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Development of an Amine-Catalyzed Regioselective Synthesis of Pyrroles

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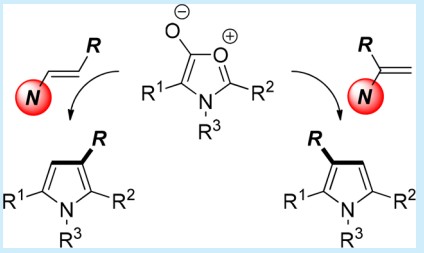
Supporting Information

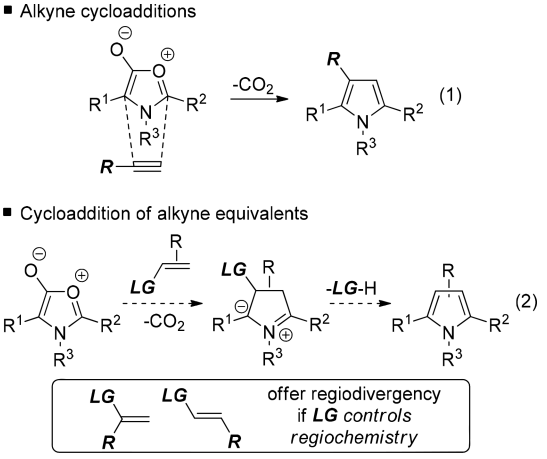
ABSTRACT: A regioselective synthesis of pyrroles has been devised through the cycloaddition of 1,3-oxazolium-5-olates and enamines. Product regiochemistry is controlled by the enamine substitution pattern. Moreover, an amine-catalyzed variant of this reaction allows aldehydes to be used directly as substrates 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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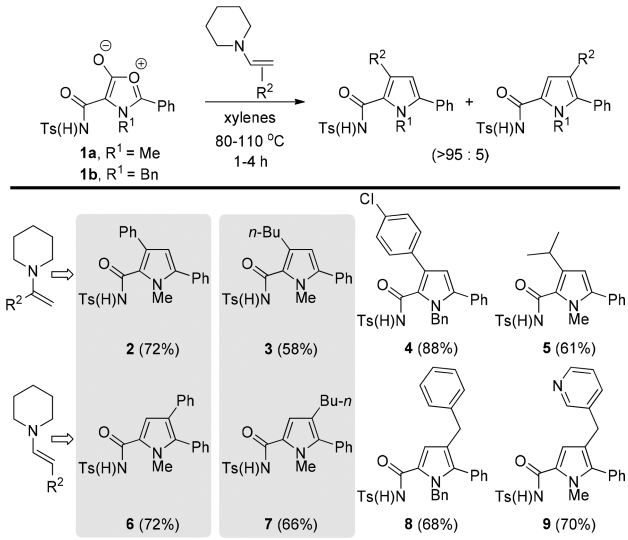
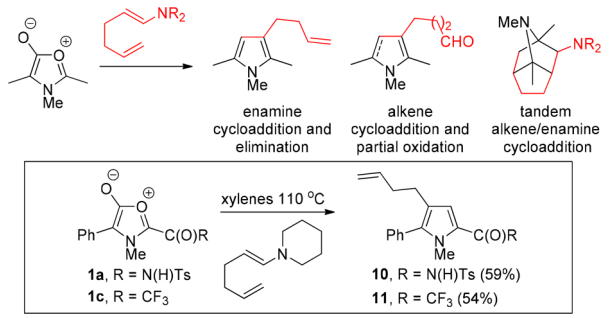
Scheme 2. Regioselective Cycloadditions of Enamines with Münchnones



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-

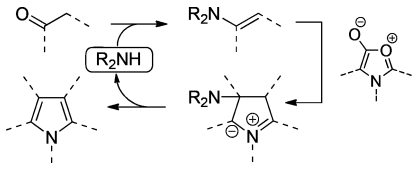
Scheme 3. Relative Reactivity of Alkenes versus Enamines



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

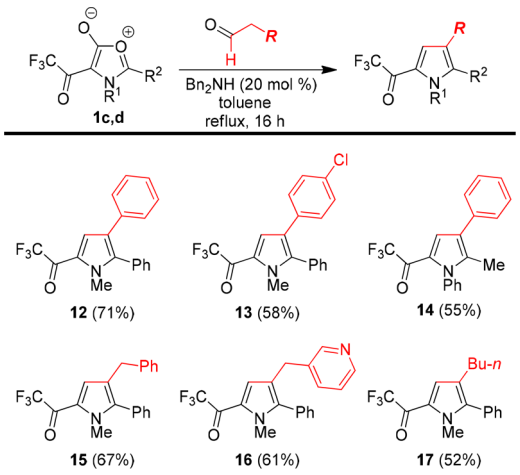
Scheme 4. Role of the Amine in the Overall Transformation



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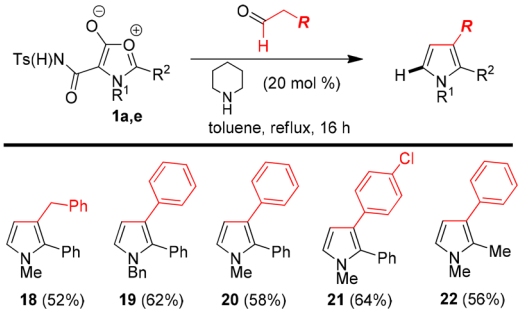
Scheme 6. Amine-Catalyzed Synthesis of 1,2,3-Substituted Pyrroles



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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(12) For a complementary catalytic pyrrole synthesis, see: Donohoe, T. J.; Race, N. J.; Bower, J. F.; Callens, C. K. A. *Org. Lett.* **2010**, *12*, 4094.

(13) The regiochemistry of pyrroles **3**, **7**, **17**, and **21** were assigned by NOE spectroscopy, and those of **19** and **20** were based on comparison with literature data. Other regiochemical assignments were made by inference.

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