Synthesis of Some Ethyl 3-Substituted-5-(1-hydroxyalkyl)-isoxazole-4-carboxylates from 4-Ethoxycarbonyl-3(2*H*)-furanones

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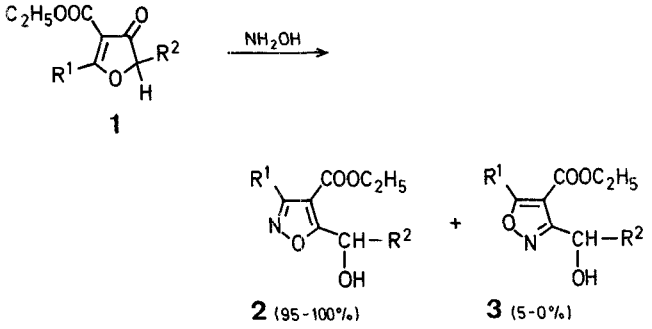
A variety of synthetic procedures have been devised for the preparation of isoxazoles, due to their utility in organic chemistry[1]. In connection with our interest in biologically active compounds related to 3,5-disubstituted isoxazole-4-carboxylic acids, we wish to describe a route to the hitherto unknown 5-(1-hydroxyalkyl) derivatives **2** from the 3(2*H*)-furanones **1**.

The reaction of hydroxylamine with 4-ethoxycarbonyl-3(2*H*)-furanones (**1**) might be expected to afford two isomeric isoxazoles, **2** and/or **3**. We have found that the reaction results in the exclusive or predominant formation of products **2**; only a small amount of the isomeric compounds **3a, b, c** (~ 5%) is detected in the crude reaction mixture by ^{1}H-N.M.R. The regiospecificity of the reaction may be rationalized by the nucleophilic addition of the N-atom of hydroxylamine to the 5-position of the furan ring leading to a ring-cleavage ring-closure rearrangement to afford compounds **2**.

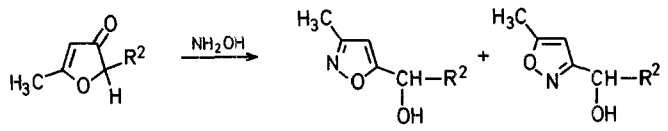


1

2 (95–100%) **3** (5–0%)

1,2,3	R^1	R^2
a	CH_3	H
b	C_2H_5	H
c	n-C_3H_7	H
d	CH_3	CH_3
e	C_6H_5	H
f	C_6H_5	CH_3

The electrophilic character of the C–5 carbon in 3(2*H*)-furanones is enhanced by the presence of the 4-ethoxycarbonyl substituent. In the case of 4-unsubstituted compounds **6a, b** the rind opening occurs more slowly; about 24 h are required for the disappearance of the starting material. The reaction is not stereospecific, since a mixture of unseparable isomeric isoxazoles **7a, b** and **8a, b** is obtained as evidenced by their ^{1}H-N.M.R. spectra on the basis of the methyl signals[7].



6a R^2 = H **6b** R^2 = CH_3 **7a** (35%) **7b** (60%) **8a** (65%) **8b** (40%)

Compounds **2** were characterized as 1,2-oxazoles (isoxazoles) by microanalyses and spectral data (I.R., ^{1}H-N.M.R., Table 1). The assignment of the isomeric structure is infered from ^{13}C-N.M.R.

Table 1. Ethyl 3-Substituted-5-(1-hydroxyalkyl)-isoxazole-4-carboxylates (**2**)

2	R^1	R^2	Yield [%]	b.p. [°C]/torr or m.p. [°C] (Solvent)	Molecular Formula[a]	I.R. ($CHCl_3$) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
a	CH_3	H	56[b]	125–130°/1 37° (water)	$C_8H_{11}NO_4$ (185.2)	3450 1700	1.40 (t, 3H, J = 7 Hz); 2.45 (s, 3H); 4.2 (br., 1H exchangeable with D_2O); 4.36 (q, 2H, J = 7 Hz); 4.91 (s, 2H)
b	C_2H_5	H	70[b]	115–120°/0.1	$C_9H_{13}NO_4$ (199.2)	3450 1690	1.29 (t, 3H, J = 7 Hz); 1.37 (t, 3H, J = 7 Hz); 2.89 (q, 2H, J = 7 Hz); 4.1 (br., 1H exchangeable); 4.37 (q, 2H, J = 7 Hz); 4.90 (s, 2H)
c	n-C_3H_7	H	61[b]	125–130°/0.5	$C_{10}H_{15}NO_4$ (213.2)	3450 1700	0.99 (t, 3H, J = 7 Hz); 1.23–1.96 (m, 5H); 2.88 (t, 2H, J = 7 Hz); 4.3 (br., 1H exchangeable); 4.35 (q, 2H, J = 7 Hz); 4.93 (s, 2H)
d	CH_3	CH_3	60	120–125°/1.5	$C_9H_{13}NO_4$ (199.2)	3420 1695	1.43 (t, 3H, J = 7 Hz); 1.61 (d, 3H, J = 7 Hz); 2.45 (s, 3H); 4.40 (q, 2H, J = 7 Hz); 4.7 (br., 1H exchangeable); 5.29 (q, 1H, J = 7 Hz)
e	C_6H_5	H	80	185–190°/0.5 57° (hexane)	$C_{13}H_{13}NO_4$ (247.2)	3450 1695	1.18 (t, 3H, J = 7 Hz); 3.7 (br., 1H exchangeable); 4.24 (q, 2H, J = 7 Hz); 4.96 (s, 2H); 7.3–7.7 (m, 5H)
f	C_6H_5	CH_3	65	175–180°/0.5	$C_{14}H_{15}NO_4$ (261.3)	3420 1690	1.12 (t, 3H, J = 7 Hz); 1.66 (d, 3H, J = 7 Hz); 4.20 (q, 2H, J = 7 Hz); 4.4 (br., 1H exchangeable); 5.26 (q, 1H, J = 7 Hz); 7.3–7.6 (m, 5H)

[a] The microanalyses were in satisfactory agreement with the calculated values: C ±0.20, H ±0.21, N ±0.36.

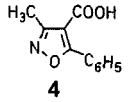
[b] Yield of isolated pure product after column chromatography.

Table 2. Pertinent ^{13}C-N.M.R. (solvent/TMS_{int}) Data of Compounds **2**, **4**, and **5**

Compound	Solvent	δ [ppm]		
		C-3	C-4	C-5
2a	$CDCl_3$	159.8 (q, ^2J = 7 Hz)	108.7	176.4[a]
2e	$CDCl_3$	161.8	109.0	177.2 (t, ^2J = 4 Hz)
4	DMSO-d_6	161.6 (q, ^2J = 7 Hz)	109.8	172.7
5	DMSO-d_6	163.2	109.7	176.7 (q, ^2J = 7 Hz)

[a] This signal is significantly broadened by the ^2J long range proton-carbon coupling with the methylene proton.

studies. Although ^{13}C-N.M.R. spectra of isoxazoles have been reported[2–5], there are no available data on the chemical shifts in isomeric 3,5-disubstituted isoxazole-4-carboxylic acids. The known isomeric acids **4** and **5** were prepared according to literature methods[6] and examined, as model compounds, to determine the shifts of the C-atoms adjacent to the O- and N-atoms, respectively, by observation of the coupled spectra. Significant differences in chemical shifts for C-3 and C-5 were observed (Table 2). The obvious similarity of the chemical shifts of compounds **2**, after examination of their coupled spectra, as compared to compounds **4** and **5**, establishes unambiguously their 5-(1-hydroxyalkyl) structure.



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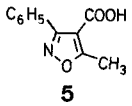

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The 3(2*H*)-furanones **6a**[8] and **6b**[9] are prepared according to known procedures.

4-Ethoxycarbonyl-3(2*H*)-furanones (1):

Compounds **1a, c–f** are prepared as previously described[10]. *4-Ethoxycarbonyl-5-ethyl-3(2H)-furanone* (**1b**) is obtained in a similar manner; yield: 60%; b.p. 112–116°C/1 torr.

$C_9H_{12}O_4$ (184.2) calc. C 58.69 H 6.57; found 58.44 6.71

I.R. ($CHCl_3$): ν = 1750, 1710, 1590 cm^{-1}

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 1.27 (t, 3H, J = 7 Hz); 1.33 (t, 3H, J = 7 Hz); 3.05 (q, 2H, J = 7 Hz); 4.30 (q, 2H, J = 7 Hz); 4.62 ppm (s, 2H).

3-Substituted 4-Ethoxycarbonyl-5-(1-hydroxyalkyl)-isoxazoles (2); General Procedure:

To a solution of a compound **1** (50 mmol) in ethanol (25 ml) is added a solution of hydroxylamine hydrochloride (4 g, 57.5 mmol) and sodium acetate (4.7 g, 57.5 mmol) in water (20 ml). After refluxing for 1 h, ethanol is evaporated under reduced pressure. Water (50 ml) is added to the residue and the mixture is extracted with ether (3 × 50 ml). The ethereal solution is dried with sodium sulfate and ether is removed. Distillation of the residue affords either product **2a, b, c** containing ~5% of **3a, b, c** or the pure product **2d, e, f**, respectively.

In the cases **a, b, c**, the mixture **2** + **3** (1.2 g) is chromatographed through a column (20 mm × 30 cm) of silica gel (50 g) using ether as eluent. Compound **3** is eluted first, and the pure compound **2** in the 100–140 ml fraction (**2a**, 1.04 g; **2b**, 1.0 g; **2c**, 0.90 g).

5-(1-Hydroxyalkyl)-3-methyl-isoxazoles (7) and 3-(1-Hydroxyalkyl)-5-methyl-isoxazoles (8):

Compounds **6a** or **6b** (10 mmol) are treated as described above for compounds **1**, the reflux time being extended to 24 h. The residue obtained on evaporation (containing **7a** + **8a** or **7b** + **8b**) is chromatographed through a column (20 mm × 30 cm) of silica gel (50 g) using ether as eluent.

Products	Fraction collected	Yield
7a + **8a**	170 → 290 ml	0.27 g (24%)
7b + **8b**	130 → 240 ml	0.76 g (60%)

Compounds **7a** + **8a**:

I.R. (CCl_4): ν = 3610, 3380, 1610 cm^{-1}

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 2.29 (s, 1.05H, CH_3 of **7a**); 2.43 (s, 1.95H, CH_3 of **8a**); 4.20 (br., 1H exchangeable with D_2O); 4.71 (s, 2H); 6.13 ppm (s, 1H).

Compounds **7b** + **8b**:

I.R. (CCl_4): ν = 3610, 3380, 1610 cm^{-1}

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 1.50 (d, 1.2H, J = 7 Hz, CHOH—CH_3 of **8b**); 1.55 (d, 1.8H, J = 7 Hz, CHOH—CH_3 of **7b**); 2.23 (s, 1.8H, 3-CH_3 of **7b**); 2.41 (s, 1.2H, 5-CH_3 of **8b**); 4.45 (br., 1H exchangeable with D_2O); 4.98 (q, 1H, J = 7 Hz); 6.06 ppm (s, 1H).

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