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A FACILE SYNTHESIS OF SUBSTITUTED PYRIMIDINES BY RING TRANSFORMATION OF 1,3-OXAZIN-4-ONES

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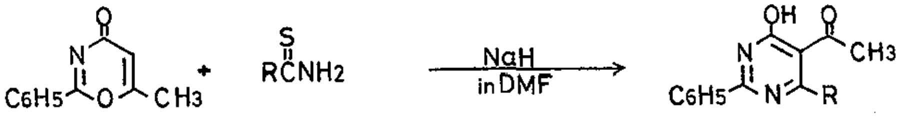
Treatment of 6-methyl-2-phenyl-4H-1,3-oxazin-4-one (1) and 2-benzyl-2-ethoxy-6-methyl-3,4-dihydro-2H-1,3-oxazin-4-one (2) with thioamides led to conversion into the corresponding 2,6-disubstituted 5-acetyl-4-hydroxypyrimidines 3a~e and 4a,b , respectively.

The ring transformations of 1,3-oxazine derivatives into various heterocycles such as pyridines,[1] pyrimidines[2,3] and pyrindines[4] were already reported. In this communication we wish to report a facile method for synthesis of substituted pyrimidines through the ring transformation of 1,3-oxazin-4-one derivatives.

The 1,3-oxazin-4-one derivatives were found smoothly to react with thioamides in the presence of sodium hydride to give substituted pyrimidines. For example, to a mixture of sodium hydride[5] (11 mmole) and phenylthioacetamide (10 mmole) in dimethylformamide (DMF) was added dropwise with stirring a solution of 6-methyl-2-phenyl-4H-1,3-oxazin-4-one (1)[2] (10 mmole) in DMF at room temperature under nitrogen atmosphere. The reaction mixture was stirred for an additional 18 hr, neutralized with 10% hydrochloric acid, and then allowed to cool in an ice-salt mixture. The precipitated product was collected by filtration. An additional quantity of the product was obtained by concentration of the filtrate. Recrystallization of the combined product from 95% ethanol gave 5-acetyl-6-benzyl-4-hydroxy-2-phenylpyrimidine (3a), mp 215° (decomp.), as colorless needles in 85% yield. The structure of 3a was confirmed by the spectral and analytical evidences (shown in Table 1). In a similar experiment, various 6-substituted 5-acetyl-4-hydroxy-2-phenylpyrimidines (3b~e) were obtained by the reaction of 1 with the corresponding thioamides as shown in Scheme 1. Spectral and experimental data were summarized in Table 1.



1

3a~e

3a: $C_6H_5CH_2$
3b: CH_3
3c: C_6H_5
3d: C_2H_5
3e: p-$CH_3OC_6H_4$

Scheme 1

In addition, the 2,3-dihydro-1,3-oxazin-4-one 2[2] also reacted with thioamides to afford the corresponding 5-acetyl-4-hydroxypyrimidines (4).

It is of interest to note that use of carboxamides such as benzamide, acetamide, propionamide and phenylacetamide

Table 1. Preparation of 6-Substituted 5-Acetyl-4-hydroxy-2-phenylpyrimidines (3a~e) and 5-Acetyl-2-benzyl-4-hydroxypyrimidines (4a,b)

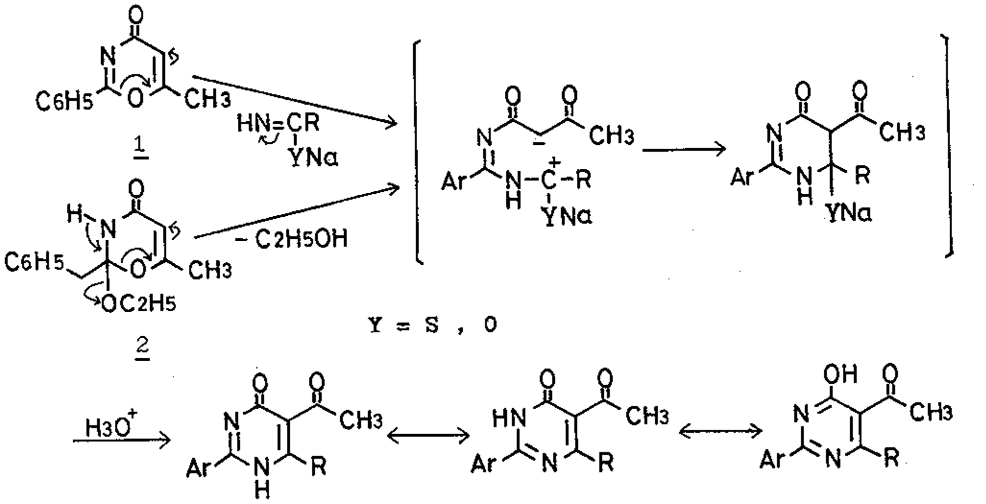
Product	R	Yield (%)	mp(°C)	Molecular formula[a)] (Mol. Wt.)	^{1}H-NMR[b)] δ(ppm)	IR (KBr)
3a	$C_6H_5CH_2$	85	215	$C_{19}H_{16}N_2O_2$ (304.4)	2.56(3H,s), 4.18(2H,s), 7.2-8.5 (10 H, m), 13.5(1H,b)	1680 (sh.), 1660
3b	CH_3	85	267 (decomp.)	$C_{13}H_{12}N_2O_2$ (228.3)	2.62(3H,s), 2.65(3H,s), 7.65-8.25 (5H,m)	1690, 1640
3c	C_6H_5	52.6	297 (decomp.)	$C_{18}H_{14}N_2O_2$ (290.3)	2.39(3H,s), 7.6-8.3 (10 H, m)	1690, 1625
3d	C_2H_5	52	215	$C_{14}H_{14}N_2O_2$ (242.3)	1.19(3H,t, J=7 Hz), 2.58(3H,s) 2.98(2H,q, J=7 Hz), 7.6-8.2(5H,m)	1690, 1640
3e	p-$CH_3OC_6H_4$	65	253 (decomp.)	$C_{19}H_{16}N_2O_3$ (320.4)	2.42(3H,s), 3.90(3H,s), 7.0-8.3(9H,m)	1695, 1625
4a	CH_3	28	188	$C_{14}H_{14}N_2O_2$ (242.3)	2.44(3H,s), 2.59(3H,s), 3.98(2H,s), 7.3-7.6(5H,m), 13.1(1H, b)	1690, 1660
4b	p-$CH_3OC_6H_4$	50	197 (decomp.)	$C_{20}H_{18}N_2O_3$ (334.4)	2.39(3H,s), 3.86(3H,s), 4.06(2H,s), 7.0-7.8(9H,m), 13.1(1H, b)	1695, 1640

a) All products gave satisfactory microanalysis (C ±0.13%, H ±0.27%, N ±0.23%).

b) Spectra were recorded on a Hitachi R-24B with TMS as internal standard; the solvents used: $CDCl_3$ (3a, 4a, 4b) or $CDCl_3$-CF_3CO_2H (9 : 1) (3b, 3c, 3d, 3e).

instead of thioamides resulted in far less yields (from 2% to 12%) of the corresponding pyrimidines.

A probable route of the ring transformation of the 1,3-oxazin-4-ones into the pyrimidines can be posturated as shown in Scheme 2.



3a~e : Ar= C_6H_5, 4a.b : Ar= $C_6H_5CH_2$

Scheme 2

REFERENCES AND NOTES

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3. T. Kato, H. Yamanaka, Y. Yamamoto, and M. Kondo, J. Pharm. Soc. Japan, 1972, 92, 886.
4. T. Kato, Y. Yamamoto, and M. Kondo, Heterocycles, 1975, 3, 293.
5. A 50% dispersion of sodium hydride in mineral oil was washed several times by decantation with purified tetrahydrofuran.

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