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# Domino Synthesis of 2-Substituted Benzothiazoles by Base-Promoted Intramolecular C–S Bond Formation

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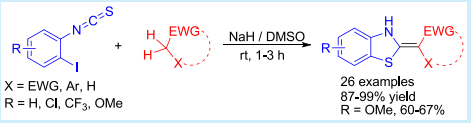
Supporting Information

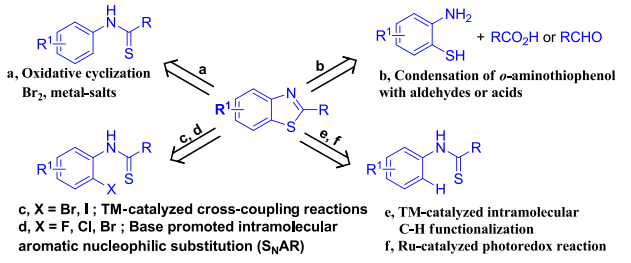
**ABSTRACT:** A new, transition-metal-free, domino synthesis of 2-substituted benzothiazoles has been developed, involving base-promoted one-pot addition of active methylene compounds to *o*-iodoarylisothioacyanates and subsequent intramolecular C–S bond formation of the resulting thioamidate anion. The reaction proceeds at room temperature within 1–3 h, affording diversely substituted benzothiazoles in high yields. A possible radical intermediate pathway, via an $S_{RN}1$ mechanism, has been proposed for intramolecular C–S bond formation.




2-Substituted benzothiazoles make up an important class of nitrogen- and sulfur-containing heterocycles, present in several important natural products and synthetic compounds, displaying a broad range of biological activities,[1,2] such as anticancer, anti-Alzheimer's, antibacterial, and antimicrobial activities,[2] and have also found application in material science.[3] Therefore, the development of new, efficient synthetic methods for diversely functionalized benzothiazoles has attracted much attention among synthetic and medicinal chemists.

Among some of the oldest methods, oxidative cyclization of thiobenzanilides[4] is the most widely used route for the synthesis of benzothiazoles (Scheme 1, a). The other common

**Scheme 1. Methods for the Synthesis of Benzothiazoles**




methods involve oxidative condensation of 2-aminothiophenols with aldehydes or carboxylic acids (Scheme 1, b).[5] Recent advances in carbon–heteroatom bond formation have led to the development of several new methods for the synthesis of benzothiazoles and their analogues, involving transition-metal-catalyzed intramolecular C–S bond formation of *o*-halothiobenzanilides (Scheme 1, c).[2a,e,6] Similar transformations have also been achieved in few cases, through base-promoted intramolecular arylation reactions of these substrates, at higher temperatures ($S_NAr$ reactions) (Scheme 1, d).[7] Alternatively, benzothiazoles have also been prepared directly through transition-metal-catalyzed C–H functionalization of readily available thiobenzanilides or thiourea derivatives (Scheme 1, e).[2f,8] Recently, 2-substituted benzothiazoles have also been obtained from thiobenzanilides via photoredox single-electron transfer (SET) pathway employing Ru(I)polypyridine complexes (Scheme 1, f).[9] However, the use of toxic and expansive transition-metal catalysts/ligands, prefunctionalization of starting materials, harsh reaction conditions, and somewhat limited substrate scope diminishes the attractiveness of these methods.

To overcome these shortcomings, much attention has been paid to the development of transition-metal-free protocols, and in recent years, "transition-metal-free cross-coupling processes" for the formation of C–C, C–N, C–O, and C–S bonds have attracted considerable interest among synthetic organic chemists.[10] Several research groups have reported significant contribution in this field, including transition-metal-free C–H arylations, for the construction of biphenyl frameworks.[11] Bolm and co-workers, in their pioneering work, first reported a detailed study of intermolecular cross-coupling reactions between aryl halides and various sulfur-, oxygen-, and nitrogen-based nucleophiles (N-, O-, and S-arylation, respectively) in the presence of KOH/DMSO as "superbase" medium[12,13] under TM-free conditions. In particular, these workers and others[14,15] have also developed base-promoted transition-metal-free intramolecular C–heteroatom bond formation reactions, which showed great potential for the synthesis of heterocyclic compounds such as 2-oxobenzimidazoles,[14a] phenoxazines,[14b] indazoles,[14a,15a] benzimidazoles,[14d,15d] oxindoles,[14e] indoles,[15b] and benzofurans.[15c] Some of these transition-metal-free coupling reactions are shown to proceed by direct nucleophilic aromatic substitution ($S_NAr$ reaction) or via a benzyne mechanism, whereas others were proposed to occur via single-electron reduction of aryl halides, involving radical or radical ion species ($S_{RN}1$ reactions),[10,11] sometimes also termed "electron-catalyzed reactions".[11d,12f,15b]

During the course of our ongoing work on the synthesis of five- and six-membered heterocycles and their benzo-fused

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analogues,[16] employing organosulfur intermediates, we now report a facile transition-metal-free protocol for the synthesis of 2-substituted benzothiazoles via base-promoted tandem addition−intramolecular cyclization of *o*-iodoarylisothiocyanates with various active methylene compounds in DMSO.

Substituted benzothiazoles bearing an active methylene group at position 2 have not been much explored in the literature.[17] A few of these compounds have found applications in medicinal chemistry as well as in material science. Thus, 2-[benzothiazol-2(3*H*)-ylidene]-2-(pyrimidin-2-yl)acetamides and their salts are shown to display "Aurora Kinase, VEGFR2[18a] and C-jun-N-terminal (JNK) kinase[18b] inhibitor" activity (**A** and **B**) and are useful in the treatment of cancer (Figure 1). Similarly, few benzothiazolo-fused 5-oxo-6-

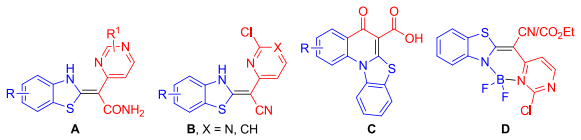
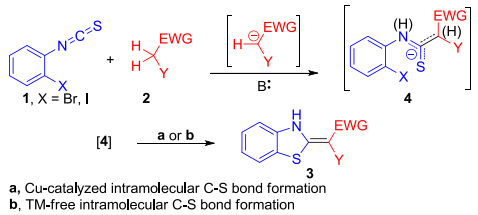



**Figure 1.** Biologically important 2-substituted benzothiazoles.

carboxyquinoline and naphthyridine scaffolds (**C**) also exhibit antibacterial properties.[19] Recently, a few of the benzothiazole−pyrimidine bidentate ligand-based boron difluoride[20a] and BODIPY complexes[20b] (**D**) have been synthesized, which are found to be selective and sensitive fluorescent sensors for cysteine (Figure 1). Some of these multifunctional benzothiazoles have also been employed as synthetic intermediates for fused heterocycles.[17,19b,21] These compounds have been synthesized in the literature by nucleophilic displacement of the corresponding polarized ketene dithioacetals by 2-aminothiophenols.[17,18,19b]

Our proposed synthesis of benzothiazoles **3** is shown in Scheme 2. Thus, we anticipated that the carbanion generated

**Scheme 2. Proposed Synthesis of 2-Substituted Benzothiazoles**



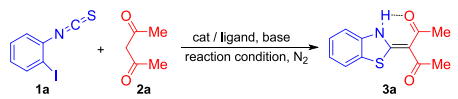

by deprotonation of active methylene compounds **2** will add to 2-halophenylisothiocyanate **1**, yielding a stabilized thioamidate anion **4**, which would undergo copper-catalyzed intramolecular C−S bond formation, yielding the desired 2-substituted benzothiazoles **3**. Alternatively, we also envisioned that thioamidate anion **4** could also undergo intramolecular C−S bond formation, leading to 2-substituted benzothiazoles **3** under transition-metal-free conditions via either nucleophilic aromatic substitution ($S_NAr$) or through a radical pathway mechanism (Scheme 2).

We therefore initiated our studies by reacting *o*-iodophenylisothiocyanate **1a** with acetylacetone **2a** as model substrates for the optimization of reaction conditions, for the synthesis of [2-benzothiazol-2(3*H*)-ylidene]acetylacetone **3a** under copper catalysis (Table 1). Thus, when **1a** and **2a** were reacted in the presence of NaH (2 equiv) as the base, CuI (10 mol %) as the catalyst, and proline as the ligand (20 mol %) in DMF, at rt for 5 h, **3a** was obtained in only 47% yield (Table 1, entry 1). At higher temperatures, the yield of **3a** was increased to 75% (Table 1, entry 2). Similarly, changing the ligand from proline to 1,10-phenanthroline resulted in higher yields of **3a** (Table 1, entry 3). However, a dramatic increase in the yield of **3a** was observed, when the reaction was conducted in the presence of CuI, in DMSO as a solvent, even at rt (Table 1, entry 4). The reaction also proceeded smoothly in DMSO under ligand-free conditions, furnishing **3a** in a comparable yield (Table 1, entry 5). We therefore started wondering whether copper catalysis was necessary for this cyclization, and indeed, to our delight, when **1a** and **2a** were reacted in the absence of CuI under identical conditions in DMSO, starting materials were consumed within 1 h at rt and **3a** was isolated in 92% yield (Table 1, entry 6).

With these unexpected results in hand, we further examined the effect of various solvents and bases on the yield of **3a** under transition-metal-free reaction conditions (Table S1). Thus, the reaction of **1a** and **2a** was found to be slower at rt in the presence of bases like *t*-BuOK, KOH, $K_2CO_3$, and $Cs_2CO_3$, in DMSO as the solvent, whereas reasonably good yields of **3a** were obtained at higher temperatures after 5−12 h (Table S1, entries 2−6). However, poor yields of **3a** were obtained by employing other solvents (DMF, toluene, THF, and $CH_3CN$) even at higher temperatures (Table S1, entries 7−10, respectively), whereas use of 1 equiv of NaH resulted in a diminished yield of **3a** (Table S1, entry 11). We therefore employed NaH (2 equiv) as a base in DMSO at rt as optimal reaction conditions for further studies (Table S1, entry 1).

We next explored the scope of this novel transition-metal-free synthesis for other 2-substituted benzothiazoles **3** by

**Table 1. Optimization of Reaction Conditions for the Synthesis of Benzothiazole 3a**




| entry | catalyst (10 mol %) | ligand (20 mol %) | base (2 equiv) | solvent | temp (°C) | time (h) | % yield (**3a**)[a] |
|---|---|---|---|---|---|---|---|
| 1 | CuI | proline | NaH | DMF | rt | 5 | 47 |
| 2 | CuI | proline | NaH | DMF | 60 | 5 | 75 |
| 3 | CuI | 1,10-phen | NaH | DMF | 60 | 5 | 81 |
| 4 | CuI | proline | NaH | DMSO | rt | 5 | 91 |
| 5 | CuI | – | NaH | DMSO | rt | 4 | 90 |
| 6 | – | – | NaH | DMSO | rt | 1 | 92 |

[a]Yields of pure isolated product.



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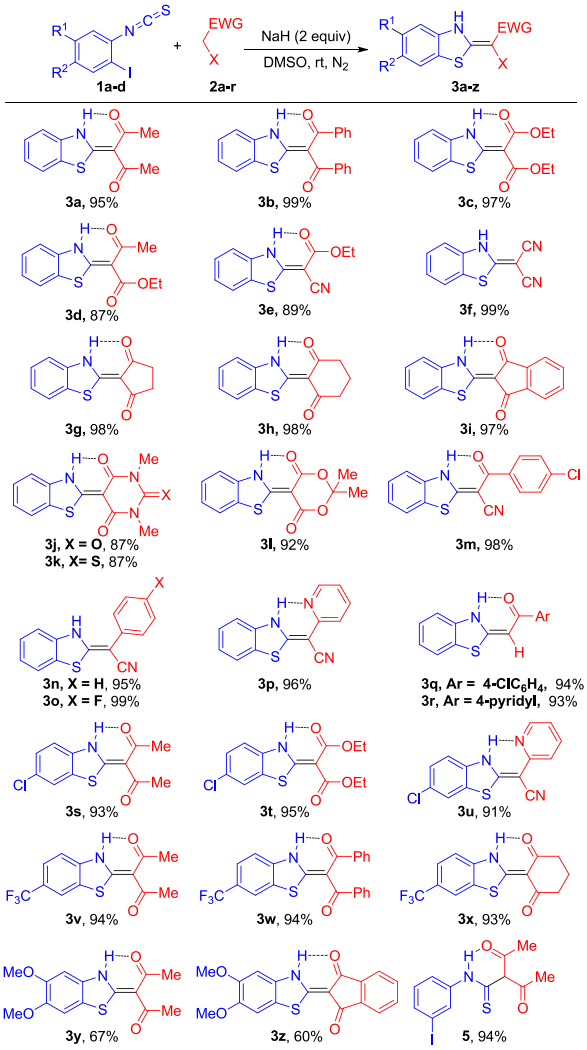
reacting various active methylene compounds with *o*-iodoarylisothiocyanates **1** in DMSO under optimized reaction conditions (Scheme 3). Thus, acyclic active methylene

**Scheme 3. Substrate Scope for the Synthesis of 2-Substituted Benzothiazoles 3**[a]



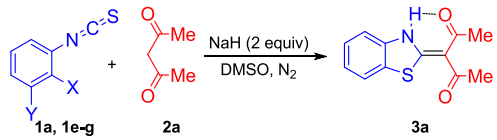

[a]Reaction conditions: **1** (1 mmol), **2** (1 mmol), and NaH (2 equiv) in DMSO under $N_2$ stirred at rt for 1−3 h. Yields of pure isolated product. The reaction was complete after the mixture had been stirred at 60 °C for 6 h.

compounds such as dibenzoylmethane, diethylmalonate, ethyl acetoacetate, ethyl cyanoacetate, and malononitrile **2b−f** reacted efficiently with *o*-iodophenylisothiocyanate **1a** under optimal conditions, yielding the corresponding 2-substituted benzothiazoles **3b−f** in excellent yields. The reaction was found to be equally facile with cyclic 1,3-diketones **2g−i**, furnishing the corresponding sterically crowded [2-benzothiazol-2(3*H*)-ylidene]-1,3-diketones **3g−i** in nearly quantitative yields (Scheme 3). Further variation in substrate structures by employing sterically incumbent cyclic 1,3-dimethyluracil, thiouracil, and meldrum's acid **2j−l** also did not affect the yields of benzothiazole products **3j−l**, respectively. The structure of these products was further confirmed by X-ray crystallographic data of compound **3h** (see Figure S1). The corresponding unsymmetrically substituted active methylene compounds such as 4-chlorobenzoylacetonitrile **2m**, phenylacetonitriles **2n** and **2o**, and 2-pyridylacetonitrile **2p** also underwent smooth tandem addition−cyclization with *o*-iodophenylisothiocyanate **1a** under identical conditions, affording various 2-functionalized benzothiazoles **3m−p** in high yields (Scheme 3). The use of less acidic ketones such as 4-chloroacetophenone **2q**, or 4-acetylpyridine **2r**, also did not affect the yields of the corresponding product **3q** or **3r**, respectively, each of which was obtained in overall high yields.

We next investigated the effect of substituents on *o*-iodoarylisothiocyanates **1b−d** bearing both electron-withdrawing and electron-donating substituents on the aryl ring (Scheme 3). Thus, the reaction of isothiocyanates **1b** and **1c** bearing either 4-chloro or 4-(trifluoromethyl) groups with acetylacetone or other active methylene compounds proceeded smoothly under identical conditions within 1 h, furnishing the corresponding [2-benzothiazol-2(3*H*)-ylidene]carbonyl/nitrile compounds **3s−x** in high yields (Scheme 3). On the other hand, the corresponding 4,5-(dimethoxy)-2-iodophenylisothiocyanate **1d** bearing electron-donating groups afforded cyclized benzothiazoles **3y** and **3z** in decreased yields upon reaction with **2a** and **2i**, respectively, although the reaction was complete within 3 h (Scheme 3).

The reactivity of few *o*-halophenylisothiocyanates **1e−g** bearing bromine, chlorine, and fluorine, respectively, was also examined toward acetylacetone, along with few additional experiments to provide some insight into the mechanism of this facile transition-metal-free coupling reaction (Table 2 and

**Table 2. Base-Mediated Reactions of Various *o*-Halophenylisothiocyanates 1a and 1e−g with Acetylacetone**

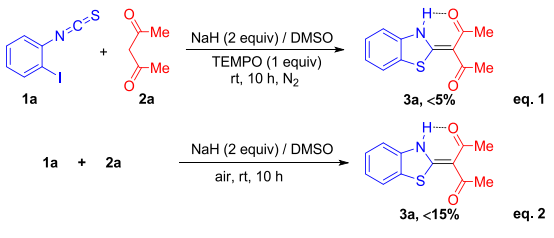



| entry | 1 | X | Y | temp (°C) | time (h) | % yield (**3a**) |
|---|---|---|---|---|---|---|
| 1 | **1a** | I | H | rt | 1 | 92 |
| 2 | **1e** | Br | H | rt | 12 | – |
| 3 | **1e** | Br | H | 90 | 12 | 57 |
| 4 | **1f** | Cl | H | rt | 12 | – |
| 5 | **1f** | Cl | H | 90 | 12 | 60 |
| 6 | **1g** | F | H | rt | 12 | 30 |
| 7 | **1g** | F | H | 60 | 12 | 70 |
| 8 | **1h** | H | I | rt | 24 | –[a] |

[a]The isolated product was found to be thioamide **5** (Scheme 3).

Scheme 4). Thus, no trace of **3a** was observed in the reaction mixture, when the corresponding *o*-bromo- and *o*-chlorophenylisothiocyanates (**1e** and **1f**, respectively) were reacted with

**Scheme 4. Reaction of *o*-Iodophenylisothiocyanate with Acetylacetone in the Presence of TEMPO and Air**



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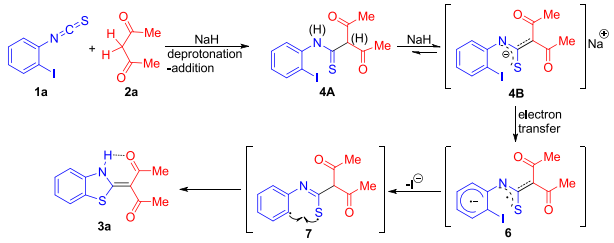
**2a** at rt under optimized conditions, even after a prolonged time (Table 2, entries 2 and 4). However, at a higher temperature of 90 °C, **3a** was obtained in 57% and 60% yields after prolonged heating (Table 2, entries 3 and 5, respectively). On the other hand, the corresponding *o*-fluorophenylisothiocyanate **1g** gave an only 30% yield of benzothiazole **3a** at rt even after 12 h (Table 2, entry 6), whereas at 60 °C, **3a** was obtained in a higher yield (70%) (Table 2, entry 7). The addition of TEMPO, a common trapping agent for free radicals, nearly completely inhibited the cyclization (Scheme 4, eq 1). Similarly, when **1a** and **2a** were reacted in the absence of a nitrogen atmosphere in air, product **3a** was isolated in only 15% yield (Scheme 4, eq 2). These observations point toward the involvement of radical intermediates and/or a SET process, in this transformation. Also, when *m*-iodophenylisothiocyanate **1h** was reacted with acetylacetone **1a** under standard reaction conditions, no trace of benzothiazole **3a** was formed even after a prolonged time (Table 2, entry 8), thus demonstrating that the benzyne intermediate is not involved in this cyclization reaction.

On the basis of the previous reports and our own observations, we propose a possible radical intermediate pathway through an $S_{RN}1$ mechanism for this transition-metal-free domino synthesis of benzothiazoles **3** (Scheme 5).

**Scheme 5. Proposed Mechanism for Base-Mediated Formation of Benzothiazole 3a from 1a and 2a**




Thus, the addition of a carbanion (generated by deprotonation of **2a**) to *o*-iodophenylisothiocyanate **1a** affords, initially, thioamide intermediate **4A**, which is transformed into its conjugate base **4B**, under basic conditions. Anionic intermediate **4B** serves as an electron donor, to initiate the radical process and undergoes intramolecular electron transfer to the aryl part of **4B**, to give radical anion intermediate **6**. Finally, the loss of the iodide ion from intermediate **6** affords diradical intermediate **7**, which undergoes intramolecular radical combination to furnish product **3a** (Scheme 5). Because only *o*-iodoarylisothiocyanate derivatives **1a−d** cyclized efficiently to benzothiazoles **2**, whereas *o*-bromo, *o*-chloro, and *o*-fluoro derivatives (**1e−g**, respectively) were found to be either completely inert or sluggish under identical conditions (Table 2, entries 2, 4, and 6, respectively), we consider that an intramolecular nucleophilic substitution pathway ($S_NAr$) is unlikely, because the reactivity of *o*-halophenylisothiocyanates **1a** and **1e−g** does not follow the expected order of reactivity (F > Cl > Br > I) for a standard $S_NAr$ mechanism. The decreased yields of benzothiazoles **3y** and **3z** obtained from 4,5-dimethoxy-2-iodophenylisothiocyanate **1d** (Scheme 3) appear to be due to the destabilization of radical anion intermediate **6**, because of the presence of two electron-donating methoxy groups.

In summary, we have developed a facile transition-metal-free domino protocol for the synthesis of 2-substituted benzothiazoles, involving base-mediated tandem addition−intramolecular cyclization of *o*-iodoarylisothiocyanates and active methylene compounds. The key features of the synthesis are that the reaction proceeds at rt, within 1−3 h, in high yields, in the absence of any ligand or additive. On the basis of various studies, a reasonable mechanism involving formation of radical intermediates ($S_{RN}1$) has been proposed. To the best of our knowledge, such a transformation involving intramolecular C−S bond formation at rt,[14c] leading to benzothiazoles, under mild transition-metal-free conditions has not been reported in the literature.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02855.

Experimental details, table of the optimization of reaction conditions for the synthesis of **3a** (Table S1), melting points, $^1$H and $^{13}$C NMR spectra, IR spectra for all products, and analytical data (PDF)

### Accession Codes

CCDC 1952893 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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## ■ DEDICATION

This paper is dedicated to Prof. C. N. R. Rao, FRS, on the occasion of his 85th birthday.

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