[Chem. Pharm. Bull. 20(5)1047—1049(1972)]

UDC 547.831.2'412.04 : 546.33.04

Studies on Organic Fluorine Compounds. X.[1] Reaction of Trifluoromethyl Group in Heterocycles with Sodium Amide[2]

Yoshiro Kobayashi, Itsumaro Kumadaki, Shigeru Taguchi, and Yuji Hanzawa

Tokyo College of Pharmacy[3]

(Received February 3, 1972)

In the reactions of (trifluoromethyl)pyridines and (trifluoromethyl)benzopyridines with sodium amide, trifluoromethyl group, which has been considered to be very stable, was substituted with amino group and an unexpected reaction was observed. We propose mechanisms for these reactions.

There have been few reports on the investigation of the reactivity of trifluoromethyl groups on heterocycles, such as pyridine and its analogues. In our recent work, we found an interesting interaction of the trifluoromethyl group and the ring nitrogen. That is, we examined the reactions of trifluoromethyl groups on the heterocycles such as alcoholysis with sodium alkoxide[4] and reduction with metal hydride,[1] and we proposed reaction mechanisms which involve the interaction between the trifluoromethyl group and a heteroatom. In this paper, the reactions of (trifluoromethyl)pyridines and (trifluoromethyl)benzopyridines with sodium amide are reported.

The reaction was carried out in liquid ammonia by treating (trifluoromethyl)heterocycles with sodium amide, whereupon novel reactions of trifluoromethyl groups were found. First, when 2-(trifluoromethyl)quinoline (I) was treated with sodium amide, 2-aminoquinoline (II) was obtained. This reaction seems to proceed through nucleophilic substitution of the trifluoromethyl group with an amino group involving fission of carbon-carbon bond. Similarly, 2-(trifluoromethyl)pyridine (III) and 1-(trifluoromethyl)isoquinoline (V) gave the corresponding amino compounds (IV and VI). This is the first example of the trifluoromethyl group being observed as a leaving group, though it had been expected, since the trifluoromethyl group had often been referred as a pseudohalogen.[5]

In contrast to the formation of α-aminocompounds from α-(trifluoromethyl)heterocycles, treatment of 3-(trifluoromethyl)quinoline (VII) with sodium amide produced, not the corresponding 3-aminocompound, but 3-cyano- (VIII) and 4-amino-3-cyanoquinoline (IX). These results fully agree with our data of the mass spectra of (trifluoromethyl)pyridine derivatives;[6] that is, in mass spectra of (trifluoromethyl)pyridine, the trifluoromethyl group in α-position is easily lost and that in β-position shows fluorine elimination with α-hydrogen. The above results and the fact that benzotrifluoride was recovered unchanged from treatment with sodium amide show that the reaction mechanisms necessarily involve the participation of the trifluoromethyl group and heteroatom. In the case of 3-(trifluoromethyl)quinoline, the reaction mechanism is not a simple substitution at the carbon atom of trifluoromethyl group with the amino group but is a more complex one which proceeds through a 1,4-dihydro

1) Part IX: Y. Kobayashi, I. Kumadaki, and S. Taguchi, *Chem. Pharm. Bull.* (Tokyo), **20**, 823 (1972).
2) Preliminary communication: Y. Kobayashi, I. Kumadaki, S. Taguchi, and Y. Hanzawa, *Tetrahedron Letters*, **1970**, 3901; Presented at the 90th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, July 1970.
3) Location: *Kitashinjuku 3-chome, Shinjuku-ku, Tokyo.*
4) Y. Kobayashi, I. Kumadaki, and S. Taguchi, *Chem. Pharm. Bull.* (Tokyo), **19**, 624 (1971).
5) W.A. Sheppard and C.M. Sharts, "Organic Fluorine Chemistry," W.A. Benjamin, New York, 1969, p. 62.
6) Y. Kobayashi, F. Nakano, and E. Chinen, *Chem. Pharm. Bull.* (Tokyo), **15**, 1901 (1967).

form mentioned in our earlier paper[1] (Chart 1). The structure of (IX) was identified by comparison with an authentic sample which was obtained from 4-chloro-3-cyanoquinoline.[7] In addition to the data obtained from 3-(trifluoromethyl)quinoline, it is interesting to note that the 3-cyanoquinoline did not give 2-amino-3-cyanoquinoline but a 4-amino-3-cyanoquinoline under treatment with sodim amide.

In the case of 4-(trifluoromethyl)quinoline (X), normal Chichibabin-like reaction product, 2-amino-4-(trifluoromethyl)quinoline (XI), and an unexpected compound with an open ring, *o*-formylaminophenylethyne (XII), were obtained. This reaction mechanisms was explained as follows: the amino anion attacked the α-position in the first step and the 1,2-dihydro compound was oxidized to give XI on one hand, and on the other the ring was cleaved by the electron back-polarization from the nitrogen atom between 2- and 3-positions to form a new compound with a triple bond and then a part of the amidine was hydrolyzed to give XII, as shown in Chart 1. The structure of XII was confirmed by infrared (IR) and nuclear magnetic resonance (NMR) spectra, elemental analysis, and chemical reactions. Its IR spectrum showed typical absorption bands at 3375, 3295 cm^{-1} (ν_{N-H}), 2120 cm^{-1} ($\nu_{C\equiv C}$), and 1700 cm^{-1} ($\nu_{C=O}$). In the NMR spectrum, the two peaks at δ 3.45 and 3.58, and four unanalizable peaks at δ 8.38, 8.48, 8.78 and 8.88 which were observed at room temperature appeared as a singlet at 3.43 (1H) (C≡CH) and 8.58 (1H) (N-CHO), respectively, by the measurement at 60°. The above spectral data are the good evidence of the fact that the free rotation of N-formyl group was hindered at room temperature. Chemically, this structure was confirmed by the reduction of *o*-formylaminophenylethyne with palladium charcoal to *o*-ethylformanilide, which was completely identical with an authentic sample obtained from the formylation of *o*-ethylaniline.[8]

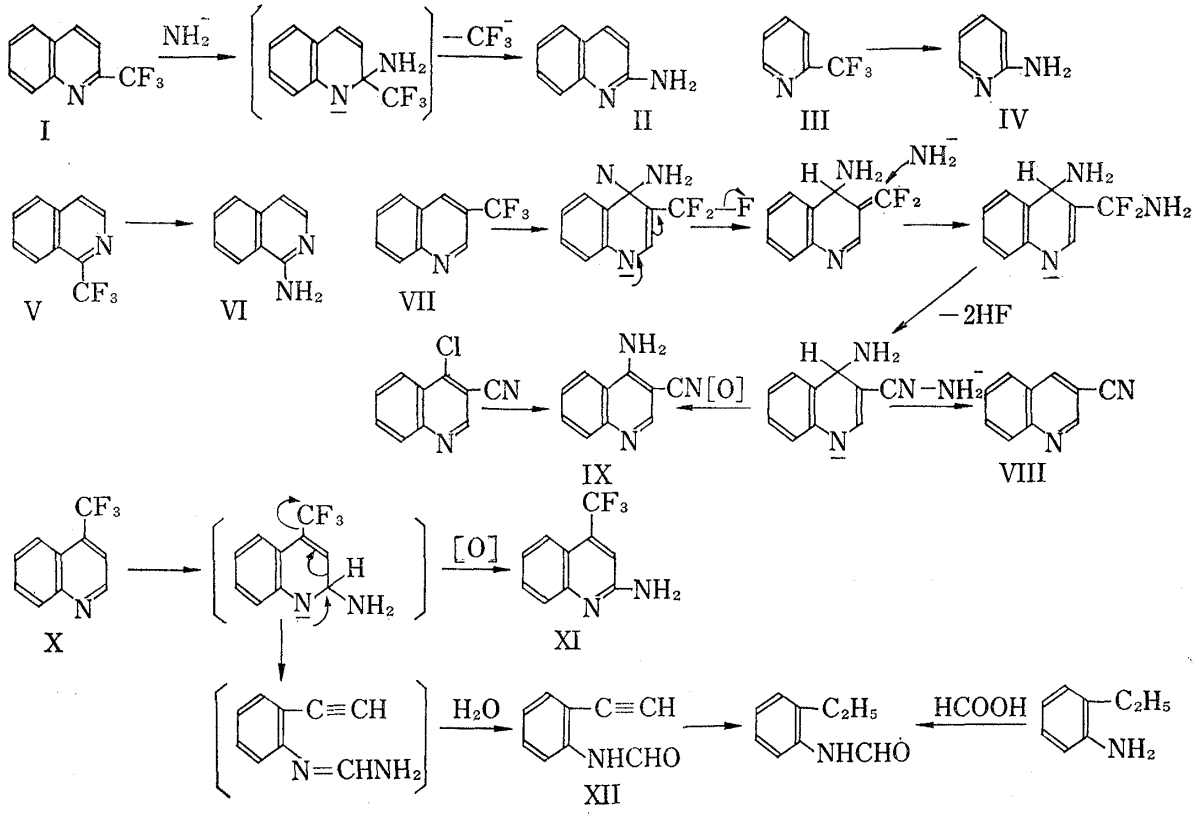

Chart 1

7) M. Hamana and S. Urabe, Abstract of the 21st Annual Meeting of the Pharmaceutical Society of Japan, Tokushima, 1965, p. 275.
8) R.B. Kelly, W.T. Taylor, and K. Wiesner, *J. Chem. Soc.*, **1953**, 2094.

In the series of reactions of the trifluoromethyl group on heterocycles, it became clear that the action of the trifluoromethyl group on heterocycles differs according to its position on the ring and all the products expected from the previously proposed three kinds of mechanism[4] were obtained in the series of our present studies of nucleophilic reactions.

All the results are summarized in Chart 1.

Experimental

General——$NaNH_2$ 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) as in the case of Birch-reduction.

Amination of 2-(Trifluoromethyl)quinoline (I)——To a solution of $NaNH_2$ (from Na (0.5 g)) in liq. NH_3 (15 ml), a solution of I (0.28 g) in ether (10 ml) was added dropwise and stirred for 2 hr. NH_3 was evaporated and the residue was treated in 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-aminoquinoline (II), mp 128—129°; yield, 0.14 g (69.5%). This substance was identified with an authentic sample by admixture and comparison of IR spectra.

Amination of 2-(Trifluoromethyl)pyridine (III)——III (1.46 g) was treated with $NaNH_2$ (from Na (1 g)) as in the case of I. After the evaporation of NH_3 at room temperature with stirring, ether containing H_2O was added slowly to the residue, and the insoluble substance was filtered off. The H_2O layer was saturated with NaOH and continuously extracted with ether. After the ether solution was dried over Na_2SO_4, ether was evaporated to give crude crystals. Recrystallization from pet. ether gave pale yellow leaflets of 2-aminopyridine (IV), mp 59—60°; yield, 0.825 g (88%). This substance was identified with an authentic sample by admixture and comparison of IR spectra.

Amination of 1-(Trifluoromethyl)isoquinoline (V)——V (0.33 g) was treated with $NaNH_2$ (from Na (1 g)) as in the case of I. The ether solution was concentrated and passed through SiO_2 column. Effluent with ether gave crude crystals, which were recrystallized from benzene–hexane to give leaflets of 1-aminoisoquinoline (VI), mp 123—124°; yield, 0.132 g (57%). This substance was identified with an authentic sample by admixture and comparison of IR spectra.

Amination of 3-(Trifluoromethyl)quinoline (VII)——VII (1 g) was treated with $NaNH_2$ (from Na (1 g)) as in the case of I. The ether extract was concentrated and the residue was recrystallized from MeOH to give pale yellow needles of 4-amino-3-cyanoquinoline (IX), mp 250—260° (dec.); yield, 0.013 g (2.5%). IR ν_{max}^{KBr} cm^{-1}: 2245 (C≡N), 3300 (broad, N-H). *Anal.* Calcd. for $C_{10}H_7N_3$: C, 70.99; H, 4.17; N, 24.84. Found: C, 70.55; H, 4.31; N, 24.96.

The mother liquor was concentrated and the residue was passed through Al_2O_3-column in CH_2Cl_2 solution. The effluent was recrystallized from *n*-hexane to give colorless needles of 3-cyanoquinoline (VIII), mp 105—106°; yield, 0.094 g (20%). This substance was identified with an authentic sample[9] by admixture and comparison of IR spectra.

Amination of 4-(Trifluoromethyl)quinoline (X)——X (0.69 g) was treated as in the case of I. The ether solution was concentrated to dryness and chromatographed over SiO_2 with CH_2Cl_2. The first effluent gave colorless crystals, which were recrystallized from hexane to give colorless needles of *o*-formylaminophenylethyne (XII), mp 103—104°; yield, 34 mg (6.0%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3375, 3295 (N–H), 2120 (C≡C), 1700 (C=O). NMR ($CDCl_3$) at 60° δ: (1H, s, CHO), 7.5—6.98 (4H, m, ar-H), 3.43 (1H, s, C≡CH). *Anal.* Calcd. for C_9H_7ON: C, 74.48; H, 4.82; N, 9.65. Found: C, 74.00; H, 4.92; N, 9.55.

2-Amino-4-(trifluoromethyl)quinoline (XI, 29.6 mg, 4.0%) was obtained from the second effluent and was recrystallized from hexane, mp 127—128°. The IR spectrum of this compound was completely identical with that of an authentic sample.

Reduction of XII——XII (30 mg) was dissolved in 30 ml MeOH and shaken with 10% Pd-C (0.1 g) in H_2. After the absorption of H_2 was over, the Pd-C was filtered off and concentrated to dryness. The residue was recrystallized from *n*-hexane to give colorless needles, mp 73—77°; yield, 28 mg (93.9%). This substance was identified with an authentic sample obtained by formylation of *o*-ethylaniline.[8]

4-Amino-3-cyanoquinoline (IX)——4-Cl-3-cyanoquinoline[7] (0.1 g) was heated in concd. NH_3 (5 ml) with $CuSO_4$ (0.1 g) in a sealed tube at 150° for 3 hr. After being cooled, the tube was opened and the reaction mixture was poured on ice and rinsed with MeOH. The mixture was concentrated to dryness and the residue was recrystallized from EtOH to give IX (0.05 g, 56.1%).

Acknowledgement We express our sincere gratitude to Sankyo Co. for elemental analyses. Part of this work was supported by the grants from the Ministry of Education of Japan and Hoansha Foundation.

9) H. Gilman and S.M. Spatz, *J. Am. Chem. Soc.*, **63**, 1557 (1941).