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Synthesis of trifluoromethyl aryl derivatives via difluorocarbene precursors and nitro-substituted aryl chlorides

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Abstract

Treatment of aryl chlorides containing electron-withdrawing groups with methyl fluorosulfonyl difluoroacetate or methyl halodifluoroacetate in the presence of potassium fluoride and copper iodide gave the corresponding trifluoromethyl derivatives in moderate to high yields.

Introduction

Although the trifluoromethylation of aryl iodides and bromides has been shown to be successful [1], few reports on the trifluoromethylation of aryl chlorides have appeared. Burton's reagent, CF_2Br_2/Zn(Cd)/CuI, can transform aryl chlorides containing electron-withdrawing substituents into the corresponding trifluoromethylated products in the presence of charcoal [2]. In our previous reports, methyl fluorosulphonyl difluoroacetate[3a] and methyl halodifluoroacetates[3b] were shown to be very efficient trifluoromethylating agents for vinyl, allylic, aryl iodides or bromides. As the aryl chlorides are cheaper and more readily available than the corresponding iodides and bromides, it would be of considerable interest to transform aryl chlorides into the corresponding trifluoromethyl compounds. The results obtained in such studies are reported here.

Experimental

All boiling points are uncorrected. ^{1}H NMR spectra were obtained on a Varian EM-360A (60 MHz) or an XL-200 (200 MHz) spectrometer. Chloroform-*d* was used as solvent with TMS as the external reference. ^{19}F NMR spectra were obtained on a Varian EM-360L (60 MHz) spectrometer with CCl_3F as the external reference (positive for upfield shifts).

Mass spectra were recorded with a Finnigan GC–MS 4021 mass spectrometer. All reagents and solvents were dried and purified prior to use.

Methyl halodifluoroacetates and methyl fluorosulfonyl difluoroacetate were prepared according to the method described in ref. 1b.

Typical procedure for the reaction of aryl chlorides with methyl chlorodifluoroacetate (4a)

A mixture consisting of $ClCF_2CO_2Me$ (**4a**) (2.89 g, 20 mmol), KF (0.58 g, 10 mmol), CuI (2 g, 10 mmol), 2,4-dinitro-1-chlorobenzene (**1b**) (2 g, 10 mmol) and 30 ml DMF was placed in a 50 ml three-necked round-bottomed flask fitted with a magnetic stir-bar, dry ice condenser and thermometer. The solution was heated to 100 °C for 8 h under an N_2 atmosphere. The mixture was filtered and the filtrate poured into ice water. The aqueous layer was extracted three times with ethyl ether (3×20 ml). The combined extracts were washed with water (30 ml) and dried over Na_2SO_4. After the ether had been evaporated, distillation *in vacuo* gave 1.9 g (90%) of compound **3b**.

The procedures employed for **4a** and **4b** were similar except that the reaction temperatures were 100 °C and 90 °C, respectively.

Compound **3a**: M.p. 40–42 °C (lit. value [2], 40–41 °C). ^{19}F NMR δ: 66.2 ppm. ^{1}H NMR δ: 8.70 (d, $J=6.8$ Hz, 2H); 7.50 (d, $J=6.8$ Hz, 2H) ppm. MS m/z: 191 (M^+); 172 (M^+-F); 145 (M^+-NO_2); 76 ($M^+-NO_2-CF_3$); 69 (CF_3^+).

Compound **3b**: B.p. 84–86 °C/0.3 mmHg. IR ν_{max} (cm^{-1}): 3050; 1600; 1540; 1500; 1350; 1150. ^{1}H NMR δ: 7.71–8.66(m) ppm. ^{19}F NMR δ: 66.5 ppm. MS m/z: 236 (M^+); 144 (M^+-2NO_2); 143 (M^+-2NO_2-1); 132; 125; 94; 75. Analysis: Calc. for $C_7H_3F_3N_2O_4$: C, 35.61; H, 1.28; N, 11.86; F, 24.14%. Found: C, 35.29; H, 1.26; N, 12.01; F, 24.30%.

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Compound **3c**: ^{1}H NMR δ: 8.25 (s) ppm. ^{19}F NMR δ: 59.1 ppm. MS *m/z*: 281 (M^+); 235 ($M^+ - NO_2$); 212 ($M^+ - CF_3$). IR ν_{max} (cm^{-1}): 3050; 1600; 1540; 1500; 1360; 1140. Analysis: Calc. for $C_6H_2F_3N_3O_6$: C, 29.91; N, 14.95; F, 20.28%. Found: C, 29.99; N, 14.59; F, 20.70%.

Compound **3d**: B.p. 54–56 °C/0.3 mmHg. ^{1}H NMR δ: 7.85 (s) ppm. ^{19}F NMR δ: 63 ppm. IR ν_{max} (cm^{-1}): 3100; 1600; 1570; 1500; 1350; 1190. MS *m/z*: 259 (M^+); 213 ($M^+ - NO_2$); 163 ($M^+ - NO_2 - CF_2$). Analysis: Calc. for $C_8H_3F_6NO_2$: C, 37.08; H, 1.17; N, 5.41; F, 43.99%. Found: C, 37.21; H, 1.08; N, 5.55; F, 43.80%.

Compound **3e**: M.p. 77–79 °C. ^{1}H NMR δ: 8.20 (s) ppm. ^{19}F NMR δ: 58 (s, 3F); 64.6 (s, 3F) ppm. IR ν_{max} (cm^{-1}): 3150; 1570; 1600; 1500; 1350; 1190. MS *m/z*: 304 (M^+); 285 ($M^+ - F$); 258 ($M^+ - NO_2$); 235 ($M^+ - CF_3$); 212 ($M^+ - 2NO_2$); 162 ($M^+ - 2NO_2 - CF_2$); 143 ($M^+ - 2NO_2 - CF_3$); 69 (CF_3^+); 46 (NO_2^+). Analysis: Calc. for $C_8H_2F_6N_2O_4$: C, 31.60; H, 0.66; N, 9.21; F, 37.48%. Found: C, 31.51; N, 8.93; F, 37.95%.

Results and discussion

Treatment of aryl halides **1** with methyl fluorosulfonyldifluoroacetate (**2**) in the presence of catalytic amounts of copper iodide in DMF at 70–80 °C under an N_2 atmosphere for 5 h gave the corresponding trifluoromethylated products **3** in high yield. The results are listed in Table 1.

$$\underset{(1)}{\mathrm{ArCl}} + \underset{(2)}{\mathrm{FSO_2CF_2CO_2Me}} \xrightarrow[80\ ^\circ\mathrm{C}]{\mathrm{CuI}} \underset{(3)}{\mathrm{ArCF_3}} + \mathrm{SO_2} + \mathrm{CO_2} + \mathrm{MeCl}$$

ArCl: (**a**) *p*-$NO_2C_6H_4Cl$
(**b**) 2,4-dinitro-1-chlorobenzene
(**c**) 2,4,6-trinitro-1-chlorobenzene
(**d**) 2-nitro-4-trifluoromethyl-1-chlorobenzene
(**e**) 2,6-dinitro-4-trifluoromethyl-1-chlorobenzene

Scheme 1.

In the presence of potassium fluoride and copper iodide, methyl chlorodifluoroacetate (**4a**) and methyl bromodifluoroacetate (**4b**) also reacted with aryl chlorides at 100–110 °C for 7–10 h and at 90 °C for 8–9 h, respectively, to afford the corresponding trifluoromethylated compounds with comparable yields. The results are listed in Table 2.

$$\underset{(1)}{\mathrm{ArCl}} + \mathrm{KF} + \underset{(4)}{\mathrm{XCF_2CO_2Me}} \xrightarrow{\mathrm{CuI}} \underset{(3)}{\mathrm{ArCF_3}} + \mathrm{KX} + \mathrm{MeX}$$

(**a**) X = Cl; (**b**) X = Br

Scheme 2.

TABLE 1. Reaction of **1** with **2** [**2**/**1**(molar ratio) = 2:1][a]

ArCl	Time (h)	Conversion[b] (%)	Yield of **3** (%)[c]
1a	12	15	95
1b	8	90	90
1c	5	100	80
1d	10	80	90
1e	5	100	93
1e[d]	5	100	94

[a] In DMF unless indicated otherwise.
[b] Determined by recovery of ArCl.
[c] Isolated yields based on the conversion of ArCl.
[d] In HMPA.

TABLE 2. Reaction of **1** with **4** with the presence of KF and CuI (**1**/**4**/KF/CuI = 1:2:1:1)[a]

ArCl	Compound **4**	Temperature (°C)	Time (h)	Conversion (%)[b]	Yield of **3** (%)[c]
1a	**4a**	100–110	10	21	87
1b	**4a**	100–110	8	95	90
1c	**4a**	100–110	7	100	90
1d	**4a**	100–110	10	75	93
1e	**4a**	100–110	7	100	90
1a	**4b**	90	10	17	90
1b	**4b**	90	9	85	88
1c	**4b**	90	8	100	92
1d	**4b**	90	8	75	90
1e	**4b**	90	8	100	85
1e[d]	**4b**	90	8	100	90
1e[e]	**4b**	90	8	60	95

[a] In DMF unless indicated otherwise.
[b] Determined by recovery of ArCl.
[c] Isolated yields based on the conversion of ArX.
[d] In HMPA.
[e] Without KF.

The presence of CuI was essential to the reaction. In its absence, compound 3 was not obtained from the reaction of either **2** or **4** with **1**. Both DMF and HMPA may be used as solvents for the reaction. Although compound **4** reacted with **1** to give **3** in the absence of KF, the yield was lower. The results listed in Tables 1 and 2 indicate that the more electron-withdrawing the substituents on the aryl ring, the more reactive is the latter, i.e. **1c** ≈ **1e** > **1d** ≈ **1b** ≫ **1a**, indicating the obvious nucleophilic substitution character of the reaction.

The following mechanism is proposed [1b] for the reaction. Methyl esters **2** or **4** are first attacked by copper(I) iodide to form the copper(I) salt and methyl iodide. The salt then decomposes in a concerted manner to afford difluorocarbene and copper halide with the elimination of CO_2 (and SO_2 for **2**). The $CF_2^{:}$ formed and the fluoride ion added or generated *in situ* are in equilibrium with CF_3^-. In the presence of copper halide, the equilibrium shifts to the right to form a trifluoromethyl copper complex which then reacts with aryl chloride to afford the final trifluoromethylated product.

$$XCF_2CO_2Me + CuI \longrightarrow XCF_2CO_2Cu + MeI$$

$(X = Cl, Br, SO_2F)$

$$XCF_2CO_2Cu \longrightarrow CuX + CF_2^{:} + CO_2 + SO_2 \; (X = SO_2F)$$

$$CF_2^{:} + F^- \rightleftharpoons CF_3^-$$

$$CF_3^- + CuI \longrightarrow CF_3CuI^-$$

$$CF_3CuI^- + ArCl \longrightarrow ArCF_3 + CuI + Cl^-$$

In the absence of potassium fluoride, **4** reacts with **1** to form the trifluoromethyl copper complex, with the fluoride ion being generated *in situ* through the following reactions [1a].

$$CF_2^{:} + HCONMe_2 \longrightarrow HCF_2NMe_2 + CO$$

$$HCF_2NMe_2 \longrightarrow HCF{=}NMe_2^+ + F^-$$

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