Pergamon

Tetrahedron Letters, Vol. 38, No. 41, pp. 7181-7182, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01705-X

Enantioselective Protonation of Amide Enolates Derived from Piperidine-2-Carboxylic Acid

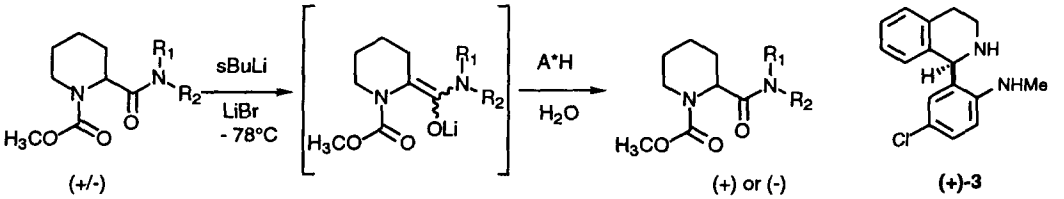
Juliette Martin,[a] Marie-Claire Lasne,*[a] Jean-Christophe Plaquevent,[b] Lucette Duhamel[b]

[a]Laboratoire de Chimie Moléculaire et Thioorganique, UMR CNRS 6507, ISMRA, Université de Caen-Basse Normandie, 6 Boulevard du Maréchal Juin, 14050 Caen Cedex, France. E-Mail : lasne@ismra.unicaen.fr ; Fax : (33) 2 31 45 28 77.

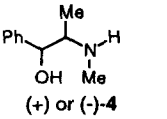
[b]Université de Rouen, Institut de Recherche en Chimie Organique Fine, UPRES -A 6014, 76821 Mont St Aignan Cedex, France.

Abstract: Enantioselective protonation was applied on amide enolates **1a** and **2a**, derived from piperidine-2-carboxylic acid. High enantioselectivity was obtained with diamine (+)-**3**, as chiral source, and in presence of LiBr. Up to 95±1% ee for amide **1** and >99% for amide **2** were reached. Moreover, (S)-**1** and (R)-**1** were obtained with 89% and 93% ee using (+) and (-) ephedrine respectively. © 1997 Elsevier Science Ltd.

Enantioselective protonation firstly described on enamines[1] and then on prostereogenic enolates,[2] is now a well known method[3] to prepare highly enriched enantiomers of different functional compounds. However, few works have been reported in the preparation of optically active amides,[4] and only on unsaturated substrates. In all the examples studied, the transferred proton was ensured by a chiral amine.[5] Searching for the synthesis of both enantiomers of carboxamide **1**, intermediates of a selective M_2 muscarinic receptor antagonist [(+) and (-)-AF-DX 384],[6,7] enantioselective protonation was studied on amide enolate **1a**.



	NR_1R_2		A*H		ee (%)
1	$N[(CH_2)_2CH_3]_2$	**1a**	(+)-**3**	(-)-S-**1**	95
			(+)-**4**	(-)-S-**1**	89
			(-)-**4**	(+)-R-**1**	93
2	$N(CH_2)_5$	**2a**	(+)-**3**	(-)-S-**2**	> 99



(+) or (-)-**4**

Sec-BuLi was the ideal base reagent for a complete and rapid deprotonation at -78°C. When diamine (+)-**3**[8] or ephedrine (+)-**4** or (-)-**4** was added to the enolates **1a** or **2a**, in the presence of lithium bromide,[5b] enantiomeric excess (ee)[9] up to 99% was obtained. Other chiral proton sources such as tartaric, mandelic,

camphoric, dipivaloytartaric, diadamantyltartaric acids or naphthylethylamine were not efficient. Among the different solvents used, THF gave the best results. In the presence of diethylether (mixture 1/1) or directly in toluene, hardly no deracemization was observed. The ee were shown to be very dependent on both reaction and hydrolysis temperatures. High ee were obtained at -78°C. Under the best conditions but in the absence of lithium bromide, the compound **1** was formed in a lower ee (87%). A similar value resulted from the reaction of **1a** with the diamine (+)-**3** in the presence of $BF_3.Et_2O$ as a Lewis acid.[4] However, the amide **1** was only recovered, in this case, with a 26% isolated yield.

A typical experimental procedure is as follows. Under nitrogen atmosphere, a solution of *sec*-BuLi in cyclohexane (1.3 M, 0.4 mL, 0.5 mmol) was added to amide **1** (80 mg, 0.3 mmol) in THF (c 0.15 M) with LiBr (45 mg, 0.52 mmol) cooled at -78°C. The resulting mixture was stirred for 15 min, then diamine (+)-**3** (162 mg, 0.592 mmol, 2 equiv.) in THF (c 0.15 M) was added, dropwise, within 20 min at -78°C. The solution was allowed to stand at -78°C for 30 min, then warmed to -20°C and immediately cooled at -78°C to be quenched with water (0.5 mL). After warming to room temperature, the solvents were evaporated, and the residue treated with ethyl acetate using conventional basic and acid extractions. The amide (-)-**1** was isolated with 74% yield (ee : 95%).[10]

Attempts of enantioselective deprotonations of the amides **1** or **2** using *sec*-BuLi in the presence of (-)-sparteine[11] are underway.

Acknowledgments - This work was supported by the "Réseau Interrégional de Chimie Organique Fine" (Contrat de Plan Etat Bassin Parisien - Régions Haute Normandie, Basse Normandie).

References and Notes

1. a) Duhamel, L. *C. R. Acad. Sciences* **1976**, *282C*, 125 -127; b) Matsushita, H.; Tsujino, Y.; Noguchi, M.; Saburi, M.; Yoshikawa, S. *Bull. Soc. Chim. Jpn.* **1978**, *51*, 862-865 and references cited therein.
2. Duhamel, L.; Plaquevent, J.-C. *J. Am. Chem. Soc.*, **1978**, *100*, 7415-7416.
3. a) Duhamel, L.; Duhamel, P.; Launay, J.-C.; Plaquevent, J.-C. *Bull. Soc. Chim. Fr.*, **1984**, *II*, 421-430. b) Fehr, C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2567- 2587 and references cited therein.
4. a) Vedejs, E.; Lee, N. *J. Am. Chem. Soc.* **1991**, *113*, 5483-5485; b) Vedejs, E.; Lee, N.; Sakata, S.T. *J. Am. Chem. Soc.* **1994**, *116*, 2175-2176; c) Vedejs, E.; Lee, N. *J. Am. Chem. Soc.* **1995**, *117*, 891-900.
5. Enantioselective protonation under the influence of a chiral amine (or its salt): a) Duhamel, L.; Plaquevent, J.-C. *Tetrahedron Lett.* **1980**, *21*, 2521-2524. b) Hogeveen, H.; Zwart, L. *Tetrahedron Lett.* **1982**, *23*, 105-108; c) Yasukata, T.; Koga, K., *Tetrahedron: Asymmetry* **1993**, *4*, 35-38; d) Fuji, K.; Tanaka, K.; Miyamoto, H. *Tetrahedron: Asymmetry* **1993**, *4*, 247-249.
6. 5,11-dihydro-11-[2-[2-[(N,N-dipropylaminomethyl)piperidine-1-yl]ethylamino]carbonyl]-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one.
7. Perrio-Huard, C.; Ducandas, C.; Lasne, M.-C.; Moreau B. *J. Chem. Soc. Perkin I* **1996**, 2925-2931.
8. Diamine (+)-**3** was obtained from recrystallized 1-[5-chloro-2-(methylamino)-phenyl]-1,2,3,4-tetrahydroisoquinoline tartrate (Aldrich).
9. The enantiomeric excess was determined by HPLC on chiral OD-type or Chirose-Bond stationary phase, l x d: 250 x 4.6 mm; eluents : n-heptane/ iPrOH (v: v 95:5); flow : 0.6 mL.min^{-1}; λ : 220 nm. The configurations were deduced from independent syntheses of both enantiomers using commercially available (R)- or (S)- piperidine-2-carboxylic acid.
10. NMR ($CDCl_3$): ^1H (250 MHz) δ **1**: 5.1-4.7(m, 1H), 4.1-3.8(m, 1H); 3.62(s, 3H); 3.6-3.3(m, 1H); 3.3-2.9(m, 4H); 1.9-1.2(m, 10H); 0.85(t, J=7Hz, 3H); 0.80(t, J=7Hz, 3H); **2**: 5.06(m, 1H); 3.94(m, 1H); 3.69(s, 3H); 3.45-3.39(m, 3H); 1.84-1.43(m, 14H). ^{13}C (62 MHz) δ **1**: 172.2, 157.2, 51.3, 50.9, 49.5, 47.6, 26.8, 24.9, 20.9, 19.3, 11.3; **2**: 170.6, 157.1, 52.7, 51.1, 46.8, 43.3, 42.1, 26.9, 26.5, 25.8, 24.9, 19.7. IR (NaCl) νmax/cm^{-1}: **1** : 1698, 1650; **2**: 1698, 1658. $[\alpha]^{22}_D$ (*c* 4, $CHCl_3$) (S)-**1**: -24.6; (S)-**2**: -40.
11. Hoppe, D.; Hintze, F.; Tebben, P.; Paetow, M.; Ahrens, H.; Scwerdtfeger, J.; Sommerfeld, P.; Haller, J.; Guarnieri, W.; Kolczewski, S.; Hense, T.; Hoppe, I. *Pure & Appl. Chem.* **1994**, *66*, 1479.

(*Received in France* 23 *July* 1997; *accepted* 18 *August* 1997)