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One-Pot Synthesis of Substituted Homoallylic Alcohols (3-Alkenols) and 1,1-Dideuterio-3-alkenols

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The reaction of the lithium enolate of ethyl acetate with various α -chlorocarbonyl compounds followed by *in situ* reduction with lithium aluminium hydride or deuteride and then lithiation with lithium powder leads, after hydrolysis, to homoallylic alcohols in a regioselective manner.

Recently, we reported a new method to transform α -chlorocarbonyl compounds into olefins by successively adding a Grignard reagent and lithium powder¹. This method was extended to the use of a hydride or deuteride as nucleophilic agent instead of the organomagnesium compound¹.

In the present communication, we report the application of this reaction to the preparation of 3-alkenols (homoallylic alcohols) via addition of a lithium enolate to the same starting materials followed by reduction and lithiation.

When α -chloroaldehydes (1, $R^2 = H$) or α -chloroketones (1, $R^2 \neq H$) were allowed to react successively with the lithium enolate of ethyl acetate (generated *in situ* by treatment of ethyl acetate with lithium diisopropylamide), lithium aluminium hydride, and finally lithium powder, the substituted homoallylic alcohols 2 were isolated. The use of lithium aluminium deuteride, instead of the corresponding hydride, in the reduction step led to the expected substituted 1,1-dideuterio-3-alkenols 3.

Table 1. 3-Alkenols 2 and 3 prepared

Prod- uct	R¹	R ²	Yield [%] ^a	b.p. [°C]/torr ^b	Molecular Formula ^c or Lit. b.p. [°C]/torr
2a 2b 2c 2d 2e 2f	C ₂ H ₅ <i>i</i> -C ₃ H ₇ —(Cl	H	47 46(1/1) 43(1/2) 54(1/4) 52 53	43-45°/15 51-53°/15 62-64°/15 61-63°/0.1 53-55°/0.1 65-67°/0.1	78°/95 ³ 135-145°/760 ⁴ 64°/16 ⁵ C ₇ H ₁₄ O(114.2) 77°/9 ⁶ 88°/8 ⁷
3b 3c 3d 3e	CH ₃ C ₂ H ₅ <i>i</i> -C ₃ H ₇ —(Cl	Н	51 (1/1) 45 (1/2) 50 (1/4) 53	51-53°/15 61-64°/15 61-63°/0.1 53-56°/0.1	C ₆ H ₁₀ D ₂ O(102.2) C ₆ H ₁₀ D ₂ O(102.2) C ₇ H ₁₂ D ₂ O(116.2) C ₇ H ₁₀ D ₂ O(114.2)

- ^a Yield of isolated product, based on the starting α-chlorocarbonyl compound 1. In parentheses the Z/E ratio from ¹³C-N. M. R. analysis.
- ^b Distillation interval.
- Satisfactory microanalyses were obtained: C, ±0.15; H or D, ±0.3.

3-Alkenols 2 and 3; General Procedure:

To a stirred solution of lithium diisopropylamide (1.176 g, 11 mmol) in tetrahydrofuran (20 ml) is added dry ethyl acetate (0.881 g, 10 mmol) at $-78\,^{\circ}\mathrm{C}$ under argon and stirring is continued for 30 min. Then, the α -chlorocarbonyl compound I (10 mmol) is added at $-100\,^{\circ}\mathrm{C}$ (bath temperature) for aldehydes or $-78\,^{\circ}\mathrm{C}$ for ketones, the mixture is stirred for 30 min, an ether solution of lithium aluminium hydride (6 mmol) is added, and stirring is continued for 3.5 h at $-60\,^{\circ}\mathrm{C}$. Then, lithium powder (25 mmol) is added and the mixture stirred overnight, allowing the temperature to rise to $20\,^{\circ}\mathrm{C}$. The mixture is then hydrolyzed with aqueous hydrochloric acid (10 ml), and extracted with ether (3 × 10 ml). The organic layer is washed with water (10 ml), dried with sodium sulfate, and evaporated (15 torr). The residue is distilled at reduced pressure to afford the alcohol 2 or 3.

Cl OLi THF,
$$\frac{1}{C} - \frac{1}{C} - \frac{1}{C} - \frac{1}{C} - \frac{1}{C} = \frac{1}{C} - \frac{$$

The reaction proceeds via the intermediate 4 which is formed by addition of the lithium enolate of ethyl acetate (ethyl lithioacetate) to the α -chlorocarbonyl compound 1. In fact, when the reaction mixture is hydrolyzed after this addition step the 4-chloro-3-hydroxyalkanoic ester 5 (e.g., 5a) can be isolated. *In situ* reduction of the intermediate 4 with lithium alanate or its deuterio analog followed by lithiation gives rise to a second intermediate 6^2 which on acid hydrolysis undergoes spontaneous β -elimination to afford the final 3-alkenol 2 or 3, respectively.

Ethyl 4-Chloro-3-hydroxy-3-methylbutanoate (5a):

To a stirred solution of lithium disopropylamide (1.176 g, 11 mmol) in tetrahydrofuran (20 ml) is added dry ethyl acetate (0.881 g, 10 mmol) at $-78\,^{\circ}\mathrm{C}$ under argon and stirring is continued for 30 min. Then, chloroacetone (1 a; 0.925 g, 10 mmol) is added at $-78\,^{\circ}\mathrm{C}$ and stirring is continued for 30 min. The mixture is then hydrolyzed with dilute hydrochloric acid (10 ml), and extracted with ether (3 × 10 ml). The organic layer is washed with water (10 ml), dried with sodium sulfate, and evaporated (15 torr). The residue is distilled in vacuo; yield: 0.83 g (46 %); b. p. 22-24 $^{\circ}\mathrm{C}/0.001$ torr.

Table 2. Spectral Data of 3-Alkenols 2 and 3

Product	I.R. (film) ^a v[cm ⁻¹]	1 H-N.M.R. (CCl ₄ , TMS _{int}) b δ [ppm]	13 C-N. M. R. (neat + $D_2O_{capillary}$) ^b δ [ppm]
2a	3400(OH); 3050, 1640 (HC=C)	1.7 (s, 1H, OH); 1.8 (s, 3H, CH ₃); 2.3 (t, 2H, $J = 7$ Hz, CH ₂ —C=C); 3.8 (t, 2H, $J = 7$ Hz, O—CH ₂); 4.8–5.0 (m, 2H, H ₂ C=C)	23.3, 41.6, 61.1, 112.8, 143.0
2 b	3360 (OH); 3030, 1660 (HC=C)	1.4–1.9 (m, 6H, 2CH ₃); 2.0–2.4 (m, 2H, CH ₂ —C=C); 2.3 (s, 1H, OH); 3.6 (t, 2H, $J = 7$ Hz, O—CH ₂); 5.1–5.5 (m, 1H, CH)	23.6, 34.8, 42.6, 60.4, 120.8, 132.3°
2c	3320 (OH); 3040, 1640 (HC=C)	1.0 (t, 3 H, $J = 7$ Hz, CH ₃); 1.8-2.5 (m, 4H, 2CH ₂ —C=C); 2.4 (s, 1 H, OH); 3.6 (t, 2H, $J = 7$ Hz, O—CH ₂); 5.3-5.7 (m, 2H, 2CH)	14.1, 26.1, 36.3, 62.4, 125.6, 134.6°
2d	3380 (OH); 3020, 1650 (HC=C)	1.0 (d, 6H, $J = 7$ Hz, 2CH ₃); 2.2 (t, 2H, $J = 6$ Hz, CH ₂ —C=C); 2.1–2.4 (m, 1H, CH—CH ₃); 2.7 (s, 1H, OH); 3.6 (t, 2H, $J = 7$ Hz, O—CH ₂); 5.2–5.6 (m, 2H, 2CH=C)	22.9, 31.6, 36.5, 62.4, 123.9, 139.8°
2e	3340 (OH); 3040, 1640 (HC=C)	1.5–2.5 (m, 8 H, 3 CH _{2ring} , CH ₂ —C=C); 3.1 (s, 1 H, OH); 3.6 (1, 2 H, $J = 7$ Hz, O—CH ₂); 5.2–5.5 (m, 1 H, CH)	23.2, 32.4, 34.1, 35.1, 60.3, 125.0, 140.
2f	3410 (OH); 3060, 1640 (HC=C)	1.3–2.4 (m, 10 H, $4CH_{2ring}$, CH_2 – C = C); 3.1 (s, 1 H, OH); 3.8 (t, 2 H, J = 7 Hz, O– CH_2); 5.6–5.9 (m, 1 H, CH)	23.4, 23.9, 26.2, 29.5, 42.1, 61.5, 123.3 135.5
3b	3400 (OH); 3030, 1620 (HC=C)	1.4–1.9 (m, 6H, 2CH ₃); 2.0–2.4 (m, 3H, \dot{CH}_2 — \dot{C} =C, OH); 5.3–5.7 (m, 1H, CH)	23.8, 35.0, 42.8, 61.6 (quin, CD_2 , $J_{CD} = 25$ Hz), 120.4, 132.7°
3c	3340 (OH); 3040, 1640 (HC=C)	1.0 (t, $3\dot{H}$, $J = 7$ Hz, CH_3); 1.7–2.3 (m, $4\dot{H}$, $2CH_2$ — $C=C$); 3.0 (s, $1\dot{H}$, $O\dot{H}$); 5.3–5.6 (m, $2\dot{H}$, $2C\dot{H}$)	13.6, 25.5, 35.6, 61.1 (quin, CD_2 , $J_{CD} = 25$ Hz), 125.3, 134.0°
3d	3400 (OH); 3040, 1650 (HC=C)	$0.9 \text{ (d, 6H, } J = 7 \text{ Hz, 2CH}_3\text{); } 2.0-2.4 \text{ (m, 3H, CH}_2-\text{C=-C, CHCH}_3\text{); } 2.2 \text{ (s, 1H, OH); } 5.2-5.5 \text{ (m, 2H, 2CH=-C)}$	23.8, 32.6, 37.6, 62.9 (quin, CD ₂ · J _{CD} = 22 Hz), 125.1, 142.5°
3e	3400 (OH); 3050, 1650 (HC=C)	1.5–2.5 (m, 8H, 3CH _{2ring} , CH ₂ —C=C); 2.9 (s, 1H, OH); 5.5–5.8 (m, 1H, CH)	23.2, 32.3, 34.2, 35.2, 60.1 (quin, CD ₂ $J_{CD} = 23 \text{ Hz}$), 125.1, 141.6

^a Recorded in a Perkin-Elmer 298 infrared spectrometer.

C₇H₁₃ClO₃ calc. C 46.54 H 7.25 (180.6) found 46.4 7.3 I.R. (film): v = 3450 (OH); 1720 cm⁻¹ (C=O). ¹H-N.M.R. (CCl₄ + D₂O capillary): $\delta = 1.3$ (ι, 3 H, J = 7 Hz, O—CH₂—CH₃); 1.3 [s, 3 H, C(OH)—CH₃]; 2.5, 2.7 (2 d, 2 H, J = 18 Hz, CH₂—C=O); 3.5 (s, 2 H, CH₂Cl); 4.2 (q, 2 H, J = 7 Hz, O—CH₂—CH₃); 4.3 ppm (s, 1 H, OH). ¹³C-N.M.R. (neat + D₂O capillary): $\delta = 14.9$, 25.8, 43.6, 53.2, 61.5, 72.0, 172.3 ppm.

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^b Recorded in a Varian FT-80A spectrometer.

^c For the major isomer.

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² Intermediates of this type are stable species only at low temperature: see, for instance, Barluenga, J., Flórez, J., Yus, M. J. Chem. Soc., Perkin Trans. 1 1983, 3019; and literature cited therein.

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