Monofluoroalkylation and alkylation of alcohols using non-volatile reagents

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ABSTRACT

Non-volatile S-Alkyl-S-phenyl-2,3,4,5-tetramethylphenylsulfonium triflate or tetrafluoroborate salts have been used to alkylate alcohols in the presence of sodium hydride. This is a simple and efficient method for the synthesis of ethers from complex alcohols and an alternative to the usual O-alkylation methods. This method was especially important for the preparation of monofluoromethyl ethers of a wide range of alcohols. Some alkylated derivatives of the precursors of some bioactive compounds were also prepared using these reagents.

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1. Introduction

The introduction of fluorine atoms into a molecule has an impact on its physical and chemical properties, with consequences to the biological activity it exhibits. This is especially important for the modulation of the pharmacological profile of a molecule and it explains why many medicines and pesticides are fluorinated compounds.[1] Volatile fluorinated reagents are prohibited and the use of non volatile ones is an active research area.

Recently a number of new trifluoromethylation, difluoromethylation and monofluoromethylation processes have been described.[2–9] O-Trifluoromethylations with 2-tert-butyl-O-(trifluoromethyl)dibenzofuranium hexafluoroantimonate have been reported for some aryl alcohols and 2-phenylethanol and n-tetradecanol.[10] These reagents are unstable and difficult to manipulate.[11] Zinc-mediated trifluoromethylation of primary and secondary alkyl alcohols using hypervalent iodine reagents afforded the corresponding CF3 ethers in fair to excellent yields.

Electrophilic monofluoromethylation of O-, S-, and N-nucleophiles with volatile chlorofluoromethane has been described.[12] Fluoromethyl ethers were efficiently obtained using this method, however the examples studied were all phenols. Another synthetic strategy to prepare monofluoromethyl ethers is based on the O-alkylation of enolates derived from β-ketoesters using N,N-(dimethylamino)-S-phenyl-S-monofluoromethyloxosulfonium trifluoromethanesulfonate or hexafluorophosphate, followed by hydrogenation of the double bond of the resulting enolether.[13] A direct monofluoromethylation of naphthols, phenols and phenyl-hexafluoro-2-propanol was also described in the same work, using cesium carbonate as the base. However, less acidic hydroxy groups as in diphenylmethanol and (3,5-dinitrophenyl)methanol did not react under the same reaction conditions.

Two step methods to prepare monofluoromethyl ethers have been reported.[14] Acetolysis of a MOM ether afforded the oxymethyl acetate moiety, which was then treated with HF/pyridine to give the monofluoromethyl ether. Similarly the methyl thiomethyl ethers have been converted into fluoromethyl ethers using IF5-pyridine-HF as the fluorinating agent.[15]

Similar electrophilic mono- and difluoromethylating sulfonium salts **1** and **2** (Fig. 1) have been described by Prakash and Olah and shown to be useful for the alkylation of heteroatoms in organic compounds.[16,17] These reagents are stable solids and were effective

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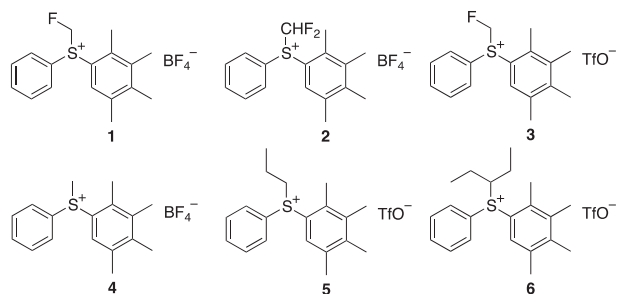E-mail address: maycock@itqb.unl.pt (C.D. Maycock).

Fig. 1. Electrophilic sulfonium alkylating reagents.

for the introduction of a monofluoromethyl or difluoromethyl group into sulfonic acids, tertiary amines, imidazole derivatives and phosphines. However, the reaction of hydroxyl groups to form the corresponding monofluoromethyl ethers was restricted to phenols (naphthols, perfluorophenol, thiophenol) and fluorinated alcohols, in the presence of cesium carbonate. The monofluoromethylation of alcohols with pKa (>10),[17] has not been reported using these reagents. Alkylations with these bulky reagents avoids the use of volatile reagents and may be used for selective alkylations at hindered heteroatoms. A study was made to determine further applications for these compounds.

2. Results and discussion

Using the same Olah/Prakash reagents, we have extended their utility to the monofluoromethylation of alcohols using sodium hydride as the base. The conditions were mild enough to allow the presence of labile groups in the substrate. *S*-methyl-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium tetrafluoroborate **4**[18] and *S*-propyl-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium triflate **5** (Fig. 1) were also used to alkylate alcohols. The results are shown in Table 1. Triflates **5** and **6**, having β protons, were prepared following the procedure of Prakash and Olah,[17] but are described for the first time in this work (Fig. 1).

Treatment of (2R,3R,5R,6R)-2,3-dihydroxymethyl-5,6-dimethoxy-5,6-dimethyl-[1,4]-dioxane **7**[19] with sodium hydride and the methylating reagent **4** afforded the corresponding dimethyl ether **8** (Table 1, entry 1) in very high yield. The sulfide byproduct was easily removed by chromatography, being much less polar than the product **8**.

Alkylation of acetylenic alcohols **9** and **12** also afforded the corresponding ethers in excellent yields (Table 1, entries 2–5). These compounds are intermediates in the synthesis of (*S*)-4,5-dihydroxypentane-2,3-dione (DPD) and analogues.[20,21] DPD is the uncyclized precursor of AI-2, a signalling molecule for bacterial inter-species communication ("quorum sensing").[22–25] Propylation of racemic **12** with sodium hydride and a propyl halide afforded propyl ether **14** in only 18% yield.[21] Using the sulfonium salt **5** the yield was considerably higher (60%, Table 1, entry 5).

Fluorinated sugars have received significant attention due to their potential applications as enzyme inhibitors, nucleosides with antiviral and antitumor properties and labelled sugars for medical imaging, among others.[1] Usually these are deoxyfluoro sugars, however monofluoromethyl ethers of sugars might show interesting biological properties as well. The fluoromethylation at the 2-OH of methyl glucoside **15** afforded **16** in 95% yield (Table 1, entry 6). The thioglucoside **17** was also successfully alkylated at the primary hydroxyl furnishing the fluorinated thioglucoside **18** (64% yield, Table 1, entry 7). Using the same method, galactoside **20** was obtained in 62% yield (Table 1, entry 8).

Finally, the fluoromethylation of PEG[550] monomethyl ether

afforded the expected fluoromethyl ether **22** in 81% yield (Table 1, entry 9).

Attempted *O*-alkylations of hydroxyl groups with reagent **6** were not successful, probably due to competing elimination reactions and steric hyndrance, however, it reacted with nicotinic acid in the presence of cesium carbonate to afford the corresponding ester **24**, in 30% yield (Scheme 1).

3. Conclusions

Using the stable and non-volatile Prakash/Olah electrophilic fluoromethylating reagent and sodium hydride as the base, monofluoromethyl ethers have been prepared from alcohols. Modification of the reagent for the introduction of other alkyl groups, some having β protons, afforded the corresponding alkyl ethers in very good to excellent yields. Bulky sulfonium salts were only useful for the esterification of carboxylic acid salts. Some of the alkylated compounds were previously very difficult to obtain in good yields using more conventional alkylating reagents. Although not very atom economic these reagents provide a conversion-efficient *O*-alkylation process using non-volatile reagents.

4. Experimental section

4.1. General information

^{1}H NMR spectra were obtained at 400 MHz in CDCl$_3$ or DMSO-d_6 with chemical shift values (δ) in ppm downfield from tetramethylsilane, ^{13}C NMR spectra were obtained at 100.61 MHz and ^{19}F NMR spectra were obtained at 376.5 MHz. Assignments are supported by 2D correlation NMR studies. Medium pressure preparative column chromatography: Silica Gel Merck 60 H. Analytical TLC: Aluminium-backed Silica Gel Merck 60 F254. Reagents and solvents were purified and dried according to Ref. [27]. All the reactions were carried out under an inert atmosphere (argon).

4.1.1. S-phenyl-S-propyl-2,3,4,5-tetramethylphenylsulfonium triflate 5

To a solution of phenyl propyl sulfoxide[28] (1.990 g, 0.012 mol) and 1,2,3,4-tetramethylbenzene (1.94 mL, 0.013 mol) in Et$_2$O (40 mL), at −78 °C, triflic anhydride (1.94 mL, 0.012 mol) was added, and the mixture was stirred at −78 °C for 2 h. Water was added (20 mL) and the aqueous phase was extracted with AcOEt (3 x 30 mL) and the combined organic extracts were dried (MgSO$_4$), filtered and the solvent was evaporated to afford **5** (4.573 g, 89%) as an oil. ^{1}H NMR (CDCl$_3$): δ 7.89–7.86 (2H, m), 7.66–7.62 (4H, m), 4.23–4.13 (1H, m), 4.07–4.01 (1H, m), 2.52, 2.52 (3H, s), 2.41 (3H, s), 2.27 (6H, s), 1.84–1.78 (2H, m), 1.04 (3H, t, *J* = 7.4 Hz). ^{13}C NMR (CDCl$_3$): δ 143.2, 138.7, 136.7, 134.0, 131.4, 130.1, 129.5, 126.7, 125.3, 124.7, 118.9, 60.4, 46.3, 20.8, 18.4, 17.3, 16.8, 16.7, 12.6. FT-IR (film): 2962, 2929, 2871, 1585, 1481, 1438 cm^{-1}. HR-MS: calcd for C$_{19}$H$_{25}$S$^+$ [M$^+$- OTf]: 285.1671; found: 285.1658.

4.1.2. Phenyl 3-pentyl sulfoxide

To a solution of the phenyl 3-pentyl sulfide[29] (4.798 g, 26.6 mmol) in MeOH/H$_2$O 5:1 (120 mL) at 0 °C, NBS (7.10 g, 39.9 mmol) was added and the mixture was stirred at 0 °C for 2 h. 10% Na$_2$SO$_3$ aqueous solution (100 mL) and saturated NaHCO$_3$ aqueous solution (50 mL) were added and the aqueous phase was extracted with AcOEt (3 x 100 mL) and the combined organic extracts were dried (MgSO$_4$), filtered and the solvent was evaporated. The crude mixture was purified by flash column chromatography (20/80 AcOEt/Hex) to afford the sulfoxide (4.33 g, 83% yield) as a colourless oil. ^{1}H NMR (CDCl$_3$): δ 7.61–7.49 (m, 5H),