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Synthesis with organoboranes

V *. Hydroxymethylation and formylation of cycloalkenes via allylic organopotassium and organoboron compounds

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Abstract

Allylic hydroxymethylation of cyclohexene and cyclooctene was achieved by metallation with trimethylsilylmethylpotassium followed by the reaction with formaldehyde. 1-Methylcycloalkenes were transformed into 2-methylenecycloalkane-1-methanols by the reaction of formaldehyde with allylic diethylboranes derived from these olefins via metallation–transmetallation. Conjugated cycloalkenecarboxaldehydes were obtained by oxidation of the hydroxymethylation products.

Introduction

Allylic hydroxymethyl derivatives of cycloalkenes and the closely related cycloalkene-1-carboxaldehydes are important synthetic intermediates [2–7]. They are also found in nature [8]. The direct approach to these compounds by one carbon atom homologation of cycloalkenes is used in the Prins reaction [9–12]. Although the reaction provides in some cases single products [13–15], its synthetic potential is limited by the frequent formation of product mixtures and low yields [12,14,16]. Clearly, new procedures for hydroxymethylation of olefins are desirable. In the preceeding papers of this series it was shown that allylic diethylboranes obtained from olefins by metallation–transmetallation react readily with aldehydes to give homoallylic alcohols [1,17,18]. The reaction of these organoboranes and their organopotassium precursors with formaldehyde is now employed for hydroxymethylation of cycloalkenes.

Results

Metalation of **1a–d** (Scheme 1) carried out with trimethylsilylmethylpotassium in an excess of olefin provided the corresponding allylic organopotassium compounds

* For Part IV see ref. 1.

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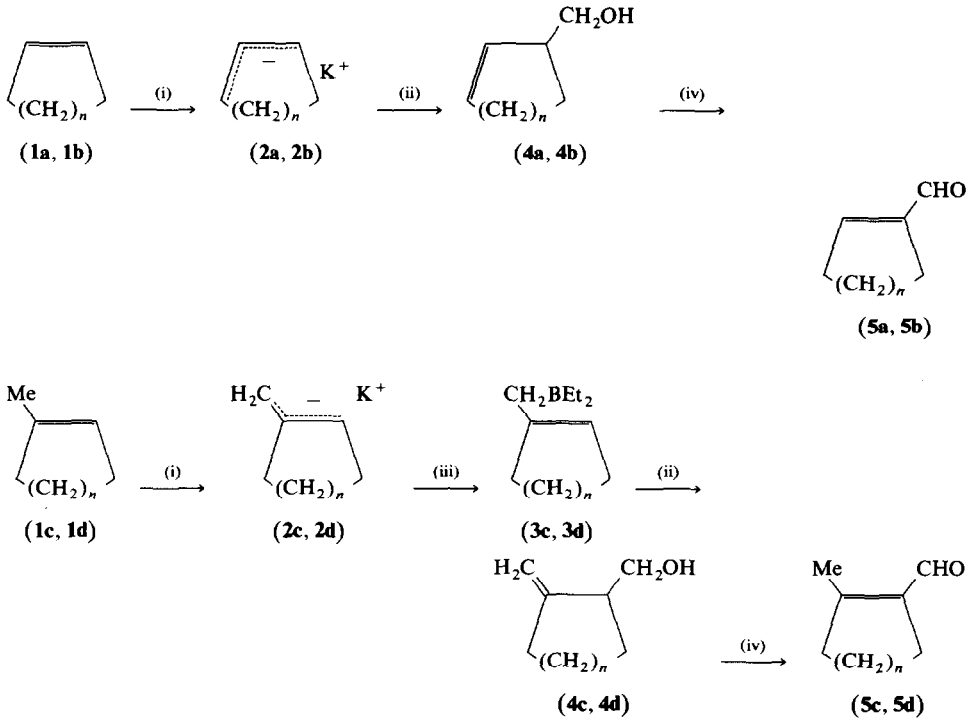

(**1a–5a**, $n = 2$; **1b–5b**, $n = 4$; **1c–5c**, $n = 1$; **1d–5d**, $n = 2$; (i) Me_3SiCH_2K; (ii) $HCHO/Et_2O$; (iii) $ClBEt_2/Et_2O$; (iv) $DMSO/(COCl)_2$)

Scheme 1

2a–d. These compounds are solids and the excess of olefin can be recovered either by removing it under vacuum or by decantation and washing the solid with n-hexane. The allylic organopotassium compounds **2a** and **2b** derived from cyclohexene and cyclooctene reacted with formaldehyde to give the corresponding hydroxymethylation products **4a** and **4b**, easily isolated by distillation in overall yield of 84 and 81%, respectively, calculated on the reacted olefin. The allylic organopotassium compounds **2c** and **2d** derived from 1-methylcycloalkenes reacted with formaldehyde to give mixtures of 2-methylenecycloalkane-1-methanol and 2-(1-cycloalkenyl)ethanol. Fortunately, **2c** and **2d** were cleanly transformed into the allylic diethylboranes **3c** and **3d**. These organoboranes combined with formaldehyde with allylic rearrangement affording the 2-methylenecycloalkane-1-methanols **4c** and **4d**. Similarly, α-pinene was transformed into *trans*-2-methylene-6,6-dimethylbicyclo[3.1.1]heptane-3-methanol (**6**). Oxidation of **4a–d** and **6** with PCC/CH_2Cl_2 or PCC/alumina [19] yielded the corresponding aldehydes **5a–d** and 2,6,6-trimethylbicyclo[3.1.1]hept-2-ene-3-carboxaldehyde (**7**), respectively. However, only **5c** and **7** were cleanly formed and could be isolated by simple distillation. Alcohols **4a**, **4b** and **4d** gave mixtures of products requiring GLC separation for the isolation of aldehydes. Oxidation with DMSO/oxalyl chloride [20] gave better results. Alcohols **4a–d** and **6** were oxidized by this reagent to aldehydes **5a–d** and **7**, respectively which were then isolated by distillation.

The hydroxymethylation procedures described above provide access to homoallylic alcohols from readily available cycloalkenes. In contrast to the Prins reaction, in all instances, single products were obtained and the yields were higher. The procedure employing the reaction of allylic organopotassium compounds with formaldehyde is suitable for unsubstituted and symmetrically substituted cycloalkenes, whereas 1-methylcycloalkenes are hydroxymethylated via allylic diethylboranes. Oxidation of the homoallylic alcohols involving the double bond migration to the conjugate position provides access to cycloalkene-1-carboxaldehydes from the same olefinic precursor.

Experimental

All glassware used for work with organoboranes and organopotassium compounds was stored in an oven at 150 °C overnight and assembled in a stream of dry argon gas. ^{1}H NMR spectra were recorded on a Tesla 80 MHz spectrometer and ^{13}C NMR spectra on a Tesla BS 567 spectrometer at 25 MHz. Mass spectra were obtained with MX-1320 spectrometer (EI, 70 eV). GLC analyses were performed on a Chrom-4 instrument using a 2.5 m column packed with 5% Carbowax 6000 on Chromosorb G. Elemental analyses were performed by the Analytical Laboratory, Institute of Chemistry, Nicolaus Copernicus University, Torun.

Chlorodiethylborane [21] and bis(trimethylsilylmethyl)mercury [22] were prepared by standard procedures. Diethyl ether, THF and olefins were distilled from $LiAlH_4$ prior to use. DMSO, CH_2Cl_2 and triethylamine were distilled from calcium hydride and stored over molecular sieves 4Å.

Synthesis of cycloalk-2-ene-1-methanol

General procedure. Bis(trimethylsilylmethyl)mercury (4.68 g, 12.5 mmol) was added in portions to a stirred mixture of potassium sand (1.00 g, 25.5 mmol) and cycloalkene (125.0 mmol) at 20–25 °C under argon atmosphere. Stirring was continued for 48 h at room temperature. The mixture was centrifuged, the liquid was decanted and the solid allylic organopotassium derivative was kept under vacuum at room temperature to remove the remaining olefin. The solid was added with stirring to 50 ml of diethyl ether at −78 °C followed by gasous formaldehyde (0.90 g, 30 mmol) at −40 to −30 °C. The mixture was allowed to warm to 0 °C and 20 ml of water was added. The organic layer was separated and the aqueous layer was extracted with 25 ml of diethyl ether. The ether solutions were combined and dried over magnesium sulphate. The product was isolated by distillation.

Synthesis of 2-methylenecycloalkane-1-methanol

General procedure. The allylic organopotassium compound derived from 1-methylcycloalkene following the procedure described above was added to a solution of chlorodiethylborane (2.60 g, 25 mmol) in 50 ml of diethyl ether at −78 °C. The mixture was allowed to warm to room temperature and was left for 3 h. The solution was separated from the precipitated material by centrifugation and decantation, the precipitate was washed with diethyl ether (2 × 25 ml) and the ether solutions were combined. Distillation afforded an allylic organoborane intermediate which was dissolved in 25 ml of diethyl ether and gaseous formaldehyde (0.90 g, 30 mmol) was introduced into the solution at 0 °C. The mixture was left for 1 h at

room temperature, aqueous 3 *M* sodium hydroxide solution (10 ml, 30 mmol) was added and the mixture was stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with 25 ml of diethyl ether. The ether solutions were combined, dried over magnesium sulphate and the product was isolated by distillation.

Oxidation of the hydroxymethylation products

Oxidation was carried out with DMSO/oxalyl chloride following the standard procedure [20].

Products identification

Products were characterized by ^{1}H NMR, ^{13}C NMR and mass spectra. Only spectroscopic data not previously available in the literature or differing from the reported data are given here. Yields of **4a–d** and **6** are calculated on the reacted olefin, yields of **5a–d** and **7** are for the oxidation step.

Compound **4a** [12,23]: yield 84%. ^{13}C NMR ($CDCl_3$): δ 129.45 (d); 127.88 (d); 67.00 (t); 38.30 (d); 25.61 (t); 25.35 (t); 21.02 (t). MS $m/z = 112$ (5%, M^+), 94 (34), 81 (100), 79 (46), 67 (11), 53 (16), 41 (19); [lit. 24].

Compound **4b** [16]: yield 81%. ^{13}C NMR ($CDCl_3$): δ 131.73 (d); 131.62 (d); 67.79 (t); 39.57 (d); 32.25 (t); 29.34 (t); 26.76 (t); 25.53 (t).

Compound **4c** [12,25]: yield 70%. ^{13}C NMR ($CDCl_3$): δ 153.53 (s); 106.05 (t); 65.25 (t); 46.36 (d); 33.67 (t); 29.71 (t); 24.52 (t). MS $m/z = 112$ (4%, M^+), 94 (38), 81 (100), 80 (20), 79 (73), 67 (47), 53 (23), 41 (23), 39 (18).

Compound **4d** [12,25]: yield 67%. ^{13}C NMR ($CDCl_3$): δ 149.79 (s); 107.32 (t); 64.02 (t); 45.65 (d); 34.56 (t); 30.31 (t); 28.41 (t); 24.11 (t). MS $m/z = 126$ (2%, M^+), 108 (44), 95 (100), 93 (58), 81 (34), 79 (37), 67 (59), 55 (57), 41 (39), 39 (30).

Compound **6** [14,17,26*]: yield 68%. ^{1}H NMR ($CDCl_3$): δ 0.75 (s, 3H, CH_3); 1.16 (d, $J = 6$ Hz, 1H, CH_2 cyclobutane ring); 1.25 (s, 3H, CH_3); 1.37–2.80 (m, 6H, CH, CH_2); 2.27 (s, 1H, OH); 3.58 (d, $J = 7$ Hz, 2H, CH_2O); 4.77 (m, 2H, $=CH_2$). ^{13}C NMR ($CDCl_3$): δ 152.52 (s); 108.92 (t); 69.69 (t); 52.26 (d); 40.72 (d); 40.72 (s); 37.70 (d); 28.18 (t); 27.99 (t); 25.94 (q); 21.59 (q). MS $m/z = 166$ (0.4%, M^+), 135 (38), 105 (45), 93 (100), 79 (26), 77 (17), 69 (39), 43 (21), 41 (51), 39 (18).

Compound **5a** [27,28]: yield 61%. ^{13}C NMR ($CDCl_3$): δ 194.25 (d); 151.25 (d); 141.73 (s); 26.50 (t); 22.10 (t); 21.35 (t); 21.35 (t).

Compound **5b** [29]: yield 64%.

Compound **5c** [30]: yield 67%.

Compound **5d** [31,32]: yield 70%. MS $m/z = 124$ (100%, M^+), 109 (55), 95 (98), 93 (19), 91 (20), 81 (44), 79 (33), 77 (20), 67 (61), 55 (31), 53 (23), 41 (35), 39 (35).

Compound **7**: yield 76%. ^{1}H NMR ($CDCl_3$): δ 0.77 (s, 3H, CH_3); 1.12 (d, $J = 7$ Hz, 1H, CH_2 cyclobutane ring); 1.31 (s, 3H, CH_3); 2.17 (s, 3H, CH_3); 2.12–2.35 and 2.35–2.62 (m, 5H, CH, CH_2); 10.11 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$): δ 189.55 (d); 167.79 (s); 130.53 (s); 50.65 (d); 39.68 (d); 38.78 (s); 30.46 (t); 28.74 (t); 26.02 (q); 20.68 (q); 18.89 (q). MS $m/z = 164$ (8%, M^+), 149 (88), 123 (47), 121 (30), 120 (22), 119 (20), 107 (29), 105 (21), 93 (100), 91 (65), 83 (19), 82 (18), 81 (46), 79 (49), 67 (19), 65 (17), 43 (23), 41 (50), 39 (38). Anal. Found: C, 80.40; H, 9.85. $C_{11}H_{16}O$ calc.: C, 80.44; H, 9.83%.

* A reference number with an asterisk indicates a note in the list of references.

Acknowledgements

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