[Chem. Pharm. Bull. 23(3) 636—639 (1975)]

UDC 547.546'546.16.04

Studies on Organic Fluorine Compounds. XVII.[1] Reaction of Benzotrifluoride Derivatives with Sodium Amide[2]

Yoshiro Kobayashi, Itsumaro Kumadaki, Yuji Hanzawa, and Masataka Mimura

Tokyo College of Pharmacy[3]

(Received September 13, 1974)

Reaction of benzotrifluoride derivatives with sodium amide was examined. *o*-Nitro- and *p*-amino-benzotrifluoride gave the corresponding benzonitriles. *m*-Nitrobenzotrifluoride gave 3,3'-bis(trifluoromethyl)azoxybenzene and 3,8-bis(trifluoromethyl)benzo[*c*]cinnoline 5-oxide. *p*-Nitrobenzotrifluoride gave *p*-nitrobenzonitrile, 2,2'-dinitro-5,5'-bis(trifluoromethyl)biphenyl and 4,4'-dicyanoazoxybenzene. Reaction mechanism for each product is proposed.

A trifluoromethyl (CF_3) group on an aromatic ring has been regarded as a very stable substituent;[4] however, in the previous papers,[5] we disclosed the fact that the trifluoromethyl group on a quinoline or an indole ring shows an interesting reactivity when treated with nucleophiles due to the interaction of the electronic effects of the trifluoromethyl group and the heteroaromatic ring. Such effects should be observed with benzotrifluoride derivatives, if the proper substituent is present. In this paper, we report some interesting information, besides what was easily expected from known results, which was obtained from our investigation of reactions of nitro- and aminobenzotrifluoride with sodium amide used as a nucleophilic reagent.

In the case of π-electron deficient pyridine-series, interesting pieces of information, such as trifluoromethyl group leaving as an anion depending on its position, were obtained.[5] Therefore, the reaction of nitrobenzotrifluorides with sodium amide was first carried out. When *o*-nitrobenzotrifluoride (I) was treated with sodium amide in liquid ammonia, a little amount of *o*-nitrobenzonitrile (II) was produced, although most of the starting material was recovered. The fact can be attributed to this: S_N2 type substitution reaction on the carbon atom of trifluoromethyl group was facilitated by the electron-withdrawing effect, as seen with quinolines, since the starting material was completely recovered in the case of benzotrifluoride (Chart 1).

Next, in the case of *m*-nitrobenzotrifluoride (III), 3,3'-bis(trifluoromethyl)azoxybenzene (IV) and 3,8-bis(trifluoromethyl)benzo[*c*]cinnoline 5-oxide (V) were obtained with some recovery of the starting material. It should be noted that a completely new type of reaction took place, such as an intermolecular reaction that had never been observed in the reaction of a heteroaromatic ring with trifluoromethyl group. The mechanism of formation of each product is thought to be as in Chart 1. The formation of V must proceed as follows: the acidity of the ortho-proton to the nitro group of III is increased by the electron-withdrawing effect

1) Part XVI: Y. Kobayashi, I. Kumadaki, A. Ohsawa, M. Honda, and Y. Hanzawa, *Chem. Pharm. Bull.* (Tokyo), **23**, 196 (1975).
2) Presented at the 93rd Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1973.
3) Location: *Kitashinjuku 3-chome, Shinjuku-ku, Tokyo.*
4) W.A. Sheppard and C.M. Sharts, "Organic Fluorine Chemistry," W.A. Benjamin, New York, 1969, p. 410.
5) *a*) Y. Kobayashi, I. Kumadaki, and S. Taguchi, *Chem. Pharm. Bull.* (Tokyo), **19**, 627 (1971); *b*) Y. Kobayashi, I. Kumadaki, and S. Taguchi, *Chem. Pharm. Bull.* (Tokyo), **20**, 823 (1972); *c*) Y. Kobayashi, I. Kumadaki, S. Taguchi, and Y. Hanzawa, *Chem. Pharm. Bull.* (Tokyo), **20**, 1047 (1972); *d*) Y. Kobayashi, I. Kumadaki, Y. Hirose, and Y. Hanzawa, *J. Org. Chem.*, **39**, 1836 (1974).

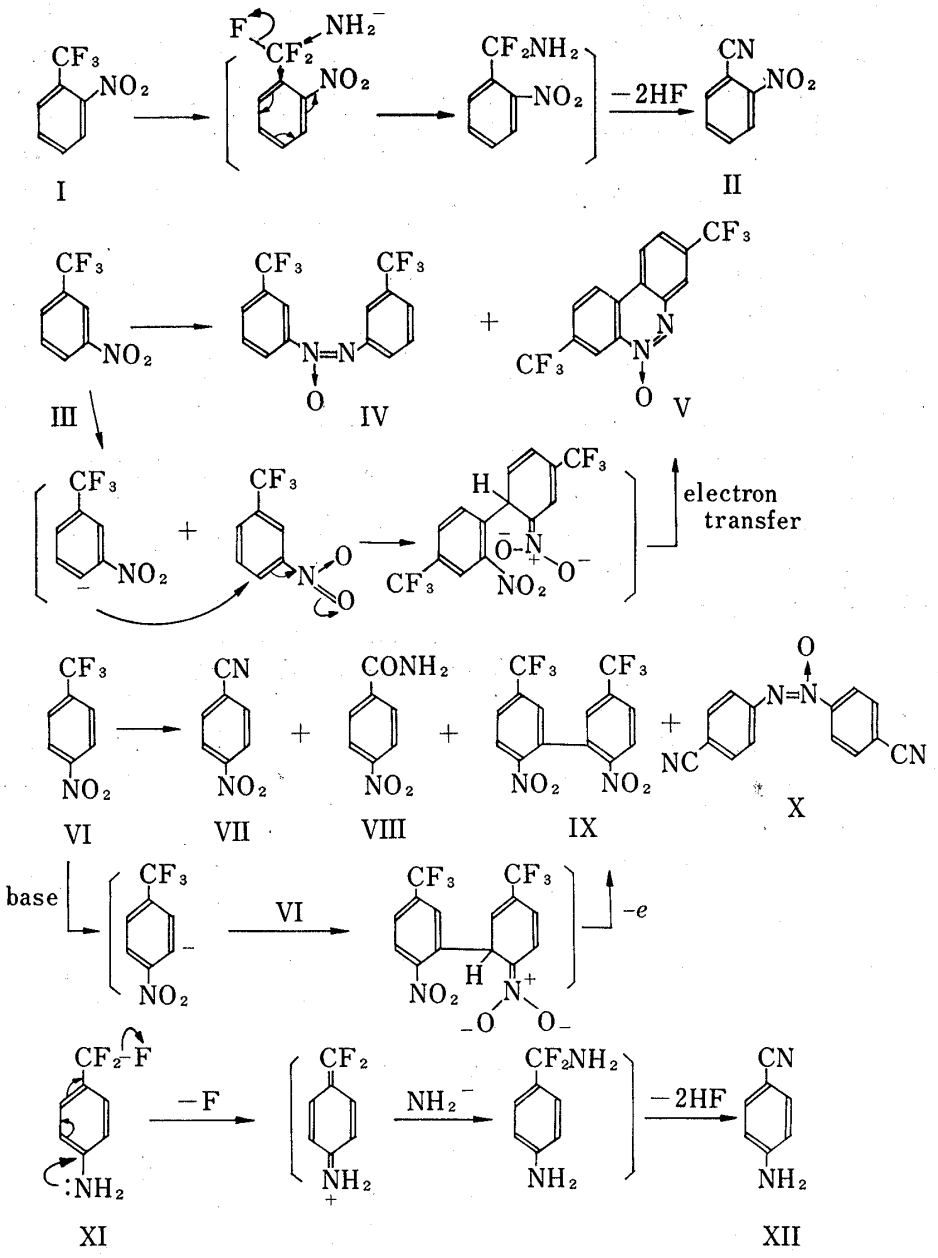

Chart 1

of the nitro and trifluoromethyl groups and is abstracted by base; the anion produced in this way is added to another molecule of III, and ring-closure takes place by oxidation-reduction reaction through some kind of electron-transfer reaction. On the other hand, IV must have been produced because of the partial reduction of the nitro group in the course of electron-transfer reaction. In this reaction, since a large amount of tarry product was obtained, the greater part of the starting material underwent the oxidation-reduction reaction and must have been used in the production of this tarry matter.

Under the same condition, *p*-nitrobenzotrifluoride (VI) yielded *p*-nitrobenzonitrile (VII), *p*-nitrobenzamide (VIII), 2,2′-dinitro-5,5′-bis(trifluoromethyl)biphenyl (IX), and 4,4′-dicyanoazoxybenzene (X). The formation of VII, as with I, is presumably due to the electron-withdrawing effect of the nitro group, which facilitated the S_N2 type substitution reaction on the carbon atom of the trifluoromethyl group, followed by dehydrofluorination by base. VIII must have been produced by hydrolysis of VII during the work-up. The formation of IX is thought to have been like this: α-proton was abstracted to the nitro group by base, as with

III, and the anion thus produced reacted with another molecule of the starting material VI and was oxidized. X was presumably produced from VII by the conjugate reduction of such an oxidation reaction. The fact that biphenyl derivative and azoxybenzene were not isolated when nitrobenzene alone was treated in the same condition should be taken into consideration on the production of IX; this fact shows that the trifluoromethyl group contributed in some way in the addition reaction of arylanion to VI.

As has been described, in the case of benzotrifluoride with a nitro group, not only the reaction at the trifluoromethyl group is activated by the nitro group, but also it involves interesting reactions as dimerization followed by oxidation-reduction and cyclization owing to the combination of the positions of nitro and trifluoromethyl groups. Next, when *p*-aminobenzotrifluoride with an electron-donating substituent, an amino group, at *p*-position was treated in the same condition, the reaction proceeded to afford only *p*-aminobenzonitrile. This is a product easily expected from the result in the case of indoles and the reaction must have proceeded in S_N1 type mechanism. The case of aminobenzotrifluoride with metal hydride as an analogous reaction was reported, where only *para*-isomer was reduced.[6] By inference of the result of indoles, sodium amide was thought to be weaker in activity in such a reaction. Accordingly, we did not try with other aminobenzotrifluorides.

The structure of each product was estimated from spectral data, and also identified with the authentic sample commercially available or synthesized *via* another route shown in the Experimental. In the course of the synthesis of 2,2′-dinitro-5,5′-bis(trifluoromethyl)biphenyl as an intermediate for V, 3-nitro-4-chlorobenzotrifluoride was heated with copper powder to a surprising result that 3,8-bis(trifluoromethyl)benzo [*C*] cinnoline was obtained in one step.

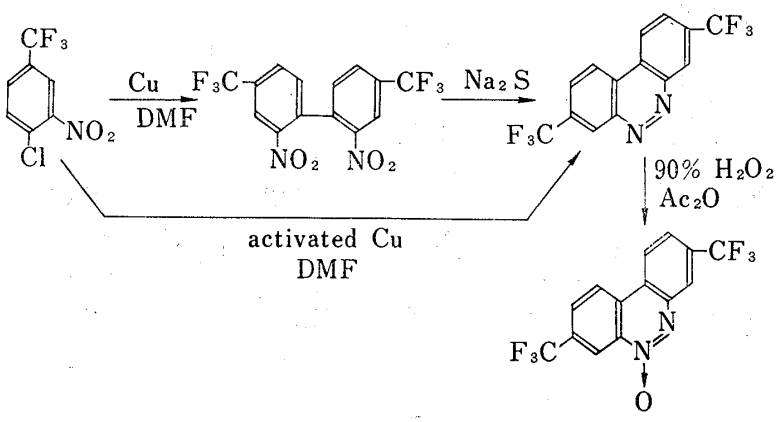

Chart 2

Experimental

Preparation of $NaNH_2$ Solution——$NaNH_2$ was freshly prepared by adding Na (1 g) to a solution of $Fe(NO_3)_3$ (0.1 g) in liq. NH_3 (20—30 ml).

Reaction of *o*-Nitrobenzotrifluoride (I) with $NaNH_2$——To a stirred solution of $NaNH_2$ in liq. NH_3, a solution of (I) (2.76 g) in $(C_2H_5)_2O$ (10 ml) was added dropwise and the mixture was stirred for 3 hr. After the evaporation of NH_3, the residue was poured on ice-water and extracted with $(C_2H_5)_2O$. The $(C_2H_5)_2O$ layer was dried over Na_2SO_4 and the $(C_2H_5)_2O$ solution was concentrated to dryness. The residue in *n*-hexane-CH_2Cl_2 (5 : 1) was passed through SiO_2-column. The effluent with *n*-hexane–CH_2Cl_2 (5 : 1) gave crude crystals of *o*-nitrobenzonitrile (II), which were recrystallized from *n*-hexane to give yellow crystals, mp 106—108°; yield, 0.02 g (1%).

The other effluent was mainly the starting material and a trace of an unidentified tarry substance. II was identified with an authentic sample by admixture and comparison of infrared (IR) spectra.

6) N.W. Gilman and L. Sternbach, *Chem. Commun.*, **1971**, 465.

Reaction of *m*-Nitrobenzotrifluoride (III) with $NaNH_2$——III (1.85 g) was treated with $NaNH_2$ as in the case of I. The $(C_2H_5)_2O$ solution was concentrated to dryness and the residue was passed through SiO_2-column in *n*-hexane–CH_2Cl_2 (4: 1) solution. The first effluent gave crude crystals, which were purified by sublimation to give orange crystals of 3,3′-bis(trifluoromethyl)azoxybenzene (IV), mp 46—47°; yield, 0.26 g (16.3%). IR ν_{max}^{KBr} cm^{-1}: 1330 (N–O), 1130—1180 (C–F). *Anal.* Calcd. for $C_{14}H_8ON_2F_6$: C, 50.30; H, 2.39; N, 8.38; F, 34.13. Found: C, 50.54; H, 2.42; N, 8.43; F, 34.78.

The second effluent gave crude crystals, which were recrystallized from EtOH to give colorless leaflets of 3,8-bis(trifluoromethyl)benzo[*c*]cinnoline-5-oxide (V),[7] mp 219—220°; yield, 0.016 g (1%). IR ν_{max}^{KBr} cm^{-1}: 1410, 1325 (N–O), 1140—1180 (C–F). NMR ($CDCl_3$) δ: 9.15 (1H, bs, 4-H), 8.69 (1H, d, J=7.5 Hz, 1-H), 8.53 (1H, d, J=8.7 Hz, 10-H), 8.25 (7H, s, 7-H), 8.2 (1H, d, J=7.5 Hz, 2-H), 7.95 (1H, d, J=8.7 Hz, 9-H). Mass Spectrum *m/e*: 332 (M^+). *Anal.* Calcd. for $C_{14}H_6ON_2F_6$: C, 50.60; H, 1.81; N, 8.43; F, 34.34. Found: C, 50.41; H, 1.68; N, 8.18; F, 33.93.

V was identified with an authentic sample[7] by admixture and comparison of IR spectra.

Synthesis of 3,8-Bis(trifluoromethyl)benzo[*c*]cinnoline——A solution of 4-chloro-3-nitrobenzotrifluoride (5 g) in dimethyl formamide (DMF) (40 ml) was heated with activated Cu powder in a stainless steel tube at 150° for 13 hr. The reaction mixture was poured on ice-water and the mixture was submitted to steam distillation. The distillate was extracted with $(C_2H_5)_2O$ and the $(C_2H_5)_2O$ layer was dried over Na_2SO_4. Evaporation of $(C_2H_5)_2O$ gave crude crystals, which were recrystallized from EtOH to give yellow powder of 3,8-bis(trifluoromethyl)benzo[*c*]cinnoline, mp 193—194°; yield, 0.357 g (10.2%). This substance was identified with an authentic sample[7] by admixture and comparison of IR spectra.

Synthesis of V——To a suspension of 3,8-bis(trifluoromethyl)benzo[*c*]cinnoline (0.2 g) in Ac_2O (2 ml), 90% H_2O_2 (0.5 ml) was added and the mixture was heated at 40—50° for 2 days. The reaction mixture was diluted with H_2O and concentrated to half the original volume. After this operation was repeated until the peracid could no longer be detected, the solution was neutralized with 10% NaOH. The extraction with CH_2Cl_2 gave crude crystals, which were recrystallized from EtOH to give colorless leaflets of V, mp 214—215°; yield, 0.111 g (54.3%). The structure was confirmed by admixture and comparison of IR spectra with an authentic sample.[7]

Reaction of *p*-Nitrobenzotrifluoride (VI) with $NaNH_2$——VI (1.23 g) was treated with $NaNH_2$ as in the case of I. $(C_2H_5)_2O$ solution was concentrated to dryness and passed through SiO_2-column in *n*-hexane–CH_2Cl_2 (2: 1) solution. The first effluent with *n*-hexane–CH_2Cl_2 (2: 1) gave crude crystals, which were recrystallized from *n*-hexane to give pale yellow crystals of 2,2′-dinitro-5,5′-bis(trifluoromethyl)biphenyl (IX), mp 105—106°; yield, 0.028 g (3%). IR ν_{max}^{KBr} cm^{-1}: 1530, 1430 (N–O), 1130—1150 (C–F). NMR (CCl_4) δ: 8.4 (2H, d, J=0.8 Hz, 3-H and 3′-H), 7.94 (2H, d, J=0.8 Hz, 4-H and 4′-H), 7.61 (2H, s, 6-H and 6′-H). *Anal.* Calcd. for $C_{14}H_6O_4N_2F_6$: C, 44.21; H, 1.58; N, 7.37; F, 30.00. Found: C, 44.28; H, 1.89; N, 7.70; F, 30.48. The structure of IX was confirmed by another synthetic route as mentioned later.

The second effluent gave crude crystals, which were recrystallized from *n*-hexane to give orange leaflets of *p*-nitrobenzonitrile (VII), mp 147—148°; yield, 0.25 g (26.2%). VII was identified with an authentic sample by admixture and comparison of IR spectra.

The CH_2Cl_2 effluent gave yellow crude crystals. Recrystallization from *n*-hexane–CH_2Cl_2 gave yellow crystals of 4,4′-dicyanoazoxybenzene (X), mp 223—224°; yield, 0.102 g (12.6%). IR ν_{max}^{KBr} cm^{-1}: 2230 (C≡N). NMR (CCl_4) δ: 8.49 (2H, d, J=8.75 Hz, 2′-H and 6′-H), 8.25 (2H, d, J=8.75 Hz, 2-H and 6-H), 7.89 (2H, d, J=8.75 Hz, 3′-H and 5′-H), 8.7 (2H, d, J=8.75 Hz, 3-H and 5-H). Mass Spectrum *m/e*: 248 (M^+). High Mass Calcd. for $C_{14}H_8ON_4$: 248.069. Found: 248.068.

Further effluent with CH_2Cl_2–MeOH gave *p*-nitrobenzamide (X), mp 198—200°; yield, 0.0104 g (1%). This substance was identified with an authentic sample by admixture and comparison of IR spectra.

Synthesis of 2,2′-Dinitro-5,5′-bis(trifluoromethyl)biphenyl (IX)——To a solution of 3-iodo-4-nitrobenzotrifluoride (3.29 g) in DMF (20 ml), Cu powder (4 g) was added and the mixture was shaken at 140—150° for 9 hr. After the filtration of excess Cu powder, the filtrate was poured on ice-water and extracted with $(C_2H_5)_2O$. The $(C_2H_5)_2O$ solution was washed with 10% HCl and saturated NaCl solution. After being dried over Na_2SO_4, $(C_2H_5)_2O$ was evaporated at atmospheric pressure. The residual crystals were recrystallized from *n*-hexane–CH_2Cl_2. The yellow leaflets obtained melt at 110°; yield, 1.8 g (91%). The IR spectrum of this substance was completely identical with that of IX.

Reaction of *p*-Aminobenzotrifluoride (XI) with $NaNH_2$——XI (0.73 g) was treated with $NaNH_2$ as in the case of I. The $(C_2H_5)_2O$ solution was concentrated to dryness and the residue was passed through SiO_2-column in *n*-hexane–CH_2Cl_2 (1: 3) solution. The effluent was recrystallized from cyclohexane to give colorless needles of *p*-aminobenzonitrile (XII), mp 83—84°; yield, 0.023 g (4.4%). XII was identified with an authentic sample by admixture and comparison of IR spectra.

Acknowledgement We express our sincere gratitude to Mr. M. Kumazaki for carrying out some part of the experiment, Mr. Y. Shida for mass spectral measurement, and Sankyo Co. for elemental analyses. Part of this work was supported by the grants from the Ministry of Education of Japan.

7) S.D. Ross and I. Kuntz, *J. Am. Chem. Soc.*, **74**, 1297 (1952).