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Elemental Sulfur Mediated Decarboxylative Redox Cyclization Reaction of *o*-Chloronitroarenes and Arylacetic Acids

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Supporting Information

ABSTRACT: A decarboxylative redox cyclization strategy has been developed for the synthesis of 2-substituted benzothiazoles by the reaction of *o*-chloronitroarenes and arylacetic acids in the presence of elemental sulfur/*N*-methylmorpholine under metal- and solvent-free conditions.

In recent years, decarboxylative reactions have attracted a great deal of attention in organic synthesis for the construction of C−C and C−X bonds, as carboxylic acids are common, inexpensive, and readily available in great structural diversity.[1] Numerous excellent investigations have been realized via a transition-metal-catalyzed decarboxylative approach;[2] however, the development of metal-free protocols for the synthesis of value added products is still desirable. In this regard, we have recently described a sulfur mediated decarboxylative thioamidation reaction.[3]

Benzothiazoles represent an important class of heterocyclic compounds ubiquitously found in natural products; especially 2-substituted benzothiazoles are used as versatile substrates and manifest broad biological and pharmaceutical properties.[4,5] Common methods for the synthesis of 2-arylbenzothiazoles involve the reaction of *o*-aminothiophenols[6] or benzothiazoles[7] with aldehydes or equivalent compounds, transition-metal-catalyzed cyclization of *o*-halothiobenzanilides,[8] and oxidative or transition-metal-catalyzed cyclization of thiobenzanilides.[9] Recently 2-aryl benzothiazoles have also been synthesized by the reaction of *N*-benzyl-2-haloaniline with potassium sulfide,[10] and *o*-halonitrobenzene with picoline[11] or benzylamine.[12] However, these methods sometimes require prefunctionalization of the starting materials, use of a metal/excess oxidant, harsh reaction conditions, and a long reaction time. Therefore, a metal-free and mild protocol for the synthesis of 2-substituted benzothiazoles using simple and readily available starting materials is highly exigent.

In light of the above and as a part of our recent interest in sulfur mediated reactions[13] and other protocols,[14] we disclose herein an elemental sulfur mediated decarboxylative redox cyclization of *o*-chloronitroarenes and arylacetic acids for the synthesis of 2-arylbenzothiazoles under metal- and solvent-free conditions (Scheme 1).

The reaction was optimized by varying different parameters using a model reaction of *o*-chloronitrobenzene (**1a**) and phenylacetic acid (**2a**) in the presence of elemental sulfur (Table 1). The study commenced using K_2CO_3 in DMSO at 100 °C for 15 h, which led to the formation of desired product 2-arylbenzothiazole (**3a**) in 51% yield (entry 1). Increasing the reaction temperature to 110 °C increased the product yield considerably (67%, entry 2). However, a further increase in the reaction temperature (120 °C) and time (24 h) did not show any beneficial effect (entries 3 and 4), but a decrease in the reaction time (12 h) decreased the product yield greatly (entry 5). The effect of different bases such as Na_2CO_3, K_3PO_4, *t*-BuOK, and $NaHCO_3$ was then screened on the reaction profile, but none of these could match the efficacy of K_2CO_3 (entries 6−9). The formation of product was not observed in the absence of the base (entry 10). Various organic bases such as DABCO, *N*-methylpiperidine, and *N*-methylmorpholine in DMSO were also found to be inferior (entries 11−13). Interestingly, when the reaction was carried out using *N*-methylmorpholine under solvent-free conditions, it improved the yield a little (entry 14). The use of solvents such as

Scheme 1. Recent Reports and Present Strategy

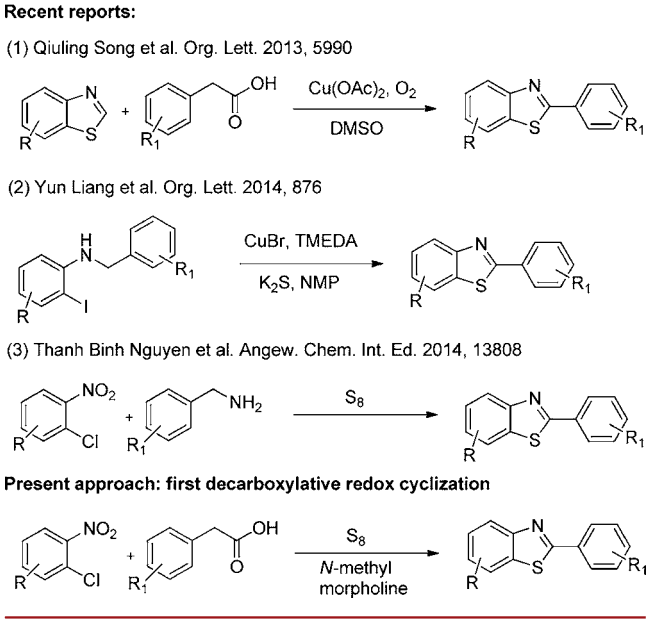

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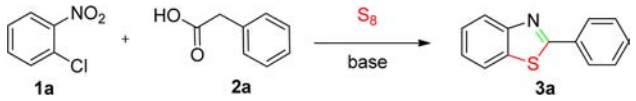
Table 1. Reaction Optimization[a]



entry	base	solvent	temp (°C)	yield (%)[b]
1	K_2CO_3	DMSO	100	51
2	K_2CO_3	DMSO	110	67
3	K_2CO_3	DMSO	120	66
4	K_2CO_3	DMSO	110	67[c]
5	K_2CO_3	DMSO	110	55[d]
6	Na_2CO_3	DMSO	110	56
7	K_3PO4	DMSO	110	36
8	*t*-BuOK	DMSO	110	39
9	$NaHCO_3$	DMSO	110	53
10	–	DMSO	110	0
11	DABCO	DMSO	110	51
12	*N*-methylpiperidine	DMSO	110	54
13	*N*-methylmorpholine	DMSO	110	59
14	*N*-methylmorpholine	–	110	69
15	*N*-methylmorpholine	pyridine	110	49
16	*N*-methylmorpholine	DMF	110	53
17	*N*-methylmorpholine	NMP	110	51
18	*N*-methylmorpholine	–	110	75[e]
19	*N*-methylmorpholine	–	110	74[f]
20	*N*-methylmorpholine	–	110	73[g]

[a]Conditions: phenylacetic acid (1 mmol), *o*-chloronitrobenzene (1 mmol), base (2 mmol), sulfur (3 mmol, 96 mg) for 15 h. [b]Isolated yield. [c]24 h. [d]12 h. [e]*N*-Methylmorpholine (3 mmol). [f]*N*-Methymorpholine (4 mmol). [g]Sulfur (4 mmol).

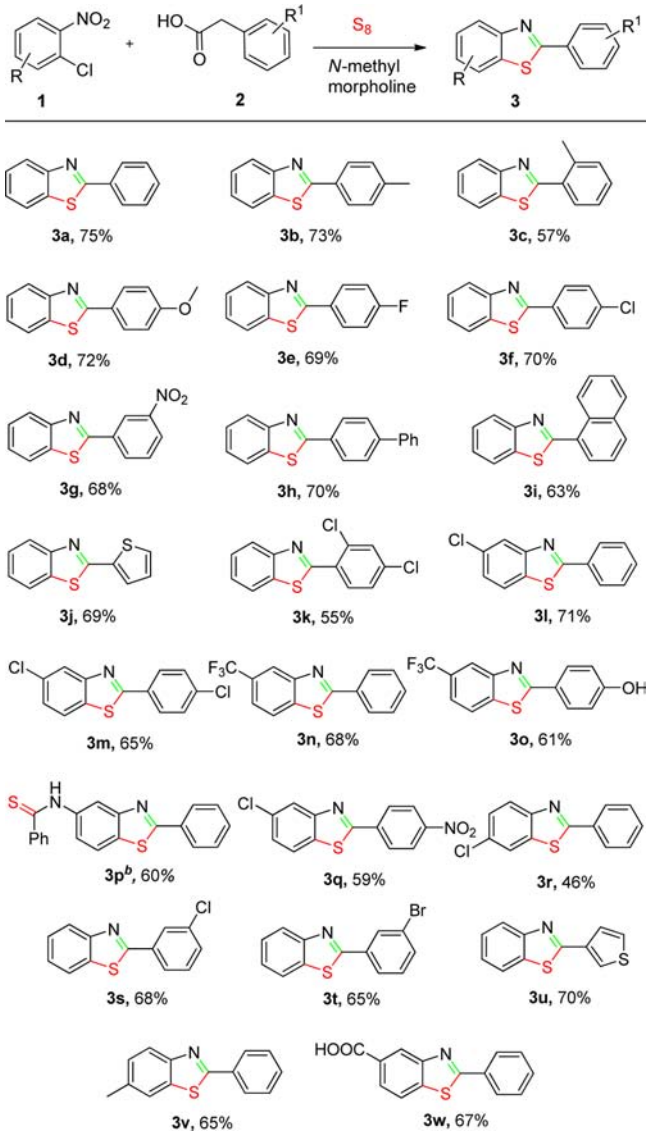
pyridine, DMF, and NMP also did not help (entries 15−17). When the molar ratio of the base was increased (3 equiv) under solvent-free conditions, an increase in the yield was observed (entry 18). A further increase in the mole equivalents of base and elemental sulfur led to no increment in the yield (entries 19 and 20).

With the optimized reaction conditions in hand (entry 18), the scope and versatility of the reaction were explored in detail (Scheme 2). A wide variety of arylacetic acids having substituents such as fluoro, chloro, bromo, methyl, methoxy, phenyl, hydroxyl, and nitro at different positions were made to react under the stipulated conditions to afford the desired products **3** in reasonably good yield. Ortho-substituted arylacetic acids gave lesser yields as compared to para- or meta-substituted reactants, perhaps due to steric hindrance. Bicyclic acid namely 2-naphthylacetic acid and heteroaromatic acids such as 2- and 3-thiopheneacetic acids also underwent the reaction smoothly. The aliphatic acids such as valeric, heptanoic, and 3-(3,4-dimethoxyphenyl)propanoic acids, however, failed to go through the reaction under the present conditions.

To further extend the adaptability of the reaction, different *o*-chloronitroarenes containing a variety of substituents such as chloro, methyl, trifluoromethyl, carboxyl, and nitro were subjected under the reaction conditions to give the corresponding products. Interestingly, the nitro function on the arylacetic acid component remained intact (**3g** and **3q**), whereas both the nitro groups of 1-chloro-2,4-dinitrobenzene participated well in the reaction to provide the *N*-(2-phenylbenzo[*d*]thiazol-5-yl)benzothioamide (**3p**) in 60% yield.

In order to gain insight into the reaction mechanism, a number of radical trapping and control experiments were

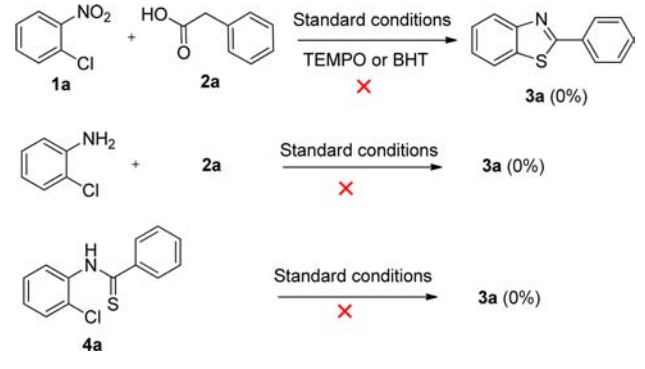
Scheme 2. Reaction Scope and Versatility[a]



[a]Conditions: arylacetic acid (1 mmol), *o*-chloronitroarene (1 mmol), *N*-methylmorpholine (3 mmol), sulfur (3 mmol, 96 mg) for 15 h. [b]Phenylacetic acid (2 mmol), *N*-methylmorpholine (6 mmol), sulfur (6 mmol, 192 mg).

conducted (Scheme 3). Radical scavengers such as TEMPO or BHT completely inhibited the reaction under standard

Scheme 3. Radical Trapping and Control Experiments



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conditions, thereby approving the involvement of the radical pathway. Control experiments involving the reaction of 2-chloroaniline with **2a**, and the reaction of thioamide **4a**, under the standard conditions, could not produce the product at all, which excludes the intermediacy of 2-chloroaniline and thioamide **4a** during the course of the reaction. The starting material **1a** was recovered as such when put alone under the standard reaction conditions.

Based on the above experiments and existing literature,[11] a plausible mechanism is outlined in Figure 1. In the presence of

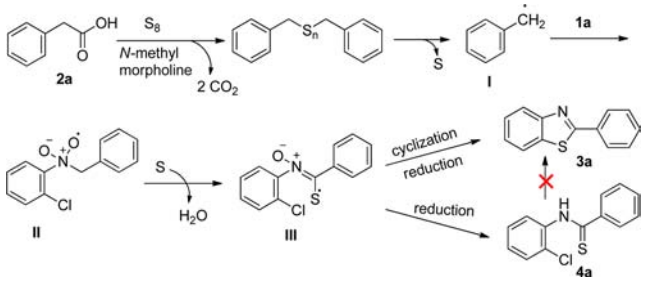

Figure 1. Plausible mechanism.

elemental sulfur and base, phenylacetic acid undergoes successive decarboxylation and sulfur extrusion to generate the radical intermediate **I**, which on subsequent reaction with the NO_2 group of the substrate **1a** followed by dehydration affords **III** via **II**. The intermediate **III** eventually undergoes cyclization reduction to provide the desired product **3a**. A trace amount of thioamide **4a** is also formed as a side product.

In conclusion, an efficient sulfur mediated decarboxylative redox cyclization approach has been developed for the synthesis of 2-substituted benzothiazoles using the reaction of *o*-chloronitroarenes and arylacetic acids. The reaction is free from the use of metal, an external oxidant, and solvent, which makes the process attractive and practical.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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