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α-AMINO CARBANIONS. A SECOND GENERATION FORMAMIDINE FOR FACILE DEPROTONATION LEADING TO α-QUATERNARY SUBSTITUTION

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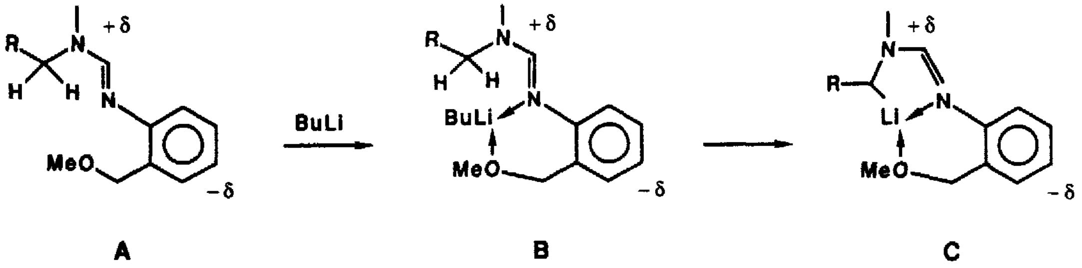
Summary - Formamidines derived from *o*-methoxymethylaniline (MMA) allow proton removal of tertiary protons in 1-substituted-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines.

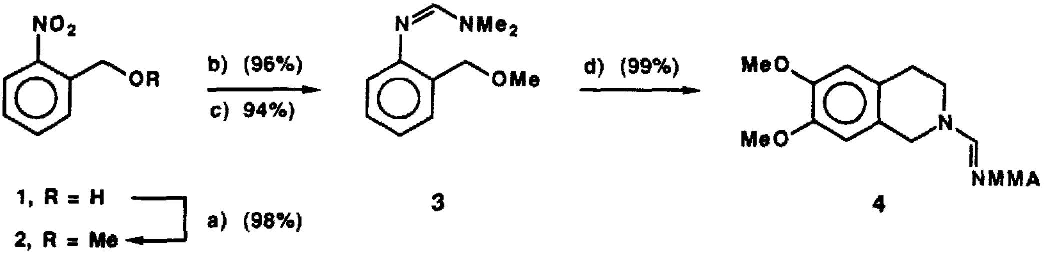
In the previous **Letter**,[1] we outlined a study which led to the emergence of a new and more powerful activating group, **A**, based on increased polarization of the formamidine moiety. The ability of the π-system in the latter to delocalize into the aromatic ring is considered a major factor responsible for the increased acidity of the α-protons. When this effect is added to the chelation properties of the methoxymethylaniline group (MMA), as shown in **B**, the result is increased base strength of the butyllithium and facile metalation to the carbanion, **C**. Because of this combination of factors in the MMA formamidine, weaker bases now become useful (*n*-BuLi in place of *sec* or *tert*-butyllithium) and lead to metalation in cases where none were possible in our earlier attempts.



We can now report the use of the MMA formamidine in α-alkylation of alkoxy substituted tetrahydroisoquinolines **7** and in *bis*-alkylation of these systems (**9**). The latter are important precursors to a variety of isoquinoline alkaloids containing quaternary centers.[2]

The requisite MMA auxiliary, which we have designated as a "second generation formamidine," was prepared in the efficient manner shown in Scheme 1. Commercially available

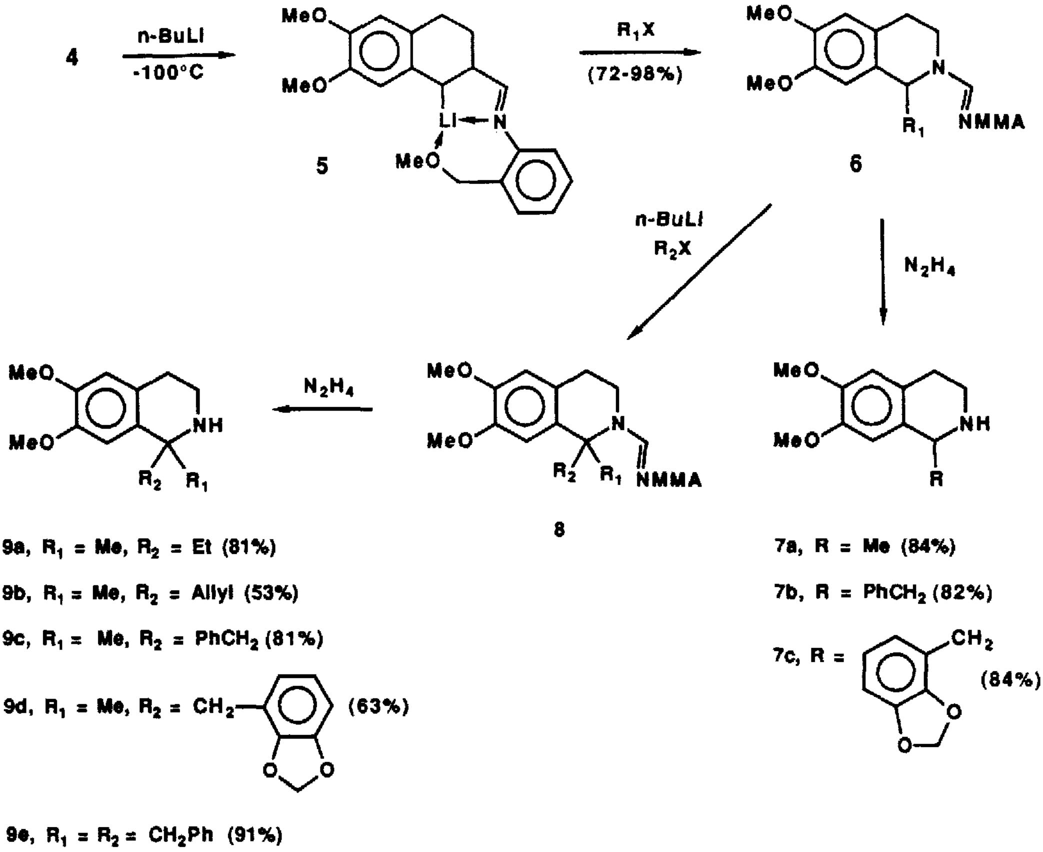
SCHEME 1



a) Me_2SO_4, $PhCH_2NEt_3Cl$, KOH-H_2O-CH_2Cl_2. b) H_2-Pd. c) $Me_2NCH(OMe)_2$, 25°, 15 h, d) 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline (Aldrich), toluene, 110°, 36 h.

o-nitrobenzyl alcohol **1** was transformed into its methyl ether using phase transfer conditions.[3] Pd-catalyzed reduction followed by treatment with DMF acetal gave the formamidine **3** in good yield and exchange[4] with the tetrahydroisoquinoline provided **4**, the precursor to our alkylation products.

To illustrate the enhanced acidity of the MMA formamidine **4**, treatment with *n*-butyllithium at –80°C for 15-30 min produced the lithiated species **5**. With previous formamidines[5] *sec*-butyllithium at -78°C and 1-2 h were the minimum conditions required to successfully produce the lithiated anion. In the present case, if alkylation of **5** was carried out at –80°C polyalkylations were observed (*vide infra*) after the alkyl halide was introduced. This reflects the ability of the MMA group to support the generation of the tertiary anion - an event never observed with the earlier formamidines. The lithiated species **5** was alkylated at -100°C affording good yields of **6** (70-98%) and, as before,[5] hydrazine treatment gave the monoalkylated isoquinolines **7a-7c** in 80-84% yields. Thus, these systems may now be reached in yields comparable to deoxyisoquinoline formamidines using the convenient base, *n*-butyllithium. The monoalkylated material **6** was again treated with *n*-butyllithium (–80°C, THF) and metalation allowed to proceed for 3 h. Introduction of various alkyl halides gave good yields of **8** which, without purification, were submitted to hydrazinolysis furnishing **9a-9e** in 53-80% yields.[6,7] Interestingly, the use of *tert*-butyllithium, a much stronger base than *n*-butyllithium, failed to deprotonate <u>any</u> of the monosubstituted derivatives, **6**. This is presumably due to the encumbered tertiary proton and the inability of the bulkier base to approach bonding distance.



This work is now progressing toward quaternary substituted isoquinoline alkaloids and efforts to incorporate a chiral element into the MMA group.

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6. Recovery of *o*-methoxymethylaniline in good yield was accomplished during the hydrazine step. Yields in this study to date have not been optimized.
7. All new compounds were completely characterized and gave satisfactory spectral and combustion analyses.

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