Synthesis of chiral amino acid - derived nitrones and 1,3-dipolar cycloadditions with acrylic acid methyl ester

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To Miha Tišler on the occasion of his 75th birthday
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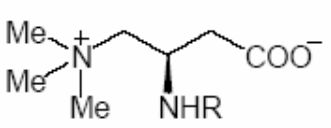
Abstract
The chiral nitrones derived from α-amino acids react with acrylic acid methyl ester to afford the corresponding diastereomeric isoxazolidines **9a-d**. The major products are in the C-3/C-4 *erythro*- and C-3/C-3a *trans*-configuration. The nitrones **3-8** were prepared from the corresponding α-amino aldehydes, starting from L-phenylalanine and L-valine.

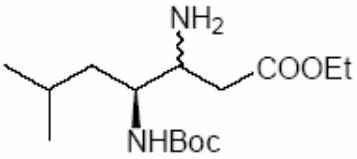
Keywords: Cycloaddition, nitrones, isoxazolidines, α-amino aldehydes

Introduction

The nitrone-olefin 1,3-dipolar cycloaddition is a powerful reaction in that it can create as many as three new contiguous stereogenic centers in a single step.[1] Based on an evaluation of the nitrone cycloaddition, it was felt that the stereochemistry of these new centers could be controlled if the reaction system was properly designed.[1-3] With our continuing efforts to utilize chiral 1,3-dipolar cycloadditions,[4-7] and with the goal of developing a simple route to the synthesis of proteinogenic and non-proteinogenic amino acids[8] *via* an asymmetric 1,3-dipolar cycloaddition we have chosen some α-amino acid – derived nitrones **3-8** as template for a nitron cycloaddition. Diastereoselective synthesis of β,γ,-diamino acids has received considerable attention, this is due to wide range of biological activities of these compounds e. g. emericedines A (**1a**), B (**1b**) and C (**1c**) – inhibit long chain fatty acid oxidation, aminostatine (**2**) – substrate analogue of statine led to potent aspartyl proteinase inhibitor of humane renine.[9]



1 **a** : R= CH_3CO
b : R= CH_3CH_2CO
c : R= $CH_3CH_2CH_2CO$



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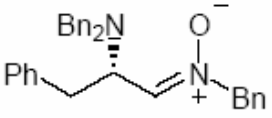
In this paper we report the synthesis of chiral nitrones derived from α-amino acids and the stereoselectivity of the cycloaddition with acrylic acid methyl ester.

Results and Discussion

The nitrones **3-8**, with a "chiral " *C*- substituent, were prepared from the corresponding α-amino aldehydes,[10] by treatment with the *N*-benzyl hydroxylamine in dichloromethane in the presence of anhydrous magnesium sulfate,[11] starting from L-phenylalanine and L-valine. A single isomer was isolated in all cases in pure state, and the expected *Z* configuration was confirmed by nuclear Overhauser effect (NOE) difference spectroscopy. The nitrones **5, 8** were already described by P. Merino,[12] the nitrones **3**, **4, 6** and **7** are originals from our laboratory. α-Amino aldehydes are mainly obtained from α-amino acids.[10] The first synthetic approach is based on the reduction of corresponding esters or amides of α-amino acids to aldehydes. In this work we have used the second method, the oxidation of α-amino alcohols obtained from α-amino acids (Scheme 1).[13,14]



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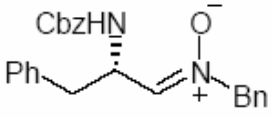

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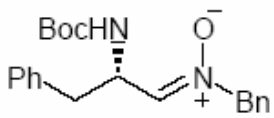

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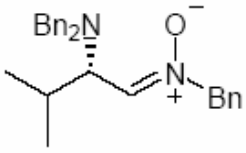

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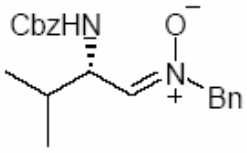

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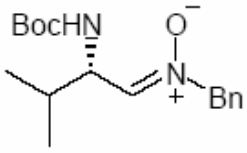

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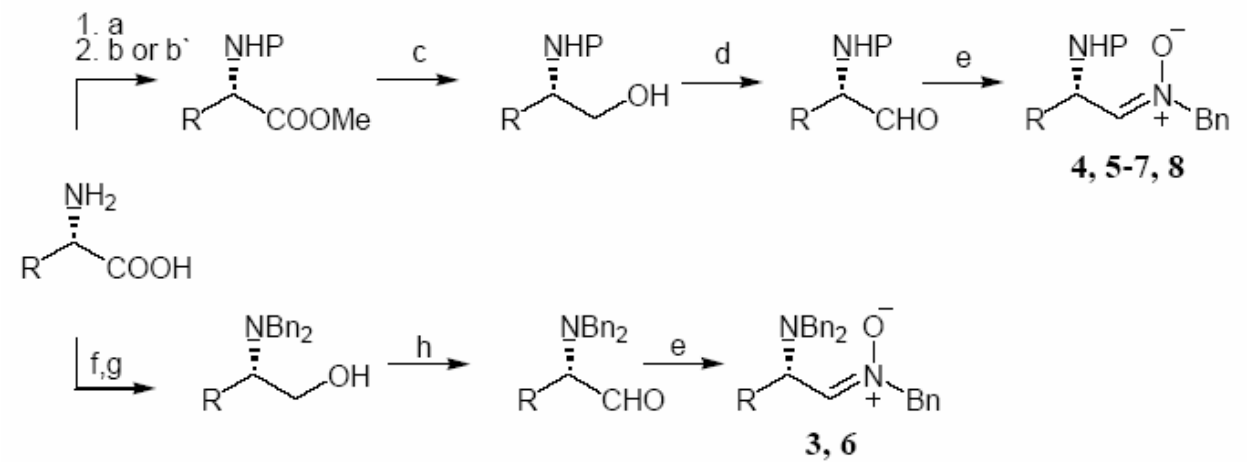
The *N*-Boc, Cbz-protected α-amino alcohols were prepared by LiBH4 or NaBH4 – LiCl reduction of the corresponding methyl esters. TEMPO – 2,2,6,6-tetramethylpiperidin-1-yloxy radical with NaOCl was used as the oxidizing reagent in the next step.[13] The *N*-Bn2-protected α-amino alcohols were prepared from corresponding parent amino alcohols by the methode of Beaulieu and Wernic.[14] Pyridine-sulfur trioxide was used as the oxidizing reagent in the Swern oxidation (results are given in Table 1).



Scheme 1

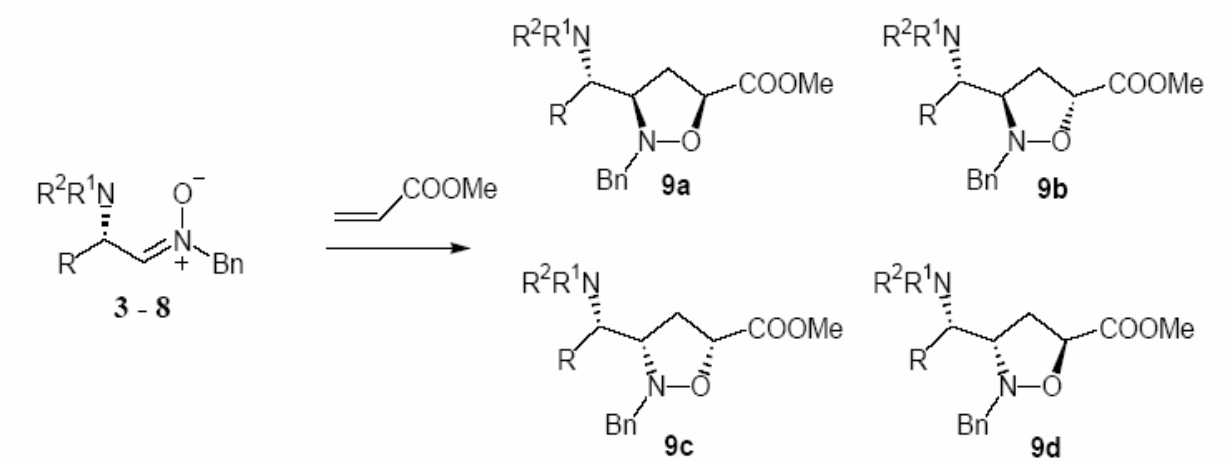
Reagents and reaction conditions: (a) $SOCl_2$, MeOH, -78ºC; (b)CbzCl, $NaHCO_3$, AcOEt, 0ºC; (b`) Boc_2O, $NaHCO_3$, RT; (c) $LiBH_4$, EtOH-THF, 0ºC; (d) TEMPO, NaOCl, NaBr, $NaHCO_3$, H_2O, toluene AcOEt, 0ºC;(e) BnNHOH, $MgSO_4$, CH_2Cl_2, RT; (f) $NaBH_4$, H_2SO_4, RT; (g) BnBr, K_2CO_3, EtOH; (h) $Pyr.SO_3$, DMSO, Et_3N, 15ºC.

Table 1. Synthesis of chiral amino acid - derived nitrones **3-8**

Entry	Nitrone	α-Amino Acid	NH_2 - Protecting group	Yield %[1]	Yield %[2]
1	**3**	L-phenylalanine	Bn_2	86	87
2	**4**	L-phenylalanine	Cbz	67	85
3	**5**	L-phenylalanine	Boc	70	83
4	**6**	L-valine	Bn_2	72	80
5	**7**	L-valine	Cbz	65	79
6	**8**	L-valine	Boc	71	77

[1] Overall yield from amino acid to amino alcohol. [2] Overall yield from amino alcohol to nitrone.

Next, we report some examples of the 1,3-dipolar cycloaddition of chiral nitrones **3-8** with acrylic acid methyl ester with purpose to apply their cycloadducts to the synthesis of γ-substituted β,γ-diamino acids (Scheme 2). Our objective was the study of diastereoselectivity of cycloadditions stemming from the nitrone part. The cycloadditions afforded the corresponding diastereomeric isoxazolidines **9a-d** as a mixture of four diastereoisomers in a good overall yield (Table 2). The regioselectivity of cycloaddition was high, indeed 5-substituted isoxazolidines were formed exclusively. The stereoselectivity of cycloaddition was dependent on minor structural changes in starting nitrone as well as to the reaction conditions (refluxing toluene or at high pressure,[15] 10 Kbar in toluene at 60 °C or RT, Table 2).



Scheme 2

Table 2. 1,3-Dipolar cycloaddition of chiral amino acid - derived nitrones to acrylic acid methyl ester

Entry	Nitrone	Reaction condition	Ratio[a]	Yield %
1	**3**	RT, 1.5 d., toluene, 10 Kbar	62:14:13:11	94
2	**3**	60 °C, 1.5 d., toluene, 10 Kbar	60:16:14:10	90
3	**3**	110 °C, 1h., toluene	60:15:13:12	89
4	**4**	RT, 2 d., CH_2Cl_2, 10 Kbar	45:26:19:10	87
5	**4**	60 °C, 2 d., CH_2Cl_2, 10 Kbar	48:24:21:6	82
6	**4**	60 °C, 2 d., toluene, 10 Kbar	51:21:21:7	89
7	**5**	RT, 2 d., toluene, 10 Kbar	47:27:13:13	76
8	**5**	60 °C, 2 d., toluene, 10 Kbar	50:28:12:10	78
9	**5**	60 °C, 2 d., CH_2Cl_2, 10 Kbar	47:-:29:24	80
10	**5**	110 °C, 1h., toluene	58:21:11:10	88
11	**6**	RT, 2 d., toluene, 10 Kbar	54:19:14:13	84

Table 2. Continued

12	**6**	60 °C, 2 d., toluene, 10 Kbar	52:20:15:13	80
13	**6**	110 °C, 1h., toluene	49:25:15:11	90
14	**7**	RT, 2 d., CH_2C_2, 10 Kbar	57:31:7:5	85
15	**8**	110 °C, 1h., toluene	53:27:12:8	92

[a] The ratio of diastereoisomers was determined from ^{13}C NMR spectra

The detailed study of the stereoselectivity of these cycloadditions and elucidation of the structures of the obtained cycloadducts is in progress.

Experimental Section

General Procedures. All starting materials and reagents are commercially available (Fluka, Merck or Avocado) and were used without further purification. Solvents were dried before use. Thin-layer chromatography (TLC, on aluminium plates coated with silica $60F_{254}$, 0.25 mm thickness, Merck) was used for monitoring of reaction courses; eluents are given in the text. For column chromatography done the flash chromatography technique was employed using silica 60 (0.040 – 0.063 mm, Merck). Melting points (m.p.) were determined on a Kofler hot plate apparatus. The ^1H and ^{13}C NMR spectra of deuterochloroform solutions were obtained using Varian VXR 300 (300 MHz) and Bruker DRX-400 (400 MHz) instruments, tetramethylsilane being the internal reference. Optical rotations [α] were measured on an IBZ Messtechnik Polar-LμP polarimeter at the sodium D line (589 nm) using a 1 dm cell with chloroform as solvent. *N*-Protected alcohols were prepared according to the already published procedures. analytical and spectral data for *N*-protected alcohols were identical with those already published.[14]

TEMPO oxidation of alcohols to aldehydes. General procedure

To a cold (0 °C), rapidly stirred biphasic mixture consisted of an alcohol (1 mmol), TEMPO free radical (0.02 mmol), NaBr (1 mmol), toluene (3 mL), ethyl acetate (3 mL) and water (0.5 mL), an aqueous solution of NaOCl (1.1 mmol) containing $NaHCO_3$ (2.9 mmol) was added dropwise over a period of 1-2 h. The aqueous layer was separated and washed with Et_2O (5 mL). The combined organic layers were washed with a solution of KI (8 mg), dissolved in 10% aqueous $KHSO_4$ (2 mL), then with 10% aqueous sodium thiosulfate (1 mL), brine (2 mL) and dried (Na_2SO_4). Filtration and concentration in vacuo afforded a desired aldehyde which was immediately used for further reactions.

Swern oxidation of alcohols to aldehydes. General procedure

By the method of Beaulieu and Wernic, pyridine-sulfur trioxide complex (1.7 mmol) in DMSO (10 mL) was added in small portions over 10-20 mins to a solution of an alcohol (1 mmol) and Et_3N (1.9 mmol) in DMSO (10 mL) at 0 °C. The mixture was allowed to warm to 15 °C, and after 2 h the reaction was quenched with ice water (20mL) and extract with CH_2Cl_2 (3 x 15 mL). The extracts were washed with water (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a crude aldehyde,which was immediately used for further reactions.

Synthesis of α-amino nitrones. General procedure

To a well-stirred solution of the corresponding α-amino aldehyde (1 mmol) in dichloromethane (10 mL), anhydrous magnesium sulfate (1.5 mmol) and *N*-benzylhydroxylamine (1 mmol) were added sequentially and resulting mixture wasstirred at RT overnight. Filtration and concentration *in vacuo* afforded a crude product which was purified by columm chromathography on silica gel to yield the pure product (eluent : EtOAc/*i*-hexane).

(*Z*)-*N*-[(2*S*)-2-(Benzyloxycarbonylamino)-3-phenylpropylidene] benzylamine *N*-oxide (4). Colourless crystals m. p. = 145-147 °C, $[\alpha]_D^{25}$ = + 25.5 (c = 1.0, $CHCl_3$), R*f* = 0.18 (EtOAc/*i*-hexane 50:50). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.15 (m, 2H, H-3), 4.75 (m, 1H, H-2), 4.85(s, 2H, $COOCH_2Ph$, 5.10 (s, 2H, NCH_2Ph), 6.28 (d, *J* = 6.4 Hz, 1H, H-NH), 6.76 (d, *J* = 5.3 Hz, 1H, H-1), 7.40-7.12 (m, 10H, H-Ph); ^{13}C NMR ($CDCl_3$, 50 MHz): δ36.9 (C-3), 50.9 (C-2), 67.4, 70.3 (2C-*C*H_2Ph), 127.3, 128.5, 128.6, 129.0, 129.1, 129.5, 129.7, 129.9 (15C, 2-6CPh), 132.8 (C-1), 136.9 (C, 1-CPh), 137.5 (2C, 1-CPh), 156.3 (C=O).

(*Z*)-*N*-[(2*S*)-2-(*tert*-Butoxycarbonylamino)-3-phenylpropylidene] benzylamine *N*-oxide (5). Colourless crystals m. p. = 128-130 °C, $[\alpha]_D^{25}$ = + 32.6 (c = 1.0, $CHCl_3$), R*f* = 0.22 (EtOAc/*i*-hexane 50:50). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.43 (s, 9H, $C(CH_3)_3$), 3.14 (m, 2H, H-3), 4.68 (ddd, *J* = 7.3, 6.7, 5.7 Hz, 1H, H-2), 4.87 (s, 2H, CH_2Ph), 5.95 (bs, 1H, H-NH), 6.75 (d, *J* = 5.7 Hz, 1H, H-1), 7.40, 7.27, 7.14 (3xm, 10H, H-Ph); ^{13}C NMR($CDCl_3$, 50 MHz): δ20.3 ($C(CH_3)_3$), 36.9 (C-3), 50.5 (C-2), 70.3 (C-*C*H_2Ph), 80.3 ($C(CH_3)_3$), 127.2, 129.0, 129.4, 129.6, 129.7, 129.9(10C, 2-6CPh), 132.9 (C-1), 137.8, 138.0 (2C, 1-CPh), 155.4 (C=O).

(*Z*)-*N*-[(2*S*)-2,2-(Dibenzylamino)-3-phenylpropylidene] benzylamine *N*-oxide (3). Colourless crystals m. p. = 109-110 °C, $[\alpha]_D^{25}$ = + 100.5 (c = 1.0, $CHCl_3$), R*f* = 0.26 (EtOAc/*i*-hexane 50:50). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.94, 3.07 (2 x dd, *J* = 8.5, 6.7, 14.0 Hz, 2 x 1H, H-3), 3.63, 3.87 (2 x d, *J* = 13.7 Hz, 2 x 2H, 2 x CH_2Ph), 4.55 ("q", ddd, *J* = 7.0 Hz, 1H, H-2), 4.85 (2 x d, *J* = 13.4 Hz, 2H, CH_2Ph), 6.77 (d, *J* = 7.3 Hz, 1H, H-1), 7.41-7.12 (m, 20H, H-Ph); ^{13}C NMR (CDCl3, 100 MHz): δ35.9 (C-3), 55.5 (2C-*C*H_2Ph) 57.5 (C-2), 70.3 (C-*C*H_2Ph), 126.6, 127.4, 128.6, 128.7, 128.8, 129.1, 129.3, 129.4, 129.5, 129.7, 129.9(20C, 2-6C_{Ph}), 133.4 (C-1), 138.7 (2C, 1-C_{Ph}), 139.7 (2C, 1-C_{Ph}).

(*Z*)-*N*-[(2*S*)-2-(Benzyloxycarbonylamino)-3-methylbutylidene] benzylamine *N*-oxide (7). Colourless crystals, m. p. = 153-154 °C, $[\alpha]_D^{25}$ = + 12.8 (c = 0.5, $CHCl_3$), R*f* = 0.10 (EtOAc/*i*-

hexane 50:50) ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.95, 0.92 (2xd, *J* = 7.9 Hz, 2 x 3H, H-4,4′), 2.39 (m, 1H, H-3), 4.26 (ddd, *J* = 7.9, 5.5, 8.9 Hz 1H, H-2), 4.90, 5.12 (2 x s, 2 x 2H, 2 x CH_2Ph), 6.55 (d, *J* = 8.9 Hz, 1H, H-NH), 6.85 (d, *J* = 5.5 Hz, 1H, H-1), 7.41-7.36 (m, 10H, H-Ph); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.7, 20.2 (2C-4, 4′), 30.8 (C3), 55.3 (C-2), 67.4, 70.5 (2C-*C*H_2Ph), 128.5, 128.9, 129.6, 129.7, 129.9 (10C, 2-6CPh), 132.8 (C-1), 137.4, 137.5 (2C, 1-CPh), 156.3 (C=O).

(*Z*)-*N*-[(2*S*)-2-(*tert*-Butoxycarbonylamino)-3-methylbutylidene] benzylamine *N*-oxide (8). Colourless crystals, m. p. = 98-100 °C, $[\alpha]_D^{25}$ = + 15.7 (c = 1.0, $CHCl_3$), R*f* = 0.12 (EtOAc/*i*-hexane 50:50) ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.87, 0.91 (2xd, *J* = 6.8 Hz, 2 x 3H, H-4,4′), 1.41 (s, 9H, H- $C(CH_3)_3$), 2.30 (m, 1H, H-3), 4.16 (m, 1H, H-2), 4.87 (s, 2H, CH_2Ph), 6.18 (bs, 1H, H-NH), 6.85 (d, *J* = 5.4 Hz, 1H, H-1), 7.38 (m, 15H, H-Ph); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.7, 19.1 (2C-4, 4′), 28.3 ($C(CH_3)_3$), 30.2 (C-3), 54.2 (C-2), 69.8 (C-*C*H_2Ph), 79.3 ($C(CH_3)_3$), 128.9, 129.2, (5C, 2-6C_{Ph}), 132.7 (C-1), 137.7 (C, 1C_{Ph}), 155.8 (C=O).

(*Z*)-*N*-[(2*S*)-2-(Dibenzylamino)-3-methylbutylidene] benzylamine *N*-oxide (6). Colourless crystals, m. p. = 102-104 °C, $[\alpha]_D^{25}$ = - 26.0, (c = 1.0, $CHCl_3$), R*f* = 0.13 (EtOAc/*i*-hexane 50:50) ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.77, 1.03 (2xd, *J* = 6.7 Hz, 2 x 3H, H-4,4′), 1.90 (m, 1H, H-3), 3.49, 3.80 (2 x d, *J* = 13.4 Hz, 2 x 2H, 2 x CH_2Ph), 3.89 (“t“, dd, *J* = 9.6 Hz, 1H, H-2), 4.96 (s, 2H, CH_2Ph), 6.73 (d, *J* = 8.8 Hz, 1H, H-1), 7.40 (m, 15H, H-Ph); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.5, 20.7 (2C-4, 4′), 30.2 (C-3), 55.5 (2C-*C*H_2Ph) 61.2 (C-2), 70.8 (C-*C*H_2Ph), 126.9, 127.3, 128.5, 128.9, 129.0, 129.3, 129.4, 129.9 (15C, 2-6C_{Ph}), 134.6 (C, 1-C_{Ph}) 140.4 (C-1).

General procedure for high pressure cycloadditions[15]

Reactions of nitrones with dipolarophiles were carried out at RT or 60 °C in toluene or in CH_2Cl_2 for several days under 10 Kbar pressure. The reaction mixture (1 mmol of nitrone, 2 mmol of dipolarophile and 0.5 mL of solvent) was placed in a Teflone ampoule which was inserted into the high-pressure vessel filled with hexane as a transmission medium. After decompression, the mixture was purified by flash columm chromathography.

General procedure for atmospheric pressure cycloadditions

To a stirred solution of the nitrone 1a (1.0 mmol) in toluene (5 mL) was added acrylic acid methyl ester, (2 mmol), and the solution was heated at reflux (110 °C) for 2 h. The resulting mixture was evaporated under reduced pressure. The crude mixture was purified and separated by column chromatography on silica gel.

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