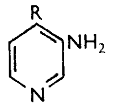
149. *A Simple Preparation of Acid Anhydrides.*

By R. K. SMALLEY and H. SUSCHITZKY.

Acid anhydrides, unaffected by cold water, have been made in high yield and purity by shaking an aqueous solution of the alkali-metal carboxylate with an acyl halide at room temperature in the presence of a tertiary amine. Related reactions of preparative value are also described.

ATTEMPTS to benzoylate various substituted 3-aminopyridines (I; *e.g.*, R = piperidino) by the Schotten–Baumann method were unsuccessful, but produced a mixture of benzoic anhydride, benzoic acid, and unchanged aminopyridine (I). From a systematic investigation of the reaction conditions it was found that pure benzoic anhydride could be obtained quantitatively by slow addition of benzoyl chloride (1 mol.), with shaking, to an aqueous solution of sodium benzoate (1 mol.), or another soluble benzoate, in the presence of a catalytic amount of base (I). Other tertiary amines, such as pyridine, 3-aminopyridine, and pyridine *N*-oxide, proved equally efficient as catalysts; the picolines, however, gave lower yields (80%), while 2- and 4-amino- and 2-fluoro-pyridine, as well as the monocarboxylic acids of pyridine, gave no yield. Impairment of the catalytic activity of pyridine by α-substitution for the reverse reaction, *i.e.*, anhydride hydrolysis, has recently been reported.[1]



(I)

The method was also applicable to the preparation of a number of symmetrical and mixed-aromatic, as well as some aliphatic, anhydrides (cf. Table), provided that the acyl halide and anhydride were not rapidly attacked by cold water. Practically no temperature increase was observed during the reactions. Yields compared favourably with those of reported procedures which are invariably more complex. For instance, the accepted preparation of benzoic anhydride[2] involves more stages (and gives inferior yields) than the simple procedure of benzoylating an aqueous solution of sodium benzoate, as described here. The utility of a tertiary base in the preparation of an acid anhydride from an acyl halide is recognised, and several variations of the method have been given. Adkins and Thompson,[3] who studied this procedure methodically to find the optimum conditions, concluded that the presence of water in the initial stages of the reaction was actually harmful, since it was thought to inhibit formation of the intermediate complex (amine–acyl halide). This very unstable addition compound, originally postulated by Minunni[4] as the effective acylating agent, was later successfully made[5] from benzoyl chloride and pyridine under anhydrous conditions. We were able to prepare an analogous intermediate from benzoyl chloride and pyridine *N*-oxide in dry benzene. It was stable

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[1] Butler and Gold, *J.*, 1961, 4362.

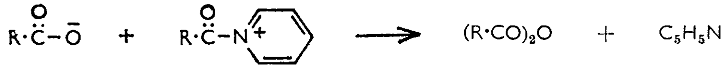
[2] Clarke and Rahrs, *Org. Synth.*, Coll. Vol. I, 91.

[3] Adkins and Thompson, *J. Amer. Chem. Soc.*, 1949, **71**, 2242.

[4] Minunni, *Gazzetta*, 1892, **22**, 213.

[5] Zeavin and Fisher, *J. Amer. Chem. Soc.*, 1932, **54**, 3738.

when kept dry; it efficiently benzoylated an aqueous solution of sodium benzoate to give benzoic anhydride, and reacted with water to give benzoic acid.

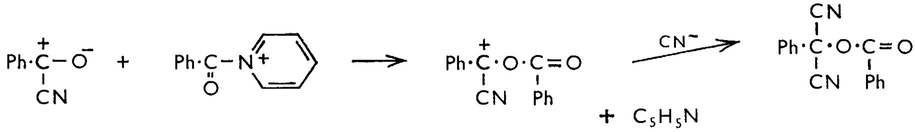


(II)

The pyridine-catalysed formation of an acid anhydride from the halide and sodium salt of the acid, in an aqueous medium, can be envisaged as being due to nucleophilic substitution by a carboxylate ion on the intermediate acylpyridinium ion (II). Excess of sodium hydroxide was found to lower the yield of anhydride in favour of acid, presumably because hydroxyl ions successfully compete with carboxylate ions in the anionic attack on the intermediate (II).

It was thought possible that sodium salts of inorganic acids, whose anions are capable of combining with an acyl moiety, might also react in a purely aqueous medium with the pyridinium ion (II), in preparative yield. This was found to be the case for sodium azide, which gave benzoyl azide in a similar yield (85%) to that recently claimed [6] (86%) for a complicated preparation of this compound in an organic solvent. Our method, of course, does not differ very much from the established procedure for making acyl azides, in which aqueous acetone is used as solvent.[7]

When an aqueous solution of sodium cyanide was treated with benzoyl chloride in the presence of pyridine, a white solid of m. p. 96° was obtained which gave the correct analysis for benzoyl cyanide (m. p. 32°). A study of its infrared spectrum, however, followed by synthesis, showed this substance to be identical with the dimer whose structure was formulated by Marvel *et al.*[8] as (III). Dimerisation presumably takes place when the initially formed benzoyl cyanide reacts with benzoylpyridinium cyanide as shown below.



(III)

The method of benzoylation by use of the pyridine complex (II) was not successful for the preparation of the sulphonic acid anhydride from equimolar quantities of the chloride and sodium salt of benzenesulphonic acid, and it also failed for the preparation of dibenzoyl sulphide from benzoyl chloride and sodium sulphide.

EXPERIMENTAL

Benzoic Anhydride.—To an aqueous solution (150 ml.) of sodium benzoate (14·4 g., 0·1 mol.) containing 2 drops of pyridine, benzoyl chloride (14 g., 0·1 mol.) was slowly added with shaking. The resulting solid was filtered off, washed with water, then with light petroleum (b. p. 40—60°), and dried to give the pure anhydride (97·5%), m. p. 40—41°. Various amines were also used as catalysts (see text), and potassium or ammonium benzoate gave similar results.

Other Anhydrides.—The procedure for the preparation of other aromatic acid anhydrides was as for benzoic anhydride and results are given in the Table. Heptanoic anhydride was made from heptanoic acid (52 g., 0·4 mol.) which had been carefully neutralised (phenolphthalein) with sodium hydroxide solution. Slow addition of heptanoyl chloride (59 g., 0·4 mol.)

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[6] M. Ratz, G.P. 845,507 (1952).

[7] Barrett and Poster, *J. Amer. Chem. Soc.*, 1941, **63**, 3434; Lindemann and Schultheis, *Annalen*, 1927, **451**, 241.

[8] Marvel, Brace, Miller, and Johnson, *J. Amer. Chem. Soc.*, 1949, **71**, 34.

Preparation of acid anhydrides from an acyl chloride ($R\cdot COCl$; 1 mol.) and an aqueous solution of a sodium salt ($R'\cdot CO_2Na$; 1 mol.), with pyridine as catalyst.

		Anhydrides					Anhydrides		
$R\cdot COCl$ R	$R'\cdot CO_2Na$ R′	M. p.	Yield (%)	Lit. yield (%)	$R\cdot COCl$ R	$R'\cdot CO_2Na$ R′	M. p.	Yield (%)	Lit. yield (%)
Ph	Ph	41°	97·5	70 [2]	Ph	*m*-$NO_2\cdot C_6H_4$	103	70	75 § [5]
Ph	*o*-$Cl\cdot C_6H_4$	49	79	new cpd.*	Ph	*p*-$NO_2\cdot C_6H_4$	131	64	65 ¶ [5]
o-$Cl\cdot C_6H_4$	Ph	49	96	new cpd.†	Ph	3,5-$(NO_2)_2C_6H_3$	114	80	60 [5]
Ph	*p*-$Cl\cdot C_6H_4$	68—70	75	69 [5]	*p*-MeC_6H_4	*p*-$Me\cdot C_6H_4$	95	94	80 [9]
Ph	*p*-$Br\cdot C_6H_4$	82	75	80 [5]	$Me\cdot[CH_2]_5$	$Me\cdot[CH_2]_5$	b. p. 170/ 15 mm.	60	80
Ph	*p*-$F\cdot C_6H_4$	43	70	new cpd.‡					
Ph	*o*-$NO_2\cdot C_6H_4$	65	70	65 [5]	$Me\cdot[CH_2]_{10}$	$Me\cdot[CH_2]_{10}$	40	66	75 [10]
					$Me\cdot[CH_2]_{14}$	$Me\cdot[CH_2]_{14}$	64	75	79 [11]

* Found: C, 64·9; H, 3·8. $C_{14}H_9ClO_3$ requires C, 64·5; H, 3·5%. † Found: C, 64·9; H, 3·8%. ‡ Found: C, 68·7; H, 3·3. $C_{14}H_9FO_3$ requires C, 68·8; H, 3·7%. § Found: C, 62·2; H, 3·6. Calc. for $C_{14}H_9O_5$: C, 62·0; H, 3·3%. ¶ Found: C, 61·5; H, 3·4%.

to the agitated reaction mixture precipitated the oily impure anhydride. It was extracted with ether and the extract was fractionally distilled to yield the colourless anhydride (58 g., 68%), b. p. 256—260°/760 mm. Its purity was assessed by infrared analysis, details of which will be published elsewhere.

Benzoyl Azide.—To an aqueous solution (50 ml.) of sodium azide (1·3 g., 0·02 mol.) containing 1 drop of pyridine, benzoyl chloride (2·3 ml., 0·02 mol.) was added with shaking. A colourless oil separated which solidified on cooling. The solid was recrystallised from light petroleum (b. p. 40—60°) to yield benzoyl azide (2·5 g., 85%), m. p. 32°. The use of pyridine *N*-oxide as catalyst gave a similar result.

Benzoyl Cyanide Dimer.—To an aqueous solution (50 ml.) of sodium cyanide (2·5 g., 0·05 mol.) containing 2 drops of pyridine, was added benzoyl chloride (7 g., 0·05 mol.), and the mixture was shaken until a yellow oil separated. After decantation of the mother-liquor, the oil solidified on contact with light petroleum (b. p. 40—60°). The solid was recrystallised from light petroleum (b. p. 40—60°) to give α-benzoyloxy-α-phenylmalononitrile, m. p. 96°, undepressed on admixture with authentic material,[8] and identical infrared spectrum.

Reaction between Benzoyl Chloride and Pyridine N-*Oxide.*—Pyridine *N*-oxide (1·9 g., 0·02 mol.), which had been dried by azeotropic distillation with benzene, was dissolved in dry benzene (150 ml.) and treated with benzoyl chloride (2·8 g., 0·02 mol.). The white precipitate of N-*benzoyloxypyridinium chloride* which was formed was filtered off and dried *in vacuo*. It had m. p. 135° (Found: C, 60·7; H, 4·6. $C_{12}H_{10}ClNO_2$ requires C, 61·1; H, 4·2%. Cl and N present).

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[9] Autenrieth and Thomae, *Ber.*, 1924, **57**, *B*, 423.

[10] Mannich and Nadelmann, *Ber.*, 1930, **63**, 797.

[11] Rankov, *Ann. Univ. Sofia*, II, 1937, **33**, 221 (*Chem. Abs.*, 1938, **32**, 3335).