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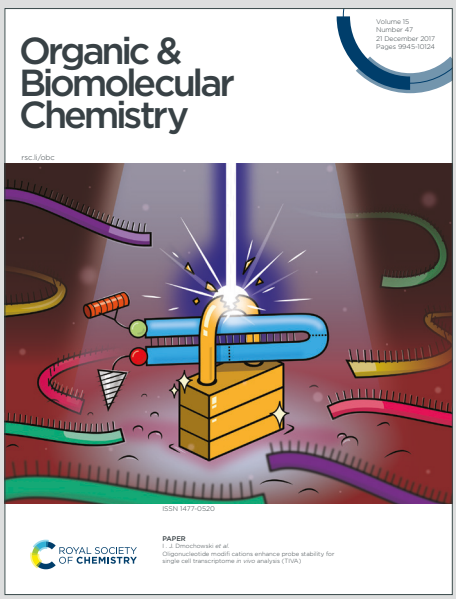

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COMMUNICATION

An Efficient Imidation of Thioethers with Nitrene in Water

Tao Feng, Zhihui Tang, Xiaoli Luo, and Junming Mo*[a]

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The first imidation of thioethers with free nitrene in water was realized. *N*-Cbz sulfilimines are formed via imidation of thioethers with free nitrene generated from α elimination of nosyloxycarbamates. In this work, water is successfully applied as solvent for free nitrene, and transition metal catalyst is not needed.

In recent years, sulfoximines have received a lot of attention owing to their interesting biological activities.[1] Methionine sulfoximine (MSO) and buthionine sulfoximine (BSO) can be employed as inhibitors of glutathione biosynthesis.[2] Sulfoximines are also potential drugs as prophylactic antiasthmatics[3] and HIV-1 protease inhibitors.[4] In addition, in the field of organic synthesis, sulfoximines have been widely used to synthesize pseudopeptides[5] and as directing groups for C-H activation.[6] Chiral sulfoximines with stereogenic sulfur atoms can also be utilized as efficient chiral ligands.[7]

These interesting applications of sulfoximines prompted chemists to develop various synthesis strategies for the preparation of sulfoximines. At present, there are two main synthetic routes for sulfoximines.[8] One route is to imidize sulfides followed by oxidation of sulfilimines.[9] The other way is imidation of sulfoxides which usually come from oxidation of sulfides.[10] Recently, synthesis of NH-sulfoximines from sulfides by one-pot N- and O-transfers was developed.[11] No matter which route is taken, imidation of sulfur is the key step to generate sulfoximines. Despite many strategies are available for imidation of sulfides and sulfoxides, there are still many challenges. Many imidating reactions of sulfides and sulfoxides usually need toxic or explosive reagents such as azides,[12] *t*-BuOCl[13] and *O*-mesitylenesulfonylhydroxylamine (MSH),[14] or require transition metal catalysts with iminoiodinanes reagents.[15] In recent year, the use of water as solvent attracted attention in organic synthesis because it have benefits on avoiding use of volatile organic solvents, improving reactivity and simplifying product isolation.[16] However, most of successful sulfur imidations rely on water sensitive reagents or water sensitive nitrene transfer reactions.[12,15] So organic solvents are needed for most of sulfur imidations, and using water as solvent is rare.[11b] In addition, many of the protecting groups introduced into sulfoximine groups are sulfonyl group[15a,17] which are difficult to be deprotected. Only a few preparations of NH sulfoximines were reported.[10b,11,15d,15f] Therefore, it is still necessary and attractive to develop safe, environmentally friendly and efficient synthetic methods of sulfoximines.

Transition metal catalyzed nitrene transfer reactions are powerful tools for imidation of thioethers (Scheme 1a, 1b).[8] Compared with nitrene transfer, methods for imidation of thioethers via direct free nitrene addition are limited. Ethyl nosyloxycarbamate is a well-developed and versatile aminating agent for C-N bond formation.[18] Nitrene generated from α elimination of ethyl nosyloxycarbamate is reactive species that reacts quickly with many substrates via nitrene addition without transition metal catalysts. As a safe, stable and low cost nitrene precursor, nosyloxycarbamate is a suitable candidate of iminating agent for green sulfur imidation. In recent years several *N*-OSO_2R carbamates have been applied to imidation of sulfides via different types of reaction. Acid catalyzed imidation of sulfides with ethyl trifluoromethanesulfonyloxycarbamate (TfONHCO$_2$Et) via nucleophilic substitution was disclosed by Tamura.[19] Lebel reported rhodium catalyzed nitrene transfer of chiral *N*-mesyloxycarbamates to sulfilimines (Scheme 1c).[9d] Herein we disclose an efficient and environmentally friendly thioether imidation in water (Scheme 1d). *N*-Cbz sulfilimines are formed via imidation of thioethers with free nitrene generated from α elimination of nosyloxycarbamates. As we know, free nitrenes are sensitive to water and easily hydrolyzed in aqueous media. Although several examples of catalytic nitrene transfer reactions in water have been reported,[20] reactions of free nitrenes with substrates in water are still challenging. In the present study, water is successfully applied as solvent in the

[a] *Guangxi Key Laboratory of Chemistry and Engineering of Forest Products, College of Chemistry and Chemical Engineering, Guangxi University for Nationalities, Nanning 530006 (China), moandli@163.com.*

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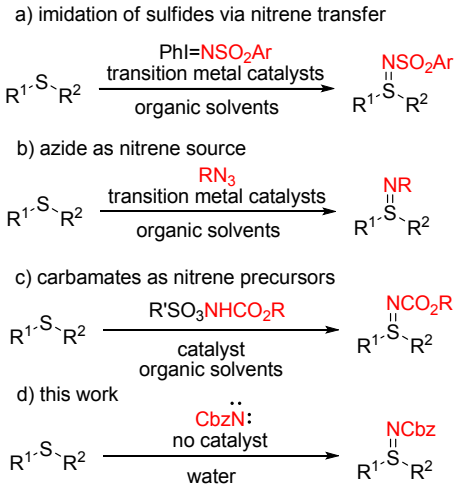
addition of free nitrene to thioethers, and transition metal catalyst is not needed.



Scheme 1. Imidation of sulfides via nitrene transfer and nitrene addition.

To avoid unexpected side reactions in further synthetic transformations, protected sulfilimines and sulfoximines are required. Cbz group is a good choice as the protecting group of sulfilimines and sulfoximines owing to its stability and easy deprotection.[21] In order to introduce Cbz group to sulfilimines, we started our study by using benzyl nosyloxycarbamate as imidating agent. Experimentally, we treated thioether **1a** with benzyl nosyloxycarbamate **2** using CH_2Cl_2 as solvent. Not surprisingly, no desired sulfilimine product **3a** was observed without any acid catalyst or acid binding agent due to stability of benzyl nosyloxycarbamate (Table 1, entry 1). Different from acid catalyzed imidation of thioethers with $TfONHCO_2Et$ reported by Tamura,[19] acid did not promote the reaction effectively (Table 1, entry 2). Fortunately, with Na_2CO_3 as base, we observed the formation of sulfilimine product **3a** with low but encouraging yield after 12 hours (32%, Table 1, entry 3). When this proof-of-principle result was established, we next attempted to optimize the reaction conditions. Among the bases screening, weaker bases like DIPEA and Et_3N, were not effective in giving the sulfilimine product (Table 1, entry 4-5). Also, NaOH was not good acid binding agent in this reaction (Table 1, entry 6). The possible reason was benzyl nosyloxycarbamate and sulfilimine would decompose quickly in strong basic solution. Encouraging result emerged when CaO was used as base. The yield of **3a** increased from 32% to 47% (Table 1, entry 7). With CaO as base, effect of some common solvents in this reaction were studied. THF, acetonitrile and toluene was not effective in promoting this reaction (Table 1, entry 8-10). Surprisingly, when water was used as solvent, the reaction was completed quickly in 40 minutes with 53% yield (Table 1, entry 11). The shorter reaction time (40 mins) in water may be the reason why the yield increases. TLC and NMR analysis of the reaction mixture revealed the benzyl nosyloxycarbamate was consumed quickly in basic aqueous solution. To obtain more sulfilimine product, two equivalent benzyl nosyloxycarbamate was added. However, complex product was observed and cannot be isolated (Table 1, entry 12). The reason may be the decomposition of **3a** via addition of the nitrene to the S=N bond. Further attempt was to use more thioether to capture nitrene. Sulfilimine product **3a** was obtained in good yield with two equivalent thioether **1a** (75%, Table 1, entry 13). Similarly, adding **2** in 4 portions (0.25 equiv each time) can also give a good result (70%, Table 1, entry 14). Higher temperature will accelerate hydrolysis of nitrene and lead to lower yield (33%, Table 1, entry 15).

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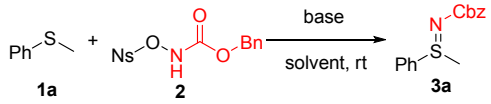
Table 1. Optimization of the imidation of thioethers[a].

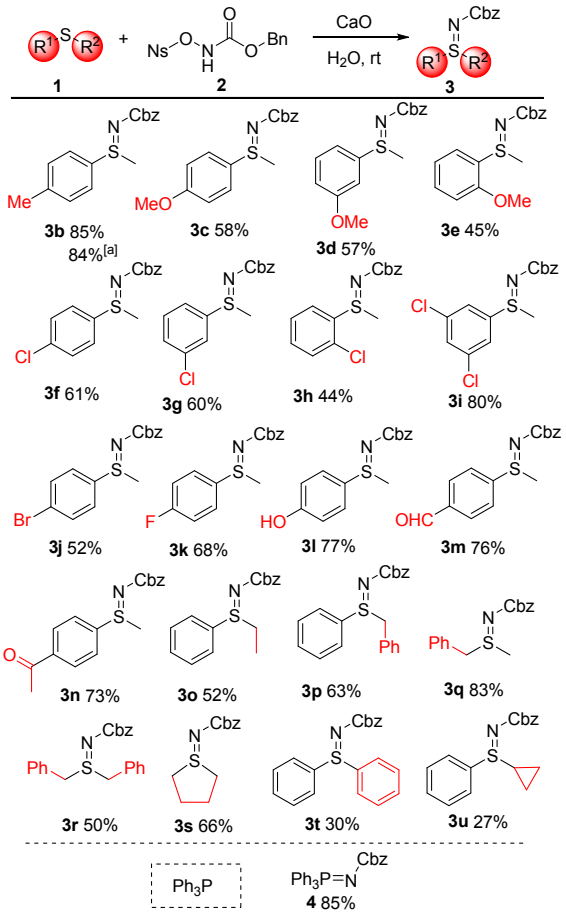


entry	base/acid	solvent	yield (%)[b]
1	-	CH_2Cl_2	0
2	CF_3COOH	CH_2Cl_2	0
3	Na_2CO_3	CH_2Cl_2	32
4	DIPEA	CH_2Cl_2	<5
5	Et_3N	CH_2Cl_2	<5
6	NaOH	CH_2Cl_2	<5
7	CaO	CH_2Cl_2	47
8	CaO	THF	12
9	CaO	MeCN	10
10	CaO	toluene	17
11	CaO	H_2O	53
12	CaO	H_2O	0[c]
13	CaO	H_2O	75[d]
14	CaO	H_2O	70[e]
15	CaO	H_2O	33[f]

[a] Reaction condition: **1a** (0.1 mmol, 1.0 equiv), **2** (0.1 mmol, 1.0 equiv), base (1.0 equiv), solvent (1.0 mL), room temperature; entry 1-10:12 h; entry 11-13: 40 min. [b] Isolated yield based on **2**. [c] **2** (2.0 equiv), CaO (2.0 equiv). [d] **1a** (2.0 equiv). [e] **1a** (1.2 equiv), **2** (1.0 equiv) was divided into 4 portions and added every 10 mins. [f] **1a** (2.0 equiv), reaction temperature: 50 °C.

With optimized reaction condition in hand, the scope of the thioether substrate reacting with benzyl nosyloxycarbamate was examined (Scheme 2). Both electron-donating and electron-withdrawing substituents installed on the *S*-phenyl unit of thioether **1a** were tolerated (**3b**-**3k**). Substrates bearing active functional groups (hydroxyl, formyl and acetyl group) were also obtained in good yields (**3l**-**3n**). Replacing methyl group of thioether **1a** with other aliphatic groups, such as ethyl and benzyl group, did not significantly affect efficiency of the reaction (**3o**, **3p**). Dialkyl thioether substrates also reacted well with good yields (**3q**-**3s**). When thioether **1a** was changed to bulky substrates like diphenyl thioether and phenyl cyclopropyl thioether, notable decreases in yields were

observed (**3t**, **3u**). Large scale reaction was also tested. Under similar reaction condition, product **3b** was obtained in good yield (2.41 g, 84 %). When Ph_3P was used as starting material, useful phosphinimine ylide **4** was also obtained in good yield. Imidation of sulfoxides cannot occur under this condition. The possible reason is weak nucleophilic ability of sulfoxide.

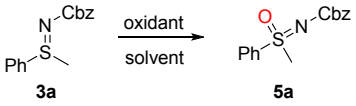


Scheme 2. Reaction scope with thioethers. Reaction condition: **1** (0.2 mmol, 2.0 equiv), **2** (0.1 mmol, 1.0 equiv), CaO (1.0 equiv), water (1.0 mL), room temperature, 40 min. [a] Gram scale: **1b** (20 mmol, 2.0 equiv), **2** (10 mmol, 1.0 equiv), CaO (1.0 equiv), water (20 mL), room temperature, 40 min.

Oxidation of *N*-Cbz sulfilimines could provide *N*-Cbz sulfoximines. To find out efficient oxidative method, a number of reaction conditions were tested with *N*-Cbz sulfilimines **3a**. With water as solvent, H_2O_2, NaOCl, *m*CPBA and *t*BuOOH were not effective in oxidative process (Table 2, entry 1-4). When $KMnO_4$ was used with water as solvent, an excellent yield was obtained (Table 2, entry 5). Using ethanol as solvent gave different results among oxidants screening (Table 2, entry 6-10). In these cases, $KMnO_4$ was inefficiency, and *m*CPBA was the best oxidant with 83% yield (Table 2, entry 8).

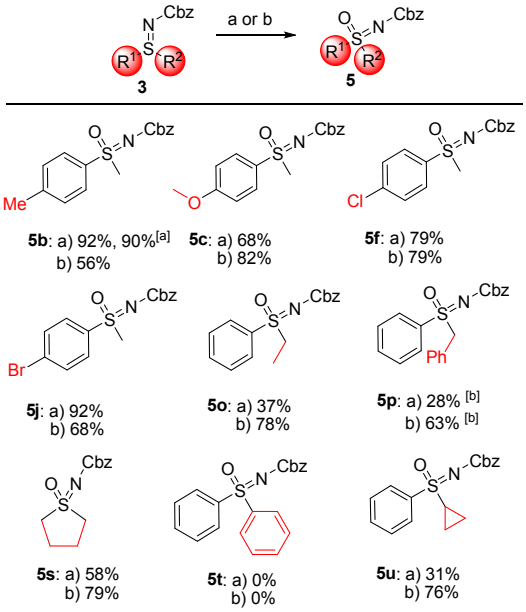
Once optimal protocols of oxidation were established, selected *N*-Cbz sulfilimines were examined with $KMnO_4$ condition and *m*CPBA condition respectively. Under both condition, *N*-Cbz sulfilimines derived from aryl substituted thioanisole and tetrahydrothiophene gave good to excellent yields (Scheme 3, **5a**-**5c**, **5f**, **5j**). $KMnO_4$ was not efficient oxidant in the case of **5o**, **5p** and **5u**. Interestingly, with *m*CPBA as oxidant, substrates **5o**, **5p** and **5u** were obtained with higher yield compared with $KMnO_4$ condition. At room temperature, oxidation of bulky sulfilimine **3p** is very inefficient (yield of **5p** < 5%). Raising temperature to 50 °C can increase yield of **5p** to 63%. Bulky diphenyl *N*-Cbz sulfilimine **3t** resulted in no conversion under both conditions. Starting material **3t** could be recovered from reaction mixture. Oxidation could be realized to obtain the products **5b** in gram scale with excellent yield (2.71 g, 90 %).

Table 2. Optimization of the oxidation of sulfilimines[a].



entry	oxidant	solvent	yield (%)[b]
1	H_2O_2 (10 equiv)	H_2O	0
2	NaOCl (5 equiv)	H_2O	<5
3	*m*CPBA (5 equiv)	H_2O	0
4	*t*BuOOH (5 equiv)	H_2O	<5
5	$KMnO_4$ (5 equiv)	H_2O	86
6	H_2O_2 (10 equiv)	EtOH	0
7	NaOCl (5 equiv)	EtOH	<5
8	*m*CPBA (5 equiv)	EtOH	83
9	*t*BuOOH (5 equiv)	EtOH	0
10	$KMnO_4$ (5 equiv)	EtOH	<5

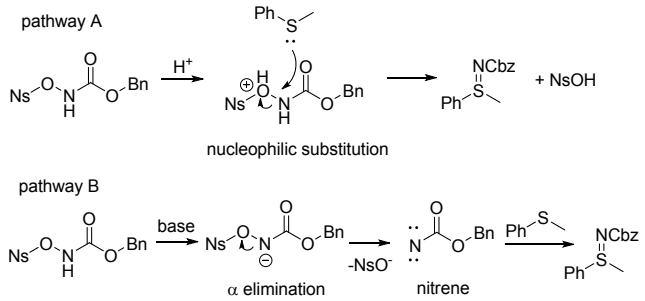
[a] Reaction condition: **3a** (0.1 mmol, 1.0 equiv), oxidant, solvent (1.0 mL), room temperature, 24h. [b] Isolated yield based on **3a**.



Scheme 3. Synthesis of *N*-Cbz sulfoximines via oxidation. Reaction condition: method a: **3** (0.1 mmol, 1.0 equiv), $KMnO_4$ (0.5mmol, 5.0

equiv), water (2.0 mL), room temperature, 24 h. method b: **3** (0.1 mmol, 1.0 equiv), *m*CPBA (0.5 mmol, 5.0 equiv), EtOH (2.0 mL), room temperature, 24 h. [a] Gram scale: **3b** (10.0 mmol, 1.0 equiv), $KMnO_4$ (50.0 mmol, 5.0 equiv), water (50.0 mL), room temperature, 24 h. [b] Reaction temperature: 50 °C.

Two distinct reaction pathways are possible for the imidation of thioethers with benzyl nosyloxycarbamate (Scheme 4). The pathway A involves nucleophilic substitution, and the pathway B involves free nitrene intermediate. In the pathway A, nucleophilic substitution can occur without any additive and be promoted by acids as Tamura's work.[19] No additive condition and several common acid catalysts were tested in this study, and no desired sulfilimine product was observed at all (Table 1, entry 1, 2).[22] This result indicated that nucleophilic substitution pathway seemed unlikely. The only probable pathway was addition of thioether to free nitrene, generated from common α elimination of benzyl nosyloxycarbamate. Replacing benzyl group of nosyloxycarbamate **2** to ethyl or *t*Bu group led to no product.[23] This result suggested that benzyl group may play a key role in stabilizing the free nitrene in water.



Scheme 4. Proposed mechanism for the imidation of thioether.

In summary, we have disclosed the first imidation of thioethers with free nitrene in water. Free nitrene generated from α elimination of benzyl nosyloxycarbamate reacted with thioethers to give *N*-Cbz sulfilimines under aqueous media without transition metal catalysts. Useful *N*-Cbz sulfoximines are accessible via simply oxidation of *N*-Cbz sulfilimines. We expect this imidation to offer green, concise, low price and/or better strategies for the development of new and useful transformations.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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22 CF_3COOH, AcOH, TfOH, TsOH, PhCOOH and HCl were tested, and no conversion was observed.

23 Reaction condition: **1a** (0.2 mmol, 2.0 equiv), nosyloxycarbamate (0.1 mmol, 1.0 equiv), CaO (1.0 equiv), water (1.0 mL), room temperature, 40 min.