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N-Chlorosuccinimide-Promoted Regioselective Sulfenylation of Imidazoheterocycles at Room Temperature

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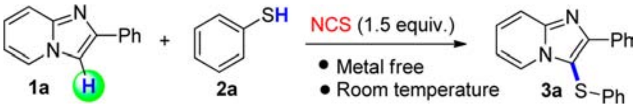
Supporting Information

ABSTRACT: Regioselective sulfenylation of imidazoheterocycles with thiophenols at room temperature is reported. Sulfenylation is promoted by *N*-chlorosuccinimide under metal-free conditions with a broad range of substrate scopes.

Imidazoheterocyclic compounds are well established as "privileged scaffolds". Subsequently, a number of these molecular frameworks have shown interesting biological activities.[1] For example, they exhibit good antiviral,[2] antibacterial,[3] fungicidal,[4] and anti-inflammatory properties[5] and also as bradykinin B2-receptor[6] as well as CXC-chemokine receptor 4 (CXCR4) antagonists.[7] Because of their diverse biological activities, many commercially available drugs (Figure S1, Supporting Information) including alpidem, olprinone, minodronic acid (to treat anxiety, heart failure, and osteoporosis), zolimidine (peptic ulcer), necopidem, and saripidem are derived from imidazo[1,2-*a*]pyridine (**IP**) core entities.[8] They are also potentially used in material science as charge transporters,[9] and hence, remarkable progress has been made by various groups,[10] including our own group,[11] on the synthesis of **IP** derivatives

The biological profile is mainly reliant on the nature of the substituents and introduction of sulfenyl groups on the azaheterocyclic rings that could impart marked biological properties.[12] As a result, the synthesis of sulfenated imidazoheterocyclic molecules has gained much attention. However, few reports are available for the synthesis of these molecules employing preparative sulfonating agents in the presence of transition-metal catalysts and others.[13] The separation of metal catalyst from products is of particular importance for the synthesis of pharmaceuticals because their residual toxicity in the target compound is a central issue to consider. Moreover, transition-metal-catalyzed reactions also generate hazardous waste, which is environmentally problematic and, hence, should be avoided wherever possible. Furthermore, it is also highly desirable to develop environmentally benign chemical processes to access pharmacologically potent sulfenated imidazoheterocyclic compounds without requirement of any metal catalyst. In continuation of our efforts on the development of green and sustainable methods for the synthesis of **IPs**,[11] we report herein an efficient *N*-chlorosuccinimide (NCS)[14] promoted synthesis of sulfenated azaheterocycles at room temperature under transition-metal-free conditions[15] (Scheme 1).

Scheme 1



For the direct sulfenylation of 2-phenylimidazo[1,2-*a*]pyridine **1a** to 2-phenyl-3-(phenylthio)imidazo[1,2-*a*]pyridine **3a**, thiophenol **2a** and NCS were chosen to determine the optimum reaction conditions (Table 1). Initially, with 1 equiv of **2a** and NCS, 40% of the desired product 2-phenyl-3-(phenylthio)imidazo[1,2-*a*]pyridine **3a** was isolated in acetonitrile along with 3-chloro-2-phenylimidazo[1,2-*a*]pyridine as the chloro-substituted product (Table 1, entry 1). By increasing the amount of **2a** and NCS (1.7 and 1.5 equiv, respectively) with respect to **1a**, the yield of desired product **3a** was also increased (Table-1, entries 2 and 3). In toluene as solvent, the yield was further increased to 79% (Table 1, entry 4). A marginal improvement of yield (81%) was observed when 2 equiv of **1a** was employed (Table 1, entry 5). There was no advantage when chlorobenzene used as solvent (Table 1, entry 6). A clear improvement in yield (87%) was observed in dichloroethane (Table 1, entry 7). Shifting the solvent system to dichloromethane, **3a** was isolated in 94% yield under the same conditions (Table 1, entry 8). Further, no improvements were observed when the reactions were carried out in other solvents (Table 1, entries 9−11). We then tested with other halogen sources such as *N*-bromosuccinimide (NBS), *N*-iodosuccinimide (NIS), and without halogen source for this transformation, they were either poorly effective or entirely ineffective (Table-1, entries 12−14). The reaction with NBS and NIS resulted diphenyl disulfide as major product compared to desired **3a**, which may be due to the high reactivities of the corresponding sulfenyl halide (Br, I) intermediates. Hence,

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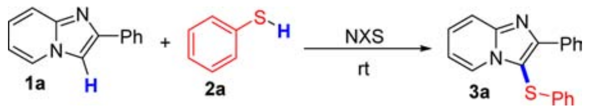
Table 1. Optimization of Reaction Conditions[a]



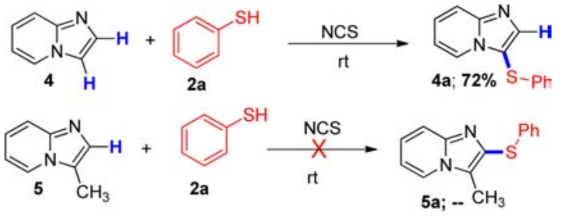
entry	NXS (equiv)	thiophenol (equiv)	solvent	yield[b] (%)
1	NCS (1)	1	CH_3CN	40
2	NCS (1.4)	1.2	CH_3CN	49
3	NCS (1.5)	1.7	CH_3CN	66
4	NCS (1.5)	1.7	toluene	79
5	NCS (1.5)	2	toluene	81
6	NCS (1.5)	2	PhCl	78
7	NCS (1.5)	2	DCE	87
8	**NCS (1.5)**	**2**	**DCM**	**95**
9	NCS (1.5)	2	EtOH	NR
10	NCS (1.5)	2	DMF	trace
11	NCS (1.5)	2	DMSO	NR
12	NBS (1.5)	2	DCM	43
13	NIS (1.5)	2	DCM	32
14		2	DCM	NR

[a] Reaction conditions: Thiophenol and *N*-halosuccinimide under a nitrogen atmosphere in solvent (2−3 mL) at rt for 30 min for the first step; 2-phenylimidazo[1,2-*a*]pyridine (1.0 mmol) was added and the mixture reacted at rt for 30 min for the second step. [b] Isolated yield. NR = no reaction.

NCS was found to be the best selective and efficient halogen source for the present transformation.

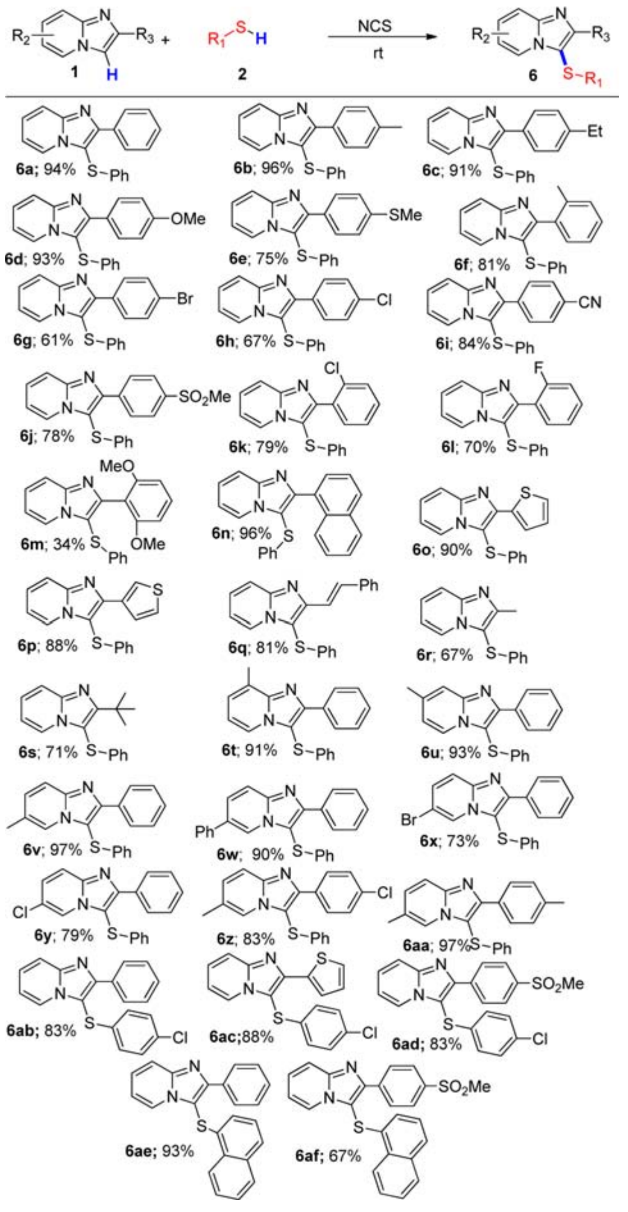
Before extension of the substrate scope for the present transformation, we performed a reaction with unsubstituted imidazo[1,2-*a*]pyridine **4** with thiophenol under optimized conditions (Table 1, entry 8), the selective C-3 sulfenated product **4a** was isolated in 72% yield (Scheme 2). When C-3-substituted substrate 3-methylimidazo[1,2-*a*]pyridine **5** was subjected to the same reaction conditions, no product **5a** formation was observed. These experiments (Scheme 2) indicate that if the C-3 position of imidazo[1,2-*a*]pyridine **IP** is substituted by any group, no reaction takes place to yield the sulfenylation product. The present transformation proceeds with only unsubstituted **IP** core units at the C-3 position to yield sulfenated imidazo[1,2-*a*]pyridine derivatives. Hence, the present transformation is highly desirable for selective synthesis of structural isomers.

Scheme 2. Selective Sulfenylation



Under this set of optimized conditions (Table 1, entry 8), the sulfenylation of various imidazo[1,2-*a*]pyridines **1** was examined (Scheme 3). The results in Scheme 3 demonstrate that the reaction has a high degree of functional group tolerance with broad substrate scope. Initially, 2-arylimidazo[1,2-*a*]pyridines bearing electron-donating groups (Me, Et, OMe, and SMe) at the *para* and *ortho* positions of the phenyl ring could react smoothly and afford the selective C-3 sulfenated products **6b−f** in good to excellent yields (75−96%). Similarly, the presence of electron-withdrawing groups (SO_2Me, Cl, Br, and CN) at either *o*/*p* position of the phenyl ring 2-phenylimidazo[1,2-*a*]pyridines provided the corresponding sulfenated products (**6g−l**) in good yields. As evident from the yields of products **6b−l**, the electronic effects associated with electron-donating/-withdrawing substituents on the phenyl ring of 2-phenylimidazo[1,2-*a*]pyridines do not affect the efficiency of the reaction. However, *o*-dimethoxyphenyl gave 34% isolated yield of desired product **6m**. Interestingly, naphthyl-substituted imidazo[1,2-*a*]pyridines **6n** and the important heterocycles such as 3-(phenylthio)-2-(thiophene-2-yl)imidazo[1,2-*a*]pyridine **6o**, 3-(phenylthio)-2-(thiophene-3-yl)imidazo[1,2-*a*]pyridine **6p**, and (*E*)-3-(phenylthio)-2-styrylimidazo[1,2-*a*]pyridine **6q** were obtained in excellent yields under the present conditions. The reactions with various substituted imidazo[1,2-

Scheme 3. Substrate Scope of Sulfonation Reactions[a]



[a] Reaction conditions: thiophenol and *N*-halosuccinimide under a nitrogen atmosphere in solvent (2−3 mL) at rt for 30 min for the first step; 2-phenylimidazo[1,2-*a*]pyridine (1.0 mmol) was added and the mixture reacted at rt for 30 min for the second step. [b] Isolated yield.

a]pyridines [groups such as aliphatic (methyl and 2-*tert*-butyl), halogens, and aryl at different positions] and thiophenol also successfully provided the corresponding C-3 sulfenated products **6r−aa** in good to excellent yields (67−97%), and one of the products **6x** was further confirmed by single-crystal XRD (Figure 1). To check the feasibility of the present system, reactions with other thiophenols (chlorothiophenol and naphthalene-1-thiol) were subjected to this procedure, and the desired products **6ab−af** were obtained in excellent yields (83−93%).

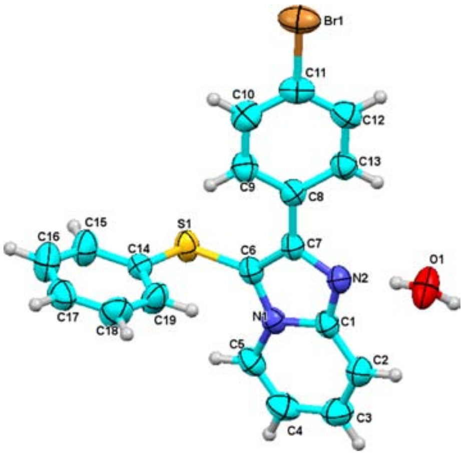
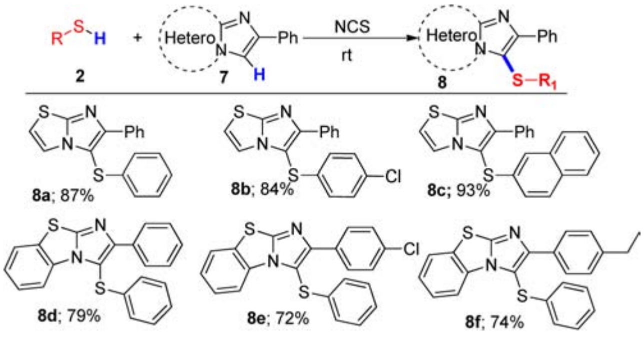


Figure 1. Crystal structure of **6x**.

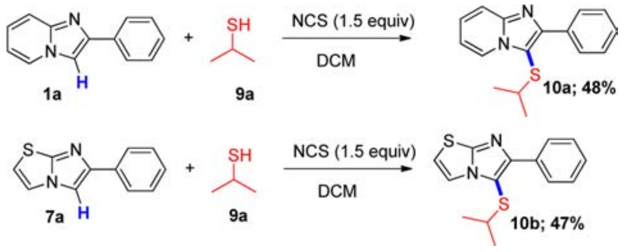
Furthermore, the optimal reaction conditions for sulfenylations were extended to other imidazoheterocyclic compounds to ascertain the scope of the methodology (Scheme 4). The reaction of various thiophenols with 6-phenylimidazo[2,1-*b*]thiazole **7** gave the corresponding 6-phenyl-5-(phenylthio)-imidazo[2,1-*b*]thiazoles (**8a−c**) in excellent yield (84−93%). Further, 2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole also gave good yields of sulfenylated products **8d−f** in 72−76% yield, respectively. Interestingly, the reactions of aliphatic secondary thio-2-propanol with **1a** and **7a** proceeded smoothly to afford the corresponding sulfenylated products **10a** and **10b** in 48% and 47% yield (Scheme 5).

Scheme 4. Substrate scope for Sulfenylation of Imidazoheterocyclic Compounds[a]



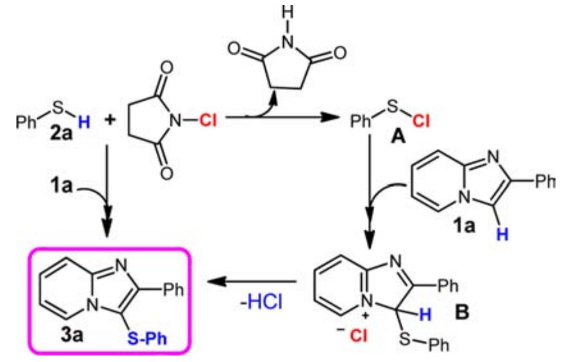
[a]Reaction conditions: Thiophenol and *N*-halosuccinimide under a nitrogen atmosphere in solvent (2−3 mL) at rt for 30 min for the first step; imidazoheterocyclic compounds (1.0 mmol) were added, and the mixture was reacted at rt for 30 min for the second step. [b]Isolated yield.

Scheme 5



Based on the literature reports and our observation in the present work, a plausible reaction mechanism has been proposed (Scheme 6). Initially, sulfenyl chloride intermediate **A** is formed by the reaction of NCS with benzenethiol **2** under the present conditions. Subsequently, regioselective electrophilic attack of PhSCl[16] on the C-3 position of **1a** yields the imidazolenium intermediate **B**. Finally, dehydrochlorination of **B** provides the final product 2-phenyl-3-(phenylthio)imidazo[1,2-*a*]pyridine **3a**.

Scheme 6. Plausible Mechanism



In conclusion, we have developed an efficient strategy for the regioselective sulfenylation of imidazo[1,2-*a*]pyridine derivatives without transition-metal catalysts at room temperature with a high degree of functional group tolerance. The scope of the methodology has been extended to imidazo[2,1-*b*]thiazoles and 2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole derivatives.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data for compound **6x** (CCDC-998765) can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Notes

The authors declare no competing financial interest.

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