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Nucleophilic fluorination of amino alcohols and diols using Deoxofluor

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Dedicated to Prof. D.W.A. Sharp in recognition of his contribution to J. Fluorine Chemistry

Abstract

Various fluorinated chiral compounds were synthesized using bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor) as a nucleophilic fluorinating reagent. Reactions of Deoxofluor (**1**) with amino alcohols (**2a–d**) and diols (**2e–g**) in methylene chloride at room temperature led to the formation of the corresponding fluoro derivatives (**3a–g**) in good yields.

Keywords: Amino alcohols; Diols; Chiral fluorinated compounds; Nucleophilic fluorination; Bis(2-methoxyethyl)aminosulfur trifluoride

1. Introduction

Synthetic and structural aspects of organofluorine compounds derived directly from non-fluorinated precursors by using electrophilic and/or nucleophilic fluorinating agents have been the focal points of vigorous research as evidenced by the appearance of a large number of publications [1]. The incorporation of a fluorine atom or a fluorine-containing group into organic molecules alters their physical, chemical and biological properties dramatically making them suitable for diverse applications in material sciences, and agrochemistry, as well as in the pharmaceutical industry (for the general applications of organofluorine compounds see [2], for the use of organofluorine compounds in medicinal and biomedical chemistry see [3], for the use of organofluorine compounds in agrosciences see [4], the ability of fluorine to change the properties of organic molecules has been discussed extensively elsewhere, for example, see [5]). The syntheses of chiral fluorinated compounds play a very important role in the development of medicines due to the influence of the unique properties of fluorine [3]. While a wide variety of methods have been developed for introducing one or more fluorine atoms into organic compounds (for general discussion on the synthesis of organofluorine compounds see [6]), the use of bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor) as a nucleophilic fluorinating reagent is gaining in popularity [7–9].

In general, Deoxofluor appears to be a somewhat more effective fluorinating reagent than either diethylaminosulfur trifluoride (DAST) or sulfur tetrafluoride [7–9]. The higher thermal stability of Deoxofluor especially makes its applicability much wider ranging. The greater reactivity of Deoxofluor with some of the substrates, such as β-diketones, has been also observed recently [9a]. In our continuing efforts to introduce fluorine into organic compounds nucleophilically, we now have extended the scope of Deoxofluor to prepare various fluorinated chiral compounds directly from their non-fluorinated chiral precursors. The details of this chemistry are described in the following sections.

2. Results and discussions

Deoxofluor is a very useful reagent [7–9] for introducing one or more fluorine atoms into organic molecules in a single step reaction. During the course of our research in the area of nucleophilic perfluoroalkylation [10], it was realized that the use of Deoxofluor with chiral precursors could provide a straightforward route to the corresponding fluorinated chiral compounds.

In this work, the reactions of Deoxofluor (**1**) with acyclic amino alcohols (**2a**, **b**) were carried out in methylene chloride between 0 and 25 °C in 1.2:1 molar ratio, respectively. The reactions were monitored by GC/MS. After 15 h, the reaction was quenched with sodium bicarbonate and after work up (see Section 3), the fluorinated products (**3a**, **b**) were obtained in >70% isolated yield. The reactions were

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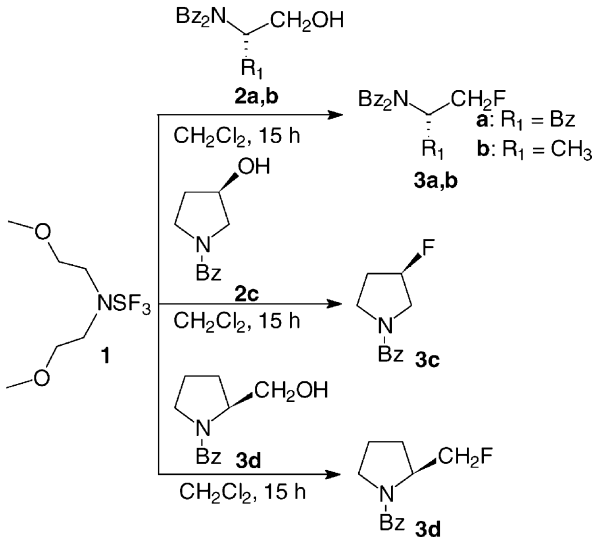
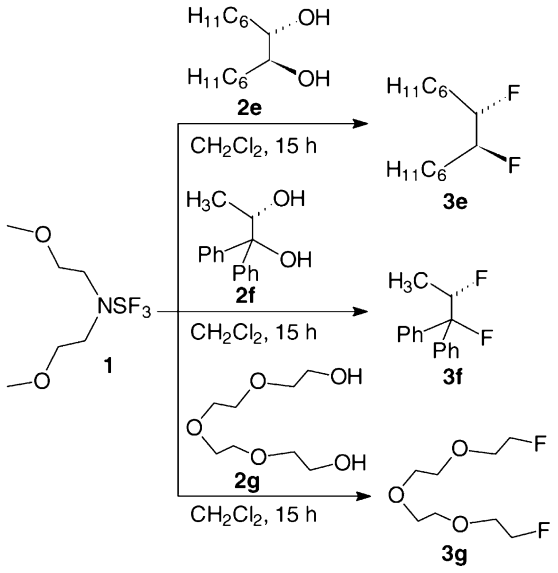


Scheme 1.



Scheme 2.

found to be very clean but flash chromatography was needed to purify the products from bis(2-methoxyethyl)amine which was formed upon hydrolysis of Deoxofluor. When DAST was reacted with **2a**, the product **3a** was obtained in 45% isolated yield after 24 h reaction time. Reactions proceeded smoothly with cyclic amino alcohols (**2c**, **d**) also and the final products (**3c**, **d**) were obtained in >70% isolated yield (Scheme 1, Table 1).

Optical rotation measurements indicated that the products are chiral and no racemization occurred during the reaction as checked by NMR using chiral shift reagent. The above reactions were found to show complete conversion of the starting materials when heated to 40 °C for 8 h, but concomitant decomposition and racemization of the products occurred. Therefore, lower temperatures and longer reaction times are necessary to obtain the pure chiral amino compounds.

Next, the reactions of Deoxofluor (**1**) with chiral (**2e**, **f**) and non-chiral (**2g**) diols were carried out between 0 and 25 °C in methylene chloride in 2.2:1 molar ratio, respectively. The reactions were monitored by GC/MS. After 5 h about 20–30% of starting materials were found to remain. Continuing the reaction with stirring for 12 h allowed complete conversion of the starting materials. Heating was avoided in all of the reactions in order to preclude any decomposition and racemization as was observed in the case of amino alcohols reactions. After quenching the reaction with sodium bicarbonate solution, products were extracted into methylene chloride, dried over anhydrous magnesium sulfate, and filtered. Removal of solvent gave the fluorinated products (**3e**–**g**) which were purified by flash chromatography (Scheme 2, Table 1).

In conclusion, this is a simple procedure for the preparation of various fluorinated chiral compounds using bis(2−methoxyethyl)aminosulfur trifluoride as a nucleophilic fluorinating reagent under mild reaction conditions and in good yields.

3. Experimental

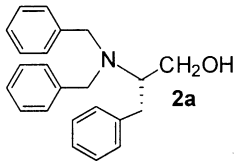
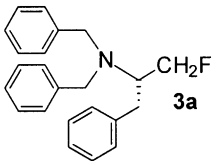
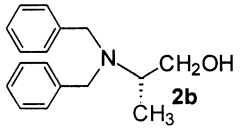
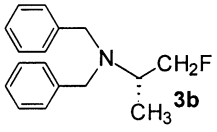
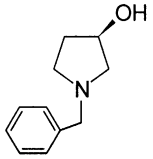
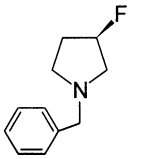
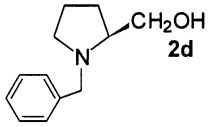
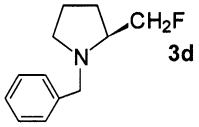
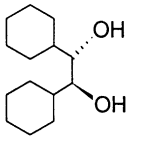
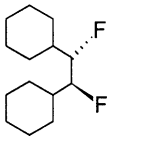
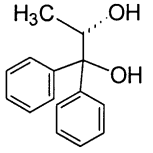
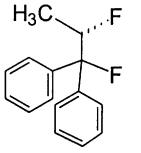
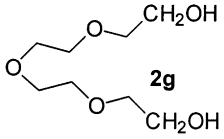
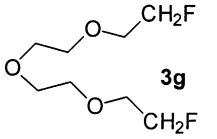
3.1. General

The amino alcohols (**2a**–**d**), diols (**2f**, **g**), and Deoxofluor (**1**) were purchased from Aldrich and used as received. Dicyclohexylethanediol (**2e**) was a gift from Prof. Donald S. Matteson at Washington State University. ^{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 and GC/MS on a Shimadzu GC/MS-QP5050 spectrometer. Optical rotations were measured in methylene chloride on a JASCO DIP-181 digital polarimeter.

3.2. General procedure for the reaction of amino alcohols and diols with Deoxofluor

To a stirred solution of amino alcohols or diols (4 mmol) in dichloromethane (4 ml) at 0 °C, Deoxofluor (4.2 mmol for amino alcohols and 8.2 mmol for diols) was added dropwise as a neat liquid. After 1 min, the cold bath was removed and reaction mixture was stirred at room temperature for 15 h. The progress of the reaction was monitored by GC/MS. On completion, the reaction was worked up by slowly adding sodium bicarbonate solution followed by washing with water. The pure product was isolated by flash

Table 1
Fluorination of diols and amino alcohols with Deoxofluor[a]

Substrate	Product	Yield[b]
 **2a**	 **3a**	78
 **2b**	 **3b**	74
 **2c**	 **3c**	82
 **2d**	 **3d**	50
 **2e**	 **3e**	80
 **2f**	 **3f**	72
 **2g**	 **3g**	91

[a] All of the reactions were carried out with 4 mmol of substrate, 4.2 mmol of Deoxofluor (in case of amino alcohols) (8.2 mmol of Deoxofluor in case of diols) in 10 ml of dichloromethane.
[b] Isolated yield.

chromatography on silica gel in pentane/dichloromethane mixture.

3.3. *3a*

Yield: 78%; viscous liquid; $[\alpha]Hg_{23}^{546} = -45°$ ($c = 1.0$, CH_2Cl_2); IR (KBr film): 2980, 1610, 1492, 1452, 1365, 1123, 1028, 1002, 742 cm^{-1}; ^1H NMR δ 2.74–3.50 (m, 2H), 3.75 (s, 4H), 3.84 (d, 2H, $J = 13.3$ Hz), 4.52 (m, 1H), 7.02–7.29 (m, 15H); ^{19}F NMR δ −226.68 (triplet of doublets, 1F, $J = 48$ Hz, 25.4 Hz); MS (EI) *m/z* (species, rel. int.): 334 ($M^+ + H$, 43), 244 [$M^+ - (C_6H_5C)$, 53], 242 ($M^+ - C_6H_5CH_2$, 10), 152 ($C_6H_5CH_2NCH_2CH_2F^+$, 30), 91 ($C_6H_5CH_2^+$, 100). Anal. Calcd. for $C_{23}H_{24}FN$: C, 82.85; H, 7.25. Found: C, 83.50; H, 7.53.

3.4. *3b*

Yield: 74%; viscous liquid; $[\alpha]Hg_{23}^{546} = -2°$ ($c = 1.1$, CH_2Cl_2); IR (KBr film): 2979, 1601, 1492, 1450, 1375, 1249, 1124, 1053, 1027, 978, 916, 829, 699 cm^{-1}; ^1H NMR δ 1.21 (ABX pattern, 3H, $J = 23.8$ Hz, 6.2 Hz), 2.61 (m, 2H), 3.63 (s, 4H), 4.79 (m, 1H), 7.17–7.36 (m, 10H). ^{19}F NMR δ −175.02 (m, 1F); ^{13}C NMR δ 19.7 (d, $J = 22.5$), 58.8 (d, $J = 22.5$ Hz), 59.6, 9.4 (d, $J = 165$ Hz), 127.6, 128.3, 128.7, 129.3, 140.0; MS (EI) *m/z* (species, rel. int.): 257 (M^+, 2), 256 ($M^+ - H$, 5), 238 ($M^+ - F$, 1], 180 ($M^+ - C_6H_5$, 6), 91 ($C_6H_5CH_2^+$, 100). Anal. Calcd. for $C_{17}H_{20}FN$: C, 79.34; H, 7.83. Found: C, 80.42; H, 8.19.

3.5. *3c*

Yield: 82%; viscous liquid; $[\alpha]Hg_{23}^{546} = -23.5$ ($c = 1.4$, CH_2Cl_2); IR (KBr film) 2962, 1490, 1448, 1379, 1251, 1128, 1082, 983, 741, 699 cm^{-1}; ^1H NMR δ 2.02 (m, 2H), 2.41 (m, 1H), 2.65 (m, 3H), 3.64 (AB pattern, 2H, $J = 16.5$ Hz, $J = 12.8$ Hz), 5.02 (m, 1H), 7.20–7.31 (m, 5H); ^{19}F NMR δ −168.54 (doublet of quartets, 1F, $J = 56$ Hz, $J = 28$ Hz); ^{13}C NMR δ 33.23 (d, $J = 21.7$ Hz), 52.6, 60.5, 60.90 (d, $J = 23.2$ Hz), 93.9 (d, $J = 174$ Hz), 127.5, 128.7, 129.2, 139.1; (MS (EI) *m/z* (species, rel. int.): 180 ($M^+ + H$, 100), 179 (M^+, 16), 178 ($M^+ - H$, 57), 160 ($M^+ - F$, 12), 159 ($M^+ - HF$, 42), 102 ($M^+ - C_6H_5$, 35), 91 ($C_6H_5CH_2^+$, 18).

3.6. *3d*

Yield: 50%; viscous liquid; $[\alpha]Hg_{23}^{546} = -12.5°$ ($c = 1.0$, CH_2Cl_2); IR (KBr film 2960, 1603, 1494, 1453, 1376, 1349, 1156, 1156, 1107, 970, 739 cm^{-1}; ^1H NMR δ 1.50–1.90 (m, 4H), 2.70–2.91 (m, 2H), 4.14–4.40 (m, 2H), 4.66 (m, 1H), 5.23 9s, 2H), 7.19–7.29 (m, 5H); ^{19}F NMR δ −221.40 (triplet of doublets, 1F, $J = 40$ Hz, 14 Hz); MS (EI) *m/z* (species, rel. int.): 194 ($M^+ + H$, 100), 193 (M^+, 29), 174 ($M^+ - F$, 12), 173 ($M^+ - HF$, 26), 116 ($M^+ - C_6H_5$, 31), 102 ($M^+ - C_6H_5CH_2$, 7), 91 ($C_6H_5CH_2^+$, 17).

3.7. *3e*

Yield: 80%; viscous liquid; $[\alpha]Hg_{23}^{546} = -88°$ ($c = 1.5$, CH_2Cl_2); IR (KBr film) 2983, 1604, 1494, 1451, 1380, 1320, 1263, 1165, 1049, 981, 917, 758, 697 cm^{-1}; ^1H NMR δ 0.93–1.89 (m, 22H), 3.32 (m, 2H); ^{19}F NMR δ −152.80 (m, 2F); MS (EI) *m/z* (species, rel. int.): 230 (M^+, 1), 191 ($M^+ - HF_2$, 5), 190 ($M^+ - 2HF$, 5), 126 [$M^+ - C_6H_{11} + HF + H$), 11]; 95 ($C_6H_{11}C^+$, 100), 83 ($C_6H_{11}^+$, 56). Anal. Calcd. for $C_{14}H_{24}F_2$: C, 73.00; H, 10.50. Found: C, 74.36; H, 11.47.

3.8. 3f

Yield: 72%; viscous liquid; $[\alpha]Hg_{23}^{546} = -58.7°$ ($c = 1.7$, CH_2Cl_2); IR (film): 2983, 1604, 1494, 1541, 1380, 1320, 1263, 1165, 1049, 981, 917, 758, cm^{-1}; ^1H NMR δ 1.53 (d, 3H, $J = 4.8$ Hz), 3.55 (m, 1H), 7.10–7.41 (m, 10H); ^{19}F NMR δ −100.82 (ABX pattern, 1F, $J = 242$ Hz), −101.97 (ABX pattern, 1F, $J = 242$ Hz); MS (EI) *m/z* (species, rel. int.): 232 (M^+, 1), 213 ($M^+ - F$, 17), 212 ($M^+ - HF$, 100), 197 [$M^+ - (HF + CH_3)$, 82], 196 [$M^+ - (CH_3 + HF + H)$, 92], 165 [$M^+ - (CH_3CHF + HF)$, 28], 77 ($C_6H_5^+$, 10). Anal. Calcd. for $C_{15}H_{14}F_2$: C, 77.57; H, 6.08. Found: C, 79.13; H, 6.78.

3.9. 3g

Yield: 91%; dense liquid; IR (KBr film): 2952, 1458, 1351, 1296, 1247, 1118, 1047, 943, 873 cm^{-1}; ^1H NMR δ 1.21 (m, 10H), 3.68 (t, 2H, $J = 4.2$ Hz), 4.36 (t, 2H, $J = 4.2$ Hz), 4.52 (t, 2H, $J = 4.2$ Hz); ^{19}F NMR δ −223.21 (m, 2F); MS (EI) *m/z* (species, rel. int.): 199 ($M^+ + H$, 1), 165 [$M^+ - CH_2F$, 1), 135 ($M^+ - OCH_2$- CH_2F, 11), 91 ($CH_2CH_2OCH_2CH_2F^+$, 11), 90 ($CHCH_2OCH_2CH_2F^+$, 11), 77 ($CH_2OCH_2CH_2F^+$, 4), 45 (OCH_2- $CH_2^+ + H$, 100).

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