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Studies on Organic Fluorine Compounds. XVIII.[1] On the Mechanism of the Conversion of Trifluoromethyl Group to Amino Group on a Quinoline Ring[2]

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The mechanism for a novel reaction of a trifluoromethyl group as a leaving group is confirmed. Reaction of 2-(heptafluoro-*n*-propyl)quinoline with sodium amide gave 2-aminoquinoline, which shows that a perfluoroalkyl group could behave as a leaving group in some SNAr reactions. Tris(trifluoromethyl)-*s*-triazine gave a 1,4-ammonia adduct, which shows that the reaction passed through addition-elimination mechanism.

In our previous papers,[4] we reported the reaction of several nucleophilic reagents with the trifluoromethyl group on the quinoline ring, along with the fact that there are three types of reaction mechanism when the reaction occurs on a trifluoromethyl group, which was believed to be very unreactive.

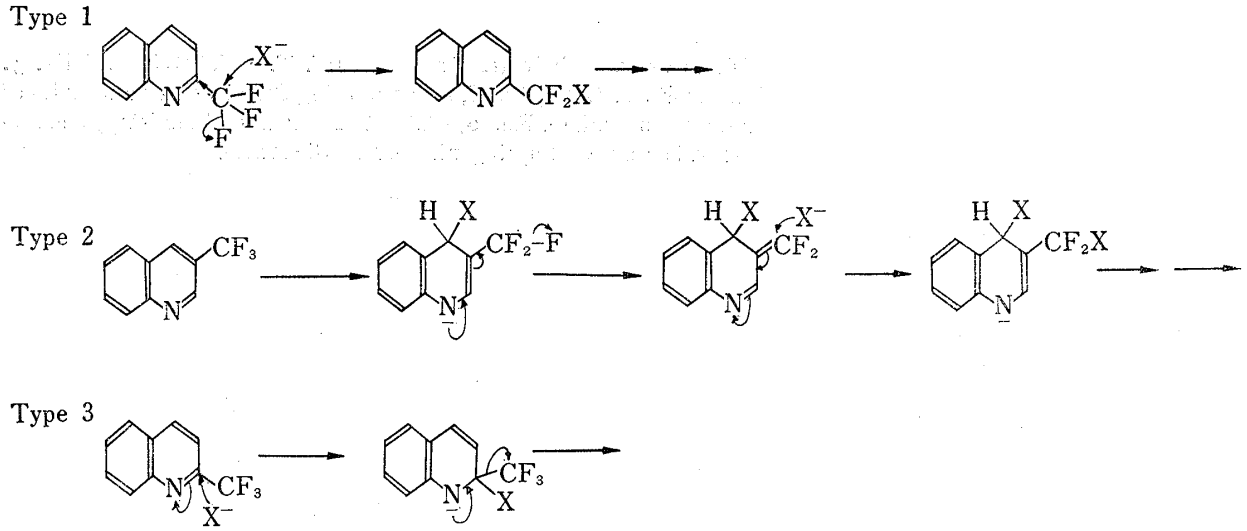

Chart 1

In this paper, we report that we obtained supporting data for the most interesting type-3 mechanism, where the trifluoromethyl group behaves as a leaving group. We proposed that a trifluoromethyl anion itself was replaced by an amino anion through an addition-elimination mechanism to produce α-amino-heterocycles. However, the following mechanism still seemed within the range of possibility: the trifluoromethyl group was first converted to a cyano group

1) Part XVII: Y. Kobayashi, I. Kumadaki, Y. Hanzawa, and M. Mimura, *Chem. Pharm. Bull.* (Tokyo), **23**, 636 (1975).
2) Presented at the 92nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April 1972.
3) Location: *Kitashinjuku 3-chome, Shinjuku-ku, Tokyo.*
4) *a*) Y. Kobayashi, I. Kumadaki, and S. Taguchi, *Chem. Pharm. Bull.* (Tokyo), **19**, 624 (1971); *b*) Y. Kobayashi, I. Kumadaki, S. Taguchi, and Y. Hanzawa, *Chem. Pharm. Bull.* (Tokyo), **20**, 1047((1972).

by SN2 reaction of a fluoride ion with an amino anion, followed by dehydrofluorination, and then the cyano group was replaced by the amino group through an addition-elimination mechanism (Chart 2). Therefore, if the reaction proceeds through the latter mechanism,

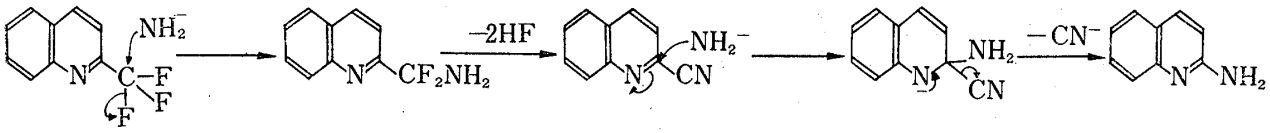

Chart 2

the cyanide ion at least should be detected in the reaction mixture. The aqueous solution after working-up was actually proved to contain cyanide ion, as it became blue when ferrous sulfate and hydrochloric acid were added. However, this fact does not necessarily show that the reaction proceeded by the latter mechanism shown in Chart 2. For, when fluoroform was bubbled into sodium amide in liquid ammonia and the reaction mixture was worked up, cyanide ion was also detected in the aqueous solution. The conversion of fluoroform to cyanide ion suggests the possibility that the trifluoromethyl anion produced by the type-3 mechanism in Chart 1 reacts with ammonia and is converted to cyanide ion as shown in Chart 3. Therefore, the detection of cyanide ion cannot tell which mechanism was responsible in the above reaction.

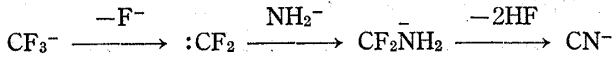

Chart 3

Next, 2-cyanoquinoline (I) and 1-cyanoisoquinoline (II) were submitted to the same reaction with the trifluoromethyl compounds under the same condition to give α-amino derivatives (III and IV). However, the yields of α-amino derivatives were much better from the trifluoromethyl compounds than from the cyano compounds, as shown in Table I. This fact supports the elimination of trifluoromethyl group by itself.

Table I

	Yield of α-amino compound
2-Cyanoquinoline (I)	(III) 22.4%
2-(Trifluoromethyl)quinoline	(III) 69.5%
1-Cyanoisoquinoline (II)	(IV) 9.1%
1-(Trifluoromethyl)isoquinoline	(IV) 57%

To confirm further the above hypothesis, quinolines with perfluoro-*n*-propyl group and perfluoro-isopropyl group, two groups which will not be converted to the cyano group, were prepared and submitted to the same reaction. First, in the case of 2-(heptafluoro-*n*-propyl) quinoline (V), 2-aminoquinoline (III) was obtained in 27% yield. The fact strongly supports the behavior of the trifluoromethyl group as leaving group in the above case. But in the case of 2-(heptafluoro-isopropyl)quinoline, the reaction was complicated and α-amino derivative was not obtained.

The result of the same reaction with other trifluoromethyl heterocycles is shown in Chart 4. In the case of tris(trifluoromethyl)-*s*-triazine (VII), diamino compound (VIII) was obtained and the reaction was presumed to proceed as shown in Chart 5 from the fact that 1,4-adduct (IX) was obtained, when ammonia gas was bubbled into the ether solution of the *s*-triazine. On the other hand, 2,6-bis(trifluoromethyl)pyridine (X) gave a monoamino compound. This fact also supports the addition-elimination mechanism. The fact that only one of the trifluoromethyl groups of 2,6-bis(trifluoromethyl)pyridine was replaced by an

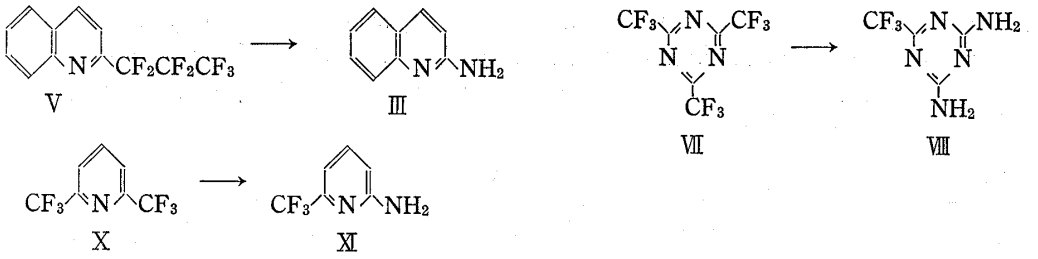

Chart 4

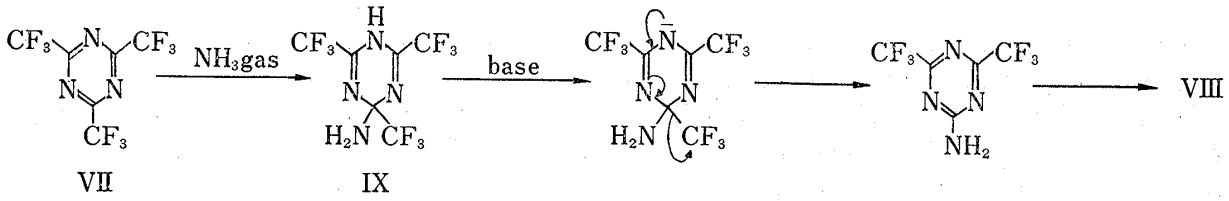

Chart 5

amino group shows that the electron-donating effect of an amino group deactivated this reaction.

In conclusion, the trifluoromethyl group was found to be a better leaving group than the cyano group in the reaction with sodium amide in liquid ammonia as far as it is in the α-position of heterocyclic ring, although it has been generally believed to be stable on the aromatic ring.

Experimental

General Preparation Procedure of $NaNH_2$ Solution——$NaNH_2$ was freshly prepared by dissolving Na (1 g) in liq. NH_3 (20—30 ml) in the presence of ferric nitrate (0.1 g).

Reaction of 2-Cyanoquinoline (I) with $NaNH_2$——To a solution of $NaNH_2$ in liq. NH_3, a solution of I (1 g) in ether (10 ml) was added dropwise and the mixture was stirred for 2 hr. After NH_3 was evaporated, the residue was treated with ice water and extracted with ether. The ether layer was dried over Na_2SO_4 and concentrated to dryness. The residue was recrystallized from benzene to give pale yellow needles of 2-amino-quinoline (III), mp 127—128°; yield, 0.21 g (22.4%). This substance was identified with an authentic sample by admixture and comparison of IR spectra.

Reaction of 1-Cyanoisoquinoline (II) with $NaNH_2$——II (0.8 g) was treated with $NaNH_2$ as in the case of I. The dried ether solution was concentrated to dryness and the residue was recrystallized from benzene to give leaflets of 1-amino-isoquinoline (IV), mp 120—122°, yield, 0.07 g (9.1%). This substance was identified with an authentic sample by admixture and comparison of IR spectra.

Synthesis of 2-(heptafluoro-*n*-propyl)quinoline (V)——A mixture of 2-iodoquinoline (2.5 g), heptafluoro-*n*-propyl iodide (5 g), and copper powder (3 g) in hexamethylphosphoric triamide (20 ml) was sealed in a stainless steel tube and shaken at 130—140° for 15 hr. The reaction mixture was poured into water and steam-distilled. The distillate was extracted with ether and the ether layer was dried over Na_2SO_4. The evaporation of ether gave a crude yellow oil. Distillation of this substance gave a pale yellow oil of 2(heptafluoro-*n*-propyl)quinoline (V), bp 126—127° (35 mmHg). Yield, 1.9 g) 65.5%). IR ν_{max}^{film} cm^{-1}: 1100—1200 (C-F). ^{19}F NMR (CCl_4)[5] +18.25 (t, 3F, CF_3), +54.25 (q, 2F, $-\underline{C}F_2-CF_2-CF_3$), +67.25 (s, 2F, $-CF_2-\underline{C}F_2-CF_3$). *Anal.* Calcd. for $C_{12}H_6NF_7$; C, 48.48; H, 2.02; N, 4.71; F, 44.78. Found: C, 47.81; H, 1.86; N, 4.51; F, 42.95.

Synthesis of 2-(Heptafluoro-isopropyl)quinoline (VI)——A mixture of 2-iodoquinoline (2.5 g), copper powder (3 g), and heptafluoro-isopropyl iodide (5.2 g) in HMPA (20 ml) was sealed in a stainless steel tube and shaken at 120—130° for 21 hr. The reaction mixture was poured into water and steam-distilled. The distillate was extracted with ether and the ether layer was dried over Na_2SO_4. The evaporation of the ether gave a crude yellow oil. This crude oil was chromatographed over SiO_2-column with CH_2Cl_2-*n*-hexane (1: 5). The effluent with CH_2Cl_2-*n*-hexane (1: 5) gave a crude yellow oil. Distillation of this substance gave a pale yellow oil of 2-(heptafluoro-isopropyl)quinoline (VI), bp 108—110° (18 mmHg). Yield, 0.866 g (29.8%). IR

5) Chemical shifts were measured in ppm from benzotrifluoride as an internal standard.

ν_{max}^{film} cm^{-1}: 1230 (C–F). ^{19}F NMR ($CDCl_3$), +12.14 (d, 6F, $-\underset{F}{\underset{|}{C}}\langle\begin{matrix}CF_3\\CF_3\end{matrix}$). *Anal.* Calcd. for $C_{12}H_6NF_7$: C, 48.48; H, 2.02; N, 4.71; F, 44.78. Found C, 48.35; H, 2.06; N, 4.56; F, 43.96.

Reaction of 2-(Heptafluoro-*n*-propyl)quinoline (V) with $NaNH_2$——V (1.08 g) was treated with $NaNH_2$ as in the case of I. The ether solution was concentrated to dryness at atmospheric pressure. The residual crude crystals were passed through SiO_2–column in CH_2Cl_2–MeOH (4%). The effluent with CH_2Cl_2–MeOH (4%) was recrystallized to give leaflets of III, mp 129°; yield, 0.144 g (27.3%). This substance was identified with an authentic sample by admixture and comparison of IR spectra.

Reaction of Tris(trifluoromethyl)-*s*-triazine (VII) with $NaNH_2$——VII (0.75 g) was treated with $NaNH_2$ as in the case of I. The ether solution was concentrated to dryness at atmospheric pressure. The residue was recrystallized from EtOH–H_2O to give colorless crystals of diamino(trifluoromethyl)-*s*-triazine (VIII), mp 250—260° (sublime); yield, 0.02 g (4.2%). IR ν_{max}^{KBr} cm^{-1}: 3400 (N–H), 1150, 1200 (C–F). Mass Spectrum *m/e*: 179 (M^+). High Mass Spectrum, Calcd. for $C_4H_4N_5F_3$: 179.042. Found: 179.041.

Reaction of Tris(trifluoromethyl)-*s*-triazine (VII) with NH_3 Gas——To a solution of VII (0.488 g) in ether (50 ml), NH_3 gas was passed for 30 min. The precipitated crystals were filtered off. These crystals were vary unstable and easily sublimable and show no constant melting point. The structure of this substance (IX) was determined as follows: IR ν_{max}^{KBr} cm^{-1}: 3340 (N–H), 1649 (C=N), 1180, 1250 (C–F). ^{19}F NMR (MeOH): +11.25 (s, 6F, $\begin{matrix}N\\N\end{matrix}\rangle C-CF_3$), +24.6 (s, 3F, $\times\begin{matrix}NH_2\\CF_3\end{matrix}$). UV λ_{max}^{EtOH} 283 nm.

Reaction of 2,6-Bis(trifluoromethyl)pyridine (X)——X (0.423 g) was treated with $NaNH_2$ as in the case of I. The ether solution was concentrated to dryness at atmospheric pressure. The residue was chromatographed over SiO_2–column with CH_2Cl_2. The effluent with CH_2Cl_2 was recrystallized with *n*–hexane to give colorless prisms of 2-amino-6-(trifluoromethyl)pyridine (XI); mp 78—80°; yield, 0.073 g (23%). IR ν_{max}^{KBr} cm^{-1}: 3300, 3210 (N–H), 1130, 1180 (C–F). NMR (CCl_4) δ: 6.6 (1H, d, 3-H, J=8 cps), 6.98 (1H, d, 5-H, J=7 cps), 7.5 (1H, d–d, 4-H, J=7 and 8 cps), 5.15 (2H, bs, NH_2). High Mass Spectrum, Calcd. for $C_6H_5N_2F_3$: 162.038. Found: 162.040.