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Synthesis of *N*-Imidoyl and *N*-Oxoimidoyl Sulfoximines from 1-Alkynes, *N*-Sulfonyl Azides, and Sulfoximines

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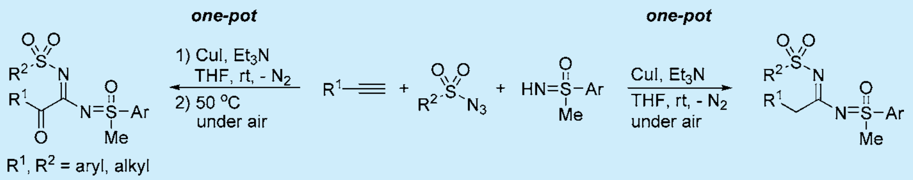
Supporting Information

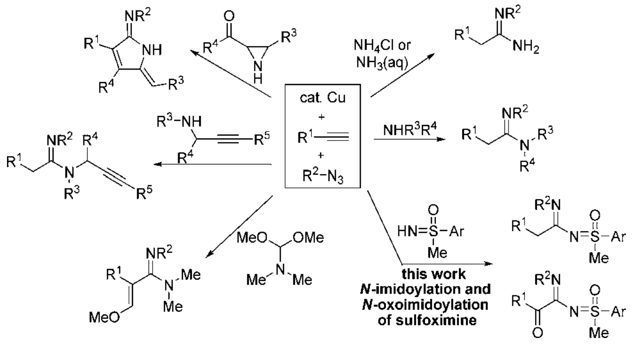


ABSTRACT: *N*-Imidoylation of sulfoximines is developed from a Cu-catalyzed three-component reaction from 1-alkynes, *N*-sulfonyl azides, and sulfoximines in THF at room temperature under air. In addition, *N*-oxoimidoylation of sulfoximines is accessed from a Cu-catalyzed three-component reaction from 1-alkynes, *N*-sulfonyl azides, and sulfoximines in THF at room temperature followed by a Cu-catalyzed oxidative reaction at 50 °C under air, producing *N*-oxoimidoyl sulfoximines.

Because sulfoximines are important privileged scaffolds in ligands,[1] chiral auxiliaries,[2] and bioactive compounds,[3] the establishment of robust synthetic approaches for the preparation of sulfoximines and their functionalizations is highly required.[4] Consequently, introduction of new functional groups onto sulfoximines has been constantly explored. Functionalization of sulfoximines is generally divided into two categories: α-C−H and N−H bond functionalizations. Among these methods, N−H bond functionalization is more attractive for synthetic interest due to the inherent nucleophilicity of the nitrogen atom. In this context, Bolm, Harmata, and many chemists have reported a wide range of N−H bond functionalizations such as *N*-silylation,[5] *N*-halogenation,[6] *N*-acylation,[7] *N*-alkylation,[7a,8] *N*-vinylation,[9] and *N*-arylation[10] of N−H sulfoximines and N−P[11] and N−S[12] bond formation. However, we are not aware of any reported examples of *N*-imidoylation of sulfoximines.

Recently, Chang and co-workers have demonstrated Cu-catalyzed three-component reactions of 1-alkynes, *N*-sulfonyl azides, and amines for the preparation of amidines.[13] In addition, several amidines were prepared through a Cu-catalyzed multicomponent reaction using nitrogen nucleophiles such as aziridines,[14] propargyl amines,[15] and *N*,*N*-dimethylformamide dimethyl acetals[16] (Scheme 1). Accordingly, we envisioned that if sulfoximines would play a role as nucleophile in the reaction with ketenimine generated in situ from a Cu-catalyzed reaction of 1-alkynes with *N*-tosyl azides, *N*-imidoyl sulfoximines would be produced. However, the fact that sulfoximines exhibit lower nucleophilic character at the nitrogen than amines and imines provides a synthetic challenge. Herein we developed *N*-imidoylation of sulfoximines from a Cu-catalyzed three-component reaction from 1-alkynes, *N*-sulfonyl azides, and sulfoximines in THF at room temperature under air. The *N*-oxoimidoylation of sulfoximines is also accessed from a Cu-catalyzed three-component reaction from 1-alkynes, *N*-sulfonyl azides, and sulfoximines in THF at room temperature followed by a Cu-catalyzed oxidative reaction at 50 °C under air, producing *N*-oxoimidoyl sulfoximines.

Scheme 1. Synthetic Approach for *N*-Imidoylation



First, we attempted *N*-imidoylation of sulfoximine from a Cu-catalyzed three-component reaction of phenylacetylene (**1a**), *N*-tosyl azide (**2a**), and *S*-methyl-*S*-phenyl sulfoximine (**3a**) (Table 1). A wide range of copper catalysts such as CuCl, CuBr, and CuI were examined to disclose that CuI was the catalyst of choice (entries 1−3). Tetrahydrofuran (THF) gave the best result among the solvents such as THF, CH_3CN, and toluene (entries 3−5). A number of bases such as Et_3N, pyridine, and K_2CO_3 were tested to reveal that Et_3N was the base of choice (entries 3, 7, and 8). The best result was obtained from the reaction between **1a** (0.2 mmol), **2a** (1.2 equiv), **3a** (1.0 equiv), and Et_3N (1.2 equiv) in the presence of

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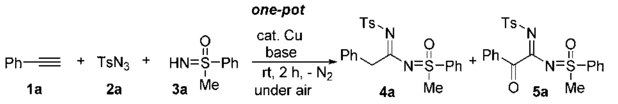
Table 1. Reaction Optimization[a]



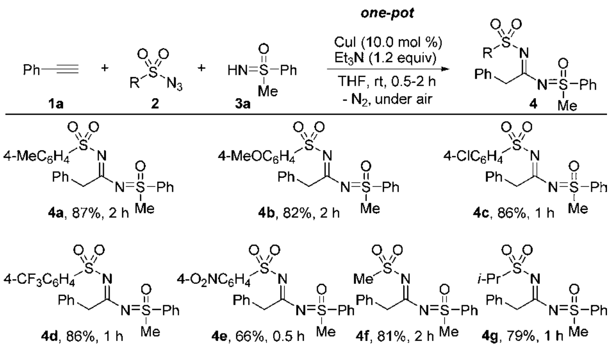
entry	cat.	base	solvent	yield (%) 4a	yield (%) 5a
1	CuCl	Et_3N	THF	67	
2	CuBr	Et_3N	THF	84	
3	CuI	Et_3N	THF	87	
4	CuI	Et_3N	CH_3CN	73	
5	CuI	Et_3N	toluene	81	
6	CuI		THF	29	
7	CuI	pyridine	THF	44	
8	CuI	K_2CO_3	THF	0	
9[b]	CuI	Et_3N	THF	59	11

[a] Reactions were carried out with **1a** (0.2 mmol), **2a** (1.2 equiv), **3a** (1.0 equiv), Cu (10.0 mol %), and base (1.2 equiv) in solvent (1.0 mL) at rt under air. [b] 50 °C.

CuI (10.0 mol %) in THF at room temperature for 2 h under air, providing *N*-imidoyl sulfoximine (**4a**) in 87% yield (entry 3).

Next, various *N*-sulfonyl azides **2** were investigated in the reaction of phenylacetylene (**1a**) with sulfoximine (**3a**) (Scheme 2). Benzenesulfonyl azide (**2b**) having an electron-donating methoxy group gave the desired *N*-imidoyl sulfoximine **4b** in 82% yield. Likewise, benzenesulfonyl azides (**2c** and **2d**) bearing electron-withdrawing chloro and trifluoromethyl groups underwent the Cu-catalyzed three-component reaction to provide the desired products **4c** and **4d** in 86% yields. However, strong electron-withdrawing nitro substituted sulfonyl azide **2e** is slightly less reactive, leading to the formation of **4e** in 66% yield. Methane- and 2-propane-sulfonyl azides (**2f** and **2g**) afforded the *N*-imidoyl sulfoximines **4f** and **4g** in 81% and 79% yields, respectively. Thus, *N*-tosyl azide **2a** was selected as best azide partner in view of yield of the reaction and its availability.

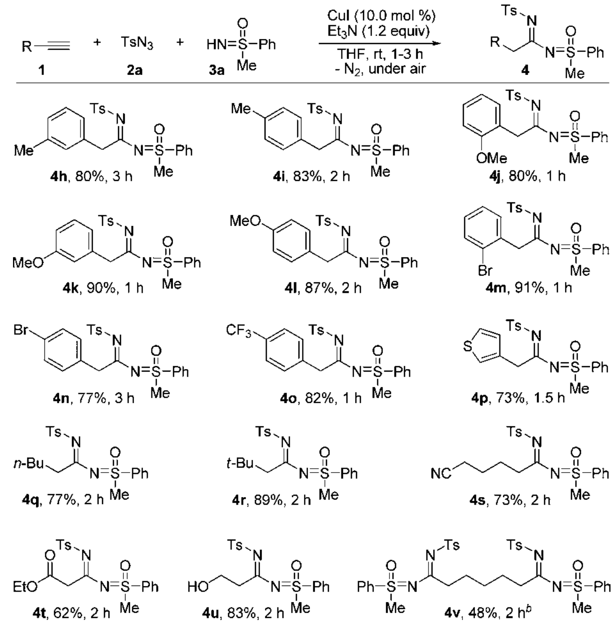
Scheme 2. Scope of *N*-Sulfonyl Azides[a]



[a] Reactions were carried out with **1a** (0.2 mmol), **2** (1.2 equiv), **3a** (1.0 equiv), CuI (10.0 mol %), and Et_3N (1.2 equiv) in THF (1.0 mL) at rt under air.

Having the promising results in hand, we studied the scope and limitation of this Cu-catalyzed three-component reaction with respect to variously substituted 1-alkynes (**1**) to react with *N*-tosyl azide (**2a**) and sulfoximine (**3a**) (Scheme 3). Electronic variation of substituents on the arene moiety of arylacetylenes **1** did not largely affect the efficiency of the *N*-imidoylation of sulfoximines. For example, arylacetylenes possessing electron-donating methyl and methoxy groups underwent the Cu-catalyzed three-component reaction, providing the corresponding *N*-imidoyl sulfoximines (**4h–l**) in good to excellent yields ranging from 80% to 90%. In addition, electron-withdrawing bromide functional group frequently employed in coupling reactions was tolerated. The fact that *o*-bromo- and -methoxy-substituted phenylacetylenes are successfully employed to the present transformation indicates that steric hindrance does not affect the reaction efficiency. 4-Trifluoromethyl-substituted phenylacetylene is suitable for the present transformation, affording to the *N*-imidoyl sulfoximine **4o** in 82% yield. Gratifyingly, Cu-catalyzed *N*-imidoylation using 3-ethynylthiophene **1p** took place to provide **4p** in 73% yield. When aliphatic alkynes such as 1-hexyne (**1q**) and 3,3-dimethyl-1-butyne (**1r**) were employed in the present conditions, the desired products were produced in good yields. It is noteworthy that alkynes (**1s** and **1t**) including nitrile and ethoxycarbonyl groups readily took part in the *N*-imidoylation to furnish the desired products **4s** (73%) and **4t** (62%). An unmasked hydroxyl group turned out to be compatible with the optimal reaction conditions (**4u**). 1,6-Hetadiyne (**1v**), sulfoximine (**3a**, 2.0 equiv), *N*-tosyl azides (**2a**, 2.4 equiv), and Et_3N (2.4 equiv) in the presence of CuI (10.0 mol %) underwent 2-fold *N*-imidoylation, resulting in the formation of **4v** in acceptable yield.

Scheme 3. Scope of Terminal Alkynes[a]



[a] Reactions were carried out with **1** (0.2 mmol), **2a** (1.2 equiv), **3a** (1.0 equiv), CuI (10.0 mol %), and Et_3N (1.2 equiv) in THF (1.0 mL) at rt. [b] Reactions were carried out with **1v** (0.2 mmol), **2a** (2.4 equiv), **3a** (2.0 equiv), CuI (10.0 mol %), and Et_3N (2.4 equiv) in THF (1.0 mL) at rt.

Encouraged by these results, we examined the influence of sulfoximines in the reaction of phenylacetylene with *N*-tosyl azide (Scheme 4). Electronic variation of a wide range of substituents on the aryl group of sulfoximines **3** displayed little effect on the reaction efficiency. Sulfoximines bearing electron-donating methyl and methoxy groups on the aryl ring smoothly underwent *N*-imidoylation to produce the desired *S*-aryl-*N*-imidoyl sulfoximines **6a** (90%) and **6b** (85%) under mild

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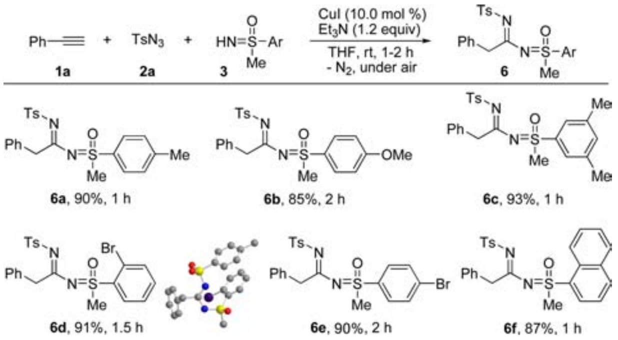
Scheme 4. Scope of Sulfoximines[a]

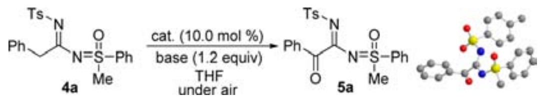


[a]Reactions were carried out with **1a** (0.2 mmol), **2a** (1.2 equiv), **3** (1.0 equiv), CuI (10.0 mol %), and Et_3N (1.2 equiv) in THF (1.0 mL) at rt under air.

conditions. The *N*-imidoylation reaction was amenable with respect to 3,5-dimethylphenyl sulfoximine to deliver the product **6c** in 93% yield. 2- and 4-bromo-substituted sulfoximines underwent the Cu-catalyzed three-component reaction, affording the desired sulfoximines (**6d** and **6e**) in 91% and 90% yields, respectively. The structure of **6d** was confirmed by X-ray crystallography. The *N*-imidoylation reaction also took place in *S*-1-naphthyl sulfoximine, leading to the fromation of *S*-1-naphthly-*N*-imidoyl sulfoximine (**6f**) in 87% yield.

When the Cu-catalyzed three-component reactions were carried out with phenylacetylene, *N*-tosyl azide, and sulfoximine at 50 °C under air, the *N*-oxoimidoyl sulfoximine **5a** was unexpectedly obtained albeit in low yield (11%) (entry 9, Table 1). The structure of **5a** was confirmed by X-ray crystallography. Because this type of compound would be a new privileged structure obtained from the Cu-catalyzed multicomponent reaction in one pot and has not been mentioned in any reports to our knowledge, we examined carefully the optimal reaction conditions for the preparation of *N*-oxoimidoyl sulfoximines (Table 2).[17] This reaction did not proceed without CuI and Et_3N under air (entries 1 and 2). Also, no desired compound was produced under nitrogen atmosphere even when CuI and Et_3N were used (entry 3). These results indicate that CuI, Et_3N, and molecular oxygen are essential for the *N*-oxoimidoylation. The optimal result was achieved from *N*-imidoyl sulfoximine **4a** (0.2 mmol) in the presence of CuI (10.0 mol %) and Et_3N (1.2 equiv) in THF at 50 °C for 20 h under air, providing the *N*-oxoimidoyl product **5a** in 66% yield (entry 4). Although molecular oxygen atmosphere acceletated the oxidative reaction, the product yield decreased slightly to 53% yield (entry 5). Next, isotopically labeled experiment was carried to examine the source of oxygen in the oxidation reaction of the *N*-imidoyl product **4a**. When the present reaction was conducted under $^{18}O_2$ atmosphere, the ^{18}O-inserted *N*-oxoimdoyl compound **5a**-[^{18}**O**] was produced in 54% yield (entry 6). These results indicate that oxygen was obtained from molecular oxygen (see the Supporting Information).

Table 2. Oxidation Conditions of *N*-Imidoyl Sulfoximines[a]

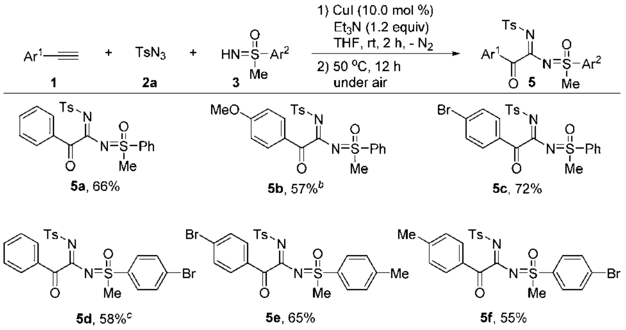


entry	cat.	base	atmosphere	temp (°C)	time (h)	yield (%)
1		Et_3N	air	50	24	0
2	CuI		air	70	24	0
3	CuI	Et_3N	N_2	50	24	0
4	CuI	Et_3N	air	50	20	66
5	CuI	Et_3N	O_2	50	8	53
6	CuI	Et_3N	$^{18}O_2$	50	8	54[b]

[a]Reactions were carried out with **4a** (0.2 mmol), CuI (10.0 mol %), and Et_3N (1.2 equiv) in THF (1.0 mL) under air. [b]**5a**[^{18}**O**] was obtained.

We examined the scope and limitations of the Cu-catalyzed *N*-oxoimidoylation from 1-alkynes, *N*-tosyl azides, and sulfoximines in one pot (Scheme 5). 4-Methoxy- and 4-bromophenylacetylenes are applicable to the present transformation, affording the desired products **5b** (57%) and **5c** (72%). When 4-bromophenyl sulfoximine was employed in the *N*-oxoimidoylation reaction of phenylacetylene with *N*-tosyl azide, the *N*-oxoimidoyl product **5d** was produced in 58% yield. 4-Bromophenylacetylene was compatible with Cu-catalyzed *N*-oxoimidoylation conditions using 4-methylphenyl sulfoximine, resulting in the formation of **5e** in 65% yield. Cu-catalyzed *N*-oxoimidoylation between 4-methylphenylacetylene, *N*-tosyl azide, and 4-bromophenyl sulfoximine under air also worked, leading to the corresponding product **5f** in 55% yield. However, when a wide range of terminal alkynes such as 1-hexyne, propargyl alcohol, ethyl propiolate, 2-methylbut-1-en-3-yne, and 1-ethynylcyclohex-1-ene were treated with *N*-tosyl azide and *S*-methyl-*S*-phenyl sulfoximine under the optimal reaction conditions, the corresponding *N*-oxoimidoyl products were not obtained.

Scheme 5. Cu-Catalyzed *N*-Oxoimidoylation from 1-Alkynes, *N*-Tosyl Azides, and Sulfoximines in One Pot[a]



[a]Reactions were carried out with **1** (0.2 mmol), **2a** (1.2 equiv), **3** (1.0 equiv), CuI (10.0 mol %), and Et_3N (1.2 equiv) in THF (1.0 mL) at rt for 2 h under air, and then the reaction mixture was heated to 50 °C. [b]For 1 h at rt. [c]For 3 h at rt.

In conclusion, we have developed an *N*-imidoylation of sulfoximines from the Cu-catalyzed three-component reaction from 1-alkynes, *N*-sulfonyl azides, and sulfoximines in THF at room temperature under air. The *N*-oxoimidoylation of sulfoximines is also described from the Cu-catalyzed three-component reaction in THF at room temperature followed by oxidative reaction from 1-alkynes, *N*-sulfonyl azides, and sulfoximines at 50 °C under air, producing *N*-oxoimidoyl sulfoximines.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, X-ray crystallography data (**5a** and **6d**), and copies of NMR spectra for all products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01553.

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Author Contributions

†W.C. and J.K. contributed equally.

Notes

The authors declare no competing financial interest.

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