

Condensation of Some 3-Methylisoxazolo[3,4-*d*]pyridazin-7(6*H*)ones with Aromatic Aldehydes

V. Dal Piaz, S. Pinzauti and P. Lacrimini

Istituto di Chimica Farmaceutica dell'Università di Firenze, Via G. Capponi 9, 50121 Firenze, Italy

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Some years ago Quilico and Musante (1,2) proved that 3-substituted-5-methyl-4-nitroisoxazoles easily condense with aromatic aldehydes in the presence of secondary amines. Kochetkov, *et al.*, (3) reported that 5-methylisoxazoles substituted in 4-position with electron-withdrawing groups different from nitro are unaffected even under extreme conditions. However, recently this limitation was overcome by using alkaline alkoxides as catalysts of the condensation between 5-methylisoxazoles and benzaldehyde (4).

In the present note we extended the investigation of the reactivity of the methyl group of 3-methylisoxazolo[3,4-*d*]pyridazin-7(6*H*)ones toward aromatic aldehydes. Compounds **1a-b** and **1e-h** were obtained by cyclization of 4-acyl-3-carbomethoxy-5-methylisoxazoles with hydrazines and substituted hydrazines (5-8).

When an equimolar mixture of aromatic aldehyde and **1** was refluxed for a short time in alcoholic medium in the presence of sodium methoxide, high melting yellow products were obtained in good yields (Table I). The structures of the 3-styrylisoxazolo[3,4-*d*]pyridazin-7(6*H*)ones were established by microanalyses, ir (bands due to a CO, 1680 cm^{-1} , and to a *trans* -CH=CH- wagging, 960 cm^{-1}), nmr and mass spectra.

In the reaction between **1a**, **1b**, **1e** and benzaldehyde the nucleophilic attack over the aldehydic CO can be due to the methyl group in the 3 or 4-position. Also if an

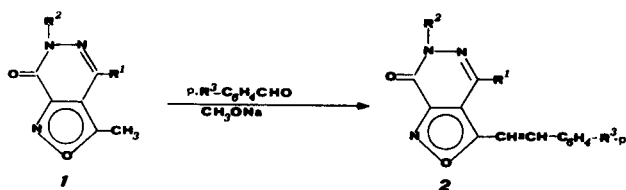
excess of aldehyde is employed, only monostyryl derivatives are obtained, proving that only one methyl group is active.

In order to assign the correct structure to the obtained styryl derivatives **2a-e**, some nmr and mass spectral data of the reaction products were examined. The nmr spectrum (9) of compound **1b** (deuteriochloroform) shows three singlets (3H) at δ 2.48, 2.84 and 3.68 ppm attributable to the methyl groups at 4, 3 and 6-positions, respectively. The spectrum of compound **2b** exhibits two singlets (3H) at δ 2.57 and 3.72 ppm for the methyl groups at 4 and 6-positions, and a multiplet (7H) between δ 7.1 and 7.52 ppm attributable to the styryl group. In this multiplet an AB pattern ($J = 16$ Hz) was easily recognizable for the *trans* olefinic protons.

The mass spectra of compounds **2a-c** (Table II) are characterized by strong molecular peaks (base peak). It is interesting to note the consistent presence of the peak corresponding to the $[M-1]^+$ ion (arising probably by loss of hydrogen from one of the -CH= groups) and the presence of the $[M+1]^+$ ion. Other prominent peaks correspond to the ions $[\text{ArCHCH}]^+$ and $[\text{Ar}]^+$.

The appearance of a peak at $m/e = 131$ was observed in the mass spectrum of 3-phenyl-5-styrylisoxazole (10) carried out for comparison. The attribution of these peaks to the $[\text{C}_6\text{H}_5\text{CHCHCO}]^+$ fragment is confirmed by its absence in the spectrum of **2c** in which the peaks of $[\text{C}_6\text{H}_5\text{CHCHCO}]^+$ ion appear. This typical fragmentation, previously observed in the mass spectra of several isoxazoles (11), is due to the cleavage of the N-O bond in the isoxazole ring.

Therefore, the presence of the fragment $[\text{ArCHCHCO}]^+$ can be used as a proof of structure for the 5-styrylisoxazoles and the 3-styrylisoxazolo[3,4-*d*]pyridazin-7(6*H*)ones. The fragmentation of the pyridazine ring takes place in all cases by loss of carbon monoxide. In the spectrum of **2a** is also observable the fragment $m/e = 224$ arising from the elimination of N_2H , while the spectra of **2b-c** reveal the fragmentation mode $[\text{M}-\text{NCH}_3]^+$.



	R ¹	R ²	R ³
2a	CH ₃	H	H
b	CH ₃	CH ₃	H
c	CH ₃	CH ₃	4-Cl
d	CH ₃	CH ₃	4-OCH ₃
e	CH ₃	C ₆ H ₅	H
f	C ₆ H ₅	H	H
g	C ₆ H ₅	CH ₃	H
h	C ₆ H ₅	C ₆ H ₅	H

Table I

3-Styrylisoxazolo[3,4-d]pyridazin-7(6H)ones

Compound	R ¹	R ²	R ³	Yield %	M.p., °C	Formula	Analyses, Calcd./Found		
							C	H	N
2a	CH ₃	H	H	70	278 (a)	C ₁₄ H ₁₁ N ₃ O ₂	66.40	4.38	16.59
							66.19	4.41	16.41
2b	CH ₃	CH ₃	H	82	224 (b)	C ₁₅ H ₁₃ N ₃ O ₂	67.41	4.90	15.72
							67.30	4.93	15.52
2c	CH ₃	CH ₃	4-Cl	76	261-262 (a)	C ₁₅ H ₁₂ ClN ₃ O ₂ (d)	59.72	4.01	13.93
							59.51	4.05	13.69
2d	CH ₃	CH ₃	4-OCH ₃	78	248 (b)	C ₁₆ H ₁₅ N ₃ O ₃	64.64	5.08	14.13
							64.67	5.08	14.36
2e	CH ₃	C ₆ H ₅	H	87	265 (b)	C ₂₀ H ₁₅ N ₃ O ₂	72.94	4.59	12.76
							73.09	4.84	12.48
2f	C ₆ H ₅	H	H	65	264 (b)	C ₁₉ H ₁₃ N ₃ O ₂	72.37	4.16	13.33
							72.21	4.25	13.20
2g	C ₆ H ₅	CH ₃	H	83	222-223 (b)	C ₂₀ H ₁₅ N ₃ O ₂	72.94	4.59	12.76
							72.74	4.75	12.80
2h	C ₆ H ₅	C ₆ H ₅	H	68	246 (c)	C ₂₅ H ₁₇ N ₃ O ₂	76.71	4.38	10.73
							76.47	4.29	10.68

(a) Recrystallized from acetic acid. (b) Recrystallized from methanol. (c) Recrystallized from acetone. (d) Analysis % for Cl, Calcd./Found: 11.75/11.49.

Table II

Mass Spectra (12) of **2a-c**
m/e (Relative Intensities %)

2a	253(a)(100), 252(59), 103(52), 77(30), 254(19), 131(18), 224(12)
b	267(a)(100), 103(82), 266(36), 67(34), 131(27), 238(23), 268(17), 239(11)
c	301(a)(100), 300(85), 302(46), 303(40), 57(37), 137(23), 71(16), 101(16), 272(11), 165(8)

(a) Molecular ion.

EXPERIMENTAL

General Procedure.

A mixture of **1** (5 mmoles) and aldehyde (10 mmoles) in dry methanol (15 ml.) was added to a solution of sodium methoxide (5 mmoles) in dry methanol (5 ml.). The reaction mixture was then refluxed for 1-3 minutes and rapidly cooled. The styryl derivatives were collected by filtration. Compound **2f** was isolated from the concentrated reaction mixture after treatment with dilute hydrochloric acid.

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