New Synthesis of Pyrazolo[4,3-*d*]pyrimidines

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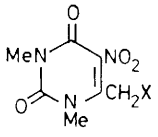
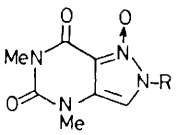
Summary Treatment of 6-bromomethyl-1,3-dimethyl-5-nitrouracil with various primary amines gave the respective 2-substituted pyrazolo[4,3-*d*]pyrimidine 1-oxides.

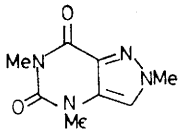
PYRAZOLO[4,3-*d*]PYRIMIDINES are interesting compounds from the physiological activity viewpoint, since their fundamental structure is present in antibiotics such as formycin.[1] Although individual pyrazolo[4,3-*d*]pyrimidines have been synthesized,[2,3] a general synthesis of this ring system is not available. Here we report a new one-step procedure for the synthesis of 2-substituted pyrazolo[4,3-*d*]-pyrimidine 1-oxides from readily available 6-bromomethyl-1,3-dimethyl-5-nitrouracil (**1**)[4] by treatment with various primary amines.



(1) X = Br
(2) X = NHR



(3)



(4)

Treatment of (**1**) with 2 equiv. of methylamine under reflux for 4 h in ethanol afforded the oxide (**3a**), m.p. 265—266 °C, in 23% yield. When the reaction was performed in ethyl acetate at 0 °C for 0·5 h, the nitrouracil (**2a**), m.p. 99—100 °C, was obtained in 34% yield. Compound (**2a**) could be converted into (**3a**) in 55% yield by refluxing for 12 h in ethanol. Catalytic reduction of (**3a**) over Pd–C in methanol (80 °C; 50 atm of H_2) gave (**4**), m.p. 265—266 °C (lit.[2] m.p. 267—269 °C) in 84% yield. Compound (**4**) was identical with an authentic sample.[3]†

Other pyrazolo[4,3-*d*]pyrimidine 1-oxides (**3b**—**g**) were similarly prepared by refluxing (**1**) and a primary amine in ethanol (see Table). When (**1**) was treated with the amine in ethyl acetate at 0 °C, the intermediates (**2b**—**d**) were obtained and upon further refluxing in ethanol ring closure occurred giving the corresponding pyrazolo[4,3-*d*]-pyrimidines (**3b**—**d**).

TABLE. Formation of pyrazolo[4,3-*d*]pyrimidine 1-oxides by reaction of (**1**) with amines.

		(2)		(3)		
	R	M.p./°C	% Yield	M.p./°C	% Yield[a]	
a	Me	99–100	34	265–266	23	(55)
b	Pr^i	88	98	183–184	19	(63)
c	CH_2=CH–CH_2	82–83	91	216–217	53	(81)
d	Furfuryl	79–80	78	219–220	59	(65)
e	$PhCH_2$	—	—	239–240	58	
f	*p*-$MeOC_6H_4CH_2$	—	—	225–226	62	
g	$PhCH_2CH_2$	—	—	219–220	61	

[a] Yield from (**1**); yield from (**2**) in parentheses.

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† All new compounds gave satisfactory elemental analyses and spectral properties consistent with the assigned structures.

[1] R. J. Suhadolnik in 'Nucleoside Antibiotics,' Wiley-Interscience, New York, 1970, p. 354.
[2] R. K. Robins, F. W. Furcht, A. D. Grauer, and J. W. Jones, *J. Amer. Chem. Soc.*, 1956, **78**, 2418; L. B. Townsend, R. A. Long, J. P. McGraw, D. W. Miles, R. K. Robins, and H. Eyring, *J. Org. Chem.*, 1974, **39**, 2023, and references cited therein; F. L. Rose, *J. Chem. Soc.*, 1952, 3448; 1954, 4116.
[3] V. Papesh and R. M. Dodson, *J. Org. Chem.*, 1965, **30**, 199.
[4] S. Senda, K. Hirota, T. Asao, and Y. Yamada, *Heterocycles*, 1976, **4**, 1765.