A Facile New Method for the Two-step Substitution of Hydroxy Groups in Primary Alcohols for Trifluoromethyl and Pentafluoroethyl Moieties

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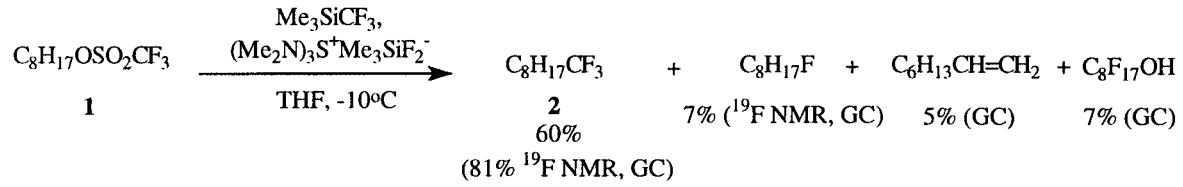
Abstract: In an efficient procedure the nucleophilic trifluoromethylation and pentafluoroethylation of alkyl triflates using (trifluoromethyl)- and (pentafluoroethyl)trimethylsilane in the presence of anhydrous tetramethylammonium fluoride is achieved giving 71-80% isolated yields.

Key words: perfluoroalkylation, (perfluoroalkyl)trimethylsilane, anhydrous tetramethylammonium fluoride, nucleophilic substitution

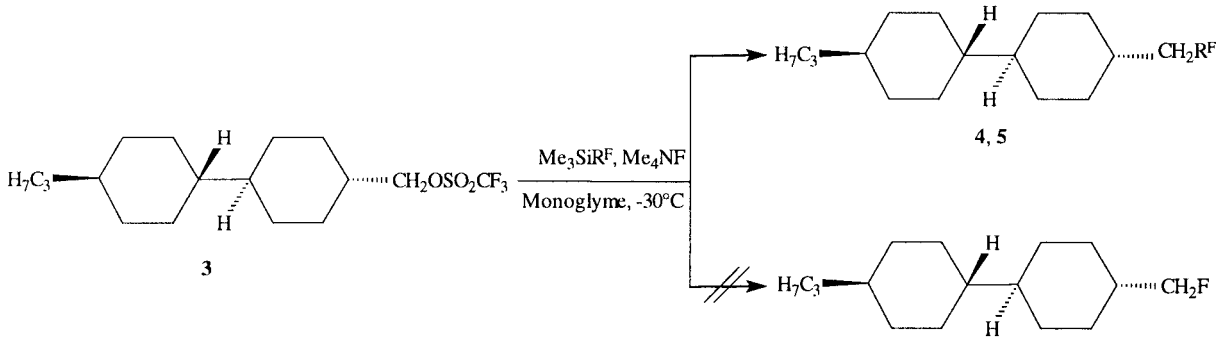
Regioselective perfluoroalkylation and, especially, trifluoromethylation of organic compounds is a well established method for synthesizing compounds applicable in agrochemistry, pharmaceutical industry and material sciences.[1,2] Numerous trifluoromethylating reactions of activated organic halides (aryl, vinyl, allyl and benzyl halides) have been reported previously.[1,3] However, the only example of trifluoromethylating non-activated alkyl halides is the reaction of aliphatic halides using a mixture of methyl chloro- or bromodifluoroacetate, an excess of potassium fluoride, copper iodide and cadmium iodide at 120 °C in HMPA,[4] where $[CF_3CuI]^-$ is supposedly the trifluoromethylating reagent. This method has several disadvantages, such as the use of a carcinogenic solvent, toxic cadmium salts, or high reaction temperature. In addition, there were difficulties in isolating the trifluoromethylated products due to moderate yields and low conversion rates of the starting alkyl halides. The unique properties of (perfluoroalkyl)trimethylsilanes as reagents for perfluoroalkylation of different organic and heteroatom electrophiles are well documented.[5] The formation of new C-C bonds during the perfluoroalkylation proceeding under fluoride anion catalysis, was achieved in the case of carbonyl compounds,[6] imines,[7] perfluoroarenes[8] and polytrifluoromethylated aromatics,[9] acyl halides[10] and carboxylic esters.[11] (Trifluoromethyl)triethylsilane was also used for in situ generation of CF_3Cu in the presence of copper halides and potassium fluoride. However, the trifluoromethyl copper species was able to trifluoromethylate only benzyl and allyl halides in 73% and 23% yield, respectively. Moreover, this procedure cannot be extended to non-activated alkyl halides.[12] Considering the good leaving group properties of the triflate group in nucleophilic substitution reactions, the availability and the costs of carbinols, alkyl triflates were chosen as the most suitable candidates for trifluoromethylation of sp^3 hybridized carbon derivatives. To the best of our knowledge, there are no methods so far for substituting hydroxy groups in alcohols directly or via their corresponding tosylates and triflates for primary perfluoroalkyl groups. It was previously reported, that phosphitylation of alcohols with $(Et_2N)_2PCl$ followed by low temperature reaction of $CFCl_3$, $CFBr_3$, CF_3CCl_3 or $(CF_3)_3CBr$ with the intermediate diamido-O-alkylphosphites, is an effective route to introduce halofluoroalkyl or perfluoro-*tert*.-butyl moieties at a sp^3-hybridized carbon.[13] Nevertheless, it proved to be impossible for the most synthetically useful perfluorinated primary alkyl groups, namely trifluoromethyl or pentafluoroethyl, since diamido-O-alkyl phosphites do not interact with trifluoromethyl- or pentafluoroethyl halides. Here, we report a new facile method for the preparation of trifluoromethylated and pentafluoroethylated alkanes starting from easily accessible alkyl triflates, (perfluoroalkyl)trimethylsilane and tetramethylammonium fluoride under very mild reaction conditions.

The treatment of primary alkyl triflates[14] with an approximately three-fold excess of R^FSiMe_3 ($R^F = CF_3$, C_2F_5) and an almost stoichiometrical amount of tetramethylammonium fluoride[15] in monoglyme at -30 °C for 2 h gave the corresponding perfluoroalkylated $AlkR^F$ derivatives in 71-80% isolated yields.[16] The nature of the fluoride ion source used significantly influenced this reaction. Initially, the trifluoromethylation reaction of octyl triflate **1** was attempted in a 2:1 ratio of CF_3SiMe_3 and TASF in THF at -10 °C for 1 h giving the targeted 1,1,1-trifluorononane **2**, 1-fluorooctane, oct-1-ene and octan-1-ol in a 81:7:5:7 ratio (GC and ^{19}F NMR) (Scheme 1).

Surprisingly, no trifluoromethylation was observed in the case of CF_3SiMe_3/KF and alkyl triflate **3** either at 0 °C or at room temperature. The only fluorinated products observed were fluoroform, trimethylfluorosilane and potassium triflate. In contrast to TASF and spray-dried KF, the application of tetramethylammonium fluoride as a fluoride anion source and performing the reaction under milder reaction conditions (-30 °C, monoglyme, 2 h) afforded the liquid crystal compound, 4-(2,2,2-trifluoroethyl)-4´-propylbicyclohexyl **4** in 71% isolated yield. The only fluorinated impurity (1% mol) observed by trifluoromethylation of the triflate **3** was 4-(2,2,3,3,3-pentafluoropropyl)-4´-propylbicyclohexyl **5** (Scheme 2).



Scheme 1



	R^F	Mesophase Sequence
4	CF_3	C –5 S_B 69 I
5	C_2F_5	C 51 S_G 65 S_B 86 I

Scheme 2 Synthesis and mesophase sequences of the liquid crystals **4** and **5**. (The phase transition temperatures are cited in °C; C = crystalline, S_B = smectic B, S_G = smectic G, I = isotropic)

The side reaction can be rationalized by considering an insertion of difluorocarbene into the Si-C bonds, formed from the "CF_3^-" containing siliconate intermediates[17,18] and generated at low temperature as it has been previously observed for CF_3Cu species.[1b]

Surprisingly, the reaction of triflate **2** with $C_2F_5SiMe_3$ gave less side-products than with CF_3SiMe_3. No fluorinated impurity was detected in the reaction mixture and the isolated yield was 80% for **5**. The difference in reactivity of these (perfluoroalkyl)trimethylsilanes reagents could be explained in terms of different thermal stability of the hypervalent pentacoordinated silicon species generated from R^FSiMe_3 and F^- at low temperature. As we have recently observed, the hypervalent bis(pentafluoroethyl)trimethyl-siliconate derived from $C_2F_5SiMe_3$ and tetramethylammonium fluoride is stable in monoglyme until 20 °C. The corresponding CF_3 containing intermediates, however, slowly decompose in monoglyme solution already at 0 °C.[17,19] The newly developed perfluoroalkylation protocol allows the exclusion of carcinogenic solvents or toxic cadmium salts. The trifluoromethylated products can be prepared under mild reaction conditions.

In summary, we have developed an efficient and general synthetic route to primary trifluoro- and pentafluoroalkanes by treating alkyl triflates with an excess of (perfluoroalkyl)trimethylsilane and almost stoichiometric amounts of anhydrous tetramethylammonium fluoride. The usefulness of this approach was demonstrated on a preparative scale by synthesizing the liquid crystal molecules **4** and **5**. Further studies of the reactive species nature, scope and applicability of this method to secondary and tertiary alcohols are presently under investigation in our laboratories.

References and Notes

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4-Trifluoro-methylsulfonylmethyl-4'-propylbicyclohexyl **3**: To a solution of 3.30 g (12 mmol) triflic anhydride in 10 mL CH_2Cl_2 at 0 °C was added a mixture of 2.62 g (11 mmol) 4-hydroxymethyl-4´-propylbicyclohexyl during 20 min and dried 0.87 g (11 mmol) pyridine in 5 mL CH_2Cl_2. After stirring for 15 min at 0 °C the reaction mixture was quenched with 100 mL cold water. After extraction with 3×10 mL CH_2Cl_2 the combined organic layers were dried over Na_2SO_4. After removal of the solvent in vacuo the residue was dissolved in 5 mL $CHCl_3$ and filtrated through silica gel (10 cm layer, eluent $CHCl_3$). Removal of the solvent in vacuo followed by crystallization from hexane afforded **3** (3.0 g, 74%) as a colorless solid. Mp 41-43 °C, ^{1}H NMR (200.13 MHz, C_6D_6): δ = 0.47-1.79 (m, 24H); 0.91 (t, 3H, CH_3, $^3J_{H-H}$ = 7.1); 3.78 (d, 2H, = CH_2, $^3J_{H-H}$ = 6.4). ^{19}F NMR (188.31 MHz, C_6D_6): δ = -76.47 (s). ^{13}C NMR (50.32 MHz, C_6D_6): δ = 14.7 (CH_3); 20.5, 28.8, 29.0, 30.3, 33.9, 40.2 and 82.1 (CH_2); 37.6, 38.0, 42.9 and 43.4 (CH); 119.4 (q, $^1J_{C-F}$ = 319.5). MS (Varian MAT 8200): 370 (M^+, 10); 125 (C_3H_7-$C_6H_{10}^+$, 100); 69 (CF_3^+, 90). HRMS: calcd. for $C_{17}H_{29}F_3SO_3$ 370.1790, found 370.1804.
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(16) **Typical procedure for the trifluoromethylation of alkyl triflates:** 4-(2,2,2-Trifluoroethyl)-4´-propylbicyclohexyl **4**: To a −30 °C solution of 1.50 g (4.1 mmol) 4-trifluoromethylsulfonylmethyl-4´-propylbicyclohexyl **3** and 1.73 g (12 mmol) (trifluoromethyl)trimethylsilane in 20 mL monoglyme was added during 1 h 0.46 g (5 mmol) tetramethylammonium fluoride. The mixture was stirred for additional 2 h at this temperature and then during 1.5 h allowed to reach 0 °C. The resulting dark mixture was quenched with 150 mL water, the aqueous layer was extracted with 3 × 15 mL CH_2Cl_2, dried over anhydrous $MgSO_4$ and was concentrated in vacuo. The residue was dissolved in 10 mL pentane and filtrated through a silica gel layer (10 cm, eluent pentane). After removal of the solvent in vacuo followed by the crystallization (from MeOH:EtOH, 10:1) yielded compound **4** (0.85 g, 71%) as colorless crystals; for the mesophase sequence see Scheme 2. ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 0.82-1.34 (m, 17H); 1.53-1.89 (m, 10H); 1.97 (q.d, 2H, CH_2, $^3J_{H-F}$ = 11.6, $^3J_{H-H}$ = 6.8). ^{19}F NMR (188.31 MHz, $CDCl_3$): δ = -64.48 (t, $^3J_{F-H}$ = 11.2). ^{13}C NMR (50.32 MHz, $CDCl_3$): 14.4 (CH_3); 20.1, 29.6, 30.1, 33.4, 33.6, 39.9 and 40.8 (q, CH_2, $^2J_{C-F}$ = 27.0); 32.9 (q, CH, $^3J_{C-F}$ = 2.3), 37.7, 42.8 and 43.3; 127.2 (q, CF_3, $^1J_{C-F}$ = 277.3). MS: 290 (M^+, 50); 247 ([M-C_3H_7]$^+$, 5); 220 ([M-CF_3H]$^+$, 13); 125 (C_3H_7-$C_6H_{10}^+$, 73); 69 (CF_3^+, 100). HRMS: calcd. for $C_{17}H_{29}F_3$ 290.2221, found 290.2220.
4-(2,2,3,3,3-Pentafluoropropyl)-4´-propylbicyclohexyl **5**, 80%, colorless crystals from methanol; for the mesophase sequence see Scheme 2. ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 0.69-1.38 (m, 18H); 1.59-1.99 (m, 11H). ^{19}F NMR (188.31 MHz, $CDCl_3$): -117.60 (t, 2F, CF_2, $^3J_{F-H}$ = 19.8); -87.26 (s, 3F, CF_3). ^{13}C NMR (50.32 MHz, $CDCl_3$): 14.4 (CH_3), 20.06, 29.7, 30.0, 33.6, 34.0, 39.8, 37.7 (t, CH_2 $^2J_{C-F}$ = 20.9); 31.3, 37.6, 42.8, 43.3 (CH); 116.7 (t.q, CF_2, $^1J_{C-F}$ = 252.1, $^2J_{C-F}$ = 37.0); 119.6 (q.t, CF_3, $^1J_{C-F}$ = 285.6, $^2J_{C-F}$ = 36.3). MS: 340 (M^+, 28); 125 (C_3H_7-$C_6H_{10}^+$, 66); 69 (CF_3^+, 100); 29 ($C_2H_5^+$, 8). HRMS: calcd. for $C_{18}H_{29}F_5$ 340.2189, found 340.2189.
The assignment of all signals in **3**, **4**, **5** was based on DEPT135 NMR spectra.
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