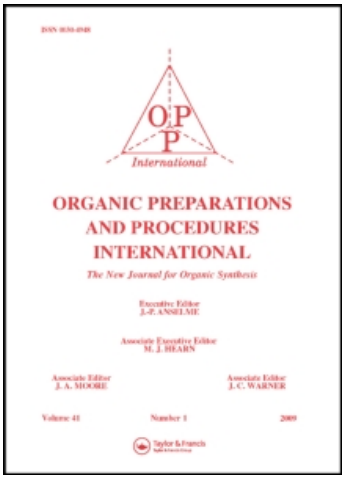

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PREPARATION OF 4-(CARBETHOXY)-5-ALKYL- AND 5-PHENYL FURAN-2-ACETIC ACIDS AND ITS METHYL ESTERS

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OPPI BRIEFS

PREPARATION OF 4-(CARBETHOXY)-5-ALKYL- AND 5-PHENYL FURAN-2-ACETIC ACIDS AND ITS METHYL ESTERS

Submitted by (03/09/87) Francisco Yuste*, Hermila Vergel, Héctor Barrios, Benjamin Ortiz and Rubén Sánchez-Obregón

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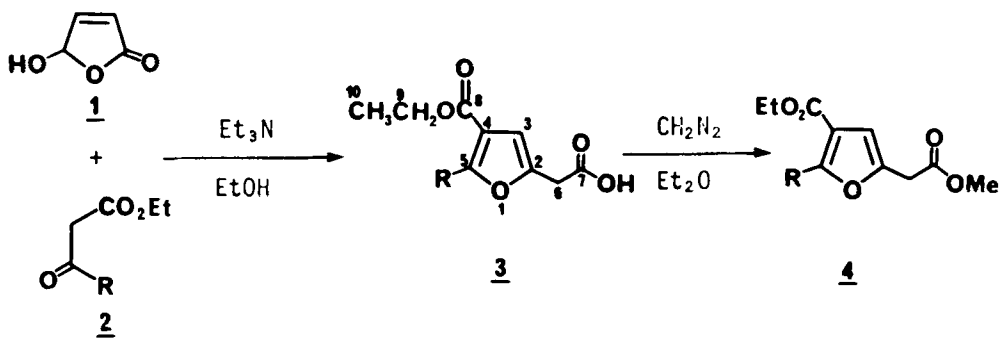
We recently described the synthesis of several heterocyclic compounds by condensation of 4-hydroxy-2-butenolide (1) with compounds containing activated methylene groups;[1] for example, the reaction of 1 and ethyl acetoacetate 2a produces the furan 3a. In order to generalize this reaction, we now report a simple preparation of 4-(carbethoxy)-5-alkyl- and 5-phenylfuran-2-acetic acids 3 by the condensation of 1 with ethyl 3-oxoalkanoates 2.



a) R = Me; b) R = Et; c) R = n-Pr; d) R = i-Pr; e) R = C_6H_5

The formation of these products has been explained[1] by a nucleophilic attack of the anion of the active methylene of 2 on the lactolic carbon of 1, followed by cyclization via a Michael addition of the enolic oxygen to the unsaturated acid and aromatization to the furan derivative 3. All the

reactions were performed in refluxing ethanol, except in the case of ethyl propionylacetate 2b which was carried out at room temperature in the presence of triethylamine. The 2-furylacetic acids 3 prepared are crystalline and may be purified by crystallization or sublimation (Table 1). The acids 3 were converted to the methyl esters 4 by methylation with diazomethane[2] (Table 2). Furans 3 and 4 were identified by IR, NMR and mass spectral data (see Tables 3 and 4).

TABLE 1. 2-Furylacetic Acids 3

Product	Reaction Time (hrs)	Yield[a] (%)	mp. (°C)	Analysis Calcd. (Found) C	H
3a	12	73	75-76	56.60 (56.68)	5.70 (5.84)
3b	26[b]	71	83-85	58.40 (58.20)	6.24 (6.36)
3c	22	90	68	59.99 (60.12)	6.71 (6.66)
3d	24	60	61-63	59.99 (59.80)	6.71 (6.41)
3e	24	56	114	65.69 (65.60)	5.15 (5.32)

a. Yield of isolated pure product. b. Carried out at room temperature.

TABLE 2. Methyl 2-Furylacetates 4

Product	Yield[a] (%)	bp.[b] (°C)/torr	bp.lit. (°C)/torr	Analysis Calcd. (Found) C	H
4a	76	86/0.3	84-85/1[3]	58.40 (58.28)	6.24 (6.38)
4b	78	115/0.2	- -	59.99 (59.85)	6.71 (6.74)
4c	85	83/0.1	85-87/0.005[3]	61.40 (61.55)	7.14 (7.22)
4d	61	95/0.3	- -	61.40 (61.49)	7.14 (7.38)
4e	80	120/0.3	- -	66.66 (66.53)	5.59 (5.70)

a. Yield of isolated pure product based on 3. b. Uncorrected, measured using a Walls apparatus.[4]

EXPERIMENTAL SECTION

Melting points were taken on a Culatti capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet FT 5X spectrometer. NMR spectra were obtained on a Varian FT-80A spectrometer in $CDCl_3$

TABLE 3. Physical Data of 2-Furylacetic Acids 3

Product	^{1}H-NMR ($CDCl_3$/TMS) δ[ppm]	^{13}C-NMR ($CDCl_3$/TMS) δ[ppm]	MS (70 eV) m/e(%)
3a	1.30 (t, 3H, J = 7 Hz); 2.50 (s, 3H); 3.60 (s, 2H); 4.25 (q, 2H, J = 7 Hz); 6.45 (s, 1H); 8.90-9.45 (br, 1H, interchangeable with D_2O).	174.53 (s, C-7); 164.17 (s, C-8); 159.05 (s, C-5); 145.15 (s, C-2); 114.58 (s, C-4); 109.46 (d, C-3); 60.27 (t, C-9); 33.56 (t, C-6); 14.36 (q, C-10); 13.71 (q, CH_3).	212 (M^+, 36); 183 (24); 167 (100); 139 (53); 121 (72).
3b	1.24 (t, 3H, J = 7 Hz); 1.33 (t, 3H, J = 7 Hz); 2.98 (q, 2H, J = 7 Hz); 3.68 (s, 2H); 4.25 (q, 2H, J = 7 Hz); 6.49 (s, 1H); 8.65-9.25 (br, 1H, interchangeable with D_2O).	174.47 (s, C-7); 164.11 (s, C-8); 163.96 (s, C-5); 145.12 (s, C-2); 113.67 (s, C-4); 109.44 (d, C-3); 60.24 (t, C-9); 33.60 (t, C-6); 21.27 (t, CH_2); 14.34 (q, C-10); 12.20 (q, CH_3).	226 (M^+, 33); 197 (100); 181 (64); 135 (29).
3c	0.95 (t, 3H, J = 7 Hz); 1.33 (t, 3H, J = 7 Hz); 1.68 (sextet, 2H, J = 7 Hz); 2.94 (t, 2H, J = 7 Hz); 3.67 (s, 2H); 4.26 (q, 2H, J = 7 Hz); 6.50 (s, 1H); 8.05-8.95 (br, 1H, interchangeable with D_2O).	174.39 (s, C-7); 164.10 (s, C-8); 162.97 (s, C-5); 145.24 (s, C-2), 114.40 (s, C-4); 109.44 (d, C-3); 60.22 (t, C-9); 33.65 (t, C-6); 29.64 (t, CH_2); 21.53 (t, CH_2); 14.36 (q, C-10); 13.65 (q, CH_3).	240 (M^+, 37); 211 (100); 195 (60); 193 (52); 43 (46).
3d	1.25 (d, 6H, J = 7 Hz); 1.33 (t, 3H, J = 7 Hz); 3.67 (s, 2H); 3.70 (septet, 1H, J = 7 Hz); 4.25 (q, 2H, J = 7 Hz); 6.48 (s, 1H); 8.40-8.90 (br, 1H, interchangeable with D_2O).	173.90 (s, C-7); 167.02 (s, C-8); 164.14 (s, C-5); 145.04 (s, C-2); 112.67 (s, C-4); 109.30 (d, C-3); 60.22 (t, C-9); 33.60 (t, C-6); 27.34 (d, CH); 20.69 (q, 2 x CH_3); 14.32 (q, C-10).	240 (M^+, 18); 225 (15); 211 (48); 107 (37); 43 (100).
3e	1.30 (t, 3H, J = 7 Hz); 3.76 (s, 2H); 4.26 (q, 2H, J = 7 Hz); 6.70 (s, 1H); 7.25-7.47 (m, 3H); 7.75-8.00 (m, 2H); 8.30-9.05 (br, 1H, interchangeable with D_2O).	174.40 (s, C-7); 163.53 (s, C-8); 157.33 (s, C-5); 146.01 (s, C-2); 129.78 (s, ipso); 129.38 (d, para); 128.50 (d, 2 x ortho); 128.08 (d, 2 x meta); 114.89 (s, C-4); 111.76 (d, C-3); 60.61 (t, C-9); 33.63 (t, C-6); 14.22 (q, C-10).	274 (M^+, 69); 229 (100); 201 (65); 105 (52).

TABLE 4. Physical Data of Methyl 2-Furylacetates 4

Product	IR (film) ν_{max} (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ[ppm]	MS (70 eV) m/e (%)
4a	1747, 1714	1.33 (t, 3H, J = 7 Hz); 2.54 (s, 3H); 3.62 (s, 2H); 3.72 (s, 3H); 4.26 (q, 2H, J = 7 Hz); 6.45 (s, 1H).	226 M^+, 54); 181 (43); 167 (100); 139 (43); 121 (63).
4b	1741, 1708[a]	1.24 (t, 3H, J = 7 Hz); 1.34 (t, 3H, J = 7 Hz); 2.97 (q, 2H, J = 7 Hz); 3.64 (s, 2H); 3.73 (s, 3H); 4.26 (q, 2H, J = 7 Hz); 6.47 (s, 1H).	240 (M^+, 28); 211 (98); 135 (89); 59 (90); 43 (100).
4c	1748, 1714	0.95 (t, 3H, J = 7 Hz); 1.34 (t, 3H, J = 7 Hz); 1.70 (sextet, 2H, J = 7 Hz); 2.95 (t, 2H, J = 7 Hz); 3.64 (s, 2H); 3.72 (s, 3H); 4.27 (q, 2H, J = 7 Hz); 6.48 (s, 1H).	254 (M^+, 36); 225 (100); 195 (52); 165 (76); 59 (52).
4d	1742, 1708[a]	1.26 (d, 6H, J = 7 Hz); 1.33 (t, 3H, J = 7 Hz); 3.63 (d, 2H, J = 1 Hz); 3.73 (s, 3H); 3.75 (septet, 1H, J = 7 Hz); 4.25 (q, 2H, J = 7 Hz); 6.45 (t, 1H, J = 1 Hz).	(254 (M^+, 24); 239 (32); 225 (84); 207 (59); 107 (65); 43 (100).
4e	1746, 1719	1.31 (t, 3H, J = 7 Hz); 3.73 (s, 5H); 4.27 (q, 2H, J = 7 Hz); 6.67 (s, 1H); 7.25-7.50 (m, 3H); 7.75-8.00 (m, 2H).	288 (M^+, 83); 229 (100); 201 (68); 105 (41).

a. In $CHCl_3$ solution.

using Me_4Si, as an internal reference, and are expressed as δ values. Mass spectra were recorded on a Hewlett-Packard 5985-B spectrometer at 70 eV.

4-(Carbethoxy)-5-propylfuran-2-acetic Acid (3c). Typical Procedure.- A solution of ethyl butyrylacetate (2c, 0.79 g, 5 mmol), lactone 1 (0.5 g, 5 mmol) and triethylamine (0.5 ml) in ethanol (10 ml) was heated at reflux for 22 hrs. The volatiles were removed in vacuo, the residue was treated with ethyl acetate (20 ml) and extracted with 5% aqueous sodium bicar-

bonate (3 X 15 ml). The aqueous phase was acidified with 10% hydrochloric acid (15 ml) and extracted with ethyl acetate (3 X 15 ml). The extracts were washed with water (3 X 15 ml), dried over sodium sulfate and evaporated to afford 1.10 g of 3c. Sublimation at 50-55°C/0.1 torr gave 1.08 g (90%) of pure material, mp. 68°C; IR ($CHCl_3$): 3500-2500 (br) and 1713 cm^{-1} (br). For other spectroscopic data, see Table 3.

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A SIMPLIFIED SYNTHESIS OF LOWER ALKYL BROMIDES

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A commonly used laboratory-scale synthesis of alkyl bromides involves the action of hydrogen bromide on the corresponding alcohol, often conveniently modified by the use of sodium or potassium bromide and