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Synthesis and Diels-Alder Reactions of N-(*tert*-Butoxycarbonyl)-3-*p*-tolylsulfinyl-1-benzoquinone-4-imine

José M. Bartolomé, M. Carmen Carreño* and Antonio Urbano

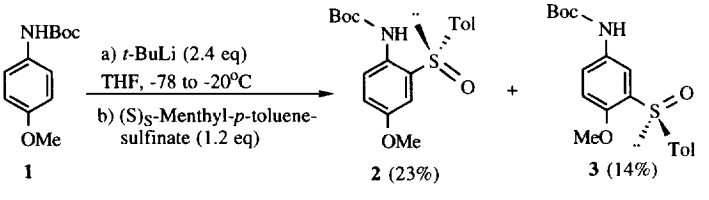
Departamento de Química Orgánica (C-I), Universidad Autónoma, Cantoblanco, 28049-Madrid, SPAIN

Abstract: The title compound was synthesized in 3 steps (regioselective sulfenylation, *m*-CPBA and $Pb(OAc)_4$ oxidations) from N-Boc-*p*-anisidine. Its Diels-Alder reactions with cyclopentadiene took place on the double bonds C_2-C_3 or C_5-C_6 depending upon the experimental conditions with total *endo*-selectivity and high π-facial diastereoselectivity. The cycloaddition with *trans*-piperylene ocurred exclusively on the sulfinylsubstituted dienophilic double bond C_2-C_3.

The ability of the sulfinyl group to control the π-facial diastereoselectivity in Diels-Alder cycloadditions[1] has been shown to be general for highly activated dienophiles such as maleates[2] or maleimides[3] as well as benzo-[4] and naphthoquinones.[5] When the quinonic system bears two dienophilic double bonds as in 2-*p*-tolylsulfinylbenzoquinones[4] and 2-*p*-tolylsulfinylnaphthazarin[6] the stereocontrol exerted by the sulfoxide in the approach of cyclopentadiene was efficient even when cycloadditions took place on the remote unsubstituted double bond. In order to extend these good results to other quinone analogues, we thought of studying the dienophilic behaviour of sulfinylquinone imines. Our interest in these systems stemed from the well known ability of the quinone imine moiety to control the regiochemistry of cycloadditions[7] which would allow regioselective reactions between the sulfinyl derivatives reacting from the unsubstituted double bond and cyclic substituted dienes. According to our previous results[4] high π-facial diastereoselectivity could also be expected. We report in this letter the synthesis and preliminary results of Diels-Alder reactions of N-(*tert*-butoxycarbonyl)-3-*p*-tolylsulfinyl-1-benzoquinone-4-imine **(5)** chosen as model compound.

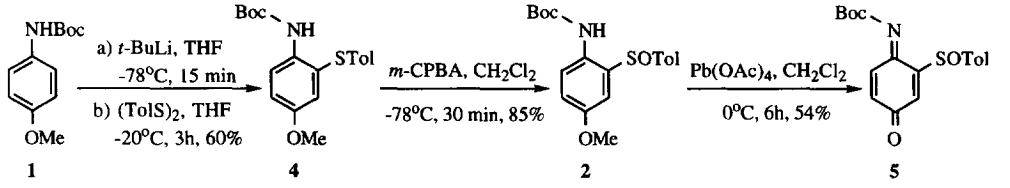
Our preceeding work on synthetic approaches to enantiomerically pure 2-*p*-tolylsulfinylquinones[4a,8] suggested a regioselective sulfinylation of N-*tert*-butoxycarbonyl-*p*-anisidine **(1)** and further controlled oxidation of the aromatic ring as the strategy. The *ortho* functionalization of **1** had been already described[9,10] through the sequence *ortho*-lithiation and reaction with several electrophiles with variable results. Different studies carried out on **1**[10] as well as on the simplest N-*tert*-butoxycarbonylaniline[11] pointed out that both the yield and regiochemistry of this sequence were strongly dependent on the base used to achieve the metallation as well as the concentration, the temperature, the solvent and the nature of the electrophile employed.

Firstly, we carried out the metallation of **1** with *t*-BuLi under the conditions described by Venuti.[11] After reaction with $(S)_S$-menthyl-*p*-toluenesulfinate[12] (Scheme 1), the resulting species were a mixture of regioisomeric sulfoxides **2**[13] (23% yield) and **3**[13] (14%). Although both compounds were isolated in optically active form, the low yield and regioselectivity obtained prompted us to check another synthetic alternative to compound **5**.



Scheme 1

So, the use of di-*p*-tolyl-disulfide, a better electrophile, after metallation of **1** in the same conditions as above (Scheme 2), allowed the regioselective formation of thioether **4**[13] (60% yield) which was oxidized to the corresponding sulfinyl derivative **2**[13] with *m*-CPBA (1 eq, 85% yield). Further oxidation of the aromatic ring of **2** with lead tetraacetate gave the desired N-(*tert*-butoxycarbonyl)-3-*p*-tolylsulfinyl-1-benzoquinone-4-imine (**5**)[13] in a 54% isolated yield (Scheme 2).

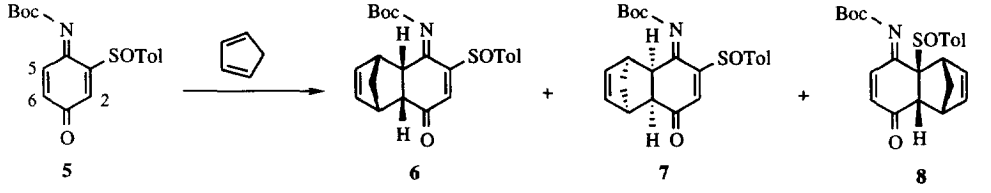


Scheme 2

The cycloadditions of **5** with cyclopentadiene, chosen as a model cyclic diene, were carried out under thermal conditions (entries 1-6 in Table) and in the presence of Lewis acids (entries 7-10). In all cases, but in the presence of $ZnBr_2$ (entries 9-10), mixtures of only two *endo* adducts **6**[13] and **7**[13] (Scheme 3) out of the eight possible diastereoisomers were formed. Their relative ratios were determined from the ^{1}H-NMR spectra of the crude reaction mixtures by integration of well separated signals. Compounds **6** and **7**, that could be separated by flash chromatography (hexane/EtOAc 85/15), resulted from the reaction on the unsubstituted dienophilic double bond C_5-C_6 in the *p*-benzoquinone monoimine system.

When the cycloadditions took place in the presence of $ZnBr_2$ (entries 9-10) adduct **8**[13] (Scheme 3), resulting from the reaction of cyclopentadiene on the substituted dienophilic double bond C_2-C_3, was obtained as major. Although **8** was not stable enough to be isolated pure, its structure and stereochemistry could be determined from the ^{1}H-NMR data of the crude reaction mixture.

The *endo* structure and relative configuration of the adducts **6**, **7** and **8** were established on the basis of their ^{1}H-NMR parameters and by comparison with those of similar adducts obtained by us[4a,c] in the cycloaddition between cyclopentadiene and (S)-2-*p*-tolylsulfinyl-1,4-benzoquinone.[14]



Scheme 3

Table. Diels-Alder reactions of **5** with cyclopentadiene.

entry	solvent	T (°C)	cat. (equiv)	time (h)	yield (%)	**6 : 7 : 8**	d.e. (%)
1	toluene	0	---------	8	97	73 : 27 : 0	46
2	CH_2Cl_2	-20	---------	5	98	77 : 23 : 0	54
3	EtOH	-20	---------	2.5	98	85 : 15 : 0	70
4	MeOH	-40	---------	4	93	88 : 12 : 0	76
5	H_2O	rt	---------	0.25	98	83 : 17 : 0	66
6	H_2O (LiCl)	rt	---------	0.08	96	85 : 15 : 0	70
7	CH_2Cl_2	-20	$Eu(fod)_3$ (2)	3.5	93	91 : 9 : 0	82
8	CH_2Cl_2	-20	$TiCl_4$ (3)	2	90	84 : 16 : 0	68
9	CH_2Cl_2	-20	$ZnBr_2$ (2)	0.5	77	17 : 8 : 75	
10	CH_2Cl_2	40	$ZnBr_2$ (2)	0.08	92	10 : 0 : 90	

Several aspects of the results presented in the Table are noteworthy. When thermal cycloadditions were carried out using solvents of distinct polarity (entries 1-6), the results indicated that both the π-facial diastereoselectivity in favor of diastereoisomer **6** and the reactivity slightly increased with solvent polarity. As expected,[15] the cycloaddition was very fast in H_2O (entry 5) and the addition of LiCl produced an instantaneous reaction (entry 6). The use of different Lewis acids improved both the reactivity and the diastereoselectivity of the cycloaddition on the unsubstituted C_5-C_6 double bond. The best results were achieved at -20°C in the presence of $Eu(fod)_3$ (entry 7) where a 91:9 mixture of **6** and **7** in excellent yield was obtained. The remote asymmetric induction which resulted in these cycloadditions on C_5-C_6 dienophilic double bond, was similar to that observed in the reactions of sulfinylbenzoquinones[4] and corroborated the ability of a sulfoxide to direct the cyclic diene approach even when situated far from the reacting centers.

In the presence of $ZnBr_2$, the chemoselectivity of the cycloaddition was temperature dependent (entries 9-10). The best result in these conditions was achieved at 40°C in CH_2Cl_2 (entry 10), being cycloadduct **8** formed in high yield and in a high diastereoselective manner.

In order to check the regiochemistry of the cycloaddition on C_5-C_6 of **5**, we performed the reactions with 1-methoxy-1,3-cyclohexadiene and 2-methylfurane. No cycloaddition products were observed, being compound **10a** (Figure 1), resulting from the easy reduction[16] of the quinone imine ring, isolated in the reaction with 1-methoxy-1,3-cyclohexadiene and **10b** (Figure 1) in the case of 2-methylfurane. The lack of Diels-Alder cycloaddition with these dienes could probably be a consequence of the disfavored transition states (**TSA** and **TSB**) that resulted in their attack both on C_2-C_3 and C_5-C_6 double bonds through the less hindered face with the expected regiochemistry (Figure 1).

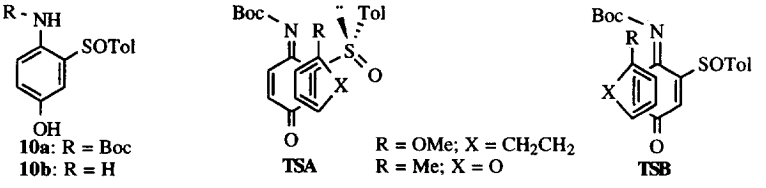
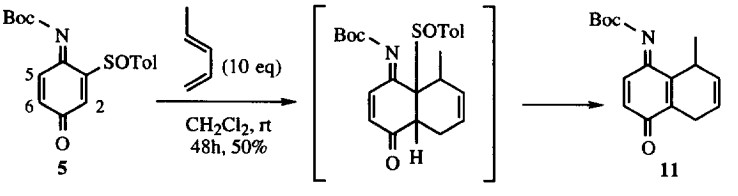


Figure 1

As can be seen in Figure 1, the *endo* diene approach to C_2-C_3 (**TSA**) is hindered by the interactions between the sulfinyl group and the ethylene ($X = CH_2CH_2$) or the oxygen (X = O) bridges in the cyclic diene. In the case of the C_5-C_6 reaction (**TSB**), the *endo* approach of the diene must be disfavoured by the interaction between the BOC protecting group and the R substituent of the diene.

However, the reaction of **5** with *trans*-piperylene, used as a model acyclic diene (Scheme 4), afforded the dihydronaphthoquinone imine **11**,[13] resulting from the exclusive cycloaddition on the substituted double bond C_2-C_3 and further elimination of the sulfinyl group in the adduct initially formed. The structure of compound **11** showed that the regiochemistry of the process was controlled by the sulfoxide[4c] and/or the imine group acting in a matched way.



Scheme 4

In conclusion, although our aim to know the regiochemistry of cycloadditions of 1-substituted cyclic dienes on C_5-C_6 double bond was not fulfilled, the substrates described in this communication open a short access to polycyclic dihydroquinone imines not easily synthesized by other ways.

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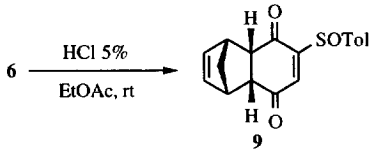
13. All new compounds were characterized on the basis of their IR, ^{1}H-NMR and ^{13}C-NMR (200 MHz, $CDCl_3$) spectral data and elemental analysis/HRMS. **2**: mp 160-1°C (hexane); ^{1}H-NMR δ 8.65 (broad s, 1H, NH), 7.84 (d, 1H, J = 9.0 Hz, H_5), 7.45 and 7.24 (AA´BB´system, 4H, tolyl group), 7.11 (d, 1H, J = 2.9 Hz, H_2), 6.96 (dd, 1H, J = 2.9 and 9.0 Hz, H_6), 3.82 (s, 3H, CH_3O), 2.35 (s, 3H, CH_3Ar), 1.42 (s, 9H, *t*-Bu). **3**: mp 206-207°C (hexane); ^{1}H-NMR δ 7.76 (broad d, 1H, J = 6.1 Hz, H_5), 7.67 (d, 1H, J = 2.6 H, H_3), 7.57 and 7.20 (AA´BB´system, 4H, tolyl group), 7.03 (broad s, 1H, NH), 6.78 (d, 1H, J = 8.8 Hz, H_6), 3.74 (s, 3H, CH_3O), 2.35 (s, 3H, CH_3Ar), 1.42 (s, 9H, *t*-Bu). **4**: mp 76-77°C (hexane); ^{1}H-NMR δ 7.96 (d, 1H, J = 9.0 Hz, H_5), 7.25 (broad s, 1H, NH), 7.06 (s, 4H, tolyl group), 7.01 (d, 1H, J = 3.0 Hz, H_2), 6.95 (dd, 1H, J = 3.0 and 9.0 Hz, H_6), 3.74 (s, 3H, CH_3O), 2.29 (s, 3H, CH_3Ar), 1.44 (s, 9H, *t*-Bu). **5**: mp 123-4°C (hexane); ^{1}H-NMR δ 7.66 and 7.26 (AA´BB´system, 4H, tolyl group), 7.40 (d, 1H, J = 2.1 Hz, H_2), 6.85 (d, 1H, J = 9.9 Hz, H_5), 6.56 (dd, 1H, J = 2.1 and 9.9 Hz, H_6), 2.37 (s, 3H, CH_3Ar), 1.57 (s, 9H, *t*-Bu). **6**: mp 147-8°C (hexane); ^{1}H-NMR δ 7.61 and 7.27 (AA´BB´system, 4H, tolyl group), 7.04 (s, 1H, H_2), 5.72 (dd, 1H, J = 2.8 and 5.6 Hz, H_7), 4.55 (dd, 1H, J = 2.8 and 5.6 Hz, H_6), 3.48 (dd, 1H, J = 3.9 and 8.2 Hz, H_{4a}), 3.39 (m, 1H, H_5), 3.15 (m, 1H, H_8), 3.10 (dd, 1H, J = 3.9 and 8.2 Hz, H_{8a}), 2.40 (s, 3H, CH_3Ar), 1.60 (s, 9H, *t*-Bu), 1.30 (m, 2H, H_{9a} and H_{9b}). **7** (from a mixture of **6** and **7**): ^{1}H-NMR δ 7.60 and 7.28 (AA´BB´system, 4H, tolyl group), 7.16 (s, 1H, H_2), 6.10 (2dd, 2H, J = 4.8 and 7.4 Hz, H_6 and H_7), 3.48 (m, 3H, H_5, H_8 and H_{8a}), 3.11 (dd, 1H, J = 4.1 and 8.4 Hz, H_{4a}), 2.37 (s, 3H, CH_3Ar), 1.59 (s, 9H, *t*-Bu), 1.52 and 1.42 (2m, 2H, H_{9a} and H_{9b}). **8**: ^{1}H-NMR δ 7.51 and 7.21 (AA´BB´system, 4H, tolyl group), 6.25 (m, 2H, H_2 and H_3), 6.19 and 5.69 (AB system, 2H, J = 10.3 Hz, H_6 and H_7), 3.96 (m, 1H, H_4), 3.63 (m, 1H, H_1), 3.08 (d, 1H, J = 3.8 Hz, H_{8a}), 2.40 (s, 3H, CH_3Ar), 2.14 (d, 1H, J = 13.2 Hz, H_{9b}), 1.67 (d, 1H, J = 13.2 Hz, H_{9a}), 1.60 (s, 9H, *t*-Bu). **11**: ^{1}H-NMR δ 6.88 and 6.53 (AB system, 2H, J = 10.0 Hz, H_2 and H_3), 5.82 (m, 2H, H_6 and H_7), 3.60 (m, 1H, H_5), 3.3-2.8 (m, 2H, H_{8a} and H_{8b}), 1.60 (s, 9H, *t*-Bu), 1.24 (d, 3H, CH_3).
14. The stereochemical assignment of **6** was confirmed by the chemical correlation shown below:



9

Treatment of **6** with HCl in EtOAc at room temperature afforded compound **9** whose stereochemistry had been demonstrated by a single-cristal determination.[4c]
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