STUDIES ON PYRIMIDINE DERIVATIVES. XXXI.[1] SYNTHESIS OF CHLOROMETHYLPYRIMIDINES BY REACTION OF MONOMETHYL-PYRIMIDINE N-OXIDES WITH PHOSPHORYL CHLORIDE

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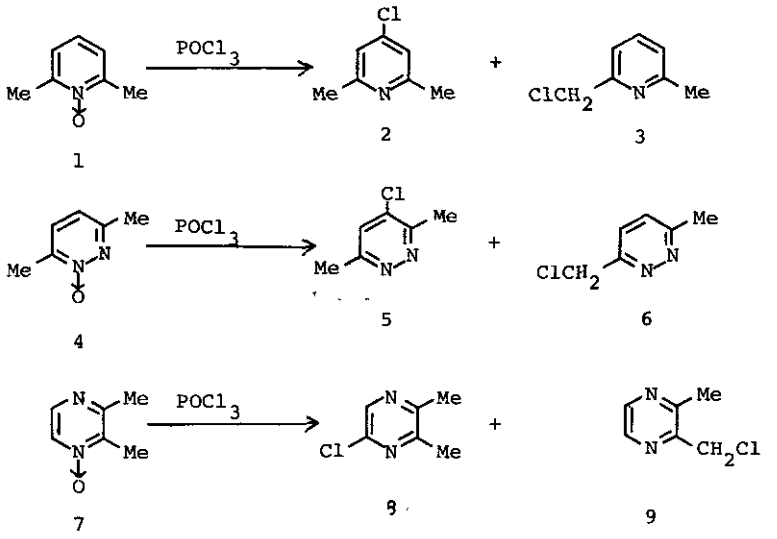
Abstract ——— The reaction of 2- and 6-methylpyrimidine 1-oxides with phosphoryl chloride underwent the selective side-chain chlorination to give 2- and 6-chloromethylpyrimidines as sole products. No by-products such as 2-chloro- and 4-chloropyrimidines were obtained even in the cases of the N-oxides having a free active position in the nucleus.

The reaction of 2,6-dimethylpyridine 1-oxide (1) with phosphoryl chloride was reported by Kato[2] to give 4-chloro-2,6-dimethylpyridine (2), together with a small amount of 2-chloromethyl-6-methylpyridine (3). The reactions of this type have been widely applied to other heteroaromatic amine N-oxides having one or two methyl groups, such as quinoline,[3,4] phenanthridine,[5] pyrazine,[6] and pyridazine N-oxides.[7] In many cases, as well as the case of 1, the reactions tend to give a mixture of the chloromethyl compounds and chloro compounds directly substituted to the rings. For example, Sueyoshi et al.[7] reported that 3,6-dimethylpyridazine 1-oxide (4) was transformed into 4-chloro-3,6-dimethylpyridazine (5) and 3-chloromethyl-6-methyl-pyridazine (6) as a 1:1 mixture, by treatment of 4 with phosphoryl chloride. Recently, Ohta et al.[6c] reported the formation of 2-chloromethyl-3-methylpyrazine (9) together with 6-chloro-2,3-dimethylpyrazine (8) from the reaction of 2,3-dimethylpyrazine 1-oxide (7). In addition to the above, various acyl halides, instead of phosphoryl chloride, are reported to be usable as chlorinating reagents,[8] but the selective formation of the chloromethyl compounds from the above mentioned N-oxide was not achieved by changing the chlorinating agents.

The reaction of methylpyrimidine N-oxides with acyl halides had not been well examined, although the reaction of 4,6-dimethylpyrimidine 1-oxide (10b) with p-toluenesulfonyl chloride was reported as only one example.[9] In the present paper,



Scheme 1

we describe the reaction of several 2-methyl- and 6-methylpyrimidine 1-oxides with phosphoryl chloride, in which the selective formation of chloromethylpyrimidines was characteristically observed.

Firstly, in order to estimate suitable reaction conditions, 6-methyl-4-phenylpyrimidine 1-oxide (10c) chosen as a representative of methylpyrimidine N-oxides was

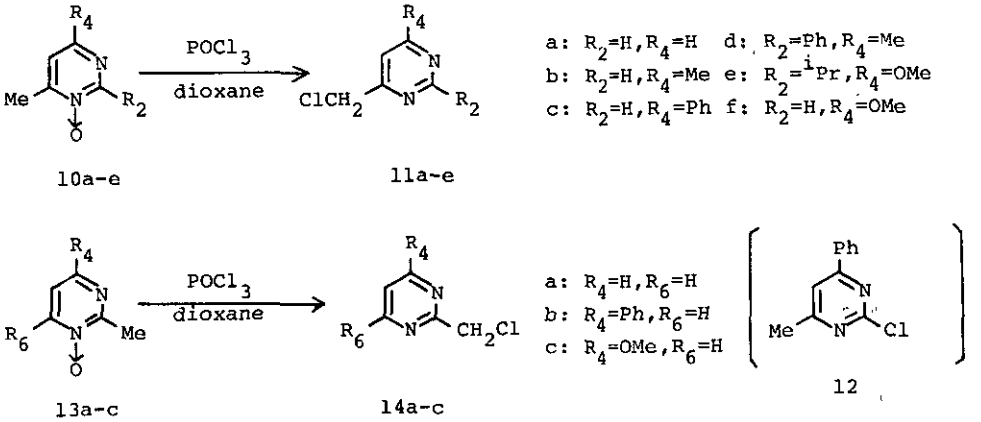
Table 1 4-Chloromethyl-6-phenylpyrimidine (11c) from 6-Methyl-4-phenylpyrimidine 1-Oxide (10c) and Acyl Halides

Run	Acyl halide	Molar ratio	Solvent	Reaction conditions		Yields of 11c (%)
				time (h)	temp. (°C)	
1	$POCl_3$	10	——	0.5	100	54
2	$POCl_3$	10	C_6H_6	0.5	reflux	58
3	$POCl_3$	3	dioxane	0.5	reflux	73
4	$POCl_3$	1	dioxane	0.5	reflux	37
5	$PhSO_2Cl$	3	dioxane	0.5	reflux	26
6	SO_2Cl_2	3	dioxane	1	reflux	0 [10] a)
7	PhCOCl	3	dioxane	1	reflux	3
8	MeCOCl	3	dioxane	1	reflux	0 [40] a)

a) Recovery

treated with various acyl halides in an appropriate solvent. A good result was obtained, when 10c was heated with three folds molecular amount of phosphoryl chloride in boiling dioxane for 0.5 h (run 3). Namely, 4-chloromethyl-6-phenylpyrimidine (11c), bp 130°C (2 mmHg) was isolated in 73 % yield, without the formation of 2-chloro-4-methyl-6-phenylpyrimidine (12). On the basis of the results listed in Table 1, the above reaction conditions were adopted as a standard method in the following investigation.

Then, several 6-methylpyrimidine 1-oxides such as 6-methyl- (10a), 4,6-dimethyl- (10b), 4,6-dimethyl-2-phenyl- (10d), and 2-isopropyl-4-methoxy-6-methyl- (10e),



Scheme 2

Table 2 Yields, Boiling Points and PMR Spectral Data for 11a-e and 14a-c

Compd. No.	Yield (%)	bp(°C) [mmHg]	PMR($CDCl_3$) δ CH_2	PMR($CDCl_3$) δ other protons
11a	39	50-51[6]	4.59(2H,s)	7.53(1H,d,J=5.5Hz),8.69(1H,d, J=5.5Hz),9.13(1H,s)
11b	52	60-61[2]	4.58(2H,s)	2.56(3H,s),7.38(1H,s) 9.03(1H,s)
11c	73	130[2]	4.65(2H,s)	7.36-7.76(3H,m),7.96(1H,s) 8.03-8.36(2H,m),9.26(1H,s)
11d	75	127[3]	4.60(2H,s)	2.60(3H,s),7.25(1H,s), 7.34-7.66(3H,m),8.30-8.67(2H,m)
11e	33	101-102[23]	4.53(2H,s)	1.30(6H,d,J=7Hz),2.66-3.46(1H,m) 4.03(3H,s),6.73(1H,s)
14a	34	101-103[26]	4.73(2H,s)	7.23(1H,d,J=5Hz), 8.74(2H,d,J=5Hz)
14b	52	144-146[2]	4.80(2H,s)	7.33-7.66(4H,m),7.89-8.36(2H,m) 8.75(1H,d,J=5Hz)
14c	57	69-70[2]	4.61(2H,s)	3.99(3H,s),6.64(1H,d,J=5.5Hz) 8.43(1H,d,J=5.5Hz)

a) mp 49-50.5°C

and 4-methoxy-6-methylpyrimidine 1-oxide (10f) were chlorinated under the standard conditions. Most of the tested compounds, except 10f, were smoothly converted into the corresponding 4-chloromethylpyrimidines (11a,b,d,e), as expected. In the case of 10f, however, the starting material was resinified, and no significant product was isolated.

Similarly, the reaction of 2-methylpyrimidine 1-oxides under the standard conditions gave 2-chloromethylpyrimidines alone. Namely, 2-methyl- (13a), 2-methyl-4-phenyl- (13b), and 4-methoxy-2-methylpyrimidine 1-oxide (13c) reacted with phosphoryl chloride in boiling dioxane to give 2-chloromethyl- (14a), 2-chloromethyl-4-phenyl- (14b), and 2-chloromethyl-4-methoxypyrimidine (14c), in satisfactory yields, respectively. The results obtained by the reaction of 2- and 6-methylpyrimidine 1-oxides are summarized in Table 2 together with the spectral data of the products.

In conclusion, it should be mentioned that the reaction of 2- and 6-methylpyrimidine 1-oxides with phosphoryl chloride provides a method for the preparation of 2- and 6-chloromethylpyrimidines, because these N-oxides, unlike methyl homologs of pyridine, pyrazine, and pyridazine N-oxides, undergo the side chain chlorination selectively.

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Received, 20th January, 1983