The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* keeping the pot temperature below 40°. The residual oil crystallized. On recrystallization from cyclohexane, 33 g. of pure *anti*-isobutyrophenone oxime was obtained, m.p. 97–100[29] (lit.[19] m.p. 95–96°), m.m.p. 56–60° with the *syn* isomer.

Attempts to prepare the *anti* isomer by ultraviolet light isomerization in ethanol or benzene for varying lengths of time led only to an inseparable mixture of *syn* and *anti* forms. Brief warming with dilute alcoholic hydrochloric acid also gave an inseparable mixture of isomers, m.p. 56–60°.

Evidence obtained from thin layer chromatography experiments indicate that the mixture of *carbamates* prepared from the *syn–anti* oxime mixture could be separated on alumina using methylene chloride as eluate.

p-Chlorobenzaldoxime Carbamate (22).—*syn-* and *anti-p*-chlorobenzaldoximes were prepared as described by Erdmann.[30] The same carbamate was obtained regardless of which isomer was used as starting material.

Benzyl Methyl Ketoxime Carbamate (23).—The ketoxime, b.p. 106° (1.5 mm.), was prepared as described by Neber.[31] No isomer of this oxime is known.

At the end of the reaction period, the reaction mixture was treated with water, and the aqueous suspension was extracted with methylene chloride. The organic solution was dried and concentrated to give an oil which slowly solidified. The semisolid material was chromatographed in ethyl acetate solution using alumina (Fisher chromatographic alumina), and the crystalline eluates were further purified by recrystallization from a mixture of chloroform and hexane.

2-(*p*-Chlorophenyl)-3-methyl-2,3-butanediol Cyclic Carbonate (25).—The starting diol[32] was treated in the standard manner. After removal of the solvent, a little water was added; then the solution was neutralized with bicarbonate, extracted with ether, dried, and concentrated to an oil that slowly set to a semisolid. The oil was dissolved in benzene and chromatographed over neutral alumina. The fractions that crystallized were combined and recrystallized from methanol, 56% yield. The infrared spectra show no –NH absorption and thus agree with the elemental analysis, which corresponds to the cyclic carbonate.

Some of the other chromatographic fractions crystallized after prolonged standing. Inspection of the infrared spectra indicates that a mixture of mono- and dicarbamates was probably present.

2-(*p*-Trifluoromethylphenyl)-3-methyl-2,3-butanediol Cyclic Carbonate (26). **A. 2-(*p*-Trifluoromethylphenyl)-3-methyl-2,3-butanediol.**[33]—To the Grignard reagent prepared from 113 g. (0.454 mole) of *p*-bromobenzotrifluoride and 12.5 g. (0.51 mole) of magnesium turnings in 1000 ml. of ether was added 21 g. (0.205 mole) of 2-methyl-2-hydroxy-3-butanone (K and K Laboratories) in 50 ml. of ether at such a rate that refluxing proceeded slowly. The mixture was stirred overnight and treated first with 100 ml. of a saturated ammonium chloride solution and then with 100 ml. of 2 *N* hydrochloric acid. After stirring for 30 min., the ethereal layer was separated and concentrated *in vacuo* to give a solid. This was recrystallized from cyclohexane, a mixture of methanol–water, and a mixture of cyclohexane and benzene. White needles were obtained, m.p. 98–99°; yield, 30 g. (59%).

Anal. Calcd. for $C_{12}H_{15}F_3O_2$: C, 58.06; H, 6.09. Found: C, 58.48; H, 6.51.

B. Preparation of the Cyclic Carbonate.—The starting diol was treated in the standard manner. The resulting oil was chromatographed over neutral alumina. The fractions that crystallized were combined and recrystallized from cyclohexane, 20% yield.

Acknowledgment.—We wish to thank Mr. Kenneth Snader for experimental assistance.

(29) We are indebted to Dr. Robert Lyle for providing us with a sample of *anti*-isobutyrophenone oxime (isolated by manual separation of crystals). It proved to be identical by mixture melting point and infrared comparisons with our material.

(30) H. Erdmann and E. Schwechten, *Ann.*, **260**, 53 (1890).

(31) P. W. Neber and A. V. Friedolsheim, *ibid.*, **449**, 109 (1926).

(32) Phenglycodol, J. Mills, *et al.*, *Proc. Soc. Exptl. Biol. Med.*, **96**, 100 (1957).

(33) The preparation of this material was carried out by Dr. Irwin Pachter of our laboratories.

Sulfonyl Fluorides as Intermediates in Organic Synthesis. I. The Synthesis of Aminobenzenesulfonyl Fluorides and Their Condensation with β-Ketonic Esters

A. DE CAT AND R. VAN POUCKE

Chemical Research Department, Gevaert Photo-Producten N.V., Antwerp, Belgium

Received February 6, 1963

Aminobenzenesulfonyl fluorides have been synthesized by deacylation of acetylaminobenzenesulfonyl fluorides or by catalytic hydrogenation of nitrobenzenesulfonyl fluorides over Raney nickel catalyst. They can be condensed in the usual way with β-ketonic esters to give N-acylacetylaminobenzenesulfonyl fluorides which can be converted into the corresponding sulfonates by alkaline hydrolysis.

The condensation of β-ketonic esters with substituted anilines to give acylacetylanilides is generally conducted in boiling xylene. Aminobenzenesulfonic acids or their salts, however, possessing very low basicity and negligible solubility in this reaction medium, fail to react. Since this excluded one-step synthesis of N-acylacetylaminobenzenesulfonates III, indirect synthetic routes had to be investigated.

Esters of N-acylacetylaminobenzenesulfonic acids IIa and IIb were expected to be interesting intermediates for the preparation of N-acylacetylaminobenzenesulfonates of type III.

However, condensation of β-ketonic esters with methyl aminobenzenesulfonates Ia gave only low yields of the expected compounds IIa, along with rather large amounts of methylaminobenzenesulfonic acids resulting from autoalkylation of methyl aminobenzenesulfonates Ia. Phenyl acylacetylaminobenzenesulfonates IIb could be obtained in high yields, but were found too resistant to alkaline hydrolysis.

Finally, the condensation of β-ketonic esters with aminobenzenesulfonyl fluorides Ic, and the subsequent alkaline hydrolysis of the resulting N-acylacetylaminobenzenesulfonyl fluorides IIc proved to be a successful

$$\mathrm{RCOCH_2COOC_2H_5} + \mathrm{H_2NArSO_2X} \xrightarrow[\text{xylene}]{\text{boiling}}$$

Ia, X = $-OCH_3$
b, X = $-OC_6H_5$
c, X = $-F$

$$\mathrm{RCOCH_2CONHArSO_2X} \xrightarrow{\text{NaOH}} \mathrm{RCOCH_2CONHArSO_2ONa}$$

IIa, X = $-OCH_3$
b, X = $-OC_6H_5$
c, X = $-F$

III

R = an aliphatic, aromatic, or heterocyclic substituent

TABLE I

NITRO- AND ACETYLAMINOBENZENESULFONYL FLUORIDES

Substituent(s)	Yield,[a] %	M.p.,[a] °C.	Recrystg.[b] solvent	N Calcd.	N Found	S Calcd.	S Found	Cl Calcd.	Cl Found	F Calcd.	F Found
3-NO_2	(89) 82	(47) 47	A							9.25	9.24
4-NO_2	(87) 78	(78) 79	A	6.86	6.96	15.62	15.92			9.25	9.68
3-NO_2, 4-Cl	(93) 82	(60) 60	A	5.86	5.80	13.36	13.59	14.82	14.73		
5-NO_2, 2-Cl	(91) 82	(43) 47	B	5.86	5.84	13.36	13.59	14.82	14.68		
4-NO_2, 3-Cl	(73) 51	(56) 57	A	5.86	5.87	13.36	13.65	14.82	14.53	7.94	7.95
2-NO_2, 5-Cl	(85) 69	(77) 77	C	5.86	5.82	13.36	13.54	14.82	14.72	7.94	7.90
4-$NHCOCH_3$[c]	(90)	(176)				14.74	14.95			8.75	8.70
5-$NHCOCH_3$, 2-OCH_3[c]	(94) 84	(162) 162	A	5.67	5.70	12.95	12.86			7.69	7.28
3-$NHCOCH_3$, 4-OCH_3[d]	(93)	(164) 164	B			12.95	12.94			7.69	7.58
5-$NHCOCH_3$, 2-CH_3[d]	(81) 71	(119) 122	C	6.06	6.20	13.85	13.88			8.22	8.20

[a] Figures in parentheses refer to yield and respective melting point of the crude sulfonyl fluorides. [b] Solvents: A, ethanol; B, ethanol–water; C, methanol–water. [c] Sulfonyl chlorides (1 mole) were added over a period of 15–30 min. to an aqueous potassium fluoride solution containing 1.5 mole of potassium fluoride per 600 ml. The reaction mixture was further boiled for 15 min. and the product was precipitated with water. [d] Sulfonyl chlorides were dissolved in boiling dioxane (300 ml. per mole) and 120 ml. of saturated potassium fluoride solution was added. The mixture was refluxed for 30 min. and the product was precipitated with water.

TABLE II

AMINOBENZENESULFONYL FLUORIDES

Position of substituent(s)	Method[a]	Yield,[a] %	M.p.,[a] °C.	Recrystg.[b] solvent	N Calcd.	N Found	S Calcd.	S Found	F Calcd.	F Found
3-NH_2	B	80	30[c]							
4-NH_2	B	(90) 77	(69) 70	A	7.99	8.10	18.29	18.64	10.86	11.00
	A[d]	(92)	(70)							
3-NH_2, 4-CH_3	B	(98) 95	(92) 94[e]	B	7.40	7.32	16.93	17.28	10.05	10.38
5-NH_2, 2-CH_3	A[f]	(97)	(62)		7.40	7.31	16.93	16.75	10.05	10.20
3-NH_2, 4-Cl	B	(86) 72	(69) 70	C	6.68	6.78	15.28	15.58	9.06	9.25
5-NH_2, 2-Cl	B	(93) 65	(60) 70	D	6.68	6.96	15.28	15.34	9.06	9.16
4-NH_2, 3-Cl	B	(90) 72	(132) 134	E	6.68	6.65	15.28	15.28	9.06	9.25
2-NH_2, 5-Cl	B	(71) 35	40	D	6.68	6.64	15.28	15.21	9.06	9.10
3-NH_2, 4-OCH_3	A[g]	(97) 88	(63) 63	F	6.83	6.81	15.61	15.71		
5-NH_2, 2-OCH_3	A[g]	(91)	(74)		6.83	6.67	15.61	15.26	9.26	8.85

[a] Method A, deacylation of acetylaminobenzenesulfonyl fluorides; method B, catalytic hydrogenation of nitrobenzenesulfonyl fluorides. Figures in parentheses refer to yield and respective melting point of the sulfonyl fluoride prior to purification. [b] Solvents:, A, ethanol–water (11:8); B, hexane–benzene (3:1); C, hexane–benzene (2:1); D, ethanol–water (1:3); E, ethanol–water (2:1); F carbon tetrachloride. [c] Purified by vacuum distillation, b.p. 160° (12 mm.). [d] Refluxing 1 mole of acetylamino derivative with 400 ml. of 10 *N* HCl and 600 ml. of ethanol. [e] Repeated recrystallization failed to give the lit.[2] m.p. 96–97°. [f] Refluxing 1 mole of acetylamino derivative with 150 ml. of 10 *N* HCl, 300 ml. of water, and 300 ml. of ethanol. [g] Refluxing 1 mole of acetylamino derivative with 300 ml. of 10 *N* HCl, 200 ml. of water, and 500 ml. of ethanol.

general procedure for the preparation of N-acylacetylaminobenzenesulfonates III.[1]

The success of this synthesis is based upon the remarkable stability of the fluorosulfonyl group in neutral or acid medium and the relative ease with which it is hydrolyzed by alkali. These properties had already been reported previously.[2,3]

The aminobenzenesulfonyl fluorides Ic were prepared either by reduction of nitrobenzenesulfonyl fluorides or by acid-catalyzed deacylation of acetylaminobenzenesulfonyl fluorides. The required nitrobenzenesulfonyl fluorides (Table I) were obtained in excellent yields by refluxing for a short time the corresponding sulfonyl chlorides with 50% excess of saturated aqueous potassium fluoride solution, according to Davies and Dick.[3]

If the same reaction conditions were applied to acetylaminobenzenesulfonyl chlorides (with melting points above the boiling point 126° of the potassium fluoride solution) a thick slurry was produced which could not be stirred efficiently, resulting in local overheating and considerable hydrolysis. However, operating in a more dilute aqueous solution or in dioxane–water afforded the expected sulfonyl fluorides in high yields (Table I).

Jenssen and co-workers[4] carried out the deacylation of 4-acetylaminobenzenesulfonyl fluoride by boiling the latter for a short time with 4 *N* hydrochloric acid, and obtained a 47% yield of the free amino derivative by basifying with sodium hydroxide. In our hands this procedure proved to be unsatisfactory, especially when larger quantities are involved. Much better results were achieved by carrying out the deacylation with hydrochloric acid in aqueous alcoholic medium. The proportion of hydrochloric acid to acetylamino derivative, the concentration of the acid, and the proportion of water to alcohol have to be determined from case to case to obtain the maximum yield and reaction rate. On account of the relative sensitivity of the fluorosulfonyl group to alkali, sodium bicarbonate was used instead of sodium hydroxide to liberate the aminobenzenesulfonyl fluorides. Yields ranged between 91 and 97% (Table II).

During exploratory attempts to hydrogenate 3-nitrobenzenesulfonyl fluoride in alcoholic solution over palladium on charcoal, the hydrogen uptake was found to be very slow and to stop long before the theoretical

(1) (a) Preliminary communication: A. De Cat, XIVth Intern. Congr. Pure and Appl. Chem., Zürich, Abstracts of Papers, 1955 p. 306; (b) A. De Cat and R. Van Poucke (Gevaert Photo-Producten N.V.) British Patent 808,276 (British Prior. 5.4.1955); *Chem. Abstr.*, **53**, 21308 (1959).

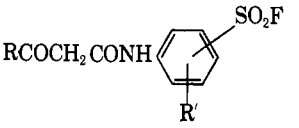
(2) W. Steinkopf, *J. prakt. Chem.*, [2] **117**, 1 (1927).

(3) W. Davies and J. Dick, *J. Chem. Soc.*, 2104 (1931).

(4) K. Jenssen, O. Hanson, I. Jörgensen, and K. Smith, *Dansk. Tidsskr. Farm.*, **18**, No. 9, 201 (1944).

TABLE III

N-ACYLACETYLAMINOBENZENESULFONYL FLUORIDES



Compd.	R	Position of substituent(s) $-SO_2F$	R'	Yield, %	M.p., °C.	Recrystg.[a] solvent	C Calcd.	C Found	N Calcd.	N Found	S Calcd.	S Found	F Calcd.	F Found
1	C_6H_5—	3	H	70	162	A	56.07	55.80	4.36	4.28	9.97	9.57	5.92	6.20
2	C_6H_5—	4	H	51	176	A	56.07	56.08	4.36	4.43	9.97	10.07		
3		3	H	55	163	A					10.29	10.22		
4	$C_{15}H_{31}$—	4	H	75	116	B	63.30	62.57	3.08	3.20	7.03	7.00		
5	3-$NO_2C_6H_4$—	3	H	85	176	C	49.18	49.53	7.65	7.53	8.75	8.78	5.19	5.15
6	3-$H_2NC_6H_4$—[b]	3	H	75	152	D	53.57	53.42	8.33	8.48	9.52	9.30	5.65	5.85
7	3-$C_{15}H_{31}CONHC_6H_4$—[c]	3	H	76	129	E			4.88	4.85			5.57	5.63
8	4-$C_{16}H_{33}OC_6H_4$—	4	H	75	135	F	66.31	65.80	2.49	2.49	5.70	5.92		
9	4-$C_{16}H_{33}OC_6H_4$—	5	2-CH_3	66	135	G					5.56	5.57		
10	4-$C_{16}H_{33}OC_6H_4$—	3	4-CH_3	62	86	E								[d]
11	4-$C_{16}H_{33}OC_6H_4$—	5	2-OCH_3	73	152	H								[d]
12	4-$C_{16}H_{33}OC_6H_4$—	3	4-OCH_3	70	115	I								[d]
13	4-$C_{16}H_{33}OC_6H_4$—	5	2-Cl	70	130	H								[d]

[a] Solvents: A, ethanol; B, ethyl acetate; C, dioxane; D, dichloroethane; E, methanol; F, methylcyclohexane; G, ligroin; H, acetone; I, methanol–acetone. [b] A 36.6-g. sample (0.1 mole) of compound 5 was hydrogenated in 300 ml. of dioxane over 3 g. of Raney nickel at 75°. The product was precipitated with water and recrystallized from dichloroethane. [c] A 33.6-g. sample (0.1 mole) of compound 6 was dissolved in 300 ml. of dioxane containing 8.7 g. (0.11 mole) of pyridine. A 27.5-g. sample (0.1 mole) of palmitoyl chloride was added over a period of 10 min. Reaction mixture stirred at 45° for 1 hr. and at 60° for 2 hr. The product was precipitated with water and recrystallized from methanol. [d] Purity of these N-acylacetylaminobenzenesulfonyl fluorides was established by titration with $NaOCH_3$ in *n*-butylamine with azoviolet as indicator. During titration, one equivalent of $NaOCH_3$ was consumed by the acidic methylene group and two further equivalents by the N-butylsulfonamide group and hydrogen fluoride resulting from the following reaction.

$$RCOCH_2CONHArylSO_2F + C_4H_9NH_2 \longrightarrow RCOCH_2CONHArylSO_2NHC_4H_9 + C_4H_9NH_2{\cdot}HF$$

amount of hydrogen had been absorbed. The contents of the autoclave had become strongly acidic, apparently due to hydrogenolysis of the fluorosulfonyl group. Raney nickel W-2[5] however, converted the nitrobenzenesulfonyl fluorides into the corresponding amino derivatives in excellent yield (Table II). Hydrogenations were conducted at pressures between 20 and 100 atm. and at temperatures between 70 and 90°. An occasional rise in temperature up to 110–120°, due to the exothermic reaction, proved to be without any harm for the fluorosulfonyl group.

The aminobenzenesulfonyl fluorides obtained were condensed in the usual way[6] with β-ketonic esters such as ethyl benzoylacetate,[7] ethyl α-furoylacetate,[8] ethyl 3-nitrobenzoylacetate,[9] methyl palmitoylacetate,[10] and methyl 4-hexadecyloxybenzoylacetate[1b] to produce the N-acylacetylaminobenzenesulfonyl fluorides of type IIc in good to excellent yields (Table III). These compounds were converted to the corresponding N-acylacetylaminobenzenesulfonates III by treating them with 3 moles of sodium hydroxide at 50 to 60°. The use of only 2 moles of sodium hydroxide resulted in incomplete saponification since the acidic methylene group which is present in the N-acylacetylaminobenzenesulfonyl fluorides as well as in the corresponding sulfonates, subtracts a mole of sodium hydroxide from the hydrolysis reaction.

Compounds of type III containing a long aliphatic chain such as those derived from methyl palmitoylacetate (R = pentadecyl) and methyl 4-hexadecyloxybenzoylacetate (R = 4-hexadecyloxyphenyl) are especially important, since they constitute yellow image color couplers used in color photography.[1b]

An alternate way of introducing the long aliphatic chain involves the catalytic hydrogenation of 3-nitrobenzoylacetylaminobenzenesulfonyl fluoride (IIc, R = 3-nitrophenyl), the condensation of the obtained amino derivative with palmitoyl chloride, and the subsequent alkaline hydrolysis of the resulting 3-palmitoylaminoacetylaminobenzenesulfonyl fluoride (IIc, R = 3-palmitoylaminophenyl).

Experimental

Melting points were determined on a Kofler hot bench melting point apparatus and are corrected.

Nitro- and Acetylaminobenzenesulfonyl Chlorides.—Most requisite sulfonyl chlorides were prepared according to the literature: 3- and 4-nitrobenzenesulfonyl chloride,[11] 4-acetylaminobenzenesulfonyl chloride,[12] 3-acetylamino-4-methoxybenzenesulfonyl chloride,[13] 5-acetylamino-2-methylbenzenesulfonyl chloride,[14] 4-chloro-3-nitrobenzenesulfonyl chloride.[15]

5-Acetylamino-2-methoxybenzenesulfonyl Chloride.—This compound was prepared by chlorosulfonation of *p*-methoxyacetanilide following the procedure described for the corresponding ethoxy derivative.[14] The crude sulfonyl chloride, which was obtained by diluting the reaction medium with ice–water, was col-

(5) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 181.
(6) C. Kibler and A. Weissberger, *ibid.*, p. 108.
(7) S. MacElvain and K. Weber, *ibid.*, p. 379.
(8) G. Barger, R. Robinson, and L. Smith, *J. Chem. Soc.*, 724 (1937).
(9) C. Bülow and E. Hailer, *Ber.*, **35**, 931 (1902).
(10) M. Viscontini and N. Merckling, *Helv. Chim. Acta*, **35**, 2280 (1952).
(11) H. Meerwein, G. Dittmar, R. Göllner, K. Hafner, F. Mensch, and O. Steinfort, *Ber.*, **90**, 841 (1957).
(12) S. Smiles and J. Stewart, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 8.
(13) R. Child, *J. Chem. Soc.*, 715 (1932).
(14) R. Johnson and S. Smiles, *ibid.*, **123**, 2384 (1923).
(15) F. Hoechst, Belgian Patent 553,871 (German Prior. 31.12.1955).

lected on a suction funnel, washed with water, and dried under vacuum over sodium hydroxide pellets (yield, 75%). The m.p. 157° remained unchanged after recrystallization from benzene.

Anal. Calcd. for $C_9H_{10}O_4NSCl$: S, 12.16; Cl, 13.50. Found: S, 12.12; Cl, 13.65.

2-Chloro-5-nitrobenzenesulfonyl Chloride.—Sodium 2-chloro-5-nitrobenzenesulfonate was refluxed with excess thionyl chloride in the presence of dimethylformamide as a catalyst, according to the general procedure of Bosshard, *et al.*[16] After distilling the excess thionyl chloride and adding ice–water, the crude sulfonyl chloride was isolated, washed, dried, and recrystallized from carbon tetrachloride. The yield was 77%, m.p. 89–90°. Fischer[17] obtained a product with the same melting point by the classical phosphorus pentachloride method.

3-Chloro-4-nitrobenzenesulfonyl Chloride.—This compound was prepared by applying the Meerwein procedure[11] to 3-chloro-4-nitroaniline.[18] Yield after recrystallization from hexane–isopropyl ether was 66%, m.p. 36°.

Anal. Calcd. for $C_6H_3O_4NSCl_2$: N, 5.47; S, 12.50; Cl, 27.69. Found: N, 5.44; S, 12.65; Cl, 27.65.

5-Chloro-2-nitrobenzenesulfonyl chloride was prepared similarly to the previous compound from 5-chloro-2-nitroaniline.[18] Yield after recrystallization from hexane–isopropyl ether was 66%, m.p. 68°.

Anal. Calcd. for $C_6H_3O_4NSCl_2$: S, 12.50; Cl, 27.69. Found: S, 12.60; Cl, 26.77.

Nitro- and Acetylaminobenzenesulfonyl Fluorides (Table I). General Procedure.—Potassium fluoride (870 g.) was dissolved in 900 ml. of warm water to give 1200 ml. of a stock solution, containing 1.5 moles (87 g.) of potassium fluoride per 120 ml. This solution (120 ml. per mole of sulfonyl chloride to be converted) was heated to boiling (126°) in a reaction flask provided with an efficient stirrer and a thermometer reaching into the liquid.

Since the nitrobenzenesulfonyl chlorides, which were used in this study, have melting points below 126°, they were dispersed very easily in the boiling solution as fine oily drops. During the reaction, the less soluble potassium chloride precipitated and this was attended with a lowering of the boiling point of the reaction medium. Generally after 20 to 30 min., the temperature had dropped down to 112–113° and this point was considered as the end point of the reaction. When the reaction mixture was diluted with cold water, the nitrobenzenesulfonyl fluorides solidified, but were found to contain variable amounts of the corresponding potassium nitrobenzenesulfonates, which result from partial hydrolysis and which are only sparingly soluble in cold water. Removing these impurities by washing with hot water produced nitrobenzenesulfonyl fluorides which, in most cases, could be used for the subsequent catalytic hydrogenation without any further purification.

For the preparation of acetylaminobenzenesulfonyl fluorides it was found preferable to operate either in more dilute aqueous medium or in dioxane–water (experimental details are given as footnotes to Table I).

Aminobenzenesulfonyl Fluorides (Table II). Method A. Deacylation of Acetylaminobenzenesulfonyl Fluorides.—The deacylations were accomplished by refluxing the acetylaminobenzenesulfonyl fluoride with hydrochloric acid in aqueous alcoholic solution. The composition of the reaction medium was selected so as to contain sufficient ethanol to obtain ready dissolution of the acetylamino derivative at the boiling point, sufficient hydrochloric acid to obtain complete deacylation in about 1 hr., and the necessary amount of water to keep the resulting amino hydrochloride in solution during deacylation.

The composition of the different reaction media is indicated in Table II. After deacylation, the reaction medium was cooled to room temperature, diluted with water to dissolve the precipitated amino hydrochloride, and neutralized with a slight excess of solid sodium bicarbonate. The precipitated aminobenzenesulfonyl fluorides were collected by suction filtration, washed with water, and dried in a vacuum desiccator. In most cases the aminobenzenesulfonyl fluorides obtained were very pure and did not need any further purification by recrystallization.

Method B. Hydrogenation of Nitrobenzenesulfonyl Fluorides.—The hydrogenations were carried out over Raney[5] nickel W-2 catalyst in ethanol, since the latter proved to be a good solvent for both the nitro- and the aminobenzenesulfonyl fluorides. Usually 10 ml. of settled Raney nickel were taken per mole of nitroderivative. Small scale hydrogenations (0.05–0.25 mole) were run in a glass Parr low-pressure hydrogenation apparatus at pressures of 2–3 atm. and temperatures of 20 to 40°. Hydrogenation of larger batches was conducted in stainless steel autoclaves, generally at temperatures between 70 and 90° and at pressures between 20 and 100 atm. (starting pressure at room temperature). In the case of nitrobenzenesulfonyl fluorides bearing nuclear chlorine substituents hydrogenation temperatures were limited to 80° by flowing cooling water through an internal cooling spiral) in view of possible dechlorination.

After absorption of the theoretical amount of hydrogen, the catalyst was filtered off, and the aminobenzenesulfonyl fluoride isolated by precipitation with water (eventually after partial removal of the solvent by distillation at reduced pressure).

Solid aminobenzenesulfonyl fluorides were purified by recrystallization from a suitable solvent. 3-Aminobenzenesulfonyl fluoride which is a low melting product (m.p. 29–30°) was preferably purified by distillation at reduced pressure. When the crude amino derivative as obtained by precipitation with water was distilled directly complete decomposition took place. However, when the crude oily amino derivative was washed with a solution of sodium bicarbonate distillation could be carried out without any difficulty, even with batches of several moles.

The aminobenzenesulfonyl fluorides which were obtained by the preceding procedure are listed in Table II.

Condensation of β-Ketonic Esters with Aminobenzenesulfonyl Fluorides.—The necessary β-ketonic esters were prepared by published procedures: ethyl benzoylacetate,[7] ethyl α-furoylacetate,[8] ethyl 3-nitrobenzoylacetate,[9] methyl palmitoylacetate,[10] and methyl 4-hexadecyloxybenzoylacetate.[1b]

Equimolecular amounts of aminobenzenesulfonyl fluorides and the appropriate β-ketonic esters were heated in dry xylene (600–800 ml. per mole of aminobenzenesulfonyl fluoride) in a flask fitted with a stirrer and a short distillation column filled with glass helices. The distillation column carried a still head with adjustable reflux. Partial reflux was utilized as long as alcohol (methanol or ethanol, depending on the β-ketonic ester used) distilled. Distillation was then continued until the temperature in the still head reached the boiling point of xylene, after which most of the solvent was removed by distillation at reduced pressure. The residue was recrystallized from the appropriate solvent. The properties of the individual acylacetylaminobenzenesulfonyl fluorides are summarized in Table III.

Alkaline Hydrolysis of N-Acylacetylaminobenzenesulfonyl Fluorides.—The following description of two typical examples will serve to illustrate the hydrolysis procedure.

Sodium N-[α-(Palmitoyl)acetyl]-4-aminobenzenesulfonate.—N-[α-(Palmitoyl)acetyl]-4-aminobenzenesulfonyl fluoride (9.1 g., 0.02 mole) was dissolved in 20 ml. of ethanol at 60°. After adding 60 ml. of *N* sodium hydroxide, the solution was further heated for 25 min. and acidified with acetic acid to pH 4. The white precipitate was collected, dried, and recrystallized twice from Methyl Cellosolve yielding fine white powder, 6.4 g. (70%).

Anal. Calcd. for $C_{24}H_{38}O_5NSNa$: S, 6.74; acidic methylene group, 2.11 mequiv./g. Found: S, 6.73; acidic methylene group, 2.10 mequiv./g. (determined by titration with $NaOCH_3$ in dimethylformamide).

Sodium N-[α-(Benzoyl)acetyl]-3-aminobenzenesulfonate.—To a stirred suspension of 312 g. (1 mole) of N-[α-(benzoyl)acetyl]-3-aminobenzenesulfonyl fluoride in 1200 ml. of water at 50° was added gradually a solution of 120 g. of sodium hydroxide in 300 ml. of water. Heating was continued for 30 min. at 70°, after which the resulting clear solution was acidified with 72 ml. of acetic acid to pH 4. Addition of saturated sodium acetate solution, and cooling caused the sulfonate to crystallize. This was collected by suction filtration, washed with methanol, and dried. There was obtained 239 g. (70%) of a white powder.

Anal. Calcd. for $C_{15}H_{12}O_5NSNa$: acidic methylene group, 2.92 mequiv./g. Found: acidic methylene group, 2.86 mequiv./g. (determined by titration with $NaOCH_3$ in dimethylformamide).

The first procedure was used for all compounds containing a long aliphatic chain. The lower molecular weight sulfonates were highly soluble in water and had to be salted out either by sodium acetate or sodium chloride, according to the procedure of the second example. Recrystallization from a suitable solvent

(16) H. Bosshard, R. Mory, M. Schmid, and H. Zöllinger, *Helv. Chim. Acta*, **42**, 1635 (1959).

(17) P. Fischer, *Ber.*, **24**, 3185 (1891).

(18) (a) H. Mayer and E. Turner, *J. Chem. Soc.*, 692 (1928); (b) R. Fuson, R. Bauman, E. Howard, and E. Marvell, *J. Org. Chem.*, **12**, 804 (1947).

(in most cases Methyl Cellosolve, mixtures of Methyl Cellosolve and ethanol, or acetic acid) gave N-acylacetylaminobenzenesulfonates with a purity of 97–99.5%. Small amounts (1 to 3%) of sodium fluoride or acetate which were found to be present by titration with perchloric acid in acetic acid, could only be removed by repeated recrystallizations.

Acknowledgment.—We wish to thank Prof. Dr. A. Van Dormael, Director of the Chemical Research Department, for his kind interest in this work. We are indebted to Dr. L. Moelants, Head of the Analytical Department, for the analyses.

The Chemistry of Bi(phosphine sulfides). II. A Convenient Method for Preparing Phosphine Oxides and Phosphine Sulfides Containing Different Groups[1a]

H. JAMES HARWOOD[1b] AND KENNETH A. POLLART

The Central Research Department, Monsanto Chemical Company, St. Louis 66, Missouri

Received November 30, 1962

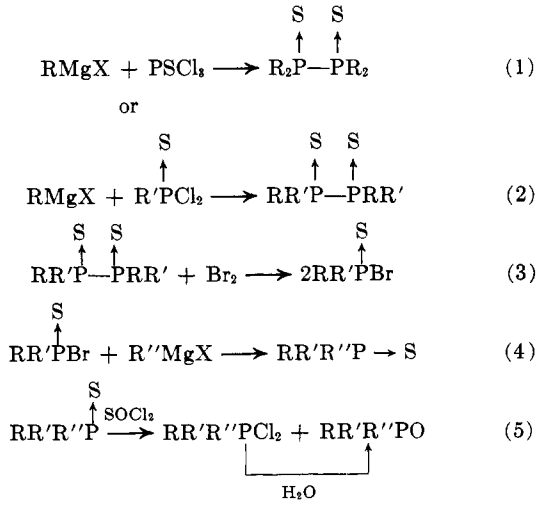
Dialkyl- and alkylarylthiophosphinic halides react with Grignard reagents to form phosphine sulfides in good yield, whereas thiophosphoryl chloride and alkyl- or arylthiophosphonic dichlorides are known to react with Grignard reagents to yield bi(phosphine sulfides). On the basis of these findings, a stepwise procedure for preparing phosphine sulfides and oxides has been developed.

Although a considerable number of symmetrical phosphines, phosphine oxides, and phosphine sulfides are described in the chemical literature, only a few of such compounds containing different groups have been reported.[2] Until recently, the preparations of unsymmetrically substituted phosphines, phosphine oxides, etc., were based, in one or more of the reactions utilized, upon reactions of halophosphines, phosphonic dihalides, or phosphinic halides with organometallic compounds. Since the degree of substitution realized in these reactions could not be selectively controlled, mixtures resulted, and intermediates necessary for preparing the unsymmetrical compounds were not obtained in high over-all yields.

In recent years, improved routes to unsymmetrical phosphines and their derivatives have been developed. The stepwise alkylation of phosphines has been refined considerably[3–5] and a number of new techniques have been developed for the synthesis of unsymmetrical phosphinic acids and their derivatives.[6–8] Unsymmetrical phosphinic halides obtained *via* these recently developed procedures may be converted to unsymmetrically substituted phosphine oxides by reaction with Grignard reagents or metal alkyls, although such reactions are sometimes difficult[2b] and may require forcing conditions.

The cleanest routes to unsymmetrically substituted phosphines, etc., however, seem to be those in which tertiary phosphines containing benzyl,[9] β-cyanoethyl,[10] or hydroxymethyl groups[11] react with alkylating agents. The quarternary phosphonium salts, thus obtained in high yield, are then degraded to new tertiary phosphines. Repetition of the alkylation–degradation sequence provides a convenient method for preparing unsymmetrically substituted phosphines. Since most of the phosphine sulfides prepared in the past have been obtained by the addition of sulfur to phosphines, the alkylation–degradation reactions can be utilized in the synthesis of unsymmetrically substituted phosphine sulfides as well. The alkylation–degradation procedure cannot be used to place aryl substituents on phosphorus, however, and aryl phosphines must be available as starting materials if unsymmetrical arylphosphines or aryl substituted phosphine sulfides are to be prepared.

This paper describes a route to unsymmetrical phosphine derivatives which seems to complement the synthetic methods discussed. For example, this route may be used to prepare phosphine derivatives which contain one or two aromatic substituents. In special cases it may perhaps also be applicable to the preparation of unsymmetrically substituted triarylphosphine derivatives. Our synthesis is based on the following series of reactions.



Bi(phosphine sulfides), the key intermediates in the synthesis, are usually prepared in good yield by treating thiophosphoryl chloride (eq. 1) or phosphinothioic

(1) (a) Presented in part before the Division of Organic Chemistry at the 136th National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1959; (b) The University of Akron, Akron 4, Ohio.

(2) (a) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950; (b) for a recent review of the synthesis of phosphine oxides, etc., see K. D. Berlin and G. B. Butler, *Chem. Rev.*, **60**, 243 (1960).

(3) F. Pass, E. Steiniger, and H. Schindlbauer, *Monatsh. Chem.*, **90**, 792 (1959).

(4) M. M. Rauhut, H. A. Curries, A. M. Semsel, and V. P. Wystrach, *J. Org. Chem.*, **26**, 5138 (1951).

(5) K. Issleib and D. Jacob, *Chem. Ber.*, **94**, 107 (1961), and other papers in this series.

(6) T. P. Dawson and K. C. Kennard, *J. Org. Chem.*, **22**, 1671 (1957).

(7) P. C. Crofts and I. S. Fox, *J. Chem. Soc.*, 2995 (1958).

(8) D. C. Morrison, *J. Am. Chem. Soc.*, **72**, 4820 (1950).

(9) (a) W. J. Bailey and S. A. Buckler, *ibid.*, **79**, 3567 (1957); (b) W. J. Bailey, S. A. Buckler, and F. Marktscheffel, *J. Org. Chem.*, **25**, 1996 (1960).

(10) M. Grayson, P. T. Keough, and G. A. Johnson, *J. Am. Chem. Soc.*, **81**, 4803 (1959).

(11) H. Hellman and O. Schumacher, *Angew. Chem.*, **72**, 211 (1960).