906. *Synthetic Uses of Polyphosphoric Acid.*

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Nuclear acylation of aromatic amines and formylation of various aromatic compounds in polyphosphoric acid are described. The reagent has also been used for preparing aromatic sulphones and in the Skraup reaction.

Intermolecular acylation catalysed by polyphosphoric acid is a known preparative method [1] for various aromatic ketones. Amino-ketones have so far not been made by this procedure, as ring-positions of aromatic amines were reported to be inactive. For instance, Snyder and Elston [2] obtained only *N*-substituted amides by reaction of aromatic amines with acids in polyphosphoric acid. We have now found that on prolonged treatment some aminobenzophenones can be made in a more convenient way and better yield than previously.[3,4] For instance, 4-aminobenzophenone was produced in 84% yield by heating benzanilide and benzoic anhydride in polyphosphoric acid at 150° for 3 hr. Other acylating agents were used less successfully with benzanilide and the method was also applied to other aromatic amines as set out in Table 1. The low yield with benzamide as the acylating source is undoubtedly due to the hydrolytic resistance of amides towards polyphosphoric acid. No ketones were obtained from *N*-heterocyclic amines.

We also studied methods of formylating aromatic compounds in polyphosphoric acid. Hexamethylenetetramine was found to be a good formylating agent at about 150°. The results differed notably in some cases from other aldehyde syntheses, including the Duff reaction which uses the same formylating agent. Thus phenol, anisole, and cresols gave a dialdehyde, easily separable from the accompanying resinous material by steam-distillation. Yields were small, but the simplicity of the method makes it more practicable than reported procedures for dialdehyde formation. Halogeno- and nitro-phenols furnished monoaldehydes which are not usually accessible by other direct formylation procedures.[5] Formation of *p*-fluorobenzaldehyde in 20% yield compares favourably

[1] Popp and McEwan, *Chem. Rev.*, 1958, **58**, 377; Uhlig and Snyder, *Adv. Org. Chem.*, 1960, **1**, 35.
[2] Snyder and Elston, *J. Amer. Chem. Soc.*, 1954, **76**, 3039.
[3] Dippy and Moss, *J.*, 1952, 2205.
[4] Grammaticakis, *Compt. rend.*, 1952, **235**, 546.
[5] Ferguson, *Chem. Rev.*, 1946, **38**, 227; Houben-Weyl, "Methoden der Organischen Chemie," Georg Thieme, Stuttgart, 1954, Vol. VII, p. 16.

TABLE 1.

Preparation of aminobenzophenones in polyphosphoric acid at 150° for 3 hr.

Starting compound	Acylating agent	Product (benzophenone)	Yield (%)
Aniline	Bz_2O	4-Amino-	55
Benzanilide	—	4-Amino-	57
Benzanilide	Bz_2O	4-Amino-	84
Benzanilide	BzOEt	4-Amino-	33
Benzanilide	$BzNH_2$	4-Amino-	17
Benzo-*o*-toluidide	Bz_2O	4-Amino-3-methyl-	70
Aniline	$(p\text{-Me}\cdot C_6H_4\cdot CO)_2O$	4-Amino-4'-methyl-	44
Benzo-*p*-toluidide	Bz_2O	2-Amino-5-methyl-	55
Benzo-*p*-fluoroanilide	Bz_2O	2-Amino-5-fluoro-	20
Benzo-*p*-chloroanilide	Bz_2O	2-Amino-5-chloro-	15

with the Gattermann–Koch reaction under normal pressure (10%).[6] Aromatic hydrocarbons, when activated by alkyl substituents, are formylated readily. For instance, *p*-tolualdehyde and *p*-isopropylbenzaldehyde were obtained in yields of the same order as are achieved by the recommended and more cumbersome practice,[7,8] while the yield of *p*-cyclohexylbenzaldehyde was increased four-fold over the recorded value.[9] *N*-Heteroaromatic compounds could not be formylated by this procedure, but 2-hydroxyxanthone gave the 1-formyl compound in the same yield as in the Duff reaction.[10] Substitution of polyphosphoric acid for phosphorus oxychloride in the Vilsmeier–Haack reaction [11] (*N*-methylformanilide) proved unattractive. Results obtained with hexamine are given in Table 2.

TABLE 2.

Formylation of aromatic compounds with hexamine in polyphosphoric acid at 150°.

Aromatic compound	Posn. of formylation	Yield (%)	Reaction time (min.)	M. p. (b. p.)
Phenol	2,4-	12	10	112°
Anisole	2,4-	12	15	116
o-Cresol	4,6-	5	5	120
p-Cresol	2,6-	5	6	132
o-Bromophenol	6-	5	5	51
p-Bromophenol	2-	15	3	103
o-Chlorophenol	4-	16	5	139
p-Chlorophenol	2-	17	5	102
o-Nitrophenol	4-	18	5	143
m-Nitrophenol	3-	9	5	53
p-Nitrophenol	2-	17	3	126
m-Nitroanisole	4-	14	5	94
Bromobenzene	4-	44	45	67
Chlorobenzene	4-	37	30	47
Fluorobenzene	4-	20	30	(186)
Benzene	1-	17	40	(179)
Toluene	4-	54	60	(204)
m-Xylene	6-	30	25	(216)
p-Xylene	2-	13	20	(218)
Isopropylbenzene	4-	46	45	(240)
Cyclohexylbenzene	4-	57	45	(236)
2-Hydroxyxanthone	1-	32	10	163

Attempts to prepare 4-amino-4'-methyldiphenyl sulphone by treatment of toluene-*p*-sulphonanilide with polyphosphoric acid, by analogy with the aminobenzophenone synthesis, yielded di-*p*-tolyl sulphone: sulphone formation in reactions involving aromatic sulphonic acids has been previously observed.[12] The action of polyphosphoric acid on sulphonic acids and their derivatives proved in fact to be a practicable way of obtaining

[6] Suschitzky, unpublished result.
[7] Coleman and Craig, *Org. Synth.*, Coll. Vol. II, p. 583.
[8] Crounse, *J. Amer. Chem. Soc.*, 1949, **71**, 1263.
[9] von Braun, Irmisch, and Nelles, *Ber.*, 1933, **66**, 1471.
[10] Davies, Lamb, and Suschitzky, *J.*, 1958, 1790.
[11] Vilsmeier and Haack, *Ber.*, 1927, **60**, 119.
[12] Snyder and Konecky, *J. Amer. Chem. Soc.*, 1958, **80**, 4388; Proctor and Thomson, *J.*, 1957, 2302.

symmetrical aromatic sulphones as shown in Table 3. The procedure was unsuccessful when applied to sulphonic acids of *N*-heteroaromatic compounds. It is noteworthy that no isomeric sulphones were obtained when ambiguity could have arisen, as, for instance, with the naphthalenesulphonic acids (cf. Table 3).

TABLE 3.

Preparation of sulphones R_2SO_2 in polyphosphoric acid.

Starting material	R	Reaction time (hr.)	Temp.	Yield (%)
p-Me·C_6H_4·SO_2·NHPh	*p*-Tolyl	1	190	85
p-Me·C_6H_4·SO_2Cl	*p*-Tolyl	1	190	34
p-Me·C_6H_4·SO_3Na	*p*-Tolyl	2	190	40
(*p*-Me·C_6H_4·SO_2)$_2$Ba	*p*-Tolyl	2·5	120	85
Ph·SO_2·NH_2	Phenyl	2	125	70
1-$C_{10}H_7$·SO_3H	1-Naphthyl	2	135	53
2-$C_{10}H_7$·SO_3H	2-Naphthyl	1	195	50

We also used polyphosphoric acid successfully for the Skraup reaction. Quinoline was prepared in 70%, and 6-nitroquinoline in 36%, yield when sulphuric acid was replaced by polyphosphoric acid in Cohn's modification.[13] It is of interest that synthesis of the latter compound has been reported to fail under similar conditions.[14]

EXPERIMENTAL

Polyphosphoric acid was commercial tetraphosphoric acid (Albright and Wilson) containing 80—85% of phosphorus pentoxide.

Preparation of Amino-ketones.—(*a*) *4-Aminobenzophenone.* Benzanilide (100 g., 0·49 mole), benzoic anhydride (80 g., 0·37 mole), and polyphosphoric acid (800 g.) were heated together at 150—155° for 3 hr. in a two-necked flask, fitted with a stirrer and a thermometer. The mixture was allowed to cool to 80°, then poured in a thin stream into water (1 l.) with stirring. The precipitate was filtered off and suspended with stirring in 40% aqueous sodium hydroxide (250 ml.), to dissolve any benzoic acid. The yellow mixture of the mono- and di-benzoyl derivative of the amino-ketone was collected (175 g.) and hydrolysed under reflux with a mixture of concentrated sulphuric acid (60 ml.) and ethanol (75 ml.) for 2 hr. The mixture was then poured into water (500 ml.), whereby the amine sulphate was precipitated. It was collected, washed with ether to remove ethyl benzoate, and hydrolysed on the water-bath for 0·5 hr. with 40% aqueous sodium hydroxide. Crude 4-aminobenzophenone (90—95 g., 90—95% based on benzanilide) had m. p. 116—118°. Recrystallisation from ethanol gave the pure ketone as pale yellow needles, m. p. 123—124°.

(*b*) Other ketones shown in Table 1 were made in a similar way.

Formylation with Polyphosphoric Acid.—To a stirred solution of polyphosphoric acid (250 g.) at 150°, hexamine (35 g.) and the substance to be formylated (25 g.) were added as quickly as possible. The mixture was stirred and heated for a time specified in Table 2, then rapidly cooled, diluted with water, and steam-distilled. Almost pure aldehyde was obtained from the distillate by extraction with ether or by filtration.

Preparation of Sulphones.—The sulphonic acid (or its derivative) was heated with *ca.* 10 times its weight of polyphosphoric acid as detailed in Table 3. When the mixture was poured into water the nearly pure sulphone separated.

Skraup Reaction with Polyphosphoric Acid.—Heating a mixture [13] of ferrous sulphate (7 g.), aniline (19 g.), nitrobenzene (14·7 g.), and boric acid (12·5 g.) in glycerol (75 g.) and polyphosphoric acid (100 g.) for 15 hr. under reflux and working up the reaction in the usual way yielded quinoline (18·3 g., 70%). By a similar procedure 6-nitroquinoline (30%) was obtained from *p*-nitroaniline.

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[13] Cohn, *J. Amer. Chem. Soc.*, 1930, **52**, 3685.
[14] Snyder and Werber, *J. Amer. Chem. Soc.*, 1950, **72**, 2965.