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A Synthesis of 2-Substituted 2-Cyclopenten-1-ones

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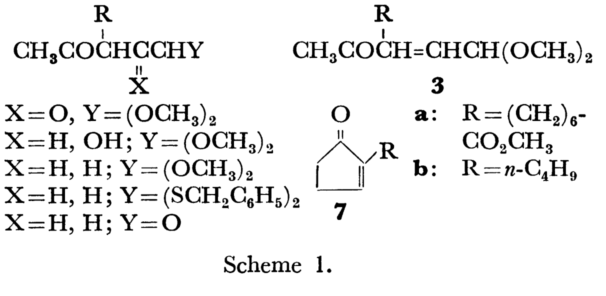
Synopsis. 2-Substituted 2-cyclopenten-1-ones, *i. e.*, 2-(6-methoxycarbonylhexyl)-2-cyclopentene-1-on and 2-butyl-2-cyclopenten-1-one were synthesized by cyclization of the corresponding 4-oxo-1-pentanals, which were obtained from 3-substituted 1,1-dimethoxy-2,4-pentadiones through several steps.

Recently a large amount of research has been devoted to developing synthetic routes to substituted 2-cyclopenten-1-ones. This has been due to the fact that many natural products possess this moiety as their major structural feature.[1)] Particularly, 2-(6-carboxyhexyl)-2-cyclopenten-1-one and its esters[2)] are valuable intermediates to 11-deoxyprostanoids[3)] which possess potential pharmacological activities. We wish to report a new synthetic route to 2-alkyl-2-cyclopenten-1-ones.

Catalytic hydrogenation of 1,1-dimethoxy-3-(6-methoxycarbonylhexyl)-2,4-pentadione (**1a**),[4)] prepared from 1,1-dimethoxy-2,4-pentadione and methyl 7-iodoheptanoate, over platinum in methanol afforded two epimeric keto alcohols **2a** and **epi-2a** in a ratio of 95 : 5 in 98% yield. Analogously, catalytic reduction of 3-butyl-1,1-dimethoxy-2,4-pentadione (**1b**) gave two epimeric alcohols **2b** and **epi-2b** in a ratio of 93 : 7 in 86% yield.[5)] Treatment of the keto alcohols **2a** and **2b** with dicyclohexylcarbodiimide and a catalytic amount of copper(I) chloride in ether[6)] gave the α,β-unsaturated ketones **3a** and **3b** in 81 and 92% yields, respectively. The ketone **3** was also obtained by treatment of the p-toluenesulfonate of the alcohol **2** with potassium acetate in aqueous *N,N*-dimethylformamide at 100 °C for 2.5 h in 60 and 55% yields, respectively. Hydrogenation of the α,β-unsaturated ketone **3** over 5% Pd–C in methanol gave the saturated ketones **4a** and **4b** in 85 and 88% yields, respectively.

Treatment of **4** with a slight excess of benzyl mercaptan and zinc chloride in dioxane at 50 °C for 1 h afforded bis(benzylthio)-derivatives **5a** and **5b** in 74 and 78% yields, respectively. Dethioacetalization of **5** was effected with mercury(II) chloride and cadmium carbonate in aqueous acetonitrile at 40 °C for 2 h to give the corresponding aldehyde **6**[7)] in good yield. Cyclization of the keto aldehydes **6a** and **6b** with potassium carbonate in methanol afforded the 2-substituted 2-cyclopenten-1-ones **7a** and **7b** in 36 and 35% yields, respectively.



$CH_3CO\overset{R}{\overset{|}{C}}H\underset{X}{\underset{\|}{C}}CHY$

$CH_3CO\overset{R}{\overset{|}{C}}H{=}CHCH(OCH_3)_2$ **3**

1: $X{=}O,\ Y{=}(OCH_3)_2$

2: $X{=}H,\ OH;\ Y{=}(OCH_3)_2$

4: $X{=}H,\ H;\ Y{=}(OCH_3)_2$

5: $X{=}H,\ H;\ Y{=}(SCH_2C_6H_5)_2$

6: $X{=}H,\ H;\ Y{=}O$

7

a: $R{=}(CH_2)_6\text{-}CO_2CH_3$

b: $R{=}n\text{-}C_4H_9$

Scheme 1.

Experimental

NMR spectra were recorded on a Varian A-60 spectrometer using TMS as an internal standard in deuterio chloroform, IR spectra were taken on a Hitachi EPI-G3 in liquid films, and the results of NMR spectra and elemental analyses are shown in Table 1.

*Catalytic Hydrogenation of **1a** and **1b**.* A solution of **1a** (633 mg, 2.11 mmol) and PtO_2 (60 mg) in MeOH (35 ml) was hydrogenated under ordinary pressure. The solution was concentrated *in vacuo* to give an oily residue (622 mg), which was chromatographed (SiO_2, 10 g, hexane–benzene, 2:1) to afford the major alcohol **2a** (590 mg, 93% yield); IR: ν 3460, 1740, 1717 and 1700 cm^{-1}. Further elution with hexane-benzene-ether (1:2:0.4) gave the minor alcohol **epi-2a** (30 mg, 4.7% yield); IR: ν 3470, 1743 and 1710 cm^{-1}.

Similar hydrogenation of **1b** (2.16 g, 10 mmol) afforded the major alcohol **2b** (1.8 g, 83% yield); IR: ν 3450 and 1705 cm^{-1}, and the minor alcohol **epi-2b** (120 mg, 5.5% yield); IR: ν 3500 and 1714 cm^{-1}.

*Dehydration of **2a** and **2b**.* A solution of **2a** (20 g, 66 mmol), DCCI (16.3 g, 79 mmol) and copper(I) chloride (300 mg) in ether (230 ml) was heated under reflux for 20 h. The mixture was filtered and washed with ether. After the filtrate was evaporated *in vacuo*, the residue (25.2 g) was chromatographed (SiO_2, 250 g, benzene) to afford **3a**, (15.2 g, 81% yield), bp 140—150 °C/0.3 Torr (bath temp); IR: ν 1743, 1680, and 1650 cm^{-1}.

Similar procedure of **2b** (44.7 g, 0.204 mol) gave **3b** (35 g, 85.5% yield), bp 96—98 °C/2 Torr; IR: ν 1680 and 1655 cm^{-1}.

*Dehydration of **2a** via Its p-Toluenesulfonate.* The *p*-toluenesulfonate of **2a**, prepared from **2a** (2.1 g, 6.9 mmol) and *p*-toluenesulfonyl chloride (1.35 g, 7.1 mmol) in pyridine, were heated with potassium acetate (4.0 g) in DMF (20 ml) and H_2O (4 ml) at 100 to 110 °C for 2.5 h. The mixture was worked up as usual and the residue (1.7 g) was chromatographed (SiO_2, 17 g) to give **5a** (1.2 g, 60.1% yield).

*Catalytic Hydrogenation of **3a** and **3b**.* A solution of **3a** (7 g, 0.024 mol) in THF (70 ml) was hydrogenated over Pd-$CaCO_3$ (5 g) under ordinary pressure. After usual work-up, an oily residue (7.05 g) was distilled *in vacuo* to afford **4a** (5.7 g, 81% yield), bp 145—155 °C/0.3 Torr; IR: ν 1745 and 1720 cm^{-1}.

Analogous hydrogenation of **3b** (10 g, 0.05 mol) afforded **4b** (8.7 g, 87% yield), bp 100—110 °C/5 Torr (bath temp); IR: ν 1716 cm^{-1}.

*Benzylthioacetalization of **4a** and **4b**.* To a solution of **4a** (3.45 g, 12 mmol), benzyl mercaptan (3.47 g, 28 mmol) and Na_2SO_4 (4 g) in dioxane (15 ml) was added powdered anhyd. $ZnCl_2$ (8 g) at room temp. The mixture was stirred at 50 °C for 1 h, and poured into cold water. The aqueous solution was extracted with ether and the extracts were washed with H_2O and dried. After evaporation of the solvent *in vacuo*, the residue was chromatographed (SiO_2, 50 g, benzene-ether, 95 : 5) to afford **5a** (4.18 g, 74.1% yield); IR: ν 1743 and 1717 cm^{-1}.

Table 1. NMR spectra and elemental analyses[a)]

Compound	NMR ($CDCl_3$) in ppm	Obsd(%)		Calcd(%)	
		C	H	C	H
2a	($+D_2O$): 2.19(3, s, $COCH_3$), 2.8(1, dt, J=3.1 and 7 Hz, COCH), 3.4 and 3.41(6, two s, OCH_3), 3.66(1, dd, J=4 and 3.1 Hz, CHOH), 4.21 (1, d, J=4 Hz, CHOMe)	59.37	8.97	59.19	9.27
epi-2a	($+D_2O$): 2.22(3, s, $COCH_3$), 2.8(1, dt, J=7 and 3.5 Hz, COCH), 3.38 and 3.5(6, two s, OCH_3), 3.7(1, dd, J=3.5 and 4.2 Hz, CHOH), 4.25 (1, d, J=4.2 Hz, CHOMe)	59.01	9.45	59.19	9.27
2b	2.19(3, s, $COCH_3$), 2.8(1, dt, J=7 and 3 Hz, COCH), 3.7(1, dd, J=3 and 4 Hz, CHOH)	60.37	10.08	60.52	10.16
epi-2b	2.22(3, s, $COCH_3$), 2.8(1, dt, J=3.5 and 7 Hz, COCH), 3.71(1, dd, J=3.5 and 4 Hz, CHOH), 4.25(1, d, J=4 Hz, CHOMe)	60.74	9.87	60.52	10.16
3a	2.22(3, s, $COCH_3$), 3.38(6, s, OCH_3), 5.16(1, d, J=6.5 Hz, CHOMe), 6.43(1, d, J=6.5 Hz, =CH)	62.88	9.23	62.91	9.15
3b	2.31(3, s, $COCH_3$), 3.34(6, s, OCH_3), 6.35(1, d, J=6.5 Hz, =CH)	65.86	10.21	65.97	10.07
4a	2.15(3, s, $COCH_3$), 3.31(6, s, OCH_3), 4.32(1, t, J=5.5 Hz, CHOMe)	62.35	9.96	62.47	9.79
4b	2.13(3, s, $COCH_3$), 3.3(6, s, OCH_3), 4.29(1, t, J=5.5 Hz, CHOMe)	65.18	10.80	65.31	10.96
5a	1.94(3, s, $COCH_3$), 3.38(1, q, J=6 and 8 Hz, COCH), 3.73 and 3.78 (4, two s, SCH_2)	68.51	7.78	68.60	7.67
5b	1.94(3, s, $COCH_3$), 3.38(1, q, J=6 and 8 Hz, COCH), 3.73 and 3.78(4, two s, SCH_2)	71.41	7.58	71.45	7.82
6a	2.18(3, s, $COCH_3$), 9.66(1, t, J=1 Hz, CHO)	64.61	9.03	64.44	9.15
6b	2.18(3, s, $COCH_3$), 9.67(1, t, J=1 Hz, CHO)	68.95	10.21	69.19	10.32
7a	0.98—1.73(3, m), 1.9—2.7(8, m), 7.13(1, m, CH=)				
7b	0.93(3, t, CH_3), 1.37(4, m, CH_2CH_2), 2.2(4, m, CH_2CH=), 2.5(2, m, CH_2CO), 7.14(1, m, CH=)	78.38	10.13	78.21	10.21

a) The NMR spectra data of the substituent "R" in compounds 2 to 7 are not described.

Similar procedure of **4b** (300 mg, 1.5 mmol) gave **5b** (447 mg, 78% yield); IR:ν 1716 cm^{-1}.

*Cyclization of **5a** and **5b**.* A solution of **5a** (4.72 g, 10 mmol), $HgCl_2$ (10 g) and $CdCO_3$ (5.4 g) in CH_3CN (50 ml) and H_2O (10 ml) was stirred under N_2 atmosphere at room temp. for 3 h. After removal of inorganic substances, the filtrate was washed with H_2O and dried. The solvent was evaporated *in vacuo* to give a crude aldehyde **6a** (2.2 g, 90% yield), which was practically usable; IR:ν 2730, 1745, 1725 and 1715 cm^{-1}. A solution of the crude **6a** (2.2 g) and anhyd. K_2CO_3 (7 g) in MeOH (100 ml) was stirred at room temp for 20 h. The mixture was neutralized with aq. AcOH and extracted with ether. The extracts were washed with H_2O and dried. After evaporation of the solvent *in vacuo*, the residue was chromatographed (SiO_2, 20 g, hexane-benzene, 2:1) to afford **7a**[2)] (720 mg, 36% yield); IR:ν 1745, 1706 and 1635 cm^{-1}.

Similar cyclization of **5b** (3.1 g, 8 mmol) gave **7b** (565 mg, 41% yield); IR:ν 1708 and 1637 cm^{-1}.

References

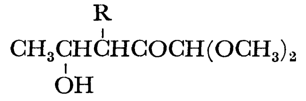
1) For recent reviews on the synthesis of 3-oxocyclopentenes and jasmoniods: see R. A. Ellison, *Synthesis*, **1973**, 397: T. L. Ho, *Synth. Commun.*, **4**, 265 (1974).

2) B. M. Trost and S. Kuroizumi, *Tetrahedron Lett.*, **1974**, 1929; K. Kondo and D. Tsunemoto, *Tetrahedron Lett.*, **1975**, 1397.

3) N. Finch, J. J. Fitt, and I. H. Hsu, *J. Org. Chem.*, **40**, 206 (1975).

4) J. Ide, K. Sakai, and Y. Yura, *Synth. Commun.*, **6**, 299 (1976).

5) In this reduction no regioisomeric alcohol **8** was found. Therefore, this hydrogenation interestingly occurred regio- and stereoselectively.



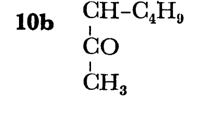
$$\underset{\text{OH}}{\text{CH}_3\text{CH}}\overset{\text{R}}{\text{CH}}\text{COCH(OCH}_3)_2$$

9

6) E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas and R. E. K. Winter, *J. Am. Chem. Soc.*, **90**, 3245 (1968).

7) Deacetalization of **4** to the aldehyde with various kinds of acids was unsuccessful. Treatment of **4** with concd. hydrochloric acid in acetone resulted in the furan derivatives **9** (**9a**: 52%, **9b**: 58% yield). Treatment of **4b** with 75% aqueous acetic acid containing catalytic amount of sulfuric acid gave the furan derivative **10b** (50.4% yield) along with a trace amount of the keto aldehyde **6**.

9



10b