ORIGINAL ARTICLE

SYNTHESIS OF NEW RACEMIC α-TETRAZOLYL α-AMINOESTERS DERIVATIVES, PART II

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ABSTRACT

Background: we report here our results concerning the synthesis of new compounds, as methyl 2-benzamido-2-(5-*p*-tolyltetrazol-1-yl)acetate and methyl 2-benzamido-2-(5-*p*-tolyltetrazol-2-yl)acetate, with the aim to have access to new active biomolecules with a good yield through *N*-alkylation reaction. **Objectives:** α-Aminoesters possess a broad range of applications ranging from agrochemistry to medicine. We developed a simple, efficient, and environmentally benign 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*-tolyl-1*H*-tetrazole. The structure of these compounds have been characterized from the rigorous analysis of their spectral ^{1}H-NMR, ^{13}C-NMR and MS. **Methods:** The *N*-alkylation reactions of 1*H*-tetrazole derivative nucleophile with *N*-benzoylated methyl α-azido glycinate **1** was performed in different solvents (acetone and acetonitrile) for 24 h at room temperature in the presence of various bases (Et_3N and DIEPA). **Results:** The products **2-3** were obtained with an improved overall yields (56.5-63%) by reaction of 1*H*-tetrazole derivative *N*u on azide derivative **1** and were characterized by MS, ^{1}H-NMR and ^{13}C-NMR spectroscopy. **Conclusions:** we have developed a simple method for the Synthesis of new racemic α-tetrazolyl α-carboxylic aminoesters by nucleophilic substitution of methyl α-azido glycinate *N*-benzoylated with *p*-tolyl-1*H*-tetrazole at room temperature under basic condition using diisopropylethylamine or triethylamine in different solvents (acetone or acetonitrile). The mild reaction conditions, rapid conversion, very satisfactory yields are the notable advantages of the present method.
Keywords: *Tetrazole, Nucleophilic substitution, α-Aminoesters, Methyl α-azidoglycinate.*

1. INTRODUCTION

Synthesis of tetrazole derivatives is very important in modern medicinal chemistry because of their structure and applications as antihypertensive, antialergic, antibiotic and anticonvulsant agents [1, 2, 3]. The development of tetrazole chemistry has been largely associated with wide scale of applications of these classes of compounds in medicine, biochemistry, agriculture [1, 2, 3, 4, 5, 6]; The tetrazole functionality plays an important role in medicinal chemistry, primarily due to its ability to serve as bioequivalent (bioisoster) of the carboxylic acid group [7]. Some of tetrazole containing compounds have been used both as anticancer and antimicrobial agents [8]. Indeed, several tetrazole [9, 10, 11] derivatives have been hardly studied as mild steel corrosion inhibitors.

Considering the interest in heterocyclic amino acids [12, 13, 14, 15, 16, 17], several structurally related non proteinogenic amino acids and their derivatives have been the subject of various investigations.

5-Substituted tetrazoles, frequently referred to as tetrazolic acids [18, 19]. Therefore, they are ionized at a physiological pH and they exist as 1*H*- and 2*H*-tautomers.

2. RESULTS AND DISCUSSION

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. In continuation of our research interest in heterocyclic amino acids [20, 21 22], we report here our results concerning the synthesis of new compounds, as methyl 2-benzamido-2-(5-p-tolyltetrazol-1-yl)acetate **4a** and methyl 2-benzamido-2-(5-p-tolyltetrazol-2-yl)acetate **4b**, 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*-tolyl-1*H*-tetrazole (Scheme 1). Azide derivative **1** was prepared using Steglich method [23] and the procedure of our team [24, 25].

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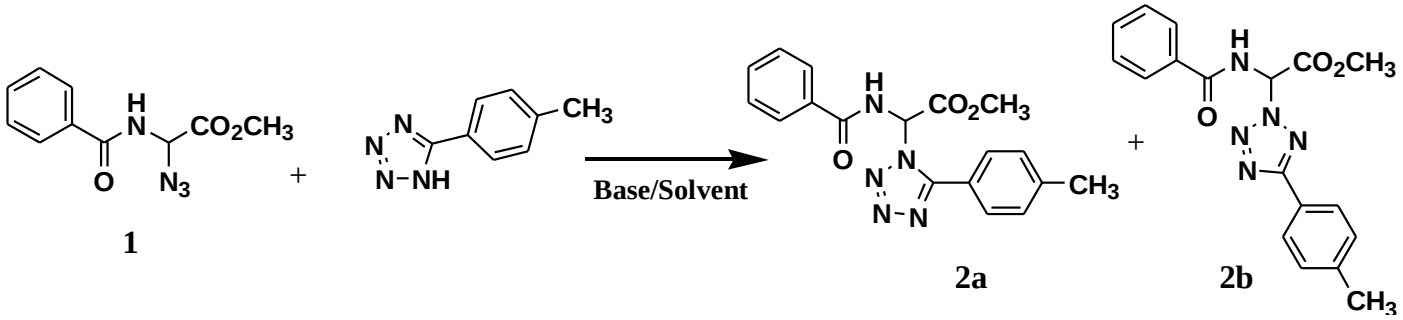


Scheme 1. The nucleophilic substitution of methyl α-azido glycinate *N*-benzoylated **1** with *p*-tolyl-1*H*-tetrazole.

The alkylation of *p*-tolyl-1*H*-tetrazole with azide derivative **1** under liquid-liquid technique such as (DIEPA/Acetone) or (Et_3N/Acetonitrile) at room temperature gave a mixture of methyl 2-benzamido-2-(5-*p*-tolyltetrazol-1-yl)acetate **2a** and methyl 2-benzamido-2-(5-*p*-tolyltetrazol-2-yl)acetate **2b**. The products **2a** and **2b** are formed in very satisfactory yields (21.5–38%) for 24 hours (Table 1).

As shown in Scheme 1, the *N*-alkylation reactions of 1*H*-tetrazole derivative nucleophile with *N*-benzoylated methyl α-azido glycinate **1** was performed in different solvents (acetone and acetonitrile) for 24 h at room temperature in the presence of various bases (Et_3N and DIEPA). The results are summarized in Table 1.

Table 1: The table presents the synthesis of new racemic α-tetrazolyl carboxylic α-aminoesters **2a**-**2b**.

Nu-H	Product	Reaction Time (h)	Et_3N Acetonitrile Yield (%)	DIPEA Acetone Yield (%)
p-tolyl-1*H*-tetrazole	**2a**	24	21.5	25
	2b		35	38

DIEPA: diisopropylethylamine, **Et_3N**: triethylamine.

The products **2a**-**2b** were obtained with an improved overall yields (56.5-63%) by reaction of 1*H*-tetrazole derivative Nu on azide derivative **1** and were characterized by MS, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

3. MATERIELS AND METHODES

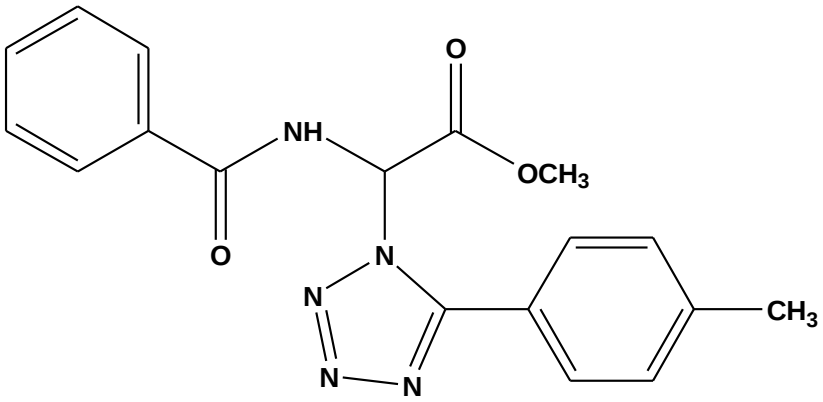
3.1. General

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 ESI Platform II and on a PolarisQ Ion Trap GC/MSn Mass Spectrometer.

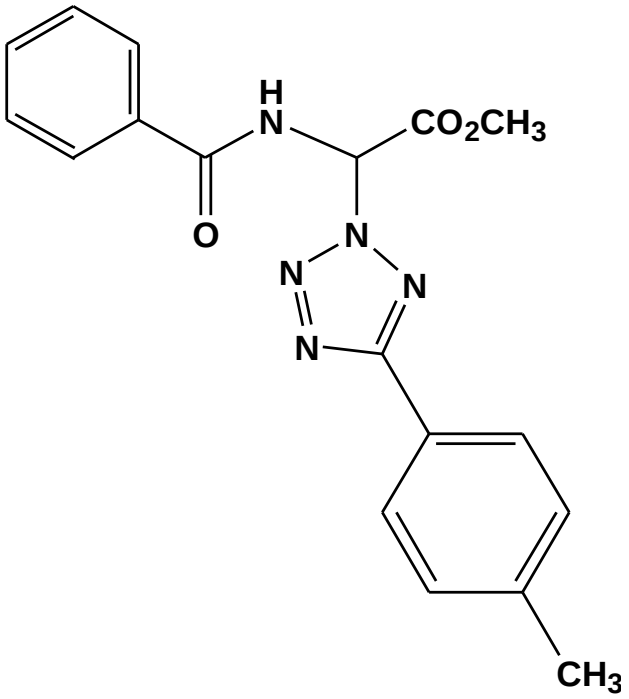
3.2. Typical procedure for N-alkylation: To a stirred solution of 2.86 mmol of 5-substituted tetrazole (nitrogen compound) and 3.12 mmol of diisopropylethylamine or triethylamine in 10 mL of dry acetone or anhydrous acetonitrile, 2.6 mmol of α-azido glycinate were added. The mixture was stirred at room 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.

3.3. Methyl 2-benzamido-2-(5-*p*-tolyltetrazol-1-yl)acetate 2a: Yield 25 %; m.p.: 218–220°C (ether/hexane); Rf: 0.45 (ether); **^{1}H NMR ($CDCl_3$): δppm:** 7.25-7.9 (2m, 9H, H_{arom}), 7.02 (d, 1H, NH_{amid}, 7.3 Hz), 5.8 (d, 1H, H_α, 7.3 Hz), 3.8 (s, 3H, OCH_3), 2.32 (s, 3H, CH_3); **^{13}C NMR ($CDCl_3$): δ ppm:** 169.3, 168.80 (2CO), 153.68($C_{tetrazole}$), 135.71(2C),

134.65, 133.51, 131.92, 129.18 (2C), 128.66 (2C), 128.28, 127.41 (2C) (C_6H_5 aromatic carbons), 63.01 (-CH-), 53.0 (OCH_3), 19.35 (CH_3); M.S-E.I: m/z = 351 ($M^{+\cdot}$); $C_{18}H_{17}N_5O_3$.



3.4. Methyl 2-benzamido-2-(5-*p*-tolyltetrazol-2-yl)acetate 2b: Yield 38 %; m.p.: 262–264°C (ether/hexane); Rf: 0.3 (ether); **^{1}H NMR ($CDCl_3$): δppm:** 7.3-7.8 (2m, 9H, H_{arom}), 7.0 (d, 1H, NH_{amid}, 7.3 Hz), 5.9 (d, 1H, H_α, 7.3 Hz), 3.8 (s, 3H, OCH_3), 2.48 (s, 3H, CH_3); **^{13}C NMR ($CDCl_3$): δ ppm:** 169.4, 168.76 (2CO), 153.25($C_{tetrazole}$), 135.8(2C), 134.7, 133.23, 131.83, 129.35 (2C), 128.68 (2C), 128.34, 127.18 (2C) (C_6H_5 aromatic carbons), 62.9 (-CH-), 52.97 (OCH_3), 19.4 (CH_3); M.S-E.I: m/z = 351 ($M^{+\cdot}$); $C_{18}H_{17}N_5O_3$.



4. CONCLUSION

In conclusion, we have developed a simple method for the Synthesis of new racemic α-tetrazolyl α-carboxylic aminoesters by nucleophilic substitution of methyl α-azido glycinate *N*-benzoylated with *p*-tolyl-1*H*-tetrazole at room temperature under basic condition using diisopropylethylamine or triethylamine in different solvents (acetone or acetonitrile). The mild reaction conditions, rapid conversion, very satisfactory yields are the notable advantages of the present method.

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