The Deoxydative Substitution of Pyridine *N*-Oxide by Mercaptans in the Presence of Carbamyl, Carbonyl and Sulfamyl Chlorides (1)

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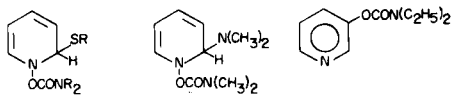
It was established, that in the presence of acylating agents, acyl-X, pyridine *N*-oxide, **1**, was substituted by mercaptans to yield a mixture of 2- and 3-pyridyl sulfides, **2** and **3**, as depicted by equation 1 in Table I. Proven acylating agents have been acetyl, benzoyl, and benzenesulfonyl chlorides (3), as well as acetic and propionic anhydrides (4,5). At this point it was desirable to explore the scope of this reaction utilizing other acylating agents, both from the point of view of the production of sulfides and potentially interesting byproducts.

The success of this reaction was very much solvent-dependent. For example, the reaction failed in hydroxylic solvents, but took place readily in excess mercaptan or in benzene (3). A large excess of mercaptan was undesirable, particularly if the thiol was a scarce commodity, or not easily removed during workup. Although, acetic anhydride, acting both as acylating agent and solvent, proved to be a good medium for this reaction, extension to other anhydrides was again impractical.

Aprotic solvents, such as DMSO and DMF, were avoided since these reacted with powerful acylating agents, particularly sulfonyl halides. Hence a solvent was sought to provide a vehicle to study the scope of the reaction, in terms of functionally different acylating agents. Ideally, reactions would be studied in homogeneous media but this could not be achieved. Therefore, benzene was chosen as the solvent for this study although it was realized that certain limitations on the solubility of all intermediates existed. Since it had been demonstrated that the inclusion of triethylamine into reactions conducted in acetic anhydride influenced the yield and distribution of **2** and **3** (5), a number of the reactions were carried out with and without this base (see Table I). Another part of this study concerned itself with finding unusual byproducts from these reactions. It was hoped that some of the reactions might yield some tetrahydropyridines (6), but no such reduced pyridines were isolated from these reactions.

Carbamyl Chlorides.

Since the stochiometry of the reaction depicted by equation 1 reveals acidic byproducts (hydrogen chloride, and an organic acid), and thus possibly tie up part of **1** as its hydrochloride, it was thought that the use of carbamyl chlorides, R_2NCOCl, might obviate this effect. Such acid chlorides would produce first pyridinium salts, $C_5H_5N^+$-$OCONR_2$ Cl^-, which would be converted by the mercaptan into **4**. Conversion of **4** to **2** and **3** (4) would release carbon dioxide and a secondary amine simultaneously. The latter could neutralize any strong acids in the reaction mixture. The results in Table I indicated a relatively good yield when diethylcarbamyl chloride was used as the acyl chloride, whether or not triethylamine was included. The yield of sulfides (60 and 75%) could be considered even higher, since it was shown that unreacted **1** could be recovered from the aqueous neutral residues. Unfortunately, when dimethyl carbamyl chloride was utilized, the yield of sulfides proved to be considerably samller and no immediate explanation for such large differences in yield can be suggested at present.



4 5 6

Some of the byproducts from the reaction of **1** with *t*-butyl mercaptan and carbamyl chlorides are briefly described. The reactions produced some ureas, R_2NCONR_2, which is neither surprising nor unexpected since the starting acid chloride would react with the secondary amine released during the reaction, or was hydrolyzed during the aqueous workup. Interestingly enough, dimethylcarbamyl chloride produced some 2-dimethylaminopyridine (10%). This compound could be found if dimethylamine formed in the decomposition of **4** attacks **7** (R = methyl) to form **5**. There is precedent for the deoxydative substitution of pyridine *N*-oxides by amines (7).

However, the use of *N,N*-diethylcarbamyl chloride in a similar reaction did not produce significant quantities of 2-diethylaminopyridine but rather a sizeable amount of 3-pyridyl-*N,N*-diethylcarbamate, **6** (3%). That this ester was formed only when the mercaptan was present was evi-

dent after it was shown that the reaction of **1** with diethylcarbamyl chloride without 2-methyl-2-propanethiol produced absolutely no **6**. It is too early to speculate on the mechanism of formation of **6**. It should be reiterated here that we had earlier also isolated a considerable quantity of 3-pyridyl benzoate from the reaction of **1** with 1-butanethiol and benzoyl chloride in benzene (3).

Carbonyl Chlorides.

Since *N,N*-diethylcarbamyl chloride proved to be such a good acylating agent, it was thought that phosgene might act as a good acid halide in this reaction. This proved to be so, provided, triethylamine was included in the reaction mixture, and its presence might have aided in the neutralization of hydrogen chloride as it is produced. Ethyl chlorocarbonate and *n*-butylthiolchlorocarbonate, *n*-C_4H_9SCOCl, however, gave only poor yields of sulfides. stitution failed. It was hoped that a salt, like $C_5H_5N^+$-$OCOSC_4H_9$-*n* Cl^-, might be able to deliver 1-butanethiol anion internally as the N-O bond began to rupture, but no sulfides could be detected.

Sulfamyl Chlorides.

One of the interesting features in studying the reaction expressed by equation 1, was that the use of sulfonyl halides always induced the formation of relatively larger proportion of **3** over **2** (3,8). This phenomena was found to be true also when *N,N*-dimethylsulfamyl chloride was utilized.

Since the sulfonate and sulfamate ions are such good leaving groups, it was suggested that they might be more effective in inducing the formation of the episulfonium ion intermediate which was advanced to explain β-substitution (4,8).

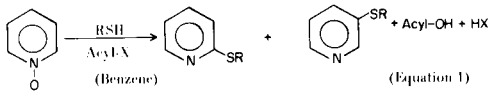
The major by products of note in the reactions of **1** with sulfamyl halides were the disulfides, RSSR. This is not unexpected since this established that the reaction of RSH with $R'SO_2Cl$ alone in the presence of a base (even pyridine) produced RSSR (8).

Related Reactions.

In a series of reactions of heteroaromatic *N*-oxides with related acid chlorides alone, deoxydative substitution products have been reported related to those described above. For example, the reaction of quinoline 1-oxide with $(C_2H_5)_2NC(=S)Cl$ in chloroform provided as the major product usually *S*-2-quinolyl-*N,N*-diethylthiocarbamate and *O*-3-quinolyl-*N,N*-diethylthiocarbamate. In the presence of triethylamine, there were also found *S*-3- and *S*-8-quinolyl-*N,N*-diethylthiocarbamate (9).

Imidoyl chlorides reacted with pyridine *N*-oxide to produce a variety of products. For example, *N*-phenylbenzimidoyl chloride and **1** furnished, among other products, 2-benzamidopyridine, 3-pyridyl benzoate and 3-chloropyridine (10).

TABLE I



1 2 3

R	Acyl-X	Catalyst	% Yield, **2** and **3**	Ratio **2**:**3**
n-C_4H_9	$(C_2H_5)_2NCOCl$	--	68	98:2
n-C_4H_9	$(C_2H_5)_2NCOCl$	$N(C_2H_5)_3$	67	100:0
t-C_4H_9	$(C_2H_5)_2NCOCl$	--	61	92:8
t-C_4H_9	$(C_2H_5)_2NCOI$	$N(C_2H_5)_3$	74	90:10
n-C_4H_9	$(CH_3)_2NCOCl$	--	37	98:2
t-C_4H_9	$(CH_3)_2NCOCl$	--	21	93:7
n-C_4H_9	$COCl_2$	--	10	81:19
n-C_4H_9	$COCl_2$	$N(C_2H_5)_3$	67	89:11
n-C_4H_9	$ClCO_2C_2H_5$	--	8	92:8
n-C_4H_9	$ClCO_2C_2H_5$	$N(C_2H_5)_3$	19	97:3
n-C_4H_9	*n*-C_4H_9SCOCl	$N(C_2H_5)_3$	20	80:20
n-C_4H_9	C_6H_5COCl (a)	--	16	85:15
n-C_4H_9	C_6H_5COCl	$N(C_2H_5)_3$	26	92:8
n-C_4H_9	$C_6H_5SO_2Cl$	$N(C_2H_5)_3$	34	68:32
t-C_4H_9	$C_6H_5SO_2Cl$	--	18	35:65
t-C_4H_9	$C_6H_5SO_2Cl$	$N(C_2H_5)_3$	35	45:55
n-C_4H_9	$(CH_3)_2NSO_2Cl$	$N(C_2H_5)_3$	57	62:38
t-C_4H_9	$(CH_3)_2NSO_2Sl$	--	31	48:52
t-C_4H_9	$(CH_3)_2NSO_2Cl$	$N(C_2H_5)_3$	37	38:62

(a) Reported in reference 3.

EXPERIMENTAL

Materials.

2-, 3- and 4-Pyridyl (*n*- and *t*-butyl) sulfides were described previously (3,4). 2-Dimethylaminopyridine, *N,N*-dimethyl- and *N,N*-diethylcarbamyl chlorides, *N,N*-dimethylsulfamyl chloride were purchased from Aldrich Chemical Co., Milwaukee, Wisconsin. 3-Pyridyl *N,N*-diethylcarbamate was prepared by treating a solution of 3-pyridinol (9.5 g., 0.1 mole) in benzene (100 ml.) with *N,N*-diethylcarbamyl chloride (13.5 g., 0.1 mole). After stirring for 18 hours at 25°, the mixture was added to cold 10% sodium hydroxide solution (60 ml.). The ester was extracted by benzene and distilled (12.1 g., 62%) b.p. 100-102° (0.3 Torr); pmr (deuteriochloroform): δ 8.52 (s, H-2), 8.60 (m, H-6), 7.67-7.17 (m, H-3, H-4), 3.62 (q, OCH_2), 1.18 (t, CH_3, J = 8.0 Hz); mass spectrum (70 eV) m/e (relative intensity): 194 (M^+, 3), 151 (2), 150 (2), 100 (45), 72 (50), 44 (30), 39 (25), 29 (100).

Anal. (By Microtech Labs, Skokie, Illinois) Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.62; H, 7.40; N, 14.49.

General Procedure for the Reaction of **1** with Acyl-X.

A solution of **1** (9.5 g., 0.1 mole) in benzene (125 ml.) was dried azeotropically by distilling off 25 ml. of solvent. The solution was chilled in an ice-water bath and stirred. The acid chloride (0.10 mole) was added at once. In some instances, a precipitate

developed, other remained homogeneous. Attempts to isolate the intermediate *N*-acyloxy- or *N*-sulfonyloxypyridinium chlorides proved to be tedious since these salts were hygroscopic and relatively unstable.

To the solution or suspension was added the mercaptan (0.15 mole) over a period of about 5 minutes. When the experiment called for the inclusion of triethylamine, a solution of the thiol in triethylamine (28 ml., 0.20 mole) were added slowly (*ca.* 20 minutes, with cooling). When the addition of the thiol was complete, the mixture was refluxed 2 hours.

The general work-up consisted of removing solvents, *in vacuo* (20 Torr) and basifying the cold residue with 10% sodium hydroxide solution (60 ml.). Basic and neutral materials were extracted by benzene (4 x 30 ml.), the extract dried (sodium sulfate) and distilled *in vacuo* (preferably at 0.1 to 1 Torr).

Continuous extraction of the aqueous solution with chloroform (44 hours) yield unreacted **1**.

Gc separations were carried isothermally (220°) out on a Varian Model 2700. Using a SE-30 column, 20 ft. x 3/8 in., with He as carrier gas, injection temp. 275°, detector temp., 250°. Fractions were either collected and identified by spectral comparison with authentic samples or identified by enrichment techiques.

Separation on a larger scale using column chromatography was achieved by the method already discussed (3).

The Reaction of **1** with Phosgene and 1-Butanethiol.

A slow stream of phosgene was bubbled for 2 hours through a boiling solution of **1** (9.5 g., 0.1 mole), 1-butanethiol (32 ml., 0.3 mole) and triethylamine (28 ml., 0.2 mole) in benzene (100 ml.). After 1 hour, additional quantities of triethylamine (14 ml.) and 1-butanethiol (16 ml.) were added. The usual work-up and distillation gave the product (12.6 g.) b.p. 141-152° (35 Torr) (see Table I for composition).

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