

STUDIES ON PYRIMIDINE DERIVATIVES. XXXI.<sup>1</sup>

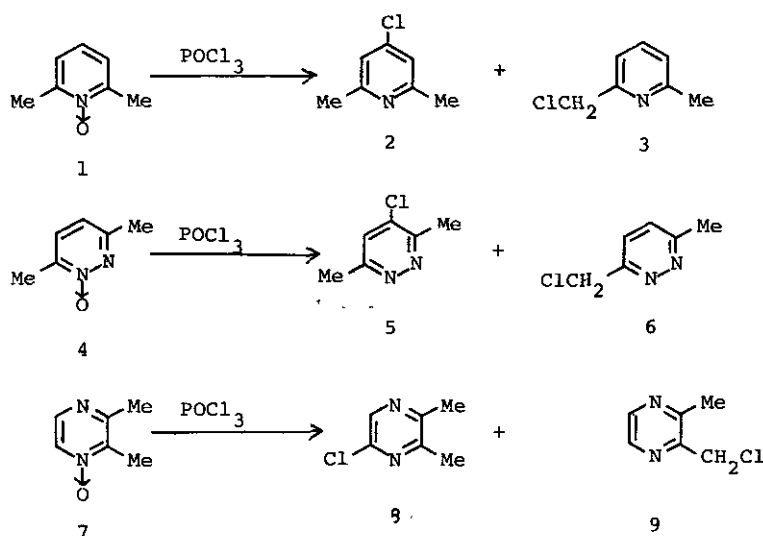
## SYNTHESIS OF CHLOROMETHYLPYRIMIDINES BY REACTION OF MONOMETHYLPYRIMIDINE N-OXIDES WITH PHOSPHORYL CHLORIDE

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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<sup>2</sup> 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,<sup>3,4</sup> phenanthridine,<sup>5</sup> pyrazine,<sup>6</sup> and pyridazine N-oxides.<sup>7</sup> 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.<sup>7</sup> reported that 3,6-dimethylpyridazine 1-oxide (4) was transformed into 4-chloro-3,6-dimethylpyridazine (5) and 3-chloromethyl-6-methylpyridazine (6) as a 1:1 mixture, by treatment of 4 with phosphoryl chloride. Recently, Ohta et al.<sup>6c</sup> 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,<sup>8</sup> 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.<sup>9</sup> 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

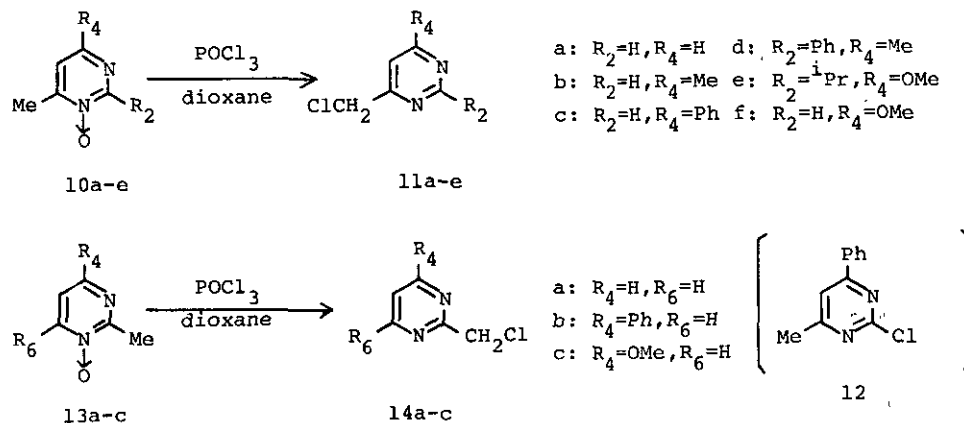
Table 1 4-Chloromethyl-6-phenylpyrimidine (11c) from 6-Methyl-4-phenylpyrimidine 1-Oxide (10c) and Acyl Halides

| Run | Acyl halide                     | Molar ratio | Solvent                       | Reaction conditions |            | Yields of llc (%)    |
|-----|---------------------------------|-------------|-------------------------------|---------------------|------------|----------------------|
|     |                                 |             |                               | time (h)            | temp. (°C) |                      |
| 1   | POCl <sub>3</sub>               | 10          | —                             | 0.5                 | 100        | 54                   |
| 2   | POCl <sub>3</sub>               | 10          | C <sub>6</sub> H <sub>6</sub> | 0.5                 | reflux     | 58                   |
| 3   | POCl <sub>3</sub>               | 3           | dioxane                       | 0.5                 | reflux     | 73                   |
| 4   | POCl <sub>3</sub>               | 1           | dioxane                       | 0.5                 | reflux     | 37                   |
| 5   | PhSO <sub>2</sub> Cl            | 3           | dioxane                       | 0.5                 | reflux     | 26                   |
| 6   | SO <sub>2</sub> Cl <sub>2</sub> | 3           | dioxane                       | 1                   | reflux     | 0 [10] <sup>a)</sup> |
| 7   | PhCOCl                          | 3           | dioxane                       | 1                   | reflux     | 3                    |
| 8   | MeCOCl                          | 3           | dioxane                       | 1                   | reflux     | 0 [40] <sup>a)</sup> |

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 <sub>3</sub> ) $\delta$ |  |
|------------|-----------|---------------|----------------------------------|--|
|            |           |               | CH <sub>2</sub>                  | 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)                                 |
| 11c        | 73        | 130 [2]       | 4.65 (2H, s)                     | 9.03 (1H, s)   |
| 11d        | 75        | 127 [3]       | 4.60 (2H, s)                     | 7.36-7.76 (3H, m), 7.96 (1H, s)                            |
| 11e        | 33        | 101-102 [23]  | 4.53 (2H, s)                     | 8.03-8.36 (2H, m), 9.26 (1H, s)                            |
| 14a        | 34        | 101-103 [26]  | 4.73 (2H, s)                     | 2.60 (3H, s), 7.25 (1H, s)                                 |
| 14b        | 52        | 144-146 [2]   | 4.80 (2H, s)                     | 7.34-7.66 (3H, m), 8.30-8.67 (2H, m)                       |
| 14c        | 57        | 69-70 [2]     | 4.61 (2H, s)                     | 1.30 (6H, d, J=7Hz), 2.66-3.46 (1H, m)                     |
|            |           |               |                                  | 4.03 (3H, s), 6.73 (1H, s)                                 |
|            |           |               |                                  | 7.23 (1H, d, J=5Hz), 8.74 (2H, d, J=5Hz)                   |
|            |           |               |                                  | 7.33-7.66 (4H, m), 7.89-8.36 (2H, m)                       |
|            |           |               |                                  | 8.75 (1H, d, J=5Hz)  |
|            |           |               |                                  | 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.

#### REFERENCES AND NOTES

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