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Preliminary Communication

Synthesis of pinacol esters of 2,3-alkadienylboronic acid via the copper(I) mediated coupling reaction of Knochel's (dialkoxyboryl)methylzinc reagents with propargylic tosylates

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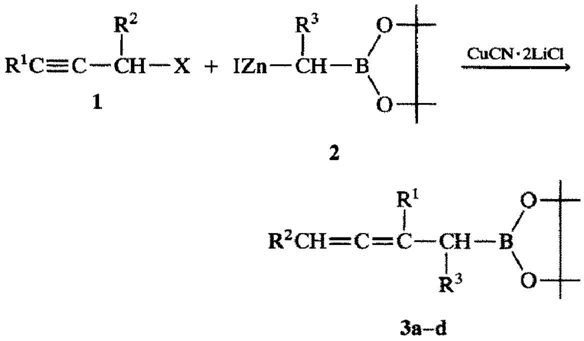
Abstract

The reaction of propargyl tosylates (1) with (dialkoxyboryl)methylcopper(I) reagents, prepared in situ from Knochel's (dialkoxyboryl)methylzinc iodide (2) and CuCN·2LiCl, produced 2,3-alkadienylboronates (3) in moderate yields. The reaction proceeded regioselectively to provide an S_N2' substitution product without contamination by other products such as 3-alkynylboronate.

Key words: Copper; Boron; Zinc; Coupling reaction; Boronic acid; Palladium

1. Introduction

Owing to the high reactivity to the carbonyl compounds, the synthesis and reaction of β,γ-unsaturated boron compounds such as the allylic [1], allenic [2], and propargylic [3] derivatives have been extensively studied. A specific feature of these reagents is their ability to transfer an organic group to the carbonyl through a six-membered cyclic transition state which provides the unsaturated alcohols with high enantioselectivity. Although the 2,3-alkadienyl boron derivatives are expected to behave similarly to other β,γ-unsaturated boron compounds, the synthesis and reaction of this reagent have not been reported to date. We previously reported that the palladium-catalyzed cross-coupling reaction of the Knochel's (dialkoxyboryl)methylzinc reagent (2) [4] offers unique advantages for the synthesis of organoboron compounds such as allylic [5] and benzylic [6] boronates. In connection with these studies, we undertook the investigation of the first preparation of some 2,3-alkadienyl boronic esters (3) via the copper(I)-induced coupling reaction of 2 with propargylic tosylates (1, X = OTs) (eqn. 1).



(1)

2. Results and discussion

Table 1 summarizes the results of the coupling reaction of 2 with representative propargylic electrophiles in THF. Recently, palladium and nickel catalysts have become increasingly popular for mediating the coupling reactions of organic halides or pseudohalides which contain sp or sp^2 carbons at or adjacent to the electrophilic center [7]. Although the palladium-catalyzed cross-coupling reaction of propargylic electrophiles with organozinc compounds was reported to provide the S_N2' type coupling with excellent regioselectivity [8], the coupling of 2 with propargyl acetate (entry 2), methyl carbonate, and tosylate (entry 5) in the presence of palladium catalyst failed. Presumably, the allene coupling products (3) are unstable in the reaction media. Because such a transition metal-catalyzed coupling reaction usually requires higher than room temperature to achieve a reasonable reaction rate, the reaction mediated by copper(I) was next chosen in order to decrease the reaction temperature of the coupling. The in situ preparation of $[(Me_2C)_2O_2BCH_2]Cu(CN)ZnI$ (1.5 equivs) from 2 and CuCN·2LiCl in THF at −20°C [9] followed by the coupling with 1 (X = OTs) was found to be effective to achieve a reasonable yield (entry 4). Under these conditions, 1 was completely consumed within 1 h. The coupling proceeded regioselectively with the γ-carbon in 1 and the regio-isomers or other by-products were not detected by GC–MS analysis (a fused silica capillary column OV-1) and ^1H NMR spectrum. The use of

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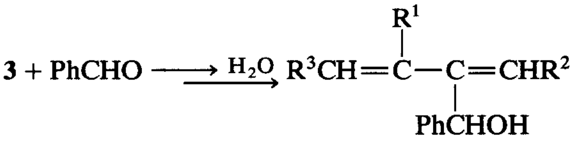
propargyl bromide instead of tosylate (entry 3) or the $CuBr \cdot SMe_2$ reagent as a copper source resulted in lower yields. The reaction can be readily extended to secondary propargyl tosylates (**1**, $R^1 = H$, $R^2 = Me$, $X = OTs$) (entry 6) and the secondary borylmethylzinc reagents (**2**, $R^3 = Me$) (entry 8). However, propargyl tosylates having a terminal alkyl substituents such as 2-butynyl tosylate (**1**, $R^1 = Me$, $R^2 = H$, $X = OTs$) resulted in a very low yield of **3** and the formation and molecular structure of which can be estimated only from the alcohol product after treatment with benzaldehyde (entry 7).

A reversible permanent allylic rearrangement is commonly observed in triallyl- and dialkyl(allyl)bron derivatives, and allylboronic esters are known to rearrange irreversibly through a [1,3] boron shift into the thermodynamically stable isomers [10]. This nature often makes it difficult to isolate pure allylic or propargylic boron compounds without rearrangement; however, the present compound (**3**) is quite stable upon heating. When **3a** and **3d** in C_6D_6 were heated in a sealed tube at 130°C, no ^1H NMR spectra change were observed. Although the spectrum gave complex broad signals after heating overnight at 160°C, there was no evidence of a 1,3-sigmatropic rearrangement to (1,3-butadien-2-yl)boronate.



$$3 + PhCHO \xrightarrow{H_2O} R^3CH{=}\overset{\displaystyle R^1}{\overset{|}{C}}{-}\underset{\displaystyle PhCHOH}{\underset{|}{C}}{=}CHR^2 \qquad (2)$$

4a: $R^1, R^2, R^3 = H$; 69%
4b: $R^1, R^2 = H$; $R^3 = Me$; 79%
4c: $R^1, R^3 = H$; $R^2 = Me$; 85%

The value of the regioselective synthesis of **3** is further evident because of its reaction with carbonyl compounds. Although their addition to aldehydes was very slow at room temperature, the reaction readily proceeded at the refluxing temperature of benzene. However, the reaction with ketones such as acetone failed. Similar reduced reactivity of the pinacol esters due to their bulkiness of the ester group was also noted in the reaction of allylboronates with carbonyls [11]. The addition of **3** to aldehydes proceeded through the allylic rearrangement to regioselectively provide a dienyl alcohol. The predominant formation of trans-dienes (> 98%) during the synthesis of **4b** and **4c** was established by ^1H NMR.

In conclusion, the sequence of transmetallation of Knochel's borylmethylzinc reagents (**2**) to the copper(I) species followed by the coupling with propargylic tosylates provides the first access to the 2,3-butenylboronate derivatives (**3**) which can be easily isolated in pure form. The reaction of **3** with aldehydes cleanly provides the dienyl alcohols (**4**) as the sole product, though these preparations from (1,3-butadien-2-yl)magnesium chloride or -lithium reagents suffer from a poor regioselectivity giving a mixture of α- and γ-adducts [12].

3. Experimental details

3.1. Material

Copper(I) cyanide purchased from Kanto Chemical was used directly. Lithium chloride was dried at 120°C in vacuo (10^{-2} mmHg). THF and benzene were dried and distilled from benzophenone ketyl or $LiAlH_4$, respectively.

The pinacol ester of iodomethylboronic acid was prepared using the method of Sadhu and Matteson [13] with the following slight modifications. To a mixture of ICH_2Cl (0.18 mol) and $(^iPrO)_3B$ (0.175 mmol) in THF (200 ml) was dropwise added a solution of ^nBuLi in hexane (1.55 M, 0.165 mol) at −78°C. The bath temperature was allowed to warm up to room temperature over a 1–2 h period and stirred for an additional 3 h. The flask was cooled again to −78°C, and acetic acid (0.175 mol) and pinacol (0.175 mol) in THF (20 ml) were then successively added. The mixture was stirred for 30 min at −78°C, followed by slow warming to room temperature, and stirred for an additional 3 h. The reaction mixture was washed with brine and dried over $MgSO_4$. Evaporation of solvent and distillation of the oily residue gave a mixture of chloro- and iodomethylboronic pinacol esters (29.6 g). bp 73–85°C/10 mmHg.

To a solution of NaI (38 g) in acetone (280 ml) was added the above boronic ester (29.6 g), and the mixture was then reflexed for 4 h. After being cooled to room temperature, the solvent was evaporated in vacuo. The product was extracted with ether, washed with brine, and dried over $MgSO_4$. Distillation of the concentrated residue gave iodomethylboronic acid pinacol ester in a 82% total yield (38.5 g). bp 93–95°C/10 mmHg.

The pinacol ester of (1-iodoethyl)boronic acid was prepared by the method of Wuts and Thompson [14]. These boronates were converted to the corresponding zinc reagent (**2**) by the procedure of Knochel [4].

3.2. A general procedure for the synthesis of 3

A oven dried flask was charged with CuCN (0.43 g, 4.8 mmol) and LiCl (0.407 g, 9.6 mmol), and flushed with nitrogen. A 10 ml of THF was added, and the mixture was then stirred for ca. 1 h to dissolve the solid. A solution of zinc reagent (**2**) in THF (0.69 M, 3.4 mmol), which concentration was estimated by titration with EDTA, was dropwise added at −20°C. The temperature of flask was slowly warmed up to 5°C to complete the transmetallation to copper. The flask was cooled again to −20°C and a solution of propargyl tosylate (**1**) (3 mmol) in THF (ca. 3 ml) was slowly added. The mixture was stirred for 30 min at −20°C, and then warmed up to ambient temperature over 2 h. Addition of hexane (20 ml) precipitated inorganic salt. Filtration of salts, concentration of filtrate, and finally distillation of the residue at 100–110°C/12 mmHg by Kugelrohr gave **3a**, **b**, **d** as viscous oil which are moderately inert to oxygen and can be handled in open air.

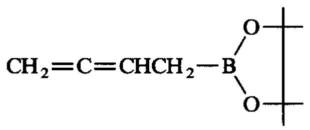
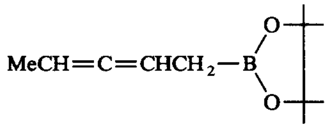
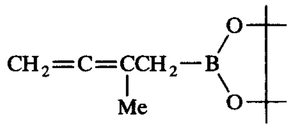
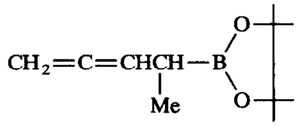
3a: ^{1}H-NMR(CDCl$_3$) δ 1.26 (s, 12H), 1.61 (ddd, 2H, $J = 3.4$, 3.4 and 6.8 Hz), 4.63 (dt, 2H, $J = 6.8$ and 3.4 Hz), 5.15 (ddd, 1H, $J = 6.8$, 6.8 and 6.8 Hz). IR (neat) 1962 cm^{-1}. MS (EI) *m/e* 83 (100), 84 (88), 94 (14), 137 (20), 165 (16), 180 (50), 181 (9). Exact mass calcd. for $C_{10}H_{17}O_2B$ 180.1321; found 180.1335.

3b: ^{1}H-NMR (CDCl$_3$) δ 1.09 (d, 3H, $J = 7.8$ Hz), 1.25 (s, 12H), 1.78 (m, 1H), 4.71 (dd, 2H, $J = 3.4$ and 6.8 Hz), 5.26 (ddd, 1H, $J = 6.8$, 6.8, and 6.8 Hz). IR (neat) 1970 cm^{-1}. MS (EI) *m/e* 84 (100), 93 (26), 101 (8), 121 (10), 137 (7), 151 (14), 179 (8), 194 (25), 195 (4). Exact mass calcd. for $C_{11}H_{19}O_2B$ 194.1478; found 194.1476.

3c: GC analysis indicated that the yield of **3c** was very low, thus the reaction mixture was directly treated with benzaldehyde (3.3 equiv.) for 12 h at refluxing temperature of benzene. The yield and the structure of **3c** in Table 1 was estimated from the addition product, 3-methyl-2-methylene-1-phenyl-3-butenol (17%): ^{1}H-NMR (CDCl$_3$) δ 1.90 (d, 3H, $J = 0.7$ Hz), 1.95 (d, 1H, $J = 4.2$ Hz), 4.96 (q, 1H, $J = 0.7$ Hz), 5.00 (s, 1H), 4.98 (d, 1H, $J = 4.2$ Hz), 5.39 (s, 1H), 5.57 (d, 1H, $J = 4.2$ Hz), 7.2–7.4 (m, 5H). IR (neat) 3350, 1595, 1495 cm^{-1}. MS (EI) *m/e* 77 (64), 79 (100), 91 (32), 107 (82), 115 (15), 129 (13), 141 (18), 143 (20), 145 (17), 156 (17), 159 (42), 174 (24). Exact mass calcd. for $C_{12}H_{14}O$ 174.1045; found 174.1025.

3d: ^{1}H-NMR(CDCl$_3$) δ 1.26 (s, 12H), 1.56–1.60 (m, 2H), 1.63 (dd, 3H, $J = 2.9$ and 6.8 Hz), 4.97–5.06 (m, 1H), 5.06–5.14 (m, 1H). IR (neat) 1975 cm^{-1}. MS *m/e*

TABLE 1. Synthesis of 2,3-Alkadienylboronates (eqn. (1))

Entry	1			2	Additive	Product	Yield(%) [a]
	R^1	R^2	X	R^3			
1	H	H	OAc	H	CuCN · 2 LiCl	 $CH_2{=}C{=}CHCH_2{-}B$ **3a**	trace
2	H	H	OAc	H	Pd(PPh$_3$)$_4$ [b]		0
3	H	H	Br	H	CuCN · 2 LiCl		28
4	H	H	OTs	H	CuCN · 2 LiCl		67
5	H	H	OTs	H	Pd(PPh$_3$)$_4$ [b]		0
6	H	Me	OTs	H	CuCN · 2 LiCl	 $MeCH{=}C{=}CHCH_2{-}B$ **3b**	59
7	Me	H	OTs	H	CuCN · 2 LiCl	 $CH_2{=}C{=}\underset{Me}{C}CH_2{-}B$ **3c**	17 [c]
8	H	H	OTs	Me	CuCN · 2 LiCl	 $CH_2{=}C{=}CH\underset{Me}{C}H{-}B$ **3d**	59

[a] Isolated yields by Kugelrohr distillation.

[b] The reaction was carried out for 24 h at room temperature by using **1** (1.0 equiv.), **2** (1.5 equiv.), and Pd-catalyst (5 mol%) in THF.

[c] After treatment of the reaction mixture with benzaldehyde at 80°C, the yield and the structure of **3c** were estimated from the alcohol product obtained, see the experimental section.

83 (100), 93 (80), 101 (28), 121 (22), 137 (56), 179 (89), 194 (33), 195 (3). Exact mass calcd. for $C_{11}H_{19}O_2B$ 194.1478; found 194.1492.

3.3. Reaction with benzaldehyde

A mixture of **3** (0.6 mmol) and benzaldehyde (1.8 mmol) in benzene (5 ml) was heated to reflux for 2 h. Water (5 ml) was added at room temperature, and then stirred for 1 h. After usual work-up, the product was isolated by chromatography over silica gel with hexane/ether = 2/1.

4a: ^{1}H-NMR ($CDCl_3$) δ 1.56 (s, 1H), 1.96 (d, 1H, $J = 3.5$ Hz), 5.05 (d, 1H, $J = 11.2$ Hz), 5.23 (d, 1H, $J = 17.8$ Hz), 5.34 (s, 1H), 5.42 (s, 1H), 5.48 (d, 1H, $J = 3.5$ Hz), 7.2–7.5 (m, 5H). IR (neat) 3375, 1595, 1492, 1450 cm^{-1}. MS (EI) m/e 77 (100), 107 (84), 115 (23), 129 (39), 142 (57), 143 (23), 160 (9). Exact mass calcd. for $C_{11}H_{12}O$ 160.0889; found 160.0872.

4b: ^{1}H-NMR ($CDCl_3$) δ 1.75 (d, 3H, $J = 4.9$ Hz), 1.97 (d, 1H, $J = 3.9$ Hz), 5.13 (s, 1H), 5.20 (broad d, 1H), 5.48 (broad t, 1H), 5.67 (d, 1H, $J = 15.2$ Hz), 5.68 (q, 1H, $J = 4.5$ hz), 7.2–7.5 (m, 5H). IR (neat), 3380, 1645, 1610, 1490 cm^{-1}. MS m/e 68 (28), 79 (71), 107 (100), 116 (29), 130 (15), 141 (9), 156 (16), 159 (4), 174 (25). Exact mass calcd. for $C_{12}H_{14}O$ 174.1045; found 174.1038.

4c: ^{1}H-NMR ($CDCl_3$) δ 1.83 (d, 3H, $J = 6.8$ Hz), 1.92 (broad s, 1H), 5.13 (d, 1H, $J = 11.2$ Hz), 5.21 (d, 1H, $J = 17.6$ Hz), 5.49 (s, 1H), 5.84 (q, 1H, $J = 7.3$ Hz), 6.56 (dd, 1H, $J = 11.2$ and 17.6 Hz), 7.2–7.4 (m, 5H). IR (neat) 3380, 1655, 1607, 1502, 1460 cm^{-1}. MS (EI) m/e 77 (76), 79 (100), 91 (38), 96 (13), 105 (52), 107 (74), 115 (18), 129 (22), 141 (23), 143 (20), 145 (18), 159 (22), 174 (21). Exact mass calcd. for $C_{12}H_{14}O$ 174.1045; found 174.1052.

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