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A theoretical investigation on the regioselectivity of the intramolecular hetero Diels–Alder and 1,3-dipolar cycloaddition reactions of 2-(vinyloxy)benzaldehyde derivatives

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Abstract: The present paper reports a systematic computational analysis study of the two possible pathways, fused and bridged, for an intramolecular hetero Diels–Alder (IMHDA) and an intramolecular 1,3-dipolar cycloaddition (IMDCA) of 2-(vinyloxy)benzaldehyde derivatives. The potential energy surface analyses for both reactions are in agreement with the experimental observations. The activation energies associated with the two regioisomeric channels in the IMHDA reaction showed that the bridged product is favored, although in the IMDCA, the most stable transition state results in the fused product. The global electronic properties of the fragments within each molecule were studied to discuss the reactivity patterns and charge transfer direction in the intramolecular processes. The asynchronicity of the bond formation and aromaticity of the optimized TSs in the Diels–Alder reaction as well as cycloaddition reaction were evaluated. Finally, the ^{1}H-NMR chemical shifts of the possible regioisomers were calculated using the GIAO method, the values of which for the most stable products were in agreement with the experimental data for both reactions.

Keywords: intramolecular hetero Diels–Alder; intramolecular 1,3-dipolar cycloaddition; charge transfer; DFT calculation; fragment electrophicity analysis.

INTRODUCTION

Pericyclic reactions are of particular interest because of their broad preparative significance in the chemistry of drugs and natural products.[1–6] Intramolecular hetero Diels–Alder reactions appeared to be a versatile strategy for the

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formation of novel polycyclic systems, which were successfully employed in the design of skeletons for some natural products and potent anti-tumor agents.[7–10] 1,3-Dipolar cycloaddition reactions (DCA) also provide an efficient approach for the synthesis of five-membered heterocyclic units in a highly regio- and stereoselective manner.[11] Five-membered heterocycles are an important class of compounds, not only because of their natural abundance, but also for their chemical and biological importance.[12]

Steric and electronic effects are two major factors that could influence the selectivity of these reactions. Domingo *et al.*[13] proposed that the global electrophilicity index introduced by Parr[14] could be used as a reliable quantity to classify the electrophilicity of a series of dienes/dipoles (D) and dienophiles/dipolarophiles (Dp) involved in intermolecular Diels–Alder and 1,3-dipolar cycloaddition reactions within a unique relative scale. Useful information about the polarity at the transition state (TS) for a given reaction could be obtained from the difference in global electrophilicity $\Delta\omega$ of the D/Dp interacting pair. Thus, small electrophilicity differences are related to non-polar mechanisms, while large electrophilicity differences are associated with polar mechanisms.[13] Soto-Delgado and coworkers established that these rules could be transferred to an intramolecular a Diels–Alder process by introducing electrophilicity and nucleophilicity indices of the fragment.[15,16] These analyses indicated that electronic effects, such as charge transfer (CT) along the reaction coordinate are invariant in both inter- and intra-molecular processes.[16]

The global electrophilicity index, ω, which measures the stabilization energy when the system acquires an additional electronic charge, ΔN, from the environment, is given by the following simple expression:[14]

$$\omega = \frac{\mu^2}{2\eta} \tag{1}$$

where μ is the electronic chemical potential and η is the chemical hardness at the ground state of the molecules. This index was used to classify the dienes/dipoles and dienophiles/dipolarophiles used in Diels–Alder and 1,3-dipolar cycloaddition reactions within a unique scale of electrophilicity.[13] Furthermore, both the electronic chemical potential and chemical hardness may be approached in terms of the one electron energies of the frontier molecular orbitals HOMO and LUMO, ε_H and ε_L, using the expressions:

$$\mu = \frac{(\varepsilon_\mathrm{H} + \varepsilon_\mathrm{L})}{2} \tag{2}$$

and

$$\eta = \varepsilon_\mathrm{L} - \varepsilon_\mathrm{H} \tag{3}$$

On the other hand, the nucleophilicity index, N, for a given system is defined as:

$$N = \varepsilon_{\mathrm{HOMO}} - \varepsilon_{\mathrm{HOMO(TCE)}} \tag{4}$$

where $\varepsilon_{\mathrm{HOMO}}$ is the HOMO energy of the nucleophile and $\varepsilon_{\mathrm{HOMO(TCE)}}$ corresponds to the HOMO energy of tetracyanoethylene (TCE), taken as reference.[17]

The fragment electrophilicity and nucleophilicity indices are given as follows:

$$\omega_{(\mathrm{fragment})} = \omega_{\mathrm{F}} = \omega \sum_{k \in \mathrm{F}} f_k^{+} \tag{5}$$

and

$$N_{(\mathrm{fragment})} = N_{\mathrm{F}} = \omega \sum_{k \in \mathrm{F}} f_k^{-} \tag{6}$$

where F = D or Dp.[15,16] The regional Fukui functions 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 molecules.[18] The direction of the electronic flux within an IMHDA and IMDCA reagent may be determined by introducing the following dual indices:

$$E1 = \omega_{\mathrm{Dp}} + N_{\mathrm{D}} \tag{7}$$

and

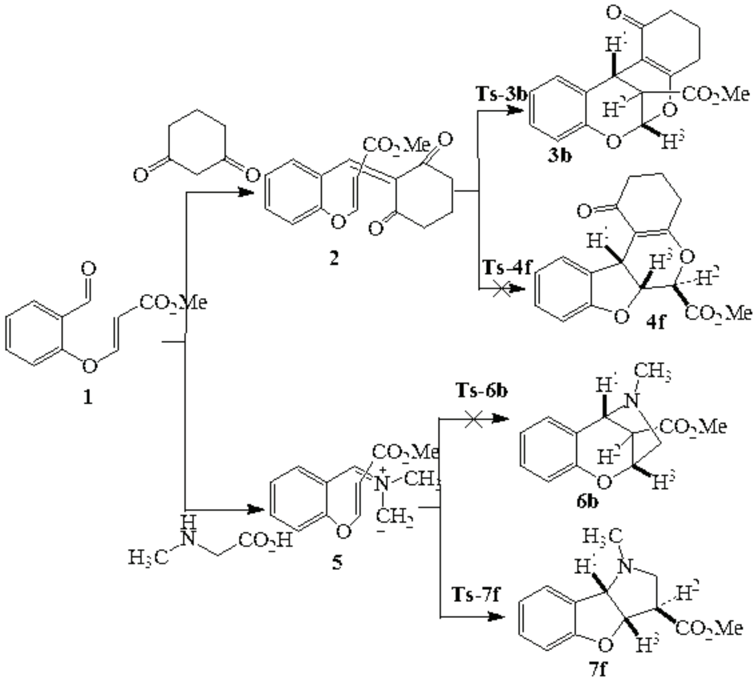
$$E2 = \omega_{\mathrm{D}} + N_{\mathrm{Dp}} \tag{8}$$

Accordingly, the charge transfer (CT) can be estimated from the relative values of $E1$ and $E2$. The process will be characterized by a Dp to D electronic flux if $E1 < E2$, whereas the electronic flux occurs from D to Dp if $E1 > E2$. The charge transfer along the reaction coordinates can be elucidated by the regional electrophilicity:[17]

$$\omega_{\Omega} = \frac{\mu_{\Omega}^{2}}{2\eta_{\Omega}} \tag{9}$$

where Ω is A or B.

In the past decades, in addition to the selectivity behavior, the understanding of the underlying principles in pericyclic reactions has grown from a fruitful interplay between theory and experiment and continues to present a real challenge.[19] Recently, Kim *et al.* reported the synthesis of benzo-fused 2,8-dioxabicyclo[3.3.1]nonane (**3**) utilizing a domino Knoevenagel condensation hetero Diels–Alder reaction of 2-(vinyloxy)benzaldehyde (**1**).[20] Then, it was expected that the 1,3-dipole (**5**), generated from **1** with sarcosine, would react with the neighboring double bond to give a structurally novel bicyclo[3.2.1]octane ring system (**6b**), Scheme 1.[21] However, contrary to anticipation, a linearly fused tricyclic compound **7f** was obtained as the major product instead (Scheme 1). In the present work, as a part of an ongoing theoretical and experimental research program on 1,3-dipolar cycloaddition reactions,[22] a theoretical study on the observed difference in regioselectivity of the above reactions was performed, in order to achieve a deeper insight to IMHDA and IMDCA.



Scheme 1. Possible reaction channels for the IMHDA and the IMDCA reactions of 2-(vinyloxy)benzaldehyde derivatives.

COMPUTATIONAL DETAILS

All calculations were performed using Gaussian09[23] suite of programs. The full geometrical optimization of all structures and transition states (TSs) was realized with the Density Functional Theory (DFT) using non-local B3LYP hybrid functional and the 6-31G(d,p) basis set. The nature of stationary geometries was characterized by calculating the frequencies in order to verify that the transition states have only one imaginary frequency with the corresponding eigenvector involving the formation of the newly created C–C bonds.

RESULT AND DISCUSSION

Energies of transition state structures

The intramolecular hetero Diels–Alder and intramolecular 1,3-dipolar cycloaddition reactions are kinetically controlled reactions with early transition states.[24] Theoretical calculations are the only way to study these TSs. For each of the IMHDA and IMDCA reactions, two regiochemical channels, namely, the fused (**TS-f**) and the bridged (**TS-b**) modes, were studied. The optimized transition structures are shown in Figs. 1 and 2. The activation energies, enthalpies and Gibbs free energies as well as energies, enthalpies, Gibbs free energies of the reactions are reported in Table I.

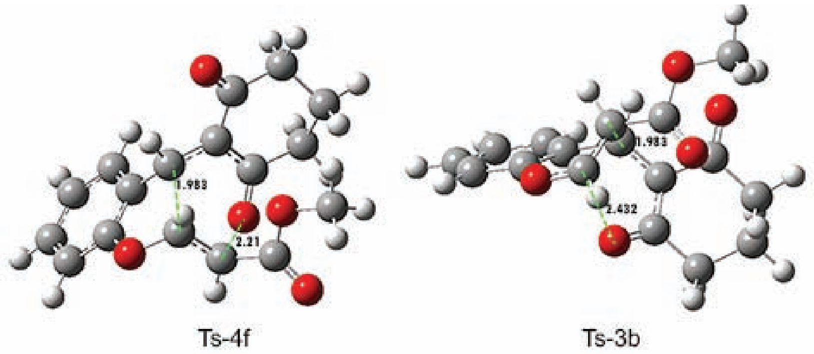


Fig. 1. Optimized structures of the transition states for the IMHDA reaction at B3lyp/6-31G(d,p) level. The lengths of the bonds directly involved in the reactions are given in angstroms.

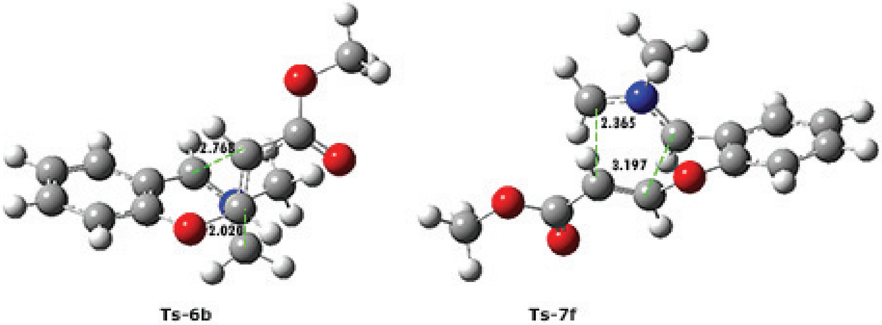


Fig. 2. Optimized structures of transition states for the IMDCA reaction at B3lyp/6-31G(d,p) level. The lengths of the bond directly involved in the reactions are given in angstroms.

TABLE I. Calculated electronic activation energies E_a, reaction Gibbs free energies ΔG, reaction enthalpies ΔH, reaction energies ΔE_{rxn}, activation Gibbs free energies $\Delta G^{\#}$, activation enthalpies $\Delta H^{\#}$ (all energies are in kcal mol^{-1}; 1 kcal = 4.184 kJ), charge transfers *CT* and nucleus-independent chemical shifts *NICS*

Structure	E_a	$\Delta G^{\#\ 1}$	$\Delta H^{\#\ 1}$	ΔE_{rxn}	ΔG	ΔH	*CT* a.u.	*NICS* ppm mol^{-1}
Ts-3b	20.33	1.03	0.84	–20.39	–21.84	–16.94	0.08[a]	–11.79
Ts-4f	31.61	1.51	1.32	–12.11	–13.49	–8.91	0.32[b]	–10.10
Ts-7f	2.87	0.19	0.10	–48.38	–49.95	–46.00	0.03[a]	–13. 94
Ts-6b	5.06	0.27	0.17	–42.61	–44.17	–40.16	0.16[a]	–12.17

[a] From D to Dp; [b] from Dp to D

The computed activation energies associated with the two regioisomeric channels for the IMHDA reaction of **2** are 31.61 (**TS-4f**) and 20.33 (**TS-3b**) kcal mol^{-1}. Therefore, the bridge mode **3b** is favored over the fused one by 11.28 kcal mol^{-1}. The activation barriers associated with the IMDCA reaction of **5** are 2.87 (**TS-7f**) and 5.06 (**Ts-6b**) kcal mol^{-1}. Accordingly, it could be predicted that the regioisomer **7f** would be formed preferentially. These results are in agreement with the experimental findings that for the IMHDA reaction of compound **2**, the bridged product **3b** is the major product[20] but for the IMDCA reaction of **5,** the fused product **7f** is favored.[21]

In order to calculate the charge transfer and reactivity indices for an intramolecular reaction, it is necessary to consider a molecule as two fragments: diene (D) and dienophile (Dp) for IMHDA and dipole (D) and dipolarophile (Dp) for IMDCA. The embedded fragments in **2** and **5** are shown in Fig. 3. For the IMHDA reaction, the calculated *CT*s present diene–dieneophile fragments electron flux in **TS-3b,** while a reversed flux was predicted for **TS-4f**. However, the calculated *CT*s in both TS of IMDCA are from dipole to dipolarophile fragments.

The extent of the asynchronicity of the bond formation in a Diels–Alder or cycloaddition reaction can be measured through the difference between the lengths of the two σ bonds that are being formed in the reaction. The computed ΔRs are 0.368, 0.227, 0.832 and 0.748 Å for **TS-3b**, **TS-4f**, **TS-7f** and **TS-6b**, respectively. This data indicates that the TSs associated with the more favorable stereoisomeric channels (**TS-3b** and **TS-7f**) have more asynchronous character than those associated with the other channels.

In order to evaluate the aromaticity of the optimized TSs, the nucleus-independent chemical shifts (*NICS*)[25] at the center of the forming ring were computed using the gauge invariant atomic orbital (GIAO)[26] approach at the B3LYP//6-31G(d,p) level. The calculated *NICS* values are presented in Table I. All of the transition structures in Table I have large negative *NICS* values, which indicate the aromatic characters of TSs due to the six electrons undergoing bond change.

Reactivity indices analysis for the IMHDA and IMDCA reactions

The computed electronic chemical potentials μ, chemical hardness η, global electrophilicities ω and nucleophilicities N of **2** and **5** are given in Table II. The global electrophilicity indices of **2** and **5** are 2.49 and 0.97 eV and their nucleophilicities are 2.72 and 4.86 eV, respectively. Compound **2** is classified as a strong electrophile and two compounds are described as excellent nucleophiles.

Frontier molecular orbital (FMO) analysis cannot be applied for IMHDA and IMDCA reactions when the HOMO and LUMO orbitals of the D and Dp fragments belong to a molecule. Thus, the electrophilicity and nucleophilicity indices of fragments were employed to analyze the polar interactions in the IMHDA and IMDCA reactions. The two considered fragments in compounds **2** and **5** are shown in Fig. 3 and their computed electrophilicity and nucleophilicity indices are given in Table III. For compounds **2**, *E1* = 2.99 and *E2* = 2.84 (Eqs. (7) and (8)) and for **5**, *E1* = 5.13 and *E2* = 1.28. The larger *E1* for both compounds indicates that CT will occur from D to Dp (Table I). The analysis of the fragment electrophilicity and nucleophilicity indices is in agreement with the estimated *CT*s for both TSs (**TS-7f** and **TS-6b**) of the IMDCA reaction (D to Dp). However for the IMHDA reaction, the analysis of fragment indices only agree with the direction of estimated charge transfer for the most stable TS (**TS-3b**) (Table I).

TABLE II. Global properties of **2** and **5**

Structure	μ / a.u	η / a.u	ω / eV	N / eV
2	–0.1641	0.1423	2.49	2.72
5	–0.0941	0.1246	0.97	4.86

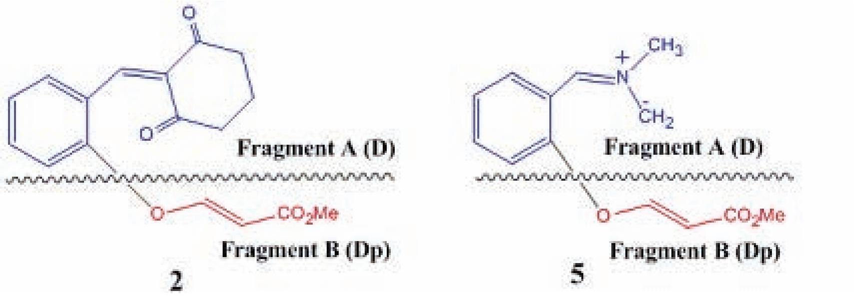


Figure 3.The diene (D)/dienophile (Dp) and dipole (D)/dipolarophile (Dp) fragments in compounds **2** and **5**.

For compounds **2** and **5**, the values of the ω_{Ω} index of the D fragments are 2.95 and 1.08 eV, and the values of the Dp fragments are 0.27 and 0.25 eV, respectively. The fragment electrophilicity difference $\Delta\omega_{\Omega} = |\omega_B - \omega_A|$ was used to estimate the *CT* at the TSs associated with the IMHDA/IMDCA reactions. The IMHDA processes involving **2** are expected to follow a polar mechanism with significant CT at the TS, $\Delta\omega_{\Omega} > 1.50$, while the IMDCA reaction in compound **5** is predicted to undergo a polar mechanism with marginal CT at the TS, $0.5 < \Delta\omega < 1.50$.

TABLE III. Local electronic properties (in eV) of the embedded fragments of **2** and **5**

Structure	ω_D	N_D	ω_{Dp}	N_{Dp}	$\omega_{(\Omega=A)}$	$\omega_{(\Omega=B)}$	$\Delta\omega_{\Omega} = |\omega_B - \omega_A|$
2	2.81	2.90	0.10	0.03	2.95	0.27	2.85
5	1.13	5.01	0.12	0.15	1.08	0.25	0.83

NMR chemical shifts

Owing to similar splitting pattern for the two regioisomers of these reactions, evaluation between the experimental data and calculated chemical shifts of possible regioisomers could be useful. Thus, the ^{1}H-NMR chemical shifts of regioisomers were calculated using the GIAO method and the results (values in ppm) are summarized in Table IV. The theoretical values of H-1, H-2 and H-3 of compound **3** for IMHDA reaction and compound **7** for IMDCA reaction are closer to the experimental values, as can be seen in Table IV. Therefore, the estimated chemical shift values of the more stable regioisomers **3** and **7** correspond well with the experimental data.

TABLE IV. Comparison of the theoretical 1H-NMR chemical shifts data (δ / ppm) of H-1, H-2 and H-3 of each pair of regioisomers with those obtained from the experimental spectroscopy

Atom number	IMHDA			IMDCA		
	3	**4**	Experimental[20]	**6**	**7**	Experimental[21]
H-1	4.7	4.3	4.54	4.0	4.9	4.59
H-2	2.8	2.1	3.12	2.9	3.0	3.52
H-3	6.4	5.6	6.30	5.1	6.0	5.67

CONCLUSIONS

A systematic theoretical study on the regioselectivity in the intramolecular hetero Diels–Alder (IMHDA) and intramolecular 1,3-dipolar cycloaddition reactions (IMDCA) of 2-(vinyloxy)benzaldehyde derivatives using DFT method was conducted. A potential energy surface analysis in the IMHDA and IMDCA reactions demonstrated that the preferred products would be bridged and fused, respectively, in agreement with experimental observations. The charge transfer direction in these intramolecular processes was studied in terms of the global electronic properties of fragments within each molecule.

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ИЗВОД

ТЕОРИЈСКО ИСПИТИВАЊЕ РЕГИОСЕЛЕКТИВНОСТИ ИНТРАМОЛЕКУЛСКЕ DIELS–ALDER И 1,3-ДИПОЛАРНЕ ЦИКЛОАДИЦИЈЕ ДЕРИВАТА 2-(ВИНИЛОКСИ)БЕНЗАЛДЕХИДА

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Извршена је систематска компјутерска анализа двају могућих реакционих путева интрамолекулске хетеро Diels–Alder (IMHDA) и интрамолекулске 1,3-диполарне циклоадиције (IMDCA) деривата 2-(винилокси)бензалдехида. Анализа површине потенцијалне енергије за обе реакције је у сагласју с експерименталним опажањима. Енергије активације за два посматрана механизма показују да је у IMHDA реакцији фаворизован премошћени продукт, док у IMDCA је то кондензовани продукт. Проучене су глобалне електронске особине фрагмената, и дискутована реактивност и правац преноса наелектрисања у интрамолекулским процесима. Одређени су асинхроницитет грађења веза и ароматичност у оптимизованим прелазним стањима истраживаних реакција. Израчуната су ^{1}H-NMR хемијска померања насталих региоизомера и нађена да су у складу са експерименталним подацима.

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REFERENCES

1. K. N. Houk, Y. Li, J. D. Evanseck, *Angew. Chem. Int. Ed.* **31** (1992) 682
2. J. March, *Advanced Organic Chemistry*, Wiley, New York, 1992
3. R. B. Woodward, R. Hoffmann, *Angew. Chem. Int. Ed.* **8** (1969) 781
4. H. E. Zimmerman, *Acc. Chem. Res.* **4** (1971) 272
5. M. J. S. Dewar, *Angew. Chem. Int. Ed.* **10** (1971) 761
6. K. Fukui, *Acc. Chem. Res.* **4** (1971) 57; G. Desimoni, G. Tacconi, A. Barco, G. P. Pollini, *Natural product synthesis through pericyclic reactions*, in *ACS monograph*, Vol. 180, American Chemical Society, Washington DC, 1983
7. A. G. Fallis, *Acc. Chem. Res.* **32** (1999) 464
8. D. Craig, *Chem. Soc. Rev.* **16** (1987) 187
9. A. G. Fallis, *Pure Appl. Chem.* **69** (1997) 495
10. J. R. Bull, R. Gordon, R. Hunter, *J. Chem. Soc.*, *Perkin Trans. 1* (2000) 3129
11. J. W. Lown, in *1,3-Dipolar Cycloaddition Chemistry*, Vol. 1, A. Padwa, Ed., Wiley, New York, 1984, pp. 653–732; W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon Press, Elmsford, New York, 1990; *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*, A. Padwa, W. H. Pearson, Eds., Wiley, New York, 2002
12. O. Tsuge, S. Kanemasa, in *Advances in Heterocyclic Chemistry*; A. R. Katritzky, Ed., Academic Press, San Diego, CA, 1989, Vol. 45, pp. 231–349
13. L. R. Domingo, M. J. Aurell, P. Pérez, R. Contreras, *Tetrahedron* **58** (2002) 4417; P. Perez, L. R. Domingo, M. J. Aurell, R. Contreras, *Tetrahedron* **39** (2003) 3117
14. P. G. Parr, L. von Szentpaly, S. Liu, *J. Am. Chem. Soc.* **121** (1999) 1922
15. J. Soto-Delgado, L. R. Domingo, R. Contreras, *Org. Biomol. Chem.* **8** (2010) 3678
16. J. Soto-Delgado, A. Aizman, L. R. Domingo, R. Contreras, *Chem. Phys. Lett.***499** (2010) 272
17. L. R. Domingo, E. Chamorro, P. Pérez, *J. Org. Chem.***73** (2008) 4615
18. R. Contreras, P. Fuentealba, M. Galván, P. Pérez, *Chem. Phys. Lett.* **304** (1999) 405; M. C. Rezende, *J. Braz. Chem. Soc*. **12** (2001) 73
19. G. Bentabed-Ababsa, A. Derdour, T. Roisnel, J. A. Saez, P. Perez, E. Chamorro, L. R. Domingo, F. Mongin, *J. Org. Chem.* **74** (2009) 2120; A. K. Nacereddine, W. Yahia, S. Bouacha, A. Djerourou, *Tetrahedron Lett.* **51** (2010) 2617; W. Benchouk, S. M. Mekelleche, M. J. Aurell, L. R. Domingo, *Tetrahedron* **65** (2009) 4644; M. Bakavoli, F. Moeinpour, A. Davoodnia, A. Morsali, *J. Mol. Struct.: THEOCHEM* **969** (2010) 139; P. Merino, J. Revuelta, T. Tejero, U. Chiacchio, A. Rescifinab, G. Romeoc, *Tetrahedron* **59** (2003) 3581; S. Špirtović-Halilović, M. Salihović, H. Džudžević-Čančar, S. Trifunović, S. Roca, D. Softić, D. Završnik, *J. Serb. Chem. Soc.* **78** (2013) 1
20. I. Kim, H.-K. Kim, S. G. Choi, G. H. Lee, *Tetrahedron* **64** (2008) 664
21. I. Kim, H.-K. Na, K. R. Kim, S. G. Kim, G. H. Lee, *Synlett* **13** (2008) 2069

22. Y. Sarrafi, M. Sadatshahabi, M. Hamzehloueian, K. Alimohammadi, M. Tajbakhsh, *Synthesis* **45** (2013) 2294; K. Alimohammadi, Y. Sarrafi, M. Tajbakhsh, S. Yeganegi, M. Hamzehloueian, *Tetrahedron* **67** (2011) 1589; Y. Sarrafi, M. Hamzehlouian, K. Alimohammadi, H. R. Khavasi, *Tetrahedron Lett.* **51** (2010) 4734; Y. Sarrafi, M. Hamzehloueian, K. Alimohammadi, S. Yeganegi, *J. Mol. Struct.* **1030** (2012) 168.
23. Gaussian 09, Revision A.1Gaussian, Inc., Wallingford, CT, 2009
24. W. R. Roush, S. E. Hall, *J. Am. Chem. Soc*. **103** (1981) 5200; F. K. Brown, K. N. Houk, *Tetrahedron Lett*. **26** (1985) 2297
25. P. V. R. Schleyer, C. Maerker, A. Dransfeld, H. Jiao, N. J. R. V. E. Hommes, *J. Am. Chem. Soc.* **118** (1996) 6317
26. K. Wolinski, J. F. Hilton, P. Pulay, *J. Am. Chem. Soc.* **112** (1990) 8251.