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On the Mechanism of Phthalimidine Formation via *o*-Phthalaldehyde Monoimines. New [1,5]-H Sigmatropic Rearrangements in Molecules with the 5-Aza-2,4-pentadienal Skeleton

Mateo Alajarín,* Pilar Sánchez-Andrada,* Carmen López-Leonardo, and Ángel Álvarez

Departamento de Química Orgánica, Facultad de Química, Campus de Espinardo, Universidad de Murcia, 30100 Murcia, Spain

alajarin@um.es

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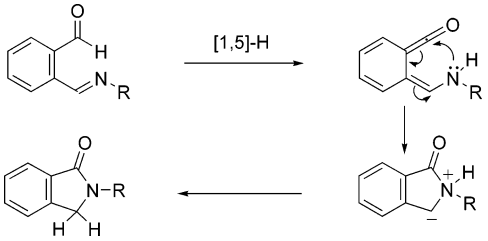

Condensation reaction of *o*-phthalaldehyde with primary amines is a classical method for the synthesis of phthalimidines. Although the intermediacy of the corresponding monoimines has been occasionally proposed, the mechanism of their transformation into phthalimidines remains to be elucidated. We present here theoretical evidence supporting a three-step mechanistic pathway for that transformation involving the [1,5]-H sigmatropic rearrangement of the aldehydic proton leading to an intermediate (aminovinyl)ketene as the key step. Other alternative routes have been calculated to be energetically less favorable. Similar transformations of related imino aldehydes enclosing a 5-aza-2,4-pentadienal skeleton via [1,5]-H shifts are also studied.

Introduction

During the last 90 years, a huge number of reactions involving *o*-phthalaldehyde have been investigated. The pioneering works of Thiele[1] and others researchers[2] have demonstrated that this compound behaves as a normal dialdehyde in some instances but more often reacts in atypical ways. Recently, Zuman has reviewed the reactions of *o*-phthalaldehyde with nucleophiles[3] such as H_2O, ammonia, amines, amino acids, thiols, etc., showing that the available information dealing with mechanisms and kinetics of these reactions is rather limited.

Phthalimidines (2,3-dihydro-1*H*-isoindol-1-ones, **1**) are heterocyclic compounds of biological relevance that have attracted considerable interest in recent years.[4] Their utilization as fluorescent markers for biochemical applications as well as precursors of electrically conductive polymers is also known.[5] The most widely used method for the synthesis of phthalimidines is the condensation of *o*-phthalaldehyde with primary amines, first reported

* To whom correspondence should be addressed. (M.A.) Phone: +34 968 367497. Fax: +34 968 364149.

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(2) (a) Amano, T.; Mizukami, S. *Yakugaku Zasshi* **1965**, *85*, 1035−1041; *Chem. Abstr*. **1966**, *64*, 8178b. (b) Amano, T.; Sakano, T. *Yakugaku Zasshi* **1969**, *89*, 164−172; *Chem. Abstr*. **1969**, *70*, 99665. (c). DoMinh, T.; Johnson, A. L.; Jones, J. E, Senise, Jr. O. P. *J. Org. Chem*. **1977**, *42*, 4217−4221. (d) Nan′ya, S.; Tange, T. Maekawa, E. *J. Heterocycl. Chem*. **1985**, *22*, 449−451. (e) Nan′ya, S.; Ishida, H.; Batsugan, Y. *J. Heterocycl. Chem*. **1994**, *31*, 1725−1726. (f) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev*. **1998**, *98*, 409−548.

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(4) See, for example: (a) Miyachi, H.; Azuma, A.; Hioki, E.; Kobayashi, Y.; Iwasaki, S.; Hashimoto, Y. *Chem Pharm. Bull*. **1996**, *44*, 1980−1982. (b) Belliotti, T. R.; Cetenko, W. A.; Connor, D. T.; Flynn, D. L.; Costlan, C. R.; Kramer, J. B.; Sircar, J. C. US Patent 4981865, 1991; *Chem Abstr*. **1991**, *114*, P206798x. (c) Funato, N.; Takayanagi, H.; Konda, Y.; Toda, Y.; Harigaya, Y.; Iwai, Y.; Omura, S. *Tetrahedron Lett*. **1994**, *35*, 1251−1254. (d) Link, J. T.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 552−553. (e) Goto, G.; Fukuda, N. *Eur. Pat. Appl*. **1994**, 602814; *Chem. Abstr*. **1994**, *121*, 134102k. (f) Grigg, R.; Gunaratne, H. Q. N.; Sridharan, V. *J. Chem. Soc., Chem. Commun*. **1985**, 1183−1184. (g) Takahashi, I.; Kawakami, T.; Hirano, E.; Yokota, H.; Kitajima, H. *Synlett* **1996**, 353−355. (h) For a review on phthalimidines, see: Kundu, N. G.; Khan, M. W.; Mukhopadhyay, R. *J. Indian Chem. Soc.* **2001**, *78*, 671−688.

(5) See, for example: (a) Ford, J. A.; Stenberg, J. F. Def. Publ. US Patent. Off. 887030, 1971; *Chem. Abstr*. **1971**, *75*, P89330b. (b) Tsuruta, Y.; Date, Y.; Kohashi, K. *J. Chromatogr*. **1990**, *502*, 178−183. (c) Azumaya, I.; Kagechika, H.; Fujiwara, Y.; Itoh, M.; Yamaguchi, K.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 2833−2838.

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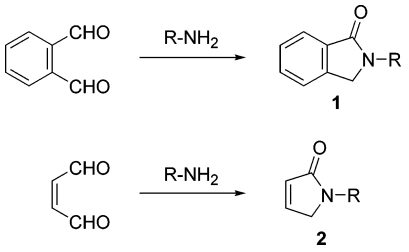
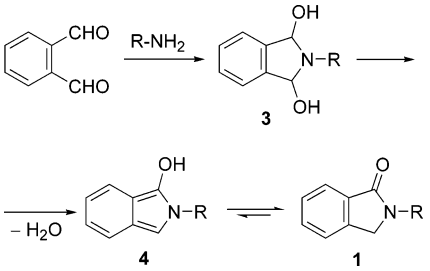
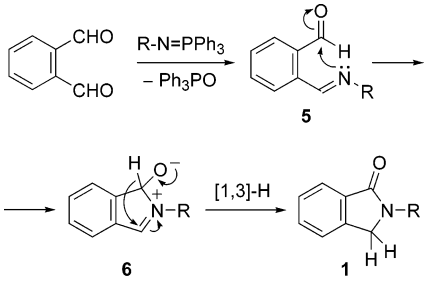
SCHEME 1. Synthesis of Phthalimidines (1) and *N*-Alkylpyrrolin-2-ones (2) from 1,2-Dicarboxaldehydes



SCHEME 2. Classical Mechanistic Proposal for the Formation of Phthalimidines from *o*-Phthalaldehyde and Amines



SCHEME 3. Guilard's Mechanistic Proposal



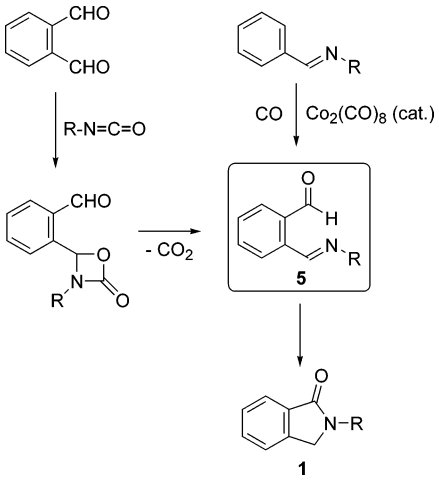
by Thiele.[1] The analogous reaction of *cis*-2-butene-1,4-dial with several amines led to the corresponding *N*-alkylpyrrolin-2-ones (**2**) (Scheme 1).[6]

The classical mechanistic proposal for explaining the formation of phthalimidines **1** in these reactions involves the participation of the corresponding 1*H*-2,3-dihydroisoindole-1,3-diols **3** as intermediates, arising from the double addition of the amine to the two formyl groups of *o*-phthalaldehyde, which then undergo dehydration to yield 1-hydroxy-2*H*-isoindoles (**4**) that promptly transform into phthalimidines by tautomerization (Scheme 2).[7]

Guilard[8] reported that the reaction of *o*-phthalaldehyde with iminophosphoranes yielded phthalimidines, suggesting the mechanism outlined in Scheme 3. First, the aza-Wittig reaction between the reactants should lead to monoimine **5**, which is proposed to convert into the dipolar intermediate **6** by nucleophilic attack of the iminic nitrogen onto the carbonylic carbon atom. A subsequent [1,3]-hydride shift would finally lead to phthalimidine **1**.

To our knowledge, this is the only report where monoimines **5** are proposed as precursors of phthalimidines **1**. Note that the reaction with amines (Scheme 2) could be also formulated as initially forming **5**. We agree with Guilard that monoimines **5** are key intermediates in the formation of phthalimidines, but we envisaged a different mechanistic sequence for its conversion into **1** (see below). Our proposal is based on two main facts: first, an exhaustive substructure search in chemical databases (CAS Registry file, CCDC database) retrieved no hits corresponding to the structure of monoimines **5** (where R = alkyl or aryl).[9] This would be quite surprising unless they are unstable compounds involved in further transformations. And second, we are aware of some synthetic sequences (others than those in Schemes 2 and 3) leading to **1** where monoimines **5** seem to be the most reasonable intermediates, such as the carbon monoxide insertion into benzylideneanilines,[10] and the reaction of *o*-phthalaldehyde with aromatic isocyanates[11] (Scheme 4).

SCHEME 4. Carbon Monoxide Insertion onto Benzylideneanilines and the Reaction of *o*-Phthalaldehyde with Aromatic Isocyanates Leading to Phthalimidines



To our knowledge, no computational studies dealing with iminoaldehydes **5** have been reported so far. We here consider a mechanistic proposal for explaining the transformation of **5** into **1** alternative to that in Scheme 3. Our approach is summarized in Scheme 5 and involves the initial [1,5]-H migration of the formyl H atom to the iminic nitrogen leading to (aminovinyl)ketene **7** and its cyclization to the zwitterion **8** which, after acid–base equilibrium, provides finally phthalimidine **1**.

Apparently, the key step of this pathway should be the first one, i.e., the [1,5]-H sigmatropic shift furnishing the (aminovinyl)ketene **7**. The [1,5]-H shifts are a class of sigmatropic rearrangements which were recognized by Woodward and Hoffmann in their chief 1965 publication on pericyclic reactions as orbital symmetry allowed, concerted processes involving suprafacial transfer of

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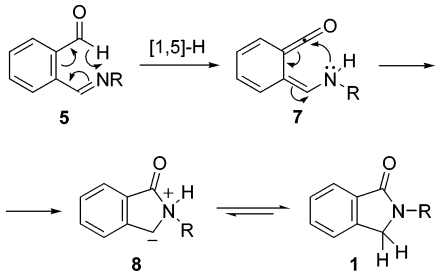
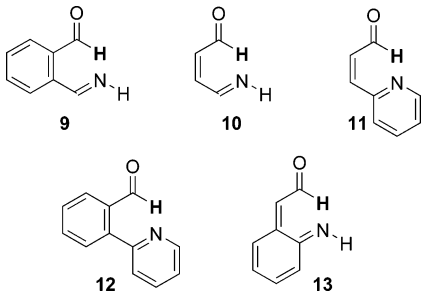
SCHEME 5. New Mechanistic Proposal for the Conversion of Iminoaldehydes 5 into Phthalimidines



hydrogen across a pentadienyl π-system.[12] They are unimolecular isomerizations and, often, most difficult to identify among the pericyclic reactions.[13] Other [1,5]-H shifts of the formyl proton in ortho-substituted benzaldehydes that have been previously reported, closely related to that discussed herein, are as follows: the transformation of *o*-phthalaldehyde into an enol−ketene which further cyclizes into phthalide,[14] the conversion of *o*-nitroso- and *o*-nitrobenzaldehyde into the respective oxime−ketene and acinitro ketene,[15] and that of *o*-vinylbenzaldehyde into a ketene−methide.[16] To our knowledge, no computational studies on these themes have been disclosed.

Here, we report the study by computational methods on the transformation of some imino-aldehydes by the pathway proposed in the literature (Scheme 3) as well as by our mechanistic proposal (Scheme 5). To this end, we selected the prototypical systems 2-(iminomethyl)-benzaldehyde (**9**) and (*E*)-4-imino-(*Z*)-2-butenal (**10**). In addition, to test the influence of the structure of the imino-aldehydes on the energy barrier corresponding to the key [1,5]-H shift process, we included in our study the following molecules: (*Z*)-3-(2-pyridyl)propenal (**11**), 2-(2-pyridyl)benzaldehyde (**12**), and the vinylogous *o*-quinoneimine (**13**), all containing the 5-aza-2,4-pentadienal skeleton (Chart 1).

CHART 1. Prototypical Aldehydes Selected for the Theoretical Study



Results and Discussion

All of the systems were studied computationally with the B3LYP[17] and RHF[18] theories in Gaussian 98[19] using the 6-31+G* and the 6-31G* basis set, respectively. Second-order perturbation analyses were achieved with the NBO (natural bond orbital) method.[20] NICS values were obtained at the B3LYP/6-31+G*//B3LYP/6-31+G* level with the GIAO (gauge-independent atomic orbital) method.[21] All energies discussed in the text are electronic energies at the B3LYP/6-31+G*//B3LYP/6-31+G* level unless otherwise noted. Zero-point vibrational energy corrections have been applied, but not scaled. The calculated energy barriers are gathered in Table 1. Geometry-optimized structures at the B3LYP/6-31+G* level for transition structures are shown in Figures 1−4. CASSCF[22](2,2)/6-31G*//B3LYP/6-31+G* calculations were performed in order to assess the possible biradical character of the transition states transforming the imino-aldehydes **9**−**13** into the corresponding ketenes via the [1,5]-H sigmatropic rearrangement. The results show that the closed-shell S_0 wave function is largely the predominant one (91−96%). Therefore, we can conclude that these TSs are described adequately with a single reference wave function.

2-(Iminomethyl)benzaldehyde (**9**) was our initial starting point. The intensive search along the potential energy surface provided three different paths connecting **9** with 2*H*-phthtalimidine (**16**) and 2*H*-isoindol-1-ol (**17**) (Figure 1), which are fully discussed below. We could not locate stationary points corresponding to the path converting **9** into **16** via a dipolar intermediate similar to **6** as proposed by Guilard[8] (Scheme 3).

Path *a*: [1,5]-H Sigmatropic Rearrangement and Further N−C Bond Formation. For the transformation of **9** into the (aminovinyl)ketene **14** via the transition state **TS1a** the computed energy barrier at the B3LYP/

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TABLE 1. Energy Barriers and Reaction Energies (ΔE_a and ΔE_{rxn} in kcal·mol^{-1}) Computed at the B3LYP/6-31+G* Theoretical Level with Zero-Point Vibrational Energy Correction Computed at the Same Level (the Marcus Barriers (Parentheses) Are Also Included)

	path ***a***				path ***b***	path ***c***
	via **TS1**	via **TS2**			via **TS3**	vi a**TS4**
ΔE_a (ΔE_{Marcus})	**9 → 14**	**14 → 15**	**15 → 16**	**15 → 17**	**9 → 17**	**9 → 15**
ΔE_{rxn}	37.79 (*24.17*) +27.04	0.0 −5.03	−51.12	−22.25	52.96 −0.24	48.64 +22.01
ΔE_a (ΔE_{Marcus})	**10 → 18**	**18 → 19**	**19 → 20**	**19 → 21**	**10 → 21**	**10 → 19**
ΔE_{rxn}	28.64 (*28.39*) +0.37	*a* *b*	−29.85[c]	−16.63[d]	42.75 −16.26	38.95 +0.37[e]
ΔE_a (ΔE_{Marcus})	**11 → 22**				**11 → 23**	**11 → 24**
ΔE_{rxn}	40.70 (*29.10*) +23.03				53.16 −0.13	52.96 +34.25
ΔE_a (ΔE_{Marcus})	**12 → 25**					
ΔE_{rxn}	50.90 (*26.71*) +48.14					
ΔE_a (ΔE_{Marcus})	**13 → 26**					
ΔE_{rxn}	16.85 (*27.41*) −21.29					

[a] **TS2b** could not be optimized at the B3LYP/6-31+G* level; see text for details. [b] **19** could not be optimized at the B3LYP/6-31+G* level; see text for details. [c] Energy difference between **18** and **20**. [d] Energy difference between **18** and **21**. [e] Energy difference between **18** and **9**.

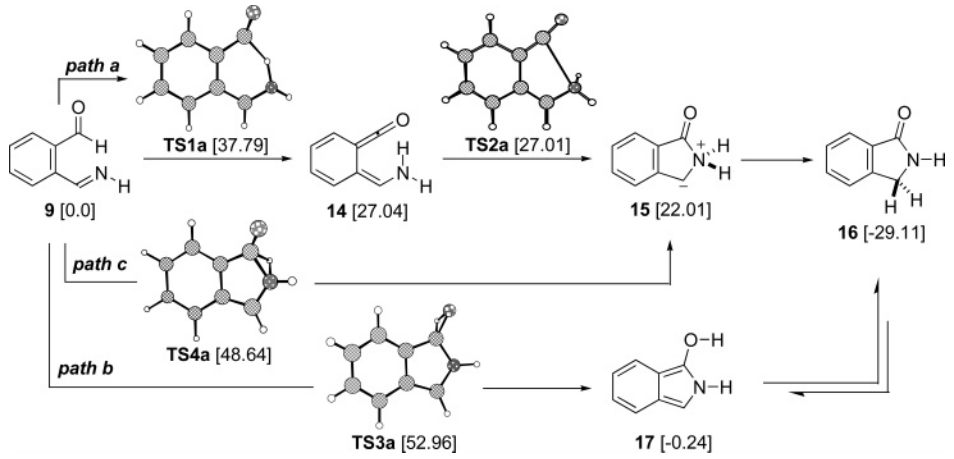


FIGURE 1. B3LYP/6-31+G*-optimized geometries and energetics for the transformation of 2-(iminomethyl)benzaldehyde (**9**) into 2*H*-phthalimidine (**16**) and 2*H*-isoindol-1-ol (**17**). In this and the following figures that include ball-and-stick representations, atoms are represented by increasing depth of shading in the order H, C, O and N.

6-31+G* level is 37.8 kcal·mol^{-1}. As shown in Figure 1, this process is endothermic by 27.0 kcal·mol^{-1}, probably due to the interruption of the aromaticity of the original benzene ring.[23] The second step is the attack of the iminic nitrogen onto the electrophilic sp-hybridized ketene carbon, via the transition structure **TS2a**, leading to the zwitterionic intermediate **15**. After the zero-point correction, **TS2a** is 0.03 kcal·mol^{-1} *below* (aminovinyl)ketene **14**; there is no barrier for this transformation,[24] as the intermediate **15** is 5.0 kcal·mol^{-1} lower in energy than ketene **14**. In the last step, an acid−base equilibrium would furnish 2*H*-phthalimidine (**16**). This conversion is exothermic by 51.1 kcal·mol^{-1}, and the global process is exothermic by 29.1 kcal·mol^{-1}. An acid−base equilibrium could also convert the zwitterion **15** into 2*H*-isoindol-1-ol (**17**), 22.2 kcal·mol^{-1} lower in energy.

Path *b*: [1,2]-H Sigmatropic Rearrangement with Simultaneous N−CO Bond Formation. We also located the stationary point **TS3a**, 53.0 kcal·mol^{-1} higher than 2-(iminomethyl)benzaldehyde (**9**). The analysis of the animation of its imaginary vibration revealed that the nuclear motion has no components associated with the formation of the N−CO bond but corresponds exclusively to the transfer of the hydrogen atom between the carbonyl carbon and the oxygen atoms. IRC calculations show that this transition state connects 2*H*-isoindol-1-ol (**17**) with a polar intermediate whose structure could be that of the molecule **6** (R = H) represented in Scheme 3. However, all attempts to optimize this structure without constraints resulted in the reactant aldehyde **9**. It is

(23) As supported by the magnetic properties of the six-membered ring in **14**; see the Supporting Information.
(24) As we will report in due course, our calculations support the pseudopericyclic nature of this 5-center, 6π-electron cyclization.

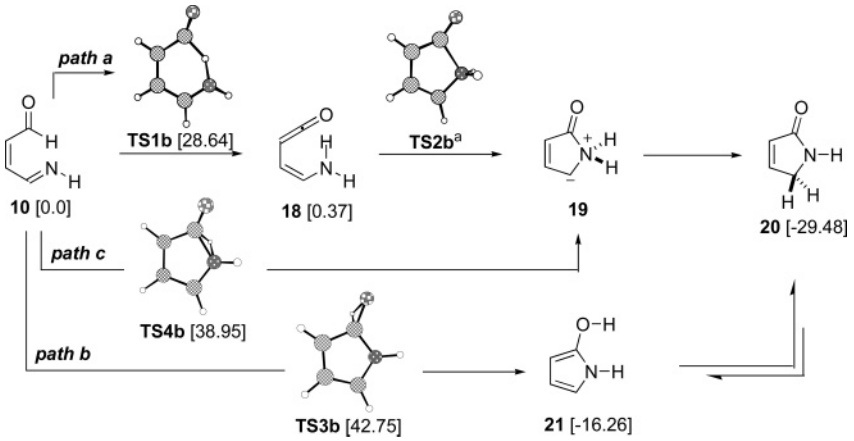


FIGURE 2. B3LYP/6-31+G*-optimized geometries and energetics for the transformation of *(E)*-4-imino-*(Z)*-2-butenal (**10**) into pyrrolin-2-one (**20**) and 1*H*-pyrrol-2-ol (**21**). [a]HF/6-31G*-optimized geometry.

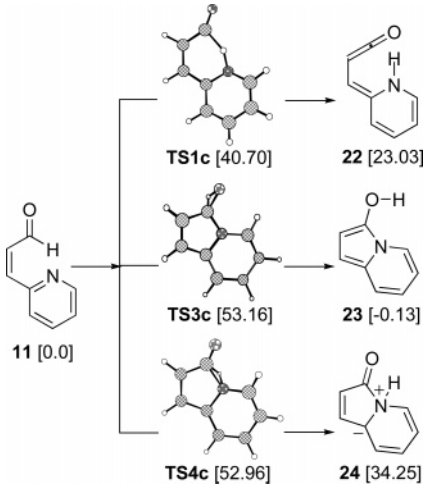


FIGURE 3. B3LYP/6-31+G*-optimized geometries and energetics for the three reaction paths found for the evolution of (*Z*)-3-(2-pyridyl)propenal (**11**).

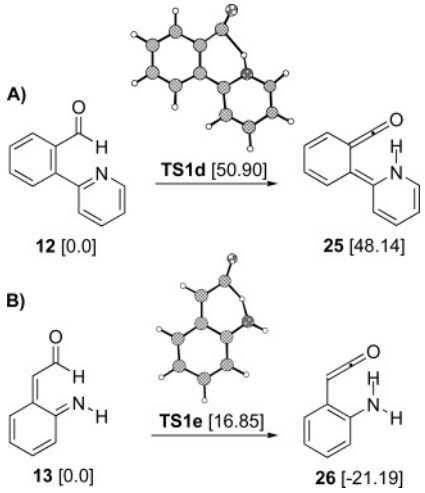


FIGURE 4. B3LYP/6-31+G*-optimized geometries and energetics for the [1,5]-H shift in (A) 2-(2-pyridyl)benzaldehyde (**12**) and (B) vinylogous *o*-quinonimine **13**.

worth recognizing that 2*H*-isoindol-1-ol (**17**) should exist predominantly in the tautomeric form 2*H*-phthalimidine (**16**).[25]

Path *c*: [1,3]-H Sigmatropic Rearrangement with Simultaneous N−CO Bond Formation. The conversion of **9** into the zwitterionic intermediate **15** may also occur via transition structure **TS4a** involving the formation of the N−CO bond with simultaneous migration of the formyl hydrogen to the nitrogen atom, the calculated energy barrier being 48.6 kcal·mol^{-1}. Again, the animation of the imaginary vibration calculated for **TS4a** only shows the movement of the hydrogen atom between the carbonylic carbon and the nitrogen atoms but does not exhibit components corresponding to the N−CO bond formation. IRC calculations show the connection of **TS4a** with the dipolar structure **6** (R = H) and the zwitterionic intermediate **15** (R = H).

According to the heights of the computed energy barriers for these three pathways (see Table 1), the transformation of **9** into **16** is predicted to be easier via the pathway ***a***, the mechanism represented in Scheme 5, the step involving the highest energy barrier being the first one, the [1,5]-H shift leading to **14**. The two other pathways (***b*** and ***c***) are energetically disfavored in relation to path ***a***. On the other hand, 2*H*-isoindol-1-ol (**17**) is 28.9 kcal·mol^{-1} higher in energy than 2*H*-phthalimidine (**16**), and therefore, this latter compound should be both the thermodynamically and kinetically controlled product.

Next, we explored the potential energy surface associated with the transformation of (*E*)-4-imino-*(Z)*-2-butenal (**10**) into pyrrolin-2-one (**20**) and 1*H*-pyrrol-2-ol (**21**). Here also the three-step pathway (path ***a***) is the energetically most favorable (see Figure 2 and Table 1). The energy barrier associated with the first step leading to the ketene (**18**), i.e., the [1,5]-H sigmatropic rearrangement, is 28.6 kcal·mol^{-1}, considerably lower than that calculated above for the conversion of **9** into **14**. We failed to locate **TS2b** and to optimize the zwitterionic intermediate **19** at correlated theory levels. All attempts for optimizing intermediate **19** without constraints resulted in the (aminovinyl)ketene **18**. Probably, this later compound easily transforms into the zwitterion,[24] which is converted by acid−base equilibrium into the pyrrolin-2-one (**20**),

(25) Katritzky, A. R.; Taylor, P. J. In *Physical Methods in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1971; Vol. 4, p 265.

this compound being 29.8 kcal·mol^{-1} lower in energy than the ketene **18**.

The transformation of the iminoaldehyde **10** into 1*H*-pyrrol-2-ol (**21**) (path ***b***) takes place via **TS3b**, the energy barrier being 39.0 kcal·mol^{-1} and the process exothermic by 16.3 kcal·mol^{-1}. Therefore, as in the preceding transformation, that of **9** into **16** and **17**, pyrrolin-2-one (**20**) is the thermodynamically and kinetically favored product.

Concerning to path ***c***, the transition structure **TS4b** is 42.7 kcal·mol^{-1} higher in energy than the iminoaldehyde **10**. IRC calculations show that this transition state connects with a polar intermediate similar to **6** in Scheme 3 and with the zwitterionic intermediate **19**. Again, all attempts to optimize these two structures without constraints resulted in the reactant aldehyde **10** and the (aminovinyl)ketene **18**, respectively.

Next, we explored the PES of (*Z*)-3-(2-pyridyl)propenal **11**. We located the transition structure **TS1c** corresponding to the [1,5]-H sigmatropic shift leading to the ketene **22**; the computed energy barrier was 40.7 kcal·mol^{-1} and the process was calculated to be endoergonic by 23.0 kcal·mol^{-1}. We assumed that the transformation of ketene **22** into the final 7*H*-indolizin-3-one should occur by the same pathway described for the two previous conversions **9** → **16** and **10** → **20** along path ***a***. The calculations predict that the alternative paths ***b*** and ***c*** for the evolution of the aldehyde **11** are, as in the preceding cases, energetically disfavored. Thus, the energetic cost for the cyclization of **11** into pyrido[2,1-*a*]-isoindol-6-ol (**23**) via **TS3c** was calculated to be 53.2 kcal·mol^{-1}, and the computed energy barrier associated to its conversion into the zwitterion **24**, through the transition structure **TS4c**, was 53.0 kcal·mol^{-1} (Figure 3).

Once we verified that the pathways ***b*** and ***c*** cannot compete with the reaction path ***a*** for the three previous conversions, for aldehydes **12** and **13** we investigated only the [1,5]-H sigmatropic shift for converting into the corresponding ketenes **25** and **26**. As expected, the value of the computed energy barrier for the [1,5]-H shift in 2-(2-pyridyl)benzaldehyde (**12**) was the largest one among all studied herein (50.9 kcal·mol^{-1}), whereas that corresponding to the conversion of vinylogous *o*-quinomethaneimine **13** into the ketene **26** was the lowest, only 16.8 kcal·mol^{-1} (Figure 4). The conversion of **12** into **25** implies the aromaticity loss in two rings, benzene and pyridine and that of **13** into **26** the formation of an aromatic benzene ring. These are the reasons that explain their respective energy barriers and why these two transformations were chosen for the present study.

There is an obvious correlation between the height of the energy barriers associated with the [1,5]-H sigmatropic rearrangement and the endo- or exothermicity of that process, which in turn depends largely on the gain or loss of aromaticity along the reaction coordinate. Thus, the lowest energy barrier is that corresponding to the transformation of **13** into **26**, the computed reaction energy being of −21.18 kcal·mol^{-1}. In contrast, the largest barrier is that associated with the conversion of 2-(2-pyridyl)benzaldehyde (**12**) into the ketene **25**, which is endothermic by 48.14 kcal·mol^{-1}. With the aim of excluding the effects of the different thermodynamic contributions to the energy barriers in these [1,5]-H shifts, we have used the Marcus theory.[26] Accordingly, the activation energy of a reaction (ΔE_a) is the sum of the intrinsic barrier and the thermodynamic contributions. The intrinsic barrier (ΔE_{Marcus}) represents the barrier of a thermoneutral process ($\Delta E_{rxn} = 0$), and can be calculated by applying the Marcus equation: $\Delta E_a = \Delta E_{Marcus} + 1/2\ \Delta E_{rxn} + (\Delta E_{rxn})^2/16(\Delta E_{Marcus})$. The values shown in Table 1 suggest that the presence of a benzene ring connecting the formyl and the imino-methyl functions by two ortho positions lowers the intrinsic barrier (ΔE_{Marcus} = 24.4 kcal·mol^{-1} for **9** → **14** vs 28.3 kcal·mol^{-1} for **10** → **18**, and 29.1 kcal·mol^{-1} for **11** → **22** vs 26.7 kcal·mol^{-1} for **12** → **25**). When the carbons 3 and 4 of the 5-aza-2,4-pentadienal skeleton form part of a benzene ring a modest decrease of the intrinsic barrier takes place (ΔE_{Marcus} = 27.4 kcal·mol^{-1} for **13** → **26** vs 28.3 kcal·mol^{-1} for **10** → **18**). By contrast, when the imino function belongs to a pyridine ring an increase in the intrinsic barrier is observed (ΔE_{Marcus} = 24.4 kcal·mol^{-1} for **9** → **14** vs 26.7 kcal·mol^{-1} for **12** → **25** and ΔE_{Marcus} = 28.3 kcal·mol^{-1} for **10** → **18** vs 29.1 kcal·mol^{-1} for **11** → **22**).

In relation to the geometry of these [1,5]-H shifts, it is worth pointing out that in the prototypical transition structure of the suprafacial [1,5]-H in 1,3-pentadiene, which has been studied extensively, the migrating hydrogen projects out of the plane, the HCCC dihedral angle being 30°.[27] The geometrical analyses of transition states **TS1a-e** show that all these [1,5] hydrogen shifts are also suprafacial. However, the value of the dihedral angle CCC(=O)H is notably lower (2°-11°) than the value of the dihedral angle CCNH (18°−26°). The nature of the atomic centers directly involved in the hydrogen shift in **TS1a**−**e** could affect the orbital topology of these transition states. Thus, the direct intervention of the nitrogen lone pair abstracting the hydrogen, or the transformation of the native formyl H−C bond in part of the LUMO ketene orbital, could make these transitions states *pseudopericyclic*[28] in nature. The results of the second-order perturbation analysis in **TS1a**,**b**, which shows the delocalization energies of electrons from filled NBOs into empty NBOs, as well their magnetic behavior, which has been obtained by calculating the NICS values along the *z*-axis perpendicular to the molecular plane, the intersection point being the (3,+1) ring critical point of the electron density (RCP) defined by Bader,[29] both show that these sigmatropic [1,5]-H shifts might be borderline cases in the continuum which must exist between pericyclic and pseudopericyclic [1,5]-H shifts (see the Supporting Information). Further studies on the orbital topology of a number of other [1,5]-H processes are currently in progress in our group.

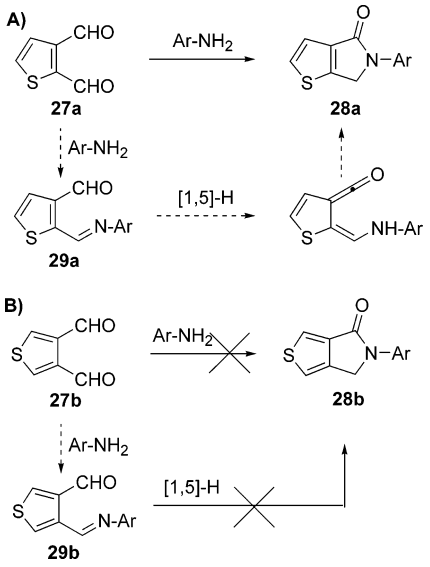
(26) For early reports on the Marcus theory, see: (a) Marcus, R. A. *J. Chem. Phys.* **1956**, *24*, 966−978. (b) Marcus, R. A. *Annu. Rev. Phys. Chem*. **1964**, *15*, 155−196. (c) Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891−899. For recent reports, see, for example: (d) Alabugin, I. V.; Manoharan, M.; Breiner, B.; Lewis, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 9329−9342. (e) Hayase, S.; Hrovat, D. A.; Borden, W. T. *J. Am. Chem. Soc.* **2004**, *126*, 10028−10034.

(27) See, for example: (a) Hess, B. A.; Baldwin, J. E. *J. Org. Chem*. **2002**, *67*, 6025−6033. (b) Jursic, B. S. *THEOCHEM* **1998**, *423*, 189−194. (c) Saettel, N. J.; Wiest, O. *J. Org. Chem.* **2000**, *65*, 2331−2336. (d) Jensen, F.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 3139−3140.

(28) For reports on pseudopericyclic [1,5] shifts, see, for example: (a) Birney, D. M. *J. Org. Chem.* **1996**, *61*, 243−251. (b) Zhou, C.; Birney, D. M. *J. Org. Chem.* **2004**, *69*, 86−94. (c) Bibas, H.; Koch, R.; Wentrup, C. *J. Org. Chem*. **1998**, *63*, 2619−2626. (d) Koch, R.; Wong, M. H.; Wentrup, C. *J. Org. Chem*. **1998**, *61*, 6809−6813.

(29) Bader, R. F. W. *Atoms in Molecules-A Quantum Theory*; Clarendon Press: Oxford, 1990; pp 13−52.

SCHEME 6. Reactions of Thiophene Dicarbaldehydes 27a (A) and 27b (B) with Arylamines



Despite our mechanistic proposal has not been previously considered in the literature, we have found several works,[30,31,32] besides those mentioned above, in which the results of some synthetic sequences can be easily explained by a mechanism including as key step a [1,5]-H shift analogous to that here proposed in mechanistic pathways ***a***. We will only emphasize the work of Guilard[32] describing that thiophene-2,3-dicarbaldehyde (**27a**) reacts with arylamines yielding thieno[2,3-*c*]pyrrol-4-ones (**28a**) (Scheme 6A), whereas similar reactions of thiophen-3,4-dicarbaldehyde (**27b**) did not lead to the expected bicycles **28b** (Scheme 6B).

If the transformation of dialdehydes **27** into bicycles **28** is assumed to occur either by a mechanism similar to that in Scheme 2 or by the intermediacy of imino-aldehydes **29** by a reaction path analogous to that represented in Scheme 3, it is difficult to explain the reluctance of the dialdehyde **27b** for transforming into **28b**. On the contrary, within the frame of our mechanistic proposal (Scheme 5) these results can be rationalized: the first step consisting of the concerted [1,5]-H shift may occur in **29a** but not in **29b** as this last compound lacks of the 5-aza-2,4-pentadienal skeleton (Scheme 6).

(30) Davies, L. S.; Jones, G. *Tetrahedron Lett*. **1970**, *11*, 3475−3478.
(31) Davies, L. S.; Jones, G. *J. Chem. Soc. C* **1971**, 2572−2576.
(32) Benachenchou, F.; Mesli, M. A.; El Borai, M.; Hanquet, B.; Guilard, R. *J. Heterocycl. Chem*. **1988**, *25*, 1531−1534.

Conclusions

In summary, these computational studies demonstrate that the three-step mechanism beginning with the [1,5] sigmatropic rearrangement of the formyl hydrogen atom (path ***a***) is a viable reaction pathway for the conversion of imino-aldehydes **9**−**13** into products enclosing a pyrrol-2-one moiety. These transformations can alternatively occur by two other reaction paths involving the simultaneous N−CO bond formation and an hydrogen shift (paths ***b*** and ***c***), but they cannot compete energetically with pathway ***a***. There is a noticeable influence of the electronic structure of the 5-aza-2,4-pentadienal skeleton of the imino-aldehydes **9**−**13** in the energy barrier of the [1,5]-H shift process leading to their corresponding (aminovinyl)ketenes. The gain or the loss of aromaticity in the aromatic rings on going from the imino-aldehydes to the respective ketenes causes either a decrease or an increase, respectively, of the computed energy barrier.

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Supporting Information Available: Table S1 including the chief electronic and energetic features for all stationary points discussed in the text. Cartesian coordinates of local minima and transition structures discussed in the text, selected orbital interactions of the NBO analysis, and NICS values. This material is available free of charge via the Internet at http://pubs.acs.org.

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