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# DIPOLE STABILIZED α-AMINO CARBANIONS. III.
# METALATION-ALKYLATION OF INDOLINES, TETRAHYDROQUINOLINES AND N-METHYLANILINES.

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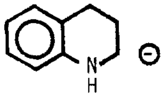
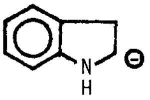
SUMMARY: Metalation of the 2-position in indolines and tetrahydroquinolines is feasible via their formamidine derivatives using *tert*-butyllithium. The N-methyl group in N-methylanilines is also metalated using this base.

The formamidine derivatives of secondary amines have shown versatility in C-C bond forming reactions by allowing the carbanions α- to the nitrogen to form readily and alkylate to homologated amines.[1,2] We now describe further progress using this methodology to generate the important synthetic equivalents A-C which are capable of being elaborated, via their formamidines, to C-substituted derivatives. In the accompanying letter,[2] metalation of tetrahydroisoquinolines was successfully achieved using LDA or *sec*-BuLi, however, the enhanced $pK_a$ of the 1-position undoubtedly was important in proton removal. To assess the generality of the formamidine activation toward α-amino carbanions, it was necessary to determine if protons of weaker carbon acids would also undergo deprotonation. In this regard, the formamidine derivative of 1,2,3,4-tetrahydroquinoline 1 was prepared via its formamide (ethyl formate, 3 equiv, reflux)[3]. Treatment with triethyloxonium fluoroborate (1.1 equiv, $ClCH_2CH_2Cl$, reflux, 16 h) was followed by addition of 1.1 equiv *tert*-butylamine. Aqueous alkali (10% KOH) wash and chloroform extraction gave 1 (97%, bp 100-105°/0.01 mm).[4] Treatment of 1 with 1.1 equiv *t*-butyllithium (-78°, THF) and allowing the solution to warm to -20±5° and maintaining that temperature for 45 min. gave a deep red anion solution. The solution was cooled to -78° and the electrophile added as a THF solution. The color faded as the temperature was allowed to warm to -30° (~1 h) and the solution quenched in water. Extraction with chloroform, drying ($Na_2SO_4$), and concentration gave the alkylated formamidine as an oil which was either purified or carried on to the final product 2 (Table 1) using KOH-MeOH, lithium aluminum hydride, or hydrazine.



A



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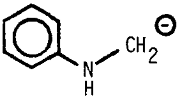

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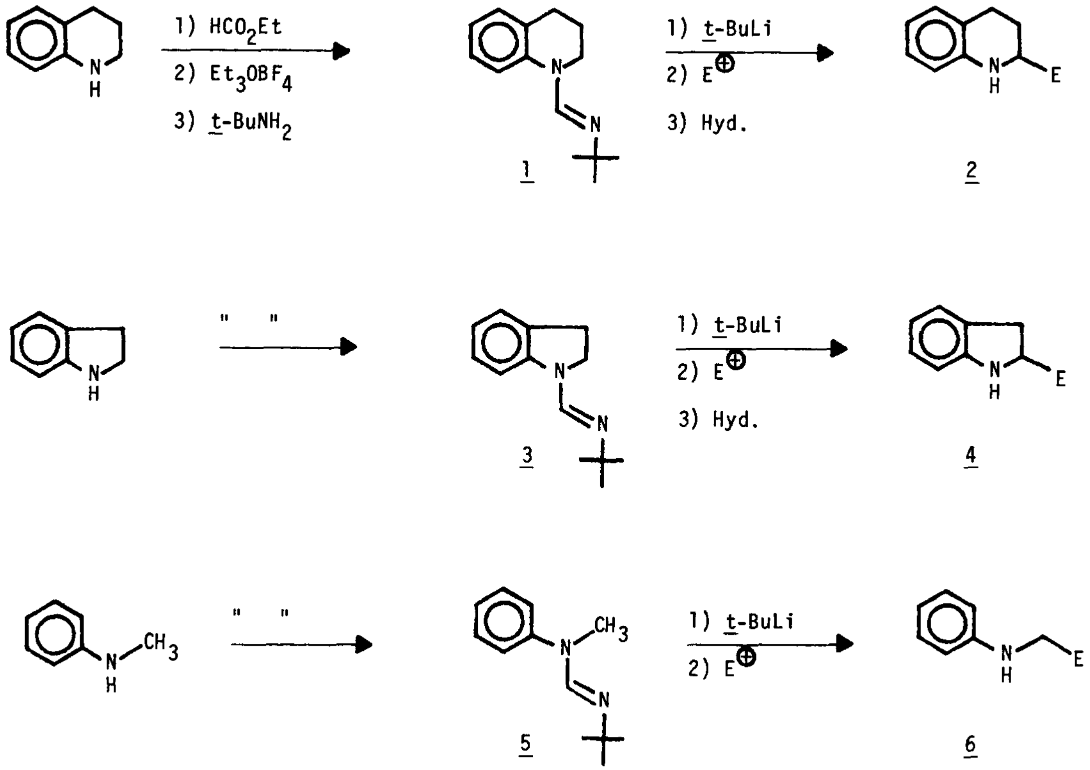
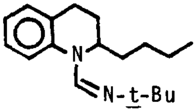
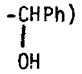
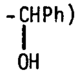
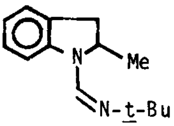
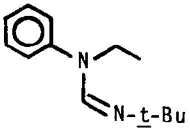


In a similar fashion, the indoline system 3 was prepared and metalated to a deep red anion and alkylated by various electrophiles to produce 4 (Table 1). It is noteworthy that the quinoline adduct with benzaldehyde 2 (E = -CH(OH)Ph) was isolated as a 1:1 mixture of diastereomers, whereas the indoline adduct 4 (R = -CH(OH)Ph) gave a 97:3 mixture of threo to erythro isomers. This high degree of selectivity encourages us to examine further examples and poses a possible route to enantiomerically pure derivatives under the influence of chiral adjuvants. The third case studied, namely formamidine 5, gave, on treatment with *t*-butyllithium, the lithio anion which was readily alkylated with methyl iodide or *n*-butyliodide. The former product was identical to an authentic sample prepared from N-ethyl formanilide (from treatment of formanilide with ethyl iodide, KOH, DMSO) using triethyloxonium tetrafluoroborate and *tert*-butyl amine as described above. The latter example was converted to aniline 6 (E = *n*-Bu) using hydrazine.

The formamidine moiety, after alkylation, was transformed back to the secondary amines 2, 4, and 6 by either heating in 2N KOH (25 ml) and DMSO (10 ml) for 3.5 h, or warming (50°) in hydrazine (95%, 3 equiv) with acetic acid (3 equiv) in 60% aq. EtOH (5 ml), or heating a THF solution of the formamidine and $LiAlH_4$ (3 eqiv Li) at reflux overnight.[6] The reductive cleavage was found to be successful for the hydroxyamines 2 (E = CH(OH)Ph) and 4 (E = CH(OH)Ph), whereas hydrolytic cleavage using KOH or hydrazine worked well for the other examples in the table.

The extensive utility of these α-amino carbanions to form C-C bonds adjacent to nitrogen has as its only synthetic precedent, the elegant work of Seebach[7] using N-nitroso amines.[8] However, the lack of physiological danger using formamidines coupled with their high

Table 1 - Alkylation of Quinolines, Indolines, and Anilines

| Amidine | $E^{\oplus}$ | Product | % Overall Yield From 1, 3, 5 | $Bp^a$ (mp) |
|---|---|---|---|---|
| 1 | MeI | 2 (E = Me) | $65^f$ | 100°/11 mm |
| 1 | n-BuI |  | 84 | $72°/0.05\ mm^e$ |
| 1 | PhCHO | 2 (E =  $-\underset{\text{OH}}{\underset{\vert}{\text{CH}}}\text{Ph}$) | $64^b$ | $(138\text{-}141°)^{c,e}$ |
| 3 | EtI | 4 (E = Et) | $66^g$ | 85°/0.2 mm |
| 3 | PhCHO | 4 (E =  $-\underset{\text{OH}}{\underset{\vert}{\text{CH}}}\text{Ph}$) | $73^d$ | $(199\text{-}201°)^{c,e}$ |
| 3 | MeI |  | 83 | $67°/0.02\ mm^e$ |
| 5 | MeI |  | 90 | $120°/0.05\ mm^e$ |
| 5 | n-BuI | 6 (E = n-Bu) | 68 | $130°/11\ mm^h$ |

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a) Bulb-to-bulb distillation temperature, mp of hydrochloride salts; b) Mixture of diastereomers determined by integration of doublets at δ 4.62 (J=6 Hz) and 4.70 (J=6 Hz); c) Recrystallized from ethanol-ether; melts with decomposition; d) Diastereomeric ratio 97% threo:3% erythro determined by doublets at δ 4.40 (threo, J=8 Hz) and 4.59 (erythro, J=5.4) and confirmed by hplc analysis (97:3) using ethyl acetate-hexane; e) Satisfactory (±0.3%) elemental analyses were obtained; f) G. N. Fisher and H. P. Schultz, J. Org. Chem., 39, 635 (1974); g) G. Smolinsky and B. I. Feur, J. Org. Chem., 29, 3097 (1964); h) Beilstein, II, Vol. 12, 96.

nucleophilicity, renders this methodology potentially very valuable.

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## REFERENCES AND NOTES

1. For Part I, c.f. A. I. Meyers and W. Ten Hoeve, J. Am. Chem. Soc., 102, 7125 (1980).
2. A. I. Meyers, S. Hellring, and W. Ten Hoeve, previous article in this issue.
3. J. Moffat, M. V. Newton, and G. J. Papenmeier, J. Org. Chem., 27, 4058 (1962).
4. This method was used to prepare formamidines 1 (bp 100-105°; 0.01 mm), 3 (bp 125°; 0.2 mm; mp 54-56° from pentane), and 5 (bp 60°; 0.03 mm) in 97, 87, and 91% yields, respectively. All three formamidines gave satisfactory elemental analyses.
5. Synthesis of 5 was also performed starting with commercially available N-methylformanilide in the manner described for 1 and 3.
6. The conditions in parentheses refer to quantities used on a 5 mmole scale. The $LiAlH_4$ cleavage was worked up by addition of $Na_2SO_4 \cdot 10\ H_2O$ to the ice-cold reaction mixture, stirring at ambient for ∿6 h, filtering the salts and washing them with THF. The combined THF solutions were concentrated to give the crude product which was purified by MPLC.
7. D. Seebach and D. Enders, Angew. Chem. Int. Ed., 14, 15 (1975).
8. For an excellent review on other related methods using dipole-stabilized anions, see P. Beak and D. R. Reitz, Chem. Rev., 78, 275 (1978).

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