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Cu-Promoted Sydnone Cycloadditions of Alkynes: Scope and Mechanism Studies

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Abstract: Cu salts have been found to promote the cycloaddition reaction of sydnones and terminal alkynes, providing significant reduction in reaction times. Specifically, the use of $Cu(OTf)_2$ is found to provide 1,3-disubstituted pyrazoles, whereas simply switching the promoter system to $Cu(OAc)_2$ allows the corresponding 1,4-isomers to be produced. The mechanism of the Cu-effect in each case has been investigated by experimental and theoretical studies, and they suggest that $Cu(OTf)_2$ functions by Lewis acid activation of the sydnone, whereas $Cu(OAc)_2$ promotes formation of reactive Cu^I acetylides.

Introduction

Sydnones are the most prominent members of the mesoionic class of heteroaromatic compounds, and they undergo a wide range of functionalization reactions.[1] From a synthesis standpoint, the cycloaddition reaction of these compounds with alkynes offers an effective method to prepare pyrazoles, and this chemistry has attracted a great deal of attention since its initial discovery by Huisgen.[2] A limitation of sydnone cycloadditions is the requirement to conduct these reactions at elevated temperatures over extended time periods. Nonetheless, such processes can provide the corresponding pyrazoles with excellent levels of regiocontrol, especially for terminal alkyne substrates.

Several examples of this chemistry have been reported in the literature. In 2007, González-Nogal and co-workers reported the generation of *N*-phenyl-3-silylpyrazoles through cycloaddition reactions of *N*-phenylsydnone with trialkylsilyl-substituted alkynes in refluxing toluene, giving moderate to good yields. This transformation has been shown to work with both internal and terminal alkynes, the latter being, in most cases, highly regioselective for formation of 3-substituted pyrazoles.[3] This chemistry has also been exploited for the synthesis of 2*H*-indazoles by Larock. In this case, the [3+2] cycloaddition of *N*-arylsydnones and arynes proceeds under mild conditions (THF, room temperature), which is quite unusual for these reactions.[4,5] In addition, the synthesis of N-unsubstituted pyrazoles can also be achieved using this methodology; Yli-Kauhaluoma recently reported the use of solid-phase techniques whereby N-linked amino acids were employed in the sydnone synthesis and subsequent 1,3-dipolar cycloaddition with disubstituted alkynes. The products were then easily isolated after cleavage from the solid support.[6]

We have previously described examples of cycloaddition reactions of sydnones with alkynylboronate and found these to offer excellent regioselectivities towards the 3-substituted-4-boronate pyrazole,[7,8] although regioselectivity is highly substituent-dependent under thermal conditions. This is a useful method for the generation of polysubstituted pyrazoles, since sydnones can be functionalized through cross-coupling reactions at the C4-position.[5,9,10] An advantage of the alkynylboronate methodology is the opportunity to perform post-cycloaddition functionalization, and this has been exemplified in the divergent synthesis of the withasomnine class of natural products.[11]

Studies in our laboratories have provided evidence that sydnones bearing electron-withdrawing groups undergo rapid cycloaddition reactions with alkynes, which indicates that these substrates react through an inverse-electron-demand cycloaddition–cycloreversion mechanism.[7] On this basis, it occurred to us that sydnones could be subjected to Lewis acid activation, thereby promoting reactions with alkynes at lower temperatures and/or over shorter reaction times. Indeed, Turnbull has proposed that the failure of $AlCl_3$-promoted Friedel–Crafts reactions of sydnones and acid chlorides is due to preferential complexation of the Lewis acid to sydnone substrates, resulting in deactivation of the heterocycle towards electrophilic aromatic substitution.[12] During the latter stages of our investigations into the Lewis acid promoted cycloaddition of sydnones, Taran and co-workers reported the use of Cu^I catalysts to promote these reactions (Scheme 1).[13,14] We report herein our own findings in this area that highlight the importance of

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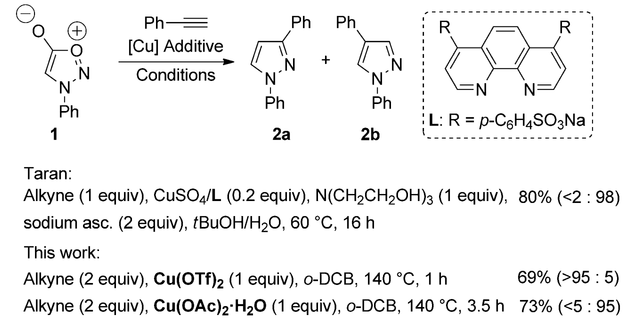
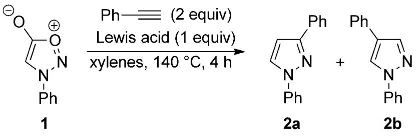


Scheme 1. Summary of copper-promoted cycloaddition reactions between sydnones and alkynes.

the Cu-promoter with respect to reaction efficiency and regiochemistry.

Results and Discussion

Table 1. Lewis Acid screening for the cycloaddition reaction of **1** and phenylacetylene.



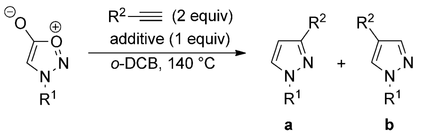
Entry	Lewis acid (LA)	% Conversion of **1** to **2 a,b**[a] 1 h	2 h	3 h	4 h
1	no LA	37	59	74	78
2	ZnI_2	0	0	0	2
3	$InBr_3$	4	6	12	18
4	$In(OTf)_3$	2	14	15	17
5	TMSOTf	49	61	72	83
6	$Zn(OAc)_2$	59	74	84	90
7	$MgBr_2$	86	92	95	100
8	$Cu(OTf)_2$	100	100	100	100

[a] Conversion estimated by GCMS analysis of the crude reaction mixture.

To ascertain if there was any beneficial effect of adding a Lewis acid to the cycloadditions, *N*-phenylsydnone **1** (0.25 mmol) and an equimolar amount of a Lewis acid were heated with ethynylbenzene (0.5 mmol) at 140 °C in a sealed vessel. The conversion of each reaction was measured hourly by GCMS, as a ratio of the sydnone **1** against the pyrazole products **2** (Table 1). When the reaction was conducted in the absence of Lewis acid, 78% conversion to pyrazoles **2** was recorded after four hours (Table 1, entry 1). The observed ratio of **2 a** and **2 b** was > 10:1, which was maintained in all examples. The conversion was found to decrease upon addition of ZnI_2, $InBr_3$ or $In(OTf)_2$ (entries 2–4), while TMSOTf and $Zn(OAc)_2$ provided only a small improvement to the background reaction (entries 5 and 6).

The employment of $MgBr_2{\cdot}OEt_2$ was highly advantageous, giving full conversion to **2** within the four hours (Table 1, entry 7). Even more remarkably, full conversion occurred within the first hour using $Cu(OTf)_2$ (entry 8). On further investigation of the additive effects of $Cu(OTf)_2$, it was discovered that complete conversion actually occurred within 20 min, compared to a 13% conversion within the same time in the absence of Lewis acid. Accordingly, we decided to explore the scope of the $Cu(OTf)_2$-promoted reaction, and to compare this to the reaction conducted in the absence of promoter. Our results are summarised in Table 2.

Table 2. Cycloaddition reactions between sydnones and alkynes in the presence and absence of $Cu(OTf)_2$.



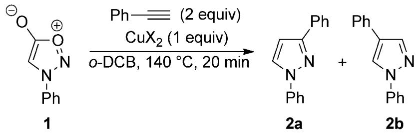
Entry	$R^{1[a]}$	R^2	No additive (**a**/**b**)	$Cu(OTf)_2$ (**a**/**b**)[b]
1	Ph, **1**	Ph	24 h; **2**, 62% (10:1)	1 h; **2**, 69% (> 95:5)
2	PMP, **3**	Ph	24 h; **9**, 76% (10:1)	1 h; **9**, 57% (> 95:5)
3	Bn, **4**	Ph	–[c]	3 h; **10**, 11% (> 95:5)
4	*i*Pr, **5**	Ph	–[c]	3.5 h; **11**, 51% (> 95:5)
5	Et, **6**	Ph	–[c]	2 h; **12**, 56% (> 95:5)
6	Me, **7**	Ph	–[c]	2 h; **13**, 56% (> 95:5)
7	Ph, **1**	EtO_2C	16 h; **14**, 59% (2:1)	20 min; **14**, 56% (2:1)
8	PMP, **3**	EtO_2C	24 h; **15**, 57% (2:1)	20 min; **15**, 51% (2:1)

[a] PMP = 4-methoxyphenyl. [b] Isolated yield after column chromatography. [c] Cycloadditions in the absence of promoter were not conducted in this case.

To our delight, a dramatic acceleration of the reaction rate was observed when adding the Lewis acid, dropping reaction times from > 12 to < 2 h in general but maintaining similar yields and regioselectivities as compared to the reactions conducted in the absence of promoter. In addition, aliphatic sydnones were also found to be suitable substrates, but reaction times were longer and yields were more modest (entries 3–6).

Having observed useful rate enhancements using $Cu(OTf)_2$ as a promoter, we next decided to carry out a screen of Cu salts in an effort to further improve the cycloaddition reaction conditions. Our results are summarised in Table 3. Surprisingly, not only did we see promotion of the cycloaddition in most cases, but we found the copper salts also had an effect on reaction regioselectivity. Specifically, the reactions could proceed with good to high levels of regioselectivity for the 1,3-pyrazole (Table 3, entries 1–3), with poor selectivity (entry 4) or with moderate to high selectivity for the 1,4-isomer (entries 5–10). This preliminary study suggested that $Cu(2\text{-ethylhexanoate})_2$ (entry 9) offered the best combination of high conversion and good regioselectivity; however, we found it difficult to purify the pyrazole products away from the 2-ethylhexanoic acid by-product during preparative scale runs. We therefore decided to explore the scope of this Cu-promoted reaction using $Cu(OAc)_2{\cdot}H_2O$, as an inexpensive alternative that simplified pyrazole purification.

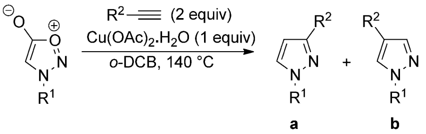
Table 3. Lewis acid screening for the cycloaddition reaction between **1** and phenylacetylene.



Entry	Copper source	**1**/**2**[a]	**2a**/**2b**[a]
1	$Cu(OTf)_2$	0:100	90:10
2	$Cu(TFA)_2$	25:75	80:20
3	$Cu(BF_4)_2$	56:44	64:36
4	$CuCl_2{\cdot}4H_2O$	26:74	48:52
5	$Cu(CO_3)_2$	71:29	27:73
6	$[Cu(acac)_2]$[b]	81:19	20:80
7	$CuBr_2$	9:91	19:81
8	$Cu(OAc)_2$	61:39	17:83
9	[Cu(2-ethylhexanoate)$_2$]	12:88	8:92
10	$[Cu(hfacac)_2]$[b]	87:13	3:97

[a] Ratio estimated by GCMS analysis of the crude reaction mixture. [b] acac = acetylacetonate; hfacac = hexafluoroacetylacetonate.

Table 4. Cycloaddition reactions between sydnones and alkynes in the presence of $Cu(OAc)_2{\cdot}H_2O$.



Entry	R^1[a]	R^2	*t* [h]	Yield [%] (**a**/**b**)
1	PMP, **3**	Ph	5	**9**, 53 (<5:95)
2	Ph, **1**	CO_2Et	1	**14**, 96 (<5:95)
3	PMP, **3**	CO_2Et	2	**15**, 81 (<5:95)
4	Ph, **1**	*n*Hex	3.5	**16**, 73 (<5:95)
5	PMP, **3**	*n*Hex	3.5	**17**, 54 (<5:95)
6	Ph, **1**	cyclohexyl	4	**18**, 100 (<5:95)
7	PMP, **3**	cyclohexyl	2.5	**19**, 71 (<5:95)
8	Ph, **1**	cyclohex-1-enyl	2.5	**20**, 71 (<5:95)
9	PMP, **3**	cyclohex-1-enyl	2.5	**21**, 60 (<5:95)
10	Ph, **1**	cyclopropyl	4	**22**, 96 (<5:95)
11	Ph, **1**	3-thiophenyl	2.5	**23**, 95 (<5:95)
12	4-FC_6H_4, **8**	CO_2Et	4	**24**, 95 (<5:95)
13	Bn, **4**	CO_2Et	4	**25**, 60 (<5:95)

[a] PMP = 4-methoxyphenyl.

As shown in Table 4, several sydnones and alkynes were subjected to the cycloaddition reaction in the presence of $Cu(OAc)_2{\cdot}H_2O$ to generate the corresponding pyrazoles in good to excellent yields, and in excellent regioselectivities (Table 4). Notably, although the reaction times were found to be longer than in the case of the Cu^{II} triflate, an increase in yield was generally observed as well as delivering pyrazoles with complementary regiochemistry.

As highlighted in Table 4, the scope of the cycloaddition of *N*-aryl sydnones is quite general, allowing alkynes bearing aryl, alkyl and ester groups to participate with high efficiency to give the 1,4-disubstituted heterocycles with excellent regioselectivity.

Once again, the Cu-promoter offers a decrease in the reaction times in comparison to reactions conducted in the absence of additives (Table 2). Finally, cycloaddition reactions between sydnones and ethyl propiolate ($R^2 = COOEt$) in the presence of $Cu(OAc)_2{\cdot}H_2O$ provided the corresponding 1,4-disubstituted pyrazole product in excellent regioselectivities in all cases, compared to the reaction without additives or with $Cu(OTf)_2$, for which the ratio between isomers is generally 2:1 (Table 2).

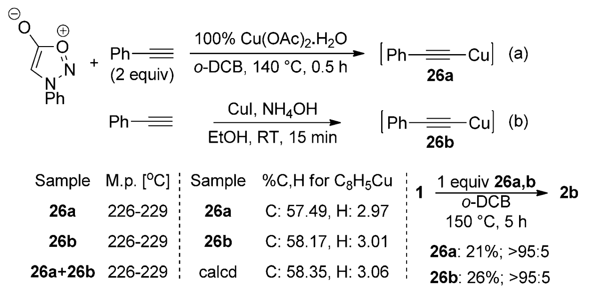
To summarize, our exploration of the use of Lewis acids to promote the sydnone cycloaddition of alkynes highlighted copper salts as useful additives, resulting in significant rate enhancements. Moreover, we were surprised to observe that the nature of Cu-promoter can have an impact of the regiochemical course of the cycloaddition process. In this context, and during the course of our work, Taran and co-workers reported a mild Cu-catalysed sydnone cycloaddition that also proceeded to deliver 1,4-pyrazole products. Scheme 1 summarizes all of these findings.

The observation that the use of Cu^{II} salts comprising acetate and triflate counterions deliver contrasting regiochemical insertion modes was intriguing and suggested that these processes operated by different reaction mechanisms. Our original hypotheses was centred on Lewis acid activation of the sydnone and so we attempted to gather evidence for this by preparing 1:1 complexes of sydnones and the Cu salts. Unfortunately we were unable to grow crystals of these complexes but IR analysis of the 1:1 adducts highlighted that, unlike $Cu(OAc)_2$, $Cu(OTf)_2$ had a significant impact on the C–O stretching frequency of sydnone **1**, which suggested that Lewis acid activation is possible in this case (Table 5).

Table 5. C–O stretching frequencies for **1** in the presence and absence of copper(II) salts.

Sample	ν_{C-O} [cm^{-1}]
1	1756
1 + $Cu(OAc)_2{\cdot}H_2O$	1757
1 + $Cu(OTf)_2$	1698

In the case of copper acetate, the formation of the 1,4-disubstituted pyrazole with high levels of regiocontrol suggested a similar reaction process to that proposed by Taran and co-workers whereby a Cu–phenanthroline-catalysed reaction proceeded via a Cu^{I} acetylide in a manner akin to alkyne–azide click reactions.[15,16,17] Indeed, when performing $Cu(OAc)_2{\cdot}H_2O$-mediated cycloaddition reactions, the formation of coloured precipitates is observed. In the case of phenylacetylene, a bright yellow precipitate forms during the course of the cycloaddition reaction. We speculated that this precipitate was likely an alkynyl–copper intermediate and therefore attempts were made to isolate and characterize this compound. We therefore heated a mixture of sydnone **1**, phenylacetylene and $Cu(OAc)_2{\cdot}H_2O$ for 0.5 h and isolated the yellow precipitate **26a** that formed during the reaction (Scheme 2a). In addition, we independently prepared an authentic sample of phenylethynyl-



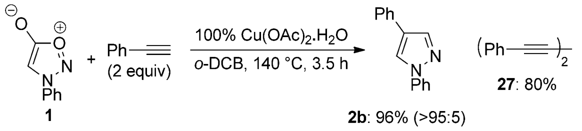
Sample	M.p. [°C]	Sample	%C,H for C_8H_5Cu
26a	226-229	26a	C: 57.49, H: 2.97
26b	226-229	26b	C: 58.17, H: 3.01
26a+26b	226-229	calcd	C: 58.35, H: 3.06

Scheme 2. Phenylethynylcopper synthesis, characterization and participation in cycloaddition reactions.

copper **26b** according to the procedure reported by Lei (Scheme 2b).[18]

Melting-point analysis (including mixed melting point) suggested that these samples were identical, although elemental analysis suggested that **26a** was less homogeneous than **26b**.[19,20,21] In addition, when both acetylides **26a** and **26b** were heated in the presence of the sydnone, 1,4-disubstituted pyrazole **2b** was detected with $<5\%$ of the corresponding 1,3-pyrazole isomer (**2a**). The product yields were found to be rather low and reaction times were relatively long in both cases, possibly due to the low solubility of the copper acetylide in *o*-DCB (DCB = dichlorobenzene, Scheme 2). Fokin also reported that Cu^{I} acetylides tend to form oligomeric thermodynamically stable aggregates, which are much less reactive than the monomeric form, thus leading to a decrease in the reaction rate. However, a higher population of the reactive monomeric Cu^{I} acetylide can be achieved by using polar-coordinating solvent, such as acetonitrile and by adding monodentate ligands.[22]

The formation of **26a** shown in Scheme 2a formally requires an in situ reduction of the copper salt. In this regard, the direct formation of Cu^{I} acetylides from Cu^{II} acetates and terminal alkynes has been reported by Heaney[23] and Lei.[24] Moreover, they showed that this combination was found to successfully catalyse alkyne–azide click reactions. Indeed, upon repeating the $Cu(OAc)_2$-promoted cycloaddition of **1** and phenylacetylene, we were able to isolate the resulting Glaser coupled 1,4-diphenylbuta-1,3-diyne in 80% yield, highlighting that a significant proportion of the Cu^{II} catalyst is reduced during the reaction (Scheme 3).



Scheme 3. In situ reduction of copper via Glaser coupling.

Overall therefore our experiments suggest that $Cu(OTf)_2$ serves to promote the cycloaddition of sydnones and alkynes by Lewis acid activation of the mesoionic compound. In contrast, $Cu(OAc)_2$ undergoes in situ reduction to Cu^{I} by Glaser coupling of the alkyne and cycloaddition proceeds by a Cu^{I} acetylide, leading to pyrazoles with complementary regiochemistry.

Computational results

To support these hypotheses, we undertook further study of these processes by DFT methods.[25] The reaction between sydnone **1** and phenylacetylene was analysed, in its uncatalysed form (absence of metal salts), as well as in the presence of Cu^{II} triflate and Cu^{II} acetate. These three reaction conditions have shown experimentally the most distinguishing results in terms of rate and regioselectivity. The geometry optimizations of all structures were performed at B3LYP/6-31G** (LANL2DZ for Cu atom)[26] and the energy values were single-point refined at M06/6-311++G** (SDD for Cu)[27] level making use of a solvation model (CPCM, *o*-dichlorobenzene).[28] All energies shown in following next figures and text correspond to Gibbs-Free energy values (ΔG), relative to the sum of the sydnone (**1**), alkyne, and the copper salt ($G_1 + G_{alkyne} + G_{Cu} = 0$).

The uncatalysed reaction was examined first, and the computational results show that the pyrazole products are formed through a two-step mechanism. The first one involves a concerted [3+2] cycloaddition (i.e. **TS-1a**, Figure 1) to form a bicyclic intermediate (i.e. **INT-1a**), followed by a fast detachment of a carbon dioxide molecule, rendering pyrazoles **2a** and **2b**. This mechanistic pathway is similar to those found in our previous studies for related cycloaddition reactions between sydnones and other types of alkynes.[7] In that case, we concluded that the regioselectivity and the reaction rate are determined in the first step, whereas the second step is almost barrierless, and does not influence the outcome of the reaction. Thus, in the present study, the transition states **TS-1a** and **TS-1b** were located (Figure 1), corresponding to concerted and highly synchronous cycloaddition processes. Their Gibbs Free energies are high, over 30 kcal mol^{-1}, in agreement with the experimentally reported high temperatures (140 °C) and long reaction

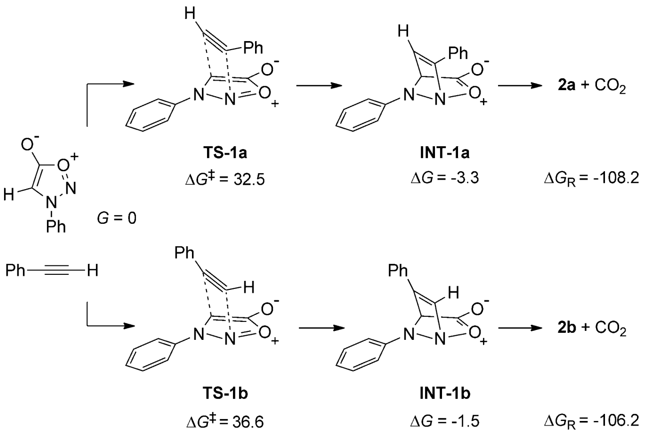


Figure 1. Activation barriers and reaction energies for the uncatalysed cycloaddition. Gibbs Free energy values were obtained at M06/6-311++G**(SDD)(CPCM,o-dichlorobenzene)//B3LYP/6-31G**(LANL2DZ).

times that are needed to complete the reaction. More interestingly, **TS-1 a** shows a 4.1 kcal mol^{-1} lower energy than its regiosiomeric structure **TS-1 b**, justifying the experimental regioselective formation of **2 a**. Whilst the formation of the bicyclic intermediates (**INT-1 a/b**) is only slightly exergonic (-3.3 and -1.5 kcal mol^{-1} respectively), and thus, potentially reversible, the overall reaction to **2 a/b** is highly exothermic, with reaction Free energies of -108.2 and -106.2 kcal mol^{-1} respectively. These extremely high negative values are due to the CO_2 release and ring aromatization that take place during the second step.

The analysis of the frontier orbitals of the two reactants shows that the sydnone is the electrophile (electrophilicity index $\omega = 2.04$ eV)[29] of the reaction, and phenylacetylene is the nucleophile ($\omega = 1.14$ eV). The reaction takes place by interaction of the alkyne/HOMO orbital with the sydnone/LUMO orbital. Thus, the addition of Lewis acids that are able to coordinate to the sydnone would be beneficial for the reaction rate, by decreasing the energy of the sydnone/LUMO and increasing its electrophilicity. Experimentally, the significant acceleration of the reaction rate (Table 3), and the C–O bond weakening observed in the IR stretching frequencies in the presence of Cu(OTf)$_2$ support this hypothesis. We computationally checked this mode of action for Cu^{II} triflate, by locating the possible sydnone–Cu(OTf)$_2$ complexes with all available lone pairs in the oxygen and nitrogen atoms of the molecule (see the Supporting Information). A structure in which copper is coordinated to the exocyclic oxygen atom through its most outer lone pair (**COM-1**, Figure 2) was found to be the most stable complex, showing a binding energy of 9.9 kcal mol^{-1}. Also, the computed frequencies for the C–O bond show a shift from 1811 cm^{-1} (free sydnone) to 1703 cm^{-1} (sydnone:Cu(OTf)$_2$ complex **COM-1**), in fair agreement with the IR shift observed experimentally (from 1756 to 1698 cm^{-1}, Table 5). These frequency data are in line with a weakening and lengthening of the C–O$_{exocyclic}$ bond, as shown by the computed distances of 1.21 Å in the sydnone and 1.25 Å in the complex.

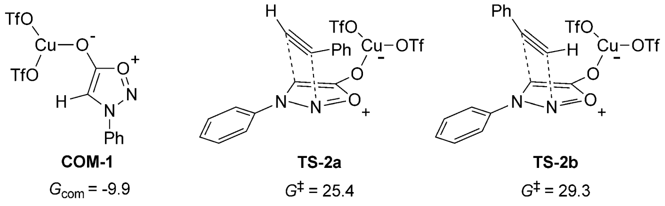


Figure 2. Sydnone:Cu(OTf)2 complex, and transition structures for its cycloadditioncomputed at M06/6-311++G**(SDD)(CPCM) level of theory.

The transition states for the cycloaddition of phenylacetylene with the sydnone/Cu(OTf)$_2$ complex **COM-1** were computed next. Not surprisingly, the absolute activation energy values were significantly lower than those corresponding to the non-catalysed reaction (**TS-2 a** = 25.4, **TS-2 b** = 29.3 kcal mol^{-1}, Figure 2), in parallel to the increase in the electrophilicity value of the sydnone-metal complex **COM-1**, which is 6.74 eV (2.04 eV in the free sydnone). The mentioned activation energies nicely explain the experimental regioselective formation of the 1,3-isomer **2 a** (Table 3), since the energy difference between **TS-2 a** and **TS-2 b** is 3.9 kcal mol^{-1} in favour of the former. This value is also very close to the energy difference of the uncatalysed transition states (4.1 kcal mol^{-1}, Figure 1), which means that the addition of the copper salt only influences the reaction rate and not the regioselectivity.

We also wanted to check if the complexation of the sydnone with the Cu^{II} metal centre would have an effect on the coordination pattern on copper. In fact, triflate anions are known to be poor coordinating ligands, and the potential detachment of one TfO– would form a cationic complex **COM-2** (Figure 3), even more electrophilic and reactive than **COM-1**. However, the computed equilibrium between both species shows a clear shift towards the neutral bis-triflate complex **COM-1**, by more than 24 kcal mol^{-1}. This high value alone should be enough to discard the participation of **COM-2** in the reaction. However, this cationic complex is extremely reactive, and its reaction with the alkyne presents an activation barrier of only 10.5 kcal mol^{-1} (from **COM-2** to **TS-3 a**, Figure 3). Thus, although its formation is remarkably unfavoured, we cannot definitively rule out its involvement in the reaction. It is plausible, for example, that during the cycloaddition, one of the triflate ligands momentarily leaves the coordination sphere of copper, facilitating the reaction. The similarity of the absolute values of **TS-2 a** (25.4 kcal mol^{-1}) and **TS-3 a** (24.8 kcal mol^{-1}) seems to support this possibility, which in any case, does not have any influence on the regioselectivity of the reaction.

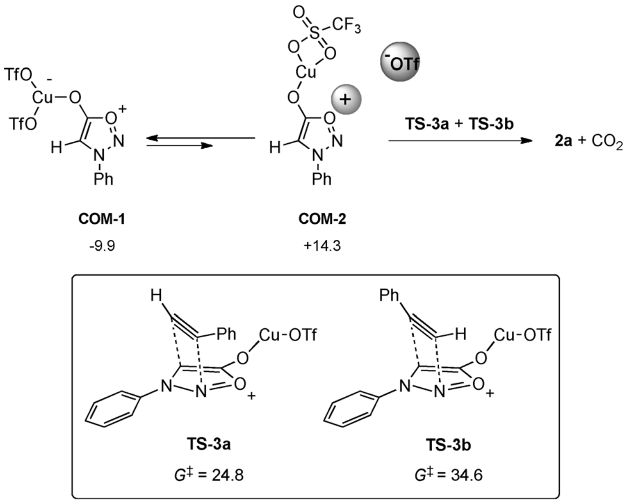
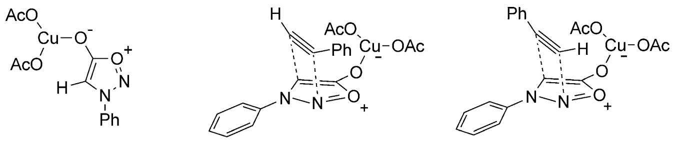


Figure 3. Formation of the mono-triflate complex and transition structures for its cycloaddition reactions at M06/6-311++G**(SDD)(CPCM) level of theory.

The most intriguing experimental results were those obtained in the presence of Cu^{II} acetate (Table 4), especially because it induces a complete reversal of regioselectivity, with preferential formation of 1,4-isomer **2 b**. Other copper salts exert the same effect (Table 3, entries 5–10), all of them presenting the common feature of a lower Lewis acid character than Cu(OTf)$_2$. Therefore, it was not surprising to find that the



COM-3 +2.8

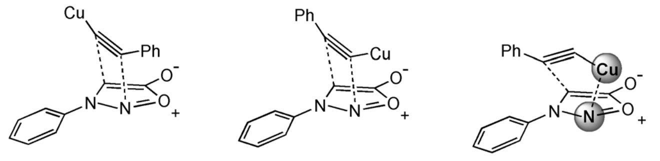
TS-4a $G^{\ddagger} = 41.4$

TS-4b $G^{\ddagger} = 45.2$

Figure 4. Complex formation and transition structures in the presence of $Cu(OAc)_2$ computed at M06/6-311++G**(SDD)(CPCM) level of theory.

formation of a sydnone:$Cu(OAc)_2$ complex (**COM-3**, Figure 4) was highly disfavoured, showing an uphill energy of +2.8 kcal mol^{-1}. This data explains why the addition of copper acetate does not have any impact on the C–O stretching frequency of sydnone **1** (Table 5). Furthermore, the computed activation energies for the transition states **TS-4a** and **TS-4b** (Figure 4), corresponding to Lewis acid activation, are over 40 kcal mol^{-1}, far too high to account for the formation of the products. Finally, the conclusive data that allows us to discard this mechanistic option is the lower activation energy of **TS-4a** than **TS-4b**, which would predict the formation of the experimentally not observed regioisomer **2a**.

Alternatively, we had envisioned the possibility that the reaction proceeded via the phenyl–alkynyl–Cu^{I} species, which has often been proposed as an active intermediate in related Cu^{II} cycloaddition chemistry.[15,16,17] As mentioned before, we have gathered experimental evidence to support this mechanistic alternative (Scheme 2). To further analyse this option, we performed and exhaustive transition state search for the reaction between sydnone and phenyl–alkynyl–Cu^{I} intermediate, resulting in the location of three structures with feasible activation energies (Figure 5). The first two, **TS-5a** and **TS-5b**, correspond to the standard synchronous cycloaddition, in which the metal is apparently playing a spectator role. Notably, they are unable to explain the experimental reactivity and selectivity, since **TS-5a** is preferred over **TS-5b**, and both are over 30 kcal mol^{-1}. In contrast, a more interesting transition state (**TS-6b**) was located, wherein a tight copper–nitrogen interaction is responsible for the lowering in the activation barrier (25.4 kcal mol^{-1}), in agreement with the faster reaction in the presence of copper acetate (Figure 5). Furthermore, this interaction is only possible in the pathway leading to 1,4-isomer **2b**, correctly predicting its experimental preference over **2a**. Structure **TS-6b** is closely related to the transition states located for the Cu^{I}-catalysed cycloaddition of azides (click chemistry).[13,30] Besides, IRC calculations show that **TS-6b** corresponds to a concerted but asynchronous formation of the pyrazole, through initial C–C bond formation followed by Cu–N dissociation and C–N bonding. Thus, no intermediates were located for this process.



TS-5a $G^{\ddagger} = 33.6$

TS-5b $G^{\ddagger} = 36.0$

TS-6b $G^{\ddagger} = 25.4$

Figure 5. Transition structures for the reaction of sydnone with alkynyl-Cu^{I} complex, computed at M06/6-311++G**(SDD)(CPCM) level of theory.

Finally, Figure 6 shows the 3D representations[31] of the productive transition states leading to the major regioisomer in each of the computed reaction systems; uncatalyzed reaction (**TS-1a**), in the presence of Cu^{II} triflate (**TS-2a**) and in the presence of Cu^{II} acetate (**TS-6b**). The first two structures (**TS-1a** and **TS-2a**) present the same level of asynchronicity, whereby the C–C bond is more advanced than the C–N during the transition state. On the other hand, **TS-6b** is significantly more asynchronous, since only C–C bond is forming to some extent during TS, whilst the strong Cu–N interaction delays the formation of the C–N bond to a later stage of the cycloaddition.

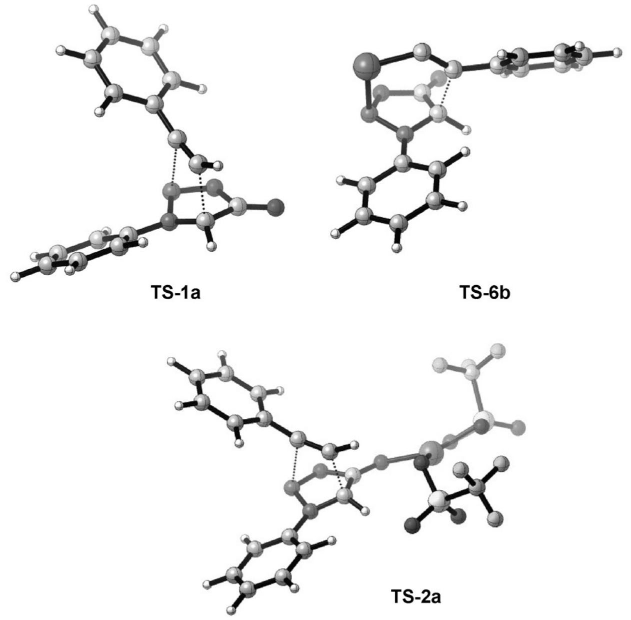


Figure 6. 3D representation of the productive transition states for each reaction system.

Conclusion

We have developed two Cu^{II}-mediated methodologies to synthesise disubstituted pyrazoles with control of the regiochemistry of the products through 1,3-dipolar cycloaddition reactions of sydnones and terminal alkynes. The 1,3-disubstituted isomer is generated with $Cu(OTf)_2$ as an additive. In contrast, $Cu(OAc)_2{\cdot}H_2O$ allows access to the 1,4-disubstituted isomers with excellent regioselectivity.

Computational results show that **TS-1a** (uncatalysed reaction), **TS-2a** (copper triflate) and **TS-6b** (copper acetate) are responsible for the major experimental isomers obtained in each of the reaction conditions. Copper(II) triflate accelerates the reaction by tight coordination to the sydnone as a Lewis acid, maintaining the regioselectivity of the uncatalysed reaction, whereas Cu^{II} acetate seems to be a precursor of the reactive Cu^{I} acetylide, which leads to the formation of the opposite regioisomer through a productive Cu–N interaction during the rate-determining transition state.

Experimental Section

General procedure for the Cu(OAc)$_2$-mediated cycloaddition of sydnones and alkynes: Synthesis of 2 b

Phenylacetylene (270 μL, 2.47 mmol) was added to a stirring solution of *N*-phenylsydnone **1** (200 mg, 1.23 mmol) and Cu(OAc)$_2$ monohydrate (432 mg, 1.23 mmol) in *o*-dichlorobenzene (0.21–0.25 M) under N_2 at room temperature. The mixture was left stirring at room temperature for 15–20 min and afterwards, heated at 150 °C for 3.5 h. After cooling, the reaction mixture was quenched with 10% HCl (aq.) and water. The organic layer was extracted with CH_2Cl_2, neutralized with saturated $NaHCO_3$ (aq.), washed with NaOH (1 M) and brine, dried over $MgSO_4$, and filtered. Finally, the volatiles were removed in vacuo. The crude product was purified by flash chromatography on silica gel (eluting solvent: 5% ethyl acetate in 60–40 petroleum ether). 1,4-Diphenyl-1*H*-pyrazole **2 b** was isolated as a yellow solid after recrystallisation from CH_2Cl_2/petroleum ether (60:40) (199 mg, 73% yield, regioselectivity $>$95:5). Melting point: 92–94 °C (lit: 95–96 °C[4]). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.17$ (s, 1H; Pyzl*H*), 8.01 (s, 1H; Pyzl*H*), 7.80–7.71 (m, 2H; Ph*H*), 7.61–7.54 (m, 2H; Ph*H*), 7.53–7.45 (m, 2H; Ph*H*), 7.44–7.36 (m, 2H; Ph*H*), 7.36–7.27 ppm (m, 2H; Ph*H*); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 140.2$, 138.9, 132.2, 129.6, 129.1, 127.0, 126.7, 125.8, 125.0, 123.4, 119.2 ppm.

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Keywords: cycloadditions · density functional calculations · pyrazole · regioselective reactions · sydnones

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FULL PAPER

Organic Chemistry

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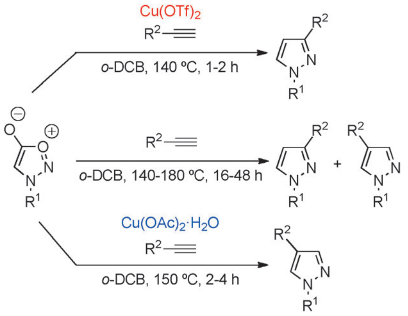
■■ – ■■

Cu-Promoted Sydnone Cycloadditions of Alkynes: Scope and Mechanism Studies



Vamos Cobre! Cu salts promote the cycloaddition of sydnones and terminal alkynes, providing significant reduction in reaction times. While Cu(OTf)$_2$ is found to provide 1,3-disubstituted pyrazoles, Cu(OAc)$_2$ allows the corresponding 1,4-isomers to be produced. Experimental and theoretical studies suggest that Cu(OTf)$_2$ functions by Lewis acid activation of the sydnone, whereas Cu(OAc)$_2$ promotes formation of reactive Cu^{I} acetylides (see scheme; o-DCB = 1,2-dichlorobenzene).