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THE REACTIONS OF 4-PYRIMIDINONE DERIVATIVES WITH SODIUM AMIDE AND WITH HYDRAZINE : SYNTHESIS OF TRIAZOLE

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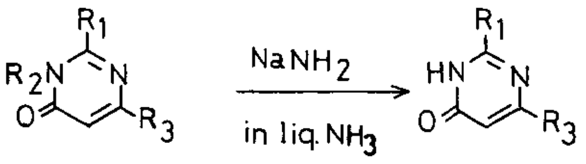
Abstract ----- The 3,6-dialkyl-2-isopropyl-4-pyrimidinones (1)-(3) and 3,6-dimethyl-2-phenyl-4-pyrimidinone (6) were converted to the N-dealkylated 4-pyrimidinones (4), (5), and (7) by reaction with sodium amide in liq. ammonia. Also, these 4-pyrimidinones (1)-(3) and (6) were converted to the triazoles (10)-(12) by heating with hydrazine, respectively.

During the studies of regioselective alkylation of 4-pyrimidinone derivatives, we found that 3,6-dimethyl-2-isopropyl-4-pyrimidinone (1) reacted with sodium amide in liq. ammonia to give quantitatively the N-dealkylated compound (4). This promoted us to examine the reaction of 4-pyrimidinones with nucleophilic reagent, such as hydrazine or guanidine. In this paper we report the reactions of 4-pyrimidinone derivatives with sodium amide and with hydrazine.

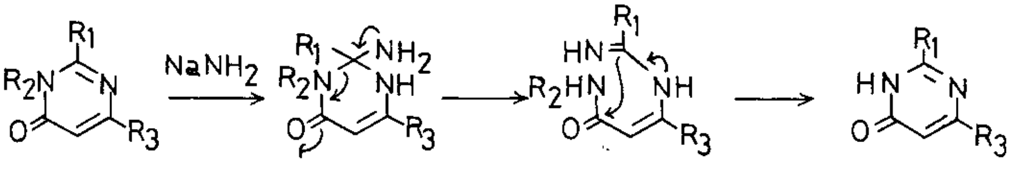
When the 3-alkyl-2-isopropyl-6- methyl-4-pyrimidinones (1) and (2) were treated with 1.1 eq. sodium amide, the same N-dealkylated compound (4) was obtained in 95 and 97% yield, respectively. Also, 3,6-diethyl-2-isopropyl-4-pyrimidinone (3) and 3,6-dimethyl-2-phenyl-4-pyrimidinone (6) were converted to (5) and (7) by similar method in 95 and 98% yield, respectively.



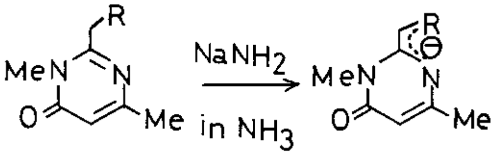
(1) R_1 = i-Pr, R_2 = R_3 = Me
(2) R_1 = i-Pr, R_2 = Et, R_3 = Me
(3) R_1 = i-Pr, R_2 = R_3 = Et
(6) R_1 = Ph, R_2 = R_3 = Me

(4) R_1 = i-Pr, R_3 = Me
(5) R_1 = i-Pr, R_3 = Et
(7) R_1 = Ph, R_3 = Me

On the other hand, when 2,3,6-trimethyl-4-pyrimidinone (8) and 3,6-dimethyl-2-ethyl-4-pyrimidinone (9) were similarly treated with sodium amide, both the starting materials were recovered. From these results, the reaction mechanism is explained as follows; primarily the ring opened intermediate (a) was formed by attack of amide anion at the 2-position of 4-pyrimidinone, followed by recyclization to afford N-dealkylated compounds. In the case of (8) and (9), abstraction of the proton from methyl or methylene group on position 2 of the 4-pyrimidinones (8) and (9) by amide anion might give anionic intermediate (b), which wouldn't be attacked by amide anion.



(a)

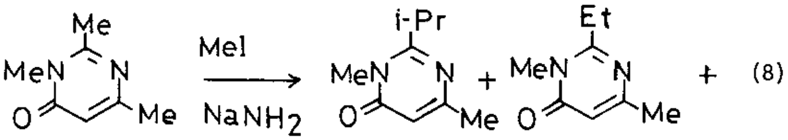


(8) R = H

(9) R = Me

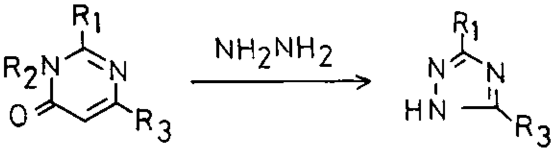
(b)

The predominant formation of the anionic intermediate (b) was supported by the following experiment. When 2,3,6-trimethyl-4-pyrimidinone (8) was treated with 1 eq. methyl iodide with sodium amide in liq. ammonia, (1), (9), and (8) were obtained in the same proportions. Also, the alkylation of (9) afforded (1) selectively in 98% yield under the similar condition.[2]



(8) (1) (9)

Next, we examined the reactions of the 4-pyrimidinones (1)-(3) and (6) with hydrazine.[3] When the 4-pyrimidinones (1) and (2) were heated with hydrazine hydrate at 130-140°C for 12h in a sealed tube, the same 1,2,4-triazole (10)[4] was obtained in 95 and 96% yield, respectively. 3,6-Diethyl-2-isopropyl-4-pyrimidinone (3) also affored the 1,2,4-triazole (11)[5] in a similar manner. Similarly, 3,6-dimethyl-4-pyrimidinone (6) was converted to 5-methyl-3-phenyl-1,2,4-triazole (12)[6] by heating with hydrazine hydrate (130-140°C, 12h) in quantitative yield.7)



(1) R_1 = i-Pr, R_2 = R_3 = Me

(2) R_1 = i-Pr, R_2 = Et, R_3 = Me

(3) R_1 = i-Pr, R_2 = R_3 = Et

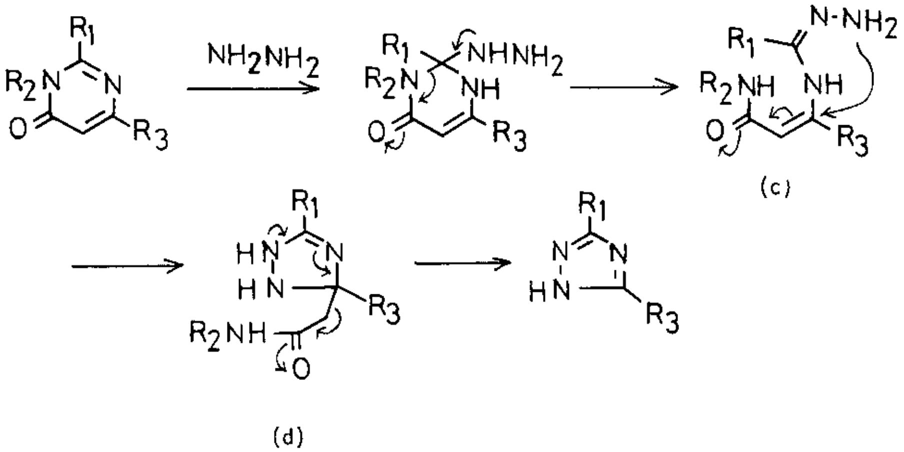
(6) R_1 = Ph, R_2 = R_3 = Me

(10) R_1 = i-Pr, R_3 = Me

(11) R_1 = i-Pr, R_3 = Et

(12) R_1 = Ph, R_3 = Me

Presumably, the ring-opened intermediate (c) is formed by attack of hydrazine at the 2-position of the 4-pyrimidinone derivatives (1)-(3) and (6), and then internal 1,4-addition of the hydrazine moiety to the α,β-unsaturated amide moiety yields the intermediate (d), which causes retro-Michael reaction to the 1,2,4-triazole (10)-(12).



The 4-pyrimidinones (8) and (9) afforded the complicated reaction mixtures by heating with hydrazine hydrate.

This reaction provides a new method for the preparation of 1,2,4-triazole derivatives from 3,6-dialkyl-2-isopropyl-4-pyrimidinones or 3,6-dialkyl-2-phenyl-4-pyrimidinones which can be readily avaiable8).

The reaction of 4-pyrimidinone derivatives with other nucleophiles are now in progress.

REFERENCES AND NOTES

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2. H. Yamanaka and his co-workers have reported the regioselective nitrosation and acylation of 2,3,6-trimethyl-4-pyrimidinone: H. Yamanaka, H. Abe, H. Hiranuma, and T. Sakamoto, *Chem. Pharm. Bull.*, 1978, **26**, 842.
3. The reactions of 1,3-oxazin-4-one and uracil with hydrazine and with other nucleophilic reagents are well known: K. Hirota, Y. Kitada, and S. Senda, *J. Org. Chem.*, 1981, **46**, 846; K. Hirota, K. A. Watanabe, and J. J. Fox, *ibid.*, 1978, 13, 1193; K. Hirota, Y. Kitada, and S. Senda, *J. Am. Chem. Soc.*, 1979, **101**, 4423; T. Kato, U. Izumi, and N. Katagiri, *J. Heterocyclic Chem.*, 1978, **15**, 1475.
4. *Ger.*, 1,076,136, 1960; The spectral datas of (10) are described as follows: IR(nujol) 3450cm^{-1}; ^{1}H NMR(60MHz, ppm, CDCl$_3$) 1.33(6H, d J=7Hz), 2.40(3H, s), 3.0(1H, q J=7Hz) 8.55-10.0(1H, br.s); Mass $^{m}/_{e}$ 125(M^{+}).
5. IR(nujol) 3459 cm^{-1} ; ^{1}H NMR(60MHz, ppm, CDCl$_3$) 1.33(3Hz, t J=7Hz), 1.35(6H, d J=7Hz), 2.80 (2H, q J=7Hz), 3.20(1H, q J=7Hz), 8.45-9.90(1H, br.s); Mass $^{m}/_{e}$ 139(M^{+}).
6. K. T. Potts, *J. Chem. Soc.*, 1954, 3461; IR(nujol) 3400 cm^{-1}; ^{1}H NMR(60MHz, ppm, CDCl$_3$) 2.47 (3H, s), 5.70-6.70(1H, br.s), 7.17-7.66(3H, m, ArH), 7.80(2H, m, ArH).
7. During our studies, the transformation of pyrimidine derivative to 1,2,4-triazole was reported by S. K. Pobev [*Tetrahedron Lett.*, 1982, **23**, 2983].
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