The Synthesis of Carbonates and Related Compounds

from Carbon Dioxide

by

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A thesis submitted in partial fulfilment of the requirements for the

degree of Doctor of Philosophy in Chemistry

University of Warwick, Department of Chemistry

August 2001

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ACKNOWLEDGEMENTS

DECLARATION

I hereby declare that all the work presented is my own unless otherwise referenced. The work was carried out in the department of chemistry at the University of Warwick between 1st October 1997 and 18th September 2000 and has not been submitted previously for another degree or at another institution.

ABSTRACT

The manufacture of carbonates and carbamates is essential due to their wide range of applications from polymers in foams, elastomers and engineering plastics to agrochemicals. Since there is a high demand for both types of compound, there is a commercial justification for use of phosgene in their synthesis. However, phosgene is highly toxic in small quantities. The development of an alternative reagent is therefore most desirable.

This thesis relates our attempts to overcome the problem of phosgene use by utilising CO_2. Chapter One highlights previous research concerning the synthesis of carbonates and their derivatives from CO_2. Chapter Two details the development of the reaction of CO_2 to form methanesulfonyl carbonates ($RO(CO)OSO_2Me$) and carbamates ($R_2N(CO)OSO_2Me$), which are precursors of carbonates and carbamates respectively. Alcohols or amines are reacted with CO_2 at atmospheric pressure in acetonitrile to generate carbonate and carbamate anions *in situ*. Reaction with methanesulfonic anhydride leads to the methanesulfonyl carbonates and carbamates which are observed spectroscopically but are not isolable. Chapter Three explains the successful conversion of methanesulfonyl carbonates and carbamates to carbonates and carbamates, as well as testing the scope of the reaction. Chapter Four demonstrates the transfer of the synthetic methodology to multifunctional compounds to generate dendritic carbamates and highlights the various approaches used to achieve this goal. Chapter Five is the experimental section.

ABBREVIATIONS

Bisphenol A	2,2-bis-(4'-hydroxyphenyl) propane
BOC	*t*-butyloxycarbonyl
BPVA	4,4 - bis (4'-hydroxyphenyl) valeric acid
Bu	butyl
CBz	Carbonyl benzyloxy
CDI	*N,N*-carbonyl diimidazole
CI	Chemical ionisation
DEADC	Diethyl azadicarboxylate
DIBAL	di-isobutylaluminium hydride
DMAC	Dimethyl acetamide
DMAP	4-dimethylamino pyridine
DMC	Dimethyl carbonate
DMF	*N,N*-Dimethyl Formamide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
EI	Electronic ionisation
Et	ethyl
GC	Gas chromatography
GC-MS	Gas chromatography-mass spectrometry
HEAP	1-bis-(2-hydroxyethyl)amino-2-propanol
Me	methyl
Ms	methanesulfonyl
MS	Mass spectrometry
NMR	Nuclear magnetic resonance
Ns	*p*-nitrobenzenesulfonyl

PAMAM	polyamidoamine
ppm	parts per million
Sc CO_2	Supercritical carbon dioxide
THF	Tetrahydrofuran
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
Ts	*p*-toluenesulfonyl
Tsoc	Trisopropylsilyloxycarbonyl

CHAPTER 1 - INTRODUCTION

1.1 Introduction

Carbonate esters and carbamate esters (trivially known as urethanes) have proven to be useful functional groups both in small molecules and in macromolecules. [1,2]
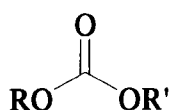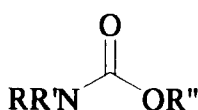
Carbonate   Carbamate

Figure 1.1: Carbonate and carbamate

Carbonates and carbamates are the esters of carbonic and carbamic acid (R = R'= R''= H) respectively (figure 1.1). Both acids decompose in the presence of a catalytic amount of water to carbon dioxide, accompanied by water in the case of carbonic acid [3] and ammonia in the case of carbamic acid. Thus, these functional groups are most commonly seen in the form of the esters mentioned above or as salts of the acids.

The monoesters of the acids are formed by the reaction of an alcohol or an amine with carbon dioxide, but both of these decompose spontaneously like the parent acids. One exception is a report of the isolation of dibenzyl carbamic acid. [4]

The diesters are normally referred to as the respective carbonate or carbamate. They are more prone to hydrolysis and saponification than esters[1b] or amides, but will undergo analogous reactions to these compounds. Due to the nature of the synthesis of carbonates and carbamates within molecules, which involves hazardous or expensive reagents, their occurrence is much less common than that of esters and amides.

1.2 Carbonate and Urethane Synthesis

As can be noted from the structure of carbonates and carbamates, they are derived from alcohols and amines respectively. Virtually all laboratory reagents used to effect the transformation to carbamate or carbonate esters are derived from toxic phosgene (figure 1.2).[1b,5] Furthermore, in the case of triphosgene, two moles of phosgene are produced in the process, so even more care is required (scheme 1.1).[6] A versatile use of 1,1'-carbonyl diimidazole (CDI) was demonstrated by Rannard and Davis.[7] By reacting primary, secondary and tertiary alcohols with CDI, they generated imidazole carboxylic esters which are chloroformate analogues. Depending which alcohol the esters were derived from, they could selectively react with diols, triols and aminodiols at specific sites without protection. The same researchers applied this methodology to the synthesis of carbonates, carbamates and amides.

The introduction of carbamates is usually *via* isocyanates (by reaction with alcohols), chloroformates or dicarbonates (by reaction with amines). Isocyanates can only form secondary carbamate esters.[2]
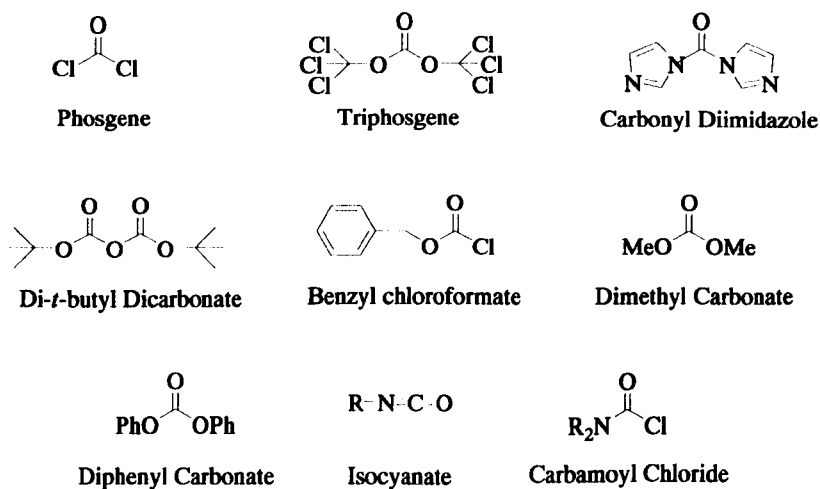
Figure 1.2: Commercial carboxylating reagents and phosgene substitutes
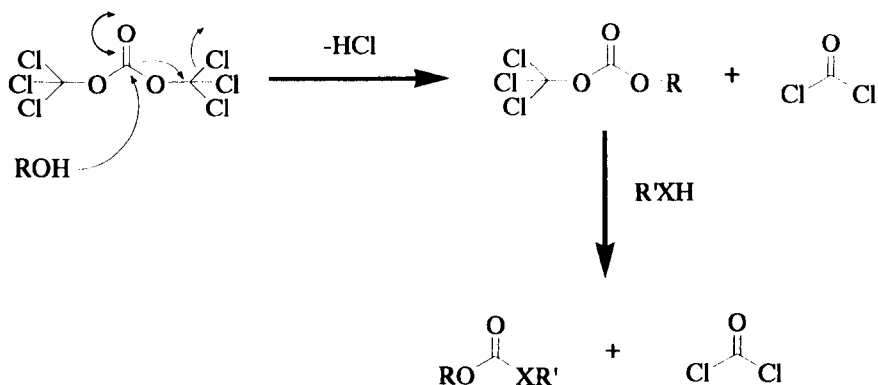
Scheme 1.1: The reaction of triphosgene

On the industrial scale, phosgene itself is used more than 80% of the time for the synthesis of carbonates, dimethyl carbonate is used for the other 20%.[8] Due to the extremely toxic nature of phosgene and isocyanates (synthesised *in situ* from phosgene), its use is hazardous to workers and populace alike. For example methyl isocyanate leaked by Union Carbide killed 8000 people in Bhopal, India [9] and phosgene use in World War I prompted the abolition of chemical weapons under the Geneva Protocol.[10] Thus the replacement of phosgene is a highly desirable goal. Alternative carbonylation technology, using carbon monoxide in place of phosgene, is applicable only to symmetrical carbonates, mainly dimethyl carbonate.[1b] However, carbon monoxide is toxic as well as flammable.

While alicyclic carbonates originate from phosgene, or, (in the case of dimethyl carbonate) carbon monoxide, cyclic carbonates can be synthesised by reaction of epoxides with carbon dioxide in the presence of a catalyst.[11] This last instance is most commonly used on an industrial scale.

The carbonate functionality is seen most commonly in high impact resistance polymers based on bisphenol A or as a diethylene glycol diallyl dicarbonate unit for lens, compact disc and toughened glass applications.[1,12] In this case, phosgene use

can be moderated by first reacting it with phenol to form diphenyl carbonate which is used in the actual polymerisation (scheme 1.2).
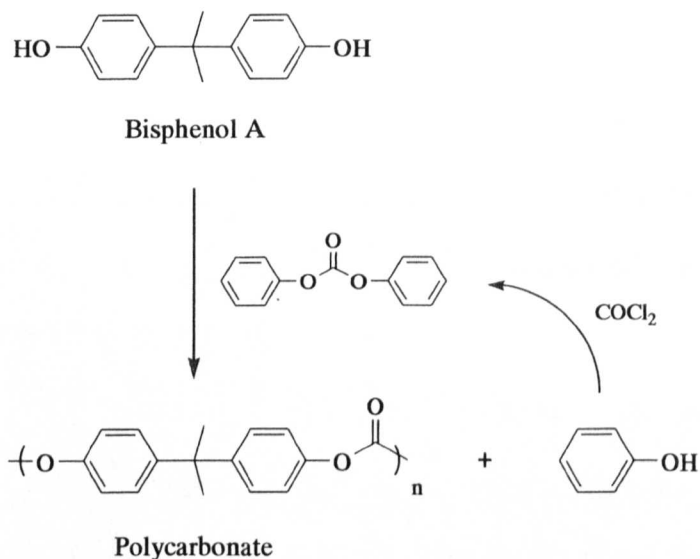
Scheme 1.2: Synthesis of polycarbonate

1.3 Applications of Carbonates and Derivatives

Carbamate esters are familiar in organic synthesis as protecting groups in peptide[13] or natural product synthesis[14], or as agrochemicals such as pesticides and herbicides.[15] The most commonly used are *t*-butyl carbamate (Boc) and benzyl carbamate (Cbz or Z) esters, introduced using di-*t*-butyl dicarbonate and benzyl chloroformate respectively (scheme 1.3).
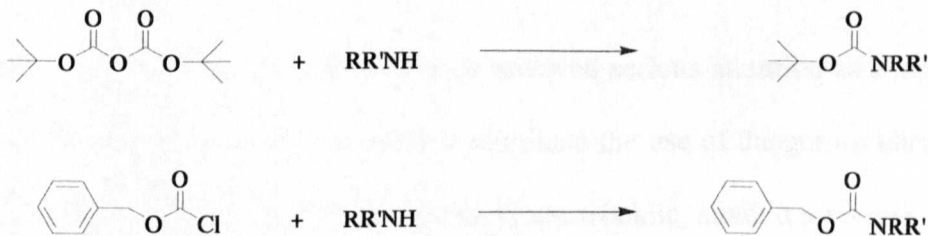
Scheme 1.3: (Top) Introduction of the Boc group. (Bottom) Introduction of the CBz group

Carbamate esters are also found in polyurethane polymers where they are useful as foams and coatings, the monomers being diols and diisocyanates such as toluene diisocyanate.[8] Trace water is used as a foaming agent due to carbon dioxide being generated on the reaction of water with isocyanates.

Organic carbonates are used less frequently than carbamates in natural product synthesis; again the main use is as a protecting group.[16] Dimethyl carbonate and higher homologues can be used as chloroformate equivalents[86] or as synthons for esters when reacted with carbanions.

Carbonates are most commonly used within polymers.[1] As mentioned above, polycarbonate (Lexan®) is synthesised *via* diphenyl carbonate. These type of polymers are used as engineering resins for CDs and DVDs [1b] and where high abrasion resistance is required, lightweight protective helmets being another example. A bio-degradable polycarbonate derived from 1,4 –pentanediol is routinely used in medicine as temporary sutures which dissolve after a given time period.[17]

Simple carbonates are frequently found as fuel additives and stable, high boiling point solvents.[1,12] Despite all the uses, the large majority of carbonates still are made from phosgene and this has prompted the search for alternative synthetic routes.

1.4 Synthesis of Carbonate Derivatives using CO_2

1.4.1 Introduction

Only in the last 20 years has carbon dioxide received serious attention as a carbonyl source, the main impetus being the need to eliminate the use of dangerous chemicals such as phosgene. Carbon dioxide is a carbonyl electrophile, albeit a poor one, and is relatively non-toxic, easy to handle and cheap.[18] Replacing a very toxic reagent such as phosgene is an important advance but utilising a greenhouse gas [19] meets two ends.

This idea is not new as the reaction between amines and carbon dioxide has been known for some time. Even in 1911 ammonium carbamate salts were made by bubbling carbon dioxide through primary amine solutions.[20] The reaction of alcohols with carbon dioxide is not as widespread because of their lower nucleophilicity. However, carbon dioxide is a thermodynamically stable end product of many processes, such as fermentation, respiration, and combustion and, as such, special techniques or reactive species need to be used to incorporate the carbonyl unit into products, typically carbonates, carbamates and their derivatives.

1.4.2 Reaction with Epoxides
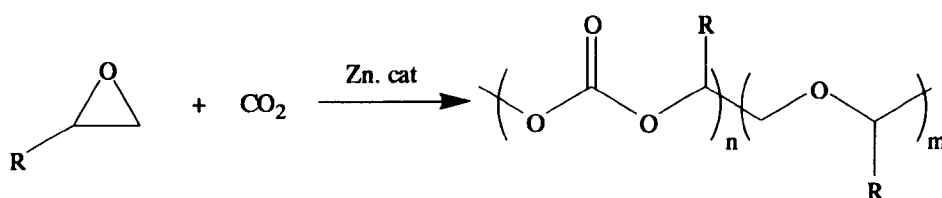
Scheme 1.4: Polymerisation of CO_2 with epoxides

As mentioned in Section 1.2, cyclic carbonates can be synthesised by reaction of epoxides with carbon dioxide in the presence of a catalyst. This reaction is used on an industrial scale. The other possible reaction of CO_2 with epoxides is formation of carbonate co-polymers, although this has only been in the research lab at high pressure (scheme 1.4).[11, 21]

1.4.3 Reaction of CO_2 via Ammonia

Ball made symmetrical alkyl carbonates[22] and polymers using harsh conditions. Urea reacts with alcohol at 150 –200°C, the most efficient reagents being Ph_3P and DIBAL, liberating two equivalents of ammonia which can be envisaged to recombine with

carbon dioxide to make urea again (scheme 1.5). Such conditions are unlikely to tolerate other functional groups.
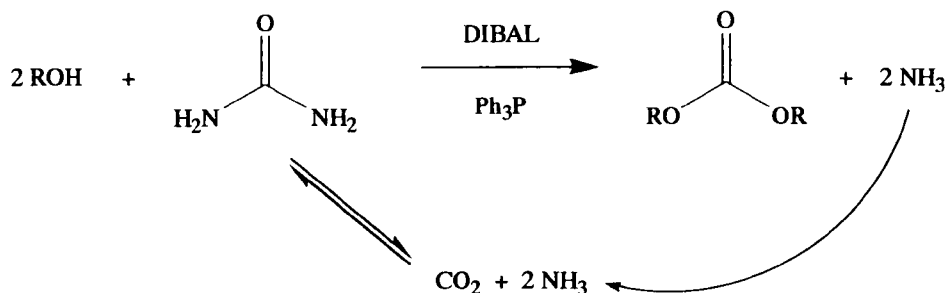
Scheme 1.5: Carbonate synthesis *via* urea

1.4.4 Use of Catalysts to make Dimethyl Carbonate
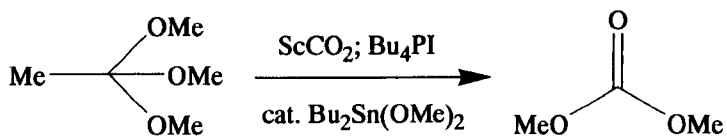
Scheme 1.6: Formation of DMC from orthoesters

Attempts to catalyse the formation of dialkyl carbonates from the corresponding alcohol and carbon dioxide have been most successful using tin-based catalysts, such as $Bu_2Sn(OMe)_2$, but the by-product, water, deactivates the catalyst. Also, the high pressures (25-66 atm) involved prevent this procedure being used in most laboratories.[23, 24] Japanese workers have used dehydrated methanol derivatives (e.g. trimethyl orthoesters, dimethyl ether) with the same catalyst to successfully yield dimethyl carbonate[25] (70%) (scheme 1.6) but the pressure (300 atm) puts this route mainly into the industrial domain. The group of Vahrenkamp used a carbonic anhydrase mimic based on zinc and tested its catalytic activity. Diethyl carbonate was

made from ethanol and supercritical carbon dioxide in 1% yield (scheme 1.7).[26] This work was primarily aimed at mimicking the enzyme rather than being a serious attempt at phosgene replacement.
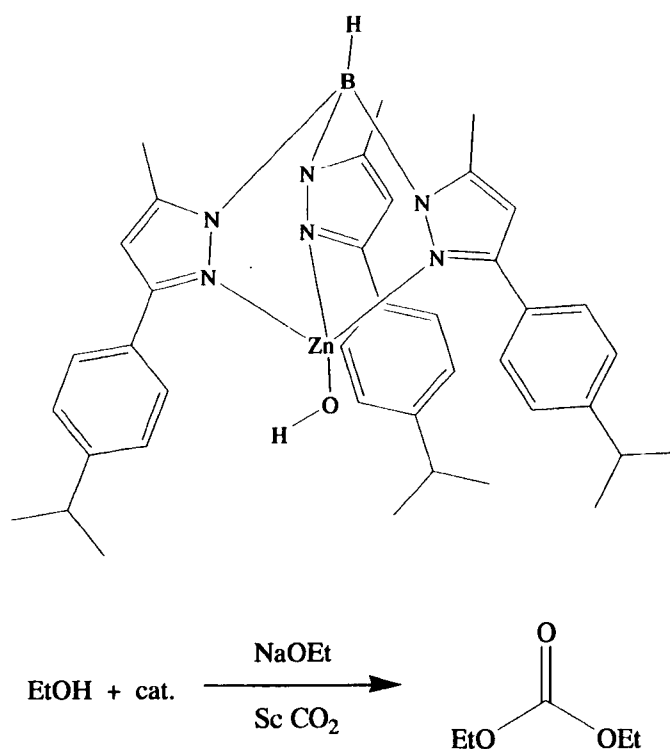
Scheme 1.7: Zinc Tris(pyrazolyl)borate catalyst as a carbonic anhydrase mimic

1.4.5 Use of Phosphines in Synthesis using CO_2

The first example of a synthesis of carbonates using alcohols and carbon dioxide was reported by Hoffman[27], who transferred the Mitsunobu reagents Ph_3P and DEADC from esterifications to carbonation without elevated pressure (scheme 1.8 (iii)). This was led to the first example of a synthesis with no special conditions that made carbonates, albeit only symmetrical ones, in good yield from carbon dioxide and an alcohol.

i) H_2N ‿ OH + CO_2 $\xrightarrow[\text{EtO}_2\text{C-N=N-CO}_2\text{Et}]{\text{Ph}_3\text{P}}$

ii) RNH_2 + CO_2 $\xrightarrow[\text{Pr}^i\text{O}_2\text{C-N=N-CO}_2\text{Pr}^i]{\text{Ph}_3\text{P}}$ $R-N=C=O$

iii) $2\,ROH$ + CO_2 $\xrightarrow[\text{EtO}_2\text{C-N=N-CO}_2\text{Et}]{\text{Ph}_3\text{P}}$
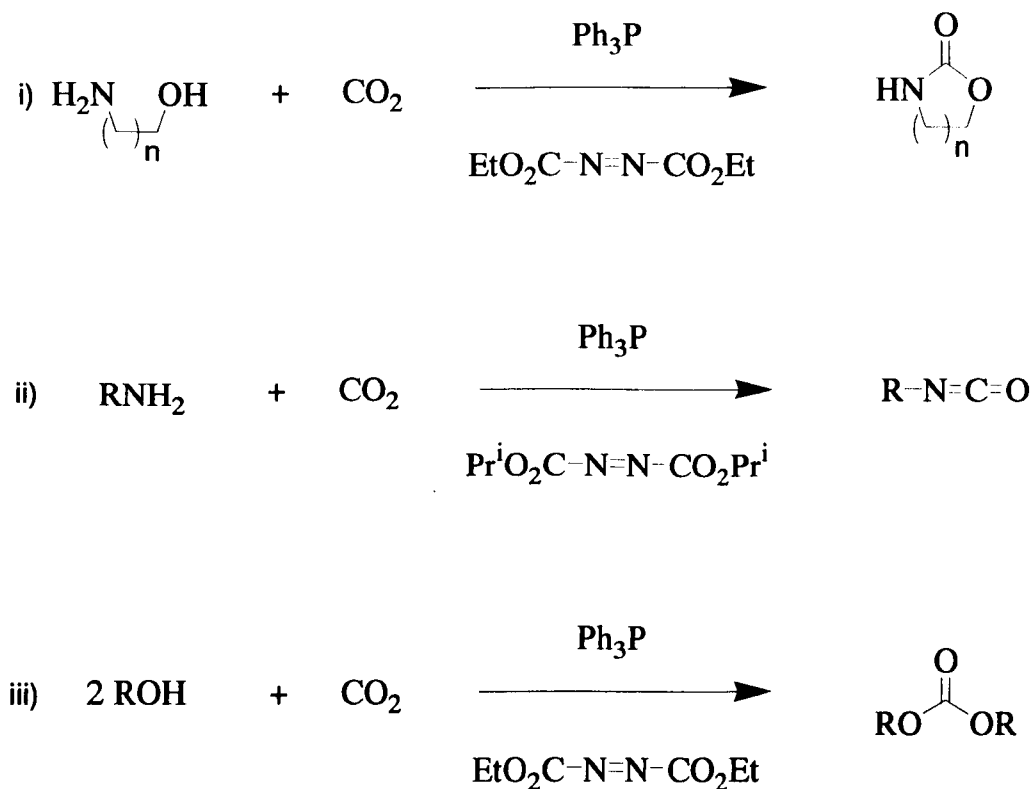
Scheme 1.8: Use of phosphines with CO_2; i) Oxazolidinones by Kodaka ; ii) Isocyanates by Jackson; iii) Symmetrical carbonates by Hoffman

Another group adopted this approach using phosphine reagents in conjunction with carbon dioxide in a new method for the synthesis of oxazolidones (cyclic urethanes) from amino alcohols, either with DEADC or CCl_4 as co-reagents (scheme 1.8(i)).[28] Other researchers have made isocyanates from primary amines (scheme 1.8 (ii))[29] and symmetrical dialkyl carbonates using Ph_3P, CBr_4 and pentaalkyl guanidines.[30] This last method is even less atom economic than the Hoffman route, uses DMF, which is less convenient to work up, and does not develop the reaction any further. None of the above examples are useful for unsymmetrical carbonate or tertiary carbamate synthesis.

1.4.6 Use of Multiple Bonds as "Handles" for CO_2 as a Reagent

Other methods use alkynes as a "handle" to drive the reaction. Dixneuf and Bruneau used propargylic alcohols with a catalytic amount of Ph_3P to synthesise α-methylenic cyclic carbonates (scheme 1.9).[31] This method is unsuitable for saturated alcohols as the alkyne group is required as a "handle".
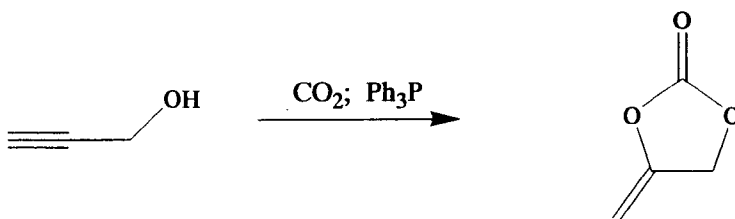
Scheme 1.9 : Use of a triphenyl phosphine catalyst with carbon dioxide

Acetylene itself can be used to generate vinyl carbamates, requiring the use of $RuCl_3$ to catalyse the reaction with carbon dioxide and secondary amines.[32] Another method uses acetylene, an alcohol, a tertiary amine and carbon dioxide at ca. 49 atmospheres. (scheme 1.10).[33] Symmetrical carbonates were produced as well as carbamate by-products. If the alcohol substituent was different to the amine substituents, that is R ≠ R', mixtures of carbonates and carbamates were formed. So there was no selectivity or control. Furthermore, these methods do not further the search for a general carbamate synthesis.

McGhee and co-workers used palladium as an activator for nucleophilic attack of carbamate anions at 5-7 atmospheres on dienes[34] and subsequently allylic chlorides (scheme 1.11).[35] The alkenes were coordinated to the metal, which made them relatively more electrophilic and gave the unsaturated urethanes.
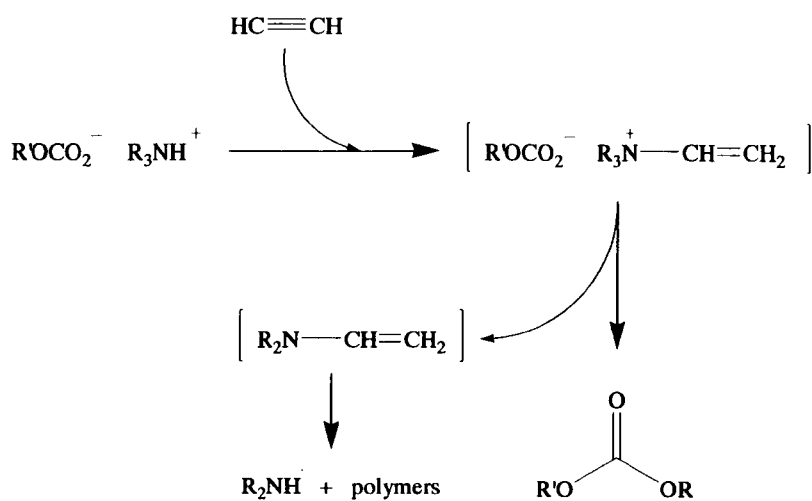
Scheme 1.10: Acetylene promoted formation of carbonates
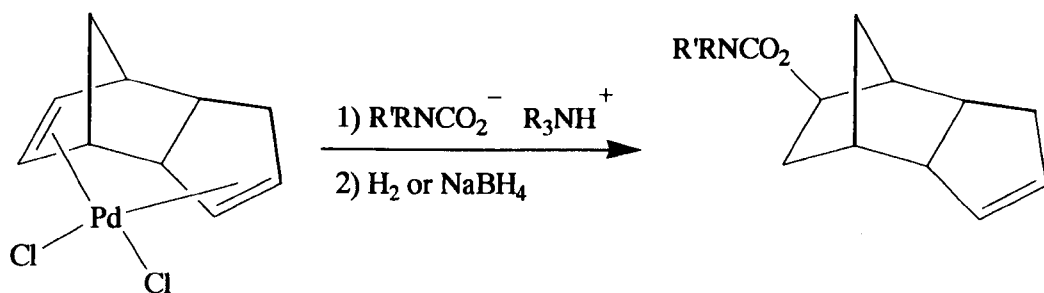
Scheme 1.11: Palladium activated carbamate synthesis

1.4.7 Use of CO_2 with "Dehydrating", Halogenating and Sulfonating Reagents
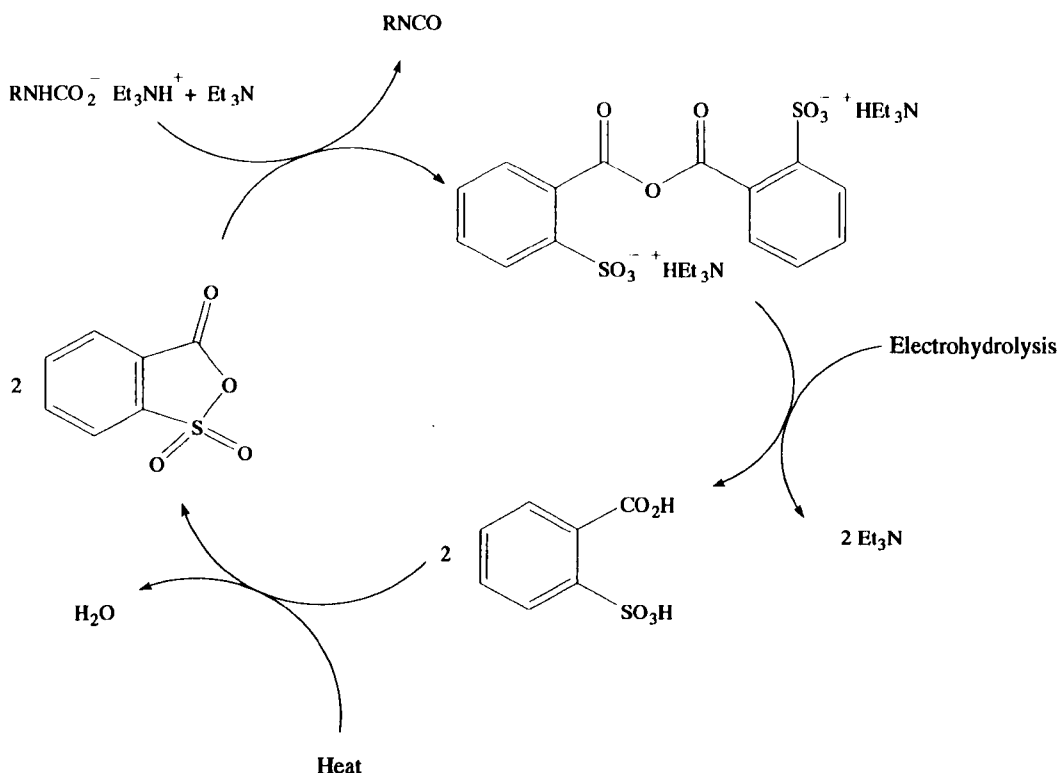
Scheme 1.12: *o*-Benzosulfonic anhydride as "dehydrating" reagent in isocyanate synthesis

A "waste-free" process to make isocyanates was envisaged by the same workers from Monsanto by using *o*-benzosulfonic anhydride, with acids and bases regenerating reagents which were in turn reformed by electrolysis (scheme 1.12).[36] Benzenesulfonic anhydride was also mentioned in passing as a dehydrating reagent, but no examples or experimental details were given.
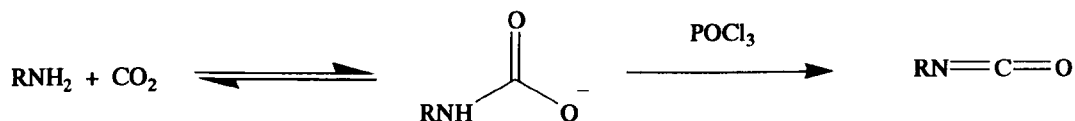
Scheme 1.13: Isocyanate synthesis from primary amines and CO_2

Another method of isocyanate formation by Monsanto was to use "dehydrating" agents such as $SOCl_2$ or $POCl_3$ with carboxylated primary amines (scheme 1.13).

$$R_2NH + CO_2 \rightleftharpoons R_2NCO_2^- \xrightarrow{SOCl_2} R_2N-\overset{\overset{O}{\|}}{C}-Cl$$
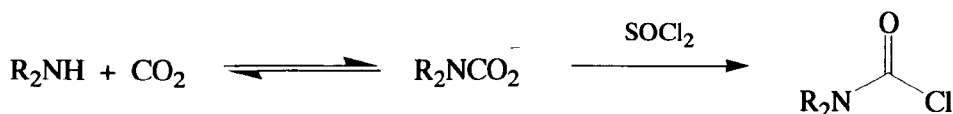
Scheme 1.14: Carbamoyl chloride synthesis from CO_2

If secondary amines were used instead, the carbamoyl chloride was produced (scheme 1.14).[38] The advantage of the reaction, as compared with previous carbamate syntheses using carbon dioxide, was that the gas could be bubbled through the solution rather than added using elevated pressure. This new reaction did not require any special equipment such as an autoclave and circumvented the need for using phosgene, which previously was the only way to make these type of compounds. The best yields were when toluene was the solvent, DBU (pK_a 12-13) or guanidine bases (pK_a 13-16) were used.[39] However, (comparing the GC results) there was a dramatic drop in yield (> 30%) on isolation of the product and a stoichiometric amount of pyridine was necessary, the reason why not being convincingly explained. Another group used this reaction to make isotopically labelled carbamoyl chlorides using $^{14}CO_2$ but yields were no better than 35%.[40]

Very recently Casadei and co-workers applied the chemistry of an electrogenerated base, to synthesise oxazolidinones (cyclic urethanes).[41] Intramolecular reaction takes place between the hydroxy group and *in situ* generated toluenesulfonyl carbamate (scheme 1.15). There have been previously published oxazolidinone syntheses from carbon dioxide and phosphines[28] (see section 1.4.5) which are superior and do not need specialist electrochemical apparatus. Results shown here later will demonstrate

that use of *p*-toluenesulfonyl chloride does not translate to synthesis of acyclic carbamates or carbonates, but dicarbonates, which verifies the work of Rosnati.[42] By adding one equivalent of *p*-toluenesulfonyl chloride to two equivalents of sodium ethylcarbonate, diethyl dicarbonate was made, ethyl toluenesulfonyl carbonate being suggested as an unisolated intermediate. Acyl chlorides and thionyl chloride gave no dicarbonate.
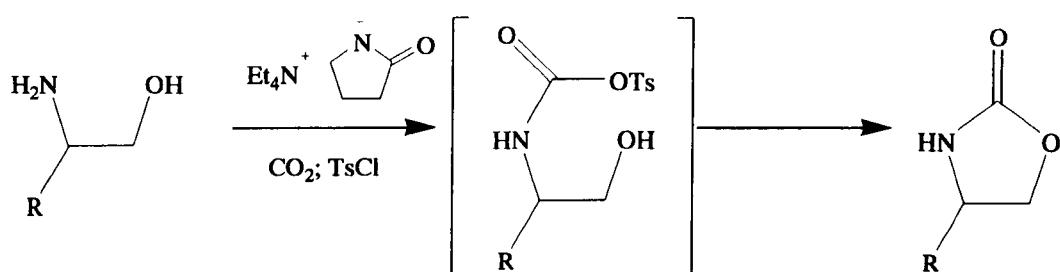
Scheme 1.15: Synthesis of oxazolidinones using electrogenerated base

A novel amine protecting group using carbon dioxide has been developed by workers at the University of California. The carbamate anion was trapped at −78 °C with triisopropylsilyl triflate (TIPSOTf), giving the triisopropylsilyloxycarbonyl (Tsoc) group (figure 1.3).[43] The functional group is stable to trifluoroacetic acid (TFA), hydrogen over Pd/C and morpholine, typical reagents for cleavage of carbamate protecting groups. Deprotection to regenerate the amine was carried out using tetrabutylammonium fluoride.
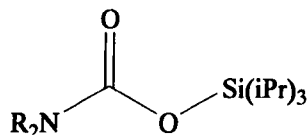
Figure 1.3: Tsoc protecting group

1.4.8 Alkylations of Anions Generated Using CO_2

1.4.8.1 Introduction

The majority of other carbonate forming reactions have been variations on the theme of alkylating the carbonate anion with an alkyl halide or an epoxide, whether the reactions were intermolecular or intramolecular. The carbamate or carbonate anion is made more nucleophilic by use of strong, delocalisable bases which can enhance the nucleophilicity of the charged oxygen atom (*vs.* the nitrogen atom in the case of carbamates), phase transfer catalysts and dipolar aprotic solvents such as DMF, acetonitrile and *N*-methylpyrrolidone, which solvate the cation more effectively and "free-up" the anion.

1.4.8.2 Alkylation of Carbonate Salts

Metal carbonate salts can also be used as a source of the carbonyl group. Under normal conditions, the carbonate anion is not very nucleophilic. Lissel and Dehmlow successfully used K_2CO_3 to make symmetrical carbonates in good yields with the aid of a catalytic amount of $KHCO_3$, primary alkyl bromides and a ten-fold excess of methyl tri-*n*-octyl ammonium chloride in toluene (figure 1.4).[44] Alkyl chlorides were not tested and attempts at preparing unsymmetrical carbonates gave low yields of mixed carbonates.

A similar method using tin catalysts and K_2CO_3 was effective only in DMF. One example using acetonitrile was reported, but only with a co-catalyst 18-crown-6 and using 1,2-dibromoethane as the substrate to give ethylene carbonate.[45] Researchers at General Electric improved this approach however, by managing to synthesise symmetrical carbonates in good yield above 100 °C.[46] They used both primary bromides and chlorides with tetrabutylammonium bromide and $KHCO_3$ in

dimethylacetamide. Use of two different alkyl halides gave mixtures of products. Using activated aryl halides led only to ethers due to decarboxylation of the intermediate aryl carbonate ions.

Whilst trying to alkylate secondary amines with alkyl bromides under phase transfer catalysed conditions Sanchez and co-workers discovered that there was a small amount of carbamate by-product.[47] Increasing the amount of tetrabutylammonium hydrogensulfate catalyst from 5% to 80% in the presence of K_2CO_3 reversed this result to yield the carbamate as the major product with no added carbon dioxide. The proposed mechanism is that the dialkylcarbonate forms first due to excess alkyl bromide, followed by substitution of the alcohol by the amine. Surprisingly, using a polar solvent such as acetonitrile favoured the *N*-alkylation product and *n*-heptane was the solvent of choice.
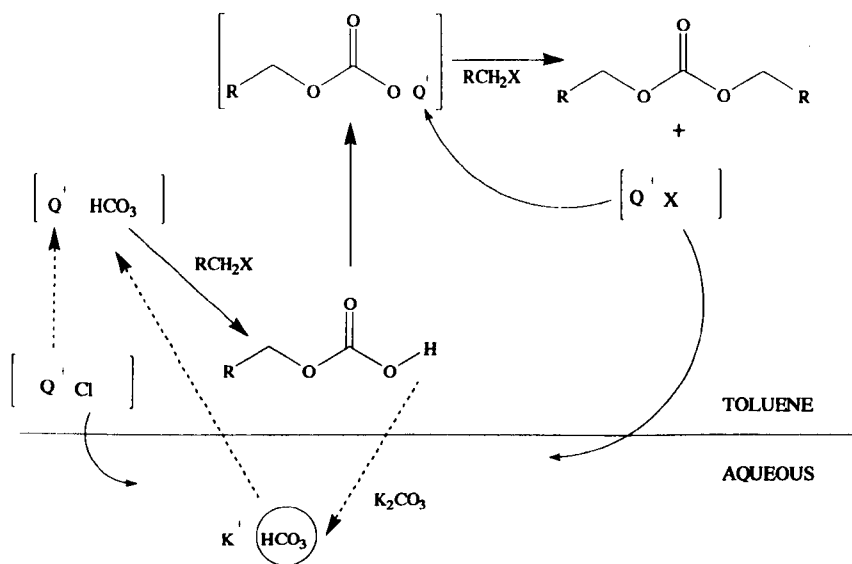
Figure 1.4: Carbonate synthesis by phase transfer catalysis

Similarly, during attempted tertiary amine synthesis from secondary amines and potassium carbonate as a base, carbamates were observed as by-products in up to 40%

yield.[48] The proposed explanation was that alkylation of secondary amines occurred first, assisted by potassium carbonate. The carbon dioxide generated then reacted with unreacted secondary amine to form the carbamate anion which was itself alkylated (scheme 1.16). Bubbling carbon dioxide into the reaction mixture increased yields of carbamates by 20%. Change of base to caesium carbonate increased this further, typically up to 70-96% and decreased tertiary amine yield to between 0-3%. Change of solvent from DMF gave no carbamate products.
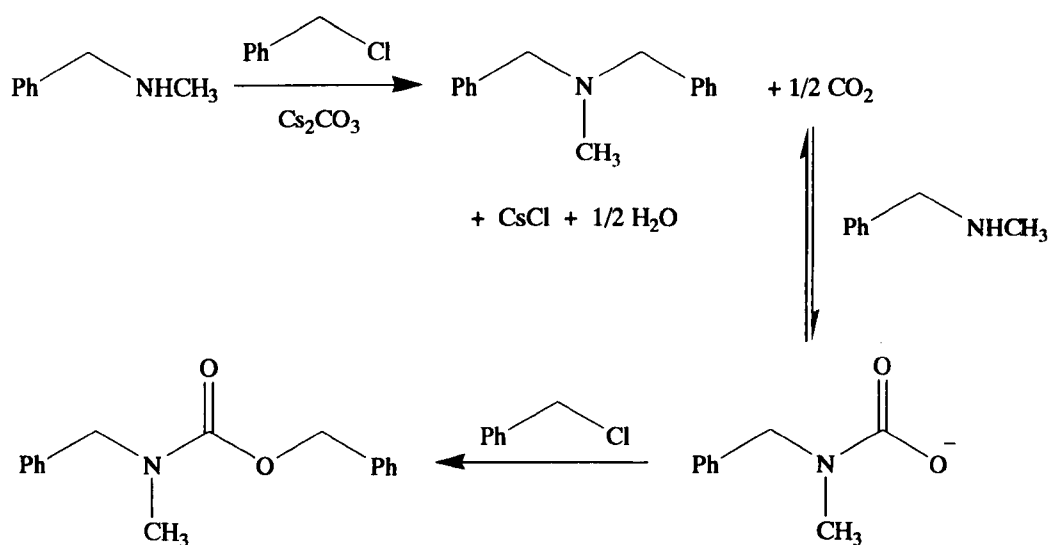
Scheme 1.16: Carbamate synthesis promoted by caesium carbonate

1.4.8.3 Metal Alkoxides as Nucleophiles, Alkyl Halides and Epoxides as Electrophiles

Alcohols do not react appreciably with carbon dioxide due to their low basicity and there is no isocyanate analogue as oxygen is not capable of isolable trivalent states, so slightly different methods have been devised to make carbonates from carbon dioxide. Most involve metal alkoxides, which are generated from an alcohol and strong base such as BuLi, rather than alcohols themselves reacting with carbon dioxide, forming

the metal hemicarbonate. Subsequently the compound is alkylated with an alkyl halide. The larger the cation, the better the yield, for example the silver (I) cation is better than the lithium cation.[49] Examples include use of allylic or homoallylic alcohols that undergo iodocarbonation (analogous to iodolactonisation). The alcohol is carbonated, the double bond reacts with iodine and the carbonate anion cyclises to form the iodocarbonate (scheme 1.17).[50] The principle is the same for epoxy alcohols, which after carbonation, cyclise to hydroxycarbonates.[51]
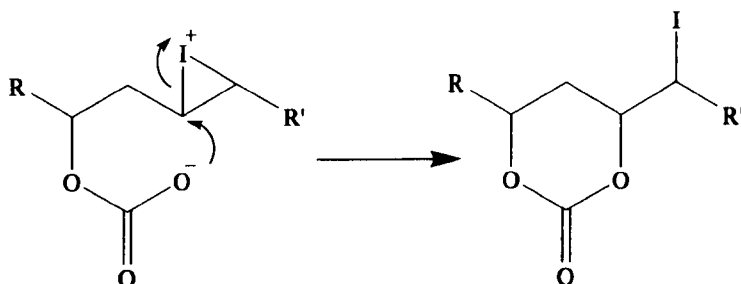
Scheme 1.17: Iodocarbonation

1.4.8.4 Alkylation Using High Pressure

$$2\,R_2NH + CO_2 \longrightarrow \left[\,R_2NH_2\,\right]^{+} \left[\,R_2NCO_2\,\right]^{-}$$
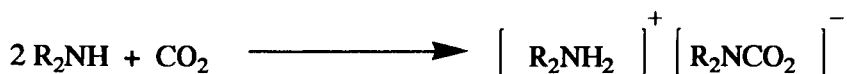
Scheme 1.18: Ammonium carbamate formation

On reaction of carbon dioxide with primary or secondary amines, an alkyl ammonium carbamate salt forms (scheme 1.18).[20] The carbamate salt can then be used as a nucleophile with alkyl halides to form urethanes in low yield, as alkylation of the nitrogen atom is the main reaction, with carbon dioxide being evolved. Whether alkylation occurs as a result of the ambident nature of the carbamate anion or whether

it is due to uncarboxylated amine reacting directly with the alkyl halide is not known (scheme 1.19).[52]
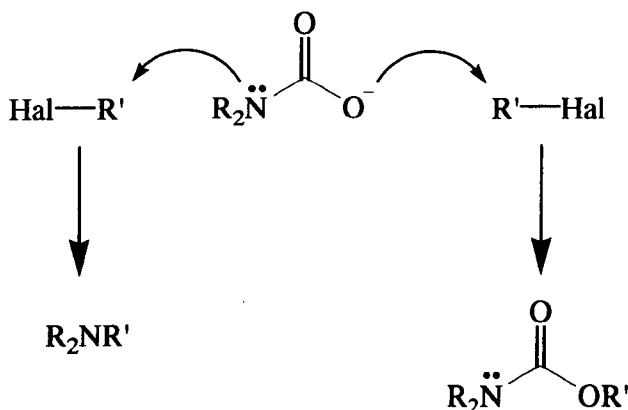
Scheme 1.19: Amine vs. carbamate formation

Improvements can be made by using higher pressure to force the equilibrium to the right, hence reducing the amount of starting material. More extensive work has been done using carbamate salts, the reaction of carbonate anions being less widespread.[55,85] The formation of carbamate esters by alkylation was initially improved by using high pressure (in excess of 40 atm).[53] These reactions are restricted to autoclaves and give low yields, unless alkyl bromides are used, in which case the upper limit on the yield is in the region of 40%, moving up to around 50% specifically for secondary amines reacting with secondary alkyl bromides.[54]

A superior series of methods for alkylation of carbamate anions was developed when McGhee and co-workers at Monsanto turned their attention to the synthesis of urethanes. They developed the methodology so palladium was no longer needed and instead strong, bulky guanidine bases were used to drive pressurised carbon dioxide reactions (5-10 atm) to form carbamate and carbonate anions from the respective alcohol or amine, which were alkylated in high yield (scheme 1.20).[52, 55] However, the

methodology did not extend to tertiary alkyl or aromatic alcohols or the analogous halides, that is any molecule that would not normally react via an S_N2 mechanism. Also, pentaalkylguanidine bases are not commercially available but have to be synthesised (usually from phosgene or other oxychloride halogenating agents) and the range of alkyl halides available is less than that of alcohols. Amidine and tertiary amine bases caused more than a 25% drop in yield. Generally, however, the yields were very good and the process efficient.

$$RXH + CO_2 \xrightleftharpoons{\text{CyTMG}} \underset{RX}{\overset{O}{\|}}{C}{-}O^- \xrightarrow{\text{R'Hal}} \underset{RX}{\overset{O}{\|}}{C}{-}OR'$$
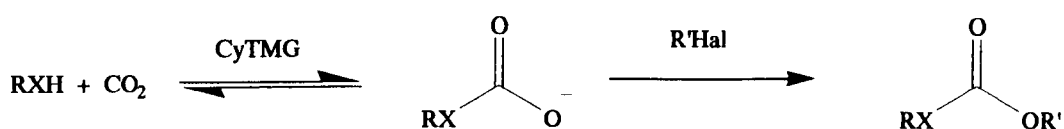
Scheme 1.20: Alkylation of anions using alkyl halides; X = O, NR

1.4.8.5 Cation Complexation to Enhance Carbamate Anion Nucleophilicity

The usual products of the reaction between a carbamate salt and an alkyl halide are N-alkylated tertiary amines or quaternary ammonium salts,[56] accompanied by evolution of carbon dioxide. Regardless of the cation, attempts to form carbamate esters have involved complexing the counterion. The reasoning behind this is to reduce the ion-pairing between ions by lowering cationic charge density. The relative nucleophilicity of a "naked" carbamate ion increases. Belforte and Calderazzo first demonstrated the approach of preforming alkali metal carbamates (Et_2NCO_2M, M = Na, K), followed by complexation of the metal cation with crown ethers or cryptands.[57] This reversed the selectivity of metal carbamates reacting with methyl iodide, so that carbamates were the major product instead of tertiary amines or ammonium salts. Transfer of the carbamate group was similarly accomplished very soon afterwards by Aresta and Quaranta. Carboxylation of aminophosphines and then

reaction of phosphocarbamate products with alkyl halides in the presence of KF and crown ethers gave carbamates (scheme 1.21).[58] No other metal halides proved useful. In the same vein, a few years later, the same researchers used crown ethers to complex primary alkylammonium carbamates which were formed by bubbling carbon dioxide into a solution of a primary amine with a stoichiometric amount of crown ether.[56] Further reaction of the carbamate-crown ether complex yielded the alkyl carbamate. The disadvantages are that expensive crown ethers are required, in stoichiometric quantities, the processes are not atom-economic and aminophosphines are difficult to synthesise.

$$P(NR_2)_3 + x\,CO_2 \longrightarrow P(NR_2)_{3-x}(R_2NCO_2)_x \xrightarrow{R'X} R_2NC(O)OR'$$
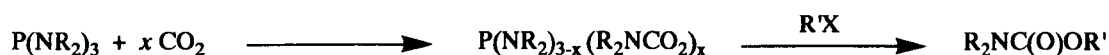
Scheme 1.21: Phosphocarbamates as intermediates to carbamates

1.4.8.6 Electrochemical Activation of CO_2
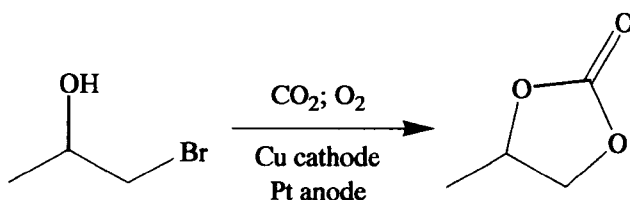
Scheme 1.22: Use of electrolysis in cyclic carbonate synthesis

The groups of Casadei and Inesi in collaboration have used a different approach to carbonate synthesis. Instead of using high pressure, complexing or phase-transfer agents, carbon dioxide is electrochemically activated with oxygen simultaneously bubbling into the reaction. Reaction of the anion can occur with either ethyl iodide to yield the carbonate,[59] or an intramolecular reaction takes place with β-halo or β-

sulfonate alcohols, to give the cyclic carbonate (scheme 1.22).[60] GC yields of acyclic carbonates were more than 30% lower than cyclic carbonates (80-90%). This is not unsurprising for an intermolecular *vs.* an intramolecular reaction. The same groups further developed the reaction by electrochemically generating the base (2-pyrrolidone) instead of activating carbon dioxide. Again, ethyl iodide was the alkylating reagent.[61] Yields were extremely variable and the reaction very non-specific for diols giving three carbonate products, monosubstituted, di-substituted and cyclic, as well as starting material. Aromatic or tertiary alkyl carbonates were not accessible (scheme 1.23; R = alkyl). Further development used amines converted to carbamate anions which were then alkylated with ethyl iodide.[62, 63] Though interesting, none of this work really improved on the work of McGhee's group as yields were generally worse, the approach was the same (alkylation of the anion) and the method does not seem appropriate for scale-up as electrochemistry is expensive.
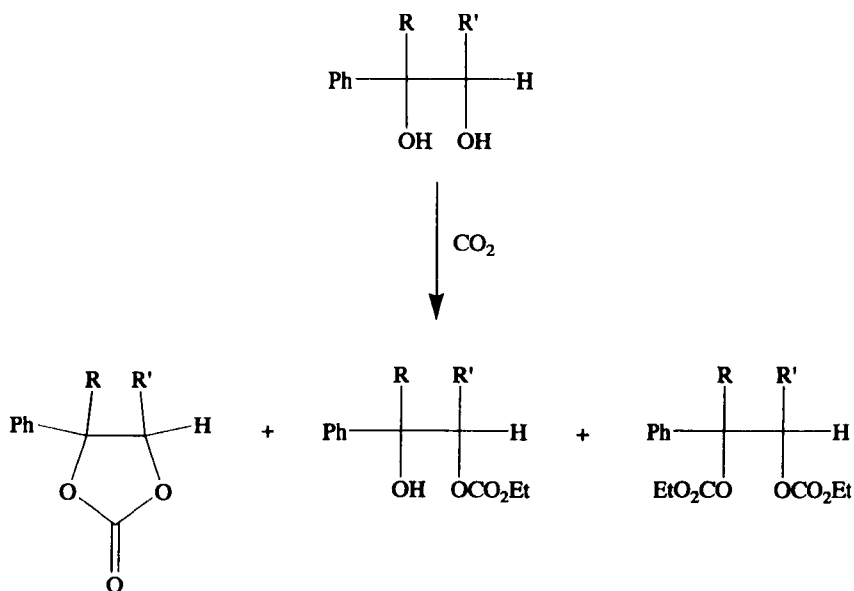
Scheme 1.23: Electrochemical synthesis using CO_2

1.5 Further Developments

The direct synthesis of unsymmetrical acyclic organic carbonates from alcohols and carbon dioxide has not been reported to our knowledge and neither have aromatic carbonates in any form. This would be most advantageous as it would allow replacement of phosgene whilst retaining the versatility of its reactions; two different alcohols could be used to make unsymmetrical carbonates. Furthermore, urethanes could be made by starting with an alcohol and adapting the said method to use an amine instead of a second alcohol.

As yet, reactions using carbon dioxide have not moved away from the use of alkyl halides, toxic halogenating reagents or isocyanates. Furthermore, very little general utility has been demonstrated, all examples have been restricted to alkyl carbonates and carbamates in various guises.

A further gap in the ensemble of routes to carbonates from carbon dioxide is that phenols can not be incorporated. Variations have only been based on longer alkyl chains with benzene rings located remotely at the terminus, using Cs_2CO_3.[64] This latter approach was also used on solid phases.

At the moment, the most general and reproducible routes for carbonate and urethane formation are based on reagents originating from phosgene such as isocyanates, chloroformates or carbamoyl chlorides. These latter intermediates all have a good leaving group adjacent to the carbonyl group. Obvious substitutes for halogen leaving groups are sulfonates, which would be expected to react in a similar fashion to produce carbonate derivatives.

$$\text{R} \underset{\displaystyle}{\overset{\displaystyle O}{\|}} \text{C} - \text{OSO}_2\text{R}' \qquad \text{RX} \underset{\displaystyle}{\overset{\displaystyle O}{\|}} \text{C} - \text{OSO}_2\text{R}'$$

Carboxylic-Sulfonic Anhydride   Carbonic/Carbamic Sulfonic Anhydride

Figure 1.5: Acyl and alkoxycarbonyl sulfonates; R = Alkyl, aryl; R' = alkyl, aryl; X =

O, NR''

The occurrence of mixed carboxylic-sulfonic,[65-68] carbonic-sulfonic[68-70] or carbamic

sulfonic anhydrides (figure 1.5),[71] where a sulfonate group is adjacent to a carbonyl

group, is sparse. The reason for this may be due to no synthetic advantage being

gained in their formation compared to the precursors that have been used to make

them. These would be carboxylic acid derivatives in the former case, chloroformates

or isocyanates in the latter. The mixed anhydrides would give the same products on

reaction with nucleophiles as acid chlorides, chloroformates or isocyanates.

Excluding rearrangements, chloroformates and isocyanates have been the only

reagents used to make carbonic or carbamic sulfonic mixed anhydrides of any type

thus far.

CHAPTER 2 - SYNTHETIC METHODOLOGY FOR THE PREPARATION OF SULFONYL CARBONATE DERIVATIVES

2.1 Synthesis of Diethyl Carbamoyl Chloride Using the Monsanto Procedure

2.1.1 Introduction

$$R_2NH + CO_2 \rightleftharpoons R_2NCO_2^- \xrightarrow{SOCl_2} \underset{R_2N}{\overset{O}{\underset{}{\bigparallel}}}Cl$$
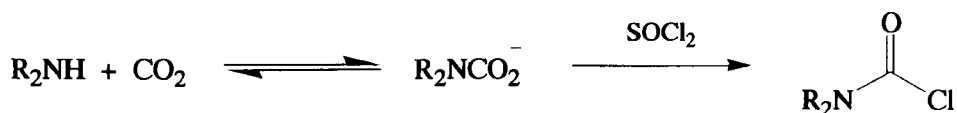
Scheme 2.1: Carbamoyl chloride synthesis by Monsanto

This project arose from our group's programme in synthesis of dendritic polycarbonates and polycarbamates. To synthesise carbamates, it was decided to initially follow the Monsanto synthesis of carbamoyl chlorides from amines, carbon dioxide and thionyl chloride (scheme 2.1).[38] The procedure seemed to be reproducible, simple and only required carbon dioxide to be bubbled into the reaction rather than specialised pressure equipment. Instead of using penta-alkyl guanidines, which have to be made using a non-trivial synthesis, we proposed to use commercially available DBU. Guanidine and amidine bases are strong, and on protonation form delocalisable cations, which form weak ion pairs and so enhance nucleophilicity of the anion. Even though bases such as triethylamine are of comparable strength and sterically hindered, this latter attribute does not seem to be a dominant contributing factor to the reaction.

The reaction could be followed as initially the solution is clear and, as carbon dioxide is bubbled in, becomes more turbid. This is in agreement with reports of carbamate salts with triethylammonium[36] or guanidinium cations.[52] In dipolar

aprotic solvents, the ammonium salts are insoluble and the guanidinium salt completely soluble, so the amidinium salt would be expected to be somewhere in between.

2.1.2 Results and Discussion

Using diethylamine, the Monsanto procedure was followed but isolation of the carbamoyl chloride proved difficult as at the end of the reaction as thick tars were recovered. Work up had to be carried out quickly to prevent hydrolysis of carbamoyl chloride product, which was troublesome if unreacted thionyl chloride had to be neutralised. Thus, to isolate the crude product by vacuum distillation the reaction had to be done on a multi-gram scale and yields were low. This was also in line with findings by another group using secondary amines, achieving maximum yields of 35%.[40]

Instead of isolating the carbamoyl chloride, it was decided to react the compound *in situ* with an alcohol. Since dendrimer synthesis was a goal, phenol was used as a model for the proposed branched monomer, 4,4 - bis (4'-hydroxyphenyl) valeric acid (BPVA) (figure 2.1). This monomer had been previously used in dendritic ester construction.[72]
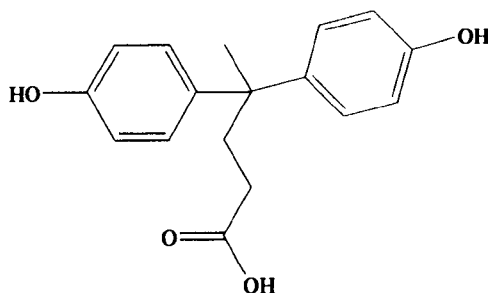
Figure 2.1: , 4,4 - Bis (4'-hydroxyphenyl) valeric acid (BPVA)

On initial formation of diethyl carbamoyl chloride, addition of phenol and an equivalent amount of pyridine gave phenyl *N,N*-diethyl carbamate **1**, isolated in 20% yield. As a comparison, reaction of phenol with diethyl carbamoyl chloride purchased from Aldrich yielded the urethane in 61% yield, identical to the product using carbon dioxide. This would mean that formation of diethyl carbamoyl chloride from diethylamine occurs in approximately 33% yield.

2.2 Trifluoromethanesulfonyl Carbonates and Carbamates as Synthetic Targets

2.2.1 Introduction
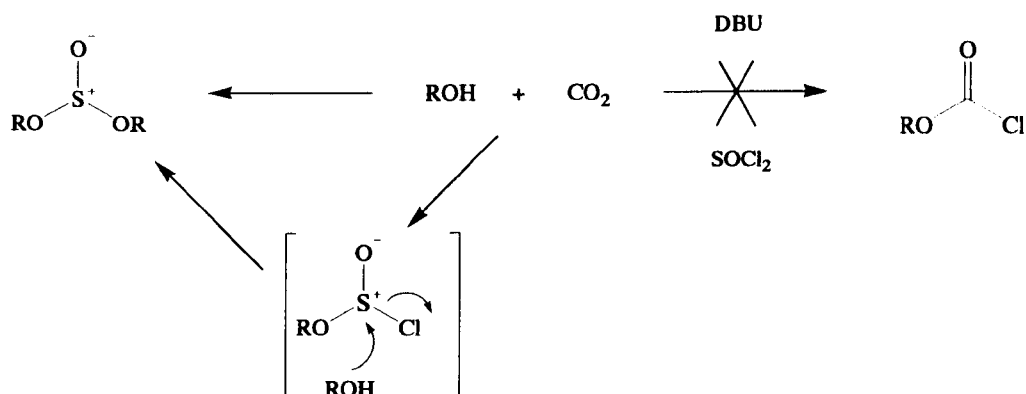
Scheme 2.2: Transfer of carbamoyl chloride methodology to alcohols

A number of factors arising from experimental observation prompted the search for a milder procedure for carbamate and carbonate synthesis; thionyl chloride is volatile, unpleasant to handle and produces sulfur dioxide when it reacts; commercial diethyl carbamoyl chloride could not be selectively reacted with BPVA to form the dicarbamate; earlier work in the group concerned with

applying the Monsanto carbamoyl chloride synthesis to synthesise chloroformates from alcohols had been shown not to work, as dialkyl sulfites were the only products (scheme 2.2).[73] These products arise probably due to thionyl chloride reacting only with alcohol and not the carbonate anion. Once the chlorosulfite ester has been formed, a second alcohol can displace a chloride ion adjacent to the sulphur-oxygen bond, giving rise to a dialkyl sulfite.
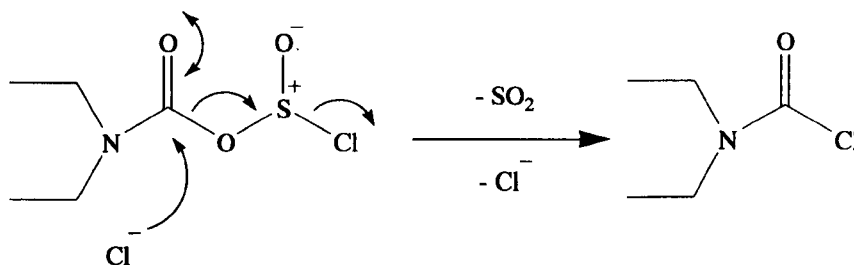
Scheme 2.3: Mechanism of the Monsanto carbamoyl chloride synthesis

The patented Monsanto method[38] involves a rearrangement of the initially formed chlorosulfite ester (similar to alkyl chloride synthesis from alchohols), to the carbamoyl chloride with loss of sulfur dioxide and a chloride ion (scheme 2.3).
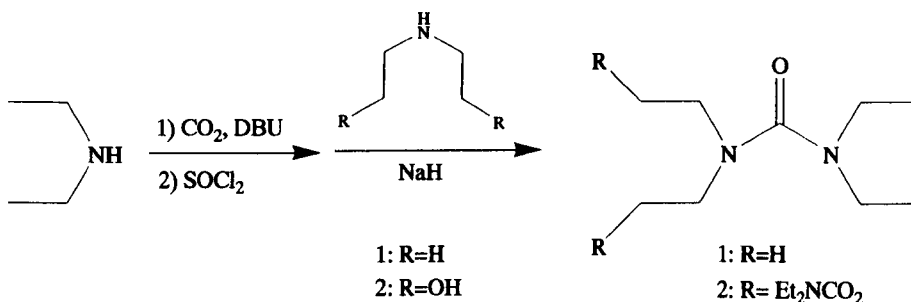
Scheme 2.4: Urea formation using the Monsanto carbamoyl chloride synthesis

Concurrent work had shown that this method was incompatible with functionalised amines, such as diethanolamine (scheme 2.4).[73] Whether this was due to the steric crowding of the amine or harshness of thionyl chloride decomposing the molecule was not known; there was also an indication of tetraethyl urea by-product arising from the reaction of unreacted diethyl amine with diethylcarbamoyl chloride. The evidence for this was a deshielded carbonyl signal around 165 ppm in a ^{13}C NMR spectrum and a parent ion at 172 in mass spectroscopic data.

So, we decided to use an alternative strategy using carbon dioxide. A milder reaction procedure was required that complemented both amines' and alcohols' reaction with carbon dioxide to make carbonates as well as urethanes. The intention was to eventually apply the reaction to dendrimer synthesis using commercial polyfunctional molecules, not any containing halides as they would probably have to be synthesised and are not very versatile. Alkylation was an option if no other methods were developed, but a change of monomer would be required that contained functional groups that would not interfere with the alkylation, which ruled out aryl halides.
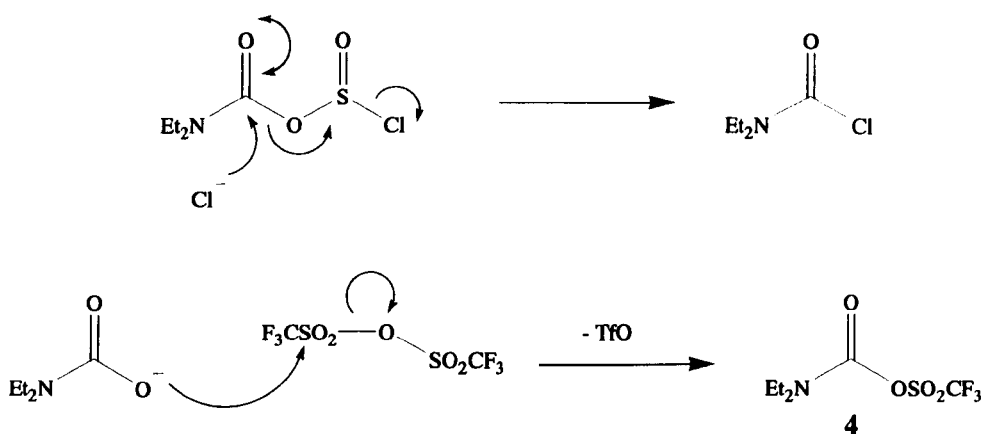
Scheme 2.5: Chlorosulfite rearrangement (Bottom) Sulfonation of a carbamate anion

It was envisaged that conversion of the charged oxygen atom, in a carbamate or carbonate ion, to a triflate group would be easier than introducing a chlorine atom into the molecule *via* a rearrangement, as the carbamate oxygen atom would immediately be incorporated into the leaving group *via* an S_N2 reaction (scheme 2.5). Also, a suitably reactive precursor to a carbamate ester (analogous to carbamoyl chlorides) would be formed.

We decided to change the solvent used in the Monsanto procedure from toluene to acetonitrile, which was expected to be superior for S_N2 reactions due to good cation and poor anion solvation, as well as being easier to remove.

Due to the lower nucleophilicity of alcohols as compared with amines, it was anticipated that bubbling carbon dioxide through the reaction mixture would not be sufficient, as most examples of carboxylation at ambient pressure have to use metal alkoxides.[46, 49]

2.2.2 Results and Discussion

PrOH + CO₂   DBU   ⟶̸   PrO–C(=O)–OTf

3.5 bar   Tf₂O   **2**
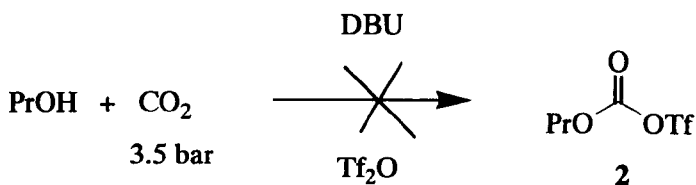
Scheme 2.6: Attempted synthesis of *n*-propyl triflyl carbonate

The first experiment was carried out in a pressure vessel under 3.5 bar carbon dioxide pressure with DBU in acetonitrile. *n*-Propanol was chosen as a test alcohol as dipropyl carbonate has a sufficiently high boiling point (167 °C) so as not to be removed with solvent *in vacuo*, but any unreacted *n*-propanol would

easily be removed. After being pressurised with carbon dioxide, the reaction was cooled before addition of triflic anhydride (scheme 2.6). Initially it was thought that the product was propyl triflyl carbonate **2** as there were three proton NMR signals indicative of a propyl group, the most deshielded triplet at δ 4.23 suggesting a very electron poor environment. Also four carbon NMR signals supported these conclusions as three were identical to propyl signals and there was a carbonyl signal (148 ppm), suggesting carboxylation had actually occurred. ^{19}F NMR and mass spectroscopy failed to confirm this inference. Comparison with authentic dipropyl carbonate also ruled this compound out. It took several experiments to discover what compound had been made (see section 2.3.2).

After this initial failure it was decided to switch to using amines, since they could be reacted by bubbling carbon dioxide into the reaction. Triflic anhydride was used in place of thionyl chloride and the Monsanto procedure for formation of carbamoyl chloride was followed, except at lower temperature (-40 °C internal temperature using MeCN cold bath) to account for the greater reactivity of the sulfonating reagent. Subsequent *in situ* reaction with phenol at the same temperature gave phenyl *N,N*-diethyl carbamate ester **1** in 35% yield on isolation (scheme 2.7). The spectra of the product matched those from an authentic sample synthesised from diethyl carbamoyl chloride.
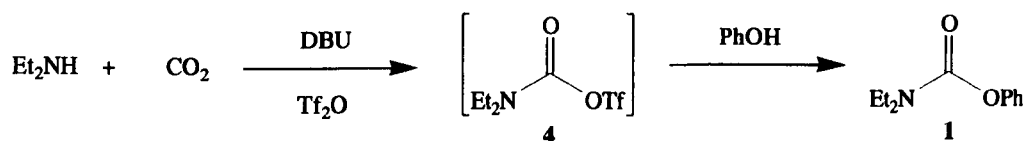
Scheme 2.7: Synthesis of phenyl *N,N*-diethyl carbamate from CO_2

Based on this successful experiment, several other amines were reacted using the same conditions, isolation of half of the intermediate was attempted and phenol was reacted with the other half. None gave analogous carbamate esters as judged from the absence of aromatic signals.

Attempted isolation of the intermediate triflyl carbamates from these reactions at first hinted at success. In long relaxation time ^{13}C NMR experiments, two types of carbonyl signal were seen, around 165 and 150 ppm; the latter is in the right region for a sulfonyl carbamate. Also present was a quartet at 119 ppm indicative of a trifluoromethyl group. However, triflyl carbamates should be at least as reactive as carbamoyl chlorides, but synthesis of carbamates was unsuccessful for all amines except diethyl amine.

The reaction using dibutyl amine showed the same signals at 166 and 119 ppm, suggesting a carbonyl group and CF_3 moiety respectively, but the carbonyl signal at 150 ppm was missing. This suggests that the signal at 150 ppm and CF_3 signal are not connected as first thought, in fact they are not even in the same molecule. This hypothesis was confirmed when analysing mass spectra of the reaction involving diethyl amine, carbon dioxide and triflic anhydride. No parent ion was present for either diethyl triflamide or *N,N*-diethyl triflyl carbamate 4. Parent ions present were m/z = 216, 172 and 149, with the largest fragment at m/z = 100. This fragment is very likely to be a diethyl carbamoyl group ($Et_2NC=O$), seen in the mass spectrum of diethyl phenyl urethane using authentic commercial diethyl carbamoyl chloride and carbon dioxide chemistry. From these results, it was apparent that the amine was being carboxylated but no trifluoromethyl groups were present in the products. In the absence of adding a different nucleophile to the reaction mixture, the data suggested that unreacted

diethylamine was attacking triflyl carbamate to yield tetraethyl urea (m/z = 172) and *N,N*-diethyl carbamate anion was reacting faster with triflyl carbamate **4** than triflic anhydride to produce tetraethyl carbamic anhydride **5** (m/z = 216) (scheme 2.8). The CF$_3$ quartet in the ^{13}C NMR spectrum is explained by triflate ion (m/z = 149). These findings also explain the carbon NMR signals, with urea carbonyls typically occurring around 165 ppm and carbamic anhydride displaying an unusually placed signal at 150 ppm.[74]
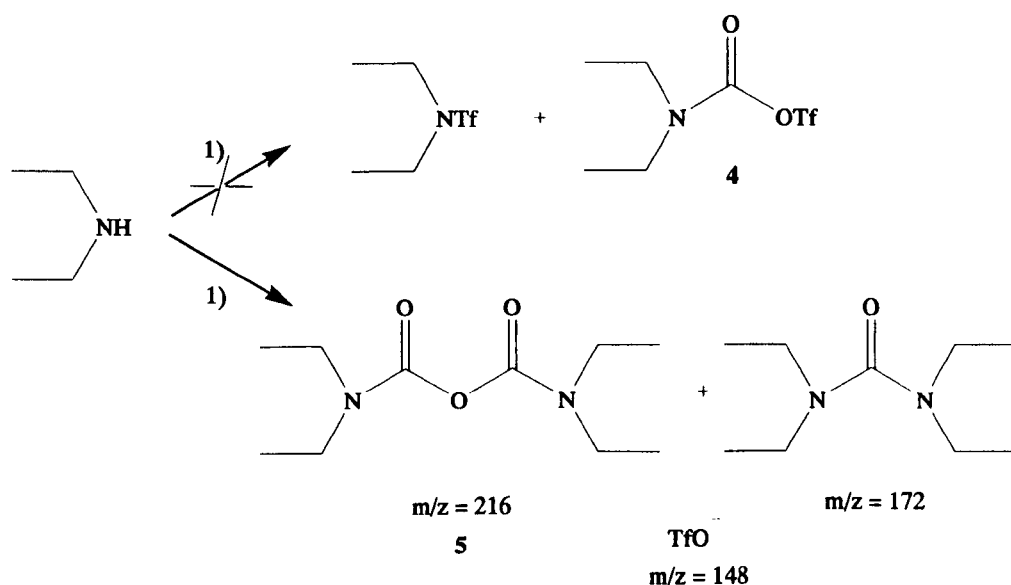
Scheme 2.8: Attempted synthesis of a triflyl carbamate

1) CO$_2$, DBU, Tf$_2$O

It was obvious that carboxylation of alicyclic amines was occurring, even though the intermediate could not be isolated. It was decided to re-investigate *n*-propanol as carboxylation had occurred with this alcohol before and this was a novel approach to potential synthesis of carbonates and related compounds. This time, after addition of a stoichiometric amount of triflic anhydride, the pressure was

released and more *n*-propanol was added. Still, no dipropyl carbonate was formed, as judged by comparison with the proton and carbon NMR of the commercial product. Rather, the unidentified product was identical to the one synthesised in the previous experiment using *n*-propanol. A hypothesis was that the aqueous hydrochloric acid work up could be displacing the triflate with a chloride ion to give the chloroformate. To rule this out, the reaction was repeated and aqueous sulphuric acid was used in work up on half the reaction and the same result was found. Addition of diethylamine to the remainder after addition of triflic anhydride, produced the expected *n*-propyl *N*,*N*-diethyl carbamate **6** as identified by MS and proton NMR of the crude product (scheme 2.9). Unfortunately, the high reactivity of triflic anhydride and triflate intermediates seemed to be causing many side reactions and by-products and purification was thus not possible.
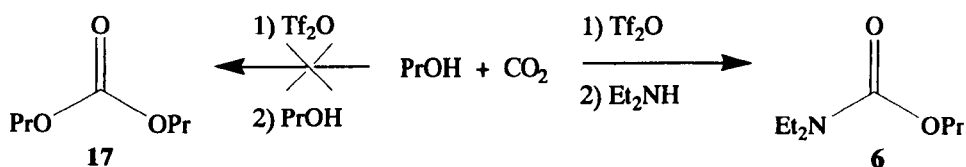
Scheme 2.9: Attempted carbamate and carbonate synthesis using Tf$_2$O

Even reactions conducted with bubbling carbon dioxide, as opposed to under pressure, were unsuitable. Adding one or more equivalents of triflic anhydride to a solution of propyl carbonate salt at −42 °C gave dipropyl dicarbonate **3** with unknown by-products increasing on using more triflic anhydride. Adding half the amount of triflic anhydride gave an unexpected result with the appearance of *i*-propyl signals in the spectrum. Dipropyl carbonate was the major product but

there were also signals present to suggest *n*-propyl-*i*-propyl carbonate had formed (scheme 2.10) by comparison with other experiments. There was no *i*-propyl triflate as the signals were all below 5.0 ppm in the ^{1}H NMR spectrum, whereas the methine septet would be expected to occur above 5.0 ppm. This procedure was unsatisfactory as presumably a rearrangement was occurring. ^{19}F NMR experiments showed more than ten fluorine containing organic compounds in all instances so this approach was discontinued.
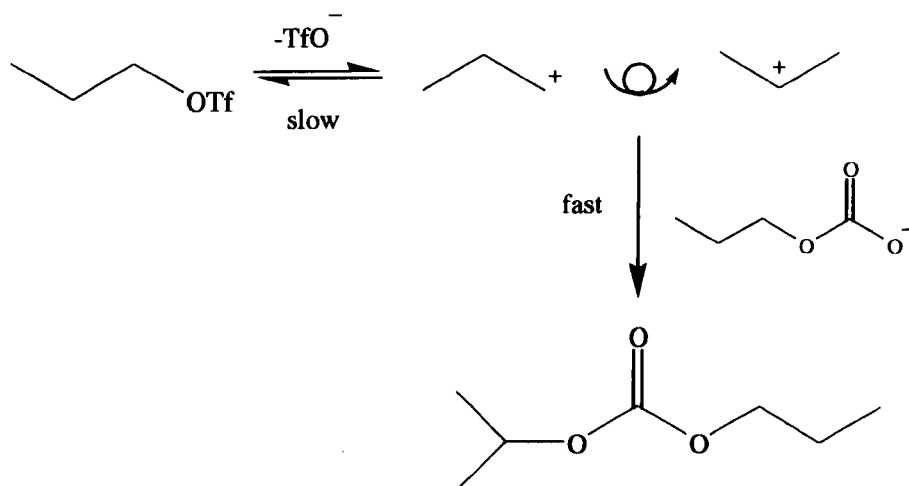
Scheme 2.10: Possible Mechanism of Isomeric Dipropyl Carbonate Formation

The very high reactivity of our proposed intermediates is consistent with a report of carbonyl ditriflate (figure 2.2)[75] (the only reported compound with a carbonyl and triflate group connected together) decomposing above –20 °C. We thus looked for a somewhat less reactive reagent.
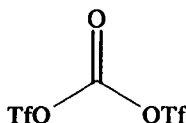
Figure 2.2: Carbonyl Ditriflate

2.3 Methanesulfonyl Carbamates and Carbonates as Synthetic Targets

2.3.1 Introduction

A different sulfonating agent seemed a good idea as preliminary results with triflic anhydride had been encouraging. Methanesulfonic anhydride was chosen for the following reasons: its products could be easily identified spectroscopically in the proton and carbon NMR spectra with no special experiments required and connectivity more easily determined by chemical shift change when attached to an alkyl or carbonyl group; the methanesulfonate ion by-product should not displace anything due to its poor nucleophilicity; it is more atom efficient than triflic anhydride and *p*-toluenesulfonyl chloride; the mesylate group is less reactive than the triflate group, so any sulfonyl carbonate intermediates should be more stable at room temperature and to the reaction conditions.

2.3.2 Results and Discussion

We decided first to test an amine substrate, as it would be easier to control the reaction using only bubbling carbon dioxide. Adapting the triflic anhydride procedure, diethyl amine and DBU were stirred below 0 °C in acetonitrile with carbon dioxide bubbling subsurface. Methanesulfonic anhydride was added and the reaction allowed to warm overnight. Half the reaction was worked up for analysis and the other half added to phenol (scheme 2.11) (see section 3.1.2.2).
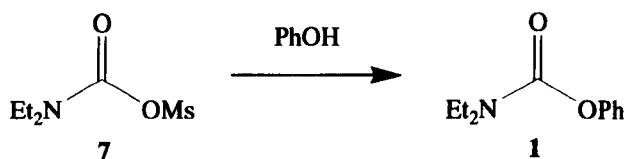
Scheme 2.11: *N,N*-Diethyl Mesyl Carbamate Reaction with Phenol

Analysis of the intermediate showed a mixture of products, the most interesting of which showed a sharp singlet at δ 3.4 ppm. A signal was already present at δ 2.8, consistent with diethyl methanesulfonamide,[76] so it had to be another methanesulfonyl containing compound. Previous reports of carboxyl mesylates had the methanesulfonyl singlet in the same position (figure 2.3).[66, 67] The ^{13}C NMR spectrum showed a shielded carbonyl resonance at 148.00 ppm. Like the result using triflic anhydride, the alternative explanation could be down to two different moieties, one being a mesylate ion or unreacted methanesulfonic anhydride and diethyl carbamic anhydride being responsible for the carbonyl resonance.

The experiment was repeated, but no phenol was added, with a view to positively identifying the intermediates of the three compounds observed. The major component was tentatively assigned as *N*,*N*-diethyl mesyl carbamate **7**. As before the same singlet at 3.4 ppm integrated in the correct ratio with the major *N*-methylene signals and two signals in the ^{13}C NMR spectrum, at 148.00 and at 40.65 ppm (where the methanesulfonyl signal should come) supported the assignments.

^{1}H NMR: δ 3.42

^{13}C NMR: δ 40.3
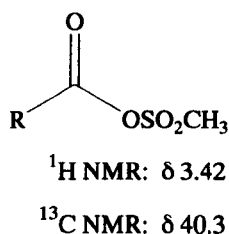
Figure 2.3: Generic NMR shift of the mesyl signal in carboxylic mesylates

The methanesulfonyl and carbonyl NMR signals were both in good agreement with values for similar compounds, cumbersomely named, carboxylic

methanesulfonic mixed anhydrides.[66] The other products were matched with literature values for diethyl methanesulfonamide,[76] tetraethyl urea[77] and possibly some carbamic anhydride **5** (scheme 2.12).[74]
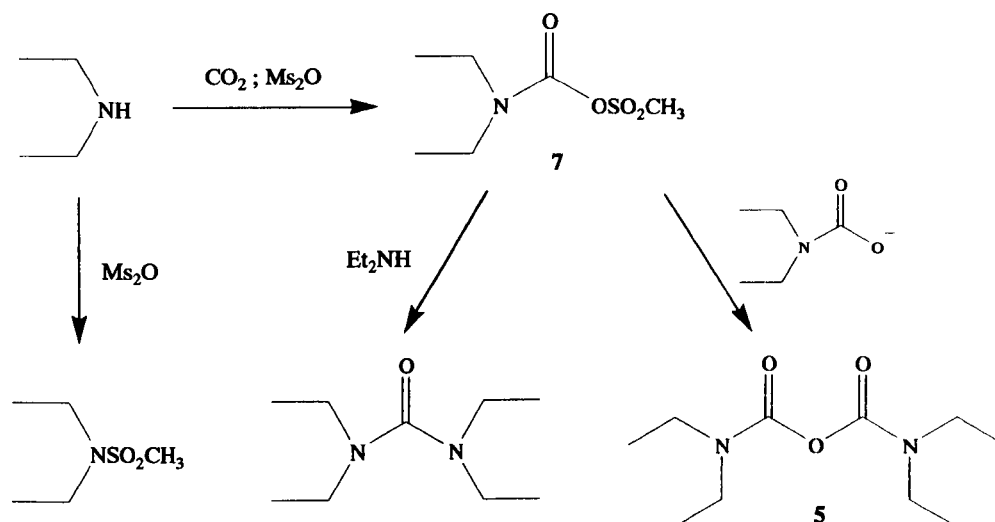
Scheme 2.12: Possible Products from the Formation of *N,N*-Diethyl Mesyl Carbamate

The intermediate was subjected to different work up procedures, which gave differing results. If the reaction mixture was washed with acid and brine, there was much more mesylate compound at 3.4 ppm present than compared to diethyl methanesulfonamide. If a neutral water wash was carried out first, sulfonamide content was higher suggesting the other mesyl compound was being removed or even hydrolysing in the isolation procedure. All the methyl signals for a proposed *N,N*-diethyl methanesulfonyl carbamate intermediate **7** were still present in the correct ratios in both ^1H and ^{13}C NMR spectra in both instances. This implies that they are all part of the same molecule. If tetraethyl carbamic anhydride **5** was the active intermediate, the extra methanesulfonyl signal would

not be reduced in intensity to the same extent as the N-methylene signals, if hydrolysis was occurring. This was clearly not the case as the methyl singlet at 3.4 ppm was consistently in the same ratio as the N-methylene signals.
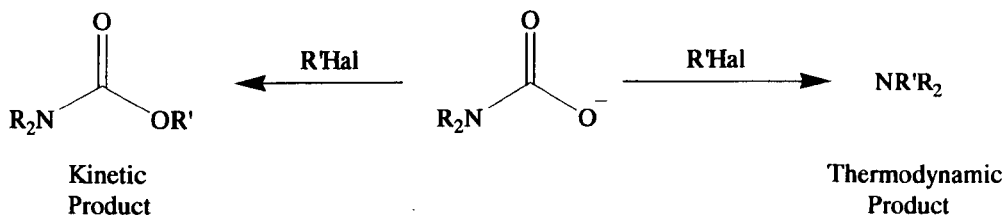
Scheme 2.13: Kinetic and thermodynamic products of the reaction between carbamate anions and alkyl halides

Belforte and Calderazzo claim that the equilibrium of diethylamine and carbon dioxide lies almost exclusively to the side of the carbamate salt.[57] They further suggest that in alkylation reactions, N-alkylation of carbamate anions to form tertiary amines is thermodynamically favoured but slow and carbamates are the kinetically controlled products (scheme 2.13). Whether adding a different base to the system affects the amine-carbon dioxide equilibrium is not mentioned. Nevertheless, our observations show that sulfonation occurs quite easily on the nitrogen atom of carbamate anions at cool temperatures.

We thus had good evidence of the existence of a target carbonyl sulfonate intermediate. Formation of *N,N*-diethyl methanesulfonyl carbamate **7** using a more concentrated methanesulfonic anhydride solution followed by reaction with *n*-propanol (see section 3.1.2.3), gave *n*-propyl *N,N*-diethyl carbamate **6** and only trace amounts of diethyl methanesulfonamide and tetraethyl urea (scheme 2.14). It had already been shown that reaction with phenol yielded the corresponding

carbamate ester **1** and thus, the beginnings of a carbamoyl chloride and phosgene alternative seemed to be emerging.
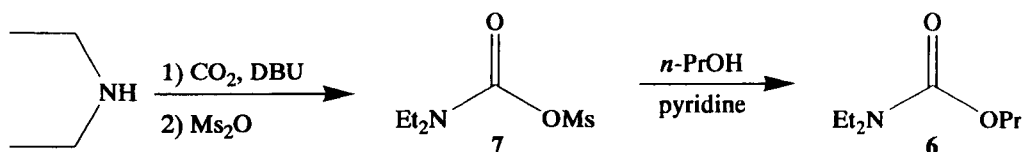
Scheme 2.14: Synthesis of *n*-Propyl *N,N*-Diethyl Carbamate

Since *n*-propyl *N,N*-diethyl carbamate **6** could also be envisaged to be synthesised from diethyl amine and *n*-propyl mesyl carbonate (see section 3.1.5), attention was turned to the reaction of carbonate anions with methanesulfonic anhydride to attempt to form a methanesulfonyl carbonate (scheme 2.15). This intermediate would be a precursor to both carbamates and carbonates, leading to greater synthetic utility than mesyl carbamates. However, due to the nature of the set-up of the pressure vessel, methanesulfonic anhydride had to be added from an attached addition funnel to the carbonate salt solution. Addition of the carbonate anion to methanesulfonic anhydride was not possible.
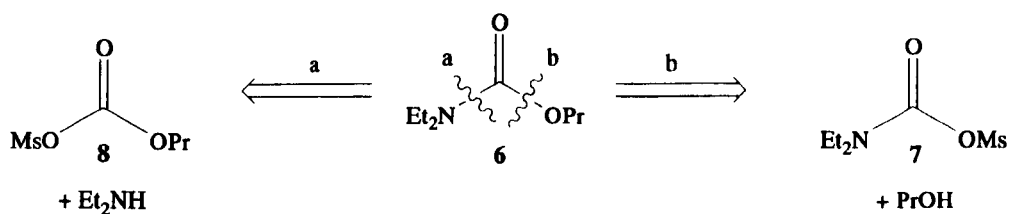
Scheme 2.15: Retrosynthesis of *n*-propyl *N,N*-diethyl carbamate

After pressurising *n*-propanol and DBU with carbon dioxide at 0 °C, the resulting carbonate salt was reacted with methanesulfonic anhydride and after warming and release of pressure, an aliquot was removed and the remainder reacted with diethylamine (see section 3.1.3.1). Analysis of the aliquot indicated a mixture of two methanesulfonyl compounds, dipropyl carbonate and a further unidentified compound. *n*-Propyl mesylate was identified as one of the components and *n*-propyl mesyl carbonate **8** speculated to be the other. This still left a propyl derivative that hadn't been identified.
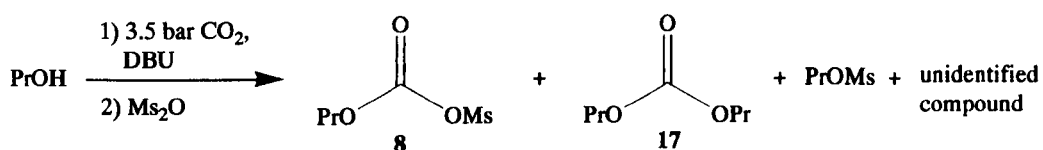
Scheme 2.16

The reaction with *n*-propanol, DBU and carbon dioxide followed by mesylation was repeated and the intermediate analysed. The addition time of methanesulfonic anhydride, changed from instantaneous to 2 minutes had shown drastic differences. Comparing the NMR spectra of the intermediate with that of the *n*-propanol reaction above showed no singlet at 3.4 ppm, yet the reaction had still proceeded to form carbamate and carbonate products. The only difference between them had been the addition rate of methanesulfonic anhydride. We attempted to optimise the procedure with respect to dipropyl carbonate **17**, but yields were sporadic and low. Dipropyl carbonate **17** still formed without addition of *n*-propanol after reaction of methanesulfonic anhydride, which was detrimental for synthetic purposes, so another approach was needed.

At this point, there were problems with the pressure vessel so the reaction was attempted by just bubbling carbon dioxide subsurface to a stirring mixture of *n*-propanol and DBU in MeCN at –42 °C. A low temperature was chosen to maximise carbon dioxide solubility in the absence of pressure. Adding 1.1 equivalents of methanesulfonic anhydride without addition of another nucleophile gave an unexpected result. The reaction had actually worked to an extent, but four compounds were apparent, not two as was originally predicted (the mesyl carbonate and the mesylate). Two had methanesulfonyl groups and three had shielded carbonyl signals in the ^{13}C NMR spectrum (155.5, 148.7 and 147.9 ppm). Three were immediately identified by integration of signals, as dipropyl carbonate **17**, *n*-propyl mesylate and *n*-propyl mesyl carbonate **8** (scheme 2.17). The carbonyl NMR signal for *n*-propyl mesyl carbonate is consistent with more shielding than normal and is in a similar position as the signal for imidazole carboxylic esters.[7c, d]
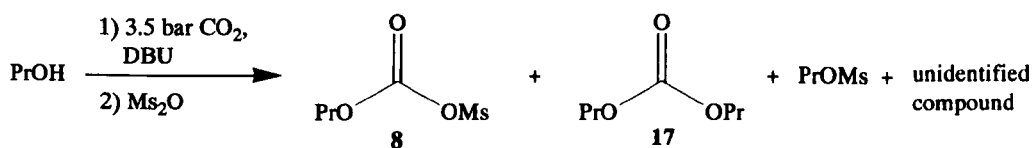
Scheme 2.17

The fourth compound remained elusive, a shielded carbonyl signal was the only clue, until GC-MS (Appendix) clarified matters. There were two minor peaks which were shown to be *n*-propyl mesylate (m/z = 138) and dipropyl carbonate (m/z = 146), confirming the NMR interpretation. Two major peaks then appeared about 3 minutes later but the mass spectrum of each showed them to be

propyl mesylate and dipropyl carbonate as well! What appeared to be happening was decarboxylation of the major compounds which by inference were therefore propyl mesyl carbonate **8** and dipropyl dicarbonate **3**. It was only at this point that the formation of this latter compound had even been considered. When care was taken, these latter two compounds could be seen in the mass spectrum (at $m/z = 182$ and 190 respectively) but after the third scan they disappeared and the two minor compounds' mass ions ($m/z = 138$ and 146 respectively) increased to become the major ions, suggesting decarboxylation of the two compounds as the difference between the parent ions was 44 mass units. From these results, we were also able to deduce exactly what was occurring in this reaction. Now all four products had been identified, the ^{1}H NMR could be fully interpreted (Appendix).

The ratios of propyl mesyl carbonate/ dipropyl dicarbonate / propyl mesylate/ dipropyl carbonate were calculated to be roughly 7 : 3.5 : 2 : 1 and a mechanistic scheme could now be constructed (figure 2.4).

As shown, the alcohol / alkyl carbonate equilibrium means that mesylation of two compounds can occur. If alkyl mesyl carbonate forms, two reactions can take place. Alkyl carbonate salt can react to yield a dicarbonate **3** or unreacted alcohol can displace mesylate to yield dialkyl carbonate. This latter route is more unlikely than the former as excess methanesulfonic anhydride is always present, so any unreacted alcohol would be minimal. Dicarbonate can react in exactly the same way as alkyl mesyl carbonate with alcohols, carbonates being the product.

If uncarboxylated alcohol is mesylated, it can then further alkylate alkyl carbonate salt to produce dialkyl carbonate.

With a proposed mechanism, experiments could be carried out to confirm its validity and attempt to maximise a particular component, in our case n-propyl methanesulfonyl carbonate **8**.
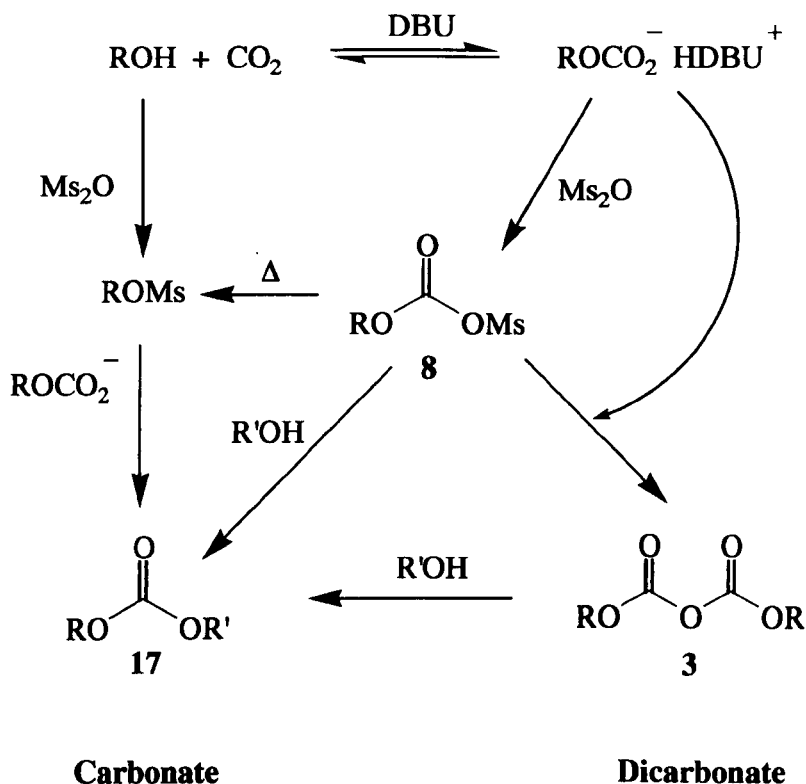
Figure 2.4 : Possible reaction routes using mesyl carbonates

A series of test experiments were carried out using n-propanol, DBU and methanesulfonic anhydride in, primarily, acetonitrile. Factors such as reaction and addition temperature, method of addition, concentration, reactant stoichiometry and reaction time were altered (table 2.1). All reactions carried out below room temperature had CO_2 bubbled subsurface and were slowly cooled.

Entry	Transfer Conditions	Reaction Conditions [c]	Concentration Propanol/Ms$_2$O	Ms$_2$O : Propanol Ratio	Mesyl carbonate [d]	
					Yield (%)	Selectivity [e] (%)
1[a]	30 min, -42°C	48h, 40°C	0.89M / 1.2M	1.13	29	37
2[a]	2 min, -42°C	36h, RT	0.67M / 0.55M	0.5	0[f]	0
3[a]	15 min, -42°C	1h, -10°C then 60h, 40°C	0.89M / 0.82M	0.76	6	9
4[a]	30 min, -42°C	1h, -42°C then 16h, RT	1.2M / 0.33M	0.55	0[f]	0
5[a]	Instantaneous, -20°C	<1 min, -20°C	0.45M / 2.67M	2	44	68
6[a]	Instantaneous, -42°C	1h, -42°C	0.54M / 2.7M	0.51	0[f]	0
7[a]	Instantaneous, -42°C	5 min, -42°C	0.54M / 2.7M	2	42	89
8[b]	25 min, RT	5 min (48h), RT	0.54M / 2.5M	1.4	(0)[f]	(0)
9[b]	30 min, -42°C	24h, RT	0.89M / 0.58M	1.08	43	60
10[b]	55 min, -42°C /	30 min, RT	0.54M / 2.67M	2	37	59
11[b]	30 min, -20°C	10 min, -20°C	0.45M / 2.67M	2	46	86
12[b]	5 min, -20°C	<1 min, -20°C	0.45M / 0.53M	2	19	67
13[b]	Instantaneous, -25°C	20 min, -25°C	0.38M / 0.71M	2	37	71
14[b]	10 min, -20°C	3 min, -20°C	0.38M / 1.07M	2	49	79
15[b]	2h, -20°C	5 min, -20°C	0.38M / 2.15M	2	40	80

Table 2.1: Optimisation of *n*-Propyl Mesyl Carbonate Formation

[a] denotes addition of Ms$_2$O to carbonate anion. [b] denotes addition of carbonate anion to Ms$_2$O. [c] Work up occurred immediately after this time [d] Yield and selectivity[78] determined by NMR after acid wash of ethereal layer. [e] relative to all products. [f] Only propyl mesylate or dipropyl carbonate and propyl mesylate formed.

It was discovered that by slowing addition of methanesulfonic anhydride to the carbonate anion, unreacted carbonate anion had time to react with the mesyl carbonate **8** to form the dicarbonate **3** (entries 1, 3 and 4). That is, the rate of dicarbonate formation is faster than the rate of mesylation in this case, so dicarbonate formation was a dominant factor (scheme 2.18). Fast addition of methanesulfonic anhydride gave more of a mixture (entries 2 and 6) as mesylation of the anion was occurring, in all likelihood, at a faster rate, implying the concentration dependance of methanesulfonic anhydride in the rate of mesylation.
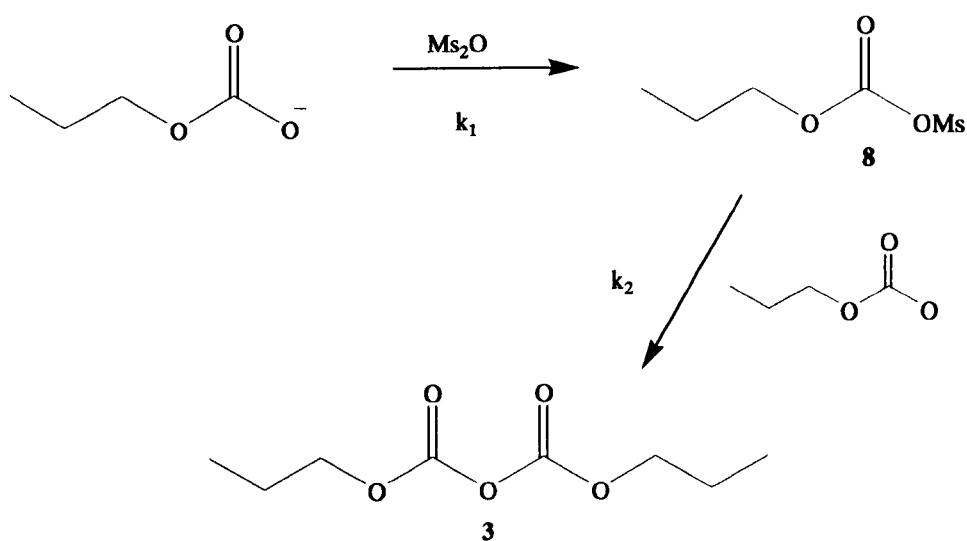
Scheme 2.18

Addition and rate of addition of reagents became important, as the rate of mesylation of the alkyl carbonate anion appears to be faster, compared to reaction of mesyl carbonate with alkyl carbonate anion to form a dicarbonate. If this hypothesis was correct, then addition of the preformed carbonate anion to a solution of methanesulfonic anhydride (the reverse of previous reactions) should

greatly reduce the yield of dipropyl carbonate **17** and dipropyl dicarbonate **3** in relation to *n*-propyl mesyl carbonate **8**.

2.4 Optimisation of Synthesis of *n*-Propyl Mesyl Carbonate

Addition of the preformed carbonate anion to methanesulfonic anhydride did lead to total exclusion of dipropyl carbonate and dipropyl dicarbonate (scheme 2.19), being dependant on reaction temperature, duration of addition and ratio of methanesulfonic anhydride to *n*-propanol. Thus, difficult to remove symmetrical carbonate by-product could be eliminated in future experiments (entries 8-15). Dicarbonate could be eliminated to further extents by increasing the ratio of mesyl anhydride to *n*-propanol.
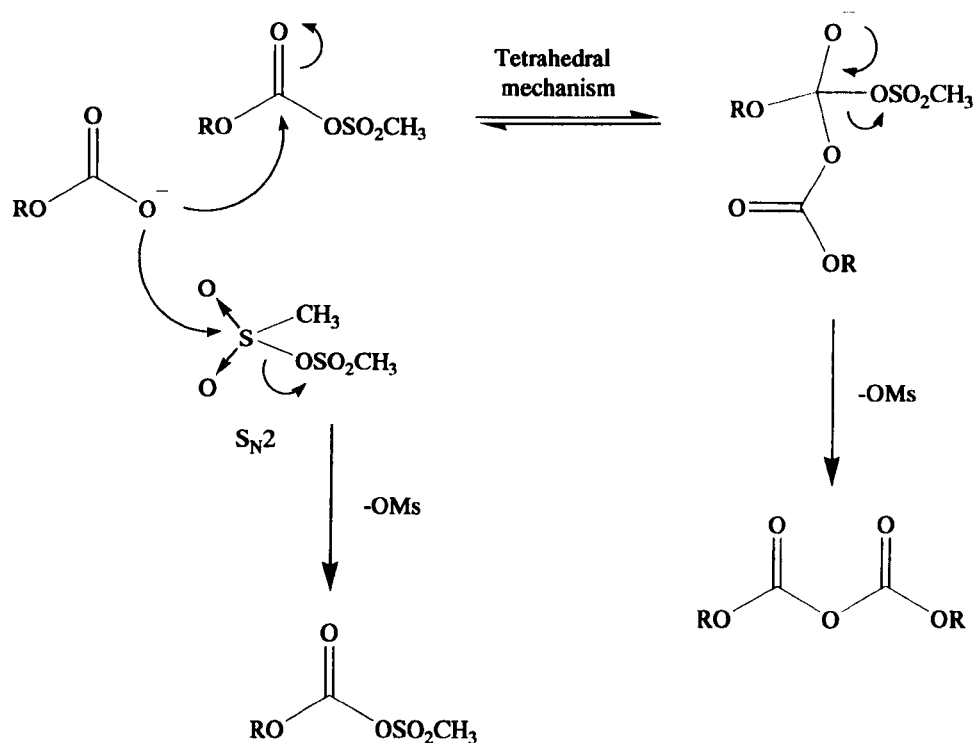
Scheme 2.19: Mechanism of formation of *n*-propyl mesyl carbonate and dipropyl dicarbonate

Every reaction led to propyl mesylate as a by-product but the selectivity in mesylation of *n*-propanol *vs* the carbonate anion varied according to reaction temperature and order of addition. At room temperature the ratio was 1.2:1 in favour of mesyl carbonate (after 48 hours only *n*-propyl mesylate was present, entry 8) and at –42 °C the ratio was even more in favour of mesyl carbonate (3:1 to 4:1, entry 9). Mesyl carbonate ratio increased from 3.4:1 (entry 1) to 11.6:1 when transferring the carbonate, instead of the mesyl anhydride, over the same length of time at –20 °C instead of -42° C (entry 11). Dicarbonate would form in very small quantities, reducing selectivity, if concentration of methanesulfonic anhydride was too low (entries 2 and 4). Addition of methanesulfonic anhydride to carbonate anion could give high selectivity and moderate yield (entries 5 and 7) so long as: it was in concentrated solution; in two-fold excess; below –20 °C; the reaction was quenched and isolated within five minutes. This procedure would not be enhanced by reducing the mesyl anhydride ratio, as this had already been shown to increase side reactions. Equally good yield and selectivity could be attained by adding carbonate anion to methanesulfonic anhydride (entries 11, 14 and 15), but there was more control over this procedure and it could lend itself more readily to further development, for example by reducing the excess of reagent. Three steps could be combined in one experiment without isolation procedures being required in between.

A possible explanation of mesylation selectivity in relation to temperature is that as temperature decreases, carbon dioxide solubility increases so mesylation of the carbonate anion occurs rather than mesylation of the alcohol. However, the ratios of mesyl carbonate **8** to mesylate at temperatures in between the top and bottom are higher. This could be due to the reaction rate of mesyl carbonate

formation from the anion increasing more than the decrease in the rate of alcohol carboxylation.

The more concentrated anhydride solutions (typically >1 M) gave higher selectivity with less propyl mesylate (entries 5, 7, 10, 11, 13-15). Due to the above findings, the reactions were continued without the pressure vessel as its construction did not allow addition of carbonate anion under pressure to methanesulfonic anhydride, as well as being less convenient.

Change of base (e.g. pyridine) gave no carboxylation whatsoever. Change of solvent to DMF or DMAC gave no selectivity advantage (as well as being more cumbersome solvents to remove) and using acetone or THF gave propyl mesylate as the major product.

2.4.1 Summary

The conditions settled on were carbon dioxide bubbling subsurface to an alcohol (ca. 0.35-0.5M) and 1-1.25 molar equivalents of DBU in acetonitrile, cooling the solution to −42 °C for 30-45 minutes, then warming to −20 °C for transferral to an acetonitrile solution of methanesulfonic anhydride (2 eq.; 2.6-3.3 M) over 30-120 minutes (entry 10), depending on volume. Entries 11 and 14 gave similar yields and selectivities but entry 11 gave propyl mesylate in much lower yield. Concentrations were dependant on how much alcohol and anhydride were actually used.

Whilst carrying out the reactions with carbon dioxide, it was noticed that continued bubbling to an acetonitrile solution at −42°C for several hours produced no cloudiness, but on warming above −30°C, a slight precipitate formed. The precipitate formed at room temperature within 5 minutes in

acetonitrile and almost instantaneously in DMF and acetone. However, it was also noted that a precipitate formed when no alcohol but just DBU was present in solution with bubbling CO_2. If DBU was in slight excess and no precipitate formed, typically yield and selectivity of mesyl carbonate (and carbonate / carbamate synthesis) was very poor (0-5%). If DBU was used in stoichiometric quantities, the solution turned cloudy but no solid precipitated. Even so, reactions were usually successful in these instances. This can be explained by the reaction of the amidine base (DBU) with CO_2 to form a salt. This reaction is known but has not been published in the literature.

2.5 Re-investigation of Methanesulfonyl Carbamate Synthesis

Until now, mesyl carbamates had been made by addition of mesyl anhydride to the carbamate anion. It was likely that this led to more by-products such as ureas, than carbonate anions, as amines are better nucleophiles. So, in close analogy with alcohols, subsequent reactions were carried out by addition of pre-formed carbamate salts to mesyl anhydride. This approach was not useful if addition of the carbamate anion occurred above –20 °C, as either the yield was very low or mesyl carbamate was the minor product A greater mixture of products was apparent, tetraethyl urea usually being the major one, indicated by a quartet at 3.15 ppm. Other by-products were diethyl methanesulfonamide and another set of signals similar to *N,N*-diethyl mesyl carbamate but no mesyl singlet was present in the ^{1}H-NMR spectrum. Comparison with earlier experiments that had the same pattern, chemical shift and carbonyl at 150 ppm, confirmed that the compound was tetraethyl carbamic anhydride. Adding carbamate salt all at once at –8 °C to methanesulfonic anhydride yielded only diethyl

methanesulfonamide. Clearly, different conditions were needed compared to alcohols, probably due to the more nucleophilic nature of the amines and hence higher reactivity with mesyl carbamate and methanesulfonic anhydride. Also, the possibility that the amine was acting as a base and decomposing the product could not be ruled out (see section 2.6.2) (scheme 2.20), as two reactions gave almost no organic product. Adding methanesulfonic anhydride instead to the carbamate anion produced mesyl carbamate **7**, the mixture of products increasing the warmer the addition temperature. Addition at -42 °C gave no product, the range of -20 to -25 °C being best over a few hours. Adding n-propanol gave a good yield of carbamate **6** (see section 3.1.2.3) and few by-products. This procedure was the one used for attempted dendron synthesis.
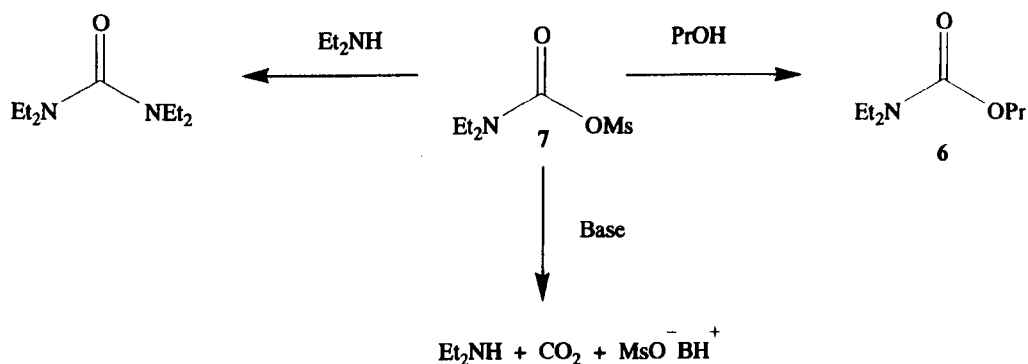
Scheme 2.20: Side reactions of N,N-diethyl mesyl carbamate

Change of solvent to toluene gave no product, whereas adapting a procedure for silylation of a carbamate anion[43] substituting methanesulfonic anhydride for TIPS and triethyl amine for DBU in dichloromethane, yielded mesyl carbamate but in worse yield compared to the carboxylation of alcohols.

Due to the mixtures of by-products using diethylamine, it was decided to follow the cleaner route of adding amines to mesyl carbonates for future carbamate synthesis.

2.6 Possible Mechanisms and Side Reactions

2.6.1 Introduction

The use of methanesulfonyl chloride as a mesylating reagent in the presence of base, usually a tertiary amine, frequently has a sulfene[79] cited as the active intermediate. The sulfene arises from base-induced attack on mesyl chloride to form a cumulene type compound, with a chloride ion as the leaving group (scheme 2.21).
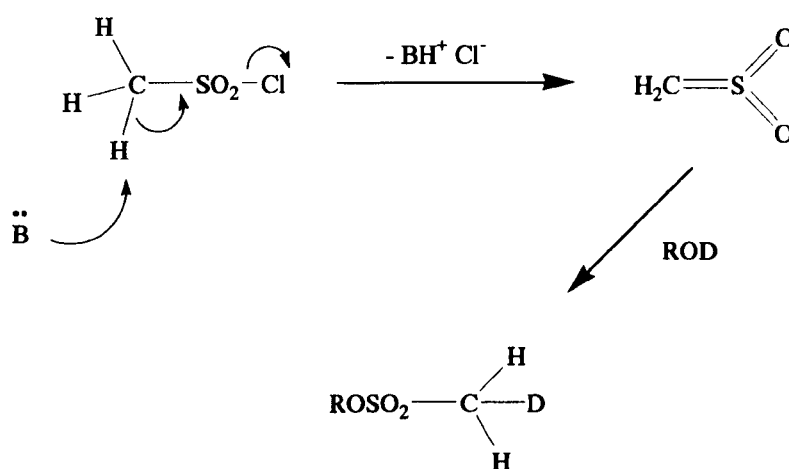
Scheme 2.21: Sulfene mechanism of sulfonation

Experiments with deuterated alcohols have given much support to this mechanism. The simple sulfene in this case is not isolable, being very reactive, but usually reacts as an electrophile with any nucleophile present. Methanesulfonic anhydride would be expected to react in a similar way as mesylates are better leaving groups than chlorides.[80]

2.6.2 Results and Discussion

Only once was the propyl carbonate salt added to a solution containing methanesulfonic anhydride and DBU. Addition of the base to mesyl anhydride solution was highly exothermic and reaction of carbonate anion gave low yield of mesyl carbonate, dicarbonate and mesylate.
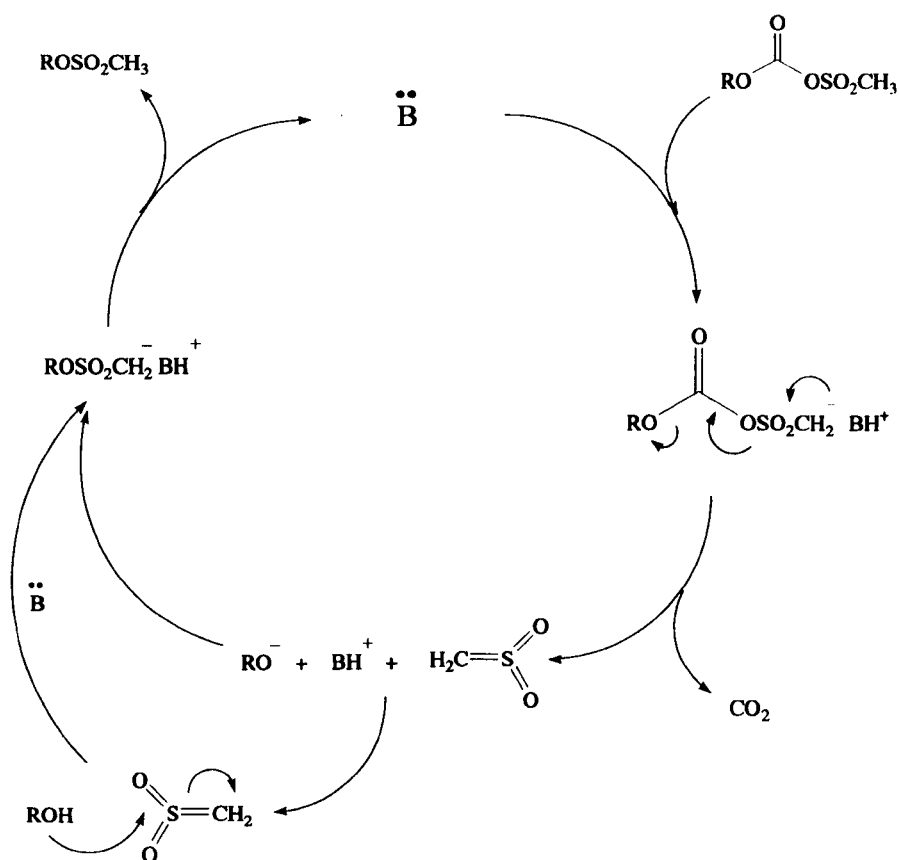
Scheme 2.22: Possible base catalysed decomposition of sulfonyl carbonates

Since bases react with mesyl compounds,[79, 80] it is also conceivable that base could react with mesyl carbonates. Alkoxide ion, carbon dioxide and sulfene would be the products and given the reactivity of sulfene, it is possible it reacts with alkoxide to produce the alkyl mesylate (scheme 2.22). This explanation would support observations of reactions that contain slight excesses of base only

yielding propyl mesylate after 48 hours at ambient temperature. If all the base is removed, mesyl carbonates still remain after 72 hours. Working on this premise, all reactions making and further reacting mesyl carbonates had amounts of base kept to a minimum.

It was thought that stoichiometric amounts of base would be needed to decompose mesyl carbonates, but only slight excess of strong base present in the reaction gave alkyl mesylates if the reaction was stirred for over two days. A couple of explanations were possible. The mesyl carbonate could decarboxylate at ambient temperature, analogously to 1,3-ketoacids. However, propyl mesyl carbonate seemed to be stable for at least a few days when isolated with varying ratios of propyl mesylate.

Another possibility was that base decomposition was actually catalytic. This hypothesis was supported when triethyl amine was added to an excess of benzyl mesyl carbonate. The singlets indicating an oxycarbonyl methylene group and a carbonyl mesylate had both disappeared completely. A new singlet indicative of either an alkyl mesylate or mesylate anion had appeared. Triethyl amine could have acted as a nucleophile on the mesyl carbonate, followed by dealkylation, but this would not explain complete absence of mesyl carbonate NMR signals as triethyl amine was the limiting reagent. To rule out nucleophilic attack, DBU was added to methyl mesyl carbonate. Both signals of this compound disappeared by the time a proton NMR experiment had taken place and two new singlets had appeared at 3.7 and 2.8 ppm. The latter signal is usually where mesylate ions are found in solution. Such a decomposition could be considered catalytic if the base is subsequently deprotonated by any alkoxide or alkyl

mesylate anion, as the pKa of alcohols (~16)[81] is higher than all bases used (12-13).[39]

2.7 Use of Other Sulfonating Reagents

2.7.1 Introduction

Methanesulfonic anhydride is more expensive per mole than other common sulfonating reagents. So different reagents[130] were used to determine whether similar results with respect to the synthesis of sulfonyl carbonates were possible. Also, it was hoped that if other types of sulfonyl carbonates could be made, their stability could be compared with a view to possible isolation and characterisation. The three sulfonating reagents used were: methanesulfonyl chloride as this would directly show whether leaving group attached to the sulfonyl moiety affected the rate of reaction or distribution of products; *p*-toluenesulfonyl chloride as it would not be susceptible to base effects since it has no α proton and so had the potential to be more stable; *p*-nitrobenzenesulfonyl chloride, because it would be a good comparison to *p*-toluenesulfonyl chloride and there was a likelihood the intermediate nosyl carbonate would be solid and hence easier to isolate.

2.7.2 Reaction of Propylcarbonate Anion with Methanesulfonyl Chloride
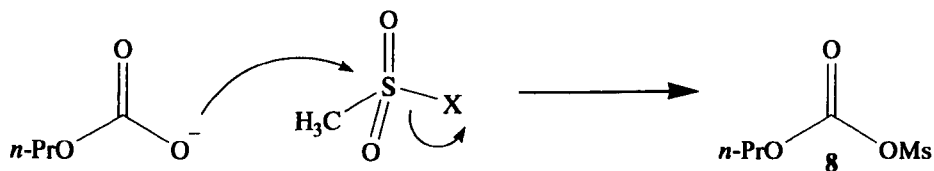
Scheme 2.23: Nucleophilic attack of mesylating reagents; X = Cl, OMs

Use of methanesulfonyl chloride subsequent to the carboxylation of n-propanol (scheme 2.23) gave n-propyl mesylate as the major product in two experiments. The insinuation is that direct nucleophilic attack on the sulfonating agent by the carbonate anion takes place as opposed to a sulfene mechanism,[79] and since a mesylate group is a better leaving group than a chloride ion, methanesulfonic anhydride is a better reagent than methanesulfonyl chloride. Formation of the reactive sulfene species by an E_2 mechanism cannot be ruled out, but it is more likely to form when excess or unreacted base is present. If sulfene formation occurs, it is likely to occur faster from methanesulfonic anhydride than methanesulfonyl chloride. The reaction would follow a nucleophilic addition pathway. If this is the case, the product distribution would not be expected to change with the different sulfonating reagents. However, the experimental evidence counters this view since n-propyl mesyl carbonate was the major product when methanesulfonic anhydride was used.

2.7.3 Reaction of n-Propylcarbonate Anion with p-Toluenesulfonyl Chloride
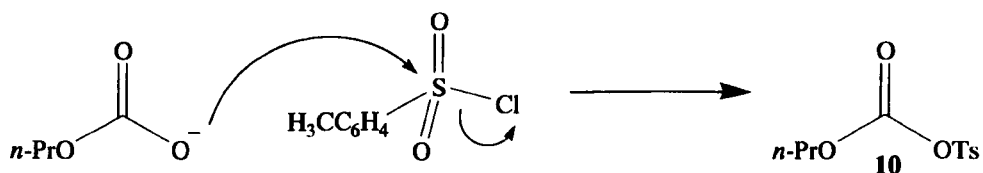
Scheme 2.24: Attempted synthesis of a p-tosyl carbonate

On substitution of methanesulfonic anhydride with p-toluenesulfonyl chloride (scheme 2.24), two compounds were isolated after the reaction on two occasions. One was p-toluenesulfonic acid and the other was dipropyl dicarbonate. No p-

toluenesulfonyl carbonate was isolated as confirmed by integration in the ^{1}H-NMR spectrum and long range proton-carbon correlation (HMBC) experiments. Just as no triflyl carbonates were detected because they reacted to form dicarbonates too quickly, so is the case using p-toluenesulfonyl chloride, but with cleaner products.

2.7.4 Reaction of Propylcarbonate Anion with p-Nitrobenzenesulfonyl Chloride
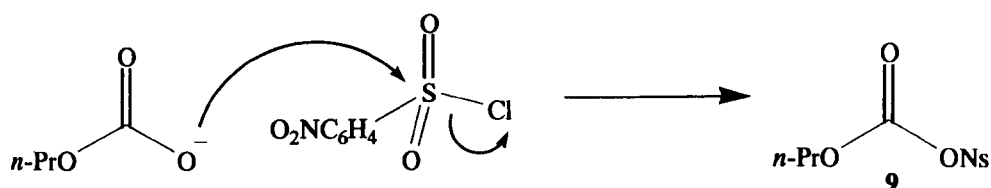
Scheme 2.25: Attempted synthesis of a p-nosyl carbonate

Both experiments involving the attempted nosylation of the n-propylcarbonate anion (scheme 2.25) yielded almost no n-propanol derived products on comparison of the p-nitrobenzenesulfonyl integration and chemical shifts of n-propyl type signals in the ^{1}H NMR spectra. These results would suggest that under the same conditions as used in the standard reaction, no nosylation was occurring, which could be due to a side reaction. This could arise from activation of the sulfonyl group by the nitroaromatic, making the reagent much more reactive than the analogous p-tosyl chloride.

2.7.5 Summary

Since the same conditions were maintained for the sulfonating reagents mentioned above as for methanesulfonic anhydride, these experiments

highlighted the fact that leaving group, the nature of the sulfonyl substituent and possibly steric bulk of the sulfonyl group affect the reaction of the carbonate anion. This is especially true of p-toluenesulfonyl chloride, which gave the dicarbonate product, compared to methanesulfonyl chloride which gave mainly n-propyl mesylate. The only difference between these two reagents is the bulk of the methylphenyl group compared to a methyl group. The unhindered nature of the charged oxygen atom in the carbonate ion in relation to n-propanol could explain why no n-propyl tosylate was observed.

CHAPTER 3 - REACTIONS OF METHANESULFONYL CARBAMATES AND METHANESULFONYL CARBONATES WITH NUCLEOPHILES

3.1 Synthesis of Carbamates

3.1.1 Introduction

The use of acyl mesylates[65-67] and sulfonyl carbonates[69, 70] as acyl chloride and chloroformate replacements (scheme 3.1) respectively is not unprecedented. There are a few reports of sulfonyl carbonates being synthesised and two examples of carbamate synthesis being further exhibited from such intermediates.[69, 70] However, the methods used to synthesise such molecules were either low yielding with a long reaction time or involved chloroformates. In the latter case, no synthetic advantage could be gained by this approach.
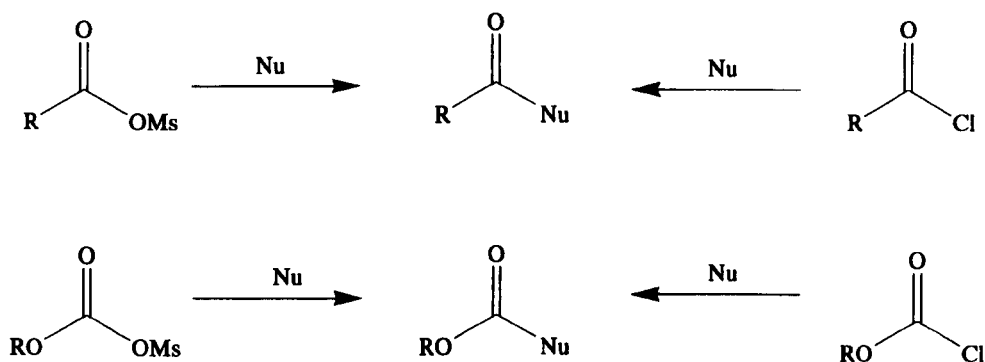
Scheme 3.1: Acyl mesylates and mesyl carbonates as acyl chloride and chloroformate analogues

Very similar compounds comprising of a sulfonyl group attached to an ester (alkoxycarbonyl sulfones)[82] have been made and one example shows their conversion to carbonates on addition of methanol (scheme 3.2). However, the products could not be isolated.
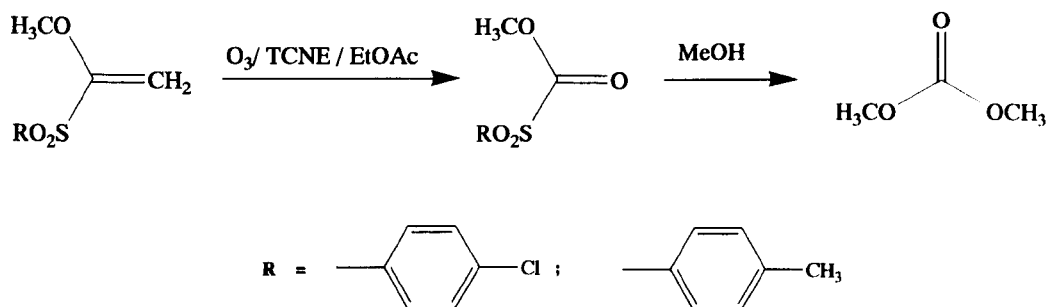
Scheme 3.2: Alkoxy carbonyl sulfones as precursors to carbonates

There are three examples in the literature of conversion of carboxylic acids to carboxylic mesylates followed by reaction with nucleophiles.[65-67] In one instance, the intermediates were reacted with amines and alcohols to form amides and esters respectively.[65] Carboxylic mesylates have even been cited in the synthesis of ceftazidime[66] where an acyl chloride procedure has been less successful. However, work by the group of Nicolaou[67] has suggested an alternative mechanism to acetylation of nucleophiles when fairly simple carboxylic acids are used (scheme 3.3). Instead of carboxylic mesylates being the active intermediate, this compound reacts very quickly with another carboxylic acid molecule to form the acid anhydride. It is contested that it is the anhydride that acylates, then the newly formed acid is sulfonated with remaining reagent and forms the anydride *in situ* again. However, if in their case the carboxylic acid is complex, for example a vancomycin derivative and very hindered, the anhydride is prevented from forming and the acyl mesylate is the active reagent. It is claimed that they could not synthesise acyl mesylates of simple carboxylic acids, such as cinnamic and benzoic acid. A similar observation has been reported when using TsCl.[83]

These precedents gave impetus to the method in principle, as both examples were not very structurally different to the molecules we intended to synthesise; mixed anhydrides of carboxylic and sulfonic acids in the former case,[65-67] carbonic and sulfinic acids in the latter.[82]
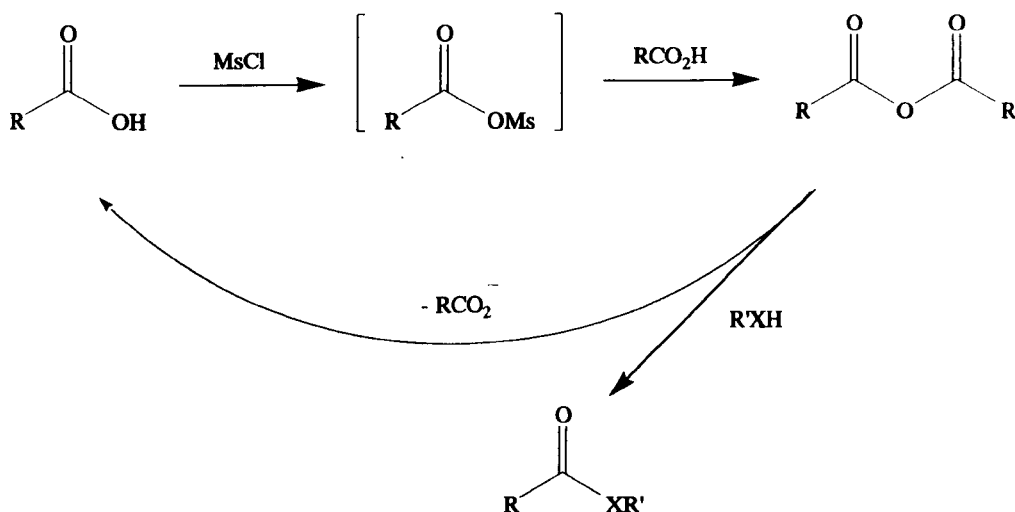
Scheme 3.3: Nicolaou's explanation of acylation using acyl mesylates

Some comparisons and contrasts can be made with our observation and that of Nicolaou's group. If methanesulfonic anhydride was added to alkyl carbonate anion over more than five minutes and allowed to react over more than one hour, not insubstantial amounts of dicarbonate was formed. This was especially true if less than 10% excess methanesulfonic anhydride was used or its concentration was less than 1.1 M. If alkyl carbonate anion was added to methanesulfonic anhydride, no dicarbonate was observed if either concentration of methanesulfonic anhydride was more than 2 M, or a two-fold excess was used.

It would be envisaged that methanesulfonyl carbonates would be less reactive than acyl mesylates, in the same way that chloroformates are less reactive than acyl chlorides, due to the lone pair of electrons on the saturated oxygen atom

increasing the electron density on the carbonyl group and decreasing its electrophilicity. Thus, this would explain the possibility of our observations and spectral evidence of mesyl carbonates without concurrently observing dicarbonates. Also, addition of excess amounts of the chosen nucleophile, for example an amine, would react with all unreacted Ms_2O which would prevent further reaction with unreacted carbonate anion.

If the propyl mesyl carbonate reaction mixture is left without addition of a nucleophile, dipropyl carbonate will form. Generally, the tendency for a carbonate to form in the reaction increases the more reactive the alcohol is. For example, using the same conditions to synthesise benzyl mesyl carbonate as for *n*-propyl mesyl carbonate, dibenzyl carbonate was present in a higher ratio compared to the main product. If addition of benzyl carbonate anion to methanesulfonic anhydride was carried out at –30 °C, then a much lower ratio of dibenzyl carbonate was formed.

We decided to start our investigation with carbamates as targets, since it had already been shown that their synthesis using carbon dioxide[20,29,36,38,48] was possible without elevated pressure, unlike the majority of work on carbonates. Carbamoyl chlorides can react with most alcohols, including aromatic ones, to form carbamates, so it made sense to adapt this methodology. As explained in Chapter 2, carboxylation of diethyl amine followed by further reaction yielded phenyl *N,N*-diethyl carbamate **1**. However, earlier work in our group showed the Monsanto procedure to be less versatile than we hoped. Carbamoyl chloride synthesis from more complex amines failed, either because the reaction was unsuccessful or because ureas formed as well as when using polyfunctional compounds (scheme 2.4).

Using our methodology, the generation of mesyl carbonates and mesyl carbamates would give simple precursors to carbonates and related compounds which usually require noxious reagents. The intention would be to extend the scope and versatility of the reaction so that various nucleophiles could be used to generate not just simple carbamates, but also di-substituted and branched products. This approach could lead to construction of molecules with a dendritic character that would be impossible to prepare by an isocyanate route.

3.1.2 Reaction of Alcohols with Sulfonyl Carbamates
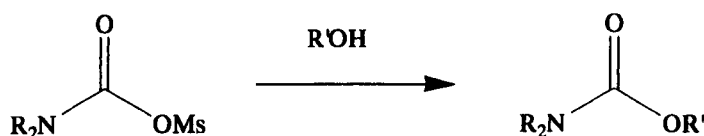
Scheme 3.4: Conversion of mesyl carbamates to carbamates

3.1.2.1 Introduction

In Chapter 2 it was reasoned that conversion of carbamate anions to sulfonyl carbamates should offer two advantages: firstly, the reaction is a simple substitution, unlike the rearrangement required with thionyl chloride which may require more forcing conditions; secondly, the sulfonyl carbamate products should be excellent electrophiles, allowing subsequent reactions to be carried out under milder conditions.

We had originally attempted to use triflyl carbamates **4**, but with little success. Following our work on carbonates, we now suspected that triflyl carbamates were too reactive. A second carbamate anion could react to form a carbamic anhydride and then react with phenol in an analogous way, halving any yields

(scheme 3.5). Hence, we decided to prepare and react methanesulfonyl carbamates 7.
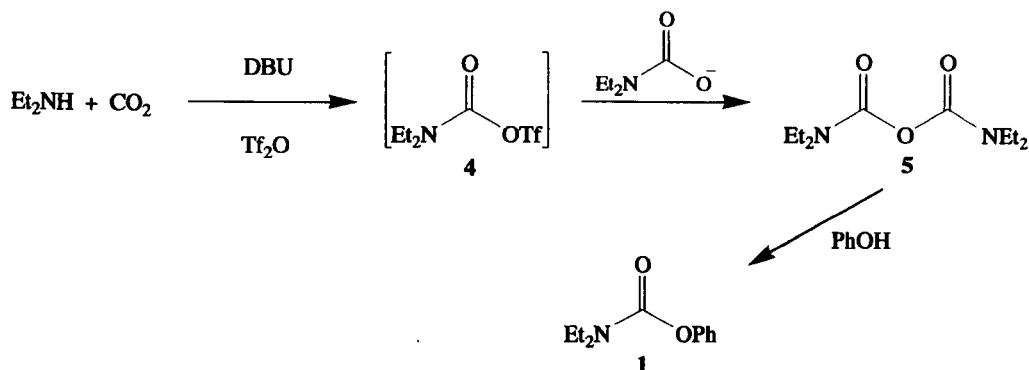
Scheme 3.5: Carbamates *via* carbamic anhydrides

3.1.2.2 Synthesis of Phenyl *N,N*-Diethyl Carbamate 1
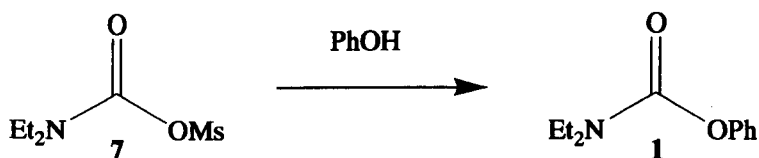
Scheme 3.6: Successful synthesis of phenyl *N,N*-diethyl carbamate

Adding a solution of mesyl anhydride to diethyl carbamate anion at reduced temperature and then reacting the mesyl carbamate *in situ* with phenol (scheme 3.6) at reflux temperature produced phenyl *N,N*-diethyl carbamate 1 at the first attempt in 21% yield (based on phenol), with only traces of by-products seen in the NMR spectrum. Analysis of the ^{1}H and ^{13}C NMR spectra of the intermediate gave support for the existence of mesyl carbamates. Two overlapping triplets at 1.21 ppm integrated in the ratio 3:2 with two identical overlapping multiplets at 3.35 ppm. A singlet at 3.42 ppm was in the ratio 1:2 with the signals that occurred where methyl groups would be expected to appear. This signal is about 0.5 ppm higher than where common methanesulfonyl signals would be apparent,

adding weight to the hypothesis of it being adjacent to a carbonyl group. The carbonyl signal in the ^{13}C NMR spectrum at 148 ppm was very low, indicative of either a carbamic anhydride or other carbamoyl group adjacent to an electronegative environment (such as carbamoyl chloride). The methylene signals were at a higher chemical shift than those seen for tetraethyl carbamic anhydride and rather than observing one signal due to symmetry, two signals were apparent (42.9 and 43.0 ppm). This would arise from restricted rotation due to delocalisation of the carbamoyl group, leading to inequivalent chemical shifts.

3.1.2.3 Synthesis of *n*-Propyl *N,N*-Diethyl Carbamate 6

Scheme 3.7: Successful synthesis of *n*-propyl *N,N*-diethyl carbamate
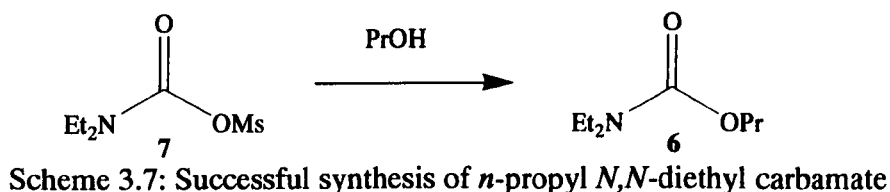
Deprotonated phenols are more nucleophilic than alcohols, so the scope of the reaction was tested by using *n*-propanol. On reaction with *N,N*-diethyl mesyl carbamate (generated *in situ* by addition of mesyl anhydride) propyl *N,N*-diethyl carbamate 6 was produced (scheme 3.7) as determined by analysis of NMR and mass spectra and comparison with published data.[54] The yield was in excess of 60% as judged by the ^{1}H NMR spectrum and the reaction was cleaner than observed on synthesis of the same product using triflic anhydride. It was clear that methanesulfonic anhydride was the reagent of choice for trapping carbamate anions and it had been shown that carbamates could be synthesised from the respective amine and alcohol, with CO_2 providing the carbonyl function.

Extending the addition time of methanesulfonic anhydride to the diethyl carbamate salt at –20 °C, followed by addition of *n*-propanol, gave no product within 16 hours as judged by tlc. However, addition of triethylamine and heating to reflux temperature, gave comparable yield to above within two hours with very little urea or sulfonamide. This procedure was the one that would be used for making branched carbamates (see Chapter 4).

3.1.3 Reaction of Amines with Mesyl Carbonates
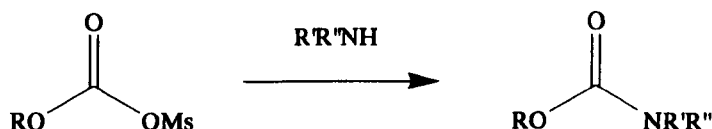
Scheme 3.8: Conversion of mesyl carbonates to carbamates

3.1.3.1 Synthesis of *n*-Propyl *N,N*-Diethyl Carbamate Under Pressure

By disconnecting *n*-propyl *N,N*-diethyl carbamate, it could be envisaged that an equally valid synthesis was to make *n*-propyl mesyl carbonate using carbon dioxide and react this compound further with diethyl amine. A solution of the alcohol and DBU was pressurised with carbon dioxide and reacted *in situ* with a solution of mesyl anhydride. An aliquot was removed and the remainder was reacted with diethylamine (scheme 3.8) so direct comparisons could be made between reactions before and after addition of a nucleophile, to observe if the intermediates were similar between mesylation of carbonate anion compared to carbamate anions.

The major product was *n*-propyl *N,N*-diethyl carbamate **6** in over 30% yield by ^{1}H NMR spectroscopy. A minor product was di-*n*-propyl carbonate **17**, which

was present in a 3:1 ratio with the major carbamate product The carbamate was identical to the one synthesised from diethylamine, carbon dioxide and *n*-propanol respectively.

Analysis of the removed aliquot indicated a mixture of two methanesulfonyl compounds, di-*n*-propyl carbonate **17** and di-*n*-propyl dicarbonate **3**.   On examination of the product from the reaction of *n*-propyl mesyl carbonate **8** with diethylamine, the major component was *n*-propyl *N,N*-diethyl carbamate, albeit in lower yield and with more impurities, (one of which was dipropyl carbonate) than the reaction of *n*-propanol with *N,N*-diethyl mesyl carbamate **7**.   On comparison with the reaction mixture from before the amine was added, it was clear that the unidentified product and *n*-propyl mesyl carbonate **8** had been consumed.   Column chromatography gave both di-*n*-propyl carbonate and *n*-propyl *N,N*-diethyl carbamate together.   Nevertheless, in principle the methodology had been proven.

3.1.4 Attempted Synthesis of Dicarbamates
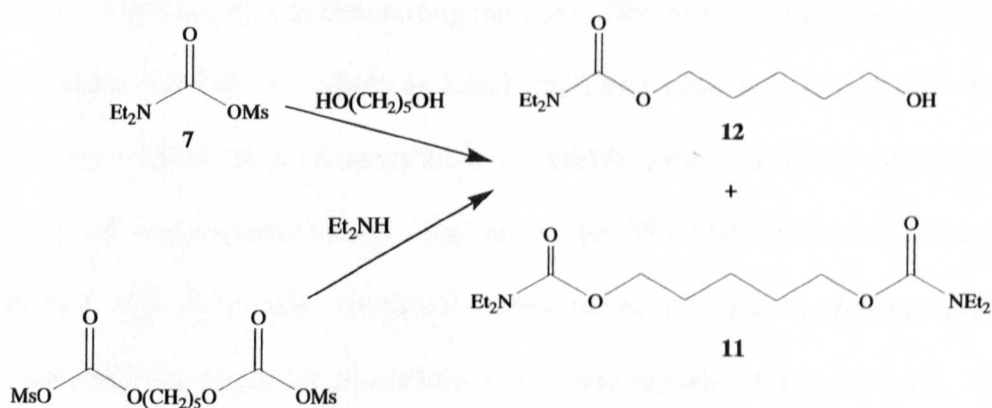
Scheme 3.9: Two attempted syntheses of dicarbamates

A previously attempted synthesis of the 1,5 dicarbamic ester **11** from the reaction of 1,5-pentanediol with *N,N*-diethyl mesyl carbamate occurred in very low yield and the product was not isolated, the mono substituted product **12** was the main isolated component as confirmed by NMR and mass spectral data. Amines are better nucleophiles than alcohols, so it was decided to synthesise a di-mesyl carbonate from 1,5-pentanediol and then addition of excess diethylamine would ensure some disubstituted product (scheme 3.9). Reduced yields were speculated to be due to diethylamine acting as a base, driving carbamate formation, as well as acting as a nucleophile. To overcome this, it was decided to use triethylamine as this was a strong enough base to deprotonate any intermediates. It was not known if pyridine was a strong enough base to drive the reaction to completion, so this was not considered in the first instance. After two days there was no change in the reactions by tlc. Substantial amounts of methanesulfonyl derived by-products were arising from the use of two equivalents of methanesulfonic anhydride, which hampered purification as the minority of the crude product was the required compound. A comparison between identical reactions was made, using 1,5-pentanediol as the starting material. One reaction used two equivalents of methanesulfonic anhydride as usual, the other used 1.2 equivalents. Using two equivalents of methanesulfonic anhydride produced more material than using 1.2 equivalents, though analysis of the ^{1}H-NMR of the two reactions showed that both had comparable conversions of diol to dicarbamate, by comparing the ratios of methylene and mesyl signals of the products. Less monocarbamic ester was produced using methanesulfonic anhydride in two-fold excess because the second hydroxy group had been mesylated. So, using less mesylating reagent and not more was shown to be more advantageous as the

product made up more than 50% of the material recovered by mass with less impurities. Purification led to mono and disubstituted carbamate esters **11** and **12**, confirmed by high resolution mass spectra, in 33% and 31% yield respectively. This result demonstrated good reproducibility of the above procedure making *n*-propyl *N,N*-diethyl carbamate from *n*-propanol just by bubbling carbon dioxide into the reaction.

Repeating the reaction with 1,5-pentanediol and a stoichiometric amount of triethyl amine in the carbamate forming reaction gave less dicarbamate ester and more mono-substituted product, again hinting that excess base could be detrimental to the mesyl carbonate intermediate.

Later work using bis(2-hydroxyethyl) 4-nitrobenzenesulfonamide **27** instead of 1,5-pentanediol (section 4.2.2), showed that side by side carbamate forming reactions comparing pyridine with triethylamine as the base, gave more of the desired product and less by-products using pyridine.

3.1.5 Synthesis of Carbamates Using *n*-Propyl Mesyl Carbonate 8

3.1.5.1 Introduction

Initally, *n*-propyl mesyl carbonate was formed using carbon dioxide under pressure, then split into three fractions after the pressure had been released. *n*-Propylamine and diethylamine were then reacted with equal fractions to see if there was any difference between the formation of carbamates derived from a primary amine against a secondary amine. *n*-Propanol was added to a third fraction as a standard.

O

PrNH₂

O   O

PrO   OMs   PrNH   OPr   +   PrO   OPr

8   17
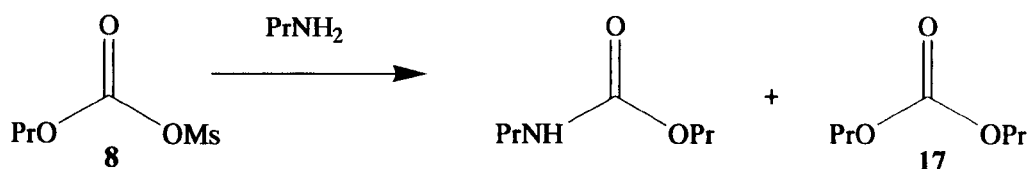
Scheme 3.10: *In situ* reaction of *n*-propyl mesyl carbonate with *n*-propylamine

The amines, which are better nucleophiles, gave mixtures of products. The reaction of diethylamine with *n*-propyl mesyl carbonate yielded the respective carbamate and diethyl methanesulfonamide as by-product. The reaction of *n*-propylamine had almost equal amounts of di-*n*-propyl carbonate and *n*-propyl *N*-*n*-propyl carbamate (scheme 3.10). This reaction gave less than 10% of the amount of organic material possible. Analysis of the aqueous layer showed that all organic products had been extracted, so incomplete conversion must be the answer. Directly comparing the control reaction of *n*-propanol to form di-*n*-propyl carbonate showed that much less of the carbonate had been made as by-product than was possible. A destructive side reaction must be occurring such that a secondary amine is less detrimental than a primary amine and alcohols not detrimental to the reaction at all. Both reactions were successful in so far as the respective carbamates were made, but both had di-*n*-propyl carbonate by-product, which it was not possible to remove, due to the similarity in polarity and boiling points of carbamates and carbonates.

One explanation is that propyl mesylate alkylated the propylcarbonate anion. Propyl mesyl carbonate and dipropyl dicarbonate both reacted with *n*-propanol to form dipropyl carbonate. In this way, all products of the mesylation step could react to form the symmetrical carbonate (scheme 3.11), although how much of a

contribution the alkylation route made compared to nucleophilic attack on the mesyl carbonate was not known.

Symmetrical carbonate formation had to be reduced as far as possible. As shown in Chapter 2, reactions did not have to be carried out using elevated pressure to form propyl mesyl carbonate in moderate yield or with good selectivity. Thus, using standard equipment it was possible to add the carbonate anion to mesyl anhydride under various conditions which prevented symmetrical carbonate formation.
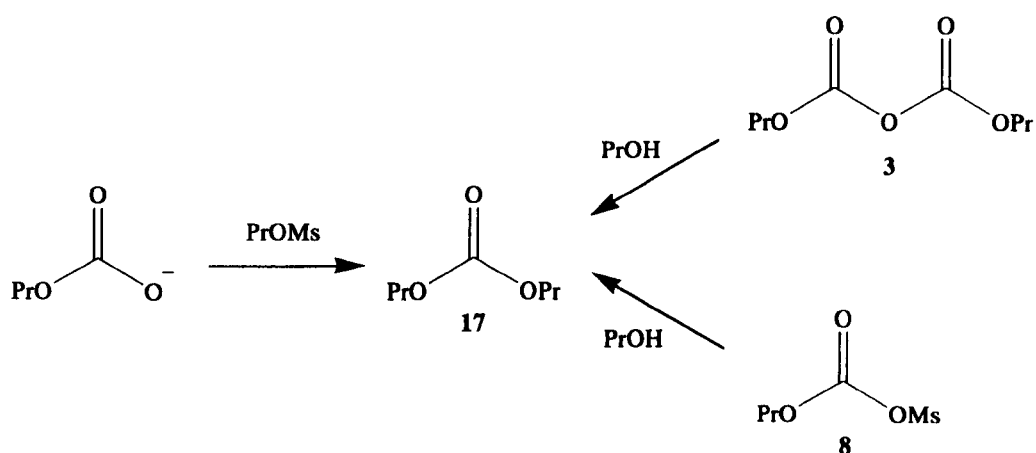
Scheme 3.11: Side reactions leading to dipropyl carbonate formation

Following the new procedure of generating n-propyl mesyl carbonate by bubbling carbon dioxide into an alcohol and DBU solution and adding the carbonate anion to mesyl anhydride, diethylamine was subsequently added at room temperature. Thin layer chromatography (tlc) after 20 hours showed no product, so a stoichiometric amount of pyridine was added. This would act as a base to drive the reaction but be sufficiently weak as to not decompose the n-propyl mesyl carbonate. After another 24 hours, n-propyl N,N-diethyl carbamate 6 had formed in 35% yield as judged by ^{1}H-NMR. However, an equal amount of

diethyl methanesulfonamide was also present. The reduced yield could be due to diethylamine also acting as a base, decomposing the mesyl carbonate intermediate (section 2.6.2), or concurrently acting as a base in promoting sulfonamide formation.

Work described in section 3.1.4 meant that all subsequent reactions used only 1.2 equivalents of methanesulfonic anhydride and pyridine as the base in reactions of mesyl carbonates. Analogously to reactions of acid anhydrides and chloroformates, pyridine presumably increased the reaction rate by acting as a nucleophile with the mesyl carbonate (scheme 3.12) and generating a more reactive intermediate *in situ*. Rapid displacement of the pyridinium ion leaves the protonated product which is deprotonated by pyridine. Usually when acylating-type reagents are used with alcohols, pyridine is also used.[80] Due to the supposition that mesyl carbonates were base sensitive, it was decided to use pyridine when amines were used as nucleophiles also.
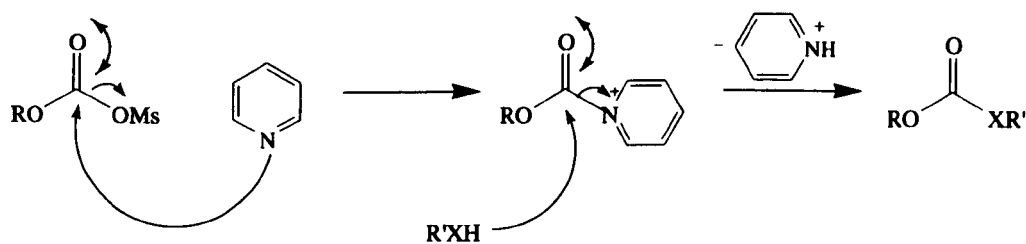
Scheme 3.12: Pyridine promoted reaction of mesyl carbonates

3.1.5.2 Synthesis of *n*-Propyl *N*-*n*-Butyl Carbamate 13
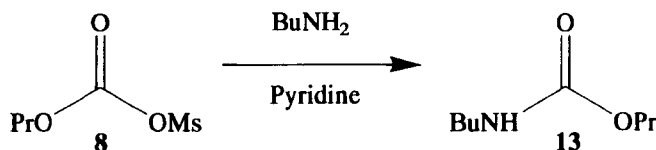
Scheme 3.13: Synthesis of *n*-propyl *N*-*n*-butyl carbamate

Generating *n*-propyl mesyl carbonate with carbon dioxide and 1.2 equivalents methanesulfonic anhydride, followed by addition of *n*-butylamine and a stoichiometric amount of pyridine gave *n*-propyl *N*-*n*-butyl carbamate **13** in 42% yield (scheme 3.13) after flash chromatography. The estimated crude yield from comparison of ^{1}H-NMR signals of all products was about 44%, which is in the right region of conversion that had been observed when making mesyl carbonate from *n*-propanol. The implication is that the conversion of mesyl carbonate to carbamate is very nearly quantitative.

3.1.5.3 Synthesis of Benzyl *N*-Phenyl Carbamate 14
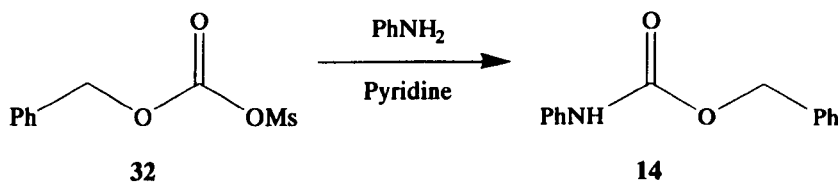
Scheme 3.14: Synthesis of benzyl *N*-phenyl carbamate

That conversion of mesyl carbonate to carbamate is quantitative is supported by the formation and reaction of benzyl mesyl carbonate with excess aniline (scheme 3.14). Analysis of the crude product by ^{1}H-NMR spectroscopy and tlc

indicated only three compounds; benzyl *N*-phenyl carbamate **14**, phenyl methanesulfonamide and benzyl alcohol. As for **13**, flash chromatography gave the required product in 43% yield. In theory, this still leaves more than 0.5 equivalents of aniline, which easily reacts with the slight excess of methanesulfonic anhydride, to form the methanesulfonamide as confirmed by the ^{1}H-NMR spectrum after isolation from the chromatographic column. The lack of other benzyl derived compounds, including benzyl mesylate, cannot be explained. Concurrent reaction of benzyl mesyl carbonate with phenol and *n*-propanol (see section 3.2.3.2) did contain dibenzyl carbonate in both cases and a small amount of benzyl mesylate in the latter reaction.

3.1.5.4 Synthesis of *n*-Propyl *N*-Phenyl Carbamate 15
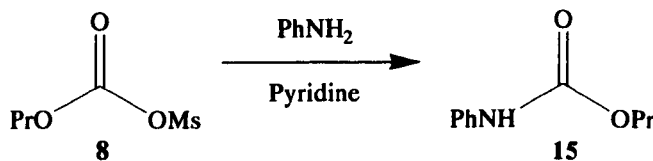
Scheme 3.15: Synthesis of *n*-propyl *N*-phenyl carbamate

The reaction of aniline with *n*-propyl mesyl carbonate (scheme 3.15) was successful but results were mixed. The reaction was carried out twice under similar conditions, the only difference being the amount of DBU used. The first time the reaction was carried out, 1.14 equivalents of DBU was used to assist carboxylation of *n*-propanol, resulting in 38% yield as calculated from the ^{1}H-NMR spectrum of *n*-propyl *N*-phenyl carbamate **15** after addition of aniline. After purification and crystallisation, the final yield had fallen to 21% due to removal of phenyl sulfonamide impurity by crystallisation, which had persisted

after chromatography. Repetition of the reaction but using a stoichiometric amount of DBU with *n*-propanol gave a crude yield of 68%, but with more sulfonamide impurity and less *n*-propyl mesylate. This observation adds more weight to the hypothesis of decomposition of mesyl carbonates by base. Excess strong base seems to be detrimental to the reaction.

In both reactions, aniline was added first, followed by pyridine. In both cases, after aniline addition, the reactions were noted to be very exothermic and required cooling in an ice bath. The reactions also became extremely viscous, to the extent of a gel-like state and stirring became difficult. Addition of more solvent and reaction overnight gave rise to a solution again with a precipitate present. This consisted of mesylate salts and was filtered and washed to remove any adsorbed products.

3.1.5.5 Synthesis of Benzyl *N-n*-Propyl Carbamate 16
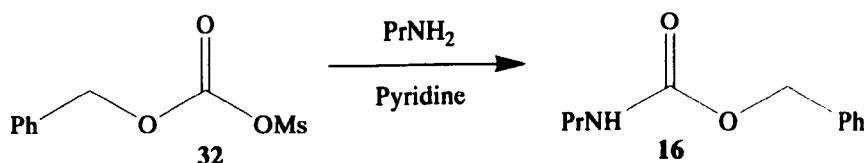
Scheme 3.16: Synthesis of benzyl *N-n*-propyl carbamate

The first attempt at the reaction of *n*-propylamine with benzyl mesyl carbonate (scheme 3.16) was successful but the yield by NMR spectroscopy of 18% was much lower than usual. This was judged to be due to the storage of the mesyl carbonate intermediate in a freezer at −30 °C not being sufficiently cold to prevent gradual decomposition. Surprisingly, there was no benzyl mesylate formed in this reaction, only *n*-propyl methanesulfonamide and unreacted benzyl

alcohol. Repetition of the reaction with immediate addition of *n*-propylamine and pyridine on formation of benzyl mesyl carbonate gave about a 39% yield after 45 minutes as judged by the ^{1}H NMR spectrum. This time the yield was higher, but benzyl mesylate and dibenzyl ether had formed, the latter compound confirmed by comparison with authentic material. No adequate resolution could be achieved by thin layer chromatography. Attempts to crystallise the material were mixed. Formation of two layers was achieved on heating the oil in hexane. Residue that did not dissolve in hot hexane still contained benzyl *N-n*-propyl carbamate and *n*-propyl methanesulfonamide, but much less benzyl alcohol. On cooling of the hexane layer, a white precipitate appeared. On analysis by ^{1}H NMR and high resolution mass spectroscopy, benzyl *N-n*-propyl carbamate was still the major component with less *n*-propyl methanesulfonamide but more benzyl derived products. This was also confirmed in the ^{13}C NMR spectra but no more resources could be dedicated to finding an alternative recrystallisation procedure.

3.1.6 Summary of Carbamate Synthesis

An unambiguous synthesis of carbamates from carbon dioxide, the first to use *either* amines or alcohols as starting materials has been demonstrated. This method does not use phosgene or use isocyanates as intermediates nor does the mechanism involve nucleophilic attack of the carbon dioxide adduct, that is formation of carbamates by alkylation of the carbamate anion. Evidence for this comes from the use of amines and phenol as nucleophiles, which under the reaction conditions, cannot act as or be converted to electrophiles capable of reacting by a S_N2 mechanism.

Yields of carbamates were typically between 20-45%, lower yields occurring in cases where there was a purification problem. This was usually due to sulfonamide impurities which arose from the reaction of excess methanesulfonic anhydride with excess amine. If decomposition of mesyl carbonate intermediates was occurring, sulfenes could be generated which would increase the likelihood of mesylation of substrated occurring and hence, increasing impurity levels.

3.2 Synthesis of Carbonates

3.2.1 Introduction

Since conditions had been optimised for the synthesis of propyl methanesulfonyl carbonate, we decided to investigate the reactions of this type of compound as it was a suitable precursor to carbonates and their derivatives. It was not known at this time whether synthesis of unsymmetrical carbonates was possible without also forming the symmetrical compound as a by-product. It was already known that to make any use of *n*-propyl mesyl carbonate, it had to be reacted with a nucleophile within 48 hours if kept under reaction conditions, as after this time only propyl mesylate remained (see Chapter 2).

The next stage of development was to find conditions for the synthesis of carbonates by subsequently adding an alcohol to the mesyl carbonates. The majority of reactions were carried out using DBU and *n*-propanol in acetonitrile. Initially, reactions were carried out under 3.5 bar of carbon dioxide to generate the mesyl carbonate, the second stage of the reaction to make carbonates was carried out at atmospheric pressure.

3.2.2 Synthesis of Unsymmetrical Carbonates

3.2.2.1 Development from Symmetrical Carbonate Synthesis – Unsuccessful Attempts
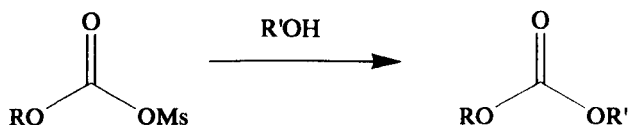
Scheme 3.17: Attempted unsymmetrical carbonate synthesis

Adding mesyl anhydride to *n*-propanol and DBU pressurised with carbon dioxide, followed by an excess of more *n*-propanol reacted at reflux temperature for 3 days, led to dipropyl carbonate **17** in 36% yield with no other products present in the gas chromatogram or ^{1}H NMR spectrum. Following the same procedure it was envisaged that adding a different alcohol should yield an unsymmetrical carbonate (scheme 3.17), as should reacting a different alcohol with carbon dioxide.

By generating substantial amounts of *n*-propyl methanesulfonyl carbonate, improvement of conditions needed for subsequent nucleophilic attack on the carbonyl compound could be accelerated by splitting the mixture and using different nucleophiles on each aliquot. In this way direct comparisons could be made between each nucleophile on the activated carbonyl compound.

The previous experiment was repeated, pressurising *n*-propanol with carbon dioxide, but three different alcohols were added to the reaction, once it had been split into three aliquots, to directly compare the reactivity of a primary alcohol (*n*-propanol), a secondary alcohol (*i*-propanol) and benzyl alcohol (scheme 3.18). Barely any organic material was recovered from the reaction of *n*-propanol. *i*-

Propanol barely reacted, the major product was di-n-propyl carbonate with only a trace amount of the unsymmetrical carbonate.

Benzyl n-propyl carbonate was made, but due to the large excess of benzyl alcohol remaining, the material was lost on attempts at purification.

On another attempt with faster addition of methanesulfonic anhydride to n-propyl carbonate anion, results were better, but still not useful. Di-n-propyl carbonate formed, but whether this was due to added n-propanol or it had formed *in situ* was not known. i-Propanol yielded equal amounts of n-propyl-i-propyl carbonate[129] and di-n-propyl carbonate, the isomers being inseparable. Benzyl n-propyl carbonate had no other carbonates present, but again, excess benzyl alcohol could not be completely removed.

Generally reactions using i-propanol were worse compared to n-propanol. i-Propanol gave mixtures following the carboxylating and mesylating procedure as for n-propanol. On addition of n-propanol to the reaction mixture, the unsymmetrical carbonate was produced but in the same ratio as i-propyl mesylate and a small amount of di-n-propyl carbonate, which could not be separated.

Formation of di – i-propyl carbonate was poor, yielding i-propyl mesylate and i-propyl carbonate in less than 2% yield by NMR. Adding benzyl alcohol to a similar aliquot did give benzyl i-propyl carbonate, but over three-quarters of recovered material was benzyl alcohol, which would not have been a useful general procedure to adopt.
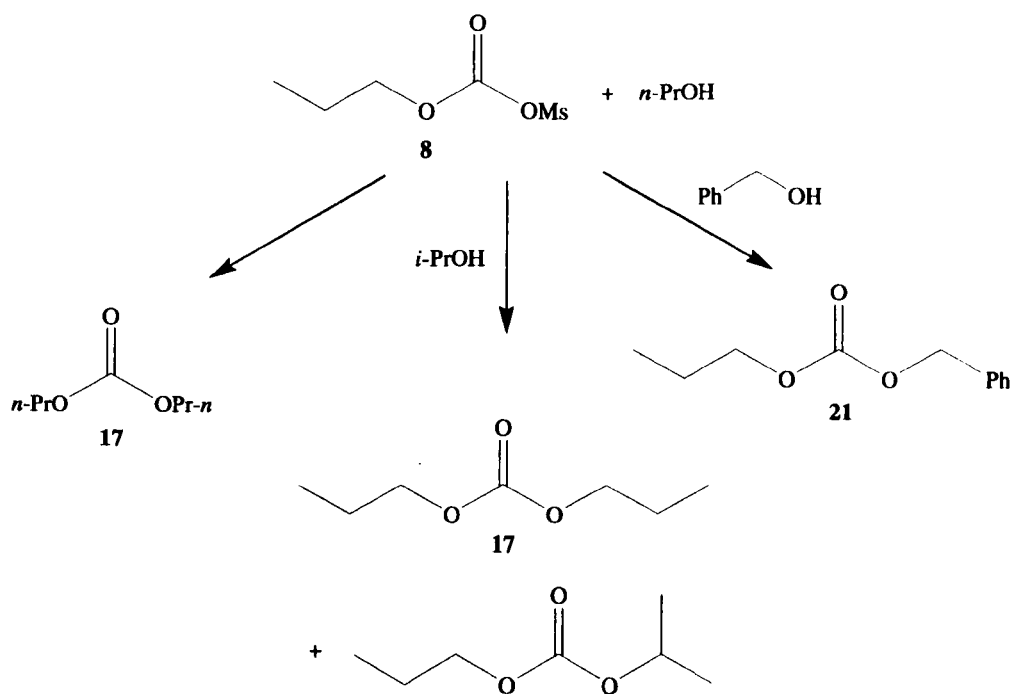
Scheme 3.18: Initial results of unsymmetrical carbonate formation

Attempts at unsymmetrical carbonate formation (using *n*-propanol, *i*-propanol and benzyl alcohol) gave mixed results. Either the symmetrical carbonate formed or as a mixture with the required product making isolation of the pure required product difficult. Reaction of benzyl alcohol was good but there was a trace amount of dibenzyl carbonate[30,87] and so much benzyl alcohol as to give <10% yield after isolation and not enough material for microanalysis.

3.2.2.2 Optimisation of Di-*n*-Propyl Carbonate Synthesis

It was decided to focus on optimising the conditions for the synthesis of di-*n*-propylcarbonate, as it was easily identified by spectroscopy and distinguishable from by-products, which it was hoped, would speed up optimisation. The first reaction of *n*-propanol and DBU pressurised with carbon dioxide followed by

addition of methanesulfonic anhydride and a second amount of *n*-propanol gave dipropyl carbonate and propyl mesylate in 26% and 13% yield respectively. However, even though the reaction worked in low yield, it was noticed that using bubbling carbon dioxide and no further addition of *n*-propanol still yielded dipropyl carbonate. The indication was that not all the *n*-propanol was being carboxylated and furthermore, propyl mesyl carbonate was being consumed as it was being synthesised. Further attempts at carbonate synthesis were halted until the procedure for propyl mesyl carbonate formation had been optimised. Otherwise, all attempts at unsymmetrical carbonate synthesis would have symmetrical carbonate contaminating the product.

It was decided to follow the procedure which gave the minimum amount of by-products (Table 2.1, entry 11), balanced with the highest yield of mesyl carbonate. Then, alcohols could be added under a variety of conditions to see what the best method for carbonate synthesis from mesyl carbonates was.

As a comparison reaction, *n*-propyl mesylate was synthesised and isolated, then later slowly added to an excess of preformed *n*-propyl carbonate salt in acetonitrile in a cold bath. Di-*n*-propyl carbonate was produced in 51% yield, in unoptimised conditions. Unlike the Monsanto procedure, where pressure and heat were required using alkyl chlorides as electrophiles,[55] alkyl mesylates did not need either. This result would go some way to explaining earlier mixtures of symmetrical and unsymmetrical carbonates.

3.2.2.3 Attempted Synthesis of Tertiary Carbonates

As the stability of the mesyl carbonates was still speculative, initial experiments that used *t*-butanol were carried out without base. After two hours *n*-propyl

mesyl carbonate was still the major component in the reaction. So, 10 mol% 4-dimethylamino pyridine (DMAP) was added to the reaction and it was heated to 40 °C. After 3 days, *t*-butanol still hadn't reacted, the only change being the increase of *n*-propyl mesylate in relation to *n*-propyl mesyl carbonate.
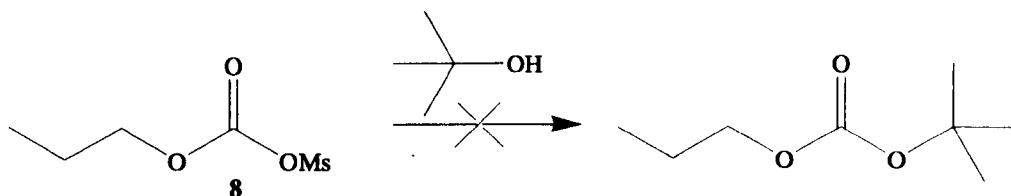
Scheme 3.19: Unsuccessful conversion to tertiary carbonates

The experiment was repeated but the carbonate anion transfer time was decreased from 2 hours to 30 minutes and no DMAP was added. Again *t*-butanol still had not reacted after 3 days (scheme 3.19), the major product being *n*-propyl mesylate with minor products of dipropyl carbonate, dicarbonate and some residual mesyl carbonate. Since it was likely that the steric bulk of the *t*-butyl group was responsible for no reaction occurring with propyl mesyl carbonate, the same reasoning suggests that *t*-butanol shouldn't yield *t*-butyl mesylate with methanesulfonic anhydride[81] but, the less sterically encumbered *t*-butyl carbonate anion should have no difficulty in being mesylated. Also, *t*-butanol should be a better nucleophile with carbon dioxide than *n*-propanol. However, on reaction of *t*-butanol with carbon dioxide and methanesulfonic anydride, almost no organic product was recovered. Repetition of the reaction, followed by addition of *n*-propanol gave propyl mesylate and *t*-butanol only. In light of these results it was decided to concentrate on primary and secondary alcohols only.

3.2.2.4 Synthesis of Aromatic Carbonates – Phenyl *n*-Propyl Carbonate 18
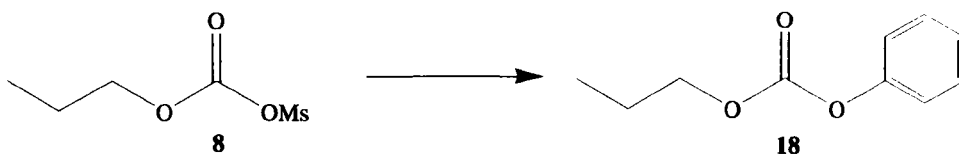
Scheme 3.20: Synthesis of phenyl *n*-propyl carbonate

Under identical conditions to the reactions using *t*-butanol, phenol had reacted with *n*-propyl mesyl carbonate successfully to yield the required carbonate **18** (scheme 3.20). By inspection of the proton NMR, there was less phenyl propyl carbonate than *n*-propyl mesylate, which was contrary to the results that had been observed developing the reaction thus far.

By decreasing the transfer time of the carbonate anion, after further reaction for 22 hours at 40 °C, phenyl propyl carbonate **18** was the major product in 35% yield. No mesyl carbonate remaining as judged by absence of a singlet at 3.4 ppm in the ^{1}H NMR spectrum. Doing the same experiment at 50 °C for 20 hours gave *n*-propyl mesylate as 90% of the product as determined by ^{1}H NMR spectroscopy.

### 3.2.3 Development of the Reaction of Alcohols with *n*-Propyl Mesyl Carbonate 8

All reactions that involved the synthesis of *n*-propyl mesyl carbonate, followed by attempted carbonate formation with benzyl alcohol or *i*-propanol, following the same procedure as for phenyl *n*-propyl carbonate, failed to give the unsymmetrical carbonate as the major product in any instance. The highest yield

was ~ 8% of benzyl *n*-propyl carbonate along with di-*n*-propyl carbonate, which was inseparable

The probable reason for low yields and mixtures were either no added base to drive the reaction or not enough alcohol was being added to react with all mesylate compounds (it was assumed, incorrectly, that the mesyl carbonate would be more reactive than the mesyl anhydride). The excess of methanesulfonic anhydride was leading to large amounts of alkyl mesylates of both the starting alcohol and added alcohol which was reducing carbonate formation. Mesylation of the added alcohol seemed to be occurring to a greater extent than the carbonate forming reaction even though no extra base was being added.

The reactions of *n*-propyl mesyl carbonate with *i*-propanol and benzyl alcohol were repeated but 10 mol% DMAP was added since its participation in acetylation reactions is well documented,[88] but gave no advantage in carbonate formation. Adding excess benzyl alcohol and *i*-propanol with stoichiometric amounts of triethyl amine did produce small quantities of benzyl propyl carbonate (typically less than 5%), but no *i*-propanol derived carbonates.
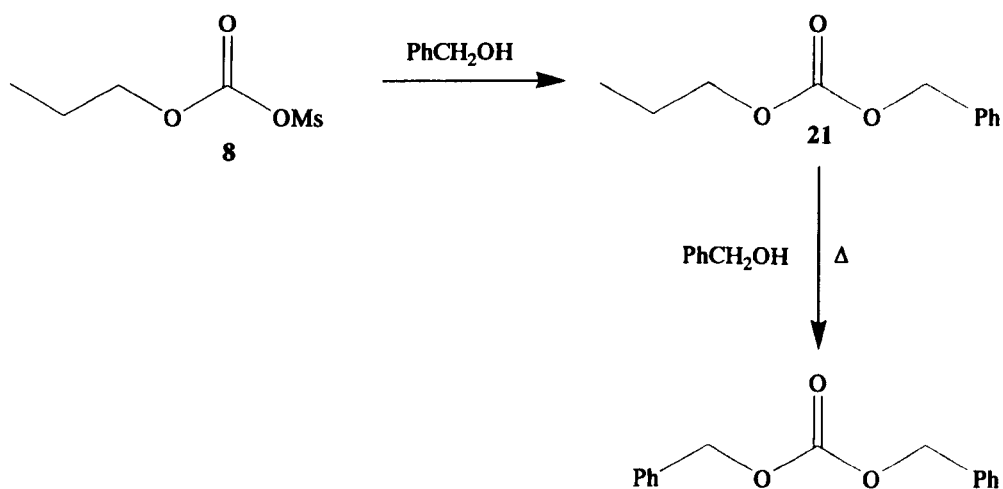
Scheme 3.21: Side reaction of dibenzyl carbonate formation

The problem with the synthesis of benzyl *n*-propyl carbonate was that small amounts of dibenzyl carbonate were being produced also, probably due to the large excess of benzyl alcohol used and the heating of the reaction (scheme 3.21). Flash chromatography isolated the two compounds together (due to almost identical polarity), but the low recovery ruled out further purification by vacuum distillation, as the two carbonates have very similar boiling points.

A satisfactory method for carbonate synthesis still had not materialised due to low yield and many by-products. Mesylate by-products were easily separated by chromatography but carbonate by-products were not. Similarly, the reaction of *i*-propanol with *n*-propyl mesyl carbonate gave the inseparable mixture of di-*n*-propyl carbonate and the isomeric *n*-propyl-*i*-propyl carbonate. Still, it had been shown that base definitely led to an improvement in the reaction.

### 3.2.3.1 Reactions of Benzyl Mesyl Carbonate 32

Initial reactions of benzyl alcohol with carbon dioxide fared the same as for *n*-propyl mesyl carbonate. In the absence of base, no benzyl phenyl carbonate was synthesised after addition of phenol, the main products were dibenzyl dicarbonate, inferred from the ^{13}C NMR spectrum, and benzyl mesylate. Using *n*-propanol as a nucleophile on the supposed benzyl mesyl carbonate gave no carboxylated products at all. Adding 10 mol% DMAP gave little improvement. Only when the reaction was done with triethylamine as a base after the second alcohol was added, was a difference made. However, less than 5% benzyl propyl carbonate was produced from analysis of the ^{1}H NMR spectrum. In the presence of base, phenol proved to be the better nucleophile as expected, yielding benzyl

phenyl carbonate along with dibenzyl carbonate. Repeated chromatography could not separate these two compounds.

3.2.3.2 Reactions of *i*-Propyl Mesyl Carbonate 33

Reactions making *i*-propyl mesyl carbonate suffered similar problems. *n*-Propanol and phenol did not react with *i*-propyl mesyl carbonate in the absence of base, the only products were mesylates of the alcohols. Using pyridine improved conversion to benzyl *i*-propyl carbonate on reaction with benzyl alcohol, but dibenzyl ether could not be separated from the product. Reaction of phenol with *i*-propyl mesyl carbonate gave no required products either at room temperature or at reflux temperature.

The approach of using the less nucleophilic alcohol as the reactant with carbon dioxide was also successful using *i*-propanol to yield benzyl *i*-propyl carbonate **19** (scheme 3.22), with very little di-*i*-propyl carbonate and no dibenzyl carbonate.
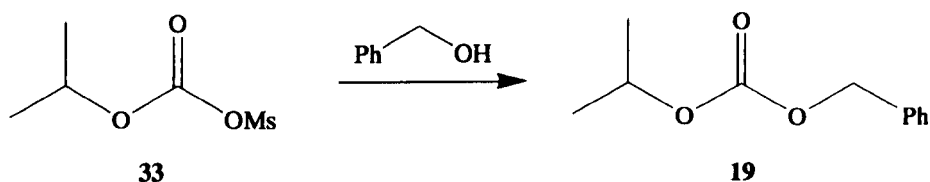
Scheme 3.22: Synthesis of benzyl *i*-propyl carbonate

The nature of the benzyl derived products, viscous oils, made isolation in sufficient quantities for full characterisation impossible due to poor yields after two chromatographic separations trying to remove dibenzyl ether.

3.2.4 Improved Synthesis of Unsymmetrical Carbonates

3.2.4.1 Introduction

It was observed from carbamate synthesis that in side-by-side reactions of mesyl carbonates, using triethylamine in one reaction and pyridine in the other, that pyridine gave the cleaner reaction. It was decided that after adding the second alcohol to the mesyl carbonate, pyridine would be added and the reaction would not be heated at all.

3.2.4.2 Reactions of Benzyl Mesyl Carbonate 32
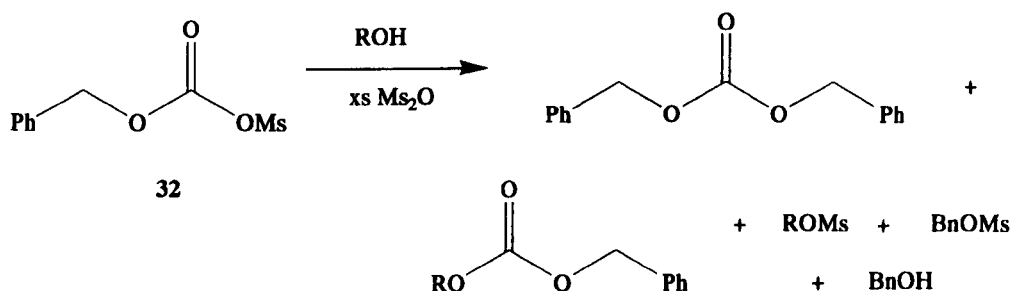
Scheme 3.23: Synthesis and reaction of benzyl mesyl carbonate using excess Ms$_2$O

Using benzyl alcohol as the substrate to react with carbon dioxide, benzyl mesyl carbonate was generated using 1.8 equivalents of methanesulfonic anhydride and was added to *n*-propanol, *i*-propanol and phenol. All reactions gave the respective unsymmetrical carbonates, but also mesylates of both alcohols in each reaction, dibenzyl carbonate and residual benzyl alcohol (scheme 3.23). Attempts to separate the carbonates always gave some dibenzyl carbonate remaining in the product. Nevertheless, the reaction using pyridine at no higher

than room temperature had shown promise. However, even when a four-fold excess of *n*-propanol was added, dibenzyl carbonate persisted as a by-product. It was not possible to isolate pure benzyl *n*-propyl carbonate as repeated chromatography proved futile. The purest fraction obtained still contained about 10% dibenzyl carbonate as judged by the ^{1}H NMR spectrum.

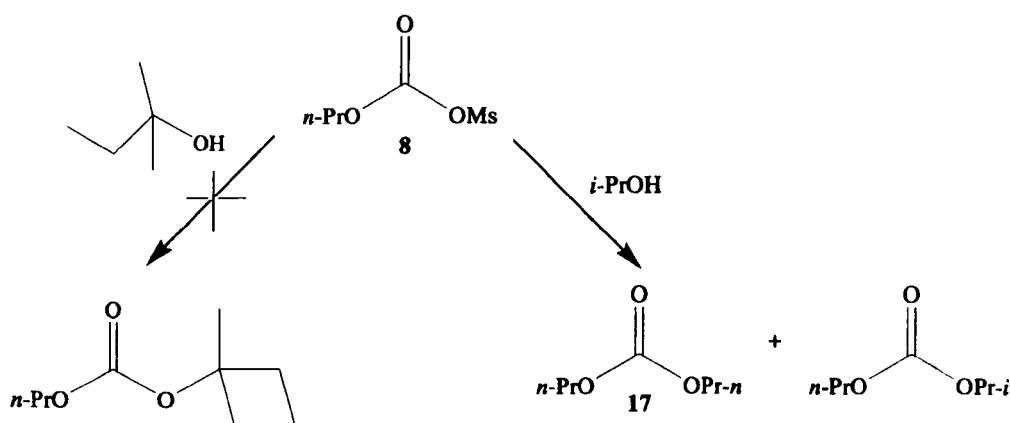### 3.2.4.2.1 Synthesis of Benzyl Phenyl Carbonate 20
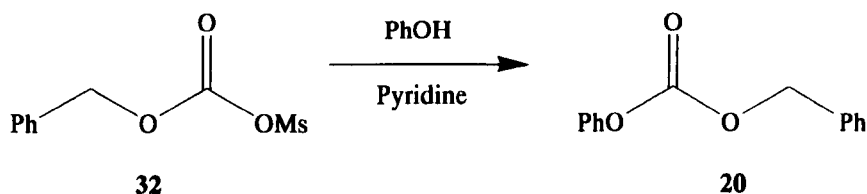
Scheme 3.24: Synthesis of benzyl phenyl carbonate

Repeating the reaction using only 1.2 equivalents of methanesulfonic anhydride, but at higher concentration, at −30 °C followed by addition of phenol and *n*-propanol to equal aliquots seemed to reduce a lot of negative factors. The cooler transfer temperature limited dibenzyl carbonate formation in between finishing carbonate anion transfer and adding the second alcohol. Less methanesulfonic anhydride reduced the yields of mesylates, thus making the crude product easier to isolate by flash chromatography, as a higher proportion of loaded material would be product. Indeed, benzyl phenyl carbonate **20** was isolated and fully characterised in 25% yield (scheme 3.24). Some remaining product was not isolated due to the extremely similar polarity to dibenzyl carbonate.
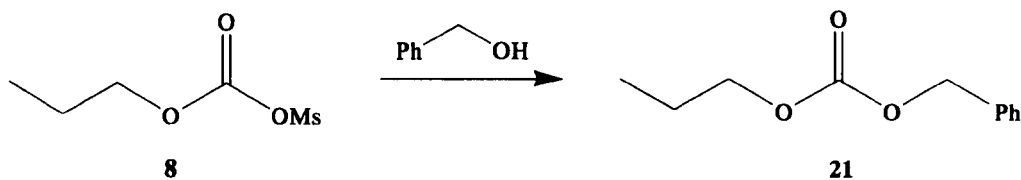
3.2.4.3 Reactions of *n*-Propyl Mesyl Carbonate 8

Using a method that seemed to give good results, the synthesis of *i*-propyl-*n*-propyl carbonate was attempted. However, even when a four fold excess of *i*-propanol was used, a mixture of the symmetrical and unsymmetrical carbonates was produced. Tertiary alcohols still did not react with *n*-propyl mesyl carbonate. Addition of amyl alcohol gave no amyl derived products. Only di-*n*-propyl carbonate and *n*-propyl mesylate were observed (scheme 3.25).

Scheme 3.25: Reaction of amyl alcohol with *n*-propyl mesyl carbonate

3.2.4.3.1 Synthesis of Benzyl *n*-Propyl Carbonate 21

Scheme 3.26: Synthesis of benzyl *n*-propyl carbonate

Since benzyl alcohol tended to react with benzyl mesyl carbonate when generated *in situ* unless a more nucleophilic substrate was added to the reaction, the logical conclusion was to react the less nucleophilic alcohol with carbon dioxide and add benzyl alcohol to the mesyl carbonate. When *n*-propyl mesyl carbonate was prepared and reacted, benzyl *n*-propyl carbonate **21** was the major product (scheme 3.26) along with residual benzyl alcohol. Some dipropyl carbonate was present but the product was easily separated by flash chromatography in 28% yield and in more than 99% purity.

3.2.4.4 Reaction of Methyl Mesyl Carbonate 22

3.2.4.4.1 Introduction

Since methyl phenyl carbonate has been cited as an alternative to phosgene derived reagents,[89] it was decided to attempt its synthesis from carbon dioxide. The aim was to demonstrate the utility of the reaction, not by just synthesising an unsymmetrical carbonate from CO_2, since this in itself had already been demonstrated and was precedented,[55,64] but to take another step forward and make a useful carbonate which was derived from phenol.

3.2.4.4.2 Synthesis of Methyl Phenyl Carbonate 23
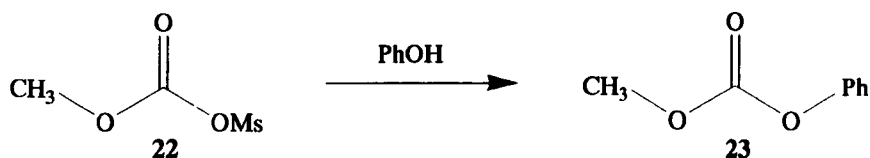
Scheme 3.27: Synthesis of methyl phenyl carbonate

Using methanol, carbon dioxide and 1.2 equivalents of methanesulfonic anhydride, methyl mesyl carbonate **22** was synthesised. Addition of 1.2 equivalents of phenol and pyridine at 7 °C immediately led to a rise in temperature to 24 °C, such that the reaction needed further cooling. However, the result was a very clean reaction with only two products detected by tlc, ^{1}H-NMR and mass spectroscopy. Methyl phenyl carbonate **23** had been produced (scheme 3.27) in 25% yield in a ratio of 27:1 with phenyl mesylate. This was the first synthesis of methyl phenyl carbonate from carbon dioxide and one of the few reports of this product being synthesised from phenol at ambient temperature.[90]

3.3 Synthesis of Thiocarbonates

3.3.1 Introduction

Thiocarbonates have been shown to be useful as pesticides[91], insecticides[92] and antibiotics.[93] In the same way that carbonates and carbamates can be synthesised from alkyl mesyl carbonates analogously to chloroformates, so too can thiocarbonates simply by using any suitable thiol as a nucleophile.[94] Thiols are better nucleophiles than amines, so it was trivial to extend the scope of the reaction to synthesise thiocarbonates.

In analogous fashion to alcohols and amines, both aromatic and aliphatic thiols, 3,5-dichlorothiophenol and ethane thiol respectively, were used in reactions with propyl and benzyl mesyl carbonate. As a result, using 1.1-1.2 equivalents of methanesulfonic anhydride, three new thiocarbonates **24, 25** and **26** were made from carbon dioxide in varying yields.

3.3.2 Synthesis of *n*-Propyl *S*-3,5-Dichlorophenyl Thiocarbonate 24
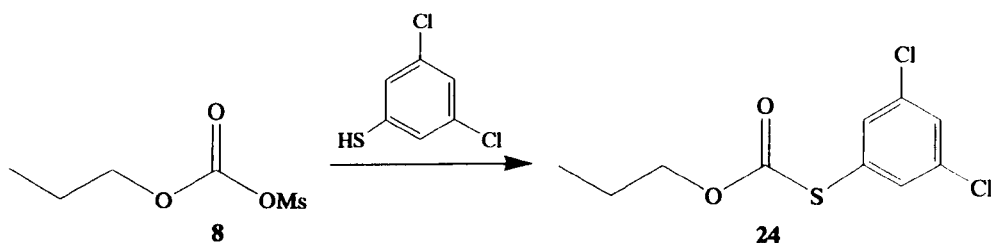
Scheme 3.28: Aryl thiocarbonate formation from *n*-propyl mesyl carbonate

The best example of using a thiol nucleophile was formation of propyl *S*-3,5-dichlorophenyl thiocarbonate **24** (scheme 3.28) in 37% yield (based on *n*-propanol). This demonstrated that mesyl carbonates could still react with relatively electron deficient nucleophiles in respectable yield. If, as was suggested earlier that the optimised mesyl carbonate yield was in the region of 45%, attack on the carbonyl compound would be occurring in excess of 80% yield. The reaction would best be utilised synthetically then if the cheapest or more abundant component was carboxylated and sulfonated, followed by reaction with a pre-made nucleophile, for example, an intermediate thiol or amine. In this way, biologically active compounds , such as pesticides, could be made simply with no need for phosgene or isocyanates.
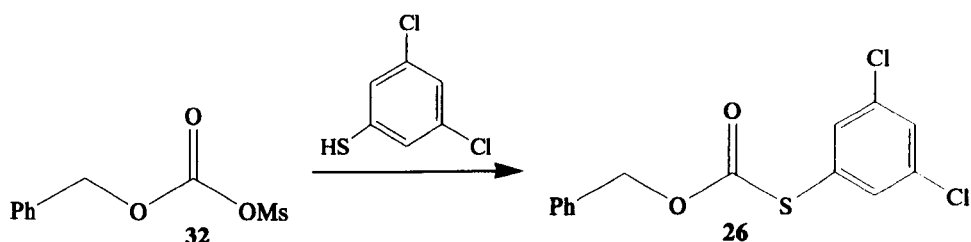
3.3.3 Synthesis of Benzyl *S*-Ethyl Thiocarbonate 25
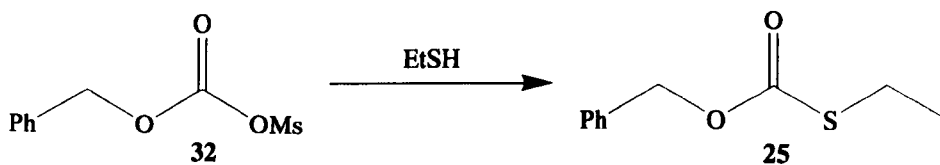
Scheme 3.29: Synthesis of benzyl *S*-ethyl thiocarbonate

Ethanethiol reacted as expected with benzyl mesyl carbonate to yield benzyl *S*-ethyl thiocarbonate **25** within one hour of its addition (scheme 3.29). The reaction and isolation in 25% yield were successful at the first attempt and so were not optimised.

### 3.3.4 Synthesis of Benzyl *S*-3,5-Dichlorophenyl Thiocarbonate 26

Scheme 3.30: Synthesis of benzyl *S*-3,5-dichlorophenyl thiocarbonate

Standard formation of benzyl mesyl carbonate followed by reaction with 3,5-dichlorobenzene thiol successfully produced the corresponding thiocarbonate (scheme 3.30) as proven by high resolution mass spectroscopy and NMR spectra. However, repeated chromatography could not separate the product from 3,5-dichlorophenyl disulfide, which was a by-product of the reaction and very prominent in the mass spectra.

3.4 Summary

Generating mesyl carbamates gave a precursor which could react analogously to carbamoyl chlorides. This meant that it was possible to synthesise both alkyl and aryl carbamates. The reaction was not restricted solely to simple carbamates but to difunctionalised molecules also (scheme 3.31).
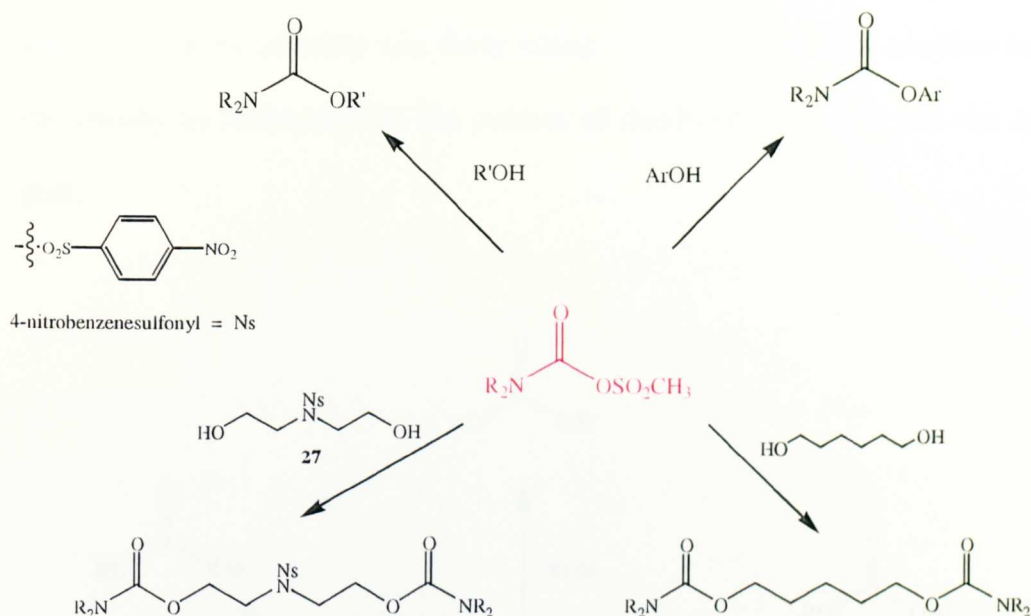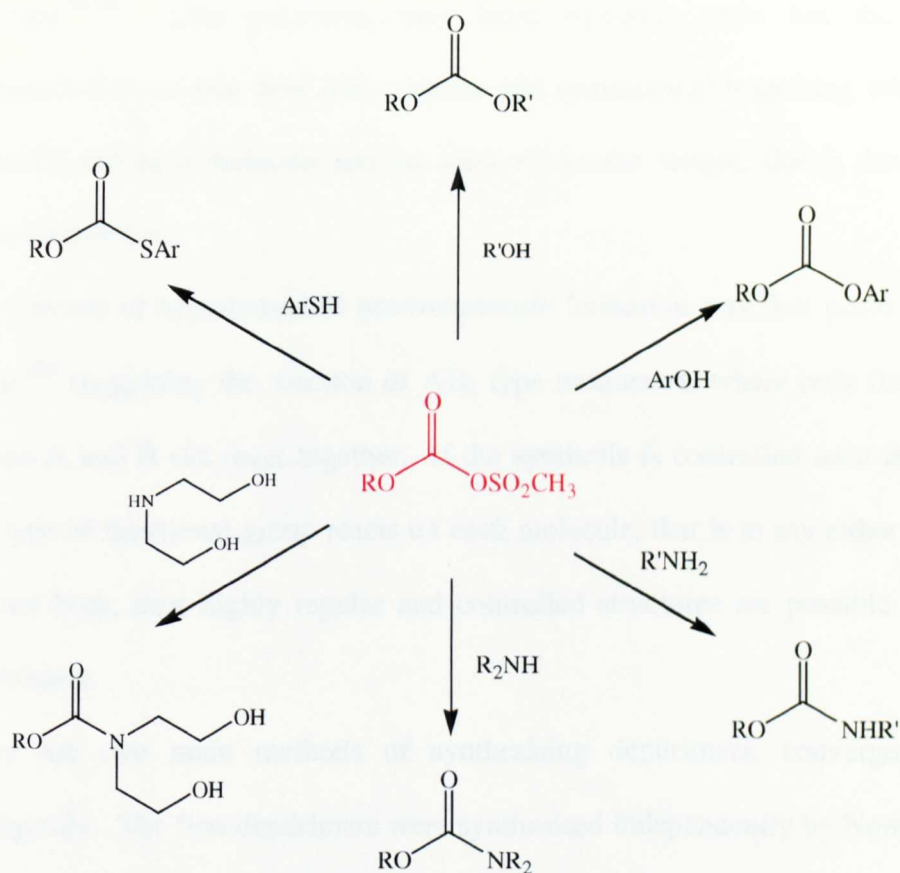
Scheme 3.31: Reactions of mesyl carbamates

By a simple adaption of the methodology, alcohols could also be made to react with carbon dioxide and the intermediate trapped as a reactive mesyl carbonate. A viable synthetic analogue to chloroformates has been demonstrated using CO_2 as a carbonyl source under mild conditions. Exhibited for the first time are the syntheses of unsymmetrical carbonates derived from the alcohols, including aryl carbonates which typically require heat to be formed.

Carbonates and carbamates are easy targets by reaction of mesyl carbonates with alcohols and amines respectively; it is viable to use aliphatic as well as aromatic nucleophiles. Less common but no less viable products are thiocarbonates and functionalised carbamates (scheme 3.32). As would be expected, amines are better nucleophiles than alcohols and this can be demonstrated simply by the reaction of diethanolamine with n-propyl mesyl carbonate (see section 4.3.2).

The scope of the reaction was fairly broad so applying the new reaction more specifically to carbamates in the context of dendrimer synthesis was the next goal.

Scheme 3.32: Reactions of mesyl carbonates

# CHAPTER 4 – ATTEMPTED APPLICATION OF METHODOLOGY TO DENDRIMER SYNTHESIS

4.1 Introduction

Dendrimers are highly branched molecules that have a regular geometrical structure.[95-99] Like polymers, they have repeating units but their main characteristics are that they have regular and symmetrical branching within the molecule and each molecule has the same molecular weight, that is dendrimers are monodisperse.

The concept of hyperbranched macromolecule formation was first postulated by Flory,[100] suggesting the reaction of AB_2 type monomers, where only functional groups A and B can react together. If the synthesis is controlled such that only one type of functional group reacts on each molecule, that is to say either A or B but not both, then highly regular and controlled structures are possible, named dendrimers.

There are two main methods of synthesising dendrimers, convergently or divergently. The first dendrimers were synthesised independently by Newkome[99] and Tomalia[96,97] by divergent methods. This usually involves beginning with a molecule that has 2,3 or 4 fold symmetry and identical functional groups, which are then completely reacted with an AB_2 monomer, whether A or B reacts being dependant on the reaction chosen. Every repeating unit that increases the number of branches is referred to as a generation. So, the exhaustive reaction of the core forms the first generation as the branching usually increases from two to four, or three to six. The sequence is then repeated, although sometimes protection-deprotection or activation steps are required in between, until the required generation number is reached. Generation four or five is usually the upper

practical limit to most dendrimers,[101] although higher generations have been
reported.
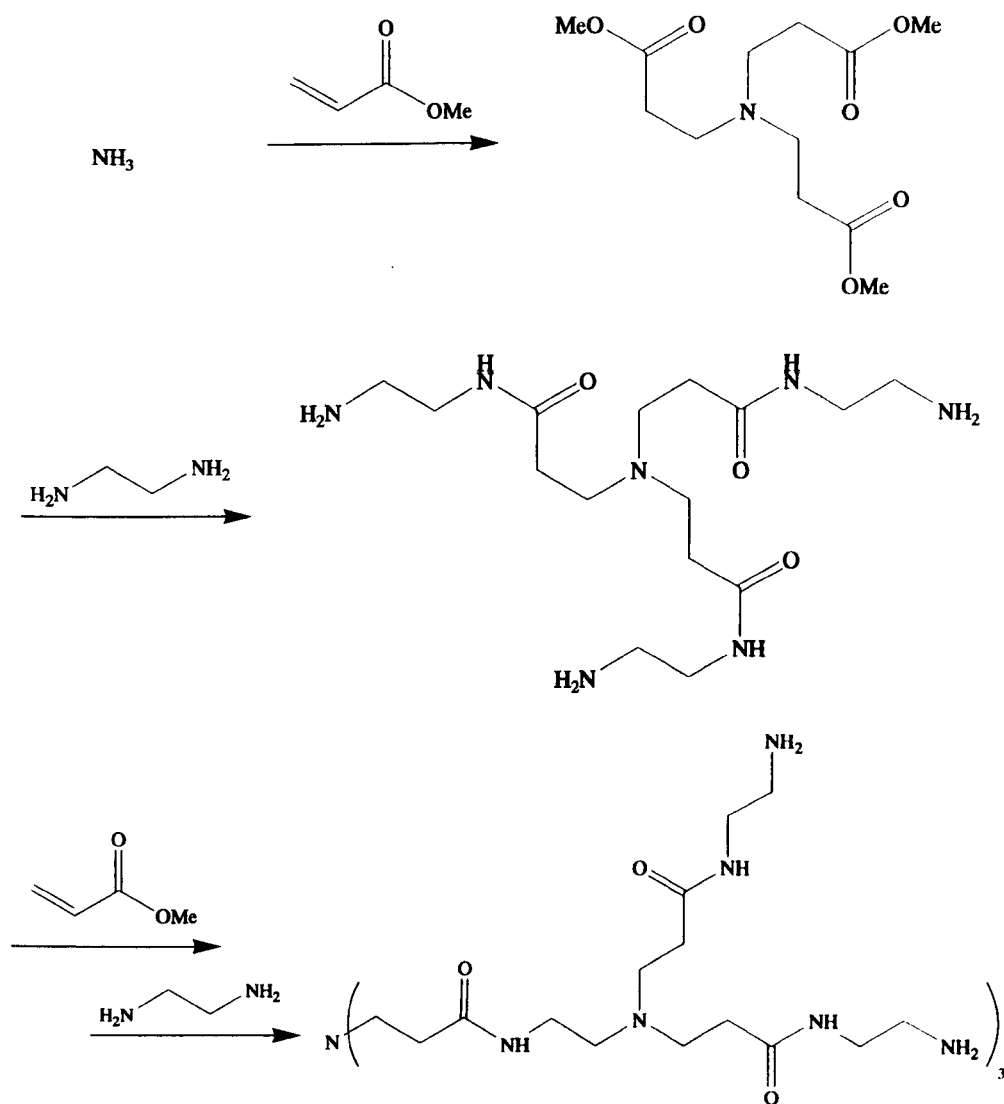
Scheme 4.1: Tomalia's StarBurst™ PAMAM Dendrimer

Newkome and co-workers coined the term *arborols*[99] as their compounds were
tree-like molecules with alcohol functional groups. Dendrimers (Gr: dendr =
branched, mer = unit) suggested by Tomalia,[96] was a more fully encompassing
term and is widely accepted. The synthesis of the Tomalia group's PAMAM
(*poly*ami*doa*mine) dendrimer (scheme 4.1), also called Starburst™ dendrimer, is

simple and hence the dendrimer is one of only two in commercial production. The other, Astramol by DSM, utilises an improved process of the original approach by Vogtle[95] to synthesise polyamines. Tomalia's approach was to react ammonia with methyl acrylate in a pseudo-Michael addition, to yield the *N*-branched tri-ester. Subsequent reaction with excess ethylene diamine yielded the tri-amide-triamine. The sequence of reactions with methyl acrylate and ethylene diamine is then repeated. Variations are possible using different amines and/or cores.

The convergent approach to dendrimer construction was first described by Frechet and Hawker.[102] Instead of beginning with a core and increasing the degree of branching by iterative sequences, dendritic wedges or dendrons are synthesised by reacting two terminal units with one monomer, usually possessing a protected functionality. After the deprotection step, the new molecule is attached to 0.5 equivalents of monomer. When required, each dendron can be tethered to a common core. This method uses less reagents but careful selection of protecting group is required as build up of the dendron leads to greater steric hindrance, which can affect reactivity.

Dendrimers now appear with many different functional groups, at different generation numbers and have different surface functional groups which affects reactivity and solubility.[103, 104] However, given the variety and breadth of research in this field, there have been very few reports of urethane and carbonate dendrimers. The fact that excessive amounts of phosgene would normally have to be used and lack of discrimination when reacting with different functional groups may have precluded this line of work thus far. Also, there would normally

be more than three reactive sites per molecule which could add in the problem of crosslinking.

Frechet demonstrated accelerated dendritic wedge construction by using different functional groups between generations,[105] one of which was the urethane linkage, generated from phosgene. In this way, generation three wedges were made from first generation monomers in one pot.
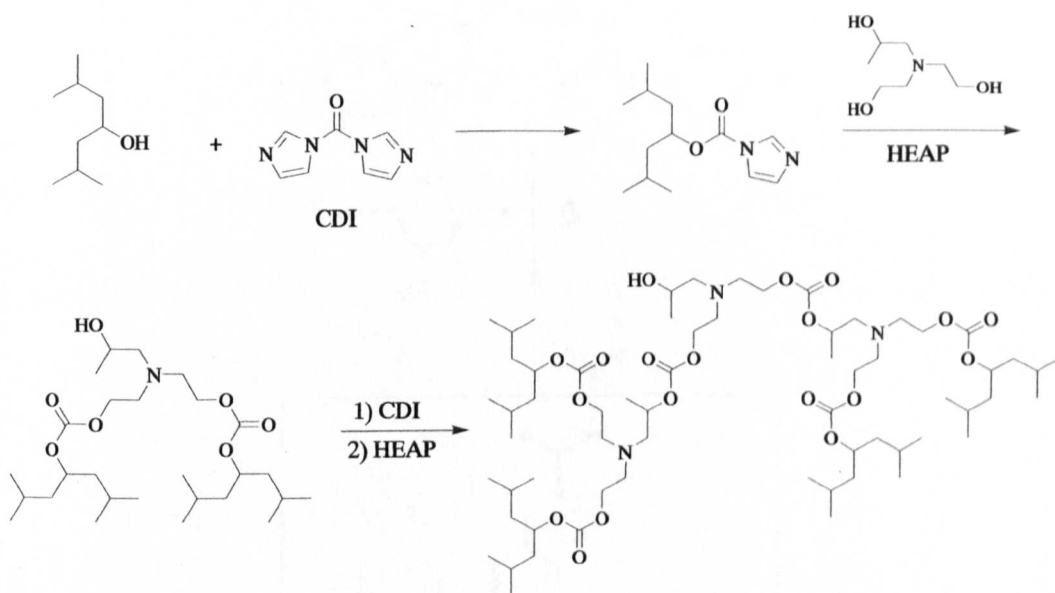
Scheme 4.2: Carbonate dendrimer synthesis using CDI

Rannard and Davis used carbonyl diimidazole (CDI) in a convergent synthesis (scheme 4.2),[106] as a safer and more selective phosgene substitute, to selectively react between primary and second alcohols. Initial isolable intermediates were imidazole carboxylic esters which could then react further with branched alcohols to give up to third generation carbonate dendrimers. No aromatic carbonates can be generated *via* this method as phenoxides are better leaving groups than imidazolides.[107]
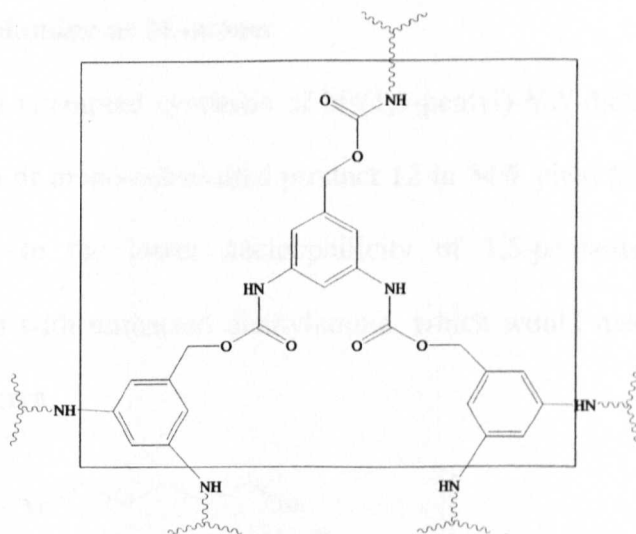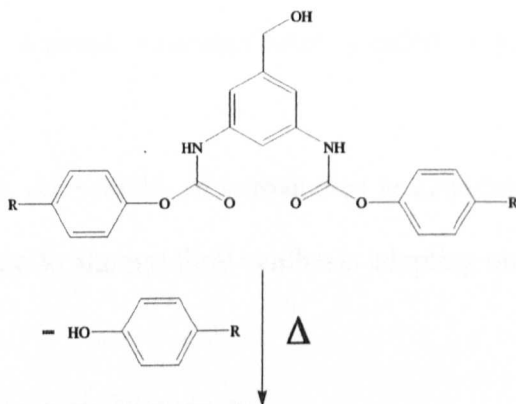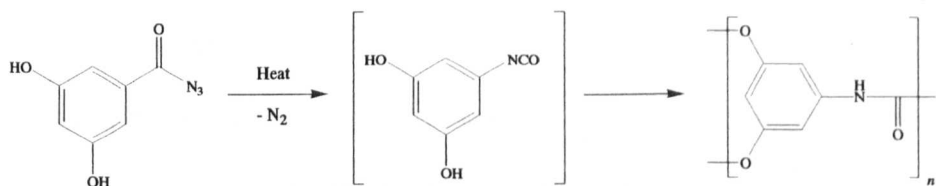
Scheme 4.3: Hyper branched polyurethanes; (Top) By Curtius Rearrangement.

(Bottom) By Decomposition of Aryl Carbamates to Isocyanates

The only other example of a urethane functional group in a hyperbranched macromolecule also utilised CDI. Woolley's group used this reagent to make aryl carbonate polymers in this instance, but silver fluoride had to be used to

simultaneously drive the reactions by precipitating silver imidazolide and remove silyl ether protecting groups.[107]

Other examples of urethane hyperbranched polymers use benzyl alcohol diaryl carbamates which decompose on heating to form isocyanates and then self polymerise.[108] Similarly, decomposition of dihydroxybenzoyl azides to isocyanates by the Curtius rearrangement yielded hyperbranched urethanes (scheme 4.3).[109]

As mentioned above, the scarcity of carbamates in dendrimers or hyperbranched polymers was a reason to attempt their synthesis adapting our procedure.

4.2 Attempted Convergent Approach

4.2.1 Diethanolamine as Monomer

The previously attempted synthesis of bis(1,5-pentyl)-*N,N*-diethyl carbamate **11** led to isolation of mono-substituted product **12** in 34% yield (scheme 4.4). This could be due to the lower nucleophilicity of 1,5-pentanediol with mesyl carbamate than with unreacted diethylamine, which would react faster than the diol, to give a urea.
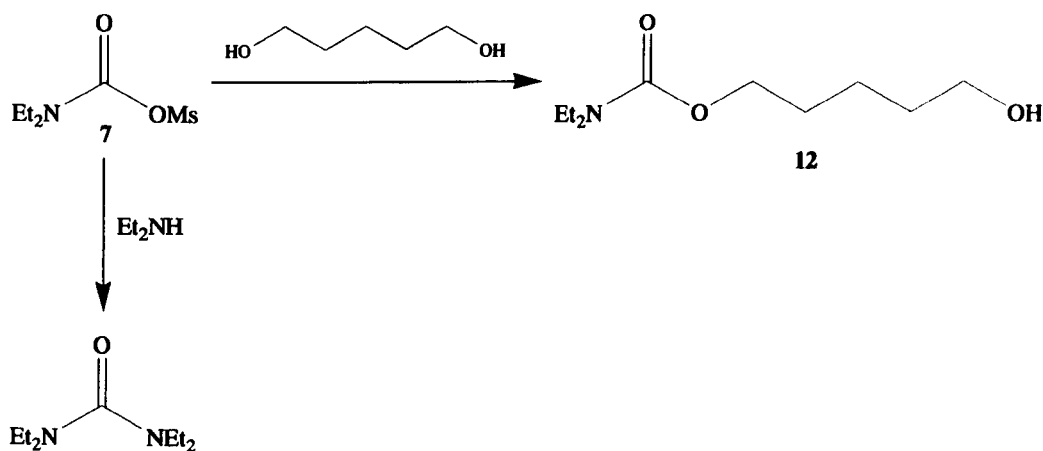
Scheme 4.4: Attempted synthesis of a dicarbamate

Since the reaction of *N,N*-diethyl mesyl carbamate with 1,5-pentanediol was successful, a simple extension of the procedure was to use a branched diol, such as diethanolamine, but selectively react the less nucleophilic hydroxy sites instead of the more nucleophilic amine by forming the di-alkoxide *in situ*. Even though yields of mesyl carbamates so far were variable, the cost of the reagents did not make scale up of the reaction a problem.

The goal was to generate carbamates with a free amine group, available for subsequent reaction with carbon dioxide. To realise this, diethyl mesyl carbamate would be generated and transferred to the metal salt of diethanolamine (scheme 4.5). No protection would be required if the addition was carefully monitored and controlled.
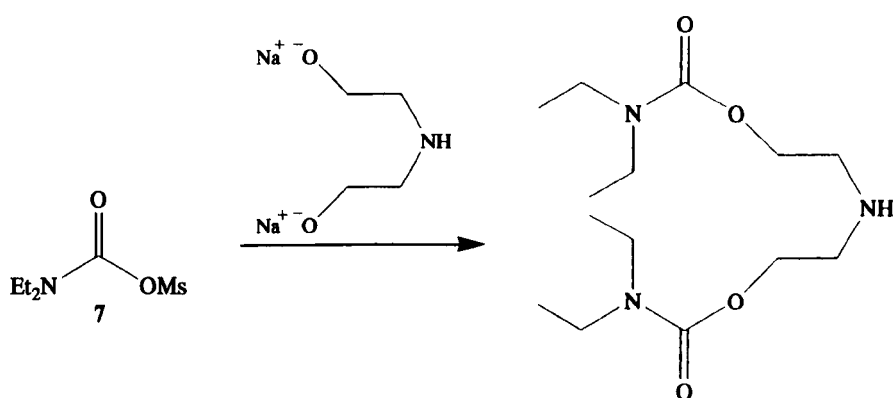
Scheme 4.5: Intended route to convergent dendrimers

Initially, diethyl carbamate anion was generated and the mesyl carbamate made from it. This was subsequently added to a hot, stirring suspension of sodium hydride and diethanolamine in acetonitrile. Following the reaction by tlc over two days gave no diethanolamine derived products, in the organic or aqueous layers. The only products determined by ^{1}H NMR were diethyl methanesulfonamide,[76] urea[77] and carbamic anhydride.[74] The reaction was

repeated using sodium hydride in DMF, but again, the reaction was unsuccessful as there was no methylene triplet at or above 4.00 ppm, which would indicate the carbamate. All significant signals were at or below 3.80 ppm in the ^{1}H NMR spectrum. Also, the ^{13}C NMR spectrum showed a signal at 150 ppm, which is too low for a carbamate ester and is more likely to be the carbamic anhydride.

Earlier work within the group had shown the convergent approach using carbon dioxide to be problematic and in the process the exhaustive reaction of diethanolamine had occurred, yielding a dicarbamate ester urea (scheme 4.6). This compound had been used to monitor reactions of diethanolamine by detecting when its reaction had proceeded too far.
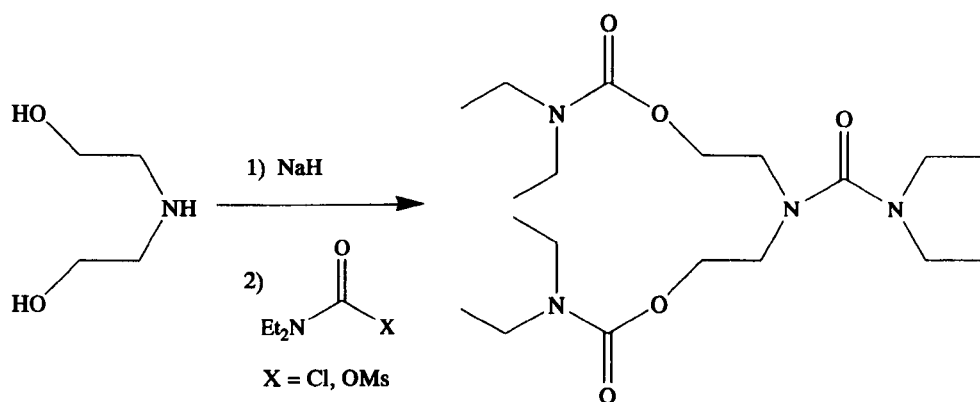
Scheme 4.6: Attempted carbamoylation of diethanolamine

Instead of trying to selectively form the free amine of a dicarbamate, it was decided to deliberately make the tri-substituted product using sodium hydride to determine whether this approach was suitable and see if a more inherent problem was occurring, for example, very low mesyl carbamate yields. Assuming less than 50% yield for conversion of diethylamine to mesyl carbamate, a sufficient

amount was used so as still to be present to react and form either the dicarbamate ester, urea derivative or mixture thereof. However, on analysis of the crude product after one day, no carbamate was present as compared with the trisubstituted product above. The problem seemed to be the deprotonation of the hydroxy groups of diethanolamine. The reaction was repeated using potassium hydride and using sodium ethoxide. On comparison of the respective ^{1}H NMR spectra with the carbamate signals of the trisubstituted diethanolamine, the reaction was deemed to have failed in both instances. To assist in understanding what some problems might be, it was decided to acetylate diethanolamine selectively with acetyl chloride to make the diester without making the amide (scheme 4.7).
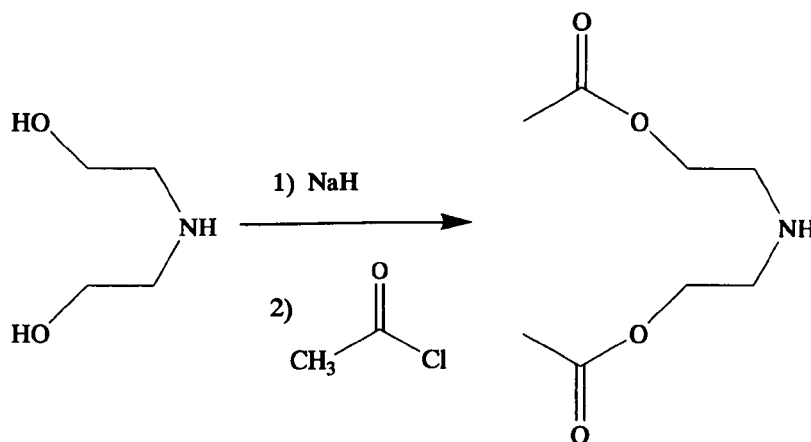
Scheme 4.7: Attempted reaction of selective acetylation of diethanolamine

Since two solvents had been used in the attempt to synthesise a carbamate from diethanolamine, acetonitrile for the carboxylation step and DMF for the deprotonation, single solvents were used next for both reactions to eliminate any negative effect that using a binary solvent system might have. Three reactions were run in parallel as direct comparisons. Sodium hydride was the base and

diethanolamine the substrate used in all three instances but the reaction conditions were different. Two reactions were run in THF, one of which was sonicated to activate the sodium hydride before stirring. The third reaction was run in DMF. To each stirring solution was slowly added 1.1 equivalents of acetyl chloride to minimise the chance of amide formation. After stirring overnight, none of the reactions showed any signals in the ^{1}H NMR spectrum above 3.9 ppm, strongly suggesting no ester had formed. However, for the stirred reaction in THF, a singlet around 2 ppm and a parent ion of 148 in the CI mass spectrum indicated the possibility of mono-acetylation occurring, albeit most likely on the nitrogen atom. No selectivity had occurred.

Another attempt to form the dianion of diethanolamine using a literature procedure,[110] followed by acetylation also failed, again, judged by no ester signal relating to the methylene group in the NMR spectrum. After this, selective acetylation was abandoned as it was possible that it was not a suitable model for the reaction of *N,N*-diethyl mesyl carbamate with diethanolamine.

A procedure for generating *N,N*-diethyl mesyl carbamate as the major product was repeated in acetonitrile and added to a stirring suspension of sodium hydride in DMF with diethanolamine. As before, no carbamate was formed as compared to the trisubstituted product. Using DMF as the solvent for both the reaction with carbon dioxide and sodium hydride gave no improvement. A hypothesis was that the sodium or potassium cation was coordinating to diethanolamine which could act as a podand. This coordination would lower the reactivity of the hydroxy or alkoxide moiety of diethanolamine. Thus, this route to selective reaction at the oxygen atoms of diethanolamine was stopped and other routes to branched molecules devised instead.

4.2.2 Use of a Protecting Group – bis(2-hydroxyethyl) 4-nitrobenzenesulfonamide as a monomer
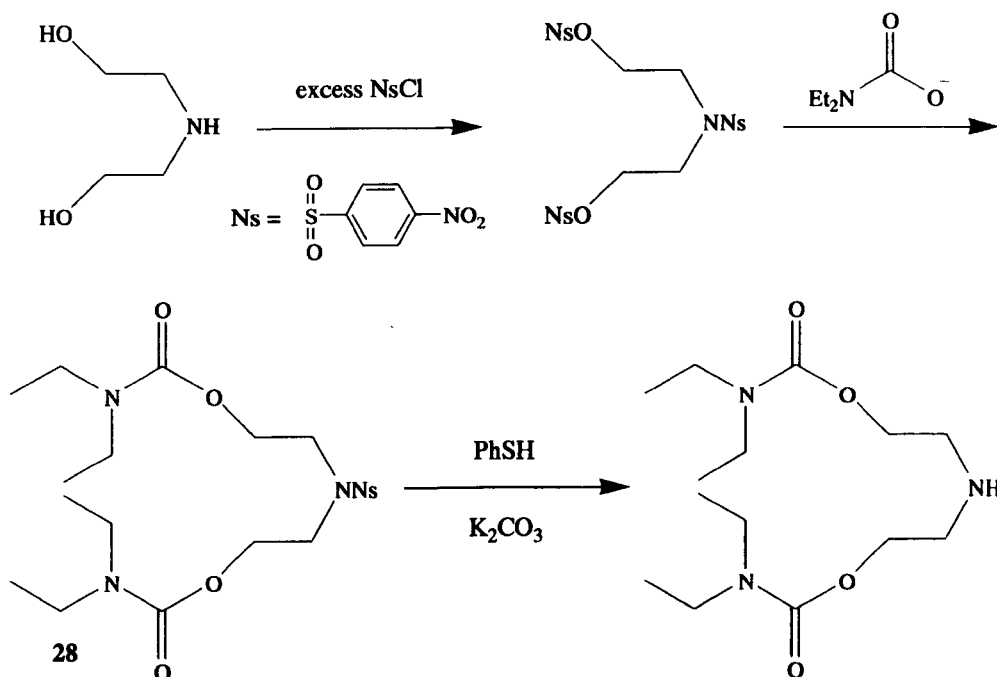

Scheme 4.8: Dendron synthesis using nosyl activating and protecting groups

4.2.2.1 Reaction with *N,N*-Diethyl Mesyl Carbamate

Earlier work done by the group had shown that the amine of diethanolamine could be protected as a 4-nitrobenzenesulfonamide group (nosylamide),[111] chemistry carried out on the substrate and the 4-nitrobenzene sulfonyl group removed to give the free amine by the action of thiophenol (scheme 4.8).[113] It was the intention to selectively protect the amine group of diethanolamine, leaving the hydroxy functional groups untouched, so later the molecule could be effectively used as a diol to react with *N,N*-diethyl mesyl carbamate. Once the dicarbamate had been made (scheme 4.9), the nosyl group would be removed and the free amine would be available for further reaction. Ideally this reaction would

occur with carbon dioxide and methanesulfonic anhydride to generate a reactive dendron intermediate.
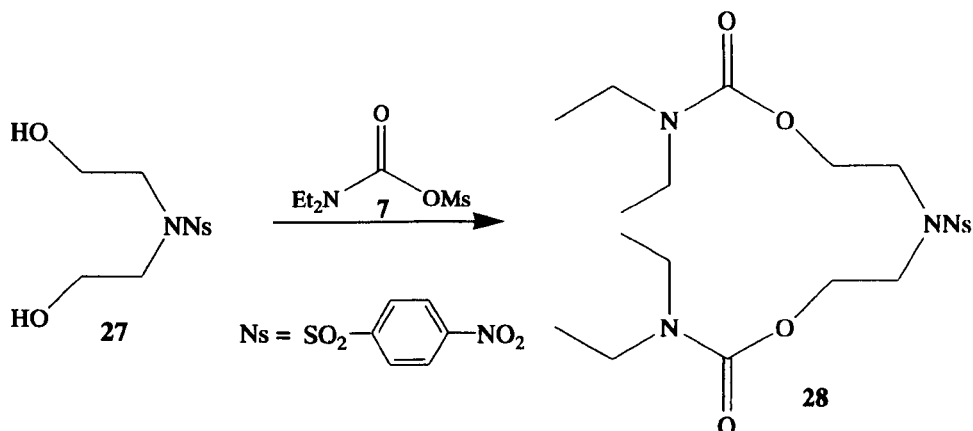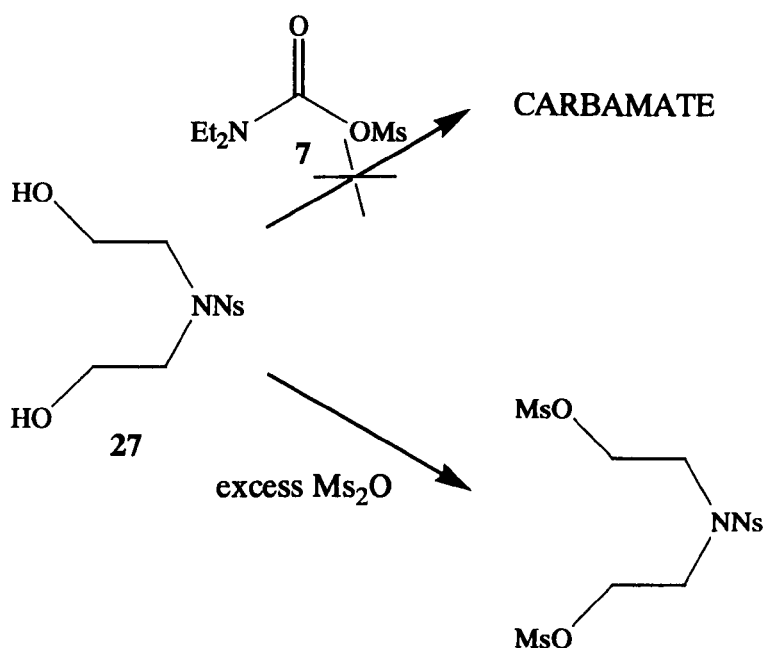

Scheme 4.9: Carbamoylation of protected diethanolamine

The first attempt at this approach, using diethyl amine to make the mesyl carbamate followed by reaction with Ns-protected diethanolamine and triethylamine as the base, gave no ^{1}H NMR signals above 3.9 ppm, suggesting no reaction at the alcohols of the protected amine to give carbamates, much like the attempted acetylations of diethanolamine.

Carboxylation of diethylamine was carried out again, but at -10°C. The mesyl carbamate was split into equal portions and reacted with Ns-protected diethanolamine at 70 °C but using two different bases, triethylamine in one reaction and pyridine in the other. Both reactions successfully yielded carbamates as indicated by NMR experiments and mass spectral data, which gave two distinct parent ions, corresponding to mono and di-substituted carbamate esters.

The reaction using pyridine as a base gave a cleaner reaction, with much less diethyl methanesulfonamide as a by-product. However, due to the small scale, low yield and large number of products indicated by tlc for both reactions, isolation was not practical. Nevertheless, the reaction had shown that making carbamates this way was possible, but complete reaction of the protected aminodiol would be required for it to be a viable option for dendrimer synthesis. Repeating the reaction was problematic as the bis (2-hydroxyethyl) nosylamide had to be the limiting reagent, but the free hydroxy groups competed for reaction with excess methanesulfonic anhydride instead of diethyl carbamoyl mesylate (scheme 4.10). No evidence of carbamates was found. Also, amines had not been as consistent as alcohols thus far upon carboxylation and mesylation, perhaps due to the effect of amine acting as a base and, hence decomposing the intermediate (scheme 2.22).

Scheme 4.10: Side reaction of attempted carbamoylation

The reaction was attempted again using a stoichiometric amount of methanesulfonic anhydride to minimise the side reaction with protected diethanolamine. Pyridine was used to help drive the carbamoylation by displacing the mesylate group and activating the carbamoyl group. However, very little material was recovered.

It was not known what effect the presence the nosyl group was having on the reactivity of the hydroxy groups. If the reaction of the alcohols was being slowed down with carbamoyl mesylate, then it was possible that after pyridine displaced mesylate from the molecule, the intermediate was decomposing. So, carbamoyl mesylate was made again and split into two fractions. Nosyl protected diethanolamine was added to both fractions, one with pyridine and the other with potassium carbonate.[113] Reaction of both overnight at ambient temperature gave no carbamate signals in the ^{1}H-NMR spectrum, even though the aromatic signals were still present. There seemed to be tetraethyl urea and carbamic anhydride as in earlier reactions, so evidently, unreacted diethylamine was excluding carbamate formation by reacting with mesyl carbamate first (scheme 4.11). This route to dendrimers was proving troublesome and so was abandoned.
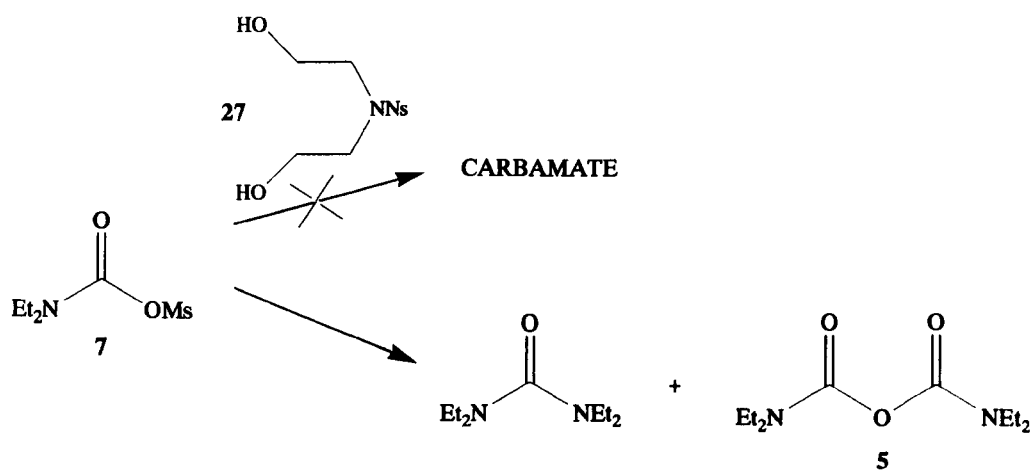
Scheme 4.11: Side reactions of *N,N*-diethyl mesyl carbamate

4.2.2.2 Reaction of nosyl protected diethanolamine with carbon dioxide

Since it had already been shown that simple carbamates could successfully be made from mesyl carbonates and extended to diols, it was decided to use nosyl protected diethanolamine as a diol and form a di-mesyl carbonate (scheme 4.12). Diethylamine had been used before as a nucleophile with mesyl carbonates, using stoichiometric amounts of pyridine to successfully make carbamates. It seemed that the effect of the amine as a base, which could decompose the intermediate, was lessened if the amine was utilised as the second substrate. Another advantage was that diethylamine was inexpensive and commercially available, so scale wasn't a problem and excesses could be used to ensure disubstitution.
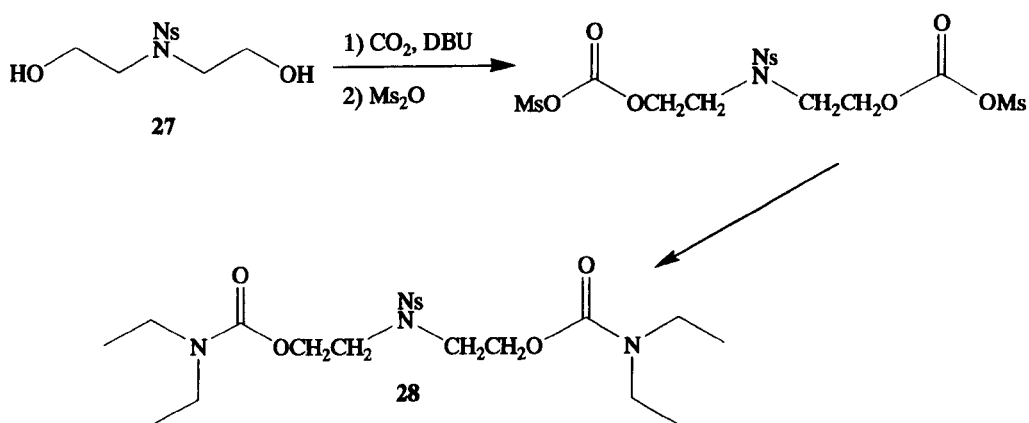
Scheme 4.12: Proposed route to protected carbamate dendrons

Initially, compared to simple alcohols, more acetonitrile than usual had to be used to dissolve nosyl protected diethanolamine and on introduction of carbon dioxide, no turbidity was observed at all, even with excess DBU, suggesting no reaction as explained above. Even on extended reaction at cold temperatures, no cloudiness was observed at all, which compared to all previous reactions indicates no carboxylation. The reaction was repeated with less nosyl protected

diethanolamine and kept at −42 °C until a precipitate formed. This time, methanesulfonic anhydride was added to the solution in portions and when this reaction was complete, diethylamine was slowly added with pyridine after the reaction had warmed to −25 °C. The aim was to minimise any chances of the intermediate decomposing. After the reaction, methylene signals were observed that were in the correct region of the ^{1}H-NMR spectrum that could be adjacent to a carbamate group. By comparison, the ^{13}C-NMR spectrum showed one major electronegative methylene signal that could be part of a carbamate but, two mesyl signals were also present. Since direct mesylation of the substrate always seemed to occur as well as mesylation of the carboxylated species, it was more than likely that the signal at 67.09 ppm was that of the mesylated nosylamide diol, the same product as in scheme 4.10. Comparing the proton NMR spectrum of the crude nosyl protected generation one dendron **28**, evidence for the formation of the product is increased by the shift of the methylene signals. Looking at the methyl region of the spectrum, two major signals can already be accounted for by diethyl methanesulfonamide by both chemical shift and integration ratio with a methanesulfonyl signal at 2.77 ppm. On comparison of the integration of the smaller methyl signal with the minor methylene peaks, it is highly unlikely that disubstitution has occurred, if the reaction occurred at all. If so, the low yield and material recovery made this route unviable also.

Using protected diethanolamine was creating more problems than it was solving, so a route to dendrimers was planned that wouldn't need any protecting groups.

4.3 Divergent Dendrimer Synthesis

4.3.1 Introduction

Due to the higher nucleophilicity of amines, a convergent approach to a carbamate dendrimer was problematic since there was a lot of urea, sulfonamide and carbamic anhydride by-products from the carboxylation reaction. Also, the selective reaction of the hydroxy groups of diethanolamine without protection of the amino function had been shown to be unsuccessful, even using a variety of methods.

A simple step forward would be to see if selectivity was possible in the reaction of diethanolamine with a mesyl carbonate at the amino group instead of trying to reverse the normal reactivity. Diethanolamine was chosen as it is an example of an AB_2 type monomer and would be an appropriate model for divergent dendrimer synthesis. In theory, the amine function would react preferentially to give the carbamate, the hydroxy groups should remain unreacted and hence, be available for carboxylation in another reaction. It had already been shown earlier that using 1,5-pentanediol and diethylamine could give carbamates by generating mesyl carbonates. This time, there would be other alcohols present in the molecule, which should be less reactive than the amine.

4.3.2 Use of diethanolamine as a repeat unit
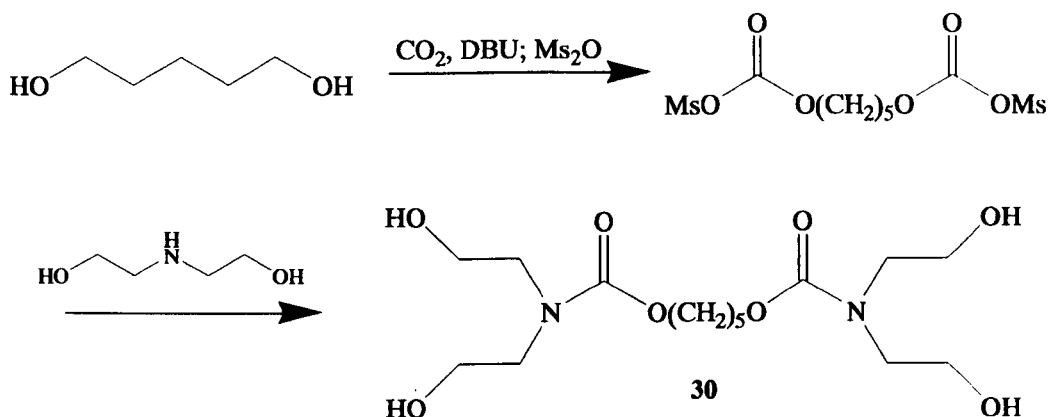
Scheme 4.13: Proposed divergent synthesis of functionalised carbamates

The di-mesyl carbonate was made *in situ* using the same method as before. A neat excess of diethanolamine was added at about −30 °C and the reaction kept cool, then allowed to warm to ambient temperature (scheme 4.13). The mixture was warmed for 24 hours and work-up attempted with different solvents. Results observed from NMR spectra indicated that a sulfonamide-type product was in an eight-fold excess by integration compared to a carboxylated product. Comparison of the carbamate *O*-methylene signals with those in the alkyl region showed them to be too disparate for carboxylation of both ends to have occurred solely. The ratio of *O*-methylene to alkyl methylene integrals should be 4:6 but was in fact 1:10. The ^{13}C NMR spectrum displayed two carbonyl signals. The formation of oligomers of 1,5-pentanediol could not be ruled out.

Since all reactants and products would contain pendant hydroxy groups and the mode of addition of diethanolamine increased the chance of side reactions, purification was not attempted as conclusive proof of the product was not found.

Other problems were the oiling out of diethanolamine from acetonitrile at cold temperatures, diethanolamine acting as a base in the reaction as no base was added and the possibility of decomposition postulated earlier due to a medium strength base being present.

The reaction was modified so the concentration of 1,5-pentanediol was decreased to reduce the chance of oligomerisation. Once the di-mesyl carbonate was made, it was transferred to a stirring, dilute solution of diethanolamine (due to solubility problems) so both mesyl carbonate groups would react with the local excess of amine groups. Excess diethanolamine was used as the base for the reaction also. Results were more encouraging this time as one carbonyl signal was present in the correct chemical shift region of the ^{13}C NMR spectrum. One other carbonyl type signal was present around 165 ppm, but whether this was due to a urea or DBU could not be determined. Morpholine-type signals were present in the proton NMR spectra, but these could not be rationalised in the mass spectrum. Mass spectroscopy did indicate major peaks at 367 and 368 in the EI and CI spectra respectively, whether this was due to excess protonation in the ionisation chamber or the product was somehow already protonated is a matter of conjecture. The data was not conclusive or corroborative.

Other peaks of note were at 335, indicating a drop of 31 mass units pertaining to potential loss of CH_2OH from the tetrol dicarbamate 30. A peak at 236 was apparent which could be either the M+1 ion for the monocarbamate or the urea of diethanolamine. This latter suggestion would account for the second carbonyl signal at higher chemical shift.

It was surmised that the peak at 132 could be the M+1 parent ion for an oxazolidinone, arising from internal transesterification of the monosubstituted

carbamate,[114] but the same peak of value 132 was both EI and CI spectra so it is also possible to arise from a fragmentation of a larger molecule (scheme 4.14).
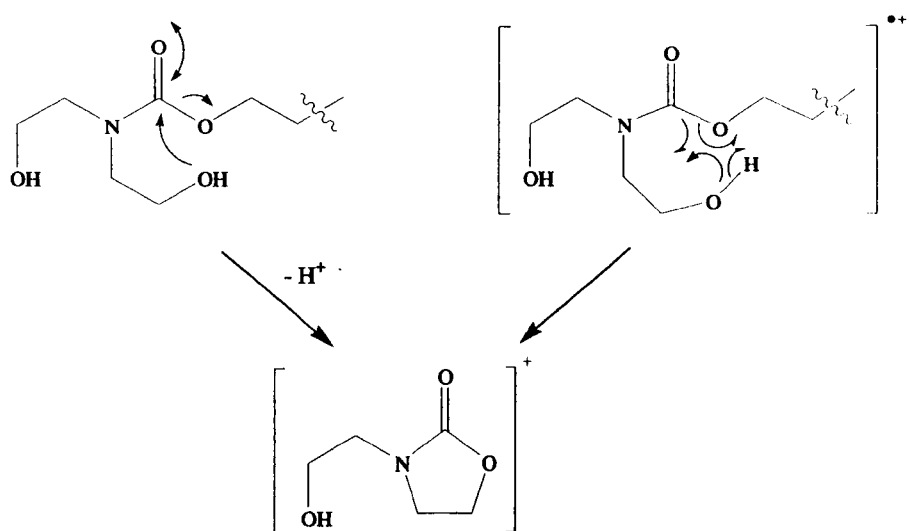
Scheme 4.14: Hypothesised reactions to explain the presence of an oxazolidinone

Again, purification was unsuccessful as flash chromatography gave no recognisable isolated products, probably due to the nature of all reactants and products being so similar. What is more, DBU was among the first compounds to elute, suggesting a strong affinity of the products for silica, so an alternative purification would probably be needed. Attempting the same reaction at a warmer temperature (-18°C) indicated little evidence of carboxylated products.

Transferral of the mesyl carbonate to diethanolamine at room temperature was one way in which the solubility problem was remedied. Extracting the crude product however did not give any leads no matter what solvent was used. Chromatography through a silica column with ethyl acetate did not yield anything useful until 50% methanol was added, then evidence of the correct product was very strong, albeit as an inseparable mixture with 1,5-pentanediol. NMR

spectroscopy produced the following clues: carbamate methylene signals were present in the correct region (4.10 ppm); a very large carbonyl signal was present at 157 ppm and all major alkyl peaks fit in with a dicarbamate of structure **30**; HMQC and COSY two dimensional spectra indicated the correct connectivity for ^{1}H-^{1}H and ^{1}H-^{13}C linkages. The parent ion was present but not much larger than noise in the mass spectrum. Addition of water to the mixture, separation and removal of water showed removal of impurities but there was a strong indication of 1,5-pentanediol still remaining. Chromatography or solvent extraction could not separate the product from the diol. Using CH_2Cl_2 and acetonitrile to solubilise diethanolamine gave no improvements in yield or selectivity. Extracting the crude oil with either CH_2Cl_2 or diethyl ether, followed by aqueous dissolution of the residue gave clearer spectra but, again, no product improvements. More morpholine-type signals were seen, that is to say a cyclic structure was most likely, but no other evidence supported this hypothesis.

To simplify matters, *n*-propyl mesyl carbonate was to be made rather than using a diol, as there would be only one site of reaction and it would be easier to determine how the reaction had proceeded. This would be a suitable model for developing the reaction for diols and increasing the degree of branching from two to four. Also, some general properties of such a molecule might be ascertained on isolation, which it was theorised, would be easier. On reaction of *n*-propyl mesyl carbonate with diethanolamine, the di-hydroxy terminated carbamate ester (scheme 4.15) was successfully separated as indicated by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. IR signals also confirmed the presence of both hydroxy and carbonyl groups. This reaction also scaled up to gram scale in 31 % yield, after extractions of the crude residue with ethyl acetate and diethyl

ether, followed by column chromatography on alumina. The small scale reaction was purified on silica but the product had to be obtained by flushing the column. Alumina had a lower affinity for the carbamate diol and so a purer product was retrieved.
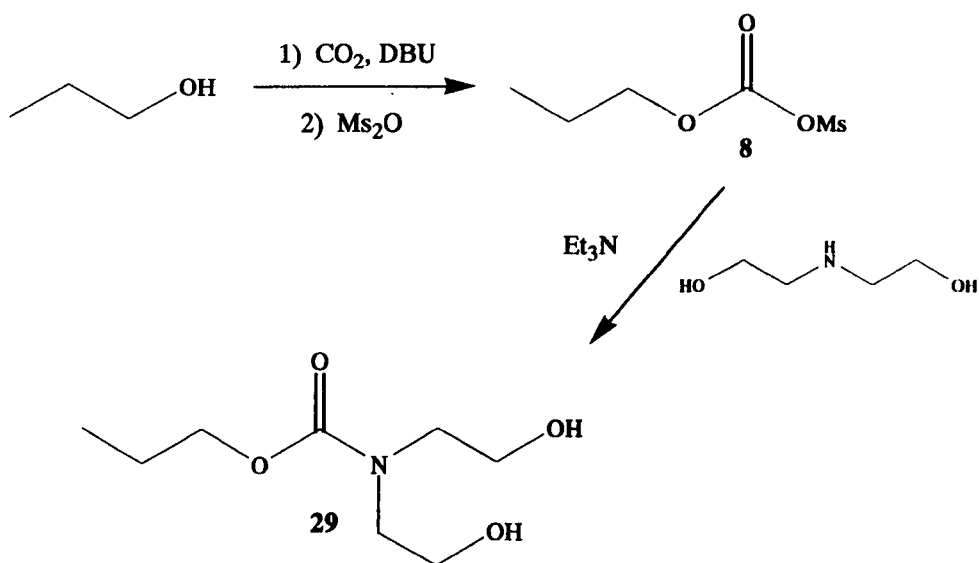
Scheme 4.15: Synthesis of a hydroxy terminated carbamate

Using 1,3-propanediol as the starting material was unsuccessful in carbamate synthesis. No cyclised or linear products were found. Transferring the carboxylation and mesylation reaction to 1,5-pentanediol was successful, followed by reaction with diethanolamine and pyridine. Triethylamine could potentially decompose the mesyl carbonate intermediate, so pyridine was used to generate a more reactive intermediate and also act as a weak base. After completion of the reaction, the NMR spectra indicated a very strong possibility of the a tetrahydroxy-dicarbamate having been made, but the mass spectrum gave no satisfactory parent ion or prominent fragments that matched up in EI and CI

experiments. The product was derivatised with a large excess of acetyl chloride and subsequently, the parent ion of the tetra-acetate of the dicarbamate **30** (figure 4.1) was confirmed in the CI mass spectrum at 535 (M+1)and 552 (M+18). All corresponding peaks in the NMR spectra (including 2-dimensional connectivity experiments) were consistent with the proposed structure. However, whilst trying to remove solvent from the bulk sample, a completely insoluble solid formed which was hypothesised to be polymer arising from crosslinking of unreacted hydroxy groups with the ester termini.
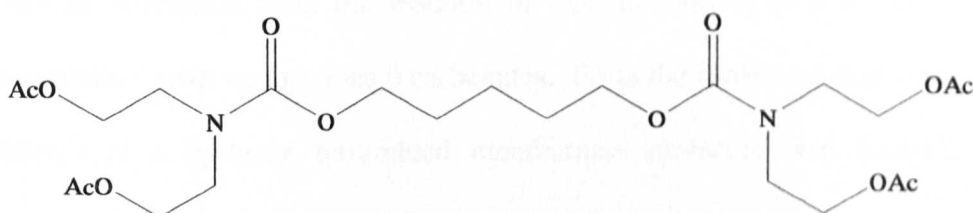
Figure 4.1: Ester terminated dicarbamate

Complications in identification of the product came about in part from the unresolvable peaks attributed to the alkyl chains. By using 1,4-benzenedimethanol,[115] it was hoped this substrate would simplify the NMR spectra and be a more reactive substrate with carbon dioxide. On reaction of benzene dimethanol, spectroscopic analysis of the products gave no indication of the dibenzyl diol derived carbamate, either from integration in the NMR spectrum or fragments in the mass spectrum. One parent ion was observed at $m/z =132$ (M+1) that was corroborated by a M+18 peak in the CI spectrum, that would correspond to N-(2-hydroxyethyl) oxazolidinone. This could arise from formation of the carbamate between diethanolamine and benzenedimethanol, followed by an intramolecular transesterification of one of the aminoalcohol

groups leading to the N-substituted oxazolidinone (scheme 4.14). Peaks consistent with a cyclised product were present in the crude ^{1}H NMR spectrum; two triplets from the hydroxyethyl group and pseudo-triplets indicative of protons bonded in a ring from the oxazolidone moiety. No further work was carried out using this substrate.

4.4 Summary of Dendrimer Synthesis

On observation of reactions of diethanolamine and derivatives in attempted carbamate formation from the reaction of diethanolamine, very mixed results were obtained with various mesyl carbonates. From the analytical data presented, synthesis of a hydroxy terminated dicarbamate molecule was possible but subsequent isolation from impurities was the major stumbling block.

Yields from the use of nosyl-protected diethanolamine were too low to usefully be able to purify the products and carry through another reaction stage. With regards to a strategy based on diethanolamine as the major branching unit, a divergent route seemed to suit this reaction methodology best, as well as obviating the need for protecting group chemistry which would possibly reduce the usefulness of the reaction.

For future consideration, a better methodology would be to separate the formation of mesyl carbonates from the reaction of multi-nucleophiles with mesyl carbonates until a better grasp of the chemistry could be had. Purification of the reaction to yield just mesyl carbonate and propyl mesylate would eliminate many side reactions, such as mesylation of the added nucleophile. In this way, there would be a clearer indication of how difunctionalised mesyl carbonates react with multifunctional nucleophiles.

The potential to create hydroxy terminated carbamates from CO_2 is present. [116] This has been achieved by discriminating between the reactivity of the amine and hydroxy functional groups of diethanolamine, whilst requiring no protecting groups. Whether this approach is best served by creating dendrimers or attempting to create hyperbranched polymers from diethanolamine and carbon dioxide in one step needs further research.

CHAPTER 5 - EXPERIMENTAL

Materials

All chemicals were used as received from Aldrich chemical company. Anhydrous acetonitrile was purchased from Aldrich chemical company. "Hi-Dry" methanol was supplied by Romil. Trifluoromethanesulfonic anhydride was used as received from Avocado. Carbon dioxide was supplied by BOC gases (99%+). NMR spectra were obtained in $CDCl_3$ or acetone-d[6] with TMS as internal standard. THF was dried over calcium hydride.

Analytical

Elevated pressure reactions were carried out in a Buchi glasuster autoclave. ^1H NMR spectra were carried out on Bruker ACF 250, DPX 300 and ACP 400 spectrometers running at 250, 300 and 400 MHz respectively, ^{13}C at 50.6, 75.5 or 100.6 MHz and ^{19}F at 376.5 MHz. NMR spectra were assigned using COSY, HMQC, PENDANT or HMBC experiments. IR spectra were acquired from a Mattson 1000 or Perkin-Elmer Paragon 1000 FT-IR spectrometer and run on 16 and 4 scans respectively. Mass spectrometry data were run on a MicroMass AutoSpec machine using NH_3 as a carrier gas for CI experiments.

5.1 Experimental Procedures (Chapter 2)

5.1.1 Experimental for Section 2.1.2

**Phenyl N, N-Diethyl Carbamate 1[117]**
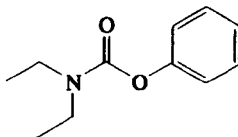
Method A: A solution of Et_2NH (2.6 mL, 25 mmol), pyridine (2.1 mL, 26 mmol) and DBU (3.8 mL, 25.5 mmol) in toluene (40 mL) was stirred with CO_2 bubbling subsurface. The solution was cooled to -10 °C in an ice-salt bath and CO_2 was bubbled continuously for 30 minutes, whereupon the solution turned cloudy white. The solution was then added by cannula to a solution of $SOCl_2$ in toluene at -10 °C and stirred at this temperature for 45 min. The reaction mixture was warmed to ambient temperature and then heated with phenol (2.98 g, 32 mmol) and DMAP (1.15 g, 9.4 mmol) in pyridine (75 mL) at 95 °C under N_2 for 24 hours. The mixture was added to ice (30g), diethyl ether (30 mL) and 1M HCl (20 mL). The mixture was extracted with diethyl ether (3 x 30 mL), the ethereal layers were combined and washed with 2M NaOH solution (30 mL) and a solution of saturated aqueous KCl. The solution was dried ($MgSO_4$), filtered and solvent removed *in vacuo* to give a light yellow oil. Phenyl N,N-diethyl carbamate was isolated after flash chromatography (SiO_2, CH_2Cl_2) as a yellow oil (0.97 g, 20%): ^1H NMR (250 MHz, $CDCl_3$) δ 1.22 (6H, 2 overlapping br t, J = 7 Hz, CH_3), 3.40 (4H, 2 overlapping br q, J = 7 Hz, CH_2), 7.08 -7.20 (3H, m, J = 8 Hz, Ar), 7.30 - 7.38 (2H, m, J = 8 Hz, Ar); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.39 (CH_3), 14.22 (CH_3),[118] 41.92 (CH_2), 42.25 (CH_2), 121.77 (C-2), 125.00

(C-4), 129.20 (C-3), 151.57 (C-1), 154.27 (C=O); MS (EI) m/z = 193 (M$^+$), 100% (100).

Method B: In pyridine (40 mL), *N,N*-diethyl carbamoyl chloride (12.7 mL. 0.10 mol) was stirred with phenol (9.55 g, 0.10 mol) under N$_2$. The solution was heated to 90 °C and left overnight. The hot mixture was then added to diethyl ether (50 mL), ice (50 g) and 1 M HCl (20 mL) and extracted with diethyl ether (3 x 20 mL). The combined ethereal layers were washed successively with 1 M NaOH solution (20 mL) and saturated aqueous KCl solution (20 mL). The solution was dried (MgSO$_4$), filtered and the solvent was removed *in vacuo* to give a light yellow oil. Phenyl *N,N*-diethyl carbamate was isolated after flash chromatography (SiO$_2$, 5:1 hexane/Et$_2$O) as a yellow oil (11.95 g, 61.5 %).

5.1.2 Experimental for Section 2.2.2

Dipropyl Dicarbonate 3[119] *via* propyl trifluoromethanesulfonyl carbonate 2
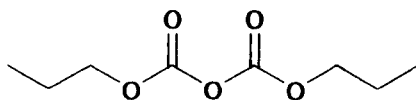
DBU (7.5 mL, 0.05 mol) was added to *n*-propanol (3.8 mL, 0.05 mol) in MeCN (30 mL) in an autoclave and stirred under CO$_2$ (3.5 bar) at -40 °C for 30 min. Trifluoromethanesulfonic anhydride (8.5 mL, 0.05 mol) in MeCN (10 mL) was added dropwise over 20 min at −40 °C. The mixture was kept at this temperature for 1h then allowed to warm to RT and the pressure released. Solvent was removed *in vacuo* from a portion and the mixture diluted with CH$_2$Cl$_2$. The solution was then washed with 10% HCl (3 x 10 mL), saturated aqueous NaHCO$_3$ (2 x 10 mL) and brine (10 mL). The solution was dried (MgSO$_4$),

filtered and solvent again removed *in vacuo*^{1}H NMR (400 MHz, CDCl$_3$) δ 0.99

(6H, t, *J* = 7 Hz, CH$_3$), 1.75 (4H, tq, *J* = 7 Hz, 7 Hz, C*H*$_2$CH$_2$O), 4.23 (4H, t, *J* = 7

Hz CH$_2$O); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 9.98 (CH$_3$), 21.68 (OCH$_2$*C*H$_2$CH$_3$),

71.39 (OCH$_2$), 148.64 (C=O); MS (EI) m/z = 190.

Phenyl *N,N*-Diethyl Carbamate 1

Method C: Et$_2$NH (1 mL, 9.65 mmol) was added to DBU (1.5 mL, 10 mmol) in

MeCN (15 mL). Carbon dioxide was bubbled subsurface, the solution was cooled

to -40 °C and CO$_2$ addition continued at this temperature for 1 h.

Trifluoromethanesulfonic anhydride (1.6 mL, 9.47 mmol) in MeCN (10 mL)

was transferred by cannula at –40 °C to the carbamate solution and the mixture

stirred under CO$_2$ for a further 90 min. A 25% aliquot was removed and added to

phenol (206 mg, 2.19 mmol) in MeCN (10 mL) by cannula, allowed to warm to

RT and stirred overnight. The solvent was removed *in vacuo*, the mixture

dissolved in CH$_2$Cl$_2$ (20 mL) and washed with 1 M NaOH solution (3 x 20 mL).

The solution was dried (MgSO$_4$), filtered and solvent removed *in vacuo* to give a

light yellow oil. The *O*-phenyl carbamate product was isolated after flash

chromatography (SiO$_2$, 30:1 CH$_2$Cl$_2$/EtOAc) as a yellow oil (0.15 g, 35%). ^{1}H

and ^{13}C NMR data and mass spectrometric data as for method A above.

N, N, N', N'-Tetraethyl Carbamic Anhydride 5[74] *via N,N*-Diethyl Triflyl Carbamate 4
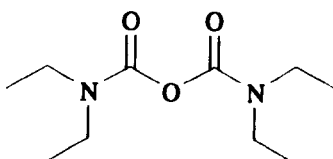
Et$_2$NH (1.1 mL, 10.6 mmol) and DBU (1.6 mL , 10.7 mmol) were stirred in anhydrous MeCN (20 mL) with CO$_2$ bubbling subsurface. The mixture was cooled to –40 °C for 1h. The solution was then transferred by cannula to triflic anhydride (1.8 mL, 10.6 mmol) in anhydrous MeCN (10 mL) at -40 °C. The solution was kept at this temperature for 20 min under CO$_2$ atmosphere, then allowed to warm to RT. The solvent was removed *in vacuo* and the mixture diluted with CH$_2$Cl$_2$. The solution was then washed with 1 M HCl (2 x 20 mL), saturated aqueous NaHCO$_3$ (2 x 20 mL) and brine (20 mL). ^{1}H NMR (CDCl$_3$) δ 1.19 (12H, 2 overlapping t, *J* = 7 Hz, CH$_3$), 3.29 (4H, q, *J* = 7 Hz, CH$_2$), 3.37 (4H, q, *J* = 7 Hz, CH$_2$). ^{13}C NMR (CDCl$_3$) δ 12.79 (C*H$_3$*CH$_2$N), 13.90 (C*H$_3$*CH$_2$N), 42.07 (CH$_2$N), 42.16 (CH$_2$N), 150.42 (C=O); MS (EI) *m/z* = 216. The product was identified as *N,N,N',N'*- tetraethyl carbamic anhydride.

n-Propyl *N, N*-Diethyl Carbamate 6[54]
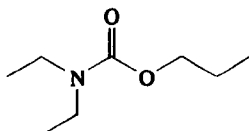
Method A: DBU (0.45 mL, 3 mmol) was added to *n*-propanol (0.2 mL, 2.67 mmol) in anhydrous MeCN (30 mL) in an autoclave and stirred under CO$_2$ (3.5 bar) at –40 °C for 30 min. Trifluoromethanesulfonic anhydride (0.45 mL, 2.66 mmol) in MeCN (10 mL) was added dropwise over 10 min at –40 °C. The mixture was kept at this temperature for 30 min then allowed to warm to RT and the pressure released after 20 min. Et$_2$NH (0.3 mL, 2.9 mmol) was added to anhydrous MeCN (5 mL). The system was pressurised with CO$_2$ (0.5 bar) and stirred overnight. The solvent was removed *in vacuo* from an aliquot of the

reaction and the mixture diluted with CH_2Cl_2. The solution was then washed with 10% H_2SO_4 (3 x 10 mL), saturated aqueous $NaHCO_3$ (2 x 10 mL) and brine (10 mL). The solution was dried ($MgSO_4$), filtered and solvent again removed *in vacuo*. The product was not isolated but NMR and mass spectroscopy data matched the literature compound.

5.1.3 Experimental for Section 2.3.2

N,N-Diethyl Methanesulfonyl Carbamate 7
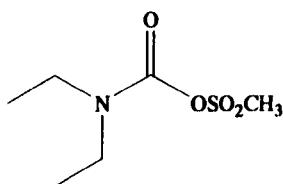
Et_2NH (0.5 mL, 4.8 mmol) and DBU (0.9 mL, 6.03 mmol) were added to anhydrous MeCN (10 mL). The system was purged with CO_2 then CO_2 was bubbled subsurface whilst the mixture was cooled to –10 °C and stirred for 40 min. A solution of methanesulfonic anhydride (0.85 g, 4.88 mmol) in acetonitrile (4 mL) was transferred by cannula at –10 °C to the carbonate solution. The mixture was stirred at this temperature for a further 25 min and then stirred at 0 °C for 25 min. The stream of CO_2 was halted and the mixture was allowed to warm overnight. The crude mixture was split into two aliquots and the solvent was removed *in vacuo* and diluted with CH_2Cl_2. One aliquot was washed with H_2SO_4 (0.5 M, 2 x 25 mL) and brine (30 mL). The second aliquot was washed with distilled water (2 x 25 mL), H_2SO_4 (0.5 M, 2 x 25 mL) and brine (30 mL). The product could not be separated from diethyl methanesulfonamide: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.21 (6H, 2 overlapping t, J = 7 Hz, CH_3CH_2N), 3.35 (4H, 2 overlapping q, J = 7 Hz, CH_3CH_2N), 3.42 (3H, s, CH_3SO_2); ^{13}C NMR ($CDCl_3$)

δ 14.01 (CH_3CH_2N), 14.25 (CH_3CH_2N), 40.65 (CH_3SO_2), 42.86 (CH_2N), 42.96 (CH_2N), 148.00 (C=O).

Propyl Methanesulfonyl Carbonate 8
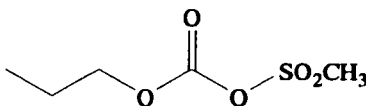
n-Propanol (0.4 mL, 5.35 mmol) and DBU (1 mL, 6.70 mmol) were dissolved in anhydrous MeCN (12 mL). CO_2 was bubbled subsurface and the solution was cooled to −42 °C for 45 minutes. The mixture was allowed to warm to −20 °C and was transferred by cannula over 30 minutes to methanesulfonic anhydride (1.86 g, 10.7 mmol; 2 eq.) in MeCN (4 mL) at the same temperature. The mixture was stirred for 10 min then diluted with Et_2O (50 mL) and washed with H_2SO_4 (0.5 M, 2 x 50 mL) and brine (60 mL). The ethereal solution was dried with anhydrous potassium carbonate, filtered and the solvent was removed *in vacuo* to give an oil (493 mg). The product could not separated from n-propyl mesylate.[120] Integration of the methanesulfonyl signals of the product and n-propyl mesylate in the ^{1}H-NMR spectrum showed that the product was 90% of the oil, overall yield 45 ^{1}H NMR (CDCl$_3$) δ 1.00 (3H, t, J = 7 Hz, CH_3CH$_2$CH$_2$O), 1.77 (2H tq, J = 7Hz, 7 Hz, CH$_3$CH_2CH$_2$O), 3.39 (3H, s, CH$_3$SO$_2$), 4.27 (2H, t, J = 7 Hz, CH$_3$CH$_2$CH_2O); ^{13}C NMR (CDCl$_3$) δ 9.94 (CH$_3$CH$_2$CH$_2$O), 21.61 (CH$_3$CH$_2$CH$_2$O), 39.65 (CH$_3$SO$_2$), 72.37 (CH$_3$CH$_2$CH$_2$O), 147.83 (C=O); MS (EI) m/z = 182. Addition of 1 drop of Et$_3$N or DBU to the NMR sample gave no n-propyl mesyl carbonate on re-analysis.

5.1.4 Experimental for Section 2.7: Attempted Synthesis of Sulfonyl Carbonate variants

n-Propyl Mesyl Carbonate 8a

n-Propanol (0.2 mL, 2.67 mmol) and DBU (0.5 mL, 3.35 mmol) were dissolved in anhydrous MeCN (4 mL). CO_2 was bubbled subsurface and the solution was cooled to −42 °C for 30 minutes. The mixture was allowed to warm to −25 °C and transferred to 1.4 molar eq. of methanesulfonyl chloride in MeCN (5 mL). The stirring mixture was allowed to warm to RT overnight and analysed by ^{1}H NMR spectroscopy. The major product was n-propyl mesylate as compared with literature data.[120]

n-Propyl Nosyl Carbonate 9

As for **8a** using 1.4 molar eq. of 4-nitrobenzenesulfonyl chloride. ^{1}H NMR spectroscopy indicated no presence of any n-propanol derivatives.

n-Propyl Tosyl Carbonate 10

As for **8a** but the carbonate was anion added to TsCl (0.56g, 2.94 mmol; 1.1 eq) in MeCN (2.5 mL) over the course of 50 minutes. After warming to RT, the reaction was stirred for 75 min. ^{1}H NMR spectroscopy indicated a 1:1 mixture of dipropyl dicarbonate[119] and TsOH only.

5.2 Experimental Procedures (Chapter 3)

5.2.1 Experimental for Section 3.1

Phenyl *N,N*-Diethyl Carbamate 1

Method D: Et_2NH (0.5 mL, 4.8 mmol) and DBU (0.8 mL, 5.36 mmol) were added to anhydrous MeCN (10 mL). The system was purged with CO_2 and then CO_2 was bubbled subsurface with stirring whilst the solution was cooled to 0 °C. This was continued for 40 min, then methanesulfonic anhydride (0.85 g, 4.88 mmol) in dry MeCN (5 mL) was transferred by cannula to the carbamate mixture at 0 °C. The solution was kept cool for 15 min then allowed to warm to RT and stirred overnight in the dark. Two-thirds of the solution was added to phenol (0.21 g, 2.23 mmol) and pyridine (1mL), stirred for 5 min and then heated to reflux for a further 42 h. The mixture was allowed to cool and the solvent was removed *in vacuo*, diluted with CH_2Cl_2 (20 mL) and washed with H_2SO_4 (0.5 M, 2 x 25 mL), NaOH (1 M, 2 x 25 mL) and brine (25 mL). The solution was dried $(MgSO_4)$, filtered and solvent removed *in vacuo*. No further purification was required. The *O*-phenyl carbamate product was isolated as a yellow oil (92 mg, 21%). ^1H and ^{13}C NMR data and mass spectral data as for method A above.

n-Propyl *N,N*-Diethyl Carbamate 6
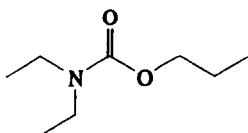
Method B: Diethylamine (0.5 mL, 4.83 mmol) and DBU (0.9 mL, 6.03 mmol; 1.25 eq) were stirred in anhydrous MeCN (8 mL). The flask was purged with CO_2 before cooling to −20 °C, then CO_2 bubbled subsurface for 1h. Methanesulfonic anhydride (0.96 g, 5.51 mmol) in anhydrous MeCN (3 mL) was

then transferred dropwise to the carbamate solution. After addition was complete, the solution was kept cool for 30 minutes, then allowed to warm to RT with stirring. *n*-Propanol (0.4 mL, 5.35 mmol) and Et$_3$N (0.7 mL, 5.02 mmol) were added and, after stirring for 1h, the reaction was heated at reflux overnight. After cooling, the solvent was removed *in vacuo* and the residue was dissolved in CH$_2$Cl$_2$ (100 mL), solids were filtered off and the organic solution was washed with H$_2$SO$_4$ (0.125 M, 2 x 100 mL) and brine (100 mL). The crude product was dried (MgSO$_4$) , filtered and concentrated to dryness (510 mg). ^{1}H NMR spectroscopy indicated a 24:1:1 ratio of carbamate/tetraethyl urea/ diethyl methanesulfonamide. Flash chromatography (SiO$_2$, 4:1 hexane/EtOAc) gave the product as a clear oil (200 mg, 26%): ^{1}H NMR (250 MHz, CDCl$_3$) δ 0.95 (3H, t, *J* = 7 Hz, C*H*$_3$CH$_2$CH$_2$O), 1.12 (6H, t, *J* = 7 Hz, C*H*$_3$CH$_2$N), 1.65 (2H, tq, *J* = 7 Hz, 7 Hz, CH$_3$C*H*$_2$CH$_2$O), 3.29 (4H, br m, CH$_3$C*H*$_2$N), 4.03 (2H, t, *J* = 7 Hz, CH$_3$CH$_2$C*H*$_2$O); ^{13}C NMR (CDCl$_3$) δ 10.54 (*C*H$_3$CH$_2$CH$_2$O), 14.25 (*C*H$_3$CH$_2$N), 14.39 (*C*H$_3$CH$_2$N), 22.49 (CH$_3$*C*H$_2$CH$_2$O), 41.43 (CH$_3$*C*H$_2$N), 41.74 (CH$_3$*C*H$_2$N), 66.59 (CH$_3$CH$_2$*C*H$_2$O), 156.20 (C=O); MS (CI) m/z = 160 (MH$^+$). Anal. Calcd. for C$_8$H$_{17}$NO$_2$: C, 60.35; H, 10.76; N, 8.80. Found: C, 59.90; H, 10.76; N, 8.55.

n-Propyl *N,N*-Diethyl Carbamate 6

Method C: DBU (1.75 mL, 11.72 mmol) was added to *n*-propanol (0.7 mL, 9.36 mmol) in anhydrous MeCN (10 mL) in an autoclave and stirred under CO$_2$ (3.5 bar) at 0 °C for 60 minutes. Methanesulfonic anhydride (1.67, 9.58 mmol) in MeCN (4 mL) was added all at once to the stirring mixture. The mixture was kept at 0 °C until no more precipitate remained, then allowed to warm to RT (60 minutes) then the pressure was released after a further 15 min. The reaction mixture was transferred to a two-necked flask and then added to it were Et$_2$NH (1

mL, 9.65 mmol) and pyridine (1.7 mL, 21 mmol). The reaction was then heated to reflux for 21h. Solvent was removed *in vacuo* and the mixture was diluted with CH_2Cl_2 (30 mL). The solution was then washed with H_2SO_4 (0.5 M, 3 x 30 mL), saturated aqueous $NaHCO_3$ (2 x 40 mL) and brine (40 mL). The solution was dried ($MgSO_4$), filtered and solvent again removed *in vacuo*. The product was not isolated but NMR and mass spectroscopy data matched the literature compound[54] and material synthesised from Et_2NH and CO_2.

1,5-Pentyl bis(*N,N*-diethylcarbamate) 11
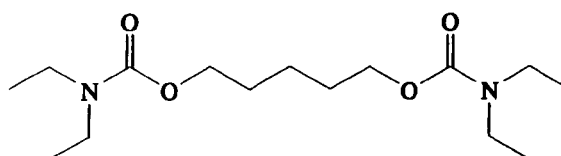
1,5-Pentanediol (0.14 mL, 1.34 mmol) and DBU (0.5 mL, 3.35 mmol) were dissolved in anhydrous MeCN (4 mL). CO_2 was bubbled subsurface and the solution cooled to –20° C for 1h. The carbonate salt solution was transferred to a solution of methanesulfonic anhydride (0.56g, 3.2 mmol) in MeCN (2 mL) at the same temperature over 5 min. After 5 min, Et_2NH (0.35 mL, 3.38 mmol) was added and the reaction was kept cool for 20 min under N_2. The reaction was then allowed to warm to ambient temperature. Tlc showed incomplete reaction. Et_3N (0.2 mL, 1.43 mmol) was added and the mixture stirred for 2 days. Heating the reaction after this time showed no change by tlc. EtOAc (30mL) was added, the organic layers washed with HCl (0.5 M, 2 x 30 mL) and brine (2 x 30 mL). The solution was dried ($MgSO_4$), solvent removed *in vacuo* and purification by flash chromatography (SiO_2, 3:1 EtOAc / hexane) gave an oil (127mg, 31%): IR (film) 1698 cm^{-1} (C=O); ^1H NMR: δ 1.12 (12H, t, J = 7 Hz, CH$_3$), 1.45 - 1.68 (6H, overlapping m, OCH$_2$C*H$_2$*C*H$_2$*C*H$_2$*CH$_2$O), 3.24 (8H, br m, CH$_2$N), 4.08 (4H, t, J

= 7 Hz, CH_2O); ^{13}C NMR: δ 13.57 (CH_3CH_2N), 14.15 (CH_3CH_2N), 22.62 ($CH_2CH_2CH_2O$), 28.76 (CH_2CH_2O), 41.15 (CH_2N), 41.64 (CH_2N), 64.79 (CH_2O), 155.92 (C=O); HRMS (EI) Calculated 302.2206 Found 302.2208

The mono substituted product below was also isolated.

1-Hydroxypentyl 5-*N*,*N*-diethylcarbamate 12
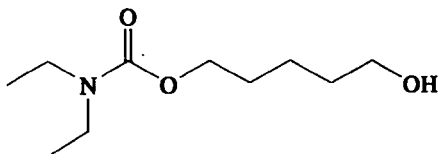
The product was isolated as an oil (90mg, 33%): IR (film) 3428 cm^{-1} (OH), 1682 cm^{-1} (C=O); ^1H NMR δ 1.11 (6H, t, J = 7 Hz, CH_3), 1.39 - 1.72 (6H, overlapping m, $OCH_2CH_2CH_2CH_2CH_2O$), 2.10 (1H, br, OH), 3.26 (4H, br m, CH_2N), 3.65 (2H, t, J = 6 Hz CH_2OH), 4.08 (2H, t, J = 7 Hz, NCO_2CH_2); ^{13}C NMR: δ 13.46 (CH_3CH_2N), 13.91 (CH_3CH_2N), 22.16 ($OCH_2CH_2CH_2CH_2CH_2O$), 28.83 ($OCH_2CH_2CH_2CH_2CH_2OH$), 32.21 ($OCH_2CH_2CH_2CH_2CH_2OH$), 41.18 (CH_2N), 41.59 (CH_2N), 62.52 (CH_2OH), 64.84 ($Et_2NCO_2CH_2$), 156.11 (C=O); HRMS (EI) Calcd. for $C_{10}H_{21}NO_3$ 203.1521, found 204.1596 ($C_{10}H_{22}NO_3$, MH$^+$).

n-Propyl *N*-*n*-Butyl Carbamate 13
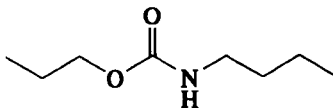
n-Propanol (0.7 mL, 9.36 mmol) and DBU (1.75 mL, 11.57 mmol; 1.24 eq) were dissolved in anhydrous MeCN (12 mL), CO_2 was bubbled subsurface and the solution cooled to –42 °C for 45 minutes. The mixture was allowed to warm to –30 °C and was transferred by cannula over 60 minutes to methanesulfonic

anhydride (2.03g, 11.65 mmol; 1.25eq.) in MeCN (6 mL) at the same temperature. Once the reaction reached RT, it was split into three equal fractions and had added butylamine (1.3 eq) and pyridine (1.4 eq) dissolved in MeCN (1 mL). The resulting reaction was exothermic and required cooling in ice-water. The reaction was subsequently stirred at ambient temperature overnight. EtOAc (50 mL) was then added and the solution was washed with H_2SO_4 (0.2 M, 2 x 50 mL) and brine (50 mL). The organic layer was dried (K_2CO_3), filtered and solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, CH_2Cl_2) yielded a clear oil (208 mg, 42%); IR (film) 3336, 1695; ^{1}H NMR ($CDCl_3$) δ 0.89-0.96 (6H, 2 overlapping t, CH_3), 1.27–1.55 (4H, 2 overlapping m, CH_2CH_2CH$_2$N), 1.62 (2H, tq, J = 7 Hz, 7 Hz, CH_2CH$_2$O), 3.17 (2H, m, J = 6 Hz, CH$_2$N), 4.01 (2H, t, J = 7 Hz, CH$_2$O), 4.69 (1H, br, N-H); ^{13}C NMR (50.6 MHz, $CDCl_3$) δ 10.29 (CH$_3$CH$_2$CH$_2$O), 13.69 (CH$_3$CH$_2$CH$_2$CH$_2$NH), 19.84 (CH$_3$$CH_2CH_2CH_2$NH), 22.34 (CH$_3$$CH_2CH_2$O), 32.05 (CH$_3CH_2$$CH_2CH_2$NH), 40.62 (CH$_3CH_2CH_2$$CH_2$NH), 66.25 (CH$_3CH_2$$CH_2$O), 156.79 (C=O); HRMS (CI) calcd. 160.1337, found 160.1332. Anal. Calcd. for $C_8H_{17}NO_2$: C, 60.35; H, 10.76; N, 8.80. Found: C, 60.05; H, 10.71; N, 8.68.

Benzyl *N*-Phenyl Carbamate 14[52, 121]
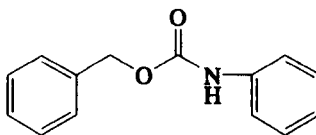
Followed procedure as for **13** but using benzyl alcohol in place of *n*-propanol and aniline in place of *n*-butylamine. Purification by flash chromatography (SiO_2, CH_2Cl_2) and recrystallisation from diethyl ether/hexane gave a white solid (316mg, 43%): IR 1726 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.21 (2H, s, CH$_2$), 6.65 (1H,

br, N-H), 7.04 – 7.09 (1H, m, J = 7 Hz, *para* H of PhNH), 7.28 – 7.40 (9H,

overlapping m, Ar); ^{13}C NMR (CDCl$_3$) δ 66.89 (CH$_2$), 118.70 (Ph C-4), 123.40

(Bn C-2), 128.16 (Ar), 128.21 (Ar), 128.49 (Ar), 128.91 (Ar), 135.92 (Bn C-1),

137.68 (Ph C-1), 153.44 (C=O); HRMS (EI) calcd. 227.0946 , found. 227.0945

Anal. Calcd. for C$_{14}$H$_{13}$NO$_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.02; H,

5.81; N, 6.17

n-Propyl *N*-Phenyl Carbamate 15[122]
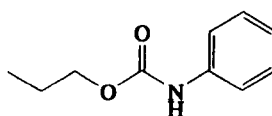
Followed procedure as for **13** using aniline instead of *n*-butylamine and a

stoichiometric amount of DBU. Crystallisation from cyclohexane yielded a

white solid (88 mg, 21 %): IR (CH$_2$Cl$_2$) 1709 cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$) δ

0.98 (3H, t, J = 7 Hz, CH$_3$), 1.70 (2H, tq, J = 7 Hz, 7 Hz, CH_2CH$_2$O), 4.13 (2H, t,

J = 7 Hz, CH$_2$), 6.64 (1H, br, NH), 7.03 – 7.08 (1H, apparent t, J = 7 Hz, H-4),

7.27 – 7.40 (4H, m, Ar); ^{13}C NMR (CDCl$_3$) δ 10.33 (CH$_3$), 22.24 (CH$_2$), 66.83

(CH$_2$), 118.58 (C-2), 123.29 (C-4), 129.01 (C-3), 137.93 (C-1), 153.69 (C=O);

MS (EI) m/z = 179. Anal. Calcd. for C$_{10}$H$_{13}$NO$_2$: C, 67.02; H, 7.31; N, 7.82.

Found: C, 67.05; H, 7.33; N, 7.81.

Benzyl *N*-*n*-Propyl Carbamate 16[123]
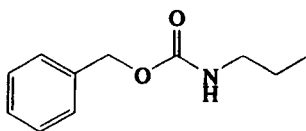
Procedure as for **13** using benzyl alcohol in place of *n*-propanol. Crystallisation from hexane gave 292mg, no further purification was possible. Yield by ^{1}H NMR was 48% (204 mg) and purity was 70%. ^{1}H NMR (CDCl$_3$) δ 0.91 (3H, t, J = 7 Hz, CH$_3$), 1.51 (2H, tq, J = 7 Hz, 7 Hz, CH_2CH$_2$N), 3.15 (2H, br m, CH$_2$N), 5.09 (2H, s, CH$_2$O), 7.28 – 7.37 (5H, m, Ph); ^{13}C NMR (CDCl$_3$) δ 11.15 (CH$_3$), 23.13 (CH$_2$), 66.52 (CH$_2$), 126.92 (Ar), 127.93 (Ar), 128.36 (Ar), 136.53 (C-1), 156.37 (C=O); HRMS (CI) calcd. 194.1180, found 194.1181

5.2.2 Experimental for Section 3.2

Di-*n*-propyl carbonate 17[30]
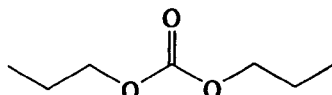
Procedure as for **13** but *n*-propanol was added instead of an amine. The product was extracted with Et$_2$O. **17** was also synthesised by two other similar methods.

1) *n*-Propyl mesylate was synthesised by a standard procedure using methanesulfonic anhydride.[120] *n*-propanol (0.4 mL, 5.35 mmol) and DBU (1 mL, 6.70 mmol) were stirred in anhydrous acetonitrile (6 mL). Carbon dioxide was continually bubbled subsurface and the mixture cooled to –42 °C. After 50 minutes, propyl mesylate (0.5 mL, 4.03 mmol) in acetonitrile (5 mL) was added dropwise over three minutes. After 15 minutes, the mixture was allowed to warm to room temperature slowly, whilst stirring over 2.5 hours. The reaction was then heated to 40 °C for 3 days. Dipropyl carbonate was the only product (300 mg, 51%).

2) *n*-Propanol (0.4 mL, 5.35 mmol) and DBU (1 mL, 6.70 mmol) were stirred in anhydrous MeCN (6 mL) and cooled to 0 °C. Methanesulfonic anhydride (311

mg, 1.78 mmol) was dissolved in MeCN (4 mL) and added dropwise over 10 min to the stirring alcohol solution. After addition was complete, the mixture was cooled to – 40 °C and CO_2 was bubbled subsurface for 1 h, then warmed to –20 °C with CO_2 bubbling subsurface for another hour. The mixture was stirred for a further 30 min after warming to RT. Tlc showed some propyl mesylate. The reaction was heated to 50 °C overnight and after cooling, extracted with Et_2O following the procedure for **13**. The product was identified as dipropyl carbonate with residual propyl mesylate. Integration of mesyl signals in the ^1H NMR spectrum indicated a 28 % yield of dipropyl carbonate.

All products were identical to authentic material with matching NMR signals.

^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (6H, t, J = 7 Hz, CH_3), 1.70 (4H, tq, J = 7 Hz, 7 Hz, CH_2CH$_2$O), 4.09 (4H, t, J = 7 Hz, CH_2O); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 10.21 (CH_3), 22.08 (CH_2), 69.45 (CH_2), 155.48 (C=O); HRMS (EI) calcd. 146.0943, found 146.0949.

Phenyl *n*-Propyl carbonate 18[124]
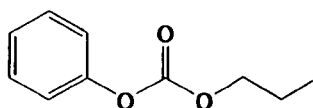
Procedure as for **13**, but phenol was added instead of an amine with no pyridine. The reaction was heated with phenol to 40 °C for 22h. The crude oil was purified by flash chromatography (SiO_2, CH_2Cl_2) and isolated as a clear oil: (170 mg, 35%): IR (film) 1761 cm^{-1} (C=O); ^1H NMR: δ 1.00 (3H, t, J = 7 Hz, CH_3), 1.77 (2H, tq, J = 7 Hz, 7 Hz, CH_2CH$_2$O), 4.22 (2H, t, J = 7 Hz, CH_2O), 7.16 - 7.48 (5H, overlapping m, Ph); ^{13}C NMR: δ 10.20 (CH_3), 22.00 (CH_2), 70.34 (CH_2), 121.10 (Ar), 125.97 (C-4), 129.47 (Ar), 151.19 (C-1), 153.81 (C=O); MS

(EI) m/z = 180 (M⁺). Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found C, 66.31; H, 6.66.

Benzyl *i*-Propyl Carbonate 19[125]
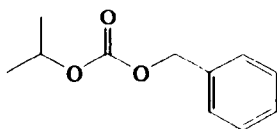
*i*-Propanol (0.4mL, 5.22 mmol) was dried over 4Å molecular sieves and then stirred with DBU (0.78mL, 5.22 mmol) in MeCN (7mL). CO_2 was bubbled subsurface and then the reaction was cooled to –42 °C. CO_2 was bubbled for a further 45 minutes at this temperature. The resulting carbonate suspension was transferred to a solution of methanesulfonic anhydride (1.052g, 6.04mmol; 1.16eq) in MeCN (3.5mL) at the same temperature, over 90 minutes, by cannula. After warming to 5 °C, the reaction was split into two aliquots. Benzyl alcohol (0.35mL, 3.38mmol) and pyridine (0.25 mL, 3.13 mmol) were added to an aliquot. After one minute, a precipitate formed and the temperature rose to 23 °C. The reaction was cooled to 5 °C again and stirred overnight. The reaction was filtered and added to Et_2O (30mL). The organic layer was washed with HCl (0.2M, 2 x 30mL) and brine (30mL). The solvent was removed in vacuo to give 282 mg. Analysis indicated the required product, benzyl alcohol, benzyl mesylate and a small amount of di-*i*-propyl carbonate in the ratio 26:39:2:1. Yield by ¹H NMR was 108 mg (21%): ¹H NMR (CDCl₃) δ 1.30 (6H, d, *J* = 6 Hz, CH₃), 4.89 (1H, septet, *J* = 6 Hz, CH), 5.14 (2H, s, CH₂), 7.35-7.39 (5H, overlapping m, Ar); ¹³C NMR (CDCl₃) δ 21.73 (CH₃), 69.25 (CH₂), 72.10 (CH), 128.27 (Ar), 128.40 (C-4), 128.51 (Ar), 135.32 (C-1), 154.59 (C=O); HRMS (CI) Calcd. for $C_{11}H_{14}O_3$ 195.1021 , found 195.1019

Benzyl Phenyl Carbonate 20[131]
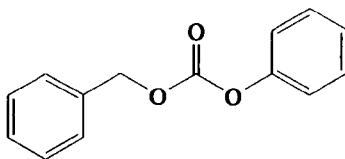
Procedure as for **13** using benzyl alcohol in place of *n*-propanol and phenol instead of an amine. The product was extracted with Et$_2$O. Yield by ^{1}H NMR was 31%. The crude oil was purified by flash chromatography (SiO$_2$, 5:4 cyclohexane/ CH$_2$Cl$_2$) and isolated as clear oil (25%, 182mg): IR (thin film) 1762; ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.27 (2H, s, CH$_2$), 7.16 - 7.47 (10H, overlapping m, Ar); ^{13}C NMR (75.5 MHz, CDCl$_3$) 70.32 (CH$_2$), 121.01 (Ar), 126.04 (Ar), 128.54 (Ar), 128.67 (Ar), 128.75 (Ar), 129.46 (Ar), 134.73 (Bn, C-1), 151.08 (Ph, C-1), 153.65 (C=O); MS (EI) *m/z* = 228. Anal. Calcd. for C$_{14}$H$_{12}$O$_3$: C, 73.67; H, 5.30. Found: C, 73.49; H, 5.23.

Benzyl *n*-Propyl Carbonate 21[126]
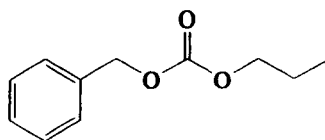
Procedure as for **13** using benzyl alcohol in place of *n*-propanol and *n*-propanol in place of an amine. A 5 mL (2.3 mmol) aliquot of the reaction was removed when at 0 °C , followed by addition of benzyl alcohol (0.3 mL, 2.90 mmol; 1.3eq.) and then pyridine (0.25 mL, 3.09 mmol; 1.39eq.) to the aliquot removed. Tlc after 1h showed a product spot. There was no further change in the reaction during 3d. The reaction was diluted with Et$_2$O (40 mL), washed with HCl

(0.125 M, 2 x 40 mL), brine (40 mL), dried (K_2CO_3) and filtered. Isolation by flash chromatography (SiO2, 1:1 cyclohexane / CH_2Cl_2) yielded a colourless oil (122 mg, 28%): IR (film) 1745 cm^{-1} (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7 Hz, CH_3CH$_2$CH$_2$O), 1.69 (2H, tq, J = 7 Hz, 7 Hz, CH$_3$CH_2CH$_2$O), 4.10 (2H, t, J = 7 Hz, CH$_3$CH$_2$CH_2O), 5.15 (2H, s, PhCH_2O), 7.31 – 7.41 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 10.18 (CH$_3$CH$_2$CH$_2$O), 22.01 (CH$_3$CH$_2$CH$_2$O), 69.81 (PhCH$_2$O), 70.08 (CH$_3$CH$_2$CH$_2$O), 128.32 (Ar), 128.49 (C-4), 128.59 (Ar), 135.36 (C-1), 155.27 (C=O); MS (EI) m/z = 194; Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.68; H, 7.18

Methyl Methanesulfonyl Carbonate 22
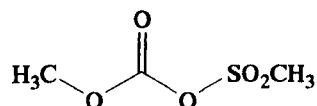
"Hi-Dry" MeOH (0.15 mL) and DBU (0.55 mL, 3.86 mmol) were stirred in anhydrous MeCN (5 mL). Carbon dioxide was bubbled subsurface and the reaction was cooled to – 42 °C for 45 min. The carbonate solution was allowed to warm to – 30 °C and was transferred at the same temperature by cannula to a solution of methanesulfonic anhydride (768 mg, 4.41 mmol) in MeCN (3 mL) over 75 min. An aliquot of the reaction was quenched with distilled water (4 mL), extracted with CH_2Cl_2 (2mL) and solvent removed *in vacuo* to yield crude **22** which could not be purified further: ^{1}H NMR ($CDCl_3$) δ 3.39 (3H, s, CH$_3$SO$_2$), 3.96 (3H, s, CH$_3$O); ^{13}C NMR: δ 39.45 (CH$_3$SO$_2$), 54.92 (CH$_3$O), 146.62 (C=O); MS (CI) m/z = 172 (M$^+$ + 18).

Methyl Phenyl Carbonate 23[127]
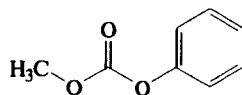
The procedure was followed as for **22** with the following amendment. After the addition of the carbonate salt was complete, the reaction was allowed to warm to 7 °C. Phenol (424 mg, 4.51 mmol) was dissolved in MeCN (1 mL) with pyridine (0.35 mL, 4.33 mmol) and added to the mesyl carbonate. A temperature increase to 24 °C was noted and the reaction was cooled back to 7 °C. A precipitate had formed within 30 s, no further change was observed within 48 hours. The reaction was diluted with Et$_2$O (40 mL) and washed with HCl (0.2 M, 2 x 40 ml), NaOH (0.125 M, 40 mL) and brine (40 mL). The product was isolated as a colourless oil (147 mg, 26%), purity by ^{1}H NMR spectroscopy was >95%: IR (film) 1763 cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$) δ 3.91 (3H, s, CH$_3$), 7.16-7.41 (5H, m, Ph); ^{13}C NMR (CDCl$_3$) δ 55.37, 121.01 (Ar), 126.06 (C-4), 129.48 (Ar), 151.07 (C-1), 154.28 (C=O); HRMS (EI) Calcd. 152.0473, found 152.0429.

5.2.3 Experimental for Section 3.3

n-**Propyl *S*-3,5-Dichlorophenyl Thiocarbonate 24**
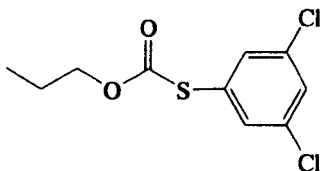
Procedure as for **13** but 1.25 eq 3,5-dichlorothiophenol was added instead of an amine. The reaction needed cooling after addition of the thiol. Analysis by tlc after 1h showed a negligible amount of thiol remaining. The reaction was stirred overnight at ambient temperature. The crude mixture was diluted with Et_2O (50mL), washed with H_2SO_4 (0.2 M, 2 x 50mL), NaOH (0.1 M, 2 x 50mL) and brine (50mL). The solution was dried (K_2CO_3), filtered and the solvent was removed *in vacuo*. Purification by flash chromatography (SiO_2, 24:1 cyclohexane/CH_2Cl_2) yielded a clear oil (307mg, 37%): IR (film) 1731 cm^{-1} (C=O); ^{1}H NMR (250 MHz, CDCl$_3$) δ 0.96 (3H, t, J = 7 Hz, CH$_3$), 1.72 (2H, tq, J = 7 Hz, 7 Hz, CH$_2$), 4.23 (2H, t, J = 7 Hz, CH$_2$), 7.40 (1H, t, J = 2 Hz, H-4), 7.44 (2H, apparent d, J = 2 Hz, H-2 and H-6); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 10.21 (CH$_3$), 22.00 (CH$_2$CH$_2$O), 70.15 (CH$_2$CH$_2$O), 129.67 (C-4), 130.92 (C-1), 132.57 (C-2), 135.14 (C-3), 168.05 (C=O); HRMS (EI) calcd. 263.9779, found 263.9774. Anal. Calcd. for C$_{10}$H$_{10}$Cl$_2$O$_2$S: C, 45.30; H, 3.80. Found: C, 45.25; H, 3.71.

Benzyl *S*-Ethyl Thiocarbonate 25
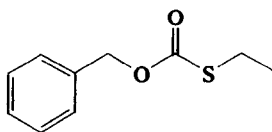
Procedure as for **13** using benzyl alcohol in place of *n*-propanol and ethanethiol in place of an amine. Purification by flash chromatography (SiO_2, 24:1 cyclohexane/CH_2Cl_2) gave the isolated product as a clear oil (118 mg, 25%): IR (film) 1702 cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$) δ 1.32 (3H, t, J = 7 Hz, CH_3CH$_2$S), 2.88 (2H, q, J = 7 Hz, CH$_2$S), 5.23 (2H, s, CH$_2$O), 7.32-7.37 (5H, m, Ph); ^{13}C

NMR (CDCl$_3$) δ 14.96 (CH$_3$), 25.38 (CH$_2$S), 68.71 (CH$_2$O), 128.56 (Bn), 128.52 (Bn), 128.44 (Bn), 135.23 (C-1), 164.31 (C=O); HRMS (EI) calcd. 196.05580, found 196.05581. Anal. Calcd. for C$_{10}$H$_{12}$O$_2$S: C, 61.20; H, 6.16. Found: C, 61.05; H, 6.11.

Benzyl *S*-3,5-Dichlorophenyl Thiocarbonate 26
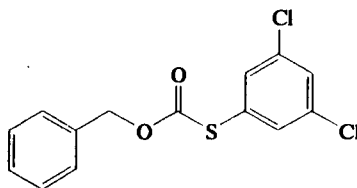
Procedure used as for **13** using benzyl alcohol in place of *n*-propanol and 3,5-dichlorothiophenol in place of an amine. A NaOH wash (0.1 M, 40 mL) was also carried out. Crude yield was 675 mg containing a 1:2 ratio of the product to the aromatic disulfide, yield by ^{1}H NMR spectroscopy 33%. Flash chromatography (SiO$_2$, 24:1 cyclohexane/CH$_2$Cl$_2$) of the crude oil gave 127 mg (19%) of product: IR (film) 1731 cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$) δ 5.27 (2H, s, CH$_2$), 7.35 – 7.41 (6H, overlapping m, Ar), 7.44 (2H, apparent d, *J* = 2 Hz, H'-2 and H'-6); ^{13}C NMR (CDCl$_3$) 70.01 (CH$_2$), 128.59 (Bn), 128.71 (Bn), 128.83 (Bn), 129.80 (Ar, C-4), 130.62 (Ar C-1), 132.60 (Ar C-2), 135.19 (Ar C-3, C-Cl), 135.76 (Bn C-1), 168.09 (C=O); HRMS (CI) calcd. (M$^+$ +18) 330.0122, found 330.0127.

5.3 Experimental Procedures (Chapter 4)

5.3.1 Experimental for Section 4.2

Bis-(2-hydroxyethyl)-4-nitrobenzenesulfonamide 27[111]
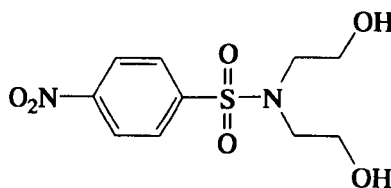
Diethanolamine (0.6mL, 6.26 mmol) was dissolved in CH_2Cl_2 (20 mL) with Et_3N (0.7 mL, 5.02 mmol). An addition funnel was connected to the flask containing 4-nitrobenzenesulfonyl chloride (1.00 g, 4.51 mmol) in CH_2Cl_2 (50mL). The reaction was purged with N_2 and cooled in an ice bath. The sulfonyl chloride solution was added dropwise to the diethanolamine solution over 3 hours. The reaction was kept cool for a further hour, then allowed to warm to ambient temperature. The solvent was removed *in vacuo* and the solid was recrystallised twice from water at 70 °C to yield white needles (1.118 g, 85%): m.p. 120-121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.15 (2 x OH), 3.35 (4H, t, J = 5 Hz, CH_2N), 3.90 (4H, t, J = 5 Hz, CH_2O), 8.03 (2H, d, J = 9 Hz, Ar), 8.39 (2H, d, J = 9 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 51.05 (CH_2N), 60.13 (CH_2OH), 123.36 (Ar), 127.75 (Ar), 144.19 (C-1), 149.13 (C-4); HRMS (CI) calculated 291.0651 found 291.0647; Anal. Calcd. for $C_{10}H_{14}NO_6S$ C, 41.38; H, 4.86; N, 9.65. Found C, 41.20; H, 4.79; N, 9.54.

Bis-(2-ethylenediethylcarbamate)-4-nitrobenzenesulfonamide 28[128]
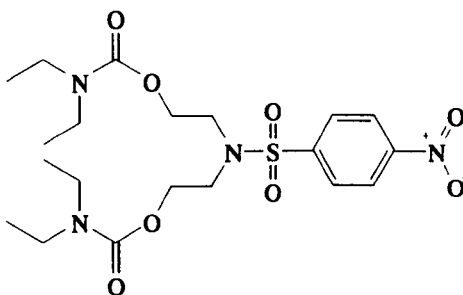
Et_2NH (0.2mL, 1.93 mmol) and DBU (0.36 mL, 2.4mmol; 1.25eq) were both added to anhydrous MeCN (8 mL) in a 3-neck flask with a pressure-equalising addition funnel. The mixture was cooled in an ice-salt bath to –15 °C with CO_2 bubbling subsurface for 1h. Methanesulfonic anhydride (0.355 g, 2.04 mmol)

was dissolved in anhydrous MeCN (2mL) and transferred to the addition funnel. The solution was added dropwise to the carbamate salt solution over 1h keeping the reaction below –10 °C.

The reaction was allowed to warm to ambient temperature after addition was complete and split into two portions. Bis(2'-hydroxyethyl) 4-nitrobenzenesulfonamide (40mg, 0.138 mmol) was added to each aliquot with Et₃N (2.1 eq) in one and pyridine (2.2 eq) in the other and heated to 70°C overnight. No bis(2'-hydroxyethyl) 4-nitrobenzene sulfonamide remaining by tlc. Added EtOAc (25 mL) to each and washed with HCl (0.1 M, 2 x 25 mL) and brine (25 mL). Tentatively assigned ^{1}H NMR (d^6-acetone): δ 1.14 (12H, t, J = 7 Hz, CH₃), 3.21 (, 8H, br q, J = 7 Hz, CH₂N), 3.75 (4H, br t, J = 6 Hz, CH₂NNs), 4.38 (4H, br t, J = 6 Hz , CH₂O), 8.04 (2H, d, J = 11Hz, Ar), 8.32 (2H, d, J = 11Hz, Ar); MS (CI) m/z = 489 (M$^+$ + 1), 506 (M$^+$ + 18).

5.3.2 Experimental for Section 4.3

n-Propyl bis-(2-hydroxyethyl) Carbamate 29
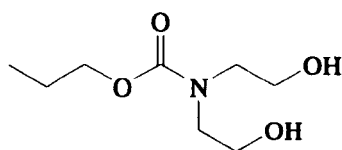
n-Propanol (1 mL, 13.4 mmol) and DBU (2.5 mL, 16.75 mmol) were dissolved in anhydrous MeCN (20 mL). Carbon dioxide was bubbled subsurface and the solution was cooled to –42 °C. After 1h, the solution was allowed to warm to -25 °C and transferred at this temperature over 100 min to methanesulfonic anhydride (2.83 g, 16.25 mmol) in dry MeCN (18 mL). When addition was complete, the reaction was allowed to warm to RT and purged with N₂. An addition funnel was attached and an acetone solution (50 mL) of diethanolamine

(2 mL, 20.9 mmol) and Et$_3$N (2 mL, 14.35 mmol) added slowly dropwise over several hours. The solvents were removed *in vacuo*, the crude residue was taken up in EtOAc 4-5 times and solvent was removed *in vacuo* again. The crude oil was extracted with Et$_2$O, followed by removal of the solvent *in vacuo* of this extract. Purification by flash chromatography twice (alumina, EtOAc, then 8:1 EtOAc/MeOH) gave a clear oil (0.79 g, 31%): IR (film) 3046 cm^{-1} (OH), 1678 cm^{-1} (C=O); ^{1}H NMR (d^6 - acetone) δ 0.92 (3H, t, *J* = 4 Hz, CH$_3$), 1.61 (2H, tq, *J* = 7 Hz, 7 Hz, CH$_3$C*H$_2$*CH$_2$O), 3.42 (4H, t, *J* = 4 Hz, CH$_2$N), 3.68 (4H, t, *J* = 4 Hz, C*H$_2$*OH), 3.98 (4H, overlapping t, CH$_3$CH$_2$C*H$_2$*O and 2 x OH); ^{13}C NMR: δ 10.76 (CH$_3$), 23.04 (CH$_3$*C*H$_2$CH$_2$O), 51.84 (CH$_2$N), 52.36 (CH$_2$N), 61.23 (CH$_2$OH), 61.46 (CH$_2$OH), 67.18 (CH$_3$CH$_2$*C*H$_2$O), 157.18 (C=O); HRMS (CI) Calcd for C$_8$H$_{17}$NO$_4$ 192.1236, found 192.1232

1,5-Pentyl bis-(2-hydroxyethyl) Dicarbamate 30
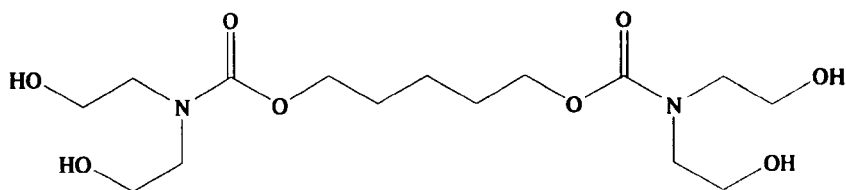
1,5-pentanediol (0.15mL, 1.43 mmol) was dissolved with DBU (0.5 mL, 3.35 mmol; 2.4 eq.) in anhydrous MeCN (3mL). CO$_2$ was bubbled subsurface and the solution cooled to –42 °C. After 30 minutes, methanesulfonic anhydride (0.837 g, 4.8 mmol; 3.36eq) in MeCN (2.5mL) at –42 °C was added all at once to the carbonate solution. This solution was transferred by cannula to diethanolamine (0.45 mL, 4.7 mmol; 3.3 eq) and pyridine (0.35 mL, 4.33 mmol; 3 eq) in anhydrous MeCN (5 mL)at 0 °C over 45 minutes. After addition was complete, the reaction was kept at 0 °C for 10-15 minutes, then allowed to warm to RT

overnight. The solvent was removed *in vacuo*, saturated aqueous brine added to the crude oil and the aqueous was extracted twice with THF. Found (CI) m/z = 236 (M^+ + 1), indicating mono substituted product. Removed solvent *in vacuo* and dissolved the residue in MeCN with 20 mol % pyridine. Acetyl chloride (0.9 mL, 12.66 mmol; 8.8eq) in MeCN (10 mL) was added over 20 minutes to the reaction in an ice bath. After warming to RT over 3 h, the reaction was diluted with EtOAc (100 mL), washed with 1 M HCl (2 x 100mL), dried (K_2CO_3), and the solvent removed *in vacuo*. An insoluble solid formed with some oil. Oil: ^1H NMR ($CDCl_3$) δ 1.45 (2H, m, J = 7 Hz, $OCH_2CH_2CH_2CH_2CH_2O$), 1.68 (4H, m, J = 7 Hz, $OCH_2CH_2CH_2CH_2CH_2O$), 2.07 (12H, s, CH_3CO), 3.54-3.63 (8H, br t, CH_2N), 4.09 (4H, m, J = 7 Hz, $CH_2O(CO)N$), 4.22 (8H, m, J = 4 Hz, CH_2OAc); MS (CI) m/z = 535 (M^+ + 1), 552 (M^+ + 18) indicating tetra-acetylation of the dicarbamate tetrol product.

Attempted Synthesis of *p*-Xylylene bis-(2-hydroxyethyl)-dicarbamate 31
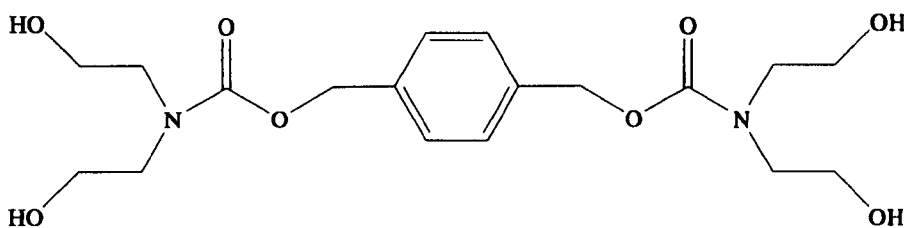
1,4-benzenedimethanol (116mg, 0.84 mmol) and DBU (0.3 mL, 2 mmol) were dissolved in 5 mL anhydrous MeCN. CO_2 was bubbled subsurface whilst the solution was cooled to –42 °C for 30 min. The solution was then held as –30 °C and transferred by cannula over 90 min to a 5 mL anhydrous MeCN solution of Ms_2O (358 mg, 2.08 mmol; 2.48 eq) at the same temperature. The reaction mixture was then warmed to *ca.* 0 °C.

Diethanolamine (0.2 mL, 2.1 mmol) and pyridine (0.17 mL, 2.1 mmol) were dissolved in 5 mL anhydrous MeCN. This solution was added dropwise to the mesyl carbonate solution over 15-20 min. The reaction was kept cool and stirred overnight. No expected product was found in NMR or mass spectra. Product detected by mass spectroscopy was tentatively assigned as N-(2-hydroxyethyl)-2-oxazolidinone; MS (CI) m/z = 132 (M$^+$ + 1), 149 (M$^+$ + 18).

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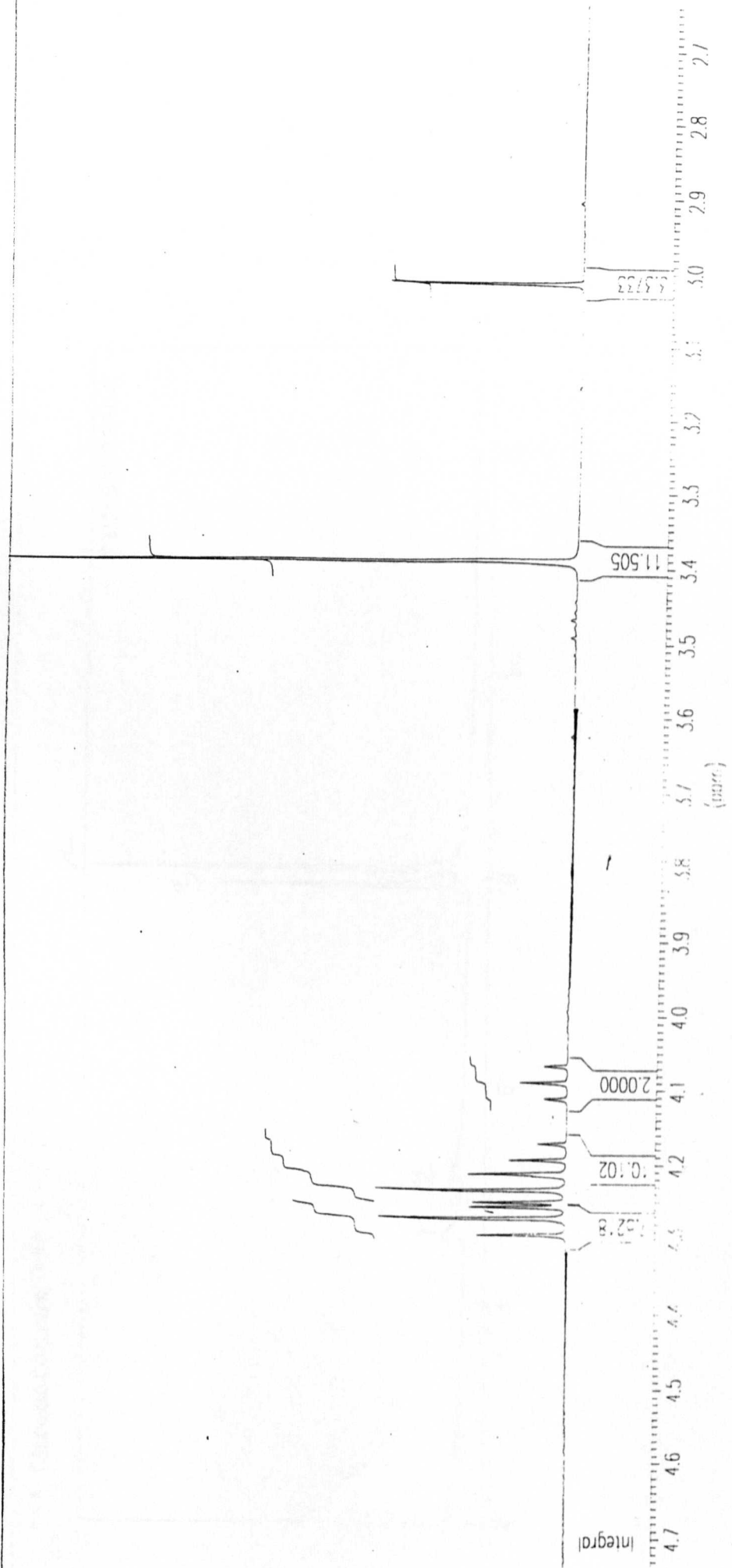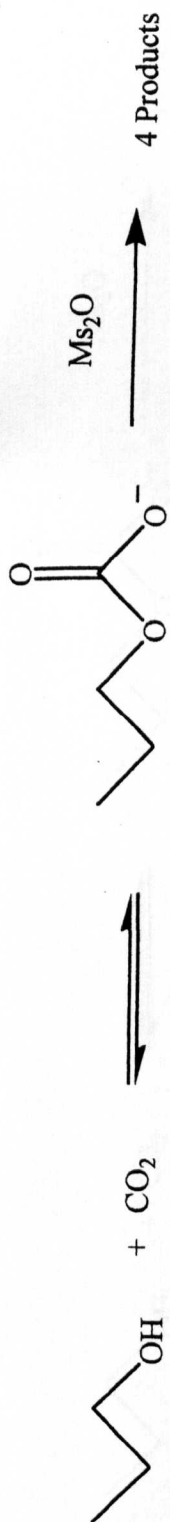(85) Fang, S.; Fujimoto, K. *Appl. Cat. A*, **1996**, *142*, L1

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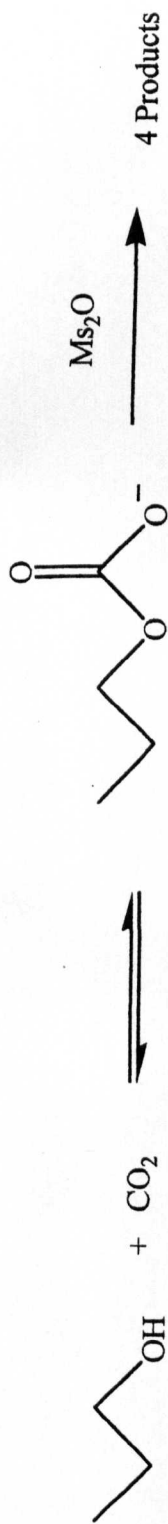
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APPENDIX

Ms$_2$O

4 Products

+ CO$_2$

OH

11.505

2.0000

0.102

Integral

$$\text{\raisebox{1ex}{$\diagdown\!\diagup\!\diagdown$}}\!\!-\!\!OH \;+\; CO_2 \;\rightleftharpoons\; \text{[carbonate]} \xrightarrow{\;Ms_2O\;} \text{4 Products}$$

*** Chromatogram ***

TIC=58773504

TIC