Tetrahedron 65 (2009) 5328–5336

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Microwave-assisted reactions of nitroheterocycles with dienes. Diels–Alder and tandem hetero Diels–Alder/[3,3] sigmatropic shift

M. Victoria Gómez[a], Ana I. Aranda[a], Andrés Moreno[a,*], Fernando P. Cossío[b,‡], Abel de Cózar[a], Ángel Díaz-Ortiz[a], Antonio de la Hoz[a,†], Pilar Prieto[a]

[a] Departamento de Química Orgánica, Universidad de Castilla-La Mancha, E-13071 Ciudad Real, Spain
[b] Kimika Organikoa Saila, Kimika Fakultatea, Universidad del País Vasco-Euskal Herriko Unibertsitatea, P.K. 1071, 20080 San Sebastián-Donostia, Spain

ARTICLE INFO

Article history:
Received 26 March 2009
Received in revised form 17 April 2009
Accepted 20 April 2009
Available online 24 April 2009

Keywords:
Microwave irradiation
Diels–Alder
Diels–Alder/[3,3] sigmatropic shift
Computational studies

ABSTRACT

Diels–Alder cycloaddition of 3-nitro-1-(*p*-toluenesulfonyl)indole **1** with dienes **2**–**6** under microwave irradiation in solvent-free conditions gave carbazole derivatives after elimination of the nitro group and in situ aromatization. While 3-nitro-1-(*p*-toluenesulfonyl)pyrrole **11** afforded indole derivatives, 4-nitro-1-(*p*-toluenesulfonyl)pyrazole **13** with cyclohexadiene **2** did not afford the expected cycloadduct but instead gave 1-cyclohexen-2-ylpyrazole **16**. This process occurred by hydrolysis of the 1-(*p*-toluenesulfonyl) group, protonation of the diene and nucleophilic addition of the pyrazolate ion, as elucidated by computational studies. Reaction of nitroindole **1** with cyclohexadiene **2** afforded exclusively the *endo* stereoisomer (**10*endo***) in a tandem hetero Diels–Alder/[3,3] sigmatropic shift, as determined by computational calculations.

1. Introduction

Since the first original paper from Wenkert,[1] indole derivatives have attracted attention as dienophiles for the preparation of carbazoles, because its structure is related to several natural products such as (−)-aspidospermine[2] or plumerene-type alkaloids.[3] Although indoles participate as dienophiles in inverse-demand Diels–Alder reactions, only a few examples of cycloaddition reactions with electron-rich dienes have been described.[4] These reactions require electron-withdrawing groups both in positions 1 and 3 of the indole,[1,2] high temperatures (150–200 °C),[1] long reaction times (26 h to 4 days) and the use of electron-rich and reactive dienes such as 1-(*N*-acetyl-*N*-propylamino)-1,3-butadiene[3] or Danishefsky[5] and Rawal dienes.[5,6]

The long reaction times and high temperatures can be somewhat reduced by applying high pressure (10–11.5 kbar) due to the negative activation volume of Diels–Alder reactions.[7] In a similar way to indoles, Diels–Alder reactions of pyrrole derivatives as dienophiles in normal-demand cycloaddition reactions require electron-withdrawing groups in positions 1 and 3, high temperatures or pressures[8] and long reaction times.[1]

Microwave irradiation has been successfully applied in chemistry since 1975 and a large number of examples have been described in organic synthesis.[9,10] With the aid of microwave irradiation, cycloaddition reactions have been performed with great success[11] because they otherwise require the use of harsh conditions that are not compatible with sensitive compounds.

Moreover, the applicability of Diels–Alder reactions is limited by the reversibility of the reaction in cases where a long reaction time is required. All of these problems can be conveniently solved by the rapid heating produced by microwave irradiation, a situation not accessible by classical methods.

Some results obtained cannot be explained by the effect of rapid heating alone, and this has led various authors to postulate the existence of a so-called ‘microwave effect’[12] Hence, acceleration or changes in reactivity and selectivity could be explained by a specific radiation effect and not merely by a thermal effect. This is still a controversial matter and several reports show that thermal effects can explain most reported improvements found on using microwaves.[13] However, in several reports the selectivity (chemo-, regio- and stereoselectivity) of a reaction has been modified in relation to that obtained with conventional heating.[14,15] These results show that microwave irradiation can be used as an alternative to conventional heating to obtain different results to those afforded by classical methods.

---

[*] Corresponding author. Tel.: +34 926 29 5300; fax: +34 926 29 5318.
E-mail addresses: fp.cossio@ehu.es (F.P. Cossío), antonio.hoz@uclm.es (A. de la Hoz).
[†] Tel.: +34 926 29 5300x3463; fax: +34 926 29 5318.
[‡] Tel.: +34 943 01 5442.

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.04.065

2. Discussion

Reactions were performed under solvent-free conditions in a monomode reactor and in closed vessels in order to avoid the evaporation of low boiling dienes. Indole, pyrrole, pyrazole and imidazole derivatives were chosen as dienophiles because of the importance of their benzoderivatives. Firstly, we chose 3-nitro-1-(*p*-toluenesulfonyl)indole **1** as a substrate because the nitro group may enhance the cycloaddition by favouring aromatization, thus preventing the retrocycloaddition. We performed the cycloaddition with a variety of dienes including cyclohexadiene **2**, 1-methoxy- and 2-methoxycyclohexadienes **3** and **4**, cyclopentadiene **5** and 1-(*N*-acetyl-*N*-isopropylamino)-1,3-butadiene **6** (Scheme 1 and Table 1). The series of dienes (**2**–**4**, **6**) can, through in situ elimination or retro-Diels–Alder reaction, produce the aromatic benzene ring easily. Finally, we studied the reaction with cyclopentadiene **5** in order to elucidate the mechanism of the cycloaddition and the stereochemical outcome of this process. An excess of diene was used in order to minimize the effect of its evaporation and polymerization. A 1:12 molar ratio of indole to diene was found to give the best results.

Yields of carbazole **7** were improved to 71% by using a more reactive diene, *N*-acetyl-*N*-isopropylamine-1,3-butadiene **6** (Table 1, entry 4). This result represents a clear improvement on those previously obtained under thermal conditions, where a yield of 11% was achieved when the reaction was performed at 90 °C for 7 days, with an increase to a maximum of 55% at 200 °C for 24 h. Reaction with a 65:35 mixture of 1-methoxy-1,3-cyclohexadiene **3** and 2-methoxy-1,3-cyclohexadiene **4** showed that the cycloaddition is regioselective, producing exclusively carbazoles **8** and **9**, respectively, in a global yield of 61% (Table 1, entry 2). Aromatization is not possible in the cycloaddition with cyclopentadiene **5** and, as a consequence, cycloadduct **10** was obtained in 29% yield (entry 3) without loss of the nitro group. The reaction is stereoselective and produces exclusively the *endo* stereoisomer. The stereochemistry of this product was inferred by NOE difference experiments. The spectroscopic data for **10** include a broad signal (3.51–3.50 ppm) for the bridgehead methines (H-1, H-4). Addition of methanol as a solvent that can form hydrogen bonds with the nitro group enabled the differentiation of the two bridgehead protons and the assignment of the stereochemistry. In an attempt to explain the preference for the *endo* stereoisomer, we performed theoretical calculations for this reaction and the results confirmed the differences observed in the reaction with indole **1** and in the stereoselectivity.

Table 1
Reaction of 3-nitro-1-(*p*-toluenesulfonyl)indole **1** with dienes **2**–**6**

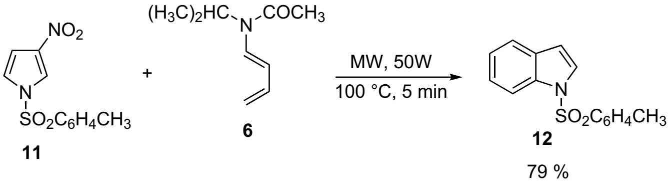
Entry	Diene	Molar ratio[a]	Time (min)	Yield (%) (product)
1	**2**	1:12	45	44 (**7**)
2	**3**+**4**	1:12	30	25 (**8**)+36 (**9**)
3	**5**	1:12	30	29 (**10**)
4	**6**	1:12	30	71 (**7**)

[a] Indole:diene molar ratio. Power 50 W, temperature 100 °C.

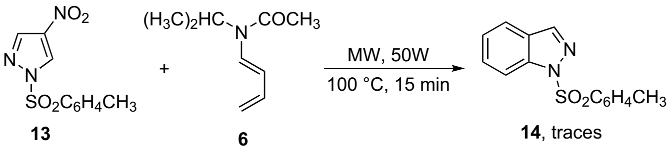
It should be noted that the reaction did not occur when performed with conventional heating under comparable conditions (45 min, 100 °C) to microwave irradiation. These results again demonstrate the utility of the microwave methodology.

We extended these conditions to other nitroheterocycles. Reaction of 3-nitro-1-(*p*-toluenesulfonyl)pyrrole **11** with diene **6** in a 1:6 molar ratio under microwave irradiation afforded the expected indole **12** in 79% yield in only 5 min (Scheme 2).

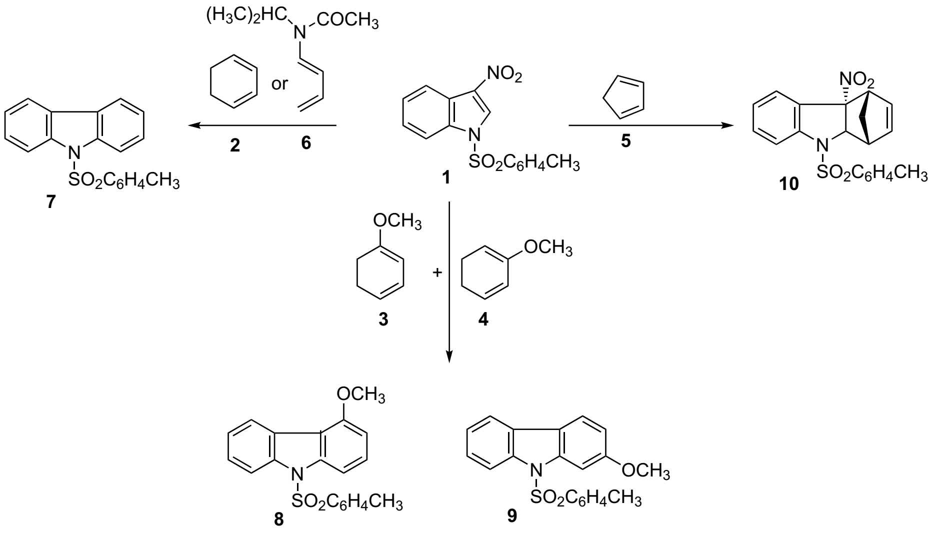
Once again this reaction does not occur with conventional heating under similar conditions (5 min, 100 °C) and the reaction at 120 °C for 72 h gave only 53% of the aromatic product **12**.[16] Reaction of 4-nitro-1-(*p*-toluenesulfonyl)pyrazole **13** with *N*-acetyl-*N*-isopropyl-1,3-butadiene **6** under several sets of reaction conditions produced only traces of the expected indazole **14** (Scheme 3).



Scheme 2.



Scheme 3.



Scheme 1.

The use of cyclohexadiene **2** as the diene in a 1:3 ratio produced an unexpected result, with 1-cyclohexen-3-ylpyrazole **16** obtained in 72% yield (Scheme 4). This yield was improved to 80% on using a 1:1 molar ratio. This reaction involves removal of the *p*-toluenesulfonyl group and addition of the nitropyrazole to the diene. As a consequence, the reaction is even more favourable on using 4-nitropyrazole **15** (Scheme 4). The reaction under conventional heating at 100 °C produced only 5% of the addition product. However, the reaction did not occur with 1-(*p*-toluenesulfonyl)pyrazole **17** or pyrazole **18**, both of which are better nucleophiles than 4-nitropyrazole **15**. A more strongly acidic azole, such as 4-nitroimidazole **19**, and a better nucleophile, such as imidazole **20**, did not react. As a consequence, we performed computational studies in order to elucidate the mechanism for the formation of 1-cyclohexen-3-ylpyrazole **16**.

3. Computational studies

All calculations included in this paper were carried out using the Gaussian 03[17] series of programs, with the standard 6-31G* basis set.[18] In order to include electron correlation at a reasonable computational cost, Density Functional Theory (DFT)[19] was used. In this study, these calculations were carried out by means of the three-parameter functional developed by Becke et al.,[20] which is usually denoted as B3LYP. This method has been shown to produce reliable results in pericyclic reactions and, in particular, in [4+2] cycloadditions.[21] Zero-point vibrational energies (ZPVEs) were computed at the B3LYP/6-31G* level and were not scaled. All transition structures and minima were fully characterized by harmonic analysis. For each located transition structure, only one imaginary frequency was obtained in the diagonalized Hessian matrix, and the corresponding vibration was found to be associated with nuclear motion along the reaction coordinate. Reaction paths were checked by Intrinsic Reaction Coordinate (IRC) calculations.[22]

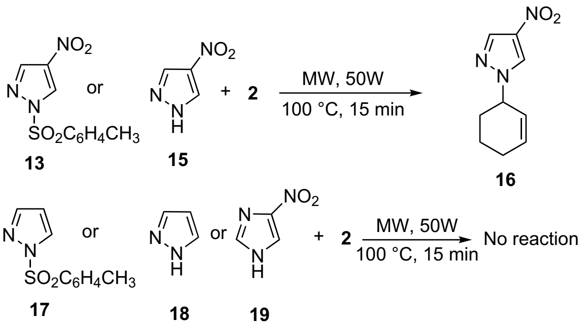
The molecular hardness (η) of each of the species was computed according to the following approximate expression (Eq. 1).[23]

$$\eta = \frac{1}{2}(\varepsilon_L - \varepsilon_H) \tag{1}$$

Where ε_L and ε_H are the energies of the LUMO and HOMO, respectively.

The solvent effect in DFT calculations was introduced by means of the Polarizable Continuum Model (PCM).[24] In all cases included in this study the model solvent was benzene (ε=2.25).

We have been interested in the theoretical study of cycloaddition reactions for a long time.[25] In this context, the aim of the present study was (a) to elucidate the *exo*/*endo* stereocontrol of the Diels–Alder reaction between 3-nitro-1-(*p*-toluenesulfonyl)indole **1** and cyclopentadiene **5** (Scheme 1) and (b) to find a possible mechanism that explains the different reactivity observed in the reaction between 4-nitro-1-(*p*-toluenesulfonyl)pyrazole **13** and cyclohexadiene **2** (Scheme 4).



Scheme 4.

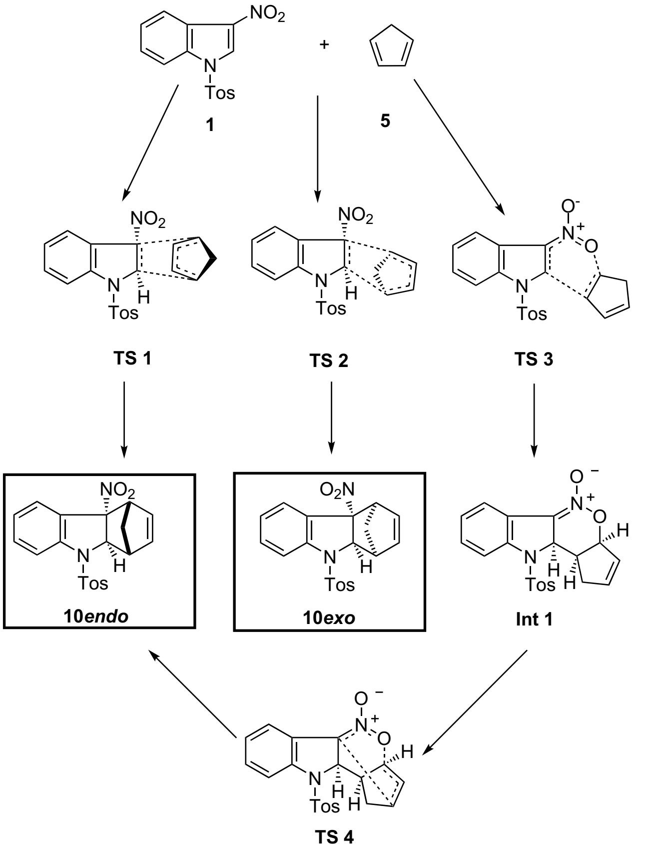
In order to reproduce the reaction conditions and geometric features of the substituents, structural simplifications were not introduced. Experimentally, significant excesses of dienes (cyclopentadiene and cyclohexadiene) were used and the dienes can therefore act as solvents. We chose benzene as the solvent for computational studies because of its similarity with our dienes and the fact that it is also conveniently parameterized.

3.1. Reaction of 3-nitro-1-(*p*-toluenesulfonyl)indole 1 and cyclopentadiene 5

We initially studied the stereocontrol observed in the reaction between **1** and **5**. In this case two possible reaction paths are therefore possible and these correspond to a normal [4+2] cycloaddition and a tandem hetero Diels–Alder cycloaddition/[3,3] sigmatropic shift (Scheme 5). They represent an example of cross-[4+2] cycloaddition reactions.

In the literature some examples of this kind of reaction are collected. Yamabe et al.[26] studied the reaction of butadiene with acrolein in the presence of Lewis acids by using ab initio calculations. They demonstrated that the reaction leads to a vinyldihydropyran, but not through the expected Diels–Alder cycloaddition. The transition state corresponded to an inverse-demand [4+2] cycloadduct where butadiene acts as a dienophile and acrolein as a 1-azadiene. This adduct was transformed to a normal-electron-demand [4+2] product through a Claisen rearrangement.

Other cross-Diels–Alder reactions were studied in the reaction of phenylsulfonyl-1,3-dienes and pyridones with dienes.[27] The



Scheme 5. Possible mechanisms for the reaction between 3-nitro-1-(*p*-toluenesulfonyl)indole **1** and cyclopentadiene **5**.

use of electron-rich dienes produced the normal Diels–Alder cycloaddition, whereas the use of the more restricted cyclopentadiene yielded an inverse Diels–Alder product.

Denmark et al.[28] have shown that reactions of nitroalkenes with cyclopentadiene can lead to mixtures of Diels–Alder and hetero-Diels–Alder cycloadducts. In the thermal reaction cyclopentadiene acts as a 4π component, but the presence of a Lewis acid reverse the periselectivity. A computational study by Houk et al.[29] on this reaction showed that in the thermal conditions reaction proceeded by an *endo* Diels–Alder transition state and a Claisen rearrangement of the *endo* adduct accounts for the formation of the hetero-Diels–Alder cycloadduct. However, no Claisen rearrangement transition state could be found in acid catalyzed conditions.

Similar results were described by Domingo et al.[30] in the reaction of 4-aza-6-nitrobenzofuroxan with cyclopentadiene. At −20 °C the inverse electron demand Diels–Alder reaction was observed while at 0 °C the normal-electron-demand Diels–Alder reaction occurs. Conversion of the [2+4] cycloadduct to the *endo* [4+2] cycloadduct is associated to a Claisen rearrangement, a [3,3] sigmatropic shift.

In this context, we performed a computational study of our reaction. The two possible reaction paths mentioned above were located at the B3LYP/6-31G* and B3LYP(PCM)/6-31G* levels using benzene as the solvent. The most important stationary points of both reaction profiles are shown in Figure 1 and the activation and reaction energies in the gas phase and in solution are shown in Table 2.

Experimentally, only the **10*endo*** stereoisomer was observed. Our calculations show that the *endo* approach (**TS 3**) always leads to a nitronate intermediate (**Int 1**), which corresponds to a [2+4] cycloadduct, and there was no evidence for the corresponding [4+2] transition state (**TS 1**).

This study also shows that the *endo* approach corresponds to a tandem reaction as it was previously reported by other authors. **TS 3** is formed by a [4+2] cycloaddition with the nitrovinylindole **1** system acting as the diene and cyclopentadiene **5** as the dienophile, a situation that leads to a nitronate intermediate (**Int 1**). A [3,3] sigmatropic shift produces **TS 4** and this finally gives the **10*endo*** stereoisomer (Scheme 5 and Fig. 1). In contrast, the *exo* approach of cyclopentadiene **5** to the nitro group is a concerted process and corresponds to a normal [4+2] cycloaddition. The exploration of this energy hypersurface yields **TS 2** as the only saddle point connecting reactant and products. This transition state is asynchronous; the two critical distances are 1.85 and 2.85 Å (Fig. 1). The *exo* approach in the [2+4] heterocycloaddition would lead to an intermediate in which the reactive centres for the [3,3] sigmatropic shift are at very long distance (4.5 Å) from one another. Moreover, the [3,3] sigmatropic shift would lead not to the experimentally observed **10*endo*** product, but to a highly hindered *trans*-fused indolizine system.

Table 2

Activation energies (ΔE_a, kcal/mol), reaction energies (ΔE_{rxn}, kcal/mol) computed at the B3LYP/6-31G*+ΔZPVE level and at B3LYP(PCM)/6-31G* using benzene as solvent

Reaction		ΔE_{a_1}	ΔE_{a_2}	ΔE_{rxn}
1+**5**→*endo* (**10*endo***)	Gas phase (1 atm)	22.90	25.38	1.85
	Benzene (1 mol/l)	22.35	24.30	−0.95
1+**5**→*exo* (**10*exo***)	Gas phase (1 atm)	25.74	—	0.86
	Benzene (1 mol/l)	25.35	—	0.19

The results shown in Table 2 indicate that activation barriers are lower for the formation of the *endo* cycloadduct **10*endo*** than for the *exo* cycloadduct **10*exo*** (22.35 and 24.30 kcal/mol vs. 25.35 kcal/mol).

Moreover, similarly to that found by Domingo et al.[30] theoretical values in solution showed that formation of the **10*endo*** cycloadduct is exothermic (0.95 kcal/mol), while formation of the **10*exo*** cycloadduct is endothermic (−0.19 kcal/mol). These outcomes indicate that the **10*endo*** cycloadduct is the kinetic and the thermodynamic product.

Differences in the activation barriers are not sufficient to explain the stereochemical outcome of the cycloaddition, so kinetic analyses of the computed activation energies were therefore carried out. The rate constants given in Table 3 were calculated using the Eyring equation (Eq. 2), where $\Delta G_n^{\neq}$ is the activation barrier calculated at B3LYP(PCM)/6-31G*+ΔZPVE and K_B and h are the Boltzmann and Planck constants, respectively.

$$k_n = \frac{k_B T}{h} \exp\left(-\frac{\Delta G_n^{\neq}}{RT}\right) \tag{2}$$

Numerical simulations were performed as the calculated kinetic constants are of the same order (Table 3). Integration of the concentration versus time curve yields the almost exclusive formation

Table 3

Calculated kinetic constants (k_n, mol/s) associated with the reaction between 3-nitro-1-(*p*-toluenesulfonyl)indole **1** and cyclopentadiene **5** computed at the B3LYP(PCM)/6-31G*+ΔZPVE level according to Eq. 2

		k_i	k_{-i}
10*endo*	Step 1	2.56 E-4	1.78 E-5
	Step 2	9.54 E-6	2.71 E-5
10*exo*		1.62 E-6	2.23 E-6

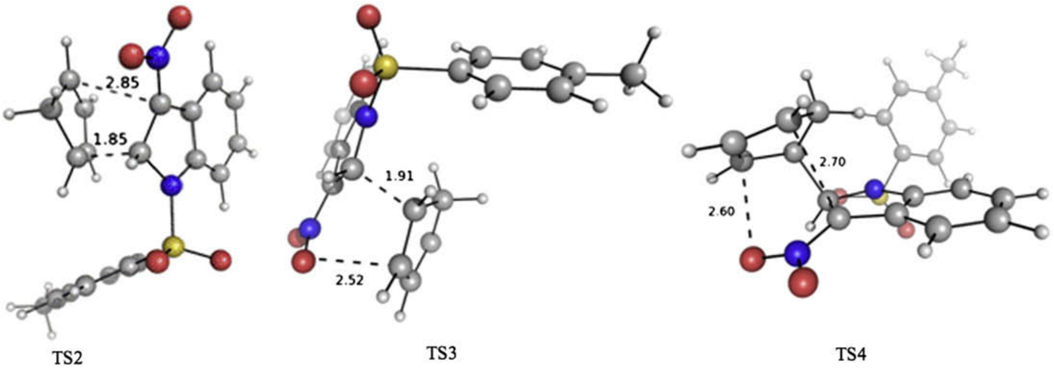


Figure 1. Fully optimized B3LYP(PCM)/6-31G* (using benzene as solvent) structures of the different transition states for the reaction between 3-nitro-1-(*p*-toluenesulfonyl)indole **1** and cyclopentadiene **5**.

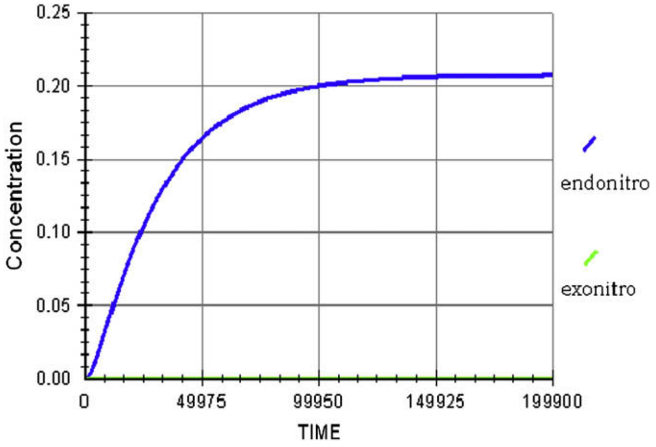


Figure 2. Simulated stereochemical outcome associated with the reaction between 3-nitro-1-(*p*-toluenesulfonyl)indole **1** and cyclopentadiene **5**.

Table 4
Dipole moments (μ, D), hardnesses (η, eV), average polarizability volumes (α'_{av}, Bohr^3) of ground and transition structures for the reaction between **1** and **5**

	μ	α'_{av}	η
1	8.869	226.73	0.0732
5	0.4892	51.88	0.1009
TS 2	11.741	309.63	0.0507
TS 3	11.042	311.34	0.0516
TS 4	11.006	311.26	0.0485

Table 5
Energy barriers (ΔE_a, kcal/mol) computed at the B3LYP(PCM)/6-31G*+ΔZPVE level for all possible mechanisms of the reaction between 4-nitropyrazole **15** and cyclohexadiene **2**

Mechanism	ΔE_a
Addition mechanism 1	29.5
Diels–Alder (*endo*)	33.5
Diels–Alder (*exo*)	35.9
Hetero [2+4]	34.5

of **10*endo*** (Fig. 2), a situation in excellent agreement with the experimental evidence.

It has also been reported that the modification of selectivity under microwave irradiation depends on the hardness and polarizability of the transition state, with the harder and less polarizable transition state favoured under microwaves.[31] As a result, we calculated the polarity, hardness and polarizability of all saddle points and the results are collected in Table 4.

The polarity values of all transition states are of the same order, although **TS 2** (corresponding to a [4+2] cycloaddition) is more polar (11.74 D) and less polarizable than **TS 3** (11.04 D) and **TS 4** (11.06 D), both of which correspond to hetero Diels–Alder reactions. In pericyclic reactions such as Diels–Alder or [3,3] sigmatropic shift, changes in polarity are not expected from ground to transition states. Therefore, all outcomes indicate that microwave irradiation led to the thermodynamic product.

3.2. Reaction of 4-nitropyrazoles 13, 15 and 4-nitroimidazole 19 with cyclohexadiene 2

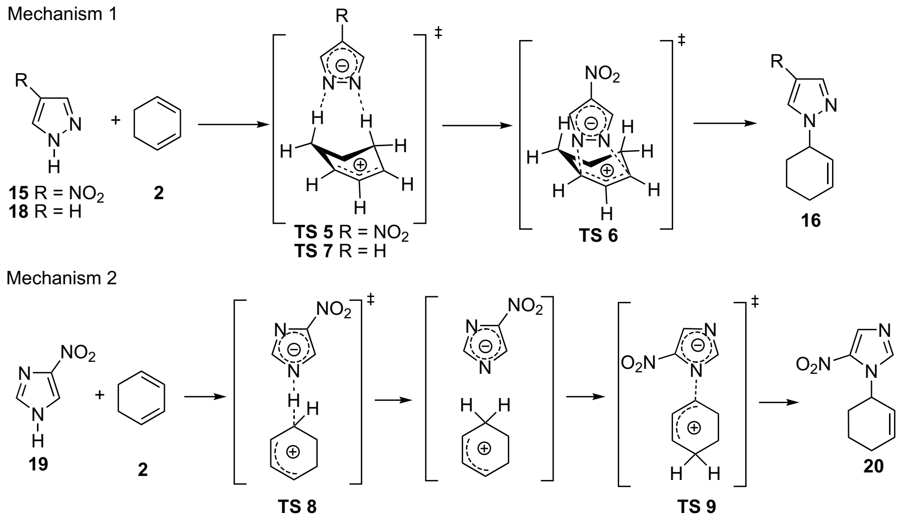
We performed a computational study aimed at explaining the different reactivities of 3-nitro-1-(*p*-toluenesulfonyl)indole **1**, 4-nitropyrazoles **13**, **15** and 4-nitroimidazole **19** with cyclohexadiene **2**. As stated above, 4-nitro-1-(*p*-toluenesulfonyl)pyrazole **13** and 4-nitropyrazole **15** react with cyclohexadiene **2** to give 1-cyclohexen-3-ylpyrazole **16** and the expected cycloadduct is not observed (Scheme 4). Furthermore, pyrazoles **17** and **18** and 4-nitroimidazole **19** do not react under similar conditions.

Formation of compound **16** from **13** implies a previous hydrolysis of the tosyl group; this is not surprising since acyl pyrazoles are used as acylation agents in mild and neutral conditions because pyrazole is a good leaving group. The mechanism may involve the protonation of cyclohexadiene and subsequent nucleophilic attack of the pyrazolate anion (Scheme 6, mechanism 1).

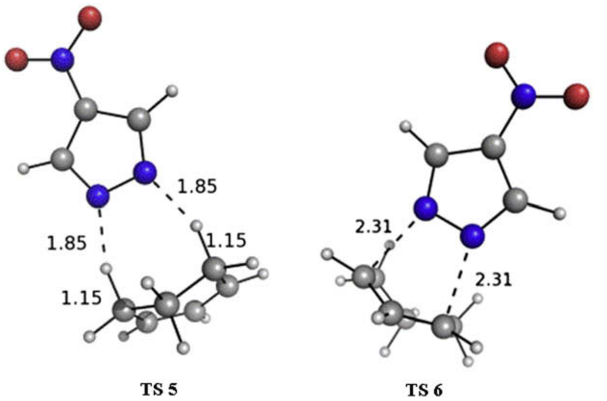
Experimentally only compound **16** was observed and the product of a Diels–Alder or hetero [4+2] cycloaddition was not detected. In order to justify this result, all possible reaction paths at the B3LYP(PCM)/6-31 G* level were computed using benzene as solvent. The activation energies are given in Table 5.

The activation energy for mechanism 1 is 4 kcal/mol lower than that of the Diels–Alder cycloaddition and 5 kcal/mol lower than that of the possible hetero [4+2] process.

The main features of the transition structures in the reaction between 4-nitropyrazole **15** and cyclohexadiene **2** are shown in Figure 3.

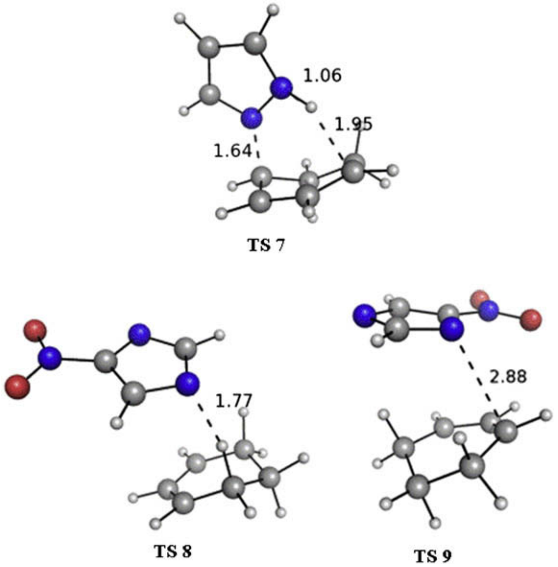


Scheme 6.



TS 5 TS 6

Figure 3. Main features of transition structures calculated at the B3LYP(PCM)/6-31G*+ΔZPVE level of theory for the reaction between 4-nitropyrazole **15** and cyclohexadiene **2**.



TS 7

TS 8 TS 9

Figure 4. Main features of transition structures calculated at the B3LYP(PCM)/6-31G*+ΔZPVE level for the reactions of pyrazole **18** and 4-nitroimidazole **19** with cyclohexadiene **2**.

Transition structures **TS 5** and **TS 6** are highly organized, with both nitrogen atoms involved in the proton transfer and identical N···H distances in **TS 5** and N···C distances in **TS 6**. In the same way, the imaginary frequency of **TS 6** corresponds to the nucleophilic attack of both nitrogen atoms to the allyl system of the cyclohexadienyl fragment. Once again, both critical distances are equal (2.31 Å). Recently, Dalko et al.[32] described how the exceptional enantioselectivity of proline-mediated reactions can be rationalized by the capacity of this molecule to promote the formation of highly organized transition states.

A product was not observed when pyrazole **18** or 4-nitroimidazole **19** were used (Scheme 4), despite these having higher pK_a values (pK_a=14.21 and 14.4, respectively) than 4-nitropyrazole **15** (pK_a=9.64). The main features of the transition structures for these reactions are shown in Figure 4 and the activation energies in solution are given in Table 6.

Table 6
Energy barriers (ΔE_a, kcal/mol) of transition structures indicated in Figures 3 and 4 computed at the B3LYP(PCM)/6-31G*+ΔZPVE level

Compound	ΔE_a (kcal/mol)
Pyrazole **18**	40.4
4-Nitroimidazole **19**	35.3
4-Nitropyrazole **15**	29.5

Table 7
Dipole moments (μ, D), hardnesses (η, eV) and average polarizability volumes (α'_{av}, Bohr^3) of ground and transition structures. Polarity increases from ground to transition states ($\Delta\mu$, D)

Entry		μ	α'_{av}	η	$\Delta\mu$
1	**2**	1.003	65.38	0.1017	
2	**15**	5.472	60.80	0.1460	
3	**18**	2.626	41.60	0.1090	
4	**19**	8.647	61.26	0.0926	
5	**TS 5**	14.967	169.86	0.0563	8.49
6	**TS 6**	10.396	148.34	0.0834	
7	**TS 7**	4.711	132.98	0.0524	1.08
8	**TS 8**	15.245	173.14	0.0317	
9	**TS 9**	10.310	157.20	0.0385	5.59

Reaction with pyrazole **18** is again concerted. However, only one asynchronous TS was detected (**TS 7**)—in contrast to 4-nitropyrazole **15**, where two synchronous and product-like TSs were detected. The reaction with 4-nitroimidazole **19** again has two TSs, one for the protonation of cyclohexadiene **2** (**TS 8**) and a second for the nucleophilic attack of the imidazole anion (**TS 9**). However, the 1,3-disposition of the nitrogen atoms in the imidazole ring prevents the occurrence of a concerted mechanism and a stepwise mechanism is detected in the reaction with 4-nitroimidazole **19**.

The calculated values of the activation barriers (Table 6) are very high in both cases (40.4 and 35.3 kcal/mol), in contrast to those calculated for the reaction of 4-nitropyrazole (29.5 kcal/mol).

The polarity, hardness and polarizability of all saddle points were calculated and compared with those of the starting materials. The results are collected in Table 7.

As expected for the proposed mechanism, there is an increase in the polarity from the starting material to the TS. Considering the polarities of transition structures, **TS 7** (which corresponds to a concerted mechanism) is less polar (4.7 D) (Table 7, entry 7) than transition structures that correspond to stepwise mechanisms (**TS 5**, **TS 6**, **TS 8** and **TS 9**) (Table 7, entries 5, 6, 8 and 9).

However, regardless of the polarity of the TS, only the reaction of 4-nitropyrazole **15** actually occurs. These results are in agreement with a thermal effect and with our calculations,[33] showing that under microwave heating reactions with high activation energies (29.5 kcal/mol) can be successfully performed. However, when the activation energies are above 30 kcal/mol the processes do not occur.

It is remarkable that the reaction between 4-nitropyrazole **15** and cyclohexadiene **2** afforded 80% of **16** under microwave irradiation while only 5% of the addition product was obtained under conventional heating.

The theoretical results are therefore in good agreement with the experimental ones and they are compatible with the exclusive formation of **16**.

4. Conclusion

In conclusion, we have shown that under microwave irradiation the cycloaddition reactions of nitroindoles and nitropyrroles in solvent-free conditions give good yields of the aromatic carbazoles and indoles, respectively, through elimination of the nitro group and subsequent aromatization. The mechanism and stereoselectivity of the cycloaddition of indole **1** with cyclopentadiene **5** were determined by computational methods and these indicate that the reaction takes place through a tandem hetero [4+2] cycloaddition/[3,3] sigmatropic shift. This mechanism gives the *endo* stereoisomer.

The reaction of 4-nitropyrazole **15** with cyclohexadiene **2** gave 1-cyclohexen-2-ylpyrazole **16** as the product. The mechanism of this reaction was also elucidated by computational methods. In this case, after hydrolysis of the tosyl group, the mechanism involves protonation of cyclohexadiene **5**, followed by nucleophilic attack of the anionic pyrazolyl group through a concerted mechanism.

Reactions were greatly improved under microwave irradiation.

5. Experimental section

5.1. General

Microwave irradiations were performed in a CEM Discover microwave reactor in standard closed vessels. Temperature was monitored during the reaction by the standard IR pyrometer included in the microwave reactor. Analysis by thin layer chromatography was performed on aluminium oxide 60 F_{254} and separations by column chromatography were carried out on silica gel type 60 (0.040–0.063 mm).

All NMR spectra were recorded on a 500 MHz spectrometer in $CDCl_3$ at 298 K and at 499.769 MHz and 125.678 MHz for ^{1}H and ^{13}C NMR, respectively. Chemical shifts were referenced to internal TMS at 0 ppm. Assignment of spectra was carried out using NOESY-1D, g-COSY and g-HSQC experiments. The NOESY-1D spectra were recorded with the following acquisition parameters: mixing time 800 ms and number of scans 256. Two-dimensional NMR spectra were acquired using 4 scans and 128 increments. The pulse programs were taken from the standard Varian pulse sequence library. All spectra were Fourier transformed with MestReNova 5.1.0 software.

1,3-Cyclohexadiene **2**, 1-methoxy-1,3-cyclohexadiene **3**, dicyclopentadiene, 4-nitroimidazole **19**, pyrazole **18**, indole and pyrrole are commercially available. Commercial 1-methoxy-1,3-cyclohexadiene **3** contains 35% of the isomeric 2-methoxy-1,3-cyclohexadiene **4**.

The following compounds were prepared by previously reported procedures: 1-(*p*-toluenesulfonyl)indole,[4] 1-(*p*-toluenesulfonyl)-3-nitroindole **1**,[1] 1-(*p*-toluenesulfonyl) pyrrole,[34] 3-nitro-1-(*p*-toluenesulfonyl)pyrrole **11**,[35] 2-nitropyrrole,[36] 3-nitropyrrole,[36] 2-nitro-1-(*p*-toluenesulfonyl)pyrrole,[37] 4-nitropyrazole **15**,[38] 4-nitro-1-(*p*-toluenesulfonyl)imidazole,[39] *N*-2-butenylideneisopropylamine,[40] 1-(*N*-acetyl-*N*-isopropylamino)-1,3-butadiene **6**.[41] Cyclopentadiene **5** was prepared from dicyclopentadiene by cracking. In a round-bottomed flask dicyclopentadiene was heated and fractionally distilled. The fraction boiling at 39 °C was collected and used fresh.

Silica-supported Lewis acids [Si(Al), Si(Ti) and Si(Zn)]. The catalysts were obtained by treatment of silica with $ZnCl_2$ [Si(Zn)],[42] Et_2AlCl [Si(Al)],[43] or $TiCl_4$ [Si(Ti)].[44]

5.1.1. *4-Nitro-1-(p-toluenesulfonyl)pyrazole* ***13***

In a round-bottomed flask potassium *tert*-butoxide (0.79 g, 7.0 mmol), 4-nitropyrazole (0.8 g, 7.0 mmol) and two drops of water were stirred at 20 °C for 45 min. Tetrabutylammonium bromide (TBAB) (0.23 g, 0.7 mmol) and *p*-toluenesulfonyl chloride (1.3 g, 7.0 mmol) were added and stirring was continued at 20 °C for 24 h. Chloroform (50 ml) was added and the mixture was filtered. The filtrate was purified by column chromatography on silica gel using hexane/ethyl acetate (5:1) as the eluent to give 1.31 g of **13** (70%) as a white solid. Mp 116–117 °C (ethanol).[45] δ_H (500 MHz, DMSO-d_6) 7.93 (2H, s, H3, H5), 7.5 (2H, d, *J* 7.8, H2′, H6′), 7.1 (2H, d, *J* 7.8, 3′-H, 5′-H), 2.49 (s, 3H, CH_3). δ_C (125 MHz, DMSO-d_6) 147.5 (C4′), 139.6 (C3), 136.8 (C1′), 136.7 (C4), 131.5 (C5), 130.5 (C3′, C5′), 128.5 (C2′, C6′), 21.1 (CH_3).

5.1.2. *Diels–Alder reactions of N-substituted indoles as dienophiles: general procedure*

A mixture of 3-nitro-1-(*p*-toluenesulfonyl)indole **1** and the diene was submitted to microwave irradiation in a closed flask (for reaction conditions see Table 1). Crude products were purified by column chromatography on silica gel and analyzed by ^{1}H NMR spectroscopy.

5.1.2.1. Reaction of 3-nitro-1-(p-toluenesulfonyl)indole ***1*** *with 1,3-cyclohexadiene* ***2****. In the absence of catalyst.* In a similar way to the general procedure, a mixture of indole **1** (0.16 g, 0.5 mmol) and 1,3-cyclohexadiene **2** (0.48 g, 6 mmol) was submitted to microwave irradiation. The pure product was obtained as a white solid by column chromatography on silica gel using hexane/ethyl acetate (13:1) as the eluent. Yields were determined by ^{1}H NMR by integration of the 1-H signal of 9-*p*-toluenesulfonylcarbazole **7** (δ 4.93 ppm) and using CH_2Br_2 as internal standard. Mp 129–129.5 °C (ethanol/water) (lit. 130–133 °C).[46] δ_H (500 MHz, $CDCl_3$) 8.33 (2H, d, *J* 8.3, H1, H8), 7.9 (2H, d, *J* 7.1, H4, H5), 7.7 (2H, d, *J* 8.3, H2′, H6′), 7.47 (2H, dd, *J* 8.3, 7.1, H2, H7), 7.35 (2H, t, *J* 7.1, H3, H6), 7.08 (2H, d, *J* 8.3, H3′, H5′), 2.25 (s, 3H, CH_3). δ_C (125 MHz, $CDCl_3$) 144.9, 138.4, 135.07, 126.5 (C4′, C1′, C1a, C8a, C4a, C5a), 129.81 (C3′, C5′), 127.5 (C2, C7), 126.6 (C2′, C6′), 123.9 (C4, C5), 120.1 (C3, C6), 115.3 (C1, C8), 21.7 (CH_3). HRMS (EI, M^+) (*m*/*z*) calcd for $C_{19}H_{15}NSO_2$: 321.0823. Found: 321.0585.

In the presence of catalyst. In a similar way to the general procedure, 3-nitro-1-(*p*-toluenesulfonyl)indole **1** (0.126 g, 0.39 mmol), cyclohexadiene **2** (0.38 g, 4.74 mmol) and silica-supported Lewis acid [Si (Ti) and Si (Zn)] (0.25 g) were used. The crude product was extracted with CH_2Cl_2 and the catalyst was separated by filtration.

5.1.2.2. Reaction of 3-nitro-1-(p-toluenesulfonyl)indole ***1*** *with 1-methoxy-1,3-cyclohexadiene* ***3*** *and 2-methoxy-1,3-cyclohexadiene* ***4****. In the absence of catalyst.* In a similar way to the general procedure using 3-nitro-1-(*p*-toluenesulfonyl)indole **1** (0.158 g, 0.5 mmol) and a 65:35 mixture of 1-methoxy-1,3-cyclohexadiene **3** and 2-methoxy-1,3-cyclohexadiene **4** (0.66 g, 6 mmol). The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (9:1) as the eluent to give an inseparable mixture of 4-methoxy-9-*p*-toluenesulfonylcarbazole **8** and 2-methoxy-9-*p*-toluenesulfonylcarbazole **9** as an oil. Yields were determined by ^{1}H NMR by integration of the $–OCH_3$ signal (δ 3.99 ppm) and using CH_2Br_2 as internal standard. HRMS (EI, M^+) (*m*/*z*) calcd for $C_{20}H_{17}NSO_3$: 351.0929. Found: 351.0946.

Data for **8**: δ_H (500 MHz, $CDCl_3$) 8.32 (1H, d, *J* 8.3, H8), 8.22 (1H, d, *J* 7.8, H5), 7.95 (1H, d, *J* 7.8, H1), 7.68 (2H, d, *J* 8.3, H2′, H6′), 7.46–7.43 (1H, m, H7), 7.42–7.40 (1H, m, H2), 7.38–7.36 (1H, m, H6), 7.06 (2H, d, *J* 7.8, H3′, H5′), 6.8 (1H, d, *J* 8.3, H3), 4.00 (3H, s, OCH_3), 2.23 (3H, s, CH_3). δ_C (125 MHz, $CDCl_3$) 155.7, 144.7, 139.5, 137.6, 134.9, 125.6, 115.4 (C1a, C4a, C5a, C8a, C4, C1′, C4′), 129.7 (C3′, C5′), 128.0 (C2), 126.9 (C2′, C6′), 126.5 (C6), 126.5 (C7), 123.5 (C5), 114.9 (C8), 108.0 (C1), 106.0 (C3), 55.5 (OCH_3), 22.0 (CH_3).

Data for **9**: δ_H (500 MHz, $CDCl_3$) 8.26 (1H, d, *J* 8.3, H8), 7.88 (1H, d, *J* 2.4, H1), 7.78 (1H, d, *J* 7.8, H5), 7.74 (1H, d, *J* 8.8, H4), 7.68 (2H, d, *J* 8.3, H2′, H6′), 7.39–7.37 (1H, m, H7), 7.31–7.29 (1H, m, H6), 7.08 (2H, d, *J* 8.3, H3′, H5′), 6.94 (1H, dd, *J* 2.4, 8.8, H3), 3.95 (3H, s, OCH_3), 2.25 (3H, s, CH_3). δ_C (125 MHz, $CDCl_3$) 159.7, 144.8, 139.6, 138.3, 134.8, 126.4, 120.5, (C1a, C4a, C5a, C8a, C2, C1′, C4′), 129.7 (C3′, C5′), 126.9 (C2′, C6′, C7), 124.8 (C6), 121.0 (4C), 119.7 (C5), 114.8 (C8), 112.9 (C3), 100.0 (C1), 56.0 (OCH_3), 22.0 (CH_3).

5.1.2.3. Reaction of 3-nitro-1-(p-toluenesulfonyl)indole ***1*** *with cyclopentadiene* ***5****.* Following the general procedure from indole **1** (0.16 g, 0.5 mmol) and cyclopentadiene **5** (0.5 ml, 6 mmol). The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (9:1) as the eluent. Yields of carbazole **10** were determined by ^{1}H NMR by integration of the 2-H signal (δ 6.4 ppm) using CH_2Br_2 as internal standard. Mp 141–143 °C (hexane/ethyl acetate). δ_H (500 MHz, $CDCl_3$) 7.73–7.68 (1H, m, H5), 7.70 (2H, d, *J* 8.5, H2′, H6′), 7.41–7.38 (1H, m, H6), 7.37–7.34 (1H, m, H8), 7.2 (2H, d, *J* 8.5, H3′, H5′), 7.1 (1H, *pseudo* t, *J* 7.55, H7), 6.42–6.39 (1H, m, H2), 6.22–6.19 (1H, m, H3), 4.77–4.76 (1H, m, H9a), 3.50 (2H, br s, H1, H4), 2.35 (3H, s, CH_3), 1.75–1.72 (1H, m, H10b), 1.50 (1H, d, *J* 10, H10a). δ_C (125 MHz, $CDCl_3$) 145.0, 144.7, 133.4, 127.1, 102.7 (C4a, C5a, C8a, C1′, C4′), 138.0 (C2), 136.0 (C3), 132.2 (C8), 129.8 (C3′, C5′), 127.6 (C2′, C6′), 124.4 (C7), 123.8 (C6), 115.8 (C5), 72.0 (C9a), 52.0 (C1), 51.0 (C4), 44.0 (C10), 22.0 (CH_3). HRMS (EI, M^+) (*m*/*z*) calcd for $C_{20}H_{18}N_2SO_4$: 382.0987. Found: 382.1077.

*5.1.2.4. Reaction of 3-nitro-1-(p-toluenesulfonyl)indole **1** with N-acetyl-N-isopropyl-1,3-butadiene **6**.* Indole **1** (0.237 g, 0.75 mmol) and diene **6** (1.376 g, 9 mmol) were submitted to microwave irradiation in a closed vessel at 100 °C for 5 min. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (13:1) as the eluent, to give carbazole **7** in 71% yield.

5.1.3. Diels–Alder reactions of other N-substituted heterocycles as dienophiles: general procedure

A mixture of the corresponding *N*-substituted heterocycle and the appropriate diene was submitted to microwave irradiation for the appropriate time.

*5.1.3.1. Reaction of 3-nitro-1-(p-toluenesulfonyl)pyrrole **11** with N-acetyl-N-isopropylamine-1,3-butadiene **6**.* Pyrrole **11** (0.199 g, 0.75 mmol) and diene **6** (0.688 g, 4.5 mmol) were submitted to microwave irradiation (50 W) in a closed vessel at 100 °C for 5 min. The crude product was purified by column chromatography using hexane/ethyl acetate (25:1) as the eluent to give *N*-(*p*-toluenesulfonyl)indole **12** as a white solid. Yields were determined by ^{1}H NMR by integration of the 3-H signal (δ 6.65 ppm) using CH_2Br_2 as internal standard. Mp 78–80 °C (dichloromethane/hexane). δ_H (500 MHz, $CDCl_3$) 7.99 (1H, d, *J* 8.3, H7), 7.75 (2H, d, *J* 8.5, H2′, H6′), 7.56 (1H, d, *J* 0.7, H2), 7.52 (1H, d, *J* 7.8, H4), 7.30 (1H, dd, *J* 7.4, 8.3, H6), 7.25 (1H, dd, *J* 7.8, 7.4, H5), 7.20 (1H, d, *J* 8.5, H3′, H5′), 6.65 (1H, d, *J* 0.7, H3), 2.33 (3H, s, CH_3). δ_C (125 MHz, $CDCl_3$) 145.0, 135.3, 134.7, 130.7 (C4′, C1′, C3a, C8a), 129.8 (C3′, C5′), 126.7 (C2′, C6′), 126.2 (C2), 124.6 (C6), 123.2 (C4), 121.3 (C5), 113.9 (C7), 108.9 (C3), 21.5 (CH_3). MS (EI) *m*/*z*: 271 (M^+).

*5.1.3.2. Reaction of 4-nitropyrazole **15** and 4-nitro-1-(p-toluenesulfonyl)pyrazole **13** with 1,3-cyclohexadiene **2**.* Pyrazole **13** or **15** (0.88 mmol) and 1,3-cyclohexadiene **2** (0.07 g, 0.88 mmol) were submitted to microwave irradiation (50 W) in a closed vessel at 100 °C for 15 min. Yields of 1-cyclohexen-3-ylpyrazole **16** were determined by ^{1}H NMR by integration of the H1′ signal (δ 4.91 ppm) using CH_3NO_2 as internal standard. Mp 57.5–59.8 °C (hexane). δ_H (500 MHz, $CDCl_3$) 8.19 (1H, s, H3), 8.10 (1H, s, H5), 6.25–6.22 (1H, m, H3′), 5.83–5.80 (1H, m, H2′), 4.91 (1H, br s, H1′), 2.26–2.17 (2H, m, CH_24'), 2.15–1.99 (2H, m, CH_26'), 1.77–1.55 (2H, m, CH_25'). δ_C (125 MHz, $CDCl_3$) 135.9 (C3), 135.3 (C5), 127.4 (C3′), 124.0 (C4), 122.9 (C2′), 58.2 (C1′), 29.7 (C4′), 24.7 (C6′), 18.5 (C5′). HRMS (EI, M^+) (*m*/*z*) calcd for $C_9H_{11}N_3O_2$: 193.0851. Found: 193.0703.

Acknowledgements

Financial support from the DGICYT of Spain through project CTQ2007-60037/BQU and from the Consejería de Ciencia y Tecnología JCCM through projects PBI-06-0020 and PCI-08-0040 is gratefully acknowledged. M.V.G. acknowledges the Ministerio de Educacion y Ciencia for financial support.

Supplementary data

NMR spectra of compounds **7**, **8**, **9**, **10**, **12** and **16**. Total electronic energies, zero-point correction of energies and number of imaginary frequencies of all stationary points. Cartesian coordinates of all the stationary points. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.04.065.

References and notes

1. Wenkert, E.; Moeller, P. D. R.; Piettre, S. R. *J. Am. Chem. Soc.* **1988**, *110*, 7188–7194.
2. Biolatto, B.; Kneeteman, M.; Mancini, P. *Tetrahedron Lett.* **1999**, *40*, 3343–3346.
3. Biolatto, B.; Kneeteman, M.; Mancini, P. M. *Molecules* **2000**, *5*, 393–395.
4. (a) Lee, L.; Snyder, J. K. *Adv. Cycloaddit.* **1999**, *6*, 119–171; (b) Hsieh, M.-F.; Rao, P. D.; Liao, C.-C. *Chem. Commun.* **1999**, 1441–1442; (c) Benson, S. C.; Lee, L.; Yang, L.; Snyder, J. K. *Tetrahedron* **2000**, *56*, 1165–1180; (d) Padwa, A.; Brodney, M. A.; Dimitroff, M. *J. Org. Chem.* **1998**, *63*, 5304–5305.
5. (a) Kraus, G. A.; Zhang, N.; Melekhow, A.; Jensen, J. H. *Synlett* **2001**, 521–522; (b) Kishbaugh, T. L. S.; Gribble, G. W. *Tetrahedron Lett.* **2001**, *42*, 4783–4795.
6. (a) Pelkey, E. T.; Gribble, G. W. *Chem. Commun.* **1997**, 1873–1874; (b) Gribble, G. W.; Pelkey, E. T.; Simon, W. M.; Trujillo, H. A. *Tetrahedron* **2000**, *56*, 10133–10140.
7. (a) Le Noble, W.; Kelm, H. *Angew. Chem.* **1980**, *19*, 841–856; (b) Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1–26; (c) Isaacs, N. *Tetrahedron* **1991**, *47*, 8463–8497; (d) Biolatto, B.; Kneeteman, M.; Paredes, E.; Mancini, P. M. E. *J. Org. Chem.* **2001**, *66*, 3906–3912; (e) Chataigner, I.; Hess, E.; Toupet, L.; Piettre, S. R. *Org. Lett.* **2001**, *3*, 515–518.
8. (a) Chrétien, A.; Chataigner, I.; Piettre, S. R. *Chem. Commun.* **2005**, 1351–1353; (b) Chrétien, A.; Chataigner, I.; Piettre, S. R. *Tetrahedron* **2005**, *61*, 7907–7915.
9. (a) Bose, A. K.; Manhas, M. J.; Banik, B. K.; Robb, E. W. *Res. Chem. Intermed.* **1994**, *20*, 1–11; (b) Caddick, S. *Tetrahedron* **1995**, *52*, 10403–10432; (c) Galema, S. A. *Chem. Soc. Rev.* **1997**, *25*, 233–238; (d) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283; (e) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284; (f) Hayes, B. L. *Aldrichimica Acta* **2004**, *37*, 66–77.
10. (a) *Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2006; (b) Hayes, B. L. In *Microwave Synthesis: Chemistry at the Speed of Light*; CEM: Matthews, NC, 2002; (c) *Microwave-Assisted Organic Synthesis*; Lidstöm, P., Tierney, J. P., Eds.; Blackwell Scientific: Oxford, 2005; (d) Kappe, C. O.; Stadler, A. Microwaves in Organic and Medicinal Chemistry. In *Methods and Principles in Medicinal Chemistry*; Mannhold, R., Kubinyi, H., Folkers, G., Eds.; Wiley: Weinheim, 2005; Vol. 25.
11. (a) de la Hoz, A.; Díaz-Ortiz, A.; Moreno, A.; Langa, F. *Eur. J. Org. Chem.* **2000**, 3659–3673; (b) de la Hoz, A.; Díaz-Ortiz, A.; Moreno, A.; Langa, F. In *Microwaves in Cycloadditions in Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002; Chapter 9; (c) Bougrin, K.; Soufiaoui, M.; Bashiardes, G. In *Microwaves in Cycloadditions in Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2006, Chapter 11.
12. (a) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199–9223; (b) de la Hoz, A.; Díaz-Ortiz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 168–178.
13. (a) Raner, K. D.; Strauss, C. R.; Vyskoc, F.; Mokbel, L. *J. Org. Chem.* **1993**, *58*, 950–953; (b) Stuerga, D. In *Microwave-Material Interactions and Dielectric Properties, Key Ingredients for Mastery of Chemical Processes in Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2006; Chapter 1; (c) Herrero, M. A.; Kremsner, J. M.; Kappe, C. O. *J. Org. Chem.* **2008**, *73*, 36–47.
14. Díaz-Ortiz, A.; de la Hoz, A.; Moreno, A. *Curr. Org. Chem.* **2004**, *8*, 903–918; Langa, F.; de la Cruz, P.; de la Hoz, A.; Díaz-Ortiz, A.; Díez-Barra, E. *Contemp. Org. Synth.* **1997**, *4*, 373–386.
15. (a) de la Hoz, A.; Díaz-Ortiz, A.; Fraile, J. M.; Gómez, M. V.; Mayoral, J. A.; Moreno, A.; Saiz, A.; Vázquez, E. *Synlett* **2001**, 753–757; (b) Díaz-Ortiz, A.; Fraile, J. M.; de la Hoz, A.; Gómez, M. A.; Mayoral, J. A.; Moreno, A.; Prieto, P.; Salvatella, L.; Saiz, A.; Vázquez, E. *Eur. J. Org. Chem.* **2001**, 2891–2899; (c) Moreno, A.; Gómez, M. V.; Vázquez, E.; de la Hoz, A.; Díaz-Ortiz, A.; Prieto, P.; Mayoral, J. A.; Pires, E. *Synlett* **2004**, 1259–1263.
16. Della Rosa, C.; Kneeteman, M.; Mancini, P. *Tetrahedron Lett.* **2007**, *48*, 1435–1438.
17. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Gui, Q.; Baboul, A. G.; Clifford, S.; Gioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision A. 1*; Gaussian: Pittsburgh, PA, 2003; p 18.
18. Hehre, W. J.; Radom, L.; Schleyer, P. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, NY, 1986; pp 65–88 and references therein.

19. Parr, R. G.; Yang, W. *Density-Functional Theory of Atoms and Molecules*; Oxford University Press: New York, NY, 1994.
20. (a) Kohn, W.; Becke, A. D.; Parr, R. G. *J. Phys. Chem.* **1996**, *100*, 12974–12980; (b) Becke, A. D. *J. Chem. Soc., Chem. Commun.* **1993**, 5648–5652; (c) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098–3100.
21. (a) Goldstein, E.; Beno, B.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 6036–6043; (b) Wiest, O.; Montiel, D. C.; Houk, K. N. *J. Phys. Chem. A* **1997**, *101*, 8378–8388; (c) García, J. I.; Martinez-Merino, V.; Mayoral, J. A.; Salvatellla, L. *J. Am. Chem. Soc.* **1998**, *120*, 2415–2420; (d) Paddon-Row, M. N.; Moran, D.; Jones, G. A.; Sherburn, M. S. *J. Org. Chem.* **2005**, *70*, 10841–10853.
22. González, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154–2161; (b) González, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523–5527.
23. (a) Parr, R. G.; Donelly, R. A.; Levy, M.; Palke, W. E. *J. Chem. Phys.* **1978**, *68*, 3801–3807; (b) Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512–7516; (c) Mulliken, R. S. *J. Chem. Phys.* **1934**, *2*, 782–793.
24. (a) Miertus, S.; Scrocco, E.; Tomasi, J. *J. Chem. Phys.* **1981**, *55*, 117–129; (b) Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *106*, 5151–5158; (c) Cammi, R.; Mennucci, B.; Tomasi, J. *J. Phys. Chem. A* **2000**, *104*, 5631–5637.
25. (a) Vivanco, S.; Lecea, B.; Arrieta, A.; Prieto, P.; Morao, I.; Linden, A.; Cossío, F. P. *J. Am. Chem. Soc.* **2000**, *122*, 4179–4187; (b) Prieto, P.; Cossío, F. P.; Carrillo, J. R.; de la Hoz, A.; Díaz-Ortiz, A.; Moreno, A. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1257–1263; (c) Pinto, D. C. G. A.; Silva, A. M. S.; Brito, C. M.; Sandulache, A.; Carrillo, J. R.; Prieto, P.; Díaz-Ortiz, A.; de la Hoz, A.; Cavaleiro, J. A. S. *Eur. J. Org. Chem.* **2005**, 2973–2986.
26. Yamabe, S.; Dai, T.; Minato, T. *J. Am. Chem. Soc.* **1995**, *117*, 10994–10997.
27. (a) Chou, T. S.; Hung, S. C. *J. Org. Chem.* **1988**, *53*, 3020–3027; (b) Teyssot, M.-L.; Lormier, A.-T.; Chataigner, I.; Piettre, S. R. *J. Org. Chem.* **2007**, *72*, 2364–2373; (c) Chou, S.-S. P.; Chen, P.-W. *Tetrahedron* **2008**, *64*, 1879–1887.
28. Denmark, S. E.; Kesler, B. S.; Moon, Y. C. *J. Org. Chem.* **1992**, *57*, 4912–4924.
29. Çelebi-Ölçum, N.; Ess, D. H.; Aviyente, V.; Houk, K. N. *J. Org. Chem.* **2008**, *73*, 7472–7480.
30. Arroyo, P.; Picher, M. T.; Domingo, L. R.; Terrier, F. *Tetrahedron* **2005**, *61*, 7359–7365.
31. Langa, F.; de la Cruz, P.; de la Hoz, A.; Espíldora, E.; Cossío, F. P.; Lecea, B. *J. Org. Chem.* **2000**, *65*, 2499–2507.
32. (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175; (b) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475–2479.
33. Cossío, F. P.; de Cózar, A.; Díaz-Ortiz, A.; de la Hoz, A.; Prieto, P. Unpublished results.
34. Catalán, J.; Abboud, J. L. M.; Elguero, J. Basicity and Acidity of Azoles. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: New York, NY, 1987; Vol. 41.
35. Anderson, H. J.; Loader, C. C.; Xun Xu, R.; Le, N.; Gogan, N. J.; McDonald, R.; Edwards, L. G. *Can. J. Chem.* **1985**, *63*, 896–902.
36. Morgan, K. J.; Morrey, D. P. *Tetrahedron* **1966**, *22*, 57–62.
37. Kwast, E.; Makosza, M. *Tetrahedron Lett.* **1990**, *31*, 121–122.
38. Hill, H. B.; Torrey, J. *Am. Chem. J.* **1899**, *22*, 89–96.
39. Suwinski, J.; Salwinska, E. *Tetrahedron* **1994**, *50*, 5741–5752.
40. Ayerbe, M.; Arrieta, A.; Cossío, F. P.; Linden, A. *J. Org. Chem.* **1998**, *63*, 1795–1805.
41. Oppolzer, W.; Bieber, L.; Francote, E. *Tetrahedron Lett.* **1979**, *11*, 981–984.
42. Rhodes, C. N.; Brown, D. R. *J. Chem. Soc., Faraday Trans.* **1993**, *89*, 1387–1391.
43. Cativiela, C.; Figueras, F.; García, J. I.; Mayoral, J. A.; Pires, E.; Rojo, A. J. *Tetrahedron: Asymmetry* **1993**, *4*, 621–624.
44. Cativiela, C.; Fraile, J. M.; García, J. I.; Mayoral, J. A.; Pires, E.; Rojo, A. J.; Figueras, F. *Tetrahedron* **1993**, *43*, 4073–4084.
45. Heinisch, G.; Holzer, W. *Heterocycles* **1988**, *27*, 2443–2457.
46. Abid, M.; Teixeira, L.; Toeroek, B. *Tetrahedron Lett.* **2007**, *48*, 4047–4050.