Oxidative Ring Opening of 2-Oxoisoxazolo[2,3-*a*]pyrimidines. Formation of Pyrimidin-2-yl Phenyl Ketones

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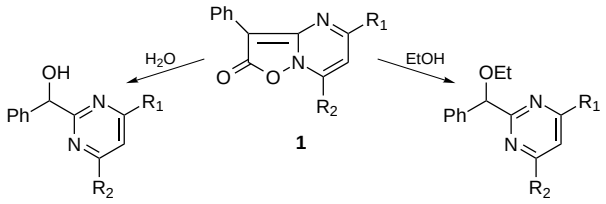
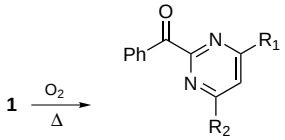
The synthesis of 2-oxo-3-phenylisoxazolo[2,3-*a*]pyrimidines **1** and their rearrangement in nucleophilic solvents was described recently.[1] Upon heating in water or ethanol, under nitrogen, the isoxazole ring was opened and a spontaneous decarboxylation led to the formation of pyrimidinylphenylmethanols **2** and their ethyl ethers **3**, respectively.



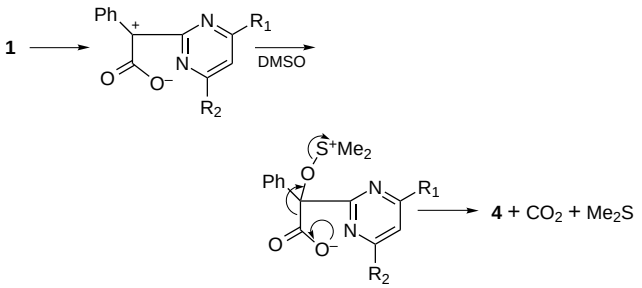
In the present work a new rearrangement of the same isoxazolo[2,3-*a*]pyrimidines is described. It was observed that when the reaction was carried out without the exclusion of air and light traces of an additional product was observed. It was identified as a 2-benzoylpyrimidine derivative **(4)**. Upon bubbling oxygen through the heated aqueous solutions of these isoxazolopyrimidine derivatives **1**, these ketones became the major products. One of these ketones **(4a)** was recently described.[2] The presence of a carbonyl group in **4c** was demonstrated by the ^{13}C signal at 192 ppm, a carbonyl stretching vibration in the IR spectrum at 1690 cm^{-1}, and the condensation of **4b** and **4c** with (2,4-dinitrophenyl)hydrazine to produce the hydrazone derivatives.



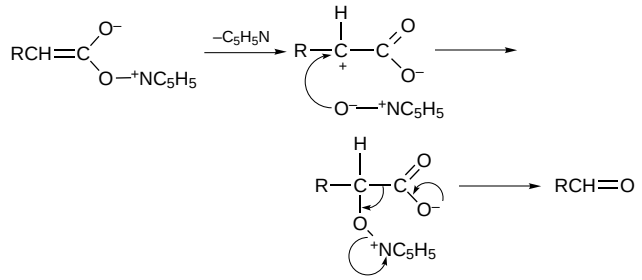
4a: R_1 = H, R_2 = H
4b: R_1 = Me, R_2 = H
4c: R_1 = Me, R_2 = Me
4d: R_1 = Me, R_2 = Ph

Heating the pyrimidinylphenylmethanols **2** in the presence of oxygen as above did not bring about any oxidation of the secondary alcohols to a ketone. This excluded alcohols being intermediates in the formation of **4**.

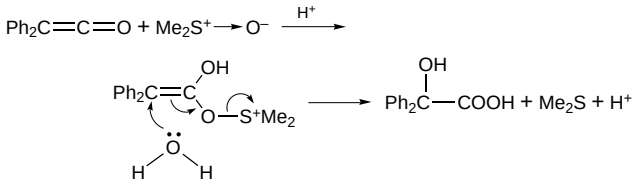
Scheme 1



Scheme 2



Scheme 3



This oxidative cleavage in boiling water is completed in about 10−24 h. Upon heating at 135° in dimethyl sulfoxide, it takes about 10 min even without bubbling of oxygen. Presumably the solvent is the oxidizing agent as is shown in Scheme 1. This mechanism is supported by the detection of dimethyl sulfide in the reaction mixture, by gas chromatography and NMR.

An analogous mechanism (Scheme 2) which involves oxidation with an amine oxide was described earlier by Cohen[3] and in turn is related to that which was proposed by Lillien[4] to account for the production of benzilic acid in the oxidation of diphenylketene by aqueous dimethyl sulfide (Scheme 3).

Experimental Section

General Methods. Melting points are uncorrected. Chromatographic separation was carried out with silica gel (230−400 mesh) on a 450 × 20 mm column.

Oxidative Rearrangement of 2-Oxo-3-phenylisoxazolo-[2,3-*a*]pyrimidines in Water. 2-Oxo-3-phenylisoxazolo[2,3-*a*]-pyrimidine (**1**, 0.001 mol) was suspended in a mixture of 6:1 water−acetonitrile (100 mL), which was previously saturated by oxygen. The mixture was refluxed with bubbling of oxygen for 24 h. The solvent was evaporated under reduced pressure, and the residue which contained **4** and **2** (5:1) was resolved by silica gel chromatography. Results and NMR data are summarized in Table 1.

(1) Zvilichovsky, G.; Gurvich, V.; Segev, S. *J. Org. Chem.* **1995**, *60*, 5251.
(2) Bátori, S.; Messmer, A. *J. Heterocycl. Chem.* **1994**, *31*, 1041.
(3) Cohen, T.; Song, I. H.; Fager, J. H.; Deets, G. L. *J. Am. Chem. Soc.* **1967**, *89*, 4968.
(4) Lillien, I. *J. Org. Chem.* **1964**, *29*, 1631.

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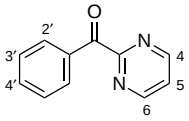
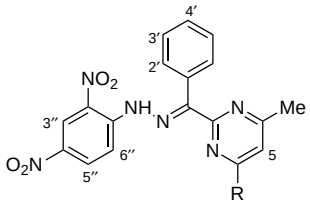
Table 1. Analytical and Spectral Data of 2-benzoylpyrimdines 4



	4a	4b	4c[a]	4d
yield, %	78	75	77	80
mp, °C	90−91	semisolid	semisolid	semisolid
formula	$C_{11}H_8N_2O$	$C_{12}H_{10}N_2O$	$C_{13}H_{12}N_2O$	$C_{18}H_{14}N_2O$
found (calcd)				
C	71.79 (71.73)	72.55 (72.79)	73.48 (73.57)	78.57 (78.81)
H	4.18 (4.38)	5.32 (5.08)	5.53 (5.70)	5.04 (5.14)
N	14.90 (15.21)	14.14 (14.13)	12.97 (13.20)	9.93 (10.21)
^{1}H NMR ($CDCl_3$)				
position 4	8.96 (d, $J = 4.88$)	8.75 (d, $J = 5.12$)	2.58 (s, Me)	2.70 (s, Me)
position 5	7.53 (t, $J = 4.88$)	7.34 (d, $J = 5.12$)	7.18 (s)	7.72 (s)
position 6	8.96 (d, $J = 4.88$)	2.65 (s, Me)	2.58 (s, Me)	8.12[b] (m, *o*-Ph), 7.51[c] (m, *m*- + *p*-Ph)
position 2′	8.04 (dd, $J_{3',2'} = 6.98$, $J_{4',2'} = 1.55$)	8.04 (dd, $J_1 = 7.46$, $J_2 = 1.59$)	8.03 (dd, $J_{3',2'} = 7.50$, $J_{4',2'} = 1.75$)	8.12[d] (m)
position 3′	7.52 (m)	7.47 (dd, $J_1 = 7.03$, $J_2 = 7.46$)	7.47 (dt, $J_1 = 6.96$, $J_2 = 7.50$)	7.51[e] (m)
position 4′	7.61 (tt, $J_{3',4'} = 6.98$, $J_{2',4'} = 1.55$)	7.58 (tt, $J_{3',4'} = 7.03$, $J_{2',4'} = 1.59$)	7.56 (tt, $J_{3',4'} = 7.50$, $J_{2',4'} = 1.75$)	7.62 (tt, $J_{3',4'} = 6.96$, $J_{2',4'} = 1.65$)

[a] For product **4c** also ^{13}C NMR (DMSO-d_6) was carried out: 23.4, 121.0, 127.8, 128.6, 130.1, 133.9, 162.0, 166.9, 192.2. [b] Together with 2′. [c] Together with 3′. [d] Together with *o*-Ph. [e] Together with *m*- + *p*-Ph.

Table 2. Analytical and Spectral Data of (Dinitrophenyl)hydrazones of Phenyl Pyrimidinyl Ketones



	R = H	R = Me
Mp, °C	201−2	186−7
formula	$C_{18}H_{14}N_6O_4$	$C_{19}H_{16}N_6O_4$
found (calcd)		
C	56.95 (57.14)	57.88 (58.16)
H	3.69 (3.73)	4.00 (4.11)
N	21.92 (22.21)	21.09 (21.42)
^{1}H NMR ($CDCl_3$)		
position 5	7.30 (d, $J_{6,5} = 5.16$)	7.16 (s)
position 2′	7.74 (dd, $J_{3',2'} = 6.56$, $J_{4',2'} = 2.51$)	7.76 (dd, $J_{3',2'} = 6.64$, $J_{4',2'} = 2.46$)
position 3′ + 4′	7.48 (m)	7.46 (m)
position 3″	9.19 (d, $J_{5'',3''} = 2.41$)	9.17 (d, $J_{5'',3''} = 2.30$)
position 5″	8.36 (dd, $J_{6'',5''} = 6.74$, $J_{3'',5''} = 2.41$)	8.32 (dd, $J_{6'',5''} = 6.90$, $J_{3'',5''} = 2.30$)
position 6″	8.32 (d, $J_{5'',6''} = 6.74$)	8.30 (d, $J_{5'',6''} = 6.90$)
position Me	2.82 (s)	2.68 (s)
position R	8.86 (d, $J_{5,6} = 5.16$)	2.68 (s)
position NH	15.12 (s)	14.89 (s)

Oxidative Rearrangement of 2-Oxo-3-phenylisoxazolo-[2,3-*a*]pyrimidines 1 in Dimethyl Sulfoxide. 2-Oxo-3-phenylisoxazolo[2,3-*a*]pyrimidines **1** (0.001 mol) were dissolved in DMSO (5 mL) and heated for 5 min at 135 °C. The reaction mixture was loaded on a silica gel column, and the products were eluated with ethyl acetate−petroleum ether (1:1). Analytical results and ^{1}H NMR are summarized in Table 1.

Condensation of Pyrimidin-2-yl Phenyl Ketones 4b and 4c with (2,4-Dinitrophenyl)hydrazine. 2-Oxo-3-phenylisoxazolo[2,3-*a*]pyrimidines **4b** and **4c** (0.005 g) were dissolved in ethanol (1 mL), and (2,4-dinitrophenyl)hydrazine reagent[5] (2 mL) was added and boiled for 4 min. The product precipitated on cooling. Analytical results and ^{1}H NMR are summarized in Table 2.

Detection of Dimethyl Sulfide in Dimethyl Sulfoxide Oxidation. (a) By ^{1}H NMR. 2-Oxo-3-phenyl-5,7-dimethylisoxazolo[2,3-*a*]pyrimidine (**4c**, 0.05 g) was dissolved in DMSO (1 mL) and boiled for 5 min with trapping of outgoing gases in $CDCl_3$. Dimethyl sulfide in outgoing gases was identified by ^{1}H NMR.

(b) By GC. 2-Oxo-3-phenyl-5,7-dimethylisoxazolo[2,3-*a*]-pyrimidine (**4c**, 0.02 g) was dissolved in DMSO and heated in a stoppered vial at 135 °C for 5 min. The gaseous phase was transferred to a GC with a POROPAK N column. The t_R was compared with that of an authentic sample of dimethyl sulfide.

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(5) Vogel, A. I. *A Text-book Of Practical Organic Chemistry*; Longmans, Green and Co.: London New York Toronto, 1989; p 923.