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A general synthesis of *N*-aryl- and *N*-alkyl-2-aminobenzoxazoles

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Abstract—An efficient and practical synthetic procedure is described for the preparation of a variety of *N*-substituted aryl- and alkyl-2-aminobenzoxazoles. This new method offers broad utility and provides desired products in good to excellent yield. The title compounds are formed in a one-pot, two step reaction sequence that is safe and operationally straightforward.

The 2-aminobenzoxazole moiety is a popular building block for the construction of phamaceutically interesting compounds. Numerous potential drug candidates containing a substituted *N*-aryl- or *N*-alkyl-2-aminobenzoxazole fragment have been or are currently under investigation for the treatment of a wide variety of disorders such as HIV, neurodegeneration and inflammatory diseases.[1]

While several methods exist for the synthesis of 2-aminobenzoxazoles, these procedures suffer from a number of disadvantages. For example, the 2-aminobenzoxazole fragment can be prepared via the reaction of an appropriately substituted 2-chlorobenzoxazole with an amine in the presence of base. However, the 2-chlorobenzoxazole portion may require preparation via an inconvenient multi-step procedure.[2] A more general method for the synthesis of the title compounds is through the cyclodesulfurization of *N*-substituted-2-hydroxy-phenylthioureas (Fig. 1). These thiourea intermediates are easily derived from the condensation of an appropriately substituted 2-aminophenol and any of a number of synthetically or commercially available alkyl- or arylisothiocyanates.[3,4]

Several cyclodesulfurization methods have appeared in the literature. Procedures, which incorporate metallic reagents such as HgO,[5] NiO_2[4] and $AgNO_3$[6] have been reported, but are undesirable for large-scale preparation due to the use of heavy metals in stoichiometric amounts. Oxidative cyclodesulfurization of a thiourea in the presence of KO_2 is precedented.[7] However, this reagent has been reported to catalyze detonation, specifically in the presence of 2-aminophenols and therefore is not an option.[8] Recently, salts of transition metals were applied for this transformation.[9] In many of the examples, the cyclodesulfurization required many days for complete reaction and chromatographic purification of desired compounds was necessary.

For our own investigations, we required substantial amounts of a variety of *N*-substituted alkyl- and; aryl-2-aminobenzoxazoles. Initially, we relied on the previously reported carbodiimide-mediated cyclodesulfurization of

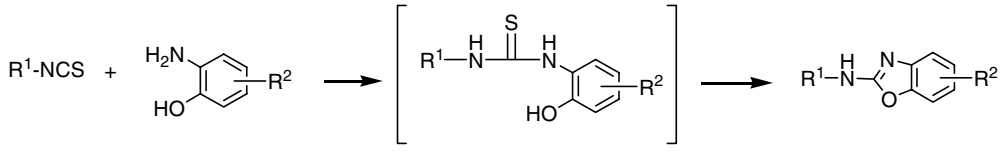

Figure 1. Formation of *N*-substituted-2-aminobenzoxazoles.

Keywords: Aminobenzoxazoles; Benzooxazolylamines.
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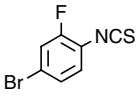
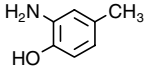
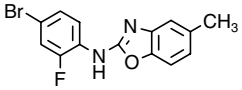
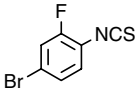
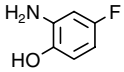
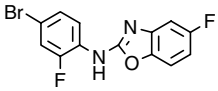
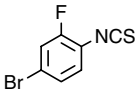
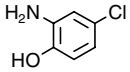
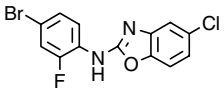
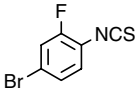
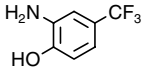
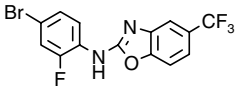
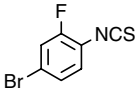
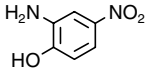
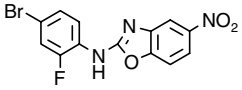
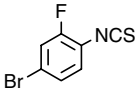
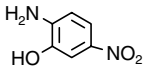
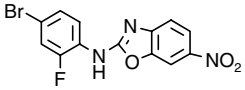
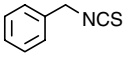
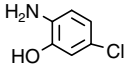
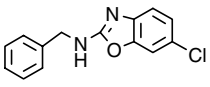
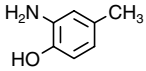
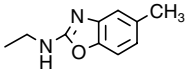
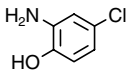
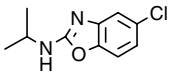
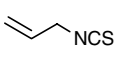
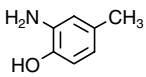
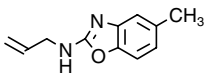
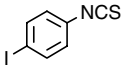
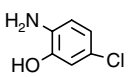
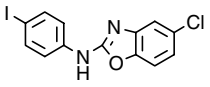
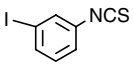
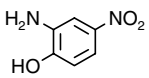
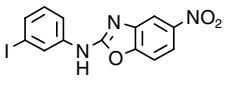
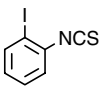
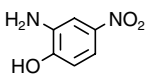
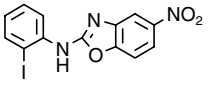
2-hydroxyphenylthioureas,[10] but discovered that the efficiency and overall yield of the transformation was dependent on the electronic nature of the substituents on the 2-aminophenol fragment.

In particular, when the aminophenol substituent R^2 was electron withdrawing, the cyclization of the corresponding thiourea afforded a lower yield of the desired product, due to the formation of impurities (see Table 1, entries 1[a]–4[a]). This procedure, therefore was considered to be unreliable for our purposes and we sought a more general, safe and robust method for the cyclodesulfurization.

Oxidative cyclodesulfurization of the thiourea intermediate with KO_2[7] was demonstrated to be successful in some of our examples, but the use of this reagent in the presence of 2-aminophenols is not recommended for safety reasons.[8] In consideration of the success of the KO_2 procedure, we reasoned that the basic nature of the reaction in conjunction with the oxidation of the sulfur facilitated the cyclization. Inspired by this pre-

Table 1. *N*-alkyl- or *N*-aryl-2-aminobenzoxazoles produced via the reaction in Figure 1

Entry	Isothiocyanate	Aminophenol	Product	Yield (%)
1				62[a], 89[b]
2				50[a], 92[b]
3				35[a], 90[b]
4				0[a], 88[b]
5				88[b]
6				87[b]
7				75[b]
8				89[b]
9				75[b]
10				85[b]
11				90[b]
12				82[b]
13				72[b]

[a] EDAC method.
[b] $LiOH/H_2O_2$ method.

sumption, we examined other basic/oxidative conditions and discovered that a mixture of aqueous hydrogen peroxide and LiOH mediated the oxidative cyclodesulfurization to cleanly and rapidly form desired *N*-alkyl- and *N*-aryl-2-aminobenzoxazoles in high yield.

The general utility of these new conditions (2.0 equiv of LiOH and 5.0 equiv of commercial 30% aqueous H_2O_2) versus the carbodiimide method was examined and the results are listed in Table 1. For example, *N*-aryl-(5-methyl-), (5-fluoro-), (5-chloro-) and (5-trifluoromethyl)-2-aminobenzoxazoles were prepared in 62%, 50%, 35% and 0% yields from their corresponding thioureas using 1-(3-dimethyl aminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC, entries 1(a)–4(a)). The yields of these compounds climbed to 89%, 92%, 90% and 88%, respectively, using $LiOH/H_2O_2$ for the cyclo desulfurization (entries 1(b)–4(b)). This method can also be used for the preparation of *N*-alkyl-2-aminobenzoxazoles, as in entries 7–10. The electronic nature of the isothiocyanate *N*-substituent appears to be independent on the success of the cyclization. However, the steric makeup of the isothiocyanate may affect a variation in the yield of desired cyclization products (entries 11–13). Additionally, positional substitution on the aminophenol portion poses insignificant effects on the efficiency of the cyclization (entries 5–6). In all cases, desired products were isolated in good yields by simple crystallization from acetonitrile. Higher isolated yields could be achieved in most cases by chromatographic purification.[11]

In conclusion, we have developed and demonstrated a simple, general and efficient one-pot method for synthesis of substituted *N*-alkyl- and *N*-aryl-2-aminobenzoxazoles from their corresponding isothiocyanates and 2-aminophenols. The utility of this procedure has been demonstrated by the preparation of a variety of aminobenzoxazoles from their corresponding isothiocyanates and 2-aminophenols on greater than a 100 g scale.

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11. Satisfactory spectral (^{1}H NMR, ^{13}C NMR, MS) and analytical data were obtained for all new compounds. General procedure: preparation of *N*-2-(2-fluoro-4-bromophenyl)-5-fluoro-1,3-benzoxazol-2-amine. 2-Amino-4-fluorophenol (64.4 g, 507 mmol, 1.15 equiv), 2-fluoro-4-bromophenyl isothiocyanate (102.3 g, 440.8 mmol, 1.0 equiv) and anhydrous THF (1.5 L) were combined and stirred at room temperature overnight. The resulting thiourea solution was cooled to −15 °C and solid lithium hydroxide monohydrate ($LiOH{\cdot}H_2O$, 37.0 g, 882 mmol, 2 equiv) was added in one portion. Aqueous hydrogen peroxide (30%, 264 mL, 2.2 mol, 5 equiv) was added dropwise, maintaining the internal temperature between 15 and 25 °C. The reaction mixture was stirred at ambient temperature until the thiourea was consumed. A solution of sodium sulfite (Na_2SO_3, 1 M) was added to the stirring reaction mixture slowly while keeping the temperature below 30 °C. The solution was checked for residual peroxide using 'Baker Testrips®'. The crude reaction was combined with water (1500 mL) and EtOAc (2000 mL). Layers were separated, and the organic layer was washed with water (4×400 mL) and brine (1×500 mL). The combined aq washes were back extracted with EtOAc (2 L). The combined organic extracts were concentrated under reduced pressure. To the residue obtained was added acetonitrile (250 mL), and the suspension was stirred for 30 min and left in refrigerator overnight. The resultant solid was collected and washed with hexanes (1×300 mL), dried under vacuum. Product obtained (131.5 g, 92% yield), mp 188–189 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.67 (s, 1H), 8.20 (t, $J = 8.8$ Hz, 1H), 7.63 (d, $J_1 = 10.7$, 1H), 7.52–7.46 (m, 2H), 7.31 (dd, $J_1 = 8.9$, $J_2 = 1.9$, 1H), 6.99–6.94 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.9 (C), 158.8 (C), 157.6 (C), 153.2 (C), 150.7 (C), 143.1 (C), 142.5 and 142.4 (C), 127.10 and 127.06 (CH), 125.5 and 125.4 (C), 122.4 (CH), 118.4 and 118.2 (CH), 114.0 and 113.9 (C), 109.1 and 109.0 (CH), 108.1 and 107.9 (CH), 103.5 and 103.3 (CH). HRMS: calcd for $C_{13}H_8BrF_2N_2O$: 324.9788, found 324.9803 (MH^+). Anal. Calc'd for $C_{13}H_7BrF_2N_2O$: C, 48.03; H, 2.17; Br, 24.58; F, 11.69; N, 8.62. Found: C, 47.83; H, 1.95; Br, 24.32; F, 11.80; N, 8.49.