SYNLETT Spotlight 394

(Trifluoromethyl)trimethylsilane

Compiled by Thi Minh Ha Vuong

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

(Trifluoromethyl)trimethylsilane (TMSCF₃) is a flammable liquid with a boiling point of 54–55 °C, a flash point of –17 °C and density of 0.926 g/mL at 20 °C. It may be harmful if inhaled, swallowed, absorbed through skin and may cause respiratory tract, skin and eye irritation. TMSCF₃ was firstly synthesized by Rupert¹ in 1984 via the condensation reaction of CF₃Br and TMSCl with (Et₂N)₃P. Nowadays, there are various synthetic methodologies to yield this compound. Among them, the approach of Pawelke is considered as the most efficient

method.² Following this method, the reaction of CF₃I and tetrakis(dimethylamino)ethylene formed an in situ mediated complex which reacted directly with TMSCl to afford TMSCF₃ in 94% yield. TMSCF₃ is versatile reagent for trifluoromethylation, such as transition-metal-catalyzed reaction, miscellaneous trifluoromethylation, and addition to carbonyl and imine groups. These reactions are extremely useful approaches in the pharmaceutical and agrochemical industry,³ because they enhance metabolic stability (metabolic blocking) and alter the compound properties (lipophilicity, binding selectivity).

Abstract

(A) Oxidative Trifluoromethylation of Terminal Alkynes and Heteroarenes:

Qing and co-worker described a powerful method for the synthesis of a broad range of trifluoromethylated acetylenes in good yields by using the copper-mediated protocol.⁴ Recently, they have developed an alternative copper-catalyzed trifluoromethylation.⁵ This method is also applied to the oxidative trifluoromethylation of heteroarenes and highly electron-deficient arenes via C–H activation.⁶

(B) Oxidative Trifluoromethylation of Boronic Acids:

Copper-mediated or -catalyzed oxidative cross-couplings of aryl- and alkenylboronic acids with TMSCF₃ under mild condition have been reported.^{5,7} This procedure can be employed in the various ranges of functionalized aryl, heteroaryl and alkenyl boronic acids.

(C) Cu-Catalyzed Reaction of Arylboronic Acid with TMSCF₃ and S₈:

This study provides an efficient and convenient protocol for the synthesis of aryl trifluoromethyl thioethers.⁸

(D) Cu-Mediated Nucleophilic Trifluoromethylation of Allyl Halides:

The trifluoromethylated allylic products have been synthesized in good yields.⁹

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(E) *Ag-Mediated Trifluoromethylation of Arenes:*

The innovative procedures for silver-mediated CH trifluoromethylation of aromatic substrates were developed by Melanie S. Sanford and co-workers.¹⁰ The mechanism of these reactions is suggested to proceed via an AgCF_3 intermediate.

(F) *Pd-Catalyzed Trifluoromethylation of Aryl Halides and Vinyl Sulfonates:*

Hartwig,¹¹ Sanford,¹² Grushin¹³ and Buchwald^{14,15} have contributed to a notable feature of this reaction.

(G) *Pd-Catalyzed Intermolecular Oxidative Aryltrifluoromethylation of Activated Alkenes:*

The powerful synthesis of oxidole derivatives containing CF_3 was explored by Liu and colleagues.¹⁶ The desired products were obtained via initial arylpalladation of alkenes, continued by sequential oxidation and reductive elimination of $\text{Csp}^2 \text{Pd}^{\text{IV}}\text{CF}_3$ species.

(H) *Synthesis of $\alpha\text{-CF}_3$ N-Heterocycles Through Tandem Nucleophilic Additions:*

A powerful strategy for the synthesis of precursors of biologically important unnatural cyclic amino acids and fluorinated N-heterocycles by tandem reactions based on amination and trifluoromethylation catalyzed by AgF was reported by Hammond.¹⁷

(I) *Addition to the Carbonyl Group:*

The catalytic nucleophilic enantioselective trifluoromethylation of carbonyls, including aldehydes,¹⁸ ketones¹⁸ (alkynylketones¹⁹ and aryl ketones²⁰), acyltrifluoromethane,²¹ acylphosphonates²² and acylsilanes^{23,24} was reported. The addition to related carbonyl compounds (enones, amides, esters, sulfonic, sulfinic, selenic esters and α -keto esters) was also described.¹⁸

(J) *Addition to Imines, Nitrones, Thiocyanate and Selenocyanate:*

This series of trifluoromethylation by addition allows for generating promising candidates for the pharmaceutical and agrochemical industry.¹⁸

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