Notes

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Studies on Pyrimidine Derivatives. XXXIV.[1] Substituent Effect on the Reaction of 4-Substituted 2,6-Dimethylpyrimidine 1-Oxides with Acetic Anhydride

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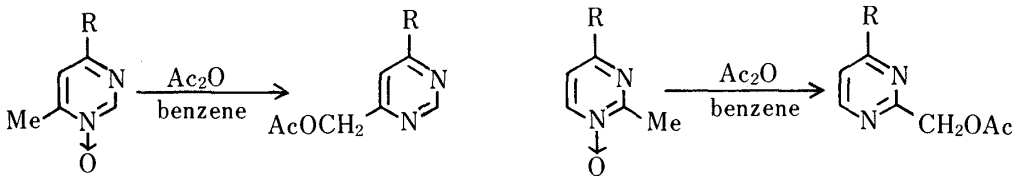
The reaction of 2-methyl- and 4-methylpyrimidine *N*-oxides with acetic anhydride proceeded smoothly in benzene solution to give 2-acetoxymethyl- and 4-acetoxymethylpyrimidines, respectively. The same reaction of 4-methoxy-2,6-dimethylpyrimidine 1-oxide afforded 2-acetoxymethyl-4-methoxy-6-methylpyrimidine as a sole product. Other examples of such site-selective acetoxylation of pyrimidine *N*-oxides are also described.

Keywords——substituent effect; site-selective reaction; acetoxymethylpyrimidine; active methyl group; pyrimidine *N*-oxide

It is well known that the reaction of pyridine *N*-oxides having alkyl substituents at the 2- or 4-position with acetic anhydride generally leads to side-chain acetoxylation.[2] In the case of methylpyrimidine *N*-oxides, however, the reaction of this type has scarcely been investigated except for the work on 4,6-dimethylpyrimidine 1-oxide (**1c**) by McOmie *et al.*[3] They obtained a small amount of a product and proposed its structure to be 4-acetoxymethyl-6-methylpyrimidine (**2c**) on the basis of only the elemental analyses of the product and its picrate. As an extension of our studies on pyrimidine derivatives, the present paper describes the reaction of methylpyrimidine *N*-oxides having one or two active methyl groups at the 2-, 4-, and/or 6-positions.

Firstly, the reaction of monomethylpyrimidine *N*-oxides such as 2-methyl- and 4-methylpyrimidine 1-oxide with acetic anhydride was investigated. Since the reaction of 6-methyl-4-phenylpyrimidine 1-oxide (**1a**) with acetic anhydride alone at 100—120 °C resulted in the formation of a resinous material, **1a** was heated with acetic anhydride in benzene under reflux, and 4-acetoxymethyl-6-phenylpyrimidine (**2a**) was successfully obtained. Similarly, 4-methoxy-6-methylpyrimidine 1-oxide (**1b**) and **1c** reacted with acetic anhydride under the same conditions to afford 4-acetoxymethyl-6-methoxypyrimidine (**2b**) and **2c**, respectively.



1a—c **2a—c** **3a,b** **4a,b**

a: R=Ph, **b**: R=OMe, **c**: R=Me

Chart 1

The structures of these products were easily determined from their proton magnetic resonance (^{1}H-NMR) and infrared (IR) sepctra. In addition, the melting point of the picrate of **2c** coincided with the reported value.[3]

Like the 6-methyl derivatives, 2-methylpyrimidine 1-oxides reacted smoothly with acetic anhydride. Namely, 2-methyl-4-phenyl- (**3a**) and 4-methoxy-2-methylpyrimidine 1-oxide (**3b**) reacted with acetic anhydride in benzene to give 2-acetoxymethyl-4-phenyl- (**4a**) and 2-acetoxymethyl-4-methoxypyrimidine (**4b**), respectively. In the cases of **1a**—**c** and **3a, b**, no by-products due to direct acetoxylation of the pyrimidine ring were isolated, though the yields of the acetoxymethyl compounds were not always satisfactory.

Secondly, the reaction of 4-substituted 2,6-dimethylpyrimidine 1-oxides was investigated in order to examine the site-selectivity of the reaction. When a benzene solution of 2,6-dimethyl-4-methoxypyrimidine 1-oxide (**5b**) and acetic anhydride was heated under reflux, 2-acetoxymethyl-4-methoxy-6-methylpyrimidine (**6b**) was obtained in 74% yield, as a sole product. The structure of the product was unequivocally determined by the alternative synthesis of **6b**, along with the satisfactory spectral data for an acetoxymethyl-methylpyrimidine structure. The authentic **6b** was obtained by the acetylation of 4-methoxy-6-methyl-2-pyrimidinemethanol prepared by the homolytic hydroxymethylation of 4-methoxy-6-methylpyrimidine in the reported manner.[4]

In contrast to the above, the reaction of 2,6-dimethyl-4-phenylpyrimidine 1-oxide (**5a**) under the same conditions gave a mixture of two positional isomers, 4-acetoxymethyl-2-methyl-6-phenyl- (**7a**) and 2-acetoxymethyl-6-methyl-4-phenylpyrimidine (**6a**), in a total yield of 58%. The separation of the mixture into **7a** and **6a** was unsuccessful, but the approximate ratio of **7a** and **6a** was determined to be 1 : 2 with the aid of ^{1}H-NMR spectroscopy. The authentic **7a** and **6a** employed in the ^{1}H-NMR analysis were prepared by the acetylation of the corresponding pyrimidinemethanols.

The reaction of 2,4,6-trimethylpyrimidine 1-oxide (**5c**) with acetic anhydride in benzene also gave a mixture of 4-acetoxymethyl-2,6-dimethyl- (**7c**) and 2-acetoxymethyl-4,6-dimethylpyrimidine (**6c**), of which the latter (**6c**) was shown to be the main product by similar analysis.

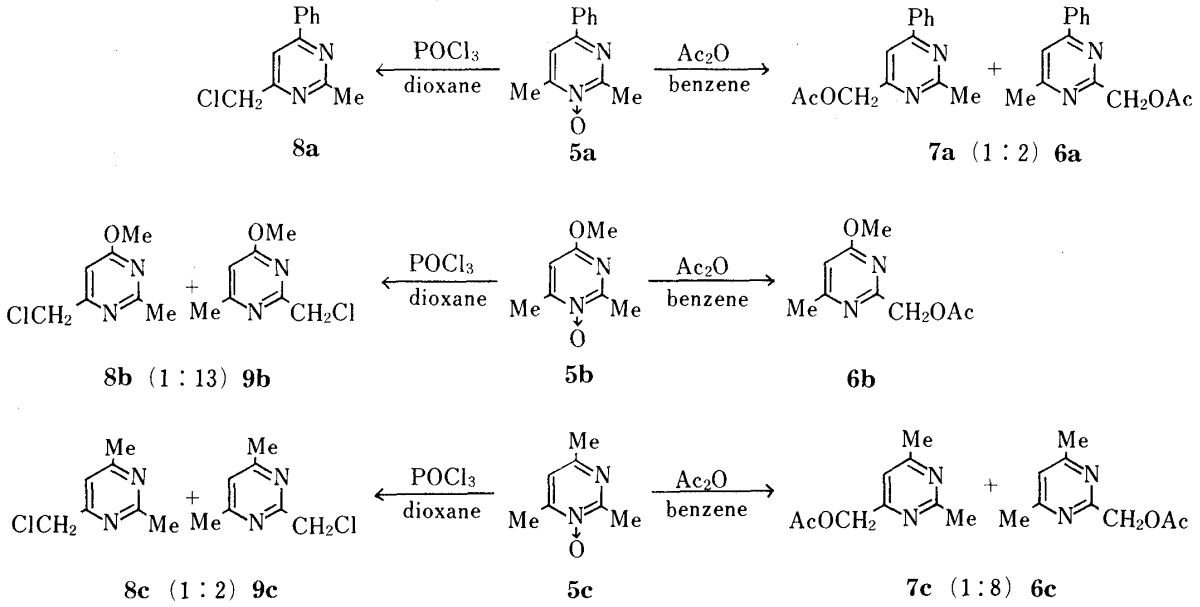


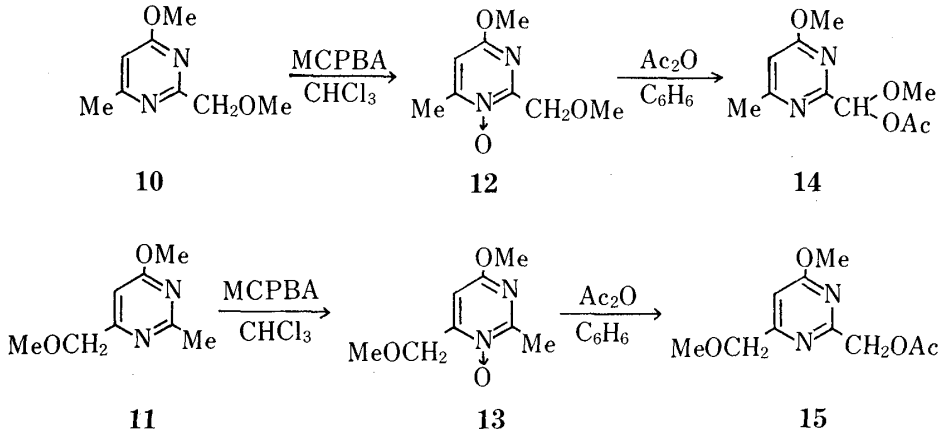
Chart 2

It is of interest to compare the results of the present investigation with those obtained by the reaction of the same substrates with phosphoryl chloride. As reproted in the preceding

paper,[1] the reaction of **5a** with phosphoryl chloride in dioxane gave **8a** exclusively. In contrast, the same reaction of **5b** resulted in the predominant formation of the 2-chloromethyl compound (**9b**). In the case of **5c**, a mixture of the 2-chloromethylpyrimidine (**9c**) and the 4-chloromethylpyrimidine (**8c**) was obtained, in which **9c** was a main product.

On the bases of these findings, it may be concluded that the reaction of methylpyrimidine *N*-oxides with acetic anhydride tends to give the 2-isomers, whereas the chlorination with phosphoryl chloride gave the 4-isomers preferentially, and that the presence of a 4-methoxyl group causes the reaction to give 2-isomers in both reaction. Since the mechanism proposed for the reactions of methylpyridine *N*-oxides with acetic anhydride[5] or with phosphoryl chloride[6] does not account for the site-selectivity of these reactions or explain the role of the 4-methoxyl group, the theoretical explanation of the above findings is now under investigation.

Finally, in order to utilize the effect of the 4-methoxyl group in the synthesis of pyrimidine derivatives, the following experiments were carried out. The *N*-oxidation of 4-methoxy-2-methoxymethyl-6-methyl- (**10**) and 4-methoxy-6-methoxymethyl-2-methylpyrimidine (**11**) with *m*-chloroperbenzoic acid (MCPBA) in chloroform afforded the *N*-oxides (**12** and **13**). The position of the *N*-oxide was proved by ^{1}H-NMR spectroscopy as reported previously.[7] On treatment with acetic anhydride under the same conditions as above, **12** and **13** were respectively transformed into 2-(1-acetoxy-1-methoxymethyl)-4-methoxy-6-methyl- (**14**) and 2-acetoxylmethyl-6-methoxy-4-methoxymethylpyrimidine (**15**), as expected. In both cases, the formation of the corresponding isomers was hardly detected.



10 **12** **14**

11 **13** **15**

Chart 3

Experimental

All melting points and boiling points are uncorrected. IR spectra were measured with a JASCO IRA-1 spectrometer. ^{1}H-NMR spectra were taken at 60 MHz with a JEOL JNM-PMX 60 spectrometer. Chemical shifts are expressed in δ values. The following abbreviations are used: s = singlet, d = doublet, and m = multiplet.

The following pyrimidine *N*-oxides were synthesized according to the literature: 6-methyl-4-phenyl- (**1a**),[8] 4-methoxy-6-methyl- (**1b**),[9] 4,6-dimethyl- (**1c**),[9] 2-methyl-4-phenyl- (**3a**),[10] 4-methoxy-2-methyl- (**3b**),[10] 2,4-dimethyl- (**3c**),[10] 2,6-dimethyl-4-methoxy- (**5b**),[8] 2,6-dimethyl-4-phenyl- (**5a**),[7] and 2,4,6-trimethylpyrimidine 1-oxide (**5c**).[11]

4-Methoxy-2-methoxymethyl-6-methylpyrimidine 1-Oxide (13)——4-Methoxy-2-methoxymethyl-6-methylpyrimidine (**12**) (1.68 g, 10 mmol) was added to a solution of MCPBA (2.07 g, 12 mmol) in $CHCl_3$ (40 ml). The mixture was allowed to stand for 24 h at room temperature and was then washed with 30% K_2CO_3. The crude product from the $CHCl_3$ layer was purified by Al_2O_3 column chromatography using $CHCl_3$ as an eluent. Recrystallization from ether–hexane gave colorless needles, mp 90—90.5 °C. Yield 0.78 g (42%). IR (KBr) cm^{-1}: 1220. ^{1}H-NMR ($CDCl_3$): 2.50 (3H, s), 3.57 (3H, s), 4.00 (3H, s), 4.85 (2H, s), 6.67 (1H, s). *Anal.* Calcd for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.57; N, 15.21. Found: C, 52.00; H, 6.59; N, 15.08.

4-Methoxy-6-methoxymethyl-2-methylpyrimidine 1-Oxide (**16**) was similarly synthesized from 4-methyl-6-

methoxymethyl-2-methylpyrimidine (**15**) (1.41 g, 8.4 mmol) as colorless needles, mp 107—108 °C, which were recrystallized from ether–hexane. Yield 0.79 g (51%). IR (KBr) cm^{-1}: 1230. ^{1}H-NMR ($CDCl_3$): 2.64 (3H, s), 3.51 (3H, s), 3.93 (3H, s), 4.64 (2H, s), 6.80 (1H, s). *Anal.* Calcd for $C_8H_{12}N_2O_3$: 52.16; H, 6.57; N, 15.21. Found: C, 51.95; H, 6.57; N, 15.07.

General Procedure for the Reaction of Methylpyrimidine *N*-Oxides with Acetic Anhydride——A solution of a pyrimidine *N*-oxide (5 mmol) and Ac_2O (25 mmol) in C_6H_6 (10 ml) was refluxed for 2—8 h. After removal of the C_6H_6, the residue was made alkaline with 3 N Na_2CO_3 and extracted with $CHCl_3$. Distillation of the $CHCl_3$ extract under reduced pressure gave a liquid.

4-Acetoxymethyl-6-phenylpyrimidine (**2a**):According to the general procedure, **2a** was obtained from **1a** as a pale yellow liquid, bp 160—164 °C (3 mmHg). Yield 0.54 g (47%).

4-Acetoxymethyl-6-methoxypyrimidine (**2b**): According to the general procedure, **2b** was obtained from **1b** as a colorless liquid, bp 135—138 °C (22 mmHg). Yield 0.3 g (33%).

4-Acetoxymethyl-6-methylpyrimidine (**2c**): According to the general procedure, **2c** was obtained from **1c** as a colorless liquid, bp 125—128 °C (22 mmHg). Lit.[3] bp 100—110 °C (15 mmHg). Yield 0.25 g (30%)

2-Acetoxymethyl-4-phenylpyrimidine (**4a**): According to the general procedure, **4a** was obtained from **3a** as a pale yellow liquid, bp 162—165 °C (2 mmHg). Yield 0.7 g (61%).

2-Acetoxymethyl-4-methoxypyrimidine (**4b**): According to the general procedure, **4b** was obtained from **3b** as a pale yellow liquid, bp 130—132 °C (19 mmHg). Yield 0.5 g (55%).

2-Acetoxymethyl-4-methoxy-6-methylpyrimidine (**6b**): According to the general procedure, **6b** was obtained from **5b** as a colorless liquid, bp 136—137 °C (21 mmHg). Yield 0.73 g (74%).

2-(1-Acetoxy-1-methoxymethyl)-4-methoxy-6-methylpyrimidine (**14**): According to the general procedure, **14** was obtained from **13** as a colorless liquid, bp 123—125 °C (2 mmHg). Yield 0.3 g (83%).

2-Acetoxymethyl-4-methoxy-6-methoxymethylpyrimidine (**17**): According to the general procedure, **17** was obtained from **16** as a colorless liquid, bp 125—128 °C (3 mmHg). Yield 0.37 g (82%).

Acetylation of Pyrimidinemethanols——2-Acetoxymethyl-4-methyl-6-phenylpyrimidine (6a): A mixture of 4-methyl-6-phenyl-2-pyrimidinemethanol (**10a**) (0.75 g, 3.8 mmol), Ac_2O (1.94 g, 19 mmol), and AcONa (0.8 g) was stirred at 80—90 °C for 6 h. The reaction mixture was made alkaline with 3 N Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was distilled under reduced pressure to give a pale yellow liquid, bp 160—170 °C (2 mmHg). Yield 0.56 g (61%).

TABLE I. Spectral and Elemental Analysis Data for Acetoxymethylpyrimidines

Compd. No.	IR ($CHCl_3$) cm^{-1} >C=O	^{1}H-NMR (CCl_4) δ	Formula	Analysis (%) Calcd (Found)		
				C	H	N
2a	1740	2.17 (3H, s), 5.15 (2H, s), 7.2—7.7 (4H, m) 7.9—8.3 (2H, m), 9.11 (1H, s)	$C_{13}H_{12}N_2O_2$	68.41 (68.46	5.30 5.58	12.27 12.64)
2b	1740	2.22 (3H, s), 4.01 (3H, s), 5.13 (2H, s) 6.76 (1H, s), 8.76 (1H, s)	$C_8H_{10}N_2O_3$	52.74 (52.81	5.53 5.59	15.38 15.56)
4a	1740	2.16 (3H, s), 5.24 (2H, s), 7.2—7.6 (4H, m) 7.8—8.2 (2H, m), 8.57 (1H, d, J=5 Hz)	$C_{13}H_{12}N_2O_2$	68.41 (68.59	5.30 5.38	12.27 12.42)
4b	1750	2.12 (3H, s), 3.93 (3H, s), 5.07 (2H, s) 6.53 (1H, d, J=6 Hz), 8.30 (1H, d, J=6 Hz)	$C_8H_{10}N_2O_3$	52.74 (52.89	5.53 5.72	15.38 15.71)
6a	1740	2.26 (3H, s), 2.61 (3H, s), 5.17 (2H, s) 7.1—7.6 (4H, m), 7.7—8.2 (2H, m)	$C_{14}H_{14}N_2O_2$	69.40 (69.52	5.83 5.91	11.56 11.33)
6b	1750	2.10 (3H, s), 2.37 (3H, s), 3.85 (3H, s) 4.97 (2H, s), 6.29 (1H, s)	$C_9H_{12}N_2O_3$	55.09 (55.32	6.17 6.12	14.28 14.15)
6c	1740	2.10 (3H, s), 2.38 (6H, s), 5.06 (2H, s) 6.81 (1H, s)	$C_9H_{12}N_2O_2$	59.98 (59.64	6.71 6.88	15.55 15.48)
7a	1740	2.16 (3H, s), 2.70 (3H, s), 5.10 (2H, s) 7.1—7.6 (4H, m), 7.7—8.2 (2H, m)	$C_{14}H_{14}N_2O_2$	69.40 (69.09	5.83 5.74	11.56 11.65)
7c	1740	2.12 (3H, s), 2.41 (3H, s), 2.56 (3H, s) 4.93 (2H, s), 6.77 (1H, s)	$C_9H_{12}N_2O_2$	59.98 (59.56	6.71 6.89	15.55 15.70)
14	1750	2.06 (3H, s), 2.36 (3H, s), 3.47 (3H, s) 3.90 (3H, s), 6.24 (1H, s), 6.36 (1H, s)	$C_{10}H_{14}N_2O_4$	53.09 (53.49	6.24 6.28	12.38 12.42)
17	1750	2.09 (3H, s), 3.42 (3H, s), 3.92 (3H, s) 4.36 (2H, s), 5.01 (2H, s), 6.62 (1H, s)	$C_{10}H_{14}N_2O_4$	53.09 (53.27	6.24 6.30	12.38 12.38)

2-Acetoxymethyl-4-methoxy-6-methylpyrimidine (**6b**) was similarly synthesized from 4-methoxy-6-methyl-2-pyrimidinemethanol (**10b**) (1.55 g, 10 mmol) as a colorless liquid, bp 162—163 °C (48 mmHg). Yield 1.46 g (74%).

2-Acetoxymethyl-4,6-dimethylpyrimidine (**6c**) was similarly synthesized from 4,6-dimethyl-2-pyrimidinemethanol (**10c**) (0.35 g, 2.5 mmol) as a colorless liquid, bp 136—137 °C (20 mmHg). Yield 0.42 g (93%).

4-Acetoxymethyl-2-methyl-6-phenylpyrimidine (**7a**) was similarly synthesized from 2-methyl-4-phenyl-6-pyrimidinemethanol (**11a**) (1.7 g, 8.5 mmol) as a pale yellow liquid, bp 164—166 °C (2 mmHg). Yield 1.3 g (63%).

4-Acetoxymethyl-2,6-dimethylpyrimidine (**7c**) was similarly synthesized from 2,4-dimethyl-6-pyrimidinemethanol (**11c**) (0.17 g, 1.2 mmol) as a pale yellow liquid, bp 134—137 °C (26 mmHg). Yield 0.19 g (88%).

References and Notes

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