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Photochemical Trifluoromethylation of Some Aromatic and Heteroaromatic Compounds with Trifluoromethyl Bromide

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The photochemical introduction of trifluoromethyl group with CF_3Br in aromatic and heteroaromatic rings was investigated for 9 compounds. Naphthalene, anthracene, anisole, *N*,*N*-dimethylaniline, ferrocene, benzo[*b*]thiophene, isoquinoline, and *N*-methylpyrrole gave trifluoromethylated products in 6.5—100% yields. In one step from uracil, a pharmacologically important 5-trifluoromethyluracil can be synthesized by this method in 11% yield. Based on the mechanistic study carried out for the naphthalene-CF_3Br-CH_3CN system, the reaction is found to proceed via the electron transfer from an excited singlet state of naphthalene to CF_3Br.

The introduction of trifluoromethyl group into aromatic and heteroaromatic compounds has been of recent interest,[1,2] because the strong electron-withdrawing ability and the high lipophilicity of the trifluoromethyl group will enhance the biological activity of the molecule. Several synthetic methods[3–16] including coupling reactions in the presence[3–8] and in the absence[9] of metal catalysts and several photochemical reactions[10–16] have been reported.

The photochemical trifluoromethylation hitherto reported requires expensive CF_3I[11,12,15,16] or hazardous[13,14] reagents so that a simple trifluoromethylation with a cheap, less hazardous and easy to handle reagent is needed. In view of this interest, we have undertaken a direct trifluoromethylation of aromatic and heteroaromatic compounds by a photochemical method using trifluoromethyl bromide, a cheap and easily available reagent.

We wish to report here the results of a one step photochemical trifluoromethylation of some aromatic and heteroaromatic compounds, together with the results of a mechanistic study of the excited states involved in the phototrifluoromethylation of these compounds.

Experimental

Materials. Bromotrifluoromethane was used as received from Japan Halon Co. Naphthalene (Wako Junyaku Co., G.R.) was recrystallized from ethanol. Anthracene (BDH Chemical Co., microanalytical reagent), *N*-methylpyrrole (Tokyo Kasei Co., G.R.), benzo[*b*]thiophene (Tokyo Kasei Co., G.R.), and ferrocene (Tokyo Kasei Co., G.R.) were used as purchased. Anisole (Wako Junyaku Co., G.R.), *N*,*N*-dimethylaniline (Junsei Yakuhin Co., G.R.), isoquinoline (Wako Junyaku Co., G.R.) were distilled under reduced pressure just before use. Uracil and 5-trifluoromethyluracil were supplied from Japan Halon Co. and were used as received. Acetonitrile (Wako Junyaku Co., G.R.) was dried over calcium hydride (Wako Junyaku Co., G.R.) and distilled twice in the presence of a small amount of phosphorus pentaoxide (Wako Junyaku Co., G.R.). Then the distillate was redistilled just before use with a 1 m Widmer distilling column in the presence of potassium carbonate (Junsei Yakuhin Co., G.R.). This distillate was used for photoreactions and measurements.

Measurements. IR-spectra were obtained by use of a Hitachi 260-50 grating spectrophotometer. ^1H NMR spectra were taken on a Hitachi R-22 (90 MHz) spectrometer or a JEOL-FX-200 (200 MHz) spectrometer. ^{19}F NMR spectra were obtained by using a Varian XL-100A spectrometer. GC-MS spectra were obtained by using JEOL JMA D-300 GC-MS spectrometer. Quantitative gas chromatography was performed on a Shimadzu GC-6A gas chromatograph, and preparative gas chromatography was done on a Shimadzu GC-5A gas chromatograph. UV-spectra were obtained on a Hitachi 228 spectrophotometer.

For the measurement of the fluorescence spectra, two sample solutions were prepared: one is the hexane solution of naphthalene (4.0×10^{-4} mol dm^{-3} deaerated with Ar by bubbling for 10 min), and the other is the similarly prepared hexane solution (4.0×10^{-3} mol dm^{-3}, deaerated with Ar) into which CF_3Br was bubbled for 10 min. The fluorescence spectra were recorded for these two solutions (excitation: 310 nm; recording wavelength range: 315—440 nm) on a Hitachi 650-60 fluorescence spectrophotometer.

Continuous Irradiation. An acetonitrile solution (170 cm^3) of aromatic or heteroaromatic compound (0.4—6.1 mmol) was irradiated in an immersion type photoreactor with a high pressure mercury lamp (a 100 W lamp of Taika Kogyo Co., with a pyrex jacket for water cooling) for 6 h under bubbling of CF_3Br (equipped with a cooling trap using Dry Ice-acetone at the outlet of the photoreactor).

In the cases of *N*-methylpyrrole and uracil the acetonitrile solutions of the substrates in a quartz tube (50 cm^3, equipped with a septum to introduce CF_3Br) was irradiated from outside of the tube with a low pressure mercury lamp (Riko-sha, UVL-160LA, 160 W) for 3 h.

Work-up Procedure. After the irradiation, water (ca. 300 cm^3) was added to the reaction mixture and the products were extracted with diethyl ether. The etherial solution was washed well with water to remove acetonitrile, then ether was removed under reduced pressure. The residual solid or liquid was dissolved in a small amount of diethyl ether and the etherial solution was submitted to preparative gas chromatography (for the photoproducts from naphthalene, 1-bromonaphthalene, anthracene, anisole, *N*-methylpyrrole, benzo[*b*]thiophene, and isoquinoline), or to column chromatography (for the photoproducts from ferrocene and *N*,*N*-dimethylaniline), or to thin-layer chromatography (for the photoproducts from uracil).

Isolation of the Products. Except for the photoproducts from uracil, the isolation of the trifluoromethylated products were all done by means of gas chromatography using a Shimadzu GC-5A (column, PEG-20M, 20%, 2 m, temp, 190 °C, for the photoproducts from naphthalene; PEG-20M, 5%, 2 m, temp, 230 °C, for the photoproducts from anthracene; PEG-20M, 20%, 2 m, temp, 130 °C, for the photoproducts from anisole; PEG-20M, 5%, 2 m, temp, 120 °C, for the photoproducts from *N*,*N*-dimethylaniline; OV-1, 5%, 2 m, temp, 160 °C, for the photoproducts from ferrocene; PEG-20M, 20%, 2 m, temp, 80 °C, for the photoproducts from *N*-methylpyrrole; PEG-20M, 20%, 2 m, temp, 190 °C, for the photoproducts from isoquinoline; and PEG-20M, 20%, 2 m, temp, 160 °C, for the photoproducts from benzo[*b*]thiophene). In the case of uracil the photoproduct was isolated by means of TLC (Merck, RP-18 F_{254}) and the quantitative analysis was done by using HPLC (Hitachi 655 liquid chromatograph, column: RP-18, solvent, CH_3CN-H_2O=3 : 7; monitoring wavelength, 254 nm; pressure, 3.5 kg cm^2) with 4-cyanopyridine as an internal standard.

Identification of the Photoproducts. Trifluoromethylnaphthalenes: 1- and 2-Trifluoromethylnaphthalene were obtained as a mixture (colorless oil, 153.5 mg, 0.78 mmol). ^{19}F NMR spectra of the mixture show one singlet ($CDCl_3/CFCl_3$, $\phi=-62.64$) and one doublet peak ($CDCl_3/CFCl_3$, $\phi=-60.19$, $J_{\text{F-H}}=2$ Hz). The latter peak is identical with that observed for 1-trifluoromethylnaphthalene by Matsui[7] ($\phi=-60.40$, $J_{\text{F-H}^8}=2$ Hz). The chemical shifts of the two peaks were in nearly the same region as the reported ones[5] ($\phi=-60.6$ for 2-CF_3, and -58.5 for 1-CF_3). The isomer ratio, 1-CF_3: 2-CF_3, calculated based on the peak area of ^{19}F NMR spectra was 78 : 22. Found: *m*/*z* 196.0492.

Trifluoromethylanthracenes: 9-, 1-, and 2-Trifluoromethylanthracene were obtained as a mixture (pale yellow oil, 19.6 mg, 0.08 mmol): ^{1}H NMR (200 MHz, $CDCl_3$) $\delta=7.45$ (m, 4H, H^2, H^7, H^3, and H^6), 8.01 (d, $J=8.0$ Hz, 2H, H^5 and H^4), 8.51 (d, $J=10$ Hz, 2H, H^1 and H^8) and 8.59 (s, 1H, H^{10}); ^{19}F NMR ($CDCl_3/CFCl_3$) $\phi=-48.91$ (t, $J_{\text{F-H}}=1.5$ Hz, 9-CF_3), -60.73 (d, $J_{\text{F-H}}=2.0$ Hz, 1-CF_3), and -63.20 (s, 2-CF_3). The ratio of the isomer, 9-CF_3: 1-CF_3: 2-CF_3, calculated based on the peak area of ^{19}F NMR spectra is 85 : 12 : 3. GC-MS (PEG-20M, 5%, 1 m, 200 °C, 70 eV) (rel intensity) 246 (M^+, 100), 227 ($(M-F)^+$, 7.4), 196 ($(M-CF_2)^+$, 21.4), and 177 ($(M-CF_3)^+$, 1.8). Found: *m*/*z* 246.0656. Calcd for $C_{15}H_9F_3$: M, 246.0657. Based on the GC-MS data a small amount of bis(trifluoromethyl)anthracene was also found.

Trifluoromethylanisole: 2-Trifluoromethylanisole was obtained as a colorless liquid substance (70 mg, 0.40 mmol): IR (neat) 3080, 2960, 2940, and 2840 cm^{-1} ($\nu_{\text{C-H}}$), 1320, 1170, and 1120 cm^{-1} ($\nu_{\text{C-F}}$); 1060 and 1040 ($\nu_{\text{C-O-C}}$), and 808, 760, and 740 cm^{-1} (out of plane C–H stretching); ^{1}H NMR (90 MHz, $CDCl_3$) $\delta=3.89$ (s, 3H, -OCH_3), 6.96—7.03 (m, 2H, H^3 and H^5), and 7.57 (m, 2H, H^4 and H^6); GC-MS (PEG-20M, 20%, 1 m, 110 °C, 70 eV) (*m*/*z*, rel intensity) 176 (M^+, 100), 157 ($(M-F)^+$, 4.4), 145 ($(M-OCH_3)^+$, 17.0), 126 ($(M-CF_2)^+$, 5.6), and 107 ($(M-CF_3)^+$, 3.6). Found: *m*/*z* 176.0453. Calcd for $C_8H_7OF_3$: M, 176.0448.

3-Trifluoromethylanisole was obtained as a colorless liquid substance (27.5 mg, 0.156 mmol): IR (neat) 3080, 3020, 2970, and 2850 cm^{-1} ($\nu_{\text{C-H}}$), 1300, 1170, and 1130 cm^{-1} ($\nu_{\text{C-F}}$), 1070 and 1040 cm^{-1} ($\nu_{\text{C-O-C}}$), 880, 860, and 755 cm^{-1} (out of plane C–H stretching); ^{1}H NMR (90 MHz, $CDCl_3$) $\delta=3.80$ (s, 3H, -OCH_3), 7.08—7.43 (m, 4H, H^2, H^4, H^5, and H^6); GC-MS (PEG-20M, 20%, 1 m, 110 °C, 70 eV) (*m*/*z*, rel intensity) 176 (M^+, 100), 157 ($(M-F)^+$, 8.3), 145 ($(M-OCH_3)^+$, 23.0), 126 ($(M-CF_2)^+$, 4.1), and 107 ($(M-CF_3)^+$, 2.4). Found: *m*/*z* 176.0452. Calcd for $C_8H_7OF_3$: M, 176.0448.

Trifluoromethyl-*N*,*N*-dimethylanilines: 2-Trifluoromethyl-*N*,*N*-dimethylaniline was obtained as a colorless liquid substance (47.6 mg, 0.252 mmol): IR (neat) 3100, 2950, and 2850 cm^{-1} ($\nu_{\text{C-H}}$), 1320, 1180, and 1110 cm^{-1} ($\nu_{\text{C-F}}$), 770 cm^{-1} (out of plane C–H stretching of 1,2-disubstituted benzene); ^{1}H NMR (90 MHz, $CDCl_3$) $\delta=2.73$ (s, 6H, -$N(CH_3)_2$), 7.02—7.79 (m, 4H, H^3, H^4, H^5, and H^6); GC-MS (PEG-20M, 5%, 1 m, 100 °C, 70 eV) (*m*/*z*, rel intensity) 189 (M^+, 63), 188 ($(M-H)^+$, 100), 170 ($(M-F)^+$, 3.2), 145 ($(M-N(CH_3)_2)^+$, 10.6), 138 ($(M-CF_2)^+$, 3.5), 127 ($(M-N(CH_3)_2-F+H)^+$, 14), 120 ($(M-CF_3)^+$, 2.2), and 95 ($(M-N(CH_3)_2-CF_2)^+$, 3.2). Found: *m*/*z* 189.0764. Calcd for $C_9H_{10}NF_3$: M, 189.0766.

4-Trifluoromethyl-*N*,*N*-dimethylaniline was obtained as a white crystalline solid (92.4 mg, 0.489 mmol): mp 69.0—69.4 °C (lit.[18] 70.3—70.8 °C). Found: *m*/*z* 189.0763.

Bis(4-dimethylaminophenyl)methane was obtained as a white crystalline solid (142 mg, 0.559 mmol): mp 86.5—87 °C (lit.[19] 88.5—89.5 °C). ^{1}H NMR spectra of this compound are identical with the reported spectra.[19]

Trifluoromethylferrocene: This compound was obtained as a yellow liquid substance (115.6 mg, 0.455 mmol): IR (KBr) 3100, 2950, 2930, and 2860 cm^{-1} ($\nu_{\text{C-H}}$), 1310, 1145, and 1120 cm^{-1} ($\nu_{\text{C-F}}$), 1100, 1020, and 1000 cm^{-1} (monosubstituted ferrocene); ^{1}H NMR (90 MHz, $CDCl_3$) $\delta=4.15$ (m, 7H, H_β to -CF_3, and unsubstituted ring 5H), and 4.37 (t, 2H, H_α to -CF_3); GC-MS (PEG-20M, 5%, 1 m, 140 °C, 70 eV) (*m*/*z*, rel intensity) 254 (M^+, 54), 235 ($(M-F)^+$, 3.6), 189 ($(M-C_5H_5)^+$, 4.8), 140 ($(M-C_5H_4CF_2)^+$, 75), and 121 ($(M-C_5H_4CF_3)^+$, 3.0). Found: *m*/*z* 254.0001. Calcd for $C_{11}H_9F_3Fe$: M, 254.0005.

2-Trifluoromethyl-*N*-methylpyrrole: The compound was obtained as a colorless oily substance (51 mg, 0.34 mmol). The ^{1}H NMR spectral data of this compound are consistent with those reported by Kobayashi.[12]

2-Trifluoromethylbenzo[*b*]thiophenes: 2-Trifluoromethylbenzo[*b*]thiophene was obtained as a white crystalline solid (18.2 mg, 0.09 mmol): mp 49.2—49.8 °C; IR (KBr) 3080, 2940, and 2870 cm^{-1} ($\nu_{\text{C-H}}$), 1310, 1170, and 1120 cm^{-1} ($\nu_{\text{C-F}}$), 880, 860, 760, and 740 cm^{-1} (out of plane C–H bending); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta=7.43$—7.48 (m, 2H, H^5 and H^6), 7.70 (s, 1H, H^3), and 7.85—7.91 (m, 2H, H^4 and H^7); GC-MS (PEG-20M, 5%, 1 m, 90 °C, 70 eV) (*m*/*z*, rel intensity) 202 (M^+, 100), 201 ($(M-H)^+$, 7.4), 183 ($(M-F)^+$, 29.2), 152 ($(M-CF_2)^+$, 20.0), and 101 ($(M-S-CF_3)^+$, 7.6). Found: *m*/*z* 202.0058. Calcd for $C_9H_5SF_3$: M, 202.0063.

3-Trifluoromethylbenzo[*b*]thiophene was obtained as a colorless oil (6 mg, 0.03 mmol): IR (neat) 3120, 3080, 2930, and 2870 cm^{-1} ($\nu_{\text{C-H}}$), 1320, 1170, and 1120 cm^{-1} ($\nu_{\text{C-F}}$), 850, 810, 760 and 740 cm^{-1} (out of plane C–H bending); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta=7.43$—7.49 (m, 2H, H^5 and H^6), 7.87—7.94 (m, 2H, H^4 and H^7), and 7.91 (s, 1H, H^2); GC-MS (PEG-20M, 5%, 1 m, 90 °C, 70 eV) (*m*/*z*, rel intensity) 202 (M^+, 100), 201 ($(M-H)^+$, 10.4), 183 ($(M-F)^+$, 28.6), 152 ($(M-CF_2)^+$, 17.0), and 101 ($(M-S-CF_3)^+$, 6.4). Found: *m*/*z* 202.0060. Calcd for $C_9H_5SF_3$: M, 202.0063.

4-Trifluoromethylbenzo[*b*]thiophene was obtained as a colorless oil (17 mg, 0.084 mmol): IR (neat) 3100 and 2940 cm^{-1} ($\nu_{\text{C-H}}$), 1310, 1170, and 1120 cm^{-1} ($\nu_{\text{C-F}}$), 870, 840, 780, and 710 cm^{-1} (out of plane C–H bending); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta=7.38$—7.70 (m, 4H, H^2, H^3, H^5, and H^6), and

8.06 (d, J=8 Hz, 1H, H^7); GC-MS (PEG-20M, 5%, 1 m, 90 °C, 70 eV) (m/z, rel intensity) 202 (M$^+$, 100), 183 ((M−F)$^+$, 22.4), 152 ((M−CF_2)$^+$, 20.6), 133 ((M−CF_3)$^+$, 3.4), 101 ((M−S−CF_3)$^+$, 7.1), and 89 ($C_6H_4CH^+$, 7.7). Found: m/z 202.0064. Calcd for $C_9H_5SF_3$: M, 202.0063.

7-Trifluoromethylbenzo[*b*]thiophene was obtained as a colorless oil (34 mg, 0.168 mmol): IR (neat) 3100 and 2940 cm^{-1} ($\nu_{\text{C-H}}$), 1310, 1170, and 1120 cm^{-1} ($\nu_{\text{C-H}}$), 870, 840, 800, 780, and 710 cm^{-1} (out of plane C-H bendiing); ^{1}H NMR (200 MHz, $CDCl_3$) δ=7.33—7.67 (m, 4H, H^2, H^3, H^5, and H^6), and 7.94 (d, J=8 Hz, 1H, H^4); GC-MS (PEG-20M, 10%, 2 m, 120 °C, 70 eV) (m/z, rel intensity) 202 (M$^+$, 100), 183 ((M−F)$^+$, 22.6), 152 ((M−CF_2)$^+$, 15.8), 133 ((M−CF_3)$^+$, 3.4), 101 ((M−S -CF_3)$^+$, 6.1), and 89 ($C_6H_4CH^+$, 6.6). Found: m/z 202.0049. Calcd for $C_9H_5SF_3$: M, 202.0063.

Trifluoromethylisoquinolines: The compounds were obtained by means of repeated preparative gas chromatography.

1-Trifluoromethylisoquinoline was obtained as a colorless liquid substance (3.1 mg, 0.015 mmol): IR (neat) 3040 cm^{-1} ($\nu_{\text{C-H}}$), 1310, 1170, and 1120 cm^{-1} ($\nu_{\text{C-F}}$), 980, 940, 820, 790, and 740 cm^{-1} (out of plane C-H bending); ^{1}H NMR (200 MHz, $CDCl_3$) δ=7.58—8.20 (m, 5H, H^4, H^5 H^6 and H^8), and 8.60 (d, J=5.5 Hz, 1H, H^3); GC-MS (PEG-20M, 5%, 1 m, 130 °C, 70 eV) (m/z, rel intensity) 197 (M$^+$, 100), 196 ((M−H)$^+$, 9.9), 178 ((M−F)$^+$, 11.7), 147 ((M−CF_2)$^+$, 25.4), and 128 ((M−CF_3)$^+$, 7.2). Found: m/z 197.0451. Calcd for $C_{10}H_6NF_3$: M, 197.0452.

4-Trifluoromethylisoquinoline was obtained as a colorless liquid substance (3.4 mg, 0.017 mmol): IR (neat) 3040 cm^{-1} ($\nu_{\text{C-H}}$), 1320, 1170, and 1120 cm^{-1} ($\nu_{\text{C-F}}$), 980, 930, 900, 820, 780, and 730 cm^{-1} (out of plane C-H bending); GC-MS (PEG-20M, 5%, 1 m, 130 °C, 70 eV) (m/z, rel intensity) 197 (M$^+$, 100), 196 ((M−H)$^+$, 10.2), 178 ((M−F)$^+$, 12.7), 147 ((M−CF_2)$^+$, 27.1), and 128 ((M−CF_3)$^+$, 23.3). Found: m/z 197.0449. Calcd for $C_{10}H_6NF_3$: M, 197.0452.

5-Trifluoromethylisoquinoline was obtained as a colorless liquid substance (17.4 mg, 0.088 mmol): ^{1}H NMR (200 MHz, $CDCl_3$) δ=7.39—8.20 (m, 5H, H^3, H^4, H^6, H^7, and H^8), and 8.94 (d, J=3.1 Hz, 1H, H^1). The compound readily converted to an unknown product in air.

8-Trifluoromethylisoquinoline was obtained as a colorless liquid substance (4.5 mg, 0.023 mmol): IR (neat) 3050 cm^{-1} ($\nu_{\text{C-H}}$), 1310, 1180, and 1120 cm^{-1} ($\nu_{\text{C-F}}$), 980, 940, 830, 810, 790, and 740 cm^{-1} (out of plane C-H bending); ^{1}H NMR (200 MHz, $CDCl_3$) δ=7.38—8.19 (m, 5H, H^3 H^4, H^5, H^6, and H^7), and 8.93 (dd, $J_{\text{H}^1\text{H}^3}$=4.3 Hz, $J_{\text{F-H}^1}$=1.5 Hz, 1H, H^1); GC-MS (PEG-20M, 5%, 1 m, 130 °C, 70 eV) (m/z, rel intensity) 197 (M$^+$, 100), 196 ((M−H)$^+$, 5.1), 178 ((M−F)$^+$, 11.7), 147 ((M−CF_2)$^+$, 17.5), and 128 ((M−CF_3)$^+$, 33.0). Found: m/z 197.0452. Calcd for $C_{10}H_6NF_3$: M, 197.0452.

5-Trifluoromethyluracil: The compound was isolated from the second fraction of TLC (Merck, RP-18 F_{254}, developing solvent: CH_3CN-H_2O=4 : 6). ^{1}H NMR spectra ($CDCl_3$, δ=7.78, s, H^6) and mass spectra (70 eV, m/z 180 (M$^+$)) are identical with those of the authentic sample.

Flash Photolysis. An acetonitrile solution of naphthalene (1.0×10^{-3} mol dm^{-3}, 5 cm^3) in a quartz cell (1 cm×1 cm, equipped with a solvent reservoir) was degassed by repeated (4 times) freeze-pump-thaw cycles, and the glass neck was sealed. The sample solution containing CF_3Br was prepared by introduction of CF_3Br into the degassed solution prepared as described above using needle and septum. These sample solutions were irradiated with a pulse of 266 nm light from a Nd-YAG laser and the transient absorption was monitored in the wavelength region of 360—670 nm.

Calculations by means of CNDO/2. Th CNDO/2 calculations of naphthalene, benzo[*b*]thiophene, and isoquinoline were carried out at Tokyo University Computer Center according to the Tokyo University Computer Center Library Program YT/TC/CB03 prepared by J.A. Pople, D.L. Beveridge, and P.A. Dobosh (Q.C.P.E. 141) arranged by H. Kihara, T. Fujikawa, and T. Aoyama.

Results and Discussion

Photo-Trifluoromethylation of Aromatic Compounds. The acetonitrile solution of aromatic compound was irradiated with a high-pressure mercury lamp for 1.5—6 h under bubbling of CF_3Br. Naphthalene, anthracene, anisole, *N*,*N*-dimethylaniline, and ferrocene gave trifluoromethylated products in 6.5—100% yields (Table 1).

The photo-trifluoromethylation of naphthalene occurs quantitatively and the ratio of the 1- and 2-trifluoromethylnaphthalene is 78 : 22.

In the case of anisole, 2- and 3-trifluoromethylanisole were obtained in 20 and 8% yields, respectively. Although 4-trifluoromethylanisole was detected by

Table 1. Photo-Trifluoromethylation of Some Aromatic Compounds with CF_3Br

Aromatic compound		Solvent[b)]	Irrad. time	Conversion	Substituent introduced	Yield[c)]
10^{-3} mol			h	%		%
Naphthalene	(6.0)	CH_3CN	6	13	1-CF_3	78[d)]
					2-CF_3	22[d)]
Anthracene	(0.6)	CH_3CN	1.5	16	9-CF_3	70[d)]
					1-CF_3	10[d)]
					2-CF_3	3[d)]
Anisole	(6.1)	CH_3CN[a)]	6	32	2-CF_3	20
					3-CF_3	8
N,*N*-Dimethylaniline	(6.1)	CH_3CN[a)]	1.5	77	2-CF_3	5.5
					4-CF_3	11
					(p-Me_2N-C_6H_4)$_2$-CH_2	12
Ferrocene	(5.4)	CH_3CN	6	19	1-CF_3	43

a) Sodium acetate (2.4 mmol) was added. b) 170 cm^3. c) Yields are calculated based on the consumed aromatic compounds. d) Calculated based on the peak area of ^{19}F NMR spectra.

Table 2. Photo-Trifluoromethylation of Some Heteroaromatic Compounds with CF$_3$Br

Heteroaromatic compound		Solvent$^{b)}$	Irrad. time	Conversion	Substituent introduced	Yield$^{c)}$
10^{-3} mol			h	%		%
N-Methylpyrrole	(6.0)	CH$_3$CN$^{a)}$	3	85	2-CF$_3$	6.5
Benzo[*b*]thiophene	(6.0)	CH$_3$CN	6	20	2-CF$_3$	7.5
					3-CF$_3$	2.5
					4-CF$_3$	7.0
					7-CF$_3$	14
Isoquinoline	(6.0)	CH$_3$CN	6	18	1-CF$_3$	1.5
					4-CF$_3$	1.6
					5-CF$_3$	8.2
					8-CF$_3$	2.1
Uracil	(0.1)	CH$_3$CN	6	56	5-CF$_3$	11

a) Sodium acetate (2.4 mmol) was added. b) 170 cm^3. c) Yields are calculate based on the consumed starting material.

GC-MS analysis, the isolation of this isomer was not possible because of the contamination of the recovered anisole.

The photo-trifluoromethylation of *N*,*N*-dimethylaniline afforded 2- and 4-trifluoromethyl-*N*,*N*-dimethylaniline in 5.5 and 11% yields, respectively. Together with the trifluoromethylated products bis(4-dimethylaminophenyl)methane[19] was obtained in 12% yield.

The photo-trifluoromethylation of ferrocene gave selectively 1-trifluoromethylferrocene in 43% yield.

Photo-Trifluoromethylation of Heteroaromatic Compounds. In Table 2 are shown the results of the photo-trifluoromethylation of three heteroaromatic compounds and uracil.

In the case of *N*-methylpyrrole, only 2-trifluoromethyl-*N*-methylpyrrole was obtained in 6.5% yield.

In the case of benzo[*b*]thiophene and isoquinoline, the photo-trifluoromethylation occurs both in the heteroaromatic ring and benzene ring. The site reactivity of these compounds will be discussed later.

5-Fluorouracil has attracted much attention because of its significant tumor-inhibition activity and one-step fluorination of uracil has been developed.[1] However, little has been investigated about the biological activities of 5-trifluoromethyluracil, which is similar to 5-fluorouracil, because of difficulties of preparation of the compound.[20] Recently a convenient synthetic method of 5-trifluoromethyluracil has been reported by Fuchikami.[21] The convenient one-step trifluoromethylation of uracil might be possible if this photochemical trifluoromethylation can be applied for uracil. The photo-trifluoromethylation of uracil gave 5-trifluoromethyluracil in 11% yield.

Mechanistic Study on the Photo-Trifluoromethylation of Naphthalene. The excited state involved in the photo-trifluoromethylation of the aromatic compounds was examined using the naphthalene-CF$_3$Br-CH$_3$CN system, since the emission and T-T absorption spectra of naphthalene have been well-investigated.[22]

On the basis of the fact that the photoreaction proceeds under the irradiation with the light of wavelength longer than 300 nm, which is not absorbed by CF$_3$Br, the excited states which initiate the reaction can be considered as follows: (1) an excited state of a CT complex which is formed between naphthalene and CF$_3$Br in the ground state, and (2) the excited singlet state or the excited triplet state of naphthalene.

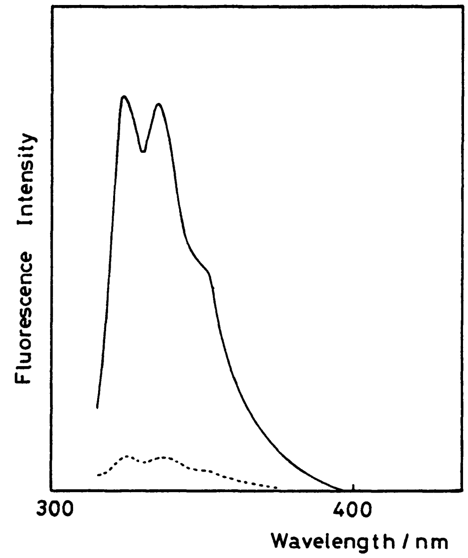


Fig. 1. Fluorescence spectra of naphthalene (4×10^{-4} mol dm^{-3} in CH$_3$CN) (excitation: 310 nm). (——): in the absence of CF$_3$Br, (------): in the presence of CF$_3$Br.

The first possibility can be excluded on the basis of the following results: the careful examination of the independently measured UV-spectra of naphthalene and CF$_3$Br in acetonitrile and those of the mixture of them in the same solvent shows no indication of the formation of CT complex between the two components in the ground state. In the cases of other aromatic and heteroaromatic compounds used in this photo-trifluoromethylation, except for uracil and *N*-methylpyrrole, similar results were obtained.

One of the second possibilities, in which the excited triplet state is involved, can also be excluded, based on the following results: (1) the fluorescence intensity of naphthalene is strongly lowered by addition of CF_3Br (Fig. 1), (2) no increment of T-T absorption intensity was observed in the system containing CF_3Br (Fig. 2, —●—) compared to the system without CF_3Br (Fig. 2, ···●···), (3) the energy required for cleaving C-Br bond of CF_3Br (289 kJ mol^{-1})[23] is higher than the triplet energy of naphthalene (E_T=254 kJ mol^{-1}).[24]

In order to obtain further evidence for the excited states and reactive intermediates involved in this reaction, flash photolysis experiments (with 266 nm light from Nd-YAG laser) were carried out for the naphthalene-CF_3Br system.

The transient absorption spectra at 50—100 ns after a flash and their assignments[25d] are shown in Fig. 2. The lifetimes of fluorescence and $S_n \leftarrow S_1$ absorption are also shown in Table 3. The results obtained from flash photolysis experiments are as follows: (1) in the presence of CF_3Br, the lifetimes of fluorescence are agreed with those of $S_n \leftarrow S_1$ absorption, (2) no new absorption which rises with the same rate as that of fluorescence decay was observed under this flash photolysis conditions, and (3) the intensity of T-T absorption was unchanged when CF_3Br was introduced and the T-T absorption decays with a second order rate constant (T-T annihilation: $k/\varepsilon l=(1.0\pm0.1)\times10^{-5}\ \mathrm{s}^{-1}$) both in the presence and in the absence of CF_3Br.

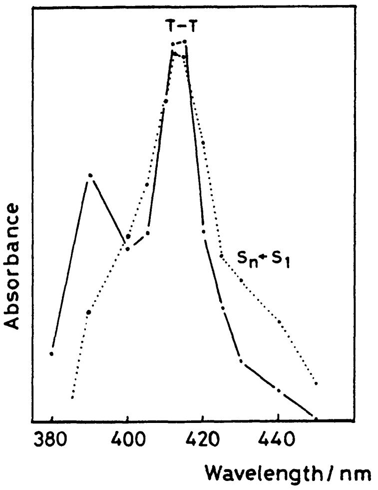


Fig. 2. Transient absorption spectra of naphthalene (1×10^{-3} mol dm^{-3} in CH_3CN). Irradiation: 266 nm light from Nd-YAG laser. (····●····): in the absence of CF_3Br, (—●—): in the presence of CF_3Br. 405—420 nm: T-T absorption; 420—450 nm: $S_n \leftarrow S_1$ absorption.[25d]

These results indicate that excited singlet state of naphthalene initiates the reaction. No new absorption which can be ascribed to an exciplex of naphthalene and CF_3Br, a cation radical of naphthalene,[25a-c] or to the CF_3 adduct to naphthalene formed by the addition of $\cdot CF_3$ to the cation radical of naphthalene was observed. These facts indicate that the process between the interaction of the singlet state of naphthalene with the ground state of CF_3Br and the product formation are so rapid that transient spectra of intermediates are not observed under our experimental conditions. However, an electron-transfer process from the excited singlet state of naphthalene to CF_3Br can be postulated based on the approximate oxidation potential of the excited singlet state of naphthalene (−2.45 V vs. SCE)[26] and the reduction potential of CF_3Br (−0.92 V vs. SCE) estimated from the reported values of CF_2BrCF_2Br,[27] since this process is an exothermic one from an energetic point of view ($\Delta G_{et}=E^{ox}(D^+/D)-E^{red}(A/A^-)-E_{0\text{-}0}-C<0$).[28]

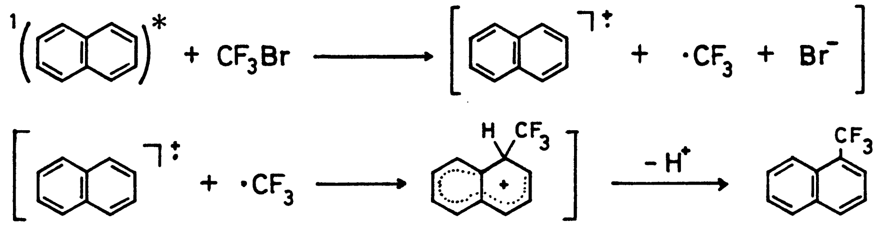
As the oxidation potentials of excited singlet state of anthracene,[26] anisole,[26] isoquinoline,[27] and aniline[26] are all lower than −2.0 V (vs. SCE), the similar energetic relations can be considered for these compounds. On the basis of the results described above, the most probable reaction pathway for the photo-trifluoromethylation of naphthalene can be considered as illustrated in Scheme 1.

Site Reactivities of Naphthalene, Benzo[*b*]thiophene, and Isoquinoline. As discussed in the reaction mechanism, the photo-trifluoromethylation of naphthalene proceeds via the electron transfer from the excited singlet state of naphthalene to the ground state-CF_3Br to give a cation radical of substrate and

Table 3. The Lifetimes of Fluorescence and $S_n \leftarrow S_1$ Absorption of Naphthalene in the Absence and in the Presence of CF_3Br in Acetonitrile Solutions[a]

[Naphthalene] 10^{-4} mol dm^{-3}	Fluorescence Wavelength nm	Fluorescence Lifetime ns	Absorption Wavelength nm	Absorption Lifetime ns	Atmosphere
5	330	73.02	—	—	N_2
10	330	67.98	—	—	degasesd
5	330	21.98	—	—	CF_3Br
10	330	20.99	—	—	CF_3Br
5	350	72.11	—	—	N_2
5	350	20.95	—	—	CF_3Br
5	—	—	435 ($S_n \leftarrow S_1$)	61.19	N_2
5	—	—	435 ($S_n \leftarrow S_1$)	25.41	CF_3Br

a) Excitation with 266 nm light from Nd-YAG laser.



Scheme 1.

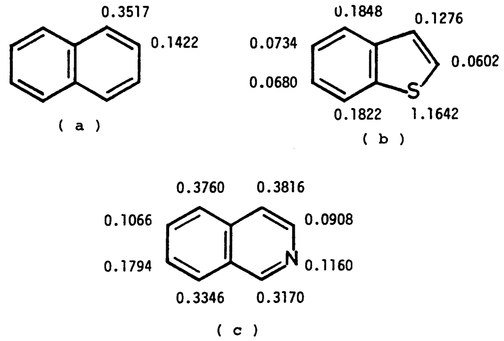


Fig. 3. HOMO Electron densities of naphthalene(a), benzo[*b*]thiophene(b), and isoquinoline(c).

a trifluoromethyl radical. The orientation of the trifluoromethylation should be determined by the succeeding process: the combination of the radical cation and $\cdot CF_3$. Thus, the site reactivities of the trifluoromethylation would be correlated with the densities of unpaired electron in HOMO orbital of the substrate. The HOMO electron densities of naphthalene, benzo[*b*]thiophene, and isoquinoline calculated by CNDO/2 method are shown in Fig. 3. In the case of benzo[*b*]thiophene, a good correlation between the site selectivity and the electron densities in HOMO was obtained: the 4- and 7-positions which are in the benzene ring and 3-position in the heteroaromatic ring with higher electron densities are trifluoromethylated.

In the case of isoquinoline, a similar tendency is found: The sites where the higher electron density in HOMO orbital is found(1-, 4-, 5-, and 8-positions) are preferentially trifluoromethylated.

In the case of naphthalene, 1-position where the higher electron density in HOMO orbital was found is preferentially trifluoromethylated. These results also support the reaction mechanism in which an electron transfers from the excited singlet state of substrate to CF_3Br and then forms a cation radical of the substrate and a $\cdot CF_3$ radical.

Mechanistic Study on the Photo-Trifluoromethylation of *N*-Methylpyrrole and Uracil. In the cases of *N*-methylpyrrole and uracil, on the other hand, the excitation of the charge transfer complexes between the substrates and CF_3Br initiates the reaction. The UV-spectra of *N*-methylpyrrole and uracil in acetonitrile solutions to which CF_3Br was introduced showed increments of absorptions in the wavelength region of 300—500 nm. These absorptions could not be observed in the spectra measured independently for each of the components. When the photo-trifluoromethylation of *N*-methylpyrrole was carried out using a low pressure mercury lamp (16 W, 3 h) only a trace of trifluoromethylated product was obtained (conversion: 99%) and the decomposition of the substrate occurred, whereas the irradiation of the *N*-methylpyrrole-CF_3Br-CH_3CN system with a high pressure mercury lamp afforded 6.5% of 2-trifluoromethyl-*N*-methylpyrrole (conversion: 85%). In the case of uracil, the similar effect was also observed. In contrast to the irradiation with a high pressure mercury lamp (5-trifluoromethyluracil: 11%, conversion: 56%), the irradiation of the uracil-CF_3Br-CH_3CN system with a low pressure mercury lamp (16 W, 3 h) brought about the lowering of the yield of trifluoromethylated product (6.4%, conversion: 56%) accompanied by the decomposition of uracil. These results indicate that the direct excitation of *N*-methylpyrrole and uracil using 254 nm light brings about decomposition, whereas the excitation of the charge transfer complexes between the substrate and CF_3Br using the light of wavelength longer than 300 nm affords the trifluoromethylated products. The results described above seemed to suggest that in these two cases the reaction proceeds via the mechanism different from that considered for naphthalene. However, the reason for the difference of these mechanisms in the same type of reactions is not clear.

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A mechanism similar to that described in the reference above can be considered for the formation of bis(4-dimethylaminophenyl)methane:

$$[{}^1(\text{Ph-NMe}_2)^*+\text{Ph-}\overset{+}{\text{N}}\text{H(Me)}_2] \rightarrow [(\text{Ph-}\overset{+}{\text{N}}\text{Me}_2)+\text{Ph-NH(Me)}_2]_{\text{cage}}$$

$$[\text{Ph-}\overset{+}{\text{N}}\text{Me}_2+\text{Ph-NH(Me)}_2]_{\text{cage}} \rightarrow \text{PhH}+\text{HN(Me)}_2+\text{PhN(Me)}\overset{+}{\text{C}}\text{H}_2$$

$$\text{Ph-N(Me)}\overset{+}{\text{C}}\text{H}_2+\text{Br}^- \rightarrow \text{Ph-N(Me)CH}_2\text{Br}$$

$$\text{Ph-N(Me)CH}_2\text{Br}+\text{H}_3\text{O}^+ \rightarrow \text{Ph-NHMe}+\text{CH}_2\text{O}+\text{HBr}$$

$$2\,\text{Ph-NMe}_2+\text{CH}_2\text{O}+\text{H}^+ \rightarrow (\text{Me}_2\text{-C}_6\text{H}_4)_2\text{CH}_2+\text{H}_3\overset{+}{\text{O}}$$

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