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Synthesis of Functionalized 1-Alkenylboronates via Hydroboration-Dealkylation of Alkynes with Diisopinocampheylborane

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SYNTHESIS OF FUNCTIONALIZED 1-ALKENYLBORONATES VIA HYDROBORATION-DEALKYLATION OF ALKYNES WITH DIISOPINOCAMPHEYLBORANE

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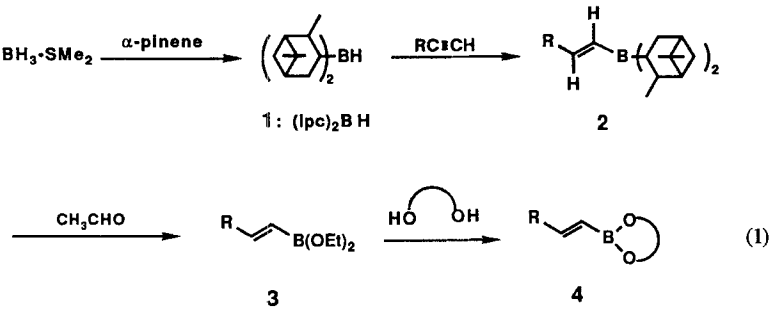
Abstract: Hydroborations of propargyl chloride, ethyl propiolate, 3-trimethylsilyloxy-1-butyne, 1,1-diethoxy-2-propyne, 1-iodo- and 1-bromo-1-hexyne, and 1-bromo-3-chloro-1-propyne with diisopinocampheylborane **1**, followed by dealkylation of the isopinocampheyl groups with acetaldehyde provide the corresponding 1-alkenylboronates in high yields with high regioselectivity.

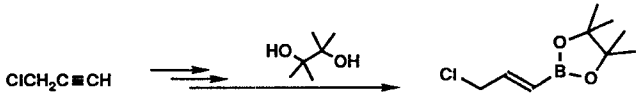
1-Alkenylboronic acids and their esters are valuable precursors in organic synthesis.[1] They can be prepared by several methods, most notably by the hydroboration of alkynes with catecholborane[2] or dihaloboranes,[3] followed by hydrolysis to boronic acids or alcoholysis to boronic esters. Although these methods have been widely accepted for the synthesis of a variety of functionalized 1-alkenylboronates, the difficulties are often encountered by the lack of regioselectivity or chemoselectivity upon addition to functionalized alkynes. On the other hand, Vaultier and co-workers[4] have recently shown that a sequence of alkyne hydroboration with diisopinocampheylborane **1** and dealkylation of the isopinocampheyl groups with acetaldehyde provides an alternative and convenient method for the synthesis of functionalized 1-alkenylboronates (Eq. 1). Although

this borane has been developed for the asymmetric hydroboration of alkenes,[5] it has several attractive features as a hydroboration reagent for alkynes, e.g., the inertness to many functional groups except aldehyde and ketone carbonyls, the high regioselectivity resulting from its bulkiness, and the ease of dealkylation to the boronic esters under neutral conditions. Thus, this procedure can be used to achieve the selective synthesis of functionalized 1-alkenylboronates which are not readily available by conventional hydroboration technique.



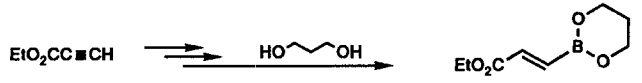
(1)

The difficulties that arise during the selective synthesis of 1-alkenylboron compounds from terminal alkynes are often encountered by alkynes having electron-withdrawing groups attached directly to the triple bond or placed at the propargylic carbon, because electronic effects direct the addition of the boron atom to the internal carbon versus to the steric effects favoring the terminal carbon. For example, it is reported that the hydroboration of propargyl chloride with catecholborane produces an inseparable mixture of internal and terminal boron adducts in a ratio of 19:81[6] and the addition of disiamylborane to ethyl propiolate results in a 33:67 ratio in favoring the terminal boron adduct.[7]



(2)

5 *73%*

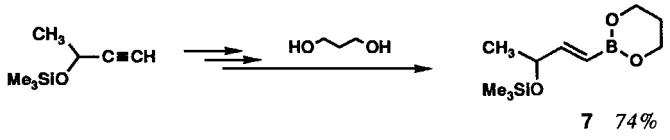


(3)

6 *70%*

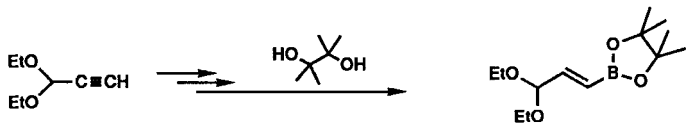
The hydroborations of both alkynes with **1** proceed to provide terminal boron derivatives in 73% and 70% yields with excellent regioselectivity. Similar high regioselectivity due to the steric bulkiness of **1** was reported for the hydroboration of (phenylsulfonyl)ethyne,[4] 2-methyl-1-buten-3-yne,[8] and 3-propioloyloxazolidinone.[9]

Although catecholborane is tolerant to many functional groups under conditions for the hydroboration of alkynes, the C-O bond of acetals or ethers at the allylic or propargylic carbon can be readily cleaved.[10] We previously found that the acetal of 7,7-ethylenedioxy-3-methyl-3-octen-1-yne is reductively cleaved with catecholborane at 70 °C in preference to hydroboration of the terminal triple bond.[11] Thus, hydroborations of the trimethylsilyl, benzyl, and tetrahydropyranyl ethers of propargylic alcohols or the acetylenic acetals with catecholborane have not been previously reported. The successful method that allows the hydroboration with catecholborane requires a protection of propargyl alcohols with sterically hindered t-butyldimethylsilyl group.[12] It is known that catalytic hydroboration with catecholborane in the presence of Rh, Pd, or Ni catalysts extremely moderates the reaction conditions,[13] but the applications of the catalytic method to both alkynes do not provide good results. In contrast, the sequence of hydroboration with **1** followed by dealkylation with acetaldehyde is sufficiently mild enough to permit such functionalities on 1-alkenylboronates (Eqs. 4 and 5).



(4)

7 *74%*

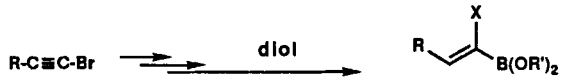


(5)

8 *52%*

1-Halo-1-alkenylboronates are valuable intermediates for stereodefined internal 1-alkenylboronates and have been synthesized by the hydroboration of 1-*halo*-1-alkynes with the dibromoborane-dimethylsulfide complex followed by alcoholysis.[14] Although quite high yields of over 80% were reported, the yields

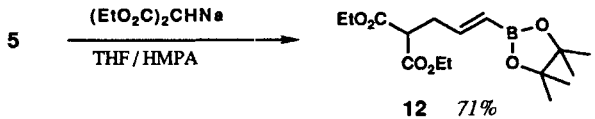
are often lower, presumably due to the side reactions caused by hydrogen bromide evolved upon alcoholysis.[15] However, the present procedure provides a more general and reliable route to such boronates from 1-iodo- or 1-bromo-1-alkynes (Eq. 6).



(6)

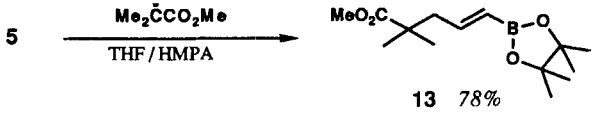
9: X = Br, R = C_4H_9 , R'$_2$ = -$(CH_2)_3$- *65%*
10: X = I, R = C_4H_9 , R'$_2$ = -CMe_2CMe_2- *90%*
11: X = Br, R = $ClCH_2$, R'$_2$ = -$(CH_2)_3$- *82%*

Some of the boronates synthesized in the present study are valuable as precursors for the other functionalized 1-alkenylboronates. The alkylation of **5** with sodium malonate or the lithium enolate of isobutylic ester provides the ester derivatives of 1-alkenylboronates in 71% and 78% yields (Eqs. 7 and 8). Although the cross-coupling with allylic halides is known to be accelerated by a catalytic amount of $Pd(PPh_3)_4$,[16] the alkylation with sodium malonate results in a mixture of (E)- and (Z)-**12** in a ratio of 71:29.



12 *71%*

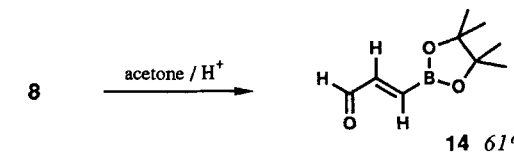
(7)



13 *78%*

(8)

Deprotection of **8** by treatment with a catalytic amount of HCl in acetone affords a novel acrolein derivative of boronate **14** in 61% yield (Eq. 9).



14 *61%*

(9)

In conclusion, the sequence of hydroboration of alkynes with **1** followed by dealkylation with acetaldehyde provides new access to functionalized 1-alkenylboronates which can be easily isolated in pure form. The procedure appears to better tolerate various functional group variations than the conventional hydroboration reactions using catecholborane and dihaloboranes. The bulkiness of the isopinocampheyl moiety can serve as a nonparticipating dummy group which allows the extremely high regioselectivity by adding boron to the less hindered carbon of the alkynes. This bulky dummy group can be readily removed by acetaldehyde under neutral conditions.

Experimental

Materials. Alkynes were prepared by the method of Brandsma.[17] α-Pinene was dried by distillation from CaH_2. The borane-methyl sulfide complex (BMS) purchased from Aldrich Chemical Co. was purified by trap-to-trap distillation in vacuo (10^{-2} mmHg).

General procedure. A dry 200-ml flask equipped with a septum inlet, a reflux condenser, a magnetic stirring bar, and an oil bubbler was charged with the borane-methyl sulfide complex (8.0 ml, 84 mmol) and THF (40 ml) under nitrogen. Then, α-pinene (186 mmol) was dropwise added at 0 °C. The mixture was stirred for 1 h, followed by 2 h at room temperature. The solution of **1** thus obtained was cooled to -35 °C, and the alkyne (79 mmol) was added slowly. After being stirred for 1.5 h at -35 °C and for 5 h at room temperature, a freshly distilled acetaldehyde (64 ml) was added at 0 °C (exothermic). The mixture was refluxed for 12 h to dealkylate isopinocampheyl groups. Acetaldehyde, solvent, and any other volatiles were evaporated in vacuo at room temperature (10 mmHg for 1 h), and then a solution of diol (80 mmol) in THF (40 ml) was added to the residue. After 3 h of stirring at room temperature, the flask was attached to the Claisen head distillation apparatus. Distillation in vacuo gave the desired 1-alkenylboronate. The product contaminates a few percent of isopinocampheylboronic ester as a by-product, that may often require the repeated distillations to improve the purity of 1-alkenylboronates.

The following 1-alkenylboronates (**5-11**) were synthesized by the above procedure.

5: Bp 69-73°C/0.22mmHg: IR (film) 1640, 1350, 970, 845 cm^{-1}; ^1H NMR δ 1.27 (s, 12 H), 4.09 (d, J = 6.0 Hz, 2H), 5.72 (d, J = 17.7 Hz, 1H), 6.64 (dt, J= 17.7 and 6.0 Hz, 1H); MS, m/e 81 (100), 103 (61), 125 (15), 145 (10), 153 (18), 159 (29), 167 (46), 187 (44), 202 (2); exact mass calcd for $C_9H_{16}O_2BCl$ 202.0932, found 202.0937.

6: Bp 76 °C/0.32 mmHg; IR (film) 1720, 1625, 1160, 1000 cm^{-1}; ^1H NMR δ 1.28 (t, J = 7.3 Hz, 3H), 1.80-2.10 (m, 2H), 4.06 (t, J = 5.7 Hz, 4H), 4.20 (q, J = 7.1 Hz, 2H), 6.47 (d, J= 17.7 Hz, 1H), 6.72 (d, J = 17.7 Hz, 1H); MS, m/e 82 (77), 111 (39), 128 (11), 139 (100), 185 (23); exact mass calcd for $C_8H_{13}O_4B$ 184.0907, found 184.0918.

7: Bp 57 °C/0.09 mmHg; IR (film) 1645, 1250, 1095, 950 cm^{-1}; ^1H NMR δ 0.104 (s, 9H), 1.21 (d, J = 6.4 Hz, 3H), 1.95 (t, J = 5.5 Hz), 4.03 (t, J = 5.5 Hz, 4H), 4.18-4.37 (m, 1H), 5.44 (d, J = 17.8 Hz, 1H), 6.47 (dt, J = 17.8 and 4.8 Hz); MS, m/e 73 (100), 95 (14), 113 (38), 131 (13), 139 (30), 143 (20), 155 (32), 171 (6), 185 (8), 213(46), 228 (4); exact mass calcd for $C_{10}H_{21}O_3BSi$ 228.1353, found 228.1325.

8: Bp 89 °C/0.18 mmHg; IR (film) 1655, 1140, 970 cm^{-1}; ^1H NMR δ 1.21 (t, J = 5.94 Hz, 6H), 1.26 (s, 12H), 3.40-3.75 (m, 4H), 4.88 (d, J = 4.4 Hz, 1H), 5.76 (d, J = 18.5 Hz, 1H), 6.53 (dd, J= 18.5 and 4.4 Hz, 1H); MS, m/e 83 (67), 95 (11), 103 (95), 111 (15), 127 (27), 136 (11), 183 (54), 211 (100), 227 (32), 241 (15), 256 (3); exact mass calcd for $C_{13}H_{25}O_4B$ 256.1846, found 256.1842.

9: Bp 84 °C/0.1 mmHg; IR (film) 1630, 810, 655 cm^{-1}; ^1H NMR δ 0.908 (t, J = 5.94 Hz, 3H), 1.22-1.51 (m, 4H), 1.85-2.10 (m, 2H), 2.15-2.40 (m, 2H), 4.09 (t, J = 5.5 Hz, 4H), 6.76 (t, J = 6.7 Hz, 1H); MS, m/e 81 (100), 97 (21), 111 (24), 125 (16), 139 (7), 151 (8), 167 (47), 179 (10), 190 (23), 192 (22), 246 (15), 248 (15) ; exact mass calcd for $C_9H_{16}O_2BBr$ 246.0427, found 246.0418.

10: Bp 110°C/0.1 mmHg (oven temperature of Kugelrohr); IR (film) 1620, 850, 650 cm^{-1}; ^1H NMR δ 0.92 (t, J = 6.4 Hz, 3H), 1.29 (s, 12H), 1.30-1.65 (m, 4H), 2.15-2.40 (m, 2H), 6.77 (t, J = 6.6 Hz, 1H). The mass spectrum do not display a molecular ion peak. The compound cause thermal decomposition, thus distillation in high vacuo using Kugelrohr is essential for the isolation.

11: Bp 87-91 °C/0.07 mmHg; IR (film) 1630, 1290, 800, 685, 650 cm^{-1}; ^1H NMR δ 1.99 (t, J = 5.6 Hz, 2H), 4.10 (t, J = 5.6 Hz, 4H), 4.24 (d, J = 6.8

Hz, 2H), 6.89 (t, J = 6.8 Hz, 1H); MS, m/e 79 (54), 101 (25), 115 (32), 123 (13), 131 (13), 159 (82), 205 (100), 238 (7) and 239 (8); exact mass calcd for $C_6H_9O_2BClBr$ 237.9567, found 237.9549.

Preparations of 12 and 13. To a solution of **5** (5 mmol) in THF (10 ml) was added a solution of sodium malonate in THF (5.5 mmol) at -78°C. The reaction mixture was allowed to warm up to room temperature over 3 h and then was stirred for an additional hour. The reaction mixture was diluted with benzene, washed with brine, and dried over $MgSO_4$. The product **12** was isolated in 71% yield by Kugelrohr distillation; Bp 120-130 °C / 0.1 mmHg (oven temperature); IR (film) 1745, 1650, 1220, 830 cm^{-1}; ^1H NMR δ 1.25 (t, J = 7.0 Hz, 6H), 1.25 (s, 12H), , 2.74 (dd, J = 7.7 and 6.4 Hz, 2H), 3.46 (t, J = 7.7 Hz, 1H), 4.19 (q, J = 7.0 Hz, 4H), 5.50 (d, J = 17.8 Hz, 1H), 6.55 (dt, J = 17.8 and 6.4 Hz, 1H); MS, m/e 81 (30), 109 (22), 125 (19), 135 (7), 153 (100), 166 (8), 181 (16), 199 (5), 226 (40), 239 (4), 266 (4), 281 (6), 311 (11), 326 (4); exact mass calcd for $C_{16}H_{27}O_6B$ 326.1901, found 326.1909.

To a solution of diisopropylamine (6.5 mmol) in THF (7 ml) was added a solution of n-butyllithium in hexane (6.5 mmol) at -78 °C. Then, a solution of methyl isobutyrate (6.5 mmol) in THF (3 ml) was added slowly over 30 min. After being stirred for 30 min at -78 °C, HMPA (1.4 ml) and **5** (5 mmol) were added successively. The mixture was stirred for 1 h at -78 °C, and then was warmed-up slowly to room temperature. After standing for over night, the mixture was diluted with benzene, washed with brine, and dried over $MgSO_4$. The distillation by Kugelrohr gave **13** in a 78% yield. Bp 80-90 °C / 0.1 mmHg (oven temperature); IR (film) 1730, 1640, 1190, 970 cm^{-1}; ^1H NMR δ 1.18 (s, 6H), 1.25 (s, 12H), 2.39 (d, J = 7.0 Hz, 2H), 3.66 (s, 3H), 5.44 (d, J = 17.8 Hz, 1H), 6.50 (dt, J = 17.8 and 7.0 Hz, 1H); MS, m/e 83 (37), 95 (12), 101 (23), 109 (33), 125 (15), 137 (8), 153 (100), 168 (77), 193 (4), 209 (13), 237 (5), 253 (18), 268 (8); exact mass calcd for $C_{14}H_{25}O_4B$ 268.1846, found 268.1860.

Preparation of 14. To a solution of **8** (6 mmol) in dry acetone (12 ml) was added two drops of HCl solution in ether (2 M) at 0 °C. GLC analysis indicated that the deprotection was completed within 30 min. The mixture was treated with powdered K_2CO_3 (0.5 g) for 30 min at 0 °C to remove the acid. The filtration of solid, evaporation of the filtrate, and finally Kugelrohr distillation gave **14** in 61% yield. Bp 110-120 °C / 10 mmHg (oven temperature); This

boronate is highly sensitive to protodeboronation with water, thus the washing with aqueous base should be avoided. **14**: IR (film) 1695, 1620, 970 cm^{-1}; ^1H NMR δ 1.31 (s, 12H), 6.61 (d, J = 18.5 Hz, 1H), 6.85 (dd, J = 18.5 and 6.8 Hz, 1H), 9.60 (d, J = 6.8 Hz, 1H); MS, m/e 81 (50), 95 (27), 109 (83), 125 (81), 140 (52), 167 (100), 183 (57); exact mass calcd for $C_9H_{15}O_3B$ 182.1115, found 182.1109.

Acknowledgement. We appreciate Professor Vaultier for sending us their original procedure for the hydroboration of alkynes with diisopinocampheylborane.

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