

A DFT study for the regioselective 1,3-dipolar cycloadditions of nitrile *N*-oxides toward alkynylboronates

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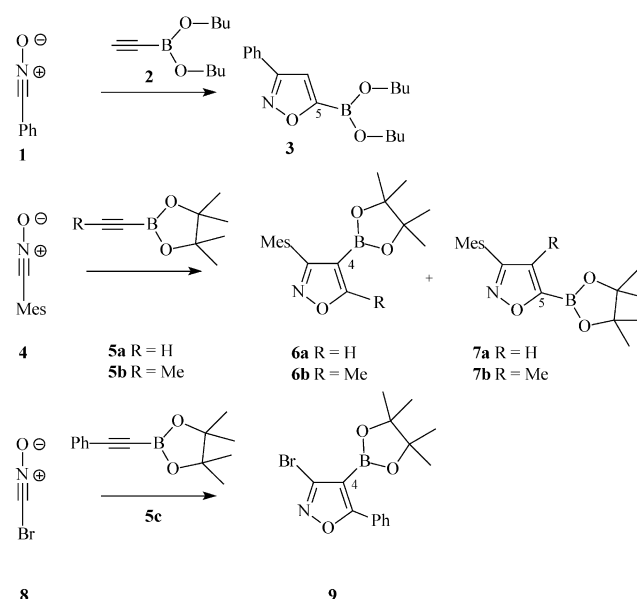
Abstract—The mechanism for the 1,3-dipolar cycloaddition of benzonitrile oxide toward ethynyl and propynylboronate has been studied by using density functional theory (DFT) at B3LYP/6-31G* level. These cycloadditions are concerted [3+2] processes. The presence of the two oxygens on the boronic ester precludes the participation of the boron atom on [3+3] processes. The two regioisomeric channels associated to the formation of the isoxazoles bearing the boronic ester unit on the 4- or 5-positions have been characterized. The B3LYP/6-31G* activation parameters are in acceptable agreement with the experiments, allowing to explain the factors controlling these regioselective cycloadditions. © 2003 Elsevier Ltd. All rights reserved.

1. Introduction

The construction of the isoxazoline and isoxazole rings by a 1,3-dipolar cycloaddition (13DC) of a nitrile oxide to an alkene or alkyne has proven to be extremely useful in the preparation of compounds in organic chemistry.^{1,2} Among the various classes of compounds which are prepared from these cycloadducts are enones,^{2a} 1,3-amino alcohols,^{2b} β,γ-dihydroxy ketones^{2c} and β-hydroxy ketones.^{2a} The boronic ester functionality has also enjoyed considerable use in organic syntheses.³ In spite of the fact that procedures exist for the direct conversion of boronic esters into alcohols, carboxylic acids, and amines, not much 13DC reactions involving vinyl⁴ or alkynyl^{5–7} boronic esters as dipolarophiles were described.

The 13DC reaction of nitrile oxides with alkynylboronates has received scant attention. Bianchi et al.⁵ reported the cycloaddition of benzonitrile oxide **1** with the ethynylboronate **2** to give the 5-substituted isoxazole **3** as a single regioisomer (Scheme 1). Recently, Davies et al.⁶ studied the regioselective 13DC reaction of mesitylenecarbonitrile oxide (**4**) with the ethynylboronate **5a** to yield the isoxazole **7a** bearing the boronic ester unit in the 5-position in 59% yield, with only 23% of the alternative 4-regioisomer **6a** (Scheme 1). However, with the propynylboronate **5b** the reaction proceeded cleanly to the 4-regioisomer **6b**, remarkably, with complete reversal regioselectivity. A similar regioselectivity was found for the 13DC reaction

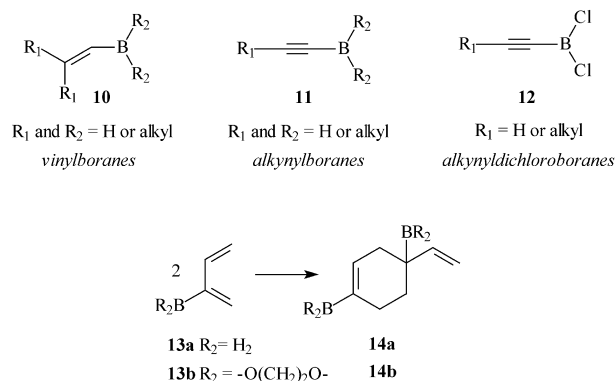
of benzonitrile oxide **1** with the alkynylboronates **5a** and **5b**.⁶ More recently, Harrity et al.⁷ studied the 13DC reaction between bromonitrile oxide (**8**) and the phenylethynylboronate **5c** to give the 4-substituted isoxazole **9** as single regioisomer in a yield of 69% (Scheme 1). The identical 4-regioselectivity was obtained using the methyl and the *n*-butylethynylboronate as dipolarophiles.⁷ Accordingly, while ethynylboronates give predominantly isoxazoles bearing the boronic ester unit in the 5-position, substitution of the hydrogen atom by a bulky alkyl or phenyl group change the regioselectivity to obtain only the 4-isomer.



Scheme 1.

Keywords: 1,3-dipolar cycloadditions; nitrile oxides; alkynylboronates; calculations; DFT.

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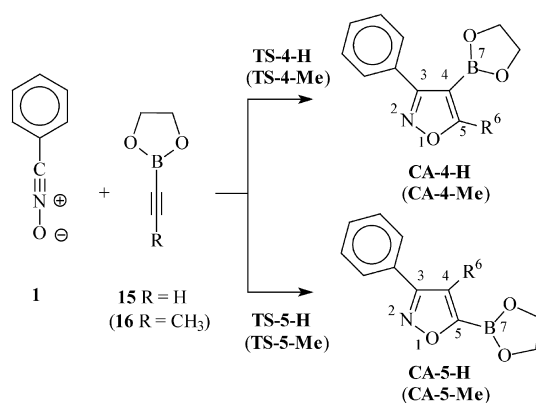


Scheme 2.

The cycloaddition reaction of 1,3-butadienes with vinylboranes, **10**,⁸ alkynylboranes, **11**,⁹ and alkynyldichloroboranes, **12**,¹⁰ has been widely theoretically studied. These studies suggest that these cycloadditions can take place through transition structures (TS) with a large [4+3] character due to the participation of the boron along the bond formation process. The participation of ethynylboronates as dienophiles has been less studied. Very recently, Carreaux, Cossío et al.¹¹ have studied the [4+2] and [4+3] mechanisms in the dimerization of 2-boryl-1,3-butadienes **13a** and **13b** (Scheme 2). The B3LYP/6-31G* study performed on the thermal cycloaddition of **13a** suggests that the [4+3] pathway predominates in the initial stage of the reaction profile. However, beyond a distance of ca. 2.1 Å the [4+2] mechanism is preferred. This behavior disappears when the 1,3-dioxolane moiety is included in the dienophile, **13b**, and the TS associated to the cycloaddition of the boronic ester has a large [4+2] character.

The 13DC reaction of nitrones with vinylboranes has been studied by Rastelli et al.¹² Analysis of the stationary points found at the B3LYP/6-31G* suggests that these cycloadditions take place along asynchronous concerted TSs, which can be associated to [3+3] processes because the large X...B (X=O or C of the nitron) interactions.

In this paper, the 13DC reaction between the benzonitrile oxide **1** and the ethynyl and propynylboronates **15** and **16** has been studied (Scheme 3).⁶ Our aim was to characterize the mechanism of these cycloadditions involving boronic esters, and to explain the origin of the regioselectivity experimentally observed.



Scheme 3.

2. Computational methods

DFT calculations have been carried out using the B3LYP¹³ exchange-correlation functionals, together with the standard 6-31G* basis set.¹⁴ The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method.¹⁵ All calculations were carried out with the Gaussian 98 suite of programs.¹⁶ The values of the relative enthalpies, ΔH , entropies, ΔS and free energies, ΔG , have been calculated based on the total energies and the thermochemical analysis at the B3LYP/6-31G* level.¹⁴

3. Results and discussions

An analysis of the gas phase results indicates that these cycloadditions take place along concerted processes. Therefore two TSs, **TS-4-H** and **TS-5-H**, and **TS-4-Me** and **TS-5-Me**, and two cycloadducts, **CA-4-H** and **CA-5-H**, and **CA-4-Me** and **CA-5-Me**, associated to the two regioisomeric channels for the two cycloadditions have been located and characterized. These acronyms are related with the formation of the 4- or 5-regioisomers, named as **4** and **5**, and to the cycloadditions with the dipolarophiles **15** or **16**, named as **H** and **Me**, respectively.

In gas phase, the activation barriers associated to these cycloadditions are: 13.5 kcal/mol (**TS-4-H**), 11.7 kcal/mol (**TS-5-H**), 15.2 kcal/mol (**TS-4-Me**) and 16.9 kcal/mol (**TS-5-Me**) (Table 1). Substitution of the hydrogen atom by the methyl group on the acetylene moiety increases the activation energy associated to the cycloaddition in 3.5 kcal/mol. These activation barriers show the change on the regioselectivity for the two 13DC reactions. Thus, while for the reaction between **1** and **15**, **TS-5-H** is 1.8 kcal/mol lower in energy than **TS-4-H**, favoring the formation of the 5-regioisomer, for the reaction between **1** and **16**, **TS-4-Me** is 1.7 kcal/mol lower in energy than **TS-5-Me**, favoring the formation of the 4-regioisomer. These energetic results agree with the change of regioselectivity experimentally observed with the methyl substitution.⁶

Since steric factors appear to be responsible for the reversal regioselectivity of the propynylboronate **16** (see latter), the influence of the methyl substitution on the dioxaborolane moiety on the 13DC reaction between **1** and **5b** was studied.

Table 1. Relative^a energies (in vacuo, ΔE_{vacuo} , and in diethyl ether, ΔE_{ether} , kcal/mol), and relative^a enthalpies (ΔH , kcal/mol), entropies (ΔS , cal/mol K) and free energies (ΔG , kcal/mol) calculated^b at 307.6 K and 1 atm in vacuo, for the 13DC reactions between of benzonitrile oxide **1** and the alkynylboronates **15** and **16**

	ΔE_{vacuo}	ΔE_{ether}	ΔH	ΔS	ΔG
TS-4-H	13.5	14.3	13.8	-44.4	27.4
TS-5-H	11.7	12.1	11.9	-42.6	25.0
CA-4-H	-75.3	-74.1	-72.0	-53.0	-55.7
CA-5-H	-75.3	-75.1	-72.8	-54.2	-56.1
TS-4-Me	15.2	16.4	16.0	-41.8	28.8
TS-5-Me	16.9	16.9	17.7	-40.2	30.0
CA-4-Me	-69.9	-71.7	-69.5	-50.8	-53.9
CA-5-Me	-68.6	-68.2	-65.2	-51.1	-49.5

^a Relative to **1+15** or **1+16**.

^b Scaled by 0.96.¹⁷

The relative energy between the TSs associated to the two regioisomeric channels, 1.3 kcal/mol, was slightly lower than that between **TS-4-Me** and **TS-5-Me**, 1.7 kcal/mol. Therefore, these results indicate that the methyl groups present on the dioxaborolane has not a decisive influence on the regioselectivity.

The activation enthalpies associated to the two regioisomeric channels predict the same regioselectivities (Table 1). The activation entropies for these intermolecular cyclo-additions range from -40.2 to -44.4 cal/mol K. These values raise the activation free energies to 25.0 kcal/mol for the reaction between **1** and **15**, and to 28.8 kcal/mol for the reaction between **1** and **16**. These cycloadditions are very exergonic processes, between -49.5 and -56.1 kcal/mol, because of the aromatic character of the isoxazole ring.

The lengths of the O1–C5 and C3–C4 forming bonds at the TSs are: 2.147 and 2.343 Å at **TS-4-H**, 2.219 and 2.302 Å at **TS-4-Me**, 2.519 and 2.165 Å at **TS-5-H** and 2.425 and 2.157 Å at **TS-5-Me**, respectively (Fig. 1). The distances between the B7 boron and the C4 carbon or O1 oxygen at these TSs are large, between 2.543 and 2.995 Å. At **TS-5-Me** the distance between the methyl C6 carbon and the phenyl substituent, 3.18 Å, is lower than the sum of the van der Waals radii of the methyl group (2.0 Å) and the carbon atom (1.2 Å). Therefore, the hindrance that appears between the alkyl substituent on ethylene and the phenyl substituent on the nitrile oxide can be responsible for the reversal regioselectivity with formation of the 4-isomer.

The BO values¹⁸ of the O1–C5 and C3–C4 forming bonds at the TSs are: 0.26 and 0.23 at **TS-4-H**, 0.23 and 0.25 at **TS-4-Me**, 0.15 and 0.29 at **TS-5-H**, and 0.18 and 0.31 at **TS-5-Me**, respectively. The TSs associated to the formation of the 5-regioisomers are more asynchronous than those associated to the formation of the 4-ones. The very low BO values between the B7 boron and the O1 oxygen or the C3 carbon at the TSs, between 0.06 and 0.01, indicate that there

are not any appreciable covalent interaction between the boron and the extreme of the dipole, excluding the [3+3] processes. The non-direct participation of the boron atom on these cycloadditions was confirmed by analysis of the intrinsic reaction coordinate (IRC)¹⁹ paths from the TSs to the two associated minima.

The charge transferred²⁰ from benzonitrile oxide **1** to the alkynylboronates **15** or **16** at the TSs is: 0.03e (**TS-4-H**), 0.02e (**TS-5-H**), 0.01e (**TS-4-Me**), and 0.00e (**TS-5-Me**), thereby indicating the non-polar character of these cycloadditions.

Inclusion of solvent effects, diethyl ether, by the polarizable continuum model (PCM)²¹ does not modify the gas phase geometries (Fig. 1). In addition, an analysis of the energies given in Table 1 indicates that in diethyl ether the activation barriers are between 0.0 and 1.2 kcal/mol higher than those obtained in gas phase. These results are a consequence of a larger solvation of the reactants than TSs, and they are in agreement with the non-polar character of these cycloadditions.

Recent studies devoted to Diels–Alder²² and 13DC²³ reactions have shown that the global indexes defined in the context of density functional theory²⁴ are a powerful tool to understand the behavior of these cycloadditions. The simplest nitrile oxide (**17**) has a low electrophilicity power,²⁵ $\omega=0.73$ eV, it being classified as a marginal electrophile.²³ However, substitution at the carbon site by a phenyl group renders the nitrile oxide **1** as a moderate electrophile ($\omega=1.46$ eV) (Table 2). Therefore, it is expected that **1** will easily react with electron-rich dipolarophiles, nucleophiles, in a polar process. For the mesitylenecarbonitrile oxide **4**, the electrophilicity power, 1.31 eV, is lesser than that for **1** because the electron-releasing character of the methyl groups present on the aryl substituent.

The alkynylboranes present a wide range of electrophilicity values. The ethynylborane **18** (**11**, R₁ and R₂=H) has an electrophilicity power of $\omega=2.24$ eV, it being classified as a strong electrophile. Therefore, it reacts with marginal electrophiles, nucleophiles, through polar processes.²³ Substitution of the two hydrogens by two electron-releasing methyl groups decreases the electrophilicity of **19** (**11**, R₁=H and R₂=Me) to 1.51 eV. On the other hand, the presence of two chlorides in **20** increases the electrophilicity

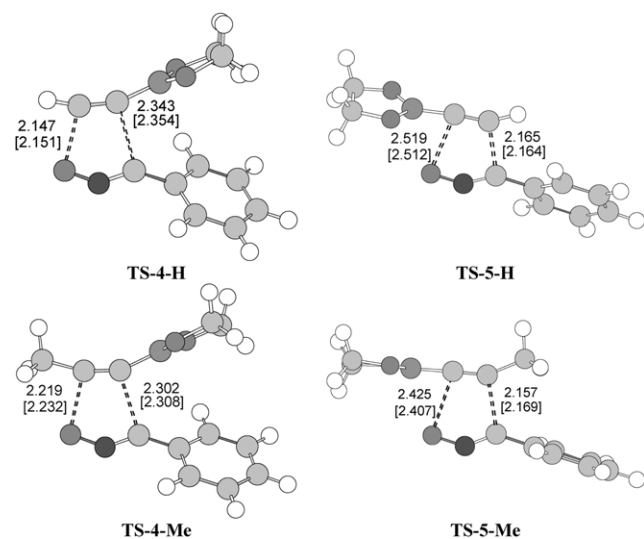


Figure 1. Optimized geometries of the TSs corresponding to the 13DC reaction between benzonitrile oxide **1** and the alkynylboronates **15** and **16**. The bond lengths directly involved in the reaction are given in angstroms. The values obtained using the PCM approach to simulate diethyl ether are given in brackets.

Table 2. Global electrophilicity²³ (ω , in eV), electronic chemical potential²⁴ (μ , in a.u.) and chemical hardness²⁴ (η , in a.u.) of the nitrile oxides **1**, **4**, and **17**, the alkynylboranes **18**, **19**, **20**, and the alkynylboronates **15** and **16**^a

	ω	μ	η
20	2.38	-0.1925	0.2118
18	2.24	-0.1788	0.1945
19	1.51	-0.1545	0.2157
1	1.46	-0.1406	0.1847
4	1.31	-0.1311	0.1790
15	1.05	-0.1433	0.2667
16	0.87	-0.1283	0.2567
17	0.73	-0.1249	0.2919

^a For computational details see Refs. 22 and 23.

of ethynylchloroborane to 2.38 eV. A more drastic effect causes the presence of the two oxygens on the boronic esters. These alkynyl derivatives present low electrophilicity values, 1.05 eV (**15**) and 0.87 eV (**16**), compared with the ethynylborane **18**. This behavior can be explained by the large delocalization of the oxygen lone pairs located on pz atomic orbitals on the unoccupied pz atomic orbital of the boron. This electronic delocalization decreases the Lewis acid character of the boron atom on the boronic ester, and it avoids the participation of this atom on a [3+3] mechanism.

Finally, the low $\Delta\omega$ values computed for these cycloadditions, 0.41 eV for **1**+**15** reaction and 0.59 eV for **1**+**16** reaction, allow to explain the non-polar character of these processes.²³ The benzonitrile oxide **1** and the ethynyl and propynylboronates **15** and **16** present similar electronic chemical potential values, μ , and in consequence, along the cycloaddition either of them has any tendency to supply electron density to the other. This analysis is in complete agreement with the unappreciable charge transfer found at corresponding TSs.

4. Conclusions

The mechanism for the 13DC reaction between benzonitrile oxide and ethynyl and propynylboronates has been studied by using DFT methods. These cycloadditions are concerted [3+2] processes with a non-polar character. The TSs associated with the formation of 5-isomers are more asynchronous and more advanced than those related with the formation of 4-ones. The former is the preferred for the reaction with ethynylboronates. However, the presence of a bulky alkyl group on the acetylene moiety causes a hindrance with the aromatic ring of benzonitrile oxide along the channel associated to the formation of the 5-isomer, it being responsible for the complete reversal regioselectivity experimentally observed. For these cycloadditions the [3+3] process with participation of the boron is not suitable because the large delocalization of the lone pairs of the two oxygens of the boronic ester on the boron.

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