TCFH – a safe, affordable reagent for ester and difficult amide synthesis

Since its original description[1] chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (TCFH) has been used as a precursor for the preparation of N-[(1H-benzotriazol-1-yl)-(dimethylamino)methylene]-N methylmethanaminium hexafluorophosphate N-oxide (HBTU)[2]. It has also been used to synthesize fluoro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (TFFH) which is an efficient reagent for the synthesis of acid fluoride and their use in peptide synthesis.[3] In fact, TFFH and related formamidinium compounds have been recently deemed as coupling reagents suitable for greener peptide synthesis (DOI: 10.1021/acs.joc.8b03001) and these compounds have also been rendered as ''most preferred'' from process safety standpoint (DOI: 10.1021/acs.oprd.8b00193). Further, TCFH is used to synthesize 1-[bis(dimethylamino)methylen]-5-chlorobenzotriazolium 3-oxide hexafluorophosphate (HCTU)[4] , and for the preparation of O-[(ethoxycarbonyl)cyanomethylenamino]-N,N,N′,N′-tetramethyluronium hexafluorophosphate (HOTU)[5] (Figure 1).

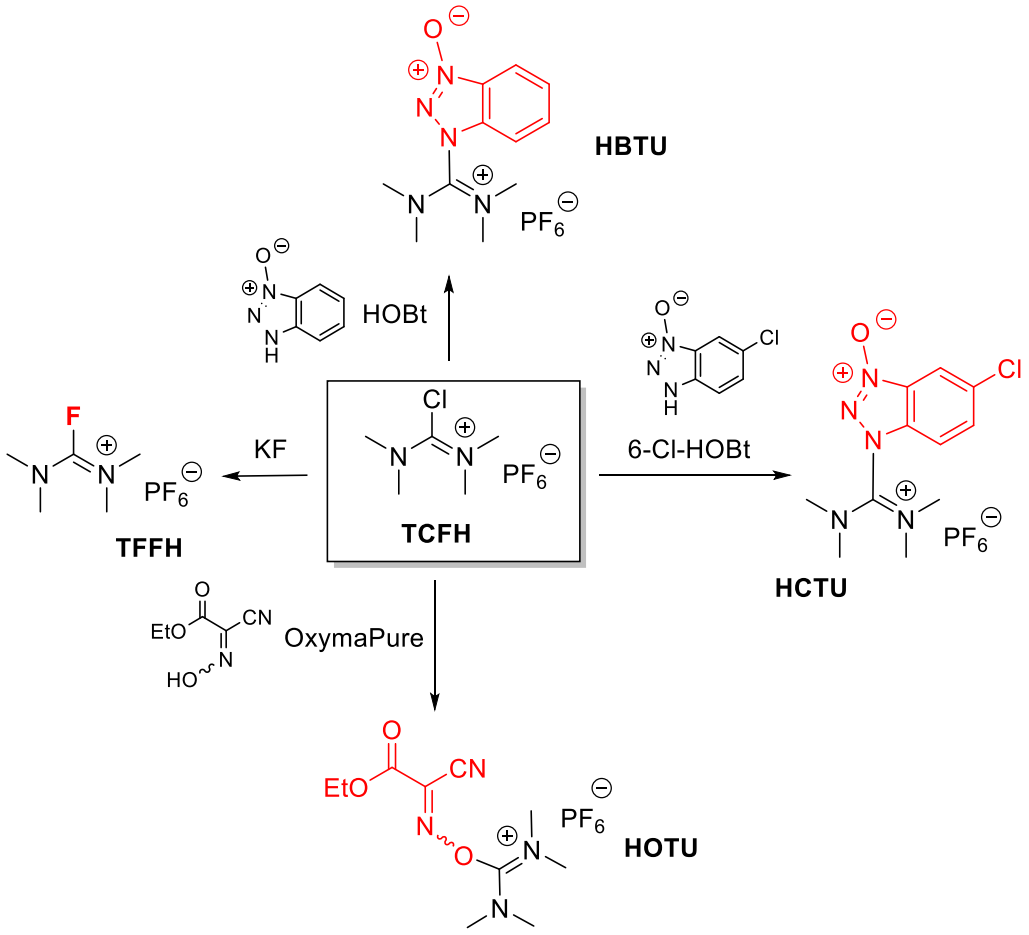

Figure 1: *TCFH as an intermediate of other coupling reagents*

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TCFH is unique in the sense that it is able to convert carboxylic acids into acid chlorides which are considered potent acylating reagents. At the same time, in the presence of reagents such as OxymaPure, HOAt, HOBt, 6-Cl-HOBt or HOSu[6], TCFH easily gives the corresponding active esters. Thus, TCFH can be used to provide a wide range of reactivities which can be applied to a broad number of different synthetic applications.

As an activated ester forming reagent its coupling potential had been recognized in the acylation of a quinolinol carboxylamide, either alone, or in combination with 1-hydroxy-7-azabenzotriazole (HOAt)[7] (Figure 2).

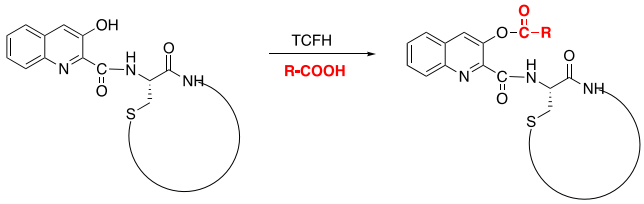

Figure 2. *Formation of a quinolinol ester*

TCFH activation was found effective in the *in situ* formation of acid chlorides to acylate the mono-2-(trimethylsilyl)ethoxycarbonyl (Teoc) protected piperazic acid derivative[8] (Figure 3).

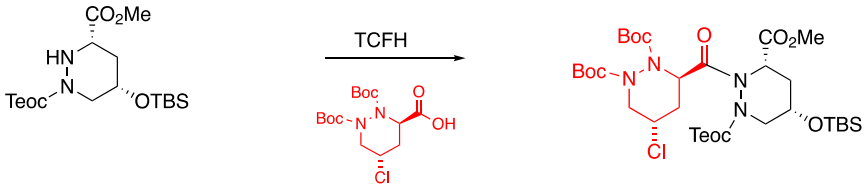

Figure 3. *Acylation of a hindered acyl hydrazide*

Beutner and coworkers at Bristol-Myers Squiib[9] demonstrated that highly reactive N-acyl imidazoliums can be formed under mild, neutral conditions.

In comparative studies they showed that the acylation efficiency of the complex generated from α-methyl phenylacetic acid, TCFH and N-methyl imidazole (NMI) outperformed HATU, TFFH in the acylation of a 4-amino-benzonitrile, Figure 4.

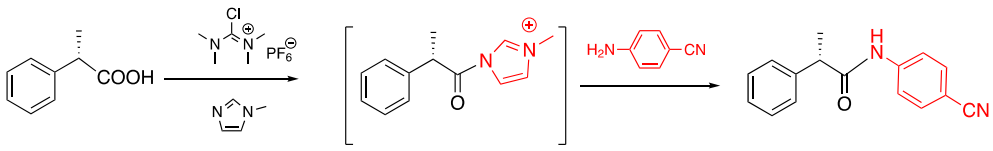

Figure 4. *TCFH-NMI combination for aromatic amine acylation*

Under optimized conditions, the epimerization of the α-methyl phenylacetic acid was below 1%, whereas with the normally effective bromo-tripyrrolidinophosphonium hexafluorophosphate (PyBrOP)[10] 9% epimerization was observed. In this study, TCFH-NMI has been also shown to

constitute a highly efficient coupling reagent for the amide bond formations involving extremely hindered peptide couplings, such as those involving aminoisobutyric acid (Aib) residues.

TCFH had been the only reagent in the acylation of 6-amino-2-cyanobenzothiazole[11] capable of providing a near quantitative yield (Figure 5). The sophisticated onium salt reagents like COMU and HATU yielded only traces of the targeted product, whereas the structural analog TFFH provided more than 50% conversion.

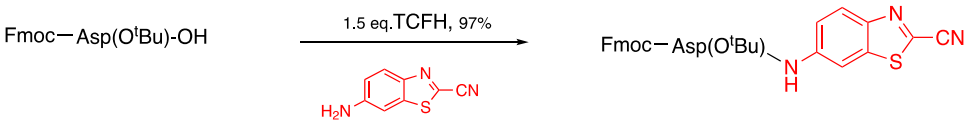

Figure 5. *Aromatic amine acylation with Fmoc-amino acid derivative*

Luxembourg Bio Technologies has made this coupling agent available for industrial production.

TCFH as a reagent has several advantages beside being economical:

- Due to is high coupling potency, it might be used in reactions previously only accomplished using carbodiimide-mediated couplings, extending in this manner its application for the formation of esters, diacyl amides and acylation of non-reactive amines
- It is solid, reasonably stable compound, when stored around 0°C
- Using the widely available coupling additives[6] the chemist can find optimal reagent ratio to balance between the product yield and the side reactions including epimerization.

In summary, the industrial availability of the highly reactive TCFH allows: esterification and amide formation in high yield, and via the use of optional additives, allows for fine-tuning of reaction conditions to achieve optimum results thus providing unprecedented synthetic flexibility for the preparative chemist.

References

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