Addition of Allylmagnesium Bromide to ROPHy/SOPHy Aldoximes: Asymmetric Synthesis of Protected β-Amino Acids

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Abstract: A new asymmetric synthesis of protected β-amino acids is described in which the key step is the diastereoselective addition of allylmagnesium bromide to *O*-(1-phenylbutyl) aldoximes.

The occurrence of β-amino acids as constituents of a range of biologically active natural products, together with their role as precursors to β-lactams, and their incorporation into β-peptides with defined secondary structure,[1] has focused attention on these homologues of α-amino acids.[2] The development of new methods for the asymmetric synthesis of β-amino acids is therefore of current interest, and several methods have been reported.[2] Among these are: the homologation of α-amino acids using the Arndt-Eistert procedure,[3] the asymmetric conjugate addition of amines and amides to α,β-unsaturated carboxylic acid derivatives,[4] and the diastereoselective addition of ester enolate equivalents or allyl organometallic reagents to the C=N double bond of imines or hydrazones.[5,6] In the last context we have recently reported the highly diastereoselective addition of organometallic reagents to the C=N bond of (R)- and (S)-*O*-(1-phenylbutyl) oximes (ROPHy and SOPHy oximes),[7] and their application in the asymmetric synthesis of the piperidine alkaloid coniine,[8] and of α-amino acids.[9] We now report an extension of this methodology in a new asymmetric synthesis of β-amino acids based on the addition of allylmagnesium bromide to a range of ROPHy/SOPHy aldoximes.

The *E*-oxime ethers **1**, precursors of the β-amino acids, were readily prepared by reaction of the appropriate aldehyde with (R)- or (S)-*O*-(1-phenylbutyl) hydroxylamine (ROPHy or SOPHy);[7] in the case of isobutyraldehyde, the *Z*-oxime was also formed (16%) but this was readily separated by chromatography. The oxime ethers **1** underwent addition of allylmagnesium bromide in the presence of boron trifluoride etherate to give the hydroxylamines **2** in excellent yield (Table).[10] The diastereoselectivity of the addition was determined from the ^{1}H NMR spectra of **2**, and with the exception of the isobutyraldoxime **1d** was greater than 92%. The configuration of the new asymmetric centre in hydroxylamines **2** was assumed to be the same as the auxiliary on the basis of our previous results, and in the case of **2a** was confirmed by conversion into the *N*-protected (R) β-amino ester **4a**. The conversion was achieved by cleavage of the N-O bond using the zinc/acetic acid/ultrasound method;[11] the resulting amines were not isolated but were immediately converted into the benzyl carbamates **3** by reaction with benzyl chloroformate (Scheme, Table).[12,13] At this stage the enantiomeric purity of the amine derivatives **3** was established by HPLC on a chiral stationary phase (Table). Finally the double bond was cleaved by ozonolysis in methanolic sodium hydroxide to give the *N*-Cbz amino esters **4** in moderate yield (Scheme, Table).[13-15] The configuration of the β-phenyl-β-alanine derivative **4a** was confirmed as (R) by comparison of its optical rotation with a literature value.[16]

In summary, we have established a simple method for the asymmetric synthesis of both homoallylamines and protected β-amino acids.

Acknowledgements

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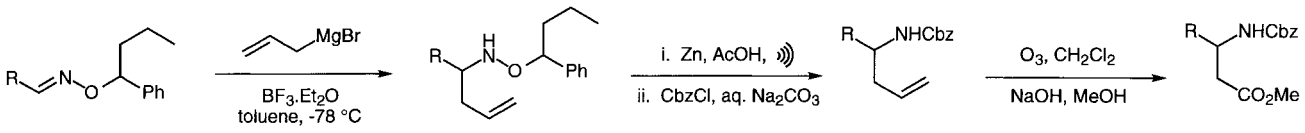
References and Notes

(1) For an account of Seebach's work on β-peptides, see: Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015.

(2) For reviews on the asymmetric synthesis of β-amino acids, see: Cole, D. C. *Tetrahedron* **1994**, *50*, 9517; Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117; *Enantioselective Synthesis of β-Amino Acids*, ed. Juaristi, E. Wiley-VCH, New York, 1997.



1 **2** **3** **4**

a, R = Ph; **b**, R = 4-MeO-C_6H_4; **c**, R = *c*-C_6H_{11}; **d**, R = *i*-Pr; **e**, R = $CHEt_2$

Scheme

Table

	Oxime **1**		Hydroxylamine **2**		*N*-Cbz-amine **3**		*N*-Cbz-amino ester **4**	
R	Yield / %	R/S[a]	Yield / %	de / %	Yield / %	ee / %[b]	Yield / %	R/S[c]
Ph	100	R	100	92	66	95	41	R
4-$MeOC_6H_4$	75	S	80	>96	62	98	33	S
c-C_6H_{11}	71	R	80	96	67	92	39	R
i-Pr	54[d]	R	78	86	47	78	36	R
$CHEt_2$	78	R	100	96	75	91	52	R

[a] Configuration of starting oxime; [b] determined by HPLC on a Chiral Pak AD column using hexane/2-propanol as solvent (99.5 : 0.5 to 92 : 8); [c] configuration of β-amino ester; [d] 16% of *Z*-oxime also obtained

(3) For recent examples of the Arndt-Eistert homologation of α-amino acids, see: Seebach, D.; Overhand, M.; Kuhnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913; Guibourdenche, C.; Seebach, D.; Natt, F. *Helv. Chim. Acta* **1997**, *80*, 1; Leggio, A.; Liguori, A.; Procopio, A.; Sindona, G. *J. Chem. Soc. Perkin Trans. 1* **1997**, 1969; Marti, R. E.; Bleicher, K. H.; Bair, K. W. *Tetrahedron Lett.* **1997**, *38*, 6145.

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(10) The oxime ether **1** (3.9 mmol) was dissolved in toluene (10 mL) under nitrogen and cooled to -78 °C. Boron trifluoride etherate (11.8 mmol) was added and the mixture was stirred for 15 min. Allylmagnesium bromide (11.8 mmol) was added dropwise over 15 min. and the mixture was stirred until all starting material was consumed (typically 2-12 hours). The reaction mixture was quenched at -78 °C with water, allowed to warm to room temperature, and extracted with ether (3 x 15 mL). The extracts were combined, dried (K_2CO_3), filtered and evaporated. The residue was purified by flash chromatography on silica gel using dichloromethane-light petroleum (1:2) as eluent to give the hydroxylamine **2**.

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(12) The N-O bond cleavage and *N*-protection steps were carried out exactly as described in ref. 9.

(13) *Selected data*
Carbamate **3a**, mp 68-69 °C (light petroleum), $[\alpha]^{22}_D$ +43.6 (*c* 0.55, CH_2Cl_2).
Carbamate **3b**, mp 67-68 °C (light petroleum), $[\alpha]^{22}_D$ -36.6 (*c* 0.7, CH_2Cl_2).
arbamate **3c**, mp 70-71 °C (light petroleum), $[\alpha]^{22}_D$ -16.0 (*c* 0.5, CH_2Cl_2).
Carbamate **3d**, oil, $[\alpha]^{22}_D$ -30.0 (*c* 2.0, CH_2Cl_2).
Carbamate **3e**, oil, $[\alpha]^{22}_D$ -29.7 (*c* 0.97, CH_2Cl_2).
Amino ester **4a**, mp 65-66 °C (hexane), (lit.,[16] 65 °C), $[\alpha]^{22}_D$ +17.1 (*c* 1, $CHCl_3$) (lit.,[16] $[\alpha]^{21}_D$ -15.8 (*c* 0.55, $CHCl_3$) for (S)-enantiomer).
Amino ester **4b**, mp 76-77 °C (hexane), $[\alpha]^{24}_D$ -26.0 (*c* 0.5, $CHCl_3$).
Amino ester **4c**, mp 71-72 °C (hexane), $[\alpha]^{25}_D$ -14.0 (*c* 0.7, $CHCl_3$).
Amino ester **4d**, oil, $[\alpha]^{24}_D$ -24.6 (*c* 1.4, $CHCl_3$).
Amino ester **4e**, oil, $[\alpha]^{25}_D$ -18.0 (*c* 0.4, $CHCl_3$).

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(15) Ozone was passed through a solution of the Cbz-protected amine **3** (1.64 mmol) in CH_2Cl_2 (13 mL) and methanolic sodium hydroxide (2.5 M; 3.3 mL) at -78 °C. After 2 h a yellow precipitate had formed. Ether (5 mL) and water (5 mL) were added and the mixture was allowed to warm to room temperature, and extracted with ether (5 x 5 mL). The extracts were combined, dried (Na_2SO_4), filtered and evaporated. Column chromatography on silica gel eluting with ether-light petroleum (1:1) gave the amino ester **4**.

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