Silica Gel-Catalyzed Air Oxidation of Cyclopentenones

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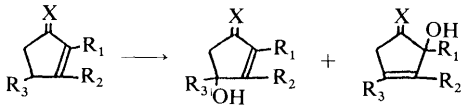
Cyclopentenones with an ester function at C_2, an alkyl function at C_3, and an ester (or alkyl) function at C_4 undergo facile oxidation during silica gel column chromatography using AcOEt–hexane as the eluent to afford oxygenated products with an OH function at C_2 or C_4.

Keywords silica gel; air oxidation; functionalized cyclopentenone; column chromatography; electron-withdrawing group

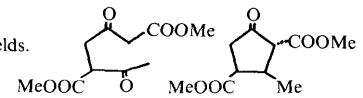
Previously, we reported that base -catalyzed cyclization[1] of the 1,4-diketone (**1**) followed by purification by silica gel column chromatography (eluent; 1—2% ether (v/v) in benzene) afforded the cyclopentenone (**2**). However, when 5—10% AcOEt–hexane was used as an eluent and the elution required more than 5 h, two oxygenated products (**2A**, **2B**)[2] were obtained.[3] Compound **2A** seems to have attractive functional groups for the synthesis of natural products. For example, this compound has a conjugated enone, required for 1,4-addition. Further, the C_4-center with two substituents (OH and ester) corresponds to a masked carbonyl function, which may be converted to a carbonyl group *via* reduction of the ester function and subsequent oxidation with $NaIO_4$. In addition, it is also possible to introduce appropriate substituents at each position on the five-membered ring. The above structural advantages were proved by the synthesis of biologically active compounds based on a five-membered ring, such as α and β-cuparenone, cuparene, and laurene.[4] Thus, we have further examined the structural requirements of this facile, practical silica gel-catalyzed air oxidation.

TABLE I. Silica Gel-Catalyzed Air Oxidation

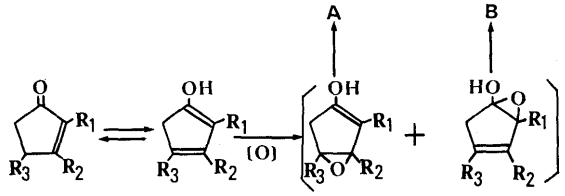


substrate	A (yield)[a]	B (yield)[a]
2 (X=O, R_1=COOMe, R_2=Me, R_3=COOMe)	**2A** (80%)	**2B** (3%)
3 (X=O, R_1=COOMe, R_2=$(CH_2)_6$COOMe, R_3=COOMe)	**3A** (41%)	**3B** (15%)
4 (X=O, R_1=COOMe, R_2=C_5H_{11}, R_3=COOMe)	**4A** (61%)	**4B** (6%)
5 (X=O, R_1=COOMe, R_2=Me, R_3=Me)	**5A** (50%)	**5B** (not detected)
6 (X=O, R_1=COOMe, R_2=Ph, R_3=COOMe)	Complex mixture	
7, **8**, **9** (**8**: X=–SCH_2CH_2S–, R_1=COOMe, R_2=Me, R_3=COOMe) (**9**: X=O, R_1=H, R_2=Me, R_3=COOMe)	Recovery	
10 (**10**: X=O, R_1=COOMe, R_2=Me, R_3=H)	Dimer	

a) Isolated yields.



1 **7**



R_1=$COOCH_3$; R_2=Alkyl; R_3=$COOCH_3$ or alkyl

Chart 1

Substrates[5] and the results of their silica gel-catalyzed oxidation are summarized in Table I. This oxidation seems to require two electron-withdrawing groups with a conjugated double bond; a single electron-withdrawing group is not enough for this oxidation, as shown by the cases of substrates **8** and **9**. The result with **7** suggests the necessity of a conjugated double bond for this oxidation reaction. As the C_3 substituent, an alkyl function is favorable, because **6** with a phenyl group at C_3 afforded a complex mixture. It may be concluded that the presence of an ester group at C_4 accelerates this oxidation, in comparison with the case of **5** with a methyl function at C_4; the oxidation reaction of **5** proceeded very slowly, requiring more than 15 h. As shown in **10**, the lack of a substituent at C_4 resulted in formation of the dimer.[6]

Reaction conditions[7] for the silica gel-catalyzed air oxidation were also examined. Air was bubbled with stirring into a solution of **2** in AcOEt in the presence of silica gel for 12 h, but only trace amounts of the oxygenated products were observed on thin layer chromatography (TLC), and most of **2** was recovered. The use of Florisil (100—200 mesh) instead of silica gel afforded a complex mixture. As an eluent, AcOEt–hexane was found to be superior to any other solvent system tested. For example, elution with 10% AcOEt in benzene (v/v) resulted in recovery of most of **2**. The oxidative mechanism is tentatively proposed to be as shown in Chart 1. Compounds A and B may be produced *via* intermediates formed by air-oxidation.

The above silica gel-catalyzed air oxidation coupled with the facile preparation of the substrates[1] may provide new chiral synthons[8] for the synthesis of natural products based on a five-membered ring.

Experimental

Infrared (IR) spectra were measured on a JASCO A-202 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured on a JEOL JNM-PS-100 spectrometer, and mass spectra (MS) were taken on a JEOL JMS-D 300 spectrometer. The melting points were measured with a Yanaco micro melting point apparatus and are uncorrected. For column chromatography, silica gel 70—230 mesh (Merck, Kieselgel 60) and distilled hexane and AcOEt were used. TLC was performed on Silica gel 60 F_{254} plates (Merck).

General Procedure for Silica Gel-Catalyzed Air Oxidation About 20-

fold excess (w/w) of silica gel over substrates (300—400 mg) was used for column chromatography, and each substrate was eluted slowly with 5—10% AcOEt in hexane (v/v) over 5—10 h. Compound A was obtained as the more polar fraction, and compound B as the less polar fraction. Each oxygenated product was obtained as a colorless oil, except for **2A** (mp 76.5—78.5 °C) and **2B** (mp 108—110 °C).

Selected Spectroscopic Data of Oxygenated Products 4-Hydroxy-2,4-bis(methoxycarbonyl)-3-methylcyclopent-2-en-1-one (**2A**): IR (neat): 3500, 1720, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s), 2.71, 2.91 (1H each, d, J=18 Hz), 3.83, 3.88 (3H each, s). MS m/z: 228 (M^+), 197, 169.

2-Hydroxy-2,4-bis(methoxycarbonyl)-3-methylcyclopent-3-en-1-one (**2B**): IR (neat): 3470, 1745, 1645 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.13 (3H, t, J=2 Hz), 3.35, 3.37 (1H each, m), 3.81, 3.83 (3H each, s). MS m/z: 228 (M^+) (FD), 196, 169.

4-Hydroxy-2,4-bis(methoxycarbonyl)-3-(6-methoxycarbonylhexyl)-cyclopent-2-en-1-one (**3A**): IR (neat): 3430, 1720, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.1—1.9 (10H, m), 2.31 (2H, t, J=7 Hz), 2.70, 2.89 (1H each, d, J=18 Hz), 3.67, 3.81, 3.87 (3H each, s). MS m/z: 357 (M^++1) (FD), 297.

2-Hydroxy-2,4-bis(methoxycarbonyl)-3-(6-methoxycarbonylhexyl)-cyclopent-3-en-1-one (3B): IR (neat): 3450, 1720—1730, 1635 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.1—1.8 (10H, m), 2.30 (2H, t, J=7 Hz), 3.30, 3.35 (1H each, m), 3.66, 3.80, 3.82 (3H each, s). MS m/z: 356 (M^+) (FD), 297.

4-Hydroxy-2,4-bis(methoxycarbonyl)-3-pentylcyclopent-2-en-1-one (**4A**): IR (neat): 3460, 1725—1740, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=6 Hz), 1.1—1.9 (6H, m), 2.66, 2.93 (1H each, d, J=18 Hz), 3.81, 3.87 (3H each, s). MS m/z: 284 (M^+), 241, 235.

2-Hydroxy-2,4-bis(methoxycarbonyl)-3-pentylcyclopent-3-en-1-one (**4B**): IR (neat): 3460, 1740, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6 Hz), 3.30, 3.35 (1H each, m), 3.80, 3.82 (3H each, s). MS m/z: 284 (M^+), 252, 224.

4-Hydroxy-3,4-dimethyl-2-methoxycarbonylcyclopent-2-en-1-one (**5A**): IR (neat): 3450, 1735, 1625 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.54 (3H, s), 2.35 (3H, s), 2.66 (2H, s), 3.84 (3H, s). MS m/z: 184 (M^+), 169, 166.

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References and Notes

1) K. Kojima, S. Amemiya, H. Suemune, and K. Sakai, *Chem. Pharm. Bull.*, **33**, 2750 (1985).
2) K. Okano, Y. Mizuhara, H. Suemune, H. Akita, and K. Sakai, *Chem. Pharm. Bull.*, **36**, 1358 (1988).
3) The structures of **2A** and **2B** were determined by X-ray analysis and examination of the spectroscopic data. See ref. 2.
4) K. Okano, H. Suemune, and K. Sakai, *Chem. Pharm. Bull.*, **36**, 1379 (1988).
5) See ref. 1 for the preparation of **2**, **3**, **4**, **6**, and **7**. For **5**, see R. Baker, D. L. Selwood, C. J. Swain, N. M. H. Webster, and J. Hirshfield, *J. Chem. Soc., Perkin Trans. 1*, **1988**, 471. Compound **8** was prepared by thioacetalization of **2** with BF_3/1,2-ethanedithiol, and **9**, was obtained by decarboxylation (DMSO/NaI) of **2**. For **10**, see M. A. Guaciaro, P. M. Wovkulich, and A. B. Smith, III, *Tetrahedron Lett.*, **1978**, 4661.
6) N. Finch, J. J. Fitt, and I. H. C. Hsu, *J. Org. Chem.*, **36**, 3191 (1971).
7) An oxidizing agent such as SeO_2 or *m*-chloroperbenzoic acid afforded a complex mixture, when used in place of silica gel.
8) It is also possible to prepare the optically pure compound (A) by kinetic resolution using an enzymatic procedure. See ref. 2.