Synthetic Communications

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Gregory H PRoos & Sundari Balasubramaniam (1998) Synthesis of α-Amino Phosphonates Under Diastereocontrol by Imidazolidin-2-One Auxiliaries, Synthetic Communications, 28:20, 3877-3884, DOI: 10.1080/00397919808004941

To link to this article: http://dx.doi.org/10.1080/00397919808004941

Published online: 23 Aug 2006.

SYNTHETIC COMMUNICATIONS, 28(20), 3877-3884 (1998)

SYNTHESIS OF α-AMINO PHOSPHONATES UNDER DIASTEREOCONTROL BY IMIDAZOLIDIN-2-ONE AUXILIARIES

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ABSTRACT : Ephedrine derived (4*R*,5*S*)-imidazolidin-2-one auxiliaries demonstrate phenomenal diastereocontrol in the addition of phosphite to chiral imine derivatives.

A focus of our research programme has been to extend the utility of the ephedrine-derived imidazolidin-2-one **1**. Features such as the ease of preparation, high stability and crystallinity, allied with the ease of cleavage and recycling have recently been reviewed.[1] In addition, the steric and electronic nature of the primary controlling C4-substituent may be readily modified by hydrogenation of the phenyl moiety to give the more sterically demanding cyclohexyl analogue **2**.[2]

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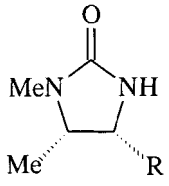
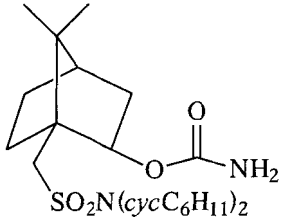
One target of this work was the stereoselective synthesis of α-amino phosphonates via the addition of diethylphosphite to imines, modified by auxiliaries **1** and **2**. α-Amino phosphonic acids have been reported to serve as important surrogates for α-amino carboxylic acids and, as such, they have been the target of diverse synthetic approaches.[3] This, along with the recent appearance of a directly related publication,[4] prompts us to report our results in this area. In their study, Chung and Kang investigated the efficiency of a range of chiral auxiliaries in controlling the stereoselectivity of the phosphite addition step. They found that the greatest levels of stereoselection were obtained with the carbamate based on the relatively labour-intensive Oppolzer camphorsulfonamide auxiliary **3** (Scheme, X = **3**).[5]



1 R = Ph = $\mathbf{X_p}$
2 R = *cyc*C_6H_{11} = $\mathbf{X_c}$

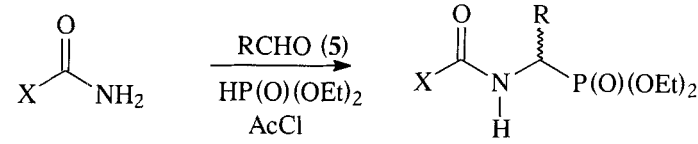


3

We now report the synthesis of the analogous urea derivatives **4** of the auxiliaries **1** and **2**, and their subsequent application in the stereoselective, one-pot, formation of α-aminophosphonates (Scheme). The results of these reactions

are collected in the Table. As might be anticipated, the poorest diastereomeric excess was obtained in the low sterically demanding case of acetaldehyde (leading to **6c**) where facial discrimination in the intermediate *N*-acylimine is most challenging.

Scheme



4 a X = X_p
b X = X_c

6 a-d

Table: Stereoselective α-Amino Phosphonate Formation

Urea	R	Yield 6 (%)[a]	d.r.%[b]	$[\alpha]_D$
4a	Ph	**6a** (70)	>100:1	-48.4
4b	Ph	**6b** (52)	>100:1	-1.2
4a	Me	**6c** (42)	66:34	-6.4
4a	*p*-NO_2Ph	**6d** (68)	>100:1	-19.1

[a] Isolated yield after recrystallization. [b] As determined by HPLC on a silica column

A correlation of the absolute sense of stereochemistry of the α-aminophosphonates was provided by hydrolysis of **6a** to give the corresponding phosphophenylglycine. This product gave a rotation that is in agreement with reported values for the (S)-configuration, and is consistent with frontside attack of the phosphorous nucleophile on the *s-cis/E* conformation of the *N*-acylimine intermediate.

EXPERIMENTAL:

General: The imidazolidin-2-one auxiliaries **1** and **2** were prepared as previously described.[6] Other reagents were obtained commercially and used without further purification. Melting points are reported uncorrected. All N.M.R. spectra were recorded on a Bruker ADVANCE DPX 300 spectrometer at 25°C in $CDCl_3$, unless otherwise indicated.

General Procedure I: Preparation of Ureas (4)

A stirred solution of the appropriate imidazolidin-2-one (1 equiv.) in dry THF was treated with *n*-BuLi at 0°C. After 30 min, ethyl chloroformate (1 equiv.) was added and the mixture stirred for 1 hr at 0°C before quenching with saturated $NaHCO_3$. The THF was removed under reduced pressure and the residue partitioned between H_2O and CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated to give the crude ethyl formate derivative. This intermediate was taken up in further THF and treated with excess concentrated aqueous NH_3 (≈25 equiv) and the mixture stirred at room temperature overnight. The white precipitated product was filtered, washed with H_2O, and recrystallized from EtOAc.

(4R,5S)-1,5-Dimethyl-3-formamido-4-phenylimidazolidin-2-one (4a)

According to General Procedure I, imidazolidin-2-one **1** (5.00g, 26.3mmol) gave the product **4a** as a white solid (5.8g, 95%), m.p. 240°C. $[\alpha]_D$ –2.3° (*c* 1.0,

CH_2Cl_2). Found: C, 61.71; H, 6.49; N, 17.96. $C_{12}H_{15}N_3O_2$ requires C, 61.79; H, 6.48; N, 18.01%. δ_H 0.84 (3H, d, *J* 6.6 Hz), 2.80 (3H, s), 3.85 (1H, dq, *J* 6.6 and 8.7 Hz), 4.95 (1H, br s), 5.30 (1H, d, *J* 8.7 Hz), 7.10-7.40 (5H, m), 8.1 (1H, br s). δ_C 14.8, 28.2, 54.5, 59.0, 126.8, 128.1, 128.5, 136.7, 153.7, 157.7

(4R,5S)-4-Cyclohexyl-1,5-dimethyl-3-formamidoimidazolidin-2-one **(4b)**

According to General Procedure I, imidazolidin-2-one **2** (5.00g, 25.5mmol) gave the product **4b** as a white solid (5.8g, 95%), m.p. 130°C. $[\alpha]_D$ –1.1° (*c* 1.0, CH_2Cl_2). Found: C, 60.21; H, 8.86; N, 17.61. $C_{12}H_{21}N_3O_2$ requires C, 60.23; H, 8.84; N, 17.56%. δ_H 0.82-1.36 and 1.52-1.82 (11H, m), 1.32 (3H, d, *J* 7Hz), 2.76 (3H, s), 3.76 (1H, dq, *J* 7 and 9 Hz), 4.33 (1H, dd, *J* 7 and 3 Hz), 4.95 (1H, br s), 8.1 (1H, br s). δ_C 11.1, 24.2, 24.3, 25.0, 25.6, 26.0, 29.1, 37.4, 53.5, 56.8, 152.3, 156.4

General Procedure II: Preparation of α-Amino Phosphonates (6)

To a mixture of urea **4** (1mmol), diethyl phosphite (1.5mmol), and acetyl chloride (5ml) at 0°C under dry argon, was added the aldehyde (1.5mmol) over 10 min. The reaction mixture was stirred at this temperature for 30 min, and then for 1 hr at room temperature. Volatile components were removed under vacuum and the oily residue dissolved in EtOAc. The organic phase was sequentially washed with sat. $NaHCO_3$ and H_2O, dried ($MgSO_4$), and reduced under vacuum

to give the crude product. Diastereomeric purity was checked by HPLC (Silica column; Eluant: 0.1% MeOH in EtOAc) prior to flash chromatography.

***(4S,5R)-1-[N-(R)-(α-diethylphosphanato)benzyl]carboxamido-3,4-dimethyl-5-phenylimidazolidin-2-one* (6a)**

According to General Procedure II, urea **4a** (233mg) and benzaldehyde gave the product **6a** as white needles (321mg, 70%), m.p. 110°C (EtOAc/hexane). $[\alpha]_D$ – 48.4° (*c* 0.3, CH_2Cl_2). Found: C, 60.08; H, 6.59; N, 9.12 $C_{23}H_{30}N_3O_5P$ requires C, 60.12; H, 6.58; N, 9.15%. δ_H 0.80 (3H, d, *J* 6.6Hz), 1.10-1.20 (6H, dt, *J* 7Hz), 2.84 (3H, s), 3.75-4.10 (5H, m), 5.20 (1H, d, *J* 8.8Hz), 5.25-5.40 (1H, m), 7.15-7.45 (10H, m), 9.30 (1H, br s). δ_C 14.8, 16.1, 28.1, 49.8, 51.8, 54.5, 59.2, 62.9, 126.9, 127.8, 127.9, 128.1, 128.4, 128.5, 135.3, 136.7, 151.9, 157.7

***(4S,5R)-1-[N-(R)-(α-diethylphosphanato)benzyl]carboxamido-5-cyclohexyl-3,4-dimethylimidazolidin-2-one* (6b)**

According to General Procedure II, urea **4b** (239mg) and benzaldehyde gave the product **6b** as a colourless oil (242mg, 52%). $[\alpha]_D$ –1.2° (*c* 1.0, CH_2Cl_2). Found: C, 59.32; H, 7.81; N, 9.11 $C_{23}H_{36}N_3O_5P$ requires C, 59.34; H, 7.79; N, 9.03%. δ_H 0.82-1.36 and 1.52-1.82 (11H, m), 1.33 (3H, d, *J* 7Hz), 2.76 (3H, s), 3.80-4.20 (5H, m), 3.78-4.23 (2H, m), 7.15-7.40 (5H, m), 9.30 (1H, br s). δ_C 12.8, 26.1, 26.2, 26.8, 27.5, 27.8, 29.6, 39.1, 54.7, 58.5, 62.3, 154.3, 158.2.

***(4S,5R)-1-[N-(R)-(α-diethylphosphanato)ethyl]carboxamido-3,4-dimethyl-5-phenylimidazolidin-2-one* (6c)**

According to General Procedure II, urea **4a** (233mg) and acetaldehyde gave the product **6c** as white needles (169mg, 42%), m.p. 102°C (EtOAc). $[\alpha]_D$ –6.4° (*c* 0.58, CH_2Cl_2). Found: C, 59.61; H, 8.53; N, 10.45 $C_{18}H_{34}N_3O_5P$ requires C, 53.59; H, 8.49; N, 10.41%. δ_H 0.90 (3H, d, *J* 6.6Hz), 1.10-1.20 (6H, dt, *J* 7Hz), 2.84 (3H, s), 3.75-4.10 (5H, m), 5.20 (1H, d, *J* 8.8Hz), 5.25-5.40 (1H, m), 7.15-7.40 (5H, m), 9.30 (1H, br s). δ_C 14.8, 16.5, 20.8, 28.1, 49.3, 51.6, 54.6, 59.8, 62.2, 126.8, 127.8, 128.9, 135.3, 151.3, 157.6

***(4S,5R)-1-[N-(R)-(α-diethylphosphanato)p-nitrobenzyl]carboxamido-3,4-dimethyl-5-phenylimidazolidin-2-one* (6d)**

According to General Procedure II, urea **4a** (233mg) and *p*-nitrobenzaldehyde gave the product **6d** as a colourless oil (347mg, 68%). $[\alpha]_D$ –19.1° (*c* 0.86, CH_2Cl_2). Found: C, 54.03; H, 6.86; N, 10.91 $C_{18}H_{34}N_3O_5P$ requires C, 54.11; H, 6.91; N, 10.97%. δ_H 0.80 (3H, d, *J* 6.6Hz), 1.10-1.25 (6H, dt, *J* 7Hz), 2.84 (3H, s), 3.75-4.10 (5H, m), 5.25 (1H, d, *J* 8.8Hz), 5.35-5.50 (1H, dd, *J* 9.1 and 13.4Hz), 7.15-8.30 (9H, m), 9.40 (1H, br s). δ_C 14.8, 16.1, 28.1, 49.8, 51.8, 54.5, 59.3, 62.9, 126.9, 127.8, 127.9, 128.1, 128.4, 128.5, 135.3, 136.7, 151.9, 157.7

(S)-(-)-Phosphophenylglycine

Diester **6a** (115mg) was stirred with 8N HCl (5ml) at 25°C for 12 hrs and then

poured into EtOAc (20ml). The organic layer was dried ($MgSO_4$) and the solvent removed. Chromatography of the crude residue (Silica gel; 2% MeOH/EtOAc) afforded the product as a white solid (32mg, 47%), m.p. 272°C. $[\alpha]_D$ –17.4° (*c* 0.2, 1N NaOH), lit[4] $[\alpha]_D$ –17.8° (*c* 1.0, 1N NaOH).

ACKNOWLEDGEMENTS: The authors thank Murdoch University for financial support (MRG for GHPR and OSPR for SB).

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(Received in the USA 27 April 1998)