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Synthesis of 5-Methylene-1,3-cyclohexadienes (*o*-Isotoluenes) via Electrocyclization of (4Z)-1,2,4,6-Heptatetraenes

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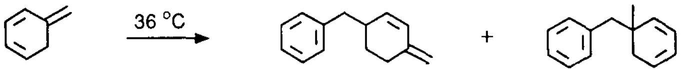
Abstract: Treatment of alkenyldicyclohexylborane **5** with 1-lithio-3,4-pentadien-1-ynes derived from **10** followed by trimethyltin chloride and acetic acid furnished *o*-isotoluenes **13** in a single operation. The reaction proceeded through an initial formation of diene-allenes **11**, which underwent facile electrocyclizations to produce **12** leading to *o*-isotoluenes **13**.

As an alicyclic isomer of toluene, 5-methylene-1,3-cyclohexadiene (*o*-isotoluene, **1**) possesses an additional 24 kcal/mol in energy,[1] which is mainly responsible for its unusual chemical reactivity. Dimerization of **1** via concerted ene reactions to the corresponding ene dimers **2** and **3** (75 % yield, **2**:**3** = 2:1) occurs under mild thermal conditions.[2] Unlike the usual ene reactions which require high reaction temperatures,[3] the formation of an aromatic system during dimerization of **1** greatly facilitates the rate of reaction. Treatment of **1** with tetracyanoethylene also produced the corresponding ene adduct.[4] Similarly, reaction with styrene at 80 °C furnished 1,2-diphenylpropane and 1,3-diphenylpropane in a 3:1 ratio in 90 % total yield.[4b] The *o*-isotoluene **1** is also sensitive to acid and oxygen, being rapidly converted to toluene[4b] and benzyl hydroperoxide,[5] respectively.



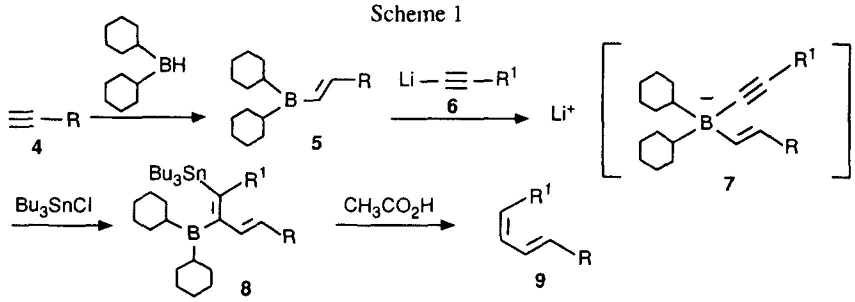
1 **2** **3**

The high reactivities of **1** and its derivatives put severe constraints on possible synthetic methods for these fascinating compounds. Thermolysis of suitable precursors, obtained by multistep syntheses, immediately prior to the formation of *o*-isotoluenes has been employed to accomplish this difficult task.[4,6] Alternatively, facile electrocyclization of the transient (Z)-1,2,4,6-heptatetraene (diene-allene) has also been shown to produce **1**.[7] We recently reported a simple and versatile route to (Z)-diene-allenes, thus providing a practical synthesis of *o*-isotoluenes.[7b] We now report a new method for the synthesis of a variety of (Z)-diene-allenes, leading to the corresponding *o*-isotoluenes with diverse structures.

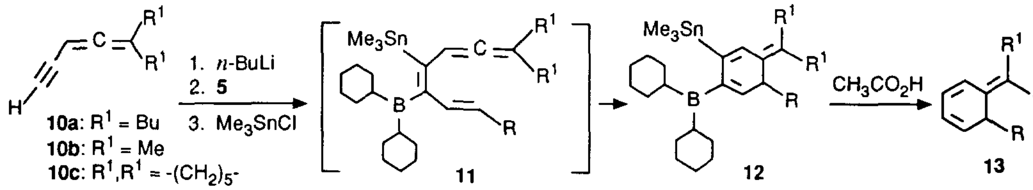
It was previously reported that treatment of alkenyldicyclohexylboranes **5**, readily prepared from terminal alkynes **4** and dicyclohexylborane, with 1-lithio-1-alkynes **6** provided 1-alkynylalkenyldicyclohexylborates **7** (Scheme 1).[8] Exposure of **7** to tributyltin chloride promoted a selective migration of the alkenyl group from the boron atom to the adjacent acetylenic carbon atom to furnish **8**, which on treatment with acetic acid was converted to dienes **9** with high geometric purity.

We envisioned that by using the readily available 3,4-pentadien-1-ynes **10**[9] to produce 1-lithio-3,4-pentadien-1-ynes for the subsequent formation of the organoborate complexes, the reaction sequence outlined in Scheme 1 could be easily adopted for the synthesis of (Z)-diene-allenes **11** as transient intermediates toward *o*-isotoluenes **13** (Scheme 2). Indeed, this synthetic route was found to be successful for the preparation of a variety of *o*-isotoluenes (Table 1). Unlike the parent compound **1** and *o*-isotoluenes without an R group on the six-membered ring, *o*-isotoluenes **13** having an R group on the ring were stable to oxygen and could be isolated and purified by column chromatography as observed previously.[7b]

Scheme 1

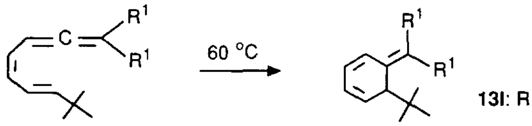


Scheme 2



The rates of electrocyclization of diene-allenes **11** to **12** were generally very facile,[10] giving rise to *o*-isotoluenes **13** after treatment of **12** with acetic acid. However with the presence of a sterically demanding *tert*-butyl group as the R group, the rate of electrocyclization was significantly reduced, allowing isolation of diene-allenes **14a** (41%) and **14b** (35%)[11] after treatment with acetic acid. On heating in $CDCl_3$ at 60 °C for 96 h ($t_{1/2}$ = ca. 12 h), **14b** was smoothly converted to *o*-isotoluene **13l** in 91% isolated yield.

14a: R^1 = Bu, 41%
14b: R^1,R^1 = $-(CH_2)_5-$, 35%

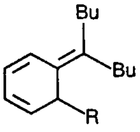


13l: R^1,R^1 = $-(CH_2)_5-$, 91%

The conjugated allenynes **10** were synthesized according to the reported procedures.[9] To 7.326 g (48.2 mmol) of the readily available 3-butyl-1,2-heptadiene[12] in 150 mL of THF at -60 °C under an N_2 atmosphere was added 19.3 mL of a 2.5 M solution of *n*-butyllithium in hexanes. After 1 h at -60 °C, 7.61 g (53.0 mmol) of anhydrous CuBr in 60 mL of THF was introduced via cannula, and the mixture was allowed to warm to -20 °C. The mixture was then cooled to -40 °C, and 11.88 g (53 mmol) of 1-iodo-2-(trimethylsilyl)acetylene[13] was added dropwise over 1 h. After an additional 1 h at -40 °C, the mixture was allowed to warm to 0 °C and then was poured into a saturated NH_4Cl solution. Pentane (30 mL) was added and the mixture was filtered. The organic layer was separated, and the aqueous layer was extracted with pentane (3 x 40 mL). The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated. The residue was distilled (bp 75 °C, 0.2 Torr) to afford 8.658 g (73%) of 1-(trimethylsilyl)-5-butyl-3,4-nonadien-1-yne as a colorless liquid.[9a] To 3.754 g (15.14 mmol) of 1-(trimethylsilyl)-5-butyl-3,4-nonadien-1-yne in 140 mL of ethanol under a nitrogen atmosphere was added 36 mL of a 0.1 N aqueous NaOH solution. After 24 h at rt, the mixture was poured into ice/water and was extracted with pentane. The organic layer was washed with a saturated NH_4Cl solution, dried over $MgSO_4$, and concentrated. The residue was distilled (bp 38 °C, 0.09 Torr) to furnish 2.383 g (90%) of **10a** as a colorless liquid: IR (neat) 3314, 2105, 1955, 1466, 1379 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.30 (1 H, sextet, J = 2.8 Hz), 2.75 (1 H, d, J = 2.4 Hz), 1.99 (4 H, m), 1.37 (8 H, m), 0.90 (6 H, t); ^{13}C ($CDCl_3$) δ 210.47, 107.34, 78.32, 76.20, 74.98, 31.89, 29.44, 22.32, 13.85; MS (m/e) 161 (M^+-CH_3), 147, 134, 119, 105, 91, 77. Alternatively, 5-methyl-1-(trimethylsilyl)-3,4-hexadien-1-yne[9a] was synthesized in 93% isolated yield by sequentially treating a slurry of CuBr and triethylamine in DMF under an N_2 atmosphere with (trimethylsilyl)acetylene and 1-bromo-3-methyl-1,2-butadiene[14] at 0 °C followed by 10 h at 30 °C.[9b] Desilylation with NaOH/EtOH furnished **10b** in 28% isolated yield. The low isolated yield for **10b** was due to its high volatility. Similarly, 5,5-(pentamethylene)-1-(trimethylsilyl)-3,4-pentadien-1-yne

Table 1. Synthesis of *o*-Isotoluenes **13**

o-isotoluenes, **13**, isolated yield[a,b]



13a-g

13a, R = Bu, 60%

13b, R = *n*-C_5H_{11}, 54%

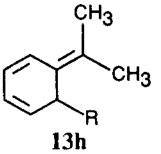
13c, R = *i*-Pr, 38%

13d, R = Ph, 16%

13e, R = 1-cyclohexenyl, 41%

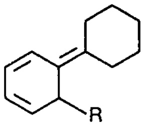
13f, R = methoxymethyl, 20%

13g, R = cyclohexylmethyl, 30%



13h

13h, R = Pr, 41%



13i-l

13i, R = Pr, 43%

13j, R = Ph, 25%

13k, R = *i*-Pr, 38%

13l, R = *t*-Bu, 32%[c]

[a] The isolated products were characterized by IR, ^1H (270 MHz) and ^{13}C (67.9 MHz) NMR,[16] and MS.

[b] In addition to *o*-isotoluenes **13**, ca. 5% of the 1-cyclohexyl-1,3,4-pentatriene derivatives arising from a competing migration of the cyclohexyl group were also isolated.

[c] The overall isolated yield from **10c**.

was prepared from 1-bromo-3,3-(pentamethylene)-1,2-propadiene[14] and (trimethylsilyl)acetylene in 85% isolated yield. Desilylation with NaOH/EtOH furnished **10c** in 86% isolated yield.

The following procedure for the synthesis of *o*-isotoluene **13a** is representative. To 1.5 mL of a 2.0 M solution of $BH_3{\cdot}SMe_2$ (3.0 mmol) in 8 mL of THF under a nitrogen atmosphere was added 0.61 mL (0.492 g, 6.0 mmol) of cyclohexene at 0 °C. After 30 min, a white slurry of dicyclohexylborane appeared.[15] The mixture was kept at 0 °C for an additional 30 min before cooling to -15 °C. A solution of 0.246 g of 1-hexyne (3.0 mmol) in 3 mL of THF was then introduced. After 2 h at 0 - 5 °C, the reaction mixture became homogeneous and was used immediately to form the organoborate complex. To a second flask containing 0.528 g of **10a** (3.0 mmol) in 3 mL of THF at -25 °C was added 1.2 mL of a 2.5 M solution of *n*-butyllithium (3.0 mmol) in hexanes. After 15 min at -25 °C, the resulting 1-lithio-5-butyl-3,4-nonadien-1-yne was introduced via cannula to the flask containing (*E*)-1-hexenyldicyclohexylborane at -25 °C. The reaction mixture was stirred at rt for 1 h before cooling to 0 °C. A solution of trimethyltin chloride (3.0 mL, 1.0 M, 3.0 mmol) in THF was then introduced with a syringe. After an additional 1 h at rt, 2 mL of glacial acetic acid was added and the mixture was heated to 50 °C for 1 h before cooling to rt. Methanol (5 mL), 6.3 mL of a 6 N NaOH solution, and 1.74 mL of 30% H_2O_2 were then introduced sequentially, and the reaction mixture was heated to 50 °C for 1 h. The mixture was then extracted with pentane (3 x 10 mL), and the combined organic layers were washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel / hexanes) to furnish 0.465 g (60 %) of **13a** as a light yellow liquid: IR (neat) 1636, 1466, 1378, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.34 (1 H, d, J = 9.9 Hz), 5.94 (1 H, dd, J = 3 and 1 Hz), 5.93 (1 H, dd, J = 3 and 1 Hz), 5.72 (1 H, dt, J = 9.9 and 3 Hz), 3.23 (1 H, m), 2.2 (2 H, m), 2.07 (1 H, m), 1.95 (1 H, m), 1.5 (1 H, m), 1.3 (13 H, m), 0.92 (9 H, m); ^{13}C NMR ($CDCl_3$) δ 141.05, 132.82, 131.71, 124.76, 122.51, 121.09, 37.81, 37.46, 31.82, 31.66, 31.40, 30.90, 28.14, 23.22, 23.04, 23.01, 14.12, 14.09, 14.07; MS (*m*/*e*) 260 (M^+), 203, 161, 147, 133, 119, 105, 91.

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11. **14a**: ^{1}H (CDCl$_3$) δ 6.38 (1 H, dd, *J* = 15.3 and 11.0 Hz), 6.22 (1 H, dd of quintet, *J* = 11.1, 2.8, and 1 Hz), 5.87 (1 H, t, *J* = 10.8 Hz), 5.73 (1 H, d, *J* = 15.2 Hz), 5.68 (1 H, t, *J* = 10.9 Hz), 1.97 (4 H, dt, *J* = 2.8 and 8.1 Hz), 1.45 - 1.25 (8 H, m), 1.05 (9 H, s), 0.89 (3 H, t); ^{13}C δ 205.42, 146.47, 127.95, 124.79, 120.20, 105.50, 90.93, 33.46, 32.39, 29.81, 29.56, 22.40, 13.99; **14b**: ^{1}H (CDCl$_3$) δ 6.39 (1 H, dd, *J* = 15.0 and 11.1 Hz), 6.13 (1 H, dm, *J* = 11.3 and 1 Hz), 5.89 (1 H, tt, *J* = 10.9 and 1 Hz), 5.73 (1 H, dt, *J* = 15 and 0.8 Hz), 5.70 (1 H, tt, *J* = 10.9 and 0.8 Hz), 2.14 (4 H, m), 1.65 - 1.45 (6 H, m), 1.06 (9 H, s); ^{13}C δ 202.60, 146.42, 128.18, 124.58, 120.18, 103.23, 88.16, 33.43, 31.42, 29.56, 27.34, 26.10.
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16. The ^{1}H and ^{13}C NMR spectra (CDCl$_3$) of **13c-f**, **13h-i**, and **13l**. **13c**: ^{1}H δ 6.35 (1 H, d, *J* = 9.7 Hz), 6.01 (1 H, dd, *J* = 9.5 and 5.2 Hz), 5.84 (1 H, dd, *J* = 9.5 and 5.6 Hz), 5.66 (1 H, dd, *J* = 9.8 and 5.2 Hz), 3.18 (1 H, t, *J* = 5.4 Hz), 2.27 (2 H, m), 2.02 (1 H, m), 1.89 (1 H, m), 1.64 (1 H, m), 1.35 (8 H, m), 0.904 (3 H, d, *J* = 6.9 Hz), 0.901 (3 H, t, *J* = 6.7 Hz), 0.85 (3 H, d, *J* = 6.7 Hz); ^{13}C δ 142.02, 131.36, 129.75, 125.80, 124.27, 121.19, 43.51, 36.63, 31.93, 31.79, 31.23, 30.77, 23.21, 23.06, 20.25, 17.35, 14.10; **13d**: ^{1}H δ 7.25 (5 H, m), 6.53 (1 H, d, *J* = 9.7 Hz), 5.87 (2 H, m), 5.78 (1 H, dt, *J* = 9.7 and 4.4 Hz), 4.33 (1 H, d, *J* = 3.7 Hz), 2.19 (2 H, m), 1.99 (1 H, m), 1.80 (1 H, m), 1.34 (4 H, m), 1.18 (4 H, m), 0.91 (3 H, t, *J* = 7.1 Hz), 0.77 (3 H, t, *J* = 7.1 Hz); ^{13}C δ 146.34, 143.88, 132.41, 129.77, 128.59, 127.04, 126.18, 125.07, 120.92, 120.65, 44.59, 32.65, 31.68, 31.38, 30.22, 23.14, 23.06, 14.04, 13.96; **13e**: ^{1}H δ 6.38 (1 H, d, *J* = 10.1 Hz), 5.91 (1 H, m), 5.67 (1 H, m), 5.49 (1 H, br s), 3.84 (1 H, d, *J* = 5.4 Hz), 2.3 - 2.1 (4 H, m), 2.0 (4 H, m), 1.6 - 1.2 (12 H, m), 0.9 (6 H. m); ^{13}C δ 143.28, 140.80, 131.39, 128.61, 125.31, 121.85, 120.94, 120.53, 47.37, 32.43, 31.75, 31.61, 31.47, 30.83, 25.53, 24.44, 23.31, 23.08, 22.52, 14.13, 14.04; **13f**: ^{1}H δ 6.33 (1 H, d, *J* = 9.9 Hz), 6.00 (2 H, m), 5.73 (1 H, dt, *J* = 9.6 and 3.3 Hz), 3.58 (1 H, dt, *J* = 9.6 and 4.5 Hz), 3.40 (1 H, t, *J* = 9.3 Hz), 3.32 (3 H, s), 3.13 (1 H, dd, *J* = 8.9 and 5.2 Hz), 2.21 (2 H, m), 2.08 (1 H, m), 1.95 (1 H, m), 1.45 - 1.25 (8 H, m), 0.92 (3 H, t), 0.91 (3 H, t); ^{13}C δ 143.06, 130.74, 127.38, 124.74, 123.40, 121.17, 78.05, 58.94, 38.30, 31.76, 31.36, 31.03, 23.18, 22.97, 14.10, 14.05; **13h**: ^{1}H δ 6.38 (1 H, d, *J* = 9.9 Hz), 5.93 (2 H, m), 5.71 (1 H, dt, *J* = 9.7 and 4.3 Hz), 3.33 (1 H, br), 1.81 (3 H, s), 1.77 (3 H, s), 1.5 (1 H, m), 1.35 (2 H, m), 1.26 (1 H, m), 0.88 (3 H, t, *J* = 7.1 Hz); ^{13}C δ 132.31, 131.59, 131.16, 124.51, 122.38, 120.70, 39.06, 37.73, 20.28, 19.85, 18.88, 14.30; **13i**: ^{1}H δ 6.43 (1 H, d, *J* = 9.7 Hz), 5.92 (2 H, m), 5.72 (1 H, dd, *J* = 9.7 and 5.4 Hz), 3.34 (1 H, dt, *J* = 8.1 and 4.7 Hz), 2.29 (2 H, m), 2.20 (2 H, m), 1.56 (6 H, m), 1.48 (1 H, m), 1.36 (2 H, m), 1.24 (1 H, m), 0.88 (3 H, t); ^{13}C δ 140.14, 132.42, 128.50, 123.95, 122.46, 121.16, 40.08, 37.13, 30.28, 29.76, 28.58, 28.29, 27.02, 18.74, 14.42; **13l**: ^{1}H δ 6.52 (1 H, d, *J* = 9.8 Hz), 6.07 (1 H, ddt, *J* = 9.5, 5.1, and 0.8 Hz), 5.93 (1 H, ddq, *J* = 9.5, 5.9, and 0.8 Hz), 5.71 (1 H, dd, *J* = 10.0 and 5.0 Hz), 3.13 (1 H, d, *J* = 5.9 Hz), 2.44 (1 H, m), 2.33 (2 H, m), 2.12 (1 H, m), 1.65 - 1.45 (6 H, m), 0.85 (9 H, s); ^{13}C δ 143.71, 130.29, 126.31, 126.21, 124.26, 121.43, 45.80, 38.83, 31.32, 30.09, 28.20, 27.88, 26.99, 26.92.

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