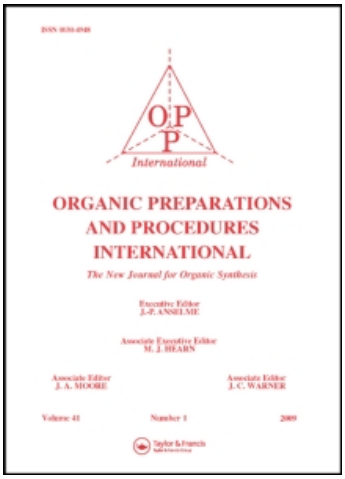

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FACILE SYNTHESIS OF 5-(DIHYDROXYBORYL)-2,4-*bis*(ALKOXY)PYRIMIDINES AND N(1)-SUBSTITUTED 5-(DIHYDROXYBORYL)URACILS

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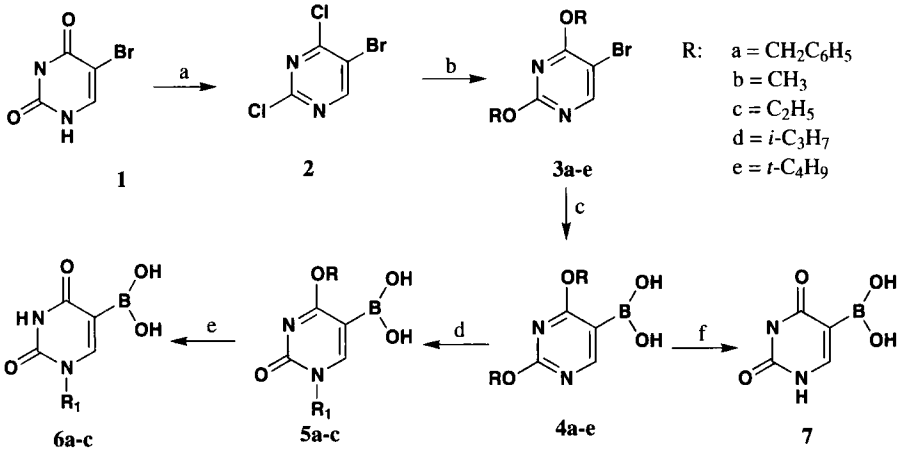
Recently there has been increased interest in the preparation of boron compounds because of their potential medical and biochemical applications,[1,2] such as their possible use in cancer therapy based on the phenomenon of boron neutron capture (BNCT).[3,4] During the last decade, considerable attention has been focused on the synthesis of boron containing pyrimidines and base-modified or sugar-modified nucleosides and oligonucleotides.[5-7] Interest in the boronic acid group stems from the fact that this functionality has been incorporated in many diverse structures, which has resulted in a range of biological activities.[8,9] The search for improved syntheses of boronic acid derivatives of pyrimidines is still in progress, for example, by palladium-catalyzed coupling reactions of halogenated nucleosides with aryltin compounds having a dihydroxyboryl substituent,[10] by reaction of carbanions with trialkyl borates[11-13] or by reaction of pyrimidines with 4-bromobutylboronic acid.[14] Nevertheless, recent interest in organoboron chemistry has been directed to the use of boron pyrimidines as a synthetic tool.[15] The procedure for the synthesis of 5-(dihydroxyboryl)pyrimidines gave the desired products in low yields and isolation of these products as cyclic iminodiethanol derivatives gave only moderate yields.[12-13] This paper describes a facile synthesis of 5-(dihydroxyboryl)-2,4-*bis*(alkoxy)pyrimidines in high yields. These compounds are easily converted to N(1)-alkyl-5-(dihydroxyboryl)uracils as shown below.

The alternative methods[16-17] for the preparation of N(1)-substituted uracils from 5-(dihydroxyboryl)uracil have been unsuccessful as the carbon-boron bond appears to be unstable under the conditions used in these reactions. Great caution has to be taken in the conversion of commercially available 5-bromouracil (**1**) to 5-bromo-2,4-dichloropyrimidine (**2**),[18] since **2** is highly allergenic. Treatment of **2** with sodium alkoxide afforded the corresponding 5-bromo-2,4-*bis*(alkoxy)pyrimidines (**3a-e**). Lithium-halogen exchange in THF at -80° followed by boronation at -100° and hydrolysis gave the desired products **4a-e** in excellent yields. The success of this approach is dependent on the hydrophobic properties of 5-(dihydroxyboryl)-2,4-*bis*(alkoxy)pyrimidines and the ease of isolation. Nearly quantitative yields were achieved for compounds with bulky alkyl groups. The subsequent Hilbert-Johnson reaction with methyl iodide,[19] ethyl iodide and benzyl bromide allowed us to



a) $POCl_3$, 110° b) RONa c) 1. n-BuLi, -80°, 2. $B(OC_2H_5)_3$, -100°, 3. 0.25M HCl.
d) $C_6H_5CH_2Br$, 25° for **4a**, CH_3I, 25° for **4b**, C_2H_5I, 25° for **4c** e) Pd/H_2 for **5a**, $AlBr_3$ for **5b,c**
f) 1M HCl for **4e**

introduce an alkyl group at the N(1) position of **5a-c**. Finally, deprotection afforded the N(1)-substituted-5-(dihydroxyboryl)uracils (**6a-c**). Unfortunately, the *t*-butoxy protecting group is so readily hydrolyzed that the reaction of **4e** with methyl iodide led to a mixture of N(1), N(3) and N(1)-N(3) alkylated products. The dealkylation of 5-(dihydroxyboryl)-2,4-*bis*(*t*-butoxy)pyrimidine under acidic conditions gives 5-(dihydroxyboryl)uracil (**7**) in high yield.

EXPERIMENTAL SECTION

Melting points are uncorrected. All ^{1}H-NMR spectra were recorded at 300 MHz in DMSO-d_6 with TMS as an internal reference. Mass spectra were obtained under electron impact conditions.

Synthesis of 5-(Dihydroxyboryl)-2,4-*bis*(alkoxy)pyrimidines (4a-e). Preparation of Compounds 3a-e.- Compounds **3a**[12], **3b,c**[20] and **3e**[21] were prepared by treatment of **2** with an alkoxide and purified as described. Compound **3d**, mp. 46-48° was synthesized (75% yield) in a similar manner. ^{1}H NMR: δ 1.31 and 1.33 (2d, 12, $C(CH_3)_2$), 5.10 and 5.12 (2h, 2, CH), 8.45 (s, 1, 6-H).

Anal. Calcd for $C_{10}H_{15}BrN_2O_2$: C, 43.65; H, 5.49; N, 10.18. Found: C, 43.83; H, 5.59; N, 10.29

Preparation of Compounds 4a-e.- A solution of 6 mmoles of **3a-e** in 40 mL of dry, freshly distilled THF was cooled to -80° (liquid N_2 / hexane) under a nitrogen atmosphere. Over the course of 5 min, 4.33 mL (6.9 mmoles) of 1.6 M solution of *n*-butyllithium in hexane was injected through a septum at such a rate that the internal temperature did not exceed -70°. After stirring for an additional 5 min, 1.32 mL (7.5 mmoles) of triethyl borate was injected into the yellow solution at -100°. The mixture was allowed to warm to room temperature over a period of 2 h and then concentrated to near dryness under reduced pressure. The residue was dissolved in 20 mL of H_2O, the solution was filtered and acidified to pH 3.5-3.0 with 0.25M HCl. Only in the case of compound **4e** was the hydrolysis carried

out under weakly alkaline conditions. Under acidic conditions, the hydrolysis of **4e** gives compound **7** in nearly quantitative yield. Compounds **4c-e** precipitated from the colorless aqueous solution. They were collected and washed with a few portions of H_2O. The filtrate was neutralized with saturated solution of $NaHCO_3$ to give a second crop of precipitate. Compounds **4a,b** were extracted into methylene chloride and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure furnish an oily residue. In the case of **4b**, the oil was dissolved in a mixture of hexane and methylene chloride (4:1) and was left at about -70° for 1h. The white fine precipitate formed was collected and washed with hexane. In the case of **4a**, the oil was dissolved in a small amount of methanol and poured into 400 mL of H_2O. After one day, a pure white precipitate formed was collected. Analytically pure samples were obtained by crystallization from ethanol or ethanol/H_2O mixture. The crystals were dried under reduced pressure at 56° and characterized.

Compound **4a**, mp. 99-101°, lit.[12] mp. 99-102°, 62% yield. ^{1}H NMR: δ 5.40 and 5.44 (2s, 4, CH_2), 7.61 (m, 10, C_6H_5), 7.92 (s, 2, $B(OH)_2$), 8.46 (s, 1, 6-H); MS, *m/e* 292 (M^+- HBO_2); UV (C_2H_5OH) λ_{max} 280 nm, ε_{max} 5300.

Anal. Calcd for $C_{18}H_{17}BN_2O_4$: C, 64.31; H, 5.10; N, 8.33. Found: C, 64.29; H, 5.13; N, 8.26

Compound **4b**, mp. 113-115°, 81% yield. ^{1}H NMR: δ 3.89 and 3.90 (2s, 6, CH_3), 7.90 (s, 2, $B(OH)_2$), 8.42 (s, 1, 6-H); MS, *m/e* 140 (M^+- HBO_2); UV (C_2H_5OH) λ_{max} 261 nm, ε_{max} 5200.

Anal. Calcd for $C_6H_9BN_2O_4$: C, 39.17; H, 4.93; N, 15.23. Found: C, 38.96; H, 4.86; N, 15.11

Compound **4c**, mp. 111-113°, 89% yield. ^{1}H NMR: δ 1.32 and 1.33 (2t, 6, CH_3), 4.33 and 4.37 (2q, 4, CH_2), 7.81 (s, 2, $B(OH)_2$), 8.40 (s, 1, 6-H); MS, *m/e* 212 (M^+); UV (C_2H_5OH) λ_{max} 262 nm, ε_{max} 6600.

Anal. Calcd for $C_8H_{13}BN_2O_4$: C, 45.32; H, 6.18; N, 13.21. Found: C, 45.13; H, 6.02; N, 13.16

Compound **4d**, mp. 119-121°, 95% yield. ^{1}H NMR: δ 1.31 and 1.33 (2d, 12, $C(CH_3)_2$), 5.19 and 5.30 (2h, 2, CH), 7.69 (s, 2, $B(OH)_2$), 8.40 (s, 1, 6-H); MS, *m/e* 240 (M^+); UV (C_2H_5OH) λ_{max} 263 nm, ε_{max} 6700.

Anal. Calcd for $C_{10}H_{17}BN_2O_4$: C, 50.03; H, 7.14; N, 11.67. Found: C, 50.20; H, 6.92; N, 11.57

Compound **4e** is without a sharp melting point, undergoing slow decomposition, 91% yield. ^{1}H NMR: δ 1.56 and 1.59 (2s, 18, $C(CH_3)_3$), 7.62 (s, 2, $B(OH)_2$), 8.35 (s, 1, 6-H); MS, *m/e* 268 (M^+); UV (C_2H_5OH) λ_{max} 263 nm, ε_{max} 6800.

Anal. Calcd for $C_{12}H_{21}BN_2O_4$: C, 53.76; H, 7.90; N, 10.45. Found: C, 53.59; H, 7.78; N, 10.21

Synthesis of N(1)-alkyl-5-dihydroxyboryluracils (6a-c). Preparation of Compounds 5a-c.- To a solution of 0.55 g (3 mmoles) of 5-(dihydroxyboryl)-2,4-*bis*(methoxy)pyrimidine (**4b**) in 3 mL of methylene chloride was added 3 mL of freshly distilled methyl iodide. The mixture was stirred for 2 days at a room temperature. Then 100 mL of hexane was added and the crystalline white precipitate of **5b** was collected. It was twice reprecipitated with hexane from methylene chloride. 5-(Dihydroxyboryl)-2,4-*bis*(ethoxy)-pyrimidine (**4c**) was allowed to react with 10 molar excess of ethyl iodide to give **5c** in a manner analogous to that for **5b** over the period of 28 days. 5-(Dihydroxyboryl)-2,4-*bis*(benzoxy)pyrimidine (**4a**) was reacted with 5 molar excess of benzyl bromide to give **5a** over the period of 2 days.

Compound **5a**, mp. 133-135°, 69% yield. ^{1}H NMR: δ 5.05 and 5.36 (2s, 4, CH_2), 7.54 (m, 10, C_6H_5), 7.78 (s, 2, $B(OH)_2$), 8.25 (s, 1, 6-H); MS, *m/e* 292 (M^+- HBO_2); UV (C_2H_5OH) λ_{max} 281 nm, ε_{max} 6300.
Anal. Calcd for $C_{18}H_{17}BN_2O_4$: C, 64.31; H, 5.10; N, 8.33. Found: C, 64.12; H, 4.98; N, 8.14.
Compound **5b**, mp. 116-118°, 91% yield. ^{1}H NMR: δ 3.37 and 3.82 (2s, 6, CH_3), 7.69 (s, 2, $B(OH)_2$), 8.11 (s, 1, 6-H); MS, *m/e* 140 (M^+- HBO_2); UV (C_2H_5OH) λ_{max} 277 nm, ε_{max} 4900.
Anal. Calcd for $C_6H_9BN_2O_4$: C, 39.17; H, 4.93; N, 15.23. Found: C, 39.03; H, 4.83; N, 15.01
Compound **5c**, mp. 113-114°, 82% yield. ^{1}H NMR: δ 1.18 and 1.30 (2t, 6, CH_3), 3.82 and 4.31 (2q, 4, CH_2), 7.63 (s, 2, $B(OH)_2$), 8.10 (s, 1, 6-H); MS, *m/e* 212 (M^+); UV (C_2H_5OH) λ_{max} 279 nm, ε_{max} 5400.
Anal. Calcd for $C_8H_{13}BN_2O_4$: C, 45.32; H, 6.18; N, 13.21. Found: C, 45.16; H, 6.03; N, 12.99

Preparation of Compounds 6a-c.- To a solution of 0.67 g (2 mmole) of **5a** in 60 mL of dry ethanol was added 100 mg of 10% palladium on a charcoal and the compound was hydrogenated at room temperature for 30 min under pressure (0.4 MPa). The mixture was then filtered through a celite pad. After evaporation of solvent, the desired compound was obtained as a white powder. The product was crystallized from ethanol yielding white needles of N(1)-benzyl-5-(dihydroxyboryl)uracil (**6a**). 2 Mmole of **5b-c** were added to a solution of 0.54 g (4 mmoles) of $AlCl_3$ in 10 mL of dry toluene. The mixture was stirred at 50° for 2 hours and cooled. Ice water was added and the raw product **6b-c** was filtered off and dried. Crystallization from ethanol gave white crystalls of N(1)-methyl-5-(dihydroxyboryl)uracil (**6b**) and N(1)-ethyl-5-(dihydroxyboryl)uracil (**6c**).
Compound **6a**, mp. 198-199°, 66% yield. ^{1}H NMR: δ 4.97 (s, 2, CH_2), 7.33 (m, 5, C_6H_5), 8.08 (s, 1, 6-H), 8.14 (s, 2, $B(OH)_2$), 11.72 (s, 1, N-H); MS, *m/e* 202 (M^+-HBO_2); UV (C_2H_5OH) λ_{max} 274 nm, ε_{max} 11100.
Anal. Calcd for $C_{11}H_{11}BN_2O_4$: C, 53.70; H, 4.47; N, 11.39. Found: C, 53.54; H, 4.31; N, 11.43
Compound **6b**, mp. 176-177°, 43% yield. ^{1}H NMR: δ 3.30(s, 3, CH_3), 7.97 (s, 1, 6-H), 8.13 (s, 2, $B(OH)_2$), 11.62 (s, 1, N-H); MS, *m/e* 170 (M^+); UV (C_2H_5OH) λ_{max} 273 nm, ε_{max} 9000.
Anal. Calcd for $C_5H_7BN_2O_4$: C, 35.34; H, 4.15; N, 16.48. Found: C, 35.21; H, 4.14; N, 16.27
Compound **6c**, mp. 170-172°, 39% yield. ^{1}H NMR: δ 1.17 (t, 3, CH_3), 3.78 (q, 2, CH_2), 8.01 (s, 1, 6-H), 8.14 (s, 2, $B(OH)_2$), 11.62 (s, 1, N-H); MS, *m/e* 184 (M^+); UV (C_2H_5OH) λ_{max} 273 nm, ε_{max} 9200.
Anal. Calcd for $C_6H_9BN_2O_4$: C, 39.18; H, 4.93; N, 15.23. Found: C, 39.01; H, 4.69; N, 15.01

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