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A Mild and Efficient One-Pot Synthesis of 2-Aminated Benzoxazoles and Benzothiazoles

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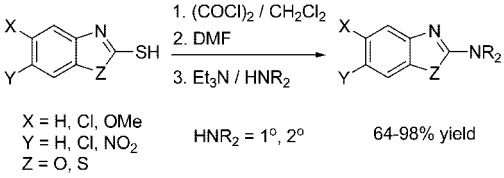

Previous syntheses of the biologically active 2-aminated benzoxazoles have relied on forcing thermal conditions to generate the products directly from the corresponding thiols. The resulting yields have ranged from moderate to poor. A mild and high-yielding alternative one-pot chlorination−amination procedure is described. Compounds with a variety of substitution patterns are reported and the methodology has been successfully extended to benzothiazoles. Palladium catalysis on suitably activated examples has been employed to generate the desired compounds of interest.

5-Hydroxytryptamine (**1**, serotonin, 5-HT, Figure 1) is an important compound that is involved in several biological pathways.[1] Selective 5-HT_3 receptor antagonists effectively prevent radiation- and chemotherapy-induced emesis.[2,3] They have also been used successfully as a novel therapeutic agents for diarrhea-predominant irritable bowel syndrome (IBS).[4] However, up to 30% of IBS patients have reported significant side effects. It has been proposed that 5-HT_3 receptor partial agonists may alleviate these side effects by the control of gastroenteric motility.[5−7] Benzoxazole derivatives with a nitrogen-containing heterocyclic substituent at the 2-position have been found to act as selective 5-HT_3 receptor partial agonists.[5−7] A facile and efficient synthesis of these compounds is therefore highly desirable. During the course of a recent project we became interested in the synthesis of such compounds. Herein we wish to report a mild and efficient one-pot synthesis of 2-aminated benzoxazoles and benzothiazoles. In addition, halogenated variants of these core motifs are shown to be excellent substrates for palladium-catalyzed reactions, allowing for the rapid construction of complex compounds.

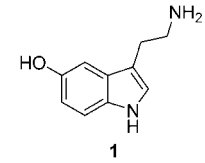

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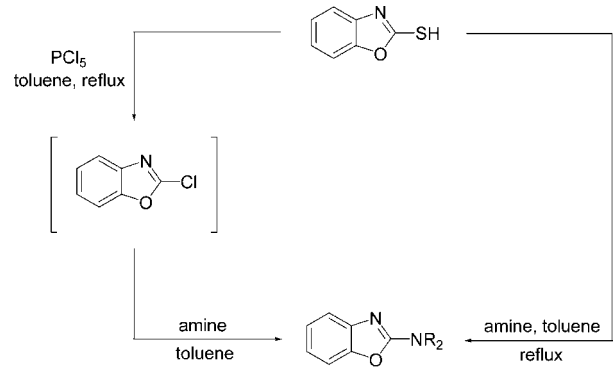
FIGURE 1. Serotonin (5-HT).

Existing methods toward 2-aminated benzoxazoles and benzothiazoles have involved nucleophilic displacement of the thiol moiety with an appropriate amine at elevated temperature (refluxing toluene, Scheme 1). We discounted this approach as the yields ranged from moderate to poor. Moreover, hydrogen sulfide is liberated, which is both highly toxic and flammable.

SCHEME 1. Typical Existing Literature Routes to 2-Aminated Benzoxazoles



A more indirect route to these compounds is preparation of the chloride followed by displacement with an amine to form the compounds of interest (Scheme 1). However, the literature examples with this strategy rely on the use of PCl_5 at elevated temperatures. These forcing conditions often necessitate that the chloride intermediate is isolated prior to the displacement reaction. Unfortunately, in many cases, these chlorides are unstable once isolated. We hypothesized that if it was possible to prepare this chloride using a milder set of reaction conditions, the amine could be added to the reaction mixture and potentially generate the desired product in a one-pot procedure.

After careful experimentation, we discovered that preparation of the Vilsmeier reagent in situ by addition of oxalyl chloride ($(COCl)_2$, 1.5 equiv) to a solution of 2-mercaptobenzoxazole in dichloromethane (CH_2Cl_2), followed by dropwise addition of *N*,*N*-dimethylformamide (DMF), led to complete conversion to the corresponding 2-chlorobenzoxazole within 1 h at room temperature. It is noteworthy that employing solely $(COCl)_2$ or thionyl chloride ($SOCl_2$) in the absence of DMF led to

(1) Kilpatrick, G. J.; Bunce, K. T.; Tyers, M. B. *Med. Res. Rev.* **1990**, *10*, 441–475, and references cited therein.
(2) Sanger, G. J.; Nelson, D. R. *Eur. J. Parmacol.* **1989**, *159*, 113–124.
(3) Butler, A.; Hill, J. M.; Ireland, S. J.; Jordan, C. C.; Tyers, M. B. *Br. J. Pharmacol.* **1988**, *94*, 397–412.
(4) Camilleri, M.; Northcutt, A. R.; Kong, S.; Dukes, G. E.; McSorley, D.; Mangel, A. W. *Lancet* **2000**, *355*, 1035–1040.
(5) Yasuo, S.; Megumi, Y.; Satoshi, Y.; Tomoko, S.; Midori, I.; Tetsutaro, N.; Kokichi, S.; Fukio, K. *J. Med. Chem.* **1998**, *41*, 3015–3021.
(6) Sato, Y.; Imai, M.; Amano, K.; Iwamatsu, K.; Konno, F.; Kurata, Y.; Sakakibara, S.; Hachisu, M.; Izumi, M.; Matski, X.; Saito, H. *Biol. Pharm. Bull.* **1997**, *20*, 752–755.
(7) Yoshida, S.; Shiokawa, S.; Kawano, K.; Ito, T.; Murakami, H.; Suzuki, H.; Sato, Y. *J. Med. Chem.* **2005**, *48*, 7075–7079.

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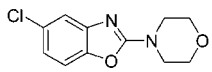
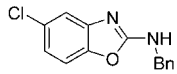
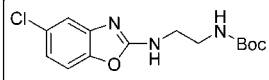
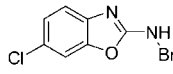
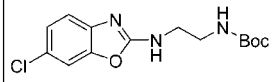
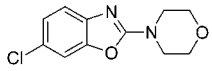
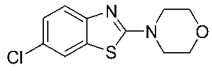
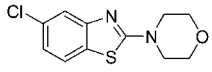
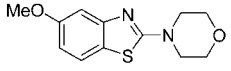
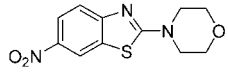
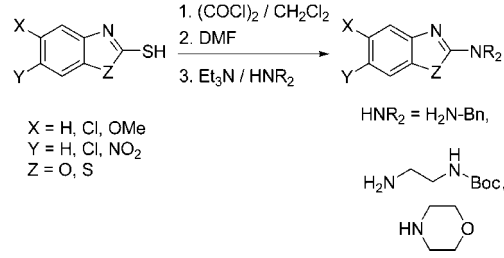
TABLE 1. Substituted Benzoxazoles/Benzothiazoles

Entry	Product	Assay Yield (%)[a]
1		77
2		64
3		82
4		76
5		67
6		88
7		75
8		69
9		68
10		98

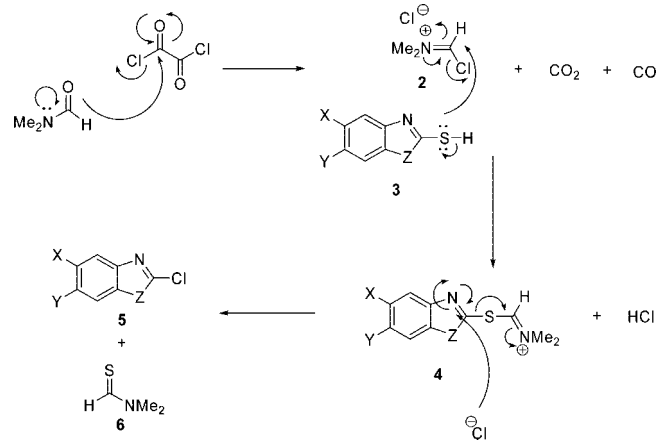
[a] Analytical samples were obtained by chromatography and/or recrystallization.

unsuccessful reactions. Likewise, a combination of $SOCl_2$ and DMF also gave disappointing results at room temperature. The order of addition of the reagents was found to be critical to the success of the reaction. If the $(COCl)_2$ was added to a mixture of the 2-mercaptobenzoxazole in CH_2Cl_2/DMF, incomplete reactions were observed which were attributed to the poor mobility of the reaction mixture (viscous slurries were formed). Attempts to reinitiate stalled reaction streams were unsuccessful. However, if the DMF was added last, the chlorination was complete within 1 h at room temperature. It was necessary to maintain a reaction temperature of less than 25 °C during the addition of DMF to avoid generating the corresponding 2-dimethylamino derivative (decomposition of DMF generates dimethylamine).[8] After complete chlorination, the reaction mixture was then treated with triethylamine (3 equiv) and a primary or secondary amine (1.2 equiv). Temperature control was also found to be important during the addition of triethylamine to avoid formation of the corresponding diethylamino derivative.[10]

SCHEME 2. Chlorination/Amination of Substituted Benzoxazoles/Benzothiazoles



SCHEME 3. Proposed Mechanism



Bearing these important points in mind, stirring this reaction mixture for 2 h led to complete amination at the 2-position. The reaction was found to be general for a number of substituted benzoxazoles and benzothiazoles with selected primary (Table 1, entries 2, 3, 4, and 5) and secondary amines (Table 1, entries 1, 6, 7, 8, 9, and 10) affording aminated products in good to excellent yields (Scheme 2, Table 1).

The proposed mechanism for chloride formation (Scheme 3) involves the generation of Vilsmeier reagent **2** that then reacts with the thiol **3** to give the activated sulfide **4**. Breakdown of **4** leads to the chlorinated product **5** with concomitant formation of *N*,*N*-dimethylthioformamide **6**, which is observed as a byproduct in the final reaction mixture.

With the mild one-pot chlorination/amination in hand attention was turned to further elaboration of the heterocyclic core. We surmised that the substituted benzoxazoles and benzothiazoles bearing an aryl halide could be aminated under conditions developed by Buchwald (Scheme 4).[11] Applying these conditions to our system and using XPhos as the ligand of choice, both the 5- and 6-chloro compounds were found to generate the desired coupled product in excellent yields (Table 2). In addition, both primary and secondary amines were found to be well tolerated in this reaction.

Finally, these halides were also found to be amenable to Suzuki couplings. Treatment of 5-chlorobenzoxazole **7** with pyridine-3-boronic acid **8** gave access to cross-coupled product **9** in 65% yield under standard conditions[12] (Scheme 5).

In summary, we have developed a mild and high-yielding one-pot chlorination/amination of substituted 2-mercaptobenzoxazoles and benzothiazoles. This method obviates the need

(8) Sharpe, C. J.; Palmer, P. J.; Evans, D. E.; Brown, G. R.; King, G.; Shadbolt, R. S.; Trigg, R. B.; Ward, R. J. *J. Med. Chem.* **1972**, *15*, 523–529.
(9) Sato, Y.; Yamada, M.; Yoshida, S.; Soneda, T.; Ishikawa, M.; Nizato, T.; Suzuki, K.; Konno, F. *J. Med. Chem.* **1998**, *41*, 3015–3021.
(10) Advani, S. P.; Sam, J. *J. Pharm. Sci.* **1968**, 1693–1696.
(11) Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7*, 3965–3968.
(12) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358–3366.

SCHEME 4. Amination of Aryl Halides

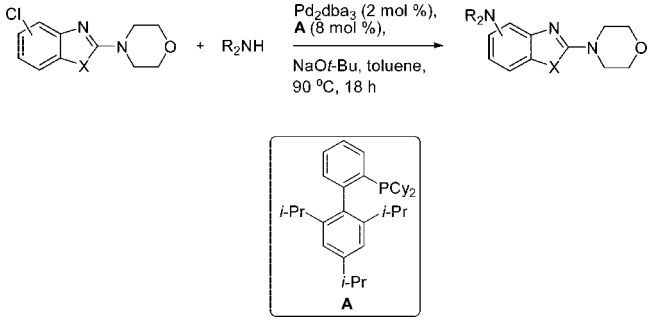
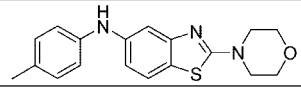
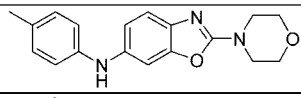
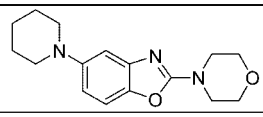
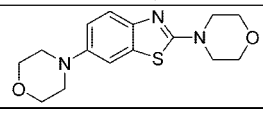
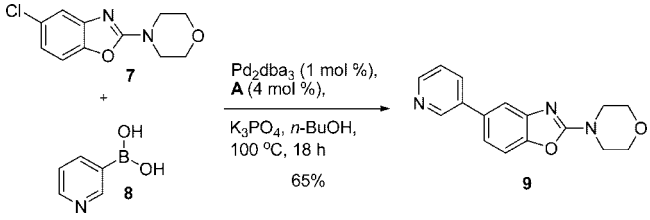


TABLE 2. Aminated Benzoxazoles/Benzothiazoles

Entry	Product	Yield (%)
1		85
2		74
3		83
4		83

SCHEME 5. Suzuki coupling



for forcing conditions and/or the isolation of the unstable chloride intermediates. Products bearing an aryl halide can be further elaborated by using palladium-mediated reactions to generate compounds of biological interest in a short and efficient manner.

Experimental Section

5-Chloro-2-morpholin-4-yl-1,3-benzoxazole (Table 1, Entry 1). To a mixture of 5-chloro-2-mercaptobenzoxazole (564 mg, 3.04 mmol) in dichloromethane (5 mL) was added oxalyl chloride (0.40 mL, 4.56 mmol). The reaction was cooled to 0 °C and *N*,*N*-dimethylformamide (2 mL) was added dropwise at 0−5 °C. The reaction was warmed to 20 °C, aged for 1 h, then recooled to 0 °C. Triethylamine (1.27 mL, 9.12 mmol) was added dropwise at 0−10 °C followed by morpholine (0.29 mL, 3.34 mmol). The reaction was warmed to 20 °C and aged for 1 h. The reaction was diluted with water (5 mL) and dichloromethane (5 mL). The phases were separated and the aqueous layer was extracted with dichloromethane (5 mL). The combined organics assayed for 560 mg of the title compound (77%). A pure analytical sample was obtained by recrystallization from acetonitrile/water. Mp 109−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.32 (1 H, d, J = 2.0 Hz), 7.17 (1 H, d, J = 8.6 Hz), 7.01 (1 H, dd, J = 2.0, 8.6 Hz), 3.83 (4 H, m), 3.70 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 162.8, 147.4, 144.3, 129.4, 120.7, 116.6, 109.3, 66.1, 45.6; HRMS (ESI+) calcd for $C_{11}H_{11}ClN_2O_2$ 239.0587, found 239.0595.

General Procedure 1 for the Pd-Catalyzed Amination of Benzoxazoles and Benzothiazoles. To a flask containing a magnetic stir bar was added the aryl halide, sodium *tert*-butoxide, $Pd_2dba_3 \cdot CHCl_3$, ligand **A**, and amine in cases where this was solid. The flask was evacuated and backfilled with nitrogen twice. The amine was added with a syringe in cases where this was liquid followed by toluene. The flask was evacuated and backfilled with nitrogen twice, then heated to 90 °C for 16 h. The reaction mixture was cooled to room temperature, then purified by silica gel chromatography (100% hexane to 80% ethyl acetate in hexane) to provide the products.

(2-Morpholin-4-yl-benzothiazol-5-yl)-*p*-tolylamine (Table 2, Entry 1). Following general procedure 1, 5-chloro-2-morpholin-4-yl-benzothiazole (70 mg, 0.28 mmol), 4-methylaniline (35 mg, 0.33 mmol), sodium *tert*-butoxide (37 mg, 0.39 mmol), $Pd_2dba_3 \cdot CHCl_3$ (5.0 mg, 0.0055 mmol, 2 mol %), ligand **A** (10.5 mg, 0.0220 mmol, 8 mol %), and toluene (2 mL) were stirred at 90 °C for 16 h. After silica gel chromatography the title compound was isolated as a pale brown solid (75.4 mg, 85%). Mp 163−168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.43 (1H, d, J = 8.4 Hz), 7.29−7.26 (1H, m), 7.07 (2H, d, J = 8.4 Hz), 7.01 (2H, d, J = 8.4 Hz), 6.79 (1H, dd, J = 8.4, 2.0 Hz), 5.67 (1H, br s), 3.84−3.80 (4H, m), 3.62−3.58 (4H, m), 2.30 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.1, 153.9, 143.1, 140.7, 130.8, 130.0, 122.1, 121.2, 118.8, 112.9, 107.8, 66.4, 48.5, 20.8; HRMS (ESI+) calcd for $C_{18}H_{19}N_3OS$ 326.1327, found 326.1313.

2-Morpholin-4-yl-5-pyridin-3-yl-benzoxazole (9). To a flask containing a magnetic stir bar was added the 5-chloro-2-morpholin-4-ylbenzoxazole (50 mg, 0.21 mmol), pyridine-3-boronic acid (39 mg, 0.31 mmol), potassium phosphate tribasic (89 mg, 0.42 mmol), $Pd_2dba_3 \cdot CHCl_3$ (1.9 mg, 0.0021 mmol, 1 mol %), and ligand **A** (4.0 mg, 0.0084 mmol, 4 mol %). The flask was evacuated and backfilled with nitrogen twice. *n*-Butanol (2 mL) was added then flask was evacuated and backfilled with nitrogen twice and then heated to 100 °C for 18 h. The reaction mixture was cooled to room temperature, then filtered through a pad of Celite, eluting with EtOAc. The solution was concentrated, then purified by silica gel chromatography (100% hexane to 80% ethyl acetate in hexane) to provide the title compound as a white solid (38.5 mg, 65%). Mp 150−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.85 (1H, d, J = 1.6 Hz), 8.57 (1H, dd, J = 4.8, 1.2 Hz), 7.87 (1H, dt, J = 7.6, 1.6 Hz), 7.56 (1H, d, J = 1.6 Hz), 7.38−7.34 (2H, m), 7.25 (1H, dd, J = 8.0, 1.6 Hz), 3.86−3.82 (4H, m), 3.74−3.71 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 162.8, 149.2, 147.7, 147.4, 144.1, 137.6, 135.4, 134.1, 124.0, 120.4, 115.3, 109.4, 66.3, 45.9; HRMS (ESI+) calcd for $C_{16}H_{15}N_3O_2$ 282.1243, found 282.1238.

Acknowledgment. We thank Simon Hamilton and Alexia Bertrand for mass spectrometry work.

Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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