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Solvent-Free Thermal and Microwave-Assisted [3 + 2] Cycloadditions between Stabilized Azomethine Ylides and Nitrostyrenes. An Experimental and Theoretical Study

Ana Arrieta,[†] Dorleta Otaegui,[†] Aizpea Zubia,[†] Fernando P. Cossío,*[,†] Angel Díaz-Ortiz,*[,‡] Antonio de la Hoz,[‡] M. Antonia Herrero,[‡] Pilar Prieto,[‡] Concepción Foces-Foces,[§] José L. Pizarro,[¶] and María I. Arriortua[¶]

Kimika Organikoa I. Saila, Kimika Fakultatea, Universidad del País Vasco-Euskal Herriko Unibertsitatea, P.K. 1071, 20080 San Sebastián-Donostia, Spain, Facultad de Química, Universidad de Castilla-La Mancha, E-13071 Ciudad Real, Spain, Dpto. Cristalografía, Instituto de Química-Física 'Rocasolano', CSIC, Serrano 119, E-28006 Madrid, Spain, and Mineralogia eta Petrologia Saila, Zientzia eta Teknologia Fakultatea, Universidad del País Vasco-Euskal Herriko Unibertsitatea, P.K. 644 Bilbao, Spain

fp.cossio@ehu.es

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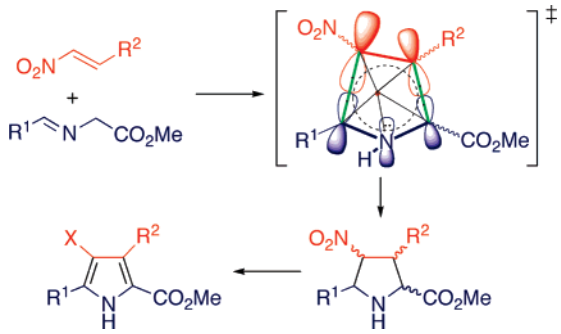

The stereochemical outcomes observed in the thermal and microwave-assisted [3 + 2] cycloaddition between stabilized azomethine ylides and nitrostyrenes have been analyzed using experimental and computational approaches. It has been observed that, in the absence of solvent, three stereoisomers are formed, both under classical heating conditions and under microwave irradiation. This result contrasts with that observed in solution under classical thermal conditions. The 4-nitropyrrolidines obtained in this way can be aromatized under further microwave irradiation to yield mixtures of pyrroles and 4-nitropyrroles. It is found that ground state cycloadditions between imines and nitrostyrenes take place by three-step mechanisms. The first step involves enolization of the starting imine, and this is followed by a pseudopericyclic 10-electron [1.4]-hydrogen shift. Finally, the cycloaddition takes place by a relatively asynchronous aromatic six-electron *supra*−*supra* thermal mechanism.

Introduction

Microwave radiation is an alternative to conventional heating for the introduction of energy into reactions and has clear benefits in many chemical transformations,[1] including cycloadditions.[2] Microwave-assisted organic synthesis is known for the spectacular accelerations produced in many reactions as a consequence of the heating rate, a phenomenon that cannot be easily reproduced by classical heating. As a result, higher yields, milder reaction conditions, and shorter reaction times can often be achieved. Under microwave irradiation, superheating to temperatures above the conventional boiling point of a solvent can be produced,[3] and decreases in reaction time are not surprising. Consequently, interest in microwave irradiation as a technique in organic chemistry has increased considerably in recent years.

1,3-Dipolar cycloadditions represent one of the most versatile tools for the construction of five-membered heterocycles.[4] Imines derived from α-aminoesters can be isomerized to

[†] Kimika Fakultatea, Universidad del País Vasco-Euskal Herriko Unibertsitatea.
[‡] Universidad de Castilla-La Mancha.
[§] CSIC.
[¶] Zientzia eta Teknologia Fakultatea, Universidad del País Vasco-Euskal Herriko Unibertsitatea.

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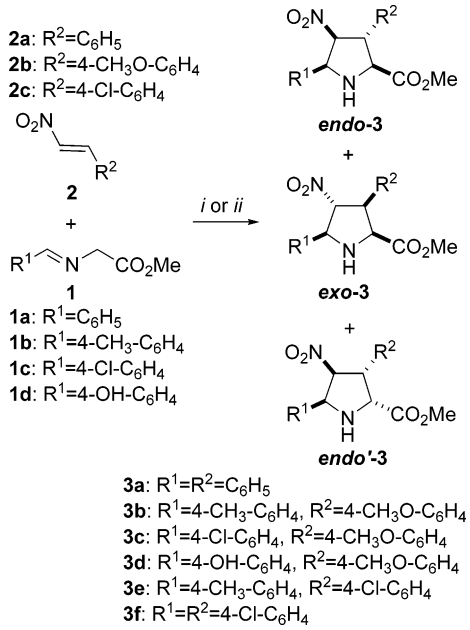
azomethine ylides[5] that undergo 1,3-dipolar cycloadditions with dipolarophiles to afford pyrrolidine derivatives.[6] The effective and eco-friendly microwave methodology to generate azomethine ylides from α-aminoester imines avoids harsh reaction conditions and the use of silver or lithium salts.[7] On classical heating in the absence of a Lewis acid catalyst, these cycloadditions can require long reaction times (24 h) and high temperatures (toluene reflux) to afford moderate yields (ca. 45%).[8]

The importance of substituted prolines[9] in the design of new catalysts[10] or in the chemical synthesis of pharmacologically[11] or biologically interesting[12] molecules is widely recognized. The [3 + 2] reaction of azomethine ylides and alkenes is one of the most useful methods for the preparation of these molecules in a convergent manner.[13]

Attention has recently been directed toward pyrrole-2-carboxylates as lead structures for the development of effective anticonvulsants,[14] but these compounds have long been important as analgesics and anti-inflammatory agents.[15] Likewise, some pyrrole-2-carboxylates bearing a substituted phenyl group have found potential applications as glycine antagonists[16] or as anti-HIV-1 agents (Delavirdine analogues).[17]

Recently, we reported a preliminary combinatorial chemistry application of the 1,3-dipolar cycloaddition between imines derived from α-aminoesters and nitroalkenes under focused microwaves in the absence of solvent.[18] We wish to report here a complete study of this reaction. Likewise, we have developed an efficient process for the aromatization of these pyrrolidines to give highly substituted pyrroles of potential interest.

SCHEME 1[a]



[a] Reagents and conditions: (i) microwaves, 210−270 W, 110−120 °C; (ii) classical heating, 120 °C; all pyrrolidines are racemic mixtures.

Results and Discussion

Experimental Studies. In the absence of solvent, microwave irradiation induces the thermal isomerization of imines **1a**−**d** to the corresponding azomethine ylides. The subsequent 1,3-dipolar cycloadditions with substituted *β*-nitrostyrenes **2a**−**c**, which occur within 10−15 min, afford the corresponding pyrrolidines **3** in 81−87% yield (Scheme 1). Three stereoisomers, namely, *endo*-**3**, *exo*-**3**, and *endo′*-**3**, were obtained in each cycloaddition. The reaction conditions, yields, and stereoisomer ratios are summarized in Table 1. Reactions were performed in open vessels at atmospheric pressure in monomode microwave

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TABLE 1. Cycloaddition Reactions between Imines 1a−d and *β*-Nitrostyrenes 2a−c under Microwave Irradiation in the Absence of Solvent

reactants	products	reaction conditions power/temp/time	yield[a] (%)	stereoisomer ratio[b] *endo*-**3**/*exo*-**3**/*endo′*-**3**
1a + **2a**	**3a**	210 W/120 °C/10 min	87	38/43/19
1a + **2a**	**3a**	−/120 °C/10 min	79	33/44/23
1b + **2b**	**3b**	210 W/120 °C/10 min	86	33/44/23
1c + **2b**	**3c**	210 W/110 °C/10 min	84	31/45/24
1d + **2b**	**3d**	270 W/120 °C/15 min	84	39/41/20
1b + **2c**	**3e**	240 W/120 °C/13 min	82	31/49/20
1c + **2c**	**3f**	270 W/120 °C/10 min	81	37/42/21

[a] Combined yield of isolated cycloadducts. [b] Determined by ^{1}H NMR spectroscopy.

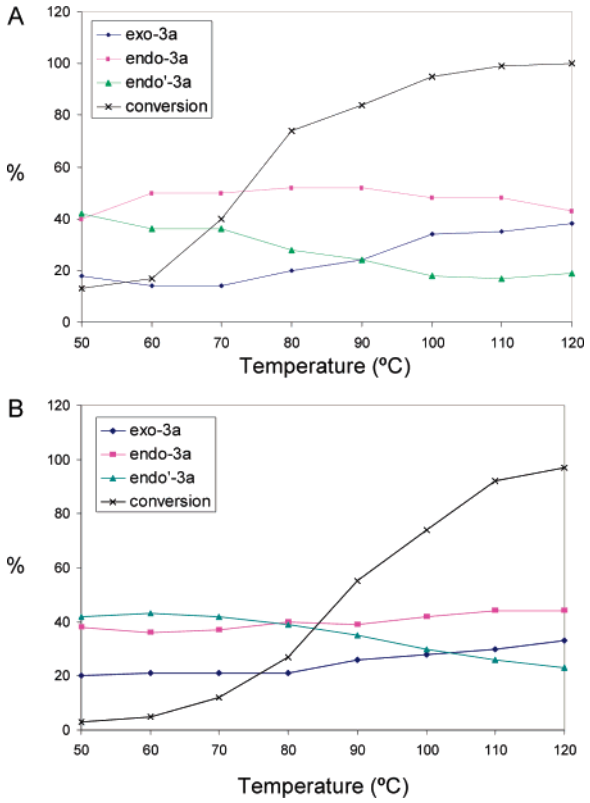


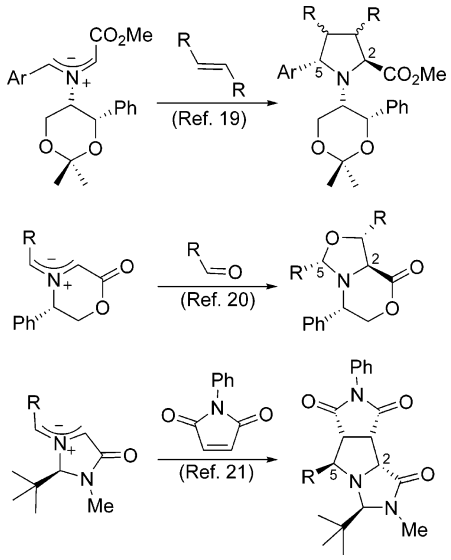
FIGURE 1. A [3 + 2] cycloaddition reaction between **1a** and **2a**: (A) microwave irradiation, 210 W, 10 min; (B) classical heating, 10 min.

reactors with total control of power and temperature by means of an infrared sensor. Conditions were optimized until complete disappearance of the imine was achieved.

In the absence of any catalyst and using classical heating with an oil bath, these cycloadditions require refluxing toluene for 24 h to afford yields below 50%. Moreover, under these conditions, only stereoisomers *endo*-**3** and *exo*-**3** were obtained.[8] However, when the reaction between imine **1a** and nitrostyrene **2a** was repeated under classical heating, but in the absence of solvent, the presence of *endo′*-**3a** was also observed in the crude reaction mixture.

In order to determine both the efficiency of the [3 + 2] cycloaddition reaction between **1a** and **2a** as well as the stereoselectivity of the reaction at different temperatures, the **1a** + **2a** → **3a** transformation was studied under both classical heating and microwave irradiation at different temperatures during 10 min. The results obtained are reported in Figure 1.

SCHEME 2. Selected Examples of Synthesis of Pyrrolidines with Substituents at C-2 and C-5 in a *trans* Relationship



Our results indicate that both profiles are similar, within the experimental error. The formation of diastereoisomers *endo′*-**3** is quite surprising, although pyrrolidines having a *trans*-relationship between the substituents at C-2 and C-5 are known[19−21] (Scheme 2). However, in these cases, the nitrogen atoms of the corresponding azomethine ylides have bulky substituents[19] or are conformationally restricted by the presence of cyclic chiral structures,[20,21] whereas in the present case, only *NH*-azomethine ylides are present.

The stereochemistry of adducts *endo*-**3** and *exo*-**3** was easily deduced by comparison with the products obtained by classical heating. The stereochemistry of cycloadducts *endo′*-**3** could only be inferred by X-ray crystallography of derivatives **5** and **7** (see the Supporting Information) obtained from inseparable mixtures of *exo*-**3a,b** and *endo′*-**3a,b** (Scheme 3).[22]

With cycloadducts **3** in hand, we decided to explore their aromatization to the corresponding 1*H*-pyrroles under microwave irradiation.

In recent years, 5-arylpyrrole-2-carboxylates have been prepared in moderate to good yields from their corresponding pyrrolidines by treatment with chloranil in refluxing xylene for 2−36 h[23] or DBU in hot DMF for 1 h.[24]

After several attempts, we found that pyrrolidines **3** can be aromatized to the corresponding 3,5-diaryl-1*H*-pyrrole-2-carboxylates **8** and **9** under microwave irradiation by oxidation with DDQ in refluxing xylene for 45 min (Scheme 4 and Table 2). This procedure represents a simple and fast method to obtain excellent yields of a wide range of pyrrole-2-carboxylates with different substitution patterns by using microwave irradiation.

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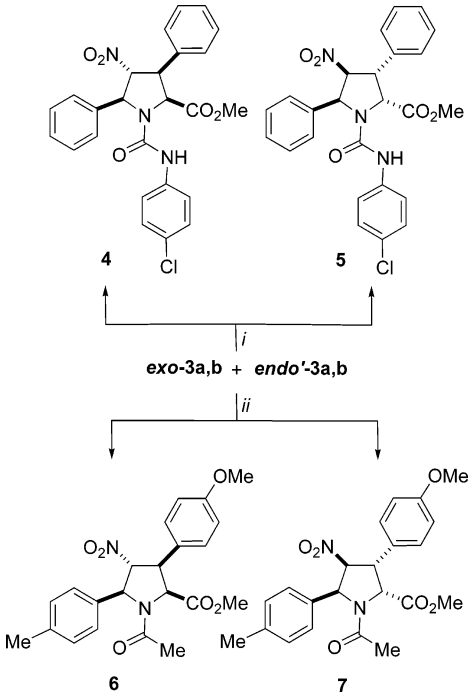
SCHEME 3. Acetylation and Carbamoylation Reactions of the Inseparable Mixtures of Stereoisomers *exo*-3a,b and *endo′*-3a,b[a]



[a] Reagents and conditions: (i) **3a**, OCN−C_6H_4−4Cl, MeCN, rt; (ii) **3b**, TFA, Ac_2O, rt.

TABLE 2. Aromatization of Pyrrolidines 3 with DDQ in Refluxing Xylene under Microwave Irradiation

substrates	products [yield[a] (%)]
endo-**3a** + *exo*-**3a** + *endo′*-**3a**	**8a** (89)
endo-**3b** + *exo*-**3b** + *endo′*-**3b**	**8b** (68) + **9b** (15)
endo-**3c** + *exo*-**3c** + *endo′*-**3c**	**8c** (74) + **9c** (14)
endo-**3d** + *exo*-**3d** + *endo′*-**3d**	**8d** (35)
endo-**3e** + *exo*-**3e** + *endo′*-**3e**	**8e** (82) + **9e** (12)
endo-**3f** + *exo*-**3f** + *endo′*-**3f**	**8f** (71)

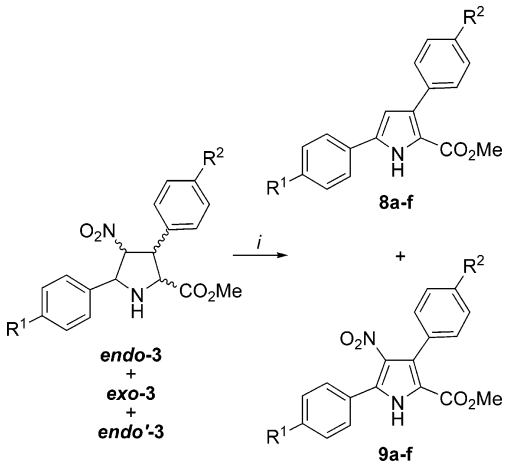
[a] Isolated yields of pure products.

When these transformations were carried out under the same reaction conditions, but with classical heating, at least 90 min was required to obtain similar yields and product distributions.

Aromatization of pure *endo*-**3b**, *exo*-**3b**, or a mixture of stereoisomers *exo*-**3b** and *endo′*-**3b** gave similar results (products and yields) in each case. It appears that, under these conditions, the elimination processes are not sensitive to the relative stereochemistries of the leaving groups. For this reason, all of the aromatizations were performed using the mixture of stereoisomers obtained in the cycloaddition. In some cases, 1*H*-pyrroles **8b**, **8c**, and **8e** were obtained along with a minor amount of the 4-nitropyrrole. However, with pyrrolidines **3a**, **3d**, and **3f**, aromatization took place with complete loss of the nitro group.

Computational Studies. All of the calculations reported in this paper were performed within Density Functional Theory,[25] using the hybrid three-parameter functional commonly denoted as B3LYP.[26] The standard 6-31G* basis set,[27]

SCHEME 4. Aromatization Reactions of Pyrrolidines 3 with DDQ under Microwave Irradiation[a]



[a] Reagents and conditions: (i) DDQ, xylene, microwaves.

as implemented in the GAUSSIAN 03[28] suite of programs, was used in all cases. Houk et al.[29] have shown that the B3LYP/6-31G* level is a convenient method for the computational study of pericyclic reactions in terms of computational cost and accuracy.

The synchronicity[30] of the reactions was calculated using a previously described approach.[31] For a given concerted reaction, "synchronicity" (Sy) is quantified as

$$\mathrm{Sy} = 1 - (2n-2)^{-1}\sum_{i=1}^{n}\frac{|\delta B_i - \delta B_{av}|}{\delta B_{av}} \qquad (1)$$

where n is the number of bonds directly involved in the reaction and δB_i is the relative variation of the bond index B_i at the

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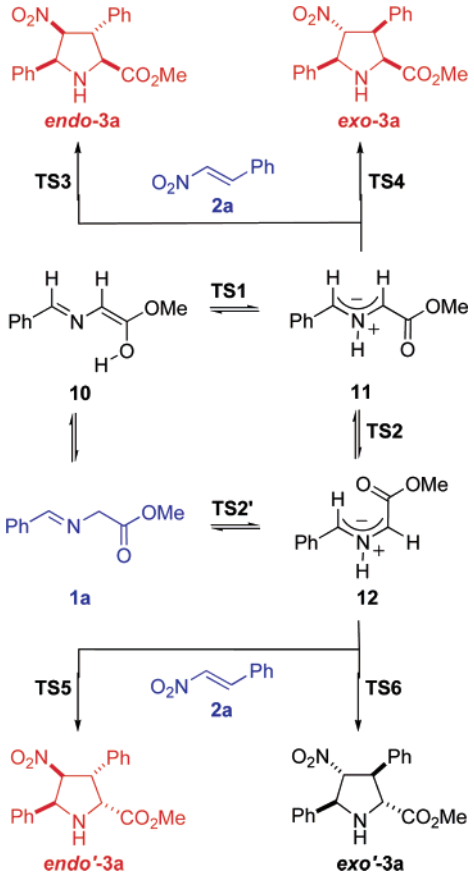
SCHEME 5. Reactants, Intermediates, Cycloadducts, and Reaction Profiles Included in the Computational Studies[a]



[a] Reactants and observed products are depicted in blue and red, respectively. Reaction intermediates and cycloadducts that are not observed are represented in black.

transition structure (TS) relative to the reactant(s) (R) and product (P), according to the following expression:

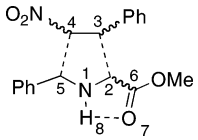
$$\delta B_i = \frac{B_i^{TS} - B_i^R}{B_i^P - B_i^R} \qquad (2)$$

The average value of δB_i, denoted as δB_{av}, in eq 2 is therefore

$$\delta B_{av} = n^{-1} \sum_{i=1}^{n} \delta B_i \qquad (3)$$

Wiberg indices B_i were employed;[32] these were evaluated using the natural bond orbital (NBO) method.[33] According to eq 1, for a perfectly synchronous reaction, Sy = 1 since for any given bond index $\delta B_i = \delta B_{av}$. Similarly, according to eqs 2 and 3, early and late transition structures will be characterized by $\delta B_{av} < 0.5$ and $\delta B_{av} > 0.5$, respectively.

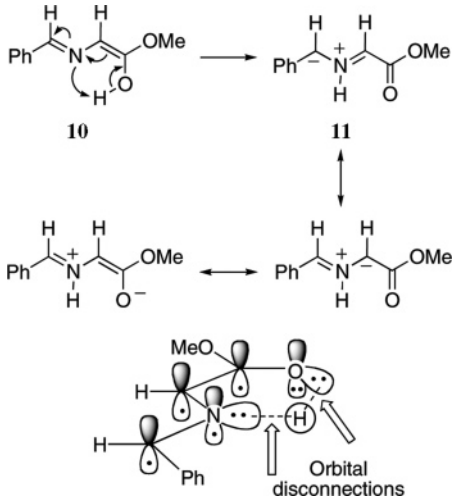
TABLE 3. Bond Indices[a] **for Reactants, Intermediates, Transition Structures, and Products Indicated in Scheme 5**



structure	$B_{1,2}$	$B_{2,3}$	$B_{3,4}$	$B_{4,5}$	$B_{5,1}$	$B_{2,6}$	$B_{6,7}$	$B_{7,8}$	$B_{1,8}$
1a	1.03	0.00	0.00	0.00	1.83	0.97	1.74	0.00	0.00
2a	0.00	0.00	1.76	0.00	0.00	0.00	0.00	0.00	0.00
endo-**3a**	0.98	0.97	0.97	0.95	0.98	0.94	1.75	0.00	0.81
exo-**3a**	0.99	0.96	0.96	0.94	0.98	0.96	1.76	0.00	0.80
endo′-**3a**	0.99	0.94	0.98	0.94	0.99	0.96	1.72	0.02	0.79
exo′-**3a**	1.00	0.96	0.96	0.95	0.97	0.95	1.75	0.01	0.79
10	1.17	0.00	0.00	0.00	1.66	1.54	1.06	0.66	0.05
11	1.23	0.00	0.00	0.00	1.39	1.19	1.57	0.03	0.72
12	1.21	0.00	0.00	0.00	1.37	1.20	1.59	0.00	0.77
TS1	1.18	0.00	0.00	0.00	1.54	1.36	1.26	0.35	0.37
TS2	0.92	0.00	0.00	0.00	1.68	1.31	1.55	0.01	0.75
TS3	1.15	0.39	1.39	0.18	1.35	1.07	1.67	0.02	0.73
TS4	1.14	0.41	1.37	0.17	1.36	1.07	1.66	0.02	0.74
TS5	1.11	0.45	1.34	0.14	1.37	1.06	1.66	0.00	0.90
TS6	1.13	0.41	1.39	0.18	1.34	1.05	1.69	0.00	0.77

[a] Calculated at the B3LYP/6-31G(d) level.

SCHEME 6. Electronic Circulations and Orbital Disconnections in the Pseudopericyclic Transformation of Enol 10 into Azomethine Ylide 11



Donor−acceptor interactions were also computed using the NBO method. The energies associated with these two-electron interactions were computed by means of the second-order perturbation energy, $\Delta E^{(2)}_{\phi\phi^*}$, according to the following equation:

$$\Delta E^{(2)}_{\phi\phi^*} = -n_\phi \frac{\langle \phi^* | \hat{F} | \phi \rangle^2}{\epsilon_{\phi^*} - \epsilon_\phi} \qquad (4)$$

where ϕ^* and ϕ are the non-Lewis and Lewis localized orbitals, $\hat{F}$ is the Fock operator, n_ϕ is the occupation of the ϕ localized orbital, and ϵ_{ϕ^*} and ϵ_ϕ are the respective energies.

Nucleus-independent chemical shifts (NICS) as defined by Schleyer[34] were computed using the gauge invariant atomic

(30) (a) Borden, W. T.; Loncharich, R. J.; Houk, K. N. *Annu. Rev. Phys. Chem.* **1988**, *39*, 213. (b) Moyano, A.; Pericàs, M. A.; Valentí, E. *J. Org. Chem.* **1989**, *54*, 573.

(31) (a) Cossío, F. P.; Morao, I.; Jiao, H.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1999**, *121*, 6737. (b) Morao, I.; Lecea, B.; Cossío, F. P. *J. Org. Chem.* **1997**, *62*, 7033. (c) Lecea, B.; Arrieta, A.; Roa, G.; Ugalde, J. M.; Cossío, F. P. *J. Am. Chem. Soc.* **1994**, *116*, 9613. (d) Lecea, B.; Arrieta, A.; Lopez, X.; Ugalde, J. M.; Cossío, F. P. *J. Am. Chem. Soc.* **1995**, *117*, 12314.

(32) Wiberg, K. B. *Tetrahedron* **1968**, *24*, 1083.

(33) (a) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899. (b) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735.

(34) Schleyer, P. v. R.; Maerker, C.; Dransfeld, A.; Jiao, H.; Hommes, N. J. R. v. E. *J. Am. Chem. Soc.* **1996**, *118*, 6317.

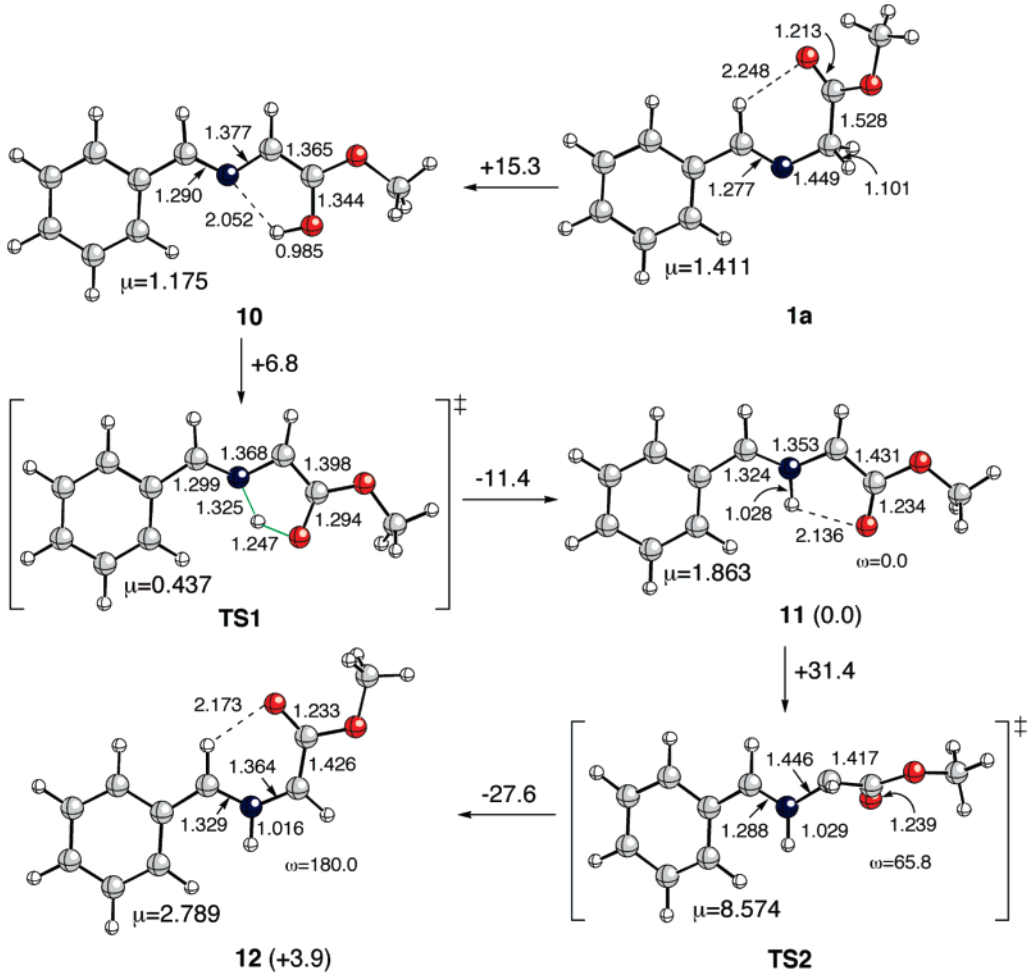


FIGURE 2. Fully optimized structures [B3LYP/6-31G(d) level of theory] of the stationary points found in the thermal conversion of imine **1a** to azomethine ylides **11** and **12**. Bond distances are given in Å. Dipole moments (μ) are reported in Debyes (D). The numbers on the arrows indicate the relative energies, in kcal/mol, of the stationary points connected by the arrow [B3LYP/6-31G(d)+ΔZPVE level of theory]. Numbers in parentheses are the relative energies between azomethines **11** and **12**, in kcal/mol.

orbital[35] (GIAO) approach at the GIAO-B3LYP/6-31G*//B3LYP/6-31G* level.

All of the stationary points were characterized by harmonic analysis.[36] Activation energies (ΔE_a) and reaction energies (ΔE_{rxn}) were computed at the B3LYP/6-31G* level including zero-point vibrational energy (ZPVE) corrections.

In a previous investigation,[8] we studied several model [3 + 2] cycloadditions involving stabilized azomethine ylides and nitroethylene. It was found that the substitution pattern has a strong influence on the reaction profiles, and for this reason, we decided to compute the structures shown in Scheme 5, which are the most important reactants, cycloadducts, and intermediates. These stationary points include all of the functional groups and general substituents included in the experimental studies. The corresponding Wiberg bond indices are collected in Table 3.

We studied the generation of azomethine ylides **11** and **12** first. As described previously, formation of these 1,3-dipoles starts with the enolization of imine **1a** to yield the intermediate imino enol **10**, which lies ca. 15 kcal/mol above **1a** at the B3LYP/6-31G(d) level (Figure 2). From this local minimum, conversion to the azomethine ylide is readily accomplished through a pseudopericyclic [1,5]-hydrogen shift, as can be seen by the planar geometry of **TS1** and the low activation energy

TABLE 4. Activation Energies[a] (ΔE_a, kcal/mol), Reaction Energies[a] (ΔE_{rxn}, kcal/mol), Average Bond Index Changes[a,b] (δB_{av}), Synchronicities[a,c] (Sy), and Nucleus-Independent Chemical Shifts[d] (NICS, ppm/mol) Associated with the Formation of [3 + 2] Cycloadducts Indicated in Scheme 5

reaction	TS[e]	ΔE_a	ΔE_{rxn}	δB_{av}	Sy	NICS (**TS**)	NICS (**3**)
11 + **2a** → *endo*-**3a**	**TS3**	5.0	−22.0	0.30	0.74	−16.76	−6.82
11 + **2a** → *exo*-**3a**	**TS4**	4.1	−24.6	0.31	0.71	−13.70	−5.70
12 + **2a** → *endo*′-**3a**	**TS5**	3.8	−26.0	0.32	0.61	−14.01	−6.09
12 + **2a** → *exo*′-**3a**	**TS6**	7.7	−31.0	0.29	0.66	−12.69	−5.86

[a] Computed at the B3LYP/6-31G(d)+ΔZPVE level. [b] Computed at the B3LYP/6-31G(d) level according to eqs 2 and 3 and using the bond indices reported in Table 3. [c] Computed at the B3LYP/6-31G(d) level according to eq 1. [d] Computed [GIAO-B3LYP/6-31G(d) level of theory] at the ring point of electron density of the corresponding transition structure or cycloadduct **3**. [e] Calculated NICS corresponding to transition structures and cycloadducts are denoted as NICS (**TS**) and NICS (**3**), respectively. For each structure, these NICS were calculated at the ring point of electron density.

(35) Wolinski, K.; Hilton, J. F.; Pulay, P. *J. Am. Chem. Soc.* **1990**, *112*, 8251.

(36) McIver, J. W., Jr.; Komornicki, A. *J. Am. Chem. Soc.* **1972**, *94*, 2625.

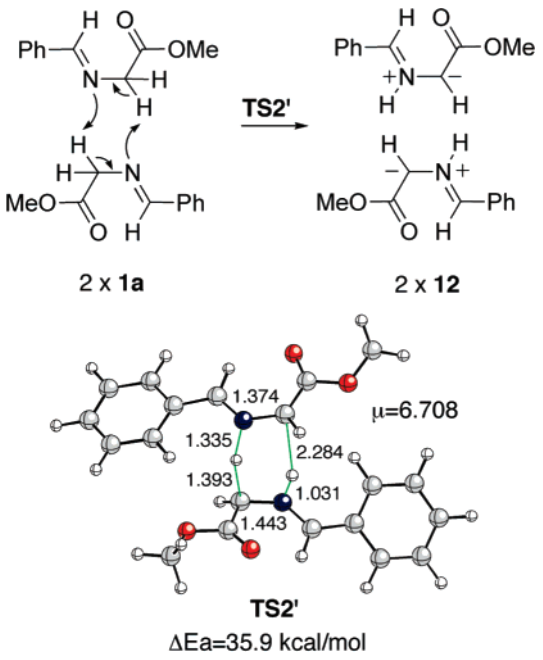


FIGURE 3. Formation of azomethine ylide **12** via bimolecular double hydrogen transfer from imine **1a**. Main geometric features of the corresponding transition structure **TS2′** (B3LYP/6-31G* level). ΔE_a is the activation energy for this process, calculated at the B3LYP/6-31G(d)+ΔZPVE level. See caption of Figure 2 for additional details.

associated with the **10**→**11** transformation (Figure 2). The pseudopericyclic nature of this reaction[37] can be readily appreciated considering the two orbital disconnections between the five-membered π-array of p AOs and the system formed by the 1s AO of the migrating hydrogen atom and the lone pairs of the nitrogen and oxygen atoms (Scheme 6).

We also calculated the synchronicity of this 10-electron pseudopericyclic hydrogen shift by analyzing the variation of the bond indices along the **10**−**TS1**−**11** sequence. As reported in Table 3, the bond indices considered were $B_{1,2}$, $B_{2,6}$, $B_{6,7}$, $B_{7,8}$, $B_{1,8}$, and $B_{1,5}$. According to eq 3, and considering that $n = 6$ from the data included in Table 3, the value $\delta B_{av} = 0.41$ is obtained. This means that **TS1** is an almost halfway, slightly early transition structure. The computed synchronicity is 0.87, which indicates that this pseudopericyclic reaction is quite synchronous in spite of the large number of electrons and different bonds and lone pairs involved.

A less stable stereoisomer **12** can be formed from azomethine ylide **11** by rotation about the C2−C6 bond (Table 3). This process is easier than the alternative rotation around the C5−N1 bond since in **11** $B_{1,5} > B_{2,6}$ (Table 3).[38] The activation energy associated with the formation of **12** from **11** is calculated to be 24.6 kcal/mol higher than that corresponding to formation of azomethine ylide **11** from enol **10** (Figure 2). In addition, **11** is calculated to be ca. 4 kcal/mol more stable than its stereoisomer **12**.

Azomethine ylide **12** can also be formed by a bimolecular mechanism involving a double proton transfer from two molecules of imine **1a**. According to this alternative mechanism, both protons are transferred in a very asynchronous manner,[39] as it can be appreciated in Figure 3, in which the chief geometric features of the corresponding transition structure **TS2′** are shown. The activation energy for this process is comparable, although slightly higher, than that computed for the formation

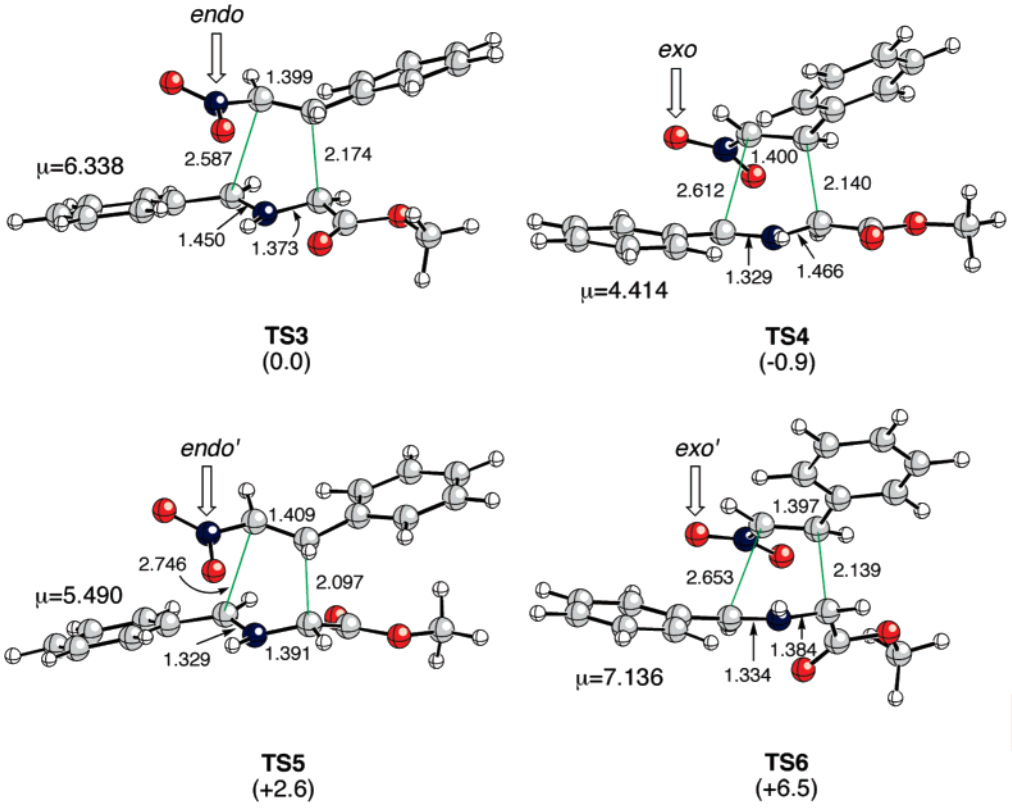


FIGURE 4. Main features of transition structures **TS3**−**6**. Numbers in parentheses are the relative energies with respect to **TS3**, calculated at the B3LYP/6-31G(d)+ΔZPVE level. See caption of Figure 2 for additional details.

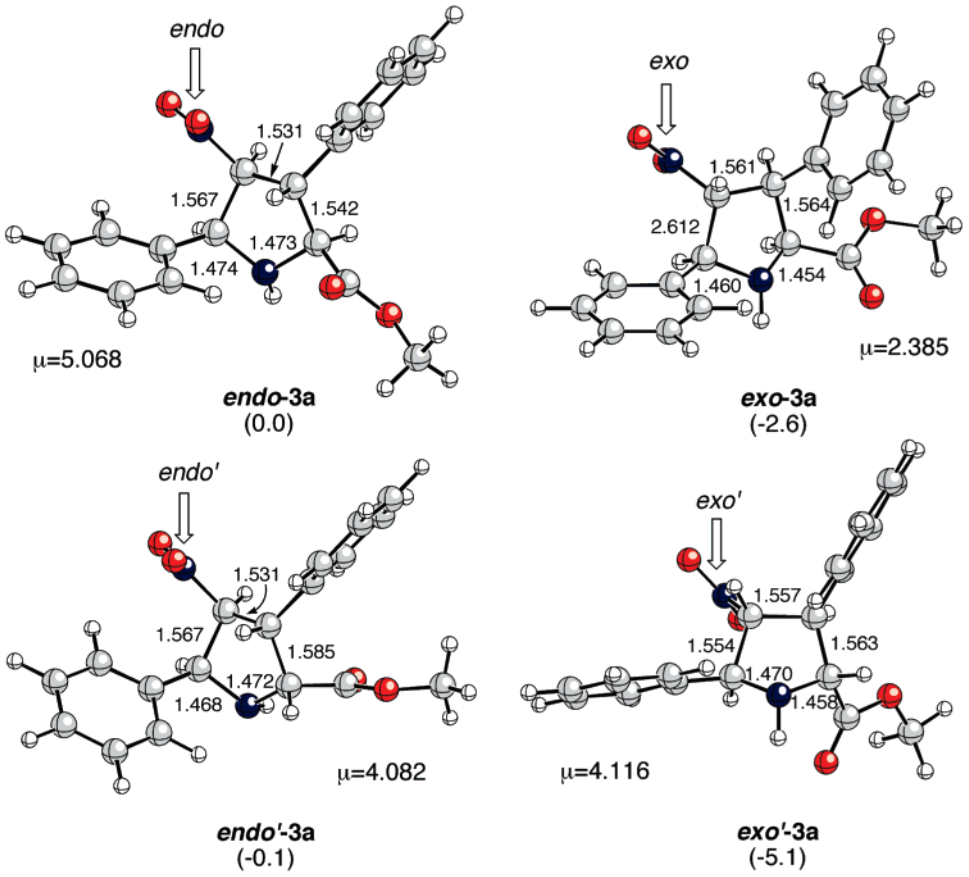


FIGURE 5. Main features of cycloadducts *endo*-, *exo*-, *endo′*-, and *exo′*-**3**. Numbers in parentheses are the relative energies with respect to *endo*-**3**, calculated at the B3LYP/6-31G(d)+ΔZPVE level. See caption of Figure 2 for additional details.

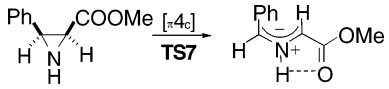
of **12** via **TS2**. It is likely that this bimolecular mechanism, together with that associated with **TS2**, contributes to the formation of an appreciable proportion of azomethine ylide **12** in the absence of solvent. As a consequence, formation of cycloadduct(s) derived from **12** could be expected under solvent-free conditions in spite of the large activation energy associated with this process.

We proceeded to study the [3 + 2] cycloaddition reactions of azomethine ylides **11** and **12** with nitrostyrene **2a** to yield the corresponding cycloadducts **3a**. On the basis of our previous results for this reaction and on our experimental results, only the regioisomers reported in Scheme 5 were considered since the reaction paths that lead to the four alternative regioisomers are of much higher energy. The chief features of the four possible transition structures and cycloadducts are shown in Figures 4 and 5, respectively. The activation and reaction energies, as well as synchronicities and NICS, are shown in Table 4.

According to our results, all transition structures **TS3**−**6** correspond to [$_{\pi}4_s$+$_{\pi}2_s$] mechanisms. However, the studied reactions are quite asynchronous, with an average Sy value of ca. 0.7 (Table 4). These values were obtained from eqs 1−3 and by considering bond indices $B_{1,2}$, $B_{2,3}$, $B_{3,4}$, $B_{4,5}$, and $B_{5,1}$ (Table 3) with $n = 5$. The activation energies associated with these cycloadditions are lower than those corresponding to the formation of the dipoles, thus confirming that this latter reaction is the limiting step of the whole process, although the kinetic treatment of the alternative reaction paths is quite complex. Transformations involving dipole **11** are slightly more synchronous than those involving dipole **12**. Within each subset, the most asynchronous transition structures are of lower energy than the most synchronous ones.

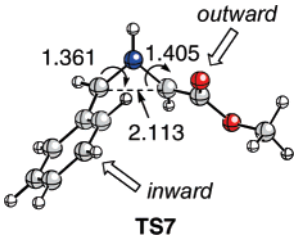
(37) Zhou, C.; Birney, D. M. *J. Am. Chem. Soc.* **2002**, *124*, 5231.

(38) The calculated transition structure associated with rotation around C5−N1 collapses to that associated with the conrotatory electrocyclic opening of the corresponding *cis*-aziridine **10**, according to the following reaction:



10 **11**

All our attempts to locate a genuine TS associated only with rotation about C5−N1 failed. **TS7** was computed to lie 5.7 kcal/mol above **TS2** and 25.7 kcal/mol above **TS1** at the B3LYP/6-31G(d)+ΔZPVE level. In this saddle point, the phenyl and methoxycarbonyl groups are inward and outward, respectively, with respect to the aziridine ring:



TS7

The high energy associated with **TS7**, together with its relatively low calculated polarity (μ = 2.632 D), indicates that this TS is not associated with the stereochemical outcome of the reaction. For the stereochemistry of conrotatory electrocyclizations, see: Niwayama, S.; Kallel, E. A.; Spellmeyer, D. C.; Sheu, C.; Houk, K. N. *J. Org. Chem.* **1996**, *61*, 2813.

(39) The connection between **TS2′** and reactants (2 × **1a**) and products (2 × **12**) was verified by IRC computations.

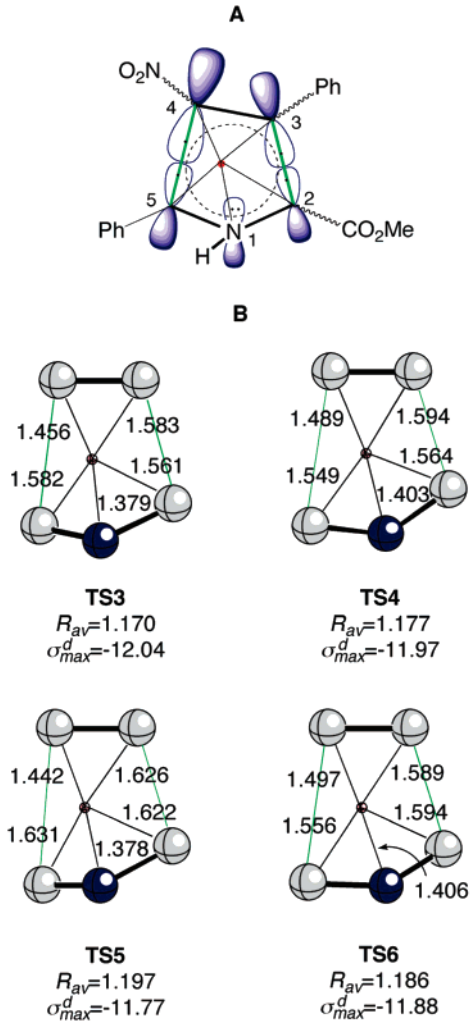


FIGURE 6. (A) Schematic definition of an in-plane ring current for transition structures **TS3**−**6**. The ring current of radius R_{av} is shown by a dashed line. The (3, +1) ring point of electron density and the radii R_i are shown in red and black, respectively. Bonds being formed and participating p AOs are represented in green and blue, respectively. (B) R_i, R_{av} (in Å), and σ^d_{max} (in ppm/mol) values for transition structures **TS3**−**6**.

Our calculations also indicate that saddle points **TS3**−**6** are aromatic.[31a,40,41] Thus, all of these transition structures have large negative NICS values (Table 4), calculated at the (3, +1) ring points of electron density.[31a,40,41] In contrast, cycloadducts **3a** have only slightly negative NICS values, probably because of local diamagnetic effects.

In previous studies,[31a,41] we reported that transition structures corresponding to aromatic thermally allowed cycloadditions can be described by a diamagnetic ring current of radius R_{av} according to the following expression:

$$R_{av} = n^{-1}\sum_{i=1}^{n}\left(R_i - \frac{4}{Z_i}a_0\right) \qquad (5)$$

where n is the number of atoms involved in the electronic circulation (in our case $n = 5$), R_i is the distance between the (3, +1) ring point and the i atom, Z_i is the corresponding atomic number (therefore, $Z_C = 6$ and $Z_N = 7$ for carbon and nitrogen atoms, respectively), and a_0 is the Bohr radius. The diamagnetic shielding σ^d_{max} at the (3, +1) ring point[40] induced by this in-plane ring current is

$$\sigma^d_{max} = -\frac{e^2\mu_0}{8\pi m_e}R_{av}^{-1} \qquad (6)$$

where m_e and e are the mass and charge of the electron and μ_0 is the permeability of vacuum.

We computed the R_{av} and σ^d_{max} values for **TS3**−**6**, and the results are shown in Figure 6. According to these results, the computed σ^d_{max} values are quite close to the previously obtained NICS values (Table 4). This result indicates that the aromatic character of these asynchronous [$_\pi4_s+_\pi2_s$] transition structures can be almost completely described in terms of diamagnetic ring currents. Therefore, it can be concluded that transition states associated with thermal 1,3-dipolar reactions between azomethine ylides and nitroalkenes exhibit in-plane aromaticity.

The experimentally observed cycloadduct ratios follow the relative energies of transition structures **TS3**−**6** and not those calculated for cycloadducts *endo*-, *exo*-, *endo*′-, and *exo*′-**3** (Figures 4 and 5). Therefore, we conclude that this reaction takes place under kinetic control, a result compatible with the exothermicity of the cycloaddition reaction (Table 4). The energy order found for the transition structures is **TS4** < **TS3** < **TS5** < **TS6**, and this is consistent with the *exo*-**3a**/*endo*-**3a**/*endo*′-**3a** ratios obtained under classical heating and microwave irradiation. The lower energies of saddle points **TS4** and **TS3** can be rationalized in terms of steric repulsion and secondary orbital interactions between the different substituents. Thus, in **TS3**, the nitro group has stabilizing two-electron interactions with the N1−H moiety [$\Delta E(2) = -0.35$ kcal/mol] and with the phenyl group at C5 [$\Delta E(2) = -0.75$ kcal/mol] since both moieties are in a *cis* disposition with respect to the nitro group. In the case of **TS4**, the main secondary orbital interactions take place between the phenyl group at C3 and the carbonyl group, which are *cis* with respect to one another, with $\Delta E(2) = -0.98$ kcal/mol. However, the latter saddle point is earlier than **TS3** (Table 3), and therefore, the destabilizing four-electron interactions are less important. The final result of this situation is a lower energy for **TS4**, which is in good agreement with the experimental observations. Saddle point **TS5** benefits from both interactions present in **TS3** and **TS4** since in this case the nitro group is *cis* with respect to the N1−H group and the phenyl group at C5, whereas the phenyl group at C3 is also *cis* with respect to the carbonyl group. Therefore, the combined $\Delta E(2)$ terms yield a value of −2.03 kcal/mol. However, the repulsive four-electron interactions are larger than those in the preceding cases because this latter saddle point is later than **TS3** and **TS4** (Table 4). The result is a relative destabilization of **TS5** with respect to **TS3** and **TS4**.

In summary, the stereochemical outcome of this reaction is the result of a delicate balance between stabilizing and destabilizing interactions. In addition, as we have previously mentioned, formation of the *endo*′-**3a** cycloadduct can be related to the bimolecular formation of the more polar azomethine ylide **12**, which is the limiting step of the whole reaction.

(40) Bader, R. F. W. *Atoms in Molecules: A Quantum Theory*; Clarendon Press: Oxford, 1990; pp 13−52.
(41) Morao, I.; Cossío, F. P. *J. Org. Chem.* **1999**, *64*, 1868.

Conclusions

Microwave irradiation induces the 1,3-dipolar cycloaddition of imines derived from α-aminoesters with β-nitrostyrenes in the absence of solvent within 10−15 min. The reaction proceeds to give yields in the range of 81−87%, and three isomeric pyrrolidines are obtained in the cycloaddition. The stereochemical outcome of the reaction is similar under microwave irradiation and thermal heating in the absence of solvent. Thermal cycloadditions between imines and nitrostyrenes take place by three-step mechanisms. The first step involves enolization of the starting imine, and this is followed by a pseudopericyclic 10-electron [1.4]-hydrogen shift. Finally, the cycloaddition takes place by a relatively asynchronous aromatic six-electron *supra*−*supra* thermal mechanism. Formation of a third stereoisomer is observed in the absence of solvent. It is proposed that formation of this stereoisomer involves an azomethine ylide resulting from isomerization of the previous one or from a double highly asynchronous proton transfer between two starting imine molecules.

Experimental Section

Imines **1a**−**d** and nitrostyrenes **2a**−**c** were prepared as previously reported.[8,42] Cycloadducts *endo*-**3a**−**c** and *exo*-**3a**−**c** are also known compounds. Characterization of these pyrrolidines was performed by comparison of the physical and spectroscopic properties with the published ones.[8,42]

Cycloaddition of Imine 1a with β-Nitrostyrene (2a). A mixture of methyl *N*-benzylidene glycinate (**1a**) (354 mg, 2 mmol) and β-nitrostyrene (**2a**) (298 mg, 2 mmol) was irradiated in a focused microwave reactor (Prolabo MX350), modified to achieve the measurement and control of power and temperature by infrared detection, at 210 W for 10 min (final temperature 120 °C) to give a mixture of three stereoisomers *endo*-**3a**, *exo*-**3a**, and *endo*′-**3a** (568 mg, 87%, stereoisomer ratios 38/43/19). The crude product was purified by silica gel flash column chromatography using hexane/ethyl acetate as the eluent. Three fractions containing stereoisomers *endo*-**3a**, *exo*-**3a**, and an inseparable mixture of *exo*-**3a** and *endo*′-**3a** were isolated.

Data for (2*S,3*R**,4*S**,5*S**)-3,5-Diphenyl-2-methoxycarbonyl-4-nitropyrrolidine, *endo*-3a:** yellow solid, mp 120−122 °C; IR 3314, 1735, 1545, 1370 cm^{-1}; ^1H NMR (δ ppm, $CDCl_3$) 3.35 (s_b, 1H), 3.80 (s, 3H), 4.14 (d, 1H, $J = 7.4$ Hz), 4.21 (dd, 1H, $J = 7.6$ Hz, $J' = 3.1$ Hz), 4.91 (d, 1H, $J = 6.6$ Hz), 5.27 (dd, 1H, $J = 6.5$ Hz, $J' = 3.2$ Hz), 7.25−7.44 (m, 10H); ^{13}C NMR (δ ppm, $CDCl_3$) 52.6, 55.3, 67.3, 67.7, 96.9, 126.4, 127.4, 128.0,128.7, 129.2, 134.4, 138.5, 171.7. Anal. Calcd for $C_{18}H_{18}O_4N_2$: C, 66.24; H, 5.57; N, 8.58. Found: C, 66.41; H, 5.74; N, 8.58.

Data for (2*S,3*S**,4*R**,5*S**)-3,5-Diphenyl-2-methoxycarbonyl-4-nitropyrrolidine, *exo*-3a:** yellow solid, mp 113−115 °C; IR 3355, 1743, 1544, 1347 cm^{-1}; ^1H NMR (δ ppm, $CDCl_3$) 2.73 (s_b, 1H), 3.27 (s, 3H), 4.37 (t, 1H, $J = 7.7$ Hz), 4.50 (d, 1H, $J = 9$ Hz, $J' = 3.1$ Hz), 4.75 (d_b, 1H, $J = 8.2$ Hz), 5.21 (dd, 1H, $J = 8.0$ Hz), 7.20−7.58 (m, 10H); ^{13}C NMR (δ ppm, $CDCl_3$) 51.8, 53.7, 64.2, 67.6, 95.0, 126.8, 127.8, 128.1,128.7, 128.9, 129.0, 135.8, 137.6, 171.8. Anal. Calcd for $C_{18}H_{18}O_4N_2$: C, 66.24; H, 5.57; N, 8.58. Found: C, 66.70; H, 5.56; N, 8.58.

Data for (2*R,3*R**,4*S**,5*S**)-3,5-Diphenyl-2-methoxycarbonyl-4-nitropyrrolidine, *endo*′-3a:** ^1H NMR (δ ppm, $CDCl_3$) 2.68 (s_b, 1H), 3.28 (s, 3H), 4.53 (dd, 1H, $J = 11.3$ Hz, $J' = 7.8$ Hz), 4.74 (d, 1H, $J = 8.2$ Hz), 5.46 (d, 1H, $J = 8.0$ Hz), 5.64 (dd, 1H, $J = 7.7$ Hz, $J' = 6.4$ Hz), 7.17−7.44 (m, 10H).

Synthesis of Carbamoyl Derivatives 4 and 5. A mixture of *exo*-**3a** and *endo*′-**3a** cycloadducts (1.0 g, 3 mmol) was transformed into a solid derivative by means of reaction with 4-chloriphenyl isocyanate (0.47 g, 3 mmol) in CH_3CN (30 mL) overnight at room temperature and under argon atmosphere. Then CH_2Cl_2 (30 mL) was added, and the resulting mixture was filtered through a Celite pad. The filtrate was washed with saturated aqueous NH_4Cl solution (2 × 10 mL) and water (4 × 10 mL). The organic extract was dried with Na_2SO_4, and the organic solvent was evaporated under reduced pressure. The resulting residue was triturated in Et_2O (yield 79%), and the isomers were separated by preparative TLC.

Data for (2*S,3*S**,4*R**,5*S**)-1-(4-Chlorophenylcarbamoyl)-3,5-diphenyl-2-methoxycarbonyl-4-nitropyrrolidine, 4:** white solid, mp 229−231 °C; IR 3407, 1748, 1648, 1532, 1341, 1030 cm^{-1}; ^1H NMR (δ ppm, $CDCl_3$) 3.37 (s, 3H), 4.46 (dd, 1H, $J = 12.0$ Hz, $J' = 9.5$ Hz), 5.22 (d, 1H, $J = 9.5$ Hz), 5.32 (d, 1H, $J = 8.6$ Hz), 5.79 (dd, 1H, $J = 12.0$ Hz, $J' = 8.6$ Hz), 5.97 (s_b, 1H), 6.82 (d, 2H, $J = 8.8$ Hz), 7.13 (d, 2H, $J = 8.8$ Hz), 7.24−7.31 (m, 2H), 7.32−7.39 (m, 3H), 7.53−7.60 (m, 3H), 7.89 (d_b, 2H, $J = 5.7$ Hz); ^{13}C NMR (δ ppm, $CDCl_3$) 49.7, 52.1, 63.9, 65.8, 92.9, 120.7, 127.5, 127.7, 128.6, 128.8, 128.9, 129.0, 130.3, 130.7, 130.8, 136.1, 136.3, 152.8, 171.4. Anal. Calcd for $C_{25}H_{22}O_5N_3Cl$: C, 62.57; H, 4.62; N, 8.76. Found: C, 62.57; H, 4.56; N, 8.80.

Data for (2*R,3*R**,4*S**,5*S**)-1-(4-Chlorophenylcarbamoyl)-3,5-diphenyl-2-methoxycarbonyl-4-nitropyrrolidine, 5:** white solid, mp 112−113 °C; IR 3427, 1723, 1673, 1557, 1331, 1095 cm^{-1}; ^1H NMR (δ ppm, $CDCl_3$) 3.40 (s, 3H), 4.60 (dd, 1H, $J = 12.3$ Hz, $J' = 8.69$ Hz), 5.00 (d, 1H, $J = 8.7$ Hz), 5.76 (d, 1H, $J = 9.31$ Hz), 5.99 (s_b, 1H), 6.23 (dd, 1H, $J = 12.3$ Hz, $J' = 9.4$ Hz), 6.97 (d, 2H, $J = 8.8$ Hz), 7.13 (d, 2H, $J = 8.8$ Hz), 7.24−7.28 (m, 2H), 7.32−7.38 (m, 3H), 7.46−7.52 (m, 5H); ^{13}C NMR (δ ppm, $CDCl_3$) 45.8, 52.2, 62.4, 63.8, 87.5, 120.8, 127.5, 127.5, 128.8, 129.0, 129.8, 130.6, 131.4, 133.9, 136.2, 153.1, 171.7. Anal. Calcd for $C_{25}H_{22}O_5N_3Cl$: C, 62.57; H, 4.62; N, 8.76. Found: C, 62.46; H, 4.61; N, 8.9.

Aromatization of *endo*-3a, *exo*-3a, and *endo*′-3a. A mixture of *endo*-**3a**, *exo*-**3a**, and *endo*′-**3a** (653 mg, 2 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (681 mg, 3 mmol) in xylene (20 mL) was irradiated in a focused microwave reactor (Prolabo MX350), modified to achieve the measurement and control of power and temperature by infrared detection, at 255 W for 45 min (max temperature 140 °C). After cooling, the resulting brown solution was concentrated in vacuo. The products were purified and separated by column chromatography on silica gel using hexane/ethyl acetate as the eluent to yield pyrrole **8a** (494 mg, 89%).

Data for 2-Methoxycarbonyl-3,5-diphenyl-*NH*-pyrrole, 8a: white solid, mp 179−180 °C; IR 3427, 3306, 1666 cm^{-1}; ^1H NMR (δ ppm, $CDCl_3$) 3.77 (s, 3H), 6.61 (d, 1H, $J = 3.3$ Hz), 7.33 (m, 2H), 7.41 (m, 4H), 7.59 (m, 4H), 9.51 (s_b, 1H); ^{13}C NMR (δ ppm, $CDCl_3$) 51.3, 109.9, 118.2, 124.7, 125.8, 127.1, 127.7, 127.9, 128.9, 129.0, 129.3, 129.4, 130.9, 133.6, 1135.0, 135.5, 161.6; MS *m*/*z* (EI) 321 (M^+). Anal. Calcd for $C_{18}H_{15}O_2N$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.65; H, 5.39; N, 4.96.

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Supporting Information Available: Complete Experimental Section with the characterization of all compounds, copy of ^1H and ^{13}C spectra of all new compounds, X-ray crystallographic data for compounds **5** and **7**, Cartesian coordinates and energies (including zero-point vibrational energies) of all reactants, intermediates, products, and transition structures discussed in this work can be found in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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