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Barbier-type reaction of fluoroalkyl iodides with aldehydes without activation

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Abstract

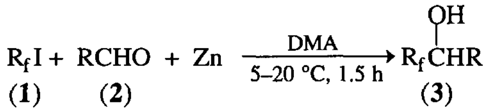
Fluoroalkyl iodides react with aldehydes in the presence of zinc in *N,N*-dimethylacetamide without activation, giving a variety of fluoroalkylated carbinols in 72%–90% yield. The reaction provides a convenient method for the synthesis of these compounds.

Introduction

Fluoroalkyl halides were useful reagents for the fluoroalkylation of organic molecules. Barbier-type reactions of fluoroalkyl halides with aldehydes in the presence of zinc are important methods for the preparation of various fluoroalkylated compounds [1]. However, all the reported Barbier-type reactions of fluoroalkyl iodides need some activation, for example, ultrasonic irradiation [2], catalysis by metal complexes [3] or catalysis by electron mediators [4], and the yields are only moderate.

Results and discussion

We have found that fluoroalkyl iodides are able to react with aldehydes in the presence of zinc in *N,N*-dimethyl acetamide (DMA) without activation, giving a variety of fluoroalkylated carbinols in 72%–90% yield. The reaction is shown below and the corresponding results summarized in Table 1. DMA, DMF, DMSO and THF could be used as solvents in this reaction, but DMA could also be used to give good yields without activation.



$$R_fI + RCHO + Zn \xrightarrow[5\text{–}20\ ^\circ C,\ 1.5\ h]{DMA} R_fCH(OH)R$$

(1) (2) (3)

3a : $R_f = n\text{-}C_4F_9$; R = Ph

3b : $R_f = n\text{-}C_4F_9$; R = $4\text{-}FC_6H_4$

3c : $R_f = Cl(CF_2)_4$; R = Ph

3d : $R_f = Cl(CF_2)_4$; R = $4\text{-}FC_6H_4$

3e : $R_f = Cl(CF_2)_4$; R = Pr

3f : $R_f = n\text{-}C_6F_{13}$; R = $4\text{-}CH_3C_6H_4$

3g : $R_f = n\text{-}C_6F_{13}$; R = Pr

TABLE 1. Preparation of fluoroalkylated carbinols **3**

Compound	R_f	R	Solvent	Yield (%)[a]
3a	$n\text{-}C_4F_9$	Ph	DMA	83
3a	$n\text{-}C_4F_9$	Ph	DMSO	70
3a	$n\text{-}C_4F_9$	Ph	DMF	60
3a	$n\text{-}C_4F_9$	Ph	THF	45
3b	$n\text{-}C_4F_9$	$4\text{-}FC_6H_4$	DMA	90
3c	$Cl(CF_2)_4$	Ph	DMA	80
3d	$Cl(CF_2)_4$	$4\text{-}FC_6H_4$	DMA	82
3e	$Cl(CF_2)_4$	Pr	DMA	72
3f	$n\text{-}C_6F_{13}$	$4\text{-}CH_3C_6H_4$	DMA	78
3g	$n\text{-}C_6F_{13}$	Pr	DMA	75

[a]Isolated yield.

Small amounts of fluorinated organozinc reagents remain at the end of these reactions. This is identical with previously reported results [1]. If tetraglyme was used as the solvent, only solvated organozinc reagents which were incapable of reacting with aldehydes were formed. ESR spectroscopy showed that fluoroalkyl radicals are formed rapidly in the reaction mixture. It has been reported [5] that tetrakis(triphenylphosphine)palladium initiates the reaction of perfluoroalkyl iodides with alkenes via a single-electron-transfer process. In order to confirm whether fluoroalkyl radicals were capable of reacting with aldehydes or not, tetrakis(triphenylphosphine)palladium was used to initiate the reaction of nonafluorobutyl iodide with

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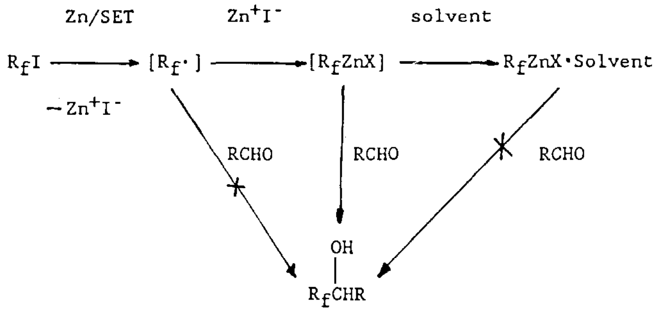

Scheme 1.

benzaldehyde. After 5 h at 80 °C, nonafluorobutyl iodide was consumed but the desired product was not obtained. On the basis of these facts, we propose that the reaction may involve nascent organometallic reagents [6] reacting near the zinc surface rather than solvated organozinc compounds or fluoroalkyl radicals (Scheme 1).

As far as convenience is concerned, the present method provides a convenient introduction of fluoroalkyl groups into aldehydes and should be useful in the synthesis of fluorinated biologically active compounds.

Experimental

All melting and boiling points were uncorrected. Infrared (IR) spectra of all products were obtained as a film on a Perkin-Elmer 983G spectrometer. NMR spectra (δ in ppm from TMS for ^{1}H NMR and from external TFA for ^{19}F NMR, positive for upfield shifts) were recorded on a JEOL FX-90Q FT NMR spectrometer at 90 MHz in $CDCl_3$. Mass spectra were measured on a Finnigan GC–MS 4021 spectrometer.

General procedure for the preparation of fluoroalkylated carbinols 3

Fluoroalkyl iodides (4.8 mmol) were added slowly with stirring to a solution of aldehyde (4.0 mmol), and acid-washed zinc dust (6.0 mmol) in dry *N*,*N*-dimethylacetamide (4.0 ml) at 5 °C (ice–water bath) under nitrogen. The reaction mixture was allowed to warm to room temperature over 1 h, quenched with 1 N HCl (8 ml) and extracted with dichloromethane (3×10 ml). The extractant was washed with aqueous NaCl solution (2×10 ml) and dried. Evaporation of the solvent gave a residue which was purified by flash column chromatography to give the pure product (**3**).

1-(Nonafluorobutyl)-1-phenyl carbinol (**3a**): 83% yield, b.p. 60–62 °C/4.0 mmHg [lit. value [2], 81–83 °C/36 mmHg]. ^{1}H NMR δ: 7.36 (s, 5H); 5.10 (dd, 1H, J=8.0, 15.2 Hz); 2.64–2.82 (br s, 1H) ppm. ^{19}F NMR δ: 4.1 (s, 3F); 45.2 (s, 2F): 49.3 (d, 2F, J=12.4 Hz); 41.3 and 48.9 (AB, 2F, J=291.1 Hz) ppm. IR (film) (cm^{-1}): 3576 (s); 3036 (s); 1493 (s). MS *m*/*e*: 326 (M$^+$); 309 (M$^+$ −OH); 108.

1-(Nonafluorobutyl)-1-(4-fluoro)-phenyl carbinol (**3b**): 90% yield, m.p. 30–31 °C. ^{1}H NMR δ: 7.28–7.50 (m, 2H); 6.92–7.24 (m, 2H); 5.14 (dd, 1H, J=8.0, 15.2 Hz); 2.70–3.10 (br s, 1H) ppm. ^{19}F NMR δ: 4.2 (s, 3F); 34.8 (s, 1F); 45.2 (s, 2F); 49.3 (d, 2F, J=12.4 Hz); 41.4 and 49.0 (AB, 2F, J=284.9 Hz) ppm. IR (film/CH_2Cl_2) (cm^{-1}): 3576 (s); 1606 (s); 1228 (s). MS *m*/*e*: 344 (M$^+$); 343 (M$^+$ −1); 328; 325; 125. Analysis: Calc. for $C_{11}H_6F_{10}O$: C, 38.31; H, 1.74%. Found: C, 38.12; H, 1.73%.

1-(ω-Chloro-octafluorobutyl)-1-phenyl carbinol (**3c**): 80% yield, b.p. 80 °C/4.0 mmHg [lit. value [7], 45–47 °C/0.3 mmHg]. ^{1}H NMR δ: 7.23 (br s, 5H); 4.74–5.10 (m, 1H); 2.60 (br s, 1H) ppm. ^{19}F NMR δ: −9.1 (s, 2F); 42.5–43.5 (m, 4F); 41.0 and 48.7 (AB, 2F, J=278.8 Hz) ppm. IR (film) (cm^{-1}): 3450 (w); 3036 (s); 1490 (s). MS *m*/*e*: 341 (M$^+$ −1); 325 (M$^+$ −OH); 107.

1-(ω-Chloro-octafluorobutyl)-1-(4-fluoro)-phenyl carbinol (**3d**): 82% yield, m.p. 37.5–38.5 °C. ^{1}H NMR δ: 7.20–7.46 (m, 2H); 6.88–7.16 (m, 2H); 5.12 (dd, 1H, J=8.0, 15.2 Hz); 2.70–2.96 (br s, 1H) ppm. ^{19}F NMR δ: −9.0 (t, 2F, J=12.5 Hz); 34.8 (s, 1F); 43.3 (m, 4F); 41.4 and 48.7 (AB, 2F, J=291.2 Hz) ppm. IR (film/CH_2Cl_2) (cm^{-1}): 3450 (w); 1610 (s); 1190 (s). MS *m*/*e*: 361 (M$^+$ +1); 359 (M$^+$ −1); 343 (M$^+$ −OH); 125. Analysis: Calc. for $C_{11}H_6ClF_9O$: C, 36.61; H, 1.66%. Found: C, 36.55; H, 1.55%.

1-(ω-Chloro-octafluorobutyl)-1-butanol (**3e**): 72% yield, b.p. 46–48 °C/3.0 mmHg. ^{1}H NMR δ: 3.90–4.28 (m, 1H); 2.08 (s, 1H); 1.30–1.80 (m, 4H); 0.99 (t, 3H, J=7.0 Hz) ppm. ^{19}F NMR δ: −9.0 (s, 2F); 43.4–43.9 (m, 4F); 44.3 and 49.7 (AB, 2F, J=291.2 Hz) ppm. IR (film) (cm^{-1}): 3400 (w); 2950 (s); 1190 (s). MS *m*/*e*: 309 (M$^+$ +1); 307 (M$^+$ −1); 291 (M$^+$ −OH); 235; 73. Analysis: Calc. for $C_8H_9ClF_8O$: C, 31.12; H, 2.91%. Found: C, 31.32; H, 2.90%.

1-(Tridecafluorohexyl)-1-(4-methyl)-phenyl carbinol (**3f**): 78% yield, b.p. 85 °C/1.0 mmHg. ^{1}H NMR δ: 7.20–7.30 (m, 4H); 4.92–5.28 (dd, 1H, J=8.0, 15.0 Hz); 2.38 (s, 3H); 1.50–1.68 (m, 1H) ppm. ^{19}F NMR δ: 3.89 (s, 3F); 44.17 (s, 2F); 45.06 (s, 2F); 45.79 (s, 2F); 49.10 (s, 2F); 41.02 and 48.72 (AB, 2F, J=278.8 Hz) ppm. IR (film) (cm^{-1}): 3500 (s); 1260 (s); 1210 (s). MS *m*/*e*: 441 (M$^+$ +1); 423 (M$^+$ −OH); 403; 121. Analysis: Calc. for $C_{14}H_9F_{13}O$: C, 38.18; H, 2.04%. Found: C, 38.19; H, 1.81%.

1-(Tridecafluorohexyl)-1-butanol (**3g**): 75% yield, b.p. 55 °C/3.0 mmHg. ^{1}H NMR δ: 4.10–4.28 (m, 1H); 3.35 (s, 1H); 1.40–1.72 (m, 4H); 0.97 (t, 3H, J=7.0 Hz) ppm. ^{19}F NMR δ: 4.34 (s, 3F); 44.61–45.94 (m, 6F); 49.47 (s, 2F); 42.98 and 49.71 (AB, 2F, J=278.8 Hz) ppm. MS *m*/*e*: 391 (M$^+$ −1); 375 (M$^+$ −OH); 355; 73.

Analysis: Calc. for $C_{10}H_9F_{13}O$: C, 30.61; H, 2.29%. Found: C, 30.58; H, 2.22%.

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