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Spotlight 328

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Hexafluoroacetone: An Appealing Key Player in Organic Chemistry

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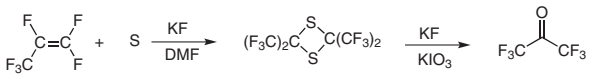
Introduction

Hexafluoroacetone (HFA, CAS: 684-16-2), a colorless, non-flammable, musty odour gas with a boiling point of –28 °C, is an efficient site-selective reagent in organic synthesis.[1] It is also found in liquid form and is used in the synthesis of solvents, adhesives and pharmaceutical products. It is a highly reactive electrophile. It reacts with activated aromatic compounds and can be condensed with olefins, dienes, ketenes, and acetylenes. HFA is a very important reagent in the solid-phase synthesis and modification of peptides, glyco- and depsipeptides.[2] In contrast to the conventional protecting groups for peptide synthesis, it is a bidentate reagent and protects simultaneously the carboxyl group and the α-functionality. Hexafluoroacetone is widely used in the synthesis of monomers that are used to prepare speciality polymers.[3] In analytical studies, HFA can be used as a reagent in ^{19}F NMR spectroscopy of compounds comprising active hydrogens.[4]

Preparation

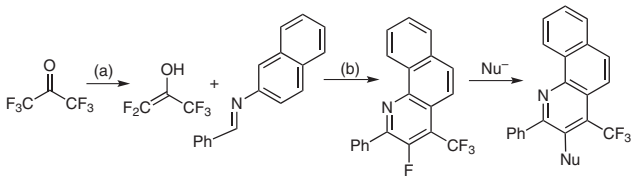
HFA can be prepared from perfluoropropene and elemental sulfur in the presence of KF.[5] It can be obtained in the laboratory by drop-wise addition of its commercially available trihydrate to concentrated sulfuric acid at 80–100 °C.[1]



Scheme 1

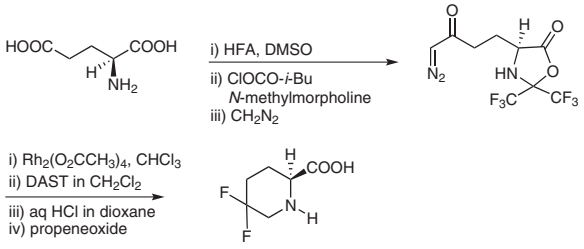
Abstracts

(A) *Synthesis of Quinolines:*
Uneyama and co-workers developed the one-pot synthesis of highly bioactive quinolines. Pentafluoropropen-2-ol (PFP) formed from HFA facilitates the synthesis of substituted quinolines via tandem Mannich addition–Friedel–Crafts cyclization–aromatization followed by nucleophilic defluorinative substitution.[6]



(a) i) Mg, TMSCl, DMF, –20 to 0 °C, 2 h; ii) concd H_2SO_4, –30 to 0 °C, 4 h.
(b) i) CH_2Cl_2, –30 °C to r.t.; ii) PhMe, reflux; iii) TFA–PhMe, reflux, 7 h.

(B) *Synthesis of Fluoro-Substituted Pipecolic Acids:*
Burger and co-workers reported a new route for the synthesis of substituted pipecolic acids from hexafluoroacetone-protected (*S*)-glutamic acid.[7] Pipecolic acids can be used as investigative tools for the *cis–trans* isomerization of the peptide bond as well as protein folding.



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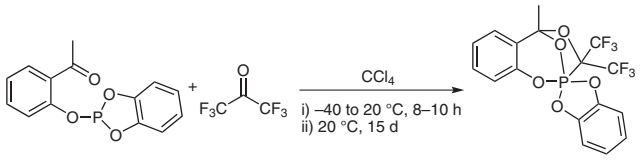
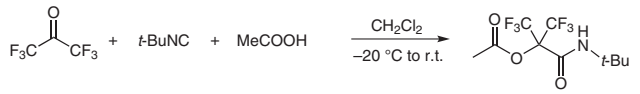
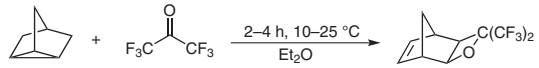
(C) *Stereoselective Synthesis of Spirophosphoranes:*
Highly stereoselective tricyclic phosphoranes were prepared by the group of Mironov by reacting dioxaphosphole with hexafluoroacetone.[8]



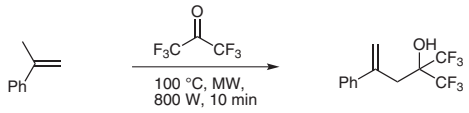
(D) *Approach to Depsipeptides:*
Gulevich et al. has reported a high-yielding synthetic approach for the synthesis of depsipeptides via Passerini three-component condensation of isocyanide, carboxylic acid and hexafluoroacetone.[9]



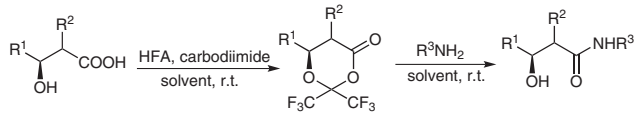
(E) *Oxetane Formation:*
Petrov et al. reported the cycloaddition of quadricyclanes and HFA to give oxetanes which are stable in both acidic and basic medium.[10]



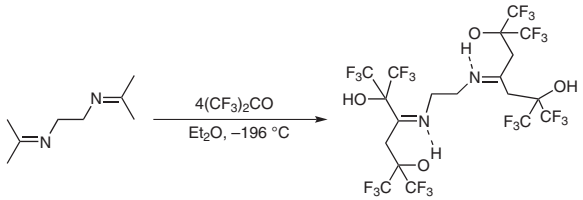
(F) *Preparation of Hexafluoroisopropanol-Functionalized Derivatives:*
Recently, Sridhar et al. used hydrated hexafluoroacetone for an efficient carbonyl-ene reaction with alkenes having allylic hydrogens.[11]



(G) *Lactone and Amide Formation:*
The reactions of β-hydroxy acids with HFA and carbodiimide have been used to obtain carboxy-activated six-membered lactones in good yields which in turn afforded the corresponding amides.[12]



(H) *β-Hydroxy-β-bis(trifluoromethyl)imines:*
In an enamine-mediated addition, selected imines with HFA gave the corresponding β-hydroxy-β-bis(trifluoromethyl)imines in good to excellent yields.[13] These imines are versatile synthons for the synthesis of bioactive compounds.



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