ORGANIC LETTERS

2000
Vol. 2, No. 6
733−736

Synthesis and Diels–Alder Reactions of a New Kind of Chiral Dienophiles: Cyclic Vinyl-*p*-tolylsulfilimines

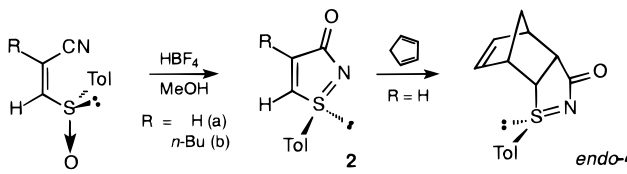
José L. García Ruano,*,† Antonio Esteban Gamboa,† Lorena González Gutiérrez,† Ana M. Martín Castro,† Jesús H. Rodríguez Ramos,*,† and Francisco Yuste‡

Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain, and Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Cd. Universitaria, Coyoacán 04510, México D.F.

joseluis.garcia.ruano@uam.es jesus.rodriguez@uam.es

Received November 5, 1999

ABSTRACT



A new kind of chiral dienophiles, cyclic vinyl-*p*-tolylsulfilimines (2a and 2b), were obtained from the corresponding (*Z*)-sulfinylacrylonitriles with HBF_4 and methanol. The asymmetric Diels–Alder reaction of optically pure 2a with cyclopentadiene under mild thermal or catalyzed conditions afforded only the *endo*-4a adduct with complete *endo* and π-facial selectivities. The ability of the sulfilimine moiety to enhance the dienophilic reactivity of the double bond is similar to that of the sulfinyl group.

Enantiomerically pure vinyl sulfoxides have been widely used as dienophiles in Diels−Alder reactions.[1] By contrast the use of vinyl sulfilimines, nitrogenated equivalents of vinyl sulfoxides, as dienophiles so far has not been reported. The lower configurational stability of these compounds with respect to the sulfoxides[2] and the fact that their synthesis in an optically pure form usually involves the corresponding sulfoxides as the starting materials[3] could explain why sulfilimines have never been used as chiral dienophiles.[4] Nevertheless, on the basis of the double bond character of the S−X bond, smaller in sulfilimines than in sulfoxides,[5] it could be expected that the former compounds exhibited a larger electronic deficiency at sulfur, thus determining that dienophilic reactivity of vinyl sulfilimines was even higher than that of vinyl sulfoxides, despite the lower electronegativity of the nitrogen as compared with that of the oxygen. On this assumption, the study of configurationally stable vinyl sulfilimines in asymmetric Diels−Alder reactions would be highly interesting.

In the course of our studies on the use of vinyl sulfoxides in asymmetric cycloadditions,[6] we have recently reported the dienophilic behavior of enantiomerically pure (*Z*)-3-*p*-tolylsulfinylacrylonitriles in Diels−Alder reactions with cyclopentadiene.[7] When the reactions catalyzed by $BF_3{\cdot}OEt_2$ were quenched with methanol before their completion, we found that variable amounts of a side product, instead of

† Universidad Autónoma de Madrid.
‡ Universidad Nacional Autónoma de México.

(1) For recent reviews, see: (a) Garcia Ruano, J. L.; Cid, B. In *Topics in Current Chemistry*; Page, P. C. B., Ed.; Springer: Berlin, 1999; vol 204, p 1−126 and references cited. (b) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717 and references cited.

(2) Kikuchi, K.; Furukawa, N.; Oae, S. *Phosphorus Sulfur Relat. Elem.* **1985**, *25*, 155.

(3) Oae, S. *Organic Sulfur Chemistry: Structure and Mechanism*; CRC Press: Boca Raton, FL **1991**, 87.

(4) Structurally related sulfinylacrilamides and cyclic *N*-acylsulfinamides have been studied as dienophiles; see ref 1a.

(5) Oae, S.; Furukawa, N. *Sulfilimines and Related Derivatives*; ACS Monograph 179; American Chemical Society, Washington, DC, 1983; p 75.

(6) (a) Garcia Ruano, J. L.; Carretero, J. L.; Carreño, M. C.; Cabrejas, L. M.; Urbano, A. *Pure Appl. Chem.* **1996**, *68*, 925 and references cited. (b) Carreño, C.; García Ruano, J. L.; Remor, C. Z.; Urbano, A.; Fischer, J. *Tetrahedron Lett.* **1997**, *38*, 9077 and references cited. (c) Garcia Ruano, J. L.; Fraile, A.; Martín, M. R. *Tetrahedron: Asymmetry* **1996**, *7*, 1943.

(7) García Ruano, J. L.; Esteban Gamboa, A.; Martín Castro, A. M.; Rodríguez, J. H.; López-Solera, M. I. *J. Org. Chem.* **1998**, *63*, 3324.

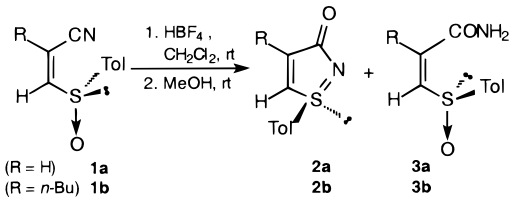
10.1021/ol991224t CCC: $19.00
Published on Web 02/23/2000

the starting material, were isolated. Its spectroscopical data suggested a sulfilimine structure bearing an endocyclic S−N bond. These results prompted us to develop experimental conditions allowing us to synthesize these compounds in high yields to investigate their properties and chemical behavior. We report herein an easy method for the preparation of this family of chiral compounds, some results concerning their configurational stability, and the behavior of the simplest one, **2a**, as a chiral dienophile with cyclopentadiene.

As the starting compounds we have used (*Z*)-sulfinylacrylonitriles **1a** and **1b**, synthesized following the previously described procedure[7,8] by hydrocyanation of their corresponding alkynyl sulfoxides with Et_2AlCN.

Treatment of sulfinylacrylonitriles **1a** and **1b** with HBF_4 (2 equiv)[9] at room temperature for 2.5 h and then quenching with anhydrous methanol for 1.5 h (conditions A, entries 1 and 2 in Table 1) afforded mixtures of the corresponding

Table 1



entry	R	conditions[a]	**2**:**3** ratio[b,c]
1	H	A	63 (47):37 (31)
2	*n*-Bu	A	93 (72):7 (6)
3	H	B	93 (64):7 (−)
4	*n*-Bu	B	100 (98):0

[a] See text. [b] Determined by ^{1}H NMR. [c] Isolated yield in brackets.

sulfilimines **2** and sulfinylacrylamides **3**. Under these conditions, the formation of **2b** (R = *n*-Bu) seems to be easier than that of **2a** (R = H). Better results were obtained under conditions B (entries 3 and 4 in Table 1) consisting of an increase in the amount of HBF_4 (4 equiv in the first step and a further addition of 2 equiv after treatment with methanol in the second step). Under the latter conditions **2b** was the only product detected from **1b** (entry 4), whereas **1a** yielded a 93:7 mixture of **2a** and **3a**. These ratios suggested that sulfinylacrylamides were precursors of sulfilimines, which could be confirmed by the independent conversion of **3a** and **3b** into **2a** and **2b**, respectively, by treatment with HBF_4, under conditions similar to those used in the reactions starting from **1a** and **1b** (conditions A).[10] To our knowledge, this method is applied for the first time to the preparation of optically pure sulfilimines from sulfoxides and amides under acidic conditions.[11]

The structure and absolute configuration of vinyl sulfilimine **2a** was unequivocally determined by X-ray crystallography (Figure 1).[12] The S−N bond distance is 1.636 Å, very similar to that corresponding to other previously reported sulfilimines, and the angles around the sulfur atom evidence its tetrahedral structure. Although the optical purity

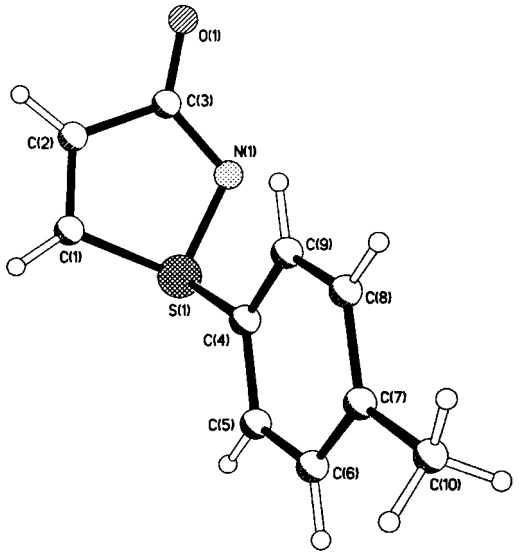
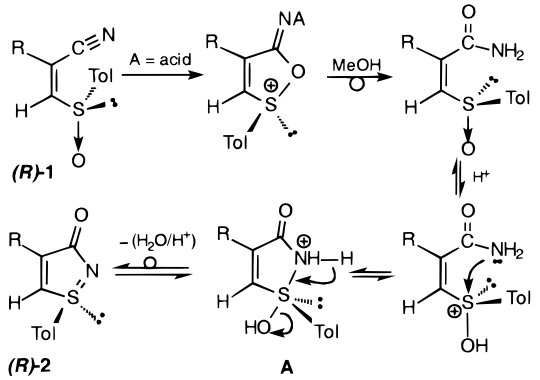


Figure 1. X-ray structure of sulfilimine **2a**.

of **2a** could not be determined (HPLC or NMR), its ee of >97% could be inferred from the optical purity of the adduct *endo*-**4a** (see below).

Taking into account that the conditions used to obtain **2** and **3** from **1** are quite similar to those previously reported for the hydrolysis of saturated β-sulfinylnitriles into β-sulfinylcarboxamides,[13] a reasonable pathway explaining the formation of the vinyl sulfilimines (*R*)-**2a** and (*R*)-**2b** from their corresponding sulfinylnitriles (*R*)-**1** is outlined in Scheme 1. It would proceed by hydrolysis of the cyano group

Scheme 1



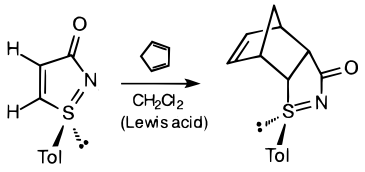
into carboxamide with anchimeric assistance of the sulfinyl group, resulting in the inversion of the configuration at sulfur (see ref 7). Once the sulfinylamide is formed under acidic conditions able to protonate the sulfinyl oxygen, the lone electron pair at nitrogen could attack the positively charged sulfur atom, displacing the OH group to yield sulfilimines (*R*)-**2**. Substitution at sulfur could take place, involving a sulfurane intermediate species **A**, bearing the sulfur atom at

the center of a trigonal bipyramid (Scheme 1) or as an intramolecular nucleophilic substitution at sulfur, but in both cases the inversion at the sulfur configuration must take place. This mechanistic proposal is similar to that reported by Oae[14] using basic conditions.

Acyclic sulfilimines have been found to undergo easier thermal racemization than sulfoxides upon heating.[15] To examine the configurational stability of our cyclic vinyl-*p*-tolylsulfilimines, **2a** and **2b** were refluxed in chloroform or methanol and their specific rotations were measured at regular intervals. After 24 days under these conditions, specific rotations of **2a** (which is slighly decomposed) and **2b** remained practically unaltered. These results suggest that these cyclic sulfilimines are configurationally more stable than the corresponding acyclic ones.[14,16] Anyway, we can assume that the degree of racemization of **2a** and **2b** is not significant in asymmetric reactions conducted under conditions milder than those used in these experiences.

The Diels−Alder reaction of **2a** with cyclopentadiene (16 equiv) in methylene chloride for 24 h at room temperature afforded cycloadduct *endo*-**4a** (84% isolated yield) along with unaltered substrate in a 95:5 ratio, respectively (Scheme 2).

Scheme 2



2a *endo*-**4a**

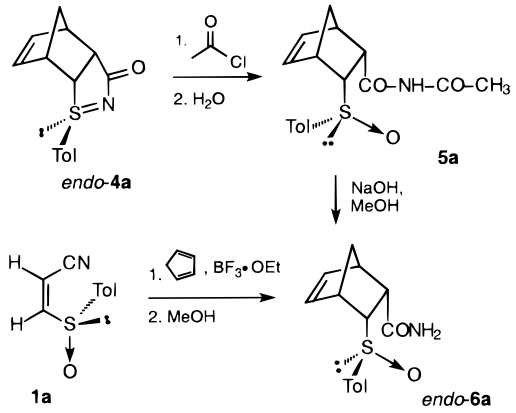
Catalyst	T(°C)	t(h)	yield (%)
—	rt	24	84
$ZnBr_2$	rt	2	98
$ZnBr_2$	-20	6	98
BF_3	-20	3	97

Addition of Lewis acids such as $ZnBr_2$ or BF_3 improved the reactivity. Thus, the complete transformation of **2a** into *endo*-**4a** (98% isolated yield) was achieved after 2 h at room temperature (or 6 h at −20 °C) in the presence of $ZnBr_2$ (1.2 equiv). The use of $BF_3{\cdot}OEt_2$ as a catalyst also led to the same cycloadduct (97% yield) after 3 h at −20 °C.[17]

The ee of the adduct **4a** was >97% (HPLC) suggesting that no racemization at sulfur had taken place either during the formation of **2a** or in its Diels−Alder reaction with cyclopentadiene.

The *endo* stereochemistry of the obtained cycloadduct **4a** was established from its ^{1}H NMR parameters,[18] and the relative configuration at their chiral carbons was established by chemical correlation (Scheme 3).

Scheme 3



Reaction of **4a** with acetyl chloride and then H_2O yielded the imide **5a** by hydrolysis of the sulfilimine moiety with inversion at the sulfur configuration. It was easily transformed (NaOH/MeOH) into carboxamide *endo*-**6a**. This compound is spectroscopically identical (and shows the same value and sign of its optical rotation) to the cycloadduct reported from the reaction of sulfinylacrylonitrile **1a** with cyclopentadiene in the presence of $BF_3{\cdot}OEt_2$.[7] Configuration at sulfur for *endo*-**4a** must be identical to that of the starting dienophile **2a** (Diels−Alder reaction conditions must not affect such a configuration) but opposite to that of the sulfinyl amide *endo*-**5a** (and therefore *endo*-**6a**), as a result of the inversion at sulfur configuration provoked by hydrolysis of the sulfilimide grouping.

The π−facial selectivity of the Diels−Alder reaction can be easily explained by assuming a steric approach control

(8) Special attention must be paid to the crystallization of **1a** following the procedure described in ref 7 to obtain it in an enantiomerically pure form. The $[\alpha]_D$ values obtained for different samples of **1a** with ee values of >96% (determined by NMR using Yb(hfc)$_3$ as LSR) fluctuates randomly (−400 ± 40, $CHCl_3$ 0.69). Hence, analysis by NMR but not specific rotation must be used as optical purity criteria.

(9) With this acid the sulfilimines are obtained in higher yields than with $BF_3{\cdot}OEt$.

(10) **2a:** ^{1}H NMR ($CDCl_3$) δ 7.93 (d, 1H, J = 5.5), 7.42 and 7.33 (AA′BB system, 4H), 7.05 (d, 1H, J = 5.5), 2.43 (s, 3H). **2b:** ^{1}H NMR ($CDCl_3$) δ 7.40 (t, 1H, J = 1.4 Hz), 7.34 and 7.26 (AA′BB system, 4H), 2.53 (m, 2H), 2.36 (s, 3H), 1.56 (m, 2H), 1.34 (m, 2H), 0.87 (t, 3H, J = 7.1).

(11) Different electrophilic activating reagents for such a condensation, including H_2SO_4 and BF_3, have been reported (Varkey, T. E.; Whitfield, G. F.; Swern, D. *J. Org. Chem.* **1974**, *39*, 3365. Sharma, A. K.; Ku, T.; Dawson, A. D.; Swern, D. *J. Org. Chem.* **1975**, *40*, 2758), but their use is limited to the presence of DMSO.

(12) The authors have deposited atomic coordinates for **2a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

(13) García Ruano, J. L.; Martín Castro, A. M.; Rodríguez Ramos, J. H.; Rubio Flamarique, A. C. *Tetrahedron: Asymmetry* **1997**, *8*, 3503.

(14) (a) Moriyama, M.; Yoshimura, T.; Furukawa, N.; Numata, T.; Oae, S. *Tetrahedron* **1976**, *32*, 3003. (b) Moriyama, M.; Oae, S.; Numata, T.; Furukawa, N. *Chem. Ind.* **1976**, 163. (c) Oae, S.; Kikuchi, K.; Moriyama, M.; Furukawa, N. *Chem. Lett.* **1982**, 1723. (d) Kikuchi, K.; Furukawa, N.; Moriyama, M.; Oae, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1934.

(15) (a) Furukawa, N.; Harada, K.; Oae, S. *Tetrahedron Lett.* **1972**, 1377. (b) Darwish, D.; Datta, S. K. *Tetrahedron* **1974**, *30*, 1155.

(16) The precise determination of the activation parameters of **2a** and **2b** is in progress.

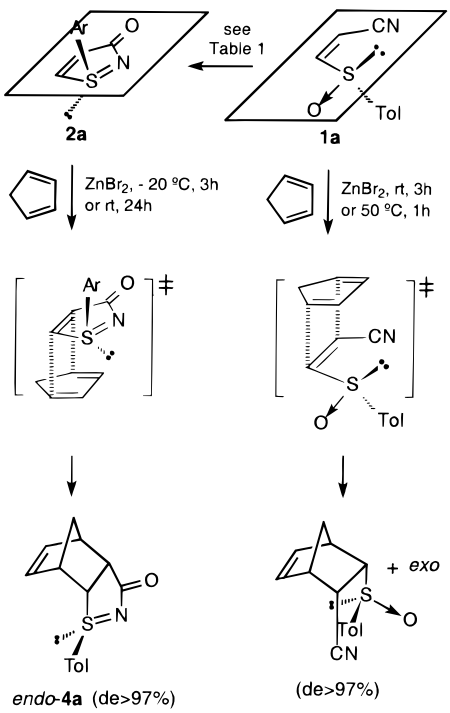
(17) Reactivity of **2b** with cyclopentadiene is clearly lower than that of **2a**. Its synthetic usefulness is only related to 1,3-dipolar cycloadditions, which are currently being investigated.

(18) *endo*-**4a:** ^{1}H NMR ($CDCl_3$) δ 7.45 and 7.30 (AA′BB′ system, 4H), 6.40 (dd, 1H, J 3.0 and 5.9), 6.30 (dd, 1H, J 3.0 and 5.9), 4.05 (dd, 1H, J 5.5 and 8.7), 3.56 (dd, 1H, J 5.5 and 8.7), 3.60−3.40 (m, 2H), 2.40 (s, 3H), 1.85−1.65 (m, 1H) and 1.60−1.40 (m, 1H).

of the diene from the less hindered face of the dienophile (that supporting the lone electron pair at sulfur). The bulky *p*-tolyl group completely hinders one of the faces of the cyclic sulfilimine, thus precluding the approach of the diene on it and justifying the complete stereoselectivity observed in these reactions.

This can be easily observed in Scheme 4 where the comparison is shown of the results obtained in reactions of

Scheme 4



2a and **1a**[7] with cyclopentadiene under thermal and $ZnBr_2$-catalyzed conditions. Both dienophiles exhibit complete but opposite π-facial selectivities, as expected from their different configuration. In this sense cyclic vinyl sulfilimines **2** can be considered as complementary dienophiles to their precursor sulfinylacrylonitriles **1** for the preparation of cycloadducts containing sulfinyl and carboxamide groups with the required configuration.

Concerning the *endo*−*exo* selectivity, the *endo* orientating character of the cyclic sulfilimine **2a** is clearly higher (only *endo*-**4a** is detected) than that of the acyclic sulfinyl acrylonitrile **1a**, mainly when reactions take place in the absence of catalysts (a 1:1 mixture of *endo* and *exo* adducts is formed).[7] The planarity of the cyclic system must facilitate the secondary interactions favoring the *endo* transition states.

Finally, results in Scheme 4 suggest that **1a** and **2a** exhibit a similar reactivity. As the positive influence of the CN group on the dienophilic character of **1a** must be similar or even higher than that of the amide group at **2a**, we can conclude that the activating effect of the sulfilimine group at **2a** will be similar or even higher than that of the sulfinyl group at **1a**. This fact can only be explained as a consequence of the lower bond order of the S═N bond (higher electronic deficiency at sulfur) with respect to the S→O one (see the Introduction).

As a conclusion we can establish that cyclic sulfilimines such as **2** can be easily prepared by cyclization of the corresponding (*Z*)-sulfinylacrylonitriles catalyzed by acids. They are configurationally stable under conditions of their Diels−Alder reactions with cyclopentadiene, evolving with complete *endo* and π-facial selectivity. The activating influence of the S═N grouping in the dienophilic character of double bonds is similar or even larger than that of the sulfinyl group. This research is ongoing in regard to the use of these substrates in other cycloaddition reactions and nucleophilic additions. These results will be published in due course.

Acknowledgment. We thank CAICYT (grant PB96-0035) for financial support. L.G.G. thanks Consejo Nacional de Ciencia y Tecnología (CONACYT-México) for a fellowship.

Supporting Information Available: Experimental Section containing characterization and carbon spectra for compounds **2**, **3**, and *endo*-**4a** (2 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

OL991224T