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'Counter-intuitive' regioselectivity, subtle steric and solvation effects in lithiation of cyclic tertiary aralkylamines☆

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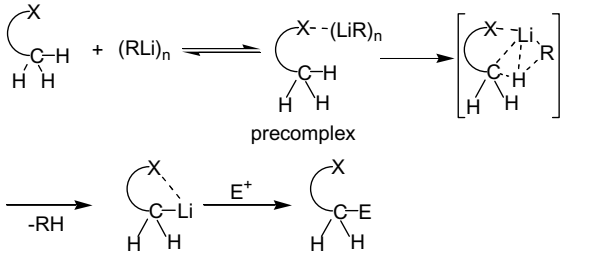
Abstract—Lithiation of a series of cyclic aralkyl tertiary amines with *sec*-BuLi in various solvents has been studied. There is a subtle sensitivity to steric factors and lithium coordinating solvents/additives have an adverse effect. *ortho*-Lithiation is observed only in the case of an eight-membered cyclic amine and the ease of benzylic lithiation with respect to nitrogen is in the surprising order $\gamma > \beta \gg \alpha, \delta$. These observations are discussed in the context of nitrogen coordination promoted lithiation.

The deprotonative lithiation-electrophile reaction sequence is a widely used method for forming new bonds at weakly acidic carbon centers.[1–5] Heteroatoms play a pivotal role in such metalations through their electronic effects and by coordination with lithium in the transition state and, arguably,[6] in a prelithiation complex (Scheme 1). In spite of studies spread over seven decades, some aspects of this chemistry remain unsettled. Notably, there is a surprising lack of understanding and systematic data on regioselectivity and its correlation with through space distance between heteroatom coordinated lithium and the reacting C–H center.[7,8] For cyclic systems, where conformational variations in distance may be less, even qualitative level studies are rare.[9] The area is complicated by superimposition of electronic effects,[10] the presence of multiple rapidly equilibrating moieties and other variables, which are difficult to delineate precisely. Lithium coordination itself can vary with the donor ability and steric environment of the substrate heteroatom. Solvents/additives which coordinate strongly with RLi can increase its reactivity due to deaggregation but this can be countered by many factors, including sequestration of the substrate and net effect may vary among the different classes of compounds.[11] The state of RLi aggregation can also have a role in regioselectivity, particularly in promoting distal lithiation.[12]



Scheme 1.

The lithiations reported here are of synthetic interest, for tertiary amines in general, and cyclic aralkylamines in particular,[13] and could be especially revealing in the context discussed above because (i) competing benzylic and aryl sites amenable to easy lithiation are present; (ii) the heteroatom is part of a medium-sized ring; (iii) the net electronic effect of nitrogen, unlike those of O, S, and P is not marked,[14,15] and coordinative effects might be more important. In the event, treatment of amines **1a**–**4a** in toluene–Et_2O (1:1) with 2.2 equiv of *sec*-BuLi (−78 → 0 °C, 1 h → −78 °C) followed by reaction with benzophenone (2.2 equiv) afforded alcohols **1c**–**4c** (Table 1, entries 1–4).[16,17] The relative ease of lithiation at competing benzylic sites, with respect to nitrogen, is in the surprising order $\gamma > \beta \gg \alpha, \delta$.

Keywords: Regioselectivity; Lithiation; Amines; Solvent effects; Steric effects.

☆ Details of the experimental procedure are available in Supplementary data.

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Table 1. Lithiation/benzophenone reaction of amines **1a**–**4a**,**d**, **5**, **6a**, and **7a** in toluene–Et_2O (1:1) (conditions A), with addition of 2.2 equiv of TMEDA (conditions B), in THF (conditions C), and in pure toluene (conditions D)

Entry	Substrate (available sites)[a]	Lithiation position[b]	Product (conditions, % yield)[c]
1	**1a** (α, β, *o*)	β	**1c** (A, 60); (B, 62); (C, 62)
2	**2a** (α, γ, *o*)	γ	**2c** (A, 31); (C, 5)
3	**3a** (β, γ, *o*)	γ	**3c** (A, 42); (B, –); (C, –); (D, –)
4	**4a** (α, δ, *o*)	*o*	**4c** (A, 55); (B, –); (C, –); (D, –)
5	**4d** (α, δ)	(–)	(A, –)
6	**5** (α, γ, *o*)	(–)	(A, –); (C, –)
7	**6a** (α, *o*)	*o*	**6c** (A, 63); (B, 20); (C, 60)
8	**7a** (α, *o*)	(–)	(A, –); (C, –)
9	**10a** (α, γ, *o*)	α	**10d** (A, 50)
10	**11a**	(–)	(A, –)

[a] *o* Denotes *ortho* position.
[b] (–) Denotes insignificant product formation (HPLC/TLC).
[c] Yields are for isolated pure compounds.

ortho-Lithiation was observed only in the case of **4a** although directed *ortho*-metalation (D*o*M) is the norm with open chain benzylamines or if the nitrogen is directly attached to the aromatic ring.[3] It seems that in **4a**, but not in **3a**, the greater flexibility of an eight-membered ring allows coordination-assisted lithiation at an *ortho* position. Although **4a** delineates the minimum proximity requirement for *ortho*-lithiation in this series, the relevant centers still seem to remain, in models, somewhat far apart. In the case of **4d**, in which the reactive *ortho*-position is blocked by a trimethylsilyl group, lithiation at neither the α nor δ position was observed. In fact, products corresponding to lithiation at the α-benzylic position, for example, **8c** from **1a**, were not formed to an appreciable extent in any of the amine reactions in toluene–ether (1:1), in contrast to oxygen and sulfur analogues **9** and **10** (Table 1, entry 9 and Ref. 18). It may be inferred that not only the electronic but also the coordinative effects of nitrogen do not favor α-lithiation. Amines **5** and **7a** were inert (Table 1, entries 6 and 8), which could be due to steric inhibition of coordinative lithiation. The steric demand of **7a** is only slightly higher than that of **2a** and it could also undergo *ortho*-lithiation on the appended benzene ring, but it was unreactive under the conditions studied (Fig. 1).

To study the effect of solvents and additives on the metalation of these amines, reactions of **4a** were carried out in pure toluene, in toluene–Et_2O (1:1) alone or with added TMEDA and in THF (Table 1, entry 4).[19] While

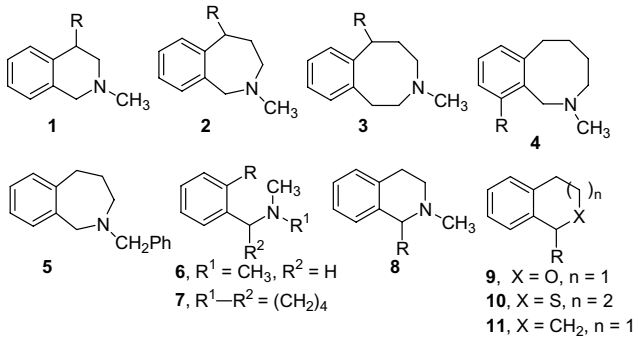

Figure 1.

suppression of lithiation by TMEDA was to be expected,[11] the dramatic curtailment in THF seemed surprising especially in comparison with the open-chain amine **6a** (Table 1, entry 7). The adverse effect of THF on the yield of the major product was also observed in the lithiation of cyclic amine **3a** and to a lesser extent in the case of **2a** (Table 1, entries 3 and 2). In contrast to lithiation of **2a**–**4a**, metalation of the analogous six-membered ring amine **1a** proceeded readily in THF (Table 1, entry 1 and Ref. 20), which is a remarkable reversal of solvent effect within a closely related series of substrates (**1a**–**4a**). Moreover, addition of other strongly lithium coordinating additives (TMEDA, PMDTA, and HMPA) or the use of Schlosser's base in THF had no adverse effect on the major product of this reaction,[16] a feature characteristic of acidity-driven metalations.[21] Whatever the factors are in **1b** or the transition state leading to it, which are responsible for the distinctive lithiation of **1a** is not clear at this stage.[22]

In conclusion, we have found that lithiation of these cyclic tertiary amines (a) exhibits subtle sensitivity to steric factors, (b) strongly lithium coordinating solvents/additives have an adverse effect except in the case of **1a**. In terms of regioselectivity (c) *ortho*-lithiation is observed only in **4a** while benzylic lithiation prevails in **1a**–**3a** and (d) its relative ease is $\gamma > \beta \gg \alpha, \delta$. Some findings of this comparative study, apparently the first in which the heteroatom is enclosed in a ring, are indeed surprising but may be specific to an extent to the chosen set. There is an urgent need for additional studies on the spatial dependence of the coordinative component of the heteroatom effect and its related areas.[23]

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.07.110.

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