SYNLETT 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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NMe₂

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),¹ and the iodide salt **2** was later developed by Eschenmoser.² 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.³

Salt **1** is prepared by cleavage of N,N,N',N'-tetramethylmethanediamine by AcCl⁴ or cleavage of methyl dimethylaminomethyl ether by TMSCl.⁵ Salt **2** is prepared by thermolysis of (iodomethyl)trimethylammonium iodide² or cleavage of N,N,N',N'-tetramethylmethanediamine by TMSI.⁶ Salt **3** is prepared by Polonovski reaction of trimethylamine oxide with TFAA or cleavage of N,N,N',N'tetramethylmethanediamine with TFA.⁷



salt (2)

r.t., 65%

OTMS

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.⁸

(B) Enolates generated by the decomposition of α -diazo ketones in the presence of trialkylborane provide Mannich bases in excellent regioselectivity from simple unsymmetrical ketones.⁹



SYNLETT 2004, No. 7, pp 1321–1322 Advanced online publication: 10.05.2004 DOI: 10.1055/s-2004-825600; Art ID: V08803ST © Georg Thieme Verlag Stuttgart · New York (C) Salts 1–3 serve as excellent one-carbon equivalents for an α -methylene group. The dimethylamino group can be easily eliminated by quaternization 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

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