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Experimental and theoretical push-pull Chemo- and regioselectivity in 1,3-Dipolar cycloaddition reactions: The case of benzotriazepin-5-one with mesitylnitrile oxide

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ABSTRACT: A novel heterocyclic compound 3-mesityl-5-methyl-4,5,11,11a-tetrahydro-6H-[1,2,4]oxadiazolo [5,4-b][1,3,4]benzotriazépin-6-one **4** has been synthesised by a 1,3 dipolar cycloaddition (13DC) reaction of 1,3,4-benzotriazepin-5-one **1** with mesitylnitrile oxide **3**. The reaction, beside its synthetic interest, has shown to be completely chemo- and regioselective. The structure of the compound was determined by X-ray crystallography and analysed by spectral methods (NMR and mass spectrometry). The molecular mechanism for the reaction has been studied using quantum mechanical calculations at the B3LYP/6-31G* theory level. Two mechanisms are possible for the formation of the cycloadduct **4**. The first one involves a 13DC reaction between **1**, as dipolarophile and **3**, as dipole. Analysis of the results indicates that it takes place along asynchronous concerted bond-formation process with a very low polar character. The regioselectivity obtained from the calculations are in complete agreement with the unique formation of the cycloadduct **4**. The second mechanism is initiated by the nucleophilic attack of the N3 nitrogen of the tautomer form of **2**, to the C5 carbon of the nitrile oxide **3** to yield an amidoxime. However, the large energy involved in this addition prevents this mechanism. The large energy difference between the tautomers **1** and **2**, makes that only the C═N site of benzotriazepin-5-one **1** could act as a dipolarophile site. This fact makes the 13DC reaction to be chemoselective. The analysis of global electrophilicity of the reagents allows explaining the low polar character of these 13DC reactions. Copyright © 2007 John Wiley & Sons, Ltd.
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KEYWORDS: 1,3-dipolar cycloaddition; Benzotriazepines; chemo- and regioselectivity; synthesis; quantum mechanical calculations

INTRODUCTION

The 1,3-dipolar cycloaddition (13DC) reaction constitutes one of the most important way used, in organic reaction, for the synthesis of a variety of five-membered heterocyclic systems.[1–10] 13DC reactions were long been drawing the attention of both experimental and theoretical chemists since their introduction by Huisgen in the early 1960s.[11] In view of such a myriad of possibilities, much effort has been devoted towards the development of synthetic methods using heteroatomic systems.[12] Among them, 2-isoxazolines, obtained by reaction of nitrile oxides with alkene dipolarophiles, have been extensively studied due to their usefulness in medicine and agriculture, as well as their synthetic versatility.[13] Isoxazoline systems are often used in total synthesis as latent synthons, such as masked new heterocyclic or aromatic rings.

Owing to their well-established role as psychotherapeutics,[14] benzodiazepines have been the object of intense investigation in medicinal chemistry. The area of biological interest of this family of compounds has been extended recently to various diseases such as cancer,[15] viral infections (HIV)[16] and cardiovascular disorders.[17] Such a versatile biological activity of the benzodiazepine pharmacophore has prompted investigations into their

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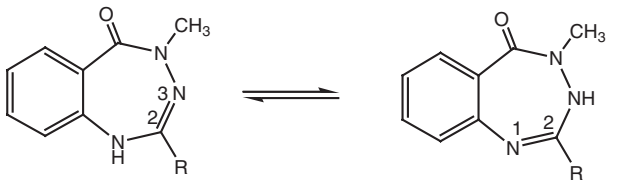
nitrogen homologues, the benzotriazepines,[18] in order to find new therapeutical leads. The fusion of heterocyclic rings to different faces of the heptatomic nucleus was shown to enhance or modify activity profiles.[19–21]

Selectivity in 13DC reactions has become the subject of theoretical investigations by means of good level of theory directed to the calculation of TSs and activation parameters.[22–24] It depends on electronic and steric effects. The specific direction of the electronic interaction is not well defined and identifying unequivocally electrophilic and nucleophilic centres has been difficult.

In general, the reactivity has been explained in terms of Frontier Molecular Orbital (FMO) theory.[25] However, although HOMO–LUMO interaction has proved to be very useful to explain the chemical reactivity and regioselectivity of Diels–Alder reactions, a satisfactory rationalisation of 13DC reactions is not available.[26] An alternative to FMO theory to address the reactivity in 13DC reactions is the formulation of the interaction energy in terms of density functional theory (DFT)[27] and the use of the global[28] and local[29] electrophilicity indexes.

In this paper, we report the experimental and theoretical results of the 13DC reaction between 1,3,4-benzotriazepin-5-one **1** (R═H) and mesitylnitrile oxide **3** (Scheme 1). Our purpose is to contribute to a better understanding of the mechanistic features of these processes, especially by locating and characterising all stationary points involved on the reactive potential energy surface (PES). The structural and energetic information obtained by theoretical methods based on quantum mechanical calculations of possible intermediates and transition structures provide powerful assistance in the study of organic reaction mechanisms.[30] These methods are accepted as reliable tools for the interpretation of experimental results, since such data are rarely available from experiments.[31] We intend, in this work, to characterise the mechanism of the studied reaction and to explain the origin of the selectivity experimentally observed.

It is noteworthy that the benzotriazepinone **1** can exist in equilibrium with the tautomeric form **2** (Scheme 2). Because both structures have different dipolarophile sites with a similar reactivity, the C2═N3 at **1** and N1═C2 at



1 **2**

Scheme 2

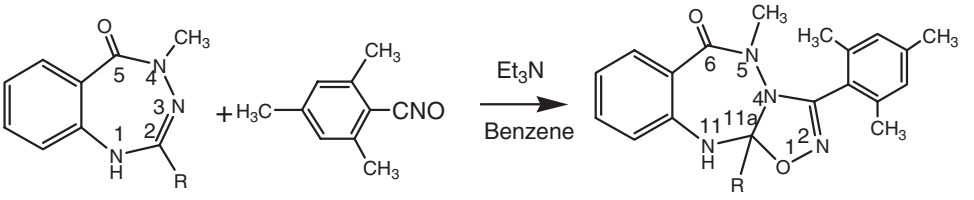
2, two 13DC reactions are feasible. Recently, we have reported the reactivity of **1** as dipolarophiles towards nitrilimines in order to access rapidly to new benzotriazepines of biological interest.[9] This 13DC reaction was found to be chemoselective (reactivity of N1═C2 or C2═N3 double bonds as dipolarophiles towards the dipole) and regioselective (different orientation along the approach of the asymmetric dipole to the C2═N3 bond) and leads to [1,2,4] triazolo[1,3,4]benzotriazepinones.[9]

RESULTS AND DISCUSSIONS

Experimental results

The reaction of 1,3,4-benzotriazepin-5-one **1** (R═H) with mesitylnitrile oxide **3** was performed in dry benzene at reflux during 8 h. After purification by chromatography on silica gel column (hexane/ethylacetate), the cycloadduct 3-mesityl-5-methyl-4,5,11,11a-tetrahydro-6H-[1,2,4]oxadiazolo[5,4-b][1,3,4]benzotriazepin-6-one **4** ($C_{19}H_{20}O_2N_4$) was isolated in 30% yield (Scheme 1). The structural identification of the reaction product was based on spectral data (^{1}H NMR, ^{13}C NMR and mass spectrometry) and X-ray crystallographic analysis.

We also observed that the substituent effect of the benzotriazepine has a large influence on the cycloaddition reactivity. So in the case of phenyl substituent (R═C_6H_5), the cycloadduct is observed but in no isolable quantity. On the other hand, when R═CH_3, the cycloaddition does not proceed out and we obtained only the benzotriazepine and the dipole dimer.



1 **3** **4**

Scheme 1

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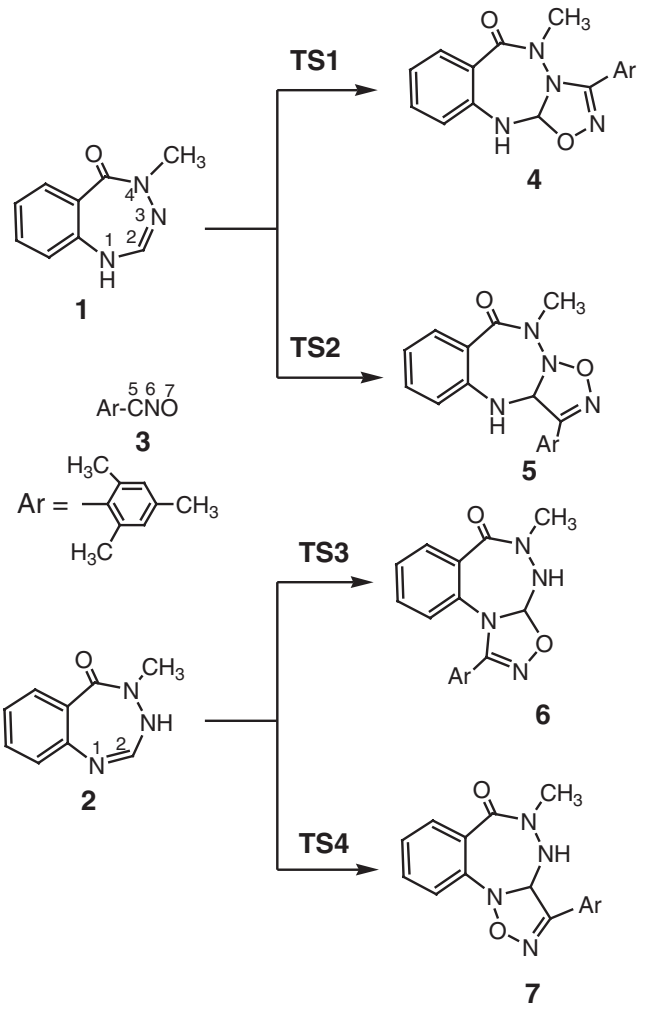

Scheme 3

Spectral data allowed the preferential C2═N3 attack site of the benzotriazepinone **1** (chemoselectivity) and the predominant orientation of the addition $N_{dipole} - C_{dipolarophile}$ (regioselectivity). So, the ^{13}C NMR spectra (spin echo) of the cycloadduct **4** (R═H) shows the chemical shift of the carbon atom C6 at about 172.6 ppm and excludes categorically the addition on the oxo group. Concerning the orientation of addition of the dipole, the chemical shift of the carbon C11a at 100.8 ppm indicates the sense of the addition ($O_{dipole} - C_{dipolarophile}$) and rules out unambiguously the formation of the other possible regioisomer. It is noteworthy that the observed value is in good agreement with those described in the literature for a similar environment.[32] In the same spectra, we can moreover detect four signals at about 19.7, 20.6, 21.5 and 38.1 ppm assigned to methyl carbons of mesityl group, and to the carbon in N—CH_3 respectively. The signals of aromatic carbons were also observed in this spectrum. Additionally, the regioselectivity was confirmed by the singlet at 6.65–6.75 ppm in the ^1H NMR spectra assigned to the proton at C11a for the cycloadduct. In the same spectra, the chemical shifts at about 1.30, 2.15, 2.25 and 3.25 ppm were assigned to methyl protons of mesityl group and hydrogen in N—CH_3 respectively. In the mass spectra (FAB), we noted essentially molecular peaks to $m/z = 337$ (100%) $[M + H]^+$ in agreement with mono-condensation reaction. Even though the spectral data were in good agreement with the proposed structure, and because of the existence of two possible dipolarophile sites (N1═C2 and C2═N3), it is difficult to make a choice between structure **4** and possible alternative chemoisomeric structure **6** (such as referred in Scheme 3, by cycloaddition across the 1,2 positions of the benzotriazepinone ring). Finally, the exact structure was determined on the basis of the X-ray crystallographic analysis of a single crystal of **4** (Fig. 1).

X-ray crystallographic analysis. The molecular structure of **4** ($C_{19}H_{20}O_2N_4$, monoclinic) determined in this work is shown in Fig. 1. There are eight formula units in the unit cell. There are intermolecular contacts O—H, N—H, H—H and π—H which lead to forming somehow a ''dimmer'' mainly through the rotation axis, as most of these contacts are through the mentioned axis. Translations along the b-axe define columns along this direction. Sheets are distributed along the diagonal (a + c), and pile up to form the crystal through centres of symmetry and helicoidally axis. Thus the packing in the crystal is a distorted closed hexagonal one.

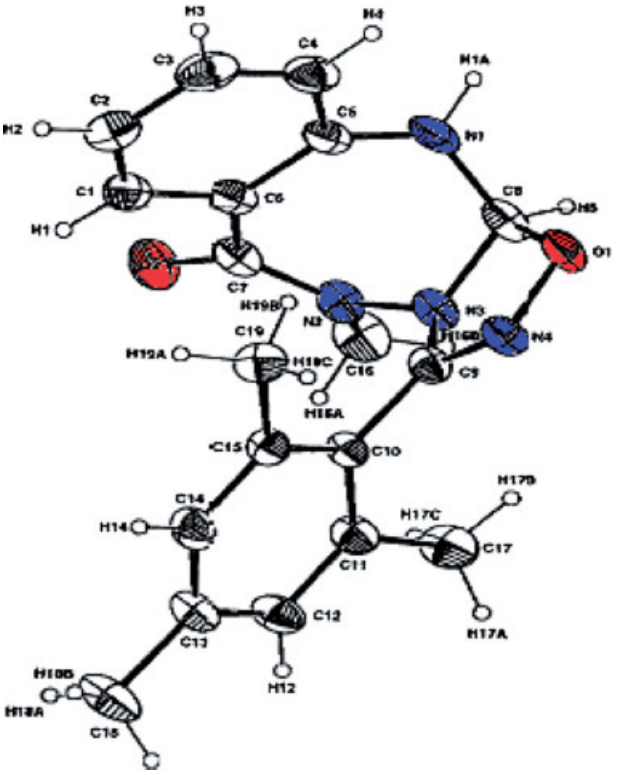

Figure 1. The molecular structure of compound 4(R═H) (ORTEP: XTAL 3.6) with the numbering scheme. Displacement ellipsoids are drawn at 30% probability.

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Theoretical results

Study of the PES for the reaction of 1 and 2 with 3. Due to the asymmetry of dipolarophiles **1** and **2** and dipole **3**, these 13DC reactions can take place along two regioisomeric pathways. Both channels have been studied. The analysis of the gas phase results for these 13DC reactions indicates that they take place along concerted bond-formation processes. Therefore four TSs, **TS1**, **TS2**, **TS3** and **TS4**, associated to the two regioisomeric channels for the 13DC reactions of **1** and **2** with **3** and the corresponding cycloadducts **4**–**7**, have been located and characterised. The stationary points corresponding to the cycloaddition reaction have been presented in Scheme 3. The relative energies are summarised in Table 1.

Early studies devoted to the tautomerism of benzotriazepinones indicated that in solution, these compounds appear to exist as the 3,4-dihydro structure **2**.[33,34] However, recently, studies carried out by Boese *et al*., using X-ray diffraction and quantum chemical calculations at the HF/6-31G** level, have indicated that these compounds exist as the 1,4-dihydro tautomeric form **1**.35 B3LYP/6-31G* calculations give the tautomer **2**, 8.1 kcal/mol higher in energy than **1** (see Table 1). This energy difference remains with the inclusion of solvent effects (8.2 kcal/mol in benzene). This DFT energy difference was confirmed by performing single point calculations at CCSD(T)/6-31G* level, 7.5 kcal/mol. These large energy differences indicate that the tautomer **1** is the major isomer of the two tautomeric forms, in agreement with the Boese studies.[35]

Two mechanisms are feasible for the interconversion between both tautomers. The first one involves an intramolecular proton transfer between the N1 and N3 nitrogen atoms through a concerted process. The second one is a stepwise mechanism involving an external acid/base catalyst. We have considered only the concerted process. The TS associated to this process, **TStau**, has a very high energy; it is located 71.3 kcal/mol higher than the tautomer **1**. Similar results have been found in related intramolecular tautomerisation processes, where the concerted process is forbidden energetically.[36] This large energy is due mainly to the strain associated to the four-membered TS. Therefore, if the two tautomeric forms are in equilibrium, the interconversion between these species must take place through a stepwise process.

For the 13DC reactions of the benzotriazepinone **1** with the nitrile oxide **3**, the activation energies associated to the two regioisomeric pathways are 18.9 kcal/mol (**TS1**) and 29.8 kcal/mol (**TS2**), while for the reactions of the tautomer **2** with **3**, they are 15.2 kcal/mol (**TS3**) and 27.9 kcal/mol (**TS4**), respectively. These cycloadditions present a large regioselectivity; the TSs associated to the formation of the cycloadducts **4** and **6** are 11 and 13 kcal/mol lesser in energy than those associated to the formation of the regioisomeric cycloadducts **5** and **7**.

The activation energy associated to the formation of the cycloadduct **6** via **TS3** is 3.7 kcal/mol lower in energy than that associated to the formation of **4** via **TS1**. However, if we consider the easy equilibrium between both isomers, the more favourable reactive channel corresponds to the formation of **4** via **TS1**, with activation energy of 18.9 kcal/mol.[37] Note that the activation energy associated to **TS3** from **1** plus **3** is 23.3 kcal/mol. This energetic result is in clear agreement with the experimental outcome; only the formation of the cycloadduct **4** is observed. Formation of the cycloadducts **4** and **6** are exothermic processes, −19.5 (relative to **1** plus **3**) and −27.8 (relative to **2** plus **3**) kcal/mol, respectively, whereas the formation of the regioisomers **5** and **7** are endothermic in *ca.* 9–11 kcal/mol. Therefore, the formation of the cycloadduct **4** is kinetically favoured.

Inclusion of the thermal corrections to the energy and the entropy to the reaction temperature (80 °C) arises the relative free energy for these 13DC reactions between 17 and 19 kcal/mol, due to the bimolecular nature of these cycloadditions. The activation free energy for the formation of the cycloadduct **4** via TS1 arises to 36.3 kcal/mol. However, the relative free energies between the four TSs of these cycloadditions are similar to those found using the relative energies. Formation of the cycloadduct **4** is slightly exergonic, −1.7 kcal/mol.

An alternative pathway for the reaction between benzotriazepinone **2** and the nitrile oxide **3** leading to the formation of the cycloadduct **4** was considered (Scheme 4). This pathway is initiated by the nucleophilic attack of the N3 nitrogen of **2** to the C5 carbon of the nitrile oxide **3** to give an amidoxime **8** via **TS5**. This type of compounds has been obtained by addition of amines to the nitrile oxides.[38] While the addition of nucleophilic

Table 1. B3LYP/6-31G* relative energies[a,b] (ΔE, in kcal/mol) and relative free energies[a] (ΔG°, in kcal/mol, 80 °C) in gas phase and relative[a] energies (ΔE, in kcal/mol) in benzene for the stationary points involved in the reaction of benzotriazepinones **1** and **2** with the mesitylnitrile oxide **3**

	Gas phase		Benzene
	ΔE	ΔG°	ΔE
2	8.1	8.5	8.2
TStau	71.3	71.2	76.9
TS1	18.9	36.3	19.4
TS2	29.8	47.1	31.4
4	−19.5	−1.7	−21.4
5	11.1	29.0	10.6
TS3	23.3	41.0	24.6
TS4	36.0	52.8	38.0
6	−19.7	−1.8	−21.3
7	17.4	36.1	17.6
TS5	29.9	47.2	35.0
8	1.6	18.2	4.7
TS6	32.8	50.9	38.0

[a] Relative to **1** or **1** plus **3**.
[b] Including ZPE corrections.

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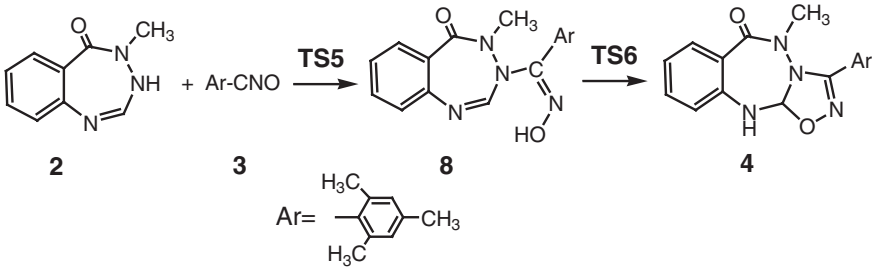

Scheme 4

carbons has a stepwise mechanism,[39] the addition of nucleophilic oxygen or nitrogen atoms have concerted mechanism.[40] Then the intramolecular attack of the O7 to the C2 with concomitant proton transfer will afford the experimentally observed cycloadduct **4**, via **TS6**.

The activation energy associated to the nucleophilic attack via **TS5** is 21.8 kcal/mol, and the formation of the amidoxime **8** is exothermic in −6.5 kcal/mol. This barrier is closer than that computed for the nucleophilic addition of ammonia to fulminic acid at the MP4/6–31G** level (22.0 kcal/mol).[40] However, the formation of the five-membered heterocycle present in **4**, via **TS6**, has a very large barrier (31.2 kcal/mol) (Fig. 2). The strain associated to the four-membered geometry demanded at this intramolecular proton transfer process is responsible of this high energy (see later). Alternatively, the cyclisation process can take place by a stepwise mechanism involving an initial N1 protonation that can catalyse the addition of the oxime oxygen atom. However, due to the large barrier found for the first nucleophilic addition, this acid-catalysed pathway was not considered.

The geometries of the TSs involved in these 13DC reactions are given in Fig. 3. The lengths of the forming bonds at the TSs are: 2.235 Å (C2—O7) and 2.005 Å (N3—C5) at **TS1**, 1.981 Å (C2—C5) and 2.313 (N3—O7) Å at **TS2**, 2.072 Å (N1—C5) and 2.158 Å (C2—O7) at **TS3** and 2.343 Å (N1—O7) and 1.919 Å (C2—C5) at **TS4**. The extent of the asynchronicity on the bond-formation can be measured by means of the difference between the lengths of the two σ bonds that are being formed in the cycloaddition that is, $\Delta r = d1 - d2$.[41] Because of different set of bonds are

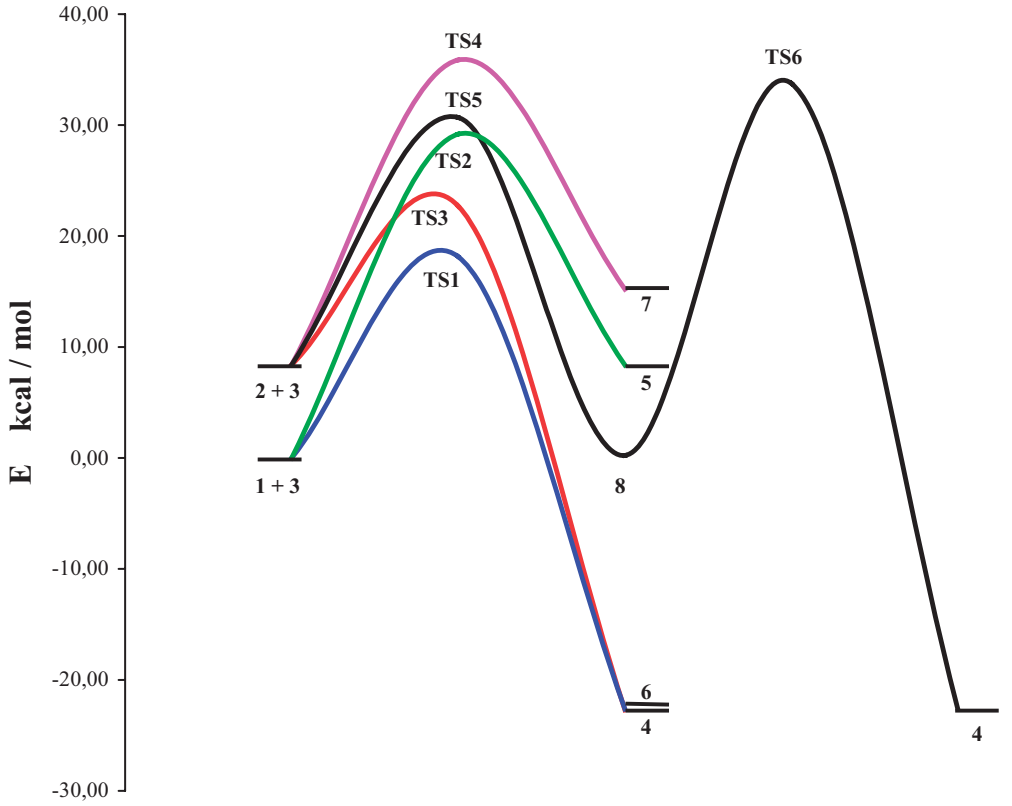

Figure 2. Energy profiles for the reaction between benzotriazepinones (**1** and **2**) and mesitylnitrile oxide **3**

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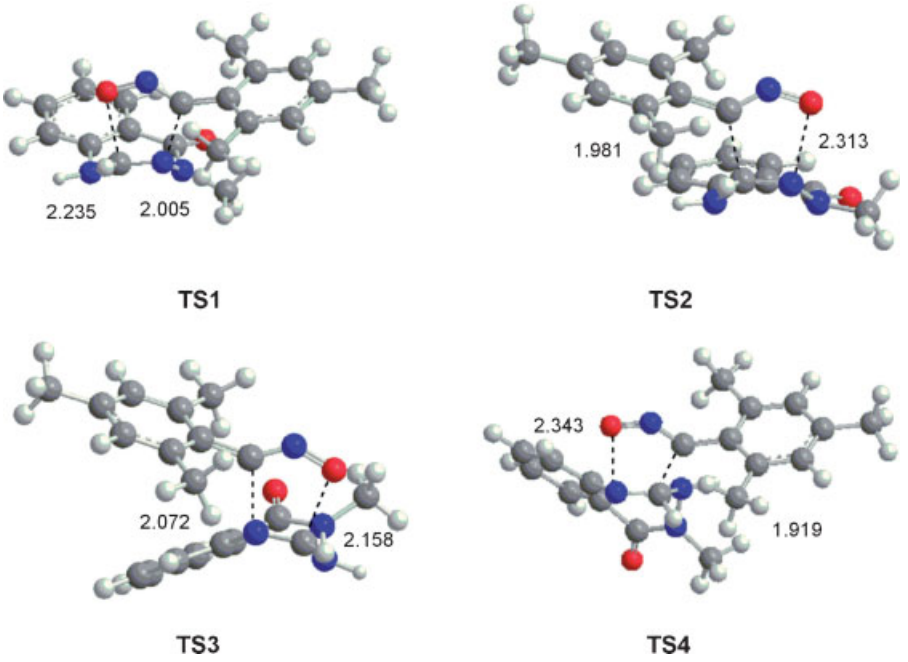

Figure 3. Selected geometrical parameters (in È) for transition structures corresponding to 13DC reaction between benzotriazepinones (**1** and **2**) and mesitylnitrile oxide **3**

involved in these 13DC reactions, C—C, C—N, C—O and N—O, we have selected $d1$ as the large bond-length, and $d2$ as the short one. The values of Δr are 0.23 (**TS1**), 0.33 (**TS2**), 0.09 (**TS3**) and 0.42 (**TS4**). While for the most favourable regioisomeric TS for the reaction of **1** with **3,** $\Delta r = 0.23$ points to an asynchronous concerted process, this value at the TS associated to the reaction of **2**, 0.09, points to a synchronous concerted process. The TSs associated to the regioisomeric pathway present larger asynchronicity.

The geometries of the TSs involved in the reaction between **2** and **3** to give **4** are presented in Fig. 4. For the TS associated to the formation of the amidoxime **8**, **TS5**, the length of the N3—C5 forming-bond is 1.914 Å, while the lengths of the N3—H breaking and O7—H forming bonds are 1.126 Å and 1.469 Å, respectively. At **TS6**, the length of the O7—C2 bond is 1.572 Å, while the lengths of the O7—H breaking and the N1—H forming bonds are 1.520 Å and 1.141 Å, respectively. The O7—C2 length indicates that this bond is readily formed at this TS. An analysis of the atomic motion at the unique imaginary frequency for **TS6**, 1,421.8 cm^{-1}, indicates that this TS is mainly associated to the proton transfer from the O7 oxygen to the N1 nitrogen. The O7—C2 bond formation takes place in an early step. However, all attempts to locate the TS associated to the formation of the five-membered ring were unsuccessful. At **TS6**, the N1—C2—O7 bond angle, 96.7 degree shows the strain associated to this four-membered TS.

The geometry of the TS involved in the intramolecular tautomerisation between **1** and **2**, **TStau**, is given in Fig. 5. The lengths of the N1—H and N3—H forming and breaking bonds at the TS are 1.539 and 2.104 Å, respectively; the N3—H breaking bond being more advanced than the N1—H forming bond. At this TS, the seven-membered heterocyclic ring has a planar arrangement, the process can be classified as a suprafacial [1,3] hydrogen shift. This process, which is forbidden by symmetry,[42] presents a large activation energy. Note that although the antarafacial process is allowed by symmetry, it is forbidden by geometric requirements.

The extent of bond formation along the reaction pathway is provided by the concept of bond order (BO).[43] The BO values of the forming bonds at the TSs associated to the 13DC processes are: 0.24 (C2—O7) and 0.37 (N3—C5) at **TS1**, 0.46 (C2—C5) and 0.23 (N3—O7) at **TS2**, 0.32 (N1—C5) and 0.27 (C2—O7) at **TS3** and 0.23 (N1—O7) and 0.49 (C2—C5) at **TS4**. These data indicate that while **TS3** is associated to synchronous bond formation process, the others TSs are associated to asynchronous concerted bond formation processes, where the bond formation involving the C5 carbon atom of nitrile oxide is more advanced than that involving the O7 oxygen. In addition, the more unfavourable regioisomeric **TS2** and **TS4** are more advanced and more asynchronous than the **TS1** and **TS3**; a similar trend is observed by analysis of Δr at the TSs.

At the TS associated to the formation of the amidoxime **8**, **TS5**, the BO value of the N3—C5 forming-bond is 0.43, while the BO values of the N3—H breaking and O7—H forming bonds are 0.52 and 0.24, respectively. These values show the concerted character of the C—N bond formation and hydrogen transfer. At **TS6**, the BO value of the O7—C2 bond is 0.70, while the BO value of

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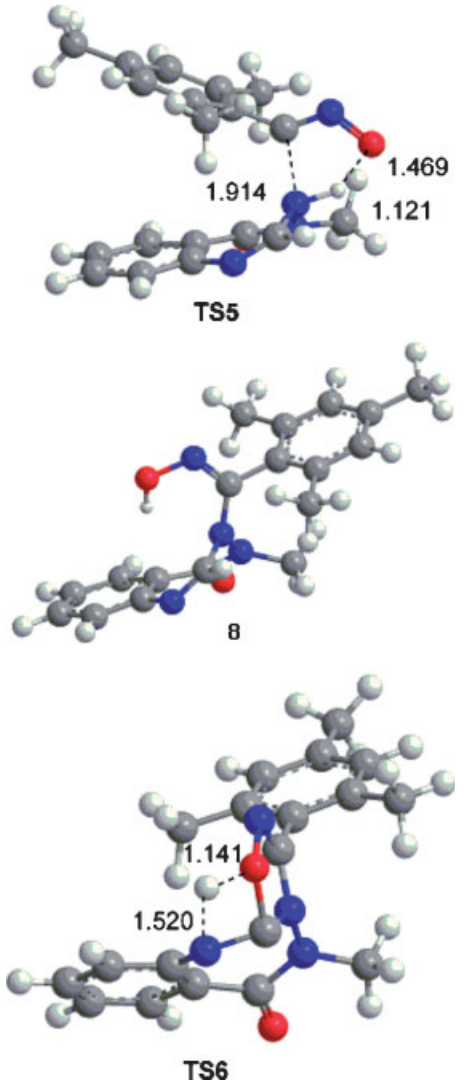

Figure 4. Selected geometrical parameters (in Å) for transition structures and amidoxime **8** corresponding to the alternative chemoselective pathway for the reaction between benzotriazepinone **2** and the mesitylnitrile oxide **3**

the O7—H breaking and N1—H forming bonds are 0.43 and 0.26, respectively.

At the TS involved in the intramolecular tautomerisation between **1** and **2**, **TStau**, the BO value of the N1—H and N3—H forming and breaking bonds are 0.20 and 0.01, respectively. Therefore, the breaking bond is more advanced than the forming one. The BO values of the N1—C2 and C2—N3 bonds are 1.06 and 1.34.

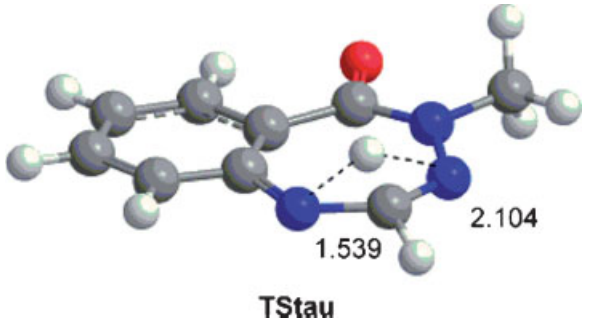

Figure 5. The TS structure involved in the intramolecular tautomerisation between **1** and **2.** The lengths of the forming bonds are given in Å

The natural population analysis (NPA) allows us to evaluate the charge transfer along these concerted 13DC reactions. The natural charges at the TSs appear shared between the dipole, **3**, and the dipolarophiles, **1** or **2**. The charge transferred at the TSs is: 0.08 e at **TS1**, 0.05 e at **TS2**, 0.00 e at **TS3** and −0.08 e at **TS4**. These low values indicate the low polar character of these 13DC reactions, in clear agreement with the low difference of electrophilicity, $\Delta\omega$, between the reagents (see later).

Finally, as these 13DC reactions were experimentally carried out in benzene, and the solvent effects can produce some alteration of both activation energies and regioselectivity, they were considered by means of single point calculations over the gas phase optimised geometries using the Polarizable Continuum Model (PCM). Table 1 reports the relative energies in benzene. Solvent effect stabilises all structures between 2 and 5 kcal/mol. The more stabilised species are the dipolarophiles **1** and **2**, *ca*. 5 kcal/mol. As a consequence, the activation energies in benzene are slightly larger than those in gas phase, *ca*. 2 kcal/mol. This poor solvent effect is in agreement with the unappreciable charge transfer found at the TSs of these 13DC reactions indicating that solvent effect does not modify substantially the gas phase results.

Global electrophilicity analysis. These 13DC reactions have been also analysed using the global indexes. Recent studies devoted to Diels–Alder[44] and 13DC[45] reactions have shown that the global indexes defined in the context of density functional theory are a powerful tool to understand the behaviour of these cycloadditions. In Table 2, the static global properties, electronic chemical potential (μ), chemical hardness (η) and global electrophilicity (ω) for the benzotriazepinones, **1** and **2** and nitrile oxide **3**.

The values of the electronic chemical potential of benzotriazepinones **1** and **2**, −0.1270 and −0.1362 au, respectively, are closer than that for the nitrile oxide **3**, −0.1311 au. Therefore, along the 13DC reactions between **1** or **2** and **3**, any of them will have some trend to provide electron density to the other and non-polar 13DC reactions will be expected in clear agreement with the NPA analysis.

Table 2. Electronic chemical potential (μ, in au), chemical hardness (η, in au) and global electrophilicity (ω, in ev) of the benzotriazepinone **1** and **2**, and nitrile oxide **3**

	μ	η	ω
1	−0.1270	0.1613	1.36
2	−0.1362	0.1772	1.42
3	−0.1311	0.1791	1.31

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The simplest nitrile oxide has a low electrophilicity power, $\omega = 0.73$ eV, it being classified as a marginal electrophile.[45] This dipole may be further converted into a poorer electrophile or probably as a good nucleophile by substitution at the carbon site by a methyl group, $\omega = 0.55$ eV.[45] However, substitution at the same site by phenyl group renders benzonitrile oxide as a moderate electrophile, $\omega = 1.46$ eV. Trimethyl substitution on the phenyl group renders mesitylnitrile oxide **3** to have a lower electrophilicity value, $\omega = 1.31$ eV, as a consequence of the electron-releasing character of the methyl group. On the other hand, the benzotriazepinone **1** and **2** present electrophilicity values of 1.36 and 1.42 eV, respectively. Therefore, they are classified also as moderate electrophiles.

As regard to the $\Delta\omega$ values computed for the studied 13DC reactions, which have been proposed as a measure of the polar character of the cycloadditions,[45] our results indicate clearly the non-polar character of these processes. Note that for the 13DC reactions of **1** and **2** with **3**, the $\Delta\omega$ values are 0.05 and 0.11 eV respectively. The mesitylnitrile oxide **3** and the benzotriazepinone **1** and **2** present similar electrophilicity values, and in consequence, either of them has any tendency to supply electron density to the other. This analysis is in clear agreement with the very low charge transfer found at the TSs, and with low solvation of the corresponding TSs by benzene.

CONCLUSIONS

The 13DC reaction of mesitylnitrile oxide **3** to benzotriazepin-5-one **1** proceeds with complete chemo- and regioselective reaction. Only one cycloadduct **4** was obtained in 30% yield and it has been characterised using NMR, mass spectroscopy, and X-ray crystallography. The molecular mechanism of the reaction has been studied using DFT calculation at B3LYP/6–31G* level. Formation of the cycloadduct **4** can take place along two alternative mechanisms. The first one involves a 13DC reaction between the C=N double bond of the benzotriazepin-5-one **1** and mesitylnitrile oxide **3**. An analysis of the gas phase results indicates that this 13DC reaction takes place along an asynchronous concerted process, the formation of the experimental [3 + 2] cycloadduct **4** being kinetically favoured. The cycloaddition presents a total regioselectivity. The second mechanism is initiated by the nucleophilic attack of the N3 nitrogen atom of the tautomer form of **2**, to the C5 carbon of the nitrile oxide **3** to give an amidoxime **8**. The subsequent intramolecular attack of the O7 oxygen atom to the C2 carbon atom with concomitant proton transfer will afford the experimentally observed cycloadduct **4**. However, the strain associated to the four-membered geometry demanded for the intramolecular proton transfer process makes the second reaction to have a very large energy barrier. The large energy difference between the tautomers **1** and **2**, makes that only the C=N site of benzotriazepin-5-one **1** could act as a dipolarophile site. This fact does the 13DC reaction to be chemoselective. The natural population analysis at the TSs associated to these 13DC reactions points to the low polar character of these cycloadditions. This analysis is in clear agreement with the small difference in the electrophilicity, $\Delta\omega$, between the reagents, and with the increase of the reaction barrier observed in benzene.

CALCULATION DETAILS

In the present study, geometrical optimisations of the stationary points along the potential energy surface (PES) were carried out using the corrected functional of Becke, Lee, Yang and Parr (B3LYP),[46] for exchange and correlation together with the 6–31G(d)[47] basis. The stationary points were characterised by harmonic vibrational frequency analysis in order to verify that minima and transition structures have zero and one imaginary frequency, respectively. The corresponding zero point energy (ZPE) corrections were calculated for all optimised structures and scaled by the empirical factor 0.98.[48] Free energies, computed at 80 °C, have been estimated by means of the potential energy barriers along with the B3LYP/6–31G* harmonic frequencies. The enthalpy and entropy changes are calculated from standard statistical thermodynamic formulas.[47] Starting from a transition structures, the intrinsic reaction coordinate (IRC)[49] pathway has also been constructed in order to verify further its identity and also map out a minimum energy reaction pathway. The optimisations were carried out using the Berny analytical gradient optimisation method.[50] Several conformations for all stationary points have been considered and those presented correspond to the most stable ones. The electronic structures of stationary points were analysed by the natural bond orbital (NBO) methods.[51] All calculations were carried out with Gaussian 98 Suite of program.[52] The solvent effects have been considered by B3LYP/6–31G* single point calculations over the gas phase optimised structures using a self-consistent reaction field[53] (SCRF) based on the PCM method of the Tomasi's group.[54] Since these reactions are carried out in benzene, we have selected its dielectric constant at 298.0 K. The global electrophilicity ω [28] is given by the expression $\omega = (\mu 2/2\eta)$, in terms of the electronic chemical potential μ and the chemical hardness η.[28] Both quantities may be approached in terms of the one electron energies of the HOMO and LUMO molecular orbitals, ε_H and ε_L, as $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $\eta \approx (\varepsilon_L + \varepsilon_H)$, respectively. The HOMO and LUMO energies have been calculated at the ground state of the molecules at the B3LYP/6–31G* level.[43]

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EXPERIMENTAL SECTION

Uncorrected melting points were taken on a Buchi 510 apparatus. The ^{1}H NMR spectra were recorded with a Bruker WP 400 CW. Me_4Si was used as an internal standard and $CDCl_3$ as the solvent. The ^{13}C NMR spectra were measured on a Varian FT 80 (100 MHz). Mass spectra was recorded with an Jeol JMS DX 300. The X-ray structure was solved by direct methods using the SHELXS and it was refined by least-squares analysis using the SHELXL (SHELX97) program.[55] Scattering factor, dispersion corrections and absorption coefficients were taken from International Tables for Crystallography.[56] Column chromatography was carried out using E-Merck silica gel 60F 254. Reagents and solvents were purified in the usual way.

The benzotriazepin-5-ones were prepared by reaction of isatoic anhydride and methylhydrazine, and then reacted with appropriate ortho esters according to a literature method.[52]

Cycloadduct **4** was obtained by reaction of 1,3,4-benzotriazepinone (0.0107 mol) **1** with mesitylnitrile oxide (0.011 mol) **3** at reflux in dry benzene (40 ml) during 8 h. The residue was concentrated under reduced pressure and purified by chromatography on silica gel column (hexane/ethyl acetate). The isolated product **4** was recrystallised at room temperature by adding a few drops of ethyl acetate to hexane saturated solution.

3-mésityl-5-méthyl-4,5,11,11a-tetrahydro-6H-[1,2,4] oxadiazolo[5,4-b][1,3,4]benzo- triazépin-6-one 4.

Rdt: 30% **F** = 209–210 °C (Ethanol)

RMN^{1}H; $CDCl_3$; (δppm): 1.30, 2.15, 2.25 (3s, 9H, Ar-C$\underline{H}_3$); 3.25 (s, 3H, N5-C$\underline{H}_3$); 4.65 (s, 1H, N11-H); 6.65–6.75 (3s, 3H, 2HAr, H-C11a); 6.85 (d, 1H,C10); 7.05 (t, 1H, H-C8); 7.35 (t, 1H, H-C9); 7.65 (d,1H, H-C7).

RMN^{13}C; $CDCl_3$; (δppm): 19.7, 20.6, 21.5 (Ar-$\underline{C}H_3$); 38.1 (N5-$\underline{C}H_3$); 100.8 (C11a); 123.3, 124.5, 129.1, 129.6, 132.6, 133.8 (C10, C8, 2CHAr, C9, C7); 119.1, 138.1, 139.4, 140.3, 140.9 (C6a, 4CAr, C10a); 153.7 (C3); 172.6 (C6).

Masse (FAB): m/z 337 (100%) $[M+H]^+$.

Crystal data: Monoclinic, space group C2/c, T = 293(2) K, $a = 14.642(10)$, $b = 8.031(5)$, $c = 28.659(21)$, $\alpha = 90.00°$, $\beta = 98.18(1)°$, $\gamma = 90.00°$, $V = 3335.9(4)$ Å^3, $Z = 8$, observed reflections, 2,708 with $I > 2\sigma(I)$, $R = 0.0507$, wR = 0.1389.

SUPPLEMENTARY MATERIAL

Table given B3LYP/6-31G* total energies, zero-point corrections, thermal corrections to enthalpy and entropy in gas phase and total energies in benzene, and B3LYP/6-31G* Cartesian coordinates for the stationary points involved in the reaction of benzotriazepinones **1** and **2** with the mesitylnitrile oxide **3**.

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