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Complex-Induced Proximity Effects. Temperature-Dependent Regiochemical Diversity in Lithiation–Electrophilic Substitution Reactions of *N*-BOC-2-Azabicyclo[2.1.1]hexane. 2,4- and 3,5-Methanoprolines

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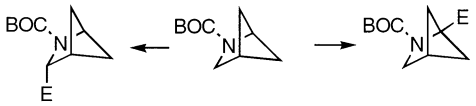
ABSTRACT



E = COOH, COOMe, CHO, CH_2OH

Azabicycle 4 and *sec*-butyllithium/TMEDA afford the C_1 bridgehead α-lithio anion at 0 °C. Anion quenching with carbon dioxide, methyl chloroformate, or DMF provide the bridgehead acid 8a (*N*-BOC-2,4-methanoproline), ester 8b, or aldehyde 8c, respectively. By contrast, at −78 °C these same reagents give a mixture of regioisomeric methylene and bridgehead anions whose quenching leads to mixtures of regioisomeric methylene and bridgehead acids 6a/8a, esters 6b/8b, or aldehydes 6c/8c, respectively. The previously unknown 3,5-methanoproline was prepared as its *N*-BOC methyl ester 6b.

The naturally occurring amino acid proline (**1**), which has the α-amino substituent incorporated into a five-membered ring, is an important component of numerous biologically significant proteins such as collagen,[1] gramicidin,[2] α-melanotropin,[3] and phosmidosine,[4] as well as pharmaceutically produced *N*-acyl derivatives used to treat hypertension and congestive heart failure such as Captopril,[5] Enalapril,[6] and Lisinopril.[6] Conformationally constrained molecules that mimic naturally occurring amino acids have importance in helping us to understand the substrate−receptor interactions of bioactive peptides.[1,7] They also have importance as synthons for generation of new bioactive molecules.[8] We desired derivatives of the more conformationally constrained 3-carboxy-2-azabicyclo[2.1.1]hexane **2** as part of a study of conformational effects on collagen stability[1] and as a synthon

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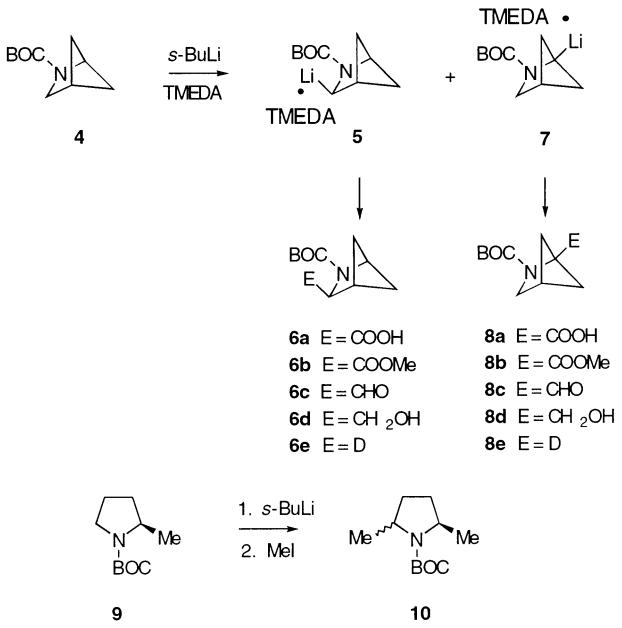
for the preparation of new nicotinic receptor agonists[9] and antibiotics.[10] Amino acid **2**, a 3,5-methanoproline, is isomeric with the naturally occurring 2,4-methanoproline **3**.[11]

1 **2** **3**

We have recently described a simple four-step route from pyridine to the 2-azabicyclo[2.1.1]hexane ring system.[12] It was envisioned that application of the protocol of Beak[13a] to the *N*-BOC-2-azabicyclo[2.1.1]hexane **4** could be used to generate a lithio anion **5** and that subsequent addition of electrophiles (CO_2, ClCOOMe, DMF) could be used to generate structures **6a**−**d**, desirable derivatives of 3,5-methanoproline **2**. However, would azabicycle **4** lose a methylene proton to give anion **5**, or would a bridgehead proton be lost to afford the lithio anion **7**, whose quenching would provide isomeric structures **8**?[14]

The established conformational principle for reactions that provide α-lithioamine derivatives of amides is that "*an orthogonal relationship between the lithio carbanion and the pi system of the amide. . . (is) favorable.*"[15] In the case of *N*-BOC-2-methyl-pyrrolidine **9**, this means that lithiation followed by methylation occurs *only at the methylene position* to afford a stereochemical mixture of 2,5-dimethyl-pyrrolidines **10**.[13a] However, the system **9** has flexibility not found in azabicycle **4**. The objective of the present study was to determine the regiochemical outcome of α-substitution reactions of the rigid ring azabicycle **4** with the goal of finding a new route to 3-substituted methanobridged proline derivatives **6**.[15]



N-BOC-2-azabicyclo[2.1.1]hexane **4** was prepared according to our previously described procedure from its *N*-(benzyloxycarbonyl) analogue[12] by hydrogenolysis of the benzyloxy group in the presence of $(BOC)_2O$.[17] To generate the lithio anions **5** and **7**, the azabicycle **4** in ether, which had been dried by passing through a Glass Contour alumina column, was reacted with 1.1−1.6 equiv of *sec*-butyllithium (*s*-BuLi)/TMEDA for 2 h at either −78 or 0 °C.[13a] The anions were then quenched. The electrophilic reagent carbon dioxide was bubbled in excess into the anion mixture over 5−15 min by warming of dry ice and passing the gas sequentially through dry calcium chloride and then concentrated sulfuric acid.[18] Methyl chloroformate (5 equiv) was injected by syringe into the preformed anion(s) **5**/**7**. Formylations were carried out by adding a mixture of the lithio anions **5**/**7** to dry precooled DMF (5 equiv) in ether. Following addition of the electrophile, the reaction mixture was maintained at the target temperature for 0.5 h and then allowed to warm to room temperature. The carbon dioxide addition product was acidified to give acid **8a**, which could be converted to ester **8b** using Me_3SiCHN_2.[19a] Aldehyde products either were isolated as aldehydes **6c**/**8c**, reduced with sodium borohydride to form alcohols **6d**/**8d**, or oxidized with sodium

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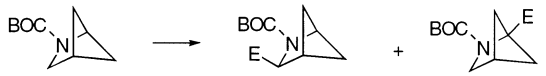
Table 1. Lithiation of Azabicycle **4** and Electrophile Additions to Provide Methylene **6** and Bridgehead **8** E-Substituted Products[a]



4 6 8

entry	reagent	*s*-BuLi (equiv)	*T* (°C)	E	product	ratio[b] of **6**:**8**	yield[c] (%)
1	CO_2	1.1	0	COOH	**8a**		98
2	CO_2	1.2	−78	COOMe[d]	**6b/8b**	43:57	76
3	$ClCO_2Me$	1.2[f]	0	COOMe	**8b**		70
4	$ClCO_2Me$	1.2	−78	COOMe	**6b/8b**	50:50	81 (95)
5	DMF	1.2	0	CHO	**8c**		38 (57)
6	DMF	1.2	−78	CHO	**6c/8c**	50:50	32 (40)[e]
7	DMF	1.6	−78	CHO	**6c/8c**	49:51	71 (83)
8	DMF	1.2	−78	CH_2OH[f]	**6d/8d**	50:50	51
9	DMF	1.2	−78	CO_2Me[g]	**6b/8b**	47:53	31[h]
10	CD_3OD	1.2	0	D	**8e**		63
11	CD_3OD	1.2	−78	D	**6e/8e**	45:55[i]	87
12	CD_3OD	1.2	−78 to 0[j]	D	**6e/8e**	44:56	98

[a] Lithium anions were generated and quenched from **4** containing TMEDA at either 0 or −78 °C in ether solvent dried using a Glass Contour alumina column. Electrophiles CO_2 and ClCOOMe were added to the cold solution of anion before warming to room temperature, neutralization, and isolation of the products. Anions were added to DMF in ether via cannula. CO_2 was dried by passing over $CaCl_2$ and anhydrous sulfuric acid. DMF was dried by passing through a commercially available Glass Contour alumina column for DMF (LaGuna Beach, CA). [b] Ratios refer to crude mixtures prior to chromatographic purification and are based upon integration of appropriate H_1 and H_3 ^1H NMR resonances. [c] Isolated yields. Numbers in parentheses are corrected yields based upon recovered **4**. [d] Workup with trimethylsilyl diazomethane afforded the ester. [e] Chromatography afforded 20% **6c** and 12% **8c**. [f] Workup includes sodium borohydride. [g] Workup includes NaOCl oxidation and Me_3SiCHN_2 esterification. [h] Isomers were not separated. [i] Average of two runs (±2). [j] See ref 23.

hypochlorite[19b] and esterified to give esters **6b**/**8b**. The identities of azabicycles **6** and **8** and their ratios in the crude reaction mixtures were determined by NMR. Methylene-substituted structures **6** retain the resonance for H_1 at δ 4.1−4.4. Bridgehead-functionalized structures **8** lack H_1 and have planar symmetry, which simplifies their ^1H and ^{13}C NMR spectra.

As shown in Table 1, anion generation from carbamate **4** at 0 °C followed by addition of carbon dioxide and acidification afforded only the bridgehead acid **8a** (entry 1). By contrast, at −78 °C, addition of carbon dioxide, acidification, and esterification afforded a 4:6 mixture of esters **6b**/**8b** (entry 2).[20] The same esters could be formed directly by quenching of the anions with methyl chloroformate. At 0 °C, only the 1-ester **8b** was obtained (entry 3), while at −78 °C, a 1:1 mixture of esters **6b**/**8b** was observed (entry 4). The above preparations of the methyl ester of *N*-BOC-2,4-methanoproline **8b**[21a] serve as formal syntheses of 2,4-methanoproline **3**, found in the seeds of *Ateleia herberet smithii* Pittier (Leguminosae)[11] and previously synthesized by photochemical routes using acyclic precursors.[21]

When carefully dried DMF[22] was used to quench the reaction of **4** with *sec*-butyllithium (1.2 equiv) at 0 °C, only the 1-formyl structure **8c** (entry 5) was observed. When the reaction was carried out at −78 °C, NMR of the crude reaction mixture indicated nearly equal amounts of the 3-formyl and 1-formyl isomers **6c**/**8c** were formed. It was observed that separation of the aldehyde mixture by silica gel column chromatography resulted in loss of a portion of the 1-CHO isomer **8c** (trial 6). The same regiochemical mixture was obtained with 1.6 equiv of *s*-BuLi (trial 7). To facilitate isolation without material loss, the mixture of 3-CHO/1-CHO **6c**/**8c** isomers was reduced to the separable alcohols **6d**/**8d** (trial 8). Alternatively, the mixture of aldehydes **6c**/**8c** was oxidized using sodium hypochlorite and converted to the corresponding esters **6b**/**8b** (entry 9); however, the esters were not conveniently separated.

To estimate the ratio of anions **5** and **7**, an anionic mixture at 0 °C was quenched with CD_3OD quench (entry 10). NMR integration of deuterated **4** indicated loss of solely the H_1 proton. Repetition of the experiment at −78 °C resulted in loss of 43% of an H_3 proton and 47% loss of the H_1 proton (entry 11). Generation of the anionic mixture of **5** and **7** at −78 °C and then allowing the mixture to stir for 40 min at 0 °C prior to addition of $DOCD_3$ (entry 12) resulted in 43% loss of an H_3 proton and 54% loss of an H_1 proton.

Dynamic regioisomeric discrimination in the reactions of **4** are the result of complex-induced proximity effects operating through preequilibrium complexes. The transformations shown in Scheme 1, as previously outlined by Beak in his studies of dynamic diastereomeric equilibrations,[15a] depict the key species leading from structure **4** to the products **6**/**8**. A mixture of *s-cis*- and *s-trans*-carbamates **4** is present.[14d,24] Each of these conformations is expected to be in rapid equilibrium with an *s*-BuLi/TMEDA complex prior to the irreversible deprotonation steps to afford the TMEDA complexed anions **5** and **7**. Quenching of the anions affords the products **6**/**8**.

(20) Our first anion quenching experiment with *s*-BuLi (1.6 equiv) at −78 °C using CO_2 passed only through dry $CaCl_2$ afforded only bridgehead acid **8a** (49%). Traces of water may have selectively quenched the 3-anion **5**.

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(22) Our initial experiments, which used DMF distilled from CaH_2, gave erratic results. In one trial at −78 °C with *sec*-BuLi (1.6 equiv), azabicycle **4** afforded only aldehyde **8c** (31%). In another trial, a 15:85 mixture of aldehydes **6c**/**8c** (57%) was observed. Under the same conditions except with less base (1.05−1.10 equiv), there were numerous failures to observe any reaction; one trial gave unreacted **4**/**6c**/**8c** = 67:0:33 (23%). These results may reflect selective quenching of the less stable 3-anion **5** with a proton source (water, dimethylamine?). In a trial in which reaction was allowed to continue overnight rather than 2 h, the 3-isomer was found to predominate: **6c**/**8c** = 97:3 (41%). This result is consistent with the preferential loss of bridgehead aldehyde **8c** noted during purification.

(23) It is important to use ether dried with a Glass Contour alumina column to obtain the results shown in Table 1. Azabicycle **4** was reacted with *s*-BuLi (1.2 equiv) in ether distilled from sodium/ benzophenone at −78 °C for 2 h, and half of the solution was then allowed to warm to 0 °C for 40 min. Quench of the −78 °C solution with $DOCD_3$ over 30 min resulted in 60% loss of an H_1 proton (56% recovery), and quench of the 0 °C solution resulted in 79% loss of an H_1 proton (90% recovery). No H_3 exchange was observed in either case.

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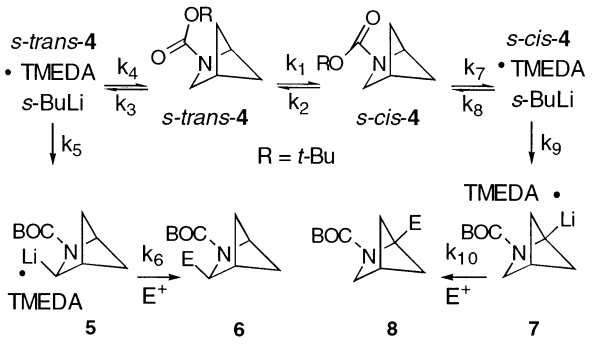
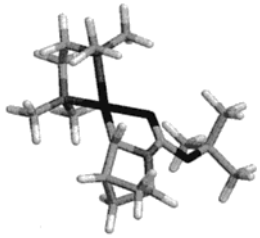
Scheme 1. Key Species in Dynamic Regioisomeric Discrimination

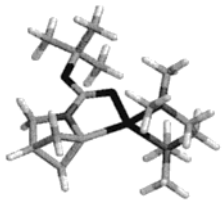


To gain information about the *s*-cis/*s*-trans conformational preference of the *N*-BOC carbonyl group in azabicycle **4**, we carried out low-temperature ^{1}H NMR experiments (See Supporting Information). No observed change in the resonance of the *tert*-butyl substituent was observed at the range of temperatures used (296−178 K). However, the bridgehead proton H_1, found at δ 4.26 (dt, J = 6.8, 1.6 Hz) at 0 °C, coalesced into a broad peak at δ 4.28 at −31 °C. At −76 °C, it separated into two separate resonances at δ 4.31 (d, $J_{1,4}$ = 6.8 Hz) and δ 4.26 (d, J = 6.8 Hz) with a relative intensity of 58:42. Calculations using the B3LYP/6-31G(d) method[25] indicate a 0.02 kcal energy difference favoring the *s*-cis over the *s*-trans conformation of azabicycle **4** (activation energy to interconversion uncorrected for zero point energies = 16.2 kcal/mol). Clearly, significant populations of carbamate conformations having the carbonyl oxygen directed toward either H_1 or H_3 are present at −78 °C, and these are averaged at 0 °C.

To gain insight into anion stabilities and geometries, we performed calculations of ground-state energies for the *N*-BOC-α-anions **5** (C_3-anion) and **7** (C_1-anion) at the B3LYP-631G(d) level[25] as their TMEDA−lithium complexes. At this level, the 1-lithio species **7** is calculated to be 5.9 kcal/mol *lower* in energy than the 3-lithio species **5**. Notably, both regioisomeric anions have the carbon−lithium bond nearly in the desired orthogonal relationship to the carbamate π-system.[15a] The minimized secondary methylene anion **5** has a Li−C−N−(C)═O dihedral angle of 11.8°, while the tertiary bridgehead lithium anion **7** has a Li−C−N−(C)═O dihedral of 0.34°.[26]



Anion **5** (Li^+-TMEDA)



Anion **7** (Li^+-TMEDA)

The results in Table 1 might then be explained in the following way using Scheme 1. At 0 °C, k_1, k_2, k_3, k_4, k_7, and k_8 are fast relative to the deprotonation steps k_5 and k_9 and the conformational equilibria between *s*-*cis*-***4***/*s*-*trans*-**4** and their TMEDA/*s*-BuLi complexes is maintained throughout the reaction. Under these sets of conditions, the Curtin−Hammett principle applies to the reaction.[27] The product ratio of **6**/**8** will reflect the difference in free energies of the transition states for formation of anions **5**/**7** and the proportions of the *s*-*cis*-***4***/*s*-*trans*-**4**/TMEDA/*s*-BuLi complexes in solution. Clearly, the formation of the more stable anion **7** from a complex of the favored *s*-*cis*-**4** conformation controls the product formation at the higher temperature. At −78 °C, interconversion of *s*-*cis*-***4***/*s*-*trans*-**4**/TMEDA/*s*-BuLi complexes is slow relative to the subsequent deprotonation steps to afford anions **5**/**7**. In this circumstance, the relative formation of products **6**/**8** partially reflects the 58:42 equilibrium population of *s*-*cis*-***4***/*s*-*trans*-**4**.

The lithiation of *N*-BOC carbamate **4** has been shown to occur with temperature-dependent dynamic *regioisomeric* discrimination. The synthetic utility of dynamic *diastereomeric* thermodynamic equilibration of α-lithio amine anions has been clearly identified previously.[13c,28]

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Supporting Information Available: All experimental procedures, spectroscopic data, as well as copies of ^{1}H NMR and ^{13}C NMR for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) Geometrical access to both anionic structures is not surprising. Both *N*-acetyl-2,4-methanoproline-*N*-methyl amide [11b,c] and *N*-(methoxycarbonyl)-5,6-*anti*-dibromo-3-methyl[2.1.1]hexane[16c] are somewhat pyramidal.

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