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Studies on Organic Fluorine Compounds. VII.[1] Trifluoromethylation of Aromatic Compounds[2]

Yoshiro Kobayashi, Itsumaro Kumadaki, Susumu Sato, Nobutoshi Hara, and Eiichi Chikami

Tokyo College of Pharmacy[3]

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Trifluoromethyl iodide reacts with aryl halide in the presence of copper powder to give aryltrifluoromethane derivatives in a fairly good yield. This newly observed reaction is applicable to heterocyclic halides as well as benzene derivatives. Activities of halides are in the following order of readiness: iodide>bromide>chloride. Effects of solvents and natures of copper were examined.

The known methods to introduce trifluoromethyl group into the desired position of the aromatic ring are the following two ways. One is to substitute the chlorine atoms in trichloromethyl group, which has been derived from methyl group, with fluorine using antimony trifluoride or hydrogen fluoride.[4] The other is to fluorinate carboxyl group by sulfur tetrafluoride with hydrogen fluoride as catalyst.[5] These methods involve the modification on the carbon atom originally existing in the compound and their application is limited. Moreover, both methods have technical difficulties with hydrogen fluoride which has been used or generated during the reaction; besides, sulfur tetrafluoride is toxic.

$$\text{(a)}\quad ArCH_3 \xrightarrow{Cl_2} ArCCl_3 \xrightarrow{SbF_3 \text{ or } HF} ArCF_3$$

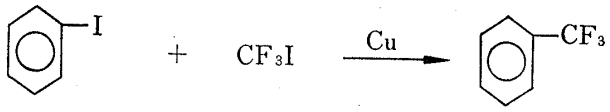
$$\text{(b)}\quad ArCOOH \xrightarrow[(HF)]{SF_4} ArCF_3$$

As regards the methods to introduce perfluoroalkyl group directly into the aromatic ring, there are such as follows: to heat aromatic compounds with perfluoroalkyl iodide,[6] to treat them with perfluoroacyl halides in the presence of nickel carbonate,[7] and to treat aryl fluoride with perfluoro-olefins at high temperature in the presence of cesium fluoride.[8] But these are synthetic methods of small interest, because isomers are obtained by them in the cases of aromatic ring, which already has substituents, or heterocyclic ring.

Recently, McLoughlin and Thrower[9] showed the way to introduce a perfluoroalkyl group possessing more than three carbon atoms into the desired position of the aromatic ring by heating the perfluoroalkyl halide, the aromatic halide, and copper metal in an aprotic solvent.

1) Part VI: Y. Kobayashi, I. Kumadaki, and S. Taguchi, *Chem. Pharm. Bull.* (Tokyo), **17**, 2335 (1969).
2) Preliminary communication: Y. Kobayashi, and I. Kumadaki, *Tetrahedron Letters*, **1969**, 4095. Most of this work was presented at the 89th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1969.
3) Location: *600 Kashiwagi 4-chome, Shinjuku-ku, Tokyo.*
4) J.H. Simons and C.J. Lewis, *J. Am. Chem. Soc.*, **60**, 492 (1938).
5) W.R. Hasek, W.C. Smith, and V.A. Engelhardt, *J. Am. Chem. Soc.*, **82**, 543 (1960).
6) G.V.D. Tiers, *J. Am. Chem. Soc.*, **82**, 5513 (1960).
7) J.J. Drysdale and D.D. Coffman, *J. Am. Chem. Soc.*, **82**, 5111 (1960).
8) R.D. Chember, R.A. Storey, and W.K.R. Musgrave, *Chem. Comm*, **1966**, 384.
9) V.C.R. McLoughlin and I. Thrower, U. S. Patent 3408411 (1968).

However, their patent does not refer to trifluoromethyl group,[10] compounds of which are quite different from higher perfluoroalkyl homologues in both chemical and physical characters. Namely, trifluoromethyl iodide is a gas at room temperature though perfluoropropyl is a liquid, and the procedure in the patent of carrying out the reaction in an open vessel is not applicable whereas that of using a sealed glass tube involves some risk and trouble. Besides, there is a considerable difference in the reactivity of trifluoromethyl iodide and higher perfluoroalkyl iodide to form their respective perfluoroalkyl lithium[11] and Grignard reagent;[12] the reaction of higher perfluoroalkyl iodide is not always applicable to trifluoromethyl iodide. Therefore, it was of great interest not only as a synthetic method but also theoretically to investigate whether the reaction would proceed with trifluoromethyl iodide.



First, iodobenzene and trifluoromethyl iodide with copper metal in a solvent of dimethylformamide was heated at 140° in a stainless steel tube under mechanical shaking, and benzotrifluoride was found to have been produced. The reaction can be regarded as an application of Ullmann reaction, where the quality of the copper metal used will influence the result. The following cases using four different kinds of copper were, therefore, compared to examine the effect of copper metal on the reaction: commercially available copper powder without pretreatment, the same substance treated with iodine-acetone,[13] copper powder precipitated from the aqueous solution of copper sulfate by adding zinc powder,[14] and the powder of copper–zinc alloy commercially available as copper bronz. Reactions were carried out with iodobenzene as substrate and dimethylformamide as solvent at 130—140°. Yield was obtained from gas chromatograph. The result is shown in Table I. It is clear from Table I that copper powder precipitated is the most effective and other three kinds are of equally low effect.

Table I

Nature of Cu	Yield (%)
Commercial Cu	36.8
Commercial Cu Treated with I_2-acetone	31.5
Precipitated Cu	72.0
Cu-Zn-alloy	38.0

Using the copper powder obtained by precipitation mentioned above, the reactions with the iodides of various aromatic compounds were carried out in dimethylformamide. The result is shown in Table II.

10) In McLoughlin's paper (V.C.R. McLoughlin and J. Thrower, *Tetrahedron*, **25**, 5921 (1969)) published after our preliminary communication[2] was published, he reports that the reaction proceeds with trifluoromethyl iodide using a sealed borosilicate glass tube and describes a single example of the reaction with iodobenzene, but there is no investigation of the reaction conditions in detail and the yield is poorer than ours.
11) O.R. Pierce, E.T. McBee, and G.F. Judd. *J. Am. Chem. Soc.*, **74**, 474 (1954).
12) R.N. Haszeldine, *J. Chem. Soc.*, **1954**, 1273.
13) R.C. Fuson and E.A. Cleveland, "Organic Syntheses," Coll. Vol. III, Jone Wiley and Sons, New York, 1955, p. 339.
14) R.Q. Brewster and T. Groening, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, 1948, p. 445.

Table II

Starting material	Product	Yield (%)
o-Iodotoluene	*o*-(trifluoromethyl)toluene	28
m-Iodotoluene	*m*-(trifluoromethyl)toluene	68
o-Diiodobenzene	*o*-bis(trifluoromethyl)benzene	32
o-Iodobenzotrifluoride	*o*-bis(trifluoromethyl)benzene	80
m-Iodobenzotrifluoride	*m*-bis(trifluoromethyl)benzene	62
p-Iodoanisole	*p*-(trifluoromethyl)anisole	86
p-Iodonitrobenzene	*p*-nitrobenzotrifluoride	51

o-Bis(trifluoromethyl)benzene was not obtained directly by method (a) mentioned above, and the same reaction had to be repeated twice. To obtain it in one step, phthalic acid alone could be used as material. But, now, two new materials are found to be available. *o*-(Trifluoromethyl)toluene was not synthesized by method (a) and the yield was very poor by method (b), whereas it was obtained in fairly good yield by this method. As for *p*-nitrobenzotrifluoride,[15] its synthesis required many steps by the known methods, method (b) being the only one-step method, but a material is found for this one-step method. The reaction was attempted with aryl halides other than iodide, but it did not proceed or its yield was so poor that it could only be recognized by gas chromatography.

Next, under similar conditions, the application of the reaction to heteroaromatic halides was attempted. The result is shown in Table III.

Table III

Starting material	Yield of CF_3-derivative (%)	Starting material	Yielb of CF_3-derivative (%)
2-Chloroquinoline	10	4-Chloroquinoline	11
2-Iodoquinoline	60	6-Bromoquinoline	28
3-Bromoquinoline	trace	1-Chloroisoquinoline	30
3-Iodoquinoline	30	1-Iodoisoquinoline	8.5

Table IV

Starting material	Solvent	Product	Yield (%)
Bromobenzene	DMF	starting material	
	HMPA	benzotrifluoride	trace
Chlorobenzene	pyridine	benzotrifluoride	11
	HMPA	benzotrifluoride	trace
	pyridine	benzotrifluoride	trace
p-Chloronitrobenzene	DMF	*p*-nitrobenzotrifluoride	trace
	HMPA	*p*-nitrobenzotrifluoride	20
	pyridine	—	—
3-Bromoquinoline	DMF	3-(trifluoromethyl)quinoline	trace
	HMPA	3-(trifluoromethylquinoline	74
	pyridine	3-(trifluoromethyl)quinoline	63

As regards 4-(trifluoromethyl)quinoline[1] in Table III, although the known method required the use of highly toxic sulfur tetrafluoride, it was obtained from 4-chloroquinoline by

15) M.R. Pettit and J.C. Tatlow, *J. Chem. Soc.*, **1954**, 1071.

this method in one step. And as for 1-(trifluoromethyl)isoquinoline, although the known method required three steps using sulfur tetrafluoride, the new method is in two steps, the starting material being isoquinoline 2-oxide in both cases.

In all the above experiments, dimethylformamide was used as solvent. But next, with the materials which gave no yields or very poor yields when the above-mentioned solvent was used, other aprotic solvents were tried. The result is shown in Table IV.

As a result, bromobenzene, *p*-nitrochlorobenzene, and 3-bromoquinoline, which could not serve as the starting material for syntheses with dimethylformamide, were found to give fairly good yields by changing the solvent. As for halobenzene, reactions took place in the following order of readiness (when the yields were poor, the starting materials were recovered): pyridine>HMPA≫DMF>acetonitrile. *p*-Nitrochlorobenzene, which is assumed to have reacted with the solvent pyridine, gave no desired product and the starting material was not recovered either.

The mechanism of this reaction is assumed, as McLoughlin[16] referred concerning perfluoroalkyl, as follows: first, trifluoromethyl iodide and copper form complex with solvent as ligand and this complex reacts with aryl iodide to introduce trifluoroalkyl group into the aromatic ring. The solvent effect mentioned above can be explained by this assumption.[17]

Experimental[18]

Benzotrifluoride (BTF)——A typical Procedure is as Follows: Iodobenzene (5 g) was dissolved in DMF (10 ml) in a stainless steel tube and commercial copper powder (10 g) was added. The tube was cooled in an acetone–dry-ice bath. Then CF_3I (30 g) was added by the vacuum line method. The reaction tube was sealed and shaken at 120 —130° for 14 hr. After cooling, the tube was opened and the reaction mixture was taken out with ether and H_2O and steam-distilled. The distillate was saturated with NaCl and ex-

Table V

Amount of C_6H_5X (g)		Nature of Cu	Cu powder (g)	CF_3I (g)	Solvent (ml)	Temp. (°C)	Time (hr)	Amount[a] of C_6H_5-CF_3 (g)
X: I	5	commercial	10	30	DMF (10)	120—130	14	1.32[b]
	3	treated with[13] I_2-acetone	5	13	DMF (10)	130—140	20	0.68
	5	Cu-Zn-alloy	10	25	DMF (10)	120—130	12.5	1.36
	3	precipitated[14] Cu	5	12	DMF (10)	130—140	20	1.55
	3	precipitated[14] Cu	5	12	CH_3CN (10)	130—140	20	1.24
X: Br	2	precipitated[14] Cu	5	7	pyridine (20)	130—140	20	0.21[c]
	2	precinitated[14] Cu	5	7	HMPA (20)	130—140	20	trace[c,d]
	2	precipitated[14] Cu	5	7	DMF (20)	130—140	20	none[c,d]

a) Estimated by GC.
b) This reaction was repeated and the cooled tube was equipped with distilling apparatus. The oil distilled at 90—110° (bath temp.) was collected and identified with commercial BTF by comparing IR spectrs and retention time in GC.
c) Most of C_6H_5Br was recovered.
d) Only a small peak was observered in GC.

16) Private communication.
17) In McLoughlin's latest paper,[10] isolation of perfluoroheptyl copper is reported and this mechanism is proved.
18) Since all new compounds are too volatile to give satisfactory elemental analyses, they were analyzed by mass spectrometry.

tracted with ether. The ether layer was dried over Na_2SO_4 and analyzed by gas chromatography (GC), using Shimazu GC-3AF (column: 15% DEGS on Shimalite, 3 m. Carrier gas: N_2, flow rate 50 ml/min. Quantitative estimation was made by the internal standard method using C_6H_6 and peak areas were measured by the half-width procedure). BTF (1.32 g) was obtained.

The other experiments to examine the effects of copper powders and solvents are summarized in Table V.

o-Bis(trifluoromethyl)benzene——i) *o*-$C_6H_4I_2$ (1 g), freshly precipitated Cu powder (3 g), and CF_3I (14 g) in DMF (7.5 ml) were shaken at 140° for 24 hr and treated by the same procedure as with BTF. The product was also analyzed by GC(column temp.: 80°. Internal standard: C_6H_5Cl). *o*-$C_6H_4(CF_3)_2$(0.26 g) was obtained.

ii) *o*-$CF_3C_6H_4I$ (3.52 g), freshly precipitated Cu powder (3 g), and CF_3I (10 g) were treated in DMF (10 ml) at 140° for 24 hr as above. *o*-$C_6H_4(CF_3)_2$ (2.2 g) was obtained.

IR spectrum of the product was imposable to that of the authentic sample.[5]

m-Bis(trifluoromethyl)benzene——*m*-$CF_3C_6H_4I$ (3 g), Cu-Zn alloy powder (5 g), and CF_3I (10 g) in DMF (10 ml) were shaken at 125—135° for 12 hr, treated by the same procedure as with BTF, and analyzed by GC(column temp. :80°. Internal standard: C_6H_5Cl.) *m*-$C_6H_4(CF_3)_2$ (1.5 g) was obtained.

o-(Trifluoromethyl)toluene——i) *o*-$CH_3C_6H_4I$ (5 g), freshly precipitated Cu powder (5 g), and CF_3I (15 g) were shaken at 130—140° for 11 hr by the same method as with BTF. The ether-extract was concentrated and distilled. *o*-$CH_3C_6H_4CF_3$ (1.04 g) was obtained. bp 130—134°. Mass Spectrum *m/e*: Calcd. for $C_8H_7F_3$: 160. Found: 160. IR ν_{max}^{film} cm^{-1}: 1320, 1130 (CF_3). This oil was identified by the retention time in GC with the sample obtained from *o*-toluic acid and SF_4 as shown below. From the distillate with higher boiling point, 1.6 g of the starting material was recovered.

ii) *o*-Toluic acid (5 g) and SF_4 (20 g) were heated in a Hasteloy-C autoclave at 140—150° for 10 hr. After evaporation of materials with low boiling points at 0°, the reaction mixture was poured on ice, neutralized with $NaHCO_3$, and steam-distilled. The distillate was extracted with ether and analyzed by GC. A small peak of *o*-(trifluoromethyl)toluene was observed.

m-(Trifluoromethyl)toluene——*m*-$CH_3C_6H_4I$ (5 g), freshly precipitated Cu powder (5 g), and CF_3I (15 g) in DMF (10 ml) were shaken at 130—140° for 20 hr and treated by the same method as with *o*-$CH_3C_6H_4CF_3$. *m*-$CH_3C_6H_4CF_3$ (2.55 g) was obtained. bp 130—135°. Mass Spectrum *m/e*: Calcd. for $C_8H_7F_3$: 160. Found: 160. IR ν_{max}^{film} cm^{-1}: 1335, 1130 (CF_3). From the distillate with higher boiling point, 0.6 g of the starting material was recovered.

p-(Trifluoromethyl)anisole——*p*-$CH_3OC_6H_4I$ (1 g), freshly precipitated Cu powder (3 g), and CF_3I (10 g) in DMF (10 ml) were shaken at 130—140° for 20 hr. From the ether extract *p*-$CH_3OC_6H_4CF_3$ (0.65 g) was obtained. bp 163—165°. Mass Spectrum *m/e*: Calcd. for $C_8H_7OF_3$: 176. Found: 176. IR ν_{max}^{film} cm^{-1}: 1330, 1180—1160, 1120 (CF_3); 1260.

p-Nitrobenzotrifluoride——A Typical Method is as Follows: *p*-$NO_2C_6H_4I$ (1.8 g), freshly precipitated Cu powder (5 g), and CF_3I (10 g) in DMF (10 ml) were shaken at 135° for 30 hr. After cooling, the tube was opened and the reaction mixture was steam-distilled. The distillate was extracted with ether and the ether layer was dried over Na_2SO_4. After evaporation of ether, the residue was distilled. *p*-$NO_2C_6H_4CF_3$ (0.7 g) was obtained. bp 110—120°/20 mmHg. This was identified with the authentic sample[15] by comparing IR spectra.

Solvent effect was examined as follows: *p*-$NO_2C_6H_4Cl$ (1 g), freshly precipitated Cu powder (3 g), and CF_3I (7 g) in the solvent shown below were shaken at 130—140° for 20 hr. *p*-$NO_2C_6H_4CF_3$ (0.24 g) was obtained in HMPA, but in DMF only a trace of the product was checked in GC. None of the product was obtained in pyridine.

2-(Trifluoromethyl)quinoline——i) 2-Chloroquinoline (2 g), freshly precipitated Cu powder (5 g), and CF_3I (10 g) in DMF (10 ml) were shaken at 120—130° for 24 hr and treated as with BTF. The ether extract was concentrated and distilled. 2-(Trifluoromethyl)quinoline (0.24 g) was obtained. bp 120—130°/20 mmHg (bath temp.). This was identified with the authentic sample[1] by comparing IR spectra.

ii) 2-Iodoquinoline (3 g), freshly precipitated Cu powder (3 g), and CF_3I (10 g) in DMF (10 ml) were shaken at 135° for 20 hr and treated as in i). 2-(Trifluoromethyl)quinoline (2.3 g) was obtained.

3-(Trifluoromethyl)quinoline——i) 3-Iodoquinoline (2 g), freshly precipitated Cu powder (1.3 g), and CF_3I (10 g) in CH_3CN (10 ml) were shaken at 120° for 20 hr and treated as with BTF. The ether extract was concentrated and the saturated solution of picric acid in ether was added to the residue. The precipitate was recrystallized from MeOH. 3-(Trifluoromethyl)quinoline picrate (0.31 g) was obtained. This was identified with the authentic sample[1] by the mixture melting point.

Solvent effect was examined as follows: 3-bromoquinoline (2 g), freshly precipitated Cu powder (5 g), and CF_3I (7 g) in the designated solvents were shaken at 130—140° for 20 hr. Solvents and grams of the distilled 3-(trifluoromethyl)quinoline were as follows: pyridine, 1.21; HMPA, 1.41; DMF, trace in GC.

4-(Trifluoromethyl)quinoline——4-Chloroquinoline (1 g), freshly precipitated Cu powder (3 g), and CF_3I (10 g) in DMF (10 ml) were shaken at 140° for 36 hr and treated as 3-iodoquinoline. 4-(Trifluoromethyl)-quinoline picrate (0.28 g) was obtained. The product was identified with the authentic sample[1] by the mixture melting point.

6-(Trifluoromethyl)quinoline——6-Bromoquinoline (1 g), freshly precipitated Cu powder (1.8 g), and CF_3I (7 g) in DMF (10 ml) were shaken at 140° for 24 hr and treated as 3-iodoquinoline. 6-(Trifluoromethyl)-

quinoline picrate (0.49 g) was obtained. The product was identified with the authentic sample[4] by the mixture melting point.

1-(Trifluoromethyl)isoquinoline——i) 1-Chloroisoquinoline (2.6 g), freshly precipitated Cu powder (3 g), and CF_3I (10 g) in DMF (10 ml) were shaken at 135—140° for 20 hr and treated as BTF. The ether extract was concentrated and distilled *in vacuo* and 1-(trifluoromethyl)isoquinoline (1 g) was obtained. The product was identified by comparing IR spectra with the authentic sample obtained from isoquinaldic acid and SF_4 as shown in iii).

ii) 1-Iodoisoquinoline (1 g), freshly precipitated Cu powder (3 g), and CF_3I (7 g) in DMF (10 ml) were shaken at 130—140° for 20 hr and treated as in i). 1-(Trifluoromethyl)isoquinoline (0.065 g) was obtained.

iii) Isoquinaldic acid (15 g), SF_4 (21 ml), and HF (5 ml) were stirred in Hasteloy-C autoclave at 140—170° for 15 hr. After cooling the material with low boiling point was evaporated at 0°, and the residue was neutralized with 10% NaOH and steam-distilled. The distillate was extracted with ether. After it was dried over Na_2SO_4, ether was evaporated and the residue was distilled to give colorless oil, bp 135°/20 mm. Yield, 5 g. *Anal.* Calcd. for $C_{10}H_6NF_3$: C, 60.91; H, 3.07; N. 7.11. Found: C, 60.80; H, 2.97; N, 6.97.

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