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A General and Regioselective Synthesis of 5-Trifluoromethyl-pyrazoles

Robert S. Foster,[†] Harald Jakobi,[‡] and Joseph P. A. Harrity*[,†]

Department of Chemistry, University of Sheffield, Sheffield, S3 7HF, U.K., and Bayer CropScience AG, Research – Weed Control Chemistry, 65926 Frankfurt am Main, Germany

j.harrity@sheffield.ac.uk

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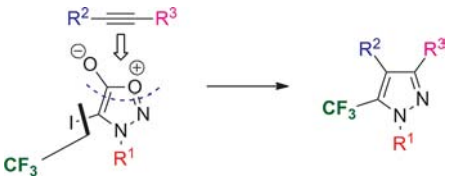
ABSTRACT



Two synthetic approaches to 4-trifluoromethylsydnones, a novel class of these mesoionic reagents, are reported. These compounds undergo regioselective alkyne cycloaddition reactions, thereby providing a general approach to 5-trifluoromethylpyrazoles. This method has been employed in a short formal synthesis of the herbicide fluazolate.

Pyrazoles bearing fluorocarbon substituents are becoming increasingly prevalent as synthetic targets and building blocks within the fine chemicals sector.[1] Many examples of bioactive fluorinated pyrazoles have emerged in recent years, and among these, the NSAID celecoxib (Celebrex)[2] and the herbicide fluazolate[3] (Figure 1) are particularly noteworthy examples.

Pyrazoles are most commonly accessed via cyclocondensation of a hydrazine with 1,3-diketones or α,β-unsaturated carbonyl compounds. However, this approach often suffers from the formation of regioisomeric mixtures with respect to substituents incorporated at the pyrazole 3- and 5-positions.[4] In the context of trifluoromethylpyrazoles, these compounds are typically synthesized using 1,1,1-trifluoromethyl-1,3-diketones, as this approach exploits the ready availability of trifluoroacetic acid derived precursors.[5] Such reactions also very often provide mixtures, although some regiocontrol can be achieved by careful choice of solvent.[6]

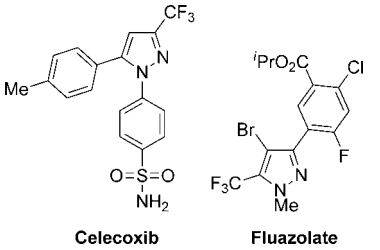


Figure 1. Bioactive trifluoromethylpyrazoles.

[†] University of Sheffield.
[‡] Bayer CropScience AG.

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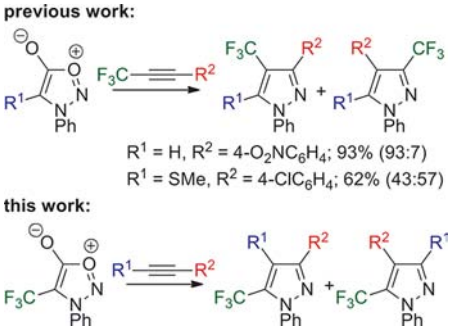
The preparation of pyrazoles via cycloaddition of alkynes with sydnones represents a convenient approach for the regioselective synthesis of these azoles.[7,8] In this regard, Meazza reported the synthesis of 3- and 4-trifluoromethylpyrazoles through cycloadditions with trifluoromethylacetylenes,[9] complementing traditional approaches to these motifs. However, elaboration of this chemistry to provide the analogous 5-trifluoromethylpyrazoles has not been developed (Scheme 1).

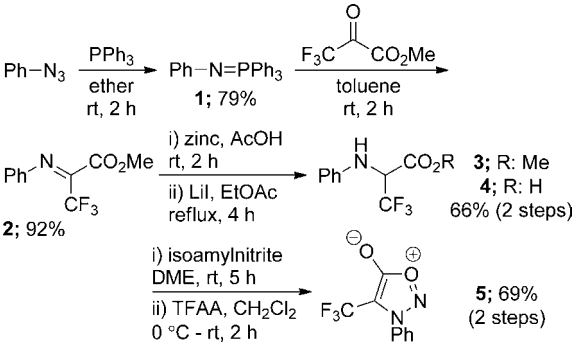
Scheme 1. Trifluoromethylpyrazoles from Sydnones



Recent studies in our laboratory have endeavored to develop the scope of sydnone functionalization and alkyne cycloaddition chemistry, with the goal of establishing this area as enabling chemistry for pyrazole synthesis.[10] We envisaged that this chemistry could provide a convenient and general solution to the regiocontrolled synthesis of 5-trifluoromethylpyrazoles. Our studies toward this end are outlined herein.

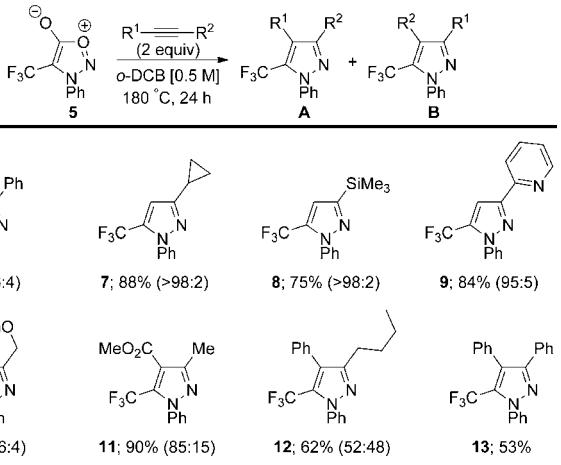
We began our investigations by developing a scalable route to the requisite 4-trifluoromethylsydnone, and our results are shown in Scheme 2. Condensation of iminophosphorane **1** with methyl trifluoromethylpyruvate furnished imine **2**,[11] which was reduced to the amino ester **3** using zinc metal.[12] Hydrolysis of **3** proved to be challenging; saponification provided a complex mixture whereas hydrolysis under acid catalysis proved to be capricious. Ultimately, however, we found that heating the amino ester **3** at reflux with lithium iodide in ethyl acetate for 4 h[13] consistently delivered the amino acid **4** in 85% yield. Finally, 4-trifluoromethyl-*N*-phenylsydnone **5** was prepared from **4** using the standard method of nitrosation followed by cyclodehydration. This procedure allowed gram quantities of **5** to be produced in an overall yield of 33%.

Scheme 2. Synthesis of 4-Trifluoromethylsydnone **5**



The cycloaddition of 4-CF_3 substituted sydnone **5** with alkynes was investigated, and our results are summarized in Scheme 3. We were pleased to find that the reaction was quite general, furnishing a selection of *N*-phenyl-5-trifluoromethyl pyrazoles in good yields and with excellent regiocontrol. In this respect, the selectivity of formation of **9** is notable; cycloadditions of 4-Me- and 4-Pr^i-substituted sydnones with 2-pyridylacetylene proceed with lower levels of regiocontrol (< 6:1)[10f] suggesting that the CF_3-group can enhance cycloaddition regioselectivity in some cases. The reaction was also found to proceed with disubstituted alkynes, although the products were formed with lower levels of selectivity in unsymmetrical cases.

Scheme 3. Regioselective Synthesis of 5-Trifluoromethylpyrazoles[a]



[a] Values in parentheses refer to **A:B** selectivities. *o*-DCB = 1,2-dichlorobenzene.

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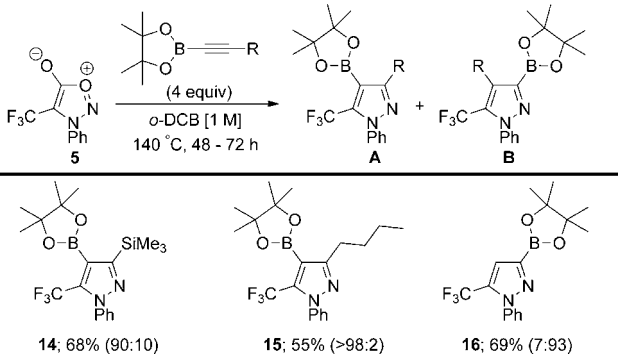
To improve regioselectivities in the formation of tetrasubstituted pyrazoles, we opted to explore the use of alkynylboronates, as these typically afford high selectivites for the 4-borylated isomer.[10d,f] In the event, the reactions required heating at 140 °C over a period of 48−72 h (Scheme 4); however, the corresponding products were generated in good yield and with useful levels of regiocontrol. Notably, the terminal alkyne exhibited the opposite regiochemical insertion mode, inline with our previous observations.

Scheme 4. Synthesis of 5-Trifluoromethylpyrazole Boronic Esters[a]



[a] Values in parentheses refer to **A:B** selectivities. *o*-DCB = 1,2-dichlorobenzene.

With respect to implementing a general approach to trifluoromethyl pyrazoles, the route outlined in Scheme 2 has the limitation that the *N*-substituent is incorporated early on and carried through a number of steps before the alkyne cycloaddition reaction. We envisaged that a more convenient strategy would be to develop a late-stage trifluoromethylation of sydnones, as this would provide a simpler means to incorporate a range of *N*-substituents.

By analogy to studies highlighting the successful trifluoromethylation of aryl iodides,[14] we chose to investigate the trifluoromethylation of 4-iodo-*N*-phenylsydnone **17**. Our results are summarized in Table 1. Copper-promoted trifluoromethylations using Ruppert's reagent are perhaps the most widely used; however, the reaction gave only the parent sydnone **18** under a range of conditions. Similarly Goossen's[15] copper-catalyzed trifluoromethylation using the potassium salt of Ruppert's reagent[16] did not result in 4-CF_3 sydnone **5**, and the transformation also failed when sodium trifluoromethylacetate was used as the CF_3 source. In contrast however, treatment of **17** with methyl

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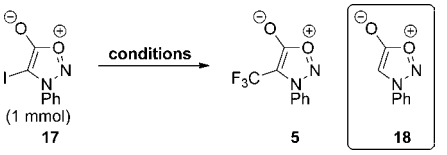
Table 1. Trifluoromethylation of 4-Iodo-*N*-phenylsydnone **17**



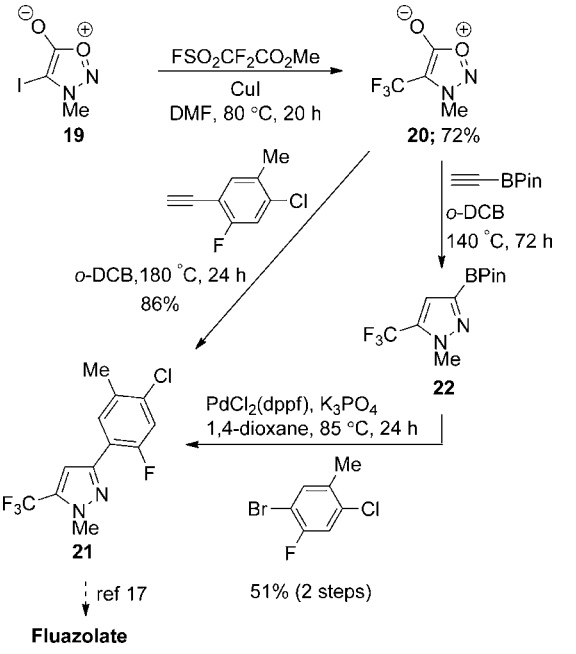
conditions	yield of **5** (%)
$TMSCF_3$ (5 equiv), CuI (1 equiv), KF (1 equiv), DMF, air, 100 °C, 24 h	0
$CF_3B(OMe)_3K$ (1 equiv), CuI (0.1 equiv), phen. (0.1 equiv), DMSO, 60 °C, 48 h, sealed tube	0
CF_3CO_2Na (1 equiv), CuI (1 equiv), NMP, 160 °C, 4 h	0
$FSO_2CF_2CO_2Me$ (5 equiv), CuI (1 equiv), DMF, 80 °C, 20 h	60
$FSO_2CF_2CO_2Me$ (5 equiv), CuI (1 equiv), DMF, 80 °C, 20 h[a]	79

[a] 5 mmol scale.

fluorosulfonyldifluoroacetate and copper iodide yielded **5**, and optimization of this reaction delivered the product in consistently high yields.

Finally, we wanted to demonstrate the applicability of the direct trifluoromethylation and cycloaddition methods in target synthesis, and we opted to explore the synthesis of fluazolate. Our synthetic route is outlined in Scheme 5. Pleasingly, the direct trifluoromethylation could be extended

Scheme 5. Formal Synthesis of Fluazolate[a]



[a] *o*-DCB = 1,2-dichlorobenzene.

to *N*-Me sydnone **19** and delivered the corresponding CF_3-substituted mesoionic reagent **20** in good yield. The key fluazolate intermediate **21** could be accessed directly by a regioselective cycloaddition with 1-chloro-4-ethynyl-5-fluoro-2-methylbenzene in 86% yield. Fluazolate is subequently prepared by bromination of the pyrazole ring followed by oxidation of the arylmethyl group and esterification of the resulting benzoic acid.[17] However, our strategy also has the flexibility to offer further diversification of the 3-aryl moiety by employing alkynylboronates in the cycloaddition. In the event, pyrazole boronic ester **22** was prepared from sydnone **20** in low yield (44%) because of the tendency of this compound to undergo rapid protodeboronation during chromatography. Accordingly, a telescoped cycloaddition–coupling was attempted that delivered **21** in an acceptable overall yield, thereby confirming the potential of this approach to generate fluazolate analogs.

In conclusion, we have demonstrated that 4-trifluoromethylsydnones can be prepared by ring synthesis and ring functionalization approaches. These compounds function as valuable precursors to 5-trifluoromethylpyrazoles via highly regioselective cycloaddition reactions.

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Supporting Information Available. Full experimental details for the syntheses reported are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.