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Graphical Abstract

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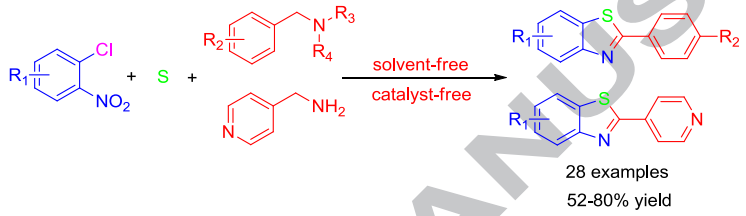

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A simple approach to benzothiazoles from 2-chloronitrobenzene, elemental sulfur, and aliphatic amine under solvent-free and catalyst-free conditions

Yao Tong [a], Qiang Pan [a],Zengqiang Jiang [a], Dazhuang Miao [a], Xuesong Shi [a], and Shiqing Han [a,b,*]

[a] College of Biotechnology and Pharmaceutical Engineering, Nanjing Tech University, Nanjing 211816, China
[b] Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, CAS, 345 Lingling Road, Shanghai 200032, China

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ABSTRACT

A novel solvent-free and catalyst-free synthesis of benzothiazoles from 2-chloronitrobenzene, elemental sulfur and aliphatic amine has been developed. The reaction tolerated a wide range of functionalities, and various benzothiazoles were synthesized in moderate to good yields in the absence of external oxidant or reductant.

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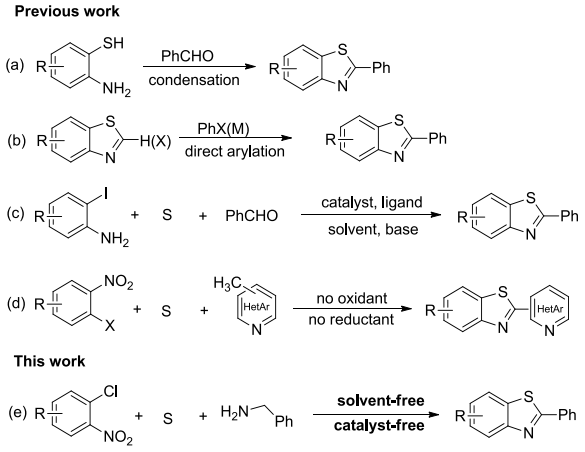
2-Substituted azoles such as benzothiazoles have attracted much attention because of their wide range of biological properties, such as their antitumor,[1] antimicrobial,[2] antiinflammatory,[3] and anticonvulsant activities.[4] Consequently, efficient preparation of substituted benzothiazole derivatives represents a worthwhile goal of heterocyclic synthesis. Traditional methods for their syntheses typically involve the condensation of 2-aminothiophenols with aryl aldehydes, carboxylic acids, or its derivatives (Scheme 1a).[5] However, this method suffers that the starting 2-aminothiophenols are not conveniently available. Alternative approaches employ direct arylation via C-H bond functionalization catalyzed by transition-metal between benzothiazoles and aryl halides or 2-halide-substituted benzothiazoles with aryl metals (Scheme 1b).[6] However, these methods often employ expensive metal catalysts and drastic reaction conditions which limit their synthetic applications. To overcome these drawbacks, some novel methods for the synthesis of benzothiazoles by means of one-pot three-component reactions have been also developed, in which elemental sulfur (Scheme 1c), hydrated sodium sulfhydrate ($NaHS{\cdot}nH_2O$), disodium disulfide (Na_2S_2) or sodium sulfide nonahydrate ($Na_2S{\cdot}9H_2O$) were used as the source of sulfur.[7] Nevertheless, these methods are associated with several limitations such as usage of toxic and unstable aldehydes, complex ligands and considerable amounts of base. Recently, Nguyen's group developed a simple and atom economic approach to 2-hetarylbenzothiazoles starting from 2-halonitroarene, methylhetarene, and elemental sulfur (Scheme 1d),[8] which is highlighted by the direct redox nitro-methyl reaction for carbon-nitrogen bond formation under mild conditions without an added oxidant or reductant. Inspired by recent reports that the methylene of benzylamine is easy to be oxidized which can construct some important heterocycles,[9] we envision the methylene of benzylamine also can act as a carbon synthon and a similar transformation can be achieved between 2-chloronitrobenzene, elemental sulfur and benzylamine (Scheme 1).



Scheme 1. Different routes for the synthesis of benzothiazoles.

With this idea in mind, we optimized the reaction conditions using 2-chloronitrobenzene **1a**, elemental sulfur, andbenzylamine **2a** as model substrates under solvent-free conditions (Table 1).

* Corresponding author. Tel: +86-25-58139970; Fax: 86-25-58139369.
*E-mail address:*hanshiqing@njtech.edu.cn (S. Han).

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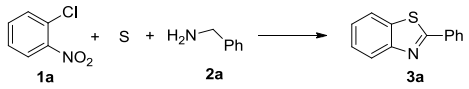
Initially, the reaction was carried out with 2-chloronitrobenzene **1a** (1 mmol), sulfur (1 equiv), benzylamine **2a** (3 equiv) at 120 ^{o}C and we were pleased to observe that these conditions afforded desired product benzothiazole **3a** in 55% (Table 1, entry 1). The desired product was obtained in 67% when 1.5 equiv sulfur was used (Table 1, entry 2). A slightly higher yield was obtained when increased the amount of sulfur to 2 equiv (Table 1, entry 3) while further increase the sulfur to 3 equiv resulted in a lower yield (Table 1, entry 4). To increase the efficiency of the reaction, the temperature was increased to 130 ^{o}C, as a result, the reaction yield could be improved to 78% (Table 1, entry 5). However, the reaction yield remarkably decreased to 63% when the temperature was increased to 140 ^{o}C (Table 1, entry 6).

Table 1. Reaction conditions optimization[a]



1a 2a 3a

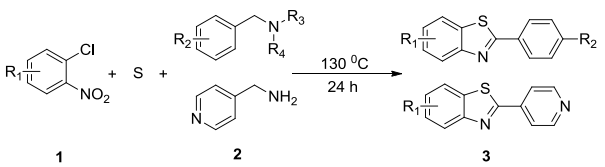
Entry	S (equiv)	**2a** (equiv)	Temp (^{o}C)	Yield[b] (%)
1	1	3	120	55
2	1.5	3	120	67
3	2	3	120	70
4	3	3	120	66
5	2	3	130	78
6	2	3	140	63

[a] Reaction conditions: 2-chloronitrobenzene **1a** (1 mmol), benzylamine **2a** (3 mmol), 24 h under nitrogen.

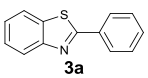
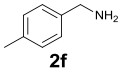
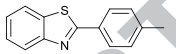
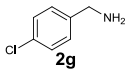
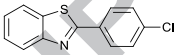
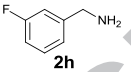
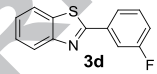
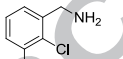
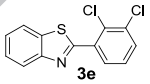
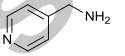
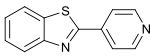
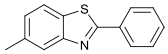
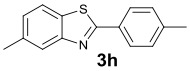
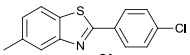
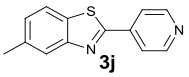
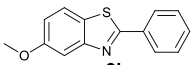
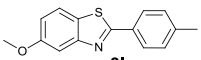
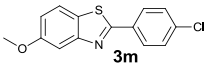
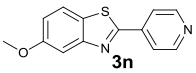
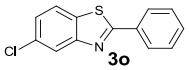
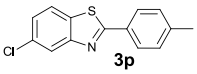
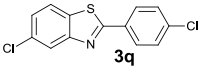
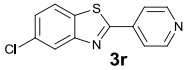
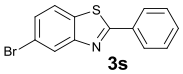
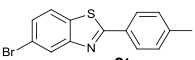
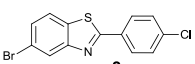
[b] Isolated yield.

With the optimal conditions established, we explored the scopeof the three-component reactions of 2-chloronitrobenzenes, elemental sulfur, and various amines under optimized conditions (Table 2). We found that in most examined cases the three-component reactions occurred smoothly and furnished the corresponding products in moderate to good yields. It turned out thatbenzylamine **2a**, 4-methyl-benzylamine **2f**, 4-chloro-benzylamine **2g**, 3-fluoro-benzylamine **2h**, and 2,3-dichloro-benzylamine **2i** were all good substrates for the formation of benzothiazoles (Table 2, entries 1, 6-9, 12-13, 16-17, 20-21, 24-25). A series of functional groups including methyl, methoxy, chloro, and bromo on the phenyl moiety of 2-chloronitrobenzene were well tolerated under the optimal reaction conditions, and the desired products were obtained in moderate to good yields (Table 2, entries 11, 15, 19, 23, 27-28). In addition, Benzylamines *N*-mono- and di-substituted by methyl or benzyl groups also underwent this transformation smoothly, although the products were formed in slightly lower yields and the higher temperatures were required (Table 2, entries 2-5). To further investigate the substrate scope, the aromatic heterocyclic amine was also tested. Interestingly, the 4-picolinamine **2j** proved to be a suitable substrate (Table 2, entries 10, 14, 18, 22, 26) and the yield could be up to 80% (Table 2, entry 10).

Table 2. Synthesis of benzothiazoles from 2-chloronitrobenzenes, elemental sulfur and aliphatic amines[a]



1 2 3

Entry	Nitrobenzene **1**	Amine **2**	Product **3**	Yield[b] (%)
1	**1a**, R_1 = H	**2a,** R_2 = R_3 = R_4 = H	 **3a**	78
2	**1a**	**2b,** R_2 = R_3 = H, R_4 = Me	**3a**	67
3	**1a**	**2c,** R_2 = H, R_3 = R_4 = Me	**3a**	65
4[c]	**1a**	**2d,** R_2 =R_3 = H, R_4 = Bn	**3a**	63
5[d]	**1a**	**2e,** R_2 = H, R_3 = R_4 = Bn	**3a**	55
6	**1a**	 **2f**	 **3b**	75
7	**1a**	 **2g**	 **3c**	55
8	**1a**	 **2h**	 **3d**	61
9	**1a**	 **2i**	 **3e**	52
10	**1a**	 **2j**	 **3f**	80
11	**1b**, R_1 = 5-Me	**2a**	 **3g**	72
12	**1b**	**2f**	 **3h**	70
13	**1b**	**2g**	 **3i**	52
14	**1b**	**2j**	 **3j**	62
15	**1c**, R_1 = 5-OMe	**2a**	 **3k**	80
16	**1c**	**2f**	 **3l**	76
17	**1c**	**2g**	 **3m**	58
18	**1c**	**2j**	 **3n**	75
19	**1d**, R_1 = 5-Cl	**2a**	 **3o**	78
20	**1d**	**2f**	 **3p**	76
21	**1d**	**2g**	 **3q**	60
22	**1d**	**2j**	 **3r**	70
23	**1e**, R_1 = 5-Br	**2a**	 **3s**	60
24	**1e**	**2f**	 **3t**	58
25	**1e**	**2g**	 **3u**	62

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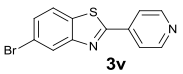
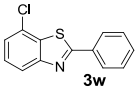
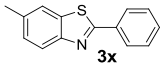
26	**1e**	**2j**	 **3v**	65
27	**1f**, R_1 = 3-Cl	**2a**	 **3w**	54
28	**1g**, R_1 = 4-Me	**2a**	 **3x**	79

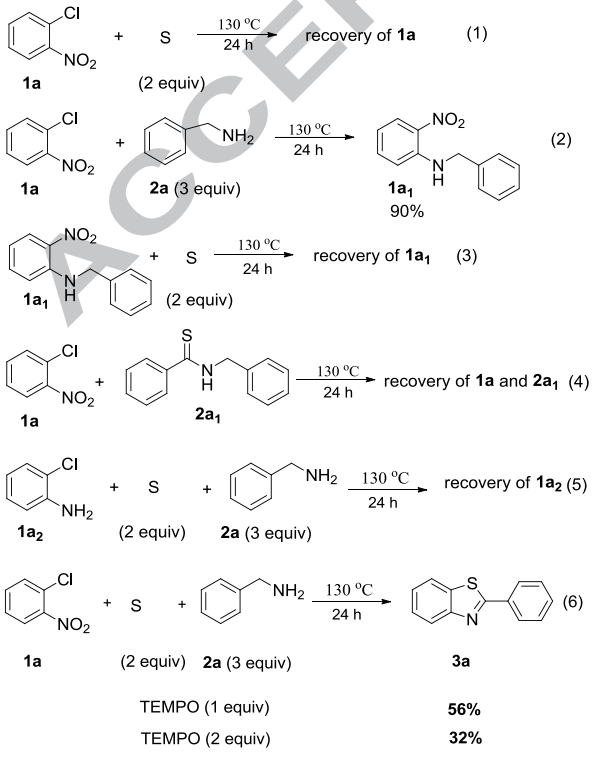
[a] Reaction conditions: 2-chloronitrobenzenes (1 mmol), sulfur (2 equiv), amines (3 equiv), 24 h, 130 °C.

[b] Isolated yield.

[c] At 140 °C.

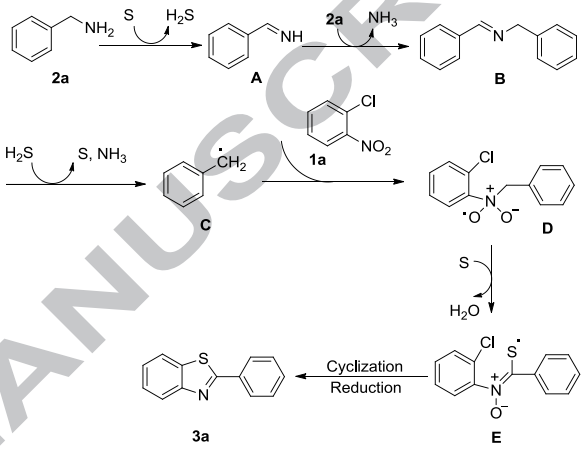
[d] At 150 °C.

To further clarify the mechanism, some control experiments were carried out, as shown in Scheme 2. Sulfur with **1a** was heated together, and **1a** was recovered unchanged (Scheme 2, eq 1). When **1a** was heated with **2a**, the expected product *N*-benzyl-2-nitroaniline **1a$_1$**was obtained in 90% yield (Scheme 2, eq 2). Treatment of **1a$_1$** with sulfur did not work and all starting materials wererecovered unchanged (Scheme 2, eq 3). *N*-benzylthiobenzamide **2a$_1$** is a byproduct during the reaction, which we speculated it may be the intermediate of the reaction. However, reaction of **1a** with **2a$_1$** did not give the desired product (Scheme 2, eq 4). When 2-chloroaniline **1a$_2$** was heated with sulfur and **2a** under optimized reaction conditions, the starting **1a$_2$** was recovered unchanged (Scheme 2, eq 5). On the basis of these results, sulfur could not reduce **1a** to **1a$_2$** and some possible intermediates such as *N*-benzyl-2-nitroaniline **1a$_1$** and *N*-benzylthiobenzamide **2a$_1$** did not play a significant role in the formation of benzothiazoles. It should be noted that when 1 equiv radical scavenger 2,2,6,6-tetramethylpiperidinooxy (TEMPO) was added under the standard reaction conditions, the desired product **3a** was obtained in 56% yield. Futher increased TEMPO to 2 equiv, the yield of **3a** was only 32%, indicating that a free radical perhaps was involved in the present reaction process (Scheme 2, eq 6).



Scheme 2. Control experiments.

Though the exact mechanism of the transformation is still not clear at present, on the basis of the above observations and previous literature a plausible mechanism is proposed and shown in Scheme 3. Firstly, benzylamine **2a** can be oxidized by elemental sulfur to generate imine **A**,[10] imine **A** reacted with **2a** to form *N*-benzylbenzaldimine **B** via transimination reaction.[11] Subsequently, in the presence of a protonic acid medium, **B** underwent a hydrogenolysis process and benzyl radical **C** may be formed during the transformation.[12] This highly active radical **C** could be trapped by the nitro group of **1a** to generate **D**. Finally, sulfuration the methylene of **D** afforded intermediate **E**, which followed by a cascade reaction of cyclization and reduction[13] to furnish 2-phenylbenzothiazole **3a**.



Scheme 3. Proposed mechanism.

In conclusion, we have developed a green and simple method for the synthesis of 2-substituted benzothiazoles by using inexpensive, readily available 2-chloronitrobenzenes, elemental sulfur and aliphatic amines as starting materials. In most cases, the corresponding 2-substituted benzothiazoles were obtained in moderate to good yields in the absence of external oxidant or reductant. The high efficiency and easy manipulation make it superior in both academic and industrial application. Further investigation of the reaction mechanism and the synthetic applications of this method is on going in our group.

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14. *General procedure for the synthesis of benzothiazoles* : A mixture of 2-chloronitrobenzene (1 mmol), amine (3 mmol) and elemental sulfur (2 mmol) was stirred in a sealed tube under nitrogen atmosphere at indicated temperature for 24 h (See Table 2). After being cooled to room temperature, the crude reaction mixture was triturated and dissolved in ethyl acetate, then filtered and the filtrate was concentrated, and the residue was purified by column chromatography on silica gel to afford the desired product. Selected spectral data for 2-Phenylbenzothiazole (Table 2, entry 1): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (t, 1 H), 7.48−7.51 (m, 4 H), 7.91 (d, J = 9.0 Hz, 1 H), 8.07−8.12 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 121.6, 123.2, 125.1, 126.3, 127.5, 129.0, 130.9, 133.7, 135.0, 154.1, 171.8.

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