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R E S E A E C H A R T I C L E

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

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A B S T R A C T

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-benzoylated 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

A R T I C L E I N F O

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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

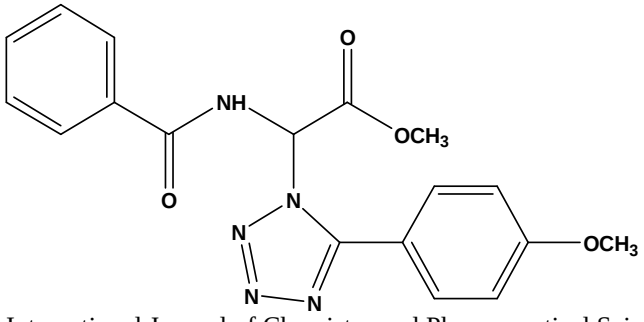
General:

Melting points were determined with an Electrothermal melting point apparatus and are uncorrected. NMR spectra (^{1}H, ^{13}C) were recorded on a Bruker AM 300 (operating at 300.13 MHz for ^{1}H, at 75.47 MHz for ^{13}C) spectrometer. NMR data are listed in ppm and are reported relative to tetra-methylsilane (^{1}H, ^{13}C); 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 ESl Platform II and on a PolarisQ Ion Trap GC/MSn Mass Spectrometer.

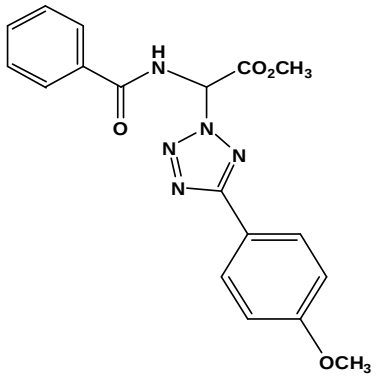
Typical procedure for N-alkylation:

To a stirred solution of 2.86 mmol of 5-substituted tetrazole (nitrogen compound) and 3.12 mmol of diisopropylethylamine or triethylamine in 10 mL of dry acetone or anhydrous acetonitrile, 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 in sodium sulfate (Na_2SO_4) 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); **^{1}H NMR ($CDCl_3$):δppm**: 7.34-7.88 (2m, 9H, H_{arom}), 6.9 (d, 1H, NH_{amid}, 7.3 Hz), 5.76 (d, 1H, H_α, 7.3 Hz), 3.8 (s, 3H, OCH_3), 3.7 (s, 3H, OCH_3); **^{13}C NMR ($CDCl_3$):**δ ppm:170.4, 168.26 (2CO),156.16($C_{tetrazole}$), 152.9, 134.12(2C), 132.82, 131.93, 129.54 (2C), 128.70 (2C), 128.14, 125.26 (2C) (C_6H_5 aromatic carbons),62.7 (-CH-), 56.1,52.3(OCH_3);M.S-E.I: *m/z* = 367 ($M^{+\cdot}$);$C_{18}H_{17}N_5O_4$.



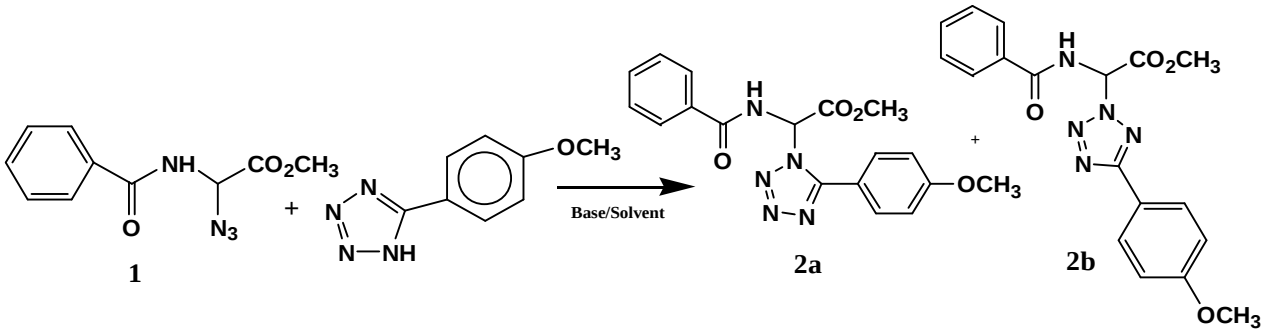
Methyl 2-benzamido-2-(5-(4-methoxyphenyl)tetrazol-2-yl)acetate 2b: Yield 37 %;Rf:0.4(ether); **^{1}H NMR ($CDCl_3$):δppm**: 7.25-7.90 (2m, 9H, H_{arom}), 7.0 (d, 1H, NH_{amid}, 7.3 Hz), 5.8 (d, 1H, H_α, 7.3 Hz), 3.78 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3); **^{13}C NMR ($CDCl_3$):**δ ppm:169.8, 168.12 (2CO),156.22($C_{tetrazole}$), 152.81, 134.27(2C), 133.02, 132.7, 129.42 (2C), 128.76 (2C), 128.52, 125.31 (2C) (C_6H_5 aromatic carbons),78.6 (-CH-), 56.5,53.7(OCH_3);M.S-E.I: *m/z* = 367 ($M^{+\cdot}$);$C_{18}H_{17}N_5O_4$.



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*-benzoylated **1** and *p*-methoxyphenyl-1*H*-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-1*H*-tetrazole with azide derivative **1**has been performed in an acetonitrile in the presence of triethylamine Et_3N or in an acetone in the presence of diisopropylethylamine 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, ^{1}H-NMR and ^{13}C-NMR spectroscopy (Scheme 1). As shown in Scheme 1, the *N*-alkylation reactions of *p*-methoxyphenyl-1*H*-tetrazole nucleophile with *N*-benzoylated methyl α-azido glycinates **1** was performed in different solvents (acetone and acetonitrile) for 48 h at room temperature in the presence of various bases (Et_3N 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-1*H*-tetrazole *N*u on azide derivative**1** and were characterized by MS, ^{1}H-NMR and ^{13}C-NMR spectroscopy.



Scheme 1. The nucleophilic substitution of methyl α-azido glycinate *N*-benzoylated **1** with *p*-methoxyphenyl-1*H*-tetrazole

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

Nu-H	Product	Reaction Time (h)	Et_3N	DIPEA
			Acetonitrile	Acetone
			Yield(%)	Yield(%)
p-methoxyphenyl-1*H*-tetrazole	**2a**	48	20	23
	2b		32	37

DIEPA: diisopropylethylamine, Et_3N: 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 withvery satisfactory yields using a simple and an efficient method by nucleophilic substitution of methyl α-azido glycinate*N*-benzoylated with *p*-methoxyphenyl-1*H*-tetrazole at room temperature under basic condition in different solvents (acetone or acetonitrile).

5. Acknowledgement

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