[Chem. Pharm. Bull. 25(11)3009—3012(1977)]

UDC 547.728.2.04 : 547.136.25.04

Studies on Organic Fluorine Compounds. XXII.[1] Synthesis and Reactions of (Trifluoromethyl)benzofurans[2]

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(Received March 25, 1977)

2- and 3-(Trifluoromethyl)benzofurans (III and V) were synthesized by the reaction of 2- and 3-bromobenzofurans with trifluoromethyliodide in the presence of copper powder. Reaction of III and V with alcoholic sodium hydroxide, lithium aluminum hydride, and sodium amide showed that the trifluoromethyl group on the benzofuran ring is much less reactive than that on the indole ring. The remarkable point of reactions of the (trifluoromethyl)benzofurans is the addition of the nucleophile of C2,C3-double bond, which might be ascribed to the localization of the double bond.

Keywords——(trifluoromethyl)benzofuran; trifluoromethylation with trifluoromethyl iodide and copper powder; sulfur tetrafluoride; nucleophilic substitution reaction with sodium amide and alcoholic sodium hydroxide; synthesis of benzofuran derivatives; trifluoromethyl group on aromatic ring

In our previous papers we reported the nucleophilic substitution reactions of a trifluoromethyl group on π-electrondeficient quinoline ring[4] and π-electron-excess indole ring.[5] In the former case, a trifluoromethyl group underwent three kinds of interesting reactions and in the latter a substitution reaction took place through elimination-addition mechanism. A trifluoromethyl group on 3-position of indole was found to be more reactive than that on 2-position. This result was consistent with what was expected from the structures of intermediates (Chart 1) and from π-electron densities calculated by the molecular orbital method.[6]

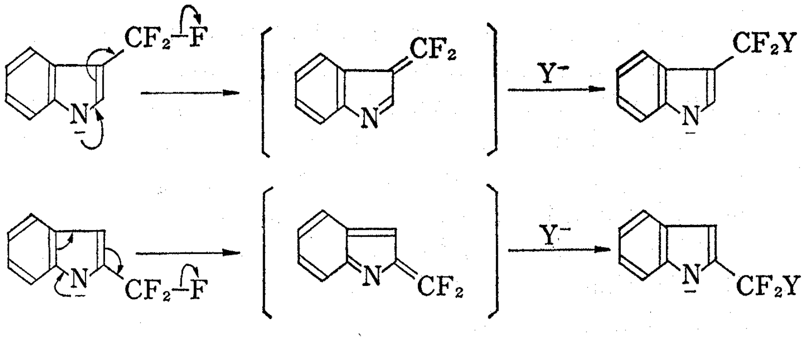

Chart 1

Thus, it seemed interesting to examine the reactions of a trifluoromethyl group on the benzofuran ring, where the π-electron density at 2-position had been reported to be higher than that at 3-position,[6] while from the resonance structure 3-isomer seemed to be more

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[1] Part XXI: Y. Kobayashi and A. Ohsawa, *Chem. Pharm. Bull.* (Tokyo), **24**, 2225 (1976).
[2] Presented at the 7th Symposium on Heterocyclic Chemistry, Chiba, Japan, October 1974.
[3] Location: *Horinouchi, Hachioji-shi, Tokyo, 192-03, Japan.*
[4] *a*) Y. Kobayashi, I. Kumadaki, and S. Taguchi, *Chem. Pharm. Bull.* (Tokyo), **19**, 629 (1971); *b*) *Idem, ibid.*, **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. Hanzawa, and M. Mimura, *Chem. Pharm. Bull.* (Tokyo), **23**, 2044 (1975).
[5] Y. Kobayashi, I. Kumadaki, Y. Hirose, and Y. Hanzwa, *J. Org. Chem.*, **39**, 1836 (1974).
[6] P.O. Lowdin and B. Pullman, "Molecular Orbitals in Chemistry, Physics and Biology," Academic Press, New York, N.Y., 1964, p. 492.

reactive than 2-isomer; the intermediate from the latter must have *o*-quinonoid structure as in the case of 2-(trifluoromethyl)indole.

First, we examined the synthesis of 2- and 3-(trifluoromethyl)benzofurans, which had not been synthesized before. Treatment of 2- and 3-benzofurancarboxylic acids (I and II) with sulfur tetrafluoride did not give satisfactory results; only 20% of 2-(trifluoromethyl)-benzofuran (III) was obtained from 2-carboxylic acid with the acid fluoride (IV) and much of polymer. The structure of III was confirmed by mass spectrum and nuclear magnetic resonance (NMR) spectrum. The structure of IV was assumed from NMR, infrared (IR), and mass spectra. Further, only a trace of 3-(trifluoromethyl)benzofuran (V) from II was observed in ^{19}F–NMR spectrum and much of the acid fluoride (VI) was formed. To increase the yield of V, the condition was made more drastic, but only the formation of a tarry substance was increased with no improvement in the yield of V. This might be due to the high reactivity of the benzofuran ring for Friedel-Crafts type acylation catalyzed by the existing hydrogen fluoride (Chart 2).

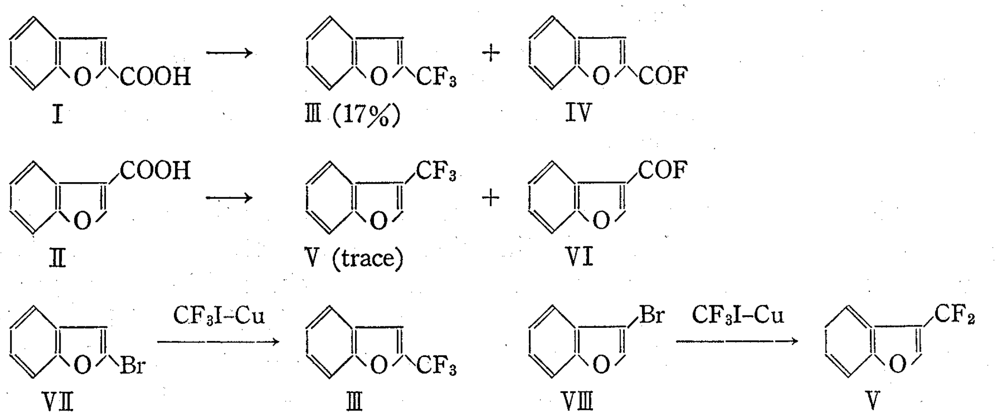

Chart 2

Next, we tried the application of our method7) of trifluoromethylation with trifluoromethyl iodide and copper powder to 2- and 3-bromobenzofurans (VII and VIII). Compounds VII and VIII were shaken with trifluoromethyl iodide and copper powder in dimethylformamide at 110—130° to give III and V in the yields of 53% and 60%, respectively. Spectral data of III and V obtained by this method and the former method using sulfur tetrafluoride were identical with each other and the structure of III and V were determined. In the latter method, III and V could be obtained for investigation of reactions (Chart 2.)

Then, we tried the reactions of III and V with nucleophiles. When III and V were refluxed with alcoholic sodium hydroxide, both gave the corresponding carboxylic acids (I and II), but the yields were very poor and a large amount of tarry substance was formed. Since benzotrifluoride was recovered unchanged in this condition, activation by the benzofuran ring must have taken part in this reaction as in the case of (trifluoromethyl)indoles. The difference between the reactivities of 2- and 3-isomers was not apparent, since the yields of carboxylic acids were poor. Formation of much tarry substance might be explained as follows: addition of the nucleophile to the rather localized C2-C3-double bond took place first, followed by ring-opening and polimerization. Actually, products from the addition and ring-opening were isolated in the reaction of III with sodium amide as shown below (Chart 3).

Treatment of III with sodium amide in liquid ammonia gave an adduct (IX), *o*-hydroxybenzoylacetonitrile (X), and *o*-hydroxybenzylcyanide (XI) in the yields of 8%, 20%, and

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7) Y. Kobayashi, I. Kumadaki, S. Sato, N. Hara, and E. Chikami, *Chem. Pharm. Bull.* (Tokyo), **18**, 2334 (1970).

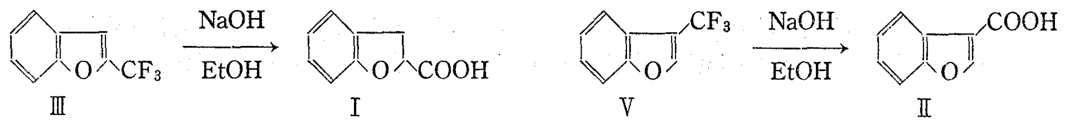

Chart 3

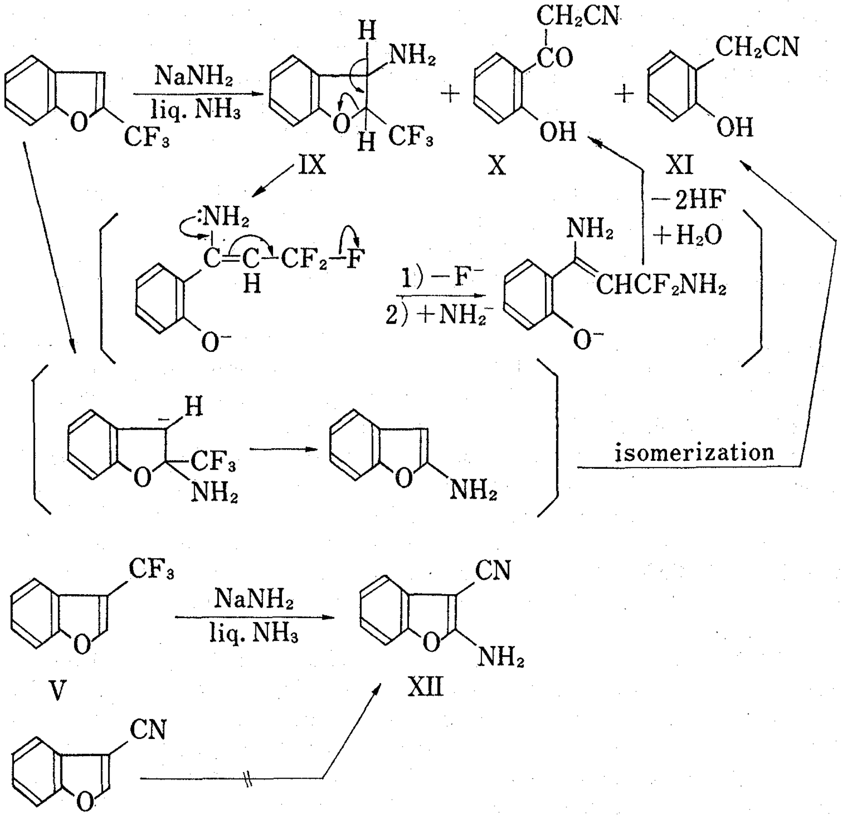

Chart 4

2%, respectively. The structure of IX was determined from mass spectrum (M^+ 203) and NMR spectrum (δ 3.00 and 3.61, both doublet, $J=17$ Hz). The structures of X and XI were assumed from spectral data and determined by comparison with the authentic samples synthesized according to literature.

Remarkable features of the result were isolation of the adduct (IX) of the nucleophile to the aromatic double bond and of open-ring compounds (X and XI). Treatment of IX in this reaction condition gave X. Thus, mechanism of production of X was assumed as shown in Chart 4. The mechanism of formation of XI might be as follows: an amino anion attacked 2-position, followed by the loss of the trifluoromethyl group and ringopening as shown in Chart 4.

Treatment of V as in the case of III gave 2-amino-3-cyanobenzofuran (XII) in a very low yield. In this case, too, addition of an amino anion occurred at 2-position, followed by oxidation, substitution of an amino anion for a fluoride ion and dehydrofluorination. Treatment of 3-cyanobenzofuran in this condition did not give XII, thereby excluding the alternative mechanism through 3-cyanobenzofuran.

Attempted reduction of III and V with lithium aluminum hydride resulted in the recovery of the starting materials.

These results show that a trifluoromethyl group on the benzofuran ring is much less reactive than that on the indole ring. This might be due to the less degree of delocalization of lone-pair electrons on the oxygen atom than those on the nitrogen atom. The localization of C2-C3-double bond and the addition of a nucleophile to this double bond is favored by the electron-attracting trifluoromethyl group. The addition of a nucleophile to the aromatic double bond is characteristic of the reactions of (trifluoromethyl)benzofurans.

Experimental

2-(Trifluoromethyl)benzofuran (III)——a) From 2-Benzofurancarboxylic Acid (I): The compound (I) (10 g) was heated with sulfur tetrafluoride (25 ml) and H_2O (0.5 ml) at 125° for 12 hr in a Hastelloy-C autoclave with stirring. After cooling, gaseous products were degassed and the residue was poured into ice-water, neutralized with $NaHCO_3$, and extracted with ether. The ether solution was dried over Na_2SO_4 and evaporated. Distillation of the residue gave a pale-yellow oil (III), bp 148°, 2.3 g (20%). ^{19}F-NMR ($CDCl_3$) ppm[8]; +2.05 (s, CF_3). Mass spectrum (MS); *m/e* 186 (M^+). High mass; Calcd. for $C_9H_5F_3O$: 186.029. Found: 186.031.

b) From 2-Bromobenzofuran (VII): The solution of VII (3 g) in DMF (20 ml) was shaken with Cu-powder (5 g) and CF_3I (5 ml) at 110—130° for 20 hr. After cooling, the reaction mixture was distilled with steam and extracted with ether. The ether solution was dried over Na_2SO_4 and evaporated. The distillation of the residue gave a pale-yellow oil, bp 148°, 1.5 g (53%). This oil was identified with III obtained by the method a).

3-(Trifluoromethyl)benzofuran (V)——The solution of 3-bromobenzofuran (VIII) (3 g) in DMF was treated as in the case of VII. Pale-yellow oil (V), 1.7 g (60%), was obtained. bp 160—162°, ^{19}F-NMR ($CDCl_3$) ppm; −2.8 (s, CF_3). MS *m/e* 186 (M^+). High mass; Calcd. for $C_9H_5F_3O$: 186.029. Found: 186.031.

Reaction of III with Alcoholic NaOH——Compound III (1 g) was refluxed in 10% alcoholic NaOH for 5 hr. After evaporation of the solvent under vacuum, the residue was diluted with H_2O, acidified with 10% HCl and extracted with ether. After the ether solution was dried over Na_2SO_4 and evaporated, the residue was recrystallized from C_6H_6 to give colorless needles, 0.05 g (5.7%), mp 190°. This was identified with the authentic sample of 2-benzofuran carboxylic acid by comparison of IR spectra and mixture melting point.

Reaction of V with Alcoholic NaOH——The same treatment of V(1 g) as III gave 3-benzofurancarboxylic acid (II), 0.062 g (8.5%), mp 155°. This was identified with the authentic sample by comparison of IR spectra and mixture melting point.

Reaction of III with $NaNH_2$——To the solution of $NaNH_2$ in liq. NH_3 (Na (1.5 g) to liq. NH_3 (30 ml)), III (3 g) in abs. ether (15 ml) was added dropwise under stirring and cooled in dry ice-acetone. Stirring was continued for further 2 hr. NH_3 was allowed to evaporate. The residue was treated with ice-water and extracted with ether. The ether extract was dried over Na_2SO_4 and concentrated to dryness. The residue was passed through SiO_2-column in C_6H_6 solution. The effluent was recrystallized from C_6H_6 to give yellow powder (IX), mp 108—109°, 0.268 g (8.2%). NMR ($CDCl_3$) δ: 7.5—6.6 (4H, m, Ar-H), 3.00 (1H, d, 2-H, $J=17$ Hz), 3.61 (1H, d, 3-H, $J=17$ Hz), 2.21 (2H, b.s., NH_2, disappears by addition of D_2O). ^{19}F-NMR ($CDCl_3$) ppm; 23.6 (s, CF_3). MS: *m/e* 203 (M^+).

The aqueous solution was acidified with d. HCl and extracted with ether. The ether extract was dried over Na_2SO_4 and evaporated. The residue was passed through SiO_2 column in benzene solution. The first effluent was recrystallized from EtOH to give pale-yellow needles[9] (X), mp 107—108°, 0.515 g (19.8%). This was identified with the authentic sample by the comparison of IR spectra and mixture melting point. The second effluent was recrystallized from EtOH to give colorless needles (XI), mp 118—120°, 0.050 g (2.3%). This was identified with the authentic sample[10] by comparison of IR spectra and mixture melting point.

Reaction of V with $NaNH_2$——Treatment of V (0.85 g) with $NaNH_2$ in liq. NH_3 (Na (1 g) in liq. NH_3 (20 ml)) as in the case of III gave yellow needles (XII) after recrystallization from C_6H_6–*n*-hexane, mp over 270°, 0.0057 g (0.7%). IR (KBr) cm^{-1}; 3400, 3360 (ν_{N-H}), 2200 ($\nu_{C\equiv N}$). MS: *m/e* 158 (M^+). High mass, Calcd. for $C_9H_6N_2O$: 158.0480. Found: 158.0511.

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[8] BTF as an internal standard.

[9] S. Cecchi and L.P. Vettori, *Gazz. Chim. Ital.*, **96**, 874 (1966) [*C.A.*, **65**, 16932 (1966)].

[10] H.A. Offe and H. Jatzkewitz, *Chem. Ber.*, **80**, 469 (1947).