure 4, pp. 3-29)

3.2.1. *Results:*

Table of results: Oxidation of DCPCAP with hydrous peroxyacetic acid.

Reaction temp. (°C)	Reaction time* (h)	% Conversion* of DCPCAP	% Triclosan ester	% Triclosan	% By-products (not identified)
25	68	3	3,0	0	0
55	46	84,3	22,1	62,2	0
60	66	89,7	29,8	56,1	3,8
75	21	55,0	0	55,0	0
75	32	90,9	0	51,7	37

*Reaction time was the time taken for all peroxide species to decompose.

* % Conversion of DCPCAP was the mole % converted in the reaction time.

3.2.2. Discussion:

At 25°C very little reaction occurred. At temperatures up to 60°C very little of the DCPCAP was dissolved into the acetic acid solvent. The slow reaction rates at these temperatures are probably due to solubility limitations. At 65° all of the DCPCAP dissolved, indicating that the solution existed as a dissolved melt. At 75°C the rate of thermal decomposition of the peroxide species was rapid. All peroxides decomposed before the oxidation reaction was complete. The last reaction in the table was carried out at 75°C with 5 mole equivalents of peroxyacetic acid. Even with a large excess of peroxide, all of the peroxides thermally decomposed before the reaction was complete.

3.2.3. Conclusion:

At lower temperatures DCPCAP had limited solubility in acetic acid, extending the reaction rate to an unacceptably long time. The higher temperatures needed to dissolve DCPCAP caused rapid decomposition of peroxyacetic acid. The hydrous peroxyacetic acid system did not appear to be a viable option for this reaction.

3.3. Oxidation of DCPCAP with anhydrous peroxyacetic acid.

In order to circumvent solubility limitations, dichloromethane was used as the reaction solvent. As previously discussed, an anhydrous system must be used to prevent aqueous and organic phases from separating. Anhydrous peroxyacetic acid is miscible in a solution of DCPCAP in dichloromethane and the Baeyer-Villiger oxidation reaction was tested in this system.

A series of reactions in dichloromethane were conducted to test the use of peroxy acetic acid in an anhydrous system. See experimental procedure 5, pp. 3-30.

3.3.1. Results:

Table of results: Oxidation of DCPCAP with anhydrous peroxyacetic acid.

Exp. no	Reaction temp. °C	% conversion of DCPCAP	Reaction time* (hours)	H_2SO_4 added (g)
1	40	1,6	33,3	0
2	30	83,0	49	2
3	40	95,6	34	2
4	50	92,1	22	2
5	60	73,2	19	2

* Reaction time = time taken for all peroxides to decompose.

3.3.2. Discussion:

As suggested in the literature, without the aid of a strong acid catalyst, the reaction (Exp. no.1) rate was very slow with 1,6% conversion in 33,3 hours of reaction. The rest of the reactions with a catalytic amount of sulphuric acid added, progressed well. However at 30°C (Exp. no.2) the reaction rate was too slow to be useful and at the higher temperatures, all of the peroxide species decomposed before the oxidation reaction was complete. In all cases the reaction product, Triclosan ester, underwent a transesterification reaction with acetic acid to form Triclosan. See chapter 4 – reaction step 3.

3.3.3. Conclusion:

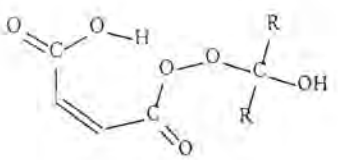
It was decided that the anhydrous peroxy acetic acid system was not suitable for this reaction due to slow reaction rates and decomposition of the peroxyacid under the reaction conditions.

4. Peroxymaleic acid

4.1. Introduction

Peroxymaleic acid has been found to be a stronger oxidant than peroxyacetic, peroxyformic and other aromatic peroxyacids [25]. It has been shown that the rate-determining step of the Baeyer-Villiger oxidation is the rearrangement of the peracid-ketone complex (Creejee intermediate). White and Emmons[22] have postulated that the enhanced activity of peroxymaleic acid is due to the ease at which the ketone-peroxyacid intermediate rearranges. See diagram 7

Diagram 7: Peroxymaleic Creejee intermediate.



An examination of the molecular model of the peroxymaleic-ketone intermediate shows that the acidic maleic acid proton is in close proximity to a peroxidic oxygen. This oxygen develops a negative charge during rearrangement and the proton stabilizes the intermediate. This results in a transition state with a more favourable entropy of activation for the rearrangement as compared to other peroxyacids.

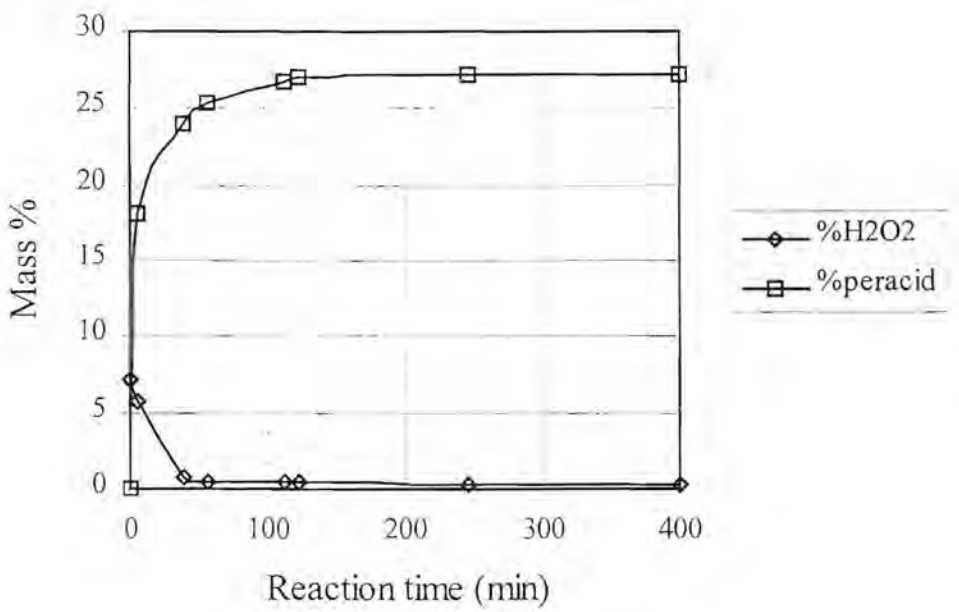
No data on explosions or ignition of peroxymaleic acid could be found, therefore in order to gather safety data, small samples of the peroxy acid were subjected to rapid heating and hammer impact tests. Under no conditions could a detonation or ignition be initiated. These results led to the conclusion that peroxymaleic acid was safe to use without fear of explosions or fires.

4.1.1. The formation of peroxymaleic acid from maleic anhydride

The peroxy acid was made by the oxidation of maleic anhydride with hydrogen peroxide in dichloromethane (see experimental procedure 6, pp. 3-31). The reaction mixtures were made anhydrous by adding sufficient anhydride to react with the water present in the hydrogen peroxide. The formation of peroxymaleic acid at 40°C with time, was monitored, the results are represented in graph 4.

4.1.1.1. Results

Graph 4: The formation of peroxymaleic acid.



4.1.1.2. Discussion

The concentration of peroxymaleic acid was found to reach equilibrium at 27.2% (m/m) after 2 hours of reaction. The same reaction was left at 40°C overnight, after 21.2 hours the peroxy acid concentration had fallen to 14.4% (m/m) showing that 47% of the peroxyacid had decomposed in this time. This figure implied that if the oxidation of DCPCAP were to take 21 hours to complete, two mole equivalents of peroxy acid

would be required to complete the reaction before the complete decomposition of peroxides.

4.1.2. The formation of peroxymaleic acid from maleic acid

After the oxidation reaction, maleic acid is recovered from the reaction mixture as a 40% aqueous solution by a water extraction. To determine if the maleic acid could be recycled, the preparation of the peroxy acid by the oxidation of maleic acid with hydrogen peroxide was investigated. (See experimental procedure 7, pp. 3-31)

4.1.2.3. Results

An aqueous and an organic phase were evident; most of the peroxide species were found in the water layer. An equilibrium of 3,8 % peroxy maleic acid was found after 3,5 hours. The addition of extra sulphuric acid as catalyst and peroxide phase transfer catalysts, tetra-isooctyl and tetraoctyl ammonium bromide[26] did not improve the yield.

4.1.2.4. Discussion

The yield of peroxymaleic acid was low due to the water in the peroxide shifting the reaction equilibrium away from the peroxy acid. It was decided that the recycle of maleic acid to the peroxy acid was not feasible and that recovered maleic acid would be sent back to the maleic anhydride plant for recycling. The production facility dehydrates aqueous maleic acid by the azeotropic removal of water with xylene followed by the distillation of the anhydride under vacuum.

4.2. Oxidation of DCPCAP with anhydrous peroxymaleic acid.

The use of anhydrous peroxymaleic acid as oxidant for this reaction was investigated. The anhydrous peroxymaleic acid was formed in situ by the addition of hydrogen peroxide to a solution of DCPCAP and maleic anhydride in dichloromethane. By slowly adding the peroxide last, the accumulation of reagents and the possibility of a run-away exothermic reaction were prevented.

A sample of DCPCAP was pre-treated to remove metal contamination using experimental procedure 1, pp. 3-27 and oxidized with anhydrous peroxymaleic acid. (See experimental procedure 8, pp. 3-32).

4.2.1. Results:

The product obtained was a light brown amorphous solid of purity 95.91% (m/m). The yield based on DCPCAP was 98.52%. Qualitative analysis by FTIR, GC-MS and NMR confirmed that the product was Triclosan ester (2-acetoxy-2',4',4-trichlorodiphenyl ether).

4.2.2. Discussion:

The reaction was complete in 22.2 hours and proceeded without the formation of by-products. Decomposition of the peroxides, other than that due to the oxidation reaction, was comparable to the thermal decomposition examined previously (paragraph 4.1.1.2).

4.2.3. Conclusion:

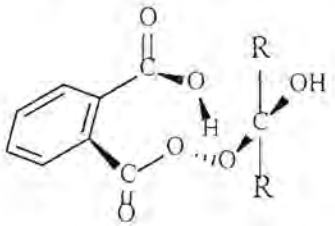
Peroxymaleic acid was found to be an excellent oxidant for DCPCAP. Optimization of the reaction parameters would lead to a viable synthesis.

5. Peroxyphthalic acid and its' salts.

5.1. Introduction

Peroxyphthalic acid should be a strong oxidant for the Baeyer-Villiger oxidation of DCPCAP. As with peroxymaleic acid, stabilization of the peroxy acid - ketone intermediate should occur. The acidic maleic acid proton will be in close proximity to the peroxidic oxygen and stabilize the negative charge that must develop for the intermediate to rearrange to the ester and free acid (see diagram 8).

Diagram 8: Peroxyphthalic Creejee intermediate.



Magnesium monoperoxyphthalate is commercially available as a stable salt and it has been used as the oxidant in the Baeyer-Villiger oxidation of ketones [7,27]. Likewise sodium monoperoxyperphthalate is also commercially available as a stable salt. Although no references were found pertaining to its' use in the Baeyer-Villiger oxidation it was thought that it should be as effective as the peroxy acid. Monoperoxyphthalic acid has been prepared by the oxidation of phthalic anhydride with hydrogen peroxide[28] in yields of 65%. Phthalic anhydride is readily available and relatively inexpensive. The use of monoperoxyphthalic acid and its' salts as oxidants for DCPCAP was investigated.

5.2. Oxidation of DCPCAP with peroxyphthalic acid and its' sodium and magnesium salts.

Samples of the sodium and magnesium salts were obtained from Aldrich Chemicals. Analyses by iodometric titration showed 52 and 56 % (m/m) peroxy acids respectively. A sample of monoperoxyphthalic acid in DCM was made, according to the method given by Royals and Harrell [28], by the oxidation of phthalic anhydride with hydrogen peroxide. Analysis showed the formation of 64% (m/m) of the peroxy acid after 2.5 hours at 35°C. Samples of DCPCAP were oxidized using these three oxidants (See experimental procedure 9, pp. 3-34).

5.2.1. Results:

The conversion of DCPCAP to TCSE after 16 hours of reaction was tabulated.

Oxidant	% conversion	Temp.(°C)
Monoperoxyphthalic acid	1.35	35
	1.42	50
Sodium peroxyphthalate	1.12	35
	1.21	50
Magnesium bisperoxyphthalate	0.4	35
	0.5	50

5.2.2. Discussion:

Peroxyphthalic acid and its' sodium and magnesium salts were not found to be suitable oxidants for this reaction. The addition of a catalytic amount of sulphuric acid did not increase the reaction rate. At 50°C some oxygen evolution was seen, signifying the decomposition of the peroxy acid. It was decided that higher temperatures were not worth investigating due to the increasing rate of decomposition with temperature.

5.2.3. Conclusion:

Peroxyphthalic acid and its' sodium and magnesium salts were not suitable oxidants for the Baeyer-Villiger oxidation of DCPCAP.

6. Conclusion: The selected peroxy acid.

Anhydrous peroxymaleic acid was found to be the most suitable reagent for oxidizing DCPCAP to Triclosan ester. It was inexpensive and the starting material, maleic anhydride, was freely available being a product this company. Recovered maleic acid could also be recycled to the anhydride reducing the environmental impact and cost of waste disposal and reducing raw material costs. It was decided that the anhydrous peroxymaleic acid route would be optimized.

7. Experimental

7.1. Procedure 1: Pre-treatment of DCPCAP - removal of metal impurities.

A sample of DCPCAP was dissolved with stirring in dichloromethane in a round bottom glass reactor. 36% Hydrochloric acid was added and the stirrer speed was increased to emulsify the aqueous HCl / DCM mixture. After 30 minutes demineralized water was added to dilute the acid and stirring was maintained for another 30 minutes. The stirring was stopped and the phases were allowed to separate. The phase separation took 7 minutes at 20°C. The bottom organic phase was drained off and the aqueous acid was recycled to the first step. The organic phase was returned to the reactor and washed by vigorous stirring with a second volume of demineralized water to remove traces of acid. The phase separation took 12 minutes at 20°C. The bottom organic phase was drained and the wash water recycled to step one. The organic phase was returned to the reactor for the oxidation reaction.

Table of reagents:

Chemical	Mass (g)	% Purity	Moles
DCPCAP	644	98,0	2
Dichloromethane	1940	100	-
HCl	50	36	-
Dilution water	250	100	-
Wash water	250	100	-

The product was a light brown solution of DCPCAP with a pH of 6,5.
DCM extraction of both water phases showed no loss of DCPCAP.

7.2. Procedure 2: Baeyer-Villiger oxidation of DCPCAP with peroxyformic acid.

A sample of DCPCAP was pre-treated as in procedure 1 and the solvent was evaporated. The sample was placed in a glass round bottom reactor equipped with a thermometer, a magnetic follower stirrer, a dropping funnel and an overhead condenser. Formic acid was added and the reactor was heated to 30°C in a thermostatically controlled water bath. Hydrogen peroxide was slowly added, over two hours, to the reactor from the dropping funnel. Once all of the peroxide was added, samples were analyzed by GC for product formation. When it was found that after 2,5 hours that only 0,5% conversion had occurred, the temperature was increased to 45° C and reaction monitoring was continued.

Table of reagents.

Chemical	moles	equivalents	% purity	Mass (g)
DCPCAP	0,1	1	99,5	31,7
Formic acid	-	-	99,9	85
Hydrogen peroxide	0,2	2	60,0	11,3

7.3. Procedure 3: Rate of formation of peroxyacetic acid from acetic anhydride.

Acetic anhydride and dichloromethane were placed in a glass three-necked flask equipped with a magnetic stirrer bar, an overhead condenser, a thermometer and a dropping funnel. The reaction flask was heated to 40°C in a water bath. While stirring well, 60% hydrogen peroxide was slowly added from the dropping funnel. The reaction exotherm, seen by the reflux rate of dichloromethane was controlled by the rate of peroxide addition. Once all of the peroxide had been added, samples were periodically withdrawn and analyzed for free peroxide and peroxy acid. The results were plotted on a graph.

Table of reagents:

Chemical	Equivalents	Moles	% purity	Mass (g)
Acetic anhydride	2,25	0,451	100	46,1
Hydrogen peroxide	1	2,0	60,0	11,3
Dichloromethane	-	0,45	100	39,3

7.4. Procedure 4: Oxidation of DCPCAP with hydrous peroxyacetic acid.

A sample of DCPCAP was pre-treated as in procedure 1 and the solvent was evaporated. The DCPCAP sample and glacial acetic acid were placed in a glass three-necked flask equipped with a magnetic stirrer bar, an overhead condenser, a thermometer and a dropping funnel. The reaction flask was heated to reaction temperature in a thermostated water bath. While stirring well, peroxyacetic acid was slowly added to the reaction flask. Once all of the peroxy acid had been added, samples were periodically withdrawn and analyzed by gas chromatography.

Table of reagents.

Reaction temp. (°C)	Moles DCPCAP	Mass glacial acetic (g)	Mole equivalents of peroxyacetic acid
25	0,15	52,5	2
55	0,15	52,5	2
60	0,2	70	2
75	0,15	52,5	2
75	0,15	52,5	5

Peroxyacetic acid: 36,5% peroxyacetic acid, 15% water, 1% sulphuric acid, balance acetic acid.

DCPCAP: P = 99,5%.

Added sulphuric acid: 1g.

Table of results:

Reaction temp. (°C)	Reaction time* (h)	% Conversion* of DCPCAP	% Triclosan ester	% Triclosan	% By-products (not identified)
25	68	3	3,0	0	0
55	46	84,3	22,1	62,2	0
60	66	89,7	29,8	56,1	3,8
75	21	55,0	0	55,0	0
75	32	90,9	0	51,7	37

*Reaction time was the time taken for all peroxide species to disappear.

% Conversion of DCPCAP was the mole % converted in the reaction time.

7.5. Procedure 5: Oxidation of DCPCAP with anhydrous peroxyacetic acid.

A solution of DCPCAP in DCM was pre-treated as is procedure 1 and acetic anhydride was added. The solution was placed in a glass three-necked flask equipped with a magnetic stirrer bar, an overhead condenser, a thermometer and a dropping funnel. The reaction flask was heated to reaction temperature in a thermostated water bath. While stirring well, hydrogen peroxide was slowly added to the reaction flask. Once all of the peroxide had been added, samples were periodically withdrawn and analyzed by gas chromatography for the formation of Triclosan ester.

Table of reagents:

Exp. no	Reaction temp °C	Moles DCPCAP	Eq. DCPCAP	Eq. Acetic anhydride	Eq. H_2O_2	DCM (g)	Catalyst /mass (g)
1	40	0,2	1	4,6	2	76	0
2	40	0,2	1	4,6	2	76	2
3	50	0,2	1	4,6	2	76	2
4	60	0,4	1	4,6	2	120	5

7.6. *Procedure 6: Formation of peroxymaleic acid by oxidation of maleic anhydride.*

Maleic anhydride (46g, 0,46 moles) was dissolved in 40g of dichloromethane in a 3-necked, glass round bottomed flask equipped with a stirrer, thermometer, cold condenser and a dropping funnel. 60% Hydrogen peroxide (11,4 g, 0,2 moles) was added over 5 minutes, via the dropping funnel. Samples were periodically withdrawn and analyzed[29 30]. The reaction was monitored by the disappearance of hydrogen peroxide and the formation of peroxymaleic acid.

7.7. *Procedure 7: Formation of peroxymaleic acid by oxidation of maleic acid*

A 40% (m/m) aqueous maleic acid solution was placed in beaker and the pH was adjusted to pH 6 with sodium carbonate. Monosodium maleic acid precipitated out of solution as a white crystalline material. The crystals were filtered on a Buchner vacuum filter and dried in an airflow. The dried material was suspended in dichloromethane in a 3-necked, glass round bottomed flask equipped with a stirrer, thermometer, cold condenser and a dropping funnel. One mole equivalent of anhydrous sulphuric acid was added, while stirring, to convert the sodium salt to anhydrous maleic acid. 1,5 Mole equivalents of hydrogen peroxide (60%) was added over 5 minutes, via the dropping funnel. Samples were periodically withdrawn and analyzed by titration[27 28]. The reaction was monitored by the disappearance of hydrogen peroxide and the formation of peroxymaleic acid.

7.8. Procedure 8: Oxidation of DCPCAP with anhydrous peroxymaleic acid.

A solution of DCPCAP (63.8g; 99.0% P; 0.2 moles; 1 equivalent) in DCM (50g) was pre-treated as described in experimental procedure 1. Maleic anhydride (92.3g; 98% P; 0.92 moles; 4.61 equivalents) was added and stirred until dissolved. The solution was placed in a glass three-necked flask equipped with a magnetic stirrer bar, an overhead condenser, a thermometer and a dropping funnel. The reaction flask was heated to 45°C in a thermostated water bath. While stirring, hydrogen peroxide (22.7g; 60.0% P; 0.4 moles; 2 equivalents) was slowly added over 20 minutes to the reaction mixture via the dropping funnel. Once all the peroxide had been added, samples were periodically withdrawn and analyzed by gas chromatography for the formation of Triclosan ester. After 22.2 hours, 0.6% (based on GC area %) of the DCPCAP remained, 98.8% Triclosan ester and 0.2% Triclosan had formed.

Reaction work-up:

De-mineralized water (80ml) was added to the reaction and the stirrer was speeded up to form an emulsion. The mixture was poured into a separating funnel and left standing to allow the phases to separate. The bottom organic phase was drained and the water was saved. The water wash was repeated with another 80ml portion of water. After the second water wash, the pH of the organic phase was 7 and no trace of peroxides was detected. The two portions of wash water were combined and extracted with 25ml of DCM. This DCM extract was added to the rest of the organic phase and the solvent was removed at 60°C in a rotary evaporator. Vacuum was applied to remove the last traces of solvent. The product was a light brown amorphous solid of purity 95.91% (m/m) with a yield (based on DCPCAP) of 98.52%.
For qualitative analysis, the product was crystallized in 60ml of methanol to yield a white crystalline material of 99.2% purity.

Analysis of re-crystallized Triclosan ester.

GC: (see appendix A-1, pp. 3-36, for chromatograph)

R.t. = 5.981 minutes.

GC-MS: (see appendix B-1, pp. 3-38, for mass spectrum)

Mass [ion fragment]:

330 $[M]^+$; 288 $[M - C_2H_2O]^+$;

252 $[M - C_2H_3O, - Cl]^+$; 218 $[M - C_2H_3O, - 2Cl]^+$;

FTIR: (see appendix C-1, pp. 3-39, for spectrum)

ν (cm^{-1}), KBr

1775, C=O stretch, aryl-alkyl ester.

1200, C-O stretch, diaryl ether.

NMR: (see appendix d-1, pp. 3-40, for spectrum)

δ 7.433 (1H, d, J=2.4 Hz. Ar-H)

δ 7.176 (1H, d, J=2.4 Hz. Ar-H)

δ 7.157 (1H, dd, J= 5.4 Hz, J=2.7 Hz. Ar-H)

δ 7.140 (1H, dd, J= 6.0 Hz, J=3.6 Hz. Ar-H)

δ 6.858 (1H, d, J=8.7 Hz. Ar-H)

δ 2.206 3H, s, C-CH_3)

7.9. Procedure 9: Oxidation of DCPCAP with monoperoxyphthalic acid and its' sodium and magnesium salts.

A large sample of DCPCAP was pre-treated to remove metal contamination using experimental procedure 1. The solvent was removed and the molten DCPCAP was poured onto a plastic sheet to harden. The solid material was flaked and stored for later use. The quantities of reagents used are shown in the table of reagents. The three oxidants were placed in glass three-necked flasks equipped with magnetic stirrer bars, overhead condensers, thermometers and powder funnels. DCM was added and the reaction flasks were heated to reaction temperature in thermostated water baths. While stirring, DCPCAP was added to the reaction mixtures via the powder funnels. Once the DCPCAP had been added, samples were periodically withdrawn and analyzed by gas chromatography for the formation of Triclosan ester

Table of reagents:

Reagent	Equivalents	Moles	%P	Mass (g)
DCPCAP	1	0.1	99.5	13.5
DCM	-	-	100	60
(1) Perphthalic	3	0.3	62	88.1
(2) Na-salt	3	0.3	52	117.8
(3) Mg-salt	1.5	0.15	56	132.5

7.10. Appendix A: Gas chromatography

Instrument:	Hewlett-Packard 6890 series GC
	Hewlett-Packard 3396 A integrator

Column:

Capillary column:	J&W Scientific DB-1
Length:	30m
ID:	0.53mm
Film thickness:	3µm
Carrier gas:	Helium

Temperature program:

Initial temp:	200°C
Initial time:	1.00min.
Ramp:	15°C/min
Final temp:	270°C
Hold time:	12min

Injection port:

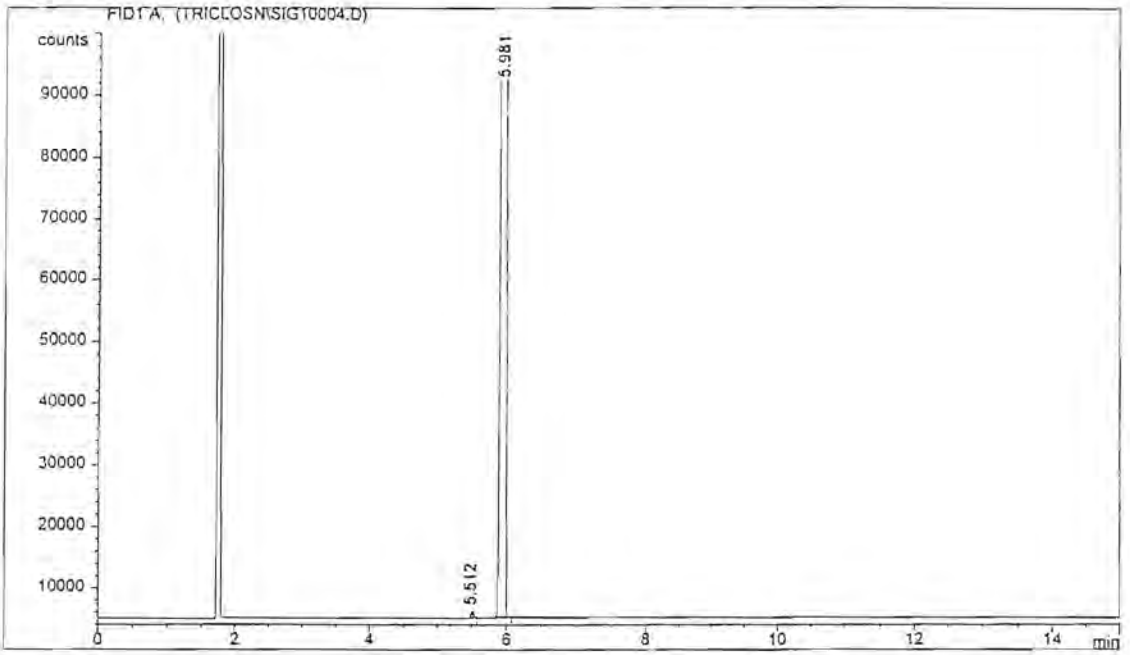
Mode:	Split
Split ratio:	35:1
Splitter flow:	32 ml/min
Septum purge:	2.5 ml/min
Temperature:	270°C
Head pressure:	55kPa

Detector:

Type:	FID
Temperature:	280°C

7.11. *Appendix A-1: Gas chromatogram of Triclosan ester (TCSE)*

```
Sample Name      : TCSE                                    Vial :   1
Acq. Operator    : Les
                                                  Inj Volume : 1 µl
Method           : C:\HPCHEM\3\METHODS\TRICLOSN.M
Last changed     : 11/16/00 11:14:01 AM by Les
                   (modified after loading)
Triclosan
```




```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount         :      1.00000  [ng/5ul]   (not used in calc.)


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  counts*s   [counts]      %
----|-------|----|-------|----------|----------|--------|
   1   5.512 PB   0.0320 2554.25635 1242.44470  0.13604
   2   5.981 PB   0.0456 1.87507e6  5.39208e5  99.86396

Totals :                  1.87763e6  5.40451e5
```

7.12. Appendix B: GC-Mass spectroscopy

Instrument: Hewlett-Packard 6890 series GC-MS

GC parameters:

Column:

Capillary column:	(Silica) HP-1
Length:	30m
I.D:	0.2mm
Film thickness:	0.2µm
Outlet pressure:	Vacuum
Carrier gas:	Helium

Temperature program:

Initial temp:	50°C
Initial time:	1.00min
Ramp:	10°C/min
Final temp:	300°C
Final time:	14min.
Total flow:	32 ml/min

Injection port:

Temperature:	250°C
Pressure:	50kPa
Mode:	Split
Split ratio:	30:1
Split flow:	29 ml/min

Mass spectrograph parameters:

Ionization source:

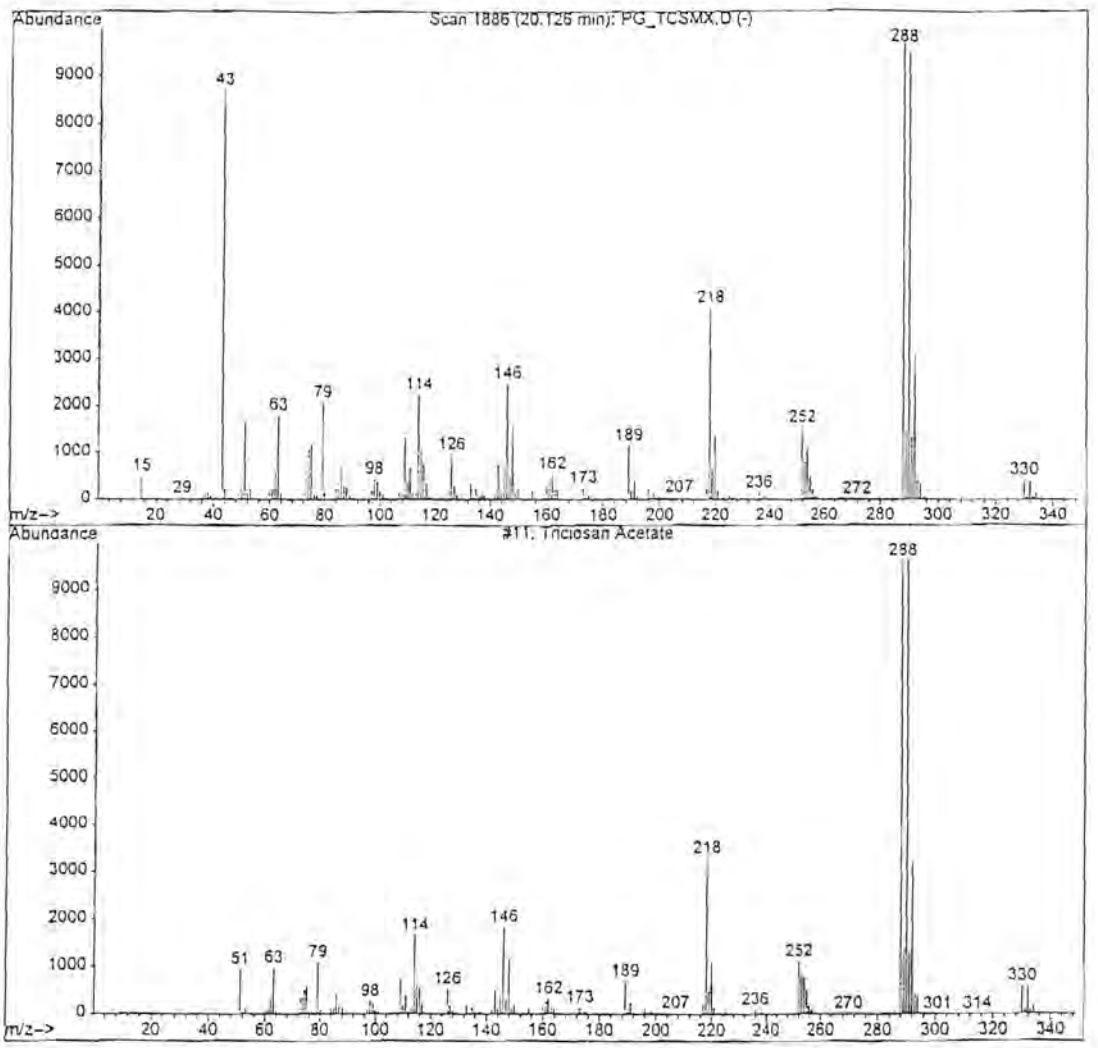
Mode:	Electron impact
Electron energy:	70 eV

Detector:

Type:	Quadropole positive ion mass selective detector with horn electron photo-multiplier.
System vacuum:	0.0015 kPa

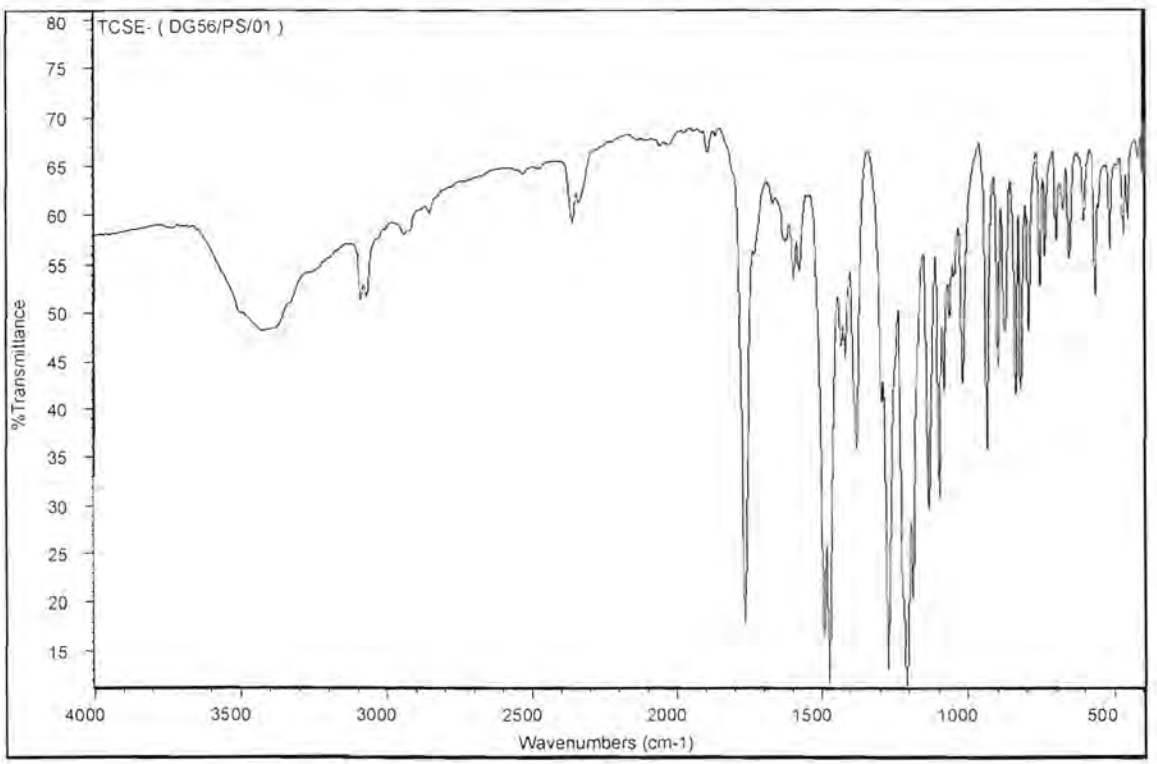
7.13. Appendix B-1: GC-MS of TCSE

Library Searched : C:\DATABASE\DG.L
Quality : 99
ID : Triclosan Acetate



7.14. Appendix C: FTIR spectrum of TCSE (KBr disk)

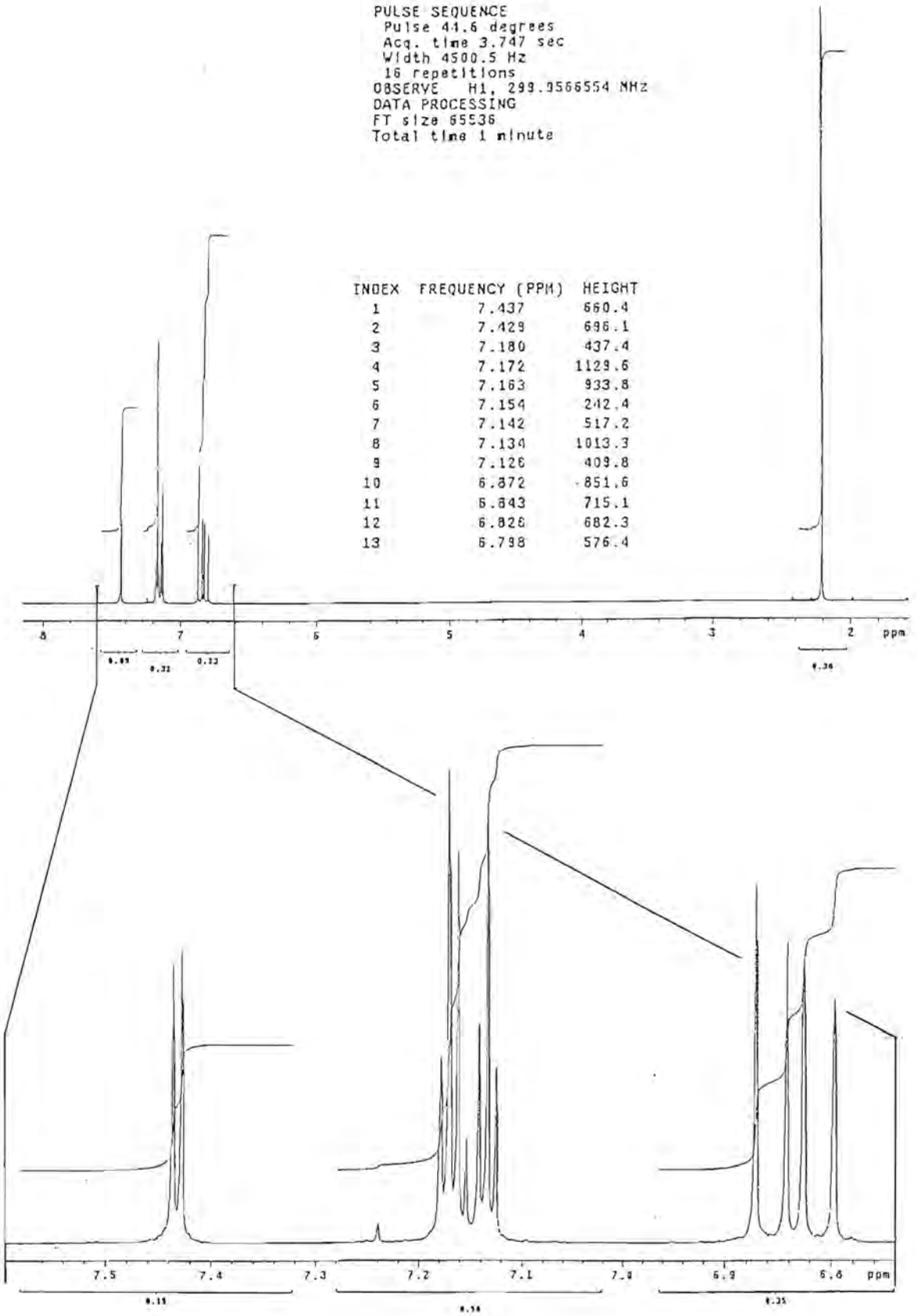
Instrument: Nicolet Avatar 360 FT-IR



7.15. *Appendix D: H-NMR spectrum of TCSE*

TCSE in CDCl3 26Jun99
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "NMR300"
PULSE SEQUENCE
Pulse 44.6 degrees
Acq. time 3.747 sec
Width 4500.5 Hz
16 repetitions
OBSERVE H1, 299.9566554 MHz
DATA PROCESSING
FT size 65536
Total time 1 minute

INDEX	FREQUENCY (PPM)	HEIGHT
1	7.437	660.4
2	7.429	696.1
3	7.180	437.4
4	7.172	1129.6
5	7.163	933.8
6	7.154	242.4
7	7.142	517.2
8	7.134	1013.3
9	7.126	409.8
10	6.872	851.6
11	6.843	715.1
12	6.828	682.3
13	6.798	576.4



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Chapter 4

Optimization of the peroxymaleic acid oxidation of DCPCAP

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1 Introduction:

This chapter describes the optimization of the laboratory synthesis of Triclosan ester (TCSE), via the Baeyer-Villiger oxidation of DCPCAP with peroxymaleic acid. This optimization was conducted with the aim of scaling up the reaction size to commercial production. By this stage of the development of this project, some criteria had been established in order to ensure a financially viable process. The general categories of these criteria were:

1. **Economics:**
   The marketing and financial departments had determined a maximum production cost of the final product. Apart from determining the optimum reaction conditions, this optimization was aimed at reducing production costs to a minimum. The optimized process also provided the information required to make a good estimate of the total production costs. In this reaction step, production costs were limited by reducing reagent excesses, reducing chemical waste by recycling, minimizing solvent volumes and utilizing simple and inexpensive processing equipment.

2. **Product quality:**
   As a new producer in the global Triclosan market it was necessary to have an advantage over the existing producers. Instead of entering into a price war with other Triclosan producers, it was decided that our product should be sold at the current market price. In order to have a competitive advantage the product had to be the purest on the market. This was done to ensure that the product would be easy to sell and therefor make an easy entry into the established marketplace.

3. **Safety:**
   No compromise was made to ensure that the final process was as safe as possible. This was done to ensure the safety of production personnel, to prevent damage to the environment via unexpected releases, excessive waste generation and to ensure continuous production.

4. **Engineering:**

   This process was developed to allow for the use of simple, cheap and easily maintained processing equipment. By limiting reagent excesses and solvent volumes, smaller and cheaper equipment could be used. As far as possible, extreme conditions of pressure, vacuum and temperature were avoided to allow for the use of standard production equipment instead of expensive custom manufactured equipment. In order to continuously asses equipment costs, possible choices of production equipment were made based on the handling procedures required to conduct the experimentation.

1.1 Optimization of reaction temperature

1.1.1 Introduction

Controlling the temperature of an exothermic reaction in large-scale production equipment can be difficult and usually requires complicated and expensive equipment. A heating circuit must supply heat to start the reaction and to maintain the reaction temperature once the reaction slows down towards the end. A cooling circuit must also be included to remove excess heat during the exothermic stage of the reaction. The simplest and least expensive method of controlling the temperature of an exothermic reaction is by utilizing the boiling point of the reaction mixture. In this case, heating is supplied to the reactor walls and a cooling unit supplying an overhead reflux condenser removes excess reaction heat.

During the acid wash pre-treatment of DCPCAP (Experimental procedure 1, chapter 3), 3 grams of dichloromethane per gram of DCPCAP were required to ensure complete dissolution of DCPCAP and a clear phase separation between organic and aqueous phases. This ratio of solvent to reagents gave a boiling point of 40°C. In order to increase the boiling point and thus reaction temperature, solvent was distilled from the reaction mixture. Measurement of the volume of solvent removed was extremely difficult because the dew point of DCM is zero at minus 42°C. This made it very difficult to quantitatively condense the dichloromethane during distillation. On a

production scale, this problem is exacerbated by ice build-up in the sub-zero temperature condensers required for complete condensation. The boiling point of the reaction mixture before the addition of hydrogen peroxide therefore was chosen as a quantitative measure of the amount of dichloromethane remaining during solvent distillation.

During the course of oxidation reactions it was seen that after about 60% conversion, the reaction rate slowed to the extent that the reaction exotherm did not supply sufficient heat to maintain to the reaction. At this stage heat was applied to maintain the reaction at a slow solvent reflux. In the planned production equipment this heat was to be supplied by a steam heated reactor jacket and the temperature control would be coupled to a flow meter that measured the rate of solvent reflux. This set-up would allow for just enough heat to be applied to maintain the reaction at the boiling point under a slow solvent reflux.

Also during the course of the reaction, peroxymaleic acid was reduced to maleic acid which is insoluble in DCM. As the acid precipitated out of solution, the boiling point of the reaction mixture dropped. However, by using a coolant temperature of 2°C in the overhead condenser, solvent losses caused by incomplete condensation caused the boiling point to remain virtually constant throughout the reaction. For the design of plant equipment, it was envisaged that a pressure swing, carbon adsorption bed or a compressor condenser would be used to recover the lost solvent down-stream of the process. This second-stage solvent recovery system would in any case be required to prevent the release of DCM into the environment.

In order to determine the optimum reaction temperature (boiling point), the oxidation of DCPCAP with varying quantities of solvent was studied (see experimental procedure 1, pp. 4-21). The reactions were assumed to be complete at 99.8% conversion of DCPCAP to Triclosan ester, measured by gas chromatography as the integrated area %.

1.1.2 Results.

The results of the solvent optimization experiments were tabulated:

Reaction number.	Bp. (°C)	g DCM/g DCPCAP	Reaction time* (h)
1	58	0.5	-
2	55	0.64	-
3	52.5	0.8	17.2
4	51	1.0	18.7
5	50	1.2	19.1
6	49	1.407	22.4
7	45	1.72	25.8
8	41	2.015	27.1

*Reaction time = time taken for complete reaction.

1.1.3 Discussion.

Reaction 1, with a starting boiling point of 58°C became too viscous to stir efficiently after about 70% conversion of DCPCAP. Maleic acid that had crystallized during the reaction formed a thick slurry that was mobile in close proximity to the stirrer blades but further away remained static. This reaction was discontinued due to the lack of efficient stirring.

Reaction 2, with a starting boiling point of 55°C was incomplete because all peroxides had decomposed before the oxidation reaction was complete. It was found that at 55°C, the rate of the thermal decomposition of peroxides was greater than that of the oxidation reaction.

Reactions 3, 4 and 5, with starting boiling points between 50 and 52.5°C remained fluid enough for efficient stirring throughout the reaction and the oxidation reactions were complete in 17 to 19 hours.

Reactions 6,7 and 8 took in excess of 20 hours to complete. It was decided that these reaction times were too long and would limit production capacity or require a greater capital outlay to include larger or more reactors in the plant design.

1.1.4 Conclusion.

It was decided that solvent would be distilled from the reaction mixture until a boiling point of between 50 to 52.5°C was attained. The exact temperature was to be determined during the scale-up of this process in the pilot plant. The reaction temperature and volume of solvent required were therefore considered optimized.

1.2 Optimization of reagent quantities.

1.2.1 Introduction

During all reactions, oxygen evolution caused by peroxy acid or hydrogen peroxide decomposition was detected in the reactor headspace, by GC analysis. The amount of hydrogen peroxide (and thus also maleic anhydride) required to complete the reaction before the peroxides decomposed was investigated. All reactions were conducted following experimental procedure 8, chapter 3, pp. 3-32 utilizing a starting boiling point of 52°C.

1.2.2 Results

Since there were small variations in the results of identical experiments, the average reaction time for two experiments was reported. The results were tabulated:

Table: Optimization of peroxide quantity

Reaction no.	Mole equivalents* H_2O_2	Reaction time (h)
1	1.5	(Incomplete)
2	2	17.2
3	3	15.8
4	4.5	13.3

*Mole equivalents = moles H_2O_2 per mole DCPCAP

1.2.3 Discussion

Reaction 1 was not complete because all peroxides had decomposed before the oxidation reaction was complete. This is in agreement with the investigation into the formation and decomposition of peroxymaleic acid reported on in chapter 3. There it was estimated that, due to the rate of the peroxide decomposition reaction, two equivalents of hydrogen peroxide would be required to complete the oxidation reaction at 40° C.

Reaction 2 was completed in 17.2 hours (average of 3 experiments). 0.08 equivalents of peroxides remained after the oxidation reaction was complete.
Reaction 3 was completed in 15.8 hours and 0.92 equivalents of peroxide remained.
Reaction 4 was completed in 13.3 hours and 2.1 equivalents of peroxide remained unreacted.

1.2.4 Conclusion

It was decided that two equivalents of hydrogen peroxide (based on DCPCAP) was the optimized, minimum amount for this reaction. Correspondingly, the optimum quantity of maleic anhydride became two equivalents plus the amount needed to create anhydrous conditions. This was based on the concentration of water in the hydrogen peroxide used. The rate of the oxidation reaction at this peroxide concentration was sufficient to complete the reaction before the complete decomposition of peroxides. A reaction time of 17.2 hours was also acceptable.

1.3 Optimization of maleic acid recovery

1.3.1 Introduction

As previously discussed, during the oxidation reaction peroxymaleic acid was reduced to maleic acid that was insoluble in DCM. The acid had to be removed from the reaction mixture for recycling to the anhydride at our maleic anhydride production facility.

The optimized recovery method had to comply with the following criteria:

- A complete removal of the acid from the organic layer had to be affected.
- The TCSE product stream had to be free from peroxides.
- The recovered maleic acid had to be free of organic material.
- And as pure as possible.
- The acid stream was to be introduced into the maleic anhydride production facility as a 40% aqueous solution to fit into the process stream, although it could be transported as a concentrated slurry or a solid.

1.3.2 Maleic acid recovery

1.3.2.1 Recovery by filtration

Once an oxidation reaction was complete, the reaction mixture was cooled to room temperature and filtered to remove the crystalline maleic acid. The maleic acid was washed with fresh DCM on a Buchner filter and dried in a flow of air. A DCM extraction of an aqueous solution of the acid yielded 0.23 % (mass) of TCSE.
Since the recovered solid, maleic acid, contained TCSE it was decided that recovery by filtration was not suitable.

1.3.2.2 Recovery by water extraction

After the completion of an oxidation reaction, distilled water was added to the reaction mixture. The quantity of water used was calculated to give a 40% maleic acid solution as required for the maleic acid plant. After ten minutes of stirring, the agitator was switched off and the mixture was left standing to allow the organic and aqueous phases to separate.

The denser organic layer was drained from the bottom of the reactor into a separating vessel. The remaining water extract, consisting of approximately 40% maleic acid, was extracted with a 10% volume of DCM to recover any residual TCSE. This DCM fraction was then drained and added to the rest of the organic phase and extracted a further four times with water. In order to determine the extraction efficiency, the organic layer was analyzed for residual peroxides and pH while the five water extractions were analyzed for maleic acid by titration with a base. The analytical results are tabulated.

Results of water extraction of the reaction mixture.

Extraction no.	Aqueous phase	Organic phase	
	Mass % maleic acid	pH	Peroxide (ppm as H_2O_2)
1	39.3	2	>200
2	0.34	2.6	28
3	0.07	4.5	9
4	(pH=4.9)	7.0	0
5	(pH=6.1)	7.0	0

As seen in the table, the organic phase was free of peroxides and maleic acid after four water extractions. A DCM extraction of the combined water phases yielded 0.012 mass % TCSE. Due to the high extraction efficiency it was decided that the first water extraction would be sent for recycling the maleic acid. The second and subsequent water extractions would be recycled to extract the following reactions.

The recycle of the second and subsequent water extractions for following reactions was examined to ensure that the extraction efficiency was not compromised. Four oxidation reactions were completed and the maleic acid in each reaction mixture was extracted four times with recycled water. The recycle of the water extraction was conducted as show in the diagram:

(The letters A to D were the four reaction mixtures while the numbers 1 to 4 are the four water extractions. The arrows show the recycle of the extracts to the next batch.)

A			
1	B		
2 →	1	C	
3 →	2 →	1	D
4 →	3 →	2 →	1
	4 →	3 →	2
		4 →	3
			4

Each extract was analyzed for maleic acid content by titration with a base. The first water extraction of each reaction mixture was extracted once with a 10% volume of DCM to recover residual TCSE. These first water extractions were analyzed for remaining organic materials by performing a further two solvent extractions. The solvents were then analyzed by GC-MS and no organic material was detected indicating a complete extraction.

The results of the analysis of maleic acid in the water extractions are represented in the following table:

A			
39.3	B		
0.34 →	38.7	C	
0.07 →	0.43 →	40.6	D
pH=4.9 →	0.01 →	0.30 →	39.46
	pH=4.5 →	0.02 →	0.33
		pH=4.7 →	0.04
			pH=4.8

(Results are given as mass % maleic acid)

As seen in the table of results, recycling did not compromise the efficiency of the water extraction of maleic acid. Analysis of the organic phases after the four extractions showed no detectable peroxides and a pH of 7 indicating a complete removal of maleic acid from the product.

1.3.3 Conclusion

Water extraction was the chosen as the best method to recover maleic acid from the reaction mixture. Four successive water extractions were required to extract all of the peroxides and maleic acid. Recycling of the second and subsequent extracts for the next reaction work up was an effective method of reducing the aqueous waste generated by the process.

For the future plant design either the same four-batch extraction process or a series of four mixer-settlers was envisaged for maleic acid recovery.

1.4 Optimization of TCSE purification

1.4.1 Introduction

After the water extraction of maleic acid from the reaction mixture, the solvent was removed by distillation. The product was a heavy brown oil, typically 94 to 96 % pure, that solidified on standing for a day.

To test if a purification of TCSE was required, a typical sample of this product was used to synthesize Triclosan. The product that was formed required two crystallizations in order to achieve the required purity. A sample of TSCE that had been crystallized once yielded Triclosan that met the purity requirements after one crystallization. This implied that both the TSCE and Triclosan could be purified once each or the Triclosan could be purified twice. It was decided that the TCSE should be purified by crystallization in order to have it in a free flowing crystalline form. To ensure continuos production of Triclosan, it would be necessary to maintain a stock of TCSE to act as a buffer to absorb discontinuations in the process. In a crystalline form it is easy to handle and can be stored in cheap bulk storage bags. If stored as a solid mass, the entire contents of a storage tank would have to be melted before use. Through experience this process can take up to a day or more to achieve a complete melt. A large bulk storage tank equipped with heating would also increase equipment costs.

1.4.2 Choice of solvent for crystallization of TCSE

The next reaction step in this process is the transesterification of TCSE and an alcohol to yield Triclosan and an alkyl acetate. The acetate and the remaining alcohol were to be removed from the product by distillation. Screening experiments and raw materials costing determined that either methanol or ethanol was the reagent of choice. Armed with this information, the marketing department found a market for a blend of methanol and methyl acetate. The sale of the recovered solvent blend was a cheaper option than installing distillation columns to separate the two. Since the solvent /

reagent required for the next reaction step was to be methanol, it was tested as the solvent for the crystallization of TCSE. Normally a crystallized material must be dried to prevent contamination of the next reaction by carry over of solvent residues. By using the same solvent to crystallize TCSE as that required for the next reaction step, drying of the crystallized material became unnecessary and the cost of drying equipment in the plant was avoided.

1.4.3 Optimization of TCSE crystallization from ethanol.

1.4.3.1 Introduction

It is extremely difficult to fully optimize a crystallization process in the laboratory that will work in large-scale production equipment. The complexity and geometry of commercial crystallization equipment is impossible to simulate in the laboratory. The best way to choose the correct crystalliser is to send the material to equipment manufacturers for pilot tests. The choice is then based on the results of these tests.

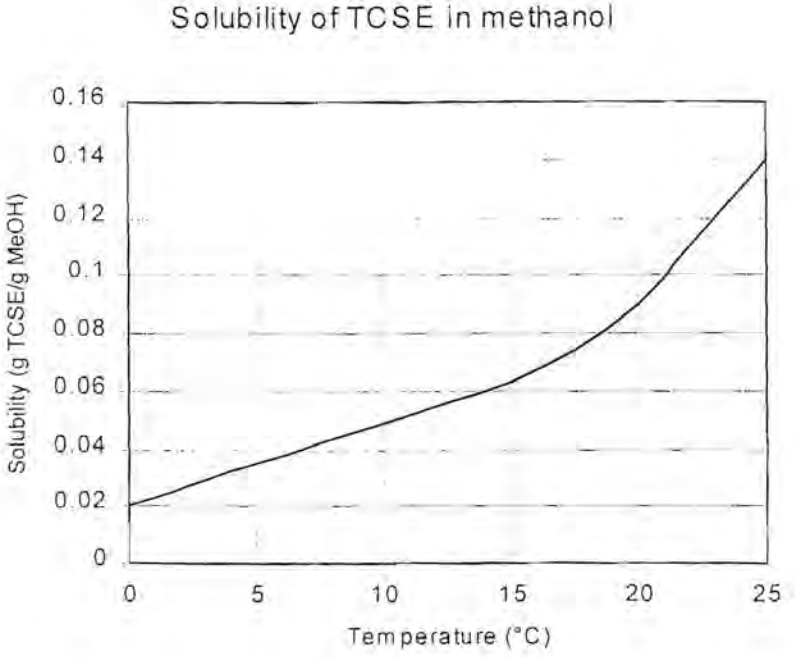
With this in mind, this crystallization optimization was aimed at providing as much information as possible that would aid in the choice of future equipment. Another aim of this optimization was to provide material of sufficient purity for the next reaction step. In order to determine the required purity of the crystallized TCSE, Triclosan was synthesized from batches of TCSE of differing purity. The product was crystallized once and analyzed in order to determine if the final product met the purity requirements. This optimization was done by my colleague Vladimir Cucan and will therefore not be reported on. The purity specification for crystallized TCSE was set at a minimum of 99.0 %.

1.4.3.2 Solubility of TCSE in methanol.

In order to establish the final temperature for the crystallization, the solubility of TSCE in methanol in the temperature range of 0 to 40°C was determined. From the solubility determinations, the losses of TCSE in the crystallization filtrate could be

calculated. A final temperature of 5°C was chosen because that was the lowest temperature that could be achieved in the existing pilot plant equipment. Obviously the final temperature would be reassessed based on the crystallizer chosen for the plant.

The results were plotted on a graph for easy reference.



1.4.3.3 Optimization of solvent to TCSE ratio.

Experiments were conducted to determine an optimum volume of methanol per unit mass of TCSE required for crystallization in a stirred reactor. The maximum yield of product and a minimum purity of 99 % were required. In all of the experiments, the same batch of flaked crude TCSE was used (purity = 93.3%). The TCSE was added to a volume of methanol and heated while stirring until dissolved. The solution was allowed to cool, while stirring, to 25°C and then cooled in a cold water bath to 5°C and held at that temperature for ten minutes. The crystals were vacuum filtered on a chilled Buchner funnel and washed through with 0.2 ml of cold methanol (2°C) per gram of TCSE. Samples were dried in a vacuum oven and analyzed by GC for purity.

The results of the crystallization experiments were tabulated:

g MeOH /g TCSE	0.5	1	1.5	2	2.5
% Purity	99.54	99.56	99.5	99.58	99.6
% Yield	91.0	89.7	88.5	84.2	82.4

All of the crystalline products were above the minimum 99% purity specification. Although the least amount of solvent gave the highest yield, the crystal slurry was extremely viscous and a thick crust of crystalline material formed on the walls of the reactor. In the laboratory the crust can simply be broken up with a glass rod but in large-scale reactor vessels this is impossible to do. There are commercially available crystallizes that are designed specifically to break up such crusts. This type of equipment would probably be utilized in the planned production facility. However, since only stirred reactors were available for scale-up operations, more solvent was used to create a mobile slurry that prevented the formation of crusts. One litre of methanol per kilogram of TCSE was chosen as the optimum amount of solvent that gave the highest yield without crust formation.

1.4.3.4 Recycle of crystallization filtrate

By reusing the filtrate and crystal cake wash-solvent for following crystallizations, yields could be increased, although impurities built up in the solvent and the purity of the product was compromised. The recycle of the combined filtrate and wash solvent from one crystallization was tested by crystallizing successive batches from it. The same crystallization procedure as described in paragraph 1.4.3.3 was used. Small losses of solvent were made up with fresh methanol.

The results of the filtrate recycle were tabulated.

Recycle number	0	1	2	3	4
Mass TCSE in (g)	200.0	200.0	200.0	200.0	200.0
% Purity	93.02	93.02	93.02	93.02	93.02
MeOH Clean (ml)	200	3	3.1	2.8	2.9
MeOH recycled (ml)	0	197	196.9	197.2	197.1
Mass TCSE out (g)	168.47	186.21	181.2	190.4	181.1
% Purity	99.54	99.09	99.7	98.68	82.34
% Yield	89.74	99.18	97.11	100.99*	84.75

* Carry-over of product from recycle two caused high value.

The results in the table show the trends of increasing yield and decreasing purity with the increasing number of solvent recycles. By the third cycle, the purity of the crystallized TCSE was below the required 99%. By the fourth cycle, both the purity and the yield were unacceptably low.

Based on these findings it was decided that 20% of the solvent would be recycled to the next crystallization, allowing for a more constant batch purity. The total volume of methanol used to rinse the filter cake was to be utilized and the balance of the 20% was to be made up with filtrate. The remaining solvent was to be recovered by distillation. The distillation bottoms would be disposed of as waste or regained by crystallization at another facility with spare equipment. It was decided that due to time constraints, this option could only be tested once the production plant was operational.

1.4.4 Conclusion

One liter of methanol per kilogram of TCSE was the optimum amount of solvent for the crystallization of TCSE in a stirred reactor. The crystallization solution would be cooled down to 5°C before filtration and 20% of the filtrate would be recycled to the next batch. The crystallization equipment of choice for the plant would have to provide a means of breaking up crusts and agglomerated crystals.

1.5 Materials of construction for production equipment

1.5.1 Introduction

It is essential to specify the correct materials of construction for production equipment in order to eliminate corrosion or any catalytic effects on the materials' surface. The various processing steps required for the production of TSCE were identified and the materials of construction of the equipment for each step were determined. As a standard, PTFE (Teflon) is specified as gasket material for all joints and reactor seals in our production equipment. PTFE is extremely inert and therefor did not require compatibility testing.

1.5.2 Materials for the oxidation reactor.

The catalytic decomposition of peroxides by various metals has already been discussed. However, Titanium, Tantalum and 316 and 304 stainless steel were tested for use as the materials of construction for the oxidation reactors, all were found to vigorously decompose peroxy maleic acid. Glass was the only material commonly used in the manufacture of reactors that was found to be suitable for use with peroxymaleic acid at the reaction conditions. Glass-lined steel was specified for the oxidation reactors and associated equipment.

1.5.3 Materials for the maleic acid recovery.

By consulting with the maleic anhydride plant engineers it was determined that fibre-reinforced plastic, 316 or 304 stainless steel were suitable for handling aqueous maleic acid solutions. The catalytic decomposition of peroxides by stainless steel was an added benefit. Simply by using stainless steel equipment, residual peroxides in the maleic acid solution were destroyed. 316 or 304 Stainless steel were specified for the maleic acid related equipment such as piping and pumps. Stainless steel or fibre-reinforced plastic, as a cheaper option, was specified for the storage tanks.

1.5.4 Materials for crystallization of TCSE.

Once the water extraction of maleic acid was complete, the reaction solvent, dichloromethane (DCM), was removed by distillation in the oxidation reactor. In the laboratory, it was found that a temperature of 55°C and a vacuum of minus 50 kPa were required to remove all traces of DCM. The remaining TCSE melt would then be transferred to the crystallization vessel. The methanol, used as the crystallization solvent, was to be added to the oxidation reactor and transferred via the same line to the crystalliser. This was to be done in order to flush out the oxidation reactor, transfer pump and piping before the material solidified and caused blockages. In effect, TCSE would come into contact with the crystalliser and associated piping as a melt at 55°C.

Since the TCSE was neutral and no corrosion was expected, stainless steel was tested, as it was the cheapest material used in the manufacture of commercial crystalliser equipment. A typical batch of TCSE was melted in glass flasks and weighed turnings of 316 and 304 stainless steel were added. The molten TCSE was maintained at 75°C for five days as an accelerated compatibility test. After five days the samples were visually inspected for discoloration. The metal turnings were washed in acetone and the dry weights were compared with their starting masses for loss by corrosion. The impurity profiles and quantified purity of the TCSE samples were compared with the original material. The colour, impurity profile and purity of the TCSE samples were not affected. No corrosion of either of the stainless steel samples was measured.

314 or 304 stainless steel was specified as the material of construction for the crystalliser and associated equipment.

2 Conclusion.

The optimization of the peroxymaleic acid oxidation of DCPCAP to TCSE was considered complete. The expected production costs were well within financial margins allowed, so the go-ahead for a scale-up to a 250-liter reactor was given. The scale-up of the entire process is described in chapter 6 of this document.

3 Experimental

3.1 Procedure 1: Optimization of reaction temperature.

A large sample of DCPCAP was pre-treated to remove metal contamination (See experimental procedure 1, chapter 3) and stored as a solution in DCM for later use. For each reaction, maleic anhydride was added to a sample of this solution according to the table of reagents. The reaction mixture was placed in a glass, three-necked flask equipped with a magnetic stirrer bar, a distillation condenser, a thermometer and a dropping funnel. The reaction flask was heated in a water bath until DCM began distilling. The distillations were continued until the required boiling points were reached, then the condensers were changed to reflux. While stirring, hydrogen peroxide (22.7g; 60.0% P; 0.4 moles; 2 equivalents) was slowly added via the dropping funnel, over 20 minutes. Once the peroxide had been added, samples were periodically withdrawn and analyzed by gas chromatography for the formation of Triclosan ester with time. The starting time of the reaction was taken at the commencement of peroxide addition.

Table of reagents.

Chemical	Mole equiv.	Moles	% Purity	Mass (g)
DCPCAP	1	0.2	99.5	63.4
Maleic anhydride	4.6	0.92	98.4	91.7
H_2O_2	2	0.4	60.0	22.7
DCM	See table for DCM quantity.			

Table of DCM quantities:

Boiling pt. of mixture (°C)	g DCM / g DCPCAP
58	0.5
55	0.64
52.5	0.8
51	1.0
50	1.2
49	1.407
45	1.72
41	2.015

Chapter 5

Transesterification of TCSE to Triclosan

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1. Introduction

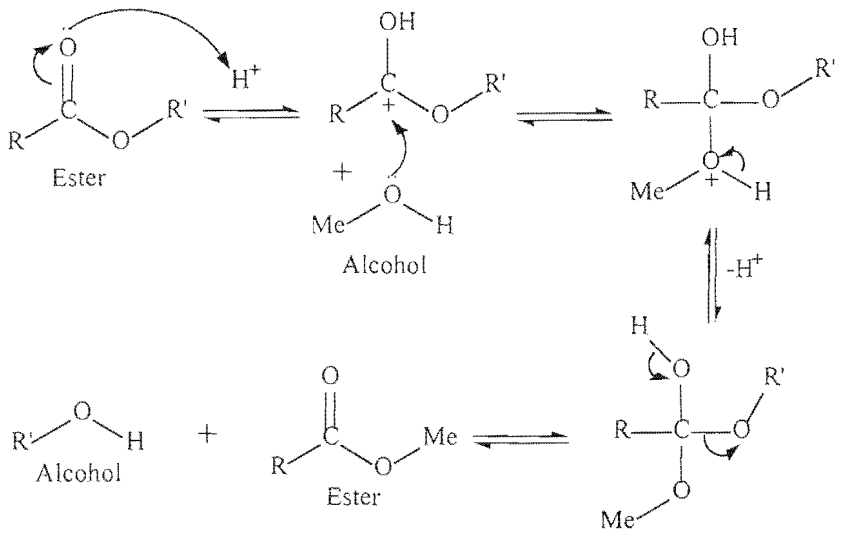
This chapter describes the third and last reaction step of this synthesis of Triclosan. This reaction is the alcoholysis of a carboxylic ester, otherwise known as a transesterification reaction. Triclosan ester (TCSE) synthesised in the previous reaction step was transesterified with methanol to form Triclosan (2,4,4'-trichloro-2'-hydroxydiphenyl ether) and methyl acetate as by-product. For ease of use, Triclosan was given the abbreviation, TCS. Methanol was chosen as the reagent for this reaction because the mixture of the excess methanol and the by-product, methyl acetate could be sold as a solvent blend. This was a cheaper option than installing a distillation column required to separate and recover methanol.

1.1. Mechanism of transesterification reaction

The transesterification reaction occurs by mechanisms identical to those of ester hydrolysis except that it is an alcoholysis. The transesterification reaction can be acid or base catalysed[1, 2], for this synthesis acid catalysis was chosen. The reactions of weak nucleophiles, like methanol, with the relatively unreactive carbonyl carbon are slow. There is much evidence to show that acids catalyse this reaction by protonation of the carbonyl carbon making it more positive and therefor more susceptible to attack by the weak nucleophile[3, 4(review)].

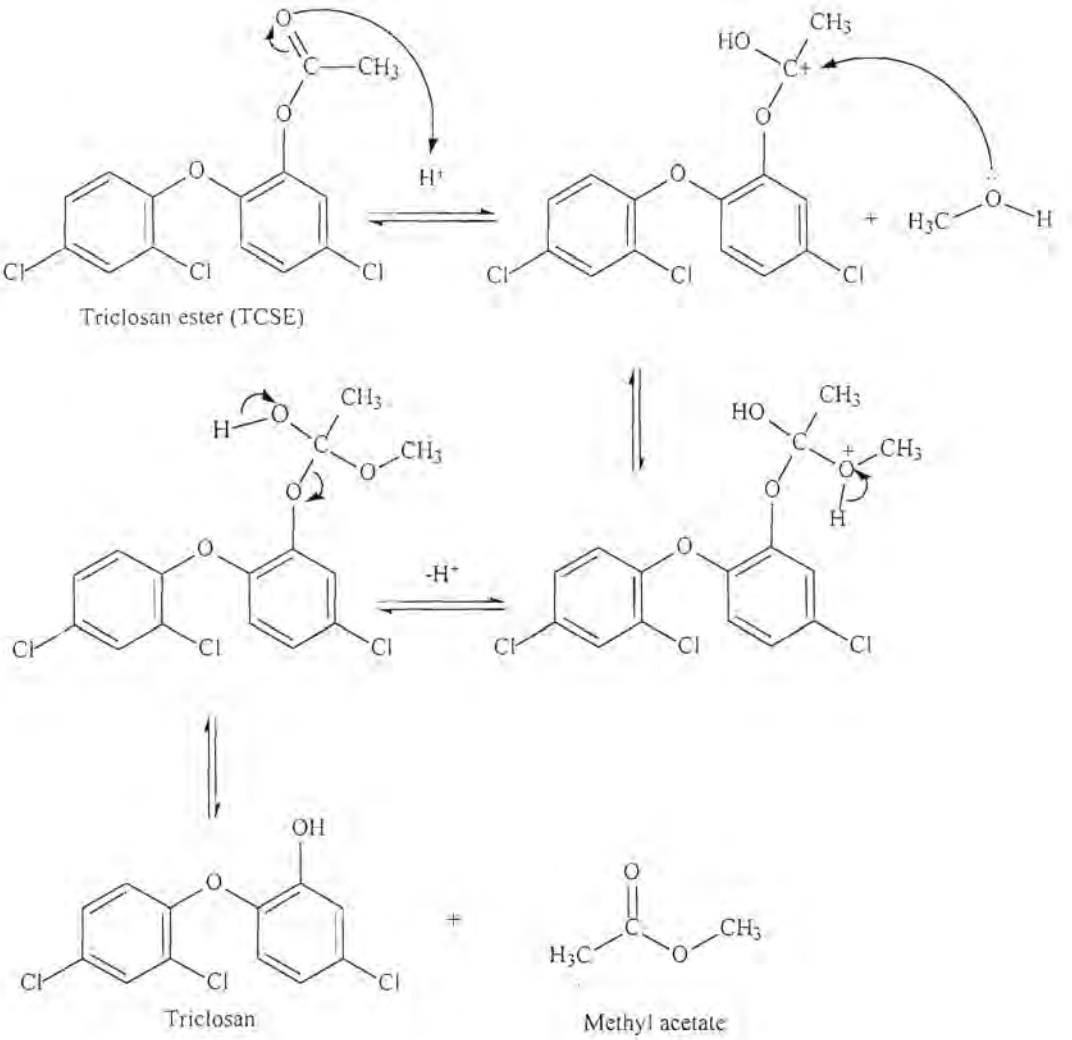
Transesterification is an equilibrium reaction, the equilibrium was shifted to achieve a complete conversion by using a large excess of methanol. Analysis of the reaction products from the transesterification of TCSE showed that only the aryl alcohol (Triclosan) and the ester of the alcohol (methyl acetate) were formed. The general mechanism of this transesterification can be represented as shown in [diagram 1].

Diagram 1: General mechanism for transesterification reaction.



The mechanism for the transesterification of Triclosan ester (TCSE) with methanol can be represented as shown in [diagram 2].

Diagram 2: Mechanism for the transesterification of TCSE to Triclosan.



1.2. Choice of acid catalyst

Many strong acids have been used as catalysts for esterification and transesterification reactions [5 and references]. Hydrochloric, sulphuric, alkyl, aryl sulphonic acids and acidic ion-exchange resins [6] are most commonly used. It was found that hydrochloric, sulphuric and methane sulphonic acids all catalysed the reaction equally well. Sulphuric and methane sulphonic acids were excluded because they caused some discoloration of the product during solvent removal by distillation. The complete removal of these acids from the product was also complicated: The product was

dissolved in a non-polar solvent and the acid extracted with water. Two water extractions were required to remove all traces of the acid and this lead to increased volumes of acidic wastewater.

Hydrochloric acid was chosen as the catalyst because it did not cause discoloration of the product. The acid was also easily removed from the product by co-distillation with the methanol, methyl acetate solvent mixture and later neutralized.

1.3. Optimised transesterification reaction

My colleges, Vladimir Cukan, Linda van Schalkwyk and Magrieta Snyman optimised the reaction parameters, therefore optimisation will not be discussed here.

One large-scale reaction was conducted in order to obtain a large, single batch of crude Triclosan, to be used for the investigation of methods of purification. (See experimental procedure 1, pp. 4-21).

1.4. Purification of Triclosan (TCS)

Triclosan was obtained after evaporating the solvent from a completed reaction as a pale yellow oil, of purity of 99.1 to 99.4%. In order to meet product purity specifications, a purification step had to be included. The purity specifications for Triclosan were determined by taking the lowest values from the United States Federal Drug Administration (FDA) registration and Ciba-Geigy product specifications.

The product specifications were set as follows:

Measurement	Specification
1. Appearance	Fine powder
2. Colour	White
3. Odour	Trace aromatic
4. Identity (I.R. spectroscopy)	Confirm
5. Purity	99.0 – 100 % (m/m)
6. Hazen value (0.05 M solution in 0.1N NaOH)	Max. 150 alpha units.
7. Solubility (0.05 M soln. In 0.1 N NaOH)	Trace turbidity.
8. 2,4-dichlorophenol	Max 10 ppm.
9. p-Chlorophenol	Max 50 ppm.
10. 4,4'-Dichloro-2-hydroxydiphenyl ether	Max. 0.1% (m/m)
11. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (GC-MS)	Max. 1 ppb.
12. 2,3,7,8-Tetrachlorodibenzofuran (GC-MS)	Max. 1 ppb.
13. 2,8-Dichlorodibenzo-p-dioxin	Max. 0.5 ppm.
14. 2,3,7-Trichlorodibenzo-p-dioxin	Max. 0.25 ppm.
15. 2,8-Dichlorodibenzofuran	Max. 0.25 ppm.
16. 2,4,8-Trichlorodibenzofuran	Max. 0.5 ppm.
17. Melting point	56 – 58° C
18. Residue on ashing.	Max. 0.1%
19. Mercury (ICP).	Max. 1 ppm
20. Arsenic (ICP).	Max 2 ppm.
21. Antimony (ICP).	Max. 10 ppm.
22. Lead (ICP).	Max. 10 ppm.
23. Cadmium (ICP).	Max. 5 ppm.
24. Nickel (ICP).	Max. 10 ppm.
25. Copper (ICP).	Max. 10 ppm.
26. Chrome (ICP).	Max. 2 ppm.
27. Sum of heavy metals.	Max 20 ppm.

The first specification given in the table is that a fine powder is required. The simplest method of getting the molten product into powder form was by crystallisation. Other methods such as flaking and grinding are, through experience, prone to cause contamination and thus were excluded from consideration. In order to meet the purity specifications shown in the table, various methods of purification were tested.

1.4.1. Purification by crystallization

Hexane and heptane were found to be the best solvents for the crystallization of TCS. The crude molten TCS obtained after solvent removal was mixed with hexane. While stirring, the solution was allowed to cool to room temperature, then cooled in a cold water bath to 5°C. After maintaining the temperature and agitation for ten minutes, the crystal slurry was then vacuum filtered using a chilled Buchner filter. The filter cake was washed through with a 1/3 volume of cold hexane (2°C).
Used in a ratio of 2.5: 1 (ml hexane to grams of TCSE), a purity of 99.7% and a yield of 96.5% were achieved. A full analysis of the purified TCS showed that all specifications except colour had been met. The crystalline material had a pale yellow colour when observed in direct sunlight. Column chromatography and GC-MS failed to isolate or detect the colour causing impurity/s.

Various purification methods were tested for removal of the colour causing impurity/s. The following methods were followed by crystallization in order to obtain the TCS in the required fine powder form.

1.4.2. Purification with activated carbon

Prior to crystallization, the hexane solution of TCS was treated with activated carbon. The carbon was stirred in the solution for 30 minutes, then removed by filtration. The TCS was crystallised as described in paragraph 1.4.1. Activated carbon did not remove the coloured impurities since no change in the colour of the crystalline material was observed.

1.4.3. Purification by salt formation.

An attempt was made to purify TCS by formation of the sodium TCS salt. TCS was dissolved in toluene at room temperature and added to an aqueous solution of one molar equivalent of sodium hydroxide. The two phases were vigorously stirred for 30 minutes. The stirrer was then stopped and the phases were allowed to separate. The aqueous phase was drained and extracted with a portion of clean toluene. The combined organic phases were extracted with a portion of water and the water extract was added to the aqueous phase. The combined aqueous phases, containing the sodium salt of TCS were neutralised with HCl and twice extracted with toluene. The toluene was evaporated and the molten TCS remaining was quantified by GC. The yield of recovered Triclosan was 88.3%. The crystallization required to obtain the material in a crystalline form would have lead to further losses of material. This purification method was not considered to be financially viable due to increased effluent volumes and a low yield.

1.4.4. Purification by distillation

Crude molten TCS obtained after solvent removal was distilled in a high vacuum distillation apparatus in an attempt to remove coloured contaminants. A 25 cm long packed column with a 2 cm internal diameter was used to affect the separation. The optimized distillation conditions were a vacuum of 0.010 to 0.015 mbar and a bottom temperature of 175 to 180°C.

Under these conditions a small, low boiling fraction was initially removed. This fraction was dark yellow in colour and represented ~3% of the total mass. Analysis of this material showed it to contain 98% Triclosan. The main fraction of the material collected was pale yellow in colour and was typically 99.5% pure. The residue was dark brown and did not exceed 1.5% of the total mass. The yield of distilled Triclosan was 95.9 to 96.4%.

The distilled material was crystallized as before from hexane and dried in flow of air. The crystalline material passed all of the purity specifications including colour.

The total yield, for the combined distillation and crystallisation, was 91.9 to 92.2%. This two step purification was the only method of achieving Triclosan that met the product specifications. The yield of purified Triclosan was high enough to ensure an economically viable process.

2. Conclusion

The transesterification of TCSE with methanol, catalysed by hydrochloric acid, was considered to be optimized. The material was best purified by high vacuum distillation followed by crystallization from hexane. The Triclosan produced using the described methods complied with all product specifications and was an economically viable process. It was decided that this process could be a commercial success and should be scaled-up in a 250 litre reactor.

3. Experimental

3.1. Procedure 1: Transesterification of TCSE

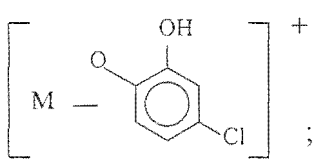
1000g of crystalline TCSE (99.68% pure, 3.007 moles) was dissolved in 1200 ml of methanol and placed in a jacketed glass reactor vessel equipped with an overhead reflux condenser and an overhead stirrer. 12 g of 32% hydrochloric acid (0.105 moles) was added and the mixture was heated to boiling by circulating heated oil through the reactor jacket. Samples were periodically withdrawn and analysed by gas chromatography to monitor the progress of the reaction. When the reaction was complete (3.87 hours), the reflux condenser was changed to distil and the solvent was removed. The product was 867.947g of pale yellow oil of 99.38 % purity giving a yield of 99.07%.

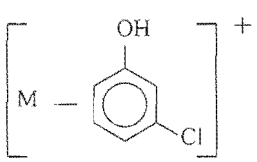
3.2. Analysis of recrystallized material

GC-MS (E.I): (See appendix A-1, pp. 5-14, for spectrum)

Mass, [ion fragment]:

288 $[M]^+$; 252 $[M-H,-Cl]^+$; 218 $[M-2Cl]^+$;

146 

; 162 

Gas Chromatogram: (See appendix B-1, pp. 5-16, for chromatogram)

One peak. Rt. = 5.617 minutes.

Melting point:

58.1°C (Ciba-Geigy official registration of Triclosan: 55 – 60°C)

IR: (See appendix C-1, pp. 5-17, for FTIR spectrum)

ν (cm^{-1}), KBr

3310 cm^{-1} (O-H stretch – phenol)

1220 cm^{-1} (CO stretch - diaryl ether)

H-NMR: (300MHz) in CDCl3: (see appendix D-1, pp 5-18, for spectrum)

δ 7.457 (1H, d, J= 2.4 Hz, Ar-H)

δ 7.198 (1H, dd, J= 8.7 Hz, J= 2.7 Hz, Ar-H)

δ 7.043 (1H, d, J= 2.4 Hz, Ar-H)

δ 6.917 (1H, d, J= 8.7 Hz, Ar-H)

δ 6.787 (1H, dd, J= 8.4 Hz, J=2.4 Hz, Ar-H)

δ 6.635 (1H, d, J= 8.7 Hz, Ar-H)

δ 5.707 (1H, s, -O-H)

3.2.1. Appendix A: GC-Mass spectroscopy

Instrument: Hewlett-Packard 6890 series GC-MS

GC parameters:

Column:

Capillary column:	(Silica) HP-1
Length:	30m
I.D:	0.2mm
Film thickness:	0.2µm
Outlet pressure:	Vacuum
Carrier gas:	Helium

Temperature program:

Initial temp:	50°C
Initial time:	1.00min
Ramp:	10°C/min
Final temp:	300°C
Final time:	14min.
Total flow:	32 ml/min

Injection port:

Temperature:	250°C
Pressure:	50kPa
Mode:	Split
Split ratio:	30:1
Split flow:	29 ml/min

Mass spectrograph parameters:

Ionisation source:

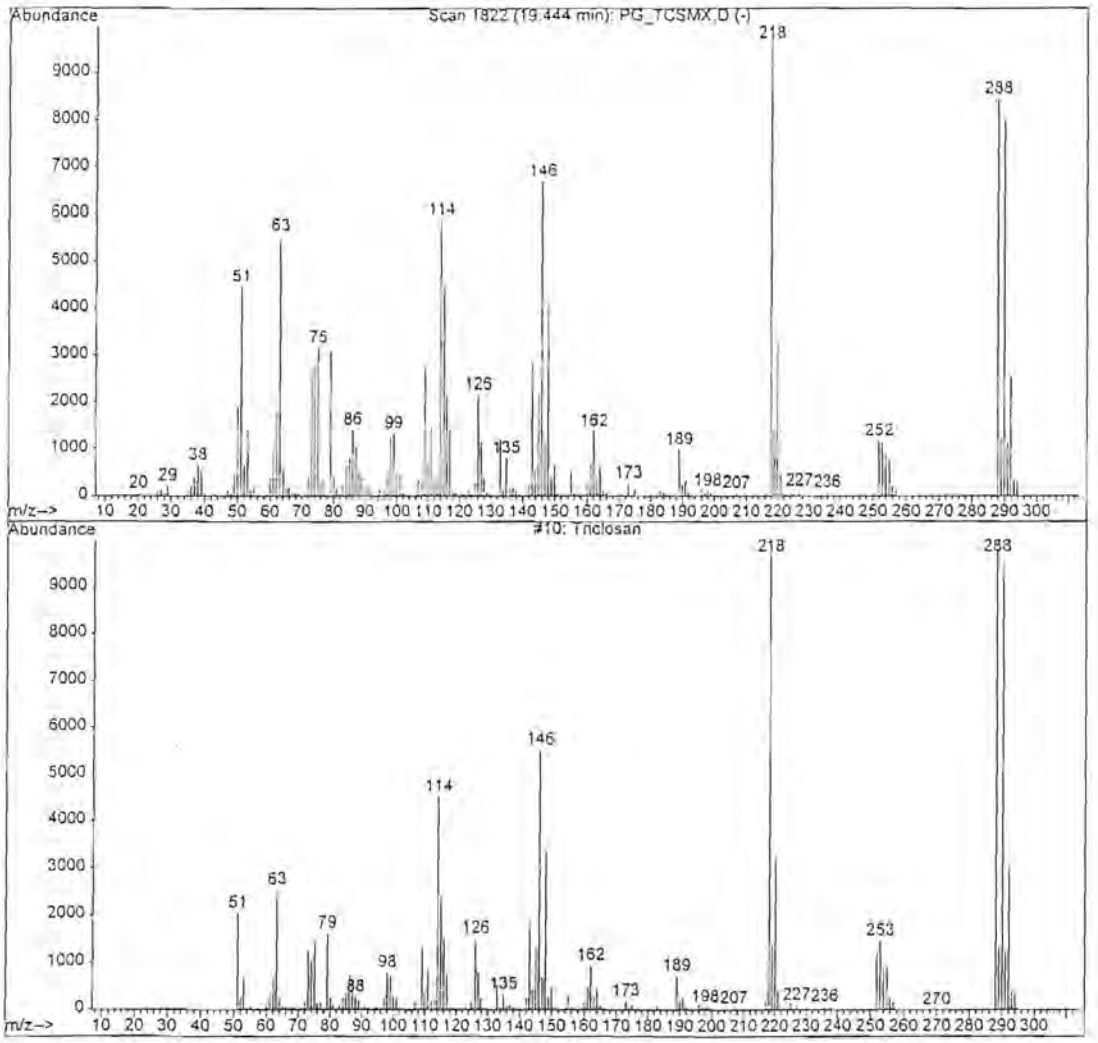
Mode:	Electron impact
Electron energy:	70 eV

Detector:

Type:	Quadropole positive ion mass selective detector with horn electron photo-multiplier.
System vacuum:	0.0015 kPa

A-1: Mass spectrum of Triclosan (2,4,4'-trichloro-2'-hydroxydiphenyl ether)

```
Library Searched : C:\DATABASE\DG.L
Quality          : 99
ID               : Triclosan
```



3.2.2. Appendix B: Gas chromatography

Instrument:	Hewlett-Packard 6890 series GC Hewlett-Packard 3396 A integrator
Column:	
Capillary column:	J&W Scientific DB-1
Length:	30m
ID:	0.53mm
Film thickness:	3µm
Carrier gas:	Helium

Temperature program:

Initial temp:	200°C
Initial time:	1.00min.
Ramp:	15°C/min
Final temp:	270°C
Hold time:	12min

Injection port:

Mode:	Split
Split ratio:	35:1
Splitter flow:	32 ml/min
Septum purge:	2.5 ml/min
Temperature:	270°C
Head pressure:	55kPa

Detector:

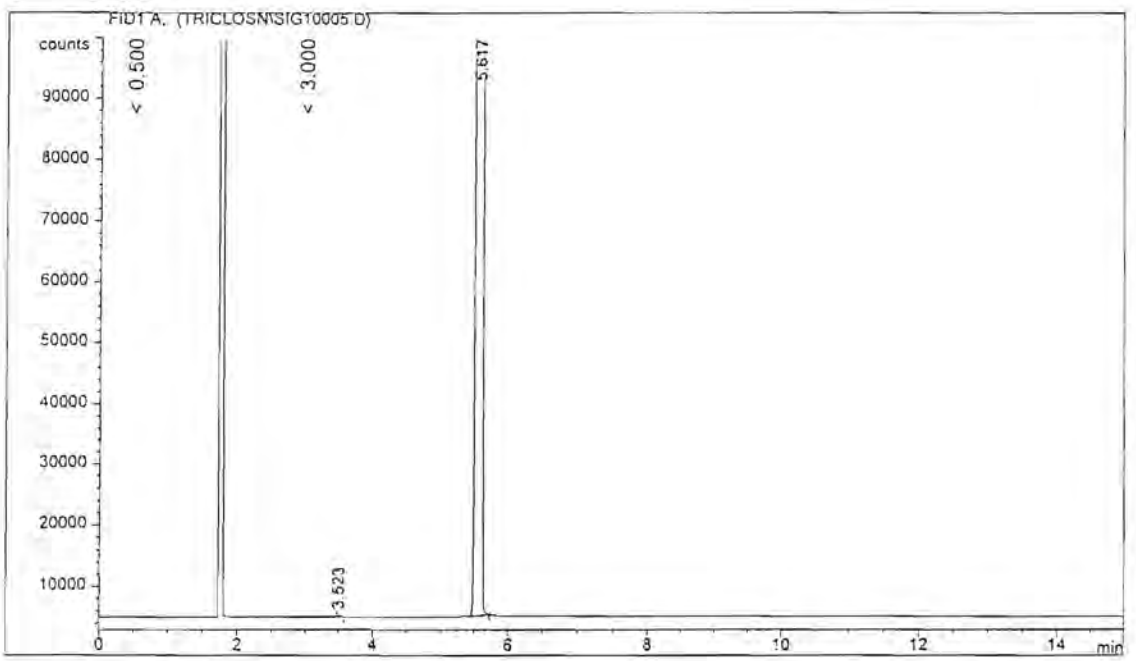
Type:	FID
Temperature:	280°C

B-1: Gas chromatogram of Triclosan

Data File C:\HPCHEM\3\DATA\TRICLOSN\SIG10005.D Sample Name: TCS

```
==========================================================================
Injection Date  : 11/16/00 11:52:44 AM
Sample Name     : TCS                                    Vial :   1
Acq. Operator   : Les
                                                  Inj Volume : 1 µl
Acq. Method     : C:\HPCHEM\3\METHODS\TRICLOSN.M
Last changed    : 11/16/00 11:14:01 AM by Les
```

Triclosan

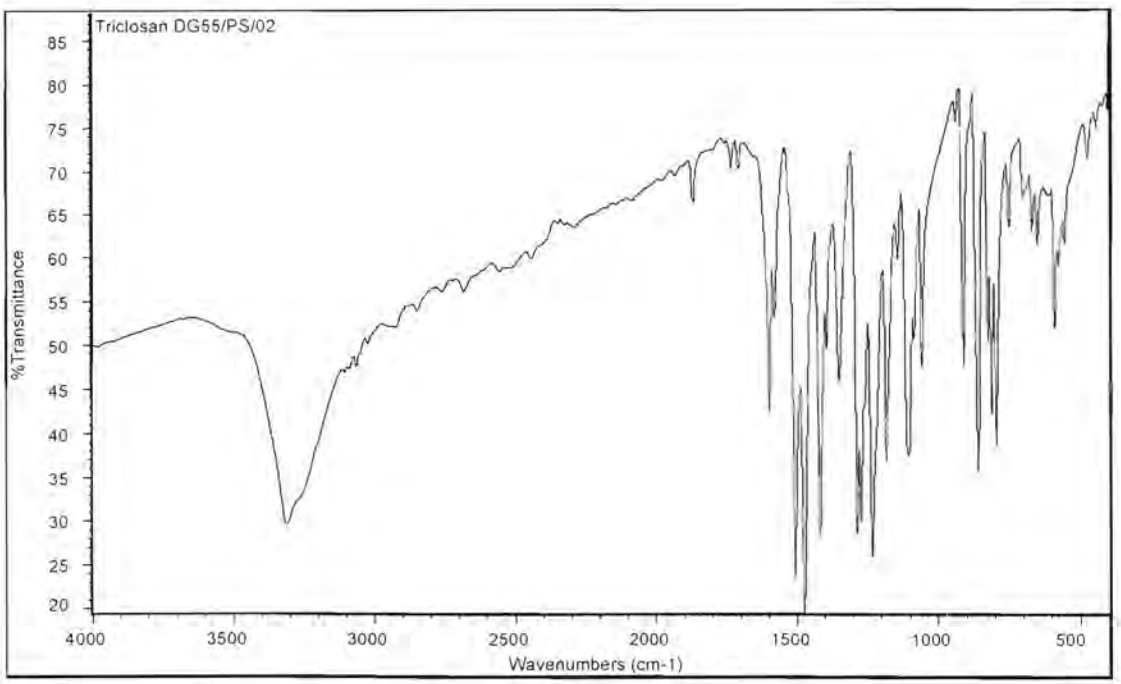



```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount         :      1.00000  [ng/5ul]    (not used in calc.)

Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]      [min]  counts*s    [counts]      %
----|-------|----|-------|----------|----------|--------|
   1   3.523 BP    0.0293  675.14069  337.78436  0.01895
   2   5.617 PB    0.0531 3.56298e6  8.46351e5  99.98105
```

3.2.3. Appendix C: Infra red spectroscopy.

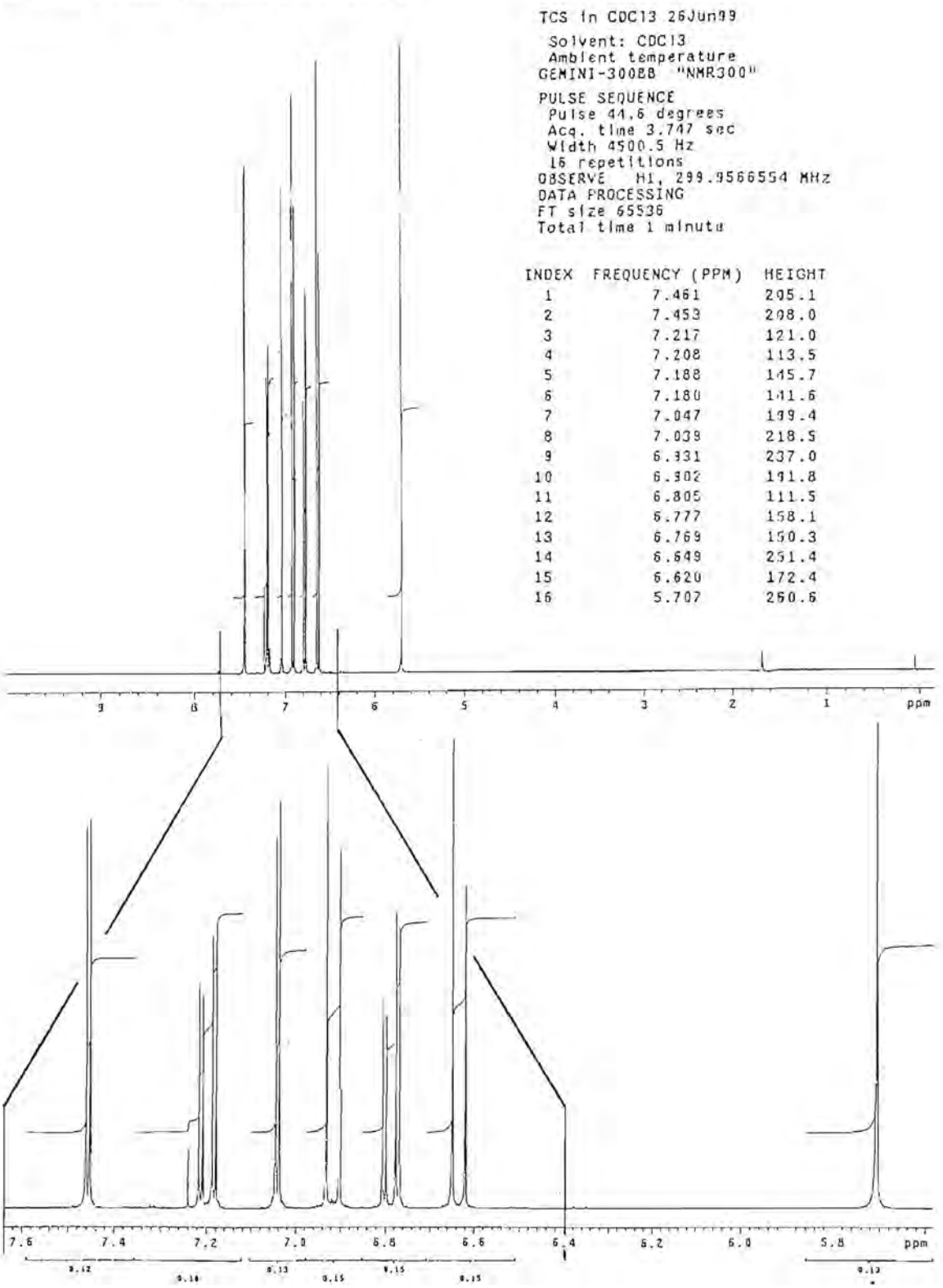
Instrument: Nicolet Avatar 360 FT-IR

C-1: FTIR spectrum of Triclosan (in KBr disk.)



3.2.4. Appendix D: Nuclear magnetic resonance

D-1: H-NMR spectrum of Triclosan.



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Chapter 6

Process scale-up

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1 Introduction

The purpose of this scale-up was to demonstrate the practicality of this synthesis on a large scale, to collect large samples of material for marketing efforts and to accumulate data that would assist in the design of a full-scale production facility. For the purpose of this dissertation, the equipment design and handling procedures used will only be briefly described in order for the reader to understand how the scaled-up reactions were conducted.

The equipment required for the scale-up of this synthesis was identified during the laboratory optimization of the three reaction steps, described in chapters two, three and four of this dissertation. For this scale-up, a 250-litre reactor and associated equipment was set up as required in an existing multipurpose pilot facility.

2 Step one: Scale-up of DCPCAP synthesis.

2.1 Unit operation 1: DCPCAP synthesis

2.1.1 Equipment description

The Ullmann Ether Synthesis of DCPCAP was carried out in a 250 litre, glass-lined reactor equipped with an agitator and a glass over-head reflux condenser fitted with an azeotrope trap. All associated pumps, valves and piping were manufactured from glass, Teflon or glass-lined steel. Liquid reagents were added by pumping the required amount into the reactor from drums. A platform electronic balance was used to measure the quantity pumped from the drums. The reagent quantities used for the reactions are shown in the following table:

Table of reagents

Chemical	Mass (kg)	Purity (%)
2,5-dichloroacetophenone	50.0	97.3
2,4-dichlorophenol	46.6	99
Sodium carbonate	18.2	91.9
Copper chloride ($CuCl_2.2H_2O$)	1.8	97
Toluene (reaction)	24.3	'100'
Toluene (reaction work-up)	40	'100'
Water (per extraction)	70	'100'
HCl	8.4	32
Fluidar*	61.6	'100'
Fluidar wash	20.5	'100'

*Fluidar – solvent blend (approximately 30% aromatics) supplied by Engen.

'100' – assumed to be 100% pure.

2.1.2 Operating procedure

2,5-Dichloroacetophenone and a solution of 2,4-dichlorophenol in toluene were pumped into the reactor and the agitator was switched on. The solid materials, sodium carbonate and copper(II)chloride were loaded manually through a manhole on the top of the reactor. The manhole was sealed and the reactor was heated to a steady toluene reflux by introducing steam into the reactor jacket. Water was constantly removed from the azeotrope trap in order to keep the reaction anhydrous. To monitor the progress of the reaction, samples were periodically withdrawn and analyzed by GC for the formation of DCPCAP and the disappearance of 2,5-dichloroacetophenone. The reaction was considered complete when 3% (GC area %) of the acetophenone remained.

2.2 Unit operation 2: Reaction work-up

Once the reaction was complete, the reactor contents were cooled to 80°C by circulating cooling water through the reactor jacket. Toluene, water and hydrochloric acid were added via air actuated pumps while the temperature was controlled at 80°C. After 30 minutes the agitator was switched off to allow the organic and aqueous

phases to separate. The heavier organic phase was transferred to a stainless steel tank equipped with an agitator and a sight-glass. The sight glass was used to observe the phase boundary when separating the two phases. The organic phase was drained into a holding tank and the aqueous phase was pumped to a waste holding tank. The organic phase was returned to the extraction vessel where two further water extractions were done to remove traces of the copper catalyst and hydrochloric acid. The organic phase was then pumped to a holding tank serving a vacuum distillation unit.

2.3 Unit operation 3: Distillation

The DCPCAP / toluene organic phase was transferred into a high vacuum distillation unit. Toluene was recovered by distillation at 130°C and atmospheric pressure. A low boiling fraction was removed by distillation at 4 millibar vacuum and a bottom temperature of 170°C. When the removal of the light fraction was complete, the bottoms of the distillation pot, containing the product, was drained into a holding vessel. The crystallization solvent, Fluidar, was pumped into the distillation pot then drained into the product holding vessel. This was done to recover DCPCAP remaining in the distillation unit and to rinse the product from the transfer lines. While still warm (60 to 70°C) the solution of DCPCAP in Fluidar was pumped into a preheated reactor that served as the crystallizer.

2.4 Unit operation 4: Crystallization and filtration

The agitator of the crystalliser was set to low speed and switched on. The contents of the reactor were gradually cooled, over a period of two hours, to 5°C by circulating chilled water through the crystallizer's jacket. The temperature was maintained at 5°C for 30 minutes to ensure complete crystallization. The crystallized DCPCAP was then filtered using a vertical, peeler centrifuge. The crystal cake was spin-dried then rinsed with a portion of cold Fluidar (2°C) and spin-dried again. The crystal cake was unloaded from the centrifuge using the peeler and stored in plastic bags.

2.5 *Results and discussions*

2.5.1 Results of DCPCAP synthesis scale-up

The results of the scaled-up DCPCAP reactions are tabulated.

Table of results

Batch no.	Reaction time (h)	Reaction yield (%)	Distillation yield (%)	Crystallization yield (%)	Overall yield (%)
1	48	63.9	88.6	67.4	38.16
2	40	73.3	82.7	95.5	57.89
3	40	72.2	94.5	68.4	46.67
4	34	72.5	92.6	67.2	45.11
5	29	75.2	97.6	66.6	48.88
6	28	72.7	92.0	141.4	95.57
7	24	61.1	97.5	89.8	53.50
8	27	77.4	93.6	81.1	58.75
9	30	73.7	93.01	107.5	73.69
10	23	62.2	95.5	87.6	52.04
11	27	72.3	92.8	79.7	53.47
Scale-up average	31.5	70.6	93.0	86.6	56.80
Laboratory average	30	70	97	90	62.3

2.5.2 Discussion of results

Reaction time:

Reaction batches 1, 2 and 3 took longer to complete than the rest of the batches. Improved temperature control and a faster rate of reflux for the remaining batches

shortened the reaction time to an average of 27.75 hours. This was 2.25 hours shorter than the average time for laboratory reactions and considered acceptable.

Reaction yield:

The reaction yield (DCPCAP in the reaction mixture) obtained in the 250 litre reactor was marginally better than the average of laboratory reactions.

Distillation yield:

The average performance of the distillation step was 93% compared to 99% for the average laboratory distillation. The greatest loss of DCPCAP was in the low boiling fraction that was removed from the product. The distillation column used had 1.5 theoretical plates compared to the laboratory distillation column with eight. It is obvious that a distillation unit with more theoretical plates will be required for the proposed production facility to prevent product losses.

Crystallization and filtration yields:

The average yield of DCPCAP in the crystallization step was lower than that of the laboratory experiments. This occurred because the ratio of solvent to DCPCAP had to be doubled in order to prevent crust formation and pipe blockages in the crystalliser. The increased volume of solvent caused product to be lost in the filtrate due to increased solubility. A custom designed crystallization unit will allow for the use of less solvent and thus increase the yield at the crystallization step. The erratic values shown in the table attest to the unsuitability of using a general-purpose reactor as a crystallizer. Batch number 6 gave a yield of 141.4%, this implied that DCPCAP must have been held up in the system and came out with this batch.

Overall yield:

The overall yield of DCPCAP, based on 2,5-dichloroacetophenone, was 56.80% compared to the laboratory average of 62.3%. An improved distillation unit and a custom designed crystallization unit would increase the overall yields to close to the

yields achieved in the laboratory. If a distillation yield of 99% and a crystallization yield of 90% could be achieved, as in the laboratory, the average yield for this scale-up would have been 62.9%.

2.6 Conclusion to DCPCAP scale-up

The Ullmann Ether Synthesis of DCPCAP was easily scaled up. The equipment used for the distillation and crystallization of the product were however not suited for this product. A crystalliser designed to prevent or break up crusts and a more effective distillation unit will be required to increase the yield of this synthesis step.

3 Step two: Scale-up of Triclosan Ester synthesis

3.1 Unit operation 1: Pre-reaction work-up and TCSE synthesis

The Baeyer-Villiger oxidation of DCPCAP to TCSE was conducted in a 250 litre, glass lined reactor equipped with a glass-lined agitator and a glass overhead condenser. All associated pumps, valves and piping were manufactured from glass, glass-lined steel or Teflon.

As already discussed in chapter 3 of this dissertation, during this reaction, oxygen is evolved due to decomposition of peroxides. A nitrogen purge was used to prevent the oxygen concentration in the reactor headspace from increasing, to form an explosive mixture with dichloromethane. An oxygen detector was installed, just after the over-head condenser unit, to measure the concentration of oxygen in the system. The nitrogen flow rate was manually adjusted to keep the oxygen concentration in the system below 10%. Based on explosive limit tests conducted by another laboratory, the maximum allowable oxygen concentration for the reaction, with a 50% safety margin, was set at 10%.

Liquid reagents were added by pumping the required amount into the reactor from drums. A platform electronic balance was used to measure the quantity of reagents loaded. Hydrogen peroxide was dosed into the reactor in 500g batches using a Teflon

air actuated diaphragm pump. The pause time between additions was based on the rate of solvent reflux (indicating extent of exotherm) and the concentration of oxygen in the system. The reagent quantities used for the reactions are shown in the following table:

Table of reagents

Chemical	Mass (kg)	Purity %
DCPCAP	53.1	96.07
Dichloromethane	153.2	100
HCl	10	32
Maleic anhydride	75	98
H_2O_2	18.4	60
Water (per extraction)	130	'100'
Methanol (crystallization)	44	'100'
Methanol (crystal wash)	14.7	'100'

'100 ' – assumed to be 100% pure.

Dichloromethane was pumped into the reactor, the agitator was switched on and DCPCAP was manually loaded into the reactor through a manhole in the reactor lid. Once the DCPCAP was dissolved, the manhole was closed and 10 kg of HCl was pumped into the reactor. The mixture was stirred for two hours, 50 kg of water was then added and stirred for a further 5 hours. The agitator was switched off, and the aqueous and organic phases were separated. This extraction was repeated with 50kg of water. The bottom, organic phase was transferred to a holding tank and the aqueous phase was extracted with 20 kg of DCM to recover entrained DCPCAP. The DCM extract was added to the rest of the organic phase and the aqueous HCl phase was pumped to a waste holding tank. The organic phase was then returned to the reactor, the agitator was switched on and maleic anhydride was manually loaded into the reactor through the manhole.

The reactor was heated and DCM was distilled from the reaction mixture until a boiling point of 50°C was achieved. The condenser system was switched to reflux, nitrogen purging and hydrogen peroxide dosing were started. The rate of solvent

reflux was controlled at a steady flow by introducing steam or cooling water into the reactor jacket. The peroxide addition took about seven hours to complete, after which reaction monitoring was started. Samples were periodically withdrawn and analyzed by gas chromatography for the formation of TCSE and the disappearance of DCPCAP. The reaction was considered to be complete when less than 1% (GC area %) of DCPCAP remained.

3.2 Unit operation 2: Water extraction of Maleic acid

Once the reaction was complete, water was pumped into the reactor to extract maleic acid and any residual peroxides. The mixture was stirred for one hour then left standing to allow the organic and aqueous phases to separate. The heavier, organic phase was transferred to a holding tank and the aqueous phase was drained into storage tank no. 1. The organic phase was returned to the reactor for the next water extraction. The second water extract was stored in storage tank no.2. This process was repeated four times with each water extract stored in a separate storage tank.

The first water extract, containing approximately 40% maleic acid was pumped into drums and stored for later recycle of the acid to maleic anhydride. The other three water extracts were recycled to subsequent reactions in a cascade manner. That is, the second extract was used for the first extraction of the next reaction, and so on.

3.3 Unit operation 3: Solvent recovery and crystallization.

After the fourth water extraction the organic phase was transferred to an agitated reactor that served as a crystallizer. This crystallizer was heated with agitation to distil the solvent, dichloromethane, from the product. The final temperature was controlled at 70°C in order to remove all traces of solvent.

The product was then cooled to 60°C, the condenser was switched to reflux and the crystallization solvent, methanol, was pumped into the crystallizer. With the agitator set on slow speed, the contents of the reactor were allowed to cool unaided to 37°C. At this temperature, 200g of TCSE seed crystals were added and the mixture was

At this temperature, 200g of TCSE seed crystals were added and the mixture was allowed to cool further to 25°C. Chilled water was then circulated through the reactor's jacket until the crystal slurry would not cool any further. With the available equipment, the minimum temperature achieved was 9°C. This temperature was maintained for one hour, then the product was filtered using a vertical, peeler centrifuge. The cake of TCSE crystals was spin-dried then rinsed with a portion of cold methanol (2°C) and spin-dried again. The filter cake was removed with the peeler and stored in plastic bags for the next reaction step.

3.4 Results and discussion

3.4.1 Results of TCSE synthesis scale-up

The results of the scale-up of the synthesis of Triclosan ester are tabulated:

Table of results

Batch no.	Reaction Time (h)	H_2O_2 Addition time (h)[1]	Crystallization Yield (%)	% TCS formed[2]	Corrected Yield[3] (%)
1	20	7.5	66.5	-	-
2	24	7.5	65.5	7.82	78.3
3	22	10	75.7	-	-
4	34	7.5	75	-	-
5	17	8	57.4	20.5	80.8
6	10.5	6.5	57.8	13.3	71.7
7	11.5	7.5	57.8	16.2	71.8
8	30	9.5	66.8	-	-
Average	20.5	7.6	65.3	14.5	73.3
Lab. average	18	6	90	0.3	90

[2]TCS was formed by non-catalyzed transesterification due to re-heating and extended times at elevated temperatures during crystallization (lab average was 0.3%).
[3]The corrected yields were calculated by adding the TCS lost in the filtrate.

3.4.2 Discussion of results

Reaction time:

The reaction time was dependent on the reaction temperature (i.e. boiling point of the reaction mixture or reaction dilution) and the rate of solvent reflux during the reaction. A high rate of solvent reflux caused the reaction mixture to become more concentrated due to greater solvent losses caused by incomplete condensation of the solvent. Batches 4 and 8 showed long reaction times due to low rates of solvent reflux and thus less solvent losses. The actual solvent losses were never quantified but by inspection of the reactor, it could be seen that a greater volume of reaction mixture remained at the end of these two batches.

Peroxide dosing time:

The hydrogen peroxide dosing time was manually controlled according to the oxygen concentration in the reactor (reaction exotherm was not a limiting factor).

Batches 3 and 8 showed excessive oxygen evolution, caused by metal catalyzed peroxide decomposition, due to incomplete metals removal.

Batch 3 was worked-up and restarted to remove metal contamination.

Batch 8 - Half a batch of maleic anhydride was added and half a batch of peroxide was dosed into the reactor in order to complete the reaction.

Crystallization and filtration yields:

As with DCPCAP, crusts of TCSE formed on the walls of the crystallizer and associated piping causing blockages. The ratio of solvent to TCSE was doubled in an effort to alleviate these problems. The increased ratio of methanol to TCSE did minimize agglomeration but increased solubility leading to greater losses of TCSE in the filtrate. Further losses of product were experienced due to the transesterification of TCSE to Triclosan. It was found that by re-heating the crystallization mixture to re-dissolve crystal agglomerations and extended periods at higher temperatures caused the formation of TCS. Triclosan that was formed was lost in the filtrate due to its high solubility in methanol.

3.5 Conclusion to TCSE scale-up

This reaction was easily scaled-up, however a crystallizer designed to break up crusts and crystal agglomerations will be required for a more effective crystallization of TCSE.

4 Step 3: Scale-up of Triclosan synthesis

4.1 Unit operation 1: Synthesis of Triclosan

The transesterification of TCSE to Triclosan was conducted in a 250 litre, glass-lined reactor equipped with an agitator and a glass overhead reflux condenser. All associated pumps, valves and piping were manufactured from glass, glass-lined steel or Teflon.

Liquid reagents were pumped into the reactor from drums positioned on a platform electronic balance. Quantities loaded were measured by mass loss of the drums.

Crystalline reagents were pre-weighed and manually loaded into the reactor through a manhole in the lid of the reactor.

The quantities of reagents used are shown in the following table

Table of reagents

Chemical	Mass (kg)	Purity (%)
TCSE	162.0	93.1
Methanol	71.5	'100'
HCl	2.9	32
Heptane	81	'100'
Heptane rinse	25	'100'

'100' – assumed to be 100% pure.

Methanol was pumped into the reactor and the agitator was switched on. Pre-weighed TCSE was manually loaded into the reactor through the manhole and the manhole was then sealed. The reactor contents were heated to 50°C by introducing low-pressure steam into the reactor jacket. The required amount of hydrochloric acid catalyst was pumped into the reactor and the reaction mixture was heated to boiling and maintained there (65°C) throughout the reaction. The reaction was monitored by the disappearance of TCSE and the formation of TCS by GC analysis. The reaction was complete when no TCSE remained unconverted.

4.2 Unit operation 2: Solvent recovery and distillation

Once the reaction was complete, the overhead condenser was switched from reflux to distil and the methyl acetate / methanol solvent blend was removed by distillation. The temperature of the reaction mixture was raised to 100°C to ensure the complete removal of all solvents. The hydrochloric acid catalyst co-distilled and was collected with the solvent blend. The molten product was then transferred to the bottom receiver of a high vacuum distillation unit.

The product was distilled at a vacuum of < 0.1 mbar and a temperature of 170°C. Small fractions of product (about 500 ml) were collected and analyzed by GC until no dichloro and monochlorophenol were detected. These first fractions, containing ~ 90% Triclosan, were combined and stored in a drum for later recovery. The remainder of the product was distilled and collected in the distillation columns' top receiver. The residue left in the distillation unit was drained into drums for disposal.

The product was drained into a holding vessel and to ensure quantitative transfer of the product, the top receiver and piping were flushed with heptane into the same vessel. In order to increase the batch size for the following crystallization step, two batches were combined in the holding vessel. The contents of the holding vessel were heated to 50°C, to dissolve any TCS crystals that had formed, and transferred to a pre-heated, agitated reactor serving as the crystallizer.

4.3 Unit operation 3: Crystallization and filtration of Triclosan

The agitator of the crystallizer was switched on and the solution of TCS in heptane was allowed to cool unaided to 39°C. 200 Grams of TCS seed crystals were then added through the manhole and the solution was cooled further by circulating chilled water through the reactor jacket. Due to refrigeration unit limitations, the lowest temperature reached was 8°C. This temperature was maintained for one hour, then the crystal slurry was filtered using a vertical basket, peeler centrifuge. The crystal cake was spun-dried for 20 minutes then rinsed with chilled heptane (2°C) and spun-dried again for 30 minutes. The centrifuge was unloaded using the peeler and the product was dried at 35°C in a drying oven.

4.4 *Results and discussion*

4.4.1 Results of TCS synthesis scale-up

The results of the Triclosan synthesis scale-up are tabulated. (Yields of batches combined for crystallization step are given)

Table of results

Batch no.	Reaction time (h)	% Yield of TCS	% Purity
1	4.25	62.5	99.8
2	4.1		
3	3.8	75.3	99.8
4	4.1		
5	4.4	73.3	99.7
6	3.7		
7	4.0	74.6	99.6
8	3.9		
Average	4.0	71.4	99.7
Lab. Av.	4.0	81.0	99.9

4.4.2 Discussion of results

Reaction

The reaction yields (TCS in reaction mixture) were quantitative. The reaction times achieved were the same as those achieved in laboratory reactions.

Distillation

Yields of the distillation alone were not available because distilled batches were combined to increase batch sizes. Recovery of the product in the light fraction was also not done due to equipment availability constraints.

Crystallization

As with the previous two synthesis steps, crusts of crystals formed on the wall and in the piping of the reactor crystallizer. The ratio of solvent to Triclosan used for crystallization was doubled to minimise crust formation. This resulted in losses of product in the filtrate due to increased solubility and lower yields. This again lead to the conclusion that a custom designed crystallizer will be required for the planned production facility.

Yield of Triclosan

The yields were about 10% lower than those achieved in the laboratory. Most of the yield losses occurred in the crystallization step where more solvent had to be used to minimise crust formation. The yield of the first combined batch of Triclosan is lower because fresh solvent was used. The other three combined batches showed increased yields because the solvent used to rinse the crystal cake in the centrifuge and a portion of the filtrate was recycled to make up half of the crystallization solvent volume. This recycle reduced the solubility of the product in the filtrate and resulted in increased yields. The average yield for the last three combined batches was 74.4%.

4.5 Conclusion

This reaction was easily scaled-up, the reaction times and yields were the same as those achieved in the laboratory. With a custom designed crystallization unit the yields of Triclosan will be similar to lab yields.

The purity of the Triclosan produced met all of the set specifications except for the impurity profile. It was discovered that due to the comparatively long residence time in the scaled-up distillation unit, an isomer of Triclosan was formed. This isomer was identified by others using NMR as 2,4',6-trichloro-2'-hydroxydiphenyl ether (Triclosan has chlorine atoms in the 2,4,4'- positions).

The impurity profile was required to be identical to that of the Triclosan already sold on the market. This was required for faster and cheaper, United States Federal Drug Administration, registration purposes. Data from previous toxicity testing can be purchased and used if the impurity profile of the new product is the same. This is a much faster, cheaper and more humane option than conducting new, animal toxicity tests required for a completely new registration.

To limit the residence time of Triclosan in the distillation unit, and thus the formation of the Triclosan isomer, a falling, thin film or wiped film continuos evaporator could be used. This equipment should be tested for inclusion in the planned production facility.

5 Conclusion

This novel synthesis of Triclosan was scaled-up without any major difficulties. The yield of Triclosan was lower than that achieved in the laboratory, however with automated temperature control for each of the three reaction steps and better-suited equipment, the yields could easily be increased to equal those achieved in the laboratory.