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Synthesis of new α-heterocyclic α-aminoesters

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Summary. α-Heterocyclic α-aminoesters were obtained in good yields by reaction of a glycine cation equivalent and different heterocyclic nucleophiles; diastereoselectivity using a carbohydrate (galactopyranose) as N-protecting group was modest.

Keywords: Heterocyclic α-aminoesters – Chiral auxiliary – Galactopyranose

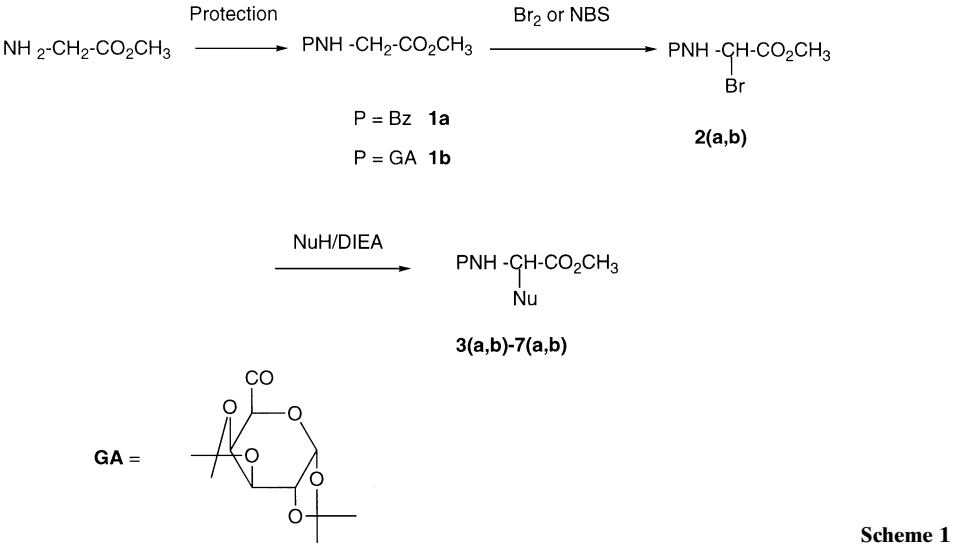
Introduction

Heterocyclic amino acids present a large spectrum of biological activities (Schenk and Werner, 1991; Monn et al., 1993; Lee et al., 1999) and are of special interest to biochemistry, ecology and neurochemistry. Several papers were published concerning these compounds (Murray et al., 1998; Kim et al., 1999; Ferreira et al., 1999; Welch and Phillips, 1999; Pajouhesh and Curry, 1998; Barbaste et al., 1998). For example L-quisqualic acid (Fletcher and Lodge, 1996) present in Quisqualis species (*Combretaceae*) is a neuroexcitatory amino acid, agonist at metabotropic receptors (m-GluRs) and is also used as a vermicide in Chinese medicine; (S)-2-amino-3-(5-methyl-3-hydroxy isoxazol-4-yl) propanoïc acid (AMPA) is a selective AMPA receptor antagonist (Jane et al., 1997; Bettler and Mulle, 1995) and 1H-tetrazol-5-yl glycine is a selective NMDA receptor agonist (Schoepp et al., 1991). β-(3-amino-1,2,4-triazol-1-yl)-L-alanine is a metabolite of the herbicide 3-amino-1,2,4-triazole (Ikegami and Murakoshi, 1994) and pyrazolylalanine presents an hypoglycemic activity (Dunnil and Fowden, 1965). Continuing our work concerning the obtention of heterocyclic carboxylic and phosphonic α-amino acids (Alami et al., 1998; Achamlale et al., 1997; Achamlale et al., 1999) we report here the synthesis of α-heterocyclic α-aminoesters.

Results

Synthetic equivalents of amino acid α-cation synthons have enormous potentiel in the synthesis of a wide range of amino acids, peptides and other nitrogen-containing compounds (Bailey et al., 1996; Duthaler, 1994) and we have applied this methodology using heterocycles as nucleophiles and α-bromo glycine derivatives **2a** and **2b** (Scheme. Carbohydrates constitute a class of inexpensive natural products of high chiral content and we want to explore the stereochemical control of the carbohydrate derivative in asymmetric synthesis. Action of benzoyl chloride on methyl glycinate in CH_2Cl_2 in the presence of NEt_3 gave compound **1** in 90% yield. Oxidation of 1, 2 : 3, 4-di-*O*-isopropylidene α-D-galactopyranose (Tipson et al., 1963) by potassium permanganate in basic medium gave the acid which was coupled with methylglycinate in the presence of BOP reagent.

(1H-(Benzotriazol-1-yloxy)tris (dimethylamino) phosphonium hexafluorophosphate) (Castro et al., 1975) to afford N-protected methyl glycinate **1b** in 85% yield. Bromination of **1a** and **1b** using Steglich's method (Kobler and Steglich, 1983) gave **2a** and **2b** in 90% and 92% yields respectively which were used without purification.



Scheme 1

Table 1. Synthesis of α-heterocyclic α-aminoesters

Compound	P	Nu-H	Yield %	d.e. %
3a	Bz	benzimidazole	83	
3b	GA	–	78	41
4a	Bz	pyrazole	84	
4b	GA	–	56	33
5a	Bz	imidazole	81	
5b	GA	–	69	36
6a	Bz	1,2,4-triazole	69	
6b	GA	–	55	30
7a	Bz	imidazolidinone	75	
7b	GA	–	74	25

Reaction of different heterocyclic nucleophiles (benzimidazole, pyrazole, imidazole, 1,2,4-triazole and imidazolidinone) on **1a** and **1b** were conducted at room temperature in acetone in the presence of DIEPA (diisopropylethylamine); results are summarized in the Table 1.

Chemical yields were fair to good starting from **1a** or **1b**. Using galactopyranose derivative as N-protecting group and chiral auxiliary, the diastereoisomeric compounds were inseparable by silica gel column chromatography and diastereomeric excess determined by ^{1}H NMR (methoxy signals) was modest.

In conclusion a new access to α-heterocyclic α-aminoesters has been investigated; this process should allow the rapid preparation of a number of compounds in good yields. However, galactopyranose derivative used as N-protecting group and chiral auxiliary afforded disappointing results concerning diastereoisomeric excesses.

Experimental section

Melting points determined on electrothermal apparatus are uncorrected. Column chromatography was performed on silica gel 60 (Merck 230–400 mesh) and reactions were monitored on Kieselgel 60F254 (Merck), detection was effected by examination under UV light. ^{1}H NMR spectra were recorded at 250 MHz; Mass spectra were performed on a JEOL JMX DX 300.

Oxidation of 1,2 : 3,4-di-O-isopropylidene-α-D-galactopyranose: 1,2 : 3,4-di-O-isopropylidene-α-D-galactopyranose (1 mmol) was added at a NaOH solution (3 mmol in 6 ml H_2O). After stirring 15 min. at room temperature, $KMnO_4$ solution (1.5 mmole in 8 ml H_2O) was added, the mixture was stirred for 12 h and MnO_2 was filtered off. The filtrate was extracted with ethyl acetate (3×25 ml). The aqueous layer was acidified using diluted sulfuric acid and extracted with ethyl acetate (3×25 ml). The combined organic phases were dried ($MgSO_4$) and the solvent was removed under reduced pressure.

Yield: 80%. m.p. 156–158°C (diethyl ether/hexane)

^{1}H NMR ($CDCl_3$) δ: 1.30 (s, 3H); 1.32 (s, 3H); 1.35 (s, 3H); 1.41 (s, 3H); 4.35–4.75 (m, 4H); 5.65 (d, 1H, J = 7.00 Hz); 7.70 (s, 1H).

Coupling reaction was performed using Castro's method (Castro et al., 1975) to afford compound **1b**.

Yield: 85%

^{1}H NMR ($CDCl_3$) δ: 1.31 (s, 3H); 1.32 (s, 3H); 1.36 (s, 3H); 1.40 (s, 3H); 3.74 (s, 3H); 4.00–4.70 (m, 6H); 5.60 (d, 1H, J = 5.00 Hz); 7.10 (s, 1H)

Compound **2b** was obtained by bromination of **1b** using Steglich's method (Kober and Steglich, 1983)

Yield: 92%

^{1}H NMR ($CDCl_3$) δ: 1.30–1.75 (m, 12H); 3.90 (s, 3H); 4.35–4.80 (m, 4H); 5.66 (d, 1H, J = 5.00 Hz); 6.50 (d, 1H, J = 10.00 Hz); 7.80 (d, 1H, J = 10.00 Hz)

Reaction of nucleophiles on **2** (General method)

To a solution of N-protected methyl bromoglycinate (2.6 mmole) and diisopropylethylamine (3.12 mmol) in acetone (10 ml) was added the nucleophile (2.86 mmole). The mixture was stirred at room temperature during 12 h. The solvent was removed under reduced pressure, the residue was dissolved in $CHCl_3$ (20 ml) and washed three times with a NH_4Cl saturated solution. The organic phase was dried (Na_2SO_4), the solvent was removed and the crude

product was chromatographed on silica gel using a mixture ethyl acetate/hexane (1/1)
Compound **3a**: Yield: 83%. m.p. 124–126°C (ethyl acetate/diethyl ether)
^{1}H NMR ($CDCl_3$) δ: 3.70 (s, 3H); 7.05–7.90 (m, 10H); 8.45 (s, 1H); 9.70 (d, 1H, J = 6.35 Hz).
M.S. (FAB^+): 310 $(M + H)^+$
Compound **3b**: Yield: 78% (oil)
^{1}H NMR ($CDCl_3$) δ: 1.10–1.50 (m, 12H); 3.75–3.78 (2s, 3H); 4.20–4.70 (m, 4H); 5.60–5.63 (2d, 1H, J = 5.00 Hz); 6.75–6.90 (m, 1H); 7.20–8.40 (m, 6H).
M.S. (FAB^+): 462 $(M + H)^+$
Compound **4a**: Yield: 84%. m.p. 117–119°C (ethyl acetate) Litt: 115–117° (Mazurkiewicz and Grymel, 1999)
^{1}H NMR ($CDCl_3$) δ: 3.85 (s, 3H); 6.25–6.35 (m, 1H): 6.00 (d, 1H, J = 7.08 Hz); 7.35–7.85 (m, 8H).
M.S. (FAB^+): 260 $(M + H)^+$
Compound **4b**: Yield: 56% (oil)
^{1}H NMR ($CDCl_3$) δ: 1.15–1.55 (m, 12H); 3.82–3.85 (2s, 3H); 4.30–4.75 (m, 4H); 5.58–5.63 (2d, J = 4.90 Hz); 6.22–6.30 (m, 1H); 6.64–6.72 (2d, 1H, J = 8.30 Hz); 7.51–7.57 (2d, 1H, J = 1.65 Hz); 7.72 (d, 1H, J = 1.65 Hz); 8.00–8.10 (m, 1H).
M.S. (FAB^+): 412 $(M + H)^+$
Compound **5a**: Yield: 81% m.p. 177–179°C (diethyl ether)
^{1}H NMR (DMSO-d_6) δ: 3.76 (s, 3H); 6.91 (m, 1H); 6.97 (s, 1H); 7.38 (s, 1H); 7.50–7.70 (m, 3H); 7.95 (m, 3H).
M.S. (FAB^+): 260 $(M + H)^+$
Compound **5b**: Yield: 69% (oil)
^{1}H NMR (DMSO-d_6) δ: 1.15–1.50 (m, 12H); 3.62–3.65 (2s, 3H); 4.10–4.70 (m, 4H); 5.60 (m, 1H); 6.49–6.52 (2d, 1H, J = 7.90 Hz); 6.90 (s, 1H); 7.25 (s, 1H); 7.84–7.87 (2s, 1H); 9.40 (m, 1H).
M.S. (FAB^+): 412 $(M + H)^+$
Compound **6a**: Yield: 69% m.p. 159–161°C (ethyl acetate)
^{1}H NMR (DMSO-d_6) δ: 3.75- (s, 3H); 7.03 (d, 1H, J = 7.18 Hz); 7.40–7,95 (m, 5H); 8.05 (s, 1H); 8.72 (s, 1H); 9.50 (m, 1H).
M.S. (FAB^+): 261 $(M + H)^+$
Compound **6b**: Yield: 55% (oil)
^{1}H NMR (DMSO-d_6) δ: 1.05–1.50 (m, 12H); 3.72–3.74 (2s, 3H); 4.20–4.77 (m, 4H); 5.67 (d, 1H, J = 5.00 Hz); 6.69–6.89 (2d, 1H, J = 8.20 Hz); 8.00–8.03 (2s, 1H); 8.60 (s, 1H); 9.25 (m, 1H).
M.S. (FAB^+): 413 $(M + H)^+$
Compound **7a**: Yield: 75%. m.p. 139–141°C (ethyl acetate/diethyl ether)
^{1}H NMR ($CDCl_3$) δ: 3.20–3.65 (m, 4H); 3.70 (s, 3H); 5.83 (d, 1H, J = 7.46 Hz); 5.91 (s, 1H); 7.25–7.90 (m, 5H); 8.17 (d, 1H, J = 7.44 Hz).
M.S. (FAB^+): 278 $(M + H)^+$
Compound **7b**: Yield: 74% (oil)
^{1}H NMR (DMSO-d_6) δ: 1.20–1.45 (m, 12H); 3.15–3.50 (m, 4H); 3,62–3.65 (2s, 3H); 4.10–4.70 (m, 4H); 5.60 (d, 1H, J = 5.00 Hz); 5.65–5.90 (2d, 1H, J = 7.70 Hz); 8.24–8.45 (2d, 1H, J = 7.70 Hz).
M.S. (FAB^+): 430$(M + H)^+$

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