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Studies of chemoselectivity in Diels–Alder reactions of 2-(*p*-tolylsulfinyl)-1,4-benzoquinone and styrenes: formation of (*p*-tolylsulfinyl)-1,4-phenanthrenequinones

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Abstract

Diels–Alder reactions of 2-(*p*-tolylsulfinyl)-1,4-benzoquinone **1** with 4-methoxystyrenes **2a**–**b** in polar solvents afforded 2- and 3-(*p*-tolylsulfinyl)-1,4-phenanthrenequinones **4a**–**b** and **5a**–**b** as major compounds. A second cycloaddition of **5a** and **4a** with 3,4-dimethoxystyrene **2a** gave access to C- and S-shaped pentacyclic molecules **10** and **11** in a highly regioselective way.

Keywords: cycloadditions; quinones; sulfoxides; chemoselectivity.

Polycyclic aromatic hydrocarbons has been the subject of attention due to their potent carcinogenic properties.[1] One of the methods employed for their syntheses is based on Diels–Alder reactions of quinones with styrene derivatives.[2] In particular, 1,4-phenanthrenequinones, obtained using *p*-benzoquinone as dienophile,[3] are also interesting en route to helical derivatives.[4] Additionally, some naturally occurring 1,4-phenanthrenequinones are biologically active.[5]

In the course of our work related to the study of Diels–Alder reactions with sulfinylquinones,[6] we have shown that ambident dienophile 2-(*p*-tolylsulfinyl)-1,4-benzoquinone **1** reacts chemoselectively with cyclic dienes on the unsubstituted C5–C6 double bond,[7] whereas reactions with semicyclic and acyclic ones occur on the sulfinyl-substituted C2–C3 double bond.[7a,b,8] We recently described the cycloadditions between **1** and differently substituted vinylarenes[9] as an improved access to 1,4-phenanthrenequinones. In all cases but one the reaction took place on the substituted C2–C3 double bond of **1** to afford, after elimination of the sulfinyl group and further aromatization, a wide range of substituted 1,4-phenanthrenequinones. When 3,4-dimethoxystyrene **2a** was the diene, a small but significant reaction on the unsubstituted C5–C6 double bond of **1** was observed, yielding the corresponding sulfinyl-substituted 1,4-phenanthrenequinones. After this unexpected result, we decided to investigate such a process. In this communication we report the chemoselectivity of Diels–Alder reactions of 2-(*p*-tolylsulfinyl)-1,4-benzoquinone **1**[10] with 3,4-dimethoxy- and 4-methoxystyrenes **2a** and **2b** and show that a second

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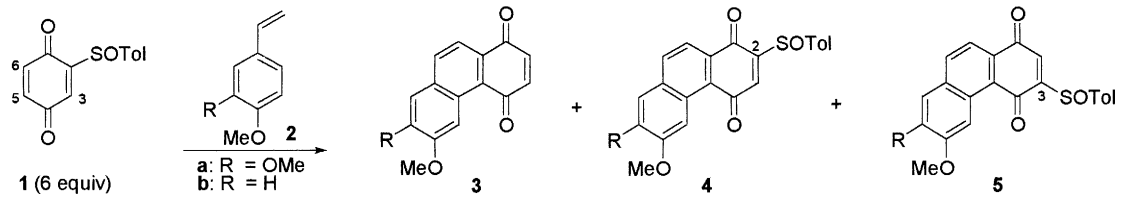
cycloaddition on the resuting sulfinyl-1,4-phenanthrenequinones opens a regiocontrolled access to S- and C-shaped pentacyclic aromatic systems.

All cycloadditions were performed under thermal conditions in solvents of different polarity using 6 equivalents of quinone to facilitate further aromatization of the intermediates. Under these conditions, Diels–Alder reactions of quinone **1** and styrenes **2a**–**b** gave variable mixtures of 1,4-phenanthrenequinones **3a**–**b**, resulting from the attack on sulfinyl-substituted double bond C2–C3 of **1**, and the regioisomeric[11] 2- and 3-(*p*-tolylsulfinyl)-1,4-phenanthrenequinones **4a**–**b** and **5a**–**b**, which resulted from the reaction on unsubstituted C5–C6 double bond of **1** (Scheme 1). The **3**:**4**:**5** ratios were determined directly from the crude reaction mixtures by ^{1}H NMR and are collected in Table 1.



Scheme 1.

Table 1
Diels–Alder reactions of 2-(*p*-tolylsulfinyl)-1,4-benzoquinone (**1**) and 4-methoxystyrenes **2a**–**b**

Entry	Diene	Solvent	Temp. / °C	Time (h)	C2-C3 (**3**)	:	C5-C6	(**4** : **5**)	Yield / %
1[a]	**2a**	toluene	110	24	**64**	:	36	(16 : 20)	80
2	**2a**	$CHCl_3$	60	24	41	:	59	(27 : 32)	60
3	**2a**	CH_3CN	80	24	38	:	62	(28 : 34)	95
4	**2a**	H_2O	20	48	22	:	**78**	(34 : 44)	74
5	**2b**	toluene	110	24	**62**	:	38	(13 : 25)	40
6	**2b**	$CHCl_3$	60	24	36	:	64	(29 : 35)	30
7	**2b**	CH_3CN	80	24	32	:	68	(32 : 36)	35
8	**2b**	H_2O	20	48	10	:	**90**	(45 : 45)	48

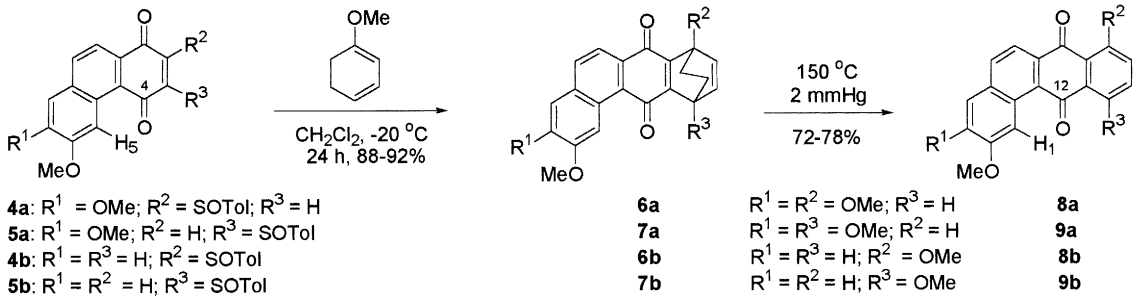
[a] Data taken from ref. 9

The reaction of **1** and **2a** in refluxing toluene (entry 1) afforded a 64:36 mixture of **3a**[3a] and **4a**:**5a** (16:20)[12] in 80% yield. The major formation of **3a** was inverted by increasing the solvent polarity. Thus, when the reaction was conducted in $CHCl_3$ (entry 2), a 60% yield of a 41:59 mixture of **3a** and **4a**:**5a** (27:32) was obtained. A slightly better result was observed in CH_3CN (entry 3) where a 38:62 mixture of **3a** and **4a**:**5a** (28:34) was formed in 95% yield. Finally, the best chemoselectivity through C5–C6 was observed using H_2O as solvent (entry 4) where a 22:78 mixture of **3a** and **4a**:**5a** (34:41) was formed. Compound **3a** was easily separated from sulfinyl derivatives **4a** and **5a**, but this mixture was difficult to separate, and only a small amount of major derivative **5a** could be obtained pure after crystallization in EtOH.

When cycloadditions were performed with 4-methoxystyrene (**2b**), the results were very similar (entries 5–8), obtaining in all cases variable mixtures of phenanthrenequinones **3b**,[3a] **4b**[12] and **5b**[12] although in lower yields (30–48%), probably due to the lower reactivity of **2b** if compared with that of **2a**. Again, reaction at sulfinyl-substituted C2–C3 double bond of **1** was preferred in refluxing toluene (entry 5), whereas in the more polar solvents (entries 6–8) the reaction was mainly on the C5–C6 double bond of **1**. The best chemoselection was reached in H_2O (entry 8) where a 10:90 mixture of **3b** and **4b**:**5b** (45:45) was obtained. All these quinones were readily separated by flash chromatography.

The comparison of the results obtained in cycloadditions using styrenes **2a** and **2b** with those observed in reactions between **1** and other styrenes,[9] shows that chemoselectivity is strongly depending on the aryl substitution. The most remarkable fact corresponds to the cycloaddition of **1** with 2,3-dimethoxystyrene in refluxing toluene,[9] which gave only reaction with the sulfinyl-substituted C2–C3 double bond of **1**. Apparently, the presence of a strongly electron donor such as the methoxy group in the *para*-position with respect to the vinyl one in styrene is essential to modify the chemoselectivity of the process. Although not easy to rationalize, these observations could suggest a major influence of electronic factors in controlling the chemoselection.

The structural assignment of **4a**–**b** and **5a**–**b** was established after the chemical correlation indicated in Scheme 2. Thus, the mixture of **4a** and **5a** reacted in a regiocontrolled way[13] with 1-methoxy-1,3-cyclohexadiene to afford, after pyrolytic elimination of the sulfoxide in the initially formed cycloadducts, a 92% of a mixture of the corresponding 1,4-dihydroquinones **6a**[12] and **7a**,[12] that could be separated by flash chromatography. In a similar way, derivatives **6b**[12] (88% yield) and **7b**[12] (91% yield) were, respectively, obtained from **4b** and **5b**. Vacuum pyrolysis[14] of **6a**–**b** and **7a**–**b** at 150°C and 2 mmHg produced complete aromatization to give the benz[*a*]anthracenediones **8a**–**b** and **9a**–**b** in good yields (72–78%). The structural assignment of **8a**[12] and **9a**[12] was effected by comparison of their ^{1}H NMR parameters[15] with those of known **8b**[11b] and **9b**.[11b]



Scheme 2.

Finally, en route to pentacyclic aromatic systems, we were interested in knowing the ability of these new sulfinyl-1,4-phenanthrenequinones to control the regioselectivity in a second cycloaddition with styrenes. Thus, the reaction between **5a** and 3,4-dimethoxystyrene **2a** in refluxing CH_3CN (Scheme 3) afforded a 60% yield of a single product identified as the C-shapped molecule **10**,[12,16] showing that sulfoxide directs the regiochemical course of the Diels–Alder reaction.[17] When cycloaddition was performed under the same conditions using a 50:50 mixture of regioisomeric **5a** and **4a** as dienophiles, we obtained a 50:50 mixture of derivative **10** and the S-shapped molecule **11** in a regioselective way.[12,16]

In conclusion, we described for the first time the preparation of several sulfinyl-substituted 1,4-phenanthrenequinones from the chemoselective Diels–Alder reactions of 2-(*p*-tolylsulfinyl)-1,4-benzoquinone **1** and 4-methoxy-substituted styrenes. This selectivity seemed to be influenced by electronic factors and could be enhanced working in polar solvents. Dienophiles **5a** and **4a** further reacted with 3,4-dimethoxystyrene to afford regioselectively C- and S-shaped molecules **10** and **11**.

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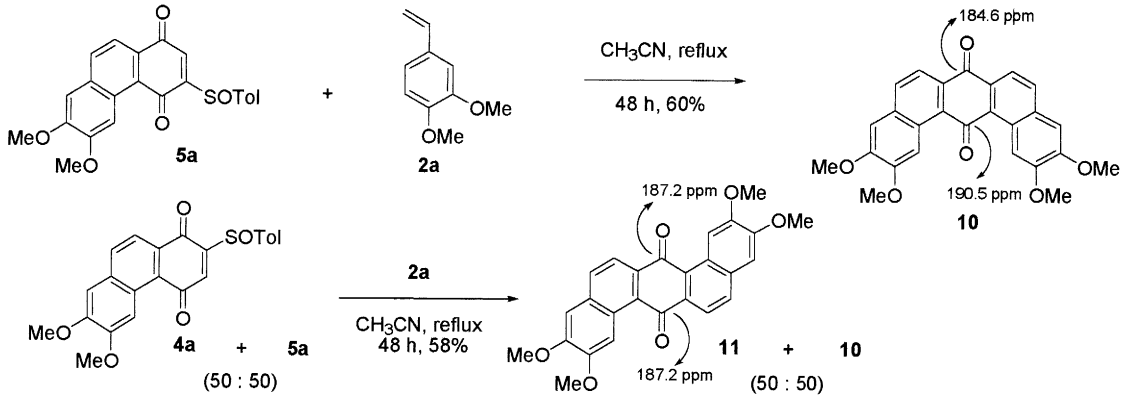

Scheme 3.

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12. All new compounds were characterized on the basis of their IR, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) spectral data, elemental analysis and/or HRMS.
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15. In the ^{1}H NMR spectrum of **9b** H_1 appeared shielded (δ=9.02 ppm) if compared with the same proton in **8b** (δ=9.20 ppm) probably due to the loss of planarity of the carbonyl group at C-12 as a consequence of the closeness with the methoxy

substituent at C-11 in **9b**. The same effect was observed for H_1 in **9a** (δ=9.00 ppm) in comparison with the same proton in **8a** (δ=9.16 ppm). A similar difference in the chemical shifts of H_5 was evident for sulfinylphenanthrenequinones **4a**–**b** and **5a**–**b**. In compounds **5**, having the sulfinyl group at C-3 close to the carbonyl at C-4, H_5 appeared at 8.88 and 8.86 ppm, respectively, whereas in **4a** and **4b** with the sulfoxide at C-2, H_5 resonated more deshielded at 9.00 ppm.

16. The structural assignment of compounds **10** and **11** was based on the differences observed in their ^{13}C NMR spectra. So, derivative **10** exhibited two different signals for its two carbonyl groups which appeared at 184.6 and 190.5 ppm respectively, whereas **11** showed only one at 187.2 ppm due to its C_2 simmetry (see Scheme 3).
17. Similar molecules have been prepared in a non-regioselective way, see: (a) Muschik, G. M.; Kelly, T. P.; Manning, W. B. *J. Org. Chem.* **1982**, *47*, 4709–4712. (b) Blatter, K.; Schlüter, A. D.; Wegner, G. *J. Org. Chem.* **1989**, *54*, 2396–2401.