Hexafluoroacetone: An Appealing Key Player in Organic Chemistry

Compiled by Kirandeep Kaur

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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 19F NMR spectroscopy of compounds comprising active hydrogens.3

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

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 defluorinating substitution.6

(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.
(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.

References

(10) Petrov, V. A.; Davidson, F.; Smart, B. E. J. Fluorine Chem. 2004, 125, 1543.