[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLLEGE OF LIBERAL ARTS AND SCIENCES, TEMPLE UNIVERSITY]

The Synthesis of Some Trifluoromethyl Derivatives of *p*-Aminobenzoic Acid, Sulfanilamide and *p,p'*-Diamino Diphenyl Sulfone

BY WILLIAM T. CALDWELL AND A. NURI SAYIN[1]

3-Trifluoromethyl-4-aminobenzoic acid, 2-trifluoromethyl-4-aminobenzenesulfonamide and 2,2'-bis-(trifluoromethyl)-4,4'-diaminodiphenyl sulfone have been synthesized. Pharmacological tests show that they are in general ineffective or but slightly active.

Comparatively few trifluoromethyl derivatives of compounds of recognized physiological or chemotherapeutic activity have been prepared. The strongly electronegative nature of the trifluoromethyl radical, its peculiar chemical stability and striking effect upon physical properties of compounds containing it, as exemplified in their low boiling points and melting points, impelled us to introduce it into a variety of substances, some of which are described in this paper. Certain irregularities encountered during conventional reactions will be noted in the experimental part where appropriate procedural details are included.

A convenient source for the preparation of 3-trifluoromethyl-4-aminobenzoic acid is *m*-aminobenzotrifluoride which has been converted by Rouche[2] and by Jones[3] into 3-trifluoromethyl-4-nitroacetanilide. From this, after hydrolysis, 3-trifluoromethyl-4-aminobenzonitrile was obtained by the method of Hodgson and Walker[4] for the diazotization of a weak base followed by a Sandmeyer reaction in which potassium nickel cyanide[5] gave a much better yield (40–45%) than cuprous cyanide (10%). Hydrolysis and then reduction produced the final product.

The derivatives of *p,p'*-diaminodiphenyl sulfone were prepared from *o*-chlorobenzotrifluoride (I) by nitrating first to form 2-chloro-5-nitrobenzotrifluoride (II) which with sodium disulfide gave, besides the expected 2,2'-bis-(trifluoromethyl)-4,4'-dinitrodiphenyl disulfide (III), 2,2'-bis-(trifluoromethyl)-4,4'-dinitrodiphenyl sulfide (IV) in high yield.

The 2-trifluoromethyl-4-aminobenzenesulfonamide (XI) was made from (V) by the action of phosphorus pentachloride upon its sodium salt (VIII) which yielded the chloride (IX). The latter with ammonia formed the amide (X) and, ultimately, reduction with iron dust in dilute acetic acid gave (XI). The formation of (IV) was confirmed by oxidizing the crude reaction product with fuming nitric acid. This oxidation took place vigorously at room temperature and yielded together with 2-trifluoromethyl-4-nitrobenzenesulfonic acid (V) the corresponding 2,2'-bis-(trifluoromethyl)-4,4'dinitrodiphenyl disulfone (VI). However, when pure 2,2'-bis-(trifluoromethyl)-4,4'-dinitrodiphenyl disulfide was submitted to the same oxidation only one product, namely, the sulfonic acid (V), was obtained. The same sulfone (VI) was prepared by an independent synthesis from pure 2,2'-bis-(trifluoromethyl)-4,4'-dinitrodiphenyl sulfide (IV) by hydrogen peroxide oxidation.[6] A mixture of the two sulfones showed no depression of melting point. Direct conversion of the same crude mixture of (III) and (IV) into the corresponding sulfonyl chloride, either by the action of chlorine in acetic acid at 50°[7] or in a mixture of concentrated hydrochloric and nitric acid at 70°,[8] gave unsatisfactory yields and it was found preferable to treat the sodium salt of 2-trifluoromethyl-4-nitrobenzene sulfonic acid with phosphorus pentachloride.[8,9]

The pharmacological tests carried out with these compounds indicated that they were generally ineffective. 3-Trifluoromethyl-4-aminobenzoic acid made up into agar solutions ranging from 50 mcg./ml. to 0.1 mcg./ml. plates containing the following organisms indicated no antibacterial or antifungal activity: *B. subtilis*, *Corynebacterium gravis*, *Corynebacterium pseudodiphtheriae*, *Micrococcus flavus*, *Staph. albus*, *Streptococcus faecalis*, *Aerobacter aerogenes*, *E. coli*, *Micrococcus catarrhalis*, *Shigella paradysenteriae*, *Mycrobacterium avum*, *Mycrobacterium tuberculosis*, *Canadida albicans*, *Trichophyton rubrum*, *Trichophyton intergitale*. It was also ineffective in typhus infected embryonated eggs at 4.0 mg. × 1.

2,2'-Bis-(trifluoromethyl)-4,4'-diaminodiphenyl sulfone was ineffective in mice against influenza and MM virus, against *Streptococcus hemolyticus* and typhoid.

2-Trifluoromethyl-4-aminobenzenesulfonamide was ineffective in mice against influenza and MM virus, slightly effective against *Streptococcus hemolyticus* and very slightly effective against typhoid.

We wish to thank Eli Lilly and Company for carrying out the pharmacological tests, the Hooker Electrochemical Co. for a gift of chemicals, and the Temple University Committee on Research and Publications for a Grant-in-aid.

Experimental[10]

2-Nitro-5-aminobenzotrifluoride (B).—*m*-Trifluoromethylacetanilide was prepared by acetylation of *m*-aminobenzotrifluoride hydrochloride in aqueous solution with acetic anhydride and sodium acetate. The anilide, obtained as white crystals from aqueous ethanol, melted at 99–100° although Rouche,[2] probably through a misprint, gives 203°. This was then nitrated by the method of R. G. Jones, whereby brilliant yellow needles, m.p. 126–127° (m.p.

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[1] Taken from a thesis submitted by A. Nuri Sayin in partial fulfillment of the requirement for the degree of Doctor of Philosophy.

[2] H. Rouche, *Bull. acad. roy. sci. Belg.*, **13**, 346 (1927).

[3] R. G. Jones, THIS JOURNAL, **69**, 2346 (1947).

[4] H. H. Hodgson and J. Walker, *J. Chem. Soc.*, 1620 (1933).

[5] F. R. Storrie, *ibid.*, 1746 (1931).

[6] A. Pomerantz and R. Connor, THIS JOURNAL, **61**, 3388 (1939).

[7] H. J. Barber, *J. Chem. Soc.*, 101 (1943).

[8] R. S. Schreiber and R. L. Shriner, THIS JOURNAL, **56**, 114 (1934).

[9] "Organic Syntheses," John Wiley and Sons, Inc., Vol. 1, New York, N. Y., p. 21.

[10] All analyses were performed by Clark Microanalytical Laboratory, Urbana, Illinois. All melting points and boiling points are uncorrected.

Rouche, 129°; Jones, 126–127°) were obtained in 80% yield.

3-Trifluoromethyl-4-nitrobenzonitrile (C).—Since we have encountered some difficulty in diazotizing this and other aromatic amines containing the trifluoromethyl group, we are including details of one procedure. A solution of 21 g. of (B) in 160 ml. of glacial acetic acid was gradually poured into a solution of 6.9 g. of sodium nitrite in 52 ml. of concentrated sulfuric acid keeping the temperature at 10–20°. The excess of nitrous acid was decomposed with urea, and then the clear diazonium solution was poured slowly with vigorous stirring into a cold solution of potassium nickel cyanide prepared from 35 g. of potassium cyanide in 150 ml. of water and 30 g. of nickel sulfate in 50 ml. of water to which 300 ml. of water and 150 g. of anhydrous sodium carbonate had been added. During the pouring a further 300 ml. of water and about 50 g. of anhydrous sodium carbonate were added (until the reaction mixture was neutral) and the temperature was allowed to rise to 30–35°. The temperature was then raised to 90° and, after stirring for half an hour, the flask was cooled to room temperature. The solid was separated by filtration, washed and steam distilled. The white crystalline 3-trifluoromethyl-4-nitrobenzonitrile (C) weighed 9 g., a yield of 41%. The product was recrystallized from alcohol and water; long white needles, m.p. 84–85°.

Anal. Calcd. for $C_8H_3O_2N_2F_3$: N, 12.96. Found: N, 12.89.

3-Trifluoromethyl-4-nitrobenzoic Acid (D).—Three and one-half grams of (C) was added in small portions through the top of a reflux condenser to 25 ml. of 75% sulfuric acid solution at 150–160°, shaking vigorously after each addition. The mixture was heated first at 160° for 30 minutes, then at 190° for another 30 minutes; after cooling, it was poured on 100 g. of cracked ice. The precipitate formed was washed and treated with 10% sodium hydroxide solution and insoluble amide removed by filtration. Acidification of the filtrate with concentrated hydrochloric acid produced the 3-trifluoromethyl-4-nitrobenzoic acid (D); yield 3 g., or 79%. The product was recrystallized from solution in aqueous acetone, m.p. 160–161°.

Anal. Calcd. for $C_8H_4O_4NF_3$: N, 5.96. Found: N, 6.27.

3-Trifluoromethyl-4-aminobenzoic Acid (E).—Three grams of (D) was added in portions to a stirred mixture of 4 g. of iron powder and a solution of 2 g. of ammonium chloride in 50 ml. of water at 50°. The mixture was stirred and refluxed for three hours. After treating with 25 ml. of 10% sodium hydroxide solution, the alkaline solution was filtered and neutralized with concentrated hydrochloric acid. This produced the 3-trifluoromethyl-4-aminobenzoic acid (E); yield 2.2 g., or 86%. After purification by dissolving in dilute sodium hydroxide and reprecipitating with hydrochloric acid, it melted at 206–207°.

Anal. Calcd. for $C_8H_6O_2NF_3$: N, 6.83. Found: N, 7.06.

2-Chloro-5-nitrobenzotrifluoride (II).—To a stirred mixture of 81 g. of fuming nitric acid (sp. gr. 1.59) and 200 g. of concentrated sulfuric acid, 179.5 g. (1 mole) of *o*-chlorobenzotrifluoride was added at such a rate that the temperature was maintained at 30–35°. During the addition the flask was cooled from time to time with cold water. The mixture was next stirred for half an hour at room temperature, then heated with stirring in a water-bath at 60° for an additional 30 minutes. After cooling to room temperature, the lower spent acid layer was removed and the crude organic product washed successively with water, 2% sodium carbonate solution, and finally with water. The product, after drying over anhydrous magnesium sulfate, was fractionated and the 2-chloro-5-nitrobenzotrifluoride (II) boiling at 230–233° was collected; yield 157.5 g., or 70%; b.p. 231° (760 mm.), 108° (10 mm.), (lit.[11] 102–103° (0.5 mm.)). The corresponding amine melted at 36–37°, colorless crystals, (lit. 36–37°). Its acetyl derivative melted at 115–116°.

2,2′-Bis-(trifluoromethyl)-4,4′-dinitrodiphenyl Disulfide (III).—One hundred and twelve grams (0.5 mole) of (II) was dissolved in 200 ml. of 95% ethyl alcohol and the solution was boiled under a reflux condenser on a steam-bath. To this solution, a melt obtained by fusing together 65 g. of dry crystalline sodium sulfide (to obtain a high yield it was essential to use dry crystalline material), and 12.5 g. of powdered sulfur was added dropwise at such a rate as to maintain constant boiling under reflux without further application of heat. The reaction mixture was refluxed for two hours, then cooled overnight. The yellow precipitate formed was filtered with suction, washed with a little cold alcohol, then with water and dried at room temperature. The product weighed 90 g. and was used directly for further conversion. To obtain pure disulfide (III) for identification 9 g. of this crude substance was refluxed with 80 ml. of 95% ethyl alcohol for 15 minutes. A concentrated solution of 2.5 g. of crystalline sodium sulfide and 1.3 g. of solid sodium hydroxide, was added through the condenser.[12] The mixture was boiled until the whole had formed a deep, reddish-brown, homogeneous solution (15–20 minutes). This solution was then diluted with about 200 ml. of water and the solid material filtered off. To the filtrate, excess of concentrated hydrochloric acid was added; this caused the solution to change color to a bright yellow with precipitation of the yellow mercaptan. The precipitate was filtered off and dissolved in warm dilute sodium hydroxide containing a little alcohol. This was again treated with concentrated hydrochloric acid. The mercaptan was filtered off and dissolved in hot glacial acetic acid and oxidized to disulfide by heating 15 minutes with a concentrated solution of ferric chloride; on cooling, the disulfide precipitated as a light yellow solid. It was recrystallized again from glacial acetic acid, m.p. 152–154°; yield 4.8 g., or 43%.

Anal. Calcd. for $C_{14}H_6N_2O_4S_2F_6$: S, 14.40. Found: S, 14.92.

2-Trifluoromethyl-4-nitrothiophenol.—Two grams of the yellow mercaptan, obtained as described above, was recrystallized from glacial acetic acid; yellow crystals, m.p. 72–73°.

Anal. Calcd. for $C_7H_4O_2NSF_3$: S, 14.34. Found: S, 14.79.

2,2′-Bis-(trifluoromethyl)-4,4′-dinitrodiphenyl Sulfone (VI).—Seventy-four grams of well-dried reaction product from (II) with sodium disulfide, was added in small portions to a flask containing 167 ml. of fuming nitric acid (sp. gr. 1.59), with constant swirling and thorough mixing after each addition. After the first violent reaction had subsided, the mixture was heated on a steam-bath for 2 hours under the hood. At the end of the reaction practically all of the organic compound had dissolved. The precipitate produced by dilution was filtered off and washed several times with water to remove nitric acid. The pure 2,2′-bis-(trifluoromethyl)-4,4′-dinitrodiphenyl sulfone (VI) recrystallized from acetone, was obtained as long needles; m.p. 171–172°, yield 29 g.

Anal. Calcd. for $C_{14}H_6O_6N_2SF_6$: N, 6.31. Found: N, 6.32.

From the filtrate 2-trifluoromethyl-4-nitrobenzenesulfonic acid was separated as described later.

2,2′-Bis-(trifluoromethyl)-4,4′-dinitrodiphenyl Sulfide (IV).[13]—Three and six-tenths grams of sodium sulfide 9-hydrate (0.015 mole) was dissolved in 20 ml. of 95% ethanol. To this a solution of 6.36 g. of (II) (0.03 mole) was added. The solution was refluxed for half an hour, allowed to stand at room temperature, then cooled in an ice-bath overnight and the resulting yellow precipitate filtered off next day. The precipitate was washed with a little cold alcohol, then with water. Three grams of product was obtained. After recrystallization from 95% ethanol the product melted at 136–137°.

Anal. Calcd. for $C_{14}H_6O_4N_2SF_6$: N, 6.79. Found: N, 6.99.

2,2′-Bis-(trifluoromethyl)-4,4′-diaminodiphenyl Sulfide.—Three grams of (IV) was dissolved in 50 ml. of equal volumes of alcohol and water. To this solution 3 g. of iron powder and 2 g. of ammonium chloride were added. The mixture was refluxed at 60–70° for three hours, more alcohol was added and the hot solution filtered off. On cooling, the diamine precipitated as white crystals which were purified by dissolving in 10% hydrochloric acid, treating the solution with charcoal, filtering and neutralizing with 20% sodium carbonate; yield 2 g. A sample recrystallized from aqueous alcohol melted at 73–74°.

Anal. Calcd. for $C_{14}H_{10}N_2SF_6$: N, 7.95. Found: N, 7.92.

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[11] *Chem. Zentr.*, **104**, II, 2061 (1933).

[12] Th. Zincke and S. Lenhardt, *Ann.*, **400**, 2 (1913).

[13] M. J. J. Blanksma, *Rec. trav. chim.*, **20**, 400 (1901).

2,2'-Bis-(trifluoromethyl)-4,4'-dinitrodiphenyl Sulfone from (IV).[6]—Two and one-tenths gram of (IV), m.p. 136–137°, was dissolved in a mixture of equal parts by volume of glacial acetic acid and acetic anhydride (18 ml.). The solution was cooled in an ice-bath and maintained at approximately 0° while 2 ml. of 30% hydrogen peroxide was added slowly. The mixture was allowed to come slowly to room temperature as the ice melted and to stand for four days while the 2,2'-bis-(trifluoromethyl)-4,4'-dinitrodiphenyl sulfone precipitated as long needles. The product was already essentially pure, m.p. 171–172°; yield almost quantitative. A sample, recrystallized from acetone, melted at 172–173°. A mixed melting point of this product with (VI) showed no depression.

2,2'-Bis-(trifluoromethyl)-4,4'-diaminodiphenyl Sulfone (VII).—Twenty-two and two-tenths grams (0.05 mole) of (VI) was added to 300 ml. of 50% acetic acid and heated on a steam-bath at 70–80° while 18.7 g. of iron powder was added with constant stirring. After heating and stirring for three hours the mixture was filtered while still hot and the filtrate diluted with 800 ml. of water. This threw out the 2,2'-bis-(trifluoromethyl)-4,4'-diaminodiphenyl sulfone as a white precipitate which was purified by dissolving in 10% hydrochloric acid solution, treating the solution with charcoal, filtering and neutralizing with 20% sodium carbonate. The yield of 2,2'-bis-(trifluoromethyl)-4,4'-diaminodiphenyl sulfone 17.5 g. or 91%. A sample recrystallized from alcohol-water gave white needles, m.p. 211–212°.

Anal. Calcd. for $C_{14}H_{10}O_2N_2SF_6$: S, 8.34. Found: S, 8.39.

Sodium 2-Trifluoromethyl-4-nitrobenzenesulfonate (VIII).—The filtrate, after separation of (VI), was evaporated to half its volume. About 100 ml. of distilled water was then added and the solution was evaporated again. This operation was repeated four or five times to remove nitric acid. The free 2-trifluoromethyl-4-nitrobenzenesulfonic acid (V) may be isolated from the mother liquor by evaporating to incipient crystallization as light yellow, very hygroscopic needles. The sodium salt was prepared by neutralizing the acidic solution with 15% sodium hydroxide solution. Evaporation of the mother liquor to a small volume precipitated the sodium salt of (V) as yellow crystals. This precipitate was filtered off and washed with a little cold alcohol and dried at 120°. It was practically pure, and used for conversion to the sulfonyl chloride without further crystallization. A yield of 30 g. of sodium 2-trifluoromethyl-4-nitrobenzenesulfonate (VIII) was obtained. The corresponding *p*-toluidine[14] salt after recrystallization from water melted at 237–238°, forming white, brilliant crystals.

2-Trifluoromethyl-4-nitrobenzenesulfonyl Chloride (IX).—Twenty-nine and three-tenths grams (0.1 mole) of (VIII) which had previously been dried for two hours at 120° was mixed with 50 g. (0.25 mole) of phosphorus pentachloride. The mixture was heated in an oil-bath at 160–170° for ten hours. From the resulting pasty mass, the phosphorus oxychloride formed was removed by distillation at 105–110°. The residue was cooled and drowned in 300 ml. of ice-water. The crude 2-trifluoromethyl-4-nitrobenzenesulfonyl chloride (IX) precipitated as a red-brown solid which was filtered, washed with cold water, sucked as dry as possible and dried *in vacuo* over concentrated sulfuric acid; yield 22 g., or 76%. This product was recrystallized from ethylene trichloride, m.p. 80–81°.

Anal. Calcd. for $C_7H_3O_4NSClF_3$: Cl, 12.24. Found: Cl, 12.24.

2-Trifluoromethyl-4-nitrobenzenesulfonamide (X).—Five grams of pure (IX), m.p. 80–81°, was added in small portions to 20 g. of 28% ammonia solution at room temperature. The mixture was stirred after each addition and allowed to stand for 90 minutes. After evaporating at 40–45° on a water-bath to dryness, the residue was dissolved in 200 ml. of hot water, treated with charcoal and the solution filtered. Upon cooling, 2-trifluoromethyl-4-nitrobenzenesulfonamide (X) separated which, after recrystallizing from water, melted at 160–161°; yield 3 g., or 64%.

2-Trifluoromethyl-4-aminobenzenesulfonamide (XI).—To a mixture of 3 g. of iron powder in 80 ml. of water and 2 ml. of glacial acetic acid, heated at 70–80° on a steam-bath, 2 g. of (X) was added in portions with continuous stirring. Stirring and heating at 70–80° was continued for three hours whereupon about 60 ml. of ethyl alcohol was added and the mixture boiled, filtered, and the hot filtrate neutralized with 20% solution of sodium carbonate. The solution was treated with charcoal, boiled, and filtered. Upon cooling, 2-trifluoromethyl-4-aminobenzenesulfonamide precipitated as white crystals; yield 1.4 g., m.p. 196–197° from aqueous alcohol.

Anal. Calcd. for $C_7H_7O_2N_2SF_3$: N, 11.66. Found: N, 11.68.

Attempts to condense 2-aminopyrimidine with 2-trifluoromethyl-4-nitrobenzenesulfonyl chloride were unsuccessful.

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[14] L. F. Fieser, *Org. Syntheses*, **16**, 65 (1936); THIS JOURNAL, **51**, 2460 (1929).

PHILADELPHIA 22, PENNA. RECEIVED MAY 21, 1951

[CONTRIBUTION FROM THE WHITMORE LABORATORY, THE PENNSYLVANIA STATE COLLEGE]

Preparation of Organofluorosilanes Using Aqueous Hydrofluoric Acid[1]

BY N. S. MARANS,[2] L. H. SOMMER AND F. C. WHITMORE[3]

A series of organofluorosilanes has been prepared by reaction of the corresponding organoalkoxysilanes and trialkylchlorosilanes with aqueous hydrofluoric acid.

Organofluorosilanes have been prepared by the following reactions: (1) alkylmagnesium halides and silicon tetrafluoride,[4] (2) hexaalkyldisiloxane and ammonium fluoride–sulfuric acid,[5] (3) dialkyldichlorosilanes and trialkylchlorosilanes with anhydrous hydrogen fluoride,[6] and (4) organochlorosilanes with zinc fluoride or antimony trifluoride.[7–10]

This investigation reports the preparation of organofluorosilanes from organoalkoxysilanes and trialkylchlorosilanes using aqueous hydrofluoric acid. For the most part these reactions were carried out at 0°.

By this method tri-*n*-propylethoxysilane, di-*n*-propyldiethoxysilane, tri-*n*-butylethoxysilane, di-*n*-butyldiethoxysilane, trimethylethoxysilane, diphenyldiethoxysilane, phenylmethyldiethoxysilane, hexadecyltriethoxysilane, triethylchlorosilane and tri-*n*-propylchlorosilane have been converted to

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[1] Paper XXVIII in a series on organosilicon chemistry. For paper XXVII, see THIS JOURNAL, **73**, 882 (1951).

[2] Taken in part from a thesis submitted by N. S. Marans in partial fulfillment of the requirements for the M.S. degree, February, 1947.

[3] Deceased.

[4] J. A. Gierut, F. J. Sowa and J. A. Nieuwland, THIS JOURNAL, **58**, 897 (1936); *cf.* also H. V. Meddoks and N. Z. Kotelkov, *J. Gen. Chem.* (*U. S. S. R.*), **7**, 2007 (1937) or *C. A.*, **32**, 531 ((1938) and H. V. Meddoks and N. Z. Kotelkov, *ibid.*, **8**, 291 (1938) or *C. A.*, **32**, 5392 (1938).

[5] E. A. Flood, THIS JOURNAL, **55**, 1735 (1933).

[6] W. H. Pearlson, T. J. Brice and J. H. Simons, *ibid.*, **67**, 1769 (1945).

[7] A. E. Newkirk, *ibid.*, **68**, 2736 (1946).

[8] P. A. McCusker and C. E. Green, *ibid.*, **70**, 2807 (1948).

[9] H. S. Booth and P. H. Carnell, *ibid.*, **68**, 2650 (1946).

[10] H. S. Booth and R. L. Jarry, *ibid.*, **71**, 971 (1949).