Diacylation of Water and of Hydrogen Sulfide with Acyl Chloride–Pyridine Compounds

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Minunni[1] prepared benzoic anhydride in 78% yield through the reaction of a mixture of benzoyl chloride and pyridine with water. He formulated the reaction as: $2C_6H_5COCl \cdot C_6H_5N + H_2O \rightarrow (C_6H_5CO)_2O + 2C_5H_5NHCl$. Wedekind[2] suggested that a radical was formed from the acyl chloride by the removal of the elements of hydrogen chloride to give pyridine hydrochloride. The postulated radical $R_2C\!-\!C\!=\!O$ would be equivalent to a ketene. In fact Staudinger[3] prepared diphenyl ketene in quantitative yield through the reaction of diphenylacetyl chloride and tripropylamine. Hanford and Sauer[4] have summarized the work on the preparation of a variety of ketenes by this method.

Ipatieff and Friedman[5] suggested that the formation of an acid anhydride, from an acyl halide in pyridine, proceeds through the reaction of the acyl halide with acid, present as an impurity in the acyl halide or formed from it by hydrolysis.[6] The preparation of anhydrides through the reaction of an acyl halide and an acid in the presence of a base is a well established procedure of wide application.

A study of the preparation of acid anhydrides from acyl halides through the agency of tertiary amines has resulted in improvement in the yields obtainable and extension of the application of the method. An addition product such as was postulated by Minunni has been obtained analytically pure by the addition of pyridine at −20° to furoyl chloride dissolved in petroleum ether. The compound was a white solid, melting with decomposition at about 60°. Furoic anhydride was obtained by the reaction of water with the addition compound. An analytically pure sample of the addition product of n-propionyl chloride and triethylamine was also obtained. Solid addition products, in varying degrees of purity were obtained from acetyl chloride and pyridine, benzoyl chloride and pyridine, acetyl chloride and triethylamine, propionyl chloride and pyridine and from furoyl chloride and triethylamine.

Procedure for Preparation of Addition Compounds.— α-Furoyl chloride (5 ml.) in 50 ml. of dry petroleum ether (b. p. 40–60°) was cooled to −20° over solid carbon dioxide. Pyridine (5 ml.) was added, whereupon a solid

product separated. The product was separated by filtration, precautions being taken to avoid moisture or drawing air through the product. The product was dried on a porous plate in a desiccator over phosphorus pentoxide.

Anal. Calcd. for $C_{10}H_2ClNO_2$: Cl, 16.93. Found: Cl, 16.85.

Thus the analysis corresponds to an addition compound in which the ratio of acyl chloride to pyridine is 1:1.

The addition compound of propionyl chloride and triethylamine, as a white powder was prepared as above, except that the solvent and excess reactants were removed at 15° and 10 mm.

Anal. Calcd. for $C_9H_{20}ClNO$: Cl, 18.30. Found: Cl, 18.41.

Five other solid addition compounds were prepared by the procedure outlined above, i. e., acetyl chloride with pyridine and with triethylamine, benzoyl chloride with pyridine, furoyl chloride with triethylamine, and propionyl chloride with pyridine. The solid products obtained were not pure, the analysis for chloride being ±2% the content calculated for a compound containing one molecule of acid chloride and one of amine.

α-Furoyl Chloride-Pyridine Compound with Water.— Pyridine (7 ml.) was added to 6.5 g. of α-furoyl chloride in 60 ml. of dry petroleum ether held at −20°. The addition compound separated immediately, but the mixture was allowed to stand ten minutes before the solid product was separated by filtration. The moist solid was dried on a porous plate in a desiccator for two hours. The solid (approximately 7.5 g.) was added at 5° with good mixing to 35 ml. of acetone containing 1 ml. of water. After standing for five minutes, the solution was poured into 300 ml. of cold water containing 10 ml. of concentrated hydrochloric acid. The yield of furoic anhydride (3.3 g., m. p. 71–73°) amounted to 64% of the theoretical based upon the amount of α-furoyl chloride used. The relatively low yield was mainly due to losses in isolating and handling the addition product.

Several variations in the procedure for the preparation of benzoic anhydride were made in seeking the optimum conditions. The yields obtained (73–83%) by the standard method,[6] in which the anhydrous mixture of benzoyl chloride and pyridine was warmed and then poured into dilute hydrochloric acid on cracked ice, were somewhat variable. A lower yield (62%) was obtained if an amount of water molecularly equivalent to one-half the benzoyl chloride was present in the pyridine. Thus the presence of water in the pyridine at the time of the formation of the benzoyl chloride–pyridine compound was disadvantageous. The use of equal molecular amounts of benzoyl chloride and benzoic acid with pyridine gave only an 82% yield of anhydride. An excess of water in the decomposition step was also disadvantageous. Similarly the use of a large excess of pyridine, as the reaction medium, lowered the yields. Almost quantitative yields (95–99%) of benzoic anhydride were obtained when the addition compound from benzoyl chloride (1 mole) and pyridine (1.5 mole), was allowed to react with water (0.5 mole) in an inert solvent

(1) Minunni, *Gazz. chim. ital.*, **22**, 213 (1892).

(2) Wedekind, *Ber.*, **34**, 2070 (1901); *Ann.*, **318**, 91 (1901); **323**, 246–264 (1902).

(3) Staudinger, *Ber.*, **40**, 1148 (1907).

(4) Hanford and Sauer in Adams "Organic Reactions," Vol. III, p. 124, John Wiley and Sons, Inc., New York, N.Y., 1946.

(5) Ipatieff and Friedman, THIS JOURNAL, **61**, 686 (1939).

(6) The editor (H. A.) of Vol. 26 of "Organic Syntheses" inserted this explanation (incorrectly as it now appears) in Note 1, p. 2 of the procedure for the preparation of p-chlorobenzoic anhydride.

such as benzene or dioxane. The water was added over a period of twenty minutes to the well-stirred solution, kept at a temperature below 10°.

The use of benzene or dioxane as a reaction medium is not essential in the preparation of benzoic anhydride. However, it is convenient and makes possible a better quality product, through facilitating the reaction with water without a rise in the temperature. A reaction medium seems to be essential for the best yields in the preparation of o-chlorobenzoic and certain , other anhydrides. For solid anhydrides which do not react readily with water dioxane is the preferred medium. The solid anhydride may be obtained by pouring the dioxane solution into water. Liquid anhydrides and those sensitive toward water are perhaps best prepared in benzene. Other solvents such as acetone, petroleum ether and diethyl ether have not given good yields. Ether undergoes cleavage and in one case ethyl 9-undecylenate was obtained in 21% yield when diethyl ether was being used as the solvent for an attempted preparation of 9-undecylenic anhydride.

High yields (90–99%) of benzoic anhydride were also obtained when triethylamine was substituted for the pyridine in the procedure outlined above. However, benzoyl chloride and triethylamine gave colored products which contaminated the benzoic anhydride. This was true even when a carefully purified sample of triethylamine was used. Triethylamine has given colored products and low yields with aliphatic acyl chlorides, presumably due to ketene formation. For the preparation of acid anhydrides pyridine is apparently preferable to more basic amines, such as triethylamine or to less basic amines such as dimethylaniline. The latter do not form sufficiently stable addition products with acyl halides while triethylamine is the preferred amine for dehydrohalogenation of acyl halides to ketenes.

Procedure for Benzoic Anhydride.—Freshly distilled benzoyl chloride (14 g., 0.1 mole) was added to 40 ml. of dry dioxane and cooled to 5°. Dry pyridine (10 ml.) was added and the mixture swirled for a few seconds while the mixture was kept below 10°, 1 ml. of water was added dropwise with vigorous agitation. After the addition of the water the mixture was allowed to stand with occasional stirring in the ice-bath for ten minutes. A mixture of 75 ml. of concd. hydrochloric acid, 75 g. of cracked ice and 350 ml. of water was prepared. The reaction mixture was then poured into the ice mixture. The solid benzoic anhydride was separated by filtration. The solid was stirred with 50 ml. of a 5% cold solution of sodium bicarbonate for a minute. The anhydride was then filtered off and washed with cold water. The product was then dried on a clay plate. The yield was 11.0 g. of product, m. p. 42–43° or 97% of the theoretical. After recrystallization from a mixture of ether and petroleum ether, 9.3 g., m. p. 43°, was obtained.

In another preparation the procedure was modified in that 12.2 g. of benzoic acid (0.1 mole) in 40 ml. of dioxane was added instead of water, to the benzoyl chloride–pyridine solution. There was obtained 19.5 g. of benzoic anhydride m. p. 42° or a yield 85% of the theoretical. A similar per cent. yield was obtained when 0.05 mole each of

benzoyl chloride and benzoic acid were used instead of 0.10 mole of benzoyl chloride in the procedure first described.

Procedure for α-Ethylcaproic Anhydride.—α-Ethylcaproyl chloride, b. p. 70° (9 mm.) (32.5 g., 0.2 moles), was mixed with 150 ml. of dry benzene and cooled below 10°. The mixture was stirred rapidly and 20 ml. (0.25 mole) of anhydrous pyridine added dropwise from a dropping funnel to the mixture kept below 10°. After the addition of the pyridine 2 ml. of water was added dropwise to the rapidly stirred mixture kept below 10°. The precipitated pyridine hydrochloride was filtered off one-half hour after the addition of the water. The solid was dissolved in 120 ml. of water and extracted twice with 50-ml. portions of benzene. The 100 ml. of benzene was washed three times with 75-ml. portions of a 5% solution of sodium bicarbonate and three times with 75-ml. portions of water. The original benzene filtrate was similarly washed, twice with 100-ml. portions of 5% bicarbonate solution and twice with water. The two benzene solutions were combined and the benzene distilled at 740 mm. and the anhydride (22.5–23.5 g.) at 149–152° (8 mm.). The anhydride so prepared was identical in properties with the product from a reaction of the acyl chloride and the sodium salt. The anhydride was characterized by conversion to the amide, m. p. 101–102°.[7]

Two other anhydrides were prepared by the procedure and on the scale described for benzoic anhydride above, i. e., o-chlorobenzoic anhydride (14.6 g., m. p. 77–79°; 11.8 g., m. p. 79°, after recrystallization) and α-furoic anhydride (9.5 g., m. p. 72–73°; 8.4 g., m. p. 73° after recrystallization). p-Iodobenzoic anhydride was prepared on 0.05 molar scale, the yield being 10.9 g., m. p. 227–229° or 8.35 g., m. p. 229° after recrystallization.

Acetic anhydride (9.8–11.6 g.), b. p. 136–139°, and propionic anhydride (15.1–16.3 g.) b. p. 163–166°, were prepared from 39.3 g. of acetyl chloride and 37 g. of propionyl chloride, respectively, following the procedure described for α-ethylcaproic anhydride. Calcium carbide, was used in these cases for removal of free acid from the benzene solution before distilling it from the acid anhydride.

Attempts to prepare the anhydride of 9-undecylenic acid were unsuccessful. Reactions took place apparently in the usual way but the product was a high molecular weight oil which could not be distilled. In one case the oil polymerized to a rubber-like solid. Presumably a ketene was formed, which like all aldoketenes dimerized, and then polymerized when subjected to more drastic conditions in the attempted distillations.

The reaction, as formulated by Minunni, seemed to us rather improbable, but all our observations are in accord with it. Reasonably stable addition compounds of various acyl halides and amines have been isolated. They react with water to give anhydrides. The best yields of anhydrides were obtained when the reaction mixture of acyl chloride and amine was free of water, or acid, so that the reaction cannot be rationalized as *depending* upon the reaction of an acyl chloride and an acid. The best yields are obtained by

(7) Raper, *J. Chem. Soc.*, **91**, 1837 (1907).

forming the addition compound and then hydrolyzing it with one-half mole of water per mole of acyl halide. The formation of the anhydride cannot be formulated as depending upon the intermediate formation of a ketene in the case of benzoyl and other aroyl chlorides. Moreover, triethylamine, the preferred reagent for dehydrohalogenating acyl halides to ketenes, is inferior to pyridine for the preparation of anhydrides. It appears that the formation of a ketene before the addition of water to the amine-acyl chloride compound, as in the case of 9-undecylenoyl chloride, prevents anhydride formation.

Since the benzoyl chloride-pyridine addition compound is so powerful an acylating agent that both of the hydrogens in a molecule of water are replaced by benzoyl groups, an attempt was made to benzoylate both of the hydrogens in hydrogen sulfide, $i.$ $e.$

$$2C_6H_5COCl \cdot C_5H_5N + H_2S \longrightarrow$$
$$(C_6H_5CO)_2S + 2C_5H_5NHCl$$
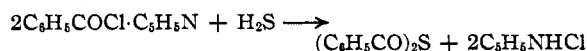
The benzoyl chloride-pyridine compound in petroleum ether was treated with hydrogen sulfide at about $-20°$. Dibenzoyl sulfide was obtained in a yield of 85% of the theoretical. Dibenzoyl sulfide reacted with hydrogen sulfide at 25°, in the presence of pyridine, to give thiobenzoic acid in a yield of above 70% of the theoretical. The sulfhydrolysis did not occur in the absence of pyridine. Since thiobenzoic acid is readily oxidized to dibenzoyl disulfide, the latter has been obtained in a yield of about 66% from benzoyl chloride without isolating the intermediate dibenzoyl sulfide or thiobenzoic acid.

Dibenzoyl Sulfide.—Benzoyl chloride (14 g. 0.1 mole) in 74 ml. of petroleum ether (b. p. 40–60°) was cooled to $-20°$ and 10 ml. of dry pyridine added. Dry hydrogen sulfide was bubbled through the reaction mixture, kept at $-20°$ or lower, for one hour. Dibenzoyl sulfide and pyridine hydrochloride separated. The petroleum ether was filtered off and discarded. Water (200 ml.) was added to the solid products and the insoluble dibenzoyl sulfide separated by filtration. The crude product was washed with 100 ml. of cold 0.1 molar ammonium hydroxide solution in order to remove thiobenzoic acid. The product (10.5 g., m. p. 46–48° and 8.9 g., m. p. 48° after recrystallization from ether) was identical with that obtained by the reaction of sodium sulfide and benzoyl chloride.[8]

(8) Blake, U. S. Patent 2,331,650, C. A., **38**, 1533 (1944).

Thiobenzoic Acid from Dibenzoyl Sulfide.—Dibenzoyl sulfide (6.5 g.) with 4 ml. of pyridine in 65 ml. of chloroform was treated with hydrogen sulfide for one hour at room temperature. The thiobenzoic acid was extracted with five 50-ml. portions of a 5% solution of sodium bicarbonate. The water solution was then acidified with hydrochloric acid and the thiobenzoic acid extracted with three 50-ml. portions of ether. The acid was converted to the benzanilide[9] (3.2 g., m. p. 159°) and the yield estimated as 33% of the theoretical.

Dibenzoyl Disulfide.—Dibenzoyl sulfide and thiobenzoic acid were successively prepared as described above, except that the preparation of dibenzoyl sulfide was carried out in chloroform, in which all products of the reaction are soluble. The thiobenzoic acid was extracted with 280 ml. of 1 molar ammonium hydroxide in seven portions. The solution at 0° was acidified with concentrated hydrochloric acid. The oily thiobenzoic acid was kept emulsified by rapid stirring. The acid at 0° to $-5°$ was oxidized wit i 30% hydrogen peroxide (8 ml.), the latter being added in 2-ml. portions at intervals of five minutes. The yellow color of the thiobenzoic acid disappears when the oxidation is complete. The crude dibenzoyl disulfide (4.5 g., m. p. 128°) was separated by filtration and dried at 80°. After recrystallization from acetone 3.2 g. of product m. p. 129–130° was obtained. The yields given were obtained from 7 g. of benzoyl chloride and are 66 and 52.5%, respectively, of the theoretical.

Summary

Benzoyl chloride, furoyl chloride, propionyl chloride and other acyl chlorides form solid addition compounds with pyridine and other amines. These addition compounds are powerful acylating agents at low temperatures. They react with water to give anhydrides and with hydrogen sulfide to give disulfides at temperatures below 0°. A study of the reactions has resulted, in procedures which give excellent yields of anhydrides and disulfides, and in confirming the postulations of Minunni regarding the formation of addition compounds rather than other intermediates which were suggested by later investigators. Pyridine appears to be the preferred amine since it is sufficiently basic to form an addition compound with the acyl chloride but does not dehydrohalogenate acyl chlorides to ketenes under the conditions used. Pyridine is an effective catalyst for the sulfhydrolysis of diacyl sulfides.

(9) Wheeler, THIS JOURNAL, **23**, 446 (1901).