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Fluorous dimethylthiocarbamate (^{F}DMTC) protecting groups for alcohols

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Abstract—*N*,*N*-Bis(perfluoroalkyl)thiocarbamoyl chlorides (^{F}DMTC-Cls) were synthesized as reagent for the protection of alcohols. Using the crystalline ^{F}DMTC-Cls, the ^{F}DMTC groups were introduced into the alcohol molecules in excellent yields in the presence of sodium hydride in THF at room temperature. The products were separated from the excess alcohols by solid-phase extraction with a fluorous reverse-phase silica gel column (Fluorous Solid Phase Extraction; FSPE). The ^{F}DMTC groups were readily removed by oxidation with *m*-chloroperbenzoic acid (*m*-CPBA) and subsequent hydrolysis with $KHCO_3$.

Fluorous compounds that bear one, two, or three perfluoroalkylchains are easily separated from organic compounds by liquid–liquid extraction using a fluorous solvent or solid-phase extraction with a fluorous reverse-phase silica gel column.[1] In order to apply the technologies to total, parallel and combinatorial synthesis of complex molecules, various fluorous protecting groups such as Cbz,[2] Boc,[3] *t*-Bu,[4] Bn,[5] THP,[6] Msc,[7] acyl-type,[8] silyl-type,[9] alkoxyethyl ether,[10] and Troc[11] have been synthesized so far, and some of them are commercially available. Utilizing these protecting groups, natural products including oligosaccharides, oligonucleotides and peptides have successfully been synthesized.[2b,8,12] Recently, we have also reported an expeditious synthesis of bistratamide H using a new 'highly' fluorous amino protecting group, tris(perfluorodecyl)silylethoxycarbonyl (^{F}Teoc) group.[13] The synthetic intermediates were easily isolated by liquid–liquid extraction with FC-72.[14] Optimization of the reaction conditions was carried out as usual by monitoring the reactions with TLC. In addition, the ^{F}Teoc group was demonstrated to be recyclable.

Protection of a functional group with protecting groups is inevitable to synthesize a complicated molecule,[15] so finding a more convenient and efficient protecting group is still a challenging target. Recently, Falck's group has proposed an *N*,*N*-dimethylthiocarbamate (DMTC) group as a useful protecting group for alcohols.[16] The DMTC group is moderately to highly stable under a wide range of reaction conditions, including metal hydrides, hydroboration, ylides, base, acid, organolithiums, Grignards, DDQ, PCC, Swern, *n*-Bu_4NF, $CrCl_2$, heat, and Lewis acids. The protecting group is selectively removed with $NaIO_4$ or H_2O_2 without damaging other common protecting groups. Accordingly, we synthesized fluorous DMTC-Cl and used it for the protection of various alcohols. Fluorous protecting reagents, bis(perfluoroalkyl)thiocarbamoyl chlorides (**6a**–**d**; ^{F}DMTC-Cl), were prepared by the route shown in Scheme 1. Four kinds of ^{F}DMTC groups in which the length of the perfluoroalkyl chain differed were synthesized in order to apply them for a fluorous mixture synthesis as well.[17] In these compounds, a three-carbon spacer between nitrogen and perfluorinated alkyl groups was also introduced instead of a two-carbon spacer to effectively insulate the strong electron-withdrawing effect of the perfluorinated alkyl parts.

3-(Perfluoroalkyl)propyl iodides **3a**–**d**[18] were synthesized according to a modified Fish's method[19] from the corresponding $C_nF_{2n+1}I$ ($n = 4, 6, 8, 10$) via three-step reactions. The iodides **3a**–**d** were reacted with benzylamine in the presence of potassium carbonate to give the corresponding tertiary amines **4a**–**d**.[20] Compounds **4a**–**d** were hydrogenated with 10% Pd–C in EtOAc to give secondary amines **5a**–**d**. To avoid forming tetraalkylthiourea, compounds **5a**–**d** (1.0 equiv) were reacted

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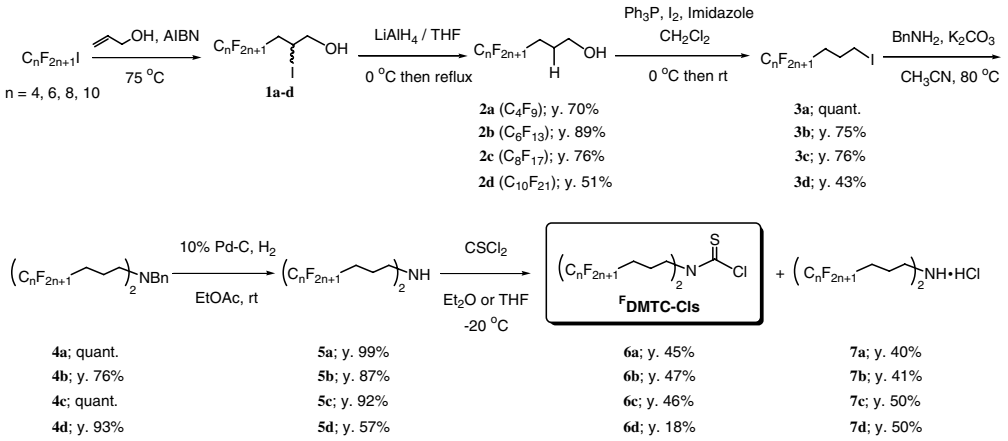


Scheme 1. Preparation of ^{F}DMTC-Cls.

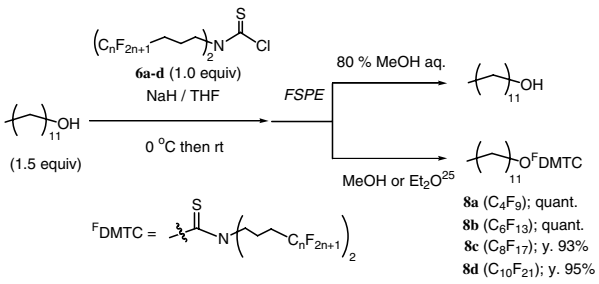
with thiophosgene (0.5 equiv) in Et_2O or THF.[21] After the reaction, the precipitated amine hydrochlorides **7a–d** were filtered off and the filtrates were concentrated. After recrystallization of the crude products from chloroform and petroleum ether, ^{F}DMTC-Cls **6a–d**[22] were obtained in 45% (**6a**), 47% (**6b**), 46% (**6c**) and 18% (**6d**) yields as colorless solids. However, since compounds **4d** and **5d** were insoluble in organic solvents, the yields of products **5d** and **6d** were decreased.

We next examined the introduction of ^{F}DMTC groups into primary alcohol (1-dodecanol), secondary alcohol (1-phenyl-2-propanol) and sugar derivatives using ^{F}DMTC-Cls **6a–d**.

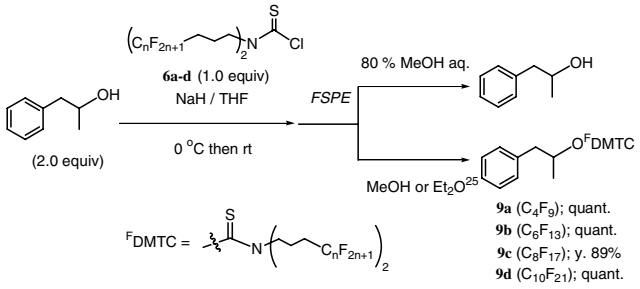
1-Dodecanol (1.5 equiv) was reacted with ^{F}DMTC-Cl **6a** (1.0 equiv) and NaH in THF at room temperature. After 12 h, the reaction was quenched with saturated NH_4Cl aq and then the reaction mixture was extracted with Et_2O. The Et_2O layer was washed, dried, and concentrated. The residue including ^{F}DMTC-protected product **8a** and excess 1-dodecanol was loaded onto a fluorous reverse-phase silica gel (Fluoro*Flash*®) column and then the column was eluted successively with 80% MeOH aq and MeOH. The MeOH fraction was concentrated to give ^{F}DMTC-protected compound **8a** in quantitative yield (Scheme 2). Similarly, 1-dodecanol was reacted with ^{F}DMTC-Cls **6b–d**. After separation of the crude products by FSPE, ^{F}DMTC-protected compounds **8b–d** were obtained in quantitative (**8b**), 93% (**8c**), 95% (**8d**) yields (Scheme 2). Next, 1-pheny-2-propanol (2.0 equiv) was reacted with ^{F}DMTC-Cls **6a–d** (1.0 equiv) under similar reaction conditions and the results are summarized in Scheme 3. The reactions proceeded smoothly to give the corresponding ^{F}DMTC-protected compounds **9a–d** in excellent yields (89%-quantitative). ^{1}H NMR spectra of **8a** and **9a**, which were isolated by FSPE, are shown in Figure 1. As seen from the spectra, the ^{F}DMTC-protected compounds were almost pure.[23]

Since ^{F}DMTC groups were successfully introduced into the simple alcohols, we also examined the protection of hydroxyl groups in various sugar derivatives in order to demonstrate the versatility of ^{F}DMTC groups. The results are summarized in Table 1. As seen from the table, the ^{F}DMTC-protected compounds (**10b**, **10c**, **11c**, **12b**, **12c**, and **13c**) were obtained in high yields from the MeOH fraction by FSPE. The unreacted starting alcohols were also recovered from 80% MeOH aq fraction by FSPE.

To find the optimal reaction conditions for ^{F}DMTC group cleavage, we initially examined deprotection of a non-fluorous DMTC group in the model compound **14** under Falck's conditions ($NaIO_4$ or H_2O_2)[16] and Mukaiyama's conditions (*m*-CPBA).[24] As shown in Table 2, ester **15** was obtained as a by-product under Falck's conditions (entries 1 and 2). On the other hand, deprotection of the DMTC group with *m*-CPBA gave 1-dodecanol in good yield (entry 3).



Scheme 2. Introduction of ^{F}DMTC groups into 1-dodecanol with **6a–d**.



Scheme 3. Introduction of ^{F}DMTC groups into 1-phenyl-2-propanol with **6a–d**.

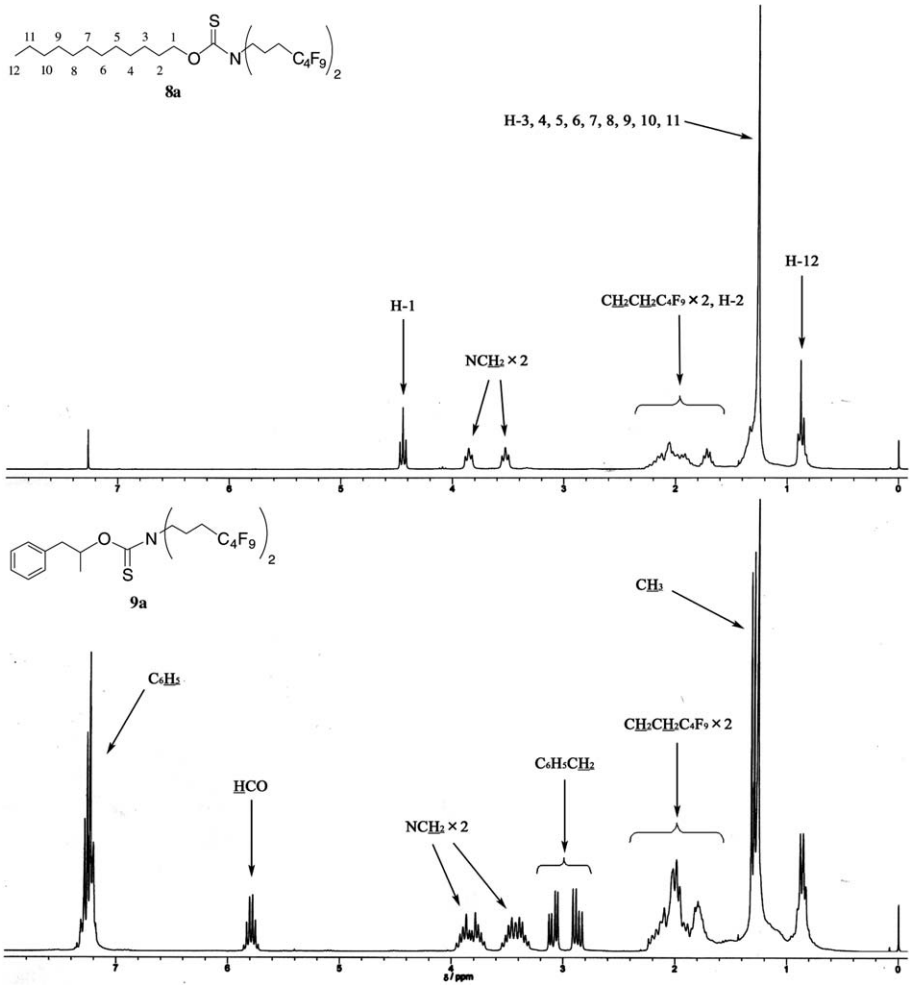
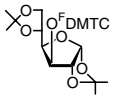
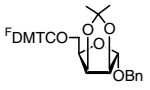
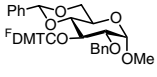
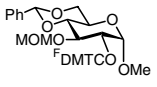


Figure 1. ^{1}H NMR spectra of compounds **8a** and **9a** (250 MHz, $CDCl_3$).

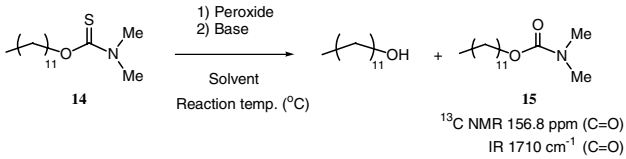
Table 1. Introduction of ^{F}DMTC groups into sugar derivatives[a]

Entry	Product	Yield (%)	Recovered yield (%) of starting alcohol
1		**10b** C_6F_{13}; 92 **10c** C_8F_{17}; 93	C_6F_{13}; 88 C_8F_{17}; quant.
2		**11c** C_8F_{17}; 97	C_8F_{17}; quant.
3		**12b** C_6F_{13}; 99 **12c** C_8F_{17}; quant.	C_6F_{13}; 98 C_8F_{17}; quant.
4		**13c** C_8F_{17}; quant.	C_8F_{17}; quant.

[a] Sugar derivatives (2.0 equiv) and ^{F}DMTC-Cls (**6b** or **6c**; 1.0 equiv) were used for the reaction.

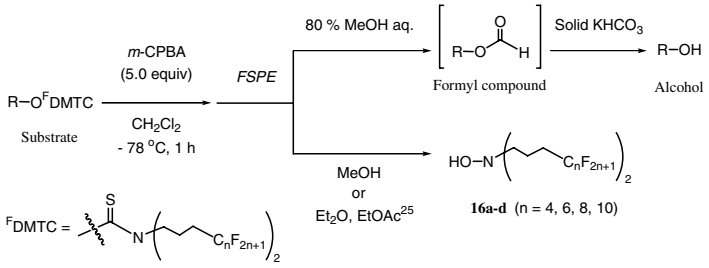
Finally, we tried to deprotect the ^{F}DMTC group under the optimal reaction conditions (entry 3 in Table 2). The results are summarized in Table 3. ^{F}DMTC-protected compounds were reacted with *m*-CPBA (5.0 equiv) in CH_2Cl_2 at −78 °C. After 1 h, the reaction was quenched with saturated $NaHCO_3$ aq and then the reaction

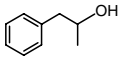
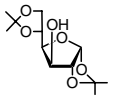
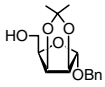
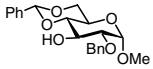
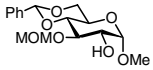
Table 2. Deprotection of DMTC group with various peroxides



Entry	Peroxide	Base	Solvent	Reaction temperature (°C)	Yield (%)	
					1-Dodecanol	**15**
1	$NaIO_4$	Na_2CO_3	$MeOH/H_2O$	45	81	7
2	H_2O_2	2 N NaOH aq	THF	50	14	48
3	*m*-CPBA	$KHCO_3$	CH_2Cl_2	−78	85	15

Table 3. Deprotection of ^{F}DMTC groups with *m*-CPBA



Entry	Substrate	Alcohol	Yield (%)
1	**8a**		82
2	**8b**		quant.
3	**8c**		92
4	**8d**		77
5	**9a**		86
6	**9b**		90
7	**9c**		85
8	**9d**		88
9	**10b**		75
10	**10c**		85
11	**11c**		78
12	**12b**		91
13	**12c**		86
14	**13c**		75

mixture was extracted with Et_2O. The Et_2O layer was washed with 1 N NaOH aq and then with brine, dried, and concentrated. The residue including the intermediate formyl compound was loaded onto a Fluoro*Flash*® column and then the column was eluted successively with 80% MeOH aq and MeOH, Et_2O or EtOAc.[25] The 80% MeOH aq layer was treated with solid $KHCO_3$ to give the corresponding alcohols in good yields. The reaction conditions for the ^{F}DMTC group cleavage are compatible with several protecting groups such as Bn, MOM, isopropylidene, and benzylidene (entries 9–14). On the other hand, fluorous hydroxylamines **16a**–**d** were obtained from the MeOH, Et_2O or EtOAc layer as a main product. Currently, we are examining reduc-

tive cleavage of the N–O bond in order to convert the hydroxylamines **16a–d** to the corresponding secondary amines **5a–d**.

In conclusion, we have developed fluorous dimethylthiocarbamate (^{F}DMTC) groups as a new fluorous protecting group for alcohols. The ^{F}DMTC groups were easily introduced into the simple alcohols and carbohydrates in high yields, and selectively cleaved with *m*-CPBA. The isolation of the ^{F}DMTC-protected products by FSPE was very easy and quick. The fluorous compounds were also purified by normal silica gel column chromatography, if necessary. Optimization of the reactions was carried out as usual by monitoring the reactions with TLC. Considering these attributes, the ^{F}DMTC groups may find valuable and versatile use in synthetic organic chemistry.

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22. Compound **6a**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.97 (2H, t, $J = 7.2$ Hz, NCH_2), 3.85 (2H, t, NCH_2), 2.16 (8H, m, CH_2CH_2C$_4$F$_9$ × 2); ^{13}C NMR (63 MHz, $CDCl_3$): δ 175.23 (*C*=S), 54.39 (NCH_2 × 2), 28.10, 27.93 (each t, $J = 22.6$ Hz, CH_2C$_4$F$_9$ × 2) 19.18, 17.20 (*C*H_2CH$_2$C$_4$F$_9$ × 2); IR (KBr, disk) ν (cm^{-1}): 2949, 1508, 1465, 1425, 1379, 1358, 1299, 1236, 1150, 1132, 1105, 1013, 990, 878, 853, 733, 719, 592. Compound **6b**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.97 (2H, t, $J = 6.8$ Hz, NCH_2), 3.85 (2H, t, NCH_2), 2.16 (8H, m, CH_2CH_2C$_6$F$_{13}$ × 2); ^{13}C NMR (63 MHz, $CDCl_3$): δ 175.24 (*C*=S), 54.41 (NCH_2 × 2), 28.20, 28.03 (each t, $J = 22.6$ Hz, CH_2C$_6$F$_{13}$ × 2) 19.23, 17.24 (*C*H_2CH$_2$C$_6$F$_{13}$ × 2); IR (KBr, disk) ν (cm^{-1}): 1507, 1421, 1368, 1299, 1246, 1209, 1144, 1123, 1103, 1082, 1034, 984, 846, 792, 746, 700, 655. Compound **6c**: ^{1}H NMR (250 MHz, C_6D_6/C_6F_6 (1:1)): δ 3.45 (2H, t, $J = 6.7$ Hz, NCH_2), 3.19 (2H, t, NCH_2), 1.79 (8H, m, CH_2CH_2-C$_8$F$_{17}$ × 2); ^{13}C NMR (63 MHz, C_6D_6/C_6F_6 (1:1)): δ 175.03 (*C*=S), 54.58, 54.40 (NCH_2 × 2), 28.60, 28.40 (each t, $J = 22.6$ Hz, CH_2C$_8$F$_{17}$ × 2) 19.30, 17.45 (*C*H_2CH$_2$-C$_8$F$_{17}$ × 2); IR (KBr, disk) ν (cm^{-1}): 2981, 1506, 1463, 1442, 1420, 1372, 1335, 1297, 1247, 1204, 1151, 1117, 1038, 978, 959, 705, 661. Compound **6d**: ^{1}H NMR (250 MHz, C_6D_6/C_6F_6 (2:3)): δ 3.40 (2H, t, $J = 6.4$ Hz, NCH_2), 3.12 (2H, t, NCH_2), 1.79 (8H, m, CH_2CH_2C$_{10}$F$_{21}$ × 2); ^{13}C NMR (63 MHz, C_6D_6/C_6F_6 (2:3)): δ 174.96 (*C*=S), 54.49, 54.32 (NCH_2 × 2), 28.51, 28.35 (each t, $J = 22.1$ Hz, CH_2C$_{10}$F$_{21}$ × 2) 19.25, 17.43 (*C*H_2CH$_2$C$_{10}$F$_{21}$ × 2); IR (KBr, disk) ν (cm^{-1}): 1506, 1463, 1420, 1374, 1344, 1298, 1214, 1152, 1113, 1084, 1038, 984, 885, 664, 647, 557.
23. Compound **8a**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.45 (2H, t, $J = 6.7$ Hz, H-1), 3.86, 3.53 (4H, each t, $J = 7.4$ Hz, NCH_2 × 2), 2.06 (8H, m, CH_2CH_2C$_4$F$_9$ × 2), 1.72 (2H, m, H-2), 1.26 (18H, s, H-3, 4, 5, 6, 7, 8, 9, 10, 11), 0.88 (3H, t, $J = 6.8$ Hz, H-12); ^{13}C NMR (63 MHz, $CDCl_3$): δ 188.97 (*C*=S), 72.09 (C-1), 51.90, 47.86 (NCH_2 × 2), 31.89, 29.70, 29.60, 29.56, 29.49, 29.33, 29.27, 28.63, 26.08, 22.66, 14.01 (C-2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12), 28.55, 28.19 (each t, $J = 22.1$ Hz, CH_2C$_4$F$_9$ × 2) 19.17, 18.04 (*C*H_2CH$_2$-C$_4$F$_9$ × 2); IR (NaCl, neat) ν (cm^{-1}): 2928, 2857, 1464, 1356, 1235, 1167, 1134, 1071, 930, 880, 736, 720. Compound **9a**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.35–7.18 (5H, m, aromatic protons), 5.79 (1H, ddq, $J = 6.0$, 6.3, 7.0 Hz, OC*H*), 3.83, 3.43 (4H, each m, NCH_2 × 2), 3.09 (2H, dd, $J = 6.3$, 13.6 Hz, PhCH_2), 2.87 (2H, dd, $J = 7.0$, 13.6 Hz, PhCH_2), 1.98 (8H, m, CH_2CH_2-C$_4$F$_9$ × 2), 1.31 (3H, d, $J = 6.3$ Hz, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 187.97 (*C*=S), 137.12, 129.34, 128.36, 126.59 (aromatic carbon), 78.59 (OCH), 51.71, 47.61

($NCH_2 \times 2$), 41.90 ($PhCH_2$), 28.14 (t, $J = 22.5$ Hz, $CH_2C_4F_9 \times 2$) 19.04, 18.04 ($CH_2CH_2C_4F_9 \times 2$), 18.94 (CH_3); IR (NaCl, neat) ν (cm^{-1}): 2924, 2835, 1496, 1456, 1357, 1235, 1133, 1012, 880, 746, 719, 701.

24. Mukaiyama, T.; Hirano, N.; Nishida, M.; Uchiro, H. *Chem. Lett.* **1996**, 99–100.
25. Usually 80% MeOH aq is used to elute organic compounds and then MeOH is used to elute light fluorous compounds from the column. In the case of highly fluorinated compounds, the column is eluted first with 80% MeOH aq to get organic compounds and then Et_2O or EtOAc is used to elute the highly fluorinated compounds.