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Tetramethylfluoroformamidinium Hexafluorophosphate (TFFH) Deoxofluorination

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Introduction

Tetramethylfluoroformamidinium Hexafluorophosphate (TFFH) was first introduced by Carpino and El-Faham in 1995, which is a nonhygroscopic white crystalline salt stable to handling under ordinary conditions [1]. Differential scanning calorimetry (DSC) analysis of TFFH revealed a decomposition temperature (T_{max}) at 370 °C with an exothermic heat (–ΔH) of 146 J/g [2]. Comparing with the -ΔH values of XtalFluor-E (1260 J/g) at T_{max} = 205 °C and XtalFluor-M (773 J/g) at T_{max} = 243 °C [3], TFFH is significantly more stable and safe. Not surprisingly, TFFH is an easily handled reagent that possesses long shelf life and has found many applications in organic synthesis [4].

Preparation of TFFH

TFFH can be readily prepared from 1,1,3,3-tetramethylurea with three steps. First, tetramethylchloroformamidinium chloride is prepared from 1,1,3,3-tetramethylurea with various chlorination agents, such as phosgene, oxalyl chloride, and $POCl_3$. Second, the chloride counter ion is replaced by a hexafluorophosphate ion, where both KPF_6 and HPF_6 can be used. Third, KF is used for F/Cl exchange reaction with tetramethylchloroformamidinium hexafluorophosphate (TCFH) at room temperature in acetonitrile (Scheme 1) [1, 4, 5]. This reaction can be scaled up to more than hundred grams scale [4].

Deoxofluorination with TFFH

TFFH was first used as a coupling reagent for solution and solid phase peptide synthesis [1]. It could react rapidly with carboxylic acids, especially for amino acids, to give the corresponding acid fluorides under basic conditions (Scheme 2) [1, 5], sometimes mixed

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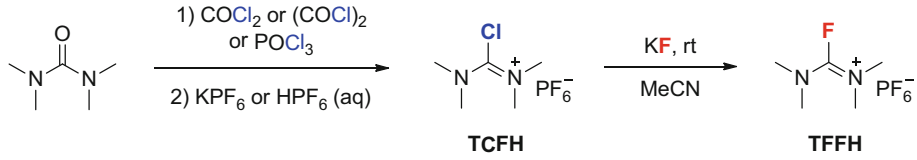
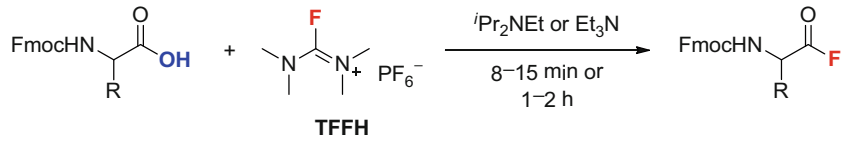
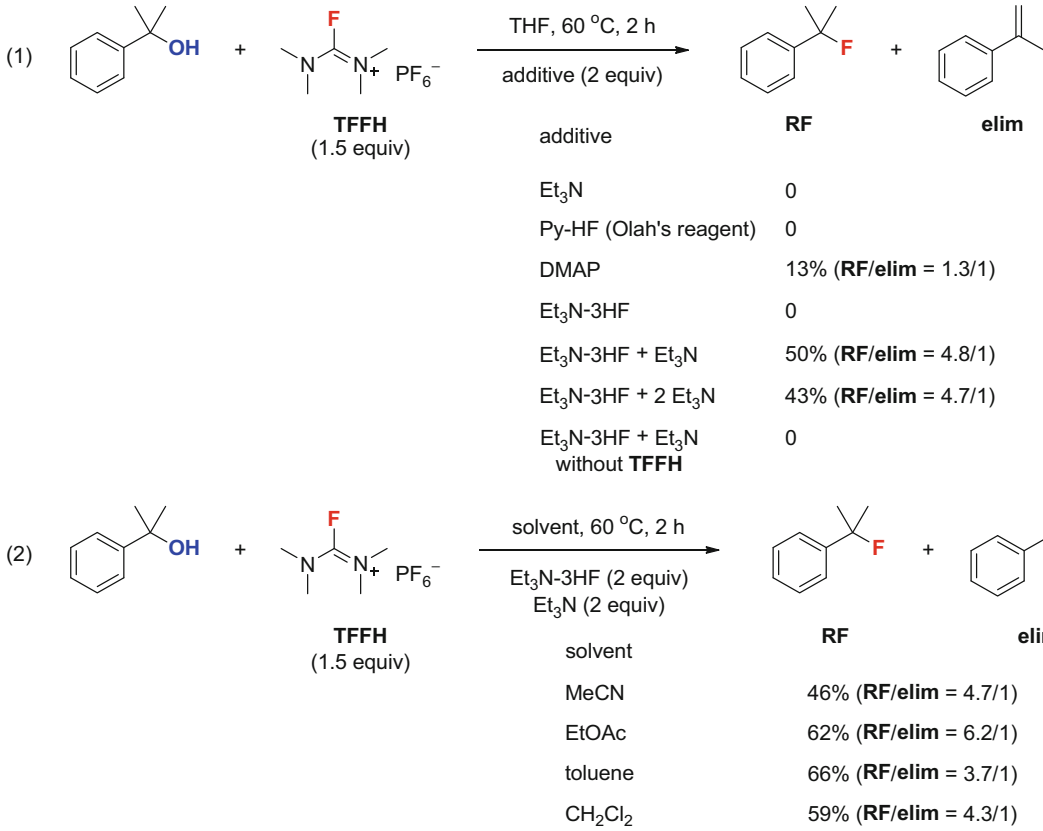


Tetramethylfluorofor-mamidinium Hexafluorophosphate (TFFH) Deoxofluorination, Scheme 1 Synthesis of TFFH



Tetramethylfluorofor-mamidinium Hexafluorophosphate (TFFH) Deoxofluorination, Scheme 2 Deoxofluorination of carboxylic acids with TFFH

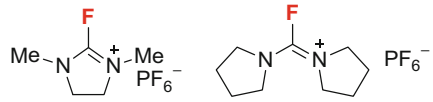


Tetramethylfluorofor-mamidinium Hexafluorophosphate (TFFH) Deoxofluorination, Scheme 3 Optimization of the deoxofluorination conditions with TFFH

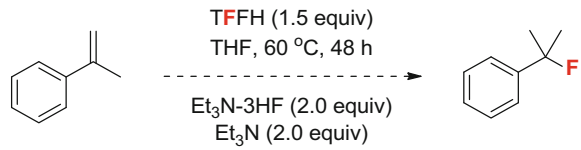
anhydrides could also be generated depending on the reaction conditions [4, 6]. By using acid fluorides as intermediates, various carboxylic acid derivatives could be prepared with high efficiency in one pot.

Although TFFH was first introduced in 1995, it had been limited to be used as a coupling reagent to prepare carboxylic acid derivatives for nearly 20 years. In 2012, Dubé and co-workers reported the use of TFFH as deoxofluorination agent of alcohols (Scheme 3) [2]. Initially, 2-phenylpropan-2-ol was used to optimize the reaction conditions. It was found that both Et_3N-3HF and Et_3N were needed as additives; otherwise, no fluorination product was obtained (Scheme 3, Eq. 1). Further screening on the solvent showed that EtOAc was optimal for the reaction in terms of both the efficiency and ease of workup (Scheme 3, Eq. 2). Although toluene gave a slightly better result than EtOAc, a gum was generated during the reaction process, which can make the isolation of the fluorination product difficult.

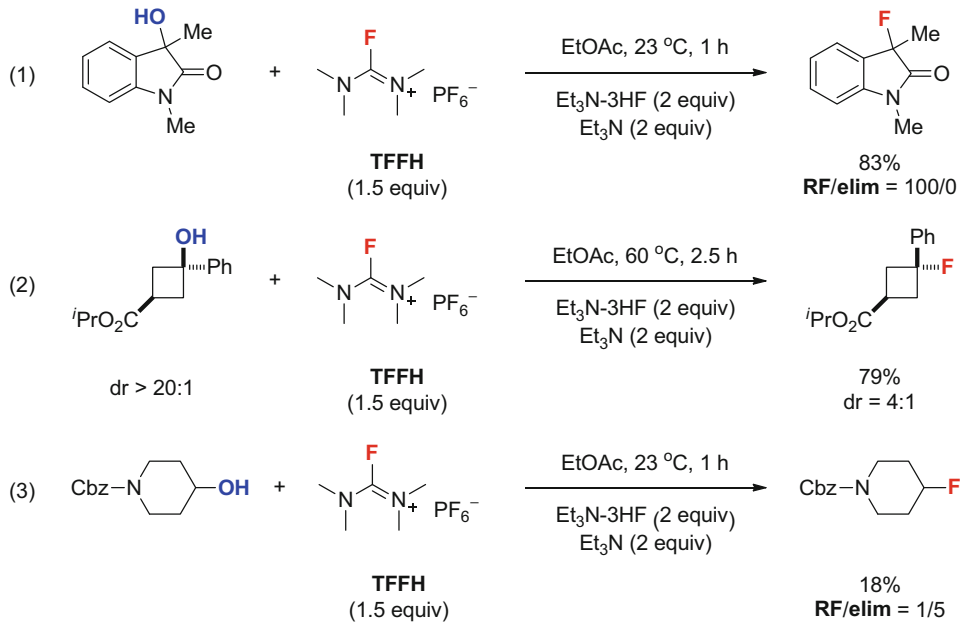
The fluorination property of some TFFH analogues (Scheme 4) were also tested: however, the results only supported the superiority of TFFH



Tetramethylfluorofor-mamidinium Hexafluorophosphate (TFFH) Deoxofluorination, Scheme 4 TFFH analogues



Tetramethylfluorofor-mamidinium Hexafluorophosphate (TFFH) Deoxofluorination, Scheme 5 Reaction of α-methylstyrene under the same deoxofluorination conditions



Tetramethylfluorofor-mamidinium Hexafluorophosphate (TFFH) Deoxofluorination, Scheme 6 Deoxofluorination of alcohols with TFFH

[2]. Recently, Ritter and coworkers disclosed that further modifying the structure of the fluoroiminium cation can significantly improve its deoxofluorination ability [7–9].

The deoxofluorination of tertiary alcohols with TFFH was examined in detail since it was usually challenging due to the ready formation of alkenes via a competitive elimination reaction. To rule out the possibility of fluorination with TFFH through an alkene intermediate, α-methylstyrene was subjected to the same deoxofluorination conditions for 48 h (Scheme 5) [2]. It was found that no fluorinated product was formed and α-methylstyrene was recovered, suggesting that the fluorinated product was generated directly from the deoxofluorination of alcohols.

By using the optimized deoxofluorination conditions, structurally diverse alcohols could be converted into the corresponding alkyl fluorides (Scheme 6) [2]. Of note, several tertiary alcohols could readily undergo the reaction in high yields (Scheme 6, Eqs 1 and 2). However, a large amount of elimination products (via dehydration) were afforded when cyclic secondary alcohols were used as substrates (Scheme 6, Eq. 3). When benzaldehyde and acetophenone were used as substrates, the corresponding *gem*-difluoro products were not obtained, and the substrates could be recovered in >95% yields [2].

Conclusion and Future Directions

In conclusion, TFFH is a stable, readily available, and mild deoxofluorination reagent with moderate fluorination ability. TFFH has been used for effective deoxofluorination of some tertiary alcohols. This reagent may find application in the selective fluorination of alcohols containing carbonyl functional groups.

Cross-References

- 2,2-Difluoro-1,3-Dimethylimidazolidine (DFI) Deoxofluorination
- α,α-Difluorobenzylamines Deoxofluorination
- CpFluor Deoxofluorination
- Fluoroolefin-Amine Adduct Deoxofluorination
- PhenoFluor Deoxofluorination

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