

Reaction of 2-Dimethylaminomethylene-1,3-diones
with Dinucleophiles. II.

Synthesis of 5-(Alkyl)(Phenyl)-4-acylisoxazoles and
6,7-Dihydro-1,2-benzisoxazol-4(5H)-ones

Giulia Menozzi, Pietro Schenone* and Luisa Mosti

Istituto di Scienze Farmaceutiche dell'Università, Viale Benedetto XV-3,
16132 Genova, Italy

Received July 14, 1982

The reaction of open-chain and cyclohexane *sym*-2-dimethylaminomethylene-1,3-diones with hydroxylamine hydrochloride in refluxing methanol gave in good to moderate yields a series of 5-(alkyl)(phenyl)-4-acylisoxazoles and 6,7-dihydro-1,2-benzisoxazol-4(5H)-ones, respectively. As 3-unsubstituted isoxazoles, all these compounds easily isomerized with sodium methoxide to the corresponding 2-cyano-1,3-diones in high yields.

J. Heterocyclic Chem., **20**, 645 (1983).

In the first paper of the series (1) we reported the facile synthesis of *sym*-2-dimethylaminomethylene-1,3-diones III and their use as synthons in the building up of heterocyclic systems by reaction with dinucleophiles such as methyl and phenyl hydrazine.

In this connection, hydroxylamine appeared to us as another interesting dinucleophile by way of its centers of different reactivity, the nitrogen and oxygen atoms. The former should react at the electrophilic extra-chain carbon atom, whereas interaction of the latter with a carbonyl group should give 5-substituted 4-acylisoxazoles IV.

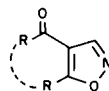
Although a number of methods are available for the synthesis of functionalized isoxazoles (2), a survey of the literature revealed that among open-chain compounds, a sole IV was synthesized to our knowledge, namely 4-acetyl-5-

methylisoxazole IVa. This was prepared by reaction of hydroxylamine hydrochloride with the most active synthon available in the open-chain series, namely Claisen' 3-ethoxymethylene-2,4-pentanedione (I, X = Y = CH₃) [(3); cf. also (1)]. In the cyclic series, and specifically among the cyclohexane derivatives, the available synthons were 2-phenylaminomethylene-1,3-cyclohexanediones II_n [cf. (1)], but these compounds gave only the corresponding 2-hydroxyaminomethylene derivatives by reaction with hydroxylamine. Heating with acids or acetic anhydride of these intermediates afforded only 2-cyano-1,3-cyclohexanediones Vf-h (4,5).

In this paper we wish to report the reaction of synthons IIIa-i with hydroxylamine to give in a sole step 5-(alkyl)(phenyl)-4-acylisoxazoles IVa-d and 6,7-dihydro-1,2-benzis-

Table I

5-Substituted 4-Acylisoxazoles IVa-d and 6,7-Dihydro-1,2-benzisoxazol-4(5H)-ones IVf-h



Formula Number	R or R' R	Yield %	Bp °C/mm or Mp °C	Molecular Formula	C	Analyses %		N
						Calcd./Found	H	
IVa	-CH ₃	73	90-95/12 (a)	C ₆ H ₇ NO ₂				
IVb	-CH(CH ₃) ₂	87	65-70/0.5	C ₁₀ H ₁₅ NO ₂	66.27	8.34	7.73	
					66.38	8.20	7.65	
IVc	-C(CH ₃) ₃	80	60-65/0.4	C ₁₂ H ₁₉ NO ₂	68.87	9.15	6.69	
					69.10	9.24	6.81	
IVd	-C ₆ H ₅	94	155-160/0.3	C ₁₆ H ₁₁ NO ₂	77.10	4.45	5.62	
					77.33	4.21	5.81	
IVf	-(CH ₂) ₃ -	40	65 (b)	C ₇ H ₇ NO ₂	61.31	5.14	10.21	
					61.19	5.17	10.40	
IVg	-CH ₂ -C(CH ₃) ₂ -CH ₂ -	27	88 (c)	C ₉ H ₁₁ NO ₂	65.44	6.71	8.48	
					65.34	6.76	8.63	
IVh	-CH ₂ -CH(C ₆ H ₅)-CH ₂ -	42	100 (c)	C ₁₃ H ₁₁ NO ₂	73.23	5.20	6.57	
					73.41	5.23	6.56	

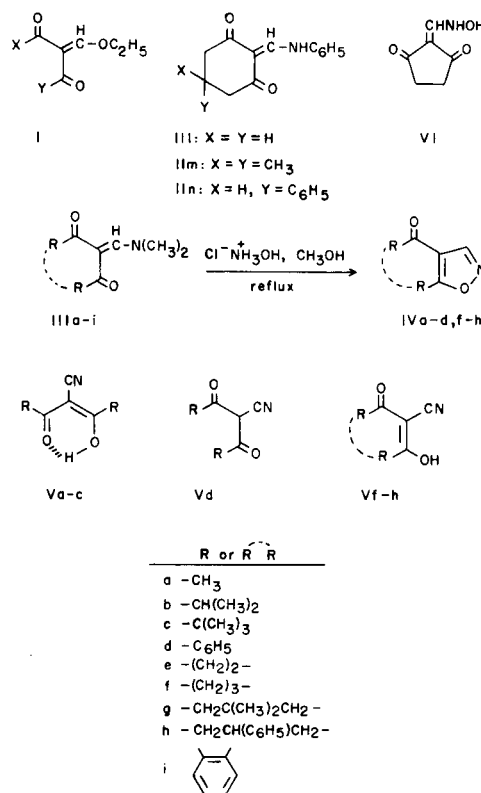
(a) Ref (3) bp 102-106°/20, mp 29-30°, yield 60%. (b) From anhydrous diethyl ether — petroleum ether (bp 40-60°). (c) From anhydrous diethyl ether.

oxazol-4(5*H*)-ones IVf-h (Table I). The reaction was carried out under acid catalysis by simply refluxing a methanol solution of both III and hydroxylamine hydrochloride. Yields were good for open-chain synthons IIIa-d, also in the case of severe steric hindrance (IIIc), and moderate for cyclohexane synthons IIIf-h. Synthons IIIe,i, namely those containing a cyclopentane moiety, did not react (IIIi) or gave the hydroxyamino derivative VI in the case of IIIe: this was another example of the poor reactivity in the cyclization reactions of cyclopentane derivatives containing $O=C(R)-C(R)=CH-NR_2$ groups [cf. (1)].

The structure of isoxazoles IVa-d, f-h was ascertained through their spectral data (Table II) and the well known, facile isomerization with base (sodium methoxide in the cold) to the corresponding 2-cyano-1,3-diones Va-d,f-h (Table III), which they underwent as 3-unsubstituted isoxazoles, carrying moreover an electron-withdrawing substituent in position 4 (6).

The structure of nitriles V was ascertained chiefly by their nmr spectral data (Table IV). Nitriles Va-c exist as chelated enol tautomers [cf. (9,10) for Va], whereas Vd was in the form of 1,3-diketo tautomer. Nitriles Vf-h exist as simple enols, as it was shown by the chemical shifts of OH proton (δ 8-11) in comparison with those of Va-c (δ 17-19). Also the ir spectra (Table IV) confirmed the proposed structures, showing in the case of Va-c a conjugated nitrile absorption (2218 cm^{-1}) more shifted than in the case of Vf-h ($2225\text{-}2230\text{ cm}^{-1}$), and a broad absorption in the $3400\text{-}3500\text{ cm}^{-1}$ region.

In conclusion, the reaction of III with hydroxylamine represents another example of the utility of these synthons



in the reactions with dinucleophiles to give in a sole step the required heterocycle, in high yield in the case of open-chain compounds, and as the best possibility in the case of cyclohexane derivatives. A limiting factor could be the size of the cycle, at least as can be seen from the unreactivity of cyclopentane derivatives.

Table II

UV, IR and NMR Spectral Data of Compounds IVa-d, f-h

	UV λ max nm (log ϵ)	IR, cm^{-1} (Chloroform)	NMR, δ (Deuteriochloroform)
IVa	232 (3.80), 275 (3.07)	1687, 1593, 1485, 1408, 1390	2.50 (s, CH ₃ CO), 2.76 (s, CH ₃ -5), 8.57 (near s, CH-3)
IVb	238 (3.87)	1683, 1580, 1487, 1470, 1388, 1367	1.22 [d, J ~ 6.5, (CH ₃) ₂ CHCO], 1.36 [d, J ~ 7, (CH ₃) ₂ CH-5], 3.14 (h, J ~ 6.5, COCHMe ₂), 3.90 (h, J ~ 7, CHMe ₂ -5), 8.52 (near s, CH-3)
IVc	227 (3.72), 280 (2.60)	1680, 1565, 1480, 1462, 1396, 1368	1.30 [s, (CH ₃) ₃ CCO], 1.42 [s, (CH ₃) ₃ C-5], 8.50 (near s, CH-3)
IVd	252 (4.18), 284 (4.04)	1662, 1567, 1467, 1450, 1392, 1368	7.50 (mc, 4 H aryl m + 2 H aryl p), 7.88 (mc, 4 H aryl o), 8.52 (s, CH-3)
IVf	229.5 (3.95), 270 (2.83)	1692, 1600, 1488, 1425, 1412	2.0-2.9 (m, CH ₂ -6 + CH ₂ -7), 3.08 (t, J = 6, CH ₂ -5), 8.57 (s, CH-3)
IVg	231 (3.90), 271.5 (3.77)	1693, 1600, 1485, 1423, 1408	1.18 (s, 2 CH ₃ -6), 2.45 (s, CH ₂ -7), 2.92 (s, CH ₂ -5), 8.53 (near s, CH-3)
IVh	216 sh (4.07), 230 sh (3.98)	1693, 1602, 1490, 1422, 1410	2.70-3.45 (m, CH ₂ -5 + CH ₂ -7), 3.5-3.9 (m, CH-6), 7.35 (mc, C ₆ H ₅), 8.57 (near s, CH ₃)

Table III
2-Cyano-1,3-diones Va-d, f-h



Formula Number	R or R∩R	Yield %	Mp °C or Bp °C/mm	Molecular Formula	Analyses %		
					C	H	N
Va	—CH ₃	78	56 (a)	C ₆ H ₇ NO ₂			
Vb	—CH(CH ₃) ₂	81	30	C ₁₀ H ₁₅ NO ₂	66.27	8.34	7.73
Vc	—C(CH ₃) ₃	78	55-60/0.4	C ₁₂ H ₁₉ NO ₂	66.33	8.19	8.07
					87 (b)	68.87	9.15
Vd	—C ₆ H ₅	82	163 (c)	C ₁₆ H ₁₁ NO ₂	68.67	9.15	6.62
					77.10	4.45	5.62
Vf	—(CH ₂) ₃ —	63	213 (d)	C ₇ H ₇ NO ₂	77.30	4.46	5.69
					61.31	5.14	10.21
Vg	—CH ₂ —C(CH ₃) ₂ —CH ₂ —	63	224 (e)	C ₉ H ₁₁ NO ₂	60.95	5.06	10.09
					65.44	6.71	8.48
Vh	—CH ₂ —CH(C ₆ H ₅)—CH ₂ —	78	224 (f)	C ₁₃ H ₁₁ NO ₂	65.50	6.78	8.21
					73.23	5.20	6.57
					73.15	5.30	6.47

(a) From petroleum ether; ref (7,8) mp 52-54°; ref (3,9) mp 54-55°. (b) From 95% ethanol. (c) From ethyl acetate; ref (11) mp 156.5°; ref (7) mp 159-160°. (d) From ethyl acetate; ref (5) mp 208.5-210°. (e) From ethyl acetate; ref (5) mp 220-222°. (f) From water; ref (5) mp 221-222°.

Table IV
UV, IR and NMR Spectral Data of Compounds Va-d, f-h

	UV λ max nm (log ε)	IR, cm ⁻¹	NMR, δ
Va	232 sh (3.45), 278 (4.03)	2220, 1603 (a)	2.42 (s, 2 CH ₃), 16.85 (broad s, OH; disappears with deuterium oxide) (c)
Vb	280.5 (4.06)	2218, 1565 br (a)	1.24 (d, J = 6.6, 4 CH ₃), 3.15 (near h, J = 6.6, 2 CHMe ₂), 17.43 (broad s, OH; disappears with deuterium oxide) (c)
Vc	285 (4.04)	2218, 1545 br (a)	1.42 [s, 2 (CH ₃) ₃ C], 18.80 (near s, OH; disappears with deuterium oxide) (c)
Vd	233 (4.03), 327 (4.09)	2218, 1515 br (b)	7.45-7.85 (m, 4 H aryl m' + 2 H aryl p + CH—2), 7.9-8.2 (m, 4 H aryl o) (d)
Vf	259.5 (4.22)	3450 br, 2225, 1648, 1593 (b)	1.6-2.1 (m, CH ₂ —5), 2.20-2.65 (m, CH ₂ —4 + CH ₂ —6), 8.20 (near s, OH; disappears with deuterium oxide)
Vg	233.5 (3.95), 268 (4.25)	3530 br, 2230, 1650, 1585 (b)	1.02 (s, 2 CH ₃ —5), 2.41 (s, CH ₂ —4 + CH ₂ —6), 11.10 (near s, OH; disappears with deuterium oxide) (d)
Vh	231 (3.96), 272 (4.30)	3400 br, 2230, 1632, 1615, 1548 (b)	2.45-2.95 (m, CH ₂ —4 + CH ₂ —6), 3.1-3.6 (m, CH—5), 7.35 (near s, C ₆ H ₅), 9.53 (near s, OH; disappears with deuterium oxide) (d)

(a) In chloroform. (b) In potassium bromide. (c) In deuteriochloroform. (d) In DMSO-d₆.

EXPERIMENTAL

The uv spectra were measured in 95% ethanol with a Hitachi-Perkin-Elmer Model EPS-3T spectrophotometer. The ir spectra were taken on a Perkin-Elmer Model 398 spectrophotometer; the nmr spectra were recor-

ded on a Perkin-Elmer Model R-12 instrument (60 MHz, TMS as the internal standard, J in Hz). Melting points were determined with a Fisher-Johns apparatus.

General Procedure for 5-Substituted 4-Acylisoxazoles IVa-d and 6,7-Dihydro-1,2-benzisoxazol-4(5H)-ones IVf-h.

A solution of III (30 mmoles) and hydroxylamine hydrochloride (2.1 g, ~30 mmoles) in methanol (15 ml) was refluxed for 1 hour (3 hours in the case of IIIg). After cooling, the reaction mixture was diluted with ice-water (30 ml) and extracted thoroughly with diethyl ether. The ether extracts were dried (sodium sulfate) and evaporated (in the case of IVf, the residue treated with a little chloroform-diethyl ether (1:1) separated the cyanodione Vf in 11% yield). The residue was chromatographed on Florisil (diethyl ether) and the product was further purified by distillation *in vacuo* or recrystallization from a suitable solvent (Table I).

2-Hydroxyaminomethylene-1,3-cyclopentanedione (VI).

When the above reaction was carried out with IIIe the final product could not be obtained pure. A more satisfactory result was achieved without heating by stirring the reaction mixture at 0° for 1 hour. The precipitate and the product obtained by concentrating the mother liquor were recrystallized from water, mp 162-163° (89%). The following spectral data were obtained with a sample dehydrated *in vacuo* at 80° for 1 hour: ir (potassium bromide): ν max 3250, 1662, 1593 cm^{-1} ; nmr (DMSO- d_6): δ 2.50 (s, $\text{CH}_2\text{-4} + \text{CH}_2\text{-5}$), 7.45 (s, =CHN), 7.8-9.2 (broad s, NH + OH; disappears with deuterium oxide).

Anal. Calcd. for $\text{C}_6\text{H}_7\text{NO}_3 \cdot \text{H}_2\text{O}$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.19; H, 5.73; N, 8.54.

General Procedure for 2-Cyano-1,3-diones Va-d,f-h.

A methanol solution of sodium methoxide, prepared from sodium (0.35 g, 15 mmoles) and anhydrous methanol (10 ml), was slowly added with stirring to an ice-cooled solution of IV (10 mmoles) in anhydrous diethyl ether (100-200 ml). The reaction mixture was stirred at room temperature for 8-12 hours, filtered and the precipitate was dissolved in cold water (5-10 ml). The solution was acidified with 6*N* hydrochloric acid, the precipitate was filtered and recrystallized from a suitable solvent (Table III).

Acknowledgement.

The authors wish to thank Mr. A. Panaro for the microanalyses and Dr. S. Morasso and Mr. F. Fasce for the uv, ir and nmr spectra.

REFERENCES AND NOTES

- (1) P. Schenone, L. Mosti and G. Menozzi, *J. Heterocyclic Chem.*, submitted.
- (2) Reviews: (a) A. Quilico in "Five- and Six-Membered Compounds with Nitrogen and Oxygen", R. H. Wiley, ed, Interscience, New York, 1962, p 1; (b) N. K. Kochetkov and S. D. Sokolov, *Adv. Heterocyclic Chem.*, **2**, 365 (1963); (c) B. J. Wakefield and D. J. Wright, *ibid.*, **25**, 147 (1979).
- (3) P. Vita Finzi, P. L. Caramella and P. Grünanger, *Ann. Chim. (Rome)*, **55**, 1233 (1965); see also Y. Tamura, Y. Miki, Y. Sumida and M. Ikeda, *J. Chem. Soc., Perkin Trans. I*, 2580 (1973).
- (4) A. A. Akhrem, A. M. Moiseenkov, M. B. Andaburskaya and A. Ya. Strakov, U. S. S. R. Patent 371,209 (1973); *Chem. Abstr.*, **79**, 18210j (1973).
- (5) A. A. Akhrem, A. M. Moiseenkov, A. Ya. Strakov and M. B. Andaburskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 836 (1973); *Chem. Abstr.*, **79**, 31545s (1973).
- (6) Ref (3a), p 44; ref (3b), p 398; ref (3c), p 170.
- (7) C. Musante, *Gazz. Chim. Ital.*, **69**, 523 (1939).
- (8) D. Martin and S. Rackow, *Chem. Ber.*, **98**, 3662 (1965).
- (9) M. Tanaka, T. Shono and K. Shinra, *Bull. Chem. Soc. Japan*, **42**, 3190 (1969).
- (10) Z. Yoshida, H. Ogoshi and T. Tokumitsu, *Tetrahedron*, **26**, 5691 (1970).
- (11) E. von Meyer, *J. Prakt. Chem.*, **42**[2], 267 (1890).