New CO_2 Chemistry for Fine Chemical Synthesis

By

Ath'enkosi Msutu

Thesis presented for the degree of

Master of Science

In the Department of Chemistry

University of Cape Town

January 2011

Supervisor: Professor Roger Hunter

Plagiarism Declaration

1. I know that plagiarism is wrong. Plagiarism is to use another's work and pretend that it is one's own.

2. I have used the Royal Society of Chemistry convention for citation and referencing. Each contribution to, and quotation in, this thesis from the work(s) of other people has been attributed, and has been cited and referenced.

3. This thesis is my own work.

4. I have not allowed, and will not allow, anyone to copy my work with the intention of passing it off as his or her own work.

5. I acknowledge that copying someone else's work, or part of it, is wrong, and declare that this is my own work.

Abstract

There is a great need in the chemical industry for developing CO_2 as a C_1 building block as an important step towards “green chemistry”. CO_2 is also attractive as a chemical feedstock because it is readily available, inexpensive, nontoxic and it can replace toxic building blocks such as phosgene and CO. Industrially, megatons of CO_2 are used each year for the production of urea, inorganic carbonates, salicylic acid, and polycarbonates, yet this is still miniscule compared to the immense potential that is still yet to be harnessed in using this versatile building block.

This thesis discusses how a novel methodology was developed for synthesising a benzotriazole (Bt) urea directly from CO_2 in a two-step, one-pot synthesis. The procedure involves trapping CO_2 with a primary or secondary amine in the presence of DBU, and reaction of the resultant carbamate salt with triphenylphosphine and chlorobenzotriazole (BtCl) to produce Bt ureas in moderate to high yields.

The Bt group may serve as a leaving group in nucleophilic substitution reactions, therefore it is also shown here how the Bt urea presents itself as a precursor for an array of useful organic intermediates. These intermediates include ureas, amides, *S*-thiocarbamates and sulfonylureas.

Acknowledgements

I would like to acknowledge the following people and institutions for their support throughout this project:

My parents for being constant sources of wisdom, strength and support. Thank you for giving me the freedom and courage to follow my dreams. My brother and sister, the rest of my family and close friends, who have been shoulders to cry on and sources of fun distraction when I really needed it.

Professor Roger Hunter for being a teacher, mentor and even psychiatrist. More than anything, I thank you for consistently inspiring me and believing in me even when I found it hard to believe in myself.

The marvellous members of the Roger Hunter group for the invaluable amount of help throughout this project and most importantly, the laughs!

The staff and fellow postgraduate students from the Department of Chemistry for giving me support whenever I needed it and for sustaining a culture of learning and excellence that continues to motivate me.

Noel Hendricks, Pete Roberts, Gianpiero Benincasa and Bertus Moolman (Stellenbosch) for their analytical services.

Sasol (and its warm, helpful staff) for the financial support throughout my studies. My wonderful Sasol mentors (Raymond Hunt and Ben Bezuidenhoudt) for the support and encouragement, and for being constant reminders of the bright future that lies ahead.

The NRF for additional funding, which has made my journey that much easier.

Abbreviations

Bn	benzyl
Boc	*N-tert*-butoxycarbonyl
Bu	butyl
J	coupling constant
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DPPA	diphenylphosphoryl azide
d	doublet
dd	doublet of doublets
eq	equivalent(s)
HRMS	High-resolution Mass Spectroscopy
hr(s)	hour(s)
Hz	hertz
i	iso
m/z	mass-to-charge ratio
MHz	megahertz
m.p.	melting point
MsCl	methanesulfonyl chloride
min	minute(s)
n	normal
NMR	nuclear magnetic resonance
p	para
p	pentet
Pr	propyl
RT	room temperature
s	singlet
sext	sextet
tlc	thin layer chromatography
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Ts	4-toluenesulfonyl
t	tert
t	triplet

Contents

Chapter 1: CO_2 and Other C_1 Building Blocks

1.1 Introduction

Carbon dioxide (CO_2) is a stable, non-flammable gas existing in the earth's atmosphere in trace amounts (0.039% of the atmosphere) and its contribution to the greenhouse effect has resulted in it being labelled as a greenhouse gas (along with water vapour, methane, nitrous oxide, and ozone). There is currently increased awareness in the world that the concentrations of greenhouse gases are increasing and CO_2, our planet's major carbon source is the worst in this regard.[1] CO_2 circulates in the environment through a variety of processes known as the carbon cycle, and industrial processes, volcanoes and living systems release vast amounts of CO_2 into the atmosphere. There are various natural processes that can absorb CO_2, such as photosynthesis. However CO_2 in the atmosphere is accumulating much faster than natural processes can absorb it.[2] It has been proposed that in order to decrease the greenhouse effect there needs to be: (i) an improvement in the efficiency of energy production and consumption processes; (ii) a significant decrease in the carbon intensity of our economies; and (iii) an improvement in atmospheric CO_2 storage and sequestration. Above all, these goals must be achieved whilst maintaining worldwide economic growth and living standards.[1] As far as CO_2 consumption is concerned, the use of this gas as a chemical building block has been highlighted as a key initiative.

Besides the greenhouse effect, there are a number of motivations for the usage of CO_2 as a C_1 building block: (i) it is a cheap, nontoxic feedstock that can replace toxic and unstable building blocks such as phosgene, CO or isocyanates; (ii) CO_2 is a totally renewable feedstock compared to oil or coal; (iii) using CO_2 to make valuable existing chemical intermediates results in new synthetic methodologies that may be more efficient and/or economical than existing ones.[1] However, one of the major problems associated with the use of CO_2 as a building block is that it is a thermodynamic end product of many chemical processes (e.g. combustion of hydrocarbons).[3] Also, because CO_2 is the most oxidized state of carbon, it is very stable and has a low energy level. Thus, a large energy input is required to transform CO_2. Nevertheless, as Aresta insightfully points out:

> "The bad thermodynamics of the carbon dioxide conversion reaction has been so far a justification for avoiding the important investment (human resources, time and budget) necessary for developing efficient technologies for its utilization. On the other hand, there was no urgency to develop such technologies because chemicals were

prepared by other ways. Today we are facing a different reality: there may be a convenience in developing synthetic strategies based on carbon dioxide, for avoiding taxes and for saving resources and also energy. The chemistry of carbon dioxide has received much less attention than that of carbon monoxide in the last century. CO_2 has been considered so far as a waste, CO as a resource. An innocuous waste, already abundant in Nature and Nature was expected to get us free of it. But it appears now that carbon dioxide is not innocent and Nature needs our cooperation for the elimination of CO_2."[4]

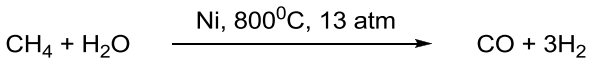
The use of CO_2 for chemicals production mostly involves it acting as a C_1 source. However, there are various other C_1 building blocks competing with CO_2 for this role in synthetic chemistry. This chapter explores the most important C_1 building blocks for organic materials in industry as well as in research.

1.2 C_1 Building Blocks in Industry

1.2.1 Natural Gas

Natural gas is a fossil fuel consisting of mainly methane (85% of its composition). It is found beneath the earth's surface associated with fossil fuels and is renowned as one of the cleanest, safest and most useful energy sources on the planet.

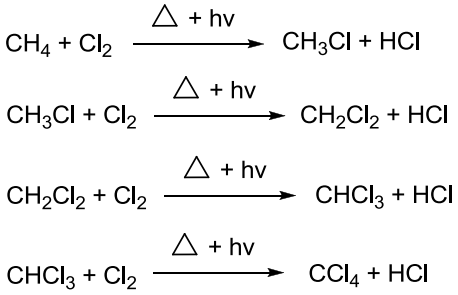
As a C_1 building block, natural gas is the principle feedstock for producing one-carbon chlorinated chemicals, hydrogen cyanide, carbon black and acetylene. It is also important for producing synthesis gas (a mixture of carbon monoxide and H_2) by decomposition of methane in the presence of steam and a catalyst (steam reforming) as shown in Scheme 1.1.[5]



Scheme 1.1: Natural gas steam reforming to produce synthesis gas

Methane can also undergo thermal chlorination. This is an exothermic, free-radical process that is difficult to control. Photochemical dissociation of chlorine improves the control of this process and the result is the formation of methyl chloride, methylene dichloride, chloroform and even carbon tetrachloride (as shown in Scheme 1.2). However, hydrogen chloride (HCl)

is the undesirable by-product of this process, which may be recycled by oxychlorination (in the presence of methane and oxygen to form chlorine) or sold as aqueous or anhydrous HCl. The hazardous nature of these chlorinated products as well as the contribution of chlorofluorocarbons (CFCs) to the depletion of the ozone layer has however led to a steady decline in their levels of production in the past 25 years.[5]



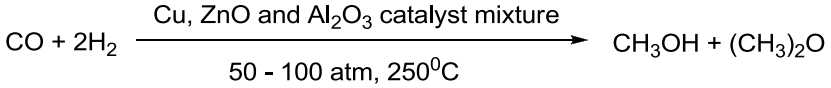
Scheme 1.2: Chlorination of methane

Fluorination (replacement of hydrogen atoms by fluorine) of these chloromethanes can also occur when thermal chlorination is conducted in the presence of hydrogen fluoride.[5]

1.2.2 Carbon Monoxide and Synthesis Gas (Syngas)

Syngas is a gas mixture containing varying amounts of CO and H_2. It is produced through the following ways: (i) steam reforming of natural gas and petroleum; (ii) gasification of coal; (iii) gasification of biomass; separation, purification and the water gas-shift reaction of syngas to yield (where required) hydrogen-enriched syngas; and (iv) as a by-product of metallurgical and ammonia processes.[5]

Syngas is an important C_1 building block. Under conditions of high temperature and pressure, and in the presence of a metal catalyst it can be used to produce methanol (another important C_1 building block), with dimethyl ether as a by-product (Scheme 1.3).



Scheme 1.3: Production of methanol from synthesis gas

Syngas can also be used to hydroformylate olefins via homogenous catalysis using cobalt complexes. Another important application of syngas is the production of the dipolar, high boiling solvent dimethyl formamide (DMF) by reaction with methylamine in methanol. Syngas is also a feedstock in the Fischer-Tropsch (F-T) process, which involves the conversion of syngas to liquid hydrocarbons. Scheme 1.4 shows the formation of alkanes via the F-T process. However, competing reactions lead to alkene and alcohol formation. Therefore (where required) the reaction conditions and catalysts can be manipulated in order to produce more of these products. Sasol (a South African based petrochemical company) is a global pioneer in F-T technology.

$$nCO + (2n+1)H_2 \xrightarrow[\text{high temperature and pressure}]{\text{Co, Fe, Ru or Ni catalyst}} C_nH_{(2n+2)} + nH_2O$$

Scheme 1.4: The F-T production of alkanes

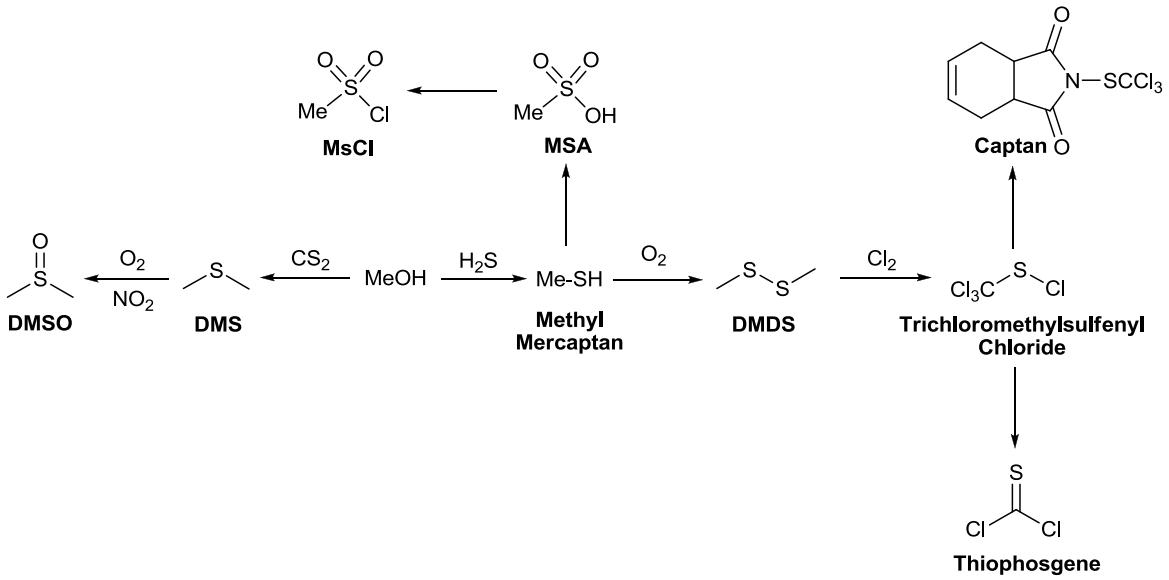
As far as CO on its own is concerned, hydroxide and alkoxide ions (in the presence of their conjugate acids) add to CO to give formate salts and esters. The formate can then be treated with water to give formic acid. CO can act as a formylating agent under strongly acidic conditions, and the formation of benzaldehyde from benzene in the Gattermann-Koch reaction is an example. CO (in the presence of water) is a carbonylating agent and can thus produce: hydroxyacetic (glycolic) acid by reacting with formaldehyde; neoacids by reacting with olefins; and α-keto acids by reacting with alkyl halides. Also, a free-radical chain reaction between CO and chlorine produces phosgene, another building block that will be discussed in Section 1.1.9.[5]

1.2.3 Methanol

Prior to 1926, methanol (also known as “wood alcohol”) was produced from the dry distillation of wood. Currently, methanol is usually produced from syngas (as previously shown in Scheme 1.3).[5]

As a building block, methanol can be used to produce methyl ethers, halomethanes, acetic acid and acetic anhydride. “Alcohol amination” is the process by which methylamines are produced through the dehydrogenation/hydrogenation of methanol in the presence of ammonia and an appropriate catalyst. Methanol is also the building block of a range of useful sulfur-containing compounds, Scheme 1.5. Treatment of methanol with carbon disulfide (CS_2) over alumina at high temperatures produces dimethyl sulphide (DMS). DMS

can in turn be oxidised by oxygen in the presence of nitrogen dioxide to the popular dipolar solvent, dimethyl sulfoxide (DMSO). The initial product of the reaction of methanol with hydrogen sulfide is methyl mercaptan, which is oxidised in the air in the presence of a metal catalyst to dimethyl disulfide (DMDS). Extensive chlorination of DMDS produces trichloromethylsulfenyl chloride. This sulfenyl chloride is the building block of captan (a fungicide) as well as thiophosgene. The oxidation of methyl mercaptan with hypochlorite generates methanesulfonic acid (MSA) (the precursor to mesyl chloride).



Scheme 1.5: The conversion of methanol to sulfur-containing compounds

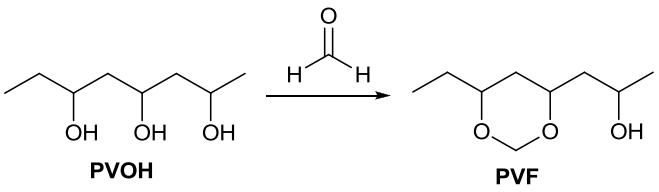
Methanol can also be used to make another C_1 building block, formaldehyde, via oxidation in the air in the presence of a silver gauze catalyst. Lastly, methanol can be reacted with CO and oxygen in the presence of a copper catalyst to yield dimethyl carbonate, a precursor to isocyanates. These are just a few useful applications of methanol as an organic building block.[5]

1.2.4 Formaldehyde

Formaldehyde is the simplest aldehyde and despite its high toxicity and volatility, it is an important compound in the chemical industry and is synthesised via the oxidation of methanol.[5]

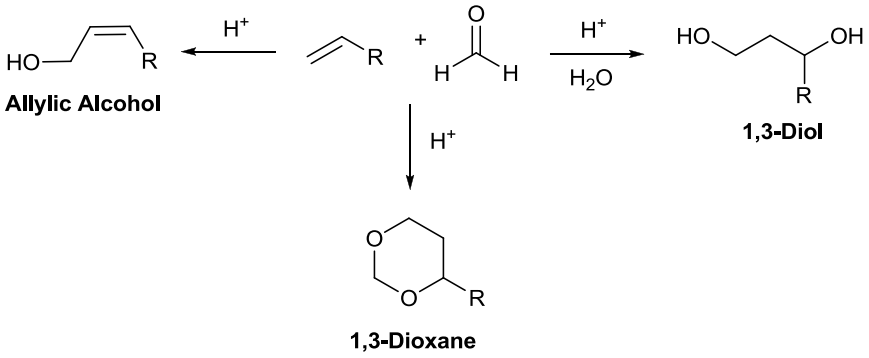
Most of the industrial formaldehyde consumption is dedicated to producing polymers such as phenol-formaldehyde, urea-formaldehyde, poly(oxymethylene) and melamine-formaldehyde

(the first three are thermoset resins). Other major chemicals include 1,4-butanediol, 1,1,1-trimethylproprane, pentaerythritol, hexamethylenetetramine and 1,4-methylenedianiline, all of which are the building blocks of polymeric organic materials. Formaldehyde is also used to make acetals and hemiacetals via acid catalysis. For example (Scheme 1.6), poly(vinylalcohol) (PVOH) is converted to the acetal poly(vinyl formal) (PVF), which is used as a wire-coating material.



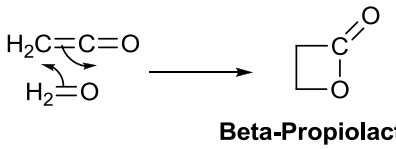
Scheme 1.6: Conversion of a fragment in PVOH to its acetal form (PVF)

Formaldehyde also undergoes aldol condensations to give methylol (-CH_2-OH) derivatives. The dehydration of these methylol species in a subsequent step results in vinyl derivatives. Another important feature of formaldehyde as a C_1 building block is its ability to undergo addition reactions with unsaturated species. An example is the Prins reaction (Scheme 1.7), which involves addition of protonated formaldehyde to olefins to produce 1,3-diols, allylic alcohols or dioxanes, depending on the reaction conditions.



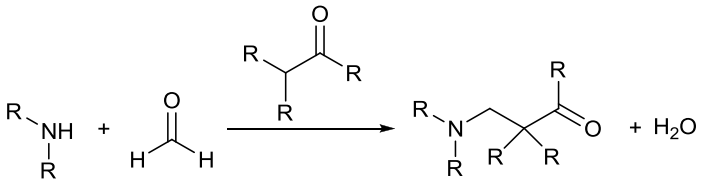
Scheme 1.7: The Prins reaction

Another example is its cycloaddition to ketene to give *β*-propiolactone, Scheme 1.8.



Scheme 1.8: The cycloaddition of formaldehyde to form *β*-propiolactone

Formaldehyde participates in the Mannich reaction (amino alkylation), as shown in Scheme 1.9, to produce fine chemicals that are important intermediates in the pharmaceutical and pesticide industries.[5]

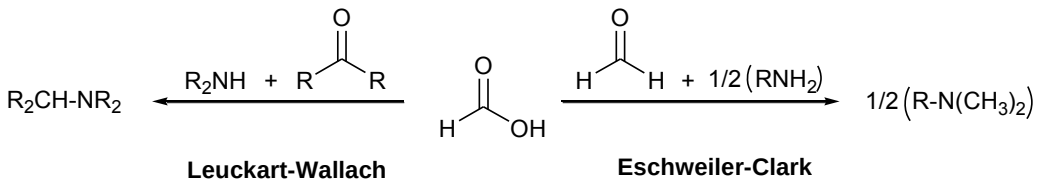


Scheme 1.9: The Mannich reaction

1.2.5 Formic Acid

Formic acid, the simplest carboxylic acid, is an important chemical intermediate that also occurs naturally in the venom of bee stings. It is produced by the hydrolysis of methyl formate (the simplest ester).[5]

As a C_1 building block, formic acid is a source of formyl and methyl moieties. It is also used as a ketone and aldehyde reductant in the Leuckart-Wallach and Eschweiler-Clark amine alkylation reactions, respectively (Scheme 1.10). These reactions play an important role in the synthesis of fine chemicals, and they account for the majority of formic acid use in synthesis.[5]

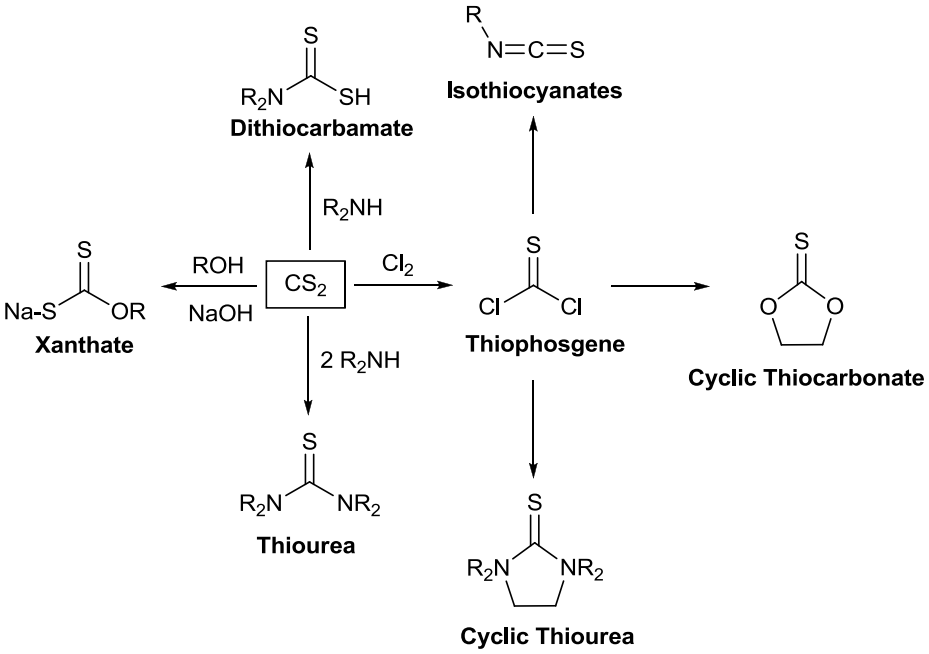


Scheme 1.10: The Leuckart-Wallach and Eschweiler-Clark reaction

1.2.6 Carbon Disulfide (CS_2)

CS_2 is a colourless, volatile and highly toxic liquid that also serves as an important chemical building block. It is obtained from the high-temperature reactions of sulphur (S_8) and methane.[5]

CS_2 is a more reactive, unstable (it spontaneously ignites in the presence of air and sunlight) and versatile alternative to its sister compound, CO_2, contributing a variety of structural moieties to sulfur-containing synthetic organic chemicals. As shown in Scheme 1.11, the reaction of CS_2 with amines, for instance, produces dithiocarbamates and thioureas. CS_2 also reacts with chlorine to give thiophosgene or carbon tetrachloride. The latter reaction makes it the preferred source of CCl_4 since it doesn't produce other chlorinated carbon compounds as by-products. Thiophosgene is in turn the building block for isothiocyanates, cyclic thioureas and cyclic thiocarbonates. CS_2 is also used to produce xanthates through its reaction with alcohols in the presence of sodium or potassium hydroxide.[5]



Scheme 1.11: The reactions of CS_2 that produce useful chemical building blocks

1.2.7 Urea

Urea is produced by the reaction of CO_2 with ammonia. An older route to urea is the nitrification of calcium carbide. Substituted ureas can be produced through the reaction of amines with CO and O_2, or CO_2 in the air, in the presence of catalysts and under harsh conditions of high pressure and high temperatures.[6]

The main use of urea as a building block is in the synthesis of amino resins. Urea can also react with substituted malonic acid esters to yield barbiturates (Figure 1.1).

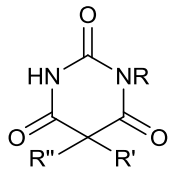
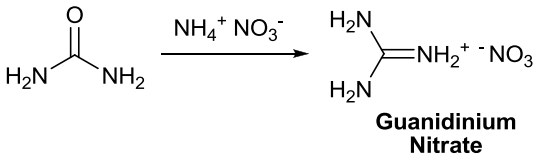


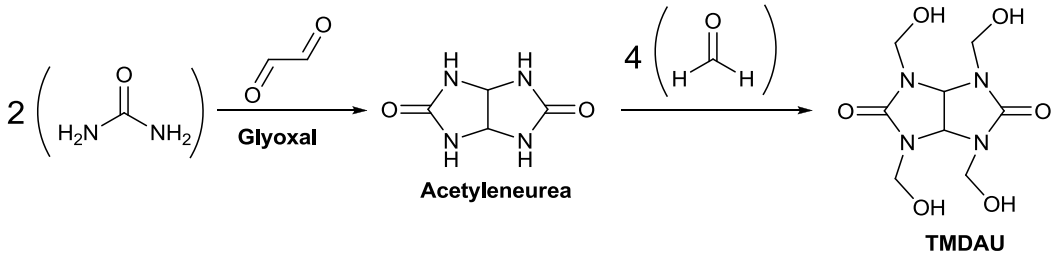
Figure 1.1: The general structure of barbiturates.

Guanidine (guanidinium nitrate) is produced by the reaction of urea with ammonium nitrate (Scheme 1.12), and it is the building block of sulfa drugs of the sulfadiazine family.



Scheme 1.12: The synthesis of guanidinium nitrate

Urea in the presence of ethylenediamine gives ethylene urea, whose derivatives are used as modifiers of formaldehyde-derived resins. Two moles of urea can react with glyoxal (the simplest dialdehyde) to produce acetyleneurea (Scheme 1.13), which is a scavenger of formaldehyde and thus forms trimethylolacetylenediurea (TMDAU), which is a cross-linking agent for urea-formaldehyde resins.



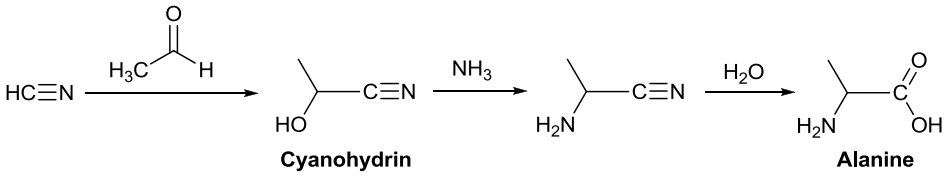
Scheme 1.13: The formation of TMDAU from urea

At high temperatures urea can decompose to, amongst other chemicals, cyanamide (H_2NCN), which is the building block for chemicals such as melamine, thiourea, substituted guanidines, and dicyanamide.[5]

1.2.8 Hydrogen Cyanide (HCN)

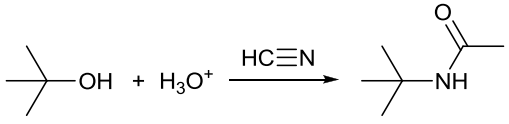
HCN is a highly toxic, low-boiling liquid (boiling at 25.6^0C). It is produced by a high temperature treatment of ammonia with methane and oxygen. It can also be produced as a by-product in the ammoxidation of propylene (the major product is acrylonitrile).[5]

HCN is a multifaceted C_1 building block. Through its reaction with 1,3-butadiene it produces adiponitrile, which is primarily used to make hexamethylenediamine and adipic acids which are in turn the building blocks of nylon 6,6. As shown in Scheme 1.14, HCN also has the ability to be added to multiple-bond-containing systems. Its addition to aldehydes and ketones leads to cyanohydrins that can subsequently be converted to α-aminocarboxylic acids by treatment with an amine and then water. Thus, HCN is responsible for the synthesis of amino acids such as alanine and glycine.



Scheme 1.14: The reaction of HCN with acetaldehyde to produce alanine

The cyanide anion in HCN is an ambident nucleophilic with the nitrogen end being “hard” (due to its higher electronegativity) and the carbon end being “soft” according to the HSAB (hard and soft acids and bases) principle. In the Ritter reaction (Scheme 1.15), the hard nitrogen seeks out the hard carbocation generated in the presence of a mineral acid and an olefin or an alcohol, giving rise to new C-N bonds.



Scheme 1.15: The Ritter reaction using an alcohol

The action of the softer carbon end of the cyanide anion is demonstrated by its addition to epoxides (producing cyanohydrins) as well as to C-C triple bonds. The nucleophilic carbon can also substitute the hydroxyl group in *N*-methylols to generate substituted aminoacetonitriles, which serve as building blocks for a range of important compounds such as substituted glycine, *α*-aminoacetoamides, *α*-aminoacetamides and *β*-aminothylamines. On the other hand, the electrophilic protonated HCN can react with an amine and then H_2S to yield thioformamide. Chlorination of HCN gives the toxic but useful synthetic reagent, cyanogen chloride (Cl-CN), which is used to introduce cyano groups onto electron-rich substrates.[5]

1.2.9 Phosgene

Phosgene is a colourless, toxic gas. Despite its uses as a chemical building block, phosgene is infamous for its high toxicity and is widely recognized as one of the most acutely toxic substances used in the chemical industry. As previously mentioned, phosgene is produced by the reaction of CO and chlorine in a free-radical chain reaction. The trimer of phosgene, triphosgene (Figure 1.1), is prepared by the exhaustive chlorination of dimethyl carbonate (DMC). Because it is a solid at room temperature, it is considered a safer alternative to phosgene and is sold commercially for research purposes.

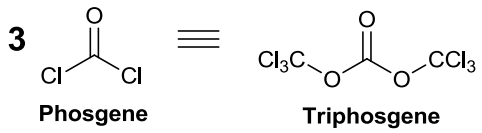
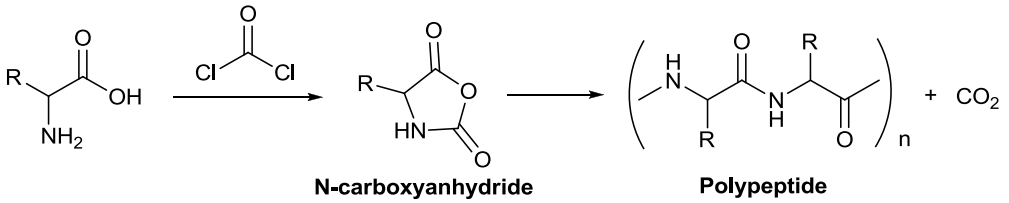


Figure 1.2: Phosgene and its trimer, triphosgene

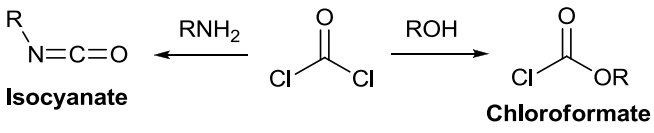
Phosgene is a widely used C_1 building block. Most of the phosgene produced is used in the polymer industry to make polycarbonates. Simple organic carbonates such as dimethyl carbonate, ethylene and propylene glycols and others are derived from the reaction of phosgene with appropriate hydroxy compounds. The reaction of alpha-amino acids with phosgene gives rise to *N*-carboxyanhydrides which can be polymerised to polypeptides, as shown in Scheme 1.16.



Scheme 1.16: Polypeptide synthesis from phosgene

Phosgene can also participate in Friedel-Crafts acylations with aromatic systems to give an acid chloride (an isolable intermediate product) and then a diaryl ketone. Disubstituted dithiocarbonates as well as tetrasubstituted ureas (e.g. tetramethylurea, TMU) are also derived from phosgene.

Another use of phosgene is in the synthesis of two important C_1 building blocks: isocyanates and chloroformates (Scheme 1.17). Phosgene reacts with amines or amine salts to produce isocyanates, which are used as industrial building blocks for the synthesis of ureas, urethanes, polyurethanes, carbamic acid, amides and carbodiimides. Methyl isocyanate (MIC), specifically, is an important building block for insecticides. In industry, isocyanates are mainly used as polymer building blocks. (The applications of isocyanates as building blocks in research shall be discussed in Section 1.3.1.) Phosgene reacts with alcohols to produce chloroformates (oxycarbonyl chlorides). These chloroformates are used in the synthesis of peroxy-group-containing vinyl polymerization catalysts. Thiochloroformates react with amines to give *S*-thiocarbamates, which are important herbicides. Chloroformates are also used to introduce protecting groups such as Cbz (carboxybenzyl) and Fmoc (fluorenylmethyloxycarbonyl). (The applications of chloroformates as building blocks in research shall be discussed in Section 1.3.3.)



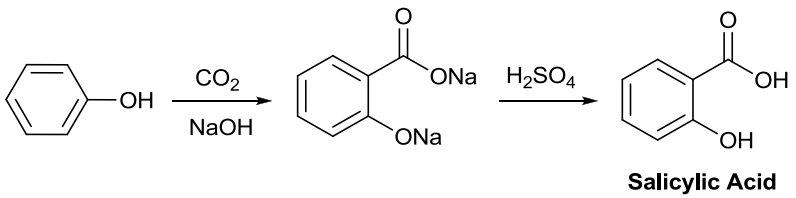
Scheme 1.17: The phosgene synthesis of isocyanates and chloroformates

The major drawbacks of phosgene processes are: (i) the high toxicity of phosgene, which is controlled by the international treaty concerning chemical weapons; and (ii) the disposal of the coproduced hydrogen chloride.[7] This is why extensive research is being conducted to explore other building blocks, such as CO_2, as phosgene alternatives.

1.2.10 CO_2

As stated earlier, CO_2 is a gas naturally present in the earth's atmosphere. Therefore, it can be sequestered from the air by distillation, but this only yields small amounts of CO_2. In fact, CO_2 is mostly obtained as a by-product of many chemical processes, particularly the combustion of all carbon-containing fuels (such as natural gas).

As an industrial C_1 building block, CO_2 provides the carbonyl, carboxylic acid, carbonate and carbamate moieties.[5] Approximately 120 MT (megatons) per year of CO_2 are currently used for chemical synthesis annually to make products such as urea, salicylic acid, cyclic carbonates, and polycarbonates. Urea production constitutes the highest amount of CO_2 industrial consumption and it reached a level of approximately 70 MT per year in 2007.[1,4,8] The production of urea is a high temperature and high pressure reaction of the gas with ammonia. In a similar fashion, ethylenediamine reacts with CO_2 to give 2-imidazolidinone, a cyclic urea. In the Kolbe-Schmitt reaction the phenolate anion reacts with CO_2 via electrophilic substitution to give salicylic acid, which is the starting material of aspirin, salicylic amide, phenyl salicylates and other useful materials.



Scheme 1.18: The Kolbe-Schmitt reaction

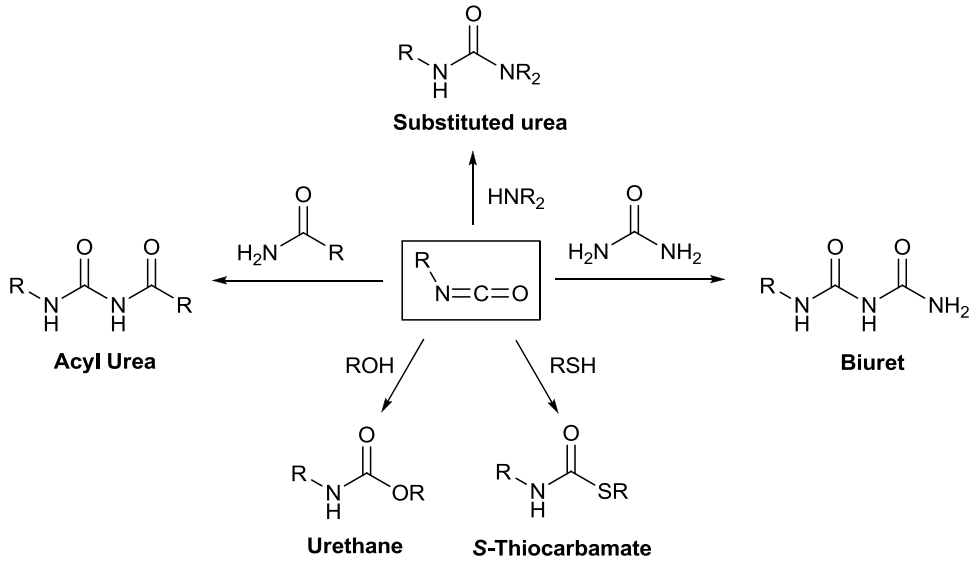
CO_2 also reacts with alcohols under base-catalysed, pressure conditions to produce dialkyl carbonates. This has led to the production of DMC (dimethyl carbonate) without using phosgene. The reaction of CO_2 and epoxides leads to monomeric- and polymeric-carbonates, once again replacing phosgene and DMC as building blocks. In this regard, CO_2 is viewed as an attractive polymer building block due to its low cost, high contribution to final product mass as well as its relative benignity.[1]

1.3 C_1 Building Blocks in Research

1.3.1 Isocyanates

As previously mentioned, the most common method of isocyanate production is the reaction of an amine (or amine salt) with phosgene.[9] Isocyanates can also be produced by the thermal decomposition of ureas and urethanes.[10] The hygroscopicity of isocyanates as well as the resulting decomposition to urea makes their handling and storage very difficult. They also tend to be highly toxic, especially the lower molecular weight variety.

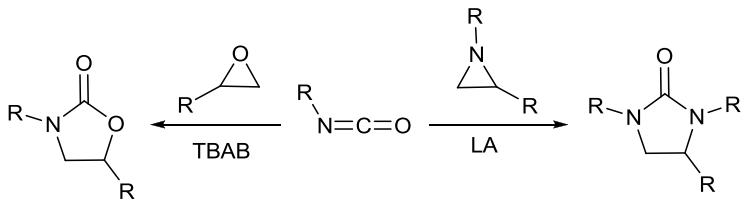
Isocyanates are nevertheless highly versatile C_1 building blocks. Compounds containing hydrogen attached to nitrogen react readily with isocyanates: amines react with isocyanates to give substituted ureas, amides give acyl ureas and ureas react with isocyanates to give biurets. Alcohols react with isocyanates to produce urethanes and thiol groups react in a similar way to give the sulfur analogues, thiocarbamates.[9] These reactions are shown in Scheme 1.19



Scheme 1.19: The reaction of isocyanates with nitrogen-containing compounds, alcohols and thiols

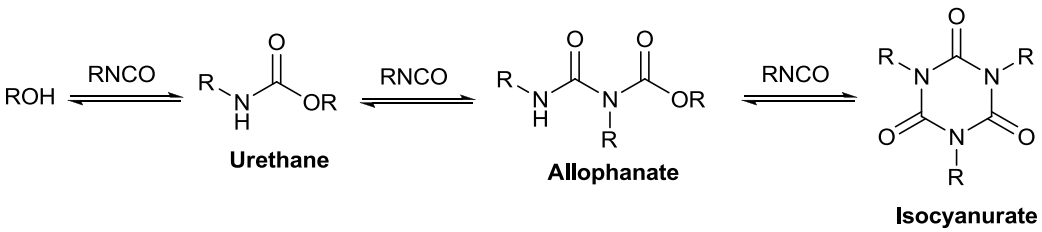
Isocyanates can also undergo a Friedel-Crafts reaction in the presence of an aryl species as well as $AlCl_3$ to give aryl amides. They react readily with Grignard reagents to produce amides and they also react with halogen acids to produce carbamoyl halides. More recently, isocyanates have been used to produce substituted oxazolidin-2-ones via

tetrabutylammonium bromide (TBAB) catalysed cycloaddition reactions with epoxides.[11] Similarly, aziridines react with isocyanates in the presence of Lewis acids (LA) to produce substituted imidazolidin-2-ones.[12] These reactions are illustrated in Scheme 1.20.



Scheme 1.20: The cycloaddition of epoxides and aziridines into isocyanates

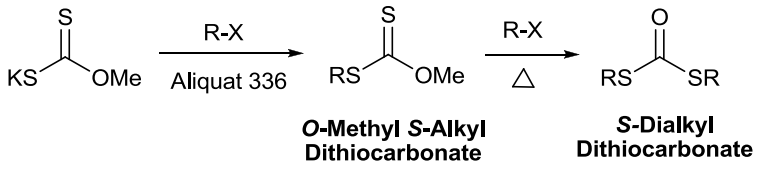
The reaction of isocyanates with *α*-olefins in the presence of a Ni catalyst to produce acrylamides has also been reported.[13] Isocyanates can also react with alcohols and phenols in a series of consecutive reactions to produce carbamates, allophanates and isocyanurates, as shown in Scheme 1.21.[14,15,16]



Scheme 1.21: The reaction of isocyanates with alcohols

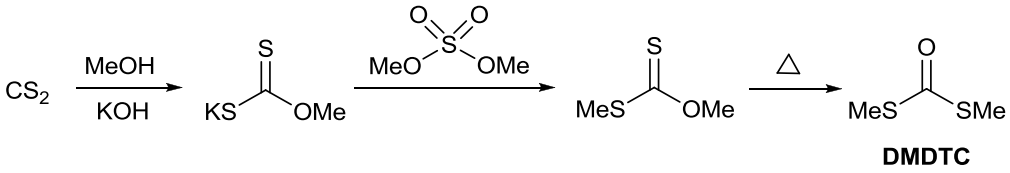
1.3.2 Dimethyl Dithiocarbonate (DMDTC)

DMDTC and other *S,S*-dialkyl, *S,S*-diaryl and *S*-aryl *S*-alkyl dithiocarbonates are a class of compounds especially known for their applications in the pesticide industry.[17] They are usually synthesised from the reactions of phosgene and thiols. Various other syntheses have also been reported. It has been shown that symmetrical *S,S*-dialkyl dithiocarbonates can be synthesised via an acid-, or base-catalysed, thermal rearrangement of *O*-methyl *S*-alkyl dithiocarbonates.[17,18] This rearrangement has also been achieved by Degani et al. in the presence of a phase-transfer catalyst (Aliquat 336), as shown in Scheme 1.22.[19]



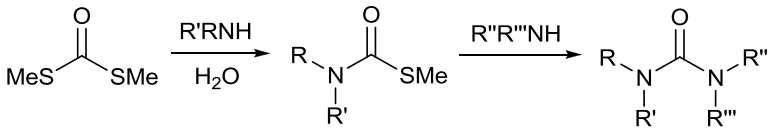
Scheme 1.22: The synthesis of symmetrical *S,S*-dialkyl dithiocarbonates by rearrangement of *O*-methyl *S*-alkyl dithiocarbonates

Dimethyl dithiocarbonate (DMDTC), specifically, can also be prepared from methanol, carbon disulfide and dimethyl sulphate by a two-step sequence, as shown in Scheme 1.23.[17,19] It is a stable high boiling liquid that can be stored, handled and measured safely without foul odours. These features render it an excellent reagent for both laboratory and industrial usage.



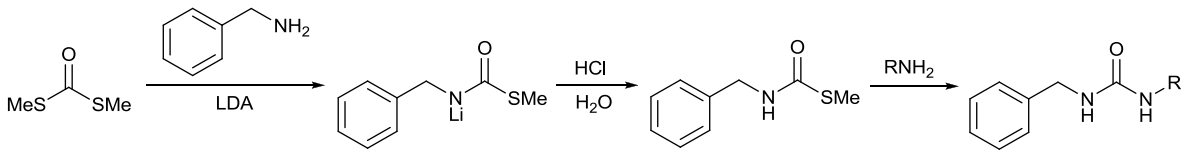
Scheme 1.23: The synthesis of DMDTC from CS_2

As C_1 building blocks, *S,S*-alkyl dithiocarbonates have the advantages of being inexpensive as well as stable, and they can be handled easily and without risk (unlike alkanethiols). They have been used in the synthesis of organic sulfides as well as β-alkylthiocarboxylic acids in excellent yields.[20,21] They have also been used to make alkenylsulfonyl chlorides via aqueous chlorination, with HCl and CO_2 being released as by-products.[22] DMDTC itself has been used as a phosgene replacement (in view of its advantageous features as a chemical reagent when compared to hazardous phosgene) in a reaction with amines in the presence of water to produce *N*-alkylthiocarbamates, Scheme 1.24.[23] As Scheme 1.24 shows, further heating of N-alkylthiocarbamates in the presence of an appropriate aqueous primary or secondary aliphatic amine produces di- and tri-substituted ureas.[6]



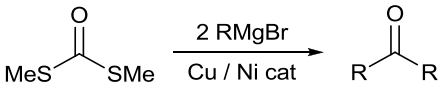
Scheme 1.24: The synthesis of *N*-alkylthiocarbamates and substituted ureas from DMDTC

Leung et al. have found that the reaction of DMDTC with one equivalent of benzylamine led to production of the symmetrical dibenzyl urea as the major product, instead of the desired thiocarbamate.[24] Mechanistic studies that followed found that substitution of the second benzylamine was a faster step than the initial thiocarbamate formation step. The solution to this problem was carrying out the reaction in the presence of a base (LDA, lithium diisopropylamide), since the deprotonated thiocarbamate was more stable towards nucleophilic substitution at ambient temperature and did not react further to form the symmetrical urea. The thiocarbamate was then quenched by an acid, isolated, and finally treated with a different primary amine to produce the desired unsymmetrical ureas (Scheme 1.25). They have also shown that hydroxy- or amino-substituted amines react with DMDTC in a dilute solution in order to give the desired symmetrical ureas (without the need for protecting groups), as well as cyclic ureas and cyclic carbamates.



Scheme 1.25: The synthesis of tri-substituted ureas from DMDTC, using LDA

In another publication, Leung et al. have shown that DMDTC, due to its structural similarity to phosgene, can also replace phosgene as a carbonyl dication synthon for ketone synthesis.[25] DMDTC was treated with Grignard or organolithium reagents in the presence of an appropriate transition metal catalyst to yield ketones as well as thioesters, thus illustrating its versatility as a C_1 building block. This ketone synthesis is depicted in Scheme 1.26.

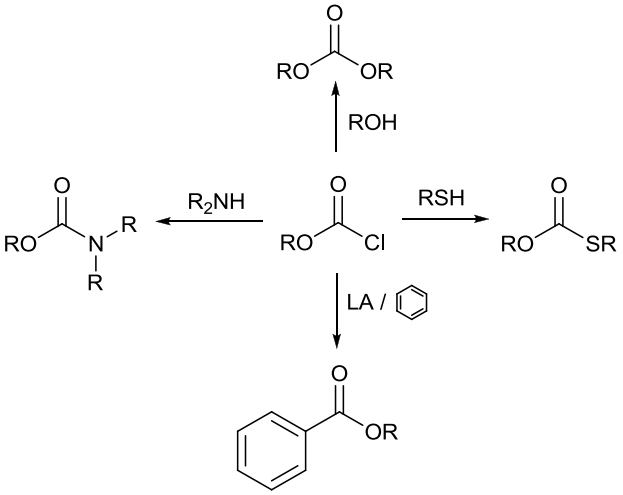


Scheme 1.26: Ketone synthesis using DMDTC

1.3.3 Chloroformates

The industrial applications of chloroformates as C_1 building blocks were previously discussed in Section 1.2.9. In research, the most useful conversions of chloroformates as C_1 building blocks are illustrated in Scheme 1.27. Aliphatic alcohols react with chloroformates to produce carbonates, although faster reactions are observed when the hydroxide of the

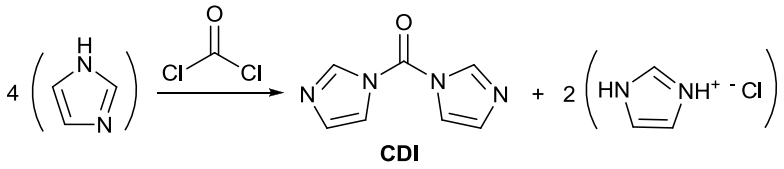
alcohol is used or when a tertiary amine is added to scavenge the HCl formed as a reaction by-product. Phenols react with chloroformates only sluggishly at room temperature and even at elevated temperatures. Therefore a base has to be added in order for the reaction to be successful. Similarly, the reaction of chloroformates with alkyl thiols in the presence of a base yields *S*-alkyl thiocarbonates. Chloroformates also react with amines to produce urethanes. Aromatic chloroformates tend to be stable in the presence of Lewis acids (in contrast to aliphatic chloroformates) and therefore acylate aromatic ring through the Friedel-Crafts reaction. Another important use of chloroformates is in the synthesis of polymers, especially polycarbonates and polyurethanes.[26]



Scheme 1.27: Compounds synthesised using chloroformates as building blocks

1.3.4 Carbonyl Diimidazole (CDI)

CDI is a white crystalline compound synthesised from the reaction of phosgene with four equivalents of imidazole, as illustrated in Scheme 1.28.

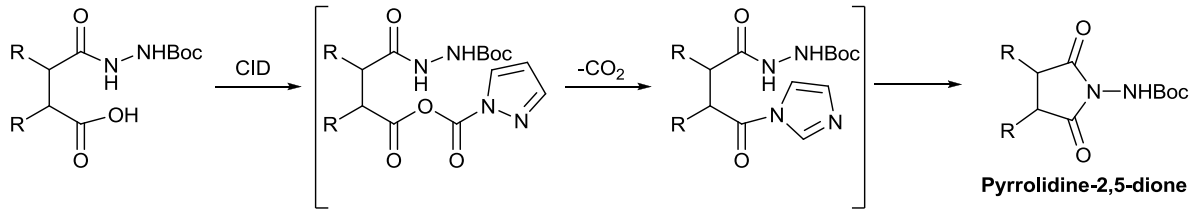


CDI

Scheme 1.28: Synthesis of CDI from phosgene

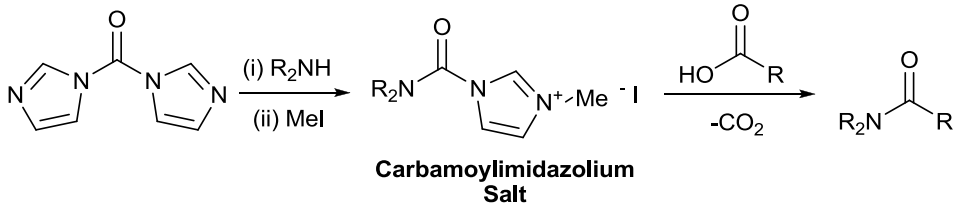
In synthesis it is used as a C_1 building block due to the imidazole groups leaving group ability, thus the majority of its reactions involve nucleophilic substitution. CDI can be used as

an alternative to poisonous phosgene, or difficult to handle acid chlorides. Similarly to phosgene, it can react with alcohols, amines, carboxylic acids, Grignard reagents (or combinations of these) to produce carbonates, [27] ureas, carbamates, [28,29] amides,[29,30] esters[31] and ketones (Scheme 1.29). As such, it can be used to synthesise substituted heterocycles such as substituted pyrrolidine-2,5-diones.[32]



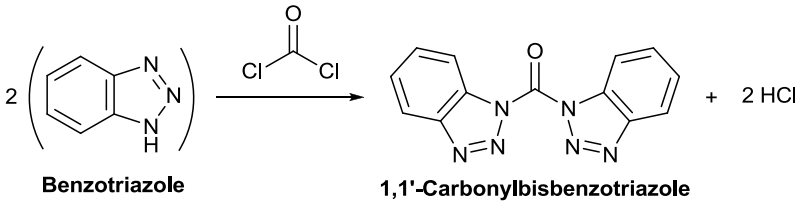
Scheme 1.29: Synthesis of substituted pyrrolidine-2,5-diones from CDI

CDI can react with formic acid to produce formylimidazole, which acts as a formylating agent. Carbamoylimidazolium salts (Scheme 1.30) are prepared by the sequential treatment of CDI with secondary amines and iodomethane, and they have been shown to be efficient carbamoylating reagents. These salts are more electrophilic than their unmethylated form and are thus more effective as carbamoylating agents. They react very well with amines, thiols, alcohols, and carboxylic acids to produce ureas, thiocarbamates, urethanes, and amides, respectively in excellent yield.[33]



Scheme 1.30: Carbamoylimidazolium salt synthesis of an amide

CDI's sulfur analogue, *N,N'*-thiocarbonyldiimidazole (TCDI), is also widely used for similar transformations.[33,34] Another compound very similar to CDI is 1,1'-carbonylbisbenzotriazole, the benzotriazole (Bt) analogue which is also synthesised from phosgene as shown in Scheme 1.31. This compound is in fact very significant to this project and will be discussed later in Section 2.2.

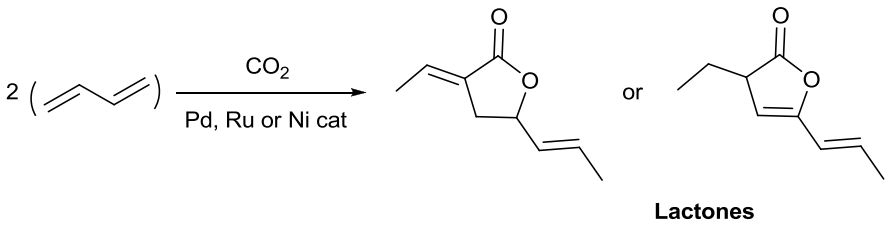


Scheme 1.31: 1,1'-Carbonylbisbenzotriazole synthesis from phosgene

1.3.5 Carbon Dioxide

In addition to the commercial CO_2 processes outlined in Section1.1.10, there are a number of reactions currently under study in various laboratories that hold promise. Listed below are just a few interesting examples found in the open literature.

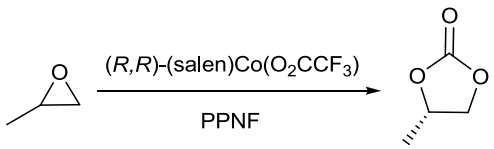
A lot of effort has been put into using CO_2 as a phosgene replacement in the synthesis of carbonates and polycarbonates. Substituting phosgene with CO_2 would drastically reduce environmental concern, as the by-product for the phosgene reactions is HCl (as opposed to water in the CO_2 case).[7] There have been many development made with regards to this area. These include the nickel-catalysed conversion of terminal and internal alkynes into pyrones, as well as the metal (Pd, Rh and Ni) catalysed conversion of butadiene to lactones and linear esters (Scheme 1.32).[8]



Scheme 1.32: The carboxylation of butadiene with CO_2 to produce lactones

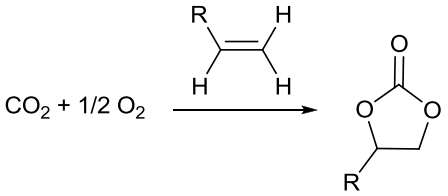
The asymmetric ring opening of epoxides using CO_2 to generate cyclic carbonates under catalytic (using a (salen)M-based catalyst), solvent-free conditions has been developed.[35,36,37] The absence of solvent, as well as the use of CO_2 as a building block make this a very environmentally-friendly protocol. This protocol is also valuable to chemistry in general since they address the issue of the feasibility of CO_2 as a C_1 building block for asymmetric synthesis.[35] The Scheme 1.33 below represents the opening of a racemic epoxide catalysed by (*R,R*)-(salen)Co(O_2CCF_3) and a nucleophilic cocatalyst (PPNF,

Bis(triphenylphosphoranylidene)ammonium fluoride) to produce propylene carbonate in an ee of 83%.



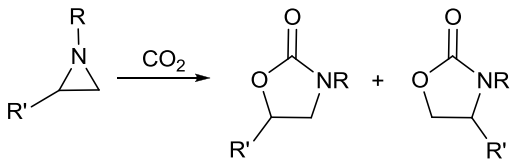
Scheme 1.33: Asymmetric cyclic carbonate synthesis using a salen catalyst

The industrial formation of carbonates using CO_2 and epoxides is hampered by the requirement of large volumes of epoxide, which itself is produced by environmentally unfriendly techniques.[8] A "greener" route involves the oxidative carboxylation of olefins using oxygen, as shown in Scheme 1.34.[38] A number of new catalysts have been developed for copolymerization of CO_2 and epoxides to form polycarbonates. These studies have increased the productivity of this reaction by approximately 102 times.[1,39, 40]



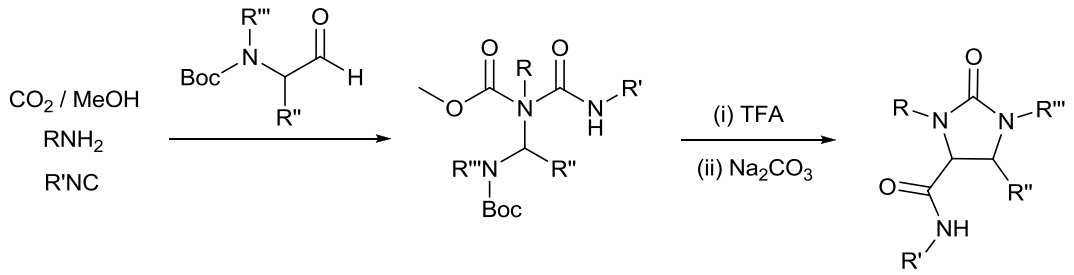
Scheme 1.34: The production of carbonates using CO_2 and O_2

CO_2 can serve as a building block for oxazolidinones. This can be achieved by: (i) CO_2 reaction with propargylamines,[41,42] or propargyl alcohols in the presence of amines[43,44] or amino alcohols (via a Mitsunobu reaction);[45] (ii) CO_2 insertion into aziridines.[46] Du et al. have developed a recyclable catalyst for the cycloaddition of aziridines to CO_2 under solvent-free conditions.[47] Recently, Wang et al. have improved upon this by developing this cycloaddition under solvent-free, as well as catalyst-free conditions to yield 5-aryl-2-oxazolidinones.[48] The *in situ* generated aziridine-CO_2 adduct is assumed to act as the catalysing agent as shown in Scheme 1.35.



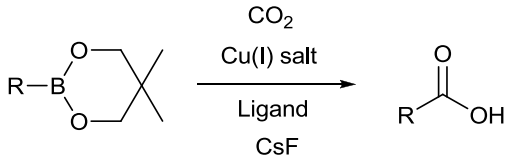
Scheme 1.35: Oxazolidinone synthesis from aziridines under solvent- and catalyst-free conditions

It has also been shown that CO_2 can be applied to Ugi multi-component reactions to yield Ugi five-component condensation (5CC) reaction products.[49,50] Scheme 1.36 shows the Hulme et al. strategy in which the CO_2/MeOH reagent combination is coupled with the UDC (Ugi/DeBOC/Cyclize) strategy. According to their protocol, the Ugi 5CC affords carbamate protected amino-amides and when one of the supporting reagents possesses a tethered amino-Boc-protected functional group, subsequent acid treatment and proton scavenging results in rapid cyclization to cyclic ureas. Additionally, treatment of the 5CC product with base affords hydantoins in good yield.[51]



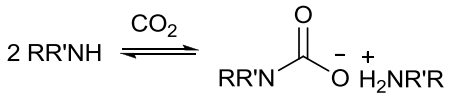
Scheme 1.36: Application of the UDC strategy to CO_2

CO_2 can also be used to produce carboxylic acids without using its reaction Grignard reagents, which is the usual route. Takaya et al. have recently shown copper(I) catalysts to be effective in the carboxylation of aryl- and alkenylboronic esters in the presence of an excess of CsF as an essential additive, Scheme 1.37.[52]



Scheme 1.37: Copper-catalysed carboxylation of boronic esters

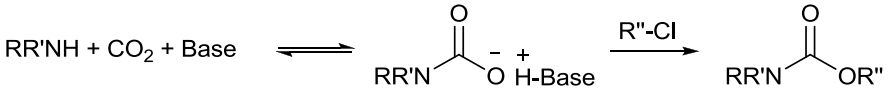
A common way to trap CO_2 gas is to react it with a primary or secondary amine to form a carbamate salt as shown in Scheme 1.38. When two moles of amine are added, an ammonium carbamate salt is formed, in which the cation is an ammonium species. However, when a metal (e.g. Na^+, K^+ and Cs^+) amide is used, a metal cation is obtained.



Scheme 1.38: Ammonium carbamate salt formation using CO_2 and an amine

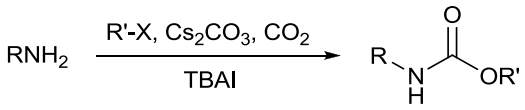
In recent years, carbamate salts thus generated have been successfully employed in preparative organic chemistry thus providing an alternative synthetic equivalent to phosgene.[2] However there are some issues to be considered in using these salts. Carbamate salts are thermally unstable and release CO_2 upon heating. (This thermal instability can also be useful in industry where polymer-bound amines are employed as reusable 'CO_2 scrubbers' removing CO_2 from industrial exhaust streams.[53,54]) Also, the nucleophilicity of the carbamate alkoxide oxygen tends to be lower than that of the carbamate nitrogen. Thus the activation of the alkoxide oxygen has been accomplished through the addition of metal catalysts, crown ethers and strong bases. In general, these additives serve to stabilize the carbamate anion thus activating the nucleophilicity of the oxygen centre.[55,56] This method of CO_2 beneficiation is particularly significant since it was the strategy employed in this project, as will be discussed further in Chapter 2. For now, the examples that follow show how products such as urethanes, substituted ureas, isocyanates, carbamoyl chlorides and carbamoyl azides have been synthesised using carbamate salts.

Urethanes are usually synthesised by the addition of an alcohol to an isocyanate. It has been shown that they can be synthesised via the reaction of ammonium or alkali metal carbamate salts with alkyl halides (RX). However the alkylating agent RX raises problems, since the electrophile "R^+" reacts at the nitrogen atom of the carbamate anion more than at the oxygen atom. The *N*-alkylation is avoided if the reaction between the amine and CO_2 is carried out in the presence of a crown-ether[55,57], cryptand[58] or strong base.[56] McGhee et al. has synthesised urethanes in high yield by adding strong amidine and guanidine bases as carbamate stabilising agents (Scheme 1.39). They also showed that the procedure can also be extended to the synthesis of di- and triurethanes.[56,59]



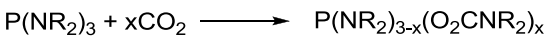
Scheme 1.39: Synthesis of urethanes using base-stabilized ammonium carbamate salts

Perez et al. made a slight modification to the usual urethane synthesis procedure. They pre-formed (and characterised) a DBU-CO_2 complex, which then underwent trans-carboxylation with primary amines and subsequent *O*-alkylation with alkyl iodides.[60] A range of urethanes were thus made in high yields (without any *N*-alkylations) and, more importantly, DBU was shown to be an efficient trap for the fixation and storage of CO_2. Scheme 1.40 shows how Chu et al. alternatively used $CsCO_3$ as a carbamate stabilising agent. In an earlier publication they developed a protocol for the synthesis of alkyl carbonates from alkyl halides, alcohols, TBAI and $CsCO_3$ (which served both as a base and CO_2 source).[61] They then improved on this methodology by adding CO_2 gas and found that this not only improved product yields, but it also expanded the versatility of the procedure. Thus a wide range of not only carbonates, but also urethanes, were synthesised in excellent yields.[62,63] TBAI (*N,N,N*-tributyl-1-butanaminiuiodide) was found to be an essential reagent as its addition prevented the formation of *N*-alkylation side-products. They were able to expand this system to the synthesis of urethanes and carbonates on solid supports.[64]



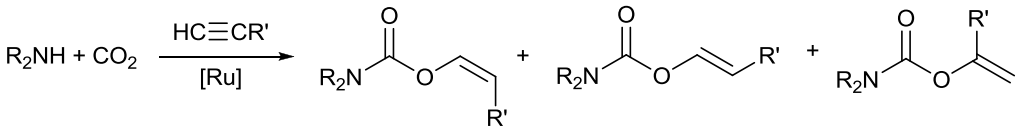
Scheme 1.40: Urethane synthesis in the presence of $CsCO_3$ and TBAI

CO_2 has been shown to insert into P-N bonds and yield phosphocarbamates as shown in Scheme 1.41. These can react with alkali metal halides and alkyl halides to give urethanes.[65,66] This reaction occurs via carbamic group transfer to the alkali metal cation in the presence of a crown-ether to give a carbamate salt $[ML]^+[O_2CNR_2]^-$ (where L is the crown-ether), which is then alkylated by the alkyl halide.



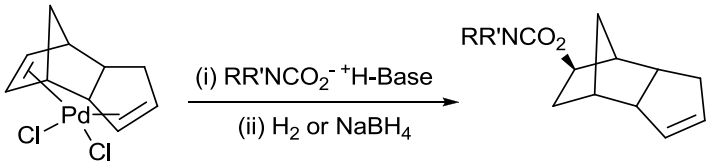
Scheme 1.41: Insertion of CO_2 into P-N bonds, where x = 1 or 2

Transition-metals have also been employed to facilitate the carbamate anion alkylation in urethane synthesis. Examples include Dixneuf's report on the ruthenium catalysed conversion of secondary amines, carbon dioxide, and terminal alkynes into *O*-vinylic urethanes, Scheme 1.42.[67]



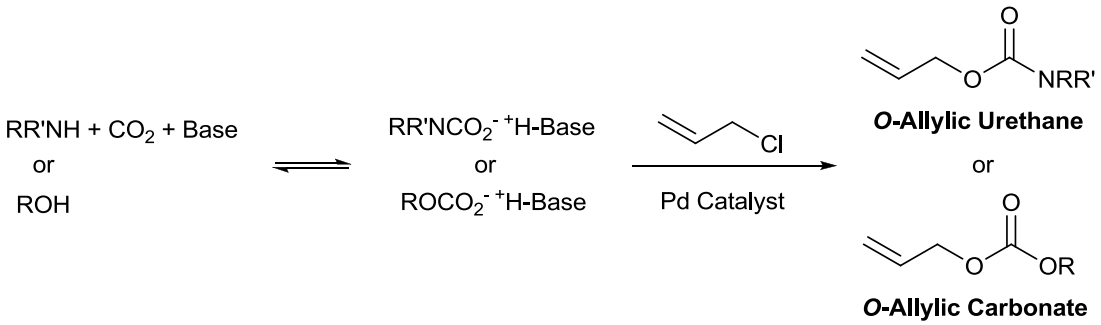
Scheme 1.42: Vinyl urethane synthesis using Pd(II)-activation

Similarly, McGhee et al. have reported a stoichiometric system based on nucleophilic attack of a premade carbamate anion on a palladium(II)-activated diolefin complexes.[68] It is suggested that the role of palladium is to activate the olefin towards nucleophilic attack by the carbamate anion, and the hydride is responsible for hydrogenolysis of the metal-carbon bond. The reaction conversion is illustrated below in Scheme 1.43.



Scheme 1.43: Urethane synthesis using Pd(II)-activation

They also used amidine- and guanidine-stabilized carbamate salts to make *O*-allylic urethanes via palladium catalysis (Scheme 1.44).[69] This procedure was extended to carbonate salts (formed by the reaction of alcohols with CO_2) to give *O*-allylic carbonates (Scheme 1.44).

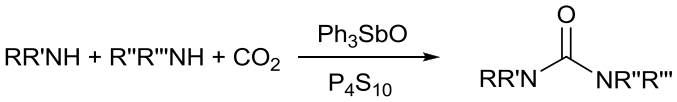


Scheme 1.44: *O*-allylic urethanes and carbonates from CO_2 via palladium catalysis

Yoshida et al. have shown that onium salts (such as tetrabutylammonium bromide) catalyse selective urethane production from amines and alkyl halides in supercritical carbon dioxide

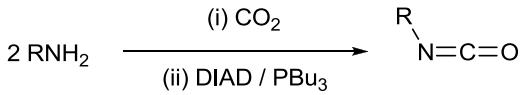
($scCO_2$), which not only acts as an alternative to organic solvents, but also as a phosgene replacement.[70] The use of CO_2 as a super-critical liquid is widely reported since: (i) $scCO_2$ is greatly miscible with organic substrates; (ii) it has a relatively high heat conductivity, leading to better dissipation of reaction heat; (iii) the separation of products and solvent ($scCO_2$) can easily be performed by depressurization, and the separated CO_2 can be reused by pressurization; and (iv) the flexible physical properties of $scCO_2$ allow for its usage at various conditions. It has also been said that these and other advantages of dense CO_2 (such as high reaction rates and unique product selectivities) can compensate for the high costs involved in its usage.[71]

The synthesis of substituted ureas via direct carbonylation of amines with CO_2 under mild conditions, and without the use of dehydrating agents (such as carbodiimides and organophosphites) had been elusive until a novel catalytic procedure was developed by Nomura et al (Scheme 1.45). They found triphenylstibine oxide (Ph_3SbO, 5 or 10 mol%) with assistance from tetraphosphorus decasulfide (P_4S_{10}, 10 or 20 mol%) to be a suitable catalytic system for the synthesis of substituted and cyclic ureas.[72]



Scheme 1.45: Synthesis of substituted ureas

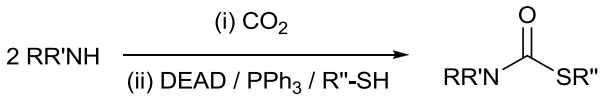
McGhee has shown that a base-stabilised carbamate salt generated from a primary amine can react with dehydrating agents such as $POCl_3$ and PCl_3 to produce isocyanates and polyisocyanates in high yields.[73] The Mitsunobu reaction has also been successfully applied to isocyanate synthesis. Saylik et al. showed that primary amines give high yields of isocyanates when reacted with carbon dioxide under Mitsunobu conditions (DIAD and Bu_3P).[74] This procedure is outlined in Scheme 1.46 below.



Scheme 1.46: Isocyanate synthesis using the Mitsunobu reaction

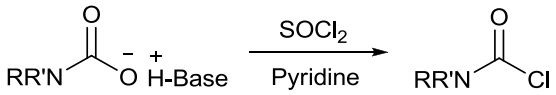
Scheme 1.47 shows how Mitsunobu conditions have also been used by Chaturvedi et al. to synthesise *S*-thiocarbamates from CO_2, a primary or secondary amine and an alkyl thiol.[75]

Interestingly enough, they claim that the intermediate formed by the reaction of the amine with CO_2 is a carbamic acid, as opposed to the ammonium carbamate salt. Unfortunately, no evidence was presented in order to substantiate this claim.



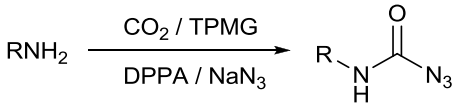
Scheme 1.47: Synthesis of *S*-thiocarbamates using the Mitsunobu reaction

Carbamate salts have also been employed in the phosgene-free synthesis of carbamoyl chlorides.[76] Scheme 1.48 depicts how secondary amines were reacted with CO_2 in the presence of guanidine or amidine bases to generate a carbamate salt, which was then reacted *in situ* with thionyl chloride. It was found that the addition of pyridine as an additional base improved the yield significantly. This may be a result of pyridine trapping the sulfur dioxide which forms during the reaction.



Scheme 1.48: Synthesis of carbamoyl chlorides from CO_2

Finally, carbamoyl azides are aminating agents (e.g. in the synthesis of biotin)[77] notorious for their explosive nature as well as the harsh conditions required in order to prepare them. However, Garcia-Egido et al. have shown that the low-temperature treatment of primary amines under a carbon dioxide atmosphere with tetramethylphenylguanidine (TMPG) and diphenylphosphoryl azide (DPPA) provides carbamoyl azides in high to excellent yields.[78] This is illustrated in Scheme 1.49 below.



Scheme 1.49: Synthesis of carbamoyl azides from CO_2

Knowledge of these syntheses paved the way for this project. The chapters that follow discuss the objectives and results of the project.

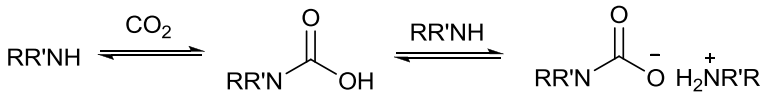
Chapter 2: CO_2 Fixation

The key objective of this research was to develop a methodology for transforming CO_2 gas into a stable, easily stored reagent that would be useful for organic synthesis. From the literature it was clear that one of the most attractive ways to do this, on paper, was to react CO_2 with a primary or secondary amine and trap the gas as an ammonium carbamate salt. This salt would then be transformed into a chemical reagent for use in synthesis. Thus, the first phase of the project studied the properties of these salts.

2.1 Carbamate Salt Study

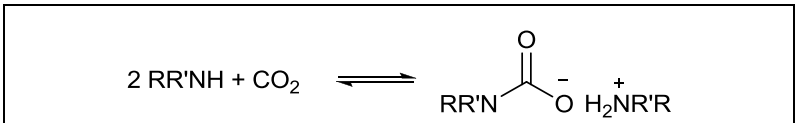
2.1.1 Salt Formation

The carbamate salt formation involves a nucleophilic addition of an amine (primary or secondary) into carbon dioxide, to form a carbamic acid, which is deprotonated by a second equivalent of an amine to form an ammonium carbamate salt (Scheme 2.1).



Scheme 2.1: The equilibria involved in carbamate salt formation using an amine and CO_2

The primary and secondary amines chosen for this study were benzylamine, diethylamine, dicyclohexylamine and piperidine. All four amines were reacted separately with CO_2 in THF, DCM or acetonitrile. Thus, on a 2 mmol scale the amines were dissolved in each of the respective solvents at a concentration of 0.4 M, and CO_2 was then bubbled through these solutions. Benzylamine and dicyclohexylamine both formed precipitates in all three solvents within a few minutes (the rate being fastest in CH_3CN for both amines). However, piperidine and diethylamine gave homogenous solutions that gave solid material on evaporation of solvent. The isolation of the precipitate proved to be very challenging with salts tending to disintegrate as soon as they were exposed to the air. Drying under pressure also led to the loss of material, presumably due to reversal of the reaction on entropy grounds. The salts of dicyclohexylamine and benzylamine were successfully isolated by suction filtration and drying in the open air. Table 2.1 below shows the yields obtained:



	THF	DCM	CH_3CN
Dicyclohexylamine	44%	74%	41%
Benzylamine	63%	42%	74%

Table 2.1: Results from carbamate salt study using dicyclohexylamine and benzylamine

In these cases, ^{1}H NMR analysis of the salts gave satisfactory evidence that salt formation was successful. Figure 2.1 shows the ^{1}H NMR spectrum of the dicyclohexylamine salt. The deshielded protons (H-1 and H-1') α- to nitrogen in both ions were observed as one downfield multiplet at 3.06 ppm. The N-H protons of the cation exchanged with deuterium atoms from the solvent (CD_3OD). This is shown by the peak at 4.85 ppm, which is the chemical shift for the hydroxyl proton in CD_3OH.

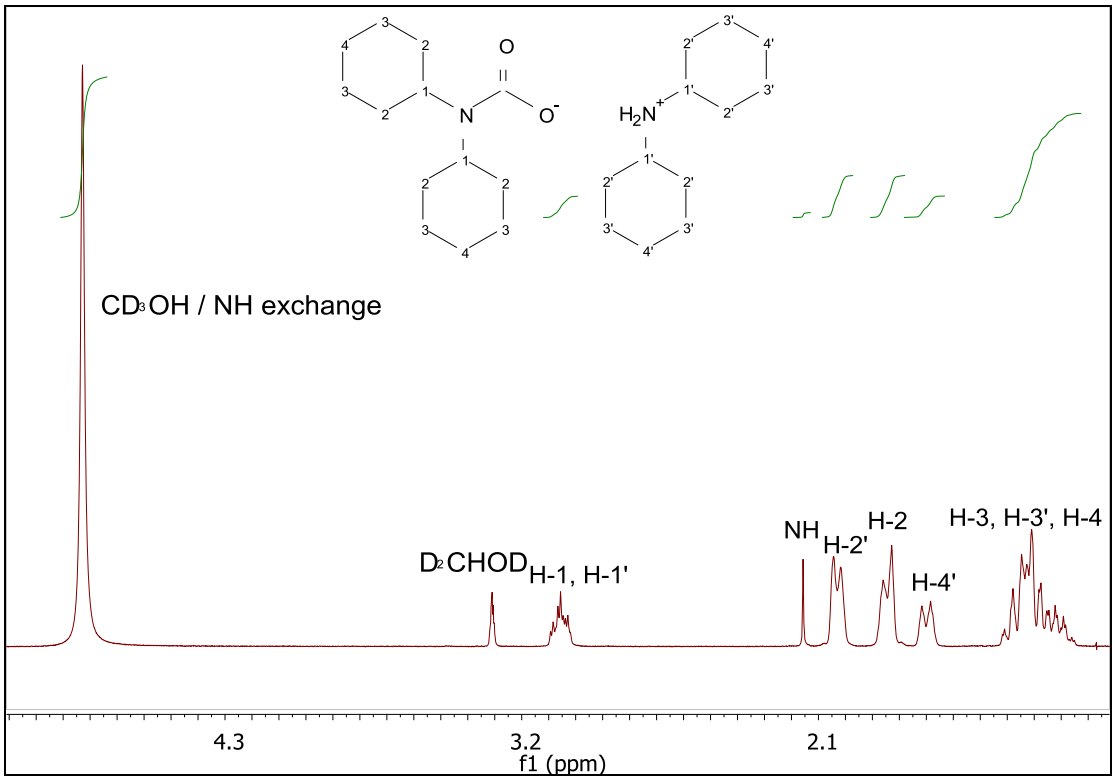
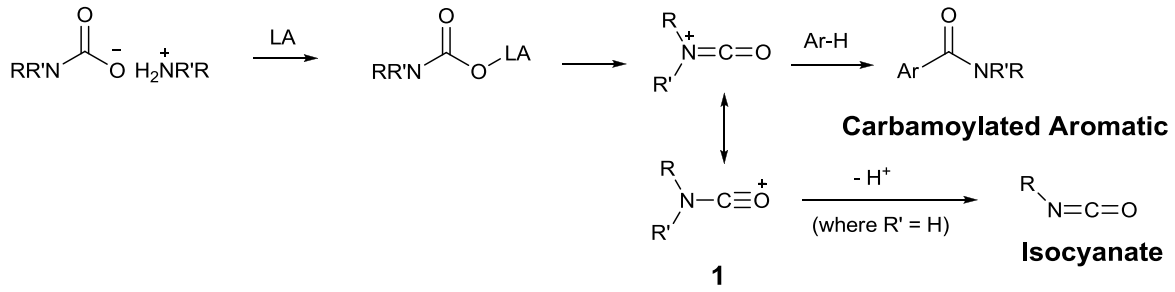


Figure 2.1: The ^{1}H NMR spectrum (CD_3OD, 400 MHz) of the dicyclohexylamine salt

The ^{13}C NMR spectrum for the dicyclohexylamine salt showed the appropriate resonances for the aliphatic cyclohexyl rings between 25.7 and 54.4 ppm. The ^{13}C NMR spectrum from the benzylamine salt showed aromatic resonances as well as two aliphatic resonances at 45.6 and 46.5 ppm for the CH_2 carbons. Curiously, the downfield carbonyl resonance was not observed for both salts. Nevertheless, it was decided that there was enough evidence to suggest successful salt formation, and so the salts were used in the next stage of the project.

2.1.2 Use of Carbamate Salts for C-C Bond Formation

The generation of carbon-carbon bonds in a simple and elegant manner is one of the key aspirations of any synthetic organic chemist. This is because C-C bonds form the backbone of virtually all organic structures. The Friedel-Crafts acylation reaction involves the acylation of an aromatic species and is one of the most famous C-C bond formation reactions. It was therefore proposed that a carbamate salt might be used in a Friedel-Crafts type of conversion in order to carbamoylate aromatic rings. The following reaction sequence was envisioned, Scheme 2.2:

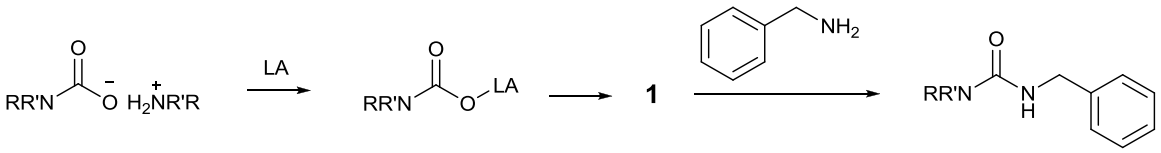


Scheme 2.2: Envisioned carbamoylation of aromatics via Lewis acid (LA) activation of a carbamate salt

The procedure entailed Lewis acid activation of the carbamate anion to generate the highly electrophilic species **1**. Electrophilic substitution of an activated aromatic with **1** would then yield the desired carbamoylated aromatic ring. However, it was thought likely that **1** would eliminate to produce an isocyanate in the case of a primary amine. At the time of this work, no analogy for this reaction sequence could be found in the literature.

Initially, TMSOTf was chosen as the oxophilic Lewis acid, the reaction solvent was DCM and the aromatic species chosen was *para*-*t*-butylphenol since: (i) the *para*-position is blocked

and this would simplify issues of regioselectivity; and (ii) it is a highly activated, π-excessive aromatic ring. The isolated benzylamine and dicyclohexylamine salts were used in this study on the basis that they had been successfully isolated and their structures had been determined. However the reactions were unsuccessful as reaction tlc's showed no conversion of starting materials, even after several hours under reflux. Changing the Lewis acid to $SnCl_4$ did not yield any better results, and it was decided that the hydroxyl group in the phenol was possibly competing with the carbamate alkoxide oxygen as a Lewis base. To avoid this, *para-t*-butylphenol was changed to anisole, which contains a methoxy group instead of a hydroxyl group. This change did not lead to any improvement even when yet another oxophilic activator ($POCl_3$) was employed. Perhaps the electrophilic iminium species **1** was not being formed, or the aromatic ring was not nucleophilic enough to react with **1**. Thus a separate experiment was performed to investigate these possibilities. The dicyclohexylamine salt was treated with $SnCl_4$, followed by a more reactive nucleophile (benzylamine) to see whether a urea (instead of the carbamoylated aromatic) would be generated as shown in Scheme 2.3. However, there was still no reaction.



Scheme 2.3: Using the carbamate salt for the formation of an unsymmetrical urea

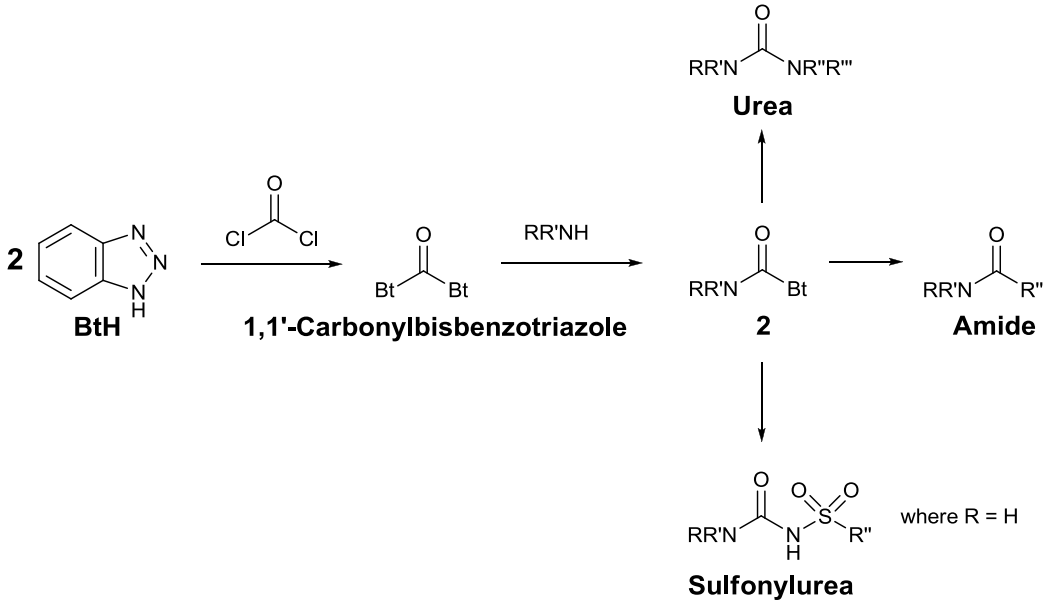
The study allowed the following conclusions to be made: (i) the insolubility of the dried carbamate salts was often an issue at room temperature; (ii) it is possible that the carbamate salt was unstable under the chosen reaction conditions, equilibrating back to the amine and releasing CO_2. Consequently, it was decided that a better approach would be to convert the salt *in situ* to a stable but reactive and isolable product for use as a reagent in synthesis.

2.2 Bt Ureas

2.2.1 The PPh_3 / BtCl System

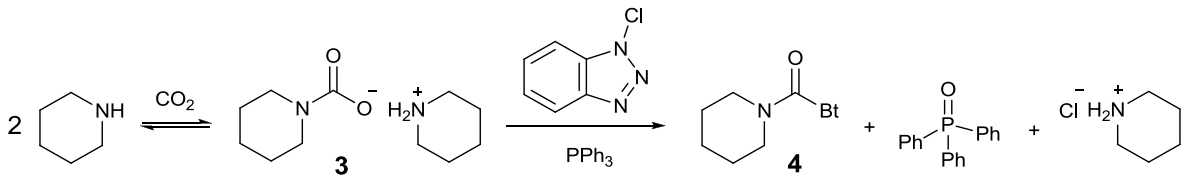
As mentioned in Chapter 1, Katritzky used phosgene to generate 1,1'-carbonylbisbenzotriazole (a compound similar to carbonyl diimidazole), which was then reacted with a primary or secondary amine to give Bt (benzotriazole) urea **2** (see Scheme 2.4).[79] The Bt urea **2** can be reacted with other amines or with Grignard reagents to give ureas and amides respectively. Butula et al. have also shown that Bt urea **2** (derived

similarly from phosgene, BtH and primary amines) can be reacted with sulfonamides to produce sulfonyl ureas, also shown in Scheme 2.4.[80]



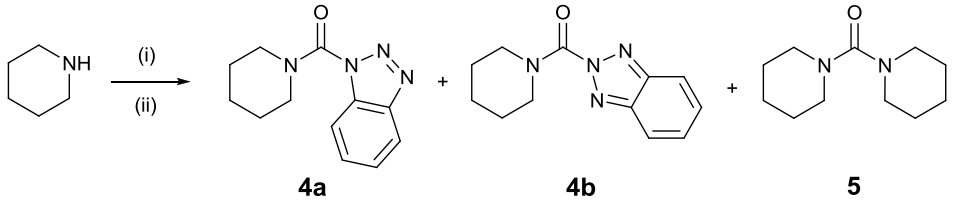
Scheme 2.4: The synthesis of Bt urea **2** from phosgene, BtH and an amine, and the types of compounds that can be produced from Bt urea **2**

Cognisant of the usefulness of Bt urea **2**, it was thus decided to investigate whether **2** could be made from CO_2 without using phosgene. As previously mentioned, Saylik et al. have shown that carbamate salts from primary amines can undergo phosphonium-ion activation (under Mitsunobu conditions with PPh_3 and DIAD) to produce isocyanates. Therefore it was envisioned that a carbamate salt generated from CO_2 might react with PPh_3 and BtCl (chlorobenzotriazole) to produce **3**. Such a reaction would depend on the reaction of PPh_3 with BtCl to generate a chlorophosphonium ion for activating the carbamate alkoxide oxygen. BtCl is a reagent produced by the reaction of BtH and bleach (a relatively benign chlorinating agent) in acetic acid as solvent. As mentioned in section 2.1, CO_2 fixation with piperidine in DCM did not result in precipitation of the carbamate salt. Thus piperidine was considered to be an ideal amine for testing out this possibility in view of homogeneity. This reaction is outlined in Scheme 2.5 below.



Scheme 2.5: Envisioned formation of a Bt urea using CO_2

Since the yield of carbamate salt formation from piperidine had not been quantified, it was thought prudent to use the carbamate salt in excess (1.3 equivalents from 2.6 equivalents of piperidine). BtCl, although always assumed to be more than ninety-five per cent pure, is prone to decomposition to BtH over time or in the presence of light. Therefore BtCl was also used in slight excess (1.2 equivalents), with PPh_3 acting as the limiting reagent. The reaction was performed under the conditions given in Scheme 2.6 gave the Bt urea as two solid regioisomers (**4a** and **4b,** in a ratio of **4a** : **4b** = 4.5 : 1) in a moderate yield of 47%, following column chromatography. However, by-product **5** (the piperidinyl symmetrical urea) was also produced in a yield of 35%. The combined yield of 82% for conversion of the *N*-acyl piperidinyl fragment of salt **3** indicated that the yield of the salt formation in the first step was indeed high.



4a **4b** **5**

Scheme 2.6: *Reagents and conditions:* (i) piperidine (2.6 eq), CO_2 (*g*), DCM, 20 min, RT; (ii) PPh_3 (1 eq), BtCl (1.2 eq), 15 min

The structures of these three products were elucidated from ^{1}H NMR and ^{13}C NMR spectral analysis. Since **4b** is a new compound, additional analytical techniques (infrared spectroscopy and high-resolution mass spectroscopy) were employed in order to confirm its structure. Repeated recrystallization from an aprotic solvent mixture (DCM and petroleum ether) unfortunately failed to give the correct CHN microanalytical combustion data, presumably due to hydrolysis. Figures 2.2, 2.3 and 2.4 show the ^{1}H NMR spectra of **4a**, **4b** and **5** respectively. The key difference between the regioisomers is that **4a** is unsymmetrical, which results in four aromatic resonances being observed for the Bt protons, whereas **4b** is symmetrical, and thus only two aromatic resonances are observed as a result of free rotation about the bond between the carbonyl carbon and the Bt nitrogen. Obviously, **5** only showed relatively upfield resonances and no aromatic resonances.

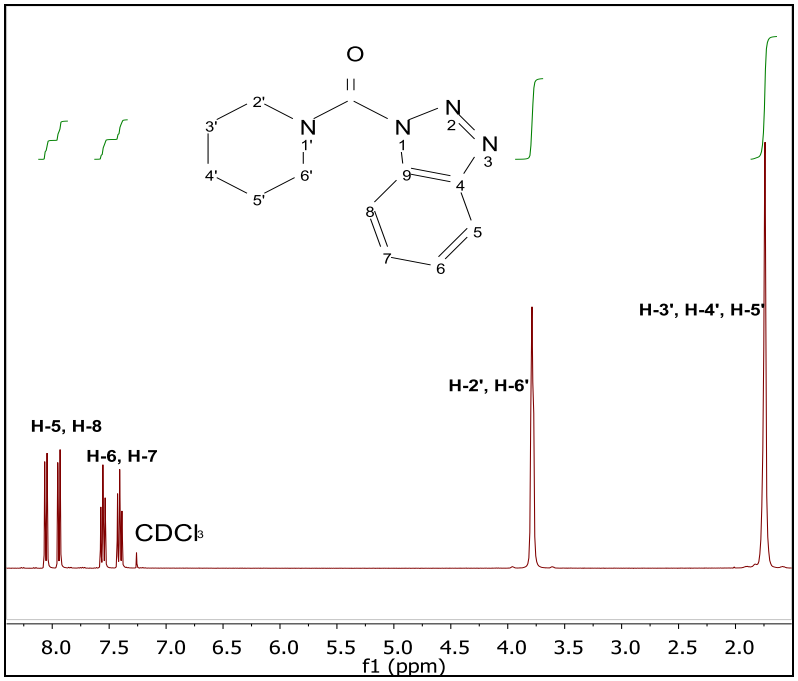


Figure 2.2: The ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of **4a**

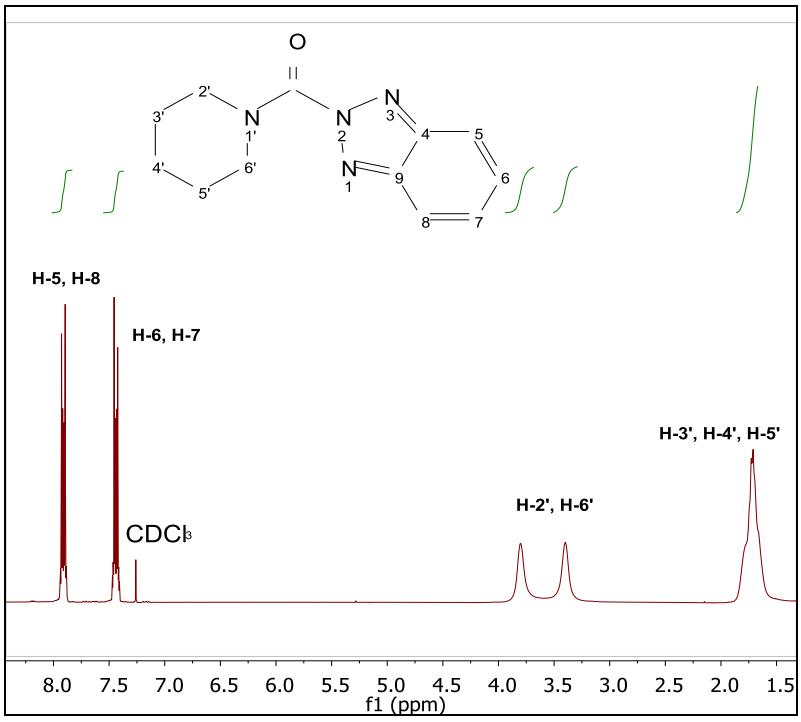


Figure 2.3: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **4b**

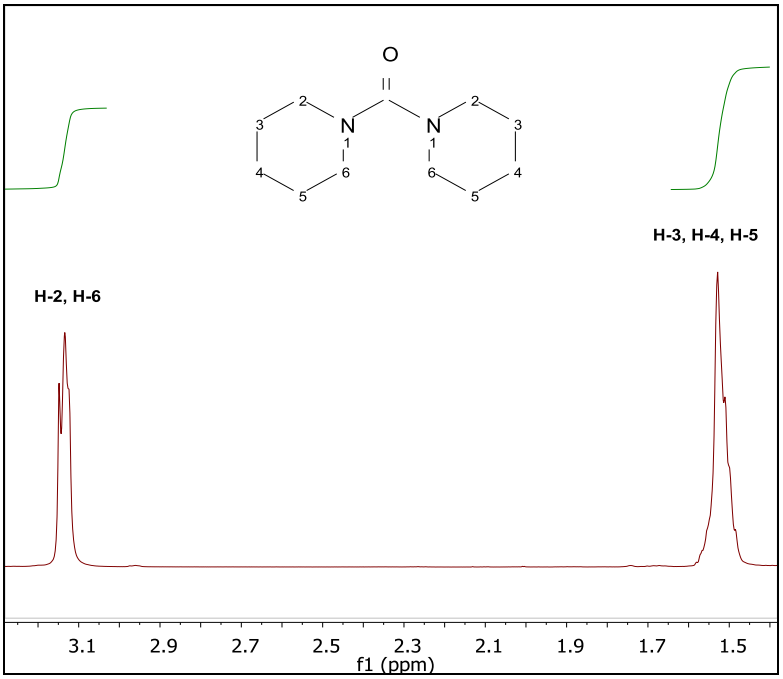
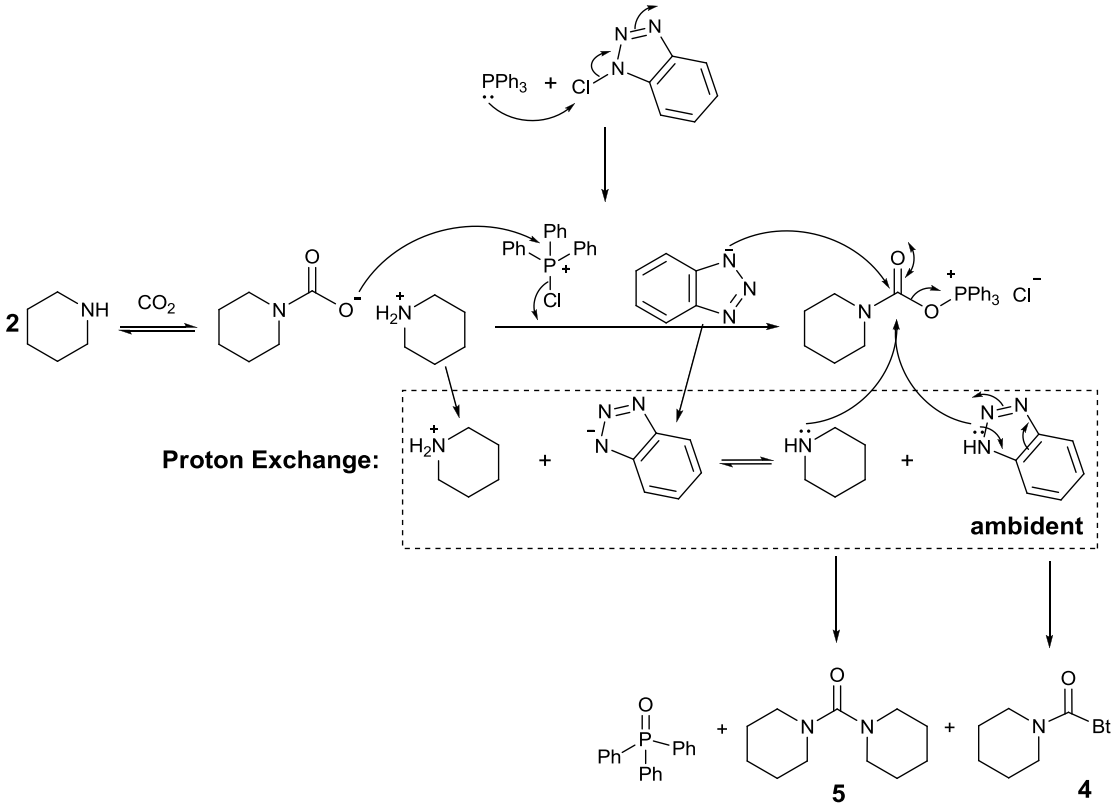


Figure 2.4: The ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of **5**

At this point, an obvious concern was the moderate yield of **4**. This led to consideration of the likely origin of **5**, which was addressed by evaluating the mechanism of the reaction, shown in Scheme 2.7.

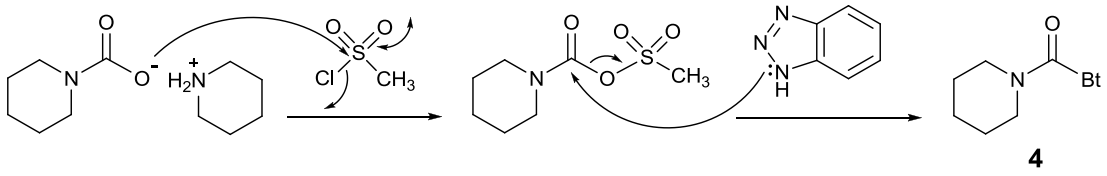


Scheme 2.7: The proposed reaction mechanism for Bt urea formation

In situ activation of the carbamate anion by the highly electrophilic and oxophilic chlorophosphonium ion and subsequent nucleophilic attack by the Bt anion (an ambident nucleophile) leads to Bt urea **4** as two regioisomers. However, the presence of by-product **5** suggests acid-base exchange between the Bt anion and the piperidinium cation to produce piperidine, which competes with BtH as a nucleophile to produce **5**. This mechanism accounts for the moderate yield of **4**.

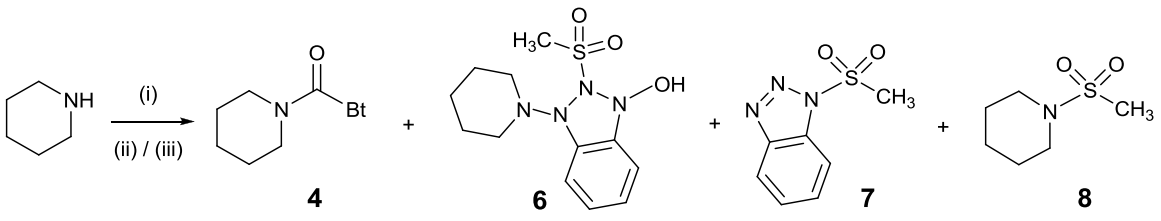
2.2.2 The MsCl / BtH System

In a separate study, the possibility of substituting the BtCl / PPh_3 system with mesyl chloride (MsCl) and BtH was investigated. Mesylation of the carbamate was expected to convert the alkoxide oxygen into a good leaving group (see Scheme 2.8). This would offer two advantages: (i) it would minimise reagent usage as BtCl synthesis would be avoided; and (ii) the mesylation by-products would be removable by aqueous extraction (in contrast to triphenylphosphine oxide, which requires column chromatography).



Scheme 2.8: The proposed mechanism for the MsCl / BtH procedure

As in the PPh_3 / BtCl case, the carbamate salt was used in excess but in this case the BtH was used as the limiting reagent, with MsCl being in a 1 : 1 ratio with the salt (i.e. 0.5 : 1 with piperidine), as shown in Scheme 2.9. The MsCl was added separately from the BtH since it reacts with BtH.



Scheme 2.9: *Reagents and conditions:* (i) piperidine (2.6 eq), CO_2 (*g*), DCM, 20 min, RT; (ii) MsCl (1.3 eq), 1 hr; (iii) BtH (1 eq), 18 hrs

The result was formation of **4** as two regioisomers (**4a** : **4b** = 2 : 1) in an isolated yield of 12%. The major product isolated was in fact **6** (48% yield), whose ^{1}H NMR spectrum is given in Figure 2.5, showing aromatic and upfield resonances whose proton ratios indicated the presence of Bt, mesyl methyl and piperidinyl moieties in the structure. In conjunction with analysis of the ^{13}C NMR spectrum, the structure of **6** was tentatively assigned to that shown in Scheme 2.9. There were also minor by-products **7** (11%) and **8** (17%), which resulted from the reaction of MsCl with BtH and piperidine (once again indicating deprotonation of the ammonium cation) respectively. The presence of these by-products suggested that the reaction of the carbamate anion with MsCl was sluggish and needed more time.

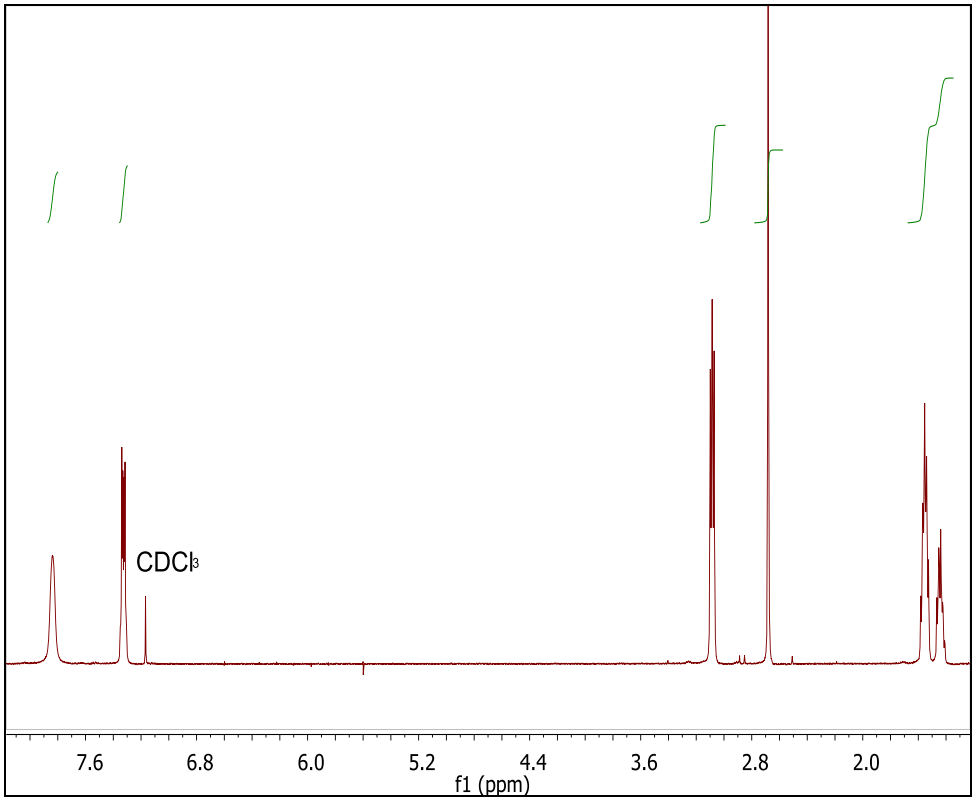


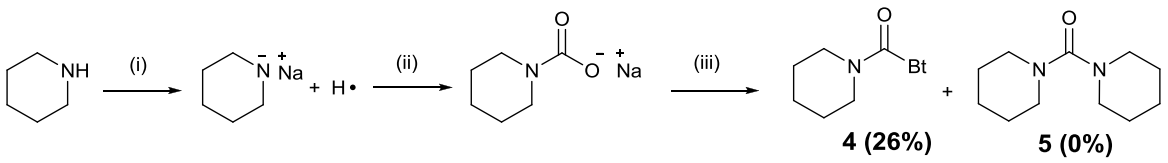
Figure 2.5: The ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of **6**

In the next experiment the procedure was modified in the following ways: (i) MsCl was reacted as one equivalent; (ii) the MsCl was given one and a half more hours to react with the carbamate salt (two and half hours in total); and (iii) two equivalents of triethylamine were added together with the BtH in the final step. These modifications were successful in removing by-products **6**, **7** and **8**. However, the yield of **4** decreased to a dismal 3%, while symmetrical urea **5** appeared as the major product in a yield of 66%. This indicated that triethylamine deprotonated the ammonium cation, resulting in a relatively higher

concentration of free piperidine for nucleophilic substitution. These results indicated that the PPh_3 / BtCl system was more suitable, and that a way to replace the ammonium cation needed to be found since its presence inevitably resulted in competing side-reactions from the free amine it generates.

2.2.3 Changing to a Metal Cation

As stated in Chapter One, there is precedence in the literature of alkali metals acting as the cation in carbamate salts and thus sodium and lithium salts were chosen for this investigation. Scheme 2.10 shows results from the formation of the carbamate salt using a slight excess of sodium metal and piperidine, which reacted (supposedly via homolysis) to give the piperidinyl anion as a sodium salt. Application of the PPh_3 / BtCl methodology in the third step gave the Bt urea **4** in a 26% yield, without the formation of by-product **5**.

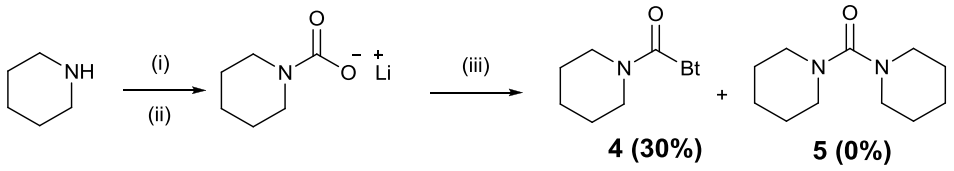


Scheme 2.10: *Reagents and conditions:* (i) piperidine (1.3 eq), Na (1.5 eq), THF, 15 min, RT; (ii) CO_2 (*g*), 20 min; (iii) PPh_3 (1 eq), BtCl (1.2 eq), 20 min

Alternatively, the sodium salt was formed using NaH (Scheme 2.11). In this case piperidine and NaH were made the limiting reagents in order to avoid having an excess of base. Accordingly, **4** was produced in a 29% yield together with 8% of **5**.

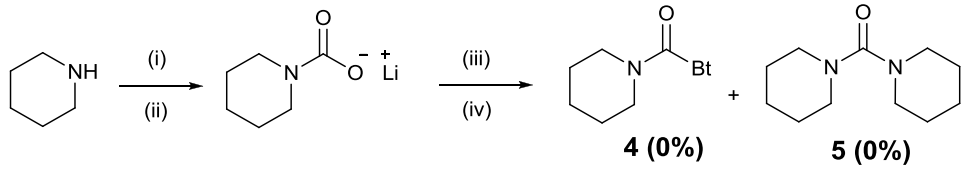
Scheme 2.11: *Reagents and conditions:* (i) piperidine (1 eq), NaH (1 eq), THF, 15 min, RT; (ii) CO_2 (*g*), 20 min; (iii) PPh_3 (1.3 eq), BtCl (1.3 eq), 20 min

Finally, the lithium carbamate salt was formed using *n*-BuLi (Scheme 2.12). For the same reason as stated above, BuLi and piperidine were the limiting reagents. This resulted in the formation of only **4**, but again in low yield (30%).



Scheme 2.12: *Reagents and conditions:* (i) piperidine (1 eq), *n*-BuLi (1 eq), THF, 15 min, 0^0C; (ii) CO_2 (*g*), 20 min; (iii) PPh_3 (1.3 eq), BtCl (1.3 eq), 20 min, 0^0C to RT

As Scheme 2.13 shows, forming the lithium salt with *n*-BuLi followed by reaction with MsCl and BtH did not result in any product formation



Scheme 2.13: *Reagents and conditions:* (i) piperidine (1 eq), *n*-BuLi (1 eq), THF, 15 min, 0^0C; (ii) CO_2 (*g*), 20 min; (iii) MsCl (1 eq), 3 hrs, 0^0C to RT; (iv) BtH (1.2 eq), triethylamine (2 eq), 20 min

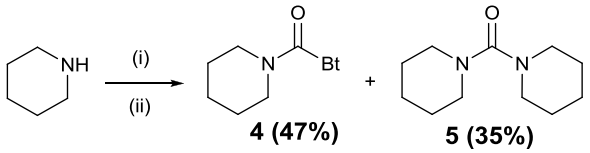
These results show that even though the percentage of **5** was reduced drastically (or even eliminated), the yield for **4** was also compromised. Thus it was decided to revisit the original PPh_3 / BtCl reaction and try to optimise the conditions.

2.2.4 PPh_3 / BtCl Reaction Optimisation Studies

Different parameters in the reaction conditions were reinvestigated, whilst keeping the stoichiometry the same as for the original model reaction (which produced **4** in a 47% yield and **5** in a 35% yield). Firstly, the time for CO_2 bubbling was increased to one hour in order to make sure that carbamate salt formation was maximised. As shown in the first entry of Table 2.2, this resulted in a 22% isolated yield of **4**, with 25% of **5**. Next, the reaction work-up was evaluated. Prior to this stage, the reaction had been processed simply by removal of solvent under reduced pressure, followed by direct column chromatography. However, HCl is a reaction by-product that was possibly promoting side-reactions, therefore a base work-up was used. Quenching the reaction with a base (aqueous Na_2CO_3) resulted in a 38% yield of **4**. In the experiments that followed, the temperature of the PPh_3 / BtCl addition step was reduced in order to slow down (or even halt) the formation of by-product **5**. When the reaction was cooled to -78^0C preliminary tlc studies showed that hardly any product was

formed. The temperature was then changed to -10^{0}C and this yielded 46% of **4** and 10% of **5**. Finally, the temperature was changed to 0^{0}C, which yielded **5** in only 9% but, strangely enough, product **4** was also reduced to 20%. Thus a decrease in temperature definitely led to a decrease in the formation of by-product **5** but this occurred at the expense of the yield for **4** (except in the -10^{0}C case).

Original Reaction Conditions:



4 (47%) **5 (35%)**

(i) piperidine (2.6 eq), CO_2 (*g*), DCM, 20 min, RT; (ii) PPh_3 (1 eq), BtCl (1.2 eq), 15 min

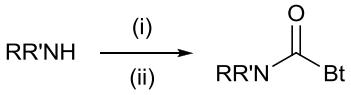
Change in Reaction Conditions	**4**	**5**
CO_2 bubbling increased to 1hr	22%	25%
Base work-up performed	38%	32%
Temperature of the second step reduced to -10^{0}C	46%	10%
Temperature of the second step reduced to 0^{0}C	29%	9%

Table 2.2: Changing parameters in the reaction conditions

From the above study, ironically, it was concluded that the original reaction conditions were the best in terms of maximising the yield of product **4**.

At this stage an investigation into the applicability of this methodology to other amines (primary, secondary, hindered and unhindered) was conducted. The solvent for each reaction was varied as THF, DCM or acetonitrile, as it was also important to see what effect a change in the reaction solvent would have on product yield. In this regard, the following amines were chosen: piperidine diethylamine, dicyclohexylamine, diisopropylamine, *n*-butylamine and benzylamine. As in the original piperidine / DCM reaction, the reaction mixture was column chromatographed directly, without an aqueous work-up. Table 2.3 summarises the yields from this study, from which it became clear that although the reaction was applicable to a range of amines, secondary amines performed the best, in which the

dicyclohexylamine / THF combination gave the best yield to date (58% yield). As far as the reaction solvent was concerned, THF proved to be the best for the secondary amines, whilst DCM was the best solvent for the primary amines. This investigation showed that the methodology was versatile and that further optimization studies would indeed be a worthwhile objective.



(i) amine (2.6 eq), CO_2 (*g*), DCM, 20 min, RT; (ii) PPh_3 (1 eq), BtCl (1.2 eq), 15 min

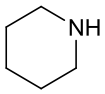
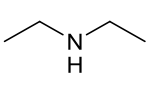
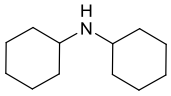
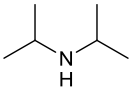
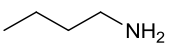
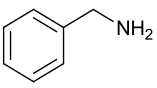
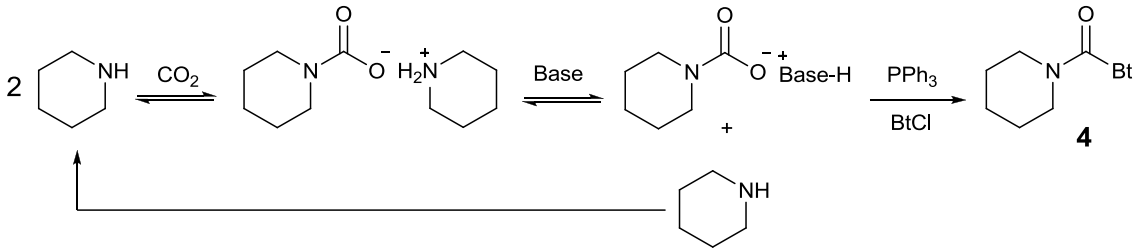
						
THF	43%	53%	58%	35%	11%	4%
DCM	47%	40%	29%	13%	26%	9%
CH_3CN	11%	28%	15%	22%	12%	7%

Table 2.3: Yields of Bt urea obtained from different amines

An issue which still had not yet been satisfactorily addressed was the high yield of by-product **5**. The most obvious way to address this was to increase the concentration of the Bt anion in the reaction medium. Thus the salt was made the limiting reagent (i.e. only two equivalents of piperidine were added), the amount of PPh_3 was increased to 1.3 equivalents, BtCl was increased to 1.6 equivalents, and the reaction was carried out in DCM, which had given the highest yield with piperidine as the amine (as shown in Table 2.3). This led to an increase in Bt urea **4** yield from 47% to 62% (the best yield to date). In the next experiment, one equivalent of BtH was also added in addition to the 1.6 equivalents of BtCl, in order to increase the concentration of the Bt nucleophile, and to also help quench the HCl formed during the reaction. The result was a 55% product yield and a 20% yield for by-product **5**, which was not good enough to justify the addition of an additional reagent. The fact that the product yield increased significantly even though the carbamate salt was reacted as the limiting reagent showed that the salt formation step was indeed more efficient than initially thought.

In a final effort to further improve the product yield and minimise by-product **5** formation, a further and exhaustive review of the literature was conducted, which resulted in an important idea. It was discovered that Aresta et al. had postulated that ionic association phenomena are present in ammonium carbamate salts due to hydrogen bonding between the carbamate anion and the ammonium cation. This interaction lowers the nucleophilicity of the oxygen centre. Complexing agents such as crown-ethers form a complex with the cation, which weakens the anion-cation interaction, thereby increasing the nucleophilicity of the anion. Crown-ethers also stabilize the equilibrium formation of the carbamate salt species.[55] McGhee et al. also found that strong, hindered, non-nucleophilic bases (such as amidines and guanidines) can help increase the nucleophilicity of the carbamate anion. These bases are capable of a greater charge delocalization and thus drive the equilibrium reaction between the amine and CO_2 forward, and they are also capable of forming highly polarisable counterions that are very hindered. This increases ionic separation of the salt in solution, thus exposing the oxygen as a "naked" anion and a more reactive nucleophile, since an increase in charge separation raises the ground-state energy of the anion. In contrast, systems with a tight ion pair (for example when trialkylamine bases are used), have a lower ground-state energy and the reactivity of the oxygen centre is thus attenuated.[56]

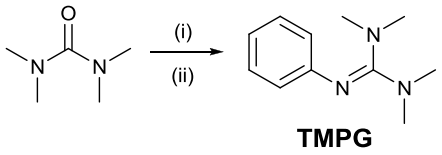
These ideas were applied to the PPh_3 / BtCl system. Scheme 2.14 below illustrates the general idea.



Scheme 2.14: Using a bulky base for carbamate salt formation in the PPh_3 / BtCl reaction

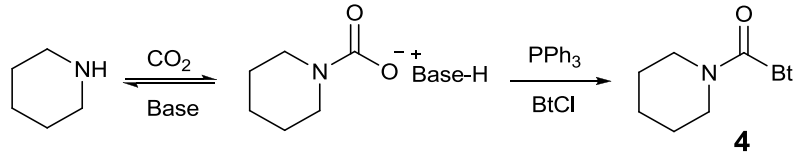
In this case only one equivalent of the amine would be required and a slight excess of the base (1.25 equivalents) would be added. Indeed, as reported by McGhee et al. the addition of trialkylamine bases did not result in a higher product yield. Triethylamine gave a 35% yield of **4** (37% of **5**), while Hünig's Base (EtN(*i*-Pr)$_2$) gave a 28% product yield (even though 0% of **5** was produced). This demonstrated that trialkylamine bases are not very good at driving the equilibrium involved in carbamate salt formation. Therefore the investigation moved to using a bulky amidine or guanidine base. DBU and DBN were commercially available, while tetramethylphenylguanidine (TMPG) was synthesised according to Mark's patented

procedure, Scheme 2.15 (although, as shown in the experimental, Chapter 5, slight modifications were made to this procedure).[81]



Scheme 2.15: *Reagents and conditions:* (i) tetramethylurea (1 eq), $POCl_3$ (1.1 eq), toluene, 18 hrs, RT; (ii) aniline (1.5 eq), 6 hrs, 80^0C

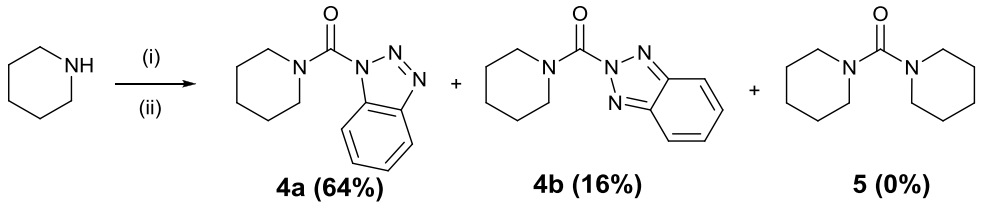
As shown in Table 2.4, DBU was tested against TMPG in three different solvents (DCM, THF and CH_3CN). In contrast to McGhee's work, DBU was found to be superior to TMPG in terms of product yield (80%) as well as in eliminating the symmetrical urea by-product. The THF experiment was applied to DBU's sister compound, DBN, and this also resulted in a high yield (76%) and no urea was isolated (although trace amounts were observed in the reaction tlc's).



	DBU		TMPG	
	% Yield 4	**% Yield 5**	**% Yield 4**	**% Yield 5**
THF	**80**	**0**	64%	10%
DCM	76%	4%	69%	4%
CH_3CN	35%	20%	48%	3%

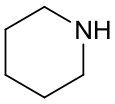
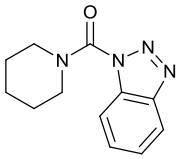
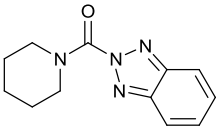
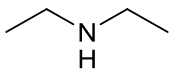
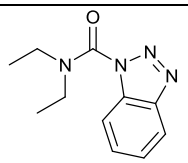
Table 2.4: The effect on the yield of products **4** and **5** of adding bulky amidine and guanidine bases

Based on this study it was determined that the optimised conditions would entail making piperidine the limiting reagent and adding 1.25 equivalents of DBU in order to maximise product yield and minimise by-product formation. The final optimised reaction conditions are shown in Scheme 2.16.



Scheme 2.16: *Reagents and conditions:* (i) piperidine (1 eq), DBU (1.25 eq), CO_2 (*g*), THF, 20 min, RT; (ii) PPh_3 (1.3 eq), BtCl (1.6 eq), 15 min

As a final aspect in the optimisation studies, these optimised reaction conditions were applied to four other amines (diethylamine, dicyclohexylamine, *n*-butylamine and benzylamine). The results of this study are shown in Table 2.5. A key conclusion that can be drawn from these findings is that the optimised reaction conditions can be applied to primary amines in some cases (benzylamine gave an equally good product yield of 79%). Another interesting result was the fact that only secondary amines produced the Bt urea as two regioisomers. For primary amines, only the unsymmetrical Bt urea was observed.

Amine	Product	Yield
 **Piperidine**	 **4a**	64%
	 **4b**	14%
	 **9a**	44%

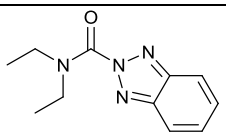
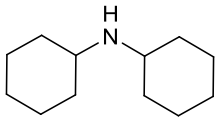
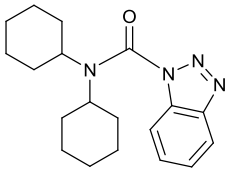
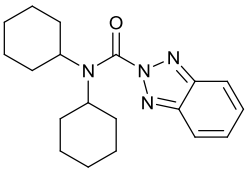
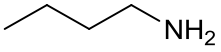
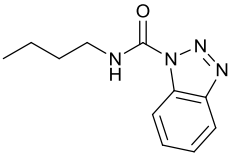
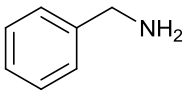
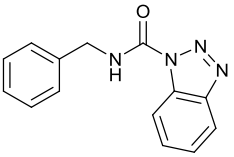
Diethylamine	 **9b**	25%
 **Dicyclohexylamine**	 **10a**	41%
	 **10b**	20%
 ***n*-Butylamine**	 **11**	46%
 **Benzylamine**	 **12**	79%

Table 2.5: Application of the optimised reaction conditions to other amines

Most of the above Bt ureas were new compounds, with the exception of **4a**, **9a**, **11** and **12**, therefore their structures were determined using a range of analytical techniques (infrared spectroscopy and high-resolution mass spectroscopy) in addition to ^{1}H and ^{13}C NMR spectroscopy. The melting points of these new solids were also determined. In all cases repeated recrystallization from aprotic DCM and petroleum ether mixtures failed to give the correct CHN microanalytical data, presumably due to hydrolysis. As an example, Figure 2.6 shows the ^{13}C NMR spectra for **9a** and **9b** in order to highlight the differences between the two regioisomers. **9a** has six aromatic resonances for the Bt carbons with two of them as quaternary carbons, whilst its regioisomer, **9b**, only shows three aromatic resonances since

it is more symmetrical. Interestingly enough, **9a** shows more symmetry in the upfield aliphatic region (10 to 50 ppm) as it has half as many (two) resonances for the ethyl carbons (as opposed to four upfield resonances for **9b**). Infrared spectroscopy of **9b** showed the diagnostic C=O resonance at 1728 cm^{-1}.

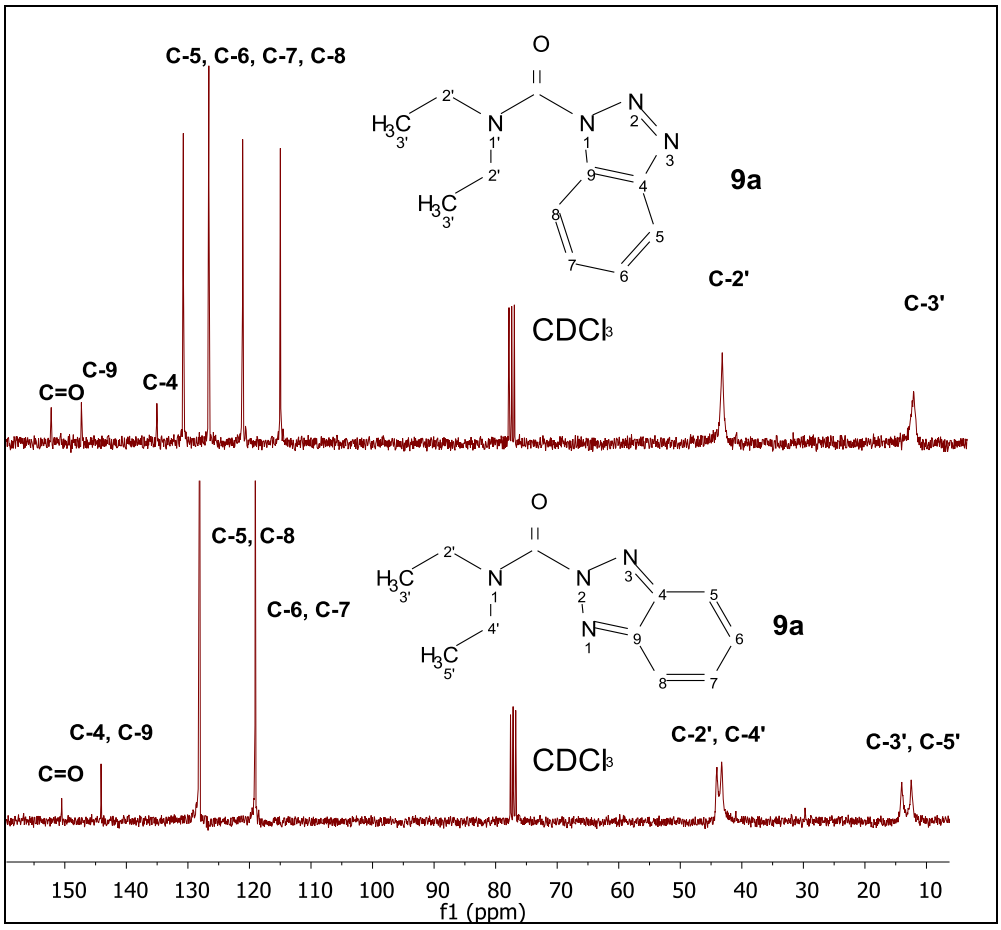


Figure 2.6: The ^{13}C NMR spectrum ($CDCl_3$, 75.5 MHz) of **9a** and **9b**

Figure 2.7 shows the ^{1}H NMR spectrum for Bt urea **11**, which was obtained as one regioisomer. All of the expected resonances were observed including the four unsymmetrical Bt protons, the four different aliphatic proton resonances, as well as the downfield N-H resonance.

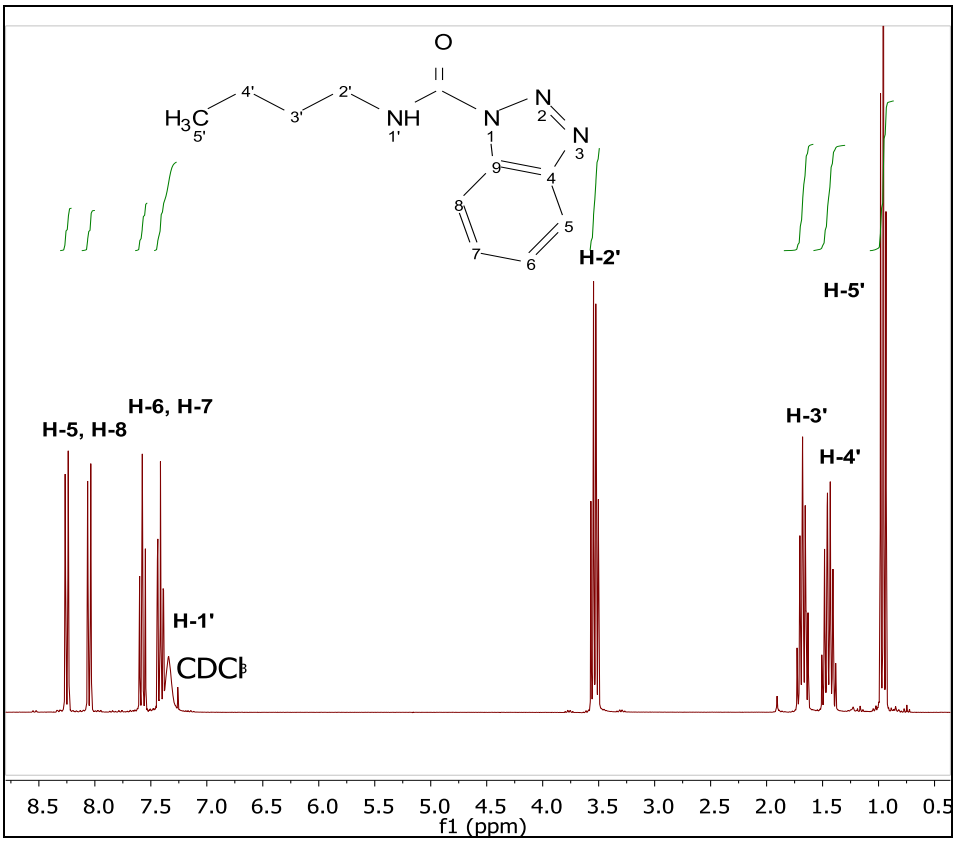


Figure 2.7: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **11**

With the various Bt urea products obtained and the novel procedure for their synthesis optimised, it was time to study their reactivity and use in the synthesis of valuable organic molecules.

Chapter 3: Use of the Bt Urea for Synthesis

This chapter reports on studies of the substitution reactions of Bt ureas in the synthesis of ureas, amides, *S*-thiocarbamates and sulfonyl ureas. The piperidinyl Bt urea **4** (Figure 3.1), as a mixture of regioisomers, was chosen for this study because it could be synthesised in high yield (even on a 10 mmol scale) and could be easily isolated as a crystalline solid. The procedures that will be discussed here have an important aspect in that the BtH that is released as a reaction by-product can be recycled and used to remake BtCl, thus affording the methodology a degree of "green" character in terms of atom efficiency.

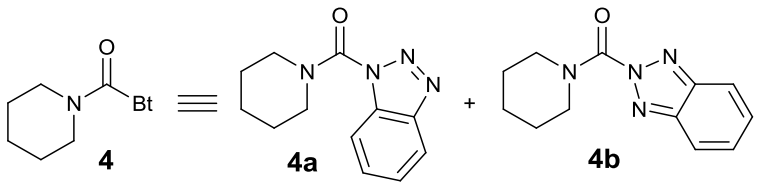
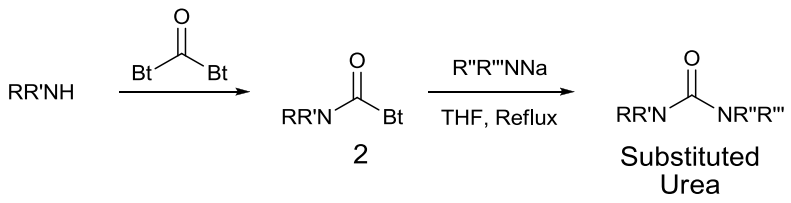


Figure 3.1: Bt urea **4**

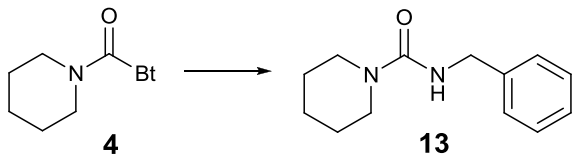
3.1 Urea Synthesis

Substituted ureas have varied applications in hair dyeing, cellulose fibres, as gasoline antioxidants and as corrosion inhibitors.[82] They also have biological applications as plant growth inhibitors, pesticides and tranquilizers, as well as providing pharmacophores for anti-HIV protease inhibitors.[82, 83] Katritzky et al. have shown that Bt-ureas (synthesised from phosgene) can be used to make tri- and tetrasubstituted ureas,[79] via a nucleophilic substitution by the sodium adduct of a primary or secondary amine respectively, under reflux conditions in THF (Scheme 3.1). The reaction times are long (ranging from one to four days), and the yields variable (from 25% to 82%), depending on steric factors and the nucleophilicity of the amine used. Therefore Bt-derivative **4** was similarly used to synthesise tri- and tetrasubstituted ureas, in order to improve on the efficiency of this important transformation.



Scheme 3.1: The Katritzky synthesis of unsymmetrical ureas

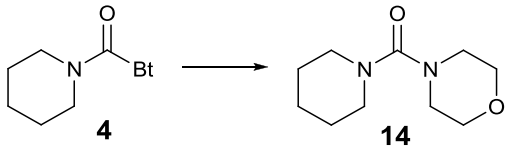
In the first experiment, Bt urea **4** was reacted with benzylamine and refluxed in THF, as shown in Scheme 3.2. The reaction was followed by tlc and from twenty-four hours onwards there was no observable increase in product formed. After twenty-seven hours the reaction was worked up despite the incomplete conversion of **4** and column chromatography gave trisubstituted urea **13** in a moderate yield of 51%. However, 13% of Bt urea **4** was also recovered from the column, giving the reaction only an 87% conversion rate.



4 **13**

Scheme 3.2: *Reagents and conditions:* **4** (1 eq), benzylamine (1.1 eq), THF, 70^0C, 27 hours

Similarly this time, tetrasubstituted urea **14** was synthesised using morpholine. As Scheme 3.3 shows, the reaction was conducted in toluene at a higher temperature (110^0C) in an attempt to improve the product yield, which marginally improved to 63%, with complete conversion of Bt urea **4**.



4 **14**

Scheme 3.3: *Reagents and conditions:* **4** (1 eq), morpholine (1.1 eq), toluene, 110^0C, 27 hours

Both ureas **13** and **14** are known solid compounds and their structures were confirmed using melting point determination and comparison with literature values, as well as ^{1}H and ^{13}C NMR spectroscopy. Figure 3.2 shows the ^{1}H NMR spectrum for **13**. The presence of the carbonyl group was confirmed by the downfield resonance at 157.7 ppm. Four aromatic resonances as well as the benzylic methyl resonances were observed, confirming the presence of the benzyl group.

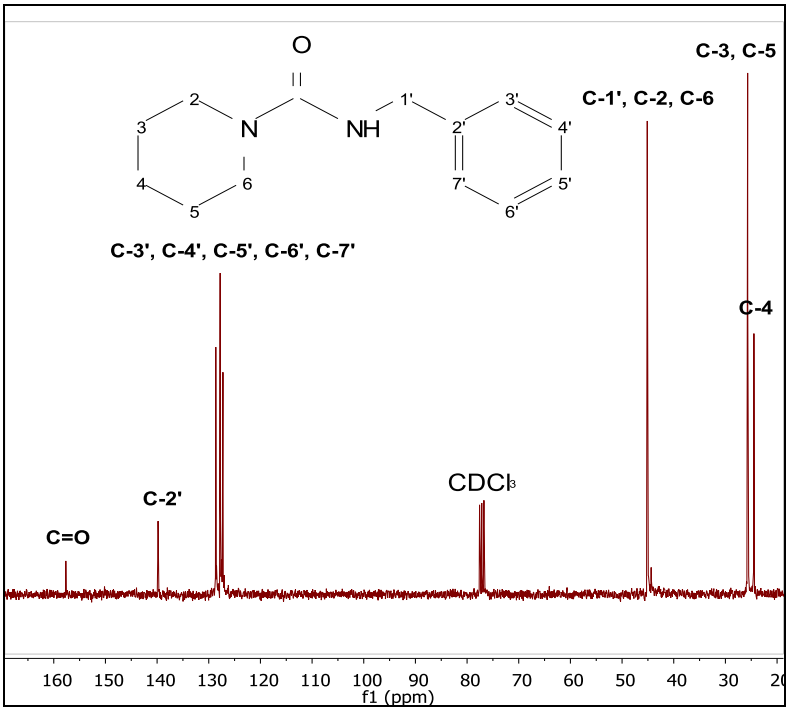


Figure 3.2: The ^{13}C NMR spectrum ($CDCl_3$, 75.5 MHz) of **13**

Similarly, Figure 3.3 shows the ^{1}H NMR spectrum for **14**. The protons α- to oxygen were observed as the most deshielded (3.59 ppm). All eight protons α- to nitrogen were observed as one resonance at 3.15 ppm.

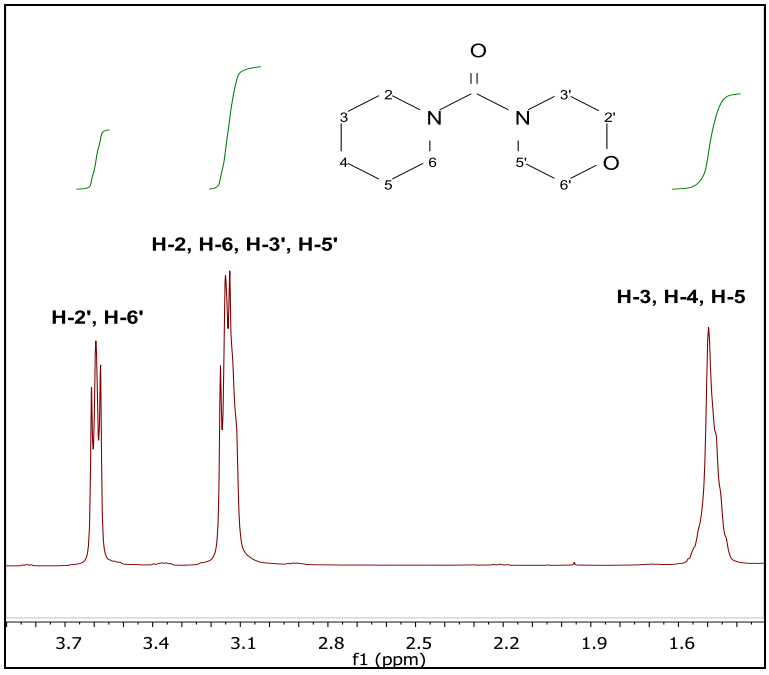
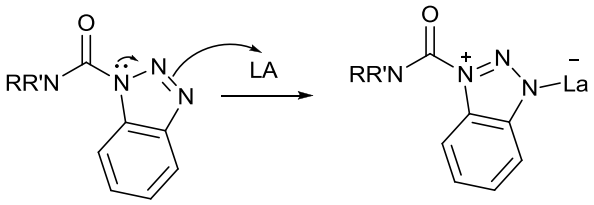


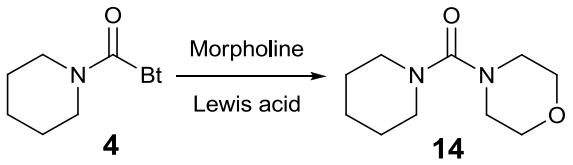
Figure 3.3: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **14**

From these moderate yields it became clear that an optimization study of this reaction was required. The Bt group, besides being a leaving group, contained a Lewis basic nitrogen site. Thus it was decided to investigate whether Lewis acid catalysis could be used to enhance the leaving group ability of the Bt group and enhance the electrophilicity of the carbamoyl group carbon also, as depicted in Scheme 3.4.



Scheme 3.4: The complexation of a Bt urea with a Lewis acid

A preliminary qualitative (tlc) study of the urea **14** reaction under such conditions was conducted. In each case, one equivalent of a Lewis acid ($SnCl_4$, TMSOTf, CuI, CsF and $ZnBr_2$) was added at 0^0C. The reaction was followed by tlc and when no conversion of Bt urea **4** was observed, the temperature was gradually increased until the reaction was under reflux. The results of these experiments are shown in Table 3.1. The addition of $SnCl_4$ did lead to the release of BtH, however, no urea was formed. This suggested hydrolysis of Bt urea **4** by the Lewis acid, since the Bt urea is stable under these conditions in the absence of $SnCl_4$. A similar result was observed with TMSOTf. No reaction product (not even BtH) was observed with CuI, CsF and $ZnBr_2$. The last entry of the table shows that addition of an organic acid (tosic acid, *p*-TsOH) actually led to product formation. However, tlc showed that the amount of product was far less than that of the original reaction.



4 **14**

Reagents and conditions: 4 (1 eq), morpholine (1.2 eq), Lewis acid (1 eq), toluene, 0^0C to 110^0C

Acid Added	Result
$SnCl_4$	**4** hydrolysed to BtH, but no urea **14** observed
TMSOTf	**4** hydrolysed to BtH, but no urea **14** observed
CuI	No reaction
CsF	No reaction
$ZnBr_2$	No reaction
p-TsOH	Product formed but in relatively low yield

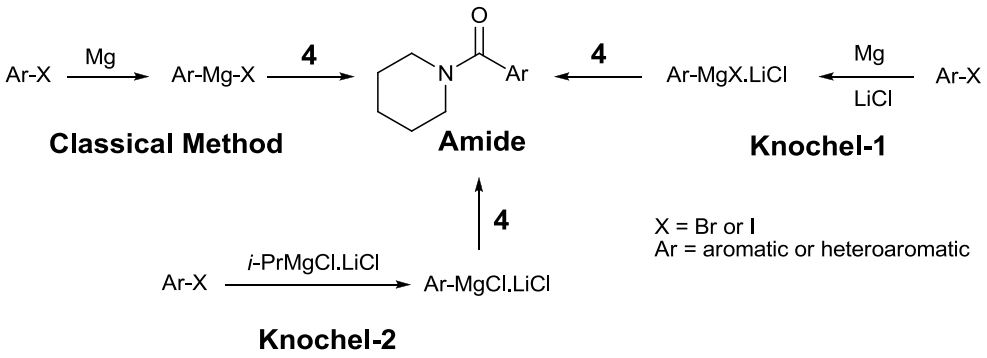
Table 3.1: Addition of Lewis and organic acids in order to optimize the urea formation reaction

The results from the optimization study clearly showed that Lewis acid activation was not suitable for this reaction, probably because it interfered with the amine nucleophilicity. As there were other issues to be explored, further optimization studies were unfortunately beyond the scope of this thesis. Nevertheless, the synthesis of unsymmetrical ureas is currently an area of great interest to synthetic organic chemists, so further optimisation studies (which will include Bronsted acid and base catalysis) are a key objective for the future.

3.2 Amide Synthesis

Aromatic and heteroaromatic amides (carboxamides) are an important class of compounds, since they show biological activity as melatonin analogues,[84] anti-fungal agents,[85] potential anti-HIV drugs and anti-tumour agents.[86] Katritzky has shown that these compounds can be made from Bt ureas in good yield via nucleophilic substitution of the Bt group with a

carbanion in the form of magnesium (Grignard) and lithio derivatives. Therefore, a study of the synthesis of aromatic and heteroaromatic amides from Grignard reagents was conducted. As illustrated in Scheme 3.5, the Grignard reagent was produced using three different procedures: (i) the classical oxidative addition method of refluxing a bromide (or iodide) with Mg turnings;[87] (ii) reacting the bromide with Mg turnings in the presence of LiCl, another procedure by Knochel et al.;[88] (iii) a metal / halogen exchange achieved by reacting the bromide with *i*-propylmagnesium chloride lithium chloride (*i*-PrMgCl.LiCl, a commercially available reagent) according to Knochel et al.[89] Knochel's one-pot procedures have an advantage over the classical method in that the Grignard reagent may be formed even with substrates containing reactive functional groups, as well as highly deactivated (hetero)aromatic halides that would ordinarily not be suitable for Grignard reactions.

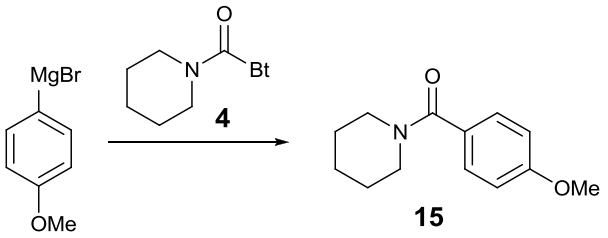


Scheme 3.5: Three Grignard methodologies for amide synthesis

3.2.1 The Classical Method

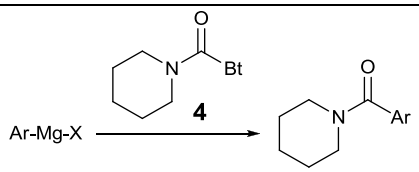
According to this method, a halide (in this case a bromide or an iodide) undergoes oxidative addition in the presence of magnesium turnings in an appropriate solvent (THF or Et_2O). Once this normally exothermic reaction is complete, the Grignard reagent is then acquired as a solution, the exact molarity of which is determined by titration. In this present study, the molarities varied between 0.23 M and 0.96 M, and this was due to the differing solubilities of the various Grignard reagents in THF or Et_2O. An excess of this reagent was then reacted with Bt urea **4** in order to generate the required amide.

The first Grignard reagent was made using 4-bromoanisole, and its molarity was determined to be 0.48 M. Reaction of **4** with 1.5 equivalents of the Grignard reagent gave the amide within fifteen minutes (see Scheme 3.6) at around 0^0C. Aqueous extraction, followed by column chromatography gave **15** in an excellent yield of 94%.



Scheme 3.6: *Reagents and conditions:* Grignard Reagent (0.48M in THF, 1.54 eq), **4** (1 eq), THF, 0^0C to RT, 15 min

Table 3.2 shows the results for other aromatic and heteroaromatic species, where amides **16**, **17** and **18** were produced in high yield as well. In these reactions the amount of Grignard reagent that was added varied between 1.5 and 2 equivalents, depending on the amount of Grignard required for full conversion of **4**, as determined by tlc studies. For iodothiophene, however, even though two equivalents of its Grignard reagent were added, only a 90% conversion of **4** was realised, as evidenced by chromatographic recovery.



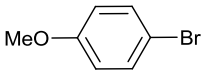
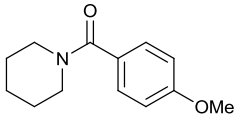
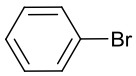
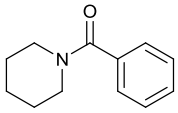
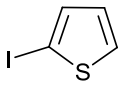
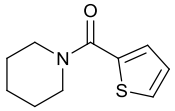
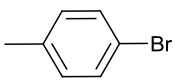
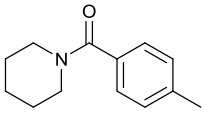
Halide	Product	Yield
	 **15**	94%
	 **16**	85%
	 **17**	*78% (*uncorrected at 90% conversion)
	 **18**	84%

Table 3.2: Synthesis of amides using the classical Grignard formation method

All of the amides are known oils whose structures were confirmed by ^{1}H and ^{13}C NMR spectroscopy. Figure 3.5 shows the ^{1}H NMR spectrum for **17**, in which all of the expected resonances were revealed.

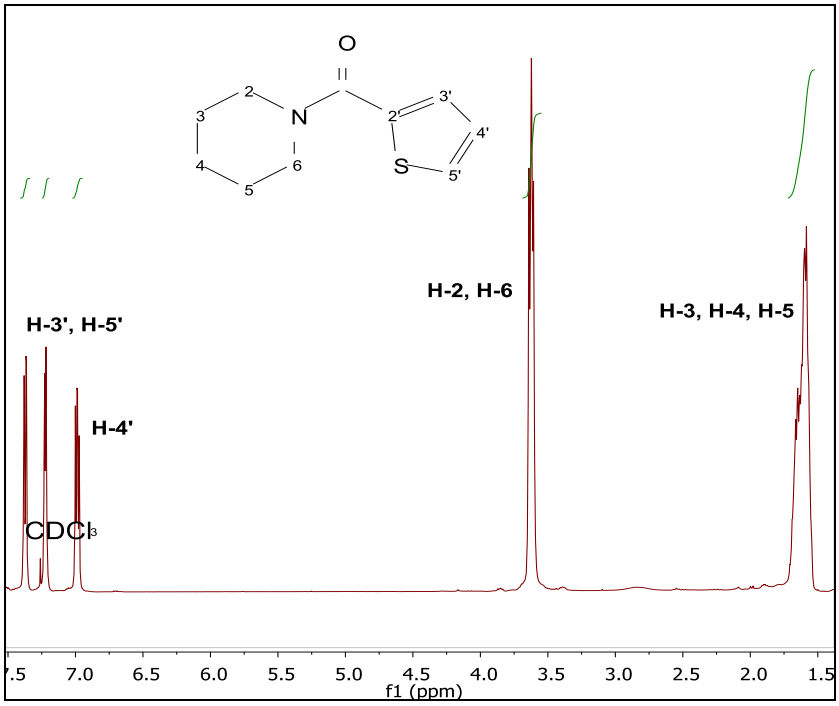
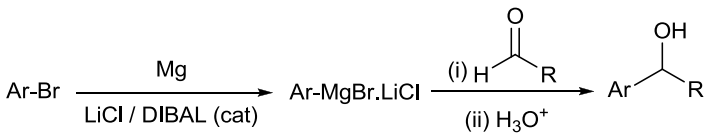


Figure 3.5: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **17**

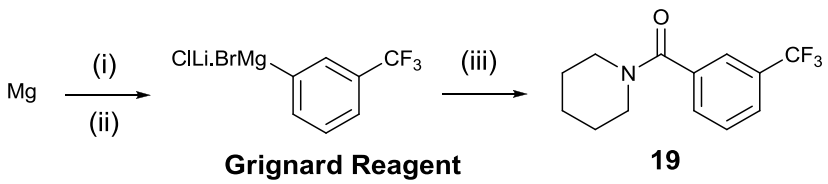
3.2.2 Knochel-1

Recently, Knochel has developed another procedure for Grignard formation. He achieved the Mg insertion into (hetero)aryl bromides by reacting an excess of Mg metal (which is activated by addition of a catalytic amount of DIBAL) with an aryl bromide in the presence of a LiCl solution, at low temperatures.[88] The LiCl was found to accelerate the metal insertion even with highly functionalised bromides that undergo Mg insertions reluctantly or sluggishly. Scheme 3.7 illustrates this procedure.



Scheme 3.7: The Knochel-1 procedure

Therefore, Grignard formation using 1-bromo-3-(trifluoromethyl)benzene and 3-bromopyridine was studied according to Knochel's conditions (Scheme 3.8). The bromide was added in a 2 : 1 ratio with Bt urea **4** in order to promote complete consumption of **4**, given that Grignard formation was assumed to be efficient but not at 100%. Tlc studies of the Grignard formation (a fast reaction for this substrate, according to Knochel) showed that not all of the bromide successfully underwent magnesium insertion. Bt urea **4** was then reacted with the Grignard reagent to give amide **20** in a moderate yield of 51%, following column chromatography. Amide **19** is a known oily compound whose structure was confirmed using ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H spectrum of this amide is shown in Figure 3.6. Once again, non-equivalence of the protons α- to nitrogen as a result of restricted rotation about the C-N bond was observed.



Scheme 3.8: *Reagents and conditions:* (i) Mg (5 eq), LiCl (2.5 eq), DIBAL (0.026 eq), 5 min, RT; (ii) 1-bromo-3-(trifluoromethyl)benzene (2 eq), 35 min, $0^{0}C$; (iii) **4** (1 eq), 2 hrs, $0^{0}C$ to RT

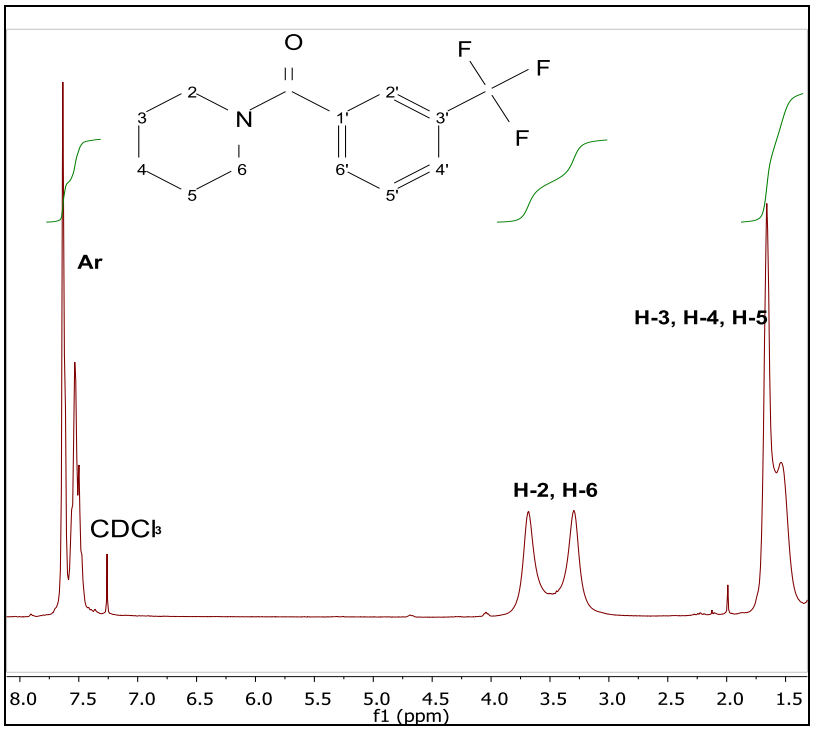
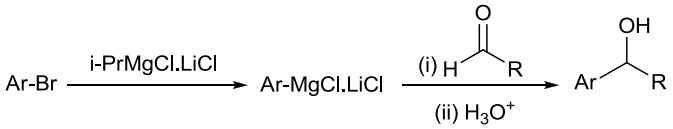


Figure 3.6: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **19**

Finally, application of Knochel's Grignard formation procedure to 3-bromopyridine gave similar results as in the trifluorobenzene case, and reaction with **4** (which in this case took 19 hours) yielded amide **20** in a yield of 59%. Amide **20** is also a known oil whose structure was confirmed using ^{1}H and ^{13}C NMR spectroscopy.

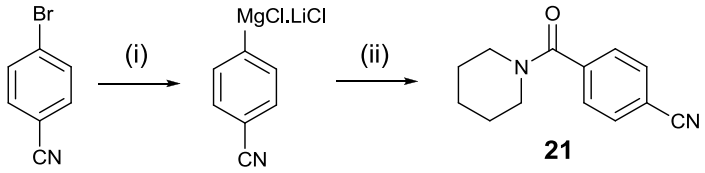
3.2.3 Knochel-2

Knochel et al. also found that the Grignard reagent *i*-PrMgCl.LiCl can achieve a metal-halogen exchange at low temperatures, even with highly deactivated (hetero)aromatic compounds.[89] As shown in Scheme 3.9, addition of *i*-PrMgCl.LiCl to an Ar-Br species leads to a Grignard reagent of the type Ar-MgCl.LiCl. This step can occur at temperatures as low as $-50^{0}C$, depending on how reactive the bromide is. An electrophile (in Knochel's case this was usually an aldehyde) is then reacted with the reagent and a product is obtained in high yield. Thus the methodology allows the formation of a Grignard reagent from substrates containing electrophilic or reactive functional groups.



Scheme 3.9: The Knochel-1 procedure

This methodology was thus applied to Bt urea **4**. The conditions for Grignard formation were identical to those stipulated in Knochel's publication.[89] An excess of the bromide (2 eq) was added as in the Knochel-1 procedure in order to consume **4**. However, the bromide was in a 1 : 1 ratio with the magnesium reagent in order to prevent an excess of the reagent from reacting with Bt urea **4**. Scheme 3.10 shows the application of this procedure to 4-bromobenzonitrile. The Grignard formation was achieved at $0^{0}C$ over two hours. This step was followed by tlc H_2O quench, which confirmed the formation of the Grignard by the appearance of the de-brominated benzonitrile, amongst several other spots. Addition of **4** led to formation of amide **21** over eight hours at $10^{0}C$ to room temperature. Amide **21** (a known oily compound) was isolated by column chromatography in a yield of 70% and its structure was confirmed using ^{1}H and ^{13}C NMR spectroscopy.



Scheme 3.10: *Reagents and conditions:* (i) 4-bromobenzonitrile (2 eq), *i*-PrMgCl.LiCl (2.1 eq), THF, 0^0C, 2 hrs; (ii) **4** (1 eq), 8 hrs, -10^0C to RT

The ^{13}C NMR spectrum of **21** is shown in Figure 3.7. All of the piperidinyl carbons were found to be non-equivalent due to restricted N-carbonyl bond rotation as a result of nitrogen electron donation into the carbonyl, which creates a partial double bond.

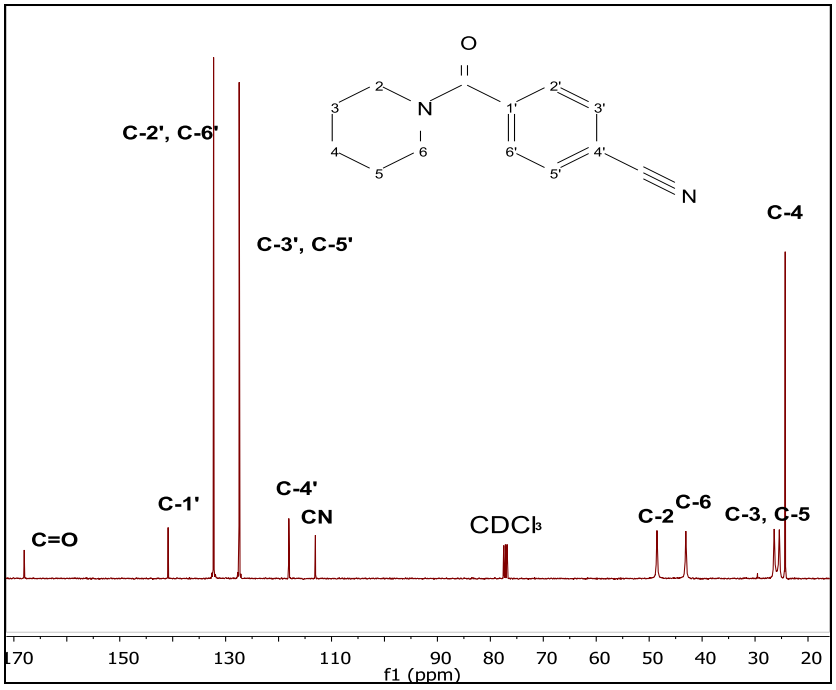
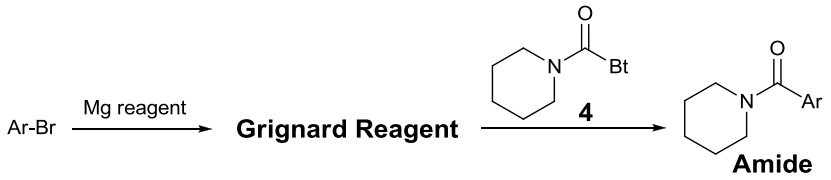


Figure 3.7: The ^{13}C NMR spectrum ($CDCl_3$, 100.6 MHz) of **21**

Table 3.3 is a summary of all the amides that were synthesised and the methods that were used to synthesise them. It is clear that the classical Grignard formation procedure was the highest yielding. This can be attributed to the fact that with this procedure the Grignard reagent is isolated and the exact amount formed is determined by titration. However, the Knochel methods are one-pot, multi-step procedures. Thus, the success of the metal exchange reaction can only be quantified by successful formation of the final product. In that case it was not absolutely clear whether the Grignard formation step or the nucleophilic substitution step was inefficient. Another complication associated with the Knochel

procedures is the fact that they require highly specialised Schlenk-type techniques in order to ensure that the reaction system is completely dry and free of oxygen. Nevertheless, the study was successful in expanding on Katritzky and Knochel's work, by showing that highly functionalised and deactivated aryl species can be used to form amides from the Bt urea.



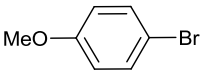
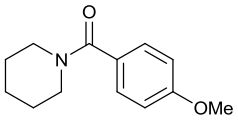
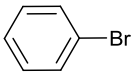
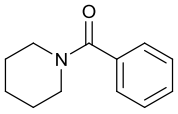
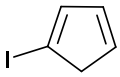
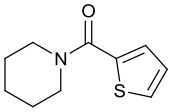
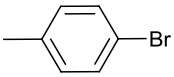
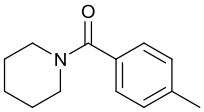
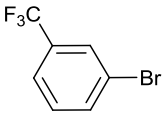
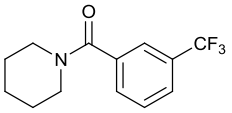
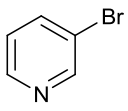
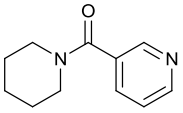
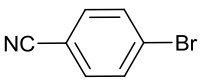
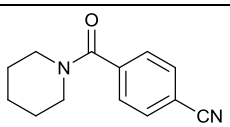
Halide	Method	Product	Yield
	Classical	 **15**	94%
	Classical	 **16**	85%
	Classical	 **17**	78%
	Classical	 **18**	84%
	Knochel-1	 **19**	51%
	Knochel-1	 **20**	59%
	Knochel-2	 **21**	70%

Table 3.3: Summary of amides synthesised and the procedures used for the Grignard formation

3.3 *S*-Thiocarbamate Synthesis

S-Thiocarbamates (Figure 3.8) are recognised as herbicides and pesticides.[90] They also show biological activity as anaesthetics, fungicides, bactericides, and antivirals.[91]

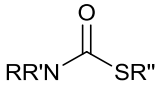
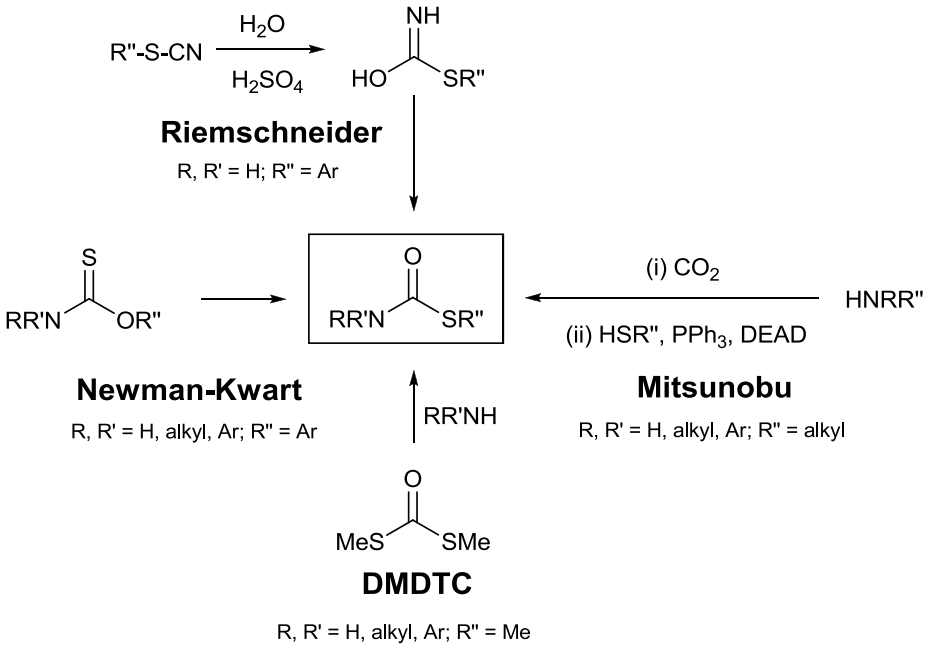


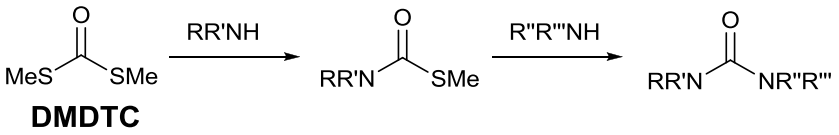
Figure 3.8: S-thiocarbamates

Scheme 3.11 is a summary of some of the popular syntheses of *S*-thiocarbamates. N-unsubstituted primary *S*-thiocarbamates (R, R' = H) are usually synthesised via the reaction of thiocyanates with water, according to the Riemschneider methodology.[92] *N*-substituted *S*-aryl thiocarbamates can be made via the Newman-Kwart rearrangement involving an O to S transposition.[93,94] As mentioned in Chapter 1, *S*-thiocarbamates can also be synthesised by thiol addition to an isocyanate, amine substitution of DMDTC (dimethylthiocarbonate)[23,24] or via Chaturvedi's synthesis from CO_2, an amine (primary or secondary) and an alkyl thiol under Mitsunobu conditions.[75]



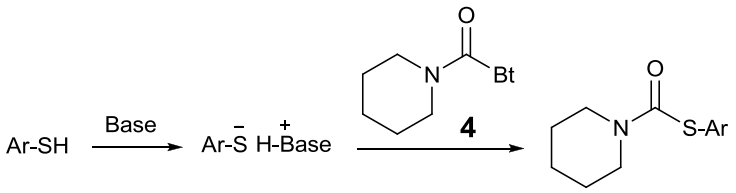
Scheme 3.11: Examples of *S*-thiocarbamate synthesis, where the variations in the R-groups are also included

As an addition to the limited use of CO_2 and its derivatives in this regard, it was hence proposed that Bt ureas**,** made directly from CO_2, might be used to synthesise *S*-aryl thiocarbamates. As mentioned in Chapter 1, Artuso and Leung have shown that *S*-methyl thiocarbamates derived from DMDTC can be used to produce ureas (Scheme 3.12). Therefore another motivation for this undertaking was to determine whether such thiocarbamates can undergo substitution reactions with amines and Grignards to produce ureas and amides, respectively. In this way, the leaving abilities of RS versus Bt could be compared.



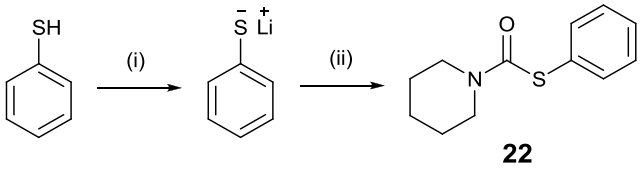
Scheme 3.12: Urea synthesis from DMDTC, via an *S*-thiocarbamate

The procedure proposed for thiocarbamate synthesis involved reaction of Bt urea **4** with nucleophilic aromatic thiols in the presence of a base (Scheme 3.13).



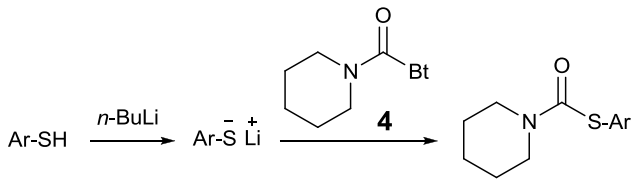
Scheme 3.13: *S*-thiocarbamate synthesis from Bt urea **4**

In the first experiment, thiophenol was reacted with one equivalent of **4** in the presence of triethylamine (0.6 eq) at room temperature. Tlc studies showed that starting material conversion was sluggish. In the next experiment KOH (1 eq) was reacted, giving the same result. Success was realised when the base was changed to *n*-BuLi. The thiol was deprotonated with *n*-BuLi at 0^0C and **4** was subsequently added after fifteen minutes (as shown in Scheme 3.14) to produce *S*-thiocarbamate **22** (87% yield after column chromatography) within two and a half hours. *S*-Thiocarbamate **22** is a known compound whose structure was confirmed using ^{1}H and ^{13}C NMR spectroscopy. This result once again confirmed the preference of the acylbenzotriazole grouping for ionic nucleophiles, in this case a much softer one than the Grignard.



Scheme 3.14: *Reagents and conditions:* (i) thiophenol (1 eq), BuLi (1 eq), THF, 0^0C, 15 min; (ii) **4** (1 eq), 2.5 hrs, 0^0C to RT

This procedure was then applied to two more thiols, namely 4-methylthiophenol and 4-fluorothiophenol. Consequently, two new compounds **23** and **24** were synthesised in excellent yields (Table 3.4). The structures of these two compounds were determined using ^{1}H and ^{13}C NMR spectroscopy, infrared spectroscopy, elemental analyses and high-resolution mass spectrometry. The melting points of these two solids were also determined.



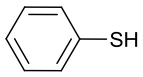
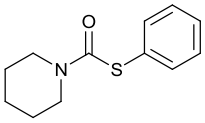
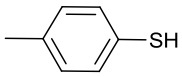
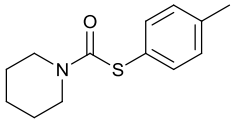
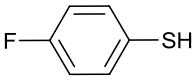
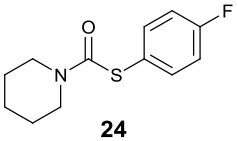
Thiol	Product	Yield
	 **22**	87%
	 **23**	82%
	 **24**	90%

Table 3.4: The formation of various *S*-thiocarbamates using **4**

Figure 3.6 shows the ^{1}H NMR spectrum of thiocarbamate **23**, where the diagnostic aromatic doublets and methyl resonance were detected.

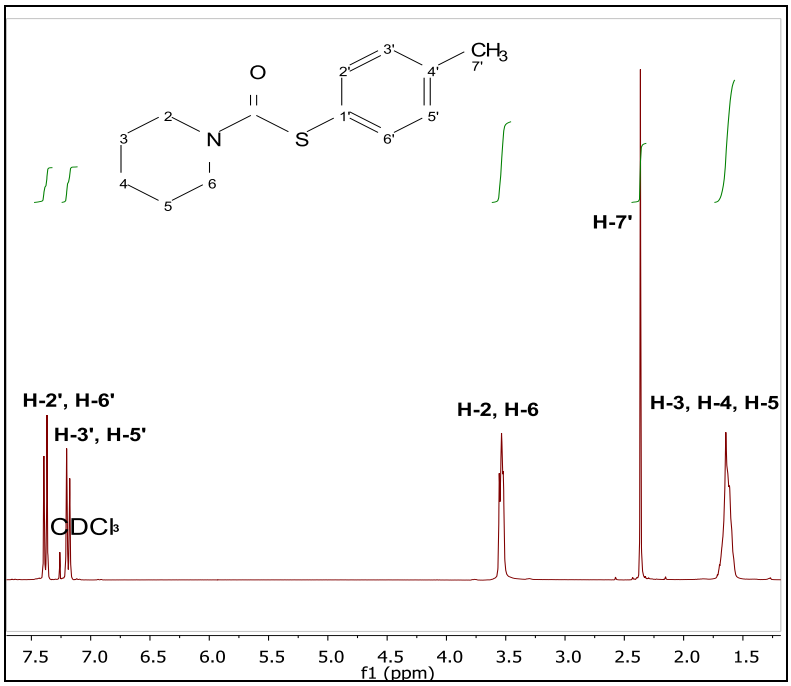
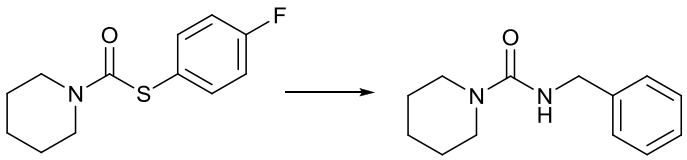


Figure 3.9: The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **23**

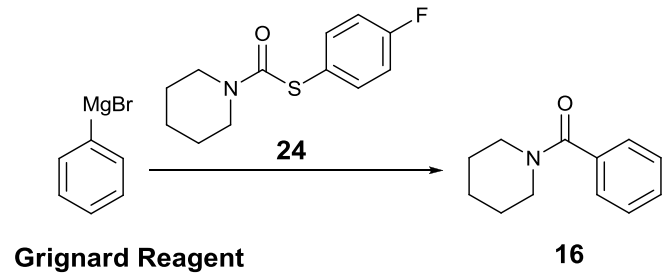
Once it had successfully been shown that Bt ureas can be used to synthesise *S*-thiocarbamates, it was then time to appraise the reactivity of the thiocarbamates against that of Bt ureas. Thus thiocarbamate **24** was subjected to urea and amide synthesis reactions under the same conditions as those used for **4**. Scheme 3.15 shows how the urea synthesis procedure was applied to thiocarbamate **24**. Refluxing **24** with benzylamine in THF for two and a half days gave the desired urea **13** in a low 14% yield (compared to 53% in the Bt urea reaction).



24 **13**

Scheme 3.15: *Reagents and conditions:* **24** (1 eq), benzylamine (1.1 eq), THF, 2.5 days, 70^{0}C

Reacting **24** with two moles of a Grignard reagent gave amide **16** in a good yield of 71%, as shown in Scheme 3.16. However, this yield was still lower than that obtained from the reaction of the same Grignard reagent with **4** (85%).



Scheme 3.16: *Reagents and conditions:* Grignard Reagent (1.5 eq), **24** (1 eq), THF, 2.5 hrs, 0^0C to RT

In both cases thiocarbamate **24** was shown to be inferior to Bt urea **4** in terms of electrophilic reactivity. Another disadvantage of the methodology is the extra thiocarbamate synthesis step.

3.4 Sulfonylurea Synthesis

Sulfonylureas are an important class of compounds as they are anti-diabetic drugs that are used to treat type II diabetes, with Figure 3.10 showing some examples. They have also been shown to have anti-cancer activity.[95]

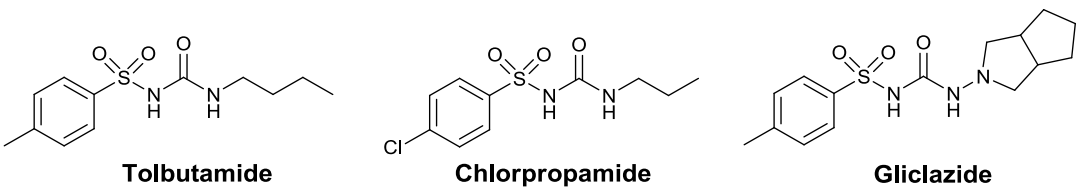
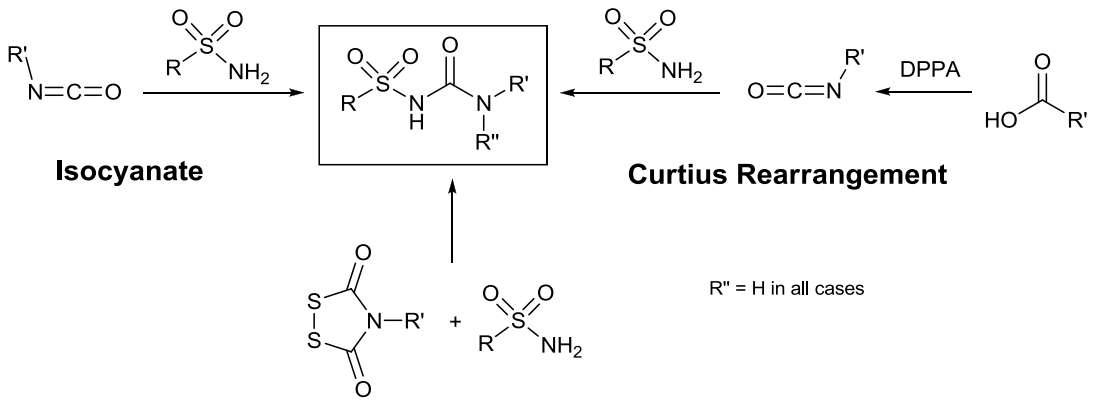


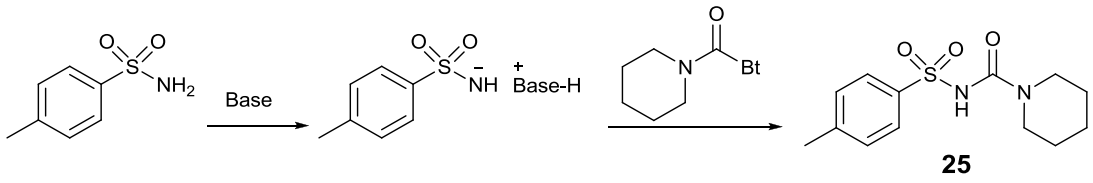
Figure 3.10: Sulfonylureas that are known anti-diabetes drugs

Various methods are known for the synthesis of sulfonylureas, as shown in Scheme 3.17. These compounds are usually synthesised by the nucleophilic addition of an *N*-sulfonamide to an isocyanate. However, a number of novel syntheses have also been reported. These include Chibale's reaction of a sulfonamide with an *N*-alkyl-1,2,4-dithiazolodone-3,5-dione,[96] as well as the reaction of sulfonamides with carboxylic acids via an *in situ* Curtius rearrangement.[97]



Scheme 3.17: Three different sulfonylurea syntheses

As mentioned in Chapter 2, Bt ureas derived from primary amines have been mentioned in a short and terse communication by Butula et al. to undergo nucleophilic substitution with sulfonamides and produce sulfonylureas in moderate yields.[80] In the present study, it was decided to investigate whether a Bt urea derived from a secondary amine (such as Bt urea **4**) could be similarly substituted by a sulfonamide anion to produce a sulfonyl urea in good yield. The study was conducted using *p*-toluenesulfonamide, which was reacted with **4** in the presence of a base (Scheme 3.18), since the nitrogen protons in sulfonamides are acidic as the sulfonamide anion is resonance-stabilised by the sulfonyl group.

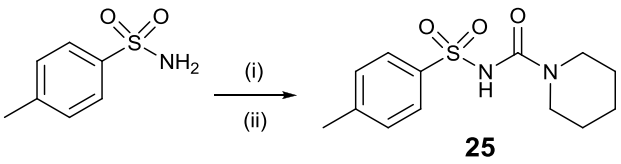


Scheme 3.18: The envisioned synthesis of sulfonyl urea **25** using Bt urea **4**

In the first experiment, 1.5 equivalents of sulfonamide was reacted with 1.2 equivalents of *n*-BuLi in THF. This led to a sulfonamide-Li salt which precipitated out of solution. Refluxing the slurry with **4** unfortunately gave no reaction product (as observed by tlc studies), even after twenty-four hours. In an attempt to address this issue of insolubility, the base was changed to a Grignard solution (PhMgBr) in the next experiment, as the carbanion in a Grignard reagent can also be used as a base. The Grignard solution was prepared according to the procedure outlined in Section 3.2.1. The sulfonamide-magnesium salt was

observed as an insoluble white salt which, as with the lithium anion, failed to give a reaction product (by tlc). The BuLi experiment was repeated with the addition of tetramethylethylenediamine (TMEDA) as a chelating additive to increase the solubility of the sulfonamide salt, since TMEDA is known to have a high affinity for the lithium cation and to convert *n*-BuLi into a reactive cluster. After refluxing overnight it was observed that the reaction mixture had started to become homogenous. After twenty-seven hours the reaction was then worked-up in an acidic medium. Column chromatography yielded the desired product **25** in a yield of 7%. Although this was a low yield, it did give an indication that the key to the success of the reaction was indeed solubility.

The base and solvent were then changed to NaH and DMF respectively, given that sodium cations are known to undergo complexation with DMF. Thus, as shown in Scheme 3.19, 1.5 equivalents of sulfonamide were reacted with 1.5 equivalents of NaH, in DMF. The mixture was then heated to 100^0C and after one hour, the reaction mixture was completely homogenous. At this point, the reaction was then cooled, **4** was added and the reaction mixture was reheated to 100^0C for three hours. Following reaction work-up and column chromatography, product **25** was isolated in a 17% yield which, although still encouraging, implied that further optimisation still needed to be done.

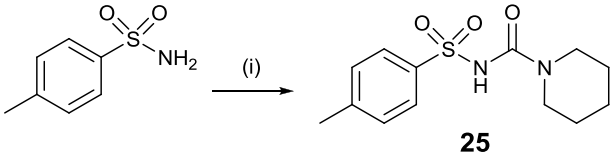


25

Scheme 3.19: *Reagents and conditions:* (i) *p*-toluenesulfonamide (1.5 eq), NaH (1.5 eq), DMF, 1 hr, 100^0C; (ii) **4** (1 eq), 3 hrs, 100^0C

Chibale's formation of sulfonylureas from sulfonamides and dithiazolidindiones (Scheme 3.14) used K_2CO_3 and toluene as base and solvent respectively.[96] Even though the mechanism of their procedure was not a straightforward nucleophilic substitution, it was still a system worth exploring. However, before the experiment was carried out, it was considered that strong bases such as NaH and K_2CO_3 might hydrolyse Bt urea **4**, as BtH was observed on tlc's of previous reactions even when product formation hadn't begun. Therefore, **4** was added to NaH (in DMF) and the mixture was heated to 100^0C. A similar reaction was set up for K_2CO_3 in toluene. In both cases there was some hydrolysis of **4** (as evidenced by the appearance of BtH on the reaction tlc's). Although this was deemed to be

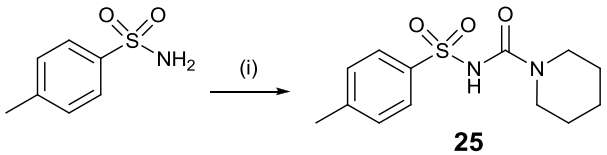
relatively minor (approximately 15% even after three days of heating), it did still suggest that perhaps the Bt urea should be added in excess in order to account for any base hydrolysis. Thus, in the K_2CO_3 / toluene experiment (as shown in Scheme 3.20) 1.5 equivalents of **4** were added and the sulfonamide was used as the limiting reagent. After 4 days of heating at 100^0C, the result was formation of the desired product in a higher yield of 26% from column chromatography. However, the most interesting result from this reaction was the definite increase in the rate of product formation that was observed on tlc as the reaction solvent evaporated. This suggested that perhaps the reaction could be done under solvent-free conditions, as a melt.



25

Scheme 3.20: *Reagents and conditions:* (i) *p*-toluenesulfonamide (1 eq), **4** (1.5 eq), K_2CO_3 (1 eq), toluene, 4 days, 100^0C,

Therefore, the sulfonamide was reacted with **4** in the presence of K_2CO_3 without solvent, as shown in Scheme 3.21. In this case the sulfonamide was used in excess in order to encourage complete consumption of Bt urea **4** (notwithstanding the issue of hydrolysis). The reaction was followed by tlc's, which showed that product formation halted after twenty-one hours., even though not all of **4** was consumed. An acid work-up and column chromatography yielded the desired product in a yield of 46%. The structure of sulfonylurea **25**, a known compound, was confirmed using ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of **25** (Figure 3.11) showed that minor amounts of the sulfonamide had co-eluted with **25**. This problem of isolating a pure product is an indication that the reaction conditions must be designed so as to consume all of the sulfonamide.



25

Scheme 3.21: *Reagents and conditions:* (i) **4** (1 eq), *p*-toluenesulfonamide (1.5 eq), K_2CO_3 (1 eq), 21 hrs, 100^0C

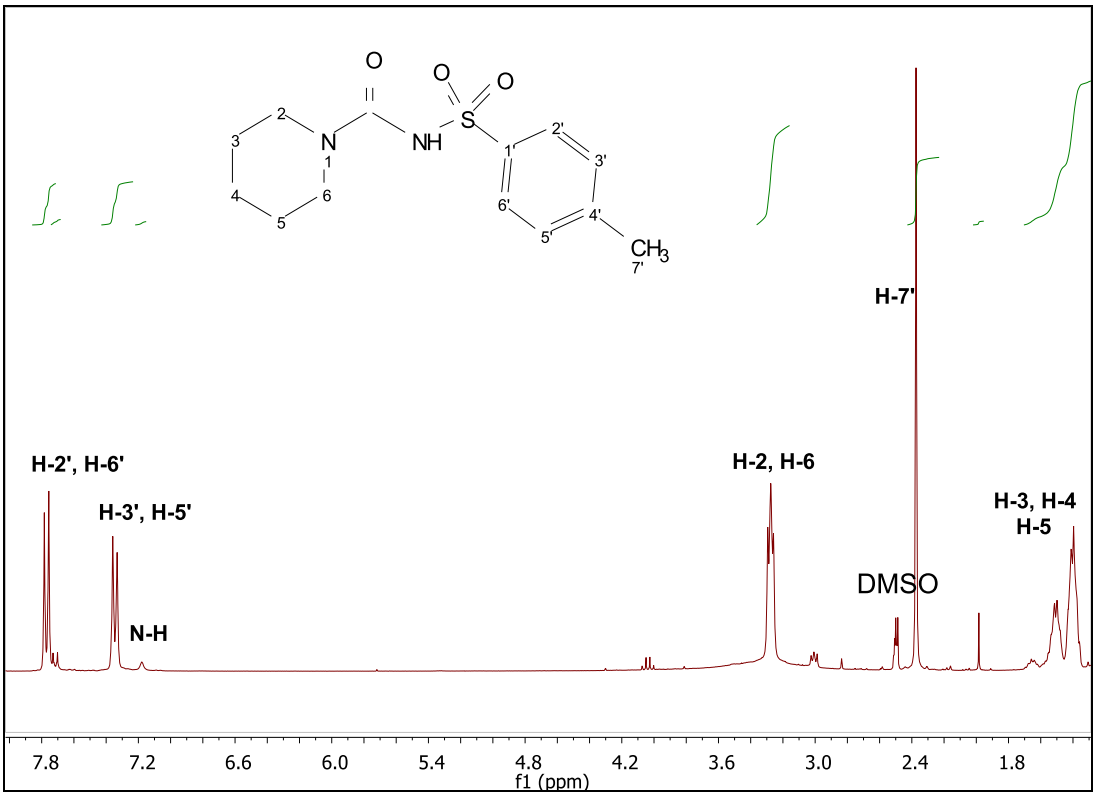
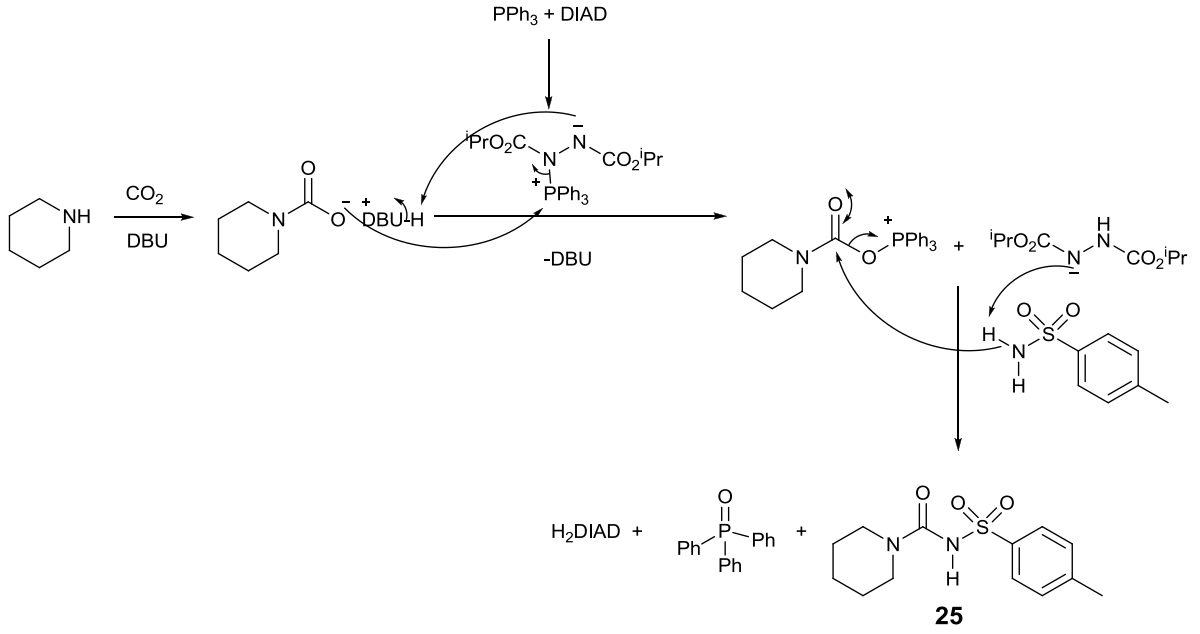


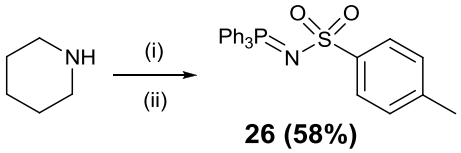
Figure 3.11: The ^{1}H NMR spectrum (D-DMSO, 300 MHz) for sulfonyl urea **25**

It was also wondered whether it would be possible to synthesise sulfonyl ureas in a one-pot reaction from CO_2 under Mitsunobu conditions (Scheme 3.22). The hope was that the PPh_3 / DIAD zwitterion would react with the carbamate salt to generate an oxophosphonium species (similar to that used in the production of Bt ureas, as described in Chapter 2), and that this species would undergo a reaction with the sulfonamide.



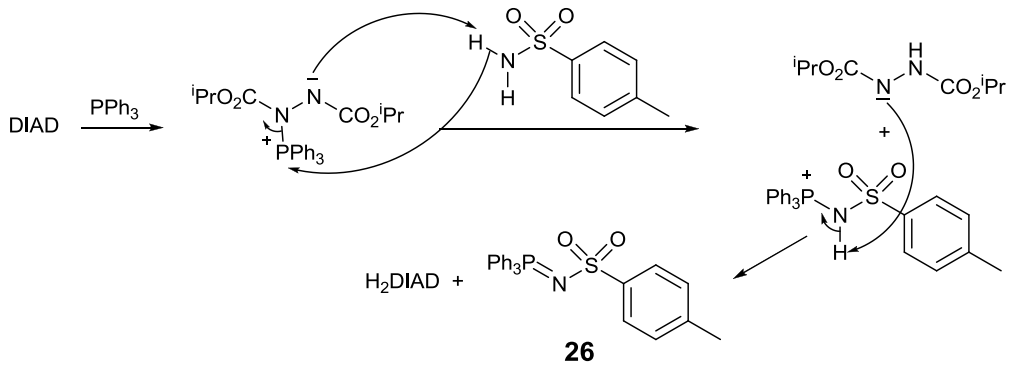
Scheme 3.22: The envisioned Mitsunobu reaction to synthesise sulfonylureas from CO_2

Therefore, the piperidine / DBU carbamate salt was generated and then reacted *in situ* with PPh_3, DIAD, and an excess of the sulfonamide (Scheme 3.23). After forty-five minutes a reaction product was observed; however it was not the desired sulfonyl urea **25**. Instead, the nitrogen ylide **26** was produced in a yield of 58%, following column chromatography.



Scheme 3.23: *Reagents and conditions:* (i) piperidine (1 eq), DBU (1.25 eq), CO_2, DCM, 20 min RT; (ii) PPh_3 (1.5), DIAD (1.5 eq), *p*-toluenesulfonamide (1.6 eq), 45 min

Formation of ylide **26** can be rationalised by the proposed mechanism in Scheme 3.24. Production of the ylide indicated that the sulfonamide anion was more nucleophilic than the carbamate salt anion and thus preferentially trapped the phosphonium species. This result implied that a phosphorus reagent was not appropriate for the sulfonamide substitution reaction. Therefore, in the future, greater ingenuity will need to be applied in order to formulate a viable procedure for sulfonylurea formation directly from CO_2.



26

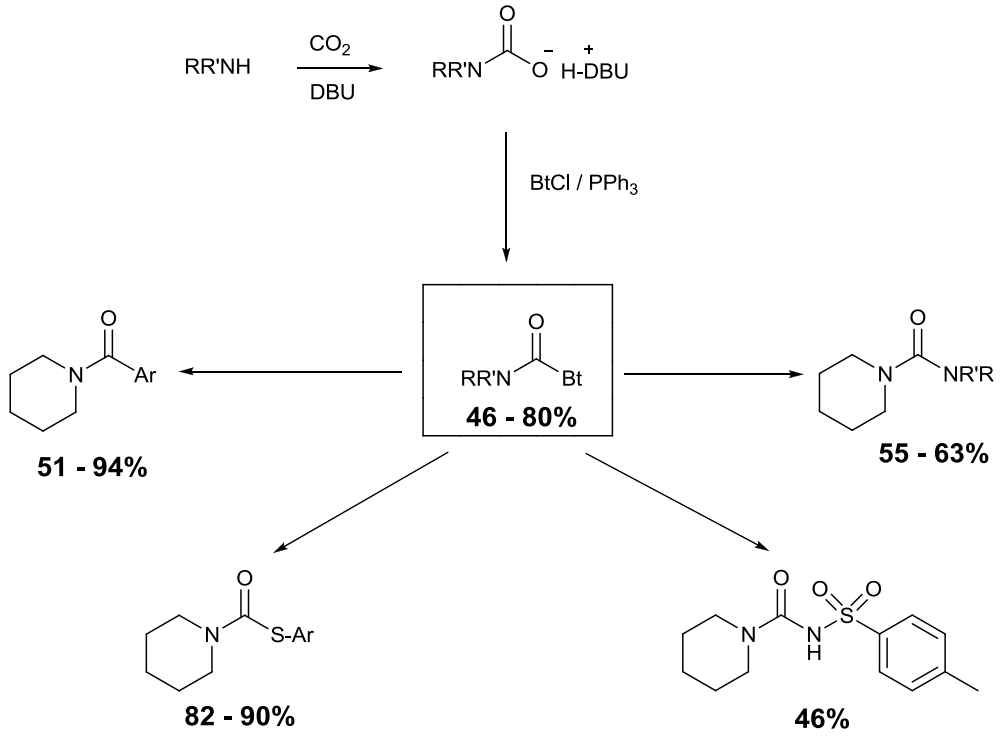
Scheme 3.24: The suggested mechanism for ylide **26** formation

As stated in Chapter 1, performing reactions under solvent-free conditions is more environmentally-friendly, thus there is an even bigger motivation to further develop the K_2CO_3 procedure in Scheme 3.21. Hence, future work will involve optimisation of the sulfonylurea synthesis from Bt ureas (or even directly from CO_2), and an attempt to develop a product isolation regime that does not utilise column chromatography.

Chapter 4: Conclusions and Future Work

4.1 Conclusions

The aim of this project was to find a way to transform CO_2 into a stable, storable reagent that would be useful for organic synthesis. Indeed, the reaction of CO_2 with an amine in the presence of a bulky, non-nucleophilic organic base, and subsequent treatment of the resultant carbamate salt with PPh_3 and BtCl gave a product (the Bt urea) that achieves this aim. As Scheme 4.1 shows, this two-step, one-pot methodology results in a chemical intermediate that is robust and can survive the necessary purification methods in order to be shelved for use in further chemical reactions. Furthermore, the development and effective optimisation of this methodology was only made possible by an appropriate use of organic mechanism.



Scheme 4.1: Synthesis of the Bt urea and its application to the synthesis of various other useful chemical entities

The robust nature of the Bt urea also had implications on its reactivity since ionised nucleophiles were required in order to exploit the Bt-moiety's leaving group capability. It was thus shown that the Bt urea is an effective precursor for the synthesis of various other useful chemical derivatives such as ureas, amides, *S*-thiocarbamates, and sulfonylureas, via

nucleophilic substitution reactions. Another advantage of the procedures described herein is the fact that BtH can be recycled, thus making the procedures more atom-economical.

4.2 Future Work

4.2.1 Cross-Coupling

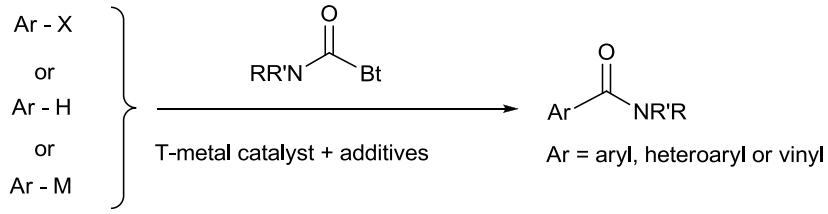
In conjunction with modern thinking on cross-coupling methodology using a transition-metal catalyst, the Bt urea offers potential as a carbamoylating agent in C-C bond formation with a range of aromatic, heteroaromatic and vinylic substrates to produce amides. Such a protocol would greatly enhance utilization of CO_2 without the intervention of phosgene. The three most likely pathways for such a substitution involve, Scheme 4.2:

(i) Ar – H activation with a metal (e.g. Fe, Cu and Ni)[98,99,100]

(ii) Ar – X oxidative addition into a metal[101]

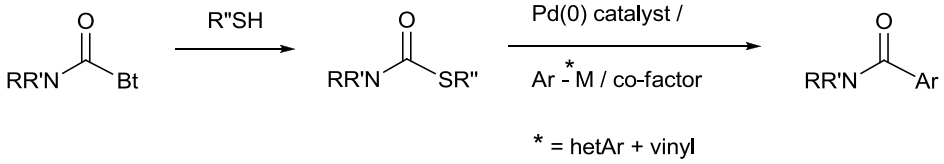
(iii) Ar – M nucleophilic substitution (e.g. boronic acids, Mg, Sn, Si and Zn)[102]

The C-H activation pathway is the ultimate goal as it is the most direct and atom-economical.



Scheme 4.2: Three possible pathways for C-C bond formation via cross-coupling, using the Bt urea

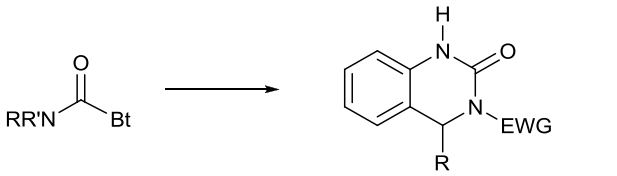
In addition, Liebeskind and Fukayama have shown that thiol esters can be converted to ketones via cross-coupling reactions using Pd(0) catalysts.[103,104,105] In a similar fashion, it is therefore proposed that *S*-thiocarbamates produced according to Chapter 3 might also be used in cross-coupling reactions for C-C bond formation to afford amides (Scheme 4.3).



Scheme 4.3: Cross-coupling using *S*-thiocarbamates

4.2.2 Functionalised Ureas

The reaction of Bt ureas with other amines in order to make substituted ureas is to be optimised in order to reduce reaction times and temperatures, and to improve product yields. The methodology for the solvent-free synthesis of sulfonylureas is also to be further optimised. Another future objective is to develop the Bt urea as an agent for the synthesis of functionalised ureas which, under normal circumstances, are difficult to synthesise. This can be achieved by an intramolecular cyclisation reaction. Compounds of the kind shown in Scheme 4.4 are important in medicinal chemistry.



Functionalised Urea

EWG = electron-withdrawing group

Scheme 4.4: Functionalised ureas to be synthesised from the Bt urea

Therefore it has been shown that the Bt urea can be synthesised using CO_2 as a C-1 building block. The Bt urea can itself be used as a building block for the synthesis of other useful chemical intermediates that would ordinarily be produced using toxic and unstable chemical building blocks (such as phosgene, isocyanates, CO and CS_2).

Chapter 5: Experimental

5.1 General methods

All solvents were freshly distilled. Tetrahydrofuran was distilled under nitrogen from sodium wire with benzophenone. Acetonitrile was distilled from calcium hydride under nitrogen. Dichloromethane was distilled from phosphorus pentoxide under nitrogen. Other reagents were purified according to standard procedures.

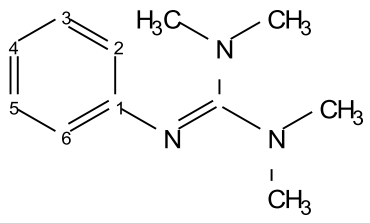
Column chromatography was performed using silica-gel 60 (Merck 7734). Thin layer chromatography was carried out on aluminium-backed Merck silica-gel 60 F_{254} plates. Compounds were visualized on tlc by using one or more of the following revealing techniques: UV lamp, iodine vapour, spraying with a 2.5% solution of anisaldehyde in a mixture of sulfuric acid and ethanol (1:10 v/v) or ninhydrin in methanol (1:19 w/w) and then heating at 250°C.

Infra-Red (IR) spectra were measured on a Bruker FT-IR Spectrometer. Nuclear Magnetic Resonance spectra were recorded on a Varian Mercury 300 MHz (75.5 MHz for ^{13}C) or a Bruker 400 MHz (100.6 MHz for ^{13}C) instrument and were carried out in chloroform-d. Chemical shifts (δ) were recorded relative to residual chloroform (δ 7.26 in ^{1}H NMR and δ 77.0 in ^{13}C NMR), or DMSO (δ 2.50 in ^{1}H NMR and δ 35.2 in ^{13}C NMR). All chemical shifts are reported in ppm and resonances are assigned according to IUPAC numbering, viz H-1 = H on C-1. All mass spectra were recorded on a Waters API Q-TOF Ultima machine in EI mode. Melting points were obtained using a Reichert-Jung Thermovar hot-stage microscope and are uncorrected. Elemental analyses were performed using a Fisons EA 1108 CHNS elemental analyzer.

All reactions were carried out under a nitrogen or argon atmosphere in dried glassware. All starting materials were purchased from Aldrich or Merck except for BtCl, which was synthesised according to the procedure of Rees et al.[106]

5.2 Synthesis and Characterisation of Products

***N,N,N',N'*-tetramethyl-*N'*-phenylguanidine**[81]



TMPG

To a solution of tetramethylurea (5.81 g, 50.0 mmol) in toluene (25 ml), was added phosphoryl chloride (8.40 g, 54.0 mmol, 1.1 eq) slowly at room temperature. The mixture was stirred overnight. Aniline (7.00 g, 75.0 mmol, 1.5 eq) was then added and the mixture was heated for six hours at 80^0C, after which the reaction mixture was cooled. Ethyl acetate (50 ml) was added and the mixture was basified to pH 14 with a concentrated solution of sodium hydroxide (5 M, 50 ml). The reaction mixture was then extracted with ethyl acetate (3 x 50 ml) and the combined organic layers were concentrated under reduced pressure. Fractional distillation, under reduced pressure on a vacuum pump (0.1 mg Hg) of the resultant oily residue gave **1** (5.31g, 56%).[81]

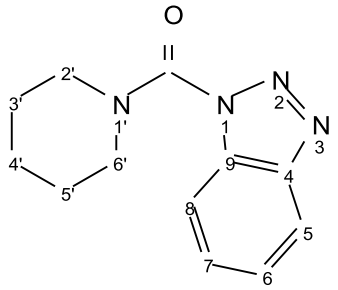
Liquid; δ_H (400 MHz, $CDCl_3$) 2.69 (12H, s, 4(CH_3)), 6.68 (1H, m, H-2/6), 6.70 (1H, m, H-2/6), 6.82 (1H, m, H-4), 7.16 (1H, m, H-3/5), 7.19 (1H, m, H-3/5); δ_C (100.6 MHz, $CDCl_3$) 39.5 4(CH_3), 119.8 (C-4), 121.6 (C-2, C-6), 128.6 (C-3, C-5), 151.6 (C-1), 159.7 (C=N).

Typical procedure for Bt-derivative synthesis (TP1):

CO_2 gas was bubbled for twenty minutes at room temperature into a mixture of amine (1.00 mmol) and DBU (190 mg, 1.25 mmol, 1.25 eq) in THF. PPh_3 (350 mg, 1.30 mmol, 1.3 eq) and BtCl (246 mg, 1.60 mmol, 1.6 eq) were then added and the mixture was stirred for fifteen minutes under a CO_2 atmosphere. The reaction mixture was then concentrated under reduced pressure to give a residue which was chromatographed on silica gel (23.0 g) with ethyl acetate / petroleum ether mixtures as eluent.

Compounds **4a** and **4b** were prepared according to **TP1** from piperidine (85.0 mg, 1.00 mmol). Column chromatography of the resultant reaction residue (ethyl acetate / petroleum ether = 1 : 9) yielded **4a** (148 mg, 0.64 mmol, 64%) and **4b** (37.0 mg, 0.16 mmol, 16%).

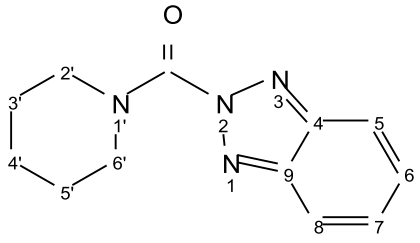
Piperidinyl-1-benzotriazolecarboxamide[107]



4a

Solid; m.p. 82-84^{0}C (from DCM / petroleum ether), no melting point reference; ν_{max}/cm^{-1} 1700 (C=O); δ_H (400 MHz, $CDCl_3$) 1.74 (6H, m, H-3', H-4', H-5'), 3.78 (4H, m, H-2', H-6'), 7.41 (1H, t, *J* = 7.7 Hz, H-6/7), 7.55 (1H, t, *J* = 7.7 Hz, H-6/7), 7.94 (1H, d, *J* = 8.3 Hz, H-5/8), 8.06 (1H, d, *J* = 8.3 Hz, H-5/8); δ_C (75.5 MHz, $CDCl_3$) 24.1 (C-4'), 25.7 (C-3', C-5'), 47.3 (C-2', C-6'), 113.2 (C-6/7), 119.5 (C-6/7), 124.8 (C-5/8), 128.9 (C-5/8), 133.0 (C-4/9), 145.2 (C-4/9), 149.3 (C=O). Anal. Cal. for $C_{12}H_{14}N_4O$: C, 62.59; H, 6.13; N, 24.33%. Found: C, 62.48; H, 6.67; N, 25.95%. HRMS (ES): *m/z* 253.1064 $[M + Na]^+$, $C_{12}H_{14}N_4NaO$ requires 253.1065.

Piperidinyl-2-benzotriazolecarboxamide



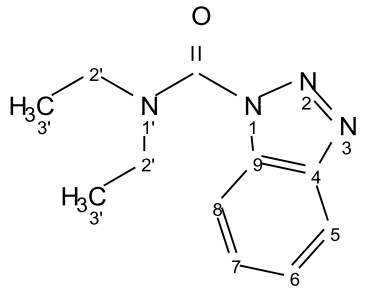
4b

Solid; m.p. 83-85^{0}C (from DCM / petroleum ether); ν_{max}/cm^{-1} 1728 (C=O); δ_H (300 MHz, $CDCl_3$) 1.72 (6 H, m, H-3', H-4', H-5'), 3.40 (2H, m, H-2'), 3.80 (2H, m, H-6'), 7.44 (2H, m, H-6, H-7), 7.91 (2H, m, H-5, H-8); δ_C (75.5 MHz, $CDCl_3$) 24.1 (C-4'), 25.3, 26.1 (C-3', C-5'), 46.5, 48.6 (C-2', C-6'), 118.9 (C-6, C-7), 128.0 (C-5, C-8), 144.1 (C-4, C-9), 149.7 (C=O).

Anal. Cal. for $C_{12}H_{14}N_4O$: C, 62.59; H, 6.13; N, 24.33%. Found: C, 62.58; H, 6.43; N, 25.73%. HRMS (ES): *m/z* 253.1056 $[M + Na]^+$, $C_{12}H_{14}N_4NaO$ requires 253.1065.

Compounds **9a** and **9b** were prepared according to **TP1** from diethylamine (73.1 mg, 1.00 mmol). Column chromatography of the resultant reaction residue (ethyl acetate / hexane petroleum ether = 1 : 11.5) yielded **9a** (96.0 mg, 0.44 mmol, 44%) and **9b** (55.0 mg, 0.25 mmol, 25%).

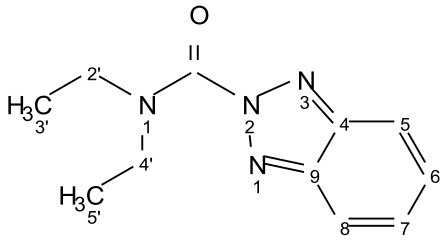
***N,N*-Diethyl-1-benzotriazolecarboxamide**[108]



9a

Semi-solid; δ_H (300 MHz, $CDCl_3$) 1.35 (6H, t, *J* = 7.1 Hz, H-3'), 3.65 (4H, q, *J* = 7.1 Hz, H-2'), 7.41 (1H, m, H-6/7), 7.55 (1H, m, H-6/7), 7.99 (1H, dt, *J* = 8.3, 1.0 Hz, H-5/8), 8.05 (1H, dt, *J* = 8.3, 1.0 Hz, H-5/8); δ_C (75.5 MHz, $CDCl_3$) 13.2 (C-3'), 43.7 (C-2'), 113.6 (C-6/7), 119.6 (C-6/7), 124.9 (C-5/8), 129.0 (C-5/8), 133.1 (C-4/9), 145.1 (C-4/9), 149.9 (C=O).

***N,N*-Diethyl-2-benzotriazolecarboxamide**

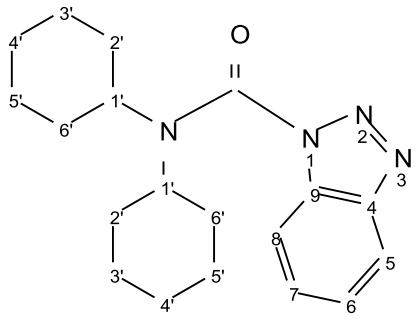


9b

Solid; m.p. 25-27^{0}C (from DCM / petroleum ether); ν_{max}/cm^{-1} 1728 (C=O); δ_H (300 MHz, $CDCl_3$) 1.32 (6H, m, H-3', H-5'), 3.48 (4H, m, H-2', H-4'), 7.42 (2H, m, H-6, H-7), 7.89 (2H, m, H-5, H-8); δ_C (75.5 MHz, $CDCl_3$) 12.3, 13.9 (C-3', C-5'), 43.1, 43.8 (C-2', C-4'), 118.9 (C-6, C-7), 127.9 (C-5, C-8), 143.9 (C-4, C-9), 149.3 (C=O). Anal. Cal. for $C_{11}H_{14}N_4O$: C, 60.53; H, 6.47; N, 25.67%. Found: C, 58.15; H, 6.86; N, 25.83%. HRMS (ES): *m/z* 241.1085 $[M + Na]^+$, $C_{11}H_{14}N_4NaO$ requires 241.1065.

Compounds **10a** and **10b** were prepared according to **TP1** from dicyclohexylamine (181 mg, 1.00 mmol). Column chromatography of the resultant reaction residue (ethyl acetate / petroleum ether = 1 : 11.5) yielded **10a** (135 mg, 0.41 mmol, 41%) and **10b** (65.0 mg, 0.20 mmol, 20%).

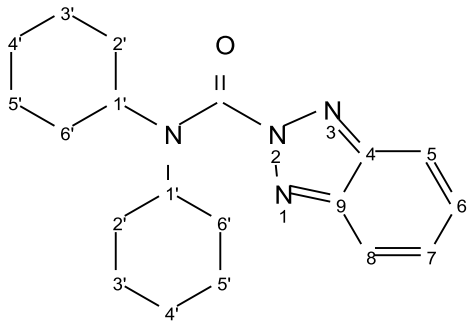
***N*,*N*-Dicyclohexyl-1-benzotriazolecarboxamide**



10a

Solid; m.p. 136-139^{0}C (from DCM / petroleum ether); ν_{max}/cm^{-1} 1699 (C=O); δ_H (300 MHz, $CDCl_3$) 1.60 (20H, m, H-2', H-3', H-4', H-5', H-6'), 3.61 (2H, s, H-1'), 7.41 (1H, m, H-6/7), 7.55 (1H, m, H-6/7), 7.92 (1H, d, *J* = 8.2 Hz, H-5/8), 8.06 (1H, d, *J* = 8.2 Hz, H-5/8); δ_C (75.5 MHz, $CDCl_3$) 25.2 (C-4'), 25.9 (C-3', C-5'), 30.6 (C-2', C-6'), 58.7 (C-1'), 113.3 (C-6), 119.6 (C-6/7), 124.7 (C-5/8), 128.7 (C-5/8), 133.3 (C-4/9), 145.3 (C-4/9), 148.8 (C=O). Anal. Cal. for $C_{19}H_{26}N_4O$: C, 69.91; H, 8.03; N, 17.16%. Found: C, 69.56; H, 8.12; N, 18.19%. HRMS (ES): *m/z* 349.2019 $[M + Na]^+$, $C_{19}H_{26}N_4NaO$ requires 349.2004.

***N*,*N*-Dicyclohexyl-2-benzotriazolecarboxamide**

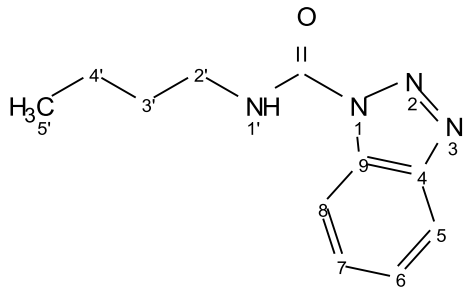


10b

Solid; m.p. 156-160^{0}C (from DCM / petroleum ether); ν_{max}/cm^{-1} 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.60 (20H, m, H-2', H-3', H-4', H-5', H-6'), 3.11 (2H, s, H-1'), 7.45 (2H, m, H-6, H-7), 7.93 (2H, m, H-5, H-8); δ_C (101.6 MHz, $CDCl_3$) 25.0 (C-4'), 25.8 (C-3', C-5'), 30.0 (C-2', C-6'), 59.0 (C-1'), 118.9 (C-6, C-7), 127.6 (C-5, C-8), 143.9 (C-4, C-9), 149.2 (C=O). Anal. Cal. for

$C_{19}H_{26}N_4O$: C, 69.91; H, 8.03; N, 17.16%. Found: C, 70.13; H, 7.84; N, 18.60%. HRMS (ES): *m/z* 349.2000 $[M + Na]^+$, $C_{19}H_{26}N_4NaO$ requires 349.2004.

_N_-Butyl-1-benzotriazolecarboxamide[109]

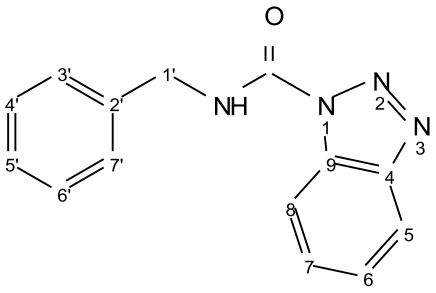


11

Compound **11** was prepared according to **TP1** from butylamine (73.1 mg, 1.00 mmol). Column chromatography of the resultant reaction residue (ethyl acetate / petroleum ether = 1 : 11.5) yielded **11** (100 mg, 0.46 mmol, 46%).

Solid; m.p. 41-43^{0}C (from DCM / petroleum ether), no m.p. given in references; δ_H (300 MHz, $CDCl_3$) 0.96 (3H, t, *J* = 7.2 Hz, H-5'), 1.44 (2H, sext, *J* = 7.2 Hz, H-4'), 1.68 (2H, p, *J* = 7.2 Hz, H-3'), 3.54 (2H, t, *J* = 7.2 Hz, H-2'), 7.34 (1H, s, H-1'), 7.41 (1H, m, H-6/7), 7.58 (1H, m, H-6/7), 8.05 (1H, dt, *J* = 8.3, 0.9 Hz, H-5/8), 8.25 (1H, dt, *J* = 8.3, 0.9 Hz, H-5/8); δ_C (75.5 MHz, $CDCl_3$) 13.5 (C-5'), 19.9 (C-4'), 31.5 (C-3'), 40.2 (C-2'), 113.8 (C-6/7), 119.8 (C-6/7), 125.2 (C-5/8), 129.7 (C-5/8), 131.6 (C-4/9), 146.2 (C-4/9), 149.1 (C=O).

_N_-Phenylmethyl-1-benzotriazolecarboxamide[110]

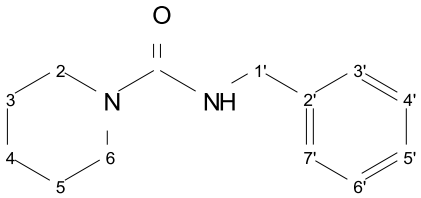


12

Compound **12** was prepared according to **TP1** from benzylamine (107 mg, 1.00 mmol). Column chromatography of the resultant reaction residue (ethyl acetate / petroleum ether = 1 : 11.5) yielded **12** (200 mg, 0.79 mmol, 79%).

Solid; m.p. 108-112^{0}C (from DCM / petroleum ether), no m.p. given in references; δ_H (400 MHz, $CDCl_3$) 4.73 (2H, d, *J* = 6.0 Hz, H-1'), 7.40 (6H, m, H-6/7, Ar), 7.61 (1H, m, H-6/7), 7.71 (1H, s, NH), 8.08 (1H, d, *J* 8.4 Hz, H-5/8), 8.29 (1H, d, *J* 8.4 Hz, H-5/8); δ_C (101.6 MHz, $CDCl_3$) 44.4 (C-1'), 113.9, 119.9, 125.3, 127.7, 127.9, 128.8, 129.8 (C-5, C-6, C-7, C-8, Bn), 131.6 (C-2'/4/9), 136.9 (C-2'/4/9), 146.2 (C-2'/4/9), 149.2 (C=O).

_N_-Methylphenylpiperidinylcarboxamide[111]

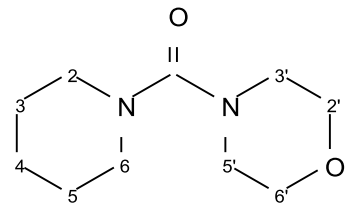


13

A mixture of **4** (230 mg, 1.00 mmol) and benzylamine (118 mg, 1.10 mmol, 1.1 eq) in THF (5 ml) was refluxed at 80^{0}C for twenty-seven hours. After cooling, the reaction mixture was quenched with a saturated solution of ammonium chloride (20 ml) and ethyl acetate (10 ml) was also added. Extraction with ethyl acetate (3 x 10 ml) followed and the combined organic layers were then concentrated under reduced pressure. The resultant oily residue was chromatographed on silica gel (23.0 g) with ethyl acetate / petroleum ether (1 : 9 to 1 : 4) mixtures as eluent to yield **13** (120 mg, 0.55 mmol, 55%).

Solid; m.p. 98-100^{0}C (from DCM / petroleum ether), lit[111] requires 103-105^{0}C; δ_H (400 MHz, $CDCl_3$) 1.51 (6H, m, H-3, H-4, H-5), 3.27 (4H, m, H-2, H-6), 4.34 (2H, s, H-1'), 4.96 (1H, s, N-H), 7.23 (5H, m, Ar); δ_C (75.5 MHz, $CDCl_3$) 24.3 (C-4), 25.5 (C-3, C-5), 44.9 (C-1'), 44.9 (C-2, C-6), 127.1, 127.6, 128.4, 139.6 (Ar), 157.5 (C=O).

4-Morphinylpiperidinylcarboxamide[79]



14

A mixture of **4** (230 mg, 1.00 mmol) and morpholine (96.0 mg, 1.10 mmol, 1.1 eq) in toluene (5 ml) was refluxed at 110^{0}C for twenty-seven hours. After cooling, the reaction mixture was

quenched with a saturated solution of ammonium chloride (20 ml) and ethyl acetate (10 ml) was also added. Extraction with ethyl acetate (3 x 10 ml) followed and the combined organic layers were then concentrated under reduced pressure. The resultant oily residue was chromatographed on silica gel (23.0 g) with ethyl acetate / petroleum ether (1 : 9 to 1 : 1) mixtures as eluent to yield **14** (125 mg, 0.63 mmol, 63%).

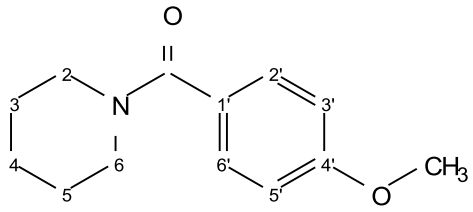
Solid; m.p. 39-41^{0}C (from DCM / petroleum ether), lit[79] requires 40-43^{0}C; δ_H (300 MHz, $CDCl_3$) 1.50 (6H, m, H-3, H-4, H-5), 3.15 (8H, m, H-2, H-6, H-3', H-5'), 3.59 (4H, m, H-2', H-6'); δ_C (75.5 MHz, $CDCl_3$) 24.4 (C-4), 25.5 (C-3, C-5), 47.2 (C-2, C-6), 47.5 (C-3', C-5'), 66.4 (C-2', C-6'), 164.1 (C=O).

Typical procedure for amide synthesis using a Grignard reagent (TP2):

To a reaction flask containing magnesium turnings (1.46 g, 60.0 mmol, 1.2 eq) and 5 ml THF or diethyl ether, was added 5 ml of a mixture of aryl- or heteroaryl halide (50.0 mmol) in 20 ml of solvent (THF or diethyl ether). The reaction mixture was then stirred and heated to 65^{0}C (THF) or 40^{0}C (diethyl ether). Once the initial violent reaction had subsided, the rest of the halide / solvent mixture was added drop-wise at a rate such that the reaction mixture refluxed gently. The reaction mixture was then refluxed for a further thirty minutes, after which it was cooled and more solvent was added in order to form a homogeneous mixture. The molarity of the Grignard mixture was determined by quenching with water and subsequent titration against dilute hydrochloric acid (0.1 M).

A flask containing a mixture of **4** (230 mg, 1.00 mmol) and THF (3 ml) was cooled to 0^{0}C with an ice bath and the Grignard mixture (1.5 or 2 eq) was added drop-wise. The ice bath was then immediately removed and the reaction mixture was allowed to stir at room temperature for fifteen minutes. The reaction mixture was then quenched with a saturated solution of ammonium chloride (20 ml) and ethyl acetate (10 ml) was also added, after which it was extracted with ethyl acetate (3 x 10 ml). The combined organic layers were then concentrated under reduced pressure and the resultant residue was purified by column chromatography.

(4-Methoxyphenyl)piperidinylmethanone[112]

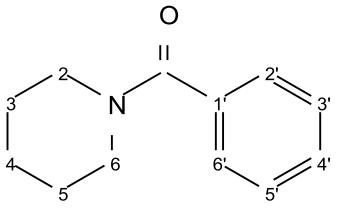


15

Compound **15** was prepared according to **TP2**. A 0.48 M THF solution of the Grignard reagent was prepared using 1-bromo-4-methoxyphenyl (9.35 g, 50.0 mmol). Treatment of **4** with the Grignard solution (3.2 ml, 1.54 mmol, 1.5 eq) and subsequent work-up gave a residue which was chromatographed on silica gel (23.0 g) with ethyl acetate / petroleum ether (1 : 9 to 1 : 4) mixtures as eluent to give **15** (206 mg, 0.94 mmol, 94%).

Oil; δ_H (400 MHz, $CDCl_3$) 1.61 (6H, m, H-3, H-4, H-5), 3.50 (4H, m, H-2, H-6), 3.78 (3H, s, OCH_3), 6.86 (2H, d, *J* = 8.7 Hz, H-3', H-5'), 7.33 (2H, d, *J* = 8.7 Hz, H-2', H-6'); δ_C (101.6 MHz, $CDCl_3$) 24.5 (C-4), 25.9 (C-3, C-5), 46.3 (C-2, C-6), 55.1 (OCH_3), 113.5 (C-3', C-5'), 128.4 (C-4'), 128.7 (C-2', C-6'), 160.4 (C-1'), 170.2 (C=O).

Phenylpiperidinylmethanone[112]

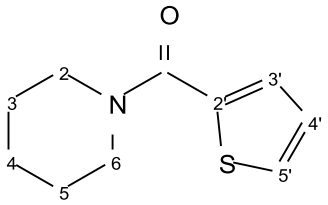


16

Compound **16** was prepared according to **TP2**. A 0.96 M THF solution of the Grignard reagent was prepared using 1-bromophenyl (7.85 g, 50.0 mmol). Treatment of **4** with the Grignard solution (1.6 ml, 1.54 mmol, 1.5 eq) and subsequent work-up gave a residue which was chromatographed on silica gel (23.0 g) with ethyl acetate / petroleum ether (1 : 9 to 1 : 5.6) mixtures as eluent to give **16** (160 mg, 0.85 mmol, 85%).

Oil; δ_H (400 MHz, $CDCl_3$) 1.60 (6H, m, H-3, H-4, H-5), 3.34 (2H, m, H-2/6), 3.69 (2H, m, H-2/6), 7.38 (5H, s, Ar); δ_C (101.6 MHz, $CDCl_3$) 24.6 (C-4), 25.7 (C-3/5), 26.4 (C-3/5), 43.0 (C-2/6), 48.8 (C-2/6), 126.8, 128.3, 129.3, 136.5 (Ar), 170.3 (C=O).

2-Thienylpiperidinylmethanone[112]

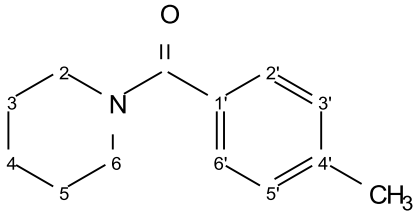


17

Compound **17** was prepared according to **TP2**. A 0.23 M diethyl ether solution of the Grignard reagent was prepared using 2-iodothiophene (10.5 g, 50.0 mmol). Treatment of **4** with the Grignard solution (8.9 ml, 2.05 mmol, 2 eq) and subsequent work-up gave a residue which was chromatographed on silica gel (23.0 g) with ethyl acetate / petroleum ether (1 : 9) mixtures to give **17** (153 mg, 0.78 mmol, 78%).

Oil; δ_H (300 MHz, $CDCl_3$) 1.63 (6H, m, H-3, H-4, H-5), 3.62 (4H, m, H-2, H-6), 6.99 (1H, dd, *J* 5.0, 3.5 Hz, H-4'), 7.22 (1H, dd, *J* = 3.5, 0.8 Hz, H-3'), 7.37 (1H, dd, *J* = 5.0, 0.8 Hz, H-5'); δ_C (75.5 MHz, $CDCl_3$) 24.4 (C-4), 26.0 (C-3, C-5), 46.2 (C-2, C-6), 126.4 (C-3'/4'/5'), 127.9 (C-3'/4'/5'), 128.1 (C-3'/4'/5'), 137.4 (C-2'), 163.3 (C=O).

(4-Methylphenyl)piperidinylmethanone[113]

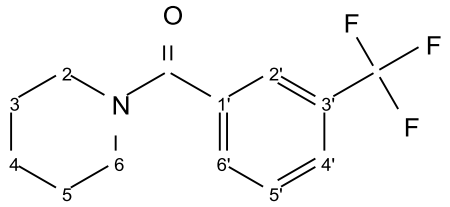


18

Compound **18** was prepared according to **TP2**. A 0.58 M THF solution of the Grignard reagent was prepared using 4-bromotoluene (8.55 g, 50.0 mmol). Treatment of **4** with the Grignard solution (3.5 ml, 2.03 mmol, 2 eq) and subsequent work-up gave a residue which was chromatographed on silica gel (23.0 g) with ethyl acetate / petroleum ether (1 : 9 to 1 : 7.3) mixtures as eluent to give **18** (170 mg, 0.84 mmol, 84%).

Oil; δ_H (300 MHz, $CDCl_3$) 1.62 (6H, m, H-3, H-4, H-5), 2.33 (3H, s, CH_3), 3.49 (4H, m, H-2, H-6), 7.15 (2H, d, *J* = 7.8 Hz, H-3', H-5'), 7.26 (2H, d, *J* = 7.8 Hz, H-2', H-6'); δ_C (75.5 MHz, $CDCl_3$) 21.2 (C-4), 24.4 (CH_3), 25.9 (C-3, C-5), 43.4 (C-2/6), 48.1 (C-2/6), 126.7 (C-3', C-5'), 128.8 (C-2', C-6'), 133.4 (C-4'), 139.2 (C-1'), 170.3 (C=O).

(3-Trifluoromethylphenyl)piperidinylmethanone[114]

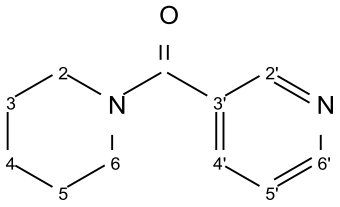


19

To a reaction flask containing magnesium turnings (122 mg, 5.01 mmol, 5 eq), were added lithium chloride (0.5 M in THF, 5 ml, 2.50 mmol, 2.5 eq) as well as DIBAL (1.3 M in toluene, 0.02 ml, 2.60 x 10^{-2} mmol, 2.6 x 10^{-2} eq) and the mixture was stirred for five minutes at room temperature. It was cooled to 0^0C, after which 1-bromo-3-(trifluoromethyl)benzene (450 mg, 2.00 mmol, 2 eq) was added and the reaction mixture was stirred for a further thirty-five minutes. Compound **4** (230 mg, 1.00 mmol) was then added and the reaction mixture was allowed to warm up to room temperature. After two hours of stirring, the reaction mixture was quenched with a saturated solution of ammonium chloride (20 ml) and ethyl acetate (10 ml) was also added. It was then extracted with ethyl acetate (3 x 10 ml). The combined organic layers were then concentrated under reduced pressure and the resultant residue was chromatographed on silica gel (23.0 g) with ethyl acetate / petroleum ether (1 : 7.3) mixtures to yield **19** (131 mg, 0.51 mmol, 51%).

Oil; δ_H (300 MHz, $CDCl_3$) 1.60 (6H, m, H-3, H-4, H-5), 3.30 (2H, m, H-2/6), 3.68 (2H, m, H-2/6), 7.60 (4H, m, Ar); δ_C (75.5 MHz, $CDCl_3$) 24.4 (C-4), 25.6 (C-3/5), 26.3 (C-3/5), 43.1 (C-2/6), 48.7 (C-2/6), 100.1 (CF_3), 123.7, 126.1, 128.9, 130.0, 137.2 (Ar), 168.6 (C=O).

3-Pyridinylpiperidinylmethanone[115,116]



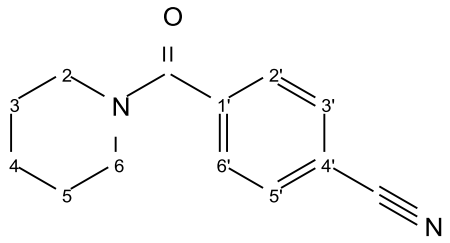
20

To a reaction flask containing magnesium turnings (122 mg, 5.01 mmol, 5 eq), were added lithium chloride (0.5 M in THF, 5 ml, 2.50 mmol, 2.5 eq) as well as DIBAL (1.3 M in toluene, 0.02 ml, 2.60 x 10^{-3} mmol, 2.6 x 10^{-3} eq) and the mixture was stirred for five minutes at room temperature. The reaction mixture was cooled to 0^0C, after which 3-bromopyridine (328 mg, 2.00 mmol, 2.00 eq) was added and the reaction mixture was stirred for a further three

hours. Compound **4** (230 mg, 1.00 mmol) was then added and the reaction mixture was allowed to warm up to room temperature. After 19 hours stirring, the reaction mixture was quenched with a saturated solution of ammonium chloride (20 ml) and ethyl acetate (10 ml) was also added. It was then extracted with ethyl acetate (3 x 10 ml). The combined organic layers were then concentrated under reduced pressure and the resultant residue was chromatographed on silica gel (23 g) with ethyl acetate / petroleum ether (1 : 9 to1 : 1) mixtures as eluent to yield **20** (112 mg, 0.59 mmol, 59%).

Oil; δ_H (300 MHz, $CDCl_3$) 1.56 (6H, m, H-3, H-4, H-5), 3.46 (4H, m, H-2, H-6), 7.28 (1H, m, H-4'/5'), 7.67 (1H, m, H-4'/5'), 8.60 (2H, m, H-2', H-6'); δ_C (75.5 MHz, $CDCl_3$) 24.2 (C-4), 25.4 (C-3/5), 26.3 (C-3/5), 43.1 (C-2/6), 48.6 (C-2/6), 123.3, 132.2, 134.6, 147.5, 150.2 (Ar), 167.4 (C=O).

(4-Benzonitrile)piperidinylmethanone[116]

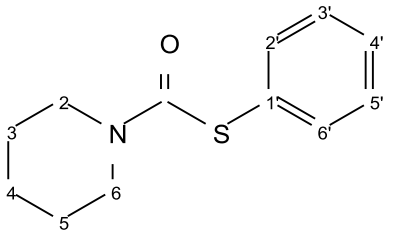


21

To a reaction flask containing *i*-PrMgCl.LiCl (1.6 ml of a 1.3 M solution in THF, 2.08 mmol, 2 eq) and 5 ml of THF at 0^0C, 4-bromobenzonitrile (364 mg, 2.00 mmol, 2 eq) was added and reaction mixture was stirred for two hours. The reaction mixture was then cooled to -10^0C and compound **4** (230 mg, 1.00 mmol) was added, after which it was allowed to warm up to room temperature and left stirring for a further eight hours. The reaction was then quenched with a saturated solution of ammonium chloride (20 ml) and ethyl acetate (10 ml) was also added. Extraction was then performed with ethyl acetate (3 x 10 ml) and the combined organic layers were then concentrated under reduced pressure and the resultant residue was chromatographed on silica gel (23.0 g) with ethyl acetate / petroleum ether (1 : 9 to 1 : 7) mixtures as eluent to yield **21** (150 mg, 0.70 mmol, 70%).

Oil; δ_H (300 MHz, $CDCl_3$) 1.54 (6H, m, H-3, H-4, H-5), 3.21 (2H, m, H-2), 3.63 (2H, m, H-6), 7.43 (2H, d, *J* = 8.0 Hz, H-2', H-6'), 7.64 (2H, d, *J* = 8.0 Hz, H-3', H-5'); δ_C (101.6 MHz, $CDCl_3$) 24.1 (C-4), 25.2 (C-3/5), 26.2 (C-3/5), 42.9 (C-2/6), 48.3 (C-2/6), 112.9 (CN), 117.9 (C-1'/4'), 127.2 (C-3', C-5'), 132.1 (C-2', C-6'), 140.7 (C-1'/4'), 167.8 (C=O).

Phenylpiperidinecarbothioate[90]

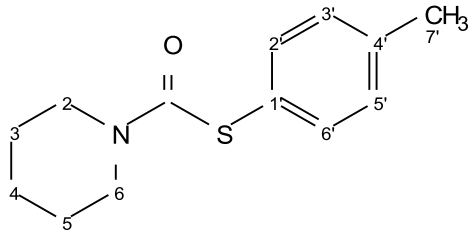


22

n-Butyllithium (1.3 M solution in THF, 0.8 ml, 1.04 mmol, 1 eq) was added to a mixture of thiophenol (0.1 ml, 1.00 mmol, 1 eq) and THF (5 ml), and the mixture was left stirring for fifteen minutes. Compound **4** (230 mg, 1.00 mmol) was then added, after which the reaction mixture was warmed to room temperature and left stirring for a further two and a half hours. The reaction mixture was quenched with a saturated solution of ammonium chloride (20 ml) and ethyl acetate (10 ml) was also added. It was then extracted with ethyl acetate (3 x 10 ml) and the combined organic layers were then concentrated under reduced pressure. The resultant oily residue was chromatographed on silica gel (23.0 g) with ethyl acetate / petroleum ether (1 : 48 to 1 : 9) mixtures as eluent to yield **22** (192 mg, 0.87 mmol, 87%).

Oil; δ_H (400 MHz, $CDCl_3$) 1.66 (6H, m, H-3, H-4, H-5), 3.55 (4H, m, H-2, H-6), 7.38 (3H, m, H-3', Ar), 7.50 (2H, m, Ar); δ_C (101.6 MHz, $CDCl_3$) 24.5 (H-4), 25.7 (H-3, H-5), 46.2 (H-2, H-6), 128.8, 129.0, 135.8 (Ar), 165.4 (C=O).

(4-Methylphenyl)piperidinecarbothioate



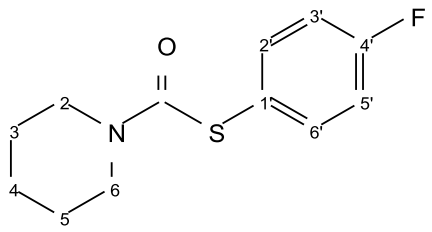
23

n-Butyllithium (1.5 M solution in THF, 0.7 ml, 1 mmol, 1 eq) was added to a mixture of 4-methylthiophenol (124 mg, 1.05 mmol, 1.05 eq) and THF (5 ml), and the mixture was left stirring for fifteen minutes. Compound **4** (230 mg, 1.00 mmol) then added, after which the reaction mixture was warmed to room temperature and left stirring for a further two hours. The reaction mixture was then quenched with a saturated solution of ammonium chloride (20 ml) and ethyl acetate (10 ml) was also added. It was then extracted with ethyl acetate (3 x 10 ml) and the combined organic layers were then concentrated under reduced pressure. The

resultant oily residue was chromatographed on silica gel (23.0 g) with ethyl acetate / petroleum ether (1 : 48 to 1 : 9) mixtures as eluent to yield **23** (194 mg, 0.82 mmol, 82%).

Solid; m.p. 72-74^{0}C (from DCM / petroleum ether); ν_{max}/cm^{-1} 1662 (C=O); δ_H (300 MHz, $CDCl_3$) 1.63 (6H, m, H-3, H-4, H-5), 2.36 (3H, s, H-7'), 3.54 (4H, m, H-2, H-6), 7.19 (2H, d, *J* = 8.0 Hz, H-3', H-5'), 7.38 (2H, d, *J* = 8.0 Hz, H-2', H-6'); δ_C (75.5 MHz, $CDCl_3$) 21.2 (C-7'), 24.5 (C-4), 25.7 (C-3, C-5), 46.0 (C-2, C-6), 125.2 (C-4'), 129.6 (C-3', C-5'), 135.7 (C-2', C-6'), 139.2 (C-1'), 165.7 (C=O). Anal. Cal. for $C_{13}H_{17}NOS$: C, 66.34; H, 7.28; N, 5.95; S, 13.62. Found: C, 66.39; H, 7.15; N, 5.66; S, 13.43%. HRMS (ES): *m/z* 258.0922 $[M + Na]^+$, $C_{13}H_{17}NNaOS$ requires 258.0929.

(4-Fluorophenyl)piperidinecarbothioate

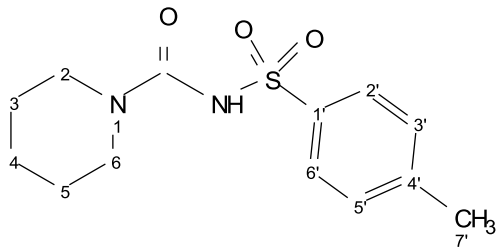


24

n-Butyllithium (1.5 M solution in THF, 0.7 ml, 1.05 mmol, 1 eq) was added to a mixture of 4-flourothiophenol (0.11 ml, 1.00 mmol, 1 eq) and THF (5 ml), and the mixture was left stirring for fifteen minutes. Compound **4** (230 mg, 1 mmol) was added, after which the reaction mixture was warmed to room temperature and left stirring for a further one and a half hours. The reaction mixture was then quenched with a saturated solution of ammonium chloride (20 ml) and ethyl acetate (10 ml) was also added. It was then extracted with ethyl acetate (3 x 10 ml) and the combined organic layers were then concentrated under reduced pressure. The resultant oily residue was chromatographed on silica gel (23.0 g) with ethyl acetate / petroleum ether (1 : 48 to 1 : 9) mixtures as eluent to yield **24** (215 mg, 0.90 mmol, 90%).

Solid; m.p. 74-76^{0}C (from DCM / petroleum ether); ν_{max}/cm^{-1} 1669 (C=O); δ_H (300 MHz, $CDCl_3$) 1.65 (6H, m, H-3, H-4, H-5), 3.54 (4H, m, H-2, H-6), 7.07 (2H, m, H-2', H-6'), 7.46 (2H, m, H-3', H-5'); δ_C (75.5 MHz, $CDCl_3$) 24.4 (C-4), 25.7 (C-3, C-5), 46.0 (C-2, C-6), 115.8, 116.1 (C-2', C-6'), 124.1 (C-1'), 137.7, 137.8 (C-3', C-5'), 161.7 (C-4'), 165.0 (C=O). Anal. Cal. for $C_{12}H_{14}FNOS$: C, 60.23; H, 5.90; N, 5.85; S, 13.40. Found: C, 61.76; H, 5.79; N, 5.02; S, 13.40%. HRMS (ES): *m/z* 240.0847 $[M + H]^+$, $C_{12}H_{15}FNOS$ requires 240.0858.

(4-Methylphenyl)sulfonylpiperidinecarboxamide[117]



25

A mixture of **4** (230 mg, 1.00 mmol), *p*-toluenesulfonamide (257 mg, 1.50 mmol, 1.5 eq) and K_2CO_3 (138 mg, 1.00 mmol, 1 eq) was stirred at 100^0C for twenty-one hours. Subsequent to cooling, the solidified reaction mixture was dissolved in ethyl acetate (10 ml) and then quenched with a saturated solution of ammonium chloride (20 ml). It was then extracted with ethyl acetate (3 x 10 ml) and the combined organic layers were concentrated under reduced pressure. The resultant oily residue was chromatographed on silica gel (23.0 g) with ethyl acetate / petroleum ether (1 : 9 to 1 : 1) mixtures as eluent to yield **25** (129 mg, 0.46 mmol, 46%).

Oil; δ_H (300 MHz, DMSO) 1.44 (6H, m, H-3, H-4, H-5), 2.37 (3H, s, C-7'), 3.28 (4H, m, H-2, H-6), 7.18 (1H, s, N-H), 7.35 (2H, d, *J* = 8.2 Hz, Ar), 7.77 (2H, d, *J* = 8.2 Hz, Ar); δ_C (75.5 MHz, DMSO) 20.6 (C-4), 23.4 (C-3, C-5), 25.0 (C-7'), 44.2 (C-2, C-6), 125.3 (C-4'), 127.0, 128.6 (C-2, C-3, C-5, C-6), 142.2 (C-1), 151.8 (C=O).

Chapter 6: References

1 H. Arakawa, M. Aresta, J. N. Armor, M. A. Barteau, E. J. Beckman, A. T. Bell, J. E. Bercaw, C. Creutz, E. Dinjus, D. A. Dixon, K. Domen, D. L. DuBois, J. Eckert, E. Fujita, D. H. Gibson, W. A. Goddard, D. W. Goodman, J. Keller, G. J. Kubas, H. H. Kung, J. E. Lyons, L. E. Manzer, T. J. Marks, K. Morokuma, K. M. Nicholas, R. Periana, L. Que, J. Rostrup-Nielson, W. M. Sachtler, L. D. Schmidt, A. Sen, G. A. Somorjai, P. C. Stair, B. R. Stults and W. Tumas, *Chem. Rev.*, 2001, **101**, 953-996.

2 D. M. Rudkevich and H. Xu, *Chem. Commun.*, 2005, 2651-2659.

3 P. Braunstein, D. Matt and D. Nobel, *Chem. Rev.*, 1988, **88**, 747-764.

4 M. Aresta, *ACS Symp. Ser., Ser. 852*, Carbon Dioxide Recovery and Utilization, ed. M. Aresta, 2003, pp. 2-39.

5 H. H. Szmant, *Organic Building Blocks of the Chemical Industry*, John Wiley and Sons, New York, NY, 1989, pp. 61-187.

6 E. Artuso, I. Degani, R. Fochi and C. Magistris, *Synthesis*, 2007, 3497-3506.

7 T. Sakakura, J. Choi and H. Yasuda, *Chem. Rev.*, 2007, **107**, 2365-2387.

8 M. Aresta and A. Dibenedetto, *Dalton Trans.*, 2007, 2975-2992.

9 J. H. Saunders and R. J. Slocombe, *Chem. Rev.*, 1948, **43**, 203-218.

10 R. Arnold, J. Nelson and J. Verbanc, *Chem. Rev.*, 1957, **57**, 47-76.

11 J. A. Demaray, J. E. Thuener, M. N. Dawson and S. J. Sucheck, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4868-4871.

12 M. S. Kim, Y. Kim, H. S. Hahm, J. W. Jang, W. K. Lee and H.J. Ha, *Chem. Commun.*, 2005, 3062-3064.

13 K. D. Schleicher and T. F. Jamison, *Org. Lett.*, 2007, **9**, 875-878.

14 K. Schwetlickt and R. Noacks, *J. Chem. Soc., Perkin Trans. 2*, 1995, 395-402.

15 S. J. Peters J. R. Klen, and N. C. Smart, *Org. Lett.*, 2008, **10**, 4521-4524.

16 H. Duong, M. J. Cross and J. Louie, *Org. Lett.*, 2004, **6**, 4679-4681.

17 I. Degani, R. Fochi and V. Regondi, *Synthesis*, 1980, 375-378.

18 K. Komaki, T. Kawata, K. Harano and T. Taguchi, *Chem. Pharm. Bull.*, 1978, **26**, 3807-3814.

19 I. Degani, R. Fochi and V. Regondi, *Synthesis*, 1981, 149-151.

20 S. Cadamuro, I. Degani, R. Fochi and V. Regondi, *Synthesis*, 1986, 1070-1074.

21 I. Degani, R. Fochi and V. Regondi, *Synthesis*, 1983, 630-632.

22 M. Barbero, S. Cadamuro, I. Degani, R. Fochi and V. Regondi, *Synthesis*, 1989, 957-958.

23 E. Artuso, G. Carvoli, L. Degani, R. Fochi and C. Magistris, *Synthesis*, 2007, 1096-1102.

24 M. Leung, J. Lai, K. Lau, H. Yu and H. Hsiao, *J. Org. Chem.*, 1996, **61**, 4175-4179.

25 C. Chen, *Tetrahedron*, 1998, **54**, 9067-9078.

26 M. Matzner, R. P. Kurkjy and R. J. Cotter, *Chem. Rev.*, 1964, **64**, 645–687.

27 S. P. Rannard and N. J. Davis, *Org. Lett.*, 1999, **1**, 933-936.

28 R. Vaidyanathan, V. G. Kalthod, D. P. Ngo, J. M. Manley and S. P. Lapekas, *J. Org. Chem.*, 2004, **69**, 2565-2568.

29 S. Rannard and N. Davis, *Org. Lett.*, 2000, **2**, 2117-2120.

30 E. K. Woodman, J. G. K. Chaffey, P. A. Hopes, D. R. J. Hose and J. P. Gilday, *Org. Proc. Res.Dev.*, 2009, 106-113.

31 T. Werner and A. G. M. Barrett, *J. Org. Chem.*, 2006, **71**, 4302-4304.

32 M. M. Krayushkin, F. M. Stoyanovich and S. V. Shorunov, *Mendeleev Commun.*, 2003, 5-6.

33 J. Grzyb, M. Shen, C. Yoshinaishii, W. Chi, R. Brown and R. Batey, *Tetrahedron*, 2005, **61**, 7153-7175.

34 M. R. Wood, D. J. Duncalf, S. P. Rannard and S. Perrier, *Org. Lett.*, 2006, **8**, 553-6.

35 P. J. Walsh, H. Li and C. A. de Parrodi, *Chem. Rev.*, 2007, **107**, 2503-2545.

36 X. Lu, B. Liang, Y. Zhang, Y. Tian, Y. Wang, C. Bai, H. Wang and R. Zhang, *J. Am. Chem. Soc.*, 2004, **126**, 3732-3733.

37 A. Berkessel and M. Brandenburg, *Org. Lett.*, 2006, **8**, 4401-4.

38 M. Aresta, C. Fragale, E. Quaranta and I. Tommasi, *Chem. Commun.*, 1992, 315-317.

39 D. J. Darensbourg, *Chem. Rev.*, 2007, **107**, 2388-2410.

40 M. Cheng, E. B. Lobkovsky and G. W. Coates, *J. Am. Chem. Soc.*, 1998, **120**, 11018-11019.

41 M. Feroci, M. Orsini, G. Sotgiu, L. Rossi and A. Inesi, *J. Org. Chem.*, 2005, **70**, 7795-7798.

42 M. Shi and Y. Shen, *J. Org. Chem.*, 2002, **67**, 16-21.

43 Y. L. Gu, Q. H. Zhang, Z. Y. Duan, J. Zhang, S. G. Zhang and Y. Q. Deng, *J. Org. Chem.*, 2005, **70**, 7376-7380.

44 H. Jiang and J. Zhao, *Tetrahedron Lett.*, 2009, **50**, 60-62.

45 C. J. Dinsmore and S. P. Mercer, *Org. Lett.*, 2004, **6**, 2885-2888.

46 A. W. Miller and S. T. Nguyen, *Org. Lett.*, 2004, **6**, 2301-2304.

47 Y. Du, Y. Wu, A. Liu and L. He, *J. Org. Chem.*, 2008, **73**, 4709-4712.

48 X. Dou, L. He, Z. Yang and J. Wang, *Synlett*, 2010, 2159-2163.

49 T. A. Keating and R. W. Armstrong, *J. Org. Chem.*, 1998, **63**, 867-871.

50 I. Ugi and C. Steinbruckner, *Chem. Ber.*, 1961, **94**, 2802-2814.

51 C. Hulme, *Tetrahedron Lett.*, 2000, **41**, 1889-1893.

52 J. Takaya, S. Tadami, K. Ukai and N. Iwasawa, *Org. Lett.*, 2008, **10**, 2697-700.

53 E. Sada, H. Kumazawa and Z. Han, *Chem. Eng. J.*, 1985, **31**, 109-115.

54 C. Bowman, *Chem. Eng. Sci.*, 1996, **51**, 4781-4789.

55 M. Aresta and E. Quaranta, *Tetrahedron*, 1992, **48**, 1515-1530.

56 W. D. McGhee, D. Riley, K. Christ, Y. Pan, B. Parnas, M. Company, N. L. Boulevard and S. Louis, *J. Org. Chem.*, 1995, **60**, 2820-2830.

57 M. Aresta, A. Dibenedetto and E. Quaranta, *J. Chem. Soc., Dalton Trans.*, 1995, 3359-3363.

58 A. Belforte and F. Calderazzo, *J. Chem. Soc., Dalton Trans.*, 1989, 1007-1009.

59 W. D. McGhee, Y. Pan and D. P. Riley, *J. Chem. Soc., Chemical Commun.*, 1994, 699-700.

60 E. R. Perez, M. Odnicki Da Silva, V. C. Costa, U. P. Rodrigues-Filho and D. W. Franco, *Tetrahedron Lett.*, 2002, **43**, 4091-4093.

61 F. Chu, E. E. Dueno and K. W. Jung, *Tetrahedron Lett.*, 1999, **40**, 1847-1850.

62 R. N. Salvatore, F. Chu, A. S. Nagle, E. A. Kapxhiu, R. M. Cross and K. W. Jung, *Terahedron*, 2002, **58**, 3329-3347.

63 R. N. Salvatore, S. I. Shin, A. S. Nagle and K. W. Jung, *J. Org. Chem.*, 2001, 66, 1035-1037.

64 R. N. Salvatore, V. L. Flanders, D. Ha and K. W. Jung, *Org. Lett.*, 2000, **2**, 2797-2800.

65 M. Aresta and E. Quaranta, *J. Org. Chem.*, 1988, **53**, 4153-4154.

66 M. Aresta and E. Quaranta, *J. Chem. Soc., Dalton Trans.*, 1992, 1893-1899.

67 P. H. Dixneuf, R. Mahe, Y. Sasaki and C. Bruneau, *J. Org. Chem.*, 1989, **54**, 1518-1523.

68 W. D. McGhee and D. P. Riley, *Organometallics*, 1992, **11**, 900-907.

69 W. D. McGhee, D. P. Riley, M. E. Christ and K. M. Christ, *Organometallics*, 1993, **12**, 1429-1433.

70 M. Yoshida, N. Hara and S. Okuyama, *Chem. Commun.*, 2000, 151-152.

71 T. Seki and A. Baiker, *Chem. Rev.*, 2009, **109**, 2409-2454.

72 R. Nomura, Y. Hasegawa, M. Ishimoto, T. Toyosaki and H. Matsuda, *J. Org. Chem.*, 1992, **57**, 7339-7342.

73 W. D. McGhee and T. E. Waldman, *Chem. Commun.*, 1994, 957-958.

74 D. Saylik, M. J. Horvath, P. S. Elmes, W. R. Jackson, C. G. Lovel and K. Moody, *J. Org. Chem.*, 1999, **64**, 3940-3946.

75 V. M. D. Chaturvedi and N. Mishra, *Synthesis*, 2008, 355-357.

76 W. D. McGhee, Y. Pan, and J. J. Talley, *Tetrahedron Lett.*, 1994, **35**, 839-842.

77 F. D. Deroose and P. J. De Clercq, *J. Org. Chem.*, 1995, **60**, 321–330.

78 E. García-Egido, M. Fernandez-Suarez and L. Muñoz, *J. Org. Chem.*, 2008, **73**, 2909-2911.

79 A. R. Katritzky, D. P. M. Pleynet and B. Yang, *J. Org. Chem.*, 1997, **62**, 4155-4158.

80 I. Butula, V. Vela and M. V. Prostenik, *Croat. Chem. Acta*, 1979, **52**, 47-49.

81 V. Marks, *United States Patent,* 1961, US 4358613.

82 E. V. G. T. P. Vishnyakova and I. A. Golubeva, *Russ. Chem. Rev.*, 1985, **54**, 429-449.

83 G. A. D. P. Getman, M. DeCrescenzo, R. M. Heintz, K. L. Reed, J. J. Talley, M. L. Bryant, M. L. V. Clare, K. A. Houseman, J. J. Marr, R. A. Mueller and R. A. S. H. S. Shieh, W. C. Stallings, *J. Med. Chem.*, 1993, **36**, 288-291.

84 D. S. P. J. Garratt, S. Travard, S. Vonhoi and A. Tsotinis, *J. Med. Chem.*, 1996, **39**, 1797-1805.

85 J. F. J. Bartroli, E. Turmo, M. Alguero, E. Boncompte, M. L. Vericat, L. Conte, J. Ramis, M. Merlos and J. Garcia-Rafanell, *J. Med. Chem.*, 1998, **41**, 1855-1868.

86 F. D. A. Dasettimo, A. M. Marini, G. Primo¢ore and F. Dasettimo, *Farmaco*, 1995, **50**, 321-326.

87 B. J. Wakefield, *Organomagnesium Methods in Organic Synthesis*, Academic Press Limited, San Diego, CA, 1995, pp. 1-81.

88 P. Knochel, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin and F. M. Piller, *Chem. Eur. J.*, 2009, **15**, 7192-7202.

89 P. Knochel and A. Krasovskiy, *Angew. Chem. Int. Ed.*, 2004, **43**, 3333-3336.

90 Y. Nishiyama, H. Kawamatsu and N. Sonoda, *J. Org. Chem.*, 2005, **70**, 2551-2554.

91 T. Mizuno, T. Iwai and Y. Ishino, *Tetrahedron*, 2005, **61**, 9157-9163.

92 R. Riemschneider, F. Wojahn and G. Orlick, *J. Am. Chem. Soc.*, 1951, **73**, 5905–5907.

93 M. S. Newman and H. A. Karnes, *J. Org. Chem.*, 1966, **31**, 3980–3984.

94 H. Kwart and E. R. Evans, *J. Org. Chem.*, 1966, **31**, 410–413.

95 F. Mohamadi and M. Spees, *J. Med. Chem.*, 1992, **35**, 3012-3016.

96 R. K. Gessner and K. Chibale, *Synlett*, 2009, 2839-2843.

97 C. A. Luckhurst, I. Millichip, B. Parker, J. Reuberson and M. Furber, *Tetrahedron Lett.*, 2007, **48**, 8878-8882.

98 A. S. Dudnik and V. Gervogyn, *Angew. Chem. Int. Ed.*, 2010, **49**, 2096-2098.

99 H. Hachiya, K. Hirano, T. Satoh and M. Miura, *Angew. Chem. Int. Ed.*, 2010, **49**, 2202-2205.

100 W. Liu, H. Cao and A. Lei, *Angew. Chem. Int. Ed.*, 2010, **49**, 2004-2008.

101 A. Correa and R. Martin, *J. Am. Chem. Soc.*, 2009, **131**, 15974-15975.

102 D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174-238.

103 J. M. Villalobos, J. Srogl and L. S. Liebeskind, *J. Am. Chem. Soc.*, 2007, **129**, 15734-15735.

104 H. Li, H. Yang and L. S. Liebeskind, *Org. Lett.*, 2008, **10**, 4375-4378.

105 T. Fukuyama and H. Tokuyama, *Aldrichim. Acta*, 2004, **37**, 87-96.

106 C. W. Rees and R. C. Storr, *J. Chem. Soc.*, 1969, 1474-1477.

107 Known and registered compound with no literature references.

108 A. Kreutzberger and H. Van Der Goot, *Arch. Pharm.*, 1974, **307**, 824-828.

109 I. Butula, M. V. Prostenik and V. Vela, *Croat. Chem. Acta*, 1977, **49**, 837-842.

110 S. Petry, G. Zoller, N. Tennagels and G. Mueller, *German Patent*, 2007, DE10200504.

111 A. Yagodkin, K. Löschcke, J. Weisell and A. Azhayev, *Tetrahedron*, 2010, **66**, 2210-2221.

112 S. Das, D. Addis, S. Zhou, K. Junge and M. Beller, *J. Am. Chem. Soc.*, 2010, **132**, 1770-1771.

113 Y. Jo, J. Ju, J. Choe, K. H. Song and S. Lee, *J. Org. Chem.*, 2009, **74**, 6358-6361.

114 M. Mitzlaff, K. Warning and H. Jensen, *Justus Lieb. Ann. Chem.*, 1978, **11**, 1713-1733.

115 G. Deguest, A. Devineau, L. Bischoff, C. Fruit and F. Marsais, *Org. Lett.*, 2006, **8**, 5889-5892.

116 L. R. Odell, J. Sävmarker and M. Larhed, *Tetrahedron Lett.*, 2008, **49**, 6115-6118.

117 C. King, *J. Org. Chem*., 1960, **25**, 352-356