ECLÉTICA QUÍMICA

Eclet. Quim. 49 | e-1479, 2024

Original Article

https://doi.org/10.26850/1678-4618.eq.v49.2024.e1479

Identification and theoretical study of the regioselectivity of the synthesis reaction of an α-heterocyclic α-amino ester

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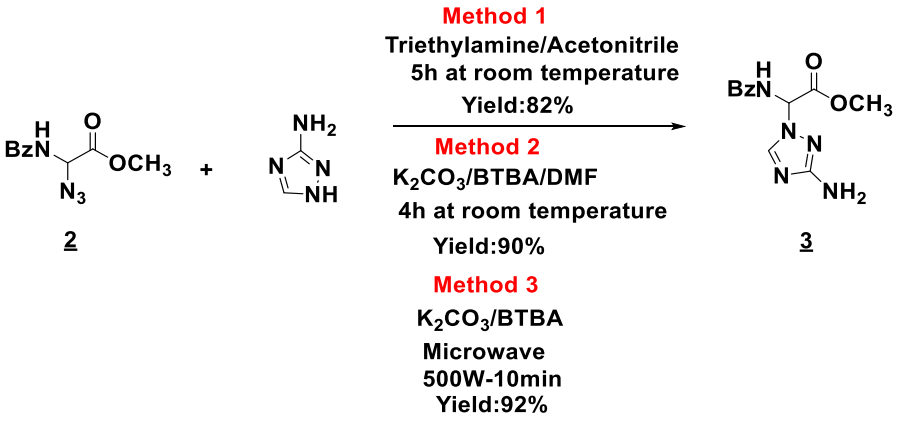
Abstract

The interest of amino acids no longer needs to be demonstrated, given the involvement of these compounds in various fields, both as basic elements of peptide and protein structures and as independent entities. We report the regioselective synthesis of an N-protected α,α-diamino carboxylic ester derived from glycine. Our synthetic strategy is based first on the preparation of methyl 2-azido-2-benzamidoacetate and then on the N-alkylation reaction between the latter and the 1H-1,2,4-triazole-3-amine with three methods. The theoretical study by the DFT method and Marvinsketch software explains well the reaction's regioselectivity and good compatibility between the experimental and computational results. The products synthesized during this strategy are identified and characterized by spectral analysis: mass spectrometry, ^{1}H NMR and ^{13}C NMR.



Article History

Received February 28, 2023
Accepted August 27, 2024
Published December 26, 2024

Keywords

1. 1H-1,2,4-triazole-3-amine;
2. heterocyclic compounds;
3. carboxylic amino esters.

Section Editors

Michelle Jakeline Cunha Rezende

Highlights

- α-Heterocyclic α-amino esters were synthesized by three methods and characterized.
- The synthesis of N-protected α,α-diamino carboxylic ester derived was reported.
- The regioselective synthesized compound was obtained from glycine.
- The theoretical study was done by the DFT method and Marvinsketch software.
- This method and the software were explored to explain the reaction regioselectivity.

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1. Introduction

Heterocyclic compounds represent most molecules used in industry and are the subject of very active research worldwide. They have an important role in biological, pharmacological, and agrochemical industrial processes (vitamins, hormones, antibiotics, dyes, etc.) (Azimi *et al.*, 2021; Rhazi *et al.*, 2022), and they also constitute the basic structures of many alkaloids, at the origin of a large variety of drugs. From a chemical point of view, most heterocyclic compounds' stability is due to a conjugated or aromatic system. Nitrogenous heterocyclic compounds are important because they often constitute the active principle of various substances used in the pharmacological, biological, and industrial fields (Faisal *et al.*, 2019).

Five-membered heterocyclic systems are very active, triazoles constitute a class among them that have found, since their discovery, diversified applications in the fields of medicine, agrochemical, industrial and catalysis (Khilkovets *et al.*, 2022; Ramesh *et al.*, 2011). Triazole molecules do not exist in nature; various methods synthesize them. Triazoles have a pseudo-aromatic structure, which results in an interaction between π bonds, a large dipole moment, and a great capacity to form hydrogen bonds (Abboud *et al.*, 2001). They are very stable compounds concerning other chemical reagents, oxidation, and reduction. Triazole derivatives have been reported to have various biological activities such as antidiabetic (Ouyang *et al.*, 2008), antitubercular (Cetin *et al.*, 2018; Radi *et al.*, 2017), anti-inflammatory, antifungal (Kumar *et al.*, 2013; Ramirez-Prada *et al.*, 2017), and antibacterial (Diculescu *et al.*, 2016; Graillot *et al.*, 2012) properties. Today, various triazole drugs have been widely used in medicine, such as antifungals (Fluconazole, Voriconazole, and Itraconazole) (El-Sabbagh *et al.*, 2009), anticancer drugs (Letrozole and Anastrozole) (Perez-Fernandez *et al.*, 2014) as well as antivirals (Ribavirin) (Bandgar *et al.*, 2009). Recently, 1,2,4-triazole derivatives have benefited from several agricultural and medical studies due to their interesting structural features and biological activities. These derivatives have various biological properties, in particular antimicrobial activity, antimalarial activity, anticonvulsive activity, anti-leishmanial activity, anti-Alzheimer activity, and antidiabetic activity (Abdu *et al.*, 2017; Abu-Hashem *et al.*, 2016; Ansari *et al.*, 2017; Insuasty *et al.*, 2010; Karrouchi *et al.*, 2018; Knorr *et al.*, 1883; Ozdemir *et al.*, 2015; Shilpy *et al.*, 2018; Zarrouk *et al.*, 2012).

Non-proteinogenic amino acids are becoming of greater industrial importance with the development of new methods of synthesis leading to a wide range of substances present, including alkaloids, antibiotics, and proteins (Ngo *et al.*, 2011). Most heterocyclic amino acids (Banno *et al.*, 2017; Christian *et al.*, 2005) of plant origin exhibiting various biological properties (Schenk *et al.*, 1991) are fundamental in biological processes (Costantino *et al.*, 2004; Jorgensen *et al.*, 2007).

Triazolic amino acids are bioactive heterocycles (Boibessot *et al.*, 2016; Stanley *et al.*, 2010; Thirumurugan *et al.*, 2013) representing an interesting class of amino acids that have few physiological activities (Albada *et al.*, 2017; Cativiela *et al.*, 2007; Dondoni *et al.*, 2006; Hughes *et al.*, 2007a; b; Nájera and Sansano 2007; Risseeuw *et al.*, 2013; Vogt *et al.*, 2007).

The work presented in this article first aims to identify a triazole α-aminoester synthesized by three methods and then to study the regioselectivity of this reaction. The valorization of this product by the evaluation of its activities and its applications will be the subject of subsequent work.

2. Experimental

2.1. General

All the chemicals used are commercial and analytical grade, and do not require further purification. The TLC is used to monitor the progress of the reactions (Merck, silica gel 60 F254), while UV light is utilized to see the spots (VILBER LOURMAT, VL-215.LC). Nuclear Magnetic Resonance (NMR) spectra (^{1}H, ^{13}C) were recorded employing a Bruker AM 300 spectrometer operating at frequencies of 300.13 MHz (for ^{1}H) and 75.47 MHz (for ^{13}C). NMR data is reported in parts per million (ppm) and is referenced to tetramethylsilane (for ^{13}C). Mass spectra were recorded using a PolarisQ Ion Trap GC/MSn mass spectrometer.

2.2. Typical procedure for nucleophilic substitution

2.2.1. Method 1

2.73 mmol of methyl 2-azido-2-benzamidoacetate were added to a mixture of 3.0 mmol of 1H-1,2,4-triazole-3-amine, 3.3 mmol of triethylamine, and 8 mL of dry acetonitrile stirred for 45 min. The reaction was carried out at room temperature for five hours. After removal of the solvent under reduced pressure, the residue was quenched with a saturated aqueous solution of ammonium chloride or sodium hydrogenocarbonate (15 mL) and extracted with dichloromethane (15 mLx 3). The organic phase was dried in sodium sulfate (Na_2SO_4) and the solvent was evaporated under reduced pressure. The product was purified by column chromatography on silica gel using hexane/ether (2:1) as eluent. Yield: 82%.

2.2.2. Method 2

To 10 mmol of 1H-1,2,4-triazole-3-amine in 30 mL of dimethyl-formamide or acetone, 15 mmol (2.10 g) of potassium carbonate are added in small portions and a catalytic amount of tetra-n-butylammonium bromide (1 mmol, 0.34 g BTBA). The mixture was stirred for 15 min and then 9.09 mmol of the methyl 2-azido-2-benzamidoacetate were added. The reaction was left for four hours at room temperature. At the end of the reaction and after evaporation of the solvent, the residue obtained was washed with hexane. The organic phase was then dried and purified by column chromatography on silica gel using an ether/hexane mixture (1:2) as eluent. Yield: 90%.

2.2.3. Method 3

A mixture of 1H-1,2,4-triazol-3-amine (5.0 mmol), methyl 2-azido-2-benzamidoacetate (4.55 mmol), tetrabutylammonium bromide (0.17 g, 0.50 mmol, and potassium carbonate (2.8 g, 20 mmol) on silica (or clay) as support was heated in a domestic microwave oven in an employing Meyer flask with a power of 500 W for 10 min. After cooling down, the reaction mixture was extracted with dichloromethane (3 x 15 mL). Then the organic layer was dried with Na_2SO_4, filtered, and the solvent was evaporated to dryness. The solid material was purified by using flash chromatography or recrystallization from hexane or ethanol to afford the desired product:2-(3-amino-1H-1,2,4-triazol-1-yl)-2-benzamidoacetate. Yield: 92%.

2.3. Product characterization data

2.3.1. Methyl 2-azido-2-benzamidoacetate 2

White solid; M.p.: 81 °C; Yield 92%; M.S-E.I: m/z ($C_{10}H_{10}N_4O_3$)=234 [M]; **^{13}C NMR** ($CDCl_3$, δ(ppm)): 167.73, 167.21 (CO, 2C); 132.90, 132.84, 129.02, 128.03 (C_{arom}, 6C); 65.64 (Cα, 1C); 53.41 (CH_3). **^{1}H NMR** ($CDCl_3$, δ(ppm)): 9.8(1H, d, NH, *J*=7.8 Hz); 7.5-7.9 (5H, 3m, $5H_{arom}$); 5.8 (1H, d, Hα, *J*=7.8 Hz); 3.7 (3H, s, CH_3).

2.3.2. Methyl 2-(3-amino-1H-1,2,4-triazol-1-yl)-2-benzamidoacetate 3

White solid;M.p.: 215 °C; M.S-E.I: m/z ($C_{12}H_{13}N_5O_3$)= 275.1013 [M]; **^{13}C NMR** ($CDCl_3$, δ(ppm)):168.15, 165.62, (CO, 2C); 155.73, 149.86, 133.00, 128.92, 127.36, 106.40 (C_6H_5 aromatic carbons); 60.72 (Cα, 1C); 54.01 (CH_3). **^{1}H NMR** ($CDCl_3$, δ(ppm)): 7.5–8.1 (7H, 3 m, $1NH_{amid}$ +$1H_{triazol}$+$5H_{arom}$); 6.5 (1H, d, Hα, *J*=7.2 Hz); 5.6 (2H, br s, NH_2); 3.9 (3H, s, CH_3).

2.3.3. Methyl 2-((1H-1,2,4-triazol-3-yl)amino)-2-benzamidoacetate 4

White solid;M.p.: 208 °C; **^{13}C NMR** ($CDCl_3$, δ(ppm)): 171.21, 168.91, (CO, 2C); 149.79, 146.00, 134.79, 131.90, 128.94, 127.63 (C_6H_5 aromatic carbons); 71.92 (Cα, 1C); 50.90 (CH_3). **^{1}H NMR** ($CDCl_3$, δ(ppm)): 7.5–8.1 (7H, 3 m, $1NH_{amid}$ +$1H_{triazol}$+$5H_{arom}$); 5.8 (1H, d, Hα, *J*=7.2 Hz); 4.7 (1H, s, NH); 3.9 (3H, s, CH_3).

The signal from the NH proton of the triazole ring is not observed on the spectrum, its value is greater than the 8.3 maximum value on our spectrum.

3. Results and discussion

By continuing our research work on the synthesis of heterocycles (Mabrouk *et al.*, 2010; 2013; 2020); we present in this manuscript our strategy for the preparation of a heterocyclic α-aminoester with three methods.

After the preparation and protection of the methyl ester of glycine according to the reaction (**Fig. 1**), the brominationof the latter is carried out following a radical reaction by N-bromosuccinimide or by dibromine in the presence of α,α'-azo-bis-isobutyronitrile (AIBN) in catalytic quantity, under the irradiating action of a 300 W lamp. The methyl 2-azido-2-benzamidoacetate **2** is obtained by substitution of the bromide nucleofuge by the azide group (**Fig. 1**). Methyl 2-azido-2-benzamidoacetate **2** contains a nucleofuge (azido) which is a good leaving group. The use of 1H-1,2,4-triazole-3-amine which contains two active sites leads to nucleophilic substitution (Achamlal *et al.*, 1997; Steglich *et al.*, 1983). The last step in this synthetic strategy is the nucleophilic substitution of methyl 2-azido-2-benzamidoacetate **2** by 1H-1,2,4-triazole-3-amine according to three modes of activation (**Fig. 1**).

Our estimate was to have two products with the predominance of one over another, but the spectroscopic data (MS, ^{13}C NMR, and ^{1}H NMR) obtained showed the existence of only a single product: 2-(3-amino-1H-1,2,4-triazol-1-yl)-2-benzamidoacetate **3** (**Fig. 2**). In what follows, we will discuss the modes of activation of the synthesis of this product and present our point of view on the regioselectivity of this reaction.

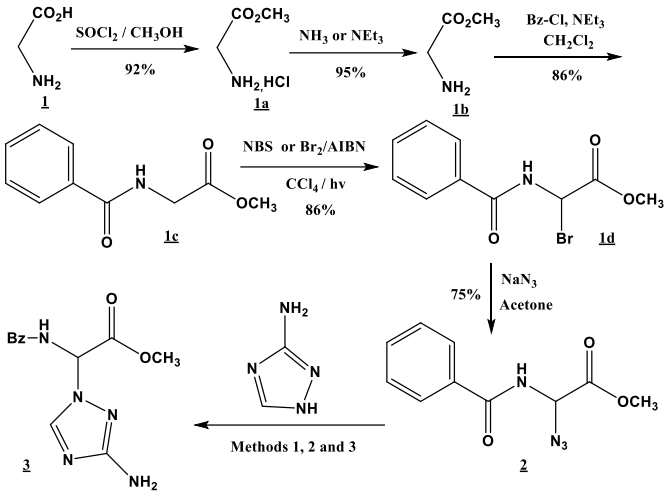

Figure 1. Different steps in the synthesis strategy of 2-(3-amino-1H-1,2,4-triazol-1-yl)-2-benzamidoacetate **3**.

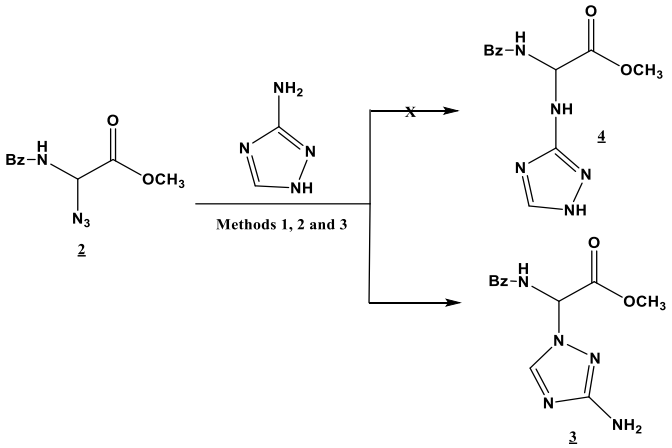

Figure 2. Regioselectivity of the synthesis reaction.

The substitution reaction of methyl 2-azido-2-benzamidoacetate **2** by 1H-1,2,4-triazole-3-amine using the mode of activation in the presence of triethylamine as a base in acetonitrile, leads to 2-(3-amino-1H-1,2,4-triazol-1-yl)-2-benzamidoacetate **3** after five hours at room temperature, with 82% yield (**Fig. 3**). Phase transfer catalysis is another method of activating the synthesis of 2-(3-amino-1H-1,2,4-triazol-1-yl)-2-benzamidoacetate **3** which consists of carrying out the reaction in the DMF, potassium carbonate, and BTBA catalyst for four hours at room temperature. The N-alkylated product **3** is obtained in this case with a yield of 90% (**Fig. 3**).

The procedure by microwave irradiation is selected to compare its effectiveness as the best mode of activation of this reaction to optimize the result of synthesis and the experimental conditions. Indeed, the N-alkylation product **3** is prepared by irradiating a mixture of 1H-1,2,4-triazole-3-amine, methyl 2-azido-2-benzamidoacetate **2**, K_2CO_3, and BTBA on silica as support under a power of 500 W for 10 min with 92% (**Fig. 3**).

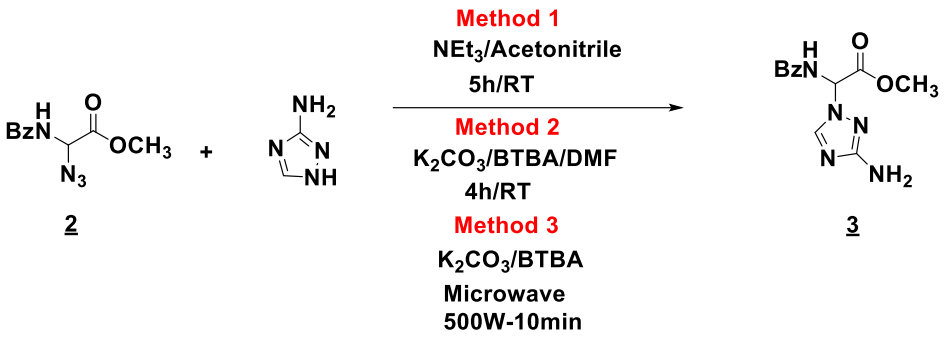

Figure 3. Different methods for activating the 2-(3-amino-1H-1,2,4-triazol-1-yl)-2-benzamidoacetate 3 synthesis reaction.

Based on the different mesomeric forms (Fig. 4) and under the mild conditions of this reaction, we see that the NH_2 group is not active and therefore, there will be no N-alkylation through this site. This result is proven experimentally. Under the reaction conditions (use of a base, room temperature), isomer (e) is more stable than isomer (a) (Fig. 4).

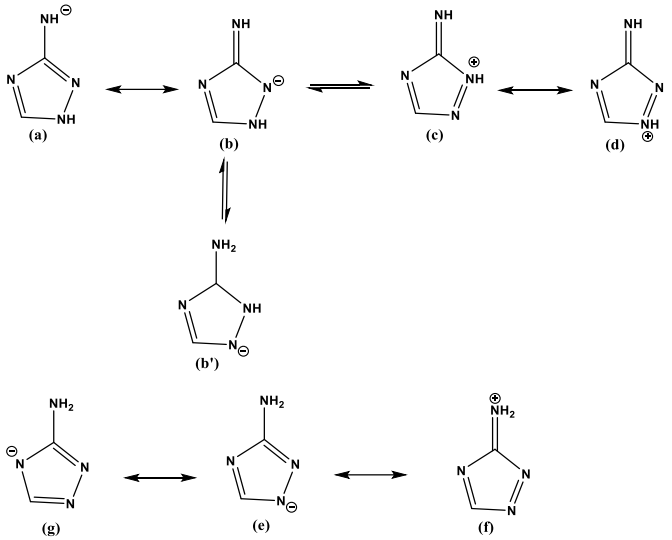

Figure 4. Different mesomeric forms of isomers (a) and (e).

From these observations, it can be concluded that the basicity and nucleophilicity of isomer (e) are greater than that of isomer (a). These results are confirmed by the theoretical study (Table 1) and by the Marvinsketch software (Table 2). Therefore, the results obtained experimentally coincide well with those obtained theoretically.

We gather the variations of free reaction enthalpy ΔG_r characterizing the reactions taking place between methyl 2-azido-2-benzamidoacetate 2 and the isomers (a) and (e) (Table 1).

The free enthalpy variations ΔG_r of reactions (1) and (2) are negative, therefore these two reactions are possible and favored thermodynamically. The free enthalpy value ΔGr corresponding to reaction (1) is lower than that corresponding to reaction (2). But the reaction with isomer (e) is preferentially favored over the reaction with isomer (a).

According to the optimized structure of the amine used (Fig. 5), it can be seen that the proton bound to the N(1) atom is more acidic than that bound to NH_2, which justifies the formation of the anionic form (e) instead of obtaining the form (a).

Table 1. Thermodynamic quantities characterizing the possible reactions between methyl 2-azido-2-benzamidoacetate 2 and isomers (a) and (e) calculated by DFT/B3LYP 6-31G (d, p).

Reactions	ΔGr (Kcal/mol)
(1) from isomer (a)	−30.66
(2) from isomer (e)	−9.72

Table 2. Percentage of the basic form (e) in the range of pH 11-13.5.

Atoms	11	12	12.5	13	13.5
(e)	55.93%	88.53%	95.10%	99.72%	99.99%

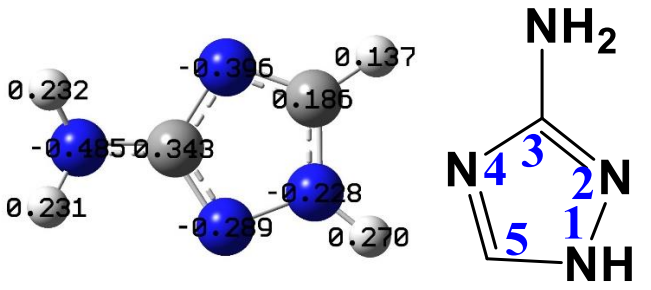

Figure 5. Structure of 1H-1,2,4-triazole-3-amine optimized by DFT/B3LYP/6-31G (d, p).

The Marvinsketch software gives the distribution (%) and the domain of predominance of the acid/base forms of a molecule or an ion according to the pH. The simulation made by the Marvinsketch software shows the existence of a single basic form of 1H-1,2,4-triazole-3-amine in the range of pH 11-13.5 (Table 2), which explains the unexpected regioselectivity of the reactivity of the secondary amine relative to the primary amine. The product formed is the result of nucleophilic substitution of the secondary amine.

The selective addition of 1H-1,2,4-triazole-3-amine to azide 2 was difficult due to the presence of several competing nucleophilic centers on 1H-1,2,4-triazole-3-amine. Regioselective addition was found to occur only at the endocyclic N-1 atom of

1H-1,2,4-triazole-3-amine when the reaction was carried out under kinetic control at room temperature. The increase in temperature can lead to the formation of a thermodynamically more stable compound (Junaid *et al.*, 2019). Indeed, the reaction was carried out at reflux by methods 1 and 2 under the same experimental conditions (Fig. 6) led to the desired product 4 which is thermodynamically more stable and whose spectroscopic and physicochemical characteristics (melting point, frontal ratio) are different from those of product 3. The yields of these reactions are successively 84.5% and 91.5%.

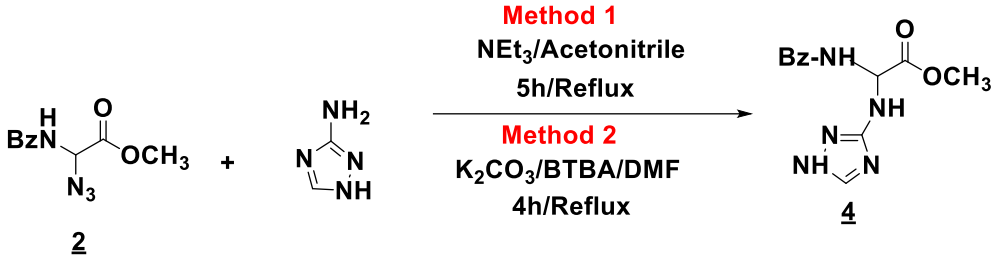

Figure 6. Synthesis of methyl 2-((1H-1,2,4-triazol-3-yl)amino)-2-benzamidoacetate 4 by thermodynamic control.

4. Conclusions

The synthesis of heterocyclic systems is currently an important research axis, not only from the point of view of the fundamental research of heterocycles but also because of the broadening of the practical applications of these compounds. It is necessary to develop new methods and procedures to easily and quickly construct complex heterocyclic molecules from simple precursors.

Triazole and its derivatives represent an important class in the family of heterocycles since these molecules of particular structures are found in important biological building blocks.

The three modes of activation of the synthesis reaction of 2-(3-amino-1H-1,2,4-triazol-1-yl)-2-benzamidoacetate 3 are effective. Microwave irradiation has increasingly become a preferable, economical, and environmental method. The use of computational studies is a new approach to fully understanding the regioselectivity of the reaction and its reaction mechanism. Methyl 2-(3-amino-1H-1,2,4-triazol-1-yl)-2-benzamidoacetate 3 is the product obtained regioselectively by kinetic control. On the other hand, methyl 2-((1H-1,2, 4-triazol-3-yl)amino)-2-benzamidoacetate 4 is the product synthesized by thermodynamic control.

Authors' contributions

Conceptualization: El Houssine Mabrouk; **Data curation**: Mohammed El Mesky; Hicham Zgueni; **Formal Analysis**: El Houssine Mabrouk; Nabil Amri; **Funding acquisition**: Not applicable; **Investigation**: El Houssine Mabrouk; Nabil Amri; Driss Chebabe; **Methodology**: El Houssine Mabrouk; Mohamed Jabha; **Project administration**: El Houssine Mabrouk; Mohamed Azrour; **Resources**: El Houssine Mabrouk; Mohammed El Mesky; Youssef Youssefi; **Software**: Not applicable; **Supervision**: El Houssine Mabrouk; Mohamed Jabha; **Validation**: El Houssine Mabrouk; Nabil Amri; **Visualization**: El Houssine Mabrouk; M'barek Azdouz; Ahmad Oubair; **Writing – original draft**: El Houssine Mabrouk; M'barek Azdouz; **Writing – review & editing**: El Houssine Mabrouk.

Data availability statement

All data sets were generated or analyzed in the current study.

Funding

Not applicable.

Acknowledgments

The authors are grateful to the "Moroccan Association of Theoretical Chemists" (AMCT) for its pertinent help concerning the programs.

Conflict of interest

The authors declare that there is no conflict of interest.

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