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Control of the Ring Selectivity in Diels-Alder Reactions of Naphthazarins mediated by Sulfur Functions

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Abstract: Ring selectivity of Diels-Alder reactions of naphthazarin thioderivatives with cyclopentadiene is controlled by choosing the adequate sulfur substituent: p-tolylsulfenyl and p-tolylsulfinyl (under $BF_3{\cdot}OEt_2$ catalysis) derivatives give cycloaddition only on the C-6 substituted tautomer. The opposite ring selectivity (exclusive reaction on the C-2 substituted tautomer) is achieved in the reaction of the p-tolylsulfonyl derivative at -78ºC.

Since the pioneering report of Fariña,[1] naphthazarin (5,8-dihydroxy-1,4-naphthoquinone) and other substituted derivatives have been widely used as dienophiles in the synthesis of tetracyclic systems related to anthracyclinones.[2] The tetracyclic framework of these antibiotics can be constructed via two Diels-Alder cycloadditions taking advantage of the tautomeric equilibrium showed by free naphthazarin ($R^1 = R^2 = H$) (Scheme 1) or its acyl derivatives ($R^1 = H$; $R^2 = COR$). For 2-substituted naphthazarins the electronic character of the substituents has a great influence on the relative stability of the tautomers: **A**, in Scheme 1, is favoured when R^1 is an electron withdrawing group[3,4] whereas **B** is more stable when R^1 is an electron donating group.[4,5] However, the composition of the equilibria must not be only the factor controlling the ring selectivity of naphthazarin cycloadditions, because there are several reports indicating that Diels-Alder reactions can take place through the less stable tautomer.[1,6] In order to evaluate the influence of the substituents on the ring selectivity of these reactions, their effects on both, stability and reactivity of tautomers, must be considered.

In the course of our work related to the synthesis[7] and Diels-Alder reactions[7a,8] of enantiomerically pure sulfinylquinones, we were faced with the synthesis of sulfenyl, sulfinyl and sulfonyl naphthazarins.[4] A detailed study of ^{13}C-nmr spectra of these sulfur derivatives allowed us to establish the qualitative composition of their tautomeric equilibrium which, agreeing with the previously reported work,[3,5] strongly depended on the nature of the sulfur substituent. Considering that the electronic effect of the sulfur functions studied (STol, SOTol and SO_2Tol) must modify the dienophilic reactivity of each tautomer making more reactive the less stable one, it was interesting to study the Diels-Alder reactions of these compounds to know the relative importance of both factors (tautomer population and reactivity) on the course of these processes and to check the possibility to get a total control of the ring selectivity only by changing the oxidation state at sulfur. The results obtained in the reaction of naphthazarins **1-3** (Scheme 1) with cyclopentadiene and the conditions in which the different functions evolve with complete ring selectivity are described herein.

Diels-Alder reactions of **1-3** were conducted in CH_2Cl_2 both under thermal and catalytic conditions. The results obtained are collected in Scheme 1 and Table 1. As can be seen, naphthazarin thioether **1** reacted with cyclopentadiene to yield only *endo* compound **4A**,[9,10] resulting from the exclusive reaction on the unsubstituted double bond of tautomer **1A** (entry 1). The increase of the temperature did not modify the ring selectivity whereas the presence of $BF_3{\cdot}OEt_2$ only had an effect on the reaction rate (and therefore the reaction time) but not on the ring selectivity which remained unaltered (entry 2). In spite of the scarce population of tautomer **1A** in its equilibrium,[4] the exclusive formation of the adduct **4A**, although was not unexpected due to the low dienophilic reactivity of the major tautomer **1B** (showing a strong electron donating STol group at C-2 of the quinonic system), evidenced that the ring selectivity of the cycloaddition of **1** was mainly controlled by the relative reactivity of the tautomers, being less important the composition of the tautomeric equilibrium.

Scheme 1

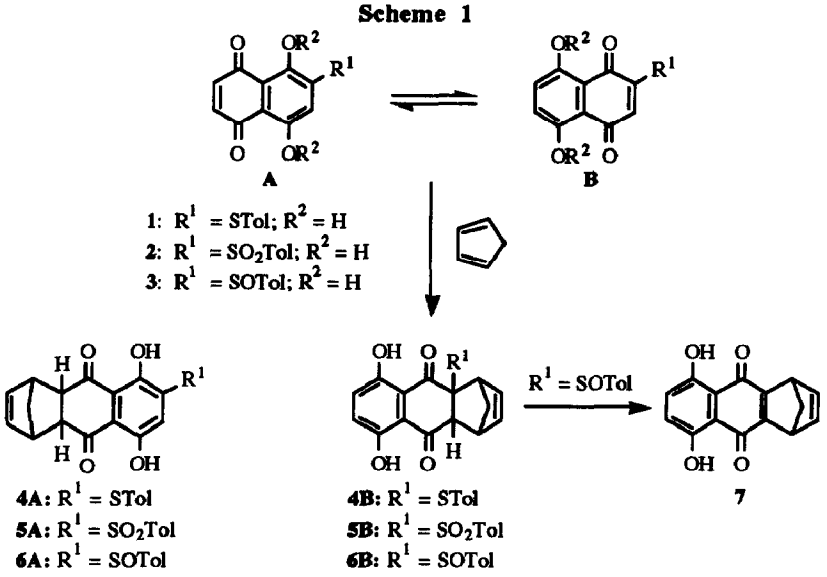

Table 1. Results of Diels-Alder reactions with naphthazarin thioderivatives **1-3**.

Entry	Substrate	Cat.	T (°C)	Time	Yield (%)	Adducts	Ratio
1	**1**	-----	20	24 h	87	**4A** : **4B**	100 : 0
2	**1**	BF_3·OEt_2	20	12 h	76	**4A** : **4B**	100 : 0
3	**2**	-----	-78	72 h	90	**5A** : **5B**	0 : 100
4	**2**	-----	-30	24 h	92	**5A** : **5B**	20 : 80
5	**2**	-----	20	1 h	87	**5A** : **5B**	25 : 75
6	**2**	-----	60[a]	5 min	82	**5A** : **5B**	25 : 75
7	**2**	BF_3·OEt_2	20	5 min	80	**5A** : **5B**	50 : 50
8	**3**	-----	-30	24 h	81	**6A**[b] : **7**	77 : 23
9	**3**	-----	20	3 h	91	**6A**[b] : **7**	63 : 37
10	**3**	-----	60[a]	5 min	88	**6A**[b] : **7**	50 : 50
11	**3**	$ZnBr_2$	-20	1 h	80	**6A**[b] : **7**	60 : 40
12	**3**	$Eu(fod)_3$	20	1 h	82	**6A**[b] : **7**	73 : 27
13	**3**	BF_3·OEt_2	-20	1 h	78	**6A**[b] : **7**	100 : 0

[a] $CHCl_3$ as solvent.

[b] Obtained as a mixture of diastereoisomeric *endo* adducts

The composition of the reaction mixtures obtained from the sulfone **2** was dependent on the temperature. At -78°C the *endo* adduct **5B**[10] was exclusively formed (entry 3). In these conditions, the adduct formed also derived from the evolution of the minor tautomer **2B**[4], whose dienophilic reactivity must be now enhanced by the strong electron withdrawing character of the SO_2Tol group. The increase of the temperature (entries 4-6) produced a decrease of the ring selectivity, giving mixtures of *endo* adducts **5A** and **5B** from which the minor component **5A**[10] (derived from the attack of cyclopentadiene on the major but less reactive tautomer **2A**) could be isolated. The addition of BF_3·OEt_2 to the reaction mixture decreased the reaction time and gave a significant increase of the amount of **5A** (entry 7).

More complexes were the results obtained from the sulfoxide **3**, which exhibits diastereotopic faces due to the chirality of the sulfinyl group. Its reaction with cyclopentadiene in thermal conditions (entries 8-10)

yielded mixtures of compounds **6A**[10] and **7**.[11] Adduct **6A** was a mixture of diastereoisomers derived from the *endo* approach of the diene on each diastereotopic face of the tautomer **3A**. Compound **7** resulted in the in situ pyrolytic elimination of the SOTol group from the mixture of the*endo* adducts **6B**, which could not be detected, resulting in the approach of the diene on the two faces of tautomer **3B**.[12] The configurational assignement of adducts **6A** could not be unequivocally established from their nmr parameters because the differences between them were too small[13].

In thermal conditions (entries 8-10), adducts **6A** were the major component of the reaction mixtures, but this ring selectivity decreased when the temperature increased (77:23 at -30°C and 50:50 at 60°C), indicating that the reactivity of the C-2 substituted tautomer **3B** must be slightly lower than that of C-6 substituted **3A** (both with similar population),[4] despite the electron withdrawing character of the sulfinyl group. This suggested that the activating electronic effect of this substituent must be overrided by steric interactions between the methylene bridge of the cyclopentadiene and the substituents around sulfur during the *endo* approach on the tautomer **3B**.[14]

The use of $ZnBr_2$ and $Eu(fod)_3$ as catalysts (entries 11 and 12) only determined small changes in the ring selectivity suggesting that the influence of these catalysts on both reactivity and composition of the tautomeric equilibrium must be low. By the contrary, the addition of $BF_3{\cdot}OEt_2$ strongly modified the ring selectivity of the reaction which only yielded adduct **6A** (entry 13). Taking into account that the coordination of the Lewis acid with the carbonylic oxygens would have a similar effect on the reactivity of both tautomers, the effect of the $BF_3{\cdot}OEt_2$ on the ring selectivity of the cycloadditions of sulfone **2** and sulfoxide **3** must be mainly attributed to their different ability for coordination induced by the presence of the sulfur function. The association of the Lewis acid to the quinonic oxygens at C-1 of tautomers **2B** and **3B** must be difficulted by the steric hindrance of the close sulfonyl (scarcely associated) or sulfinyl group (strongly associated[15] and therefore with a larger size). This fact determines a more effective association with the carbonylic oxygens of tautomers **2A** and **3A** whose reactivity must be largely enhanced. Moreover, the increase of the sulfinyl group size as a consequence of its association with the $BF_3{\cdot}OEt_2$, must decrease the reactivity of the tautomer **3B** because the steric interactions with the cyclic diene above mentioned become larger.

In conclusion, we have succeeded in controlling the ring selectivity of Diels-Alder reactions on naphthazarin systems by using sulfur functions in different oxidations states (S, SO and SO_2). The results obtained evidence that the effect of the substituents on the dienophilic reactivity of substituted naphthazarin tautomers have a larger influence on the ring selectivity of the cycloaddition than those on their stability and therefore the composition of the tautomeric equilibria. Moreover, they alert about the important role of the steric interactions on the relative reactivity of the tautomers in reactions with cyclic dienes. We are currently applying these results to the synthesis of tetracyclic systems related to anthracyclinones.

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REFERENCES AND NOTES

1. Fariña, F.; Vega, J.C. *Tetrahedron Lett.* **1972**, 1655.
2. a) Echavarren, A.; Fariña, F.; Prados, P. *Tetrahedron* **1984**, *40*, 4561. b) Kelly, T.R.; Gillard, J.W.; Goerner Jr., R.N.; Lyding, J.M. *J. Am. Chem. Soc.* **1977**, 5513. c) Kelly, T. R.; Vaya, J.; Ananthasubramanian, L. *J. Am. Chem. Soc.* **1980**, *102*, 5983. d) Kelly, T.R.; Ananthasubramanian, L.; Borah, K.; Gillard, J.W.; Goerner Jr., R.N.; King, P.F.; Lyding, J.M.; Tsang, W.G.; Vaya, J. *Tetrahedron* **1984**, *40*, 4569. e) Krohn, K. *Tetrahedron* **1990**, *46*, 291 and ref. cited therein. f) de Bie, J.F.M.; Peperzak, R.M.; Daenen, M.J.; Scheeren, H.W. *Tetrahedron* **1993**, *49*, 6463.
3. Escobar, C.; Fariña, F.; Martínez-Utrilla, R.; Paredes, M.C. *J. Chem. Research (S)* **1977**, 266. b) Bloomer, J.L.; Stagliano, K.W. *Tetrahedron Lett.* **1993**, *49*, 757.
4. Carreño, M.C.; García Ruano, J.L.; Urbano, A. *Tetrahedron* **1994**, in press.
5. Moore, R.E.; Scheuer, P. *J. Org. Chem.* **1966**, *31*, 3272.
6. Echavarren, A.; Fariña, F.; Prados, P. *An. Quím.* **1980**, *76*, 222.
7. a) Carreño, M.C.; García Ruano, J.L.; Urbano, A. *Tetrahedron Lett.* **1989**, *30*, 4003. b) Carreño, M.C.; García Ruano, J.L.; Mata, J.M.; Urbano, A. *Tetrahedron* **1991**, *47*, 605. c) Carreño, M.C.; García Ruano, J.L.; Urbano, A. *Synthesis* **1992**, 651.
8. Carreño, M.C.; García Ruano, J.L.; Urbano, A. *J. Org. Chem.* **1992**, *57*, 6870.

9. In the case of the adducts **4**, **5** and **6**, the notations **A** or **B** indicate the tautomeric form of the dienophile **1-3** from which they are formed.

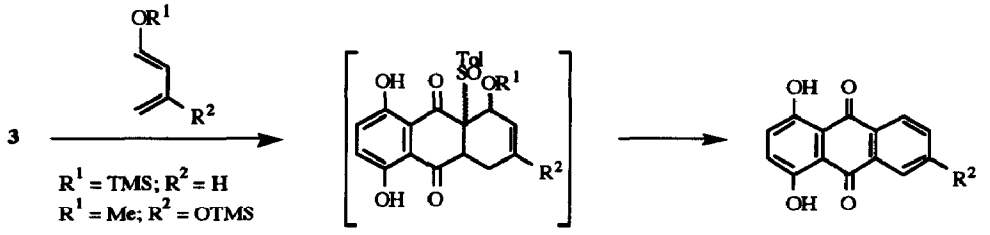
10. All new compounds described in this paper were fully characterized on the base of their IR, ^{1}H-NMR (200 MHz, $CDCl_3$), ^{13}C-NMR (50.3 MHz, $CDCl_3$) spectral data and elemental analysis / HRMS. Compound **4A**: mp 101-2°C (methanol); ^{1}H-NMR δ 1.55 (m, 2H, H_{11a} and H_{11b}), 2.42 (s, 3H, CH_3Ar), 3.40 (m, 2H, H_{4a} y H_{9a}), 3.66 (m, 2H, H_1 y H_4), 6.04 (m, 2H, H_2 and H_3), 6.42 (s, 1H, H_7), 7.28 and 7.43 (AA´BB´ system, 4H, tolyl group), 12.79 and 13.32 (2s, 2H, OH). Compound **5A**: ^{1}H-NMR δ 1.51 and 1.59 (2m, 2H, H_{11a} and H_{11b}), 2.43 (s, 3H, CH_3Ar), 3.42 (m, 2H, H_{4a} y H_{9a}), 3.68 (m, 2H, H_1 y H_4), 6.03 (m, 2H, H_2 and H_3), 7.32 and 7.93 (AA´BB´ system, 4H, tolyl group), 8.08 (s, 1H, H_7), 12.36 and 13.39 (2s, 2H, OH). Compound **5B**: mp 178-80°C (hexane); ^{1}H-NMR δ 1.60 (dt, 1H, J = 9.4 and 1.5 Hz, H_{11b}), 2.43 (s, 3H, CH_3Ar), 2.47 (m, 1H, H_{11a}),3.72 and 3.77 (2m, 2H, H_1 y H_4), 4.29 (d, 1H, J = 3.8 Hz, H_{9a}), 6.06 and 6.20 (2H, 2dd, J = 2.9 and 5.6 Hz, H_2 and H_3), 7.16 and 7.22 (AB system, 2H, J = 9.4 Hz, H_6 and H_7), 7.31 and 7.67 (AA´BB´ system, 4H, tolyl group), 11.89 and 12.45 (2H, 2s, OH).Compounds **6A** (the major component could be separated by flash chromatography CH_2Cl_2:acetone 40:1): **Major diastereoisomer**: mp 128-130°C (methanol); ^{1}H-NMR δ 1.51 and 1.59 (2m, 2H, H_{11a} and H_{11b}), 2.35 (s, 3H, CH_3Ar), 3.38 (m, 2H, H_{4a} and H_{9a}), 3.68 (m, 2H, H_1 and H_4), 6.08 (t, 2H, J = 1.6 Hz, H_2 and H_3), 7.24 and 7.65 (AA´BB´ system, 4H, tolyl group), 7.92 (s, 1H, H_7), 12.59 and 12.89 (2s, 2H, OH). **Minor diastereoisomer**: ^{1}H-NMR δ 1.54 (2H, 2m, H_{11a} and H_{11b}), 2.37 (3H, s, CH_3Ar), 3.43 (2H, m, H_{4a} y H_{9a}), 3.65 (2H, m, H_1 y H_4), 5.96 and 6.02 (2H, 2dd, J = 2.8 and 5.7 Hz, H_2 and H_3), 7.30 and 7.68 (4H, AA´BB´ system, tolyl group), 7.90 (1H, s, H_7), 12.58 and 12.91 (2H, 2s, OH).

11. Tandon, V.K.; Rajesihwar, S.; Wharnna, J.M.; Anand, N. *Ind. J. Chem.* **1972**, *15B*, 839.

12. We could expect a very high π-facial diastereoselectivity for this approach because the sulfinyl group has shown to be very efficient to control it in the case of other 2-sulfinylquinones (see ref. 7) as well as in 2-sulfinylmaleates (Alonso, I.; Carretero, J.C.; García Ruano, J.L. *J. Org. Chem.* **1993**, *58*, 3231. *ibid* **1994**, in press). Nevertheless, the quick elimination of the sulfinyl group giving rise to the achiral quinone **7** precluded to check this assumption.

13. A significant π-facial diastereoselectivity was observed for the cycloaddition on **3A**. The ratio of both diastereoisomeric *endo* adducts ranged from 12 to 40% of diastereoisomeric excess. The role of steric effects, used in other related quinonic systems to explain similar diastereoselective reactions[7a], must be minimized in **3A** due to the long distance existing between the sulfinyl group and the dienophilic double bond in this tautomer. Therefore electronic factors, such as the different electronic density of both faces of these quinones, could be also responsible of the observed diastereoselectivity.

14. In order to confirm this point we have studied the reaction of p-tolylsulfinylnaphthazarin **3** with the acyclic dienes, 1-trimethylsyliloxy-1,3-butadiene and Danishefsky's diene:



Compounds **9**, resulting from adducts **8B** by elimination of both sulfinyl and OR^1 groups, were exclusively formed. This complete ring selectivity, just the opposite to that observed with cyclopentadiene, indicated that the sulfinyl group substantially increases the dienophilic behaviour of the double bond as expected from its withdrawing electron character. Therefore, the inversion of the ring selectivity observed in reactions of **3** with cyclopentadiene suggested that steric interactions mentioned in the text could counterbalance the electronic activation inverting the ring selectivity. 2-p-Tolylsulfinyl-1,4-benzoquinone had shown similar differences in the reaction with cyclic and acyclic dienes.[7a]

15. This association will also increase the electron withdrawing character of the sulfoxide, which could determine the shift of the tautomeric equilibrium of **3** towards **A** form. We have investigated the composition of these equilibria in the presence of Lewis acids by ^{13}C-nmr. Nevertheless, as the chemical shifts of all the signals are strongly affected by the acid, no conclusions could be extracted from this study.

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