Preparation of (1-Norbornylmethyl)lithium

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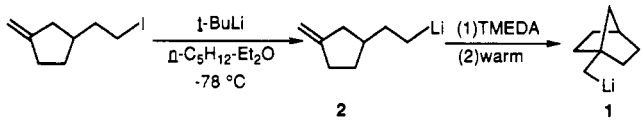
Summary: Room-temperature cyclization of the organolithium (4) derived from 4-(iodomethyl)-1-methylenecyclohexane (3), by low-temperature lithium–iodine exchange, produces (1-norbornylmethyl)lithium (1) in 94–96% yield.

We recently reported that (1-norbornylmethyl)lithium (1) may be prepared, as shown, by cyclization of the olefinic

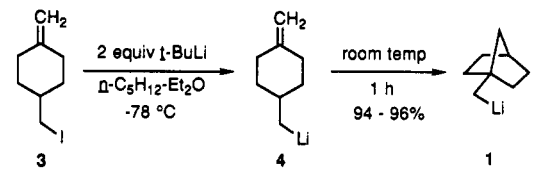


alkyllithium (2) derived from 3-(2-iodoethyl)-1-methylenecyclopentane.[1] While this route offers a viable method for the preparation of 1, it suffers from the fact that the cyclization step is slow relative to side reactions that consume anions. As a result, even in the presence of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA), the sluggish isomerization of 2 → 1 requires 40 min at room temperature and the yield of 1 is a moderate 60–70%.[1]

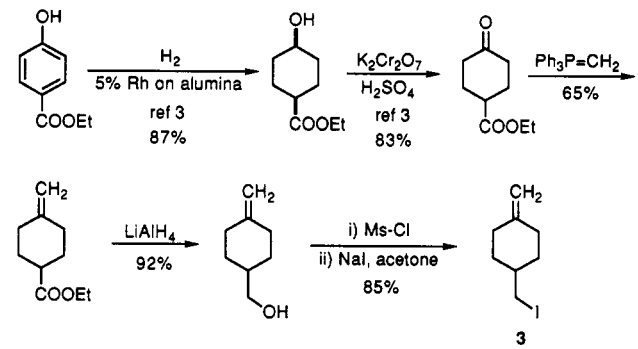
Herein we report a highly efficient, alternative route to (1-norbornylmethyl)lithium that provides 1 in yields of 94–96%. The two-step, one-pot synthetic sequence, involving 5-exo cyclization of the 5-hexenyllithium derived from 4-(iodomethyl)-1-methylenecyclohexane (3), is summarized in Scheme I. The iodide precursor, 3, is prepared from ethyl 4-hydroxybenzoate, via commercially available ethyl 4-oxocyclohexanecarboxylate, as depicted in Scheme II.

Treatment of an approximately 0.1 M solution of 3 in dry *n*-pentane–diethyl ether (3:2 by volume) at −78 °C with 2.0–2.2 molar equiv of *tert*-butyllithium (*t*-BuLi) following our general protocol for low-temperature lithium–iodine interchange[2] serves to generate the corresponding olefinic alkyllithium (4) in essentially quantitative yield. Isomerization of 4 to 1 was easily accomplished by allowing the reaction mixture to warm and stand at ambient temperature (ca. +22 °C) for 1 h under an atmosphere of dry argon. The yield of (1-norbornylmethyl)lithium (1), assayed as 1-methylbicyclo[2.2.1]heptane[4] following quench of such reaction mixtures with deoxygenated water or methanol, was typically 94–96%: the balance of the reaction mixture (4–6%) was 4-methyl-1-methylenecyclohexane generated, as noted elsewhere,[2] as a byproduct of the initial lithium–iodine exchange. By way of comparison, the much slower cyclization of (2-(3-methylenecyclopentyl)ethyl)lithium (2) to 1 proceeds to less than 10% completion when solutions of 2 in *n*-pentane–diethyl ether are allowed to stand at room temperature for 1 h. Indeed, as noted above, it is necessary to add TMEDA to facilitate the ring-closure of 2 to 1.[1]

Scheme I



Scheme II



The cyclization of 4 to 1 is also accelerated significantly in the presence of TMEDA. Addition of 2.0 molar equiv of dry, deoxygenated TMEDA to a cold solution of 4 in *n*-pentane–ether followed by removal of the cooling bath afforded 1 virtually quantitatively after only 11 min at room temperature. Quench of such a reaction mixture with CH_3OD gave a 96% yield of 1-methylbicyclo[2.2.1]-heptane having a deuterium content of 86%. Under identical reaction conditions the isomerization of 2 to 1 is only 24% complete after the same period of time.[1]

The rapid cyclization of 4 to 1 is attributable to the relatively low-energy transition state for the process. Recently reported molecular orbital calculations indicate that the 5-exo ring closure of 5-hexenyllithiums involves a fairly rigid activated complex in which the lithium atom is coordinated with the olefinic π-bond.[5] Apparently, the thermodynamically favorable Li–olefin coordination that initiates the ring closure is sufficient to offset the energy increase accompanying the conformational change required for cyclization of 4 to 1.

In summary, the facile isomerization of 4 to 1, which is much more rapid than is the cyclization of 2, provides the method of choice for the preparation of (1-norbornylmethyl)lithium. As detailed in our previous report,[1] 1-substituted bicyclo[2.2.1]heptanes are readily prepared by reaction of 1 with any of a variety of electrophiles.

Experimental Section

Reactions involving alkyllithiums were performed in glassware that had been flame-dried under an atmosphere of dry argon, and all manipulations of organolithiums were conducted using

(1) Bailey, W. F.; Khanolkar, A. D. *J. Org. Chem.* **1990**, *55*, 6058.
(2) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404.
(3) (a) Bachman, P. L.; Finnegan, R. A. *J. Org. Chem.* **1965**, *30*, 4145. (b) Petit, G. R.; Harvey, J. B. *Synth. Commun.* **1981**, *11*, 167.
(4) Della, E. W.; Pigou, P. E. *J. Am. Chem. Soc.* **1984**, *106*, 1085.
(5) Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K.; Ovaska, T. V.; Rossi, K.; Thiel, Y.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 5720 and references therein.

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standard syringe/cannula techniques under an atmosphere of dry, oxygen-free argon. Diethyl ether was freshly distilled from dark-purple solutions of sodium/benzophenone; dry, olefin-free *n*-pentane was obtained as previously described;[1] TMEDA was distilled under nitrogen from calcium hydride. The concentrations of commercial solutions of *t*-BuLi in *n*-pentane (Aldrich) were determined immediately prior to use by the method of Watson and Eastham.[6] Literature procedures were followed for the preparation of ethyl 4-oxocyclohexanecarboxylate from ethyl 4-hydroxybenzoate.[3]

Ethyl 4-Methylenecyclohexanecarboxylate. A suspension of 5.10 g (45.2 mmol) of potassium *tert*-butoxide and 16.2 (45.2 mmol) of methyltriphenylphosphonium bromide in 45 mL of dry diethyl ether was stirred at 0 °C for 1 h under an atmosphere of nitrogen. A solution of 7.00 g (41.1 mmol) of ethyl 4-oxocyclohexanecarboxylate[3] in 20 mL of dry diethyl ether was then added to the ylide solution, and the resulting mixture was stirred at room temperature for 15 h. The reaction mixture was filtered, the filtrate was concentrated by rotary evaporation, and the residue was taken up in 50 mL of hexanes and cooled in an ice bath to precipitate the residual triphenylphosphine oxide. The mixture was then filtered, the filtrate was concentrated, and the residue was purified by flash chromatography on silica gel using 10% ethyl acetate–hexanes as eluent to give 4.50 g (65%) of the pure ester: R_f = 0.54 (25% ethyl acetate–hexanes); IR (neat) 3067, 1724, 1649, 1444, 1209, 1163, 1034 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.61 (apparent s, 2H), 4.90 (q, J = 7.12 Hz, 2H), 2.47–2.24 (m, 3H), 2.09–1.89 (m, 4H), 1.63–1.45 (m, 2H), 1.22 (t, J = 7.12 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 175.34, 147.65, 107.85, 60.17, 42.61, 33.63, 30.13, 14.21; mass spectroscopic molecular weight calcd for $C_{10}H_{16}O_2$ m/e 168.1150, found m/e 168.1152.

(4-Methylenecyclohexyl)methanol. A solution of 4.20 g (25.0 mmol) of ethyl 4-methylenecyclohexanecarboxylate in 20 mL of dry diethyl ether was added in a dropwise manner to an ice-cold suspension of 1.00 g (26.4 mmol) of lithium aluminum hydride in 30 mL of dry diethyl ether. The resulting suspension was stirred at room temperature for 1 h and then hydrolyzed by sequential dropwise addition of 1.00 mL of water, 1.00 mL of 15% aqueous sodium hydroxide, and 3.00 mL of water. The mixture was filtered, the solids were washed with fresh diethyl ether, and the combined filtrate and washings were concentrated by rotary evaporation to give an oil. Purification by flash chromatography on silica gel (15% ethyl acetate–hexanes) gave 2.90 g (92%) of the known[7] title alcohol: R_f = 0.18 (25% ethyl acetate–hexanes); IR (neat) 3340, 3067, 1649, 1444, 1034, 882 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.60 (apparent s, 2H), 3.45 (d, J = 6.41 Hz, 2H), 2.38–2.26 (m, 2H), 2.10–1.80 (m, 4H), 1.72–1.57 [overlapping patterns, i.e., 1.72–1.54 (m, 1H), 1.54 (br s, exchanges with D_2O 1H)], 1.12–0.94 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 149.34, 107.02, 67.77, 39.93, 34.08, 30.71.

4-(Iodomethyl)-1-methylenecyclohexane (3). Following the general procedure of Crossland and Servis,[8] 1.50 g (11.9 mmol) of (4-methylenecyclohexyl)methanol was converted into its mesylate and added to a solution of 2.30 g (15.3 mmol, 1.25 equiv) of sodium iodide in 25 mL of acetone. The resulting mixture was stirred at gentle reflux for 14 h under a blanket of nitrogen. Inorganic salts were then removed by filtration and washed with dry acetone. The combined filtrate and washings were concentrated under vacuum, and the residue was taken up in 50 mL of hexanes and washed with 10% aqueous sodium thiosulfate and brine. After drying ($MgSO_4$), solvents were removed by rotary evaporation and the residue was purified by flash chromatography on silica gel using hexanes as eluent to afford 2.20 g (85%) of the pure title iodide: R_f = 0.54 (hexanes); ^{1}H NMR ($CDCl_3$) δ 4.63 (apparent s, 2H), 3.09 (d, J = 6.25 Hz, 2H), 2.34–2.21 (m, 2H), 2.13–1.89 (m, 4H), 1.74–1.50 (m, 1H), 1.18–0.96 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 148.20, 107.54, 39.57, 34.36, 33.96, 14.53; mass spectroscopic molecular weight calcd for $C_8H_{13}I$ m/e 236.0064, found m/e 236.0067.

Preparation of (1-Norbornylmethyl)lithium (1). An approximately 0.1 M solution of 4-(iodomethyl)-1-methylenecyclohexane in *n*-pentane–diethyl ether (3:2 by volume) was cooled to −78 °C under an atmosphere of dry, oxygen-free argon, and with stirring, 2.2 molar equiv of *t*-BuLi was added via syringe over a 5-min period. The reaction mixture was stirred for an additional 5 min at −78 °C before being treated in one of the following ways. (A) The solution was allowed to warm and stand at room temperature under the blanket of argon for 1 h to complete the isomerization of **4** to **1** (Scheme I). Addition of deoxygenated methanol or water afforded 1-methylbicyclo[2.2.1]heptane[4] in 94–96% yield. (B) The solution of **4** in *n*-pentane–diethyl ether was maintained at −78 °C, and 2.0–2.2 molar equiv of dry, deoxygenated TMEDA was added via syringe. The resulting pale-yellow mixture was stirred at −78 °C for an additional 5 min, the cooling bath was then removed, and the solution was allowed to warm and stand at +22 °C for 11 min to afford **1** in 95% yield (assayed as 1-methylbicyclo[2.2.1]heptane). As previously described, addition of an excess of an electrophile to solutions of **1** affords functionalized 1-substituted bicyclo[2.2.1]heptanes.[1]

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(6) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.
(7) Haggis, G. A.; Owen, L. N. *J. Chem. Soc.* **1953**, *33*, 404.
(8) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.