A New Synthesis of 3-Oxazolin-5-ones (5-Oxo-2,5-dihydro-1,3-oxazoles)

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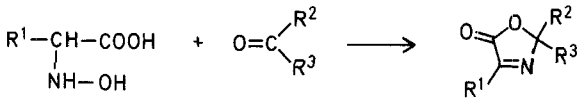
The 3-oxazolin-5-one ring system, without 2-alkylidene substitution, has been so far prepared by irradiation of suitably 3-substituted 2*H*-azirines in the presence of carbon dioxide[1-5], or by even less direct routes[6,7]. Only in two particular cases[8,9], has cyclodehydration of *N*-acylamino acids afforded heterocycles of this type.

In this paper, a simple and general synthesis of the 3-oxazolin-5-ones **3** from the easily available starting compounds **1** and **2** is described.



1 **2** **3**

α-Hydroxyamino acids **1**[10,11] were allowed to react under mild conditions with carbonyl compounds **2**, which were generally also used as solvents. When aliphatic aldehydes were employed (Method A), the reaction was catalyzed by small amounts of triethylamine; with ketones (Method B) an equimolecular quantity of the base was preferred. The oxazolinones **3** were isolated as oily or low melting materials and purified by crystallization or by column chromatography (see Table).

As previously reported[12], aromatic aldehydes under the above conditions reacted to afford the expected nitrones[13]; in contrast, aromatic ketones reacted to give compounds **3**, but in lower yields.

I.R. spectra were measured on a Perkin-Elmer Model 157 spectrophotometer. ^{1}H-N.M.R. spectra were recorded on a Perkin-Elmer R-12B spectrometer using TMS as internal standard. Mass spectra were taken on a Varian MAT 112 spectrometer at 70 eV, 1.5 ma. Column chromatographic separations were performed on silica gel (Merck, 70–230 mesh) using hexane/ethyl acetate mixtures as eluent. The yields refer to pure isolated products.

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Table. 3-Oxazolin-5-ones **3**

Product	R^1	R^2	R^3	Reaction conditions temp./time/solvent	Method	Yield [%]	m.p.	Molecular formula[a] or Lit. m.p. or b.p./torr	I.R. (film) $\nu_{C=O}$ [cm^{-1}]
3a	C_6H_5	H	*i*-C_3H_7	80 °C/4 h/excess **2**	A	33	oil	b.p. 130 °C/0.05[9]	1775[b]
3b	C_6H_5	H	*n*-C_4H_9	r.t./18 h/THF	A	20	oil	$C_{13}H_{15}NO_2$ (217.3)	1775
3c	CH_3	CH_3	CH_3	r.t./60 h/excess **2**[c]	B	3	oil	$C_6H_9NO_2$ (127.1)	1800
3d	C_6H_5	CH_3	CH_3	r.t./18 h/excess **2**	B	80	36–38 °C	m.p. 38–40 °C (pentane)[5]	1780[d]
3e	C_6H_5	CH_3	C_2H_5	r.t./18 h/excess **2**	B	70	oil	$C_{12}H_{13}NO_2$ (203.2)	1775
3f	C_6H_5	CH_3	*i*-C_4H_9	r.t./18 h/excess **2**	B	43	oil	$C_{14}H_{17}NO_2$ (231.3)	1775
3g	C_6H_5	CH_3	C_6H_5	80 °C/18 h/benzene	B	15	oil	$C_{16}H_{13}NO_2$ (251.3)	1775

[a] All new products gave satisfactory microanalyses (C ±0.3, H ±0.2, N ±0.3); I.R., ^{1}H-N.M.R., and mass spectra were consistent with the assigned structures.

[b] I.R. of isomeric 2-isopropyl-4-phenyl-2-oxazolin-5-one: $\nu_{C=O}$ = 1835 cm^{-1} in CCl_4, see Ref. [9].

[c] Reaction performed in the presence of 4 Å molecular sieves as water scavengers.

[d] Nujol mull.

2-Butyl-4-phenyl-3-oxazolin-5-one (3b):

Method A: A two-necked reaction flask equipped with magnetic stirrer and calcium chloride valve is charged with α-hydroxyaminophenylacetic acid (1 g, 5.98 mmol), tetrahydrofuran (8 ml), and triethylamine (0.08 ml, 0.59 mmol). The resultant solution is stirred at room temperature and treated dropwise with pentanal (1.03 g, 11.96 mmol) in tetrahydrofuran (5 ml). Stirring is continued at room temperature for 18 h, then the solvent is removed under reduced pressure. The oily residue is purified by column chromatography to give **3b**; yield: 0.27 g (20%).

$C_{13}H_{15}NO_2$	calc.	C 71.86	H 6.96	N 6.45
(217.3)	found	71.68	6.96	6.47

^{1}H-N.M.R. (CCl_4): δ = 8.52–8.30 and 7.57–7.38 (m, $5H_{arom}$); 5.91 (t, 1H, *J* = 6 Hz, $CH-C_4H_9$); 2.10–1.20 [m, 6H, $-(CH_2)_3-$]; 0.94 ppm (t, 3 H, *J* = 5.0 Hz, CH_3).

M.S.: *m/e* = 217 (M^+).

2-Ethyl-2-methyl-4-phenyl-3-oxazolin-5-one (3e):

Method B: The apparatus described above is charged with α-hydroxyaminophenylacetic acid (0.5 g, 2.99 mmol) and 2-butanone (5 ml). The resultant suspension is stirred at room temperature and triethylamine (0.41 ml, 2.99 mmol) is added dropwise. The reaction mixture is stirred at room temperature for 18 h (complete solution occurs after 1 h) and evaporated in vacuo. The oily residue is purified by column chromatography to give **3e**; yield: 0.42 g (70%).

$C_{12}H_{13}NO_2$	calc.	C 70.92	H 6.45	N 6.89
(203.2)	found	70.75	6.46	6.87

^{1}H-N.M.R. ($CDCl_3$): δ = 8.70–8.31 and 7.57–7.36 (m, $5H_{arom}$); 2.00 (q, 2H, *J* = 7.3 Hz, CH_2CH_3); 1.63 (s, 3H; $CH_3-C-C_2H_5$); 0.86 ppm (t, 3H; *J* = 7.3 Hz, CH_2CH_3).

M.S.: *m/e* = 203 (M^+).

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