ChemPubSoc Europe

DOI: 10.1002/ejoc.201600486

EurJOC European Journal of Organic Chemistry

Communication

Cycloadditions

Synthesis and Cycloaddition Reactions of Stabilized Münchnones

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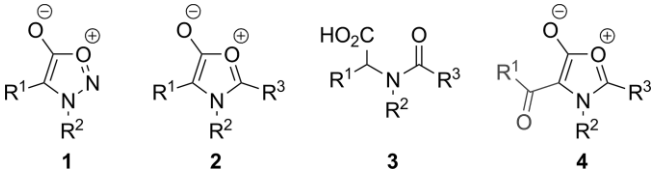
Abstract: A family of stabilized münchnones bearing an acyl group at C4 have been prepared and studied in alkyne cycloaddition reactions. These reactions are highly regioselective, and the method represents a rapid and straightforward route to densely substituted pyrroles. Finally, the C4-stabilizing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

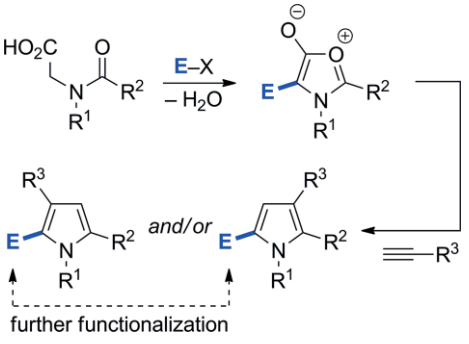
Introduction

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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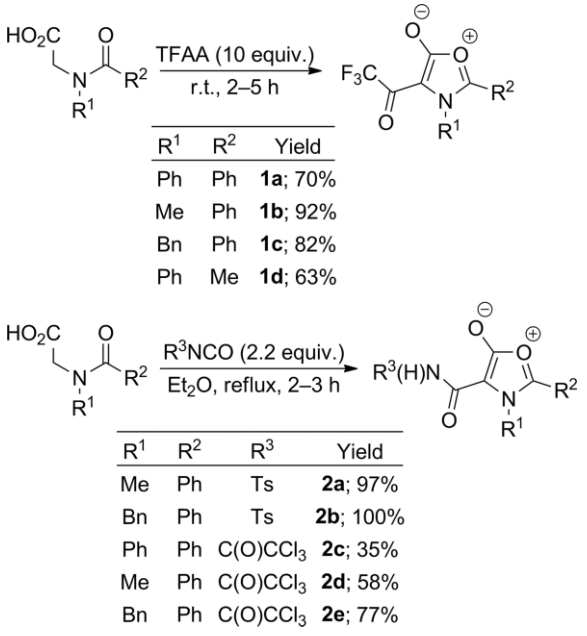
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201600486.

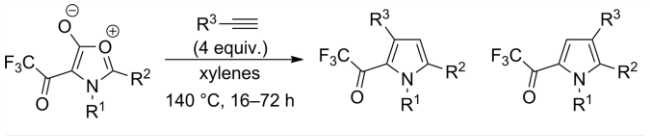


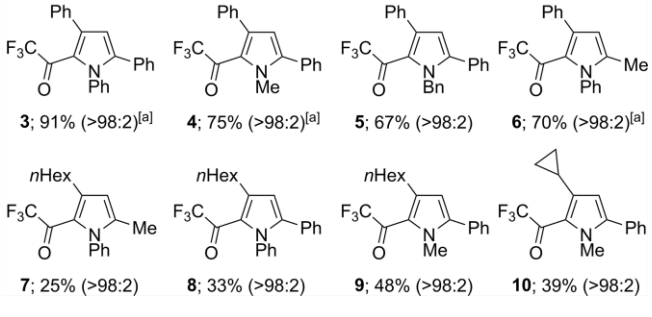
R^1	R^2	Yield
Ph	Ph	**1a**; 70%
Me	Ph	**1b**; 92%
Bn	Ph	**1c**; 82%
Ph	Me	**1d**; 63%

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.

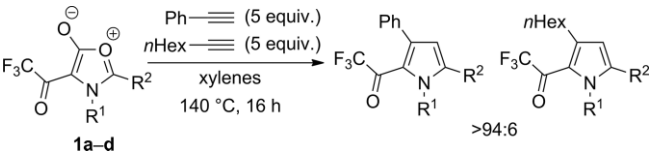
With a selection of mesoionic compounds in hand, we turned our attention to the alkyne cycloaddition reactions of these compounds. We began our studies by exploring the reactivity of 4-trifluoroacetylated substrates, and our results are shown in Scheme 4. Münchnones **1a**–**d** underwent efficient reaction 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).



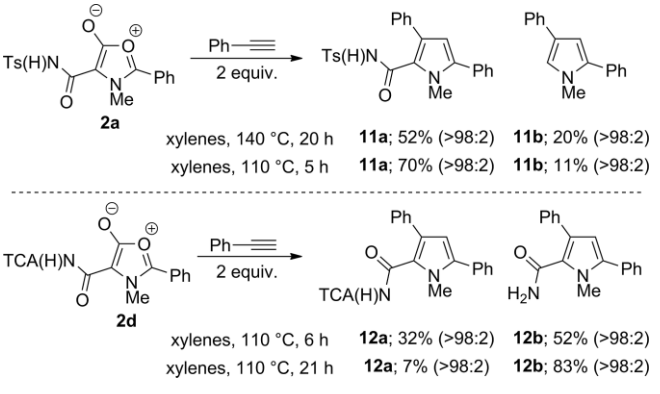
Scheme 5. Relative reactivity of phenylacetylene and 1-octyne.

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.

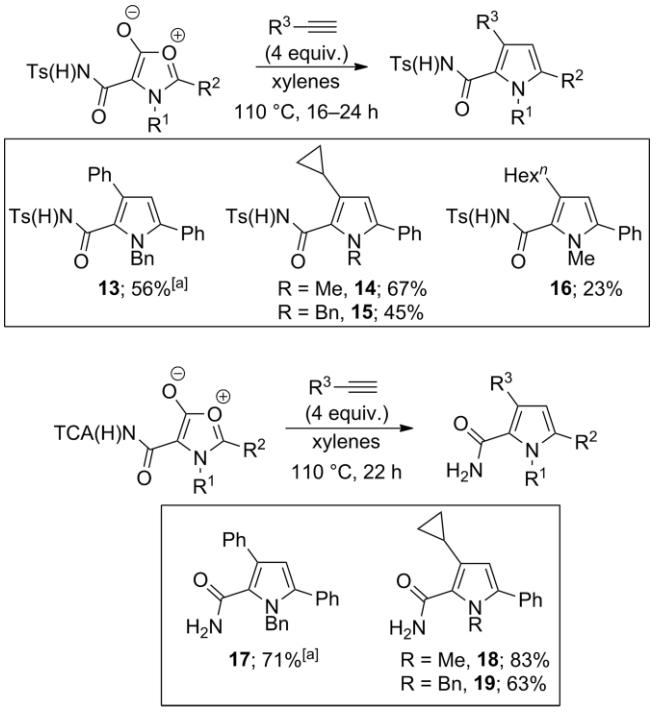
We were pleased to note that the reaction regioselectivities are uniformly high across all substrates examined. Interestingly, the incorporation of the stabilizing groups does not appear to play a significant role with respect to regiochemistry, and the trends observed here reflect the known regiochemical 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

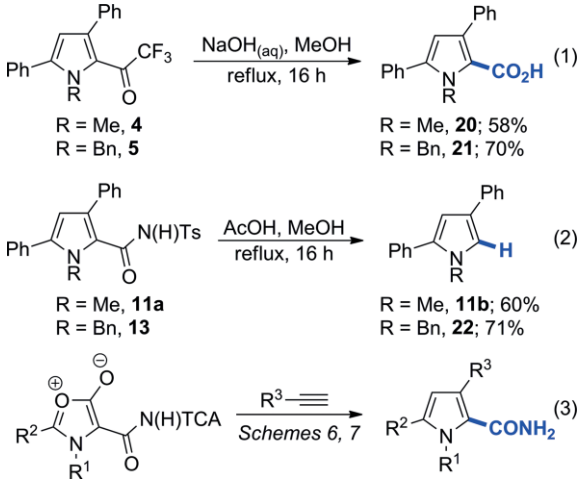


Scheme 6. Cycloaddition reactions of 4-imide-substituted münchnones. Ts = 4-tolylsulfonyl; TCA = trichloroacetyl.

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

We are grateful to The Higher Committee for Education Development in Iraq and the University of Sheffield SURE Scheme for financial support.

Keywords: Münchnones · Cycloaddition · Pyrroles · Regioselectivity · Heterocycles

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Received: April 19, 2016
Published Online: May 20, 2016

