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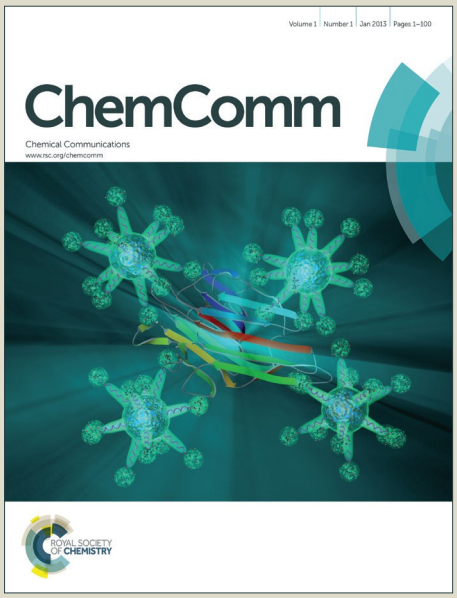

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A Metal-Free Synthesis of 2-Aminobenzothiazoles through Aminyl Radical Addition to Aryl Isothiocyanates

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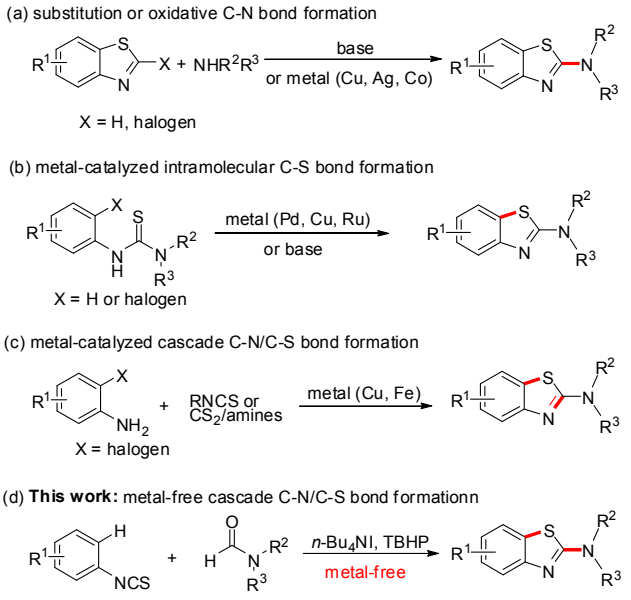
A convenient synthesis of 2-aminobenzothiazoles, starting from aryl isothiocyanates and formamides under metal-free conditions, is described. Various secondary and tertiary amine- and even α-amino acid-derived formamides can be used as amino scources in this process. Mechanistic studies suggest that the reaction is initiated by decarbonylative aminyl radical formation in the presence of *n*-Bu_4NI and TBHP, followed by aminyl radical addition to isothiocyanates and cyclization via sulfur centred radical intermediates.

The development of efficient methods for the construction of C-S bond has received much attention due to the ubiquitous existence of sulfur atom in biologically relevant molecules. Direct C-H bond sulfuration is considered as one of the powerful methods for the construction of C-S bond in terms of atom economy and step efficiency.[1] Over the past decade, great progress has been made in this field, mainly focusing on transition-metal catalysis.[2] In view of green chemistry, it is attractive to develop alternative transition-metal-free C-H sulfuration reactions.[3] Isothiocyanates are versatile building blocks used frequently for the synthesis of ureas, carbamates and various heterocycles, mostly triggered by nucleophilic addition.[4] On the other hand, isothiocyanate-participated radical reactions are less documented.[5] In general, C, Si, or Sn-centred radicals were used to attack the sulfur or carbon centre of isothiocyanates to generate the corresponding imidoyl or sulfur radical intermediates for further transformations. For example, Zanardi et al. described a cascade radical process for the construction of benzothieno[2,3-*b*]quinolines from 2-alkynyl-substituted aryl radicals and aryl isothiocyanates via imidoyl radical intermediates.[5c] Yadav et al. reported a copper-catalyzed 2-alkylbenzothiozole synthesis through addition of alkyl radicals to the carbon centre of aryl isothiocyanates, followed by cyclization of the sulfur radical intermediate.[6] However, reaction of *N*-centred radicals with isothiocyanates was scarce in literature. Recently, Jiang's group reported a novel access to 2-aminothiazoles, in which a possible mechanism involving iminium radical addition to isothiocyanates followed by C-S bond formation of the resulting sulfur radical with the α-carbon of the imine moiety was proposed.[7]

Scheme 1. Approaches for the Preparation of 2-Aminobenzothiazoles



The scaffold of 2-aminobenzothiazole can be found in many natural products and biologically active compounds,[8] and therefore considerable efforts have been made for their synthesis (Scheme 1). Major approaches include: (a) base promoted substitution reaction of 2-halobenzothiozoles or transition-metal-catalyzed oxidative coupling of 2-unsubstituted benzothiazoles with amines;[9] (b) transition-metal-catalyzed cyclization of *N*-aryl thioureas through intramolecular C-S bond formation;[10] (c) tandem condensation and cyclization of 2-haloanilines with isothiocyanates or three-component reaction of 2-haloanilines, amines and CS_2 under transition-metal catalysis.[11] In these methods, transition-metal catalysts or bases are generally needed. We report herein a convenient synthesis of 2-aminobenzothiazoles under transition-metal-free conditions starting from readily available aryl isothiocyanates and formamides (d, Scheme 1).

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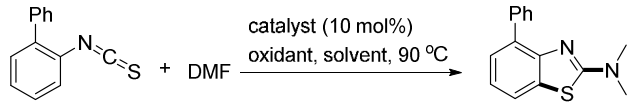
Recently, the combination of *n*-Bu_4NI and TBHP has been applied successfully in C-H functionalization due to the high reaction efficiency and environmental benignity.[12,13] For instance, Wan[14] and Qu[15] independently developed oxidative coupling of formamides with aldehydes or acetophenones catalyzed by *n*-Bu_4NI in the presence of TBHP as an oxidant. As part of our continuing interest in heterocycles synthesis through C-H functionalization, we hypothesized that *N*-centred radical produced from decarbonylation of formamide would react with aryl isothiocyanates to deliver 2-aminobenzothiazoles after cyclization.

Table 1. Optimization of the Reaction Conditions[a]



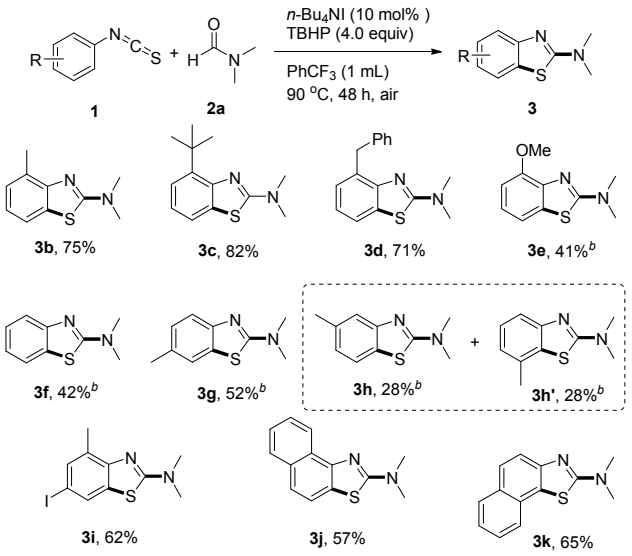
1a **2a** **3a**

entry	catalyst (10 mol%)	oxidant	**2a** (equiv)	solvent	yield[b] (%)
1	*n*-Bu_4NI	TBHP[c]	1 mL	--	87
2	*n*-Bu_4NI	TBHP[d]	1 mL	--	62
3	*n*-Bu_4NI	TBPB	1 mL	--	44
4	*n*-Bu_4NI	H_2O_2	1 mL	--	58
5	*n*-Bu_4NI	TBHP[c]	10	$PhCF_3$	58
6	*n*-Bu_4NI	TBHP[c]	10	CH_3CN	44
7	*n*-Bu_4NI	TBHP[c]	10	DCE	42
8[e]	*n*-Bu_4NI	TBHP[c]	10	$PhCF_3$	75
9[e]	I_2	TBHP[c]	10	$PhCF_3$	21
10[e]	NIS	TBHP[c]	10	$PhCF_3$	0
11[e]	--	TBHP[c]	10	$PhCF_3$	0
12[e]	*n*-Bu_4NI	--	10	$PhCF_3$	0

[a] Reaction conditions: **1a** (0.2 mmol), catalyst (10 mol%), oxidant (1.2 equiv), 90 °C, 48 h, in air. [b] Isolated yield based on **1a**. [c] TBHP = *tert*-butyl hydroperoxide in decane (5.5 M). [d] 70% TBHP in water. [e] oxidant (4.0 equiv). TBPB: *tert*-butyl peroxybenzoate.

Our investigation started with 2-isothiocyanato-1,1'-biphenyl (**1a**) as a substrate and *N*,*N*-dimethylformamide **2a** (DMF, 1mL) as an amino source in the presence of 10 mol% of *n*-Bu_4NI and 1.2 equiv of TBHP (5.5 M in decane) at 90 °C (entry 1, Table 1). To our delight, the desired product, *N*,*N*-dimethyl-4-phenylbenzo[d]thiazol-2-amine **3a**, was obtained in 87% isolated yield. Other oxidants were proved to be less effective in this transformation (entries 2-4). To develop a general and practical procedure applicable to other formamides, less amount of DMF (10.0 equiv) in different solvent was examined. It was found that the reaction in $PhCF_3$ proceeded better than those in CH_3CN and DCE (58%, entries 5-7). When TBHP was used in 4.0 equiv in $PhCF_3$, the yield of **3a** was improved to 75% (entry 8). Molecular iodine (I_2) and NIS were tested in place of *n*-Bu_4NI, but they were found much less effective (entries 9-10). A set of control reactions revealed that both *n*-Bu_4NI and TBHP were necessary for this amination cyclization reaction (entries 11-12). It was notable that TBHP had to be added in several portions; otherwise the desired product **3a** was partially demethylated to form *N*-methylbenzo[d]thiazol-2-amine.

Scheme 2. Scope of Aryl Isothiocyanate[a]



[a] Reaction conditions: **1** (0.2 mmol), *N*, *N*-dimethylformamide **2a** (2.0 mmol), *n*-Bu_4NI (10 mol%), TBHP (0.8 mmol, 5.5 M in decane), trifluoromethylbenzene (1 mL), 90 °C, 48 h, isolated yield. [b] **1** (0.2 mmol), *N*, *N*-dimethylformamide **2a** (1 mL), Bu_4NI (10 mol%), TBHP (0.24 mmol, 5.5 M in decane), 90 °C, 48h.

The scope of aryl isothiocyanates was first examined under the optimized reaction conditions (Scheme 2). It was found that both the position and electronic nature of the substituent on the phenyl ring affected the outcome of the reaction significantly. For example, *ortho* methyl, *tert*-butyl, or benzyl substituted aryl isothiocyanates could afford the corresponding products smoothly (**3b**-**3d**). However, more electron-rich 1-isothiocyanato-2-methoxybenzene was less compatible with the oxidative conditions, affording **3e** in lower yield (41%). Disappointingly, isothiocyanates substituted with electron withdrawing groups such as chloro or nitro group at the *ortho* position couldn't produce the desired product. Phenyl isothiocyanate and *para*-methyl phenyl isothiocyanate gave the corresponding products **3f** and **3g** in moderate yields. The reaction was non-regioselective for *meta*-methyl substituted aryl isothiocyanate, delivering a mixture of **3h** and **3h'** in a 1:1 ratio. The iodo group could survive the reaction condition, making further diversification on the scaffold possible. Interestingly, when 2-isothiocyanatonaphthalene was used as a substrate, only one of the isomeric products **3k** was obtained in 65% yield.

Then, different formamides were tested in reactions with 1-isothiocyanato-2-methylbenzene **1b** (Scheme 3). *N*,*N*-Diethylformamide and morpholine-4-carbaldehyde could be served as excellent amino sources, while steric hindered *N*,*N*-diisopropylformamide was less efficient in the desired product formation (**3o**). Moreover, primary amine derived formamides including *N*-*sec*-butylformamide, *N*-*tert*-butylformamide, *N*-

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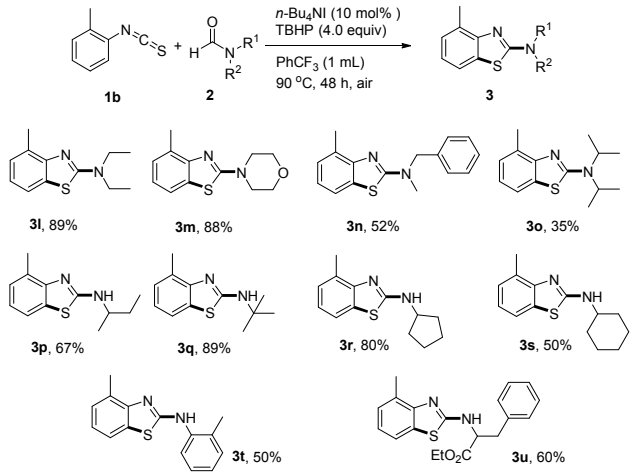
cyclopentylformamide, and *N*-cyclohexylformamide were well tolerated under the metal-free conditions, delivering the corresponding N-H free 2-aminobenzothiazole derivatives **3p**–**3s** in moderate to good yields. Notably, *N*-*o*-tolylformamide was also a suitable substrate for the reaction to afford **3t** in 50% yield. Importantly, benzothiazole derivative **3u**, bearing an α-amino acid moiety, was also accessible by applying this method. Unfortunately, reaction of isocyanatobenzene with DMF under the standard conditions couldn't give the corresponding aminated benzooxazole.

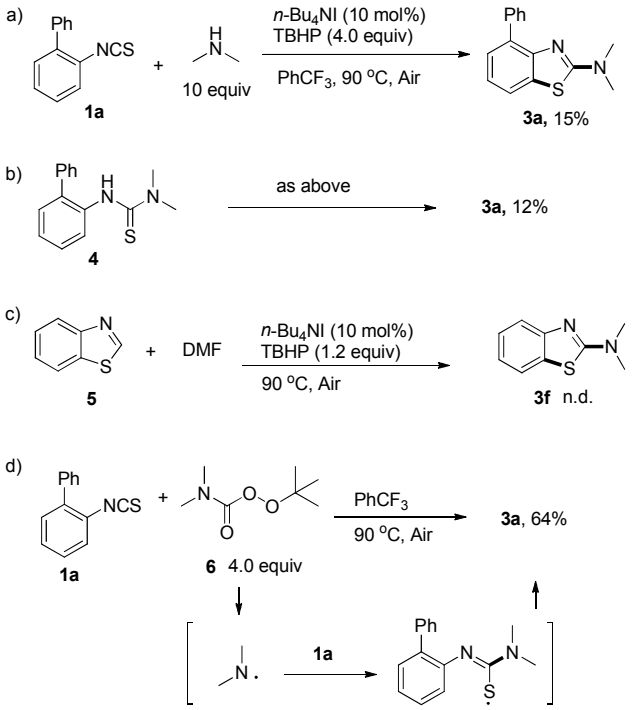
Scheme 3. Scope of Formamide[a]



[a]Reaction conditions: **1b** (0.2 mmol), formamide (2.0 mmol), *n*-Bu_4NI (10 mol%), TBHP (0.8 mmol), trifluoromethylbenzene (1 mL), 90 °C, 48 h, isolated yield.

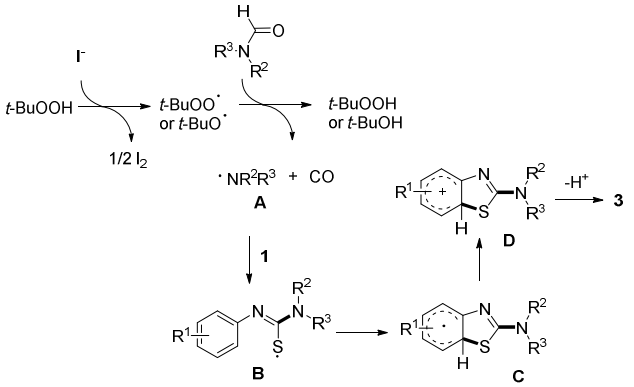
To gain insight into the reaction mechanism, several control experiments were conducted (Scheme 4). Treatment of biphenylisocyanate **1a** with dimethylamine under the standard conditions gave the desired product **3a** in only 15% yield. When the performed 3-([1,1'-biphenyl]-2-yl)-1,1-dimethylthiourea **4** was subjected to the reaction, the reaction mixture was messy and **3a** was obtained in 12% yield. Meanwhile, the desired product **3f** cannot be observed when benzothiazole **5** was used as a substrate under the standard reaction conditions. These control reactions indicated that dimethylamine, thiourea **4,** or benzothiazole **5** was unlikely to be reaction intermediate in this transformation. When TEMPO, a radical-trapping reagent, was added to the reaction, the generation of **3a** was mostly suppressed. It is known that *N*,*N*-dimethyl aminyl can be produced upon thermal decomposition of *tert*-butyl dimethylcarbamoperoxoate **6**.[14,16] When a mixture of **6** and **1a** was heated at 90 °C in trifluoromethylbenzene, the same aminated benzothiazole **3a** was obtained in 64% yield. The results strongly suggested that it was aminyl radical rather than amine the reaction intermediate.

Scheme 4. Mechanistic Studies



Based on the experimental results, a plausible reaction mechanism was proposed in Scheme 5. Initially, *tert*-butoxyl and *tert*-butylperoxy radicals are generated by decomposition of TBHP in the presence of TBAI. Then, *tert*-butoxyl or *tert*-butylperoxy radical abstracts a hydrogen atom from formamides to form the aminyl radical intermediate **A** after releasing CO.[14, 16] Subsequently, addition of the aminyl radical to the central carbon of the isothiocyanate moiety leads to a sulfur radical **B**. Intramolecular addition of sulfur radical to the pendant aromatic ring provides a cyclohexadienyl radical **C** followed by SET oxidation to cation **D**. Finally, the desired product is formed by deprotonation.

Scheme 5. Proposed Reaction Mechanism



In conclusion, we have developed a facile and efficient protocol for the synthesis of functionalized 2-

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aminobenzothiazoles from readily available aryl isothiocyanates and formamides in the presence of *n*-Bu_4NI and TBHP. The reaction proceeds through aminyl radical initiated addition to isothiocyanate and cyclization. Various secondary and tertiary amine- and even α-amino acid-substituted benzothiazoles are accessed efficiently under the metal-free conditions.

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Notes and references

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† Electronic supplementary information (ESI) available: Experimental procedure, spectral data, and copies of the NMR spectra of products. See DOI: 10.1039/c0ccxxxxxx

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