Stereoselective synthesis of methyl (*S*)-2-amino-3-(6-chloro-3-ethoxycarbonylimidazo[1,2-a]pyridin-2-yl) propanoate

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Stereoselective synthesis of methyl *(S)*-2-amino-3-(6-chloro-3-ethoxycarbonylimidazo[1,2-a]pyridin-2-yl)propanoate was carried out by alkylation of (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine with ethyl 2-bromomethyl-6-chloroimidazo[1,2-a]pyridine-3-carboxylate. The latter was obtained by radical bromination of ethyl 6-chloro-2-methylimidazo[1,2-a]pyridine-3-carboxylate

Key words: imidazo[1,2-a]pyridine, Schöllkopf's auxiliary, stereoselective synthesis, α-amino acid ester

INTRODUCTION

Heteroaromatic α-amino acid derivatives are important as bioactive compounds and useful tools in developing highly selective peptide ligands. Some naturally occurring neuroexcitatory amino acids of kainoid type, such as *(S)-(-)-acromelobic acid* and *(S)-acromelobinic acid,* are derivatives of (*S*)-3-(4- and 3-pyridyl)alanine [1]. (*S*)-(3)-(2-Pyridyl)alanine [2] and (*S*)-3-(2-thienyl)alanine [3] are valuable precursors for the preparation of *Angiotesin II* and *Bradkynin*, respectively. (*S*)-3-(5-Hydroxy-2-pyridyl)alanine is known as a potent antitumor antibiotic [4].

The recent completion of the first draft of the human genome will reveal thousands of new polypeptide ligands and their receptors, thus opening unprecedented opportunities in amino acid, peptide and protein research. The aromatic and heteroaromatic moieties of the peptide side-chain groups may play important roles in the molecular recognition processes between ligands and specific receptors as well as receptor subtypes. Therefore, aromatic and heteroaromatic ring substituted unnatural α-amino acids can provide valuable tools in developing highly selective peptide ligands. As examples of such type of α-amino acids, recently synthesized derivatives of aryltryptophans [5, 6], 2-(3-isoxazolyl)- and 2-(3-thiazolyl)glycines [7, 8] could serve.

Except for glycine, α-amino acids are chiral compounds and many efforts have therefore been devoted to their preparation in enantiomerically pure form [9]. The main current method for the preparation of optically active heterocyclic α-amino acids is asymmetric synthesis using chiral reagents or auxiliaries [5–7, 10–13].

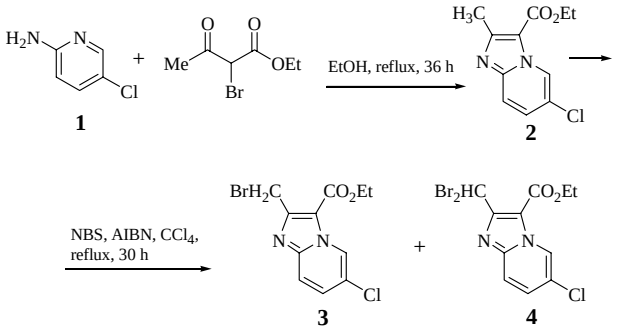
The asymmetric synthesis of β-heteroaromatic-substituted alanines was carried out by the reaction of lithiated (*2S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (Schöllkopf's auxiliary) with halogenmethyl derivatives of five- and six-membered aromatic heterocycles [13]. The scope of the present work is the preparation of β-heteroaromatic-substituted alanine derivatives containing a bicyclic imidazo[1,2-a]pyridine moiety. The imidazo[1,2-a]pyridine ring system is present in various compounds exhibiting biological activity [14, 15]. However, to our knowledge, the synthesis of β-(imidazo[1,2-a]pyridine)-substituted alanines has not yet been investigated. In the present work, the strategy for stereoselective synthesis of the target β-(imidazo[1,2-a]pyridine)-substituted alanine was based on the methodology of Schöllkopf's asymmetric α-amino acid synthesis [16].

RESULTS AND DISCUSSION

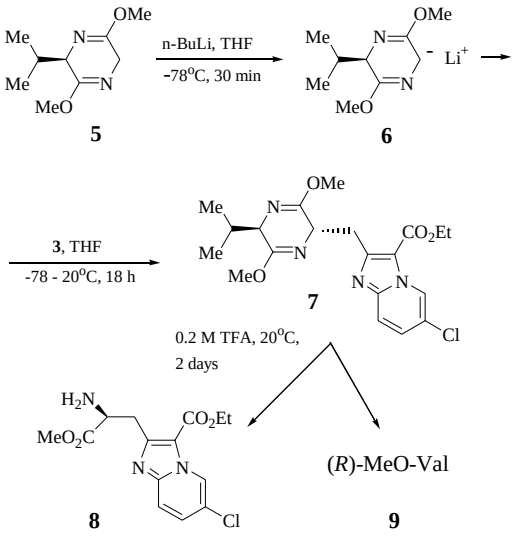
The imidazo[1,2-a]pyridine ring system can be easily obtained by the condensation of 2-aminopyridine with α-halocarbonyl compound [17]. Thus, condensation of 2-aminopyridine and ethyl 2-chloroacetoacetate proceeded smoothly to give a good yield of ethyl 2-methylimidazo[1,2-a]pyridine-3-carboxylate in one step [18]. In the present work, the starting ethyl 6-chloro-2-methylimidazo[1,2-a]pyridine-3-carboxylate **1** was synthesized analogously by the reaction of 2-amino-5-chloropyridine with ethyl 2-bromoacetoacetate.

In order to prepare bromomethylated precursor **3**, the bromination of ethyl 6-chloro-2-methylimidazo[1,2-a]pyridine carboxylate **2** was investigated. It is known that halogenation of a side chain of aromatic hydrocarbons can be easily achieved by their reaction with N-bromosuccinimide in the presence of a catalytic amount of radical initiator [19, 20]. However, similar free-radical substitution reactions of methylheterocycles very often give a mixture of bromomethyl and dibromomethyl derivatives together with ring bromo products [21–23].

The reaction of compound **2** with *N*-bromosuccinimide was carried out in reflux carbon tetrachloride with the presence of a catalytic amount of AIBN (Scheme 1). The separation of the reaction mixture by flash chromatography furnished bromomethyl derivative **3** in 40% yield and dibromomethyl derivative **4** in 2% yield. The characteristic signal in the ^{1}H NMR spectrum of compound **3** is the singlet of $BrCH_2$ group at 4.90 ppm, while the signal of the Br_2CH group of compound **4** is present at 7.51 ppm. In the ^{13}C NMR spectrum the signals of the carbon atoms of the groups mentioned above are situated at 25.22 and 31.76 ppm, respectively.



The reaction of bromomethyl derivative **3** with chiral auxiliary **5** was carried out in accordance with Schöllkopf's method of alkylation [16]. In the first stage of synthesis *(R)*-bislactim ether **5** was treated with n-BuLi at –78 °C (Scheme 2). Deprotonation at C-5 gave the almost planar dihydropyrazine anion **6** which was further treated with bromomethyl derivative **3**. According to ^{1}H NMR spectrum, the d.e. of the crude product **7** was excellent, over 95%. The absolute configuration of the introduced stereocenter was assigned in accord with the normal findings in Schöllkopf's asymmetric amino acid synthesis [16]. It is known that the isopropyl group of the valine residue imposes a strong facial bias by hindering the lower face of the enolate, thereby directing the electrophile to the upper face [24]. However, it has been previously observed [13] that for the reactions of lithiated chiral bislactim ether with bromomethyl derivatives of pyridine, thiazole, furane, isothiazole or isoxazole d.e. did not exceed 74–91%.



Therefore, highly diastereoselective alkylation of chiral dihydropyrazine anion **6** with bromomethyl derivative **3** can be attributed to steric interactions imposed by the bulky 3-(ethylcarbonyl)imidazo[1,2-a]pyridine moiety of the electrophile.

Hydrolysis of compound **7** with trifluoroacetic acid gave methyl ester of (*S*)-2-heteroarylalanine **8** together with methyl valinate **9**. Compounds **8** and **9** were readily separated by flash chromatography on silica gel. The structure of the obtained ester **8** was proved by spectral data. Absorption bands at 3400 br (NH_2), 1750 (C=O) and 1700 cm^{-1} (C=O) are observed in the IR spectrum of **8**. The ^{1}H NMR spectrum of **8** contains a characteristic pattern of alanine $CHCH_2$ group protons at 3.38 (1H, dd, J = 8.9 and 14.7 Hz), 3.61 (1H, dd, J = 4.4 and 14.7 Hz) and 4.08 ppm (1H, dd, J = = 4.4 and 8.9 Hz).

EXPERIMENTAL

All melting points were determined on a Kleinfeld melting point apparatus and are uncorrected. Infrared spectra were obtained on a Specord M80 spectrometer with KBr pellets. ^{1}H NMR spectra were measured with a Bruker DRX 500 (500 MHz) spectrometer. The ^{13}C spectra were recorded at 125 MHz using the instrument mentioned above. The chemical shifts are reported in ppm downfield from tetramethylsilane, using residual $CHCl_3$ (7.24 ppm) as reference for the proton spectra and $CDCl_3$ (77 ppm) as reference for the carbon spectra. The optical rotations were measured with a Krüss P300 electronic polarimeter at ambient temperature. For thin layer chromatographic (TLC) analyses, Merck precoated TLC plates (silica gel 60 F254) were used. Flash chromatography was performed with Silica Gel 60 (230–400 mesh) from Merck. All reagents were purchased from Aldrich Chemical Co. or Merck and used without further purification.

Ethyl 6-chloro-2-methylimidazo[1,2-a]pyridine-3-carboxylate (2). Ethyl 2-bromoacetoacetate (10.45 g, 50 mmol) was added dropwise to a solution of 2-amino-5-chloropyridine (5.00 g, 38.9 mmol) in dry ethanol (50 ml). The mixture was heated under reflux for 48 h, after which the solvent was evaporated off on a rotary evaporator. The obtained crystalline material was washed with acetone (20 ml) and dissolved in water (50 ml). The resulted solution was neutralized with saturated aqueous Na_2CO_3 solution (to pH = 8–9), the precipitated product was filtered off and dried to give 4.83 g (52%) of compound **2** as a white crystalline material, mp 121–122 °C (from ethanol). Found: C, 54.97; H, 4.86. Calculated for $C_{11}H_{11}ClN_2O_2$: C, 55.36; H, 4.65%. IR spectrum: 1700 cm^{-1} (C=O). ^{1}H NMR spectrum (500 MHz, $CDCl_3$): δ 1.49 (3H, t, J = 7.1 Hz, CH_3); 4.48 (2H, J = 7.1 Hz, CH_2); 7.38 (1H, dd, J = 2.0 and 9.4 Hz, 7-H); 7.57-7.59 (1H, m, 8-H); 9.43 (1H, m, 6-H). ^{13}C-NMR ($CDCl_3$): δ 14.84 (CH_3), 17.05 (CH_3), 60.98 (CH_2), 113.49 (C), 117.26 (CH), 122.31 (C), 126.40 (CH), 129.12 (CH), 145.54 (C), 153.62 (C), 161.60 (C=O).

Ethyl 2-bromomethyl-6-chloroimidazo[1,2-a]pyridine-3-carboxylate (3) and ethyl 2-dibromomethyl-6-chloroimidazo[1,2-a]pyridine-3-carboxylate (4). To a stirred solution of ethyl 6-chloro-2-methylimidazo[2,1-b]pyridine-3-carboxylate **2** (2.98 g, 12.5 mmol) in carbon tetrachloride (200 ml), *N*-bromosuccinimide (crystallised) (2.79 g, 15.7 mmol) and 2,2'-azobis(2-methylpropionitrile), AIBN, (40 mg) were added and the mixture was refluxed for 30 h. The reaction mixture was then cooled to room temperature, succinimide was removed by filtration and the solvent was evaporated off on a rotary evaporator. The crude product was chromatographed on silica gel using gradient (from 30 to 50% ethyl acetate in hexane, elution was completed with methanol) to give 1.59 g (40%) of bromomethyl derivative **3** and 0.10 g (2%) of dibromomethyl derivative **4**.

The compound **3**, mp 139–140 °C; found: C, 41.69; H, 3.44. Calculated for $C_{11}H_{10}BrClN_2O_2$: C, 41.60; H 3.17%. IR spectrum: 1690 cm^{-1} (C=O). ^{1}H NMR spectrum (500 MHz, $CDCl_3$): δ 1.50 (3H, t, J = 7.1 Hz, CH_3); 4.50 (2H, q, J = 7.1 Hz, OCH_2); 4.90 (2H, s, CH_2Br); 7.42 (1H, dd, J = 2.0 and 9.5 Hz, 7-H); 7.63 (1H, m, 8-H); 9.40 (1H, m, 5-H). ^{13}C NMR spectrum (125 MHz, $CDCl_3$): δ 14.35 (CH_3), 25.22 (CH_2Br), 61.30 (OCH_2), 112.97 (C), 117.92 (CH), 123.06 (C), 126.12 (CH), 129.60 (CH), 145.13 (C), 150.79 (C), 160.13 (C=O).

The compound **4**, mp 158–160 °C; found: C 33.11; H 2.65. Calculated for $C_{11}H_9Br_2ClN_2O_2$: C, 33.32; H 2.29%. IR spectrum: 1695 cm^{-1} (C=O). ^{1}H-NMR spectrum (500 MHz, $CDCl_3$): δ 1.51 (3H, t, J = 7.1 Hz, CH_3); 4.53 (2H, q, J = 7.1 Hz, OCH_2); 7.47 (1H, dd, J = 2.0 and 9.5 Hz, 7-H); 7.51(1H, s, Br_2CH); 7.76 (1H, m, 8-H); 9.35 (1H, m, 5-H). ^{13}C-NMR ($CDCl_3$): δ 14.39 (CH_3), 31.76 (Br_2CH), 61.81 (OCH_2), 108.77 (C), 118.52 (CH), 123.65 (C), 126.13 (CH), 130.20 (CH), 145.18 (C), 151.60 (C), 159.49 (C=O).

(2*R*,5*S*)-5-[(6-Chloro-3-ethoxycarbonylimidazo[1,2-a]pyridin-2-yl)methyl]-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine (7). n-Butyllithium (1.5 ml, 1.5 mmol, 1 M in hexane) was added dropwise to a solution of (*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine **5** (0.30 g, 1.5 mmol) in dry THF (20 ml) under argon at –78 °C. After 30 min a solution of compound **3** (0.48 g, 1.5 mmol) in dry THF (15 ml) was added dropwise over 15 min. The mixture was stirred at –78 °C for 2 h and then left to reach ambient temperature overnight. The THF was removed on a rotary evaporator and the residue dissolved in ethyl acetate (25 ml). The solution was washed with a solution of ammonium chloride (10%, 15 ml), dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by flash chromatography on silica gel, using a mixture of hexane with ethyl acetate (2:1) as eluent to give 0.40 g (63%) of compound **7** as a pale yellow crystalline material, mp 80–81 °C. Found: C, 56.98; H, 6.13. Calculated for $C_{20}H_{25}ClN_4O_4$: C 57.07; H, 5.99%. [α_D = –24 (c = 0.35, $CHCl_3$). IR spectrum: 1700 cm^{-1} (C=O). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.68 (3H, d, J = = 6.8 Hz, CH*C*H_3); 1.05 (3H, d, J = 6.8 Hz, CH*C*H_3); 1.42 (3H, t, J = 7.1 Hz, CH_2*C*H_3); 2.24–2.27 (1H, m, *C*HCH_3); 3.27 (1H, dd, J = 9.5 and 13.5, C*H*H); 3.52 (3H, s, OCH_3); 3.70 (1H, dd, J = = 4.7 and 13.5 Hz, C*H*H); 3.73 (3H, s, OCH_3); 3.93 (1H, t, J = 3.4 Hz, 2-H pyrazine); 4.42 (3H, t, J = = 7.1, *C*H_2CH_3); 4.53-4.56 (1H, m, 5-H pyrazine); 7.34 (1H, dd, J = 2.0 and 9.4 Hz, 7-H imidazo[1,2-a]pyridine); 7.58 (1H,dd, J = 0.5 and 9.4 Hz, 8-H imidazo[1,2-a]pyridine); 9.43 ppm (1H, dd, J = 0.5 and 2.0 Hz, 5-H imidazo[1,2-a]pyridine). ^{13}C-NMR ($CDCl_3$): 14.32, 16.56, 19.11, 31.55, 35.62, 52.32, 52.48, 55.69, 60.61 (2C), 113.80, 117.28, 121.90, 126.07, 128.62, 145.21, 153.85, 161.24, 163.54, 163.61 ppm.

Methyl (*S*)-2-amino-3-(6-chloro-3-ethoxycarbonylimidazo[1,2-a]pyridin-2-yl)propanoate 8. The compound **7** (0.67 g, 1.59 mmol) was stirred with trifluoroacetic acid (39.8 ml, 7.95 mmol, 0.2 M) at ambient temperature for 2 days. The solution was brought to pH 10 by addition of conc. ammonia, the mixture was extracted with dichloromethane (3 × × 20 ml). The combined organic extracts were dried (Na_2SO_4), the solution was evaporated almost to dry-

ness and the product was isolated by flash chromatography using ethylacetate:ethanol:conc. ammonia (9:1:0.01), affording 0.35 g (68%) of the title compound **8** as a pale yellow crystalline material; mp 68–70 °C. Found: C 51.96; H 5.27. Calculated for $C_{14}H_{16}ClN_3O_4$: C 51.62; H 4.95%. [α_D = –7 (c=0.29, $CHCl_3$). ^{1}H NMR spectrum (500 MHz, $CDCl_3$): δ 1.46 (3H, t, J = 7.1, CH_2CH_3); 2.07 (2H, br s, NH_2); 3.38 (1H, dd, J = 8.9 and 14.7, C*H*H); 3.61 (1H, dd, J = 4.4 and 14.7, C*H*H); 3.75 (3H, s, OCH_3); 4.08 (1H, dd, J = 4.4 and 8.9, *CH*CH_2); 4.46 (2H, q, J = 7.1, CH_2CH_3); 7.38 (1H, dd, J = = 2.0 and 9.4 Hz, 7-H imidazo[1,2-a]pyridine); 7.59 (1H, m, 8-H); 9.41 ppm (1H, m, 5-H). ^{13}C NMR ($CDCl_3$): δ 14.38, 34.91, 52.18, 54.04, 60.90, 113.54, 117.34, 122.32, 126.10, 129.03, 145.23, 152.84, 160.82, 175.41 ppm.

CONCLUSIONS

1. The main product of the bromination of ethyl 6-chloro-2-methylimidazo[2,1-b]pyridine-3-carboxylate with *N*-bromosuccinimide in reflux carbon tetrachloride with the presence of a catalytic amount of AIBN is a corresponding bromomethyl derivative.

2. The alkylation of lithiated Schöllkopf's bislactim ether chiral auxiliary with ethyl 2-bromomethyl-6-chloroimidazo[1,2-a]pyridine-3-carboxylate proceeds with high diastereoselectivity and good chemical yield.

3. A practical method of the stereoselective synthesis of β-heteroaromatic-substituted alanine methyl ester bearing the imidazo[1,2-a]pyridine moiety was developed.

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STEREOSELEKTYVI METIL-(*S*)-2-AMINO-3-(6-CHLORO-3-ETOKSIKARBONILIMIDAZO[1,2-A]PIRIDIN-2-IL)PROPANOATO SINTEZĖ

S a n t r a u k a

Radikaliniu būdu brominant etil-6-chloro-2-metilimidazo[1,2-a]piridin-3-karboksilatą buvo gautas etil-2-brommetil-6-chlorimidazo[1,2-a]piridin-3-karboksilatas. Pastaruoju junginiu alkilinant (2*R*)-2,5-dihidro-3,6-dimetoksi-2-izopropilpiraziną, stereoselektyviai susintetintas metil-(*S*)-2-amino-3-(6-chloro-3-etoksikarbonilimidazo[1,2-a]piridin-2-il)propanoatas.