

SYNLETT Spotlight 92

Dimethyl(methylene)ammonium Salts: Mannich Reagents

Compiled by Heedong Yun



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

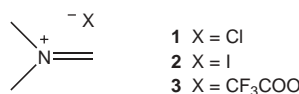
Heedong Yun was born in Kumi, Korea, in 1975. He received a B.S. in 1999 from Seoul National University in Seoul, Korea. He obtained an M.A. from Columbia University in 2003 and he is currently pursuing a Ph.D. on the total synthesis of biologically active marine natural products under the guidance of Prof. Samuel J. Danishefsky.

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Introduction

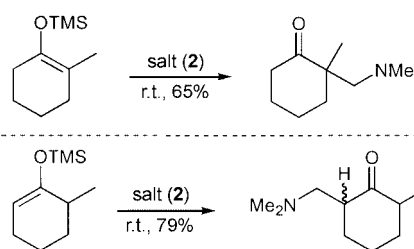
These reagents comprise a family of preformed iminium salts which have been extensively utilized in condensation reactions with carbonyl and aromatic compounds in a variant of the Mannich reaction. Böhme prepared the first dimethyl(methylene)ammonium chloride (**1**),¹ and the iodide salt **2** was later 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 AcCl^4 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

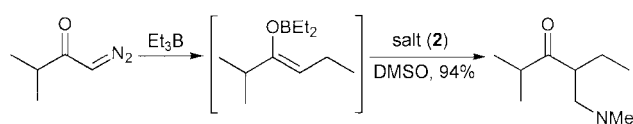


Abstracts

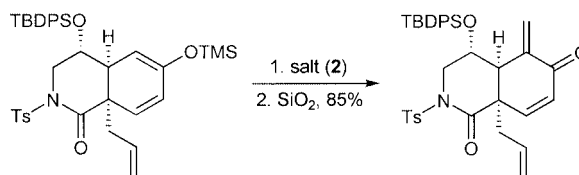
(A) Trimethylsilyl enol ethers derived from ketones and aldehydes add to salts **1–3** and the reaction proceeds via a silyloxonium ion which hydrolyzes on aqueous workup. This method has been used for the synthesis of the two regioselective Mannich bases of 2-methylcyclohexanone.⁸



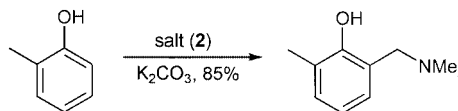
(B) Enolates generated by the decomposition of α -diazo ketones in the presence of trialkylborane provide Mannich bases in excellent regioselectivity from simple unsymmetrical ketones.⁹



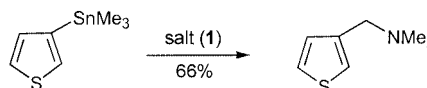
(C) Salts **1–3** serve as excellent one-carbon equivalents for an α -methylene group. The dimethylamino group can be easily eliminated by quaternization with iodomethane followed by treatment with base or direct purification on silica-gel chromatography. This method was successfully applied to an elegant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



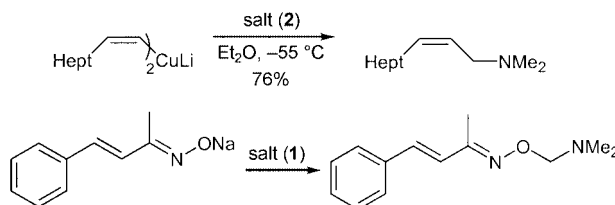
(D) Electron-rich aromatic and heteroaromatic compounds have been shown to undergo condensation reactions with salts **1–3** with excellent regiocontrol. Monosubstituted phenols, which usually afford mixtures of *ortho*, *para* and diaminomethylated products under conventional methods, react with **1** 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



References

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