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

MAHDIEH DARROUDI, 1 YAGHOUB SARRAFI,[[1]](#footnote-1),\* MAHSHID HAMZEHLOUEIAN 2

*1 Department of Organic Chemistry, Faculty of Chemistry, University of Mazandaran, 47416 Babolsar, Iran*

*2 Department of Chemistry, Jouybar Branch, Islamic Azad University, Jouybar, Iran*

*Abstract:* In this work, synthesis of novel triazole derivatives with barbituric motifs in good yields was described. The alkyne was prepared through Knoevenagel reaction of barbituric derivatives with ortho and para O-propargylated hydroxyl-benzaldehyde. Mechanism and regioselectivity of this [3+2] cycloaddition (CA) reaction were investigated using density functional theory (DFT) 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 most preferred pathway. The regioselectivity has been explained in terms of frontier molecular orbital (FMO) interactions, local and global electrophilicity and nucleophilicity indices. Accordingly, the favoured interactions for di-copper acetylide are in good agreement with the observed regioselectivity, while completely opposite results are obtained for possible uncatalysed reaction.

*Keywords:* *Triazoles*; *Barbituric derivatives*; *DFT study;* *Mechanism.*

RUNNING TITLE: NOVEL TRIAZOLES INCORPORATING BARBITURIC MOTIFS

INTRODUCTION

1,2,3–Triazole has been known as an important five-membered heterocycle which is 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 treatment of tumors2,3, HIV4, allergy5, fungal infection6,7 and microbial diseases8–12. The first 1,4-disubsituted triazole was prepared through [3+2] cycloaddition (CA) of terminal or internal alkynes and azides by Huisgen13, which is well-known as an important class of the click reaction. The applications of click reactions are wide in scope. The click reactions give excellent yields and generate inoffensive 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 this reaction began with the pivotal discovery by the groups of Meldal15 and Sharpless,16 in which copper(I) catalysis was found to dramatically accelerate the reaction under mild conditions. On the other hand, 1,4-triazoles are generated through these Cu(I) catalyzed azide-alkyne CA (CuAAC) reactions with a 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 ligands15,23–25 or more often generated from copper(II) salts with reducing agents. 26 Barbituric acid derivatives are also used for the treatment of epilepsy and seizures.27,28 Substituted barbituric27,29,30 or thiobarbituric31,32 acids with heterocyclic/aryl increases the antiepileptic activity. The interest in using barbituric acid derivatives is mainly the lack of E/Z isomer formation in Knoevenagel condensation.33



SCHEME 1. Regioselective synthesis of triazoles

Based on the pharmacological properties associated with barbituric acid derivatives and triazole heterocycles, we became interested in combining these heterocyclic moieties through a CuAAC reaction, catalyzed by copper(I) species34,35 which generated in situ from copper(II) and ascorbate,36,37,38. The barbituric derivatives were generated via the Knoevenagel condensation of propargylated hydroxyl-benzaldehyde and barbituric acid (Scheme 1). In addition, we were carried out a theoretical study on the mechanism of this click reaction, by means of the density functional theory (DFT).

EXPERIMENTAL

*General information and apparatus:*

Melting points were measured on an Electrothermal 9100 apparatus. NMR spectra were recorded with a Bruker DRX-400 AVANCE instrument (400.1 MHz for 1H, 100.6 MHz for 13C) with DMSO as solvent. IR spectra were recorded on an FT-IR Bruker vector 22 spectrometer. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were carried with a Perkin-Elmer 2400II CHNS/O Elemental Analyzer

Synthesis:

*Propargylation of hydroxybenzaldehyde derivatives* ***2a – b****:*

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

*General procedure for Knoevenagel condensation:*

Preparation of (**4a-d**): Propargylated aldehydes **2a–b** (1 mmol) were added to a stirred solution of barbituric acid derivatives (1.2 mmol) in aqueous HCl (25 ml, 10%) at room temperature. After stirring for 2–15 h, the pure substances was collected by filtration, and washing with hot ethanol. 39

Propargylated aldehydes **2a–b** (1 mmol) were added to a stirred solution of N,N-dimethylbarbituric acid (**3c**) (1.2 mmol) in water (20 ml) containing (NH4)2HPO4 (20 mol%) at room temperature. After stirring for 4–12 h, the yellow precipitated 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 benzyl bromide derivatives **5a-c** (1 mmol) in DMF. The mixture was heated at 100° C and, after completion (3h), was quenched with an aqueous solution of NH4Cl (15 mL) and extracted with ethyl acetate (3 -20 mL). The organic extracts were washed with brine (3 -20 mL) and dried over MgSO4. After evaporation of the solvent at reduced pressure, pure azides were isolate. 40

*General procedure for click cycloaddition reaction:*

Alkynes **4a-f** (1.2 mmol) and benzyl azide **6a-c** (1 mmol) were added to a solution of CuSO4 (0.2 equiv) DMSO (10 mL) in a capped ﬂask at room temperature. The reaction mixture was stirred at 80°C and, after completion (12h), the reaction was quenched with a saturated aqueous solution of NH4Cl (30 mL) and extracted with ethyl acetate (3- 40 mL). The organic extracts were washed with brine (3 -30 mL), dried over Na2SO4 and concentrated under vacuum.

RESULTS AND DISCUSSION

Initially, compounds **2a-b** were prepared from hydroxyl-benzaldehyde **1a-b** and propargyl bromide in the presence of K2CO3(Scheme 2a).41 Then, the alkyne **4a** was synthesized through the Knoevenagel condensation of barbituric derivative **3a** and propargylated hydroxyl-benzaldehyde **2a** under reflux condition in good yield (Scheme 2b).42,43 (Table 1). The general procedure for the preparation of organic azides is shown in Scheme 2c. 40







SCHEME 2. Preparation of dipole **6a-d** and dipolarophiles **4a-f**

TABLE 1. Knoevenagel condensation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Entry | OCH2CCH | X | R | Yield, % |
| 4a | Ortho | O | H | 85 |
| 4b | Para | O | H | 90 |
| 4c | Ortho | S | H | 80 |
| 4d | Para | S | H | 87 |
| 4e | Ortho | O | Me | 84 |
| 4f | Para | O | Me | 79 |

Then the cycloadduct **7** was prepared from (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 DMSO15. The synthetic route is outlined in Scheme 3. The progress of 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 2).



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

TABLE 2. 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 |
| 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 |  |

A facile and rapid access to a wide range of novel 1,2,3-triazoles containing a wide range of functional groups has been developedin good yield. The structure of the cycloadduct **7** was determined by various spectroscopic techniques. So, the IR spectrum of **7** demonstrated absorption at 3438 cm-1, indicating the presence of a NH group, 1677 cm-1 and 1159 cm-1 which correspond to the CO and ether group, respectively. The 1H NMR spectrum of **7** exhibited a singlet peak of -CH2 group at 5.22 for Ha and a singlet at 5.71 ppm for two Hc protons of OCH2 group. A singlet peak at *δ* =8.06 for Hb of triazole heterocyclic compound and a singlet peak at 8.37 ppm of CH is referred to Hd of methine group, respectively (Scheme 3). Two signals at 10.99 and 10.97 were assigned for NH groups of barbituric acid. The 13C NMR of cycloadduct **7** showed a peak at *δ* =52.04 ppm owing to the CH2 group and a peak at *δ* =61.89 ppm for the CH2 attached to the oxygen group. This suggests that the triazole **7** is formed. It is well known that in the presence of copper catalyst the preferred regioisomeric products are 1,4-triazoles. 15–22 So, it can be proposed that **7a** is produced in the CuAAC cycloaddition reaction studied here. This can be verified with computational study on the NMR spectra of two possible regioisomers and compared 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:

*Computational details:*

In this study, the geometry optimization of all ground states and transition states (TSs) were carried out using B3LYP44 functional with 6-31+G(d) basis set as implemented in the Gaussian09 program package.45 Solvent effects are considered by means of CPCM calculations in DMSO.46–49 All the geometry optimizations were performed without any symmetry constraint. The stationary geometries has been 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 selected reaction pathways, an IRC calculation was carried out to fully characterize the located transition state structures.50,51 The 1H chemical shifts were also studied by means of the GIAO method using the tetramethylsilane (TMS) as 1H reference at the 6-311+G(d) level.52 The reported energies are include zero-point vibrational corrections, thermal and entropy corrections at 298 K and solvation energies.

*1H NMR spectral analysis:*

Two possible regioisomers of these reactions have similar splitting pattern. Thus, 1H-NMR of the possible triazoles **7a** and **7a'** were calculated and compared with our experimental results. As shown in Table 6, the calculated values of Ha, Hc and Hd of the **7a** are closer to the experimental values. Accordingly, the cycloadduct of this reaction could be 1,4-triazole **7a**.

****

**TABLE 6:** Comparison of the experimental and theoretical 1H-NMR chemical shifts data (δ / ppm) of Ha, Hb, Hc and He of cycloadducts

|  |  |  |  |
| --- | --- | --- | --- |
| Atom number | **7a** | **7a'** | Experimental |
| **He** | **5.10** | 5.6 | 5.22 |
| **Hb** | 7.51 | 7.31 | 8.06 |
| **Hc** | **5.40** | 4.90 | 5.71 |
| **Hd** | **8.5** | 9.15 | 8.37 |

*Uncatalyzed concerted cycloaddition:*

The uncatalyzed 1,3-dipolar cycloaddition of organic azides with alkynes was also studied by means of DFT calculations. Due to asymmetry of reagents, two regioisomeric adducts can be formed in the [3+2] CA reaction (Fig. 1). The study found high energy barriers for both the 1,4- and 1,5-approaches. We have also calculated the energy barriers for the coupling of **6a** and **4** in order to properly compare its energetics with the catalytic pathways described through this paper. Our 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, respectively. This energy difference explains the lack of regioselectivity when the cycloaddition is carried out in the absence of any catalyst as well as the slowness of the transformation. The formation of triazoles **7a** and **8** are exergonic more than 30 kcal/mol. The optimized geometries of the transition states are shown in Fig. 1.

C:\Users\Mahdi\Desktop\fig1.tif

FIG. 1. The uncatalyzed CA pathways. Energies are in (kcal/mol). Distances in angstroms (Å).

*Di-copper catalyzed stepwise cycloaddition:*

The analysis of alkyne /Cu reaction pathways between alkyne **4a** and azide **6a** shows that the CA reaction occurs through a stepwise mechanism (Scheme 4). Consequently, the reactants, transition states, and intermediates are located and characterized. The optimized geometries of the transition states and intermediates are presented in Figure 1.



SCHEME 4. Probable reaction mechanism of deprotonation of alkyne

In the reaction conditions, alkyne **4** is acidiﬁed considerably through coordinating with one CuL and formation of complex **D**, that calculations show this coordination is endergonic by 5.1 kcal/mol. The deprotonation of complex **D** to aﬀord di-copper acetylide **4a**, using triethylamine as a base is exergonic by 5.5 kcal/mol (Scheme 4). In other words, the deprotonation process of alkyne in the presence of two copper ions is 0.4 kcal/mol more favorable than in the presence of one copper ion. This complexation likely increases alkyne activity toward CA reaction.

C:\Users\Mahdi\Desktop\scheme 5.tif

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 was suggested as the preferred pathway.53,54 The stepwise di-copper reaction is initiated with coordination of atom N15 of azide **6a** and atom Cu of acetylide **4a** to provide intermediate **F**. Our calculations show that rate-determining step of this reaction is formation of intermediate **F**, although it has lower barrier than uncatalyzed manner (23.94 *vs* 43.83 kcal/mol). In the following, the formation of carbon−nitrogen bond between azide and alkyne will be occurred, leading to the six-membered ring **G**. Then, the five-membered ring **H** is formed through ring contraction of **G**.

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

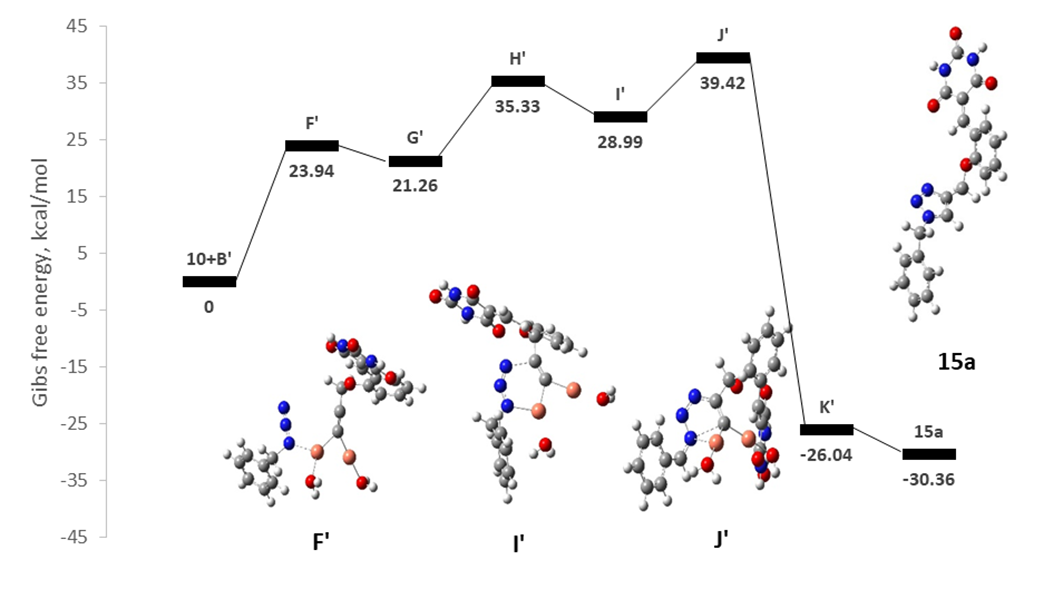


FIG. 2. The di-copper stepwise CA pathway. The relative energies are in (kcal/mol).

*Analysis of global and local properties:*

The frontier molecular orbital (FMO)55–58 analysis was performed at HF/6-311++G(d,p)//B3LYP/6-31G(d) level to explain the regioselectivity and reactivity in [3+2] CA of benzyl azide **6a** and alkynes **4** and **4a**. According to the FMO theory, the interactions between orbitals is favored when they are closer in term of their energies.59,60 To better visualize the FMO approach, two possible interactions HOMOdipolarophile -LUMOdipole and HOMOdipole - LUMOdipolarophile for uncatalyzed and catalyzed reactions are shown in Figure 3. In the absence of copper catalyst, the HOMOazide–LUMOalkyne 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 sustman classification.).61–64 In comparison with alkyne **4**, the HOMO and LUMO energy gaps of alkyne **4a** are decreased. (Figure 3). This can be explained by the involvement of copper as a soft metal.

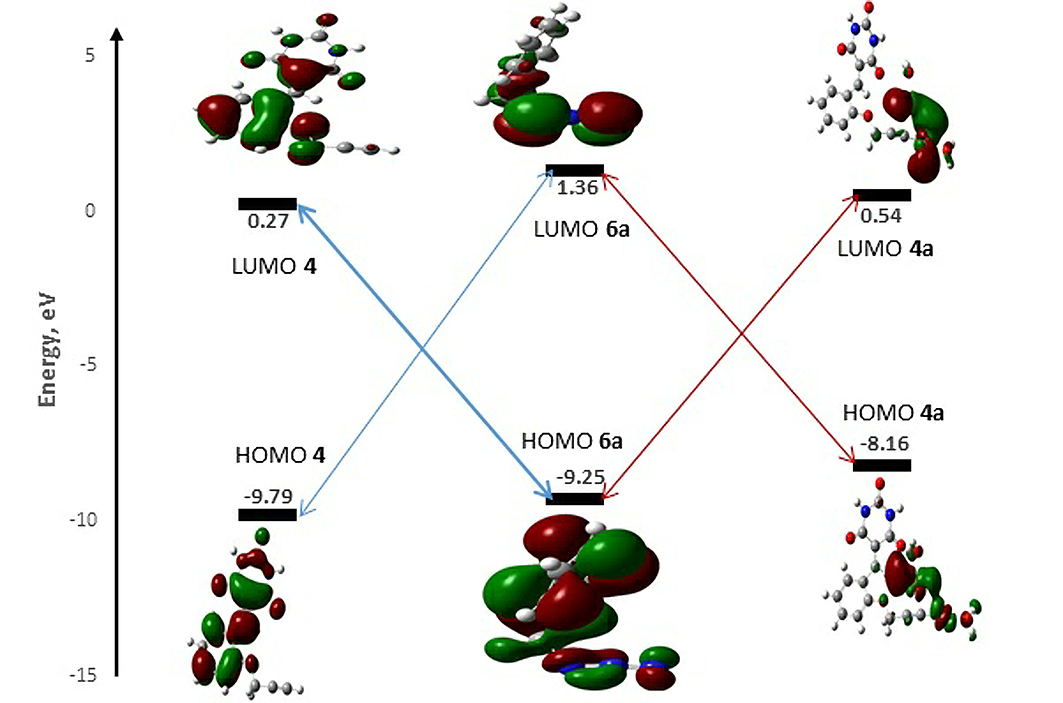


FIG. 3.HOMO and LUMO energies of dipolarophiles **4** and **4a** and azide **6a** calculated at the HF/6-311++G(d,p)//B3LYP/6-31G(d) level.

As shown in Table 4, for the dipole **6a** the HOMO coefficient of N15 is 0.40 and that of N17 is 0.03 and the LUMO coefficients of dipolarophile **4** on the reactive sites C28 and C29 are 0.07 and 0.20, respectively. According to Houk’s rule,65 the most favored large-large interaction would be occurred between C29 of the alkyne **4** and N15 of the azide **6a**, which is in agreement with the experimental observation.66 For di-copper acetylide **4a**, the analysis of HOMOazide **6a**–LUMOalkyne **4a** interaction shows that the coefficient of C29 is higher than C28 (Table 4). Therefore, the most favored interaction will take place between C29 and N15, in accordance with the experimentally favored product. Also, for the HOMO alkyne **4a**–LUMO azide **6a** interaction, the LUMO coefficient of N17 and the HOMO coefficient of C28 at di-copper acetylide **4a** and azide **6a** are higher than N15 and C29, respectively and the interaction between C28and N17 is in harmonic with the proposed regioselectivity.

|  |
| --- |
| TABLE 3:The calculated electronic chemical potential *μ*, chemical hardness *η*, global electrophilicity *ω,* global nucleophilicity *N* and global softnessindices S, for azide **6a**, alkynes **4** 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 |

The regioselectivity of CA reaction can be analyzed using the local and global indices defined in the context of DFT. The static global properties, namely electronic chemical potential (*μ*), chemical hardness (*η*), global electrophilicity (*ω*) and global nucleophilicity (*N*) indices of alkyne **4**, di-copper acetylide **4a** and azide **6a** are reported in Table 3. The global electrophilicity index, is the ratio , which measures the total ability to attract electrons from the environment. Electronic chemical potential (*µ*), is the mean value of HOMO (*ε*H) and LUMO energies (*ε*L) as and is 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 , the global softness computed as: and the relative global nucleophilicity index *N*, based on the HOMO energies defined as where TCE is tetracyanoethylene.67,68,69,70 According to Table 3, the electronic chemical potential and nucleophilicity of azide **6a** is greater than alkyne **4**, thus the electron flux can take place from azide **6a** to alkyne **4** in accordance with FMO analysis. As expected, di-copper acetylide **4a** has an electronic chemical potential higher than azide **6a**, which means that the electronic ﬂow is from the dipolarophile **4a** to dipole **6a**. Di-copper acetylide **4a** can also behave as a medium nucleophile in polar processes (*N* = 2.99 eV) and it has greater nucleophilicity value than **4** and **6a**.

|  |
| --- |
| TABLE 4: The calculated local properties of for azide **6a**, alkyne **4** and **4a.** |

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

The Fukui functions guess favorable interactions between two molecules of the donor and the acceptor. The local electrophilicity indices ωk, was extracted from . The value of *ƒ*+ and ƒ- are the electrophilic and nucleophilic Fukui functions, respectively, obtained through the analysis of the Mulliken charges analysis of the radical cation and the radical anion.71–76 The Fukui functions of *ƒ*± at the atomic center *k* for electrophilic () and nucleophilic ( 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 4, the largest nucleophilic and electrophilic activation of azide **6a** are at the N15 ((*fk- =*0.91) and (*fk+ =*0.71)). In the absence of copper, alkyne **4** has the largest electrophilic activation at the C28 atom. So, the C28 of alkyne **4** will be the preferred position for a nucleophilic attack of the N15 of azide **6a**, which is completely opposite with the observed regioselectivity of click reaction. The di-copper acetylide **4a,** at the C29 has the larger electrophilic and nucleophilic activation than C28, (*fk- =*0.31 *vs* 0.16) and (*fk+ =*0.47 *vs* 0.36), respectively. Therefore, the C29 of di-copper acetylide **4a** will be the preferred position for a nucleophilic attacks to the N15 of azide. All of these interactions of di-copper acetylide are in good agreement with the observed regioselectivities.

|  |
| --- |
| TABLE 5: The calculated hard and soft acids and bases (HSAB) |

|  |  |  |  |
| --- | --- | --- | --- |
| Structure |  |  |  |
| Alkyne **4**- Azide **6a** |  | 1.02  0.16  0.08  1.25 | **1.18**  1.34 |
| Alkyne **4a**-Azide **6a** |  | 0.35  0.09  0.02  0.18 | 0.44  **0.19** |
| Azide **6a**- Alkyne **4a** |  | 0.43  0.10  0.18  0.30 | 0.53  **0.48** |

The hard and soft acids and bases (HSAB) principle and local softness can be used in predicting the regioselectivity of CA reactions.77–79 The local softness's s*k* are calculated through S*k±* =S*.fk±.*80The softness matching index is calculated by = (- )2 + (- )2 where the lower value of showed the favored pathway. For CA of azide **6a** and alkyne **4**, the value for the generation of 1,5-triazole **C** 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.81 In the presence of two coppers, the value for both directions of the generation 7a is smaller than that for another one. This suggests a preference for the generation of **7a** which is in agreement with the regioselectivity experimentally observed.16 The mentioned values are given in Table 4.

CONCLUSION

In summary, we have developed a general method for the synthesis of novel triazoles with barbituric motifs *via* the [3+2] CA reaction in DMSO. The investigation proceeds using alkynes as dipolarophile and azides as dipoles in the presence of copper (I). Finally, mechanism and the regiochemistry of the reaction have been studied in terms of global and local reactivity indices, FMO analysis and characterization of relevant transition states at the B3LYP/6-31+G(d) level of theory. Analyses of global and local properties are in agreement with the regioselectivity of the experimental results.

SUPPLEMENTARY MATERIAL

Electronic Supplementary Information (ESI) are available electronically from <http://www.shd.org.rs/JSCS/>, or from the corresponding author on request.

*Acknowledgements:* The authors acknowledge the University of Mazandaran for financial support of this research

И З В О Д

НАСЛОВ РАДА

ПРВИ А. АУТОР, ДРУГИ Б. АУТОР1 и ТРЕЋИ В. АУТОР2

*Афилијација првог аутора*

*1Афилијација другог аутора*

*2Афилијација трећег аутора*

(Домаћи аутори морају доставити Извод (укључујући имена аутора и афилијацију) на српском језику, исписане ћирилицом, иза Захвалнице, а пре списка референци.) For authors outside Serbia, the Editorial Board will provide a Serbian translation of their English abstract.

REFERENCES

1. C.-K. Sha, A. K. Mohanakrishnan, *Azides*, in *Synth. Appl. 1,3-Dipolar Cycloaddit. Chem. Towar. Heterocycles Nat. Prod.*, John Wiley & Sons, Inc., New York, USA, 2003, pp. 623–679.

2. R. Alvarez, S. Velazquez, A. San-Felix, S. Aquaro, E. De Clercq, C.-F. Perno, A. Karlsson, J. Balzarini, M. J. Camarasa, *J. Med. Chem.* **37** (1994) 4185–4194.

3. F. de C. da Silva, M. C. B. V de Souza, I. I. P. Frugulhetti, H. C. Castro, S. L. de O. Souza, *Eur. J. Med. Chem.* **44** (2009) 373–383.

4. D. R. Buckle, C. J. Rockell, H. Smith, B. A. Spicer, *J. Med. Chem.* **29** (1986) 2262–7.

5. J. C. Fung-Tomc, E. Huczko, B. Minassian, D. P. Bonner, *Antimicrob. Agents Chemother.* **42** (1998) 313–318.

6. R. Périon, V. Ferrières, M. Isabel García-Moreno, C. Ortiz Mellet, R. Duval, J. M. García Fernández, D. Plusquellec, *Tetrahedron* **61** (2005) 9118–9128.

7. D. J. Anderson, M. R. Barbachyn, D. E. Emmert, S. a Garmon, D. R. Graber, *J. Med. Chem.* **43** (2000) 953–970.

8. M. Hoshino, *Nature* **186** (1960) 174–175.

9. A. M. Thompson, A. Blaser, R. F. Anderson, S. S. Shinde, S. G. Franzblau, Z. Ma, W. A. Denny, B. D. Palmer, *J. Med. Chem.* **52** (2009) 637–645.

10. A. K. Jordão, V. F. Ferreira, E. S. Lima, M. C. B. V de Souza, E. C. L. Carlos, *Bioorganic Med. Chem.* **17** (2009) 3713–3719.

11. D.-R. Hou, S. Alam, T.-C. Kuan, M. Ramanathan, T.-P. Lin, M.-S. Hung, *Bioorg. Med. Chem. Lett.* **19** (2009) 1022–5.

12. J. Shen, R. Woodward, J. P. Kedenburg, X. Liu, M. Chen, L. Fang, D. Sun, P. G. Wang, *J. Med. Chem.* **51** (2008) 7417–7427.

13. A. Padwa, *1, 3-Dipolar cycloaddition chemistry*, Wiley, New York, 1984.

14. H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chemie Int. Ed.* **40** (2001) 2004–2021.

15. C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **67** (2002) 3057–64.

16. V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chemie Int. Ed.* **41** (2002) 2596–2599.

17. S. Quader, S. E. Boyd, I. D. Jenkins, T. A. Houston, *J. Org. Chem.* **72** (2007) 1962–1979.

18. F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.* **127** (2005) 210–216.

19. Q. Wang, S. Chittaboina, H. N. Barnhill, *Lett. Org. Chem.* **2** (2005) 293–301.

20. S. Díez-González, H. C. Kolb, M. G. Finn, K. B. Sharpless, *Catal. Sci. Technol.* **1** (2011) 166.

21. J. E. Hein, V. V. Fokin, *Chem Soc Rev* **39** (2010) 1302–1315.

22. V. D. Bock, H. Hiemstra, J. H. van Maarseveen, *European J. Org. Chem.* **2006** (2006) 51–68.

23. T. R. Chan, R. Hilgraf, K. B. Sharpless, V. V Fokin, *Org. Lett.* **6** (2004) 2853–2855.

24. S. Díez-González, A. Correa, L. Cavallo, S. P. Nolan, *Chem. - A Eur. J.* **12** (2006) 7558–7564.

25. N. Candelon, D. Lastécouères, A. K. Diallo, J. Ruiz Aranzaes, D. Astruc, *Chem. Commun.* **41** (2008) 741–743.

26. V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chemie - Int. Ed.* **41** (2002) 2596–2599.

27. M. R. Shiradkar, M. Ghodake, K. G. Bothara, *Med. Chem. (Los. Angeles).* **2007** (2007) 58–74.

28. L. L. Brunton, J. S. Lazo, K. L. Parker, *Goodman & Gilman’s The Pharmacological Basis of Therapeutics*, McGraw-Hill, Health Professions Division, 2006.

29. H. PANWAR, A. AGARWAL, A. KUMAR, *Indian J. Pharm. Sci* **67** (2005) 194–199.

30. A. Archana, P. Rani, K. Bajaj, V. Srivastava, R. Chandra, A. Kumar, *Arzneimittelforschung* **53** (2011) 301–306.

31. K. P. Gupta, R. C. Gupta, K. P. Bhargava, B. Ali, *Chem. Informationsd.* **14** (1983) 448–452.

32. G. R. Sarma, J. V. Rao, *Indian J.* (1999).

33. J. W. Daly, *J. Med. Chem.* **25** (1982) 197–207.

34. M. Meldal, C. W. Tomøe, *Chem. Rev.* **108** (2008) 2952–3015.

35. V. O. Rodionov, V. V. Fokin, M. G. Finn, *Angew. Chemie* **117** (2005) 2250–2255.

36. M. B. Davies, *Polyhedron* **11** (1992) 285–321.

37. C. Creutz, *Inorg. Chem.* **20** (1981) 4452–4453.

38. M. Darroudi, Y. Sarrafi, M. Hamzehloueian, *Tetrahedron* **73** (2017) 1673–1681.

39. M. J. Khoshkholgh, S. Balalaie, R. Gleiter, F. Rominger, *Tetrahedron* **64** (2008) 10924–10929.

40. Y. Kitamura, K. Taniguchi, T. Maegawa, Y. Monguchi, Y. Kitade, H. Sajiki, *Heterocycles* **77** (2009) 521–532.

41. G. Bashiardes, I. Safir, F. Barbot, J. Laduranty, *Tetrahedron Lett.* **45** (2004) 1567–1570.

42. H. Behbehani, H. M. Ibrahim, S. Makhseed, M. H. Elnagdi, H. Mahmoud, *Eur. J. Med. Chem.* **52** (2012) 51–65.

43. A. Pałasz, *Monatshefte Für Chemie - Chem. Mon.* **143** (2012) 1175–1185.

44. P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **82** (1985) 270.

45. M. Robert, *Bull. Physiopathol. Respir. (Nancy).* **11** (2009) 79–170.

46. A. Klamt, G. Schüürmann, *J. Chem. Soc., Perkin Trans. 2* (1993) 799–805.

47. J. Andzelm, C. Kölmel, A. Klamt, *J. Chem. Phys.* **103** (1995) 9312.

48. V. Barone, M. Cossi, *J. Phys. Chem. A* **102** (1998) 1995–2001.

49. M. Cossi, N. Rega, G. Scalmani, V. Barone, *J. Comput. Chem.* **24** (2003) 669–681.

50. C. Gonzalez, H. B. Schlegel, *J. Chem. Phys.* **90** (1989) 2154.

51. C. Gonzalez, H. B. Schlegel, *J. Phys. Chem.* **94** (1990) 5523–5527.

52. K. Wolinski, J. Hinton, P. Pulay, *J. Am. Chem.* **112** (1990) 8251–8260.

53. B. T. Worrell, J. A. Malik, V. V. Fokin, *Science (80-. ).* **340** (2013) 457–460.

54. D. Cantillo, M. Ávalos, R. Babiano, P. Cintas, J. L. Jiménez, J. C. Palacios, *Org. Biomol. Chem.* **9** (2011) 2952.

55. Y.-H. Sheng, D.-C. Fang, Y.-D. Wu, X.-Y. Fu, Y. Jiang, *J. Mol. Struct. THEOCHEM* **467** (1999) 31–36.

56. K. Marakchi, H. Abou El Makarim, O. K. Kabbaj, N. Komiha, *Phys. Chem. News* **52** (2010) 129–137.

57. S. Stecko, K. Paśniczek, C. Michel, A. Milet, S. Pérez, M. Chmielewski, *Tetrahedron: Asymmetry* **19** (2008) 1660–1669.

58. J. Tomasi, M. Persico, *Chem. Rev.* **94** (1994) 2027–2094.

59. A. D. Becke, *J. Chem. Phys.* **98** (1993) 5648.

60. C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **37** (1988) 785–789.

61. R. Sustmann, *Tetrahedron Lett.* **12** (1971) 2717.

62. R. Sustmann, H. Trill, *Tetrahedron Lett.* **42** (1972) 4271.

63. R. Sustmann, *Pure Appl. Chem.* **40** (1974) 569–593.

64. R. Sustmann, *Tetrahedron Lett.* **12** (1971) 2721.

65. K. N. Houk, J. Sims, C. R. Watts, L. J. Luskus, *J. Am. Chem. Soc.* **95** (1973) 7301–7315.

66. S. Stecko, A. Mames, B. Furman, M. Chmielewski, *J. Org. Chem.* **74** (2009) 3094–3100.

67. M. Rahm, T. Brinck, *J. Phys. Chem. A* **112** (2008) 2456–2463.

68. K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* **98** (1998) 863–910.

69. D. M. Andrada, A. M. Granados, M. Solà, I. Fernández, *Organometallics* **30** (2011) 466–476.

70. Z. Chen, L. Lin, M. Wang, X. Liu, X. Feng, *Chem. - A Eur. J.* **19** (2013) 7561–7567.

71. L. R. Domingo, J. Andrés, *J. Org. Chem.* **68** (2003) 8662–8668.

72. L. R. Domingo, M. José Aurell, *J. Org. Chem.* **67** (2002) 959–965.

73. L. R. Domingo, *Tetrahedron* **58** (2002) 3765–3774.

74. L. R. Domingo, M. J. Aurell, P. Pérez, R. Contreras, *J. Phys. Chem. A* **106** (2002) 6871–6875.

75. L. R. Domingo, A. Asensio, P. Arroyo, *J. Phys. Org. Chem.* **15** (2002) 660–666.

76. L. R. Domingo, M. J. Aurell, P. Pérez, R. Contreras, *Tetrahedron* **58** (2002) 4417–4423.

77. A. K. Chandra, M. T. Nguyen, *Int. J. Mol. Sci.* **3** (2002) 310–323.

78. Loc Thanh Nguyen, F. De Proft, A. K. Chandra, T. Uchimaru, Minh Tho Nguyen, P. Geerlings, *J. Org. Chem.* **66** (2001) 6096–6103.

79. R. G. Pearson, *J. Am. Chem. Soc.* **85** (1963) 3533–3539.

80. H. Chermette, *J. Comput. Chem.* **20** (1999) 129–154.

81. M. M. Ghorab, F. A. Ragab, H. I. Heiba, M. G. El-Gazzar, S. S. Zahran, *Eur. J. Med. Chem.* **92** (2015) 682–692.

1. \*Corresponding author. E-mail: [ysarrafi@umz.ac.ir](mailto:ysarrafi@umz.ac.ir) [↑](#footnote-ref-1)