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

Ac	acetyl
Ar	aryl group
Bn	benzyl
^{n}Bu	*n*-butyl
^{t}Bu	*tert*-butyl
Boc	tert-butoxycarbonyl
Cbz	carboxybenzyl
DMAD	dimethyl acetylenedicarboxylate
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DIPC	*N,N*'-diisopropylcarbodiimide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMF	*N*,*N*-dimethylformamide
dba	*Trans, trans*-dibenzylideneacetone
Et	ethyl
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimi
EWG	electron-withdrawing group

E	electrophile
et al.	et alia
eq/equiv	equivalent
ee	enantiomeric excess
FTIR	Fourier-Transform Infrared Spectroscopy
FMO	Frontier Molecular Orbital Theory
g	gram
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
^{n}Hex	*n*-hexyl
HOMO	Highest Occupied Molecular Orbital
h	hours
LUMO	Lowest Unoccupied Molecular Orbital
L_n	Ligand
LG	Leaving group
LC-MS	Liguid chromatography-mass spectrometry
Min	minutes
Me	methyl
MHz	Mega Hertz
Nu	nucleophile

NOE/nOe	Nuclear overhauser effect
OTBS	tert-butyldimethylsilyl ethers
Ph	phenyl
^{i}Pr	*iso*-propyl
RT or rt	room temperature
TFAA	Trifluoroacetic anhydride
Tf	Trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
Tol	toluene
TOF ES	Time of Flight Electrospray
UV	Ultra violet

Chapter I. Introduction

Part 1: Mesoionic compounds and pyrroles.

1. Pyrroles

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]

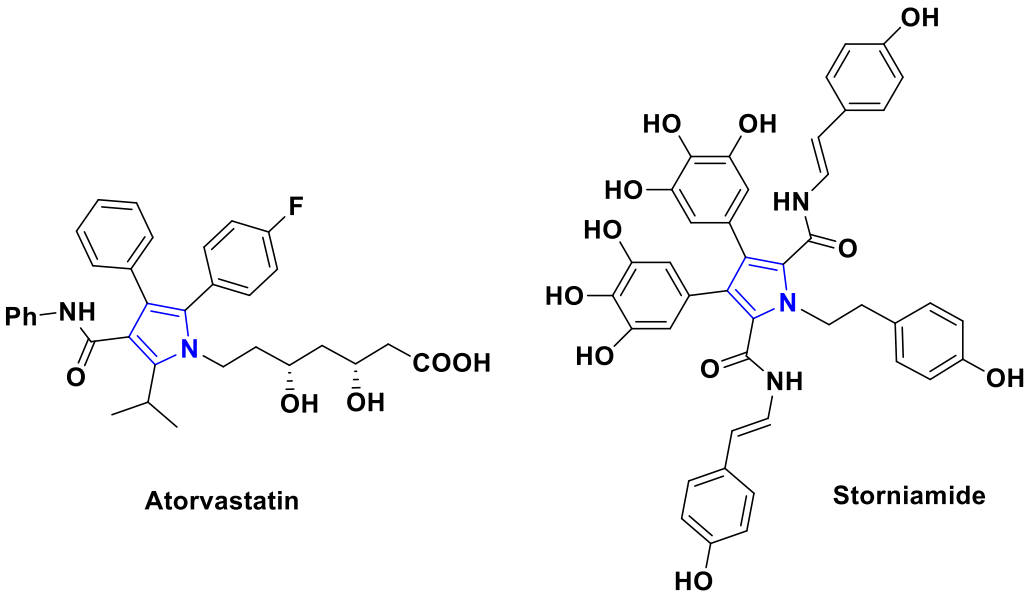
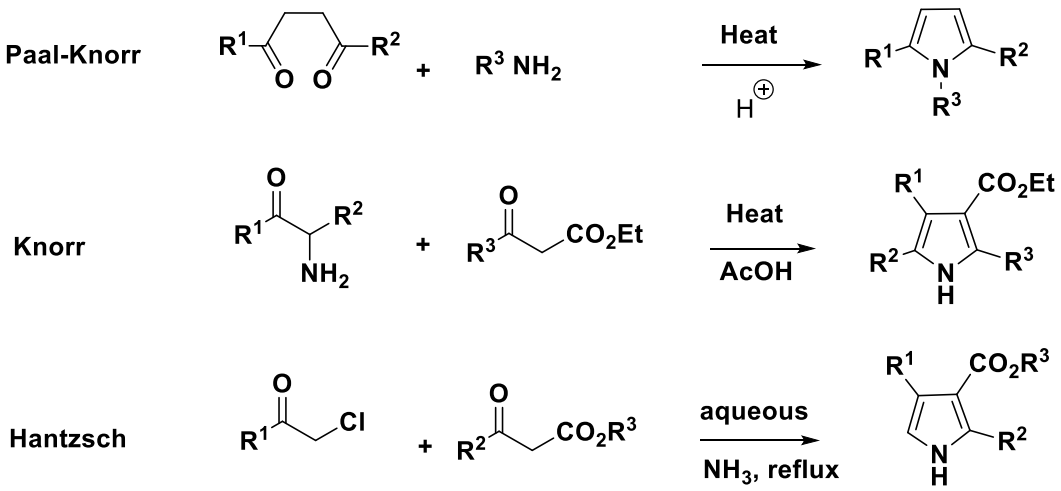


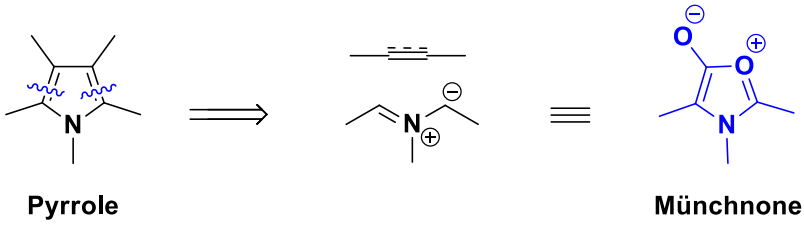
Figure I.1: Some natural and non-natural pyrrole therapeutics.

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).



Scheme I.1: Classical methods to synthesise pyrroles.

However, an alternateve 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).[17]



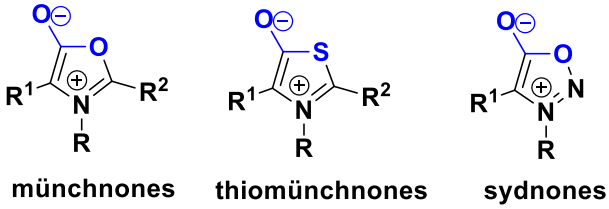
Scheme I.2: Pyrroles from münchnones and dipolarophiles.

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.[18] They allow access to a range of 5-membered ring heterocyclic products in an atom economical way, under mild conditions.[19]

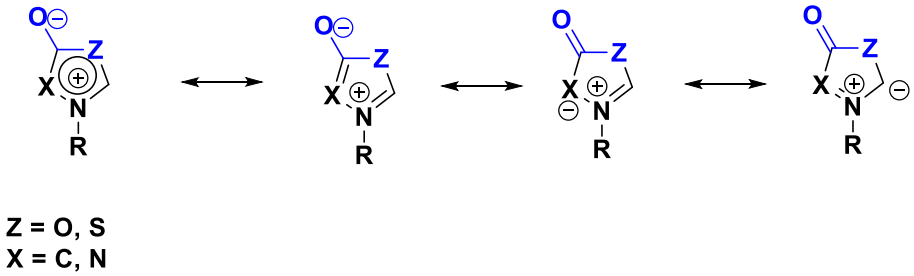
A range of dipolar compounds are available. Among these, there are mesoionic compounds, which have been found to function as useful synthetic intermediates for

the synthesis of many heterocyclic compounds. Scheme I.3 shows some prominent classes of these mesoionic heterocycles.[20]



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).

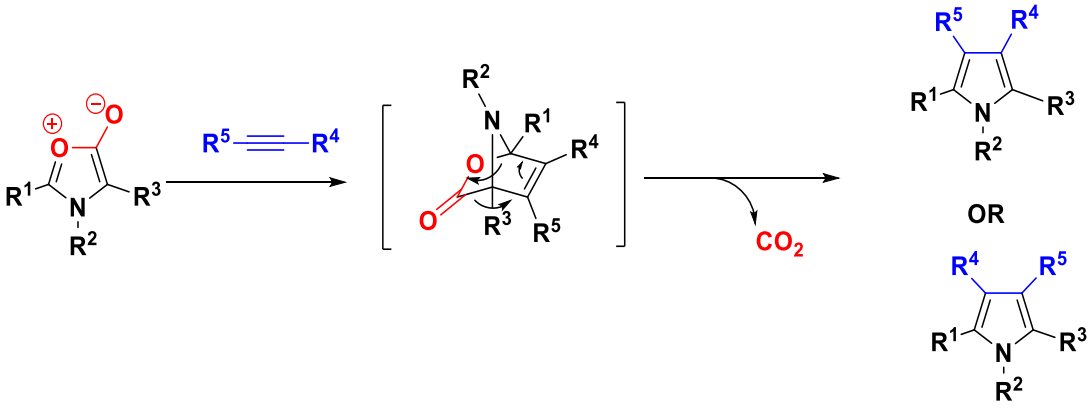


Scheme I.4: Commonly accepted mesoionic structures.

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

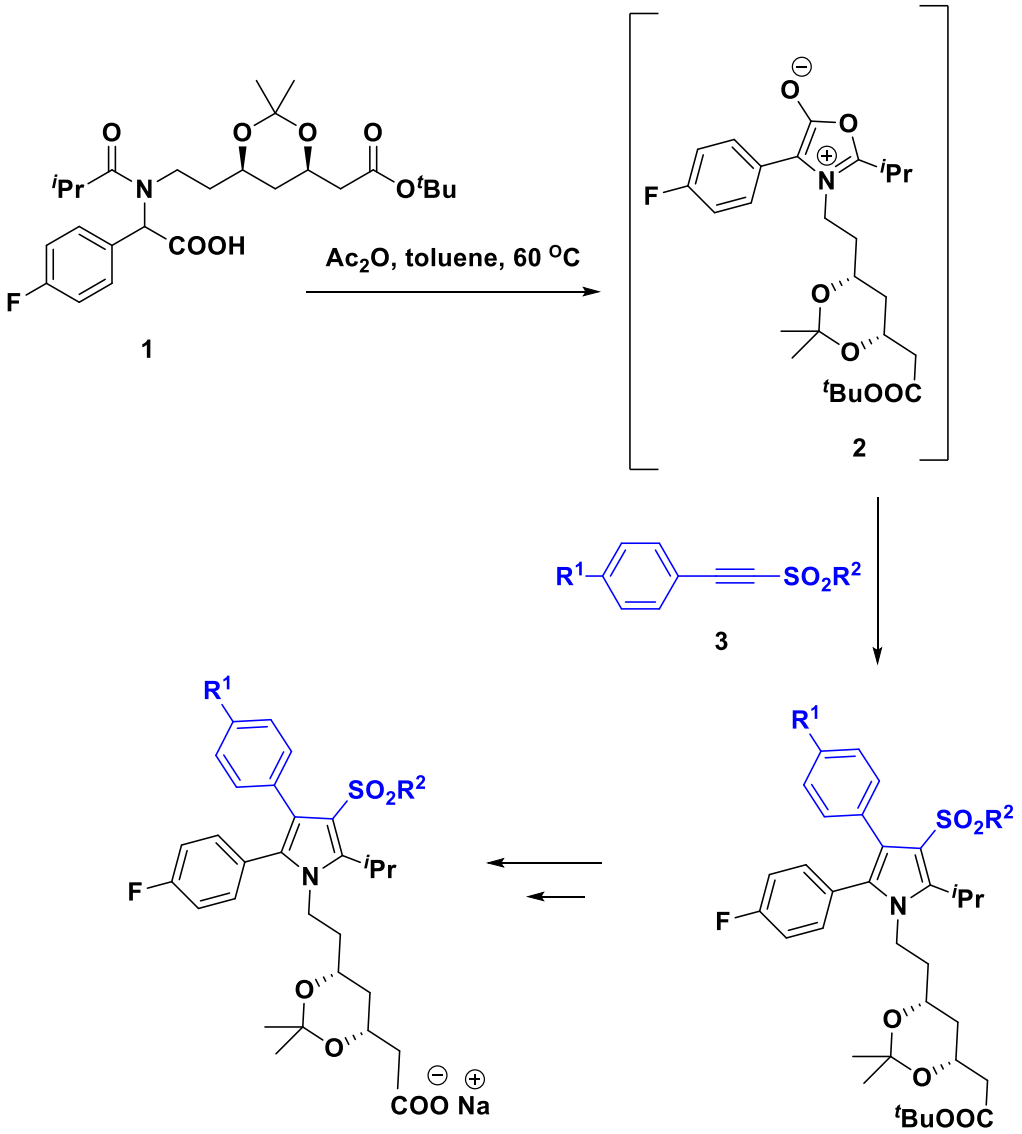
Münchnones (1,3-oxazolium-5-olates) are one of the most heavily studied classes of mesoionic compounds, and they are synthetically valuable. This is due to their reactivity in 1,3-dipolar cycloaddition reactions for the formation of a broad range of useful products and pharmacologically relevant molecules including pyrroles and imidazoles.[21-24] Interestingly, münchnones are named after their city of discovery in honour of Münich, Germany, where they were first formulated by Hüisgen in 1964.[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".[25-26] Hüisgen found that münchnones 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.[27] These processes therefore confirmed that münchnones provide a direct method to access useful molecules of value to biological chemistry, pharmaceuticals and natural products.[28]



Scheme I.5: 1,3-Dipolar cycloaddition of münchnones.

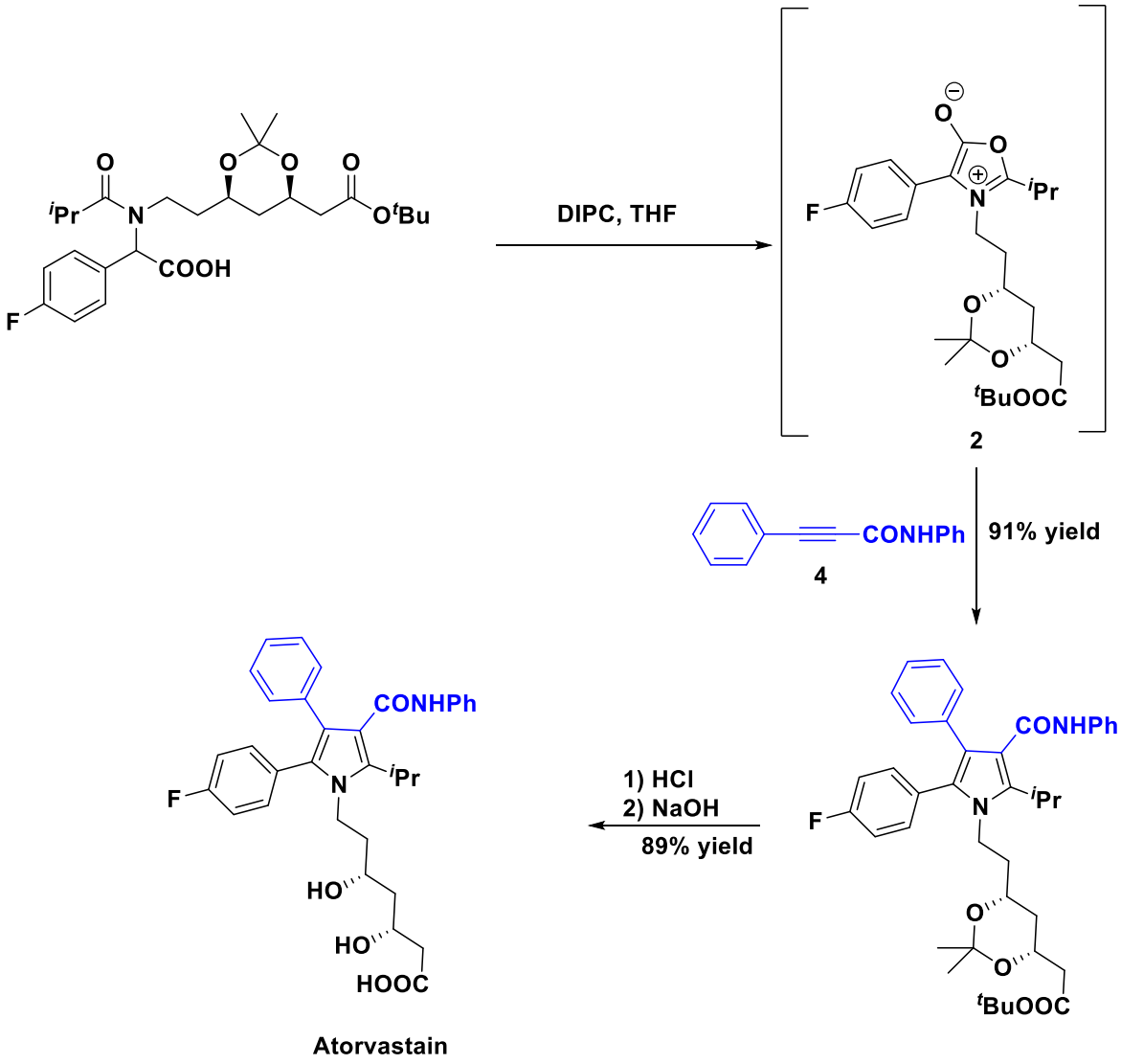
Indeed, the application of münchnones in the synthesis of pyrrole-based pharmaceuticals such as atorvastain analogs has been reported. For instance, in 2008, Park et al.[29] employed acetic anhydride to dehydrate the *N*-acylamino acid **1**

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.

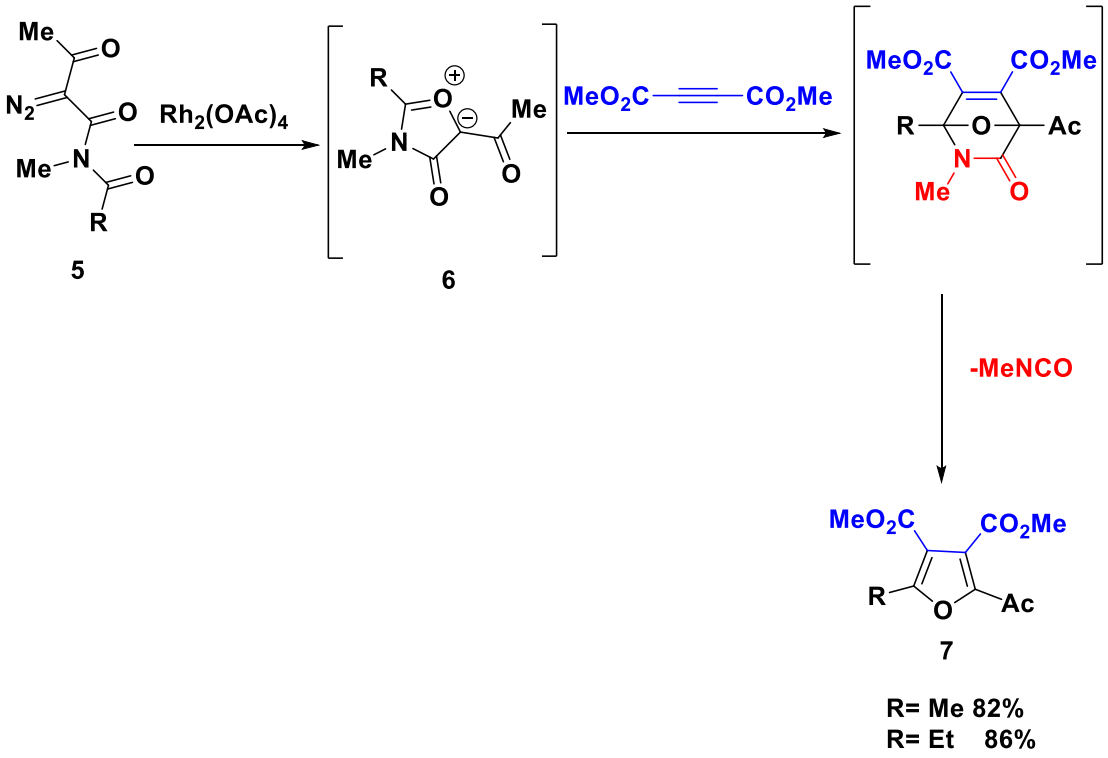
In 2015, Gribble et al.[30] also employed münchnone intermediate **2** to obtain atorvastatin by a route comprising a cycloaddition reaction with alkyne **4**; their synthetic procedures are shown in scheme I.7.



Scheme I.7: Synthesis of atorvastain.

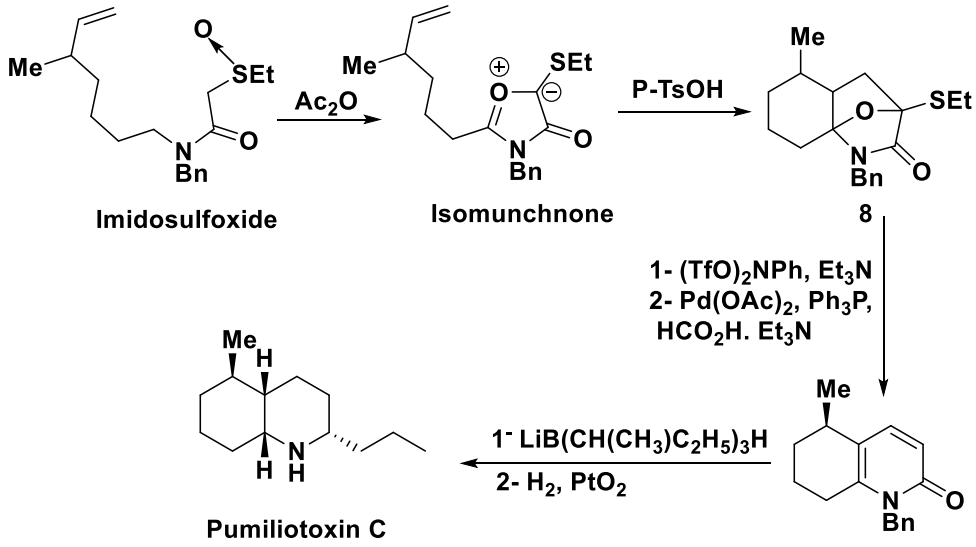
2.2. Isomünchnones

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.[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]



Scheme I.9: Synthesis of pumiliotoxin C.

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).

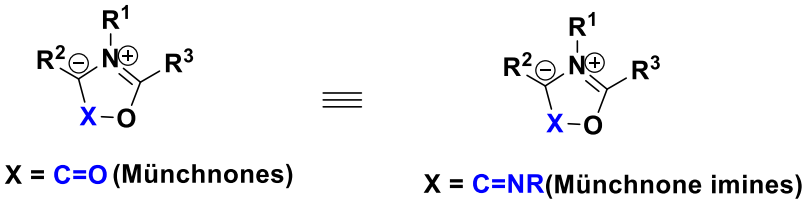


Figure I.2: Design of münchnone imines.

Münchnone imines can be obtained by a multi-component coupling process comprising the reaction of acid chlorides, isocyanides and imines[33] (Figure I.3).

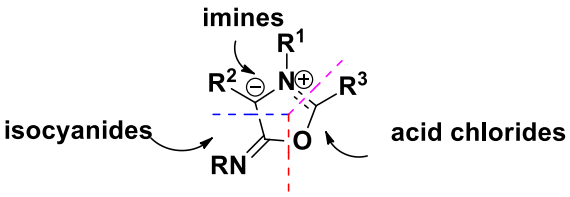
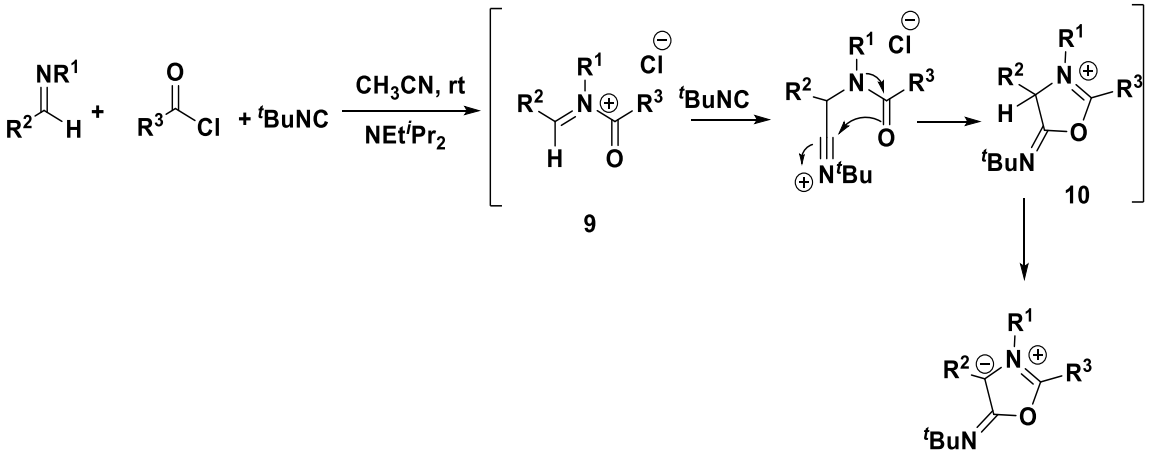


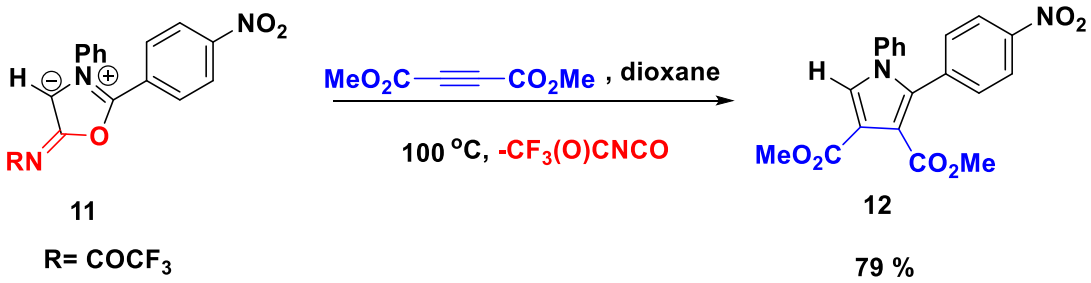
Figure I.3: Münchnone imine synthesis.

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).

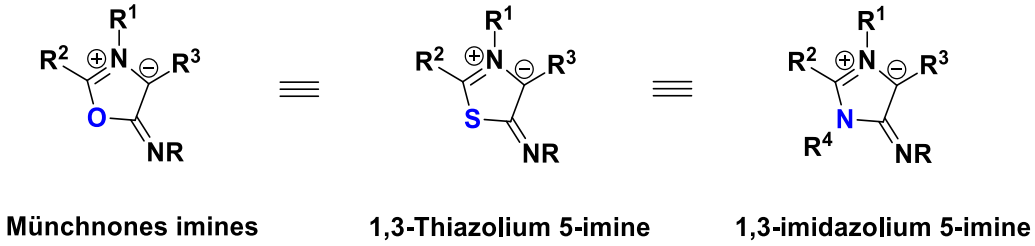
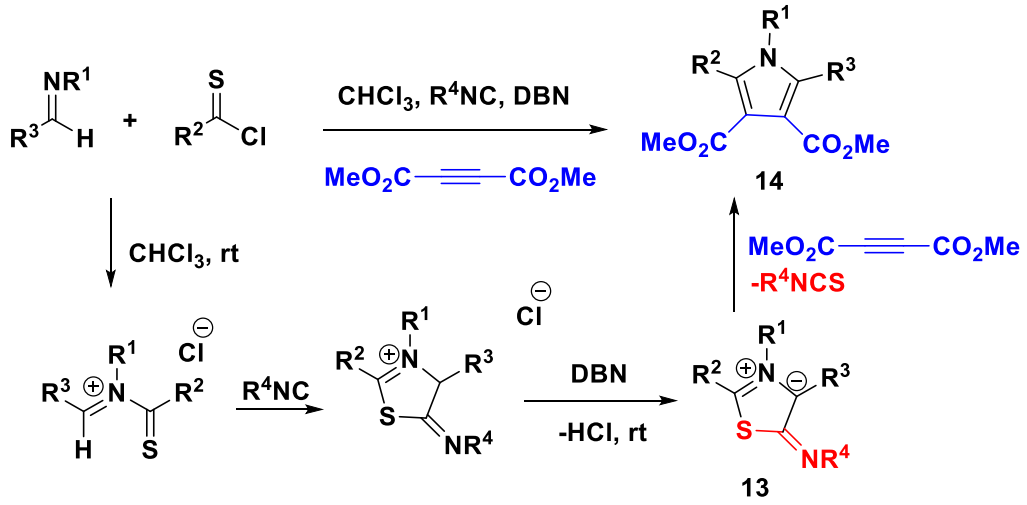


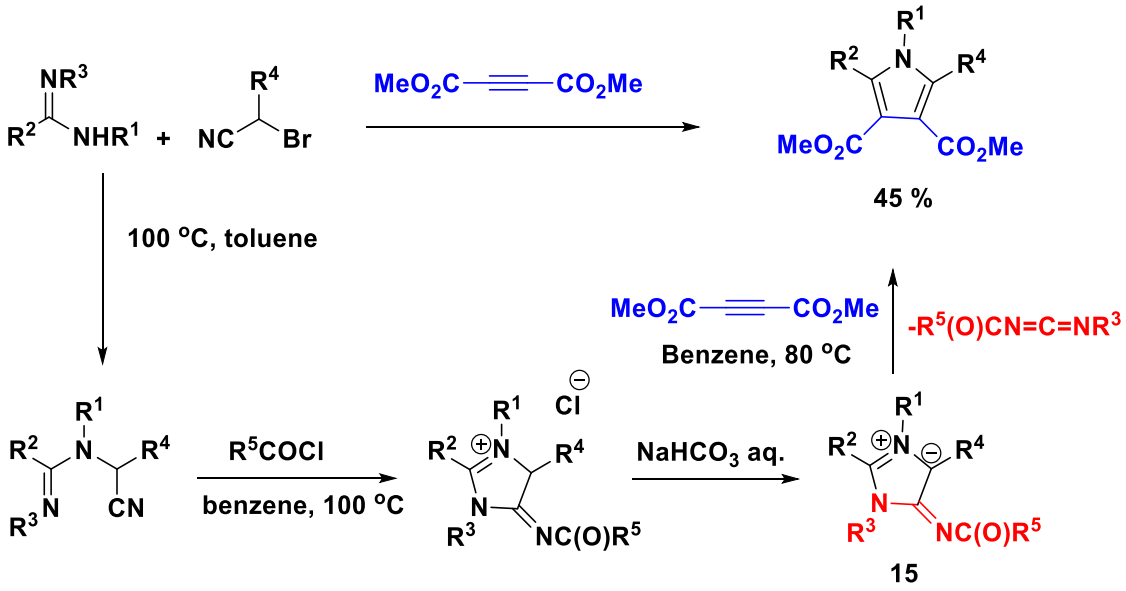
Figure I.4: Design of alternative mesoionic heterocycles.

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.[35] 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).[36]



Scheme I.12: Pyrrole synthesis through 1,3-thiazolium 5-imines.

1,3-Imidazolium 5-imines **15** also undergo 1,3-dipolar cycloadditions with electron poor dipolarophiles (eg 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.

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 PR_3 unit gave phospha-münchnones (Figure I.5).

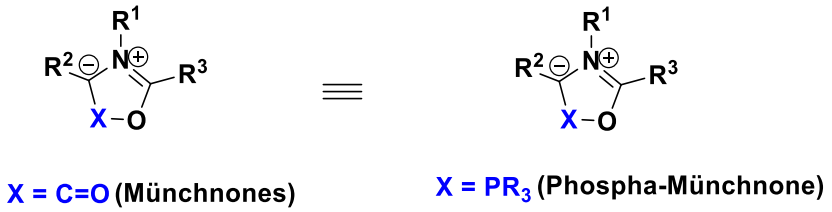


Figure I.5: Design of mesoionic structure.

Using the same building blocks as employed in the synthesis of münchnone imines, phospa-münchnones can be generated by a three component coupling comprising imines, acid chlorides and a PR_3 reagent (Figure I.6).

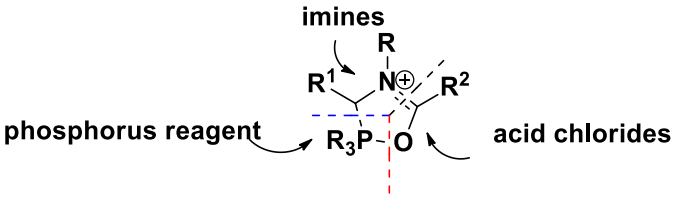
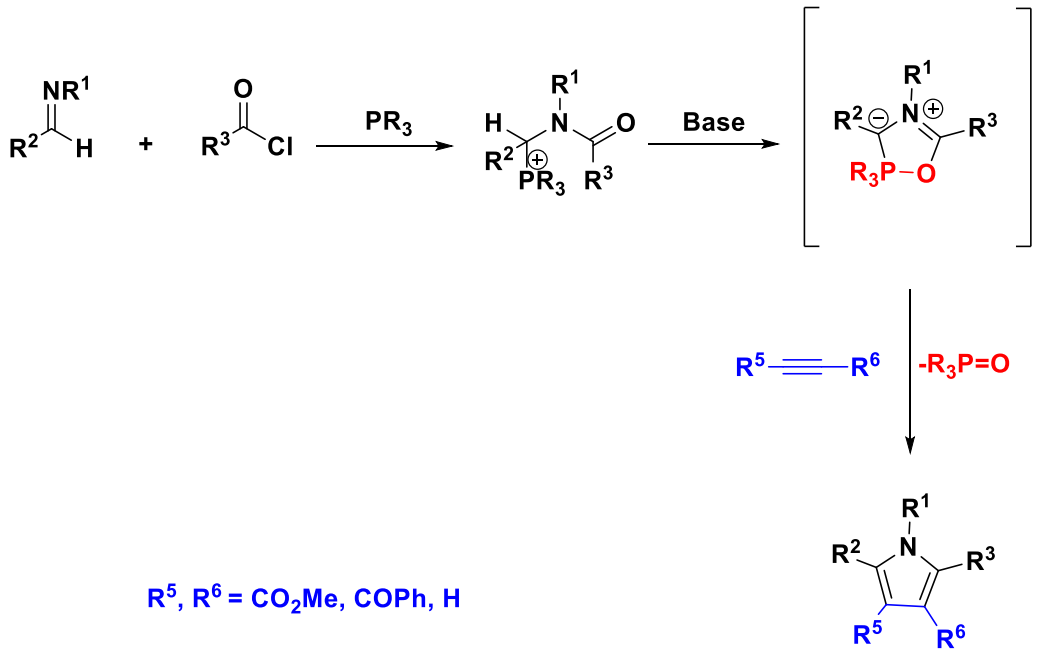


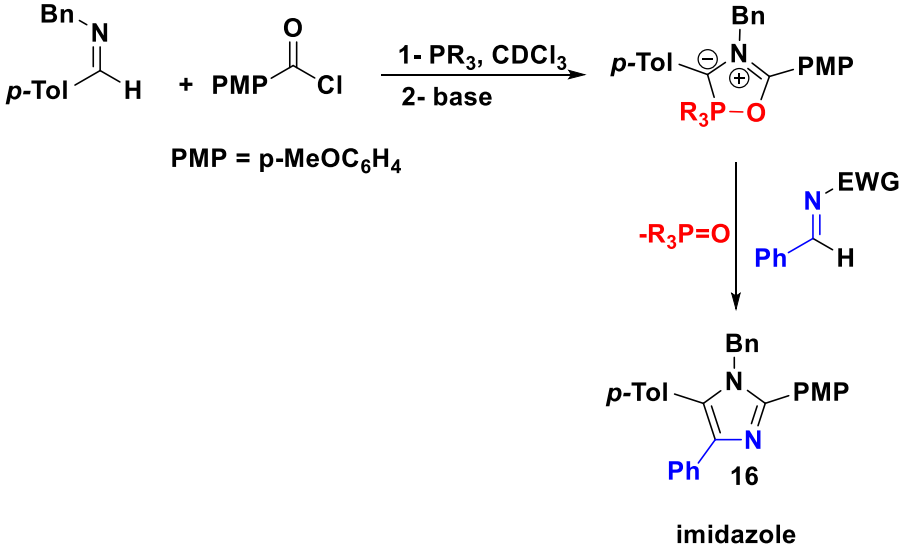
Figure I.6: Synthesis of phospha-münchnones.

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.[39] 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 allowingcontrol of the regioselectivity. For example, by using an alkyne as dipolarophile, a novel route to highly substituted pyrroles can be achieved (Scheme I.14).



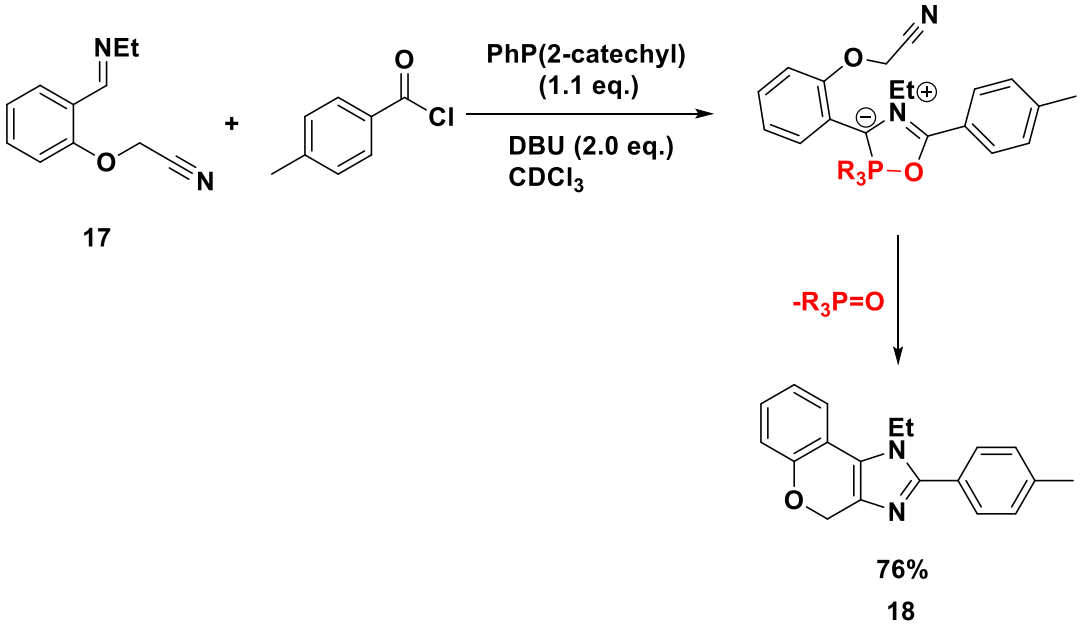
Scheme I.14: In situ synthesis of phosph-münchnones and subsequent pyrrole formation.

Furthermore, imines can also be used as reactive dipolarophiles in phopha-münchnone cycloadditions, which in this case allows imidazoles **16** to be formed (Scheme I.15).[40]



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]



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).

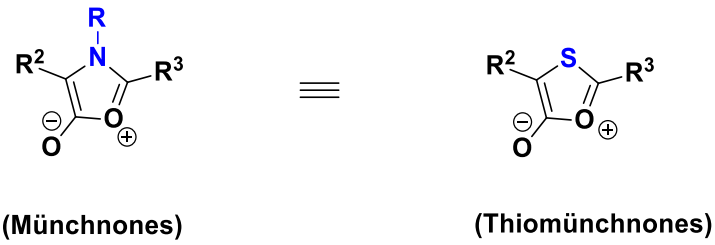
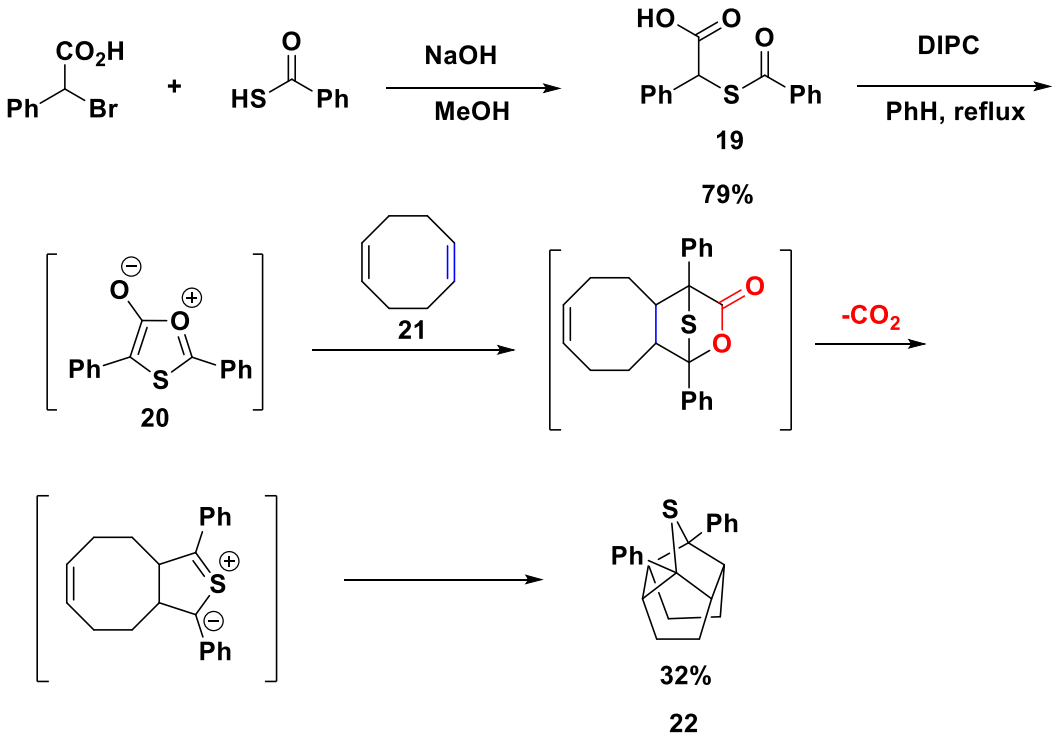


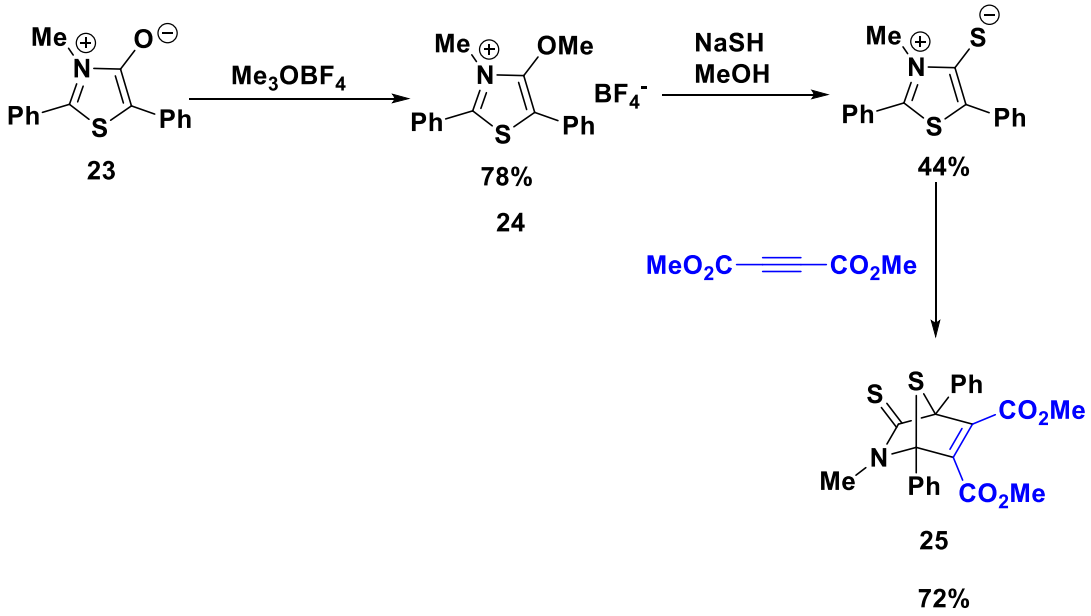
Figure I.7: Design of thiomünchnones.

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).



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.[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

3. Conclusion

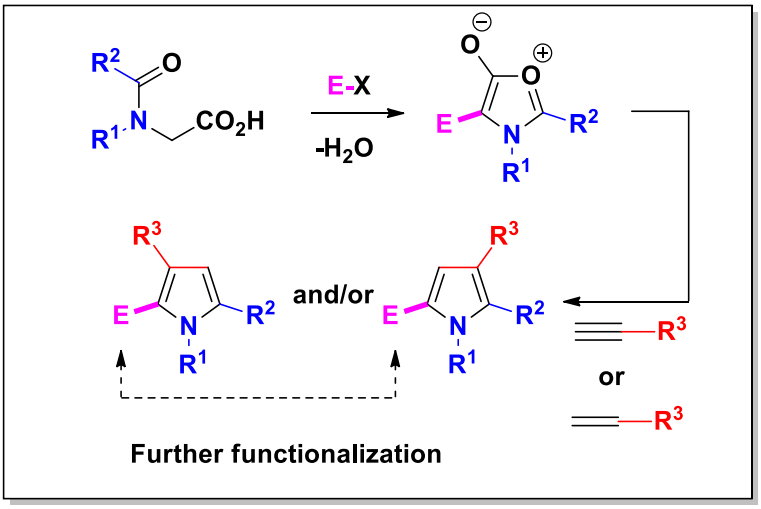
To summarise, a number of mesoionic heterocycles have been developed. These compounds are important building blocks in the synthesis of useful molecules such as pyrroles. However, each of these mesoionic heterocycles has associated limitations such as multistep syntheses, precursor availability, and 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 mesoionic 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).



Scheme I.19: Synthesis of functionalized pyrroles from stabilized münchnones.

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]

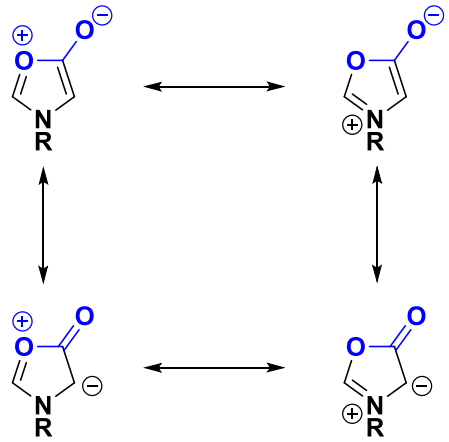
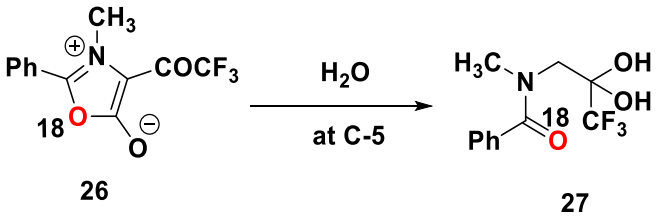


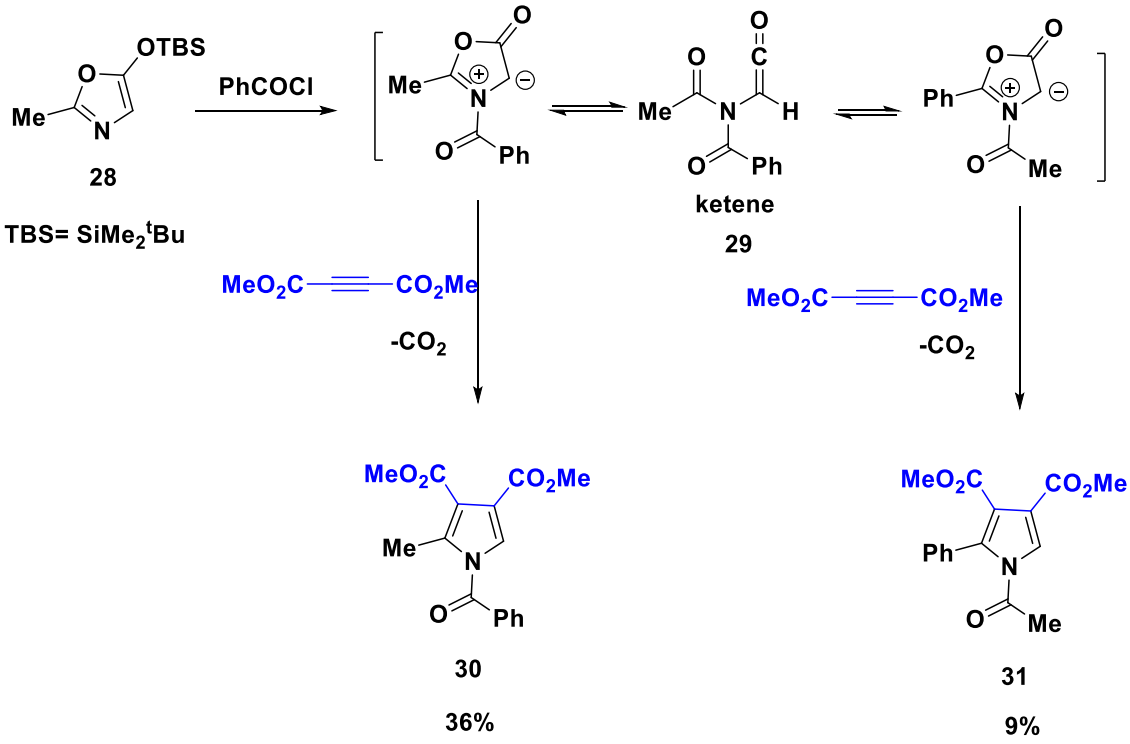
Figure II.1: Münchnone resonance structures.

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_2O at the C5 position providing trifluoromethyl ketone hydrate **27** after 3 h at 60 °C (Scheme II.1).



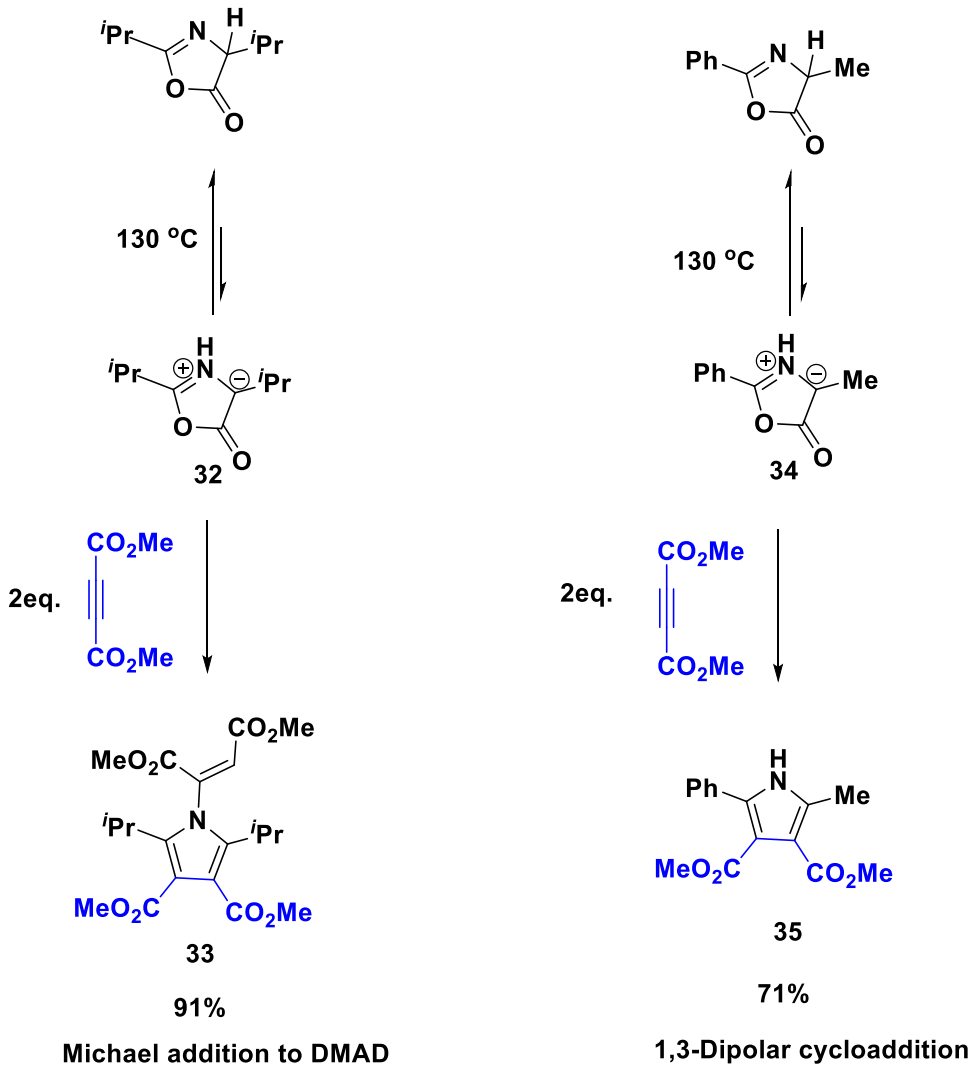
Scheme II.1: Hydrolysis of münchnones.

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 pyrroles **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]

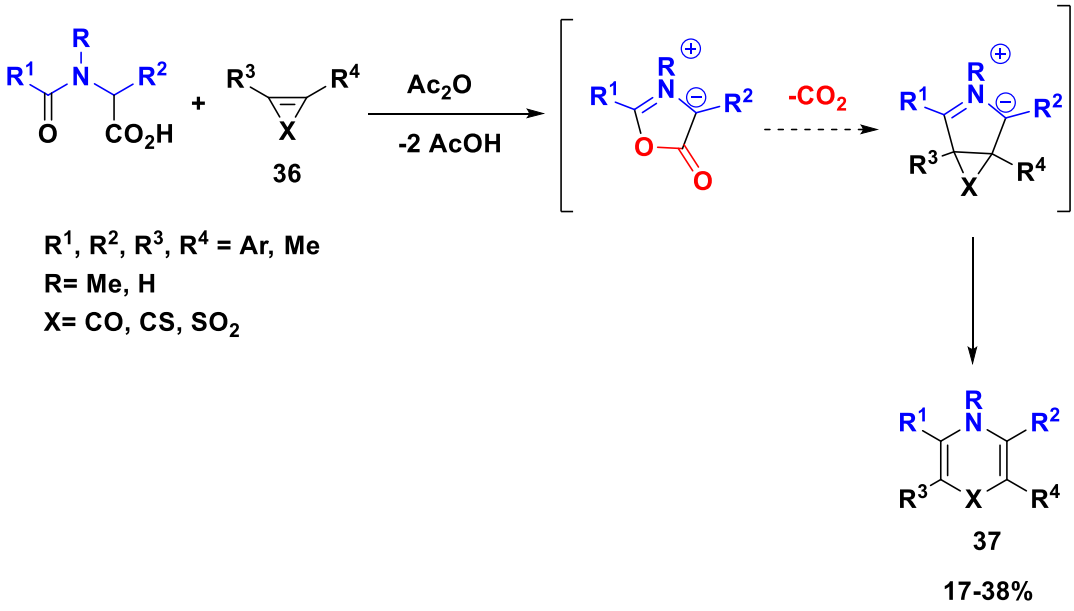


Scheme II.3: The effect of substitution on *NH*-münchnone cycloaddition reactions.

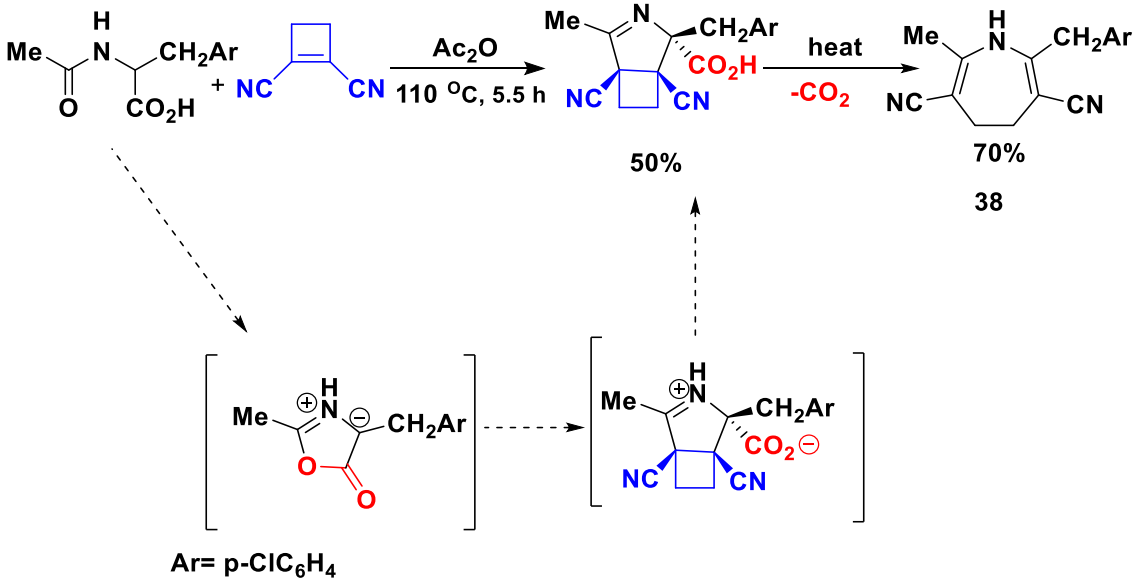
2. General reactivity of münchnones

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, cyclopropenes **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]

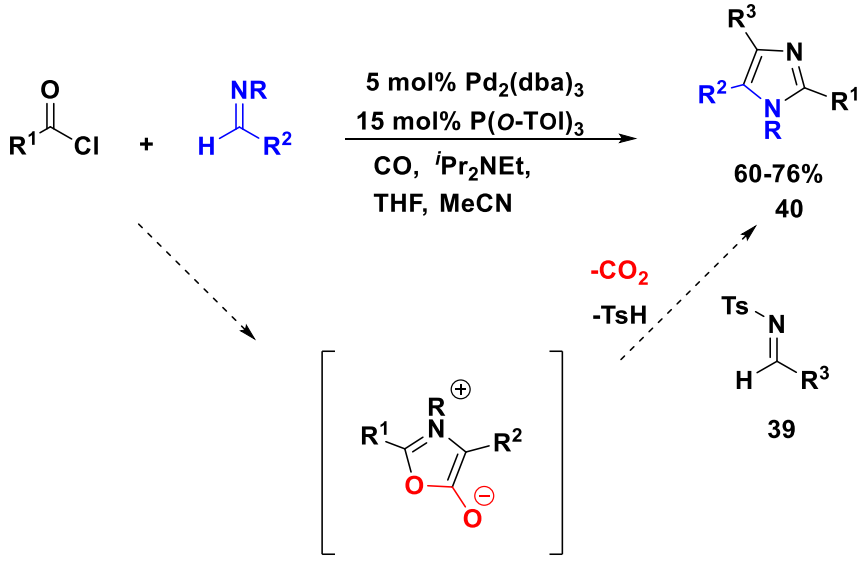


Scheme II.4: Cycloaddition of münchnones and cyclopropenes.



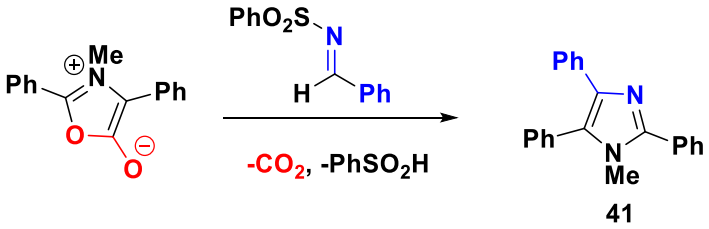
Scheme II.5: Synthesis of 7-membered ring heterocycles from münchnones.

Another important class of heterocyclic product available via in situ synthesis of münchnones is imidazoles. For instance, imidazole **40** is formed from the cycloaddition of *N*-tosyl imines **39** with münchnones; the latter were generated in situ via palladium catalysis (Scheme II.6).[52]



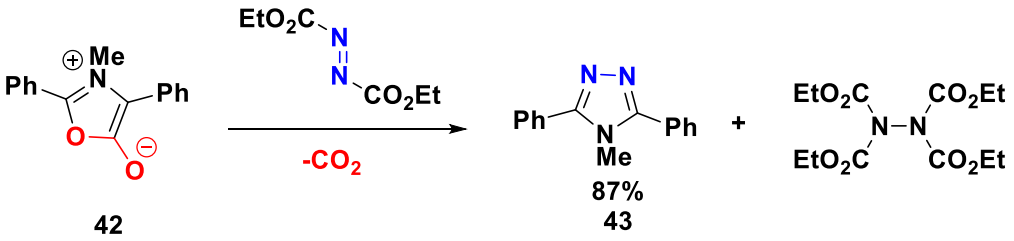
Scheme II.6: Münchnone cycloadditions in imidazole synthesis.

The use of *N*-benzenesulfonyl imines as dipolarophiles for münchnone cyclodditions also provides imidazoles in good yields. Thus, the cycloaddition of münchnones and imines delivered a direct synthesis of imidazole **41** (Scheme II.7).[53]



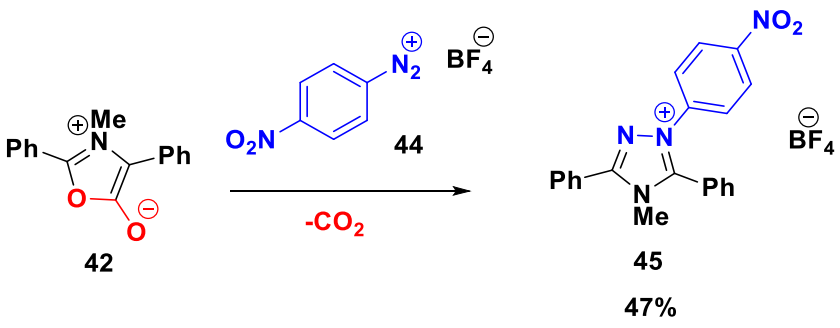
Scheme II.7: Münchnone/imine cycloaddition in imidazole synthesis.

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).[54]



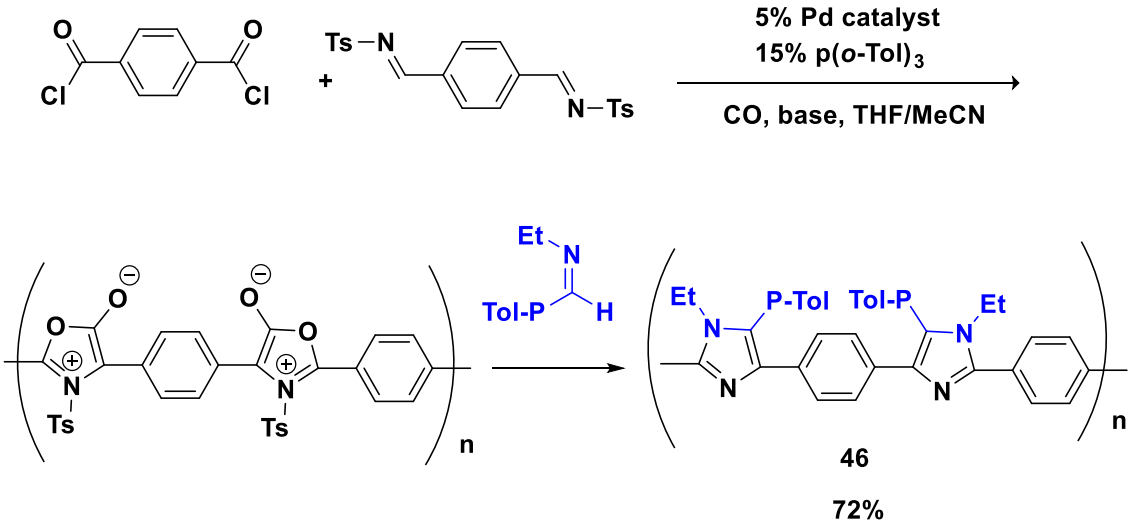
Scheme II.8: 1,3,4-Triazole synthesis from münchnones and ethyl diazodicarboxylate.

Moreover, diazo compound **44** undergoes cycloaddition with münchnone **42** to form triazolium salt **45** in 47% yield (Scheme II.9).[55]



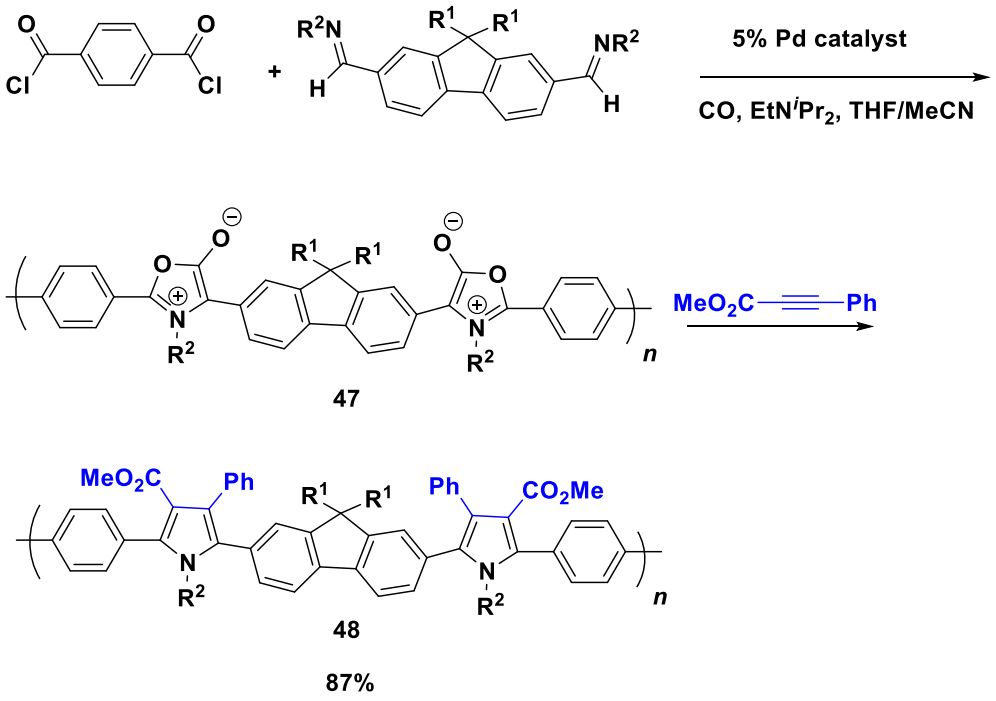
Scheme II.9: Triazolium salt synthesis via münchnone cycloaddition.

A similar protocol reported the use of carbon monoxide, acid chlorides and imines in 1,3-dipolar cycloadditions with münchnones. For example, in 2011 Arndtsen et al.[56] developed an interesting approach to the synthesis conjugated polymers containing imidazoles **46** (Scheme II.10).



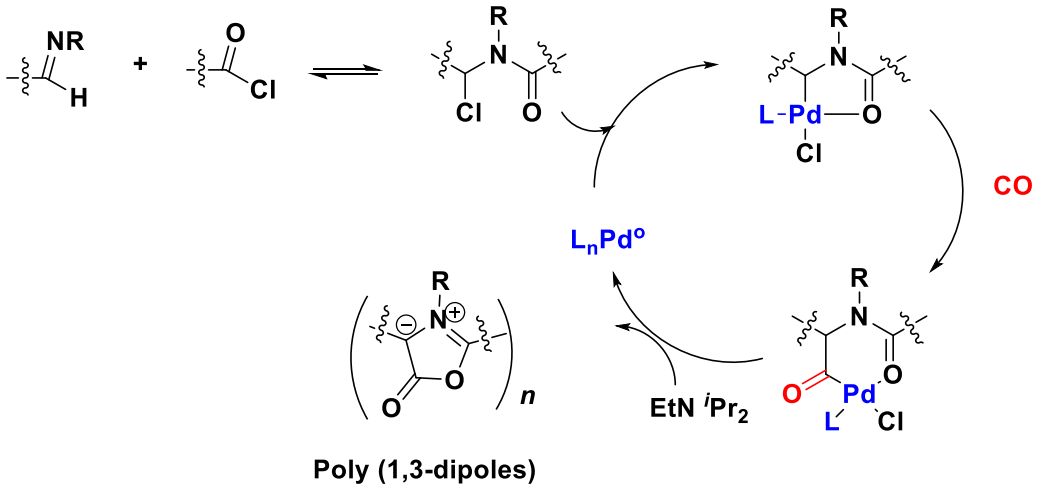
Scheme II.10: Synthesis of conjugated polymers with imidazoles from polymeric münchnones.

More recently, a synthesis of a conjugated polymer containing pyrroles **48** via 1,3-dipolar cycloaddition of polymeric münchnone **47** with dipolarophiles has also been reported by Arndtsen group (Scheme II.11).[57]



Scheme II.11: Synthesis of polymeric pyrroles via polymeric münchnones.

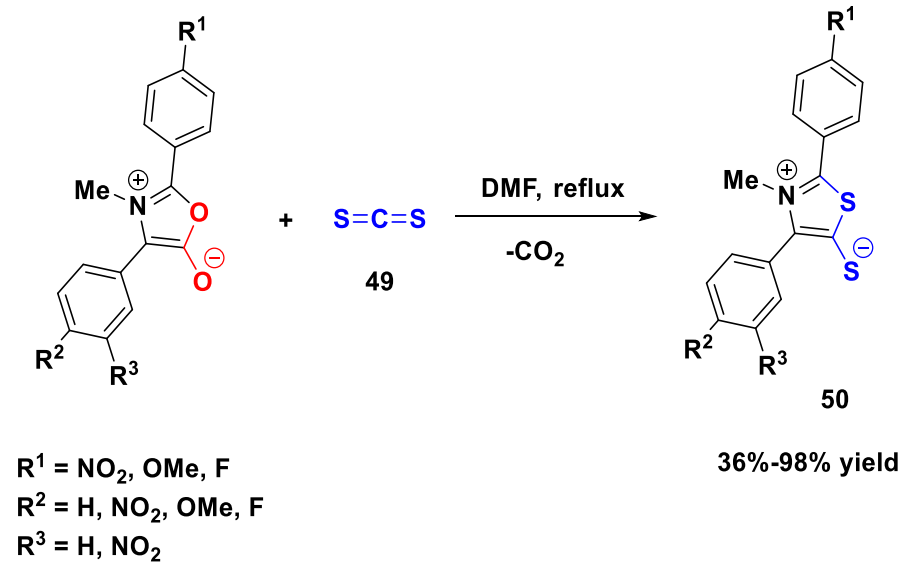
The possible mechanism for the palladium-catalyst coupling route used to generate poly(1,3-dipoles) from acid chlorides, imines and carbon monoxide is shown in scheme II.12.



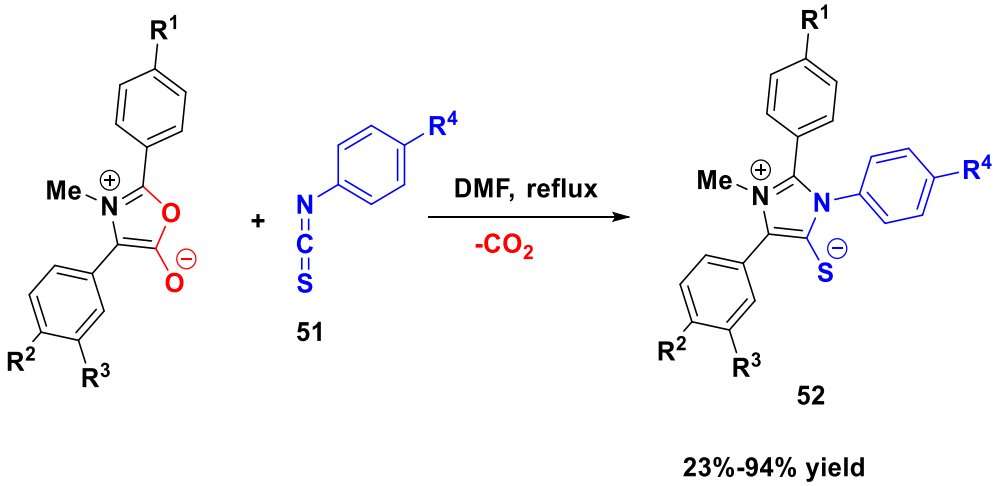
Scheme II.12: A potential transformation to polymers via münchnones.

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

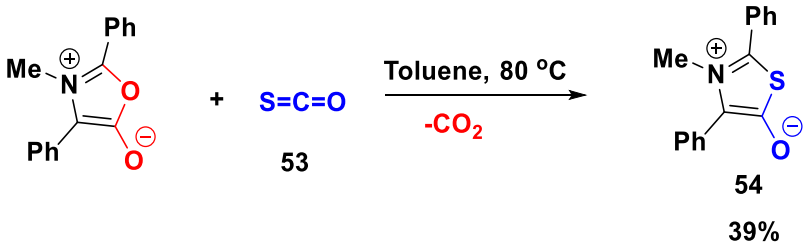
be synthesized through the cycloaddition reactions of münchnones with multiple bond dipolarophiles such as carbon disulfide[58] (CS_2) **49**, isothiocyanates[59] (S=C=NR) **51** and carbonyl sulfide [60-61] (S=C=O) **53**.



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



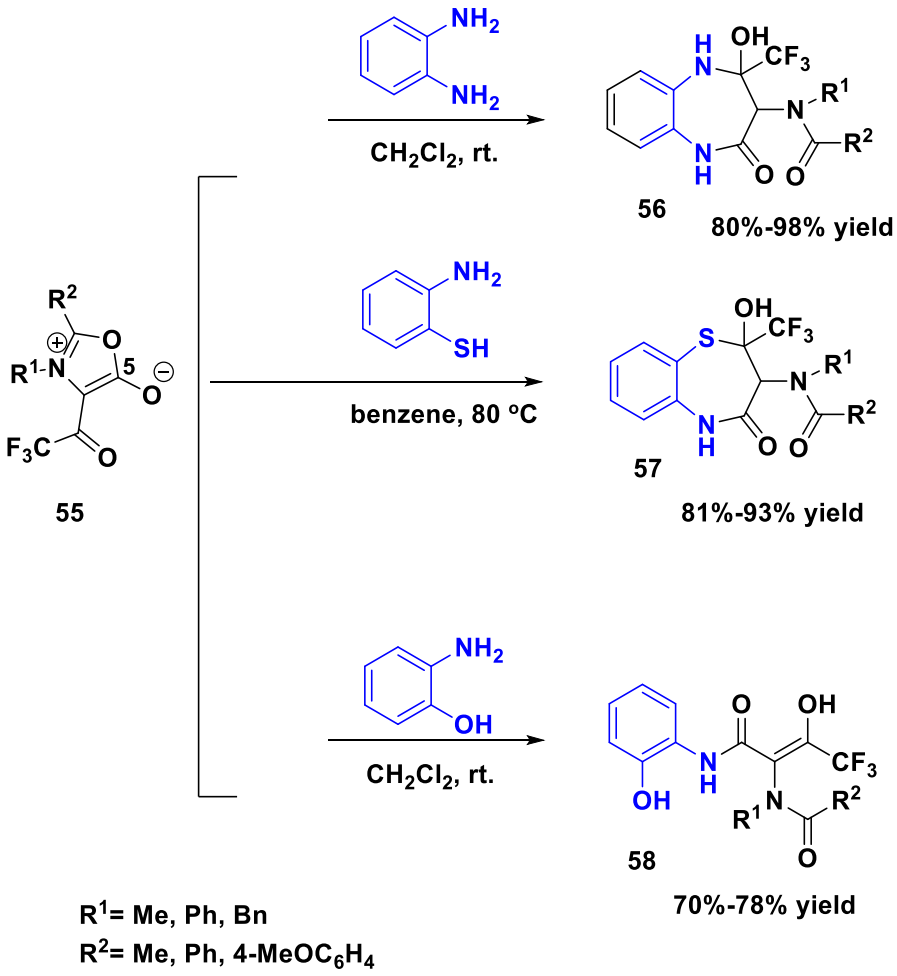
Scheme II.14: Cycloaddition of münchnones and isothiocyanates.



Scheme II.15: Cycloaddition of münchnones and carbonyl sulphide.

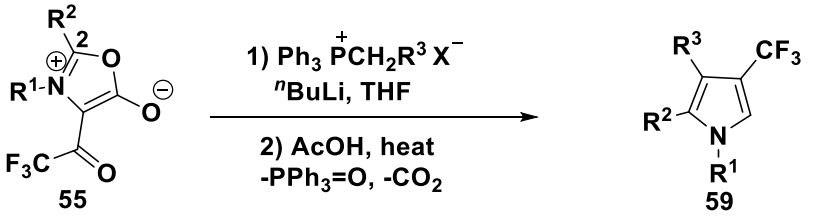
4-Trifluoroacetyl-1,3-oxazolium-5-olates **55** have been found to be a remarkably stable class of münchnones, and they can be readily isolated. These compounds appear to have unique properties and methods have emerged for their use in the synthesis of many different products.

In 2001, Kawase et al.[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).



Scheme II.16: Reaction of 4-trifluoroacetyl münchnones.

In 2010, Kawase et al.[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).



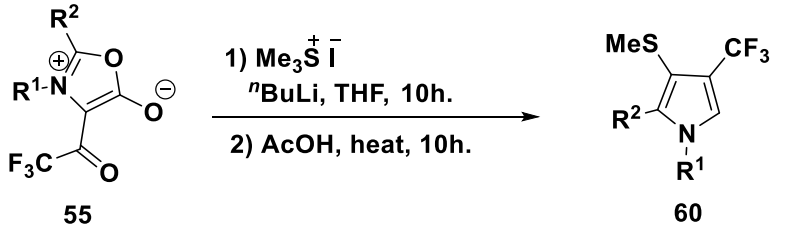
R^1= Me, Ph, Bn, 4-$MeOC_6H_4CH_2$

R^2= Me, ^{t}Bu, Ph, 4-$MeOC_6H_4$

R^3= H, Me, Pr, OMe

Scheme II.17: Pyrrole formation from 4-trifluoroacetyl münchnones.

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).[64]



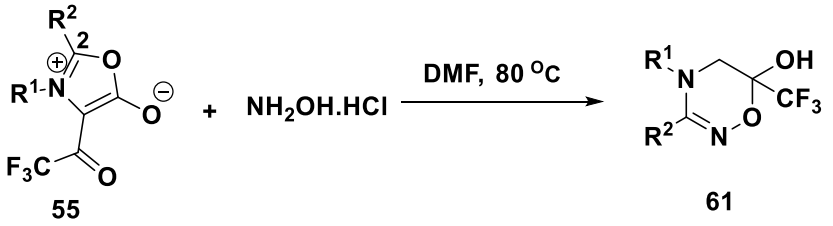
R^1= Me, Ph, Bn, 4-$MeOC_6H_4CH_2$

R^2= Me, Ph, 4-$MeOC_6H_4$

R^3= Me, Ph

Scheme II.18: Münchnone/sulfur ylide cycloadditions in pyrrole synthesis.

Futhermore, 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).[65]



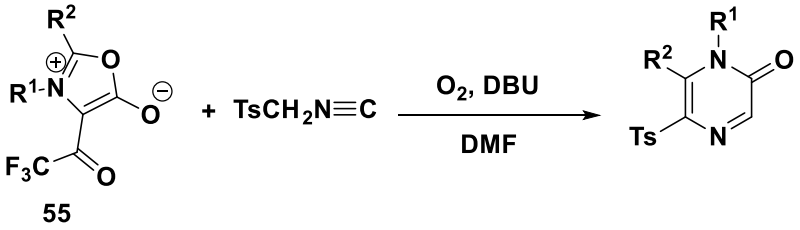
R^1= Me, Ph, Bn

R^2= Me, ^{t}Bu, Ph

54%-95% yield

Scheme II.19: Reaction of münchnones with hydroxylamine.

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).[66]



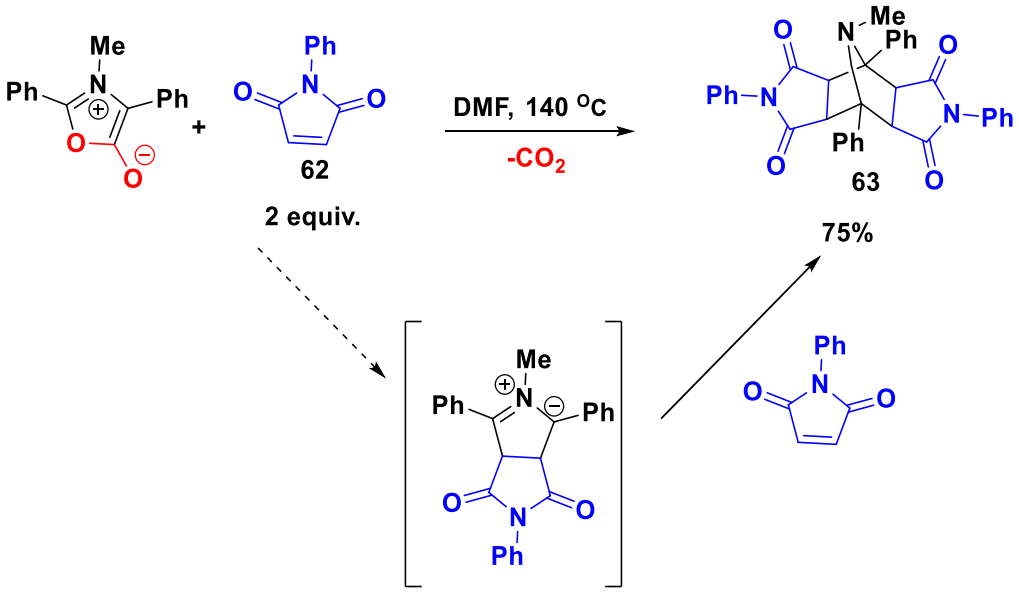
R^1= Me, Ph, Bn, 4-$MeOC_6H_4$

R^2= Me, Ph, 4-$MeOC_6H_4$, 4-BrC_6H_4

19%-78% yield

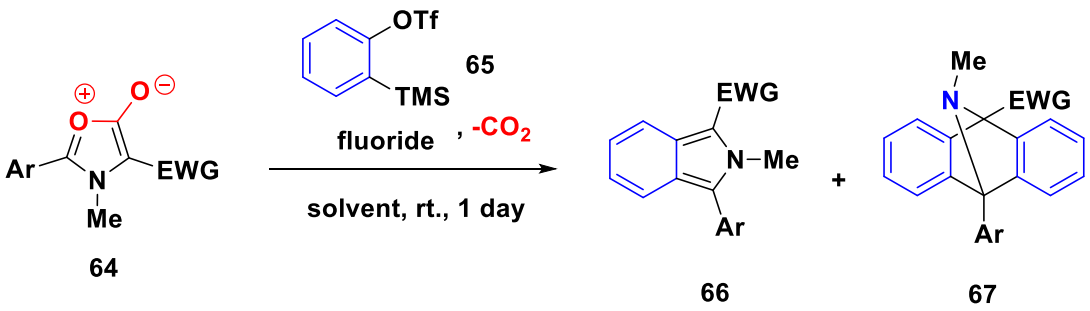
Scheme II.20: Pyrazinone synthesis via münchnones.

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).[67]



Scheme II.21: Reaction of münchnones with *N*-phenyl maleimide.

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.[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).



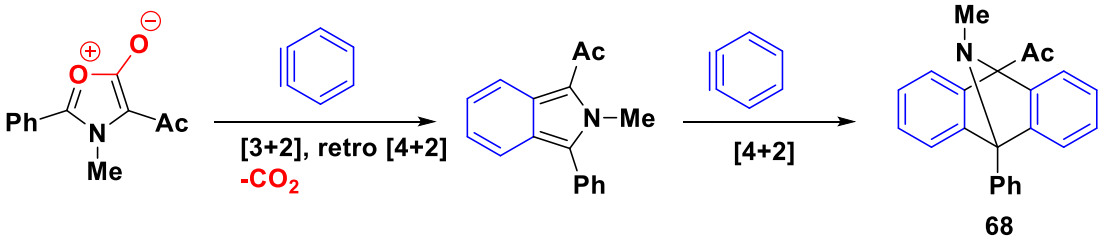
EWG= Acyl, $COCF_3$, $CO(CH_2)_2CH_3$, etc.

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

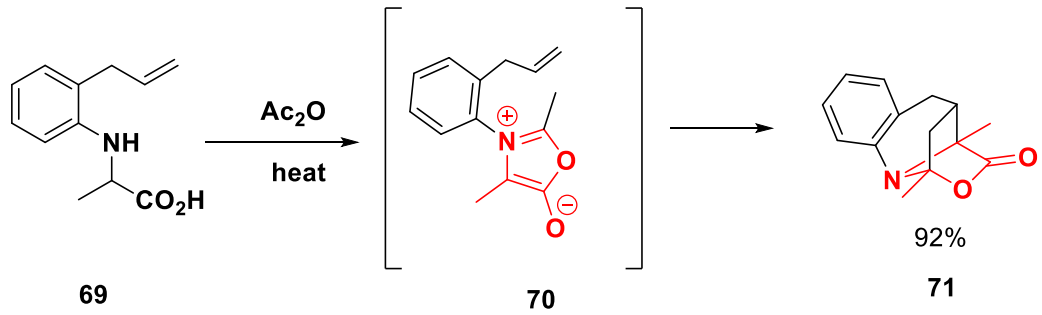
exclusive product when using an excess of benzyne, due to the high reactivity of the latter in the [4+2] cycloaddition reaction.

The mechanism of this process involves an initial [3+2] cycloaddition, followed by [4+2] cycloreversion with extrusion of CO_2 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).



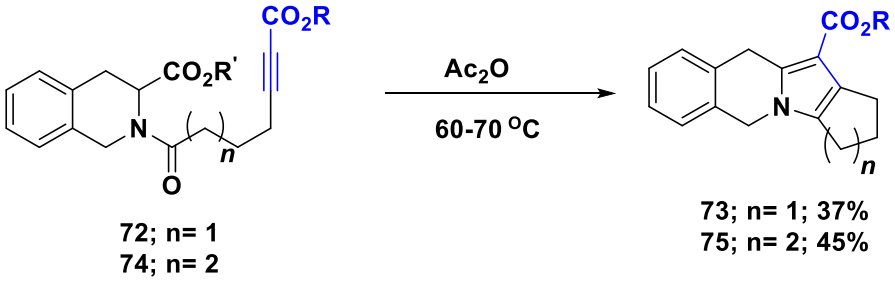
Scheme II.23: Münchnone/aryne cycloaddition.

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).[69,70]



Scheme II.24: Intramolecular münchnone cycloadditions.

Sainsbury at al.[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).



Scheme II.25: Synthesis of tetracyclic products via intramolecular münchnone cycloadditions.

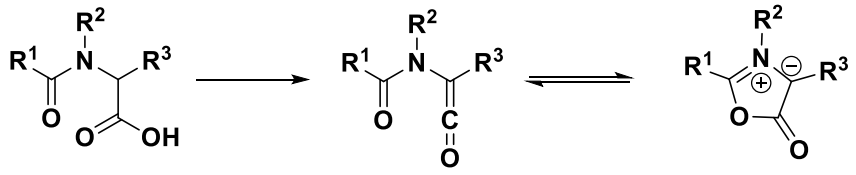
3. Conclusion

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

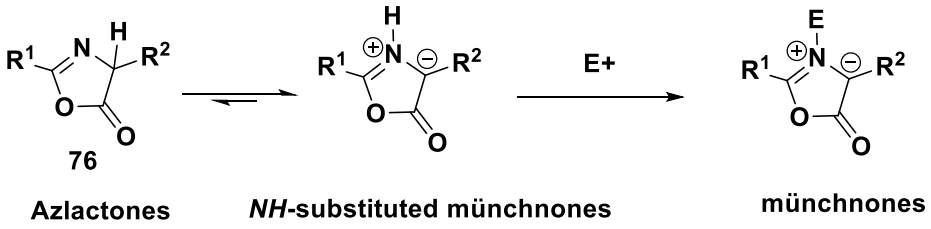
1. Previous synthesis of münchnones

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.



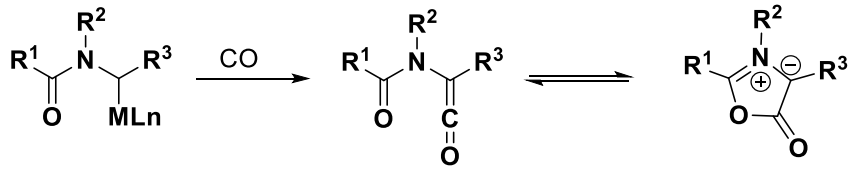
Scheme III.1: Münchnone synthesis from amino acid derivatives.

Alternatively, oxazol-5-(4*H*)-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.

Finally, metal mediated routes to münchnones involve of use of α-metalated amide precursors, which undergo carbonylation (Scheme III.3).

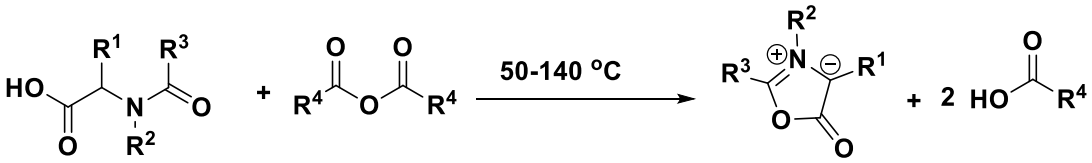


Scheme III.3: General organometallic strategy for synthesis of münchnones.

Examples of these three strategies will be illustrated in the following sections.

1.1. Synthesis of münchnones from amino acids

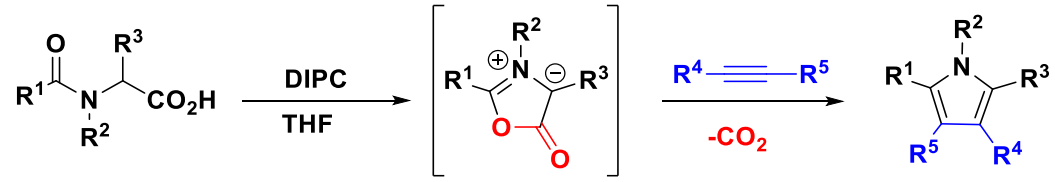
Traditionally, münchnones were synthesized by the cyclodehydration of *N*-alkyl amino acids using acid anhydrides (Scheme III.4).[72]



Scheme III.4: General strategy for the synthesis of münchnones (Hüisgen).

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.[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*-ethyl-*N*'-dimethyl aminopropyl carbodiimide (EDC) or $SiCl_4$.[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 münchnones.

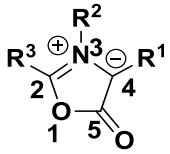
Since their discovery, a range of *N*-alkyl or *N*-aryl münchnones have been generated. However, many authors have reported that most of these 1,3-dipoles are too unstable to be isolated. Therefore, these münchnones can be reacted in situ with dipolarophiles. For example, symmetrical and unsymmetrical münchnones were prepared and reacted in situ with a range of dipolarophiles using *N,N'*-diisopropylcarbodiimide (DIPC) as shown in Scheme III.5.[74]



$R^1 = R^3 = Me$
$R^1 = R^3 = Ph$
$R^1 = Ph, R^3 = Me$
$R^1 = Me, R^3 = Ph$
$R^2 = Me, Bn$

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

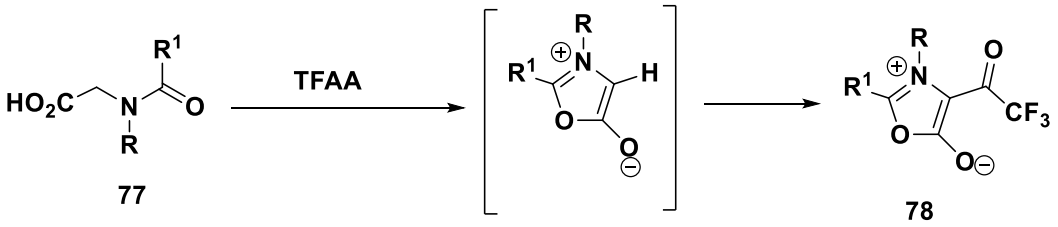
Many synthetic routes have been developed towards more stable münchnone analogues. For instance, the effects of substitution on münchnone stability have been investigated. It was discovered that only in cases where münchnones contained aryl substituents at C2 and C4 positions, or when the C4 position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



$R^1, R^3 = Ar$
$R^1 = COCF_3, R^3 = Ar$ or Alkyl
$R^2 = Me, Bn$

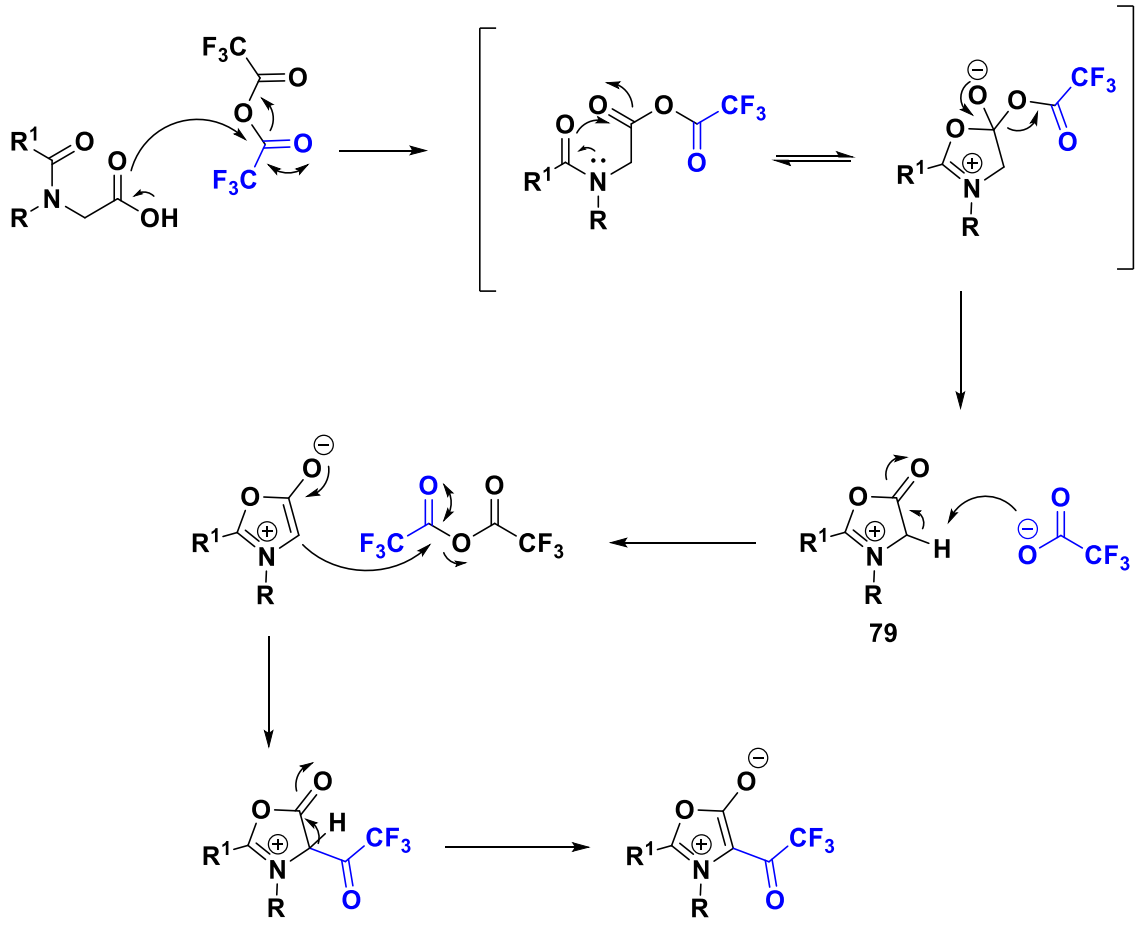
Figure III.1: Isolable münchnones.

In 1964, Singh et al.[76] reported an efficient route to stable münchnones **78**, by reacting *N*-alkyl *N*-acyl glycines **77** with trifluoroacetic anhydride at room temperature (Scheme III.6).



Scheme III.6: Stabilized münchnones.

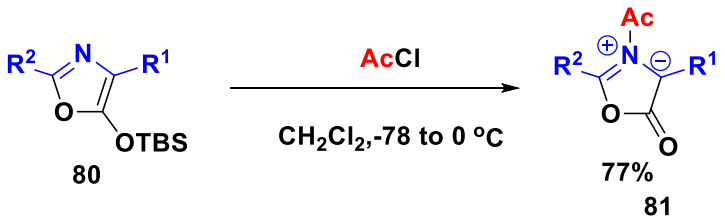
A possible mechanism for these reactions is illustrated in scheme III.7. These reactions are initiated by attack of the carboxylic acid on the anhydride to form oxazolium ion as the intermediate **79**. These intermediates have an unsubstituted C4 position, which can undergo acylation after being deprotonated by the trifluoroacetate to furnish the desired münchnone.



Scheme III.7: Proposed mechanism of münchnone formation.

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.[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).



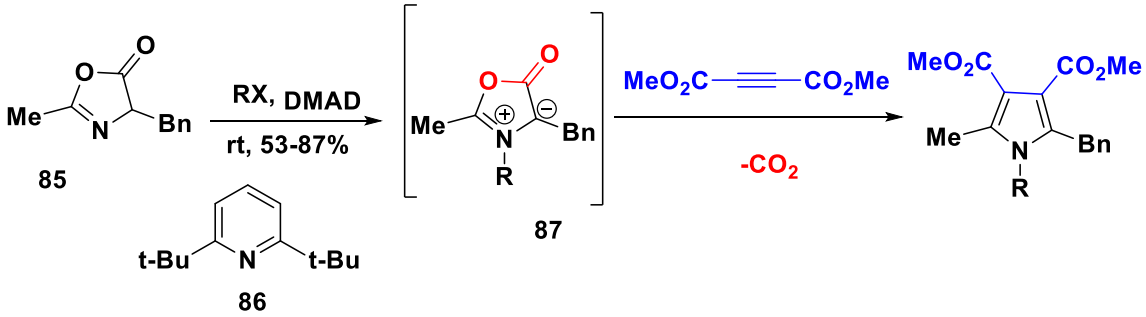
Scheme III.8: Synthesis of *N*-Acyl münchnones.

Wilde et al.[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**.

z

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

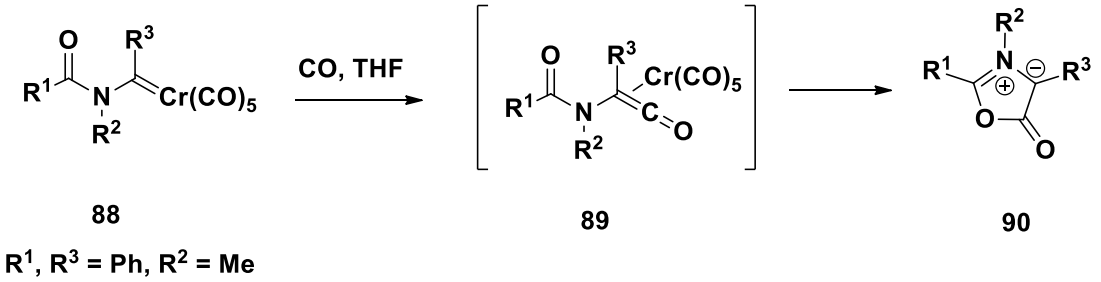
In a protocol similar to that reported by Wilde, Hershenson et al.[78] observed the formation of münchnone **87** by use of an azalactone **85**, which underwent *N*-alkylation followed by deprotonation by 2,6-di-*tert*-butylpyridine **86**. Trapping of **87** with DMAD gave the corresponding pyrrole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



Scheme III.10: Formation of münchnones by use of azalactones.

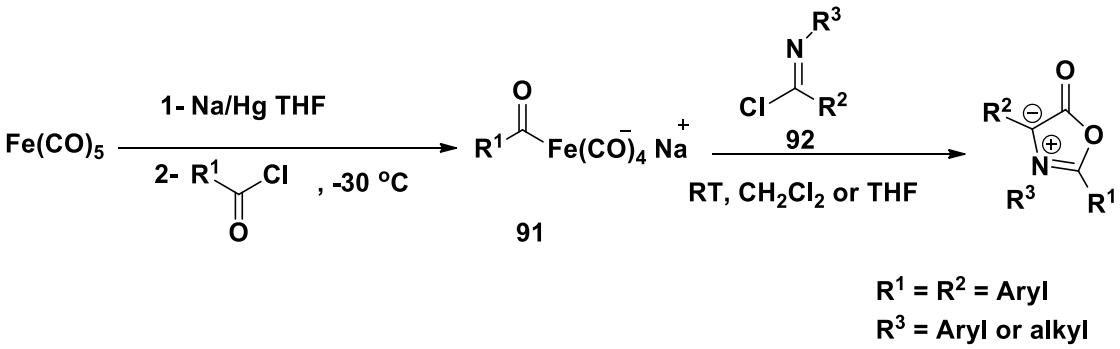
1.3. Synthesis of münchnones from metal-mediated routes

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).[79]



Scheme III.11: Generation of münchnones from *N*-acylaminochromium carbenes.

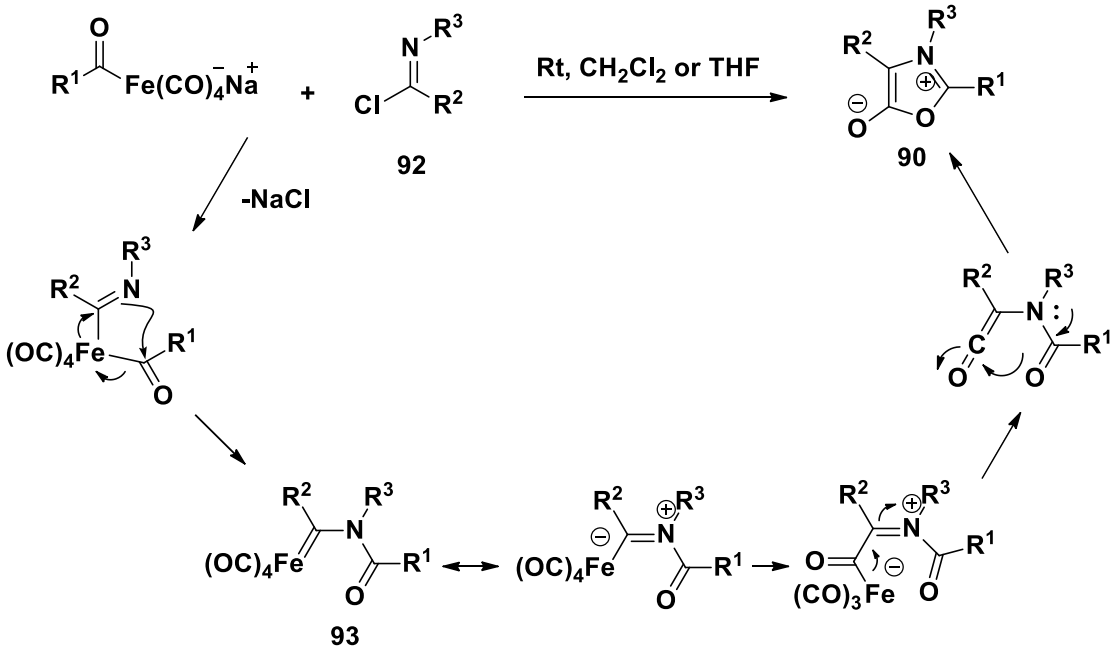
Similarly, iron acyl complexes can be used to form münchnones. The reaction of sodium acyltetracarbonylferrate **91** with imidoyl chlorides **92** followed by cyclisation results in the production of these mesoionic compounds in moderate to good yields (Scheme III.12).[80]



Scheme III.12: Generation of münchnones from acyltetracarbonyl ferrates.

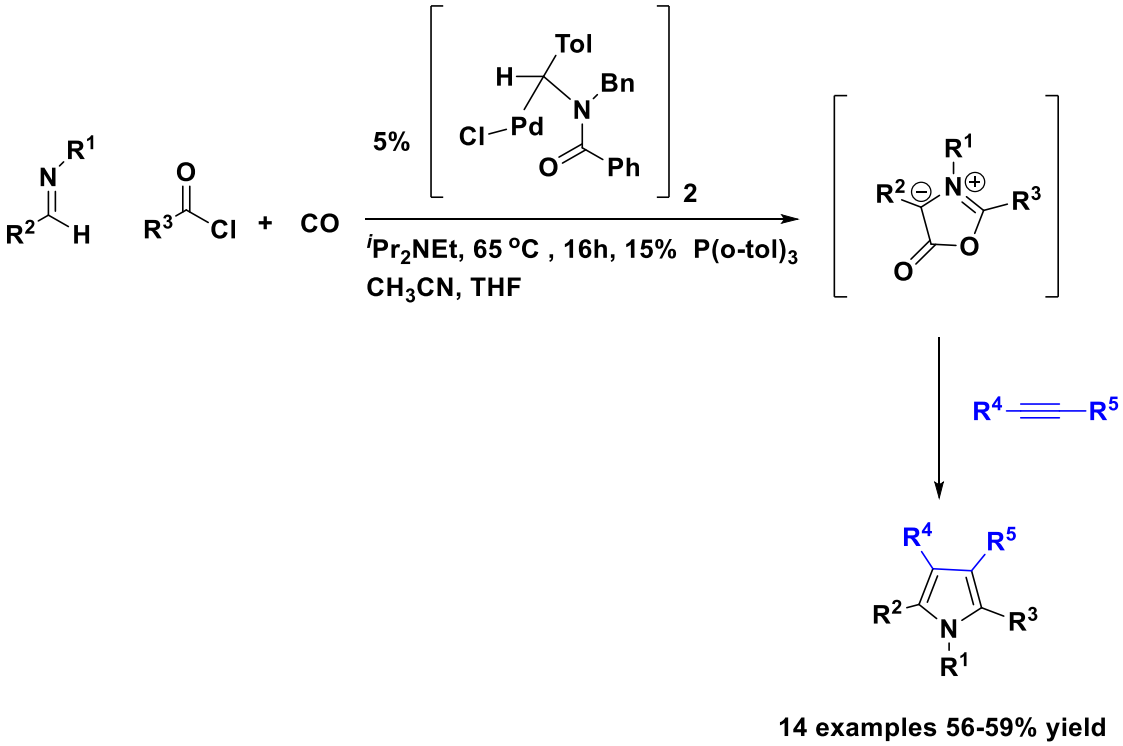
The postulated mechanism is illustrated in scheme III.13, and involves initial displacement of the chloride from the imidoyl chloride **92** to provide **93** followed by

migration of the carbene complex. After CO insertion, the desired münchnone **90** was obtained.



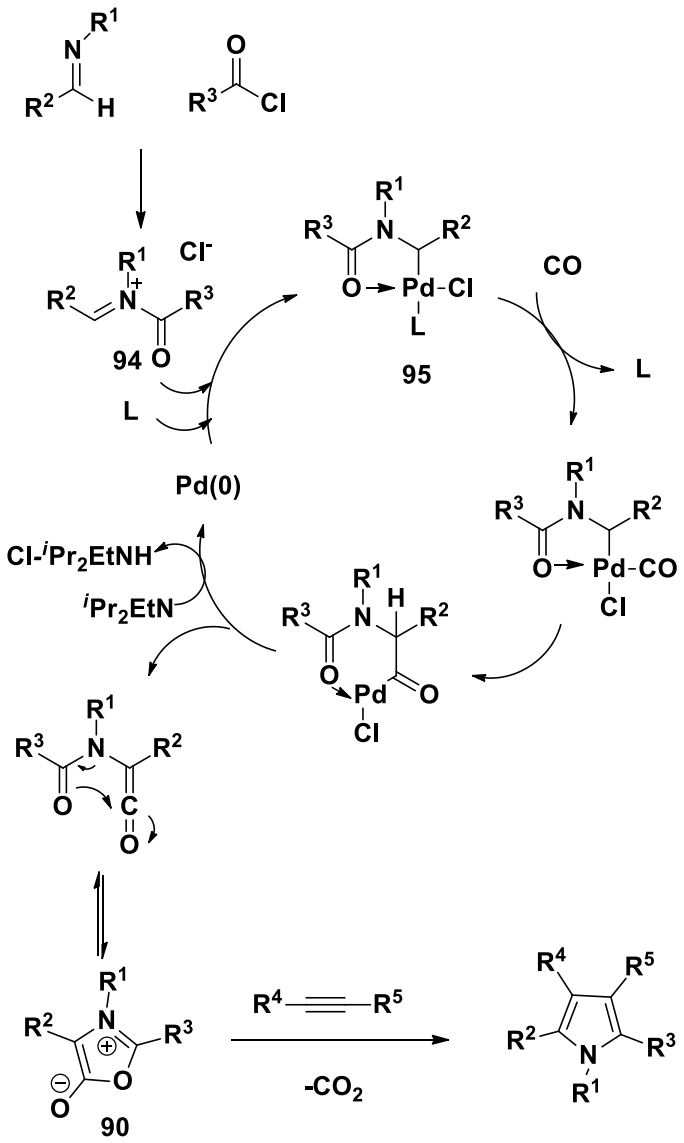
Scheme III.13: Proposed mechanism for münchnone synthesis.

More recently, Arndtsen et al.[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).

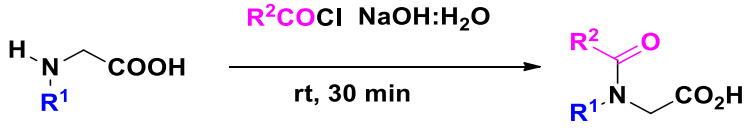


Scheme III.15: Mechanism for the synthesis of pyrroles via münchnones.

2. Substrate synthesis

Initial results and optimisation

As described previously, most reactions of münchnones requires 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,[24] our initial work aimed to access a small selection of *N*-acyl amino acids. They were synthezised 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 *N*-methyl amino acids **96** and *N*-benzyl amino acids **98** a mixture of two rotamers obtained (Table III.1).



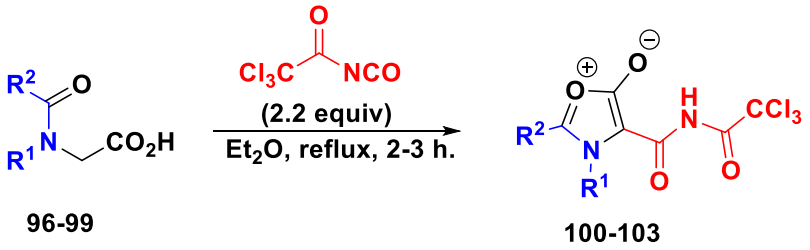
96-99

Entry	R^1	R^2	Product	Yield %
1	Me	Ph	96	84%
2	Ph	Me	97	80%
3	Bn	Ph	98	67%
4	Ph	Ph	99	89%

Table III.1: Synthesis of substituted *N*-acyl-*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.[24] The corresponding 4-trifluoroacetylated münchnones **100**-**103** were obtained in a good yield by the use of TFAA (trifluoroacetic anhydride) as an electrophile (Table III.2).



Entry	R^1	R^2	Product	Yield %
1	Me	Ph	100	92%
2	Ph	Me	101	63%
3	Bn	Ph	102	82%
4	Ph	Ph	103	70%

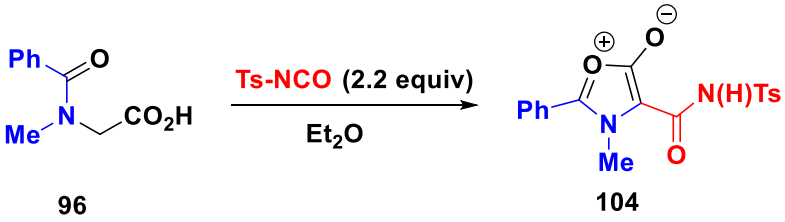
Table III.2: Synthesis of 4-trifluoroacetylated münchnones.

The principal advantage of preparing münchnones **100**-**103** is the wide variety of substituents available for R^1 and R^2, which can be reflected in the corresponding substitution of the resulting product. Thus, the münchnone precursors are air and bench stable for extremely long periods of time. Furthermore, the cyclisation of these münchnones 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 münchnones 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 münchnones, 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.[82] Tosyl isocyanate was tested first with *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_2O as the most effective solvent for the formation of münchnone **104**.

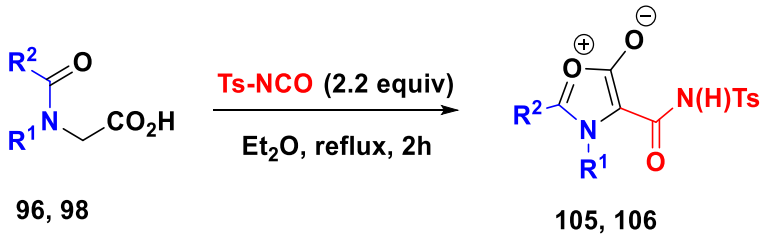


96 **104**

Reaction (time)	Conditions	Yield%
10 min	rt	65%
2h	rt	86%
2h	reflux	97%

Table III.3: Synthesis of *N*-methyl C4-imide substituted münchnones. Ts=4-toluenesulfonyl.

The *N*-benzyl C4-imide substituted münchnones **105** and **106** were also obtained in excellent yield using the same conditions described above (Scheme III.16).

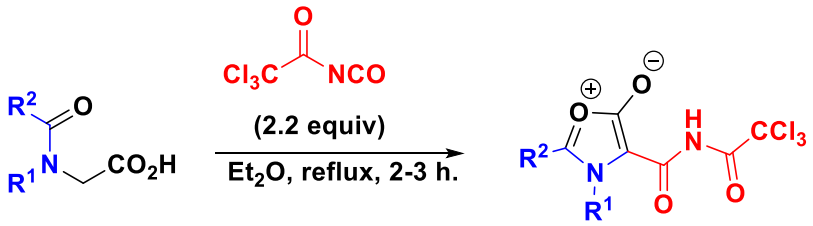


96, 98 105, 106

Entry	R^1	R^2	Product	Yield %
1	Bn	Ph	105	100%
2	Me	Me	106	80%

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).



96-98 107-109

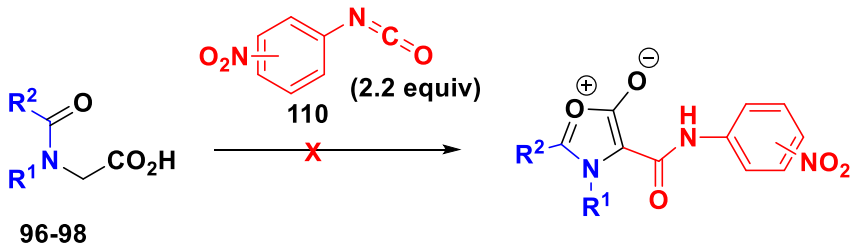
Entry	R^1	R^2	Compound	Yield%
1	Me	Ph	107	58%
2	Bn	Ph	108	77%
3	Ph	Ph	109	35%

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

Compounds **107**-**109** were isolated after precipitation from cold Et_2O 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.

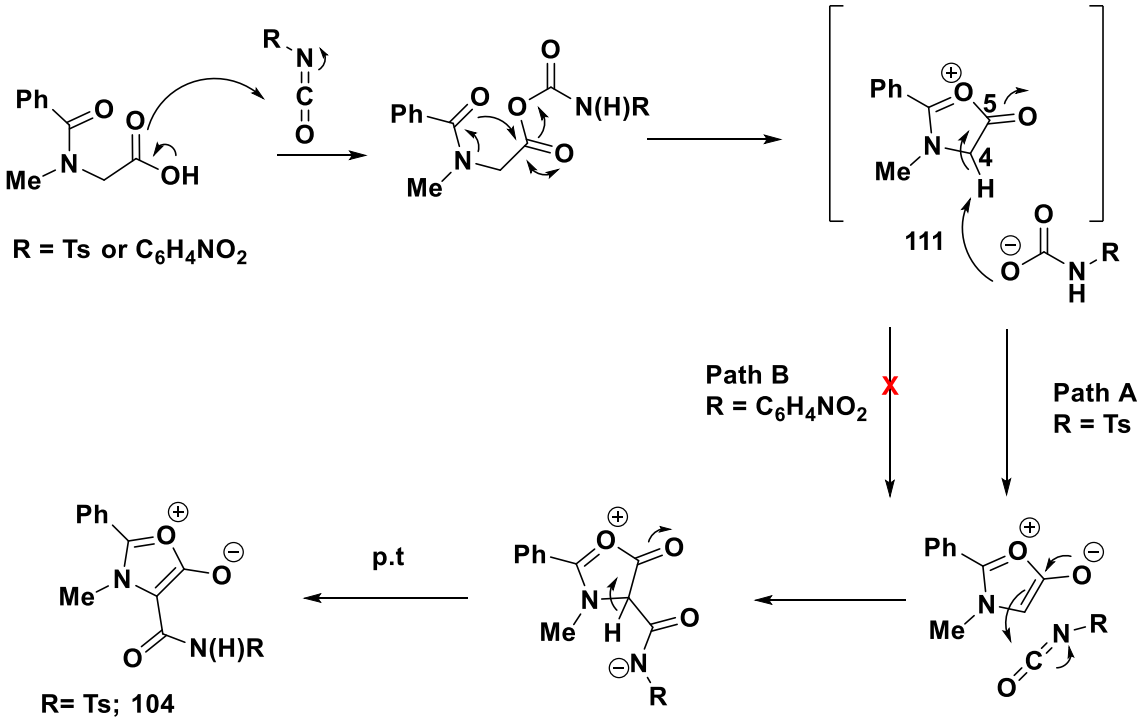
In order to explore the efficiency of other isocyanate reagents as electrophiles for münchnone formation, a range of alternative commercial isocyanates were tested. Disappointingly, using nitrophenyl isocyanate **110** as the electrophile under the general conditions described above, no desired product 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).



Entry	R^1	R^2	Con.	Time	Solvent	nitroarene Isomer used
1	Me	Ph	Reflux	4 h	Et_2O	Para
2	Me	Ph	Reflux	4 h	THF	Para
3	Me	Ph	RT	3 h	Et_2O	Para
4	Ph	Me	Reflux	16 h	THF	Para
5	Bn	Ph	Reflux	2 h	Et_2O	Para
6	Me	Ph	Reflux	2 h	Et_2O	Meta

Table III.5: Attempted synthesis of nitrophenylmünchnones.

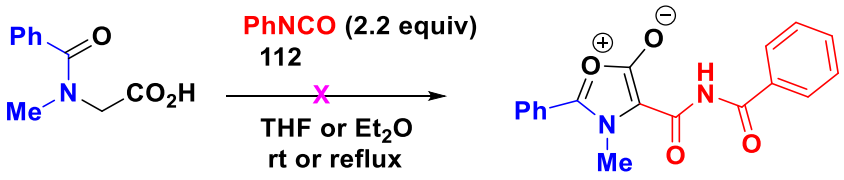
The lack of reactivity observed with nitrophenyl isocyanate **110** was unexpected and is difficult to explain. We believe that the mechanism of formation of the C4-imide substituted münchnones is essentially the same as that proposed for the 4-trifluoroacetyl münchnones as illustrated in scheme III.7.



Scheme III.17: Proposed mechanism for münchnone cyclization.

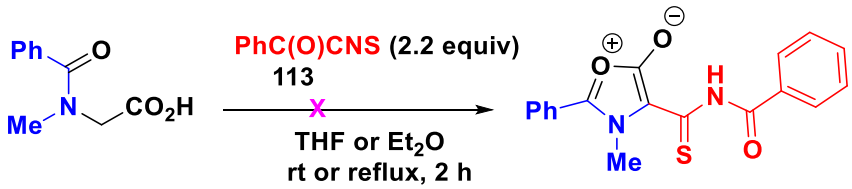
As shown in scheme III.17, the cyclisation step provides intermediate **111** which undergoes electrophilic aromatic substitution to generate the product **104** (Scheme III.17, bath A). It may simply be that nitrophenyl isocyanates are too poorly electrophilic to promote this process, and that the unsubstituted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



Scheme III.18. Unsuccessful münchnone cyclization reaction.

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).



Scheme III.19: Unsuccessful münchnone cyclization reaction.

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

3. Conclusion

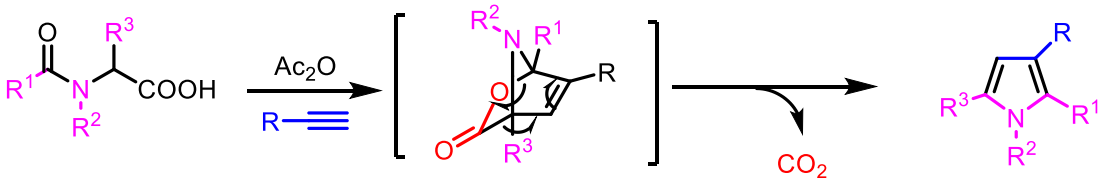
Overall, a new set of münchnones **104 - 109** were synthesized using a novel methodology from readily available amino acids and isocyanates. Although some isocyanates such as nitrophenyl isocyanate **110** and phenyl isocyanate **112** were unsuccessful in generating the desired products, those münchnones 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

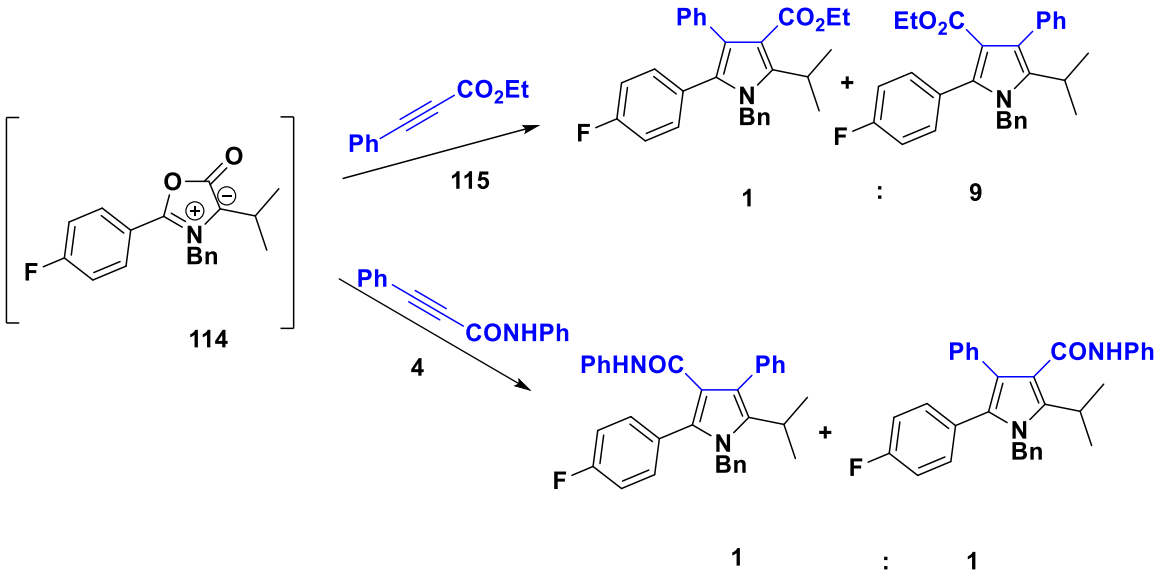
1. Introduction

Developing new strategies to access functionalised pyrroles has been subject of many studies in organic synthesis.[83-85] 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.[86] With regard to dipolarphiles employed in reactions of münchnones, the use of alkynes to form pyrroles is by far the most common approach.[87,88] 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).[22]



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.[20] For example, Pandey et al.[89] 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).

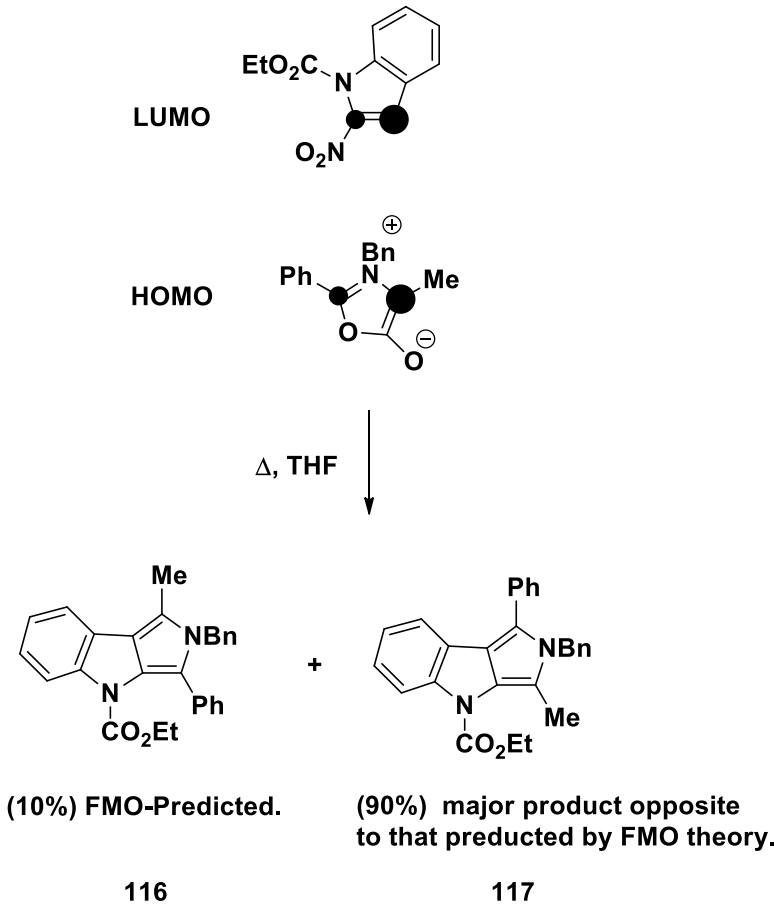


Scheme IV.2: Unpredictable regioselectivity in dipolar cycloaddition of münchnones.

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.[90]

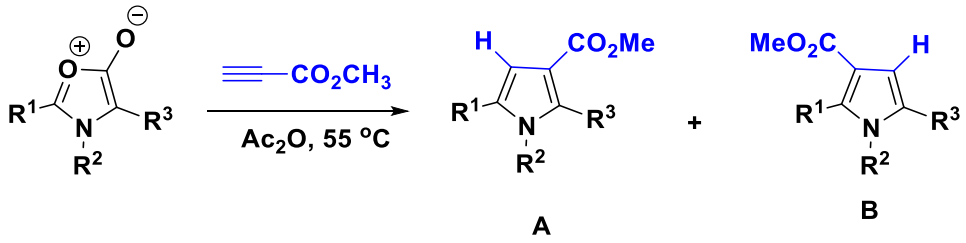
In general, the reactivity of 1,3-dipolar compounds can be explained by frontier molecular orbital theory (FMO), which is a useful tool to help predict the regioselectivity of 1,3-dipolar cycloaddition reactions. This theory explains that the cycloaddition occurs between the reactants that have the lowest 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.[20,91] However, in practice, FMO theory fails to predict product regioselectivity of münchnone cycloaddition with dipolarophiles.[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).[92]



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

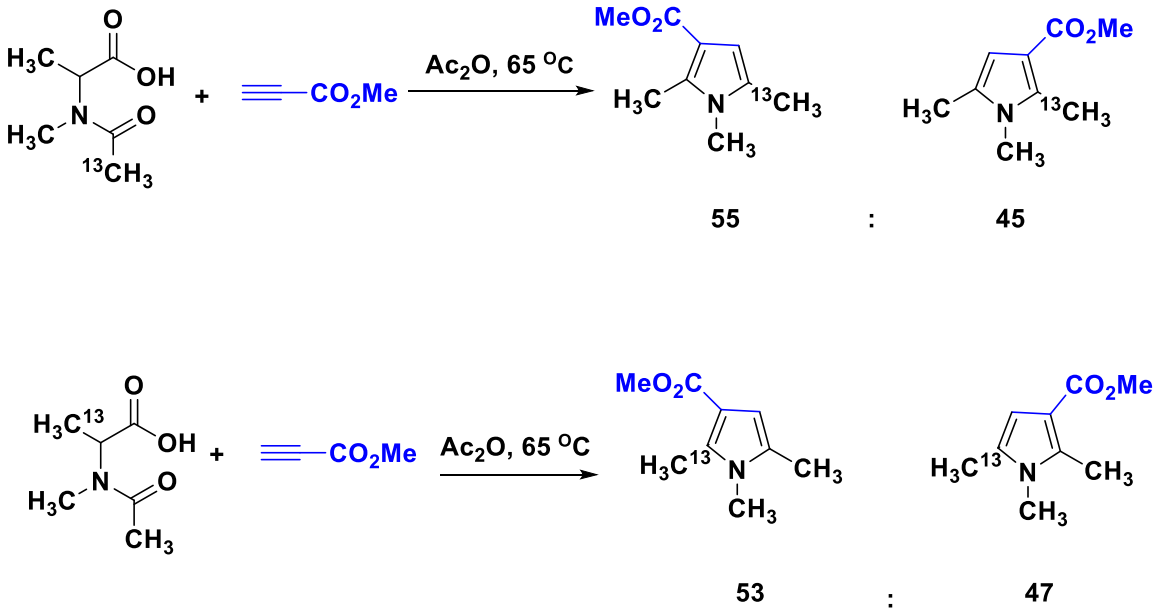
The same sporadic regiochemical trends were observed by Trost et al.[93] in his studies of münchnone cycloadditions with methyl propiolate. Upon treatment of a series of unsymmetrical münchnones with this alkyne, it was found that the regiochemistry appeared to be heavily influenced by steric factors 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).



Entry	R^1	R^2	R^3	Regioisomeric ratio A:B
1	$(CH_3)_2CH$	CH_3	H	25 : 75
2	CH_3	CH_3CH_2	H	25 : 75
3	Bn	CH_3	H	16 : 84
4	Ph	CH_3CH_2	H	25 : 75
5	H	CH_3	$(CH_3)_2CH$	67 : 33
6	H	CH_3	Bn	83 : 17
7	H	CH_3CH_2	CH_3	84 : 16
8	H	CH_3CH_2	Ph	86 : 14

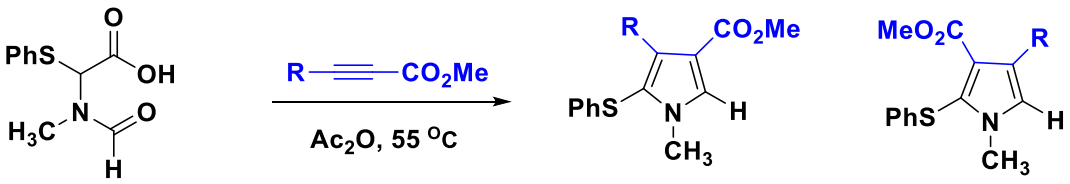
Table IV.1: cycloadditions of unsymmetrical münchnones with methyl propiolate.

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 (^{12}C- versus ^{13}C-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 ß-carbon. When dipolarophiles bearing substituents of different steric bulk were investigated (R = H, CH_3, 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.

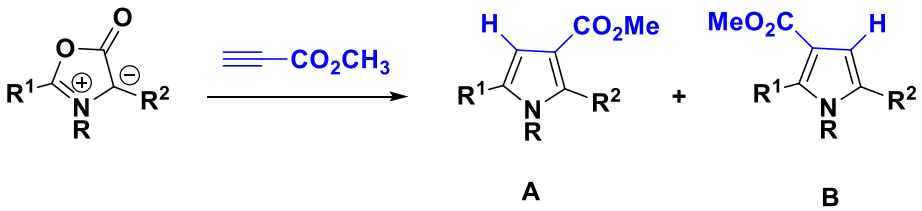


R = H	18	:	82
R = CH_3	75	:	25
R = Ph	100	:	0

Scheme IV.5: Product distribution from different substituents on the dipolarophile.

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).

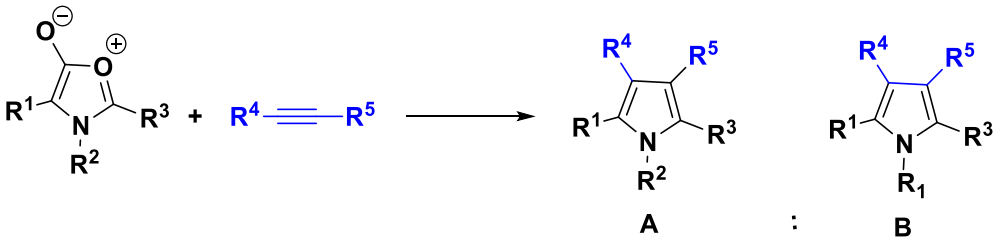


A B

Entry	R^1	R	R^2	Regioisomeric ratio A :B
1	CH_3	Ph	H	1 : 3
2	CF_3	Ph	H	9 : 1
3	CH_3	CH_3	Ph	1 : 1
4	CH_3	CH_3	Bn	1 : 1

Table IV.2: Regioselectivity study of münchnone cycloadditions.

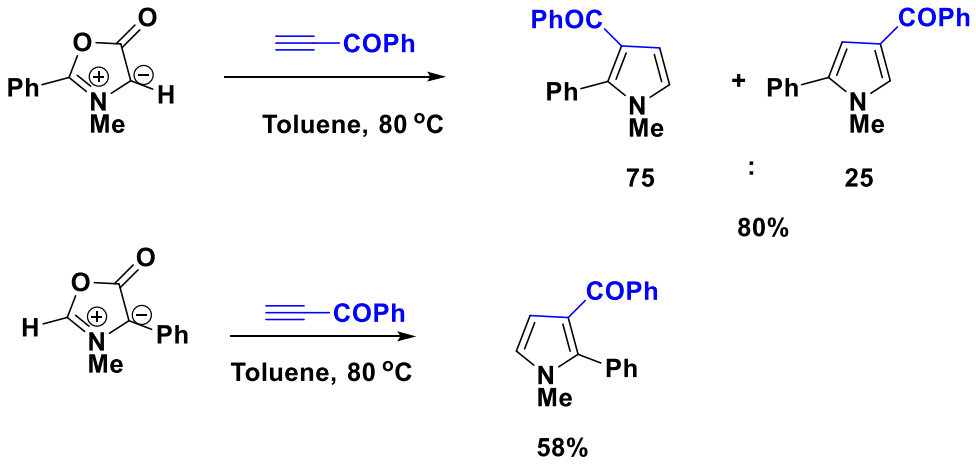
Rosa et al.[95] also examined the influence of münchnone substitution patterns on cycloaddition regioselectivities. These researchers used symmetrical and unsymmetrical münchnones with arylsulfonyl alkynes. It was suggested that steric and electronic influences combine to determine the course of reaction 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.



Entry	R^1	R^2	R^3	R^4	R^5	Yield	Regioisomeric ratio A : B
1	Ph	Me	Ph	H	SO_2Ph	72%	—
2	Ph	Me	Ph	Me	SO_2Ph	63%	—
3	Ph	Me	Ph	Ph	SO_2-o-Tol	55%	—
4	H	Ph	H	H	SO_2Ph	61%	—
5	H	Ph	H	Me	SO_2Ph	62%	—
6	H	Ph	H	Ph	SO_2-o-Tol	68%	—
7	Ph	Me	Me	H	SO_2Ph	62%	100 : 0
8	Ph	Me	Me	Me	SO_2Ph	67%	100 : 0
9	Ph	Me	Me	Ph	SO_2-o-Tol	72%	100 : 0
10	Me	Me	Ph	H	SO_2Ph	86%	25 : 75
11	Me	Me	Ph	Me	SO_2Ph	92%	10 : 90
12	Me	Me	Ph	Ph	SO_2-o-Tol	83%	12 : 88

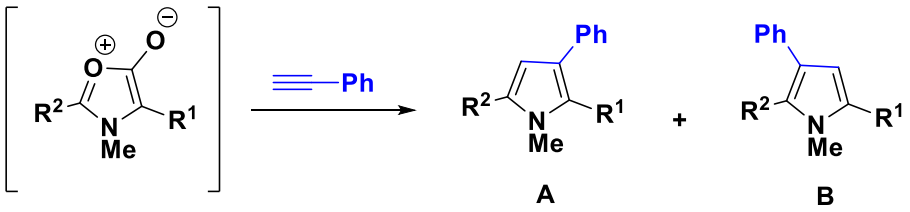
Table IV.3: Substituent effects on regioselectivity of münchnone cycloadditions.

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]



Scheme IV.6: Substituent effects on regioselectivity.

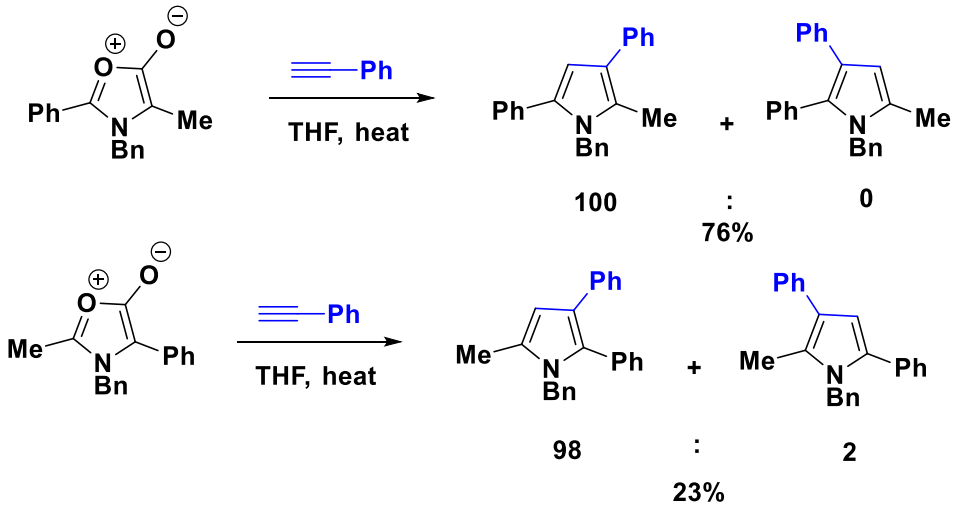
Futhermore, Dalla and La Rosa showed that unsymmetrical münchnones could be reacted with phenylacetylene to give the pyrrole products in moderate to good yields. The reaction is commonly regioselective with the major pyrrole isomer from the connection of the negative charge of C4 of the münchnone and the α-carbon of the dipolarophile (Table IV.4).[97]



Entry	R^1	R^2	Yield %	Regioisomeric ratio A : B
1	Ph	H	34	100 : 0
2	CH_3	H	4	100 : 0
3	Ph	CH_3	50	98 : 2
4	CH_3	Ph	44	99 : 1

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

Morever, Gribble et al.[20] observed the same behavior when *N*-benzyl münchnone was used in the cycloaddition of phenylacetylene (Scheme IV.7).



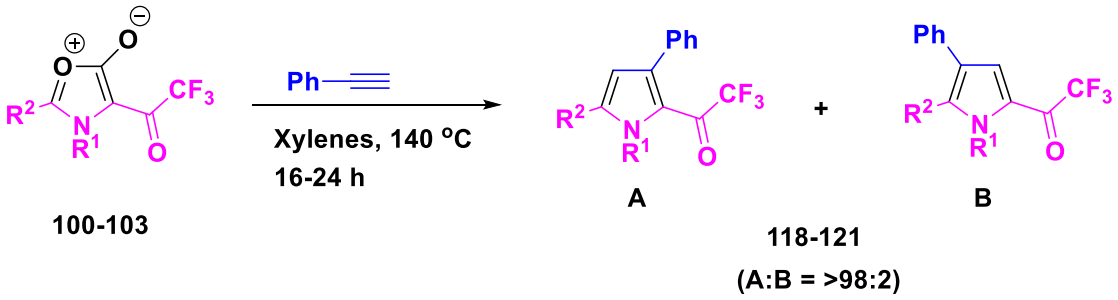
Scheme IV.7: Pyrrole formation from phenylacetylene as a dipolarophile.

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.



Entry	R^1	R^2	[a]Products	[c]Yield %
1	Me	Ph	**118**	75%
2	Ph	Me	[b]**119**	70%
3	Bn	Ph	**120**	67%
4	Ph	Ph	**121**	91%

[a]Product ratios were determined by ^{1}H NMR integration; [b]Regiochemistry was determind by NOE interaction of R^2 and the pyrrole ring proton; [c]Yields 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).

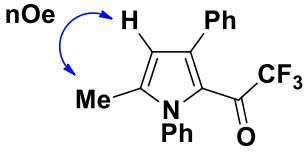
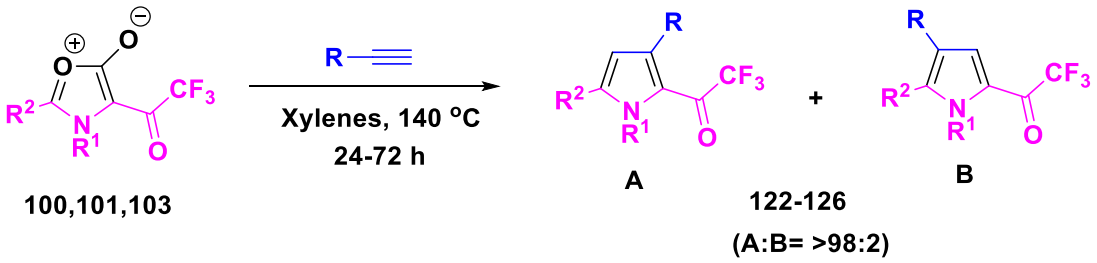


Figure IV.1: Characterization of pyrrole regiochemistry by NOE.

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).



Entry	R^1	R^2	R	Products	Yield %
1	Me	Ph	^{n}Hex	122	48%
2	Ph	Me	^{n}Hex	123	25%
3	Ph	Ph	^{n}Hex	124	33%
4	Me	Ph	^{n}Bu	125	44%
5	Me	Ph	cyclopropayle	126	39%

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.

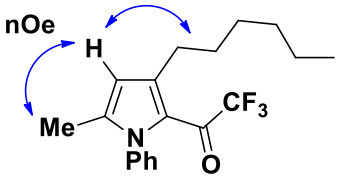
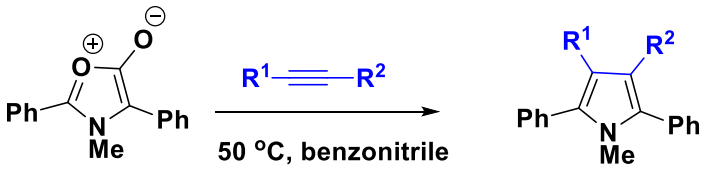


Figure IV.2. Characterization of pyrrole regiochemistry by NOE.

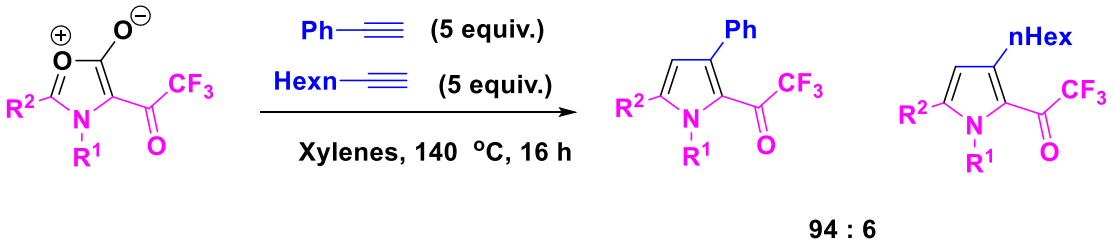
These results obtained from trifluoroacetylated münchnone cycloadditions with alkynes suggested that pyrrole formation proceeded with high selectivity to connect the C4 carbon of the münchnone to the α-C2 carbon of the alkyne. Futhermore, these reactions reflected literature precedent that suggests there is a decrease in reactivity from electron poor to electron rich alkynes.[27] Figure IV.3 summarizes the reactivity order of alkynes in cycloadditions with münchnones from the most reactive to the least reactive dipolarophiles.



$MeO_2CC{\equiv}CCO_2Me > HC{\equiv}CCO_2Me > PhC{\equiv}CCO_2Me > PhC{\equiv}CH > C_6H_{13}C{\equiv}CH$

Figure IV.3: Different alkyne reactivity with münchnones.

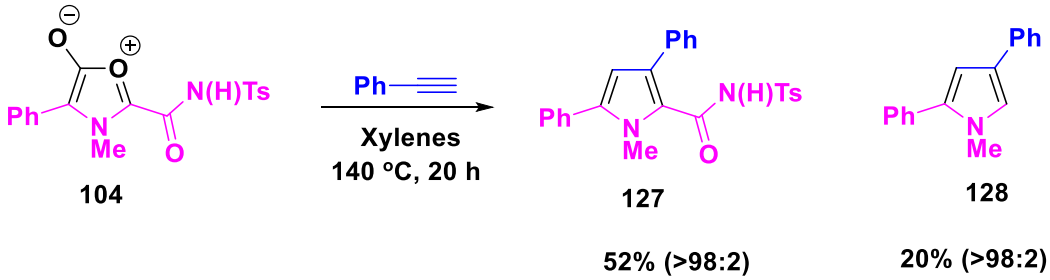
To quantify the lower reactivity of alkyl-substituted alkynes relative to aryl-substituted alkynes in our reactions, a series of competition reactions were conducted. For münchnones **100-103**, using an excess of a stoichiometric mixture of 1-octyne and phenylacetylene in cycloaddition resulted in a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



Scheme IV.8: Competition reaction of phenylacetylene and 1-octyne with münchnones.

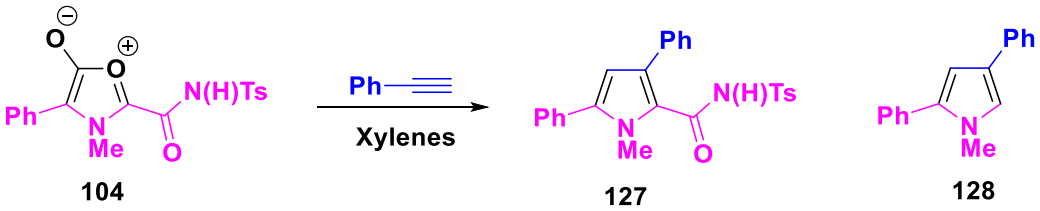
As preliminary investigations looked promising, the efficiency of the cycloaddition reaction of C4-imide substituted münchnones **104** and **103** was then explored.

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).

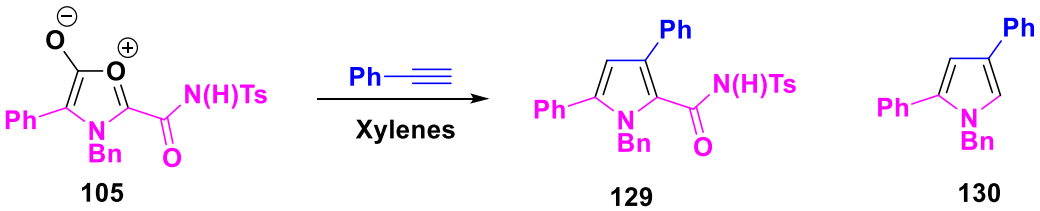


104 127 128

Entry	Temp.	Time	eq.	Yield%	
				127	128
1	140	20 h	4 eq	52%	20%
2	140	28 h	4 eq	43%	36%
3	140	24 h	6 eq	50%	32%
4	140	18 h	6 eq	60%	25%
5	100	24 h	6 eq	40%	33%
6	110	6 h	6 eq	64%	14%
7	110	5 h	2eq	70%	11%

Table IV.7: Optimisation reaction to minimise loss of the imide group during the cycloadditon 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).

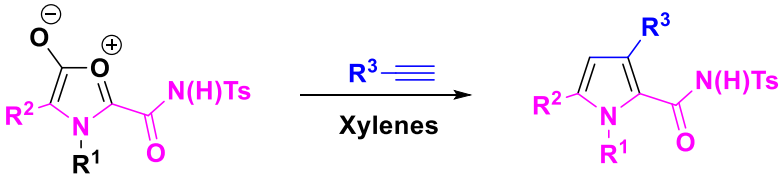


105 129 130

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).



104; R^1= Me, R^2= Ph
105; R^1= Bn, R^2= Ph

Entry	R^1	R^2	R^3	Product	Yield%
1	Me	Ph	^{n}Hex	131	23%
2	Me	Ph	^{n}Bu	132	20%
3	Me	Ph	cyclopropyl	133	67%
4	Bn	Ph	cyclopropyl	134	45%

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.

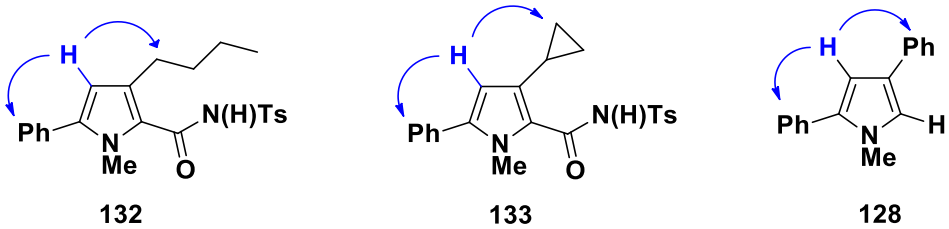
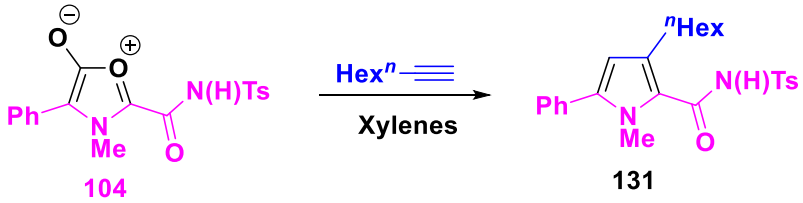


Figure IV.5: Characterization of pyrrole regiochemistry by NOE.

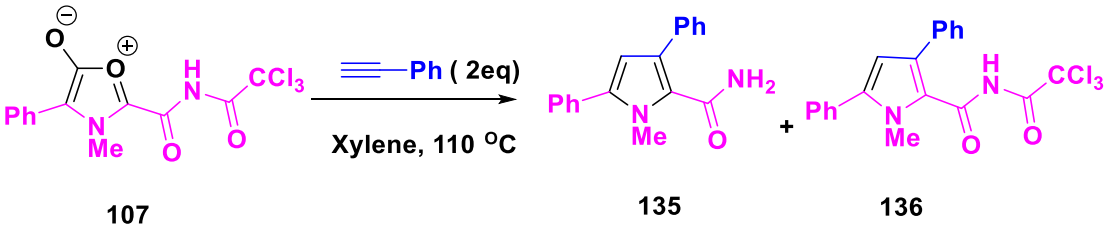
In order to increase product yield of alkyl-substituted alkynes, reaction optimization was carried out by varying reaction time, temperature and the number equivalents of alkyne. Unfortunately, when the cycloaddition reaction between münchnone **104** and 1-octyne was conducted under different conditions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



Entry	eq.	Temp.	Time	Yield%
1	6	140	16 h	19%
2	4	110	16 h	14%
3	2	110	3 h	4%
4	2	110	6 h	7%
5	4	110	20 h	23%

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).

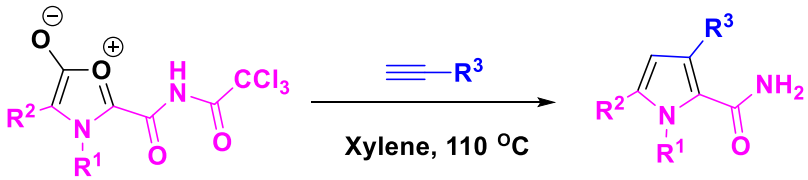


107 135 136

Entry	Time	Yield (135)	Yield (136)
1	2 h	34%	44%
2	6 h	52%	32%
3	21 h	83%	7%

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

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).



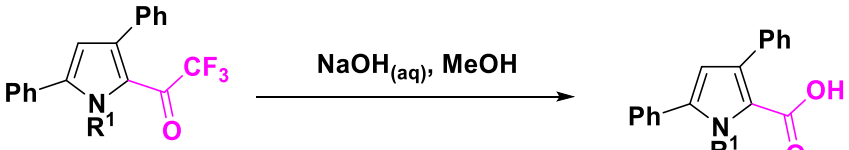
Entry	R^1	R^2	R^3	product	Yield%
1	Bn	Ph	Ph	137	71%
2	Bn	Ph	Cyclopropyl	138	63%
3	Me	Ph	Cyclopropyl	139	83%

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

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).

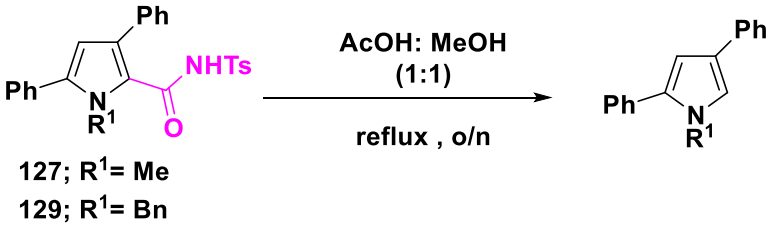


118; R^1= Me
120; R^1= Bn

Entry	R^1	Time	Products	Yield
1	Bn	3h, rt	140	18%
2	Bn	16 h, reflux	140	70%
3	Me	16 h, reflux	141	58%

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).



127; R^1= Me
129; R^1= Bn

Entry	R_1	Product	Yield%
1	Me	**128**	60%
2	Bn	**130**	71%

Table IV.12: functionalization of acylsulfonamide substituted pyrrole. Ts=4-toluensulfonyl.

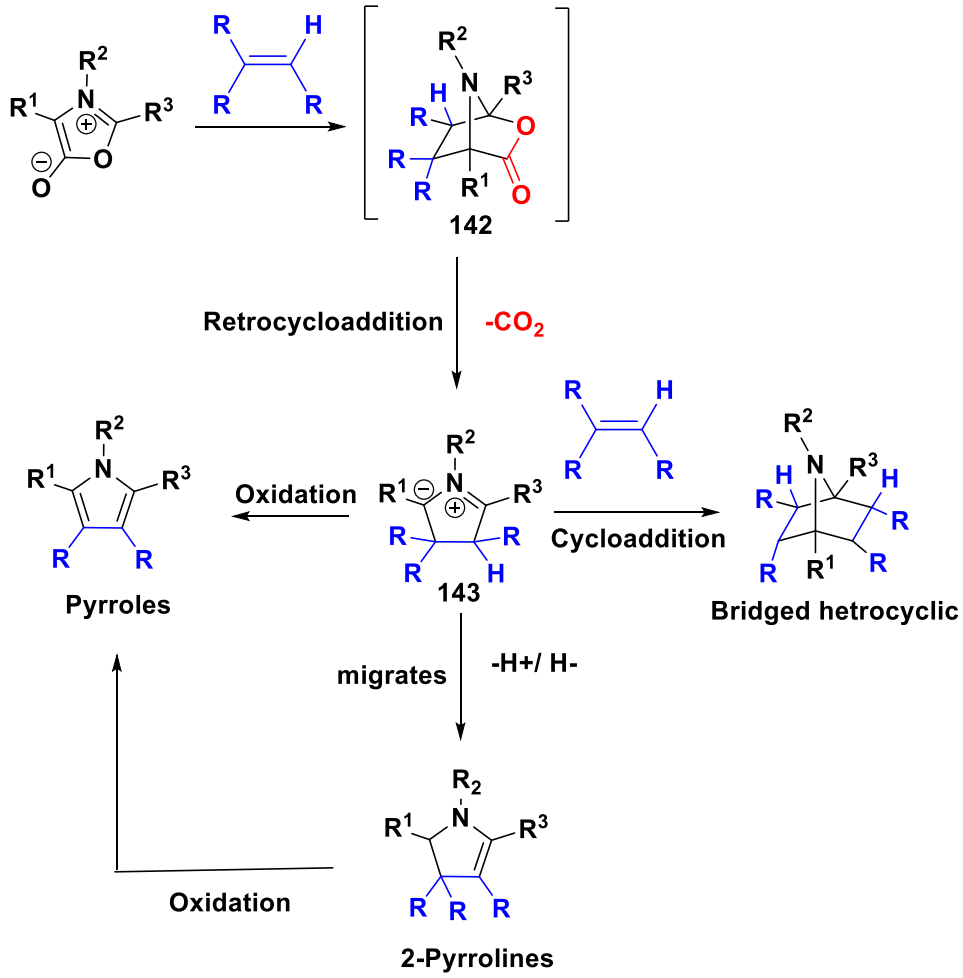
4. Conclusion

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

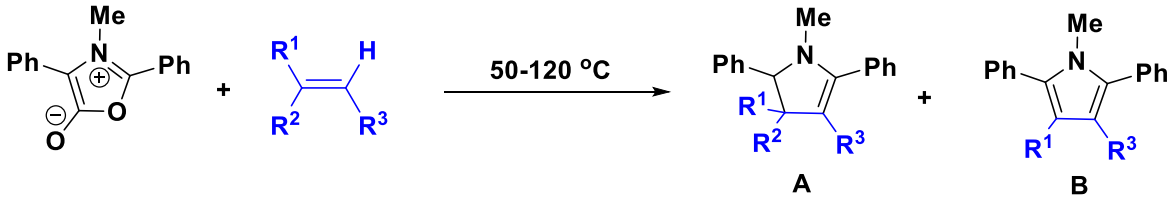
1. Introduction

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]



Scheme V.1: General münchnone cycloaddition with alkenes.

Huisgen et al. in 1964,[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).

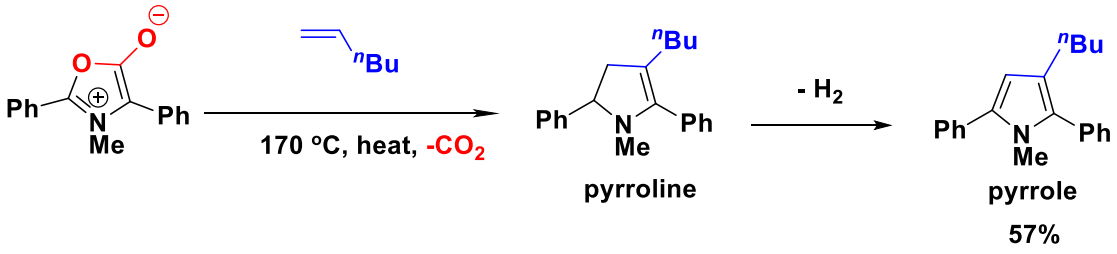


Entry	R^1	R^2	R^3	Yield% A	Yield% B
1	H	H	^{n}Bu	_	57
2	H	CO_2Me	CO_2Me	31	_
3	Me	CO_2Me	H	74[a]	_
4	CO_2Me	H	CO_2Me	43	_

[a] 40:60 *cis-trans* (relative to phenyl and ester group) mixture.

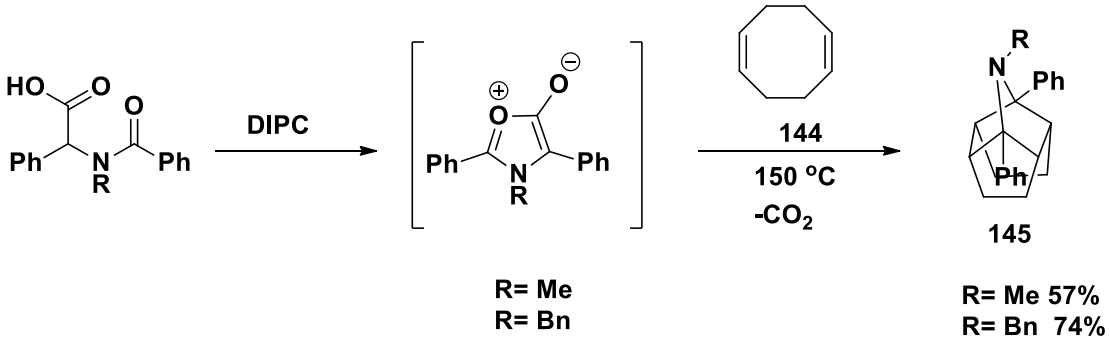
Table V.1: Münchnone-alkene cycloadditions

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).[67]



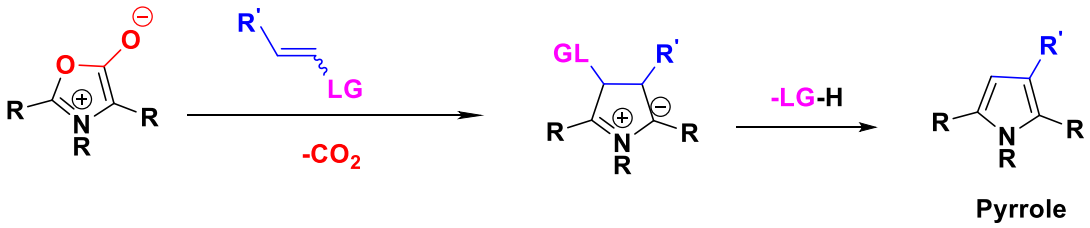
Scheme V.2: Pyrrole formation from alkene-münchnone cycloaddition followed by oxidation.

Furthermore, Gribble et al.[106] 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).



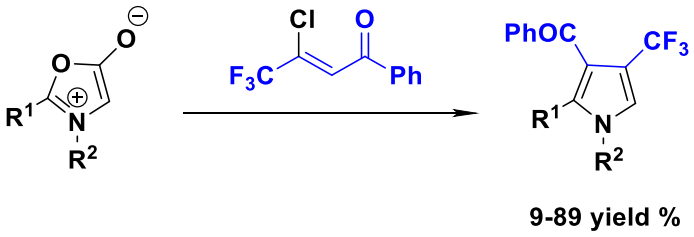
Scheme V.3: Tandem 1,3-dipolar cycloaddition reaction.

Indeed, during investigations into münchnone-alkene cycloadditions it was found that olefins substituted by electron-withdrawing leaving groups such as OAc, NO_2, CN, and Cl, $PPh_3^+Br^-$ offered the opportunity to carry out in situ oxidation level adjustment to generate pyrroles directly (Scheme V.4).[107-115]



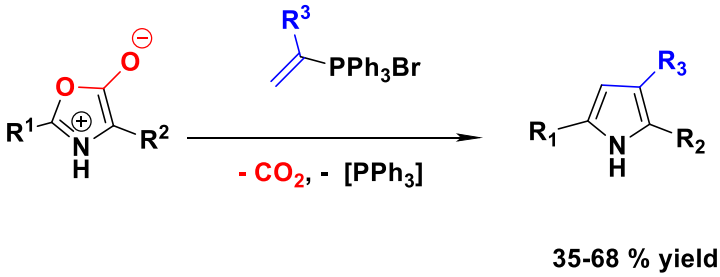
Scheme V.4: Cycloaddition between münchnones and alkenes bearing a leaving group.

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]



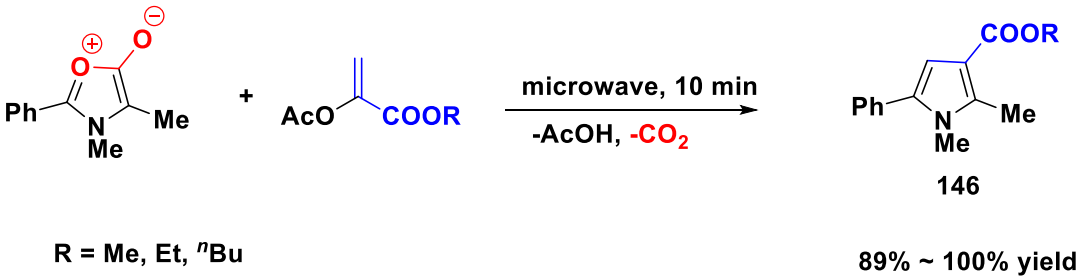
Scheme V.5: Pyrrole formation from münchnones with alkenylchlorides.

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]



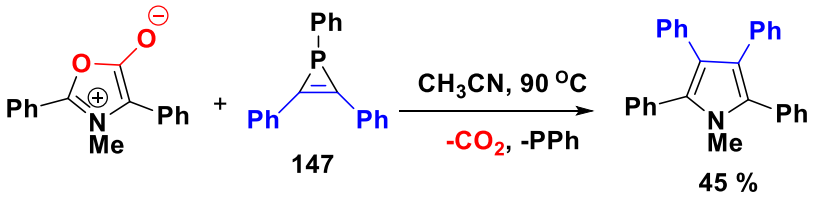
Scheme V.6: Pyrrole formation from vinyl triphenylphosphonium bromides.

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).



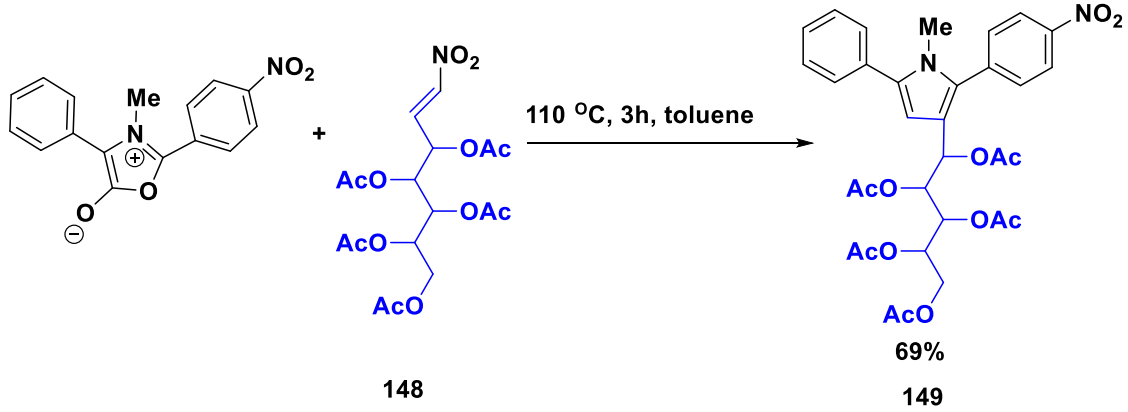
Scheme V.7: Pyrrole formation from münchnone cycloadditions.

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.

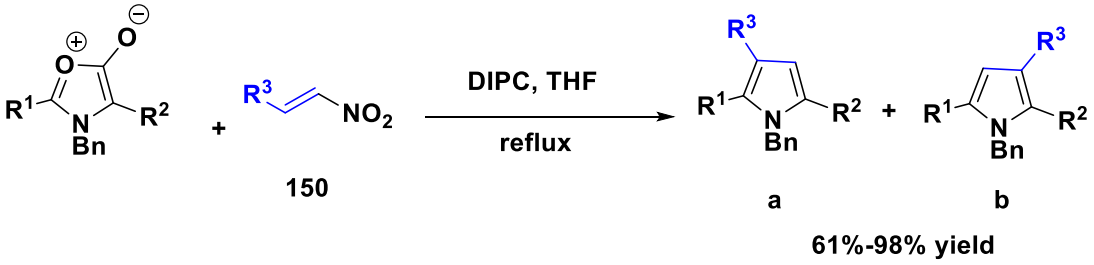
Work by Jimenez et al.[119] showed that the 1,3-dipolar cycloaddition of münchnones with nitroalkenes **148** proceeds with high regiocontrol, but with opposite selectivity to that predicted by FMO theory. The 1,3-dipolar cycloaddition delivers a single pyrrole product **149** after elimination of HNO_2 (Scheme V.9).



148 149

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.[120] showed that nitrovinyl pyridines or a quinoline **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 **150**, the reaction could proceed with high regioselectivity a:b (up to 99:1, Scheme V.10).



150 a b

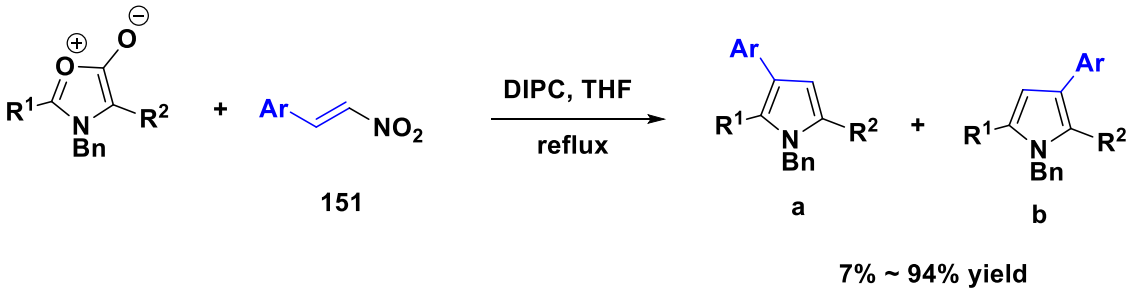
61%-98% yield

R^1, R^2 = Me, Ph; R^3 = 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl;

DIPC = (^{i}PrN=C= N^{i}Pr)

Scheme V.10: Pyrrole derivatives from the reaction of münchnones and nitroalkenes.

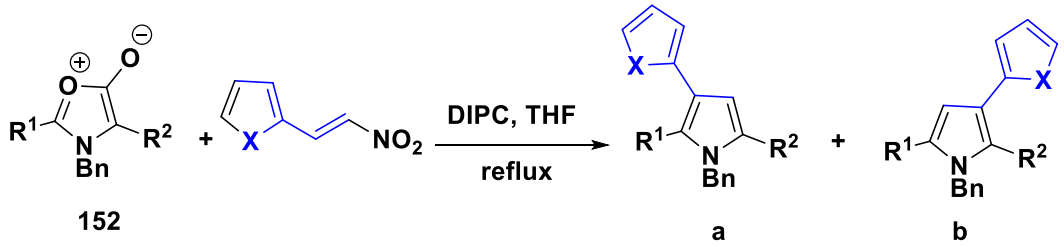
Futhermore, In 2013, Gribble et al.[120] investigated the regioselectivity of 1,3-dipolar cycloadditions between münchnone and nitroalkenes **151**, which provided a convenient synthesis of substituted pyrroles (Scheme V.11).



R^1 = Ph, R^2 = Me, a:b = 62:38 ~ 95:5
R^1 = Me, R^2 = Ph, a:b = 43:57 ~ 89:11
Ar = Ph, 4-ClC_6H_4, 3-FC_6H_4,4-$Me_2NC_6H_4$, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, P-Tol, 4-$F_3CC_6H_4$, 4-PhC_6H_4, etc.

Scheme V.11: Münchnone cycloadditions with nitroalkenes.

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 **152** with nitrovinyl heterocycles (Scheme V.12).[122]



R^1 = Ph, R^2 = Me, a:b = 77:23 ~ 88:12
R^1 = Me, R^2 = Ph, a:b = 14:86 ~ 82:18
X = O, S, NMe, NSO_2Ph

Scheme V.12: Synthesis of heteroaryl-substituted pyrroles.

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.[123] The general method for the synthesis of enamines which is commonly used today was described by Mannich and Davidsen.[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).

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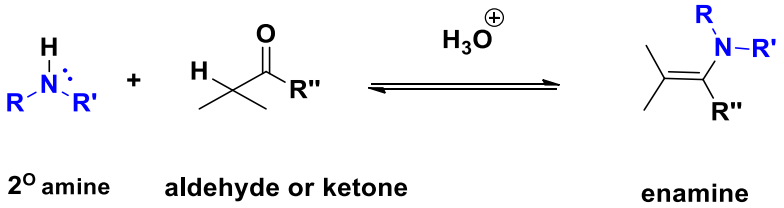
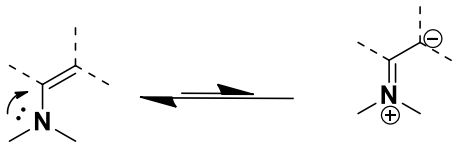


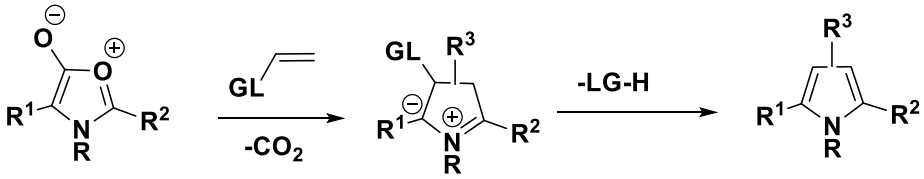
Scheme V.13: Enamine synthesis.

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).[125]



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).

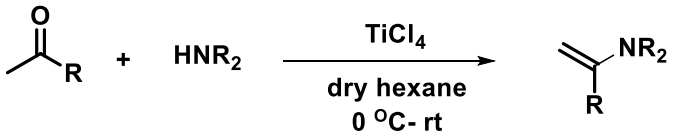


Scheme V.15: Cycloaddition of alkyne equivalents.

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.[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.[129]



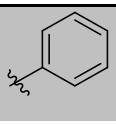
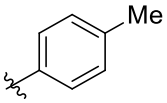
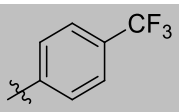
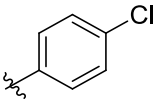
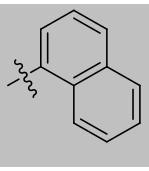
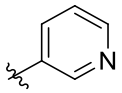
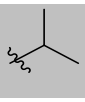
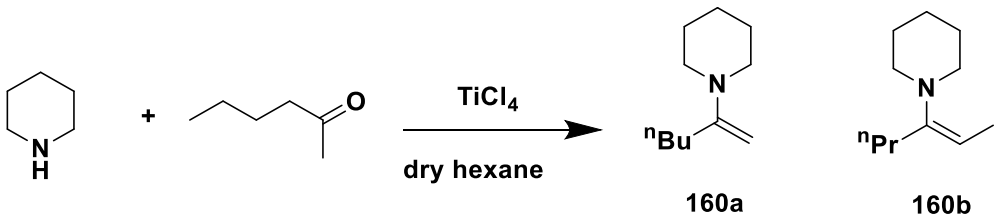
Entry	Compound	NR_2	R	Yield
1	153	piperidine		67%
2	154	piperidine		79%
3	155	piperidine		79%
4	156	piperidine		75%
5	157	piperidine		79%
6	158	diethylamine		25%
7	159	piperidine		71%

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).

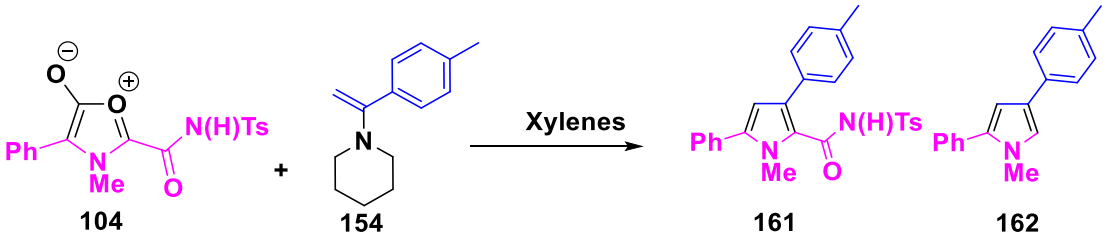


160a 160b

Scheme V.16: Synthesis of enamine from 2-hexanone.

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).[129]

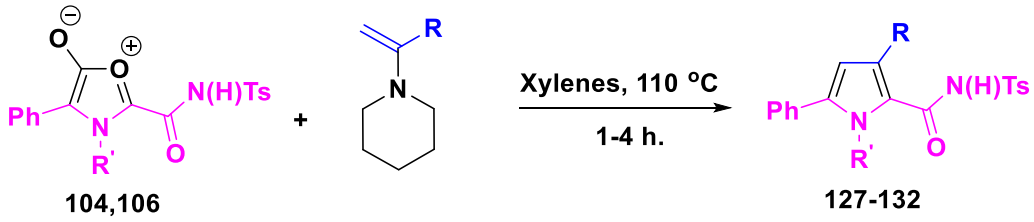


Entry	Temp.	Time	Eq.	Yield%	
				161	162
1	140	16 h	4 eq	54%	36%
2	180	24 h	4 eq	43%	32%
3	100	24 h	4 eq	50%	34%
4	80	24 h	4 eq	60%	22%
5	110	6 h	2 eq	72%	14%
6	110	40 min.	2eq	92%	trace

Table V.3: Optimisation reaction to minimise loss of the imide group during the cycloadditon 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 **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 **127, 163** and **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 **165**, **166**, **167** in excellent to moderate yield and always maintaining excellent levels of regioselectivity (Table V.4, entry 4-6).



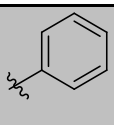
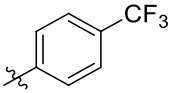
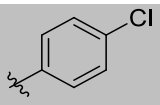
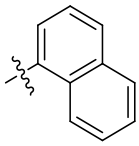
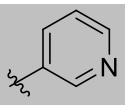
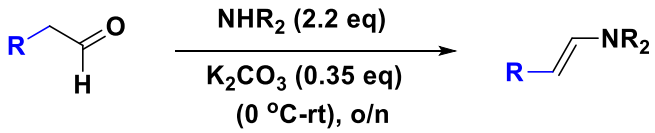
Entry	R'	R	Product	Yield%
1	Me		127	72%
2	Me		163	80%
3	Bn		164	72%
4	Me		165	84%
5	Me		166	71%
6	Me		167	61%
7[a]	Me		132	58%

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

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 münchnone 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-münchnone cycloadditions where alkyl-substituted alkynes provide the corresponding pyrroles in low yield.

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.



HNR_2 = (piperidine or diethylamine)

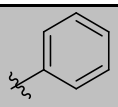
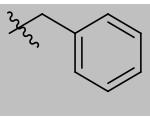
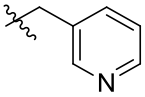
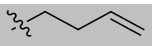
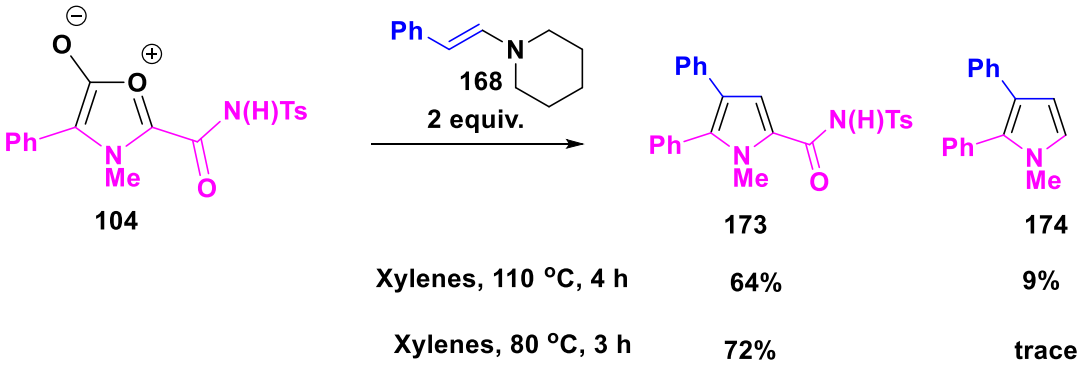
Entry	R	compound	Yield%
1		168	74%
2		169	60%
3		170	78%
4		171	84%
5		172	64%

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

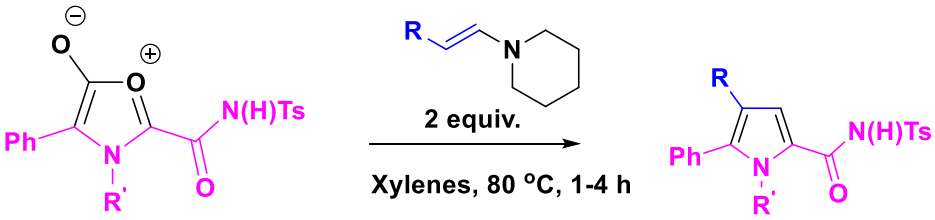
Methyl-substituted münchnone **104** and enamine **168** were chosen to investigate the cycloaddition step. It was observed that with the optimal set of conditions consisted of using one equivalent of münchnone, two equivalents of enamine in xylenes at 110 °C, providing pyrrole product **173** in 64% yield and pyrrole **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.



104

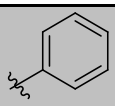
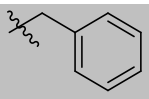
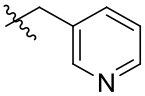
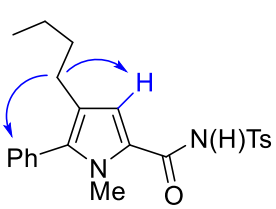
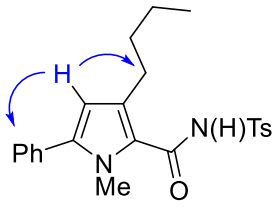
Entry	R'	R	compound	Yield%
1	Me		173	72%
2	Me		175	67%
3	Bn		176	68%
4	Me		177	70%

Table V.6: Scope of the cycloaddition reaction between münchnones and 2-substituted enamines.

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



175



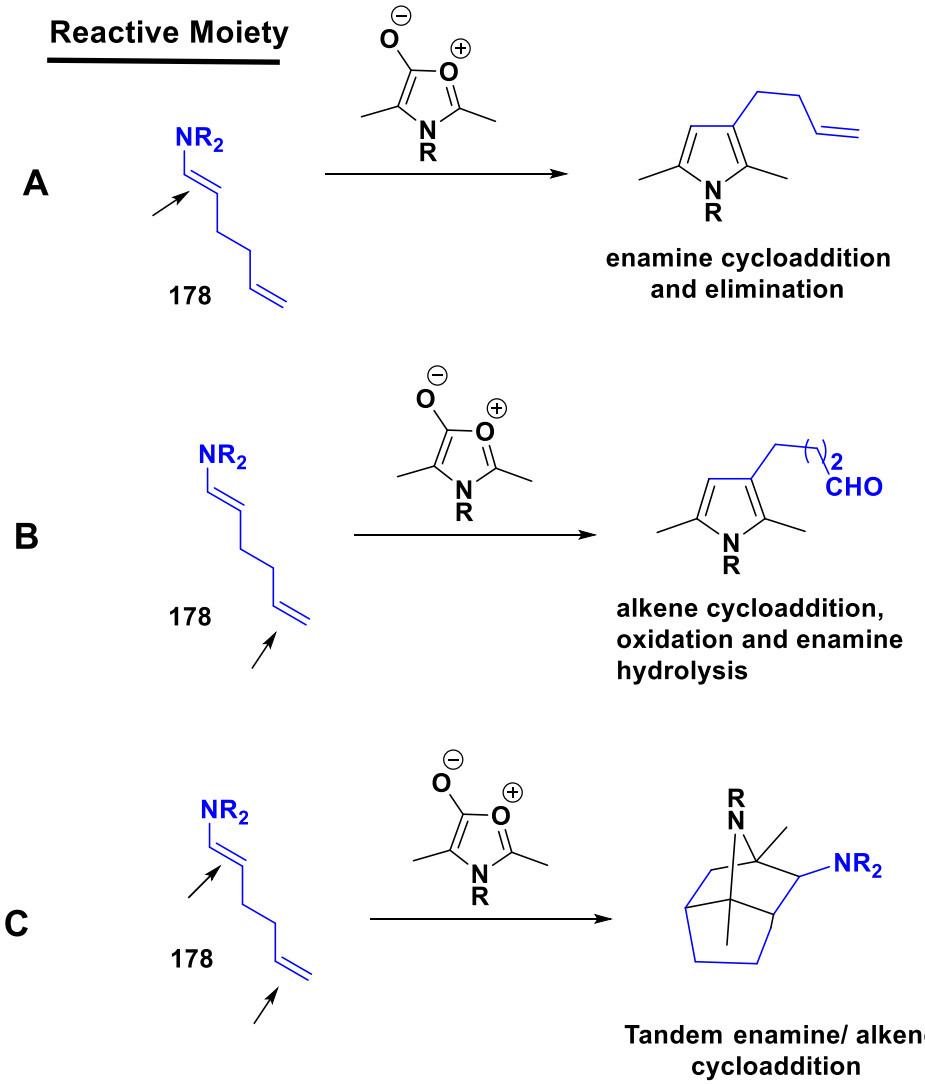
132

Figure V.1: Characterization of pyrrole regiochemistry by NOE spectrocopy.

From these experiments, it is clear the factors that govern the regioselectivity of pyrrole formation by the cycloaddition between münchnones and enamines 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.

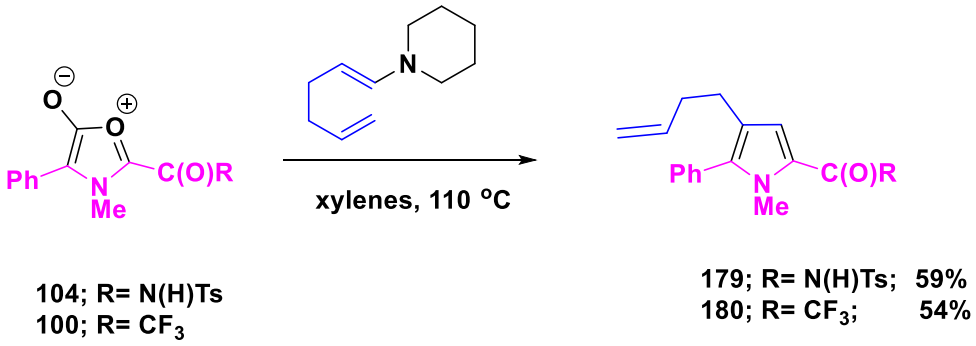
5. Reactivity of münchnones toward enamines and alkenes

Following the observation that enamines were highly reactive in cycloadditions with münchnones and as the literature shows that münchnones can also react with alkene dipolarophiles, it was decided to prepare 1-aminohexa-1,5-dienes **178**, to explore the relative reactivity of münchnones with enamines 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 alkene. It should be noted that a cage structure might also form from the cycloaddition with the alkene followed by reaction with enamine after loss of carbon dioxide, as shown in pathway C.



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

In order to test the generality of this qualitative rate difference, initial cycloadditions between münchnones **104** and **100** with 1-aminohexa-1,5-diene were attempted. Performing the reaction at 110 °C in xylenes provided pyrroles **179** and **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.



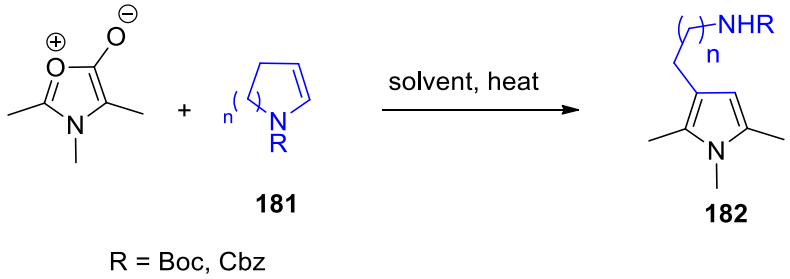
104; R= N(H)Ts
100; R= CF_3

179; R= N(H)Ts; 59%
180; R= CF_3; 54%

Scheme V.19: Relative reactivity of alkenes versus enamines.

6. Münchnone-cycloalkene cycloaddition reactions.

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).



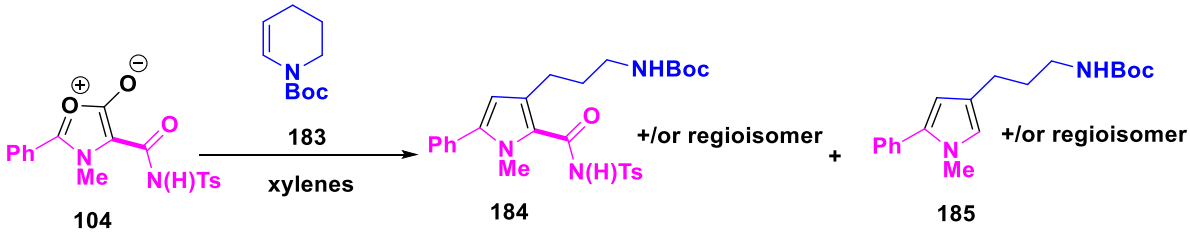
181

182

R = Boc, Cbz

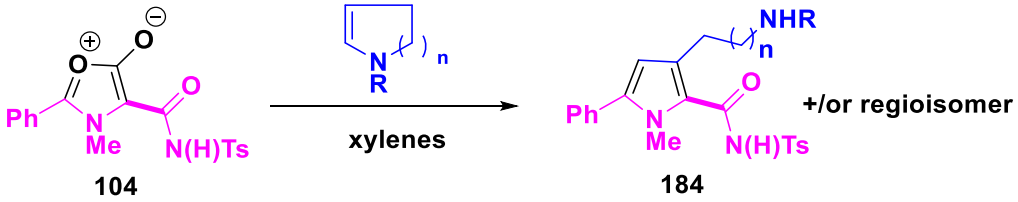
Scheme V.20: Proposed cycloaddition reaction between a münchnone and cyclic enamine.

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).

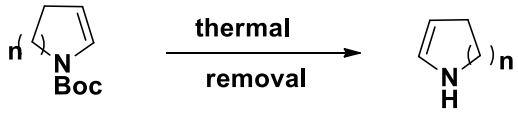


R = Boc, Cbz

Entry	R	*n*	t/ hours	T/ °C	Yield %
1	Boc	2	2	110	5
2	Boc	2	4	150	4
3	Boc	2	8	80	3
4	Boc	1	16	110	trace
5	Boc	1	4	160	trace
6	Cbz	2	20	110	Complex mixture
7	Cbz	1	16	110	Complex mixture

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

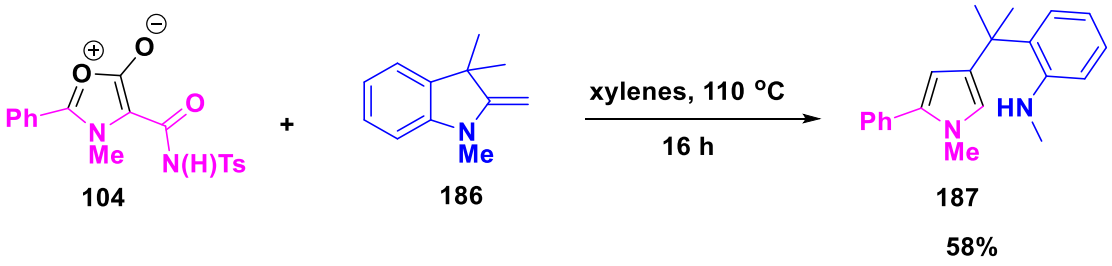
The low product yield might be caused by thermal *N*-Boc deprotection to give the amine (Scheme V.22) which could in this case undergo side reactions rather than the cycloaddition process.



Scheme V.22: Thermal boc-deprotection of an enamide.

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 pyrroles. 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).



Scheme V.23: Münchnone-dipolarophile cycloadditon/ring opening reactions.

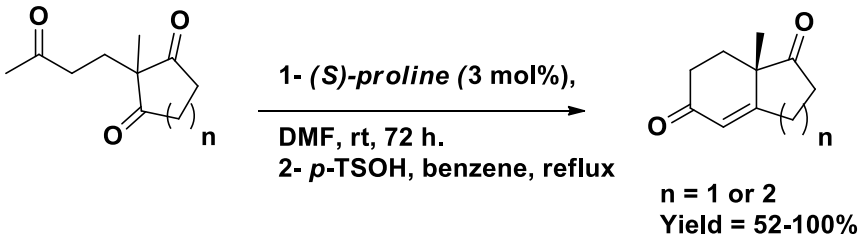
7. Conclusion

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

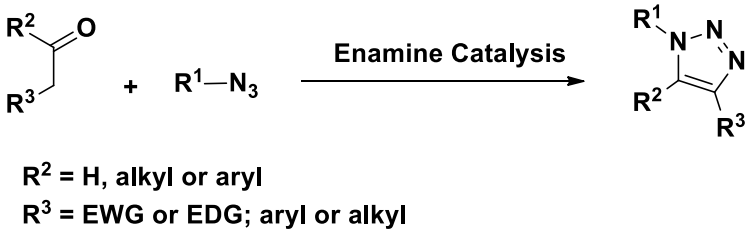
As discussed in Chapter V, the use of enamines in cycloaddition reactions with münchnones to form pyrroles with complete regiocontrol shows clear advantages when compared to the traditional alkene-münchnone cycloaddition process. Furthermore, it was deemed desirable to extend this cycloaddition strategy 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).

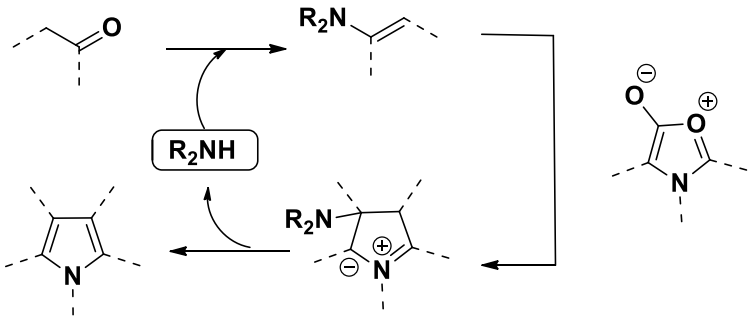
Although this reaction was discovered over 40 years ago,[134] its potential has not been fully realized until more recently. Since new catalytic reactions are constantly being discovered and the mechanistic process is becoming clearer, enamine organocatalysis has developed into a powerful strategy for 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).[138-140] However, to the best of our knowledge, an enamine-catalyzed (3+2) Huisgen cycloaddition strategy with münchnones has not been explored to date.



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 münchnones 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.

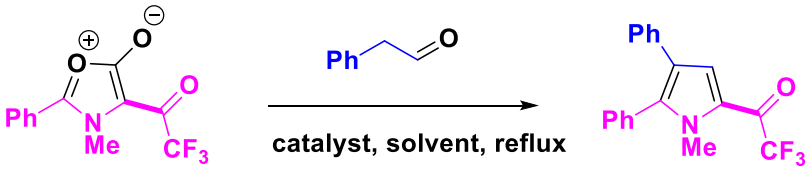


Scheme VI.3: Role of the amine in the overall enamine-münchnone cycloaddition.

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.

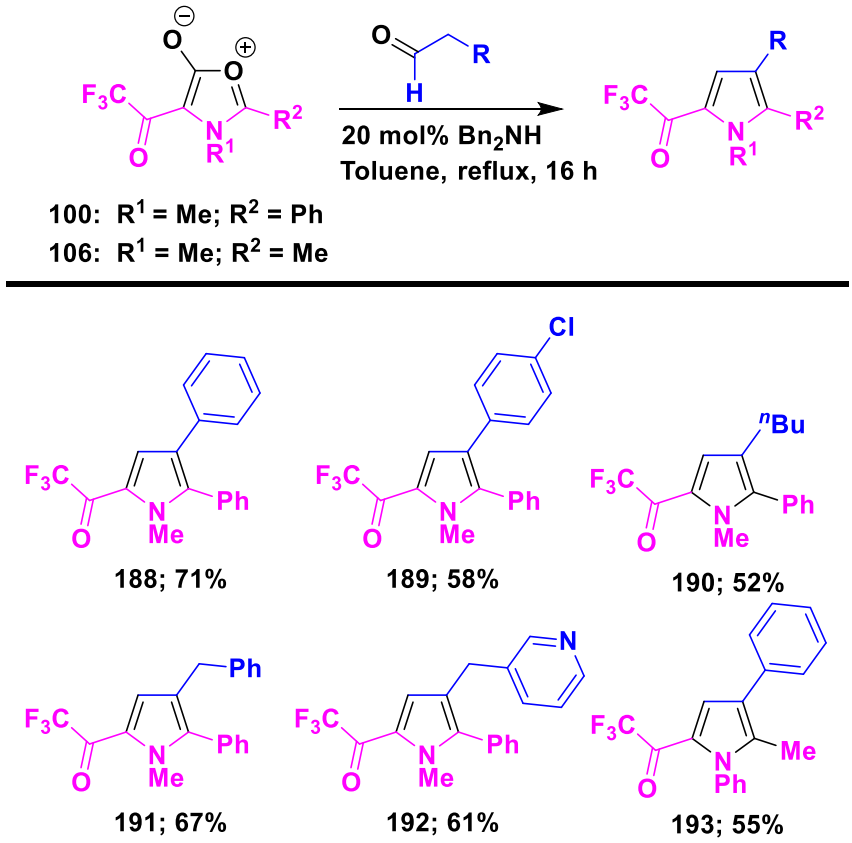


Entry	Catalyst (mol)%	Solvent	Yield (%)
1	NEt_2 (10)	xylenes	25
2	piperidine (10)	xylenes	30
3	pyrrolidine (10)	xylenes	26
4	$(PhCH_2)_2NH$ (10)	xylenes	34
5	$(^iPr)_2NH$ (10)	xylenes	28
6	piperidine (10)	Toluene	34
7	piperidine (5)	Toluene	20
8	Bn_2NH (5)	Toluene	18
9[a]	Piperidine (20)	Toluene	68
10[a]	pyrrolidine (20)	Toluene	54
11[a]	$(^iPr)_2NH$ (20)	Toluene	58
12[a]	Bn_2NH (20)	Toluene	71

a:using Dean-Stark conditions

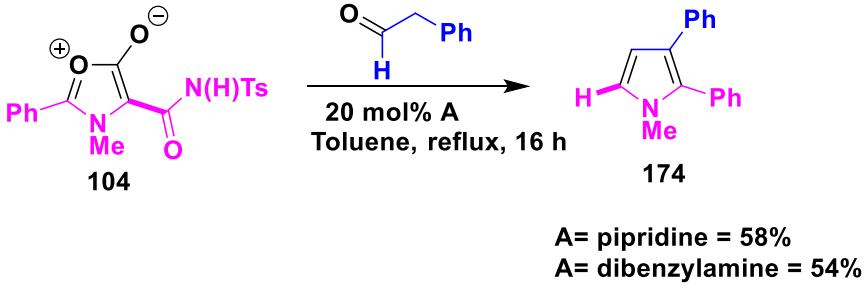
Table VI.1: Optimization of reaction conditions.

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.



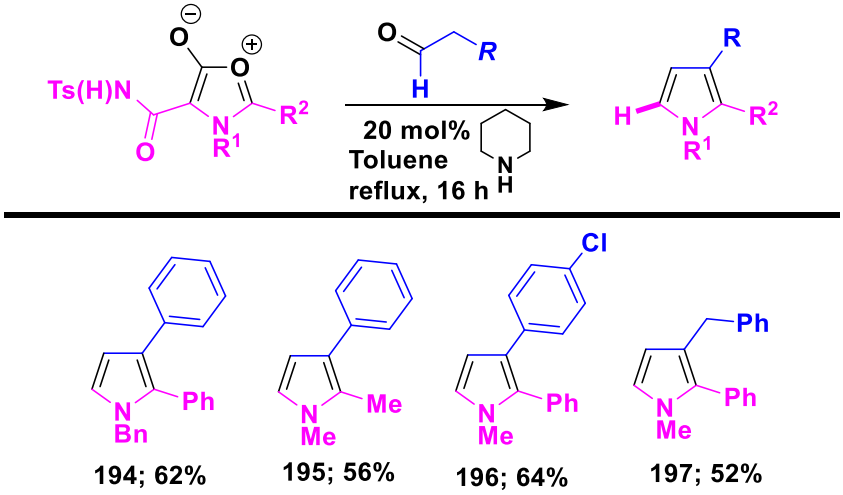
Scheme VI.4: Scope of amine-catalyzed cycloaddition between aldehydes and münchnone.

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.



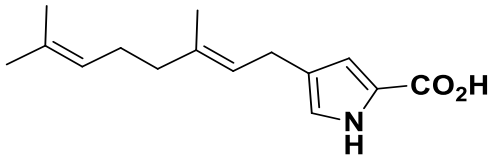
Scheme VI.5: Optimization of the reaction conditions using an *N*-tosylamide substituted münchnone.

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 münchnone 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 aldehydephenyl 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 assighned by NOE, pyrroles **174** and **194** were assigned by comparison with literature data.[141,142.] The regiochemistry of remaining pyrroles were tentatively assigned by analogy.



Scheme VI.6: Amine-catalyzed synthesis of 1,2,3-substituted pyrroles

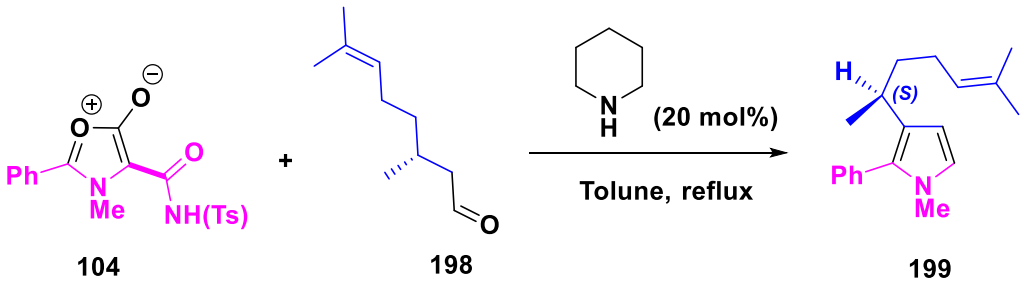
From a synthetic point of view, the preparation of α-unsubstituted pyrroles such as pyrrolostatin and its analogues remains a challenge. Pyrrolostatin, an in vitro inhibitor activity against lipid peroxidation, consists of 2-carboxylic acid substituted pyrrole with a geranyl chain group attached at the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



Pyrrolostatin

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.



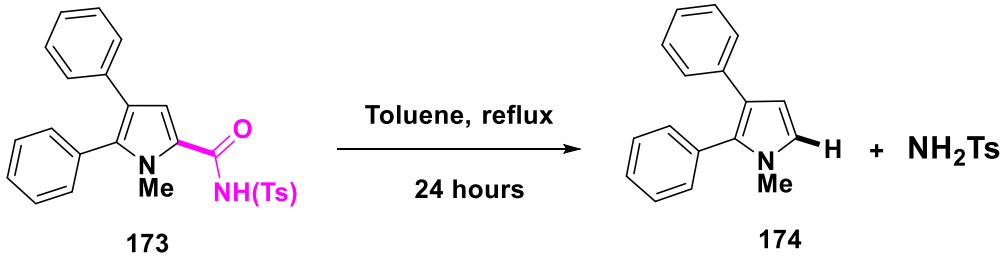
104 **198** **199**

71%, 96% ee

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.



173 174

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.

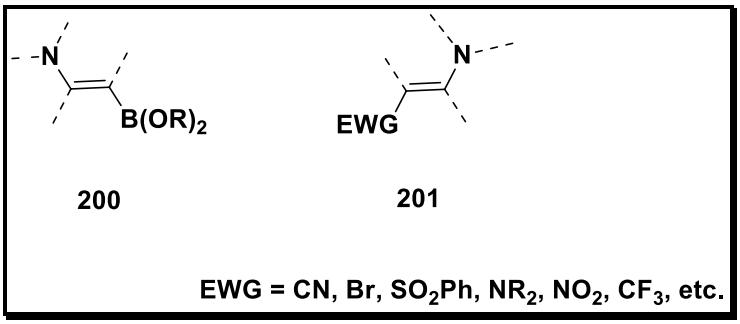


Figure VII.2: Future directions for reactive dipolarophile/münchnone cycloadditions.

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 tetramethylsilance (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_2Cl_2 solutions of the samples ν_{max} in cm^{-1}. 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 analysies, operating in Electrospray mode (TOF ES^+), or MicroMass prospec operating in FAB (FBA^+), El (El^+) or Cl (Cl^+) modes.

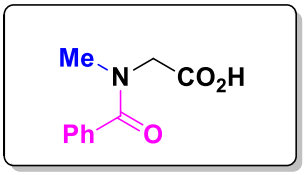
All solvents and reagents were purified using standared laboratory techniques according to methods published in Purification of Laboratory Chemicals, by Perrin and Amarego.[146]

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 cm^2 g^{-1} with concentration (c) quoted in g 100 Ml^{-1}.

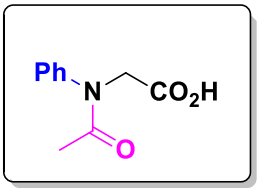
2. Synthesis of Starting Materials

Synthesis of N-benzoyl–N-methylglycine (96).[147]



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); **^{1}H NMR (DMSO, 400 MHz):** δ 12.83 (s, br, 2H), 7.47-7.9 (m, 10H, ArH), *4.14 (s, 2H, CH_2)*, 3.93 (s, 2H, CH_2), *2.98 (s, 3H, CH_3)*, 2.94 (s, 3H, CH_3); **^{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.

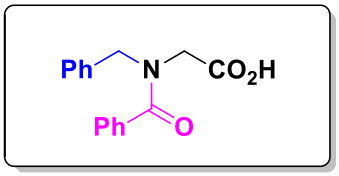
Synthesis of N-Acetyl-N-phenylglycine (97).[147]



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

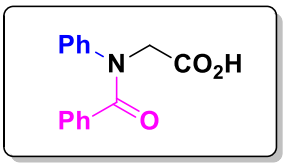
ethyl acetate and the combined organic extracts were dried over magnesium sulfate. Removal of solvent in vacuo gave the title compound as a yellow solid (982 mg, 80%). **Melting point:** 190-191 °C (lit. 193-195 °C); **^{1}H NMR (DMSO, 400 MHz):** δ 12.71 (s, br, 1H), 7.46-7.34 (m, 5H, ArH), 4.25 (s, 2H, CH_2), 1.81 (s, 3H, CH_3); **^{13}C NMR (DMSO, 101 MHz):** δ 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 hydrochlorid (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}H NMR ($DMSO_3$, 400 MHz)**: δ 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}C NMR (DMSO, 101 MHz):** δ 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.

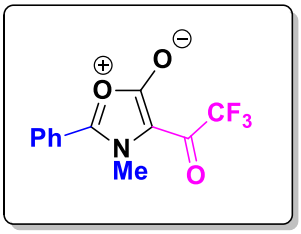
Synthesis of N-benzoyl-N-phenylglycine (99).[147]



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):** δ 12.83 (s, br, 1H), 7.29-7.15 (m, 10H, ArH), 4.49 (s, 2H, CH_2); **^{13}C NMR (DMSO, 101 MHz):** δ 170.9, 170.0, 144.1, 136.0, 130.2, 129.4, 128.8, 128.3, 127.8, 127.0, 52.3.

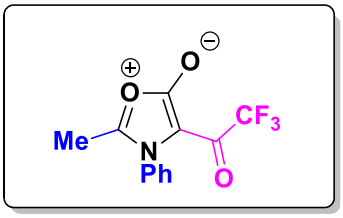
3. Synthesis of münchnones

Synthesis of 4-trifluoroacetyl-3-methyl-2-phenyl-1,3-oxazolium-5-olate (100).[148]



N-Benzoyl–*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%). **Melting point:** 160-162 ˚C (lit. 162-163 °C); **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.76-7.70 (m, 3H, ArH), 7.67-7.61 (m, 2H, ArH), 4.13 (s, 3H, NCH_3); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 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_3), 97.3, 37.6; **^{19}F NMR ($CDCl_3$, 376.5 MHz):** δ -75.3.

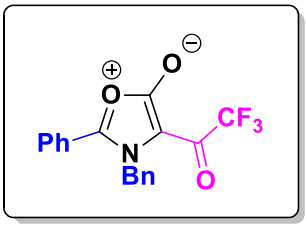
Synthesis of 4-Trifluoroacetyl-2-methyl-3-phenyl-1,3-oxazolium-5-olate (101).[148]



N-Acetyl-*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%). **Melting point:** 209-210 ˚C (lit. 211-212 °C); **^{1}H NMR ($CDCl_3$, 400**

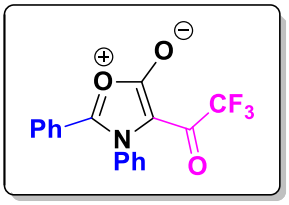
MHz): δ 7.62-7.55 (m, 3H, ArH), 7.34-7.30 (m, 2H, ArH), 2.38 (s, 3H, CH_3); **^{19}F NMR ($CDCl_3$, 376.5 MHz):** δ -75.4.

Synthesis of 4-Trifluoroacetyl-2-phenyl-3-benzyl-1,3-oxazolium-5-olate (102).[148]



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}H NMR ($CDCl_3$, 400 MHz):** δ 7.67-7.66 (m,3H, ArH), 7.59-7.54 (m, 2H, ArH), 7.43-7.36 (m, 3H, ArH), 7.17-7.13 (m, 2H, ArH), 5.79 (s, 2H, CH_2); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 167.1 (q, *J* = 38.0 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 (q, *J* = 289.0 Hz, CF_3), 96.0, 52.2; **^{19}F NMR ($CDCl_3$, 376.5 MHz):** δ -75.2.

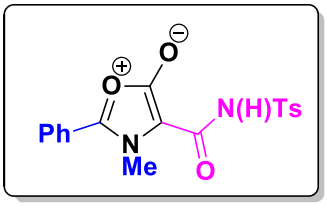
Synthesis of 4-Trifluoroacetyl-2,3-diphenyl-1,3-oxazolium-5-olate(103).[148]



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}H NMR ($CDCl_3$, 400 MHz):** δ

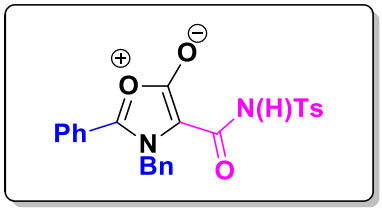
7.67-7.52 (m, 4H, ArH), 7.43-7.40 (m, 2H, ArH), 7.37-7.34 (m, 4H, ArH);**^{13}C NMR ($CDCl_3$, 101 MHz):** δ 166.4 (q, *J* = 38.0 Hz, C=O), 157.7, 152.2, 134.4, 134.2, 131.3, 130.3, 129.5, 129.4, 126.4, 120.7, 116.6 (q, *J* = 289.0 Hz, CF_3), 98.3; **^{19}F NMR ($CDCl_3$, 376.5 MHz):** δ - 75.4.

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_2O (5 mL) and the resulting solution was heated at reflux for 2 h. The mixture was added to Et_2O (10 mL) at 0 °C, and the precipitate was filtered and washed with cold Et_2O 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):** δ 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):** δ 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:** ν_{max}: 1703 (s), 1676 (s) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{18}H_{16}N_2O_5S$ requires 373.0853, found 373.0851.

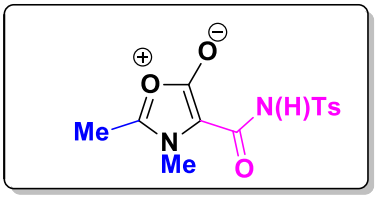
Synthesis of 3-benzyl-2-phenyl-4-(tosylcarbamoyl)-1,3-oxazolium-5-olate (105).



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_2O (5 mL) and the resulting solution was heated at reflux for 2 h. The mixture was added to Et_2O (10 mL) at 0

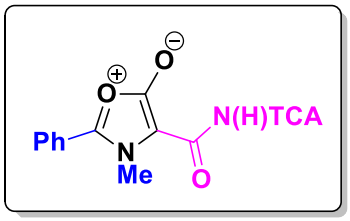
°C, and the precipitate was filtered and washed with cold Et_2O to produce the desired product (417 mg, 100%) as a pale yellow powder. **Melting point:** 136-140 °C; **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 9.89 (s, 1H, NH), 7.93 (d, *J* = 8.0 Hz, 2H, ArH), 7.64-7.48 (m, 6H, ArH), 7.31-7.28 (m, 4H, ArH), 7.06-7.00 (m, 2H, ArH), 5.75 (s, 2H, NCH_2), 2.41 (s, 3H, CH_3); **^{13}C NMR ($CDCl_3$, 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:** ν_{max}: 1708 (s), 1668 (s) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{24}H_{20}N_2O_5S$ requires 449.1166, found 449.1164.

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



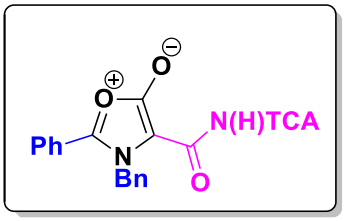
Tosyl isocyanate (0.64 mL, 4.20 mmol) was added dropwise to a solution of *N*-methyl sarcosine (250 mg, 1.90 mmol) in Et_2O (5 mL) and the resulting solution was heated at reflux for 2 h. The mixture was added to Et_2O (10 mL) at 0 °C, and the precipitate was filtered and washed with cold Et_2O to produce the desired product (470 mg, 80%) as a pale yellow powder. **Melting point:** 148-151 °C; **^{1}H NMR ($CDCl_3$, 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, CH_3), 2.53 (s, 3H, CH_3), 2.44 (s, 3H, CH_3); **^{13}C NMR ($CDCl_3$, 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:** ν_{max}: 1721 (s), 1666 (s), 1400 (m), 1307 (m), 1157 (m) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{13}H_{14}N_2O_5S$ 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 Et_2O (5 mL) and the resulting solution was heated at reflux for 3 h. The mixture was added to Et_2O (10 mL) at 0 °C and the precipitate was filtered and washed with cold Et_2O to give the title compound (274 mg, 58%) as a pale yellow powder. **Melting point:** 147-150 °C; **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 11.18 (s, 1H, NH), 7.77-7.61 (m, 5H, ArH), 4.23 (s, 3H, CH_3); **^{13}C NMR ($CDCl_3$, 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:** ν_{max}: 1759 (s), 1714 (s), 1673 (s) cm^{-1}; m/z (EI) 362 (10%, $[M(^{35}Cl_3)]^-$), 364 (20% $[M(^{37}Cl(^{35}Cl_2)]^-$); **HRMS:** calc. for $C_{13}H_9{}^{37}Cl^{35}Cl_2N_2O_4$ 364.9501, found 364.9486.

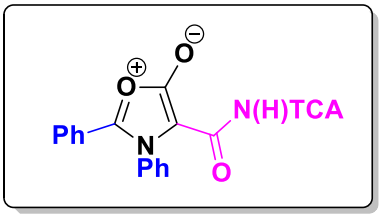
Synthesis of 3-benzyl-2-phenyl-4-(2,2,2-trichloroacetyl) carbamoyl-1,3-oxazolium-5-olate (108).



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 Et_2O (5 mL) and the resulting solution was heated at reflux for 2 hours. The mixture was added to Et_2O (10 mL) at 0 °C, and the precipitate was filtered and washed with cold Et_2O to produce the desired product (314 mg, 77%) as a pale yellow powder. **Melting point:** 110-114 °C; **^{1}H NMR ($CDCl_3$, 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, NCH_2); **^{13}C NMR ($CDCl_3$, 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:** ν_{max} : 1756 (s), 1718 (s), 1671 (s) cm^{-1}; m/z (EI) 439 (100%, $[M(^{35}Cl_3)]^+$); **HRMS:** calc. for $C_{19}H_{13}{}^{35}Cl_3N_2O_4$ requires 439.0014, found 439.0014.

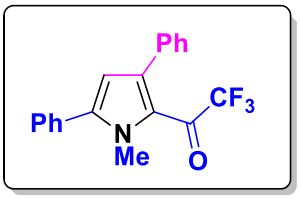
Synthesis of 2,3-Diphenyl-4-(2,2,2-trichloroacetyl) carbamoyl-1,3-oxazolium-5-olate (109).



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 Et_2O (3 mL) and the resulting solution was heated at reflux for 2 h. The mixture was added to Et_2O (10 mL) at 0 °C, and the precipitate was filtered and washed with cold Et_2O to produce the desired product (116 mg, 35%) as a pale yellow powder. **Melting point:** 133-136 °C; **^{1}H NMR ($CDCl_3$, 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); **^{13}C NMR ($CDCl_3$, 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:** ν_{max}: 1756 (s), 1740 (s), 1680 (s) cm^{-1}; m/z (EI) 425 (100%, $[M(^{35}Cl_3)]^+$), 427 (80% $[M(^{37}Cl(^{35}Cl_2)]^+$); 429 (20% $[M(^{35}Cl(^{37}Cl_2)]^+$); **HRMS:** calc. for $C_{18}H_{12}{}^{35}Cl_3N_2O_4$ requires 424.9863, found 424.9862.

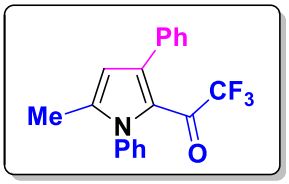
4. Synthesis of pyrrole

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 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 10% EtOAc in petroleum ether) to provide the title compound as a yellow solid (92 mg, 75%). **Melting point:** 90-93 °C; **^{1}H NMR ($CDCl_3$, 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, NCH_3); **^{13}C NMR ($CDCl_3$, 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, CF_3), 114.0, 36.0; **^{19}F NMR (CDCl3, 376.5 MHz):** δ -70.4; **FTIR:** ν_{max} 2923 (w), 1660 (s), 1628 (m), 1496 (m), 1465 (w), 1371 (w) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{19}H_{15}NOF_3$: 330.1106, found: 330.1099.

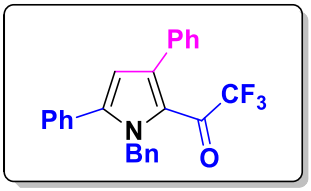
Synthesis of 5-trifluoroacetyl-1,4-diphenyl-2-methyl-1H-pyrrole (119).



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 xylenes (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; **^{1}H NMR ($CDCl_3$, 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,

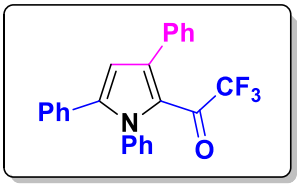
3H, CH_3); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 172.4 (q, *J* = 39.5 Hz, C=O), 141.1, 138.8, 138.3, 135.2, 129.4, 129.2, 128.6, 127.8 (x2C), 127.7, 127.3, 113.3, 116.0 (q, *J* = 289.5 Hz, CF_3), 13.0; **^{19}F NMR ($CDCl_3$, 376.5 MHz):** δ -71.1; **FTIR:** ν_{max}: 1650 (s), 1452 (m), 1378 (m), 1287 (w), 1183 (s), 1148 (s) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{19}H_{14}NOF_3$: 329.1022, found: 329.1026.

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



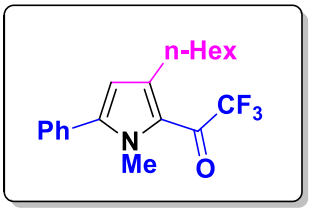
A solution of 3-benzyl-4-trifluoroacetyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.29 mmol) and ethynylbenzene (117 mg, 1.15 mmol) in xylenes (0.29 mL) in a sealed microwave vessel was heated at 140 °C for 24 hours. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to provide the title compound as a yellow oil (79 mg, 67%). **^{1}H NMR ($CDCl_3$, 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, NCH_2); **^{13}C NMR ($CDCl_3$, 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 ($CDCl_3$, 376.5 MHz):** δ -70.7; **FTIR:** ν_{max}: 1656 (s), 1603 (m), 1496 (m), 1484 (m), 1453 (s) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{25}H_{18}NOF_3$: 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):** δ 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); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 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; **^{19}F NMR ($CDCl_3$, 376.5 MHz):** δ -71.4; **FTIR:** ν_{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.

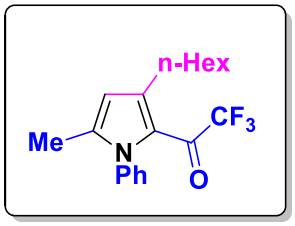
Synthesis of 5-trifluoroacetyl-1-methyl-2phenyl-4-n-hexyl-1H-pyrrole (122).



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):** δ 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),

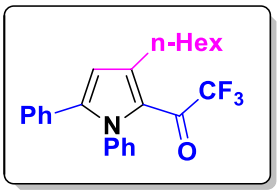
1.34-1.30 (m, 4H, CH_2), 0.9 (t, *J* = 7.0 Hz, 3H, CH_3); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 170.8 (q, *J* = 36.5 Hz), 146.2, 139.3, 131.0, 129.3, 129.0, 128.7, 120.0 (q, *J* = 289.0 Hz), 118.5, 112.8, 36.5, 31.7, 31.0, 29.3, 27.2 (q, *J* = 4.0 Hz), 22.6, 14.0; **^{19}F NMR ($CDCl_3$, 376.5 MHz):** δ -72.1; **FTIR:** ν_{max} : 1642 (s), 1542 (w), 1276 (s), 1195 (s), 1139 (s) cm^{-1}; **HRMS:** m/z [MH^+] cald. for $C_{19}H_{23}NOF_3$: 338.1732, found: 338.1721.

Synthesis of 5-trifluoroacetyl-1-phenyl-2methyl-4-n-hexyl-1H-pyrrole (123).



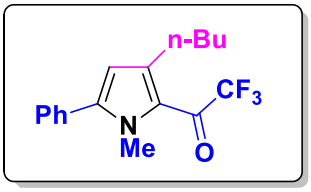
A solution of 3-phenyl-4-trifluoroacetyl-2-methyl-1,3-oxazolonium-5-olate (100 mg, 0.37 mmol) and 1-octyne (163 mg, 1.47 mmol) in xylenes (0.37 mL) in a sealed microwave vessel was heated at 140 °C for 16 hours. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 5% EtOAc in petroleum ether) to provide the title compound as a yellow oil (30 mg, 25 %). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.47-7.41 (m, 3H, ArH), 7.16-7.13 (m, 2H, ArH), 6.10 (s, 1H, pyrlH), 2.76-2.72(m, 2H, CH_2), 2.00 (s, 3H, CH_3), 1.68-1.62 (m, 2H, CH_2), 1.43-1.39 (m, 2H, CH_2), 1.35-1.31 (m, 4H, CH_2), 0.91 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 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}F NMR ($CDCl_3$, 376.5 MHz):** δ -72.3; **FTIR:** ν_{max}: 1651 (s), 1497 (s), 1196 (s), 1140 (s) cm^{-1}; **HRMS:** m/z [MH^+] cald. for $C_{19}H_{23}NOF_3$: 338.1732, found: 338.1731.

Synthesis of 5-trifluoroacetyl-1, 2-diphenyl-4-*n*-hexyl-1*H*-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%). **^{1}H NMR ($CDCl_3$, 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, CH_2), 1.72-1.70 (m, 2H, CH_2), 1.37-1.36 (m, 2H, CH_2), 1.37-1.34 (m, 4H, CH_2), 0.92 (t, *J* = 7.0 Hz, 3H, CH_3); **^{13}C NMR ($CDCl_3$, 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; **^{19}F NMR ($CDCl_3$, 376.5 MHz):** δ -72.4; **FTIR:** ν_{max} : 1675 (s), 1597 (s), 1497 (m), 1365 (m); **HRMS:** m/z [MH^+] calc. for $C_{24}H_{25}NOF_3$: 400.1888, found: 400.1906.

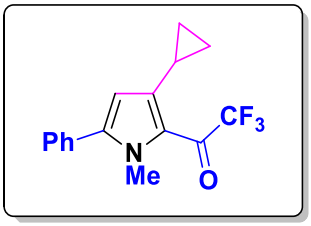
Synthesis of 5-trifluoroacetyl-1-methyl-2-phenyl-4-n-butyl-1H-pyrrole (125).



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%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.52-7.43 (m, 5H, ArH), 6.26 (s, 1H, pyrlH), 3.79 (s, 3H,

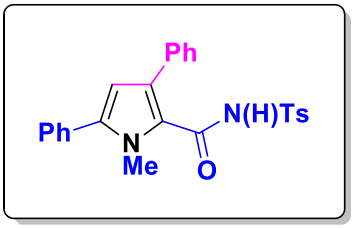
NCH_3), 2.81-2.77 (m, 2H, CH_2), 1.67-1.61 (m, 2H, CH_2), 1.48-1.45 (m, 2H, CH_2), 0.98 (t, *J* = 7.0 Hz, 3H, CH_3); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ171.0 (q, *J* = 36.0 Hz), 146.2, 139.0, 131.0, 129.3, 129.0, 128.7, 125.3, 117.0 (q, *J* = 289.0 Hz), 113.0, 36.5, 33.1, 27.0 (q, *J* = 6.0 Hz), 22.6, 14.0; **^{19}F NMR ($CDCl_3$, 376.5 MHz):** δ -72.1; **FTIR:** ν_{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).



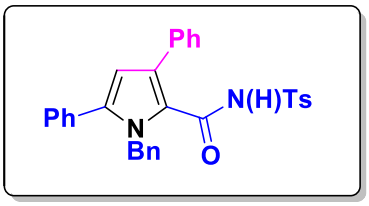
A solution of 3-methyl-4-trifluoroacetyl-2-phenyl-1,3-oxazolonium-5-olate (200 mg, 0.73 mmol) and ethynylcyclopropane (195 mg, 2.95 mmol) in xylenes (0.73 mL) in a sealed microwave vessel was heated at 140 °C for 48 hours. After cooling, the crude materials were purified by flash chromatography on silica 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):** δ 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):** δ 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):** δ -72.2; **FTIR:** ν_{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):** δ 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:** ν_{max} : 3323 (w), 1674 (s), 1416 (s), 1164 (s), 1063 (s), 699 (s), 657 (s) cm^{-1}**; HRMS:** m/z [MH^+] calc. for $C_{25}H_{22}N_2O_3S$: 431.1424, found: 431.1422.

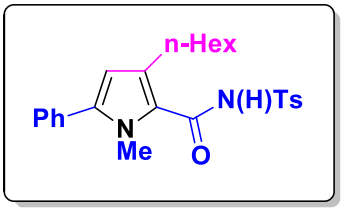
Synthesis of 5-tosylcarbamoyl-1- benzyl-2,4 diphenyl-1H-pyrrole (129).



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 ($CDCl_3$,**

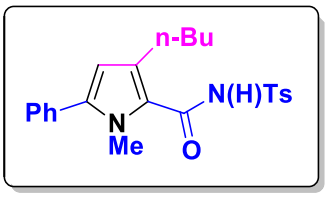
400 MHz): δ 7.80-7.73 (m, 3H, ArH), 7.50-7.35 (m, 10H, ArH), 7.29-7.27 (m, 2H, ArH), 7.28 (d, *J* = 8.0 Hz, 2H, ArH), 6.77-6.74 (m, 2H, ArH), 6.28 (s, 1H, pyrlH), 5.54 (s, 2H, NCH_2), 2.45 (s, 3H, CH_3); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 158.2, 144.6, 141.0, 138.4, 136.0, 134.2, 132.4, 131.5, 129.6, 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:** ν_{max}: 3321 (m), 1683 (s), 1426 (s),1166 (s), 1085 (s) cm^{-1}**; HRMS:** m/z [MH^+] calc. for $C_{31}H_{26}N_2O_3S$: 507.1737 found: 507.1748.

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



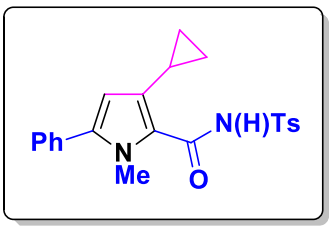
A solution of 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5- olate (200 mg, 0.53 mmol) and 1-octyne (236 mg, 2.14 mmol) in xylenes (0.5 mL) in a sealed microwave vessel was heated at 110 °C for 16 h. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to provide the title compound as a colourless oil (53 mg, 23%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.09-8.01 (m, 2H, ArH), 7.42-7.30 (m, 7H, ArH), 6.05 (s, 1H, pyrlH), 3.67 (s, 3H, CH_3), 2.74-2.67 (m, 2H, CH_2), 2.44 (s, 3H, CH_3), 1.68-1.59 (m, 2H, CH_2), 1.43-1.36 (m, 2H, CH_2), 1.33-1.30 (m, 4H, CH_2), 0.91 (t, *J* = 7.0 Hz, 3H, CH_3); **^{13}C NMR ($CDCl_3$,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:** ν_{max}: 2924 (m), 1671 (s), 1451 (s), 1421 (s), 1162 (s) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{25}H_{30}N_2O_3S$: 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}H NMR ($CDCl_3$, 400 MHz):** δ 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, pyrlH), 3.69 (s, 3H, CH_3), 2.76-2.71 (m, 2H, CH_2), 2.46 (s, 3H, CH_3), 1.69-1.60 (m, 2H, CH_2), 1.49-1.40 (m, 2H, CH_2), 0.98 (t, *J* = 7.3 Hz, 3H, CH_3); **^{13}C NMR ($CDCl_3$, 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, 126.5, 121.7, 110.9, 35.0, 32.8, 28.0, 22.6, 21.7, 13.9; **FTIR** ν_{max}: 2927 (m), 1672 (s), 1451 (s), 1422 (s), 1162 (s) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{23}H_{26}N_2O_3S$: 411.1737, found 411.1741.

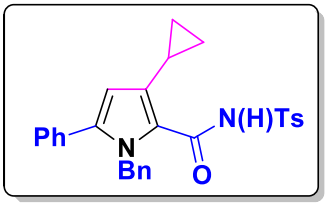
Synthesis of 5-tosylcarbamoyl-1-methyl-2-phenyl-4-cyclopropyl-1H-(133).



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}H NMR ($CDCl_3$, 400 MHz):** δ 9.58 (s, 1H, NH), 8.06-8.03 (m, 2H, ArH), 7.43-

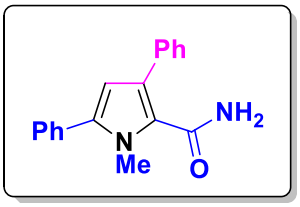
7.34 (m, 5H, ArH), 7.30–7.28 (m, 2H, ArH), 6.01 (s, 1H, pyrlH), 3.73 (s, 3H, NCH_3), 2.43 (s, 3H, CH_3), 2.01-1.94 (m, 1H, CH), 1.20-1.16 (m, 2H, CH_2), 0.85-0.82 (m, 2H, CH_2); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 158.0, 144.7, 141.5, 136.5, 131.9, 131.3, 129.6, 129.3, 128.6, 128.5, 128.4, 122.4, 110.9, 35.3, 21.7, 9.7, 7.8; **FTIR:** ν_{max}: 3312 (m), 1671 (s), 1422 (s), 657 (s) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{22}H_{22}N_2O_3S$: 395.1424, found: 395.1422.

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



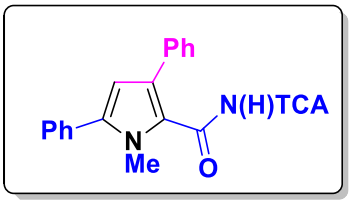
A solution of 3-benzyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium -5-olate (200 mg, 0.45 mmol) and ethynylcyclopropane (118 mg, 1.78 mmol) in xylenes (0.7 mL) in a sealed microwave vessel was heated at 110 °C for 24 h. After cooling, the crude materials were purified by flash chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to provide the title compound as a yellow oil (95 mg, 45%). **^{1}H NMR ($CDCl_3$, 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, pyrlH), 5.48 (s, 2H, CH_2), 2.43 (s, 3H, CH_3), 2.02-1.96 (m, 1H, CH), 1.20-1.15 (m, 2H, CH_2), 0.86-0.82 (m, 2H, CH_2); **^{13}C NMR ($CDCl_3$, 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:** ν_{max}: 3286 (m), 2971 (m), 1739 (s), 1673 (s) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{28}H_{26}N_2O_3S$: 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):** δ 7.50-7.32 (m, 10H, ArH), 6.21 (s, 1H, pyrlH), 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):** δ 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:** ν_{max} : 3416 (w), 3166 (w), 1638 (s), 1442 (s), 755 (s), 697 (s) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{18}H_{16}N_2O$: 277.1335, found: 277.1339.

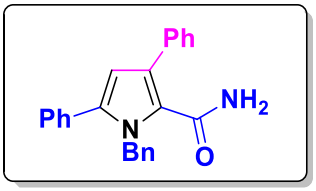
Synthesis of 5-trichloroacetyl carbamoyl-1-methyl-2,4 diphenyl-1H-pyrrole (136).



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**

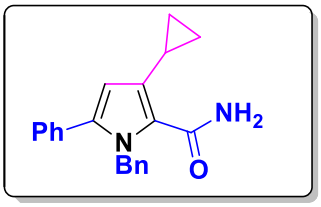
(61 mg, 52%). **131: ^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.99 (s, 1H, NH), 7.48-7.43 (m, 10H, ArH), 6.24 (s, 1H, pyrlH), 3.94 (s, 3H, CH_3); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 157.7, 157.6, 142.6, 134.6, 132.3, 131.1, 129.0, 129.7, 129.5, 128.8, 128.7 (x2C), 121.6, 116.7, 112.3, 35.7; **FTIR:** ν_{max}: 2924 (m), 1757 (s), 1645 (s), 1577 (m) cm^{-1}; m/z (EI) 421 (70%, $[M(^{35}Cl_3)]^+$), **HRMS:** calc. for $C_{20}H_{15}{}^{35}Cl_3N_2O_2$: 421.0272, found 421.0276.

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



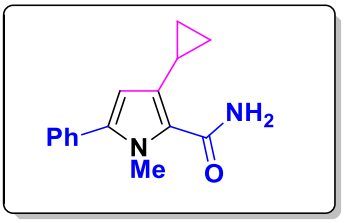
A solution of 3-benzyl-4-(2,2,2-trichloroacetyl)carbamoyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.23 mmol) and ethynylbenzene (46 mg, 0.45 mmol) in xylenes (0.35 mL) in a sealed microwave vessel was heated at 110 °C for 22 h. After cooling, the crude materials were purified by flash chromatography 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):** δ 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):** δ 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:** ν_{max}: 3474 (m), 1664 (s), 1598 (m), 1456 (s), 751 (s), 696 (s) cm^{-1}**;** HRMS: m/z $[MH^+]$ calc. for $C_{24}H_{20}N_2O$: 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:** ν_{max}: 3385 (m), 3016 (m), 1738 (s) cm^{-1}; HRMS: m/z [MH^+] calc. for $C_{21}H_{20}N_2O$: 317.1648, found: 317.1648.

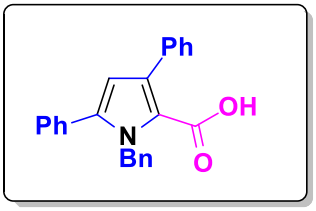
Synthesis of 5-amide-1-methyl -2-phenyl-4-cyclopropyl-1H-pyrrole (139).



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

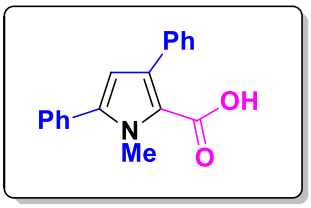
(m, 1H, CH), 0.99-0.93 (m, 2H, CH_2), 0.78-0.74 (m, 2H, CH_2); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 164.4, 139.2, 132.2, 129.8, 129.4, 128.4, 127.9, 124.6, 108.8, 35.0, 9.3, 7.4; **FTIR:** ν_{max}: 3363 (w), 3165 (w), 1638 (s), 1602 (s), 1465 (s), 764 (s), 700 (s) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{15}H_{16}N_2O$: 241.1335, found: 241.1336.

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



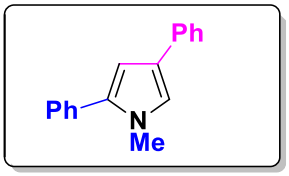
5-Trifluoroacetyl-1-benzyl-2,4-diphenyl pyrrole (100 mg, 0.25 mmol) and NaOH (197 mg) in methanol (0.7 mL) and water (0.7 mL) were heated under reflux overnight. The mixture was acidified with concentrated HCl and extracted with EtOAc. The extracts were washed with water and brine, then dried ($MgSO_4$) 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}H NMR ($CDCl_3$, 400 MHz):** δ 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, NCH_2); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 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; **FTIR:** ν_{max} : 3065 (w), 3031 (w), 2970 (w), 1653 (s), 1456 (s), 1270 (s) cm^{-1}**;** **HRMS:** m/z [MH^+] calc. for $C_{24}H_{19}NO_2$: 354.1489, 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:** ν_{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.

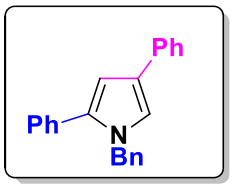
Synthesis of 1-methyl-2,4-diphenyl-1H-pyrrole (128).



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, pyrH), 6.54 (d, *J* = 2.0 Hz, 1H, pyrlH), 3.70 (s,

3H, NCH_3); **^{13}C NMR ($CDCl_3$, 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:** ν_{max}: 1681 (s), 1448 (m), 1424 (m) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{17}H_{15}N$: 234.1277, found 234.1274.

Synthesis of N-benzyl-2,4-diphenyl pyrrole (130).[149]

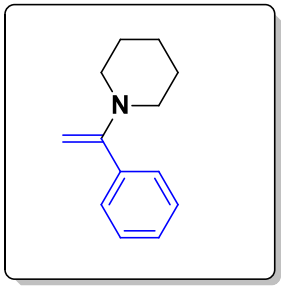


5-Tosylcarbamoyl-1-benzyl-2,4-diphenyl-1H-pyrrole (150 mg, 0.29 mmol) in methanol (1 mL) and acetic acid (1 mL) were heated under reflux overnight. The mixture was extracted with EtOAc. The extracts were washed with water and brine, then dried ($MgSO_4$) and evaporated. The crude materials were purified by flash chromatography on silica gel (eluting with 30% EtOAc in petroleum ether) to provide the title compound as a yellow solid (65 mg, 71%). **Melting point:** 93-95 ˚C (lit. 96-98 °C); **^{1}H NMR ($CDCl_3$, 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, PyrlH), 6.60 (d, *J* = 2.0 Hz, 1H, PyrlH), 5.18 (s, 2H, CH_2); **^{13}C NMR ($CDCl_3$, 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.

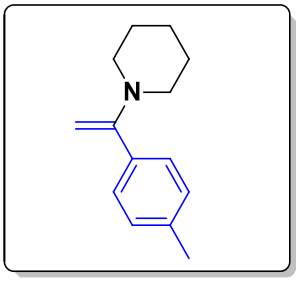
Acetophenone enamines were synthesized according to a literature method.[150]

General procedure as exemplified by the synthesis of *N*-(1-arylvinyl) piperidine (153).[151,152]



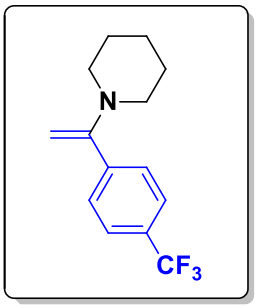
To a solution of acetophenone (2.0 g, 17.0 mmol) and piperidine (10 mL, 100.0 mmol) in anhydrous hexane (40 mL), was added $TiCl_4$ (1.8 mL, 17.0 mmol) over 30 min at 0 ^oC. The reaction mixture was stirred at room temperature for 24 h and filtered. The filtrate was evaporated under vacuum to give *N*-(1-arylvinyl)piperidine as a pale yellow oil (2.0 g, 67% yield). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 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):** δ 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).**[153]



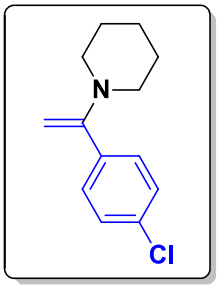
Following the general procedure using 4-methylacetophernone (500 mg, 3.7 mmol), piperidine (2.2 mL, 22.0 mmol) and $TiCl_4$ (0.4 mL, 2.3 mmol) the title compound was isolated as a yellow oil (590 mg, 79%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.37-7.34 (m, 2H, ArH), 7.14-7.12 (m, 2H, ArH), 4.21 (s, 1H, 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):** δ 158.0, 137.5, 137.4, 128.7, 127.6, 89.5, 50.5, 26.0, 24.5, 21.1.

***N*-(1-(4-(trifluoromethyl)phenyl)vinyl)piperidine (155).**[154]



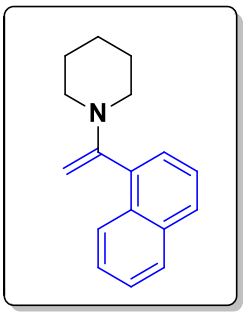
Following the general procedure using (4-trifluoromethyl)phenyl]ethanone (200 mg, 1.0 mmol), piperidine (0.6 mL, 6.0 mmol) and $TiCl_4$ (0.1 mL, 1.0 mmol) the title compound was isolated as a yellow oil (190 mg, 79%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.57 (m, 4H, ArH), 4.30 (s, 1H, CH), 4.23 (s, 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.

***N*-(1-(4-Chlorophenyl)vinyl)piperidine (156).**[153]



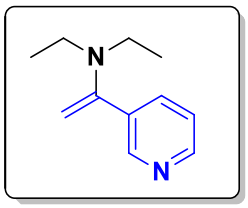
Following the general procedure using 4-chloroacetophernone (500 mg, 2.3 mmol), piperidine (1.3 mL, 14.0 mmol) and $TiCl_4$ (0.2 mL, 2.3 mmol) the title compound was isolated as a yellow oil (370 mg, 75%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.44-7.40 (m, 2H, ArH), 7.32-7.28 (m, 2H, ArH), 4.25 (s, 1H, 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).**



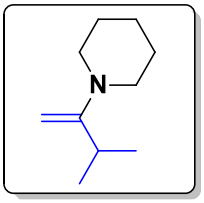
Following the general procedure using 1-acetonaphthalene (200 mg, 1.1 mmol), piperidine (0.7 mL, 7.0 mmol) and $TiCl_4$ (0.1 mL, 1.1 mmol) the title compound was isolated as a yellow oil (220 mg, 79%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.52-8.44 (m, 1H, ArH), 7.90-7.81 (m, 2H, ArH), 7.55-7.43 (m, 4H, ArH), 4.34 (s, 1H, CH), 4.09 (s, 1H, CH), 2.92–2.84 (m, 4H, CH_2), 1.60-1.48 (m, 6H, CH_2). **^{13}C NMR ($CDCl_3$, 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).**[155]



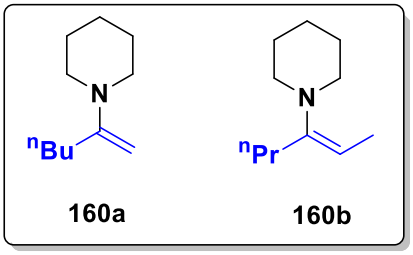
Following the general procedure using 4-acetylpyridine (200 mg, 1.6 mmol), diethylamine (1.0 mL, 10 mmol) and $TiCl_4$ (0.2 mL, 1.6 mmol) the title compound was isolated as a pale yellow oil (71 mg, 25%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.58-8.56 (m, 1H, ArH), 8.43-8.40 (m, 1H, ArH), 7.62-7.59 (m, 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, CH_2), 0.93-0.90 (m, 6H, CH_3); **^{13}C NMR ($CDCl_3$, 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).



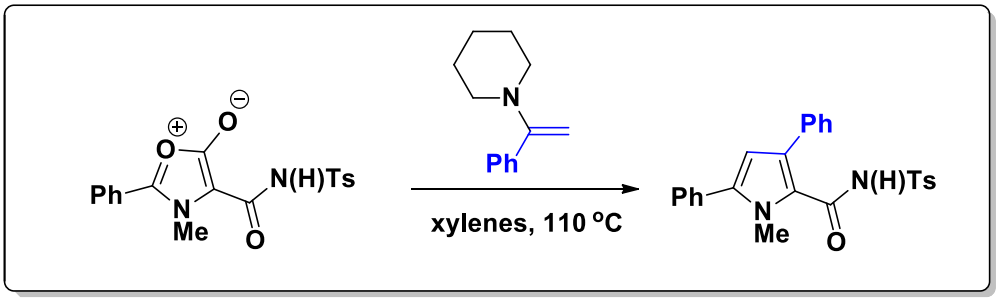
Following the general procedure using 2-acetyl propane (200 mg, 2.3 mmol), Piperidine (1.4 mL, 14.0 mmol) and $TiCl_4$ (0.3 mL, 2.3 mmol) the title compound was isolated as a yellow oil (250 mg, 71%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 3.97 (s, 1H, CH), 3.88 (s, 1H, CH), 2.86-2.81 (m, 4H, CH_2), 1.63-1.57 (m, 6H, CH_2), 1.10 (d, *J* = 7.0 Hz, 6H, CH_3). **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 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).



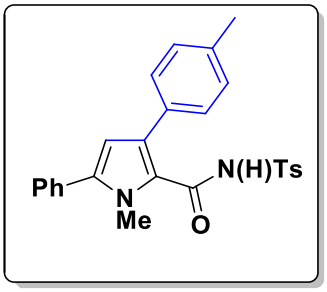
Following the general procedure using 2-hexanone (200 mg, 1.1 mmol), piperidine (1.2 mL, 12 mmol) and $TiCl_4$ (0.2 mL, 1.1 mmol) the title compound was isolated as a yellow oil and a mixture of two regioisomer (1:1; 220 mg, 84%); **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 4.29 (t, J = 7.0 Hz, 1H), 3.80 (s, 1H, CH), 3.74 (s, 1H, CH), 2.93-2.77 (m, 8H, CH_2), 2.15-2.09 (m, 4H, CH_2), 1.71 (d, *J* = 7.0 Hz, 3H, CH_3), 1.98-1.92 (m, 6H, CH_2), 1.50-1.45 (m, 12H, CH_2), 0.95-0.90 (m, 6H, CH_3); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 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.

6. Representative Procedure for 1-substituted enamine-münchnone [3+2] Cycloaddition: synthesis of 5-tosylcarbamoyl-1-methyl-2,4 diphenyl-1*H*-pyrrole (128).



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 N_2 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**.

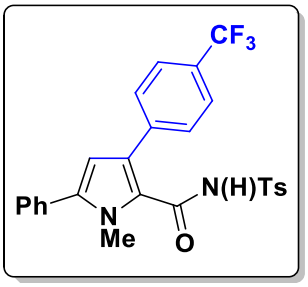
Synthesis of 5-tosylcarbamoyl-1-methyl-2-phenyl-4-p-tolyl-1*H*-pyrrole (161).



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%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.88-7.86 (m, 2H, ArH), 7.46-7.38 (m, 3H, ArH), 7.36-

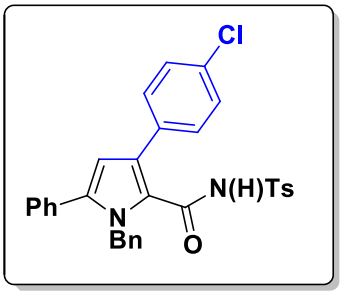
7.33 (m, 3H, ArH), 7.30-7.23 (m, 5H, ArH), 6.15 (s, 1H, pyrlH), 3.80 (s, 3H, NCH_3), 2.45 (s, 3H, CH_3), 2.44 (s, 3H, CH_3); **^{13}C NMR ($CDCl_3$, 101 MHz):** 158.2, 144.8, 141.7, 138.6, 136.2, 131.8, 131.5, 131.3, 130.1, 129.5, 129.4 (x2C), 128.6, 128.5, 128.4, 120.6, 111.6, 35.3, 21.7, 21.4.; **FTIR:** ν_{max} : 3318 (m), 2922 (m), 1677 (s), 1451 (s), 1166 (s), 1067 (s), 812 (s) cm^{-1}**;** **HRMS:** m/z [MH^+] calc. for $C_{26}H_{24}N_2O_3S$: 445.1580, found: 445.1590.

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



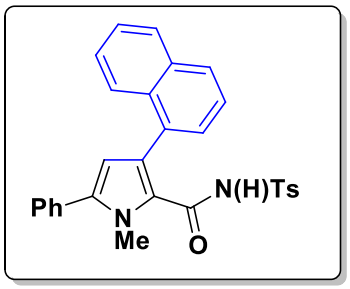
Following the general procedure using 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.27 mmol) and *N*-(1-(*p*-trifluoromethyl)vinyl)piperidine (167 mg, 0.54 mmol), the title compound was isolated as a yellow oil (92 mg, 68%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.92-7.89 (m, 2H, 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, pyrlH), 3.80 (s, 3H, NCH_3), 2.49 (s, 3H, CH_3); **^{13}C NMR ($CDCl_3$, 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; **^{19}F NMR ($CDCl_3$, 376.5 MHz):** δ -63.0; **FTIR:** ν_{max} : 2951 (w), 2927 (w), 1683 (m), 1456 (s), 1325 (s), 1166 (s), 767 (m) cm^{-1} **;** **HRMS:** m/z [MH^+] calc. for $C_{26}H_{21}F_3N_2O_3S$: 499.1298, found: 499.1308.

Synthesis of 5-tosylcarbamoyl-1-benzyl-2-phenyl-4-chlorophenyl-1*H*-pyrrole (164).



Following the general procedure using 3-benzyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olat (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):** δ 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):** δ 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:** ν_{max}: 3321 (w), 1683 (s), 1454 (m), 1167 (s), 1086 (m) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{31}H_{25}{}^{35}ClN_2O_3S$: 541.1347, found: 541.1359.

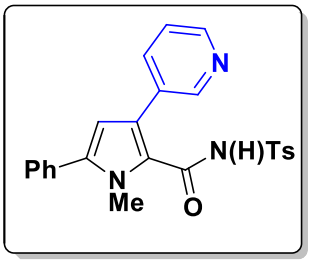
Synthesis of 5-tosylcarbamoyl-1-methyl-2-phenyl-4-naphthalene-1*H*-pyrrole (165).



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):** δ 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, PyrlH), 3.94 (s, 3H,

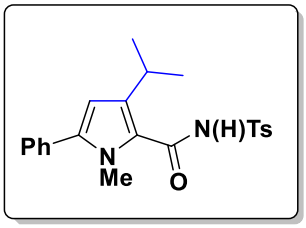
NCH_3), 2.40 (s, 3H, CH_3); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 157.9, 144.3, 142.0, 135.6, 133.9, 132.5, 132.3, 131.2, 129.7, 129.4, 129.3, 128.7, 128.6, 128.1, 128.0 127.1, 126.6, 125.8 125.7, 122.2, 112.5, 35.5, 21.6; **FTIR: ν_{max}:** 3058 (w), 2957 (w), 1678 (s), 1449 (s), 1166 (s), 1067 (s), 781 (m) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{29}H_{24}N_2O_3S$: 481.1580, found: 481.1589.

Synthesis of 5-tosylcarbamoyl-1-methyl-2-phenyl-4-pyridin-1*H*-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). **^{1}H NMR ($CDCl_3$, 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, NCH_3), 2.45 (s, 3H, CH_3); **^{13}C NMR ($CDCl_3$, 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:** ν_{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 $C_{24}H_{21}N_3O_3S$: 432.1376, found: 432.1381

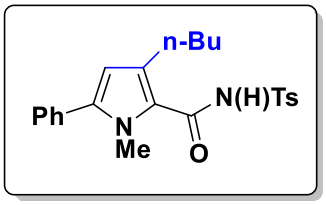
Synthesis of 5-tosylcarbamoyl-1-methyl-2-phenyl-4-isopropyl-1*H*-pyrrole (167).



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, pyrlH), 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:** ν_{max}: 3066 (w), 2961 (m), 1676 (s), 1453 (s), 1165 (s), 1079 (m) cm^{-1}**; HRMS:** m/z [MH^+] calc. for $C_{22}H_{24}N_2O_3S$: 397.1585, found: 397.1585.

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

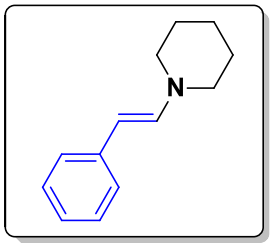


Following the general procedure using 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.27 mmol) and a mixture (1:1) of 1-(hex-1-en-2-yl)piperidine and 1-(hex2-en-3yl) piperidine (90 mg, 0.54 mmol), the title compound was isolated as a yellow oil (64 mg, 58%).**^{1}H NMR ($CDCl_3$, 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, pyrlH), 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: vmax**: 3063 (w), 2956 (m), 1672 (s), 1450 (s), 1161 (s), 1070 (m), 763 (s) cm^{-1} ; **HRMS:** m/z [MH+] calc. for $C_{23}H_{26}N_2O_3S$: 411.1737, found: 411.1746**.**

7. Preparation of isomeric 2-substituted enamines.

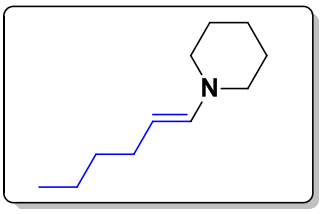
Arylacetaldehyde enamines were synthesized according to a literature method.[156]

General procedure as exemplified by the synthesis of (*E*)-1-styrylpiperidine (168).[156]



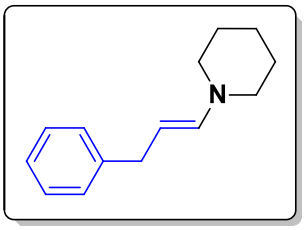
To a dried 12 mL round-bottom flask with a magnetic stir bar was added Na_2CO_3 (0.55 g, 5 mmol) and amine (3.0 g, 36 mmol), and the mixture was cooled in an ice-water bath. Phenylacetaldehyde (1.8 g, 15.0 mmol) was added dropwise to the above mixture. The reaction mixture was stirred at room temperature 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). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 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); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 140.3, 139.6, 128.5, 123.9, 123.7, 99.5, 49.7, 25.4, 24.4.

***(*E)-1-styrylpiperidine (169).**[157]



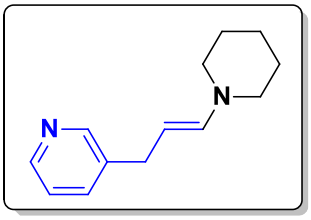
Following the general procedure using hexanal (500 mg, 4.9 mmol), pipridine (1.1 mL, 12.0 mmol) and Na_2CO_3 (0.17 g, 1.6 mmol) the title compound was isolated as a brown oil (500 mg, 60%). **^{1}H NMR ($CDCl_3$, 400 MHz):** *δ* 5.79 (d, *J* = 14.0 Hz, 1 H, CH), 4.34 (dt, *J* = 14.0 Hz, 1H, CH), 2.78-2.69 (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); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 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).**[158]



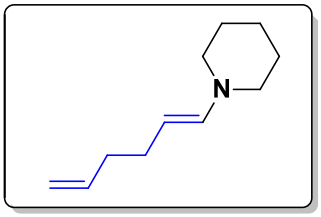
Following the general procedure using 3- phenylpropanal (500 mg, 3.7 mmol), diethylamine (0.9 mL, 9.0 mmol) and Na_2CO_3 (0.13 g, 1.2 mmol) the title compound was isolated as a yellow oil (550 mg, 78%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.39-7.12 (m, 5 H, ArH), 6.1 (d, *J* = 14.0 Hz, 1H, CH), 4.45 (dt, *J* = 14.0 Hz, 1H, CH), 3.46 (d, *J* = 7.0 Hz, 2H, CH_2), 2.91-2.85 (m, 4H, CH_2), 1.61-1.50 (m, 6H, CH_2); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 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).



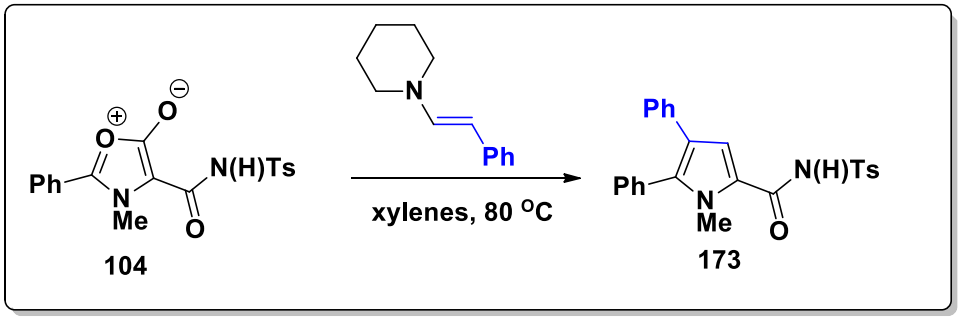
Following the general procedure using 3-pyridinepropanal (500 mg, 3.6 mmol), pipridine (0.87 mL, 9.0 mmol) and Na_2CO_3 (0.13 g, 1.2 mmol) the title compound was isolated as a brown oil (620 mg, 84%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.47-8.38 (m, 2H, ArH), 7.54-7.49 (m, 1H, ArH), 7.21-7.14 (m, 1H, 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_2), 2.81-2.75 (m, 4H, CH_2), 1.59-1.47 (m, 6H, CH_2). **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 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).



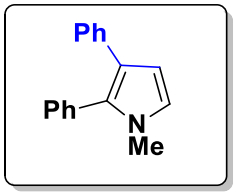
Following the general procedure using 5-hexenal (500 mg, 5.1 mmol), pipridine(1.2 mL, 12.0 mmol) and Na_2CO_3 (0.18 g, 1.6 mmol) the title compound was isolated as a yellow oil (540 mg, 64 %). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 5.89-5.73 (m, 2H, CH), 5.00-4.85 (m, 2H, CH2), 4.33 (*dt*, 1H, *J* = 14.0, 7 Hz, CH), 2.71–2.64 (m, 4H, CH_2), 2.05-1.97 (m, 4H, CH_2), 1.52-1.42 (m, 6H, CH_2). **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 140.4, 138.7, 114.1, 52.9, 49.9, 35.6, 26.5, 25.3, 24.7.

8. Representative Procedure for isomeric 2-substituted enamine-münchnone [3+2] Cycloaddition: synthesis of 5-tosylcarbamoyl-1-methyl-2,3-diphenyl-1*H*-pyrrole (173).



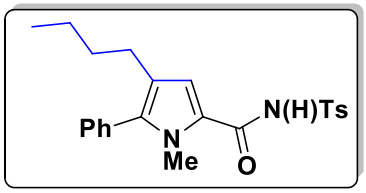
To a flame-dried two neck round bottom flask equipped with a stirrer bar and reflux condenser was added a solution of 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate **104** (100 mg, 0.27 mmol, 1.0 eq.) and 1-(2-phenylethenyl)piperidine (101 mg, 0.54 mmol, 2.0 eq.) in xylenes (2 mL) under N_2 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%). **^{1}H NMR ($CDCl_3$, 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, NCH_3), 2.46 (s, 3H, CH_3); **^{13}C NMR ($CDCl_3$, 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_{max} : 3292 (m), 2919 (s), 1680 (s), 1440 (s), 1330 (s), 1159 (s), 1038 (s), 701 (s) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{25}H_{22}N_2O_3S$: 431.1424, found: 431.1430.

Synthesis of 1-methyl-2,3-diphenyl-1*H*-pyrrole (174).



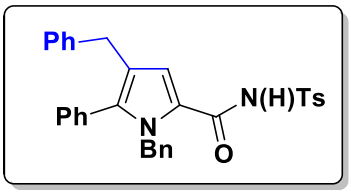
Following the general procedure using 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.27 mmol), phenylacetaldehyde (65 mg, 0.54 mmol) and piperidine (5 µL, 0.054 mmol) the title compound was isolated as a colorless oil (37 mg, 58%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.44-7.31 (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, PyrlH), 6.47 (d, *J* = 3.0 Hz, 1H, PyrlH), 3.56 (s, 3H, NCH_3); **^{13}C NMR, 101 MHz):** δ 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:** ν_{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-1*H*-pyrrole (175).



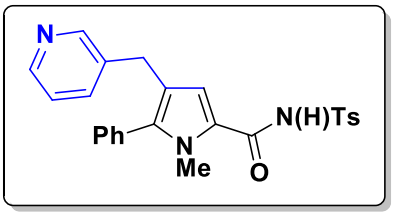
Following the general procedure using 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (100 mg, 0.27 mmol) and 1-(1-hexenyl)piperidine (90 mg, 0.54 mmol), the title compound was isolated as a yellow oil (74 mg, 67%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.15-8.07 (m, 2H, ArH), 7.48-7.36 (m, 5H, ArH), 7.25-7.21 (m, 2H, ArH), 6.91 (s, 1H, pyrlH), 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):** δ 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:** ν_{max} : 3271 (m), 2955 (m), 1679 (s), 1430 (s), 1164 (s), 703 (s) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{23}H_{26}N_2O_3S$: 411.1737, found: 411.1742.

Synthesis of 5-tosylcarbamoyl-1,3-dibenzyl-2-phenyl-1*H*-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):** δ 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)**: δ 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:** ν_{max}: 3027 (w), 2924 (m), 1679 (s), 1453 (s), 1166 (s), 700 (s) cm^{-1}; **HRMS**: m/z [MH^+] calc. for $C_{32}H_{28}N_2O_3S$: 521.1893, found: 521.1904.

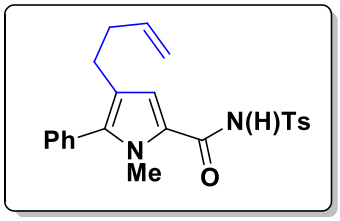
Synthesis of 5-tosylcarbamoyl-1-methyl-2-phenyl-3-(pyridine-3-ylmethyl)-1*H*-pyrrole (177).



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)ally)pyridine (108 mg, 0.54 mmol), the title compound was isolated as a yellow oil (84 mg, 70%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 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):** δ 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:** ν_{max}: 3055 (w), 2962 (m), 2920 (m), 1675 (s),

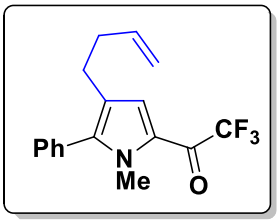
1455 (s), 1163 (s), 1075 (s), 813 (s) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{25}H_{23}N_3O_3S$: 446.1533, found: 446.1540.

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



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):** δ 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):** δ 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:** ν_{max}: 3436 (w), 2919 (m), 1676 (s), 1454 (s), 919 (m) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{23}H_{25}N_2O_3S$: 409.1580, found: 409.1582.

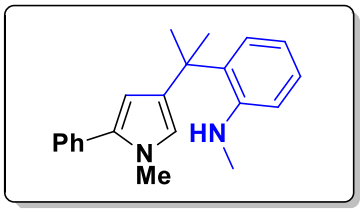
Synthesis of 5-trifluoroacetyl -1-methyl-2-phenyl-3-(but-3-en-1-yl)-1*H*-pyrrole (180).



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):** δ 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,

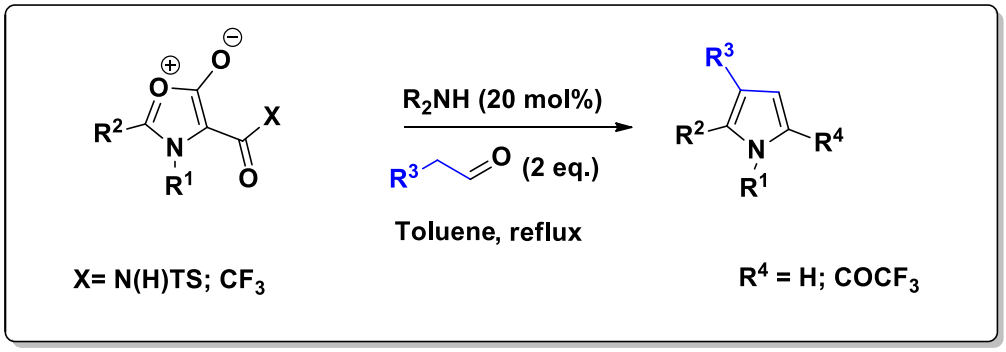
CH_3), 2.52-2.44 (m, 2H, CH_2), 2.28-2.21 (m, 2H, CH_2). **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 169.0 (q, *J* = 58.0 Hz), 144.7, 137.7, 129.0 (x2C), 129.2, 128.8, 124.6, 124.2, 122.9 (q, *J* = 4.0 Hz), 118.8, 115.2, 35.2, 34.5, 25.4; **^{19}F NMR ($CDCl_3$, 376.5 MHz):** δ -71.0; **FTIR:** ν_{max}: 3429 (w), 2925 (w), 1662 (s), 1450 (m), 1441 (m), 940 (m) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{17}H_{16}F_3NO$: 308.1257, found: 308.1257.

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



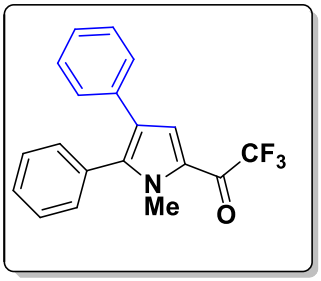
Following the general procedure using 3-methyl-4-tosylcarbamoyl-2-phenyl-1,3-oxazolonium-5-olate (50 mg, 0.13 mmol) and 1,3,3-trimethyleneindoline (47 mg, 0.26 mmol), the title compound was isolated as a brown-red oil (23 mg, 58%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.46-7.43 (m, 1H, ArH), 7.41-7.38 (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, pyrlH), 6.07 (d, *J* = 2.0 Hz, 1H, pyrlH), 4.81 (s, br, 1H, NH), 3.65 (s, 3H, CH_3), 2.66 (s, 3H, CH_3), 1.69 (s, 6H, CH_3) **^{13}C NMR ($CDCl_3$, 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 $C_{21}H_{24}N_2$: 305.2012, found: 305.2017.

9. Representative Procedure for Amine Catalyzed Münchnone Cycloadditions.



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 N_2 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.

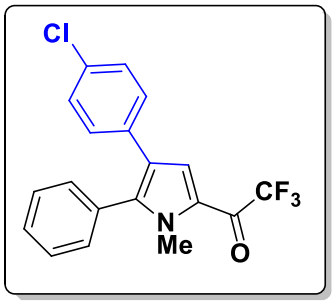
Synthesis of 5-trifluoroacetyl-1-methyl-2,3-diphenyl-1*H*-pyrrole (188).



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 dibenzylamine (14 µL, 0.074 mmol) the title compound was isolated as yellow solid (87 mg, 71%). **Melting point:** 89-92 °C; **^{1}H NMR ($CDCl_3$, 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, PyrlH), 3.88 (s, 3H, NCH_3); **^{13}C NMR ($CDCl_3$, 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,

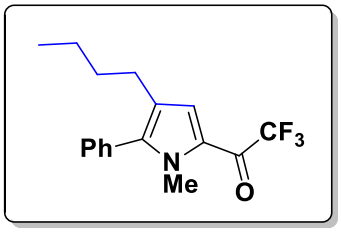
124.9, 122.6 (q, *J* = 4.0 Hz), 117.3 (q, *J* = 291.0 Hz), 35.3; **^{19}F NMR ($CDCl_3$, 376.5 MHz):** δ -71.0; **FTIR:** ν_{max}: 3061 (w), 1667 (s), 1442 (m), 1301 (m), 1174 (m) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{19}H_{14}NOF_3$: 330.1107, found: 330.1107.

Synthesis of 5-trifluoroacetyl-1-methyl-2-phenyl-3-(4-chlorophenyl) 1*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%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 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, PyrlH), 3.86 (s, 3H, NCH_3); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 170.1 (q, *J* = 35.0 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}F NMR ($CDCl_3$, 376.5 MHz):** δ -71.0; **FTIR:** ν_{max}: 3424 (w), 1666 (s), 1513 (m), 1434 (m), 1450 (m), 1173 (m) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{19}H_{13}{}^{35}$[Cl]NOF_3: 364.0711, found: 364.0718.

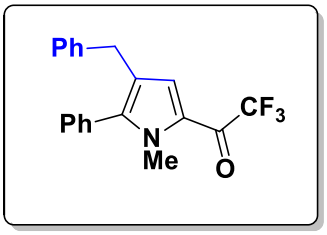
Synthesis of 5-trifluoroacetyl -1-methyl-2-phenyl-3-*n*-butyl-1*H*-pyrrole (190).



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

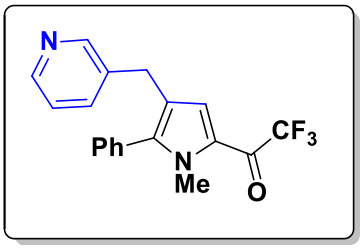
mg, 52%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.56-7.49 (m, 3H, ArH), 7.34-7.31 (m, 2H, ArH), 7.15 (s, 1H, pyrlH), 3.79 (s, 3H, NCH_3), 2.42-2.34 (m, 2H, CH_2), 1.53-1.44 (m, 2H, CH_2), 1.34-1.22 (m, 2H, CH_2), 0.86 (t, *J* = 7.0 Hz, 3H, CH_3); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 169.4 (q, *J* = 35.0 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):** δ -71.0; **FTIR:** ν_{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 -1*H*-pyrrole (191).



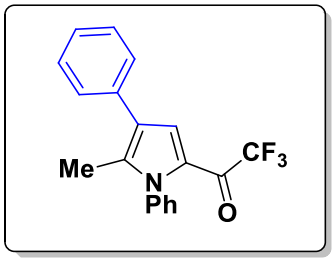
Following the general procedure using 3-methyl-4-trifluoroacetyl-2-phenyl-1,3-oxazolonium-5-olate **1c** (100 mg, 0.37 mmol), 3-phenylpropionaldehyde (99 mg, 0.74 mmol) and dibenzylamine (14 µL, 0.074 mmol) the title compound was isolated as an orange oil (85 mg, 67%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 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, PyrlH), 3.81 (s, 3H, NCH_3), 3.75 (s, 2H, CH_2); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 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):** δ -71.0; **FTIR:** ν_{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)-1*H*-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%). **^{1}H NMR ($CDCl_3$, 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, NCH_3), 3.74 (s, 2H, CH_2); **^{13}C NMR ($CDCl_3$, 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; **^{19}F NMR ($CDCl_3$, 376.5 MHz):** δ -71.0; **FTIR:** ν_{max}: 3063 (w), 2925 (w), 1664 (s), 1450 (m), 1295 (m), 1175 (m) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{19}H_{15}N_2OF_3$: 345.1209, found: 345.1209.

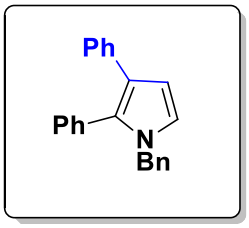
Synthesis of 5-trifluoroacetyl-1,3-diphenyl-2-methyl -1*H*-pyrrole (193).



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; **^{1}H NMR ($CDCl_3$, 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

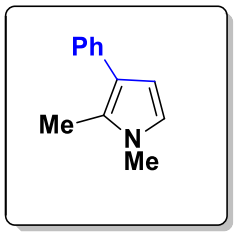
(m, 1H, ArH), 7.31-7.28 (m, 2H, ArH, PyrlH), 2.20 (s, 3H, CH_3); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 168.3 (q, *J* = 47.0 Hz), 140.6, 138.5, 134.4, 129.4, 128.9, 128.7, 128.3, 127.4, 127.0, 125.8, 124.9, 123.1 (q, *J* = 4.0 Hz), 117.2 (q, *J* = 291.0 Hz), 12.1; **^{19}F NMR ($CDCl_3$, 376.5 MHz):** δ -71.0; **FTIR:** ν_{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 ($CDCl_3$, 400 MHz):** δ 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, PyrlH), 6.55 (d, *J* = 3.0 Hz, 1H, PyrlH), 5.03 (s, 2H, CH_2). **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 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:** ν_{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.

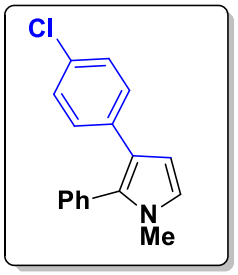
Synthesis of 1,2-dimethyl-3-phenyl-1*H*-pyrrole (195).



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

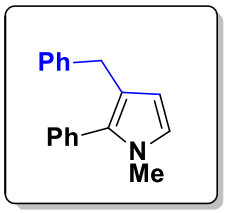
colorless oil (31 mg, 56%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.46-7.35 (m, 4H, ArH), 7.25-7.21 (m, 1H, ArH), 6.64 (d, *J* = 3.0 Hz, 1H, PyrlH), 6.28 (d, *J* = 3.0 Hz, 1H, PyrlH), 3.61 (s, 3H, NCH_3), 2.37 (s, 3H, CH_3); **^{13}C NMR, 101 MHz):** δ 137.6, 128.3, 128.0, 125.4, 125.1, 122.0, 120.6, 107.1, 34.0, 10.7; **FTIR:** ν_{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) 1*H*-pyrrole (196).



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 µL, 0.054 mmol) the title compound was isolated as a colorless oil (46 mg, 64%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 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, PyrlH), 6.41 (d, *J* = 3.0 Hz, 1H, PyrlH), 3.54 (s, 3H, NCH_3); **^{13}C NMR, 101 MHz):** δ 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:** ν_{max}: 3052(w), 1700 (w), 1600 (m), 1504 (m), 1348 (m), 701 (m) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{17}H_{14}{}^{35}$[Cl]N: 268.0888, found: 268.0891.

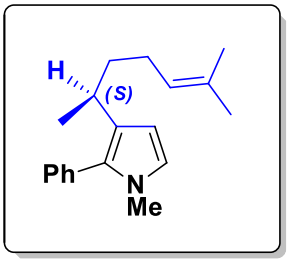
Synthesis of 1-methyl-2-phenyl-3-benzyl-1*H*-pyrrole (197).



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 µL, 0.054 mmol) the title compound was isolated as a

yellow oil (35 mg, 52%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 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, PyrlH), 6.05 (d, *J* = 3.0 Hz, 1H, PyrlH), 3.79 (s, 2H, CH_2), 3.54 (s, 3H, NCH_3); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 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:** ν_{max}: 3061 (w), 1678 (s), 1494 (m), 1451 (m), 701 (m) cm^{-1}; **HRMS:** m/z [MH^+] calc. for $C_{18}H_{17}N$: 248.1434, found: 248.1434.

Synthesis-1-methyl-2-phenyl-3-(6-methylhept-5-en-2-yl)-1*H*-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 µL, 0.054 mmol) the title compound was isolated as a colorless oil (51 mg, 71%, 96% ee). **$[\alpha]_D^{23}$** = +10 (*c* 0.5, $CHCl_3$); **Chiral HPLC:** Phenomenex ® Lux 3u Cellulose-1 column; 100% hexane; flow rate = 1.0 mL/min; detection at 220 nm. **^{1}H NMR ($CDCl_3$, 400 MHz**): δ 7.48-7.29 (m, 5H, ArH), 6.66 (d, *J* = 3.0 Hz, 1H, PyrlH), 6.12 (d, *J* = 3.0 Hz, 1H, PyrlH), 5.03-4.97 (m, 1H, CH), 3.48 (s, 3H, NCH_3), 1.92-1.78 (m, 1H, CH), 2.67-2.55 (m, 2H, CH_2), 1.63 (s, 3H, CH_3), 1.58-1.42 (m, 2H, CH_2), 1.52 (s, 3H, CH_3), 1.17 (d, *J* = 7.0 Hz, 3H, CH_3); **^{13}C NMR ($CDCl_3$, 101 MHz):** δ 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: ν_{max}**: 3053 (w), 2957 (s), 2921 (s), 1603 (m), 1489 (m), 1334 (m) 773 (s) cm^{-1}; **HRMS: m/z [MH^+]** calc. for $C_{19}H_{25}N$: 268.2060, found: 268.2060.

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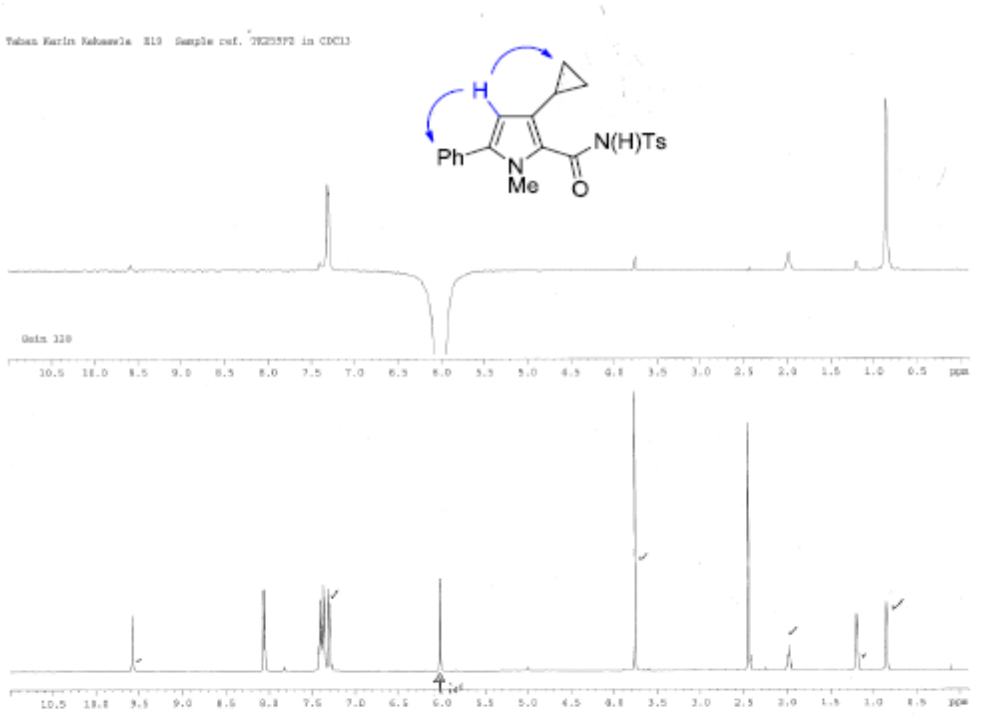
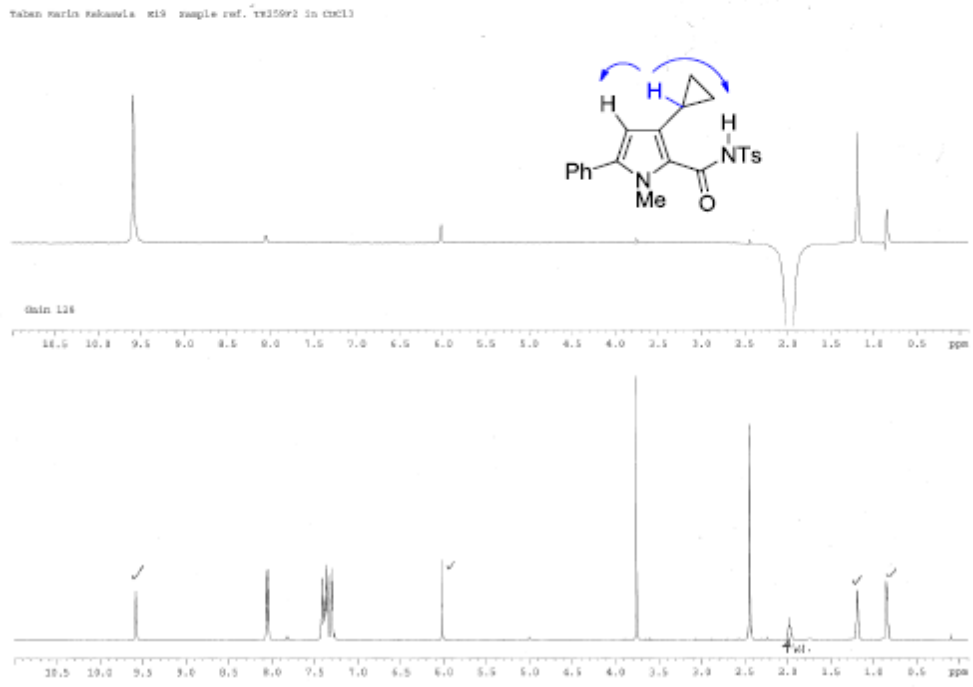
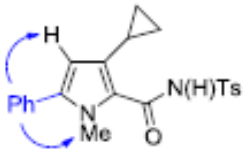
Appendix

- nOe spectra of **133**.



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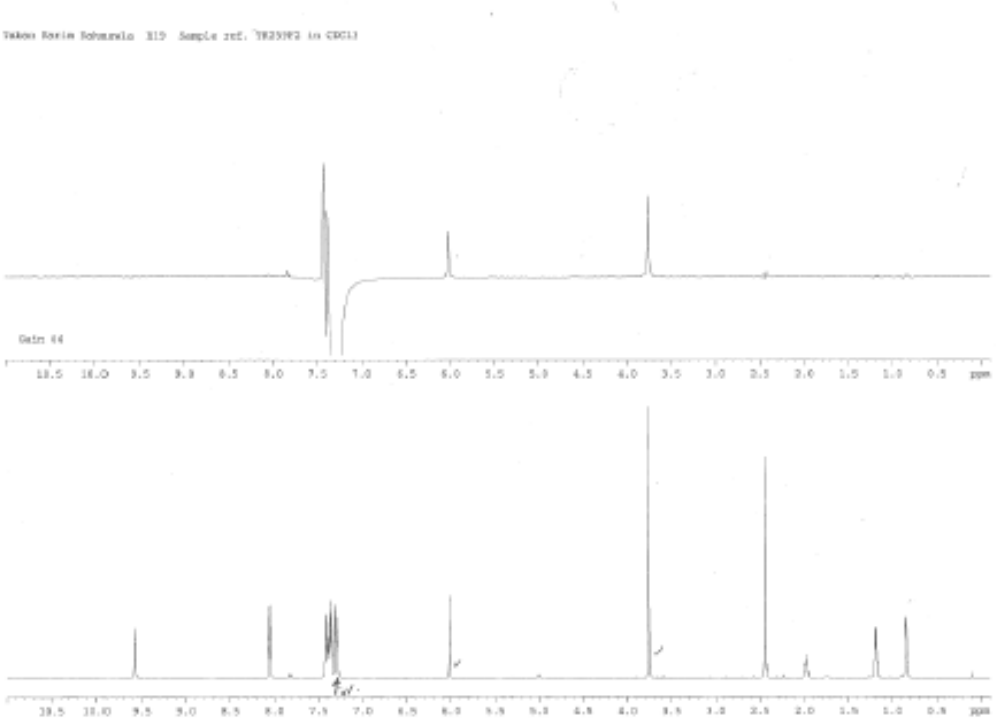
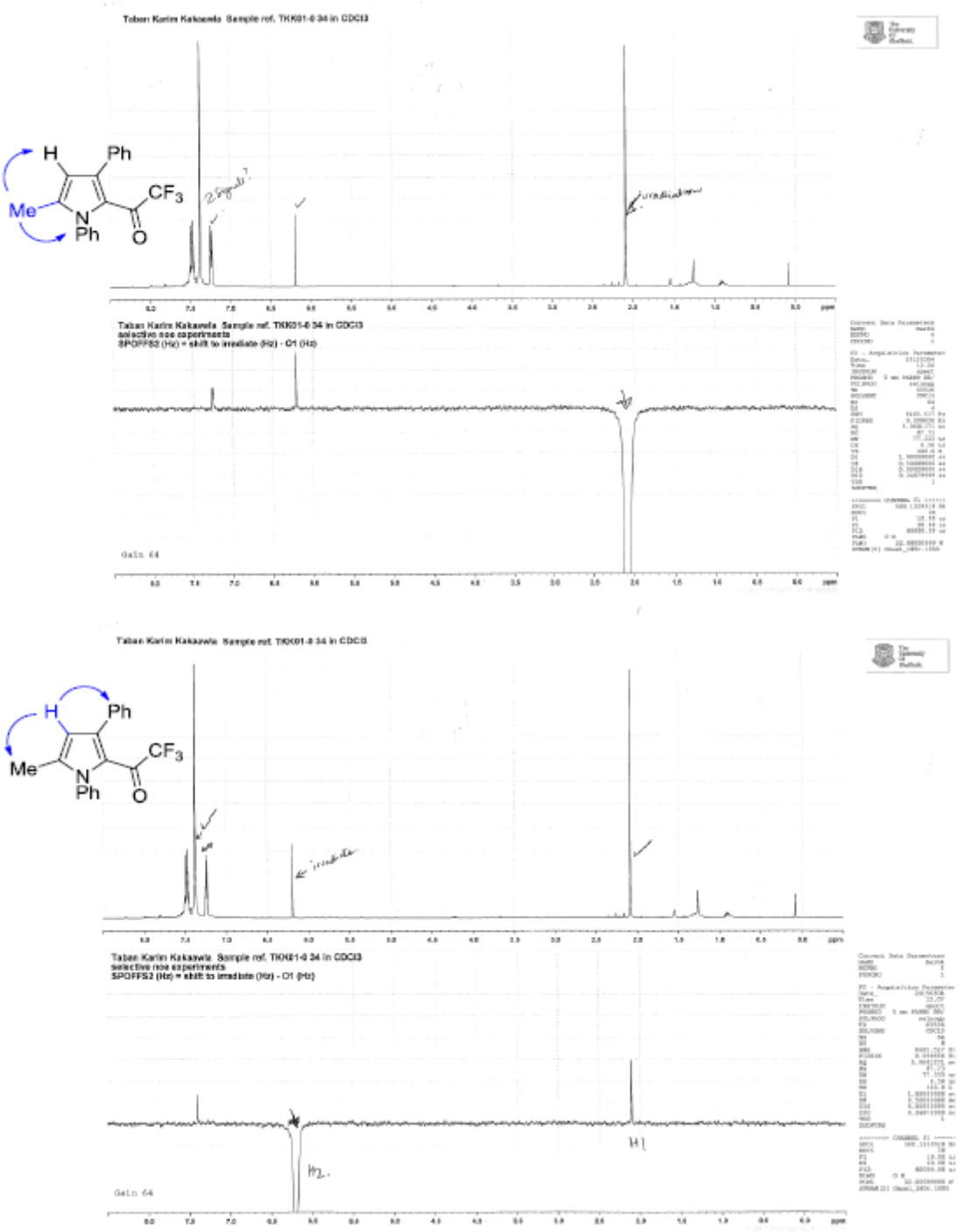
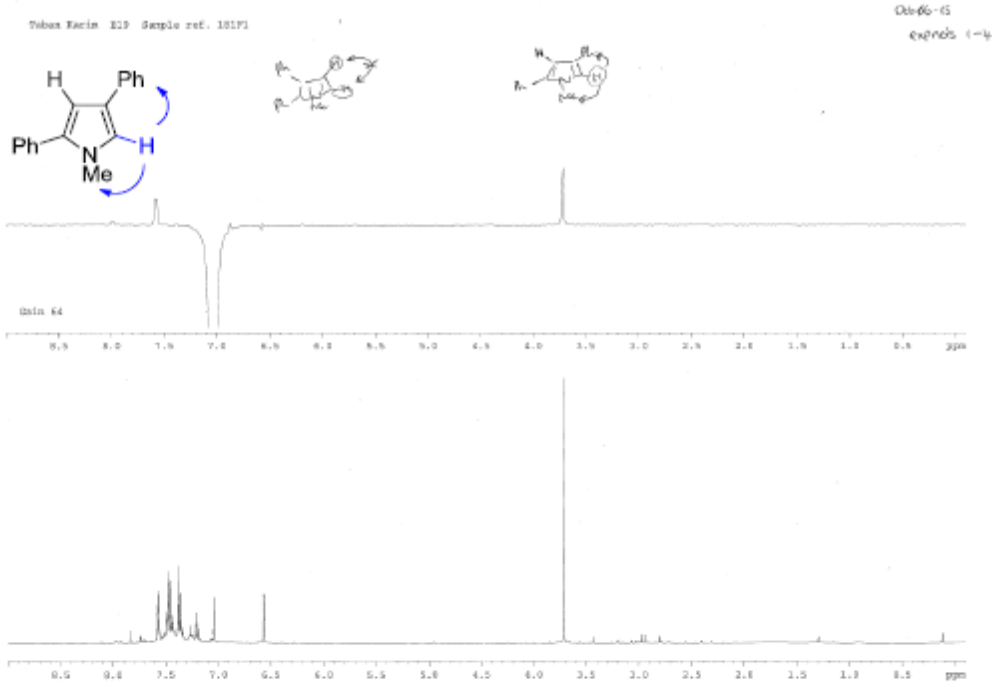
Me
N(H)Ts
O

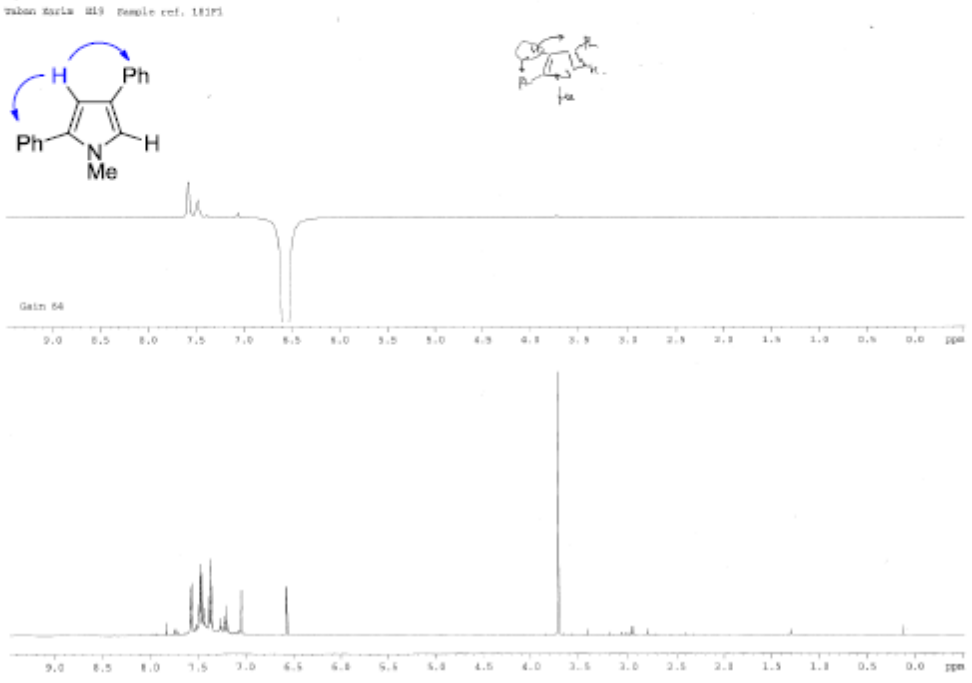


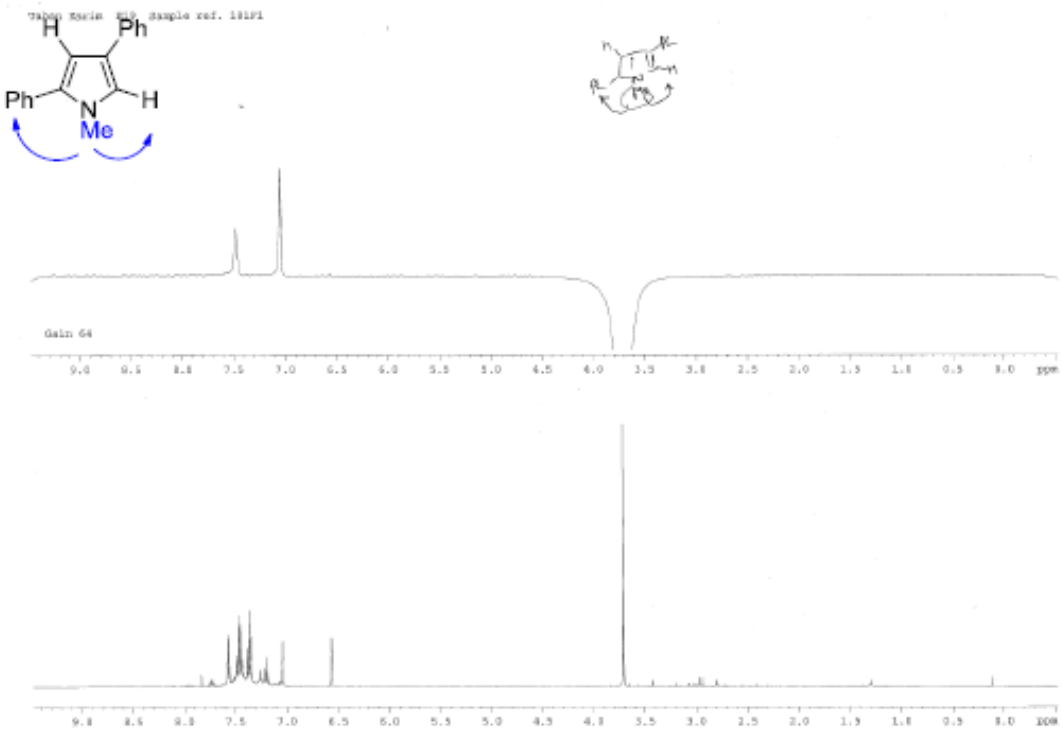
❖ nOe spectra of **119.**



❖ nOe spectre of **128.**



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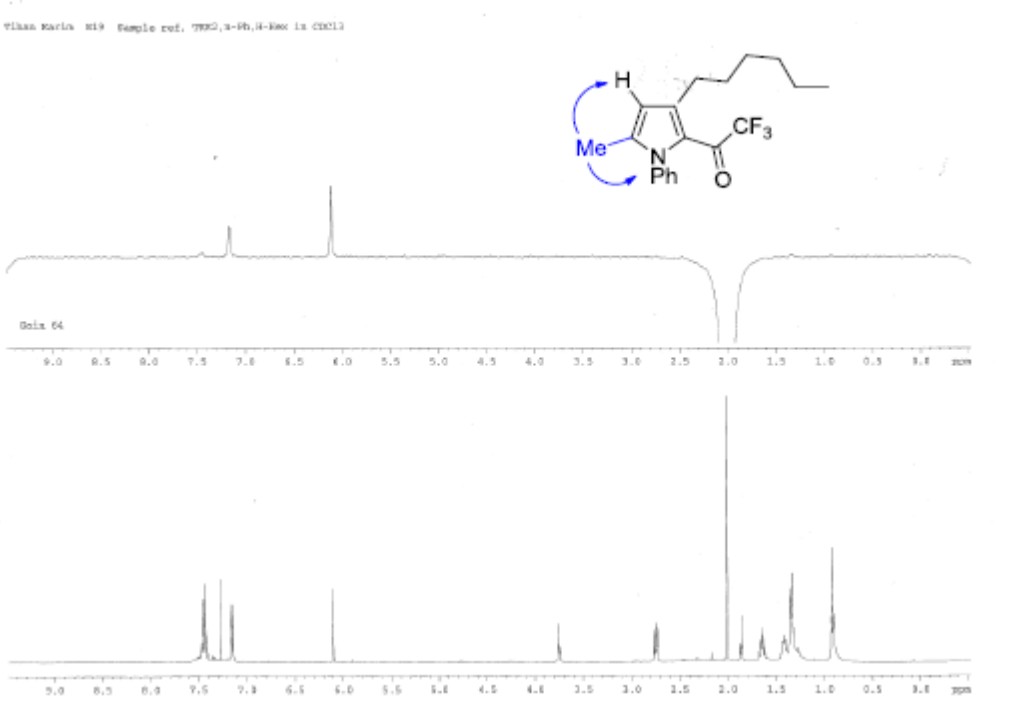
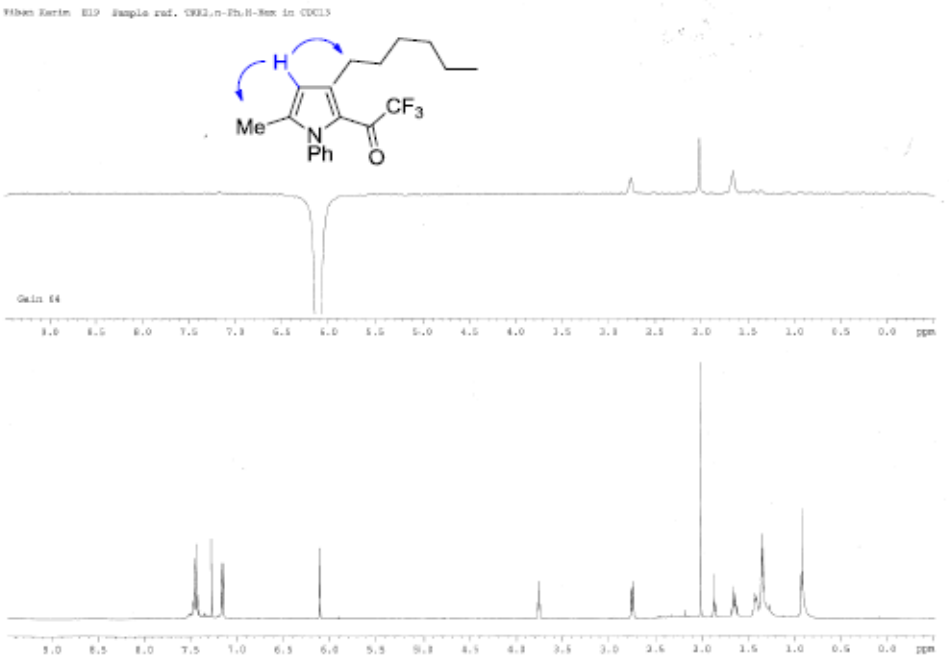
Ph
Ph
N
H
Me
Gain 64

❖ nOe spectra of **123.**





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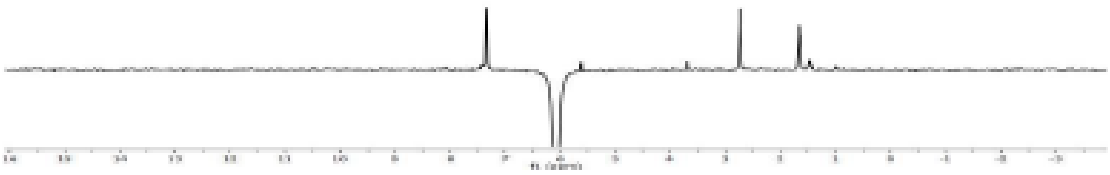
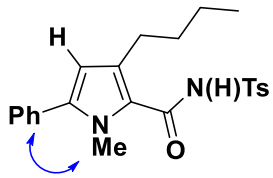
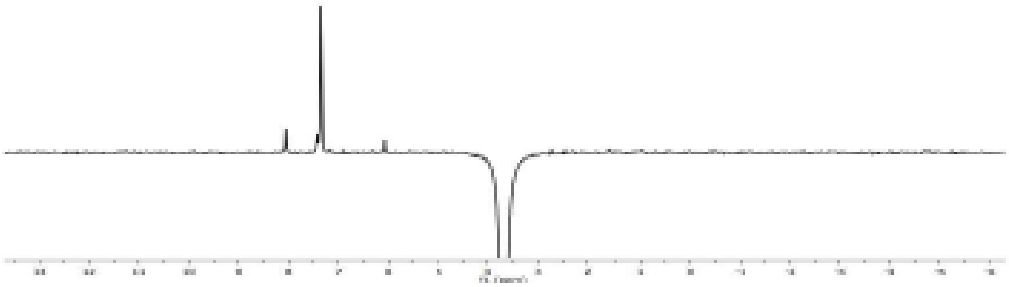
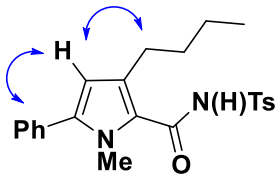
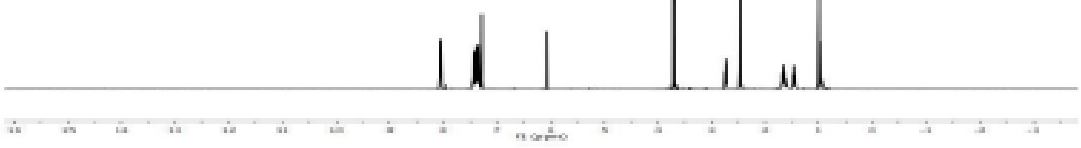


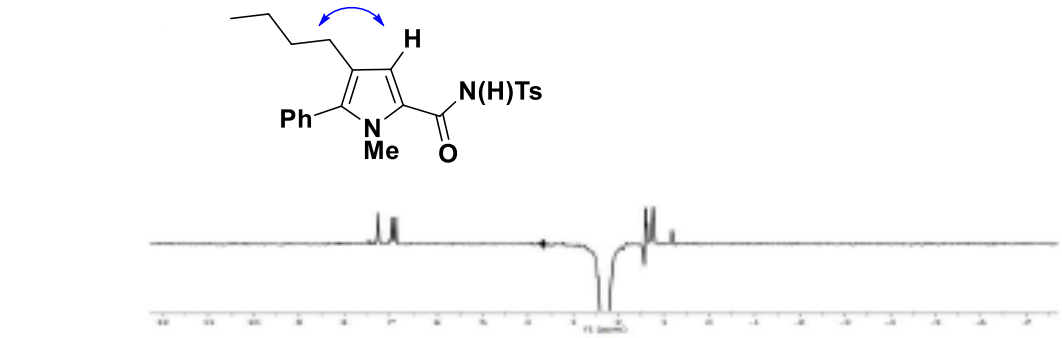


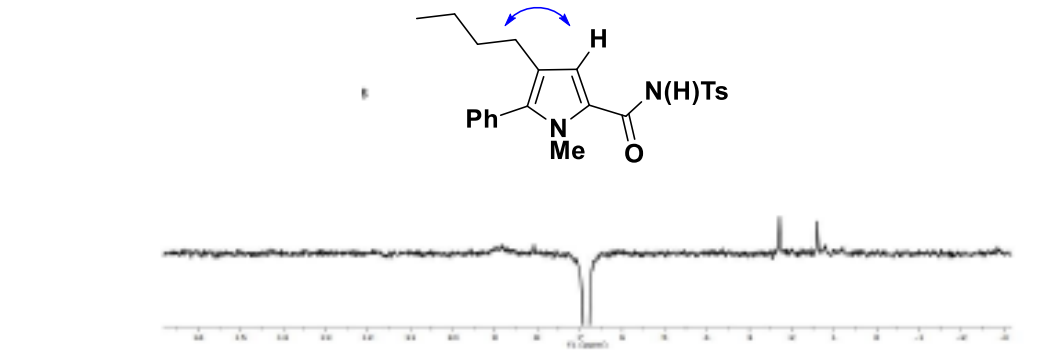


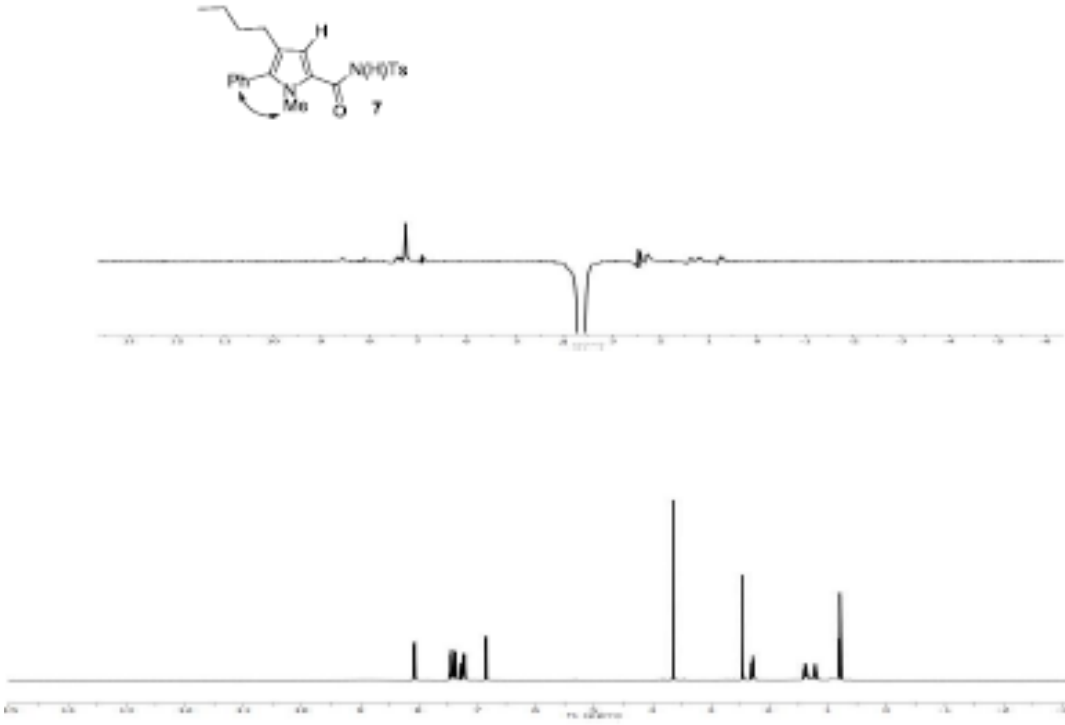




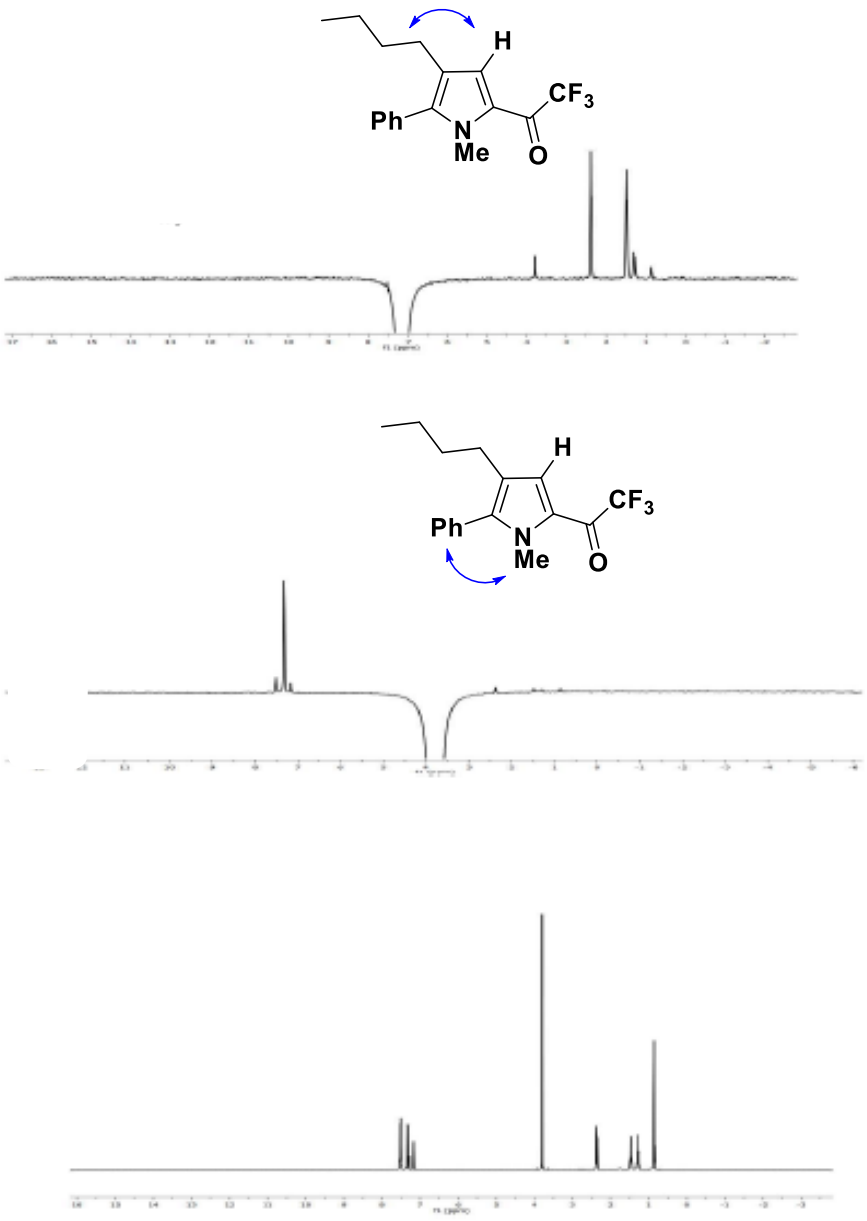
❖ nOe spectra 0f **175**.



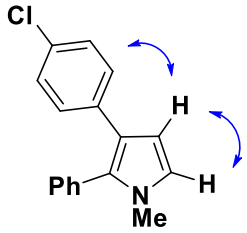


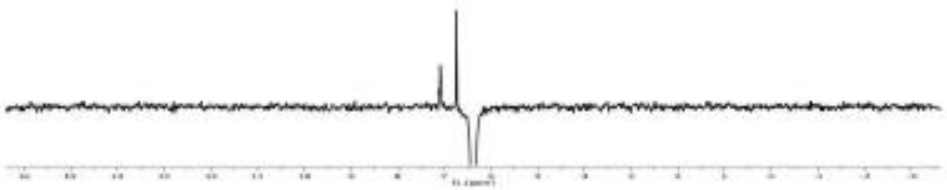


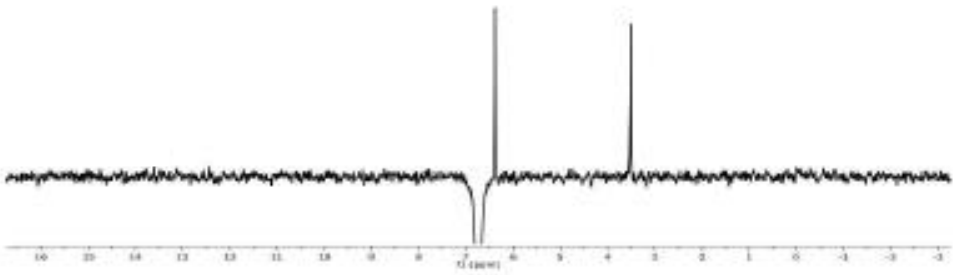
❖ nOe spectra of **190.**

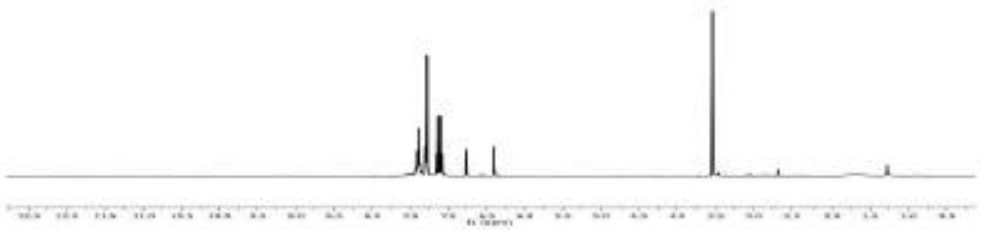


❖ nOe spectra of **196.**









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Communication

Cycloadditions

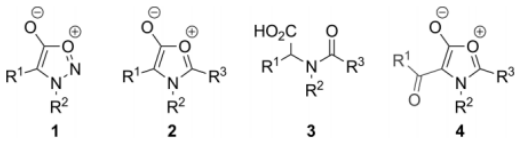
Synthesis and Cycloaddition Reactions of Stabilized Münchnones

Taban K. K. Kakaawla,[a] Will C. Hartley,[a] and Joseph P. A. Harrity*[a]

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

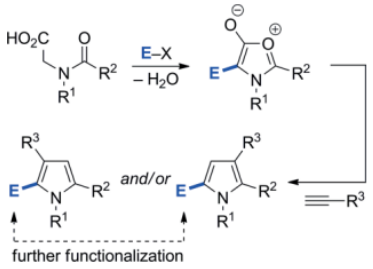
Introduction

Mesoionic compounds are five-membered dipolar heterocycles that have a rich source of chemistry, in particular with respect to reactivity and structure.[1] 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 5-oxides (münchnones) **2** have also attracted significant attention,[3] in particular in their transformation to pyrroles by cycloaddition/retrocycloaddition 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).



Scheme 1. Mesoionic heterocycles.

On the other hand, *stabilized* münchnones **4** bearing an acyl group at C4 can be significantly more stable than their non-acylated 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 pyrroles by alkyne cycloadditions has received scant attention,[6] and so the regioselectivity of this process has not been established. We therefore set out to explore the scope of alkyne cycloaddition reactions of stabilized münchnones, and report our results herein (Scheme 2).



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

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.[8] 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).

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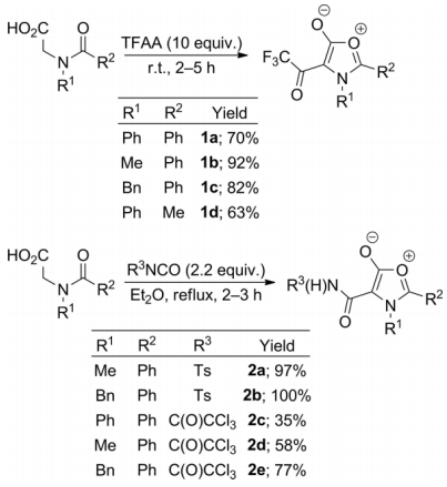
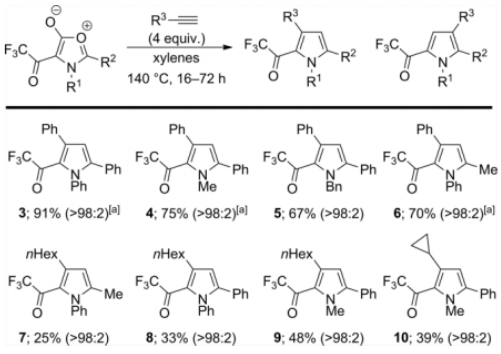


R^1	R^2	Yield
Ph	Ph	**1a**; 70%
Me	Ph	**1b**; 92%
Bn	Ph	**1c**; 82%
Ph	Me	**1d**; 63%

R^1	R^2	R^3	Yield
Me	Ph	Ts	**2a**; 97%
Bn	Ph	Ts	**2b**; 100%
Ph	Ph	$C(O)CCl_3$	**2c**; 35%
Me	Ph	$C(O)CCl_3$	**2d**; 58%
Bn	Ph	$C(O)CCl_3$	**2e**; 77%

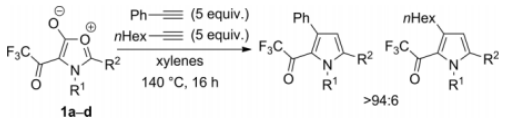
Scheme 3. Synthesis of stabilized münchnones.

With a selection of mesoionic compounds in hand, we turned our attention to the alkyne cycloaddition reactions of these compounds. We began our studies by exploring the reactivity of 4-trifluoroacetylated substrates, and our results are shown in Scheme 4. Münchnones **1a–d** underwent efficient reaction with phenylacetylene after heating in xylenes to give the corresponding pyrroles **3–6** in good yields. Moreover, we were delighted to find that the products were generated as single regioisomers. 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.[9]



Scheme 4. Cycloaddition reactions of 4-trifluoroacetylated münchnones. [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 münchnones **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 aryl-substituted alkyne (Scheme 5).



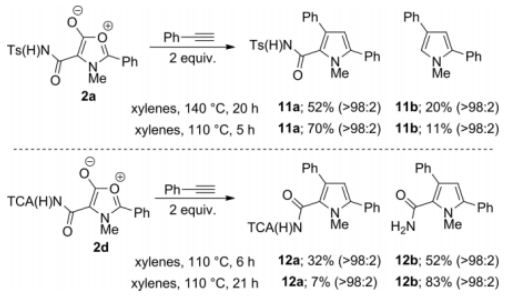
Scheme 5. Relative reactivity of phenylacetylene and 1-octyne.

We next opted to explore the cycloaddition reaction of the C4-imide-substituted münchnones and began with sulfonimide **2a** and trichloroacetimide **2d**, and using phenylacetylene 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 phenylacetylene also produced two pyrrole products. In this case amide **12b** was the predominant product when the reaction mixture was heated in xylenes 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 münchnones **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.

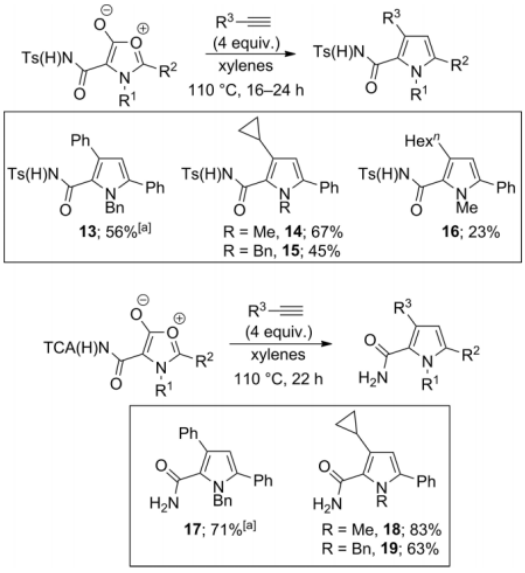
We were pleased to note that the reaction regioselectivities are uniformly high across all substrates examined. Interestingly, the incorporation of the stabilizing groups does not appear to play a significant role with respect to regiochemistry, and the trends observed here reflect the known regiochemical alkyne insertion patterns of arylacetylenes, whereby the initial cycloaddition takes place to connect the substituted alkyne carbon atom to the münchnone C4 position.[10]

The cycloaddition reactions shown in Schemes 4, 6 and 7 highlighted that the incorporation of electron-deficient groups

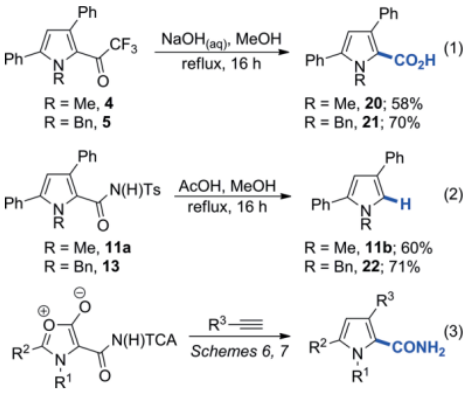


Scheme 6. Cycloaddition reactions of 4-imide-substituted münchnones. Ts = 4-tolylsulfonyl; TCA = trichloroacetyl.

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 fate of the stabilizing group. In contrast to trifluoroacetate, which proved to be stable to the reaction conditions, the *N*-acylsulfonamide underwent partial cleavage of the directing group, while the trichloroacetimide 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 8. 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*-acylsulfonamides **11a** and **13** resulted in 5*H*-pyrroles **11b** and **22** [Equation (2)]. This latter process highlighted the potential of *N*-acylsulfonamides as traceless münchnone-stabilizing groups. Finally, Equation (3) summarizes our finding that trichloroacetimides function as primary amide equivalents in the alkyne cycloaddition process.



Scheme 7. Cycloaddition scope of imide-substituted münchnones. Ts = 4-tolylsulfonyl; TCA = trichloroacetyl. [a] 2 equiv. of alkyne used in these cases.



Scheme 8. Manipulation of the directing group. Ts = 4-tolylsulfonyl; TCA = trichloroacetyl.

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 cyclodehydration functionalization reaction. The cycloadditions are highly regioselective and provide direct access to densely substituted functionalized pyrroles. 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-1*H*-pyrrole (3): A solution of 2,3-diphenyl-4-trifluoroacetyl-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 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. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.42 (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. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 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 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –71.4 ppm. FTIR: $\tilde{\nu}$ = 1661 (s), 1596 (m), 1272 (s), 1239 (s), 1195 (s) cm^{-1}. HRMS: calcd. for $C_{19}H_{15}NOF_3$ 330.1106, found 330.1099.

Acknowledgments

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Keywords: Münchnones · Cycloaddition · Pyrroles · Regioselectivity · Heterocycles

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Development of an Amine-Catalyzed Regioselective Synthesis of Pyrroles

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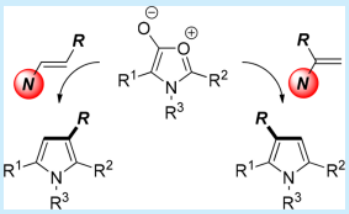
Supporting Information

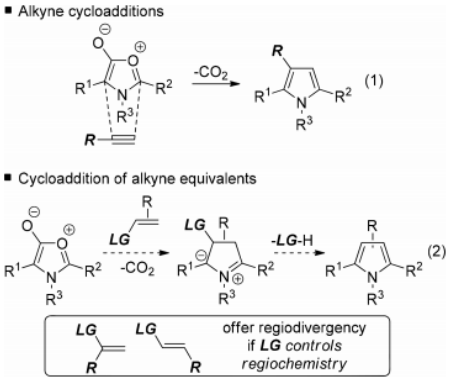
ABSTRACT: A regioselective synthesis of pyrroles has been devised through the cycloaddition of 1,3-oxazolium-5-olates and enamines. Product regiochemistry is controlled by the enamine substitution pattern. Moreover, an amine-catalyzed variant of this reaction allows aldehydes to be used directly as substrates 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.[1] The synthesis of pyrroles by traditional electrophilic aromatic substitution processes is complicated by their high reactivity, often rendering these processes difficult to control.[2] 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-oxazolium-5-olates) represent an interesting class of mesoionic heterocycles and they are known to furnish pyrroles upon cycloaddition reactions with alkynes.[3] These processes allow complex substitution patterns to be assembled very easily, and the reactions can be quite regioselective, especially when arylacetylenes are employed.[4] 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 cycloadduct reveals a dipolar intermediate that can undergo several other reactions including proton transfer (with or without ring oxidation)[5] or further cycloaddition,[6] and these can be difficult to control.[7] However, the use of alkenes 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 alkyne cycloadditions (Scheme 1, eq 2). The veracity of this idea has been demonstrated using β-nitrostyrenes, albeit with variable levels of regiocontrol.[8] 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.

Scheme 1. Cycloadditions of Alkynes and Alkyne Equivalents with Münchnones



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.[9] 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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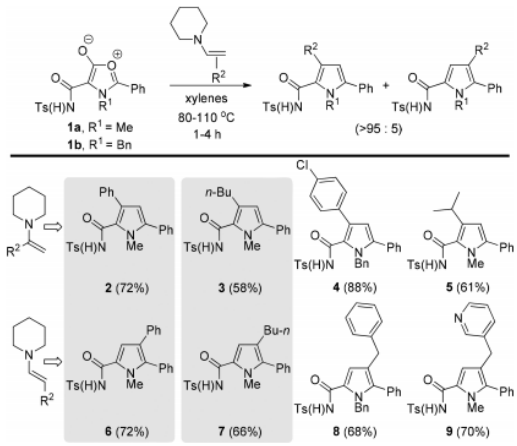
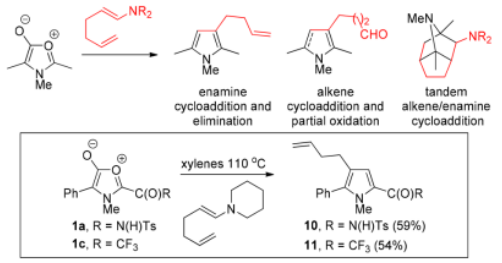
Scheme 2. Regioselective Cycloadditions of Enamines with Münchnones



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 nonchemoselective cycloaddition of münchnones and 1-

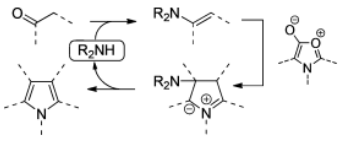
Scheme 3. Relative Reactivity of Alkenes versus Enamines



aminohexa-1,5-dienes could give rise to a range of products (formation of regioisomers is also possible although not explicitly shown).[10] In the event, the reaction of substrates **1a,c** with 1-piperidyl hexa-1,5-diene provided pyrroles **10** and **11** in reasonable yields, as single regioisomers. We noted the presence of several minor byproducts in the crude material; however, products of cycloaddition with the alkene could not be identified. Therefore, although we have been unable to rule out the potential side reactions indicated in Scheme 3, it appears that they do not significantly compete with the enamine cycloaddition−elimination pathway.

The enamines employed in the cycloaddition reactions were accessed by simple condensation chemistry, and so the amine used at the start of the sequence was ultimately expelled during the cycloaddition as depicted in Scheme 4. This raised the possibility that an amine-catalyzed variant of the cycloaddition could be devised whereby simple carbonyl compounds

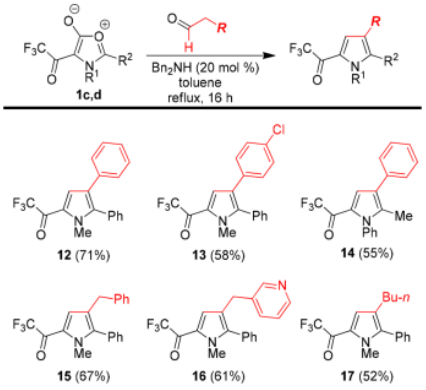
Scheme 4. Role of the Amine in the Overall Transformation



functioned as alkyne equivalents in the cycloaddition reaction.[11,12] We decided to focus on acetaldehyde derivatives as these would be expected to rapidly form 2-substituted enamines in solution, thereby generating pyrroles with complementary regioselectivity to that of alkyne cycloadditions.

Pleasingly, preliminary optimization studies showed that a range of secondary amines were effective for the catalytic cycloaddition of aldehydes, with dibenzylamine proving to be the most efficient. Exploring the scope of the reaction using stable 4-trifluoroacetyl-substituted münchnones highlighted that the process was compatible with aldehydes bearing a range of alkyl and aryl substituents, providing the corresponding pyrroles as single regioisomers (Scheme 5).[13]

Scheme 5. Amine-Catalyzed Cycloaddition of Aldehydes and Münchnones



Extending this study to the imide-substituted mesoionic 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.

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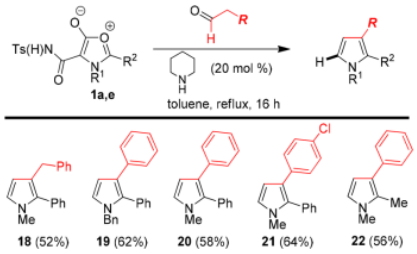
Scheme 6. Amine-Catalyzed Synthesis of 1,2,3-Substituted Pyrroles



Moreoever, this method accesses products with complementary regiochemistry to that of alkyne cycloadditions.

■ ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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