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Synthesis and applications of fluorous silyl protecting groups with improved acid stability

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Abstract

Fluorous alkoxysilyl protecting groups have been developed and evaluated for their acid stability. *tert*-Butylphenyl-1*H*,1*H*,2*H*,2*H*-heptadecafluorodecyloxysilyl (BPFOS) ethers in particular were found to be surprisingly acid stable and allow simple protection–purification–deprotection schemes by liquid–liquid extraction with FC-72/CH_3CN or by solid phase extraction with fluorous reverse phase silica gel. © 1999 Elsevier Science Ltd. All rights reserved.

Fluorous synthesis[1] schemes allow for easy purification or removal of highly fluorinated intermediates or reagents, e.g. via liquid–liquid extraction (3-phase extraction) between organic solvents, fluorinated solvents and water, or via solid phase extraction with fluorous reverse phase silica gel.[2] Ideally, one of the reactants is rendered fluorous by tagging it with a suitable fluorous protecting group which allows for easy purification in the subsequent steps of the reaction sequence. This fluorous tag should fulfill a double role as protective group and phase tag and is removed in the final step(s) of the synthesis. The viability of a fluorous synthesis plan hinges often on the availability of suitable fluorous protecting groups, but to date only a few alternatives have been described.[1,3]

For the preparation of a library of curacin A analogs we wanted to develop a fluorous silyl protecting group for alcohols readily cleavable with standard TBAF methodology but with superior acid stability compared to the known fluorous protecting groups. The classical fluorous silyl tag **1**[1] is quite acid sensitive (Fig. 1) and the corresponding silyl ethers can be cleaved with wet silica gel illustrating both acid lability and ease of nucleophilic attack.

Bis-alkoxysilyl ethers can be surprisingly acid stable,[5] so we decided to explore the viability of fluorous alkoxysilyl groups as protecting groups for alcohols. A secondary alcohol, cyclohexanol, was

Me_3Si- ~ $(C_6F_{13}CH_2CH_2)_3Si$- (**1**) < *t*-$BuMe_2Si$- < *t*-$BuPh_2Si$-

Figure 1. Acid stability of silane protecting groups for alcohols[1,4]

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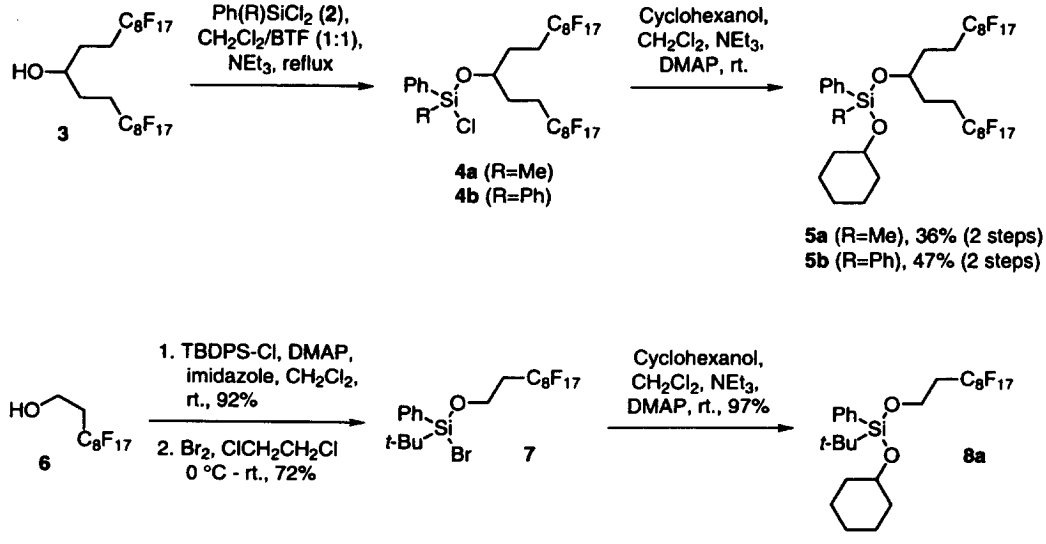
chosen as a prototypical substrate. Fluorous alkoxysilyl ethers (**5a,b**)[6] were readily prepared by reacting stoichiometric amounts of commercially available dichlorosilanes (**2**) with fluorous alcohol (**3**)[3b] to yield chlorosilanes **4a,b**, which were, however, contaminated with the bis-adduct of the fluorous alcohol (Scheme 1). Without purification, **4a,b** were used to protect cyclohexanol. The ensuing mixture was purified by solid phase extraction on fluorous reverse phase silica gel with hexane:acetone (50:1). The reported yields are isolated yields after separation from bis-adducts of the fluorous alcohol; conversion based on cyclohexanol was quantitative.



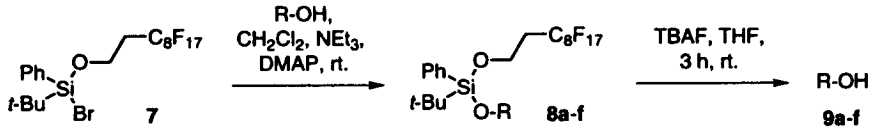
Scheme 1. Synthesis of fluorous alkoxysilyl derivatives

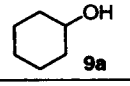
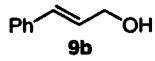
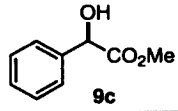
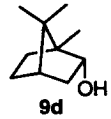
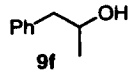
Alkoxysilyl ether **8a**[7] was derived from bromosilane **7**, which can easily be obtained in high yield and purity in a two-step sequence starting from *tert*-butyldiphenylsilylchloride (TBDPS-Cl) and alcohol **6** (Scheme 1).

Fluorous alkoxysilyl ethers (**5a,b**, **8a**) were each dissolved in a mixture of CH_2Cl_2/trifluoroacetic acid (5%), and aliquots of these solutions were quenched with MeOH:pyridine (20:1). The quenched reaction mixtures were analyzed for remaining **5a,b** and **8a** by LC–MS.[8] Not entirely unexpectedly, the stability of these alkoxysilyl ethers seems to be determined by the steric bulk around the silicon atom. While **5a** was not stable ($t_{1/2}$ ~6 min) under the acidic reaction conditions, **5b** ($t_{1/2}$ ~4 h) was moderately, and the *tert*-butyl-phenyl-1*H*,1*H*,2*H*,2*H*-heptadecafluorodecyloxysilyl ether **8a** ($t_{1/2}$ ≫6 h) completely, stable. This prompted us to investigate the chemical behavior of **8a** in somewhat greater detail. Due to the enhanced electrophilicity of the silicon atom in bis-alkoxysilyl ethers, the latter are generally more labile toward nucleophiles and bases than either the TBDPS or the *tert*-butyldimethylsilyl (TBDMS) groups.[5] Yet, after dissolving **8a** in a mixture of THF-d_8 and 0.25 M NaOD (3:1), we determined, by ^{1}H NMR, a $t_{1/2}$ of 48 h which suggests that the *tert*-butyl-phenyl-1*H*,1*H*,2*H*,2*H*-heptadecafluorodecyloxysilyl (BPFOS) tag can be used in mildly basic aqueous media. In contrast, the stability under protic acidic conditions in 5% *p*-TsOH/MeOH ($t_{1/2}$ ~40 min) is more limited. Based on these preliminary results, it appears that the BPFOS group is closely related in stability to the *tert*-butylmethoxyphenylsilyl group,[5] which is slightly more acid-labile than the TBDPS function but considerably more acid-stable than a TBDMS-ether.

We also explored the viability of the *tert*-butyl-phenyl-1*H*,1*H*,2*H*,2*H*-heptadecafluorodecyloxysilyl (BPFOS) protecting group for the protection of alcohols in a parallel synthesis experiment performed on an HP 7868 solution phase synthesizer. The silylbromide **7** was reacted with a panel of alcohols to

Table 1
Protection of alcohols **9a–f** with **7** (and deprotection of silyl ethers with TBAF)



Entry	R-OH	Yield for BPFOS attachment [%]	Yield for BPFOS cleavage [%]
1	 **9a**	79	77
2	 **9b**	77	88
3	 **9c**	24	nd
4	 **9d**	83	94
5	 **9e**	27	nd
6	 **9f**	62	100

yield the bis-alkoxysilyl ethers **8a–f** (Table 1).[9] Yields are based on isolated and characterized material (^{1}H NMR, MS) and are slightly lower than reported for the bulk synthesis of **8a** due to loss of material in the liquid–liquid extraction steps on the synthesizer. Purification in the deprotection step was via FC-72/CH_3CN liquid–liquid extraction and filtration through silica gel, and provided material of >90% purity.[10]

Primary and secondary alcohols give excellent to fair yields in the protection and deprotection steps while, probably for steric reasons, the tertiary alcohol *t*-butanol (entry 5) and the sterically demanding methyl mandelate (entry 3) provide poor yields.

In summary, we have developed a new acid stable fluorous silane label suitable for the protection of primary and secondary alcohols. The label is easily attached and removed in an automated parallel synthesis setup and allows for purification of intermediates and products via fluorous liquid–liquid or solid phase extraction.

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6. Preparation of **5b**: A solution of dichlorodiphenylsilane (0.7 mmol), alcohol **3** (0.7 mmol) and triethylamine (0.77 mmol) in a mixture of CH_2Cl_2 (2.5 mL) and benzotrifluoride (BTF, 2.5 mL) was heated at reflux for 1.5 days. Solvents were evaporated and the residue was partitioned between FC-72 and CH_2Cl_2. The FC-72 phases were combined and evaporated. The residue was dissolved in CH_2Cl_2 (5 mL). Cyclohexanol (0.47 mmol), triethylamine (0.65 mmol) and dimethylaminopyridine (DMAP, 0.02 mmol) were added and the mixture was stirred at rt overnight. 3-Phase extraction ($NaHCO_3$ solution, CH_2Cl_2, FC-72) yielded, after pooling and evaporation of the FC-72 phase, a colorless oil. Filtration over fluorous reverse phase silica (hexane:acetone, 50:1) gave 0.24 g (47%) of **5b** as a colorless oil which solidified upon standing: ^{1}H NMR ($CDCl_3$) δ 7.62–7.59 (m, 4H), 7.45–7.35 (m, 6H), 3.98–3.92 (m, 1H), 3.82–3.73 (m, 1H), 2.3–1.9 (m, 4H), 1.9–1.6 (m, 8H), 1.5–1.3 (m, 3H), 1.2–1.0 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 134.9, 132.8, 130.5, 128.0, 125–105 (m, 16C), 71.8, 70.6, 35.5, 27.4, 27.2 (b), 25.4, 23.9; MS(EI) *m/z* (rel. intensity) 1204 (M^+, 4), 1185 (5), 1126 (85).
7. Preparation of **8a**: A solution of TBDPS-Cl (26.5 mmol), alcohol **6** (24.1 mmol), DMAP (1.2 mmol) and imidazole (33.8 mmol) in CH_2Cl_2 (50 mL) was stirred at rt overnight. CH_2Cl_2 was added and the solution was washed with H_2O, 1 M HCl and brine. Drying (Na_2SO_4) and evaporation of the solvent yielded the TBDPS ether as a colorless oil: 15.5 g (92%). ^{1}H NMR ($CDCl_3$) δ 7.69–7.66 (m, 4H), 7.45–7.38 (m, 6H), 3.96 (t, 2H), 2.45–2.25 (m, 2H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 135.2, 134.9, 129.9, 127.9, 125–105 (m, 8C), 56.3, 33.9 (b), 26.6, 19.1. Bromine (26.5 mmol) was added dropwise to a solution of the TBDPS ether (22.1 mmol) in 1,2-dichloroethane (150 mL) at 0°C. Stirring continued at rt overnight. Distillation (0.03 mbar/105–110°C) yielded 11.3 g (72%) of **7** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.69–7.65 (m, 2H), 7.48–7.39 (m, 3H), 4.11–4.06 (m, 2H), 2.47–2.35 (m, 2H), 1.01 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 135.6, 134.9, 131.1, 128.1, 125–105 (m, 8C), 57.0, 34.0 (b), 25.1, 21.4. Compound **7** (1.1 mmol) was dissolved in CH_2Cl_2 (5 mL). Cyclohexanol (1 mmol), triethylamine (1.4 mmol) and dimethylaminopyridine (DMAP, 0.05 mmol) were added and the mixture was stirred at rt overnight. CH_2Cl_2 was added and the mixture was washed with $NaHCO_3$ solution. The organic phase was dried (Na_2SO_4), the solvent was removed and the residue filtered through SiO_2 (hexane:EtOAc, 98:2) to give 0.70 g (97%) of **8a** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.65–7.60 (m, 2H), 7.42–7.35 (m, 3H), 4.11 (t, 2H, *J*=6.9 Hz), 3.95–3.88 (m, 1H), 2.50–2.35 (m, 2H), 1.84–1.72 (m, 4H), 1.52–1.40 (m, 3H), 1.30–1.21 (m, 3H), 0.94 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 135.5, 132.3, 129.9, 127.8, 125–105 (m, 8C), 71.1, 55.7, 35.7, 34.1 (b), 26.1, 25.6, 23.7, 18.8; HRMS(EI) *m/z* found 723.1597; calcd 723.1587.
8. Reactions and quenching were performed on a HP 7868 solution phase synthesizer. Analysis of quenched samples was done with a HP 1100 series LC–MS. Samples eluted were compared with unreacted control samples. (R_t [min]: 2.6 (**5a**), 2.9 (**5b**), 2.3 (**8a**); Novapak C18, 3.9×150 mm, 1.2 mL/min, MeOH as eluent).
9. Alcohols **9a–f** (0.16 mmol) were added to a solution containing the appropriate amount of reagents in 0.7 mL of CH_2Cl_2. The samples were vortexed and left for 16 h. The solutions were washed with H_2O, the organic phase was evaporated and the residue was eluted with hexane through cartridges containing SiO_2.
10. Silyl ethers were added to a solution of TBAF (0.6 M) in 0.5 mL of THF. After 3 h, Et_2O was added, the solutions were washed with H_2O (3 times), the Et_2O phase was collected, evaporated and the residue was partitioned between FC-72 and CH_3CN. The organic phase was eluted with hexane/AcOEt through a SiO_2 cartridge.