1,3-DIPOLAR CYCLOADDITION OF 4-ALKOXY-6-METHYLPYRIMIDINE N-OXIDES

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While 1,3-dipolar cycloaddition of 4-ethoxy-6-methylpyrimidine N-oxide (Ia) with phenyl isocyanate gave the expected product, 2-anilino-4-ethoxy-6-methylpyrimidine (II), the reaction of Ia with phenyl isothiocyanate afforded 3-phenyl-7-methyl-2,3-dihydrooxazolo[4,5-d]pyrimidine-2-thione (IV).

The reaction of 4-alkoxy-6-methylpyrimidine N-oxides (I) with dimethyl acetylenedicarboxylate afforded methyl 4-alkoxy-6-methyl-2-pyrimidineacetates (IX).

Many investigations have been published on the 1,3-dipolar cycloaddition between pyridine or quinoline N-oxides and some dipolarophiles. Usually this type of reaction gave the products containing substituents at the 2-position of a pyridine ring, accompanied by deoxygenation of N-oxide function. For instance, Huisgen et al.[1] reported the reaction of pyridine 1-oxide with phenyl isocyanate to afford 2-anilinopyridine, and Hamana et al.[2]

described the formation of methyl α-formyl-2-quinolineacetate by means of the reaction of quinoline 1-oxide with methyl propiolate.

On the other hand, we have reported the reaction of pyrimidine N-oxides with morpholine enamines introducing a carbon substituent to the 2-position of a pyrimidine ring.[3] Thus, the interest of our laboratory was focussed on the 1,3-dipolar cycloaddition of pyrimidine N-oxides. In this communication we wish to report these results.

At first, the reaction of 4-ethoxy-6-methylpyrimidine N-oxide (Ia) with phenyl isocyanate was carried out. A mixture of Ia and phenyl isocyanate was heated at 95-105° for 5 hr to give 1,3-diphenyl-1-(4-ethoxy-6-methyl-2-pyrimidinyl)urea (III), mp 114.5-115° (40%), along with 2-anilino-4-ethoxy-6-methylpyrimidine (II), mp 70-71° (12%). The separation of II and III was achieved by alumina column chromatography using benzene as an eluant.

Compound II was identical in every respect with the authentic specimen prepared by the reaction of 2-anilino-4-chloro-6-methylpyrimidine[4] with sodium ethoxide.

The infrared (IR) spectrum (KBr) of III exhibits no band due to the N-oxide group in the range of 1200-1300 cm^{-1} and a carbonyl band at 1700 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum[5] of III indicates the presence of two phenyl groups at 7.00-7.80 (10H, m), a pyrimidine ring proton at 6.16 (1H, s), and an amide proton at 13.00-14.30 (1H, broad). Furthermore, the treatment of II with phenyl isocyanate gave III in 60% yield. Based on these data, the structure of III has been assigned 1,3-diphenyl-1-(4-ethoxy-6-methyl-2-pyrimidinyl)urea.

On the contrary, the treatment of Ia in $CHCl_3$ with phenyl isothiocyanate at room temperature for 45 hr gave an unexpected product (IV), mp 145.5-147°, instead of the 2-thioureido derivative. The structure of IV was elucidated as follows:

The empirical formula ($C_{12}H_9N_3OS$) was established by elemental analysis and by mass spectrometry (M^+= 243). The IR spectrum ($CHCl_3$) of IV shows bands at 1650 and 1120 cm^{-1} due to the C=N double bond and the thiocarbonyl group, respectively. The NMR spectrum of IV shows a signal at 8.68 (1H, s) which could be assignable to that of a proton located at the 5-position of the ring. On hydrolysis with KOH in EtOH, IV was transformed into 4-anilino-5-hydroxy-6-methylpyrimidine (V), mp 238-239° (decomp.).

According to the method reported by Bray,[6] 4-anilino-5-

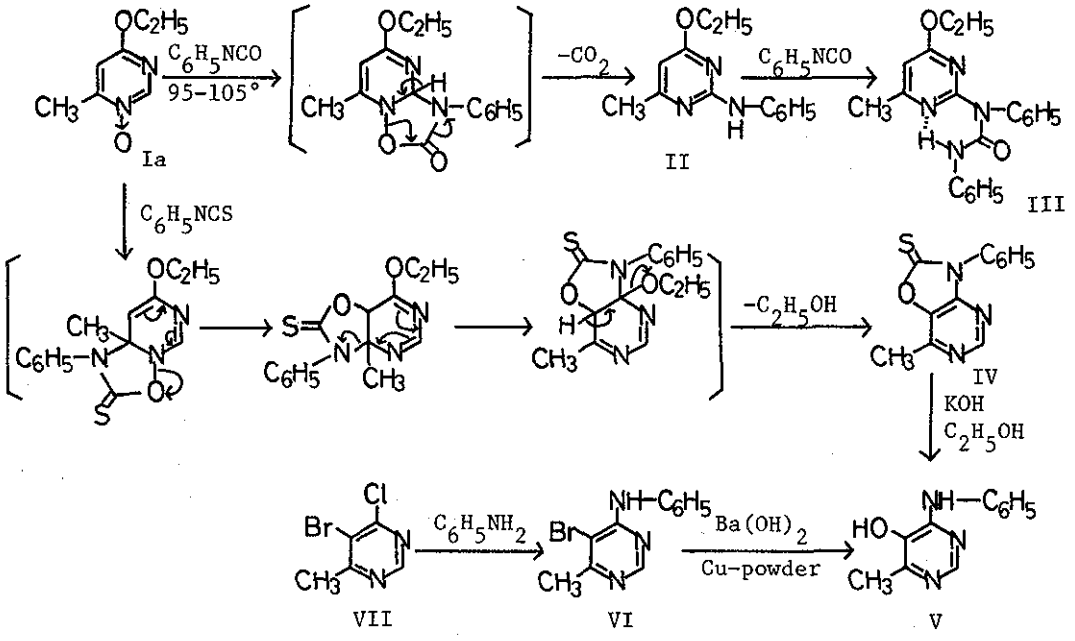


Chart 1

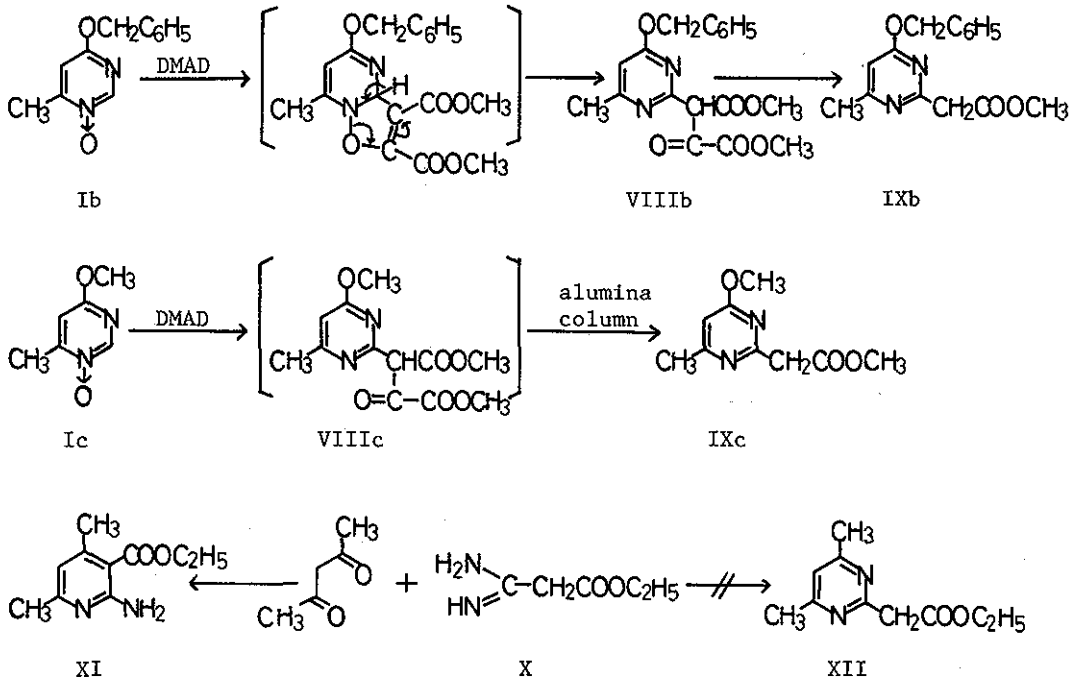
bromo-6-methylpyrimidine (VI) derived from 4-chloro-5-bromo-6-methylpyrimidine (VII) was heated with barium hydroxide in the presence of copper powder in water to give V which was identical with the compound obtained by alkaline hydrolysis of IV. Based on these data, the structure of IV could be assigned 3-phenyl-7-methyl-2,3-dihydrooxazolo[4,5-d]pyrimidine-2-thione.

A likely mechanism of this reaction is shown in Chart 1, although its details remain to be elucidated.

Then the reaction of 4-benzyloxy-6-methylpyrimidine N-oxide (Ib) with dimethyl acetylenedicarboxylate (DMAD) was tested. A solution of Ib, DMAD and a catalytic amount of hydroquinone in dioxane was allowed to stand overnight to give pale yellow crystals (VIIIb) which were purified by recrystallization from AcOEt, mp 144° (decomp.), (40%). The empirical formula of VIIIb ($C_{18}H_{18}O_6N_2$) showed this compound to be a 1:1 adduct of Ib and DMAD. In the NMR spectrum of VIIIb, are observed signals due to three methyl groups (2.39, 3.78, 3.84, each 3H, s), a methylene group (5.47, 2H, s), a pyrimidine ring proton (6.20, 1H, s) and a phenyl group (7.2-7.6, 5H, m) together with a broad signal (15.5-16.1, 1H). In the IR spectrum (KBr) of VIIIb, two carbonyl bands and a band assignable to carbon-carbon double bond are shown at 1750, 1680 and 1620 cm^{-1}, respectively.

From these data, the structure of VIIIb was assigned as shown in Chart 2.

While treated by an alumina column for purification, VIIIb was hydrolyzed to methyl 4-benzyloxy-6-methyl-2-pyrimidineacetate (IXb) whose spectral data [IR ($CHCl_3$): 1752 cm^{-1}, MMR: 2.41



Ib VIIIb IXb

Ic VIIIc IXc

XI X XII

Chart 2

(3H, s), 3.70 (3H, s), 3.88 (2H, s), 5.38 (2H, s), 6.49 (1H, s) 7.37 (5H, s)] are consistent with its structure.

In the case of the reaction of Ic with DMAD under identical conditions the product corresponding to VIIIb was not isolated. Purification of the crude product through an alumina column with Et_2O, followed by distillation under reduced pressure, afforded methyl 4-methoxy-6-methyl-2-pyrimidineacetate (IXc), bp 101-102° (2mmHg), in 46% yield. The spectral data of IXc [IR($CHCl_3$): 1753 cm^{-1}, NMR (C_6D_6): 2.04 (3H, s), 3.34 (3H, s), 3.60 (3H, s), 3.87 (2H, s), 6.09 (1H, s)] are in fair agreement with its structure.

The formation of pyrimidines containing an alkoxycarbonyl-

methyl group at the 2-position by the Pinner type reaction is restricted by the reactivity of the active methylene group attached to the aliphatic starting material. This limitation was illustrated by the condensation of ethoxycarbonylacetamidine (X) with acetylacetone[7,8] to give ethyl 2-amino-4,6-dimethylnicotinate (XI) instead of ethyl 4,6-dimethyl-2-pyrimidineacetate (XII). Thus, our investigation has provided a facile synthetic method for 2-pyrimidineacetates.

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