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Asymmetric Synthesis. XL.[1] 2,3-Disubstituted Piperidines via Chiral Non-racemic Lactams.

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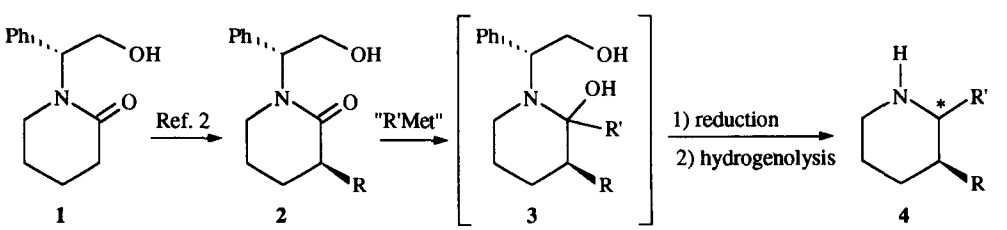
Abstract : Optically pure 2,3-cis-disubstituted piperidines **7a** and **7b** have been prepared from chiral lactams **2**. The first step involves C-2 functionalization with Grignard reagent, then a diastereoselective reduction of resulting oxazolidines **5** furnishes the desired piperidines **7**.

As part of a program dealing with the asymmetric synthesis of substituted nitrogen heterocycles, we recently reported the preparation of 3-substituted piperidines [2], 2-substituted piperazines[3] and 2-methyl-5-substituted piperidines [4] in enantiomerically pure form via a diastereoselective alkylation of non racemic lactams explained by a chelated control process.[5] We now wish to present our first results towards the preparation of optically pure 2,3-disubstituted piperidines, starting from lactam **1**[7] (scheme 1), for which no general methods have been described[6].

Alkylation of lactam **1** is known to be totally diastereoselective, leading to compounds **2**.[2] We decided to take advantage of the presence of the carbonyl group to substitute the C-2 center. The most common way to functionalize the carbonyl group of a lactam involves the preparation of a thiolactam followed by a sulfur contraction process[8] as recently exemplified for the asymmetric synthesis of 2,6-disubstituted piperidines.[9] However this reaction only allowed the preparation of vinylogous urethanes. We thought that a more rapid and versatile approach could be the direct reaction of lactams **2** with an organometallic reagent followed by the reduction of the intermediate carbinolamine **3** (scheme 1).

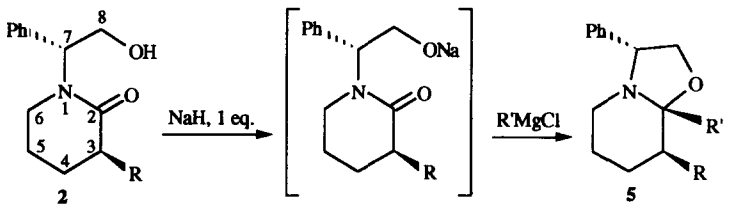


Scheme 1

Such reactivity has previously been described[10], but surprisingly, this methodology has not received many applications although it constitutes a simple access to α-substituted amines. The main reason could be the relative instability of the intermediate carbinolamine **3** which could lead to an amino ketone by a ring-opening

reaction or to an enamine by dehydration. In our case, we expected that the presence of a hydroxyl group on the chiral appendage could allow the formation of a stable oxazolidine **5** preventing side reactions.

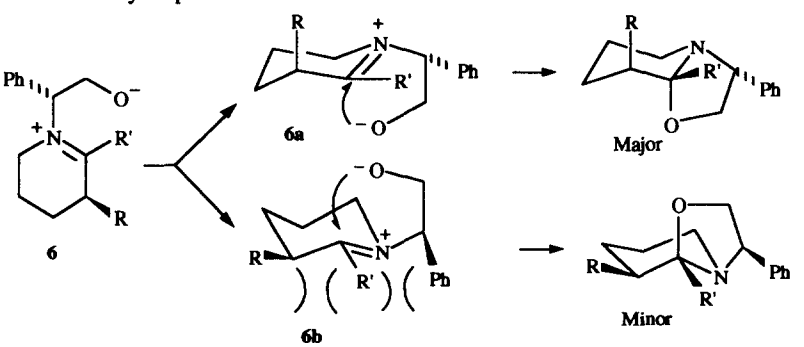
In a first series of experiments, we studied the reactivity of lactams **2** with Grignard reagents. Whatever the conditions of solvent and temperature, it has been impossible to obtain the desired products **5** in satisfactory yields, large amounts of starting material always being recovered from the reaction mixture. Since poor yields could result from the formation of alkoxymagnesium salts, increasing the aggregation state of the reactants, we decided to prepare sodium alcoholate (NaH, 1 eq.) prior to the addition of Grignard reagent. In these conditions oxazolidines **5** were obtained in moderate to good yields (Table 1).[11] In each case except one (entry 2), good to excellent diastereoselectivities were observed.



Entry	R	R'	Yield (%)	d.e. (%)	compound
1	Me	Me	79	85	**5a**
2	Me	CH_2Ph	61	0	**5b**
3	CH_2Ph	Me	87	> 95	**5c**
4	CH_2Ph	CH_2Ph	44	60	**5d**

Table 1 : C-2 alkylation of lactams **2**.

Absolute configuration of the newly created asymmetric center was determined by ^1H and ^{13}C NMR.[12] For both isomers, C-3 substituent was equatorial as indicated by the coupling constants values ($J_{H\text{-}3,H\text{-}4ax}$ = 11.5-12.6 Hz), and C-2 substituent was axial for major isomer indicating a cis relationship between R and R'. To explain the observed diastereoselectivity cyclisation of the alcoholate onto the iminium ion (scheme 2) could be proposed as the key-step.

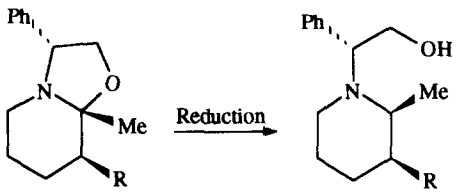


Scheme 2

As it is known that such a reaction occurs with an axial approach of the nucleophile[11], two intermediates **6a** and **6b** can be considered. Intermediate **6b** would involve strong $A^{1,2}$ interactions between C-2 substituent

R' and both R and Ph, in contrast to **6a** which could cyclize to furnish *cis*-2,3-disubstituted product, with the observed configuration after ring inversion. The reasons for the lack of stereoselectivity for 2-benzyl-3-methyl derivative (entry 2) is far from clear, but it is obvious that an augmentation of the size of C-2 substituent induced a diminution of stereoselectivity.

Diastereomeric mixtures of oxazolidines **5** were then directly reduced, since these compounds could not be obtained diastereomerically pure by flash chromatography (table 2). Whatever the conditions, only mixtures of C-2 epimeric compounds were obtained indicating that no C-3 epimerisation occurred.



5 **7**

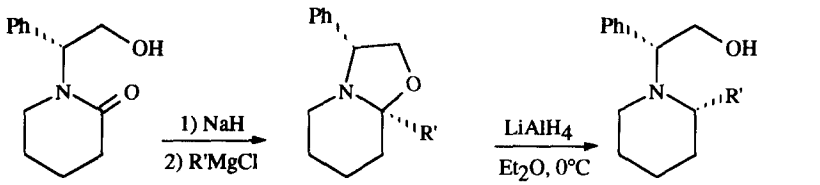
Entry	R	d.e. of starting compound (%)	reducing agents	conditions	Yield. (%)	d.e. (%)	compound
1	Me	85	$LiAlH_4$	Et_2O, 0°C	88	84	**7a**
2	Me	85	$NaBH_4$	MeOH, -78°C	80	64	**7a**
3	Me	0[14]	$LiAlH_4$	Et_2O, -78°C	86	0	
4	Me	85	$LiAlH_4$	Et_2O, rt	87	77	**7a**
5	Me	85	$NaBH_3CN$	MeOH, H_3O^+, rt	0	-	
6	Me	85	Et_3SiH	$TiCl_4$, THF, rt	0	-	
7	Me	85	H_2, Pd/C	MeOH	84[15]	0	
8	CH_2Ph	>95	$LiAlH_4$	Et_2O, 0°C	85	95	**7b**

Table 2 : reduction of oxazolidines **5**.

The best results were obtained with $LiAlH_4$ in Et_2O at 0°C. Entries 1 and 3 clearly indicate that $LiAlH_4$ reduction was diastereoselective. Furthermore, ^1H NMR analysis of the major diastereomer **7a** revealed a *cis* relationship between C-2 and C-3 substituents (J_{H2-H3} = 4.3 Hz), indicating a retention of stereochemistry probably due to a process involving a chelation of aluminium to nitrogen. When $NaBH_4$ was used, a diminution of the d.e. was observed suggesting a non-concerted mechanism through an iminium ion. Other reducing agents ($NaBH_3CN$, Et_3SiH, H_2) did not allow the preparation of pure disubstituted piperidines.

In order to study the generality of C-2 functionalization and the influence of C-3 substituent, non-substituted lactam **1** was reacted with Grignard reagents (scheme 3). When propyl magnesium bromide was used, an excellent diastereoselectivity was observed, but it has been impossible to determine the configuration of C-2 at this stage. Reduction of oxazolidines **8a** and **8b** were performed with $LiAlH_4$; in these conditions the diastereomeric ratios were preserved. C-2 configuration of **9b** was deduced by a comparison with the 2-(*S*)-isomer previously prepared in our laboratory during the synthesis of coniine.[16] The two products were clearly different (^1H and ^{13}C NMR, TLC, $[\alpha]_D$). It was concluded that **9b** possessed a 2-(*R*) configuration which would favour a different stereochemistry of **8b** compared to disubstituted products **5**. The reasons of such a difference are not obvious and would need supplementary experiments. Nevertheless, this method constitutes

an easy access to disubstituted piperidines. Applications to the synthesis of natural products or biologically active compounds are under investigation and will be reported in due time.



1

8a R' = Me
Y = 55%, d.e. = 60%

8b R' = Pr
Y = 71%, d.e. = 90%

9a R' = Me
Y = 55%, d.e. = 60%

9b R' = Pr
Y = 71%, d.e. = 80%

Scheme 3

Acknowledgments : Laurent Micouin is grateful to Roussel-Uclaf Company for a grant.

References and notes.

1. For part XXXIX see : L. Micouin, M. Bonin, M.-P. Cherrier, A. Mazurier, A. Thomas, J.-C. Quirion, H.-P. Husson, *Tetrahedron*, submitted for publication.
2. L. Micouin, T. Varea, C. Riche, A. Chiaroni, J.-C. Quirion, H.-P. Husson, *Tetrahedron Lett.* **1994**, *35*, 2529-2532.
3. V. Schanen, A. Chiaroni, C. Riche, J.-C. Quirion, H.-P. Husson *Tetrahedron Lett.* **1994**, *35*, 2533-2536.
4. T. Varea, M. Dufour, L. Micouin, C. Riche, A. Chiaroni, J.-C. Quirion, H.-P. Husson *Tetrahedron Lett.* **1995**, *36*, 1035-1038.
5. L. Micouin, J.-C. Quirion, H.-P. Husson *Angew. Chem. Int. Ed. Engl.* submitted to publication.
6. For a recent example of asymmetric synthesis of 2,3-disubstituted piperidines see D. Gnecco, C. Marazano, B.C. Das J. *Chem. Soc. Chem. Commun.* **1991**, 625-627.
7. L. Micouin, J.-C. Quirion, H.-P. Husson *Synth. Commun.* **1996**, in press
8. M. Roth, P. Dubs, E. Götschi, A. Eschenmoser *Helv. Chim. Acta* **1971**, *54*, 710-734.
9. M.J. Munchhof, A.I. Meyers *J. Am. Chem. Soc.* **1995**, *117*, 5399-5400.
10. Y.C. Hwang, M. Chu, F.W. Fowler *J. Org. Chem.* **1985**, *50*, 3885-3890.
11. The preparation of oxazolidine **5a** is representative. To a solution of lactam **2** (R = Me) (110 mg, 0.43 mmol) in THF (5 mL), NaH (1 eq) was added under N_2. Resulting mixture was stirred at rt for 20 min, then a solution of MeMgCl in THF (3 M, 1 mL, 3.0 mmol) was added. The reaction was stirred for an additional 14 h at rt. Usual work-up furnish an oil which was purified by chromatography (Al_2O_3) (EtOAc) furnishing 78 mg of **5a** as a 93/7 mixture of isomers. Major isomer : ^1H NMR, (δ, ppm) : 1.00 (d, J = 6.7 Hz, Me), 1.05 (s, Me), 2.31 and 2.61 (m, 2 H-6), 3.51, 3.92 and 4.20 (3t, 2 H-7 and H-8). ^{13}C NMR, (δ, ppm) : 9.1 (C-3 Me), 16.1 (C-2 Me), 41.4 (C-3), 42.8 (C-6), 62.9 (C-7), 72.3 (C-8), 95.8 (C-2).
12. M; Rubiralta, E. Giralt, A. Diez "*Piperidine. Structure, Preparation, Reactivity, and Synthetic Applications of Piperidine and its Derivatives*", Elsevier, Amsterdam, **1991**.
13. A. Stevens, *Acc. Chem. Res.*, **1984**, *17*, 289-296.
14. C-2 Epimeric mixture was obtained by refluxing **5a** in MeOH for 24h.
15. In these conditions, reduction was followed by hydrogenolysis of the chiral appendage. A 1/1 mixture of *cis* and *trans* 2,3-dimethyl-piperidines was obtained in 84 % yield.
16. L. Guerrier, J. Royer, D.S. Grierson, H.-P. Husson *J. Am. Chem. Soc.* **1983**, *105*, 7754-7755.

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