Tetrahedron Vol. 34, pp. 2775–2778

0040-4020/78/0915-2775/$02.00/0

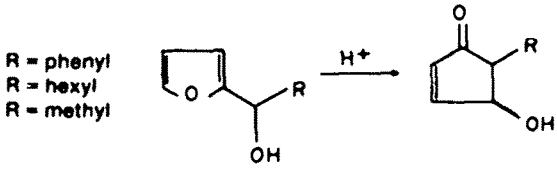
A NEW SYNTHESIS OF 3-OXOCYCLOPENTENES*

G. PIANCATELLI,† A. SCETTRI, G. DAVID and M. D'AURIA
Istituto di Chimica Organica, Università di Roma, Italia

(*Received in UK 9 March 1978; Accepted for publication 3 April 1978*)

Abstract—5 - Methyl - 2 - furylcarbinols 3 have been converted into 3-oxocyclopentene derivatives 4 through a molecular rearrangement catalyzed by $ZnCl_2$. The reaction mechanism is explained in terms of a thermal electrocyclic reaction of a $4n$ electrons system. An application relative to the synthesis of (±) allethrolone is reported. reported.

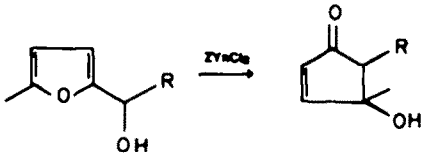
We have recently reported a new and efficient synthesis of 4-substituted 5 - hydroxy - 3 - oxocyclopentenes 2 through acid-catalyzed rearrangement of 2-furylcarbinols 1, and an application in the prostaglandin field yielded some interesting intermediates.[1]



1 2

The extension of this method to 5 - methyl - 2 - furylcarbinols 3 unexpectedly failed, since only a mixture of products was obtained and characterized by the absence of any CO function in the IR spectrum. By electron donor effect, the Me group on the furan ring increased the reactivity (and consequently the instability) of the compounds 3 in acid medium preventing the rearrangement from occurring.[b]

In this paper we wish to report a resolution of this problem, being the conversion of 3 to 3-oxocyclopentenes 4 carried out by a weak Lewis acid used as electrophilic catalyst. Zinc chloride was chosen since it did not appear to be a proton donor under the usual reaction conditions, while analogous solutions of other halides, as $SnCl_2$ or $CdCl_2$, are acid to litmus.[c]



3 4

In fact, 5 - methyl - 2 - furylcarbinols 3, after treatment with zinc chloride in acetone–water mixture at 60° for several hours, were directly converted into 4-substituted 5 - hydroxy - 5 - methyl - 3 - oxocyclopentenes 4 (Table 1). All new compounds showed spectral data (IR and ^1H NMR) completely in agreement with the ones reported for similar products:[1] e.g. 4a: IR spectrum (neat, ν_{max} cm^{-1}): 3400, 1700, 1640, 1595. ^1H NMR spectrum (CCl_4, δ): 7.20 (d, 1H, 1-H; J = 6 Hz), 5.95 (d, 1H, 2-H; J = 6 Hz), 5.75 (m, 1H, $-CH_2-CH=CH_aH_b$), 5.10 (m, 1H, $-CH_2-CH=CH_aH_b$), 4.95 (m, 1H, $-CH_2-CH=CH_aH_b$), 3.5 (broad s, 1H, 5-OH), 2.35 (m, 1H, 4-H), 1.95 (complex m, 2H, $-CH_2-CH=CH_aH_b$), 1.34 (s, 3H, 5-Me).

Zinc chloride and the compounds 3 were used in nearly equimolar ratio, while the best yields were obtained with the molar ratios $H_2O/ZnCl_2$ reported in Table 1.

When the furylcarbinols 3 contained an alkyl group as substituent R, the reaction was always characterized by an extremely low rate, poor yields, and, most of all, by the formation of unidentified by-products, which did not show any signal indicative of CO functions in their IR spectra. When R was an aromatic substituent, the reaction was much faster and the yields of 4 were excellent.

The mechanism could be explained in terms of a thermal electrocyclic reaction of a $4n$ electrons system, that is conrotatory:[1] presumably, it involved an initial electrophilic attack upon the alcoholic function by the zinc ion, leading to an intermediate 5, from which the carbonium ion 6 could be generated.

The formation of 6 (and its relative stability) seemed to be the key step towards the following rearrangement: when R was an aromatic substituent, this step was energetically favoured and the intermediate 6 was stable enough to undergo the attack of H_2O on 5C atom. When R was an alkyl group the same step was less favoured because of the lower stability of 6. This could explain the decrease of reaction rate, the poor yields of 4a–c, and the remarkable amounts of undesired by-products.

The rearrangement, in agreement with the proposed mechanism, proceeded in stereospecific manner: in fact in all ^1H NMR spectra the signals relative both to the Me group at 5 in 4a–f and to the proton at 4 in 4d–f presented as very clear singlets, sure sign of high steric purity. Between the two possible pairs (I and II), only I was formed, as indicated by ^1H NMR data.

The Me group at 5 in 4a–c was found to have the usual chemical shift (1.37 δ, for ex., in 4-cyclohexyl derivative 4c), while the same Me in 4d–f was shifted upfield (0.85 δ, for e.g. in 4-phenyl derivative 4d) because of the shielding effect induced by the aromatic ring in *cis configuration*.

Although sometimes the yields are rather low, this method always presents a real usefulness, because it

*The investigation was supported by the Italian C.N.R.

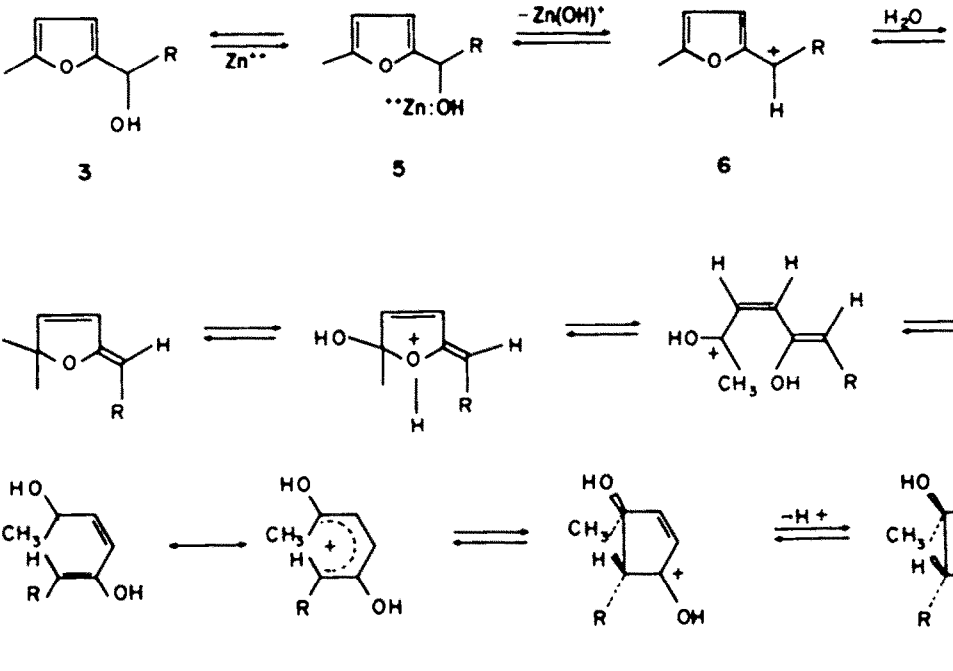
[b]2-Furylcarbinols are generally very unstable compounds.[2]

[c]The aqueous solution of $ZnCl_2$ is acid (pH ≈ 4), but, in acetone–water mixture, pH value rises to 6–7. Under the same conditions, the solution of $MgBr_2$ is neutral too, but the rearrangement of 3 to 4 did not occur.

Table 1.

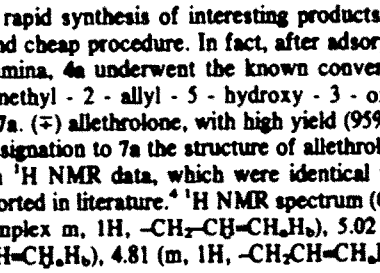
Starting materials	Molar ratio $H_2O/ZnCl_2$	Time/h	Products	Yields %*
3a R = allyl	8/1	72	4a	35
3b R = n-butyl	16/1	72	4b	18
3c R = cyclohexyl	8/1	72	4c	16
3d R = phenyl	16/1	24	4d	70
3e R = 2-thienyl	16/1	4	4e	85
3f R = p-tolyl	16/1	4	4f	65

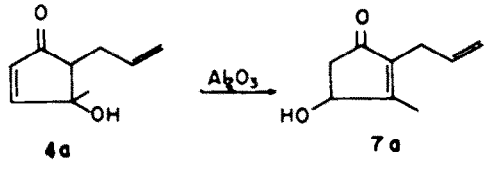
*All yields refer to isolated, chromatographically pure products.



allows a rapid synthesis of interesting products using a simple and cheap procedure. In fact, after adsorption on basic alumina, 4a underwent the known conversion[3] to (∓) 1 - methyl - 2 - allyl - 5 - hydroxy - 3 - oxocyclopentene 7a. (∓) allethrolone, with high yield (95%).

The assignation to 7a the structure of allethrolone was based on ^{1}H NMR data, which were identical with the ones reported in literature.[4] ^{1}H NMR spectrum (CCl_4, δ): 5.65 (complex m, 1H, $-CH_2-CH=CH_aH_b$), 5.02 (m, 1H, $-CH_2-CH=CH_aH_b$), 4.81 (m, 1H, $-CH_2CH=CH_aH_b$), 4.57





(m, 1H, 5-H), 2.85 (d, 2H, $-CH_2-CH=CH_aH_b$), 2.65 (dd, 1H, 4-H; J_1 = 18 Hz, J_2 = 6 Hz), 2.15 (dd, 1H, 4-H; J_1 = 18 Hz, J_2 = 3 Hz), 2.05 (s, 3H, 1-Me).

EXPERIMENTAL

^{1}H NMR spectra were taken with a Jeol 50 HL spectrometer, using CCl_4 soln with TMS as an internal standard. IR spectra were taken with a Perkin–Elmer 257 spectrometer. Mass spectra were obtained with an AEI MS-12 spectrometer at 70 eV, by using direct insertion at source temp. of 150°. Commercial Merck silica gel and Woelm alumina were used for column chromatography. Merck precoated silica gel plates were used in tlc. The chromatograms were detected by spraying with 5 N H_2SO_4 and heating at 110° for 10 min.

5 - *Methyl* - 2 - *furylallylcarbinol* 3a. 5 g of 5 - methyl - furan - 2 - carboxyaldehyde, diluted with 12 ml anhyd Et_2O, were added at 0° to the Grignard reagent prepared from 2.4 g Mg, 7.5 ml allyl bromide in 25 ml anhyd Et_2O.[5] After 1 hr, 100 ml of a cold soln, satd with NH_4Cl, were added and the mixture was stirred for

2 hr. Then the usual work-up yielded 6.6 g of crude product that was purified through chromatography on SiO_2. The elution with C_6H_6–Et_2O gave 6 g of pure, oily 3a (87%). (Found: C, 71.15; H, 8.09. Calc. for $C_9H_{12}O_2$: C, 71.03; H, 7.95%). IR spectrum (film, ν_{max} cm^{-1}): 3400, 1670, 1570. ^1H NMR spectrum (CCl_4, δ): 5.90 (d, 1H, 3-H), 5.80 (m, 1H, 4-H), 6.1–5.4 (complex m, 1H, $-CH_2-CH=CH_aH_b$), 5.10 (m, 1H, $-CH_2-CH=CH_aH_b$), 4.88 (m, 1H, $-CH_2-CH=CH_aH_b$), 4.50 (t, 1H, –CH–OH), 2.42 (m 2H, $-CH_2-CH=CH_aH_b$), 2.22 (s, 3H, 5-Me). MS, *m/e*: 152 (M^+).

5 - *Methyl* - 2 - *furylbutylcarbinol* 3b. 15 ml 1.5 N n-BuLi soln were added at 0° to 1.82 ml 5 - methyl - furan - 2 - carboxyaldehyde. After 30 min 50 ml of a cold soln, satd with NH_4Cl, were added and the mixture was stirred for 1 hr. The usual isolation procedure yielded 3.0 g of crude product which was chromatographed on SiO_2. The elution with C_6H_6–Et_2O 9:1 afforded 2.570 g of pure, oily 3b, (85%). (Found: C, 71.20; H, 9.75. Calc. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59%). IR spectrum (film, ν_{max} cm^{-1}): 3400, 1560. ^1H NMR spectrum (CCl_4, δ): 5.98 (d, 1H, 3-H), 5.80 (m, 1H, 4-H), 4.50 (t, 1H, –CH–OH) 3.55 (broad s, 1H, –CH–OH), 2.20 (s, 3H, 5-Me), 1.32 (m, 6H, 3 $-CH_2-$), 0.95 (t, 3H, $-(CH_2)_3-CH_3$). MS. *m/e*: 168 (M^+).

5 - *Methyl* - 2 - *furylcyclohexylcarbinol* 3c. 2 ml 5 - methyl - furan - 2 - carboxyaldehyde, diluted with 12.5 ml anhyd Et_2O, were added at 0° to the Grignard reactive prepared from 1.5 ml cyclohexyl bromide, 2.67 g Mg in 10 ml anhyd Et_2O.[6] The usual work-up yielded 3.5 g crude product, which was purified through chromatography on SiO_2. The elution with C_6H_6–Et_2O 4:1 gave 2.8 g of pure, oily 3c (65%). (Found: C, 74.03; H, 9.20. Calc. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34%). IR spectrum (film, ν_{max} cm^{-1}): 3400, 1560. ^1H NMR spectrum (CCl_4, δ): 5.84 (d, 1H, 3-H), 5.70 (m, 1H, 4H), 4.10 (d, 1H, –CH–OH), 2.38 (s, 1H, –CH–OH), 2.21 (s, 3H, 5-Me). MS, *m/e*: 194 (M^+).

5 - *Methyl* - 2 - *furylphenylcarbinol* 3d. 2.5 ml 5 - methyl - furan - 2 - carboxyaldehyde, diluted with 20 ml anhyd Et_2O, were added at 0° to the Grignard reactive prepared from 1.2 g Mg, 5 ml bromobenzene in 10 ml anhyd Et_2O. After 1 hr, 50 ml of a cold soln, satd with NH_4Cl, and the mixture was stirred for 1 hr; the usual isolation yielded 4.15 g crude product which was chromatographed on neutral Al_2O_3 B III. The elution with C_6H_6–Et_2O 4:1 gave 3.5 g of pure oily 3d (74%). (Found: C, 76.70; H, 6.68. Calc. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43%). IR spectrum (film, ν_{max} cm^{-1}): 3600, 3012, 1584, 1560. ^1H NMR spectrum (CCl_4, δ): 7.22 (s, 5H, phenyl protons), 5.76 (s, 2H, furan protons), 5.50 (s, 1H, –CH–OH), 3.30 (broad s, 1H, –CH–OH), 2.18 (s, 3H, 5-Me). MS, *m/e*: 188 (M^+).

5 - *Methyl* - 2 - *furyl*(2 - *thienyl*)*carbinol* 3e. 1 ml 5 - methyl - furan - 2 - carboxyaldehyde, diluted with 10 ml anhyd Et_2O, was added to the reactive prepared from 2.2 ml thiophene and 20 ml 1.5 N n-BuLi in 50 ml anhyd Et_2O. After 1 hr, 50 ml of a cold soln satd with NH_4Cl were added and the mixture was stirred for 30 min. The usual work-up yielded 1.4 g crude product which was chromatographed on neutral Al_2O_3 B III. The elution with C_6H_6–Et_2O 4:1 gave 1.25 g of pure, oily 3e (65%). IR spectrum (film, ν_{max} cm^{-1}): 3390, 1560. ^1H NMR spectrum (CCl_4, δ): 7.05 (m, 1H, thienyl 5-H), 6.75 (m, 2H, thienyl 3-H and 4-H), 5.93 (d, 1H, furan 3-H), 5.72 (m, 2H, overlapping of furan 4-H and –CH–OH), 2.98 (broad s, 1H, –CH–OH), 2.22 (s, 3H, furan 5-Me). MS, *m/e*: 194.25 (M^+ in agreement with the formula $C_{10}H_{10}O_2S$).

5 - *Methyl* - 2 - *furyl*(p - *tolyl*)*carbinol* 3f. 1.8 ml 5 - methyl - furan - 2 - carboxyaldehyde, diluted with 15 ml anhyd Et_2O, were added at 0° to the reactive prepared from 1 g Mg, 4.3 ml *p*-bromotoluene in 20 ml anhyd Et_2O. After 1 hr, 50 ml of a cold soln, satd with NH_4Cl, were added and the mixture was stirred for 1 hr. The usual isolation procedure yielded 3 g crude product which was chromatographed on neutral Al_2O_3 B III. The elution with C_6H_6–Et_2O 9:1 gave 1.6 g of pure, oily 3f (44%). (Found: C, 77.31; H, 7.14. Calc. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98%). IR spectrum (film, ν_{max} cm^{-1}): 3390, 3050, 3020, 1615, 1560. ^1H NMR (CCl_4, δ): 7.04 (m, 4H, phenyl ring protons), 5.73 (m, 2H, furan protons), 5.46 (s, 1H, –CH–OH), 3.30 (broad s, 1H, –CH–OH), 2.30 (s, 3H, –Me on benzene ring), 2.20 (s, 3H, Me on furan ring). MS, *m/e*: 202 (M^+).

4 - *Allyl* - 5 - *hydroxy* - 5 - *methyl* - 3 - *oxocyclopentene* 4a. 500 mg of 3a and 444 mg $ZnCl_2$, dissolved in mixture of 20 ml acetone and 0.48 ml H_2O, were stirred at 60° for 72 hr. The soln was acidified to pH 3 with 2 N H_2SO_4 and was extracted many times with Et_2O. The neutral combined organic extracts were dried over Na_2SO_4 and, after the removal of the solvent under reduced pressure, the crude product was chromatographed on SiO_2. The elution with C_6H_6–Et_2O 2:1 gave 175 mg of pure, oily 4a (35%). (Found: C, 71.20; H, 8.17. Calc. for $C_9H_{12}O_2$: C, 71.03; H, 7.95%). IR spectrum (film, ν_{max} cm^{-1}): 3400, 1700, 1640, 1595. ^1H NMR spectrum (CCl_4, δ): 7.20 (d, 1H, 1-H; J = 6 Hz), 5.95 (d, 1H, 2-H, J = 6 Hz), 5.75 (m, 1H, $-CH_2-CH=CH_2$), 5.10 (m, 1H, $-CH_2-CH=CH_aH_b$), 4.95 (m, 1H, $-CH_2-CH=CH_aH_b$), 3.50 (s, 1H, 5-OH), 2.35 (m, 1H, 4-H), 1.34 (s, 3H, 5-Me). MS, *m/e*: 152 (M^+).

4 - N - *Butyl* - 5 - *hydroxy* - 5 - *methyl* - 3 - *oxocyclopentene* 4b. 500 mg of 3b and 393 mg $ZnCl_2$, dissolved in a mixture of 20 ml acetone and 0.84 ml H_2O, were stirred at 60° for 72 hr. The usual isolation procedure yielded 480 mg crude product which was chromatographed on SiO_2. The elution with C_6H_6–Et_2O 1:1 gave 90 mg of pure, oily 4b (18%). (Found: C, 71.30; H, 9.68. Calc. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59%). IR spectrum (film, ν_{max} cm^{-1}): 3400, 1695, 1595. ^1H NMR spectrum (CCl_4, δ): 7.25 (d, 1H, 1-H; J = 6 Hz), 5.85 (d, 1H, 2-H; J = 6 Hz), 3.63 (s, 1H, 5-OH), 2.20 (m, 1H, 4-H), 1.25 (s, 3H, 5-Me). MS, *m/e*: 168 (M^+).

4 - *Cyclohexyl* - 5 - *hydroxy* - 5 - *methyl* - 3 - *oxocyclopentene* 4c. 500 mg of 3c and 350 mg $ZnCl_2$, dissolved in a mixture of 20 ml acetone and 0.38 ml H_2O, were stirred at 60° for 72 hr. The usual work-up yielded 350 mg crude product which was chromatographed on SiO_2. The elution with C_6H_6–Et_2O 1:1 gave 80 mg of pure, oily 4c, (16%). (Found: C, 74.30; H, 9.20. Calc. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34%). IR spectrum (film, ν_{max} cm^{-1}): 3390, 1695, 1595. ^1H NMR spectrum (CCl_4, δ): 7.20 (d, 1H, 1-H; J = 6 Hz), 5.81 (d, 1H, 2-H; J = 6 Hz), 3.35 (broad s, 1H, 5-OH), 2.10 (m, 1H, 4-H), 1.37 (s, 3H, 5-Me). MS, *m/e*: 194 (M^+).

4 - *Phenyl* - 5 - *hydroxy* - 5 - *methyl* - 3 - *oxocyclopentene* 4d. 500 mg of 4c and 350 mg $ZnCl_2$, dissolved in a mixture of 20 ml acetone and 0.8 ml H_2O, were stirred at 60° for 24 hr. After the usual work-up, the crude product, 420 mg, was chromatographed on SiO_2. The elution with C_6H_6–Et_2O 1:1 gave 350 mg of pure 4d, as a very dense oil, (70%). (Found: C, 76.40; H, 6.62. Calc. for $C_{12}H_{12}O_2$; C. 76.57; H, 6.43%). IR spectrum (CCl_4 1%, ν_{max} cm^{-1}). 3400, 1700, 1605, 1595. ^1H NMR spectrum (CCl_4, δ): 7.25 (d, 1H, 1-H; J = 6 Hz), 7.10 (m, 5H, aromatic protons), 5.98 (d, 1H, 2-H, J = 6 Hz), 4.20 (broad s, 1H, 5-OH), 3.57 (s, 1H, 4-H), 0.85 (s, 3H, 5-Me). MS, *m/e*: 188 (M^+).

4 - (2 - *Thienyl*) - 5 - *hydroxy* - 5 - *methyl* - 3 - *oxocyclopentene* 4e. 500 mg of 3e, and 350 mg $ZnCl_2$, dissolved in a mixture of 20 ml acetone and 0.8 ml H_2O, were stirred at 60° for 4 hr. After the usual isolation procedure, the crude product, 495 mg, was chromatographed on SiO_2. The elution with C_6H_6–Et_2O 1:1 gave 425 mg of pure oily 4e (85%). IR spectrum (film, ν_{max} cm^{-1}): 3400, 1700, 1590. ^1H NMR spectrum ($CDCl_3$, δ): 7.43 (d, 1H, 1-H; J = 6 Hz), 7.30–6.80 (complex m, 3H, thienyl protons), 6.15 (d, 1H, 2-H; J = 6 Hz), 4.04 (s, 1H, 4-H), 2.76 (s, 1H, 5-OH), 1.12 (s, 3H, 5-Me). MS, *m/e*: 194.25 (M^+) in agreement with the formula $C_{10}H_{10}O_2S$.

4 - n - *Butyl* - 5- *hydroxy* - 5 -*methyl* - 3 - *oxcyclopentene* 4f. 500 mg of 3f and 350 mg $ZnCl_2$, dissolved in a mixture of 20 ml acetone and 0.8 ml H_2O, were stirred at 60° for 4 hr. The usual isolation procedure yielded 470 mg crude product, which was chromatographed on SiO_2. The elution with C_6H_6–Et_2O 1:1 gave 325 mg of pure, oily 4f (65%). (Found: C, 77.39; H, 6.95. Calc. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98%). IR spectrum (film, ν_{max} cm^{-1}): 3400, 1695, 1595. ^1H NMR spectrum (CCl_4, δ): 7.27 (d, 1H, 1-H; J = 6 Hz), 6.90 (m, 4H, aromatic protons), 5.98 (d, 1H, 2-H; J = 6 Hz), 4.28 (broad s, 1H, 5-OH), 3.51 (s, 1H, 4-H), 2.25 (s, 3H, Me on benzene ring), 0.87 (s, 3H, 5-Me). MS, *m/e*: 202 (M^+).

(±) *Allethrolone* 7a. After adsorption of 125 mg of 4a on neutral Al_2O_3 B III for 24 hr the elution with C_6H_6–Et_2O 1:1 gave 118 mg pure 7a (95%). (Found: C, 70.85; H, 7.90. Calc. for $C_9H_{12}O_2$: C, 71.03; H, 7.95%). IR spectrum (film, ν_{max} cm^{-1}): 3400, 1695, 1640, 1635. For ^1H NMR data see the initial section. MS, *m/e*: 152 (M^+).

REFERENCES

[1]G. Piancatelli and A. Scettri, *Tetrahedron Letters* 1131 (1977); and refs therein.
[2]R. Laliberté, G. Medawar and Y. Lefebvre, *J. Med. Chem.* 16, 1084 (1973).
[3]G. Piancatelli and A. Scettri, *Synthesis* 116 (1977).
[4]M. Vanderwalle and E. Madeleyn, *Tetrahedron* 26, 3551 (1970).
[5]M. S. Kharasch and O. Reinmuth, *Grignard Reaction of Non-metallic Substances*, p. 27. Prentice-Hall, New York (1954).
[6]*Ibid.* p. 28.