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C-3 Sulfenylation of N-heteroarenes in water under catalyst–free conditions

Chitrakar Ravi, Abhisek Joshi, and Subbarayappa Adimurthy*

Abstract: We describe herein a catalyst-free C−H sulfenylation of imidazo[1,2–a]pyridines using sulfonothioates as odorless source of thioarylated reagent in an aqueous medium. The method works for a variety of substituted imidazo[1,2–a]pyridines with broad functional group tolerance. The methodology has been extends to sulfernylation of indoles and imidazothiazoles. The sulfonothioates are activated exclusively in aqueous medium rather than organic solvent media and the feasibility of the process for scale-up studies have been demonstrated.

Introduction

In the past decade, transition-metal-catalyzed C−H functionalization has received extensive attention in organic synthesis, due to its powerful and versatile tool for directly introducing the desired new functionalities via C−H bond transformation.[1] The cost associated with precious metal catalysts and their contamination in the products of human consumption are also the matter of concern in the synthesis of bio-organic molecules.[2] Sulfenylation of heteroarenes through C−H activation[3] for the construction of carbon-sulfur (C—S) bond has attracted special interest in various fields such as pharmaceutical, agrochemical industries, natural products and organic materials.[4] Synthesis of C-3 substituted imidazo[1,2–a]pyridines are very challenging to achieve, as these structures are widely distributed in variety of natural products and synthetic molecules with diverse pharmaceutical applications.[5] The C-3 substituted imidazo[1,2–a]pyridine derivatives such as necopidem, saripidem, and zolpidem are clinically used as neuroactive drugs including alpidem, (as an anxiolytic agent), minodronic acid[6] and optically active GSK812397 (HIV infection).[7] In addition, functionalized imidazo[1,2–a]pyridines were also recognized in medicinal chemistry for antiproliferative activity against melanoma cells, tubulin polymerization and protein kinase inhibitors.[8] In recognition of the importance of these molecules, recently many research groups have demonstrated the sulfenylation of imidazo[1,2–a]pyridines using disulfides, thiols, sulfenyl chlorides, sodium sulfinates and sulfonyl hydrazines as a source for sulfenylation.[9-11] Though these strategies have been successfully employed for the sulfenylation of imidazo[1,2–a]pyridines, they require the activators such as copper catalyst, iodine, peroxides and also these reactions are effective only in organic solvent media.

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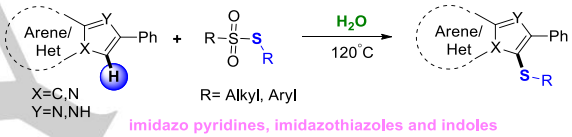
Recently, water has been employed as a solvent-cum-catalyst for the construction of heterocycles.[12] Aqueous reactions have attracted much attention due to their unique reactivity and



Scheme 1. sulfenylation of imidazo[1, 2–a]pyridine.

selectivity observed which were difficult to achieve in conventional organic solvents.[13] Organic substrates are generally insoluble in water, however reactions reported to proceed “on water” to obtain the desired products.[14]

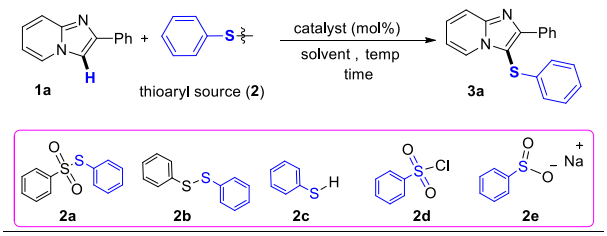
Results and Discussion

Despite the significance of these approaches, the synthetic simplicity as well as environmentally benign process, to provide the direct strategy for the synthesis of 3-sulfenyl imidazo[1,2–a]pyridines via a transition metal-free and organic solvent-free protocol is still an attractive.[15] To the best of our knowledge, the sulfenylation of imidazo[1,2–a]pyridines in water under metal-free conditions were not reported. In continuation of our interest on the synthesis of functionalized imidazo[1,2–a]pyridines,[15a] herein, we report an efficient metal−free C−H sulfenylation of imidazo[1,2-a]pyridines with S-phenyl sulfonothioates in an aqueous medium (Scheme 1). Compared to the sulfenylation in organic solvents,[15a] water has been identified as a selective solvent to activate the organic substrates to convert into desired products.

At the outset of our investigation, we selected 2-phenyl imidazo[1,2–a]pyridine (**1a**) and S-phenyl sulfonothioate (**2a**) as model substrates to optimize the reaction conditions (Table 1). Initially our hypothesis was examined by the reaction of **1a** with S-phenyl benzenesulfonothioate **2a** in the presence of 5 mol % of NaI in isopropyl alcohol (IPA) at room temperature, after 24 h, the desired sulfenylated product **3a** was isolated in 26% yield

(Table 1, entry 1).[15b,c] When the same reaction was performed at 45 °C, **3a** was isolated in 33% yield (Table 1, entry 2). Upon further raising of the reaction temperature to 60 °C and 80 °C, the desired product **3a** was isolated in 40% yield in both cases (Table 1, entries 3 and 4). In the latter entry, there was no advantage when the temperature raised to 80 °C. However, with increasing the catalyst loading to 10 mol%, at 60 °C, marginal improvement in yield was observed (Table 1, entry 5). Attempts were made to further increase the catalyst loading and reaction time, no improvement in the yield of the product was observed (Table 1, entries 6 and 7).

Table 1. Optimization of reaction conditions.[a]

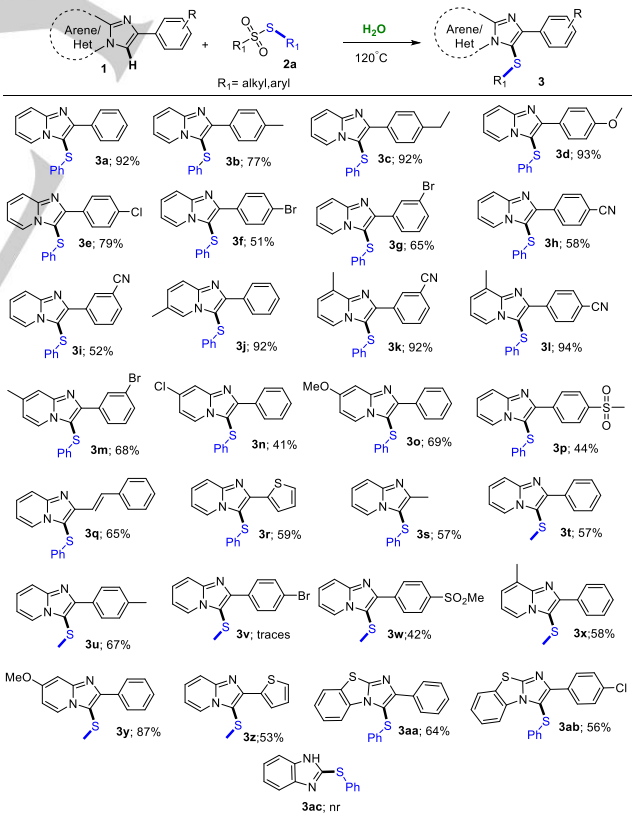


Entry	Thioaryl source (**2**)	Catalyst (mol%)	Solvent (mL)	Temp (°C)	Yield(%)
1	2a	NaI (5)	IPA	rt	26
2	2a	NaI (5)	IPA	45	33
3	2a	NaI (5)	IPA	60	40
4	2a	NaI (5)	IPA	80	40
5	2a	NaI (10)	IPA	60	46
6	2a	NaI (15)	IPA	60	42
7[b]	2a	NaI (10)	IPA	60	41
8	2b	NaI (10)	IPA	60	traces
9	2c	NaI (10)	IPA	60	nr
10	2d	NaI (10)	IPA	60	nr
11	2e	NaI (10)	IPA	60	nr
12	2a	KI (10)	IPA	60	31
13	2a	TBAI (10)	IPA	60	18
14	2a	I_2 (10)	IPA	60	39
15	2a	NaI (10)	CH_3CN	60	36
16	2a	NaI (10)	MeOH	60	12
17	2a	NaI (10)	H_2O	60	58
18	2a	NaI (10)	H_2O	80	84
19	2a	NaI (10)	H_2O	100	85
20	2a	-	H_2O	100	82
21	2a	-	H_2O	110	88
22	**2a**	**-**	**H_2O**	**120**	**92**
23[c]	2a	-	H_2O	120	84
24[d]	2a	-	H_2O	120	81
25	2a	-	ACOH	120	18
26	2a	-	MeOH	120	14
27	2a	-	EtOH	120	22

[a]Reaction conditions: 0.25 mmol of **1a**, 0.3 mmol of **2**, catalyst (10 mol %), solvent (1mL), 24 h, argon balloon, isolated yields. [b]36 h. [c]O2 balloon. [d] Closed tube.

Upon extensive screening of various sulfenylation sources (**2b**–**2e**); various iodine sources (KI, TBAI, I_2) and different solvents (acetonitrile and methanol), the yield of the product was not improved under these conditions (Table 1, entries 8–16). Fortunately, when the reaction of **1a** and **2a** was conducted in water as solvent, with NaI (10 mol %) at 60 °C, the desired product **3a** was isolated in 58% yield (Table 1, entry 17). When the reaction temperature in water was increased to 80 °C and 100 °C, gratifyingly, the yield was increased to 84% and 85% respectively (Table 1, entries 18 and 19). Surprisingly, 82% of **3a** was isolated without NaI in water at 100 °C (Table 1, entry 20). We anticipated to raise product yield further, accordingly increased the temperature to 110°C and 120°C, the desired product **3a** was obtained in 88% and 92% yield respectively (Table 1, entries 21 and 22). Also, the reaction was performed under oxygen (O_2 balloon) and closed tube instead of argon atmosphere to check the efficiency the transformation and the yield of **3a** was reduced to 84% and 81% respectively. (Table 1, entries 23 and 24). Finally, we performed the reactions in protic solvents such as acitic acid, methanol and ethanol and observed only 18%, 14% and 22% yield respectively (Table 1, entries 25-27), it indicates that, water promotes the present sulfenylation reaction.

Table 2. Substrate scope of imidazo heterocyclic compounds[a]



[a]Reaction conditions: 0.25 mmol of 1, 0.3 mmol of **2a**, Water (1mL), argon balloon, 24 h, isolated yields.

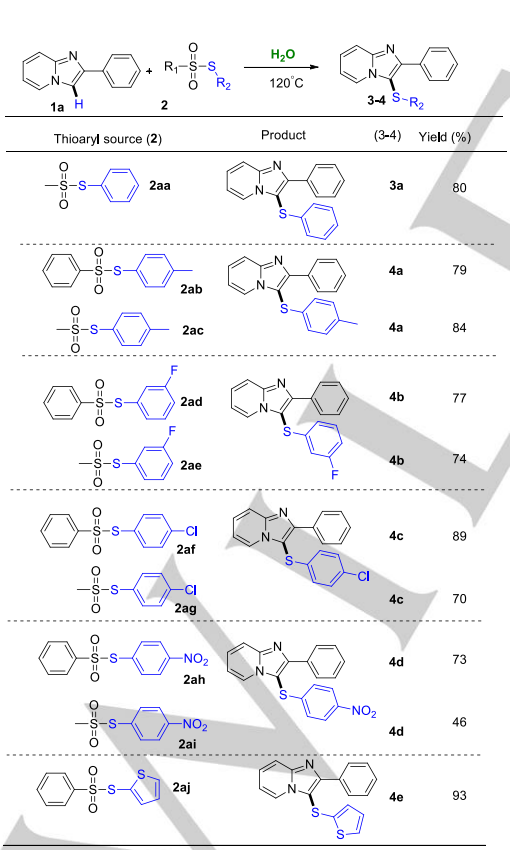
Under the set of optimized conditions (Table 1, entry 22), the sulfenylation of various imidazo[1,2-a]pyridines **1** with S-phenyl

benzenesulfonothioate **2a** was examined (Table 2). The results in Table 2 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, and OMe,) at the para position of the phenyl ring could react with **2a** smoothly and afford the C-3 sulfenylated products **3b−3d** in good to excellent yields (77−93%). Similarly, the presence of electron-withdrawing groups (Cl, Br, and CN) either at *para* or *meta* -position of the phenyl ring of 2-phenylimidazo[1,2-a]pyridines provided the corresponding sulfenylated products **3e−3i** in good yields. The reaction of S-phenyl benzenesulfonothioate **2a** with various substituted imidazo[1,2-a]pyridines, [substituents on pyridine ring of **1** such as methyl, methoxy, bromide, chloride, and cyanide] under the optimized conditions gave the C-3 sulfenylated products **3j–3o** in good to excellent yields (41 –94%). When the zolimidine drug was subjected to the present reaction conditions, it gave 44% yield of desired sulfenylated product **3p**. The electronic effects associated with (either electron-donating or electron-withdrawing groups) on the benzene ring of 2-phenyl imidazo[1,2–a]pyridines has little influence on the yield of sulfenylation reaction.

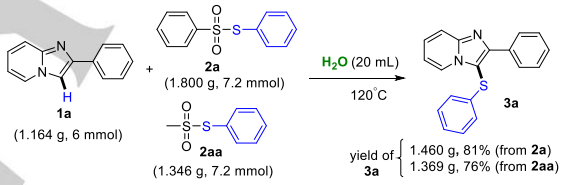
The present methodology is also applicable to alkenyl and heterocyclic substituted derivatives (E)-2-styrylimidazo[1,2-a]pyridine **3q** and 2-(thiophen-2-yl)imidazo[1,2-a]pyridine **3r** and obtained in 65% and 59% yields respectively. The 2-methylimidazo[1,2-a]pyridine also gave the desired product **3s** in 57% yield. To our delight, the reaction of alkylsulfonothioates were also reacted well with various imidazo[1,2-a]pyridines and gave moderate to good yields of corresponding 3-(methylthio)imidazo[1,2-a]pyridine derivatives **3t**-**3y** including 3-(methylthio)-2-(thiophen-2-yl)imidazo[1,2-a]pyridine **3z** in moderate to good yields (42-87%). Furthermore, the present conditions were extended to the sulfenylation of other imidazoheterocycles like benzo[d]imidazo[2,1–b]thiazole to ascertain the scope of the methodology and obtained corresponding sulfenylated products **3aa** and **3ab** in 64% and 56% yield respectively. Unfortunately the present conditions not suitable for benzimidazole **3ac**.

We then verified the reactivity of other sulfenylation sources S-phenyl alkyl/ arylsulfonothioates **2** and subjected to C-H thioarylations with **1a** under the optimized reaction conditions (Table 3). The reaction of **1a** with S-phenyl methanesulfonothioate **2aa** gave the desired product **3a** in 80% yield. Variety of S-phenyl alkyl/arylsulfonothioates **2** bearing various substituents such as methyl (**2ab** & **2ac**), fluoro (**2ad** & **2ae**), chloro (**2af** & **2ag**), nitro (**2ah** & **2ai**) and thiophene **2aj** groups were well tolerated and delivered the desired thioarylated imidazo[1,2-a]pyridine derivatives **4a-4e** in moderate to excellent yields (46- 93%).

Table 3. Scope for different sulfonothioates[a]



aReaction conditions: 0.25 mmol of 1a, 0.3 mmol of 2, Water (1mL), argon balloon, 24 h, isolated yields



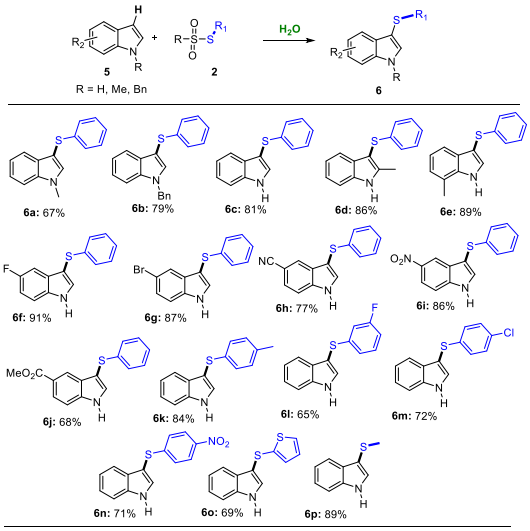
Scheme 2. Gram scale sulfenylation of 1a.

In addition, to confirm the feasibility of the process for scale-up studies, we synthesized two products (from two different sulfenylating agents) at gram scale under the same optimized conditions. The reaction of **1a** (1.164 g, 6 mmol), with two different sulfenylating agents **2a** (1.800 g, 7.2 mmol) and **2aa** (1.346 g, 7.2 mmol) were subjected and the corresponding sulfenylated product **3a** was obtained in 81% (1.460 g) and 76% (1.369 g) yield respectively (Scheme 2). This study indicates the feasibility of the method for industrial/commercial production as the reactions performed only in water.

Further, the present strategy has been extended to another important heterocyclic compounds like indoles under the set of optimized conditions. Various indoles **5** with different benzenesulfonothioates **2** were examined (Table 4). Initially the reaction of S-phenyl benzenesulfonothioate **2** was conducted with N-methyl indole **5a**, N-benzyl indole **5b** and indole **5c** these indoles reacted smoothly and gave good yields (67 –81%) of corresponding sulfenylated products (**6a**-**6c**). The presence of electron-donating/withdrawing substituted (Me, Br, F, CN, NO2, CO_2Me) indoles were also reacted well and afford the desired products (**6d**-**6j**) in good to excellent yields. Further, the different

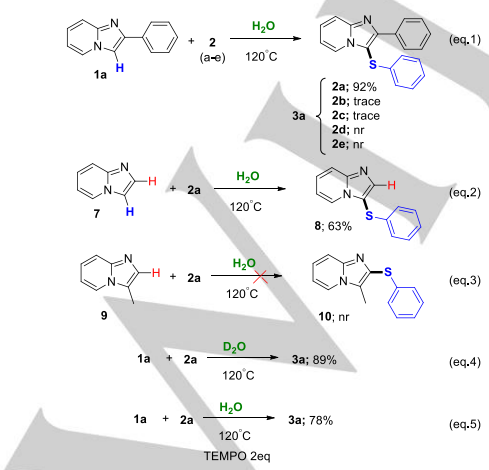
sulfernylation sources including S-(thiophen-2-yl) benzenesulfonothioate **2** were also compatible for a range of indole derivatives and provided good yields of products (**6k**-**6o**). The reactions of alkylsulfonothioate with indole also reactive and afford the corresponding 3-(methylthio)-1H-indole **6p** in good yield (89%).

Table 4. Substrate scope of indole compounds.[a]



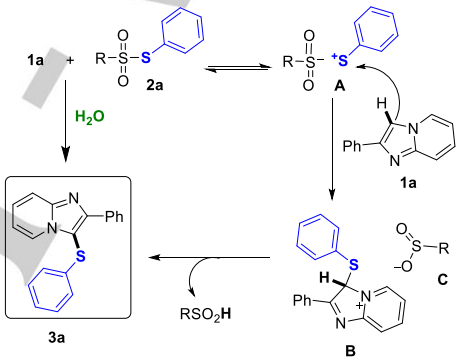
[a]Reaction conditions: 0.25 mmol of 5, 0.3 mmol of 2a, Water (1mL), argon balloon, 24 h, isolated yields.

To gain insight into the reaction mechanism, some selective and control experiments were performed (Scheme 3). Principally, we subjected the reactivity of **1a** with other sulfur sources such as 1,2-diphenyldisulfane **2b**, thiophenol **2c**, and benzenesulfonyl chloride **2d** and sodium benzenesulfonate **2e** under the standard reaction conditions, along with S-phenyl phenylsulfonothioates **2a** (Scheme 3, eq 1). No reactions or traces of product was observed with **2b-2e**, however, with **2a** 92% of desired product was obtained (Scheme 3, eq. 1).



Scheme 3. Selectivity and control experiments

These reactions indicates that other sulfur sources **2b-e** were not activated under the present conditions only **2a** selectively active to dissociation in water and also selectively **2a** was activated without need of any catalyst. Further, the reaction of unsubstituted imidazo[1,2-a]pyridine **7** was reacted with **2a**, the C-3 sulfenylated product **8** was isolated in 63% yield (Scheme 3, eq. (2)). When C-3 substituted substrate 3-methylimidazo[1,2-a]pyridine **9** was subjected to the same reaction conditions, the formation of desired product **10** was not observed (Scheme 3, eq. (3)).These experiments (Scheme 3, eqs. 2 and 3) designates that, the present transformation is highly desirable for selective synthesis of structural isomers and supports the formation of imidazolium intermediate to propose the probable reaction mechanism as shown in scheme 4. The reaction with D_2O gave 89% yield of **3a** (Scheme 3, eq. (4)) Also when the reaction was performed with TEMPO as a radical scavenger, 78% yield of **3a** was obtained under optimized conditions.[15c] It indicates that, the reaction does not proceed through radical pathway (Scheme 3, eq. (5)).



Scheme 4. Plausible Reaction Mechanism

Based on the literature reports[15,16] and our above observations in the present work, a plausible reaction mechanism has been proposed (Scheme 4). In the presence of water, S-phenyl phenylsulfonothioate **2a** disassociate into **A**. Subsequently, attack of **A** to imidazo[1,2-a]pyridine **2a** through the electrophilic attack of PhS+ on the C-3 position of **1a** and generates the imidazolium intermediates **B** and **C**. Finally, elimination of sulfinic acid from the intermediate **B** provides the desired product 2-phenyl-3-(phenylthio)imidazo- [1,2-a]pyridine **3a**. Similar plausible mechanism also applicable for the indole derivatives.

Conclusions

In conclusion, we have developed an efficient strategy for the sulfenylation of imidazo[1,2-a]pyridine, phenylbenzo[d]imidazo[2,1-b]thiazoles and indole derivatives under catalyst-free aqueous conditions with high degree of functional group tolerance. The scope of the methodology has been extended to variety of aryl and alkyl sulfonothioates and

also checked the feasibility of the reactions at gram scale preparation of sulfenylated imidazo[1,2-a]pyridines.

Experimental Section

General procedure for 3a

A clean washed boiling tube equipped with a magnetic stir bar was charged with 2-phenylimidazo[1,2-a]pyridine **1a** (0.0485 g, 0.25 mmol), S-phenyl benzenesulfonothioate **2a** (0.075 g, 0.30 mmol) and H2O (1mL), the above mixture was stirred for 24h at 120°C temperature in argon balloon. After completion of the reaction, the mixture was poured into 10mL of $NaHCO_3$ solution. The product was extracted with ethyl acetate (10 mL × 3) and dried with anhydrous Na_2SO_4. Removal of the solvent under reduced pressure, the left out residue was purified through column chromatography using silica gel (20% EtOAc/hexane) to obtain 2-phenyl-3-(phenylthio)imidazo[1,2-a]pyridine **3a** in 92 % yield (0.0696g).

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Keywords: water • imidazopyridines • sulfenylation • catalyst free • C-H Functionalisation.

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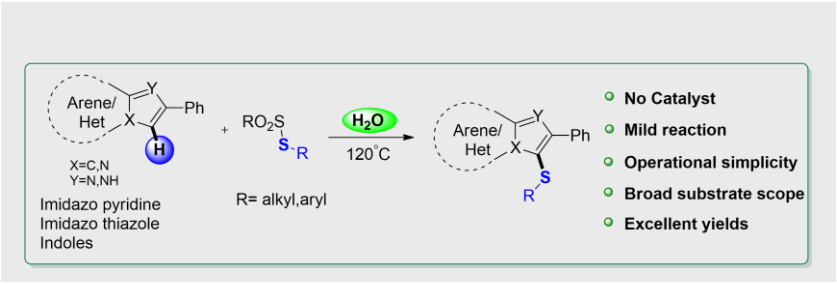

C-H Sulfenylation

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C-3 Sulfenylation of N-heteroarenes in water under catalyst–free conditions

The synthesis of sulfinylated imidazo[1,2-a]pyridine, phenylbenzo[d]imidazo[2,1-b]thiazoles and indole derivatives have been reporting under catalyst-free conditions with high degree of functional group tolerance in aqueous medium. The sulfenylation scope of the this methodology has been extended to variety of aryl and alkyl sulfonothioates.