Synlett Spotlight 73

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

Trimethylsilyldiazomethane

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Neil Hodnett was born in Chichester in 1977 and began his studies at the University of Bristol (UK) in 1995. He received his MSci in 1999, after spending a lively year at the Université de Montpellier II (France) as part of the Socrates exchange program. He enjoyed Bristol so much he decided to stay and is about to complete a PhD, under the supervision of Dr Guy C. Lloyd-Jones (Bristol), to develop a novel method for screening racemic catalysts based on kinetic resolution.

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Introduction

The commercially available reagent trimethylsilyldiazomethane\(^1\) can be used as a stable and safe alternative to diazomethane in one-carbon homologations, as in the Arndt–Eistert reaction,\(^2\) the homologation of carbonyl compounds\(^3,4\) and O-methylation of carboxylic acids, phenols and alcohols. Additionally, the reagent can serve as a C–N–N synthon for the preparation of azoles.

Abstracts

(A) Trimethylsilyldiazomethane (TMSCHN\(_2\)) reacts rapidly with carboxylic acids in benzene or toluene in the presence of methanol, at room temperature, to afford the methyl esters in very high yields.\(^6\) This method is particularly useful in quantitative analysis of fatty acids by gas chromatography.\(^7\)

(B) Both cyclic and acyclic ketones react with TMSCHN\(_2\) in the presence of boron trifluoride etherate to give the ring or chain homologated ketones. The steric bulk of the trimethylsilyl group promotes regioselective methylene insertion.\(^8\)

(C) While TMSCHN\(_2\) will only react with activated nitriles, its lithium salt, TMSC(Li)N\(_2\) reacts smoothly with aromatic, heteroaromatic and aliphatic nitriles to give the corresponding 4-substituted 5-trimethylsilyl-1,2,3-triazoles.\(^9\) Reaction of TMSC(Li)N\(_2\) with \(\alpha,\beta\)-unsaturated nitriles can also afford pyrazoles in some cases.\(^10\)
(D) TMSCHN₂ has been employed in asymmetric dipolar cycloadditions with chiral acrylates, to afford optically active Δ²-pyrazolines.¹¹ The cycloadditions proceed in high yield with a high degree of diastereoselectivity. This methodology has also been applied to the synthesis of the indolizidine metabolite stellettamide A.¹²,¹³

(E) TMSCHN₂ reacts directly with N-sulfonyl imines to furnish C-silylaziridines in good yields and high cis-stereoselectivities.¹⁴,¹⁵ The resulting products undergo substitution of the silyl group with high diastereoselectivity and ring opening by nucleophiles with complete regioselectivity.

References