SELECTIVITY ON THE HOMOLYTIC ACYLATION OF PYRIMIDINE DERIVATIVES

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Pyrimidine derivatives in which 2- and 4-positions are free, exhibited regioselectivity toward the reaction with acyl radicals. Namely, 6-phenyl-, 6-methylpyrimidine and 5,6,7,8-tetrahydroquinazoline reacted with the acyl radicals generated from aldehydes, ferrous sulfate, t-butyl hydroperoxide, and sulfuric acid to give the 4-acyl derivatives, respectively. In all the cases, the formation of 2-acyl isomers was not observed.

There has been reported by Minisci et al. that acyl radical generated in such redox systems as RCHO-t-BuOOH-Fe^{2+} in H_2SO_4[1,2] (method A) and RCOCOOH-$(NH_4)_2S_2O_8$-$AgNO_3$ in H_2SO_4[2] (method B) attacked the 2- and 4-positions of quinoline rings with favorable selectivity. For instance, acetyl radical from pyruvic acid reacted with quinoline (I) affording 2,4-diacetylquinoline (II) along with 2-acetyl- (III) and 4-acetyl-quinoline (IV). Similar results were obtained from the reaction of quinoline derivatives with acetaldehyde by method A.

method A

$$t\text{-BuO-OH} + Fe^{2+} \longrightarrow t\text{-BuO}\cdot + Fe(OH)^{2+\bullet}$$

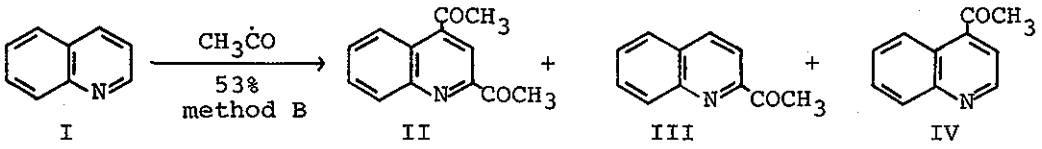
$$t\text{-BuO}\cdot + RCHO \longrightarrow t\text{-BuOH} + R\dot{C}O$$

method B

$$Ag^{+} + S_2O_8^{2-} \longrightarrow Ag^{2+} + SO_4^{-\bullet} + SO_4^{2-}$$

$$Ag^{+} + SO_4^{-\bullet} \longrightarrow Ag^{2+} + SO_4^{2-}$$

$$RCOCOOH + Ag^{2+} \longrightarrow R\dot{C}O + CO_2 + H^{+} + Ag^{+}$$



I II III IV

(II:III:IV=53:22:25)

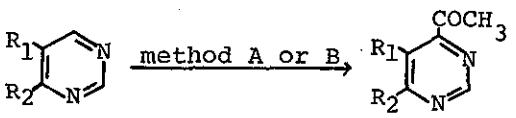
During the investigation of the synthesis of pyrimidinyl ketones, we found that the homolytic acylation of the 6-substituted pyrimidines with the acyl radicals gave 4-acylpyrimidines without accompanying 2-isomers.

Comparison of method A with method B was at first investigated. Thus 4-phenylpyrimidine (V) was treated with acetaldehyde (6 molar eq.), $FeSO_4 \cdot 7H_2O$ (6 molar eq.), t-butyl hydroperoxide (6 molar eq.) in 10 % sulfuric acid (1 molar eq.) at a temperature not exceeding 20° for 1 hr to give colorless needles (VI), $C_{12}H_{10}N_2O$, mp 53-53.5° as a sole product in 45 % yield. The same product, mp 51-52°, was obtained in 25 % yield by method B.

The NMR spectrum shown in Table, exhibits the 2-position of VI being free. Further, the Wolff-Kishner reduction of VI afforded 4-ethyl-6-phenylpyrimidine which was identical with the authentic specimen.[3] These results demonstrated the unequivocal structure of the product to be 4-acetyl-6-phenylpyrimidine.

Similarly, 4-acetyl-6-methylpyrimidine (VIII) and 4-acetyl-5,6,7,8-tetrahydroquinazoline (X) were synthesized from 6-methylpyrimidine (VII) and 5,6,7,8-tetrahydroquinazoline (IX), respec-

tively. The results obtained by method A and B were listed in the Table together with the spectral data of the products. In all the cases none of 2-acetyl isomer nor the 2,6-diacetyl compound was obtained.



V,VII,IX VI,VIII,X

Table

No.	R_1	R_2	method*	yield (%)	mp or [bp] (°C)	NMR($CDCl_3$) ppm	IR($CHCl_3$) c=o
VI	H	C_6H_5	A	45	53-53.5	2.72 (3H,s) 8.22 (1H,s) 9.28 (1H,s)	1710
			B	25	51-52		
VIII	H	CH_3	A	34	74-76	2.71 (3H,s) 2.64 (3H,s) 7.78 (1H,s) 9.25 (1H,s)	1710
			B	25	72-75		
X		$-(CH_2)_4-$	A	30	[120-130/15mmHg]	2.60 (3H,s) 8.86 (1H,s)	1710
			B	28	[85/3mmHg]		

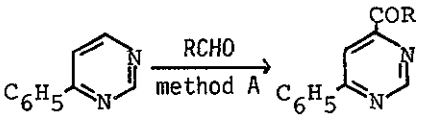
*Method A: pyrimidines (0.01 mole), aldehyde (0.06 mole), conc. H_2SO_4 (0.01 mole), t-BuOOH (0.06 mole), $FeSO_4$ (0.06 mole), H_2O 45 ml, 10-20°, 1 hr.

Method B: pyrimidines (0.01 mole), pyruvic acid (0.02 mole), $(NH_4)_2S_2O_8$ (0.02 mole), $AgNO_3$ (0.001 mole), conc. H_2SO_4 (0.01 mole), H_2O 130 ml, 50°, 1 hr.

Based on the above results, it is concluded that there was not much difference between method A and method B concerning the yield of the products. However, judging from the simplicity of the experimental conditions and the availability of the reagents, method A seemed to be more applicable for the synthesis of pyrimidinyl ketones.

Thus, 6-phenylpyrimidine (V) was treated with aldehydes such

as propionaldehyde, isobutyraldehyde and benzaldehyde under the conditions according to method A, to afford 4-propionyl- (XI), 4-isobutyroyl- (XII) and 4-benzoyl-6-phenylpyrimidine (XIII), in yields ranging from 28 to 50 %. The results of elemental analysis, NMR and IR spectra were in full agreement with the assigned structures of the products.



	R		Yield
XI	C_2H_5	bp 140-141°/5mmHg	50%
XII	$(CH_3)_2CH$	bp 120-121°/3mmHg	35%
XIII	C_6H_5	mp 78-79°	28%

Although yields of the products were not satisfactory, the regioselective acylation observed on pyrimidine derivatives might be noteworthy for synthesis of pyrimidinyl ketones.[4)]

ACKNOWLEDGEMENT We are gratefull to Mrs. C. Koyanagi, Miss K. Mushiake, Miss H. Koizumi, and Mrs. A. Sato for elemental analyses and spectral measurements.

REFERENCES

1) G. P. Gardini and F. Minisci, J. Chem. Soc. (C), 1970, 929.
2) T. Caronna, G. Fronza, F. Minisci, and O. Porta, J. Chem. Soc. Perkin II, 1972, 2035.
3) The authentic 4-ethyl-6-phenylpyrimidine was synthesized by the Grignard coupling of 4-chloro-6-phenylpyrimidine with ethylmagnesium bromide in the presence of a nickelphosphine complex.
4) Synthesis of pyrimidinyl ketones is discussed in detail in the following literature. D.J.Brown and S.F.Mason, "The Pyrimidines", The Chemistry of Heterocyclic Compounds, Vol. 16, ed. by A.Weissberger, Interscience Publisher, Inc., New York, 1962, p 415.

Received, 3rd February, 1978