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Synthesis of Optically Pure *vic*-Sulfanyl Amines Mediated by a Remote Sulfinyl Group

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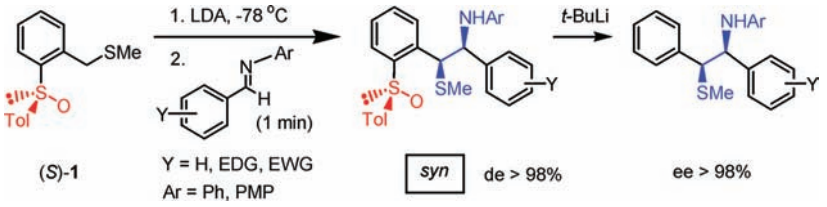
ABSTRACT



Enantiomerically pure *syn*-1,2-diaryl-1,2-sulfanylamine derivatives can be obtained in a completely stereoselective manner by reaction of the benzylcarbanion Li-(*S*)-1 with *N*-phenyl (or PMP)-arylidene aldimines and further desulfinylation with *t*-BuLi. Theoretical studies at the DFT (mPW1PW91) level with the CPCM model, by using the Gaussian09 program, provide a good explanation for the stereochemical results.

vic-Sulfanyl amines are efficient heterobidentate *N*,*S*-ligands in asymmetric reactions[1] and valuable buildings blocks,[2] which are characteristic motifs in bioactive natural products,[3] and pharmacologically important compounds.[4] Despite this interest, only two general routes have been reported for synthesizing optically pure 1,2-sulfanylamines containing two chiral centers. The Enders' approach[5] involves the sequential formation of the two chiral centers by α-alkylation of optically pure α-sulfanylated acetaldehyde-SAMP-hydrazones followed by 1,2-addition to a C=N bond (Scheme 1, upper). Our approach[6] involves the reactions of the α-methylsulfenylbenzyl carbanion Li-(*S*)-**1** with (*S*)-*N*-sulfinylaldimines, affording *anti*-1,2-sulfanylamines (Scheme 1, lower), which takes place with simultaneous formation of the two chiral centers according to a completely stereoselective double asymmetric induction process. Both approaches allow the preparation of the enantiomerically pure *anti* diastereoisomers in high de (≥96% de), but none of them is suitable for obtaining the *syn* ones. Consequently, the

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(1) For recent reviews, see: (a) Pellisier, H. *Tetrahedron* **2007**, *63*, 1297. (b) Martin, E.; Diéguez, M. *C. R. Chim.* **2007**, *10*, 188. For other references, see:(c) Le Fur, N.; Mojovic, L.; Plé, N.; Turck, A.; Reboul, V.; Metzner, P. *J. Org. Chem.* **2006**, *71*, 2609. (d) Granander, J.; Eriksson, J.; Hilmersson, G. *Tetrahedron: Asymmetry* **2006**, *17*, 2021. (e) Ekegren, J. K.; Roth, P.; Källström, K.; Tarnai, T.; Andersson, P. G. *Org. Biomol. Chem.* **2003**, *1*, 358. (f) Hage, A.; Petra, D. G. I.; Field, J. A.; Schipper, D.; Wijnberg, J. B. P. A.; Kamer, P. C. J.; Reek, J. N. H.; Van Leeuwen, P. W. N. M.; Wever, R.; Schoemaker, H. E. *Tetrahedron: Asymmetry* **2001**, *12*, 1025. (g) Petra, D. G. I.; Kamer, P. C. J.; Spek, A. L.; Schoemaker, H. E.; Van Leeuwen, P. W. N. M. *J. Org. Chem.* **2000**, *65*, 3010.

(2) (a) Yang, X.-F.; Zhang, M.-J.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* **2002**, *67*, 8097. (b) Aggarwal, V. K.; Charmant, J. P. H.; Ciampi, C.; Hornby, J. M.; O'Brien, C. J.; Hynd, G.; Parsons, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3159.

(3) (a) Schwartz, A.; Madan, P. B.; Mohacsi, E.; O'Brien, J. P.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem.* **1992**, *57*, 851. (b) Tamariz, J. In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1996; p 45. (c) Rinehart, K. L. *Med. Res. Rev.* **2000**, *20*, 1. (d) Parveen, S.; Khan, M. O. F.; Austin, S. E.; Croft, S. L.; Yardley, V.; Rock, P.; Douglas, K. T. *J. Med. Chem.* **2005**, *48*, 8087 and references therein.

(4) (a) Boge, T. C.; Georg, G. I. In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: NewYork, 1996; p 1. (b) Bae, J. H.; Shin, S. H.; Park, C. S.; Lee, W. K. *Tetrahedron* **1999**, *55*, 10041. (c) Adams, B.; Beresford, K. J. M.; Whyte, S. M.; Young, D. W. *Chem. Commun. (Cambridge, U.K.)* **2000**, 619.

(5) Enders, D.; Moll, A.; Schaadt, A.; Raabe, G.; Runsink, J. *Eur. J. Org. Chem.* **2003**, 3923 and references therein.

(6) (a) Arroyo, Y.; Meana, A.; Rodríguez, J. F.; Santos, M.; Sanz-Tejedor, M. A.; García-Ruano, J. L. *J. Org. Chem.* **2005**, *70*, 3914. (b) Arroyo, Y.; Meana, A.; Sanz-Tejedor, M. A.; Alonso, I.; García-Ruano, J. L. *J. Org. Chem.* **2009**, *74*, 764.

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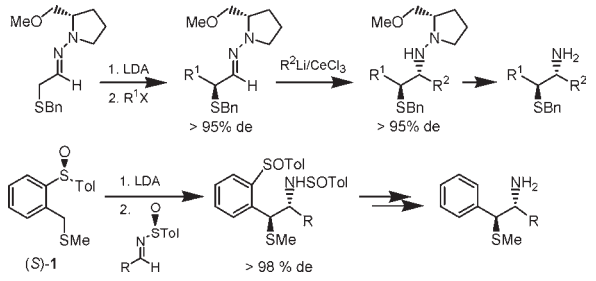
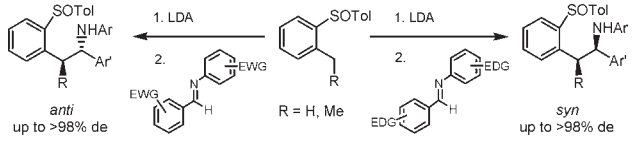
search for methods to obtain enantiomerically pure *vic*-sulfanyl amines remains a challenging task.

Scheme 1. Approaches for Synthesizing *anti* 1,2-Sulfanyl Amines



We have reported that the stereoselectivity of the reactions of alkyl 2-(*p*-tolylsulfinyl)benzyl carbanions with *N*-arylarylideneamines depends on the electronic density of the rings at the imine, with electron-donating (EDG) and electron-withdrawing groups (EWG), respectively, favoring the formation of the *syn* and *anti* stereoisomers[7] (Scheme 2). This behavior prompted us to study the reactions of (*S*)-**1** with *N*-arylimines, with the hope to find the appropriate substituents allowing the preparation of the optically pure *syn*-1,2-sulfanyl amines. The results obtained in this study are reported herein.

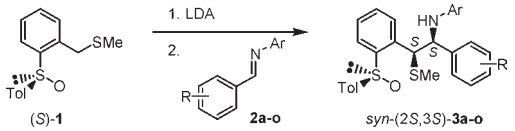
Scheme 2. Reactions of 2-(*p*-Tolylsulfinyl)benzylcarbanions with *N*-Arylarylideneimines[7]



Optically pure (*S*)-**1** was easily synthesized in two steps starting from commercially available *o*-bromotoluene.[6a] *N*-Arylarylideneamines **2a**–**u** were prepared from anilines and benzaldehydes in the presence of molecular sieves.[7]

We first studied the reactions of the benzylcarbanion derived from (*S*)-**1** with *N*-phenylbenzylideneamine **2a**. To our surprise, a completely stereoselective reaction, only yielding the *syn*-1,2-sulfanylamine **3a** in 75% isolated yield (entry 1, Table 1), was observed. This result contrasts with the 91:9 mixture of *anti*/*syn* amines obtained from 2-*p*-tolylsulfinyl ethylbenzene.[7a] We then studied the reactions with other *N*-phenylarylideneamines **2b**–**f**, bearing EDG and EWG (Table 1, entries 2–6). The NMR spectra of the reaction crudes are very clean and reveal a complete conversion and the almost exclusive formation of the *syn* stereoisomers. Signals corresponding to another product can be detected in reaction crudes obtained from **2c** and **2f** (entries 3 and 6), but their low proportion (≤2%) precludes their characterization. The behaviors of the *N*-*p*-methoxyphenyl and *N*-2,4,6-trimethoxyphenyl arylidene imines are identical, allowing optically pure *syn*-1,2-sulfanylamine derivatives to be obtained (**3g**–**3o**, entries 7–15, Table 1), which indicates that the influence of EDG enhancing the electron density on the aniline ring does not produce any significant change, regardless of the substituent at the arylidene ring. The isolated yields for compounds **3a**–**3o** ranged between 65 and 80%.

Table 1. Reactions of (*S*)-**1** with *N*-Arylarylideneamines **2a**–**o** Using a Single Asymmetric Induction Procedure



entry	Ar	R	product	de (%)[a]	yield, %[b]
1	Ph	H	**3a**	>98	75
2	Ph	4-CH_3	**3b**	>98	80
3	Ph	4-CH_3O	**3c**[c] + **3′c**	≥96[d]	65
4	Ph	3-Cl	**3d**	>98	77
5	Ph	4-CF_3	**3e**	>98	70
6	Ph	4-CN	**3f** + **3′f**	≥96[d]	80
7	PMP	H	**3g**	>98	70
8	PMP	4-CH_3	**3h**	>98	75
9	PMP	4-CH_3O	**3i**	>98	65
10	PMP	2-Br	**3j**	>98	–[e]
11	PMP	3-Cl	**3k**	>98	75
12	PMP	4-CF_3	**3l**	>98	65
13	PMP	4-CN	**3m**	>98	75
14	TMP	4-CH_3	**3n**	>98	75
15	TMP	4-CN	**3o**	>98	75

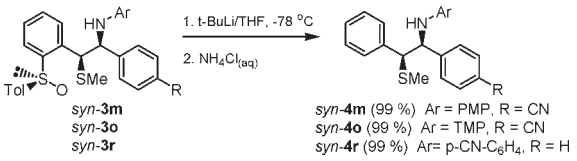
[a] Determined by ^{1}H NMR of the crude reaction mixture. [b] Isolated yield. [c] The ORTEP structure of **3c** can be found in the Supporting Information. [d] See text. [e] Compound **3j** was completely decomposed during chromatographic purification.

By assuming a similar behavior for all reactions shown in Table 1, the absolute configuration for compounds *syn*-**3** was established as (S*S*, 1*S*, 2*S*) once it was unequivocally assigned by X-ray analysis for *syn*-**3c** and for the sulfone derived from *syn*-**3p** (see Supporting Information (SI) and Table 2).

Desulfinylation of **3** into the *N*-aryl-1,2-sulfanylamines *syn*-**4** can be achieved with *t*-BuLi. These reactions were investigated with *syn*-**3m**, *syn*-**3o**, and *syn*-**3r** (Scheme 3), respectively yielding *syn*-**4m**, *syn*-**4o**, and *syn*-**4r** in quantitative yields, without affecting the benzylic C–S bond or the configurational integrity at C(1) and C(2).

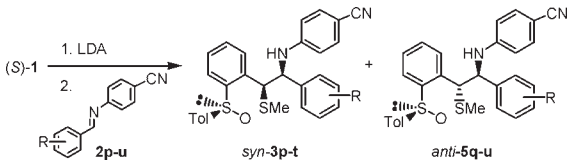
(7) (a) García-Ruano, J. L.; Alemán, J.; Alonso, I.; Parra, A.; Marcos, V.; Aguirre, J. *Chem.—Eur. J.* **2007**, *13*, 6179. (b) Alemán, J. PhD Thesis, Universidad Autónoma de Madrid, Spain. (c) Jiao, L.; Liang, Y.; Xu, J. *J. Am. Chem. Soc.* **2006**, *128*, 6060. (d) Liang, Y.; Jiao, L.; Zhang, S.; Yu, Z.-X.; Xu, J. *J. Am. Chem. Soc.* **2009**, *131*, 1542.

Scheme 3. Desulfinylation of Compounds **3m**−**3r**



Once our synthetic objective was achieved, some mechanistic explanation to the substantial changes observed in the stereochemical results shown in Table 1 (only affording *syn* isomers) with respect to those of the Scheme 2 (affording mixtures of *syn* and *anti* isomers with the same imines) deserved investigation. As the presence of the EWG at the iminic rings would favor the formation of the *anti* isomers in Scheme 2, we studied the reactions of (*S*)-**1** with *N*-*p*-cyanophenylarylideneamines **2p**−**u**. The results are collected in Table 2.

Table 2. Reactions of (*S*)-**1** with *N*-*p*-Cyanophenylarylidene Amines **2p**−**u**



entry	R	imine	dr (%)[a] *syn*-**3**/*anti*-**5**	yield, %[b]
1	CH_3O	**2p**	>98[c]:−	75
2	CH_3	**2q**	64:36	70
3	H	**2r**	63:37	99
4	3-Cl	**2s**	17:83	55
5	CF_3	**2t**	15:85	70
6	CN	**2u**	−:>98	75

[a] Determined by ^{1}H NMR of the crude reaction mixture. [b] Combined yield. [c] The ORTEP structure of sulfone **3′p** obtained from **3p** can be found in the Supporting Information.

Imine **2p**, bearing a strong EDG at the arylidene ring, evolves with a complete *syn*-stereoselectivity, only affording *syn*-**3p** in 75% isolated yield (entry 1; Table 2). However, the reaction of (*S*)-**1** with imine **2q**, supporting a weaker EDG, provides a mixture of two diastereisomers, *syn*-**3q** and *anti*-**5q** (entry 2, Table 2), with the *syn* isomer as the major one still. A similar result was obtained from **2r** (entry 3, Table 2). In contrast, reactions with imines **2s** and **2t**, bearing weakly EWG at the arylidene ring, provide mixtures with a larger proportion of the isomer *anti*-**5** (entries 4 and 5, Table 2), whereas reaction with *N*-4-cyanophenyl imine **2u** afforded *anti*-**5u** as the only isomer (entry 6, Table 2). These results, showing the dependence between stereoselectivity and the electronic character of the substituents at the benzylidene moiety of *p*-cyanophenyl imines **2p**−**2u**, are identical to that previosly observed for N-aryl imines in the Scheme 2. The *anti*-stereochemistry assigned to compounds **5** was based on their NMR data, and their absolute configuration was unequivocally established by chemical correlation (see SI). It is remarkable that the absolute configuration at the chiral carbons for compounds *anti*-**5** is different from that of the *anti* compounds at Scheme 2.

To understand the stereochemical results we must take into account that both diastereomeric amines show the same (*S*) configuration at the aminic carbon. It suggests that reactions take place through the approach of the nucleophile to the *re* face of imines **2**. By contrast, the configuration at carbon bonded to sulfur is *S* for *syn*-**3** and *R* for *anti*-**5**, indicating the imine's approach occurs at the *re* and *si* faces of carbanion (*S*)-**1**, respectively (Figure 1).

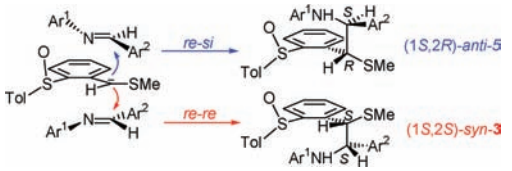


Figure 1. Approaches of the imines **2** to Li^+[(*S*)-**1**] explaining the stereochemical results.

Additionally, since *syn*-**3** amines are the only products obtained in reactions from imines derived from activated anilines (Table 1) whereas the *anti*-**5** ones become important only when highly activated imines are employed (EWG in both aromatic rings, Table 2), the energy of the resulting transition states should depend on the nature of the groups (EDG or EWG) present in imine aromatic rings. The stability of the possible structures of the carbanion and transition states, in the solvent phase, were studied theoretically at the DFT (mPW1PW91)[8] level, with the CPCM model,[9] by using the Gaussian09 program[10] (Figure 2). Carbanion model **I**[11] results from the stereoselective deprotonation of the species generated by association of the sulfinyl oxygen with the lithium at the base. It is stabilized by a hydrogen bond between benzylic carbon and the N−H

(8) (a) Perdew, J. P.; Chevary, S. H.; Vosko, K. A.; Jackson, K. A.; Pederson, M. R.; Singh, D. J.; Fiolhais, C. *Phys. Rev. B* **1992**, *46*, 6671. (b) Perdew, J. P.; Chevary, S. H.; Vosko, K. A.; Jackson, K. A.; Pederson, M. R.; Singh, D. J.; Fiolhais, C. *Phys. Rev. B* **1993**, *48*, 4978. (c) Perdew, J. P.; Burke, K.; Wang, Y. *Phys. Rev. B* **1996**, *54*, 16533. (d) Adamo, C.; Barone, V. *J. Chem. Phys.* **1998**, *108*, 664. (e) It is proposed that the mPW1PW91 can account for the likely long-range dispersive interactions as well as hydrogen bonding (see: Patil, M. P.; Sunoj, R. B. *Chem. Asian L.* **2009**, *4*, 714 and references therein).

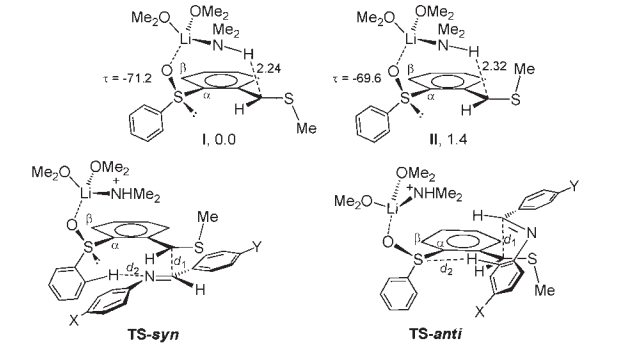
(9) (a) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995. (b) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669.

(10) Frisch, M. J. et al. *Gaussian 09, revision A.02*; Gaussian, Inc.: Wallingford CT, 2009 (see SI).

(11) Other structures for the carbanion have been studied and compared with **I** at the B3LYP level (see SI).

of the amine bonded to the lithium atom. Conformation **II**, with the Me of the SMe group oriented toward the upper face, is 1.4 kcal/mol less stable than **I** probably due to steric effects. We then calculated the TSs of the approaches of imines **2a**, **2p**, **2r**, and **2u** (Tables 1 and 2) to the carbanions **I** and **II** by the opposite face to that occupied by the Me of the SMe group. Results are also depicted in Figure 2. **TS-*syn*** corresponds to the approach of the *re* face of the imine to the less hindered *re* face of the carbanion **II**. It is stabilized by a hydrogen bond between the iminic nitrogen and the *ortho* hydrogen atom of the sulfinylated aromatic ring, which could be responsible for the preferred approach of the imine by its *re* face (Figure 2).[12] **TS-*anti*** results from the approach of the *re* face of the imine to the upper face of the carbanion **I**. It is also stabilized by a hydrogen bond between the sulfinyl sulfur and the *ortho* hydrogen of the aromatic ring joined to the iminic nitrogen.

In agreement with the de indicated in Tables 1 and 2, **TS-*syn*** is clearly favored with respect to **TS-*anti*** for **2a** and **2p** ($\Delta G_{relat.}$ = 2.7 and 2.3 kcal/mol respectively). The model predicts a 60:40 ratio of *syn*-**3r**/*anti*-**5r** ($\Delta G_{relat.}$ = 0.2 kcal/mol), comparable with experimental results (Table 2, entry 3). Finally, with imine **2u** only **TS-*anti*** could be found, thus precluding establishing the $\Delta G_{relat.}$-value.[13] Three main parameters can be used to understand the relative stability of these **TSs**. d_1 is the distance separating the reactive centers. It is inversely proportional to the imine's reactivity (increases in the order **2u** > **2r** > **2p** > **2a**, Figure 2), and it is longer for **TS-*syn*** because the hydrogen bond N···HC increases the positive charge at the iminic carbon and therefore its reactivity. d_2 indicates the formation of the hydrogen bonds C−H···N and C−H···S for **TS-*syn*** and **TS-*anti*** respectively. Although the presence of EWG at the rings scarcely changes d_2 values in Figure 2, NBO analyses[14] indicate that decreases the strength of these bonds. Also, according to these analyses, the negative charge of the carbanion moiety in TSs in which X = CN (more reactive) is mainly polarized toward the benzylic position, whereas in the case of X = H (less reactive) it is mainly located at C_α which allows its stabilization by the sulfinyl group (being higher for the **TS-*syn***[15]) which could be an important factor in determining the $\Delta G_{relat.}$-value. These orbital interactions may be mainly related to the value of the third parameter τ, the torsion angle O−S−C_α−C_β, which is very different in both TSs. It is larger (maybe due to the hydrogen bond C−H···N) and almost constant for **TS-*syn***, whereas it is lower and variable for **TS-*anti***. In this latter case, τ is also related to the steric repulsions of the imine with the sulfinyl associated to the base, becoming lower when τ decreases. Thus, steric destabilization of the **TS-*anti*** is minimized for the most reactive imines (those supporting EWG) giving rise to changes in the *syn*/*anti* selectivity.



ΔG_{relat}	Imine	X	Y	d_1	d_2	τ	ΔG_{relat}	Imine	X	Y	d_1	d_2	τ
0	**2a**	H	H	2.35	2.37	-66.3	2.7	**2a**	H	H	2.27	2.74	-44.4
0	**2p**	CN	OMe	2.52	2.38	-65.3	2.3	**2p**	CN	OMe	2.45	2.79	-34.4
0	**2r**	CN	H	2.61	2.41	-66.7	0.2	**2r**	CN	H	2.49	2.80	-33.8
---	**2u**	CN	CN	---	---	---	---	**2u**	CN	CN	2.57	2.81	-32.2

Figure 2. $CPCM_{(THF)}$/mPW1PW91/6-311G(d,p)//6-31G(d) optimized carbanion and transition states for the reaction of the imines **2** with Li^+[(*S*)-**1**].[16] ΔG (kcal/mol) and representative distance (d in Å) and torsion angles (τ in deg) are indicated.

In summary, we have demonstrated that the synthesis of enantiomerically pure *syn*-1,2-sulfanylamine derivatives **3**, (*S,S*)-1-aryl-2-(methylsulfenyl)-2-(phenyl)ethylamines, can be performed by reaction of (*S*)-α-(methylsulfenyl)-2-(*p*-tolylsulfinyl)toluene, (*S*)-**1**, with *N*-arylarylideneamines and LDA and further desulfinylation with *t*-BuLi.

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Supporting Information Available. Additional experimental details. This material is available free of charge via Internet at http://pubs.acs.org.

(12) C−H...X interactions in TSs are crucial for the diastereoselectivity (for example, see Washington, I.; Houk, K. N. *Angew. Chem., Int. Ed.* **2001**, *40*, 4485). The approach of imine **2a** by its *si*-face that would yield the diastereomeric *anti* product shown in Scheme 2, mainly formed in the case of R = Me (ref 7), was also studied. However, the corresponding TS (see structure **TS-*anti*'-2a** in the SI) was much less stable ($\Delta G_{relat.}$ = 3.9 kcal/mol) which would explain the absence of this product in the present case. The different behaviour of carbanions with R = Me, in which the C−H···N bond could have also been formed and R = SMe must be due to the different distribution of the charge, delocalized through the aromatic ring and was stabilized by the sulfinyl group or partially stabilized by the SMe group in the latter case.

(13) **TS-*syn*** and the remaining TSs were also studied with the B3LYP level (see SI). However, despite the relative stabilities of these structures showing the tendency experimentally observed, they correlate worse with experimental results.

(14) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899. The stabilizing interactions (kcal·mol^{-1}), evaluated by means of a second-order perturbational analysis of the Fock matrix, between the lone pair of a nitrogen atom in **TS-*syn*** and the C−H antibonding orbital, decreases with the presence of EWG: 2.86, 2.62, and 2.36 from **2a** to **2r**. The strength of the hydrogen bond C−H···S in **TS-*anti*** also decreases (1.50, 1.25, 1.21, and 1.21 from **2a** to **2u**). Another very weak C−H···S bond in **TS-*syn*** between the sulfur atom of SMe and the iminic hydrogen could be proposed according to its length (2.81−2.85 Å); however, taking into account the same criteria regarding its strength (less than 0.23) it was considered negligible.

(15) Stabilizing interactions (kcal·mol^{-1}) between a lone pair at C_α and the S−O and S−Ph bonds have been found for **I** (14.5), **II** (14.8), **TS-*syn*-2a** (12.2), or **TS-*anti*-2a** (10.7).

(16) Me_2O, Me_2NH, and Ph were used as simplified models for a solvent, base, and Tol group respectively.