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Synthesis of aminopyrazoles from sydnones and ynamides

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Aminopyrazoles are prepared from readily accessible sydnones and sulfonyl ynamides using either a copper-mediated sydnone alkyne cycloaddition (CuSAC) or *in situ* generated strained cyclic ynamides.

Sydnones are considered to be one of the most popular members of the family of meso-ionic heteroaromatic compounds.[1-6] They are known to participate as 1,3-dipoles in cycloaddition reactions, particularly with alkynes, as Huisgen described in the 1960s.[7, 8] These cycloadditions tend to give better results when electron-deficient dienophiles are used, usually require high reaction temperatures and long reaction times, and the regioselectivity of the pyrazole products is often substrate-dependent.[1] Previously reported attempts to try to address these issues include the use of alkynylboronates[9, 10] or copper promoters to direct the regioselectivity of the sydnone-alkyne cycloaddition reactions.[11-13] Due to the high interest towards new routes to fully functionalised pyrazoles, which are known to possess biological activities,[14, 15] we were interested in expanding the scope of the sydnone-alkyne cycloaddition reaction to increase the tolerance for activated and electron-rich alkynes. To do so, we developed the synthesis of 4-aminopyrazoles from cycloaddition reactions between sydnones and ynamides, which have not been reported to date.[15-32]

First we proceeded with the preparation of the sulfonyl ynamides *via* the dichloroenamide approach reported by Anderson and co-workers,[33] which allowed a convenient large scale synthesis of the ynamide substrates.[34] Alternative popular synthetic routes to ynamides include copper-catalysed amidative cross-coupling processes.[35-43] The sydnones could be accessed *via* a two-step procedure consisting of the nitrosation and cyclodehydration of *N*-arylglycines, as extensively reported in the literature.[1] Further functionalisation of the C4 position of the sydnone scaffold was achieved by Pd-catalysed direct arylation[44] or lithiation followed by quenching with electrophiles, affording a range of 4-substituted sydnones with different properties.

In order to improve the performance of the cycloaddition reactions between sydnones and alkynes, different strategies have been reported in the literature in the past few years. A popular approach is the use of Lewis acids, since *via* coordination to the sydnone, the reaction is favoured and the regioselectivity of the pyrazole products can be affected.[12, 45] The use of copper promoters has also been shown to affect regioselectivity and facilitate the cycloaddition reaction, commonly referred to as a Cu-mediated Sydnone Alkyne Cycloaddition (CuSAC).[11, 13] Based on these reports, we decided to undertake a screening of readily available copper catalysts and study their effect on the cycloaddition between ynamides and sydnones. Although it is known that terminal sulfonyl ynamides are water sensitive, this was not a major concern during previous studies on metal-free systems, as the desired reactions outpaced any side-reactions.[34] However, during our copper catalyst screen, we found that the presence of the copper promoters facilitated the hydrolysis of the terminal sulfonyl ynamide **1a** to its sulfonyl amide **2** (Scheme 1).

The addition of copper(II) acetate to the ynamide-based CuSAC was expected to result in the facile formation of 1,4-pyrazole **4**, but only trace amounts of pyrazole products could be identified by LCMS, together with large quantities of unreacted sydnone and hydrolysed

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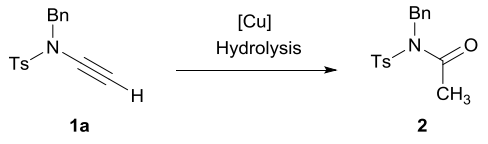


1a **2**

Scheme 1. Hydrolysis of the sulfonyl ynamide substrates.

ynamide **2** (Table 1, Entry 1). Both the anhydrous and the monohydrate salt of copper(II) acetate were found to degrade the ynamide. Even more surprising results were obtained when copper(II) triflate was added to the terminal sulfonyl ynamide **1a**. Where the copper(II) acetate reaction took several hours at elevated temperatures to hydrolyse the ynamide, the copper(II) triflate-promoted degradation of the ynamide was complete in several minutes at room temperature (Table 1, Entry 2). In a futile attempt to prevent hydrolysis, we decided to perform the reaction under strict anhydrous conditions by adding activated molecular sieves and using dry copper(I) iodide (Table 1, Entry 3). We found that under these conditions the amide formation was reduced, but the desired reaction still yielded mere traces of product, even when elevated temperatures and prolonged reaction times were employed.

Satisfactorily, when the copper(II) sulphate-mediated click chemistry-like conditions reported by Taran[11, 12] were attempted (Table 1, Entry 4), we were pleased to see full conversion of the ynamide and the formation of a 2:1 mixture of pyrazole and sulfonyl amide. Fortunately, isolation of the desired pyrazole product could be achieved by simple recrystallisation from hot methanol.

Due to the high sensitivity of terminal sulfonyl ynamides towards the copper-promoted hydrolysis, we decided to explore the use of two internal ynamides: **1b** (R = Me) and **1c** (R = CO_2Et). As these are more stable, treatment of **1b** and **1c** with copper(II) acetate or copper(II) sulphate did not lead to degradation (Table 1, entries 5&6 and 8&9). However, only traces of the desired pyrazoles could be detected, likely due to the lack of formation of key Cu(I) acetylides. Attempts to use copper(II) triflate, that was previously reported to activate the sydnone, resulted in the degradation of the internal ynamides, likely due to the elevated temperatures required (Table 1, entries 7 and 10).

Table 1. Catalyst screening.

Entry	R	[Cu] source	Time	Temp [°C]	Result[e]
1	R = H (**1a**)	$Cu(OAc)_2$[a]	3-16 h	100-140	Traces **3/4**, mostly **2**
2		$Cu(OTf)_2$[b]	15 min	RT	Only **2**
3		CuI[c]	3 days	60-100	Traces **3/4**, mostly **2**
4		$CuSO_4·5H_2O$[d]	16 h	80	2:1 mix of **4**:**2**
5	R = CH_3 (**1b**)	$Cu(OAc)_2$[a]	16 h	100	Traces **3/4**
6		$CuSO_4·5H_2O$[d]	16 h	80	Traces **3/4**
7		$Cu(OTf)_2$[b]	16 h	100	Degradation
8	R = OEt (**1c**)	$Cu(OAc)_2$[a]	16 h	100	Traces **3/4**
9		$CuSO_4·5H_2O$[d]	16 h	80	Traces **3/4**
10		$Cu(OTf)_2$[b]	16 h	100	Degradation

[a] 0.2 equiv. of $Cu(OAc)_2$, 0.2 M in *o*-DCB, [b] 1.0 equiv. of $Cu(OTf)_2$, 0.2 M in *o*-DCB, [c] 0.2 equiv. of CuI, 0.2 equiv. 1,10-phenanthroline, 1.0 equiv. Et_3N, 0.1 M in DMF, activated 4Å molecular sieves, [d] 0.2 equiv. of $CuSO_4·5·H_2O$, 0.2 equiv. 1,10-phenanthroline, 2.0 equiv. of Na-ascorbate, 1.0 equiv. Et_3N, 0.1 M in *t*BuOH : H_2O (1:1), [e] The isolation of trace amounts of pyrazole products did not allow for determination of obtained regio-isomer, e.g. **3** or **4**.

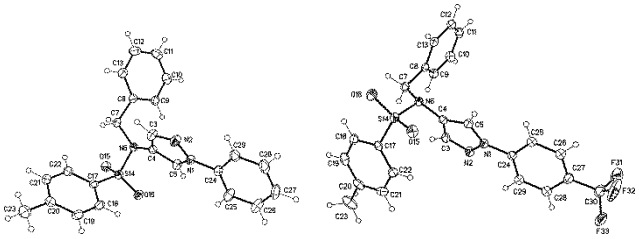
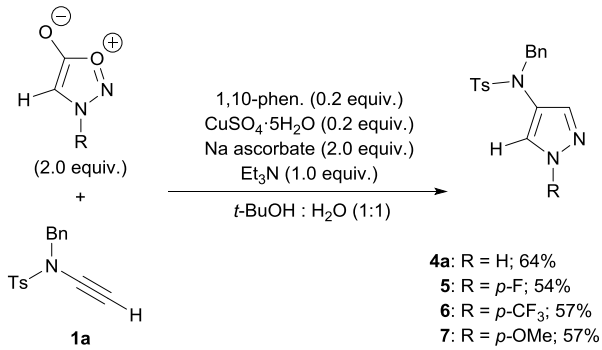


Figure 1. Molecular structure of 4-aminopyrazoles **4a** (left) and **6** (right). Displacement parameters are drawn at 50% probability level, in **6** the minor disordered part is omitted for clarity.

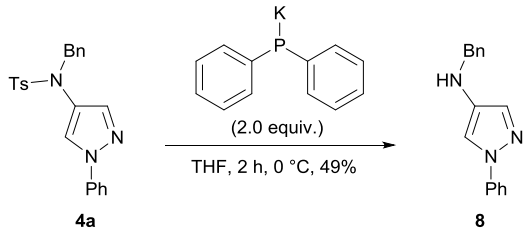


Scheme 2. Cycloaddition between sydnones and terminal ynamide **1a**.

Next we decided to investigate the scope of the CuSAC reaction in terms of suitable sydnones (Scheme 2). Using the terminal sulfonyl ynamide **1a** and the copper(II) sulphate method a variety of sydnones were screened. To our delight all the C4-unsubstituted 3-arylsydnones we had in hand reacted readily, resulting in the isolation of 4-aminopyrazoles in a moderate yields (Scheme 2), but

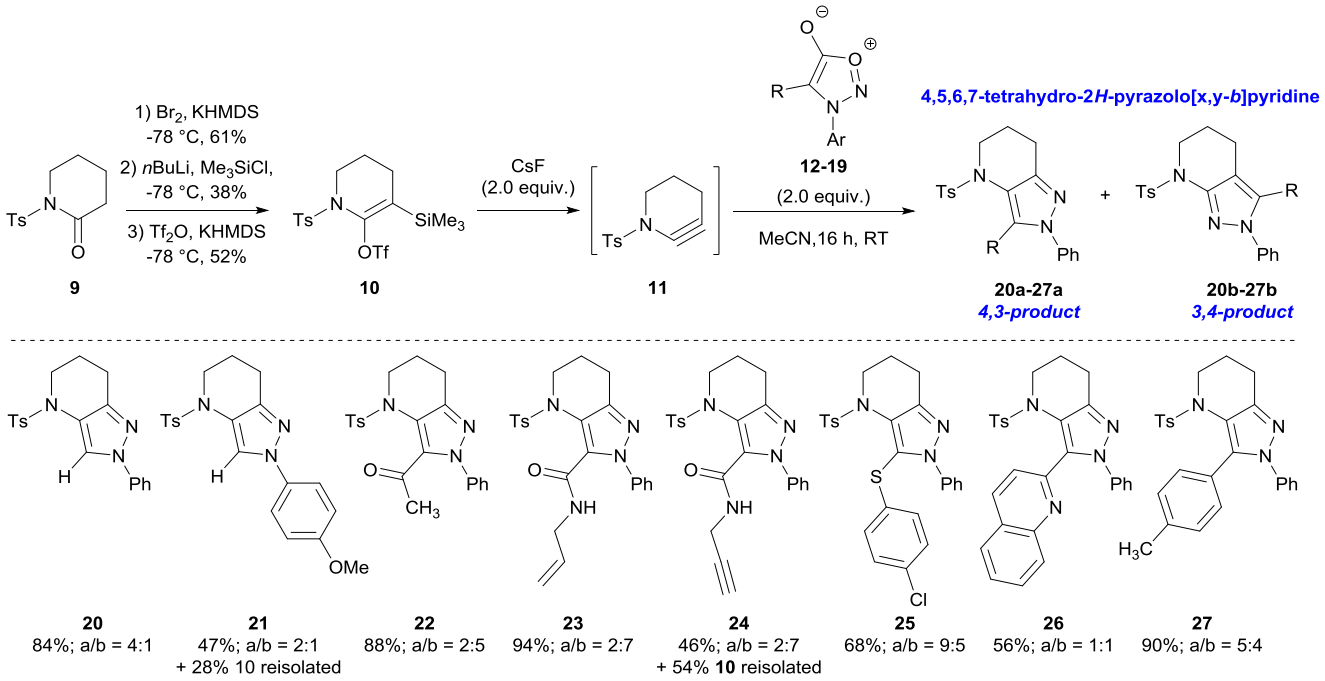
regioselective manner, as confirmed by ^{1}H and ^{13}C NMR as well as with X-ray crystallographic analysis (Figure 1). However, it appears that the ynamide CuSAC reaction is limited to C4-unsubstituted sydnones, as all attempts to use C4-substituted sydnones failed.

In order to increase the synthetic versatility for the 4-amino-pyrazoles, the removal of the tosyl and benzyl groups was investi-



4a **8**

Scheme 3. Successful removal of the *N*-tosyl group.



Scheme 4. Scope for the strained ynamide-sydnone cycloaddition process. For clarity, only the "a" isomer is shown.

gated (Scheme 3). It was found that, although the tosyl group could be removed in moderate yield using potassium diphenyl-phosphanide,[46] the benzyl group was surprisingly resistant to hydrogenation. Even when a pressure of 10 bar of hydrogen was applied, no conversion was observed. Attempts to remove the benzyl group using oxidative conditions with sodium bromide and oxone[47] also proved to be unsuccessful and unreacted starting material was recovered.

In pursuit of reaction conditions that could tolerate C4-substituted sydnones and thus would allow access to a wider substrate scope, we decided to perform the reaction under copper-free conditions. Inspired by the strain-promoted alkyne azide cycloaddition (SPAAC),[48-52] which is well-known for its efficacy despite its lack of copper, we set out to investigate the synthesis of strained cyclic ynamides as recently conceptualised by Danheiser *et al.*[53] Additionally, it was recently shown that sydnones are suitable substrates for strain-promoted cycloadditions.[54] In four steps the *N*-tosyl-azacyclohexyne precursor **10** can be prepared with relative ease following Danheiser's work (Scheme 4). Subsequently the strained cyclic ynamide **11** can be generated *in situ* by addition of caesium fluoride, a procedure best known from the preparation of arynes.[55-63]

To our delight, the strain-promoted sydnone ynamide cycloaddition tolerated a wide range of substitutions on the C4 position of the sydnone, as shown in Scheme 4. Reaction optimization revealed that slight excess of the sydnone provided best results, since when activated ynamides were used in excess, complex reaction mixtures were obtained, presumably due to side reactions.

Although in most cases complete conversion was reached after a few hours, the regioselective outcome of the reactions turned out to be rather inconsistent. Initial results showed that 4-unsubstituted sydnones favour the 4,3-disubstituted product **20a-27a** (Scheme 4). However, when 4-aryl-substituted sydnones were employed, no clear preference was observed over the product ratio. Interestingly, from these preliminary results it seemed that C-4 amide substituted sydnones tend to produce the 3,4-regio-isomer **20b-27b** preferentially. Additional experiments, molecular modelling and DFT calculations could help understand this behaviour and are currently under investigation.

In conclusion, we successfully achieved the synthesis of (fused) amino-substituted pyrazole scaffolds by means of cycloaddition reactions between sydnones and ynamides, accessing new scaffolds unexplored up to date.

Notes and references

Crystal Structure Determinations

CCDC 1484278 (**4a**), and 1484279 (**6**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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