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An efficient potassium cyanide-promoted synthesis of 2-arylbenzoxazoles from [4.3.0]boron heterobicycles

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ABSTRACT

The 2-arylbenzoxazoles **3a–f** were produced in moderate to excellent yields merely by stirring a potassium cyanide (3 equiv)-containing methanol solution of the borobicyclic compounds **1a–f** at room temperature. These compounds were fully characterized spectroscopically [IR, ^{1}H, and ^{13}C NMR and X-ray analysis (**3a**)] and by elemental analysis.

There has been a recent surge in the development of new benzoxazole syntheses because of their occurrence in a number of natural products[1], and their potential use as cytotoxic agents[2], cathepsin S inhibitors[3], HIV reverse transcriptase inhibitors[4], estrogen receptor agonists[5], selective peroxisome proliferator-activated receptor antagonists[6], anticancer agents[7], and orexin-1 receptor antagonists.[8] They have also found application as herbicides and as fluorescent-whitening agent dyes.[9] The methods which have been used to provide access to benzoxazoles include (a) conventional thermal- or microwave-accelerated condensation of 2-aminophenols with carboxylic acid derivatives under strongly acidic conditions,[10] (b) metal-catalyzed cyclization of 2-halo *N*-acylanilines,[11] and (c) oxidative cyclization of the Schiff bases derived from 2-aminophenols and aldehydes using oxidants such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[12] $PhI(OAc)_2$,[13] NiO_2,[14] $Ba(MnO_4)_2$,[15] pyridinium chlorochromate (PCC),[16] $Mn(OAc)_3$,[17] PbO_2,[18] $Pb(OAc)_4$,[19] $ThClO_4$,[20] and $Pd(OAc)_2$[21] (Fig. 1). In addition, oxidative cyclization conditions considerably milder than those referred above have been described for the generation of benzoxaxoles from the Schiff bases derived from 2-aminophenols.[22] Herein, we describe an exceptionally mild method of generating benzoxazoles from the boron-containing heterocyclic systems **1a–f**.

In continuation of our recent studies involving the boron complexes derived from Schiff bases,[23,24] we reacted a methanolic solution of the very readily available[23–26] boron-containing heterocyclic compound **1a** (see Scheme 1 for synthesis) with excess potassium cyanide at room temperature, with the expectation of obtaining the tetracyclic nitrile **2a** (Scheme 1). The only compound isolated, however, from the reaction mixture was the 2-arylbenzoxazole derivative **3a** (61 % yield). The 2-arylbenzoxazoles **3b–f** were similarly obtained from compounds **1b–f** (See Scheme 2). The structures of the benzoxazole derivatives were unequivocally

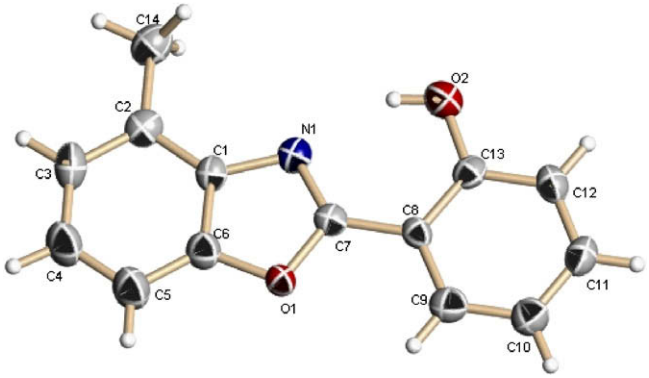

Figure 1. X-ray structure of **3a**.

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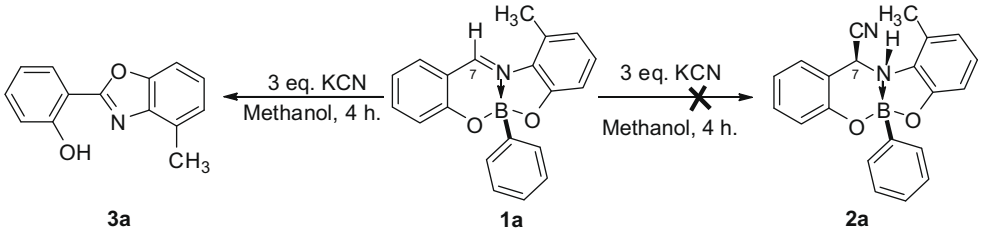
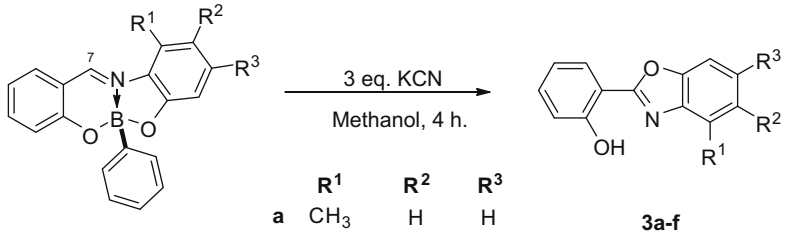


Scheme 1.



	R^1	R^2	R^3
a	CH_3	H	H
b	H	Cl	H
c	H	*t*-Bu	H
d	H	CH_3	H
e	H	H	H
f	H	H	NO_2

Scheme 2.

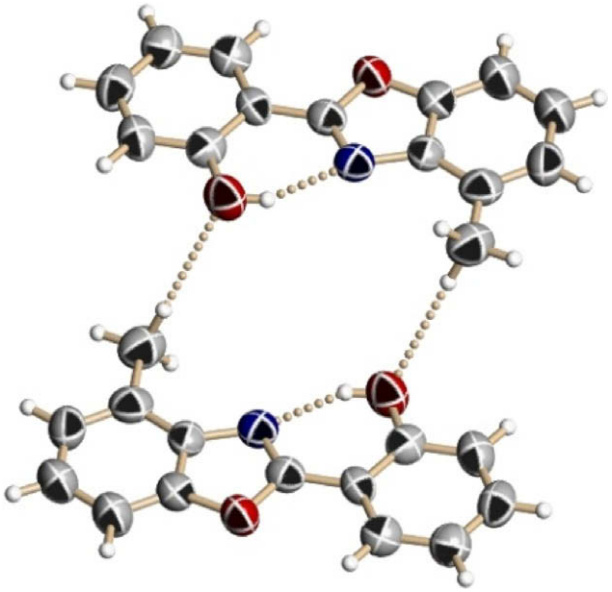


Figure 2. Dimeric structure for **3a** formed by intermolecular hydrogen bonding.

established by the usual spectroscopic means[27], as well as by an X-ray crystal structure for compound **3a** (Fig. 2, vide infra).[28] Thus, the ^{1}H NMR spectra of these compounds did not possess signals for H-7 (8.29–8.46, see Scheme 1), but did show a low field absorption at δ 11.2–11.58 typical of an H-bonded hydroxyl group (to the C=N moiety; see also Fig. 2 below). In addition, the IR spectra showed absorption bands at 1631–1627 cm^{-1} (C=N) and 1591–1557 cm^{-1} (O–C=N moiety) which are characteristic of the five-membered ring of benzoxazoles. Furthermore, the Raman spectrum of compound **3e** shows bands expected for both the C=N (1630 cm^{-1}) and O–C=N (1551 cm^{-1}) groups.

A crystal suitable for X-ray diffraction was obtained for compound **3a** and the molecular structure is shown in Figure 2.[28] The existence of an intramolecular hydrogen bond between the phenolic OH group and benzoxazole N-atom is consistent with the observed N–HO(2) distance (2.66 Å) and the N–H-(O2) angle (147.7°). The molecular packing reveals that interaction present at the oxygen (O2) and hydrogen atoms (CH_3) forms a dimeric structure in the solid state (Fig. 2). The H_3C-(O2) intermolecular distance is 3.625 Å and the C(14)–H-(O2) angle is 172.8°, characteristic of a weak intermolecular bond.

In conclusion, an efficient method for the synthesis of 2-arylbenzoxazoles has been developed from the [4.3.0] boron heterobicyclic compounds **1a**–**f** containing a dative N–B bond. This unprecedented reaction occurs rapidly at room temperature. Compounds **3a**–**f** were fully characterized by ^{1}H and ^{13}C NMR spectroscopy and by X-ray analysis for **3a**.

Acknowledgments

We are indebted to Dr. Joseph M. Muchowski for friendly, helpful discussions and to CONACyT for financial support (Grant J49336-Q).

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27. *General procedure*: In a 100 mL round-bottomed flask containing a magnetic stirring bar was placed 1 equiv of (**1a**–**f**) in 45 mL of methanol, and 3 equiv of potassium cyanide was added. The resulting solution was stirred at room temperature for 4 h and the solvent was removed in vacuo. The crude product was purified by crystallization from methanol at 0 °C. The yields are those of pure compounds. Compound **3a**: mp 113–114 °C as a brown solid [lit.[29] 102 °C] (yield: 0.22 g, 61%) IR (KBr): ν_{max} 3753, 2958, 1627, 1591, 1547, 751, 714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.58 (s, 1H, OH), 7.99 (dd, 1H, J = 7.6 Hz, J = 1.4 Hz, H-3), 7.42 (t, 1H, J = 6.5 Hz, H-5), 7.40 (d, 1H, J = 7.7 Hz, H-5′), 7.24 (t, 1H, J = 7.7 Hz, H-6′), 7.15 (d, 1H, J = 7.3 Hz, H-7′), 7.12 (d, 1H, J = 8.4 Hz, H-6), 6.99 (t, 1H, J = 7.5 Hz, H-4), 2.61 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2 (C-2′), 158.6 (C-1), 148.8 (C-7a), 139.3 (C-3a), 133.4 (C-5), 129.8 (C-4′), 127.0 (C-3), 125.5 (C-7′), 125.1 (C-6′), 119.5 (C-4), 117.3 (C-6), 110.7 (C-2), 107.9 (C-5′), 16.5 (CH_3) ppm. Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.57; H, 4.91; N, 6.48%. For **3b**: mp 146–147 °C as a purple solid [lit.[29] 140 °C] (yield: 0.25 g, 69%) IR (KBr): ν_{max} 3649, 3153, 1628, 1588, 1541, 1254, 855, 805, 755, 708 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$): δ 11.19 (s, 1H, OH), 7.95 (dd, 1H, J = 7.8 Hz, J = 1.6 Hz, H-3), 7.66 (d, 1H, J = 1.8 Hz, H-4′), 7.48 (d, 1H, J = 8.8 Hz, H-7′), 7.43 (ddd, 1H, J = 8.4 Hz, J = 6.9 Hz, J = 1.4 Hz, H-5), 7.31 (dd, 1H, J = 8.5 Hz, J = 2.0 Hz, H-6′), 7.09 (dd, 1H, J = 8.4 Hz, J = 0.7 Hz, H-6), 6.98 (td, 1H, J = 7.5 Hz, J = 1.0 Hz, H-4) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2 (C-2′), 158.9 (C-1), 147.7 (C-7a), 141.1 (C-3a), 134.0 (C-5), 130.5 (C-5′), 127.2 (C-3), 125.6 (C-6′), 119.7 (C-4), 119.2 (C-4′), 117.6 (C-6), 111.3 (C-7′), 110.1 (C-2) ppm. Anal. Calcd for $C_{13}H_8ClNO_2$: C, 63.56; H, 3.28; N, 5.70. Found: C, 62.75; H, 3.11; N, 5.41%. For **3c**: mp 263–265 °C as a yellow solid (yield: 0.25 g, 67%) IR (KBr): ν_{max} 3740, 2962, 2869, 1627, 1557, 1378, 830, 704 cm^{-1}; Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 77.00; H, 6.04; N, 5.33%. Due to insolubility in $CDCl_3$, DMSO-d_6, acetone-d_6 etc., it was impossible to obtain NMR data. For **3d**: mp 136–137 °C as a orange solid [lit.[30] 128 °C] (yield: 0.25 g, 71%) IR (KBr): ν_{max} 3648, 2966, 1631, 1590, 1543, 1256, 800, 755, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.52 (s, 1H, OH), 7.98 (dd, 1H, J = 7.8 Hz, J = 1.6 Hz, H-3), 7.48 (d, 1H, J = 0.7 Hz, H-4′), 7.44 (d, 1H, J = 8.4 Hz, H-6′), 7.42 (dd, 1H, J = 7.3 Hz, J = 1.4 Hz, H-5), 7.15 (d, 1H, J = 7.6 Hz, H-7′), 7.11 (d, 1H, J = 8.4 Hz, H-6), 6.99 (td, 1H, J = 8.0 Hz, J = 1.8 Hz, H-4), 2.47 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0 (C-2′), 158.7 (C-1), 147.4 (C-7a), 140.2 (C-3a), 134.9 (C-5′), 133.4 (C-5), 127.0 (C-3), 126.5 (C-7′), 119.5 (C-4), 119.2 (C-6′), 117.4 (C-6), 110.7 (C-2), 110.0 (C-4′), 21.5 (CH_3) ppm. Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.88; H, 4.79; N, 6.35 %. For **3e**: mp 125–126 °C as a pink solid [lit.[30] 122–124 °C] (yield: 0.21 g, 61%) IR (KBr): ν_{max} 3527, 3029, 1630, 1587, 1487, 1259, 741, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.48 (s, 1H, OH), 8.01 (dd, 1H, J = 7.8 Hz, J = 1.6 Hz, H-3), 7.72–7.70 (m, 1H, H-5′), 7.60–7.57 (m, 1H, H-6′), 7.43 (td, 1H, J = 8.0 Hz, J = 1.4 Hz, H-5), 7.38–7.35 (m, 2H, H-10, H-4′), 7.12 (d, 1H, J = 8.4 Hz, H-6), 7.0 (td, 1H, J = 7.6 Hz, J = 0.9 Hz, H-4) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9 (C-2′), 158.8 (C-1), 149.1 (C-7a), 140.0 (C-3a), 133.6 (C-5), 127.1 (C-3), 125.4 (C-7′), 125.0 (C-4′), 119.6 (C-4), 119.3 (C-5′), 117.4 (C-6), 110.7 (C-6′), 110.6 (C-2) ppm. Anal. Calcd for $C_{13}H_9NO_2$: C, 73.92; H, 4.29; N, 6.63. Found: C, 73.76; H, 4.21; N, 6.39%. For **3f**: mp 186–189 °C as a yellow solid (yield: 0.34 g, 94%) IR (KBr): ν_{max} 3736, 3112, 1589, 1542, 757, 706, 546 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.87 (s, 1H, OH), 8.70 (d, 1H, J = 2.4 Hz, H-7′), 8.32 (dd, 1H, J = 2.4 Hz, J = 8.7 Hz, H-5′), 8.04–8.00 (m, 2H, H-4′ y H-3), 7.57 (t, 1H, J = 6.8 Hz, H-5), 7.14 (d, 1H, J = 8.2 Hz, H-6), 7.10 (t, 1H, J = 8.3 Hz, H-4) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0 (C-2′), 158.7 (C-1), 149.0 (C-7a), 145.9 (C-3a), 145.4 (C-6′), 135.5 (C-5), 129.2 (C-4′), 121.6 (C-5′), 120.6 (C-4), 119.9 (C-3), 118.0 (C-6), 110.8 (C-2), 108.0 (C-7′). Anal. Calcd for $C_{13}H_8N_2O_4$: C, 60.94; H, 3.15; N, 10.93. Found: C, 60.84; H, 1.04; N, 10.81%.
28. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as a Supplementary Publication Numbers, CCDC 713665 No. for **3a** Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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