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A method for the synthesis of 2-aminobenzoxazoles

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ABSTRACT

A synthesis of 2-aminobenzoxazoles from the parent C–H compound is described. The procedure involves deprotonation at the 2-position of the benzoxazole and quenching the intermediate organolithium species with a halogen electrophile. The 2-halobenzoxazole is then treated in the same pot with an amine nucleophile to afford the desired product. The substrate scope and selectivity of the reaction are presented. The method is operationally simple and provides access to a variety of amine products bearing additional nucleophilic heteroatoms.

Introduction

The 2-aminobenzoxazole subunit is found in a number of therapeutically important molecules.[1] As such, methods which allow rapid access to a range of compounds containing this key structural feature are of broad importance. Three general approaches are most frequently used to construct the 2-aminobenzoxaole array: (a) reaction between an aminophenol and a C(*IV*) electrophile;[2] (b) oxidative coupling between a benzoxazole and an amine;[3] (c) formation of a 2-halogenated benzoxazole and subsequent amine displacement.[4]

The merit of these methods is without debate however each suffers from certain drawbacks inherent to the specific system. In the reaction of aminophenols, the electrophile must often be generated in a parallel step, and amines bearing pendant nucleophiles may not readily form the type of reactive electrophiles required. Oxidative C–N bond formation is arguably the most direct approach, but the scope of this transformation remains limited, particularly in the coupling primary amines. Amine displacement from a 2-halogenated precursor is attractive, but formation of the 2-halobenzoxazole can be tedious and require multiple operations.

Despite the drawbacks mentioned above, we were drawn to the halide displacement method, particularly in the light of the reliability with which this approach allows the coupling of primary amines bearing additional heteroatoms. Generation of the 2-halo precursor is generally accomplished through the reaction of a 2-mercaptobenzoxazole with S(*IV*) or P(*V*) (oxy)chlorides.[5] Byproducts generated in the chlorination step often necessitate workup of the reaction prior to amine addition, resulting in a negative environmental impact and increased time cycle for the overall transformation. An alternative method which complements the nucleophilic introduction of the halide would be metalation of the C–H benzoxazole followed by quenching with an electrophilic halogenating agent.[6,7] The latter approach has not been rigorously evaluated in the context of 2-aminobenzoxazole formation,[8] and may provide a more streamlined synthesis of these valuable structures. This study describes our efforts to use electrophilic halogenation of benzoxazoles as part of a practical synthesis of 2-aminobenzoxazoles.

Results and discussion

Optimization experiments were carried out with 5-chlorobenzoxazole and *N*-Boc-ethylenediamine (Table 1). Evaluation of the base demonstrated that lithium hexamethyldisilazide led to the highest conversion (entries 1–4). Of the electrophilic halogen sources examined higher conversions were observed for iodinating or brominating versus chlorinating agents (cf. entries 1, 7 and 9). Elemental bromine efficiently quenched the lithium anion, but led to increased levels of uncharacterized decomposition products (entry 8). Employing NBS led to a small amount of unreacted starting material (entry 9), but refinement around the reagent charges and order of addition improved the conversion and resulted in a high yield for the amination reaction (entry 10). The amination requires no exogenous base, as lithium succinimide generated in the bromination is well suited to act as a general base for the amine addition. Ultimately the amination process requires two

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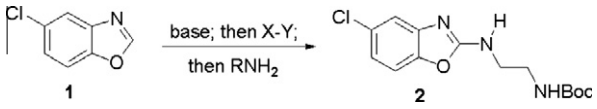
Table 1
Reaction optimization



Entry	Base	X–Y	**2**[a] (%)	**1**[a] (%)
1	LHMDS	NCS	77	18
2	NHMDS	NCS	58	18
3	KHMDS	NCS	59	21
4	$LiNH_2$	NCS	nd	89
5	LHMDS	DCDMH	48	16
6	LHMDS	TCICA	15	14
7[b]	LHMDS	I_2	85	nd
8[c]	LHMDS	Br_2	89	nd
9	LHMDS	NBS	86	6
10[d]	LHMDS	NBS	93	nd

General conditions: 1.25 equiv base, 10 vol THF, −20 °C; then 1.20 equiv X–Y and warm to rt; then 1.20 equiv amine. Notes:
[a] Starting material and product amounts were determined by quantitative HPLC.
[b] Amine addition run with 1.2 equiv TEA at 60 °C.
[c] Amine addition run with 1.2 equiv TEA.
[d] 1.5 equiv base, 14 vol THF, 1.5 equiv NBS, 1.6 equiv amine and inverse addition of anion to NBS slurry. *Abbreviations*: DCDMH, 1,3-dichloro-5,5-dimethylhydantoin; TCICA, trichloroisocyanuric acid; nd, not detected.

vessels and is comprised of three distinct chemical steps: lithiation with LHMDS, bromination with NBS and amine displacement of the 2-bromo compound.

The optimized conditions were then used to evaluate the substrate scope of the benzoxazole component with ethanolamine as the nucleophile (Table 2). The reaction performed well for a variety of 5-substituted benzoxazoles, regardless of the electronic nature of the substituent (entries 1–5). Substitution at the 4- and 6-position was also well tolerated (entries 6 and 7). One limitation of the methodology was established in the reaction of a fused aromatic substrate (entry 8). Competing halogenation of the aromatic C–H bond adjacent to oxygen was observed leading to a mixture of amine products. This observation can be rationalized in the light of the known propensity of 2-lithiated benzoxazoles to exist in equilibrium with the ring opened 2-(isocyano)phenolate.[6b] Halogenation of the ring is therefore not unexpected, but what is perhaps more interesting is why this pathway should predominate in the fused aromatic case. Interestingly, changing the position of the ring fusion restored the selectivity for bromination at the benzoxazole 2-position (entry 9).

Variation of the amine component was also evaluated. The primary goal was to establish the selectivity for primary amine alkylation in nucleophiles bearing additional heteroatoms (Fig. 1). No selectivity in the alkylation reaction was observed between primary and *N*-alkyl amines. Additionally, discrimination between primary linear and branched amines proved challenging. Good selectivity was seen for alkylation of a primary amine in the presence of an aniline, phenol, and alcohol.

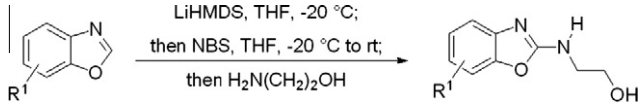
Conclusion

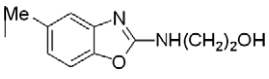
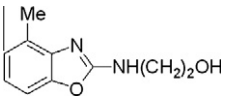
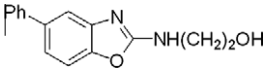
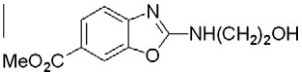
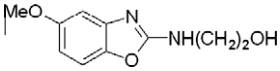
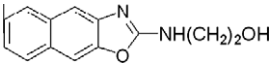
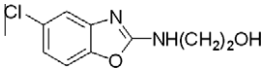
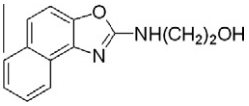
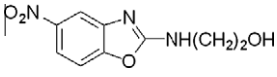
In conclusion a practical method has been developed to 2-aminobenzoxazoles via a 2-halobenzoxazole generated by electrophilic bromination. The chemistry is operationally simple requiring three separate reagent charges and two vessels to obtain the 2-aminobenzoxazole from the parent C–H compound without any intermediate isolations. This method should find utility in the preparation of benzoxazole structures which bear multiple nucleophilic sites on the amine component.

Experimental

A 500 mL 3-neck round bottom flask equipped with a septum, thermocouple, 125 mL addition funnel, inert gas inlet and magnetic stir bar was purged with nitrogen for 10 min. Hexamethyldisilazane (42 mL, 0.20 mol) and THF (78 mL) were charged against positive nitrogen pressure. The addition funnel was charged with a hexane solution of *n*-butyllithium (78.0 mL, 195 mmol). The amine solution was cooled to −52 °C and *n*-butyllithium was added over 84 min, resulting in a temperature increase to 12.5 °C over the course of the addition. The resulting lithium

Table 2
Benzoxazole substrate scope



Entry	Product	#	Yield[a] (%)	Entry	Product	#	Yield[a] (%)
1		3	80	6		7	85
2		4	71	7		8	80
3		5	84	8		9	21
4		2	84	9		10	65
5		6	84				

General conditions: 1.2 equiv LHMDS (1 M THF solution), 1.22 equiv NBS, 1.4 equiv ethanolamine, final 0.3 M starting material concentration in THF. Notes:
[a] Yields are of isolated material after silica gel chromatography.

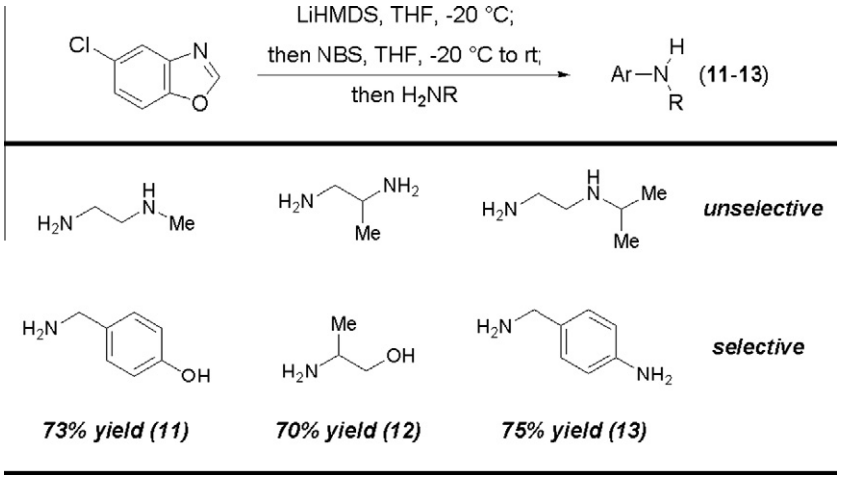


Figure 1. Selectivity of primary amine nucleophiles. General conditions: 1.2 equiv LHMDS (1 M THF solution), 1.22 equiv NBS, 1.4 equiv amine, final 0.3 M starting material concentration in THF. Notes: yields are of isolated material after silica gel chromatography.

hexamethyldisilazide solution was removed from the cooling bath and aged for 30 min.

To a 500 mL 3-neck round bottom flask equipped with a septum, thermocouple, inert gas inlet and magnetic stir bar was charged 5-chlorobenzoxazole (20.00 g, 130 mmol). The gray solid was dissolved in THF (100 mL) and the resulting colorless solution was cooled to −25 °C. The freshly prepared lithium hexamethyldisilazide solution was added via cannula over 80 min. The temperature of the anion solution was maintained between −25 and −15 °C during the addition. The resulting dark brown solution was aged for 90 min between −25 and −15 °C.

To a 1000 mL 3-neck round bottom flask equipped with a Claisen adapter, septum, thermocouple, inert gas inlet, stir shaft bearing, and blade was charged THF (100 mL) and *N*-bromosuccinimide (34.8 g, 195 mmol). The resulting slurry was cooled to −20 °C and the anion solution was added via cannula over 150 min. During the addition the anion solution and reaction mixture were maintained between −25 and −15 °C. The resulting brown slurry was removed from the cooling bath and aged for 50 min while warming to room temperature.

To the resulting bromide slurry was added a solution of ethanolamine (12.6 mL, 208 mmol) in MeCN (38 mL) via syringe pump over 5 h. During the addition the reaction temperature was maintained between 20 and 27 °C. The resulting brown slurry was aged at room temperature overnight.

The reaction mixture was cooled in an ice water bath and the septum replaced with a 50 mL addition funnel charged with concentrated HCl (32 mL, 390 mmol). The acid solution was added over 10 min, during which time the temperature increased from 10 to 20 °C. The reaction mixture was removed from the ice water bath and aged for 5 min. Charged 20 wt % aqueous K_2HPO_4 (170 mL) and the resulting biphasic mixture was transferred to a separatory funnel. The flask was washed with THF (3×, 10 mL) and the washings were added. The aqueous phase was cut. The organic phase was washed with 20 wt % aqueous K_2HPO_4 (200 mL), separated and analyzed. The crude reaction stream had a total mass of 396.47 g. By quantitative HPLC assayed 25.81 g of **2** in the organic phase, 93% assay yield, 92.74 LC peak area percent at 210 nm.

Pure **2** was obtained on a small (1 g) scale by silica gel chromatography (3:1 to 1:3 hexanes/EtOAc eluent). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.17 (t, J = 5.6 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.25 (d, J = 1.8 Hz, 1H), 6.97 (dd, J = 8.4, 1.8 Hz, 1H), 4.81 (t, J = 5.4 Hz, 1H), 3.56 (q, J = 5.7 Hz, 2H), 3.35 ppm (q, J = 5.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.5, 146.8, 145.0, 127.7, 119.5, 115.0, 109.4, 59.3, 45.0 ppm.

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