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Journal of Fluorine Chemistry 111 (2001) 153–160

JOURNAL OF FLUORINE CHEMISTRY

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Nucleophilic trifluoromethylation and difluorination of substituted aromatic aldehydes with Ruppert's and Deoxofluor^{TM} reagents

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Received 6 March 2001; accepted 13 June 2001

Abstract

Efficient, high yield syntheses of 2,2,2-trifluoro-1-(*N*,*N*-dialkylaminophenyl)-ethanols (**3a**, **b**) and 2,2,2-trifluoro-1-(hydroxyaryl)ethanols (**6c–g**) by reacting Ruppert's reagent, (trifluoromethyl)trimethylsilane (TMSCF$_3$), with appropriate substrates in the presence of a catalytic amount of cesium fluoride are described. A versatile route to the synthesis of substituted aryl difluoromethane derivatives (**8h–l**, **10m**, **12n**, **o**, **14p**) and the reactivity of substituted aromatic aldehydes towards bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor^{TM}) were also investigated. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: (Trifluoromethyl)trimethylsilane; 2,2,2-Trifluoro-1-(*N*,*N*-dialkylaminophenyl)-ethanols; 2,2,2-Trifluoro-1-(hydroxyaryl)ethanols; Bis(2-methoxyethyl)aminosulfur trifluoride; Aryldifluoromethane derivatives; Deoxofluor^{TM}

1. Introduction

The incorporation of a fluorine-containing group into an organic molecule alters dramatically its physical, chemical and biological properties [1,2]. The concomitant changes in properties make these compounds suitable for diverse applications in material sciences, and agrochemistry, as well as in the pharmaceutical industry [3–6]. The biological activity [7,8] and numerous commercial applications [9–12] of organofluorine compounds have encouraged interest in developing synthetic methods for selective and efficient incorporation of fluorine or fluorinated groups into organic compounds under mild reaction conditions. Although many practical applications of hydroxy and amino-containing aryl compounds have been reported [13], their synthetic routes tend to be cumbersome. For example, an earlier synthesis of (**6e**) was accomplished by the reaction of *p*-anislmagnesium bromide and trifluoroacetic acid, followed by demethylation and reduction (Scheme 1) [14–16]. While Kimoto et al. reported an alternative route to (**6e**) from simple phenol and trifluoroacetaldehyde ethyl hemiacetal, the products obtained after heating at 120°C for 6 h were found as isomeric mixtures [17].

Also starting from aromatic aldehydes, the general reported routes to the synthesis of alkyl or aryl difluoromethanes involve the use of sulfur tetrafluoride, [18–21] aminofluorosulfuranes [22–24] and difluorocarbenes [25]. Very recently bis(2-methoxyethyl)-aminosulfur trifluoride has been used to convert benzaldehyde into the corresponding difluorotoluene [26,27] but no study has been reported on substituted aromatic aldehydes. Also, the effect of substituents in the aromatic ring towards the reactivity with bis(2-methoxyethyl)-aminosulfur trifluoride is not described. It has been found that there exists a profound difference in the reactivity of the aldehyde chosen based upon substituents in the aromatic ring. In general, the pattern of reactivity of the aldehydes corroborates the nucleophilic mode of reaction behavior of bis(2-methoxyethyl)-aminosulfur trifluoride. Recently, we and others have reported several novel trifluoro [28–36] and difluoromethylation reactions [37,38]. In this paper, we present very efficient procedures for the syntheses of 2,2,2-trifluoro-1-(*N*,*N*-dialkylaminophenyl)-ethanols and 2,2,2-trifluoro-1-(hydroxyaryl)ethanol derivatives, and substituted aryldifluoro-methane compounds in very good yield through the use of TMSCF$_3$ and bis(2-methoxyethyl)aminosulfur trifluor-ide, respectively.

2. Results and discussion

The syntheses of 2,2,2-trifluoro-1-(*N*,*N*-dimethylaminophenyl)ethanols (**3a**) were reported earlier [17] in good yield

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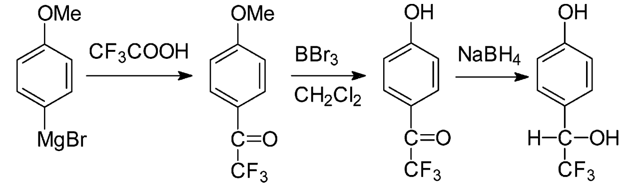
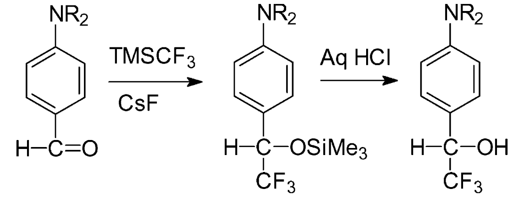
PII: S0022-1139(01)00447-X



6e

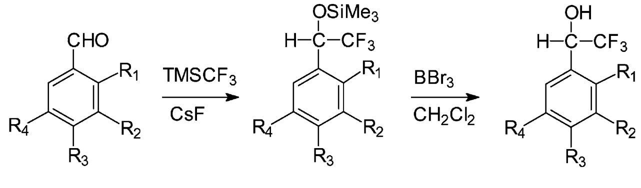
Scheme 1.



1a,b **2a,b** **3a,b**

a, R = Me
b, R = Et

Scheme 2.



4c-g **5c-g** **6c-g**

c, R_1 = OMe; R_2, R_3, R_4 = H
d, R_1 = H; R_2 = OMe; R_3, R_4 = H
e, R_1, R_2, = H; R_3 = OMe; R_4 = H
f, R_1 = H, R_2 = Me; R_3 = OMe; R_4 = H
g, R_1 = H, R_2 = Me; R_3 = OMe; R_4 = Me

Scheme 3.

but the reaction also produced another isomer in trace amounts which required purification. In the present synthesis, the reaction of dialkylamino-anisaldehyde (**1a**, **b**) in monoglyme with $TMSCF_3$ in the presence of a catalytic amount of CsF led to the formation of the corresponding trifluoromethylated silyl ethers (**2a**, **b**) in essentially quantitative yields. Hydrolysis of the silyl ethers with 6N HCl for 2 h furnished the 2,2,2-trifluoro-1-(*N*,*N*-dialkylaminophenyl)ethanols (**3a**, **b**) in 95% isolated yield (Scheme 2). No side products were observed.

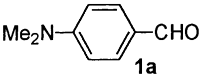
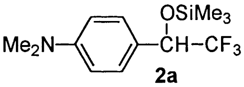
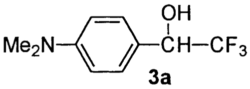
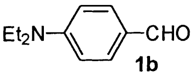
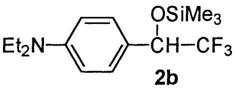
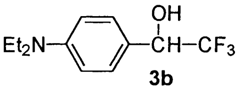
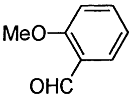
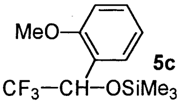
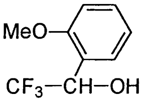
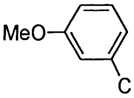
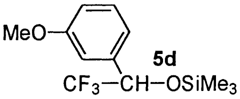
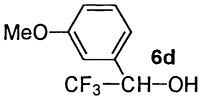
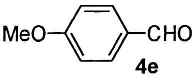
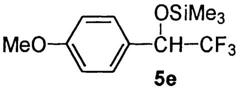
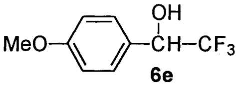
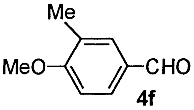
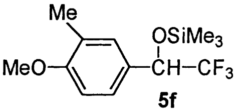
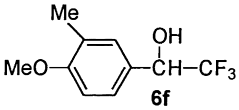
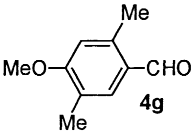
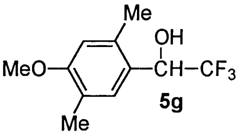
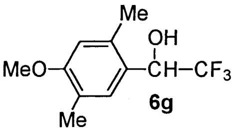
Earlier, the syntheses of 4-methoxy-2,2,2,-trifluoro-1-(hydroxyaryl)ethanol was mentioned [36], but the yield and characterization data of the compounds were not given. In the present work, the reactions of several anisaldehyde derivatives (**4c–g**) with $TMSCF_3$ in the presence of catalytic amounts of CsF were carried out at room temperature in monoglyme. The corresponding trifluoromethylated silyl ethers (**5c–g**) were obtained in almost quantitative yield. Treatment of (**5c–g**) with boron tribromide at −78°C in dichloromethane, followed by hydrolysis, resulted in 2,2,2-trifluoro-1-(hydroxyaryl)ethanols (**6c–g**) in more than 92% isolated yields (Scheme 3, Table 1).

A variety of aromatic aldehydes (**7h–l**, **9m**, **11n**, **o**, **13p**) with variations in substituents and position with respect to the aldehyde functionality were studied (Scheme 4). Bis(2-methoxyethyl)aminosulfur trifluoride was chosen as the fluorinating agent because of its enhanced thermal stability compared to DAST and its analogues. [26,27] As a result, the reaction system could be subjected to 60–80°C as required. The reactions were conducted in CH_2Cl_2 as solvent. In cases where both starting materials were liquids, the reactions were accomplished under neat conditions. However, other hydrocarbon solvents like ethyl ether and diglyme can also be used as alternative solvent systems. The reactions were carried out with 0.7 eqv. excess of bis(2-methoxyethyl)aminosulfur trifluoride. [26,27] The aryldifluoromethane products were obtained as colorless oils. The aldehyde reactants utilized in this study can be broadly classified into two classes, namely those with high to moderate electron donor(s) with their influence on the –CHO functionality and those with electron withdrawing substituents.

A critical analysis of the reaction conditions (Table 2) reveals that an electron donating substituent, such as OMe at the meta-position of the aromatic ring has no influence on the reactivity and consequently 100% conversion of the aldehyde moiety to difluoromethyl is achieved. The same substituent at the *ortho*- or *para*-position reduces the electrophilic character of the –CHO functionality. As a result, the presence of catalyst, such as HF and higher temperatures are necessary to drive such reactions in the required direction. HF could be considered most convenient as it can be generated in situ by adding EtOH. [26,27] In the case of **8h**, even drastic temperatures could not drive the reaction beyond 57% conversion. Reactants **7j** and **7k** that are isomers differing in the position of a –OMe group have comparable reactivity under identical reaction conditions. The electrophilic character of the –CHO moiety is greatly enhanced when an electron withdrawing substituent is present in the aromatic ring. For example, with **11n** and **13p**, the reactions occur in very short periods of time under ambient conditions without any catalyst. Substrate **11o** is intermediate between the extreme cases of substituent influence described. Its reaction with bis(2-methoxyethyl)aminosulfur trifluoride is quite facile and complete conversion is achieved (Scheme 4, Table 2).

In conclusion, a simple procedure for the preparation of 2,2,2-trifluoro-1-(*N*,*N*-dialkylaminophenyl)ethanols, 2,2,2-trifluoro-1-(hydroxyphenyl)ethanols and substituted difluoro toluene using (trifluoromethyl)trimethylsilane and bis(2-methoxyethyl)aminosulfur trifluoride has been described. Yields are good to excellent. The pattern of reactivity of the substituted aldehydes chosen is consistent with a nucleophilic mode of behavior for Deoxofluor^{TM}.

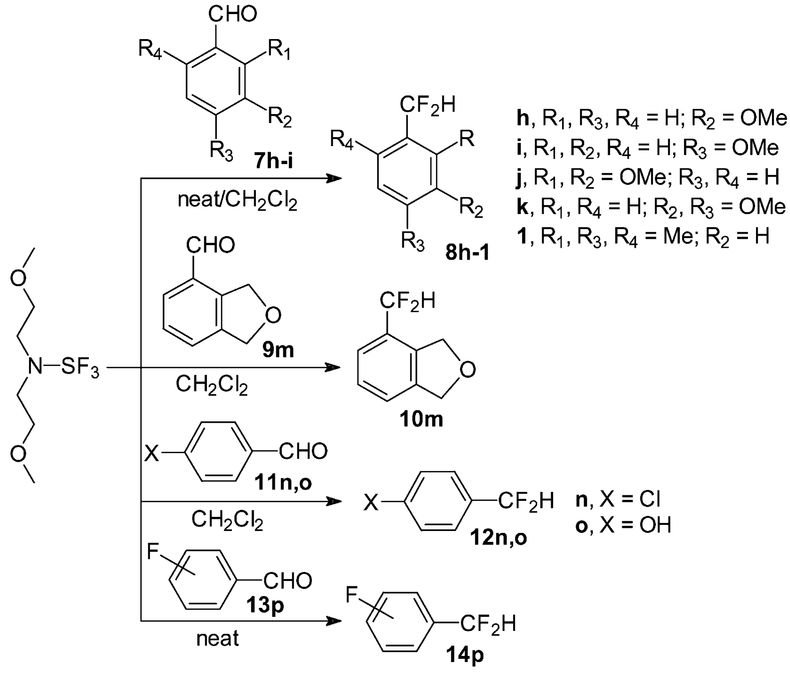
Table 1
Preparation of 2,2,2-trifluoro-1-(*N*,*N*-dialkylaminophenyl)ethanols and 2,2,2-trifluoro-1-(hydroxyaryl)ethanols using (trifluoromethyl)trimethylsilane[a]

Substrate	Intermediate[b]	Product	Yield (%)[c]
 **1a**	 **2a**	 **3a**	95
 **1b**	 **2b**	 **3b**	95
 **4c**	 **5c**	 **6c**	92
 **4d**	 **5d**	 **6d**	94
 **4e**	 **5e**	 **6e**	92
 **4f**	 **5f**	 **6f**	93
 **4g**	 **5g**	 **6g**	92

[a] All the reactions were carried out with 5.0 mmol of substrate, 5.25 mmol of $TMSCF_3$ and 0.1 mmol of CsF in 5.0 ml of monoglyme.

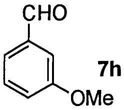
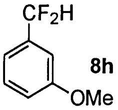
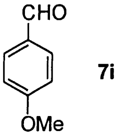
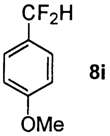
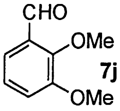
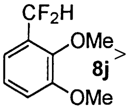
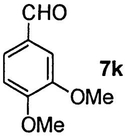
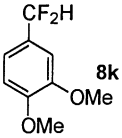
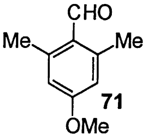
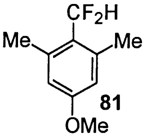
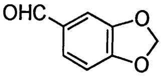
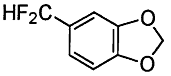
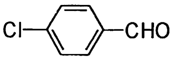
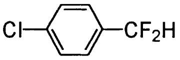
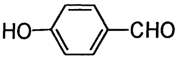
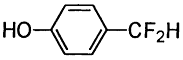
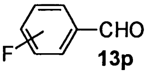
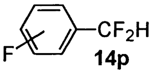
[b] Formed in quantitative yield.

[c] Isolated yield.



Scheme 4.

Table 2
Fluorination of aromatic aldehydes with bis(2-methoxyethyl)aminosulfur trifluoride[a]

Substrate	Reaction conditions	Products	Conversion[b]	Yield[c]
 7h	Neat, RT, 16 h	 8h	100	94
 7i	Neat, 75°C, 18 h	 8i	57	44
 7j	Ch_2Cl_2, 45°C, 16 h	 8j	83	70
 7k	Ch_2Cl_2, 45°C, 16 h	 8k	80	68
 71	Ch_2Cl_2, 45°C, 12 h	 81	90	62
 9m	Ch_2Cl_2, 45°C, 16 h	 10m	80	65
 11n	Ch_2Cl_2, RT, 3 h	 12n	100	90
 11o	Ch_2Cl_2, RT, 8 h	 12o	100	85
 13p	Neat, RT, 8 h	 14p	100	80

[a] All the reactions were carried out with 5 mmol of substrate, 8.5 mmol of bis(2-methoxy-ethyl)aminosulfur trifluoride in 4 ml of dichloromethane.
[b] Based on GC/MS.
[c] Isolated yield.

3. Experimental

3.1. General

All the reactions were performed under a dry nitrogen atmosphere. (Trifluoromethyl)trimethylsilane was prepared by literature procedures [39,40]. Cesium fluoride was placed in an oven at 200°C and repeatedly ground until it remained as a finely divided powder. Once this stage is reached, it may be used in the reactions. Storing in the oven at 200°C retains the compound in its finely divided state indefinitely. The aldehydes were purchased from Aldrich. Deoxofluor^{TM} was obtained from Air Products and Chemicals. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker spectrometer operating at 200, 188, and 50 MHz, respectively. Chemical shifts are reported in ppm relative to the appropriate standard, $CFCl_3$ for ^{19}F and TMS for ^{1}H and ^{13}C NMR spectra. Infrared spectra were recorded as liquid films between KBr discs using a BIO-RAD FT spectrometer. KBr pellets were prepared for solid samples. The melting points were obtained by using a Mel-Temp II apparatus. Electron impact mass spectra and HRMS were measured at 70 eV using a JEOL JMS AX505HF spectrometer.

3.2. General procedure for synthesis of 2,2,2-trifluoro-1-(dialkylaminophenyl)ethanols

The 4-(dialkylamino)benzaldehyde (5 mmol) and $TMSCF_3$ (5.25 mmol) were dissolved in monoglyme (10 ml) and the mixture was cooled with cold water (about

10°C). To the stirred solution, powdered cesium fluoride (0.1 mmol) was added. Heat was generated as the reaction began. After 15 min, the water bath was removed and the reaction mixture was stirred for 3 h. Volatile materials were removed and dry pentane (20 ml) was added. The mixture was filtered under nitrogen and washed. Removal of pentane under reduced pressure gave the trimethylsilyl ether intermediates (**2a**, **b**) in essentially quantitative yields. Hydrolysis of (**2a**, **b**) was carried out with 6N HCl in THF (5 ml) for 2 h at room temperature, and the solution was neutralized with sodium bicarbonate. Products were extracted with ethyl acetate. The ethyl acetate solution was dried over anhydrous $MgSO_4$ and filtered. Removal of solvent furnished the products (**3a**, **b**) which were further purified by crystallization from diethyl ether and pentane mixtures.

*3.3. 2,2,2-Trifluoro-1-(4-N,N-dimethylaminophenyl)trimethylsilyl ether (**2a**)*

Yield: ~100%; mp 54–55°C; IR (KBr pellet): 2950, 1618, 1531, 1359, 1253, 1125, 881 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.10 (s, 9H), 2.95 (s, 6H), 4.81 (q, 1H, $J = 6$ Hz), 6.68 (d, 2H, $J = 8.5$ Hz), 7.28 (d, 2H, $J = 8.5$ Hz); ^{19}F NMR ($CDCl_3$): δ −78.86 (d, $J = 6$ Hz). ^{13}C NMR ($CDCl_3$): $\delta = -0.23$, 40.30, 73.09 (q, $J_{C-C-F} = 13.8$ Hz), 111.77, 122.70, 124.49 (q, $J_{C-F} = 280.2$ Hz), 128.43, 150.91; MS (EI) *m/z* (species, rel. int.): 292 (M^+ +1, 11), 291 (M^+, 38), 222 (M^+ — CF_3, 100); Anal. calcd. for $C_{13}H_{20}F_3ONSi$: C, 53.58; H, 6.92; N, 4.81; Si, 9.61. Found: C, 53.67; H, 6.82; N, 4.83; Si, 9.97%.

*3.4. 2,2,2-Trifluoro-1-(4-N,N-diethylaminophenyl)trimethylsilyl ether (**2b**)*

Yield: ~100%; viscous liquid; IR (KBr disc): 2970, 1614, 1523, 1357, 1263, 1166, 1129, 883 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.13 (s, 9H), 1.19 (t, 3H, $J = 7$ Hz), 3.37 (q, 2H, $J = 7$ Hz), 4.84 (q, 1H, $J = 6.7$ Hz), 6.65 (d, 2H, $J = 8.5$ Hz), 7.26 (d, 2H, $J = 8.5$ Hz); ^{19}F NMR ($CDCl_3$): δ −78.77 (d, $J = 6$ Hz); ^{13}C NMR ($CDCl_3$): δ −0.22, 12.51, 44.25, 73.17 (q, $J_{C-C-F} = 31.7$ Hz), 111.00, 121.54, 124.60 (q, $J_{C-F} = 280.3$ Hz), 128.65, 148.31; MS (EI) *m/z* (species, rel. int.): 319 (M^+, 42), 304 (M^+ — CH_3, 96), 250 (M^+ — CF_3, 100), 73 ($SiMe_3^+$, 15).

*3.5. 2,2,2-Trifluoro-1-(4-N,N-dimethylaminophenyl)ethanol (**3a**)*

Yield: 95%; mp 98–99°C; IR (KBr pellet): 3359 (broad), 2894,1615, 1526, 1448, 1355, 1263, 1166, 1117, 1063, 907, 805 cm^{-1} ^1H NMR ($CDCl_3$): δ 2.54 (b, s, 1H), 2.95 (s, 6H), 4.86 (q, 1H, $J = 6.5$ Hz), 6.71 (d, 2H, $J = 8.6$ Hz), 7.29 (d, 2H, $J = 8.7$ Hz). ^{19}F NMR ($CDCl_3$): δ −78.58 (d, $J = 6.5$ Hz); ^{13}C NMR ($CDCl_3$): δ 40.38, 72.69 (q, $J_{C-C-F} = 31.5$ Hz), 112.31, 124.25 (q, $J_{C-F} = 280.4$ Hz), 128.39, 151.27; MS (EI) *m/z* (species, rel. int.): 219 (M^+, 51), 202 (M^+ — OH, 4), 120 (M^+ — CF_3CHOH, 41), 150 (M^+ — CF_3, 100), 69 (CF_3^+, 14). HRMS: calcd. for $C_{10}H_{12}F_3NO$ (M^+): 219.0871. Found: 219.0879. Anal. calcd. for $C_{10}H_{12}F_3ON$: C, 54.77; H, 5.52; N, 6.39. Found: C, 54.89; H, 5.63; N, 6.35%.

*3.6. 2,2,2-Trifluoro-1-(4-N,N-diethylaminophenyl) ethanol (**3b**)*

Yield: 95%; mp 35–36°C; IR (KBr pellet): 3170 (broad), 2965, 1610, 1513, 1360, 1260, 1166, 880 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.20 (t, 3H, $J = 7$ Hz), 2.50 (b, s, 1H), 3.35 (q, 2H, $J = 7$ Hz), 4.80 (q, 1H, $J = 6.7$ Hz), 6.62 (d, 2H, $J = 8.5$ Hz), 7.27 (d, 2H, $J = 8.5$ Hz). ^{19}F NMR ($CDCl_3$): δ −78.75 (d, $J = 6$ Hz); ^{13}C NMR ($CDCl_3$): δ −12.50, 44.25, 73.18 (q, $J_{C-C-F} = 31.7$ Hz), 111.10, 121.51, 124.62 (q, $J_{C-F} = 280.3$ Hz), 128.60, 148.31; MS (EI) *m/z* (species, rel. int.): 247 (M^+, 40), 230 (M^+ — OH, 3), 232 (M^+ — CF_3, 100), 69 (CF_3^+, 7). HRMS: calcd. for $C_{12}H_{16}F_3NO$ (M^+): 247.2600. Found: 247.2597.

3.7. General procedure for synthesis of 2,2,2-trifluoro-1-(hydroxyphenyl)ethanols

Anisaldehyde or its derivatives (5 mmol) and $TMSCF_3$ (5.25 mmol) were dissolved under dry nitrogen in monoglyme and cooled to about 10°C. Cesium fluoride (0.1 mmol) was added directly. After stirring for 15 min, the cold bath was removed and stirring was continued for 3 h. Volatile materials were removed and the residue obtained was dissolved in dry pentane (20 ml). It was filtered under nitrogen and washed. Removal of pentane gave the trimethylsilyl ether intermediates (**5c–f**) in nearly quantitative yields. These intermediates were further dissolved in dichloromethane and cooled to −78°C. Boron tribromide (15 mmol, 1 M solution in dichloromethane) was added dropwise. The reaction mixture was stirred at −78°C for 15 h. It was quenched with brine solution and stirred for an additional 1 h. The solution was neutralized with sodium bicarbonate and products were extracted with ethyl acetate. Further purification of the products (**6c–f**) was carried out by crystallization with ether and pentane mixtures.

*3.8. 2,2,2-Trifluoro-1-(2-methoxyphenyl)trimethylsilyl ether (**5c**)*

Yield: 99%; viscous liquid; IR (KBr disc): 2965, 1612, 1480, 1455, 1366, 1254, 1170, 1129, 1048, 868 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.12 (s, 9H), 3.80 (s, 3H), 4.85 (q, 1H, $J = 6.5$ Hz), 6.78 (m, 1H), 7.00 (s + d, 2H), 7.24 (d, 1H, $J = 5.5$ Hz); ^{19}F NMR ($CDCl_3$): δ −78.40 (d, $J = 6.5$ Hz); ^{13}C NMR ($CDCl_3$): δ −0.29, 55.10, 73.25 (q, $J_{C-C-F} = 31.8$ Hz), 111.12, 113.50, 119.81, 124.48 (q, $J_{C-F} = 280.4$ Hz), 129.36, 136.92, 159.05; MS (EI) *m/z* (species, rel. int.): 278 (M^+, 20), 209 (M^+ — CF_3, 100), 73 ($SiMe_3^+$, 14).

*3.9. 2,2,2-Trifluoro-1-(3-methoxyphenyl)trimethylsilyl ether (**5d**)*

Yield: 99%; viscous liquid; IR (KBr disc): 2960, 1604, 1490, 1457, 1367, 1257, 1171, 1130, 1047, 879 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.13 (s, 9H), 3.80 (s, 3H), 4.90 (q, 1H, $J = 6.5$ Hz), 6.95 (m, 1H), 7.00 (s + d, 2H), 7.25 (d, 1H, $J = 5.8$ Hz); ^{19}F NMR ($CDCl_3$): δ −78.55 (d, $J = 6.5$ Hz); ^{13}C NMR ($CDCl_3$): δ −0.38, 55.13, 73.15 (q, $J_{C-C-F} = 31.9$ Hz), 113.12, 114.51, 119.91, 124.50 (q, $J_{C-F} = 280.2$ Hz), 129.24, 136.95, 159.56; MS (EI) *m/z* (species, rel. int.): 278 (M^+, 24), 209 (M^+ — CF_3, 100), 73 ($SiMe_3^+$, 23).

*3.10. 2,2,2-Trifluoro-1-(4-methoxyphenyl)trimethylsilyl ether (**5e**)*

Yield: 100%; viscous liquid; IR (KBr disc): 2960, 1614, 1514, 1463, 1365, 1254, 1168, 1130, 1033, 879, 845 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.12 (s, 9H), 3.69 (s, 3H), 4.86 (q, 1H, $J = 6.5$ Hz), 6.89 (d, 2H, $J = 8.7$ Hz), 7.37 (d, 2H, $J = 8.7$ Hz); ^{19}F NMR ($CDCl_3$): δ −78.95 (d, $J = 6.5$ Hz); ^{13}C NMR ($CDCl_3$): δ −0.34, 55.13, 72.89 (q, $J_{C-C-F} = 31.9$ Hz), 113.68, 124.53 (q, $J_{C-F} = 28.0$ Hz), 127.54, 128.81, 160.21; MS (EI) *m/z* (species, rel. int.): 278 (M^+, 24), 209 (M^+ — CF_3, 100), 73 ($SiMe_3^+$, 23). Anal. calcd. for $C_{12}H_{17}F_3O_2Si$: C, 51.78; H, 6.16; Si, 10.06. Found: C, 51.58; H, 6.20; Si, 9.87%.

*3.11. 2,2,2-Trifluoro-1-(3-methyl-4-methoxyphenyl)trimethylsilyl ether (**5f**)*

Yield: 99%; viscous liquid; IR (KBr disc): 2959, 1614, 1506, 1254, 1170, 1132, 1035, 881, 843 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.10 (s, 9H), 2.22 (s, 3H), 3.81 (s, 3H), 4.90 (q, 1H, $J = 6.5$ Hz), 6.80 (d, 1H, 8.0 Hz), 7.20 (s, 1H), 7.24 (d, 1H, $J = 8.0$ Hz);^{19}F NMR ($CDCl_3$): δ −78.80 (d, $J = 6.0$ Hz); ^{13}C NMR ($CDCl_3$): δ −0.29, 16.22, 55.20, 72.93 (q, $J_{C-C-F} = 31.8$ Hz), 109.4, 113.12, 124.480 (q, $J_{C-F} = 280.7$ Hz), 126.15, 126.50, 126.93, 129.72, 158.28; MS (EI) *m/z* (species, rel. int.): 292 (M^+, 10), 223 (M^+ — CF_3, 100), 73 ($SiMe_3^+$, 8).

*3.12. 2,2,2-Trifluoro-1-(2,5-dimethyl-4-methoxyphenyl)trimethylsilyl ether (**5g**)*

Yield: 99%; viscous liquid; IR (KBr disc): 3200 (broad), 2960, 1607, 1512, 1260, 1168, 1038, 885 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.12 (s, 9H), 2.21 (s, 3H), 2.35 (s, 3H), 3.82 (s, 3H), 5.12 (q, 1H, $J = 6.5$ Hz), 6.59 (s, 1H), 7.35 (s, 1H); ^{19}F NMR ($CDCl_3$): δ −78.37 (d, $J = 6.5$ Hz); ^{13}C NMR ($CDCl_3$): δ −0.13, 16.35, 19.69, 55.54, 69.66 (q, $J_{C-C-F} = 31.0$ Hz), 111,90, 124.50, (q, $J_{C-F} = 281.0$ Hz), 124.68, 125.10, 130.76, 134.56, 158.55; MS (EI) *m/z* (species, rel. int.): 306 (*M*, 29), 237 (M^+ — CF_3, 100), 217 (M^+ — $OSiMe_3$, 10), 73 ($SiMe_3^+$, 6).

*3.13. 2,2,2-Trifluoro-1-(2-hydroxyphenyl)ethanol (**6c**)*

Yield: 92%; mp 111–112°C; IR (KBr pellet): 3336 (br), 1597, 1492, 1458, 1355, 1245, 1169, 1130, 1049, 873 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.76 (b, s, 2H), 5.16 (q, 1H, $J = 6.5$ Hz), 6.91 (m, 2H), 7.21 (m, 2H); ^{19}F NMR ($CDCl_3$): δ −78.68 (d, $J = 6.5$ Hz). ^{13}C NMR ($CDCl_3$): δ −0.34, 55.13, 72.89 (q, $J_{C-C-F} = 31.9$ Hz), 113.68, 124.53 (q, $J_{C-F} = 28.0$ Hz) 127.54, 128.81, 160.21; MS (EI) *m/z* (species, rel. int.): 192 (M^+, 48), 123 (M^+ — CF_3, 80), 95 (M^+ — CF_3CO, 100); Anal. calcd. for $C_8H_7F_3O_2$: C, 49.99; H, 3.67. Found: C, 50.24; H, 3.75%.

*3.14. 2,2,2-Trifluoro-1-(3-hydroxyphenyl)ethanol (**6d**)*

Yield: 94%; mp 103–104°C; IR (KBr pellet): 3192 (broad), 1593, 1483, 1352, 1263, 1166, 1078, 1128, 937 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.58 (b, s, 1H), 2.52 (b, s, 1H), 4.96 (q, 1H, $J = 6.6$ Hz), 6.87 (m, 1H), 7.02 (s + d, 2H), 7.26 (d, 1H, $J = 5.6$ Hz); ^{19}F NMR ($CDCl_3$): δ −78.46 (d, $J = 6.6$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ −0.34, 55.13, 72.89 (q, $J_{C-C-F} = 31.9$ Hz), 113.68, 124.53 (q, $J_{C-F} = 28.0$ Hz), 127.54, 128.81, 160.21; MS (EI) *m/z* (species, rel. int.): 192 (M^+, 49), 123 (M^+ — CF_3, 89), 95 (M^+ — CF_3CO, 100). HRMS: calcd. for $C_8H_7F_3O_2$ (M^+): 192.0398. Found: 192.0408.

*3.15. 2,2,2-Trifluoro-1-(4-hydroxyphenyl)ethanol (**6e**)*

Yield: 92%; colorless crystals; mp 125–126°C; IR (KBr pellet): 3200 (broad), 1601, 1510, 1443, 1244, 1160, 1126, 1066, 817 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.20 (b, s, 1H), 2.76 (b, s, 1H), 3.69 (s, 3H), 4.94 (q, 1H, $J = 6.6$ Hz), 6.84 (d, 2H, $J = 8.3$ Hz), 7.33 (d, 2H, $J = 8.7$ Hz). ^{19}F NMR ($CDCl_3$): δ −78.80 (d, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$): δ −0.34, 55.13, 72.89 (q, $J_{C-C-F} = 31.9$ Hz), 113.68, 124.53 (q, $J_{C-F} = 28.0$ Hz) 127.54, 128.81, 160.21; MS (EI) *m/z* (species, rel. int.): 192 (M^+, 30), 123 (M^+ — CF_3, 100), 69(CF_3^+, 2). HRMS: calcd. for $C_8H_7F_3O_2$ (M^+): 192.0398. Found: 192.0804.

*3.16. 2,2,2-Trifluoro-1-(3-methyl-4-hydroxyphenyl) ethanol (**6f**)*

Yield: 93%; mp 107–108°C; IR (KBr pellet): 3205 (broad), 1611, 1508, 1440, 1248, 1155, 1129, 1061, 815 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.40 (b, s, 1H), 3.69 (s, 3H), 4.94 (q, 1H, $J = 6.7$ Hz), 5.12 (b, s, 1H), 6.74 (d, 1H, $J = 8.1$ Hz), 7.16 (d, 1H, $J = 8.1$ Hz), 7.23 (s, 1H); ^{19}F NMR ($CDCl_3$): δ −78.68 (d, $J = 6.7$ Hz); ^{13}C NMR ($CDCl_3$): δ 15.70, 72.52, (q, $J_{C-C-F} = 31.20$, Hz), 114.98, 124.17, 124.50 (q, $J_{C-F} = 280.5$ Hz), 124.70, 126.41, 130.16, 154.77; MS (EI) *m/z* (species, rel. int.): 206 (M^+, 56), 137 (M^+ — CF_3, 100), 69 (CF_3^+, 2); Anal. calcd. for $C_9H_9F_3O_2$: C, 52.41; H, 4.40. Found: C, 52.17; H, 4.30%.

*3.17. 2,2,2-Trifluoro-1-(2,5-dimethyl-4-hydroxyphenyl)ethanol (**6g**)*

Yield: 92%; mp 114–115°C; IR (KBr pellet): 3200 (broad), 2964, 1612, 1510, 1255, 1165, 1035, 888 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.19 (s, 3H), 2.24 (s, 3H), 3.26 (b, s, 2H), 3.82 (s, 3H), 5.17 (q, 1H, $J = 6.6$ Hz), 6.56 (s, 1H), 7.29 (s, 1H); ^{19}F NMR ($CDCl_3$): δ −78.13 (d, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$): δ 15.64, 19.13, 68.89, (q, $J_{\mathrm{C-C-F}} = 31.5$ Hz), 117.11, 122.11, 124.92, 129.93, 136.03, 154.65; MS (EI) *m/z* (species, rel. int.): 220 (M^+, 19), 151 (M^+ — CF_3, 100), 69 (CF_3^+, 9); Anal. calcd. for $C_{10}H_{11}F_3O_2$: C, 54.53; H, 5.05. Found: C, 54.77; H, 5.07%.

3.18. General procedure for difluoromethylation of substituted aromatic aldehydes

A solution of aromatic aldehyde (5 mmol) in dichloromethane (2 ml) was reacted with a solution of of Deoxofluor$^{\mathrm{TM}}$ (1.88 g, 8.5 mmol) in dichloromethane (2 ml). Ethanol (46 mg, 1 mmol) was added, and the reaction was monitored by GC/MS. On completion, the reaction was worked up by slow addition of sodium bicarbonate solution followed by washing with water. The pure product was isolated by flash chromatography on silica gel in hexane/ether mixture.

*3.19. 2-Methoxy-difluorotoluene (**8h**)*

Yield: 94%; liquid; IR (KBr disc): 2964, 2841, 1492, 1461, 1372, 1269, 1195, 1170, 1039, 861, 760, 695, 663 cm^{-1}; ^{1}H NMR δ 7.37–7.33 (m, 1H), 7.08–6.98 (m, 3H), 6.60 (t, 1H, $J = 57.2$ Hz), 3.82 (s, 3H); ^{19}F NMR δ −110.8 (d, $J = 57.4$ Hz); ^{13}C NMR δ 159.8, 135.7, 129.8, 117.9, 116.6, 114.6 (t, $J = 237.5$ Hz), 110.5, 55.3; MS (EI) *m/z* (species, rel. int.): 158 (M^+, 100), 143 (M^+ — F, 10), 127 (M^+ — OMe, 80), 51 (CHF_2, 20); HRMS: calcd. for $C_8H_8F_2O$ (M^+): 158.0543. Found: 158.0535.

*3.20. 1,2-Dimethoxy difluorotoluene (**8j**)*

Yield: 70%; liquid; IR (KBr disc): 2944, 2841, 1488, 1376, 1275, 1230, 1045, 1027, 911, 791, 758, 653 cm^{-1}; ^{1}H NMR δ 7.19–7.15 (m, 2H), 7.01–6.99 (m, 1H), 6.92 (t, 1H, $J = 55.8$ Hz), 3.86 (s, 6H); ^{19}F NMR δ −114.1 (d, $J = 55.3$ Hz); ^{13}C NMR δ 152.6, 147.4, 128.2, 124.4, 117.4, 114.6 (t, $J = 236.5$ Hz), 113.5, 55.8; MS (EI) *m/z* (species, rel. int.) 188 (M^+, 100), 173 (M^+ — Me, 65), 169 (M^+— F, 10), 51 (CHF_2, 30); HRMS: calcd. for $C_9H_{10}F_2O_2$ (M^+): 188.0649. Found: 188.0639.

*3.21. 3,4-Dimethoxy difluorotoluene (**8k**)*

Yield: 68%; liquid; IR (KBr disc): 2966, 2841, 1519, 1462, 1392, 1266, 1244, 1197, 1022, 927, 860, 788, 646 cm^{-1}; ^{1}H NMR δ 7.03–7.01 (m, 2H), 6.88–6.86 (m, 1H), 6.59 (t, 1H, $J = 56.7$ Hz), 3.88 (s, 6H); ^{19}F NMR δ −108.2 (d, $J = 56.9$ Hz); ^{13}C NMR δ 150.9, 149.3, 126.9, 118.8, 116.8 (t, $J = 237.4$ Hz), 110.6, 108.0, 56.0, 55.9; MS (EI) *m/z* (species, rel. int.): 188 (M^+, 100), 173 (M^+ — Me, 70), 169 (M^+ — F, 15), 51 (CHF_2, 65); HRMS: calcd for $C_9H_{10}F_2O_2$ (M^+): 188.0649. Found: 188.0658.

*3.22. 1,1′-Dimethyl-4-methoxy difluorotoluene (**8l**)*

Yield: 62%; liquid; IR (KBr disc): 2963, 2837, 1512, 1463, 1317, 1265, 1113, 1072, 1007, 896, 848, 785, 692, 619 cm^{-1}, ^{1}H NMR δ 7.24 (s, 1H), 6.69 (t, 1H, $J = 55.3$ Hz), 6.65 (s, 1H), 3.84 (s, 3H) 2.40 (s, 3H), 2.20 (s, 3H); ^{19}F NMR δ −110.5 (d, $J = 55.7$ Hz); ^{13}C NMR δ 159.1, 135.3, 128.2, 124.1, 123.9, 114.8 (t, $J = 234.9$ Hz), 57.3, 18.4, 15.7; MS (EI) *m/z* (species, rel. int.): 186 (M^+, 100), 171 (M^+ — Me, 35), 167 (M^+ — F, 15), 51 (CHF_2, 20); HRMS: calcd for $C_{10}H_{12}F_2O$ (M^+): 186.0856. Found: 186.0852.

*3.23. 3,4-Methylenedioxy difluorotoluene (**10m**)*

Yield: 65%; liquid; IR (KBr disc): 2981, 2907, 1502, 1452, 1408, 1352, 1251, 1105, 1040, 931, 813, 869, 792, 632 cm^{-1}; ^{1}H NMR δ 6.96–6.93 (m, 2H), 6.82–6.80 (m, 1H), 6.51 (t, 1H, $J = 56.1$ Hz), 5.98 (s, 2H); ^{19}F NMR δ −108.1 (d, $J = 55.9$ Hz); ^{13}C NMR δ 149.6, 148.0, 128.3, 120.1, 114.6 (t, $J = 238.1$ Hz), 108.2, 105.8, 101.6; MS (EI) *m/z* (species, rel. int.): 172 (M^+, 100), 153 (M^+ — F, 25), 51 (CHF_2, 35); HRMS: calcd. for $C_8H_6F_2O_2$ (M^+): 172.0336. Found: 172.0337.

Acknowledgements

This work was supported by the National Science Foundation (Grant no. CHE-9720365) and donors of the American Chemical Society Petroleum Research Fund. We are grateful to Dr. G.S. Lal (Air Products and Chemicals) for a generous supply of Deoxofluor$^{\mathrm{TM}}$ reagent. We thank Dr. G. Knerr for obtaining high resolution mass spectra and Dr. Alex Blumenfeld for NMR measurements.

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