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Elemental sulfur-promoted one-pot synthesis of 2-(2,2,2-trifluoroethyl)benzoxazoles and their derivatives†

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A novel and direct strategy has been developed for the synthesis of 2-(2,2,2-trifluoroethyl)benzoxazoles by reaction of *o*-aminophenols and 2-bromo-3,3,3-trifluoropropene in the presence of elemental sulfur under metal-free conditions. The scope of this methodology was further extended to the synthesis of the trifluoroethylated benzothiazole and benzoimidazole derivatives. A plausible mechanism was proposed on the basis of isolation and characterization of a thioamide intermediate.

The occurrence of the fluorinated molecules in pharmaceuticals, agrochemicals, and advanced materials has led to unceasing research efforts toward the preparation of organofluorine compounds.[1–4] The appropriate introduction of fluorinated functional groups into lead molecules might change their affinity for biological receptors and modify their metabolic stability and lipophilicity.[5–8] One of the most important organofluorine functionalities is the trifluoroethyl group (–CH_2CF_3), which exhibits intriguing physical and biological properties. As a consequence, numerous elegant methodologies have been developed for direct trifluoroethyl functionalization.[9–11] These developments originated in 1969, when McLoughlin and Thrower reported Cu(0)-mediated reductive coupling of iodoarenes with CF_3CH_2I.[12] In recent years, a flourish of activity in the development of transition-metal-catalyzed, metal-free, or photoinduced trifluoroethylation of arylboronic acids[13–15] or esters,[16] aryl iodides,[17] arenes,[18–25] alkenes,[26–30] alkynes,[31,32] carboxylic acids,[33,34] amines,[35,36] aryl Grignard reagents,[37] and others[38] has been witnessed in the literature.

On the other hand, the benzoxazole structural motif is found in many natural products and synthetic bioactive molecules.[39] Quite a number of benzoxazole-containing compounds were documented to exhibit valuable biological activities including antitumor, antiviral, antimicrobial, anticonvulsant, antiallergic, anthelmintic, antioxidant, antidepressant, and analgesic effects.[40] Owing to these exceptional properties, further functionalization of benzoxazole derivatives such as the introduction of a trifluoroethyl group may be beneficial towards their future pharmaceutical applications. Indeed, several patented bioactive benzoxazole derivatives such as isothiazolylaminoacylbenzazole **A**,[41] benzo fused heterocycle **B**,[42] and substituted 2-amidobenzoxazole **C**[43] all contain a trifluoroethyl benzoxazole moiety as the key functionality (Fig. 1). Thus, in consideration of the prevalence of trifluoroethyl-substituted compounds in pharmaceuticals, as well as the occurrence of benzoxazole scaffolds in several biologically active molecules, the development of a facile, general, and efficient synthesis of 2-trifluoroethylated benzoxazoles is highly desirable.

Recently, the elemental sulfur-promoted synthesis of benzoxazole derivatives from the reaction of *o*-aminophenols and cinnamic acids,[44] ketones,[45] or phenylglyoxylic acid[46] has been reported. Inspired by these studies along with our recent experiences on the synthesis of fluorinated heterocyclic compounds,[47–52] we surmised that an intramolecular nucleophilic addition and elimination of 2-hydroxyphenyl propanethioamide *via* a radical anion intermediate would be a distinct and straightforward pathway to the preparation of 2-trifluoroethylated benzoxazoles (Scheme 1). Herein, we reported a novel approach for accessing 2-trifluoroethylated benzoxazoles *via* elemental sulfur-promoted cyclization between 2-bromo-3,3,3-trifluoropropene (**1**) and *o*-aminophenols (**2**).

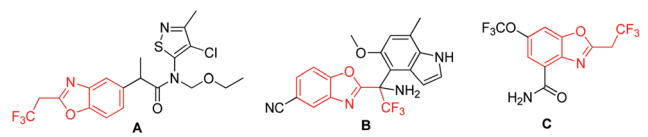

Fig. 1 Patented 2,2,2-trifluoroethyl-containg bioactive benzoxazole derivatives.

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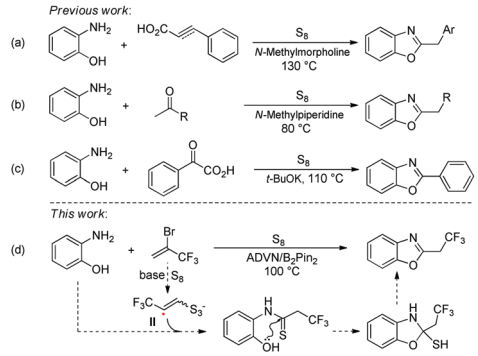
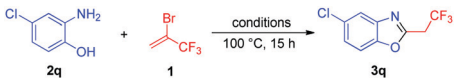


Scheme 1 Elemental sulfur-promoted synthesis of benzoxazole derivatives.

To test the reaction feasibility, we first examined the cyclization of 2-amino-4-chlorophenol (**2q**) with 2-bromo-3,3,3-trifluoropropene (**1**) under a variety of reaction conditions (Table 1). The major challenge was to identify an activator (entries 1–6) and elemental sulfur (8 equiv.) was found to be a good promoter to afford the desired product 5-chloro-2-(2,2,2-trifluoroethyl)benzoxazole (**3q**) in promising 54% yield (entry 6). The use of less than 8 equiv. of S_8 resulted in a decrease in product yield (entries 4 and 5). Among the bases evaluated (entries 5–11), $NaHCO_3$ was superior and provided the best yield of the product **3q** at 100 °C for 15 h (entries 5 and 6). A variety of solvents such as DMF, DMSO, NMP, DMAc, MeCN, and THF were also screened for optimized conditions (entries 12–16), and it was observed that DMF afforded a better yield than other solvents. The reaction efficiency could be further improved by using 2,2′-azobis-(2,4-dimethylvaleronitrile) (ADVN)

Table 1 Optimization of the reaction conditions[a]



2q 1 3q

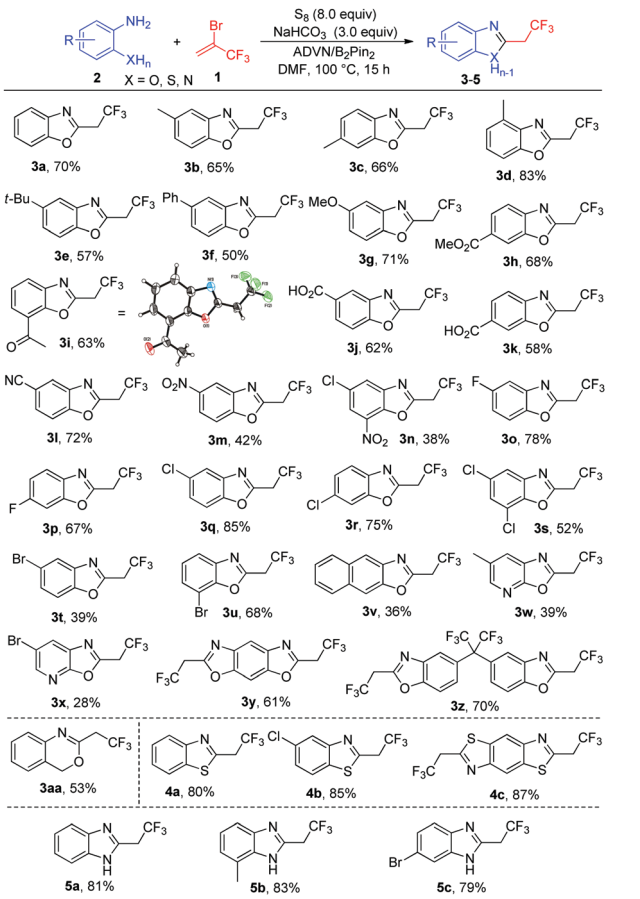
Entry	Promoter (equiv.)	Base	Additive	Solvent	Yield[b] (%)
1	I_2 (5)	$NaHCO_3$	—	DMF	0
2	KI (5)	$NaHCO_3$	—	DMF	0
3	O_2	$NaHCO_3$	—	DMF	0
4	S_8 (3)	$NaHCO_3$	—	DMF	19
5	S_8 (5)	$NaHCO_3$	—	DMF	51
6	S_8 (8)	$NaHCO_3$	—	DMF	54
7	S_8 (5)	NaOH	—	DMF	45
8	S_8 (5)	Na_2CO_3	—	DMF	8
9	S_8 (5)	KOH	—	DMF	35
10	S_8 (5)	CsF	—	DMF	16
11	S_8 (5)	DBU	—	DMF	30
12	S_8 (5)	$NaHCO_3$	—	DMSO	0
13	S_8 (5)	$NaHCO_3$	—	NMP	46
14	S_8 (5)	$NaHCO_3$	—	DMAc	41
15	S_8 (5)	$NaHCO_3$	—	MeCN	0
16	S_8 (5)	$NaHCO_3$	—	THF	0
17	S_8 (8)	$NaHCO_3$	ADVN	DMF	67
18	S_8 (8)	$NaHCO_3$	B_2Pin_2	DMF	76
19	S_8 (8)	$NaHCO_3$	ADVN/B_2Pin_2	DMF	87

[a] Reaction conditions: **1** (0.70 mmol), **2q** (0.10 mmol), base (0.30 mmol), solvent (1.0 mL), under a N_2 atmosphere. [b] The yield was determined by ^{19}F NMR spectroscopy with $PhOCF_3$ as an internal standard.

or bis(pinacolato)diboron (B_2Pin_2) as an additive (entries 17 and 18). The best result was obtained when ADVN and B_2Pin_2 (0.090 mmol : 0.070 mmol = 9 : 7) were introduced, where the product **3q** was generated in 87% yield from 2-bromo-3,3,3-trifluoropropene (**1**, 7 equiv.), *o*-aminophenol **2q** (1 equiv.), $NaHCO_3$ (3 equiv.), and S_8 (8 equiv.) at 100 °C for 15 h (entry 19). The role of ADVN/B_2Pin_2 in the cyclization might be to facilitate the formation of reactive radical intermediates.

With the optimization conditions in hand, the substrate scope of the reaction was then examined with different *o*-aminophenols (Table 2). It was found that a variety of *o*-aminophenols with electron-donating and electron-withdrawing groups substituted on the aromatic ring were tolerable, and moderate to good yields of trifluoroethylated products were obtained. For instance, the reaction of unsubstituted *o*-aminophenol (**2a**) with **1** afforded the corresponding product **3a** in 70% yield. Numerous electron-donating (*i.e.*, methyl, *tert*-butyl, phenyl, and methoxy) and electron-withdrawing (*i.e.*, acetyl, ester, carboxyl, cyano, and nitro) substituents at the positions *ortho*, *meta*, and *para* to the hydroxyl on the aryl ring were well tolerated, rendering the corresponding products **3b–3n** in 38–83% yields. The structure of **3i** was verified by the

Table 2 Scope of the reaction with *o*-aminophenols[a]

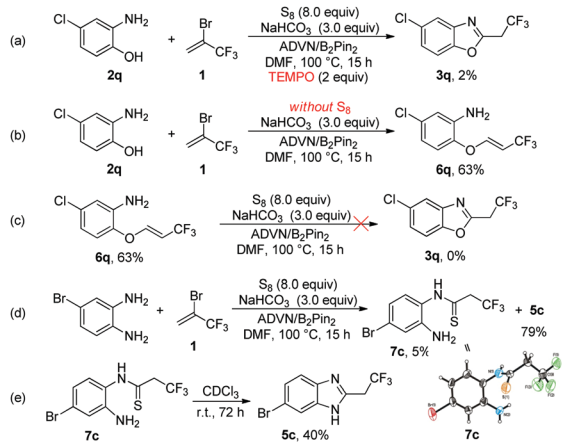


[a] Reaction conditions: **1** (2.10 mmol), **2** (0.30 mmol), S_8 (2.40 mmol), $NaHCO_3$ (0.90 mmol), ADVN (0.27 mmol), B_2Pin_2 (0.21 mmol), DMF (3.0 mL), under N_2 atmosphere; isolated yields.

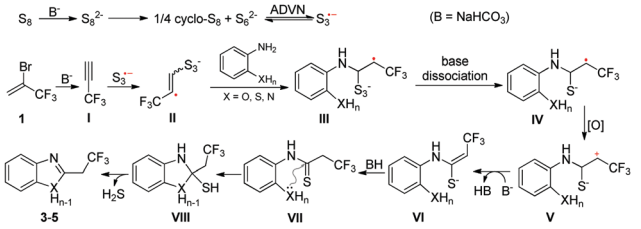
single-crystal X-ray analysis. Likewise, the *o*-aminophenols bearing halogen substitutions such as fluoro (**2o**, **2p**), chloro (**2n**, **2q**–**2s**), and bromo (**2t**, **2u**) groups were all compatible with this transformation and gave the desired products **3n**–**3u** in moderate to good yields. Similar to those disubstituted *o*-aminophenols (**2n** and **2s**), 3-amino-2-naphthol **2v** also gave the corresponding product **3v** in a lower yield (36%). Notably, heterocyclic substrates could also participate in the reaction, even with a lower yield, to provide the corresponding products **3w** and **3x** in 39% and 28% yield, respectively. Next, the bis-(*o*-aminophenol) derivatives were also tested, and the respective bis-trifluoroethylated products **3y** and **3z** were obtained in 61% and 70% yield. It is noteworthy that when the hydroxyl group of *o*-aminophenol was switched to a hydroxymethyl moiety as in *o*-aminophenylcarbinol, the corresponding cyclization product **3aa** was produced without difficulties in 53% yield.

To demonstrate the generality of the methodology, we further extended the substrates to other *o*-substituted anilines, and the results are summarized in Table 2. To our delight, a variety of *o*-aminobenzenethiols and benzene-1,2-diamines were smoothly transformed to the corresponding trifluoroethylated benzothiazoles **4a**–**4c** and benzoimidazoles **5a**–**5c** in good yields (79–87%).

To explore the mechanism of this transformation, some control experiments were carried out. The cyclization of **2q** with **1** in the presence of a radical scavenger such as TEMPO halted the formation of product **3q**, indicating a possible radical-mediated pathway (Scheme 2a). However, we did not observe any TEMPO-adduct products. In the absence of elemental sulfur, the uncyclized *O*-trifluoroallylated product **6q** was obtained instead of the desired product **3q** (Scheme 2b), suggesting that elemental sulfur plays a significant role in the cyclization. The isolated compound **6q** may presumably undergo intramolecular nucleophilic addition of the amino group to the double bond, followed by oxidation to afford the cyclized product **3q**. However, treatment of **6q** under the standard conditions failed to give the expected **3q**, and most of the starting material **6q** was recovered (Scheme 2c). These results imply that **6q** is not the putative intermediate involved in the cyclization and the proposed



Scheme 2 Mechanistic studies.



Scheme 3 Proposed mechanism.

nucleophilic addition pathway may be infeasible. Interestingly, in addition to the desired product **5c** which was generated (79% yield) during the cyclization of 4-bromobenzene-1,2-diamine with **1**, a sulfurated product **7c** (X-ray) was also isolated in *ca.* 5% yield (Scheme 2d). The intermediacy of thioamide **7c** was independently proven by intramolecular cyclization of **7c** in $CDCl_3$ at room temperature for 72 h, where the desired product **5c** was obtained in a yield of 40% (Scheme 2e).

Based on the aforementioned controlled experiments, a putative mechanism is depicted in Scheme 3. Initially, the reaction of elemental sulfur with the base in the presence of ADVN/B_2Pin_2 would generate the $S_3^{\bullet-}$ radical anion.[53] The *in situ* generated 3,3,3-trifluoropropyne **I** (resulting from a dehydrobromination reaction of **1** under basic conditions)[54] could react with $S_3^{\bullet-}$ to form the radical anion intermediate **II**. The generated radical anion **II** then reacted with the NH_2 group of the substrate, producing an alkyl radical intermediate **III**. Subsequent base dissociation of **III** generated **IV**, which underwent oxidation by sulfur species to give the carbocation intermediate **V**. Deprotonation of **V** would furnish **VI**, which subsequently underwent protonation to form a thioamide **VII**. Intramolecular nucleophilic addition of the XH_n group of **VII** to the nearby C=S double bond afforded the cyclized **VIII**. Final elimination of H_2S from **VIII** furnished the desired products **3**–**5**.

To conclude, we have described a novel and direct approach toward the preparation of 2-(2,2,2-trifluoroethyl)benzoxazole derivatives based on readily available *o*-aminophenols/*o*-aminobenzenethiols/benzene-1,2-diamines and 2-bromo-3,3,3-trifluoropropene with the latter as the source of the trifluoroethyl group. Moreover, the isolation and characterization of a sulfurated compound confirmed the involvement of a thioamide intermediate.

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Conflicts of interest

There are no conflicts to declare.

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