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Synthesis of a novel pyrrolo-benzoxaborole scaffold and its derivatization *via* Friedel–Crafts reaction catalyzed by anhydrous stannic chloride

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Abstract

A novel pyrrolo-benzoxaborole, 6-(pyrrol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, was synthesized with 27% overall yield over six steps from 2-bromo-1-methyl-4-nitrobenzene as starting material. Its derivatization was achieved *via* Friedel–Crafts reaction catalyzed by anhydrous stannic chloride with various acyl chlorides giving 3-acyl-1-phenylpyrroles as the main products.

Keywords: Benzoxaborole; Friedel–Crafts reaction; Stannic chloride; 3-Acyl-1-arylpyrrole

Benzoxaboroles have recently been drawing attention due to their newly discovered application as clinically useful agents [1]. For example, 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (AN2690, Fig. 1) exhibited excellent antifungal activity by inhibiting leucyl-tRNA synthetase (LeuRS). The boron atom of AN2690 is critical for the activity by forming a tetrahedral covalent adduct with the terminal *cis*-diol on tRNA [2]. Recently, 5-aryloxybenzoxaboroles **1** (Fig. 1) are reported to show good potency against phosphodiesterase 4 which is a therapeutic target for the treatment of inflammation such as asthma and chronic obstructive pulmonary disease [3]. Although benzoxaboroles have attracted great attention in medicinal chemistry, the reports about their synthetic methodologies are limited [4,5]. Considering the excellent biological profile of substituted benzoxaboroles and their increasing importance in pharmaceutical and biological research [4,6], we are urged to develop a convenient and versatile synthesis of novel benzoxaborole scaffolds.

We report here the design and synthesis of 6-(pyrrol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole **8**, a medicinally useful scaffold, for the first time with 27% overall yield over six steps from the commercially available 2-bromo-1-methyl-4-nitrobenzene **2**. Subsequent acylation of compound **8** catalyzed by Lewis acids was investigated. It was demonstrated that the benzoxaborole functionality well tolerated the reaction condition, and $SnCl_4$ was proved to be a more effective catalyst than $AlCl_3$ to give both 2′- and 3′-regioisomers in sufficient yields.

The retrosynthetic analysis of compound **8** showed that 2-bromo-1-methyl-4-nitrobenzene **2** can be utilized as starting material which was easily converted to methyl 4-amino-2-bromobenzoate **5**, the precursor of cyclization.

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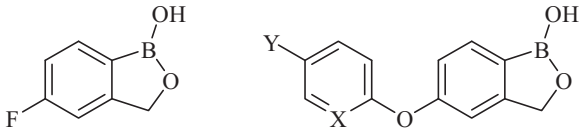
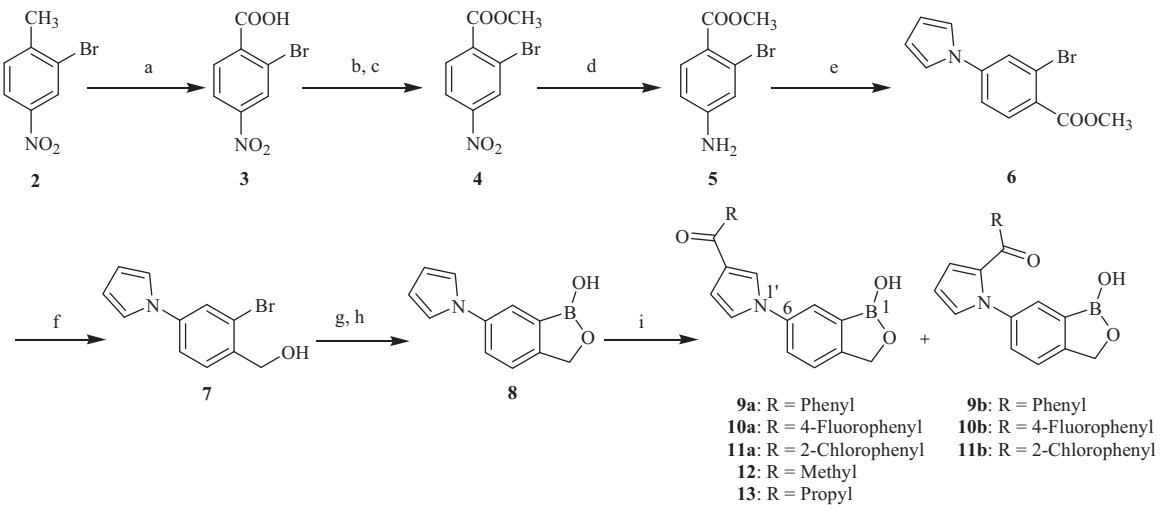


Fig. 1. Structures of AN2690 and 5-aryloxybenzoxaboroles **1**.

After the pyrrol-1-yl benzene **6** was formed by means of the Paal–Knorr reaction, the boron atom was introduced utilizing *n*-BuLi/B(i-PrO)$_3$. Subsequent intramolecular esterification of ortho-(hydroxymethyl)phenylboronic acid completed the construction of benzoxaborole skeleton **8** [4,6,7–12].

The synthetic route is outlined in Scheme 1. First, the oxidation of 2-bromo-1-methyl-4-nitrobenzene **2** with $KMnO_4$ in a mixture of pyridine and water gave acid **3** in 68% yield. Acid **3** was refluxed in thionyl chloride to give corresponding acyl chloride, which was then converted to methyl ester **4** *in situ* in dry methanol in the presence of triethylamine with 95% yield over two steps. Reduction of methyl 2-bromo-4-nitrobenzoate **4** by tin dichloride dihydrate gave amine **5** in 94% yield. Subsequent condensation of amine **5** with 2,5-dimethoxytetrahydrofuran formed pyrrol-1-ylbenzene derivative **6** with 84% yield. Reduction of ester **6** provided the benzyl alcohol **7**. To avoid involving expensive palladium catalyst, boronylation was carried out using *n*-Butyl lithium/B(*i*-PrO)$_3$ method. Subsequent hydrolysis and spontaneous cyclization in the presence of 2 mol/L HCl gave the desired scaffold 6-(pyrrol-1-yl)-benzoxaborole **8**.

Next, derivatization of compound **8** was established by the Lewis acid-catalyzed acylation of pyrrole ring. It was reported that reaction of 1-phenylpyrroles with an excess of acid anhydride catalyzed by orthophosphoric acid can give 3-acyl-1-arylpyrroles [13]. AlC1$_3$-catalyzed acylation reactions of 1-substituted pyrrole were also reported to give 3-acyl derivatives regioselectively [14]. To avoid the opening of the oxaborole ring in the presence of orthophosphoric acid, the former methodology was not employed in this case. Thus, we tried to complete the acylation of compound **8** using two Lewis acids with strong to weak Friedel–Crafts activity, *i.e.* $AlCl_3$ and $SnCl_4$, as catalysts [15]. Although both Lewis acids gave 3-acylpyrroles as main products, the reactions catalyzed by $AlCl_3$ are more complex than those catalyzed by $SnCl_4$. TLC observation of the reactions showed complex products in the case of AlC1$_3$-catalyzed



Scheme 1. Reagents and conditions: (a) $KMnO_4$, pyridine, H_2O, reflux, 12 h (68%); (b) $SOCl_2$, reflux, 6 h; (c) CH_3OH, triethylamine, 1 h (95% for two steps); (d) $SnCl_2{\cdot}2H_2O$, ethyl acetate, reflux, 1 h (94%); (e) 2, 5-dimethoxytetrahydrofuran, AcOH, reflux, 30 min (84%); (f) $LiBH_4$, THF, CH_3OH, 0 °C, 12 h (93%); (g) *n*-BuLi, (*i*-PrO)$_3$B, THF, −80 °C, 12 h; (h) 2 mol/L HCl (57% for two steps); (i) acyl chloride, $SnCl_4$, CH_2Cl_2, 12 h, (**9a**: 23%; **9b**: 12%; **10a**: 22%; **10b**: 5%; **11a**: 18%; **11b**: 7%; **12**: 28%; **13**: 38%).

reaction whereas only two main components were observed in the case of $SnC1_4$-catalyzed reactions. We reasoned that $AlCl_3$, a strong Lewis acid in terms of Friedel–Crafts activity, may have led to low substrate selectivity and side reactions such as the acylation of the benzene ring [15]. Eventually, $SnCl_4$ was employed as the catalyst for the acylation. The acetylation and butyrylation of compound **8** provided 3′-acyl product **12**, **13** and trace amount of 2′-acyl product, while various benzoylations provided 2′-acyl products **9b–11b** as well as 3′-acyl products **9a–11a** with separable yields. In the case of benzoyl chloride and 2-chlorobenzoyl chloride, the ratio of 3′- to 2′-acyl selectivity was approximately 2:1 (**9a**:**9b**, **11a**:**11b**). However, 4-fluorobenzoyl chloride gave an increased ratio of 5:1 (**10a**:**10b**). The 3′-substitution pattern of **9a–11a**, **12** and **13** are consistent with the presence of 4′-H NMR signals at 6.6–6.9 ppm (dd, J = 1–2, 2–3.2 Hz) resulting from the coupling with 2′-H and 5′-H. On the other hand, the structures of 2-acylpyrroles **9b–11b** corroborate with the 4′-H signals at 6.3–6.4 ppm (dd, J = 2.8, 3.6–4.0 Hz) arising from the coupling with two neighboring protons, 3′-H and 5′-H.

In summary, we successfully synthesized 6-(pyrrol-1-yl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole **8** with a 27% overall yield from commercially available 2-bromo-1-methyl-4-nitrobenzene **2** over 6 steps. To demonstrate the versatile application of 6-(pyrrol-1-yl)-benzoxaborole **8**, we investigated the acylation reactions on the pyrrole ring using different Lewis acids, and obtained derivatives **9a–13** [16] with various acyl substituents at 2′- or 3′-position. In light of the medicinal significance of benzoxaboroles, we believe the efficient synthesis of this new scaffold will facilitate its further application in new drug discovery.

Acknowledgments

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References

[1] D.G. Hall, Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine, Wiley-VCH, Weinheim, Germany, 2005.
[2] (a) F.L. Rock, W. Mao, A. Yaremchuk, et al. Science 316 (2007) 759;
(b) S.J. Baker, Y.K. Zhang, T. Akama, et al. J. Med. Chem. 49 (2006) 4447.
[3] Y.K. Zhang, J.J. Plattner, A. Tsutomu, et al. Bioorg. Med. Chem. Lett. 20 (2010) 2270.
[4] L. Ye, D.Z. Ding, Y.Q. Feng, et al. Tetrahedron 65 (2009) 8738.
[5] D.S. Gunasekera, D.J. Gerold, N.S. Aalderks, et al. Tetrahedron 63 (2007) 9401.
[6] D.Z. Ding, Y.X. Zhao, Q.Q. Meng, et al. ACS Med. Chem. Lett. 1 (2010) 165.
[7] K. Torssell, Ark. Kemi 10 (1957) 507.
[8] R.T. Hawkins, W.J. Lennarz, H.R. Snyder, J. Am. Chem. Soc. 82 (1960) 3053.
[9] J. Lennarz, R. Snyder, J. Am. Chem. Soc. 82 (1960) 2172.
[10] P. Tschampel, H.R. Snyder, J. Org. Chem. 29 (1964) 2168.
[11] V.V. Zhdankin, P.J. Persichini III, L. Zhang, et al. Tetrahedron Lett. 40 (1999) 6705.
[12] Y.L. Tan, A.J.P. White, D.A. Widdowson, et al. J. Chem. Soc. Perkin Trans. 1 (2001) 3269.
[13] G.N. Dorofeenko, A.P. Kucherenko, N. V. Prokaf'eva, Zh. Org. Khim 33 (1963) 586.
[14] (a) N. Ioannis, Z. Chariklia, J.D. Vassilis, J. Med. Chem. 47 (2004) 2706;
(b) M. Kakushima, P. Hamel, R. Frenette, et al. J. Org. Chem. 48 (1983) 3214.
[15] (a) G.A. Olah, S. Kobayashi, M. Tashiro, J. Am. Chem. Soc. 94 (1972) 7448;
(b) S. Kobayashi, T. Busujima, S. Nagayama, Chem. Eur. J. 6 (2000) 3491.
[16] Analytic data for compound **8–13**. Compound **8**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.27 (s, 1H), 7.79 (d, 1H, J = 2.4 Hz), 7.65 (dd, 1H, J = 8 and 2.4 Hz), 7.47 (d, 1H, J = 8 Hz), 7.29 (dd, 2H, J = 2.4 and 2 Hz), 6.25 (dd, 2H, J = 2.4 and 2 Hz) and 5.03 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 140.4, 124.4, 124.1, 122.2, 120.4, 111.9, 70.9; mp: 120–122 °C. Compound **9a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.87 (s, 1H), 7.80 (d, 1H, J = 1.6 Hz), 7.62 (m, 1H), 7.50 (m, 5H), 7.11 (dd, 1H, J = 2.8 and 2.4 Hz), 6.88 (dd, 1H, J = 2.8 and 1.6 Hz), 5.53 (s, 1H) and 5.15 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1, 152.7, 139.8, 139.3, 131.8, 129.1, 128.5, 126.6, 126.4, 124.4, 123.2, 122.6, 121.6, 112.7, 71.1; HRMS (ESI): $[M+H]^+$ calcd. for $C_{18}H_{15}BNO_3$ 304.1145, found 304.1143; mp: 148–151 °C. Compound **9b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.62 (s, 1H), 7.56 (m, 2H), 7.41 (m, 4H), 7.08 (m, 1H), 6.90 (m, 1H), 6.38 (dd, 1H, J = 3.6 and 2.8 Hz) and 5.03 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.1, 153.1, 140.0, 139.1, 132.2, 131.6, 131.3, 129.7, 128.8, 128.3, 127.4, 123.8, 121.8, 109.7, 71.2; HRMS (ESI): $[M+H]^+$ calcd. for $C_{18}H_{15}BNO_3$ 304.1145, found 304.1152; mp: 120–124 °C. Compound **10a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, 1H, J = 8.4 Hz), 7.92 (d, 1H, J = 8.4 Hz), 7.82 (d, 1H, J = 1.6 Hz), 7.63 (t, 1H, J = 2.0 Hz), 7.55 (dd, 1H, J = 8.4 and 2 Hz), 7.46 (d, 1H, J = 8 Hz), 7.18 (d, 1H, J = 8.4 Hz), 7.15 (d, 1H, J = 8.4 Hz), 7.12 (dd, 1H, J = 3.2 and 2.0 Hz), 6.86 (dd, 1H, J = 3.2 and 1.6 Hz) and 5.16 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 187.6, 164.0 (d, J = 250 Hz), 152.3, 138.1, 135.7 (d, J = 3 Hz), 131.3 (d, J = 9 Hz), 126.1, 125.0,

123.6, 122.7, 122.1, 121.8, 115.3 (d, J = 22 Hz), 111.6, 69.7; HRMS (ESI): $[M+H]^+$ calcd. for $C_{18}H_{14}BFNO_3$ 322.1051, found 322.1059; mp: 160–162 °C. Compound **10b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, 1H, J = 8.4 Hz), 7.88 (d, 1H, J = 8.4 Hz), 7.62 (s, 1H), 7.42 (dd, 1H, J = 8 and 1.6 Hz), 7.39 (d, 1H, J = 8 Hz), 7.12 (m, 3H), 6.87 (dd, 1H, J = 4.0 and 1.2 Hz), 6.35 (dd, 1H, J = 3.6 and 2.8 Hz) and 5.16 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.6, 165.3 (d, J = 250 Hz), 153.2, 140.0, 135.3 (d, J = 3 Hz), 132.1 (d, J = 9 Hz), 131.6, 131.1, 128.8, 127.3, 123.5, 121.9, 115.4 (d, J = 22 Hz), 109.7, 71.2; HRMS (ESI): $[M+H]^+$ calcd. for $C_{18}H_{14}BFNO_3$ 322.1051, found 322.1051; mp: 114–117 °C. Compound **11a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, 1H, J = 1.6 Hz), 7.50 (dd, 1H, J = 8.4 and 2.4 Hz), 7.45 (m, 6H), 7.09 (m, 1H), 6.81 (dd, 1H, J = 2.8 and 1.6 Hz) 5.42 (s, 1H) and 5.13 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 188.1, 152.5, 139.5, 137.9, 131.0, 129.9, 129.6, 128.7, 127.1, 126.9, 126.2, 123.7, 122.8, 122.6, 122.2, 110.8, 69.8; HRMS (ESI): $[M+H]^+$ calcd. for $C_{18}H_{14}BClNO_3$ 338.0755, found 338.0757; mp: 165–168 °C. Compound **11b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, 1H, J = 1.2 Hz), 7.50, (dd, 1H, J = 8 and 2.0 Hz), 7.39 (m, 5H), 7.09 (dd, 1H, J = 2 and 2.8 Hz), 6.66 (dd, 1H, J = 4.0 and 1.6 Hz), 6.35 (dd, 1H, J = 4.0 and 2.8 Hz), 5.45 (s, 1H) and 5.14 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 182.1, 153.0, 138.9, 138.8, 133.3, 131.1, 130.6, 130.0, 129.6, 129.0, 128.4, 127.2, 126.8, 124.1, 121.7, 110.1, 69.8; HRMS (ESI): $[M+H]^+$ $C_{18}H_{14}BClNO_3$ calcd. 338.0755, found 338.0757; mp: 131–135 °C. Compound **12**: ^{1}H NMR (400 MHz, CD_3OD): δ 8.00 (t, 1H, J = 2 Hz), 7.79 (d, 1H, J = 1.6 Hz), 7.67 (dd, 1H, J = 8.4 and 1.6 Hz), 7.53 (d, 1H, J = 8.4 Hz), 7.26 (dd, 1H, J = 3.2 and 2 Hz), 6.75 (dd, 1H, J = 3.2 and 1.6 Hz), 5.14 (s, 2H) and 2.47 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 192.3, 152.1, 138.2, 127.2, 125.1, 123.3, 122.7, 121.9, 121.5, 109.8, 69.7, 27.0; HRMS (ESI): $[M+H]^+$ calcd. for $C_{13}H_{13}BNO_3$ 242.0988, found 242.0990; mp: 189–191 °C. Compound **13**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.30 (s, 1H), 8.16 (m, 1H), 7.91 (d, 1H, J = 2.1 Hz), 7.78 (dd, 1H, J = 8.4 and 2.1 Hz), 7.53 (d, 1H, J = 8.4 Hz), 7.40 (m, 1H), 6.66 (dd, 1H, J = 3 and 1.5 Hz), 5.05 (s, 2H), 2.78 (t, 2H, J = 7.2 Hz), 1.61 (m, 2H) and 0.93 (t, 3H, J = 7.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 195.4, 152.6, 138.8, 127.5, 125.1, 123.8, 123.2, 122.4, 122.0, 110.4, 70.3, 41.1, 18.4, 14.3; HRMS (ESI): $[M+H]^+$ calcd. for $C_{15}H_{17}BNO_3$ 270.1301, found 270.1303; mp: 122–124 °C.