JOC*Note*

Synthesis of Functionalized 1,5-Cyclooctadienes by LICKOR Metalation

Jefferson D. Revell and A. Ganesan*

Combinatorial Centre of Excellence, Department of Chemistry, University of Southampton, Southampton SO17 1BJ, United Kingdom

ganesan@soton.ac.uk

Received March 13, 2002

Abstract: 1,5-Cyclooctadiene was lithiated under LICKOR superbase conditions followed by reaction with alkyl halides or ethylene oxide to yield 3-substituted 1,5-cyclooctadienes in high yield and purity. This procedure is suitable for preparation of 1,5-cyclooctadienes carrying pendant functional groups for immobilization on solid-phase resins.

1,5-Cyclooctadienes have found widespread application as ligands for transition metals, while their propensity for transannular reactions makes them valuable synthons for various bicyclic ring systems. For example, 1,5-cyclooctadiene is the starting material for Brown's synthetically important hydroborating agent 9-BBN[1] and a combinatorial scaffold recently reported[2] by Sharpless. To explore these and other possibilities on solid-phase, we needed to prepare 1,5-cyclooctadienes containing an alkyl tether that could be immobilized on a polystyrene resin. A literature survey revealed few examples suitable for our purposes. One notable exception[3] was Winkler and Sridar's reaction of lithiated 1,5-cyclooctadiene (prepared by 1,5-cyclooctadiene + *n*-BuLi) with alkyl halides and ethylene oxide. Although these reactions proceeded in poor yield (35% being the highest, with ethylene oxide as the electrophile), the directness of the approach was appealing. Unfortunately, we were unable to reproduce the alkylation with ethylene oxide, the product mixture largely consisting of oligomerized material.

We next investigated a nonpolymerizable electrophile, the THP derivative of 6-bromo-1-hexanol. With *n*-BuLi as the base, 1,5-cyclooctadiene deprotonation appeared to be incomplete, as direct butylation of the electrophile was a competing side reaction. Nevertheless, this byproduct was readily removed by column chromatography to give the desired alkylated 1,5-cyclooctadiene in 45% yield. While this result was gratifying, a regiosisomeric diene was also present in ~14%, and could be removed only after several rounds of chromatography.

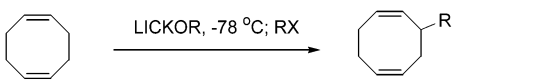
A more detailed study of the alkylation was then carried out under different conditions (Table 1). All deprotonations were carried out at −78 °C, giving rise to a thick suspension of the cyclooctadienyl anion in varying colors depending on the conditions. Upon addition of the alkylating agent, a clear yellowish-orange solution resulted in all cases. The increased reactivity of *n*-BuLi/TMEDA relative to *n*-BuLi alone in allylic deprotonations[4] was found to be beneficial in decreasing the regiosomer formation when excess TMEDA was added (entry 3). An alternative was the use of LICKOR "superbases"[5,6] formed by the addition of alkyllithiums to bulky potassium alcoholates and popularized by Schlosser for highly regioselective allylic deprotonation. With the classical LICKOR conditions using *n*-BuLi/KO*t*-Bu (entry 4), the impurity level was now reduced to ~5%. Addition of TMEDA (entry 5) gave a further slight improvement, but our cleanest product mixtures were obtained by the substitution of *t*-BuLi for *n*-BuLi, with or without TMEDA (entries 6 and 7). In these LICKOR metalations, we initially prepared the KO*t*-Bu freshly by sublimation at 5 mmHg and dissolving this in dry THF, but have found no differences when employing commercially available 1 M solutions of KO*t*-Bu in THF.

TABLE 1. Alkylation of 1,5-Cyclooctadienyllithium by $Br(CH_2)_6OTHP$

entry	deprotonation conditions[a]	color[b]	yield (%)	impurity (%)[c]
1	*n*-BuLi	bright yellow	45	14
2	*n*-BuLi, 1 equiv of TMEDA	yellow	45	16
3	*n*-BuLi, 3 equiv of TMEDA	yellow	44	7
4	*n*-BuLi, 1 equiv of KO*t*-Bu	orange	69	5
5	*n*-BuLi, 1 equiv of KO*t*-Bu, 1 equiv of TMEDA	orange	72	2
6	*t*-BuLi, 1 equiv of KO*t*-Bu	brick red	76	1−2
7	*t*-BuLi, 1 equiv of KO*t*-Bu, 1 equiv of TMEDA	dark orange	74	1−2

[a] Bases (and TMEDA, when present) were stirred at −78 °C (20 min) before dropwise addition of neat 1,5-cyclooctadiene at a rate of ~5 mL/min. [b] Color of the 1,5-cyclooctadienyl anion after stirring at −78 °C (2 h). [c] Yield of isomeric alkylated cyclooctadiene, estimated by ^{13}C NMR of the product mixture.

As far as we are aware, the use of superbases for the metalation of 1,5-cyclooctadiene is not documented. The method (eq 1) provides access to 3-substituted 1,5-cyclooctadienes in preparatively useful yields and high purity, and we have successfully prepared compounds with various alkyl tethers. Under these superbase conditions, the reaction of lithiated 1,5-cyclooctadiene with ethylene oxide itself also proceeded smoothly to give **4** in 62% yield, unlike our difficulties when using *n*-BuLi alone as the base.



(1)

1, R = $(CH_2)_3OTHP$, 62%
2, R = $(CH_2)_4OTHP$, 74%
3, R = $(CH_2)_6OTHP$, 76%
4, R = $(CH_2)_2OH$, 62%

Standard transformations served to convert **1**−**4** to other functional groups that are useful for resin attach-

(1) For recent reviews, see: (a) Stentiford, R. A. *Synlett* **2000**, 159. (b) Bracher, F.; Litz, T. *J. Prakt. Chem.* **1996**, *338*, 386−389.

(2) Converso, A.; Burow, K.; Marzinzik, A.; Sharpless, K. B.; Finn, M. G. *J. Org. Chem.* **2001**, *66*, 4386−4392.

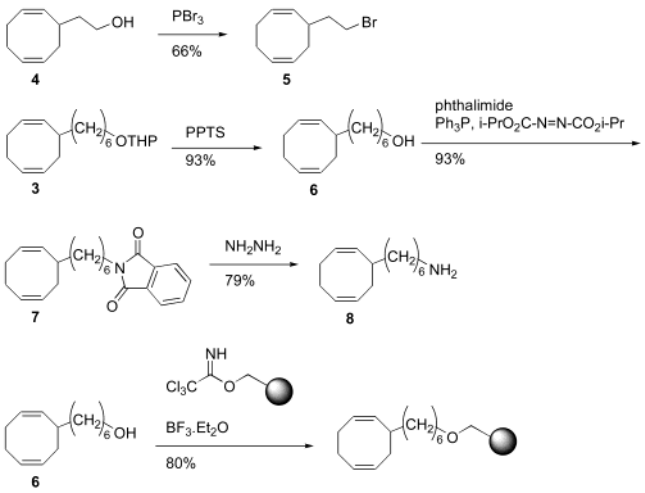
(3) Winkler, J. D.; Sridar, V. *J. Am. Chem. Soc.* **1986**, *108*, 1708−1709.

(4) Crawford, R. J.; Erman, W. F.; Broaddus, C. D. *J. Am. Chem. Soc.* **1972**, *94*, 4298−4306.

(5) For reviews, see: (a) Lochmann, L. *Eur. J. Inorg. Chem.* **2000**, 1115−1126. (b) Schlosser, M. *Pure Appl. Chem.* **1988**, *60*, 1627−1634.

10.1021/jo025715u CCC: $22.00
Published on Web 07/24/2002

SCHEME 1. Further Transformations of 3-Alkyl-1,5-cyclooctadienes



ment. The bromination of **4** (Scheme 1) provided the corresponding bromide **5**, while Mitsunobu amination of deprotected **3** afforded amine **8**. An example of solid-phase immobilization is shown by the attachment of alcohol **6** to the trichloroacetimidate[7] Wang resin.

In summary, the lithiation of 1,5-cyclooctadiene by LICKOR has proven to be a convenient route to 3-substituted homologues. The products are formed in high yield and purity, without significant contamination by regioisomers. Studies with immobilized 1,5-cyclooctadienes on solid-phase are currently in progress.

Experimental Section

General Considerations. All reactions were conducted under an inert atmosphere of dry nitrogen. Column chromatography was performed using a slight positive pressure with flash silica (0.04−0.06 mm particle size). ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, in $CDCl_3$ as the solvent. Low-resolution mass spectra were obtained by electrospray or atmospheric pressure chemical ionization techniques.

General Procedure for LICKOR Lithiation and Alkylation of 1,5-Cyclooctadiene. *tert*-Butyllithium (3.5−6 mmol in pentanes, 1.0 equiv) was transferred to a Schlenk vessel by cannula under an argon atmosphere, and the solvent was cautiously removed in vacuo. The resulting white powder was redissolved in anhydrous THF (30−50 mL) precooled to −78 °C. To the resulting yellow solution was added an anhydrous THF solution of KO*t*-Bu (1 equiv) at −78 °C, followed by the dropwise addition of neat 1,5-cyclooctadiene (1.01 mol equiv). The reaction mixture was stirred gently for 2 h, maintaining the reaction temperature at −78 °C, to give a brick red suspension. The alkyl halide or ethylene oxide (1.1 equiv) was then rapidly added dropwise with stirring, and the reaction mixture was maintained at −78 °C for an additional 1 h before warming to ambient temperature over 1 h. The reaction mixture was quenched by transfer to a stirred solution of saturated aqueous NH_4Cl, and the phases were separated. The aqueous phase was extracted with diethyl ether, and the combined extracts were dried over $MgSO_4$, concentrated, and purified by column chromatography on silica.

2-{[3-(2,6-Cyclooctadienyl)propyl]oxy}tetrahydro-2*H*-pyran (1). Obtained in 62% yield (3.8 mmol scale) as a colorless oil from the alkylation of lithiated 1,5-cyclooctadiene with 2-(3-bromopropyloxy)-tetrahydropyran: chromatography eluent 5% ethyl acetate in hexane, R_f 0.3; IR 1079, 1034 cm^{-1}; ^{1}H NMR δ 5.55 (3H, m), 5.25 (1H, dd, J = 6.8, 11.5 Hz), 4.55 (1H, m), 3.85 (1H, m), 3.72 (1H, dd, J = 6.7, 13.6 Hz), 3.49 (1H, m), 3.38 (1H, dd, J = 6.7, 13.6 Hz), 2.75 (1H, m), 2.52 (1H, m), 2.32 (4H, m), 2.15 (3H, m), 1.75−1.30 (8H, m); ^{13}C NMR δ 134.3, 128.7, 128.6, 127.7, 98.9, 67.8, 62.4, 38.8, 34.96, 33.9, 30.8, 28.1, 28.0, 27.8, 25.6, 19.8; MS 250 (M$^+$, 1%), 107 (23%), 85 (100%).

2-{[4-(2,6-Cyclooctadienyl)butyl]oxy}tetrahydro-2*H*-pyran (2). Obtained in 74% yield (3.8 mmol scale) as a colorless oil from the alkylation of lithiated 1,5-cyclooctadiene with 2-(4-iodobutyloxy)-tetrahydropyran:[8] chromatography eluent 4% ethyl acetate in hexane, R_f 0.25−0.3; IR 1080, 1035 cm^{-1}; ^{1}H NMR δ 5.5 (3H, m), 5.30 (1H, dd, J = 6.9, 11.3 Hz), 4.55 (1H, m), 3.85 (1H, m), 3.7 (1H, m), 3.45 (1H, m), 3.35 (1H, m), 2.7 (1H, m), 2.55 (1H, m), 2.32 (4H, m), 2.15 (3H, m), 1.7−1.25 (10H, m); ^{13}C NMR δ 134.4, 128.6, 128.4, 127.4, 98.8, 67.6, 62.3, 38.7, 37.1, 34.9, 30.8, 29.9, 28.02, 27.96, 25.5, 24.2, 19.7; MS 264 (M$^+$, 12%), 107 (93%), 85 (100%). Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.26; H, 10.64.

2-{[6-(2,6-Cyclooctadienyl)hexyl]oxy}tetrahydro-2*H*-pyran (3). Obtained in 78% yield (3.5 mmol scale) as a colorless oil from the alkylation of lithiated 1,5-cyclooctadiene with 2-(6-iodohexyloxy)-tetrahydropyran:[9] chromatography eluent 3% ethyl acetate in hexane, R_f 0.25; IR 1079, 1034 cm^{-1}; ^{1}H NMR δ 5.53 (3H, m), 5.30 (1H, dd, J = 6.8, 11.5 Hz), 4.55 (1H, m), 3.85 (1H, m), 3.71 (1H, ddd, J = 2.9, 6.8, 13.4 Hz), 3.48 (1H, m), 3.36 (1H, ddd, J = 2.9, 6.8, 13.4 Hz), 2.7 (1H, m), 2.55 (1H, m), 2.32 (4H, m), 2.15 (3H, m), 1.65 (2H, m), 1.65−1.25 (12H, m); ^{13}C NMR δ 134.6, 128.8, 128.5, 127.4, 98.9, 67.7, 62.4, 38.9, 37.4, 35.0, 30.9, 29.8, 29.7, 28.1, 27.5, 26.3, 25.6, 19.8, 19.7; MS 292 (M$^+$, 2%), 107 (93%), 94 (94%), 80 (100%). Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.82; H, 11.34.

2-(2,6-Cyclooctadienyl)-1-ethanol (4). Obtained in 62% yield (6.0 mmol scale) as a colorless oil from the alkylation of lithiated 1,5-cyclooctadiene with ethylene oxide: chromatography eluent 20% ethyl acetate in hexane, R_f 0.3; IR 3305, 3005 cm^{-1}; ^{1}H NMR δ 5.55 (3H, m), 5.35 (1H, dd, J = 6.9, 11.5 Hz), 3.68 (2H, t, J = 6.6 Hz), 2.92 (1H, dd, J = 5.8, 11.9 Hz), 2.53 (1H, m), 2.33 (4H, m), 2.2 (2H, m), 1.64 (2H, m); ^{13}C NMR δ 133.7, 128.8, 128.4 (2C), 61.3, 40.1, 35.5, 35.1, 28.1, 28.0; MS 152 (M$^+$, 10%), 91 (39%), 67 (100%).

2-(2,6-Cyclooctadienyl)-1-bromoethane (5). To a stirred and cooled (salt/ice−water bath) solution of **4** (400 mg, 2.63 mmol) in anhydrous diethyl ether (20 mL) was added phosphorus tribromide (175 μL, 1.84 mmol, 0.7 equiv) at a rate such that the internal reaction temperature was maintained as closely as possible to 0 °C. The reaction mixture was maintained at this temperature for 1 h under nitrogen and then both quenched rapidly and kept cold by cautious addition to ice−water. The aqueous layer was extracted, and the combined organic extracts were washed (H_2O, saturated aqueous $NaHCO_3$, and brine), dried, and concentrated. The crude bromide was applied to a short silica plug and rapidly eluted with neat hexanes (R_f 0.7−0.9) to afford **5** as a light yellow oil (373 mg, 1.73 mmol, 66%): ^{1}H NMR δ 5.6 (3H, m), 5.30 (1H, dd, J = 11.5, 7.0 Hz), 3.45 (2H, m), 3.0 (1H, m), 2.55 (1H, m), 2.35 (4H, m), 2.2 (2H, m), 1.91 (2H, dt, J = 6.8, 13.5 Hz); ^{13}C NMR δ 132.3, 129.2, 129.0, 127.9, 40.1, 37.4, 34.5, 32.1, 28.1, 28.0; MS 216 (M$^+$ + 1, 10%), 107 (45%), 79 (100%).

6-(2,6-Cyclooctadienyl)-1-hexanol (6). To a stirred solution of **3** (600 mg, 2.05 mmol) in methanol (10 mL) was added pyridinium *p*-toluenesulfonate (52 mg, 0.205 mmol, 0.1 equiv).

(6) For some recent examples of allylic deprotonations with LICKOR, see: (a) Rauchschwalbe, G.; Zellner, A.; Schlosser, M. *Eur. J. Org. Chem*. **2001**, 3903−3909. (b) Zellner, A.; Schlosser, M. *Synlett* **2001**, 1016−1018. (c) Krassnig, R.; Schmidhammer, H.; Wurst, K. *Helv. Chim Acta* **2000**, *83*, 380−383. (d) Schlosser, M.; Kotthaus, M. *Eur. J. Org. Chem*. **1999**, 459−462.

(7) (a) Hanessian, S.; Xie, F. *Tetrahedron Lett*. **1998**, *39*, 733−736. (b) Phoon, C. W.; Oliver, S. F.; Abell, C. *Tetrahedron Lett*. **1998**, *39*, 7959−7962.

(8) Shea, K. J.; Burke, L. D.; Doedens, R. J. *Tetrahedron* **1986**, *42*, 1841−1844.

(9) Uchida, K.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1977**, *33*, 2987−2992.

After 6 h, the reaction mixture was washed (saturated aqueous $NaHCO_3$) and diluted with 9:1 hexane/EtOAc and the aqueous phase extracted with hexane. The combined organic extracts were washed with brine, dried, and concentrated. Chromatography on silica (eluent 20% ethyl acetate in hexane, R_f 0.25−0.35) yielded **6** as a colorless oil (397 mg, 1.91 mmol, 93%): IR 3357 cm^{-1}; ^1H NMR δ 5.53 (3H, m), 5.31 (1H, dd, J = 6.8, 11.6 Hz), 3.59 (2H, t, J = 6.6 Hz), 2.69 (1H, m), 2.53 (1H, m), 2.30 (4H, m), 2.12 (2H, m), 1.5 (2H, m), 1.30 (8H, m); ^{13}C NMR δ 134.5, 128.7, 128.5, 127.4, 62.9, 38.8, 37.3, 35.0, 32.8, 29.7, 28.0, 27.5, 25.8; MS 208 (M^+, 7%), 94 (78%), 80 (100%).

6-(2,6-Cyclooctadienyl)-1-phthalimide (7). To a stirred solution of **6** (350 mg, 1.68 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (10 mL) were added triphenylphosphine (572 mg, 2.18 mmol, 1.3 equiv) and phthalimide (321 mg, 2.18 mmol, 1.3 equiv), followed by dropwise addition of diisopropyl azodicarboxylate (441 mg, 2.18 mmol, 1.3 equiv) with cooling (ice/water bath) over 5 min. The yellow reaction mixture was stirred under nitrogen for 16 h, after which the solvent was removed in vacuo. The resulting oil was triturated with *n*-pentanes, filtered, concentrated, and chromatographed on silica (eluent 1:1 CH_2Cl_2/hexanes, R_f 0.3−0.35) to furnish **7** as a colorless oil (526 mg, 1.56 mmol, 93%): IR 3003, 1707 cm^{-1}; ^1H NMR δ 7.83 (2H, dd, J = 3.0, 5.4 Hz), 7.7 (2H, dd, J = 3.0, 5.4 Hz), 5.53 (3H, m), 5.3 (1H, dd, 6.8, 11.6 Hz), 3.66 (2H, t, 7.3 Hz), 2.7 (1H, m), 2.52 (1H, m), 2.3 (2H, m), 2.13 (2H, m), 1.68 (2H m), 1.3 (10H, m); ^{13}C NMR δ 168.5, 134.6, 133.9, 128.8, 128.5, 127.5, 123.2, 38.8, 38.1, 37.3, 35.0, 29.5, 28.7, 28.1, 28.0, 27.5, 26.9; MS 337 (M^+, 71%), 160 (100%), 107 (78%).

6-(2,6-Cyclooctadienyl)-1-hexylamine (8). To a stirred solution of **7** (500 mg, 1.48 mmol) in ethanol (10 mL) was added hydrazine hydrate (185 μL, 5.95 mmol, 4 equiv). The reaction mixture was refluxed under nitrogen for 18 h. After cooling, the phthalhydrazide precipitate was removed by filtration and the filtrate concentrated. To the residue was added aqueous 1 M NaOH, and the resulting emulsion was extracted with CH_2Cl_2. The combined organic extracts were dried (K_2CO_3), filtered, concentrated, and chromatographed on silica (eluent 9:1 CH_2Cl_2/MeOH saturated with ammonia, R_f 0.2−0.25) to afford **8** as a colorless oil (242 mg, 1.17 mmol, 79%): IR 3373, 3290 cm^{-1}; ^1H NMR δ 5.41 (3H, m), 5.21 (1H, dd, J = 11.4, 6.8 Hz), 2.56 (2H, t, J = 6.8 Hz), 2.43 (1H, m), 2.2 (2H, m), 2.0 (2H, m), 1.3 (2H, m), 1.2 (10H, m); ^{13}C NMR δ 134.3, 128.5, 128.2, 127.1, 42.1, 38.6, 37.1, 34.8, 33.7, 29.5, 27.8, 27.3, 26.7; MS 208 (M^+, 55%), 107 (61%), 79 (100%).

Solid-Phase Immobilization of 6. To a suspension of trichloroacetimidate Wang resin (1.02 g, loading of 0.77 mmol/g, 0.79 mmol) in cyclohexane (8 mL) was added alcohol **6** (820 mg, 3.95 mmol, 5 equiv) in CH_2Cl_2 (8 mL), followed by agitation for 5 min and the addition of $BF_3{\cdot}OEt_2$ (50 μL). The progress of the reaction was monitored by the disappearance of the IR absorption at 1662 cm^{-1}. After agitation for 5 h, the resin was filtered, washed sequentially with THF, CH_2Cl_2, and cyclohexane (5 × 15 mL), and dried in vacuo to a constant mass of 1.05 g.

The level of loading of **6** was determined by cleavage. The loaded resin (1.05 g) was suspended in a solution of 5% (v/v) TFA in CH_2Cl_2 (10 mL) and agitated for 4 h. Anhydrous $NaHCO_3$ (1.0 g) was added cautiously and agitation continued for 5 min. The suspension was filtered and washed with CH_2Cl_2 and MeOH, and the combined filtrates were concentrated and dried to afford pure **6** (131 mg, 0.63 mmol), corresponding to 80% loading.

Acknowledgment. The Combinatorial Centre of Excellence is funded by an industrial consortium comprising Amersham, AstraZeneca, GlaxoSmithKline, Eli Lilly, Merck, Organon, Pfizer, and Roche, and government funding via the JIF initiative.

Supporting Information Available: ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO025715U