Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 11, pp. 2651-2654, 1995

0957-4166/95 $9.50+0.00

0957-4166(95)00348-7

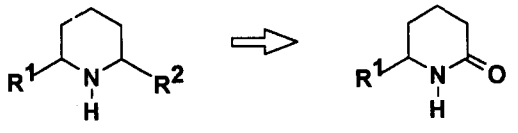
New Highly Enantioselective Synthesis of 6-Alkylpiperidin-2-ones and 2-Substituted Piperidines

Stéphanie Fréville, Jean Pierre Célérier, Vu Moc Thuy, and Gérard Lhommet*

Université P. et M. Curie. Laboratoire de Chimie des Hétérocycles, associé au CNRS.
4 Place Jussieu. 75252 Paris cedex 05. France.

Abstract : A versatile and highly enantioselective approach to 2-substituted piperidines is described using phenylglycinol as chiral auxiliary.

Mono- and di-alkylpiperidine alkaloids **1** are abundant in Nature and some of them exhibit significant biological activity[1]. Numerous racemic approaches of 2-alkylpiperidines have been described since Ladenburg's first synthesis of coniine **1b** (R^1=n-C_3H_7; R^2=H) in 1886 but only a few enantioselective preparations of these compounds have been presented. Most of these asymmetric syntheses employ aminoacid[2], sugars[3], chiral benzylic amines such as phenylglycinol[4], α-methylbenzylamine[5] as auxiliaries. A different approach has been described which uses enantioselective 1,2-addition of organoytterbium reagents to aldehyde SAMP hydrazones[6]. In connection with our studies on lactam reactions, we wish here to present a general, enantioselective, and versatile access to such compounds via the preparation of 6-alkylpiperidin-2-ones **2**.

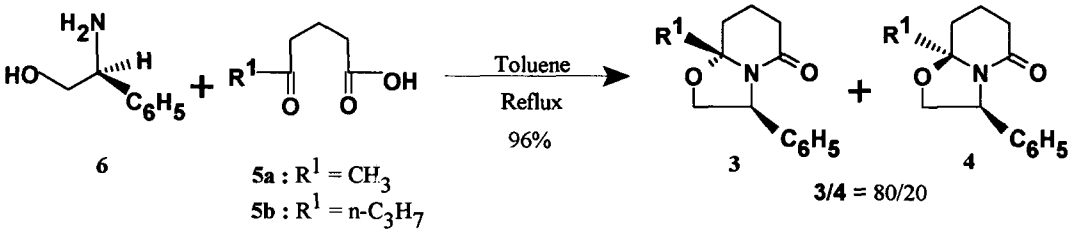


1 **2**

We have previously shown that 5-alkylpyrrolidin-2-ones can easily be obtained from commercially available (S)-pyroglutamic acid[7], but six membered ring lactams homologues cannot be prepared due to the difficulty of preparing the chiral precursor. In fact, 6-methylpiperidin-2-one **2a** (R^1=CH_3) was first prepared by a very difficult deracemization and subsequent oxidation of 2-methylpiperidine[8], or more recently by chemical homologation of alanine[9], or by oxidation of oxazolopiperidines[10]. An efficient synthesis of α-substituted pyrrolidin-2-ones and pyrrolidines has been described by Meyers *et al.*[11]. The authors obtain with an excellent diastereoselectivity oxazolopyrrolidinones by condensation of γ-keto acids with enantiomerically pure phenylglycinol, which by reductive ring opening leads to various desired products. However no extension to six membered rings was presented in this work.

We wish here to report general reactions which permit a versatile and enantioselective access to such compounds like **1** (R^2=H) and **2**.

Substituted oxazolopiperidin-2-ones **3** and **4** are prepared by condensation of δ-keto acids **5**[12] and (L)-(+)-phenylglycinol **6**[13] (Scheme 1). The diastereoisomeric excess is around 60% and does not depend on the chain length of R^1, but the diastereoisomers **3** and **4** are readily separable by chromatography on silica gel.



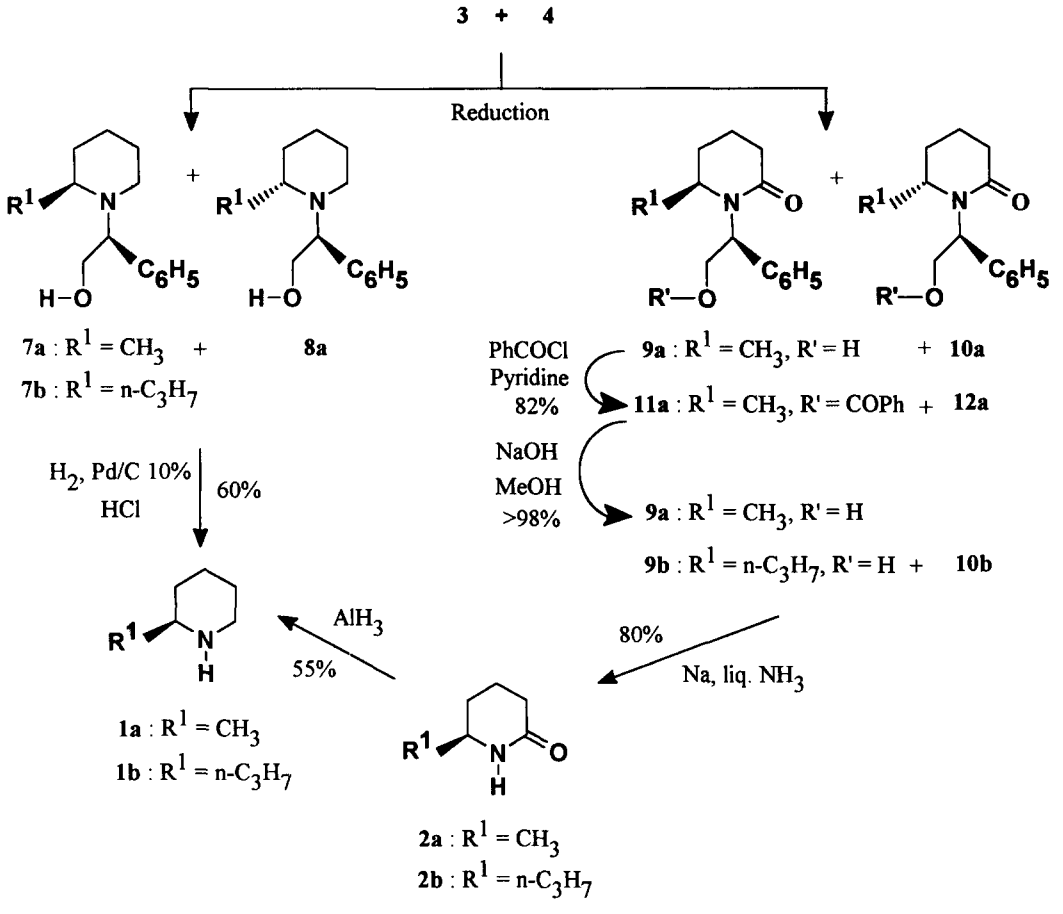
Scheme 1

Nevertheless, compounds **3** and **4** can be treated together without separation with reducing agents to lead to piperidine compounds. For the formation of compounds **7** and **8**, the oxazolopiperidin-2-ones **3** and **4** react. For the formation of compounds **9** and **10**, only the major diastereoisomer **3** is reduced (Scheme 2). These isomers are formed diastereoselectively during the reduction of the iminium intermediate[11b]. Furthermore, no equilibration between **3** and **4** is observed. It can be noted that the Meyers's reducing conditions do not give satisfactory results with these compounds.

Oxazolopiperidin-2-ones **3** are interesting precursors of enantiomerically pure natural 2-mono-alkylated-piperidines such as α-pipecoline **1a** (R^1=CH_3, R^2=H) or coniine **1b**.(R^1=C_3H_7, R^2=H). Reduction of a mixture of diastereoisomers of **3** and **4** with different reducing agents such as $LiAlH_4/AlCl_3$, $NaBH_4/TiCl_4$, or BH_3/DME leads to cyclic amino alcohols **7** and **8** with an excellent diastereoisomeric excess (d.e.>80%) (Table 1). Diastereoisomer **7a** is easily separated by chromatography on silica gel and a final hydrogenolysis of **7a** and **7b**, using palladium on carbon in acidic media permits the isolation of naturrally occurring monosubstituted piperidines **1a** and **1b**[14].

Oxazolopiperidin-2-ones **3** can also be used to prepare 6-alkylpiperidin-2-ones **2** by treatment with a large excess of triethylsilane in presence of $TiCl_4$ (d.e.>80%). When R^1=n-C_3H_7, a recrystallization leads to a single isomer **9b**. When R^1=CH_3, a reversible benzoylation is necessary to permit the separation of the two diastereoisomers **11a** and **12a** and to establish by X Ray diffraction the absolute configuration of **11a**. In this way, 1-substituted-piperidin-2-ones **9a** and **9b** are obtained with a high diastereoisomeric excess (>98%). The last step of this synthesis consists of a debenzylation. A final reduction using Na/liq. NH_3 leads with a very high enantioselectivity to 6-alkylpiperidin-2-ones **2**. 6-Methylpiperidin-2-one **2a** (R^1=CH_3) and 6-propylpiperidin-2-one **2b** (R^1=C_3H_7) are finally prepared with an overall yield respectively of 45% and 29% in a few steps [17].

2-Alkylpiperidines **1** can also be obtained by reduction of lactams **2** by AlH_3 with 55% yield.



Scheme 2

Table 1 : Reductive opening of oxazolopiperidin-2-ones.

Reducing Agent	7a R^1=CH_3			9a R^1=CH_3			7b R^1=n-C_3H_7			9b R^1=n-C_3H_7		
	Yield %	d.e.	α^{20}_D Conc Solvent	Yield %	d.e.	α^{20}_D Conc Solvent	Yield %	d.e.	α^{20}_D Conc Solvent	Yield %	d.e.	α^{20}_D Conc Solvent
$LiAlH_4/AlCl_3$ (3eq./1eq.)	65	80	+63.0 1.7 MeOH	-	-	-	53	>98	+63.3 1.1 MeOH	-	-	-
$NaBH_4/TiCl_4$ (3eq./2eq.)	60	*id.*	*id.*	-	-	-	a	a	a	a	a	a
BH_3/DME (2eq.)	60	*id.*	*id.*	-	-	-	a	a	a	a	a	a
$(Et)_3SiH/TiCl_4$ (6eq./6eq.)	-	-	-	59	80	+12.9 1.0 MeOH	-	-	-	62	90	+33.5 1.3 MeOH

a : Reduction not studied

In conclusion, we describe a general and versatile synthesis of enantiomerically pure 2-alkylpiperidines and 6-alkylpiperidin-2-ones via common oxazolopiperidin-2-one intermediate. 6-Alkylpiperidin-2-ones will be in future used to prepare natural polysubstituted piperidine alkaloids.

Acknowldgement

We are grateful to DSM ANDEMO (Netherlands) for the generous gift of L-(+)-phenylglycine.

References and notes

1. Fodor, G.B.; Colasanti, B. in *Alkaloids : Chemical and Biological Perspectives*; ed. S.W. Pelletier, Wiley, New York, **1985**, vol 3, pp 1-90.
2. Hermitage, S.A.; Moloney, M.C. *Tetrahedron Asymmetry* **1994**, *5*, 1463
3. Kunz, H.; Pfrengle, W. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1067.
4. (a) Royer, J.; Husson, H.P. *Janssen Chim. Acta* **1993**, *11*, 2, and references therein. (b) Mehmandoust, M.; Marazano, C.; Das, C. *J. Chem. Soc., Chem. Commun.* **1989**, 1185.
5. (a) Kiguchi, T.; Nakazono, Y.; Kotera, S.; Naito, T. *Heterocycles* **1990**, *31*, 1525. (b) Marx, E.; El Bouz, M.; Célérier, J.P.; Lhommet, G. *Tetrahedron Lett.* **1992**, *33*, 4307.
6. Enders, D.; Tiebes, T. *Liebigs Ann. Chem.* **1993**, 173.
7. (a)Saliou, C.; Fleurant, A.; Célérier, J.P.; Lhommet, G. *Tetrahedron Lett.* **1991**, *28*, 3365. (b) Rosset, S.; Célérier, J.P.; Lhommet, G. *Tetrahedron Lett.* **1991**, *28*, 7521. (c) Provot, O.; Célérier, J.P.; Petit, H.; Lhommet, G. *J. Org. Chem.* **1992**, *57*, 2163.
8. Cervinka, O.; Fabryova, A.; Novak, V. *Coll. Czech. Chem. Commun.* **1965**, *30*, 1742.
9. McIntosh, J.M.; Acquaah, S.O. *Can. J. Chem.* **1988**, *66*, 1752.
10. Lienard, P.; Varea, T.; Quirion, J.C.; Husson, H.P. *Synlett* **1994**, *2*, 143.
11. (a) Meyers, A.I.; Romo, D. *Tetrahedron* **1991**, *47*, 9503. (b) Meyers, A.I.; Burgess, L.E. *J. Org. Chem.* **1992**, *57*, 1656. (c) Meyers A.I.; Munchhof, M.J. *J. Am. Chem. Soc* **1995**, *117*, 5399.
12. Jpn. Kokai Tokkyo Koho JP 81,161,348; *Chem. Abst.* **1982**, *96*, 142275z.
13. Abiko, A.;Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 5517.
14. α-Pipecoline **1a**: $[\alpha]^{20}_D$ + 5.2 (c=0.5, EtOH); lit [15] : $[\alpha]^{20}_D$ + 5.6 (c=1.53, EtOH)
    Coniine **1b**: $[\alpha]^{20}_D$ + 7.9 (c=1.0, EtOH); lit [16] : $[\alpha]^{20}_D$ + 8.0 (c=1.0, EtOH)
15. Tallent, W.H.; Horning, E.C. *J. Am. Chem. Soc* **1956**, *78*, 4467.
16. Kouji, H.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749.
17. 6-methylpiperidin-2-one **2a**: $[\alpha]^{20}_D$ + 25.89 (c=2.1; H_2O); lit [9] : $[\alpha]^{20}_D$ + 25.6 (c=2.04, H_2O)
    6-propylpiperidin-2-one **2b** : $[\alpha]^{20}_D$ +14.2 (c=0.82; EtOH)

(*Received in UK* 31 *July* 1995; *accepted* 26 *September* 1995)