Metalation−Alkylation of N-Activated Pyrrolidines. Rigorous Proof of Retention for Both Steps

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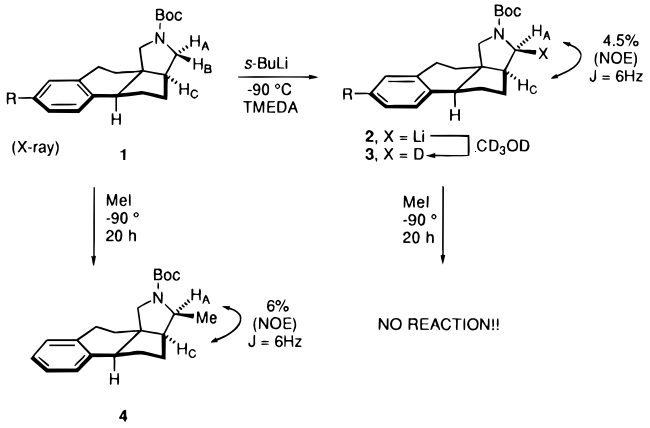
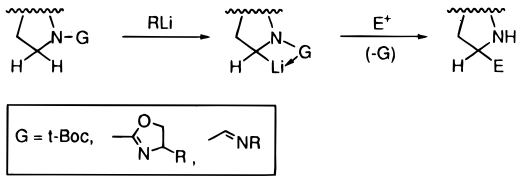
The achiral or enantioselective alkylation α to nitrogen in a number of saturated heterocycles has attracted considerable attention over the last decade.[1] Generally, the process involves activation of the nitrogen by some electron-withdrawing group that, upon treatment with a strong base, produces the α-lithio derivative, and introduction of an electrophile then completes the sequence. Removal of the activating group is the final step to the α-substituted amine (Scheme 1). This process has also been extended to the formation of chiral nonracemic pyrrolidines by deprotonation−alkylation of the *N*-Boc derivative mediated by (−)-sparteine.[2,3] The α-lithio derivatives formed during this sequence are generally believed to alkylate with retention[2ef,4] (alkyl group enters from same face as the proton removed), although some reports of an inversion process (alkyl group enters from face opposite proton removal) have appeared.[5]

During the course of a total synthesis of (+)-conessine,[6] we had the occasion to examine the methylation at C-20 of the enantiomerically pure tetracyclic pyrrolidine **1**. We found, as a result of this study, what we believe to be rigorous proof for stereoselective deprotonation and alkylation of the lithio anions of *t*-Boc-pyrrolidines. In addition, Beak has also been concerned with the stereochemistry of deprotonation and subsequent electrophilic alkylation and on the basis of some very astute experiments concluded that the key enantio-determining step was deprotonation.[7] The experiments involved deuterated N-Boc benzylamines that ultimately were cyclized to enantioenriched 2-aryl pyrrolidines. Although the conclusion about asymmetric deprotonation is sound, the stereochemistry of the lithiations substitution was not definitively assignable.



Scheme 1



In the present study, the enantiopure pyrrolidine **1** with known absolute configuration[8] also possesses a rigid ring system that allows ready assignment of all pertinent protons (H_A, H_B, H_C).[9] When a 0.3 M ethereal solution of **1** was treated at −90 °C with *sec*-butyllithium−TMEDA and then quenched with excess iodomethane, the product **4** was obtained in 50% yield with the β-methyl diastereomer predominating (>15:1, 88% de).[10] Similarly, quenching the lithio intermediate **2** with methanol-d_4 produced the deuterio derivative **3**, again with β-D predominating >15:1 over the α-D epimer.[11] The yields for the β-methyl derivative **4** were determined by integration of the methyl doublet at 1.24 ppm relative to the distinct proton signals in the deuterio derivative **3**. No products other than starting pyrrolidine **1** were present. (The low yield of **4** (∼50−60%) was due to a very slow rate of alkylation at −90 °C.)

Since both the deuteration and methylation gave the same stereochemical result on reaction with the lithiopyrrolidine **2**, it was now of interest to see what factors control this process. Therefore, we designed an experiment to assess the importance of the kinetic isotope effect (KIE) on proton removal for this system. It was felt that

(1) Reviews: (a) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275. (b) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem Rev.* **1984**, *84*, 471−573. (c) Gawley, R. E.; Rein, K. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 1.2. (d) Meyers, A. I.; Highsmith, T. Asymmetric Synthesis of Alkaloids. In *Asymmetric Syntheses of Natural Products;* Pearson, W., Ed.; JAI Press: Greenwich, 1990.

(2) (a) Beak, P.; Basu, A. *J. Am. Chem. Soc.* **1996**, *118*, 1575. (b) Beak, P.; Boys, M. L.; Park, Y. S. *J. Am. Chem. Soc.* **1996**, *118*, 3757. (c) Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755. (d) Beak, P.; Du, H. *J. Am. Chem. Soc.* **1993**, *115*, 2516. (e) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231. (f) For a recent example, see: Coldham, I.; Hufton, R.; Snowden, D. *J. Am. Chem. Soc.* **1996**, *118*, 5322.

(3) (a) Hoppe, D.; Marsch, M.; Harms, K.; Boch, G.; Hoppe, I. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2158. (b) Karsen, B.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 323. (c) Zchage, O.; Hoppe, D. *Tetrahedron* **1992**, *48*, 5657. (d) Schlosser, M.; Limat, D. *J. Am. Chem. Soc.* **1995**, *117*, 12342. (e) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075. (f) Kleine, S.; Marek I.; Poisson, J. F.; Normant, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 8853.

(4) (a) Still, W. C.; Sreekumar, C. J. *J. Am. Chem. Soc.* **1990**, *102*, 1201. (b) Hoppe, D.; Carstens, A.; Kramer, T. *Angew. Chem., Int. Ed. Engl.* **1990**, *50*, 10124. (c) Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097. (d) Pearson, W. H.; Lindbeck, A. C. *J. Am. Chem. Soc.* **1991**, *113*, 8546. (e) Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622. (f) Chong, J. M.; Park, S. B. *J. Org. Chem.* **1992**, *57*, 2220. (g) Gawley, R. E.; Zhang, Q. *J. Am. Chem. Soc.* **1993**, *115*, 7515.

(5) Gawley, R. E.; Zhang, Q. *J. Org. Chem.* **1995**, *60*, 5763. For an example of an inversion mechanism for chiral formamidines see: Meyers, A. I.; Dickman, D. *J. Am. Chem Soc.* **1987**, *107*, 1263.

(6) Meyers, A. I.; Kopach, M.; Fray, A. Submitted for publication in *J. Am. Chem. Soc.*

(7) Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715.

(8) Determined by X-ray single crystal analysis (see ref 6).

(9) At room temperature chiral pyrrolidine **1** exists as a 1:1 mixture of rotamers. However, at 150 °C in DMSO-d_6 the rotamers coalesce into one species with H_A (3.41 ppm, dd, J = 5.1, 11.0 Hz) and H_B (3.30 ppm, d, J = 11.0 Hz) as discrete resonances. A 4.5% NOE between H_A and H_C (2.21 ppm) was observed along with a 5.1 Hz *syn* coupling constant. ^{1}H and ^{13}C NMR assignments were made with the assistance of 500 MHz HMQC. Details are provided in the supporting information.

(10) The β-stereochemistry of **4** was confirmed by 6.0 Hz coupling and 6% NOE between H_A and H_C. In addition, irradiation of the C21 β-methyl group shows a 3% NOE with H_A and does not show any detectable NOE with the H_C bridgehead methine.

(11) Substituting D_2O for CD_3OD results in a significant decrease in β/α selectivity as quenching of lithiated intermediate occurs at higher temperatures. We further observed disappearance of H_B by ^{1}H NMR in DMSO-d_6 at 150 °C. H_A did not decrease in intensity and retained a 5.1 Hz coupling constant with H_C.

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direct comparison of deprotonation of the protio (**1**) and the specifically monodeuterio (**3**) systems would be a valid case to examine. Thus, an ethereal solution of **3** was treated with *sec*-butyllithium and TMEDA at −90 °C for 16 h. Similarly, the protio system **1** was subjected to the same conditions in another reaction vessel at the same time. After 16 h (complete deprotonation required these lengthy times), both reaction vessels were quenched at 90 °C with excess iodomethane and, after 20 h, worked up. The reaction of **1** with *s*-BuLi/iodomethane gave, as expected, a 50−60% yield of **4** (15:1 β-Me), whereas the reaction of **3** produced less than 2% alkylated material, the remainder being starting deuteriopyrrolidine **3**. It thus became clear that the deprotonation of **1** was highly selective for the β-H (H_B) and the large KIE present in **3** at −90 °C significantly prevented its deprotonation.[2e,12] We may further conclude that the deprotonation is rate determining as well as stereochemically significant.

Next, we proceeded to examine the effect of temperature on the deprotonation−methylation step and found, firstly, that the KIE was still a significant factor (>10) in metalations at temperatures as high as −30 °C. Deprotonations were also performed at −78, −45, and −30 °C and quenched with both CD_3OD and CH_3I in each case. In all cases, the β/α selectivity, observed at −90 °C, decreased as the temperature of methylation or deuteration was raised. Thus, at −45 °C a 2:1 β/α ratio of D (or CH_3) was observed, whereas at −30 °C a 1:1 β/α ratio of D or CH_3 was noted. Over the entire temperature range study, the deuteration and methylation stereochemical result closely parallelled each other. It is noteworthy that no dialkylation or dideuteration was observed even though excess base or electrophile was present. In addition, we noted that the warm−cool protocol of Beak[7] also resulted in significant loss of stereoselectivity in both deuteration or methylation.

Taken together, all of the above reaction characteristics point clearly to a kinetically dominated generation of a specific, configurationally stable, lithio pyrrolidine at −90 °C. This occurs by highly stereoselective removal of the β-proton in **1** to give what we believe is the β-lithio anion **2** followed by methylation with retention, the β-methylpyrrolidine **4** (or D-product **3**).

In agreement with earlier observations of Beak, Hoppe, Gawley, and others,[1−4] the stereochemically produced α-lithio derivative, which we see as a highly associated ion pair, begins to "loosen-up" as the temperature rises, allowing inversion to occur (loss of stereochemical integrity). Alkylation then takes place on this anion mixture leading to the observed lower selectivity.

It is important to note that the present study was performed without an enantiomerically pure cosolvent (e.g., (−)-sparteine), but only using the simple diamine, TMEDA.[13] The resident stereocenters present in the pyrrolidine system provided the only basis for stereocontrol for the deprotonation−alkylation.

It was also desirable to address the basis of the proton selectivity observed. Thus, why was the less accessible proton (H_B) removed in preference to the more accessible H_A?[14] We felt that CIPE[15] was responsible, in part, for this observation wherein *s*-BuLi is required to complex the Boc carbonyl group prior to proton abstraction. In order for this to occur, the Boc group must adopt a conformation whereby the carbonyl group and the accompanying BuLi complex sit over the proton to be removed (Figure 1). For the *N*-Boc system, **5A**, the BuLi complexes to the carbonyl oxygen and the base is now available to align itself with either H_B or H_A (**6** or **7**). In the alignment to remove H_B, the O-*t*-Bu residue of the Boc group is turned so it is away from the region of the remainder of the molecule and exhibits little steric problems. On the other hand, alignment **7** brings the *t*-Boc group over the top of the molecule, an area of increasing steric encumbrance. These two conformations appear to be distinctly different in their sterics such that **6** is favored for the removal of H_B even though the latter is pointed into the concave face. To achieve **6** or **7**, the Boc-BuLi complex is not more than 25−30° away from coplanarity (between N−C═O) and no severe reduction in $\pi-\sigma$ overlap need be experienced.[16]

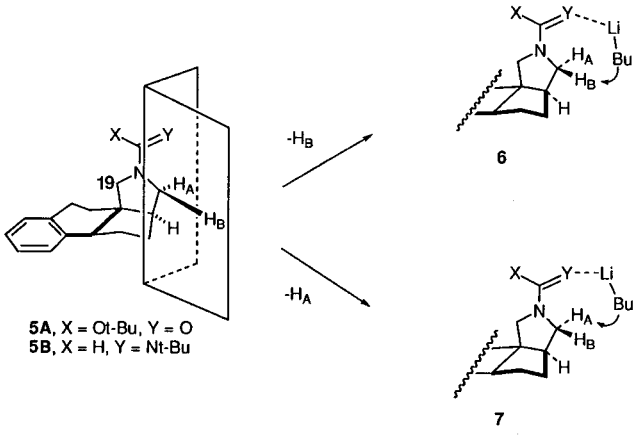

Figure 1.

If the above stereochemical argument favoring only H_B removal is valid, then use of the corresponding formamidine **5B**, with much less steric bulk, should not show this selectivity. Indeed, this is observed by metalating the formamidine **5B**, which exhibited no selectivity under any conditions when the methyl iodide was introduced. The formamidine activating group appears to access either proton (H_A, H_B) in **5B** when complexed with BuLi, thus furnishing **6** or **7** with equal facility.

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Supporting Information Available: X-ray structure of **5A**, ^{1}H NMR spectra for pyrrolidine **1** as well as an experimental procedure for synthesis of pyrrolidine **4** (7 pages).

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(12) The kinetic isotope effect at −90 °C (K_H/K_D) was estimated to be 20−21 (Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper Row: New York, 1987; p 234).

(13) In order for the alkylation reaction to proceed with high de it was necessary to use diethyl ether as the solvent. Substituting THF as solvent results in a 1:1 α/β selectivity even at −90 °C.

(14) Competitive alkylation at C19 was not observed under any conditions. Presumably this is due to the inaccessibility of both methylene protons at C19 from the bulk of the adjacent neopentyl center.

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

(16) It should be noted that the configuration of the lithiated pyrrolidine **2** is shown as occupying the β-position. Although this is not known with certainty, it is reasonable to assume that the newly formed C−Li ion pair would undergo inversion to the α-C−Li intermediate. This would then require another inversion at the methylation step and would unnecessarily increase the complexity of the process. This would be contrary to the spirit of "mechanistic economy"[17] or Ockham's razor.[18]

(17) Berson, J. A. In *Rearrangements in Ground and Excited States*; DeMayo, P., Ed.; Academic: New York, 1980; Vol. 1, p 342.

(18) Hoffmann, R.; Minkin, V. I.; Carpenter, B. K. *Bull. Soc. Chim. Fr.* **1996**, *133*, 117.