Tetrabutylammonium Butyldifluorodimethylsilicate and Difluorodimethylphenylsilicate, New Nucleophilic Fluorinating Reagents

Jaroslav Kvíčala,* Petr Mysík, Oldřich Paleta

Department of Organic Chemistry, Institute of Chemical Technology Prague, Technická 5, 166 28 Prague 6, Czech Republic

Fax 420 2 2435 4288; E-mail kvicalaj@vscht.cz

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Abstract: Tetrabutylammonium butyldifluorodimethylsilicate (TAMBS, **1a**) and tetrabutylammonium difluorodimethylphenylsilicate (TAMPS, **1b**) were conveniently prepared from the corresponding substituted fluorodimethylsilanes and tetrabutylammonium fluoride. Both fluorosilicates **1a**, **1b** are powerful nucleophilic fluorinating reagents which transform primary or secondary halides, tosylates, or mesylates to the corresponding fluorides in moderate to good yields.

Key words: nucleophilic fluorination, hypervalent silicon compounds, butyldifluorodimethylsilicate, difluorodimethylphenylsilicate

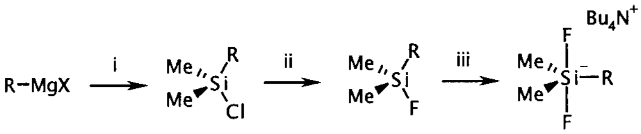
Among three general fluorination methods, namely radical, electrophilic, and nucleophilic fluorinations, the latter is still employed preferentially due to economic reasons and easy application in the laboratory.[1] From a practical point of view nucleophilic fluorinating reagents can be divided into several groups: a) cheap and easily available fluorinating reagents, which either display low efficiency (KF) or require special precautions (HF); b) fluorinating reagents with acceptable price and moderate efficiency (TBAF•3H_2O, Py•nHF, Et_3N•3HF, Gingras reagent, KF/18-crown-6 ether); c) comparably efficient reagents, which are not commercially available and their preparation involve some level of risk, e.g. use of hydrogen fluoride or insufficient stability (CuF•Bipy, $CHClF\text{-}CF_2\text{-}NEt_2$, $R_4P^+HF_2^-$); d) efficient and commercially available, but rather expensive reagents (Ishikawa reagent, DAST, TASF).

Fluorinating reagents either require the presence of a good leaving group (halogen, OSO_3R) in the substrate, or create it in the first step of fluorination reaction from the poor leaving group (OH). While the latter reagents can be used directly in combination with poor leaving group as hydroxyl, selectivity of fluorination by the former one can be improved substantially in demanding cases by using efficient leaving group (triflate).

The use of hypervalent silicon compound as the fluorinating reagent has been first reported by Doboszewski et al.,[2] who employed TASF reagent for fluorination of protected sugars. The main drawback of TASF is its high price due to its synthesis from highly toxic SF_4. Pilcher[3] synthesized tetrabutylammonium difluorotriphenylsilicate by a comparably more convenient way using aqueous hydrogen fluoride, but efficient fluorination required high excess of this reagent. Moreover, his results were not confirmed by Albanese and coworkers,[4] who also reported an improved synthesis of Pilcher reagent, TAMPS (**1b**) and other methylphenylsilicates.

The aim of our work was to develop a convenient and safe method for the synthesis of substituted difluorodimethylsilicates and to study the scope and limitations of their fluorinating abilities.

We started the syntheses from easily accessible substituted chlorodimethylsilanes, which are available commercially but can be prepared in a more economical way from cheap dichlorodimethylsilane and the corresponding Grignard reagents. Small contamination of chlorodimethylphenylsilane by the corresponding bromide arising from halogen exchange was not significant as both compounds were transformed by fluorination to the identical product (see Scheme). The key intermediates, substituted fluorodimethylsilanes, can be prepared by numerous ways. We preferred the fluorination of the starting chlorides by alkali metal fluorides,[5] which is a more safe and convenient method than fluorination of the corresponding silanols by hydrogen fluoride,[3] and cheaper than fluorination of silyl hydrides.[4] The final step of the preparation consisted of mixing fluorosilane with an acetonitrile solution of TBAF. We employed a 70% aqueous solution of TBAF from Aldrich, which after 3 h drying at 3 kPa afforded crystalline trihydrate of sufficient purity. The presence of water resulted in formation of small amounts of the corresponding silanols, whose presence did not impede subsequent fluorination reactions. The formation of difluorosilicates could be easily checked by both ^1H and ^{19}F NMR spectroscopy.[6]



1a, R = Bu
1b, R = Ph

Scheme i Me_2SiCl_2, Et_2O, reflux, R = Bu: X = Cl, 3 h, 42%, R = Ph: X = Br, 2 h, 46%; ii KF, MeCN, rt, 16 h, R = Bu: 76%, R = Ph: 47%; iii TBAF·3 H_2O, MeCN, rt, 2 h, quant.

In contrast to tetrabutylammonium difluorotriphenylsilicate (TBAT) reported by Pilcher,[3] we were not able to obtain difluorosilicates TAMBS **1a** and TAMPS **1b** in the

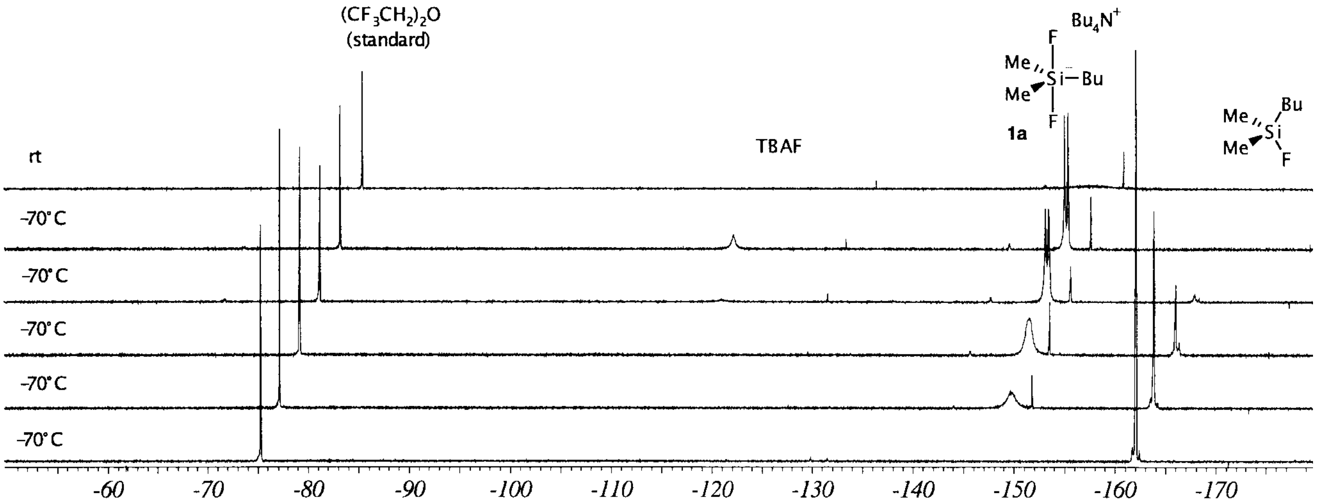


Figure Monitoring of the reaction of butylfluorodimethylsilane with TBAF by low-temperature ^{19}F NMR spectroscopy

crystalline state. To confirm that both fluorination reagents are not mixtures of TBAF and the corresponding fluorosilanes, we performed low-temperature titration of fluorosilanes with TBAF in an NMR tube and observed ^{19}F NMR spectra of the mixtures formed (Figure). Stepwise formation of difluorosilicates could be easily observed. Complexes of two molecules of fluorosilanes with one TBAF containing bridged fluorine in analogy to bridged complexes of 1,2-bis(fluorosilylated)benzenes[7] were not detected. In the case of TAMPS, no signal of fluoride anion could be observed before all fluorosilane was consumpted. On the other hand, the signal of the fluoride anion appeared before reaching the equivalent point for TAMBS (Figure) indicating that the stability of the latter silicate is lower and that it exists in equilibrium with the mixture of TBAF and fluorosilane. At room temperature, a rapid exchange of fluorine atoms between difluorosilicates **1** and TBAF resulted in coalescence of both signals.

We then compared the fluorinating ability of both difluorosilicates **1a** and **1b** with that of TBAF. Octan-1-yl and octan-2-yl mesylates and bromides were employed as representative primary and secondary compounds. The results are listed in the Table.[8] In all cases, the mesylates proved to be more efficient substrates than the corresponding bromides. In agreement with published data,[1] the secondary substrates are prone to elimination and fluorinated products were accompanied by the corresponding alkenes. Fluorinations with difluorosilicates **1** were superior to TBAF in all cases. The use of TAMPS **1b** led to better results than TAMBS **1a**. Fluorinations of octan-2-yl mesylate with TAMBS **1a** and TAMPS **1b** (87/13 mixture of 2-fluorooctane/octenes) were more selective than fluorinations of octan-2-ol with Ishikawa reagent (71/29 mixture) or of oct-2-yltrimethylsilane with DAST (71/29 mixture).[1] Fluorination of 2-bromooctane with TAMPS **1b** (44% prep. yield) afforded results comparable with fluorination with copper(I) fluoride (51% prep. yield).[1]

Table Results of fluorinations with difluorosilicates **1**

Substrate/Reagent	Products (% rel.)			Prep. yield (%)
Octan-1-yl mesylate	1-Fluorooctane	Oct-1-ene	Oct-2-ene	1-Fluorooctane
TAMBS (**1a**)	100	-	-	81
TBAF	100	-	-	77
1-Bromooctane	1-Fluorooctane	Oct-1-ene	Oct-2-ene	1-Fluorooctane
TAMBS (**1a**)	90	10	-	67
TAMPS (**1b**)	98	2	-	73
TBAF	81	19	-	62
Octan-2-yl mesylate	2-Fluorooctane	Oct-1-ene	Oct-2-ene	2-Fluorooctane
TAMBS (**1a**)	89	3	8	66
TAMPS (**1b**)	87	3	10	68
TBAF	72	8	20	40
2-Bromooctane	2-Fluorooctane	Oct-1-ene	Oct-2-ene	2-Fluorooctane
TAMBS (**1a**)	27	9	64	20
TAMPS (**1b**)	63	2	35	44
TBAF	12	13	75	10
	Products (% rel.)[a]			
	2-Fluorooctane	Oct-1-ene	Oct-2-ene	Octan-2-ol
TAMPS + 5 H_2O	34	9	40	17

[a] Based on GLC analysis of crude reaction mixture

The major advantage of difluorosilicates **1** as compared with DAST is their good tolerance to water. When water was added to the fluorination mixture (five-molar excess to TAMPS **1b**), 17% (rel. yield) of octan-2-ol was formed together with still acceptable yields of 2-fluorooctane from 2-bromooctane.

In conclusion, we have developed a method for the preparation of nucleophilic fluorination reagents, which are safe, convenient, and suitable for laboratories without any special equipment. The fluorination reagents prepared, especially tetrabutylammonium difluorodimethylphenylsilicate (TAMPS, **1b**), are comparable with or superior to commercially available reagents.

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(6) NMR data for **1**: Tetrabutylammonium butyldifluorodimethyl-silicate (TAMBS, **1a**) ^{1}H NMR δ -0.18 (s, 6H), δ 0.29 (m, 2H), δ 0.67 (t, 3H, J = 6.1 Hz), δ 0.80 (t, 12H, J = 7.1 Hz), δ 1.10 (m, 2H), δ 1.20 (sextet, 8H, J = 7.2 Hz), δ 1.45 (quintet, 8H, J = 7.1 Hz), δ 3.00 (m, 8H); ^{13}C NMR δ -0.2, δ 13.0, δ 13.2, δ 17.6, δ 19.1, δ 23.2, δ 25.0, δ 25.8, δ 58.1; ^{19}F NMR δ -152.0 (s, 2F); Tetrabutylammonium difluorodimethyldiphenylsilicate (TAMPS, **1b**) ^{1}H NMR δ 0.06 (s, 6H), δ 0.74 (t, 12H, J = 7.7 Hz), δ 1.14 (sextet, 8H, J = 7.1 Hz), δ 1.34 (quintet, 8H, J = 7.4 Hz), δ 2.86 (m, 8H), δ 7.10 (m, 2H), δ 7.24 (m, 3H); ^{13}C NMR δ 0.4, δ 13.2, δ 19.4, δ 23.4, δ 58.3, δ 127.6, δ 129.2, δ 132.8, δ 140.0; ^{19}F NMR δ -157.1 (s, 2F).

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(8) Representative example of a preparative fluorination experiment: 4.79 g (15.2 mmol) of crystalline TBAF·3H$_2$O was dissolved in 40 mL of dry acetonitrile, followed by the addition of 2.42 g (15.7 mmol) of fluorodimethylphenylsilane. The mixture was stirred for 1 h at room temperature and octan-2-yl mesylate (1.41 g, 6.77 mmol) was added to it. The mixture was heated to gentle reflux (90 °C) for 24 h, cooled, partitioned between water and pentane, pentane extracts were dried over anhydrous MgSO$_4$ and pentane was removed by careful fraction distillation. Final vacuum distillation afforded 700 mg of crude product boiling at 35-39 °C/2.5 kPa, consisting of (analysis by ^{1}H NMR) 87% of 2-fluoroctane (68% prep. yield), 3% of oct-1-ene and 10% of (*E*)-oct-2-ene.

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