Tetrahedron Vol. 41, No. 22, pp. 5141 to 5144, 1985
Printed in Great Britain.

A NEW SYNTHESIS OF 4-METHOXY-CYCLOPENT-2-EN-1-ONES

ARRIGO SCETTRI

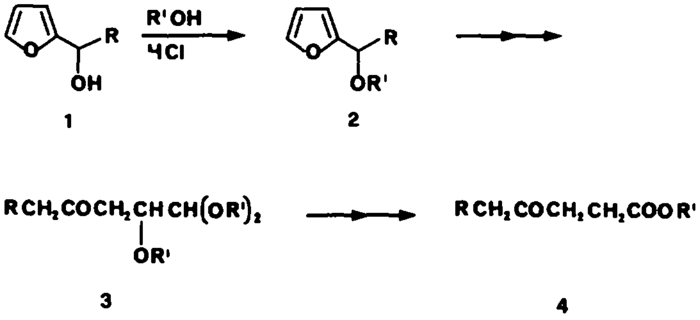
Centro di Studio per la Chimica delle Sostanze Organiche Naturali del CNR c/o Dipartimento di Chimica, Università "La Sapienza", P.le Aldo Moro 2, 00185 Roma Italy

(*Received in UK* 19 *June* 1985)

ABSTRACT: 4-methoxy-cyclopent-2-en-1-ones 6 are easily obtained through a simple procedure involving in the key-step the conversion of 2-furylcarbinols 1 into 1,1,2-trimethoxy-alkan-4-ones 3, a masked form of 1,4-dicarbonyl compounds, by treatment with Amberlyst H15 in methanolic solution. Then, the regeneration of the aldehydic function and a base-catalysed aldolic condensation lead in high yields to the final products 6.

The fission of furfuryl alcohols 1 to substituted levulinic acid esters 4 in the presence of hydrochloric acid and methanol has been throughly investigated in the past years.[1] The conversion is not always convenient from a synthetic point of view, since compounds 4 are isolated in very variable yields by rather complex mixtures of products.[2] However, the isolation and identification of several intermediates has allowed the formulation of a mechanism,[3] that is summarised in Scheme 1.

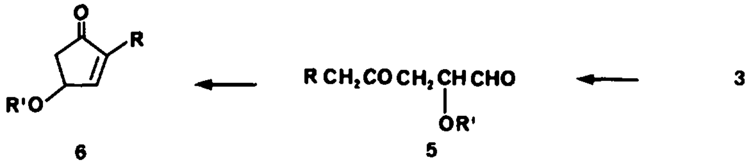
SCHEME 1



$RCH_2COCH_2CH(OR')CH(OR')_2$ → $RCH_2COCH_2CH_2COOR'$

Compounds of structure 3, which represented a masked form of 1,4-dicarbonyl compounds, attracted our interest: in fact, as resulted by a retrosynthetic analysis (Scheme 2), they could be considered useful starting materials for the synthesis of cyclopentenones of type 6. 4-Alkoxycyclopentenones show very interesting biological activity, as pharmaceuticals, agricultural chemicals and perfumes.[4]

SCHEME 2

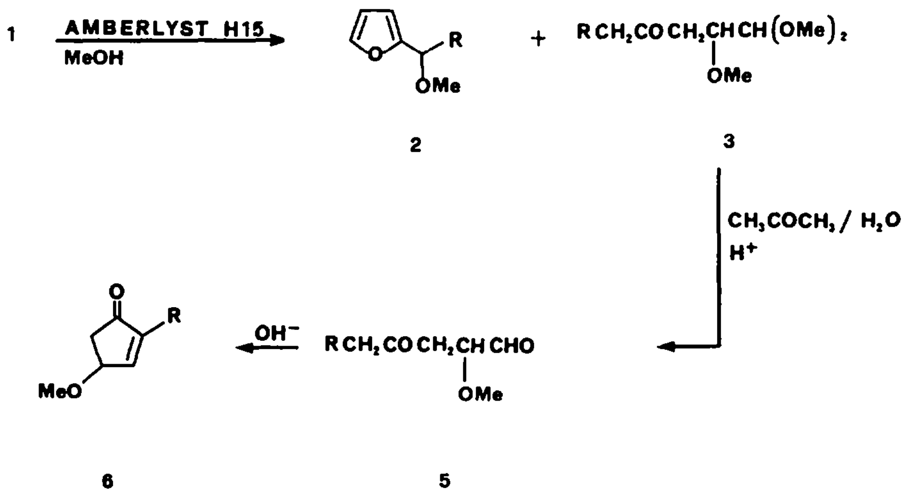


Unfortunately, under the above conditions, 3 could be isolated in rather negligible amounts.

Now, we wish to report that 2-furylcarbinols 1 can be changed into 3 with good yields by using an acid ion exchanger, Amberlyst H15, instead of hydrochloric acid. Furthermore, the conversion proceeds with much better selectivity, since this treatment leads essentially to a mixture of only two products, 2 and 3, (total yield 90-95%), while the formation of methyl 4-oxoalkanoate 4 is almost completely inhibited. The procedure proves to be particularly convenient if we consider that 2 is not a mere by-product, but a precursor of 3.

This result has allowed the achievement of a new general route to 2-substituted-4-methoxy-cyclopent-2-en-1-ones 6: in fact, (Scheme 3), the hydrolysis of the acetal function of 3 in acetone-water in the presence of catalytic amount of p-toluenesulfonic acid, affords the 2-methoxy-4-oxoalkanal 5, that, without purification, is converted into the cyclopentenone derivative 6 by a base-catalysed intramolecular condensation (85-90% from 3).

SCHEME 3



Although compounds 5 can be isolated and easily identified by spectroscopic methods (for ex. 5d: IR (CCl$_4$, ν_{max}, cm^{-1}): 3090, 3065, 3030, 1738, 1720, 1120, 700. PMR (CCl$_4$, δ): 9.40 (s, 1H), 7.0 (s, 5H), 3.75 (t, 1H; J= 6.5 Hz), 3.52 (s, 2H), 3.25 (s, 2H), 2.52 (d, 2H; J= 6.5 Hz). MS (m/e): 206 (M$^+$)), nevertheless, better yields in final products 6 are obtained carrying out the cyclisation process on the crude 5 (Table).

T A B L E

Compoun	Yield %	Compounds 6	Yield % (from 3)	
a: R= C_8H_{17}		52	a: R= C_8H_{17}	85
b: R= $C_{10}H_{21}$		53	b: R= $C_{10}H_{21}$	87
c: R= $C_{12}H_{25}$		55	c: R= $C_{12}H_{25}$	88
d: R= C_6H_5		44	d: R= C_6H_5	90

It has to be pointed out that, for R= phenyl, both furylcarbinol 1d and ketoaldehyde 5d show a remarkable tendency to decompose under the above reported treatments, so that milder reaction conditions and/or shorter reaction times are generally required for a fair occurrence of the whole sequence.

As at present a few general routes are available for the synthesis of 4-methoxy-cyclopentenones,[5,6] this procedure proves to be particularly effective for the simplicity and mildness of the involved reactions.

EXPERIMENTAL: M.ps were determined on a Kofler block and are uncorrected. IR spectra were recorded on a Perkin-Elmer 298 spectrometer, in 1% CCl$_4$ solution and are given in cm^{-1}. PMR spectra were recorded on a Varian EM-360 spectrometer, usually in CCl$_4$ solution, and shifts are reported in ppm (δ) relative to Me$_4$Si. Mass spectral data were obtained with an AEI-MS 12 spectrometer. Carlo Erba precoated silica gel plates were used in TLC.

Starting materials: 2-furylcarbinols were prepared by reacting 2-formyl-furan with an excess of the appropriate Grignard reagent and their structures were confirmed through spectroscopic (IR and PMR) data.

General procedure to 1,1,2-trimethoxy-alkan-4-ones 3: a mixture of 10 mmol of 1, 250 ml of MeOH and 5g of Amberlist H15 is stirred under N$_2$ at 50°C for 48h (24h for 1d). Then, the solution is filtered through a pad of silica gel. The solvent is removed under a reduced pressure and the crude product is purified by chromatography on SiO$_2$. The elution with 2/1 light petroleum/ethyl acetate yields the pure 3.

General procedure to 4-methoxy-cyclopent-2-en-1-ones 6: p-toluenesulfonic acid (100 mg) is added to a solution of 3 (5 mmol) in 200 ml of 2/1 acetone-water; the mixture is stirred under N$_2$ at 65°C for 36h (24h at 50°C for 3d), then it is poured into water and extracted with diethyl ether. The neutral organic phase is concentrated in vacuo and the crude ketoaldehydes 5, dissolved in 100 ml of MeOH, are treated with 10 ml of 0.1N aq. NaOH for 12h (1h for 5d). Then, the mixture is diluted with brine and extracted with AcOEt. The neutral organic phase is dried over an. Na$_2$SO$_4$ and, after the removal of the solvent, the crude product is chromatographed on silica gel. Elution with 4/1 light petroleum/diethyl ether yields the pure cyclopentenones 6.

1,1,2-trimethoxy-tridecan-4-one 3a: oil, n_D^{21}= 1.4290. IR: 2920, 2855, 1720, 1460, 1125, 1080. PMR: 4.10 (d, 1H; J= 5 Hz), 3.65 (dt, 1H; J$_1$= 6 Hz, J$_2$= 5 Hz), 3.32 (s, 6H), 3.28 (s, 3H), 2.45 (d, 2H; J= 6 Hz), 2.2 (m, 2H), 1.3 (m, 14H), 0.9 (m, 3H). MS (m/e): 288 (M$^+$). Anal. calc. for $C_{16}H_{32}O_4$: C 66.63, H 11.18. Found C 66.75, H 11.31%.

1,1,2-trimethoxy-pentadecan-4-one 3b: oil, n_D^{21}= 1.4299. IR: 2915, 2850, 1718, 1462, 1120, 1082. PMR: 4.12 (d, 1H; J= 5 Hz), 3.70 (dt, 1H; J$_1$= 6 Hz, J$_2$= 5 Hz), 3.35 (s, 6H), 3.30 (s, 3H), 2.52 (d, 2H; J= 6 Hz), 2.3 (m, 2H), 1.3 (m, 18H), 0.9 (m, 3H). MS (m/e): 316 (M$^+$). Anal. calc. for $C_{18}H_{36}O_4$: C 68.31, H

11.47. Found C 68.50, H 11.55%.

1,1,2-trimethoxy-heptadecan-4-one 3c: oil, n_D^{21} = 1.4300. IR: 2920, 2853, 1718, 1458, 1125, 1079. PMR: 4.15 (d, 1H; J= 5 Hz), 3.65 (dt, 1H; J_1= 6 Hz, J_2= 5 Hz), 3.32 (s, 6H), 3.27 (s, 3H), 2.48 (d, 2H; J= 6 Hz), 2.2 (m, 2H), 1.3 (m, 22H), 0.9 (m, 3H). MS (m/e): 344 (M^+). Anal. calc. for $C_{20}H_{40}O_4$: C 69.72, H 11.70. Found C 69.85, H 11.83%.

1-phenyl-4,5,5-trimethoxy-pentan-2-one 3d: oil, n_D^{21} = 1.4251. IR: 3090, 3070, 3035, 1718, 1601, 1478, 1112, 1075. PMR: 7.0 (m, 5H), 4.0 (d, 1H; J= 5 Hz), 3.6 (m, 1H), 3.50 (s, 2H), 3.25 (s, 9H), 2.40 (d, 2H; J= 6 Hz). MS (m/e): 252 (M^+). Anal. calc. for $C_{14}H_{20}O_4$: C 66.65, H 7.99. Found C 66.50, H 8.11%.

2-n-octyl-4-methoxy-cyclopent-2-en-1-one 6a: plates from MeOH/H_2O, mp 52-53°C. IR: 2955, 2925, 2850, 1715, 1645, 1244, 1098. PMR: 6.9 (m, 1H), 4.2 (m, 1H), 3.30 (s, 3H), 2.50 (dd, 1H; J_1= 18 Hz, J_2= 6 Hz), 2.15 (partially visible dd, J_1= 18 Hz, J_2= 2 Hz), 0.9 (m, 3H). MS (m/e): 224 (M^+). Anal. calc. for $C_{14}H_{24}O_2$: C 74.95, H 10.78. Found C 75.10, H 10.90%.

2-n-decyl-4-methoxy-cyclopent-2-en-1-one 6b: plates from MeOH/H_2O, mp 54-56°C. IR: 2950, 2922, 2853, 1715, 1647, 1465, 1190, 1100. PMR: 6.9 (m, 1H), 4.2 (m, 1H), 3.27 (s, 3H), 2.52 (dd, 1H; J_1= 18 Hz, J_2= 6 Hz), 2.10 (partially visible dd, 1H; J_1= 18 Hz, J_2= 2 Hz), 0.9 (m, 3H). MS (m/e): 252 (M^+). Anal. calc. for $C_{16}H_{28}O_2$: C 76.14, H 11.18. Found C 76.01, H 11.03%.

2-n-dodecyl-4-methoxy-cyclopent-2-en-1-one 6c: plates from MeOH/H_2O, mp 58-60°C. IR: 2952, 2925, 2854, 1716, 1645, 1465, 1195, 1100. PMR: 7.0 (m, 1H), 4.2 (m, 1H), 3.30 (s, 1H), 2.60 (dd, 1H; J_1= 18 Hz, J_2= 6 Hz), 2.20 (partially visible dd, 1H; J_1= 18 Hz, J_2= 2 Hz), 0.9 (m, 3H). MS (m/e): 280 (M^+). Anal. calc. for $C_{18}H_{32}O_2$: C 77.09, H 11.50. Found C 76.95, H 11.38%.

2-phenyl-4-methoxy-cyclopent-2-en-1-one 6d: plates from MeOH/H_2O, mp 60-63°C. IR: 3090, 3060, 3012, 2925, 1721, 1600, 1342, 1100, 990, 690. PMR: 7.6-7.0 (m, 6H)), 4.3 (m, 1H), 3.30 (s, 3H), 2.65 (dd, 1H; J_1= 18 Hz, J_2= 6 Hz), 2.25 (dd, 1H; J_1= 18 Hz, J_2= 2 Hz). MS (m/e): 188 (M^+). Anal. calc. for $C_{12}H_{12}O_2$: C 76.57, H 6.43. Found C 76.70, H 6.60%.

REFERENCES

1) F. Bosshard, C.H. Eugster, "Advances in Heterocyclic Chemistry", Academic Press, New York, (1966), vol. 7, pp 438-441
2) A.P. Dunlop, F.N. Peters, "The Furans", Reinhold Publishing Corp., (1953), New York, pp 640-652
3) K.G. Lewis, J. Chem. Soc., 4690 (1961)
4) M. Minai, T. Katsura, Ger. Offen. DE 3.217.904 (1982): C.A. 98, 106859a (1983)
5) G. Piancatelli, A. Scettri, M. D'Auria, Tetrahedron, 36, 661 (1980)
6) T.F. West, J. Chem. Soc., 239 (1944)

Acknowledgement: this research has been partially supported by the Italian MPI.