Remote Regiocontrol by a Thioether Group in Diels−Alder Reactions of Naphthazarin: Regioselective Access to Tetracyclic Polyhydroxyquinones

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The synthesis of tetracyclic polyhydroxyquinones **5a** and **5b** was achieved through a sequence involving two Diels−Alder reactions with 1-methoxy-1,3-cyclohexadiene: the first with 2-(*p*-tolylthio)naphthazarin and the second on the resulting tricyclic derivative previously transformed into a (*p*-tolylsulfinyl)naphthazarin. The success of this strategy stemmed from the efficient remote regiocontrol exerted by the thioether substituent in the first step.

The possibility of achieving double Diels−Alder cycloadditions on naphthazarin derivatives[1] has been successfully exploited in the total synthesis of anthracyclinones.[2−4] The construction of the tetracyclic framework with the adequate substitution required an efficient control of the regiochemistry in both cycloadditions. The solution of the regiochemical problem in these Diels−Alder reactions has been found in the introduction of different substituents on the two reactive double bonds[2] or in the derivatization of the 5,8-dihydroxy-1,4-naphthoquinone system through a monoester[3,4] or quinone−monoimine formation.[5]

In the course of our work related to the synthesis[6] and Diels−Alder reactions[6a,7] of enantiomerically pure sulfinylquinones, we recently reported the preparation of sulfenyl-, sulfinyl-, and sulfonylnaphthazarins.[8] The study of their Diels−Alder reactions with cyclopentadiene[9] revealed a ring selectivity for the cycloadditions mainly dependent on the oxidation state at sulfur, regardless the composition of the tautomeric equilibria in the involved naphthazarins. In the case of 2-(*p*-tolylthio)naphthazarin (**1**) (see Scheme 1), both thermal and Lewis acid-catalyzed cycloadditions took place exclusively on the unsubstituted double bond of tautomer **1B**[9] in spite of its scarce participation in the equilibrium.[8] Thus, the ring selectivity of the cycloaddition was mainly determined by the reactivity of the dienophilic double bond, higher in tautomer **1B** than in **1A**, which bears an electron-donating substituent. In order to achieve the cycloaddition at the substituted ring it was necessary to oxidize the thioether function into a sulfoxide or sulfone, which increased the dienophilic reactivity of the substituted double bond.

These results suggested a ready access to tetracyclic hydroxyquinones from **1** by a sequence involving two Diels−Alder reactions: the first with 2-(*p*-tolylthio)-naphthazarin (**1**) and the second on the resulting tricyclic derivative previously transformed into a (*p*-tolylsulfinyl)-naphthazarin. The success of this strategy to construct the tetracyclic framework would be mainly dependent on the regioselectivity of the first cycloaddition between **1** and an asymmetric diene. The regiocontrol of the second cyloaddition on an appropriate sulfinylnaphthazarin was warranted from the well-documented behavior of sulfinylquinones.[7c]

In this paper we report the remote control exerted by the thioether group on the regioselectivity of Diels−Alder reactions of 2-(*p*-tolylthio)naphthazarin (**1**) and 1-methoxy-1,3-cyclohexadiene as well as its application to the regiocontrolled formation of a polyhydroxy tetracyclic quinone, taking advantage of the efficient control that a thioether and a sulfoxide can exert on both ring selectivity and regioselectivity of the two cycloadditions.

The first cycloaddition of **1** and 1-methoxy-1,3-cyclohexadiene was carried out at 40 °C for 24 h in different solvents, and the results obtained are collected in Scheme 1 and Table 1.

Two regioisomeric adducts **2a** and **2b**, resulting from the exclusive reaction of the diene on tautomer **1B**, were formed in all cases. The major component of the reaction mixture was dependent on the nature of the solvent (Table 1). The observed ring selectivity was expected after our previous research results,[9] but the high regioselectivity achieved was surprising taking into account that in the reactive tautomer **1B** the *p*-tolylthio group was not directly linked to the reactive dienophilic double bond. A similar remote regiocontrol in a Diels−Alder reaction exerted by a substituent situated far from the dienophilic double bond has been already pointed out by Kraus *et al.*[10]

As can be seen in Table 1, the best result corresponded to the reaction carried out in CH_2Cl_2 where compound **2a** was the major adduct formed in a 90:10 ratio (Table 1, entry 1). Excellent regiocontrol is thus exerted by the remote thioether function in the cycloaddition. A similar

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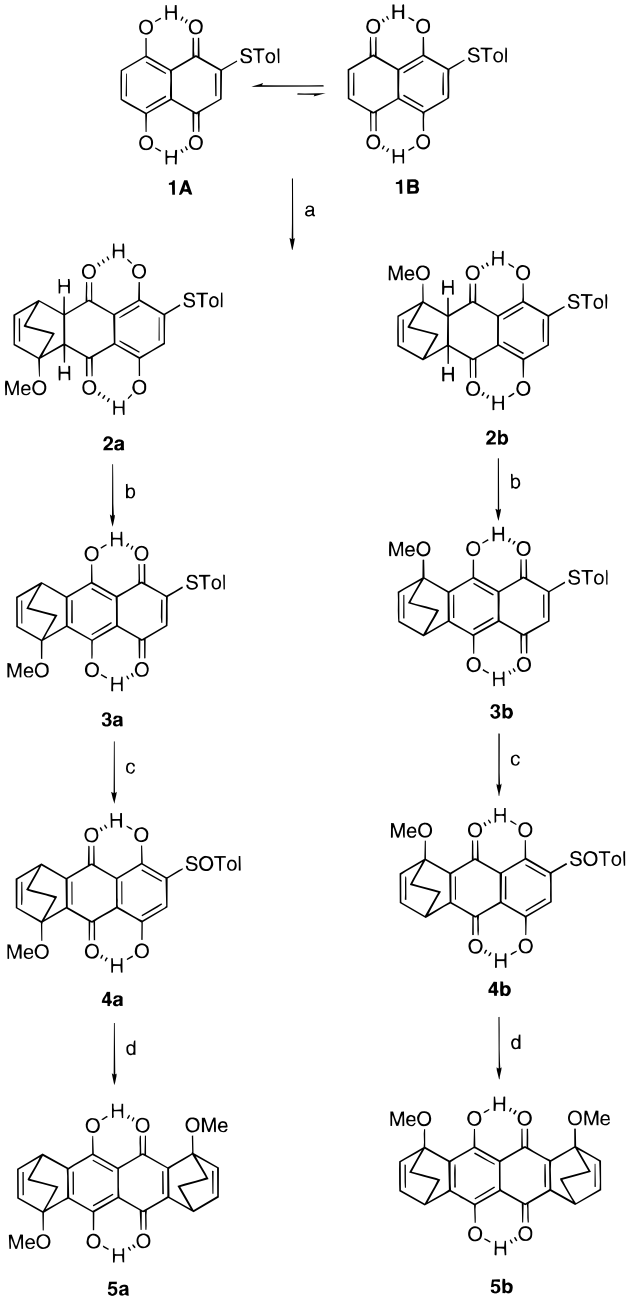
Scheme 1[a]



[a] Key: (a) 1-methoxy-1,3-cyclohexadiene (10 equiv), 40 °C, 24 h; (b) K_2CO_3 THF, H_2O, rt, 24 h, 70−88%; (c) *m*-CPBA, CH_2Cl_2, 0 °C, 2 h, 92−95%; (d) 1-methoxy-1,3-cyclohexadiene (2 equiv), $CHCl_3$, rt, 24 h, 80−82%.

Table 1. Diels−Alder Reactions of 1 and 1-Methoxy-1,3-cyclohexadiene at 40 °C

entry	solvent	yield (%)	**2a**:**2b**
1	dichloromethane	82	90:10
2	chloroform	77	80:20
3	ethyl ether	75	40:60
4	acetonitrile	80	35:65
5	ethanol	78	25:75
6	water[a]	85	50:50

[a] Room temperature, 2 h.

result, a 80:20 mixture of **2a** and **2b**, was observed when the cycloaddition was carried out in chloroform (Table 1, entry 2). The best opposite regioselectivity, a 25:75 mixture of **2a** and **2b**, was achieved in ethanol (Table 1, entry 5). The observed regioselectivity was

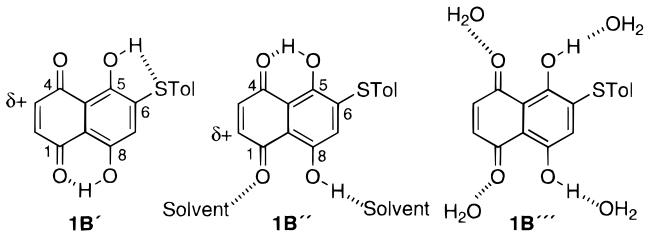


Figure 1.

lower when other solvents, such as ethyl ether (Table 1, entry 3) and acetonitrile (Table 1, entry 4), were used. Moreover, when water was the solvent of choice, the reaction took place very quickly, being completed in 2 h at rt, but with a total lack of regioselectivity (Table 1, entry 6).

The changes observed in the regioselectivity under the different conditions used could be rationalized from the different polarization of the dienophilic double bond of **1** as a result of the intramolecular hydrogen bonds strongly affected by the nature of the solvent. Thus, when the solvent was unable to be associated with the substrate through hydrogen bonds (CH_2Cl_2 and $CHCl_3$), only the intramolecular associations should be responsible of the double bond polarization. As can be seen in Figure 1, considering only the reactive tautomer **1B**, the association of the OH at C-8 with the carbonyl group at C-1 must be stronger than the one between the OH at C-5 and the carbonyl at C-4 due to the competition of the latter with the sulfur atom at C-6. As a consequence, the dienophile is mainly polarized as indicated for **1B′** in Figure 1 leading to the major formation of **2a** in the cycloaddition. When the solvents used were able to form hydrogen bonds with the OH (ethyl ether and acetonitrile) and carbonyl (ethanol) groups of the substrate, the intermolecular associations could compete with the intramolecular ones modifying the polarization of the dienophilic double bond. The presence of the STol group at C-6 would make difficult the intermolecular association of the solvent with the close OH at C-5 preserving the intramolecular hydrogen bonding shown in **1B″**. The polarization of the dienophilic double bond in **1B″** could explain the major formation of adduct **2b**. Finally, the high ability of water to form hydrogen bonds determined the breaking of all intramolecular associations, giving rise to the nonpolarized species **1B‴** that evolved in the cycloaddition without any regioselectivity.

The major regioisomeric adduct **2a** was isolated pure by flash chromatography (eluent: CH_2Cl_2) in 79% yield, and its structural assignment could only be unequivocally established after the synthesis of the tetracyclic system shown in Scheme 1.

Thus, the treatment of adducts **2a** or **2b** (as a 75:25 mixture of **2b**:**2a**) with potassium carbonate in a mixture THF/H_2O at rt afforded, respectively, pure (*p*-tolylthio)-naphthazarin **3a** in 78% yield, and a 75:25 mixture of **3b** and **3a**. Compound **3b** could be isolated pure after flash chromatography (eluent: CH_2Cl_2) in a 70% yield. The *m*-CPBA controlled oxidation of **3a** and **3b** gave the corresponding sulfoxides **4a** and **4b** as a 50:50 mixture of sulfur epimers. Finally, the Diels−Alder reaction of **4a** with 1-methoxy-1,3-cyclohexadiene at rt for 24 h gave the tetracyclic derivative **5a** in 82% yield. In a similar reaction, **4b** yielded exclusively compound **5b** (80% yield). In both cycloadditions, the adduct initially formed suffered a spontaneous pyrolysis of the sulfoxide, giving rise

to the quinonic framework in the same synthetic step.[7c,11] As expected, the regiochemistry of this second cycloaddition was in both cases fully controlled by the sulfinyl group.[7c,12]

The unequivocal regiochemical assignment of both **5a** and **5b** was based on their ^{1}H-NMR spectra. Compound **5a** showed the two associated hydroxyl groups at the same chemical shift (δ = 13.59 ppm) due to the C_2 symmetry present in this molecule. On the contrary, in compound **5b** both phenolic groups were nonequivalent and appeared at 13.02 and 14.12 ppm, respectively.

In summary, we have shown that the thioether function on the naphthazarin system is able to exert an effective remote control on the regioselectivity of the Diels−Alder cycloadditions with 1-methoxy-1,3-cyclohexadiene. Moreover, this regioselectivity can be inverted by changing the reaction medium. This ability has allowed the highly regioselective formation of tetracyclic quinonic compounds by two consecutive Diels−Alder reactions. We are currently extending this methodology to the synthesis of adequately functionalized derivatives related to anthracyclinones.

Experimental Section

Melting points were obtained in open capillary tubes and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ at 200.1 and 50.3 MHz, respectively. Diastereoisomeric adduct ratios were established by integration of well-separated signals of the diastereoisomers in the crude reaction mixtures and are listed in Table 1. All reactions were monitored by thin layer chromatography that was performed on precoated sheets of silica gel 60, and flash column chromatography was done with silica gel 60 (230−400 mesh) of Macherey-Nagel. Eluting solvents are indicated in the text. Apparatuses for inert atmosphere experiments were dried by flaming in a stream of dry argon. CH_2Cl_2 was dried over P_2O_5. All other reagent quality solvents were used without purification. For routine workup, hydrolysis was carried out with water, extractions with CH_2Cl_2, and solvent drying with Na_2SO_4.

5,8-Dihydroxy-1-methoxy-6-(*p*-tolylthio)-1,4,4a,9a-tetrahydro-9,10-anthraquinone (2a). To a solution of 2-(*p*-tolylthio)naphthazarin (**1**) (100 mg, 0.3 mmol) in 10 mL of refluxing CH_2Cl_2 was added 1-methoxy-1,3-cyclohexadiene (0.6 mL, 3 mmol, 10 equiv). After 24 h, the solvent was evaporated and the residue purified by flash chromatography (eluent: CH_2Cl_2) to afford **2a** as a brown solid (79% yield): mp 168−170 °C (MeOH); ^{1}H-NMR δ 12.97 and 12.36 (2s, 2H), 7.43 and 7.27 (4H, AA′BB′ system), 6.45 (1H, s), 6.13 (1H, dd, J = 5.6, 8.7 Hz), 6.06 (1H, dd, J = 1.8, 8.7 Hz), 3.49 (3H, s), 3.39 (1H, d, J = 9.1 Hz), 3.33 (1H, m), 3.26 (1H, dd, J = 2.8, 9.1 Hz), 2.42 (3H, s), 2.1−1.4 (4H, m); ^{13}C-NMR δ 203.6, 198.7, 155.4, 150.8, 140.6, 135.9 (2C), 135.8, 131.4, 131.2, 131.1 (2C), 124.5, 121.7, 113.2, 112.3, 80.1, 51.3, 50.9, 50.6, 36.4, 29.3, 24.2, 21.3.

5,8-Dihydroxy-1-methoxy-7-(*p*-tolylthio)-1,4,4a,9a-tetrahydro-9,10-anthraquinone (2b). Compound **2b** was obtained as above in EtOH at 40 °C as an unseparable 75:25 mixture with **2a** (78% yield): ^{1}H-NMR δ 12.78 and 12.46 (2H, 2s), 7.44 and 7.27 (4H, AA′BB′ system), 6.41 (1H, s), 6.08 (2H, m), 3.50 (3H, s), 3.41 (1H, d, J = 9.0 Hz), 3.30 (1H, m), 3.22 (1H, dd, J = 2.8, 9.0 Hz), 2.42 (3H, s), 2.1−1.4 (4H, m).

9,10-Dihydroxy-5-methoxy-2-(*p*-tolylthio)-5,8-dihydro-1,4-anthraquinone (3a). To a solution of **2a** (85 mg, 0.2 mmol) in 5 mL of THF was added K_2CO_3 (280 mg, 2 mmol, 10 equiv) in 5 mL of H_2O. After 24 h at rt, the reaction mixture was hydrolyzed with 10% HCl and extracted with ethyl ether. After workup and flash chromatography (eluent: CH_2Cl_2) compound **3a** was obtained as a red solid (88% yield): mp 120−121 °C (MeOH); ^{1}H-NMR δ 13.60 and 12.62 (2H, 2s), 7.41 and 7.30 (4H, AA′BB′ system), 6.70 (1H, dd, J = 1.4, 8.0 Hz), 6.46 (1H, dd, J = 6.1, 8.0 Hz), 6.09 (1H, s), 4.58 (1H, m), 3.72 (3H, s), 2.42 (3H, s), 1.9-1.4 (4H, m); ^{13}C-NMR δ 182.1, 181.3, 158.1, 157.1, 155.3, 146.7, 142.5, 141.0, 135.5 (2C), 135.3, 131.6, 131.1 (2C), 127.0, 123.5, 110.0, 109.7, 85.4, 55.4, 33.2, 30.8, 24.9, 21.3.

9,10-Dihydroxy-8-methoxy-2-(*p*-tolylthio)-5,8-dihydro-1,4-anthraquinone (3b). Compound **3b** was obtained as above from **2b** as a red solid (70% yield): mp 160−162 °C (MeOH); ^{1}H-NMR δ 13.25 and 12.94 (2H, 2s), 7.41 and 7.30 (4H, AA′BB′ system), 6.71 (1H, dd, J = 1.5, 8.0 Hz), 6.45 (1H, dd, J = 6.1, 8.0 Hz), 6.09 (1H, s), 4.57 (1H, m), 3.75 (3H, s), 2.43 (3H, s), 1.9-1.4 (4H, m); ^{13}C-NMR δ 182.8, 181.8, 156.1, 156.0, 155.9, 145.2, 144.3, 141.1, 135.6 (2C), 135.4, 131.8, 131.2 (2C), 128.2, 123.5, 110.0, 109.7, 85.6, 55.6, 33.2, 30.9, 25.0, 21.4.

5,8-Dihydroxy-1-methoxy-6-(*p*-tolylsulfinyl)-1,4-dihydro-1,4-anthraquinone (4a). To a solution of **3a** (42 mg, 0.1 mmol) in 5 mL of CH_2Cl_2 cooled at −20 °C was slowly added *m*-CPBA (30 mg, 0.1 mmol) in 5 mL of CH_2Cl_2. After the addition, the temperature was raised to 0 °C and the reaction was continued for 2 h. Then, the mixture was treated with $NaHCO_3$ saturated solution, and after workup, compound **4a** was obtained pure by ^{1}H-NMR as a 50:50 mixture of sulfur epimers (92% yield): ^{1}H-NMR δ 13.10, 13.00, 12.66 and 12.63 (4H, 4s), 7.88 and 7.87 (2H, 2s), 7.68 and 7.25 (8H, 2 AA′BB′ systems), 6.65 and 6.62 (2H, 2dd, J = 1.5, 6.2 Hz), 6.41 and 6.38 (2H, 2dd, J = 4.7, 6.2 Hz), 4.49 (2H, m), 3.70 and 3.68 (6H, 2s), 2.37 and 2.36 (6H, 2s), 1.9−1.2 (8H, m).

5,8-Dihydroxy-1-methoxy-7-(*p*-tolylsulfinyl)-1,4-dihydro-1,4-anthraquinone (4b). Compound **4b** was obtained as above from **3b** as a 50:50 mixture of sulfur epimers (95% yield): ^{1}H-NMR δ 13.10, 13.09, 12.56 and 12.55 (4H, 4s), 7.86 and 7.85 (2H, 2s), 7.69 and 7.25, 7.68 and 7.25 (8H, 2 AA′BB′ systems), 6.65 and 6.61 (2H, 2dd, J = 1.5, 6.2 Hz), 6.43 and 6.39 (2H, 2dd, J = 4.7, 6.2 Hz), 4.53 (2H, m), 3.68 and 3.65 (6H, 2s), 2.36 (6H, 2s), 1.9−1.2 (8H, m).

6,11-Dihydroxy-1,7-dimethoxy-1,4,7,10-tetrahydro-5,12-naphthacenequinone (5a). To a solution of compound **4a** (44 mg, 0.1 mmol) in 5 mL of dry $CHCl_3$ was added 1-methoxy-1,3-cyclohexadiene (40 μL, 0.2 mmol, 2 equiv) under argon. After 24 h at rt, the solvent was evaporated and the residue was purified by flash chromatography (eluent: CH_2Cl_2/EtOAc 90/10) to obtain the tetracyclic quinone **5a** (80% yield): ^{1}H-NMR δ 13.59 (2H, s), 6.67 (2H, dd, J = 1.0, 7.8 Hz), 6.44 (2H, dd, J = 6.0, 7.8 Hz), 4.57 (2H, m), 3.72 (6H, s), 1.9−1.3 (8H, m).

6,11-Dihydroxy-1,10-dimethoxy-1,4,7,10-tetrahydro-5,12-naphthacenequinone (5b). Compound **5b** was obtained as above from **4b** (82% yield): ^{1}H-NMR δ 14.12 and 13.02 (2H, 2s), 6.67 (2H, dd, J = 1.1, 7.9 Hz), 6.43 (2H, dd, J = 6.1, 7.9 Hz), 4.54 (2H, m), 3.72 (6H, s), 1.9−1.3 (8H, m); ^{13}C-NMR δ 169.9 (2C), 167.9 (2C), 147.6 (2C), 147.5 (2C), 146.4, 146.3, 135.4 (2C), 131.4 (2C), 85.60 (2C), 55.7 (2C), 33.1 (2C), 31.1-(2C), 25.0 (2C).

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Supporting Information Available: Copies of ^{1}H-NMR spectra of all compounds (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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