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Stereoselective Ring Opening of Chiral Oxazolidines by Reformatsky Reagents: An Enantioselective Entry to β-Amino Esters.

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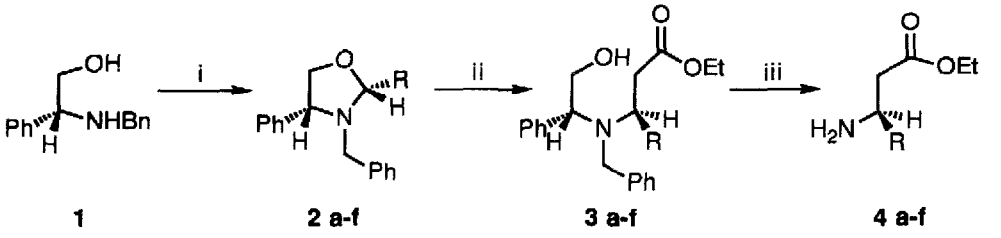
Abstract: Chiral oxazolidines obtained by condensation of aldehydes with (-).(R)- or (+).(S)-N-benzylphenylglycinol react with the Reformatsky reagent derived from ethyl bromoacetate, in mild reaction conditions (Et_2O or CH_2Cl_2, 0°C, 15-60 min), leading to ethyl β-amino carboxylates in moderate to good diastereomeric excess (60-92%). These ring opening products are transformed into primary β-aminoesters, in one step, by debenzylation with H_2/Pd on carbon without loss of their stereochemical integrity. In this way, ethyl β-amino carboxylates can be obtained in both enantiomeric forms, with chemical yields ranging 55-76% and moderate to good e.e. (60-92%).

The developement of new expedient preparation of β-amino acids or their derivatives constitutes an active area of investigation because they are valuable intermediates in organic synthesis[1] and a biologically important class of compounds.[2] Some of the most recent approaches are the diastereoselective addition of amines to chiral α,β-ethylenic esters,[3] additions of silyl ketene acetals to Schiff bases,[4,5] oxidative cleavage of chiral allyl amines obtained by reaction of imines[6,7] or N-benzylidene-p-toluenesulfinamides[8] with organometallics, the coupling of organocuprates with a β-homoserine equivalent[9] or the electrophilic additions to enolates from β-alanine-derived perhydropyrimidin-4-ones,[10] and the enantioselective hydrogenation of acyclic acid derivatives.[11]

Otherwise, chiral oxazolidines have been widely exploited as chiral templates in asymmetric synthesis,[12] but the nucleophilic ring opening of these cyclic O,N-acetals directed to the formation of a new stereocenter remains partially unexplored.[13]

Previously we have studied the regioselective ring opening of tetrahydro-1,3-oxazines by Reformatsky reagents,[14] and we present in this paper the asymmetric version of a related reaction leading to a new efficient enantioselective synthesis of β-amino esters. To this end, we have chosen as targets the chiral 1,3-oxazolidines **2a-g** prepared by condensation of aldehydes with (-).(R)-N-benzylphenylglycinol **1**.[15] These substrates have the following advantages: i) The chiral auxiliary is easily accesible in both enantiomeric forms; ii) the formation of 1,3-oxazolidines is a highly diastereoselective reaction,[12] leading to 2R diastereomers with d.e.>95%,[16] and iii) the ring opening products are dibenzylic amines, and consequently easily transformed into primary amine derivatives in only one step.

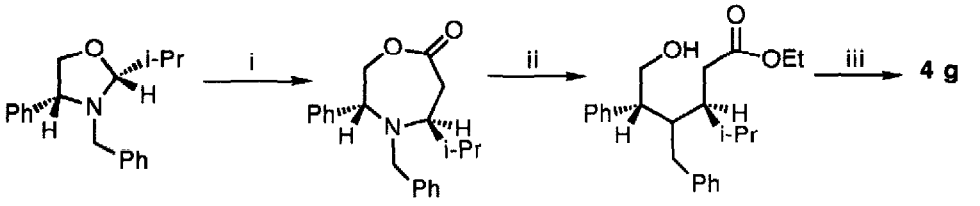
The 1,3-oxazolidines **2a-c** readily react with the zinc derivative of ethyl bromoacetate in mild conditions (diethyl ether, or CH_2Cl_2, 0° C) affording β-amino esters **3a-c** with moderate stereoselectivity entries 1-6 in table 1), whereas the substrates with larger substituents **2d-f** lead to **3d-f** in very good diastereomeric excess (entries 7-10 in table 1); moreover the change in the solvent of the reaction has only a little effect on both the chemical yields and d.e.'s (compare entries 4, 6 and 8 versus 3, 5 and 7 in table 1).[17]



1 **2 a-f** **3 a-f** **4 a-f**

Scheme 1. *Reagents and conditions* : i, RCHO, CH_2Cl_2, mol. sieves, r. t., 2-4 h.; ii, $BrZnCH_2CO_2Et$, 4 eq., Et_2O, 0°C, 30-60 min., then sat. NH_4Cl sol.; iii, H_2, 10% Pd/C, EtOH, r.t., 9 bar, 18-24 h.

A surprising exception to this behaviour corresponds to (-).(2R,4R)-4-phenyl-2-*iso*propyl-1,3-oxazolidine **2g**; this compound does not react with the Reformatsky reagent at 0°C, and it is necessary to heat the reaction mixture in ether at reflux for 3h., leading to a 69:31 mixture of epimeric perhydro oxazepinones **5g**, that is transformed into a mixture (69:31) of diastereomeric β-amino esters **3g** by heating in a HCl saturated ethanol solution, and neutralization (entry 11 in table 1).



2 g **5 g** **3 g**

Scheme 2. *Reagents and conditions* : i, $BrZnCH_2CO_2Et$, 4 eq., Et_2O, 35°C, 3 h., then sat. NH_4Cl sol.; ii, sat. HCl-EtOH, reflux, 3h.; iii, H_2, 10% Pd/C, EtOH, r.t., 9 bar, 24 h.

Otherwise, the open compounds **3a-g** were easily bisdebenzylated without lost of their stereochemical integrity, into a mixture of enantiomeric ethyl β-amino carboxylates **4a-g** by stirring for 15-24 h. at room temperature under H_2 atmosphere in the presence of 10% palladium on carbon as catalyst. The described protocol allowed to prepare the enantiomeric β-amino carboxylates starting from the easily available enantiomeric 1,3-oxazolidines. In a particular case, (2S, 4S)-3-benzyl-2-methyl-4-phenyl-1,3-oxazolidine *ent*-**2a**, obtained by condensation of (+).(S)-N-benzylphenylglycinol *ent*-**1** with acetaldehyde, was transformed into (S)-ethyl-3- amino carboxylate *ent*-**4a** in 62% e.e. (entry 2 in table 1).

Table 1. Enantioselective Synthesis of Chiral Ethyl β-Amino Carboxylates by Diastereoselective Nucleophilic Ring Opening of 1,3-Oxazolidines by Reformatsky Reagents.

entry	Substrate	R	Reaction Conditions			Product(%)[a]	Diast.	β-Amino	E.e.[c] (Conf.)[d]
			Solvent	T(°C)	t(min.)		Ratio[b]	Esters(%)[a]	
1	**2a**	Me	Et_2O	0	15	**3a** (65)	80:20	**4a** (71)	60 (R)
2	ent-**2a**		Et_2O	0	15	ent-**3a** (68)	19:81	ent-**4a** (73)	62 (S)
3	**2b**	Et	Et_2O	0	20	**3b** (80)	86:14	**4b** (69)	72 (R)
4	**2b**		CH_2Cl_2	0	20	**3b** (80)	87:13	**4b** (70)	74 (R)
5	**2c**	n-Pr	Et_2O	0	20	**3c** (77)	89:11	**4c** (70)	78 (R)
6	**2c**		CH_2Cl_2	0	20	**3c** (72)	89:11	**4c** (70)	78 (R)
7	**2d**	Bu	Et_2O	0	30	**3d** (74)	96:4	**4d** (73)	92 (R)
8	**2d**		CH_2Cl_2	0	30	**3d** (75)	95:5	**4d** (72)	90 (R)
9	**2e**	i-Bu	Et_2O	0	60	**3e** (63)	93:7	**4e** (75)	86 (R)
10	**2f**	$CH_2CH_2C_6H_5$	Et_2O	0	60	**3f** (74)	96:4	**4f** (76)	92 (R)
11	**2g**	i-Pr	Et_2O	35	180	**3g** (67)	69:31	**4g** (55)	38 (R)

[a] Yields refer to pure compounds, after column chromatography. [b] Diastereomeric ratios were measured by ^{13}C-NMR.[c] E.e. were determined by GC or HPLC as indicated in the text. [d] The given configurations correspond to the major enantiomer in the mixture.

At this stage, the enantiomeric excess (e.e.) of the aminoesters in the mixtures were determined by GC as trifluoroacetamides[18] on a chirasil-val column for compounds **4a-d** and **4g** or by HPLC, as 1-naftoyl amides[19] on a Pirkle column for compounds **4e** and **4f**, and the results are collected in table 1. Moreover, the stereochemistry of the enantiomers was assigned by the order of elution from the chiral columns, and confirmed and correlated, by optical measurements, with the corresponding 1,3-aminoalcohols for **4a** and *ent*-**4a**; thus, lithium aluminum hydride reduction[20] of the reaction mixtures leaded respectively to (-).(R)-3-amino propan-1-ol in 59% e.e.,$[\alpha]_D^{25}$= -6.6 (c= 1.5, ethanol), lit.[20] $[\alpha]_D^{25}$= -11.2 (c= 5.1, ethanol), and (+).(S)-3-aminopropan-1-ol in 62% e.e., $[\alpha]_D^{25}$= +6.5 (c=1.5, ethanol), lit.[20] $[\alpha]_D^{25}$= +10.5 (c= 5.1, ethanol).

The stereochemical outcome of the reaction can be explained by analogy to the behaviour of chiral acetals with organometallics,[21,22] and it is easily rationalized by accepting the preferential complexation of the Reformatsky reagent to the oxygen in the heterocycle, followed by an invertive substitution at C-2.

In summary, this paper describes a new methodology for nucleophilic ring opening of chiral oxazolidines providing a short an efficient entry to β-amino esters in both enantiomeric forms with good chemical yields and moderate to good enantiomeric excesses.

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17. The following procedure is representative (Table 1, entry 1): To a solution of (-).(2R,4R) 3-Benzyl-2-methyl-4-phenyloxazolidine (1.266 g, 5mmol) in diethyl ether (10 mL) cooled at 0°C, was added a previously prepared[22] 0.7M solution (28.6 mL, 20 mmol) of Reformatsky reagent in the same solvent under nitrogen. The mixture was stirred at 0°C for 15 min. and then quenched with a saturated solution of Ammonium chloride (5 mL) and extracted with diethyl ether. The extracts were dried (magnesium sulfate), evaporated, and the residue chromatographed on silicagel using ethyl acetate/hexane (1:8).
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