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CIRCULAR NO. 136

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BY

G. C. FINGER AND MARTIN KNELL

SOME FACTORS IN THE SYNTHESIS OF
3,5-DINITROBENZOTRIFLUORIDE

BY

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REPRINTED FROM THE TRANSACTIONS OF THE ILLINOIS STATE ACADEMY OF SCIENCE
VOL. 38, 1945 AND VOL. 39, 1946



PRINTED BY AUTHORITY OF THE STATE OF ILLINOIS

URBANA, ILLINOIS

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ILLINOIS STATE GEOLOGICAL SURVEY



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SOME TRISUBSTITUTED BENZOTRIFLUORIDES

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A number of highly fluorinated aliphatic compounds have been known for some time, especially, some of the chlorofluoro derivatives of methane and ethane. Due to their unique properties they have found commercial application as refrigerants, as propellants in "bug bombs," as gaseous and liquid dielectrics, and in the synthesis of some very unusual polymers. These discoveries and applications warrant research in other types of compounds. Almost immediately the field of aromatic compounds suggests itself. Very few polyfluorides of such simple molecules as benzene and toluene have been described in the literature. The synthesis of two difluorobenzotrifluorides by Finger and Reed¹ in the Survey laboratories immediately brought requests for samples and for further information on these and other aromatic compounds. This paper represents a preliminary report on some of the intermediate compounds studied in trying to find an appropriate synthesis for a trifluorobenzotrifluoride.

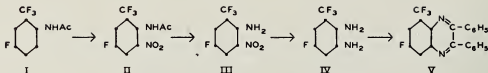
The synthesis of higher fluorinated aromatic compounds presents two problems; (1) the usual fluorine substitution reactions tend to be inoperative as the degree of substitution increases, and (2) it is necessary to know the exact structure of the final compound in order to evaluate it properly. Ordinarily the second problem is solved if the structure of the compound just preceding the introduction of a fluorine atom is definitely known. These facts are,

more or less, illustrated in this preliminary report.

As a first approach to a probable synthesis of a trifluorobenzotrifluoride, 2-acetylamino-5-fluorobenzotrifluoride (I) was used as the starting compound. This compound was available in the Survey laboratories as a result of some previous work¹.

The nitration of (I) followed by hydrolysis of the acetyl group gave 2-amino-3-nitro-5-fluorobenzotrifluoride (III). This was the compound desired although on a theoretical basis two other isomers could be formed, namely, the nitro group could have entered also into the 4 or 6 positions. These isomers were not isolated although they may have been present in small amounts. The structure of compound (III) was established by conversion to 2,3-diphenyl-6-fluoro-8-trifluoromethylquinoxaline (V). After having established the structure of 2-amino-3-nitro-5-fluorobenzotrifluoride (III), it appeared that this nitroamine may be the basis for the synthesis of 2,3,5-trifluorobenzotrifluoride.

Attempts to apply the Schiemann reaction, in the usual way, to 2-amino-3-nitro-5-fluorobenzotrifluoride (III) so as to obtain 2,5-difluoro-3-nitrobenzotrifluoride failed. The nitroamine appears to be only slightly basic although it forms an amine hydrochloride in concentrated hydrochloric acid; the hydrochloride can also be formed in absolute ether by passing in dry hydrogen chloride. Indications are that diazotization did take place; however, when



sodium fluoborate was added a precipitate of sodium chloride and sodium fluoborate was formed.

Although these results did not achieve the original objective, the nitration data is significant in predicting the results which may be obtained in nitrating 2,5-difluorobenzotrifluoride. The orientation factors are, more or less, the same thus lending credence to the formation, of 2,5-difluoro-3-nitrobenzotrifluoride as the chief product. The nitration of 2,5-difluorobenzotrifluoride gave a nitro compound and its

composition was established through the acetyl derivative of the amine resulting from reduction. Therefore, it is possible to assign a structure with some supporting evidence even though a more positive proof is necessary. The nitro compound is being studied further as to its structure and properties.

The authors are indebted to Dr. F. H. Reed, chief chemist, for suggestions, and to Mr. H. S. Clark, microanalyst, for the analyses in this investigation.

EXPERIMENTAL

2-Amino-3-nitro-5-fluorobenzotrifluoride (III).—Twenty grams of 2-acetyl-5-fluorobenzotrifluoride¹ (I) was dissolved in a mixture of 150 g. of concentrated sulfuric acid and 30 g. of glacial acetic acid at room temperature. After cooling to 10° , a solution of 12.6 g. of fuming nitric acid (sp. gr. 1.49-1.5) in 25 g. of concentrated sulfuric acid was added slowly with stirring, and the temperature maintained at $10-20^\circ$ for ninety minutes. The reaction mixture was poured slowly into an ice-water mixture giving a white precipitate. After filtering and drying, the yield of crude product was 17 g. This crude product was found to be chiefly 2-acetyl-5-fluoro-3-nitrobenzotrifluoride (II) upon recrystallizing a sample from 50 percent aqueous ethanol. The crude material was heated on a water bath for one hour with 50 cc. of concentrated sulfuric acid, and poured into an ice-water mixture giving the crude nitroamine as a yellow precipitate. After filtering and drying, recrystallization from 60 percent aqueous ethanol gave 11.5 g. (57 percent) of 2-amino-3-nitro-5-fluorobenzotrifluoride (III) as yellow needles, m.p. $68-69^\circ$.

Anal. Calculated for $\text{C}_7\text{H}_4\text{F}_3\text{N}_2\text{O}_2$: C, 37.51; H, 1.8; N, 12.50. Found: C, 37.63; H, 1.85; N, 12.56.

The acetyl compound (II) upon recrystallization from 50 percent aqueous ethanol gave white needles, m.p. $179.5-180^\circ$.

Anal. Calculated for $\text{C}_9\text{H}_6\text{F}_3\text{N}_2\text{O}_2$: C, 40.61; H, 2.27; N, 10.53. Found: C, 40.70; H, 2.26; N, 10.45.

2,3-Diphenyl-6-fluoro-8-trifluoromethylquinoxaline (V).—To a refluxing solution of 2 g. of 2-amino-3-nitro-5-fluorobenzotrifluoride (III) in 100 cc. of 50 percent aqueous acetic acid, 6 g. of powdered zinc was added in small portions. After the mixture was light yellow in color, the unreacted zinc was removed by filtration. The 2,3-diamino-5-fluorobenzotrifluoride (IV) was not isolated.

To the filtrate was added slowly, a warm solution containing 30 cc. of 40 percent aqueous sodium bisulfite, 3 g. of benzil, and 40 cc. of ethanol. The yellow flocculent precipitate which formed was removed by filtration, washed, and dried. Recrystallization from methanol gave 2,3-diphenyl-6-fluoro-8-trifluoromethylquinoxaline (V) as white needles, m.p. $133-133.5^\circ$. The formation of the quinoxaline proved the adjacency of the nitro and amino groups in III.

Anal. Calculated for $\text{C}_{27}\text{H}_{18}\text{F}_3\text{N}_2$: C, 68.48; H, 3.28; N, 7.61. Found: C, 68.46; H, 3.28; N, 7.74.

Diazotization of 2-Amino-3-nitro-5-fluorobenzotrifluoride (III).—Attempts were made to diazotize 2-amino-3-nitro-5-fluorobenzotrifluoride (III) under a variety of conditions. The amine hydrochloride may be formed in concentrated hydrochloric acid or by dissolving the nitroamine in absolute ether and passing in anhydrous hydrogen chloride. In a concentrated hydrochloric acid solution, the amine hydrochloride appears to diazotize slowly with sodium nitrite to give a clear solution. Upon the addition of a strong sodium fluoborate solution, a white precipitate of inorganic salt (probably sodium chloride or sodium fluoborate) was formed. Diazotization with nitrosyl sulfuric acid in the presence of phosphoric acid² or glacial acetic acid³ or 60 percent fluoboric acid failed to give a diazonium fluoborate.

2,5-Difluoro-3(?)-nitrobenzotrifluoride.—To a mixture of 40 cc. of fuming sulfuric acid (40 percent SO₃) and 19.3 g. of fuming nitric acid (sp. gr. 1.49-1.5), 18.3 g. of 2,5-difluorobenzotrifluoride was added at such a rate with stirring that the temperature was maintained at 50° for ninety minutes. The entire reaction mixture was poured into an ice-water mixture, and the crude nitro compound was isolated as a heavy yellow oil. The crude yield was 14.8 g. or 62 percent. A preliminary fractional distillation showed that 2,5-difluoro-3(?)-nitrobenzo-

trifluoride boils about 191-192° or 91.5-92.5°/19 mm. The sample was not pure indicating the possible presence of isomers and also a trace of a dinitro derivative.

A small sample of the crude nitro compound was reduced with iron filings in an ammonium chloride (0.78 N) solution⁴ to the amine. The amine was isolated as an oil, and converted to the acetyl derivative by the usual method. Recrystallization from high-boiling petroleum ether gave 2,5-difluoro-3(?)-acetylamino benzotrifluoride as white needles, m.p. 104.5-105.5°.

Anal. Calculated for C₇H₄F₂NO: C, 45.20; H, 2.53; N, 5.86. Found: C, 45.33; H, 2.43; N, 5.82.

SUMMARY

2-Amino-3-nitro-5-fluorobenzotrifluoride was synthesized from 2-acetylamino-5-fluorobenzotrifluoride.

Attempts to convert 2-amino-3-nitro-5-fluorobenzotrifluoride to 2,5-difluoro-3-nitrobenzotrifluoride by the Schiemann reaction failed.

The nitration of 2,5-difluorobenzotrifluoride gives a nitro compound which is probably 2,5-difluoro-3-nitrobenzotrifluoride.

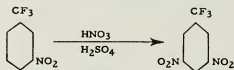
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SOME FACTORS IN THE SYNTHESIS OF 3, 5-DINITROBENZOTRIFLUORIDE

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The synthesis of certain symmetrical aromatic fluorine compounds under investigation in this laboratory necessitated the development of a large-scale laboratory preparation of 3, 5-dinitrobenzotrifluoride.



Adaptation of the original synthesis by Finger and Reed¹ of this dinitro compound to a large-scale laboratory preparation required further investigation to determine optimum yield conditions.

The synthesis of 3, 5-dinitrobenzotrifluoride involves the nitration of *m*-nitrobenzotrifluoride with a fuming nitric and sulfuric acid mixture. The nitro group entering the aromatic nucleus is directed to the meta position common to both the $-\text{CF}_3$ group and the original nitro group. The difficulty involved in nitrating *m*-dinitrobenzotrifluoride may be predicted when a comparison is made with *m*-nitrobenzene, as both compounds contain two meta directing groups in the 1,3 positions. The nitration of *m*-dinitrobenzene is extremely difficult; therefore, it would be expected that nitration of *m*-nitrobenzotrifluoride would also be difficult. This theoretical analogy was verified experimentally as it was necessary to use a fuming nitric-sulfuric acid mixture at a temperature of about 100°C . in order to obtain a satisfactory yield of 3,5-dinitrobenzotrifluoride.

To develop a standard procedure for a large-scale laboratory preparation of 3,5-dinitrobenzotrifluoride which would produce a maximum yield of product, consistent with economical use of both time and materials, required a study of the effects on the dinitro yield by the following conditions: (1) concentration and volume of sulfuric and nitric acid used in nitration; and (2) time and temperature of nitration.

An investigation of the effects of the conditions given above on the yield of 3,5-dinitrobenzotrifluoride was conducted by performing a series of nitrations in which the conditions were varied from run to run. The yield of dinitrobenzotrifluoride as affected by various concentrations and volumes of acids used are shown in Tables 1 and 2.

From the data obtained, indications are that fuming sulfuric acid (30 percent free SO_3) and fuming nitric acid (sp. gr. 1.49-1.5), a nitration temperature of 100°C ., and a heating period of three hours produced better yields of 3,5-dinitrobenzotrifluoride. Nitration temperatures higher than 100°C ., and heating periods longer than 3 hours were found to effect only negligible increases in the yield.

The crude 3,5-dinitrobenzotrifluoride, washed free of acid with dilute alkali, is still contaminated with small amounts of isomers and unreacted *m*-nitrobenzotrifluoride which make imperative an efficient purification process. Fractional crystallization of the crude product from methanol gave a pure product but

TABLE 1.—YIELDS OF 3,5-DINITROBENZOTRIFLUORIDE AS AFFECTED BY DIFFERENT ACID CONCENTRATIONS

Reagent	Concentration	Average Yield of 3, 5-Dinitrobenzotrifluoride
Fuming H ₂ SO ₄	15% SO ₃	35 Percent
Fuming H ₂ SO ₄	25% SO ₃	40 Percent
Fuming H ₂ SO ₄	30% SO ₃	45 Percent*
Fuming H ₂ SO ₄	60% SO ₃	40 Percent
Fuming HNO ₃	Sp. gr. 1.49-5	45 Percent*
Red fuming HNO ₃	40 Percent

* Procedure was standardized on these concentrations.

TABLE 2.—YIELD OF 3,5-DINITROBENZOTRIFLUORIDE VS. VOLUME OF REAGENTS

Acid	Volume Ratio Acid: C ₆ H ₄ (CF ₃) (NO ₂) 1, 3	Percent Yield of C ₆ H ₃ (CF ₃) (NO ₂) ₂ 1, 3, 5
H ₂ SO ₄ (30% free SO ₃).....	5:1	41
H ₂ SO ₄ (30% free SO ₃).....	3.6:1*	45
HNO ₃ (Sp. gr. 1.99-1.5).....	1.8:1	41
HNO ₃ (Sp. gr. 1.49-1.5).....	6.4:1*	51

* Procedure standardized on these ratios.

low recovery, due to the additional solubility effect of the unreacted *m*-nitrobenzotrifluoride. Purification by steam distillation was found to be impractical because the dinitro compound is slightly steam distillable. Fractional distillation under diminished pressure followed by recrystallization of the dinitro from methanol proved to be the most efficient method for purifying the crude dinitro product.

EXPERIMENTAL

Nitrations were carried out in a 5-liter three-necked (standard joints) round-bottomed flask submerged in a water bath containing a coil of copper tubing with connections so arranged as to permit circulation through the coil of either low or high pressure steam, tap water, or a cold brine solution. The flask was equipped with a Claisen adapter to which was attached a dropping funnel and a reflux condenser, a thermometer, and a mercury-sealed stirrer coupled to the shaft of a one-half h.p. motor.

m-Nitrobenzotrifluoride was added to

the stirred fuming nitric and sulfuric acid mixture maintaining the nitration temperature at 100° C. throughout the addition and the subsequent two-hour heating period. The efficient heat transfer system previously described makes possible precise temperature control at 100° C. of the nitration reaction which is exothermic.

A modification of the above experimental procedure involves a nitration of benzotrifluoride with the spent acid to produce enough *m*-nitrobenzotrifluoride for a subsequent large-scale dinitrobenzotrifluoride preparation. This modification is advantageous from the standpoint of more efficient utilization of materials but has the disadvantage of increasing the dinitro production time.

SUMMARY

A study was made of the nitration of *m*-nitrobenzotrifluoride to determine the conditions most favorable for obtaining good yields of 3,5-dinitrobenzotrifluoride. From the results thus obtained, a large-scale laboratory method of preparation of 3,5-dinitrobenzotrifluoride was developed.

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