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# A FACILE METHOD FOR FLUOROALKYLATION OF ANILINE AND ITS DERIVATIVES

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## SUMMARY

In the presence of tetrakis(triphenylphosphine)nickel, fluoroalkylation reactions of aniline and its derivatives occur under mild conditions, giving good yields of the corresponding o- and p-fluoroalkylaniline. The reaction shows regioselectivity. The hydrolytic behaviors of the products are also described.

## INTRODUCTION

Yagupolskii et al.[1] and Umemoto et al.[2] have achieved the fluoroalkylation of aniline and its derivatives by means of $R_FI(Ph)Cl$ and $R_FI(Ph)OSO_2$, respectively. However, the preparation of either reagent is tedious. On the other hand, Ojima [3] reported that, in the presence of copper, fluoroalkylation of anilines could take place with perfluoroalkyl iodides. A higher temperature and longer time

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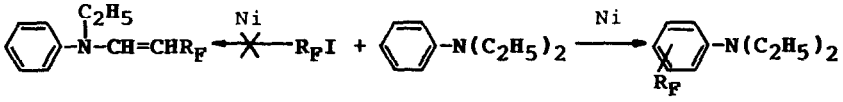
(100°C for 16h) was needed, and the yields were moderate (38-58%). Furthermore, all of the above reactions are not regioselective; the products contain ortho, meta and para isomers.

In the course of our studies on reactions of tertiary amines with fluoroalkyl iodides catalyzed by derivatives of nickel group metals[4,5], we found that when diethylaniline was used as substrate, fluoroalkylation only took place on the benzene ring.



Here, we would like to report a facile fluoroalkylation of aniline and its derivatives with a fluoroalkyl iodide in the presence of tetrakis(triphenylphosphine)nickel.

## RESULTS AND DISCUSSION

In the presence of catalytic amount of $Ni(PPh_3)_4$ (5-10% mol) fluoroalkyl iodides reacted with anilines at 80°C in dioxane solution for 6h to give o- and p-fluoroalkylanilines. (Table I).

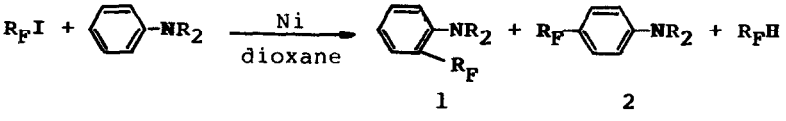


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**TABLE I**

Fluoroalkylation of aniline and its derivatives

| Entry | $R_FI$ | Aniline | Yield (%)* | | |
|---|---|---|---|---|---|
| | | | 1 | 2 | $R_FH$ |
| a | $Cl(CF_2)_6I$ | $C_6H_5NH_2$ | 40 | 45 | 15 |
| b | $Cl(CF_2)_6I$ | $o\text{-}CH_3C_6H_4NH_2$ | 34 | 48 | 9 |
| c | $Cl(CF_2)_6I$ | $p\text{-}CH_3C_6H_4NH_2$ | 79 | | 21 |
| d | $Cl(CF_2)_6I$ | $o\text{-}CH_3\text{-}p\text{-}CH_3C_6H_3NH_2$ | 71 | | 29 |
| e | $Cl(CF_2)_6I$ | $C_6H_5N(CH_3)_2$ | 20 | 30 | 50 |
| f | $Cl(CF_2)_2I$ | $C_6H_5N(C_2H_5)_2$ | 22 | 65 | 13 |
| g | $Cl(CF_2)_4I$ | $C_6H_5N(C_2H_5)_2$ | 21 | 63 | 16 |
| h | $Cl(CF_2)_6I$ | $C_6H_5N(C_2H_5)_2$ | 16 | 50 | 24 |

* determined by $^{19}F$ NMR

When the reaction was carried out in different solvents the yields of fluoroalkylation products did not vary too much, but the orientation varied significantly (Table II). In hexane, acetonitrile, dioxane and THF, both the o- and p-substituted products, the latter predominating, were obtained, while in DMF, DMSO and HMPT, the p-substituted product was obtained exclusively. Amines and aromatic compounds could not be used as solvent, because they react with $R_FI$[5].

**TABLE II**

Solvent effect in fluoroalkylation reaction [a] of aniline

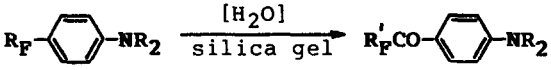
| Solvent | DN[b] | $\delta_{CF_2I}$ | 1(%) | 2(%) | $R_FH$ |
|---|---|---|---|---|---|
| $n\text{-}C_6H_{14}$ | 0.0 | 0.0 | 13 | 35 | 0 |
| $CH_3CN$ | 14.1 | 4.3 | 10 | 40 | 0 |
| dioxane | 14.8 | 5.2 | 16 | 48 | 14 |
| THF | 20.0 | 6.6 | 10 | 42 | 30 |
| DMF | 26.6 | 8.5 | 0 | 37 | 20 |
| DMSO | 29.8 | 9.4 | 0 | 24 | 17 |
| HMPT | 38.8 | 11.6 | 0 | 46 | 33 |

[a] Reaction condition: $Cl(CF_2)_6I$:Aniline:$Ni(PPh_3)_4$=1:2:0.05, 80°C/6h. The products were determined by $^{19}F$ NMR.

[b] The donor number of solvent [6].

It is noteworthy that,no matter which solvent was used, no meta orientation product was produced. The selectivity may be attributed to the interaction of solvent to fluoroalkyl iodide or to the transition state. Table II shows the increase of $\delta_{CF_2I}$ toward high field in $^{19}F$ NMR with the increase of donor number of solvent (DN).

We found that the fluoroalkylaniline could not be hydrolyzed with 50% NaOH by heating to 100°C for 10h, and concentrated $H_2SO_4$ (100°C/10h) caused the material to char. However, by passing through a column of silica gel, the p-substituted dialkylanilines **2e-2h** could be hydrolyzed to p-fluoroacylanilines (**3e-3h**), while the o-isomers (**1e-1h**) remained intact. These facts indicate that the electronic effects of $NR_2$ substituted at o- or p- positions are quite different.




**2e–2h** **3e–3h**

When **2a**, **2b** or **1a–1d** was treated with silica gel the hydrolysis did not occur. These facts show that the electron-donating power of $NH_2$ is less than $NR_2$. The intermediate for the hydrolysis of these anilines is probably of type **4** [7,8]. In the stabilization of resonance structures of type **4**, $NR_2$ is more favorable than $NH_2$.

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**TABLE III**

Hydrolysis of **2e–2h**

| | $R_F$ | R | B.p.(°C/mmHg) | Yield(%) |
|---|---|---|---|---|
| **3e** | $Cl(CF_2)_5$ | $CH_3$ | 80/0.2 | 83 |
| **3f** | $ClCF_2$ | $C_2H_5$ | 85/0.5 | 74 |
| **3g** | $Cl(CF_2)_3$ | $C_2H_5$ | 73/0.1 | 73 |
| **3h** | $Cl(CF_2)_5$ | $C_2H_5$ | 92/0.1 | 70 |

EXPERIMENTAL

$Ni(PPh_3)_4$ catalyst was prepared according to the literature [9], solvents were treated by standard methods, polyfluoroalkyl iodides and anilines were redistilled before use. All the reactions were carried out under $N_2$ atmosphere. NMR spectra were recorded on an EM-360A instrument at 60 MHz ($^1H$ NMR: $CCl_4$/TMS, $^{19}F$ NMR: $CCl_4/CFCl_3$ ext, high field is positive). IR spectra were recorded on IR-440, and MS spectra were obtained on Ms-4021 spectrometers.

All the compounds reported below are new.

2-(ω-Chloro-dodecafluorohexyl)aniline **1a** and 4-(ω-chloro-dodecafluorohexyl)aniline **2a**: **Typical Procedure:** A mixture of 925 mg (2 mmol) $Cl(CF_2)_6I$, 372 mg (4 mmol) $C_6H_5NH_2$, 110 mg (0.1 mmol) $Ni(PPh_3)_4$ in 5 ml dioxan was heated at 80°C for 6h. $^{19}F$ NMR showed that the iodide had been converted completely, and the yields of **1a** and **2a** were 40 and 45 percent (based on iodide) respectively.

After hydrolysis and extraction with ether, the mixture **1a** and **2a** was separated by column chromatography on silica gel (eluted with petroleum ether and ethyl acetate).

**1a**: b.p. 64-66°C/1 mmHg. IR (neat) 3350, 1635, 1590, 1500, 1465, 1330, 1300-1100$cm^{-1}$. MS: m/e 430, 429, 428, 427(M), 408, 392, 142(100). $^1H$ NMR: $\delta$(ppm) 4.10(s,2H), 6.30-7.40(m,4H). $^{19}F$ NMR: $\delta$(ppm) 66.2(t,2F,J=13Hz), 106.9 (t,2F,J=12.5Hz), 118.4(m,2F), 119.7(m,2F). Analysis Found: C,33.75; H,1.47; Cl,8.34; F,53.23; N,3.17. $C_{12}H_6ClF_{12}N$ Calc.: C,33.68; H,1.40; Cl,8.30; F,53.33; N,3.27.

**2a:** b.p. 73-77°C/1 mmHg. IR (neat): 3350, 1625, 1520, 1300-1100cm$^{-1}$. MS: m/e 430, 429, 428, 427(M), 408, 392, 142(100). $^{1}$H NMR: $\delta$(ppm) 3.75(s,2H), 6.53 and 7.25 ($A_2B_2$,4H,J=8.0Hz). $^{19}$F NMR: $\delta$(ppm) 66.4(t,2F,J=11Hz), 107.8(t,2F,J=11Hz), 118.6 (m,2F), 119.9(m,6F). Analysis Found: C,33.54; H,1.31; Cl,8.49; F,53.20; N,3.23. $C_{12}H_6ClF_{12}N$ Calc.: C.33.68; H,1.40; Cl,8.30; F,53.23; N,3.27.

The following compounds were prepared similarly.

2-Methyl-6-($\omega$-chloro-dodecafluorohexyl)aniline **1b:** b.p. 81-83°C/1 mmHg. IR (neat): 3450, 2900, 1632, 1475, 1300-1100cm$^{-1}$. MS: m/e 444, 443, 442, 441(M), 422, 406, 156(100). $^{1}$H NMR: $\delta$(ppm) 2.15(s,3H), 3.90(s,2H), 6.60(dt,1H,J=8Hz,$H_4$), 7.13(d,2H,J=8Hz,$H_3$,$H_5$), $^{19}$F NMR: $\delta$(ppm) 66.4(t,2F,J=12.5Hz), 106.2(t,2F,J=12.5Hz), 118.4(m,2F), 119.5(m,6F). Analysis Found: C,35.06; H,1.71; Cl,7.87; F,51.47; N,2.99. $C_{13}H_8ClF_{12}N$ Calc.: C,35.33; H,1.81; Cl,8.04; F,51.64; N,3.17.

2-Methyl-4-($\omega$-chloro-dodecafluorohexyl)aniline **2b:** b.p. 70-72°C/0.5 mmHg. IR (neat): 3420, 2850, 1632, 1520, 1312, 1300-1100cm$^{-1}$. MS: m/e 444, 443, 442, 441(M,100), 422, 406, 156. $^{1}$H NMR: $\delta$(ppm) 2.15(s,3H), 3.74(s,2H), 6.57(d,1H, J=8.4Hz,$H_6$), 7.20(d,1H,J=8.4Hz,$H_5$), 7.20(s,1H,$H_3$). $^{19}$F NMR: $\delta$(ppm) 66.8(t,2F,J=10Hz), 107.9(t,2F,J=11Hz), 118.7(m,2F), 120.0(m,6F). Analysis Found: C,36.00; H,1.82; Cl,7.85; F,51.50; N,3.19. $C_{13}H_8ClF_{12}N$ Calc.: C,35.33; H,1.81; Cl,8.04; F,51.64; N,3.17.

4-Methyl-2-(ω-chloro-dodecafluorohexyl)aniline **1c:** b.p. 65-68°C/0.5 mmHg. IR (neat): 3450, 2850, 1637, 1515, 1425, 1315, 1300-1100cm$^{-1}$. MS: m/e 444, 443, 442, 441(M,100), 422, 406, 156. $^{1}$H NMR: $\delta$(ppm) 2.20(s,3H), 4.05(s,2H), 6.45(d,1H, J=8.4Hz,$H_6$), 7.00(d, 1H,J=8.4Hz,$H_5$), 7.06(s,1H,$H_3$). $^{19}$F NMR: $\delta$(ppm) 67.0(t,2F,J=13Hz), 107.4(t,2F,J=13Hz), 119.0(m,2F), 120.0(m,6F). Analysis Found: C,35.61; H,1.93; Cl,8.00; F,52.05; N,3.13. $C_{13}H_8ClF_{12}N$ Calc.: C,35.33, H,1.81; Cl,8.04; F,51.64; N,3.17.

2,4-Dimethyl-6-(ω-chloro-dodecafluorohexyl)aniline 1d: b.p. 68-70°C/0.5 mmHg. IR (neat): 3450, 2820, 1635, 1490, 1300-1100cm$^{-1}$. MS: m/e 458, 457, 456, 455(M), 436, 420, 170, 156(100). $^{1}$H NMR: $\delta$(ppm) 2.10(s,3H), 2.20(s,3H), 3.90(s,2H), 6.90(s,2H). $^{19}$F NMR: $\delta$(ppm) 66.4(t,2F,J=12Hz), 106.3(t,2F, J=12Hz), 118.4(m,2F), 120.4(m,6F). Analysis Found: C,37.26; H,2.11; Cl,7.56; F,49.77; N,3.24. $C_{14}H_{10}ClF_{12}N$ Calc.: C,36.88; H,2.19; Cl,7.79; F,50.05; N,3.07.

2-(ω-Chloro-dodecafluorohexyl)-N,N-dimethylaniline **1e:** b.p. 78-80°C/1 mmHg. IR (neat): 2970, 1600, 1500, 1460, 1300-1100cm$^{-1}$. MS: m/e 458, 457, 456, 455(M), 436, 420, 170(100), 156. $^{1}$H NMR: $\delta$(ppm) 2.61(s,6H), 6.76-7.60(m,4H). $^{19}$F NMR:$\delta$(ppm) 66.6(t,2F,J=12Hz), 103(t,2F,J=12.1Hz), 118.7 (m,6F), 119.7(m,2F). Analysis Found: C,36.09; H,1.98, Cl,7.57; F,49.51; N,3.25. $C_{14}H_{10}ClF_{12}N$ Calc.: C,36.88; H,2.19, Cl,7.79; F,50.05; N,3.07.

2-(2-Chloro-tetrafluoroethyl)-N,N-diethylaniline **1f:**

b.p. 56°C/0.5 mmHg. IR (neat): 2950, 1600, 1495, 1445, 1380, 1300-1100cm$^{-1}$. MS: m/e 286, 285, 284, 283(M), 282, 270, 269, 268(100). $^{1}$H NMR: $\delta$(ppm) 1.00(t,6H,J=6.5Hz), 2.92(q, 4H,J=6.5Hz), 6.95-7.65(m,4H). $^{19}$F NMR: $\delta$(ppm) 66.1(s,2F), 101(s,2F). Analysis Found: C,51.24; H,5.15; Cl,12.58; F,26.69; N,4.75. $C_{12}H_{14}ClF_4N$ Calc.: C,50.79; H,4.94; Cl,12.52; F,26.81; N,4.94.

2-($\omega$-Chloro-octafluorobutyl)-N,N-diethylaniline **1g:**

b.p. 68-70°C/0.5 mmHg. IR (neat): 2980, 1600, 1495, 1450, 1385, 1300-1100cm$^{-1}$. MS: m/e 386, 385, 384, 383(M), 370, 369, 368, 348, 85, 71, 57(100). $^{1}$H NMR: $\delta$(ppm) 1.00(t,6H, J=6.5Hz), 2.92(q,4H,J=6.5Hz), 6.85-7.70(m,4H), $^{19}$F NMR: $\delta$(ppm) 66.3(t,2F,J=13Hz), 102(t,2F,J=11.5Hz), 117.5(m,2F), 118.2(m,2F). Analysis Found: C,43.72; H,3.86; Cl,9.21; F,39.35; N,3.83. $C_{14}H_{14}ClF_8N$ Calc.: C,43.80; H,3.65; Cl,9.26; F,39.63; N,3.65.

2-($\omega$-Chloro-dodecafluorohexyl)-N,N-diethylaniline **1h:**

b.p. 60°C/0.2 mmHg. IR (neat): 3000, 1610, 1500, 1460, 1390, 1300-1100cm$^{-1}$. MS: m/e 486, 485, 484, 483(M), 470, 469, 468(100), 448, 168. $^{1}$H NMR: $\delta$(ppm) 0.93(t,6H,J=6.5Hz), 2.85 (q,4H,J=6.5Hz), 6.60-7.65(m,4H). $^{19}$F NMR: $\delta$(ppm) 66.8(t,2F, J=11.5Hz), 102.4(t,2F,J=11.5Hz), 118.5(m,2F), 119.1(m,2F), 120(m,2F). Analysis Found: C,39.91, H,3.04, Cl,7.29, F,46.50; N,2.83. $C_{16}H_{14}ClF_{12}N$ Calc.: C,39.71, H,2.89; Cl,7.34; F,47.16, N,2.90.

Compounds **2e-2h** were readily converted to **3d-3h** respectively on passing through a column of silica gel, so they could not be obtained in pure state. Their existence was indicated by $^{19}F$ NMR: $\delta C_6H_4CF_2$ **2e** 108, **2f** 107, **2g** 108, **2h** 107.6. After chromatography and elution with petroleum ether and ethyl acetate **3e-3h** were obtained from **2e-2h** respectively, and the data of **3e-3h** are shown below:

4-(ω-Chloro-decafluorocaproyl)-N,N-dimethylaniline **3e:**

b.p. 80°C/0.2 mmHg. IR (neat): 2910, 1665, 1600, 1540, 1500, 1445, 1380,1300-1100cm$^{-1}$. MS: m/e 436, 435, 434, 433(M), 149, 148(100). $^1H$ NMR: $\delta$(ppm) 3.12(s,6H), 6.63 and 7.93 ($A_2B_2$,4H,J=8.4Hz). $^{19}F$ NMR: $\delta$(ppm) 66.2(t,2F,J=12Hz), 114 (t,2F,J=11.5Hz), 118.4(m,4F), 119.1(m,2F). Analysis Found: C,38.95; H,2.40; Cl,8.01; F,43.58; N,3.17. $C_{14}H_{10}ClF_{10}NO$ Calc.: C,38.75; H,2.31; Cl,8.19; F,43.83; N,3.23.

4-(2-Chloro-difluoroacetyl)-N,N-diethylaniline **3f:**

b.p. 85°C/0.5 mmHg. IR (neat): 2980, 1680, 1600, 1540, 1420, 1360, 1300-1100cm$^{-1}$. MS: m/e 264, 263, 262, 261(M), 248, 246, 177, 176(100). $^1H$ NMR: $\delta$(ppm) 1.20(t,6H,J=6.5Hz), 3.43 (q,4H,J=6.5Hz), 6.55 and 7.87($A_2B_2$,4H,J=8.4Hz). $^{19}F$ NMR: $\delta$(ppm) 57.3(s,2F). Analysis Found: C,55.24; H,5.39; Cl,13.46; F,14.80; N,5.51. $C_{12}H_{14}ClF_2NO$ Calc.: C,55.07, H,5.53; Cl,13.58; F,14.53; N,5.35.

4-(ω-Chloro-hexafluorobutyryl)-N,N-diethylaniline **3g:**

b.p. 73°C/0.1 mmHg. IR (neat): 2980, 1670, 1590, 1535, 1415, 1355, 1300-1100cm$^{-1}$. MS: m/e 364, 363, 362, 362, 361(M),

348, 347, 346(100), 326, 176, 121, 106. $^{1}H$ NMR: $\delta$(ppm) 1.10 (t,6H,J=6.5Hz), 3.30(q,4H,J=6.5Hz), 6.45 and 7.78($A_2B_2$,4H, J=8.4Hz). $^{19}F$ NMR: $\delta$(ppm) 65.4(t,2F,J=11.2Hz), 109.9(t,2F, J=11.2Hz), 117.8(s,2F). Analysis Found: C,46.48; H,4.10; Cl,9.35; F,31.92; N,4.06. $C_{14}H_{14}ClF_6NO$ Calc.: C,46.47; H,3.87; Cl,9.82; F,31.54; N,3.87.

4-(ω-Chloro-decafluorocaproyl)-N,N-diethylaniline **3h:**

b.p. 92°C/0.1 mmHg. IR (neat): 3000, 1680, 1600, 1540, 1420, 1365, 1300-1100$cm^{-1}$. MS: m/e 464, 463, 462, 461(M), 448, 447, 446, 426, 176(100). $^{1}H$ NMR: $\delta$(ppm) 1.20(t,6H,J=6.0Hz), 3.40(q,4H,J=6.0Hz). 6.51 and 7.81($A_2B_2$,4H,J=8.2Hz). $^{19}F$ NMR: $\delta$(ppm) 66.4(t,2F,J=11.2Hz), 110.5(t,2F,J=11Hz), 118.7(m,2F), 119.3(m,2F). Analysis Found: C,41.75; H,3.13; Cl,7.66; F,41.09; N,3.25. $C_{16}H_{14}ClF_{10}NO$ Calc.: C,41.60; H,3.03; Cl,7.69; F,41.17; N,3.03.

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