

SYNTHESIS OF 2-ACYLMETHYLPYRIMIDINES FROM  
2-CHLORO-4,6-DIMETHYLPYRIMIDINE

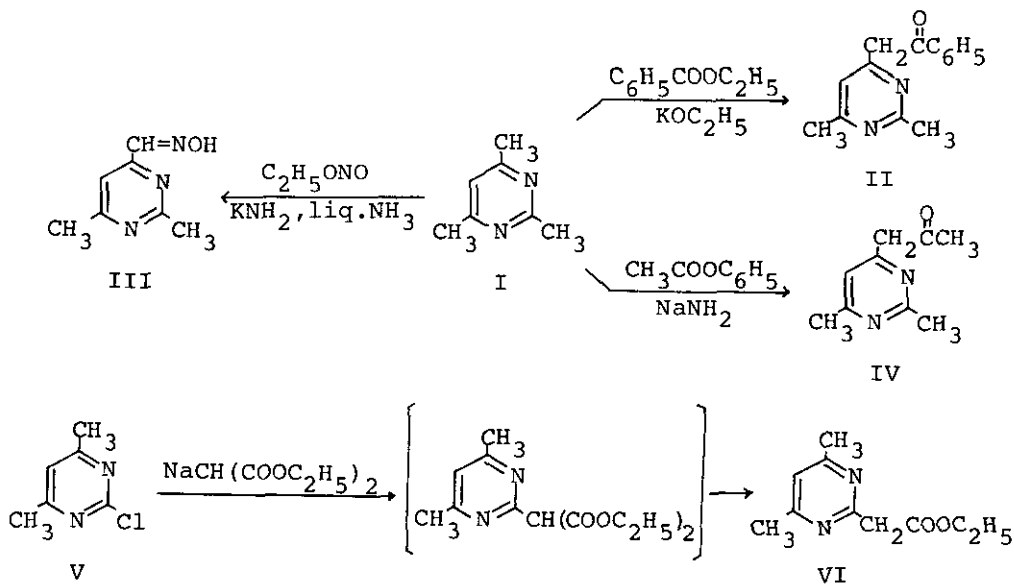
Settsuko Niitsuma, Takao Sakamoto, and Hiroshi Yamanaka\*  
Pharmaceutical Institute, Tohoku University  
Aobayama, Sendai 980, Japan

The substitution of 2-chloro-4,6-dimethylpyrimidine with dimethylsulfoxonium methylide gave rise to dimethylsulfoxonium 4,6-dimethyl-2-pyrimidinylmethylide. The pyrimidinyl-sulfur ylide was acylated with acetic anhydride, benzoyl chloride, and ethoxycarbonyl chloride to afford the respective monoacyl derivatives, which were desulfurized to 2-acetyl-, 2-phenacyl-, and 2-ethoxycarbonylmethyl-4,6-dimethylpyrimidines in good yields.

As reported previously, the selective acylation of the 2-methyl group on a pyrimidine ring under the conditions corresponding to the Claisen ester condensation is rather difficult, when another methyl group is present at the 4-(or 6-)positions of the same molecule. For instance, ethyl benzoate or ethyl nitrite reacted with 2,4,6-trimethylpyrimidine (I) in the presence of potassium ethoxide or potassium amide giving selectively 2,6-dimethyl-4-phenacylpyrimidine (II) or 2,6-dimethyl-4-pyrimidine-

aldoxime (III).<sup>1,2)</sup> Phenyl acetate has also been reported<sup>3)</sup> to react with I under basic conditions to give 4-acetyl-2,6-dimethylpyrimidine (IV).

Concerning the preparation of such pyrimidine derivatives, the reaction of chloropyrimidines with active methylene compounds are known to give a mixture of two or three products.<sup>4)</sup> The best result was obtained on the reaction of 2-chloro-4,6-dimethylpyrimidine (V) with sodium diethyl malonate to afford ethyl 4,6-dimethyl-2-pyrimidineacetate (VI) as a sole product in 20 % yield.<sup>5)</sup>



From the points of view, we wish to report herein the synthesis of the pyrimidine derivatives containing a 2-acylmethyl group, by means of the acylation of dimethylsulfoxonium 4,6-dimethyl-2-pyrimidinylmethylenide (IX) and the subsequent desulfurization of the resulting acyl-ylides.

When dimethylsulfoxonium methylide (VIII)<sup>6)</sup> generated from trimethylsulfoxonium chloride (VII), was heated with V in tetrahydrofuran, the pyrimidinyl-sulfur ylide (IX), mp 101.5-103°,  $C_9H_{14}N_2OS$ , was obtained in 70 % yield. As shown below, spectral data of IX are consistent with its methylide structure [IR(CHCl<sub>3</sub>,  $cm^{-1}$ ): 1575, 1585; NMR(CDCl<sub>3</sub>, ppm): 2.24 (6H, s), 3.47 (6H, s), 4.34 (1H, broad s), 6.29 (1H, s)]. This compound (IX) was readily acylated by treatment with acetic anhydride, benzoyl chloride, and ethoxycarbonyl chloride in dioxane at room temperature giving the corresponding acetyl (Xa), mp 131-132.5°,  $C_{11}H_{16}N_2O_2S$ , 73 %; benzoyl (Xb), mp 167-170°,  $C_{16}H_{18}N_2O_2S$ , 80 %; and ethoxycarbonyl derivative (Xc), mp 90-91°,  $C_{12}H_{18}N_2O_3S$ , 82 %, respectively. The spectral data of these products are as follows.

Xa [IR(CHCl<sub>3</sub>,  $cm^{-1}$ ): 1600, 1550; NMR(CDCl<sub>3</sub>, ppm): 2.30 (3H, s), 2.44 (6H, s), 3.66 (6H, s), 6.75 (1H, s)]

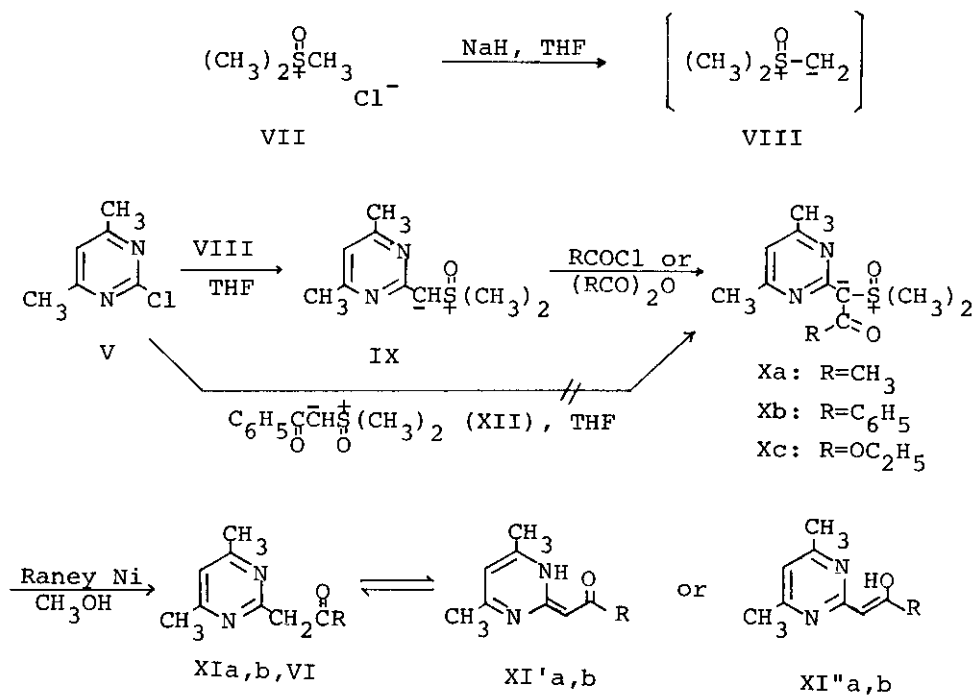
Xb [IR(CHCl<sub>3</sub>,  $cm^{-1}$ ): 1600, 1535; NMR(CDCl<sub>3</sub>, ppm): 2.21 (6H, s), 3.76 (6H, s), 6.62 (1H, s), 7.00-7.40 (5H, m)]

Xc [IR(CHCl<sub>3</sub>,  $cm^{-1}$ ): 1645, 1600; NMR(CDCl<sub>3</sub>, ppm): 1.25 (3H, t, J=7.0 Hz), 2.41 (6H, s), 3.65 (6H, s), 4.19 (2H, q, J=7.0 Hz), 6.70 (1H, s)]

In order to devise the alternative synthesis of Xb, V was treated with dimethylsulfoxonium benzoylmethylide (XII) in boiling tetrahydrofuran, however, the reaction failed to give Xb or any other product.

Desulfurization of Xa using Raney nickel in boiling methanol for 2 minutes gave rise to 2-acetonyl-4,6-dimethylpyrimidine (XIa) as yellow liquid, bp 95° (4 mmHg),  $C_9H_{12}N_2O$ , in 68 % yield. The

prolonged desulfurization probably caused the reduction of the carbonyl group on the side chain, so that the purification of XIa became difficult. In a chloroform solution of XIa, the existence of an imine-enamine tautomerism was observed. Based on the spectral data [IR(CHCl<sub>3</sub>, cm<sup>-1</sup>): 1735, 1655; NMR(CDCl<sub>3</sub>, ppm): 2.09 (0.9H, s), 2.29 (2.1H, s), 2.47 (6H, s), 4.08 (1.4H, s), 5.59 (0.3H, s), 6.77 (0.3H, s), 7.02 (0.7H, s), 13.30-14.00 (0.3H, broad)], the content of the imine-form (XIa) in this tautomerism was roughly estimated at 70 %, however, the enamine-form (XI'a) was not distinguished from another possible tautomer (XI''a).



Similarly, desulfurization of Xb,c under the same conditions afforded 4,6-dimethyl-2-phenacylpyrimidine (XIb), mp 76-77°, 46 % and VI, mp 62-66°, 71 %, whose melting points coincided with those appeared in the literature.<sup>7,5a)</sup>

Based on the above results, the replacement of active chlorine substituents with VIII seems to have wide applicability for the synthesis of both 2- and 4-acylmethylpyrimidines, because the reactivity of 4-chloropyrimidines are recognized to resemble with that of 2-isomers.

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- b) The pyrimidine (VI) was not obtained by the Pinner reaction of which synthetic utility is well known. According to our experiment, the condensation of ethoxycarbonylacetamide with acetylacetone resulted in the formation of ethyl 2-amino-4,6-dimethyl-3-pyridinecarboxylate, instead of the pyrimidine (VI).
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