<u>LETTERS</u>

Assembly of 2-Arylbenzothiazoles through Three-Component Oxidative Annulation under Transition-Metal-Free Conditions

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Supporting Information

ABSTRACT: Highly efficient methods for the synthesis of 2arylbenzothiazoles and 2-arylnaphtho[2,1-*d*]thiazoles have been developed. Readily available aromatic amines, benzaldehydes, and elemental sulfur were directly assembled through oxidative annulation and C–H functionalization under transition-metal-free conditions, where DMSO or oxygen served as the oxidant. NH₄I or KI as the catalyst was found to be effective to promote the transformations to give the annulation products in good to excellent yields with wide functional group tolerance.

B enzothiazole represents one of the privileged motifs in natural products and pharmaceuticals.^{1,2} Specifically, 2arylbenzothiazoles compose core structures of many bioactive compounds such as antitumor agents, antituberculotics, antiparasitics, and calcium channel antagonists.³ Moreover, 2arylbenzothiazoles have been extensively investigated for applications in industrial dyes, organic luminescent materials, and agrochemical compounds.⁴ Accordingly, the development of efficient methods for the synthesis of 2-arylbenzothiazoles has attracted considerable interest. The classic routes to 2arylbenzothiazoles mainly rely on the condensation of 2aminothiophenols with aldehydes and carboxylic acids⁵ and oxidative intramolecular cyclization of thiobenzanilides.⁶ Transition-metal-catalyzed direct arylation of preexisting benzothiazole cores is also an attractive research topic,⁷ which, significantly, does not require preactivated heteroaryl coupling partners.

Among the intensive efforts on the synthesis of 2arylbenzothiazoles, while the classic methods often use stoichiometric toxic oxidant or proceed through multistep operation, the direct arylations rely on expensive metal catalysts. Furthermore, the prefunctionalized substrates such as 2aminothiophenol and its analogues are expensive and not easily available chemicals.⁸ From a green chemistry perspective, it is highly desirable to develop efficient methods for the synthesis of 2-arylbenzothiazoles from readily available starting materials under mild and facile reaction conditions.⁹

Elemental sulfur widely exists in nature with nontoxic and stable properties under ambient conditions. Thus, the direct use of elemental sulfur as the sulfur source for the construction of sulfur-containing molecules is believed to be a direct, simple, and atom-economical approach.^{10–12} Meanwhile, the use of easily available anilines instead of more complex 2-aminothiophenol or



2-haloaniline substrates is apparently a more straightforward approach for the construction of benzothiazoles.¹³ Within our program on C–S bond formation using elemental sulfur,¹⁴ herein, we report the three-component synthesis of 2-arylbenzothiazoles starting from readily available aromatic amines, aldehydes, and sulfur powder. The reaction is successfully achieved in one-pot fashion under simple and facile reaction conditions.

We initiated our study by examining the reaction of naphthalen-2-amine (1a), benzaldehyde (2a), and sulfur powder in DMSO/chlorobenzene (1:3) under ambient atmosphere (Table 1). When the reaction was run at 140 °C in the presence of molecular sieves without any initiator, the desired 2phenylnaphtho[2,1-d]thiazole 3a was observed in 59% yield (entry 1). This result encouraged us to screen a series of iodide catalysts¹⁵ for this transformation. When KI and molecular iodine were added, the reaction yields were improved to 78% and 76%, respectively (entries 2,3). To our delight, 94% yield was obtained when NH₄I was used as the catalyst (entry 4), while Me₄NI also enhanced the reaction yield to 70% (entry 5). Then, we found solvent played an important role in this threecomponent annulation, and much lower yields were obtained when the reactions were carried out in NMP, toluene, and 1,4dioxane (entries 6-8). The addition of DMSO was critical to get satisfactory yield since only modest yield was observed when chlorobenzene was used as the sole solvent (entry 9). The ratio of chlorobenzene/DMSO slightly affected the reaction yield (entries 10–12), and 3 equiv of DMSO was found to be superior to give the desired product in 95% yield. The desired product was generated in 91% yield when decreasing catalyst loading of NH₄I

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Table 1. Optimization of Reaction Conditions^a

	NH ₂ + F	PhCHO S ₈ 4 Å MS, air	S N N
	1a	2a	3a
entry	catalyst	solve	nt yield ^b
1		PhCl/DMS	O (3:1) 59
2	KI	PhCl/DMS	O (3:1) 78
3	I_2	PhCl/DMS	O (3:1) 76
4	NH_4I	PhCl/DMS	O (3:1) 94
5	Me ₄ NI	PhCl/DMS	O (3:1) 70
6	NH_4I	NMP	49
7	NH_4I	toluene	26
8	NH_4I	1,4-dioxane	48
9	NH_4I	PhCl	54
10 ^c	NH_4I	PhCl/DMS	O 95
11	NH_4I	PhCl/DMS	O (1:1) 87
12	NH_4I	PhCl/DMS	O (1:3) 84
13 ^d	NH_4I	PhCl/DMS	O (3:1) 91
14 ^e	NH_4I	PhCl/DMS	O (3:1) 88
15 ^f	NH_4I	PhCl/DMS	O (3:1) 40
16 ^g	NH_4I	PhCl/DMS	O (3:1) 12

^{*a*}Reaction conditions: **1a** (0.22 mmol), **2a** (0.2 mmol), S_8 (12.8 mg, 0.4 mmol), catalyst (10 mol %), 4 Å MS (100 mg), and solvent (0.4 mL, 0.5 M) under air at 140 °C for 24 h. ^{*b*}GC yield based on **2a**. ^{*c*}DMSO (3 equiv). ^{*d*}NH₄I (5 mol %). ^{*e*}S (0.3 mmol, 1.5 equiv). ^{*f*}Without 4 Å MS. ^{*g*}At 120 °C.

to 5 mol % (entry 13). Reducing the amount of elemental sulfur to 1.5 equiv also gave good yield of **3a** (88%) (entry 14). Much lower yield was observed when the reaction was carried out in the absence of molecular sieves (entry 15), and **3a** was produced in 12% yield when the reaction was run at 120 $^{\circ}$ C (entry 16).

With the optimized reaction conditions in hand, the scope and generality of the three-component reaction was explored (Scheme 1). In general, the reactions with benzaldehydes bearing substituents at the para-, meta-, and ortho-positions worked smoothly to give the corresponding 2-arylnaphthothiazole products in excellent yields (3a-3v), and higher product yields were obtained when aromatic aldehydes bearing electrondonating groups were used (3d-3g). The position of the substituent did not affect the reaction yield in most cases. While para-bromobenzaldehyde afforded the product in 61% (3c), 3j was obtained in 90% yield when the bromo group was located at the meta-position. Notably, the hydroxyl functional group was compatible under the optimized reaction conditions (3r), affording the corresponding annulation product in 94% yield. Aromatic aldehydes with strongly electron-withdrawing nitro at the ortho-position were also highly effective to this reaction, giving the corresponding products in good to excellent yields (3s-3v). 2-(Naphthalen-2-yl)naphtho[2,1-d]thiazole 3w was obtained in 93% yield when 2-naphthaldehyde (2w) was used. Multisubstituted aldehydes efficiently reacted as well to give the products in excellent yields (3x-3z). Heteroaromatic aldehydes were also investigated under the optimized reaction conditions. While 3aa was obtained in moderate yield when pyridine-2carbaldehyde (2aa) was used, very good yield was obtained with thiophene-2-carbaldehyde (2ab). Anthracen-2-amine was also well compatible with the present system to generate the 2phenylanthra [2,1-d] thiazole **3ac** in 83% yield. Remarkably, when 5 mmol scale reactions were run under the optimized conditions,

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^{*a*}Reaction conditions: **1a** (0.22 mmol), **2** (0.2 mmol), S_8 (12.8 mg, 0.4 mmol), NH₄I (10 mol %), DMSO (3 equiv), 4 Å MS (100 mg), and PhCl (0.4 mL) under air at 140 °C for 24 h. ^{*b*}Five mmol scale reaction. ^{*c*}DMSO (0.1 mL).

the corresponding products **3a** and **3n** were obtained in 90% and 91% yields, respectively.

To further examine the scope and limitations of the reaction, we tested anilines instead of naphthalenamine in this reaction (Scheme 2). However, much lower yields were obtained when anilines were employed under the previously optimized reaction conditions. To get satisfactory yield, we used KI (20 mol %) as the catalyst with an increased amount of elemental sulfur and elevated reaction temperature. Notably, the oxygen atmosphere was better as the oxidant for anilines than DMSO, and the addition of molecular sieves could not enhance the transformation. Under the modified reaction conditions, moderate to good yields were generally obtained when alkyl-substituted anilines were employed (4a-4g). Product 4h was obtained in 84% yield when 4-methoxyaniline was used as the substrate. Other anilines bearing electron-donating groups such as ethoxy, phenoxy, and multimethoxy groups afforded the desired products in modest yields (4i-4m). Unfortunately, aliphatic aldehydes such as n-octanal did not work in both cases of naphthalenamine and aniline.

A series of control experiments were performed to gain mechanistic information on the three-component annulation. Although 2-aminothiophenol 5 combined with benzaldehyde and sulfur powder generated the desired benzothiazole 4h in excellent yield (Scheme 3a), it was not considered as the

Scheme 2. Substrate Scope with Respect to Anilines^a



^aReaction conditions: 1 (0.3 mmol), 2a (0.2 mmol), S_8 (32 mg, 1.0 mmol), KI (20 mol %), and NMP (0.5 mL) under O₂ at 150 °C.

Scheme 3. Control Experiments



intermediate product of the reaction because the direct treatment of aniline 1h in the absence of aldehyde could not afford 2aminothiophenol product (Scheme 3b). Furthermore, the generation of imine 6 was superior when the reaction was performed within 1 h (Scheme 3c). Then, we found either imine 6 or thioamide 7 could transfer into the final benzothiazole under the standard conditions (Scheme 3d,e), which indicated that this reaction probably involves two different pathways. Additionally, the annulation would not proceed through a radical pathway since the addition of radical scavengers such as BHT and TEMPO did not inhibit the desired transformation (Scheme 3f).

Based on the experimental results, a possible reaction mechanism was proposed (Scheme 4). The condensation of



amines and aldehydes is believed to be the initial step, which generates imine A. Electrophilic attack of sulfur S_n to the orthoposition of anilines affords intermediate **B**,¹⁶ which proceeds through elimination of S_{n-1} and deprotonation to give sulfurated imine C. The final 2-arylbenzothiazoles is formed through cyclization of C and subsequent oxidative aromatization. The nucleophilic attack of sulfur S_n to imine would be complementary,¹⁷ whereby intermediate E is afforded. Then, intramolecular electrophilic addition of sulfur moiety of E to arene followed by deprotonation generates dihydrobenzothiazole D, which likewise delivers final products by oxidation. While DMSO^{15c,d} served as oxidant in the case of naphthalen-2-amine, 2-arylbenzothiazoles 4 were produced through aerobic oxidation by oxygen. With respect to the role of the iodide catalyst, we suspect that it may make the imine intermediate more active and promote the oxidative aromatization.¹⁵ⁱ⁻¹

In summary, we have developed a novel oxidative approach for the synthesis of 2-arylbenzothiazoles and 2-arylnaphthothiazoles from aromatic amines, aromatic aldehydes, and elemental sulfur under metal-free conditions. NH_4I and KI as the catalyst combined with DMSO and oxygen as the oxidant were found to be effective to achieve satisfactory reaction yields. This protocol provides facile access to 2-arylbenzothiazoles from three readily available starting materials. The mechanistic studies and further synthetic applications of this methodology are currently in progress in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02168.

Experimental procedures, characterization data, and ¹H NMR and ¹³C NMR spectra for all new products (PDF)

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Notes

The authors declare no competing financial interest.

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