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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**.

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).

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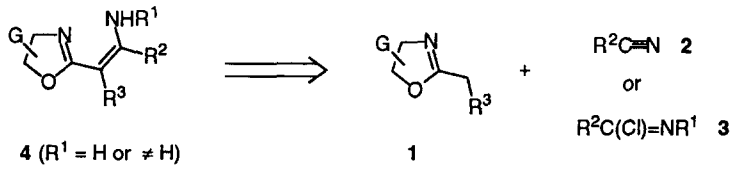
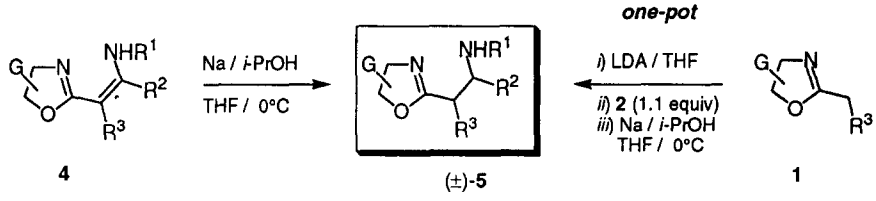
Scheme 1



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**[&] 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.

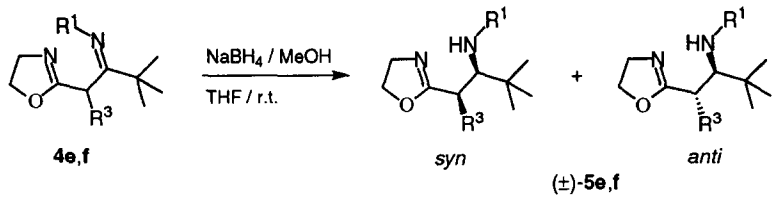
Scheme 2



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=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**.

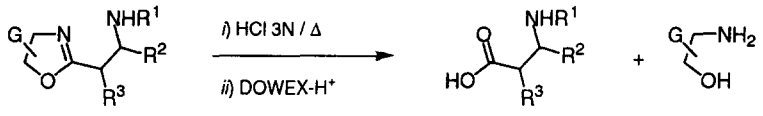
Entry	Starting Material	R^1	R^2	R^3	Product	Yield[c] (%)	*Syn:anti*[d]	m.p (°C)[e]
1	**4a**[a]	Ph	Ph	H	**5a**	99	-	137-9
2	**4b**[a]	*c*-C_6H_{11}	Ph	H	**5b**	98	-	98-100
3	**4c**[a]	Ph	*p*-$MeOC_6H_4$	H	**5c**	98	-	138-40
4	**4d**[a]	Ph	Ph	Me	**5d**	88	*17:83*	162-5
5	**4e**[a]	*p*-$MeOC_6H_4$	*t*-Butyl	H	**5e**	75	-	115-6
6	**4f**[a]	*p*-MeC_6H_4	*t*-Butyl	Me	**5f**	90	*23:77*	[f]
7	**4g**[a]	H	*p*-$MeOC_6H_4$	H	**5g**	88	-	oil
8	**4h**[b]	H	*p*-MeC_6H_4	H	**5h**	92 (97)	-	oil
9	**4i**[a]	H	*p*-MeC_6H_4	Me	**5i**	85 (90)	*18:82*	92-4[g]
10	**4j**[b]	H	2-Furyl	H	**5j**	82 (93)	-	oil
11	**4k**[a]	H	*p*-MeC_6H_4	CH_2=$CHCH_2$	**5k**	96	*35:65*	oil[h]
12	**5a**	Ph	Ph	H	**6a**	90	-	135-6[i]
13	**5e**	*p*-$MeOC_6H_4$	*t*-Butyl	H	**6e**	88	-	125-7
14	**5i**	H	*p*-MeC_6H_4	Me	(2*R**,3*S**)-**6i**	55	-	256-8[g,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



(±)-**5** (±)-**6** **7**

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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References

[1] See, for example: Sone H, Nemoto T, Ishiwata H, Ojika M, Yamada K, Tetrahedron Lett. 1993; 34: 8449-8452.
[2] Nicolaou KC, Guy RK, Angew. Chem. Int., Ed. Engl. 1995; 34: 2079-2090.
[3] Gellman SH, Acc. Chem. Res. 1998; 31: 173-180.
[4] Palomo C, Aizpurua JM, Urchequi R, Iturburu M, Ochoa A, Cuevas C, J.Org. Chem. 1991; 56: 2244-2247 and references cited therein.
[5] For a recent monograph of β-amino acids, see: Juaristi, E. in Enantioselective Synthesis of β-Amino Acids. Wiley-VCH: New York, 1997.
[6] Review: Cole D, Tetrahedron 1994; 50: 9517-9582.
[7] Review: Juaristi E, Quintana D, Escalante J, Aldrichimica Acta 1994; 27: 3-11.
[8] Bartoli G, Cimarelli C, Mercantoni E, Palmieri G, Petrini M J. Org. Chem. 1994; 59: 5328-5325.
[9] Review: Meyers AI, Gant TG, Tetrahedron 1994; 50: 2297-2360.
[10] Fustero S, Díaz MD, Barluenga J, Aguilar E, Tetrahedron Lett. 1992; 33: 3801-3804.
[11] Fustero S, Navarro A, Díaz MD, García de la Torre M, Asensio A, Sanz F, Liu M, J. Org. Chem. 1996; 61: 8849-8859.
[12] Barluenga J, Joglar J, González FJ, Fustero S, Krüger C, Tsay Y-H, Synthesis 1991; 387-393 and references cited therein.
[13] Shono T, Kise N, Sanda F, Ohi S, Tsubata K, Tetrahedron Lett. 1988; 29: 231-234.
[14] Shimano M, Meyers AI, J. Org. Chem. 1995; 60: 7445-7455.

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[#] All compounds **5** and **6** exhibited NMR and mass spectra consistent with the assigned structure. For example, (**5a**): ^{1}H 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**): ^{1}H 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**): ^{1}H 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.