Synthesis of Some 3 (or 5)-Substituted 4-Ethoxycarbonyl-5 (or 3)-(1-hydroxyalkyl)-pyrazoles

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The known methods for the synthesis of 3(or 5)-hydroxyalkylpyrazole derivatives involve the reduction of pyrazole-carboxylates with lithium aluminium hydride[1,2,3] or the addition of diazomethane or hydrazine to substituted acetylenic alcohols[1,4,5]. The applicability of these methods is limited, in the first case by the presence of other easily reducible groups in the pyrazole derivatives and by the availability of the acetylenic starting materials in the second case.

Previous studies from this laboratory established that 4-ethoxycarbonyl-2-methoxy-3(2*H*)-furanone derivatives on treatment with hydrazine hydrate undergo ring opening and then recyclization to produce 4-ethoxycarbonyl-3(or 5)-acylpyrazoles **1**[6]. In the course of these studies we considered the possibility that the 3(2*H*)-furanones **4, 5** might undergo the same reaction. The problem we encountered hereby is related to the difficulty in differentiating between the furanone-hydrazones and the isomeric pyrazoles. In order to clarify this problem, a synthesis of the pyrazoles **7a, c** was carried out by the reduction of corresponding acylpyra-

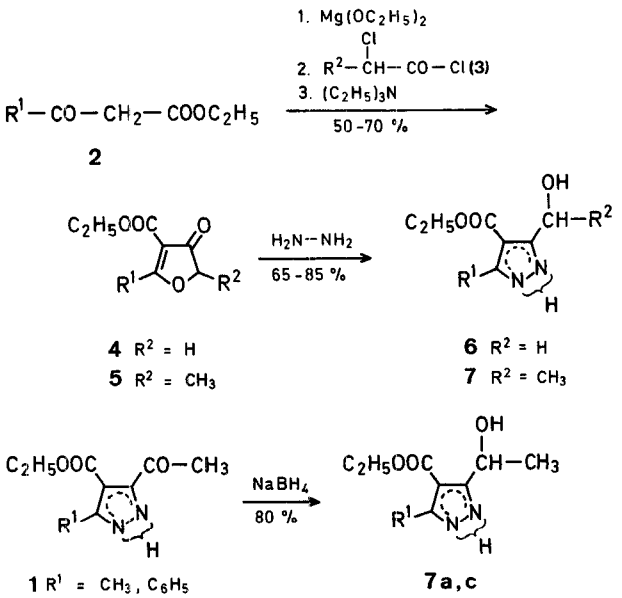

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Table 1. 4-Ethoxycarbonyl-3(2*H*)-furanones **4, 5**

Product No.	R^1	R^2	Yield [%]	b.p./torr or m.p. (solvent)	Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	I.R. ($CHCl_3$) ν [cm^{-1}]	U.V. (C_2H_5OH) λ [nm] (ε)
4a	CH_3	H	60	76° (hexane)[b]	$C_8H_{10}O_4$ (170.1)	see Ref. [8]	—	—
4b	n-C_3H_7	H	55	130°/1	$C_{10}H_{14}O_4$ (198.2)	1.01 (t, 3H, J = 7 Hz); 1.30 (t, 3H, J = 7 Hz); 1.75 (sext., 2H, J = 7 Hz); 2.90 (t, 2H, J = 7 Hz); 4.25 (q, 2H, J = 7 Hz); 4.66 (s, 2H)	1750, 1710, 1590	262 (10400), 214 (6600)
4c	C_6H_5	H	56	165°/0.1 57° (C_2H_5OAc/hexane, 4:6)	$C_{13}H_{12}O_4$ (232.2)	1.27 (t, 3H, J = 7 Hz); 4.30 (q, 2H, J = 7 Hz); 4.75 (s, 2H); 7.35–8.05 (5H)	1750, 1720, 1600	294 (12700), 248 (4500), 215 (8400)
4d	4-H_3C—C_6H_4	H	50	70° (ether)	$C_{14}H_{14}O_4$ (246.3)	1.29 (t, 3H, J = 7 Hz); 2.43 (s, 3H); 4.35 (q, 2H, J = 7 Hz); 4.71 (s, 2H); 7.30 (d, 2H, J = 8.5 Hz); 7.85 (d, 2H, J = 8.5 Hz)	1740, 1710, 1590	302 (19200), 261 (6000), 220 (11100)
4e	4-H_3CO—C_6H_4	H	70	80° (ether)	$C_{14}H_{14}O_5$ (262.3)	1.33 (t, 3H, J = 7 Hz); 3.91 (s, 3H); 4.35 (q, 2H, J = 7 Hz); 4.72 (s, 2H); 7.00 (d, 2H, J = 9 Hz); 7.98 (d, 2H, J = 9 Hz)	1740, 1710, 1590	322 (25700), 265 (4700), 226 (12000), 212 (8400)
4f	4-Cl—C_6H_4	H	64	70° (hexane)	$C_{13}H_{11}ClO_4$ (266.7)	1.31 (t, 3H, J = 7 Hz); 4.32 (q, 2H, J = 7 Hz); 4.75 (s, 2H); 7.45 (d, 2H, J = 8.5 Hz); 7.90 (d, 2H, J = 8.5 Hz)	1750, 1720, 1610	301 (17300), 260 (7100), 218 (11200)
5a	CH_3	CH_3	70	115°/0.8; 43° (hexane)[c]	$C_9H_{12}O_4$ (184.2)	1.36 (t, 3H, J = 7 Hz); 1.51 (d, 3H, J = 7 Hz); 2.95 (s, 3H); 4.32 (q, 2H, J = 7 Hz); 4.64 (q, 1H, J = 7 Hz)	1740, 1705, 1595	262 (11500), 213 (9500)
5c	C_6H_5	CH_3	70	164°/0.1[d]	$C_{14}H_{14}O_4$ (246.3)	1.22 (t, 3H, J = 7 Hz); 1.49 (d, 3H, 55% keto form, J = 7 Hz); 2.25 (s, 3H, 45% enol form); 4.28 (q, 2H, J = 7 Hz); 4.70 (q, 1H, 45% keto form); 7.30–7.58 (3H); 7.73–8.0 (2H)	1760, 1710, 1610, 1590	296 (12700), 248 (7000), 216 (11200)

[a] All products gave satisfactory microanalyses (C ±0.43, H ±0.21, N ±0.20, Cl ±0.17).
[b] Ref. [8] m.p. 76°.
[c] Ref. [9] m.p. 43°.
[d] Ref. [9] b.p. 164°/0.1 torr.

zoles **1a, c,** using sodium borohydride. The resultant compounds were identical to those obtained by action of hydrazine hydrate on the appropriate 3(2*H*)-furanones **5a, c.**

Consequently, this reaction provides a convenient route for the preparation of 3(or 5)-variously substituted-5(or 3)-(1-hydroxyalkyl)-pyrazoles **6, 7** from 3(2*H*)-furanones **4, 5** as starting materials. Our results are summarized in Table 2. Compounds **4, 5** were easily prepared from β-ketoesters **2** and α-chloroacyl chlorides **3** by a generalisation of our previous procedure[7] (Table 1).

Preparation of 4-Ethoxycarbonyl-3(2*H*)-furanones 4, 5; General Procedure:

Magnesium turnings (13 g) are converted to magnesium ethoxide with absolute ethanol (75 ml). Benzene (125 ml) is added followed by β-ketoester **2** (0.5 mol). The mixture is stirred at room temperature for 1 h, then acetonitrile (125 ml) is added and the mixture cooled to −10°. The α-chloroacyl chloride **3** (0.55 mol) is added dropwise to the stirred solution which is then kept at 0° for 1 h. The mixture is poured on to ice/water (250 ml) containing sulfuric acid (15 ml) and the resultant mixture is extracted with ether. The organic phase is separated, dried (Na_2SO_4), and triethylamine (50.5 g, 0.5 mol) in dry ether (50 ml) is added to cooled solution (0°) which is then kept at room temperature for 24 h. The precipitated salt is filtered off and the filtrate is evaporated. The residue is distillated in vacuo or recrystallized.

Preparation of 4-Ethoxycarbonyl-3(or 5)-substituted-5(or 3)-(1-Hydroxyalkyl)-pyrazoles 6, 7; General Procedure:

To a solution of **4, 5** (0.01 mol) in ethanol (20 ml) is added hydrazine hydrate (1.03 g, 0.02 mol). The resultant mixture is refluxed for 2 h. After evaporation of the ethanol, the residue is purified by recrystallization or column chromatography through a silica gel column (17 mm × 25 cm) of **6b** or **7c** (1 g) using diethyl ether or hexane/acetone 7/3 respectively as eluent. The product was obtained after elution of 100 ml to 180 ml for **6b**; 150 ml to 200 ml for **7c**.

Preparation of 5(or 3)-(1-Hydroxyethyl)-pyrazoles 7a, c By reduction:

To a solution of **1** (0.01 mol) in ethanol (10 ml) is added solid sodium borohydride (0.37 g, 0.01 mol) in one portion to the chilled solution (below 30°), then the resultant suspension is kept at room temperature for 12 h. Water (10 ml) is added, then the mixture is cautiously hydrolysed with 10% hydrochloric acid solution (5 ml). The mixture is extracted with dichloromethane. The organic extract is treated as above; yield: 80%.

Table 2. 3(or 5)-Substituted 4-Ethoxycarbonyl-5(or 3)-(1-hydroxyalkyl)-pyrazoles **6**, **7**

Product No.	R^1	R^2	Yield [%]	m.p. (solvent)	Molecular formula[a]	^{1}H-N.M.R. (DMSO-d_6)[b,c] δ [ppm]	I.R. ($CHCl_3$) ν [cm^{-1}]	U.V. (C_2H_5OH) λ [nm] (ε)
6a	CH_3	H	65	117° (C_2H_5OAc)	$C_8H_{12}N_2O_3$ (184.19)	1.32 (t, 3H); 2.43 (s, 3H); 4.31 (q, 2H); 4.81 (s, 2H)[d,e]	3460, 3220, 1700, 1580	230 (8000)
6b	n-C_3H_7	H	85[f]	61°	$C_{10}H_{16}N_2O_3$ (212.2)	0.90 (t, 3H, J = 7 Hz); 1.28 (t, 3H); 1.65 (sext., 2H, J = 7 Hz); 2.80 (t, 2H, J = 7 Hz); 4.22 (q, 2H); 4.65–4.80 (broad, 2H); 4.93–5.19 (1H, exchangeable with CF_3COOH); 13.1 (1H, broad)	3460, 3240, 1690, 1570	227 (9500)
6c	C_6H_5	H	85	106° (C_2H_5OAc/hexane, 3:7)	$C_{13}H_{14}N_2O_3$ (246.3)	1.18 (t, 3H); 4.21 (q, 2H); 4.93 (s, 2H); 5.45 (s, 1H, exchangeable with CF_3COOH); 7.40–7.87 (m, 5H); 13.5 (broad, 1H)	3450, 3220, 1690, 1570	243 (10000), 218 (8900)
6d	4-H_3C—C_6H_4	H	79	139° (C_2H_5OAc)	$C_{14}H_{16}N_2O_3$ (260.3)	1.18 (t, 3H); 2.34 (s, 3H); 4.18 (q, 2H); 4.85 (s, 2H); 5.35 (s, 1H, exchangeable with CF_3COOH); 7.25 (d, 2H, J = 8 Hz); 7.60 (d, 2H, J = 8 Hz); 13.5 (broad, 1H).	3460, 3220, 1690, 1580	243 (10000), 215 (15200)
6e	4-H_3CO—C_6H_4	H	82	127° (C_2H_5OAc/hexane, 7:3)	$C_{14}H_{16}N_2O_4$ (276.3)	1.20 (t, 3H); 3.82 (s, 3H); 4.18 (q, 2H); 4.83 (s, 2H); 7.00 (d, 2H, J = 9 Hz); 7.63 (d, 2H, J = 9 Hz)[d,e]	3450, 3220, 1690, 1590	262 (9000), 221 (12000)
6f	4-Cl—C_6H_4	H	76	139° (C_2H_5OAc/hexane, 8:2)	$C_{13}H_{13}ClN_2O_3$ (280.7)	1.18 (t, 3H); 4.19 (q, 2H); 4.85 (s, 2H); 5.51 (s, 1H, exchangeable with CF_3COOH); 7.45 (d, 2H, J = 9 Hz); 7.73 (d, 2H, J = 9 Hz); 13.6 (broad, 1H)	3450, 3220, 1690, 1620, 1590	246 (10400), 220 (14000)
7a	CH_3	CH_3	71	88° (C_2H_5OAc/hexane, 3:7)	$C_9H_{14}N_2O_3$ (198.2)	1.29 (t, 3H); 1.41 (d, 3H, J = 6.5 Hz); 2.38 (s, 3H); 4.25 (q, 2H); 5.02–5.35 broad, 2H, 1H, exchangeable with (F_3COOH)[e]	3460, 3220, 1700, 1580	229 (8500)
7c	C_6H_5	CH_3	74	oil[g]	$C_{14}H_{16}N_2O_3$ (260.3)	1.13 (t, 3H); 1.51 (d, 3H, J = 6 Hz); 4.18 (q, 2H); 5.15–5.60 (broad, 2H, 1H exchangeable with CF_3COOH); 7.30–7.75 (m, 5H); 13.45 (broad, 1H)	3460, 3240, 1690, 1570	240 (9600), 216 (13500)

[a] All products gave satisfactory microanalyses (C ±0.52, H ±0.21, N ±0.24, Cl ±0).

[b] These alcohols failed to give the expected multiplicities for the hydroxy and methylene (or methine) resonances, but, in some cases, both these signals were broadened by the incipient spin-spin coupling. Similar effect appears in alcohols which contain an electron-withdrawing group close to the —OH[10].

[c] Ethoxycarbonyl groups, coupling constant J = 7 Hz.

[d] OH proton is not observed.

[e] NH proton is not observed.

[f] Isolated by column chromatography on silica gel with diethyl ether.

[g] Isolated by column chromatography on silica gel with hexane/acetone, 7:3.

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