[CONTRIBUTION FROM THE R. B. WETHERILL LABORATORY OF CHEMISTRY, PURDUE UNIVERSITY]

Dehydrations with Aromatic Sulfonyl Halides in Pyridine.[1] A Convenient Method for the Preparation of Esters

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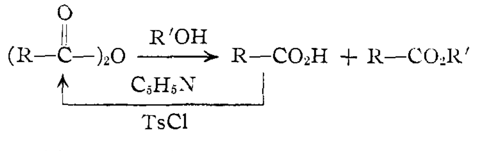
An ester is formed rapidly and in high yield when a solution of an acid and an alcohol in pyridine is treated with toluenesulfonyl chloride. This procedure is particularly useful in the esterification of tertiary alcohols and in the preparation of solid esters. The reaction appears to involve *in situ* generation of the acid anhydride; anhydride formation occurs selectively in the presence of alcohols, permitting complete utilization of the acid. This method can be adapted to the preparation of anhydrides and amides.

Aromatic sulfonyl halides in pyridine have been used as reagents for the Beckmann[2] and Lossen[3] rearrangements, the dehydration of aldoximes[4] and primary amides[5] to nitriles, for the cyclization of 1,4- and 1,5-diols to tetrahydrofurans and tetrahydropyrans,[6] and for the cyclization of a γ-hydroxy amide to a sulfonimido ether.[1] These diverse reactions appear to involve two major steps for each of which there is ample precedent: first, the formation of an O–S bond by replacement of chlorine from the sulfonyl halide, and second, the displacement, elimination or migration of the arenesulfonate ion, $ArSO_3^-$. By analogy, it would be expected that a carboxylic acid would react with an aromatic sulfonyl halide to form a mixed anhydride ($R-COOSO_2Ar$) which should be a highly reactive acylating agent. The observation that 2-hydroxycyclohexaneacetic acid is lactonized, *with retention of configuration*, on attempted tosylation[1] suggested that such anhydride formation could occur even in the presence of alcoholic hydroxy groups.

It has now been found that carboxylic acids react rapidly with aromatic sulfonyl halides in pyridine solution to form symmetrical anhydrides. Thus, benzoic acid gave a 96% yield of benzoic anhydride in five minutes when treated in pyridine solution with a half-molecular amount of benzenesulfonyl chloride. This reaction would appear to be analogous with the "diacylation of water"[7] or the acylation of acids[8] by acyl halides in pyridine, but is more convenient in that preparation and isolation of the halides is obviated. This reaction serves further as a convenient method for the *in situ* preparation of acid anhydrides in pyridine for use in the formation of amides and esters. Thus, addition of aniline to a solution prepared as above gave benzanilide nearly quantitatively; half of the benzoic acid is, of course, lost unless recovered in the isolation procedure.

The chief utility of this reaction appears to be in the preparation of esters. By using a full equivalent of the sulfonyl halide the acid can be recycled through the anhydride stage *in the presence of the alcohol* and thus be completely converted to the ester



$$(R-\overset{\overset{O}{\|}}{C}-)_2O \xrightarrow[C_5H_5N]{R'OH} R-CO_2H + R-CO_2R' \qquad (R-CO_2H \xrightarrow{TsCl} (R-CO-)_2O)$$

Esters which have been prepared in this way are listed in Table I. These products were generally obtained in yields exceeding those realized by use of the corresponding acid chlorides; the solid esters melted, before recrystallization, within two degrees of melting points reported in the literature. This procedure is particularly useful in the esterification of tertiary alcohols[9,10] and in the preparation of solid esters for characterization and identification. The present method of esterification is distinctly superior, with respect to yields and purity of product, to the closely related method of Barnett and Nixon, in which thionyl chloride is used.[11] It seems likely that the superiority of the present method results primarily from the sluggish reactivity of the sulfonyl halide toward alcohols and the relative rapidity of all other reactions in this system.

Experimental

Benzoic Anhydride.—Benzenesulfonyl chloride (8.8 g., 6.4 ml., 0.05 mole) was added with stirring to a solution of 12 g. (0.1 mole) of benzoic acid in 20 ml. of pyridine; the temperature rose to about 75°. Five minutes after addition of the sulfonyl chloride the solution was poured over 50 g. of ice in 100 ml. of water. A heavy oil separated; this was scratched to induce crystallization, collected by filtration, washed with ice-water and dried in a vacuum desiccator. There was obtained 10 g. (97%) of benzoic anhydride, m.p. 39–40°. This material can be purified by crystalliza-

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[1] Part I, J. H. Brewster and C. H. Kucera, THIS JOURNAL, **77**, 4564 (1955).

[2] P. Oxley and W. F. Short, *J. Chem. Soc.*, 382 (1947); 1519 (1948).

[3] C. D. Hurd and L. Bauer, THIS JOURNAL, **76**, 2791 (1954).

[4] A. Werner and A. Piguet, *Ber.*, **37**, 4295 (1904).

[5] (a) P. Oxley, D. A. Peak and W. F. Short, *J. Chem. Soc.*, 1618 (1948); (b) F. Hochstein, *et al.*, THIS JOURNAL, **75**, 5455 (1953); (c) C. R. Stephens, *et al.*, *ibid.*, **76**, 3568 (1954); (d) C. R. Stephens, E. J. Bianco and F. J. Pilgrim, *ibid.*, **77**, 1701 (1955).

[6] (a) D. D. Reynolds and W. O. Kenyon, *ibid.*, **72**, 1593 (1950); (b) G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, 399 (1953).

[7] G. Minunni, *Gazz. chim. ital.*, **22**, 213 (1892); H. Adkins and Q. E. Thompson, THIS JOURNAL, **71**, 2242 (1949).

[8] See, C. F. H. Allen, *et al.*, in E. C. Horning, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 28.

[9] The reaction fails with triphenylcarbinol, other products, currently under study, being formed. Authentic esters of this alcohol could not be recovered from a solution of toluenesulfonyl chloride in pyridine.

[10] Several tertiary acetylenic alcohols have been converted to their 3,5-dinitrobenzoates in 85% yield by this method; G. F. Hennion, University of Notre Dame, private communication.

[11] E. d.B. Barnett and I. G. Nixon, *Chem. News*, **129**, 190, 191 (1924); *J. Chem. Soc., Abstracts*, **126**, 1192, 1195 (1924). These workers also prepared amides by adding thionyl chloride to a mixture of an acid and an amine in pyridine. We have found that toluenesulfonyl chloride reacts much more rapidly with an amine than with an acid so that amides can be made only by preformation of the anhydride. When this is done, and care is taken that no excess of either the sulfonyl halide or amine is used, pure amides are obtained almost quantitatively; the present method, then, is useful when the acid is expendable or conveniently recovered. These workers have also described the essentially quantitative preparation of anhydrides by use of thionyl chloride in pyridine. See also, F. H. Carpenter, THIS JOURNAL, **70**, 2964 (1948).

TABLE I

PREPARATION OF ESTERS

Acid	Alcohol or phenol	Yield, %	Ester M.p., °C.	Ester Ref. m.p.
Acetic	Cholesterol	88	113–114	114[a]
Benzoic	Resorcinol	89	116–117	115[b]
p-Nitrobenzoic	Methanol	92	95–96[s]	95.1[c]
	Ethanol	90	56–57[s]	56.3[c]
	2-Propanol	96	109–110[s]	108.3[c]
	t-Butyl alcohol	85	115–116[t,s]	115.5[d]
	Furfuryl alcohol	90	75–76	75–77[e]
	Benzyl alcohol	96	84–85	85–86[f]
	Benzhydrol	90	130–131	131–132[g]
	Benzoin	90	122–123	123[h]
	Phenol	78	127–128	129[i]
	2-Naphthol	88	166–167	169[j]
3,5-Dinitrobenzoic	Methanol	90	107–108	107.9[k]
	2-Propanol	90	120–121	122.1[k]
	t-Butyl alcohol	92	140–141	141.5[l]
	2,3-Dimethyl-2-butanol	78	109–110	111[m]
	Cyclohexanol	82	111–112	112–113[l]
	l-Menthol	89	153–154	153[n]
	d-Borneol	85	154–155	156–157[o]
	1-Phenylethanol	88	95–96	95[p]
	Cinnamyl alcohol	90	120–121	121[q]
	1-Dodecanol	82	59–60	60[r]

[a] A. Windaus, *Z. physiol. Chem.*, **101**, 276 (1918). [b] J. Ross, J. H. Perry, R. L. Brandt, A. I. Gebhart, J. E. Mitchell and S. Yolles, *Ind. Eng. Chem.*, **34**, 924 (1942). [c] M. D. Armstrong and J. E. Copenhaver, THIS JOURNAL, **65**, 2252 (1945). [d] R. Adams, E. K. Rideal, W. B. Burnett, R. L. Jenkins and E. E. Dreger, *ibid.*, **48**, 1758 (1926). [e] R. D. Kleene and S. Fried, *ibid.*, **62**, 3516 (1940). [f] R. Kothe, *Ann.*, **266**, 313 (1902). [g] J. Meisenheimer and W. Schmidt, *ibid.*, **475**, 157 (1929). [h] J. Meisenheimer, *Ber.*, **38**, 874 (1905). [i] L. C. Raiford, R. Taft and H. P. Lankelma, THIS JOURNAL, **46**, 2051 (1924). [j] E. d.B. Barnett and I. G. Nixon, *Chem. News*, **129**, 190 (1924). [k] G. B. Malone and E. E. Reid, THIS JOURNAL, **51**, 3424 (1929). [l] T. Reichstein, *Helv. Chim. Acta*, **9**, 799 (1926). [m] P. Sutter, *ibid.*, **21**, 1266 (1938). [n] J. Read, W. J. Grubb and D. Malcolm, *J. Chem. Soc.*, 170 (1933). [o] W. Hückel, *Ann.*, **549**, 186 (1941). [p] F. Ashworth and G. N. Burkhardt, *J. Chem. Soc.*, 1791 (1928). [q] F. Willi and F. Knörr, *Chem. Ber.*, **85**, 841 (1952). [r] R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd Edition, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 288. [s] Mixed melting point undepressed. [t] Infrared spectrum identical with authentic sample.

tion from ether and mixed pentanes, 90% recovery, m.p. 41.5–42.5° (lit.[12] 43°).

Benzanilide.—A solution prepared by adding 6.4 ml. of benzenesulfonyl chloride to 12 g. of benzoic acid in 20 ml. of pyridine (see above) was cooled to room temperature under the tap and then 4.7 g. (0.05 mole) of aniline was added. The solution became hot; it was cooled under the tap with stirring until the reaction mixture solidified (about 10 min.). The product was treated with a solution of 10 g. of sodium hydroxide and 5 g. of sodium bisulfite in 200 ml. of water. The dead-white product was collected by filtration and dried in vacuum; yield, 9.2 g. (94%), m.p. 160.5–161° (lit.[13] 160–161°).

Other amides made in this way include acetanilide (49%, crude), m.p. 110–111° (lit.[14] m.p. 114°) and 2-furo-*p*-toluidide (90%), m.p. 107° (lit.[15] m.p. 107.5°).

When the molar ratio of the aromatic sulfonyl halide to the carboxylic acid is greater than one-half the product is orange colored and difficult to purify. The conversion of carboxylic acid to its substituted amide drops due to the formation of sulfonamide from the excess of sulfonyl halide. The sulfonamide can be recovered from the alkaline mother liquors by acidification and is obtained in the amounts to be expected from the excess of sulfonyl halide over that required for formation of the symmetrical anhydride.

Preparation of Esters.—The following procedure is the most generally successful so far devised for this reaction. With highly reactive alcohols it may prove desirable to modify this procedure by using less sulfonyl halide and to add it more slowly. The acid is dissolved in 20–50 parts of pyridine (in some cases a salt separates) and two molecular equivalents of benzenesulfonyl or toluenesulfonyl chloride is added. The solution is chilled in ice and one molecular equivalent of the alcohol or phenol is added. The solution is kept cold for about one hour and then poured into three or four volumes of an ice and water mixture. Solid esters are collected by filtration. Esters which have been prepared in this way are listed in Table I.

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(12) H. T. Clarke and E. J. Rahrs, in H. Gilman and A. H, Blatt, "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 91.

(13) C. N. Webb, *ibid.*, p. 82.

(14) J. H. Matthews, THIS JOURNAL, **39**, 1125 (1917).

(15) E. Baum, *Ber.*, **37**, 2949 (1904).

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Complex Salts of Monosubstituted Amides with the Hydrohalic Acids and the Halogens

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A number of salts of N-(*t*-butyl)-acetamide (A) corresponding to A·HX, $A_2 \cdot HX$, and $A_2 \cdot HX_3$ have been prepared (X = halogen); the latter compounds are halogenating agents. A structure is proposed for the 2:1 complexes similar to that of the carboxylic acid dimers. Complexes of this type are apparently general for monosubstituted and unsubstituted amides.

During an attempted nitrosation of N-(*t*-butyl)-acetamide (A) with nitrosyl bromide,[1,2] orange-colored crystals separated which contained active bromine and analyzed for $C_{12}H_{27}N_2O_2Br_3$. A mixture of A ($C_6H_{13}NO$) and bromine in carbon tetrachloride on recrystallization yielded only the amide; however, after exposure to the atmosphere (HBr formed) the same orange-colored crystals were obtained, suggesting that the analysis above corresponded to $(A)_2 \cdot HBr \cdot Br_2$. Subsequently the same compound was prepared by the step-wise procedure shown below, thereby confirming this partial structure. The same compound was also obtained from a mixture of standard solutions of A, bromine and hydrogen bromide in the correct proportion.

The properties of these intermediates as well as those of the related iodine complex IV are given in Table I. The hydrochlorides corresponding to I

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(1) E. H. White, THIS JOURNAL, **77**, 6008 (1955).

(2) Nitrosyl bromide is partially dissociated into bromine and nitric oxide at 0° (C. M. Blair, Jr., P. D. Brass and D. M. Yost, *ibid.*, **56**, 1916 (1934)).