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Iodine-catalyzed amination of benzothiazoles with KSeCN in water to access primary 2-aminobenzothiazoles

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ABSTRACT

A facile and sustainable approach for the amination of benzothiazoles with KSeCN using iodine as the catalyst in water has been disclosed under transition-metal free conditions. The reaction proceeded smoothly to afford various primary 2-amino benzothiazoles in up to 96% yield. A series of control experiments were performed, suggesting a ring-opening mechanism was involved *via* a radical process. This protocol provides efficient synthesis of primary 2-aminobenzothiazoles

2-Aminobenzothiazoles are important building blocks in organic synthesis [1] with wide applications in pharmaceuticals, agrichemicals, and medicinal science [2–5]. Meanwhile, 2-aminobenzothiazole derivatives also serve as fluorescent sensor in the detection of metal ions [6]. Accordingly, great effort has been made for the synthesis of 2-aminobenzothiazoles [7]. The successful approaches include transition-metal-catalyzed tandem condensation and cyclization between *o*-haloaniline and isothiocyanates or other reagents (Scheme 1a) [8–10], intramolecular cyclization of *N*-arylthioureas or 2-haloarylthioureas (Scheme 1b) [11–13], and amination of benzothiazoles with amines or formaides (Scheme 1c) [14–19]. Recently, cascade reaction between aryl isothiocyanates with amines or formamides has also proved to be an effective strategy (Scheme 1d) [20–24]. Despite the above elegant work, the aforementioned protocols mainly focused on synthesis of secondary and tertiary amino-substituted benzothiazoles. Meanwhile, transition-metal catalysts and toxic organic solvents are generally required, which is not environmentally benign. Therefore, it is highly imperative to explore a novel and facile synthetic method to access primary 2-amino-substituted benzothiazoles while meeting green and sustainable chemistry.

Facing the challenge of environmental issues and depletion of nonrenewable resources, the concept of green chemistry and principles has been proposed to reduce chemical waste. Specially, the utilization of green solvents is a key principle in the synthetic community [25,26]. As a non-toxic, commercially available, and renewable resource, water has become an excellent reaction medium for organic transformation with improved selectivity, efficiency, and work-up procedures [27–29]. On the other hand, selenocyanate potassium (KSeCN) is a cheap readily, and versatile reagent with wide applications in organic chemistry. In general, KSeCN could be utilized as selenocyano source *via* nucleophilic reactions or radical pathways [30–33]. Meanwhile, KSeCN has been applied as a selenium transfer reagent [34–37]. In our recent work, we have also reported temperature-controlled selenation and selenocyanation of imidazopyridines with KSeCN in water [38]. Nevertheless, the employment of KSeCN as the cyano synthon has not been achieved.

In accordance with principles of green chemistry, we have achieved C-H sufonylmethylation of imidazopyridines and indoles in nontoxic media [39,40]. We also have reported iodine-mediated C-H sulfonylation and sulfenylation of imidazopyridines under metal-free conditions [41]. Recently, Li and co-workers have reported iron-catalyzed arylation of benzothiazoles with aryl aldehydes (Scheme 1e) [42]. In view of the increased attention to design green and transition-metal-free methods for the formation of heterocyclic compounds, we herein develop a one-pot synthesis of primary 2-aminobenzothiazoles from benzothiazoles and KSCN through the *in-situ* formation of an aminobenzenethiol intermedi-

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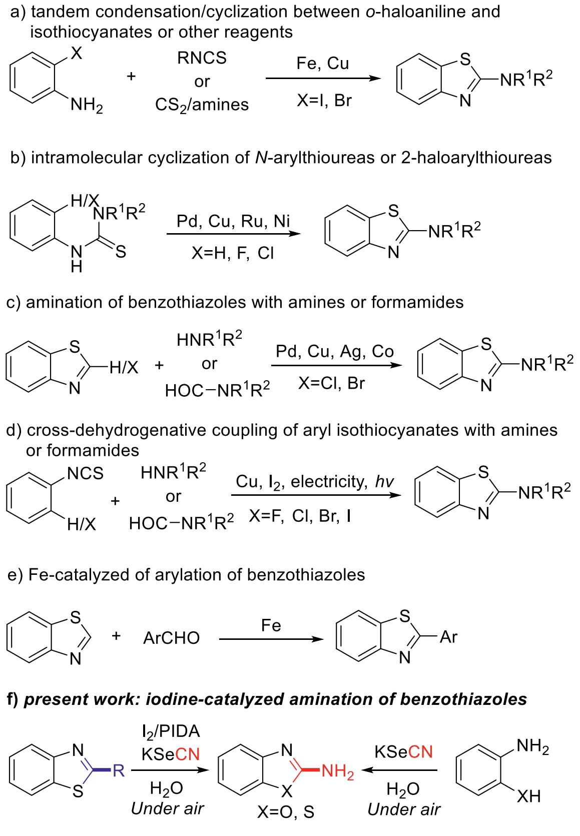


Scheme 1. Synthetic strategies for 2-substituted benzothiazoles.

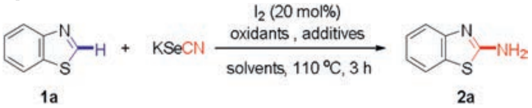
ate, intermolecular condensation, and cyclization process catalyzed by iodine (Scheme 1f). The advantages of this methodology include nonmetallic catalyst, novel CN source, green reaction media, and operational convenience.

We initiated our studies using benzothiazole **1a** (0.2 mmol) and KSeCN (0.2 mmol) as the model substrates in the presence of I_2 (20 mol%) in water (1 mL). To our delight, the aminated product **2a** was obtained in 18% yield at 110 °C for 3 h under air (Table 1, entry 1). Subsequently, various solvents, such as DMF, DMSO, and CH_3OH, were investigated, which all gave inferior results (Table 1, entries 2–4). Next, a series of oxidants were screened (Table 1, entries 5–7), indicating addition of PIDA (1.5 equiv.) was beneficial to provide **2a** in 40% yield (Table 1, entry 5). To further improve reaction efficiency, different additives were examined, such as TFA, $TsOH{\cdot}H_2O$, Tf_2O, and K_2CO_3, which gave **2a** in up to 70% yield when the reaction was heated for 6 h (Table 1, entry 10). Finally, the molar ratio of reactants and amount of solvent were examined, which gave **2a** in up to 94% yield (Table 1, entry 14). The structure of **2a** (CCDC No. 2034721) was further confirmed by X-ray crystallography analysis (see Supporting information for details).

With the optimized reaction conditions in hand (entry 14, Table 1), the substrate scope of benzothiazoles was investigated (Scheme 2). Initially, 4-halogen-substituted benzothiazoles were examined to give products **2b** and **2c** in 72% and 74% yields, respectively. Subsequently, a series of 5- and 6-substituted benzothiazoles were employed, which reacted with KSeCN to afford the desired products **2d**-**2q** in 17%–96% yields.

Especially, benzothiazoles bearing strong electron-withdrawing groups, including NO_2 and CN, were also well tolerated to give products **2i, 2o** and **2p** in 77%–91% yields. Unfortunately, for 6-hydroxy-substituted benzo-thiazole, the aminated product **2q** was isolated in 17% yield. Next, 7-bromo and 7-ester substituted benzothiazoles proceedes smoothly to provide aminated products **2r**

Table 1
Optimization of the reaction conditions.[a]



Entry	Oxidant (equiv.)	Additive (equiv.)	Solvent	**2a** (%)
1	-	-	H_2O	18
2	-	-	DMF	NR
3	-	-	DMSO	NR
4	-	-	CH_3OH	10
5	PIDA (1.0)	-	H_2O	36/40[b]
6	TBHP (1.0)	-	H_2O	36/27[b]
7	$K_2S_2O_8$ (1.0)	-	H_2O	trace
8	PIDA (1.5)	TFA (1.0)	H_2O	59
9	PIDA (1.5)	$TsOH{\cdot}H_2O$ (1.0)	H_2O	50
10	PIDA (1.5)	Tf_2O (0.5)	H_2O	63/70[c]
11	PIDA (1.5)	K_2CO_3 (1.0)	H_2O	11
12	PIDA (1.5)	Tf_2O (0.5)	H_2O	73[d]
13	PIDA (1.5)	Tf_2O (0.8)	H_2O	91[e]
14	PIDA (1.5)	Tf_2O (0.8)	H_2O	94[f]

PIDA = (diacet oxyiodo)benzene.

[a] Reaction Conditions: **1a** (0.2 mmol), KSeCN (0.2 mmol), I_2 (20 mol%), oxidant (equiv.), additives (equiv.), solvent (1 mL), under air, 110 °C, 3 h. Isolated yields.

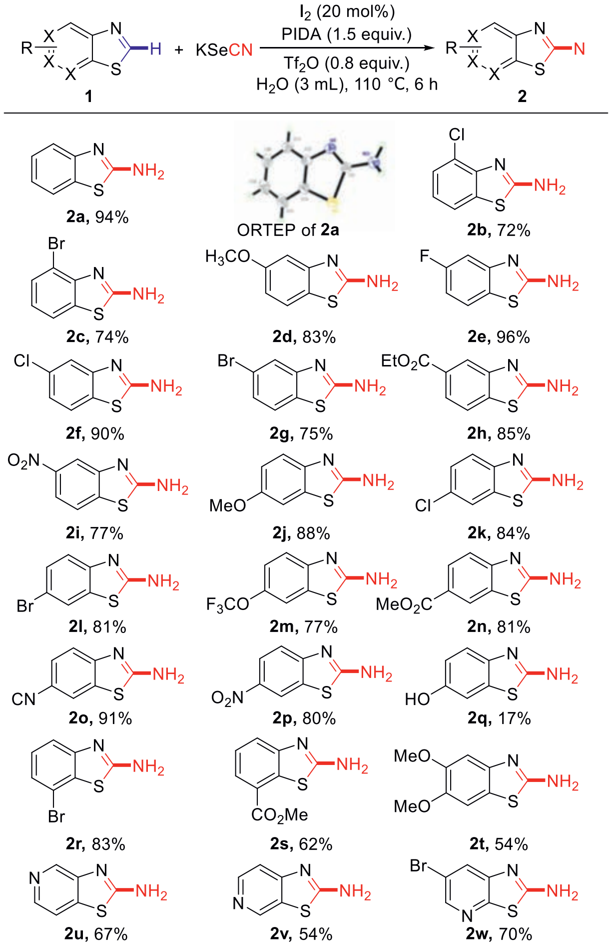
[b] Oxidant (1.5 equiv.).

[c] 6 h.

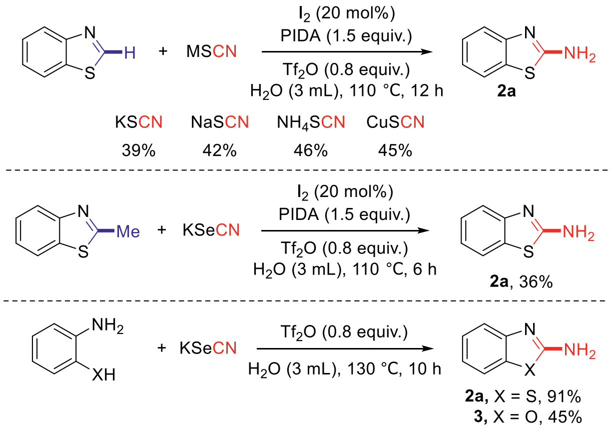
[d] H_2O (2 mL), 6 h.

[e] KSeCN (0.3 mmol), H_2O (2 mL), 6 h.

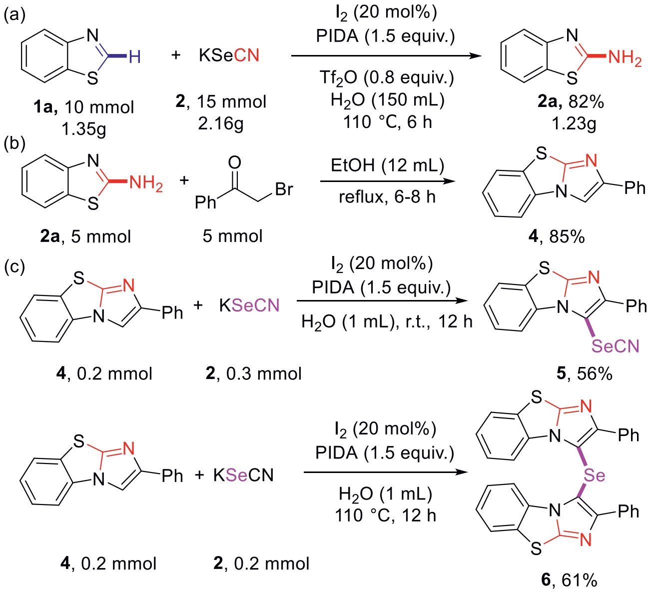
[f] KSeCN (0.3 mmol), H_2O (3 mL), 6 h.



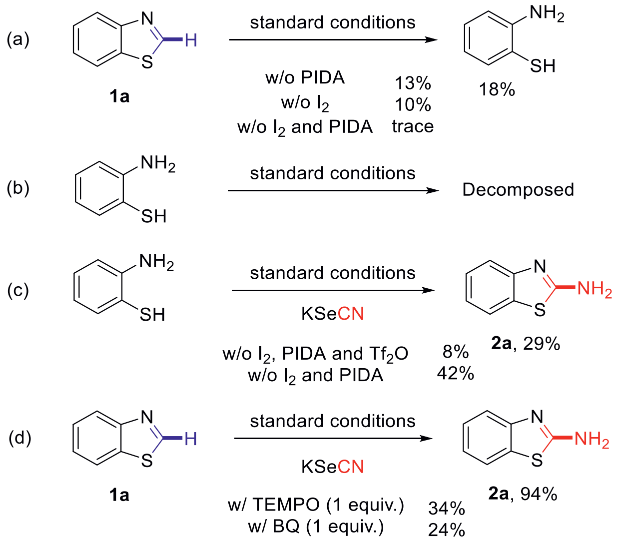
Scheme 2. Substrate scope of benzothiazolesa. Reaction conditions: **1** (0.2 mmol), KSeCN (0.3 mmol), I_2 (20 mol%), PIDA (1.5 equiv.), Tf_2O (0.8 equiv.), H_2O (3 mL), 110 °C, 6 h, under air. Isolated yield.



Scheme 3. Investigation of "CN" reagents and other substrates.



Scheme 4. Gram-scale reaction and further derivatizations.



Scheme 5. Control experiments.

and **2s** in 83% and 62% yields. Moreover, for disubstituted benzothiazole, the corresponding products **2t** was obtained in 54% yields. Finally, heterocyclic thiazoles were also compatible with the optimized conditions to deliver **2u-2w** in 54%–70% yields.

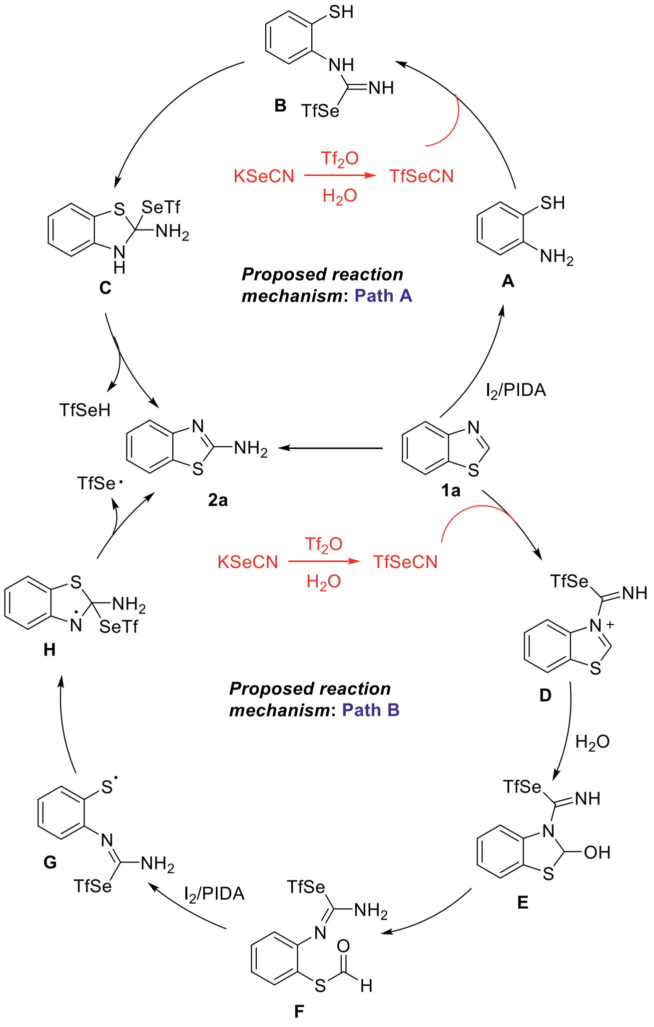
Encouraged by the above results, other thiocyanate salts were also evaluated as the cyano source (Scheme 3) [43–45]. Pleasingly, when KSCN, NaSCN, CuSCN, and NH_4SCN was employed, the aminated product **2a** was isolated in 39%–46% yields. Nevertheless, compared with thiocyanate salts, KSeCN demonstrates superior reactivity, which could be utilized as a novel CN source. Next, 2-methylbenzothiazole could also react with KSeCN to afford the desired product **2a** in 36% yield. Finally, when aminophenol and aminothiophenol were examined, the desired products **2a** and **3** [46] could be obtained in 91% and 45% yields, respectively, without I_2 and PIDA. These promising results enable the current protocol as a reliable and practical procedure to access 2-aminobenzoxazole derivatives.

To demonstrate the synthetic utility of this methodology, a gram-scale reaction was performed to give 2-aminobenzothiazole **2a** in 82% yield (Scheme 4). Meanwhile, the obtained **2a** could be converted to imidazoheterocycles **4** in 85% yield [47,48], which is difficult to realize from benzothiozole. Moreover, imidazoheterocycles **4** could undergo further functionalizations to afford the corresponding chalcogenated product **5** and chalcogenocyanated product **6** in 56% and 61%, respectively. In this case, KSeCN was utilized as SeCN and Se source selectivity.

To explore reaction mechanism, a set of control experiments were conducted (Scheme 5). Initially, **1a** could be converted to aminothiophenol in 18% yield without KSeCN under standard conditions (Scheme 5a). Aminothiophenol is not stable (decomposed) under the current conditions, which might explain the low isolated yield (Scheme 5b). Meanwhile, both I_2 and PIDA are required for this transformation. Without I_2 and PIDA, aminothiophenol could not be generated (Scheme 5a). Next, reaction between aminothiophenol and KSeCN under standard conditions would afford **2a** in 29% yield, suggesting aminothiophenol could be an intermediate in the reaction system (Scheme 5c). When the reaction was performed in the absence of I_2 and PIDA, the aminated product **2a** could be obtained in 42% yield. Finally, the radical scavenger reactions were performed (Scheme 5d). In the presence of TEMPO and BQ, the formation of corresponding amino-benzothiazole **2a** was substantially depressed, indicating a radical mechanism might be involved.

On the basis of above discussion and relevant literatures, two plausible reaction mechanisms were proposed (Scheme 6) [49–53]. In the mechanism A, benzothiazole **1a** underwent oxidative ring-opening process in the presence of I_2 and PIDA to give aminothiophenol **A** *in situ* [54], which reacted with KSeCN and Tf_2O to afford imine intermediate **B**. The subsequent intramolecular addition generated intermediate **C**, followed by aromatization to deliver the aminated product **2a**. Alternatively, the iminium species **D** was initially formed from benzothiazole in the presence of KSeCN and Tf_2O [51]. Subsequently, nucleophilic attack of iminium **D** by H_2O gave hemiacetal intermediate **E** [52]. Next, the intermediate **E** underwent ring-opening process to give intermediate **F**, which produced sulfur radical **G** through the reaction of PIDA with I_2 [53]. Finally, thioyl radical **G** underwent tautemerization and annulation process to afford intermediate **H**, followed by release of TfSe· to give the desired product **2a**.

In conclusion, we have demonstrated the direct amination of benzoxazoles with KSeCN under transition-metal-free conditions. This methodolgy provided efficient access to primary 2-benzothiazolamines using cheap and non-toxic iodine as catalyst and water as reaction media, which is more environmentally friendly. Various functional groups, including OMe, OCF_3, F, Cl, Br, COOMe, CN and NO_2, and heterocyclic thiazoles were all well tol-



Scheme 6. Proposed mechanism.

erated under the optimized conditions. Mechanism studies indicated this transformation proceeded *via* a ring-opening process. Notably, 2-methyl benzothiazole was also compatible to give the corresponding aminated product, which is less reported. This protocol featured with unique characterizations, including transition-metal free, novel CN reagent, green reaction media, operational convenience, high efficiency, and gram-scale production.

Declaration of competing interest

The authors declare no competing financial interest.

Acknowledgment

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2021.08.070.

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