Mannich Reaction of Carbonyl Compounds *via* Boron Enolates and *N,N,N′,N′*-Tetramethyldiaminomethane

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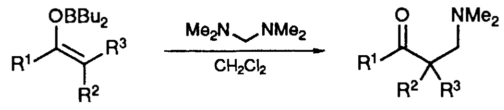
A variety of carbonyl compounds undergo *N,N*-dimethylaminomethylation in moderate to good yields by the Mannich reaction involving boron enolates and *N,N,N′,N′*-tetramethyldiaminomethane in dichloromethane.

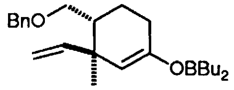
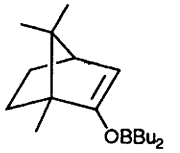
The Mannich reaction of carbonyl substrates has classically utilized an acidic mixture of dimethylamine and formaldehyde under reflux in ethanol for several days. More recently enolates[1] and silyl enol ethers[2] have been shown to react with preformed *N,N*-dimethylmethyleneiminium ions to yield Mannich bases. While such conditions offer a number of advantages such as aprotic solvents, lower reaction temperatures, and good yields, the iminium ions employed are very hygroscopic. To circumvent handling the iminium ion, silyl enol ethers[3,4] and silyl ketene acetals[5] have been used to react with the iminium ion or a similarly reactive species[4] produced *in situ* from *gem*-aminoethers by Lewis acid catalysis yielding the Mannich bases; however, these reactions typically require the preparation and isolation of the silylated starting materials.

Mannich bases have also been synthesized from aminals. The aminal, *N,N,N′,N′*-tetramethyldiaminomethane (TMDM), which is often used as the precursor for *N,N*-dimethylmethyleneiminium ion formation, has been used to form the Mannich base of alkyl aryl ketones under conditions which spontaneously eliminate the *N,N*-dimethylamino moiety providing unsaturated ketones.[6] The reaction of silyl enol ethers with TMDM under Lewis acid conditions[7] also yields Mannich bases as does the direct reaction of lithium enolates with Katritzky's benzotriazole derived aminal.[8]

We report a convenient one-pot reaction between boron enolates and TMDM. The boron of the enolate is capable o functioning as the Lewis acid component, thus complexing and activating the aminal. A typical procedure entailed formation of the boron enolate by known methods in

Table 1 Reaction of boron enolates with *N,N,N',N'*-tetramethyldiaminomethane



Entry	R^1	R^2	R^3	Yield^a (%)
a	Ph	H	Me	68
b	Et	H	Me	70
c	–(CH$_2$)$_4$–		H	67
d	Bu^i	H	Pr^i	73
e	Pr^i	Me	Me	50
f	Bu^t	H	H	63
g	Ph	H	H	70 (crude)^b
h	OBBu$_2$	H	Me	59
i	SBu^t	Et	H	61
j	OEt	H	OPh	53
k				57^d
l				39^e

[a] Based on product isolated. All products gave satisfactory ^{1}H and ^{13}C NMR, IR, and GLC–MS data. [b] Product contaminated with 45% dialkylated material. [c] Boron enolate generated from silyl enol ether by exchange with Bu$_2$BOSO$_2$CF$_3$. [d] Diastereoselectivity was undetermined. [e] Yield reflects *exo* product only.

dichloromethane,[9] which was then treated with 1.5 equivalents of TMDM at 0 °C. After stirring for 2 h at room temperature, the usual work-up[1] followed by distillation afforded the Mannich base. The reaction has also been conducted in diethylether and tetrahydrofuran as the solvent, but the yields are slightly lower. Presumably these Lewis basic solvents compete for the boron with the nitrogen of the aminal.

Good yields are obtained by this method, see Table 1, yet dimethylaminomethylation at sterically hindered positions of ketones furnishes somewhat lower yields, entries k and l, as does formation of the quarternary centre in entry e. Interestingly the *exo*-isomer is dominant when camphor is used.[10] Also alkylation at methyl (R^2 and R^3 = H) is typically difficult[4,8] and affords dialkylation with some resultant elimination of dimethylamine, entry g.

The β-aminocarboxyl functionality has also been synthesized by this procedure. Enediolates undergo *N,N*-dimethylaminomethylation as shown in entry h. Similarly thiolesters and glycolate esters afford good yields of Mannich bases, entries i and j.

It is important to note that the reaction does not proceed with the less Lewis acidic lithium enolate generated by lithium diisopropylamide (LDA) in tetrahydrofuran or benzene, whereas the reaction gave similar yields (92% from propiophenone and 66% from pentan-3-one) with the titanium enolate generated by TiCl$_4$ and diisopropylethylamine in dichloromethane.[11]

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