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

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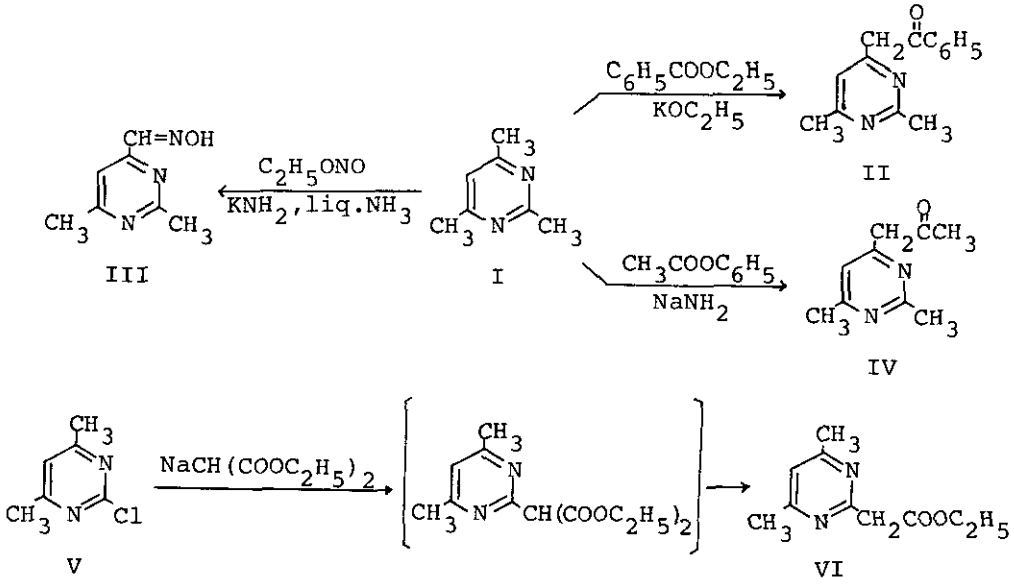
The substitution of 2-chloro-4,6-dimethylpyrimidine with dimethylsulfoxonium methylide gave rise to dimethylsulfoxonium 4,6-dimethyl-2-pyrimidinylmethylide. The pyrimidinyl-sulfur ylide was acylated with acetic anhydride, benzoyl chloride, and ethoxycarbonyl chloride to afford the respective monoacyl derivatives, which were desulfurized to 2-acetonyl-, 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).[1,2] Phenyl acetate has also been reported[3] to react with I under basic conditions to give 4-acetonyl-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.[4] 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.[5]



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-pyrimidinylmethylide (IX) and the subsequent desulfurization of the resulting acyl-ylides.

When dimethylsulfoxonium methylide (VIII)[6] 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($CHCl_3$, cm^{-1}): 1575, 1585; NMR($CDCl_3$, 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($CHCl_3$, cm^{-1}): 1600, 1550; NMR($CDCl_3$, ppm): 2.30 (3H, s), 2.44 (6H, s), 3.66 (6H, s), 6.75 (1H, s)]

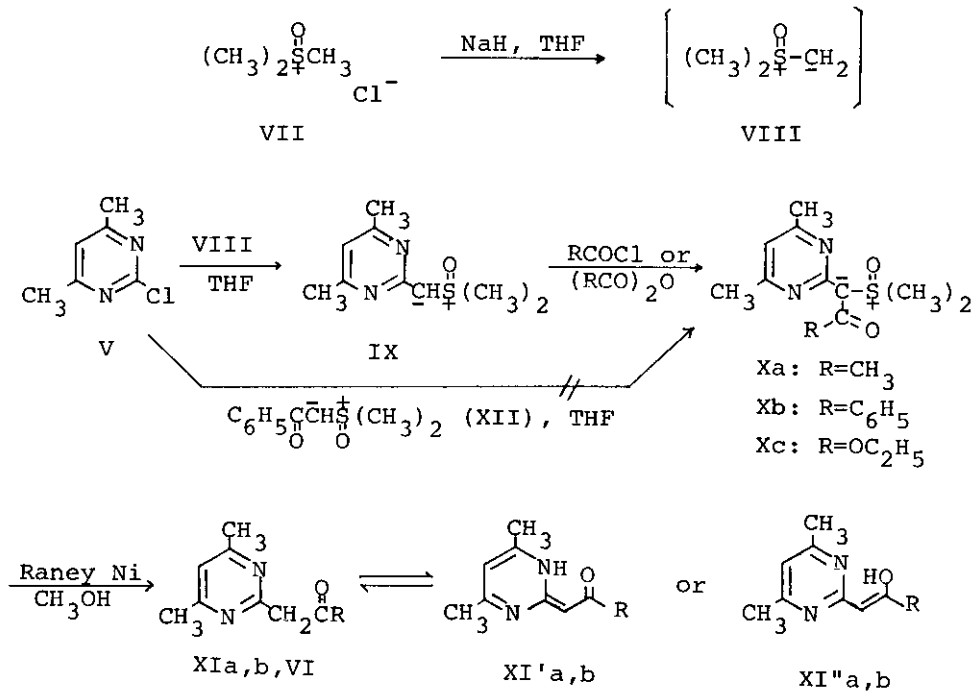
Xb [IR($CHCl_3$, cm^{-1}): 1600, 1535; NMR($CDCl_3$, ppm): 2.21 (6H, s), 3.76 (6H, s), 6.62 (1H, s), 7.00-7.40 (5H, m)]

Xc [IR($CHCl_3$, cm^{-1}): 1645, 1600; NMR($CDCl_3$, 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 device 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($CHCl_3$, cm^{-1}): 1735, 1655; NMR($CDCl_3$, 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.[7,5a)]

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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