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The Role of Steric and Electronic Interactions in the Stereocontrol of the Asymmetric 1,3-Dipolar Reactions of 5-Ethoxy-3-*p*-(*S*)-tolylsulfinylfuran-2(5*H*)-ones with Diazoalkanes: Theoretical Calculations and Experimental Evidences

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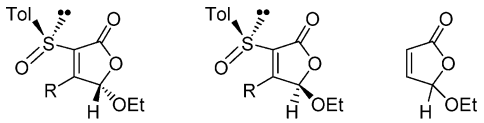
The addition of diazomethane and diazoethane to (5*S*,S*S*)- and (5*R*,S*S*)-5-ethoxy-3-*p*-tolylsulfinylfuran-2(5*H*)-ones (**1a** and **1b**) and their 4-methylderivatives (**2a** and **2b**) proceeded in almost quantitative yields and complete regioselectivity. The observed π-facial selectivity is determined by the configurations at both C-5 and the sulfinyl group, the later being the most important. The syn adducts were almost exclusively obtained from **1a** and **2a** in apolar solvents but the π-facial selectivity was strongly decreased in more polar solvents. On the other hand, the major adducts from **1b** and **2b** were the anti ones and such predominance was slightly increased with solvent polarity. The exo-selectivity was complete in all the cases except for the anti approach to compounds **2a** (in polar solvents) and **2b**. The role of the sulfinyl group in this behavior was inferred by comparison of these results with those obtained in reactions of diazoalkanes with 5-methoxyfuran-2(5*H*)-one (**3**). Steric interactions seem to be the main ones responsible for the observed exo selectivity of reactions with diazoethane, but electronic factors, which can be modulated by the solvent, are also significant in the π-facial selectivity control. DFT computational methods are able to correctly predict the reactivity, regioselectivity, and π-facial selectivity exhibited by 5-alkoxyfuranones as well as their changes with the solvent polarity. A C−H···O hydrogen bond, involving the oxygen atom of the 5-alkoxy group at dipolarophiles and the *endo*-hydrogen atom at dipoles, seems to play a key role in the electronic interactions influencing the stereochemical course of these reactions.

Introduction

Substituted vinyl sulfoxides have been widely used as chiral dienophiles in asymmetric Diels−Alder reactions due to the ability of the sulfinyl group to control their π-facial selectivity, despite its influence on the reactivity and endo/exo selectivity being not too large.[1] In contrast, the number of papers reporting the use of homochiral vinyl sulfoxides as dipolarophiles is quite low,[1,2] maybe due to the easy desulfinylation of the resulting adducts. Some years ago we initiated a program devoted to explore the behavior of optically pure vinyl sulfoxides as dipolarophiles. Our first contribution[3] concerned reactions of diazomethane with (5*S*,S*S*)- and (5*R*,S*S*)-5-ethoxy-3-*p*-tolylsulfinylfuran-2(5*H*)-ones, **1a** and **1b**, and their 4-methyl derivatives, **2a** and **2b** (Figure 1). The results of these reactions revealed that dipolarophilic features of these cyclic sulfoxides were much better than their dienophilic ones, with the sulfinyl group playing a quite significant role in the reactivity and stereoselectivity of the 1,3-dipolar reactions. In that first paper we proposed that the π-facial selectivity was complete and exclusively controlled by the sulfinyl configuration. Moreover, the steric effects appeared as the only ones responsible for the stereochemical course of the reactions. These studies revealed that substrates **1** and **2** exhibited some advantages as sulfinyl dipolarophiles in asymmetric synthesis because the primary adducts were stable enough to be isolated due to their bicyclic structure, which determined that they were not too prone to desulfinylation. Conse-



1a (R=H) **2a** (R=Me) **1b** (R=H) **2b** (R=Me) **3**

FIGURE 1. Dipolarophiles studied.

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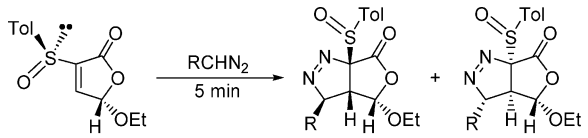
quently, we have also studied the reactions of **1a** and **1b** with some other dipoles such as nitrile oxides,[4,5] nitrones,[6] and azomethine ylides.[7]

All these studies revealed to us that electrostatic interactions also played an important role in the π-facial selectivity control of many of these 1,3-dipolar reactions, which contrasted with their apparent scarce significance that we had proposed in the reactions with diazomethane.[3] Moreover, the presence of the sulfinyl group was also decisive in determining the endo/exo selectivity. To get some evidence about these influences in the reactions of sulfinyl dipolarophiles with diazoalkanes, we initiated the study of the reactions of **1** and **2** with diazoethane. From the results obtained in this study, we inferred the significant role of the electrostatic interactions in the π-facial selectivity (by considering the influence of the solvent polarity in the reaction course), thus questioning the conclusions that we have presented in our first paper on reactions with diazomethane.[3] This prompted us to revise the available data and perform new studies on these reactions. In this paper we report a complete study of the reactions of diazoethane and diazomethane with (5*S*,S*S*)- and (5*R*,S*S*)-5-ethoxy-3-*p*-tolylsulfinylfuran-2(5*H*)-ones, **1a** and **1b** (epimers at C-5), as well as with their 4-methyl derivatives, **2a** and **2b**, under different conditions. Additionally, we present the cycloadditions of both diazoalkanes with 5-methoxyfuran-2(5*H*)-one (**3**), which lacks the sulfinyl group at C-3. The comparison of these results with those obtained from **1a** and **1b** allowed us to know the role of the sulfinyl group at C-3 in the features of these 1,3-dipolar reactions. Finally, we have also studied these reactions from a theoretical point of view, by using models able to provide a reasonable estimate of the effect of solvent polarity on the energy barriers. From these calculations, which correctly predict most of the features of these reactions, it is possible to know the nature of the different factors controlling them. A new type of C−H···O hydrogen bond, involving the oxygen atom of the 5-alkoxy group of the dipolarophile and the *endo*-hydrogen atom of the dipole, seems to play a key role in the stereochemical outcome of these reactions. This kind of interaction has been the subject of study in recent computational papers,[8] including effects on the stereoselectivity of aldol[8b] and epoxidation[8c] reactions.

Results and Discussion

We had previously reported the synthesis of compounds **1a** and **1b**,[9] as well as that of their 4-methyl derivatives **2a** and **2b**.[3] Compound **3** had been described by Schenck.[10]

TABLE 1. Additions of Diazoethane and Diazomethane to 1a



1a R=Me *syn*-**4a**-*exo* *anti*-**4a**-*exo*
R=H *syn*-**5a** *anti*-**5a**

entry	R	solvent	*T* (°C)	syn:anti
1[a]	Me	Et_2O	0	95:5
2	Me	Et_2O	−40	96:4
3	Me	Et_2O	−78	96:4
4	Me	CH_3CN/Et_2O	0	60:40
5	Me	CH_3CN/Et_2O	−40	48:52
6[b]	H	Et_2O	0	100:0
7	H	CH_3CN/Et_2O	0	50:50
8[c]	H	CH_3CN/Et_2O	−40	40:60

[a] Isolated yield of *syn*-**4a**-*exo* 80%. [b] These data are identical with those reported in ref 3. [c] Isolated yield for the mixture *syn*-**5a** + *anti*-**5a** 78%.

The results in the reactions of **1a** with an excess of diazomethane and diazoethane under different conditions are collected in Table 1. The reaction of **1a** with an ethereal solution of diazoethane was complete in 5 min at 0 °C, yielding a 95:5 mixture of $^1\Delta$-pyrazolines *syn*-**4a**-*exo*/*anti*-**4a**-*exo*[11] in an almost quantitative yield (entry 1, Table 1). Reactions were also instantaneous at lower temperatures, but diastereomeric ratios did not increase significantly (entries 2 and 3, Table 1). The reactions performed by using a 7.5:1 mixture of CH_3CN/Et_2O as the solvent (entries 4 and 5) also took place in 5 min and evolved with a clearly lower facial diastereoselection yielding mixtures of syn and anti cycloadducts, the later being slightly favored at −40 °C (entry 5). Only the exo-adduct was obtained in all these reactions.[11]

Reactions with diazomethane showed a similar behavior. The π-facial selectivity was complete in Et_2O at 0 °C (entry 6), which allowed the complete characterization of *syn*-**5a**,[3] but strongly decreased in CH_3CN (entry 7), the *anti*-**5a** being the major adduct at −40 °C (entry 8).

The reactions of **1b**[12] with diazoethane (Table 2) were also completely regioselective and exo-selective. The π-facial selectivity in Et_2O was significantly lower than that observed for **1a**. Thus, reactions conducted at 0 °C afforded a 85:15 mixture of pyrazolines *anti*-**4b**-*exo* and *syn*-**4b**-*exo* (entry 1, Table 2). Diastereomeric excesses increased as the temperature decreased (entries 2 and

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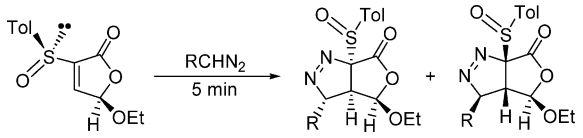
(11) The terminology syn/anti indicates the spatial arrangement of the alkoxy group at C-5 and the pyrazoline ring at the furanone moiety. It also indicates that the approach of the dipole has taken place either to the face containing the alkoxy group (syn-approach) or to the opposite one (anti-approach). Therefore, the syn/anti ratio will be indicative of the π-facial selectivity of the reaction. The term exo indicates the trans arrangement of the methyl group of the diazoethane with respect to the furanone moiety at the pyrazoline ring. It is characteristic of the exo approach of the dipole to the dipolarophile, using as the reference the carbonyl group at the later.
(12) As the isolation of **1b** in its diastereomerically pure form was very difficult these reactions were performed starting from a 94:6 mixture of **1b** and **1a**. As a consequence, in all cases we also obtained small amounts (∼6%) of the adduct *syn*-**4a**-*exo*, which could be easily separable from the **4b** adducts.

TABLE 2. Additions of Diazoethane and Diazomethane to 1b



1b | *syn*-**4b**-*exo* *syn*-**5b** | *anti*-**4b**-*exo* *anti*-**5b**

entry	R	solvent	*T* (°C)	syn:anti
1[a]	Me	Et_2O	0	15:85
2	Me	Et_2O	−40	8:92
3	Me	Et_2O	−78	7:93
4	Me	CH_3CN/Et_2O	0	8:92
5	Me	CH_3CN/Et_2O	−40	5:95
6[b]	H	Et_2O	0	17:83
7	H	Et_2O	−40	9:91
8	H	Et_2O	−78	7:93
9	H	CH_3CN/Et_2O	0	15:85
10	H	CH_3CN/Et_2O	−40	9:91

[a] Isolated yield of *syn*-**4b**-*exo* 10%. [b] Isolated yield of *syn*-**5b** 13%.

3), reaching a 86% de at −78 °C. Contrasting with the results obtained from **1a**, the π-facial selectivity slightly increased when the reactions from **1b** were conducted in CH_3CN/Et_2O mixtures (compare entries 4 and 5 with 1 and 2, respectively).

Similar results were obtained in reactions with diazomethane: the adduct *syn*-**5b** was formed in a similar proportion to that of *syn*-**4b**-*exo* in its mixture[13] (compare entries 6 and 1, Table 2). The influence of the temperature (compare entries 2 and 3 with 7 and 8) is identical for both diazoalkanes, whereas the influence of the polarity of the solvent (compare entries 6 and 1 with 9 and 4, respectively) is scarcely significant in the reactions with diazomethane.

All the initial purification trials performed on compounds **4** with use of chromatography on silica gel or crystallization were unsuccessful, due to the easy decomposition of the pyrazolines. The use of a silica gel previously treated with Et_3N for 24 h for the column chromatography avoided the decomposition of the compounds *syn*-**4a**-*exo* and *syn*-**4b**-*exo*, allowing their separation from their respective mixtures as well as their complete spectroscopic characterization. The adducts *anti*-**4** were characterized from the NMR spectra of their mixtures along with the syn-adducts, once all the signals of the later had been assigned. The adducts **5**, derived from diazomethane, are stable in silica gel, but their chromatographic separation was only possible for adducts **5b**. Compound *syn*-**5a**, which had been obtained as a sole diastereoisomer under the conditions of entry 6 (Table 1), could be easily characterized, whereas the spectroscopic parameters for its anti isomer were obtained from

(13) The data corresponding to this reaction in ref 3 indicate that *anti*-**5b** was exclusively formed under the conditions indicated in entry 6. However, taking into account that compound *syn*-**4b**-*exo* resulted from the approach of the diazoethane to the face of the dipolarophile bearing the OEt group at C-5, the absence of a similar adduct (*syn*-**5b**) in the reaction of **1b** with the less hindered diazomethane was difficult to explain. Therefore, we have repeated the later reaction and thoroughly studied the reaction crude, with the results indicated in entry 6 of Table 2. This mistake was responsible for the wrong conclusions reported in ref 3.

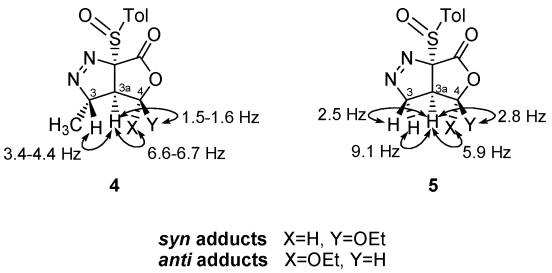
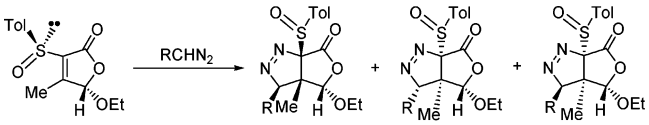


FIGURE 2. Coupling constants of adduct **4** and **5**.

TABLE 3. Additions of Diazoethane and Diazomethane to 2a



2a | *syn*-**6a**-*exo* *syn*-**7a** | *anti*-**6a**-*exo* *anti*-**7a** | *anti*-**6a**-*endo*

entry	R	solvent	time (h)	*T* (°C)	syn:anti (exo:endo)
1	Me	Et_2O	1.5	0	100:0
2	Me	CH_3CN/Et_2O	1	0	84:16 (12:4)
3	Me	CH_3CN/Et_2O	5.5	−40	82:18 (13:5)
4[a]	H	Et_2O	1.5	0	100:0
5	H	CH_3CN/Et_2O	1	0	75:25
6	H	CH_3CN/Et_2O	6.5	−40	74:26

[a] This result is identical with that reported in ref 3.

the spectra of the purified mixtures of *syn*-**5a** + *anti*-**5a**, once the signals of the first one had been completely assigned.

The syn or anti stereochemistry of the pyrazolines[11] was deduced from the values observed for $J_{3a,4}$ (5.9−6.7 and 1.5−2.8 Hz, respectively, see Figure 2), whereas the exo character[11] of all the cycloadducts was established from the values of $J_{3,3a}$ (they ranged between 2.5 and 4.4 Hz). As a reference we used the values of the coupling constants measured for pyrazolines derived from diazomethane (Figure 2), whose configurational assignment had been unequivocally established.[3] The absolute configurations of compounds **4** and **5** were assigned as indicated in Tables 1 and 2 on the assumption that the configurations at C-5 and sulfur of the starting sulfinyl furanones **1a** and **1b** remained unaltered in the course of these reactions.

The reaction of **2a** with diazoethane, in a nonpolar solvent (entry 1, Table 3) evolved with complete regio- and stereoselectivity, affording *syn*-**6a**-*exo* as the sole diastereoisomer in quantitative yield. When a 13.5:1 mixture of CH_3CN/Et_2O was used as the solvent, two new compounds, both of them with the anti-stereochemistry (*anti*-**6a**-*exo* and *anti*-**6a**-*endo*), were detected (entries 2 and 3). These cycloadditions required 90 and 60 min for completion at 0 °C, which reveals that, as expected, the dipolarophilic reactivity of the methyl derivative **2a** is lower than that of **1a** and **1b**. The reactions of **2a** with diazomethane afforded similar results, showing a complete stereoselectivity in ether[3]—only yielding the adduct *syn*-**7a**—which strongly decreased when acetonitrile was used as the solvent (entries 5 and 6).

The reaction of **2b** with an excess of diazoethane (ethereal solution) at 0 °C afforded a 2:1 mixture of two

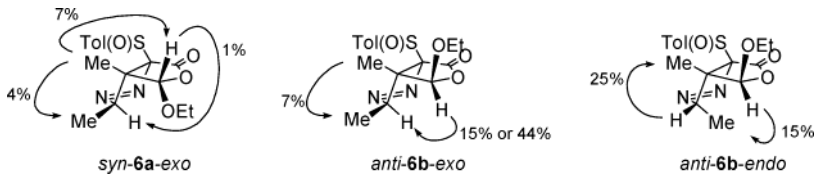
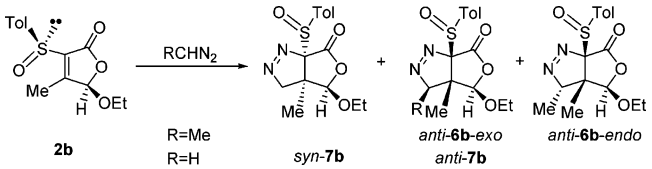


FIGURE 3. NOE effects of adducts **6**.

TABLE 4. Additions of Diazoethane and Diazomethane to 2b



entry	R	solvent	time (h)	*T* (°C)	syn:anti (exo:endo)
1	Me	Et_2O	3	0	0:100 (66:34)
2	Me	CH_3CN/Et_2O	3	−40	0:100 (78:22)
3[a]	H	Et_2O	3	0	0:100
4	H	CH_3CN/Et_2O	3	−40	5:95

[a] This result was identical with that reported in ref 3.

$^1\Delta$-pyrazolines, *anti*-**6b**-*exo* and *anti*-**6b**-*endo* (entry 1, Table 4), and required 3 h for completion, thus revealing that both reactivity and mainly exo selectivity of **2b** were lower than those for **2a**, whereas the π-facial selectivity was complete but opposite for both substrates. The increase in the solvent polarity had scarce influence. We must remark that the formation of the endo-adducts from compounds **2** only took place for the anti approaches of the dipole to **2a** and **2b**, whereas the exo-adducts were exclusively formed in the syn addition mode. The use of acetonitrile as the solvent scarcely modified the exo/endo selectivity. The reactions of **2b** with diazomethane (entries 3 and 4, Table 4) exclusively evolved into the adduct *anti*-**7b** in ethyl ether (entry 3, Table 4), but yielded a 95:5 mixture of *anti*-**7b** and *syn*-**7b** when performed in a 7.5:1 mixture of acetonitrile/ether (entry 4, Table 4).

The separation and purification of adducts **6** or **7** were not possible by column chromatography, but their characterization was made by NMR analysis of the reaction crude. The unequivocal configurational assignment of compounds shown in Figure 3 was performed on the basis of the observed NOE effects, which also confirmed the regiochemistry of the adducts.

The stereochemical results from **1a** and **1b** can only be explained by assuming a significant role of both electrostatic and steric factors, which in turn are related to the configurations at both the sulfur atom and C-5.[14] Electrostatic repulsion between sulfinyl and carbonyl oxygens completely shifts the conformational equilibria around the C−S bond toward the s-cis rotamer A (Figure 4), which arranges the *p*-tolyl group toward one of the diastereotopic faces of the dipolarophile. From a steric point of view, this orientation makes difficult the approach of the dipole to such a face. The influence of this factor must be identical for **1a** and **1b**, both exhibiting the same configuration at sulfur. By contrast, the steric

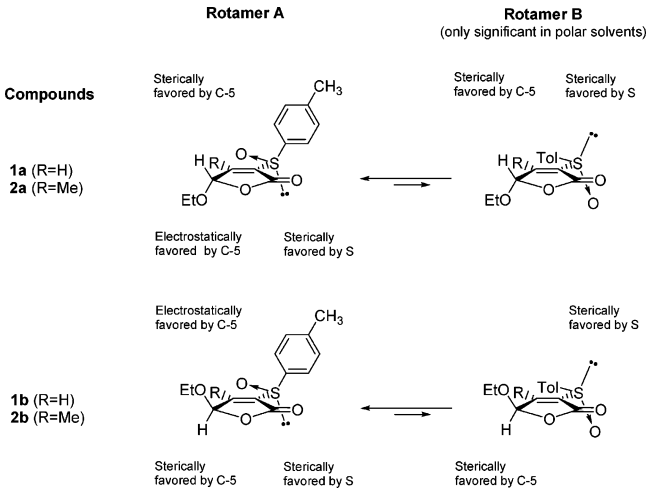


FIGURE 4. Conformational equilibrium of sulfinylfuranones **1** and **2** and substituent effects on diastereofacial selectivity.

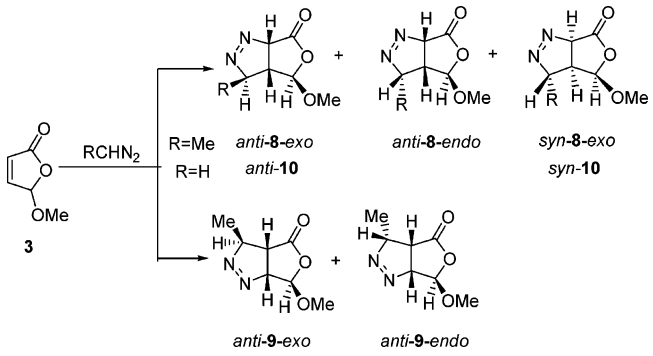
influence of the EtO group—much lower than that of the *p*-tolyl group—in the π-facial selectivity must be opposite that for both compounds, differing at the configuration at C-5. Thus, we expect a more stereoselective evolution for compound **1b** (the anti approach would be favored by both chiral centers) than for **1a** (each center favors a different approach, which would counterbalance their influence). The experimental results show that is not the case in ethyl ether (at 0 °C, de was higher than 90% for **1a** but lower than 70% for **1b**), thus suggesting that other contributions should be considered. The fact that the use of a more polar solvent (CH_3CN) lowers the proportion of the syn adducts, decreasing the de value in reactions from **1a** but increasing it in those from **1b**, suggests an electrostatic character for these interactions that favors the syn-approaches in apolar solvents, although the nature of such interactions is not so obvious.[15]

The decrease in the π-facial selectivity observed in reactions of **1a** with the change of the solvent polarity is more marked that the increase observed in reactions of **1b**. This can be explained as a consequence of the shifting of the conformational equilibria toward rotamers B (Figure 4) in polar solvents, where the electrostatic repulsion between the sulfinyl and carbonyl oxygens is lower. As we can see in Figure 4, in the case of compound **1a**, the steric effects clearly favor the anti approach to rotamer B, whose population will only be significant in polar solvents, which minimizes the importance of electrostatic interactions. As the anti approach to rotamer A was also favored in polar solvents both tendencies

(14) This contrasts with the previously reported proposal in ref 3, which assumed that the π-facial selectivity was exclusively controlled by the sulfinyl configuration through the steric effects present in the most stable conformation around the C−S bond.

(15) Taking into account that the carbonated end at the dipole supports a negative charge, initially we thought that the alkoxy oxygen could exhibit a possitive charge as a consequence of the strong anomeric effect present in 5-alkoxy-furan-2-(5*H*)-ones, but further theoretical calculations revealed that this was not the case.

TABLE 5. Additions of Diazoethane and Diazomethane to 3



entry	solvent	time (h)	*T* (°C)	R	adducts **8** or **10**[a]	adducts **9**[a]	anti:syn	regioisomeric ratio
1[b]	Et_2O	1.5	−10	Me	*anti*-**8**-*exo* (40) *anti*-**8**-*endo* (7) *syn*-**8**-*exo* (45)	*anti*-**9**-*exo* (5.5) *anti*-**9**-*endo* (2.5)	55:45	92:8
2	CH_3CN	1.5	−10	Me	*anti*-**8**-*exo* (59.6) *anti*-**8**-*endo* (9.2) *syn*-**8**-*exo* (29)	*anti*-**9**-*exo* (1.4) *anti*-**9**-*endo* (0.8)	71:29	97.8:2.2
3	CH_3CN	3	−40	Me	*anti*-**8**-*exo* (67) *anti*-**8**-*endo* (8) *syn*-**8**-*exo* (24.2)	*anti*-**9**-*exo* (0.5) *anti*-**9**-*endo* (0.3)	75.5:24.5	98.7:1.3
4	Et_2O	12	−10	H	*anti*-**10** (50) *syn*-**10** (50)	−	50:50	100:0
5	CH_3CN	12	−10	H	*anti*-**10** (73) *syn*-**10** (27)	−	73:27	100:0

[a] Relative proportion determined by ^1H NMR of the reaction crude. [b] Combined yield after column chromatography 90% (41% of *syn*-**8**-*exo* and 33% of *anti*-**8**-*exo* as pure isomers).

superimposed and strongly reduced the facial diastereoselectivity of **1a** in acetonitrile (Table 1). On the contrary, in the case of **1b**, the evolution of rotamer B must be scarcely selective (the face sterically favored by each chiral center is different), which partially compensates for the higher stereoselective evolution of rotamer A expected in polar solvents (see above). Consequently, the facial stereoselectivity of the reactions from **1b** is scarcely affected by the solvent polarity.

The results with **2a** and **2b** can be explained on the basis of the lower reactivity—and, therefore, the higher selectivity—of these substrates, by assuming a model similar to that used for compounds **1a** and **1b**, with the only difference that conformations A must be predominant in any solvent, because of the strong steric Me/*p*-tolyl interaction unstabilizing rotamers B. Thus, both compounds evolved in a completely stereoselective way in Et_2O. The increase in the solvent polarity destabilized the syn approaches causing an increase in the proportion of the anti-adducts, which is only possible for **2a**.

At this point, the study of the reactions of 5-alkoxyfuran-2(5*H*)-ones with diazoalkanes in solvents of different polarity appeared doubly interesting. First, it would allow us to establish the role of the 5-alkoxy group on the course of these cycloadditions, thus confirming or not the conclusions deduced from the above results concerning the relative importance of the steric and electrostatic grounds in the stereoselectivity control. Second, the comparison between the results from this study with those of the sulfinylfuranones **1a** and **1b** would provide direct evidence about the role of the sulfinyl group in these 1,3-dipolar reactions. To our knowledge, the only reported data are those concerning reactions of diazomethane with 5-methoxyfuran-2(5*H*)-ones[16] and 5-(*l*)-menthyloxyfuran-2(5*H*)-one[17] in apolar solvents. Moreover, although different stereoselectivities (70/30[16] and 55/45[17]anti/syn ratios) were reported in both papers, they did not include any comment about them. This prompted us to study the reactions of diazoethane and diazomethane with 5-methoxyfuran-2(5*H*)-one (**3**) in ether and acetonitrile.[18] The results are shown in Table 5.

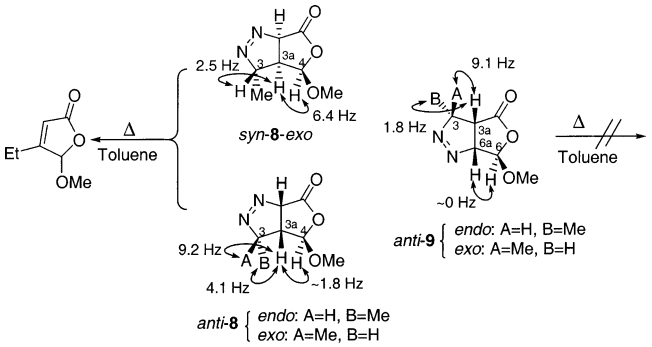
The reaction of diazoethane with **3** required 1.5 h at −10 °C, affording a mixture of five isomers (entry 1); two of them, *anti*-**9**-*endo* and *anti*-**9**-*exo*, exhibited the opposite regiochemistry to that of the adducts formed from **1** and **2**. The major adducts, *anti*-**8**-*exo* and *syn*-**8**-*exo*, isolated in 33% and 41% yields, were fully characterized. Both regioselectivity (92:8) and facial stereoselectivity (55:45) of this reaction were improved in acetonitrile (entries 2 and 3). The major adduct *anti*-**8**-*exo* obtained under the conditions of entry 3 was isolated in 60% yield. The reactions of **3** with diazomethane in ether and acetonitrile were completely regioselective (entries 4 and 5), whereas the stereoselectivity was almost nonexistent in Et_2O but increased up to 46% de in acetonitrile, with *anti*-**10** being the major adduct. Regioisomers **8** and **9** were easily separated by chromatography as mixtures of stereoisomers. Compounds *anti*-**9**-*exo* and *anti*-**9**-*endo*

(16) Fariña, F.; Martín, M. V.; Sánchez, F. *Heterocycles* **1986**, *24*, 2587−2592.

(17) Rispens, M. T.; Keller, E.; de Lange, B.; Zijlstra, R. W. J.; Feringa, B. L. *Tetrahedron*: *Asymmetry* **1994**, *5*, 607−624 and references therein.

(18) These data suggest that the results published in ref 16, concerning the π-facial selectivity of the reaction of 5-methoxy-2(5*H*)-furanone with diazomethane at −10 °C (30:70 syn:anti), could be wrong. On the other hand, the stereoselectivity reported in ref 17 for reactions of 5-(*l*)-menthyloxy-2(5*H*)-furanone with diazomethane (40:60 syn:anti) is not consistent with that of ref 16 from a steric point of view (as the menthyloxy group is bulkier than the methoxy one, a higher proportion of the anti-adduct must be expected in the former case).

SCHEME 1



were spectroscopically characterized from their mixture. It was also possible for *anti*-**8**-*endo* to be characterized from the mixture containing the three adducts **8**, once the two major exo adducts had been independently characterized.

The most significant parameters in the stereochemical and regiochemical assignment of adducts **8** and **9** are depicted in Scheme 1.

The different regiochemistry of the adducts was unequivocally established by chemical and spectroscopical methods. Thus regioisomers **8** exhibit H-3a coupled to the three protons of the bicyclic fragment, whereas the equivalent proton at **9** (now designed as H-6a) only shows one apparent coupling constant with H-3a ($J_{3a,6a}$ = 8.1 or 7.5 Hz), because the trans relationship between H-6 and H-6a determines an almost zero value for $J_{6,6a}$. As a confirmation of the so assigned regiochemistry, compounds *anti*-**8**-*exo* and *syn*-**8**-*exo* were independently transformed into 4-ethyl-5-methoxyfuran-2(5*H*)-one[19] in almost quantitative yield by heating in toluene for 1 h. The same compound was obtained as the sole product starting from the *anti*-**8**-*exo*/*syn*-**8**-*exo*/*anti*-**8**-*endo* mixture. These results unequivocally indicate that the carbon of the dipole is joined to C-4 at the dipolarophile in compounds **8**. By contrast, under the same reaction conditions, the *anti*-**9**-*exo*/*anti*-**9**-*endo* mixture remained unaltered for longer periods of time. This stability toward the extrusion of the nitrogen could be a consequence of the change in the regiochemistry. The stereochemistry syn or anti assigned to compounds **8** could be deduced from the values of $J_{3a,4}$ (<2 Hz for the anti-adducts and 6.4 Hz for the syn-adduct), which are similar to those previously reported for compounds **10**.[16] The endo or exo character was deduced from the value of $J_{3a,3}$ (≥9 and ≤4 Hz, respectively). These rules allowed us to assign the stereochemistry of compounds **9**.

As can be deduced from Table 5, the regioselectivity observed in reactions with diazoethane (92:8, entry 1) was lower than that with diazomethane (100:0, entry 4), as could be expected from a steric point of view. On the other hand, the reactivity of $MeCHN_2$ at −10 °C (1.5 h were required to reach completion) was higher than that of CH_2N_2 (12 h), which was not unexpected by FMO theory. Moreover, the π-facial selectivity, measured as the syn/anti ratio of the adducts **8**, was similar for both dipoles (45/47 for diazoethane, entry 1, and 50:50 for diazomethane, entry 4), and quite lower than that expected from a steric point of view, clearly favoring the anti approaches.[20] The increase in the π-facial selectivity (anti/syn ∼ 3:1) observed in acetonitrile suggests that some type of electrostatic interaction is able to counterbalance the steric repulsion for the syn approach. Finally, the high exo/endo ratio observed in reaction with diazoethane (∼12:1 for the major regioisomer) scarcely modified by the solvent polarity suggests that the steric factors favor the exo addition mode (vide infra).

The comparison of the results obtained in the reactions of diazomethane and diazoethane with compounds **1** (Tables 1 and 2) and **3** (Table 5) allowed us to deduce the role of the sulfinyl group in the course of these 1,3-dipolar reactions. It can be summarized as follows:

(a) It strongly increases the reactivity of the dipolarophile. Thus, reactions of **3** with diazoethane and diazomethane at −10 °C required 1.5 and 12 h, respectively, to reach completion (Table 5), whereas they are instantaneous from **1a** and **1b** (Tables 1 and 2).

(b) It improves the regiochemistry. Reactions of diazoethane with **1a** and **1b** (Tables 1 and 2) evolved with complete regioselectivity, whereas mixtures of regioisomers were obtained starting from **3** (Table 5).

(c) It is the main group responsible for the π-facial selectivity in low-polarity solvents (it was very high or even complete for compounds **1** and **2** but scarcely significant for **3**), where the sulfur configuration determines the face of the furanone ring, which is favored for the approach of the dipole, regardless the configuration at C-5.

(d) It favors the exo addition mode in reactions with diazoethane (the exo selectivity is complete for compounds **1a** and **1b**, whereas a small amount of endo adduct was formed starting from **3**).

The problem of the endo/exo selectivity observed in reactions with diazoethane deserves additional comments. The reactions of compounds **1a** and **1b** were completely exo-selective (Tables 1 and 2). This was also the case in the syn-approaches of the dipole to compounds **2a**, **2b**, and **3** (Tables 3−5). The endo-adducts were only formed as the minor ones in the anti approaches of the dipole to these later furanones (exo/endo ratios ranged between 2 and 3 for **2a** and **2b**, being ∼7 for **3**). To explain these results we assume that the most important factor controlling the exo-selectivity of these reactions must be mainly related to the steric interactions of the susbstituents at C-4 of the furanone ring (C-5 and H for **1** and **3** and C-5 and CH_3 for **2**) with those of the diazoethane (Me and H) in the transition state corresponding to each approach of the dipole to the dipolarophile. During the approach of the dipole to the face displaying the OR group, only the exo-adducts were formed from every substrate (syn-endo adducts were never detected). This can be explained by taking into account that the steric interaction of Me/C_5-OR, present in the endo modes for any substrate, is more destabilizing than that for Me/H (compounds **1** and **3**) or Me/C-H (compounds **2**) of the exo modes. During the attack of the dipole to the opposite face of that supporting the alkoxy group (anti approach)

(19) Hoffmann, N.; Buschmann, H.; Raabe, G.; Scharf, H. *Tetrahedron* **1994**, *50*, 11167−11186.

(20) The steric differentiation of the diastereotopic faces at the furanone ring produced by the OMe group at C-5 was able to control the π-facial selectivity of their reactions with cyclopentadiene (Feringa, B. L.; de Jong, J. C. *J. Org. Chem.* **1988**, *53*, 1125−1127).

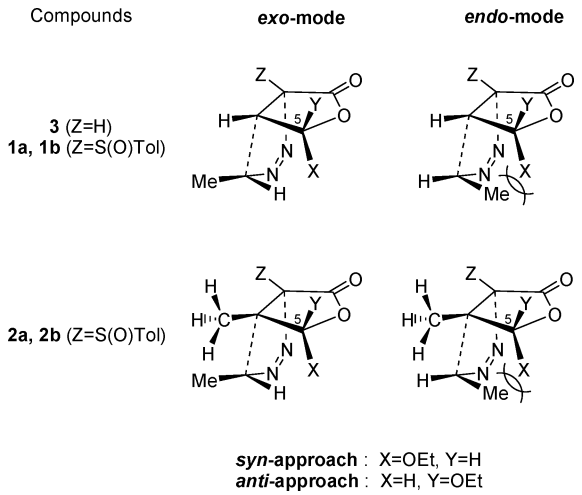


FIGURE 5. Approach of diazoethane to furanones **1**−**3**.

the exo mode is more stable than the endo one in the case of compounds **1** and **3** (Me/H and H/C_5-H interactions are preferred with respect to Me/C_5-H and H/H, Figure 5), whereas the interactions of both modes are similar for compounds **2** (Me/C-H and H/C_5-H or H/C-H and Me/C_5-H). The preference for the exo-adducts in the later case could also be due to the higher rigidity of the cyclic C_5-H fragment with respect to the exocyclic CH_3.

As on the basis of the experimental data we have not been able to establish the nature of the electrostatic interactions that have some influence on the π-facial selectivity of these reactions, we decided to explore these reactions from a theoretical point of view, to obtain some answer to this problem. Moreover, the increase in the reactivity and regioselectivity produced by the sulfinyl group experimentally observed for all these reactions could also be evaluated by analyzing the global and local indices of the reactants. The density functional theory formulation of Parr, Pearson, and Yang (PPY-DFT)[21] has introduced a number of global descriptors of electronic structure, such as the electronic chemical potential (μ), chemical hardness (η) and chemical softness (s), and electrophilicity index (ω),[22] providing modern chemistry with more quantitative concepts.

Recently, Domingo et al. have created a global electrophilicity scale,[23] based on the ω values, for dienes and dienophiles commonly used in Diels−Alder reactions (DA),[23a] as well as dipoles and dipolarophiles used in 1,3-DC reactions.[23b] Within this scale, 1,3-DC reactions between dipoles with a low ω value (marginal electrophiles or nucleophiles) and dipolarophiles with high ω values (strong electrophiles) correspond with normal electron demand cycloaddition (NED) processes and, accordingly, with a charge transfer from the dipole to the dipolarophile. The opposite interactions (electrophilic dipoles with nucleophilic dipolarophiles) are classified as inverse electron demand (IED) 1,3-DC reactions. We have analyzed our 1,3-dipolar reactions on the same basis.

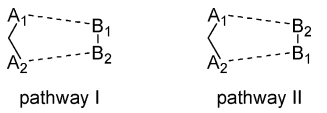


FIGURE 6. Regiochemical pathways.

TABLE 6. Global Electrophilicity (ω in eV) and Local Softness (s in eV^{-1}) for Dipoles and Dipolarophiles

	ω	s_i^α	s_j^α
diazomethane	1.405	0.386[a]	0.573[b]
diazoethane	1.245	0.390[a]	0.497[b]
1a	1.821	0.044[c]	0.087[d]
1b	1.821	0.044[c]	0.087[d]
3	1.692	0.040[c]	0.066[d]

[a] $\alpha = -$, i = N. [b] $\alpha = -$, j = C. [c] $\alpha = +$, i = 3. [d] $\alpha = +$, j = 4.

Table 6 presents the most significant global and local indices for the diazoalkanes and the dipolarophiles **1a**, **1b**, and **3** computed at the B3LYP/6-31G(d) level. The ω values indicate that the 1,3-DC of diazoalkanes and the 5-alkoxyfuranones can be classified as Sustmann Type I processes[24] in which a net charge transfer from the dipole to the dipolarohile occurs in the cycloaddition. The difference in the reactivity of **1** and **3** toward diazoalkanes could be explained in terms of electrophilicity (ω). Higher ω values make the dipolarophile more electrophilic and therefore more reactive. The opposite is also true for the different reactivity of diazoalkanes, that is, lower ω values imply higher nucleophilicity of the dipole and consequently higher reactivity (diazoethane > diazomethane).

Besides the definition of global descriptors, PPY-DFT provided local reactivity indices derived directly from the ground-state electron density. The local softness, s_k^α (local softness at atom k with α being either $-$, for an electrophilic attack, or $+$, for a nucleophilic one), is one of the most common descriptors of site reactivity.

In the case of a diene or dipole (A) that reacts with a dienophile or dipolarophile (B), two regiochemical pathways are possible (Figure 6). The regioselectivity in cycloaddition reactions with two bond-forming interactions has been recently studied by means of the local hard and soft acids and bases (HSAB) principle.[25] In these studies, successful prediction of the regioselectivity was obtained by a local softness matching square sum criterion, which can be expressed as follows: pathway I is preferred over pathway II when

$$(s_{A_1}^- - s_{B_1}^+)^2 + (s_{A_2}^- - s_{B_2}^+)^2 < (s_{A_1}^- - s_{B_2}^+)^2 + (s_{A_2}^- - s_{B_1}^+)^2 \Rightarrow \Delta s_{B_1^+B_2^+}^{A_1^-A_2^-} < \Delta s_{B_2^+B_1^+}^{A_1^-A_2^-} \quad (1)$$

(21) (a) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989. (b) Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512−7516.

(22) Parr, R. G.; von Szentpály, L.; Liu, S. *J. Am. Chem. Soc.* **1999**, *121*, 1922−1924.

(23) (a) Domingo, L. R.; Aurell, M. J.; Pérez, P.; Contreras, R. *Tetrahedron* **2002**, *58*, 4417−4423. (b) Pérez, P.; Domingo, L. R.; Aurell, M. J.; Contreras, R. *Tetrahedron* **2003**, *59*, 3117−3125.

(24) (a) Sustmann, R. *Tetrahedron Lett.* **1971**, 2717−2720. (b) Sustmann, R.; Trill, H. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 838−840. (c) Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569−593.

(25) (a) Damon, S.; Van de Woude, G.; Méndez, F.; Geerlings, P. *J. Phys. Chem. A* **1997**, *101*, 886−893. (b) Sengupta, D.; Chandra, A. K.; Nguyen, M. T. *J. Org. Chem.* **1997**, *62*, 6404−6406. (c) Chandra, A. K.; Nguyen, M. T. *J. Comput. Chem.* **1998**, *19*, 195−202. (d) Chandra, A. K.; Nguyen, M. T. *J. Phys. Chem. A* **1998**, *102*, 6181−6185. (e) Le, T. N.; Nguyen, L. T.; Chandra, A. K.; De Proft, F.; Geerlings, P.; Nguyen, M. T. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1249−1255. (f) Chandra, A. K.; Uchimaru, T.; Nguyen, M. T. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2117−2121.

TABLE 7. Regiochemical Analysis in Terms of Δs Values (in 10^{-3} eV^{-1})

	pathway	diazomethane	diazoethane
1a	I ($\Delta s_{3^+4^+}^{N^-C^-}$)	2.61	2.47
	II ($\Delta s_{4^+3^+}^{N^-C^-}$)	5.98	4.51
	I−II	−3.36	−2.04
1b	I ($\Delta s_{3^+4^+}^{N^-C^-}$)	2.59	2.45
	II ($\Delta s_{4^+3^+}^{N^-C^-}$)	5.94	4.48
	I−II	−3.35	−2.03
3	I ($\Delta s_{3^+4^+}^{N^-C^-}$)	4.84	4.33
	II ($\Delta s_{4^+3^+}^{N^-C^-}$)	6.89	5.57
	I−II	−2.05	−1.24

for a NED cycloaddition process or when

$$(s_{A_1}^+ - s_{B_1}^-)^2 + (s_{A_2}^+ - s_{B_2}^-)^2 < (s_{A_1}^+ - s_{B_2}^-)^2 + (s_{A_2}^+ - s_{B_1}^-)^2 \Rightarrow \Delta s_{B_1^-B_2^-}^{A_1^+A_2^+} < \Delta s_{B_2^-B_1^-}^{A_1^+A_2^+} \quad (2)$$

for an IED one.

In the case of our 1,3-DC, we name pathway I for the regiochemical orientation in which $N_{(dipole)}$−$C3_{(dipolarophile)}$ and $C_{(dipole)}$−$C4_{(dipolarophile)}$ bonds are created and, therefore, pathway II for the orientation with an opposite bond forming pattern. The regiochemical preference can be predicted with the aid of eq 1 and the results presented in Table 7. In all cases, pathway I is preferred over pathway II, as indicated by the lower Δ*s* values of the former. The presence of the sulfoxide group in position 3 of the dipolarophile enhances the regiochemical preference for pathway I and, in addition, a methyl substituent in the dipole (diazoethane) leads to lower preference for the same pathway. Hence, the reaction of diazoethane with **3** presents the lowest of all values for the regiochemical preference for pathway I (pathway I−II in Table 7) in agreement with the experimental results that correspond with the only case in which regioisomers from pathway II were detected.

The global and local PPY-DFT reactivity indices have been shown as very useful tools in the study of the reactivity and regioselectivity of these 1,3-DC. However, the stereochemical outcome must be studied by examination of the stationary points along the reaction path. Diastereoselectivity in 1,3-DC of **1** and **2** with diazoalkanes is strongly dependent on the polarity of the solvent, thus suggesting a significant contribution of some kind of electrostatic interactions involving the alkoxy group at C-5 favoring the syn-approaches more than expected from a steric point of view. To shed light on the nature and scope of this effect, we started our study with the reaction of diazomethane with furanone **3** (see Table 5) for which this is the only factor affecting *π*-facial selectivity of the cycloaddition.

Table 8 summarizes the results of our study in the reaction of diazomethane with **3**. At all the DFT levels of calculation, the reaction is predicted to be exothermic with 32.3 kcal/mol as the lowest energy barrier for the reverse process and, because the experimental results were taken at temperatures below 0 °C, these are 1,3-DC under kinetic control. At the B3LYP/6-31G(d) level, there is an important preference in the gas phase for the syn stereochemistry over the anti one (1.4 kcal/mol). Energy barriers for the transition structures are reduced

TABLE 8. Energy Barriers for the Transition Structures and Cycloadducts 10 at Different Levels of Calculation as well as the Energy Difference Anti−Syn in the Transition Structures (kcal/mol)

		syn-10		*anti*-10		**TS10**
	ϵ^a	TS	adduct	Ts	adduct	(anti−syn)
B3LYP/6-31G(d)	1.00	13.2	−24.2	14.6	−24.7	1.4
	4.20	10.0	−35.4	10.9	−35.9	0.9
	35.94	9.8	−37.7	10.4	−38.1	0.6
B3LYP/6-31++G(d,p)	1.00	15.1	−20.7	16.4	−21.6	1.3
	4.20	12.0	−31.9	12.7	−32.9	0.7
	35.94	11.8	−34.2	12.1	−35.3	0.3
B3LYP/6-31++G(d,p)//	1.00	15.2	−20.6	16.4	−21.5	1.2
B3LYP/6-31G(d)	4.20	12.1	−32.0	12.8	−32.9	0.7
	35.94	12.0	−34.6	12.3	−35.3	0.3
B3LYP/cc-pVTZ//	1.00	16.9	−15.4	18.2	−16.2	1.3
B3LYP/6-31G(d)	4.20	11.4	−27.9	11.9	−26.0	0.5
	35.94	10.1	−30.7	9.7	−27.6	−0.4
MP2/6-31++G(d,p)	1.00					1.0[b]
	4.20					0.9
	35.94					0.8

[a] ϵ = dielectric constant (1.00, gas phase; 4.20, Et_2O; 35.94, CH_3CN). [b] At the HF/6-31++G(d,p) level, **TS10**(syn − anti) = 1.2 kcal/mol.

with the increase in solvent polarity but this effect is higher for the cycloadducts (higher exothermicity) and, therefore, the energy barriers for the reverse process raise. Solvent effects are also involved in the stereochemistry of the addition, thus the syn approach is less favored with increasing polarity of the medium, in agreement with the experimental results. However, at this level of calculation, *syn*-**10** is always the most favored adduct whereas ∼1:1 and ∼3:1 anti:syn ratios were experimentally obtained in Et_2O and CH_3CN, respectively. In conclusion, the B3LYP/6-31G(d) method reproduces the observed directing effect of the alkoxy group in position 5 but its magnitude is overestimated.

The results with a higher basis set that includes diffuse and polarization functions on first row and hydrogen atoms (6-31++G(d,p)) exhibit a similar trend but with a slightly lower syn preference in the gas phase and a slightly higher solvent effect. However, in the most polar solvent (CH_3CN) the syn-adduct is still favored by 0.3 kcal/mol over the anti-adduct.

The lower stabilization of the transition structures and adducts with respect to the reactants found with this higher basis set suggests that a basis set superposition error (BSSE) could be significant and responsible for the overestimation of the 5-alkoxy directing effect. We then decided to use a more complete basis set but through single-point energy calculations. As a previous step, we carried out single-point energy calculations at the B3LYP/6-31++G(d,p) level (for which we have the results of the full optimization) on the B3LYP/6-31G(d) optimized geometries and used the zero-point energy correction (ZPEC) at this latter level. This procedure allowed us to validate B3LYP/6-31G(d) geometries for use in single-point energy calculations at higher levels. The obtained electronic energies plus ZPEC of all the structures are between 0.1 and 0.6 kcal/mol higher than those obtained with the B3LYP/6-31++G(d,p) geometries. These values are slightly lower in solution, from 0.0 to 0.2 kcal/mol in Et_2O, and from 0.0 to 0.4 kcal/mol in CH_3CN. However, and most significantly, the energy differences (TS−

TABLE 9. Significant Parameters (charges, *q*, in e; distances, *d*, in Å; and bond orders, BO) for TS-*syn*-10 and TS-*anti*-10

			TS-*syn*-**10**			TS-*anti*-**10**		
	$NNCH_2$ H	**3** O-5	H_{endo}	H_{exo}	O-5	H_{endo}	H_{exo}	O-5
q_{ChelpG}[a]	0.287	−0.386	0.072	0.092	−0.283	0.096	0.136	−0.442
$q_{natural}$[b]	0.243	−0.570	0.281	0.254	−0.588	0.256	0.258	−0.577
d_{H-C}	1.080		1.085	1.089		1.088	1.089	
BO_{H-C}	0.904		0.878	0.899		0.899	0.898	
d_{H-X5}[c]			2.235			2.387		
BO_{H-O}[d]			0.009	0.000		0.001	0.000	
$q_{transfer}$[e]			0.210	0.184				

[a] ChelpG charges (see Computational Methods). [b] Natural charges. [c] X5 = substituent at C5 in **3** (O in the syn approach and H in the anti one). [d] Intermolecular $H_{dipole} - O_{dipolarophile}$. [e] Charge transfer from the dipole to the dipolarophile in the transition structures (natural charges).

reactants and adducts−reactants) and stereochemical preferences are almost the same with both procedures (Table 8).

Our choice for a more complete basis set was the Dunning's triple-ζ one, cc-pVTZ, which includes polarization functions on all the atoms. In accordance with the observation in the case of 6-31++G(d,p), a more complete basis set raises the energies of transition structures and products with respect to the reactants. Finally, the most important consequence is present in the solvation effects on the stereoselectivity of the process. Now, the formation of adduct *syn*-**10** is favored in Et_2O, but with the lowest preference of all (0.5 kcal/mol), whereas the formation of *anti*-**10** is favored in CH_3CN by 0.4 kcal/mol. These are the theoretical results in best agreement with the experimental ones, but this methodology still slightly overestimates the directing effect of the 5-alkoxy group vicinal to the CC double bond.

Experimental results are successfully reproduced by DFT methods with a sufficiently large basis set. At this point, we decided to test ab initio methods versus DFT ones toward the problem of the diastereoselectivity of the cycloaddition. Full geometry optimization and frequency analysis of **TS**-*syn*-**10** and **TS**-*anti*-**10** were carried out at the HF/6-31++G(d,p) level, and taking these geometries as the starting point, subsequent optimization at the correlated MP2/6-31++G(d,p) level was performed. The results of these calculations are presented in Table 8. The values for the stereochemical preference of the reaction are very similar to those found with the DFT methods but with a slightly lower syn preference in the gas phase and lower solvent effects.

To establish the nature of the 5-alkoxy directing effect, we have explored different magnitudes in the reactants and the transition structures calculated at the B3LYP/6-31G(d) level (Table 9). Hydrogen atoms in diazomethane present notable positive charges while the oxygen atom at C-5 in **3** is negatively charged. These two atoms are the closest nondirectly bonded ones in **TS**-*syn*-**10** so an attractive Coulombic interaction could justify the 5-alkoxy effect.

Comparison of the values presented in Table 9 with the ones reported by Scheiner et al.[26] for several CH···O complexes reveals the presence of this kind of interaction controlling the stereochemistry of the cycloaddition. It should be noted that the direct comparison of the TS with the isolated reactants can lead to more profound changes than expected because in our case, both molecules are interacting in a cycloaddition process involving the atoms to which H and O are bonded. Hence, in this case, an optimal agreement is accounted for by comparing syn and anti approaches and even H_{endo} and H_{exo} in the same syn approach. In the above-mentioned paper, Scheiner et al. reported a C−H bond contraction in the CH···O complexes between 0.2 and 2.9 mÅ and, in our case, the $C-H_{endo}$ distance in **TS**-*syn*-**10** is ca. 3−4 mÅ shorter than the other C−H distances in the dipole fragment of the TS's. Additionally, CH···O complexes exhibit enhancements in the natural charges of the H and O atoms, between 16 and 33 me and between −1 to −23 me, respectively. H_{endo} in **TS**-*syn*-**10** present a natural charge value ∼25 me higher than the other H atoms in the dipole fragment of the TS's, whereas the O atom at C-5 of the dipolarophile in **TS**-*syn*-**10** presents a natural charge 11 me lower than that in **TS**-*anti*-**10**. This result refers to the concept of induction; the proximity of a negative charge to the H atom in diazomethane induces a polarization in the molecule that rises its positive charge, whereas the proximity of a positive charge to the O atom at C-5 of the furanone has the opposite effect. In contrast, the trend in ChelpG charges is just the opposite that in natural charges, which could easily be understood if this type of charge is visualized as the electrostatic effect measured at a certain distance from the nucleus. Therefore, the proximity of a charge with different sign tends to neutralize the effects, and accordingly, ChelpG charges should be lower in absolute value when H and O atoms are involved in CH···O hydrogen bonding.

An NBO analysis of the transition structures also shows the presence of the CH···O hydrogen bond by the weakening of the C−H bond (lower bond order in ∼0.011), appreciable H···O bond order (0.009), and the significant value for the $n_O \rightarrow \sigma^*_{C-H}$ second-order interaction, 1.6 kcal/mol, which is very close to the **TS10** anti − syn energy difference of 1.4 kcal/mol (Table 8).

The reactions of diazomethane with **1a**,**b** (Scheme 2) were studied following the methodology that provided the best results in the preceding case, i.e. full geometry optimization and frequency analysis of the reactants, transition structures, and cycloadducts at the B3LYP/6-31G(d) level and subsequent single-point energy calculations at the B3LYP/cc-pVTZ level. The results of these calculations are presented in Table 10. The energy barriers for the 1,3-DC are lower than those found for the 3-unsubstituted furanone **3** and the reactions are more exothermic, thus showing the higher reactivity of the 3-sulfinylfuranones.

The syn addition is greatly favored over the anti one (3.0−3.4 kcal/mol) in the reaction of diazomethane with **1a** in agreement with the high stereoselectivity found in the experiments when the reaction was carried out in the least polar solvent. On the other hand, in the reaction of diazomethane with **1b**, the stereochemical preference is significantly lower: syn addition is slightly favored over anti (0.3 kcal/mol) with the 6-31G(d) basis set, while anti addition is the favored one (0.3 kcal/mol) with the cc-pVTZ. In this case, again calculations with the shortest

(26) Gu, Y.; Kar, T.; Scheiner, S. *J. Am. Chem. Soc.* **1999**, *121*, 9411−9422.

SCHEME 2

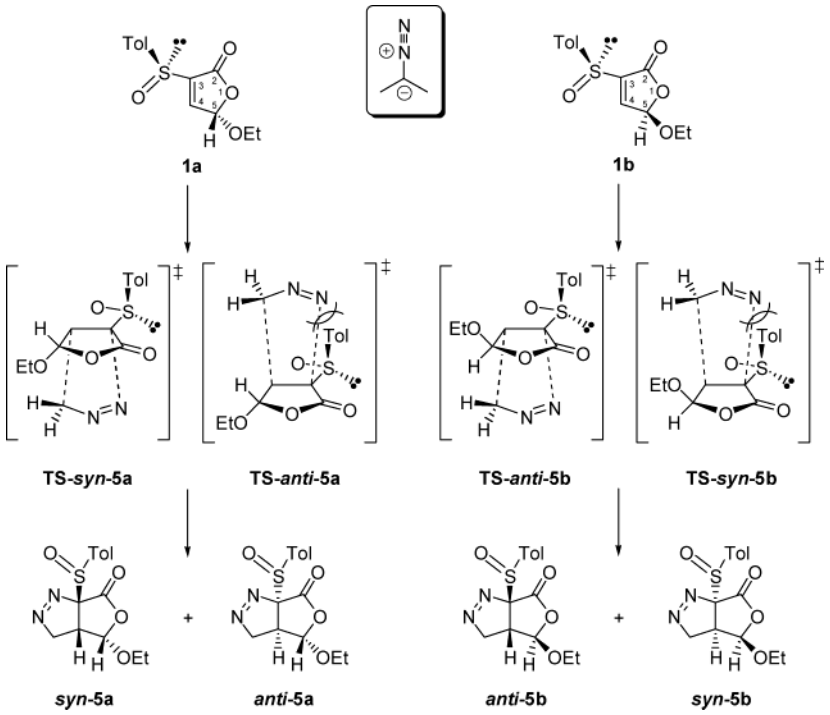


TABLE 10. Energy Barriers for the Transition Structures and Cycloadducts 5a,b at Different Levels of Calculation (kcal/mol)

		B3LYP/6-31G(d)	B3LYP/cc-pVTZ// B3LYP/6-31G(d)
syn-**5a**	TS	10.3	13.8
	adduct	−25.4	−16.3
anti-**5a**	TS	13.3	17.2
	adduct	−24.8	−16.2
syn-**5b**	TS	11.6	15.7
	adduct	−24.9	−15.8
anti-**5b**	TS	11.9	15.4
	adduct	−25.2	−16.2

basis set tend to overestimate the magnitude of the 5-alkoxy directing effect. To sum up, calculations at the B3LYP/cc-pVTZ//B3LYP/6-31G(d) reveal that the stereochemistry of the addition is mainly governed by the configuration of the S atom in position 3 (steric effects, SE) and it is modulated by the configuration in C5 (CH···O hydrogen bond, CHO). Assuming that these two effects are operating independently, the anti−syn energy difference in **TS-5a** consists of the sum of both effects favoring the syn addition

$$\Delta E(\textbf{TS-5a})_{\text{anti}-\text{syn}} = \text{SE} + \text{CHO} = 3.4 \qquad (3)$$

whereas in **TS-5b**, steric effects favor the anti-adduct and the 5-alkoxy directing effect favors the syn one

$$\Delta E(\textbf{TS-5b})_{\text{anti}-\text{syn}} = \text{SE} - \text{CHO} = 0.3 \qquad (4)$$

which yields a value of 1.85 kcal/mol for the steric effects (SE) and 1.55 kcal/mol for the 5-alkoxy directing effect (CHO). The latter is close to the anti−syn energy difference for **TS-10** in the gas phase (1.3 kcal/mol).

Table 11 presents the most significant parameters in **TS-5a** and **TS-5b** allowing the analysis of the CH···O interaction. As in the case of **TS-10**, several pieces of evidence support this hydrogen bonding (vide supra): (a) The higher absolute values of the natural charges for the H and O atoms in the *syn*-**TS** while ChelpG charges exhibit lower absolute values; (b) shortening and weakening of the C−H bond in the *syn*-**TS** over the anti one; and (c) appreciable H···O bond order.

In addition, the NBO analysis revealed significant values for the $n_O \rightarrow \sigma^*_{C-H}$ interactions, 1.16 kcal/mol in **TS**-*syn*-**5a** and 0.79 kcal/mol in **TS**-*syn*-**5b**.

It should be noted that these calculations where carried out only for the gas-phase processes since the two factors controlling the stereochemistry are affected by solvent effects. On one hand, increasing solvent polarity stabilizes charges and therefore weakens CH···O interactions. On the other hand, in high-polarity solvents, the conformational preference of the rotamers with the S → O bond in an s-cis arrangement with respect to the dipolarophilic double bond (rotamer A in Figure 4) must be lower, thus increasing the population of the other possible conformers around the C3−S (rotamers B in Figure 4) that exhibit a less significant influence of the bulky *p*-tolyl group. This fact complicates the calculations of the reactions of diazomethane with **1a** or **1b** since, to take into account all the effects, three conformations should be studied for each one of the structures presented in Scheme 2. Due to the size of the problem and the high number of structures involved, the required computational cost exceeds the aim of this work. Nevertheless, the solvent polarity effects on the outcome of these reactions could be rationalized from a qualitative point of view as previously indicated (see above).

Conclusions

We can conclude that the reactions of diazoalkanes with 5-alkoxy-3-*p*-tolylsulfinylfuran-2(5*H*)-ones are quite

TABLE 11. Significant Parameters (charges, *q*, in e; distances, *d*, in Å; and bond orders, BO) for TSs 5a and 5b

	$NNCH_2$ H	**1a** O-5	TS-*syn*-**5a** H_{endo}	TS-*syn*-**5a** O-5	TS-*anti*-**5a** H_{endo}	TS-*anti*-**5a** O-5	**1b** O-5	TS-*syn*-**5b** H_{endo}	TS-*syn*-**5b** O-5	TS-*anti*-**5b** H_{endo}	TS-*anti*-**5b** O-5
q_{ChelpG}[a]	0.287	−0.389	0.085	−0.268	0.141	−0.490	−0.455	0.073	−0.247	0.141	−0.546
$q_{natural}$[b]	0.243	−0.562	0.280	−0.598	0.260	−0.585	−0.576	0.281	−0.599	0.258	−0.585
D_{H-C}	1.080		1.084		1.088			1.084		1.087	
BO_{H-C}	0.904		0.880		0.899			0.882		0.898	
d_{H-X5}[c]			2.302		2.504			2.331		2.507	
BO_{H-O}[d]			0.006		0.000			0.005		0.000	
$q_{transfer}$[e]			0.288		0.251			0.284		0.262	

[a] ChelpG charges (see Computational Methods). [b] Natural charges. [c] X5 = substituent at C5 in **3** (O in the syn approach and H in the anti one). [d] Intermolecular $H_{dipole} - O_{dipolarophile}$. [e] Charge transfer from the dipole to the dipolarophile in the transition structures (natural charges).

interesting in asymmetric synthesis because they evolve in high yields under mild conditions affording bicyclic pyrazolines with complete regioselectivity, exo-selectivity, and very high π-facial selectivity, which can be modulated, becoming almost complete, with the solvent polarity. The sulfinyl group increases the dipolarophilic reactivity of the butenolides, as well as their regioselectivity and exo-selectivity. Moreover it is the main group responsible for the π-facial selectivity, but electrostatic interactions between dipoles and the alkoxy group at C-5 are also significant in apolar solvents. Finally, the steric interactions between the substituents at diazoethane and at C-4 of the furanone rings are the main reasons for the observed exo-selectivity. The results obtained in the theoretical study of these 1,3-dipolar reactions, making use of the density functional theory of Parr, Pearson, and Yang (PPY-DTF), are consistent with the experimentally observed behavior and suggest that the stabilizing hydrogen bonds between the negatively charged alkoxy oxygen at C-5 of the furanone and the positively charged hydrogen atoms at the dipole almost compensate for the steric interactions associated with the syn approaches of both reagents.

Experimental Section

General Methods. Flash chromatography was performed with silica gel 60 (230−400 mesh), and silica gel F_{254} plates were used for preparative TLC. The IR spectra frequencies are gives in cm^{-1}. NMR spectra were determined in $CDCl_3$ solutions at 300 (or 200) and 75.5 (or 50.3) MHz for ^1H and ^{13}C NMR, respectively; chemical shifts (δ) were reported in ppm and *J* values are gives in hertz. Optical rotations were obtained at ambient temperature in the solvent and concentration (g/100 mL) indicated in each case. Diazomethane and diazoethane were synthesized according to the procedure described in ref 27.

General Procedure for the Addition of Diazoalkanes to Furan-2(5*H*)-ones. To a solution of furanone (0.40 mmol) in diethyl ether or acetonitrile (11 mL for **1a**, **1b**, **2b**, and **3** or 20 mL for **2a**), cooled at the temperature indicated in Tables 1−5, was added an ethereal solution of diazoethane or diazomethane (1.5 mL, containing 0.6 mmol/mL). The reaction was kept at the same temperature during the period indicated in each case. The solvent was removed and the residue was analyzed by ^1H NMR (Tables 1−5) and purified as indicated in each case.

The data for adducts *syn*-**5a**, *anti*-**5b**, *syn*-**7a**, and *anti*-**7b** have been reported previously in ref 3 and the data for the adducts **10** in ref 16.

(27) Arndt, F. *Organic Syntheses*; Wiley: New York, 1941; Collect. Vol. II, pp 165−167.

(3*R*,3a*S*,4*S*,6a*R*,S*S*)-4-Ethoxy-3-methyl-6a-[(4-methylphenyl)sulfinyl]-3,3a,4,6a-tetrahydro-6*H*-furo[3,4-*c*]pyrazol-6-one (*syn*-4a-*exo*). *syn*-**4a**-*exo* was obtained from **1a** and diazoethane, after 5 min of reaction time. It was isolated as a white solid by column chromatography (silica gel was previously treated with triethylamine), 50:45:5 hexane/dichloromethane/diethyl ether. Yield 80%; mp 91−93 °C dec. $[\alpha]^{20}_D$ +416.0 (*c* 0.5, acetone); IR (KBr) 1756, 1595, 1084, 1060; ^1H NMR δ 7.60 and 7.38 (AA′BB′ system, 4H), 5.40 (qd, *J* = 7.3 and 3.7, 1H), 4.68 (d, *J* = 6.7, 1H), 3.68 (m, 1H), 3.44 (m, 1H), 2.73 (dd, *J* = 6.7 and 3.7, 1H), 2.45 (s, 3H), 1.57 (d, *J* = 7.3, 3H), 1.13 (t, *J* = 7.1, 3H); ^{13}C NMR δ 163.5, 143.7, 134.1, 130.4, 124.7, 122.3, 102.2, 88.0, 66.8, 41.7, 21.4, 17.9, 14.4. Anal. Calcd for $C_{15}H_{18}N_2O_4S$: C, 55.88; H, 5.63; N, 8.69; S, 9.95. Found: C, 55.75; H, 5.39; N, 8.61; S, 10.41.

(3*S*,3a*R*,4*S*,6a*S*,S*S*)-4-Ethoxy-3-methyl-6a-[(4-methylphenyl)sulfinyl]-3,3a,4,6a-tetrahydro-6*H*-furo[3,4-*c*]pyrazol-6-one (*anti*-4a-*exo*). *anti*-**4a**-*exo* was obtained along with *syn*-**4a**-*exo* by addition of diazoethane to a solution of **1a** in acetonitrile. It could not be isolated as a pure compound. Spectroscopic data for *anti*-**4a**-*exo* correspond to those of the crude reaction mixture (entries 4 and 5, Table 1). IR (film) 1771, 1595, 1493, 1088, 1061; ^1H NMR δ 7.53 and 7.33 (AA′BB′ system, 4H), 5.19 (d, *J* = 1.6, 1H), 4.84 (qd, *J* = 7.4 and 3.7, 1H), 3.92 (m, 1H), 3.66 (m, 1H), 2.59 (dd, *J* = 3.7 and 1.6, 1H), 2.41 (s, 3H), 1.28 (t, *J* = 7.1, 3H), 0.93 (d, *J* = 7.4, 3H); ^{13}C NMR δ 164.0, 143.5, 134.2, 129.6, 125.9, 118.1, 107.1, 93.4, 66.2, 46.1, 21.4, 17.2, 14.7.

(3a*R*,4*S*,6a*S*,S*S*)-4-Ethoxy-6a-[(4-methylphenyl)sulfinyl]-3,3a,4,6a-tetrahydro-6*H*-furo[3,4-*c*]pyrazol-6-one (*anti*-5a). *anti*-**5a** was obtained along with *syn*-**5a** by addition of diazomethane to a solution of **1a** in acetonitrile. It could not be separated from its stereoisomer by column chromatography (60:35:5 hexane/dichloromethane/diethyl ether). The data were obtained from a 59:41 mixture of *anti*-**5a** and *syn*-**5a** (entry 8, Table 1). $[\alpha]^{20}_D$ +411.6 (*c* 1.15, $CHCl_3$); IR (film) 1773, 1595, 1492, 1087, 1061; ^1H NMR δ 7.46 and 7.27 (AA′BB′ system, 4H), 5.03 (d, *J* = 2.8, 1H), 4.75 (dd, *J* = 19.2 and 2.5, 1H), 3.92 (m, 1H), 3.88 (dd, *J* = 19.2 and 9.1, 1H), 3.68 (m, 1H), 3.12 (dt, *J* = 9.1 and 2.6, 1H), 2.41 (s, 3H), 1.27 (t, *J* = 7.1, 3H); ^{13}C NMR δ 163.9, 143.5, 133.6, 129.6, 125.6, 118.7, 107.8, 84.2, 66.6, 38.8, 21.5, 14.7. Anal. Calcd for $C_{14}H_{16}N_2O_4S$: C, 54.53; H, 5.23; N, 9.08; S, 10.40. Found: C, 54.65; H, 5.41; N, 8.99; S, 10.95.

(3*S*,3a*R*,4*R*,6a*S*,S*S*)-4-Ethoxy-3-methyl-6a-[(4-methylphenyl)sulfinyl]-3,3a,4,6a-tetrahydro-6*H*-furo[3,4-*c*]pyrazol-6-one (*syn*-4b-*exo*). *syn*-**4b**-*exo* was obtained as the minor product by reaction of **1b** with diazoethane (entry 1, Table 2). It was isolated as an oil by column chromatography (silica gel was previously treated with triethylamine), 60:35:5 hexane/dichloromethane/diethyl ether, and could not be thoroughly purified. Yield 10%. IR (film) 1775, 1595, 1493, 1088, 1059; ^1H NMR δ 7.44 and 7.33 (AA′BB′ system, 4H), 5.61 (d, *J* = 6.6, 1H), 5.22 (qd, *J* = 7.4 and 4.4, 1H), 3.89 (m, 1H), 3.67 (m, 1H), 2.65 (dd, *J* = 6.6 and 4.4, 1H), 2.41 (s, 3H), 1.21 (t, *J* =

7.1, 3H), 0.70 (d, J = 7.4, 3H); ^{13}C NMR δ 164.7, 143.7, 133.9, 129.7, 125.4, 120.1, 102.5, 86.9, 67.1, 42.8, 21.5, 17.0, 14.7.

(3*R*,3a*S*,4*R*,6a*R*,*SS*)-4-Ethoxy-3-methyl-6a-[(4-methylphenyl)sulfinyl]-3,3a,4,6a-tetrahydro-6*H*-furo[3,4-*c*]pyrazol-6-one (*anti*-4b-*exo*). *anti*-**4b**-*exo* was obtained as the major adduct by reaction of **1b** with diazoethane, although it could not be isolated diastereoisomerically pure. This compound was characterized by its spectroscopic data from the crude reaction mixture (entry 3, Table 2). IR (film) 1768, 1596, 1493, 1086, 1061; ^{1}H NMR δ 7.59 and 7.34 (AA′BB′ system, 4H), 5.04 (d, J = 1.5, 1H), 4.97 (qd, J = 7.2 and 3.4, 1H), 3.31 (m, 2H), 2.44 (dd, J = 3.4 and 1.5, 1H), 2.42 (s, 3H), 1.60 (d, J = 7.2, 3H), 0.83 (t, J = 7.1, 3H); ^{13}C NMR δ 163.3, 143.1, 134.0, 129.9, 125.4, 122.7, 107.0, 93.8, 65.4, 44.4, 21.3, 18.2, 14.3.

(3a*R*,4*R*,6a*S*,*SS*)-4-Ethoxy-6a-[(4-methylphenyl)sulfinyl]-3,3a,4,6a-tetrahydro-6*H*-furo[3,4-*c*]pyrazol-6-one (*syn*-5b). *syn*-**5b** was obtained as the minor product by reaction of **1b** with diazomethane (entry 6, Table 2). It was isolated as a white solid by column chromatography (35:60:5 hexane/dichloromethane/diethyl ether). Yield 13%; mp 123−125 °C dec (hexane/ethyl acetate); $[\alpha]^{20}_D$ +383.2 (*c* 0.25, $CHCl_3$). IR (KBr) 1771, 1594, 1492, 1086, 1059; ^{1}H NMR δ 7.40 and 7.29 (AA′BB′ system, 4H), 5.51 (d, J = 5.9, 1H), 5.07 (m, 1H), 3.83 (m, 1H), 3.59 (m, 1H), 3.31 (m, 2H), 2.41 (s, 3H), 1.16 (t, J = 7.1, 3H); ^{13}C NMR δ 165.5, 143.6, 133.3, 129.7, 125.4, 119.1, 101.6, 79.5, 66.5, 35.2, 21.5, 14.5. Anal. Calcd for $C_{14}H_{16}N_2O_4S$: C, 54.53; H, 5.23; N, 9.08; S, 10.40. Found: C, 54.09; H, 5.09; N, 9.13; S, 10.59.

(3*R*,3a*S*,4*S*,6a*R*,*SS*)-4-Ethoxy-3,3a-dimethyl-6a-[(4-methylphenyl)sulfinyl]-3,3a,4,6a-tetrahydro-6*H*-furo[3,4-*c*]pyrazol-6-one (*syn*-6a-*exo*). *syn*-**6a**-*exo* was obtained as a colorless oil after 90 min of reaction time from **2a** and diazoethane in quantitative yield (entry 1, Table 3); $[\alpha]^{20}_D$ +423.0 (*c* 1.6, acetone). IR (film) 1775, 1595, 1493, 1083, 1053; ^{1}H NMR δ 7.75 and 7.42 (AA′BB′ system, 4H), 5.42 (s, 1H), 4.67 (q, J = 7.4, 1H), 3.90 (m, 1H), 3.69 (m, 1H), 2.46 (s, 3H), 1.70 (d, J = 7.4, 3H), 1.48 (s, 3H), 1.23 (t, J = 7.1, 3H); ^{13}C NMR δ 161.1, 143.2, 133.6, 129.4, 126.7, 111.9, 107.2, 89.0, 67.5, 54.5, 21.6, 14.7, 12.9, 12.0.

(3a*R*,4*S*,6a*S*,*SS*)-4-Ethoxy-3a-methyl-6a-[(4-methylphenyl)sulfinyl]-3,3a,4,6a-tetrahydro-6*H*-furo[3,4-*c*]pyrazol-6-one (*anti*-7a). *anti*-**7a** was obtained as the minor adduct by addition of diazomethane to **2a** in acetonitrile. It decomposed by column chromatography. The spectroscopic data for *anti*-**7a** correspond to those of the crude reaction mixture (entry 5, Table 3). ^{1}H NMR δ 7.76 and 7.37 (AA′BB′ system, 4H), 4.82 (s, 1H), 4.78 and 4.58 (AB system, J = 18.3, 2H), 3.91 (m, 1H), 3.65 (m, 1H), 2.45 (s, 3H), 1.64 (s, 3H), 1.27 (t, J = 7.0, 3H); ^{13}C NMR δ 162.2, 143.7, 133.6, 129.2, 128.2, 110.1, 106.7, 89.1, 67.4, 50.8, 21.6, 14.8, 11.4.

4-Ethoxy-3,3a-dimethyl-6a-[(4-methylphenyl)sulfinyl]-3,3a,4,6a-tetrahydro-6*H*-furo[3,4-*c*]pyrazol-6-one (*anti*-6b-*exo* and *anti*-6b-*endo*). Compounds *anti*-**6**-*endo* and *anti*-**6**-*exo* were obtained by reaction of **2b** with diazoethane (entries 1 and 2, Table 4) and could not be separated. A 43:57 mixture of *anti*-**6**-*endo*/*anti*-**6**-*exo* was obtained by washing the crude reaction with diethyl ether. White solid; IR (KBr) 1769, 1594, 1496, 1085, 1055. Anal. Calcd for $C_{16}H_{20}N_2O_4S$: C, 57.12; H, 5.99; N, 8.33; S, 9.53. Found: C, 57.10; H, 5.96; N, 8.39; S, 9.50. **(3*R*,3a*S*,4*R*,6a*R*,*SS*)-*anti*-6b-*exo*** (major isomer): ^{1}H NMR δ 7.72 and 7.37 (AA′BB′ system, 4H), 4.96 (s, 1H), 4.48 (q, J = 7.5, 1H), 3.81 (m, 1H), 3.55 (m, 1H), 2.44 (s, 3H), 1.66 (d, J = 7.5, 3H), 1.32 (s, 3H), 1.15 (t, J = 7.1, 3H); ^{13}C NMR δ 162.1, 142.8, 134.3, 129.3, 126.9, 112.1, 105.4, 94.6, 66.6 (or 66.3), 54.2, 21.5, 14.5, 12.9, 9.5. **(3*S*,3a*S*,4*R*,6a*R*,*SS*)-*syn*-6b-*endo*** (minor isomer): ^{1}H NMR δ 7.71 and 7.37 (AA′BB′ system, 4H), 4.96 (s, 1H), 4.81 (q, J = 7.6, 1H), 3.81 (m, 1H), 3.55 (m, 1H), 2.44 (s, 3H), 1.49 (d, J = 7.6, 3H), 1.43 (s, 3H), 1.16 (t, J = 7.1, 3H); ^{13}C NMR δ 162.7, 142.8, 134.0, 129.3, 126.9, 112.4, 103.1, 96.7, 66.3 (or 66.6), 51.6, 21.5, 14.6, 13.5, 12.2.

(3a*R*,4*R*,6a*S*,*SS*)-4-Ethoxy-3a-methyl-6a-[(4-methylphenyl)sulfinyl]-3,3a,4,6a-tetrahydro-6*H*-furo[3,4-*c*]pyrazol-6-one (*syn*-7b). *syn*-**7b** was obtained as the minor adduct by addition of diazomethane to **2b** in acetonitrile. The spectroscopic data for *syn*-**7b** correspond to those of the crude reaction mixture. ^{1}H NMR δ 7.70 and 7.37 (AA′BB′ system, 4H), 5.22 and 4.23 (AB system, J = 18.1, 2H), 5.10 (s, 1H), 3.71 (m, 1H), 3.51 (m, 1H), 2.45 (s, 3H), 1.78 (s, 3H), 1.10 (t, 3H); ^{13}C NMR δ 164.5, 143.7, 133.0, 129.1, 128.2, 109.7, 106.7, 85.6, 66.0, 50.1, 21.6, 15.5, 14.5.

4-Methoxy-3-methyl-3,3a,4,6a-tetrahydro-6*H*-furo[3,4-*c*]pyrazol-6-one (*anti*-8-*exo*). *anti*-**8**-*exo* was obtained by reaction of **3** with diazoethane. It was isolated by column chromatography (1:2 ethyl acetate/hexane) as an oil. IR (film) 1778, 1555, 1176, 1112; ^{1}H NMR δ 5.73 (dd, J = 8.8 and 2.4, 1H), 5.04 (d, J = 1.6, 1H), 4.83 (m, 1H), 3.44 (s, 3H), 2.37 (ddd, J = 8.8, 4.1, and 1.6, 1H), 1.46 (d, J = 7.3, 3H);^{13}C NMR δ 167.1, 108.1, 92.5, 91.7, 57.1, 46.6, 18.5. Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.41; H, 5.92; N, 16.46. Found: C, 49.11; H, 5.69; N 16.19.

4-Methoxy-3-methyl-3,3a,4,6a-tetrahydro-6*H*-furo[3,4-*c*]pyrazol-6-one (*anti*-8-*endo*). *anti*-**8**-*endo* was obtained as the minor product by reaction of **3** with diazoethane and could not be fully purified by column chromatography (1:2 ethyl acetate/hexane). ^{1}H NMR (from a 80:20 mixture of *anti*-**8**-*endo*/*anti*-**8**-*exo*) δ 5.64 (dd, J = 9.1 and 1.3, 1H), 5.13 (d, J = 2.0, 1H), 4.96 (m, 1H), 3.51 (s, 3H), 2.81 (td, J = 9.2 and 2.0, 1H), 1.61 (d, J = 7.6, 3H); ^{13}C NMR δ 168.0, 104.2, 93.2, 88.1, 57.3, 41.9, 13.6.

4-Methoxy-3-methyl-3,3a,4,6a-tetrahydro-6*H*-furo[3,4-*c*]pyrazol-6-one (*syn*-8-*exo*). *syn*-**8**-*exo* was obtained by reaction of **3** with diazoethane. It was isolated as an oil by column chromatography (1:2 ethyl acetate/hexane). IR (film) 1781, 1555, 1180, 1144; ^{1}H NMR δ 5.55 (dd, J = 9.0 and 2.3, 1H), 5.42 (d, J = 6.4, 1H), 5.38 (m, 1H), 3.44 (s, 3H), 2.75 (ddd, J = 9.0, 6.4, and 2.5, 1H), 1.33 (d, J = 7.3, 3H); ^{13}C NMR δ 168.0, 103.6, 92.6, 86.7, 57.7, 43.2, 17.7. Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.41; H, 5.92; N, 16.46. Found: C, 49.21; H, 6.26; N, 16.54.

6-Methoxy-3-methyl-3,3a,6,6a-tetrahydro-4*H*-furo[3,4-*c*]pyrazol-4-ones (*anti*-9-*exo* and *anti*-9-*endo*). *anti*-**9**-*exo* and *anti*-**9**-*endo* were obtained by reaction of **3** with diazoethane and could not be fully purified by column chromatography (1:2 ethyl acetate/hexane). Both isomers of **9** were characterized from their NMR data from a 32:68 mixture of *anti*-**9**-*endo*/*anti*-**9**-*exo*. *anti*-**9**-*exo*: ^{1}H NMR δ 5.76 (s, 1H), 5.26 (m, 2H), 3.61 (s, 3H), 2.78 (dd, J = 7.4 and 1.8, 1H), 1.39 (d, J = 7.2, 3H). ^{1}H NMR (C_6D_6) δ 5.28 (s, 1H), 4.83 (m, 1H), 4.54 (dd, J = 7.5 and 2.3, 1H), 2.96 (s, 3H), 1.89 (dd, J = 7.5 and 1.8, 1H), 0.61 (d, J = 7.3, 3H). ^{13}C NMR δ 175.3, 104.1, 92.9, 89.8, 57.2, 42.3, 18.3. *anti*-**9**-*endo*: ^{1}H NMR δ 5.71 (s, 1H), 5.26 (m, 1H), 4.78 (m, 1H), 3.60 (s, 3H), 3.11 (dd, J = 9.1 and 8.2, 1H), 1.69 (d, J = 7.5, 3H). ^{1}H NMR (C_6D_6) δ 5.22 (d, J = 0.6, 1H), 4.48 (ddd, J = 8.1, 2.0, and 0.6, 1H), 3.82 (m, 1H), 2.94 (s, 3H), 2.12 (dd, J = 9.1 and 8.3, 1H), 1.44 (d, J = 7.5, 3H). ^{13}C NMR δ 172.8, 103.5, 95.2, 87.7, 57.1, 39.1, 14.3.

Computational Methods

The Gaussian 98 program[28] was used to perform all of the calculations. All the geometries of the reactants, transition structures, and products were fully optimized at the well-

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established B3LYP/6-31G(d) level and characterized as minima or first-order saddle points by frequency analysis. The reported values of energy barriers in the gas phase include zero-point energy corrections (ZPEC) scaled by a factor of 0.98.[29] The same scale factor was used for the calculations at the B3LYP/6-31++G(d,p), which include ZPEC at the same level, and for the calculations with the B3LYP/6-31++G(d,p)//B3LYP/6-31G(d) and B3LYP/cc-pVTZ//B3LYP/6-31G(d) model chemistries, which include ZPEC at the same level as the optimized geometries (i.e. B3LYP/6-31G(d)). Ab initio calculations consisted of the geometry optimization and frequency analysis at the HF/6-31++G(d,p) level. Subsequent geometry optimization was performed at the correlated second-order MP2/6-31++G(d,p) level starting from the HF geometries. The reported energy values at this level include ZPEC at the HF/6-31++G(d,p) level scaled by a factor of 0.92.[29] Solvation effects were evaluated by means of single-point energy calculations with the polarizable continuum model (PCM) of Tomasi et al.[30] with dielectric constants of 4.20 (Et_2O) and 35.94 (CH_3CN).[31] While these calculations are still approximate because they do not include explicit solvent molecules, they do provide reasonable estimates of the effect of solvent polarity on the energy barriers. We expect a change in the geometries upon solvation, but the size of the system, the number of different stereochemical approaches to take into account, and the general difficulties of convergence of the geometry optimization involving the PCM method preclude a full optimization in solution at the levels of calculations used in this paper.

Charges on individual atoms were computed by using the natural population[32] and the ChelpG[33] schemes. Wiberg bond indices and the atomic orbital overlap matrix (for the calculation of the Fukui functions) were obtained from a natural bond orbital (NBO)[32,34] analysis with the BNDIDX and SAO keywords, respectively.

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Supporting Information Available: A brief explanation of the DTF global and local properties used and Cartesian coordinates of all of the structures with their computed total energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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