

Enantioselective Synthesis of α -Amino Acids From Nitroalkenes

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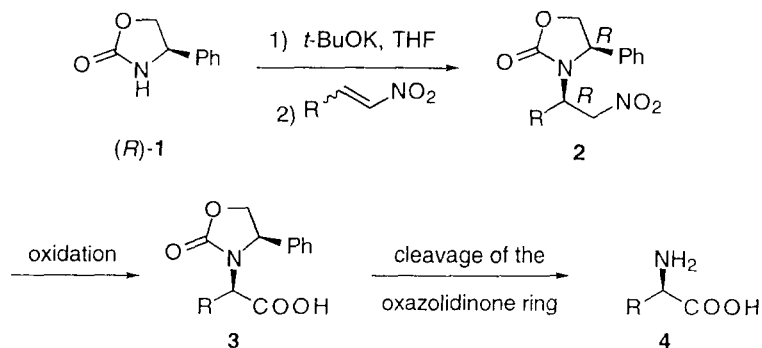
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Abstract: The products of the conjugate addition of (*R*)-4-phenyl-2-oxazolidinone on monosubstituted nitroalkenes were converted into D- α -amino acids of high enantiomeric purity. © 1998 Published by Elsevier Science Ltd. All rights reserved.

Given the importance of α -amino acids, either proteinogenic, non-proteinogenic, or unnatural in biology and chemistry, it is not surprising that many enantioselective syntheses of these products have been devised.¹ It remains an area of active research.²

Only a few stereoselective preparations of α -amino acids involve the introduction of the nitrogen atom via the conjugate addition of a nitrogen nucleophile.³ We have recently reported the completely diastereoselective addition of the potassium salt of (*R*)- or (*S*)-4-phenyl-2-oxazolidinone **1** to monosubstituted nitroalkenes.⁴ The products of this addition can be viewed as convenient precursors to α -amino acids, since the carboxylic acid function could be generated from the nitromethyl group, and since the amino function would result from the cleavage of the oxazolidinone ring, as depicted in the Scheme 1. The purpose of this communication is to describe the synthesis of several D-configured α -amino acids **4** of high enantiomeric purity from the conjugate addition products **2**, prepared from (*R*)-4-phenyl-2-oxazolidinone.



Scheme 1

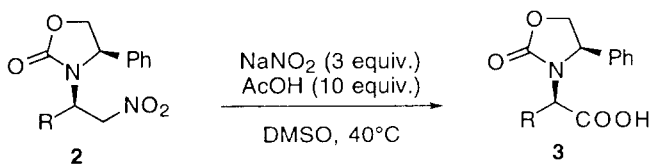
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The oxidation of compounds **2** was carried out using the recently reported procedure that allows the conversion of primary nitro compounds into carboxylic acids under mild conditions.⁵ Thus, after treatment of compounds **2** with sodium nitrite (3 equivalents) and acetic acid (10 equivalents) in DMSO at 40°C for 18-30 hours, acids **3** were isolated in 25-89% yield (Table 1).⁶ In the case of acids such as **3a** (entry 1), that do not have a large alkyl residue, the yields obtained were not good; this suggests that some loss of product might have occurred because of its solubility in the aqueous phase, and that the yields might be improved.

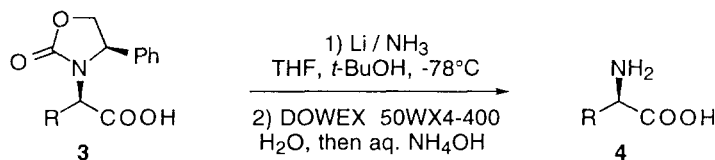
In all cases, only one diastereomer was observed by ¹H- and ¹³C-NMR spectroscopy, indicating that no epimerization of the stereogenic centers had occurred during the reaction.

Table 1. Oxidation of Nitro Compounds **2** to Carboxylic Acids **3**

					
entry	R	reaction time (h)	product	% yield	specific rotation of 3 in CHCl ₃
1	Me	18	3a	25	[α] _D ²⁹ -99 (c 0.61)
2	<i>n</i> -Pr	30	3b	48	[α] _D ²⁷ -56 (c 3.00)
3	BnOCH ₂	18	3c	43	[α] _D ³⁶ -73 (c 2.70)
4	<i>i</i> -Pr	18	3d	51	[α] _D ²⁵ -50 (c 1.94)
5	<i>t</i> -Bu	28	3e	89	[α] _D ³⁰ -35 (c 0.76)
6	cyclohexyl	27	3f	88	[α] _D ²⁸ -60 (c 2.78)

Generation of amines from *N*-substituted 4-phenyl-2-oxazolidinones can be realized using a Birch reduction^{7,8} or by reaction with trimethylsilyl iodide.⁹ The former method was recently employed in the synthesis of L-methionine that also involved an asymmetric carboxylation.¹⁰ We used it to prepare the α-amino acids **4**. Thus, treatment of oxazolidinones **3** with lithium / ammonia in THF and *t*-BuOH at -78°C for 30 minutes afforded the α-amino acids, which were isolated after ion-exchange resin purification, in 62-99% yield (Table 2).¹¹ The protecting benzyl group present in the compound **3c** was concomitantly removed, leading to D-serine **4c** (entry 3).

The enantiomeric purity of the D-α-amino acids **4**¹² was evaluated by HPLC using a Crownpak CR(+) column¹⁴ or, in the case of *tert*-leucine **4e** (entry 5), by examination of the ¹⁹F NMR of the corresponding Mosher amide.^{2a}

Table 2. Preparation of α -Amino Acids **4** by Cleavage of the Oxazolidinone Ring of Compounds **3**

entry	starting material	R	product	R	% yield	ee (%)
1	3a	Me	4a	Me	99	> 96 ^a
2	3b	<i>n</i> -Pr	4b	<i>n</i> -Pr	96	> 96 ^a
3	3c	BnOCH ₂	4c	HOCH ₂	94	> 96 ^a
4	3d	<i>i</i> -Pr	4d	<i>i</i> -Pr	62	> 96 ^a
5	3e	<i>t</i> -Bu	4e	<i>t</i> -Bu	88	95 ^b

^a Ee evaluated by HPLC using a Crownpak CR(+) column¹⁴; in each case, it was not possible to detect the L-enantiomer. ^b Ee evaluated by examination of the ¹⁹F NMR of the corresponding Mosher amide.

In conclusion, the nitro compounds **2**, which are easily obtained by the conjugate addition of (*R*)-4-phenyl-2-oxazolidinone to monosubstituted nitroalkenes, can be converted in two steps to D- α -amino acids of high enantiomeric purity. Finally, it is worthy of note that since (*S*)- as well as (*R*)-4-phenyl-2-oxazolidinone are commercially available, or may be readily prepared,¹⁵ the method can be utilized to synthesize either L- or D- α -amino acids.

Acknowledgment. We thank Mrs L. Sergent for the ee determination by ¹⁹F NMR.

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- Representative procedure for the oxidation of nitro compounds **2**: A solution of nitro compound **2e** (1.06 g, 3.62 mmol), sodium nitrite (0.75 g, 3 equiv.), and acetic acid (2.07 ml, 10 equiv.) in DMSO (25 ml)

- was heated at 40°C for 28 h. After cooling to room temperature, 1N HCl (30 ml) was added to the yellow solution; after 15 min, the aqueous phase was extracted with CH₂Cl₂ (3 x 50 ml). The combined organic phases were then dried over MgSO₄, filtered, concentrated in vacuo. The residue was purified by chromatography (silica gel, 95/05 CH₂Cl₂/CH₃OH) to yield compound **3e** (0.89 g, 89%).
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 11. Representative procedure for the reductive cleavage of oxazolidinones **3**: To a solution of oxazolidinone **3e** (0.35 g, 1.26 mmol), in THF (75 ml) and *tert*-butanol (10 ml) was added lithium (88 mg, 10 equiv.). After cooling the reaction mixture down to -78°C, NH₃ (about 110 ml) was condensed. The resulting deep-blue solution was stirred at -78°C for 30 min, then NH₄Cl (1.5 g) was added. The reaction mixture was allowed to warm to room temperature, then concentrated in vacuo. The residue was purified using a DOWEX 50WX4-400 ion-exchange resin washed beforehand with water. The resin was eluted with water, then with 0.5M NH₄OH, then with 1M NH₄OH. The content of each fraction was checked by thin layer chromatography (80/20 EtOH/10% aq. NH₄OH; ninhydrin; R_f = 0.65). D-*tert*-Leucine **4e** was obtained as a white solid (0.145 g; 88%).
 12. Specific rotations of α -amino acids **4**: **4a**: [α]_D³¹ -13 (c 0.30, 5N HCl); Lit.^{13a}: [α]_D -12.7 (c 0.51, 5N HCl); **4b**: [α]_D³⁸ -22 (c 0.82, 6N HCl); Lit.^{13b}: [α]_D²⁵ -23.0 (c 2-3, 6N HCl); **4c**: [α]_D²⁸ -13 (c 0.30, 5N HCl); Lit.^{13c}: [α]_D²³ -15.0 (c 4, 1N HCl); **4d**: [α]_D²⁶ -28 (c 0.80, 6N HCl); Lit.^{13d,e}: [α]_D²⁵ -29.04 (6N HCl); **4e**: [α]_D³² -29 (c 1.00, AcOH); Lit.^{13f}: [α]_D²⁵ -31.4 (c 1, AcOH).
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 14. Determination of the enantiomeric purity of the α -amino acids: in each case, both an authentic racemic mixture and the synthetic sample were analyzed by HPLC using a Crownpak CR(+) column. Mobile phase: pH 1.5 aq. HClO₄; flow rate: 0.4 ml / min; λ = 200 nm; compounds **4c,d** were analyzed at 0°C. Retention times: R_t(D-enantiomer) / R_t(L-enantiomer) = 3.7 min / 4.8 min (alanine); 5.9 min / 9.2 min (norvaline); 3.9 min / 4.9 min (serine); 5.8 min / 7.4 min (valine).
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