Unexpected Substitution Reaction of 1,1-Dichloro-2,2,2-trifluoroethane (HCFC-123) with Phenolates

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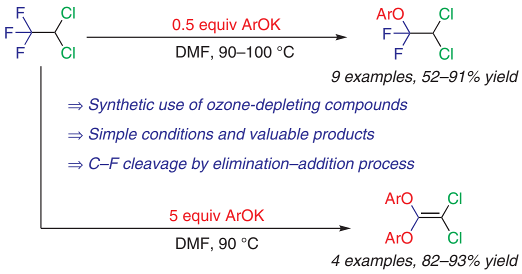

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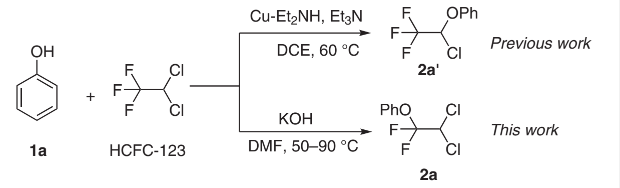
Abstract An unexpected substitution reaction of HCFC-123 with phenolates is reported. During the reaction, fluorine atoms in HCFC-123 are removed one by one in the presence of phenolates.

Key words dichlorotrifluoroethane, phenolates, elimination, substitution

In recent decades, hydrochlorofluorocarbons (HCFCs; for example, HCFC-21, HCFC-22 and HCFC-123) have been produced worldwide as transitional substitutes for chlorofluorocarbons or as starting materials for the manufacture of hydrofluorocarbons (e.g., HCFC-133a). As ozone-depleting compounds, HCFCs will be banned from use as refrigerants, aerosol propellants, and cleaning solvents by 2040 under the Montreal Protocol. Nevertheless, investigations on the reactivities of HCFCs are still attractive from the viewpoint of their chemistry. On the one hand, due to the inductive and stereoelectronic effect of the fluorine atoms, the C–Cl bonds in HCFCs tend to undergo single-electron transfer reactions[1–3] rather than S_N1 or S_N2 reactions of other alkyl chlorides.[4] On the other hand, some HCFCs are irreplaceable for the preparation of fluoroalkyl reagents.[5,6] Therefore, researches on the reactivities of HCFCs are desirable from the points of view of both fluorine chemistry and environmental protection.

As an HCFC with a lower ozone-depleting potential, 1,1-dichloro-2,2,2-trifluoroethane (HCFC-123) is widely used as the refrigerant, a cleaning solvent, or a foaming agent. Inspired by the pioneering work of Dolbier's group,[7] we have extensively investigated the Cu-mediated reactions of HCFC-123 with phenols, thiophenols,[8] alkynes,[9,10] alkenes,[11] and phosphites.[12] In particular, the Cu-mediated reaction of HCFC-123 with phenol in the presence of Et_3N afforded the phenoxylated product **2a′** [^{19}F NMR: δ = –80.8 ppm (d, J = 4.0 Hz)] through substitution of a chlorine atom with a phenoxy group when DCE or HCFC-123 was used as the solvent (Scheme 1; previous work).



Scheme 1 The reactions of HCFC-123 with phenol (**1a**) under various conditions

To our surprise, when we used DMF as the solvent and KOH as the base, and performed the reaction at 50 °C for three hours, a different product **2a** appeared in the ^{19}F NMR spectrum [δ = –80.2 ppm (d, J = 5.8 Hz)] (Scheme 1 and Table 1, entry 1). The ^{19}F NMR yield of **2a** improved to 82% when the reaction was performed at 70 °C for three hours (entry 2). The yield decreased slightly when another aprotic solvent (DMSO or HMPA) was used (entries 3 and 4). Note that a byproduct with a ^{19}F NMR peak at δ = –78 ppm was also detected; the formation of this byproduct was inhibited by increasing the amount of HCFC-123 to two equivalents (entry 5). Eventually, the isolated yield **2a** was increased to 88% by performing the reaction at 90 °C for two hours (entry 6).

With the optimized conditions in hand, we extended this reaction to other phenols (Scheme 2). Phenols bearing electron-donating groups gave the corresponding products **2a–f** in excellent yields within three hours. In contrast, phenols bearing electron-withdrawing groups afforded the desired products **2g–i** in moderate yields after prolonged reaction times.

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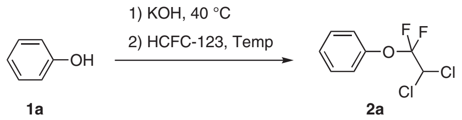
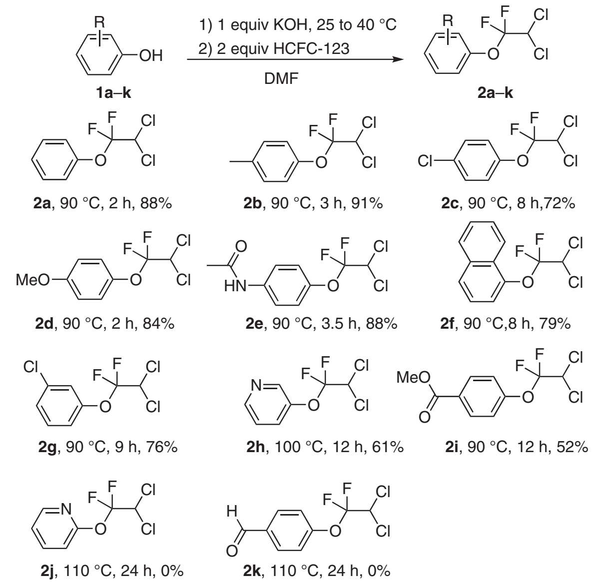
Phenols with strongly electron-withdrawing groups shut down the reaction (**2j** and **2k**). As mentioned above, a small amount of a byproduct was detected at δ = –78 ppm in the ^{19}F NMR spectrum when the molar ratio of **1m** to HCFC-123 was 1:1.2. When the molar ratio of **1m** to HCFC-123 was to 2.5:1, compound **2mm**, which appeared at δ = –78 ppm in the ^{19}F NMR spectrum, became the main product, with a 71% isolated yield (Scheme 3).

Table 1 Optimization of the Conditions for the Reaction of Phenol (**1a**) with HCFC-123[a]

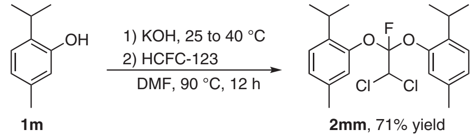


Entry	Solvent	Temp (°C)	Yield[b] (%)
1	DMF	50	trace
2	DMF	70	82
3	DMSO	70	66
4	HMPA	70	70
5[c]	DMF	70	93
6[d]	DMF	90	88[e]

[a] **1a**/KOH/HCFC-123 molar ratio = 1:1.1:1.2; [HCFC-123] = 1 mol/L, 3 h.
[b] Determined by ^{19}F NMR with $PhCF_3$ as the internal standard.
[c] **1a**/KOH/HCFC-123 molar ratio = 1:1.1:2, 3 h.
[d] **1a**/KOH/HCFC-123 molar ratio = 1:1:2, 2 h.
[e] Isolated yield.

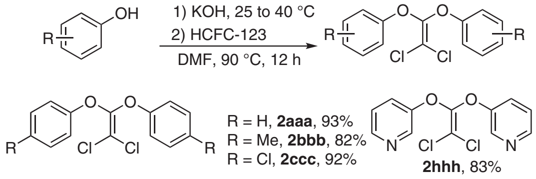


Scheme 2 Reactions of HCFC-123 with various phenols in a molar ratio of 2:1



Scheme 3 The reaction of HCFC-123 with **1m** in a molar ratio of 1:2.5

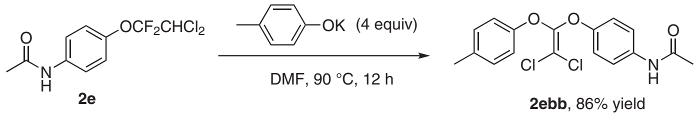
However, with the electron-deficient phenols **1c** and **1h**, although products **2cc** and **2hh** were detected in ^{19}F NMR, the defluorinated products **2ccc** and **2hhh** (Scheme 4), rather than **2cc** and **2hh**, were isolated by column chromatography on silica gel. As expected, when we increased the molar ratio of the phenolate to HCFC-123 to 5:1, the fully defluorinated products **2aaa**–**2ccc** were obtained in good to excellent yields for both electron-rich and electron-deficient phenols (Scheme 4). Taking **1b** as an example, products **2b**, **2bb**, and **2bbb** were all detected by TLC and ^{19}F NMR after 30 minutes of reaction, and **2bbb** was shown to be the sole product after 12 hours.



Scheme 4 Reactions of HCFC-123 with selected phenols at a molar ratio of 1:5

In addition, the reaction of purified **2e** with four equivalents of potassium 4-methylphenoxide gave the defluorinated product **2ebb** in 86% yield (Scheme 5).

Finally, an acid-base pathway was proposed for the reaction mechanism (Scheme 6). The key intermediate, 1,1-dichloro-2,2-difluoroethene, generated by an acid–base reaction, reacts further with the phenolate and affords the product **2a**.[13] However, a halophilic mechanism, similar to the reaction of the phenolate with CF_3CCl_3 cannot be excluded.[14,15] In this pathway, the phenolate attacks the chlorine atom in HCFC-123 and produces 1-chloro-2,2-difluoroethene, which reacts with a second phenolate ion[16] to afford the product through a chain–anion mechanism.



Scheme 5 The reaction of **2e** with potassium 4-methylphenolate at a molar ratio of 1:4

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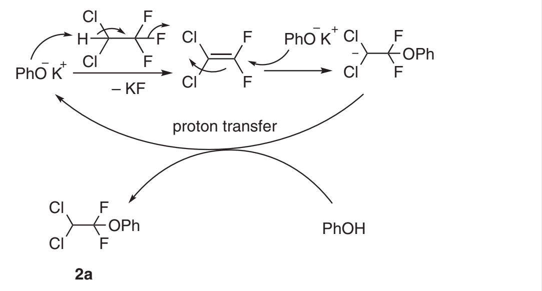

2a

Scheme 6 Proposed plausible reaction mechanisms

In summary, we have reported unexpected substitution reaction of fluorine in HCFC-123 by phenolates. By increasing the amount of the phenolate, the fluorine atoms in HCFC-123 could be removed one by one. This reaction can produce valuable fluorinated alkyl aryl ethers[17,18] and unusual tetrasubstituted alkenes from readily available HCFC-123 under simple conditions.[19]

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707291.

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(19) **(2,2-Dichloro-1,1-difluoroethoxy)benzene (2a): Typical Procedure**
A 20 mL Schlenk tube was charged with DMF (10 mL) and **1a** (5 mmol, 470 mg). KOH (5 mmol, 280 mg) was added, and the mixture was stirred at 40 °C until the KOH disappeared. The mixture was then cooled to r.t. Precooled HCFC-123 (10 mmol, 1.52 g) was added to the solution, and the mixture was stirred at 90 °C for 2 h, then cooled to r.t. The mixture was then poured into Et_2O (100 mL), washed with H_2O, dried (Na_2SO_4), and concentrated by rotary evaporation under vacuum. The residue was purified by flash column chromatography [silica gel, PE–CH_2Cl_2 (20:1)] to give a colorless oil; yield: 994 mg (88%).
^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.40 (m, 2 H), 7.21–7.29 (m, 3 H), 5.91 (t, *J* = 4.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.5, 129.6, 126.4, 121.7, 119.7 (t, *J* = 270 Hz), 67.8 (t, *J* = 42 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.2 (d, *J* = 5.8 Hz). MS (EI): *m/z* (%) = 226 (M^+, 21.51), 77 (100), 143 (50.87), 65 (38.96), 94 (30.34), 226 (21.51).

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