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A New and Mild Synthesis of β -Amino Acids From Masked β -Enamino Acid Derivatives

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Abstract

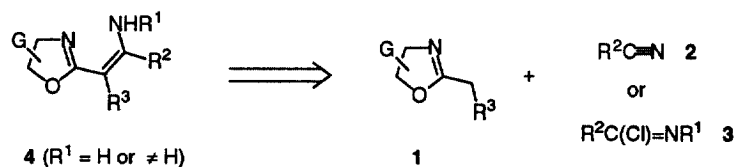
A new method of synthesis of racemic β -amino acids **6** by reduction of masked *N*-substituted and *N*-unsubstituted β -enamino acid derivatives **4** via *C*-protected β -amino acids **5** is described. The process occurs with high yields, total chemoselectivity and moderate diastereoselectivity. Readily available starting materials, inexpensive reagents and mild conditions are used to furnish derivatives **5** and **6**. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Amino acids and derivatives; oxazolines; reduction; regioselection.

Simple β -amino acids have been found as components in a variety of natural products [1] [2], most of them showing interesting biological properties [3] including β -lactam-based antibiotics [4]. In recent years, a great effort for developing new methodologies for the synthesis of β -amino acids has been carried out [5]. As a consequence, several attractive routes to these important compounds have been described [6] [7], which can be classified into the following categories: (i) Michael addition of primary or secondary amines to α,β -unsaturated esters, (ii) condensation reactions between ester enolates and imines, (iii) homologation of α -amino acids, (iv) chemoenzymatic methods, and (v) selective reduction of 3-aminoacrylates and derivatives. Among all of them, the chemoselective reduction of the enamino moiety in β -enamino acid derivatives has received much less attention due, perhaps, to the high reactivity of the ester function toward a great number of reducing agents diminishing, therefore, the regioselectivity of the process [8].

In order to deal with this problem two simple solutions can be *a priori* applied, either to find an adequate reducing agent or to protect the acid moiety. In the last case heterocyclic systems such as Δ^2 -oxazolines have been extensively used as masked carboxylic acids, showing a great stability toward a large variety of reagents [9]. Therefore, regarding this second option, we developed two new different approaches to the protected β -enamino acid derivatives **4** by reacting commercially available 2-alkyl- Δ^2 -oxazolines **1** with a variety of nitriles **2** [10] or, more recently, with imidoyl chlorides **3** [11] (Scheme 1).

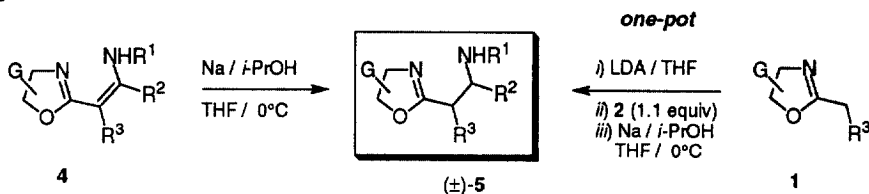
Scheme 1



Compounds **4** may be considered as precursors of the target β -amino acids by reducing the enamino function and deprotection of the masked carboxylic function. Thus, we report here a simple process to obtain racemic β -amino acids by chemoselective reduction of the enamino moiety in **4** and subsequent deprotection by hydrolysis of the oxazoline ring.

Due to its simplicity the use of dissolving metals, particularly the sodium-alcohol system, has been one of the easiest procedures employed to perform the reduction of a large number of organic compounds [8] [12]. Thus, treatment of β -enamino acid derivatives **4** with an excess of Na / *i*-PrOH in THF at 0°C for several hours (see below) gave, after work-up, the corresponding *C*-protected β -amino acid derivatives **5^a** in high yields as the only products (Scheme 2). In most instances the crude product showed satisfactory spectroscopic data and could be used in the following step without purification.

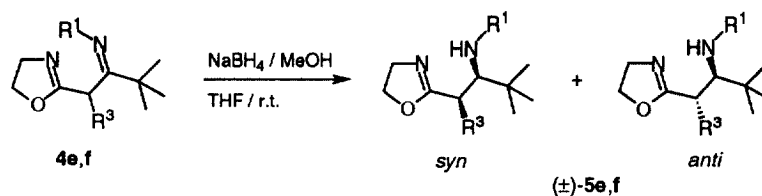
Scheme 2



The results obtained are summarised in Table 1. From the table it can be seen that the outcome is satisfactory with either *N*-substituted and *N*-unsubstituted derivatives **4** and does not depend on the nature of R^1 and R^3 substituents and Δ^2 -oxazoline system. Only when R^2 is an alkyl group is an undefined mixture, in general, obtained. Compounds **5** were prepared in high yields, the reduction went with total chemoselectivity and it was complete within 1-4 h at 0°C; however, the diastereoselectivity of the process was only moderate (entries 4, 6, 9 and 11, Table 1). It is worth noting that *C*-protected β -amino acids **5** ($R^1=\text{H}$) can also be obtained in a one-pot procedure starting from 2-alkyl- Δ^2 -oxazolines **1** (Scheme 2). This reaction is very convenient because isolation of the intermediate **4** is not necessary. Furthermore, in most examples, this one-pot reaction provides higher yields than the two-step sequence (entries 8-10, Table 1) making it the method of choice for preparing derivatives **5**.

Other reducing agents such as complex metal hydrides (*i.e.*, NaBH_4 , NaBH_3CN , LiAlH_4) have also been tested, but they were inefficient. One exception to this general behaviour is the case of β -*tert*-leucine derivatives **4e-f**. These compounds generally appear as imino tautomers, because of steric effects between the *t*-butyl and aryl ($=R^1$) groups, [11] and as a consequence they can also be reduced by other agents such as complex metal hydrides. Thus, when **4e-f** were allowed to react with NaBH_4 in a THF/MeOH mixture (3:1) at 25°C the corresponding β -amino derivatives **5e-f** were synthesised in high yields (entries 5-6, Table 1 and Scheme 3). In the case of α -substituted derivatives such as **4f**, a separable mixture of *syn/anti* (1:3) diastereoisomers (±)-**5f** was obtained (entry 6, Table 1).

Scheme 3



It also should be noted that, although the synthesis of β -amino acids is well documented, only a few examples have been described in which they have been obtained from Δ^2 -oxazoline derivatives [13,14].

Table 1. Synthesis of β -Amino acid derivatives 5 and 6.

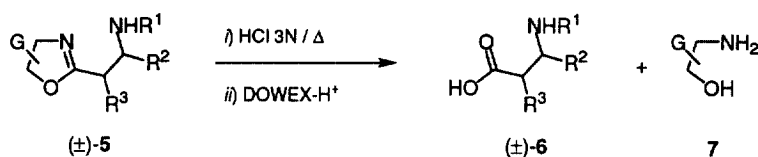
Entry	Starting Material	R ¹	R ²	R ³	Product	Yield ^c (%)	Syn:anti ^d	m.p (°C) ^e
1	4a ^a	Ph	Ph	H	5a	99	-	137-9
2	4b ^a	<i>c</i> -C ₆ H ₁₁	Ph	H	5b	98	-	98-100
3	4c ^a	Ph	<i>p</i> -MeOC ₆ H ₄	H	5c	98	-	138-40
4	4d ^a	Ph	Ph	Me	5d	88	17:83	162-5
5	4e ^a	<i>p</i> -MeOC ₆ H ₄	<i>t</i> -Butyl	H	5e	75	-	115-6
6	4f ^a	<i>p</i> -MeC ₆ H ₄	<i>t</i> -Butyl	Me	5f	90	23:77	f
7	4g ^a	H	<i>p</i> -MeOC ₆ H ₄	H	5g	88	-	oil
8	4h ^b	H	<i>p</i> -MeC ₆ H ₄	H	5h	92 (97)	-	oil
9	4i ^a	H	<i>p</i> -MeC ₆ H ₄	Me	5i	85 (90)	18:82	92-4 ^h
10	4j ^b	H	2-Furyl	H	5j	82 (93)	-	oil
11	4k ^a	H	<i>p</i> -MeC ₆ H ₄	CH ₂ =CHCH ₂	5k	96	35:65	oil ^h
12	5a	Ph	Ph	H	6a	90	-	135-6 ^l
13	5e	<i>p</i> -MeOC ₆ H ₄	<i>t</i> -Butyl	H	6e	88	-	125-7
14	5i	H	<i>p</i> -MeC ₆ H ₄	Me	(2R*,3S*)-6i	55	-	256-8 ^{h,j}

^a Derived from 2-methyl- Δ^2 -oxazoline. ^b Derived from 2,4,4-trimethyl- Δ^2 -oxazoline. ^c Yield of crude product (not optimised). ^d Calculated from crude mixture. ^e Melting points are uncorrected. ^f M.p. (*anti*) 117-8 °C; m.p. (*syn*) 130-2 °C. ^g M.p. of isolated *anti* diastereoisomer. ^h Mixture of *syn/anti* diastereoisomers. ⁱ M.p. of 6a.HCl. ^j Decomposition.

Once compounds 5 were prepared, the last step consisted of the deprotection of the carboxylic function. As described in the literature [9] [14] the most convenient method is acidic hydrolysis by using hydrochloric acid. The optimum results were achieved by treating

compounds **5** with 3N HCl at reflux for 2-3 hours. The desired β -amino acids **6** * were, in this way, obtained in moderate to good yields along with recovery of the β -amino alcohols **7**. Finally, compounds **6** were further purified by flash chromatography, recrystallization ($R^1 \neq H$) or by chromatography on ion-exchange column (Dowex-50, H^+ form) for *N*-unsubstituted β -amino acids (entries 12-14, Table 1 and Scheme 4).

Scheme 4



In summary, we have described the initial studies of a simple and convenient synthetic route for the preparation of *N*-substituted and *N*-unsubstituted β -amino acids. Further work in order to improve the diastereoselectivity in the reduction step is in progress.

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* All compounds **5** and **6** exhibited NMR and mass spectra consistent with the assigned structure. For example, (**5a**): 1H NMR (250 MHz) 2.75 (dd, $J = 1.0$ and 4.0 , 2H), 3.81 (t, $J = 9.5$, 2H), 4.20 (t, $J = 9.5$, 2H), 4.70 (m, 1H), 4.72 (br s, 1H), 6.51-6.68 (m, 3H), 7.05-7.41 (m, 7H); ^{13}C NMR (62.8 MHz) 36.8 (t), 54.3 (d), 55.3 (t), 67.4 (t), 113.5 (d), 117.5 (d), 126.1 (d), 127.3 (d), 128.7 (d), 129.0 (d), 142.6 (s), 147.3 (s), 165.5 (s); HRMS calcd for $C_{17}H_{18}N_2O$ 266.1419, found 266.1426. *anti*-(**5i**): 1H NMR (250 MHz) 0.95 (d, $J = 7.0$, 3H), 1.75 (br s, 2H), 2.34 (s, 3H), 2.69 (m, 1H), 3.88 (t, $J = 9.6$, 2H), 4.00 (d, $J = 9.4$, 1H), 4.27 (t, $J = 9.6$, 2H), 7.10-7.30 (m, 4H); ^{13}C NMR (62.8 MHz) 15.9 (q), 21.1 (q), 41.8 (d), 54.2 (t), 59.0 (d), 67.1 (t), 127.0 (d), 129.2 (d), 137.1 (s), 140.7 (s), 170.0 (s); HRMS calcd for $C_{13}H_{18}N_2O$ 218.1403, found 218.1419.

* For example: (**6e**): 1H NMR (250 MHz) 0.87 (s, 9H), 2.27 (dd, $J = 8.7$ and 15.0 , 1H), 2.56 (dd, $J = 4.7$ and 15.0 , 1H), 3.50 (m, 1H), 3.66 (s, 3H), 6.59-6.70 (dd, $J = 9.0$, 4H); HRMS calcd for $C_{14}H_{21}NO_3$ 251.1521, found 251.1517.