Asian Journal of Chemistry Vol. 21, No. 1 (2009), 541-548

O-Alkylation *versus* C-Alkylation in the Synthesis of 5,6-Dihydro-4*H*-oxacin-4-ones: Theoretical Approach

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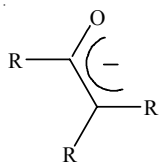
The condensation of α-ketoalkynes with *p*-nitrobenzaldehyde, in the presence of lithium diisopropyl amide (LDA) used as a strong base, results exclusively in the O-alkylation product *i.e.*, the 5,7-dialkyl-6-(4-nitro-phenyl)-2-phenyl-8-phenylethynyl-5,6-dihydro-oxacin-4-ones. No C-alkylation product was found. The energy calculation of the two possible transition states shows a preferentially low activation energy for the 8-endo-dig cyclization pathway.

Key Words: O-Alkylation, C-Alkylation, Cyclization, Oxacinones.

INTRODUCTION

The interest to synthesize substituted oxacinones have been developed and reported. This is due because of common structural is present in several natural products which are known to exhibit important biological and pharmacological activities[1,2] such as allelopathics[3], herbicides[4], activators of the protein kinase C in the Alzheimer´s therapeutics[5], (as benzolactams) amongst other.

Recently we reported a new process to reach oxacinones[6] using a nickel catalyzed addition-cyclization reaction with enolate ions as intermediates, wich constitutes useful nucleophilic species in the formation of C-C and O-C bonds based on the following delocalized system:



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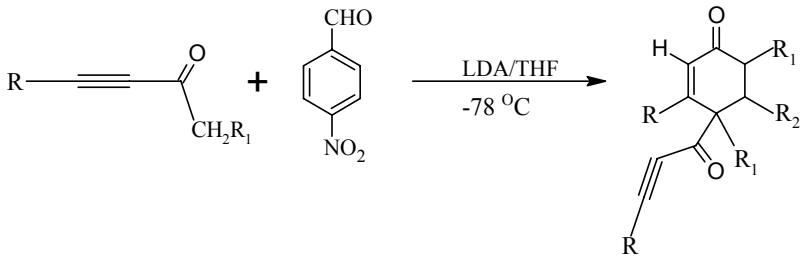
This species reacts with electrophiles, yielding C-bonded or O-bonded products. The former producing an α substituted carbonyl compound and the latter an enolic-derivative.

Although the C-alkylation represents the common pathway, the named intermediate frequently generates a mixture of both possibilities. Thus, the selective formation of one of them is a task that, when performed, would eliminate the problems associated with the separation of the reaction mixture.

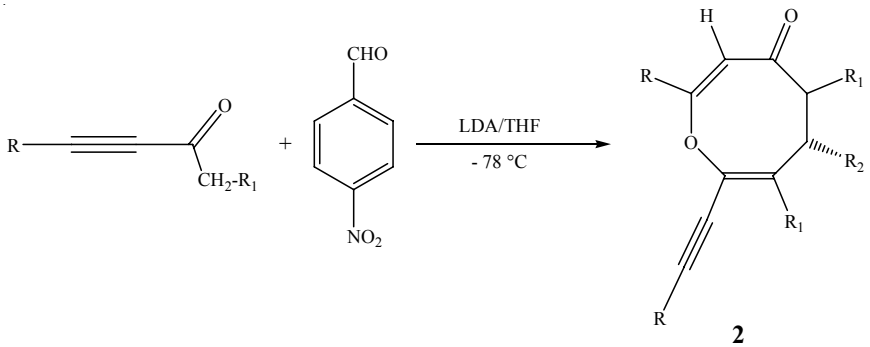
In continuation of our studies regarding the synthesis of heterocycles using aqueous catalytic methods, where iron and nickel based precursors are involved[7-11] (upon planning of the synthesis of highly substituted pyranone derivatives (**1**), in strategic positions), we concluded that an adequate one pot process consists in the condensation of α-ketoalkynes with *p*-nitro-benzaldehyde in the presence of a strong base such as lithium diisopropyl amide (LDA), according to the general reaction shown in **Scheme-I**.



R = Ph, R_1 = Et, *n*-Pr, *n*-Bu and R_2 = *p*-NO_2-C_6H_4

Scheme-I

Surprisingly, the experimental results showed no-formation of the expected pyranones (**1**), obtaining in this case an eight-membered heterocycle (**2**) showed in **Scheme-II**. R = Ph, R_1 = Et, *n*-Pr, *n*-Bu, R_2 = *p*-NO_2-C_6H_4.



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Scheme-II

Product **2** was identified as 5,7-diethyl-6-(4-nitro-phenyl)-2-phenyl-8-phenylethynyl-5,6-dihidro-oxacin-4-one, by IR spectroscopy, nuclear magnetic resonance (^{1}H and ^{13}C NMR), mass spectrometry and X-ray crystallography, Tables 1 and 2 and Fig. 5.

TABLE-1
SPECTROSCOPIC DATA OF 5,7-DIETHYL-6-(4-NITRO-PHENYL)-2-PHENYL-8-PHENYLETHYNYL-5,6-DIHIDRO-OXACIN-4-ONE (IR, NMR AND MASS SPECTROMETRY)

m.p. 150-152 °C; Mass spectrum EI: *m/z* = 477; IR (ν_{max}, selected cm^{-1}) 1686 (C=O), 2212 (C≡C), 1599 (C=C), 1461 and 1380 (N=O); ^{1}H NMR δ_H (300 MHz; $CDCl_3$; TMS ppm): 8.2 (d, 2Ha^2, *J* = 8.7 Hz), 7.8 (d, 2Hb^2, *J* = 8.7 Hz), 7.5 and 7.2 (m, 10H, 2 phenyl), 6.5 (s, 1H, CH), 3.9 (t, 1H, CH, *J* = 2.4 Hz), 3.3 (d, 1H, CH, *J* =1 1.1 Hz), 2.4 (m, 2H, CH_2), 1.9 (m, 2H, CH_2), 0.97 (t, 3H, CH_3, *J* = 7.5 Hz), 0.73 (t, 3H, CH_3, *J* = 7.5 Hz); ^{13}C NMR δ_C: 204.6 (C_4), 169.5 (C_2), 149.7 (C_{20}), 147.2 (C_{17}), 140.1 (C_9), 137.8 (C_8), 133.5 (C_7), 131.4 (C_{28}, C_{32}), 131.3 (C_{22}, C_{18}), 129.9 (C_{11}, C_{13}), 129.0 (C_{30}), 128.7 (C_{29}, C_{31}), 128.4 (C_{12}), 127.3 (C_{10}, C_{14}), 124.0 (C_{19}, C_{21}), 121.9 (C_{27}), 116.0 (C_3), 95.3 (C_{26}), 83.0 (C_{25}), 57.0 (C_5), 52.7 (C_6), 27.1 (C_{15}), 24.2 (C_{23}), 12.2 (C_{16}), 12.2 (C_{24}).

TABLE-2
CRYSTAL DATA AND STRUCTURE REFINEMENT FOR 5,7-DIETHYL-6-(4-NITRO-PHENYL)-2-PHENYL-8-PHENYLETHYNYL-5,6-DIHIDRO-OXACIN-4-ONE

Parameter	Compound	Parameter	Compound
Empirical formula	$C_{31}H_{27}NO_4$	γ°	90
Formula weight	477.54	Volume Å^3	5132.7(6)
Crystal system	Orthorhombic	Z	8
Space group	P b c a	Density (Calcd.)Mg/m^3	1.236
Crystal size (mm)	0.45 × 0.15 × 0.10	λ mm^{-1}	0.082
a Å	21.624(1)	Reflections collected	39691
b Å	8.875(1)	Independent reflections	4527
c Å	26.745(2)	R	0.0463
α°	90	GOF	0.964
β°	90	σ/e Å^{-3}	0.143/-0.121

We found the exclusive formation of the eight-membered heterocycle, rather than the apparently more convenient six-membered compound, intriguing, since both cyclizations could be allowed according to Baldwin rules applied to the preferential alkylation of ketones enolates[12].

In order to clarify the chemoselectivity of the titled reaction, a theoretical study (including HOMO calculations) with respect to the activation energy of the transition state in both possible reaction pathways was carried out.

The results show only one of the two schemes is possible. The source of this selectivity is discussed further on.

COMPUTATIONAL METHODS

All calculations were performed using the Gaussian 98 program[13]. Full geometry optimizations without symmetry constraints were carried out using density functional (DFT) calculations. Becke's gradient corrections[14] for exchange and Perdew-Wang's for correlation[15] were used for optimization and total energy evaluation. The corresponding functional is BPW91, which has demonstrated excellent performance in these kinds of systems[16,17]. All calculations were performed using the 6-31-G** basis set.

For the transition state determinations, quasi-Newton transit-guided (QSTN) computations were carried out[18]. In addition, corrections to the transition states were confirmed by intrinsic reaction coordinate (IRC) calculations, while intrinsic reaction paths (IRPs)[19,20] were traced in order to make sure that no further intermediates exist, for the MO energy calculations.

RESULTS AND DISCUSSION

The coordinates of each reaction are shown in Figs. 1 and 2, presenting the energy values for the up-hill and down-hill zones, respectively. The results are conclusive and the difference between the transition state energy values is very high, with a large difference in activation energies (427.15 and 13.7 kcal/mol) for the two pathways. Therefore, the preferred pathway is *via* the formation of the eight-membered ring.

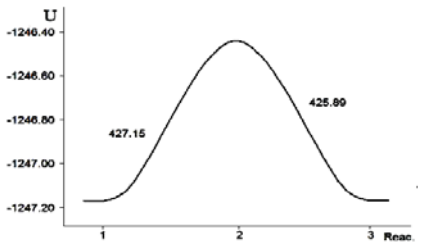


Fig. 1. Reaction profile plot of the pathway 6-endo-dig (Energy values in hartree in the axis and kcal/mol in the plots)

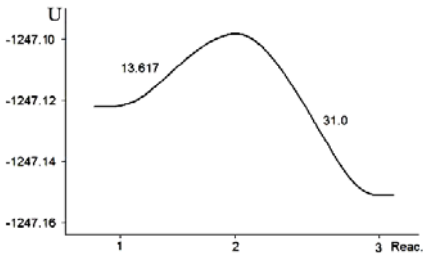
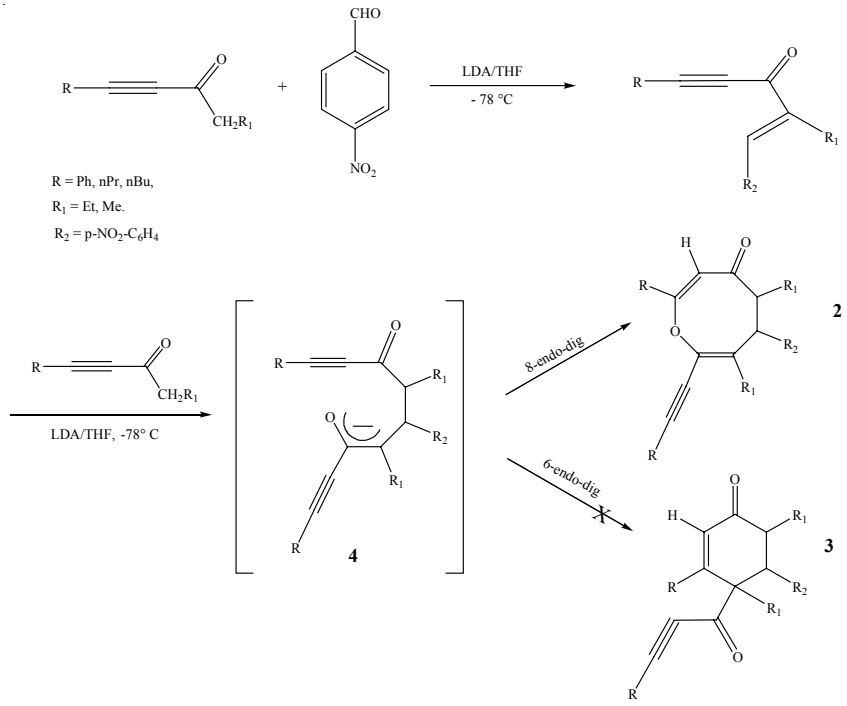


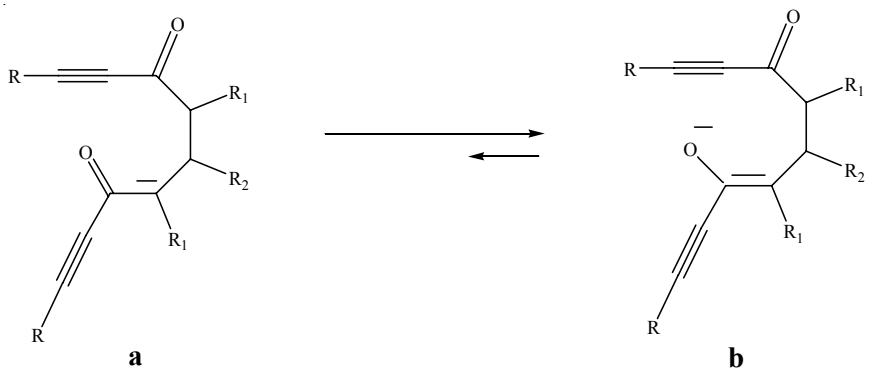
Fig. 2. Reaction profile plot of the pathway 8-endo-dig (Energy values in hartree in the axis and kcal/mol in the plots)

In an earlier report[6], a plausible mechanism involving the initial aldol condensation of an α-ketoalkyne with *p*-nitrobenzaldehyde is suggested. This yields a crossed enynone, which, by the Michael addition of a second equivalent of the α-ketoalkyl enolate, gives the intermediate **4**. The intermediate **4** cyclizes 8-endo-dig in a selective way, as shown in **Scheme-III**.



Scheme-III

The titled intermediate should be involved in a tautomeric equilibria as is shown in **Scheme-IV**.



Scheme-IV

Specie **b** is favoured in the reaction process, due to the low levels of activation energy involved. According to the HOMO calculation of **4** (Fig. 3), we observed high electron density around the oxygen atom and, therefore, the O-intramolecular Michael's type attack is the preferential pathway, as

shown in **Scheme-V**. The bulky groups involved in this conformation, also favour the approach of the electrophile in the plane of enolate in Fig. 4 (this last postulated by Baldwin rules). The stereoelectronic effect gives the 8-endo-dig cycle as the regiospecific product.

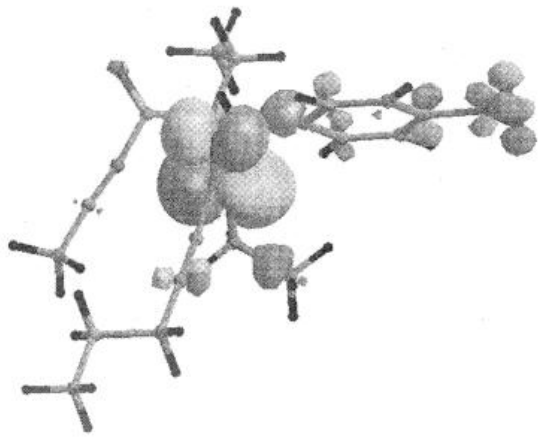


Fig. 3. HOMO calculation of intermediate **4**

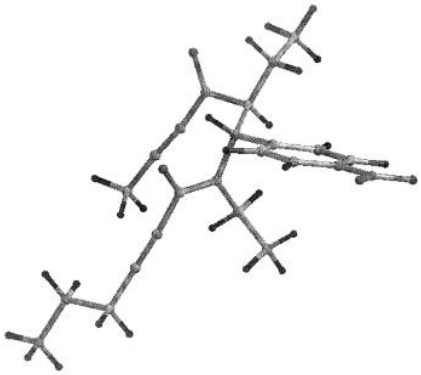
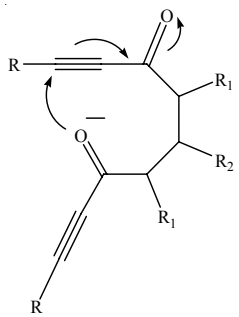


Fig. 4. Approach of the electrophile in the plane of enolate



Scheme-V

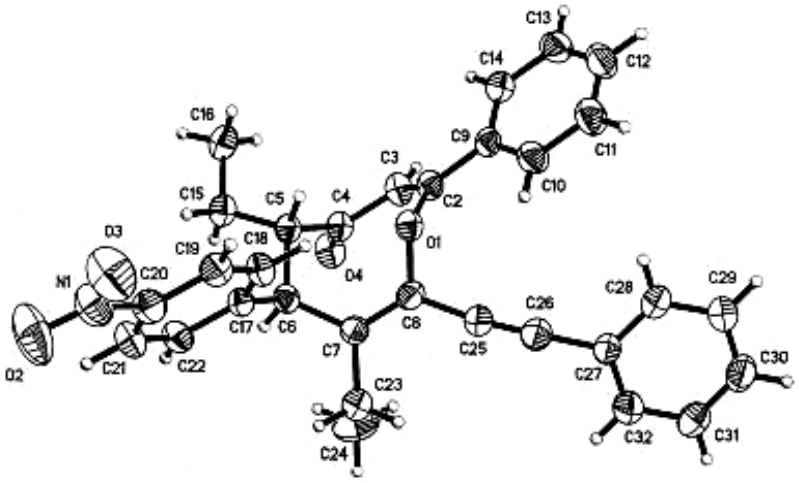


Fig. 5. Molecular structure of 5,7-diethyl-6-(4-nitro phenyl)-2-phenyl-8-phenylethynyl-5,6-dihydrooxacin-4-one

Conclusion

The reaction of α-ketoalkynes with *p*-nitrobenzaldehyde in basic media can take two different pathways. However, in the present case, the reaction yielded only the O-alkylation (8-endo-dig) cyclic product **3**, with no traces of compound **2** (six-endo-dig) being detected. This result is consistent with the values of calculated activation energy and HOMO calculations, since the more favourable enolate species in equilibria (**Scheme-IV**) seems to be responsible for the final result. We found that Baldwin rules can be applied in this particular case.

Finally, the biological behaviours of the oxacinones obtained were tested and an important activity as lipid oxidation inhibitors and moderate antiinflamatory activity were evaluated. Studies in order to clarify these biological conducts are in progress. This type heterocycles since are of interest to synthesize itself in one pot of reaction, unlike other informed methods[2,21,22].

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(*Received*: 12 January 2008; *Accepted*: 30 August 2008) AJC-6799