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Synthesis of 2-Arylmethylbenzoxazoles by S_8-Mediated Cyclization of 2-Aminophenols with Styrenes

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Abstract—A metal-free protocol to obtain 2-(arylmethyl)benzoxazoles by sulfur-mediated cyclization of 2-aminophenols and styrenes in *N*-methylpyrrolidone in the presence of K_2HPO_4 as a base has been developed. Preliminary mechanistic investigations suggest intermediate formation of *N*-(2-hydroxyphenyl)-2-phenylethanethioamide, which requires 2 equiv of the initial aminophenol.

Keywords: benzoxazoles, 2-aminophenol, styrene, cyclization, sulfur

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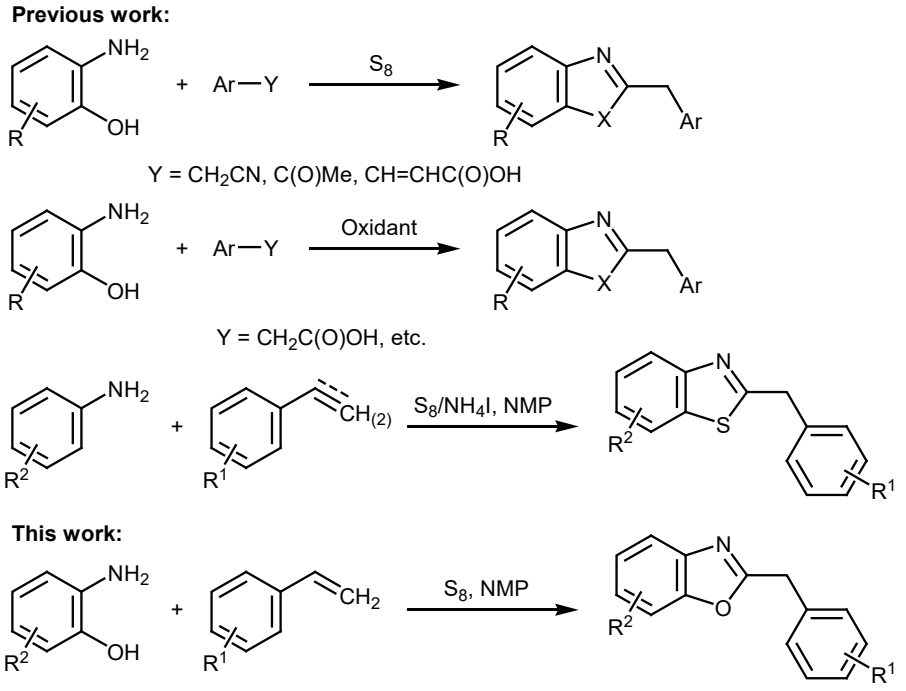
INTRODUCTION

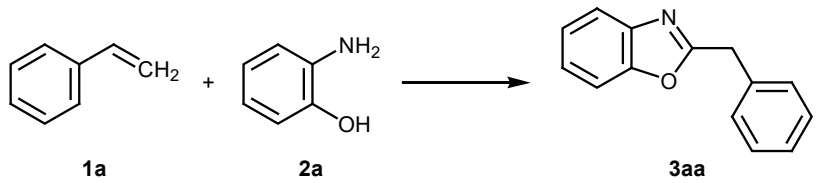
2-Substituted benzoxazoles are important building blocks that are extensively used in many areas [1–3] requiring new synthetic strategies to be developed by organic chemists. Several methods have been employed using 2-aminophenol as substrate under sulfur-mediated transition metal-free conditions (Scheme 1) [4–8]. Benzoxazole has also been reported as a substrate in these reactions [9–14]. However, literature reports on the use of styrene as a substrate are still rare [15].

Styrene has been applied widely in organic synthesis for the construction of C–C and C–X bonds in recent years [16–22], and great advances have been made recently in the construction of heterocycles [23–28]. For example, Deng et al. [26] reported *ortho*-

Scheme 1.



Scheme 2.



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

C–H sulfuration/cyclization of aniline with elemental sulfur for efficient synthesis of 2-substituted benzothiazoles (Scheme 1). Han et al. [15] recently reported elemental sulfur-promoted formation of benzoxazole/benzothiazole with carbon atoms of a C=C double bond as a one-carbon donator, but the substrate scope was not broad. However, the development of metal-free protocols for the synthesis of 2-(arylmethyl)-benzoxazoles is still pressing [4–8, 18, 19]. In view of this need and continuing with our sulfur-related research [29–34], we report here metal-free cyclization of 2-aminophenols with styrenes to give 2-(arylmethyl)benzoxazoles (Scheme 1).

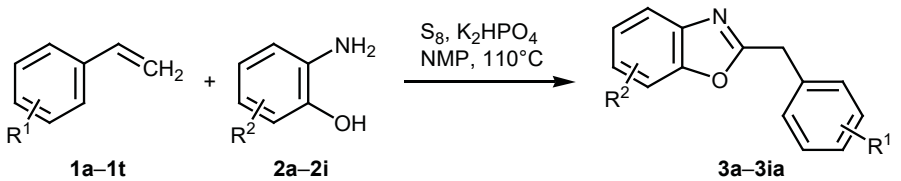
RESULTS AND DISCUSSION

Initially, we used unsubstituted styrene (**1a**), 2-aminophenol (**2a**, 2.0 equiv), elemental sulfur (2.0 equiv), and $NaHCO_3$ (1.5 equiv) in *N*-methylpyrrolidone (NMP) at 110°C under an air atmosphere to explore the reaction, and the target product, 2-benzyl-1,3-benzoxazole (**3aa**) was isolated in 57% yield (Scheme 2; Table 1, entry no. 1). We then tried other bases such as $KHCO_3$, K_3PO_4, *N*-methylpiperidine (NMPP) or pyridine (Table 1, entry nos. 2–5). To our delight, **3aa** could be obtained in 68% yield in NMP with K_2HPO_4 as a base (Table 1, entry no. 6), although lower yields were obtained when other organic solvents were used (Table 1, entry nos. 7–13). The yield was not improved by conducting the reaction at a higher (120°C) or lower temperature (100°C) (Table 1, entry nos. 14, 15). Altering the amounts of elemental sulfur, **2a**, or K_2HPO_4 did not improve the yield (Table 1, entry nos. 16–20). The yield of **3aa** was 61% when **1a** was replaced with β-bromostyrene as substrate (Table 1, entry no. 21). However, no desired product was obtained when allylbenzene was employed as substrate (Table 1, entry no. 22).

We studied the scope of the proposed protocol for the synthesis of 2-(arylmethyl)benzoxazoles **3** using a series of substituted styrenes (Scheme 3). Many substituents on the aromatic rings of the styrenes were tolerated in the reaction, and the corresponding products **3ab**–**3ar** were isolated in moderate to good yields (47–78%). In general, *meta*-substituted styrenes gave lower yields than their *para*-substituted analogs (**3ab**, **3af**–**3ai**, **3am**–**3ap**, **3ar**). Furthermore, 1- and 2-vinylnaphthalenes smoothly reacted under the optimal conditions to give the desired products **3as** and **3at** in 49 and 62% yields, respectively. We also performed the reaction of 2-aminophenol (**2a**) and 4-methylstyrene (**1b**) on a gram-scale, and compound **3ab** was isolated in 65% yield (1.16 g) from 8 mmol of **1b**. Differently substituted 2-aminophenols were also reacted with styrene (**1a**) under the optimal conditions to afford the required products **3ba**–**3ia** in moderate to good yields (45–74%); the highest yield (**3ga**, 74%) was obtained from 2-amino-5-fluorophenol (**1g**).

Special experiment was carried out to provide an insight into the reaction mechanism (Scheme 4). 2-Aminophenol (**2a**) was acylated with phenylacetyl chloride (1.0 equiv) in the presence of pyridine (1.1 equiv) in methylene chloride to give amide **4** in 82% yield [35]. Amide **4** was treated with Lawesson's reagent (1.0 equiv) in anhydrous methylene chloride to afford thioamide **4′** which was detected by mass spectrometry (see Supplementary Materials), and the

Scheme 3.



1a–1t **2a–2i** **3a–3ia**

1, R^1 = H (**a**), 4-Me (**b**), 4-Et (**c**), 4-Pr (**d**), 4-Bu (**e**), 4-OMe (**f**), 4-F (**g**), 4-Cl (**h**), 4-Br (**i**), 4-*t*-Bu (**j**), 4-Ph (**k**), 4-CF_3 (**l**), 3-Me (**m**), 3-OMe (**n**), 3-F (**o**), 3-Cl (**p**), 2-Cl (**q**), 3-Br (**r**), 2,3-benzo (**s**), 3,4-benzo (**t**); **2**, R^2 = H (**a**), 4-Me (**b**), 5-Me (**c**), 4-OMe (**d**), 4-F (**e**), 4-Cl (**f**), 5-F (**g**), 5-Cl (**h**), 4,5-benzo (**i**).

Table 1. Optimization of the reaction conditions[a]

Entry no.	Base	Solvent	Temperature, °C	Yield,[b] %
1	$NaHCO_3$	NMP	110	57
2	$KHCO_3$	NMP	110	45
3	K_3PO_4	NMP	110	Trace
4	NMPP	NMP	110	Trace
5	Pyridine	NMP	110	57
6	**K_2HPO_4**	**NMP**	**110**	**68**
7	K_2HPO_4	DMF	110	49
8	K_2HPO_4	DMA	110	58
9	K_2HPO_4	DMSO	110	Trace
10	K_2HPO_4	Dioxane	110	Trace
11	K_2HPO_4	Toluene	110	Trace
12	K_2HPO_4	Acetonitrile	110	Trace
13	K_2HPO_4	1,2-Dichloroethane	110	Trace
14	K_2HPO_4	NMP	120	64
15	K_2HPO_4	NMP	100	49
16[c]	K_2HPO_4	NMP	110	68
17[d]	K_2HPO_4	NMP	110	48
18[e]	K_2HPO_4	NMP	110	52
19[f]	K_2HPO_4	NMP	110	60
20[g]	K_2HPO_4	NMP	110	62
21[h]	K_2HPO_4	NMP	110	61

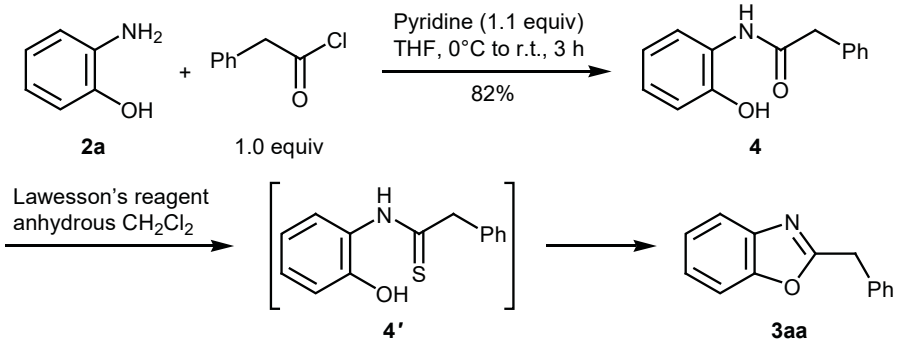
[a] Conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), elemental sulfur (0.4 mmol), base (0.3 mmol), solvent (0.6 mL), 110°C, 18 h under air.
[b] Isolated yield.
[c] Sulfur (19.2 mg, 0.6 mmol).
[d] Sulfur (6.4 mg, 0.2 mmol).
[e] **2a** (0.3 mmol).
[f] K_2HPO_4 (0.4 mmol).
[g] K_2HPO_4 (0.2 mmol).
[h] β-Bromostyrene (0.2 mmol) as substrate.

latter underwent cyclization to furnish the target product **3aa**.

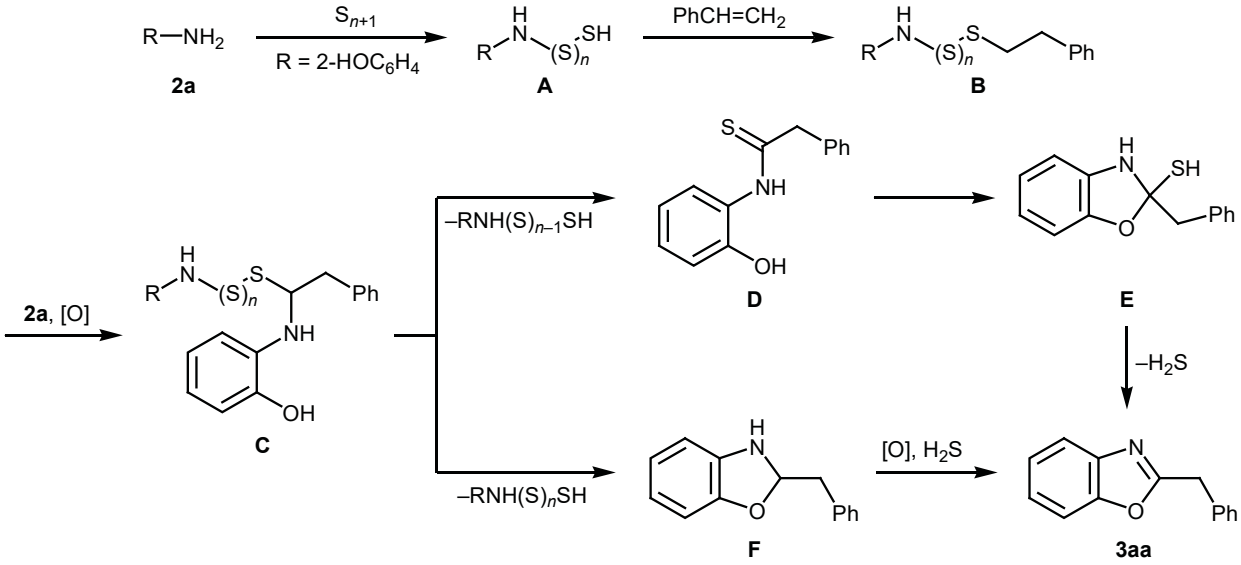
Based on known reports [25, 26, 36, 37] and our experimental results, a possible mechanism is proposed in Scheme 5. The reaction of **2a** with elemental sulfur produces intermediate **A** [38, 39], and the addition of **A** to styrene **1a** gives intermediate **B** which undergoes oxidation and reacts with another equivalent of **2a** to give **C**. *N*-(2-Hydroxyphenyl)-2-phenylethanethioamide **D** is produced from **C** via S–S bond cleavage, and the subsequent cyclization generates intermediate **E**. Loss of hydrogen sulfide from the latter yields the final product **3aa** [40]. Alternatively, S–S bond cleavage in **C**, followed by cyclization, gives oxazoline intermediate **F** which is oxidized to **3aa**.

Some chemical transformations of benzoxazole **3aa** were also studied (Scheme 6). The oxidation of **3aa** (0.5 mmol) with CuI (20 mol %) and AcOH (1.0 equiv) in DMSO for 24 h (1 atm O_2) afforded 2-benzoylbenzoxazole **5** in 89% yield. Benzoxazole **3aa** was smoothly alkylated with *n*-hexyl bromide (1.2 equiv) in the presence of K_3PO_4 (0.78 equiv) in NMP under nitrogen to give 82% of **6**. Likewise, the alkylation of **3aa** with benzyl chloride (1.2 equiv) in the presence of

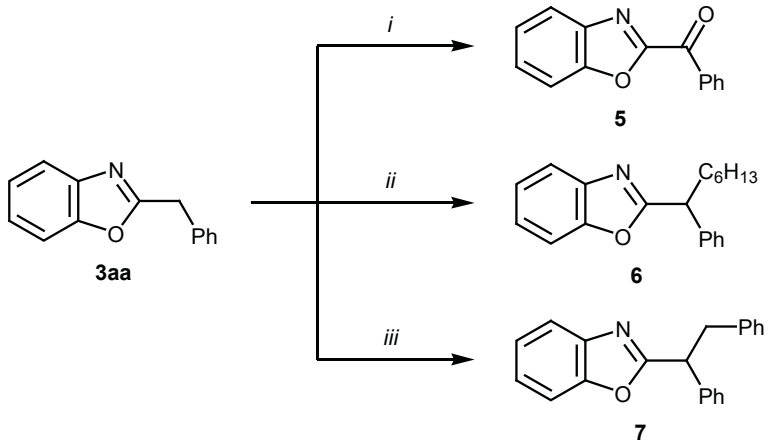
Scheme 4.



Scheme 5.



Scheme 6.



i: CuI (20 mol %), AcOH (1.0 equiv), DMSO (1 mL), O_2 (1 atm), 100°C, 24 h, 89%; *ii*: *n*-hexyl bromide (1.2 equiv), K_3PO_4 (0.78 equiv), NMP (2 mL), 100°C, 14 h, N_2, 82%; *iii*: benzyl chloride (1.2 equiv), Cs_2CO_3 (1.2 equiv), DMA (2 mL), 60°C, 16 h, N_2, 60%.

Cs_2CO_3 (1.2 equiv) in DMA under a nitrogen atmosphere afforded 2-(1,2-diphenylethyl)benzoxazole **7** in 60% (isolated) yield.

EXPERIMENTAL

Under otherwise noted, materials were obtained from commercial suppliers and used without further purification. All experiments were conducted in a sealed pressure vessel. The ^{1}H NMR spectra were recorded at 300, 400, or 500 MHz in $CDCl_3$ (δ 7.26 ppm). The ^{13}C NMR spectra were recorded at 75, 100, or 125 MHz in $CDCl_3$ (δ_C 77.0 ppm). The ^{19}F NMR spectra were recorded at 282 MHz in $CDCl_3$. The ^{1}H and ^{13}C chemical shifts were measured relative to tetramethylsilane (TMS) as internal standard. The high-resolution mass spectra were recorded using a Q-TOF mass spectrometer. Elemental analyses were carried out with a Vario MICRO cube analyzer (Germany). Flash column chromatography was performed over silica gel (200–300 mesh).

2-Benzyl-1,3-benzoxazole (3aa) [5]**.** A mixture of styrene (**2a**, 24 μL, 0.2 mmol), 2-aminophenol (**1a**, 43.6 mg, 0.4 mmol), elemental sulfur (12.8 mg, 0.4 mmol), K_2HPO_4 (52.3 mg, 0.3 mmol), and NMP (0.6 mL) was placed in a sealed pressure vessel (10 mL) containing a magnetic stirring bar. The vessel was capped, and the mixture was stirred at 110°C for 18 h under air atmosphere. After the reaction was complete (TLC), the mixture was cooled to room temperature, and treated with ethyl acetate (15 mL) and water (10 mL). The organic phase was separated, washed with brine, dried, filtered, and evaporated under reduced pressure, and the residue was purified by silica gel column chromatography using petroleum ether–ethyl acetate as eluent (20:1). Yield 28 mg (68%), light yellow solid, mp 107–109°C; published data [41]: 108–110°C; R_f 0.3 (petroleum ether–ethyl acetate, 20:1). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.67–7.71 m (1H), 7.44–7.49 m (1H), 7.27–7.40 m (7H), 4.28 s (2H).

Compounds **3ab**–**3ia** were synthesized in a similar way.

2-(4-Methylbenzyl)-1,3-benzoxazole (3ab) [5]**.** Yield 35 mg (78%), light yellow solid, mp 47–49°C, R_f 0.3 (petroleum ether–ethyl acetate, 20:1). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.67–7.70 m (1H), 7.44–7.48 m (1H), 7.26–7.31 m (4H), 7.16 d (J = 8.0 Hz, 2H), 4.24 s (2H), 2.33 s (3H).

2-(4-Ethylbenzyl)-1,3-benzoxazole (3ac). Yield 36 mg (75%), light yellow oil, R_f 0.3 (petroleum ether–ethyl acetate, 30:1). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 7.69–7.70 m (1H), 7.45–7.47 m (1H), 7.26–7.32 m (4H), 7.19 d (2H, J = 7.9 Hz), 4.25 s (2H), 2.64 q (2H, J = 7.6 Hz), 1.23 t (3H, J = 7.6 Hz). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ_C, ppm: 165.4, 151.1, 143.3, 141.4, 132.0, 128.9, 128.3, 124.6, 124.1, 119.8, 110.4, 34.9, 28.4, 15.4. Mass spectrum: m/z 238.12230 $[M + H]^+$. Found, %: C 80.66; H 6.46; N 5.99. $C_{16}H_{15}NO$. Calculated, %: C 80.98; H 6.37; N 5.90. M + H 238.12264.

2-(4-Propylbenzyl)-1,3-benzoxazole (3ad). Yield 36 mg (72%), light yellow oil, R_f 0.3 (petroleum ether–ethyl acetate, 30:1). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 7.69–7.70 m (1H), 7.45–7.47 m (1H), 7.26–7.31 m (4H), 7.16 d (2H, J = 7.9 Hz), 4.25 s (2H), 2.57 t (2H, J = 7.6 Hz), 1.60–1.67 m (2H), 0.94 t (3H, J = 7.3 Hz). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ_C, ppm: 165.4, 151.1, 141.7, 141.4, 132.0, 128.9, 128.8, 124.6, 124.1, 119.8, 110.4, 37.6, 34.9, 24.4, 13.8. Mass spectrum: m/z 252.13788 $[M + H]^+$. Found, %: C 81.06; H 6.86; N 5.63. $C_{17}H_{17}NO$. Calculated, %: C 81.24; H 6.82; N 5.57. M + H 252.13829.

2-(4-Butylbenzyl)-1,3-benzoxazole (3ae) [30]**.** Yield 35 mg (66%), light yellow oil, R_f 0.4 (petroleum ether–ethyl acetate, 20:1). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.65–7.70 m (1H), 7.42–7.46 m (1H), 7.24–7.29 m (4H), 7.15 d (2H, J = 8.0 Hz), 4.23 s (2H), 2.58 t (2H, J = 7.7 Hz), 1.53–1.61 m (2H), 1.29–1.38 m (2H), 0.91 t (3H, J = 7.3 Hz).

2-(4-Methoxybenzyl)-1,3-benzoxazole (3af) [5]**.** Yield 28 mg (58%), light yellow solid, R_f 0.2 (petroleum ether–ethyl acetate, 10:1), mp 45–47°C; published data [42]: mp 43–45°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.67–7.69 m (1H), 7.45–7.49 m (1H), 7.25–7.33 m (4H), 6.87–7.91 m (1H), 4.21 s (3H), 3.79 s (3H).

2-(4-Fluorobenzyl)-1,3-benzoxazole (3ag) [5]**.** Yield 25 mg (56%), light yellow solid, R_f (petroleum ether–ethyl acetate, 20:1), mp 35–37°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.69–7.76 m (1H), 7.31–7.48 m (5H), 7.05 d (2H, J = 7.7 Hz), 4.25 s (2H).

2-(4-Chlorobenzyl)-1,3-benzoxazole (3ah) [5]**.** Yield 32 mg (65%), light yellow solid, R_f 0.3 (petroleum ether–ethyl acetate, 20:1), mp 79–81°C; published data [43]: mp 78–80°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.68–7.69 m (1H), 7.46–7.47 m (1H), 7.26–7.32 m (6H), 4.24 s (2H).

2-(4-Bromobenzyl)-1,3-benzoxazole (3ai) [44]**.** Yield 30 mg (52%), light yellow solid, R_f 0.4 (petro-

leum ether–ethyl acetate, 20:1), mp 93–95°C; published data [44]: mp 92–95°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 7.67–7.72 m (1H), 7.46–7.48 m (3H), 7.26–7.32 m (4H), 4.22 s (2H).

2-(4-*tert*-Butylbenzyl)-1,3-benzoxazole (3aj) [13]**.** Yield 31 mg (59%), light yellow solid, R_f 0.3 (petroleum ether–ethyl acetate, 25:1), mp 71–73°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.68–7.70 m (1H), 7.45–7.48 m (1H), 7.38 d (2H, J = 8.4 Hz), 7.32 d (2H, J = 8.4 Hz), 7.28–7.30 m (2H), 4.25 s (2H), 1.31 s (9H).

2-([1,1′-Biphenyl]-4-ylmethyl)-1,3-benzoxazole (3ak) [10]**.** Yield 39 mg (69%), light yellow solid, R_f 0.2 (petroleum ether–ethyl acetate, 20:1), mp 96–98°C; published data [45]: mp 91°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.70–7.73 m (1H), 7.57–7.59 m (4H), 7.42–7.50 m (5H), 7.36 d (1H, J = 7.0 Hz), 7.30–7.32 m (2H), 4.33 s (2H).

2-[4-(Trifluoromethyl)benzyl]-1,3-benzoxazole (3al) [10]**.** Yield 31 mg (56%), light yellow solid, R_f 0.3 (petroleum ether–ethyl acetate, 30:1), mp 51–53°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.69–7.71 m (1H), 7.61 d (2H, J = 8.1 Hz), 7.45–7.51 m (3H), 7.25–7.32 m (2H), 4.32 s (2H).

2-(3-Methylbenzyl)-1,3-benzoxazole (3am) [13]**.** Yield 26 mg (59%), light yellow oil, R_f 0.3 (petroleum ether–ethyl acetate, 20:1). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.73–7.75 m (1H), 7.49–7.51 m (1H), 7.28–7.36 m (3H), 7.22 d (2H, J = 7.4 Hz), 7.13 d (2H, J = 7.3 Hz), 4.27 s (2H), 2.38 s (3H).

2-(3-Methoxybenzyl)-1,3-benzoxazole (3an) [5]**.** Yield 26 mg (54%), light yellow solid, R_f 0.2 (petroleum ether–ethyl acetate, 10:1), mp 71–73°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.68–7.72 m (1H), 7.46–7.48 m (1H), 7.25–7.32 m (3H), 6.82–6.98 m (3H), 4.25 s (2H), 3.80 s (3H).

2-(3-Fluorobenzyl)-1,3-benzoxazole (3ao) [10]**.** Yield 23 mg (50%), light yellow oil, R_f 0.3 (petroleum ether–ethyl acetate, 20:1). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.69–7.72 m (1H), 7.46–7.49 m (1H), 7.25–7.34 m (3H), 7.09–7.17 m (2H), 6.96–7.00 m (1H), 4.27 s (2H).

2-(3-Chlorobenzyl)-1,3-benzoxazole (3ap) [30]**.** Yield 27 mg (56%), light yellow oil, R_f 0.3 (petroleum ether–ethyl acetate, 20:1). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.68–7.71 m (1H), 7.45–7.48 m (1H), 7.38 s (1H), 7H), 7.10 s (1H), 4.26 s (2H), 2.45 s (3H).

2-(2-Chlorobenzyl)-1,3-benzoxazole (3aq) [5]**.** Yield 29 mg (60%), yellow oil, R_f 0.3 (petroleum ether–ethyl acetate, 30:1). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 7.71–7.73 m (1H), 7.39–7.50 m (3H), 7.26–7.33 m (4H), 4.45 s (2H).

2-(3-Bromobenzyl)-1,3-benzoxazole (3ar) [46]**.** Yield 27 mg (47%), yellow oil, R_f 0.3 (petroleum ether–ethyl acetate, 20:1). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.69–7.71 m (1H), 7.41–7.55 m (3H), 7.55–7.58 m (1H), 7.20–7.31 m (4H), 4.24 s (2H).

2-(Naphthalen-1-ylmethyl)-1,3-benzoxazole (3as) [47]**.** Yield 25 mg (49%), light yellow solid, R_f 0.2 (petroleum ether–ethyl acetate, 20:1), mp 67–69°C; published data [47]: mp 68°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 8.16 d (1H, J = 3.6 Hz), 7.80–7.85 m (2H), 7.67 d (1H, J = 3.3 Hz), 7.39–7.52 m (5H), 7.23–7.29 m (2H), 4.70 s (2H).

2-(Naphthalen-2-ylmethyl)-1,3-benzoxazole (3at) [5]**.** Yield 32 mg (62%), light yellow solid, R_f 0.2 (petroleum ether–ethyl acetate, 20:1), mp 60–62°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 7.82–7.86 m (4H), 7.69–7.72 m (1H), 7.43–7.52 m (4H), 7.28–7.34 m (2H), 4.44 s (2H).

2-Benzyl-5-methyl-1,3-benzoxazole (3ba) [48]**.** Yield 27 mg (61%), light yellow solid, R_f 0.3 (petroleum ether–ethyl acetate, 20:1). mp 48–50°C; published data [48]: mp 49.5–51°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.26–7.47 m (7H), 7.10 s (1H), 4.26 s (2H), 2.45 s (3H).

2-Benzyl-6-methyl-1,3-benzoxazole (3ca) [5]**.** Yield 29 mg (66%), light yellow solid, R_f 0.3 (petroleum ether–ethyl acetate, 20:1), mp 49–51°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.53–7.55 m (1H), 7.26–7.44 m (6H), 7.10 d (1H, J = 7.3 Hz), 4.24 s (2H), 2.45 s (3H).

2-Benzyl-5-methoxy-1,3-benzoxazole (3da) [30]**.** Yield 27 mg (56%), light yellow solid, R_f 0.2 (petroleum ether–ethyl acetate, 10:1), mp 147–149°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 7.26–7.39 m (6H), 7.18 s (1H), 6.89 d (1H, J = 8.9 Hz), 4.25 s (2H), 3.83 s (3H).

2-Benzyl-5-fluoro-1,3-benzoxazole (3ea) [13]**.** Yield 22 mg (48%), light yellow solid, R_f 0.3 (petroleum ether–ethyl acetate, 30:1), mp 46–48°C; published data [13]: mp 48–49°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 7.26–7.37 m (7H), 6.99–7.05 m (1H), 4.26 s (2H).

2-Benzyl-5-chloro-1,3-benzoxazole (3fa) [5]**.** Yield 22 mg (45%), light yellow solid, R_f 0.3 (petroleum ether–ethyl acetate, 20:1), mp 45–47°C. ^{1}H NMR

spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.67 d (1H, J = 1.9 Hz), 7.26–7.44 m (7H), 4.27 s (2H).

2-Benzyl-6-fluoro-1,3-benzoxazole (3ga). Yield 34 mg (74%), light yellow solid, R_f 0.3 (petroleum ether–ethyl acetate, 25:1), mp 124–126°C. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 7.61 d.d (1H, J = 8.7, 4.9 Hz), 7.34–7.38 m (1H), 7.28–7.31 m (1H), 7.19 d.d (1H, J = 8.0, 3.3 Hz), 7.03–7.07 m (1H), 4.26 s (2H). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ_C, ppm: 166.0, 151.1, 139.7, 134.3 d (J = 8.1 Hz), 130.5, 128.9 d (J = 12.6 Hz), 127.4, 125.0, 120.2, 119.9 d (J = 16.6 Hz), 112.2 d (J = 40.9 Hz), 111.1, 35.1. Mass spectrum: m/z 228.10199 $[M + H]^+$. Found, %: C 73.86; H 4.41; N 6.14. $C_{14}H_{10}NOF$. Calculated, %: C 74.00; H 4.44; N 6.16. M + H 228.08192.

2-Benzyl-6-chloro-1,3-benzoxazole (3ha) [5]**.** Yield 27 mg (56%), light yellow solid, R_f 0.3 (petroleum ether–ethyl acetate, 20:1), mp 50–52°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 7.59 d (1H, J = 8.6 Hz), 7.47 s (1H), 7.29–7.38 m (6H), 4.26 s (2H).

2-Benzylnaphtho[2,3-*d*][1,3]oxazole (3ia) [49]**.** Yield 35 mg (67%), light yellow solid, R_f 0.3 (petroleum ether–ethyl acetate, 20:1), mp 140–143°C; published data [49]: mp 140–142°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.77–7.82 m (2H), 7.55 s (1H), 7.44–7.46 m (1H), 7.26–7.36 m (7H), 4.50 s (2H).

***N*-(2-Hydroxyphenyl)-2-phenylacetamide (4)** [35]**.** Yield 1.862 g (82%), light yellow solid, mp 148–150°C; published data [46]: 149–150°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 9.75 br.s (1H), 9.31 br.s (1H), 7.76 d (1H, J = 7.9 Hz), 7.22–7.37 m (5H), 6.83–6.95 m (2H), 6.72–6.77 m (1H), 3.74 s (2H).

1-(1,3-Benzoxazol-2-yl)-1-phenylmethanone (5) [50]**.** Yield 99 mg (89%), light yellow solid, R_f 0.4 (petroleum ether–ethyl acetate, 30:1), mp 73–75°C; published data [51]: mp 74°C. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 8.54 d (2H, J = 7.6 Hz), 7.92 d (1H, J = 8.0 Hz), 7.64–7.69 m (2H), 7.51–7.56 m (3H), 7.43–7.46 m (1H).

2-(1-Phenylheptyl)-1,3-benzoxazole (6) [11]**.** Yield 120 mg (82%), colorless liquid, R_f 0.3 (petroleum ether–ethyl acetate, 60:1). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 7.74–7.76 m (1H), 7.43–7.48 m (3H), 7.27–7.37 m (5H), 4.26 t (1H, J = 7.8 Hz), 2.39–2.46 m (1H), 2.12–2.20 m (1H), 1.29–1.39 m (8H), 0.89 t (3H, J = 6.9 Hz).

2-(1,2-Diphenylethyl)-1,3-benzoxazole (7) [52]**.** Yield 90 mg (60%), colorless oil, R_f 0.3 (petroleum ether–ethyl acetate, 50:1). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 7.74–7.77 m (1H), 7.45–7.48 m (1H), 7.14–7.40 m (12H), 4.49 t (1H, J = 7.8 Hz), 3.81 d.d (1H, J = 7.8, 5.9 Hz), 3.43 d.d (1H, J = 7.8, 5.9 Hz).

CONCLUSIONS

A sulfur-mediated metal-free protocol has been developed to prepare 2-(arylmethyl)benzoxazoles. Dipotassium hydrogen phosphate was found to be an effective base for this transformation with broad functional group tolerance. The reactions proceeded in moderate to good yields, and a gram-scale reaction was carried out. Preliminary mechanistic investigations suggested participation of thioamide intermediate, namely *N*-(2-hydroxyphenyl)-2-phenylethanethioamide. Further application of this methodology is ongoing in our laboratory.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY INFORMATION

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REFERENCES

1. Pal, S., Manjunath, B., Ghorai, S., and Sasmal, S., *Alkaloids*, 2018, vol. 79, p. 71. https://doi.org/10.1016/bs.alkal.2017.12.002
2. Bansal, S., *Mini-Rev. Org. Chem*., 2021, vol. 18, p. 383. https://doi.org/10.2174/1570193X17999200706010457
3. Guo, Y., Huang, X., Liao, W., Meng, L., Xu, D., Ye, C., Chen, L., and Hu, T., *ACS Omega*, 2021, vol. 6, p. 15412. https://doi.org/10.1021/acsomega.1c01866
4. Nguyen, T.B. and Lung, J.C., *Eur. J. Org. Chem*., 2018, p. 5815. https://doi.org/10.1002/ejoc.201701607

5. Nguyen, T.B. and Retailleau, P., *Org. Lett*., 2017, vol. 19, p. 3887. https://doi.org/10.1021/acs.orglett.7b01775
6. Guntreddi, T., Vanjari, R., Kumar, S., Singh, R., Singh, N., Kumar, P., and Singh, K.N., *RSC Adv*., 2016, vol. 6, p. 81013. https://doi.org/10.1039/C6RA17491D
7. Jiang, J., Zou, H., Dong, Q., Wang, R., Lu, L., Zhu, Y., and He, W., *J. Org. Chem*., 2016, vol. 81, p. 51. https://doi.org/10.1021/acs.joc.5b02093
8. Kumbhar, H.S. and Shankarling, G.S., *Dyes Pigm*., 2015, vol. 122, p. 85. https://doi.org/10.1016/j.dyepig.2015.06.020
9. Li, Z.-L., Jin, L.-K., and Cai, C., *Org. Chem. Front*., 2017, vol. 4, p. 2039. https://doi.org/10.1039/C7QO00396J
10. Pan, W.-J. and Wang, Z.-X., *Asian J. Org. Chem*., 2018, vol. 7, p. 1626. https://doi.org/10.1002/ajoc.201800264
11. Ackermann, L., Barfüsser, S., Kornhaass, C., and Kapdi, A.R., *Org. Lett*., 2011, vol. 13, p. 3082. https://doi.org/10.1021/ol200986x
12. Mukai, T., Hirano, K., Satoh, T., and Miura, M., *Org. Lett*., 2010, vol. 12, p. 1360. https://doi.org/10.1021/ol1002576
13. Ji, Y.-Y., Zhang, Y., Hu, Y.-Y., and Shao, L.-X., *Tetrahedron*, 2015, vol. 71, p. 6818. https://doi.org/10.1016/j.tet.2015.07.030
14. Zhao, X., Wu, G., Zhang, Y., and Wang, J., *J. Am. Chem. Soc*., 2011, vol. 133, p. 3296. https://doi.org/10.1021/ja111249p
15. Zhang, J., Hu, L., Liu, Y., Zhang, Y., Chen, X., Luo, Y., Peng, Y., Han, S., and Pan, B., *J. Org. Chem*., 2021, vol. 86, p. 14485. https://doi.org/10.1021/acs.joc.1c01357
16. Suslick, B.A. and Tilley, T.D., *Org. Lett*., 2021, vol. 23, p. 1495. https://doi.org/10.1021/acs.orglett.1c00258
17. Choo, J.P.S., Kammerer, R.A., Li, X., and Li, Z., *Adv. Synth. Catal*., 2021, vol. 363, p. 1714. https://doi.org/10.1002/adsc.202001500
18. Oseghale, C.O., Mogudi, B.M., Akinnawo, C.A., and Meijboom, R., *Appl. Catal., A*, 2020, vol. 602, article ID 117735. https://doi.org/10.1016/j.apcata.2020.117735
19. Yang, S., Gao, P., Suo, M.-T., Gao, S.-X., Duan, X.-H., and Guo, L.-N., *Chem. Commun*., 2020, vol. 56, p. 10714. https://doi.org/10.1039/D0CC04439C
20. Keene, S.T., Fogarty, D., Cooke, R., Casadevall, C.D., Salleo, A., and Parlak, O., *Adv. Healthcare Mater*., 2019, vol. 8, article ID e1901321. https://doi.org/10.1002/adhm.201901321
21. Ma, J., Chen, K., Fu, H., Zhang, L., Wu, W., Jiang, H., and Zhu, S., *Org. Lett*., 2016, vol. 18, p. 1322. https://doi.org/10.1021/acs.orglett.6b00260
22. Chen, F., Wang, T., and Jiao, N., *Chem. Rev*., 2014, vol. 114, p. 8613. https://doi.org/10.1021/cr400628s
23. Kondoh, A., Ma, C., and Terada, M., *Chem. Commun*., 2020, vol. 56, p. 10894. https://doi.org/10.1039/D0CC04512H
24. Kim, J., Pannilawithana, N., and Yi, C.S., *ACS Catal*., 2016, vol. 6, p. 8395. https://doi.org/10.1021/acscatal.6b02186
25. Li, G., Jiang, J., Zhang, F., Xiao, F., and Deng, G.-J., *Org. Biomol. Chem*., 2017, vol. 15, p. 10024. https://doi.org/10.1039/C7OB02430D
26. Jiang, J., Li, G., Zhang, F., Xie, H., and Deng, G.-J., *Adv. Synth. Catal*., 2018, vol. 360, p. 1622. https://doi.org/10.1002/adsc.201701560
27. Xia, X.-D., Xuan, J., Wang, Q., Lu, L.-Q., Chen, J.-R., and Xiao, W.-J., *Adv. Synth. Catal*., 2014, vol. 356, p. 2807. https://doi.org/10.1002/adsc.201400527
28. Nakao, Y., Kashihara, N., Kanyiva, K.S., and Hiyama, T., *Angew. Chem., Int. Ed*., 2010, vol. 49, p. 4451; *Angew. Chem*., 2010, vol. 122, p. 4553. https://doi.org/10.1002/anie.201001470
29. Gan, H., *ChemistrySelect*, 2020, vol. 5, p. 717. https://doi.org/10.1002/slct.201904569
30. Gan, H., *ChemistrySelect*, 2019, vol. 4, p. 8598. https://doi.org/10.1002/slct.201902349
31. Gan, H. and Yang, D., *J. Saudi Chem. Soc*., 2019, vol. 23, p. 809. https://doi.org/10.1016/j.jscs.2019.03.001
32. Gan, H., *ChemistrySelect*, 2019, vol. 4, p. 2858. https://doi.org/10.1002/slct.201900550
33. Gan, H., Miao, D., Pan, Q., Hu, R., Li, X., and Han, S., *Chem. Asian J*., 2016, vol. 11, p. 1770. https://doi.org/10.1002/asia.201600355
34. Gan, H., *Asian J. Org. Chem*., 2016, vol. 5, p. 1111. https://doi.org/10.1002/ajoc.201600274
35. Sun, A., Prussia, A., Zhan, W., Murray, E.E., Doyle, J., Cheng, L.-T., Yoon, J.-J., Radchenko, E.V., Palyulin, V.A., Compans, R.W., Liotta, D.C., Plemper, R.K., and Snyder, J.P., *J. Med. Chem*., 2006, vol. 49, p. 5080. https://doi.org/10.1021/jm0602559
36. Nguyen, T.B., Tran, M.Q., Ermolenko, L., and Al-Mourabit, A., *Org. Lett*. 2014, vol. 16, p. 310. https://doi.org/10.1021/ol403345e
37. Wang, Z., Wang, Y., Zhang, W., Hou, Z., and Xi, Z., *J. Am. Chem. Soc*., 2009, vol. 131, p. 15108. https://doi.org/10.1021/ja9069419
38. Nguyen, T.B., *Asian J. Org. Chem*., 2017, vol. 6, p. 477. https://doi.org/10.1002/ajoc.201700011
39. Nguyen, T.B., *Adv. Synth. Catal*., 2017, vol. 359, p. 1066. https://doi.org/10.1002/adsc.201601329

40. Kim, Y.H., Kim, Y.I., Chang, H.S., and Yoon, D.C., *Heterocycles*, 1989, vol. 29, p. 213. https://doi.org/10.3987/COM-89-4785
41. Khalili, D. and Banazadeh, A.R., *Bull. Chem. Soc. Jpn*., 2015, vol. 88, p. 1693. https://doi.org/10.1246/bcsj.20150232
42. Rezazadeh, S., Akhlaghinia, B., and Razavi, N., *Aust. J. Chem*., 2015, vol. 68, p. 145. https://doi.org/10.1071/CH14037
43. Li, G., Arisawa, M., and Yamaguchi, M., *Chem. Commun*., 2014, vol. 50, p. 4328. https://doi.org/10.1039/C4CC00816B
44. Wagner, G. and Eppner, B., *Pharmazie*, 1980, vol. 35, p. 285.
45. Kumar, J., Gupta, A., and Bhadra, S., *Org. Biomol. Chem*., 2019, vol. 17, p. 3314. https://doi.org/10.1039/C9OB00337A
46. Fan, X., He, Y., Zhang, X., Guo, S., and Wang, Y., *Tetrahedron*, 2011, vol. 67, p. 6369. https://doi.org/10.1016/j.tet.2011.05.111
47. Isagulyants, V.I., *Kataliticheskii sintez i prevrashcheniya geterotsiklicheskikh soedinenii. Geterogennyi kataliz* (Catalytic Synthesis and Transformations of Heterocyclic Compounds. Heterogeneous Catalysis), Giller, S.A., Ed., Riga: Zinatne, 1976, p. 206.
48. Ackermann, L., *Org. Lett*., 2010, vol. 12, p. 724. https://doi.org/10.1021/ol9028034
49. Kumar, D., *Aust. J. Chem*., 2008, vol. 61, p. 881. https://doi.org/10.1071/CH08193
50. Sterckx, H., De Houwer, J., Mensch, C., Caretti, I., Tehrani Kourosch, A., Herrebout, W.A., Van Doorslaer, S., and Maes, B.U.W., *Chem. Sci*., 2016, vol. 7, p. 346. https://doi.org/10.1039/C5SC03530A
51. Pollard, C.B., *J. Am. Chem. Soc*., 1931, vol. 53, p. 996. https://doi.org/10.1021/ja01354a023
52. Xie, P., Huang, H., Xie, Y., Guo, S., and Xia, C., *Adv. Synth. Catal*., 2012, vol. 354, p. 1692. https://doi.org/10.1002/adsc.201200025