*A Novel Method of Acetylation Using Acetoxypyridines**

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Pyridoxine, cytosine, thymine, guanine and adenine, which play important roles in biological systems, have an azine or a diazine ring and also one or more hydroxyl and/or amino substituents. Though it had been known that the hydroxyl and the amino groups of these compounds are important in constructing the double spiral structure of nucleic acids by means of hydrogen bonds, the chemical meaning of these groups had not yet been known. A hydroxyl group and an amino group attached to such a heteroaromatic ring as an azine or a diazine have interesting properties. For example, 2- or 4-hydroxypyridine tends to from 2- or 4-pyridone. It may, therefore, be assumed that acyloxy derivatives of pyridine and pyrimidine behave as acylating reagents. Moreover, if so, it is expected that the hydroxyl and the amino groups of the basic components in nucleic acids will play their chemical role of offering an electrophilic reaction intermediate if they act chemically.

In this paper the satisfactory acetylation of alcohols, phenols, amines and acid compounds with 2- and 3-acetoxypyridines is reported.

Experimental

2-Acetoxypyridine.—This compound was prepared by the Tschitschibabin method[1] from acetyl chloride and the sodium salt of 2-hydroxypyridine,[2] which had been prepared from 2-aminopyridine. B. p. 110~112°C/10 mmHg.

3-Acetoxypyridine.—This compound was prepared from acetic anhydride and 3-hydroxypyridine by

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1) A. E. Tschitschibabin and P. G. Szolow, *Ber.*, **58**, 2650 (1925).

2) R. Adams and V. V. Jones, *J. Am. Chem. Soc.*, **69**, 1803 (1947).

the Fischer method,[3] b. p. 92°C/9 mmHg.

The Acetylation of Butyl Alcohol. — *The Preperation of Butyl Acetate.*—Butyl alcohol (3.96 g.) and 3-acetoxypyridine (8.23 g.) were placed in a flask equipped with a condenser and a calcium chloride tube; the mixture was refluxed for 7 hr., then cooled, acidified with dilute hydrochloric acid and extracted with ether. The ethereal extract was washed with an aqueous solution of sodium bicarbonate and then with water, and dried with anhydrous sodium sulfate. After the ether had been distilled off, the residue was combined with 10 ml. of dry xylene and fractionated under atmospheric pressure to give 5.78 g. of butyl acetate. Yield, 93%. When butyl alcohol (6.07 g.) was acetylated with 2-acetoxypyridine (10.47 g.) in tetrahydrofuran (5 ml.) at 25°C for 3 hr. and when the reaction mixture was then treated in a way similar to that described above, the same yield (92%) of butyl acetate was obtained.

The Acetylation of Amines and Phenols. — *General Method.*—In a 50 ml. flask equipped with a condenser and a calcium chloride tube, an amine or a phenol was acetylated with acetoxypyridine under various conditions. The details of reaction conditions are summarized in Table I. After the solvent had been distilled under reduced pressure at room temperature, the residue was washed with 1 N hydrochloric acid or a 1 N sodium hydroxide solution according to the case and then washed with water several times. The acetyl derivative obtained was recrystallized from an adequate solvent. The product was identified with an authentic sample. In case the product was a liquid, such as acetobutylamide or acetodiethylamide, the aqueous hydrochloric acid solution was extracted with ether and the ethereal solution was dried over anhydrous sodium sulfate. After the ether had been distilled off, the residue was fractionated in a vacuum. In the case of urea, the residue was washed with absolute alcohol and the monoacetyl derivative was obtained.

3-Benzoxypyridine.—In a flask equipped with a condenser and a calcium chloride tube, benzoic acid (6.11 g.) and 3-acetoxypyridine (7.11 g.) were placed in 5 ml. of dry xylene, and the mixture was refluxed for 1 hr. After the acetic acid produced had been distilled off, ether was added to the residue. The ethereal solution was washed with an aqueous dilute solution of sodium carbonate and then with water. After drying over anhydrous sodium sulfate, the ether was distilled off and the residue was fractionated under reduced pressure. The fraction boiling at 168~171°C/12 mmHg was collected, m. p. 49~50°C. The yield of 3-benzoxypyridine was 85% on the basis of the 3-acetoxypyridine.

The Friedel-Crafts-type Acetylation of Anisole. —In a round-bottomed three-necked flask equipped with a condenser, a calcium chloride tube, a dropping funnel, a thermometer, and a sealed stirrer there were placed anisole (13.5 g.) and 3-acetoxypyridine (13.7 g.) in 50 ml. of dry carbon disulfide. Aluminum chloride (37 g.) was added to the stirred solution over a period of 15 min., with occasional cooling with water. The solution was then stirred under gentle reflux for 2 hr. After the carbon disulfide had been distilled under reduced pressure, the residue was poured onto ice containing hydrochloric acid. The decomposed mixture was extracted with ether, and the combined ether extracts were washed with water, with a 10% aqueous solution of sodium hydroxide and again water. After drying over sodium sulfate, the ether was distilled and the residue was fractionated under reduced pressure. The yield of acetylanisole was 76% on the basis of 3-acetoxypyridine. Acetyl derivatives of benzene and toluene were obtained in similar manners; the results are shown in Table II.

3) O. Fisher and E. Renouf, *Ber.*, **17**, 1896 (1889).

Results

The remarkable differences in the reactivity of 2- and 3-acetoxypyridine are shown in Tables I and II. In general, the yields of

Table I. Acetylation of amines, alcohols and phenols

Sample	Acetylating reagent*	Solvent**	Temp. °C	Yield %
Butylamine	3	None	Reflux	70
Diethylamine	3	None	Reflux	91
Urea	3	Xylene	Reflux	80
Aniline	2	THF	25	77
Aniline	3	THF	25	78
o-Toluidine	2	THF	Reflux	81
o-Toluidine	2	THF	25	73
o-Toluidine	3	Xylene	Reflux	46
o-Toluidine	3	THF	Reflux	0
p-Toluidine	2	THF	Reflux	95
p-Toluidine	2	THF	25	88
p-Toluidine	3	THF	Reflux	93
p-Toluidine	3	THF	30	70
p-Nitroaniline	2	THF	Reflux	95
p-Nitroaniline	2	THF	25	82
p-Nitroaniline	3	Xylene	Reflux	0
β-Naphthylamine	2	THF	Reflux	96
β-Naphthylamine	2	THE	25	89
β-Naphthylamine	3	Xylene	Reflux	66
β-Naphthylamine	3	THF	Reflux	0
Diphenylamine	2	Xylene	Reflux	95
Diphenylamine	2	THF	Reflux	0
Diphenylamine	3	Xylene	Reflux	0
Benzanilide	2	Xylene	Reflux	0
Butanol	2	THF	25	92
Butanol	3	None	Reflux	93
α-Naphthol	2	THF	Reflux	45
α-Naphthol	2	THF	25	0
β-Naphthol	2	THF	Reflux	68
β-Naphthol	2	THF	25	37
β-Naphthol	3	Xylene	Reflux	33
β-Naphthol	3	THF	Reflux	0

* 2: 2-Acetoxypyridine
3: 3-Acetoxypyridine
** THF: Tetrahydrofuran

TABLE II. FREIDEL-CRAFTS TYPE ACETYLATION OF BENZENE, TOLUENE, AND ANISOLE

Sample	Acetylating reagent*	Yield %
Benzene	2	32
Benzene	3	0.7
Toluene	2	50
Toluene	3	25
Anisole	2	81
Anisole	3	76

* 2 : 2-Acetoxypyridine
3 : 3-Acetoxypyridine

acetylated compounds with 2-acetoxypyridine were higher than those with 3-acetoxypyridine. *o*-Toluidine and *p*-nitroaniline did not react with 3-acetoxypyridine under reflux in xylene, but they did reacted with 2-acetoxypyridine to give the corresponding acetyl compounds without catalyzers under mild conditions. For example, *o*-acetotoluide was obtained in a 81% yield in refluxing tetrahydrofuran and in a 73% yield at 25°C in the same solvent. The acetyl derivatives of *p*-nitroaniline, β-naphthylamine, diphenylamine and β-naphthol were obtained in good yields with 2-acetoxypyridine under mild conditions. In the Friedel-Crafts-type acetylation, it was found that the main acetyl-substituted products of aromatic compounds were *p*-derivatives and that *o*-derivatives were very small in quantity. As may be seen from Table III, interesting results were obtained. The boron trifluoride etherate was found to be a good catalyzer for this acetylation. On the other hand, because cupric sulfate and cupric acetate were sparingly soluble in dry organic solvents, they were unsuitable as catalyzers. For example, *p*-nitroaniline was acetylated with 3-acetoxypyridine in chloroform containing boron trifluoride etherate, but it was not acetylated with either cupric sulfate or cupric acetate. The solvent effect was not clear in these experiments. The interexchange reaction between benzanilide and 2-acetoxypyridine did not proceed in refluxing xylene or tetrahydrofuran containing boron trifluoride etherate as a catalyzer. The effect of the temperature and the catalyzer on the reactivity of aniline was investigated with 3-acetoxypyridine. As is shown in Table IV, the yield was little changed above 25°C, but at 10°C it decreased to the extent of 40% of the yield.

TABLE III. THE EFFECT OF CATALYZER IN ACETYLTION OF *p*-NITROANILINE WITH 3-ACETOXYPYRIDINE

Catalyzer	Solvent*	Temp. °C	Yield %
None	THF	Reflux	0
$CuSO_4$	THF	Reflux	0
$Cu(AcO)_2$	THF	Reflux	0
BF_3	THF	Reflux	70
None	$CHCl_3$	Reflux	0
$CuSO_4$	$CHCl_3$	Reflux	0
$CuSO_4$	$(Me)_2SO$	66	0
BF_3	$CHCl_3$	Reflux	72

* THF : Tetrahydrofuran

TABLE IV. THE EFFECT OF TEMPERATURE AND CATALYZER IN ACETYLATION OF ANILINE WITH 3-ACETOXYPYRIDINE

Solvent*	Catalyzer	Temp. °C	Yield %
Xylene	None	Reflux	87
Benzene	None	Reflux	91
THF	None	35	81
THF	None	25	78
THF	None	10	36
THF	CH_3I	25	83
THF	BF_3	25	76
THF	$Cu(AcO)_2$	25	72

* THF : Tetrahydrofuran

This study has not established the best experimental conditions, nor has it found the specific property in reactivity.

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