Arabian Journal of Chemistry (2013) 6, 93–96

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

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

* Corresponding author. Tel.: +212 618 788 704.
E-mail address: mabrouk.elhoussine@yahoo.fr (E.H. Mabrouk).

Peer-review under responsibility of King Saud University.
doi:10.1016/j.arabjc.2010.09.023

Production and hosting by Elsevier

Table 1 Synthesis of new α-aminoesters and α,α-diaminoesters derivatives **2**–**4**.

Product	Nu-H	m.p. (°C)	Reaction time (h)	– DCM Yield (%)	Et_3N DCM Yield (%)	Et_3N acetone Yield (%)	DIEPA DCM Yield (%)	DIEPA acetone Yield (%)
2	3-Amino-1,2,4-triazole	214–216	48	Traces	19	33	42	77.5
3	2-Tetrahydrofuran-2-ylmethanamine	130–132	48	Traces	17.5	30.5	39	72
4	2-Methylquinolin-4-amine	158–160	72	Traces	14.5	25.5	32.5	60

DCM: dichloromethane, Et_3N: triethylamine.

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 a amino acid, in order to study their biological activities. The present study describes the synthesis and characterization of novel α-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*-benzoylated **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*-benzoylated **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.

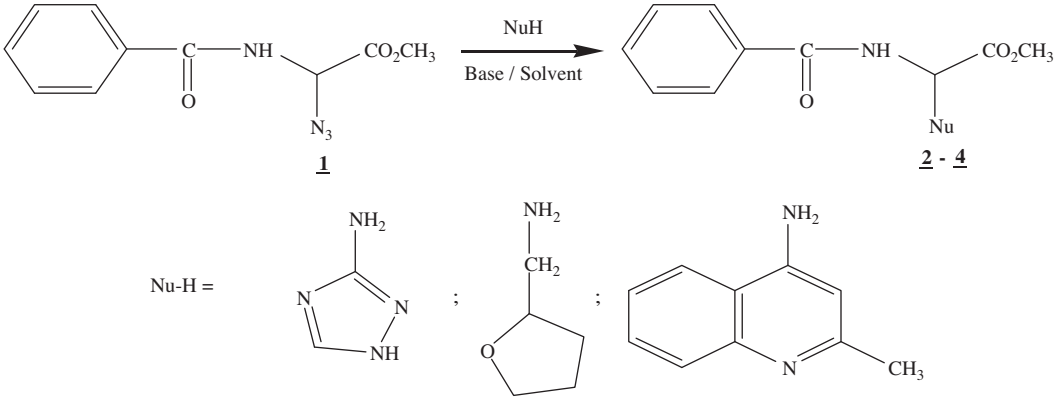
As a first step and to optimize the different reaction conditions (choice of base, solvent, ...), we conducted several test reactions. For all these tests, the reactions were followed by TLC and ^{1}H NMR. Yields are given as pure product after column chromatography on silica gel.

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, ^{13}C NMR and ^{1}H NMR.

For the reaction of 3-amino-1,2,4-triazole with azide **1**, our estimate was to have two products with the predominance of one over another, but the spectroscopic data obtained showed the existence of only a single product: methyl 2-benzamido-2-(3-amino-1,2,4-triazol-1-yl) acetate **2** (Scheme 2).

Comparing these results with the work done by our team (Boukallaba et al., 2006, 2007): synthesis of new α-heterocyclic α-aminophosphonates and synthesis of α-heterocyclic α-aminophosphonates, Part II: morpholine, piperidine, pyrrolidine,



Scheme 1