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Salicylic Acid-Promoted Three-Component Annulation of Benzimidazoles, Aryl Nitroalkenes and Elemental Sulfur

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Abstract: Herein, a three-component cyclization reaction of benzimidazoles, aryl nitroalkenes and elemental sulfur has been developed. Cheap and easily available salicylic acid found to be an efficient mediator for the present transformation. This protocol provides a facile access to structurally significant imidazo[2,1-*b*]thiazole skeleton from simple raw materials with a range of compatible synthetically useful functionalities. Furthermore, gram-scale preparation of this method is effective, which enables potential applications of it in broader fields of molecule synthesis. Mechanistically, a reaction cascade involving sequential aza-Michael addition, nucleophilic sulfuration, and deaminative aromatization was proposed.

Keywords: multi-component reaction; elemental sulfur; benzimidazoles; nitroalkenes; imidazo[2,1-*b*]thiazole

One-pot multi-component cascade assembly represents an advanced technique in modern synthesis that provides an efficient platform for rapid preparation of complex molecules from simple raw materials.[1] This strategy has also been extensively exploited in medicinal chemistry, total synthesis of naturally occurring products, and materials science.[2] In spite of the great progress, novel multi-component cascade reactions especially under facile reaction conditions remain desirable for method development in synthetic chemistry.

On the other hand, sulfur-containing frameworks widely exist in pharmaceuticals. Among the molecules in the table of top 200 pharmaceuticals by US prescription in 2012, for examples, more than 20% of them contain at least one sulfur atom.[3] Considering the pharmaceutical importance of sulfur compounds,[4] efficient methods for their construction has been intensively studied.[5] Elemental sulfur is a cheap, bench-stable, user-friendly sulfur reagent that was recently exploited to produce sulfur compounds including some valuable sulfur heterocycles such as thiophenes,[6] thiazoles,[7] benzothiazoles,[8] and among others.[9] Remarkably, the multi-component reactions through direct C–H sulfuration with elemental sulfur found to be versatile to give atom- and step-economic entries to complex sulfur-containing molecules. For example, Deng and coworkers have developed three-component heterocyclization of indoles, ketones, and elemental sulfur, which affords a novel access to indole-fused (benzo)thiophenes.[10] On the basis of this result, the same group utilized alkenes or alkynes as the coupling partner instead of ketones to construct the same heterocycle skeleton under metal-free conditions.[11] Complementarily, Fu *et al.* discovered that acrylic acids were also capable to engage into this three-component assembly and this reaction proceeded smoothly under additive-free conditions because of the acidity of reactant (Figure 1, a).[12]

Given the structurally nucleophilic resemblance between indoles and benzimidazoles, we speculated benzimidazoles could be used to replace indoles in the three-component assembly with elemental sulfur. Hence, a range of coupling partners such as acetophonone, phenylacetylene, styrene, cinnamic acid, and *β*-nitrostyrene were initially screened as the third

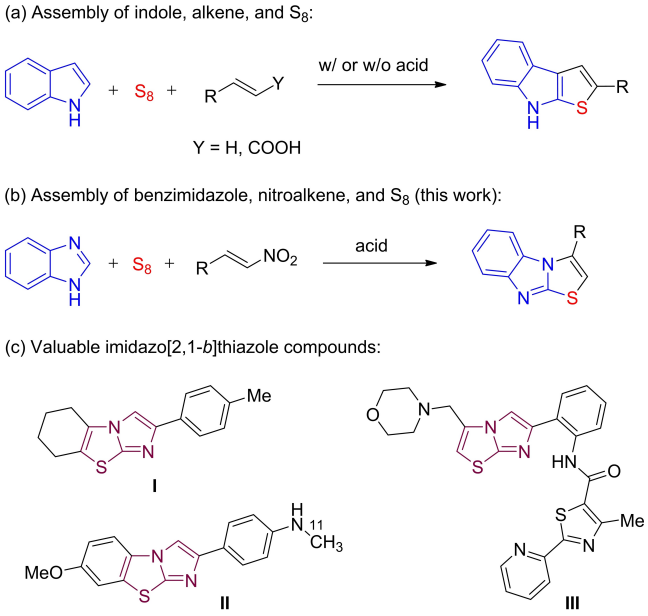
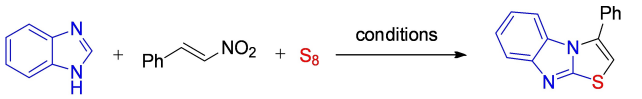


Figure 1. Three-component reactions with elemental sulfur for tricyclic heteroaromatics and valuable imidazo[2,1-*b*]thiazole compounds.

component. Among them, only *β*-nitrostyrene could deliver the target benzoimidazothiazole product (Figure 1, b). Notably, high levels of regioselectivity were observed in this reaction, in which C3-substituted heterocycle was exclusively formed, on the contrary to the result of indole assembly. More importantly, many imidazo[2,1-*b*]thiazole compounds are drugs or drug candidates.[13] For example, pifithrin-*β* (Figure 1c, **I**) is a highly efficient p53 inhibitor ($IC_{50} < 23$ nM); the ^{11}C-labeled imidazo[2,1-*b*] thiazole **II** could serve as a fluorescent probe in PET analysis of Alzheimer's disease; and the patented imidazo[2,1-*b*]thiazole compound **III** was developed as sirtuin modulator. Accordingly, it is highly attractive to develop facile methods for the construction of imidazo[2,1-*b*]thiazole motif.

With the primary results, we next conducted the optimization studies with benzimidazole **1a**, *β*-nitrostyrene **2a**, and elemental sulfur (S_8) as the model substrates under air (Table 1). Given previous reports that copper catalysts may play an essential role in C–S bond formation,[14] therefore, some copper salts were employed (entries 1–3). Of them, while $Cu(OAc)_2$ afforded the desired product **3a** in 30% yield, $CuCl_2$ and CuCl quenched the three-component assembly. These results indicate copper catalyst may not function in the current C–H sulfuration. The reaction performed with or without additional KI gave similar results (entries 4 and 5). Subsequently, an array of Brønsted acids were screened to disclose that while strong acids almost completely prohibited the desired transformation (entries 6–8), weak acids such as acetic acid (entry 9) and benzoic acid (entry 10) enhanced the

Table 1. Optimization of Reaction Conditions.[a]



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

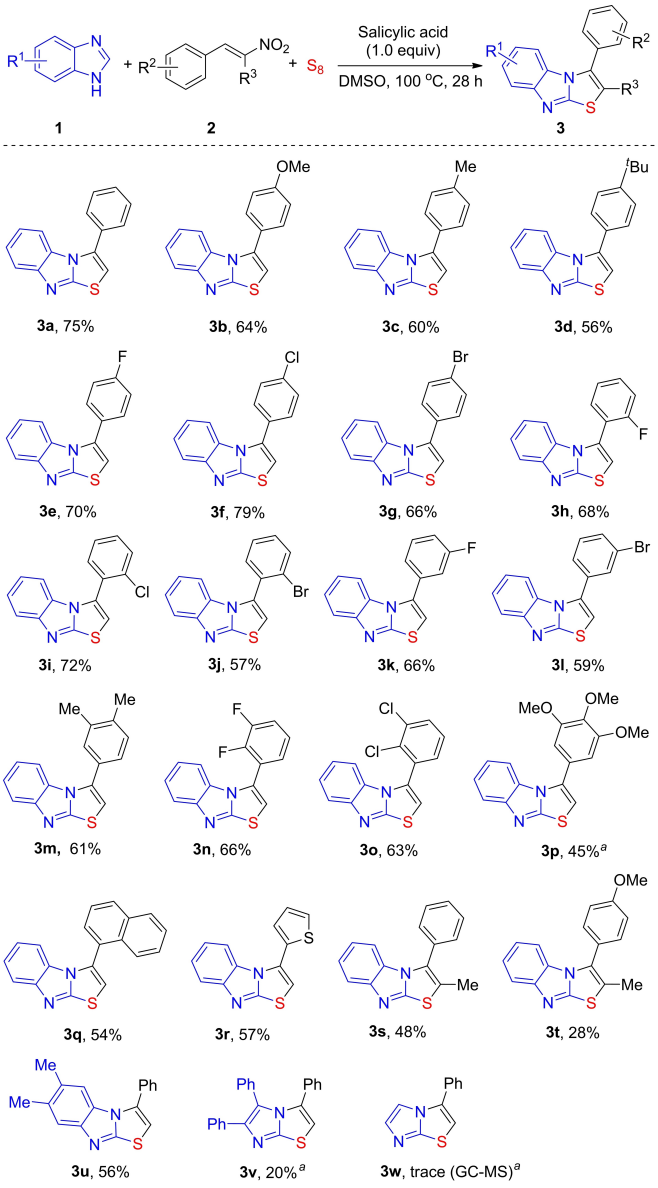
Entry	Catalyst	Additive	Solvent	Yield[b]
1	$Cu(OAc)_2$	–	DMSO	30
2	$CuCl_2$	–	DMSO	trace
3	CuCl	–	DMSO	trace
4	KI	–	DMSO	25
5	–	–	DMSO	24
6	–	TFA	DMSO	trace
7	–	TfOH	DMSO	trace
8	–	MsOH	DMSO	trace
9	–	HOAc	DMSO	36
10	–	BzOH	DMSO	48
11	–	salicylic acid	DMSO	75
12	–	2-NBA	DMSO	50
13	–	4-NBA	DMSO	35
14	–	$BF_3{\cdot}OEt_2$	DMSO	48
15	–	$Zn(OTf)_2$	DMSO	30
16	–	salicylic acid	DMF	34
17	–	salicylic acid	DMA	31
18	–	salicylic acid	NMP	60
19	–	salicylic acid	toluene	trace
20[c]	–	salicylic acid	DMSO	72
21[d]	–	salicylic acid	DMSO	56
22[e]	–	salicylic acid	DMSO	41
23[f]	–	salicylic acid	DMSO	73

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), S_8 (0.6 mmol, the mole number of sulfur based on S: 32 g/mol), catalyst (0.01 mmol, 5.0 mol%), additive (1.0 equiv.), DMSO (0.6 mL), at 100 °C under air for 28 h. NBA = nitrobenzoic acid.
[b] Isolated yield.
[c] At 110 °C.
[d] At 90 °C.
[e] Salicylic acid (0.5 equiv.) was used.
[f] Under Ar.

productivity of **3a**. Thus, substituted benzoic acids were further tested (entries 11–13). To our delight, salicylic acid found superior to others that generated **3a** in 75% yield (entry 11). Lewis acids were found also to be certain effective for this reaction, where $BF_3{\cdot}OEt_2$ (entry 14) and $Zn(OTf)_2$ (entry 15) afforded **3a** in 48% and 30% yield, respectively. The solvent effect was then studied, in which those of high polarity such as DMSO, DMF, DMA, and NMP worked with certain productivities (entries 16–18). Low-polar media such as toluene quenched the transformation (entry 19), which could be attributed to the low solubility of elemental sulfur in low-polar solvent. The reaction performed at elevated reaction temperature to 110 °C gave a similar result with that at 100 °C (entry 20); however, dramatically reduced reaction yield was

observed at 90 °C (entry 21), in line with the result obtained by reducing the amount of acid additive (entry 22). Finally, the control experiment under inner atmosphere suggests that oxygen did not participate in the present heterocyclization (entry 23).

With the optimized reaction conditions in hand, the substrate scope and generality of the Brønsted acid-promoted three-component sulfur-heterocyclization was probed (Scheme 1). First, a pad of *β*-nitrostyrenes bearing para-substituents were subjected to the acidic system. Those with electron-donating functional groups such as methoxy (**3 b**), methyl (**3 c**), and tert-butyl (**3 d**) slightly decreased the reaction efficiency. The corresponding 3-phenylbenzo[4,5]imidazo[2,1-*b*]thiazoles have been accessed in moderate yields. In the case of halogen functionalities, fluoro, chloro, and bromo were all tolerated to produce the halo-functionalized benzoimidazothiazole products (**3 e**–**g**), which provide ready opportunities for further manipulation and late stage diversification. Then, the *β*-nitrostyrenes with ortho- or meta-functionalities were employed (**3 h**–**l**). These substrates afforded the desired products with similar efficiency to that of para-variants, ruling out the steric hindrance effect of this component. Other decorated *β*-nitrostyrenes with dimethyl (**3 m**), difluoro (**3 n**), and dichloro (**3 o**) were compatible in the present system, furnishing the corresponding benzoimidazothiazoles in generally modest yields. That bearing trimethoxy function groups proceeded to afford **3 p** in 22% yield under the standard conditions while evaluated reaction temperature proved helpful. Hence, the reaction at 120 °C produced **3 p** in 45% yield. Nitroethylenes with naphthyl and thienyl moieties worked to give products **3 q** and **3 r**, respectively, with moderate efficiency. Gratefully, *β*-methyl-*β*-nitrostyrenes were also accommodated with the present system that afford 2,3-disubstituted benzo[4,5]imidazo[2,1-*b*]thiazoles, albeit in lower efficiency (**3 s** and **3 t**). Unfortunately, aliphatic nitroalkenes did not work in the present acid system.

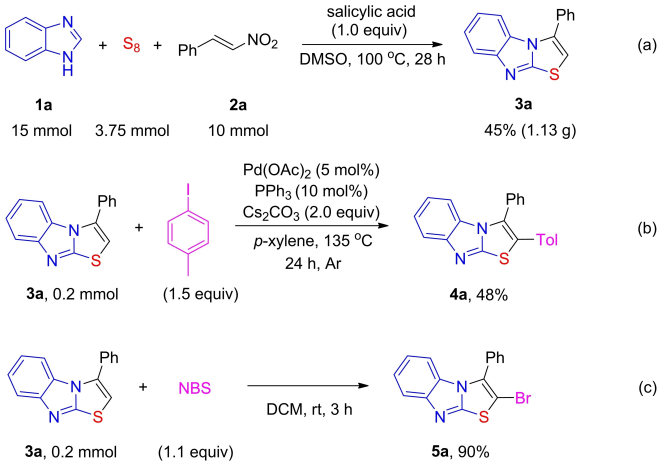


Scheme 1. Three-component reaction of benzimidazoles, *β*-nitrostyrene, and elemental sulfur. [a] Yield of reaction at 120 °C.

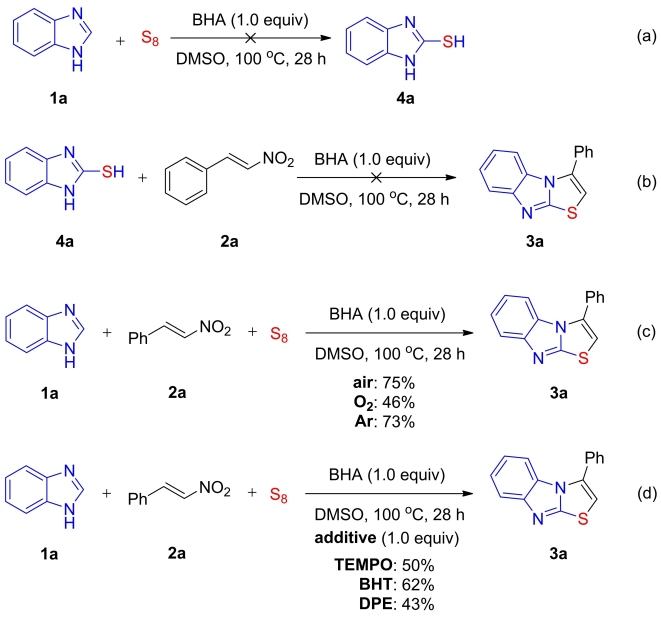
While mono-substituted benzoimidazoles gave a mixture of two isomer products with poor selectivity, 5,6-dimethyl-1H-benzo[*d*]imidazole afforded the corresponding product in good yield (**3 u**). Generally, the imidazole-type substrates featured low reactivity. For example, 3,4-diphenyl-1H-imidazole produced the target 3,5,6-triphenylimidazo[2,1-*b*]thiazole (**3 v**) in 20% yield even at 120 °C. But unsubstituted imidazole gave only trace amounts of corresponding product (**3 w**). However, the present system still provides a promising approach for the synthesis of structurally significant imidazo[2,1-*b*]thiazole motif.

The gram-scale reaction in the facile Brønsted acid system proved to be effective, where 10 mmol of *β*-nitrostyrene could afford 4.5 mmol of product **3 a** (Scheme 2, a). The product **3 a** bearing an undecorated C2 C–H, which could be readily transferred to C–C and C–Br bonds via palladium-catalyzed arylation with aryl iodide (Scheme 2, b) and bromination with the treatment of NBS (Scheme 2, c), respectively. However, because of the immature direct C–H arylation of this kind of heterocycles, the two step manipulation via sequential bromination and Suzuki-Miyaura coupling may feature advantage in productivity.

With the established reactivity of our Brønsted acid system for the three-component assembly, we were attracted by depicting the reaction model of the heterocyclization. To this end, some control experiments were carried out (Scheme 3). First, the treatment of benzimidazole **1 a** with elemental sulfur in the



Scheme 2. Synthetic applications.

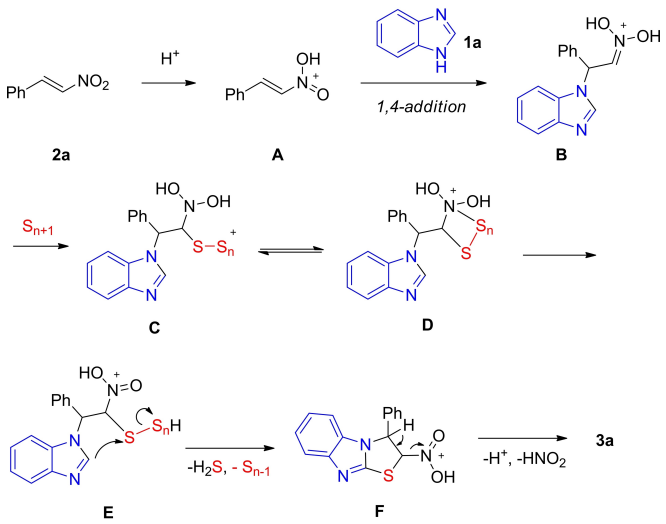


Scheme 3. Control experiments.

absence of *β*-nitrostyrene did not afford 1H-benzo[d] imidazole-2-thiol (Scheme 3, a). Further, the direct cyclization of 1H-benzo[d]imidazole-2-thiol and *β*-nitrostyrene could proceed under copper catalysis, which was discovered by Hajra and coworkers.[14] However, this reaction did not occur in our copper-free system (Scheme 3, b). These results suggest that the C–H sulfuration of 1H-benzo[d]imidazole with elemental sulfur would not occur in the initial step. Given the strong nitrogen nucleophilicity of benzo[d] imidazole, the aza-Michael addition of it to *β*-nitrostyrene may be more operative. Then, we found that oxygen atmosphere for the reaction significantly diminished the reaction productivity (Scheme 3, c), suggesting that oxidative annulation was not involved in this three-component heterocyclizaiton. Finally, the addition of radical scavenger such as TEMPO, butylated hydroxytoluene (BHT), and 1,1-diphenylethylene (DPE) has a slight effect on the reaction yield (Scheme 3, d). Hence, a radical pathway would not be mechanistically involved.

On the basis of the results from above experiments and previous reports,[10–11,15] a tentative reaction mechanism was proposed (Scheme 4). With the assistance of Brønsted acid, aza-Michael addition of benzimidazole **1a** to *β*-nitrostyrene **2a** proceeds to afford the intermediate **B** bearing an imine cation moiety. Then, nucleophilic attack of elemental sulfur to the intermediate **B** generates polysulfur intermediate **C** or **D**, with subsequent proton transfer of **D** to afford intermediate **E**. Then, intramolecular C–H sulfuration gives the annulation intermediate **F**, along with the elimination of hydrogen sulfide and elemental sulfur S_{n-1}. Finally, the thermal-driven elimination of nitrous acid moiety and deprotonation lead to the final benzo[4,5]imidazo[2,1-*b*]thiazole product **3a**.

In summary, we have developed a facile Brønsted acid-promoted three-component reaction that give a platform for the synthesis of benzo[4,5]imidazo[2,1-*b*] thiazoles from readily available benzimidazoles, nitroalkenes, and elemental sulfur. This metal-free protocol provides a straightforward entry to complex S,N-heterocycles from simple raw materials with a range of compatible functionalities. Mechanistic studies reveal a cascade reaction pathway involving sequential aza-Michael addition, nucleophilic sulfuration, and deaminative aromatization.



Scheme 4. Possible reaction mechanism.

Experimental Section

General Procedure for the Three-Component Reaction

Benzimidazole **1** (0.3 mmol), nitroalkene **2** (0.2 mmol), S_8 (19.2 mg, 0.6 mmol), salicylic acid (27.6 mg, 0.2 mmol, 1.0 equiv.), and DMSO (0.6 mL) were added successfully to a 10 mL oven-dried reaction vessel. The sealed reaction vessel was stirred at 100 °C for 28 h. After cooling to room temperature, the reaction was diluted with ethyl acetate (10 mL) and washed with saturated sodium chloride solution. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (10 mL) for three times. The combined organic layer was dried over magnesium sulfate and the volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate) to yield the desired product **3**.

Acknowledgements

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