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ARTICLE

Alkenylcopper Reagents Prepared from Stereodefined Alkenylboronate Esters. Reaction with Allylic Halides as a Convenient Route to Stereodefined 1,4-Dienes

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ABSTRACT

The stereo-defined synthesis of 1,4-dienes based on *in situ* generated stereo-defined alkenylcopper reagents is presented. The hydroboration of alkynes with dibromoborane-methyl sulfide complex followed by treatment with trimethylene glycol provides stable (*E*)-1-alkenylboronate esters. These boronate esters readily undergo “ate” complexes with a hindered base such as potassium-*tert*-butoxide. The transmetalation of the alkenyl group from boron to copper *via* the “ate” complexes retains the original stereochemistry defined from the starting alkenylboronate esters. The effect of representative bases on stereodefined alkenylboronate esters and subsequent reaction of these boronate esters in the transmetalation reaction with copper(I) bromide-methyl sulfide is investigated. The resulting stereo-defined alkenyl copper species generated *in situ* readily couple with allylic bromide to give the corresponding 1,4-dienes with retention of stereochemistry. Since (*Z*)-1-alkenylboronate esters are easily accessible, both *cis*- and *trans*-isomeric 1,4-dienes are synthesized.

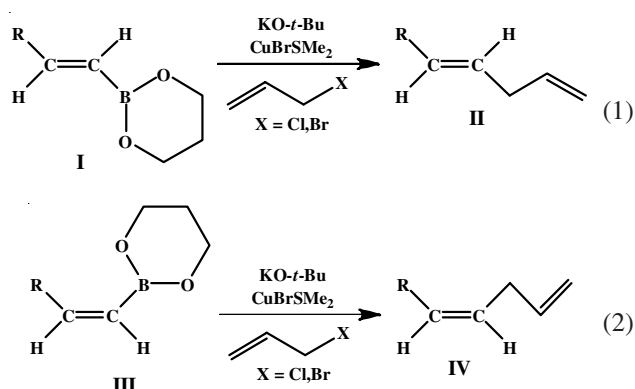
KEYWORDS

Alkenylcopper, 1,4-Dienes, Alkenylboronate esters, Trimethylene glycol, Copper(I) bromide, Methyl sulfide.

INTRODUCTION

Certain classes of natural products of current synthetic interest, such as insect pheromones [1,2] and polyunsaturated fatty acids [3] contain the 1,4-diene unit. Several recent methods have been reported to assemble such unconjugated diene structures. The coupling of allylic halides or acetates with alkenyl derivatives of aluminum [4], boron [5,6], copper [7,8], mercury [9] and nickel [10] have appeared particularly promising. However, while all of these methods achieve some degree of selectivity and usually acceptable yields, invariably there are other inherent difficulties. Sensitive functional groups are often incompatible with the organometallic reagent or the reaction conditions limiting the synthetic versatility [11]. Also unwanted byproducts may interfere, especially conjugated diene dimers, resulting from decomposition of the alkenyl organometallic reagents. Allylic transposition may or may not accompany the coupling reaction leading to mixtures of isomers [12]. Finally, many of the procedures require a large excess of one reagent to achieve satisfactory yields.

Whitesides *et al.* [13] reported a synthesis of symmetrical conjugated dienes from alkenyldialkylboranes *via* sodium methoxide addition compounds and cuprous bromide methyl sulfide. The reaction was demonstrated to probably proceed through formation of an alkenylcopper reagent which, at 0 °C, undergoes thermal decomposition stereospecifically to produce conjugated dienes. The possibility of intercepting the alkenylcopper reagent with reactive electrophilic substrates appeared promising. Such a coupling reaction with allylic halides could then provide a novel synthetic route to 1,4-dienes. Thus, an investigation was undertaken to examine the reaction of allylic halides with the alkenylcopper intermediates generated from both *E*- and (*Z*)-1-alkenylboronate esters as a synthetic route to homoconjugated dienes (eqns. 1 and 2).



EXPERIMENTAL

All glasswares were predried at 140 °C for at least 4 h, assembled hot and cooled under a stream of dry N₂. All reagents transfers, especially of boron reagents, were performed using extensively the techniques as described earlier [14]. All was prepared by treatment of lithiually available and were distilled from CaH₂ before using. Cuprous bromide methyl sulfide was prepared by the method of House *et al.* [14] sodium methoxide was prepared from potassium *tert*-butoxide was prepared from *tert*-butanol (Mallinckrodt, analytical reagent) and potassium metal in THF.

General procedure for the synthesis of 1,4-dienes from allyl bromide: The procedure for synthesis of (*E*)-7-acetoxy-1,4-heptadiene is representative *E*-1-hexenylboronate ester solution was then decanted onto a suspension of 1.72 g (31.8 mmol) of NaOC(CH₃)₃ in THF at 25 °C. After stirring for 30 min, the clear solution was decanted dropwise onto a slurry of CuBr·SMe₂ (6.3 g, 30.6 mmol) in 15 mL of THF maintained at -15 °C. Immediately following the addition, 2.85 mL (4.0 g, 33 mmol, 10% excess) of neat allyl bromide was added dropwise. The reaction was then stirred 1 h at -15 to -18 °C, 1 h at 0 °C, followed by warming to 25 °C and stirring an additional 30 min, then 10 mL of 1 N HCl was added and stirred for 10 min. The organic layer was then separated from the copper residue, with the residue washed with 3 × 50 mL of ethyl ether. Most of the volatiles were removed under aspirator vacuum and the crude product plus the boron byproduct taken up in 200 mL of ether and transferred to a large centrifuge tube. Ethanolamine (1.89 mL, 31.5 mmol) was added resulting in

the immediate precipitation of after centrifugation, a white precipitated ethanolamineboron adduct was dried (MgSO₄), the volatiles removed and the product distilled to provide [*E*]-7-acetoxy-1,4-(*E*)-1,4-heptadiene:heptadiene. b.p. 54-56 °C/3.0 mm Hg, 3.37 g (22 mmol, 73%). The purity was >97% by gas chromatography, n²⁰D = 1.4434. Anal. calcd. (found) % for 154.2 g/mol: C, 70.10 (69.99); H, 9.15 (9.34); O, 20.75 (20.67). ¹H NMR (CDCl₃) δ ppm: 6.5 (m, 3H); 4.9-5.1 (m, 2H); 4.07 (t, 2H, *J* = 7 Hz); 2.74 (m, 2H); 2.33 (m, 2H); 2.00 (s, 3H). ¹³C NMR (CDCl₃) δ ppm: 169.03; 136.35; 130.00; 126.44; 114.44; 62.98; 36.13; 31.60; 19.76. IR (neat, cm⁻¹): 1740, 1638, 1240, 1040, 970, 910.

Other 1,4-dienes were synthesized in an analogous manner and either isolated by preparative gas chromatography or distillation.

(*E*)-1,4-Nonadiene: ¹H NMR (CDCl₃) δ ppm: 5.75 (m, 4H); 5.0-5.4 (m, 3H); 2.75 (m, 2H); 2.05 (m, 2H); 1.4 (m, 4H); 0.93 (t, 3H, *J* = 6 Hz). IR (neat, cm⁻¹): 1640, 1430, 990, 910.

(*Z*)-1,4-nonadiene: n²⁰D + 1.4332; ¹H NMR (CDCl₃) δ ppm: 4.8-6.0 (m, 5H); 2.80 (t, 2H, *J* = 6 Hz); 2.06 (m, 2H); 1.31 (m, 4H); 0.89 (t, 3H, *J* = 6 Hz); ¹³C NMR (CDCl₃) δ ppm: 137.32; 131.20, 126.72, 114.51, 31.92, 31.63, 26.94, 22.40; IR (neat, cm⁻¹): 1635, 990, 905. Mass spectra: (*m/e* (% base)): 124(33) (parent); 109(5); 96(22); 95(44); 82(48); 81(100); 79(29); 54(28); 42(32); 41(43).

(*E*)-4-Ethyl-1,4-heptadiene: n²⁰D = 1.4365, ¹H NMR (CDCl₃) δ ppm: 5.7 (m, 1H); 5.1 (m, 3H); 2.70 (d, 2H, *J* = 6 Hz); 2.00 (m, 4H); 0.93 (pair of triplets, 6H, *J* = 6 Hz); ¹³C NMR (CDCl₃) δ ppm: 138.52, 137.15, 127.00, 114.94, 40.96, 22.80, 20.70, 14.22, 12.69. IR (neat, cm⁻¹): 1642, 1000, 918, 860. Mass spectra: (*m/e* (% base)): 124 (42) (parent), 109(16), 95(100), 67(87), 55(100).

(*Z*)-4-Trimethylsilyl-1,4-dodecadiene: n²⁰D = 1.4585, ¹H NMR (CDCl₃) δ ppm: 5.4-6.0 (m, 2H); 4.9 (d over m, 2H); 2.74 (d, 2H, *J* = 6 Hz); 2.05 (m, 2H); 1.27 (broadened singlet, 10H); 0.83 (t, 3H); 0.67 (s, 9H). ¹³C NMR (CDCl₃) δ ppm: 144.36, 138.51, 136.34, 114.41, 41.85, 31.96, 31.96, 31.66, 29.95, 29.14, 22.43, 13.73, 0.01. Mass spectra: (*m/e* (% base)): 239(3), 238(10), 223(10), 197(11), 195(12), 164(21), 139(25), 123(30), 99(45), 73(100).

General procedure of (*Z*)-1-alkenylboronate esters with allyl bromide: To a slurry of dry potassium-*tert*-butoxide (10.6 mmol) in THF (10 mL) was added (*Z*)-1-alkenylboronate ester (10 mmol) at room temperature. The reaction mixture was stirred for 0.5 h and the resulting solution was slowly added to a suspension of CuBr·SMe₂ (10.2 mmol) in THF (6 mL) at -15 °C. To this golden yellow slurry was then added the desired neat allyl bromide (11 mmol). The reaction solution was stirred for 1 h at -15 °C, 1 h at 0 °C and then allowed to warm to room temperature. The reaction was quenched by the addition of 1 N HCl (10 mL).

The organic phase was then transferred *via* double-ended needle to a separate flask and the remaining aqueous phase was extracted with pentane (3 × 10 mL) and combined. This pentane extract was concentrated under vacuum (25 mm Hg, 15 min), dissolved in THF (10 mL) and then oxidized by the sequential addition of 3 N NaOH (2 mL) and 30% H₂O₂ (2 mL). The solution was maintained at 50 °C for 1 h to ensure complete

oxidation. The aqueous layer was saturated with potassium carbonate, separated and extracted with pentane. The combined organic layers were washed with saturated aqueous NaCl solution (20 mL) and dried over anhydrous MgSO₄. The solvents were removed by rotary evaporation and the residue was distilled using a short path distilling column. Representative *cis*-1,4-dienes have been synthesized and the results are presented in Table-1.

(4Z)-1,4-Nonadiene: b.p.: 62-64 °C/45 mm Hg; n²¹D = 1.4315; IR (neat, cm⁻¹): 1638, 716; ¹H NMR (CDCl₃) δ ppm: 4.8-6.0 (*m*, 5H), 2.6-2.9 (*m*, 2H), 1.1-2.1 (*m*, 6H), 0.8-1.0 (*t*, *J* = 6 Hz, 3H), M⁺ 124.

(4Z)-1,4-Decadiene: b.p.: 68-70 °C/45 mm Hg; n²¹D = 1.5710; IR (neat, cm⁻¹): 1637, 724; ¹H NMR (CDCl₃) δ ppm: 4.8-6.2 (*m*, 5H), 2.6-2.9 (*m*, 2H), 1.2-2.1 (*m*, 8H), 0.8-1.0 (*m*, 3H), M⁺ 138.

(4Z)- 5-Cyclohexyl-1,4-pentadiene: b.p.: 90-92 °C/45 mm Hg; n²¹D = 1.4670; IR (neat, cm⁻¹): 1635, 907; ¹H NMR (CDCl₃) δ ppm: 4.9-6.2 (*m*, 5H), 2.7-3.0 (*m*, 2H), 0.9-2.4 (*m*, 11H), M⁺ 150.

(4Z)-6-Methyl-1,4-heptadiene: b.p.: 30-32 °C/100 mm Hg; n²¹D = 1.4175; IR (neat, cm⁻¹): 1635, 910; ¹H NMR (CDCl₃) δ ppm: 4.9-5.4 (*m*, 5H), 2.5-3.0 (*m*, 3H), 1.1-2.1 (*m*, 6H), 1.0 (*d*, *J* = 6Hz 6H), M⁺ 110. 88(100), 67(47).

RESULTS AND DISCUSSION

General reaction scheme with allylic bromides: Earlier work had shown the alkenylcopper reagent to probably be derived from a cuprous alkenyldialkylborate complex B formed by cation exchange with the corresponding sodium borate complex A [15]. At 0 °C the equilibrium between the borate complex B and the alkenylcopper compound apparently lies sufficiently to the right to allow rapid thermal decomposition of reagent to form the dimer C. However, below -15 °C, the cuprous borate complex B must be only slightly dissociated since only traces of the dimer C can be detected even after several hours [16]. Allowing a cooled (< -15 °C) reaction mixture containing the complex B to warm slowly in the presence of an allylic halide could then conceivably produce the cross-coupled product D.

To investigate this as a synthetic preparation of 1,4-dienes, distilled *E*-1-hexenylboronate ester and allyl bromide were selected as a representative substrates. Isolated *B*-1-hexenyl-

boronate ester, prepared by the hydroboration of 1-hexyne with dibromoborane-methyl sulfide complex followed by treatment with 1,3-propane diol was employed initially to avoid problems associated with the hydroboration step. Accordingly, potassium *tert*-butoxide addition compound of *E*-1-hexenyl-boronate ester was prepared followed by addition of CuBr·SMe₂ in diethyl ether at -15 °C. Allyl bromide was then added followed by immediate removal of the cooling bath with reaction mixture warming slowly to room temperature (eqn. 2). Gas chromatographic analysis revealed an 82% yield of (*4E*)-1,4-nonadiene (1) along with 4% of the decomposition dimer 2. By permitting the reaction to stir for 1 h at -15 °C before warming increased the yield of 1 to 92%. Also under these conditions, formation of dimer 2 was nearly completely suppressed (less than 1%). Pure diene 1, isolated by preparative gas chromatography, proved to be exclusively the *trans* isomer, indicating the coupling to occur with strict retention of configuration.

Reaction with allylic chlorides and allylic iodides: Reaction of copper reagent derived from *B-trans*-1-hexenylboronate ester or *trans*-1-hexenyldiboronate ester with allyl chloride proceeded only very sluggishly. Diene 1 was found only in a 6% yield accompanied by substantial amounts of the thermal decomposition diene 2. Two approaches were pursued to overcome this difficulty. The first involved attempted activation or enhancement of copper reagent reactivity. The use of HMPA as a co-solvent has been reported to promote organometallic coupling reactions, including reaction of alkenylcopper reagents with organic halides [17,18]. Thus reaction of allyl chloride with the copper reagent derived from *B*-1-hexenyl-9-BBN in the presence of three equivalents of three equivalents of HMPA afforded a 56% yield of diene 1. However, there was still 20-25% formation of the thermal decomposition of diene 2. Use of either fewer or more equivalents of HMPA did not improve the yield of 1 or significantly suppress the formation of 2.

The additional equivalent of potassium *tert*-butoxide was required to coordinate with the *B*-methoxydialkylborane released in the reaction. Also, the *tert*-butoxide must be added after the presumed copper borate complex has formed (B). Otherwise, much lower yields result.

While these results were encouraging, the potassium *tert*-butoxide might prove to be deleterious to any sensitive functional groups present. Thus, an alternative approach in which the

TABLE-1
PRAPARATION OF 1,4-DIENES FROM ALLYL BROMIDE

Alkyne	Product ^a	Yield ^d (%) (by isolation)
1-Hexyne ^b	(4E)-1,4-Nonadiene	92
1-Hexyne ^c	(4E)-1,4-Nonadiene	93
3-Hexyne ^b	(4E)-4-Ethyl-1,4-heptadiene	95
3-Hexyne ^c	(4E)-4-Ethyl-1,4-heptadiene	96
4-Acetoxy-1-butyne	(4E)-7-Acetoxy-1,4-heptadiene	(73)
1-Trimethylsilyl-(81-nonyne)	(4E)-4-Trimethylsilyl-1,4-dodecadiene	78
Cyclohexylethyne	(4E)-5-cyclohexyl-1,4-pentadiene	69
5-Chloro-1-pentyne	(4E)-8-Chloro-1,4-octadiene	72
3-Methyl-1-butyne	(4Z)-6-methyl-1,4-heptadiene	68
Cyclohexylethyne	(4Z)-5-Cyclohexyl-1,4-pentadiene	80
1-Hexyne	(4Z)-1,4-Nonadiene	76
1-Heptyne	(4Z)-1,4-Decadiene	73

^aAll products were fully characterized by spectral and physical properties. ^b9-BBN as hydroborating reagent. ^cDicyclohexylborane as hydroborating reagent. ^dGas chromatographic analysis.

TABLE-2
PREPARATION OF 1,4-DIENES FROM ALLYLIC CHLORIDE

Alkyne	Allylic chloride ^a	Product ^b	Yield (%) (by isolation)
1-Hexyne	Allyl chloride	(4E)-1,4-Nonadiene	90
3-Hexyne	Allyl chloride	(4E)-4-Ethyl-1,4-Nonadiene	93
Cyclohexyl-acetylene	2-Methylallyl chloride	(1E)-1-Cyclohexyl-4-methyl-1,4-pentadiene	(89)
5-Chloro-1-pentyne	2-Chloroallyl chloride	(4E)-2,8-Dichloro-1,4-octadiene	(83)

^aIn each case, the corresponding allylic iodide was prepared using 1.5 equivalents of NaI in THF at 25 °C and used in a 10% excess over the alkenylcopper reagent. ^bAll products were characterized by ¹H NMR, ¹³C NMR, IR and mass spectral analysis (see experimental).

reactivity of allylic chloride could be enhanced was attempted. This conceivably might be simply accomplished by conversion to the corresponding allylic iodides *via* the Finkelstein reaction. Thus, initially allyl iodide was prepared and isolated. Reaction with alkenylcopper reagent from *trans*-1-hexenyl-dicyclohexylborane gave a 92% yield of diene 1. Consequently, allylic iodides appeared to react with equal facility as allylic bromides. The reaction then of NaI with allyl chloride was examined in THF and found to approach completion within 20 h at 25 °C (~ 0.5 M in allyl chloride). Simply decanting the supernatant containing the “crude” allyl iodide into a second flask containing the copper reagent afforded the diene 1 in 91% yield (eqn. 11). Only trace of dimer diene 2 was detected. Due to the simplicity, mildness and ease of workup, this method was adopted for use with allylic chlorides (Table-2). Again, each product was found to be exclusively the *trans*-isomer indicating the reaction to be proceeding with complete retention of configuration.

Conclusion

The alkenylcopper intermediates generated from alkenylboronate esters readily undergo cross-coupling with allylic halides in a highly stereospecific manner. The stereochemistry is predefined by the starting alkenylboronate stereochemistry allowing the preparation of both *cis*- and *trans*-alkenylcopper reagents. The mildness of the reaction conditions readily permits sensitive functional groups to be tolerated.

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