Spotlight 92

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

Dimethyl(methylene)ammonium Salts: Mannich Reagents

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Introduction

These reagents comprise a family of preformed iminium salts which have been extensively utilized in condensation reactions with carbonyl and aromatic compounds in a variant of the Mannich reaction. Böhme prepared the first dimethyl(methylene)ammonium chloride (1), and the iodide salt 2 was later developed by Eschenmoser. Preformed iminium salts are sufficiently soluble in many aprotic solvents, enabling the use of highly reactive nucleophiles which ordinarily would decompose under the protic conditions of the classical Mannich reaction. A comparison study of these salts favors the trifluoroacetate salt (3) because it is the most soluble and can be transferred by syringe, although it is more tedious to prepare.

Salt 1 is prepared by cleavage of \(N,N,N',N'-\text{tetramethylmethanediamine by } \text{AcCl}\) or cleavage of methyl dimethylammonium ether by \(\text{TMSCl}\). Salt 2 is prepared by thermolysis of (iodomethyl)trimethylammonium iodide or cleavage of \(N,N,N',N'-\text{tetramethylmethanediamine by } \text{TMSI}\). Salt 3 is prepared by Polonovski reaction of trimethylamine oxide with TFAA or cleavage of \(N,N,N',N'-\text{tetramethylmethanediamine with } \text{TFA}\).

Abstracts

(A) Trimethylsilyl enol ethers derived from ketones and aldehydes add to salts 1–3 and the reaction proceeds via a silyloxonium ion which hydrolyzes on aqueous workup. This method has been used for the synthesis of the two regioselective Mannich bases of 2-methylcyclohexanone.

(B) Enolates generated by the decomposition of \(\alpha\)-diazoketones in the presence of trialkylborane provide Mannich bases in excellent regioselectivity from simple unsymmetrical ketones.

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(C) Salts 1–3 serve as excellent one-carbon equivalents for an α-methylene group. The dimethylamino group can be easily eliminated by alkylation with iodomethane followed by treatment with base or direct purification on silica-gel chromatography. This method was successfully applied to an elegant synthetic approach toward Xestocyclamine A.10

(D) Electron-rich aromatic and heteroaromatic compounds have been shown to undergo condensation reactions with salts 1–3 with excellent regiocontrol. Monosubstituted phenols, which usually afford mixtures of ortho, para and diaminomethylated products under conventional methods, react with 1 or 2 to afford the ortho-product in excellent yield, presumably because of ion pair interaction between the phenoxide anion and the iminium salt.11

(E) Aryl and heteroaryl stannanes react with salt 1 to afford an ipso-substitution product of the stannyl group. The directing effect of tin allows for the preparation of Mannich bases with an ipso substitution pattern which is not ordinarily obtained under traditional procedures.12

(F) Analogous to the enolate additions, organometallic reagents such as Grignards,13 cuprates14 and lithium reagents15 add to salt 2 to produce N,N-dimethylamine. Similarly, the salts have been added to hydrazines16 and oximes.17

References