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Expanding available pyrazole substitution patterns by sydnone cycloaddition reactions

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ABSTRACT

We report the use of alkynylsilanes for the regiocontrolled synthesis of pyrazoles from functionalised sydnones. The strategies outlined herein allow a range of pyrazoles to be accessed with substitution patterns that are otherwise not directly obtained with high selectivity by alkyne cycloadditions. Moreover, this study serendipitously highlighted a simple and convenient procedure for the synthesis of aryl monofluoromethyl ethers through the combination of TBAF and dichloromethane.

1. Introduction

Pyrazoles are a privileged class of heteroaromatic compounds and they constitute the core motif of a number of compounds of medicinal and agrochemical significance.[1] Classical approaches to pyrazoles have broadly encompassed condensation and cycloaddition reactions.[2] Work in our labs has sought to exploit both strategies for the direct formation of borylated pyrazoles where the borate is introduced during annelation, rather than through ring functionalisation.[3] With respect to cycloadditions, sydnones have emerged as effective precursors to pyrazoles, and they offer a regiocontrolled route to 1,3-disubstituted and 1,3,5-trisubstituted diazoles when reacted with terminal alkynes.[4] This product substitution pattern is the result of the innate selectivity of alkyne cycloadditions with 4-*H* and 4-substituted sydnone substrates. We have been interested in developing strategies that overturn this innate selectivity, and report herein how alkynylsilanes can access alternative substitution patterns, thereby expanding the scope of sydnone cycloaddition methodology for pyrazole synthesis (Scheme 1).[5]

2. Results and discussion

2.1. 1,5-Disubstituted pyrazoles

We initially started our investigations into expanding the scope of the preparation of 1,5-disubstituted pyrazoles. Our strategy was to employ trimethylsilylacetylene as a non-gaseous acetylene equivalent in cycloaddition reactions of 4-substituted sydnones, which were in turn prepared by direct arylation[6] or by metalation chemistry. In all cases attempted, the cycloaddition proceeded efficiently and with high (albeit ultimately inconsequential) regioselectivity favouring the 3-substituted pyrazole (Scheme 2). In contrast, TBAF-mediated removal of the trimethylsilyl group proved somewhat less general. While pyrazoles **2**, **4** and **8** were successfully prepared in good yield (see below for discussion of compound **10**), Weinreb amide-substituted pyrazole **5** only afforded a complex mixture of products. Moreover, in the case of oxazoline-substituted pyrazole **11**, product **12** was afforded in only moderate yield.

These studies highlighted some unexpected outcomes in the TBAF mediated protodesilylation of 3-trimethylsilylpyrazoles. With regard to the low yield observed in the synthesis of **12**, we were able to isolate (23%, 1:1 *E*:*Z*) and characterise a major by-product of this reaction which proved to be nitrile **13** (Scheme 3). The isolation and characterisation of **13** highlights the propensity of electron deficient pyrazoles to undergo elimination under strongly basic conditions.[7]

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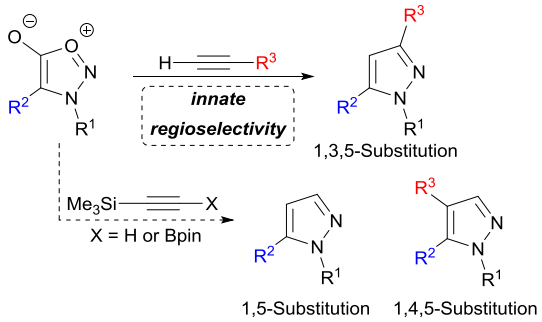
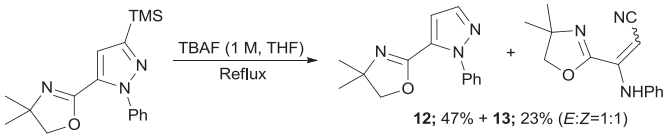


Scheme 1. Sydnone cycloadditions of alkynes to form pyrazoles.

With regard to the conversion of **9** → **10**, we noted that significantly lower yields of product were observed in the presence of CH_2Cl_2 (carried over from chromatography). Specifically, when **9** was subjected to refluxing TBAF solution, a small amount of **10** was isolated together with mono-fluoromethylated phenol **14**. In addition, fluoromethylation product **14** could be generated in higher yield when the reaction vessel was charged with dichloromethane, TBAF and heated at reflux (Scheme 4).

Current interest in developing methods for the simple incorporation of fluorous hydrocarbons suggested that this method could represent a powerful tool in the synthesis of organofluorine compounds. Monofluoromethyl ethers are much less prevalent in the literature than their difluoro- and trifluoro- counterparts. However, Hu et al. recently reported the monofluoromethylation of phenols and other nucleophiles using fluoroalkyl sulfoximines.[8] In order to explore the generality of our method for the synthesis of monofluoromethyl ethers, we attempted to repeat the reaction shown in Scheme 4 on 4-bromophenol and 3-hydroxy-4-methoxybenzaldehyde, our results are depicted in Scheme 5.

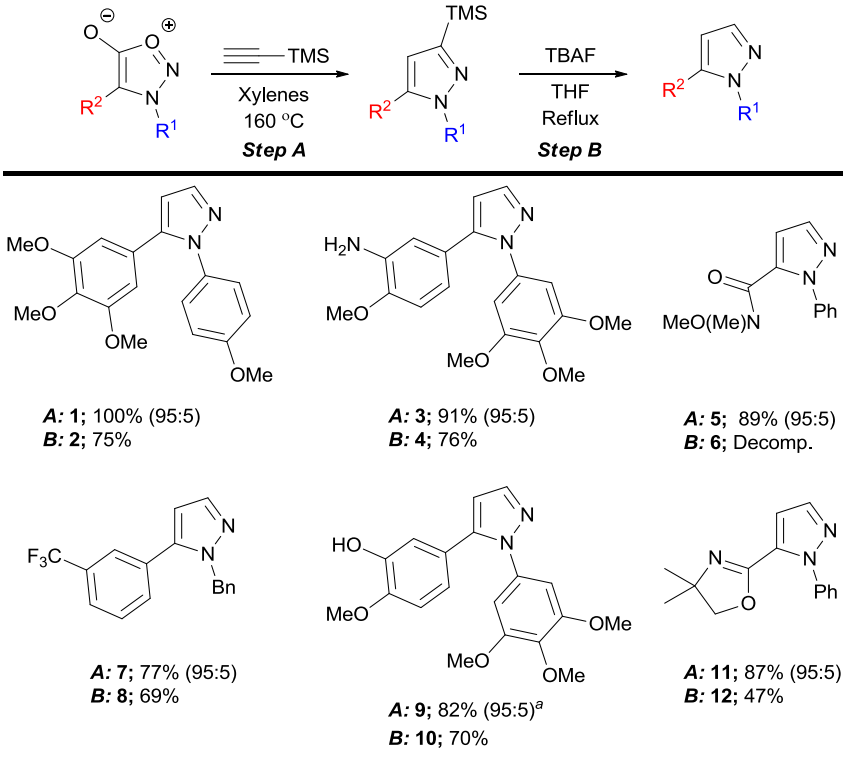


Scheme 3. TBAF-mediated elimination.

Subjecting 4-bromophenol to TBAF/CH_2Cl_2 led to fluoromethylation product **15**, as judged by ^{1}H NMR analysis of the crude reaction mixture. However, the product was found to be contaminated with the corresponding acetal **16**. Unfortunately, **15** and **16** could not be separated by chromatography. Furthermore, **15** was found to undergo conversion to acetal **16** on various chromatographic supports, or on standing. In this context, the instability of monofluoromethyl ethers has been noted by Hu and Sheng.[8,9] Interestingly however, **17** could be isolated cleanly after chromatography on Florisil®, albeit in modest yield (Scheme 5). These experiments suggested that the fluoromethyl ether formation outlined here may be useful, but only in cases where the final products undergo slow hydrolysis. Finally, with regard to the mechanism of fluoromethyl ether formation, Zhang et al. have shown that chlorofluoromethane is capable of alkylating phenols.[10] We therefore propose that CH_2Cl_2 and TBAF combine to form FCH_2Cl as an alkylating agent. The potential for fluoromethylation *via* an interrupted Reimer-Tiemann reaction[11] was discounted as CD_2Cl_2 provided the ***d*-17** with >95% D-incorporation.

2.2. 1,4,5-Trisubstituted pyrazoles

We next turned our attention to the synthesis of more heavily decorated pyrazoles. We envisaged that an alkynylboronate bearing a trimethylsilyl group could provide general access to 1,4,5-



Scheme 2. Preparation of 1,5-disubstituted pyrazoles. [a]R^2 in the starting sydnone was used as the corresponding TBS-ether.