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57. Hiroshi Yamanaka : Studies on the Synthesis of 4-Methoxypyrimidine 1-Oxide and its Reissert Reaction.

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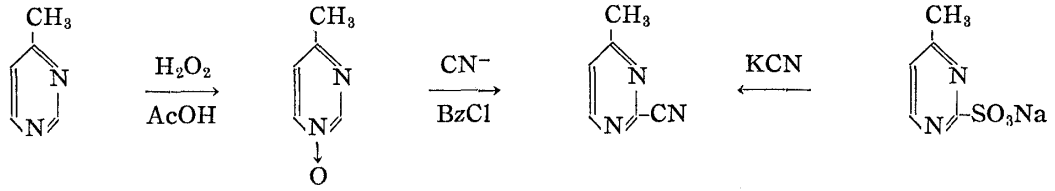
Some time ago, Ochiai and Yamanaka[1] reported that the Reissert reaction of 4-methylpyrimidine 1-oxide afforded 4-methylpyrimidine-2-carbonitrile. However, a large portion of the product became resinous and the yield was so small that it was impossible to conclude from this result alone that the activity of the 2-position in this N-oxide compound is greater than that of the 6-position.

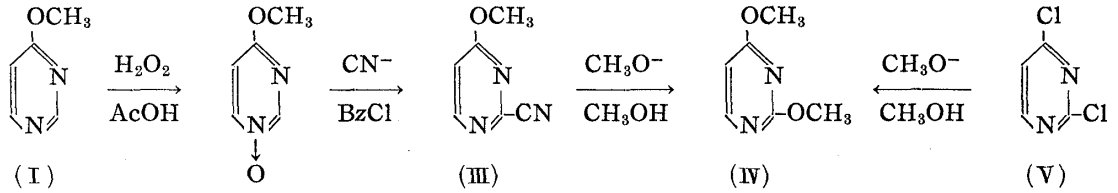


In order to clarify this point, the same reaction was carried out in the present series of work with 4-methoxypyrimidine 1-oxide (II) and 4-methoxypyrimidine-2-carbonitrile (III) was obtained in a good yield. In this reaction, there was no evidence for the formation of 6-carbonitrile and it became clear that there is a difference in activity between 2- and 6-positions of pyrimidine 1-oxide.

Oxidation of 4-methoxypyrimidine (I) in a usual manner with 30% hydrogen peroxide in glacial acetic acid at 60~65° gives 4-methoxypyrimidine 1-oxide (II) in 29% yield, which is far below the yield of 70% in the case of formation of 4-methoxy-6-methylpyrimidine 1-oxide. The reason for this low yield might be the oxidative ring cleavage of (I) at the vacant 6-position and in fact, ammonia odor is detected when the reaction mixture is basified. However, no detailed examination has been made on this point.

Treatment of (II), dissolved in water with excess of potassium cyanide, with calculated amount of benzoyl chloride affords a substance of m.p. 53° in a good yield (76%) and its analytical values agree with those calculated for 4-methoxypyrimidine-monocarbonitrile. Detailed examination of the reaction system failed to reveal the presence of a corresponding isomer.

The cyano group in 2- and 4-positions of pyrimidine ring is found to be substituted with an alkoxyl group when treated with the corresponding sodium alkoxide in alcohol.[2] This process was followed and the carbonitrile obtained as above was refluxed with sodium methoxide in methanol. Purification of the product by distillation afforded a basic liquid whose picrate, m.p. 129~130°, was found to be identical with the picrate, m.p. 129~130°, of 2,4-dimethoxypyrimidine (IV) prepared by another route. It follows, therefore, that the carbonitrile of m.p. 53° is 4-methoxypyrimidine-2-carbonitrile (III).



(I) (II) (III) (IV) (V)

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1) E. Ochiai, H. Yamanaka : This Bulletin, **3**, 175(1955).
2) H. Yamanaka : Unpublished data.

As for the synthesis of (I) used as the starting material in this reaction, following facts are known from existing literature.

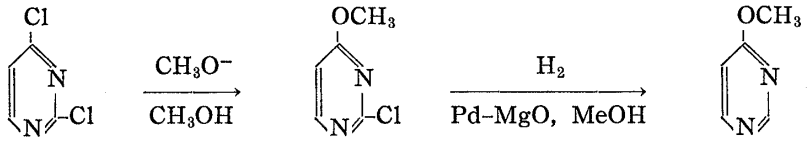
(1) Derivation of (I) from 4-chloropyrimidine, obtained by treatment of 4-pyrimidinol with phosphoryl chloride, is unsuitable as a method of preparation because of the poor yield of 4-chloropyrimidine and its instability, making it impossible to preserve this compound for any length of period.[3]

(2) If, in the above process, 4-chloropyrimidine is not isolated but methanol added directly to the reaction solution to obtain (I), the yield is still not satisfactory.[4]

(3) Direct methylation of 4-pyrimidinol with diazomethane affords only a small amount of (I) and majority of the product in this case is 3-methyl-4-pyrimidone.[5]

Under these circumstances, a simple method for laboratory preparation of (I) was felt necessary and the problem seemed near solution by the process to be described below.

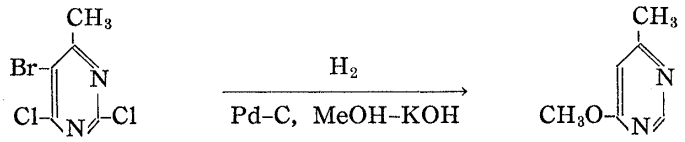
A calculated amount of sodium methoxide was added cautiously and dropwise into 2,4-dichloropyrimidine (V) by which the chlorine in 4-position alone underwent substitution to form 2-chloro-4-methoxypyrimidine (VI) in a good yield. Catalytic reduction of (IV) in methanol over palladium catalyst, with heavy magnesium oxide as a carrier, resulted in a very rapid absorption of 1 mole of hydrogen and (I) was obtained, also in a good yield.



(V) (VI) (I)

Throughout the course of this route, yield from each reaction is good and intermediates are not labile, so that the procedures are generally easy.

The halogens in 2- and 4-positions of pyrimidine ring are known to be extremely active towards anionoid substitution but the result of present series of experiments has indicated that the activity of halogen in 4-position is somewhat greater than that in 2-position. The data reported by Yanai[6] on catalytic reduction of 2,6-dichloro-3-bromo-



4-methylpyrimidine are also evidence of this fact. However, treatment of (V) according to this process results in complicated reactions and pure (I) cannot be obtained easily, producing 2,4-dimethoxypyrimidine (IV) and other by-products.

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Experimental

Reaction of 2,4-Dichloropyrimidine (V) with Sodium Methoxide; Preparation of 2-Chloro-4-methylpyrimidine—A solution of MeONa, prepared by dissolving 0.85 g. of metallic Na in 50 cc. of MeOH, was added dropwise into a solution of 5.5 g. of (V) dissolved in 60 cc. of MeOH, maintaining

3) M. P. V. Boarland, J. F. W. McOmie: J. Chem. Soc., **1951**, 1218.
4) D. J. Brown, L. N. Short: *Ibid.*, **1953**, 331.
5) D. J. Erown, *et al.*: *Ibid.*, **1955**, 211.
6) M. Yanai: Yakugaku Zasshi, **62**, 329(1942).

the temperature of the solution at 40~50° and with occasional shaking. The crystals of NaCl began to precipitate out gradually. On completion of the addition, MeOH was distilled off under a reduced pressure, 15 cc. of water was added to the residue, and this was extracted several times with Et_2O. The extract was dried over anhyd. Na_2SO_4 and Et_2O evaporated, leaving 5 g. of colorless oil. The oil underwent crystallization on being chilled in ice and recrystallization from petr. ether (b.p. 60~80°) afforded 4.1 g.(77%) of prisms, m.p. 55°.

Catalytic Reduction of 2-Chloro-4-methoxypyrimidine (VI); Preparation of 4-Methoxypyrimidine (I)—A Pd-MgO catalyst, prepared from 15 cc. of 1% $PdCl_2$ solution and 6 g. of heavy MgO, was added to a solution of 10 g. of (VI) dissolved in 50 cc. of MeOH and this was submitted to hydrogenation at ordinary temperature and pressure. When 1 mole of H_2 had been absorbed, the catalyst was filtered off and MeOH was distilled off at atmospheric pressure. When the temperature of the distillate reached 75°, distillation was stopped, 10 cc. of water was added to the residue, and the solution was extracted thoroughly with Et_2O. Et_2O extract was dried over anhyd. K_2CO_3, Et_2O was evaporated, and the residual liquid was distilled to collect a fraction of b.p. 120~160°. This fraction was redistilled to give 5.5 g.(72%) of a liquid of b.p. 152~154°. Picrate : m.p. 123~124°(from MeOH), identical with the picrate[4] of 4-methoxypyrimidine. The picrate of 2-methoxypyrimidine melts at 105~106°.

N-Oxidation of 4-Methoxypyrimidine (I)—To a solution of 3 g. of (I) dissolved in 10 cc. of glacial AcOH, 5 cc. of 34% H_2O_2 was added and the solution was warmed on a water bath at 60~65° for 7 hr. AcOH was distilled off under a reduced pressure, the residue was basified with an excess of 20% K_2CO_3 solution, and extracted thoroughly with $CHCl_3$ (marked odor of NH_3 was detected at this stage). $CHCl_3$ layer was dried over anhyd. K_2CO_3 and the solvent was evaporated, leaving 1.5 g. of white prisms. The cyrstals were dissolved in a small amount of $CHCl_3$ and passed through a short column of alumina to remove impurities. Recrystallization of the product so obtained afforded 1.0 g.(29%) of (II), m.p. 132~134°. Picrate : Pale yellow, long needles, m.p. 148~149°.

Reissert Reaction of 4-Methoxypyrimidine 1-Oxide (II); Formation of 4-Methoxypyrimidine-2-carbonitrile (III)—To a solution of 0.8 g. of (II) and 0.7 g. of KCN dissolved in 5 cc. of water, cooled in water, 0.9 g. of BzCl was added dropwise with vigorous stirring. An orange oil began to separate out as the reaction progressed and the oil gradually solidified as the stirring was continued. The reaction mixture was allowed to stand over night, the whole mixture was transferred to a separatory funnel, and extracted with benzene. The benzene layer was washed with 10% NaOH solution and water to remove acid substances, dried over anhyd. K_2CO_3, and passed through a short column of alumina. Benzene was evaporated from the effluent and the colorless oily residue crystallized on being stimulated. Recrystallization from petr. ether (b.p. 60~80°) afforded 0.66 g. of (III), m.p. 53°. *Anal.* Calcd. for $C_6H_5ON_3$ (4-Methoxypyrimidine-2-carbonitrile): C, 53.33; H, 3.73; N, 31.10. Found: C, 53.58; H, 3.83; N, 30.67.

Reaction of 4-Methoxypyrimidine-2-carbonitrile (III) with Sodium Methoxide—A solution of 0.1 g. of metallic Na dissolved in 10 cc. of MeOH was added to a solution of 0.2 g. of (III) dissolved in 5 cc. of MeOH and the solution was refluxed on a water bath for 1 hr. MeOH was evaporated under a reduced pressure, water was added to the residue, and the oily substance that precipitated out was extracted with Et_2O. After drying over anhyd. K_2CO_3, Et_2O was evaporated and 0.15 g. of the oily residue was distilled under a reduced pressure to collect a fraction of $b.p_{20}$ 100~110°(bath temp.). The picrate prepared from this oil melted at 129~130°, alone and in admixture with the picrate, m.p. 129~130°, of 2,4-dimethoxypyrimidine (IV) prepared from (V).

Preparation of Palladium Catalyst on Magnesium Oxide Carrier—A mixture of 6.0 g. of heavy MgO, 15 cc. of 1% $PdCl_2$, and 20 cc. of water is shaken in H_2 stream by which the orange mixture will turn gradually black. The catalyst is collected by filtration and washed consecutively with water and methanol, avoiding contact with air. The catalyst is used immediately after preparation.

Summary

4-Methoxypyrimidine 1-oxide was prepared and its Reissert reaction afforded 4-methoxypyrimidine-2-carbonitrile, which was derived to 2,4-dimethoxypyrimidine to confirm the structure. At the same time, difference in the nucleophilic activity of the 2- and 4-positions in pyrimidine 1-oxide was clarified. During the course of this work, a simple process for the preparation of 4-methoxypyrimidine was established.

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