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2-Aminophenols react with an array of carboxylic acids in dioxane at 180° in the presence of tin(II) chloride to afford the corresponding 2-substituted benzoxazoles in good yields. The reaction is applicable to a wide range of alkyl, alkenyl, aryl carboxylic acids.

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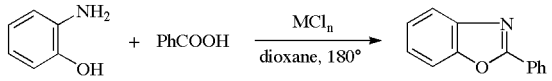
Compounds containing the benzoxazole framework have frequently been used as fluorescent brightening agents, calcium antagonists and antitumor metabolites. The structural core of benzoxazole is commonly constructed from 2-aminophenols and carboxylic acids as substrate by the aid of catalysts such as polyphosphoric acid and its ester [1,2] and boric acid [3]. Furthermore, several homogeneous transition metal-catalyzed synthetic methods have also been attempted because of the wide availability of substrate [4-7]. In connection with this report, during the course of our ongoing studies on ruthenium-catalyzed alkyl group transfer reactions between amines (amine exchange reaction) which eventually leads to indoles [8-11] and quinolines [12-17], the addition of tin(II) chloride dihydrate ($SnCl_2$•$2H_2O$) was essential for effective heteroannulation. Prompted by these findings and intrigued by the actual role of $SnCl_2$•$2H_2O$, we focused our attention on the discovery of additive activity of tin(II) halides in organic reactions. We recently found that the addition of $SnCl_2$•$2H_2O$ resulted in selective formation of *N*-monoalkylanilines for ruthenium-catalyzed *N*-alkylation of anilines with tetraalkylammonium halides [18]. Herein, as an another example for the additive activity of tin(II) halides, we report tin(II) chloride-mediated synthesis of benzoxazoles from 2-aminophenols and carboxylic acids.

The results of several reactions between 2-aminophenol (**1**) and benzoic acid (**2**) in the presence of various metallic chlorides are listed in Table 1 (Scheme 1). Typically, **1** was treated with an equimolar amount of **2** in dioxane in the presence of metallic chlorides at 180° under argon atmosphere to afford 2-phenylbenzoxazole (**3**). Table 1 shows that tin(II) chloride ($SnCl_2$) is the metallic chloride of choice for effective cyclization (runs 1-6). The absence of $SnCl_2$ proved to be ineffective for the formation of **3** and no other products were detected on TLC analysis (run 7). The yield of **3** was increased by prolonging the reaction time up to 30 hours (runs 8 and 9). The use of half an equivalent of $SnCl_2$ relative to the substrate resulted in a decreased yield (run 10). The reaction also proceeded using metallic chloride systems such as $SnCl_2$•$2H_2O$ or $SnCl_2$/LiCl, but the yields of **3** was generally lower than that obtained by the use of $SnCl_2$ (runs 11 and 12).

Scheme 1



1 **2** **3**

Table 1

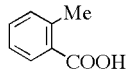
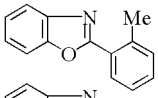
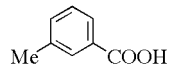
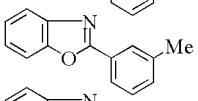
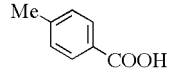
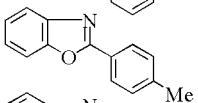
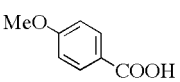
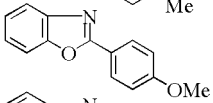
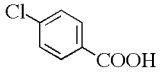
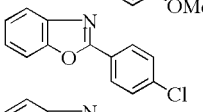
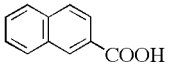
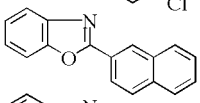
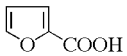
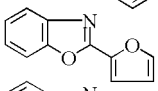
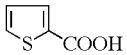
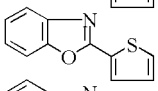
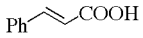
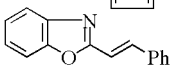
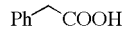
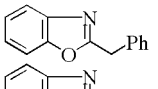
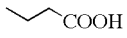
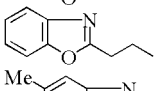
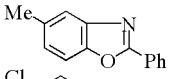
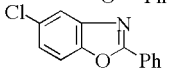
Metallic Halides-Mediated Formation of **3** from **1** and **2** [a]

Run	Metallic chloride	Time (h)	Yield of **3** [b]
1	$SnCl_2$	20	43
2	$SbCl_3$	20	9
3	$BiCl_3$	20	4
4	$LaCl_3$	20	3
5	$FeCl_3$	20	2
6	$CeCl_3$	20	5
7	-	20	trace
8	$SnCl_2$	30	60
9	$SnCl_2$	40	60
10	$SnCl_2$ [c]	30	46
11	$SnCl_2$•$2H_2O$	20	32
12	$SnCl_2$/LiCl [d]	20	17

[a] All reactions were carried out with **1** (2 mmol), **2** (2 mmol), and metallic chloride (2 mmol) in dioxane (10 mL) at 180° under argon unless otherwise stated; [b] Isolated yield; [c] $SnCl_2$ = 1 mmol; [d] LiCl = 2 mmol.

Given these results, an array of aminophenols and carboxylic acids was employed in order to investigate the scope of the reaction. The results are summarized in Table 2. Aryl carboxylic acids were readily cyclized with **1**, and these preliminary results indicate that benzoxazole yield is affected by the position of the substituent on aromatic ring of the carboxylic acid (runs 1-6). With *ortho*-substituted aryl carboxylic acid, the yield was lower than that when *meta*- and *para*-substituted aryl carboxylic acids were used. Also, the results found in runs 4-6 , may indicate that the yield is dependent on the electronic nature of the substituent as well. With heteroaryl, vinyl and alkyl carboxylic acids, the corresponding 2-substituted benzoxazoles were also formed in similar yields (runs 8-12). In the reaction between 2-amino-4-chlorophenol and **2**, the corresponding benzoxazole was formed with concomitant formation of 2-phenylbenzoxazole (**3**) (run 14).

Table 2
Synthesis of 2-Substituted Benzoxazoles from 2-Aminophenols and Carboxylic Acids [a]

Run	Carboxylic acid	Benzoxazole	Yield [b]
1	**2**	**3**	60
2			27
3			62
4			55
5			37
6			63
7			60
8			66
9			51
10			50
11			73
12			59
13 [c]	**2**		61
14 [d]	**2**		32 [e]

[a] Except as noted, all reactions were carried out with **1**; [b] Isolated yield; [c] 2-Amino-4-methylphenol was used; [d] 2-Amino-4-chlorophenol was used; [e] **3** was also formed in 18% yield.

In summary, we have demonstrated that 2-substituted benzoxazoles can be synthesized from 2-aminophenols and carboxylic acids in the presence of $SnCl_2$ in good yields. The present $SnCl_2$-mediated reaction is an alternative route to benzoxazole synthesis using 2-aminophenols and carboxylic acids.

EXPERIMENTAL

The ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker Avance Digital 400 spectrometer using TMS as an internal standard. Melting points were determined on a Thomas Scientific Capillary Melting Points Apparatus and are uncorrected. The isolation of pure products was carried out *via* column chromatography (silica gel 60 HF_{254}, 70-230 mesh, Merck). Commercially available organic and inorganic compounds were used without further purification.

Tin(II) Chloride-Catalyzed Synthesis of 2-Substituted Benzoxazoles from 2-Aminophenols and Carboxylic Acids.

A mixture of 2-aminophenol (2 mmol), carboxylic acid (2 mmol), and tin(II) chloride (2 mmol) in dioxane (10 mL) was placed in a 50 mL stainless steel pressure vessel. After the system was flushed with argon, the mixture was stirred at 180° for 30 hours. Removal of solvent under reduced pressure left a crude mixture which was separated by column chromatography (ethyl acetate/hexane = 1/10) to give 2-substituted benzoxazoles.

2-Phenylbenzoxazole (**3**).

This compound was obtained as white crystals, mp 101-102° (hexane) (lit [2] mp 102-103°); ^1H NMR ($CDCl_3$): δ 7.33-7.37 (m, 2H), 7.51-7.54 (m, 3H), 7.56-7.59 (m, 1H), 7.77-7.79 (m, 1H), 8.25-8.27 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 110.6, 120.0, 124.6, 125.1, 127.2, 127.6, 128.9, 131.5, 142.1, 150.7, 163.0.

2-(2-Methylphenyl)benzoxazole.

This compound was obtained as white crystals, mp 64-65° (hexane) (lit [19] mp 64-66°); ^1H NMR ($CDCl_3$): δ 2.81 (s, 3H), 7.32-7.43 (m, 5H), 7.56-7.59 (m, 1H), 7.78-7.82 (m, 1H), 8.16-8.18 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 22.2, 110.5, 120.1, 124.4, 125.0, 126.1, 126.2, 129.9, 130.9, 131.8, 138.8, 142.1, 150.3, 163.4.

2-(3-Methylphenyl)benzoxazole.

This compound was obtained as white crystals, mp 81-82° (hexane) (lit [20] mp 81-82°); ^1H NMR ($CDCl_3$): δ 2.44 (s, 3H), 7.31-7.41 (m, 4H), 7.54-7.58 (m, 1H), 7.75-7.79 (m, 1H), 8.04 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 21.3, 110.5, 119.9, 124.5, 124.7, 125.0, 127.0, 128.2, 128.8, 132.3, 138.7, 142.1, 150.7, 163.2.

2-(4-Methylphenyl)benzoxazole.

This compound was obtained as white crystals, mp 110-111° (hexane) (lit [20] mp 113-115°); ^1H NMR ($CDCl_3$): δ 2.42 (s, 3H), 7.31-7.34 (m, 4H), 7.55-7.57 (m, 1H), 7.74-7.77 (m, 1H), 8.14 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 21.6, 110.5, 119.8, 124.3, 124.4, 124.8, 127.5, 129.6, 142.0, 142.1, 150.6, 163.2.

2-(4-Methoxyphenyl)benzoxazole.

This compound was obtained as white crystals, mp 98-99° (hexane) (lit [3] mp 100-100.5°); ^1H NMR ($CDCl_3$): δ 3.89 (s, 3H), 7.03 (d, J = 9.0 Hz, 2H), 7.30-7.35 (m, 2H), 7.54-7.56 (m, 1H), 7.73-7.75 (m, 1H), 8.20 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 55.6, 110.6, 114.5, 119.8, 119.9, 124.6, 124.8, 129.6, 142.4, 150.8, 162.5, 163.3.

2-(4-Chlorophenyl)benzoxazole.

This compound was obtained as white crystals, mp 146-147° (hexane) (lit [3] mp 149-149.5°); ^1H NMR ($CDCl_3$): δ 7.34-7.39 (m, 2H), 7.49-7.52 (m, 2H), 7.56-7.60 (m, 1H), 7.75-7.79 (m, 1H), 8.18-8.21 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 110.6, 120.1, 124.7, 125.4, 125.6, 128.8, 129.3, 137.8, 142.0, 150.7, 162.1.

2-(2-Naphthyl)benzoxazole.

This compound was obtained as white crystals, mp 111-112° (hexane) (lit [21] mp 112°); ^1H NMR ($CDCl_3$): δ 7.34-7.38 (m, 2H), 7.53-7.62 (m, 3H), 7.79-7.83 (m, 1H), 7.86-7.88

(m, 1H), 7.95-7.98 (m, 2H), 8.29-8.32 (m, 1H), 8.76 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 110.6, 120.0, 123.9, 124.4, 124.6, 125.2, 126.9, 127.8, 127.9, 128.1, 128.8, 128.9, 133.0, 134.7, 142.2, 150.8, 163.2.

2-(2-Furanyl)benzoxazole.

This compound was obtained as white crystals, mp 84-86° (hexane) (lit [3] mp 86.5-87.5°); ^{1}H NMR ($CDCl_3$): δ 6.62 (dd, J = 3.5 and 2.0 Hz, 1H), 7.28 (d, J = 3.5 Hz, 1H), 7.32-7.38 (m, 2H), 7.54-7.59 (m, 1H), 7.65-7.67 (m, 1H), 7.73-7.78 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 110.6, 112.3, 114.3, 120.1, 124.8, 125.3, 141.6, 142.6, 145.7, 150.1, 155.3.

2-(2-Thiophenyl)benzoxazole.

This compound was obtained as white crystals, mp 104-105° (hexane) (lit [21] mp 107°); ^{1}H NMR ($CDCl_3$): δ 7.18 (dd, J = 5.0 and 3.5 Hz, 1H), 7.31-7.36 (m, 2H), 7.52-7.56 (m, 2H), 7.71-7.76 (m, 1H), 7.91 (dd, J = 3.5 and 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 110.4, 119.8, 124.7, 125.0, 128.2, 129.6, 130.0, 130.2, 142.0, 150.4, 159.0.

2-(2-Styryl)benzoxazole.

This compound was obtained as white crystals, mp 80-82° (hexane) (lit [3] mp 80.5-82°); ^{1}H NMR ($CDCl_3$): δ 7.07 (d, J = 16.6 Hz, 1H), 7.30-7.44 (m, 5H), 7.50-7.54 (m, 1H), 7.58-7.60 (m, 2H), 7.69-7.74 (m, 1H), 7.78 (d, J = 16.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 110.3, 113.9, 119.9, 124.5, 125.2, 127.6, 129.0, 129.8, 135.1, 139.5, 142.2, 150.4, 162.8.

2-Benzylbenzoxazole [5].

This compound was obtained as pale yellow oil; ^{1}H NMR ($CDCl_3$): δ 4.26 (s, 2H), 7.24-7.39 (m, 7H), 7.42-7.46 (m, 1H), 7.66-7.70 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 35.2, 110.4, 119.8, 124.1, 124.6, 127.3, 128.8, 128.9, 134.7, 141.3, 151.0, 165.1.

2-Propylbenzoxazole [5].

This compound was obtained as pale yellow oil; ^{1}H NMR ($CDCl_3$): δ 1.05 (t, J = 7.4 Hz, 3H), 1.89-1.95 (m, 2H), 2.91 (t, J = 7.4 Hz, 2H), 7.27-7.30 (m, 2H), 7.46-7.48 (m, 1H), 7.66-7.68 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 14.1, 20.6, 30.9, 110.6, 119.9, 124.4, 124.8, 141.8, 151.2, 167.6.

2-Phenyl-5-methylbenzoxazole.

This compound was obtained as white crystals, mp 101-102° (hexane) (lit [22] mp 102°); ^{1}H NMR ($CDCl_3$): δ 2.48 (s, 3H), 7.14-7.16 (m, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.49-7.53 (m, 3H), 7.55 (s, 1H), 8.21-8.26 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 21.5, 109.9, 119.9, 126.2, 127.3, 127.5, 128.9, 131.4, 134.4, 142.3, 149.0, 163.1.

2-Phenyl-5-chlorobenzoxazole.

This compound was obtained as white crystals, mp 102° (hexane) (lit [1] mp 101.1-102.1°); ^{1}H NMR ($CDCl_3$): δ 7.30 (dd, J = 8.5 and 2.0 Hz, 1H), 7.46-7.57 (m, 4H), 7.73 (d, J = 2.0 Hz, 1H), 8.20-8.23 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 111.3, 120.0, 125.3, 126.7, 127.7, 128.9, 130.0, 131.9, 143.2, 149.3, 164.3.

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