RESEARCH ARTICLE

Synthesis of methyl 2-benzamido-2-(5-(4-methoxyphenyl)tetrazol-1-yl)acetate and methyl 2-benzamido-2-(5-(4-methoxyphenyl)tetrazol-2-yl)acetate

El Houssine Mabrouk

Laboratory of Organic Chemistry, Faculty of Sciences Dhar El Mehraz, University Sidi Mohamed Ben Abdellah, B.P. 1796, Fez, Morocco

ABSTRACT

Heterocyclic amino acids represent a well-known group of organic compounds also presenting biological activity. We developed an environmentally benign, efficient, and simple method for the Synthesis of new racemic α-tetrazolyl α-carboxylic aminoesters derivatives by nucleophilic substitution of methyl α-azido glycinate N-benzyolated with p-methoxyphenyl-1H-tetrazole. The structure of the these compounds have been characterized from the rigorous analysis of their spectral 1H-NMR, 13C-NMR and MS.

Keywords: Tetrazole, Nucleophilic substitution, α-Aminoesters, Methyl α-azido glycinate

ARTICLE INFO

CORRESPONDING AUTHOR
El Houssine Mabrouk
Laboratory of Organic Chemistry, Faculty of Sciences Dhar El Mehraz, University Sidi Mohamed Ben Abdellah, B.P. 1796, Fez, Morocco

ARTICLE HISTORY: Received 29 June 2018, Accepted 18 August 2018, Available Online 27 September 2018

Copyright©2018 El Houssine Mabrouk. Production and hosting by Pharma Research Library. All rights reserved.

This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.


CONTENTS

1. Introduction ............................................. 245
2. Materials and Methods .................................. 246
3. Results and Discussion ................................ 246
4. Conclusion ............................................. 247
5. Acknowledgement ...................................... 247
6. References ............................................. 247

1. Introduction

Annually in the world about 13 million of new oncological cases are registered and more than 6.2 million deaths occur, according to WHO data. As you can see, death rate is very high. The situation with bacterial infections is no better. Nevertheless, more and more people are surviving cancer, thanks to advances in treatment and screening tests that could predict or detect it. That is why anticancer and antimicrobial agent investigations are very important and always up-to-date. Our research group is dealing with α-tetrazolyl carboxylic α-aminoesters, that were already
investigated to have various biological activities: antibacterial, antimicrobial, antifungal, anticancer, antiviral and antioxidant [1-7]. Hence, the aim of this research is to unleash the potential of new racemic α-tetrazolyl α-carboxylic aminoesters as antibacterial, antifungal and anticancer agents. Heterocyclic organic compounds such as, tetrazoles were reported to show a marked corrosion inhibition efficiency of Cu–Ni alloys in different corrosive environments [8-10].

2. Materials and Methods

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-methylsiliane (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 visualized under UV light or by exposure to vaporized iodine. Mass spectra were recorded by electrospray on a micromass ESI Platform II and on a PolarisQ Ion Trap GC/MS Mass Spectrometer.

Typical procedure for N-alkylation:
To a stirred solution of 2.86 mmol of 5-substituted tetrazole (nitrogen compound) and 3.12 mmol of disopropylethylamine or triethylamine in 10 mL of dry acetonitrile, 10 mL of dry acetonitrile and 2.6 mmol of α-azido glycinate were added. The mixture was stirred at room temperature and the reaction was followed by TLC (Kieselgel 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 in sodium sulfate (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 nucleophilic substitution product.

Methyl 2-benzamido-2-(5-(4-methoxyphenyl)tetrazol-1-yl)acetate 2a: Yield 23 %; Rf: 0.5(ether); 1H NMR (CDCl3); δ ppm: 7.34-7.88 (2m, 9H, H arom.), 6.9 (d, 1H, NH amid., 7.3 Hz), 5.76 (d, 1H, H p, 7.3 Hz), 3.8 (s, 3H, OCH3), 3.7 (s, 3H, OCH3), 1H NMR (CDCl3); δ ppm: 7.90 (2m, 9H, H arom.), 7.38 (s, 3H, OCH3), 3.67 (s, 3H, OCH3); 13C NMR (CDCl3); δ ppm:169.8, 168.12 (2C), 156.22 (C tetrazole), 152.81, 134.27 (2C), 133.02, 132.7, 129.42 (2C), 128.8 (2C), 128.52, 125.31 (2C) (C6H aromatic carbons), 78.6 (C p), 62.7 (C p). Residual solvent peaks were 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 visualized under UV light or by exposure to vaporized iodine. Mass spectra were recorded by electrospray on a micromass ESI Platform II and on a PolarisQ Ion Trap GC/MS Mass Spectrometer.

3. Results and Discussions

Heterocyclic α-Aminoesters possess a broad range of applications ranging from agrochemistry to medicine. In continuation of our research interest in heterocyclic amino acids [11-13], we report here our results concerning the synthesis of new compounds, as methyl 2-benzamido-2-(5-(4-methoxyphenyl)tetrazol-1-yl)acetate 2a and methyl 2-benzamido-2-(5-(4-methoxyphenyl)tetrazol-2-yl)acetate 2b with the aim to have access to new active biomolecules with a good yield through N-alkylation reaction, as key step, between methyl α-azido glycinate N-benzyolated 1 and p-methoxyphenyl-1H-tetrazole (Scheme 1). Azide derivative 1 was prepared using Steglich method [14] and the procedure of our team[15,16].

The reaction of p-methoxyphenyl-1H-tetrazole with azide derivative 1 has been performed in an acetonitrile in the presence of triethylamine Et3N or in an acetone in the presence of disopropylethylamine DIEPA at room temperature. Both N(1)- and N(2)-alkylated products 2a and 2b, respectively, have been isolated. The two products methyl 2-benzamido-2-(5-(4-methoxyphenyl)tetrazol-1-yl)acetate 2a and methyl 2-benzamido-2-(5-(4-methoxyphenyl)tetrazol-2-yl)acetate 2b were obtained respectively with the following yields 20% or 23% and 32% or 37% and were characterized by MS, 1H-NMR and 13C-NMR spectroscopy (Scheme 1). As shown in Scheme 1, the N-alkylation reactions of p-methoxyphenyl-1H-tetrazole nucleophile with N-benzyolated methyl α-azido glycinate was performed in different solvents (acetonitrile and acetonitrile) for 48 h at room temperature in the presence of various bases (Et3N and DIEPA). The results are summarized in Table 1. The products 2a-2b were obtained with an improved overall yields (52-60%) by reaction of p-methoxyphenyl-1H-tetrazole N on azide derivative 1 and were characterized by MS, 1H-NMR and 13C-NMR spectroscopy.
Scheme 1. The nucleophilic substitution of methyl α-azido glycinate N-benzyolated 1 with p-methoxyphenyl-1H-tetrazole

![Scheme 1](image)

Table 1: Synthesis of new racemic α-tetrazolyl carboxylic α-aminoesters 2a-2b

<table>
<thead>
<tr>
<th>Nu-H</th>
<th>Product</th>
<th>Reaction Time (h)</th>
<th>Et₃N Acetonitrile</th>
<th>DIPEA Acetonitrile</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-methoxyphenyl-1H-tetrazole</td>
<td>2a</td>
<td>48</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td></td>
<td>32</td>
<td>37</td>
</tr>
</tbody>
</table>

DIEPA: diisopropylethylamine, Et₃N: triethylamine

4. Conclusion
In order to study their biological activities, we considered it interesting to synthesize new compounds of α-carboxylic amino acid. Methyl 2-benzamido-2-(5-(4-methoxyphenyl)tetrazol-1-yl)acetate and methyl 2-benzamido-2-(5-(4-methoxyphenyl)tetrazol-2-yl)acetate were prepared with very satisfactory yields using a simple and an efficient method by nucleophilic substitution of methyl α-azido glycinate N-benzyolated with p-methoxyphenyl-1H-tetrazole at room temperature under basic condition in different solvents (acetone or acetonitrile).

5. Acknowledgement
We thank the CNR for financial support of this work (PROTARS D13/03, Morocco).

6. References


