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α-AMINO CARBANIONS. A COMPETITION STUDY TO ASSESS RELATIVE ACIDITIES IN VARIOUS FORMAMIDINES

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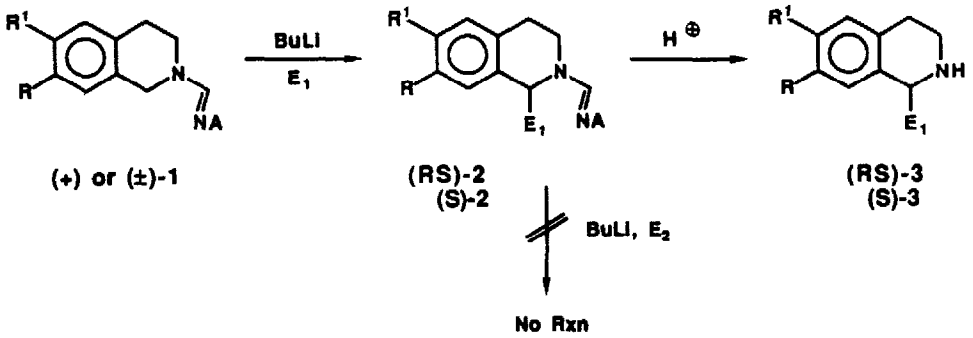
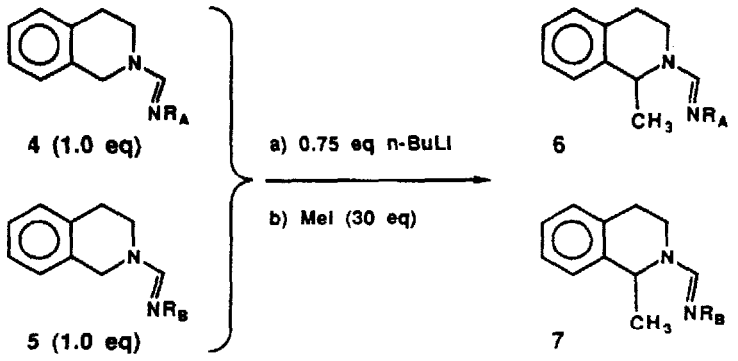
Summary - Various N-groups on formamidines have been examined to see which enhance proton removal adjacent to nitrogen.

Over the past few years we have amply demonstrated that chiral or achiral formamidines **1** may be metalated and alkylated to **2** in high yields and in high ee's. Removal of the formamidine leads to a variety of isoquinoline alkaloids **3** in > 95% ee.[1] It was not surprising that the presence

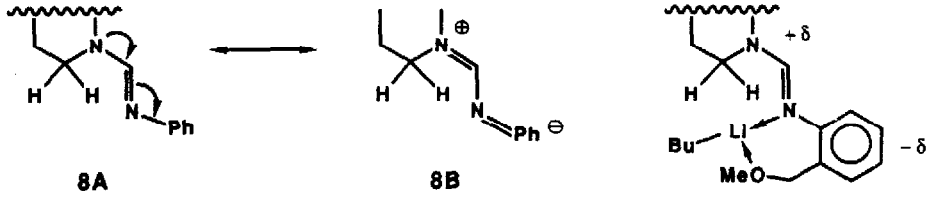


of a 6-alkoxy group in **1** (R^1 = MeO) required stronger bases to remove the proton (LDA is sufficient if R^1 = H). However, it was unfortunate that under no conditions could the tertiary proton in **2** (R^1 = MeO) be removed to allow quaternary carbon formation. Because this would result in a serious limitation in reaching a number of alkaloids, we set out to assess the factors necessary to overcome this problem and hopefully arrive at a group which would increase the acidity of **2**. It was decided to keep the formamidine moiety due to its ease of introduction, removal, and ability to carry chiral or achiral groups. These factors set the formamidine apart from the other dipole stabilized anions[2] and we did not wish to forfeit these advantages.

The study involved a head-to-head competition between two differently substituted formamidines, **4** and **5**, which were allowed to react with a deficiency of *n*-butyllithium in THF solution at -84° C. After 15 min, a large excess of methyl iodide was introduced and the ratio of products, **6** and **7**, were analyzed (Table 1).[3] Some interesting results arose out of this study which opened the way to a new and more reactive formamidine whose synthetic properties are described in the accompanying **Letter**.

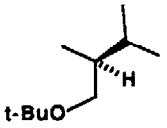
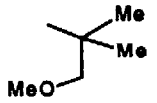
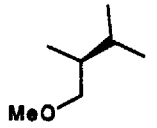
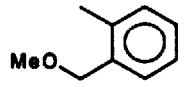
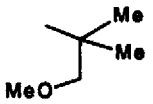
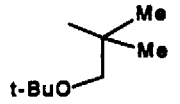
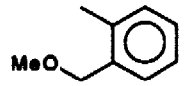


As seen from the Table, chelating groups on the formamidine are far superior to nonchelating groups (Entry 1). In a previous report, we showed that chelation, not proton removal, is most probably the rate determining step in these metalations.[5] Quite surprisingly, however, the phenyl group (Entry 2) competes reasonably well with the valinol *tert*-butyl ether (**6/7** ≅1.8). The absolute stereochemistry of some of the groups in the Table are irrelevant for this study since our concern was only over steric and electronic factors. Regarding steric factors, the gem-dimethyl moiety (Entry 3) was superior to the valinol butyl ether and this is attributed to an enhancement in chelation by virtue of the gem-dimethyl (Thorpe-Ingold) effect.[4] Altering the size of the alkyl group on the ether oxygen (Entry 4 and 6) appears to provide only moderate enhancement on the ratio 6/7. If this is indeed a steric effect, it is only of marginal importance. An even more interesting observation is seen in Entry 7 where the phenyl group is clearly superior to the *tert*-butyl group (**6/7** ≥ 25). This result, coupled with that in Entry 2 wherein the phenyl and the valinol butyl ether are nearly competitive, supported the rationalization that phenyl delocalization of the lone pair on nitrogen (**8A, 8B**) tends to increase the acidity of the α-protons. Furthermore, if a chelating group could be incorporated into the phenyl, this could be the strongest activating group



yet encountered. This was indeed the case when the head-to-head competition was performed with phenyl *vs o*-methoxymethylphenyl (Entry 8) and gave a 1:10 ratio of 6/7. Similarly, the competition between valinol ether and o-methoxymethylphenyl (Entry 5) predictably gave a product ratio favoring the latter. Thus, it would appear that the o-methoxymethyl phenyl group

TABLE 1. Head to Head Competition Study.

Entry	4 (R_A)	5 (R_B)	Methylation $\frac{6\ (R_A)^a}{7\ (R_B)}$
1.		t-Bu	> 50
2.	" "	Phenyl	1.8
3.	" "		0.15
4.	" "		0.8
5.	" "		0.1[b]
6.			1.8
7.	Phenyl	t-Bu	> 25
8.	Phenyl		0.1[b]

[a]An equimolar mixture of **4** and **5** was cooled to -84°C and treated with a deficiency of n- BuLi in THF. After 15 min, 30 equiv of MeI was added all at once and the reaction mixture analyzed for **6**/**7** *via* HPLC, GC, or NMR. [b]Metalation performed at -100°C to avoid polymethylation.

should be capable of overcoming the limitation of generating quaternary carbons in these useful C-C bond forming reactions. This aspect is presented in the accompanying **Letter**.

References

1. Meyers, A. I.; Miller, D. B.; White, F. W. *J. Am. Chem. Soc.* **1988**, *110*, 4778 and earlier references cited.
2. For a fine review on this subject see Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* 1984, *84*, 741.
3. If we can assume that the rate of alkylation with 30 equiv of CH_3I, added rapidly, is much faster than proton exchange then the ratio of **6** to **7** is a rather direct measure of the acidities.
4. Eliel, E. L; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Interscience: New York, p. 191.
5. Meyers, A. I.; Dickman, D. A. *J. Am. Chem. Soc.* **1987**, *109*, 1263.
6. The formamidines **4** and **5** with the various R groups in Table 1 were all prepared in good yield by heating the primary amine corresponding to R_A and R_B with DMF-acetal for 1.0-1.5 h at 60-100° C. The resulting dimethylamino derivative was then heated with 1,2,3,4-tetrahydroisoquinoline in toluene (110° C) affording the formamidines **4** and **5**. Further details may be found in Meyers, A. I.; Dickman, D. A.; Bös, M. *Tetrahedron* **1987**, *43*, 5095.

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