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An efficient synthesis of novel triazoles incorporating barbituric motifs *via* [3+2] cycloaddition reactions: An experimental and theoretical study

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Abstract: In this work, the synthesis of novel triazole derivatives with barbituric motifs in good yields is described. The alkyne was prepared through the Knoevenagel reaction of barbituric derivatives with *ortho* and *para O*-propargylated hydroxybenzaldehyde. The mechanism and regioselectivity of this [3+2] cycloaddition reaction were investigated using the density functional theory at the B3LYP/6-31+G(d) level of theory. The computational studies revealed that a di-copper catalyzed stepwise mechanism, involving six-membered ring intermediate, is the preferred pathway. The regioselectivity was explained in terms of frontier molecular orbital (FMO) interactions, local and global electrophilicity and nucleophilicity indices. Accordingly, the favored interactions for di-copper acetylide are in good agreement with the observed regioselectivity, while completely opposite results were obtained for a possible uncatalysed reaction.

Keywords: triazoles; barbituric derivatives; DFT study; mechanism.

INTRODUCTION

1,2,3-Triazole has been known as an important five-membered heterocycle that forms the building blocks of many biologically important compounds. These heterocyclic scaffolds are found in drugs, natural products and agrochemicals.[1] They are also utilized in many biological applications, including the treatment of tumors,[2,3] HIV,[4] allergy,[5] fungal infections[6,7] and microbial diseases.[8–12] The first 1,4-disubsituted triazole was prepared by Huisgen[13] through the [3+2] cycloaddition (CA) of terminal or internal alkynes and azides, which are well-known as an important class of a click reaction. The applications of click reactions are wide in scope. Click reactions give excellent yields and generate inoffen-

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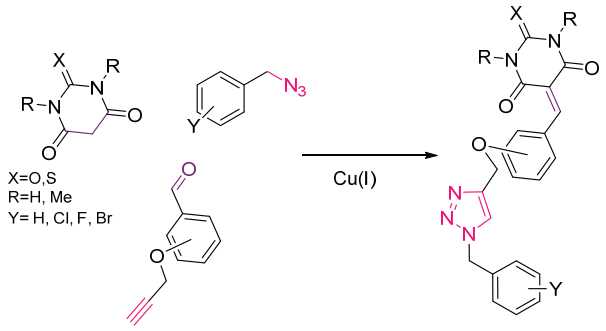
sive by-products that can be removed by convenient methods. The required process characteristics include simple reaction conditions, readily available reactants, solvent free reactions or using a solvent that is benign or easily removed, and simple product isolation.[14]

The enormous attention recently gained by these reactions began with the pivotal discovery by the groups of Meldal[15] and Sharpless,[16] in which copper(I) catalysis was found to dramatically accelerate the reaction under mild conditions. On the other hand, 1,4-substituted 1,2,3-triazoles are generated through these Cu(I) catalyzed azide-alkyne CA (CuAAC) reactions with high regioselectivity (Scheme 1).[17–22] The required copper(I) species in the CuAAC reaction are either added directly as cuprous salts, usually with stabilizing ligands,[15,23–25] or more often, generated from copper(II) salts with reducing agents.[16] Barbituric acid derivatives are also used for the treatment of epilepsy and seizures.[26,27] Substituted barbituric[26,28,29] or thiobarbituric[30,31] acids with heterocyclic/aryl substituents have increased antiepileptic activity. The interest in using barbituric acid derivatives is mainly the lack of *E*/*Z* isomer formation in the Knoevenagel condensation.[33]



Scheme 1. Regioselective synthesis of triazoles.

Based on the pharmacological properties associated with barbituric acid derivatives and triazole heterocycles, arose our interest in combining these heterocyclic moieties through a CuAAC reaction, catalyzed by a copper(I) species[33,34] generated *in situ* from copper(II) and ascorbate.[35–37] The barbituric derivatives were generated *via* the Knoevenagel condensation of propargylated hydroxybenzaldehyde and barbituric acid (Scheme 1). In addition, a theoretical study on the mechanism of this click reaction was realized by means of the density functional theory (DFT).

EXPERIMENTAL

General information and apparatus

Melting points were measured on an Electrothermal 9100 apparatus. The NMR spectra were recorded on a Bruker DRX-400 Avance instrument (400.1 MHz for ^{1}H, 100.6 MHz for

^{13}C) using DMSO as the solvent. The IR spectra were recorded on an FT-IR Bruker Vector 22 spectrometer. The mass spectra were recorded on a Finnigan MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were realized using a Perkin Elmer 2400II CHNS/O elemental analyzer.

Synthesis

*Propargylation of hydroxybenzaldehyde derivatives **2a** and **b***. Propargyl bromide (6 mmol) was added to a stirred solution of hydroxybenzaldehydes **1a** or **1b** (5 mmol) and potassium carbonate (5 mmol) in DMF (15 mL). After stirring for 4–24 h, water was added and the precipitated solid was filtered and washed with water.

General procedure for the Knoevenagel condensation

*Preparation of **4a**–**d***. To a stirred solution of barbituric acid (1.2 mmol) in aqueous HCl (25 ml, 10 %) were added propargylated aldehydes **2a** and **b** (1.0 mmol) at room temperature. After stirring for 2–10 h, the precipitated material was filtered and washed with water and ethanol.[39]

*Preparation of **4e**–**f***. Propargylated aldehydes **2a** and **b** (1.0 mmol) were added to a stirred solution of *N*,*N*-dimethylbarbituric acid (**3c**, 1.2 mmol) in water (20 ml) containing $(NH_4)_2HPO_4$ (20 mol %) at room temperature. After stirring for 4–12 h, the yellow precipitate was filtered and washed with water and ethanol.

*Preparation of alkyl azide **6a**–**c***. Sodium azide (1.2 mmol) was added to a solution of the required benzyl bromide derivative **5a**–**c** (1 mmol) in DMF. The mixture was heated at 100 °C and, after completion (3 h), the reaction was quenched with an aqueous solution of NH_4Cl (15 mL) and extracted with ethyl acetate (3×20 mL). The combined organic extracts were washed with brine (3×20 mL) and dried over $MgSO_4$. After evaporation of the solvent at reduced pressure, the pure azides were isolated.[39]

General procedure for the click cycloaddition reaction

Alkynes **4a**–**f** (1.2 mmol) and benzyl azide **6a**–**c** (1 mmol) were added to a solution of $CuSO_4$ (0.2 equiv.) in DMSO (10 mL) in a capped flask at room temperature. The reaction mixture was stirred at 80 °C and after completion (12 h), the reaction was quenched with a saturated aqueous solution of NH_4Cl (30 mL) and extracted with ethyl acetate (3×40 mL). The combined organic extracts were washed with brine (3×30 mL), dried over Na_2SO_4 and concentrated under vacuum.

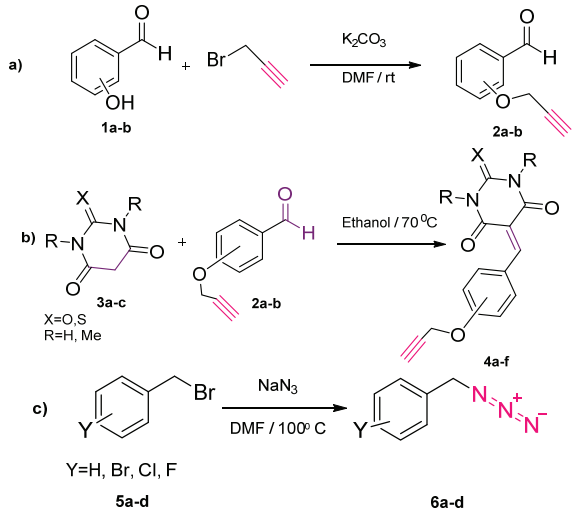
Analytical and spectral data of the synthesized compounds are given in Supplementary material to this paper.

RESULTS AND DISCUSSION

Initially, compounds **2a** and **b** were prepared from hydroxybenzaldehydes **1a** and **b** and propargyl bromide in the presence of K_2CO_3 (Scheme 2a).[40] Then, the alkyne **4a** was synthesized through the Knoevenagel condensation of barbituric derivative **3a** and propargylated hydroxybenzaldehyde **2a** under reflux conditions in good yield (Scheme 2b and Table I).[41,42] The general procedure for the preparation of organic azides is shown in Scheme 2c.[39]

Then the cycloadduct **7** was prepared from the [3+2] CA reaction of benzyl azide **6a** as a dipole and alkyne **4a** as a dipolarophile in the presence of copper(I) species, generated *in situ* from copper(II)/ascorbate in DMSO.[15] The synthetic route is outlined in Scheme 3. The progress of the reaction was monitored by thin

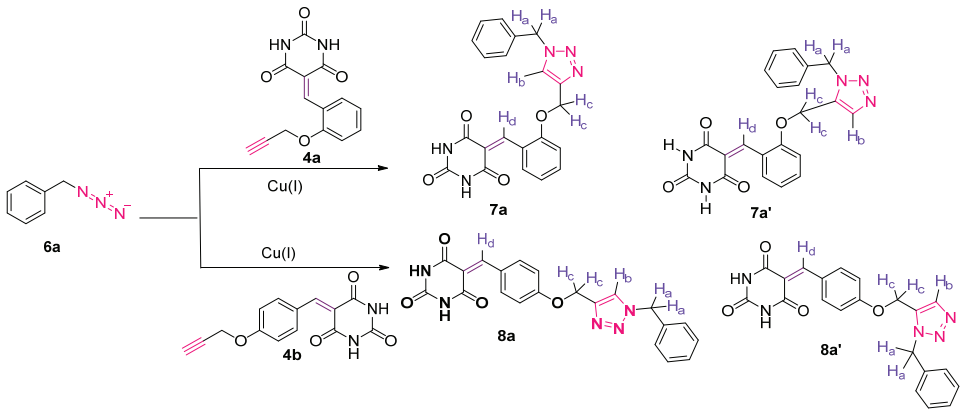
layer chromatography (TLC) and the pure cycloadduct was purified by column chromatography. This protocol was applied to a series of various derivatives of alkyne **4a**–**f** and benzyl azide **6a**–**d** under similar conditions (Table II).



Scheme 2. Preparation of dipole **6a**–**d** and dipolarophiles **4a**–**f**.

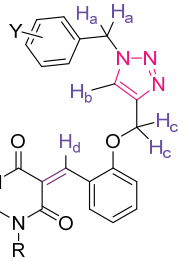
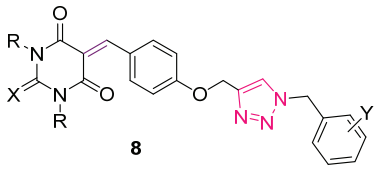
TABLE I. Knoevenagel condensation

Entry	OCH_2CCH	X	R	Reaction time, h	Yield, %
4a	Ortho	O	H	10	85
4b	Para	O	H	7	90
4c	Ortho	S	H	6	80
4d	Para	S	H	2	87
4e	Ortho	O	Me	12	84
4f	Para	O	Me	4	79



Scheme 3. Synthesis of the compounds **7** and **8**.

TABLE II. The copper-catalyzed [3+2] CA reaction of alkynes and azides

Entry	X	Y	R	Yield%	Structure
7a	O	H	H	75	
7b	O	4-Br	H	67	
7c	O	H	Me	63	
7d	O	3-F	Me	53	
7e	S	H	H	72	
7f	S	3-F	H	51	
7g	S	4-Br	H	56	
					7
8a	O	H	H	75	
8b	O	2-Cl	H	71	
8c	O	3-F	H	62	
8d	O	4-Br	H	81	
8e	O	2-Cl	Me	75	
8f	S	H	H	68	
8g	S	4-Br	H	63	
					8

A facile and rapid access to a wide range of novel 1,2,3-triazoles containing a wide range of functional groups has been developed in good yield. The structure of the cycloadducts **7a**–**g** was determined by various spectroscopic techniques. Thus, the IR spectrum of **7a** demonstrated absorption at 3438 cm^{-1}, which indicated the presence of a NH group, and at 1677 and 1159 cm^{-1}, which correspond to the CO and ether group, respectively. The ^{1}H-NMR spectrum of **7a** exhibited a singlet peak of $–CH_2$ group at 5.27 ppm for H_a and a singlet at 5.61 ppm for two H_c protons of OCH_2 group. A singlet peak at δ = 8.07 ppm for H_b of triazole heterocyclic compound and a singlet peak at 8.32 ppm of CH is referred to H_d of methine group, respectively (Scheme 3). Two signals at 10.99 and 10.75 ppm were assigned for NH groups of barbituric acid. The ^{13}C-NMR of cycloadduct **7a** showed a peak at δ =53.34 ppm owing to the CH_2 group and a peak at δ = 61.92 ppm for the CH_2 attached to the oxygen group. This suggests that triazole **7a** was formed. It is well known that in the presence of a copper catalyst, the preferred regioisomeric products are 1,4-triazoles.[15–22] Thus, it could be proposed that **7a** was produced in the CuAAC cycloaddition reaction studied here. This could be verified by a computational study on the NMR spectra of the two possible regioisomers and a comparison of the results with experimental data. The formation of the product was also confirmed by mass spectrometry. The mass spectrum of **7** showed a molecular ion peak at 402.1 (M^+).

Computational

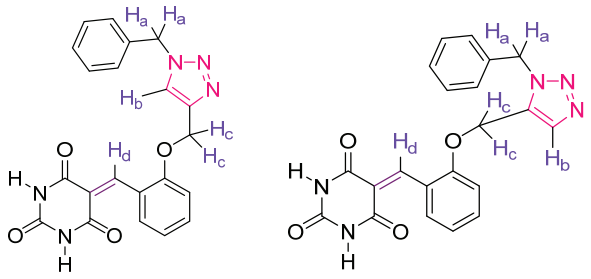
In this study, the geometry optimization of all ground states and transition states (TSs) were performed using the B3LYP[43] functional with the 6-31+G(d)

basis set as implemented in the Gaussian 09 program package.4 Solvent effects were considered by means of CPCM calculations in DMSO.[45–48] All the geometry optimizations were performed without any symmetry constraint. The stationary geometries were characterized as minima (zero imaginary frequency) or transition states (one imaginary frequency) by analytical frequency calculations at the same theory level as the geometry optimizations. In the selected reaction pathways, an IRC calculation was performed to fully characterize the located transition state structures.[49,50] The ^{1}H chemical shifts were also studied by means of the GIAO method using tetramethylsilane (TMS) as the ^{1}H reference at the 6-311+G(d) level.[51] The reported energies include zero-point vibrational corrections, thermal and entropy corrections at 298 K and solvation energies.

^{1}H-NMR spectral analysis

The two possible regioisomers of these reactions have similar splitting pattern. Thus, the ^{1}H-NMR spectrums of the possible triazoles **7a** and **7a′** were calculated and compared with the obtained experimental results. As shown in Table III, the calculated values of H_a, H_c and H_d of **7a** are closer to the experimental values. Accordingly, the cycloadduct of this reaction could be 1,4-substituted 1,2,3-triazole **7a**.

TABLE III. Comparison of the experimental and theoretical ^{1}H-NMR chemical shifts data (δ / ppm) of H_a, H_b, H_c and H_d of the cycloadducts



7a **7a'**

Atom number	**7a**	**7a′**	Experimental
H_e	5.10	5.6	5.22
H_b	7.51	7.31	8.06
H_c	5.40	4.90	5.71
H_d	8.5	9.15	8.32

Uncatalyzed concerted cycloaddition

The uncatalyzed 1,3-dipolar cycloaddition of organic azides with alkynes was also studied by means of DFT calculations. Due to the asymmetry of the reagents, two regioisomeric adducts could be formed in the [3+2] CA reaction (Fig. 1). The study found high-energy barriers for both the 1,4- and 1,5-appro-

aches. In addition, the energy barriers for the coupling of **6a** and **4a** were calculated in order to compare properly its energetics with the catalytic pathways described in this paper. The calculations gave, as expected, analogous energy barriers for the 1,4- and 1,5-regiochemistries (Fig. 1), resulting in 43.83 and 45.65 kcal* mol^{-1}, respectively. This energy difference explains the lack of regioselectivity when the cycloaddition is performed in the absence of any catalyst, as well as the slowness of the transformation. The formation of triazoles **7a** and for an ortho isomer are exergonic by more than 30 kcal mol^{-1}. The optimized geometries of the transition states are shown in Fig. 1.

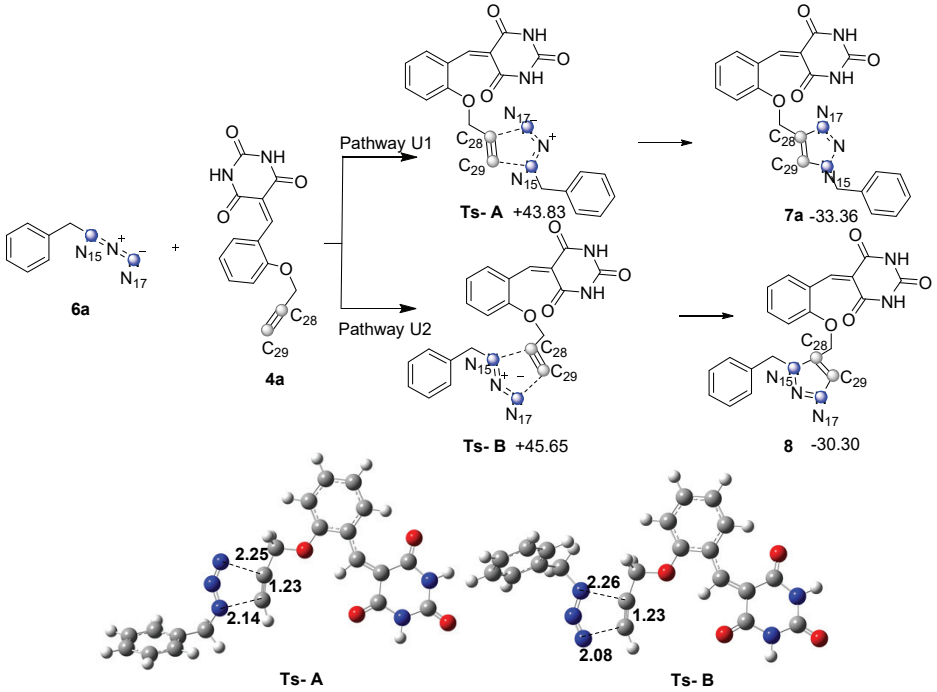


Fig. 1. The uncatalyzed CA pathways. Energies are in kcal/mol; distances in Å.

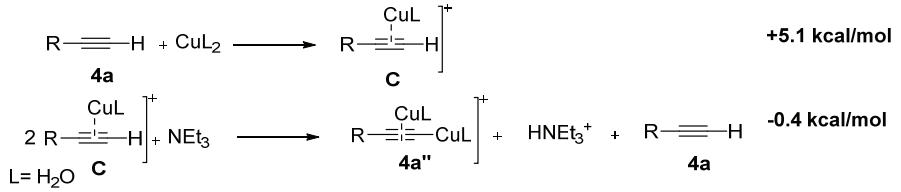
Di-copper catalyzed stepwise cycloaddition

The analysis of the alkyne/Cu reaction pathways between alkyne **4a** and azide **6a** showed that the CA reaction occurs through a stepwise mechanism (Schemes 4 and 5). Consequently, the reactants, transition states, and intermediates were located and characterized. The optimized geometries of the transition states and intermediates are presented in Fig. 2.

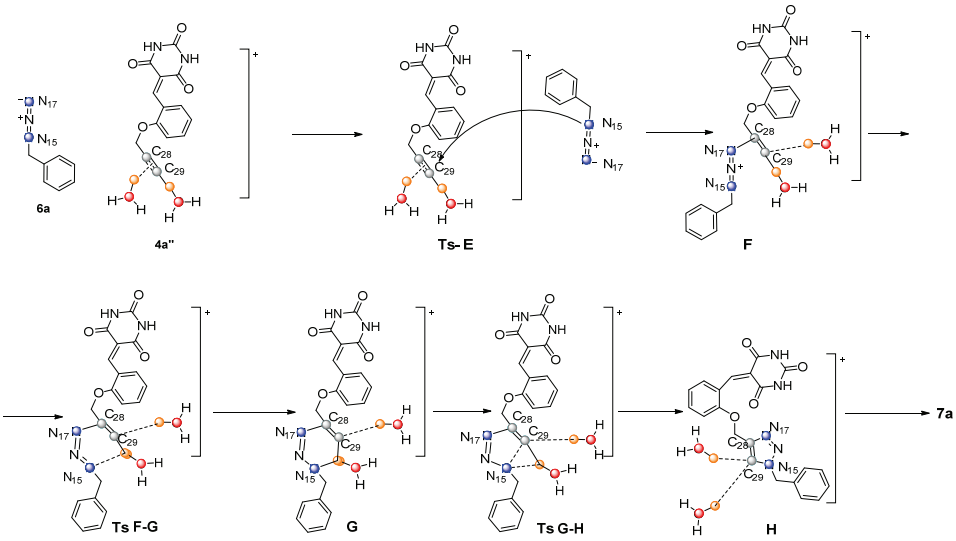
Under the reaction conditions, alkyne **4** is acidified considerably through coordination with one CuL and the formation of complex **C**, and the calculations

* 1 kcal = 4184 J

showed that this coordination is endergonic by 5.1 kcal mol^{-1}. The deprotonation of complex **C** to afford the di-copper acetylide **4a''**, using triethylamine as a base, is exergonic by 5.5 kcal mol^{-1} (Scheme 4). In other words, the deprotonation process of alkyne in the presence of two copper ions is 0.4 kcal mol^{-1} more favorable than in the presence of one copper ion. This complexation likely increases activity of the alkyne toward the CA reaction (Scheme 5).



Scheme 4. Probable reaction mechanism of deprotonation of alkyne.



Scheme 5. The di-copper stepwise CA pathway.

An in-depth analysis of all the mechanistic proposals for the Cu-catalyzed cycloadditions of azides and alkynes in aqueous media through DFT calculations showed that the di-copper catalyzed stepwise CA mechanism could be suggested as the preferred pathway.[52,53] The stepwise di-copper reaction is initiated with coordination of atom N15 of azide **6a** and Cu atom of acetylide of **4a''** to provide intermediate **E**. The calculations show that the rate-determining step of this reaction is the formation of intermediate **E**, although it has a lower barrier than the uncatalyzed manner (23.94 *vs*. 43.83 kcal mol^{-1}). In the following, the formation of a carbon–nitrogen bond between the azide and alkyne occurred, leading to the

six-membered ring **F**. Then, the five-membered ring **G** is formed through ring contraction of **G**.

The activation energy associated with the nucleophilic attack of azide **6a** on the di-copper acetylide of **4a''** *via* **Ts-D** is 23.94 kcal mol^{-1}; the formation of the corresponding intermediate **F** is endergonic, 21.26 kcal mol^{-1}. The energy barrier for ring formation from **E** is 14.07 kcal mol^{-1} *via* **Ts E–F** and this step was found to be endergonic by 7.73 kcal mol^{-1}. The activation barrier for the formation of cycloadduct **G** through the transition state **Ts F–G** is 10.43 kcal mol^{-1} and this step is exergonic by 55.03 kcal mol^{-1} (Fig. 2). Then, the decoordination of two CuL^+ at **G** leads to the triazole **7a**, which is exergonic by 4.32 kcal mol^{-1}, and the overall process is exergonic by 30.36 kcal mol^{-1}.

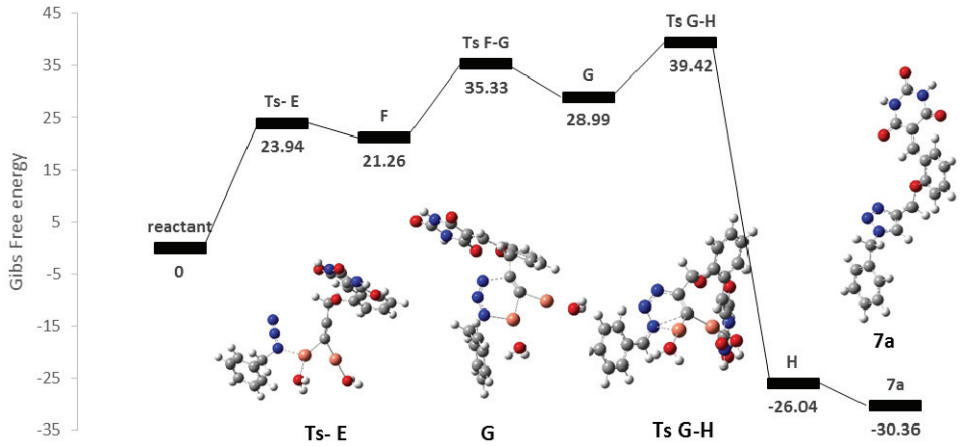


Fig. 2. The di-copper stepwise CA pathway.

Analysis of global and local properties

The frontier molecular orbital (FMO)[54–57] analysis was performed at the HF/6-311++G(d,p)//B3LYP/6-31G(d) level to explain the regioselectivity and reactivity in the [3+2] CA of benzyl azide **6a** and alkynes **4** and **4a''**. According to the FMO theory, interactions between orbitals is favored when they are closer in term of their energies.[58,59] To better visualize the FMO approach, two possible interactions $HOMO_{dipolarophile}$–$LUMO_{dipole}$ and $HOMO_{dipole}$–$LUMO_{dipolarophile}$ for the uncatalyzed and catalyzed reactions are shown in Fig. 3. In the absence of copper catalyst, the $HOMO_{azide}$–$LUMO_{alkyne}$ interaction controls the CA reaction. However, in the presence of two copper ions, the HOMO–LUMO energy gaps of the alkyne **4a** as a dipolarophile and azide **6a** as a dipole are slightly closed, therefore both HOMO–LUMO interactions are important (Type II in the Sustman classification).[60–63] In comparison, with alkyne **4''**, the HOMO and

LUMO energy gaps of alkyne **4a''** are decreased (Fig. 3). This could be explained by the involvement of copper as a soft metal.

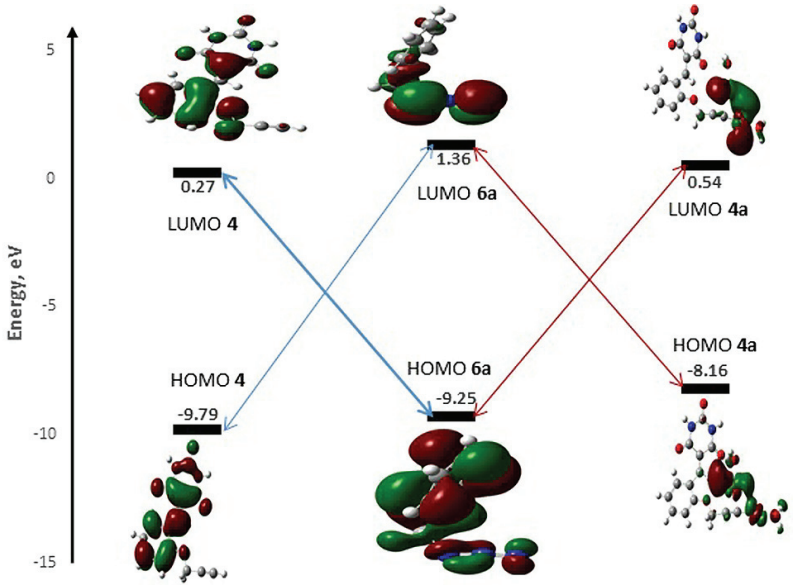


Fig. 3. HOMO and LUMO energies of the dipolarophiles **4** and **4a''** and the azide **6a**, calculated at the HF/6-311++G(d,p)//B3LYP/6-31G(d) level.

As shown in Table III, for the dipole **6a**, the HOMO coefficient of N15 is 0.40 and that of N17 is 0.03, while the LUMO coefficients of dipolarophile **4a** on the reactive sites C28 and C29 are 0.07 and 0.20, respectively. According to the Houk rule,[64] the most favored large–large interaction would occur between C29 of the alkyne **4a** and N15 of the azide **6a**, which is in agreement with the experimental observation.[65] For the di-copper acetylide **4a''**, the analysis of the $HOMO_{azide\ \mathbf{6a}}$–$LUMO_{alkyne\ \mathbf{4a}}$ interaction shows that the coefficient of C29 is higher than that of C28 (Table IV). Therefore, the most favored interaction would be between C29 and N15, which is in accordance with the experimentally favored product. In addition, for the $HOMO_{alkyne\ \mathbf{4a}}$–$LUMO_{azide\ \mathbf{6a}}$ interaction, the LUMO coefficient of N17 and the HOMO coefficient of C28 for the di-copper acetylide **4a''** and azide **6a** are higher than N15 and C29, respectively, and the interaction between C28 and N17 is in harmony with the proposed regioselectivity.

The regioselectivity of a CA reaction can be analyzed using the local and global indices defined in the context of DFT. The static global properties, namely the electronic chemical potential (μ), chemical hardness (η), global electrophilicity (ω) and global nucleophilicity (N) indices, of alkyne **4a**, the di-copper acetylide **4a''** and azide **6a** are reported in Table IV. The global electrophilicity index

is the ratio $\omega = \mu^2 / 2\eta$, which measures the total ability to attract electrons from the environment. Electronic chemical potential (μ), the mean value of the HOMO (ε_H) and LUMO energies (ε_L), is by $\mu = (\varepsilon_H + \varepsilon_L) / 2$ and is a relative measure of the molecular capacity to donate electron density. Chemical hardness (η), is the difference between the HOMO (ε_H) and LUMO (ε_L) energies as $\eta = \varepsilon_L - \varepsilon_H$, the global softness computed as $S = 1/2\eta$ and the relative global nucleophilicity index N, based on the HOMO energies, is defined as $N = \varepsilon_{H(Nu)} - \varepsilon_{H(TCH)}$, where TCE is tetracyanoethylene.[66–69] According to Table IV, the electronic chemical potential and nucleophilicity of azide **6a** is greater than those for alkyne **4a**, and thus, electron flux from the azide **6a** to the alkyne **4a** can occur, which is in accordance with the FMO analysis. As expected, di-copper acetylide **4a''** has an electronic chemical potential higher than that of azide **6a**, which means that electronic flow is from the dipolarophile **4a''** to the dipole **6a**. Di-copper acetylide **4a''** can also behave as a medium nucleophile in polar processes (N = 2.99 eV) and it has a nucleophilicity value that is greater than those of **4** and **6a**.

TABLE III. The calculated local properties for azide **6a** and for alkynes **4** and **4a**

Structure	Site	HOMO coefficient	LUMO coefficient	f_K^-	f_K^+	s^-	s^+	ω_K^+
Alkyne **4**	C28	0.02	0.07	0.11	0.11	0.14	0.15	0.004
	C29	0.10	0.20	0.05	0.03	0.06	0.04	0.001
Alkyne **4a''**	C28	0.12	0.52	0.16	0.36	0.25	0.57	0.011
	C29	0.11	0.93	0.31	0.47	0.49	0.74	0.015
Azide **6a**	N15	0.40	0.35	0.91	0.71	1.16	0.91	0.019
	N17	0.03	0.78	0.34	0.62	0.44	0.80	0.016

TABLE IV. The calculated electronic chemical potential μ, chemical hardness η, global electrophilicity ω, global nucleophilicity N and global softness indices S, for azide **6a**, and for alkynes **4a** and **4a''**

Structure	μ / a. u.	η / a. u.	Ω / eV	N / eV	S / a. u.
Alkyne **4**	−0.175	0.37	1.12	1.36	1.35
Alkyne **4a''**	−0.140	0.32	0.83	2.99	1.56
Azide **6a**	−0.145	0.39	0.73	1.90	1.28

Fukui functions guess favorable interactions between a molecule of a donor and a molecule an acceptor. The local electrophilicity indices, ω_k, were extracted from $\omega_k = \omega_{f_k}^+$. The values of f^+ and f^- are the electrophilic and nucleophilic Fukui functions, respectively, obtained through an analysis of the Mulliken charges of the radical cation and the radical anion.[70–75] The Fukui functions of $f^\pm$ at the atomic center k for electrophilic (f_K^+) and nucleophilic (f_K^-) attacks can be obtained from single point calculations at the optimized structures of the ground state of the donor and the acceptor (dipole–dipolarophile). As shown in Table III, the largest nucleophilic and electrophilic activation of azide **6a** are at

the N15 (($f_{\bar{K}}$ =0.91) and (f_{K}^{+} =0.71). In the absence of copper, alkyne **4a** has the largest electrophilic activation at the C28 atom. Hence, C28 of alkyne **4a** will be the preferred position for a nucleophilic attack of N15 of azide **6a**, which is completely opposed to the observed regioselectivity of the click reaction. The di-copper acetylide **4a''**, C29 has a larger electrophilic and nucleophilic activation than C28, ($f_{\bar{K}}$ = 0.31 *vs*. 0.16) and (f_{K}^{+} = 0.47 *vs*. 0.36), respectively. Therefore, C29 of di-copper acetylide **4a''** will be the preferred position for a nucleophilic attack on N15 of the azide. All of these interactions of di-copper acetylide are in good agreement with the observed regioselectivities.

The hard and soft acids and bases (HSAB) principle and local softness could be used in predicting the regioselectivity of CA reactions.[76–78] The local softnesses s_k are calculated through $s_k^{\pm} = s f_k^{\pm}$.[79] The softness matching index Δ_{ij}^{kl} is calculated by $\Delta_{ij}^{kl} = (s_i^{-} - s_k^{+})^2 + (s_i^{-} - s_l^{+})^2$, whereby the lower value of Δ_{ij}^{kl} showed the favored pathway. For the CA of azide **6a** and alkyne **4a**, the Δ_{ij}^{kl} value for the generation of the 1,5-disubstituted 1,2,3-triazole **H** is smaller than that for **7a** (1.18 *vs*. 1.34), which is in disagreement with the regioselectivity of the click reaction in the presence of copper complex.[80] In the presence of two coppers, the Δ_{ij}^{kl} value for both directions of the generation of **7a** is smaller than that for the other one. This suggests a preference for the generation of **7a**, which is in agreement with the experimentally observed regioselectivity.[16] The mentioned values are given in Table V.

TABLE V. The calculated hard and soft acids and bases (HSAB)

Structure	$(s_i^{-} - s_k^{+})^2$	Value	Δ_{ij}^{kl}
Alkyne **4a** – Azide **6a**	$(s_{\bar{1}5} - s_{28}^{+})^2$	1.02	1.18
	$(s_{\bar{1}7} - s_{29}^{+})^2$	0.16	1.34
	$(s_{\bar{1}7} - s_{28}^{+})^2$	0.08	
	$(s_{\bar{1}5} - s_{29}^{+})^2$	1.25	
Alkyne **4a''** – Azide **6a**	$(s_{\bar{1}5} - s_{28}^{+})^2$	0.35	0.44
	$(s_{\bar{1}7} - s_{29}^{+})^2$	0.09	0.19
	$(s_{\bar{1}7} - s_{28}^{+})^2$	0.02	
	$(s_{\bar{1}5} - s_{29}^{+})^2$	0.18	
Azide **6a** – Alkyne **4a''**	$(s_{\bar{2}8} - s_{15}^{+})^2$	0.43	0.53
	$(s_{\bar{2}9} - s_{17}^{+})^2$	0.10	0.48
	$(s_{\bar{2}9} - s_{15}^{+})^2$	0.18	
	$(s_{\bar{2}9} - s_{17}^{+})^2$	0.30	

CONCLUSIONS

In summary, a general method for the synthesis of novel triazoles with barbituric motifs *via* [3+2] CA reactions in DMSO was developed. The investigation proceeded using alkynes as dipolarophile and azides as dipoles in the presence of copper(I). Finally, the mechanism and regiochemistry of the reaction were studied in terms of global and local reactivity indices, FMO analysis and the

characterization of relevant transition states at the B3LYP/6-31+G(d) level of theory. Analyses of the global and local properties are in agreement with the experimentally found regioselectivity.

SUPPLEMENTARY MATERIAL

Analytical and spectral data are available electronically at the pages of the journal website: http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

ЕФИКАСНА СИНТЕЗА НОВИХ ТРИАЗОЛА КОЈИ УКЉУЧУЈУ БАРБИТУРНЕ МОТИВЕ [3+2] ЦИКЛОАДИЦИОНОМ РЕАКЦИЈОМ: ЕКСПЕРИМЕНТАЛНА И ТЕОРИЈСКА СТУДИЈА

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У овом раду је описана синтеза у добром приносу нових деривата триазола са барбитуратним мотивима. Алкин је добијен Кневенагеловом реакцијом барбитурних деривата са *ortho* и *para O*-пропаргилованим хидроксибензалдехидом. Механизам и региоселективност ове [3+2] циклоадиционе реакције испитивани су коришћењем теорије функционала густине на B3LYP/6-31+G(d) нивоу теорије. Рачунарске студије показују да је ди-бакром катализовани вишестепени механизам, који укључује интермедијер са шесточланим прстеном, најповољнија реакциона путања. Региоселективност је објашњена преко интеракција граничних орбитала, локалне и глобалне електрофилности, те индекса нуклеофилности. Сагласно томе, најповољније интеракције за ди-бакар-ацетилиде су у доброј сагласности са опаженом региоселективношћу, док се за некатализовану реакцију добијају потпуно супротни резултати.

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