Cedranediolborane as a Borylating Agent for the Preparation of Boronic Acids: Synthesis of a Boronated Nucleoside Analogue

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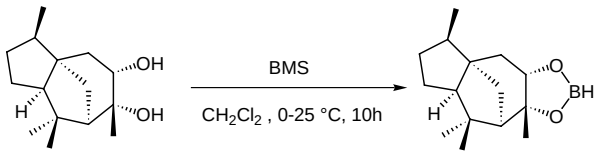
Abstract: Cedranediolborane can be cross-coupled with aryl iodides under Pd(0) catalysis to yield aryl boronates which can easily be deprotected to form the corresponding *free* boronic acids. The application of this methodology has led to the preparation of a boronated nucleoside indole analogue.

Key words: cedrane, borylation, boronic acids, boronates, nucleoside

Boronic acids and their esters (boronates) are valuable intermediates, useful in synthetic applications such as Suzuki-Miyaura couplings and Matteson asymmetric homologations. In addition, boronated analogues of biomolecules[1] are of interest for their possible use in boron neutron capture therapy (BNCT),[2] as inhibitors of serine proteases,[3] and as chemosensors during recognition events.[4,5]

Aryl boronates can be obtained from aryl halides by a metalation/borylation sequence. A newer method though, involves Pd-mediated borylations with either bis(pinacolato)-diboron[6] or pinacolborane,[7] and such cross-couplings have resulted in straightforward syntheses of clinically useful 4-borono-L-phenylalanine.[8] However, deprotection of boronate esters has not always been trouble-free,[9] and some biological evaluations had to be performed with boronates rather than the free boronic acids.[10] We now introduce cedranediolborane **1** as a new borylating agent which, after coupling with aryl iodides, easily yields the corresponding *free* boronic acids.

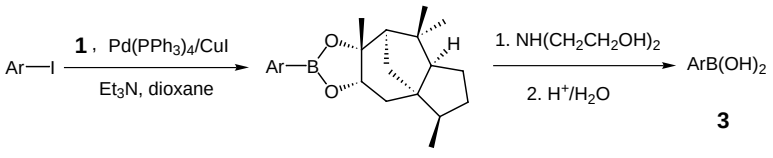


1

To prepare **1**, cedrane-8,9-diol,[11] readily obtained by dihydroxylation of (-)-α-cedrene,[12] was treated with the borane-dimethyl sulfide (BMS) complex.[13] The product decomposed upon attempted distillation under high vacuum, but crude **1**, left on evaporation of the volatiles from the reaction mixture, was of sufficient quality for the cross-coupling reactions. These reactions were carried out with aryl iodides (see Table) using catalytic amounts of tetrakis(triphenylphosphine)palladium(0) and copper(I) iodide.[14] The boronates **2** thus readily formed were found to be air- and chromatography stable compounds that could be converted to the free boronic acids **3** by transesterification with diethanolamine,[15] followed by acid treatment.[16] This procedure is compatible with functionalized aryl iodides (see Table), for example the iodopyrimidine in entry 7 which is of particular interest as the product is similar to that used in the preparation of boronated pyrimidines and nucleosides.[17]

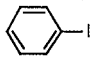
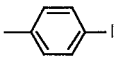
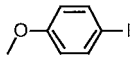
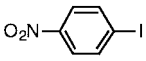
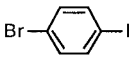
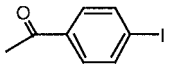
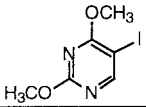
To exploit the synthetic potential of borylating agent **1**, we undertook the preparation of the boronated nucleoside **4**, which could not be obtained previously by coupling of 5-indolyl-boronates with halide **9** due to the lack of a suitable boronic acid protecting group.[18,19] The preparation of the required 5-iodoindole started with the commercially available 5-bromo derivative **5**, whose sodium salt was silylated to give **6**. After halogen exchange in **6** by quenching the corresponding lithio derivative with iodine (to give **7**) desilylation was effected by aqueous base treatement to afford **8** in 69% overall yield from **5**. This new preparation of 5-iodoindole **8** was found to be the most practical of several examined.[20]

Nucleoside formation[21] was effected by treating the sodium salt of **8** with the deoxyribosyl derivative **9**[22], which gave a single anomer **10**[23] (79%). Given the coupling constants observed for H-1' (5.6 and 8.4 Hz), the β configuration was assigned.[24] The borylation step was next carried out with cedranediolborane **1** by using the general procedure described above[14] which proceeded efficiently

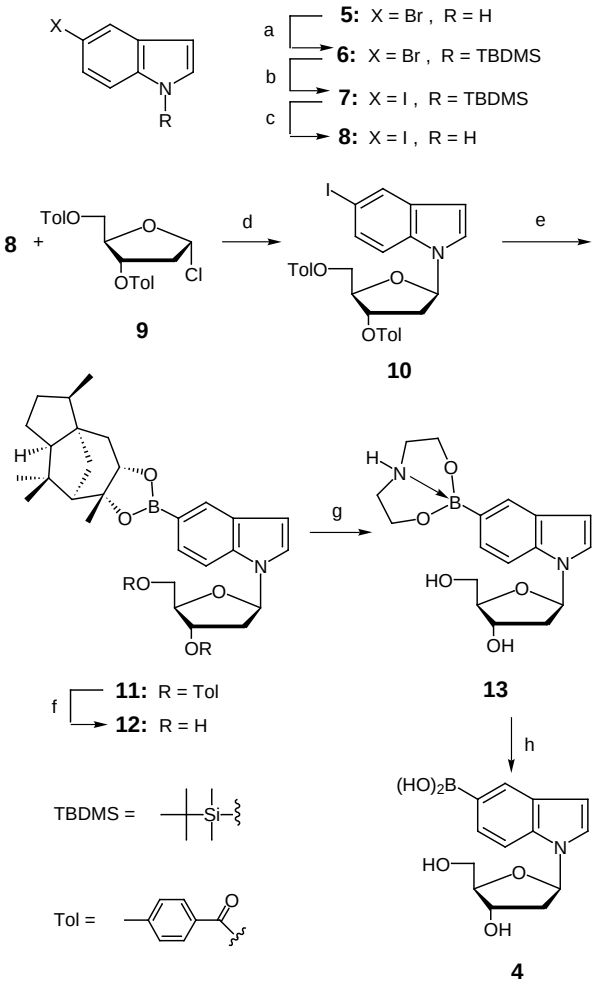


2 **3**

Table Reaction of **1** with representative aryl iodides and deprotection of the resulting boronates.

entry	aryl iodide	yield of **2** (%)	yield of **3** (%)[a]
1		81 [b]	71 [d]
2		86	70 [e]
3		87	64 [f]
4		79	72 [f]
5		89	63 [g]
6		69	58 [f]
7		c	83 [h]

[a]overall yields from aryl iodides. [b]previously obtained by esterification[12] of phenylboronic acid. [c]converted to the free boronic acid without isolation. [d]phenylboronic acid (**3**, Ar = C_6H_5) is commercially available.[e]authentic sample prepared according to ref.30. [f]characterized as known[6] pinacol boronate after reaction with pinacol. [g]authentic sample prepared according to ref. 31. [h]starting iodide prepared according to ref. 32 and product described in ref. 17.



Reagents and conditions: (a) NaH, 1.2 equiv., MeCN, 1h, then TBDMSiCl, 1.25 equiv., overnight, 96%; (b) nBuLi, 1.1 equiv., THF, - 85 °C, 1 h, then I_2 in THF,1.15 equiv., 83%; (c) 0.5 M NaOH in 1:1 THF/H_2O, overnight, 87%; (d) **9** added to preformed **8**-Na salt (**8** in 0.1 M MeCN, NaH, 1.1 equiv., 30 min.), 4 h, 79%; (e) **1,** $Pd(PPh_3)_4$/CuI, 81%; (f) NaOMe (3 equiv.), CH_3OH, overnight; 78%; (g) $NH(CH_2CH_2OH)_2$ (1.2 equiv.), Et_2O, 2 h, 93%; (h) MeOH, Amberlite IRC-50 (H^+) to pH 7, 2 h, 68%.

(81%) to give **11**. Cleavage of the toluoates to provide **12**[25] was followed by formation of "ate" complex **13** by treatment with diethanolamine. Deprotection of **13** to the free boronic acid **4**[26], could then be effected (Amberlite IRC 50 (H^+) without cleavage of the nucleoside linkage.

Nucleoside **4** is the first boronated indole nucleoside to be prepared.[27] This structurally simple nucleoside analogue, whose nucleobase is expected to display hydrophobic/ stacking interactions,[28] may be useful as well for the introduction of substituents at C-5 on the indole ring through subsequent Suzuki-Miyaura couplings,[29] in addition to possible applications in BNCT.

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(13) To a stirred suspension of cedranediol (2.38g, 10 mmol) in dry CH_2Cl_2 (4 mL) under argon at 4 °C was added dropwise *fresh* borane-dimethyl sulfide (1.1 mL of a 10 M solution in Me_2S) and the resulting mixture was allowed to warm to room temperature. After about 10 h, a clear solution was obtained, which was stirred for an additional 4 h. Evaporation of the volatiles under reduced pressure ($p < 50$ mmHg and $t < 80$ °C) afforded air-sensitive cedranediolborane **1**: ^{1}H NMR (300MHz, $CDCl_3$) δ 0.81 (d, J = 7.0Hz, 3H, CH_3), 1.04(s, 3H, CH_3), 1.14(s, 3H, CH_3), 1.41(s, 3H, CH_3), 1.10-2.25(m, 11H, CH, CH_2), 4.13(dd, J_1 = 7.0Hz, J_2 = 8.4Hz, 1H, OCH); ^{13}C NMR (75MHz, $CDCl_3$) δ 15.50, 25.63, 28.50, 28.82, 31.07, 36.14, 39.15, 42.04, 42.61, 44.27, 51.67, 57.73, 58.23, 78.21, 85.86.

(14) *Representative procedure*: To a stirred mixture of 4-iodotoluene (65 mg, 0.3 mmol), CuI (4 mg) and **1** (248 mg, 1.0 mmol) in dry 1,4-dioxane (2 mL) under argon, was added Et_3N (0.5 mL, 3.6 mmol). Ar was bubbled through the reaction mixture for 20 min before addition of $Pd(PPh_3)_4$ (4 mg). The mixture was then heated to 80 °C and stirred for 20 h. After being allowed to cool to room temperature, the reaction mixture was quenched with water and extracted with cyclohexane. The organic layer was washed with brine and dried over $NaSO_4$ and, after filtration, the volatiles were removed under reduced pressure. The residue was purified by flash chromatography (9/1 hexane/ethyl acetate) on silica gel to yield cedranediol p-tolylboronate (87 mg, 86% yield): ^{1}H NMR (300MHz, $CDCl_3$) δ 0.82(d, J = 7.0Hz, 3H, CH_3), 1.08(s, 3H, CH_3), 1.20(s, 3H, CH_3), 1.52(s, 3H, CH_3), 1.28-2.35(m, 11H, CH, CH_2), 2.40(s, 3H, Ar-CH_3), 4.28(dd, J_1 = 7.2Hz, J_2 = 8.4Hz, 1H, OCH), 7.23(d, J = 7.8Hz, 2H, Ar-H), 7.77(d, J = 7.8Hz, 2H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$) δ 15.50, 21.90, 25.64, 28.47, 28.54, 31.03, 36.20, 39.29, 42.03, 42.52, 44.06, 51.74, 58.06, 58.18, 78.80, 85.88, 128.75, 135.09, 141.72.

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(16) *General procedure*: A THF solution of **2** and diethanolamine (2 equiv.) was stirred overnight. After being acidified with 1 M HCl the reaction mixture was stirred for 30 min and then diluted with water and extracted with ethyl acetate. The combined organic layers were then extracted with 1M NaOH. After being acidified to pH 1 with 1 M HCl, the aqueous extracts were extracted with ethyl acetate to yield pure **3**, free from cedranediol. For acid sensitive compounds, after the addition of diethanolamine, purification was effected by column chromatography to remove the cedranediol. Then, to a solution of the ate complex, Amberlite IRC-50 (H^+) was added portionwise until pH 7 was reached whereupon the mixture was stirred for an additional 2 h, before final purification (cc on silica gel).

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(23) **10**: mp 136-7 °C; ^{1}H NMR (300MHz, $CDCl_3$) δ 2.43(s, 3H), 2.45(s, 3H), 2.65(m, 1H), 2.84(m, 1H), 4.57(m, 1H), 4.64(m, 2H), 5.71(m, 1H), 6.41(dd, J_1 = 5.6Hz, J_2 = 8.4Hz, 1H), 6.45(d, J = 3.3Hz, 1H), 7.23-7.30(m, 6H), 7.38(dd, J_1 = 1.7Hz, J_2 = 8.7Hz, 1H), 7.91(d, J = 8.2Hz, 2H), 7.93(s, 1H), 7.97(d, J = 8.2Hz, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ 21.86, 21.90, 38.05, 64.31, 75.08, 81.93, 84.01, 85.75, 103.00, 112.08, 124.87, 126.69, 126.98, 129.41, 129.45, 129.85, 129.94, 130.09, 130.59, 131.87, 135.19, 144.26, 144.64, 166.16, 166.38. Anal. calcd. for $C_{29}H_{26}INO_5$: C, 58.50; H, 4.40, N, 2.35. Found : C, 58.75; H, 4.43, N, 2.35.

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(25) **12**: mp 123-5 °C. ^{1}H NMR (300MHz, $CDCl_3$) δ 0.79(d, J = 7.0Hz, 3H), 1.07(s, 3H), 1.18(s, 3H), 1.51(s, 3H), 0.88-2.34(m, 11H), 2.30(m, 1H), 2.52(m, 1H), 3.64(m, 2H), 3.90(m, 1H), 4.27(t, J = 7.6Hz, 1H), 4.45(m, 1H), 6.35(t, J = 6.4Hz, 1H), 6.57(d, J = 3.2Hz, 1H), 7.19(d, J = 3.2Hz, 1H), 7.48(d, J = 8.3Hz, 1H), 7.71(d, J = 8.3Hz, 1H), 8.17(s, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 15.51, 25.63, 28.49, 28.54, 31.02, 36.17, 39.31, 40.09, 41.99, 42.55, 44.03, 51.79, 58.09(2), 62.61, 71.66, 78.78, 84.62, 85.83, 86.06, 104.31, 109.54, 124.28, 128.54, 128.97, 129.20, 138.35. FAB-HRMS, m/z $(M+H)^+$: 480.2926 (calcd. for $C_{28}H_{39}{}^{11}BNO_5$: 480.2922).

(26) **4:** $[\alpha]_D{}^{23}$ = -27° (c = 0.01, CH_3OH). ^{1}H NMR (300MHz, CD_3OD) δ 2.27(m, 1H), 2.54(m, 1H), 3.65(m, 2H), 3.91(m, 1H), 4.43(m, 1H), 6.40(t, J = 7.0Hz, 1H), 6.48(d, J = 3.2Hz, 1H), 7.40-7.49(m, 2H), 7.55(d, J = 8.4Hz, 1H), 7.83(s, 1H); ^{13}C NMR (75MHz, CD_3OD) δ 40.91, 63.56, 72.72, 86.05, 88.08, 104.38, 110.23, 125.61, 128.17, 130.16, 138.65. **4** was esterified with cedranediol to yield boronate **12**, identical to the sample prepared above.

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