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On the [2+2] Cycloaddition of 2-Aminothiazoles and Dimethyl Acetylenedicarboxylate. Experimental and Computational Evidence of a Thermal Disrotatory Ring Opening of Fused Cyclobutenes

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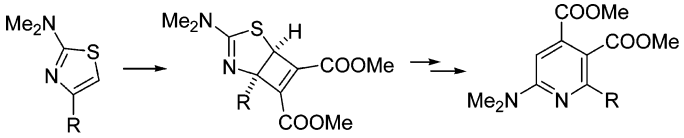
Received March 28, 2006



(R = CH=CHAr, Ar or Me)

The reaction of 2-(phenylamino)- and 2-(dimethylamino)thiazoles with dimethyl acetylenedicarboxylate led unexpectedly to dimethyl 6-(phenylamino)- and 6-(dimethylamino)-3,4-pyridinedicarboxylates. Those compounds reasonably result from a sequence of reactions initiated by a [2 + 2] cycloaddition of the alkyne to the formal C=C of the thiazole ring. These pyridines were obtained in nearly all the cases assayed as the *exclusive* reaction products under rather mild conditions and in fair to good yields. In contrast, the regioisomeric 2-amino-3,4-pyridinedicarboxylates, which would result from a [4 + 2] cycloaddition followed by sulfur extrusion, were only obtained in one particular case. The two reaction paths leading alternatively to both regioisomers were investigated computationally. The respective [2 + 2] and [4 + 2] cycloadducts were found to be formed stepwise from a common dipolar intermediate. Notably, the step following the [2 + 2] cycloaddition (i.e., the ring opening of the fused cyclobutene intermediate to give an *all*-cis 1,3-thiazepine) was found to take place in a disrotatory mode. Although geometric constraints and electronic factors may reduce the energy for the disrotation, the implication of the fused five-membered ring in the electronic reorganization leading to the 1,3-thiazepine is determinant. In this sense, this step could be regarded also as a thermally allowed six-electron five-center disrotatory electrocyclic ring opening. The proposed mechanism was experimentally supported by the isolation of several intermediates and other experimental facts.

Introduction

There is considerable interest for both synthetic and mechanistic reasons in cycloadditions where five-membered ring heterocycles participate, but only a few examples dealing with thiazoles as starting materials have been reported. This is probably due to the low reactivity of these heterocycles caused by their considerable aromatic stabilization.[1] The first cycloaddition involving thiazoles was reported in 1965[2] describing the hetero Diels−Alder reaction of 4-methyl-5-ethoxythiazoles with dimethyl fumarate at 200 °C to give pyridines after sulfur extrusion. Later on, Weiss and co-workers reported that thiazole rings reacted intramolecularly with acetylenes, leading to fused thiophenes by an intramolecular Diels−Alder followed by elimination of 1 mol of nitrile.[3] Recently, Wong and Ye described the intermolecular version of this process reacting 4-methyl and 4-phenylthiazole with bis(trimethylsilyl)acetylene and diphenylacetylene.[4]

The reaction of thiazoles with dimethyl acetylenedicarboxylate (DMAD) deserves special interest. The controversial nature

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(1) *Thiazole and its Derivatives*; Metzger, J. V., Ed.; Wiley & Sons: New York, 1979.

(2) Takeda Chem. Ind., Ltd. Fr. Patent 1,400,843, 1965; *Chem. Abstr.* **1965**, *63*, 9922.

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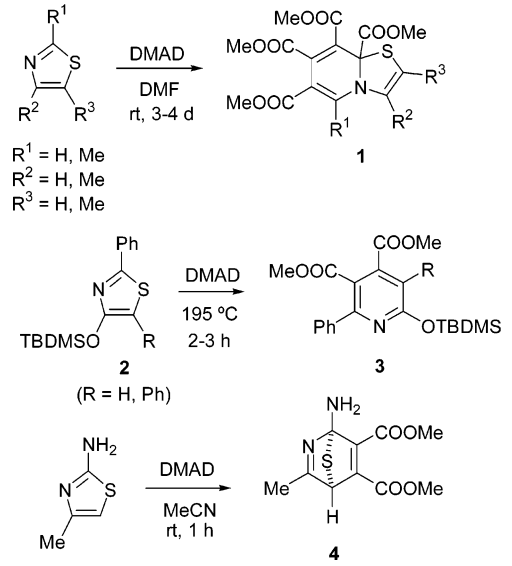
10.1021/jo060664c CCC: $33.50
Published on Web 06/16/2006

SCHEME 1. Previously Reported Reactions between Thiazoles and DMAD



of the reaction products between thiazole, 2-, 4-, or 5-methylthiazole, and 2,5-dimethylthiazole and DMAD[5] was finally established by Acheson and co-workers, who assigned their structures, on the basis of NMR spectroscopy and X-ray analysis, to the tetramethyl pyrido[2,1-*b*]thiazole-6,7,8,8a-tetracarboxylates **1** (Scheme 1).[6] These species are not the expected hetero Diels−Alder adducts but the result of two successive additions of two molecules of DMAD across the C═N bond of the heterocycle, followed by cyclization and further rearrangement of the resulting product.[6] Surprisingly, electron-donating substituents at the heterocycle change completely the course of the reaction as it was later described. Thus, the reaction of the thiazoles **2** with DMAD gives the pyridines **3** through an hetero Diels−Alder reaction and further sulfur extrusion,[7] although in this case extremely harsh conditions were required (Scheme 1).

The activating effect of the amino functionality in the reaction of 2-(dimethylamino)thiazole toward electron-poor reagents such as diethyl azodicarboxylate, tosyl isocyanate, or ketenes has been also demonstrated.[8] Nevertheless, no cycloadducts were formed in these reactions, but only Michael-type products resulting from the functionalization at the 5-position of the thiazole ring. This activating effect was evident when 2-amino-4-methylthiazole was allowed to react with DMAD. From this reaction, conducted at room temperature, a new adduct was isolated in 42% yield whose structure was assigned to the 7-thia-2-azabicyclo[2.2.1]-hepta-2,5-diene **4** (Scheme 1).[9] The formation of **4** was explained as the result of a [4 + 2] cycloaddition in which the heterocycle acts as heterodiene.

(5) (a) Reid, D. H.; Skelton, F. S. *Tetrahedron Lett.* **1964**, 1797−1802. (b) Acheson, R. M.; Foxton, M. W.; Miller, G. R. *J. Chem. Soc.* **1965**, 3200−3206.

(6) (a) Abbott, P. J.; Acheson, R. M.; Eisner, U.; Watkin, D. J.; Carruthers, J. R. *J. Chem. Soc., Chem. Commun.* **1975**, 155−156. (b) Abbott, P. J.; Acheson, R. M.; Eisner, U.; Watkin, D. J.; Carruthers, J. R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1269−1278.

(7) Kopka, I. E. *Tetrahedron Lett.* **1988**, *29*, 3765−3768.

(8) (a) Dondoni, A.; Medici, A.; Venturoli, C. *J. Org. Chem.* **1980**, *45*, 621−626. (b) Medici, A.; Pedrini, P.; Venturoli, C.; Dondoni, A. *J. Org. Chem.* **1981**, *46*, 2790−2793.

(9) The adduct **4** was isolated along with other secondary products from the reaction of the amino functionality with the acetylenic ester. See: Crank, G.; Khan, H. R. *J. Heterocycl. Chem.* **1985**, *22*, 1281−1284.

CHART 1. General Structure of 2-Aminothiazoles 5

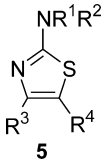


TABLE 1. 2-Amino-, 2-(Phenylamino)-, and 2-(Dimethylamino)thiazoles 5a−i

R^1	R^2	R^3	R^4	thiazole
H	H	(*E*)-4-MeC_6H_4CH═CH	H	**5a**
H	Ph	(*E*)-4-MeC_6H_4CH═CH	H	**5b**
Me	Me	(*E*)-4-MeC_6H_4CH═CH	H	**5c**
Me	Me	Ph	H	**5d**
Me	Me	4-ClC_6H_4	H	**5e**
Me	Me	4-BrC_6H_4	H	**5f**
Me	Me	4-MeC_6H_4	H	**5g**
Me	Me	4-$MeOC_6H_4$	H	**5h**
Me	Me	Ph	Me	**5i**

TABLE 2. Reaction Conditions and Yields of Pyridines 6 and 7 Obtained from 2-Aminothiazoles 5a−i and DMAD[a]

entry	2-aminothiazole	*T* (°C)	*t* (h)	product	**6** (%)	**7** (%)
1	**5a**	25	24	**a**	0[b]	0[b]
2	**5b**	25	12	**b**	36	0
3	**5c**	25	12	**c**	70	0
4	**5d**	25	12	**d**	74	0
5	**5e**	25	6 d (72[c])	**e**	86 (60)	0 (20)
6	**5f**	25	6 d	**f**	80	0
7	**5g**	25	12	**g**	85	0
8	**5h**	25	12	**h**	91	0
9	**5i**	reflux	12	**i**	10	15

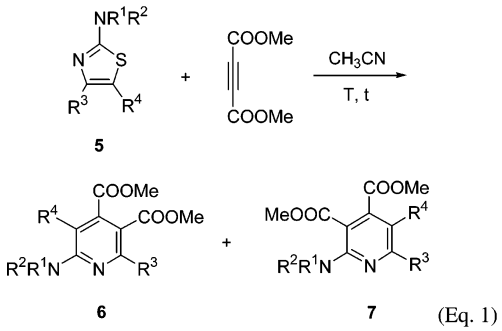
[a] The reactions were run with an excess (3 equiv) of DMAD. [b] A complex mixture of products was obtained. [c] DMAD (6 equiv) was used.

Herein, we disclose our findings in the reaction of 2-aminothiazoles **5** with DMAD. The main reaction products, 6-(phenylamino)- and 6-(dimethylamino)pyridines, are formed under rather soft conditions and in good yields. Computational data and the isolation of some intermediates support that the formation of these final products is the result of an unexpected [2 + 2] cycloaddition of the DMAD to the heterocycle across the formal C═C of the thiazole ring in the first step. Subsequent ring opening, 6π-electrocyclization, and sulfur extrusion would lead to the final products. Computational and experimental data also demonstrate that the ring-opening of the fused cyclobutene intermediate takes place in a disrotatory mode. Chart 1 shows the general structure of 2-aminothiazoles **5**.

Results and Discussion

Experimental Results. The 2-amino-, 2-(phenylamino)-, and 2-(dimethylamino)thiazoles **5a−i** (Table 1) were obtained from the corresponding α-haloketones and thioureas (Hantzsch synthesis) in good yields (see Supporting Information). The thiazoles **5a−c** were allowed to react with DMAD (3 equiv) in acetonitrile at room temperature (eq 1, Table 2, entries 1−3). Under these conditions, **5b,c** gave the pyridines **6b,c** as the only reaction products. Pyridines **6** are regioisomeric of **7**, the initially expected reaction products resulting from a [4 + 2] cycloaddition of the DMAD to the thiazole ring acting as heterodiene, and further sulfur extrusion. The best result coming from the 4-alkenyl-substituted thiazoles **5a−c** was obtained by using the 2-(dimethylamino)thiazole **5c** (entry 3). In contrast, the reaction

between the thiazole **5a**, with a free amino group at the 2-position, and DMAD led to a complex mixture of products (entry 1).



(Eq. 1)

The formation of the pyridines **6** as the exclusive reaction products is rather general. Thus, the reaction of the 2-(dimethylamino)-4-arylthiazoles **5d**−**h** with DMAD (3 equiv) under the same reaction conditions (acetonitrile, 25 °C) led to **6** as single products in fair to good yields (entries 4−8). With **5e**, an increase of the number of equivalents of DMAD (from 3 to 6) and decrease in the reaction time (from 6 d to 72 h) led to a mixture of the regioisomeric pyridines **6e** and **7e** in a 3:1 ratio (entry 5, parenthesis). Notably, aromatic groups bearing electron-donating substituents at the 4-position of the thiazole ring accelerate the reactions (entries 5 and 6 versus entries 7 and 8). The reaction of the 2-(dimethylamino)-5-methyl-4-phenylthiazole (**5i**) gave a mixture of the regioisomeric **6i** and **7i** both in low yields (entry 9). In this last case, the reaction temperature needed to be increased from 25 to 83 °C (refluxing acetonitrile).

The structural characterization of the regioisomeric pyridines **6** and **7** was done on the basis of their spectroscopic data (^{1}H- and ^{13}C NMR, and IR), mass spectra, and elemental analyses. The location of all substituents in **6** and **7** (except **6i** and **7i**, see below) was determined on the basis of the ^{1}H,^{1}H−NOESY spectra of **6c** and **7e**. The other tetrasubstituted pyridines **6b** and **6d**−**h** were identified by comparison of their ^{1}H- and ^{13}C NMR data with that of **6c**. In these terms, the proton located at the 5-position in the pyridine ring was the most informative signal, appearing at a typical chemical shift (6.70−6.84 ppm). This proton resonates at higher frequency (7.34 ppm) in the pyridine **7e**. In addition, the structure of **6c** was unambiguously determined by single-crystal X-ray diffraction analysis (see Supporting Information). The most informative NOE effects in compounds **6c** and **7e** are depicted in Figure 1. The main feature of the NOESY spectrum of **6c** was the strong NOE observed between the proton directly attached to the pyridine ring and those of the dimethylamino group, which was absent in the spectrum of **7e**. On the contrary, the NOESY spectrum of **7e** showed a cross-peak relating the proton located at the pyridine nucleus and the ortho protons of the aromatic substituent at the 6-position.

The differentiation between the regioisomeric pyridines **6i** and **7i** was done again on the basis of their ^{1}H,^{1}H−NOESY spectra. Analogously to **6c**, the spectrum of **6i** showed cross-peaks relating the methyl group at the 5-position and the protons of the dimethylamino substituent at the 6-position in the pyridine ring. On the contrary, for **7i** a strong NOE effect was observed between the methyl group located at the 5-position in the pyridine ring and the ortho protons of the phenyl group (Figure 1).

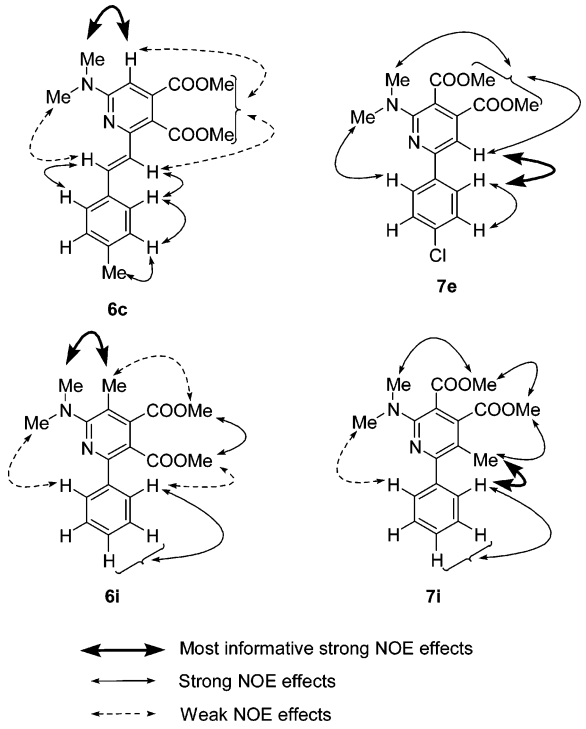


FIGURE 1. Contacts from the ^{1}H,^{1}H−NOESY spectra of **6c**, **6i**, **7e**, and **7i**.

The preparation of the dimethyl 6-(dimethylamino)-2-phenyl-(methyl)-3,4-pyridinedicarboxylates **6d** and **6j** (Scheme 2) has been previously reported in the literature, although they were obtained in low yields or as mixture of products. Thus, treatment of the 2-azavinamidinium perchlorate **8** with NaH led to the 2-azabutadiene **9**, which was reacted in situ with DMAD to give **6d** in 28% yield (Scheme 2).[10] Pyridine **6j** was prepared from the 2-azadiene **10** and DMAD, and it was isolated along with the pyridine **6k**.[11] The simultaneous formation of pyridines **6j** (32%) and **6k** (40%) was rationalized in terms of a [1,3]-shift of the Me_2N group in the initial [4 + 2] adduct **11**, followed by elimination of Me_2NH or MeSH from the intermediate **12**.

We attempted the synthesis of the pyridine **6j** by using the methodology described in this article, reacting the 2-(dimethylamino)-4-methylthiazole **5j** with DMAD (Scheme 3). However, under our standard reaction conditions (acetonitrile, 25 °C, 12 h, excess of DMAD), that reaction led to a complex mixture of products. When the reaction was run with only 1 equiv of DMAD, the 2-thia-4-azabicyclo[3.2.0]hepta-3,6-diene **13j** could be isolated in 52% yield. Under these reactions conditions, the pyridine **6j** was also formed in small amounts (10%). The structural characterization of **13j** was accomplished on the basis of its spectroscopic data (^{1}H- and ^{13}C NMR, and IR), mass spectrum, and elemental analysis. Its IR spectrum presents a band at 727 cm^{-1} typical from a cis-double bond in a strained ring.[12] Notably, the ^{1}H NMR spectrum of **13j** exhibits a signal characteristic of a bridgehead proton at δ 4.33 ppm. The stereochemistry of **13j** must be cis since a trans fusion of a cyclobutene ring to a five- or six-membered ring can be ruled

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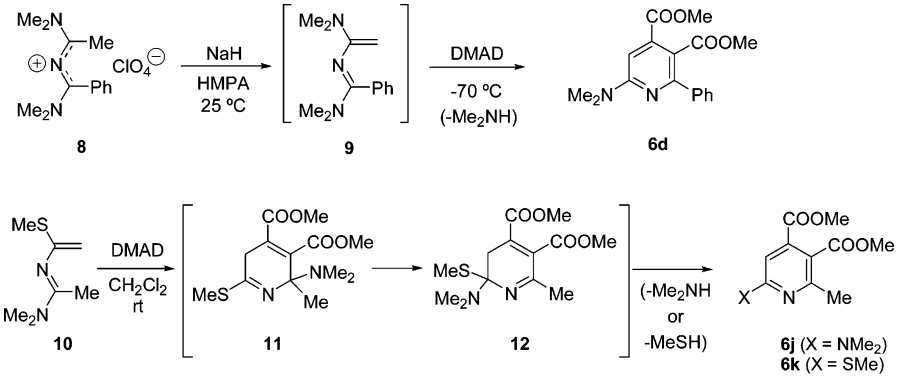
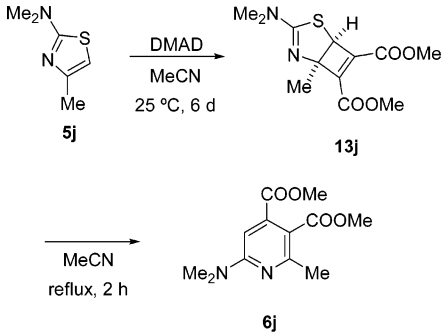
SCHEME 2. Previously Reported Methodologies for the Synthesis of 6d and 6j



SCHEME 3. Sequential Conversion of Thiazole 5j into Bicycle 13j and Pyridine 6j



out on the basis of the steric strain involved.[13] This stereochemical assignment was further confirmed by an ^{1}H,^{1}H−NOESY spectrum (see Supporting Information). Thus, a contact was observed relating both substituents, the proton and the methyl group, located at the bridgehead carbon atoms. The bicycle **13j** cleanly transformed into the pyridine **6j** in 90% yield when a solution in acetonitrile was heated at reflux temperature (Scheme 3).

The conversion of **13j** into **6j** in toluene-d_8, $CDCl_3$, and CD_3CN was followed by ^{1}H NMR spectroscopy, and their respective rates were compared. As shown in Figure 2, the reaction was faster in the more polar CD_3CN. On the contrary, there was no significant difference by using $CDCl_3$ or toluene-d_8. This reaction was also conducted in the presence of 1 equiv of CF_3COOH by using $CDCl_3$ as solvent. Under these conditions, no conversion of **13j** was observed (see below).

With all these experimental results in our hands and on the basis of the chemical knowledge and the bibliographic precedents related with this transformation, we propose the mechanism depicted in Scheme 4 for explaining the formation of the pyridines **6** and **7** in the reaction of 2-aminothiazoles **5** with DMAD. A [2 + 2] cycloaddition involving the C=C bond of the thiazole ring and the C≡C bond of the DMAD should lead to the cycloadduct **13**. Since the [2_s + 2_s] cycloaddition is not a thermally allowed process according to the Woodward−Hoffmann rules and the allowed [2_s + 2_a] requires a geometrically distorted transition state that should be unfavorable except under unusual circumstances,[14] many chemists have reasoned that [2 + 2] cycloadditions may occur in a stepwise manner involving diradical or dipolar intermediates.[15] There is experimental evidence of thermal [2 + 2] cycloadditions proceeding via two-step mechanisms through zwitterionic intermediates. Among these processes are the reactions of tetracyanoethylene with electron-rich alkenes such as enol ethers,[16] tetralkoxyethylenes,[17] and thioenolethers.[18] Dipolar intermediates have been also invoked as intermediates for the [2 + 2] cycloaddition reactions of electron-deficient acetylenes and alkenes.[19] Reinhoudt and others demonstrated that 3-amino-4,5-dihydrothiophenes,[20] 3-aminothiophenes,[21] and related heterocycles[12,22] react with DMAD similarly to normal enamines[23] giving the corresponding [2 + 2] cycloadducts which usually

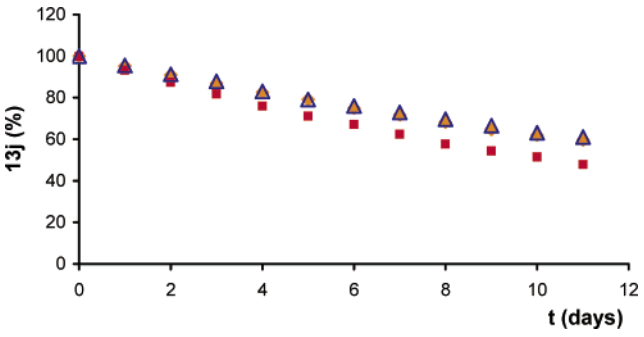


FIGURE 2. Plots representing the percentage of **13j** in the reaction mixture (**13j** + **6j**) versus the reaction time (days) in CD_3CN (red, ■), $CDCl_3$ (orange, ◆), and toluene-d_8 (△).

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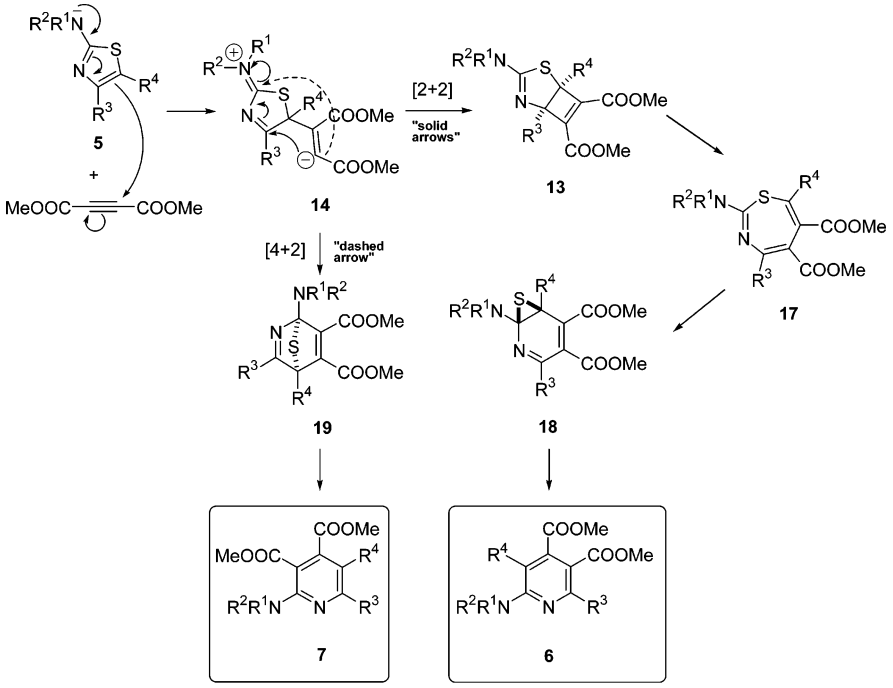
(21) (a) Reinhoudt, D. N.; Kouwenhoven, C. G. *J. Chem. Soc., Chem. Commun.* **1972**, 1233−1234. (b) Reinhoudt, D. N.; Kouwenhoven, C. G. *Tetrahedron* **1974**, *30*, 2093−2098. (c) Reinhoudt, D. N.; Trompenaars, W. P.; Geevers, J. *Tetrahedron Lett.* **1976**, 4777−4780. (d) Verboom, W.; Visser, G. W.; Trompenaars, W. P.; Reinhoudt, D. N. *Tetrahedron* **1981**, *37*, 3525−3533. (e) Reinhoudt, D. N.; Geevers, J.; Trompenaars, W. P. *J. Org. Chem.* **1981**, *46*, 424−434.
(22) (a) Paquette, L. A.; Begland, R. W. *J. Am. Chem. Soc.* **1966**, *88*, 4685−4692. (b) Reinhoudt, D. N.; Kouwenhoven, C. G. *Tetrahedron Lett.* **1972**, 5203−5204. (c) Reinhoudt, D. N.; Kouwenhoven, C. G. *J. Chem. Soc., Chem. Commun.* **1972**, 1232−1233. (d) Temciuc, E.; Hörnfeldt, A.-B.; Gronowitz, S.; Stålhandske, C. *Tetrahedron* **1995**, *51*, 13185−13196.

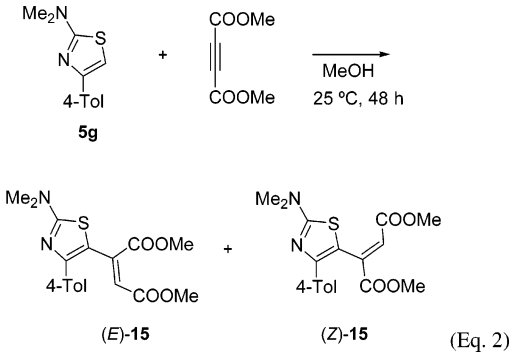
SCHEME 4. Proposed Mechanism for Rationalizing the Formation of Pyridines 6 and 7



evolve forming more stable species. Contrary to expectation, these processes take place with high levels of stereoselectivity which have been rationalized on the basis of the formation of 1,4-dipolar intermediates showing restricted rotation of the two poles caused by electrostatic interaction (tied ion pair).[21d,24]

In our case, the 5-position of the thiazole ring in **5** is activated by the presence of the amino group at carbon 2. This fact has precedents in the participation of 2-(dimethylamino)thiazoles in nucleophilic substitution reactions[8] and was, in our hands, evidenced by the apparition at low frequency of the proton at this position in the NMR spectra of thiazoles **5a**−**h** and **5j**.[25] We propose that the nucleophilic attack of the thiazole, at its 5-position, to DMAD would give the zwitterionic intermediate **14** whose cyclization would lead to the bicycle **13** (Scheme 4). A methyl substituent at the reactive position (5) as in **5i** (R^4 = Me) would make the approach of the electrophile more difficult due to steric reasons, and, consequently, higher temperature would be required as it was observed (see above). Independent of the mechanism, concerted or stepwise, the cis-stereochemistry observed for the cycloadduct **13j** is imposed by steric constraints as mentioned before.[13]

We sought evidence for the implication of the zwitterionic intermediate **14** by trapping experiments.[26] Thus, the thiazole **5g** was reacted with 1 equiv of DMAD by using methanol as solvent. Under these conditions, a mixture of the diastereomeric thiazoles (*E*)- and (*Z*)-**15** in a 24:76 ratio was formed (90% overall yield) (eq 2).[27] The structure of the diastereomer (*Z*)-**15** was unambiguously determined by single-crystal X-ray diffraction analysis (see Supporting Information). The isolation of (*E*)-**15** and (*Z*)-**15** was taken as proof of the participation of the dipolar intermediate **14** in the formation of the bicycle **13j** and thus of the stepwise nature of the mechanism in discussion also supported by computational data (see below).



Turning back to the proposed mechanistic pathway described in Scheme 4, the electrocyclic ring opening of the cyclobutene ring in **13**, or in other words, the expansion of the bicyclic skeleton, would lead to the seven-membered ring, the 1,3-thiazepine **17**. Woodward and Hoffmann[28] and Longuet-Higgins and Abrahamson[29] discussed the two possible modes of concerted thermal ring opening of cyclobutene systems, namely conrotary and disrotatory. In principle, the symmetry-allowed conrotatory opening might lead to the formation of an energetically unfavorable seven-membered ring with a trans double bond. However, it has been proposed that in compounds in which the cyclobutene ring is cis-annulated to another one possessing less than eight atoms, a conrotatory process is unlikely, and the disrotatory opening is observed.[22a,30] Through this mechanism, the more stable all-cis 1,3-thiazepine **17** would be formed.

The 1,3-thiazepines are little known compounds. Most of their bibliographic antecedents deal with the relevant biological

(23) Brannock, K. C.; Burpitt, R. D.; Goodlett, V. W.; Thweatt, J. G. *J. Org. Chem.* **1963**, *28*, 1464−1468.

(24) Epiotis, N. D.; Shaik, S. *J. Am. Chem. Soc.* **1978**, *100*, 9−17.

(25) These protons appear in the range of 5.95−6.68 ppm and, thus, at lower frequencies compared to the chemical shift of this proton in the thiazole ring (7.41 ppm).

(26) The participation of dipolar intermediates in some of these reactions is supported by the *high yields* of fumarates obtained when the reaction is conducted in methanol, where a proton is available to quench the zwitterion. See: Acheson, R. M.; Brisdon, J. N.; Cameron, T. S. *J. Chem. Soc., Perkin Trans. 1* **1972**, 968−975.

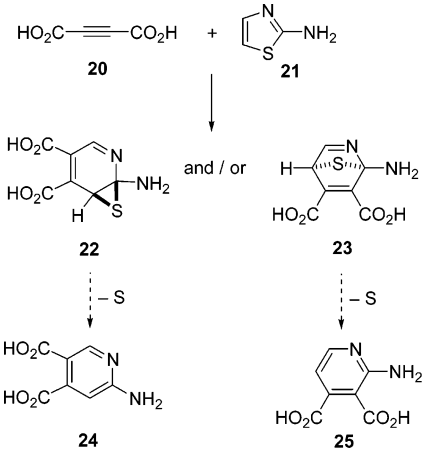
activities of their polyhydroderivatives.[31] Although little is known about the chemical behavior of 1,3-thiazepines,[32] it should be analogous to that of its isomeric 1,4-thiazepines, which show a pronounced instability caused by their ability to undergo sulfur extrusion.[33] Accordingly, we propose that the 1,3-thiazepine **17** would evolve rapidly through a symmetry-allowed disrotatory 6π-electrocyclic ring closure to give its valence isomer, the 7-thia-2-azanorcaradiene **18**. Finally, desulfurization of **18** would give rise to the pyridine **6**.

Alternatively, the zwitterionic intermediate **14** could lead to the 7-thia-2-azabicyclo[2.2.1]hepta-2,5-diene **19**, the formal [4 + 2] cycloadduct, through the attack of its carbanionic center to the 2-position of the heterocycle (Scheme 4). Further sulfur extrusion in **19** would give the regioisomeric pyridine **7**. This reaction path proved to be operative, although in low extension, only in two cases (entries 5 and 9 in Table 2).

Computational Study

As mentioned earlier, [2 + 2] cycloadditions between electron-deficient acetylenes and alkenes may occur in a stepwise manner since the [2_s + 2_s] cycloaddition is not a thermally allowed process according to the Woodward−Hoffmann rules, and the allowed [2_s + 2_a] requires an unfavorable geometrically distorted transition state.[14,15] Consequently, zwitterions have been proposed as intermediates in these types of reactions.[19−23] The mechanism of the [2 + 2] cycloaddition of electron-deficient acetylenes and π-excedent five-membered heterocycles has not yet been scrutinized computationally. In contrast, the mechanisms of the Diels−Alder reaction between DMAD and 1-methylpyrrole[34] and acetylenedicarboxylic acid and 2-methylfuran[35] have been approached by ab initio and DFT calculations showing that the reactions take place in a stepwise manner with the initial formation of zwitterionic intermediates. PM3 semiempirical methods have also showed that the reaction of 6-aminopyrimidin-4(3*H*)-ones with DMAD lead to the corresponding [4 + 2] cycloadducts on a concerted mode.[36]

SCHEME 5. Reaction between Acetylenedicarboxylic Acid (20) and 2-Aminothiazole (21) Leading to 6-Amino-3,4-pyridinedicarboxylic Acid (24) and 2-Amino-3,4-pyridinedicarboxylic Acid (25)

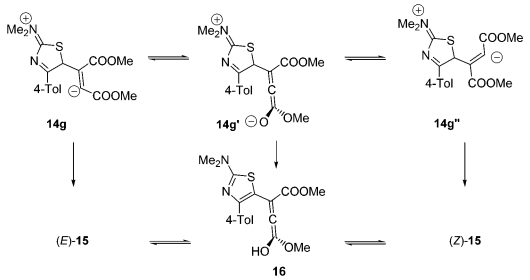


For simplicity, to model the reaction of DMAD with the thiazoles **5** presented in the experimental part of this work, we selected as reactants the more simple structures acetylenedicarboxylic acid (**20**) and 2-aminothiazole (**21**). We have carried out an intensive exploration of the potential energy surface associated with the reaction of **20** with **21** leading to the thiazanorcaradiene **22** (coming from successive transformations of the [2 + 2] cycloadduct initially formed) and 7-thia-2-azabicyclo[2.2.1]hepta-2,5-diene (**23**) (the corresponding [4 + 2] cycloadduct) (Scheme 5). The sulfur extrusions giving 6-amino-3,4-pyridinedicarboxylic acid (**24**) and 2-amino-3,4-pyridinedicarboxylic acid (**25**) as final products have not been included in this theoretical approach as it has been well-documented that the sulfur extrusion in related heterocycles takes place in several steps without appreciable energetic cost.[37]

We have found the stepwise mechanisms outlined in Figure 3 for the formation of products **22** and **23**. Both the [2 + 2] (path A, blue color) and the [4 + 2] (path B, red color) cycloaddition reactions, leading respectively to the cycloadducts **26** and **23**, take place in a stepwise manner, involving the initial formation of a common polar intermediate **INT**. No transition states corresponding to concerted [4 + 2] or [2 + 2] cycloaddition reactions between **20** and **21** could be located.

Figure 3 displays the qualitative reaction profile at the B3LYP/6-31+G* theoretical level and the location of the stationary points for the reaction between acetylenedicarboxylic

(27) The reaction pathway to give the diastereomeric compounds **15** may involve the formation of the bent dipole **14g**, which can easily equilibrate with **14g″** through the cumulenic **14g′**. The (*E*)- and (*Z*)-**15** adducts should be formed by migration of the hydrogen of the former C5 of the thiazole in **14g** and **14g″** or, alternatively, from the allenic structure **16** by a tautomeric equilibrium. See: (a) Caramella, P.; Houk, K. N. *Tetrahedron Lett.* **1981**, *22*, 819−822. (b) Dickstein, J. I.; Miller, S. I. In *The Chemistry of the Carbon−Carbon Triple Bond*; Patai, S., Ed.; Wiley: New York, 1978; pp 819−826.



(28) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395−397.

(29) Longuet-Higgins, H. C.; Abrahamson, E. W. *J. Am. Chem. Soc.* **1965**, *87*, 2045−2046.

(30) (a) Epiotis, N. D. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 751−780. (b) Seebach, D. In *Houben-Weyl, Methoden der organischen Chemie*; Müller, E., Ed.; G. Thieme Verlag: Stuttgart, 1971; Vol. IV/4, pp 418−419.

(31) See, for example: (a) Di Cesare, M. A.; Campiani, G.; Butini, S. Patent WO2005097797, 2005; *Chem. Abstr.* **2005**, *143*, 405933. (b) Patel, R. N. *Biomol. Eng.* **2001**, *17*, 167−182.

(32) (a) Mente, P. G.; Heine, H. W. *J. Org. Chem.* **1971**, *36*, 3076−3078. (b) Schmidt, R. R.; Berger, G. *Synthesis* **1974**, 187−189.

(33) (a) Yamamoto, K.; Yamazaki, S.; Osedo, H.; Murata, I. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 635−637. (b) Masquelin, T.; Obrecht, D. *Tetrahedron* **1997**, *53*, 641−646. (c) Cabarrocas, G.; Ventura, M.; Maestro, M.; Mahía, J.; Villalgordo, J. M. *Tetrahedron: Asymmetry* **2001**, *12*, 1851−1863.

(34) Domingo, L. R.; Picher, M. T.; Zaragoza, R. J. *J. Org. Chem.* **1998**, *63*, 9183−9189.

(35) (a) Domingo, L. R.; Picher, M. T.; Aurell, M. J. *J. Phys. Chem. A* **1999**, *103*, 11425−11430. (b) Domingo, L. R.; Picher, M. T.; Andres, J. *J. Org. Chem.* **2000**, *65*, 3473−3477.

(36) Cobo, J.; Melguizo, M.; Nogueras, M.; Sánchez, A.; Dobado, J. A.; Nonella, M. *Tetrahedron* **1996**, *52*, 13721−13732.

(37) (a) Gleiter, R.; Krennich, G.; Cremer, D.; Yamamoto, K.; Murata, I. *J. Am. Chem. Soc.* **1985**, *107*, 6874−6879. (b) Miller, K. J.; Moschner, K. F.; Potts, K. T. *J. Am. Chem. Soc.* **1983**, *105*, 1705−1712.

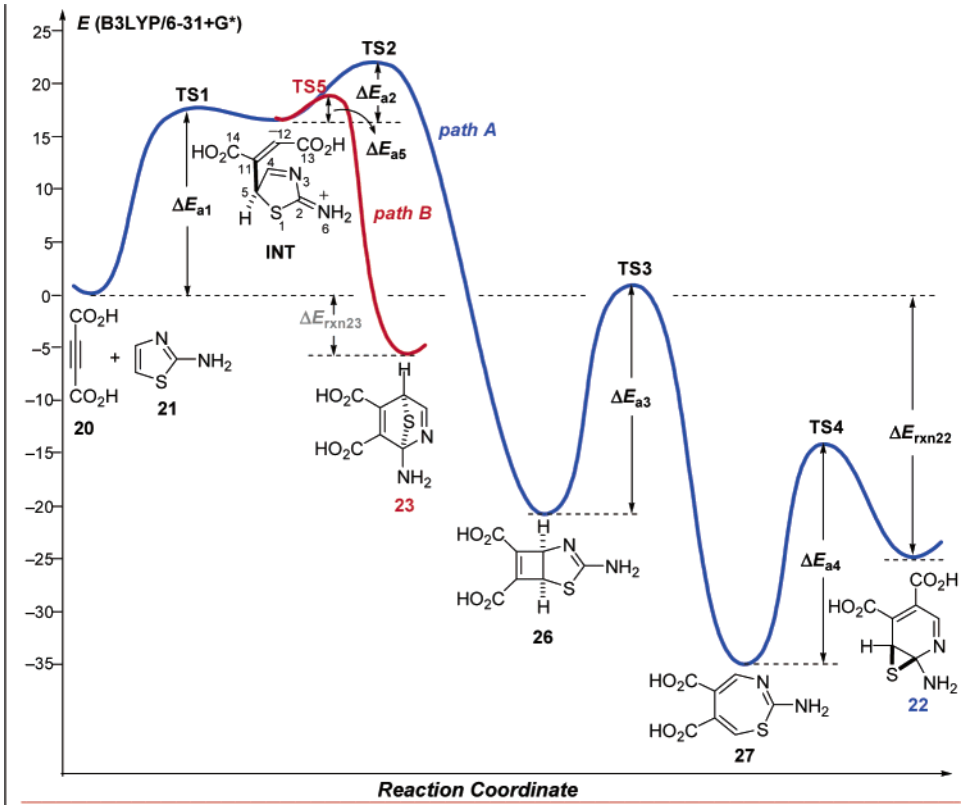


FIGURE 3. Qualitative reaction profiles at the B3LYP/6-31G+* level of reaction between acetylenedicarboxylic acid (**20**) and 2-aminothiazole (**21**) leading to the thiazanorcaradiene **22** and the 7-thia-2-azabicyclo[2.2.1]hepta-2,5-diene **23**.

acid and 2-aminothiazole: reactants **20** + **21**; products **22** and **23**, intermediates **INT**, **26** and **27**, and the transition structures **TS1**, **TS2**, **TS3**, **TS4**, and **TS5**. Figures 4 and 5 show the geometries of these stationary points, including the most relevant bond distances, while Table 3 includes the relative energies of the stationary points at the B3LYP/6-31+G*//B3LYP/6-31+G* and B3LYP-PCM/6-31+G*//B3LYP/6-31+G* theoretical levels also with the energy barriers. We will comment only the results obtained at the B3LYP/6-1+G* theoretical level, unless otherwise stated.

Pathway A: Mechanism of the Formation of the Thiazanorcaradiene 22. In this transformation, the first step consists of the formation of the C5−C11 σ-bond (see Figure 3 for numeration) through the transition state **TS1** leading to the dipolar intermediate **INT**, 17.8 kcal·mol^{-1} higher in energy than that of the reactants. The calculated barrier for this step was 18.3 kcal·mol^{-1}. As mentioned earlier, the presence of the amino group at the 2-position of the thiazole ring activates the C5 center for acting as a nucleophile attacking the conjugated acetylenic system of the other reactant. As a consequence of this attack, partial or total positive and negative charges are generated at the C4 and C12 carbon atoms, respectively, of both **TS1** and **INT**. Thus, the natural charge at C4 changes from 0.184 in **21** to 0.346 in **TS1** and 0.400 in **INT**, whereas the natural charge at C12 changes from −0.025 in **20** to −0.040 in **TS1** and −0.026 in **INT** (see Supporting Information). The presence of the carboxyl and the amino groups allows for an effective delocalization of the negative and positive partial charges, respectively.

In **TS1**, the plane containing the carboxyl group at C11 is in the plane containing the C14−C11−C12−C13 atoms, whereas the carboxyl group at C12 is perpendicular to that plane (see Figure 4). This spatial arrangement, also present in **INT**, allows for the effective delocalization of the charge being formed at C12. In both **TS1** and **INT** the thiazole ring unexpectedly deviates from planarity entailing an arrangement that places the plane containing the carboxyl group at C12 (negative charge) nearly parallel to the plane containing the C4−N3−C2−N6 fragment (charged positively). This probably allows for attractive electrostatic interactions and also the formation of a weak hydrogen bond between an oxygen atom of the carboxyl group and one of the hydrogen atoms at N6. On the other hand, it is worth pointing out that the configuration of the vinyl anionic moiety being formed as result of the change of hybridization (from sp to sp^2) at C11 and C12 is *E* in both **TS1** and **INT**. Notwithstanding, the values of the C11−C12−C13 bond angles, 159.9° and 153.4° in **TS1** and **INT**, respectively, are higher than those expected for an sp^2-hybridized C12 carbon atom. This fact indicates that the sp^2 lobe at the C12 center, filled by the electron density transferred from the thiazole to the acetylenedicarboxylic acid, is delocalized in some extension into the carbonyl oxygen of the adjacent carboxyl group. Consequently, the C12 carbon atom is cumulenic in a certain degree.

The dipolar intermediate **INT** can evolve by the two alternative pathways, A and B (see Figure 3). The formation of the σ-bond C4−C12 occurs via the transition state **TS2**, 6.0 kcal·mol^{-1} above **INT**, leading to the [2 + 2] cycloadduct **26**. This step is highly exothermic, by 39.4 kcal·mol^{-1}. The animation of the imaginary frequency in **TS2** shows that the nuclear motions are similar to that expected for the inversion of configuration (*E* to *Z*) at the C12 carbon atom, but going further until the formation of the C4−C12 bond. The cycloadduct **26** thus formed features a cis fusion at the bridgehead atoms (see Figure 4).

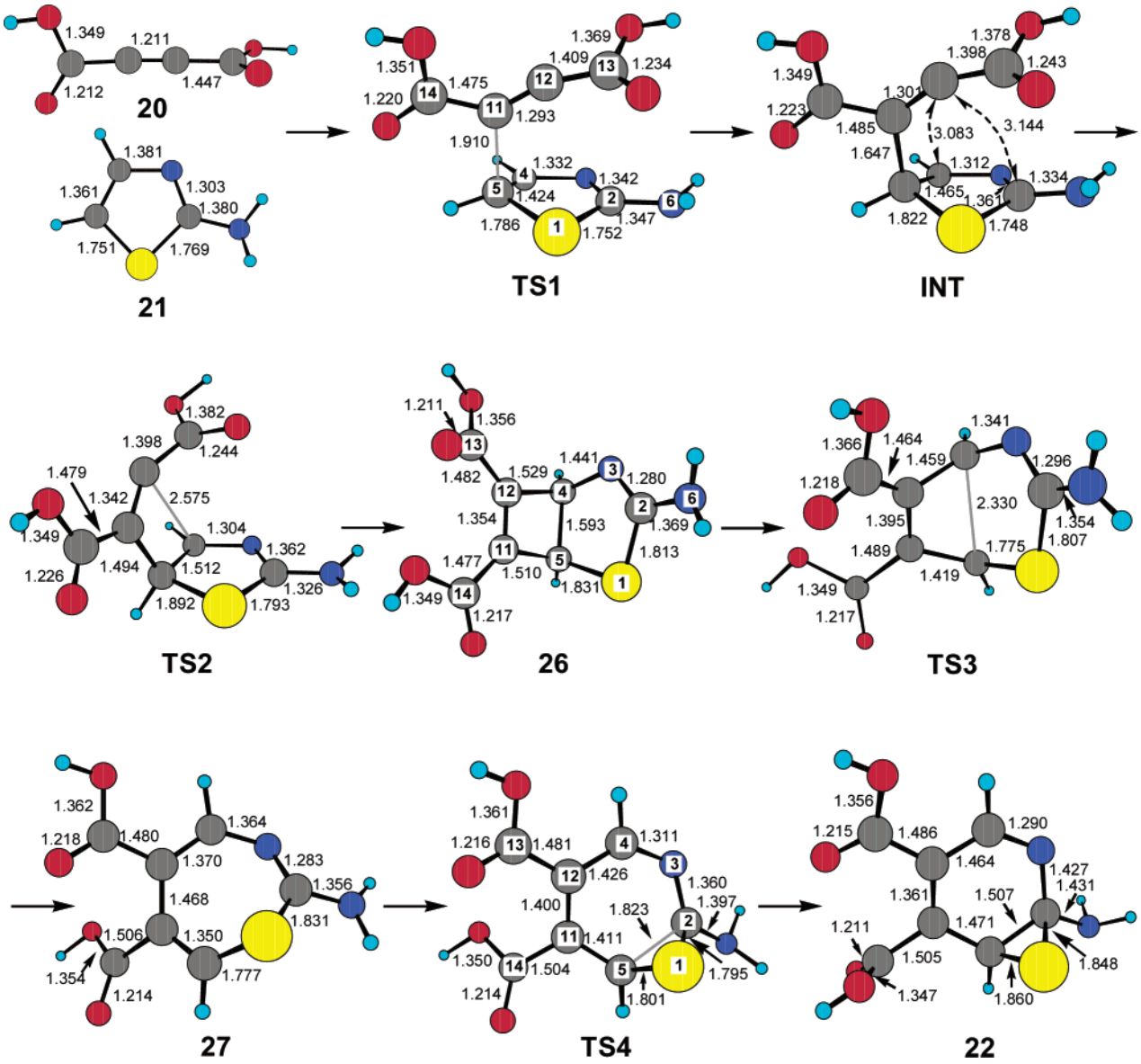


FIGURE 4. B3LYP/6-31+G*-optimized geometries of the stationary points found in the reaction of acetylenedicarboxylic acid (**20**) with 2-aminothiazole (**21**) leading to the thiazanorcaradiene **22**.

According to the cis-fusion of **26**, the opening of the cyclobutene ring of that compound by an electrocyclic, symmetry-allowed conrotatory process should lead to the corresponding *cis*,*trans*,*cis*-2-amino-1,3-thiazepine or *cis*,*cis*,*trans*-2-amino-1,3-thiazepine, depending on the clockwise or the counterclockwise conrotation along the C4−C12 and C5−C11 bonds, respectively. However, we have found the transition state **TS3** whose geometry resembles a disrotatory electrocyclic ring opening of **26**. IRC calculations confirmed that **TS3** connects with **26** and the *cis*,*cis*,*cis*-2-amino-1,3-thiazepine **27**. The computed barrier for this transformation is 24.0 kcal·mol^{-1}, and the process is exothermic by 13.8 kcal·mol^{-1}.

In the literature, there are several precedents of disrotatory ring openings of cyclobutenes. Houk and co-workers have recently confirmed[38] Roth's hypothesis that a cyclobutene forced to planarity might have a smaller preference for the conrotatory mode, demonstrating that the large energy of concert in the electrocyclic ring opening of cyclobutenes can be eroded by geometric constraints. On the other hand, for compounds in which the cyclobutene ring is cis-annulated to another system that possesses less than eight atoms, it is generally accepted that the ring opening must occur by way of the symmetry-forbidden disrotatory mode.[22a,30] Along with the geometric constraints, the electronic characteristic of the substituents can reduce the activation energy for the disrotation, in a way that Epiotis qualified as polar disrotatory ring opening.[30a] Several examples support that these predictions are correct.[22b,23,39] Thus, Reinhoudt et al.[21a,b,e,22c,40] showed that, in cis-fused [2 + 2] cycloadducts of thiophenes with acetylenes that isomerize at low temperature to the corresponding *cis*,*cis*,*cis*-thiepines, the

(38) Lee, P. S.; Sakai, S.; Hörsteman, P.; Roth, W. R.; Kallel, E. A.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 5839−5848.

(39) (a) Chapman, O. L.; Pasto, D. J.; Borden, G. W.; Griswold, A. A. *J. Am. Chem. Soc.* **1962**, *84*, 1220−1224. (b) Breslow, R.; Napierski, J.; Schmidt, A. H. *J. Am. Chem. Soc.* **1972**, *94*, 5906−5907.

(40) Reinhoudt, D. N.; Volger, H. C.; Kouwenhoven, C. G. *Tetrahedron Lett.* **1972**, 5269−5272. See also ref 22d.

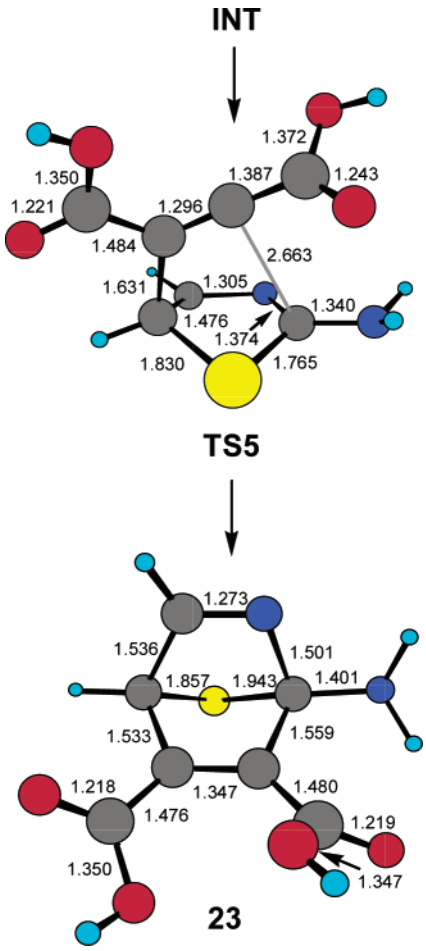


FIGURE 5. B3LYP/6-31+G*-optimized geometries of the stationary points found in the transformation of the dipolar intermediate **INT** into **23**.

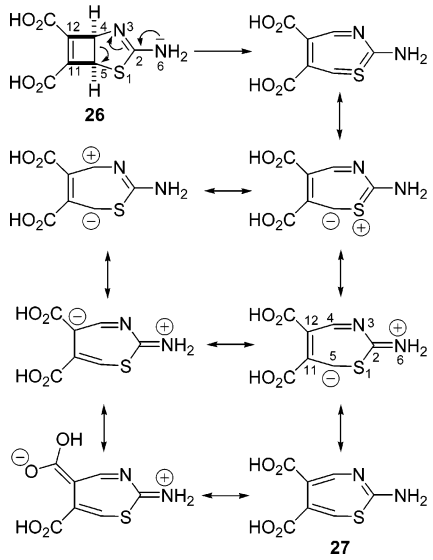
TABLE 3. Relative Energies with Zero-Point Vibrational Energy Corrections (kcal·mol^{-1}) at the B3LYP/6-31+G*//B3LYP/6-31+G* and the B3LYP-PCM/6-31+G*//B3LYP/6-31+G* Theoretical Levels, Low or Imaginary Frequencies (cm^{-1}) for the Stationary Points Found in the Conversions 20 + 21 → 22 and 20 + 21 → 23 Calculated at the B3LYP/6-31+G* Theoretical Level Also with the Calculated Energy Barriers[a] (kcal·mol^{-1})

	relative energy			energy barriers		
structure	B3LYP	B3LYP-PCM	low frequencies		B3LYP	B3LYP-PCM
20 + 21	0.0	0.00	36.0 (20) 249.9 (21)	ΔE_{a1}	18.3	9.9
TS1	18.3	9.9	−331.9	ΔE_{a2}	6.0	
INT	17.8	6.9	45.8	ΔE_{a3}	24.0	23.6
TS2	23.7	5.0	−103.9	ΔE_{a4}	20.6	22.3
26	−21.6	−30.1	37.3	ΔE_{rxn22}	−20.0	−26.4
TS3	2.4	−6.4	−197.4	ΔE_{a5}	0.6	3.6
27	−35.4	−42.5	53.3	ΔE_{rxn23}	−6.2	−10.9
TS4	−14.9	−20.2	−444.4			
22	−20.0	−26.4	30.8			
TS5	18.4	10.5	−97.7			
23	−6.2	−10.9	32.3			

[a] See Figure 3 for the notation of the energy barriers.

presence of an electron-donating group at the bridgehead carbon atom enhanced the rate of isomerization, in the same way that electron-withdrawing groups at the sp^2 carbon atoms of the cyclobutene fragment did.[13]

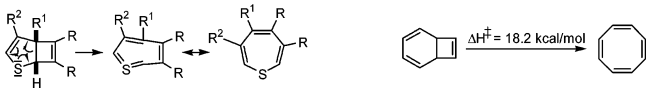
SCHEME 6. Ring Opening of Bicycle 26 Leading to 1,3-Thiazepine 27 Showing Some Resonance Forms of the Latter



We suppose that both the electronic features and the geometrical constraints of the bicycle **26** clearly favor a polar disrotatory ring opening. Thus, on the basis of the structure of **TS3** it can be seen that not only the cyclobutene ring of **26** but also the fused five-membered ring are involved in the electronic reorganization leading to **27**. This fact can be inferred by analyzing the bond distances, the natural charges, as well as the bond orders on going from **26** to **27** through **TS3**. In relation to the changes in natural charges, the most relevant is the increase of the positive charge at C4 in **TS3** (0.364) with regard to **26** (0.203) and **27** (0.339), and the increase of the negative charge at C5 (−0.162) with regard to **26** (−0.124) and **27** (−0.059). The positive charge at C4 is delocalized into C2, N6, and S1, and the negative one into C12, the carbonyl oxygen atom of the carboxyl group at this atom, and also into the vicinal S1 atom (see the values of bond orders and natural charges in the Supporting Information). These features are consistent with the fact that the breaking of the C4−C5 bond is assisted by the lone pair at the exocyclic nitrogen atom, by the intracyclic sulfur atom, and by the carboxyl group at C12. Thus, the isomerization of **26** to its valence tautomer **27** could be regarded also as a six-electron five-center disrotatory electrocyclic ring opening, thermally allowed, with simultaneous reorganization of the resultant cyclic π-system.[41] The participation of the thiazole ring in this reorganization can be easily visualized by considering the neutral resonance structure of **27** with a λ^4 sulfur atom. In fact, the values of the bond orders and the natural charges point to the contribution of several polar resonance forms to the structure of thiazepine **27** (Scheme 6).

These theoretical data are in line with those extracted from the experimental results. Thus, the conversion of the bicycle

(41) Reinhoudt has also proposed (see ref 21b) that the ring opening of thiabicyclo[3.2.0]hepta-3,6-dienes leading to the corresponding thiepines can be regarded as an electrocyclic symmetry-allowed disrotatory reaction of the dihydrothiophene ring analogous to that occurring in the isoelectronic bicyclo[4.2.0]octatriene which isomerizes rapidly to cyclooctatetraene. See: Glass, D. S.; Watthey, J. W. H.; Winstein, S. *Tetrahedron Lett.* **1965**, 377−383.



13j into the pyridine **6j** was faster in the more polar CD_3CN compared to that in $CDCl_3$ or toluene-d_8, perhaps as result of the highly polar character of the transition state of the rate-determining step, the formation of the thiazepine ring. Other experimental observations can be correctly interpreted on the basis of the data obtained from the theoretical calculations; in fact, bicyclic **13** could be isolated only when C4 bears a nonaromatic group such as in **13j** (R^3 = Me in Scheme 4). For the rest of the cases in which an alkenylic or an aromatic group is attached to this carbon atom (R^3 = CH=CHAr or Ar in Scheme 4) only the corresponding pyridine **6** was detected in the reaction mixture. Even more, it is a matter of the fact that aromatic groups bearing electron-donating substituents at the 4-position in the thiazole ring accelerate the reaction (Table 2; entries 5 and 6 versus entries 7 and 8). These observations may be interpreted by considering that the developing positive charge at C4 in the corresponding transition state **TS3** may be stabilized by resonance by the appropriate substituents, in special electron-donating ones, leading to a decrease in the activation energy of this step and thus favoring the evolution to the pyridine **6**. Finally, the conversion of **13j** into **6j** in the presence of 1 equiv of CF_3COOH did not occur at all (see the previous section). This experimental fact shows the relevant role that the lone pair at the exocyclic nitrogen atom N6 plays in assisting the cleavage of the C4−C5 bond of the bicycles type **26**.

As stated earlier, the chemical behavior of 1,3-thiazepines should be analogous to that of their isomeric 1,4-thiazepines, which show a pronounced instability caused by their ability to undergo sulfur extrusion.[33] The propensity to sulfur extrusion has been also well-documented in the related seven-membered ring thiepines.[37] The instability of the latter compounds has been rationalized as a consequence of its antiaromatic character[42] and, moreover, as due to the low activation energy required for the desulfurization reaction which converts it into the benzene nucleus, via the formation of a thianorcaradiene as intermediate.[43]

Analogous to the more stable conformation of the thiepine ring,[37,44] the optimized structure of the thiazepine **27** is boat-shaped. This conformation seems to be appropriate to allow a 6π-electrocyclic disrotatory ring closure through the transition structure **TS4**, leading finally to the thiazanorcaradiene **22**. The calculated energy barrier for this step is 20.6 kcal·mol^{-1}, and the process is endothermic by 15.4 kcal·mol^{-1}.

The transformation of the thiazanorcaradiene **22** into the final 6-amino-3,4-pyridinedicarboxylic acid (**24**), as mentioned earlier, has not been included in this theoretical study as previous works dealing with the sulfur extrusion in thiepines and other heterocycles have been already reported. These investigations revealed that this process involves a sequence of reactions entailing several intermediates in which the number of sulfur atoms increases, ending with the formation of the corresponding aromatic compound and stable forms of sulfur. The activation energy for the steps leading to the sulfur extrusion is lower than 5 kcal·mol^{-1}.[37] Therefore, if we consider a similar propensity of the thiazanorcaradiene **22** to the desulfurization reaction leading to the pyridine **24**, the formation of **22** from the thiazepine **27** can be considered as an irreversible process once the thiazanorcaradiene **22** has converted into the pyridine **24**, despite **22** being more energetic than the thiazepine **27** and even though the calculated barrier for the reversion of **22** to **27** is only 5.2 kcal·mol^{-1}.

Pathway B: Mechanism of the Formation of the 7-Thia-2-azabicyclo[2.2.1]hepta-2,5-diene 23. The alternative path for the evolution of intermediate **INT** consists of its transformation into the formal [4 + 2] cycloadduct **23** involving the nucleophilic attack of the anionic C12 center on the C2 carbon atom of the thiazole ring. At the HF/6-31G* theoretical level, we have found that this process involves the initial inversion of the configuration at the C12 carbon atom leading to the corresponding intermediate of *Z* configuration [(*Z*)-**INT**], and subsequently, the formation of the C2−C12 bond takes place through **TS5′** (see Supporting Information) leading to **23**. However, at the B3LYP/6-31+G* level we have found only a transition structure, **TS5**, that connects the polar intermediate **INT** with the bicycle **23**, whose structure resembles that expected for the *E* to *Z* configuration inversion at the C12 carbon atom. Thus, the value of the C11−C12−C13 bond angle is 176.2°,[45] and the C2−C12 bond formation is not much advanced: the bond distance is 2.663 Å and the bond order is 0.17. The animation of the imaginary frequency showed that the nuclear motions correspond to the inversion at C12 and the simultaneous approaching of the C2 and C12 atoms. IRC calculations confirmed the connection of **TS5** with **INT** and **23**, notwithstanding that the IRC curve toward the formation of **23** showed an inflection point in a small and very flat region corresponding to a structure similar to the transition state **TS5′** found at the HF level. The calculated barrier at the B3LYP/ 6-31+G* level for the conversion of **INT** into **23** through **TS5** was almost imperceptible, only 0.6 kcal·mol^{-1}, the process being exothermic by 23.9 kcal·mol^{-1}, whereas the overall transformation (i.e., **20** + **21** → **23**) is exothermic by only 6.2 kcal·mol^{-1}. It is expected that the sulfur extrusion in the bicycle **23**, leading to 2-amino-3,4-pyridinedicarboxylic acid (**25**), should occur easily without appreciable energetic cost.

By considering the calculated reaction profile for the transformations **20** + **21** → **22** and **20** + **21** → **23** (Figure 3) and the energy barriers associated with each step (Table 3), this theoretical approach predicts that the intermediate **23** should be the kinetically controlled product, whereas the thiazanorcaradiene **22** seems to be the product of thermodynamic control. Therefore, the nearly exclusive formation of pyridines **6** in the experiments described earlier can only be rationalized as resulting from the prevalence of the [2 + 2] cycloaddition pathway under thermodynamic control. To this end, the reversion of the [4 + 2] cycloadduct **23** into the dipolar intermediate **INT** should occur, and the energy barrier of this process is 24.6 kcal·mol^{-1}.

These results correspond to calculations in the gas phase but, because several stationary points along the reaction coordinates resulting in **22** and **23** are highly polarized (i.e., **TS1**, **INT**, **TS3**), it is conceivable that the solvent may alter considerably the

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(45) This value indicates that the C12 carbon atom presents an sp hybridization where the charge located at this center occupies a p atomic orbital. A similar value has been found in the transition state corresponding to the configuration inversion connecting two polar intermediates coming from the reaction of DMAD with 1-methylpyrrole (see ref 34).

values of the energy barriers. This is why we studied the influence of the solvent in the mechanism of these transformations.

Solvent Effects. We have carried out single-point calculations by using the polarized continuum model (PCM) with acetonitrile as solvent, because this is the one used in the experimental part of this work. Table 3 reports the B3LYP/6-31+G* relative energies with inclusion of solvent effects. As we expected, these data show notorious changes in the energy barriers, and they are especially significant when comparing the two competitive paths, A and B, as now the transition state **TS2** is less energetic than the transition state **TS5**. Actually, with the inclusion of the solvent, there is no barrier for the transformation of **INT** into the [2 + 2] cycloadduct **26**,[46] whereas the calculated energy barrier for the conversion of **INT** into the [4 + 2] cycloadduct **23** is now 3.6 kcal·mol^{-1}, and therefore the thiazanoracardiene **22** should be both the kinetically and thermodynamically controlled product, thus explaining the *exclusive* formation of the reaction products **6**.

It is worth pointing out that, although all the stationary points are stabilized by the inclusion of solvent in the calculations, there are no notorious changes in the energy barriers of the remaining steps in the transformation **20** + **21** → **22**, except in that of the first one leading to the dipolar intermediate **INT**, whose value decreases to 9.9 kcal·mol^{-1}.

Conclusions

The reaction of the 2-(phenylamino) and 2-(dimethylamino)-thiazoles **5** with DMAD leads to the unexpected pyridines **6** as the exclusive reaction products, except under special circumstances in which the regioisomeric pyridines **7** are isolated in small amounts. The two possible competitive pathways for the reaction between the simplified reagents 2-aminothiazole and acetylenedicarboxylic acid leading to the regioisomeric 6-amino and 2-amino-3,4-pyridinedicarboxylic acids (**24** and **25**) (i.e., those resulting from a [2 + 2] or a [4 + 2] cycloaddition, respectively) have been computationally scrutinized. The analysis of the energy profiles for both pathways at the B3LYP−PCM level of theory indicates that pyridines **24** are both the kinetically and thermodynamically controlled products. Both alternative cycloaddition processes were found to occur stepwise through a common dipolar intermediate (**INT**). Notably, the step following the [2 + 2] cycloaddition (i.e., the ring opening of the fused cyclobutene intermediate to give the *all*-cis 1,3-thiazepine) has been found to take place in a disrotatory mode. Although geometric constraints and electronic factors may reduce the energy barrier for the disrotation, the implication of the fused five-membered ring in the electronic reorganization leading to the 1,3-thiazepine seems to be determinant in this sense, since this step could be regarded also as a thermally allowed six-electron five-center disrotatory electrocyclic ring opening. The proposed mechanism is experimentally supported by the isolation of several intermediates and other experimental facts such as the influence of the polarity of the solvent on the rate of conversion of the fused cyclobutene **13j** into the pyridine **6j** and the lack of reaction of **13j** in the presence of trifluoroacetic acid.

(46) In fact, **INT** is slightly higher in energy than **TS2**, probably as consequence of using the approximation of frozen geometries. See: (a) Bonaccorsi, R.; Cammi, R.; Tomasi, J. *J. Comput. Chem.* **1991**, *12*, 301−309. (b) Tuñón, I.; Silla, E.; Tomasi, J. *J. Phys. Chem.* **1992**, *96*, 9043−9048.

Experimental Section

Synthesis of the Thiazoles 5a−j. Thiazoles **5d**,[47] **5e**,[48] **5f**,[48] **5g**,[48] **5h**,[47] and **5j**[47] were known compounds, and they were prepared following methodologies previously described in the literature. The general procedure for the synthesis of the thiazoles **5a−c** and **5i** and their structural characterization have been included in the Supporting Information.

General Procedure for the Synthesis of Pyridines 6b−i. DMAD (0.35 g, 2.45 mmol) was added to a solution of the corresponding thiazole **5** (0.82 mmol) in acetonitrile (10 mL), and the reaction mixture was stirred at 25 °C or under reflux (temperatures and reaction times depicted in Table 2). The solvent was evaporated to dryness, and the residue was purified by silica gel column chromatography.

(1*R,5*S**)-Dimethyl 3-(dimethylamino)-5-methyl-2-thia-4-azabicyclo[3.2.0]hepta-3,6-diene-6,7-dicarboxylate (13j).** DMAD (0.30 g; 0.21 mol) was added to a solution of the thiazole **5j** (0.30 g, 0.21 mol) in MeCN (15 mL), and the reaction mixture was stirred at 25 °C for 6 d. The solvent was evaporated to dryness, and the residue was purified by silica gel column chromatography eluting with 1:1 AcOEt/hexane (R_f 0.16); yield 52%; mp 89.2−90.2 °C (colorless prisms, $CHCl_3/Et_2O$); IR (Nujol) 1741, 1718, 1605, 1290, 1122 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.71 (s, 3H), 2.96 (s, 6H), 3.82 (s, 3H), 3.83 (s, 3H), 4.33 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.3 (q), 39.6 (2 × q), 52.1 (q), 52.2 (q), 57.1 (d), 86.3 (s), 138.4 (s), 148.2 (s), 160.9 (s), 161.2 (s), 162.7 (s); MS (EI, 70 eV) *m*/*z* (relative intensity) 284 (M^+, 7), 252 (52), 237 (45), 223 (100), 221 (50). Anal. Calcd for $C_{12}H_{16}N_2O_4S$ (284.33): C, 50.69; H, 5.67; N, 9.85; S, 11.28. Found: C, 50.40; H, 5.89; N, 9.66; S, 10.81.

Dimethyl 6-(dimethylamino)-2-methyl-3,4-pyridinedicarboxylate (6j). A solution of **13j** (0.12 g, 0.42 mmol) in MeCN (15 mL) was stirred under reflux for 2 h. The solvent was evaporated to dryness, and the residue was purified by silica gel column chromatography eluting with 1:2 AcOEt/hexane (R_f 0.43); yield 90%; mp 63.8−64.2 °C (lit. 64 °C)[11] (colorless prisms, Et_2O/hexane); ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3H), 3.13 (s, 6H), 3.84 (s, 3H), 3.88 (s, 3H), 6.59 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.8 (q), 37.7 (2 × q), 52.1 (q), 52.7 (q), 101.9 (d), 112.9 (s), 140.8 (s), 157.5 (s), 158.6 (s), 167.9 (s), 168.6 (s).

Reaction of the Thiazole 5g and DMAD in Methanol. DMAD (0.03 g; 0.23 mmol) was added to a solution of the thiazole **5g** (0.05 g, 0.23 mol) in methanol (10 mL), and the reaction mixture was stirred at 25 °C for 48 h. Then, the solvent was evaporated to dryness, and the residue was purified by silica gel column chromatography eluting with 1:3 AcOEt/hexane to give a mixture of (*Z*)-**15** and (*E*)-**15**.

Dimethyl (*Z*)-[2-(Dimethylamino)-4-(4-methylphenyl)thiazol-5-yl]-2-butenedioate [(*Z*)-15]: (R_f 0.18); yield 68%; mp 102.8−103.7 °C (yellow prisms, $CHCl_3$/*n*-hexane); IR (Nujol) 1720, 1618, 1253, 1216 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 3.16 (s, 6H), 3.40 (s, 3H), 3.67 (s, 3H), 6.65 (s, 1H), 7.13 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.3 (q), 40.0 (2 × q), 51.8 (q), 52.7 (q), 110.2 (s), 126.1 (d), 128.5 (2 × d), 128.9 (2 × d), 132.9 (s), 137.5 (s), 138.0 (s), 155.2 (s), 165.5 (s), 167.2 (s), 170.5 (s); MS (EI, 70 eV) *m*/*z* (relative intensity) 360 (M^+, 14), 301 (44), 300 (100), 271 (36), 269 (39), 242 (47). Anal. Calcd for $C_{18}H_{20}N_2O_4S$ (360.43): C, 59.98; H, 5.59; N, 7.77; S, 8.90. Found: C, 59.68; H, 5.74; N, 7.74; S, 8.69.

Dimethyl (*E*)-[2-(Dimethylamino)-4-(4-methylphenyl)thiazol-5-yl]-2-butenedioate [(*E*)-15]: (R_f 0.12); yield 22%; mp 84.1−85.5 °C (yellow prisms, $CHCl_3$/*n*-hexane); IR (Nujol) 1734, 1709, 1556, 1288, 1157 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 3.15 (s, 6H), 3.32 (s, 3H), 3.68 (s, 3H), 5.85 (s, 1H), 7.16 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.3 (q), 40.0

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(2 × q), 51.6 (q), 52.1 (q), 114.7 (d), 115.2 (s), 128.5 (2 × d), 129.4 (2 × d), 131.9 (s), 138.5 (s), 141.5 (s), 156.7 (s), 165.5 (s), 166.3 (s), 168.9 (s); MS (EI, 70 eV) *m*/*z* (relative intensity) 360 (M^+, 9), 301 (40), 300 (100), 271 (33), 269 (30), 242 (38). Anal. Calcd for $C_{18}H_{20}N_2O_4S$ (360.43): C, 59.98; H, 5.59; N, 7.77; S, 8.90. Found: C, 59.62; H, 5.88; N, 7.88; S, 8.66.

Computational Methods. All calculations were carried out with the Gaussian03[49] suite of programs. An intensive characterization of the potential energy surface was done at the HF/6-31G*[50] theoretical level and then with the B3LYP[51] functional using the 6-31+G* basis set. Harmonic frequency calculations at each level of theory verified the identity of each stationary point as a minimum or a transition state, and they were used to provide an estimation of the zero-point vibrational energies, which were not scaled. IRC calculations were carried out to determine what minima each transition structure connects.

The solvent effects have been considered by B3LYP/6-31+G* single-point calculations using the self-consistency reaction field[52] method, based on the polarized continuum model[53] of Tomasi and co-workers, in acetonitrile as solvent.

Natural charges and Wiberg bond indices were calculated with the natural bond orbital (NBO) method.[54]

Acknowledgment. We are grateful to the "Ministerio de Educación y Ciencia" of Spain and FEDER (Project CTQ2005-02323/BQU) and the "Fundación Séneca-CARM" (Project PI-1/00749/ FS/01) for funding. J.C. is grateful to the "Ministerio de Educación y Ciencia" of Spain for a fellowship. A.P. also thanks the "Ministerio de Educación y Ciencia" of Spain and the University of Murcia for a contract in the frame of the "Ramón y Cajal" program.

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, bond orders, and atomic natural charges from the NBO analysis. Detailed experimental procedures and full characterization of the thiazoles **5a**−**c** and **5i**. Analytical and spectroscopic data for pyridines **6b**−**i**, **7e**, and **7i**. ^{1}H,^{1}H−NOESY spectra of the pyridines **6c**, **6i**, **7e**, **7i**, and the bicycle **13j**. Crystallographic information files (CIF) for **6c** and (*Z*)-**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060664C

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