ASYMMETRIC SYNTHESIS WITH CHIRAL HYDROGENOLYSABLE AMINES: A NEW ROUTE TO ENANTIOPURE ETHANOLAMINES**

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Abstract - Enantiopure ethanolamines have been obtained via diastereoselective reduction of chiral 2,3-dihydro-6H-1,4-oxazin-2-ones

Chiral β-aminoalcohols form an important class of compounds due to their usefulness in modern organic chemistry as chiral auxiliaries[1] or chiral building blocks.[2]

Preparation of β-ethanolamines (**1**) has been described by chemical reduction of natural α-aminoacids,[3] enzymatic resolution[4] or synthetic approaches.[5]

The literature reports two general homochiral amines syntheses: addition reaction of organometallic reagents[5-7] or hydrogen[8] to chiral imines or iminiums.

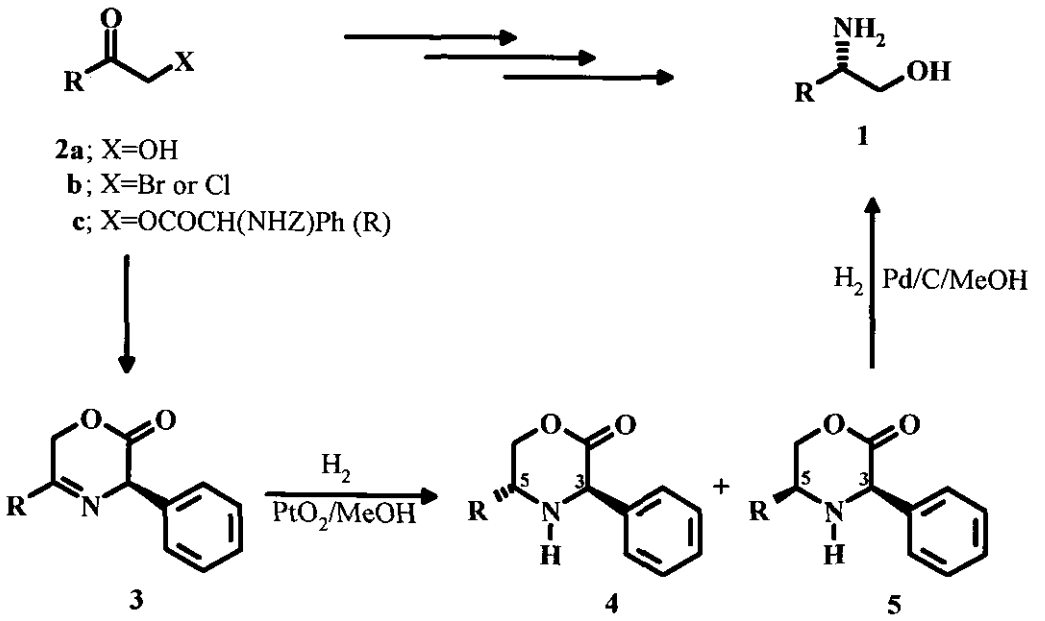
This last strategy has been applied to α-hydroxyketones (**2a**), using α-methylbenzylamine, α-phenylglycinol and methyl α-phenylglycinate as chiral hydrogenolysable amines, but we never observed the α-hydroxyimine formation. However, catalytic reductive amination of ketone (**2a**,R=CH_3) with the same chiral amines leads to a diastereomeric mixture (d.e.= 80%). Unfortunately, the results obtained with other substituents are not satisfactory.

Here we report preparation and diastereoselective reduction of cyclic imines (**3**) which have permitted to obtain optically pure ethanolamines (**1**) after reduction and debenzylation.

** Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday.

Chiral oxazinones (**3**) were readily obtained in two steps from α-halomethyl ketones (**2b**)[9] and potassium (R)-N-carbobenzyloxy-α-phenylglycinate by nucleophilic substitution in DMF,[10] leading to esters (**2c**) in good yields (83-98%).

Then cleavage of Cbz-protecting group using 33% hydrobromic acid in acetic acid and subsequent neutralisation of the resulting hydrobromides in water provided chiral oxazinones (**3**) in quantitative yields (Scheme 1).



Scheme 1

Reduction of oxazinones (**3**) was achieved by catalytic hydrogenation leading to morpholinones (**4**)+(**5**) with diastereomeric excesses between 66 and 86%. Best diastereoselectivity and chemical yields were obtained over PtO_2 in methanol at atmospheric hydrogen pressure (Table 1). Isolation of the major *cis*-morpholinone (**5**) was performed by flash chromatography on silica gel using a $CHCl_3$-Me_2CO mixture as an eluent.

Table 1. Catalytic oxazinones (3) reduction.

Oxazinones	R	Time (h)	*Cis* (5) / *trans* (4)	Morpholinones (5) (%)[a]
3a	Me	4	91 : 9	73
3b	Et	4	86 : 14	82
3c	iPr	4	90 : 10	84
3d	nBu	5	83 : 17	78
3e	iBu	5	85 : 15	76
3f	tBu	6	93 : 7	89

[a] Yields refer to chromatographed products.

Finally, hydrogenolysis of morpholinones (**5**) over 10% Pd/C (150 bars) for 72 h in methanol gave chiral β-ethanolamines (**1**) in good chemical yields (Table 2).

Table 2. β-Ethanolamines (1) formation.

Ethanolamines	R	Yields (%)	bp (°C/torr)		$[\alpha]_D^{20}$ (c, solvent)	
			Found	Ref.	Found	Ref.
1a	Me	89	76 / 16	12	+18.2 (neat)	14
1b	Et	84	87 / 22	12	+10.2 (neat)	14
1c	iPr	88	50 / 0.01	12	+17.1 (11.0, EtOH)	15
1d	nBu	78	70 / 0.01	12	+12,2 (8.7, EtOH)	12
1e	iBu	86	136 / 56	12	+01.2 (neat)	16
1f	tBu	82	60 / 0.01	13	+37.2 (3.0, EtOH)	13

As conclusion, we have developed a direct and general synthesis of enantiopure ethanolamines using α-phenylglycine as chiral auxiliary.

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