Dehydration in Liquid Sulfur Dioxide. I. Acid Amide and Acid Anhydride Synthesis in an Iodine-Pyridine-Sulfur Dioxide System

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A novel dehydrating reagent consisting of the I_2–pyridine–liq. SO_2 system has been examined in order to obtain acid amides from carboxylic acids and amines in liq. SO_2. Among the amines, aniline gave the most satisfactory results. A fairly good yield was also achieved when the SO_2Cl_2–Py–SO_2 system was used in place of the I_2–Py–SO_2 system. Various amines in the absence of acids in this system gave *N,N'*-disubstituted diaminosulfone derivatives in good yields. Benzoic acid itself in the absence of amines gave benzoic acid anhydride in this system slowly.

Liquid sulfur dioxide has been used as an unique solvent for the carbonium-ion reaction. It is an acidic dipolar aprotic solvent with a considerably small dielectric constant, 12.35 (22°C). The cationic reaction in this solvent is excellently favored. The organic reactions with negative ρ values can be successfully carried out in this solvent with unusual rapidity.[1]

The complex formations between various compounds bearing lone pairs and sulfur dioxide have been studied extensively.[2-5] Amines[2,3] and alcohols[4,5] are known to form 1:1 complexes with sulfur dioxide.

A chemical material called the Karl Fischer reagent,[6,7] consisting of iodine, pyridine, and sulfur dioxide in a 1:10:3 molar ratio, has been widely employed since 1935 for the convenient and quantitative analysis of water content in various substances in which the dehydration reaction of the organic compound is not proceeding.

The present authors have taken up a new liq. SO_2 system, consisting of iodine, pyridine, and sulfur dioxide in 1:3:100 molar ratio, or of sulfuryl chloride, pyridine and sulfur dioxide in the same ratio, in order to develop a new dehydrating reagent for organic chemistry.

Iodine is assumed to be dissociated in this system as:[8]

$$2\text{pyridine} + I_2 \rightleftarrows [\text{Py}\cdot\text{I}\cdot\text{Py}]^+ + I^- \quad (1)$$

Py=pyridine

and water is quantitatively determined as in the following equation:

$$H_2O + I_2 + 3\text{Py} + SO_2 \longrightarrow 2\text{HI}\cdot\text{Py} + SO_3\cdot\text{Py} \quad (2)$$

The dehydrating reaction of the organic compounds seems to proceed through a similar reaction series:

$$\text{RCOOH} + \text{R'NH}_2 + I_2 + 3\text{Py} + SO_2(\text{excess}) \longrightarrow \text{RCONHR'} + 2\text{HI}\cdot\text{Py} + SO_3\cdot\text{Py} \quad (3)$$

Results and Discussion

Amide Synthesis in the I_2–Py–Liq.SO_2 System. Acetic, propionic, and benzoic acids were reacted with several amines such as *n*-propyl amine and aniline. The results are listed in Table 1.

The results indicate that *n*-propyl amine is less reactive than aniline. The reaction might be accounted for by the lesser basicity of aniline as compared to that of *n*-propyl amine, the latter being solvated or complexes with sulfur dioxide to depress the reactivity of the amine greatly.[9]

$$\text{RNH}_2 + SO_2 \overset{K}{\rightleftarrows} \text{RNH}_2\cdot SO_2 \quad (4)$$

$$\text{RCOOH} + \text{R'NH}_2 \longrightarrow \text{RCOO}^-\text{NH}_3^+\text{R'} \xrightarrow[I_2\text{-Py-liq. } SO_2]{-H_2O} \text{RCONHR'} \quad (5)$$

The equilibrium constant, *K*, of the complex formation will be increased as the basicity of RNH_2 becomes larger, and the effective concentration of the amine in the solution will be decreased according to Eq. (4).

Secondly, the reaction of aniline with tetraethyl-

TABLE 1. AMIDE SYNTHESIS IN THE I_2–Py–Liq.SO_2 SYSTEM AT −70°C

Acid	Amine	Product (yield %)	
CH_3COOH	$CH_3CH_2CH_2NH_2$	No reaction	
CH_3COOH	$C_6H_5NH_2$	$CH_3CONHC_6H_5$	(80)
CH_3CH_2COOH	$CH_3CH_2CH_2NH_2$	$CH_3CH_2CONHC_3H_7$	(23)
CH_3CH_2COOH	$C_6H_5NH_2$	$CH_3CH_2CONHC_6H_5$	(36)
C_6H_5COOH	$CH_3CH_2CH_2NH_2$	$C_6H_5CONHC_3H_7$	(49)
C_6H_5COOH	$C_6H_5NH_2$	$C_6H_5CONHC_6H_5$	(85)

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Table 2. Reaction products of benzoic acid and tetraethyl ammonium benzoate with aniline in the I_2–Py–Liq.SO_2 system

Starting material	Product	
$C_6H_5COOH+C_6H_5NH_2$	$C_6H_5CONHC_6H_5$ (85)	$C_6H_5NHSO_2NHC_6H_5$ (15)
$C_6H_5COON(Et)_4+C_6H_5NH_2$	$C_6H_5CONHC_6H_5$ (18)	$C_6H_5NHSO_2NHC_6H_5$ (24)
	$C_6H_5COOCOC_6H_5$ (14)	

ammonium benzoate in the same system was carried out in order to examine the role of the benzoate ion as the attacking reagent, depicted as follows:

$$C_6H_5COON(Et)_4 \rightleftarrows C_6H_5COO^- + {}^+N(Et)_4 \quad (6)$$

$$C_6H_5COO^- + SO_2 \rightleftarrows C_6H_5COO^-\cdot SO_2 \quad (7)$$

$$C_6H_5NH_2 + SO_2 \rightleftarrows C_6H_5NH_2\cdot SO_2 \quad (8)$$

$$C_6H_5COO^- + {}^+N(Et)_4 + C_6H_5NH_2 + I_2 + Py\text{–}SO_2 \longrightarrow HI\cdot Py + SO_3\cdot Py + I^-N^+(Et)_4 + C_6H_5CONHC_6H_5 \quad (9)$$

However, the possibility of a reaction path through the benzoate anion can be disproved since the distributions of products formed from the two series of reactions are entirely different from each other, as may be seen in Table 2.

The yield of the acid amide is very small in the latter case. Moreover, benzoic acid anhydride was found in the reaction mixture of the reaction between tetraethylammonium benzoate and aniline. These results suggest that the intermediate $(C_6H_5COO)^-$ $(NH_3C_6H_5)^+$ is the most plausible one. The dehydration of benzoic acid itself has been examined in the same system. Benzoic acid is dehydrated to benzoic acid anhydride very gradually, as is shown in Table 3.

Table 3. The dehydration of benzoic acid in the I_2–Py–Liq.SO_2 system

Reaction period	Product (%)
1 hr	No reaction
24 hrs	$C_6H_5COOCOC_6H_5$ (50)
7 days	$C_6H_5COOCOC_6H_5$ (49)

The rate of the acid anhydride formation is very slow compared to that of the formation of the benzanilide; this suggests the path to the acid amide through the reaction of benzoic anhydride and aniline should also be rejected.

The authors also examined the reaction of the amine in this I_2–Py–SO_2 system.

Table 4. Reaction of amines in the I_2–Py–Liq.SO_2 system

Amine	Reaction period	Product	Yield %
Aniline	24	$C_6H_5NHSO_2NHC_6H_5$	50
Aniline+NaOTs	24	$C_6H_5NHSO_2NHC_6H_5$	81
$CH_3CH_2CH_2NH_2$	24	$C_3H_7NHSO_3NHC_3H_7$	10
Aniline	1	$C_6H_5NHSO_2NHC_6H_5$	84
Aniline+NaOTs	1	$C_6H_5NHSO_2NHC_6H_5$	95
Aniline (degassed)	1	$C_6H_5NHSO_2NHC_6H_5$	79

An inspection of Table 4 will show the following point: 1) *n*-Propyl amine gave a much smaller yield of diamino sulfone (10%) than aniline. 2) *N,N'*-Diphenyldiamino sulfone was obtained in a remarkably good yield in the presence of a catalytic amount of sodium toluenesulfonate. 3) Moreover, the yield was decreased when the reaction was prolonged for 24 hr, suggesting that an equilibrium condition will decrease the yield of the diamino sulfone. 4) The degassing of the reaction solution has little effect on the yield of the *N,N'*-diphenyldiamino sulfone. These phenomena suggest that the diamino sulfone formation in the liq. SO_2–I_2–Py system is an iodine-catalyzed dehydrogenation. The mechanism will be discussed further elsewhere.

Lastly, sulfuryl chloride was used in place of iodine in this system. A fair yield was achieved, as is shown in Table 5.

Table 5. Dehydration reaction in the SO_2Cl_2–Py–Liq.SO_2 system

Starting material	Product (yield %)
$C_6H_5COOH+C_6H_5NH_2$	$C_6H_5CONHC_6H_5$ (75)
$CH_3CH_2COOH+C_6H_5NH_2$	$CH_3CH_2CONHC_6H_5$ (27)
$C_6H_5NH_2$	$C_6H_5CHSO_2NHC_6H_5$ (70)

These results are very similar to those for the I_2–Py–liq. SO_2 system, and suggest the following intermediate, $(RCOO)^-(NH_3C_6H_5)^+$, in the reaction course. The overall reaction mechanism may be supposed to be as follows:

$$(RCOO)^-(NH_3C_6H_5)^+ + I^+ + I^- + Py\text{–}SO_2 \longrightarrow RCONHC_6H_5 + 2HI\text{–}Py + SO_3\text{–}Py \quad (10)$$

SO_2Cl_2–Py–liq.SO_2 system:

$$(RCOO)^-(NH_3C_6H_5)^+ + Cl^+ + SO_2Cl^- + Py\text{–}SO_2 \longrightarrow RCONHC_6H_5 + 2HCl\text{–}Py + SO_3\text{–}Py \quad (11)$$

Experimental

Materials. The liquid sulfur dioxide was dried over phosphorus pentoxide and distilled two times. Commercially-sold iodine, benzoic acid, and sodium *p*-toluenesulfonate of a reagent grade were used without further purification. The acetic acid, propionic acid, pyridine, and *n*-propylamine were all purified by the ordinary methods and distilled. A constant middle fraction was collected for use in the preparation.

Preparation of Tetraethylammonium Benzoate. Fowler's method was adopted.[10] Fresh silver oxide was obtained by mixing aqueous silver nitrate and aqueous sodium hydroxide solutions and was washed with water several times. Then silver oxide was added to the aqueous solution of tetraethylammonium iodide. After the removal of the precipitated silver iodide, equivalent moles of benzoic acid were added. By evaporating the water *in vacuo*, tetraethylammonium benzoate was obtained as a white crystal, which was then

10) D. L. Fowler, *J. Amer. Chem. Soc.*, **62**, 1140 (1940).

dried and stored in a dessicator.

IR (KBr) cm^{-1}: 1592, 1550, 1448, 1363, 1160, 990, and 710 cm^{-1}.

The Synthesis of an Amide in the Iodide–PyridineL–iquid SO_2 System. Into 30 ml of liq. SO_2 in a high-pressure glass vessel, 0.015 mol of iodine, 0.045 mol of pyridine, 0.015 mol of a carboxylic acid, and 0.030 mol of an amine were added at −70°C. The reaction mixture was then kept at 30°C for 1 hr. After the reaction, the reaction mixture was chille and poured into an ice-cooled aqueous solution of aboutd 1.5 molar sodium hydroxide and made alkaline. The amide was extracted by ether from the basic reaction mixture. The ethereal solution was washed with a saturated salt solution repeatedly dried over anhydrous sodium sulfate. After the evaporation of the ether, the product was purified by recrystallization and identified as an amide. The residue after the extraction was made acidic again by adding concd hydrochloric acid and was then extracted by ether. From the extract, a small amount of a diamino sulfone was obtained by a similar procedure.

Acetanilide: The reaction of acetic acid (0.9 g) and aniline (2.7 g) gave acetanilide (2.0 g, 80%, recrystallized from benzene). Mp and mixed mp with authentic specimen, 112—114°C;[11] IR (KBr) cm^{-1}: 1658(s), 1597(s), 1560(m), 1439 (m), 1325(m).

N-n-*Propylpropionamide*: The reaction of propionic acid (1.17 g) and *n*-propylamine (1.77 g) gave 0.4 g (27%) of a liquid; bp 64—65°C (0.4 Torr);[12] IR (KBr) cm^{-1}; 3250(m), 1640(s), 1560(s), 1472(s). NMR ($CDCl_3$) τ; 9.1(multiplet), 8.5(sextet), 7.8(quartet), 6.9(quartet), 2.9(singlet).

Propionanilide: The reaction of propionic acid (1.17 g) and aniline (2.70 g) gave 0.8 g (36%) of propionanilide (from benzene). Mass $m/e=149$ (M^+); mp and mixed mp, 104—106°C;[11] IR ($CDCl_3$) cm^{-1}: 1657(s), 1600(s), 1440(s), 745(m), 682(m).

N-n-*Ppropylbenzamide*: The reaction of benzoic acid (1.83 g) and *n*-propylamine (1.77 g) gave 1.2 g of a crystal (49%) (from ethanol–water); mp and mixed mp 83—85°C;[13] IR (KBr) cm^{-1}: 3250(m), 1628(s), 1540(s), 1450(s), 1370(s), NMR ($CDCl_3$) τ: 9.05(t), 8.4(sex), 6.6(q), 2.4(m), 3.15(s).

Benzanilide: The reaction of benzoic acid (1.83 g) and aniline (2.70 g) gave white crystals (from ethanol–water); 2.7 g (85%); mp and mixed mp, 158—161°C;[14] IR (KBr) cm^{-1}: 1650(s), 1530(s), 1439(s), 750(m), 682(m).

The Reaction of an Amine in the Iodide–Pyridine–Liq. SO_2 System. The reaction conditions and the procedure used were the same as those used for the amide synthesis. The molar ratio of the reagents was as follows: amine: iodine: pyridine: liq. SO_2=2: 1: 3: 100.

N,N′-*Diphenyldiamino Sulfone*: Aniline (2.70 g) gave crystals (recrystallized from benzene); 3.1 g (84%); mp and mixed mp 111—113.[15] Mass, $m/e=248$ (M^+), 92.64. IR (KBr) cm^{-1}: 3225(m), 1595(m), 1140(m), 930(m), 740(m), 690(m).

N,N′-*Di*-n-*propyldiamino Sulfone*: *n*-Propylamine (1.77 g) gave white crystals (0.3 g, 10%; recrystallized from benzene). Mp and mixed mp 118—120°C.[15] Mass, $m/e=180$ (M^+), 151.58; IR (KBr) cm^{-1}; 3250(m), 1587(m), 1446(m), 1315(s), 1135(s), NMR ($CDCl_3$), τ: 9.0(t), 8.4(sex), 7.0(q), 2.7(s).

The Dehydration Reaction in the SO_2Cl_2–Pyridine–Liq. SO_2 System. We have examined the dehydration reaction of carboxylic acid and amine using sulfuryl chloride instead of iodine. The ratio of the reagents and the reaction conditions were the same as those used in the amide synthesis in the iodine–pyridine–liq. SO_2 system.

The Synthesis of Carboxylic acid Anhydride in the Iodine–pyridine–liq. SO_2 System. The reaction conditions used for the carboxylic acid anhydride synthesis were as follows: carboxylic acid (0.030 mol), iodine (0.015 mol), and pyridine (0.045 mol) were reacted in liq. sulfur dioxide (1.50 mol) for 24 hr at 30°C. The reaction mixture was then treated as has been described in the case of amide synthesis.

Benzoic Anhydride: Benzoic acid (3.66 g) gave 1.2 g of white crystals (yield 49%); mp and mixed mp,[16] 40—42°C. IR (KBr) cm^{-1}; 1785(s), 1720(s), 1600(m), 1450(m), 1210(m), 778(m), 675(s).

The Reaction of Tetraethylammonium Benzoate in the Iodine–Pyridine–Liq.SO_2 System. Into a mixture of pyridine (0.045 mol), iodine (0.015 mol), and aniline (0.030 mol) in liq. SO_2 (1.50 mol), we added 0.015 mol of tetraethylammonium benzoate; the mixture was then reacted for one hour at 30°C. The products were isolated and separated by the usual procedure.

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