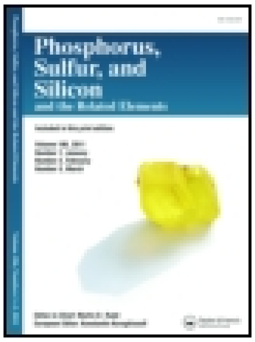

Phosphorus, Sulfur, and Silicon and the Related Elements

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Microwave-assisted and catalyst-free sulfenylation of imidazo[2,1-*b*]thiazoles with sulfonyl hydrazides in water

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ABSTRACT
An efficient microwave-assisted and catalyst-free sulfenylation of imidazo[2,1-*b*]thiazoles with sulfonyl hydrazides has been developed in water. This method is practical and environmental friendly, and can be performed within a short reaction time. The sulfenylation reaction shows high regioselectivity, and excellent functional-group compatibility, giving the desired products in moderate to good yields.

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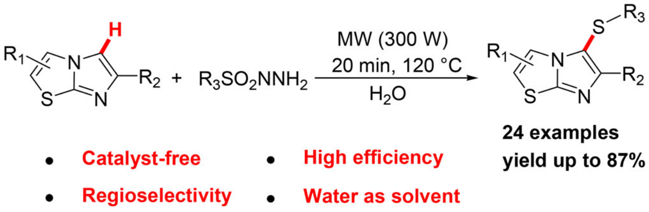
Sulfenylation; imidazo[21-b]thiazole; sulfonyl hydrazide; catalyst-free; regioselectivity

GRAPHICAL ABSTRACT



Introduction

Sulfur-containing compounds widely exist in natural products, bioactive molecules, pharmaceuticals, polymers and material sciences.[1] Therefore, the development of efficient synthetic strategies to construct C-S bonds has attracted much attention. Transition-metal-catalyzed sulfenylation processes employing copper,[2] palladium,[3] rhodium,[4] cobalt,[5] and silver,[6] as catalysts have been successfully achieved. Very recently, there has been a growing interest in exploring green, environmental and cost effective methods. Many metal-free sulfenylation processes catalyzed by I_2,[5b,7] NXS(Cl, Br),[8] KIO_3,[9] KI,[10] NH_4I,[11] DDQ,[12] or promoted by visible-light [13] have been reported which avoids toxicity and the disposal problem of metal catalysts.

Imidazo[2,1-*b*]thiazole is an important scaffold in drug, medicinal and organic synthetic chemistry because of its wide application and value.[14] In particular, sulfenylated imidazo[2,1-*b*]thiazole derivatives show diverse biological properties, such as anti-fungicide, herbicidal activities, and enhancement of cerebral functions (Figure 1). More recently, the direct sulfenylation of imidazo[2,1-*b*]thiazoles has been successfully achieved. These routes normally use thiols,[15] disulfides,[8a] sulfonyl hydrazides,[7d,16] sodium sulfinates,[7l] sulfinic acids,[13b] and DMSO[17] as sulfur source (Scheme 1). However, the long reaction time, high temperature, or yields of byproduct still present solvable challenges. It is still necessary to explore reliable and efficient methods for the sulfenylation of imidazo[2,1-*b*]thiazoles. Microwave-assisted organic synthesis (MAOS) has shown broad applications as an efficient accelerator for C–S bond formation, providing excellent yields, short reaction times, and cleaner reactions.[18] MAOS technology for organic synthesis is one of the most efficient strategies in green-chemistry area. Herein, we wish to report a fast and green method for the sulfenylation of imidazo[2,1-*b*]thiazoles with sulfonyl hydrazides in water under microwave irradiation.

The reaction between 3-methyl-6-phenylimidazo[2,1-*b*]thiazole **1a** and *p*-toluenesulfonyl hydrazide **2a** was chosen as the model reaction to optimize the reaction conditions (Table 1). Initially, the desired coupling product **3a** was obtained in 22% yield after microwave irradiation for 10 min in H_2O at 60 °C (Table 1, entry 1). Next, we examined the effect of irradiation temperature and the results showed that the temperature at 120 °C offered the product **3a** in 75% yield (Table 1, entries 2–5). Additional experiments varying the reaction time were carried out for 5, 20, 30 mins respectively, it was found that a better conversion was

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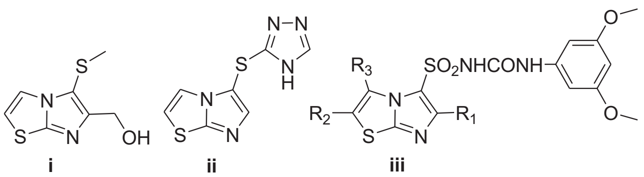
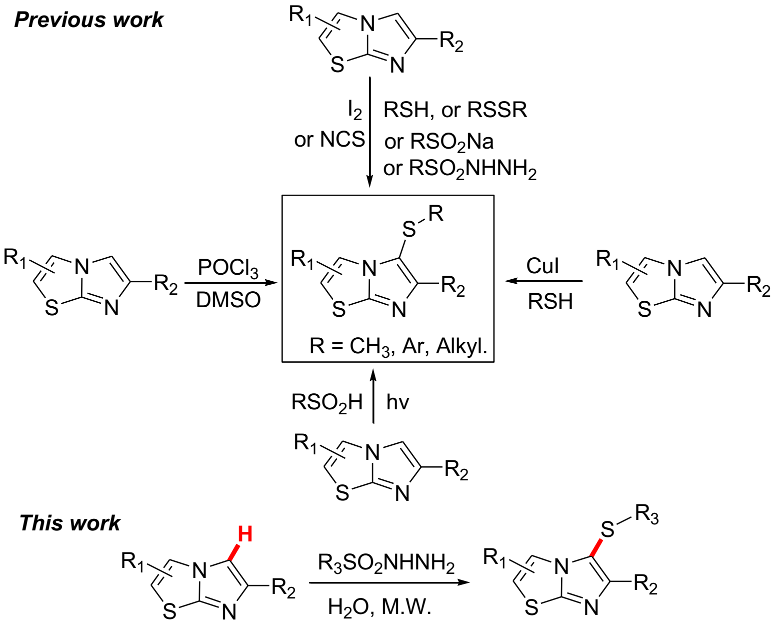


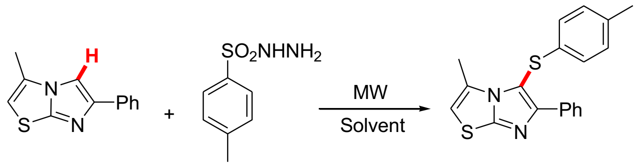
Figure 1. Imidazo[2,1-*b*]thiazole derivatives with biological activity.

generated in 20 min and the yield increased up to 83% (Table 1, entries 6–8). Encouraged by this preliminary result, we then screened different solvents. Organic solvents were ineffective, providing few amount of the desired product (Table 1, entries 9–15). The lower yields in organic solvents suggested an importance of water for this sulfenylation reac-



Scheme 1. Approaches for the sulfenylation of imidazo[2,1-*b*]thiazoles.

Table 1. Optimization of the reaction conditions.[a]



1a **2a** **3a**

Entry	T (°C)	Time (min)	Solvent	Yield (%)[b]
1	60	10	H_2O	22
2	80	10	H_2O	43
3	100	10	H_2O	67
4	120	10	H_2O	75
5	140	10	H_2O	68
6	120	5	H_2O	43
7	120	20	H_2O	83
8	120	30	H_2O	79
9	120	20	EtOH	57
10	120	20	DMF	36
11	120	20	DCE	41
12	120	20	dioxane	32
13	120	20	CH_3CN	53
14	120	20	PEG-400	46
15	120	20	THF	23
16[c]	120	20	H_2O	–
17[d]	120	30	H_2O	–
18[e]	120	12 h	H_2O	63
19[f]	120	20	H_2O	84
20[g]	120	20	H_2O	74

[a] Reaction condition: 3-methyl-6-phenylimidazo[2,1-*b*]thiazole **1a** (0.2 mmol), *p*-toluenesulfonyl hydrazide **2a** (0.24 mmol), solvent (2 mL), power (300 W). The microwave is on for all the reaction time.

[b] Isolated yield.

[c] 1,2-di-*p*-tolyldisulfane was used.

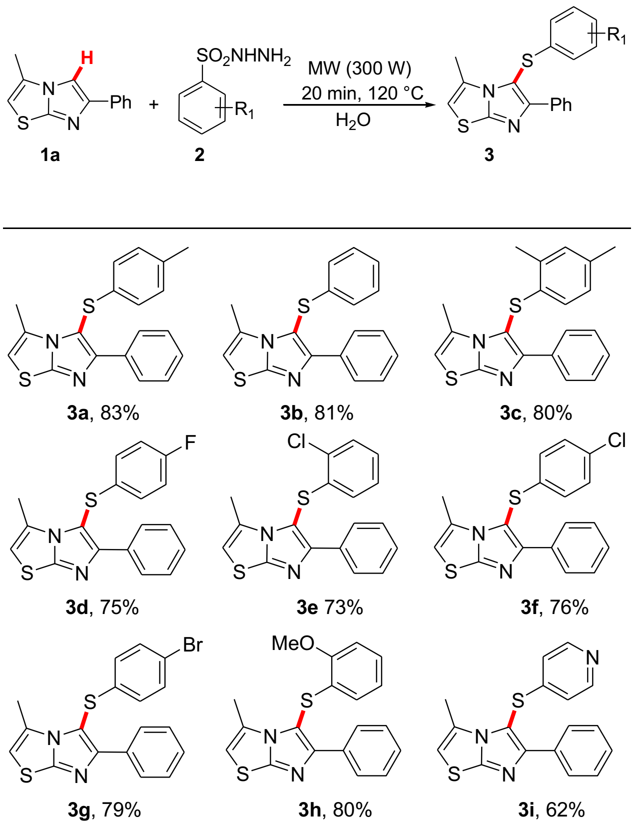
[d] 4-methylbenzenethiol was used.

[e] Oil heating.

[f] Under N_2.

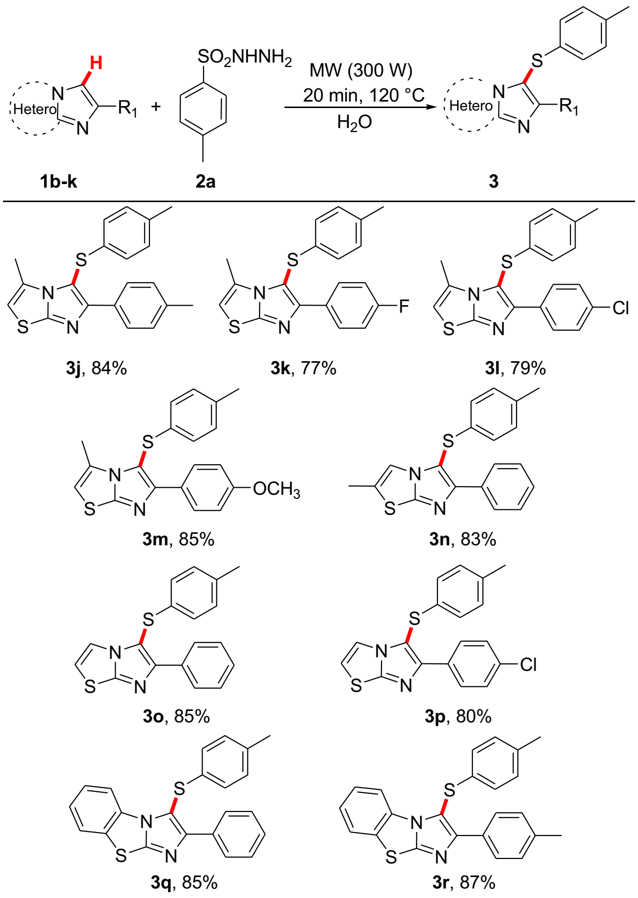
[g] Under O_2.

Table 2. Direct sulfenylation of imidazo[2,1-*b*]thiazoles with different sulfonyl hydrazides.[a]



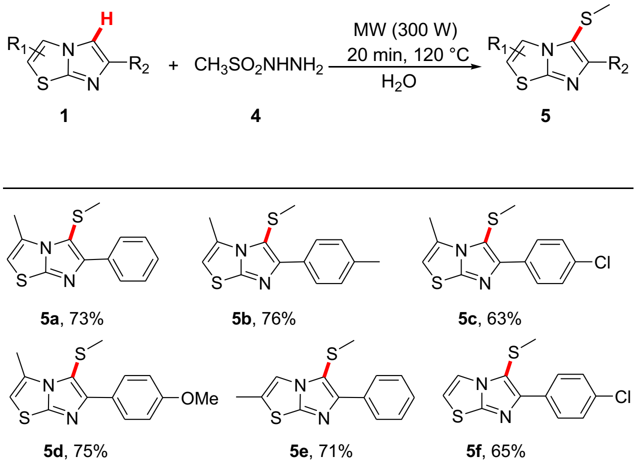
[a]All reaction were performed with **1a** (0.2 mmol), **2** (0.24 mmol) in 2 mL of H_2O at 120 °C for for 20 min under microwave irradiation. Isolated yields.

Table 3. Direct sulfenylation of imidazo[2,1-*b*]thiazoles derivatives **1 b-k** with *p*-toluenesulfonyl hydrazide **2a**.[a]



[a]All reaction were performed with **1 b-k** (0.2 mmol), **2a** (0.24 mmol) in 2 mL of H_2O at 120 °C for for 20 min under microwave irradiation. Isolated yields.

Table 4. Methylthiolation of imidazo[2,1-*b*]thiazoles with methanesulfonyl hydrazide.[a]



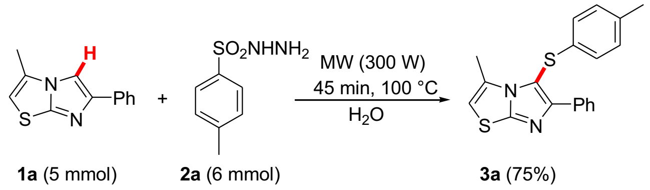
[a]All reaction were performed with **1** (0.2 mmol), **4** (0.24 mmol) in 2 mL of H_2O at 120 °C for for 20 min under microwave irradiation. Isolated yields.

tion. When the *p*-toluenesulfonyl hydrazide was replaced with disulfides or thiols as the thiol source respectively, the reactions failed (Table 1, entries 16 and 17). This sulfenylation reaction under conventional oil heating for 12 h at 120 °C generated the desired product **3a** in 63% yield (Table 1, entry 18). When the reaction was subjected to N_2 instead of air atmosphere, the product **3a** obtained almost the same yield (Table 1, entry 19). Moreover, when the reaction mixture was degassed with pure O_2, a relatively lower yield was obtained (Table 1, entry 20). The above results indicated that the MAOS technology was an efficient and practical strategy for the construction of C–S bonds.

With the optimal conditions in hand, the scope of this transformation was subsequently screened. A variety of sulfonyl hydrazides **2** were found to be applicable for this sulfenylation reaction, affording the corresponding products **3a**–**3h** with moderate to good yields (Table 2). Sulfonyl hydrazides **2** bearing methyl, fluoro, chloro, bromo, and methoxy substituents were well tolerated. Sulfonyl hydrazides with electron-withdrawing functions (such as –F, -Cl, -Br) gave slightly lower yields compared with other sulfonyl hydrazides. Ortho substituent groups (such as $-CH_3$, -Cl, -OMe) on the sulfonyl hydrazide ring smoothly participated in this transformation to provide the corresponding products **3c**, **3e**, and **3 h**. The heteroaryl sulfonyl hydrazide was also investigated and the desired product **3i** was obtained in 62% yield. It is particularly noteworthy that all reactions selectively occurred on the C-5 position of imidazo[2,1-*b*]thiazoles, and no C-2 position sulfenylated products were isolated.

Next, the scope of imidazo[2,1-*b*]thiazoles was also performed under the optimal conditions (Table 3). As expected, the desired products **3j**-**3p** were obtained in 77-85% yields. The imidazo[2,1-*b*]thiazole derivatives with *p*-fluorophenyl or *p*-chlorophenyl group at the C-6 position gave lower yields of **3k** and **3l** (77 % and 79%). Notably, this sulfenylation reaction also exhibited C-5 regioselectivity. In addition, the sulfenylation reaction of benzo[d]imidazo[2,1-*b*]thiazole ring proceeded smoothly to isolate the corresponding products **3q** and **3r**.

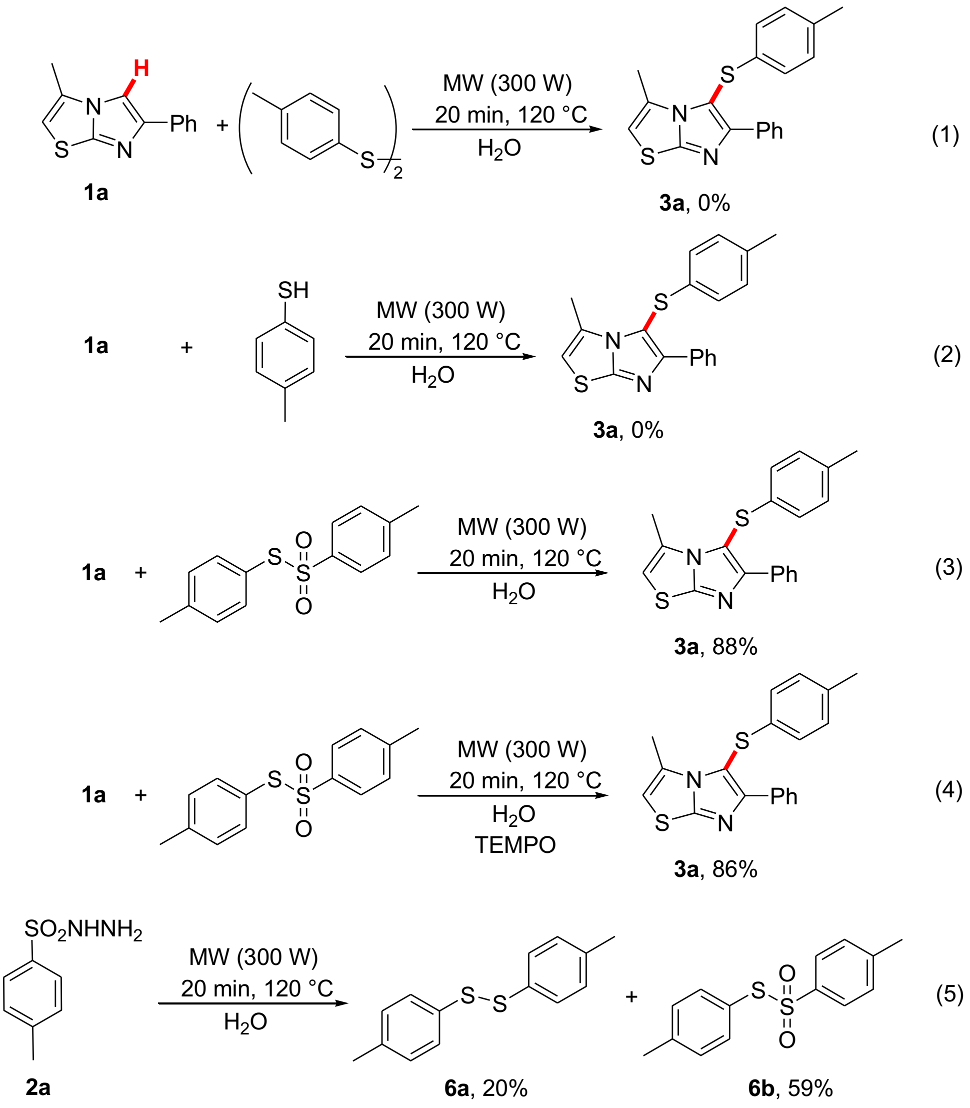
Aryl methyl thioether is highly attractive skeleton in biologically active molecules due to their application value.[19] Herein, aliphatic methylsulfonyl hydrazine ($CH_3SO_2NHNH_2$) was selected as a sulfenylating agent. It was found that the alkylsulfonyl hydrazine was also suitable under the same conditions. Imidazo[2,1-*b*]thiazole derivatives can be directly methylthiolated in this system to afford the corresponding products **5a–5f** in 63–76% yields (Table 4).



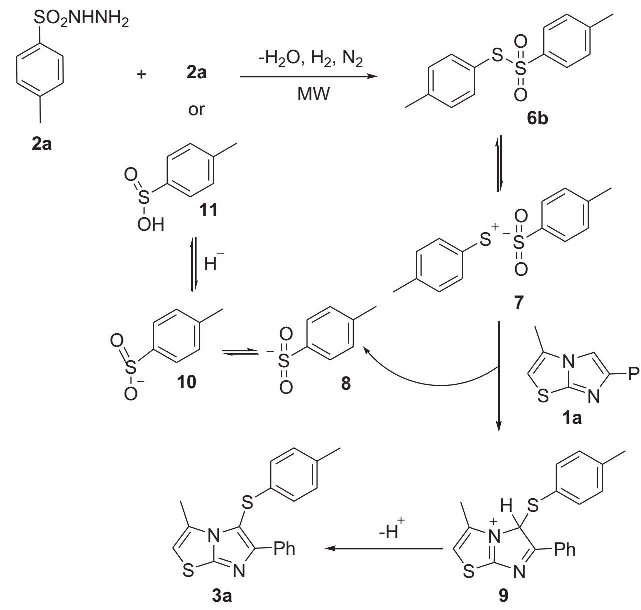
Scheme 2. Scale-up reaction between **1a** and **2a**.

To demonstrate the practical usefulness of the new method, a gram-scale reaction was carried out under the optimized reaction conditions (Scheme 2). Thereby, the reaction between 3-methyl-6-phenylimidazo[2,1-*b*]thiazole (**1a**, 5 mmol) and *p*-toluenesulfonyl hydrazide (**2a**, 6 mmol) in H_2O (25 mL)afforded the desired product **3a** in 75% yield after a reaction time of 45 min.

To establish the mechanism of the reaction, control experiments were tested. As shown in Scheme 3, 1,2-di-*p*-tolyldisulfane and 4-methylbenzenethiol as sulfenylating agents instead of sulfonyl hydrazides failed in this method (Equations (1) and (2)). The sulfenylation reaction of **1a** with *S*-p-tolyl 4-methylbenzenesulfonothioate proceeded under the optimized conditions (Equation (3)). If the reaction was performed with TEMPO as a radical scavenger, the desired product **3a** was also obtained in 86% yield (Equation (4)), which indicated that this transformation did not proceed by a radical pathway. When



Scheme 3. Control reactions.



Scheme 4. Proposed reaction mechanism.

the *p*-toluenesulfonyl hydrazide **2a** was treated alone, the reaction afforded 1,2-di-*p*-tolyldisulfane **6a** and *S*-*p*-tolyl-4-methylbenzenesulfonothioate **6b** in 20% and 59% yields, respectively (Equation (5)). On the basis of the above results and previous reports,[7d,7g,20] a plausible mechanism of this transformation was proposed and shown in Scheme 4. Initially, treatment of sulfonyl hydrazides of **2a** under the reaction condition gives the sulfonothioate **6b**. Subsequently, a regioselective Friedel-Crafts reaction on C-3 position of **1a** generates the intermediate **9**. Finally, deprotonation of intermediate **9** provides the product **3a**. In this transformation, the intermediate **8** is converted to sulfinic acid **11** in the presence of water, which can supply the active sulfonothioate **6b** in this reaction cycle.

Conclusion

In conclusion, we have developed a simple and efficient method for the sulfenylation of imidazo[2,1-*b*]thiazoles with sulfonyl hydrazides under microwave-assisted and catalyst-free conditions. This transformation exhibits a broad scope of the reaction substrates and good functional-group tolerance. Ongoing research including expanding the substrate scope and applications of MAOS technology in organic synthesis are currently underway in our lab.

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