SYNLETT Spotlight 328

Hexafluoroacetone: An Appealing Key Player in Organic Chemistry

Compiled by Kirandeep Kaur

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

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Introduction

Hexafluoroacetone (HFA, CAS: 684-16-2), a colorless, non-flammable, musty odour gas with a boiling point of $-28\text{ }^{\circ}\text{C}$, 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 depsiptides.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 $80\text{--}100\text{ }^{\circ}\text{C}$.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 $0\text{ }^{\circ}\text{C}$, 2 h; ii) concd H_2SO_4 , -30 to $0\text{ }^{\circ}\text{C}$, 4 h.
(b) i) CH_2Cl_2 , $-30\text{ }^{\circ}\text{C}$ 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.

i) $\text{Rh}_2(\text{O}_2\text{CCH}_3)_4$, CHCl_3
ii) DAST in CH_2Cl_2
iii) aq HCl in dioxane
iv) propene oxide

(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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