Asian Journal of Chemistry; Vol. 26, No. 21 (2014), 7401-7403

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.17095

Synthesis and Characterization of Novel (E)-1-(Hexa-3,5-dien-1-yl)-4-methoxybenzene *via* Boronate Complex

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Received: 21 January 2014; *Accepted*: 7 April 2014; *Published online*: 30 September 2014; AJC-16147

Novel (E)-1-(hexa-3,5-dien-1-yl)-4-methoxybenzene was synthesized through boronate complex. 3-(4-Methoxyphenyl)propyl diisopropylcarbamate was reacted with allylboronic acid pinacol ester in the presence of *N*,*N*,*N*,*N*-tetramethylethyllenediamine to give secondary boronic ester which was further reacted with (vinylsulfonyl)benzene by using Grubbs Hoveyda II. Resulting product (E)-2-(1-(4-methoxyphenyl)-6-(phenylsulfonyl)hex-5-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was then treated with 1-bromo-3,5-*bis*(trifluoromethyl)benzene in the presence of *n*-BuLi to get nucleophilic boronate complex. (E)-1-(hexa-3,5-dien-1-yl)-4-methoxybenzene was obtained in excellent yields by stirring boronate complex at 50 °C for 1 h and refluxing for 15 h.

Keywords: Lithiation borylation, Secondary boronic ester, 1-Bromo-3,5-*bis*(trifluoromethyl)benzene, Boronate complex.

INTRODUCTION

Olefin metathesis chemistry[1] has led a number of opportunities in organic synthesis. Olefin metathesis[2] involves the redistribution of fragments of alkenes by regeneration of carbon-carbon double bonds. There are numerous applications of olefin metathesis and it is an important methodology to produce reagents.

Addition of aryl lithium reagents to secondary boronic esters results to a new class of chiral organometallic-type reagents which have broad utility in asymmetric organic synthesis. Larouche-Gauthier *et al.*[3] formed intermediate boronate complex by adding an aryl lithium reagent to a secondary boronic ester. It behaved as a chiral nucleophile and maximum enantioselectivity was found by using electron withdrawing groups on aryllithium. Hussain *et al.*[4] used different aryl lithiums and studied stereoselectivity of boronate complexes by tuning steric bulk. Hoffmann[5] obtained chiral Grignard reagents from sulfoxides Mg exchange reaction of halosulfoxides. Brown *et al.*[6] investigated iodination of the ate-complexes from various B-alkoxyborinane derivatives and 1-alkynyl lithium. Vedejs *et al.*[7] synthesized ate-complexes which contained stereogenic boron by reacting trivalent boranes with nucleophiles. They noticed that stability of ate-complex depend upon the electronegativity of substituents attached to boron. Ryschkewitsch and Garrett[8] resolved chiral boronate complexes by classical methods. Bernardi *et al.*[9] determined the role of ate-complxes in aldol stereoselectivity.

In the recent paper, we reported the synthesis of novel (E)-1-(hexa-3,5-dien-1-yl)-4-methoxybenzene (**7**). It was characterized by IR, ^{1}H, ^{13}C and mass spectra. Lithiation-Borylation was used to synthesize the secondary boronic ester and by using olefin cross metathesis, it gave (E)-2-[1-(4-methoxyphenyl)-6-(phenylsulfonyl)hex-5-en-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane when reacted with (vinylsulfonyl)benzene. (E)-2-[1-(4-Methoxyphenyl)-6-(phenylsulfonyl)hex-5-en-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was converted into ate-complex which on heating produced the desired product.

EXPERIMENTAL

n-Butyl lithium (*n*-BuLi), *sec*-butyl lithium solution (*s*-BuLi) (1.6 M), pinacol, *N*,*N*,*N*,*N*-tetramethylethylenediamine (TMEDA), (vinylsulfonyl)benzene, Grubbs Hoveyda II and 1-bromo-3,5-*bis*(trifluoromethyl)benzene were taken from Sigma Aldrich. All reagents were used without further purification. To dry diethyl ether (Et_2O) and tetrahydrofuran (THF) 4 A° molecular sieves were used. All experiments were done in nitrogen atmosphere using schlenk lines.

Equipments: ^{1}H and ^{13}C spectral measurements were done by using varian NMR (400 MHz) spectrometer (model DMX 400). For protons, chemical shifts were calculated corresponding to tetramethylsilane (TMS) at $\delta = 0$ ppm.

Synthesis and characterization of 2-[1-(4-methoxyphenyl)hex-5-en-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3): To a solution of 3-(4-methoxyphenyl)propyl

diisopropylcarbamate (1 g, 3.41 mmol, 1 eq) (**1**) and *N*,*N*,*N*,*N*-tetramethylethylenediamine (0.61 mL, 4.09 mmol, 1.2 eq) (**2a**) in Et_2O (17 mL) at -78 °C, *sec*-BuLi (1.6 M in 92:8 cyclohexane/hexane, 2.9 mL, 3.75 mmol, 1.1 eq) was added dropwise and stirred for 5 h at -78 °C. Then allyl boronic acid pinacol ester (0.77 mL, 4.09 mmol, 1.2 eq) (**2**) was added dropwise to the reaction mixture and further stirred at -78 °C for 1 h and warmed to room temperature. At this stage, a solution of $MgBr_2{\cdot}OEt_2$ in Et_2O, made as follows, was added to the reaction mixture. [At room temperature, 1,2-dibromoethane (0.60 mL, 6.88 mmol, 1 eq) was added into a suspension of magnesium (0.17 g, 6.88 mmol, 1 eq) in Et_2O (8.6 mL). The reaction flask was further stirred for 2 h after placing into a water bath in order to control the moderate exotherm]. Biphasic mixture having two layers thus obtained was added to the former reaction mixture *via* syringe and then refluxed for 16 h. Reaction mixture was then cooled to room temperature. Water was used to quench the reaction. After adding diethyl ether, layers were extracted and washed with 1 N hydrochloric acid, 1 N sodium hydroxide, water and then brine. It was dried with $MgSO_4$ and concentrated. Column chromatography (SiO_2) was then used to purify the crude product. Pure(R)-2-(1-(4-methoxyphenyl)hex-5-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3**) (0.84 g, 77.60 %) was obtained as colorless oil. The reaction is given in Fig. 1.

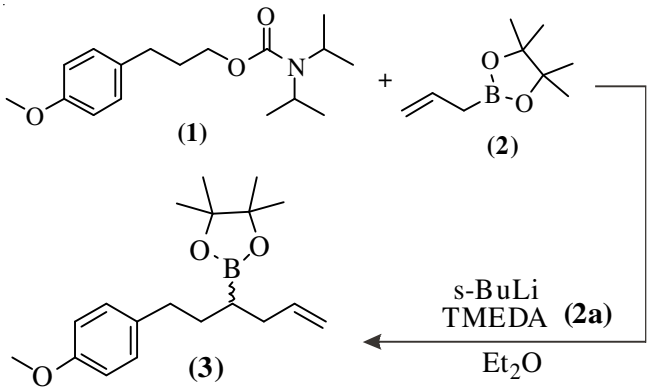


Fig. 1. Synthesis of 2-(1-(4-methoxyphenyl)hex-5-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.09 (2H, d, *J* = 8.80 Hz, 2 × ArH) 6.81 (2H, d, *J* = 8.80 Hz, 2 × ArH) 5.86-5.75 (1 H, m, $CH{=}CH_2$) 5.04 (1H, d, *J* = 2.20 Hz, CH=CHH) 4.94 (1H, d, *J* = 10.27 Hz, CH=CHH) 3.78 (3H, s, OCH_3) 2.63-2.48 (2H, m, $ArCH_2CH_2CHBCH_2$) 2.27-2.11 (2H, m, $ArCH_2CH_2CHBCH_2$) 1.78-1.58 (2H, m, $ArCH_2CH_2CHBCH_2$) 1.25 (12 H, s, 4 × CH_3) 1.08-1.18 (1 H, m, $ArCH_2CH_2CHBCH_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 157.6 (1C, -OCH_3), 138.4 (2C, 2 × ArCH), 135 (2C, 2 × ArCH), 129.2 (1C, ArC-O), 114.9 (1C, -$CH_2CH{=}CH_2$), 113.6 (1C, -CHb=CH_2), 83 (2C, 2 × $C(CH_3)_2$), 55.2 (1C, $ArCCH_2$), 35.3 (1C, -CH_2CH_2CHB), 34.5 (1C, -CH_2CHB), 33.1 (1C, -$CHBCH_2CH$), 24.9 (1C, -CH_2CH_2CHB), 24.8 (4C, 2 × $(CH_3)_2C$).

^{11}B NMR (96.23 MHz, none): δ ppm 33.24, IR (film): ν(cm^{-1}) 3026 (sp^2C-H stretch), 2977, 2924, 2852 (sp^3 C-H stretch), 1511, 1456 (sp^2 C=C stretch), 1243, 1175, 1142 (sp^3 C-O stretch), 846, 822, 670 (sp^2 C-H oop bending).

Synthesis and Characterization of (E)-2-[1-(4-methoxyphenyl)-6-(phenylsulfonyl)hex-5-en-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5): Grubbs-Hoveyda II (**4a**) (3.9 mg, 0.0063 mmol, 0.05 eq) was added to a solution of 2-[1-(4-methoxyphenyl)hex-5-en-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3**) (40 mg, 0.126 mmol, 1 eq) and (vinylsulfonyl)benzene (**4**) (0.0635 g, 0.378 mmol, 3 eq) in CH_2Cl_2 (2 mL). After fitting a condenser to the flask, reaction mixture was refluxed for 15 h under nitrogen. The reaction mixture was reduced in volume to 0.5 mL and then purified directly on a silica gel column eluting with 9:1 Pet. Ether/EtOAc to get the desired product (E)-2-(1-(4-methoxyphenyl)-6-(phenylsulfonyl)hex-5-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**5**) as dark brown solid (0.0438 g, 77.25 %)[10] m.p. 82 °C (Fig. 2).

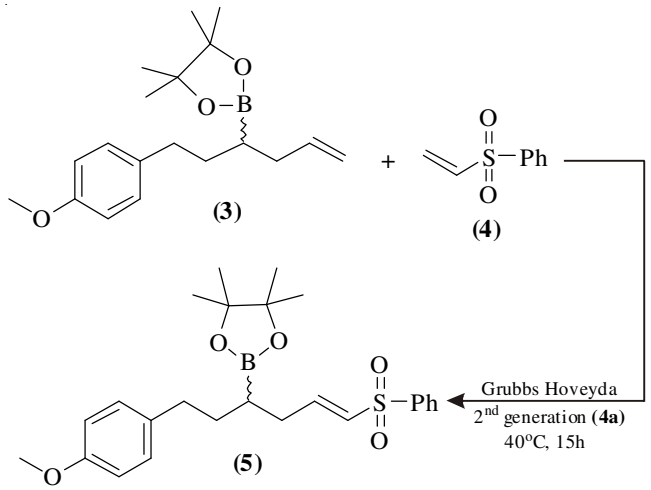


Fig. 2. Synthesis of (E)-2-(1-(4-methoxyphenyl)-6-(phenylsulfonyl)hex-5-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.88-7.84 (2H, m, 2 × ArH) 7.62-7.56 (1H, m, 1 × ArH) 7.54-7.48 (2H, m, 2 × ArH) 7.05-6.99 (2H, m, 2 × ArH) 6.96 (1H, t, *J* = 6.97 Hz, CH_2-CH=CH) 6.84-6.77 (2H, m, 2 × ArH) 6.31 (1H, dt, *J* = 15.16, 1.47 Hz, CH_2-CH=CH) 3.78 (3H, s, -CH_3) 2.59-2.45 (2H, m, CH_2-CH_2-CHB) 2.43-2.26 (2H, m, CH_2-CHB-CH_2) 1.77-1.66 (1H, m, CH_2-CHB-CHH) 1.63-1.53 (1H, m, CH_2-CHB-CHH) 1.27-1.21 (1H, m, CH_2-CHB-CH_2) 1.18 (12 H, s, 4 × CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 157.7 (1C, ArC-O) 146.9 (1C, ArC-S) 140.8 (1C, CH=CH-S) 134.2 (1C, CH=CH-S) 133.1 (1C, ArC-CH_2) 130.6 (1C, ArCH) 129.2 (2C, 2 × ArCH) 129.1 (2C, 2 × ArCH) 127.5 (2C, 2 × ArCH) 113.7 (2C, 2 × ArCH) 83.4 (2C, 2 × $C(CH_3)_2$) 55.2 (1C, OCH_3) 34.1 (1C, CH_2CHBCH_2) 33.1 (1C, CH_2CH_2CHB) 32.8 (4C, 2 × $(CH_3)_2C$) 24.8 (1C, -$CHBCH_2CH$) 24.7 (1C, CH_2CH_2CHB).

^{11}B NMR (96.23 MHz, none): δ ppm 33.24, IR (film): ν(cm^{-1}) 2977, 2924 (sp^3 C-H stretch), 1511, 1446 (sp^2 C=C stretch), 1244, 1176, 1141 (sp^3C-O stretch), 822, 730, 687 (sp^2 C-H oop bending).

Synthesis and characterization of (E)-1-(hexa-3,5-dien-1-yl)-4-methoxybenzene (7): To a solution of 3,5-$(CF_3)_2C_6H_3Br$ (24.6 mg, 0.084 mmol, 1.2 eq) in THF (1.9 mL) at -78 °C *n*-BuLi (1.6 M in hexanes, 0.053 mL, 0.084 mmol, 1.2 eq) was dropwise added. Reaction mixture was then stirred for

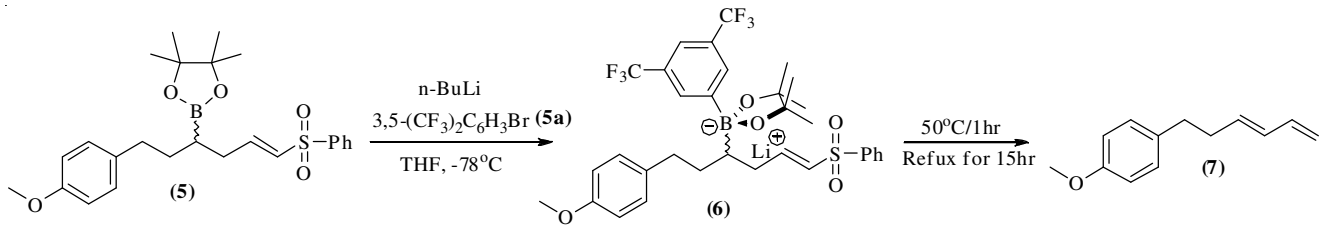


Fig. 3. Synthesis of (E)-1-(hexa-3,5-dien-1-yl)-4-methoxybenzene (**7**)

1 h at -78 °C and a solution of boronic ester (32 mg, 0.070 mmol, 1 eq) made in THF (1.5 mL) was dropwise added. The mixture was stirred at -78 °C for 0.5 h and 0.5 h at room temperature to form boronate complex. Ate-complex was further heated at 50 °C for 1 h and refluxed for 15 h (Fig. 3).

Reaction was quenched with water; EtOAc was added to separate layers. Both layers were then combined, washed with brine and dried using $MgSO_4$. After concentrating, the crude mixture was finally purified by column chromatography (SiO_2, 2:1 Pet. ether/EtOAc) to get desired product as colorless oil (19.87 mg, 62.10 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.14-7.07 (2 H, m, 2 × ArH) 6.85-6.80 (2H, m, 2 × ArH) 6.30 (1H, dt, *J* = 17, 10.21 Hz, CH=CH-CH=CH_2) 6.12-5.97 (1H, m, CH=CH-CH=CH_2) 5.78-5.69 (1H, m, CH=CH-CH=CH_2) 5.21-5.06 (1 H, m, CH=CHH) 4.99-4.95 (1H, m, CH=CHH) 3.79 (3H, s, -CH_3) 2.70-2.60 (2H, m, CH_2CH_2CH) 2.52-2.33 (2H, m, CH_2CH_2CH).

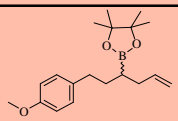
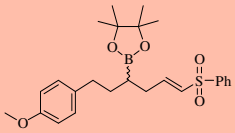
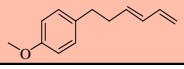
^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 157.7 (1C, ArC-O) 137.0 (1C, CH=CH_2) 133.7 (1C, CH=CH-CH=CH_2) 132 (1C, ArC-CH_2) 129.5 (1C, CH=CH-CH=CH_2) 129.1 (2C, 2 × ArCH) 114.9 (1C, CH=CH_2) 113.6 (2C, 2 × ArCH) 55.1 (1C, -CH_3) 34.6 (1C, CH_2CH_2CH) 34.5 (1C, CH_2CH_2CH), IR (film): ν(cm^{-1}) 2955, 2921, 2852 (sp^3 C-H stretch), 1737, 1461 (sp^2 C=C stretch), 1277, 1184, 1137 (sp^3 C-O stretch), 967, 805 (sp^2 C-H oop bending). HRMS (ESI) Calcd. for $C_{13}H_{17}O$ [M + H]$^+$ 189.1279, found 189.1287.

RESULTS AND DISCUSSION

Starting material 2-[1-(4-methoxyphenyl)hex-5-en-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3**) has been synthesized as colorless oil in excellent yields (77.6 %) (Table-1, entry 1) by using Lithiation-Borylation methodology; carbamate (**1**) was reacted with pinacol (**2**) by using TMEDA (2a) at suitable conditions. Spectral studies proved the structure as mentioned in literature[11]. By using application of olefin cross metathesis, boronic ester (**3**) was then reacted with (vinylsulfonyl)benzene (**4**) to give (E)-2-(1-(4-methoxyphenyl)-6-(phenylsulfonyl)hex-5-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**5**) as dark brown solid. Yield was again excellent (Table-1, entry 2) for this reaction.

Boronate complex (**6**) which acted as nucleophile was synthesized by reacting (E)-2-(1-(4-methoxyphenyl)-6-(phenylsulfonyl)hex-5-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**5**) with aryl lithium (**5a**). Boronate complex (**6**) showed best nucleophilic character by using 3,5-$(CF_3)_2C_6H_3Br$ (**5a**) as aryl lithium[11] and it was then stirred at 50 °C for 1 h and then refluxed for 15 h and desired product (E)-1-(hexa-3,5-dien-1-yl)-4-methoxybenzene (**7**) was collected.

TABLE-1
PHYSICAL STATES AND YIELDS

Entry	Substances	Physical States	Melting points	Yield (%)
1		Colorless oil	—	77.60
2		Dark brown solid	82 °C	77.25
3		Colorless oil	—	62.10

Conclusion

Novel (E)-1-(hexa-3,5-dien-1-yl)-4-methoxybenzene has been synthesized through a novel route and characterized by spectral techniques like IR, ^{1}H, ^{13}C and MS. Boronate complex was successfully converted into aromatic dienes. This novel synthetic route resulted in excellent yields.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the financial support by Higher Education Commission of Pakistan. Thanks are also due to the Department of Chemistry, University of Engineering and Technology, Lahore, Pakistan and Superior University Lahore, Pakistan for guidance, research and laboratory facilities.

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