SYNLETT
Spotlight 201

Trimethylsilyl Cyanide (TMSCN)

Compiled by Ebrahim Soleimani

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

Cyanation of carbonyl compounds is one of the most powerful procedures for the synthesis of polyfunctionalized molecules. Compared to various cyanating reagents such as KCN, NaCN, and HCN, trimethylsilyl cyanide (TMSCN) is a safer and more effective cyanide source for nucleophilic addition to carbonyl compounds under mild conditions.^{1,2} Asymmetric addition of TMSCN to carbonyl compounds and subsequent hydrolysis produces chiral cyanohydrins.³ The reaction of an epoxide with TMSCN leads to formation of either trimethylsilyloxy nitrile (C-nucleophilic attack) or trimethylsiloxy iso-

cyanide (N-nucleophilic attack) depending on the nature of the catalyst, due to the ambident nucleophilic character of TMSCN.⁴ Cyanation of nucleophilic alkynes as an easy approach to substituted α -cyanoenamines is another ability of TMSCN.⁵ Recently, TMSCN was used as a functional, yet non-classical isonitrile, for the synthesis of 3-aminoimidazo[1,2-*a*]pyridines.⁶

Abstracts

(A) The addition of TMSCN to carbonyl compounds is an area of active study due to the synthetic versatility of cyanohydrins. The reaction of TMSCN with benzaldehyde at $-20\text{ }^{\circ}\text{C}$ in the presence of proline-based *N,N'*-dioxides as catalyst afforded enantioselective cyanosilylation.⁷

(B) There are few reports on the preparation of cyanohydrin trimethylsilyl ethers of acylferrocenes except for formylferrocene. Bian et al. described the synthesis of cyanohydrin trimethylsilyl ethers of acylferrocenes via the addition of TMSCN to various acylferrocenes in the presence of ZnI_2 in dichloromethane.⁸

(C) TMSCN is a very effective cyanide anion source for the synthesis of α -amino nitriles. The reaction of aldehydes and amines with TMSCN in the presence of a catalytic amount of $\text{H}_{14}[\text{NaP}_5\text{W}_{30}\text{O}_{110}]$ afforded α -amino nitrile derivatives.⁹

(D) Recently, Schwerkoske et al. reported a novel one-step three-component procedure for the synthesis of 3-iminoarylimidazo[1,2-*a*]pyridines via the unique application of TMSCN as a functional, yet non-classical isonitrile. Reactions are performed under microwave irradiation in methanol by simply mixing α -amino-pyridines, aldehydes, and TMSCN in the presence of scandium triflate to afford the products.¹⁰

(E) β -Hydroxynitriles are useful synthetic intermediates in organic synthesis and versatile moieties for the synthesis of 1,3-amino alcohols. The ring opening reaction of epoxides with TMSCN is the most direct method for the preparation of these compounds. An asymmetric ring opening of meso epoxides with TMSCN in the presence of catalytic amounts of (pybox)YbCl₃ complexes, yielding the β -trimethylsilyloxy nitrile ring-opened products with good enantioselectivities (83–92% ee) is reported.¹¹

(F) The addition of TMSCN to a wide range of electron-rich heteroaromatic compounds such as pyrroles, thiophenes, and indoles in the presence of phenyliodine bis(trifluoroacetate) (PIFA) under mild conditions produced the selective cyanation products.¹²

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