Regioselectivity in Forming Dipole-Stabilized Anions. Sites of Metalation of Indolines, Tetrahydroquinolines, and Benzazepines Activated by *N*-Formimidoyl or *N*-Boc Groups[†]

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Summary: Metalation of the title compounds indicated that the formamidine-equipped indolines or 1,2,3,4-tetrahydroquinolines give rise solely to C-2 alkylation products (**5**, **6**) whereas the corresponding N-*t*-Boc systems give only ortho aryl alkylation (**7**, **8**).

Nearly a decade ago, we reported the metalation of and alkylation of indoline **3** and 1,2,3,4-tetrahydroquinoline **4** containing the formamidine moiety.[1] The site of metalation was shown to occur exclusively at C-2 (Scheme I) affording the elaborated indolines and/or tetrahydroquinolines **5** and **6**, respectively. In view of the recent results described by Beak[2] and Iwao[3] wherein the corresponding Boc derivatives **1** and **2** exhibited metalation–alkylation at the ortho aryl position, furnishing **7** and **8**, respectively, we felt it necessary to further examine the factors controlling this process.

In another related study from this laboratory,[4] we observed significantly different metalation behavior between formamidine (Tbf) and Boc activated secondary amines with regard to *stereochemical products*. The *regiochemistry* of metalation, however, was shown to be identical. The study dealt with piperidine and decahydroquinoline systems wherein conformational effects proved to be the major factor involved. In the present study, there are possibilities of other factors (i.e., complex induced proximity effect,[5] conformation, inductive effects, etc.) which may play various roles in determining the site of metalation.

Scheme I

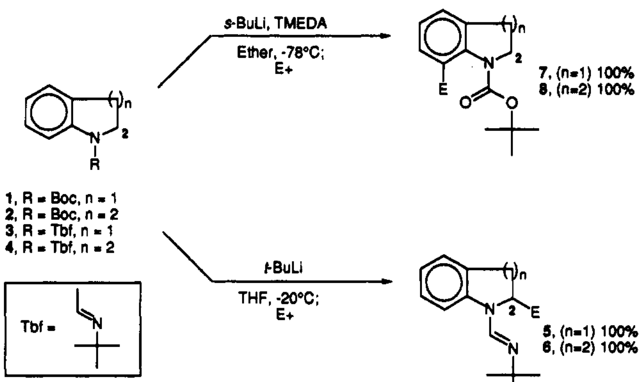
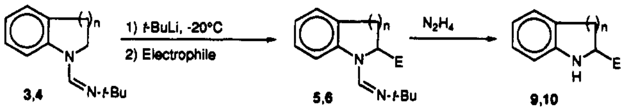


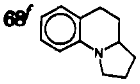
Table I



Indoline **3** ($n = 1$)

electrophile	**5** yield[a] (%)	**9** yield[b] (%)
(a) MeI	92	80
(b) Me_3SiCl	95	
(c) Me_3SnCl	89	
(d) BuI/CuC≡CPr	78	91
(e) allylBr/CuC≡CPr	70	81 (E = propyl)[c,d]
(f) $ClCO_2Et$	87	
(g) MeOD	(90% D)	
(h) $Cl(CH_2)_3I$/CuC≡CPr	85	75[f] 

tetrahydroquinoline **4** ($n = 2$)

electrophile	**6** yield (%)	**10** yield[b] (%)
(a) MeI	95	85
(b) Me_3SiCl	95	56
(c) MeOD	(90% D)	
(d) BuI/CuC≡CPr	91	80
(e) allylBr/CuC≡CPr	94	78 (E = propyl)[c,e]
(f) $Cl(CH_2)_3I$/CuC≡CPr	75	68[f] 

[a] Lithiation–alkylation were performed in THF (0.5 M) using 1.35 equiv of *tert*-butyllithium. [b] Hydrazinolysis performed as reported earlier (see ref 4). [c] Concomittant reduction of the olefin was observed. [d] 65%, E = allyl from KOH/DMSO hydrolysis (see ref 4). [e] 82%, E = allyl, from KOH/DMSO hydrolysis (see ref 4). [f] Formed during hydrazine step.

The metalation of the formamidines **3** and **4**, as 0.5 M solutions in THF, using *tert*-butyllithium are summarized in Table I. As is readily seen, only C-2 metalation and alkylation (to **5**, **6**) took place in generally good yields with no detectable trace of arene metalation. The alkylations of the lithio species proceeded smoothly with highly reactive electrophiles (MeI, Me_3SiCl, D_2O) while less reactive materials such as iodobutane, allyl bromide, or dihalides required the use of pentynyl copper.[6] These latter alkylations, presumably involving radical intermediates,[4,8b] proceeded in good yields to **5** and **6**. For synthetic purposes, the hydrazinolysis of the latter was performed furnishing the *N*-unsubstituted products **9** and **10**. It is noteworthy that the product of hydrazinolysis originating from the 2-allylindoline or 2-allyl-1,2,3,4-tetrahydroquinoline was the saturated 2-propyl derivatives **9e** and **10e**. This facile reduction of the olefinic bond has been previously observed by us[4] in related processes and presumably requires traces of copper ion to occur.

It is interesting to compare these results leading to **9** and **10** with the metalation–alkylation of the same heterocyclic systems equipped with the Boc group (**7** and

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[†] This paper is dedicated to Professor Harry M. Walborsky on the occasion of his 70th birthday.

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(1) Meyers, A. I.; Hellring, S. *Tetrahedron Lett.* **1981**, *22*, 5119.

(2) Beak, P.; Lee, W.-K. *Tetrahedron Lett.* **1989**, *30*, 1197.

(3) Iwao, M.; Kuraishi, T. *Heterocycles* **1992**, *34*, 1031. The orthometalation of N-activated anilines related to these systems has been reported by others; see: (a) Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798. (b) Katritzky, A. R.; Fan, J.-Q.; Akutagawa, K. *Tetrahedron* **1986**, *42*, 4027.

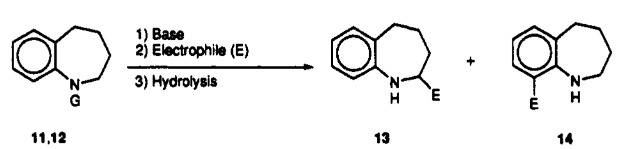
(4) Meyers, A. I.; Milot, G. *J. Am. Chem. Soc.* **1993**, *115*, 6652. This concomittant reduction of the alkene can be avoided by hydrolysis of the formamidine with aqueous KOH–DMSO in place of hydrazine (see supplementary material).

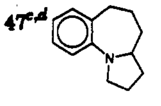
(5) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.

(6) Meyers, A. I.; Edwards, P. D.; Reiker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270.

0022-3263/93/1958-6538$04.00/0

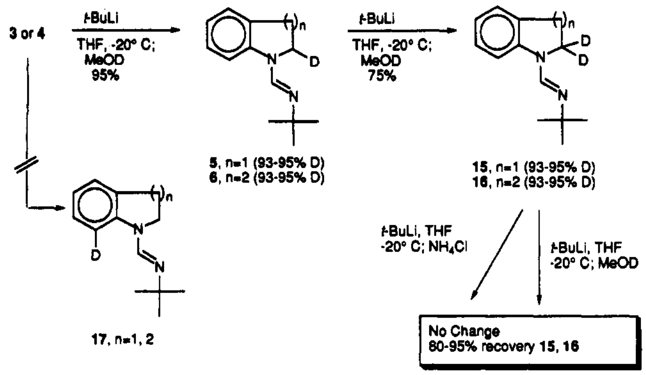
Table II. Alkylation of Benzazepines



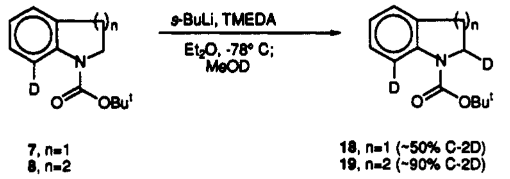
electrophile (E)[a]	% 13	% 14	% yield overall
	11, G = Boc		
(a) MeI	80	20	90
(b) Me_3SiCl	80	20	75
(c) MeOD	80	20	71
			
(a) MeI	70	30	54
(b) Me_3SiCl	70	30	72
(c) MeOD	70	30	66
(d) allylBr/CuC≡CPr	70	30	58 (E = propyl)[b]
(e) BuI/CuC≡CPr	98	2	50[d]
(f) $Cl(CH_2)_3I$/CuC≡CPr	95		47[c,d] 

[a] For 11, 1.5 equiv of *sec*-butyllithium (cyclohexane) at −78 °C in ether in the presence of 1.1 equiv of TMEDA was employed. Further details are described in the supplementary material. For 12, 1.5 equiv of *tert*-butyllithium (pentane) at −20 °C in Et_2O/THF (4:1) was used; see supplementary material. [b] See ref 4. [c] Formed during hydrazine step. [d] 20–30% of 14 (E = H) was recovered in addition to product, 13 (E = alkyl).

Scheme II



Scheme III



8).[7] The striking differences observed by changing the activating groups prompted a further study on the next higher homolog, namely the benzazepine systems 11 and 12. The respective Boc and formamidine derivatives 11 and 12 were prepared from the benzazepine[8] (G = H) and subjected to metalation–alkylation conditions as before. Surprisingly, the *N*-Boc benzazepine 11 gave a 4:1 mixture of 13:14 substitution (Table II), whereas the formamidine derivative 12 gave a 7:3 mixture of 13:14. Thus, both *N*-activating groups now led to C-2 substitution as the major event while arene deprotonation was found to be less favored. The flexible seven-membered ring in 11 or 12 may be responsible for the multiple metalation sites not observed earlier with the more rigid five- and six-membered ring systems (e.g., 1–4). Since it has been generally agreed[6,9] that deprotonation of these systems requires that the proton be orthogonal (or nearly so) to the π-system of the *N*-Boc or formamidine moiety, the flexibility or mobility of the seven-membered ring allows the α-proton (C-2H) to assume a favorable orientation to the π-system while undergoing the deprotonation. From a synthetic viewpoint, the dichotomy of the regioalkylations observed should prove useful in elaborating these ring systems. It is also seen from Tables I (entries h and f) and II (entry f) that 1-azabicyclo systems are accessible in good yield by merely using a bifunctional electrophile (e.g., α,ω-dihalide) to fuse a pyrrolidine ring onto the original heterocyclic template. The cyclization occurred spontaneously during the hydrazinolysis step. The higher selectivity using butyl iodide or chloropropyl iodide (Table II, entries e, f) is a reflection of the poor electrophilic character when alkylating 14 (E = Li) which returned significant quantities of 14 (E = H).

Experiments involving multiple metalations and deuterations to assess the relative kinetic acidities of the different sites in 3 and 4 were also performed. Scheme II further describes the highly selective nature of these metalations in the presence of the formamidine moiety. Thus, metalation and deuterium quench gave, as before, substitution solely at C-2 (93–95% D) for either 3 or 4. When 5 or 6 were again treated with *tert*-butyllithium and quenched with methanol-d_1 only the *gem*-dideuterio derivatives 15 and 16 were obtained in good yield with >93% D-incorporation (^{13}C-NMR of C-2).[10] No evidence of any aryl-D bond (^{13}C-NMR, ^{1}H-NMR) could be detected arising from this metalation. With both deuteriums in place at C-2, another metalation was attempted to see if the kinetic acidity of the adjacent aryl proton would compete with the stronger C–D bonds at C-2. Quenching with methanol-d_1 after 6, 12, and 18 h gave only starting materials 15 and 16 in 60–80% recovery, the lower recovery due to decomposition after prolonged exposure to base. To evaluate the strength of the C–D bond in 15 and 16, they were subjected to the usual metalation conditions and quenched with a proton (methanol or ammonium chloride). The deuterio derivatives 15 and 16 were recovered in greater than 95% yield (Scheme II) indicating no deuterium abstraction had occurred. Thus, under no conditions attempted could we deprotonate the ortho aromatic proton to reach 17. This, again, is in stark contrast to the *N*-Boc systems 1 and 2, which favor this metalation site. We also examined the relative kinetic acidity of the latter (Scheme III). Surprisingly, when 7

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(7) It is noteworthy that the formamidines 3 and 4 required *tert*-butyllithium, THF at −20 °C to effect metalation whereas the N-Boc systems 7 and 8 required *s*-BuLi, TMEDA, −78 °C in ether to furnish the lithio derivative. In both cases, reversing the conditions or base led to either no metalation or decomposition; thus, they could not be compared under identical metalation conditions.

(8) (a) Lansbury, P. T.; Mancuso, N. R. *Tetrahedron. Lett.* **1965**, *6*, 2445. (b) Yamamoto, H.; Maruoka, K.; Miyazaki, T.; Satoru, S. *Tetrahedron Lett.* **1983**, 4711. (c) Maruoka, K.; Ando, M.; Matsumara, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *105*, 2831. (d) Adams, G.; Andrieux, J.; Plat, M. *Tetrahedron* **1992**, *38*, 2403. Experimental details for 11 and 12 as well as all other derivatives described in this report are given as supplementary material.

(9) (a) Peak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471. (b) Gawley, R. E.; Hart, G. C.; Bartolotti, L. J. *J. Org. Chem.* **1989**, *54*, 175. (c) Seebach, D.; Wykpiel, W.; Lubosch, D.; Kalinowski, H. D. *Helv. Chim. Acta* **1978**, *61*, 3100. (d) Beak, P.; Lee, W. K. *J. Org. Chem.* **1989**, *55*, 2578.

(10) Assignment and quantitative assessment of the deuterated compounds 5, 6, 15, 16, 18, 19, 20, and 21 were made by ^{1}H and ^{13}C NMR spectra examining C-2 and Ar-H protons.

and 8 were treated to the metalation conditions and quenched with MeOD, there was indeed deuterium incorporation at the C-2 position, as determined by ^{13}C-NMR. The dideuterated indoline 18 was only formed in ~50% yield after 6 h of metalation whereas the quinoline system 19 gave a 90% yield of dideuterio product after 6 h. There is, therefore, an apparent reluctance of the indoline system to metalate at the C-2 position once the aryl-H is blocked by the isotopic substituent. The more flexible quinoline ring 8, on the other hand, proceeded to deuteriate more rapidly.[11] Thus, the *N*-Boc is capable, under certain conditions, of directing metalation to the methylene group (C-2) if the adjacent aryl proton is absent. The difference exhibited by the formamidines and Boc system 1–4 is not yet clearly understood, but suffice it to say that the kinetic acidities of the protons in question are delicately balanced and influenced by the conformational population as well as the differences in the metalating conditions and electronic nature of the two activating groups. Further experiments are planned to shed light on this behavior. The results of this study are synthetically useful, even though the origins of these effects are not yet clear.

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Supplementary Material Available: Experimental details for all compounds (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(11) Professor Beak has informed us if the aryl proton in 1 is substituted by chlorine, the metalation also proceeds at the C-2 position. We thank Professor Peter Beak for sharing these experimental results and stimulating discussions.