STUDIES ON PYRIMIDINE ANALOGUES: REACTION OF ISOXAZOLO-(3,4-d)PYRIMIDINE WITH ACTIVE METHYLENE COMPOUNDS

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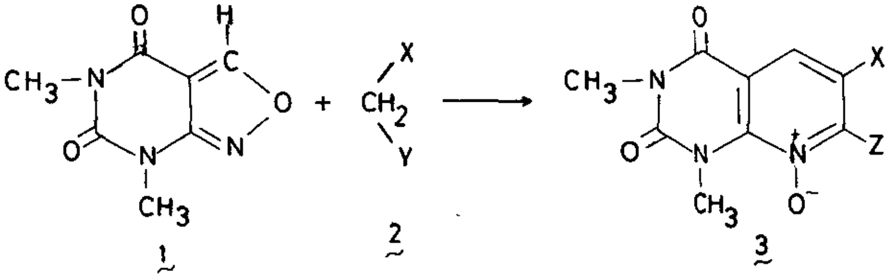
Abstract - 5,7-Dimethylisoxazolo[3,4-d]pyrimidine-4,6(5*H*,7*H*)-dione is found to react with a variety of active methylene compounds yielding novel pyrido[2,3-d]pyrimidine-2,4(1*H*,3*H*)-dione oxides.

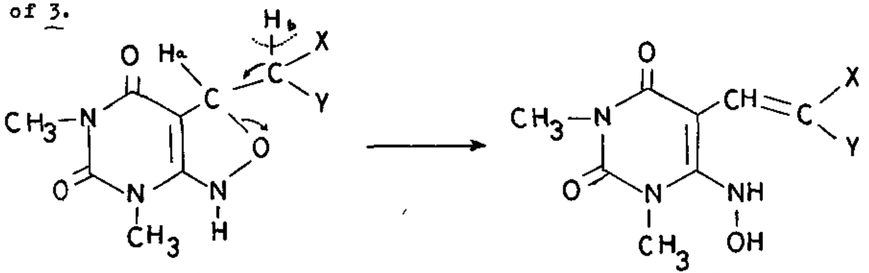
Anthranils have exceptionally low electron density at C-3 and therefore a large number of nucleophiles have been found to attack at this position of these molecules[1]. In base-catalysed reactions deprotonation at C-3 has been assumed to be the first step, followed by rupture of isoxazole ring[2]. In contrast it is also reported that C-3 proton could not be exchanged when triethylamine and D_2O were used[3]. Ethereal solution of diazomethane also did not methylate C-3 indicating that though this position is highly electron deficient the proton is not so much labile in character[4]. In this report we describe our results when a related system **1**[5] is reacted with various active methylene compounds **2** to give new pyrido[2,3-d]pyrimidine-2,4(1*H*,3*H*)-dione oxides **3**.



2	X	Y	**3**	X	Z
a =	-CN	-CN	a =	-CN	$-NH_2$
b =	$-CO_2C_2H_5$	$-CO_2C_2H_5$	b =	$-CO_2C_2H_5$	-OH
c =	$-CO_2C_2H_5$	-CN	c =	$-CO_2C_2H_5$	$-NH_2$
d =	$-CONH_2$	-CN	d =	$-CONH_2$	$-NH_2$

Equimolar quantities of **1** and **2** were refluxed for 2 h in absolute alcohol in the presence of a catalytic amount of triethylamine. After cooling the reaction mixture a white crystalline product was separated out which was filtered and recrystallised from absolute alcohol to give **3**. The yields, melting points and elemental analysis are given in table I and spectral data in table II.

In the formation of the product **3** we propose similar mechanism as in the case of anthranils i.e. formation of intermediates **4** and **5** leading to the formation of **3**.



4

5

In this case **4** is the result of direct attack of active methylene compounds (**2a**-**d**) at C-3 followed by rupture to **5** giving end product **3**.

EXPERIMENTAL

A typical experimental procedure for the reaction described is as follows: a mixture of 5,7-dimethylisoxozolo[3,4-d]pyrimidine-4,6(5*H*,7*H*)-dione, **1**, (181 mg, 1 m mole) and malononitrile, **2a**, (76 mg, 1 m mole) was refluxed for 2 h in 10 ml of absolute alcohol in the presence of catalytic amount of triethylamine and then cooled. The resultant white crystalline material separated was filtered and recrystallised from absolute alcohol to give 6-cyano-and 7-aminopyrido[2,3-d]pyrimidine-2,4(1*H*,3*H*)-dione 8-oxide, **3a**, (200 mg, 80% yield). In case of the reaction with diethyl malonate, **2b**, ethyl cyanoacetate, **2c** and cyanoacetamide, **2d**, the clear reaction mixture after reflux was chilled to get the product.

Table I. Yields, melting points, elemental analysis of pyrido[2,3-d]-pyrimidine-2,4(1H,3H)-dione oxides

Active methylene compound	Product	mp °C	Yield %	Molecular formula	Analysis % C Found (Calculated)	H	N
2a Malononitrile	3a	272	80	$C_{10}H_9N_5O_3$	48.40 (48.58)	3.61 (3.64)	22.23 (28.34)
2b Diethyl malonate	3b	205	60	$C_{12}H_{13}N_3O_6$	48.62 (48.81)	4.39 (4.41)	14.12 (14.24)
2c Ethyl cyanoacetate	3c	203-204	60	$C_{12}H_{14}N_4O_5$	48.79 (48.98)	4.72 (4.76)	18.88 (19.05)
2d Cyanoacetamide	3d	211-212	55	$C_{10}H_{11}N_5O_4$	45.12 (45.28)	4.11 (4.15)	26.26 (26.41)

Table II. Ir, Mass and ^{1}H nmr data of compounds 3a-d

Compound	ir(cm^{-1})	MS m/e M$^+$	^{1}H nmr δ
3a	3250, 2200, 1650, 1625, 970	247	3.38(s,3H), 4.07(s,3H), 7.832-8.427(m,2H), 8.9(s,1H)
3b	3450, 1675, 1650	295	1.4(t,3H), 3.3(s,3H), 3.66(s,3H), 4.3(q,2H), 8.66(s,1H)
3c	3250, 1675, 1650, 970	294	1.41(t,3H), 3.35(s,3H), 3.66(s,3H), 4.3(q,2H), 8.63(s,1H)
3d	3250, 1650, 1615, 970	265	2.84(s,3H), 3.44(s,3H), 7.4-8.0(b,4H), 8.26(s,1H)

ir (KBr); ^{1}H nmr; 3a-c, 270 MHz^6, 3d, 60 MHz; Solvent: 3a, TFA+CDCl$_3$, 3b-c, CDCl$_3$ and 3d, TFA

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6. 270 MHz nmr spectra were recorded at sophisticated nmr facility at Bangalore, India.

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