Novel and Versatile Münchnones Cycloadditions for the
Synthesis of Functionalised Pyrroles

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Abstract

Münchnones represent versatile intermediates for the synthesis of pyrroles through 1,3-dipolar cycloaddition reactions with dipolarophiles. Due to the poor stability of münchnones and their challenging isolation, a range of novel stabilized münchnones have been successfully prepared. These were used efficiently in cycloaddition reactions with alkynes to access pyrroles in a highly regioselective manner. Furthermore, the acyl substituted pyrroles were found to be useful for further functionalization. However, one limitation of this method is that alkyl acetylenes provided products in low yields. The relative reactivities of aryl and alkyl acetylenes with münchnones has been studied through a series of competition reactions.

A regioselective synthesis of pyrroles has also been developed using enamines as dipolarophiles. A range of enamine substrates were prepared and subjected to cycloaddition conditions, showing that both aliphatic and aromatic enamines could be tolerated in the reaction. Furthermore, the product pyrrole regiochemistry was found to be controlled by the enamine substitution pattern. Additionally, the cycloaddition strategy was tolerant of cyclic enamines, providing the pyrrole products in comparable yield by a cycloaddition/ring opening process.

Finally, an amine-catalyzed variant of the pyrrole synthesis has been developed using aldehydes as substrates.
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### Abbreviations

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<thead>
<tr>
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<th>Definition</th>
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<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
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<tr>
<td>Ar</td>
<td>aryl group</td>
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<td>benzyl</td>
</tr>
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<td>’Bu</td>
<td>n-butyl</td>
</tr>
<tr>
<td>’Bu</td>
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</tr>
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<td>Boc</td>
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<tr>
<td>DMAD</td>
<td>dimethyl acetylenedicarboxylate</td>
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<tr>
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<td>1,5-diazabicyclo[4.3.0]non-5-ene</td>
</tr>
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<td>DCC</td>
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</tr>
<tr>
<td>DIPC</td>
<td>N,N'-diisopropylcarbodiimide</td>
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<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>dba</td>
<td>Trans, trans-dibenzyldieneacetone</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>EDC</td>
<td>1-ethyl-3-(3-dimethylaminopropyl)carbodiimi</td>
</tr>
<tr>
<td>EWG</td>
<td>electron-withdrawing group</td>
</tr>
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<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
<td>-----------</td>
</tr>
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</tr>
<tr>
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<td>et alia</td>
</tr>
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</tr>
<tr>
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<td>enantiomeric excess</td>
</tr>
<tr>
<td>FTIR</td>
<td>Fourier-Transform Infrared Spectroscopy</td>
</tr>
<tr>
<td>FMO</td>
<td>Frontier Molecular Orbital Theory</td>
</tr>
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<td>g</td>
<td>gram</td>
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<td>HPLC</td>
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<tr>
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<td>hours</td>
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<tr>
<td>LUMO</td>
<td>Lowest Unoccupied Molecular Orbital</td>
</tr>
<tr>
<td>L&lt;sub&gt;n&lt;/sub&gt;</td>
<td>Ligand</td>
</tr>
<tr>
<td>LG</td>
<td>Leaving group</td>
</tr>
<tr>
<td>LC-MS</td>
<td>Liquid chromatography-mass spectrometry</td>
</tr>
<tr>
<td>Min</td>
<td>minutes</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MHz</td>
<td>Mega Hertz</td>
</tr>
<tr>
<td>Nu</td>
<td>nucleophile</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>NOE/nOe</td>
<td>Nuclear overhauser effect</td>
</tr>
<tr>
<td>OTBS</td>
<td>tert-butyldimethylsilyl ethers</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>iPr</td>
<td>iso-propyl</td>
</tr>
<tr>
<td>RT or rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>TFAA</td>
<td>Trifluoroacetic anhydride</td>
</tr>
<tr>
<td>Tf</td>
<td>Trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Tol</td>
<td>toluene</td>
</tr>
<tr>
<td>TOF ES</td>
<td>Time of Flight Electrospray</td>
</tr>
<tr>
<td>UV</td>
<td>Ultra violet</td>
</tr>
</tbody>
</table>
Chapter I. Introduction

Part 1: Mesoionic compounds and pyroles.

1. Pyroles

Pyrroles are five-membered heterocyclic compounds which are found in a wide variety of biologically relevant molecules including pharmaceuticals, natural, and non-natural products.\(^1\)\(^-\)\(^2\) For example, the drug Atorvastatin (Lipitor) which contains a densely substituted pyrrole core, is prescribed to reduce cholesterol levels and is one of the best-selling drugs in history. In addition, Storniamide marine alkaloids are isolated from a sponge Cliona sp and show interesting antibacterial activity (Figure I-1).\(^3\)

![Atorvastatin and Storniamide](image)

Figure I.1: Some natural and non-natural pyrrole therapeutics.

Because of the broad utility of pyrroles, the development of different methods for their synthesis has been an important topic over the last several decades. Classical approaches for the synthesis of pyrroles have been largely based on condensation reactions including the Paal-Knorr,\(^4\)\(^-\)\(^6\) Knorr\(^7\)\(^-\)\(^{12}\) and Hantzsch\(^13\)\(^-\)\(^{16}\) reactions (Scheme I.1).
However, an alternative approach for the synthesis of pyrroles in a simple and single step involves the [3+2] cycloaddition reactions of 1,3-dipole containing mesoionic heterocycles (münchnones) with assorted dipolarophiles (e.g. alkenes or alkynes) (Scheme I.2).}

Scheme I.2: Pyrroles from münchenones and dipolarophiles.

2. Mesoionic heterocycles

1,3-Dipolar cycloaddition reactions have attracted much attention from organic chemists ever since they were described more than one hundred years ago. They allow access to a range of 5-membered ring heterocyclic products in an atom economical way, under mild conditions.

A range of dipolar compounds are available. Among these, there are mesoionic compounds, which have been found to function as useful synthetic intermediates for
the synthesis of many heterocyclic compounds. Scheme I.3 shows some prominent classes of these mesoionic heterocycles.\textsuperscript{20}

\begin{center}
\begin{tikzpicture}
\node [below] at (0,0) {münchnones};
\node [below] at (1.5,0) {thiomünchnones};
\node [below] at (3,0) {sydnones};
\end{tikzpicture}
\end{center}

\textbf{Scheme I.3: Examples of mesoionic heterocycles.}

These mesoionic compounds can be represented by a five-membered mesoionic structure in which the positive charge is delocalised over the ring system while the negative charge is localised mainly on the exocyclic oxygen atom, and they cannot be drawn as a single resonance structure (Scheme I.4).

\begin{center}
\begin{tikzpicture}
\node [below] at (0,0) {Z = O, S};
\node [below] at (1.5,0) {X = C, N};
\end{tikzpicture}
\end{center}

\textbf{Scheme I.4: Commonly accepted mesoionic structures.}

The main focus in this introductory chapter will be to describe the chemistry of some mesoionic heterocycles and their development and applications in 1,3-dipolar cycloaddition reactions, which can yield a variety of useful aromatic products.
2.1. Münchnones

Münchnones (1,3-oxazolium-5-olates) are one of the most heavily studied classes of mesoionic compounds, and they are synthetically valuable. This is due to their reactivity in 1,3-dipolar cycloaddition reactions for the formation of a broad range of useful products and pharmacologically relevant molecules including pyrroles and imidazoles.\textsuperscript{21-24} Interestingly, münchenones are named after their city of discovery in honour of Münich, Germany, where they were first formulated by Hüisgen in 1964.\textsuperscript{22} Indeed, this style of nomenclature has been commonly applied to mesoionic compounds; Earl named sydnones in light of their discovery in Sydney, Australia. Moreover, phospha-münchnones and imino-münchnones were investigated in Montreal and named “Montrealones”.\textsuperscript{25-26} Hüisgen found that münchenones react smoothly with a wide range of double and triple bond-containing dipolarophiles such as alkynes and alkenes (Scheme I.5). These cycloadditions can furnish pyrrole derivatives in good yields.\textsuperscript{27} These processes therefore confirmed that münchenones provide a direct method to access useful molecules of value to biological chemistry, pharmaceuticals and natural products.\textsuperscript{28}

![Scheme I.5: 1,3-Dipolar cycloaddition of münchenones.](image)

Indeed, the application of münchenones in the synthesis of pyrrole-based pharmaceuticals such as atorvastain analogs has been reported. For instance, in 2008, Park et al.\textsuperscript{29} employed acetic anhydride to dehydrate the N-acylamino acid 1
and generate münchnone 2 in situ. Subsequent trapping of this intermediate with alkyne 3 generated atorvastain analogues in good yield (Scheme I.6).

Scheme I.6: Synthesis of atorvastains through a münchnone intermediate.

In 2015, Gribble et al.\textsuperscript{30} also employed münchnone intermediate 2 to obtain atorvastatin by a route comprising a cycloaddition reaction with alkyne 4; their synthetic procedures are shown in scheme I.7.
2.2. Isomünchnones

Isomünchnones (1,3-oxazolium-4-olates) have found utility as substrates for a number of cycloaddition processes. Isomünchnones are often unstable and so are commonly generated in situ and trapped by a dipolarophile. The metal-mediated reaction of diazo imides is one of the simplest methods to access these compounds.\textsuperscript{31} Thus, 5 smoothly forms isomünchnone 6 which can be intercepted with DMAD to provide furan 7 in high yield after the loss of methyl isocyanate (Scheme I.8).
Scheme I.8: Furan synthesis through isomünchnone cycloadditions.

A common application of isomünchnones is in their use as precursors to key intermediates in the synthesis of natural products. For instance, Pumiliotoxin C, which is a toxin isolated from the skin of poison dart frogs was generated by the intramolecular dipolar cycloaddition of an isomünchnone. The key steps in this synthesis are the formation of an oxabicyclic intermediate 8, which is formed via the intramolecular dipolar cycloaddition of an imidosulfoxide to generate the cis decahydroquinoline system of Pumiliotoxin C (Scheme I.9).³²
2.3. Münchnone imines

The replacement of the keto functional group of a münchnone (C=O) with an imine (C=NR) provides a new class of mesoionic 1,3-dipole substrates commonly referred to as a münchnone imines (Figure I.2).

![Scheme I.9: Synthesis of pumiliotoxin C.](image)

Münchnone imines can be obtained by a multi-component coupling process comprising the reaction of acid chlorides, isocyanides and imines\textsuperscript{33} (Figure I.3).
Thus, the treatment of 9 with isocyanide provides intermediate 10, which then undergoes deprotonation to form the product münchnone imine (Scheme I.10).

Scheme I.10: Synthesis of münchnone imines.

Münchnone imines display similar reactivity to münchnones and they can also undergo 1,3-dipolar cycloaddition reactions to provide pyrroles. For example, N-acylated münchnone imine 11 has been reported to be an isolable and stable compound. Treatment of this compound with DMAD led to pyrrole 12 in good yield (Scheme I.11).34

Scheme I.11: 1,3-Dipolar cycloaddition of N-acylated münchnone imines.
Similar to the münchnone imines, other mesoionic heterocycle derivatives were synthesised. For example, exchanging the oxygen atom in the oxazole ring of a münchnone imine to a sulfur or nitrogen atom led to new families of mesoionic compounds; 1,3-thiazolium 5-imines in the case of sulfur and 1,3-imidazolium 5-imines in the case of nitrogen (Figure I.4).

Figure I.4: Design of alternative mesoionic heterocycles.

These substrates can be generated in a similar fashion to münchnone imines. Thus, 1,3-thiazolium 5-imines 13 are prepared from chlorothioformate, isocyanides and imines. However, these mesoionic compounds are difficult to isolate and are typically generated and reacted in situ. They were reacted with dipolarophiles and underwent the expected cycloaddition in a similar fashion to classic 1,3-dipoles to generate pyrroles 14 (Scheme I.12).
1,3-Imidazolium 5-imines 15 also undergo 1,3-dipolar cycloadditions with electron poor dipolarophiles (e.g., DMAD) to provide pyrroles. However, only one example of this type of reaction has been reported, which provided the corresponding pyrrole in only moderate yield (Scheme I.13).37,38

![Scheme I.13: Pyrrole formation from 1,3-imidazolium 5-imines.](image)

### 2.4. Phospha-Münchnones

As described in the previous section, other units can replace the keto functional group of münchnones (C=O). This can provide efficient syntheses of a number of münchnone derived products. Thus, replacement of the exocyclic C=O of münchnone by a PR₃ unit gave phospha-münchnones (Figure I.5).

![Figure I.5: Design of mesoionic structure.](image)
Using the same building blocks as employed in the synthesis of münchnone imines, phospha-münchnones can be generated by a three component coupling comprising imines, acid chlorides and a PR$_3$ reagent (Figure I.6).

![Diagram of the reaction](image)

**Figure I.6: Synthesis of phospha-münchnones.**

Phospha-münchnones can be generated in situ and trapped by dipolarophiles to generate a diverse variety of substituted heterocyclic products with total control of regioselectivity. The regioselectivity of these 1,3 dipolar cycloadditions are dependent upon the nature of PR$_3$ group employed. Thus, the phosphorous group (PR$_3$) creates a significant electronic bias across the dipole allowing control of the regioselectivity. For example, by using an alkyne as dipolarophile, a novel route to highly substituted pyrroles can be achieved (Scheme I.14).

![Scheme I.14: In situ synthesis of phosph-münchnones and subsequent pyrrole formation.](image)
Furthermore, imines can also be used as reactive dipolarophiles in phospha-münchnone cycloadditions, which in this case allows imidazoles 16 to be formed (Scheme I.15).40

\[
\begin{align*}
\text{Bn} & \quad \text{N} \\
p-Tol & \quad \text{H} \\
+ & \quad \text{PMP} \quad \text{Cl} \\
\rightarrow & \quad \text{Bn} \quad \text{N} \\
p-Tol & \quad \text{PMP} \\
\text{R}_3\text{P} \quad \text{O} \\
\text{PMP} = p-\text{MeOC}_6\text{H}_4 \\
\end{align*}
\]

Scheme I.15: Imidazole synthesis via phospha-münchnones.

In addition to the use of imines as dipolarophiles, nitrile-tethered imines 17 have been reported as dipolarophiles. Thus, in situ generation of phospha-münchnones provide polycyclic imidazoles 18 as a products via an intramolecular cycloaddition reaction pathway (Scheme I.16).40

\[
\begin{align*}
\text{NEt} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{17} & \quad + \\
\text{PhP(2-catechyl)} & \quad \text{Cl} \\
\rightarrow & \quad \text{Et} \\
(1.1 \text{ eq.}) & \quad \text{DBU} \quad \text{(2.0 eq.)} \\
\text{CDCl}_3 & \quad \text{R}_3\text{P} \quad \text{O} \\
\text{-R}_3\text{P}=\text{O} \\
\text{76\%} & \quad \text{18}
\end{align*}
\]

Scheme I.16: Synthesis of polycyclic imidazoles through an intramolecular cycloaddition reaction.
2.5. Thiomünchnones

Replacement of the N-substituent of a münchnone (NR) with a sulfur atom (S) provides mesoionic 1,3-dipoles called thiomünchnones (Figure I.7).

![Münchnones](image1)

![Thiomünchnones](image2)

**Figure I.7: Design of thiomünchnones.**

Only one report for the synthesis of (1,3-oxathiolium-5-olates) thiomünchnones has been reported, and this was carried out by Gribble et al.41 Thus, cyclodehydration of S-acylthioglycolic acid 19 provided 2,4-diphenylthiomünchnone 20, which underwent a tandem 1,3-dipolar cycloaddition with 1,5-cyclooctadiene 21 to afford sulfide product 22 in 32% yield (Scheme I.17).

![Synthesis Scheme](image3)

**Scheme I.17: Synthesis of (1,3-oxathiolium-5-olates) thiomünchnones and 1,3 dipolar cycloaddition.**
In addition, a sulfur analogue of thioisomünchnones 23 has been reported by Yoshii et al.\textsuperscript{42} Replacement of the exocyclic oxygen unit of thioisomunchnones to sulfur via 24 gave a new class of 1,3-dipole called 1,3-thiazolium-4-thiolates. These can undergo cycloadditions with DMAD to provide unexpectedly stable cycloadducts 25 (Scheme I.18).

![Scheme I.18: Sulfur analogues of thioisomünchnones](image)

3. Conclusion

To summarise, a number of mesoionic heterocycles have been developed. These compounds are important building blocks in the synthesis of useful molecules such as pyrroles. However, each of these mesoionic heterocycles has associated limitations such as multistep syntheses, precursor availability, and difficult isolation. We will focus on the chemistry of münchnones, as these important mesoionic reagents were the subject of the research program.
4. Project overview and aims

As a result of the importance of nitrogen containing heterocycles in industrial applications, the development of novel synthetic methodologies to access these products is an important development. One of the most important classes of five membered heterocycles is that of the pyrroles. Of the several methods available to prepare these in the laboratory, 1,3-dipolar cycloaddition reactions of münchnones with dipolarophiles has proven to be particularly useful.

A literature search has shown that current synthetic approaches to münchnones, and their 1,3-dipolar cycloaddition chemistry is currently limited. Unfortunately, a narrow substrate scope, low product yields and unpredictable regioselectivities are often encountered. Thus, we envisaged that accessing a class of stable and isolable münchnones could facilitate investigations into their cycloaddition reactions, in order to address these limitations. We envisaged that this would allow access to a library of novel small molecules based around the pyrrole core.

For this purpose, the initial aims in this project were to establish stabilized münchnones and to explore the potential of these compounds to furnish pyrroles. This was to be achieved through a one-pot cyclodehydration-C4 functionalisation sequence, followed by alkyne and alkene cycloadditions which could offer an effective and modular strategy for the rapid assembly of pyrroles. The regioselectivity of this method has not been studied. For that purpose, we set out to explore the scope of mesionic substrates that undergo this novel transformation, as well as the scope of dipolarophile cycloaddition reaction of stabilized münchnones. Moreover, we hoped to take advantage of the stabilizing groups, which are essential for isolation of the münchnones, showing how these could be further manipulated in the ensuing pyrrole products (Scheme I.19).
Although the reaction of münchnones with alkene dipolarophiles has been studied for many years, the investigation of enamines as synthetic equivalents for alkynes has not been reported. Since the selectivity in münchnone cycloadditions is typically under substrate control, we reasoned that the use of specific enamine regioisomers as dipolarophiles in münchnone cycloadditions might help control the pyrrole product regioselectivity. Finally, another important aspect of this project was to extend this transformation to enamine organocatalysis to achieve pyrrole synthesis with high levels of regiocontrol by means of a simple procedure.
Part 2: Chemistry of 1,3-oxazolium-5-oxides (münchnones).

1. General features of münchnones

Due to the dipolar nature of münchnones, there are various possible ways to describe these compounds. The general structures of münchnones are illustrated in Figure II.1.43

![Münchnone resonance structures.](image)

Figure II.1: Münchnone resonance structures.

Most münchnones are unstable when isolated and they are often used in situ.44 One particularly prominent decomposition pathway of münchnones is hydrolysis. When münchnones are exposed to water or alcohols, they can readily react and revert to the corresponding α-amino acid derivatives. Kawase et al.45 investigated this hydrolysis process and found that $^{18}$O-labeled münchnone 26 could be attacked by H$_2$O at the C5 position providing trifluoromethyl ketone hydrate 27 after 3 h at 60 °C (Scheme II.1).

![Scheme II.1: Hydrolysis of münchnones.](image)
Furthermore, there is evidence to suggest that münchnones are prone to exist in equilibrium with their valence tautomer form ketene 29. For example, in situ synthesis of münchnone by N-acylation of oxazole 28 with benzoyl chloride results in the formation of two pyrrole products 30 and 31 after trapping with DMAD (Scheme II.2).46

Scheme II.2: Tautomeric equilibrium of münchnones.

Münchnones normally bear substituents at nitrogen, however the chemistry of free NH-münchnones has also been exploited. For example, münchnones 32 with alkyl groups at the C2 and C4 positions add DMAD twice to afford pyroles 33 in high yields (Scheme II.3). The nucleophilic character of these münchnones is due to the presence of the alkyl groups. Indeed, replacing one of the alkyl groups by an aryl group such as 34 results in a decrease in the nucleophilicity of the nitrogen and only cycloaddition occurs in this case to provide pyrrole 35.47
Scheme II.3: The effect of substitution on NH-münchnone cycloaddition reactions.
2. General reactivity of münchnones

Münchnones have been exploited in the preparation of a variety of compounds such as bicyclic and heterocyclic products. They may react with heterocumulenes (A=B=C) to provide a valuable entry into münchnone analogues. They can also be exploited in the synthesis of important biologically active molecules. Nevertheless, münchnones are most commonly exploited in 1,3-dipolar cycloaddition reactions with alkenes and alkynes to afford pyrroles. The utility of these reactions and other examples of products accessible from münchnones are shown below.

Seven and six membered ring heterocycles have been accessed from münchnone chemistry. For instance, cyclopropanes 36 can be used as dipolarophiles to form 6-membered ring heterocycles 37 (Scheme II.4), and in an analogous fashion, cyclobutenes provide 7-membered-ring heterocycles 38 (Scheme II.5).48—51

![Scheme II.4: Cycloaddition of münchnones and cyclopropanes.](image-url)
Scheme II.5: Synthesis of 7-membered ring heterocycles from münchenones.

Another important class of heterocyclic product available via in situ synthesis of münchenones is imidazoles. For instance, imidazole 40 is formed from the cycloaddition of \(N\)-tosyl imines 39 with münchenones; the latter were generated in situ via palladium catalysis (Scheme II.6).\(^{52}\)
The use of N-benzenesulfonyl imines as dipolarophiles for münchnone cycloadditions also provides imidazoles in good yields. Thus, the cycloaddition of münchnones and imines delivered a direct synthesis of imidazole 41 (Scheme II.7).  

\[
\begin{array}{c}
\text{Ph} \overset{\text{Me}}{\text{N}} \overset{\text{Ph}}{\text{O}} \overset{\text{C}}{\text{O}} \overset{\text{N}}{\text{Ph}} \text{Ph} + \text{PhO}_2S^{-} \overset{\text{N}}{\text{H}} \overset{\text{Ph}}{\text{Ph}} \rightarrow \text{Ph} \overset{\text{N}}{\text{Me}} \overset{\text{Ph}}{\text{N}} \overset{\text{Me}}{\text{Ph}} \text{H} \overset{-\text{CO}_2}{\text{-PhSO}_2\text{H}} \\
\end{array}
\]

Scheme II.7: Münchnone/imine cycloaddition in imidazole synthesis.

1,3,4-Triazole 43 is formed by treatment of münchnone 42 with an excess of ethyl diazodicarboxylate, adding to the list of possible heterocycles which can be formed via versatile münchnone chemistry (Scheme II.8).

\[
\begin{array}{c}
\text{Ph} \overset{\text{Me}}{\text{N}} \overset{\text{Ph}}{\text{O}} \overset{\text{C}}{\text{O}} \overset{\text{N}}{\text{Ph}} \text{Ph} + \text{EtO}_2\text{C}^{-} \overset{\text{N}}{\text{N}} \overset{\text{CO}_2\text{Et}}{\text{H}} \rightarrow \text{Ph} \overset{\text{N}}{\text{Me}} \overset{\text{Ph}}{\text{N}} \overset{\text{Me}}{\text{Ph}} 87\% \text{ 43} + \text{EtO}_2\text{C}^{-} \overset{\text{N}}{\text{N}} \overset{\text{CO}_2\text{Et}}{\text{H}} \\
\end{array}
\]

Scheme II.8: 1,3,4-Triazole synthesis from münchnones and ethyl diazodicarboxylate.

Moreover, diazo compound 44 undergoes cycloaddition with münchnone 42 to form triazolium salt 45 in 47% yield (Scheme II.9).

\[
\begin{array}{c}
\text{Ph} \overset{\text{Me}}{\text{N}} \overset{\text{Ph}}{\text{O}} \overset{\text{C}}{\text{O}} \overset{\text{N}}{\text{Ph}} \text{Ph} + \text{O}_2\text{N}^{-} \overset{\text{N}}{\text{BF}_4^{-}} \rightarrow \text{Ph} \overset{\text{N}}{\text{Me}} \overset{\text{Ph}}{\text{N}} \overset{\text{Me}}{\text{Ph}} \text{H} \overset{-\text{CO}_2}{\text{-BF}_4^{-}} \\
\end{array}
\]

Scheme II.9: Triazolium salt synthesis via münchnone cycloaddition.
A similar protocol reported the use of carbon monoxide, acid chlorides and imines in 1,3-dipolar cycloadditions with múchnones. For example, in 2011 Arndtsen et al.\textsuperscript{56} developed an interesting approach to the synthesis conjugated polymers containing imidazoles \textbf{46} (Scheme II.10).

\begin{center}
\begin{tikzpicture}
\begin{scope}[scale=0.8]
\node at (0,0) [text=black] \textbf{Scheme II.10: Synthesis of conjugated polymers with imidazoles from polymeric múchnones.}
\end{scope}
\end{tikzpicture}
\end{center}

More recently, a synthesis of a conjugated polymer containing pyrroles \textbf{48} via 1,3-dipolar cycloaddition of polymeric múchnone \textbf{47} with dipolarophiles has also been reported by Arndtsen group (Scheme II.11).\textsuperscript{57}
Scheme II.11: Synthesis of polymeric pyrroles via polymeric münchnones.

The possible mechanism for the palladium-catalyst coupling route used to generate poly(1,3-dipoles) from acid chlorides, imines and carbon monoxide is shown in scheme II.12.

Scheme II.12: A potential transformation to polymers via münchnones.

A common strategy towards a new series of mesoionic compounds 50, 52 and 54 was devised that exploited münchnones as substrates, and these are represented in schemes II.13, II.14 and II.15, respectively. These compounds can
be synthesized through the cycloaddition reactions of münchnones with multiple bond dipolarophiles such as carbon disulfide\(^{58}\) (CS\(_2\)) \(^{49}\), isothiocyanates\(^{59}\) (S=\(\text{C}\)=NR) \(^{51}\) and carbonyl sulfide\(^{60,61}\) (S=\(\text{C}\)=O) \(^{53}\).

**Scheme II.13: Cycloaddition of münchnone and carbon disulfide.**

**Scheme II.14: Cycloaddition of münchnones and isothiocyanates.**
Scheme II.15: Cycloaddition of münchnones and carbonyl sulphide.

4-Trifluoroacetyl-1,3-oxazolium-5-olates 55 have been found to be a remarkably stable class of münchnones, and they can be readily isolated. These compounds appear to have unique properties and methods have emerged for their use in the synthesis of many different products.

In 2001, Kawase et al.\textsuperscript{62} reported an efficient route to seven membered trifluoromethylated heterocycles from münchnone 55. The reaction occurs via the initial attack of bidentate nucleophiles at the C-5 position of the münchnone ring. This led to cyclized products 56 and 57, respectively. However, the reaction with o-aminophenol resulted in a ring opened compound 58 (Scheme II.16).
In 2010, Kawase et al.\textsuperscript{63} found that 4-trifluoroacetyl münchnone 55 reacts with phosphorus ylides to give pyrroles 59 in good yields. Thus, nucleophilic attack of the ylide at the C-2 position of münchnone and subsequent elimination of carbon dioxide and triphenylphosphine oxide afforded the products in good yields (Scheme II.17).
In 2012, Kawase et al. described other routes to pyrroles from the same mesoionic compound 55. Reaction of 55 with sulfur ylides generated 3-alkyl(aryl)thio-4-trifluoromethyl pyrroles 60 (Scheme II.18).  

![Scheme II.17: Pyrrole formation from 4-trifluoroacetyl münchnones.](image)

Furthermore, Kawase in 2013, reported another use of münchnones 55 to form six-membered heterocyclic compounds. Thus, 6-trifluoromethyl-1,2,4-oxadiazin-6-ols 61 were obtained from the reaction of münchnone with hydroxylamine by the addition at C-2 (Scheme II.19).  

![Scheme II.18: Münchnone/sulfur ylide cycloadditions in pyrrole synthesis.](image)
Additionally, it was found that münchnone 55 could also generate pyrazinones in moderate to good yields by their reaction with tosyl methyl isocyanide in the presence of oxygen (Scheme II.20).  

\[
\begin{align*}
R^1 &= \text{Me, Ph, Bn} \\
R^2 &= \text{Me, }{^1}\text{Bu, Ph}
\end{align*}
\]

Scheme II.19: Reaction of münchnones with hydroxylamine.

A variety of heterocyclic scaffolds can be formed from münchnones by their cycloaddition with dipolarophiles. Bicyclic adducts can also be accessed from münchnones. It has been shown that when maleimide 62 is reacted twice with a münchnone, it forms isolable bicyclic adduct 63 with a 75% yield (Scheme II.21).  

\[
\begin{align*}
R^1 &= \text{Me, Ph, Bn, 4-MeOC}_6\text{H}_4 \\
R^2 &= \text{Me, Ph, 4-MeOC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4
\end{align*}
\]

Scheme II.20: Pyrazinone synthesis via münchnones.
Furthermore, stabilized münchnones bearing electron-withdrawing groups at the 4-position were prepared and their reactivity with arynes in cycloaddition reactions was studied. In 2014, Larock et al.\textsuperscript{68} reported that an initial cycloaddition between münchnone 64 and benzyne, generated from 65, provided two products at room temperature: isoindole 66 and bicyclic adduct 67 (Scheme II.22).

\textbf{Scheme II.21: Reaction of münchnones with \textit{N}-phenyl maleimide.}

\textbf{Scheme II.22: Cycloaddition reaction between münchnones and arynes.}

Attempts to optimize the reaction conditions to obtain the isoindole as the major product were unsuccessful. However, the bicyclic adduct was obtained as the
exclusive product when using an excess of benzyne, due to the high reactivity of the latter in the [4+2] cycloaddition reaction.

The mechanism of this process involves an initial [3+2] cycloaddition, followed by [4+2] cycloreversion with extrusion of CO₂ to afford the isoindole. The isoindole intermediate was found to be very reactive and underwent a cycloaddition with another equivalent of aryne to furnish bicyclic adduct 68 in a very good yield (Scheme II.23).

The intramolecular 1,3-dipolar cycloaddition process with dipolarophiles (alkenes or alkynes) have been developed for the synthesis of a variety of synthetic products. The first example of this process involved in situ formation of münchnone 70, (formed by heating alanine 69 with acetic anhydride) which underwent an intramolecular cycloaddition with the alkene to form cycloadduct 71 with the carbon dioxide unit still present in the product (Scheme II.24).
Sainsbury at al.\textsuperscript{71} described a method for the synthesis of tetracyclic products via an intramolecular cycloaddition with an activated internal alkyne to the münchnone intermediate. Treatment of 72 in acetic anhydride at 60-70 °C provided tetracyclic anhydride 73 in 37% yield. When isoquinoline 74 was used \((n=1)\), a slightly better yield of analogue 75 \((n=2)\) was found (Scheme II.25).

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\textbf{Scheme II.25: Synthesis of tetracyclic products via intramolecular münchnone cycloadditions.}};
\end{tikzpicture}
\end{center}

3. Conclusion

The useful reactivity of münchnones has motivated their use in the synthesis of many classes of heterocyclic compounds such as imidazoles, pyrazinones and pyrroles. Due to the easy availability of münchnones, the applications and utility of these dipoles in pyrrole synthesis still has great potential. We have therefore undertaken a study of their synthesis and applications, which will be discussed in the following chapter.
Chapter II. Synthesis of münchnones

1. Previous synthesis of münchnones

Typically, there are three main precursors for the synthesis of münchnones. Dehydration of amino acid derivatives to a ketene moiety is the most common route for their synthesis as shown in scheme III.1.

![Scheme III.1: Münchnone synthesis from amino acid derivatives.](image1)

Alternatively, oxazol-5-(4H)-ones (azlactones) 76 can be isomerized to NH-substituted münchnones, which may be transformed into other münchnones by N-quaternization with electrophiles followed by deprotonation as shown in scheme III.2.

![Scheme III.2: Münchnone synthesis from azlactones.](image2)

Finally, metal mediated routes to münchnones involve use of α-metalated amide precursors, which undergo carbonylation (Scheme III.3).
Examples of these three strategies will be illustrated in the following sections.

1.1. Synthesis of münchenones from amino acids

Traditionally, münchenones were synthesized by the cyclodehydration of $N$-alkyl amino acids using acid anhydrides (Scheme III.4).\textsuperscript{72} 

Hüisgen employed this method frequently, and it remains a popular approach to these heterocycles. However, alternative approaches are known and can also be used. In 1979, Potts et al.\textsuperscript{72} were the first to use dehydrating agents such as dicyclohexylcarbodiimide (DCC) to generate these mesoionic compounds. More recently, Heider and Anderson reported the use of $N$-ethyln$N'$-dimethyl aminopropyl carbodiimide (EDC) or SiCl$_4$.\textsuperscript{73} In the case of DCC, the cyclodehydration reaction forms urea by-products that can be very difficult to remove. In contrast, EDC generates a urea by-product that is water soluble and is therefore easily removed by extraction. These two newer cyclodehydration reactions are by far the most important alternative approaches to generate münchenones.
Since their discovery, a range of $N$-alkyl or $N$-aryl münchnones have been generated. However, many authors have reported that most of these 1,3-dipoles are too unstable to be isolated. Therefore, these münchnones can be reacted in situ with dipolarophiles. For example, symmetrical and unsymmetrical münchnones were prepared and reacted in situ with a range of dipolarophiles using $N,N'$-diisopropylcarbodiimide (DIPC) as shown in Scheme III.5.\textsuperscript{74}

\[
\begin{align*}
R^1 &= R^3 = \text{Me} \\
R^1 &= R^3 = \text{Ph} \\
R^1 &= \text{Ph, } R^3 = \text{Me} \\
R^1 &= \text{Me, } R^3 = \text{Ph} \\
R^2 &= \text{Me, Bn}
\end{align*}
\]

Scheme III.5: In situ synthesis of münchnones with DIPC.

Many synthetic routes have been developed towards more stable münchnone analogues. For instance, the effects of substitution on münchnone stability have been investigated. It was discovered that only in cases where münchnones contained aryl substituents at C2 and C4 positions, or when the C4 position contained an electron-withdrawing group, can these mesoionic compounds be isolated (Figure III.1).\textsuperscript{75}

\[
\begin{align*}
R^1, R^3 &= \text{Ar} \\
R^1 &= \text{COCF}_3, R^3 = \text{Ar or Alkyl} \\
R^2 &= \text{Me, Bn}
\end{align*}
\]

Figure III.1: Isolable münchnones.
In 1964, Singh et al.\textsuperscript{76} reported an efficient route to stable münchnones \textsuperscript{78}, by reacting \textit{N}-alkyl \textit{N}-acyl glycines \textsuperscript{77} with trifluoroacetic anhydride at room temperature (Scheme III.6).

\begin{center}
\textbf{Scheme III.6: Stabilized münchnones.}
\end{center}

A possible mechanism for these reactions is illustrated in scheme III.7. These reactions are initiated by attack of the carboxylic acid on the anhydride to form oxazolium ion as the intermediate \textsuperscript{79}. These intermediates have an unsubstituted C4 position, which can undergo acylation after being deprotonated by the trifluoroacetate to furnish the desired münchnone.
1.2. Synthesis of münchnones from isomerization of oxazol-5-(4\(H\))-ones

In addition to the cyclodehydration of amino acids, alternative strategies have been reported to access münchnones. Wilde et al.\textsuperscript{77} utilised an acylation and desilylation of 5-silyloxyoxazoles 80. Specifically, 5-silyloxy oxazoles react with acetyl chloride under basic conditions to provide münchnones 81 in a good yield (Scheme III.8).
Scheme III.8: Synthesis of $N$-Acyl münchnones.

Wilde et al.\textsuperscript{77} also reported an in situ synthesis of münchnone 83 using methyl triflate 82 (Scheme III.9). Thus, DMAD was used to trap the münchnone to give 39\% of pyrrole 84.

Scheme III.9: Synthesis of a $N$-methyl münchnone.

In a protocol similar to that reported by Wilde, Hershenson et al.\textsuperscript{78} observed the formation of münchnone 87 by use of an azalactone 85, which underwent $N$-alkylation followed by deprotonation by 2,6-di-tert-butylpyridine 86. Trapping of 87 with DMAD gave the corresponding pyrrole product in a good yield (Scheme III.10).

Scheme III.10: Formation of münchnones by use of azalactones.
1.3. Synthesis of münchnones from metal-mediated routes

A novel approach to münchnones involving the use of organometallic complexes has been devised that exploits the chemistry of Fischer chromium carbenes. In this reaction, exposure of the chromium complexes 88 to CO generates chromium bound ketene 89, which can cyclize to provide the isolated münchnone 90 (Scheme III.11)\(^7\).

![Scheme III.11: Generation of münchnones from N-acylaminochromium carbenes.]

Similarly, iron acyl complexes can be used to form münchnones. The reaction of sodium acyltetracarbonylferrate 91 with imidoyl chlorides 92 followed by cyclisation results in the production of these mesoionic compounds in moderate to good yields (Scheme III.12)\(^8\).

![Scheme III.12: Generation of münchnones from acyltetracarbonyl ferrates.]

The postulated mechanism is illustrated in scheme III.13, and involves initial displacement of the chloride from the imidoyl chloride 92 to provide 93 followed by
migration of the carbene complex. After CO insertion, the desired münchnone 90 was obtained.

More recently, Arndtsen et al.\textsuperscript{81} reported that münchnones could be synthesised by palladium-catalyzed multicomponent coupling of acid chlorides, imines and carbon monoxide. The latter formed pyrroles by trapping with alkynes in a 1,3-dipolar cycloaddition (Scheme III.14).
Scheme III.14: Palladium-catalyzed münchnone synthesis.

The mechanism of this reaction is believed to involve the generation of $N$-acyliminium salt 94. This is followed by oxidative addition to Pd(0) to give 95. CO insertion, followed by ketene formation results in equilibration to münchnone 90. Finally, the 1,3-dipolar cycloaddition between this münchnone and alkyne yields the desired pyrrole (Scheme III.15).
Scheme III.15: Mechanism for the synthesis of pyrroles via münchnones.
2. Substrate synthesis

Initial results and optimisation

As described previously, most reactions of münchnones require their employment in situ directly after formation. However, münchnones bearing an electron withdrawing group on the C4 position can be significantly more stable, allowing them to be isolated by routine techniques such as column chromatography. With this in mind, the purpose of this project was to generate and isolate 4-trifluoroacetylated münchnones by traditional methods from amino acid derivatives. Following literature procedures, our initial work aimed to access a small selection of \textit{N}-acyl amino acids. They were synthesised from the corresponding glycine with acetyl chloride. Acetylation of the amino acid in the presence of NaOH at room temperature for 30 minutes gave very good yields of glycine derivatives 96-99 after recrystallisation from ethanol. In case of \textit{N}-methyl amino acids 96 and \textit{N}-benzyl amino acids 98 a mixture of two rotamers obtained (Table III.1).

\[
\begin{align*}
\text{H} & \text{N} \rightarrow \text{COOH} \xrightarrow{\begin{array}{c}
\text{R}^2\text{COCl} \\
\text{NaOH:} \text{H}_2\text{O}
\end{array}} \text{rt, 30 min} \xrightarrow{\text{R}^2\text{O}} \\
\text{R}^1 & \text{N} \rightarrow \text{CO}_{2}\text{H}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>Product</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Ph</td>
<td>96</td>
<td>84%</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Me</td>
<td>97</td>
<td>80%</td>
</tr>
<tr>
<td>3</td>
<td>Bn</td>
<td>Ph</td>
<td>98</td>
<td>67%</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>Ph</td>
<td>99</td>
<td>89%</td>
</tr>
</tbody>
</table>

Table III.1: Synthesis of substituted \textit{N}-acyl-\textit{N}-alkylglycines.

The scope of substitution on the glycine derivatives was specifically chosen to interrogate various features of the cyclisation reaction to generate a small family of
münchnones. With the amino acids in hand, the cyclodehydration procedure was then attempted on the substrates by the conditions reported by Kawase. The corresponding 4-trifluoroacetylated münchenones 100-103 were obtained in a good yield by the use of TFAA (trifluoroacetic anhydride) as an electrophile (Table III.2).

![Chemical structures showing the conversion of the amino acids into the corresponding 4-trifluoroacetylated münchenones.]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Product</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Ph</td>
<td>100</td>
<td>92%</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Me</td>
<td>101</td>
<td>63%</td>
</tr>
<tr>
<td>3</td>
<td>Bn</td>
<td>Ph</td>
<td>102</td>
<td>82%</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>Ph</td>
<td>103</td>
<td>70%</td>
</tr>
</tbody>
</table>

Table III.2: Synthesis of 4-trifluoroacetylated münchenones.

The principal advantage of preparing münchenones 100-103 is the wide variety of substituents available for R¹ and R², which can be reflected in the corresponding substitution of the resulting product. Thus, the münchenone precursors are air and bench stable for extremely long periods of time. Furthermore, the cyclisation of these münchenones could be carried out on ~5 g scale within 2 h, with the exception of N-Ph substrates which required 5 h.

In order to extend the scope of isolable and stable münchenones for further chemistry, and in an effort to introduce some different functionality, other electrophiles were tried for the cyclodehydration/acylation process.

Although the use of isocyanates as an electrophile had not been exploited for the formation of münchenones, we envisaged that these compounds could expand...
the range of products accessible by this chemistry. Indeed, we were pleased to find that it was possible to prepare a family of novel C4-imide substituted münchnones by the use of isocyanates bearing Ts- and trichloroacetyl groups.\textsuperscript{82} Tosyl isocyanate was tested first with \textit{N}-methyl glycine 96. To our delight, C4-imide substituted münchnone 104 was generated in 65\% yield at room temperature within a short reaction time of 10 min (Table III.3). Using the same conditions at reflux for 2 h gave the best yield, and 104 was isolated in 97\% after precipitation from cold diethyl ether. A scope of common organic solvents such as DCM, toluene, THF, DMF highlighted Et\textsubscript{2}O as the most effective solvent for the formation of münchnone 104.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Reaction (time)</th>
<th>Conditions</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 min</td>
<td>rt</td>
<td>65%</td>
</tr>
<tr>
<td>2h</td>
<td>rt</td>
<td>86%</td>
</tr>
<tr>
<td>2h</td>
<td>reflux</td>
<td>97%</td>
</tr>
</tbody>
</table>

\textbf{Table III.3: Synthesis of \textit{N}-methyl C4-imide substituted münchnones.} Ts=4-toluenesulfonyl.

The \textit{N}-benzyl C4-imide substituted münchnones 105 and 106 were also obtained in excellent yield using the same conditions described above (Scheme III.16).
Scheme III.16: Synthesis of C4-imide substituted münchnones.

We opted next to explore other isocyanates using similar conditions to the two previous reactions. Using different glycine derivatives and trichloroacetyl isocyanate, the amide-substituted münchnones 107-109 were also produced in moderate to good yields (Table III.4).

Table III.4: Scope of C4-imide substituted münchnone.

Compounds 107-109 were isolated after precipitation from cold Et₂O without the need for flash column chromatography.
These results highlighted that using electron-deficient isocyanates offered a general and efficient means for preparing highly stabilized C4-substituted münchnones bearing amide functionality.

In order to explore the efficiency of other isocyanate reagents as electrophiles for münchnone formation, a range of alternative commercial isocyanates were tested. Disappointingly, using nitrophenyl isocyanate 110 as the electrophile under the general conditions described above, no desired product was observed and an unidentified side product was obtained instead. Changing the reaction conditions by screening various solvents, reaction times, temperatures or other amino acid substrates also failed to furnish the desired products (Table III.5 entries 1-6).

![Diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Con.</th>
<th>Time</th>
<th>Solvent</th>
<th>nitroarene isomer used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Ph</td>
<td>Reflux</td>
<td>4 h</td>
<td>Et₂O</td>
<td>Para</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>Ph</td>
<td>Reflux</td>
<td>4 h</td>
<td>THF</td>
<td>Para</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>Ph</td>
<td>RT</td>
<td>3 h</td>
<td>Et₂O</td>
<td>Para</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>Me</td>
<td>Reflux</td>
<td>16 h</td>
<td>THF</td>
<td>Para</td>
</tr>
<tr>
<td>5</td>
<td>Bn</td>
<td>Ph</td>
<td>Reflux</td>
<td>2 h</td>
<td>Et₂O</td>
<td>Para</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>Ph</td>
<td>Reflux</td>
<td>2 h</td>
<td>Et₂O</td>
<td>Meta</td>
</tr>
</tbody>
</table>

Table III.5: Attempted synthesis of nitrophenylmünchnones.
The lack of reactivity observed with nitrophenyl isocyanate 110 was unexpected and is difficult to explain. We believe that the mechanism of formation of the C4-imide substituted münchnones is essentially the same as that proposed for the 4-trifluoroacetyl münchnones as illustrated in scheme III.7.

As shown in scheme III.17, the cyclisation step provides intermediate 111 which undergoes electrophilic aromatic substitution to generate the product 104 (Scheme III.17, bath A). It may simply be that nitrophenyl isocyanates are too poorly electrophilic to promote this process, and that the unsubstituted münchnones decompose upon work-up of the reaction mixture (Scheme III.17, path B).

To investigate other electrophile induced münchnone forming processes, the addition of phenyl isocyanate 112 to glycine was attempted (Scheme III.18).
Unfortunately, only traces of a possible product were observed in the crude proton NMR spectrum and no product was isolated. To optimize the reaction, the previous conditions shown in Table III.5 were examined with the reagent 112 in which two different solvents were tested. However, no improvement was observed. Moreover, no reaction was observed when benzoyl isothiocyanate 113 was added using the same conditions described above (Scheme III.19).

By observing the reactivity of the reagent used, it appeared that only electron-deficient isocyanates work as good electrophiles for these reactions.

3. Conclusion

Overall, a new set of münchnones 104 - 109 were synthesized using a novel methodology from readily available amino acids and isocyanates. Although some isocyanates such as nitrophenyl isocyanate 110 and phenyl isocyanate 112 were unsuccessful in generating the desired products, those münchnones derived from trichloroacetyl and tosyl isocyanates that were generated were found to be stable with the potential for further functionalization. Further application of these compounds was investigated and will be discussed in the following section.
Chapter III. Münchnones cycloaddition reactions.

Part 1: Generation of pyrroles from münchnones and alkynes

1. Introduction

Developing new strategies to access functionalised pyrroles has been subject of many studies in organic synthesis. Among the many methods available, the 1,3-dipolar cycloaddition of münchnones is appealing as it provides an effective method to generate highly substituted products with regiocontrol.  With regard to dipolarphiles employed in reactions of münchnones, the use of alkynes to form pyrroles is by far the most common approach. These reactions proceed via a [4+2] cycloaddition to form bicyclic or bridged intermediates, which cannot be observed. Instead, these rapidly eliminated carbon dioxide to afford the product pyrrole directly (Scheme IV.1).

Scheme IV.1: Mechanism of pyrrole formation from münchnones.

Although the use of münchnones in cycloaddition reactions to provide pyrroles is now well established, there are some challenges with this approach as these reactions can be unpredictable with regard to regioselectivity or reaction efficiency. For example, Pandey et al. reported that the reaction of münchnones with electronically similar alkynes displayed surprising regioselectivity trends. Specifically, münchnone 114 reacted with ethyl phenylpropiolate 115 to provide the corresponding pyrrole as a 1:9 ratio of isomers. However, propynamide 4 did not offer any regioselectivity in the same reaction, giving 1:1 ratio of isomeric pyrazoles (Scheme IV.2).
Scheme IV.2: Unpredictable regioselectivity in dipolar cycloaddition of münchnones.

As with other 1,3-dipolar compounds, a number of methods have been utilized to predict the reactivity and regioselectivity of münchnones in cycloaddition reactions. These investigations have comprised studying the influence of the electronic nature of the alkyne, or the effect of substituents on the 2- and 4-position of münchnones.\textsuperscript{90}

In general, the reactivity of 1,3-dipolar compounds can be explained by frontier molecular orbital theory (FMO), which is a useful tool to help predict the regioselectivity of 1,3-dipolar cycloaddition reactions. This theory explains that the cycloaddition occurs between the reactants that have the lowest unoccupied molecular orbital (LUMO) and the highest occupied molecular orbital (HOMO). Thus, the reaction of münchnones, which have a high (HOMO) orbital and the (LUMO) of the alkynes will result in cycloaddition, and should be regioselective, assuming a significant difference in orbital coefficient on each substrate.\textsuperscript{20,91} However, in practice, FMO theory fails to predict product regioselectivity of münchnone cycloaddition with dipolarophiles.\textsuperscript{87}
For example, matching the HOMO of unsymmetrical münchnones with the LUMO of nitroindole, the predicted major product would be compound 116. The cycloaddition however generates the unexpected isomer 117, which is the opposite selectivity to that predicted by FMO theory (Scheme IV.3).  

\[ \text{LUMO} \quad \text{HOMO} \]

\[ \Delta, \text{THF} \]

\[ \begin{align*}
\text{Me} & \quad \text{Ph} \\
\text{CO}_2\text{Et} & \quad \text{N} \quad \text{Ph} \\
\text{N} & \quad \text{N} \\
\text{Bn} & \quad \text{Bn}
\end{align*} \]

(10%) FMO-Predicted.  (90%) major product opposite to that predicted by FMO theory.

116 \quad 117

Scheme IV.3: FMO analysis of a münchnone cycloaddition.

The same sporadic regiochemical trends were observed by Trost et al. in his studies of münchnone cycloadditions with methyl propiolate. Upon treatment of a series of unsymmetrical münchnones with this alkyne, it was found that the regiochemistry appeared to be heavily influenced by steric factors rather than those predicted by FMO theory. Their findings showed that münchnones bearing a hydrogen atom at C2 resulted in the formation of pyrroles where the more crowded groups are found adjacent to each other (Table IV.1).
Trost also investigated the influence of the münchnone ring on reaction regioselectivity. Using a symmetrical münchnone bearing two methyl groups, and differing only by the isotope of each carbon atom on that group (¹²C- versus ¹³C-labeled), the cycloaddition of methyl propiolate was investigated. The authors assumed that the two methyl groups on the münchnone were approximately electronically equal. In the event, a slight preference for a cycloaddition that connected the C1 atom of the alkyne and the C2 atom of the münchnone was observed. Nevertheless, the cycloaddition of these münchnones with methyl propiolate provided low selectivity overall suggesting that the nature of the ring heteroatoms has relatively little influence on reaction regiochemistry (Scheme IV.4).⁹³
Scheme IV.4: Reaction of isotopically labelled münchnones with methyl propiolate.

In order to establish the importance of the electronic nature of dipolarophiles on münchnone cycloadditions, phenylthio/hydrogen-substituted münchnones were prepared. They were reacted with acetylenic esters bearing different groups attached to the β-carbon. When dipolarophiles bearing substituents of different steric bulk were investigated (R = H, CH₃, Ph), the major regioisomer was found to be the pyrrole were the two least sterically encumbered groups were formed adjacent to each other. The results of these cycloaddition reactions are shown in Scheme IV.5. Changing the R group on the dipolarophiles results in a change in product isomer distribution, whereby an increase in the size of the R group ultimately leads to a single regioisomer product.
Trost’s findings suggest that both the electronic properties of the münchnone substituents and steric effects are controlling factors for the regioselectivity. The FMO contributions, however, appear to be of minimal importance. They also concluded that "No single criterion can successfully be used to correlate the experimental observations regarding regioselectivity in münchnone cycloaddition reactions."93

Similar studies have been reported by Padwa et al.94 regarding the effect of C2 and C4 münchnone substituents on cycloaddition regioselectivity. These studies again highlighted variability of the reaction regiochemistry. However, similar trends to those observed in Trost’s study were generally recorded (Table IV.2).
Table IV.2: Regioselectivity study of münchnone cycloadditions.

Rosa et al.\textsuperscript{95} also examined the influence of münchnone substitution patterns on cycloaddition regioselectivities. These researchers used symmetrical and unsymmetrical münchnones with arylsulfonyl alkynes. It was suggested that steric and electronic influences combine to determine the course of reaction regiochemistry. When symmetrically substituted münchnones with aryl or hydrogen groups at C2 and C4 position were used, arylsulfonyl acetylenes afforded the corresponding pyrroles in good yields (Entries 1-6, Table IV.3). Unsurprisingly, isomeric mixtures were obtained when unsymmetrical münchnones were employed (Entry 7-12, Table IV.3). Nonetheless, the incorporation of aromatic groups at C4 on the münchnone appears to be particularly important as it provides pyrroles with complete regioselectivity.
<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>R⁵</th>
<th>Yield</th>
<th>Regioisomeric ratio A : B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Me</td>
<td>Ph</td>
<td>H</td>
<td>SO₂Ph</td>
<td>72%</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Me</td>
<td>Ph</td>
<td>Me</td>
<td>SO₂Ph</td>
<td>63%</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>Me</td>
<td>Ph</td>
<td>Ph</td>
<td>SO₂-o-Tol</td>
<td>55%</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>SO₂Ph</td>
<td>61%</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>Me</td>
<td>SO₂Ph</td>
<td>62%</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>Ph</td>
<td>SO₂-o-Tol</td>
<td>68%</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>SO₂Ph</td>
<td>62%</td>
<td>100 : 0</td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>SO₂Ph</td>
<td>67%</td>
<td>100 : 0</td>
</tr>
<tr>
<td>9</td>
<td>Ph</td>
<td>Me</td>
<td>Me</td>
<td>Ph</td>
<td>SO₂-o-Tol</td>
<td>72%</td>
<td>100 : 0</td>
</tr>
<tr>
<td>10</td>
<td>Me</td>
<td>Me</td>
<td>Ph</td>
<td>H</td>
<td>SO₂Ph</td>
<td>86%</td>
<td>25 : 75</td>
</tr>
<tr>
<td>11</td>
<td>Me</td>
<td>Me</td>
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<td>Me</td>
<td>SO₂Ph</td>
<td>92%</td>
<td>10 : 90</td>
</tr>
<tr>
<td>12</td>
<td>Me</td>
<td>Me</td>
<td>Ph</td>
<td>Ph</td>
<td>SO₂-o-Tol</td>
<td>83%</td>
<td>12 : 88</td>
</tr>
</tbody>
</table>

Table IV.3: Substituent effects on regioselectivity of münchnone cycloadditions.

La Rosa’s investigation of the cycloaddition of disubstituted münchnones with terminal alkynes showed similar trends to those discussed earlier in Padwa’s studies (Scheme IV.6).⁹⁶
Futhermore, Dalla and La Rosa showed that unsymmetrical münchnones could be reacted with phenylacetylene to give the pyrrole products in moderate to good yields. The reaction is commonly regioselective with the major pyrrole isomer from the connection of the negative charge of C4 of the münchnone and the α-carbon of the dipolarophile (Table IV.4).  

\[
\begin{array}{cccc}
\text{Entry} & R^1 & R^2 & \text{Yield} \% & \text{Regioisomeric ratio A : B} \\
1 & \text{Ph} & \text{H} & 34 & 100 : 0 \\
2 & \text{CH}_3 & \text{H} & 4 & 100 : 0 \\
3 & \text{Ph} & \text{CH}_3 & 50 & 98 : 2 \\
4 & \text{CH}_3 & \text{Ph} & 44 & 99 : 1 \\
\end{array}
\]

Table IV.4: Cycloaddition of unsymmetrical münchnones with phenylacetylene.

Moreover, Gribble et al.\textsuperscript{20} observed the same behavior when N-benzyl münchnone was used in the cycloaddition of phenylacetylene (Scheme IV.7).
Scheme IV.7: Pyrrole formation from phenylacetylene as a dipolarophile.

With the literature showing that the reactions of münchnones and alkynes offer a variety of regioselectivities, and in a continuous effort to improve these cycloaddition reactions, it was deemed appropriate to study cycloaddition reactions of novel stabilized münchnones bearing an electron withdrawing group at C4. These reactions have the potential to afford densely functionalized pyrroles.
2. Application of münchnone-alkyne cycloaddition reactions

Results and optimisation

With a selection of stabilized münchnone analogues in hand, it was possible to carry out 1,3 dipolar cycloaddition reactions with alkynes. Accordingly, the reaction of a range of 4-trifluoroacetylated münchnones and phenylacetylene were initially performed under thermal conditions. The best conditions consisted of using one equivalent of münchnone with two equivalents of phenylacetylene in xylenes at 140 °C. Pleasingly, as shown in Table IV.5 entries 1-4, 4-trifluoroacetylated münchnones underwent efficient cycloaddition with phenylacetylene to give the corresponding pyrroles 118-121 as a single regioisomer in good to excellent yields.

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>^aProducts</th>
<th>^cYield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Ph</td>
<td>118</td>
<td>75%</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Me</td>
<td>^b119</td>
<td>70%</td>
</tr>
<tr>
<td>3</td>
<td>Bn</td>
<td>Ph</td>
<td>120</td>
<td>67%</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>Ph</td>
<td>121</td>
<td>91%</td>
</tr>
</tbody>
</table>

^aProduct ratios were determined by ^1H NMR integration; ^bRegiochemistry was determined by NOE interaction of R² and the pyrrole ring proton; ^cYields refer to isolated products after column chromatography.

Table IV.5: Cycloaddition reactions of 4-trifluoroacetylated münchnones with phenylacetylene.
The regiochemistry of pyrrole 119 was determined by NOE spectroscopy, suggesting that the 4-Ph-isomers are formed in these cases. The pyrrole ring proton showed an interaction with the methyl group in the pyrrole ring (Figure IV.1).

![Figure IV.1: Characterization of pyrrole regiochemistry by NOE.](image)

Unfortunately, however, as shown in table IV.6, the cycloaddition reaction of 4-trifluoroacetylated münchnones with alkyl-substituted alkynes appears to be less effective. The use of 1-octyne generated the corresponding pyrrole 122-124 in a much lower yield, albeit maintaining high regioselectivities (Table IV.6 entries 1, 2 and 3). Ethynylcyclopropane and 1-hexyne also underwent cycloaddition under the same conditions; the corresponding pyrroles 125 and 126 were also obtained in low yield (Table IV.6 entries 4 and 5).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>R</th>
<th>Products</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Ph</td>
<td>²Hex</td>
<td>122</td>
<td>48%</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Me</td>
<td>²Hex</td>
<td>123</td>
<td>25%</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>Ph</td>
<td>²Hex</td>
<td>124</td>
<td>33%</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>Ph</td>
<td>²Bu</td>
<td>125</td>
<td>44%</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>Ph</td>
<td>cyclopropyle</td>
<td>126</td>
<td>39%</td>
</tr>
</tbody>
</table>

Table IV.6: Cycloaddition reaction of münchnone with alkyl-substituted alkynes.
The regiochemistry of pyrroles 123 was assigned by NOE spectroscopy, suggesting that the A isomer is formed selectively (Figure IV.2). The regiochemistry of remaining pyrroles were tentatively assigned by analogy.

![Figure IV.2. Characterization of pyrrole regiochemistry by NOE.](image)

These results obtained from trifluoroacetylated münchnone cycloadditions with alkynes suggested that pyrrole formation proceeded with high selectivity to connect the C4 carbon of the münchnone to the α-C2 carbon of the alkyne. Furthermore, these reactions reflected literature precedent that suggests there is a decrease in reactivity from electron poor to electron rich alkynes. These results obtained from trifluoroacetylated münchnone cycloadditions with alkynes suggested that pyrrole formation proceeded with high selectivity to connect the C4 carbon of the münchnone to the α-C2 carbon of the alkyne. Furthermore, these reactions reflected literature precedent that suggests there is a decrease in reactivity from electron poor to electron rich alkynes.

![Figure IV.3: Different alkyne reactivity with münchnones.](image)

MeO₂CC≡CCO₂Me > HC≡CCO₂Me > PhC≡CCO₂Me > PhC≡CH > C₆H₁₃C≡CH

To quantify the lower reactivity of alkyl-substituted alkynes relative to aryl-substituted alkynes in our reactions, a series of competition reactions were conducted. For münchnones 100-103, using an excess of a stoichiometric mixture of 1-octyne and phenylacetylene in cycloaddition resulted in a selective incorporation of the aryl-substituted alkyne (Scheme IV.8).
Scheme IV.8: Competition reaction of phenylacetylene and 1-octyne with münchnones.

As preliminary investigations looked promising, the efficiency of the cycloaddition reaction of C4-imide substituted münchnones 104 and 103 was then explored.

As highlighted in scheme IV.9, the first investigation using phenylacetylene as a substrate provided a surprising result. In fact, by heating sulfonimide substituted münchnone 104 with phenylacetylene in xylenes in a sealed tube at 140 °C, the pyrrole 127 was formed in moderate yield together with pyrrole 128 in which the imide had undergone apparent cleavage.

Scheme IV.9: Cycloaddition reaction of sulfonimide substituted münchnone with phenylacetylene.

Methyl-substituted münchnone 104 and phenylacetylene were chosen to investigate and optimize the reaction in order to minimise loss of the amide group. Our results are summarized in table IV.7. Parameters such as solvent, temperature or the number of equivalents of the alkyne were investigated. The use of high temperature (140 °C) and longer reaction times were not suitable for this reaction as this resulted in a low yield of the pyrrole bearing the imide group (Table IV.7 entries 1-5). However, by running the reaction at 110 °C and reducing the reaction time, the desired product was isolated in high yield (Table IV.7 entries 6-7).
Table IV.7: Optimisation reaction to minimise loss of the imide group during the cycloaddition reaction. Ts=4-toluenesulfonyl.

Using our optimized conditions, the scope of the cycloaddition reaction was investigated. The cycloaddition of münchnone 105 with phenylacetylene provided the corresponding product 129 in 56% yield together with pyrrole 130 in 7% yield (Scheme Table IV.10).

Scheme IV.10: Cycloaddition reaction of sulfonimide substituted münchnone with phenylacetylene.
The cycloaddition of münchnone 104 and 105 with cyclopropane-substituted acetylene provided the corresponding product in moderate to high yield and with good regiocontrol (Table IV.7 entries 3 and 4).

However, once again the cycloaddition of münchnone 104 with 1-octyne and 1-hexyne was found to be less effective and the corresponding products were formed in significantly lower yield (Table IV.7 entries 1 and 2).

\[
\begin{array}{cccccc}
\text{Entry} & \text{R}^1 & \text{R}^2 & \text{R}^3 & \text{Product} & \text{Yield}\% \\
1 & \text{Me} & \text{Ph} & \text{\textsuperscript{\textgamma}Hex} & 131 & 23\% \\
2 & \text{Me} & \text{Ph} & \text{\textsuperscript{\textgamma}Bu} & 132 & 20\% \\
3 & \text{Me} & \text{Ph} & \text{cyclopropyl} & 133 & 67\% \\
4 & \text{Bn} & \text{Ph} & \text{cyclopropyl} & 134 & 45\% \\
\end{array}
\]

Table IV.7: Scope of imide substituted münchnones. Ts=4-toluensulfonyl.

The regiochemistry of pyrroles 132, 133 and 128 was assigned by NOE spectroscopy, suggesting that the isomers in figure IV.5 were formed. The regiochemistry of remaining pyrroles were tentatively assigned by analogy.

Figure IV.5: Characterization of pyrrole regiochemistry by NOE.
In order to increase product yield of alkyl-substituted alkynes, reaction optimization was carried out by varying reaction time, temperature and the number equivalents of alkyne. Unfortunately, when the cycloaddition reaction between münchnone 104 and 1-octyne was conducted under different conditions (Table IV.8 entries 1-5), no improvement in the yield was observed and the corresponding alkyne appeared to be relatively unreactive.

![Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>eq.</th>
<th>Temp.</th>
<th>Time</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>140</td>
<td>16 h</td>
<td>19%</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>110</td>
<td>16 h</td>
<td>14%</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>110</td>
<td>3 h</td>
<td>4%</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>110</td>
<td>6 h</td>
<td>7%</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>110</td>
<td>20 h</td>
<td>23%</td>
</tr>
</tbody>
</table>

Table IV.8: Optimization to increase product yield of alkyl-substituted alkynes.
Ts=4-toluensulfonyl.

We opted next to explore the cycloaddition reaction of the trichloroacetimide substituted münchnone 107. Surprisingly, heating phenylacetylene for 2 h in xylenes at 110 °C with münchnone 107 generated two pyrrole products 135 and 136 (Table IV.9 entry 1). However, extending the reaction time from 2 h to 21 h, we were able to improve the yield of pyrrole with the amide group up to 83% yield (Table IV.9 entry 3).
After optimization of the initial conditions for the cycloaddition of münchnone 107, we explored next the scope and limitations of this process. The cycloaddition reaction of N-benzyl-substituted münchnone with phenylacetylene and cyclopropylacetylene furnished the corresponding pyrroles 137 and 138 in 71% and 63% yields respectively, and with good regiocontrol (Table IV.10 entries 1 and 2). Moreover, cyclopropylacetylene with N-methyl-substituted münchnone provided the corresponding pyrrole 139 in high yield (Table IV.10 entry 3).

**Table IV.9: Cycloaddition reaction of 4-imide substituted münchnone.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time</th>
<th>Yield (135)</th>
<th>Yield (136)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 h</td>
<td>34%</td>
<td>44%</td>
</tr>
<tr>
<td>2</td>
<td>6 h</td>
<td>52%</td>
<td>32%</td>
</tr>
<tr>
<td>3</td>
<td>21 h</td>
<td>83%</td>
<td>7%</td>
</tr>
</tbody>
</table>

**Table IV.10: Cycloaddition scope of imide substituted münchnone.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>product</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bn</td>
<td>Ph</td>
<td>Ph</td>
<td>137</td>
<td>71%</td>
</tr>
<tr>
<td>2</td>
<td>Bn</td>
<td>Ph</td>
<td>Cyclopropyl</td>
<td>138</td>
<td>63%</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>Ph</td>
<td>Cyclopropyl</td>
<td>139</td>
<td>83%</td>
</tr>
</tbody>
</table>
3. Functionalization of pyrroles

Having explored a variety of pyrrole functionality in cycloaddition reactions between münchnones and alkynes, we were interested to exploit the stabilizing group in order to form pyrroles with different functionality in the final products. With regard to the trifluoroacetate substituted pyrrole, which proved to be stable during the cycloaddition reactions, the possibility of converting the trifluoroacetate group to a carboxylic acid was explored.

Pyrroles 118 and 120 were chosen for this functionalization study. Initially, using sodium hydroxide and methanol as a solvent at room temperature provided little conversion from pyrrole trifluoroacetyl groups 120 to pyrrole carboxylic acid 140 (Table IV.11 entry 1). However, by heating under reflux for 16 h, the desired product was obtained in good yield (Table IV.11 entry 2). The same conditions were also applied to pyrrole 118 and they provided the desired pyrrole carboxylic acids 141 in 58% yield (Table IV.11 entry 3).
Table IV.11: Pyrrole trifluoroacetyl group conversion to carboxylic acids.

The possibility of further functionalization of the acylsulfonamide substituted pyrroles was also explored. In order to remove the amide group on pyrrole 127, a solution of 127 in methanol and acetic acid was heated under reflux to provide 5-H pyrrole 128 in 60% yield (Table IV.12 entry 1). The same conditions were also applied to pyrrole 129 to provide 71% yield of 130 (Table IV.12 entry 2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Time</th>
<th>Products</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bn</td>
<td>3h, rt</td>
<td>140</td>
<td>18%</td>
</tr>
<tr>
<td>2</td>
<td>Bn</td>
<td>16 h, reflux</td>
<td>140</td>
<td>70%</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>16 h, reflux</td>
<td>141</td>
<td>58%</td>
</tr>
</tbody>
</table>
Table IV.12: functionalization of acylsulfonamide substituted pyrrole. Ts=4-toluensulfonyl.

4. Conclusion

We have demonstrated a respectable substrate scope for the cycloaddition of münchnones with alkynes, in reactions which are highly regioselective and provide an efficient route to functionalized pyrroles. The cycloaddition of trifluoroacetyl münchnones 100-103, N-sulfonylamide substituted münchnones 104-106 and trichloroacetyl münchnones 107-109 with phenylacetylene and cyclopropylacetylene provided pyrroles 118 - 121, 127, 129, 133, 135, 137 - 139 in a very good yield. However, there was a limitation in the low yield associated with alkyl substituted alkynes such as 1-octyne and cyclopropylacetylene to provide pyrroles 122 - 126, 131, 132, 134 in low yield. In order to address this, we decided to study other substrates as dipolarophiles such as electron deficient olefins. It was hoped that these would be more reactive than the corresponding acetylenes and could increase the available substrate scope. We were interested to know about electron-deficient alkenes and strained olefins, since the study of these alkenes was not comprehensive in the literature.
Part 2. Generation of pyrroles from münchnones and alkenes

1. Introduction

The use of alkenes as dipolarophiles in münchnone cycloadditions can also lead to the formation of pyrroles, however this process is more complicated than the corresponding alkyne cycloadditions as they can’t furnish a pyrrole product directly. In these reactions, alkene cycloaddition often leads to the formation of an unstable bicyclic intermediate 142. The bicyclic adduct can then expel carbon dioxide to furnish the 1,3-dipolar intermediate 143, which upon proton migration forms 2-pyrrolines. Alternatively, these 2-pyrrolines or the intermediate 143 can undergo proton transfer or spontaneously oxidize to their pyrrole counterpart. Finally, a further cycloaddition between 143 and a second equivalent of alkene may also occur to yield bicyclic adducts. The fact that so many different processes can occur during alkene cycloaddition reactions of münchnones makes these reactions difficult to control (Scheme V.1). 98-103
Huisgen et al. in 1964,\textsuperscript{105} reported the first example of alkene-münchnone cycloadditions. For instance, münchnones synthesised in situ were shown to undergo cycloaddition with alkenes to generate 2-pyrrolines. While this product could be formed in moderate yields (Table V.1, entries 2 and 4), some isomeric mixtures were also generated (Table V.1, entry 3). Furthermore, within the reaction mixture a pyrrole product, which could be formed through oxidation, was observed (Table V.1, entry 1).
Another example shows that pyrroles can also be synthesised by the cycloaddition of the electron rich alkene 1-hexene with a münchnone to generate pyrroline, which can undergo spontaneous oxidation to generate pyrrole (Scheme V.2).  

**Table V.1: Münchnone-alkene cycloadditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Yield% A</th>
<th>Yield% B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>nBu</td>
<td>_</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>31</td>
<td>_</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>H</td>
<td>74&lt;sup&gt;a&lt;/sup&gt;</td>
<td>_</td>
</tr>
<tr>
<td>4</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>H</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>43</td>
<td>_</td>
</tr>
</tbody>
</table>

<sup>a</sup> 40:60 cis-trans (relative to phenyl and ester group) mixture.

**Scheme V.2: Pyrrole formation from alkene-münchnone cycloaddition followed by oxidation.**

Furthermore, Gribble et al. have reported that in situ formed münchnones can undergoes a tandem 1,3-dipolar cycloaddition reaction with 144 by sequential addition of alkene to give cycloadduct cage structure 145 in good yield (Scheme V.3).
Indeed, during investigations into münchnone-alkene cycloadditions it was found that olefins substituted by electron-withdrawing leaving groups such as OAc, NO₂, CN, and Cl, PPh₃⁺Br⁻ offered the opportunity to carry out in situ oxidation level adjustment to generate pyrroles directly (Scheme V.4). ¹⁰⁷⁻¹¹⁵

For example, the cycloaddition of münchnones with chloroalkenes generates the desired pyrroles in good yield after decarboxylation and elimination of HCl (Scheme V.5). ¹¹₆
Vinyl phosphonium salts have been found to perform as dipolarophiles with münchnones to provide pyrrole products in moderate yield, but in high regioselectivity. The product was formed after elimination of PPh$_3$ after decarboxylation (Scheme V.6).$^{117}$

![Scheme V.6: Pyrrole formation from vinyl triphenylphosphonium bromides.](image)

In addition to vinyl phosphonium salts, other types of olefin may also be substituted to react with münchnones to provide pyrroles. In 2005, Grassi et al.$^{118}$ showed that münchnones reacted with α-acetoxy acrylic acid esters and, after loss of acetic acid and carbon dioxide, pyrrole 146 could be formed with a high yield and selectivity (Scheme V.7).

![Scheme V.7: Pyrrole formation from münchnone cycloadditions.](image)

Furthermore, tetrasubstituted pyrroles are formed via the cycloaddition reaction of münchnones with the highly strained olefin 147 after elimination of CO$_2$ and the unstable PPh (Scheme V.8).$^{119}$

![Scheme V.8: Pyrrole formation from phosphirenes.](image)
Work by Jimenez et al.\textsuperscript{119} showed that the 1,3-dipolar cycloaddition of münchnones with nitroalkenes \textbf{148} proceeds with high regiocontrol, but with opposite selectivity to that predicted by FMO theory. The 1,3-dipolar cycloaddition delivers a single pyrrole product \textbf{149} after elimination of HNO\textsubscript{2} (Scheme V.9).

Scheme V.9: Regioselectivity of the münchnone cycloaddition with nitroalkenes.

A variety of pyrrole derivatives having a pyridyl group were prepared through münchnone chemistry. In 2011, Gribble et al.\textsuperscript{120} showed that nitrovinyl pyridines or a quinoline \textbf{150} reacted smoothly with symmetrical and unsymmetrical münchnones in 1,3-dipolar cycloaddition reactions. When unsymmetrical münchnones were used ($R_1 \neq R_2$) with \textbf{150}, the reaction could proceed with high regioselectivity a:b (up to 99:1, Scheme V.10).

\begin{align*}
\text{Scheme V.10: Pyrrole derivatives from the reaction of münchnone and nitroalkenes.}
\end{align*}
Furthermore, in 2013, Gribble et al.\textsuperscript{120} investigated the regioselectivity of 1,3-dipolar cycloadditions between münchnone and nitroalkenes \textsuperscript{151}, which provided a convenient synthesis of substituted pyrroles (Scheme V.11).

\[
\begin{align*}
\text{Scheme V.11: Münchnone cycloadditions with nitroalkenes.}
\end{align*}
\]

More recently, Gribble showed that a series of five membered heterocycle substituted pyrrole derivatives could be prepared via 1,3-dipolar cycloaddition of unsymmetrical münchnones \textsuperscript{152} with nitrovinyl heterocycles (Scheme V.12).\textsuperscript{122}

As mentioned above, münchnone-alkene cycloadditions can lead directly to pyrrole products without the need for an oxidant. Unfortunately, the reaction proceeds with variable levels of regiocontrol and can generate acidic by-products.
Nevertheless, these reports provide a potentially attractive protocol, that have several opportunities for improvement:

- Could less acidic leaving groups on the dipolarophile be used?
- Could more reactive dipolarophiles be designed for the synthesis of new and synthetically useful pyrroles?
- Is it possible for these new alkene dipolarophiles to show improved regioselectivity?

2. Münchnone-alkene (enamine) cycloaddition reaction

We were attracted to the use of enamines in cycloaddition reactions of münchnones as these electronically polarized alkenes offered the potential for high reactivity and regioselectivity in comparison to simple alkenes. Moreover, enamines have not been investigated as dipolarophiles in cycloaddition reactions of münchnones.

Enamines are long established and powerful enol synthons in organic chemistry. Meyer and Hopf in 1921 were the first to synthesize the simplest enamine of a carbonyl compound.\textsuperscript{123} The general method for the synthesis of enamines which is commonly used today was described by Mannich and Davidsen.\textsuperscript{124} Thus, the desired enamine can be formed by the simple condensation between a secondary amine and an aldehyde or a ketone in the presence of an acid catalyst (Scheme V.13).

\begin{minipage}{\textwidth}

\textbf{Scheme V.13: Enamine synthesis.}

\end{minipage}
Typically, enamines behave as carbon-nucleophiles through conjugation of the nitrogen lone pair into the C=C bond to give a negative charge at the β-position which can attack an electrophile (Scheme V.14).\textsuperscript{125}

\begin{center}
\includegraphics[width=0.4\textwidth]{scheme_v14}
\end{center}

Scheme V.14: Enamine conjugation.

Therefore we were interested to know whether the electron pair on the enamine nitrogen could influence the reactivity and regioselectivity of these alkenes in münchnone cycloaddition reactions, and whether they would act as alkyne equivalents (Scheme V.15).

\begin{center}
\includegraphics[width=0.7\textwidth]{scheme_v15}
\end{center}

Scheme V.15: Cycloaddition of alkyne equivalents.
3. Application of enamine-münchnone cycloaddition reactions for pyrrole synthesis

Results and optimization

All enamines employed in this study were prepared in the same manner, using previously established condensation reactions of amines with aldehydes and ketones.\textsuperscript{126-128} The substitution pattern of the ketone derivatives was chosen to examine various features of the 1,3 dipolar cycloaddition reaction. Specifically, aromatic groups bearing electron donating and withdrawing substituents (Table V.2, entries 1-4), as well as a naphthyl (Table V.2, entry 5) and heteroaryl substituted enamines (Table V.2, entry 6) and alkyl substituted examples (Table V.2, entry 7). All enamines were formed in good yield.\textsuperscript{129}
Table V.2: Scope of enamine syntheses.

Using the initial reaction conditions to synthesis of enamine from 2-hexanone, a mixture (1:1) of the two regioisomeric enamines **160a** and **160b** in 84% yield were formed (see scheme V.16).
4. Cycloaddition

In order to examine the effect of the dipolarophile on the cycloaddition step, and as münchnones are often unstable where prepared in situ, it was decided to employ stabilized münchnone analogues in this investigation where an electron acceptor groups is incorporated at the C4 position. An initial cycloaddition between münchnone 104 and aryl enamine 154 was attempted (Table V.3). Performing the reaction at 140 °C in xylenes for 16 hours provided the desired pyrrole product 161 in moderate yield (54%) together with (36%) yield of pyrrole 162, indicating that an amine leaving group is suitable in this reaction (Table V.3, entry 1). Attempts to optimise the reaction to minimise loss of the amide group by varying stoichiometry, temperature, length of reaction time were successful in delivering the desired product in very good yield (92%) after a 40 minute reaction (Table V.3, entry 6).²²

\[
\begin{align*}
\text{Entry} & \quad \text{Temp.} & \quad \text{Time} & \quad \text{Eq.} & \quad \text{Yield\%} \\
1 & 140 & 16\ h & 4\ eq & 54\% & 36\% \\
2 & 180 & 24\ h & 4\ eq & 43\% & 32\% \\
3 & 100 & 24\ h & 4\ eq & 50\% & 34\% \\
4 & 80 & 24\ h & 4\ eq & 60\% & 22\% \\
5 & 110 & 6\ h & 2\ eq & 72\% & 14\% \\
6 & 110 & 40\ min. & 2eq & 92\% & \text{trace}
\end{align*}
\]

Table V.3: Optimisation reaction to minimise loss of the imide group during the cycloaddition reaction. Ts=4-toluenesulfonyl.
With the optimised conditions in hand, the scope of the reaction with respect of the enamine partner was investigated. The cycloaddition reaction of münchnone \textbf{104} was found to be tolerant of a number of aryl substituted enamines having electron withdrawing and donating groups in the phenyl ring. The corresponding pyrroles \textbf{127, 163} and \textbf{164} were obtained in good yield (Table V.4, entries 1-3).

Pleasingly, these conditions proved to be suitable for both heteroaromatic and aliphatic groups on enamines, providing the desired pyrroles \textbf{165, 166, 167} in excellent to moderate yield and always maintaining excellent levels of regioselectivity (Table V.4, entry 4-6).
We were interested to note that the aryl group was incorporated into the same position of the pyrrole (i.e. adjacent to the stabilizing group) and that this regiochemistry reflected that of the mümchnone cycloaddition with aryl acetylenes (described in chapter IV). However, this reaction was much faster than those of the corresponding alkynes, and the yields remained quite high when alkyl-substituted enamines were employed. This is in contrast to acetylene-mümchnone cycloadditions where alkyl-substituted alkynes provide the corresponding pyrroles in low yield.

Table V.4: Scope of the cycloaddition reaction between mümchnones and 1-substituted enamines. Enamine used as a mixture of regioisomers.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R'</th>
<th>R</th>
<th>Product</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td></td>
<td>127</td>
<td>72%</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td></td>
<td>163</td>
<td>80%</td>
</tr>
<tr>
<td>3</td>
<td>Bn</td>
<td></td>
<td>164</td>
<td>72%</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td></td>
<td>165</td>
<td>84%</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td></td>
<td>166</td>
<td>71%</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td></td>
<td>167</td>
<td>61%</td>
</tr>
<tr>
<td>7a</td>
<td>Me</td>
<td></td>
<td>132</td>
<td>58%</td>
</tr>
</tbody>
</table>
Following the observation that 1-substituted enamines were highly reactive towards the cycloaddition reaction with münchnones to provide the corresponding pyrroles in good yield, it was decided to investigate isomeric 2-substituted enamines in this reaction. We hypothesized that by simple choice of the enamine isomer pattern, we might be able to force a switch in the regioselectivity of the reaction.

In this regard, aldehyde enamines were obtained by simple condensation of aldehyde with secondary amine in the presence of anhydrous potassium carbonate to give both aliphatic and aromatic enamines in good yield as shown in Table V.5.

\[
\text{RCH(OH)\text{H}NHR}_2 \xrightarrow{\text{NHR}_2 (2.2 \text{ eq})} \xrightarrow{\text{K}_2\text{CO}_3 (0.35 \text{ eq})} \xrightarrow{(0 \text{ °C-rt), o/n}} \text{R} \equiv \text{NR}_2
\]

\(\text{HNR}_2 = (\text{piperidine or diethylamine})\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>compound</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>168</td>
<td>74%</td>
</tr>
<tr>
<td>2</td>
<td>(\text{Me})</td>
<td>169</td>
<td>60%</td>
</tr>
<tr>
<td>3</td>
<td>(\text{tBu})</td>
<td>170</td>
<td>78%</td>
</tr>
<tr>
<td>4</td>
<td>(\text{Ph})</td>
<td>171</td>
<td>84%</td>
</tr>
<tr>
<td>5</td>
<td>(\text{Py})</td>
<td>172</td>
<td>64%</td>
</tr>
</tbody>
</table>

Table V.5: synthesis of isomeric 2-substituted enamines.

Methyl-substituted münchnone 104 and enamine 168 were chosen to investigate the cycloaddition step. It was observed that with the optimal set of conditions consisted of using one equivalent of münchnone, two equivalents of enamine in xylenes at 110 °C, providing pyrrole product 173 in 64% yield and pyrrrole 174 in 9% yield. Pleasingly, as shown in scheme V.17 this reaction was found to furnish pyrrole 173 in 72% yield at 80 °C and with the opposite sense of
regiochemical insertion, as well as a single regioisomer. Regiochemical assignment will be discussed later.

Scheme V.17: Optimisation reaction of the münchnone and 2-substituted enamine cycloaddition reaction. Ts=4-toluensulfonyl.

Under these conditions, as Table V.6 shows, several aromatic and aliphatic groups on enamines were found to be tolerated in the cycloaddition with münchnone 104, and generated the corresponding pyrroles 173, 175, 176 and 177 in good yields and with excellent regioselectivity.
Table V.6: Scope of the cycloaddition reaction between münchnones and 2-substituted enamines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R'$</th>
<th>$R$</th>
<th>compound</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td></td>
<td>173</td>
<td>72%</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>$\beta$Bu</td>
<td>175</td>
<td>67%</td>
</tr>
<tr>
<td>3</td>
<td>Bn</td>
<td></td>
<td>176</td>
<td>68%</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td></td>
<td>177</td>
<td>70%</td>
</tr>
</tbody>
</table>

NOE analysis of pyrrole alkyl-proton 175 and 132 showed that the isomers in figure V.1 were formed, the regiochemistry of remaining pyroles were tentatively assigned by analogy.

Figure V.1: Characterization of pyrrole regiochemistry by NOE spectroscopy.
From these experiments, it is clear the factors that govern the regioselectivity of pyrrole formation by the cycloaddition between münchenones and enamine can be dictated by simple choice of enamine substrate, a distinct advantage over traditional alkyne cycloadditions which was more complicated to deliver one regioisomer in favor of the other.

5. Reactivity of münchenones toward enamine and alkenes

Following the observation that enamine were highly reactive in cycloadditions with münchenones and as the literature shows that münchenones can also react with alkenes, it was decided to prepare 1-aminohexa-1,5-dienes 178, to explore the relative reactivity of münchenones with enamine and alkenes. We hypothesized that 178 could give rise to a range of products as illustrated in Scheme V.18. Pathway A shows that the reaction could lead to products of cycloaddition with the enamine whilst pathway B leads to products of cycloaddition with alkenes. It should be noted that a cage structure might also form from the cycloaddition with the alkenes followed by reaction with enamine after loss of carbon dioxide, as shown in pathway C.
In order to test the generality of this qualitative rate difference, initial
cycloadditions between münchnones \textbf{104} and \textbf{100} with 1-aminohexa-1,5-diene were
attempted. Performing the reaction at 110 °C in xylenes provided pyrroles \textbf{179} and
\textbf{180} in reasonable yields, as single regioisomers. The LC-MS analysis of the crude
reaction mixture showed the presence of several minor byproducts. Unfortunately
however, We were unable to characterize these minor products. Nevertheless, these
reactions highlight that the enamine cycloaddition–elimination reaction is the main
pathway.

Scheme V.18: Reactivity of münchnones toward enamines and alkenes.

Following the success employing enamines in münchnone cycloaddition reactions, attempts were made to employ a cyclic enamide in a reaction with a münchnone. It was hypothesized that the use of enamine 181 as a cyclic alkene substrate would allow a ring opening/elimination process, thus furnishing pyrrole 182 with the functional group in the final product (Scheme V.20).

An initial cycloaddition between münchnone 104 and commercially available N-Boc enamide 183 was attempted using xylenes at 110 °C for 16 hours (Scheme V.21). The desired pyrrole product 184 was obtained in 7% yield with trace amount of pyrrole 185, indicating that an amide leaving group is retained in the final product.
Scheme V.21: Münchnone-Boc protected enamide cycloadditions.

However, subsequent attempts to optimize the reaction by varying temperature, enamine ring size and reaction time were unsuccessful in delivering the desired product in reasonable yields (Table V.6).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>n</th>
<th>t/ hours</th>
<th>T/ °C</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Boc</td>
<td>2</td>
<td>2</td>
<td>110</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>Boc</td>
<td>2</td>
<td>4</td>
<td>150</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Boc</td>
<td>2</td>
<td>8</td>
<td>80</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Boc</td>
<td>1</td>
<td>16</td>
<td>110</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>Boc</td>
<td>1</td>
<td>4</td>
<td>160</td>
<td>trace</td>
</tr>
<tr>
<td>6</td>
<td>Cbz</td>
<td>2</td>
<td>20</td>
<td>110</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>7</td>
<td>Cbz</td>
<td>1</td>
<td>16</td>
<td>110</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>

Table V.6: Optimization of the reaction between münchnone 102 and cyclic enamides.

The low product yield might be caused by thermal \( N \)-Boc deprotection to give the amine (Scheme V.22) which could in this case undergo side reactions rather than the cycloaddition process.
Therefore, the use of N-Cbz enamides, with a more stable protecting group, in cycloaddition reactions with münchnones were tested to make sure that the nitrogen substituent does not affect the cycloaddition step. Disappointingly, however, the reaction of N-Cbz enamide was unsuccessful in providing any products and only complex mixtures were obtained (Table V.6 entries 6 and 7). As the lone pair on the nitrogen-enamine influences the regioselectivity of the cycloaddition steps, it might be possible to use an electron withdrawing group on the nitrogen-enamide. Therefore, cyclic-enamine dipolarophiles with either less electron withdrawing groups (such as phenyl) or more electron donating (such as methyl) at nitrogen atom were tested in an effort to improve the reactivity of the cycloaddition process.

Indeed, continuing our interest in the cycloaddition/ring opening reaction pathway in münchnone cycloaddition reactions, attempts were made to use commercially available of 2-methylene-1,3,3-trimethylindoline 186 as a dipolarophile with münchnone 104. Pleasingly, performing the reaction at 110 °C in xylenes for 16 h delivered the desired novel pyrrole product 187 by a ring opening elimination process in 58% yield, once again the reaction was found to be completely regioselective. This was only one example developed so far of this reaction sequence, but this method would provide a simple and efficient synthesis of functionalized pyroles. Therefore, the optimizations as well as the scope of the reaction with respect to the münchnone partner and dipolarophile will continue to be investigated in our group (Scheme V.23).
7. Conclusion

Although various synthetic methods have been developed for münchnone-alkene cycloadditions for pyrrole syntheses, regiocontrol in the reaction remains a concern. We have described a novel methodology for the synthesis of pyrroles under mild conditions by using enamines as dipolarophiles to react with münchnones in a highly regioselective manner. Competing reactions of two alkene-enamines with münchnones demonstrates that the products of enamine–elimination reaction are significantly more reactive than the alkene-cycloaddition-elimination pathway. Furthermore, the cycloaddition of N-Boc protected enamides with münchnones has been shown to provide pyrroles in very low yield; however, this might be a consequence of enamide Boc-deprotection which may minimize the amount of available substrate. On the other hand, the synthesis of novel functionalised pyrroles through 1,3-dipolar cycloaddition/ring opening of 2-methylene-1,3,3-trimethylindoline has been shown to proceed in a useful yield. Further investigation into applications of this enamine-cycloaddition ring opening strategy is underway in the Harrity group.
Chapter IV. Amine Catalysed pyrrole synthesis via 1,3-dipolar cycloaddition reactions

1. Introduction

As discussed in Chapter V, the use of enamines in cycloaddition reactions with münchnones to form pyrroles with complete regiocontrol shows clear advantages when compared to the traditional alkene-münchnone cycloaddition process. Furthermore, it was deemed desirable to extend this cycloaddition strategy to include enamine organocatalysis. In this instance, the term “enamine organocatalysis” refers to the catalysis of a reaction by secondary or primary amines on aldehydes or ketones via enamine intermediates.\(^{130,131}\) The first example of an asymmetric enamine catalyzed process is known as the Hajos-Parrish-Eder-Sauer-Wiechert (HPESW) reaction, which involves the intramolecular aldol reaction shown in scheme VI.1.\(^{132,133}\)

![Scheme VI.1: Intramolecular aldol reaction (HPESW process).](image)

Although this reaction was discovered over 40 years ago,\(^{134}\) its potential has not been fully realized until more recently. Since new catalytic reactions are constantly being discovered and the mechanistic process is becoming clearer, enamine organocatalysis has developed into a powerful strategy for the design of efficient, environmentally sound and economically viable reaction conditions.\(^{135-137}\) Indeed, an enamine-catalyzed (3+2) Huisgen cycloaddition strategy, employing enamine intermediates generated in situ, has been extensively investigated in many reactions over the last decade. For example, an efficient synthesis of highly substituted 1,2,3-triazoles with complete regioselectivity has been developed through an enamine-catalysis strategy, using a broad spectrum of commercially
available carbonyl compounds and azides (Scheme VI.2). However, to the best of our knowledge, an enamine-catalyzed (3+2) Huisgen cycloaddition strategy with münchenones has not been explored to date.

\[
\begin{align*}
R^2 \text{O} & + R^1 - N_3 \xrightarrow{\text{Enamine Catalysis}} R^1 \text{N} - N - N \\
R^2 & = \text{H, alkyl or aryl} \\
R^3 & = \text{EWG or EDG; aryl or alkyl}
\end{align*}
\]

Scheme VI.2: Representative examples of amine-catalyzed (3+2) Huisgen cycloadditions for the synthesis of 1,2,3-Triazoles.

In this regard, we noted that the enamine we used during the cycloaddition with münchenones was formed from the simple condensation of secondary amine with an aldehyde, and during cycloaddition process the amine fragment cleaved as depicted in Scheme VI.3. This gives rise to a situation whereby the amine can behave as a catalyst, forming pyrrole products from aldehydes and ketones via enamine intermediates.

\[
\begin{align*}
\text{R}_2 \text{N} & \xrightarrow{\text{R}_2 \text{NH}} \text{R}_2 \text{N} \\
\text{N} & \xrightarrow{\text{R}_2 \text{N}} \text{O} \\
\text{O} & \xrightarrow{\text{R}_2 \text{N}} \text{N}
\end{align*}
\]

Scheme VI.3: Role of the amine in the overall enamine-münchnone cycloaddition.
2. Application of amine-catalyst cycloaddition with münchnone towards pyrroles.

Results and discussion:

To test the application of amine organocatalysis in the enamine-münchnone cycloaddition reaction, we decided to use commercial available acetaldehyde derivatives as the carbonyl component in the presence of a catalytic amount of simple secondary amine. This could easily form the desired enamine intermediate in solution, which would then proceed to generate the pyrrole products with complete regioselectivity. Initial experiments were conducted on phenylacetaldehyde with stable 4-trifluoroacetyl-substituted münchnones in the presence of 10 mol% of amine (Table VI.1, entry 1). Pleasingly, the desired products were formed with a range of secondary amines (Table VI.1, entries 1-6) for the catalytic cycloaddition of aldehydes. Lowering the catalyst loading to 5 mol% (Table VI.1, entries 7 and 8) did not afford a good yield. However, the best yield was achieved when performing the reaction with using Dean-Stark distillation apparatus, and by increasing the catalyst loading to 20 mol% (Table VI.1, entries 9-12). Additionally, both piperidine and dibenzylamine are identified as the most active catalysts.
Having optimised the reaction conditions, different aldehydes bearing a range of alkyl and aryl substituents were tested to provide the scope shown in scheme VI.4. Pleasingly, incorporation of both aliphatic and aromatic groups on the aldehyde, in combination with münchnone 100 proved to be suitable to provide the desired pyrrole products 188, 189, 190, 191 and 192 in excellent to moderate yields with completely regioselectivity. Furthermore, using münchnone 106 under these conditions provided pyrrole 193 in 55% yield to incorporate a methyl group next to the phenyl group. The regiochemistry of pyrroles 190 were assigned by NOE spectroscopy, the regiochemistry of remaining pyrroles were tentatively assigned by analogy.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol)%</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NEt_2 (10)</td>
<td>xylenes</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>piperidine (10)</td>
<td>xylenes</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>pyrrolidine (10)</td>
<td>xylenes</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>(PhCH_2)_2NH (10)</td>
<td>xylenes</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>(iPr)_2NH (10)</td>
<td>xylenes</td>
<td>28</td>
</tr>
<tr>
<td>6</td>
<td>piperidine (10)</td>
<td>Toluene</td>
<td>34</td>
</tr>
<tr>
<td>7</td>
<td>piperidine (5)</td>
<td>Toluene</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>Bn_2NH (5)</td>
<td>Toluene</td>
<td>18</td>
</tr>
<tr>
<td>9^a</td>
<td>Piperidine (20)</td>
<td>Toluene</td>
<td>68</td>
</tr>
<tr>
<td>10^a</td>
<td>pyrrolidine (20)</td>
<td>Toluene</td>
<td>54</td>
</tr>
<tr>
<td>11^a</td>
<td>(iPr)_2NH (20)</td>
<td>Toluene</td>
<td>58</td>
</tr>
<tr>
<td>12^a</td>
<td>Bn_2NH (20)</td>
<td>Toluene</td>
<td>71</td>
</tr>
</tbody>
</table>

^a: using Dean-Stark conditions

Table VI.1: Optimization of reaction conditions.
Scheme VI.4: Scope of amine-catalyzed cycloaddition between aldehydes and münchnone.

In an attempt to extend this cycloaddition study for more münchnone substrates, an \( N \)-tosylamide substrate münchnone \( 104 \) were employed (Scheme VI.5). Interestingly, using 20 mol% loading catalyst of dibenzylamine or piperidine at 110 °C in refluxing toluene for 16 hours with phenylacetaldehyde resulted in concomitant cleavage of \( N \)-tosylamide group that was essential for stabilization of münchnone, thereby allowing access to 1,2,3-trisubstituted pyrroles \( 174 \) with good yield and complete regiocontrol.
Furthermore, this reaction can be extended, providing the desired pyrrole 194 in 62% yield where an N-benzyl group has been incorporated adjacent to the phenyl group. In addition, pyrrole 195 was formed in 56% yield where the münchenone substrate bears a pair of adjacent methyl groups. Using 4-chloroacetophenone in this catalytic cycloaddition provided desired pyrrole 196 in 64% yield. Finally, the aliphatic aldehydehydephenyl benzenepropanal also provided pyrrole product 197 in 52% yield. Gratifyingly, all these reactions remain highly regioselective for the 1,2,3-trisubstituted pyrroles (Scheme VI.6). The regiochemistry of pyrrole 196 were assigned by NOE, pyrroles 174 and 194 were assigned by comparison with literature data. The regiochemistry of remaining pyrroles were tentatively assigned by analogy.

Scheme VI.5: Optimization of the reaction conditions using an N-tosylamide substituted münchenone.

Scheme VI.6: Amine-catalyzed synthesis of 1,2,3-substituted pyrroles
From a synthetic point of view, the preparation of α-unsubstituted pyrroles such as pyrrolostatin and its analogues remains a challenge. Pyrrolostatin, an in vitro inhibitor activity against lipid peroxidation, consists of 2-carboxylic acid substituted pyrrole with a geranyl chain group attached at the 4-position (Figure VI.1).\(^{143-145}\)

![Pyrrlostatin](image)

**Figure VI.1: structure of pyrrolostatin.**

Indeed, we were interested in testing enamine catalysis with enantiopure starting materials such as (S)-(−)-citronellal 198, which could provide a pyrrole bearing an alkyl chain similar to the geranyl chain in Pyrrolostatin. Interestingly, employing (S)-(−)-citronellal under the optimised conditions with münchnone 104 in this transformation provided the desired pyrrole product 199 in very good yield, regioselectivity and with complete retention of enantiopurity (Scheme VI.7). Extension of this idea to other enantiopure aldehydes would allow facile access to a number of simple, enantioenriched pyrrole products.

![Scheme VI.7](image)

**Scheme VI.7: Synthesis of pyrrole from münchnone 104 and (S)-(−)-citronellal.**

An interesting observation made during this study was that the imide-substituted münchnone substrates were found to be cleaved during the organocatalytic cycloaddition process, thus providing the corresponding 1,2,3-
trisubstituted pyrroles. However, during the stoichiometric enamine cycloadditions this group remained intact to provide the C2-tosylamide substituted pyrroles (see Table V.4, chapter V). An obvious discrepancy between the two reactions is the length of time for which they were heated; 16 hours in refluxing toluene for the organocatalytic reactions but only 1-4 hours in refluxing xylenes while using stoichiometric quantities of enamine. This observation suggests that controlling the reaction time is essential to minimize cleavage of the amide group. Therefore, control experiments were performed using N-tosylamide pyrrole 173, which underwent conversion to the C2-unsubstituted pyrroles after heating in refluxing toluene overnight (Scheme VI.8). The different outcomes observed for the catalytic and stoichiometric reactions are therefore a consequence of the extended reaction times employed in the catalytic reaction.

Scheme VI.8: Control experiments using N-tosylamide pyrrole 173
3. Conclusion

In summary, a catalytic 1,3-dipolar cycloaddition between münchnones and aldehydes, which is catalysed by a variety of secondary amines, has been developed to generate pyrroles 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 199 with high levels of regiocontrol. These strategies can be used for the insertion of chiral centres adjacent to the pyrrole core of the products. Furthermore, this cycloaddition proceeds efficiently with readily availability of starting materials (acetaldehyde derivatives) and inexpensive catalysts. Such studies with enamines in cycloaddition reactions with other mesoionic compounds are actively underway in our laboratory. Therefore, we believe that this work will open the opportunity to develop further amine-catalysed cycloadditions with other dipolar compounds for the regioselective synthesis of useful heterocyclic compounds.
Chapter V. Concluding remarks and future outlook.

1. Concluding remarks

The synthesis of pyrroles through the 1,3-dipolar cycloaddition between functionalized münchnones and dipolarophiles has been successfully developed. Satisfactorily, we have prepared a family of novel stabilized imide-substituted münchnone analogues through the cyclodehydration reaction of readily available isocyanate substrates. Interestingly, these münchnones provide pyrroles in a highly regioselective fashion when alkynes are employed as dipolarophiles. Unfortunately, alkyl substituted alkynes were found to be less reactive than those substrates bearing aryl groups, and provide pyrrole products in low yield. Nonetheless, these pyrrole products are functionalized at the C-2 position and could be manipulated further.

In order to address the low yield associated with alkyl-substituted alkynes and to increase the substrate scope, we investigated enamines as alkyne equivalents in münchnone cycloaddition reactions. Firstly, stoichiometric quantities of enamine were investigated in cycloaddition reactions with stabilised münchnones. We have successfully developed a switchable cycloaddition reaction to access complementary regioisomers of pyrroles, depending on the regioisomer of enamine used, with good yields incorporating both alkyl and aryl groups. Secondly, the cycloaddition reaction of cyclic Boc protected enamides as dipolarophiles proceeds in low yield. Nonetheless, cyclic enamine dipolarophiles provide a novel method for ring opening to access pyrroles with the leaving group intact in the final product.

Finally, in contrast to the stoichiometric enamine reactions, we have successfully extended this chemistry to a simple and synthetically useful method under catalytic conditions for the synthesis of pyrroles. This process allows acetaldehyde derivatives to function as substrates for an amine-catalyzed cycloaddition, to generate products in excellent regioselectivity.
2. Future outlook

Different areas in this thesis have been explored; however improvements in several areas can still be pursued.

- For synthesis of münchnones, there are many other isocyanates that could be tried, to produce münchnones with alternative functionalities.
- Further investigation into applications of cyclic enamines in cycloaddition-ring opening strategies should seek to extend the scope of this novel methodology.
- A variety of other reactive dipolarophiles and münchnones remain ripe for exploration. For example, using a dipolarophile containing a boronic ester group such as 200 could provide a pyrrole which can be easily elaborated to a range of new and useful products.
- A bifunctional enamine such as 201 could be investigated in the münchnone cycloaddition. This could allow one of the leaving groups to be retained in the final product and hence provide pyrroles with an extra functional group.

Figure VII.2: Future directions for reactive dipolarophile/münchnone cycloadditions.
Chapter VI. Experimental

1. General procedure

All reactions were conducted in flame-dried glassware under an inert atmosphere of dry nitrogen or argon unless otherwise stated. Thin layer chromatography was performed on commercially available pre-coated aluminium-backed plates (Merck silica Kieselgel 60 F_{254}). Spots were made visible either by the quenching of UV fluorescence or by staining with a potassium permanganate solution. The solvent system used was graduated from 100% petroleum ether, increasing polarity towards the solvent mixture stated in the procedure. Melting points were obtained using a Gallenkamp melting apparatus and are uncorrected.

\(^1\)H NMR spectra were recorded on Bruker AVIII HD 400 (400 MHz), Bruker AVI 400 (400 MHz), Bruker AMX-400 (400 MHz) or DPX-400 (400 MHz) supported by an Aspect 3000 data system. Proton magnetic resonance chemical shift is reported in parts per million (ppm) from tetramethylsilane (TMS) with the residual protic solvent resonance as the internal standard (CDCl\(_3\): δ 7.26 ppm), unless otherwise stated. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet, dd = doublet of doublets), coupling constant in hertz (Hz), integration and assignation.

\(^{13}\)C NMR spectra were recorded on a Bruker Avance 300 (75.5 MHz), a Bruker Avance 400 (100.6 MHz) or a Bruker DRX 250 (62.9 MHz) or a Bruker Avance DRX 500 (125.8 MHz). Carbon magnetic resonance chemical shifts are reported in parts per million (ppm) from tetramethylsilane (TMS) with the solvent as the internal reference (CDCl\(_3\): δ 77.0 ppm), unless otherwise stated.

\(^{19}\)F NMR spectra were recorded on the Bruker Avance 400 (377.0 MHz), a Bruker Avance DRX 500 (471.0 MHz) and chemical shifts are reported parts per million (ppm) relative to CFCl\(_3\) as external standard.

Infrared (IR) spectra were recorded as chloroform or CH\(_2\)Cl\(_2\) solutions of the samples \(\nu_{\text{max}}\) in cm\(^{-1}\). \(\text{cxBands}\) are characterized as broad (br), strong (s), medium (m) or weak (w).
High-resolution mass spectra (HRMS) were recorded using a magnetic sector mass analyses, operating in Electrospray mode (TOF ES⁺), or MicroMass prospec operating in FAB (FBA⁺), El (El⁺) or Cl (Cl⁺) modes.

All solvents and reagents were purified using standared laboratory techniques according to methods published in Purification of Laboratory Chemicals, by Perrin and Amarego.¹⁴⁶

Enantiomer ratios were determinated by chiral HPLC (Chiral Technologies Chiralpak OD column (250 mm × 4.6 mm) or by Chiral Technologies Chiralpak AD column (250 mm × 4.6 mm) in comparison with authentic racemic material.

Optical rotation values were recorded on a perkin Elmer 241 automatic polarimeter at 589 nm (Na D-Line) with a path length of ether 1 dm or 0.1 dm and are given in 10⁻¹ deg cm² g⁻¹ with concentration (c) quoted in g 100 Ml⁻¹.
2. Synthesis of Starting Materials

Synthesis of N-benzoyl–N-methylglycine (96).\textsuperscript{147}

\[
\begin{array}{c}
\text{Me} \\
\text{N} \\
\text{H} \\
\text{Ph} \\
\text{\_CO}_2\text{H}
\end{array}
\]

Benzoyl chloride (0.41 mL, 3.56 mmol), was added portionwise over a 15-30 min period to a cold (0-10 °C) solution of sarcosine (380 mg, 4.27 mmol) and NaOH (313 mg, 7.81 mmol) in water (12 mL). After the addition was complete, the reaction was stirred for 30 min at rt and then filtered. The filtrate was cooled (ice bath) and acidified to pH 1 with concentrated HCl. The reaction mixture was extracted with ethyl acetate and the combined organic extracts were dried over magnesium sulfate. Removal of solvent in vacuo gave the title compound as a yellow solid, and a ~3:2 mixture of rotamers (578 mg, 84 %). Melting point: 101-103 °C (lit. 102-104 °C); \textsuperscript{1}H NMR (DMSO, 400 MHz): \(\delta\) 12.83 (s, br, 2H), 7.47-7.9 (m, 10H, ArH), 4.14 (s, 2H, \(\text{CH}_2\)), 3.93 (s, 2H, \(\text{CH}_2\)), 2.98 (s, 3H, \(\text{CH}_3\)), 2.94 (s, 3H, \(\text{CH}_3\)); \textsuperscript{13}C NMR (DMSO, 101 MHz): 171.5, 171.2, 171.1, 170.9, 136.6, 136.3, 130.1, 129.9, 128.1, 128.8, 127.3, 126.7, 53.0, 49.2, 38.7, 34.4.

Synthesis of N-Acetyl-N-phenylglycine (97).\textsuperscript{147}

\[
\begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{H} \\
\text{\_CO}_2\text{H}
\end{array}
\]

Acetyl chloride (0.45 mL, 6.36 mmol), was added portionwise over a 15-30 min period to a cold (0-10 °C) solution of N-phenylglycine (115 mg, 7.64 mmol) and NaOH (560 mg, 14 mmol) in water (12 mL). After the addition was complete, the reaction was stirred for 2 h at rt and then filtered. The filtrate was cooled (ice bath) and acidified to pH 1 with concentrated HCl. The reaction mixture was extracted with
ethyl acetate and the combined organic extracts were dried over magnesium sulfate. Removal of solvent in vacuo gave the title compound as a yellow solid (982 mg, 80%). **Melting point:** 190-191 °C (lit. 193-195 °C); \(^1\text{H NMR (DMSO, 400 MHz):}\) \(\delta\) 12.71 (s, br, 1H), 7.46-7.34 (m, 5H, ArH), 4.25 (s, 2H, CH\(_2\)), 1.81 (s, 3H, CH\(_3\)); \(^{13}\text{C NMR (DMSO, 101 MHz):}\) \(\delta\) 171.0, 169.9, 143.8, 129.9, 128.2, 128.1, 51.3, 22.4.

**Synthesis of N-benzoyl-N-benzylglycine (98).\(^{147}\)**

Benzoyl chloride (0.41 ml, 3.55 mmol), was added portionwise over a 15-30 min period to a cold (0-10 °C) solution of N-benzylglycine hydrochloride (860 mg, 4.26 mmol) and NaOH (312 mg, 7.80 mmol) in water (12 mL). After the addition was complete, the reaction was stirred for 2h at rt and then filtered. The filtrate was cooled (ice bath) and acidified to pH 1 with concentrated HCl. The reaction mixture was extracted with ethyl acetate and the combined organic extracts were dried over magnesium sulfate. Removal of solvent in vacuo gave the title compound as a yellow solid, and a ~1:1 mixture of rotamers (640 mg, 67%). **Melting point:** 105-107 °C (lit. 106-107 °C); \(^1\text{H NMR (DMSO\(_3\), 400 MHz):}\) \(\delta\) 12.87 (s, br, 2H), 7.47-7.33 (m, 4H, ArH), 7.32-7.21 (m, 16H, ArH), 4.70 (s, 2H, CH\(_2\)), 4.53 (s, 2H, CH\(_2\)), 4.00 (s,2H, CH\(_2\)), 3.84 (s, 2H, CH\(_2\)); \(^{13}\text{C NMR (DMSO, 101 MHz):}\) \(\delta\) 171.8, 171.0, 170.5, 167.8, 137.5, 137.1, 136.5, 136.1, 133.3, 131.2, 130.2, 129.7, 129.2, 129.0, 128.3, 127.9, 127.7, 127.3, 126.9, 126.7, 53.6, 50.6, 49.3, 47.1.
Synthesis of N-benzoyl-N-phenylglycine (99).147

Benzoyl chloride (1.65 mL, 14.22 mmol), was added portionwise over a 15-30 min period to a cold (0-10 °C) solution of N-phenylglycine (2.58 g, 17 mmol) and NaOH (1.25 mg, 31 mmol) in water (36 mL). After the addition was complete, the reaction was stirred for 2 h at rt and then filtered. The filtrate was cooled (ice bath) and acidified to pH 1 with concentrated HCl. The reaction mixture was extracted with ethyl acetate and the combined organic extracts were dried over magnesium sulfate. Removal of solvent in vacuo gave the title compound as a yellow solid (3.23 g, 89%).

**Melting point:** 190-194 °C (lit. 193-195 °C); $^1$H NMR (DMSO, 400 MHz): $\delta$ 12.83 (s, br, 1H), 7.29-7.15 (m, 10H, ArH), 4.49 (s, 2H, CH$_2$); $^{13}$C NMR (DMSO, 101 MHz): $\delta$ 170.9, 170.0, 144.1, 136.0, 130.2, 129.4, 128.8, 128.3, 127.8, 127.0, 52.3.
3. Synthesis of münchnones

Synthesis of 4-trifluoroacetyl-3-methyl-2-phenyl-1,3-oxazolium-5-olate (100).\textsuperscript{148}

\[
\text{Ph}^+\text{N}^+\text{Me}^-\text{CF}_3^-\text{O}^-\text{O}^-
\]

\textit{N}-Benzoyl–\textit{N}-methylglycine (250 mg, 1.30 mmol) was added to trifluoroacetic anhydride (1.82 mL, 13.00 mmol). The mixture was stirred for 1.5 h at room temperature. The resulting solution was poured into diethyl ether (10 mL), thereby precipitating the product which was collected by filtration as a yellow solid (324 mg, 92%). \textbf{Melting point:} 160-162 °C (lit. 162-163 °C); \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 7.76-7.70 (m, 3H, ArH), 7.67-7.61 (m, 2H, ArH), 4.13 (s, 3H, NCH\textsubscript{3}); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 101 MHz): \(\delta\) 167.7 (q, \(J = 38.0\) Hz, C=O), 157.9, 153.7, 134.2, 129.7, 129.5, 120.5, 116.8 (q, \(J = 289.0\) Hz, CF\textsubscript{3}), 97.3, 37.6; \textsuperscript{19}F NMR (CDCl\textsubscript{3}, 376.5 MHz): \(\delta\) -75.3.

Synthesis of 4-Trifluoroacetyl-2-methyl-3-phenyl-1,3-oxazolium-5-olate (101).\textsuperscript{148}

\[
\text{Me}^-\text{N}^+\text{Ph}^-\text{CF}_3^-\text{O}^-\text{O}^-
\]

\textit{N}-Acetyl-\textit{N}-phenylglycine (200 mg, 1.03 mmol) was added to trifluoroacetic anhydride (1.46 mL, 10.35 mmol). The mixture was stirred for 5 h at room temperature. The resulting solution was then poured into diethyl ether (10 mL), thereby precipitating the product which was collected by filtration as a yellow solid (176 mg, 63%). \textbf{Melting point:} 209-210 °C (lit. 211-212 °C); \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 7.76-7.70 (m, 3H, ArH), 7.67-7.61 (m, 2H, ArH), 4.13 (s, 3H, NCH\textsubscript{3}); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 101 MHz): \(\delta\) 167.7 (q, \(J = 38.0\) Hz, C=O), 157.9, 153.7, 134.2, 129.7, 129.5, 120.5, 116.8 (q, \(J = 289.0\) Hz, CF\textsubscript{3}), 97.3, 37.6; \textsuperscript{19}F NMR (CDCl\textsubscript{3}, 376.5 MHz): \(\delta\) -75.3.
MHz): δ 7.62-7.55 (m, 3H, ArH), 7.34-7.30 (m, 2H, ArH), 2.38 (s, 3H, CH3); \(^{19}\text{F NMR}\) (CDCl\(_3\), 376.5 MHz): δ -75.4.

Synthesis of 4-Trifluoroacetyl-2-phenyl-1,3-oxazolium-5-olate (102).\(^{148}\)

\[\text{N-Benzoyl-N-phenylglycine (123 mg, 0.46 mmol) was added to trifluoroacetic anhydride (0.64 mL, 4.56 mmol). The mixture was stirred for 4 h at room temperature. The resulting solution was then poured into diethyl ether (10 mL), thereby precipitating the product which was collected by filtration as a white solid (131 mg, 82%). Melting point: 140-143 °C (lit. 143-145 °C); } ^{1}\text{H NMR (CDCl}_3\text{, 400 MHz): } \delta 7.67-7.66 \text{ (m, 3H, ArH), 7.59-7.54 \text{ (m, 2H, ArH), 7.43-7.36 \text{ (m, 3H, ArH), 7.17-7.13 \text{ (m, 2H, ArH), 5.79 \text{ (s, 2H, CH}_2\text{); } } ^{13}\text{C NMR (CDCl}_3\text{, 101 MHz): } \delta 167.1 \text{ (q, } J = 38.0 \text{ Hz, C=O), 158.2, 154.7, 134.4, 133.6, 129.9, 129.4, 129.2, 128.7, 125.8, 120.7, 116.8 \text{ (q, } J = 289.0 \text{ Hz, CF}_3\text{), 96.0, 52.2; } ^{19}\text{F NMR (CDCl}_3\text{, 376.5 MHz): } \delta -75.2.}\]

Synthesis of 4-Trifluoroacetyl-2,3-diphenyl-1,3-oxazolium-5-olate (103).\(^{148}\)

\[\text{N-Benzoyl-N-phenylglycine (70 mg, 0.27 mmol) was added to trifluoroacetic anhydride (0.39 mL, 2.74 mmol). The mixture was stirred for 2 h at room temperature. The resulting solution was then poured into diethyl ether, thereby precipitating the product which was collected by filtration as a yellow solid (63 mg, 70%). Melting point: 193-195 °C (lit.194-196 °C); } ^{1}\text{H NMR (CDCl}_3\text{, 400 MHz): } \delta \]
7.67-7.52 (m, 4H, ArH), 7.43-7.40 (m, 2H, ArH), 7.37-7.34 (m, 4H, ArH); $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta$ 166.4 (q, $J = 38.0$ Hz, C=O), 157.7, 152.2, 134.4, 134.2, 131.3, 130.3, 129.5, 129.4, 126.4, 120.7, 116.6 (q, $J = 289.0$ Hz, CF$_3$), 98.3; $^{19}$F NMR (CDCl$_3$, 376.5 MHz): $\delta$ - 75.4.

Synthesis of 3-methyl-2-phenyl-4-(tosylcarbamoyl)-1,3-oxazolium-5-olate (104).

Tosyl isocyanate (0.44 mL, 2.84 mmol) was added dropwise to a solution of $N$-benzoyl sarcosine (250 mg, 1.30 mmol) in Et$_2$O (5 mL) and the resulting solution was heated at reflux for 2 h. The mixture was added to Et$_2$O (10 mL) at 0 °C, and the precipitate was filtered and washed with cold Et$_2$O to produce the desired product (470 mg, 97%) as a pale yellow powder. **Melting point:** 153-155 °C; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 9.83 (s, 1H, NH), 7.96 (d, $J = 8.0$ Hz, 2H, ArH), 7.70-7.55 (m, 5H, ArH), 7.31 (d, $J = 8.0$ Hz, 2H, ArH), 4.08 (s, 3H, CH$_3$), 2.42 (s, 3H, CH$_3$); $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta$ 161.6, 156.9, 148.9, 144.4, 136.9, 133.5, 129.7, 129.5, 129.0, 128.2, 120.7, 91.4, 36.4, 21.7; FTIR: $\nu_{\text{max}}$: 1703 (s), 1676 (s) cm$^{-1}$; HRMS: m/z [MH$^+$] calc. for C$_{18}$H$_{16}$N$_2$O$_5$S requires 373.0853, found 373.0851.

Synthesis of 3-benzyl-2-phenyl-4-(tosylcarbamoyl)-1,3-oxazolium-5-olate (105).

Tosyl isocyanate (0.31 mL, 2.04 mmol) was added dropwise to a solution of $N$-benzoyl-$N$-benzylglycine (250 mg, 0.93 mmol) in Et$_2$O (5 mL) and the resulting solution was heated at reflux for 2 h. The mixture was added to Et$_2$O (10 mL) at 0
°C, and the precipitate was filtered and washed with cold Et₂O to produce the desired product (417 mg, 100%) as a pale yellow powder. **Melting point:** 136-140 °C; **¹H NMR (CDCl₃, 400 MHz):** δ 9.89 (s, 1H, NH), 7.93 (d, J = 8.0 Hz, 2H, ArH), 7.64-7.48 (m, 6H, ArH), 7.31-7.28 (m, 4H, ArH), 7.06-7.00 (m, 2H, ArH), 5.75 (s, 2H, NCH₂), 2.41 (s, 3H, CH₃); **¹³C NMR (CDCl₃, 101 MHz):** δ 161.7, 156.5, 149.6, 144.1, 137.0, 133.7, 133.5, 129.7, 129.3, 129.2, 128.8, 128.6, 128.2, 126.3, 121.0, 90.5, 51.2, 21.6; **FTIR:** vₚmax: 1708 (s), 1668 (s) cm⁻¹; **HRMS:** m/z [MH⁺] calc. for C₉H₂₀N₂O₅S requires 449.1166, found 449.1164.

**Synthesis of 2,3-dimethyl-4-(tosylcarbamoyl)-1,3-oxazolium-5-olate (106).**

![Chemical structure](image)

Tosyl isocyanate (0.64 mL, 4.20 mmol) was added dropwise to a solution of N-methyl sarcosine (250 mg, 1.90 mmol) in Et₂O (5 mL) and the resulting solution was heated at reflux for 2 h. The mixture was added to Et₂O (10 mL) at 0 °C, and the precipitate was filtered and washed with cold Et₂O to produce the desired product (470 mg, 80%) as a pale yellow powder. **Melting point:** 148-151 °C; **¹H NMR (CDCl₃, 400 MHz):** δ 9.66 (s, 1H, NH), 7.97 (d, J = 8.0 Hz, 2H, ArH), 7.33 (d, J = 8.0 Hz, 2H, ArH), 3.88 (s, 3H, CH₃), 2.53 (s, 3H, CH₃), 2.44 (s, 3H, CH₃); **¹³C NMR (CDCl₃, 101 MHz):** δ 161.7, 156.7, 150.2, 150.3, 144.4, 136.8, 129.5, 128.2, 34.4, 21.7, 11.8.; **FTIR:** vₚmax: 1721 (s), 1668 (s), 1400 (m), 1307 (m), 1157 (m) cm⁻¹; **HRMS:** m/z [MH⁺] calc. for C₁₃H₁₄N₂O₅S requires 311.0696, found 311.0699.
Synthesis of 3-methyl-2-phenyl-4-(2,2,2-trichloroacetyl)carbamoyl-
1,3-oxazolium-5-olate (107).

Trichloroacetyl isocyanate (0.34 mL, 2.85 mmol) was added dropwise to a
solution of N-benzoyl sarcosine (250 mg, 1.30 mmol) in Et₂O (5 mL) and the resulting
solution was heated at reflux for 3 h. The mixture was added to Et₂O (10 mL) at 0
°C and the precipitate was filtered and washed with cold Et₂O to give the title
compound (274 mg, 58%) as a pale yellow powder. Melting point: 147-150 °C; ¹H
NMR (CDCl₃, 400 MHz): δ 11.18 (s, 1H, NH), 7.77-7.61 (m, 5H, ArH), 4.23 (s, 3H,
CH₃); ¹³C NMR (CDCl₃, 101 MHz): δ 161.6, 158.6, 156.6, 149.6, 133.7, 129.8, 129.2,
120.6, 92.9, 92.8, 36.7; FTIR: v_max: 1759 (s), 1714 (s), 1673 (s) cm⁻¹; m/z (El) 362
(10%, [M(³⁵Cl₃)]), 364 (20% [M(³⁷Cl(³⁵Cl₂)])); HRMS: calc. for C₁₃H₉³⁷Cl³⁵Cl₂N₂O₄
364.9501, found 364.9486.

Synthesis of 3-benzyl-2-phenyl-4-(2,2,2-trichloroacetyl) carbamoyl-1,3-
oxazolium-5-olate (108).

Trichloroacetyl isocyanate (0.34 mL, 2.85 mmol) was added dropwise to a
solution of N-benzoyl-N-benzylglycine (250 mg, 0.93 mmol) in Et₂O (5 mL) and the resulting
solution was heated at reflux for 2 hours. The mixture was added to Et₂O
(10 mL) at 0 °C, and the precipitate was filtered and washed with cold Et₂O to
produce the desired product (314 mg, 77%) as a pale yellow powder. Melting point:
110-114 °C; ¹H NMR (CDCl₃, 400 MHz): δ 11.24 (s, 1H, NH), 7.70-7.66 (m, 3H,
ArH), 7.28-7.54 (m, 2H, ArH), 7.42-7.34 (m, 3H, ArH), 7.20-7.18 (m, 2H, ArH), 5.88 (s, 2H, NCH₂); ¹³C NMR (CDCl₃, 101 MHz): δ 161.8, 158.5, 155.0, 150.4, 133.9, 133.4, 129.9, 129.5, 128.9, 128.8, 126.2, 120.7, 92.5, 91.0, 51.6; FTIR: \( \nu_{\text{max}} \): 1756 (s), 1718 (s), 1671 (s) cm⁻¹; m/z (EI) 439 (100%, [M(3⁵Cl₃)]⁺); HRMS: calc. for C₁₉H₁₃⁵Cl₃N₂O₄ requires 439.0014, found 439.0014.

**Synthesis of 2,3-Diphenyl-4-(2,2,2-trichloroacetyl) carbamoyl-1,3-oxazolium-5-olate (109).**

![Chemical structure of 2,3-Diphenyl-4-(2,2,2-trichloroacetyl) carbamoyl-1,3-oxazolium-5-olate (109).]

Trichloroacetyl isocyanate (0.21 mL, 1.72 mmol) was added dropwise to a solution of N-benzoyl-N-benzylglycine (200 mg, 0.78 mmol) in Et₂O (3 mL) and the resulting solution was heated at reflux for 2 h. The mixture was added to Et₂O (10 mL) at 0 °C, and the precipitate was filtered and washed with cold Et₂O to produce the desired product (116 mg, 35%) as a pale yellow powder. **Melting point:** 133-136 °C; ¹H NMR (CDCl₃, 400 MHz): δ 11.14 (s, 1H, NH), 7.67-7.55 (m, 3H, ArH), 7.55-7.49 (m, 1H, ArH), 7.46-7.42 (m, 2H, ArH), 7.37-7.32 (m, 4H, ArH); ¹³C NMR (CDCl₃, 101 MHz): δ 161.1, 158.3, 155.0, 148.4, 133.7, 133.6, 131.4, 130.4, 129.4, 128.9, 126.4, 120.8, 94.3, 92.5; FTIR: \( \nu_{\text{max}} \): 1756 (s), 1740 (s), 1680 (s) cm⁻¹; m/z (EI) 425 (100%, [M(3⁵Cl₃)]⁺), 427 (80% [M(3⁷Cl(3⁵Cl₂)]⁺); 429 (20% [M(3⁵Cl(3⁷Cl₂)]⁺); HRMS: calc. for C₁₈H₁₂⁵Cl₃N₂O₄ requires 424.9863, found 424.9862.
4. Synthesis of pyrrole

Synthesis of 5-trifluoroacetyl-1-methyl-2,4-diphenyl-1H-pyrrole (118).

A solution of 3-methyl-4-trifluoroacetyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.37 mmol) and ethynylbenzene (76 mg, 0.74 mmol) in xylene (0.37 mL) in a sealed microwave vessel was heated at 140 °C for 16 hours. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to provide the title compound as a yellow solid (92 mg, 75%). **Melting point:** 90-93 °C; **¹H NMR** (CDCl₃, 400 MHz): δ 7.54-7.48 (m, 5H, ArH), 7.45-7.38 (m, 5H, ArH), 6.34 (s, 1H, pyrlH), 3.86 (s, 3H, NCH₃); **¹³C NMR** (CDCl₃, 101 MHz): δ 173.5 (q, J = 36.0 Hz, C=O), 145.0, 138.2, 135.3, 130.7, 129.4, 129.1, 128.8, 128.3, 127.8, 127.7, 125.0, 116.2 (q, J = 289.5 Hz, CF₃), 114.0, 36.0; **¹⁹F NMR** (CDCl₃, 376.5 MHz): δ -70.4; **FTIR:** νₓmax 2923 (w), 1660 (s), 1628 (m), 1496 (m), 1465 (w), 1371 (w) cm⁻¹; **HRMS:** m/z [MH⁺] calc. for C₁₉H₁₅NOF₃: 330.1106, found: 330.1099.

Synthesis of 5-trifluoroacetyl-1,4-diphenyl-2-methyl-1H-pyrrole (119).

A solution of 3-phenyl-4-trifluoroacetyl-2-methyl-1,3-oxazolonium-5-olate (179 mg, 0.66 mmol) and ethynyl benzene (135 mg, 1.32 mmol) in xylene (0.66 mL) in a sealed microwave vessel was heated at 140 °C for 16 hours. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 10% EtOAc in petroleum ether), to provide the title compound as a yellow solid (152 mg, 70%). **Melting point:** 125-130 °C; **¹H NMR** (CDCl₃, 400 MHz): δ 7.50-7.46 (m, 3H, ArH), 7.39-7.36 (m, 5H, ArH), 7.25-7.23 (m, 2H, ArH), 6.20 (s, 1H, pyrlH), 2.09 (s,
3H, CH₃); $^{13}$C NMR (CDCl₃, 101 MHz): δ 172.4 (q, $J = 39.5$ Hz, C=O), 141.1, 138.8, 138.3, 135.2, 129.4, 129.2, 128.6, 127.8 (x2C), 127.7, 127.3, 113.3, 116.0 (q, $J = 289.5$ Hz, CF₃), 13.0; $^{19}$F NMR (CDCl₃, 376.5 MHz): δ -71.1; FTIR: $\nu_{\text{max}}$: 1650 (s), 1452 (m), 1378 (m), 1287 (w), 1183 (s), 1148 (s) cm⁻¹; HRMS: m/z [MH⁺] calc. for C₁₉H₁₄NOF₃: 329.1022, found: 329.1026.

**Synthesis of 5-trifluoroacetyl-1-benzyl-2,4-diphenyl-1H-pyrrole (120).**

A solution of 3-benzyl-4-trifluoroacetyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.29 mmol) and ethynylbenzene (117 mg, 1.15 mmol) in xylenes (0.29 mL) in a sealed microwave vessel was heated at 140 °C for 24 hours. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to provide the title compound as a yellow oil (79 mg, 67%).

$^{1}$H NMR (CDCl₃, 400 MHz): δ 7.44-7.37 (m, 10H, ArH), 7.28-7.27 (m, 1H, ArH), 7.25-7.18 (m, 2H, ArH), 6.91-6.83 (m, 2H, ArH), 6.40 (s, 1H, pyrlH), 5.53 (s, 2H, NCH₂); $^{13}$C NMR (CDCl₃, 101 MHz): δ 174.4 (q, $J = 37.0$ Hz), 145.2, 139.0, 138.2, 135.2, 131.0, 129.5, 129.4, 129.3, 128.9, 128.7, 128.0, 127.9, 127.4, 125.8, 123.9, 116.0 (q, $J = 290.0$ Hz), 114.2, 50.3; $^{19}$F NMR (CDCl₃, 376.5 MHz): δ -70.7; FTIR: $\nu_{\text{max}}$: 1656 (s), 1603 (m), 1496 (m), 1484 (m), 1453 (s) cm⁻¹; HRMS: m/z [MH⁺] calc. for C₂₅H₁₈NOF₃: 405.1335 found: 405.1332.
Synthesis of 5-trifluoroacetyl-1,2,4-triphenyl-1H-pyrrole (121).

A solution of 3-phenyl-4-trifluoroacetyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.30 mmol) and ethynylbenzene (61 mg, 0.60 mmol) in xylenes (0.30 mL) in a sealed microwave vessel was heated at 140 °C for 16 hours. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to provide the title compound as a yellow solid (107 mg, 91%). **Melting point:** 164-165 °C; \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.48-7.42 (m, 5H, ArH), 7.39-7.36 (m, 3H, ArH), 7.25-7.20 (m, 5H, ArH), 7.17-7.13 (m, 2H, ArH), 6.56 (s, 1H, PyrlH); \(^1^3\)C NMR (CDCl\(_3\), 101 MHz): \(\delta\) 174.1 (q, \(J\) = 37.0 Hz), 143.3, 138.3, 137.6, 134.8, 130.7, 129.3, 129.0, 128.8, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 125.5, 116.0 (q, \(J\) = 290.0 Hz), 114.0; \(^1^9\)F NMR (CDCl\(_3\), 376.5 MHz): \(\delta\) -71.4; FTIR: \(\nu_{\text{max}}\) 1661 (s), 1596 (m), 1272 (s), 1239 (s), 1195 (s) cm\(^{-1}\); HRMS: m/z [MH\(^+\)] calc. for C\(_{24}\)H\(_{17}\)NOF\(_3\): 392.1262 found: 392.1255.

Synthesis of 5-trifluoroacetyl-1-methyl-2phenyl-4-n-hexyl-1H-pyrrole (122).

A solution of 3-methyl-4-trifluoroacetyl-2-phenyl-1,3-oxazolonium-5-olate (200 mg, 0.74 mmol) and 1-octyne (326 mg, 2.96 mmol) in xylenes (0.74 mL) in a sealed microwave vessel was heated at 140 °C for 72 hours. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 5% EtOAc in petroleum ether) to provide the title compound as a yellow oil (119 mg, 48 %). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.50-7.41 (m, 5H, ArH), 6.23 (s, 1H, pyrlH), 3.77 (s, 3H, NCH\(_3\)), 2.78-2.74 (m, 2H, CH\(_2\)), 1.68-1.61 (m, 2H, CH\(_2\)), 1.45-1.38 (m, 2H, CH\(_2\)),
1.34-1.30 (m, 4H, CH₂), 0.9 (t, J = 7.0 Hz, 3H, CH₃); \(^{13}\text{C NMR (CDCl}_3, 101 \text{ MHz): } \delta 170.8 (q, J = 36.5 Hz), 146.2, 139.3, 131.0, 129.3, 129.0, 128.7, 120.0 (q, J = 289.0 Hz), 118.5, 112.8, 36.5, 31.7, 31.0, 29.3, 27.2 (q, J = 4.0 Hz), 22.6, 14.0; \(^{19}\text{F NMR (CDCl}_3, 376.5 \text{ MHz): } \delta -72.1; \text{ FTIR: } v_{\text{max}}: 1642 (\text{s}), 1542 (\text{w}), 1276 (\text{s}), 1195 (\text{s}), 1139 (\text{s}) \text{ cm}^{-1}; \text{ HRMS: m/z [MH}^+\text{] cald. for C}_{19}\text{H}_{23}\text{NOF}_3: 338.1732, \text{ found: 338.1721.}

\textbf{Synthesis of 5-trifluoroacetyl-1-phenyl-2methyl-4-hexyl-1H-pyrrole (123).}

A solution of 3-phenyl-4-trifluoroacetyl-2-methyl-1,3-oxazolonium-5-olate (100 mg, 0.37 mmol) and 1-octyne (163 mg, 1.47 mmol) in xylenes (0.37 mL) in a sealed microwave vessel was heated at 140 °C for 16 hours. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 5% EtOAc in petroleum ether) to provide the title compound as a yellow oil (30 mg, 25 %). \(^1\text{H NMR (CDCl}_3, 400 \text{ MHz): } \delta 7.47-7.41 (\text{m, 3H, ArH}), 7.16-7.13 (\text{m, 2H, ArH}), 6.10 (\text{s, 1H, pyrH}), 2.76-2.72(\text{m, 2H, CH}_2), 2.00 (\text{s, 3H, CH}_3), 1.68-1.62 (\text{m, 2H, CH}_2), 1.43-1.39 (\text{m, 2H, CH}_2), 1.35-1.31 (\text{m, 4H, CH}_2), 0.91 (\text{t, J = 7.0 Hz, 3H}); \(^{13}\text{C NMR (CDCl}_3, 101 \text{ MHz): } \delta 170.7 (q, J = 38.0 Hz), 142.4, 140.4, 139.5, 129.1, 128.3, 127.4, 125.0, 117.7 (q, J = 273.0 Hz), 112.4, 31.7, 31.0, 29.3, 27.2 (q, J = 7.0 Hz), 22.6, 14.1, 13.2; \(^{19}\text{F NMR (CDCl}_3, 376.5 \text{ MHz): } \delta -72.3; \text{ FTIR: } v_{\text{max}}: 1651 (\text{s}), 1497 (\text{s}), 1196 (\text{s}), 1140 (\text{s}) \text{ cm}^{-1}; \text{ HRMS: m/z [MH}^+\text{] cald. for C}_{19}\text{H}_{23}\text{NOF}_3: 338.1732, \text{ found: 338.1731.}
Synthesis of 5-trifluoroacetyl-1, 2-diphenyl-4-n-hexyl-1H-pyrrole (124).

A solution of 3-phenyl-4-trifluoroacetyl-2-phenyl-1,3-oxazolonium-5-olate (162 mg, 0.49 mmol) and 1-octyne (216 mg, 1.96 mmol) in xylenes (0.49 mL) in a sealed microwave vessel was heated at 140 °C for 48 hours. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 5% EtOAc in petroleum ether) to provide the title compound as a yellow oil (64 mg, 33%).

1H NMR (CDCl₃, 400 MHz): δ 7.34-7.29 (m, 3H, ArH), 7.23-7.17 (m, 3H, ArH), 7.14-7.12 (m, 2H, ArH), 7.08-7.06 (m, 2H, ArH), 6.42 (s, 1H, pyrlH), 2.83-2.79 (m, 2H, CH₂), 1.72-1.70 (m, 2H, CH₂), 1.37-1.36 (m, 2H, CH₂), 1.37-1.34 (m, 4H, CH₂), 0.92 (t, J = 7.0 Hz, 3H, CH₃); 13C NMR (CDCl₃, 101 MHz): δ 171.2 (q, J = 37.0 Hz), 144.5, 139.6, 139.1, 131.0, 129.0, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 116.5 (q, J = 289.3 Hz), 113.4, 31.7, 30.9, 29.3, 27.1 (q, J = 3.0 Hz), 22.6, 14.1; 19F NMR (CDCl₃, 376.5 MHz): δ -72.4; FTIR: νmax : 1675 (s), 1597 (s), 1497 (m), 1365 (m); HRMS: m/z [MH⁺] calc. for C₂₄H₂₅NOF₃: 400.1888, found: 400.1906.

Synthesis of 5-trifluoroacetyl-1-methyl-2-phenyl-4-n-butyl-1H-pyrrole (125).

A solution of 3-methyl-4-trifluoroacetyl-2-phenyl-1,3-oxazolonium-5-olate (200 mg, 0.73 mmol) and 1-hexyne (240 mg, 2.94 mmol) in xylenes (0.73 mL) in a sealed microwave vessel was heated at 140 °C for 48 hours. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 5% EtOAc in petroleum ether) to provide the title compound as a yellow oil (100 mg, 44%).

1H NMR (CDCl₃, 400 MHz): δ 7.52-7.43 (m, 5H, ArH), 6.26 (s, 1H, pyrlH), 3.79 (s, 3H,
NCH$_3$), 2.81-2.77 (m, 2H, CH$_2$), 1.67-1.61 (m, 2H, CH$_2$), 1.48-1.45 (m, 2H, CH$_2$), 0.98 (t, $J$ = 7.0 Hz, 3H, CH$_3$); $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta$ 171.0 (q, $J$ = 36.0 Hz), 146.2, 139.0, 131.0, 129.3, 129.0, 128.7, 125.3, 117.0 (q, $J$ = 289.0 Hz), 113.0, 36.5, 33.1, 27.0 (q, $J$ = 6.0 Hz), 22.6, 14.0; $^{19}$F NMR (CDCl$_3$, 376.5 MHz): $\delta$ -72.1; FTIR: $\nu_{\text{max}}$: 1667 (s), 1449 (s), 1380 (s), 1143 (s) cm$^{-1}$; HRMS: m/z [MH$^+$ ] calc. for C$_{17}$H$_{19}$NOF$_3$: 310.1419, found: 310.1410.

**Synthesis of 5-trifluoroacetyl-1-methyl-2-phenyl-4-cyclopropyl-$^{1}$H-pyrrole (126).**

A solution of 3-methyl-4-trifluoroacetyl-2-phenyl-1,3-oxazolonium-5-olate (200 mg, 0.73 mmol) and ethynylcyclopropane (195 mg, 2.95 mmol) in xylenes (0.73 mL) in a sealed microwave vessel was heated at 140 °C for 48 hours. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 5% EtOAc in petroleum ether) to provide the title compound as a yellow oil (82 mg, 39%).

$^{1}$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.48-7.37 (m, 5H, ArH), 5.93 (s, 1H, pyrlH), 3.77 (s, 3H, NCH$_3$), 2.20-2.13 (m, 1H, CH), 1.03-0.98 (m, 2H, CH$_2$), 0.74-0.70 (m, 2H, CH$_2$); $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta$ 170.8 (q, $J$ = 37.0 Hz), 146.2, 140.9, 130.9, 129.2, 129.1, 128.7, 126.4, 117.1 (q, $J$ = 289.0 Hz), 109.2, 36.6, 9.5, 8.5 (q, $J$ = 6.0 Hz); $^{19}$F NMR (CDCl$_3$, 376.5 MHz): $\delta$ -72.2; FTIR: $\nu_{\text{max}}$: 1641 (s), 1450 (m), 1274 (s) cm$^{-1}$; HRMS: m/z [MH$^+$ ] calc. for C$_{16}$H$_{15}$NOF$_3$: 294.1106, found: 294.1119.
Synthesis of 5-tosylcarbamoyl-1-methyl-2,4 diphenyl-1H-pyrrole (127).

A solution of 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (200 mg, 0.54 mmol) and ethynylbenzene (110 mg, 1.08 mmol) in xylenes (0.3 mL) in a sealed microwave vessel was heated at 110 °C for 5 h. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to provide the title compound as a yellow solid (163 mg, 70%) together with N-methyl-2,4-diphenylpyrrole 128 (14 mg, 11%). See later for spectroscopic data of compound 128. Melting point: 80-83 °C; \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.89-7.87 (m, 2H, ArH), 7.52-7.34 (m, 12H, ArH), 6.19 (s, 1H, pyrlH), 3.81 (s, 3H, NCH\(_3\)), 2.45 (s, 3H, CH\(_3\)); \(^{13}\)C NMR (CDCl\(_3\), 101 MHz): 158.2, 144.8, 141.7, 136.0, 134.5, 131.8, 131.3, 129.6, 129.4 (x3C), 128.7 (x2C), 128.6, 128.5, 120.8, 111.5, 35.3, 21.7; FTIR: \(\nu_{\text{max}}\): 3323 (w), 1674 (s), 1416 (s), 1164 (s), 1063 (s), 699 (s), 657 (s) cm\(^{-1}\); HRMS: m/z [MH\(^+\)] calc. for C\(_{25}\)H\(_{22}\)N\(_2\)O\(_3\)S: 431.1424, found: 431.1422.

Synthesis of 5-tosylcarbamoyl-1-benzyl-2,4 diphenyl-1H-pyrrole (129).

A solution of 3-benzyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.22 mmol) and ethynylbenzene (455 mg, 0.46 mmol) in xylenes (0.3 mL) in a sealed microwave vessel was heated at 110 °C for 16 h. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to provide the title compound as a yellow solid (62 mg, 56%) together with N-benzyl-2,4-diphenylpyrrole 130 (5 mg, 7%). See later for spectroscopic data of compound 130. Melting point: 124-127 °C; \(^1\)H NMR (CDCl\(_3\),
400 MHz): δ 7.80-7.73 (m, 3H, ArH), 7.50-7.35 (m, 10H, ArH), 7.29-7.27 (m, 2H, ArH), 7.28 (d, J = 8.0 Hz, 2H, ArH), 6.77-6.74 (m, 2H, ArH), 6.28 (s, 1H, pyrH), 5.54 (s, 2H, NCH2), 2.45 (s, 3H, CH3); 13C NMR (CDCl3, 101 MHz): δ 158.2, 144.6, 141.0, 138.4, 136.0, 134.2, 132.4, 131.5, 129.6, 129.5, 129.4, 129.3, 128.7 (x2C), 128.6, 128.4 (x2C), 127.1, 126.3, 120.5, 112.0, 49.3, 21.7; FTIR: ʋmax: 3321 (m), 1683 (s), 1426 (s), 1166 (s), 1085 (s) cm⁻¹; HRMS: m/z [MH+] calc. for C31H26N2O3S: 507.1737 found: 507.1748.

Synthesis of 5-tosylcarbamoyl-1-methyl-2-phenyl-4-n-hexyl-1H-pyrrole (131).

A solution of 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (200 mg, 0.53 mmol) and 1-octyne (236 mg, 2.14 mmol) in xylenes (0.5 mL) in a sealed microwave vessel was heated at 110 °C for 16 h. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to provide the title compound as a colourless oil (53 mg, 23%). 1H NMR (CDCl3, 400 MHz): δ 8.09-8.01 (m, 2H, ArH), 7.42-7.30 (m, 7H, ArH), 6.05 (s, 1H, pyrH), 3.67 (s, 3H, CH3), 2.74-2.67 (m, 2H, CH2), 2.44 (s, 3H, CH3), 1.68-1.59 (m, 2H, CH2), 1.43-1.36 (m, 2H, CH2), 1.33-1.30 (m, 4H, CH2), 0.91 (t, J = 7.0 Hz, 3H, CH3); 13C NMR (CDCl3, 101 MHz): δ 158.2, 144.8, 141.8, 136.2, 131.5, 131.3, 129.6, 129.3, 128.6, 128.5, 128.3, 121.6, 110.8, 35.0, 31.7, 30.7, 29.2, 28.3, 22.6, 21.7, 14.1; FTIR: ʋmax: 2924 (m), 1671 (s), 1451 (s), 1421 (s), 1162 (s) cm⁻¹; HRMS: m/z [MH+] calc. for C25H30N2O3S: 440.2081, found 440.2084.
Synthesis of 5-tosylcarbamoyl-1-methyl-2-phenyl-4-n-butyl-1H-pyrrole (132).

A solution of 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (200 mg, 0.53 mmol) and 1-hexyne (176 mg, 2.14 mmol) in xylenes (0.5 mL) in a sealed microwave vessel was heated at 110 °C for 16 h. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to provide the title compound as a colorless oil (45 mg, 20%). 

\[ ^1\text{H NMR (CDCl}_3, 400\text{ MHz):} \delta 8.11-8.02 (m, 3H, ArH), 7.46-7.43 (m, 1H, ArH), 7.42-7.40 (m, 1H, ArH), 7.39-7.36 (m, 2H, ArH), 7.35-7.34 (m, 1H, ArH), 7.34-7.33 (m, 1H, ArH), 6.08 (s, 1H, pyrH), 3.69 (s, 3H, CH\text{$_3$}), 2.76-2.71 (m, 2H, CH\text{$_2$}), 2.46 (s, 3H, CH\text{$_3$}), 1.69-1.60 (m, 2H, CH\text{$_2$}), 1.49-1.40 (m, 2H, CH\text{$_2$}), 0.98 (t, J = 7.3 Hz, 3H, CH\text{$_3$}); \]

\[ ^{13}\text{C NMR (CDCl}_3, 101\text{ MHz):} \delta 158.2, 144.8, 141.8, 136.2, 131.5, 131.3, 129.6, 129.3, 128.6, 128.5, 128.3, 126.5, 121.7, 110.9, 35.0, 32.8, 28.0, 22.6, 21.7, 13.9; \]

\[ \text{FTIR } \nu_{\text{max}}: 2927 (m), 1672 (s), 1451 (s), 1422 (s), 1162 (s) \text{ cm}^{-1}; \]

\[ \text{HRMS: m/z [MH}^+\text{]} \text{ calc. for C}_{23}\text{H}_{26}\text{N}_2\text{O}_3\text{S: 411.1737, found 411.1741.} \]

Synthesis of 5-tosylcarbamoyl-1-methyl-2-phenyl-4-cyclopropyl-1H-(133).

A solution of 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (200 mg, 0.53 mmol) and ethynylcyclopropane (142 mg, 2.15 mmol) in xylenes (0.5 mL) in a sealed microwave vessel was heated at 110 °C for 24 h. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to provide the title compound as a yellow oil (140 mg, 67%). 

\[ ^1\text{H NMR (CDCl}_3, 400\text{ MHz):} \delta 9.58 (s, 1H, NH), 8.06-8.03 (m, 2H, ArH), 7.43-
7.34 (m, 5H, ArH), 7.30–7.28 (m, 2H, ArH), 6.01 (s, 1H, pyrH), 3.73 (s, 3H, NCH₃), 2.43 (s, 3H, CH₃), 2.01-1.94 (m, 1H, CH), 1.20-1.16 (m, 2H, CH₂), 0.85-0.82 (m, 2H, CH₂); ¹³C NMR (CDCl₃, 101 MHz): δ 158.0, 144.7, 141.5, 136.5, 131.9, 131.3, 129.6, 129.3, 128.6, 128.5, 128.4, 122.4, 110.9, 35.3, 21.7, 9.7, 7.8; FTIR: v max: 3312 (m), 1671 (s), 1422 (s), 657 (s) cm⁻¹;

**Synthesis of 5-tosylcarbamoyl-1-benzyl-2-phenyl-4-cyclopropyl-1H-pyrrole (134).**

![Chemical Structure](image)

A solution of 3-benzyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium -5-olate (200 mg, 0.45 mmol) and ethynylcyclopropane (118 mg, 1.78 mmol) in xylenes (0.7 mL) in a sealed microwave vessel was heated at 110 °C for 24 h. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to provide the title compound as a yellow oil (95 mg, 45%).

**¹H NMR (CDCl₃, 400 MHz):** δ 9.34 (s, 1H, NH), 7.94-7.89 (m, 2H, ArH), 7.34-7.31 (m, 3H, ArH), 7.30-7.27 (m, 1H, ArH), 7.26-7.20 (m, 3H, ArH), 7.10-7.04 (m, 3H, ArH), 6.70-6.62 (m, 2H, ArH), 6.03 (s, 1H, pyrH), 5.48 (s, 2H, CH₂), 2.43 (s, 3H, CH₃), 2.02-1.96 (m, 1H, CH), 1.20-1.15 (m, 2H, CH₂), 0.86-0.82 (m, 2H, CH₂); ¹³C NMR (CDCl₃, 101 MHz): δ 157.7, 144.4, 142.0, 138.7, 136.4, 132.8, 131.5, 129.7, 129.4, 129.1, 128.6, 128.2, 126.8, 126.5, 126.1, 121.8, 111.1, 49.3, 21.7, 9.6, 7.9; FTIR: v max: 3286 (m), 2971 (m), 1739 (s), 1673 (s) cm⁻¹; HRMS: m/z [MH⁺] calc. for C₂₈H₂₆N₂O₃S: 471.1737, found: 471.1737.
Synthesis of 5-amide-1-methyl-2,4 diphenyl-1H-pyrrole (135).

A solution of 3-methyl-4-(2,2,2-trichloroacetyl) carbamoyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.28 mmol) and ethynylbenzene (562 mg, 0.55 mmol) in xylenes (0.15 mL) in a sealed microwave vessel was heated at 110 °C for 21 h. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to provide the title compound as a yellow solid (64 mg, 83%). **Melting point:** 165-168 °C; **$^1$H NMR (CDCl$_3$, 400 MHz):** $\delta$ 7.50-7.32 (m, 10H, ArH), 6.21 (s, 1H, pyrH), 5.61 (br, 1H, NH$_2$), 5.50 (br, 1H, NH$_2$), 3.87 (s, 3H, NCH$_3$); **$^{13}$C NMR (CDCl$_3$, 101 MHz):** $\delta$ 164.1, 139.4, 135.9, 132.1, 129.5, 129.4, 129.2, 128.8, 128.6, 128.0, 127.5, 122.9, 110.7, 35.0; **FTIR:** $\nu_{\text{max}}$: 3416 (w), 3166 (w), 1638 (s), 1442 (s), 755 (s), 697 (s) cm$^{-1}$; **HRMS:** m/z [MH$^+$] calc. for C$_{18}$H$_{16}$N$_2$O: 277.1335, found: 277.1339.

Synthesis of 5-trichloroacetyl carbamoyl-1-methyl-2,4 diphenyl-1H-pyrrole (136).

A solution of 3-methyl-4-(2,2,2-trichloroacetyl)carbamoyl- 2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.28 mmol) and ethynylbenzene (562 mg, 0.55 mmol) in xylenes (0.15 mL) in a sealed microwave vessel was heated at 110 °C for 6 h. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to provide the title compound as a yellow oil (38 mg, 32%) together with 5-amide-1-methyl-2,4 diphenyl-1H-pyrrole 135.
(61 mg, 52%). 131: \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.99 (s, 1H, NH), 7.48-7.43 (m, 10H, ArH), 6.24 (s, 1H, pyrH), 3.94 (s, 3H, CH\(_3\)); \(^{13}\)C NMR (CDCl\(_3\), 101 MHz): \(\delta\) 157.7, 157.6, 142.6, 134.6, 132.3, 131.1, 129.0, 129.7, 129.5, 128.8, 128.7 (x2C), 121.6, 116.7, 112.3, 35.7; FTIR: \(v_{\text{max}}\): 2924 (m), 1757 (s), 1645 (s), 1577 (m) cm\(^{-1}\); m/z (EI) 421 (70%, [M(\(^{35}\)Cl\(_3\)])\(^+\)), HRMS: calc. for C\(_{20}\)H\(_{15}\(^{35}\)Cl\(_3\)N\(_2\)O\(_2\): 421.0272, found 421.0276.

**Synthesis of 5-amide-1-benzyl-2,4 diphenyl-1H-pyrrole (137).**

![Diagram of 5-amide-1-benzyl-2,4 diphenyl-1H-pyrrole](image)

A solution of 3-benzyl-4-(2,2,2-trichloroacetyl)carbamoyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.23 mmol) and ethynylbenzene (46 mg, 0.45 mmol) in xylenes (0.35 mL) in a sealed microwave vessel was heated at 110 °C for 22 h. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to provide the title compound as a brown oil (58 mg, 71%). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.52-7.50 (m, 2H, ArH), 7.43-7.32 (m, 8H, ArH), 7.24-7.14 (m, 3H, ArH), 6.90-6.88 (m, 2H, ArH), 6.27 (s, 1H, pyrH), 5.65 (s, 2H, CH\(_2\)), 5.33 (br, 1H, NH\(_2\)), 5.17 (br, 1H, NH\(_2\)); \(^{13}\)C NMR (CDCl\(_3\), 101 MHz): \(\delta\) 163.8, 139.7, 139.4, 135.8, 132.2, 129.8, 129.6, 129.4, 128.7, 128.5, 128.4, 128.2, 127.4, 126.9, 126.2, 122.3, 111.3, 49.2; FTIR: \(v_{\text{max}}\): 3474 (m), 1664 (s), 1598 (m), 1456 (s), 751 (s), 696 (s) cm\(^{-1}\); HRMS: m/z [MH\(^+\)] calc. for C\(_{24}\)H\(_{20}\)N\(_2\)O: 353.1650, found: 353.1648.
Synthesis of 5-amide-1-benzyl-2-phenyl-4-cyclopropyl-1H-pyrrole (138).

A solution of 3-benzyl-4-((2,2,2-trichloroacetyl)carbamoyl)-2-phenyl-1,3-oxazolonium-5-olate (200 mg, 0.45 mmol) and ethynylcyclopropane (120 mg, 1.81 mmol) in xylenes (0.7 mL) in a sealed microwave vessel was heated at 110 °C for 22 h. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to provide the title compound as a yellow oil (90 mg, 63%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.35-7.27 (m, 5H, ArH), 7.22-7.13 (m, 3H, ArH), 6.85-6.81 (m, 2H, ArH), 6.01 (s, 1H, pyrlH), 5.62 (s, 2H, CH$_2$), 2.02-1.95 (m, 1H, CH), 1.01-0.96 (m, 2H, CH$_2$), 0.81-0.76 (m, 2H, CH$_2$); $^{13}$C NMR (CDCl$_3$, 101 MHz): δ 163.9, 139.8, 139.7, 132.3, 130.7, 129.5, 128.4, 128.3, 128.0, 126.7, 126.0, 123.8, 109.5, 49.2, 9.3, 7.6; FTIR: $\nu_{\text{max}}$: 3385 (m), 3016 (m), 1738 (s) cm$^{-1}$; HRMS: m/z [MH$^+$] calc. for C$_{21}$H$_{20}$N$_2$O: 317.1648, found: 317.1648.

Synthesis of 5-amide-1-methyl -2-phenyl-4-cyclopropyl-1H-pyrrole (139).

A solution of 3-methyl-4-((2,2,2-trichloroacetyl)carbamoyl)-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.27 mmol) and ethynylcyclopropane (73 mg, 1.10 mmol) in xylenes (0.35 mL) in a sealed microwave vessel was heated at 110 °C for 22 h. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to provide the title compound as a yellow solid (55 mg, 83%). Melting point: 138-140 °C; $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.43-7.33 (m, 5H, ArH), 5.93 (s, 1H, pyrlH), 3.84 (s, 3H, NCH$_3$), 2.02-1.93.
(m, 1H, CH), 0.99-0.93 (m, 2H, CH₂), 0.78-0.74 (m, 2H, CH₂); \(^{13}\text{C NMR (CDCl}_3, 101\text{ MHz)}\): \(\delta\) 164.4, 139.2, 132.2, 129.8, 129.4, 128.4, 127.9, 124.6, 108.8, 35.0, 9.3, 7.4; \text{FTIR: } \nu_{\text{max}}: 3363 (w), 3165 (w), 1638 (s), 1602 (s), 1465 (s), 764 (s), 700 (s) cm\(^{-1}\); \text{HRMS: } m/z \text{ [MH}^+\text{] calc. for C}_{15}\text{H}_{16}\text{N}_2\text{O}: 241.1335, \text{found: 241.1336.}

**Synthesis of 5-carboxylic acid-1-benzyl-2,4 diphenyl-1H-pyrrole (140).**

5-Trifluoroacetyl-1-benzyl-2,4-diphenyl pyrrole (100 mg, 0.25 mmol) and NaOH (197 mg) in methanol (0.7 mL) and water (0.7 mL) were heated under reflux overnight. The mixture was acidified with concentrated HCl and extracted with EtOAc. The extracts were washed with water and brine, then dried (MgSO\(_4\)) and evaporated. The crude materials were purified by flash chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to provide the title compound as a white solid (62 mg, 70%). **Melting point**: 158-161 °C; \(^1\text{H NMR (CDCl}_3, 400\text{ MHz)}\): \(\delta\) 7.51-7.48 (m, 2H, ArH), 7.39-7.32 (m, 8H, ArH), 7.24-7.18 (m, 3H, ArH), 6.87 (d, \(J = 7.0\) Hz, 2H, ArH), 6.33 (s, 1H, pyrlH), 5.60 (s, 2H, NCH₂); \(^{13}\text{C NMR (CDCl}_3, 101\text{ MHz)}\): \(\delta\) 165.1, 142.1, 139.1, 136.1, 131.8, 129.6, 129.5, 128.6, 128.5, 128.4, 127.8 (x2C), 127.0, 126.9, 125.9, 118.1, 113.0, 49.8; \text{FTIR: } \nu_{\text{max}}: 3065 (w), 3031 (w), 2970 (w), 1653 (s), 1456 (s), 1270 (s) cm\(^{-1}\); \text{HRMS: } m/z \text{ [MH}^+\text{] calc. for C}_{24}\text{H}_{19}\text{N}_2\text{O}: 354.1489, \text{found: 354.1485.}
Synthesis of 5-carboxylic acid-1-methyl-2,4 diphenyl-1H-pyrrole (141).

5-Trifluoroacetyl-1-methyl-2,4-diphenyl pyrrole (190 mg, 0.58 mmol) and NaOH (461 mg) in methanol (1.5 mL) and water (1.5 mL) were heated under reflux overnight. The mixture was acidified with concentrated HCl and extracted with EtOAc. The extracts were washed with water and brine, then dried (MgSO$_4$) and evaporated. The crude materials were purified by flash chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to provide the title compound as a yellow solid (94 mg, 58%). Melting point: 174-176 °C; $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.52-7.32 (m, 10H, ArH), 6.27 (s, 1H, pyrlH), 3.87 (s, 3H, NCH$_3$); $^{13}$C NMR (CDCl$_3$, 101 MHz): δ 166.1, 141.7, 136.3, 135.5, 131.8, 129.7, 129.5, 128.6, 128.4, 127.8, 126.9, 118.8, 112.3, 35.6; FTIR: $\nu_{\text{max}}$: 3614 (br), 3053 (w), 1709 (m), 1599 (s), 1413 (s), 1361 (s) cm$^{-1}$; HRMS: m/z [MH$^+$] calc. for C$_{18}$H$_{15}$NO$_2$: 278.1176, found: 278.1173.

Synthesis of 1-methyl-2,4-diphenyl-1H-pyrrole (128).

5-Tosylcarbamoyl-1-methyl-2,4-diphenyl-1H-pyrrole (120 mg, 0.28 mmol) in methanol (1 mL) and acetic acid (1 mL) were heated under reflux overnight. The mixture was extracted with EtOAc. The extracts were washed with water and brine, then dried (MgSO$_4$) and evaporated. The crude materials were purified by flash chromatography on silica gel (eluting with 30% EtOAc in petroleum ether) to provide the title compound as a colorless oil (39 mg, 60%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.55-7.53 (m, 2H, ArH), 7.47-7.41 (m, 4H, ArH), 7.36-7.33 (m, 3H, ArH), 7.19-7.16 (m, 1H, ArH), 7.02 (d, $J$ = 2.0 Hz, 1H, pyrlH), 6.54 (d, $J$ = 2.0 Hz, 1H, pyrlH), 3.70 (s,
3H, NCH₃); $^{13}$C NMR (CDCl₃, 101 MHz): δ 135.7, 133.1, 128.9, 128.7, 128.6, 128.4, 127.4, 127.0, 125.4, 124.0, 120.4, 106.7, 35.2; FTIR: νmax: 1681 (s), 1448 (m), 1424 (m) cm⁻¹; HRMS: m/z [MH⁺] calc. for C₁₇H₁₅N: 234.1277, found 234.1274.

**Synthesis of N-benzyl-2,4-diphenyl pyrrole (130).**

5-Tosylcarbamoyl-1-benzyl-2,4-diphenyl-1H-pyrrole (150 mg, 0.29 mmol) in methanol (1 mL) and acetic acid (1 mL) were heated under reflux overnight. The mixture was extracted with EtOAc. The extracts were washed with water and brine, then dried (MgSO₄) and evaporated. The crude materials were purified by flash chromatography on silica gel (eluting with 30% EtOAc in petroleum ether) to provide the title compound as a yellow solid (65 mg, 71%). **Melting point:** 93-95 °C (lit. 96-98 °C); $^1$H NMR (CDCl₃, 400 MHz): 7.58-7.54 (m, 2H, ArH), 7.41-7.27 (m, 10H, ArH), 7.21-7.14 (m, 1H, ArH), 7.11-7.07 (m, 2H, ArH), 7.06 (d, J = 2.0 Hz, 1H, PyrH), 6.60 (d, J = 2.0 Hz, 1H, PyrH), 5.18 (s, 2H, CH₂); $^{13}$C NMR (CDCl₃, 101 MHz): 138.5, 136.1, 135.6, 133.0, 128.9, 128.7, 128.6, 128.5, 127.4, 127.3, 126.6, 125.5, 124.0, 124.9, 119.5, 106.9, 50.9.
5. Preparation of isomeric 1-substituted enamines.
Acetophenone enamines were synthesized according to a literature method.\textsuperscript{150}

General procedure as exemplified by the synthesis of $N$-(1-arylvinyl) piperidine (153).\textsuperscript{151,152}

To a solution of acetophenone (2.0 g, 17.0 mmol) and piperidine (10 mL, 100.0 mmol) in anhydrous hexane (40 mL), was added TiCl$_4$ (1.8 mL, 17.0 mmol) over 30 min at 0 °C. The reaction mixture was stirred at room temperature for 24 h and filtered. The filtrate was evaporated under vacuum to give $N$-(1-arylvinyl)piperidine as a pale yellow oil (2.0 g, 67% yield). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.48-7.45 (m, 2H, ArH), 7.33-7.28 (m, 3H, ArH), 4.24 (s, 1H, CH), 4.15 (s, 1H, CH), 2.82-2.79 (m, 4H, CH$_2$), 1.62-1.53 (m, 6H, CH$_2$). $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta$ 158.0, 140.3, 128.0, 127.7, 127.7, 90.1, 50.5, 26.0, 24.5.

$N$-(1-(p-tolyl)vinyl)piperidine (154).\textsuperscript{153}

Following the general procedure using 4-methylacetophenone (500 mg, 3.7 mmol), piperidine (2.2 mL, 22.0 mmol) and TiCl$_4$ (0.4 mL, 2.3 mmol) the title compound was isolated as a yellow oil (590 mg, 79%). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.37-7.34 (m, 2H, ArH), 7.14-7.12 (m, 2H, ArH), 4.21 (s, 1H, CH), 4.10 (s, 1H, CH), 2.81-2.78 (m, 4H, CH$_2$), 2.35 (s, 3H, CH$_3$), 1.64-1.58 (m, 6H, CH$_2$). $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta$ 158.0, 137.5, 137.4, 128.7, 127.6, 89.5, 50.5, 26.0, 24.5, 21.1.
Following the general procedure using (4-trifluoromethyl)phenyl]ethanone (200 mg, 1.0 mmol), piperidine (0.6 mL, 6.0 mmol) and TiCl$_4$ (0.1 mL, 1.0 mmol) the title compound was isolated as a yellow oil (190 mg, 79%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.57 (m, 4H, ArH), 4.30 (s, 1H, CH), 4.23 (s, 1H, CH), 2.79-2.77 (m, 4H, CH$_2$), 1.65-1.52 (m, 6H, CH$_2$); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ: 156.8, 144.0, 129.79 (q, $J = 32.0$ Hz), 127.9, 125.1, 124.4 (q, $J = 399.0$ Hz), 92.0, 50.7, 26.1, 24.4.

Following the general procedure using 4-chloroacetophernone (500 mg, 2.3 mmol), piperidine (1.3 mL, 14.0 mmol) and TiCl$_4$ (0.2 mL, 2.3 mmol) the title compound was isolated as a yellow oil (370 mg, 75%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.44-7.40 (m, 2H, ArH), 7.32-7.28 (m, 2H, ArH), 4.25 (s, 1H, CH), 4.17 (s, 1H, CH), 2.81-2.78 (m, 4H, CH$_2$), 1.66-1.57 (m, 6H, CH$_2$); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 156.9, 138.8, 133.4, 128.9, 128.2, 90.8, 50.5, 25.9, 24.4.
**N-(1- naphthalene)vinyl)piperidine (157).**

Following the general procedure using 1-acetonaphthalene (200 mg, 1.1 mmol), piperidine (0.7 mL, 7.0 mmol) and TiCl₄ (0.1 mL, 1.1 mmol) the title compound was isolated as a yellow oil (220 mg, 79%). ^1H NMR (CDCl₃, 400 MHz): δ 8.52-8.44 (m, 1H, ArH), 7.90-7.81 (m, 2H, ArH), 7.55-7.43 (m, 4H, ArH), 4.34 (s, 1H, CH), 4.09 (s, 1H, CH), 2.92–2.84 (m, 4H, CH₂), 1.60-1.48 (m, 6H, CH₂). ^13C NMR (CDCl₃, 101 MHz): δ 155.5, 138.4, 133.4, 132.1, 128.0, 127.9, 126.9, 126.1, 125.8, 125.7, 125.2, 88.9, 49.1, 25.8, 24.5.

**N,N-Diethyl-1-(pyridin-3-yl)ethenamine (158).**

Following the general procedure using 4-acetylpyridine (200 mg, 1.6 mmol), diethylamine (1.0 mL, 10 mmol) and TiCl₄ (0.2 mL, 1.6 mmol) the title compound was isolated as a pale yellow oil (71 mg, 25%). ^1H NMR (CDCl₃, 400 MHz): δ 8.58-8.56 (m, 1H, ArH), 8.43-8.40 (m, 1H, ArH), 7.62-7.59 (m, 1H, ArH), 7.14-7.10 (m, 1H, ArH), 4.10 (s, 1H, CH), 4.06 (s, 1H, CH), 2.88-2.84 (m, 4H, CH₂), 0.93-0.90 (m, 6H, CH₃); ^13C NMR (CDCl₃, 101 MHz): δ 152.0, 149.5, 149.2, 136.8, 135.2, 123.2, 92.5, 45.4, 11.9.
1-(3-methylbut-1-en-2-yl)piperidine (159).

Following the general procedure using 2-acetyl propane (200 mg, 2.3 mmol), Piperidine (1.4 mL, 14.0 mmol) and TiCl₄ (0.3 mL, 2.3 mmol) the title compound was isolated as a yellow oil (250 mg, 71%). $^1$H NMR (CDCl₃, 400 MHz): $\delta$ 3.97 (s, 1H, CH), 3.88 (s, 1H, CH), 2.86-2.81 (m, 4H, CH₂), 1.63-1.57 (m, 6H, CH₂), 1.10 (d, $J$ = 7.0 Hz, 6H, CH₃). $^{13}$C NMR (CDCl₃, 101 MHz): $\delta$ 163.6, 83.9, 51.5, 30.1, 26.5, 25.9, 24.6.

Synthesis of 1-(hex-1-en-2-yl)piperidine (160a) and 1-(hex2-en-3yl) piperidine (160b).

Following the general procedure using 2-hexanone (200 mg, 1.1 mmol), piperidine (1.2 mL, 12 mmol) and TiCl₄ (0.2 mL, 1.1 mmol) the title compound was isolated as a yellow oil and a mixture of two regioisomer (1:1; 220 mg, 84%); $^1$H NMR (CDCl₃, 400 MHz): $\delta$ 4.29 (t, $J$ = 7.0 Hz, 1H), 3.80 (s, 1H, CH), 3.74 (s, 1H, CH), 2.93-2.77 (m, 8H, CH₂), 2.15-2.09 (m, 4H, CH₂), 1.71 (d, $J$ = 7.0 Hz, 3H, CH₃), 1.98-1.92 (m, 6H, CH₂), 1.50-1.45 (m, 12H, CH₂), 0.95-0.90 (m, 6H, CH₃); $^{13}$C NMR (CDCl₃, 101 MHz): $\delta$ 144.6, 104.6, 49.9 (x2C), 45.8, 43.5, 29.9, 29.8, 26.1, 26.0, 24.6, 23.8, 15.7, 10.7, 10.5.

To a flame-dried two neck round bottom flask equipped with a stirrer bar and reflux condenser was added a solution of 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.27 mmol, 1.0 eq.) and N-(1-phenylvinyl)piperidine (101 mg, 0.54 mmol, 2.0 eq.) in xylenes (2 mL) under N2 at room temperature. The mixture was left to stir at room temperature for 10-15 minutes and afterwards, heated at 110 °C for 1-4 h. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 5 % EtOAc in petroleum ether) to afford the title compound as a yellow solid (84 mg, 72%). For characterization data, see compound 127.

Synthesis of 5-tosylcarbamoyl-1-methyl-2-phenyl-4-p-tolyl-1H-pyrrole (161).

Following the general procedure using 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.27 mmol) and N-(1-((p-tolyl)vinyl)piperidine (109 mg, 0.54 mmol), the title compound was isolated as a yellow oil (110 mg, 92%). ¹H NMR (CDCl₃, 400 MHz): δ 7.88-7.86 (m, 2H, ArH), 7.46-7.38 (m, 3H, ArH), 7.36-
7.33 (m, 3H, ArH), 7.30-7.23 (m, 5H, ArH), 6.15 (s, 1H, pyrH), 3.80 (s, 3H, NCH₃), 2.45 (s, 3H, CH₃), 2.44 (s, 3H, CH₃); ¹³C NMR (CDCl₃, 101 MHz): 158.2, 144.8, 141.7, 138.6, 136.2, 131.8, 131.5, 131.3, 130.1, 129.5, 129.4 (x2C), 128.6, 128.5, 128.4, 120.6, 111.6, 35.3, 21.7, 21.4.; FTIR: νmax: 3318 (m), 2922 (m), 1677 (s), 1451 (s), 1166 (s), 812 (s) cm⁻¹; HRMS: m/z [MH⁺] calc. for C₂₆H₂₄N₂O₃S: 445.1580, found: 445.1590.

Synthesis of 5-tosylcarbamoyl-1-methyl-2-phenyl-4-trifluoromethyl-1H-pyrrole (163).

Following the general procedure using 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.27 mmol) and N-(1-(p-trifluoromethyl)vinyl)piperidine (167 mg, 0.54 mmol), the title compound was isolated as a yellow oil (92 mg, 68%). ¹H NMR (CDCl₃, 400 MHz): δ 7.92-7.89 (m, 2H, ArH), 7.74-7.69 (m, 2H, ArH), 7.50-7.43 (m, 5H, ArH), 7.42-7.38 (m, 4H, ArH), 6.22 (s, 1H, pyrH), 3.80 (s, 3H, NCH₃), 2.49 (s, 3H, CH₃); ¹³C NMR (CDCl₃, 101 MHz): 158.1, 145.1, 141.7, 138.1, 135.7, 130.9, 130.4, 130.2, 129.7, 129.6, 129.4, 129.3, 128.7, 128.5, 126.1 (q, J = 4.0 Hz), 121.2, 123.8 (q, J = 274 Hz), 111.3, 35.1, 21.7; ¹⁹F NMR (CDCl₃, 376.5 MHz): δ -63.0; FTIR: νmax: 2951 (w), 2927 (w), 1683 (m), 1456 (s), 1325 (s), 1166 (s), 767 (m) cm⁻¹; HRMS: m/z [MH⁺] calc. for C₂₆H₂₁F₃N₂O₃S: 499.1298, found: 499.1308.
Synthesis of 5-tosylcarbamoyl-1-benzyl-2-phenyl-4-chlorophenyl-1H-pyrrole (164).

Following the general procedure using 3-benzyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.22 mmol) and N-(1-(4-chlorophenyl)vinyl)piperidine (99 mg, 0.44 mmol), the title compound was isolated as a colorless oil (105 mg, 88%). \(^{1}H\) NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.77 (d, \(J = 8.0\) Hz, 2H, ArH), 7.42-7.38 (m, 5H, ArH), 7.35-7.31 (m, 3H, ArH), 7.30-7.27 (m, 3H, ArH), 7.12-7.05 (m, 3H, ArH), 6.74-6.66 (m, 2H, ArH), 6.23 (s, 1H, PyrH), 5.46 (s, 2H, CH\(_2\)), 2.46 (s, 3H, CH\(_3\)). \(^{13}C\) NMR (CDCl\(_3\), 101 MHz): \(\delta\) 158.1, 144.7, 141.9, 138.1, 135.8, 134.4, 132.4, 131.3, 130.5, 130.6 (x2C), 129.5, 129.4, 128.8, 128.7, 128.4, 128.3, 127.2, 126.3, 120.6, 111.7, 49.2, 21.7; FTIR: \(v_{\text{max}}\): 3321 (w), 1683 (s), 1454 (m), 1167 (s), 1086 (m) cm\(^{-1}\); HRMS: m/z [MH\(^+\)] calc. for C\(_{31}\)H\(_{25}\)ClN\(_2\)O\(_3\)S: 541.1347, found: 541.1359.

Synthesis of 5-tosylcarbamoyl-1-methyl-2-phenyl-4-naphthalene-1H-pyrrole (165).

Following the general procedure using 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.27 mmol) and N-(1-naphthalene vinyl) piperidine (158 mg, 0.54 mmol), the title compound was isolated as a yellow oil (92 mg, 71%). \(^{1}H\) NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.03 (m, 2H, ArH), 7.68-7.53 (m, 5H, ArH), 7.47-7.27 (m, 7H, ArH), 7.13-7.09 (m, 2H, ArH), 6.30 (s, 1H, PyrH), 3.94 (s, 3H,
NCH₃), 2.40 (s, 3H, CH₃); ¹³C NMR (CDCl₃, 101 MHz): δ 157.9, 144.3, 142.0, 135.6, 133.9, 132.5, 132.3, 131.2, 129.7, 129.4, 129.3, 128.7, 128.6, 128.1, 128.0 127.1, 126.6, 125.8 125.7, 122.2, 112.5, 35.5, 21.6; FTIR: v max: 3058 (w), 2957 (w), 1678 (s), 1449 (s), 1166 (s), 1067 (s), 781 (m) cm⁻¹; HRMS: m/z [MH⁺] calc. for C₂₉H₂₄N₂O₃S: 481.1580, found: 481.1589.

Synthesis of 5-tosylcarbamoyl-1-methyl-2-phenyl-4-pyridin-1H-pyrrole (166).

Following the general procedure using 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.27 mmol) and N,N-diethyl-1-(pyridin-3-yl)ethenamine (95 mg, 0.54 mmol), the title compound was isolated as brown oil (78 mg, 67% yield). ¹H NMR (CDCl₃, 400 MHz): δ 8.3-8.30 (m, 2H, ArH), 7.99-7.97 (m, 2H, ArH), 7.74-7.71 (m, 1H, ArH), 7.47-7.36 (m, 8H, ArH), 6.21 (s, 1H, PyrH), 3.78 (s, 3H, NCH₃), 2.45 (s, 3H, CH₃); ¹³C NMR (CDCl₃, 101 MHz): 159.1, 148.5, 147.1, 144.6, 144.4, 137.7, 136.5, 131.2, 131.0, 129.5, 129.3, 128.7, 128.6, 128.5, 126.8, 123.7, 122.3, 110.6, 34.9, 12.7.; FTIR: v max: 2958 (m), 2920 (m), 2853 (m), 1665 (s), 1451 (m), 1160 (s), 1085 (s), 735 (m) cm⁻¹; HRMS: m/z [MH⁺] calc. for C₂₄H₂₁N₃O₃S: 432.1376, found: 432.1381

Synthesis of 5-tosylcarbamoyl-1-methyl-2-phenyl-4-isopropyl-1H-pyrrole (167).

Following the general procedure using 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.27 mmol) and 1-(2-methyl-1-methylenepropyl)piperidine (82 mg, 0.54 mmol), the title compound was isolated as
a yellow oil (65 mg, 61%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.16 (br, 1H, NHTs), 8.08-8.04 (m, 2H, ArH), 7.49-7.32 (m, 7H, ArH), 6.14 (s, 1H, pyrH), 3.66 (s, 3H, NCH$_3$), 3.25-3.14 (m, 1H, CH), 2.46 (s, 3H, CH$_3$), 1.31 (d, J = 6.0 Hz, 6H, CH$_3$); $^{13}$C NMR (CDCl$_3$, 101 MHz): δ 165.0, 158.4, 144.9, 138.1, 136.0, 131.6, 129.6, 129.3, 128.6, 128.5, 128.3, 126.2, 107.7, 34.9, 26.9, 24.4, 21.7; FTIR: $\nu_{\text{max}}$: 3066 (w), 2961 (m), 1676 (s), 1453 (s), 1165 (s), 1079 (m) cm$^{-1}$; HRMS: m/z [MH$^+$] calc. for C$_{22}$H$_{24}$N$_2$O$_3$S: 397.1585, found: 397.1585.

**Synthesis of 5-tosylcarbamoyl-1-methyl-2-phenyl-4-n-butyl-1H-pyrrole (132).**

Following the general procedure using 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolium-5-olate (100 mg, 0.27 mmol) and a mixture (1:1) of 1-(hex-1-en-2-yl)piperidine and 1-(hex2-en-3yl) piperidine (90 mg, 0.54 mmol), the title compound was isolated as a yellow oil (64 mg, 58%).$^1$H NMR (CDCl$_3$, 400 MHz): δ 8.08-8.03 (m, 2H, ArH), 7.46-7.36 (m, 5H, ArH), 7.36-7.33 (m, 2H, ArH), 6.08 (s, 1H, pyrH), 3.69 (s, 3H, NCH$_3$), 2.77-2.72 (m, 2H, CH$_2$), 2.46 (s, 3H, CH$_3$), 1.69-1.61 (m, 2H, CH$_2$), 1.51-1.42 (m, 2H, CH$_2$), 0.99 (t, J = 7.0 Hz, 3H, CH$_3$); $^{13}$C NMR (CDCl$_3$, 101 MHz): δ 161.3, 144.3, 136.3, 135.8, 130.7, 130.5, 130.2, 129.7, 129.3, 128.3, 127.6, 121.0, 113.3, 34.5, 32.1, 25.8, 22.7, 21.7, 14.1; FTIR: $\nu_{\text{max}}$: 3063 (w), 2956 (m), 1672 (s), 1453 (s), 1161 (s), 1079 (m), 763 (s) cm$^{-1}$; HRMS: m/z [MH$^+$] calc. for C$_{23}$H$_{26}$N$_2$O$_3$S: 411.1737, found: 411.1746.
7. Preparation of isomeric 2-substituted enamines.

Arylacetaldehyde enamines were synthesized according to a literature method.\(^{156}\)

**General procedure as exemplified by the synthesis of (E)-1-styrylpiperidine (168).\(^{156}\)**

![Diagram of (E)-1-styrylpiperidine (168)]

To a dried 12 mL round-bottom flask with a magnetic stir bar was added Na\(_2\)CO\(_3\) (0.55 g, 5 mmol) and amine (3.0 g, 36 mmol), and the mixture was cooled in an ice-water bath. Phenylacetaldehyde (1.8 g, 15.0 mmol) was added dropwise to the above mixture. The reaction mixture was stirred at room temperature for 24 h and filtered. The filtrate was evaporated under vacuum to give (E)-1-styrylpiperidine as brown-red oil (2.0 g, 74% yield). ¹H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.32-7.26 (m, 4H, ArH), 7.10-7.07 (m, 1H, ArH), 6.75 (d, \(J = 14.0\) Hz, 1H, CH), 5.45 (d, \(J = 14.0\) Hz, 1H, CH), 3.12-3.08 (m, 4H, CH\(_2\)), 1.72-1.62 (m, 6H, CH\(_2\)). ¹³C NMR (CDCl\(_3\), 101 MHz): \(\delta\) 140.3, 139.6, 128.5, 123.9, 123.7, 99.5, 49.7, 25.4, 24.4.

**(E)-1-styrylpiperidine (169).\(^{157}\)**

![Diagram of (E)-1-styrylpiperidine (169)]

Following the general procedure using hexanal (500 mg, 4.9 mmol), pipridine (1.1 mL, 12.0 mmol) and Na\(_2\)CO\(_3\) (0.17 g, 1.6 mmol) the title compound was isolated as a brown oil (500 mg, 60%). ¹H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 5.79 (d, \(J = 14.0\) Hz, 1H, CH), 4.34 (dt, \(J = 14.0\) Hz, 1H, CH), 2.78-2.69 (m, 4 H, CH\(_2\)), 1.95-1.90 (m, 2 H, CH\(_2\)), 1.58-1.46 (m, 4 H, CH\(_2\)), 1.29-1.26 (m, 6 H, CH\(_2\)), 0.86 (t, \(J = 7.0\) Hz, 3 H, CH\(_3\)). ¹³C NMR (CDCl\(_3\), 101 MHz): \(\delta\) 140.1, 101.4, 50.1, 33.5, 30.2, 25.4, 24.3, 22.0, 13.9.
1-(3-phenyl-1-propenyl)piperidine (170).\textsuperscript{158}

Following the general procedure using 3-phenylpropanal (500 mg, 3.7 mmol), diethylamine (0.9 mL, 9.0 mmol) and Na\textsubscript{2}CO\textsubscript{3} (0.13 g, 1.2 mmol) the title compound was isolated as a yellow oil (550 mg, 78\%). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta 7.39-7.12\) (m, 5 H, ArH), 6.1 (d, \(J = 14.0\) Hz, 1H, CH), 4.45 (dt, \(J = 14.0\) Hz, 1H, CH), 3.46 (d, \(J = 7.0\) Hz, 2H, CH\textsubscript{2}), 2.91-2.85 (m, 4H, CH\textsubscript{2}), 1.61-1.50 (m, 6H, CH\textsubscript{2}). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 101 MHz): \(\delta 144.4, 138.9, 129.1, 128.9, 126.3, 96.4, 45.2, 35.8, 26.0, 24.6\).

1-(3-pyridinylprop-1-enyl)piperidine (171).

Following the general procedure using 3-pyridinepropanal (500 mg, 3.6 mmol), pipridine (0.87 mL, 9.0 mmol) and Na\textsubscript{2}CO\textsubscript{3} (0.13 g, 1.2 mmol) the title compound was isolated as a brown oil (620 mg, 84\%). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta 8.47-8.38\) (m, 2H, ArH), 7.54-7.49 (m, 1H, ArH), 7.21-7.14 (m, 1H, ArH), 5.93 (d, \(J = 14.0\) Hz, 1H, CH), 4.45 (dt, \(J = 14.0\) Hz, 1H, CH), 3.29 (d, \(J = 7.0\) Hz, 2H, CH\textsubscript{2}), 2.81-2.75 (m, 4H, CH\textsubscript{2}), 1.59-1.47 (m, 6H, CH\textsubscript{2}). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 101 MHz): \(\delta 149.9, 147.2, 141.8, 138.0, 135.8, 123.2, 98.2, 49.9, 34.0, 25.3, 24.3\).
Hexa-1,5-dienyl piperidine (172).

Following the general procedure using 5-hexenal (500 mg, 5.1 mmol), pipridine (1.2 mL, 12.0 mmol) and Na₂CO₃ (0.18 g, 1.6 mmol) the title compound was isolated as a yellow oil (540 mg, 64 %). \(^1\text{H NMR (CDCl}_3, \text{400 MHz)}: \delta 5.89-5.73 \ (m, 2H, CH), 5.00-4.85 \ (m, 2H, CH₂), 4.33 \ (dt, 1H, J = 14.0, 7 \ Hz, CH), 2.71-2.64 \ (m, 4H, CH₂), 2.05-1.97 \ (m, 4H, CH₂), 1.52-1.42 \ (m, 6H, CH₂). \(^{13}\text{C NMR (CDCl}_3, \text{101 MHz)}: \delta 140.4, 138.7, 114.1, 52.9, 49.9, 35.6, 26.5, 25.3, 24.7.
To a flame-dried two neck round bottom flask equipped with a stirrer bar and reflux condenser was added a solution of 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate 104 (100 mg, 0.27 mmol, 1.0 eq.) and 1-(2-phenylethenyl)piperidine (101 mg, 0.54 mmol, 2.0 eq.) in xylenes (2 mL) under N₂ at room temperature. The mixture was left to stir at room temperature for 10-15 minutes and afterwards, heated at 80 °C for 1-4 h. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 5 % EtOAc in petroleum ether) to afford the title compound as a colorless oil (84 mg, 72%).

**¹H NMR (CDCl₃, 400 MHz):** δ 8.72 (br, 1H, NHTs), 8.12-8.04 (m, 2H, ArH), 7.43-7.36 (m, 5H, ArH), 7.24-7.13 (m, 5H, ArH), 7.08-7.04 (m, 3H, ArH, pyrlH), 3.70 (s, 3H, NCH₃), 2.46 (s, 3H, CH₃);

**¹³C NMR (CDCl₃, 101 MHz):** δ 157.7, 144.9, 139.6, 136.1, 134.4, 130.9, 130.8, 129.6, 128.8 (x2C), 128.4, 128.3, 127.8, 126.1, 123.6, 122.6, 115.0, 34.5, 21.7; **FTIR:** ν<sub>max</sub>: 3292 (m), 2919 (s), 1680 (s), 1440 (s), 1330 (s), 1159 (s), 1038 (s), 701 (s) cm<sup>-1</sup>; **HRMS:** m/z [MH⁺] calc. for C₂₅H₂₂N₂O₃S: 431.1424, found: 431.1430.
Synthesis of 1-methyl-2,3-diphenyl-1H-pyrrole (174).

Following the general procedure using 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.27 mmol), phenylacetaldehyde (65 mg, 0.54 mmol) and piperidine (5 µL, 0.054 mmol) the title compound was isolated as a colorless oil (37 mg, 58%). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.44-7.31 (m, 5H, ArH), 7.24-7.17 (m, 4H, ArH), 7.15-7.09 (m, 1H, ArH), 6.79 (d, \(J = 3.0\) Hz, 1H, PyrH), 6.47 (d, \(J = 3.0\) Hz, 1H, PyrH), 3.56 (s, 3H, NCH\(_3\)); \(^{13}\)C NMR, 101 MHz): \(\delta\) 136.7, 132.8, 131.1, 130.7, 128.5, 128.1, 127.8, 127.5, 125.1, 122.8, 122.3, 107.9, 34.8; FTIR: \(\nu_{\text{max}}\): 3061 (w), 2923 (w), 1678 (s), 1448 (m), 1394 (m), 699 (m) cm\(^{-1}\); HRMS: m/z [MH\(^+\)] calc. for C\(_{17}\)H\(_{15}\)N: 234.1277, found: 234.1278.

Synthesis of 5-tosylcarbamoyl-1-methyl-2-phenyl-3-n-butyl-1H-pyrrole (175).

Following the general procedure using 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.27 mmol) and 1-(1-hexenyl)piperidine (90 mg, 0.54 mmol), the title compound was isolated as a yellow oil (74 mg, 67%). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.15-8.07 (m, 2H, ArH), 7.48-7.36 (m, 5H, ArH), 7.25-7.21 (m, 2H, ArH), 6.91 (s, 1H, pyrH), 3.65 (s, 3H, NCH\(_3\)), 2.46 (s, 3H, CH\(_3\)), 2.38-2.19 (m, 2H, CH\(_2\)), 1.45-1.34 (m, 2H, CH\(_2\)), 1.30-1.13 (m, 2H, CH\(_2\)), 0.78 (t, \(J = 7.0\) Hz, 3H, CH\(_3\)); \(^{13}\)C NMR (CDCl\(_3\), 101 MHz): \(\delta\) 157.9, 144.6, 140.5, 136.5, 130.0, 130.4, 129.6, 128.5, 128.4, 128.3, 123.4, 121.6, 115.8, 34.4, 32.9, 25.4, 22.2, 21.7, 13.8; FTIR: \(\nu_{\text{max}}\): 3271 (m), 2955 (m), 1679 (s), 1430 (s), 1164 (s), 703 (s) cm\(^{-1}\); HRMS: m/z [MH\(^+\)] calc. for C\(_{23}\)H\(_{26}\)N\(_2\)O\(_3\)S: 411.1737, found: 411.1742.
Synthesis of 5-tosylcarbamoyl-1,3-dibenzyl-2-phenyl-1H-pyrrole (176).

Following the general procedure using 3-benzyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.22 mmol) and 1-(3-phenyl-1-propenyl)piperidine (90 mg, 0.44 mmol), the title compound was isolated as a colorless oil (78 mg, 68%). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.21 (br, 1H, NHTs), 7.93-7.90 (m, 2H, ArH), 7.46-7.33 (m, 4H, ArH), 7.30-7.05 (m, 11H, ArH), 6.69-6.58 (m, 3H, ArH, pyrlH), 5.38 (s, 2H, CH\(_2\)), 3.66 (s, 2H, CH\(_2\)), 2.45 (s, 3H, CH\(_3\)); \(^{13}\)C NMR (CDCl\(_3\), 101 MHz): \(\delta\) 157.2, 144.5, 141.0, 140.9, 138.4, 136.0, 130.6, 130.4, 129.4, 128.8, 128.6, 128.5 (x2C), 128.3, 128.2, 126.9, 126.3, 126.1, 122.5, 121.8, 116.4, 49.0, 32.1, 21.7; FTIR: \(v_{\text{max}}\): 3027 (w), 2924 (m), 1679 (s), 1453 (s), 1166 (s), 700 (s) cm\(^{-1}\); HRMS: m/z [MH\(^{+}\)] calc. for C\(_{32}\)H\(_{28}\)N\(_2\)O\(_3\)S: 521.1893, found: 521.1904.

Synthesis of 5-tosylcarbamoyl-1-methyl-2-phenyl-3-(pyridine-3-ylmethyl)-1H-pyrrole (177).

Following the general procedure using 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.27 mmol) and 3-(3-piperidin-1-yl)allylpyridine (108 mg, 0.54 mmol), the title compound was isolated as a yellow oil (84 mg, 70%). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.43-8.31 (m, 2H, ArH), 8.03-7.96 (m, 2H, ArH), 7.48-7.32 (m, 6H, ArH), 7.26-7.11 (m, 3H, ArH), 6.65 (s, 1H, pyrH), 3.68 (s, 5H, NCH\(_3\), CH\(_2\)), 2.45 (s, 3H, CH\(_3\)). \(^{13}\)C NMR (CDCl\(_3\), 101 MHz): \(\delta\) 158.2, 149.4, 147.1, 144.4, 140.2, 136.8, 136.7, 136.5, 130.4, 129.5, 128.9, 128.8, 128.7, 128.3, 123.5, 122.6, 120.4, 116.0, 34.5, 29.6, 21.7. FTIR: \(v_{\text{max}}\): 3055 (w), 2962 (m), 2920 (m), 1675 (s),
1455 (s), 1163 (s), 1075 (s), 813 (s) cm$^{-1}$; HRMS: m/z [MH$^+$] calc. for C$_{25}$H$_{23}$N$_3$O$_3$S: 446.1533, found: 446.1540.

**Synthesis of 5-tosylcarbamoyl-1-methyl-2-phenyl-3-(but-3-en-1-yl)-1$H$-pyrrole (179).**

![Chemical Structure](image)

Following the general procedure using 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.27 mmol) and 1-(hexa-1,5-dien-1-yl)piperidine (89 mg, 0.54 mmol), the title compound was isolated as a yellow oil (65 mg, 59%).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 8.63 (br, 1H, NHTs), 8.12-7.98 (m, 2H, ArH), 7.50-7.35 (m, 5H, ArH), 7.26-7.18 (m, 2H, ArH), 6.77 (s, 1H, pyrH), 5.86-5.61 (m, 1H, CH), 5.00-4.80 (m, 2H, CH$_2$), 3.64 (s, 3H, NCH$_3$), 2.46 (s, 3H, CH$_3$), 2.44-2.39 (m, 2H, CH$_2$), 2.22-2.16 (m, 2H, CH$_2$). $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta$ 157.5, 144.7, 140.6, 137.0, 136.3, 130.8, 130.4, 129.6, 128.6 (x2C), 128.4, 122.4, 121.6, 115.2, 115.0, 34.7, 34.4, 25.3, 21.7; FTIR: $v_{\text{max}}$: 3436 (w), 2919 (m), 1676 (s), 1454 (s), 919 (m) cm$^{-1}$; HRMS: m/z [MH$^+$] calc. for C$_{23}$H$_{25}$N$_2$O$_3$S: 409.1580, found: 409.1582.

**Synthesis of 5-trifluoroacetyl -1-methyl-2-phenyl-3-(but-3-en-1-yl)-1$H$-pyrrole (180).**

![Chemical Structure](image)

Following the general procedure using 3-methyl-4-trifluoroacetyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.37 mmol) and 1-(hexa-1,5-dien-1-yl)piperidine (122 mg, 0.74 mmol), the title compound was isolated as a colorless oil (62 mg, 54%).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.57-7.46 (m, 3H, ArH), 7.34-7.30 (m, 2H, ArH), 7.20-7.17 (m, 1H, pyrH), 5.92-5.69 (m, 1H, CH), 5.06-4.81 (m, 2H, CH$_2$), 3.79 (s, 3H,
CH₃), 2.52-2.44 (m, 2H, CH₂), 2.28-2.21 (m, 2H, CH₂). ¹³C NMR (CDCl₃, 101 MHz): δ 169.0 (q, J = 58.0 Hz), 144.7, 137.7, 129.0 (x2C), 129.2, 128.8, 124.6, 124.2, 122.9 (q, J = 4.0 Hz), 118.8, 115.2, 35.2, 34.5, 25.4; ¹⁹F NMR (CDCl₃, 376.5 MHz): δ -71.0; FTIR: v_max: 3429 (w), 2925 (w), 1662 (s), 1450 (m), 1441 (m), 940 (m) cm⁻¹; HRMS: m/z [MH⁺] calc. for C₁₇H₁₈F₃NO: 308.1257, found: 308.1257.

Synthesis of N-methyl-2-(2-(1-methyl-5-phenyl-3-yl)propan-2-yl)aniline -1H-pyrrole (187).

Following the general procedure using 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (50 mg, 0.13 mmol) and 1,3,3-trimethyleneindoline (47 mg, 0.26 mmol), the title compound was isolated as a brown-red oil (23 mg, 58%). ¹H NMR (CDCl₃, 400 MHz): δ 7.46-7.43 (m, 1H, ArH), 7.41-7.38 (m, 4H, ArH), 7.33-7.19 (m, 2H, ArH), 6.86-6.74 (m, 1H, ArH), 6.69-6.60 (m, 1H, ArH), 6.50 (d, J = 2.0 Hz, 1H, pyrH), 6.07 (d, J = 2.0 Hz, 1H, pyrH), 4.81 (s, br, 1H, NH), 3.65 (s, 3H, CH₃), 2.66 (s, 3H, CH₃), 1.69 (s, 6H, CH₃) ¹³C NMR (CDCl₃, 101 MHz): 148.0, 134.7, 133.6, 133.2, 132.3, 128.3, 127.3, 126.6, 125.7, 120.2, 116.4, 111.2, 107.1, 37.3, 35.9, 30.9, 30.0; FTIR: ν_max: 3383 (w), 2964 (m), 2922 (m), 1712 (s), 1614 (m), 1459 (m), 1124 (m), 744 (m) cm⁻¹; HRMS: m/z [MH⁺] calc. for C₂₁H₂₄N₂: 305.2012, found: 305.2017.
9. Representative Procedure for Amine Catalyzed Münchnone Cycloadditions.

![Chemical Structure](image)

X = N(H)TS; CF₃

To a flame-dried three neck round bottom flask equipped with a stirrer bar, condenser and Dean-Stark trap was added a solution of aldehyde (2 eq.) and amine (20 mol%) in toluene 15 mL under N₂ at room temperature. The mixture was stirred at room temperature for 10-15 minutes. Münchnone (1.0 eq.) was then added and the mixture heated at reflux for 24 h. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 5% EtOAc in petroleum ether) to afford the pyrrole products.

**Synthesis of 5-trifluoroacetyl-1-methyl-2,3-diphenyl-1H-pyrrole (188).**

Following the general procedure using 3-methyl-4-trifluoroacetyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.37 mmol), phenylacetaldehyde (89 mg, 0.74 mmol) and dibenzyamine (14 µL, 0.074 mmol) the title compound was isolated as yellow solid (87 mg, 71%). **Melting point:** 89-92 °C; **¹H NMR (CDCl₃, 400 MHz):** δ 7.50-7.46 (m, 4H, ArH), 7.34-7.30 (m, 2H, ArH), 7.27-7.18 (m, 3H, ArH), 7.17-7.13 (m, 2H, ArH, PyrH), 3.88 (s, 3H, NCH₃); **¹³C NMR (CDCl₃, 101 MHz):** δ 170.0 (q, J = 35.0 Hz), 143.5, 134.0, 130.6, 130.0, 129.4, 128.9, 128.4, 128.1, 126.6, 125.8,
124.9, 122.6 (q, J = 4.0 Hz), 117.3 (q, J = 291.0 Hz), 35.3; \(^{19}\text{F NMR (CDCl}_3, 376.5 \text{ MHz)}\): \(\delta -71.0\); \(\text{FTIR: } \nu_{\text{max}}\): 3061 (w), 1667 (s), 1442 (m), 1301 (m), 1174 (m) cm\(^{-1}\); \(\text{HRMS: } m/z [\text{MH}^+]\) calc. for C\(_{19}\)H\(_{13}\)NOF\(_3\): 330.1107, found: 330.1107.

Synthesis of 5-trifluoroacetyl-1-methyl-2-phenyl-3-(4-chlorophenyl) \(1\text{H-pyrrole (189).}

Following the general procedure using 3-methyl-4-trifluoroacetyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.37 mmol), (4-chlorophenyl)acetaldehyde (114 mg, 0.74 mmol) and dibenzylamine (14 µL, 0.074 mmol) the title compound was isolated as a yellow oil (78 mg, 58%). \(\text{\(^{1}\text{H NMR (CDCl}_3, 400 \text{ MHz): } \delta 7.51-7.46 (m, 3H, ArH), 7.43-7.41 (m, 1H, ArH), 7.31-7.27 (m, 2H, ArH), 7.22-7.17 (m, 2H, ArH), 7.07-7.03 (m, 2H, ArH, PyrH), 3.86 (s, 3H, NCH}_3\}; \(\text{\(^{13}\text{C NMR (CDCl}_3, 101 \text{ MHz): } \delta 170.1 (q, J = 35.0 \text{ Hz}), 143.4, 132.5 (x2C), 130.5, 129.7, 129.6, 129.3, 129.1, 128.6, 124.9, 124.5, 122.3 (q, J = 4.0 Hz), 117.2 (q, J = 291.0 Hz), 35.3; \(^{19}\text{F NMR (CDCl}_3, 376.5 \text{ MHz): } \delta -71.0\); \(\text{FTIR: } \nu_{\text{max}}\): 3424 (w), 1666 (s), 1513 (m), 1434 (m), 1450 (m), 1173 (m) cm\(^{-1}\); \(\text{HRMS: } m/z [\text{MH}^+]\) calc. for C\(_{19}\)H\(_{13}\)\(^{35}\text{Cl}\)NOF\(_3\): 364.0711, found: 364.0718.

Synthesis of 5-trifluoroacetyl-1-methyl-2-phenyl-3-\(n\)-butyl-\(1\text{H-pyrrole (190).}

Following the general procedure using 3-methyl-4-trifluoroacetyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.37 mmol), hexanal (74 mg, 0.74 mmol) and dibenzylamine (14 µL, 0.074 mmol) the title compound was isolated as yellow oil (59
mg, 52%). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.56-7.49 (m, 3H, ArH), 7.34-7.31 (m, 2H, ArH), 7.15 (s, 1H, pyrH), 3.79 (s, 3H, NCH$_3$), 2.42-2.34 (m, 2H, CH$_2$), 1.53-1.44 (m, 2H, CH$_2$), 1.34-1.22 (m, 2H, CH$_2$), 0.86 (t, $J$ = 7.0 Hz, 3H, CH$_3$); $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta$ 169.4 (q, $J$ = 35.0 Hz), 144.7, 130.1, 129.1, 128.8, 125.7 (x2C), 124.2, 122.9 (q, $J$ = 4.0 Hz), 117.4 (q, $J$ = 291.0 Hz), 35.0, 32.8, 25.5, 22.3, 13.8; $^{19}$F NMR (CDCl$_3$, 376.5 MHz): $\delta$ -71.0; FTIR: $\nu_{\text{max}}$: 2932 (w), 1663 (s), 1451 (m), 1297 (m), 1174 (m) cm$^{-1}$; HRMS: m/z [MH$^+$] calc. for C$_{17}$H$_{18}$NOF$_3$: 310.1446, found: 310.1451.

**Synthesis of 5-trifluoroacetyl-1-methyl-2-phenyl-3-benzyl-1H-pyrrole (191).**

Following the general procedure using 3-methyl-4-trifluoroacetyl-2-phenyl-1,3-oxazolonium-5-olate 1c (100 mg, 0.37 mmol), 3-phenylpropionaldehyde (99 mg, 0.74 mmol) and dibenzylamine (14 µL, 0.074 mmol) the title compound was isolated as an orange oil (85 mg, 67%). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.52-7.48 (m, 3H, ArH), 7.30-7.24 (m, 4H, ArH), 7.22-7.18 (m, 1H, ArH), 7.17-7.13 (m, 1H, ArH), 7.09-7.06 (m, 2H, ArH, PyrH), 3.81 (s, 3H, NCH$_3$), 3.75 (s, 2H, CH$_2$); $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta$ 169.7 (q, $J$ = 35.0 Hz), 145.0, 140.7, 130.2, 129.8, 129.3, 128.8, 128.5, 128.3, 126.1, 124.4, 123.9, 123.7 (q, $J$ = 4.0 Hz), 117.3 (q, $J$ = 291.0 Hz), 35.3, 32.2; $^{19}$F NMR (CDCl$_3$, 376.5 MHz): $\delta$ -71.0; FTIR: $\nu_{\text{max}}$: 3064 (w), 1663 (s), 1451 (m), 1296 (m), 1174 (m) cm$^{-1}$; HRMS: m/z [MH$^+$] calc. for C$_{20}$H$_{16}$NOF$_3$: 344.1257, found: 344.1259.
Synthesis of 5-trifluoroacetyl-1-methyl-2-phenyl-3-(pyridine-3-ylmethyl)-1H-pyrrole (192).

Following the general procedure using 3-methyl-4-trifluoroacetyl-2-phenyl-1,3-oxazolonium-5-olate 1c (100 mg, 0.37 mmol), 3-(3-pyridinyl)propanal (50 mg, 0.74 mmol) and dibenzylamine (14 µL, 0.074 mmol) the title compound was isolated as a brown oil (78 mg, 61%). 1H NMR (CDCl₃, 400 MHz): δ 8.44-8.29 (m, 2H, ArH), 7.52-7.48 (m, 3H, ArH), 7.38-7.35 (m, 1H, ArH), 7.26-7.23 (m, 2H, ArH), 7.19-7.11 (m, 2H, ArH, PyrlH), 3.80 (s, 3H, NCH₃), 3.74 (s, 2H, CH₂); 13C NMR (CDCl₃, 101 MHz): δ 169.7 (q, J = 35.0 Hz), 149.7, 147.6, 144.8, 136.1, 135.8, 130.0, 129.5 (x2C), 129.0, 124.4, 123.4, 123.2 (q, J = 4.0 Hz), 122.6, 117.2 (q, J = 291.0 Hz), 35.3, 29.6; 19F NMR (CDCl₃, 376.5 MHz): δ -71.0; FTIR: νmax: 3063 (w), 2925 (w), 1664 (s), 1450 (m), 1295 (m), 1175 (m) cm⁻¹; HRMS: m/z [MH⁺] calc. for C₁₉H₁₅N₂OF₃: 345.1209, found: 345.1209.

Synthesis of 5-trifluoroacetyl-1,3-diphenyl-2-methyl-1H-pyrrole (193).

Following the general procedure using 3-phenyl-4-trifluoroacetyl-2-methyl-1,3-oxazolonium-5-olate 1d (100 mg, 0.37 mmol), phenylacetaldehyde (89 mg, 0.74 mmol) and dibenzylamine (14 µL, 0.074 mmol) the title compound was isolated as a yellow solid (67 mg, 55%). Melting point: 123-126 °C; 1H NMR (CDCl₃, 400 MHz): δ 7.57-7.52 (m, 3H, ArH), 7.48-7.46 (m, 4H, ArH), 7.45-7.43 (m, 1H, ArH), 7.39-7.35
(m, 1H, ArH), 7.31-7.28 (m, 2H, ArH, PyrH), 2.20 (s, 3H, CH₃); $^{13}$C NMR (CDCl₃, 101 MHz): $\delta$ 168.3 (q, $J = 47.0$ Hz), 140.6, 138.5, 134.4, 129.4, 128.9, 128.7, 128.3, 127.4, 127.0, 125.8, 124.9, 123.1 (q, $J = 4.0$ Hz), 117.2 (q, $J = 291.0$ Hz), 12.1; $^{19}$F NMR (CDCl₃, 376.5 MHz): $\delta$ -71.0; FTIR: $\nu_{\text{max}}$: 3061 (w), 1674 (s), 1497 (m), 1409 (m), 1293 (m), 1151 (s) cm$^{-1}$; HRMS: m/z [MH$^+$ ] calc. for C$_{19}$H$_{14}$NOF$_3$: 330.1108, found: 330.1108.

**Synthesis of N-benzyl-2,3-diphenyl pyrrole (194).**

Following the general procedure using 3-benzyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.22 mmol), phenylacetaldehyde (54 mg, 0.45 mmol) and piperidine (4 µL, 0.045 mmol) the title compound was isolated as a yellow solid (42 mg, 62%). **Melting point:** 92-95 °C; $^1$H NMR (CDCl₃, 400 MHz): $\delta$ 7.36-7.18 (m, 12H, ArH), 7.14-7.08 (m, 1H, ArH), 7.06-7.02 (m, 2H, ArH), 6.82 (d, $J = 3.0$ Hz, 1H, PyrH), 6.55 (d, $J = 3.0$ Hz, 1H, PyrH), 5.03 (s, 2H, CH$_2$). $^{13}$C NMR (CDCl₃, 101 MHz): $\delta$ 138.6, 136.5, 132.8, 131.3, 131.0, 128.6, 128.5, 128.1, 127.7 (x2C), 127.4, 126.8, 125.1, 122.8, 121.7, 108.5, 50.7; FTIR: $\nu_{\text{max}}$: 3061 (w), 1603 (s), 1505 (m), 1344 (m), 1073 (m), 697 (s) cm$^{-1}$; HRMS: m/z [MH$^+$ ] calc. for C$_{23}$H$_{19}$N: 310.1592, found: 310.1592.

**Synthesis of 1,2-dimethyl-3-phenyl-1H-pyrrole (195).**

Following the general procedure using 3-methyl-4-tosylcarbamoyl-2-methyl-1,3-oxazolonium-5-olate (100 mg, 0.32 mmol), phenylacetaldehyde (77 mg, 0.64 mmol) and piperidine (6 µL, 0.064 mmol) the title compound was isolated as a
colorless oil (31 mg, 56%). \( ^1H\) NMR (CDCl\(_3\), 400 MHz): \( \delta 7.46-7.35 \) (m, 4H, ArH), 7.25-7.21 (m, 1H, ArH), 6.64 (d, \( J = 3.0 \) Hz, 1H, PyrH), 6.28 (d, \( J = 3.0 \) Hz, 1H, PyrH), 3.61 (s, 3H, NCH\(_3\)), 2.37 (s, 3H, CH\(_3\)); \( ^{13}C\) NMR, 101 MHz): \( \delta 137.6, 128.3, 128.0, 125.4, 125.1, 122.0, 120.6, 107.1, 34.0, 10.7 \); FTIR: \( \nu_{\text{max}} \): 2966 (w), 1601 (s), 1504 (s), 1443 (m), 1348 (m), 701 (s) cm\(^{-1}\); HRMS: m/z [MH\(^+\)] calc. for C\(_{12}\)H\(_{13}\)N: 172.1121, found: 172.1123.

Synthesis -1-methyl-2-phenyl-3- (4-chlorophenyl) \( 1H \)-pyrrole (196).

![Structure](image)

Following the general procedure using 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.27 mmol), (4-chlorophenyl)acetaldehyde (83 mg, 0.54 mmol) and piperidine (5 \( \mu \)L, 0.054 mmol) the title compound was isolated as a colorless oil (46 mg, 64%). \( ^1H\) NMR (CDCl\(_3\), 400 MHz): \( \delta 7.44-7.37 \) (m, 3H, ArH), 7.32-7.28 (m, 2H, ArH), 7.18-7.08 (m, 4H, ArH), 6.77 (d, \( J = 3.0 \) Hz, 1H, PyrH), 6.41 (d, \( J = 3.0 \) Hz, 1H, PyrH), 3.54 (s, 3H, NCH\(_3\)); \( ^{13}C\) NMR, 101 MHz): \( \delta 135.2, 132.5, 131.0, 130.8, 130.7, 129.0, 128.6, 128.2, 127.8, 122.5, 121.7, 107.7, 34.8 \); FTIR: \( \nu_{\text{max}} \): 3052 (w), 1700 (w), 1600 (m), 1504 (m), 1348 (m), 701 (s) cm\(^{-1}\); HRMS: m/z [MH\(^+\)] calc. for C\(_{17}\)H\(_{14}^{35}\text{Cl}\)N: 268.0888, found: 268.0891.

Synthesis of 1-methyl-2-phenyl-3-benzyl-1\( H \)-pyrrole (197).

![Structure](image)

Following the general procedure using 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.27 mmol), 3-phenylpropionaldehyde (72 mg, 0.54 mmol) and piperidine (5 \( \mu \)L, 0.054 mmol) the title compound was isolated as a
yellow oil (35 mg, 52%). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 7.47-7.40 (m, 2H, ArH), 7.38-7.30 (m, 3H, ArH), 7.27-7.14 (m, 5H, ArH), 6.67 (d, \(J = 3.0\) Hz, 1H, PyrH), 6.05 (d, \(J = 3.0\) Hz, 1H, PyrH), 3.79 (s, 2H, CH\textsubscript{2}), 3.54 (s, 3H, NCH\textsubscript{3}); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 101 MHz): \(\delta\) 142.8, 132.5, 131.5, 130.5, 128.5, 128.3, 128.2, 127.2, 125.5, 121.9, 120.6, 108.5, 34.8, 32.7; FTIR: \(v_{\text{max}}\): 3061 (w), 1678 (s), 1494 (m), 1451 (m), 701 (m) cm\textsuperscript{-1}; HRMS: m/z [MH\textsuperscript{+}] calc. for C\textsubscript{19}H\textsubscript{17}N: 248.1434, found: 248.1434.

**Synthesis-1-methyl-2-phenyl-3-(6-methylhept-5-en-2-yl)-1H-pyrrole (199).**

Following the general procedure using 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate 1a (100 mg, 0.27 mmol), (S)-(−)-citronellal (84 mg, 0.54 mmol) and piperidine (5 \(\mu\)L, 0.054 mmol) the title compound was isolated as a colorless oil (51 mg, 71%, 96% ee). \([\alpha]_D^{23}\) = +10 (c 0.5, CHCl\textsubscript{3}); \textbf{Chiral HPLC:} Phenomenex \textsuperscript{®} Lux 3u Cellulose-1 column; 100% hexane; flow rate = 1.0 mL/min; detection at 220 nm. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 7.48-7.29 (m, 5H, ArH), 6.66 (d, \(J = 3.0\) Hz, 1H, PyrH), 6.12 (d, \(J = 3.0\) Hz, 1H, PyrH), 5.03-4.97 (m, 1H, CH), 3.48 (s, 3H, NCH\textsubscript{3}), 1.92-1.78 (m, 1H, CH), 2.67-2.55 (m, 2H, CH\textsubscript{2}), 1.63 (s, 3H, CH\textsubscript{3}), 1.58-1.42 (m, 2H, CH\textsubscript{2}), 1.52 (s, 3H, CH\textsubscript{3}), 1.17 (d, \(J = 7.0\) Hz, 3H, CH\textsubscript{3}); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 101 MHz): \(\delta\) 133.0, 130.9, 130.8, 130.5, 130.4, 128.1, 127.0, 125.0, 121.6, 104.8, 39.0, 34.6, 30.3, 26.3, 25.6, 23.1, 17.6.; FTIR: \(v_{\text{max}}\): 3053 (w), 2957 (s), 2921 (s), 1603 (m), 1489 (m), 1334 (m) 773 (s) cm\textsuperscript{-1}; HRMS: m/z [MH\textsuperscript{+}] calc. for C\textsubscript{19}H\textsubscript{25}N: 268.2060, found: 268.2060.
References


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Appendix

- nOe spectra of 133.
nOe spectra of 119.
**nOe spectre of 128.**
nOe spectra of 123.
nOe spectra of 132.
nOe spectra of 175.
nOe spectra of 190.
nOe spectra of 196.
Cycloadditions

Synthesis and Cycloaddition Reactions of Stabilized Münchnones

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Abstract: A family of stabilized münchnones bearing an acyl group at C4 have been prepared and studied in alkene cycloaddition reactions. These reactions are highly regioselective, and the method represents a rapid and straightforward route to densely substituted pyroles. Finally, the C4-stabilizing units can be further manipulated to furnish carboxylic acid and amide groups, or removed altogether to provide unsubstituted pyroles.

Introduction

Mesoionic compounds are five-membered dipolar heterocycles that have a rich source of chemistry, in particular with respect to reactivity and structure.[11] Amongst the many possible members of this family of compounds, sydnones 1 are the most generally studied due to their ease of synthesis and isolation.[2] The closely related 1,3-oxazolium S-oxides (münchnones) 2 have also attracted significant attention,[3] in particular in their transformation to pyroles by cycloaddition/reverscycloaddition processes.[4] Generally speaking, however, münchnones are less stable than sydnones, and they readily undergo hydrolysis to the corresponding N-amido α-amino acids 3.[5] For this reason, much of the chemistry of these compounds requires their employment in situ directly after formation (Scheme 1).

On the other hand, stabilized münchnones 4 bearing an acyl group at C4 can be significantly more stable than their nonacylated analogues, allowing them to be isolated, purified and characterized by traditional methods.[6] A relatively narrow range of C4-acyl substituents has been reported, with the trifluoroacetyl group being the most commonly employed.[7] Moreover, the potential of these compounds to function as precursors to the corresponding pyroles by alkene cycloadditions has received scant attention,[8] and so the regioselectivity of this process has not been established. We therefore set out to explore the scope of alkene cycloaddition reactions of stabilized münchnones, and report our results herein (Scheme 2).

Scheme 2. Use of stabilized münchnones in the synthesis of pyroles.

Results and Discussion

The stabilized münchnones required for the regioselective cycloaddition study were prepared by cyclodehydrative acylation reactions. Applying conditions reported by Kawase,[7] we were able to generate 4-trifluoroacetylated münchnones 1a-d bearing alkyl and aryl groups at the nitrogen atom. Although acid anhydrides are commonly employed for the formation of münchnones, isocyanates have not been exploited for this purpose.[9] However, we were pleased to find that isocyanates bearing Ts and trichloroacetyl groups performed quite well in this regard to deliver a family of novel C4-imide-substituted münchnones 2a-e. Overall, compounds 1, 2 were found to be stable and amenable to chromatographic purification (Scheme 3).

With a selection of mesoionic compounds in hand, we turned our attention to the allyl cycloaddition reactions of these compounds. We began our studies by exploring the reactivity of 4-trifluoroacetylated substrates, and we obtained a scheme that we have shown in Scheme 4. Münchones 1a-d underwent efficient reaction with phenylacetylene after heating in xylene to give the corresponding pyrroles 3-6 in good yields. Moreover, we were delighted to find that the products were generated as single regiosomers. Unfortunately, however, alkyl-substituted alkynes such as 1-octyne and cyclopropylacetylene proved to be much less reactive, and generated the corresponding heterocyclic products 7-10 in much lower yields, albeit with the same high regiocontrol.\(^1\)

Scheme 4. Cycloaddition reactions of 4-trifluoroacetylated münchones. [a] 2 equiv. of alkyne used in these cases.

The lower reactivity of alkyl-substituted alkynes relative to that of phenylacetylene was confirmed by a series of competition experiments carried out on münchones 1a-d. In all cases, performing the cycloaddition with an excess of a stoichiometric mixture of phenylacetylene and 1-octyne resulted in the selective incorporation of the alkyl-substituted alkyn (Scheme 5).

Scheme 5. Relative reactivity of phenylacetylene and 1-octyne.

We next opted to explore the cycloaddition reaction of the C4-imide-substituted münchones and began with sulfonamide 2a and trichloroacetamide 2d, and using phenyl acetylene as a reactive alkyne. In the event, 2a generated pyrrole 11a in moderate yield but excellent regioselectivity. Surprisingly, pyrrole 11b was also isolated, in which the imide had undergone apparent cleavage. Nonetheless, we were able to minimize loss of the imide group by reducing the reaction time and temperature, which allowed us to isolate the pyrrole 11a in high yield. With respect to substrate 2d, cycloaddition with phenyl acetylene also produced two pyrrole products. In this case amide 12b was the predominant product when the reaction mixture was heated in xylene over 6 h. We were able to improve the yield of this product by extending the reaction time to 21 h.

Having optimized the conditions for the cycloaddition of münchones 2, we explored the scope of this process. Pyrroles 13-15 and 17-19 were formed in moderate to high yields and with excellent regiocontrol. However, once again, alkyl-substituted alkynes were less effective; for example, compound 16 was produced in significantly lower yield.

We were pleased to note that the reaction regiosel ectivities are uniformly high across all substrates examined. Interestingly, the incorporation of the stabilizing groups does not appear to play a significant role with respect to regiochemistry, and the trends observed here reflect the known regiochemical allyne insertion patterns of arylacetylenes, whereby the initial cycloaddition takes place to connect the substituted alkyn carbon atom to the münchone C4 position.\(^1\)

The cycloaddition reactions shown in Schemes 4, 6 and 7 highlighted that the incorporation of electron-deficient groups
at the münchnone C4 position offered a convenient opportunity to isolate these mesoionic substrates, while imparting excellent levels of regiocontrol in the reactions with alkynes. In addition, an unexpected observation was made in the final step of the stabilizing group. In contrast to trifluoroacetate, which proved to be stable to the reaction conditions, the N-acetylsulfonamide underwent partial cleavage of the directing group, while the trichloroacetamide underwent conversion into the corresponding amide. These results prompted us to exploit the stabilizing group in order to expand the flexibility of the pyrrole functionality in the final cycloadducts; our results are summarized in Scheme 6. The base-mediated hydrolysis of the trifluoroacetyl groups in 4 and 5 allowed us to access pyrrolecarboxylic acids 20 and 21 (Equation [1]), whereas heating of N-acetylsulfonamides 11a and 13 resulted in SH-pyroles 11b and 22 (Equation [2]). This latter process highlighted the potential of N-acetylsulfonamides as traceless münchnone-stabilizing groups. Finally, Equation (3) summarizes our finding that trichloroacetamides function as primary amide equivalents in the alkyne cycloaddition process.

Conclusions

We report the cycloaddition reactions of alkynes and a series of stabilized münchnones, including an unusual family of amide-substituted analogues that are prepared by a novel isocyanate-mediated cyclohydridation functionalization reaction. The cycloadditions are highly regioselective and provide direct access to densely substituted functionalized pyroles. Moreover, the stabilizing groups can be further manipulated to furnish carboxylic acid and amide groups, or removed altogether to provide the unsubstituted pyrrole. A current limitation is the low yields associated with alkyl-substituted alkynes, and work is underway to develop solutions to this drawback.

Experimental Section

Typical Cycloaddition Procedure as Exemplified by the Formation of 5-Trifluoroacetyl-1,2,4-triphenyl-1H-pyrrole (3): A solution of 2,3-diphenyl-4-trifluoroacetyl-1,3-oxazolium-5-olate (100 mg, 0.30 mmol) and ethynylbenzene (61 mg, 0.60 mmol) in xylene (60.3 mL) in a sealed microwave vessel was heated at 140°C for 16 h. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to provide the title compound as a yellow solid (107 mg, 91%); m.p. 164–165°C. 1H NMR (400 MHz, CDCl3): δ = 7.46–7.42 (m, 5 H), 7.39–7.36 (m, 3 H), 7.25–7.20 (m, 5 H), 7.17–7.13 (m, 2 H), 6.56 (s, 1 H) ppm. 13C NMR (101 MHz, CDCl3): δ = 174.1 (q, J = 37.0 Hz), 143.3, 138.3, 137.6, 134.8, 130.7, 129.3, 129.0, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 125.5, 115.0 (q, J = 2900 Hz), 114.0 ppm. 19F NMR (276 MHz, CDCl3): δ = –71.4 ppm. FTR: v = 1661 (s), 1596 (s), 1272 (s), 1239 (s), 1195 (s) cm⁻¹. HRMS: calcd. for C18H13NOF3: 330.1106, found: 330.1099.

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Keywords: Münchnones · Cycloaddition · Pyroles · Regioselectivity · Heterocycles

[8] In a related example, a putative CH-unsubstituted mucochrome, formed by cyclodehydration using acetic anhydride, was treated with benzoyl isocyanate: W. Friedrichsen, W. D. Schreer, T. Debaerdemacker, Liebigs Ann. Chem. 1980, 1836.
[9] The regiochemistry of pyrroles 6, 7, 11b, and 14 was assigned by nOe spectroscopy. The remaining compounds are assigned by inference, and by analogy to the regiochemistry of related reactions.\(^{10}\)
Development of an Amine-Catalyzed Regioselective Synthesis of Pyrroles

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Supporting Information

ABSTRACT: A regioselective synthesis of pyrroles has been devised through the cycloaddition of 1,3-oxazolin-5-olates and enamines. Product regiochemistry is controlled by the amine substitution pattern. Moreover, an amine-catalyzed variant of this reaction allows aldehydes to be used directly as substrates for pyrrole synthesis.

Pyrroles are among the most important heteroaromatic compounds in the chemical sciences, and they feature in a range of products, from light harvesting materials to pharmaceuticals. The synthesis of pyrroles by traditional electrophilic aromatic substitution processes is complicated by their high reactivity, often rendering these processes difficult to control. Cycloaddition reactions offer an appealing alternative to the synthesis of multisubstituted pyrroles, as they can proceed under neutral conditions, often serving to regulate product regiochemistry. In this context, münchnones (1,3-oxazolin-5-olates) represent an interesting class of mesionic heterocycles and they are known to furnish pyrroles upon cycloaddition reactions with alkynes. These processes allow complex substitution patterns to be assembled very easily, and the reactions can be quite regioselective, especially when arylacetylenes are employed. Indeed, the regiochemical insertion process favors the addition of the substituted alkyne carbon to the münchnone C4 position (Scheme 1, eq 1).

In contrast to the cycloaddition of alkynes, the corresponding reactions of münchnones and alkenes are more complicated, as decarboxylation of the initial cycloaduct reveals a dipolar intermediate that can undergo several other reactions including proton transfer (with or without ring oxidation) or further cycloaddition, and these can be difficult to control. However, the use of alkynes bearing a potential leaving group (LG) could offer the opportunity to carry out in situ oxidation level adjustment to generate pyrroles directly. Moreover, if LG dictated reaction regiochemistry then this process would allow either regioisomer of the pyrrole to be accessed by simple choice of alkene substrate isomer, which would offer improved flexibility over the corresponding alkene cycloadditions (Scheme 1, eq 2). The veracity of this idea has been demonstrated using β-nitrostyrenes, albeit with variable levels of regiocontrol. We report herein that enamines can offer high selectivities in münchnone cycloadditions and that this approach successfully delivers a regiodivergent synthesis of pyrroles. Finally, we describe the development of this concept toward an amine-catalyzed cycloaddition of aldehydes.

We began our studies by exploring the reactions of enamines and münchnones, a cycloaddition that had not been previously investigated to the best of our knowledge. As münchnones are often unstable and require preparation and reaction in situ, we targeted stabilized analogs where an electron acceptor is incorporated at C4 in order to allow us to focus explicitly on the efficiency of the cycloaddition step. As shown in Scheme 2, we were pleased to find that these substrates underwent relatively rapid cycloaddition with 1-substituted enamines to provide the corresponding pyrroles 2–5 in good yield, and as single regioisomers. Moreover, isomeric 2-substituted enamines also provided the corresponding pyrroles 6–9, but with the opposite sense of regiochemical insertion. Indeed, examples 2 and

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Scheme 1. Cycloadditions of Alkynes and Alkyne Equivalents with Münchnones

LG

Scheme 2. Cycloaddition of Alkyne equivalents

LG
Scheme 2. Regioselective Cycloadditions of Enamines with Münchnones

Scheme 3. Relative Reactivity of Alkenes versus Enamines

Scheme 4. Role of the Amine in the Overall Transformation

Scheme 5. Amine-Catalyzed Cycloaddition of Aldehydes and Münchnones

6 as well as 3 and 7 clearly highlight that pyrrole regiochemistry can be dictated by the substitution pattern of the enamine substrate, a distinct advantage over traditional alkyne cycloadditions which cannot currently be easily diverted from their innate regioselectivities.

We next opted to explore the relative reactivity of münchnones toward enamines and alkenes. We envisaged that 1-aminohexa-1,5-dienes could represent interesting substrates toward this end. Specifically, as shown in Scheme 3, a nonchelating regioselective cycloaddition of münchnones and 1-

Extending this study to the imide-substituted mesionic reagents employed at the outset of our studies (cf. Scheme 2) revealed an interesting feature of the catalytic process. In these cases the N-tosylamide group that was essential for stabilization of the münchnone substrates was found to be cleaved during cycloaddition to provide the corresponding 1,2,3-trisubstituted pyrroles with complete regiocontrol (Scheme 6). Control reactions showed that pyrroles bearing N-tosylamides at C2 underwent conversion to the free pyrroles after heating in refluxing toluene overnight. The different outcomes highlighted in Schemes 2 and 6 are therefore due to the extended reaction times employed in the latter case.

In conclusion, we report the use of enamines in the cycloaddition—elimination reaction of münchnones for the synthesis of pyrroles. This method has several advantages over traditional alkyne cycloadditions, especially the ability of this approach to access complementary regioisomers. Moreover, this strategy allows acetaldehyde derivatives to formally function as substrates for cycloaddition via an amine-catalyzed process, generating pyrroles with excellent regioselectivities.
Moreover, this method accesses products with complementary regiochemistry to that of allene cycloadditions.

**ASSOCIATED CONTENT**

- **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.lett.7b03658.

Experimental procedures and characterization data (PDF)

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**Notes**

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