Synthesis of Sterically Hindered Long-Chain Alkenols via Organolithium Compounds

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The synthesis of sterically hindered primary, secondary and tertiary alcohols is reported. An unusual monoalkylation/reduction occurs on treatment of a fully α-substituted methyl carbonyl with t-BuLi. A mechanism not involving a ketone intermediate but a β-H abstraction from t-BuLi prior to or after alkylation is proposed.

We are currently studying the synthesis of some long-chain alkenols in which the carbon α or β to the oxygen atom bears alkyl groups of different size. Since a hindered ketone and a Grignard reagent with β-hydrogens are prone to side reactions1-3 such as enolization and reduction at the expense of the normal 1,2-addition, a synthetic route employing a ω-disubstituted ester 1a as the starting material was developed (Scheme 1). An organolithium reagent was chosen instead of a Grignard reagent since higher addition to reduction ratios are generally encountered by the use of the former.1,4,5

The ester 1a was allowed to react with t-BuLi at −70 or 0 °C. The di-tert-butyl derivative 2 was not formed even in trace amounts at either reaction temperature according to the NMR spectra measured from the crude product mixtures. The sec mono-tert-butyl alkenol 3 was isolated as the sole product in both cases instead. However, the related tri-tert-butyl carbinol 6 (Scheme 2) has been obtained from hexamethylacetone and t-BuLi at −70 °C.6 The authors say that the ketone reduction product 7 appears as a by-product only at temperatures higher than −40 °C.6,7

We found that tri-tert-butyl carbinol 6 is formed along with the di-tert-butyl carbinol derivative 7 in the ratio 2:3 at 0 °C. At −70 °C 6 and 7 were formed in the ratio 3:1. Furthermore, the tert-alkenol 8 was produced along with the ketone 9 (Scheme 3) as a 1:1 mixture from the ester 1b and t-BuLi at −70 °C or 0 °C with no traces of the corresponding sec mono-tert-butyl alkenol.

These findings clearly indicate that the long hydrocarbon chain together with the steric hindrance caused by the alkyl groups around the oxygen moiety in the ester 1a prevent the normal 1,2-addition. Obviously both these factors are required for monoalkylation-reduction to occur since aliphatic cage derivatives of 6 with adamantyl, bicyclo[2.2.2]octyl and norbornyl substituents

Scheme 1.

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Scheme 3.

have been synthesized from a ketone and an organolithium reagent.10–11

According to the literature, organolithium or Grignard reagents react with carbonyl compounds to afford addition products in high yields in the presence of anhydrous cerium(III) chloride.12–14 Thus, an attempt was made to synthesize 2 via a cerium chloride promoted nucleophilic addition14 of t-BuLi at −70 °C to the ester 1a or to the ketone 10 (Scheme 4), prepared from 1a and t-BuLi at −70 °C. In both cases only the starting material 1a or 10 was recovered.

Almost complete suppression of reduction and enolization is observed, in the absence of CeCl₃ or other additives, if a ketone is added to a solution of t-BuLi in THF at −78 °C, but not vice versa.15 In an attempt to react the ketone 10 with t-BuLi accordingly,15 mainly unchanged starting material remains even after 7 h, along with a very small amount (<5%) of the mono-tert-butylderivative 3, according to the ¹H and ¹³C NMR spectra measured from the crude product mixture. Thus it appears that in the alkylation–reduction of the ester 1a to the alcohol 3, the ketone 10 is not an intermediate.

An analogous alkylation–reduction of methyl pivalate to hexamethylethane and the sec-alcohol 7 using tert-butyl chloride and sodium has been previously mentioned with little detail and no mechanistic discussion.16 Other ester-into-sec-alcohol conversions have been performed with RMgX in the presence of LiBH₄,17 Cp₂TiCl₂,18 or DIBAL.19 A mechanism involving a ketone intermediate was suggested for the first mentioned reaction.17 Replacing RMgX by RLi produced tert alcohols.17

For the reaction of the aliphatic ester 1a and t-BuLi we suggest the following mechanism [Fig. 1(a,b)] which takes into account the fact that the ketone 10 is not reduced under our conditions. Compound 3 is formed when a β-hydrogen atom is abstracted from t-BuLi with simultaneous formation of lithium methoxide and isobutene, or alternatively, the β-hydrogen atom abstraction could occur prior to alkylation involving a reduction to an aldehyde in the first step. The normal 1,2-addition pathway is prevented by the long hydrocarbon chain. We realize that alternative single-electron processes may also be depicted for the 1a→3 reaction.

The other long-chain alkenols 4 and 5 in Scheme 1 were obtained by treating the ester 1a with CH₃Li at 0 °C or with LiAlH₄ in refluxing THF, respectively.

Scheme 4.

Fig. 1. (a), (b) Proposed mechanisms for the reduction of the ester 1a by t-BuLi.
Experimental

$^1$H, $^{13}$C and 2D NMR spectra (HSQC and HMBC) were recorded on a Varian Unity 500 MHz, Varian Inova 300 MHz or Varian Gemini 200 MHz spectrometer using CDCl$_3$ as the solvent unless otherwise stated. Infrared spectra were obtained on a Bio-Rad SPC 3200 spectrometer. Mass spectra and high-resolution mass spectra were recorded on a JEOL JMS-SX102 with an EI potential of 70 eV. Flash chromatography was carried out with Merck Silica gel 60 (0.063–0.200 mm). Preparative layer chromatography was performed on aluminium oxide 60 F 254 PLC plates (Merck). All reactions were performed under an argon atmosphere. Tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone. 11-Bromoundecene (from Lancaster), methyl isobutyrate (from Aldrich) and anhydrous CeCl$_3$ (from Fluka) were used as received. Methyl 9-decanoate (1b), synthesized by Neste, was distilled before use.

Ester la. LDA was prepared from BuLi (1 equiv.) and diisopropylamine (1 equiv.) at $-40$ °C and then kept at 0 °C for 15 min. Methyl isobutyrate (1 equiv.) was added at $-70$ °C and the mixture was stirred at that temperature for 90 min. 11-Bromoundecene (1.5 equiv.) was added to the mixture at $-70$ °C and the reaction mixture was allowed to warm to 0 °C over 1 h. It was then stirred overnight at room temperature. The reaction was quenched with 10% NH$_4$Cl (aq.) at 0 °C. The crude product was purified by flash chromatography on silica gel with gradient elution using hexane and dichloromethane as solvents. The yield of the pure ester was 4.0 g (80%).

Compound 3. The ester la was treated with t-BuLi (3.5 equiv.) in THF at 0 °C for 4 h, then left at room temperature overnight or at $-70$ °C for 5 h and then quenched as stated above. The crude product (yield 0.95 g, 80%) was purified by preparative Al$_2$O$_3$ (neutral) layer chromatography using a hexane–dichloromethane (7:3) eluent system. The yield of the pure 3 was 0.24 g (25%), its structure being assigned by 2D NMR techniques at different temperatures. The characteristic feature in these spectra is the CHOH proton resonance. When the $^1$H NMR spectrum was measured at 27 °C in CD$_2$Cl$_2$, the methane proton showed an unresolved doublet signal at $\delta$ 3.05 ppm. The OH proton resonance was a singlet of chemical shift 1.50 ppm. The coupling constant of 5.5 Hz for the CH and OH protons was determined from the $^1$H NMR spectrum measured at $-40$ °C. At that temperature the CH and OH resonances are each divided into a doublet, the former having a chemical shift of 3.05 ppm and the latter 1.62 ppm. By lowering the measurement temperature to $-70$ or $-90$ °C, the OH proton resonance was observed to shift to $\delta$ 1.75 or 1.95 ppm in the $^1$H NMR spectra. IR (KBr): $\nu_{max}$ 3519, 2922, 1639, 1473, 995, 914 cm$^{-1}$. $^1$H NMR (500 MHz, CD$_2$Cl$_2$): $\delta$ 5.80 (m, 1 H, C–CH), 4.90 (m, 2 H, CH$_2$–C), 3.05 (unresolved d, 1 H, C(POCH$_3$)), 2.00 (m, 2 H, C–C–CH$_2$), 1.50 (s, OH), 1.46 (m, 2 H), 1.36 (m, 2 H), 1.20–1.30 (br, 6 H), 1.00 (s, 9 H, t-Bu), 0.80 (s, 3 H, CH$_3$), 0.70 (s, 3 H, CH$_3$). $^{13}$C NMR (500 MHz, CD$_2$Cl$_2$): $\delta$ 139.5, 114.1, 84.0, 42.3, 40.0, 37.5, 34.0, 31.0, 29.94, 29.87, 29.7, 29.4, 29.2, 29.0, 25.9, 25.5, 24.3. HRMS: calc. for C$_{19}$H$_{33}$O$_2$ 282.2923, found 282.2909.

Compound 4. The ester la was treated with CH$_3$Li (3.5 equiv.) at 0 °C for 2 h 30 min, and then stirred at room temperature overnight. The crude product (122 mg) was purified as described above for compound 3 using dichloromethane as the eluent. The yield of 4 was 50 mg (41%). IR (KBr): $\nu_{max}$ 3443, 2932, 1642, 1470, 1378, 1115, 908 cm$^{-1}$. $^1$H NMR (500 MHz): $\delta$ 5.80 (m, 1 H, C–CH), 4.90 (m, 2 H, CH$_2$–C), 2.00 (m, 2 H, C–C–CH$_2$), 1.40 (s, OH), 1.38 (m, 2 H), 1.34–1.22 (br, 7 CH$_2$), 1.20 (s, 6 H), 0.90 (s, 6 H). $^{13}$C NMR (500 MHz): $\delta$ 139.9, 114.8, 76.4, 40.5, 37.6, 34.5, 31.6, 30.4, 30.3, 30.2, 29.8, 29.7, 29.6, 29.5, 29.2, 29.0, 23.9. HRMS: calc. for C$_{17}$H$_{36}$O 254.2690, found 254.2599.

Compound 5. The ester la was reduced with LiAlH$_4$ (1.5 equiv.) by refluxing the mixture in THF. The yield of the compound 5 after purification by flash chromatography on silica gel (CH$_2$Cl$_2$ eluent) was 0.50 g (55%). IR (KBr): $\nu_{max}$ 3352, 2916, 1643, 1410, 1041, 908 cm$^{-1}$. $^1$H NMR (200 MHz): $\delta$ 5.80 (m, 1 H, C–CH), 5.00 (m, 2 H, CH$_2$–C), 3.30 (s, 2 H, CH$_2$OH), 2.00 (m, 2 H, C–C–CH$_2$), 1.50 (s, OH), 1.20–1.40 (br, 8 CH$_2$), 0.90 (s, 6 H, CH$_3$). $^{13}$C NMR (200 MHz): $\delta$ 139.3, 114.1, 72.1, 38.7, 35.0, 33.8, 30.6, 29.7, 29.6, 29.5, 29.2, 29.0, 23.9. HRMS: calc. for C$_{16}$H$_{34}$O 226.2297, found 226.2299.

Compound 8. Methyl 9-decanoate was treated with t-BuLi (3.5 equiv.) in THF at 0 °C or $-70$ °C as described for compound 3. The raw product (0.58 g) was a 1:1 mixture of the tert-alkenol 8 and ketone 9. Compound 8 was purified by flash chromatography on neutral Al$_2$O$_3$ using a gradient elution [petroleum ether (b.p. 30–65 °C)–diethyl ether mixtures]. The yield of pure 8 was 119 mg (21%). IR (KBr): $\nu_{max}$ 3550, 2940, 1640, 1470, 1365, 1000, 920 cm$^{-1}$. $^1$H NMR (300 MHz): $\delta$ 5.80 (m, 1 H, C–CH), 5.00 (m, 2 H, CH$_2$–C), 2.00 (m, 2 H, C–C–CH$_2$), 1.58 (t, 2 H), 1.54 (s, OH), 1.20–1.40 (br, 5 CH$_2$), 1.00 (s, 18 H, t-Bu). $^{13}$C NMR (300 MHz): $\delta$ 139.2, 114.4, 79.8, 42.6, 34.2, 33.7, 30.9, 30.1, 29.7, 29.4, 28.8, 27.0. EI-MS (m/z) 250 (M–H$_2$O), 211 (M–t-Bu).

Compound 10. The ester la was treated with t-BuLi (1 equiv.) at $-70$ °C for 30 min. The crude product (119 mg) was isolated as above and purified by preparative Al$_2$O$_3$ (neutral) layer chromatography using a toluene–pentane (1:9) eluent system. The yield of 10 was 38 mg (32%). IR (KBr): $\nu_{max}$ 2931, 1682, 1482, 1047, 982, 912 cm$^{-1}$. $^1$H NMR (300 MHz): $\delta$ 5.80 (m, 1 H, C–CH), 5.00 (m, 2 H, CH$_2$–C), 2.05 (m, 2 H,
C=CH₂), 1.56 (m, 2 H), 1.36 (m, 2 H), 1.32–1.20 (br, 5 CH₃ and 5 CH₂), 1.12 (m, 2 H). ¹³C NMR (300 MHz): δ 219.1, 139.5, 114.4, 49.8, 46.0, 41.9, 34.1, 30.6, 29.9, 29.8, 29.7, 29.4, 29.2, 28.8, 26.8, 25.6. HRMS: calc’d for C₁₉H₃₆O 280.2766, found 280.2779.

**Attempted synthesis of compound 2.** A suspension of anhydrous CeCl₃ (3.5 or 1.5 equiv.) and dry THF was stirred overnight at room temperature. t-BuLi (3.5 or 1.5 equiv.) was added at −70 °C and mixed for 1.5 h at −70 °C followed by addition of the ester 1a (1 equiv.) or ketone 10 (1 equiv.). Stirring was continued for 7 h at −70 °C. Quenching and isolation of the product was performed as described earlier. In each case only the starting material was recovered.

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**References**


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