Application of Carbamoylimidazolium Salts as Carbamoyl Transfer Reagents

and

Approaches toward Esterification

and

Etherification Protocols

by

Connie Wong

A thesis submitted in conformity with the requirements for the degree of Master of Science
Graduate Department of Chemistry
University of Toronto

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Application of Carbamoylimidazolium Salts as Carbamoyl Transfer Reagents and Approaches toward Esterification and Etherification Protocols

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Abstract

The stability and reactivity of three classes of carbamoylimidazolium salts as N,N-disubstituted carbamoyl transfer reagents were examined: iodide, tetrafluoroborate and hexafluorophosphate salts. The hexafluorophosphate salt proved superior in reactivity and stability over previously established iodide salts. A library of compounds with a variety of functional groups was generated with the hexafluorophosphate salt including ureas, carbamates and amides.

In addition, the effect of a catalytic amount of lanthanide triflate on esterification and lactonization reactions using 2-methyl-6-nitrobenzoic acid was tested. Finally, a methodology to install t-amyl groups was attempted, using the convenient and commercially available 2-methyl-2-butene. Various conditions using heat and pressure were used.
Acknowledgments

I would first like to thank my research supervisor, Prof. Robert Batey for, first of all, accepting me into the lab with little research experience, for all his support, guidance and patience, and for ultimately teaching me to be a resourceful chemist.

I also thank all the past and current members of the Batey group who have kept me company and whose enthusiasm towards chemistry has been an inspiration. To all senior students and Marvin for guiding me and answering my trivial questions. To Jordan and Pjotr for their endless company at all hours of the day. To Simon for being kind, for sharing his experience and for making labwork so fun!
# Table of Contents

Contents

Acknowledgments.................................................................................................................. iii
Table of Contents.................................................................................................................. iv
List of Tables ........................................................................................................................ vi
List of Schemes ...................................................................................................................... vii
List of Figures ....................................................................................................................... viii
List of Abbreviations .......................................................................................................... ix
List of Appendices ............................................................................................................... x

Chapter 1  Stability, Synthesis and Reactivity of Carbamoylimidazolium Salts as \( N,N \)-disubstituted Carbamoyl Transfer Reagents ................................................................. 1

1.1 Introduction .................................................................................................................... 1

1.1.1 Chemistry of Carbamoyl Derivatives ................................................................. 1
1.1.2 Previous research from the Batey group ........................................................... 2
1.1.3 Hexafluorophosphate anion as a counterion .................................................... 3
1.1.4 Extension of reactivity and stability study ......................................................... 3

1.2 Results and Discussion ............................................................................................... 4

1.2.1 Synthesis of carbamoylimidazolium salts for stability study ............................. 4
1.2.2 Stability Studies ...................................................................................................... 7
1.2.3 Reactivity study ....................................................................................................... 11
1.2.4 Reactivity of Carbamoylimidazolium Hexafluorophosphate Salt ..................... 15

1.3 Conclusion .................................................................................................................... 19

Chapter 2  Approaches Toward Esterification .................................................................. 20

2.1 Introduction .................................................................................................................. 20

2.1.1 Accessing Intermolecular Esterification and Macrolactonization .................... 20
2.1.2 Approach ................................................................................................................ 20
2.2 Results and Discussion ........................................................................................................... 22
  2.2.1 Intermolecular Coupling ............................................................................................... 22
  2.2.2 Lactonization .................................................................................................................. 24
2.3 Conclusion .............................................................................................................................. 26

Chapter 3 Etherification Protocols .......................................................................................... 27
  3.1 Introduction .......................................................................................................................... 27
    3.1.1 Current t-Butyl Protection Method ............................................................................. 27
    3.1.2 Previous Work with t-Amyl Protection Method ........................................................... 28
    3.1.3 Approach ....................................................................................................................... 28
  3.2 Results and Discussion .......................................................................................................... 28
  3.3 Conclusion ............................................................................................................................ 34

References ..................................................................................................................................... 35

Appendices .................................................................................................................................... 38
List of Tables

Table 1.1: Yields of $N,N$–disubstituted carbamoylimidazoles

Table 1.2: Yields of methylations and salt metathesis

Table 1.3: Reactivity of morpholine derived carbamoylimidazolium salts

Table 1.4: Reactivity of $N$-methylaniline derived carbamoylimidazolium salts

Table 1.5: Synthesis of ureas, carbamates and amides from carbamoylimidazolium hexafluorophosphate salts and amines, aniline, phenol and carboxylic acid respectively

Table 2.1: Conditions used for attempted coupling of $N$-boc-alanine and benzyl 2-hydroxy-2-methylpropanoate

Table 2.2: Conditions for the coupling Z-Ser-(O'Bu)-OH and Z-Ser-OPac

Table 3.1: Conditions used for attempted $t$-butyl ether protection of 1-octanol.

Table 3.2: Conditions used for attempted $t$-butyl ether protection of 3-phenyl-1-propanol.

Table 3.3: Conditions used for attempted $t$-butyl ester protection of hydrocinnamic acid.

Table 3.4: Conditions used for attempted $t$-butyl ester protection of malonic acid.

Table 3.5: Microwave conditions used in attempts to $t$-butyl ester protect hydrocinnamic acid.
List of Schemes

**Scheme 1.1:** Synthesis of monosubstituted carbamoylimidazoles

**Scheme 1.2:** Synthesis and reactivity of disubstituted carbamoylimidazolium iodide salts

**Scheme 1.3:** Synthesis of carbamoylimidazolium hexafluorophosphate salts through salt metathesis

**Scheme 1.4:** Synthesis of iodide, hexafluorophosphate and tetrafluoroborate carbamoylimidazolium salts

**Scheme 1.5:** Decomposition of carbamoylimidazolium salts

**Scheme 1.6:** Synthesis of ureas from carbamoylimidazolium iodide salts and amines

**Scheme 1.7:** Synthesis of carbamates from carbamoylimidazolium iodide salts and alcohols

**Scheme 1.8:** Synthesis of amides from carbamoylimidazolium iodide salts and carboxylic acids

**Scheme 2.1:** Hypothesized MNBA and Lewis acid catalyzed ester formation

**Scheme 2.2:** Lewis acid catalyzed lactonization through chelation

**Scheme 2.3:** Attempted coupling of benzyl 2-hydroxy-2-methylpropanoate and N-boc-\(L\)-leucine hydrate

**Scheme 2.4:** Synthesis of serine precursors from free serine

**Scheme 2.5:** Synthesis of seco-acid

**Scheme 3.1:** Mechanism of \(t\)-butyl alcohol or acid protection via isobutylene gas

**Scheme 3.2:** Attempted \(t\)-amylation protections with benzyl alcohol at room temperature

**Scheme 3.3:** Attempted \(t\)-amylation protection with 3-phenyl-1-propanol

**Scheme 3.4:** \(t\)-butyl protection of malonic acid
List of Figures

**Figure 1.1**: Carbamoyl transfer reagents

**Figure 1.2**: NMR Spectrum of morpholine derived iodide, hexafluorophosphate and tetrafluoroborate carbamoylimidazolium salts after 80 days under an air atmosphere.

**Figure 1.3**: NMR Spectrum of morpholine derived iodide, hexafluorophosphate and tetrafluoroborate carbamoylimidazolium salts after 80 days under a nitrogen atmosphere.

**Figure 1.4**: NMR Spectrum of morpholine derived iodide, hexafluorophosphate and tetrafluoroborate carbamoylimidazolium salts after 44 days in deuterated dimethyl sulfoxide.

**Figure 1.5**: Percent decomposition of morpholine derived carbamoylimidazolium salts over a period of 44 days in deuterated dimethyl sulfoxide

**Figure 2.1**: Enterobactin
List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>$^1$H NMR</td>
<td>proton nuclear magnetic resonance</td>
</tr>
<tr>
<td>$^{13}$C NMR</td>
<td>carbon-13 nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>CDI</td>
<td>1,1-carbonyldiimidazole</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>EDC</td>
<td>1-ethyl-3-(3-dimethylaminopropyl)carbodiimide</td>
</tr>
<tr>
<td>FT-IR</td>
<td>Fourier transformed infrared spectroscopy</td>
</tr>
<tr>
<td>ESI MS</td>
<td>electrospray ionization mass spectrometry</td>
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<tr>
<td>HRMS</td>
<td>high resolution mass spectroscopy</td>
</tr>
<tr>
<td>iPr$_2$NEt</td>
<td>Hunig’s base/diisopropylethylamine</td>
</tr>
<tr>
<td>MeCN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>MNBA</td>
<td>2-methoxy-6-nitrobenzoic anhydride</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectroscopy</td>
</tr>
<tr>
<td>NEt$_3$</td>
<td>triethylamine</td>
</tr>
<tr>
<td>Pac</td>
<td>phenacyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
</tbody>
</table>
List of Appendices

Experimental .................................................................................................................. 38
Spectral Data .................................................................................................................. 48
Chapter 1  Stability, Synthesis and Reactivity of Carbamoylimidazolium Salts as \(N,N\)-disubstituted Carbamoyl Transfer Reagents

1.1  Introduction

1.1.1  Chemistry of Carbamoyl Derivatives

Carbamoyl groups are present in several functional groups and their members, such as ureas and carbamates, are prevalent in natural product targets and pharmaceuticals. In addition, carbamoyl groups have industrial applications including, but not limited to, pesticides, plastics, polyurethane foam and adhesives.\(^1\) It follows that carbamoyl transfer is an important class of reactions. Isocyanates 1 are a class of monosubstituted carbamoyl cation equivalents. Carbamoyl chlorides 2 are another commonly used reagent with this functionality, acting as disubstituted carbamoyl cation equivalents. However, their limited commercial availability, requirement of highly-toxic phosgene for their synthesis, susceptibility to hydrolysis and unstable nature make them undesirable reagents. Carbonyldiimidazoles (CDI) adducts 3 are a safer and more stable alternative carbamoyl transfer reagent; however their reactivity was found lacking.\(^2\)

\[
\begin{align*}
R-N=CO & \quad R_1^1\quad \text{O} \quad N^+ \quad \text{N} \quad \text{Me} & \quad R_2^1\quad \text{O} \quad R_2^2
\end{align*}
\]

Figure 1.1: Carbamoyl transfer reagents
1.1.2 Previous research from the Batey group

More recently, J. Bansagi and P. Duspara investigated CDI adducts as isocyanate or carbamoyl cation equivalents. A protocol was developed to synthesize $N$-methyl carbamoylimidazole with a variety of primary amines 3 (where $R^2 = H$), in which purification was achieved through liquid-liquid extraction. The resultant CDI adducts were storable at $-4 \, ^\circ C$, showing only trace decomposition after months, and able to form ureas, carbamates and thiocarbamates.

![Scheme 1.1: Synthesis of monosubstituted carbamoylimidazoles](image)

In pursuit of a more bench stable but also highly reactive disubstituted carbamoyl transfer reagent, the Batey group demonstrated that CDI can be activated as the corresponding $N$-methylated carbamoylimidazolium iodide salts 4 (Figure 1.1), whose increased electrophilicity functions as carbamoyl cation equivalents. These salts were formed by nucleophilic addition of a secondary amine into CDI followed by $N$-methylation with methyl iodide (Scheme 1.2). The carbamoylimidazolium salts not only react faster than their CDI analogues, but also with a larger variety of compounds. Thus, 4 reacts with alcohols, phenols, thiols, thiophenols, amines, anilines and carboxylic acids to yield ureas, thiocarbamates, carbamates and amides without chromatographic purification.

![Scheme 1.2: Synthesis and reactivity of disubstituted carbamoylimidazolium iodide salts](image)
1.1.3 Hexafluorophosphate as a counterion

Some of the N-methylated carbamoylimidazolium iodide salts were still relatively unstable, hygroscopic and prone to hydrolysis. This made them less suitable as ‘off the shelf’ reagents for long-term storage. Adeline Pham, working under previous graduate student, Laurie Joyce, demonstrated that hexafluorophosphate salts were better than their iodide salt analogs at stabilizing compounds in the case of carbene complex synthesis. Hexafluorophosphate salts are often used in organometallic and inorganic synthesis as counterions and ionic liquids. The hexafluorophosphate anion is known for its non-coordinating nature and its resistance to acid and base hydrolysis. Its larger size also enables it to delocalize its charge and also to stabilize larger cations. These characteristics make it a more desirable anion compared to the more reactive halide anions. Foglieni Baptiste, a previous student, examined the comparative reactivity and stability of the morpholine derived iodide salt and its hexafluorophosphate salt analog. He found that the hexafluorophosphate salt retained similar reactivity and was more bench stable.

![Scheme 1.4](image)

**Scheme 1.3**: Synthesis of carbamoylimidazolium hexafluorophosphate salts through salt metathesis

1.1.4 Extension of reactivity and stability study

Tetrafluoroborate has similar properties to hexafluorophosphate, and is also used in inorganic chemistry as a weakly coordinating counterion. It has low nucleophilicity and is relatively soft. Per mmol, ammonium tetrafluoroborate is less expensive than ammonium hexafluorophosphate, and consequently, a slightly more desirable counterion. As such, we decided to extend the previous study to tetrafluoroborate salts, and compare the reactivity and stability of all three salts: iodide, hexafluorophosphate and tetrafluoroborate. We predicted that the tetrafluoroborate salts would have similar stability and reactivity as the hexafluorophosphate salts, and that both these salts would be more stable than the iodide salt.
1.2 Results and Discussion

1.2.1 Synthesis of carbamoylimidazolium salts for stability study

The synthesis of carbamoylimidazolium salts is shown in Scheme 1.4. Three carbamoylimidazole reagents \(3\) were synthesized from the corresponding secondary amine and a slight excess of CDI (1.2 eq). They were then dissolved in acetonitrile or dichloromethane. Four equivalents of methyl iodide were added to ensure complete conversion to the \(N\)-methylated iodide salt \(4\). Full conversion was observed after 24 h. Two equivalents of ammonium hexafluorophosphate or ammonium tetrafluoroborate were added to a solution of the carbamoylimidazolium iodide salt, a solid precipitate was noticed immediately. The solution was allowed to stir for one hour before the precipitate was isolated as the hexafluorophosphate salts \(6\) and tetrafluoroborate salt \(7\) respectively. Letting the solution sit in the freezer overnight increased the yield of the salts. The pyrrole adducts \(3d-5d\) and isoquinoline adducts \(3f-5f\) were synthesized by another graduate student, Rivka Taylor (Table 1.1 and 1.2). Iodide salts ranged from orange oils, yellow foamy solids to white solids. The oils and foamy solids were quite hygroscopic and difficult to weigh. Hexafluorophosphate salts were all isolated as white or slightly off white crystalline powders. Tetrafluoroborate salts were all isolated as fine white or slightly off white powders.

**Scheme 1.4:** Synthesis of iodide, hexafluorophosphate and tetrafluoroborate carbamoylimidazolium salts.
Table 1.1: Yields of \(N,N\)-disubstituted carbamoylimidazoles

<table>
<thead>
<tr>
<th>Amine</th>
<th>CDI Adduct</th>
<th>Entry</th>
<th>Yield(^a) (%)</th>
</tr>
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<tr>
<td>OMe</td>
<td><img src="image1" alt="Structure" /></td>
<td>3a</td>
<td>90</td>
</tr>
<tr>
<td>MeNH</td>
<td><img src="image2" alt="Structure" /></td>
<td>3b</td>
<td>Quant</td>
</tr>
<tr>
<td>CPh</td>
<td><img src="image3" alt="Structure" /></td>
<td>3c</td>
<td>Quant</td>
</tr>
<tr>
<td>CHN</td>
<td><img src="image4" alt="Structure" /></td>
<td>3d</td>
<td></td>
</tr>
<tr>
<td>CPhNH</td>
<td><img src="image5" alt="Structure" /></td>
<td>3e</td>
<td>Quant</td>
</tr>
<tr>
<td>CPhNN</td>
<td><img src="image6" alt="Structure" /></td>
<td>3f</td>
<td></td>
</tr>
<tr>
<td>MeO-OMe</td>
<td><img src="image7" alt="Structure" /></td>
<td>3g</td>
<td>88</td>
</tr>
<tr>
<td>NH</td>
<td><img src="image8" alt="Structure" /></td>
<td>3h</td>
<td>80</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield

\(^b\) Synthesized by Rivka Taylor, graduate student
Table 1.2: Yields of methylations and salt methatheses

<table>
<thead>
<tr>
<th>Salt Adduct</th>
<th>X⁻ = I⁻</th>
<th>X⁻ = PF₆⁻</th>
<th>X⁻ = BF₄⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Entry</td>
<td>Yield (%)ᵃ</td>
<td>Entry</td>
</tr>
<tr>
<td>4a</td>
<td>5a</td>
<td>86 (86)</td>
<td>6a</td>
</tr>
<tr>
<td>4b</td>
<td>5b</td>
<td>99 (99)</td>
<td>6b</td>
</tr>
<tr>
<td>4c</td>
<td>5c</td>
<td>85 (85)</td>
<td>6c</td>
</tr>
<tr>
<td>4d</td>
<td>b</td>
<td></td>
<td>5d</td>
</tr>
<tr>
<td>4e</td>
<td>99</td>
<td></td>
<td>5e</td>
</tr>
<tr>
<td>4f</td>
<td>b</td>
<td></td>
<td>5f</td>
</tr>
<tr>
<td>4g</td>
<td>89</td>
<td></td>
<td>5g</td>
</tr>
<tr>
<td>4h</td>
<td>Quant</td>
<td></td>
<td>5h</td>
</tr>
</tbody>
</table>

ᵃ Isolated yields. Yields in parentheses are those calculated from the carbamoyl imidazole adduct 3
ᵇ Synthesized by Rivka Taylor, graduate student
ᶜ Salt was not used in stability study
1.2.2 Stability Studies

The stability studies were performed on three carbamoylimidazolium iodide salts and their hexafluorophosphate and tetrafluoroborate equivalents, the morpholine adducts 4-6a, the pyrrole adduct 4-6d and isoquinoline adduct 4-6f, of which the latter two studies were performed by another graduate student, Rivka Taylor. Three sets of conditions were envisioned to study the stability of these compounds (Methods A-C). The first method (Method A) was to store the respective salts under an air atmosphere, without the exclusion of moisture. The second method (Method B) was to store the respective salts under an inert atmosphere, nitrogen gas, after the exclusion of moisture. The third method (Method C) was to store the salts in deuterated dimethyl sulfoxide. All methods were performed at room temperature, as a previous study showed the stability of iodide salts stored in the fridge.4a For the first two methods, the compounds 4-6 were monitored by NMR Spectrum, using deuterated dimethyl sulfoxide as a solvent, every five days. For the last study the compounds 4-6 were stored in NMR tubes and sealed with parafilm to avoid the accumulation of moisture and prevent evaporation. NMR Spectrum spectra of the compounds were taken daily. To monitor the hygroscopic nature of these salts, the mass of the samples from the first two methods were taken daily. Increased mass was attributed to the absorption of water.

![Scheme 1.5: Decomposition of carbamoylimidazolium salts. The original amine and imidazolium salt is produced.](image)

Decomposition was thus monitored by $^1$H NMR, and the amount of decomposition determined by the integration ratio of the carbamoylimidazolium peaks to the imidazolium peaks.
Figure 1.2: NMR Spectrum of morpholine derived iodide, hexafluorophosphate and tetrafluoroborate carbamoylimidazolium salts after 80 days under an air atmosphere. (Method A)

Figure 1.3: NMR Spectrum of morpholine derived iodide, hexafluorophosphate and tetrafluoroborate carbamoylimidazolium salts after 80 days under a nitrogen atmosphere. (Method B)
All samples stored under an air or nitrogen atmosphere were a white powder on Day 1. Samples stored in deuterated dimethyl sulfoxide were clear and colourless.

Previously, Baptiste’s study showed that iodide salt 4a would start to decompose after 42 days under an air atmosphere. However, this study showed no decomposition of 4a after 80 days. This discrepancy may be due to the more humid summer environment during Baptiste’s study, whereas this study was performed during the drier fall term. As well, the salts in this study were stored in a well-ventilated fumehood, whereas the location of Baptiste’s studies were unspecified.

Under an inert nitrogen atmosphere, both studies were consistent in that no decomposition was seen after 42 days for both iodide and hexafluorophosphate salts. This was further extended to 80 days, and no decomposition was observed for the iodide, hexafluorophosphate and tetrafluoroborate salts.

The hygroscopic nature of the salts were quite similar. Salts under the air and nitrogen atmosphere absorbed similar amounts of water per mmol. On average, the salts placed under a nitrogen atmosphere absorbed 0.02 g of water/mmol and those under air absorbed 0.03 g of water/mmol.

However, for both the above studies, the iodide salt changed from a white powder to a yellow powder within a week. A slight yellowing was also noticed in the hexafluorophosphate salts near the end of the study. After six months, the iodide salts stored on the bench top decomposed into a dark orange oil which showed mild decomposition (9%) but a large water peak. The hexafluorophosphate and tetrafluoroborate remained as slight yellow powders. As such, though the studies were less conclusive about the hygroscopic nature of the salts, long-term storage of iodide salts as an ‘off the shelf’ reagent is not a viable option.
Figure 1.4: NMR Spectrum of morpholine derived iodide, hexafluorophosphate and tetrafluoroborate carbamoylimidazolium salts after 44 days in deuterated dimethyl sulfoxide. (Method C)

Figure 1.5: Percent decomposition of morpholine derived carbamoylimidazolium salts over a period of 44 days in deuterated dimethyl sulfoxide.
Decomposition was more noticeable in the samples stored in deuterated dimethyl sulfoxide. Though the amount of decomposition per sample is similar in all three salts, the physical colour of the samples over the evaluation period was different. The iodide sample quickly turned a pale yellow by the end of the first day. By the fifth day, the sample was a yellow colour and this colour deepened to a deep yellow-orange colour by the eighth day. The tetrafluoroborate salt also changed to a pale yellow solution after the second day. On the eighth day, it was a yellow solution and remained so until the end of the evaluation period. The hexafluorophosphate remained a clear colourless solution until the 30th day, where it became a pale yellow solution.

The study of the stability of morpholine derived carbamoylimidazolium salts was less definitive than the studies performed by Rivka Taylor, which concluded that the tetrafluoroborate and hexafluorophosphate salts were much more stable and less hygroscopic than their iodide counterpart. The above studies did demonstrate the retention of colour and physical state of the convenient and easily weighable hexafluorophosphate and tetrafluoroborate salts. The physical and chemical stabilities of the hexafluorophosphate and tetrafluoroborate salts were demonstrated, which permit a storage of compounds previously unstable in the iodide form as well as solid weighable powder alternatives to viscous, hygroscopic oils.

1.2.3 Reactivity study

Carbamoylimidazolium iodide salts are useful in that they are able to generate a variety of functional groups including ureas, carbamates, amides, thioureas and thiocarbamates. We were more interested in the first three classes of compounds. Thus the reactivity of the salts were tested with a variety of amines, naphthol, and acids as shown in Scheme 1.6 - 1.8.
Scheme 1.6: Synthesis of ureas from carbamoylimidazolium iodide salts and amines

Scheme 1.7: Synthesis of carbamates from carbamoylimidazolium iodide salts and alcohols

Scheme 1.8: Synthesis of amides from carbamoylimidazolium iodide salts and carboxylic acids
Table 1.3: Reactivity of morpholine derived carbamoylimidazolium salts

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Product nucleophile in blue</th>
<th>Entry</th>
<th>(X^- = \text{I}^-) Yield (%)</th>
<th>(X^- = \text{PF}_6^-) Yield (%)</th>
<th>(X^- = \text{BF}_4^-) Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{H}_2\text{N}-\text{C}_2\text{H}_5)</td>
<td><img src="image1" alt="Product" /></td>
<td>7a</td>
<td>79</td>
<td>82 (71)</td>
<td>72 (71)</td>
</tr>
<tr>
<td>(\text{HO}-\text{C}_6\text{H}_4)</td>
<td><img src="image2" alt="Product" /></td>
<td>9a</td>
<td>90</td>
<td>85 (73)</td>
<td>91 (89)</td>
</tr>
<tr>
<td>(\text{COOH}-\text{C}_6\text{H}_5)</td>
<td><img src="image3" alt="Product" /></td>
<td>10a</td>
<td>89</td>
<td>83 (72)</td>
<td>78 (76)</td>
</tr>
<tr>
<td>(\text{COOH}-\text{CH}=\text{CH}_2)</td>
<td><img src="image4" alt="Product" /></td>
<td>10i</td>
<td>26</td>
<td>72 (62)</td>
<td>56 (55)</td>
</tr>
</tbody>
</table>

* Isolated yields. Yields in parenthesis are calculated from the carbamoyl imidazole adduct 3.
Table 1.4: Reactivity of $N$-methylaniline derived carbamoylimidazolium salts.

The morpholine derived tetrafluoroborate salt seemed to outperform its hexafluorophosphate counterpart because of its almost quantitative yield during salt methathesis (Table 1.2). However, the hexafluorophosphate salt is generally slightly more reactive than the tetrafluoroborate salt (Table 1.3). The higher reactivity of the hexafluorophosphate salt was also exhibited by the $N$-methylaniline derived salts, having very similar overall yields to the iodide salt (Table 1.4). As such, it was concluded that the hexafluorophosphate salts were the most effective reagents for reaction with a variety of nucleophiles rather than the iodide or tetrafluoroborate salts.
1.2.4 Reactivity of Carbamoylimidazolium Hexafluorophosphate Salt

A total of eight carbamoylimidazolium hexafluorophosphate salts were synthesized. They were reacted with eight different nucleophiles including primary amine, secondary amines, an aniline, a phenol, and a carboxylic acid (Table 1.5). For the ureas, purification was achieved through a simple acidic workup with 1 M HCl. The carbamate was purified through an acidic and basic wash, followed by column chromatography with ethyl acetate and hexanes. The amides were also purified through a simple acid and basic workup. The hexafluorophosphate salts reacted well with primary and secondary amines, often with yields over 85%. Reactivity with N-methylaniline, 2-naphthol and benzoic acid were generally good, but with a few inconsistencies. The symmetric urea 8b consistently had low yields, which is unexpected as the other ureas generated from the starting salt 5b had very high yields. The N-phenyl piperazine derived salt 5h is not as soluble in dichloromethane, which may explain its lower yields.
Table 1.5: Synthesis of ureas 7 and 8, carbamates 9 and amides 10 from carbamoylimidazolium hexafluorophosphate salts and amines, aniline, phenol and carboxylic acid respectively.

<table>
<thead>
<tr>
<th>Carbamoylimidazolium</th>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;f&lt;/sup&gt; (%)</th>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;f&lt;/sup&gt; (%)</th>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;f&lt;/sup&gt; (%)</th>
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<td>5A</td>
<td>7a</td>
<td>82</td>
<td>7i</td>
<td>66</td>
<td>7q</td>
<td>quant</td>
</tr>
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<td>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</td>
<td>Entry&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</td>
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<td>Entry&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Yield&lt;sup&gt;f&lt;/sup&gt; (%)</td>
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<sup>a</sup> Imidazolium salt 5 (1.0 equiv), amine (1.0 equiv) and triethylamine (1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> were stirred at rt for 24 h
<sup>b</sup> Imidazolium salt 5 (1.0 equiv), L-Pro-OBn·HCl (1.0 equiv) and triethylamine (2.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> were stirred at rt for 24 h
<sup>c</sup> Aniline (1.0 equiv) and nBuLi (1.5 equiv) in THF were stirred at rt for 1 h. Imidazolium salt 5 (1.2 equiv) was then added, and stirred for 18 h
<sup>d</sup> Imidazolium salt 5 (1.0 equiv), phenol (1.0 equiv) and triethylamine (1.0 equiv) in acetonitrile were refluxed for 16 h.
<sup>e</sup> Imidazolium salt 5 (1.0 equiv), carboxylic acid (1.0 equiv) and triethylamine (1.0 equiv) were stirred at rt for 16 h.
<sup>f</sup> Isolated yields without flash chromatography
<sup>g</sup> Isolated yields
1.3 Conclusion

From the reactivity study and the stability study, the carbamoylimidazolium hexafluorophosphate salts were shown to be the best ‘off the shelf’ reagents and retain the best reactivity profile relative to their iodide and tetrafluoroborate salt analogs. Their convenience as solid weighable powders over the oily and sticky foamy iodide salts, outweighs the slight loss in yield during salt metathesis. From Rivka Taylor’s stability studies, the hexafluorophosphate salts are consistently higher in stability over the iodide salts, and are considerably less hygroscopic. They able to react with amines, anilines, phenols and carboxylic acids to synthesize ureas, carbamates and amides, often without the need for chromatographic purification. Their facile synthesis, high reactivity and stability allows them to be desirable and convenient disubstituted carbamoyl transfer reagents.
Chapter 2  Lewis Acid Catalyzed Approach to Sterically Hindered Esterification and Lactonization

2.1  Introduction

2.1.1 Accessing Intermolecular Esterification and Macrolactonization

Intermolecular esterification has been studied extensively. However, coupling between sterically hindered substrates remains a challenge. Macrolactonization also suffers from the slow rate of ester formation, often forming polymeric or macrodiolide products. As such, new methods which allow easy access to esters and lactones in high yields are much sought after and of fundamental importance in organic synthesis.\(^{17}\)

2.1.2 Approach

Previous studies have shown that transition metal Lewis acid catalysts, such as \(\text{Sc(OTf)}_3\) have enabled the coupling of sterically hindered alcohols with acids in 10-20% catalyst loading.\(^{13, 14}\) Tertiary alcohols, generally, had lower yields (68-76%) compared to the >90% yields of less hindered alcohols. We aimed to investigate the use of a catalytic amount of transition metal Lewis acids with the anhydride reagent, 2-methyl-6-nitrobenzoic anhydride (MNBA) \(^{12, 14, 15}\) which has proven to be efficient in esterification through activation of the acid moiety, with sterically encumbered alcohols \(^{14}\) and amino acids \(^{11}\) (Scheme 2.1). The addition of a metal based Lewis acid is proposed to further increase the reactivity of the mixed anhydride \(^{13}\) by increasing the electrophilicity of the acid moiety, thereby increasing the rate and yield of the desired reaction pathway. Of interest are the lanthanide triflates, which have been shown to activate carbonyl compounds in a variety of reactions.\(^{16}\)
Scheme 2.1: Hypothesized MNBA and Lewis Acid Catalyzed Ester Formation

Lewis acid activation would similarly increase the reactivity of the seco acid 16 for lactonization. The chelation effect may be amplified in seco acids containing multiple carbonyl moieties, arranging the substrate such that the alcohol would be in proximity of the activated acid.\textsuperscript{17-20}

Scheme 2.2: Lewis acid catalyzed lactonization through chelation

This methodology may provide effective functionalization of sterically hindered alcohols and access to difficult nine to fifteen membered macrocyclic cores, which are present in many natural products.\textsuperscript{17} A macrocyclic core of interest is enterobactin (Fig 2.1): a 12 membered ring consisting of three esters.

There have been many syntheses of enterobactin as it is the strongest siderophore known and has antibacterial properties.\textsuperscript{21} More recent syntheses by Meyer achieved a one-step synthesis of the trityl-protected enterobactin trilactone scaffold using an organotin template with over 50% yield from serine units.\textsuperscript{22} However, when the trilactone core was prepared through a single lactonization from the seco acid, cyclization occurred in just over 40% yield.\textsuperscript{24} We were interested in a pathway in which the seco acid is first synthesized and then
using the above metal catalyzed lactonization to close the ring. This pathway would also allow for alternative functionalization of the trilactone core compared to Meyer’s organotin template method.\textsuperscript{21, 22}

2.2 Results and Discussion

2.2.1 Intermolecular Coupling

The hindered coupling of $N$-Boc-L-leucine hydrate 19 and a slight excess of tertiary alcohol 18 was attempted with and without catalyst dysprosium triflate. Both conditions produced no product. This was attributed to the water molecules from the leucine hydrate destroying any mixed anhydride formation.

\begin{center}
\textbf{Scheme 2.3}: Attempted coupling of benzyl 2-hydroxy-2-methylpropanoate and $N$-boc-L-leucine hydrate.
\end{center}

The next attempt was to couple the even more hindered $N$-boc-phenylalanine to the same alcohol using similar conditions, but with 1.5 eq. of MNBA instead of 3 eq. Again, coupled product did not form. These conditions were repeated using 3 eq. of MNBA and pre-stirring all reagents except the alcohol to ensure acid activation. However, none of these conditions were able to give product formation, most likely as a result of the hindered substrates used.

The last attempt at intermolecular coupling was with the one of the least hindered amino acids, $N$-boc-alanine, and the same alcohol. A variety of conditions were used as listed in Table 2.1. None of these reactions produced the desired ester. Only the MNBA activated acid was
obtained. After the neat reactions (4-7) at 40 °C did not yield any product, we determined that the tertiary alcohol may be too hindered to couple.

**Table 2.1**: Conditions used for attempted coupling of N-boc-alanine and benzyl 2-hydroxy-2-methylpropanoate. All reactions were pre-stirred for 15 minutes without the alcohol to ensure acid activation.

\[
\text{Alcohol} \quad \text{Acid} \quad \text{DMAP} \quad i\text{Pr}_2\text{NEt} \quad \text{MNBA} \quad \text{EDC}^a \quad \text{Dy(O Tf)}_3 \quad \text{CH}_2\text{Cl}_2 \quad \text{Temp} \quad (°C)
\]

<table>
<thead>
<tr>
<th>Alcohol (eq.)</th>
<th>Acid (eq.)</th>
<th>DMAP (eq.)</th>
<th>iPr\textsubscript{2}NEt (eq.)</th>
<th>MNBA (eq.)</th>
<th>EDC\textsuperscript{a} (eq.)</th>
<th>Dy(O Tf)\textsubscript{3} (eq.)</th>
<th>CH\textsubscript{2}Cl\textsubscript{2} (mL)</th>
<th>Temp (°C)</th>
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</tr>
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<td>4</td>
<td>4</td>
<td>40\textsuperscript{c}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide is coupling agent often used yield amide bonds
\textsuperscript{b} reactions were run for 24 h
\textsuperscript{c} reactions were monitored by TLC for up to 48 h
2.2.2 Lactonization

The proposed synthetic pathway to the seco-acid 23 for the trilactone core of enterobactin is outlined below.

Scheme 2.4: Synthesis of serine precursors from free serine

Scheme 2.5: Synthesis of seco-acid 23.

Unfortunately, the synthesis of the seco-acid was not completed as we could not obtain the first coupled product 22 in a satisfactory yield. Many conditions were attempted, such as varying the equivalents of the acid and alcohol, as well as the concentration and the use of different coupling reagents (Table 3.2). All reactions were run for 24 h at 40 °C. The use of coupling reagents 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and CDI were unsuccessful. We hypothesized that the t-butyl group on 21 may have reduced the accessibility of the acid; however,
coupling with cinnamyl alcohol was performed successfully, ensuring that the acid was not too hindered for coupling.

After column chromatography for the MNBA reactions (Table 2.2, entries 1-3), an eliminated product 24 was observed, albeit in very low yields (4%). It was unclear whether this product was formed before coupling e.g., with excess Hunig’s base, or after (excess Hunig’s base or during workup). A control reaction was run without the acid to determine whether Hunig’s base was reacting with alcohol 20 before coupling (Table 2.2, entry 6). Eliminated product 24 was not formed under these conditions. Thus, we theorize that the coupled product must be reacting with the base. The number of equivalents of Hunig’s base were lowered and a milder aqueous basic solution was used during work-up. Product 22 was formed in a 1:4 ratio to eliminated product 24, but yields were unsatisfactory (12%).

Table 2.2: Conditions for the coupling of Z-Ser-(O'Bu)-OH and Z-Ser-OPac

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<th>Entry</th>
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<th>eq. 20</th>
<th>eq. MNBA</th>
<th>eq. iPr2NEt</th>
<th>eq. DMAP</th>
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<td>2</td>
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<td>1.5</td>
<td>2</td>
<td>1</td>
<td>1 mL</td>
</tr>
<tr>
<td></td>
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<td>eq. 20</td>
<td>eq. EDCb</td>
<td>eq. DMAP</td>
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<tr>
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<td>1 mL</td>
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<td></td>
<td>eq. 21</td>
<td>eq. 20</td>
<td>eq. MNBA</td>
<td>eq. iPr₂NEt</td>
<td>eq. DMAP</td>
<td>CH₂Cl₂ (mL)</td>
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<td>1.5</td>
<td>1.2</td>
<td>1</td>
<td>2 mL</td>
</tr>
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</table>

ᵃ reaction yielded product 22

2.3 Conclusion

Due to time constraints, these projects were inconclusive as to the efficacy of lanthanide triflates during intermolecular esterification and lactonization reactions with MNBA. Further investigation into intermolecular esterification could involve the use of more hindered secondary alcohols, or a more “alcohol activation” or “double activation” type approach in which the increased nucleophilicity of the alcohol could overcome its steric hindrance and attack into an activated acid. There are still many coupling agents that could be used to make the seco-acid for the lactonization investigation. The less sterically hindered methyl alcohol protected serine (Z-Ser-(OMe)-OH) may provide more facile coupling.
Chapter 3  Development of \( t \)-Amyl Protection as an Alternative to \( t \)-Butyl Protection

3.1  Introduction

3.1.1  Current \( t \)-Butyl Protection Method

\( t \)-Butyl ethers and esters are good protecting groups for alcohols and carboxylic acids. \( t \)-Butyl ethers are stable under most conditions except strong acid. \( t \)-Butyl esters are more sensitive and will hydrolyze in moderate acidic and basic conditions.\(^{28}\) A common method for mmol scale \( t \)-butyl protection is to use isobutylene. A catalytic amount of concentrated sulfuric acid is added to create a \( t \)-butyl cation which can then be trapped by an alcohol or a carboxylic acid (Scheme 3.1).

\[
\begin{align*}
\text{H} & \xrightarrow{\text{O}} \text{SO}_{3} \text{H} \\
\text{HO} & \xrightarrow{\text{R}} \text{H} & \text{HO} & \xrightarrow{\text{R}} \text{H} \\
\text{R} & \xrightarrow{\text{O}^+} \text{SO}_{3} \text{H} & \text{R} & \xrightarrow{\text{O}^+} \text{SO}_{3} \text{H} \\
\end{align*}
\]

Scheme 3.1: Mechanism of \( t \)-butyl alcohol (\( R = \text{alkyl} \)) or acid (\( R = \text{aldehyde} \)) protection via isobutylene gas and a catalytic amount of acid.

The issue with this method is that isobutylene is a flammable gas. It is difficult to replicate the molar equivalents of isobutylene when bubbling it through a reaction vessel, and a large excess is often required. It is also very hard to obtain in Canada, only available in large quantities and shipping costs are extremely high. As such, a liquid form alternative to isobutylene, such as 2-methyl-2-butene, would provide similar functional group protection, facile shipping and storage, and commercial availability.
3.1.2 Previous Work with \textit{t}-Amyl Protection Method.

On scale \textit{t}-amylation, or more generally, hydroalkoxylat ion of alkenes, is widely used in the oil and fuel processing industry.\textsuperscript{30} Generally, the \textit{t}-amylation is achieved by adding 2-methyl-2-butene, the alcohol and a catalytic amount of strong acid to a high pressure and high temperature reactor. Temperatures for these types of reactions range from 60 °C\textsuperscript{32} to 343 °C\textsuperscript{30c} and pressures up to 1.2 MPa.\textsuperscript{33}

For smaller scales in laboratory settings, Figadère \textit{et al.} reported that the \textit{t}-amyl group could be installed on alcohols with 2-methyl-1-butene and a stoichiometric about of BF$_3$·OEt$_2$ in 24 h at room temperature.\textsuperscript{34} However, we could not reproduce these results.

3.1.3 Approach

We viewed 2-methyl-2-butene as an alternative to isobutylene. We used \textit{t}-butyl protection protocols and replaced isobutylene with 2-methyl-2-butene. As industrial conditions used high heat and pressure, we decided to also pursue similar conditions with microwave flash heating.\textsuperscript{35} A common method for \textit{t}-butyl ether and ester protection is to bubble isobutylene gas through a solution of dichloromethane or ether, the alcohol and a catalytic amount of strong acid (concentrated sulfuric acid) at room temperature.\textsuperscript{36} Methods involving BF$_3$·OEt$_2$ often required low temperatures,\textsuperscript{37} which is incompatible with microwave flash heating.

3.2 Results and Discussion

Two conditions were used at room temperature to \textit{t}-amylation protect benzyl alcohol, one with concentrated sulfuric acid in dichloromethane, and the other with \textit{p}-toluenesulfonic acid in dioxane at room temperature for 24 h (Scheme 3.2). The first reaction yielded polymerized product, whereas the second reaction yielded less than one percent, by NMR, of what seemed to be the \textit{t}-amyloprotected product.
Scheme 3.2: Attempted $t$-amyl protections with benzyl alcohol at room temperature

Scheme 3.3: Attempted $t$-amyl protection with 3-phenyl-1-propanol
3-Phenyl-1-propanol was also tested under the same conditions. No conversion was seen by NMR with \( p \)-toluenesulfonic acid. This reaction was then attempted using microwave irradiation at 100 °C for 10 min. By NMR, there was no \( t \)-amyol conversion and starting material was recovered after workup. Hence, \( p \)-toluenesulfonic acid was deemed to be too weak to act as a catalyst for \( t \)-amyol protection. Polymerization was observed when 3-phenyl-1-propanol was reacted with a catalytic amount of sulfuric acid for 24 h. These results were consistent when the same reaction conditions were subjected to microwave irradiation at 100 °C for 10 min.

A variety of microwave and room temperature conditions were attempted for both \( t \)-amyol ether protection of octanol and 3-phenyl-1-propanol (Table 3.1, Table 3.2) and \( t \)-amyol ester protection of hydrocinnamic acid and malonic acid (Table 3.3, Table 3.4) using concentrated sulfuric acid. By NMR, all reactions seemed to result in 2-methyl-2-butene polymerization with complete recovery of starting material. Temperatures were reduced in attempts to slow polymerization. Column chromatography yielded recovered starting material and polymerized substrates.

**Table 3.1**: Conditions used for attempted \( t \)-amyol ether protection of 1-octanol.
Table 3.2: Conditions used for attempted \( t \)-butyl ether protection of 3-phenyl-1-propanol.

<table>
<thead>
<tr>
<th>Solvent (1 mL)</th>
<th>2-methyl-2-butene (eq)</th>
<th>Acid</th>
<th>( \mu \text{wave} ) (min)</th>
<th>( \mu \text{wave} ) (°C)</th>
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<td>H(_2)SO(_4)\ (cat)</td>
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<td>100</td>
</tr>
<tr>
<td>THF</td>
<td>5</td>
<td>H(_2)SO(_4)\ (cat)</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>THF</td>
<td>5</td>
<td>H(_2)SO(_4)\ (cat)</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>THF</td>
<td>5</td>
<td>CH(_3)COOH\ (cat)</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>THF</td>
<td>5</td>
<td>CH(_3)COOH\ (1 eq)</td>
<td>10</td>
<td>100</td>
</tr>
</tbody>
</table>

Four control reactions were set up to compare the reactivity of isobutylene and 2-methyl-2-butene in terms of polymerization. Procedurally, isobutylene \( t \)-butyl ether protection was reproduced: isobutylene was bubbled through a solution of malonic acid in a minimal amount of ether and a catalytic amount of sulfuric acid, then sealed (Scheme 3.4). After 16 h, the diprotected product 25 was extracted. No polymerized product was seen by NMR.

Scheme 3.4: \( t \)-butyl protection of malonic acid
Table 3.3: Conditions used for attempted t-butyl ester protection of hydrocinnamic acid.

<table>
<thead>
<tr>
<th>Acid (eq)</th>
<th>2-methyl-2-butene (eq)</th>
<th>Acid</th>
<th>Solvent</th>
<th>t (h)</th>
<th>T (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>H₂SO₄ cat.</td>
<td>neat</td>
<td>12</td>
<td>RT</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>H₂SO₄ cat.</td>
<td>ether</td>
<td>6</td>
<td>RT</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>H₂SO₄ cat.</td>
<td>ether</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>H₂SO₄ cat.</td>
<td>ether</td>
<td>6</td>
<td>-78°C</td>
</tr>
</tbody>
</table>

Table 3.4: Conditions used for attempted t-butyl ester protection of malonic acid.

<table>
<thead>
<tr>
<th>Acid (eq)</th>
<th>2-methyl-2-butene (eq)</th>
<th>Acid</th>
<th>Solvent</th>
<th>t (h)</th>
<th>T (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>H₂SO₄ cat.</td>
<td>neat</td>
<td>12</td>
<td>RT</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>H₂SO₄ cat.</td>
<td>ether</td>
<td>6</td>
<td>RT</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>H₂SO₄ cat.</td>
<td>ether</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>H₂SO₄ cat.</td>
<td>ether</td>
<td>6</td>
<td>-78°C</td>
</tr>
</tbody>
</table>

2-Methyl-2-butene was tested under the same conditions: A catalytic amount of sulfuric acid was added to a solution of 2-methyl-2-butene, ether and malonic acid. Polymerization was observed after 30 min.
Polymerization of isobutylene was tested with a catalytic amount of sulfuric acid: Isobutylene was bubbled through a solution of ether and a catalytic amount of sulfuric acid, then sealed. After 24 h, no polymerized product was seen. Likewise, polymerization of 2-methyl-2-butene was tested with a catalytic amount of sulfuric acid: A catalytic amount of sulfuric acid was added to a solution of 2-methyl-2-butene and ether. After 4 h, polymerization occurred to give a brown, viscous oil.

It was concluded that 2-methyl-2-butene does undergo polymerization with a catalytic amount of sulfuric acid. To avoid polymerization, more dilute conditions were attempted, and 2-methyl-2-butene was added dropwise to the solution slowly. Polymerization was not observed in these reactions, however, there was also no product formation. By NMR, no conversion occurred after 3 days. These conditions were repeated under microwave irradiation; however there was still no conversion (Table 3.5).

Table 3.5: Microwave conditions used in attempts to t-amyl ester protect hydrocinnamic acid.

<table>
<thead>
<tr>
<th>Solvent (THF)</th>
<th>2-methyl-2-butene (eq)</th>
<th>Acid</th>
<th>μwave (min)</th>
<th>μwave (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mL</td>
<td>1</td>
<td>H₂SO₄ (cat)</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>1 mL</td>
<td>1.5</td>
<td>H₂SO₄ (cat)</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>1.5 mL</td>
<td>2</td>
<td>H₂SO₄ (cat)</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>2 mL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3</td>
<td>H₂SO₄ (cat)</td>
<td>30</td>
<td>80</td>
</tr>
<tr>
<td>2 mL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3</td>
<td>H₂SO₄ (cat)</td>
<td>30</td>
<td>100</td>
</tr>
</tbody>
</table>

<sup>a</sup>Solvent was increased for optimal microwave radiation absorption.
3.3 Conclusion

Polymerization of 2-methyl-2-butene seemed unusual. It was suggested that polymerization of isobutylene should be faster than polymerization of 2-methyl-2-butene, as the extra methyl group would deter polymerization. On the other hand, the extra methylene group does stabilize the formed cation. Polymerization may also be more of a concentration related issue, as more dilute conditions showed no polymerization, but also no product formation. Further investigations into increased pressure and increased temperature reactions may force the reaction to proceed; however such harsh conditions are not as suitable for the sensitive substrates of organic synthesis.
References


Appendices

Experimental

All commercial reagents were used as received (Aldrich, Fischer Scientific Ltd., AAPPTec or VWR). All glassware was flame-dried and allowed to cool under a stream of dry nitrogen unless otherwise specified. All reactions were carried out under an atmosphere of nitrogen. Melting points are uncorrected. $^1$H and $^{13}$C NMR were recorded at 400 and 300 MHz on a Varian Unity 400 spectrometer. Proton chemical shifts were internally referenced to the residual proton resonance in CDCl$_3$ (δ 7.26) or DMSO-$d_6$ (δ 2.50). Carbon chemical shifts were internally referenced to the deuterated solvent signals in CDCl$_3$ (δ 77.2) or DMSO-$d_6$ (δ 39.5). FT-IR spectra were recorded on a Perkin-Elmer Spectrum 100 instrument equipped with a 10-bounce diamond/ZnSe ATR accessory as thin films from CH$_2$Cl$_2$. High resolution mass spectra (HRMS) were obtained on a VS 70-250S (double focusing) mass spectrometer. Bond Elute Reservoirs with a hydrophobic frit were obtained from Varian for liquid-liquid extraction.

General procedure for the preparation of carbamoyl imidazoles 3a-3h

To a cooled (ice-water bath) suspension of $N,N'$-carbonyldiimidazole (CDI, 7.1 g, 44 mmol) in CH$_2$Cl$_2$ (30.0 mL) was added amine (40 mmol) dropwise. After the solids dissolved, giving a slightly yellowish clear solution, the water bath was removed, and the mixed stirred for a further 24 h. The reaction was diluted with CH$_2$Cl$_2$ (20 mL) and washed with water (2 x 50 mL). The organic layer was dried (Na$_2$SO$_4$), filtered and concentrated in vacuo to yield the product carbamoyl imidazole 3a-3h.

Compounds 3a-3g are known compounds and spectral data obtained were consistent with previous spectra.

(1H-Imidazol-1-yl)(4-phenylpiperazin-1-yl)methanone (3h)

3h was obtained in an 80% yield. Yellow solid; mp = 92-94 °C; R$_f$ = 0.58 (EtOAc); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.91 (s, 1H), 7.30 (dd, $J$ = 8.5, 7.5 Hz, 2H), 7.24 (t, $J$ = 1.5 Hz, 1H), 7.12 (s, 1H), 6.97 – 6.94 (m, 2H), 6.93 (d, $J$ = 1.0 Hz, 1H), 3.78 (t, $J$ = 10.0, 4H), 3.26 (t, $J$ = 10.0, 4H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 150.5, 136.9, 129.9, 129.4, 121.1, 117.9, 116.9, 49.5, 46.4;
IR (thin film) 3133, 2812, 1677 cm\(^{-1}\); HRMS (DART) \(m/z\): [M + H]\(^+\) for C\(_{14}\)H\(_{17}\)N\(_4\)O calcd 257.1402; found 257.1.

**General procedure for the preparation of carbamoylimidazolium iodide salts 4a-4f**

To a solution of carbamoylimidazole 3 (8.00 mmol) in acetonitrile (15 mL) was added methyl iodide (2.0 mL, 32.0 mmol). The solution was stirred at rt for 24 h. The solvent was removed under vacuum to yield the carbamoylimidazolium iodide salts 4a-4f.

**General procedure for the preparation of carbamoylimidazolium iodide salts 4g-4h**

To a solution of carbamoylimidazole 3 (8.00 mmol) in dichloromethane (15 mL) was added methyl iodide (2.0 mL, 32.0 mmol). The solution was stirred at rt for 24 h. The solvent was removed under vacuum to yield the carbamoylimidazolium iodide salt 4g-4h.

Compounds 4a-4g are known compounds and spectral data obtained were consistent with previous spectra.

**3-Methyl-1-(4-phenylpiperazine-1-carbonyl)-1H-imidazol-3-ium iodide (4h)**

4h was obtained in a quantitative yield. Orange foamy oil; \(R_f\): 0.00 (2:8 MeOH:EtOAc); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 9.57 (s, 1H), 8.04 (t, \(J = 2.0\) Hz, 2H), 7.85 (t, \(J = 2.0\) Hz, 1H), 7.24 (dd, \(J = 9.0, 7.5\) Hz, 2H), 6.96 (dd, \(J = 9.0, 1.0\) Hz, 2H), 6.82 (tt, \(J = 7.0, 1.0\) Hz, 1H), 3.91 (s, 3H), 3.71 – 3.61 (m, 4H), 3.27 (t, \(J = 5.5\) Hz, 4H). \(^1\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 150.7, 147.2, 138.2, 129.5, 124.1, 121.5, 120.0, 116.4, 48.2, 46.2, 36.8. IR (neat) 3054, 2813, 1721. HRMS (ESI) \(m/z\): [M – I]\(^+\) for C\(_{15}\)H\(_{19}\)N\(_4\)O calcd 271.15; found 271.1546.

**General procedure for the preparation of carbamoylimidazolium hexafluorophosphate salts 5a-5f**

To a solution of 4 (4.00 mmol) in methanol (20 mL) was added ammonium hexafluorophosphate (1.3 g, 8.00 mmol) while stirring. A white precipitate formed immediately. The product was
collected by filtration and washed with small portions of cold methanol (-78°C) and dried under vacuum to yield the carbamoylimidazolium hexafluorophosphate salt.

3-Methyl-1-(morpholine-4-carbonyl)-1H-imidazol-3-ium hexafluorophosphate (5a)

5a was obtained in a 86% yield. White powder; mp = 138-140 °C; Rf: 0.00 (2:8 MeOH:EtOAc); ¹H NMR (300 MHz, DMSO-d₆) δ 9.53 (s, 1H), 7.99 (t, J = 2.0 Hz, 1H), 7.83 (t, J = 2.0 Hz, 1H), 3.88 (s, 3H), 3.67 (t, J = 5.0 Hz, 4H), 3.50 (t, J = 5.0 Hz, 4H); ¹³C NMR (101 MHz, DMSO-d₆) δ 147.2, 138.1, 124.1, 121.4, 65.8, 46.8, 36.7; IR (neat) 3115, 2862, 1718, 1437 cm⁻¹; HRMS (ESI) m/z: [M – PF₆]⁺ for C₉H₁₄N₂O₂ calcd 196.1081; found 196.1079.

3-Methyl-1-(methyl(phenyl)carbamoyl)-1H-imidazol-3-ium hexafluorophosphate (5b)

5b was obtained in a quantitative yield. Yellow powder; mp = 130-132 °C. Rf: 0.00 (2:8 MeOH:EtOAc); ¹H NMR (300 MHz, DMSO-d₆) δ 9.43 (s, 1H), 7.55 (t, J = 2.0 Hz, 1H), 7.42 (m, 4H), 7.40 – 7.31 (m, 2H), 3.81 (s, 3H), 3.45 (s, 3H). ¹³C NMR (100 MHz, DMSO-d₆) δ 146.9, 141.6, 138.7, 130.4, 128.8, 126.7, 123.6, 121.7, 40.5, 36.7; IR (neat) 3313, 1420 cm⁻¹; HRMS (ESI) m/z: [M – PF₆]⁺ for C₁₂H₁₄N₃O calcd 216.1131; found 216.1130.

1-(Indoline-1-carbonyl)-3-methyl-1H-imidazol-3-ium hexafluorophosphate (5c)

5c was obtained in an 85% yield. Yellow powder; mp = 152-153 °C; Rf: 0.00 (2:8 MeOH:EtOAc); ¹H NMR (400 MHz, DMSO-d₆) δ 9.69 (s, 1H), 8.17 (t, J = 2.0 Hz, 1H), 7.87 (t, J = 2.0 Hz, 1H), 7.77 (m, 1H), 7.40 – 7.35 (m, 1H), 7.35 – 7.27 (m, 1H), 7.19 (m, 1H), 4.20 (t, J = 8.5 Hz, 2H), 3.94 (s, 3H), 3.23 – 3.13 (t, J = 8.5 Hz, 2H). ¹³C NMR (100 MHz, DMSO-d₆) δ 145.0, 141.1, 138.2, 133.6, 127.9, 126.2, 125.9, 124.0, 121.3, 117.1, 51.0, 36.8, 28.2; IR (neat) 3157, 3096, 1711 cm⁻¹; HRMS (ESI) m/z: [M – PF₆]⁺ for C₁₃H₁₄N₃O calcd 228.1131; found 228.1132.

3-Methyl-1-(1,2,3,4-tetrahydroquinoline-1-carbonyl)-1H-imidazol-3-ium hexafluorophosphate (5e).

5e was obtained in an 85% yield. White powder; mp = 144-145 °C; Rf: 0.00 (2:8 MeOH:EtOAc); ¹H NMR (300 MHz, DMSO-d₆) δ 9.55 (s, 1H), 7.71 (t, J = 2.0 Hz, 1H), 7.67 (s, 1H), 7.32 – 7.25
(m, 1H), 7.20 – 7.06 (m, 3H), 3.87 (s, 3H), 3.79 (t, J = 6.5 Hz, 2H), 2.83 (t, J = 6.5 Hz, 2H), 2.04 – 1.93 (tt, J = 6.5, 6.5, 2H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 146.9, 138.9, 136.5, 132.8, 129.5, 126.8, 126.5, 123.8, 123.7, 121.8, 47.1, 36.8, 26.2, 23.4; IR (neat) 3169, 2945, 1731 cm$^{-1}$; HRMS (ESI) m/z: [M – PF$_6$]$^+$ for C$_{14}$H$_{16}$N$_3$O calcd 242.1288; found 242.1296.

General procedure for the preparation of carbamoylimidazolium hexafluorophosphate salts 5g-5h

To a solution of 4 (8.00 mmol) in methanol (5 mL) was added ammonium hexafluorophosphate (2.6 g, 16.00 mmol) while stirring. A yellow precipitate formed immediately and the reaction mixture was stirred at rt for 30 min. The solution was then stored at -20 °C overnight. The product was collected by filtration and washed with small portions of cold methanol (0 °C) and dried under vacuum to yield the carbamoylimidazolium hexafluorophosphate salt 5g-5h.

1-(Methoxy(methyl)carbamoyl)-3-methyl-1H-imidazol-3-ium hexafluorophosphate (5g).

5g was obtained in a 85% yield. White solid; mp = 101-104 °C; R$_f$: 0.00 (2:8 MeOH:EtOAc); $^1$H NMR (600 MHz, DMSO-$d_6$) δ 9.68 (s, 1H), 8.08 (t, J = 2.0 Hz, 1H), 7.84 (t, J = 2.0 Hz, 1H), 3.94 (s, 3H), 3.75 (s, 3H), 3.40 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 145.9, 139.2, 123.8, 122.1, 62.4, 36.8, 35.2; IR (neat) 3171, 1730 cm$^{-1}$; HRMS (ESI) m/z: [M – PF$_6$]$^+$ for C$_7$H$_{12}$N$_3$O$_2$ calcd 170.0924; found 170.0948.

3-Methyl-1-(4-phenylpiperazine-1-carbonyl)-1H-imidazol-3-ium hexafluorophosphate (5h)

5h was obtained in a 96% yield. Yellow solid; mp = 127-130 °C; R$_f$: 0.00 (2:8 MeOH:EtOAc); $^1$H NMR (300 MHz, DMSO-$d_6$) δ 9.56 (s, 1H), 8.03 (t, J = 2.0 Hz, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.30 – 7.18 (m, 2H), 7.02 – 6.93 (m, 2H), 6.88 – 6.78 (m, 1H), 3.90 (s, 3H), 3.65 (t, J = 5.0 Hz, 4H), 3.27 (t, J = 5.0 Hz, 4H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 150.7, 147.2, 138.2, 129.5, 124.1, 121.5, 120.0, 116.4, 48.2, 46.2, 36.8. IR (neat) 3171, 1735 cm$^{-1}$; HRMS (ESI) m/z: [M – PF$_6$]$^+$ for C$_{15}$H$_{19}$N$_4$O calcd 271.1553; found 271.1544.
General procedure for the preparation of carbamoylimidazolium tetrafluoroborate salts

6a-6b

To a solution of 3 (4.00 mmol) in methanol (20 mL) was added ammonium tetrafluoroborate (0.832 g, 8.00 mmol) while stirring. A white precipitate formed immediately. The product was collected by filtration and washed with small portions of cold methanol (-78 °C) and dried under vacuum to yield the carbamoylimidazolium tetrafluoroborate salt.

3-Methyl-1-(morpholine-4-carbonyl)-1H-imidazol-3-ium hexafluorophosphate (6a)

6a was obtained in a 98% yield. White powder; mp = 128-131 °C; Rf: 0.00 (2:8 MeOH:EtOAc); 
1H NMR (300 MHz, DMSO-d6) δ 9.53 (s, 1H), 7.99 (t, J = 2.0 Hz, 1H), 7.83 (t, J = 2.0 Hz, 1H), 3.88 (s, 3H), 3.67 (t, J = 5.0 Hz, 4H), 3.50 (t, J = 5.0 Hz, 4H); 13C NMR (101 MHz, DMSO-d6) δ 147.2, 138.1, 124.1, 121.4, 65.8, 46.8, 36.7; IR (neat) 3115, 2862, 1718, 1437 cm⁻¹; HRMS (ESI) m/z: [M – PF6]⁺ for C9H14N3O2 calcld 196.1081; found 196.1079.

3-Methyl-1-(methyl(phenyl)carbamoyl)-1H-imidazol-3-ium hexafluorophosphate (6b)

6b was obtained in a 59% yield. White powder; mp = 135-136 °C; Rf: 0.00 (2:8 MeOH:EtOAc); 
1H NMR (300 MHz, DMSO-d6) δ 9.43 (s, 1H), 7.55 (t, J = 2.0 Hz, 1H), 7.42 (m, 4H), 7.40 – 7.31 (m, 2H), 3.81 (s, 3H), 3.45 (s, 3H). 13C NMR (100 MHz, DMSO-d6) δ 146.9, 141.6, 138.7, 130.4, 128.8, 126.7, 123.6, 121.7, 40.5, 36.7; IR (neat) 3313, 1420 cm⁻¹; HRMS (ESI) m/z: [M – PF6]⁺ for C12H14N3O calcld 216.1131; found 216.1130.

General procedure for the preparation of ureas 7

To a solution of 5 (0.25 mmol) in CH2Cl2 (2.5 mL) was added triethylamine (0.40 mL, 0.25 mmol) and primary or secondary amine (0.25 mmol). The solution was stirred at rt for 24 h, then diluted with CH2Cl2 (5 mL) and 1 M HCl solution (5 mL). The mixture was shaken and poured into a 70 mL Bond Elute Reservoir (Varian). The organic layer was collected while the aqueous layer was left in the reservoir. The organic phase was washed again with 1M HCl and poured into the Bond Elute Reservoir. The product 7 was obtained after concentration.
Benzyl (morpholine-4-carbonyl)-L-prolinate (7i)

7i was obtained in a 66% yield. Clear oil; Rf: 0.39 (EtOAc); 1H NMR (400Hz, CDCl3) δ 7.35 (m, 5H), 5.24-5.08 (t, J = 7.5 Hz, 1H), 3.70-3.59 (m, 4H), 3.50-3.45 (m, 2H), 3.39-3.33 (m, 2H), 3.26-3.20 (m, 2H), 2.31-2.26 (m, 1H), 2.04-1.96 (m, 1H), 1.91-1.81 (m, 2H); 13C NMR (101 MHz, CDCl3) δ 161.8, 135.8, 128.5, 128.2, 128.1, 66.6, 66.5, 49.6, 46.5, 44.0, 29.5, 25.4; IR (neat) 3389, 2859, 1744, 1628 cm⁻¹; HRMS (ESI) m/z: [M + H]+ for C₁₇H₂₃N₂O₄ calcd 319.1659; found 319.1645.

Benzyl (indoline-1-carbonyl)-L-prolinate (7k)

7k was obtained in a 94% yield. Orange oil; Rf: 0.69 (EtOAc); 1H NMR (400 MHz, CDCl3) δ 7.35 – 7.31 (m, 5H), 7.25 – 7.21 (m, 1H), 7.17 – 7.07 (m, 2H), 6.88 (td, J = 7.5, 1.0 Hz, 1H), 5.17 (q, J = 12.5 Hz, 2H), 4.74 (dd, J = 8.0, 6.5 Hz, 1H), 4.02 – 3.85 (m, 2H), 3.66 – 3.57 (m, 1H), 3.47 (ddd, J = 10.5, 7.0, 4.0 Hz, 1H), 3.15 – 2.94 (m, 2H), 2.34 (d, J = 8.0 Hz, 1H), 2.09 – 1.85 (m, 3H); 13C NMR (75 MHz, CDCl3) δ 172.8, 143.9, 135.7, 131.3, 128.5, 128.2, 128.1, 127.0, 124.6, 121.8, 114.9, 66.8, 59.9, 49.9, 49.0, 29.6, 28.5, 25.2; IR (neat) 3033, 2957, 2888, 1740, 1643 cm⁻¹; HRMS (ESI) m/z: [M + H]+ for C₂₁H₂₃N₂O₃ calcd 351.1709; found 351.1702.

Benzyl (1,2,3,4-tetrahydroquinoline-1-carbonyl)-L-prolinate (7m)

7m was obtained in a 94% yield. Orange oil; Rf: 0.66 (EtOAc); 1H NMR (400 MHz, CDCl3) δ 7.41 – 7.27 (m, 6H), 7.10 – 7.01 (m, 2H), 6.90 (m, J = 7.5, 1.0 Hz, 1H), 5.25 – 5.15 (m, 2H), 4.66 (t, J = 7.5 Hz, 1H), 3.79 (dt, J = 15.5, 6.5 Hz, 1H), 3.43 (ddd, J = 15.5, 8.0, 5.5 Hz, 1H), 3.10 (m, J = 25.0 Hz, 2H), 2.82 – 2.59 (m, 2H), 2.27 (d, J = 7.0 Hz, 1H), 2.10 – 1.95 (m, 1H), 1.93 – 1.71 (m, 4H); 13C NMR (75 MHz, CDCl3) δ 172.8, 140.1, 135.7, 129.4, 128.6, 128.4, 128.2, 128.1, 126.5, 122.3, 121.1, 66.8, 60.1, 49.2, 44.6, 29.7, 26.8, 25.3, 23.9; IR (thin film) 3032, 2947, 2877, 1740, 1636 cm⁻¹; HRMS (ESI) m/z: [M + H]+ for C₂₂H₂₅N₂O₃ calcd 365.1865; found 365.1861.

Benzyl(methoxy(methyl)carbamoyl)-L-prolinate (7o)

7o was obtained in a 95% yield. Yellow oil; Rf: 0.62 (EtOAc); 1H NMR (400Hz, CDCl3) δ 7.36-7.30 (m, 5H), 5.21-5.10 (m, 2H), 4.50-4.45 (dd, J = 8.0, 4.0 Hz, 1H), 3.64-3.60 (t, J = 6.5, 6.5 Hz, 2H), 3.53 (s, 3H), 3.02 (s, 3H), 2.26-2.13 (m, 1H), 2.01-1.85 (m, 3H); 13C NMR (100 MHz,
CDCl$_3$ δ 172.8, 160.0, 135.8, 128.5, 128.2, 128.1, 66.6, 60.6, 59.2, 48.6, 35.2, 29.8, 24.2; IR (neat) 2977, 1742, 1645 cm$^{-1}$; HRMS (ESI) $m/z$: [M + H]$^+$ for C$_{15}$H$_{21}$N$_2$O$_4$ calcd 293.1501; found 293.1496.

**Benzyl (4-phenylpiperazine-1-carbonyl)-L-prolinate (7p)**

7p was obtained in a 77% yield. Yellow oil; R$_f$: 0.69 (EtOAc); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.38 – 7.26 (m, 5H), 6.94 – 6.85 (m, 5H), 5.24 – 5.07 (m, 2H), 4.62 (t, $J$ = 7.5 Hz, 1H), 3.59 – 3.46 (m, 4H), 3.45 – 3.34 (m, 2H), 3.14 (m, 4H), 2.28 (s, 1H), 2.03 (d, $J$ = 14.0 Hz, 1H), 1.87 (t, $J$ = 7.0 Hz, 2H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 172.9, 161.8, 151.2, 135.8, 129.1, 128.5, 128.2, 128.1, 120.1, 116.3, 66.6, 60.2, 49.8, 49.1, 46.0, 29.5, 25.4; IR (neat) 3063, 2997, 1734, 1641 cm$^{-1}$; HRMS (ESI) $m/z$: [M + H]$^+$ for C$_{23}$H$_{28}$N$_3$O$_3$ calcd 394.2131; found 394.2125.

**N-Methoxy-N-methyl-3,4-dihydroisoquinoline-2(1H)-carboxamide (7w)**

7w was obtained in a 90% yield. Yellow oil; R$_f$: 0.50 (EtOAc); $^1$H NMR (400Hz, CDCl$_3$) δ 7.22 – 7.10 (m, 4H), 4.60 (s, 1H), 3.70 – 3.66 (t, $J$ = 6.0, 6.0 Hz, 2H), 3.62 (s, 3H), 3.00 (3H, s), 2.92 – 2.88 (t, $J$ = 6.0, 6.0, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 162.2, 134.8, 133.6, 133.6, 128.6, 126.5, 126.2, 58.8, 47.6, 43.6, 36.2, 28.9; IR (neat) 2929, 1651 cm$^{-1}$; HRMS (ESI) $m/z$: [M + H]$^+$ for C$_{13}$H$_{20}$N$_3$O$_2$ calcd 250.1556; found 250.1558.

**Indolin-1-yl(4-phenylpiperazin-1-yl)methanone (7aa)**

7aa was obtained in a 97% yield. Orange foamy solid; R$_f$: 0.71 (EtOAc); mp = 118-120 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.38 (s, 4H), 7.24 – 7.12 (m, 2H), 7.12 – 7.03 (m, 2H), 6.93 (td, $J$ = 7.5, 1.0 Hz, 1H), 3.97 (t, $J$ = 8.0 Hz, 2H), 3.75 (s, 4H), 3.35 (s, 4H), 3.05 (t, $J$ = 8.0 Hz, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 159.0, 157.4, 143.3, 131.7, 129.6, 127.2, 125.1, 122.1, 118.2, 113.1, 105.0, 50.3, 45.5, 45.4, 27.8; IR (neat) 2891, 1654 cm$^{-1}$; HRMS (ESI) $m/z$: [M + H]$^+$ for C$_{19}$H$_{22}$N$_3$O calcd 308.1763; found 308.1758.

**Benzyl (1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-L-prolinate (7dd)**

7dd was obtained in a quantitative yield. Yellow oil; R$_f$: 0.69 (EtOAc); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.48 – 7.26 (m, 5H), 7.23 – 7.03 (m, 4H), 5.32 – 5.01 (m, 2H), 4.64 (t, $J$ = 7.0 Hz, 1H), 4.47 (d, $J$ = 3.0 Hz, 2H), 3.75 – 3.39 (m, 4H), 3.00 – 2.73 (m, 1H), 2.28 (dt, $J$ = 8.0, 5.5 Hz, 1H),
$2.17 \text{ (s, 1H)}, 2.09 – 1.78 \text{ (m, 3H)}$; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 173.1, 162.1, 135.8, 134.7, 133.8, 128.7, 128.5, 128.1, 128.0, 126.4, 126.4, 126.1, 66.6, 60.3, 49.6, 48.0, 44.1, 29.5, 28.9, 25.4; IR (neat) 3032, 2953, 1740, 1631 cm$^{-1}$; HRMS (ESI) $m/z$: [M + H]$^+$ for C$_{22}$H$_{25}$N$_2$O$_3$ calcld 365.1865; found 365.1861.

$N$-Methoxy-$N$-methyl-4-phenylpiperazine-1-carboxamide (7ee)

7ee was obtained in a 74% yield. Red oil; R$_f$: 0.61 (EtOAc); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36-7.16 (m, 5H), 3.85 (s, 4H), 3.61 (s, 3H), 3.29 (s, 4H), 3.03 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 161.7, 151.1, 129.2, 120.3, 116.4, 58.7, 49.4, 45.5, 36.1; IR (thin film) 3177, 2965, 1660 cm$^{-1}$; HRMS (ESI) $m/z$: [M + H]$^+$ for C$_{12}$H$_{17}$N$_2$O$_2$ calcld 221.1290; found 221.1285.

General procedure for the preparation of ureas 8

To a solution of amine (0.25 mmol) in THF (6 mL) was added $n$-BuLi (0.19 mL, 2.0 M, 0.38 mmol), and the reaction was stirred for 1 h. Then the carbamoylimidazolium salt 5 (0.30 mmol) was added. The mixture was stirred at rt for 18 h, then diluted with CH$_2$Cl$_2$ (10 mL) and washed with 0.2 M HCl (15 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 20 mL) and brine (15 mL), the organic layer dried (Na$_2$SO$_4$), filtered and concentrated in vacuo to yield ureas 8.

General procedure for the preparation of carbamates 9

To a solution of carbamoylimidazolium salt 5 (0.25 mmol) in acetonitrile (6 mL) was added the phenol (0.25 mmol) and triethylamine (0.25 mmol). The reaction was refluxed overnight. The solvent was removed under vacuum and the residue was dissolved in CH$_2$Cl$_2$ (15 mL) and 0.1 M HCl (15 mL) was added. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 15 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL). The organic layer was dried (Na$_2$SO$_4$), filtered and concentrated in vacuo to yield carbamate 9.
Naphthalen-2-yl indoline-1-carboxylate (9b)

9b was obtained in an 85% yield. White solid; mp = 175-176 °C; Rf: 0.78 (EtOAc); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.95 – 7.79 (m, 3H), 7.67 (s, 1H), 7.48 (ddd, J = 8.5, 6.0, 2.0 Hz, 2H), 7.36 (d, J = 9.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.03 (t, J = 7.5 Hz, 2H), 4.30 (d, J = 9.0 Hz, 2H), 3.25 (d, J = 9.0 Hz, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 151.4, 148.4, 142.2, 133.8, 131.4, 131.0, 129.4, 127.8, 127.7, 127.6, 126.5, 125.6, 124.7, 123.2, 121.4, 118.6, 115.2, 47.9, 27.7; IR (neat) 3058, 2918, 2851, 1703 cm$^{-1}$; HRMS (DART) m/z: [M + H]$^+$ for C$_{19}$H$_{16}$NO$_2$ calcd 290.1181; found 290.1173.

Naphthalen-2-yl 3,4-dihydroisoquinoline-2-(1H)-carboxylate (9f)

9f was obtained in a 66% yield. Beige solid; mp = 130-132 °C; Rf: 0.77 (EtOAc); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.87 – 7.77 (m, 3H), 7.60 (d, J = 2.5 Hz, 1H), 7.20 (dd, J = 13.5, 4.0 Hz, 4H), 4.90 (s, 1H), 4.75 (d, J = 6.0 Hz, 1H), 3.06 – 2.90 (dd, J = 6.0, 6.0 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 154.0, 149.0, 134.5, 133.8, 133.2, 131.2, 129.2, 128.9, 127.7, 127.6, 126.7, 126.4, 126.2, 125.4, 121.6, 118.5, 46.3, 42.4, 29.1; IR (neat) 2925, 2850, 1708 cm$^{-1}$; IR (neat) 3058, 2918, 2851, 1703 cm$^{-1}$; HRMS (DART) m/z: [M + H]$^+$ for C$_{20}$H$_{18}$NO$_2$ calcd 304.1338; found 304.1336.

Naphthalen-2-yl methoxy(methyl)carbamate (9g)

9g was obtained in a 71% yield. Beige solid; mp = 56-58 °C; Rf: 0.71 (EtOAc); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.89 – 7.67 (m, 3H), 7.62 (d, J = 2.5 Hz, 1H), 7.52 – 7.36 (m, 2H), 7.30 (dd, J = 9.0, 2.5 Hz, 1H), 3.85 (s, 3H), 3.33 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 155.2, 148.5, 133.7, 131.4, 129.3, 127.6, 126.5, 121.2, 118.7, 61.8, 35.7; IR (neat) 3062, 2939, 2824, 1718 cm$^{-1}$; HRMS (DART) m/z: [M + H]$^+$ for C$_{13}$H$_{14}$NO$_3$ calcd 232.0974; found 232.0965.

Naphthalen-2-yl 4-phenylpiperazine-1-carboxylate (9h)

9h was obtained in a 38% yield. White solid; mp = 185-187 °C; Rf: 0.80 (EtOAc); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.87 – 7.77 (m, 3H), 7.60 (d, J = 2.5 Hz, 1H), 7.52 – 7.42 (m, 2H), 7.35 – 7.27
(m, 3H), 7.01 – 6.90 (m, 3H), 3.83 (d, J = 47.0 Hz, 4H), 3.27 (s, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 153.8, 151.1, 148.9, 133.8, 131.2, 129.2, 129.2, 127.7, 127.5, 126.4, 125.4, 121.4, 120.6, 118.5, 116.8, 49.4, 29.9; IR (neat) 3068, 2920, 2845, 1716 cm$^{-1}$; HRMS (ESI) m/z: [M + H]$^+$ for C$_{21}$H$_{21}$N$_2$O$_2$ calcd 333.1603; found 333.1589.

### Preparation of ester 22

To a solution of the acid 21 (0.30 g, 1 mmol) in CH$_2$Cl$_2$ (1.5 mL) was added iPr$_2$NEt (0.17 g, 1 mmol), MNBA (0.41 g, 1.2 mmol) and DMAP (0.12 g, 1 mmol). The solution was stirred at rt for 15 min. The alcohol 20 (0.35 g, 1.2 mmol) was dissolved in CH$_2$Cl$_2$ (2 mL) and added dropwise to the solution. The solution was refluxed for 24 h then diluted with 10 mL of CH$_2$Cl$_2$, washed with 1 M HCl (15 mL), 0.2 M NaOH (15 mL), brine (15 mL) and dried with Na$_2$SO$_4$. It was then filtered, concentrated in vacuo to yield a residue in which the product 22 was obtained after flash column chromatography (1:1 EtOAc:Hexanes).

2-(((Benzyloxy)carbonyl)amino)-3-oxo-3-(2-oxo-2-phenylethoxy)propyl N-((benzyloxy)carbonyl)-O-(tert-butyl)serinate (22)

22 was obtained in a 12% yield. White solid; mp = 100-101 °C; R$_f$: 0.31 (1:1 Hexanes:EtOAc); $^1$H NMR (300 MHz, Chloroform-$d$) δ 7.96 – 7.86 (m, 2H), 7.70 – 7.62 (m, 1H), 7.56 – 7.46 (m, 2H), 7.42 – 7.26 (m, 10H), 5.79 (d, J = 9.0 Hz, 2H), 5.72 (d, J = 16.5 Hz, 1H), 5.32 (d, J = 16.5 Hz, 1H), 5.14 (s, 2H), 4.69 – 4.56 (m, 1H), 4.33 (d, J = 12.0 Hz, 2H), 3.90 (d, J = 12.0 Hz, 1H), 3.63 (s, 2H), 1.69 – 1.53 (m, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 155.2, 148.5, 133.7, 131.4, 129.3, 127.6, 126.5, 125.6, 121.2, 118.7, 61.8, 35.7; IR (thin film) 3329, 3230, 3184, 3057, 1751, 1687 cm$^{-1}$; HRMS (ESI) m/z: [M + H]$^+$ for C$_{34}$H$_{38}$N$_2$O$_{10}$ calcd 635.2569; found 635.2564.
Spectral Data

![Chemical Structure](image)

3h
5a
7i
$7m$
7ee