Pergamon

Tetrahedron Letters 43 (2002) 8759–8763

TETRAHEDRON LETTERS

Pyrrolidinic and piperidinic ring fission by conjugate elimination

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Received 26 June 2002; accepted 23 September 2002

Abstract—Treating *N*-substituted pyrrolidines and piperidines bearing an allylic chain α to the nitrogen with strong bases leads to the opening of the heterocycle and provides 1,3-dienes disubstituted with an alkoxy and an aminoalkyl chain. The effects of the base and the solvent have been studied, as well as the influence of the ring size and the nitrogen substituent. The results obtained suggest a possible pre-chelation of the base cation before the deprotonation.

Non-aromatic nitrogen heterocycles such as pyrrolidines and piperidines are found in an extremely large number of natural and non-natural products.[1] Functionalized pyrrolidines and piperidines are also potent synthons that have found a broad spectrum of synthetic applications, particularly in the field of alkaloids and more generally cyclic and polycyclic natural products.[2] These heterocycles undergo little ring tension; therefore, they are very stable and only a few ways to convert the cyclic core into its linear aminoalkyl equivalent (Fig. 1) have been described to date.[3] Would it rely on a simple chemistry, such a process could be synthetically useful as long as it takes advantage of the good chimio and stereocontrols generally associated with reactions on cyclic molecules before the ring-opening step.

In this context, we decided to apply the conjugated elimination reaction to various pyrrolidines or piperidines bearing an allylic chain α to the nitrogen in the hope to prepare a set of functionalized aminodienes. Those could be regarded, after, for instance, acylation of the amino group, as simple precursors of medium-ring lactams through an intramolecular [4+2] cycloaddition (Fig. 2). The eventual interest of this approach would rely on the simplicity and the stereoselectivity of the transformation. Previous results had shown that oxygenated heterocycles (acetals such as dioxolanes or dioxanes,[4b] allylic epoxides[4c] or tetrahydrofurans[4d]) can be disrupted following a similar procedure and transformed into medium-ring lactones.

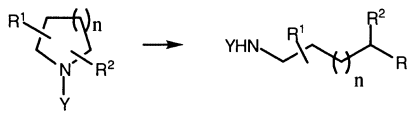

Figure 1.

However, the extension of this reaction to nitrogen heterocycles was not guaranteed since (i) the difference between the acidity of the protons α to the *Z* (Y = COOBn) or Boc (Y = COO*t*-Bu) protected nitrogen and those α to the oxygen seems relatively low and therefore the deprotonation site may be ambiguous; (ii) no ring tension release upon fission can be expected to act as a driving force; (iii) the expelled lithium amide could behave as a powerful nucleophile, undergoing an addition onto the newly formed dienic moiety and therefore returning to the original carbanion. Such a hypothesis had already been proposed in the case of the basic treatment of comparable α,β-unsaturated aminals[5] and could be anticipated applying the microreversibility principle in conjunction with Baldwin's ring closure

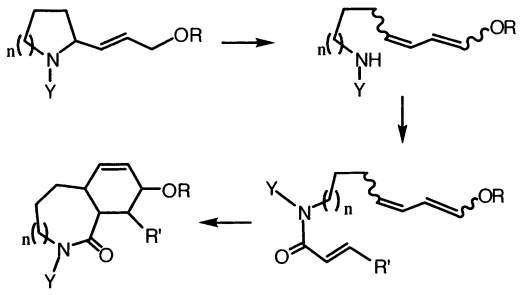

Figure 2.

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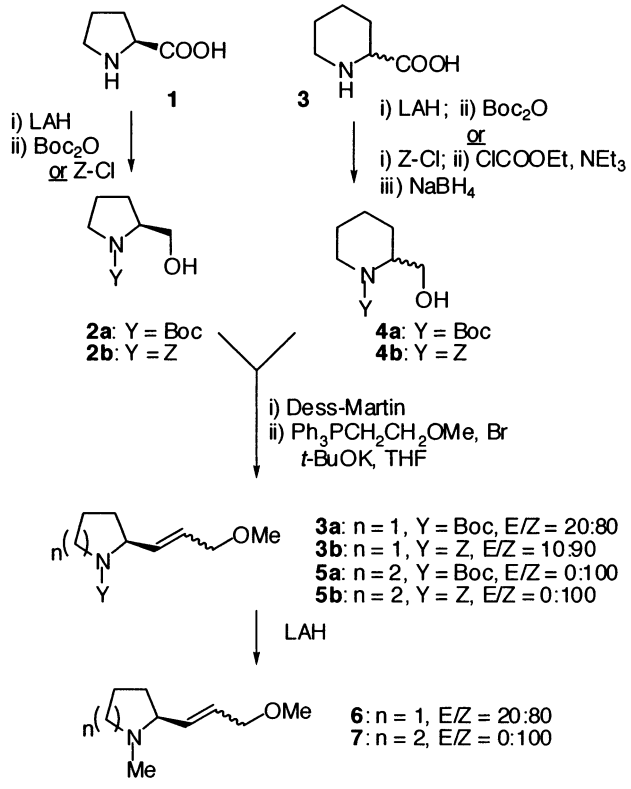
0040-4039/02/$ - see front matter
PII: S0040-4039(02)02155-X

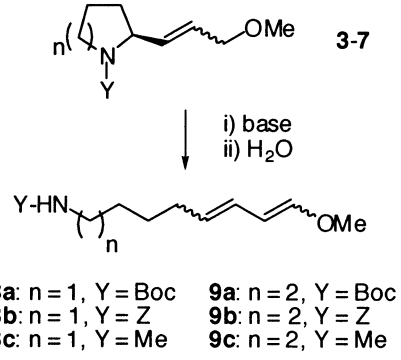
rules.[6] We wish to describe the results we have obtained with model pyrrolidines and piperidines and present the effects of a few parameters on the efficiency and the selectivity of this reaction.

The starting α-allyl heterocycles were prepared following Scheme 1 from (L)-Proline **1** or racemic pipecolic acid **3**. Both aminoacids could be reduced ($LiAlH_4$) and protected following an efficient one-pot procedure,[7] except for *N*-benzyloxycarbonyl pipecolinol **4b**, where a complex mixture of products was recovered. In this case, we resorted to Yang's procedure[8] that consists in the preliminary *Z*-protection of pipecolic acid followed by ethylchloroformate treatment and direct $NaBH_4$ reduction. The expected product **4b** was recovered in satisfactory yields. Alcohols **2** and **4** were then cleanly oxidized to the corresponding (known) aldehydes using Dess–Martin periodinane[9] in methylene chloride at room temperature. These were isolated, purified and kept in the freezer under nitrogen for reasonable periods of time. The allyl-chain was obtained by a Wittig reaction with 1.3 equivalents of (2-methoxyethyl)triphenylphosphonium bromide, prepared in a sealed tube in 98% yield from 2-bromoethanol and triphenylphosphine in methanol at 100°C. The corresponding ylid was obtained in THF by deprotonating the phosphonium salt between −78°C and 0°C with freshly sublimed *t*-BuOK. The Wittig reaction then afforded olefins **3** and **5** in 68–95% yield. The stereoselectivity of the condensation was in favor of the *Z* isomers,[10] either mainly (with the pyrrolidine) or totally (with the piperidine), as detailed in Scheme 1. To extend the scope of our investigation to *N*-alkyl heterocycles,[11] the Boc-protected amines **3a** and **5a** were also reduced by LAH in THF, providing the *N*-methyl pyrrolidine **6** and piperidine **7** in 72 and 50% yields, respectively. This also simplified the determination of the *E*/*Z* ratio on the *N*-Boc and *N*-Z derivatives **3** and **5** rendered difficult by the presence of two rotamers into solution.



Scheme 1.

The elimination reaction was then studied in standard basic conditions (Scheme 2). The stereoselectivities were assessed by 500 MHz ^1H NMR measurement of the ethylenic coupling constants or resorting to NOE experiments, either on the crude mixture or on purified samples. We first examined the influence of the exact structure of the base on a single substrate, viz. the *N*-Boc pyrrolidine **3a**. Albeit this substrate was stereochemically heterogeneous (*E*/*Z* = 20:80), previous results on relatively similar compounds had shown that the original double bond has little if any influence on the stereochemistry of the final diene.[12] It is clear from Table 1 that in THF, the deprotonation of this type of



Scheme 2.

Table 1. Influence of the base on the conjugate elimination reaction of **3a**

Entry	Base	Eq.	Temp (°C)	Conv. (%)	*EE*/*EZ*/*ZE*/*ZZ*
1	*t*-BuOK	1.2	0	–	–
2	LDA	1.2	−78/20	–	–
3	KHMDS	1.5	0/70	–	–
4	BTPP[a]	1.1	20/70	–	–
5	BuLi[b]	3.0	−78	≈33	n.d.
6	BuLi/*t*-BuOK	3.0	−78	≈90	12:9:19:60
7	*t*-BuLi	3.0	−78	≈90	7:60:33:0

[a] BTPP (Schwezinger's base): phosphazene base P1-*t*Bu-tris-(teramethylene).
[b] Experiment done with **5b** instead of **3a**.

allylic ether required very strong bases such as bimetallic superbases[13] or *t*-BuLi that triggered the elimination in almost quantitative yields at low temperature. The milder bases had no effect, even upon raising of the temperature. Three equivalents of *n*-BuLi induced only a partial ring fission of **3a** at −78°C. The dienol ether **8a** being very prone to hydrolysis, the yields dropped after chromatography on silica gel, even in the presence of triethylamine. From a stereochemical point of view, the two efficient bases led to very different results: while the *t*-BuLi favored the 1*E*,3*Z* isomer (60%), the bimetallic system yield mainly to 1*Z*,3*Z* **8a** (60%). The enol ether double bond remained *Z* in both cases.

We retained *t*-BuLi and considered the possible effect of the solvent on this reaction, still at −78°C. Three among the most common solvents for deprotonations, pentane, diethyl ether and THF, were compared (Table 2). The variations between reported chemical yields are not to be taken into account since the data correspond to the crude mixture in the case of *t*-BuLi and to purified products in the two other cases. In these latter solvents, a chromatography was indeed necessary because the crude mixture contained by-products interfering with the measurement of the isomers ratio. Despite this artifact, the stereoselectivity of the elimination reaction seemed more or less insensitive to the solvent, as can be seen on Table 2, the 1*Z*,3*E* isomer being always favored over the 1*E*,3*Z* one while the two other isomers were hardly or not detected at all. THF was therefore used in the rest of the study.

Table 2. Influence of the solvent on the conjugate elimination of **3a**

Entry	Solvent	Yd (%)	*EE*/*EZ*/*ZE*/*ZZ*
1	Pentane	34[a]	4:59:37:0
2	Et_2O	34[a]	12:58:30:0
3	THF	90[b]	7:60:33:0

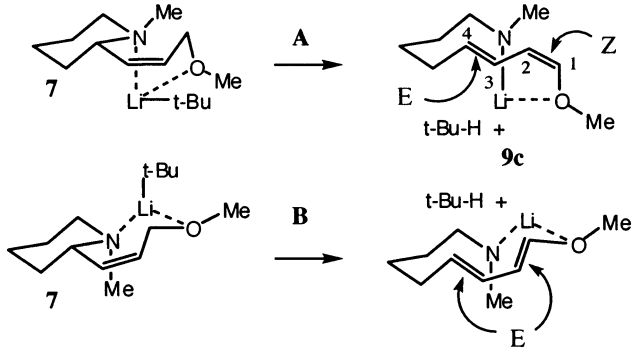
[a] Yields after flash chromatography.
[b] Crude yields.

Then, the effects of both ring size and of nitrogen substituent were examined (Table 3). Following above conclusions, the reaction was run with 3 eq. *t*-BuLi in THF at −78°C in 90 min. A clean reaction medium being recovered in all cases (90% conversion), the stereoselectivity was determined from the NMR data on the crude mixtures.

Let us first consider the case of the *N*-methylated compounds **6** and **7** for which a selectivity in favor of the *E* 3,4-double bond was observed, for **8c** as well as **9c** (entries 1 and 2). Assuming that the configuration of the double bond is mainly depending on the conformation of the heterocycle during the fission process, this selectivity suggests that the allylic ether chain is oriented toward the nitrogen atom.

Discussing the selectivities on the basis of intermediates such as **6-Li** or **7-Li** conformations can be speculative since the behavior of these carbenoid-type compounds is difficult to predict. Elements of rationalization can instead be suggested taking into account possible pre-transition states in which the *t*-BuLi lithium would be chelated by the amine and the methoxy. Assuming that the elimination is very rapid once the deprotonation has occurred, and limiting the discussion to the major *Z* isomer, two complexes between **7** and *t*-BuLi can be drawn, in which the *N*-methyl substituent adopts an equatorial (A) or an axial (B) arrangement (Scheme 3). In the first case, the orientation of the oxygen is such that the resulting diene **9c** should be 1*Z*,3*E*, in agreement with the experimental data. By contrast, situation B (with an axial methyl group) forces the oxygen in a position such that a 1*E*,3*E* diene should be recovered. Only 8% of this isomer are found in the mixture, suggesting that a pre-transition state with an equatorial methyl group is favored. This reasoning is unable to account for the results obtained with pyrrolidine **5**, for which the axial/quatorial arrangements can be ambiguous.

Carbamates **3** and **5** have to be considered separately. Would a pre-chelation of the lithium cation take place, it should now occur between the oxygen of the carbamate carbonyl (positioning the metal in the NCO

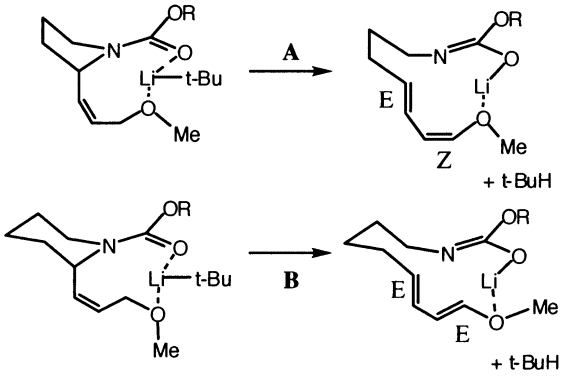


Scheme 3.

Table 3. Influence of the ring size and *N*-substituent on the elimination

Entry	Y	*n*	*E*/*Z* (SM)	Diene	*EE*/*EZ*/*ZE*/*ZZ*
1	Me	1 (**6**)	20:80	**8c**	**57**:0:43:0
2	Me	2 (**7**)	0:100	**9c**	8:0:**92**:0
3	Boc	1 (**3a**)	20:80	**8a**	7:33:**60**:0
4	Boc	2 (**5a**)	0:100	**9a**	**60**:0:40:0
5	*Z*	1 (**3b**)	10:90	**8b**	16:4:**75**:5
6	*Z*	2 (**5b**)	0:100	**9b**	**83**:0:17:0

plane) and that of the methoxy, leading to nine-membered pre-transition cyclic complexes. In the absence of specific mechanistic studies or calculations, attempts to rationalize the isomer ratios can appear very unrealistic. It is however known that *N*-carbamate piperidines tend to place their α-substituent into an axial orientation (the Paulsen effect).[14] When one takes into account this preference, the *Z*-configuration of the double bond in the major isomers of **3** and **5**, and the necessity for the lithium to lie in the CNCO plane, the number of degrees of freedom decreases sharply and only two chelated transition states can be built from a molecular model (Scheme 4). In the first one (A), the nine-membered ring is roughly chair-like (the tether standing 'remote' of the carbamate moiety) while it is the opposite in situation B, the chelation ring adopting a more or less boat 'folded' conformation (the tether staying this time 'close' to the carbamate). From the measured selectivities, it seems that the A situation is preferred for pyrrolidines **3** while the B arrangement would be associated to piperidines **5**. We cannot, with the data we have in hand, really interpret these results but we would like to note that the Z-substituted compounds **3b** and **5b** provide a slightly better selectivity than their Boc counterparts **3a** and **5a**, maybe indicative of steric interferences in the chelated models. Let us finally stress that (1*E*,3*E*)-**9b** is obtained with an attractive selectivity, and that this diene is particularly fit for inter- or intra-molecular cycloaddition reactions.



Scheme 4.

In conclusion, the conjugated elimination reaction on α-allylic heterocycles furnishes, in good yields and average to good selectivities, aminoalkyl 1,4-disubstituted dienes. The ring-fission is efficient even with *N*-methyl pyrrolidine **6** and piperidine **7**. The overall selectivities observed can be partly interpreted through pre-transition state models. Our observations are in fine agreement with those by Sardina and colleagues about β-lithiopyrrolidines and piperidines who have reported that these compounds are less stable, in DME, than the corresponding azetidines.[6b] The propensity of our systems (vinilogues of those of Sardina) to undergo a ring opening suggests that the vinilogy decreases the stability brought by the gem-lithioalkoxy moiety. Finally, the driving force for the heterocycle fission is likely to be found in the difference between the electronegativities of the carbon and that of the nitrogen. Extensions to the opening of (strained) carbocycles or to unsaturated heterocycles (such as that described by Ishimaru and Kojima)[3c] would also set the stage for a new access to 1,3-disubstituted dienes of which reactivity has already been studied.[15] These developments are on the way.

Acknowledgements

The Consiglio Nazionale delle Ricerche and the Centre National de la Recherche Scientifique are thanked for an exchange grant (CNR-CNRS #8724, 2000–2003).

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