Tetrahedron Letters, Vol. 33, No. 42, pp. 6359-6362, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Stereoselective Cyclization of δ-Alkenylamines Catalyzed with Butyllithium. Synthesis of *cis*-*N*-Methyl-2,5-disubstituted Pyrrolidines

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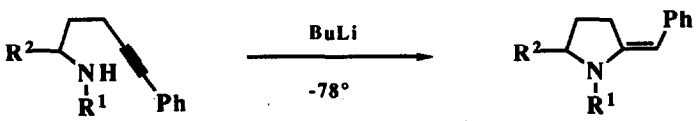
Abstract: Treatment of δ-alkenylamines (**1a-1d**) with a catalytic amount of butyllithium gave *cis*-*N*-methyl-2,5-disubstituted pyrrolidines (**2a-2d**) stereoselectively in good yields.

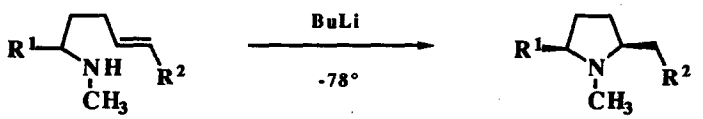
The syntheses of substituted pyrrolidines by the intramolecular cyclization of δ-alkenylamines have been achieved by photolysis of the corresponding *N*-chloroamines or *N*-nitrosoamines,[1] or by anodic oxidation of the corresponding lithium amides[2] or the corresponding hydroxylamines.[3] The synthesis of pyrrolidines has also been achieved by the reaction of δ-alkenylamines with the assistance of metal ions, such as Hg^{2+} (amino-mercuration),[4] or Pd^{2+} (aminopalladation).[5] However, the synthesis of cyclic amines by intramolecular nucleophilic cyclization has been rare, since the nucleophilic addition of amines to simple alkenes is usually difficult and requires a catalyst and high temperature.[6] Only the cyclization of complex amines, such as 6-(methylamino)-12-methylene-5,6,7,12-tetrahydrodibenzo[*a*,*d*]cyclooctene, has been reported.[7] On the other hand, we previously reported that the enamine pyrrolidines having an exo double bond can be prepared in high yields by the treatment of δ-alkynylamines with butyllithium (Scheme 1).[8]



Scheme 1

We wish to report that a similar cyclization of δ-alkenylamines can also be achieved upon treatment of δ-alkenylamines with a catalytic amount of butyllithium to give *cis*-*N*-methyl-2,5-disubstituted pyrrolidines stereoselectively as outlined in Scheme 2.

The treatment of δ-alkenylamines (**1a-1d**) with 1.0-1.2 equiv. of butyllithium at -78 °C, thus, gave *cis*-*N*-methyl-2,5-disubstituted pyrrolidines (**2a-2d**) in 12-65% yields. Table 1 summarizes the structures and yields of the pyrrolidines obtained in these cyclizations. Intramolecular cyclization of the amine to olefins carrying a phenyl group at their terminal carbons of the double bonds thus readily took place to give **2a**, **2b**, and **2d**.[9] We found



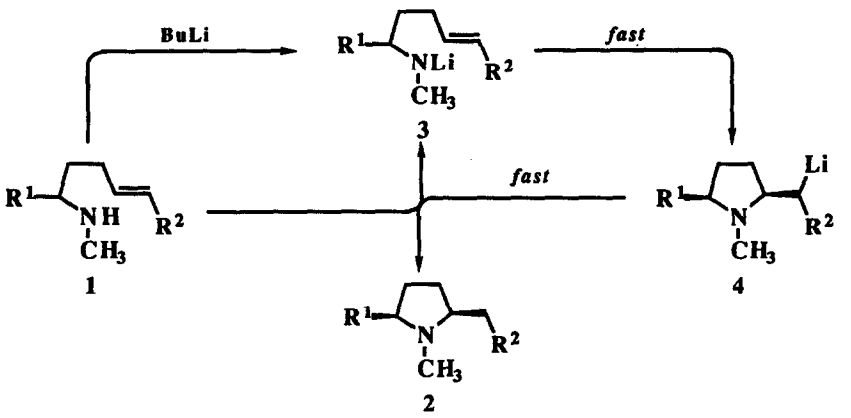
Scheme 2

that an unactivated olefin, such as **1c**, was also susceptible to cyclization to give **2c**.[9] All of these cyclizations took place highly stereoselectively to give *cis*-2,5-disubstituted pyrrolidines (**2a, 2b, 2c**) exclusively. The cyclization of a 3:1 mixture of *cis*- and *trans*-**1d** also gave a mixture of the corresponding single *cis*-**2d** and single *trans*-**2d** with probably the same configurations regarding the benzyl substituent at C-2 position and the cyclohexane methylene group at C-5 as those of **2a-2c**.

Cyclization was found to be achieved more efficiently to give higher yields of the products when a catalytic amount of butyllithium was used; the treatment of **1a** with 0.1 equiv. of butyllithium gave a 99% yield of **2a** and the treatment of alkenylamines **1b**, **1c**, and **1d** with 0.3 equiv. of butyllithium gave the best yields of the cyclization products.

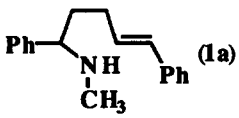
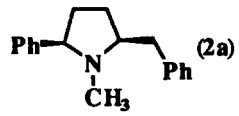
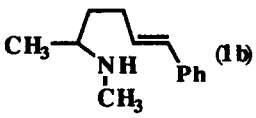
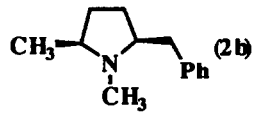
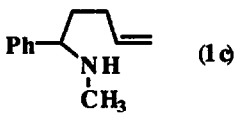
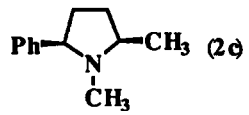
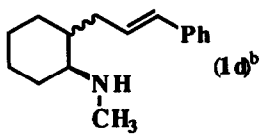
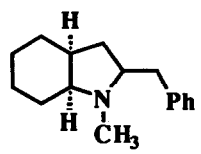
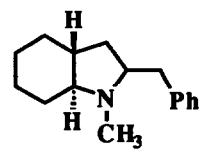
Typically, to a 0.067 M solution of *N*-methyl-1,5-diphenylpent-4-enylamine (**1a**) (100 mg, 0.4 mmol) in THF (6 ml) was added butyllithium in hexane (0.3 ml, 0.48 mmol) at -78 °C under a nitrogen atmosphere and the solution was stirred for 30 min at -78 °C and another 30 min at 0 °C. Quenching of the reaction mixture with water at 0 °C, followed by the usual work-up, gave a crude product which was subjected to TLC separation (silica gel; CH_2Cl_2/ MeOH/NH_3=200/10/1) to give *cis*-2-benzyl-1-methyl-5-phenylpyrrolidine (**2a**) (65 mg, 65% yield).

The present cyclization of δ-alkenylamines to the pyrrolidines propably proceeds *via* the reaction pathways outlined in Scheme 3. Thus, the addition of butyllithium to δ-alkenylamine **1** gives lithium amide **3**, which undergoes a facile anionic cyclization to afford **4**. The intermediate **4** abstracts a proton from the starting amine **1**



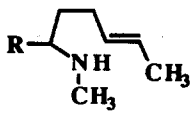
Scheme 3

Table 1. Cyclization of δ-Alkenylamines (1)

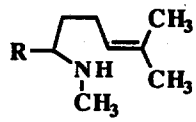
Amine	BuLi (mol/mol of 1)	Product	Yield (%)[a]
 (1a)	1.2 0.5 0.3 0.1	 (2a)	65 87 91 99
 (1b)	1.0 0.3	 (2b)	20 51
 (1c)	1.2 0.5 0.3	 (2c)	12 34 49
 (1d)[b]	1.0 0.5 0.3 0.1	 (*cis*-2d)  (*trans*-2d)	44 (95: 5)[c] 72 (74:26)[c] 84 (72:28)[c] 53 (92: 8)[c]

a) Isolated yields. b) *cis* : *trans* = 74 : 26. c) Ratios of *cis*-2d to *trans*-2d.

to give product 2 with a regeneration of 3. Both the cyclization to 4 and the following protonation to the product 2 should be very fast, since an attempted trapping of 4 at -78 °C with various electrophiles such as methyl iodide, allyl bromide, benzyl bromide, chlorotrimethylsilane, or acetyl chloride all failed and gave only product 2. Moreover, the following results suggest that the addition step of 3 to 4 is anionic. Treatment of δ-alkenylamines **5a**, **5b**, **6a**, and **6b** with 1.0-0.3 equiv. of butyllithium, which results in the formation of unstable *secondary* and *tertiary* carbanions, gave no product arising from the cyclization. The stereoselectivity of the present cyclizations is in good accordance with that of the intramolecular anionic cyclization of C-Li bond to an unactivated alkenes, recently reported by Bailey and colleagues.[11]



5a R=Ph
5b R=CH_3



6a R=Ph
6b R=CH_3

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(Received in Japan 1 June 1992)