

Synthesis and Characterization of a Novel Biheterocyclic α -amino Acid Precursor of the Triazole-Tetrazole Type, via the Copper (I) Catalyzed Alkyne-Azide Cycloaddition Reaction (CuAAC)

Khadim Dioukhane, Younas Aouine, Salaheddine Boukhssas, Asmae Nakkabi, Hassane Faraj, and Anouar Alami

ABSTRACT

In this paper, we describe the regioselective synthesis of a novel triheterocyclic compound, a biheterocyclic amino acid precursor, derived from both triazole and tetrazole. The key step of our synthesis approach was the Huisgen 1,3-dipolar cycloaddition reaction, catalyzed by the copper (I) formed in situ by reduction of Cu(II) salts (CuSO_4 , $5\text{H}_2\text{O}$) by sodium ascorbate, and using as dipole the oxazoline azide derivative 4-(azidomethyl)-4-ethyl-2-phenyl-4,5-dihydrooxazole (4) and as dipolarophile 5-(4-methoxyphenyl)-2-(prop-2-yn-1-yl)-2H-tetrazole (3). The Cu(I) catalysis allowed us to carry out the cycloaddition at room temperature during a reaction time of only 8 hours and also to selectively obtain the 1,4-regioisomer; one of the two possible isomers, with a yield of 90% after chromatography on a silica gel column (ether/hexane: 1/2), and recrystallization in an ether/acetone mixture. The desired compound, 4-ethyl-4-((4-((5-(4-methoxyphenyl)-2H-tetrazol-2-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)-2-phenyl-4,5-dihydrooxazole (5) was analyzed by 1D magnetic resonance spectroscopy (^1H , ^{13}C), and characterized physico-chemically by mass spectrometry and elemental analysis.

Keywords: Tetrazole, alkyne, oxazoline azide, Triazole, CuAAC.

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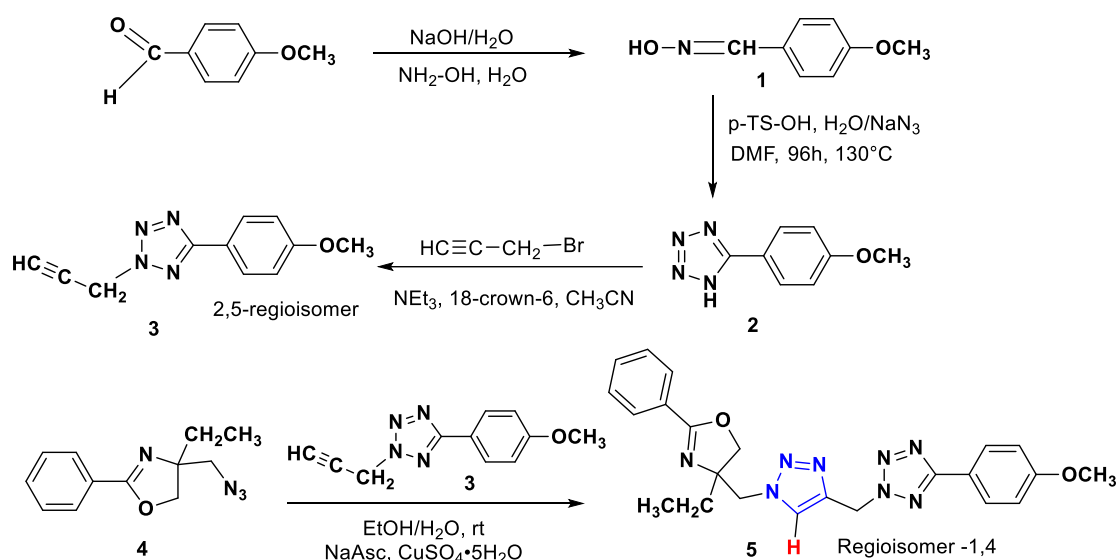
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I. INTRODUCTION

Tetrazole derivatives have been of great interest in recent years because of their potential pharmacological properties [1]-[10]. They can act as bioisosters of the carboxylate group [11], since they have a similar pKa and are deprotonated at physiological pH. This characteristic enables them to resist metabolic degradation. For example, Losartan and Candesartan are two angiotensin II receptor antagonists. These compounds show better binding affinity and action when administered orally. The increased binding strength to the receptor is due to the high capacity of tetrazole to distribute a negative charge at physiological pH, allowing for better interaction with the positive charge at the receptor [12]. Thus, the major advantage of tetrazoles over carboxylic acids is that they resist several biological processes of metabolic degradation. Benzoic acid derivatives often undergo the formation of covalent bonds with the transferred enzymes to form activated species. The same activation process does not occur with aromatic or aliphatic tetrazoles.

Due to the extensive applications of tetrazole derivatives, much effort has been devoted to the development of various preparation methods for the establishment of many tetrazole derivatives [13], [14]. Of these, the cyclocharge reaction [3+2] between nitriles or oximes and an azide source is the most commonly used procedure for accessing 5-substituted tetrazole derivatives. In the light of these observations and in the continuity of our previous work on the synthesis of 2,5-disubstituted tetrazolic compounds [15]-[18], we have focused in this work on the regioselective synthesis of 5-(4-methoxyphenyl)-2-(prop-2-yn-1-yl)-2H-tetrazole (**3**), which will subsequently be used as a dipolarophile in a Cu(I)-

catalyzed cycloaddition reaction with the dipole 4-(azidomethyl)-4-ethyl-2-phenyl-4,5-dihydrooxazole (**4**). Indeed, in our laboratory, starting from 4-methyl-2-phenyloxazoline, EL HAJJI [19] has developed a method of preparation of precursor triheterocyclic systems of α -amino acids and α -amino aldehydes by action of certain acetylenic derivatives on various azides. ZAID [20], for his part, took up and continued this work and obtained new triheterocyclic systems, which enabled him to eventually develop α -amino aldehydes and bitriazolic α -amino acids. For our part, starting from the same starting synthon, we report in this paper the synthesis of a new tri-heterocyclic compound, a biheterocyclic α -amino acid precursor of the triazole-tetrazole. The key step in our synthesis strategy (Scheme 1), was the Huisgen 1,3-dipolar cycloaddition reaction between the oxazoline azide derivative (**4**) and the 5-(4-methoxyphenyl)-2-(prop-2-yn-1-yl)-2H-tetrazole (**3**). This is catalyzed by copper (I) formed in situ by reduction of Cu(II) salts (CuSO₄, 5H₂O) by sodium ascorbate in a water-ethanol solvent mixture (1/1). Cu(I) catalysis allowed us to carry out the cycloaddition at room temperature during a reaction time of only 8 hours and also to selectively obtain the triazole 1,4-regioisomer; one of the two possible isomers, with a yield of 90% after chromatography on silica gel column (ether/hexane: 1/2), and recrystallization in an ether/acetone mixture. The triheterocyclic compound (**5**) is obtained pure with an excellent yield. Its structure has been established on the basis of NMR spectroscopy (¹H, ¹³C), mass spectrometry and elemental analysis.



Scheme 1. Synthesis strategy adopted for the preparation of the tri-heterocyclic compound (**5**).

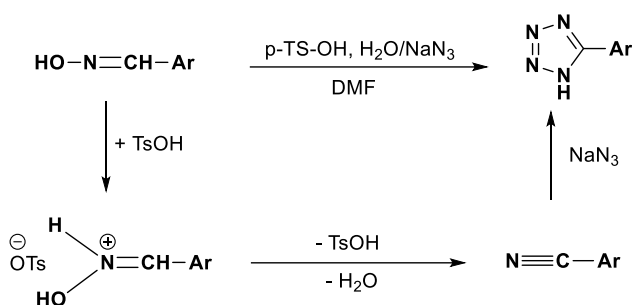
II. RESULTS AND DISCUSSION

The azide compound, 4-(azidomethyl)-4-ethyl-2-phenyl-4,5-dihydrooxazole (**4**) is prepared from the commercial product, 2-amino-2-methyl propan-1,3-diol (CAS No. [115-69-5]) according to the same reaction protocol adopted by EL HAJJI [22] and HAJIB [23].

The synthesis of tetrazolic alkyne first requires the preparation of 5-(4-methoxyphenyl)-1H-tetrazole. Thus, for

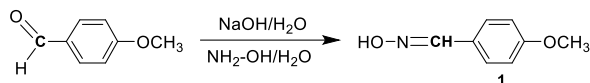
its preparation, we based ourselves on the method described by LIPPMANN and KÖNNECKE [24] and taken up in our laboratory by ALAMI [15] then by ACHAMALE [17] using aldoxime as starting material. This method consists first of preparing the tosylated oxime salt, which is then transformed into the corresponding nitrile. The latter is used as a dipolarophile in a cycloaddition reaction in the presence of sodium azide as a dipole. Thus, for the preparation of 5-(4-methoxyphenyl)-1H-tetrazole (**2**), we have preferred to use a

monotope or one-pot synthesis. This is a chemical synthesis in which a reagent undergoes several successive reactions in a single reaction mixture. It thus avoids long separation and purification processes of intermediate compounds. This type of reaction is actively sought after by chemists because it allows them to save time and increase the overall chemical yield. The process by which a multi-step synthesis is reduced to a single-step synthesis is called telescoping. Thus, the tosylated oxime salt and nitrile are prepared "in situ" in the same cycloaddition reaction with sodium azide, starting with an oxime as starting material (Scheme 2).



Scheme 2. Reaction protocol for the synthesis of 5-substituted tetrazoles.

Thus, commercially available 4-methoxy benzaldehyde oxime (CAS No. [3717-22-4]) was prepared in our laboratory with a yield of 89% from commercially available 4-methoxybenzaldehyde (CAS No. [123-11-5]). The reaction is carried out in an aqueous medium in the presence of sodium hydroxide and hydroxylamine hydrochloride (Scheme 3).



Scheme 3. Oxime synthesis route (1).

The isolated oxime (1) was characterised by 1D NMR of proton and carbon 13 (Fig. 1 and 2) and by comparison with data from the literature. Thus, its proton NMR spectrum shows the following signals:

- A singlet around 3.84 ppm corresponding to the 3 protons of the methoxy group -OCH₃.
- A doublet split around 6.93 ppm corresponding to the 2 aromatic protons ($J_1 = 6.9$ Hz and $J_2 = 2.1$ Hz).
- A doublet split to 7.55 ppm corresponding to the 2 aromatic protons ($J_1 = 6.9$ Hz and $J_2 = 2.1$ Hz).
- A singlet around 8.17 ppm corresponding to the proton -CH=N-.
- A signal widened to 9.42 ppm corresponding to the hydroxyl proton -OH.

As for its ¹³C NMR spectrum, it is characterized by the following signals (Fig. 2):

- A signal around 55.35 ppm corresponding to the carbon of the methoxy group -OCH₃.
- An intense signal around 114.31 ppm corresponding to the 2 aromatic carbons.
- A signal around 124.56 ppm corresponding to the quaternary aromatic carbon bound to -CH=N-OH.
- An intense signal around 128.63 ppm corresponding to the 2 aromatic carbons.
- A signal around 150.03 ppm corresponding to carbon -CH=N-OH.

- A signal around 161.10 ppm corresponding to the quaternary aromatic carbon linked to the methoxy group.

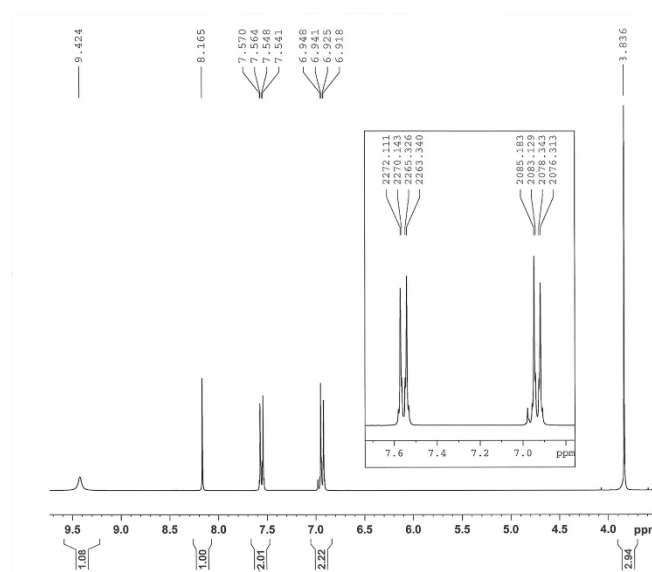


Fig. 1. ¹H-NMR 1D spectrum of compound (1).

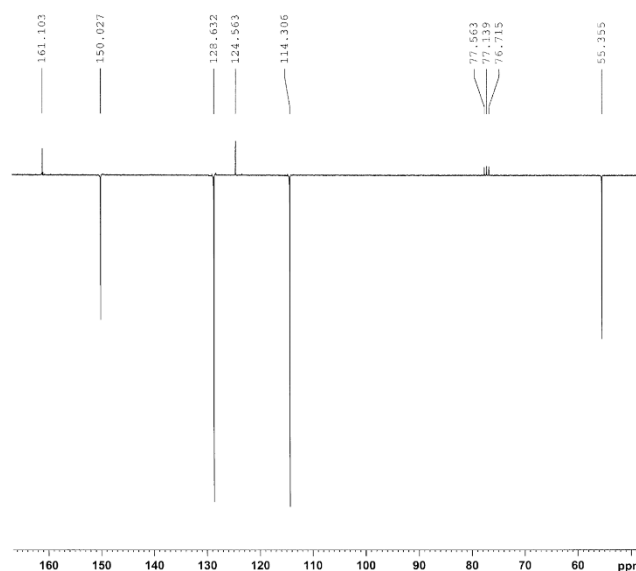
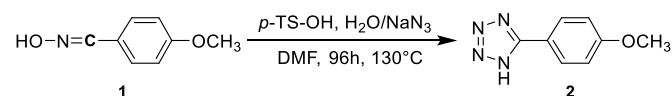


Fig. 2. ¹³C-NMR 1D spectrum of compound (1).

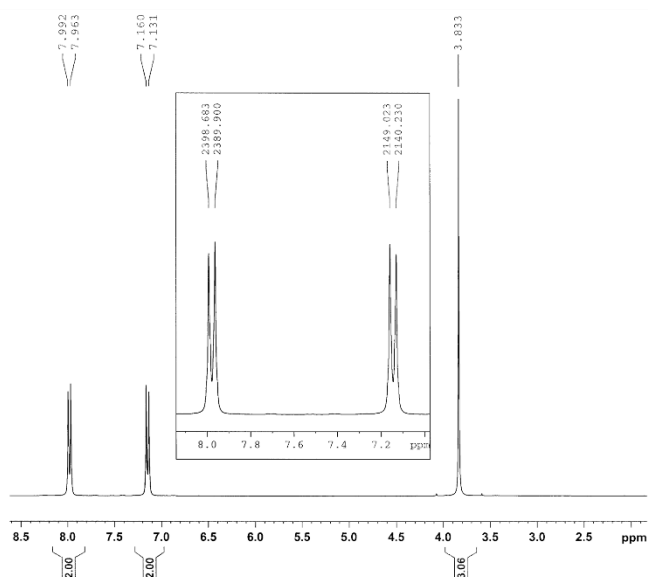
The oxime thus obtained was transformed in a single step into tetrazole by the action of sodium azide in the presence of paratoluenesulfonic acid monohydrate in *N,N*-dimethylformamide (DMF) (Scheme 4). The reaction mixture was stirred for 96 hours at 130 °C.



Scheme 4. Synthesis route of 5-(4-methoxyphenyl)tetrazole (2).

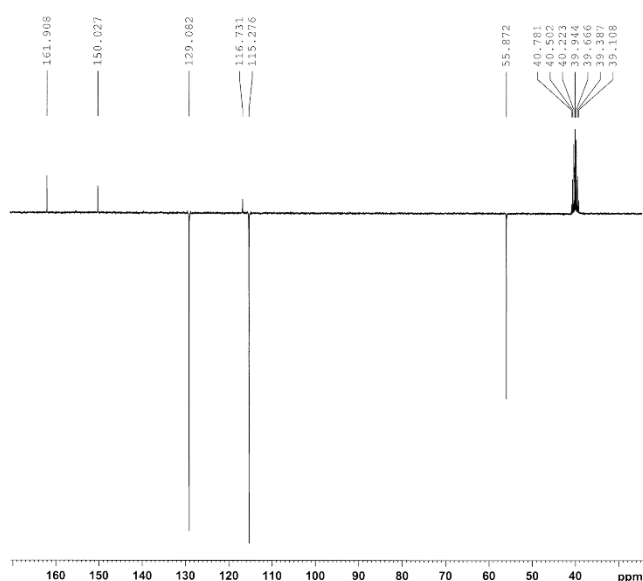
5-(4-methoxyphenyl)tetrazole (2) was obtained pure after recrystallisation in ethyl acetate with a yield of 75%. It has been identified on the basis of the analysis of its ¹H and ¹³C 1D NMR spectra and by comparison with data from the literature [24], [15]. Thus, its ¹H NMR spectrum (Fig. 3) shows the following signals:

- A singlet around 3.83 ppm corresponding to the 3 protons of the methoxy group $-OCH_3$.
- A doublet around 7.14 ppm corresponding to the two 2 aromatic protons ($J = 8.8$ Hz).
- A doublet around 7.98 ppm corresponding to the two 2 aromatic protons ($J = 8.8$ Hz).

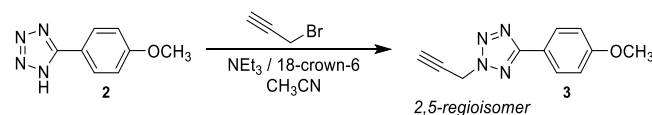
Fig. 3. ^1H -NMR 1D spectrum of compound (2).

Its ^{13}C NMR spectrum (Fig. 4) also shows the following signals:

- A signal around 55.87 ppm corresponding to the carbon of the methoxy group $-OCH_3$.
- An intense signal around 115.27 ppm corresponding to the 2 aromatic carbons.
- A signal around 116.73 ppm corresponding to the quaternary aromatic carbon linked to the tetrazole ring.
- An intense signal around 129.08 ppm corresponding to the 2 aromatic carbons.
- A signal around 150.03 ppm corresponding to the carbon of the tetrazole cycle.
- A signal around 161.91 ppm corresponding to the quaternary aromatic carbon linked to the methoxy group.

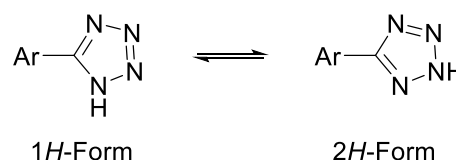
Fig. 4. ^{13}C -NMR 1D spectrum of compound (2).

The action of 5-substituted tetrazole on propargyl bromide is carried out in acetonitrile in the presence of triethylamine and 18-crown-6 in catalytic quantity, at room temperature for 4 hours (Scheme 5). Only the 2,5-disubstituted tetrazole regioisomer is isolated pure after chromatography on a silica gel column (ether/petroleum ether (20/80)) with a yield of 85%. The 18-crown-6 ether is used to promote nucleophilic substitution by preventing the pairing of ions, which act as naked nucleophiles.



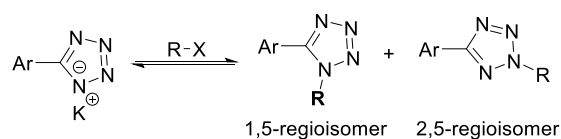
Scheme 5. Dipolarophile synthesis pathway (3).

The structure of the dipolarophile has been confirmed, in addition to ^1H and 2D HSQC NMR, by mass spectrometry (DCI/ NH_3), by weight analysis, and taking into account the data in the literature concerning the orientation of the *N*-alkylation of the 5-substituted tetrazole. 5-substituted tetrazoles are characterized by the presence of an acidic proton, which can occupy two different positions in the heterocycle [8] according to the following tautomeric equilibrium (Scheme 6).



Scheme 6. Tautomerism of tetrazole derivatives.

We can therefore expect to obtain two regioisomers during alkylation reactions where the tetrazole will play the role of a nucleophilic entity. According to data from the literature [25]-[29], the *N*-alkylation of tetrazole substituted in the 5-position by alkyl, aryl, sulphonic ester or ester groups [25], leads to the formation of two regioisomers 1,5- and 2,5- (Scheme 7).

Scheme 7. *N*-alkylation reaction of 5-aryl-tetrazole.

The regioselectivity of the *N*-alkylation of 5-substituted tetrazole is strongly dependent on the electronic structure of the substituent carried by the carbon atom [26]. In the majority of cases of alkylation of tetrazoles substituted in position 5 by an attracting group, the 2,5-regioisomer [27]-[29] was obtained in the majority of cases. In the case of nitrotetrazole only the 2,5-regioisomer is obtained. On the other hand, the use of tetrazoles [30], unsubstituted or substituted by an electron-donating group, preferentially leads to the formation of the 1,5-regioisomer. Moreover, concerning ^{13}C NMR, the literature [31]-[33] reports that the chemical shift of the carbon in position 5 of the aromatic-substituted tetrazole derived from benzene ($-C_6H_5$, *p*-Me-

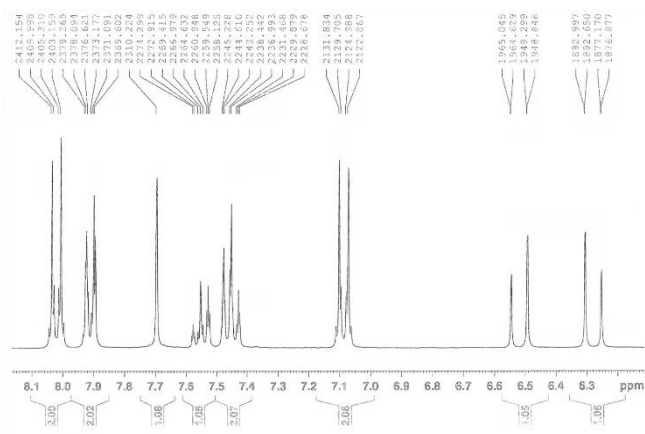


Fig. 8. Enlargement of the ^1H -NMR spectrum of compound (5) between 6.2 ppm and 8.1 ppm.

Thus, its ^1H NMR spectra (Fig. 7 and 8) were characterized by the presence of the following signals:

- A triplet towards 1.03 ppm corresponding to the 3 protons of methyl $-\text{CH}_3$ ($J = 7.4$ Hz).
- A quadruplet towards 1.87 ppm corresponding to the 2 protons of methylene $-\text{CH}_2-\text{CH}_3$ ($J = 7.4$ Hz).
- A singlet around 3.88 ppm corresponding to the 3 protons of the methoxy group $-\text{OCH}_3$.
- An AB system around 4.54 ppm corresponding to the 2 protons of methylene $-\text{CH}_2(\text{Oxaz})$ ($J = 9.3$ Hz).
- An AB system around 4.91 ppm corresponding to the 2 protons of the methylene $-\text{CH}_2\text{-Triaz}$ ($J = 14.7$ Hz).
- An AB system around 6.28 ppm corresponding to the 2 protons of methylene $-\text{CH}_2\text{-Tetraz}$ ($J = 0.3$ Hz).
- A doublet split around 7.08 ppm corresponding to the 2 aromatic protons ($J_1 = 6.9$ Hz and $J_2 = 2.1$ Hz).
- A multiplet towards 7.43-7.55 ppm corresponding to the 3 aromatic protons of the benzene nucleus.
- A singlet around 7.7 ppm corresponding to the proton of the triazole nucleus $=\text{C}^5\text{-H}$.
- A multiplet towards 7.89-7.92 ppm corresponding to the 2 aromatic protons of the benzene nucleus.
- A doublet split around 8.02 ppm corresponding to the 2 aromatic protons ($J_1 = 6.9$ Hz and $J_2 = 2.1$ Hz).

Thus, contrary to the data in the literature [35], including the work carried out in our laboratory [36], the triazole proton H-5 resonates at 7.7 ppm and is therefore less deshielded. This inverse phenomenon can be justified by the fact that the H-5 proton does not undergo the anisotropic effect of the tetrazole nucleus.

Its ^{13}C NMR spectrum (Fig. 9) has, among others, the following characteristic signals:

- A signal around 5.04 ppm corresponding to methyl carbon $-\text{CH}_3$.
- A signal around 30.17 ppm corresponding to the carbon of the methylene $-\text{CH}_2-\text{CH}_3$.
- A signal around 45.36 ppm corresponding to the carbon of the methylene $-\text{CH}_2\text{-Triaz}$.
- A signal around 54.51 ppm corresponding to the carbon of the methylene $-\text{CH}_2\text{-Tetraz}$.
- A signal around 54.88 ppm corresponding to the carbon of the methoxy group $-\text{OCH}_3$.
- A signal around 72.37 ppm corresponding to the quaternary carbon $-\text{Cq}(\text{Oxaz})$.

- A signal around 72.78 ppm corresponding to the carbon of the methylene $-\text{CH}_2(\text{Oxaz})$.
- An intense signal around 114.38 ppm corresponding to the 2 aromatic carbons.
- A signal around 115.7 ppm corresponding to the carbon $=\text{C}^5\text{-H}$ of the 1,2,3-triazole nucleus.
- An intense signal around 119.73 ppm corresponding to the quaternary aromatic carbon linked to the tetrazole.
- A signal around 127.14 ppm corresponding to the carbon $=\text{C}^4$ of the 1,2,3-triazole nucleus.
- An intense signal around 128.18 ppm corresponding to the two aromatic carbons.

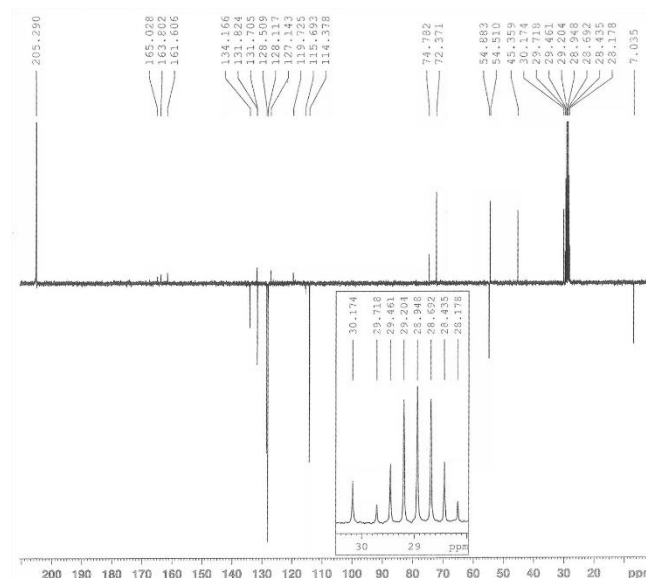


Fig. 9. ^{13}C -NMR 1D spectrum of compound (5).

III. MATERIALS AND METHODS

All solvents were purified following the standard techniques and commercial reagents were purchased from Sigma-Aldrich (St. Louis, MO, USA). Melting point was determined with an electrothermal melting point apparatus and was uncorrected. NMR spectra (^1H and ^{13}C) were recorded on a Bruker AM 300 spectrometer (operating at 300.13 MHz for ^1H , at 75.47 MHz for ^{13}C) (Bruker Analytische Messtechnik GmbH, Rheinstetten, Germany). NMR data are listed in ppm and are reported relative to tetramethylsilane (^1H , ^{13}C); residual solvent peaks being used as an internal standard. All reactions were followed by thin-layer chromatography (TLC). TLC analyses were carried out on 0.25 mm thick pre-coated silica gel plates (Merck Fertigplatten Kieselgel 60F₂₅₄) and spots were visualized under UV light or by exposure to vaporized iodine. Mass spectra were measured on a JEOL-JMS-DX 300 FAB instrument and Desorption in chemical ionisation with NH_3 DCI instrument. Elemental analysis was performed with a Flash 2000 EA 1112, Thermo Fisher Scientific-Elemental Analyzer (CNRST-Rabat, Morocco).

4-methoxybenzaldehyde oxime (I)

To 35 mmoles of sodium hydroxide (NaOH) and 20 mmoles of aldehyde in 4 mL of water, 22 mmoles of hydroxylamine hydrochloride were added in small portions. The mixture was kept stirred at room temperature for 4 hours. After reaction, the solution was filtered and the rest of the

oxime in the aqueous phase was extracted with ether. The resulting solution was dried and then evaporated. The resulting solid was recrystallized in an ether/petroleum ether mixture.

Yield = 90% (White solid); $R_f = 0.35$ AcOEt/hexane (1/4); m.p. = 52°C.

$^1\text{H-NMR}$ (CDCl_3 , ppm): 3.84 (3H, s, $-\text{OCH}_3$); 6.93 (2H, dd, $J_1 = 6.9$ Hz, $J_2 = 2.1$ Hz, 2H_{arom}); 7.55 (2H, dd, $J_1 = 6.9$ Hz, $J_2 = 2.1$ Hz, 2H_{arom}); 8.17 (1H, s, $-\text{CH}=\text{N}-$); 9.42 (1H, e, $-\text{OH}$). $^{13}\text{C-NMR}$ (CDCl_3 , ppm): 55.35 ($-\text{OCH}_3$); 114.31 ($2\text{C}_{\text{arom-H}}$); 124.56 ($1\text{C}_{\text{arom-CH}=\text{N}}$); 128.63 ($2\text{C}_{\text{arom-H}}$); 150.03 ($-\text{CH}=\text{N}-\text{OH}$); 161.10 ($1\text{C}_{\text{arom-O}}$).

5-(4-methoxyphenyl)-1H-tetrazole (2)

10 mmoles of 4-methoxybenzaldehyde oxime and 10 mmoles of paratoluenesulfonic acid monohydrate in 12 mL of *N,N*-dimethylformamide (DMF) are stirred with 0.65g (10 mmoles) of NaN_3 . After reaction water was added to the reaction residue, the aqueous phase was extracted three times with methylene chloride or ether and then acidified with a solution of 3M hydrochloric acid. The precipitated tetrazole was filtered, the rest of the product in the aqueous phase was extracted with ethyl acetate, the organic phase was dried on Na_2SO_4 and then evaporated to dryness. The solid obtained was added to the precipitate and then the whole was recrystallized in ethanol.

Yield = 75% (White solid); m.p. = 235°C.

$^1\text{H-NMR}$ (DMSO-d_6 , ppm): 3.83 (3H, s, $-\text{OCH}_3$); 7.14 (2H, d, $J = 8.8$ Hz, 2H_{arom}); 7.98 (2H, d, $J = 8.8$ Hz, 2H_{arom}).

$^{13}\text{C-NMR}$ (DMSO-d_6 , ppm): 55.87 ($-\text{OCH}_3$); 115.27 ($2\text{C}_{\text{arom-H}}$); 116.73 ($1\text{C}_{\text{arom-Tetraz}}$); 129.08 ($2\text{C}_{\text{arom-H}}$); 150.03 ($1\text{C}_{\text{q-Tetraz}}$); 161.91 ($1\text{C}_{\text{arom-O}}$).

5-(4-methoxyphenyl)-2-(prop-2-yn-1-yl)-2H-tetrazole (3)

To 10 mmoles of 5-(4-methoxyphenyl)-1H-tetrazole suspended in 10 mL of acetonitrile, 11 mmoles of triethylamine and 4 mmoles of 18-crown-6 ether were added. Propargyl bromide (10 mmoles) was then added and the reaction mixture was stirred at room temperature for 4 hours. After reaction, the solution was filtered, the solvent was evaporated and the residue obtained is chromatographed on a silica gel (hexane ether) column. The solid obtained was recrystallized in a petroleum ether/methylene chloride mixture.

Yield = 82%, m.p. = 71°C, $R_f = 0.73$ (ether/petroleum ether: 2/1)

$^1\text{H-NMR}$ (acetone- d_6 , ppm): 3.23 (1H, t, $J = 2.62$ Hz, $-\text{C}\equiv\text{CH}$); 3.89 (3H, s, $-\text{OCH}_3$); 5.68 (2H, d, $J = 2.62$ Hz, $-\text{CH}_2-\text{C}\equiv\text{CH}$); 7.11 (2H, dd, $J_1 = 6.8$ Hz, $J_2 = 2.2$ Hz, 2H_{arom}); 8.08 (2H, dd, $J_1 = 6.8$ Hz, $J_2 = 2.2$ Hz, 2H_{arom}).

MS [DCI/NH_3]: $[\text{M}+\text{H}]^+ = 215$ and $[\text{M}+\text{NH}_4]^+ = 232$.

Anal. Calcd. for $\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}$ (%): C, 61.67; H, 4.71; N, 26.15; Found (%): C, 61.64; H, 4.75; N, 26.19.

4-ethyl-4-((4-((5-(4-methoxyphenyl)-2H-tetrazol-2-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)-2-phenyl-4,5-dihydrooxazole (5)

2.2 mmoles of alkyne (3) and 2.2 mmoles of oxazoline azide (4) were stirred in 10 mL of an ethanol-water mixture (1/1), 0.05 equivalent of copper sulphate pentahydrate ($\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$) and 0.1 equivalent of sodium ascorbate (Na-Asc) were added. The TLC analysis indicated complete consumption of the reactants after 8 hours of stirring at room

temperature. After filtration of the precipitate formed, the solvent was evaporated under pressure and the crude was washed with water and extracted with methylene chloride. The organic phase is then dried with magnesium sulphate and the solvent was removed under reduced pressure. The oil obtained was purified by chromatography on a silica gel column (ether/hexane: 1/2). The solid obtained was recrystallized in an ether/acetone mixture.

Yield = 90% (White solid); $R_f = 0.4$ (ether/acetone 5%); m.p. = 160°C.

$^1\text{H-NMR}$ (Acetone- d_6 , δ ppm): 1.03 (3H, t, $J = 7.4$ Hz, $-\text{CH}_3$); 1.87 (2H, q, $J = 7.4$ Hz, $-\text{CH}_2-\text{CH}_3$); 3.88 (3H, s, $-\text{OCH}_3$); 4.54 (2H, AB, $J = 9.3$ Hz, $-\text{CH}_2-\text{Oxaz}$); 4.91 (2H, AB, $J = 14.7$ Hz, $-\text{CH}_2-\text{Triaz}$); 6.28 (2H, AB, $J = 0.3$ Hz, $-\text{CH}_2-\text{Tetraz}$); 7.08 (2H, dd, $J_1 = 6.9$ Hz, $J_2 = 2.1$ Hz, 2H_{arom}); 7.43-7.55 (3H, m, 3H_{arom}); 7.7 (1H, s, $=\text{C}^5-\text{H}$); 7.89-7.92 (2H, m, 2H_{arom}); 8.02 (2H, dd, $J_1 = 6.9$ Hz, $J_2 = 2.1$ Hz, 2H_{arom}).

$^{13}\text{C-NMR}$ (Acetone- d_6 , δ ppm): 5.04 ($-\text{CH}_3$); 30.17 ($-\text{CH}_2-\text{CH}_3$); 45.36 ($-\text{CH}_2-\text{Triaz}$); 54.51 ($-\text{CH}_2-\text{Tetraz}$); 54.88 ($-\text{OCH}_3$); 72.37 ($-\text{C}_{\text{q}}-\text{Oxaz}$); 72.78 ($-\text{CH}_2-\text{Oxaz}$); 114.38 ($2\text{C}_{\text{arom-H}}$); 115.7 ($=\text{C}^5-\text{H}(\text{Triaz})$); 119.73 ($1\text{C}_{\text{arom-Tetraz}}$); 127.14 ($=\text{C}^4(\text{Triaz})$); 128.18 ($2\text{C}_{\text{arom-H}}$); 128.51 ($2\text{C}_{\text{arom-H}}$); 131.70 ($1\text{C}_{\text{arom-Oxaz}}$); 131.82 ($2\text{C}_{\text{arom-H}}$); 134.17 ($2\text{C}_{\text{arom-H}}$); 161.61 ($-\text{C}=\text{N}(\text{Oxaz})$); 163.8 ($1\text{C}_{\text{arom-O}}$); 165.03 ($=\text{C}^5(\text{Tetraz})$).

MS [DCI/NH_3]: $[\text{M}+\text{H}]^+ = 445$.

Anal. Calcd. for $\text{C}_{23}\text{H}_{24}\text{N}_8\text{O}_2$ (%): C, 62.15; H, 5.44; N, 25.21; Found (%): C, 62.18; H, 5.41; N, 25.24.

IV. CONCLUSION

In summary, the 1,3-dipolar cycloaddition reaction between azide (4) and heterocyclic (3) terminal alkyne, catalyzed by copper (I), provided regioselective access to the 1,4-regioisomer (5) with an excellent yield. The structural characterization was determined by Proton nuclear magnetic resonance ($^1\text{H-NMR}$), Carbon-13 nuclear magnetic resonance ($^{13}\text{C-NMR}$), mass spectrometry, and elemental analysis. The chemical shift of the triazole proton H-5, which resonates at 7.7 ppm can be justified by the fact that the H-5 proton does not undergo the anisotropic effect of the tetrazolic cycle. The evaluation of the anti-corrosion and biological activities of the synthesized product is under way.

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