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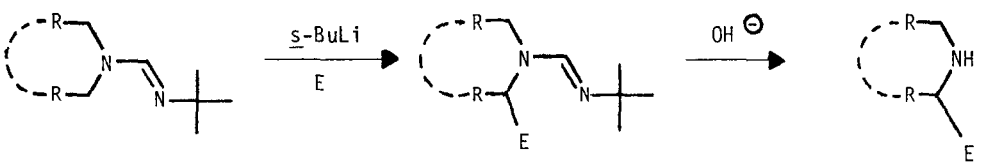
DIPOLE STABILIZED α-AMINO CARBANIONS. II. ALKYLATION OF TETRAHYDROISOQUINOLINES IN THE 1-POSITION.

A. I. Meyers,* Stuart Hellring, and Wolter Ten Hoeve
Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

SUMMARY: N-Formamidine derivatives of tetrahydroisoquinolines are metalated and alkylated to give 1-substituted derivatives. Regeneration of the parent amine is accomplished by several different reagents.

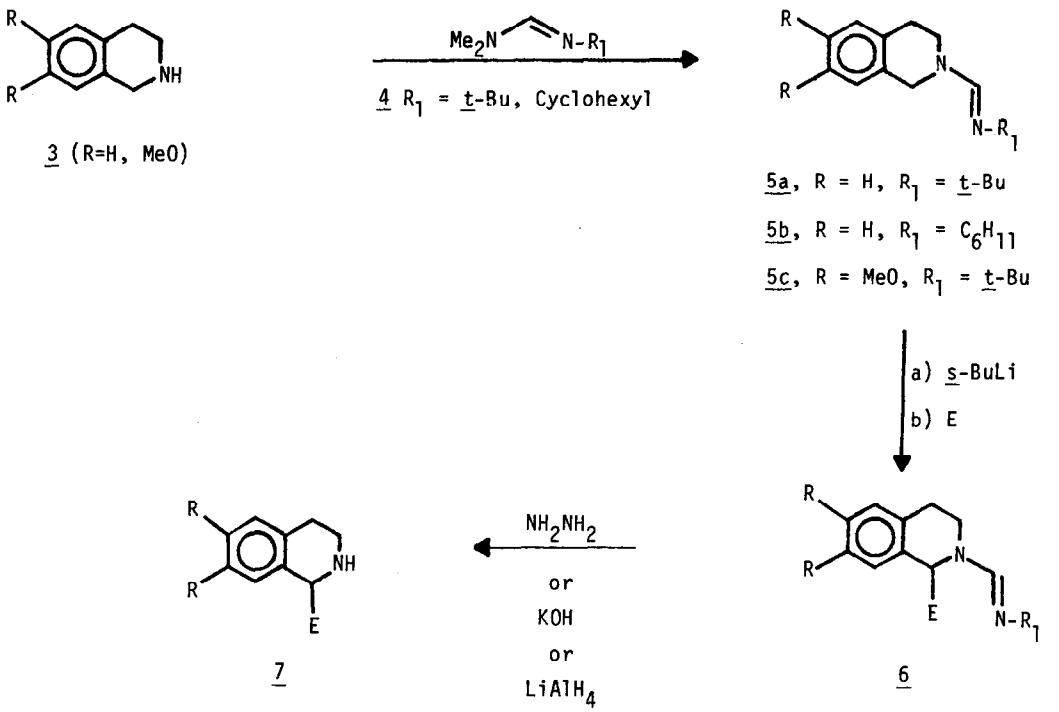
Our recently described methodology for metalating formamidines 1 and alkylation with various electrophiles has provided a new route to α-substituted amines 2, after hydrolytic removal of the formamidine group.[1] Further studies on this useful process has now led to the



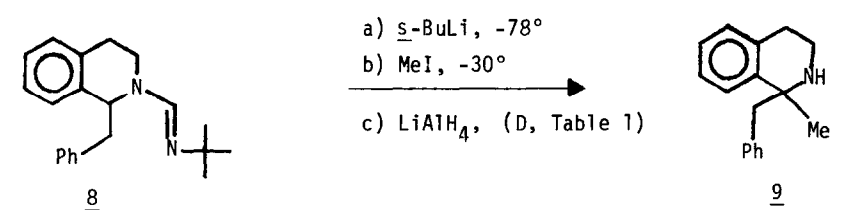
1 2

finding that tetrahydroisoquinolines may also be efficiently alkylated at the 1-position, a synthetic goal which has considerable importance in medicinal chemistry.[2] The isoquinolines 3 were readily transformed into their formamidine derivatives either by a) heating with the dimethyl formamidines 4[1] in toluene to furnish 5a (89%) or 5b (95%) or b) treatment of the N-formyl derivative of 3 (R = MeO) with $Et_3O^+ BF_4^-$ in dichloroethane followed by t-butylamine and heating at reflux overnight. Quenching in alkali, extraction (chloroform), drying (Na_2SO_4), and concentration gave 5c in 90% yield.[3]

Metalation of 5 (a-c) was generally performed using 1.1 equiv of s-butyllithium in THF at -78° followed by introduction of the electrophile and allowing the solution to warm to -20°±10° over 2-3 h. Aqueous quench, chloroform extraction, drying (Na_2SO_4) and concentration afforded the alkylated tetrahydroisoquinoline 6 in high yield.[4] Without further purification, crude 6 was treated with either hydrazine, KOH-MeOH, or $LiAlH_4$ to regenerate the free amine (Table 1). From the table it may be seen that the representative array of alkylated isoquinolines clearly supports the versatility of this method. Of particular note is the formation of N-methyl 1-carboethoxy tetrahydroisoquinoline (last entry in table) which arose by formamidine cleavage using aluminum-amalgam in moist ether. Obviously, the formamidine in this instance could not



be removed using any of the three cleavage methods mentioned above. This technique is also applicable to geminal alkylation of the 1-position in the isoquinolines as seen by treatment of 8 with sec-butyllithium, methyl iodide and finally with $LiAlH_4$ to furnish 9 in 53% yield (mp of HCl salt, 218-220°). A facile synthesis of benzo[b]quinolizidines 11 was demonstrated by treating 3 with s-BuLi (-78°) and adding 1-chloro-4-bromobutane, warming to -30°, and quenching the reaction in water. After chloroform extraction, crude 10 was treated with $LiAlH_4$ and gave 11 in 71% yield.[5] Further utility concerning this route to alkylated N-heterocycles is described in the accompanying letter.



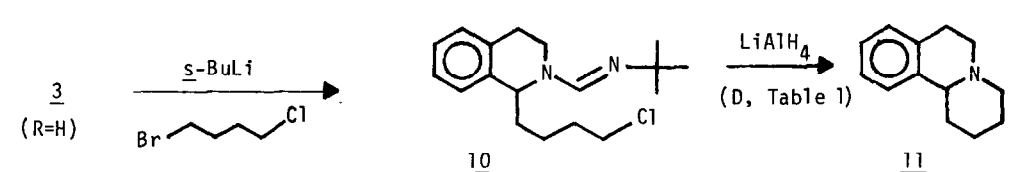
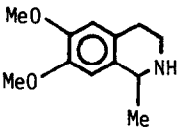
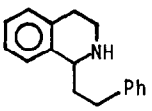
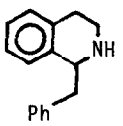
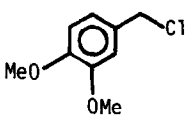
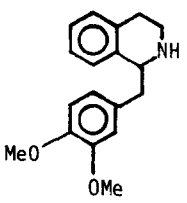
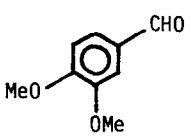
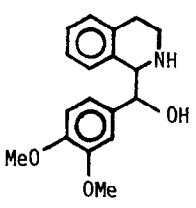
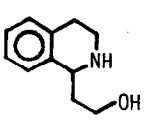
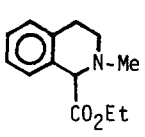


Table 1 1-Substituted Tetrahydroisoquinolines 7

Formamidine	Electrophile	Cleavage 6 → 7	Product	Overall Yield	Mp (bp)[6]
5c[7]	MeI	A		52%	188-189°
5a		B		61%	171-173°
5b		A		52%	166-167°
5b		A		52%	228-230°
5b		A		53%[9]	198-200°
5a		B		67%	(140°/2mm)
5b[8]	$ClCO_2Et$	C		62%	(89-90/0.2mm)

A = 95% NH_2NH_2-CH_3CO_2H-60% aq. EtOH (1:1.6:10) heated to 53° overnight.

B = 10% aq. KOH-MeOH (1:1) heated to reflux, 24 h.

C = Al-Hg reagent described by A. I. Meyers and J. R. Durandetta, J. Org. Chem., 40, 2021 (1975).

D = $LiAlH_4$ (3 equiv Li), THF, reflux, 16 h.

ACKNOWLEDGEMENT - The authors are grateful to both the National Science Foundation and the Army Research Office (Durham) for financial assistance.

REFERENCES AND NOTES

1. A. I. Meyers and W. Ten Hoeve, J. Am. Chem. Soc., 102, 7125 (1980).

2. Alkylation adjacent to amino groups has been reported by a) J.-J. Lohmann, D. Seebach, M. A. Syfrig, and M. Yoshifuji, Angew. Chem. Int. Ed., 20, 128 (1981) and earlier references cited; b) T. Shono, Y. Matsumura, and K. Tsubata. J. Am. Chem. Soc., 103, 1172 (1981) and earlier references cited.

3. 5a, bp 170° (0.15 mm); 5b bp 106-109° (0.2 mm), mp 79-81° (pentane); 5c, bp 115° (0.02 mm), mp 93-95° (ether-hexane). Elemental analyses were within ±0.3%.

4. In several instances 6 was purified (tlc) and gave correct elemental anlysis.

5. M. Uskokovic, H. Bruderer, C. Von Planta, T. Williams, and A. Brossi, J. Am. Chem. Soc., 86, 3364 (1964). ^{1}H nmr comparison showed product to be identical.

6. Mp of hydrochloride salts which agreed with literature values or gave satisfactory elemental analysis if not previously reported. Values in parentheses are bp's (bulb-to-bulb) for free base.

7. KDA (potassium diisopropylamide) used as metalating base.

8. LDA (lithium diisopropylamide) used as metalating base. All of the examples in Table 1 could be metalated with LDA in place of sec-butyllithium. However, the metalation time for the latter (∿45 min) was more convenient than the former (2-3 h).

9. Mixture of diastereomers (∿1:1).

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