Synthesis of the new carboxylic α,α-diamino ester: Methyl 2-benzamido-2-(N-benzyl N-ethylamino) acetate

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ABSTRACT
A simple synthetic approach to racemic methyl 2-benzamido-2-(N-benzyl N-ethylamino) acetate in high yield is reported. This synthesis involves the N-alkylation reaction between methyl α-bromo glycinate or methyl α-azido glycinate N-benzyolated and N-benzyl-N-ethylamine in different solvents in the presence of various bases. The structure of this product was established on the basis of NMR spectroscopy (¹H, ¹³C), and MS data.

Keywords: Amine; N-alkylation; α-Amino acids; Methyl α-azido glycinate, methyl α-bromo glycinate.

1. Introduction
Amino acid derivatives are an important group of peptidomimetics [1]. They exhibit several applications in medicinal chemistry (antibiotics, antiepileptics, antivirals, antiprotozoals, cardiovascular, atherosclerosis, renal failure and diabetes, neuroexciters) [2-6]. The amino acids were used as starting keys for synthesis peptides, are known to contribute to various chemotherapeutic effects, as antileukemic [7], antitumor [8], antimicrobial [9], and antiviral agents [10]. The reactions of amines have been a topic of immense research interest due to their synthetic utility [11] and biological activity [12]. Amines are widely used as intermediates to prepare solvents, fine chemicals,
agrochemicals, pharmaceuticals and catalyst for polymerization [13]. Organic azides have proved to be efficient key intermediates in organic synthesis for the construction of heterocyclic systems by cycloaddition reactions, while the substitution of the azide group has received much less attention. Continued our investigations on the use of organic azides [14-17], we focused in this work on the synthesis of new carboxylic α,α-diamino ester derivative with the aim to have access to new active biomolecule with a good yield.

2. Experimental
2.1 General: Melting points were determined with an Electrothermal melting point apparatus and are uncorrected. NMR spectra (1H, 13C) were recorded on a Bruker AM 300 (operating at 300.13 MHz for 1H, at 75.47 MHz for 13C) spectrometer. NMR data are listed in ppm and are reported relative to tetra-methylsilane (1H, 13C); residual solvent peaks being used as internal standard. All reactions were followed by TLC. TLC analyses were carried out on 0.25 mm thick precoated silica gel plates (Merck Fertigplatten Kieselgel 60F254) and spots were visualised under UV light or by exposure to vaporised iodine. Mass spectra were recorded by electrospray on a micromass ESI Platform II and on a PolarisQ Ion Trap GC/MSn Mass Spectrometer.

2.2 Typical procedure for N-alkylation
To a stirred solution of 2.86 mmol of amine (nitrogen compound) and 3.12 mmol of diisopropylethylamine in 10 mL of dry acetone, 2.6 mmol of α-azido glycinate were added. The mixture was stirred at room temperature and the reaction was followed by TLC (Kiesegel Merck 60F524). The solvent was evaporated under reduced pressure. The residue was quenched with saturated aqueous solution of ammonium chloride (20 mL) and extracted with dichloromethane (20 mL × 3). The organic phase was dried (Na2SO4) and the solvent was removed under reduced pressure. The product was purified by column chromatography on silica gel using ether/hexane as eluant to afford pure N-alkylated product.

2.3. Methyl 2-benzamido-2-(N-benzyl N-ethylamino) acetate 2: Yield 80 %; m.p.: 218-220°C (ether/hexane); RF: 0.75 (ether); 1H NMR (CDCl3): δppm: 7.8 (d, 1H, NHαazid 7.3 Hz), 7.5 (m, 10H, H arom), 5.55 (d, 1H, Hα, 7.3 Hz), 4.0 (s, e, 2H, NCH2), 3.8 (s, 3H, OCH3); 2.6 (q, 2H, NCH2, 7Hz), 1.3 (t, 3H, CH3, 7Hz); 13C NMR (CDCl3): δ ppm: 171.1, 168, 2 (2CO), 137.7, 133.3, 132.1, 129.1, 128.74, 128.46, 128.25, 127.12 (C6H5 aromatic carbons), 68.7 (-CH-); 55.6 (CH3), 52.8 (OCH3); 42.1 (NCH2); 14.03 (CH3); M.S.E.I: m/z = 326 (M+); C17H22N2O5.

3. Results and Discussions
Our strategy is based on the N-alkylation of N-benzyl N-ethylamine with methyl α-bromo glycinate 1a or methyl α-azido glycinate 1b (scheme 1). Azide derivative 1b was prepared using Achamlale’s procedure [18,19]. Methyl α-azido glycinate 1b was obtained by the reaction of sodium azide with the methyl α-bromo glycinate 1a. The title compound is stable and can be stored for an unlimited time without any signs of decomposition. The methyl α-bromo glycinate 1a also can be used and gives satisfactory results; The azide 1b is used especially for its stability.

As shown in Scheme 1, the reaction of N-benzyl N-ethylamine with methyl α-bromo glycinate 1a or methyl α-azido glycinate 1b was conducted at room temperature in dry solvent in the presence of base. After several attempts of reactions without base or in the presence of bases such as triethylamine, reaction with diisopropylethylamine (DIEPA) gave the best results. The reaction was carried out in dry acetone at room temperature. Results are summarized in Table 1 and Table 2.

4. Conclusion
This work describes the synthesis of a novel α,α-diamino ester by a simple and efficient method. The nucleophilic substitution of carboxylic azide or methyl α-bromo glycinate with N-benzyl-N-ethylamine was occurred under very mild conditions and led after about 48 h to the methyl 2-benzamido-2-(N-benzyl N-ethylamino) acetate with a satisfactory yield.

5. Acknowledgements
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Table 1. Synthesis of new α,α-diamino ester derivative 2 by N-alkylation of N-benzyl N-ethyamine with methyl α-bromo glycinate 1a.

<table>
<thead>
<tr>
<th>Nu-H</th>
<th>Entry</th>
<th>Product</th>
<th>M.P. (°C)</th>
<th>Reaction Time (h)</th>
<th>DCM</th>
<th>DCM</th>
<th>Acetone</th>
<th>DCM</th>
<th>Acetone</th>
<th>Yield (%)</th>
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<tr>
<td>N-benzyl N-ethyamine</td>
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<td>218-220</td>
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The product 2 was obtained in high chemical yield by N-alkylation of N-benzyl N-ethyamine with methyl α-bromo glycinate N-benzoylated 1a or methyl α-azo glycinate N-benzoylated 1b in dry acetone for 48 h at room temperature in the presence of diisopropylethylamine (DIPEA) and was characterized by MS, 1H-NMR and 13C-NMR spectroscopy.

Table 2. Synthesis of new α,α-diamino ester derivative 2 by N-alkylation of N-alkylation of N-benzyl N-ethyamine with methyl α-azo glycinate 1b.

<table>
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6. References


