Tetramethylfluoroformamidinium Hexafluorophosphate (TFFH) as a Mild Deoxofluorination Reagent

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Abstract: The solid, air-stable peptide coupling reagent TFFH (tetramethylfluoroformamidinium hexafluorophosphate) was found to activate a variety of alcohols towards deoxofluorination. These conditions are compatible with carbonyl functional groups thus offering interesting possibilities for the application to sensitive molecules.

Key words: deoxofluorination, fluoroformamidinium, fluoride, TFFH, fluorination

The introduction of fluorine atoms into molecules has received an increasing interest in the literature.[1] In particular, the conversion of alcohols to the corresponding fluorinated analogues via deoxofluorination is now part of the chemical toolkit.[1a,2] If DAST and Deoxo-Fluor have become the standard reagents for such a transformation (Figure 1),[3] few applications on larger scale have been reported due to their limited chemoselectivity and functional group tolerance.[4] Moreover, the physical properties of these fuming liquids further restricts their applicability.[5] In response to these limitations, aminodifluorosulfinium salts offer similar reactivity with enhanced thermal stability. These crystalline salts based on the reactivity of the sulfur–fluorine bond have emerged as novel reagents for a variety of deoxofluorination reactions.[6] Nonetheless, the discovery of new classes of reagents based on the reactivity of a different motif is of interest.

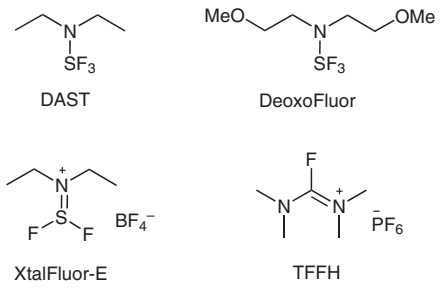
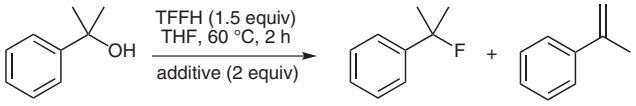


Figure 1 Structures of common deoxofluorination reagents compared with TFFH

We were thus interested by reports on the use of TFFH, a stable white crystalline solid,[7] to generate acyl fluorides for the preparation of amide bonds.[8] Interestingly, only limited applications of this reagent have been reported despite its remarkable functional group tolerance. We envisioned that TFFH could be used to promote the deoxofluorination of alcohols under suitable conditions. Our objectives were to identify these conditions and further underline their limitations in prevision to the use of this reagent for the deoxofluorination of complex drug candidates in our pipeline. 2-Phenylpropan-2-ol was thus chosen as benchmark substrate for the optimization hoping its sensitivity towards elimination would lead us to identify mild conditions for the desired transformation (Table 1). As only elimination was observed with TFFH alone,[9] we sought to buffer the HPF_6 by-product by the addition of a base, thus hoping to minimize side reactions. Interestingly, triethylamine proved ineffective while modest albeit encouraging results were obtained using DMAP. Based on this finding we hypothesized that the presence of exogenous fluoride would enhance the reactivity and favor substitution over elimination. Following the findings of Couturier et al.,[6] decent conversion to the

Table 1 Optimization of the Additive



Entry	Additive	Conv. (%)	Ratio of **2**/**3**	Yield of **2** (%)[a]
1	–	15	–	0[b]
2	Et_3N	10	–	0
3	DMAP	23	1.3:1	13
4	KF	0	–	0
5	TBAF	0	–	0
6	Py–HF	48	–	0[b]
7	Et_3N–3HF	0	–	0
8	Et_3N–3HF + Et_3N	55	4.8:1	50
9[c]	Et_3N–3HF + 2 Et_3N	53	4.7:1	43
10[d]	Et_3N–3HF + Et_3N	0	–	0

[a] In situ GC yield based on internal standard (PhCl).
[b] Only elimination was observed.
[c] Corresponds to 2 equiv of Et_3N–3HF + 4 equiv of Et_3N vs. **1**.
[d] Reaction was carried out without TFFH.

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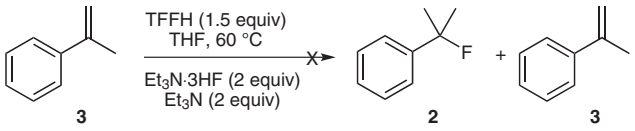
desired tertiary fluoride **2** was finally obtained when using Et_3N–3HF[10] with additional Et_3N (entries 8 and 9).

To gain a better understanding of the reaction and product ratio α-methylstyrene was submitted to the reaction conditions (Scheme 1). Interestingly, no conversion was observed and the styrene was recovered intact after 48 hours at 60 °C. This result highlights that under these conditions the products arising from the deoxofluorination of alcohols is of kinetic origin; the reaction does not proceed via dehydration followed by subsequent hydrofluorination of the styrene.[11]



Scheme 1 Reaction of α-methylstyrene under the deoxofluorination conditions

We then sought to gain understanding of the fate of TFFH in the presence of additional HF with the rationale that an equilibrium with the corresponding difluoromethylene diamine (**4**) species might be existing in solution (Equation 1). The exact nature of the active reagent is of interest given the published ability of such reagents to perform deoxofluorination reactions but also in light of potential intellectual property rights governing their use.[12]

Equation 1 Potential equilibrium of TFFH with the difluoromethylene diamine analogue

A series of ^{19}F NMR studies were undertaken using the commercially available 2,2-difluoro-1,3-dimethyl imidazolidine (DFI) as reference to monitor the *gem*-difluoro moiety. Our data supports the presence of the fluoroformamidinium function as resting species of this reaction mixture and a difluoromethylene diamine unit was not detected (Figure 2).[13]

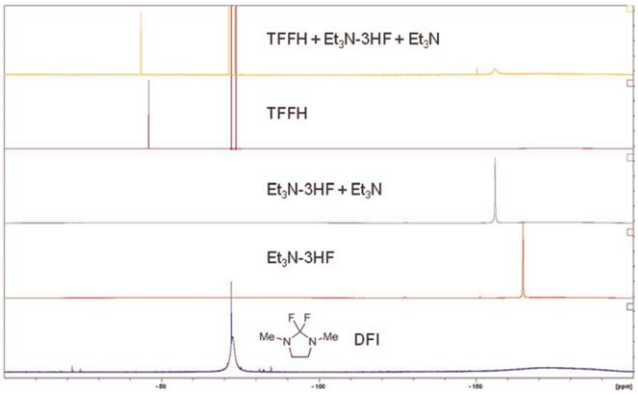


Figure 2 Comparative ^{19}F NMR of fluorinated species

Based on these findings, we screened a variety of haloformamidinium salts in order to identify other potential activators sharing this motif (Figure 3). This evaluation rapidly highlighted ability of chloro iminium salts to promote the incorporation of the chlorine atom in a deoxochlorination reaction. The evaluation of alternative fluoroformamidinium salts only supported the superiority of TFFH to mediate the desired deoxofluorination. Focus was thus put on the optimization of the reaction featuring TFFH as the key promoter given its commercial availability and stability.[14]

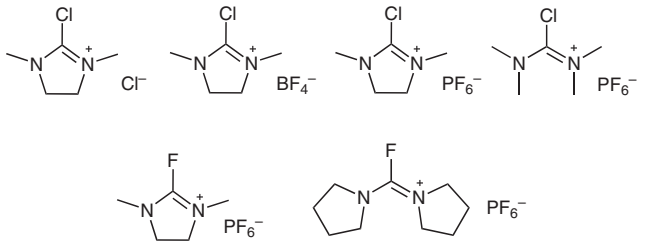
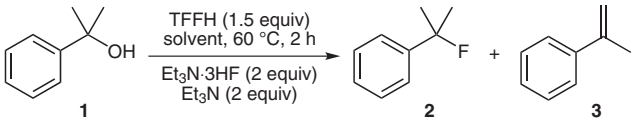


Figure 3 Structures of haloformamidinium reagents evaluated for the deoxofluorination of alcohols

The optimization of the reaction solvent was examined next (Table 2). Although conversions were not optimized, it is interesting that a variety of solvents can produce similar ratio of products and in situ yields. The compatibility of these conditions to such an array of solvents can be appealing when the solubility of starting alcohols is restricted. Nonetheless, EtOAc was selected for the remaining of our study.[15]

Table 2 Solvent Screen



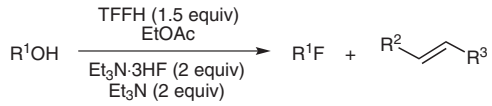
Entry	Solvent	Conv. (%)	Ratio of **2**/**3**	Yield of **2** (%)[a]
1	THF	55	4.8:1	50
2	2-MeTHF	41	4.3:1	33
3	*i*-PrOAc	42	4.6:1	35
4	MeCN	56	4.7:1	46
5	EtOAc	71	6.2:1	62
6	toluene	84	3.7:1	66
7	CH_2Cl_2	73	4.3:1	59
8	DMF	32	2.1:1	22

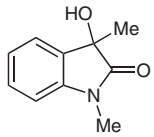
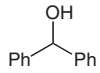
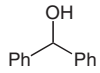
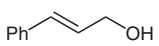
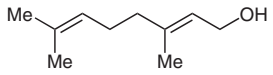
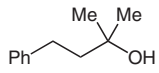
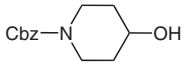
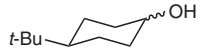
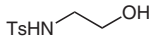
[a] In situ GC yield based on internal standard (PhCl).

We next evaluated the generality of the reaction by examining a variety of alcohols, again with the intent to understand the limitations of the method (Table 3). The reaction was found to proceed readily with benzylic alcohols, providing the corresponding benzylic fluorides in high yields

after less than hour at ambient temperature. Allylic alcohols could also be converted under similar conditions to mixtures of allylic fluorides. In an attempt to define the reactivity limits of this system, an aliphatic tertiary alcohol was subjected to the deoxofluorination conditions (entry 6). Although the reaction required prolonged heating, we were delighted to observe the desired tertiary fluoride in 67% in situ yield. Finally, these conditions seem incompatible with cyclic secondary alcohols and an ethanol amine derivative as they were found to favor dehydration vs. deoxofluorination.

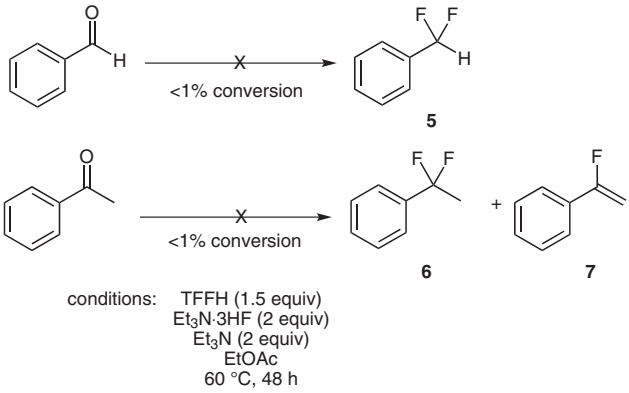
Table 3 Scope of Alcohols



Entry	ROH	Temp (°C)	Time (h)	Ratio[a] of **RF/elim**	Yield (%)[b]
1		23	1	100:0	83
2		23	1	100:0	83
3		23	1	10:1	(90)
4		23	1	100:0	(>99)[c]
5		23	1	8:1	(51)
6		60	16	2.5:1[d]	(67)
7		23	1	1:5	(18)
8[e]		23	1	0:100	0
9		23	1	0:100	0

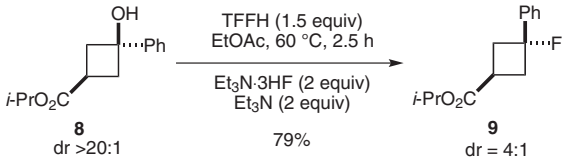
[a] Ratio of products determined by GC–MS.
[b] Isolated yields unless otherwise noted. Yields between parentheses are in situ GC yields based on an internal standard (PhCl).
[c] A mixture of fluorinated isomers (1:1) was obtained.
[d] A mixture of elimination products was obtained.
[e] Both *cis*- and *trans*-isomers gave the same results.

With an understanding of the scope of alcohols, we sought to evaluate the sensitivity of carbonyl species to these conditions (Scheme 2). Benzaldehyde and acetophenone were thus independently subjected to the TFFH-promoted deoxofluorination conditions at 60 °C to stress any potential reactivity. We were pleased to find that both compounds could be recovered in high yields (>95%) even after prolonged exposure to the reagents. Given the ability of common reagents based on S–F chemistries to transform carbonyl groups to *gem*-difluoro moieties, the inability of TFFH to promote such a transformation even under forcing conditions should open the way for the application of our method to complex systems.[16]



Scheme 2 Reactivity of benzylic carbonyl functions

Having defined the limitations and some opportunities, we were particularly interested to apply the method to a model substrate of a drug candidate in development at Pfizer. When subjected to our conditions, **8** provided the corresponding fluorocyclobutane **9** in 79% isolated yield as a 4:1 mixture of diastereoisomer favoring overall inversion of stereochemistry (Scheme 3). Interestingly, the opposite diastereoisomer of **8** (ester and phenyl *syn*) also provided the same diastereomeric ratio of **9**. This result suggests the presence of a common carbocationic intermediate accessed by an S_N1 mechanism.



Scheme 3 Model study for drug candidate

In summary, we have developed novel conditions for the deoxofluorination of alcohols by using the bench-stable TFFH as a promoter in the presence of added HF reagents that are commercially available.[17] The mildness of these conditions should allow their application to complex systems featuring carbonyl functions, offering an alternative reactivity to existing methods. The application of this deoxofluorination method to a drug candidate is underway and will be reported in due course.

Acknowledgment

We are grateful to David R. Bill of Pfizer for performing the DSC analysis of TFFH.

References and Notes

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(7) Differential scanning calorimetry (DSC) analysis of TFFH revealed a generation of 146 J/g at T_{max} of 370 °C. See reference 6a for comparative data with other reagents.

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(11) This conclusion can only be applied to a subset of the reactions studied as this behavior could be substrate dependent.

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(13) ^{19}F NMR experiments were collected using a Bruker-Biospin 5 mm BBFO probe on Bruker AVANCE III NMR spectrometer operating at 400 MHz. Limit of detection evaluated at 0.1%.

(14) The activity of commercial TFFH was found to vary among suppliers. Material from TCI and Oakwood consistently provided reproducible results.

(15) Toluene provided slightly better results but the formation of a gum was deemed undesirable especially in potential scale up of this reaction.

(16) The mildest of the sulfur fluoride based reagents, XtalFluor, was found to transform carbonyls into *gem*-difluoro moieties at ambient temperatures. This reaction in bifunctional substrates could be mitigated by using cryogenic temperatures (–78 °C).

(17) **Typical Procedure**: The alcohol (1 equiv) was dissolved in EtOAc (concentration of 0.5 M) at ambient temperature. The solution was cooled to 5 °C and $Et_3N{\cdot}3HF$ (2 equiv) and Et_3N (2 equiv) were successfully added in a dropwise manner. After stirring for 5 min, TFFH was added in one portion (1.5 equiv). The solution was then allowed to stir at the necessary temperature. Upon completion, the reaction was quenched with sat. $NaHCO_3$ to pH 7 and diluted with additional EtOAc. Layers were separated and the organic layer was concentrated to a crude residue. The crude residue could be purified by flash chromatography or partitioned between MTBE and H_2O to remove the tetramethylurea by-product.

