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

MAHDIIEH DARROUDI1, YAGHOUB SARRAFI1* and MAHSHID HAMZEHLLOUEIAN2

1Department of Organic Chemistry, Faculty of Chemistry, University of Mazandaran, 47416 Babolsar, Iran and 2Department of Chemistry, Jouybar Branch, Islamic Azad University, Jouybar, Iran

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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 infections6,7 and microbial diseases.8–12 The first 1,4-disubstituted triazole was prepared by Huisgen13 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-
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.

The enormous attention recently gained by these reactions began with the pivotal discovery by the groups of Meldal and Sharpless, 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).

The required copper(I) species in the CuAAC reaction are either added directly as cuprous salts, usually with stabilizing ligands, or more often, generated from copper(II) salts with reducing agents. Barbituric acid derivatives are also used for the treatment of epilepsy and seizures. Barbituric or thiobarbituric 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.

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 generated in situ from copper(II) and ascorbate. 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 1H, 100.6 MHz for
\(^{13}\text{C})\) 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\(_4\))\(_2\)HPO\(_4\) (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\(_4\)Cl (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\(_4\)Cl (30 mL) and extracted with ethyl acetate (3×40 mL). The combined organic extracts were washed with brine (3×30 mL), dried over Na\(_2\)SO\(_4\) 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\(_2\)CO\(_3\) (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).

**TABLE I. Knoevenagel condensation**

<table>
<thead>
<tr>
<th>Entry</th>
<th>OCH2CCH</th>
<th>X</th>
<th>R</th>
<th>Reaction time, h</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>Ortho</td>
<td>O</td>
<td>H</td>
<td>10</td>
<td>85</td>
</tr>
<tr>
<td>4b</td>
<td>Para</td>
<td>O</td>
<td>H</td>
<td>7</td>
<td>90</td>
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<tr>
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<td>S</td>
<td>H</td>
<td>6</td>
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<tr>
<td>4d</td>
<td>Para</td>
<td>S</td>
<td>H</td>
<td>2</td>
<td>87</td>
</tr>
<tr>
<td>4e</td>
<td>Ortho</td>
<td>O</td>
<td>Me</td>
<td>12</td>
<td>84</td>
</tr>
<tr>
<td>4f</td>
<td>Para</td>
<td>O</td>
<td>Me</td>
<td>4</td>
<td>79</td>
</tr>
</tbody>
</table>

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

**Scheme 3. Synthesis of the compounds 7 and 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 ¹H-NMR spectrum of 7a exhibited a singlet peak of –CH₂ group at 5.27 ppm for Hₐ and a singlet at 5.61 ppm for two Hₖ protons of OCH₂ group. A singlet peak at δ = 8.07 ppm for H₉ of triazole heterocyclic compound and a singlet peak at 8.32 ppm of CH is referred to H₈ of methine group, respectively (Scheme 3). Two signals at 10.99 and 10.75 ppm were assigned for NH groups of barbituric acid. The ¹³C-NMR of cycloadduct 7a showed a peak at δ = 53.34 ppm owing to the CH₂ group and a peak at δ = 61.92 ppm for the CH₂ 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 B3LYP⁴³ functional with the 6-31+G(d)
basis set as implemented in the Gaussian 09 program package. Solvent effects were considered by means of CPCM calculations in DMSO. 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. 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. 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 patterns. 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 ($\delta$ / ppm) of $H_a$, $H_b$, $H_c$ and $H_d$ of the cycloadducts |
|-------------|-------------|-----------------|
| Atom number | 7a          | 7a′             | Experimental  |
| $H_a$       | 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.

![Image](image.jpg)

**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

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*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.](https://www.shd.org.rs/JSCS/)

**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\( \text{dipolarophile} \)–LUMO\( \text{dipole} \) and HOMO\( \text{dipole} \)–LUMO\( \text{dipolarophile} \) for the uncatalyzed and catalyzed reactions are shown in Fig. 3. In the absence of copper catalyst, the HOMO\( \text{azide} \)–LUMO\( \text{alkyne} \) 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.

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,\textsuperscript{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.\textsuperscript{65} For the di-copper acetylide $4a''$, the analysis of the HOMO$_\text{azide}$ $6a$–LUMO$_\text{alkyne}$ $4a$ 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$_\text{alkyne}$ $4a$–LUMO$_\text{azide}$ $6a$ 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 ($\mu$), chemical hardness ($\eta$), global electrophilicity ($\omega$) 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 ($\mu$), the mean value of the HOMO ($\epsilon_H$) and LUMO energies ($\epsilon_L$), is by $\mu = (\epsilon_H + \epsilon_L) / 2$ and is a relative measure of the molecular capacity to donate electron density. Chemical hardness ($\eta$), is the difference between the HOMO ($\epsilon_H$) and LUMO ($\epsilon_L$) energies as $\eta = \epsilon_L - \epsilon_H$, the global softness computed as $S = 1 / 2\eta$ and the relative global nucleophilicity index $N$, based on the HOMO energies, is defined as $N = \epsilon_{H(\text{TCE})} - \epsilon_{H(\text{TCH})}$, where TCE is tetracyanoethylene. 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

<table>
<thead>
<tr>
<th>Structure</th>
<th>Site</th>
<th>HOMO coefficient</th>
<th>LUMO coefficient</th>
<th>$f^+_k$</th>
<th>$f^-_k$</th>
<th>$s^-$</th>
<th>$s^+$</th>
<th>$\omega_k$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkyne 4</td>
<td>C28</td>
<td>0.02</td>
<td>0.07</td>
<td>0.11</td>
<td>0.11</td>
<td>0.14</td>
<td>0.15</td>
<td>0.004</td>
</tr>
<tr>
<td>Alkyne 4a''</td>
<td>C28</td>
<td>0.12</td>
<td>0.52</td>
<td>0.16</td>
<td>0.36</td>
<td>0.25</td>
<td>0.57</td>
<td>0.011</td>
</tr>
<tr>
<td>Azide 6a</td>
<td>N15</td>
<td>0.40</td>
<td>0.35</td>
<td>0.91</td>
<td>0.71</td>
<td>1.16</td>
<td>0.91</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>N17</td>
<td>0.03</td>
<td>0.78</td>
<td>0.34</td>
<td>0.62</td>
<td>0.44</td>
<td>0.80</td>
<td>0.016</td>
</tr>
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</table>

TABLE IV. The calculated electronic chemical potential $\mu$, chemical hardness $\eta$, global electrophilicity $\omega$, global nucleophilicity $N$ and global softness indices $S$, for azide 6a, and for alkynes 4a and 4a''

<table>
<thead>
<tr>
<th>Structure</th>
<th>$\mu$ / a. u.</th>
<th>$\eta$ / a. u.</th>
<th>$\Omega$ / eV</th>
<th>$N$ / eV</th>
<th>$S$ / a. u.</th>
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<tbody>
<tr>
<td>Alkyne 4</td>
<td>−0.175</td>
<td>0.37</td>
<td>1.12</td>
<td>1.36</td>
<td>1.35</td>
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<tr>
<td>Alkyne 4a''</td>
<td>−0.140</td>
<td>0.32</td>
<td>0.83</td>
<td>2.99</td>
<td>1.56</td>
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<tr>
<td>Azide 6a</td>
<td>−0.145</td>
<td>0.39</td>
<td>0.73</td>
<td>1.90</td>
<td>1.28</td>
</tr>
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</table>

Fukui functions guess favorable interactions between a molecule of a donor and a molecule an acceptor. The local electrophilicity indices, $\omega_k$, 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. 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_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_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. The local softnesses s_k are calculated through s_k^+ = s f_k^+ . The softness matching index Δ^kl is calculated by Δ^kl = (s^-i - s^+k)^2 + (s^-l - s^+i)^2, whereby the lower value of Δ^kl showed the favored pathway. For the CA of azide 6a and alkyne 4a, the Δ^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. In the presence of two coppers, the Δ^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. The mentioned values are given in Table V.

<table>
<thead>
<tr>
<th>Structure</th>
<th>(s^-i - s^+k)^2</th>
<th>Value</th>
<th>Δ^kl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkyne 4a – Azide 6a</td>
<td>(s^-15 - s^+28)^2</td>
<td>1.02</td>
<td>1.18</td>
</tr>
<tr>
<td></td>
<td>(s^-17 - s^+29)^2</td>
<td>0.16</td>
<td>1.34</td>
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<td>(s^-17 - s^+28)^2</td>
<td>0.08</td>
<td></td>
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<td></td>
<td>(s^-15 - s^+29)^2</td>
<td>1.25</td>
<td></td>
</tr>
<tr>
<td>Alkyne 4a'' – Azide 6a</td>
<td>(s^-15 - s^+28)^2</td>
<td>0.35</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td>(s^-17 - s^+29)^2</td>
<td>0.09</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>(s^-17 - s^+28)^2</td>
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<tr>
<td></td>
<td>(s^-15 - s^+29)^2</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Azide 6a – Alkyne 4a''</td>
<td>(s^-28 - s^+15)^2</td>
<td>0.43</td>
<td>0.53</td>
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<tr>
<td></td>
<td>(s^-29 - s^+17)^2</td>
<td>0.10</td>
<td>0.48</td>
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<td></td>
<td>(s^-29 - s^+15)^2</td>
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<tr>
<td></td>
<td>(s^-20 - s^+17)^2</td>
<td>0.18</td>
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</table>

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] ЦИКЛОАДИЦИОНИЈАМ РЕАКЦИЈОМ: ЕКСПЕРИМЕНТАЛНА И ТЕОРИЈСКА СТУДИЈА

МАХДИЕ ДАРОУДИ1, ЯГОУБ САРАФИ1 И МАХШИД ХАМЗЕЛОУЕИАН2

1Department of Organic Chemistry, Faculty of Chemistry, University of Mazandaran, 47416 Babolsar, Iran
2Department of Chemistry, Jouybar Branch, Islamic Azad University, Jouybar, Iran

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 каталлизовани 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-ацилид су у доброј сагласности са опаженом региоселективношћу, док се за некатализовану реакцију добијају попутно супротни резултати.


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