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To cite this version:

HAL Id: hal-00782572
https://hal.archives-ouvertes.fr/hal-00782572
Submitted on 25 May 2021

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Synthesis of new racemic α-heterocyclic α,α-diaminoesters and α-aminoester carboxylic

El Houssine Mabrouk a,*, Elachqar Abdelrhani a, El Hallaoui Abdelilah a, Alami Anouar a, El Hajji Soumia a, Martinez Jean b, Rolland Vallery b

a Laboratoire de Chimie Organique, Faculté des Sciences Dhar El Mehraz, Université Sidi Mohamed Ben Abdellah, Fès, Morocco
b Laboratoire des Aminoacides, Peptides et Protéines (LAPP), UMR5810-CNRS, Université Montpellier II, France

Received 27 July 2010; accepted 23 September 2010
Available online 1 October 2010

KEYWORDS
Amino acid;
Amine;
Heterocyclic molecules;
Nucleophilic substitution;
Methyl α-azido glycinate

Abstract
New racemic α-aminoester and α,α-diaminoesters derivatives were synthesized by nucleophilic substitution of methyl α-azido glycinate N-benzoylated with 3-amino-1,2,4-triazole, 2-tetrahydrofuran-2-ylmethan-amine and 2-methyl quinolin-4-amine.

1. Introduction
The investigation of amino acids is of fundamental interest to scientists from many diverse fields. This interest derives from their role as the basic constituents of proteins in addition to their ability to serve as building blocks for the production of many classes of secondary metabolites.

α-Amino acids play an important role in different areas because of the wide spectrum of activity they have (enzymology, medicine and pharmacology, industry, asymmetric synthesis, ...) (Beers et al., 1996; Mikolajczyk, 2005; Joly and Jacobsen, 2004; Leite et al., 2006; Moreira et al., 2007).

This has led to the development of numerous synthetic methods for a variety of compounds (Haemers et al., 1989).

The recent literature is enriched with progressive findings about the synthesis and pharmacological action of fused heterocycles. Heterocycles bearing a symmetrical triazole and furan are reported to show a broad spectrum of pharmacological properties such as anti-inflammatory, antiviral and antibacterial activities (Boschelli et al., 1993; Unangst et al., 1992; Hung and Chen, 2001; Srivastava et al., 1984; Saad, 1996; Hui et al., 2002).

Because of their multiple functionalities, amino acids heterocyclics play a considerable role in the biologic processes (Costantino et al., 2004; Jorgensen et al., 2007). So a large number of between them isolated of plants have a very varied biologic activity (Schenk and Werner, 1991).

Over the past decades, nitrogen-containing heterocyclic molecules have been considered as the privileged synthetic targets in the pharmaceutical and veterinary industries (Katritzky et al., 1996; Undheim and Benneche, 1999; Joule and Mills, 2000; Katritzky et al., 2003) because of their diverse
biological properties and a wide variety of applications, e.g., anticancer, diuretic, anticonvulsant, anti-inflammatory and anti-hypertensive activities (Chan et al., 1997; Gackenheimer et al., 1996; Dempcy and Skibo, 1991).

The 1,2,4-triazole and its derivatives were reported to exhibit various pharmacological activities, such as antimicrobial, analgesic, anti-inflammatory, anticancer and antioxidant properties (Padmavathi et al., 2008; Amir et al., 2008; Sztanke et al., 2008; Kus et al., 2008). Some of the present day drugs, such as Ribavirin (antiviral agent), Rizatriptan (antimigraine agent), Alprazolam (anxiolytic agent), Fluconazole and Itraconazole (antifungal agents) are the best examples for potent molecules possessing triazole nucleus.

Quinaldine derivatives are very important photographic sensitizers; they are used as dyes (textile, printing inks, and food), drugs, cosmetics and indicators (Finar, 1995; Sanyal et al., 1979; Shashidhar, 1974).

For this reason, we considered it interesting to synthesize new compounds containing [1,2,4]-triazole nucleus, 2-tetrahydrofuran-2-ylmethanamine and 2-methylquinolin-4-amine fused with an amino acid, in order to study their biological activities. The present study describes the synthesis and characterization of novel aminoesters derivatives.

2. Results

We continued our investigations on the use of organic azides (Boukallaba et al., 2006, 2007) in heterocyclic synthesis; we reported in this paper another part of our investigations concerning the preparation of new carboxylic α,α-diaminoesters carrying a variety of heterocyclic in position α.

Our strategy is based on the nucleophilic substitution of methyl α-azido glycinate N-benzyolated 1 with amines (Scheme 1). Azide derivative 1 was prepared using Steglich method (Steglich and Kober, 1983) and Achamlale’s procedure (Achamlale et al., 1997, 1999).

Methyl α-azido glycinate N-benzyolated 1 was obtained by the reaction (Achamlale et al., 1997, 1999) of sodium azide with the methyl α-bromo glycinate. The title compound is stable and can be stored for an unlimited time without any signs of decomposition. The methyl α-bromo glycinate also can be used and gives satisfactory results; the azide 1 is used especially for its stability.

The reaction of different amines Nu on azide derivative 1 results in Compounds 2-4 carrying heterocyclic amines.

As a first step and to optimize the different reaction conditions (choice of base, solvent, ...), we conducted several test reactions. For all these tests, the reactions were followed by TLC and 1H NMR. Yields are given as pure product after column chromatography on silica gel.

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.

The products 2-4 were obtained in 60–77.5% overall yield from 1 and were analyzed by MS, 13C NMR and 1H NMR.

<table>
<thead>
<tr>
<th>Product</th>
<th>Nu-H</th>
<th>m.p. (°C)</th>
<th>Reaction time (h)</th>
<th>DCM Yield (%)</th>
<th>Et3N DCM Yield (%)</th>
<th>Et3N acetone Yield (%)</th>
<th>DIEPA DCM Yield (%)</th>
<th>DIEPA acetone Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>3-Amino-1,2,4-triazole</td>
<td>214–216</td>
<td>48</td>
<td>Traces</td>
<td>19</td>
<td>33</td>
<td>42</td>
<td>77.5</td>
</tr>
<tr>
<td>3</td>
<td>2-Tetrahydrofuran-2-ylmethanamine</td>
<td>130–132</td>
<td>48</td>
<td>Traces</td>
<td>17.5</td>
<td>30.5</td>
<td>39</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>2-Methylquinolin-4-amine</td>
<td>158–160</td>
<td>72</td>
<td>Traces</td>
<td>14.5</td>
<td>25.5</td>
<td>32.5</td>
<td>60</td>
</tr>
</tbody>
</table>

DCM: dichloromethane, Et3N: triethylamine.
tetrahydrofurylmethylamine, N-benzyl-N-methylamine, and aniline derivatives, we see that we have obtained almost the same results.

The methyl glycinate may be protected by different protecting groups: trifluoroacetic anhydride, trichloroethoxycarbonyl chlorides, acetyl chloride, and benzoyl chloride. The protection reaction is carried out in dichloromethane in the presence of triethylamine or pyridine. After column chromatography on silica gel, the aminoesters N-protected are obtained in good yields.

3. Conclusion

In conclusion, this method provides general and convenient access to a wide range of α,α-diaminoesters and α-aminoester carboxylic derivatives starting from the appropriate azide derivative 1. The nucleophilic substitution of methyl α-azido glycinate N-benzoylated 1 with different amines (3-amino-1,2,4-triazole, 2-tetrahydrofuran-2-ylmethan-amine, and 2-methylquinolin-4-amine) occurred under very mild conditions and led to the desired products in good yields.

4. Experimental

4.1. General

Melting points were determined with an electrothermal melting point apparatus and are uncorrected. NMR spectra (1H, 13C) were recorded on an Bruker AM 300 (operating at 300.13 MHz for 1H, at 75.47 MHz for 13C) spectrometer (Centre Universitaire Régional d’Interface, Fès). NMR data are listed in ppm and are reported relative to tetramethylsilane (1H, 13C); residual solvent peaks being used as an 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 on a PolarisQ Ion Trap GC/MSn Mass Spectrometer (Centre Universitaire Régional d’Interface, Fès); except for the product 3 which was identified by electrospray on a micromass ESI Platform II (Université Montpellier II, France). Methyl α-azidoglycinate 1 was prepared using Achamlale’s method (Achamlale et al., 1997, 1999).

4.2. Typical procedure for nucleophilic substitution

To a stirred solution of 2.86 mmoles of amines (nitrogen compounds) and 3.12 mmoles of diisopropylethylamine in 10 ml of dry acetone, 2.6 mmoles of methyl 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 wherever necessary by column chromatography on silica gel using ether/hexane as eluant to afford pure nucleophilic substitution product.

4.3. Methyl 2-benzamido-2-(3-amino-1,2,4-triazol-1-yl) acetate 2: yield: 77.5%; mp 214–216 °C (ether/hexane); Rf: 0.3 (ether)

1H NMR (CDCl3): δ ppm: 3.9 (s, 3H, OCH3); 5.6 (br s, 2H, NH2); 6.45 (d, 1H, J = 7.2 Hz, H a); 7.47–8.05 (3 m, 7H, Ar + H triazol + NH amid). 13C NMR (CDCl3): δ ppm: 54.04 (OCH3); 60.67 (–CH–); 106.42, 127.42, 128.92, 133.01, 149.92, 155.70, (C6H5 aromatic carbons); 165.62, 168.16 (2CO). M.S-E.I: m/z = 275.8 [M]; C12H13N5O3.

4.4. Methyl 2-benzamido-2-{(tetrahydro-furan-2-ylmethyl)amino} acetate 3: yield 72%; m.p.: 130–132 °C (ether/hexane); Rf: 0.6 (ether)

1H NMR (CDCl3): δ ppm: 1.2–1.75 (2 m, 5H, HT.H.F); 2.9 (m, 2H, NCH2); 3.75 (s, 3H, OCH3); 4.1–4.45 (2 m, 3H, HT.H.F + NH); 5.6 (br s, 1H, Hj); 7.4–8.02 (3 m, 5H, Ar + NH amid). 13C NMR (CDCl3): δ ppm: 4× (CH2) 24.13, 27.07, 50.25, 66.12; 54.49 (OCH3); 71.32 (–CH–); 128.34, 129.54, 131.33, 135.77 (C6H5 aromatic carbons); 169.07, 171.98 (2CO). MS (electrospray) m/z = 293.3 [M + 1]; 292.3 [M]; C14H20N2O4.
4.5. Methyl 2-benzamido-2-(2-methylquinolin-4-ylamino) acetate 4

yield: 60%; m.p.: 158–160 °C (ether/hexane); Rf: 0.6 (ether);

$^1$H NMR (CDCl$_3$): δ ppm: 3.57 (3H, s, CH$_3$); 3.88 (s, 3H, OCH$_3$); 4.9 (br s, 1H, NH); 5.8 (d, 1H, $J = 9.0$ Hz, H$_a$); 6.2 (br s, 1H, Ar); 6.7–7.9 (3 m, 10H, Ar + NH$_{amid}$).

$^{13}$C NMR (CDCl$_3$): δ ppm: 24.13 (CH$_3$); 53.08 (OCH$_3$); 56.98 (–CH–); 78.69, 109.23, 116.34, 120, 125.33, 127.25, 128.77, 132.38, 133, 149.12, 149.23, 159.77, (C$_6$H$_5$ aromatic carbons); 168.58, 171 (2CO) M.S-E.I: m/z = 349.1 [M]; C$_{20}$H$_{19}$N$_3$O$_3$.

Acknowledgement

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

References
