The Direct Acylamination of Pyridine 1-Oxides. Effect of Substituents in *N*-Phenylarylimidoyl Chloride. Trapping with Thiols

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The effect of a *para*-substituent in the benzoic acid portion of the arylimidoyl chloride on the nature and yield of products in the reaction with pyridine 1-oxide has been studied. When an electron-withdrawing substituent is present no acylamination product is formed and only 2- and 3-chloropyridine are isolated. When benzenethiol is added a respectable yield of 3-phenylthiopyridine is obtained, but alkanethiols gave low yields of 3-alkylthiopyridines.

The direct acylamination of pyridine 1-oxides using imidoyl chlorides or nitrilium salts has been described (1) and the effect of some substituents in the *N*-aryl portion of the imidoyl chloride (1) and of 3-substituents in the pyridine ring (2) upon the nature and orientation of the products has been determined. In most of the cases studied, the reagent was a benzimidoyl chloride, though in a few cases an acetimidoyl chloride was used (1). We now report a brief study of the influence of a *para*-substituent in the benzoic acid portion of the imidoyl chloride upon the nature and the yields of products formed with pyridine 1-oxide.

First, the influence of solvent on the yields of products formed with *N*-phenylbenzimidoyl chloride itself was studied. The results are summarized in Table I from which it is seen that the highest yields of 2-*N*-benzoylanilinopyridine (**1**) were obtained in DMF solution, while the lowest yield of byproduct, 3-chloropyridine (**2**), was formed in that solvent. We suspect that this may be due to the increased basicity of this solvent as compared with the other two, which facilitates proton abstraction from the 1,2-dihydro intermediate, thus increasing the yield of 2-acylamination product and decreasing that of byproduct arising from the 1,2-dihydro intermediate (1).

The influence of added external chloride was also studied briefly. Addition of triethylamine hydrochloride, tetrabutylammonium iodide (source of I^-) (no 3-iodopyridine isolated), tetrabutylammonium dichloroiodide (3) or thionyl chloride, all in ethylene chloride, had no beneficial influence on the yield of **2** and only slowed down the reaction considerably. Addition of lithium chloride or tetraethylammonium chloride to the reaction mixtures in

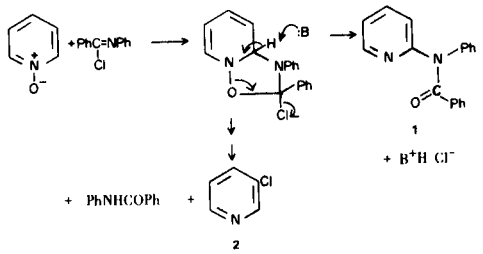


Table I

Effect of Solvent on Yields of **1** and **2** in the Reaction of Pyridine 1-oxide with *N*-Phenylbenzimidoyl Chloride

Solvent	**1** (%) (a)	**2** (%) (b)
Ethylene chloride	42.8	30.3
Acetonitrile	55.0	25.0
Dimethylformamide	70.1	8.1

(a) Isolated yield. (b) Determined by glc.

Table II

Reaction of p-$XC_6H_4C(Cl)=NPh$ with Pyridine 1-Oxide in Ethylene Chloride

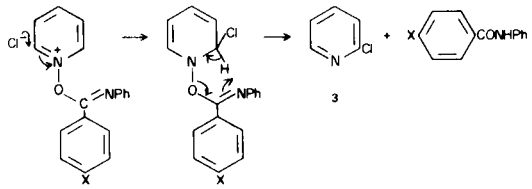
X	**1** (%) (a)	**2** (%) (a)	2-Chloropyridine (**3**) (%) (a)
H	42.8	30.3	
CH_3	58.8	1.7	
OCH_3	52.3	14.7	
Cl		11.3	13.4
NO_2		~15 (b)	21.8

(a) Estimated by glc. (b) Glc peak contaminated slightly by other product.

DMF or acetonitrile stopped the reaction altogether. These results may be due to a common ion effect or to a medium effect *e.g.* solvation of the *N*-oxide oxygen by the cations, thus reducing its reactivity.

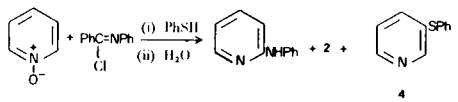
The reaction of pyridine 1-oxide with *N*-phenylarylimidoyl chloride bearing a *para*-substituent in the benzoic acid portion of the molecule gave the results summarized in Table II. The amides formed were hydrolyzed and the 2-anilinopyridine was analyzed.

The interesting feature emerges that electron-withdrawing substituents seem to inhibit aromatization of the 1,2-dihydro intermediate while decreasing somewhat its intra- or intermolecular (1) reaction with chloride at C-3, and some 2-chloropyridine (**3**) is formed simultaneously. The latter may be explained if it is assumed that the electron-withdrawing substituent slows down the intramolecular cyclization sufficiently for the initially formed imidoyloxypyridinium salt to undergo intramolecular attack by chloride ion.



The formation of 3-chloropyridine has been visualized as either an intramolecular transfer of chloride in the 1,2-dihydro intermediate or an intermolecular attack by Cl^- upon a stabilized 1,2-dihydro intermediate carbenium ion (produced by loss of Cl^- from the initial adduct) (1). Conceivably, then, it should be possible to intercept this intermediate by suitable external nucleophiles. These could react at various stages: with the initial imidoyl chloride, with the initial 1,2-dihydropyridine intermediate followed by intramolecular attack at the β-position of the pyridine by the new nucleophile, or by intermolecular attack upon the intermediate 1,2-dihydrocarbenium ion. Preliminary experiments using thiols were explored briefly here (4).

Addition of benzenethiol to a mixture of *N*-phenylbenzimidoyl chloride and pyridine 1-oxide gave, after hydrolysis, 2-anilinopyridine (49%), 3-chloropyridine (**2**) (1%) and 3-phenylthiopyridine (**4**) (35%) (5). An authentic sample of the latter was obtained from 3-aminopyridine *via* the diazonium salt and benzenethiol, and was formed in lower yield than in the imidoyl chloride reaction. The latter is, therefore, the more convenient method for its preparation. The yield of acylamination product is not affected significantly, but that of **2** decreased markedly. It appears, therefore, that **4** is formed at the expense of **2**. When *t*-butylmercaptan was used, 3-*t*-butylthiopyridine was obtained in only 4% yield, while **2** (1.5%) and 2-anilinopyridine (46%) were also formed. *n*-Decylmercaptan gave even lower yields of thioether (0.9%). It remains to be determined whether conditions can be found to improve the yield of thioether in these cases.



EXPERIMENTAL

Acylamination of Pyridine 1-Oxide.

The procedure was essentially the same as that described previously (1). The imidoyl chloride (0.01 mole) in 30 ml. of either ethylene chloride, acetonitrile or DMF in a dry box was treated with freshly distilled pyridine 1-oxide (1.8 g.) in one portion. When the solvent was ethylene chloride or acetonitrile the solution was boiled under reflux for 5 hours. When it was DMF the solution was kept at 90-95° with stirring for 5 hours. The solvent was then evaporated and the residue was hydrolyzed with 10% hydrochloric acid (15 ml.) on a steam bath for 1.5 hours. 2-Chloropyridine survived this treatment. The solution was filtered, basified with 15% aqueous sodium hydroxide and extracted with ether (3 x 50 ml.). The dried (magnesium sulfate) extract was analyzed by gas chromatography on a 7 ft. x ¼ in. 20% SE-30 on Gas Chrom Q column operated at 100° for 12 minutes and then raised to 235° over a 4 minute period and run isothermally thereafter. Samples were collected as eluted and their infrared spectra compared with those of authentic samples. 2-Chloropyridine picrate was also prepared and found to be identical with an authentic sample. 2-Bromopyridine was used as the internal standard.

Acylamination in the Presence of Benzenethiol.

N-Phenylbenzimidoyl chloride (3 g.) in ethylene chloride (50 ml.) was treated with freshly distilled pyridine 1-oxide (4 g.) and the solution was kept at room temperature for 1 hour. Benzenethiol (6.6 g.) was then added and the solution boiled under reflux for 8 hours in a dry box. The solvent was evaporated and the residue hydrolyzed with 10% hydrochloric acid (20 ml.) on a steam-bath for 1 hour. The mixture was filtered, basified with 20% aqueous sodium hydroxide and extracted with ether (3 x 100 ml.). A portion of the extract was analyzed by glc on a 6 ft. x ¼ in. column packed with 15% Apiezon L on Chromosorb W at 200°. 3-Bromopyridine was the internal standard. Compounds were collected and the infrared spectra compared with those of authentic samples. Thus were obtained 3-chloropyridine (1.3%), 3-phenylthiopyridine (35.4%), and 2-anilinopyridine (49.2%). The bulk of the ether extract could be resolved on a silica gel column. Light petroleum (b.p. 30-60°) eluted 3-chloropyridine. Benzene eluted 3-phenylthiopyridine, b.p. 190°/0.65 mm; nmr (carbon tetrachloride): δ 8.54 (d, 1, $J_{2,4}$ = 2 Hz, H_2), 8.39 (dd, 1, $J_{5,6}$ = 4.5 Hz, $J_{4,6}$ = 1 Hz, H_6), 7.6-7.0 (m, 6H); mass spectrum: 187 ($M^{+\cdot}$), 77 (Ph-).

Anal. Calcd. for $C_{11}H_9NS$: C, 70.64; H, 4.81; N, 7.48. Found: C, 70.78; H, 4.95; N, 7.31.

Further elution gave 2-anilinopyridine.

Acylamination in the Presence of *t*-Butylmercaptan and 3-*n*-Decylmercaptan.

The acylamination was carried as above using ten times the amounts used earlier and adding *t*-butylmercaptan (100 g.) instead

of benzenethiol. The products were resolved by column chromatography on silica gel. Light petroleum (b.p. 30-60°) eluted 3-*t*-butylthiopyridine (0.96 g., 4.1%), b.p. 50°/0.18 mm, identical with an authentic sample (6).

Anal. Calcd. for $C_9H_{13}NS$: C, 64.41; H, 7.83; N, 8.37. Found: C, 64.46; H, 7.65; N, 8.49.

Elution with light petroleum: benzene (9:1 v/v) gave 2-anilinopyridine (10.9 g., 46%).

Gas chromatographic analysis of the original reaction mixture revealed the presence of 3-chloropyridine (1.5%).

When the reaction was carried out using *n*-decylmercaptan (100 g.), 3-chloropyridine (1.7%), 2-anilinopyridine (47.3%), and 3-*n*-decylthiopyridine (0.9%), b.p. 83-85°/0.19 mm were obtained; m/e 251 ($M^{+\cdot}$).

Anal. Calcd. for $C_{15}H_{25}NS$: C, 71.77; H, 10.02; N, 5.57. Found: C, 71.60; H, 10.14; N, 5.39.

3-Phenylthiopyridine.

A solution of 3-aminopyridine (4.3 g.) in concentrated hydrochloric acid (10 ml.) at 0° was diazotized with sodium nitrite (3.5 g.) in water (20 ml.). The solution was poured into a hot solution of benzenethiol (5 ml.) in water (50 ml.) containing sodium hydroxide (10 g.). When the evolution of nitrogen ceased the solution was extracted with ether (3 x 50 ml.), the extract dried (magnesium sulfate) and evaporated to give 3-phenylthiopyridine (1.8 g., 21%) as a yellow oil, b.p. 113-114°/0.65 mm, identical with the sample obtained above. Some red dye is also formed in this reaction but remains in the alkaline layer.

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(4) Preliminary reactions were carried out by Dr. Elizabeth M. Smith, whom we thank.

(5) Since this work was completed it was reported [K. F. King and L. Bauer, *J. Org. Chem.*, 36, 1641 (1971)] that reaction of pyridine 1-oxide and thiophenol in the presence of benzenesulfonyl chloride gave a mixture of 2- and 3-phenylthiopyridine together with some disulfide.

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