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Copper-Catalyzed *N*-Alkynylations of Sulfoximines with Bromoacetylenes

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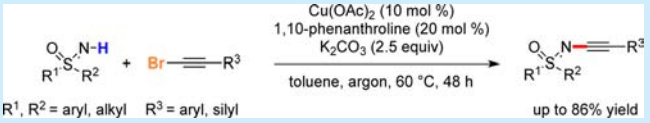
Supporting Information

ABSTRACT: *N*-Alkynylated sulfoximines have been obtained by copper-catalyzed cross-coupling reactions starting from *N*H-sulfoximines and bromoacetylenes in moderate to good yields. The reaction conditions are mild, and the substrate scope is wide.

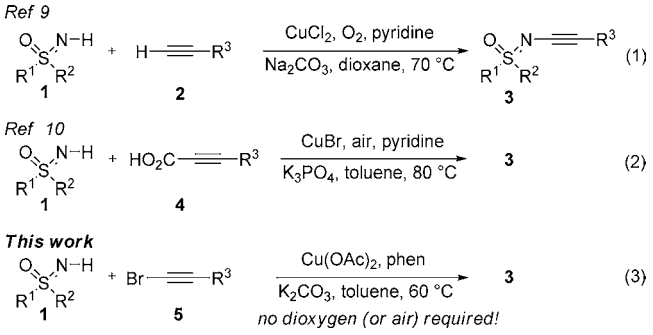


Sulfoximines have come a long way since their discovery in 1950.[1] Starting as a structural oddity, the sulfonimidoyl unit, which consists of a central sulfur atom bound to an oxygen, a nitrogen, and two (mostly differently substituted) carbon atoms, is now found in many areas of contemporary chemistry.[2] Those include classical auxiliary-supported asymmetric synthesis,[3] ligand-assisted (stereoselective) metal catalysis,[4] and organocatalysis.[5] Furthermore, sulfoximines are present in other fields where, for example, they have shown promising bioactivities being relevant in medicinal or agricultural chemistry.[6]

Realizing that *N*-alkynylated sulfoximines **3** could be regarded as chiral analogues of ynamides and thus offer rich prospects for sequential functionalizations,[7] this essentially unfathomed type of compound piqued our interest.[8]

To date, only two synthetic approaches are known (Scheme 1, eqs 1 and 2).[9−12] Both are copper-catalyzed oxidative cross-coupling reactions starting from *N*H-sulfoximines **1**. They differ in the required coupling partners, which are either terminal alkynes **2** or propiolic acids **4**. In both reactions, dioxygen (pure or in form of air) is used as terminal oxidant at elevated temperature (70 and 80 °C), which raises safety concerns in large-scale applications. We hypothesized that sequential processes with decoupled oxidation/cross-coupling steps could reduce this potential danger in the preparation of **3**. As readily available bromoalkynes **5** were known to undergo alkynylating cross-couplings in related systems,[13,14] they became our first-choice reagents in the search for an improved and safe(r) synthetic access to **3**. The realization of this idea is presented here.

Scheme 1. Synthetic Approaches toward *N*-Alkynylated Sulfoximines 3



For the initial phase of the project, *S*-methyl-*S*-phenylsulfoximine (**1a**) and 1-bromo-2-phenylacetylene (**5a**) were chosen as substrates, which we expected to provide *N*-alkynylated sulfoximine **3a** after the coupling. Because of the particular properties of the sulfoximines, an extensive screening of reaction conditions was necessary to get the first positive results. Ultimately, a slightly modified procedure of Hsung's original protocol[13d] as described by Yorimitsu, Oshima, and coworker[15] for the coupling of aryl sulfonamides with 1-bromoalkynes worked best (Scheme 1, eq 3). It involved the use of $CuSO_4 \cdot 5H_2O$ (10 mol %), 1,10-phenanthroline (phen, 20 mol %), and K_2CO_3 (2 equiv), which were applied in toluene at 60 °C. In this manner, product **3a** was obtained in 64% yield after 24 h (Table 1, entry 1). Control reactions confirmed that no product was formed in the absence of either the copper salt or the ligand. Next, the reactivities of different Cu(I) and Cu(II) salts were tested (entries 2−6). Neither the oxidation state nor the presence or absence of coordinated water had a distinct impact on the product formation, and in all cases, product **3a** was obtained in similar yields (58−68%). Since the use of anhydrous $Cu(OAc)_2$ provided the highest yield (entry 4), it was chosen for the following studies. Raising or lowering the reaction temperature from 60 to 80 °C or 40 °C, respectively, as well as utilizing a catalytic amount of pyridine instead of 1,10-phenanthroline resulted in diminished yields of **3a** (entries 7−9). Next, the effects of base, reaction time, solvent, and substrate ratio were investigated (entries 10−25).

Compared to K_2CO_3 (68% yield of **3a**, Table 1, entry 4), all other bases proved less efficient (Table 1, entries 10−16). To our surprise, this was also true for the reactions with Na_2CO_3 and Cs_2CO_3, which led to **3a** in only 8% and 6% yield,

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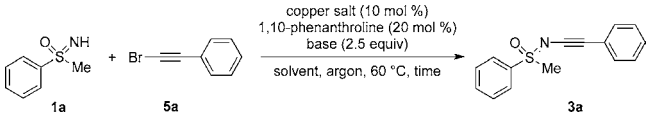
Table 1. Development of Optimal Reaction Conditions[a]



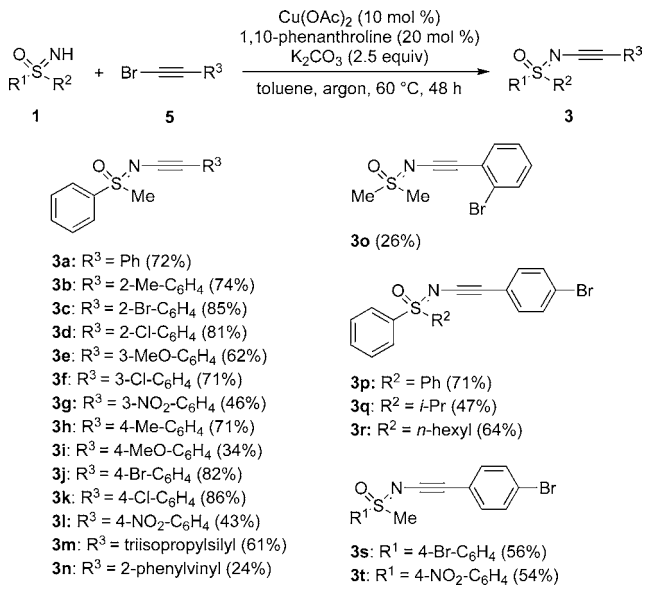
entry	copper salt	base	solvent	time (h)	yield (%)
1	$CuSO_4 \cdot 5H_2O$	K_2CO_3	toluene	24	64
2	$CuSO_4$	K_2CO_3	toluene	24	58
3	$Cu(OAc)_2 \cdot H_2O$	K_2CO_3	toluene	24	60
4	$Cu(OAc)_2$	K_2CO_3	toluene	24	68
5	$CuCl_2$	K_2CO_3	toluene	24	65
6	CuI	K_2CO_3	toluene	24	67
7[b]	$Cu(OAc)_2$	K_2CO_3	toluene	24	48
8[c]	$Cu(OAc)_2$	K_2CO_3	toluene	48	44
9[d]	$Cu(OAc)_2$	K_2CO_3	toluene	24	31
10	$Cu(OAc)_2$	Na_2CO_3	toluene	24	8
11	$Cu(OAc)_2$	Cs_2CO_3	toluene	24	6
12	$Cu(OAc)_2$	*t*-BuOK	toluene	24	2
13	$Cu(OAc)_2$	KOH	toluene	24	5
14	$Cu(OAc)_2$	pyridine	toluene	24	51
15	$Cu(OAc)_2$	KOAc	toluene	48	0
16	$Cu(OAc)_2$	K_3PO_4	toluene	48	30
17	$Cu(OAc)_2$	K_2CO_3	toluene	48	72
18	$Cu(OAc)_2$	K_2CO_3	toluene	72	74
19	$Cu(OAc)_2$	K_2CO_3	DCE	48	50
20	$Cu(OAc)_2$	K_2CO_3	1,4-dioxane	48	55
21	$Cu(OAc)_2$	K_2CO_3	DMF	48	8
22[e]	$Cu(OAc)_2$	K_2CO_3	toluene	48	60
23[f]	$Cu(OAc)_2$	K_2CO_3	toluene	48	73
24[g]	$Cu(OAc)_2$	K_2CO_3	toluene	48	62
25[h]	$Cu(OAc)_2$	K_2CO_3	toluene	48	50

[a]Conditions used: **1a** (0.6 mmol), **5a** (0.5 mmol), copper salt (0.05 mmol, 10 mol %), base (1.25 mmol), stirred in solvent (1 mL) under argon at 60 °C for indicated time. [b]Conducted at 80 °C. [c]Conducted at 40 °C. [d]With 20 mol % of pyridine instead of 1,10-phenanthroline. [e]Use of **1a** (0.5 mmol) and **5a** (0.75 mmol). [f]Use of **1a** (0.75 mmol) and **5a** (0.5 mmol). [g]Performed in air. [h]Performed with 0.025 mmol (5 mol %) of $Cu(OAc)_2$.

respectively (Table 1, entries 10 and 11).[16] The only noteworthy yields of **3a** were obtained from reactions with pyridine or K_3PO_4 instead of K_2CO_3 providing **3a** in 51% and 30% yield, respectively (Table 1, entries 14 and 16). Prolonging the reaction time from 24 h to 48 h and 72 h increased the yield of **3a** from 68% to 72% and 74%, respectively (Table 1, entries 4, 17, and 18). Considering this only minor change, the evaluation of the substrate scope (Scheme 2) was later done with a reaction time of 48 h. With respect to the solvent, toluene proved superior to DCE, 1,4-dioxane, and DMF, which all gave **3a** in lower yields (Table 1, entries 4, 19–21). Varying the ratio of **1a** and **5a** showed that using a slight excess of the sulfoximine was beneficial for the yield of **3a** (Table 1, entries 4, 22, and 23). Finally, it is important to note that the coupling could be performed in air (instead of argon as inert atmosphere; Table 1, entry 24) and that the catalyst loading could be reduced from 10 to 5 mol % (Table 1, entry 25). Although compared to the standard conditions (Table 1, entry 4) the yields of **3a** were slightly lower (62% and 50%, respectively, versus 68%), these observations might prove valuable for a possible scale-up of the coupling process.

Having identified optimal conditions for the coupling of **1a** and **5a** to give **3a** with respect to yield per time (Table 1, entry 17), the general applicability of the protocol using various sulfoximines **1** and bromoacetylenes **5** was explored (Scheme 2). First, arylbromoacetylenes with an electron-donating or -withdrawing group at the 2-, 3-, or 4-position of the arene were coupled with sulfoximine **1a**. Irrespective of the substitution pattern, the reactions proceeded well leading to the corresponding products (**3b–l**) in moderate to high yields. Although no clear reactivity trend was observed, it appeared as if reactions with halo-substituted substrates gave the best results as reflected by the high yields (71–86%) of products **3c**, **3d**, **3f**, **3j**, and **3k** (Scheme 2). An electron-withdrawing nitro group seemed to hamper the coupling, and the yields of **3g** and **3l** were lower (46% and 43%, respectively) compared to the unsubstituted product **3a** (72%). Whereas methyl groups on the arene had essentially no effect (**3b**: 74%, **3h**: 71%), methoxy substituents gave nonuniform results (**3e**: 62%, **3i**: 34%).[17]

Scheme 2. Scope of the Copper-Catalyzed *N*-Alkynylation of Sulfoximines 1 with Bromoacetylenes 5



Finally, a triisopropylsilyl- and a *β*-styrenyl-substituted bromoacetylene were applied in the coupling with sulfoximine **1a**. These reactions proceeded well, and the corresponding products, **3m** and **3n**, were obtained in 61% and 24% yields, respectively. The former result is of particular interest because cleavage of the silyl substituent could prove useful for the synthesis of a monosubstituted terminal.

With the goal to evaluate the applicability of other sulfoximines, products **3o–t** were targeted (Scheme 2). Probably because of the low solubility of *S*,*S*-dimethyl sulfoximine (**1b**) in toluene, *N*-alkynylated **3o** was obtained in only 26% yield. In light of the analogous experiment with sulfoximine **1a** as starting material, which led to **3c** in 85% yield, this result was disappointing. Higher yields were achieved in couplings of other sulfoximine/alkyne combinations. For example, applying *S*,*S*-diphenyl sulfoximine (**1c**) in a coupling with (2-bromoethynyl)-4-bromobenzene led to **3p** in 71% yield. Both the alkyl as well as the aryl substituent of the sulfoximine could be modified as reflected by the syntheses of *N*-alkynylated products **3q–t**, which were obtained in yields ranging from 47% to 64%. Analyzing these data in detail suggested that steric effects dominated over electronic ones.

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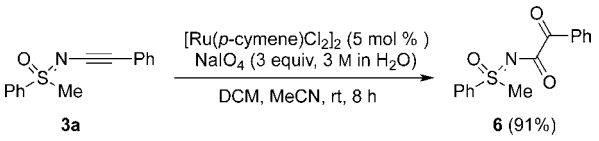
As noted in our previous work, *N*-alkynylated sulfoximines **3** were prone to undergo acid-catalyzed hydroysis providing *N*-acylsulfoximines.[9] Furthermore, we reported a (*Z*)-selective reduction of **3a** to the corresponding *N*-vinylsulfoximine[10] and demonstrated thermal [2 + 2]-cycloadditions leading to cyclobutenone derivatives.[10,11] It was now decided to attempt an oxidative transformation (Scheme 3). To this end, *N*-alkynylsulfoximine **3a** was subjected to similar conditions as described by Al-Rashid, Hsung, and co-workers for the formation of α-ketoimides from ynamides.[18] The ruthenium-catalyzed oxidation of the triple bond with $NaIO_4$ worked very well providing diketo derivative **6** in excellent yield (91%).

Scheme 3. Transformation of *N*-Alkynyl Sulfoximine 3a into Diketo Derivative 6 under Oxidative Conditions



In conclusion, we have developed an alternative approach toward *N*-alkynylated sulfoximines avoiding the use of potentially hazardous gaseous dioxygen. The copper-catalyzed transformations proceed under mild reaction conditions involving the use of readily available bromoacetylenes in combination with diversely substituted *NH*-sulfoximines. In an initial experiment, an efficient ruthenium-catalyzed oxidative transformation of the C−C-triple bond into an α-diketo moiety was demonstrated.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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