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Fluorous TBAF: A Convenient and Selective Reagent for Fluoride-Mediated Deprotections

Santos Fustero,*[,†,‡] Amador García Sancho,[‡] José Luis Aceña,[‡] and Juan F. Sanz-Cervera[†,‡]

[†]*Departamento de Química Orgánica, Universidad de Valencia, E-46100 Burjassot, Spain, and* [‡]*Laboratorio de Moléculas Orgánicas, Centro de Investigación Príncipe Felipe, E-46012 Valencia, Spain*

santos.fustero@uv.es

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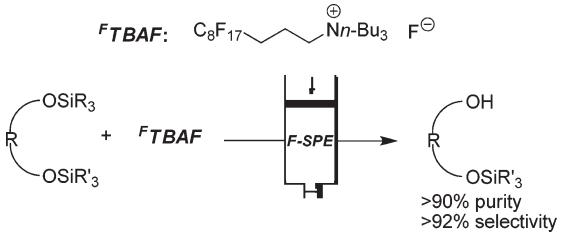

A fluorous analogue of TBAF has been developed for its use in the clean removal of silicon-derived protecting groups. Purification of the crude mixtures by fluorous solid-phase extractions allowed alcohols, amines, and carboxylic acids to be obtained in high purity, with no need of chromatographic separations. The moderate reactivity of fluorous TBAF was exploited in selective deprotections of several bifunctional molecules.

The purification of reaction products often constitutes the most time-consuming step within a synthetic sequence.[1] Several techniques have been developed in order to make this part of the process faster and simpler, including the use of solid-supported tags, reagents, and scavengers, all of which facilitate the purification of reaction products by means of simple washings and filtrations of the crude reaction mixtures.[2] In a similar manner, fluorous procedures employ highly fluorinated (fluorous) reagents and materials which can then be easily separated from nonfluorous species through liquid−liquid or solid−liquid extractions, depending on the number of fluorine atoms introduced. Thus, among the many applications of fluorous chemistry are the use of fluorous reagents as protecting groups, scavengers, and tags for conventional, parallel, or mixture syntheses.[3]

Silicon-derived reagents are routinely employed in syntheses of complex molecules for the convenient protection of alcohols (TMS and derived groups), carboxylic acids [2-(trimethylsilyl)ethyl (TMSE) group], and amines [2-(trimethylsilyl)ethoxycarbonyl (Teoc) group].[4] Many reaction conditions for their removal that are compatible with other functional groups have been described, but these usually involve treatment with fluoride reagents. In the case of acid-sensitive substrates, tetra-*n*-butylammonium fluoride (TBAF) is the reagent of choice. However, TBAF-mediated deprotections often suffer from the drawback that the elimination of excess TBAF and/or tetra-*n*-butylammonium (TBA) salts can be somewhat difficult. This is particularly problematic in the case of water-soluble products or when standard chromatographic separations are not possible. Several solutions to this problem involve the precipitation of insoluble TBA salts[5] or the use of polymer-supported scavengers.[6] In these cases, filtration techniques can then be used to isolate pure, TBAF-free, deprotected products.

These challenges motivated us to design and synthesize a fluorous analogue of TBAF (^{F}TBAF, **1**) with the aim of facilitating the separation of TBA byproducts. Thus, the replacement of an *n*-butyl chain in TBAF with a perfluoroalkyl derivative would afford a light fluorous molecule that would be suitable for purification through fluorous solid-phase extractions (F-SPE)[7] (Figure 1).

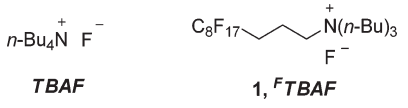

FIGURE 1. Structures of TBAF and ^{F}TBAF.

The synthesis of fluorous TBAF **1** was easily carried out in two steps from commercially available iodide **2** (Scheme 1) on a multigram scale. While treatment of **2** with *n*-Bu_3N in refluxing MeCN led to moderate yields of fluorous TBAI **3**,[8] the reaction was considerably more efficient when performed in a sealed vessel at 150 °C. Subsequent reaction of **3** with excess aqueous HF was followed by treatment of the organic extracts with solid KF. After filtration, the ethereal phase was carefully concentrated to afford a 0.1−0.3 M solution of ^{F}TBAF in THF. The concentration of the resulting ^{F}TBAF solution was quantified with the aid of ^{1}H NMR integration of the perfluoroalkyl and THF signals. Subsequent ^{19}F NMR analysis confirmed that full conversion was achieved, as judged by the integration of both fluoride (−155.2 ppm) and fluorous signals.

(1) Curran, D. P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1174–1196.
(2) (a) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc. Perkin Trans. 1* **2000**, 3815–4195. (b) Solinas, A.; Taddei, M. *Synthesis* **2007**, 2409–2453.
(3) (a) Zhang, W. *Tetrahedron* **2003**, *59*, 4475–4489. (b) *Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horváth, I. T., Eds.; Wiley-VCH: Weinheim, Germany, 2004. (c) Zhang, W. *Chem. Rev.* **2004**, *104*, 2531–2556. (d) Zhang, W. *Curr. Opin. Drug Discovery Dev.* **2004**, *7*, 784–797. (e) Zhang, W. *Chem. Rev.* **2009**, *109*, 749–795.
(4) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; John Wiley and Sons: Hoboken, NJ, 2007.
(5) Craig, J. C.; Everhart, E. T. *Synth. Commun.* **1990**, *20*, 2147–2150.
(6) (a) Parlow, J. J.; Vazquez, M. L.; Flynn, D. L. *Biorg. Med. Chem. Lett.* **1998**, *8*, 2391–2394. (b) Kaburagi, Y.; Kishi, Y. *Org. Lett.* **2007**, *9*, 723–726.
(7) (a) Curran, D. P. *Synlett* **2001**, 1488–1496. (b) Curran, D. P. *Aldrichim. Acta* **2006**, *39*, 3–9. (c) Zhang, W.; Curran, D. P. *Tetrahedron* **2006**, *62*, 11837–11865.
(8) For the synthesis of similar fluorous TBAI analogues, see: Gupta, O. D.; Armstrong, P. D.; Shreeve, J. M. *Tetrahedron Lett.* **2003**, *44*, 9367–9370.

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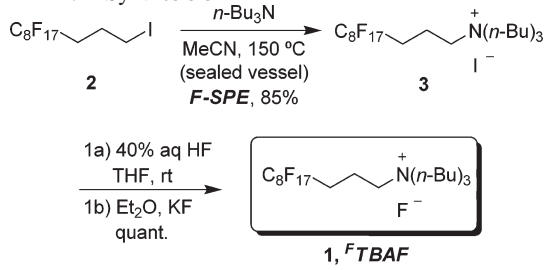
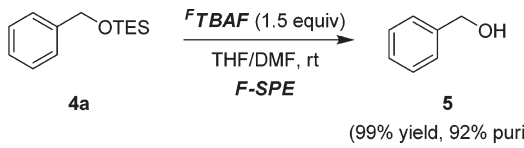
SCHEME 1. Synthesis of ^{F}TBAF



SCHEME 2. Deprotection of BnOTES



We next tested the synthetic applications of ^{F}TBAF, as well as the ease with which the reaction products could be purified, using silyl-protected benyl alcohols as model systems. The first experiment was a deprotection of BnOTES (**4a**) (THF/DMF, rt, 30 min), which resulted in the isolation of benzyl alcohol **5** (Scheme 2) in high yield and with high purity (as per GC-MS analysis), with no trace of TBA salts after a simple purification through F-SPE[9] (Figure 2). In contrast, a similar reaction with nonfluorous TBAF typically requires a chromatographic separation.

Other silicon-derived protecting groups such as TBS or TIPS proved to be much more resistant than a TES group when removed with ^{F}TBAF under the same reaction conditions (Table 1, entries 1−3). In contrast, BnOTBS (**4b**) and BnOTIPS (**4c**) were easily deprotected with nonfluorous TBAF in only 10 or 30 min, respectively (entries 4 and 5). For the complete removal of TBS and TIPS groups with ^{F}TBAF much longer reaction times were needed at room temperature (entries 6 and 7) or alternatively the reaction was more conveniently carried out under microwave irradiation (entries 8 and 9). The latter conditions were also applied for the simultaneous removal of a primary and a secondary TBS groups in compound **6** (Scheme 3).

After obtaining these results, we focused on molecules which are commonly difficult to separate from TBA byproducts, such as amines or carboxylic acids, which were obtained in high purity after F-SPE (Table 2, entries 1 and 2). Conversely, transesterification of TMSE-protected α-imino ester **12** through reaction with ^{F}TBAF/BnBr easily afforded the corresponding benzyl ester **13** (entry 3).[10]

(9) The crude mixture was eluted through fluorous silica gel with 67% aqueous MeOH to afford pure BnOH, whereas all fluorous species remained adsorbed onto the solid support. The low solubility of the TES-F byproduct precluded its elution in the fluorophobic fraction.

(10) The α-imino acid was too unstable to allow its isolation, see: Fustero, S.; Sánchez-Roselló, M.; Rodrigo, V.; García, A.; Catalán, S.; del Pozo, C. *J. Org. Chem.* **2008**, *73*, 5617–5620.

(11) (a) Studer, A.; Curran, D. P. *Tetrahedron* **1997**, *53*, 6681–6696. (b) Röver, S.; Wipf, P. *Tetrahedron Lett.* **1999**, *40*, 5667–5670. (c) Palmacci, E. R.; Hewitt, M. C.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4433–4437. (d) Nakamura, H.; Linclau, B.; Curran, D. P. *J. Am. Chem. Soc.* **2001**, *123*, 10119–10120. (e) Zhang, W.; Luo, Z.; Chen, C. H.-T.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 10443–10450. (f) Manzoni, L. *Chem. Commun.* **2003**, 2930–2931. (g) Manzoni, L.; Castelli, R. *Org. Lett.* **2004**, *6*, 4195–4198. (h) Crich, D.; Grant, D.; Bowers, A. A. *J. Am. Chem. Soc.* **2007**, *129*, 12106–12107. (i) Carrel, F. R.; Seeberger, P. H. *J. Org. Chem.* **2008**, *73*, 2058–2065. (j) García Sancho, A.; Wang, X.; Sui, B.; Curran, D. P. *Adv. Synth. Catal.* **2009**, *351*, 1035–1040.

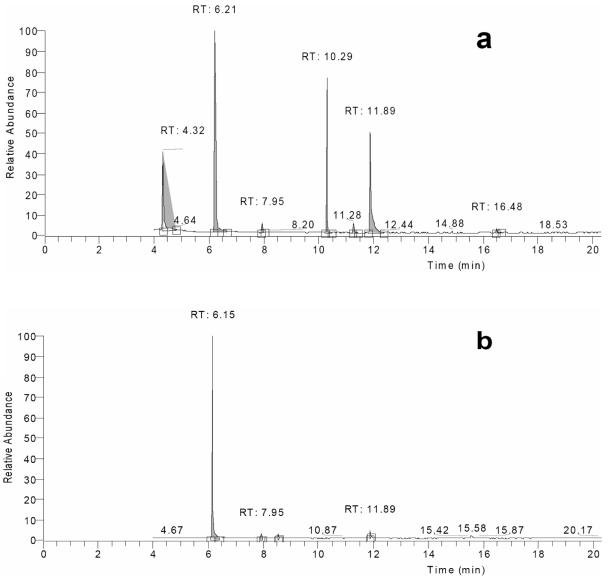
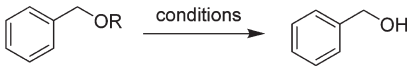


FIGURE 2. GC analysis of the reaction of BnOTES (**4a**) with ^{F}TBAF: (a) crude reaction mixture and (b) after purification by F-SPE.

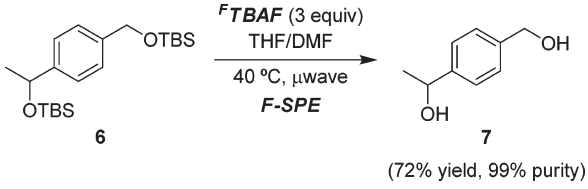
TABLE 1. Deprotection of Silylated Derivatives of Benzyl Alcohol



entry	R		conditions[a]	time (h)	*t* (°C)	yield (%)[b]	purity (%)[c]
1	TES	**4a**	A	0.5	25	99	92
2	TBS	**4b**	A	0.5	25	4[d]	
3	TIPS	**4c**	A	0.5	25	1[d]	
4	TBS	**4b**	B	0.15	25	100[d]	
5	TIPS	**4c**	B	0.5	25	100[d]	
6	TBS	**4b**	A	18	25	92	93
7	TIPS	**4c**	A	48	25	88	94
8	TBS	**4b**	A	0.75	60[e]	85	96
9	TIPS	**4c**	A	0.75	40[e]	83	91

[a]Conditions A: ^{F}TBAF (15equiv), THF/DMF, purification by F-SPE. Conditions B: TBAF (1.5 equiv), THF/DMF. [b]Isolated yield after F-SPE purification [c]Measured with the aid of GC-MS [d]Conversion determined in the crude mixture through GC-MS; F-SPE was not carried out[e]Reaction performed under microwave irradiation

SCHEME 3. Deprotection of Primary and Secondary TBS Groups



Fluorous silyl protecting groups have recently been developed for the convenient protection of alcohols,[11] carboxylic acids,[12] and amines.[13] Still, when TBAF is used for their

(12) Fustero, S.; García Sancho, A.; Chiva, G.; Sanz-Cervera, J. F.; del Pozo, C.; Aceña, J. L. *J. Org. Chem.* **2006**, *71*, 3299–3302.

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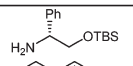
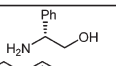
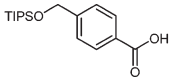
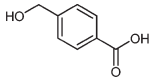
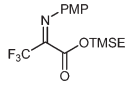
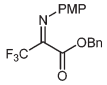
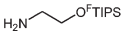
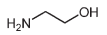
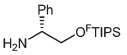
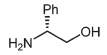
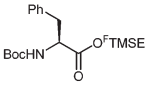
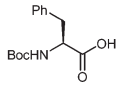
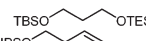
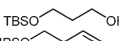
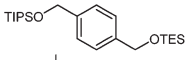
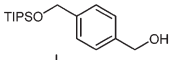
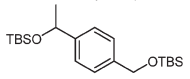
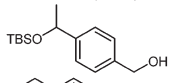
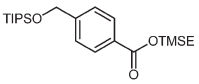
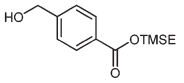
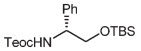
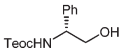
TABLE 2. ^{F}TBAF-Mediated Deprotection of Silylated Substrates

entry	substrate		equiv of ^{F}TBAF	time (h)	*t* (°C)	product		yield (%)[a]	purity (%)[b]
1		**8**	1.5	12	25		**9**	88	93
2		**10**	2.0	12	25		**11**	95	92
3[c]		**12**	2.0	2	25		**13**	94	92
4		**14**	1.5	3	25		**15**	86	93
5		**16**	1.5	3	25		**9**	84	94
6		**17**	4.0	1	40[d]		**18**	72	>99

[a]Isolated yield after F-SPE purification[b]Measured with the aid of GC-MS or HPLC[c]Reaction performed with 10equiv of BnBr. [d]Reaction performed under microwave irradiation^{F}TIPS = Si(*i*-Pr)$_2$(CH$_2$)$_2$C$_8$F$_{17}$. ^{F}TMSE = (CH$_2$)$_2$SiMe$_2$(CH$_2$)$_3$C$_8$F$_{17}$.

TABLE 3. ^{F}TBAF-Mediated Selective Deprotections

entry	substrate		equiv of ^{F}TBAF	time (h)	*t* (°C)	product		yield (%)[a]	purity (%)[b]
1		**19**	1.1	0.15	0		**20**	79	98
2		**21**	1.1	0.15	0		**22**	100[c,d]	
3		**6**	1.1	12	0		**23**	97[c,e]	
4		**24**	2.0	12	0 to 25		**25**	87	>99
5		**26**	2.5	16	0 to 25		**27**	95	97

[a]Isolated yield after F-SPE purification [b]Measured with the aid of GC-MS[c]Conversion determined in the crude mixture through GC-MS; F-SPE was not carried out[d]92:8 ratio of TIPS-protected diol and free diol[e]98:2 ratio of mono-TBS-protected diol and starting material

removal, further purification may be needed after F-SPE in order to remove the TBA salts completely. In this kind of process, however, the combination of ^{F}TIPS group[11c–e] protection and ^{F}TBAF deprotection is extremely useful for the efficient deprotection of alcohols (entries 4 and 5). In a similar fashion, the ^{F}TMSE group developed by our group[12] was also easily and efficiently cleaved by the action of ^{F}TBAF (entry 6).

The observed moderate reactivity of ^{F}TBAF is probably a consequence of the electron-withdrawing effect of the perfluoroalkyl chain. This prompted us to undertake several selective deprotections,[14] all of which proceeded smoothly in several bis-silylated subtrates with careful control of the amount of ^{F}TBAF and the reaction conditions (Table 3). For instance, a primary TES group was selectively cleaved in the presence of primary TBS or TIPS groups in compounds **19** and **21**, respectively (entries 1 and 2). Furthermore, it was possible to discriminate between primary and secondary TBS groups of compound **6** by the action of ^{F}TBAF (entry 3). On the other hand, silyl-protected alcohols **24** and **26** were completely deprotected in the presence of a TMSE ester or a Teoc carbamate, respectively (entries 4 and 5).[15] It should be noted that all those selective deprotections are more difficult to achieve with nonfluorous TBAF, and usually need to be buffered with AcOH.[16] For instance, deprotection of compound **6** afforded an almost equimolecular mixture of starting material and monoprotected products **23** and **28** when TBAF/AcOH was used, in stark contrast with the results achieved with ^{F}TBAF (Scheme 4).

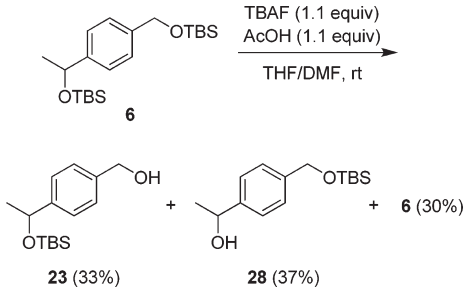
In summary, fluorous tetra-*n*-butylammonium fluoride (^{F}TBAF) has been easily prepared in two steps from commercial sources and tested in the efficient cleavage of silicon-based protecting groups. The deprotected products

(14) For reviews, see: (a) Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031–1069. (b) Crouch, R. D. *Tetrahedron* **2004**, *60*, 5833–5871. For selected examples, see: (c) Shah, S. T. A.; Singh, S.; Guiry, P. J. *J. Org. Chem.* **2009**, *74*, 2179–2182. (d) Chen, M.-Y.; Lee, A. S.-Y. *J. Org. Chem.* **2002**, *67*, 1384–1387. (e) Schwarz, S.; Schumacher, M.; Ring, S.; Nanninga, A.; Weber, G.; Thieme, I.; Undeutsch, B.; Elger, W. *Steroids* **1999**, *64*, 460–471. (f) Collington, E. W.; Finch, H.; Smith, I. J. *Tetrahedron Lett.* **1985**, *26*, 681–684.

(15) Both the TMSE and Teoc groups in compounds **24** and **26** (Table 3, entries 4 and 5) were stable even in the presence of a larger excess of FTBAF. In contrast, 2 equiv of nonfluorous TBAF fully deprotected both substrates.

(16) For examples, see ref [14b] and: Yashunsky, D. V.; Borodkin, V. S.; Ferguson, M. A. J.; Nikolaev, A. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 468–474.

SCHEME 4. Nonselective Deprotection with TBAF



are obtained in high yields and with high purities after a rapid, simple purification through F-SPE, making this method particularly useful in the case of polar compounds such as amines and carboxylic acids. The lower reactivity of ^{F}TBAF compared to TBAF allowed the selective deprotection of specific silyl groups. Further applications of this novel reagent are currently under study in our laboratories.

Experimental Section

Synthesis of ^{F}TBAI (3). *n*-Bu_3N (0.79 mL, 3.3 mmol) was added to a solution of **2** (1.80 g, 3 mmol) in MeCN (30 mL). The reaction was heated in a sealed tube at 150 °C. After 24 h the solvent was removed under reduced pressure and the crude material was purified with F-SPE to afford 1.98 g of **3** as a white solid (85% yield). Mp 82−83 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, J = 7.4 Hz, 9H), 1.25−1.35 (m, 6H), 1.57 (br, 6H), 1.93 (br, 2H), 2.18−2.33 (m, 2H), 3.24−3.30 (m, 6H), 3.47−3.53 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.1, 14.1, 19.1, 23.9, 27.2 (t, J = 22.0 Hz), 57.5, 59.1, (the signals from the C_8F_{17} group were obscured due to their low intensity). ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −81.4 (t, 3F, J = 9.9 Hz), −113.8 (br, 2F), −122.1 (s, 6F), −123.2 (s, 2F), −123.4 (s, 2F), −126.7 (s, 2F). HRMS (FAB) calcd for $C_{23}H_{33}F_{17}N$ $[M - I]^+$ 646.2341, found 646.2331.

Synthesis of ^{F}TBAF (1). HF (40% aqueous, 20 mL, 460 mmol) was added to a solution of **3** (1.55 g, 2 mmol) in THF (40 mL). After 6 h, the mixture was diluted with Et_2O, and the aqueous layer was extracted with Et_2O several times. The organic extracts were stirred in the presence of KF (26.7 g, 460 mmol). The mixture was filtered then the filtrates were diluted with THF and concentrated to a residual volume of ca. 10 mL. This process was repeated three times to ensure the full evaporation of Et_2O. The final concentration of the ^{F}TBAF solution in THF (typically 0.1−0.3 M) was measured by ^{1}H NMR analysis. This solution was stored under argon at room temperature and used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (t, J = 7.5 Hz, 9H), 1.19−1.26 (m, 6H), 1.50 (br, 6H), 1.83−1.85 (m, 2H), 2.18 (br, 2H), 3.14−3.16 (m, 6H), 3.37−3.42 (m, 2H). ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −81.4 (br, 3F), −113.7 (br, 2F), −122.1 (br, 6F), −122.9 (s, 2F), −123.3 (s, 2F), −126.4 (s, 2F), −155.2 (br, 1F).

General Procedure for the ^{F}TBAF-Mediated Deprotections. ^{F}TBAF (THF solution) was added to a solution of the protected substrate (1 equiv) in DMF (0.05M). The reaction was stirred at the temperature and time indicated in each case. Then, the THF was removed under a N_2 stream and the crude material was purified by F-SPE. The deprotected products were identified by comparison with commercially available samples or previously reported compounds.

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Supporting Information Available: Experimental procedures and copies of NMR spectra and GC-MS and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.