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CHEMISTRY OF 1,4-DIOXENE II [1]

A NEW METHOD FOR THE TWO-CARBON HOMOLOGATION OF ALDEHYDES AND KETONES TO α-HYDROXYMETHYL KETONES

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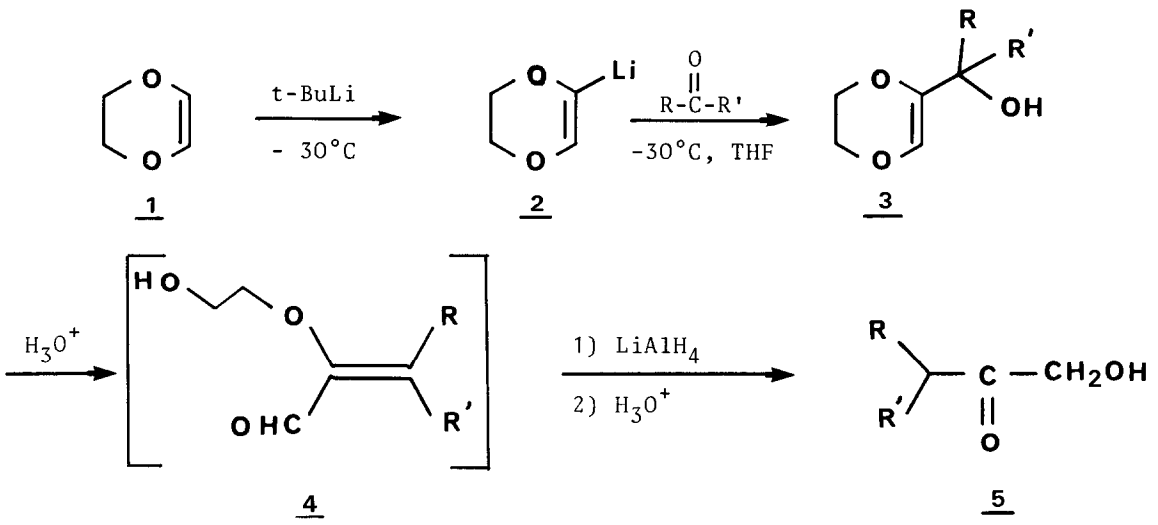
Summary : 1,4-Dioxen-2-yl lithium 2 reacts with ketones or aldehydes to give alcohols 3 which lead after an allylic rearrangement under mild conditions, followed by reduction and hydrolysis to α-hydroxymethyl ketones in fair yields .

1,4-Dioxene 1 [2], which is readily available from diethylene glycol, and can be stored in the cold for years, is an attractive substrate for a variety of investigations. In a previous paper [1], we reported the introduction of a new protective group of alcohols, by acid-catalyzed addition of hydroxyl groups to 1,4-dioxene . In this communication, we describe our first results concerning the synthetic use of 1,4-dioxene for the preparation of α-hydroxymethyl ketones [3] from carbonyl compounds .

Although lithiation of vinyl ethers has been extensively used in organic chemistry [4], when our investigation was initiated, only one report on the lithiation of 1,4-dioxene was recorded [5] . 1,4-Dioxen-2-yl lithium, which is fairly stable even at room temperature, reacts with a variety of electrophiles .

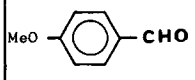
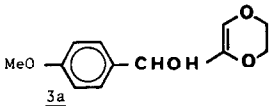
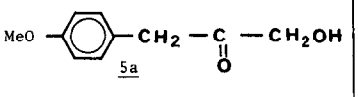
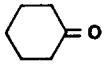
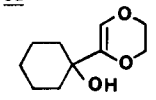
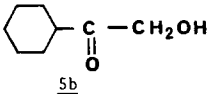
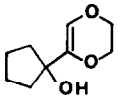
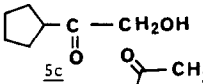
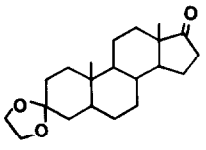
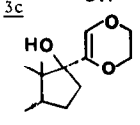
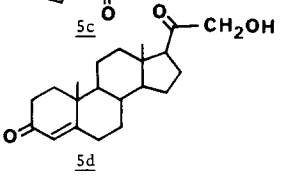
Thus, treatment of 1,4-dioxene with t-butyllithium at - 30°C affords a white precipitate which slowly reacts with aldehydes or ketones in tetrahydrofuran, leading to alcohols 3 [6] in good to moderate yields (Table) . These compounds are not too stable, and undergo an allylic rearrangement under very mild conditions, in some cases in the course of an attempted purifica-

SCHEME



1 2 3 4 5

TABLE

Entry	R - C(=O) - R'	Adduct 3	Yield*	Hydroxymethyl ketone 5	Yield*
1		 3a	62***	 5a	72
2		 3b	54	 5b	70
3		 3c	56	 5c	85
4		 3d	60	 5d	40

* The yields (not optimized) are given for the pure products .

*** 3a undergoes a partial transformation to 4a on the flash chromatography column .

tion by flash chromatography . At any rate, wet acidic silica gel (i.e. silica gel containing a small amount of oxalic acid) always converts adducts 3 into intermediates 4 . LAH reduction of crude 4, followed by hydrolysis of the enol ether moiety, gives α-hydroxymethyl ketones 5 . As shown in the table, the overall conversion yields of 3 to 5 range from moderate to excellent .

This sequence, a two-carbon homologation process of carbonyl compounds, is illustrated by the preparation of 21-hydroxyprogesterone 5d (entry 4) .

A typical experiment is as follows . t-BuLi (1.9 M, pentane, 20 mmol) was added to stirred 1,4-dioxene (22 mmol) cooled at - 30°C . After stirring the resulting white precipitate for 2 h at - 20°C, a solution of cyclohexanone (20 mmol) in THF (5 ml) was added over a period of 15 min . The mixture was stirred at - 20°C to 0°C for 2 h before adding a small amount of water . The mixture was extracted with ether and the isolated crude material was purified by flash chromatography (eluant : ethyl acetate/pentane 1 : 4) to give the pure adduct 3b (2 g, 54 %) .

To a stirred suspension of silica gel (70-230 mesh, 2 g) in dichloromethane (5 ml) was added an aqueous solution of 5 % oxalic acid (7 drops) . After 5 min, a solution of the adduct 3b (300 mg) in dichloromethane (3 ml) was added and stirring was continued until the disappearance of starting material . Solid sodium hydrogenocarbonate was added and the solid phase was separated by suction filtration . Evaporation of the solvent under reduced pressure gave crude 4b (320 mg) which was dissolved in THF (4 ml) and added to a stirred solution of $LiAlH_4$ (100 mg) in THF . Stirring was continued for 10 min and a solution of 30 % HCl was carefully added . The reaction mixture was then stirred at room temperature and extracted with ether . Flash chromatography of the crude product afforded the α-hydroxymethyl ketone 5b (160 mg, 70 %) as a colorless oil [6] .

References and Notes

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6 . All new compounds gave satisfactory analytical and spectral data .

3a : oil, I.R. (CCl_4) 3610, 1615, 1605, 1240 cm^{-1} ; ^1H NMR (60 MHz, $CDCl_3$) δ 7.28 (d, 2H, J = 8 Hz), 6.80 (d, 2H, J = 8 Hz), 5.95 (s, 1H), 4.96 (s, 1H), 4.0 (s, 4H), 3.76 (s, 3H), 2.50 (m, 1H) ; ^{13}C NMR (25 MHz, $CDCl_3$) δ 158.7 (s), 137.9 (s), 132.3 (s), 127.5 (d), 124.7 (d), 113.3 (d), 71.5 (d), 64.3 (t), 63.8 (t), 54.9 (q) .

3b : oil, I.R. (CCl_4) 3600, 1680, 1450 cm^{-1} ; ^1H NMR (60 MHz, $CDCl_3$) δ 6.10 (s, 1H), 4.0 (m, 4H), 1.86 (s, 1H,), 1.58 (m, 10H) ; ^{13}C NMR (25 MHz, $CDCl_3$) δ 141.3 (s), 122.1 (d), 70.7 (s), 64.1 (d), 63.5 (t), 34.4 (t), 21.5 (t), 25.3 (t) .

3c : oil, I.R. (CCl_4) 3600, 1680 cm^{-1} , ^1H NMR (60 MHz, $CDCl_3$) δ 6.13 (s, 1H), 4.0 (m, 4H), 1.93 (s, 1H), 1.75 (m, 8H) ; ^{13}C NMR (20 MHz, $CDCl_3$) δ 140.4 (s), 122.5 (d), 80.5 (s), 65.2 (t), 64.0 (t), 38.4 (t), 24.0 (t) .

3d : m. p. 135-137° (hexane), I.R. (CCl_4) 3580, 1670, 1095 cm^{-1} ; ^1H NMR (60 MHz, $CDCl_3$) δ 5.93 (s, 1H), 5.30 (m, 1H), 4.0 (br. s, 4H); 3.90 (s, 4H), 1.98,(s, 1H), 1.00 (s, 3H), 0.87 (s, 3H) ; ^{13}C NMR (25 MHz, $CDCl_3$) δ 139.9 (s), 138.8 (s), 124.5 (d); 121.7 (d), 109.2 (s), 83.5 (s), 64.17 (t), 64.07 (t), 63.9 (t), 63.52 (t), 49.3, 46.3, 41.5, 36.3, 36.1, 33.8, 33.4, 32.3, 31.2, 30.8, 22.7, 20.7, 18.7, 14.1 .

5a : m. p. 76-77° (pentane-ether), I.R. (CCl_4) 3500, 1720, 1615, 1510-1250 cm^{-1} ; ^1H NMR (60 MHz, $CDCl_3$) δ 7.03 (d, 2H, J = 8 Hz), 6.75 (d, 2H, J = 8 Hz), 4.20 (s, 2H), 3.73 (s, 3H), 3.56 (s, 2H), 3.20 (m, 1H) ; ^{13}C NMR (25 MHz, $CDCl_3$) δ 207.7 (s), 158.6 (s), 130.2 (d), 124.4 (s), 114.1 (d), 67.3 (t), 55.1 (q), 44.7 (t) .

5b : oil, I.R. (CCl_4) 3500, 1715 cm^{-1} ; ^1H NMR (60 MHz, $CDCl_3$) δ 4.30 (s, 2H), 3.20 (br. s, 1H), 2.34 (m, 1H), 2.16-1.0 (m, 10H) ; ^{13}C NMR (20 MHz, $CDCl_3$) δ 212.7 (s), 66.5 (t), 47.2 (d), 28.4 (t), 25.5 (t), 25.7 (t) .

5c : oil, I.R. (CCl_4) 3500, 1715 cm^{-1} ; ^1H NMR (60 MHz, $CDCl_3$) δ 4.26 (s, 2H), 3.11 (m, 1H), 2.10-1.50 (m, 9H) ; ^{13}C NMR (25 MHz, $CDCl_3$) δ 212.3 (s), 67.1 (t), 47.0 (d), 28.9 (t), 25.7 (t) .

5d : The analytical and spectral data of this compound are identical with those of an authentic sample .

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