Cross-Coupling

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Copper-Catalyzed Oxidative Cross-Coupling of Sulfoximines and Alkynes**

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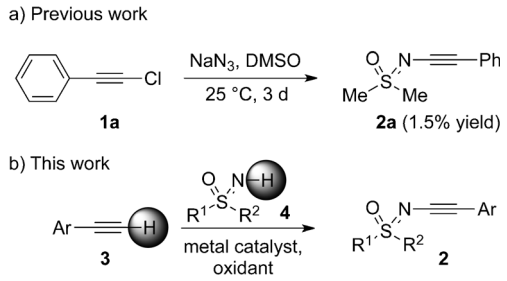
Until recently, the cross-coupling of two electron-rich nucleophilic substrates presented a significant challenge for synthetic organic chemists.[1] In the past decade, however, several breakthroughs have been reported for such processes, such as employing transition-metal catalysts to facilitate the formation of either a new C–C or C–N bond between two nucleophiles.[2] Realizing that this approach could also open access to N-alkynylated sulfoximines (**2**), which represent an essentially unexplored substrate class, we considered oxidative cross-coupling methods for the construction of the respective C–N bonds (Scheme 1).



Scheme 1. a) The only previously reported preparation of an N-alkynyl sulfoximine.[3] b) The approach reported herein. DMSO = dimethylsulfoxide.

A necessity of such dual C–H/N–H activation cross-coupling procedures is the inclusion of an oxidant, often in stoichiometric amounts, to remove two electrons during the bond-forming process. Molecular oxygen appears as an ideal oxidant, thus avoiding the subsequent generation of additional waste.[4] Furthermore, it is desirable that the transition-metal catalysts employed for the activation of the two nucleophiles are cheap and readily available. To this end, we herein report the development of a high-yielding oxidative cross-coupling method for the preparation of N-alkynylated sulfoximines. This protocol employs dioxygen as oxidant and a copper(II) salt as catalyst. Furthermore, through a simple modification in the purification procedure, the corresponding N-acyl sulfoximines can also be obtained selectively in good yields.

The sulfoximidoyl moiety is found in various bioactive compounds currently examined in both medicinal and agricultural chemistry.[5] In asymmetric metal catalysis, sulfoximines have proven useful as chiral ligands for a range of catalyzed processes.[6] Functionalization of the sulfoximine N–H bond enriches the diversity of sulfoximine libraries and provides access to a plethora of potentially useful compounds. By applying the currently available methods, alkyl, alkenyl, and aryl groups can be introduced.[7] N-Alkynylations of sulfoximines, however, are unknown. In this context it is also noteworthy that the only reported representative of the expected product class **2** is *N*-(phenylethynyl)-*S*,*S*-dimethylsulfoximine (**2a**), which was obtained through nitrene addition to DMSO and isolated in only 1.5% yield (Scheme 1).[3]

In light of the rich chemistry of the structurally related ynamides,[8] the scarcity of N-alkynylated sulfoximines is even more surprising. The development of new synthetic protocols for the preparation of stable and potentially chiral derivatives of these ynamide-type products appears critical to allow further progress to be made in this burgeoning field of synthetic chemistry.

Considering the advances in copper-catalyzed syntheses of N-alkynylheterocycles and N-alkynylamides,[2,9] we decided to apply those methods to the preparation of the corresponding sulfoximine derivatives. In Table 1, the most significant steps of this screening are summarized. In all cases, racemic methyl phenyl sulfoximine (**4a**) served as the NH-coupling partner and **2b** was the expected product.

Initially, the N-alkynylation of the sulfoximine **4a** was tried with (bromoethynyl)benzene (**1b**)[9a–d] as an alkynylation reagent (Table 1, entries 1–3), but under these reaction conditions, only the homocoupled diyne (not shown) was identified in the reaction mixture. To our delight, however, the application of the reaction conditions reported by Stahl and co-workers for the oxidative amidation of terminal alkynes[2a] (Table 1, entry 5), and Evano and co-workers for the oxidative alkynylation of diaryl imines[2b] (Table 1, entry 6) proved effective, thus leading to the yne sulfoximine **2b**, with the former protocol being slightly higher yielding. The use of copper(II) chloride as a catalyst and sodium carbonate as a base in 1,4-dioxane proved optimal to afford synthetically useful yields of **2b** starting from **4a** and phenylacetylene (**3a**). With toluene as the solvent (Table 1, entry 6) similar results to those obtained with 1,4-dioxane were observed, however the starting materials were initially more soluble in 1,4-dioxane, and as such, this was used as the

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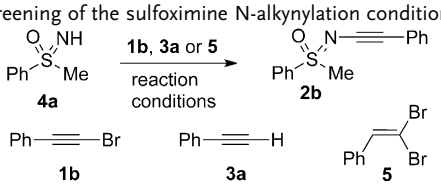
Table 1: Screening of the sulfoximine N-alkynylation conditions.

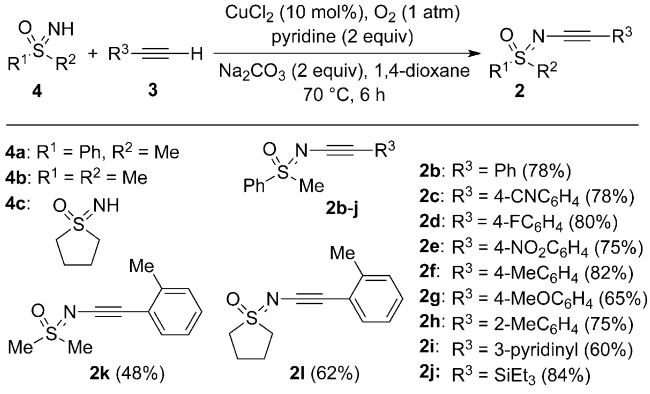


Entry	Alkynylation reagent	Reaction conditions[a]	Yield [%]
1	**1b**	CuI (5 mol%), 2-acetylcyclohexanone (20 mol%), Cs_2CO_3 (2 equiv), 1,4-dioxane, 4 Å M.S., 50°C	–
2	**1b**	$CuSO_4{\cdot}5H_2O$ (5 mol%), 1,10-phenanthroline (20 mol%), K_3PO_4 (2 equiv), toluene, 60°C	–
3	**1b**	CuCN (5 mol%), DMEDA (20 mol%), K_3PO_4 (2 equiv), toluene, 110°C	–
4	**3a**	$CuCl_2$ (10 mol%), Na_2CO_3 (2 equiv) 1,4-dioxane, 70°C, O_2	59
5	**3a**	$CuCl_2$ (10 mol%), pyridine (2 equiv), Na_2CO_3 (2 equiv), 1,4-dioxane, 70°C, O_2	78
6	**3a**	$CuCl_2$ (10 mol%), pyridine (2 equiv), Na_2CO_3 (2 equiv), toluene, 70°C, O_2	75
7	**5**	CuI (12 mol%), DMEDA (18 mol%), Cs_2CO_3 (4 equiv), 1,4-dioxane, 70°C	–

[a] Use of 2 equiv of sulfoximine to alkynylation reagent. O_2 employed at a pressure of 1 atm. DMEDA = *N*,*N*′-dimethylethylenediamine.

solvent for the remainder of the study. The use of molecular oxygen was also essential for the reaction to proceed. Furthermore, it was determined that the presence of two equivalents of pyridine provided higher yields (compare entries 4 and 5), by preventing homocoupling of the alkyne to form the Glaser–Hay dimer.[10] Attempts to employ (2,2-dibromovinyl)benzene (**5**)[9e] as the alkynylation reagent remained unsuccessful (Table 1, entry 7).

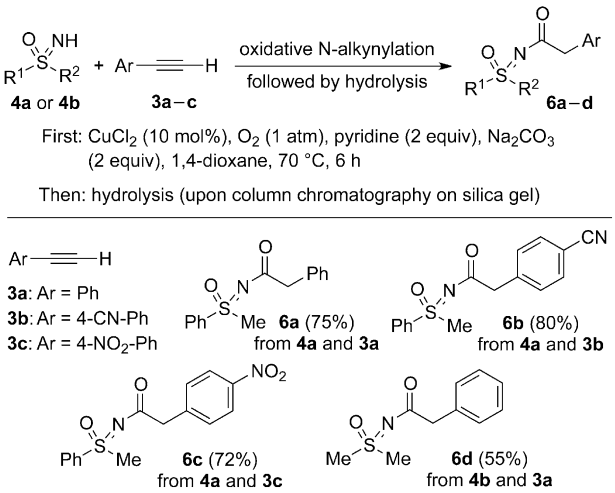
Following optimization of the reaction conditions, the substrate scope of the alkynylation protocol was investigated (Scheme 2). Initially, *S*,*S*-methylphenyl sulfoximine [(*S*,*S*)-**4a**] was coupled with a range of terminal alkynes to afford the yne sulfoximines **2b–j**. In general, the products were obtained in moderate to high yields. Various electron-donating and electron-withdrawing moieties on the aryl alkynes were well tolerated in this reaction process, and overall the electronic



Scheme 2. Substrate scope of the oxidative N-alkynylation.

properties of the terminal alkyne coupling partner did not significantly affect the yield. Substrates bearing a 3-pyridinyl or a triethylsilyl group also reacted well, thus affording the corresponding products **2i** and **2j** in 60 and 84% yield, respectively. It is important to note that all the products were obtained after purification by column chromatography using triethylamine-deactivated silica gel.[11] In addition to (*S*,*S*)-**4a**, reactions with *S*,*S*-dimethyl sulfoximine [(*S*,*S*)-**4b**] and *S*,*S*-tetramethylene sulfoximine [(*S*,*S*)-**4c**] worked well, thus affording the yne sulfoximines **2k** and **2l** in moderate yields. Attempts to employ alkyl-substituted terminal alkynes (1-hexyne and 1-octyne) under the previously optimized reaction conditions remained unsuccessful.

During the investigation into the scope of the N-alkynylation of sulfoximines it was observed in some cases that the yne sulfoximines were sensitive to hydrolysis, in particular on silica gel. To further exploit this, reaction mixtures containing newly formed yne sulfoximines were subjected to normal silica gel chromatography, which led, to our delight, to the corresponding N-acyl sulfoximines **6** in good overall yields (Scheme 3).



Scheme 3. Products of sequential oxidative N-alkynylations and hydrolyses.

As confirmed by X-ray crystal structure analysis of **6b** (see the Supporting Information),[11,12] the hydrolysis of the yne sulfoximines was regioselective, thereby providing access to products which commonly involve reactions with highly active acyl donors such as acyl halides.[13,14] This novel oxidative coupling protocol, in contrast, is mild and utilizes alternative starting materials (alkynes), which might prove beneficial in many target-driven syntheses involving sensitive substrates and products.

In conclusion, we have developed a synthetically useful protocol for the preparation of yne sulfoximines through copper-catalyzed oxidative couplings of sulfoximines and terminal alkynes.[15] The mild reaction conditions involve a cheap catalyst and molecular dioxygen as the oxidant. Various yne sulfoximines can be generated from the corresponding sulfoximines whereby both electron-rich and electron-deficient terminal alkynes are well tolerated. A modified

work-up (chromatography) opens up straightforward access to the respective N-acyl sulfoximines by acid-mediated hydrolysis of the yne sulfoximines during chromatography. Various chemical transformations and applications of the scarcely reported yne sulfoximines (which we consider ynamide analogues accessible in enantiopure form) are envisaged and these will be reported in due course.

Experimental Section

Typical procedure for the N-alkynylation of sulfoximines: A 100 mL three-necked flask equipped with a stirring bar was loaded with $CuCl_2$ (6 mg, 10 mol%), sulfoximine (1.0 mmol) and Na_2CO_3 (106 mg, 1.0 mmol). Under an oxygen atmosphere (1 atm), a solution of pyridine (1.0 mmol) in 1,4-dioxane (5 mL) was added. After heating to 70 °C, a solution of the terminal alkyne (0.5 mmol) in 1,4-dioxane (3 mL) was added slowly to the reaction mixture using a syringe pump over 4 h. After the addition, the reaction mixture was stirred at 70 °C for an additional 2 h, and then cooled to room temperature. The reaction mixture was filtered over a plug of triethylamine-deactivated silica gel and washed with dichloromethane and concentrated. Purification by triethylamine-deactivated silica gel column chromatography afforded the yne sulfoximine.

Typical Procedure for the N-alkynylation of sulfoximines: As above, however, the crude reaction mixture was subjected to normal silica gel column chromatography to afford the corresponding N-acyl-sulfoximines.

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