Synthesis of Furo[3,4-d]-1,2-oxazole Derivatives

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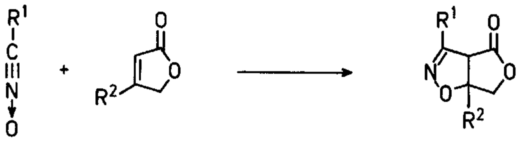
The 1,3-dipolarophilic activity of $\Delta^{\alpha,\beta}$-butenolides has been little investigated; e.g., the reaction with 2-diazopropane has been reported[1] to yield only one of the two possible structurally isomeric pyrazolines. Pursuing our studies on the reactivity of nitrile oxides, we report here on the reaction of benzo- and mesito-nitrile oxides **1** with the double bond of some $\Delta^{\alpha,\beta}$-butenolides **2** in absolute ether solution. The cycloaddition takes place readily, yielding variable amounts of monoadducts, according to the general equation:



1 **2** **3**

When $R^1 = C_6H_5$, notable yields of diphenylfuroxan, the benzonitrile oxide dimer, were also obtained.

Whereas the cycloaddition of nitrile oxides with open-chain α,β-unsaturated esters[2] often yields a mixture of the two structural isomeric 2,5-dihydro-1,2-oxazoles, the reaction with butenolides always led to 4-oxo-3-aryl-3a,4,6,6a-tetrahydrofuro[3,4-d]-1,2-oxazoles, and represents an easy synthesis of this heterocyclic system. No significant amount of isomeric products was detected in the reaction mixtures. The yields of adducts **3**, whatever the nature of R^1, decreased on passing from the unsubstituted **2** ($R^2=H$) to the substituted derivatives. The better yields reported with mesitonitrile oxide are due to its extremely low tendency to dimerization[3]. Characterization data are given in Table 1.

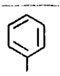
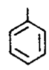
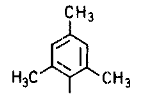
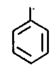
The structures assigned to products **3** rely upon spectral data. The I.R. spectra show the γ-lactone band and lack any absorption band in the region 3600–3200 cm^{-1}. The U.V. spectra are consistent with a 3-aryl-1,2-oxazoline ($Ar-\overset{|}{C}=N-$ absorption band) structure. The N.M.R. spectra, the significant data of which are given in Table 2, clearly support structure **3** and exclude the isomeric struture containing the γ-lactone group adjacent to the 5-position of the 1,2-oxazoline ring.

Attempted hydrolytic cleavage of the γ-lactone ring of **3a–f** with bases gave an alkali salt which invariably, on mild acidification, re-cyclized to give the starting compound **3**. Prolonged heating of **3a** with 20% hydrochloric acid led with loss of carbon dioxide to 5-hydroxymethyl-3-phenyl-1,2-oxazole[5] in low yield, whilst the bulk of the product remained unchanged.

General Procedure:

Method A. An ethereal solution of benzonitrile oxide, prepared from benzhydroximic acid chloride (0.03 mol) and triethylamine (0.03 mol)[6] was rapidly added, at room temperature, to a solution of butenolide (0.03 mol) in absolute ether (10 ml). The crystalline adduct **3** slowly precipitated (5–6 days) and was isolated by filtration. An additional amount of product was obtained by column chromatography on silica gel [eluent: cyclohexane/ethyl acetate (4/1)] of the residue left after complete evaporation of the solvent.

Table 1. Characterization Data of Compounds 3[a,b]

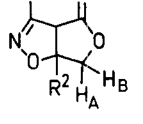
R^1	R^2	Method	Adduct	Yield[c] %	m.p.	I.R. (®Nujol) $\nu_{C=O}$ [cm^{-1}]	U.V. (C_2H_5OH) λ_{max} [nm]	log ε
	H	A B	**3a**	54 50	157–158° (ethanol)	1765	265	4.08
	CH_3.	A B	**3b**	23 18	127–128° (benzene/petroleum ether)	1760	265	4.10
		A B	**3c**	15 15	139–140° (ethanol)	1760	264	4.10
	H	C	**3d**	72	109–112°	1770	240 (sh)	3.78
	CH_3	D	**3e**	73	107–108° (benzene/petroleum ether)	1755	239 (sh)	3.81
		D	**3f**	64	159–160° (benzene/petroleum ether)	1770	240 (sh)	3.85

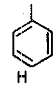
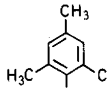
[a] Satisfactory elemental analyses have been obtained for all substances.

[b] The $\Delta^{\alpha,\beta}$-butenolides have been prepared according to literature[4].

[c] The yields refer to equimolar amounts of reagents for sake or comparison, and might be optimized by varying the reagents ratio.

Table 2. N.M.R. Data of Compounds 3[a]



Compound	R^1	R^2	H_A	H_B	H_C	$R^2=H$	J_{AB}	J_{CD}	$J_{AC}+J_{BD}$
3a		H	4.65 d	4.65 d	4.62 d	5.640		9.6	7.6
3b		CH_3	4.32 d	4.59 d	4.27 s	–	–10.5		
3c			4.75 d	4.87 d	4.61 s	–	–10.5		
3d		H	4.50 d	4.50 d	4.33 d	5.520		9.5	8.1
3e		CH_3	4.58 d	4.27 d	3.98 s	–	–10.5		
3f			4.85 d	4.72 d	4.31 s	–	–10.5		

[a] Recorded on a Varian-60 spectrometer, $CDCl_3$, TMS as internal standard, δ values in ppm, J in c. p. s.; s=singlet; d=doublet; o=octet.

Method B. To a vigorously stirred solution of butenolide (0.03 mol) and benzhydroximic acid chloride (0.03 mol) in absolute ether (15 ml) was added, dropwise and with stirring at room temperature over a period of 2 hr, an ethereal solution of triethylamine (0.03 mol). The mixture was allowed to stand overnight. Cold water was added, the organic layer separated, and dried over magnesium sulfate. The solvent was evaporated and the adduct (**3**) isolated by column chromatography of the residue as described above.

Method C. A solution of mesitonitrile oxide[3] (0.01 mol) and butenolide (0.01 mol) in absolute ether (25 ml) was allowed to stand at room temperature for 7 days. The adduct **3** crystallized out completely; from the mother liquor, no adduct could be isolated.

Method D. A solution of mesitonitrile oxide (0.01 mol) and butenolide (0.01 mol) in absolute ether (20 ml) was kept at 35° for one month. After evaporation of the solvent, the adduct **3** was isolated by column chromatography of the residue as described above.

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[1] M. Franck-Neumann, Angew. Chem. **80**, 42 (1968); Angew. Chem., Internat. Edit. **7**, 65 (1968).

[2] M. Christl, R. Huisgen, Tetrahedron Letters **1968**, 5209.
F. Monforte, G. Lo Vecchio, Gazz. Chim. Ital. **83**, 416 (1953).
M. Arbasino, P. Vita Finzi, Ric. sci. **36**, 1339 (1966).

[3] C. Grundmann, J. M. Dean, J. Org. Chem. **30**, 2809 (1965).