JOC Note

Regiospecificity in the Synthesis of Diaryl Sulfones[†]

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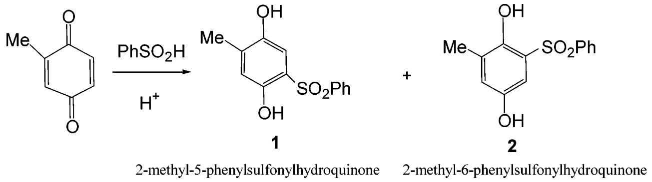
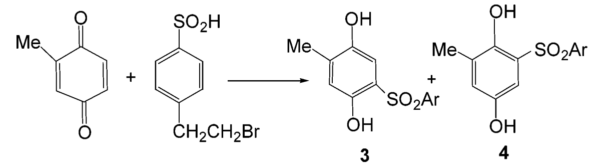
Abstract: The addition of arylsulfinic acids to 2-methyl-1,4-benzoquinone provides high yields of sulfones in a wide variety of solvents. The distribution of isomeric products obtained is strongly influenced by either (1) the acidity of aqueous solvents or (2) the water content of alcohol solvents. The distribution of isomeric products does not change in the various anhydrous, aprotic solvents examined.

The addition of benzenesulfinic acid to 2-methyl-1,4-benzoquinone leads to two isomeric sulfones (Scheme 1):

SCHEME 1



SCHEME 2



The literature of quinone addition reactions has been extensively reviewed and shows that the Michael adducts from monosubstituted 1,4-benzoquinones, are not formed in equal amounts.[1] We wish to present appropriate conditions for the preparation of each of these regioisomers and analogous compounds.

In an earlier study of quinonoid electrochemistry,[2] we carried out this reaction in aqueous acetic acid as described by Wanzlick,[3] who had followed the original method of Otto Hinsberg.[4] No evidence was found for compound **1**, and since a good yield of compound **2** was obtained, we did not pursue the subject further. The NMR coupling constants of the hydroquinone ring protons, as described by Gates et al.,[5] were used to establish that the structure was sulfone **2**. The ease with which compound **2** was obtained was surprising since both resonance theory[6] and frontier molecular orbital theory[7] predict **1** as the dominate isomer. Compound **1** is usually referred to as the 2,5-adduct and has been reported as the principal product in a similar reaction. Spinner et al. used 4-(2-bromoethyl)benzenesulfinic acid to obtain a 55% yield of compound **3** (Scheme 2).[8] Since aqueous ethanol was used in this instance, it seemed important to examine the extent to which solvent and acidity can shift the proportion of isomeric products.

Two other examples of the regiospecificity of nucleophilic sulfur addition to 2-methyl-1,4-benzoquinone have been reported. Gates and his collaborators studied the addition of 1-phenyl-5-mercaptotetrazole in methanol and found the 2,5-adduct analogous to compound **1** to predominate in a 2 to 1 ratio. In this instance, a total yield of only 38% was obtained.[5] Lau and Kestner found that thiourea adds to 2-methyl-1,4-benzoquinone in strongly acidic solvents and produces an overall yield of 89% and the 2,6-adduct corresponding to compound **2** in a 9 to 1 ratio.[9]

In 1992, Bruce and Lloyd-Williams repeated the addition shown in Scheme 1.[10] Using a two-phase dichloromethane/water system made strongly acidic with trifluoroacetic acid, they found a 3 to 1 excess of compound **2**. Their evidence demonstrates that the protonated quinone is the reactive species and that selective protonation of the two carbonyl groups explains the observed product ratios.

The only aprotic solvent reported for the addition of benzenesulfinic acid to a quinone is THF.[11] This work involved 1,2-benzoquinone and raises questions of regiospecificity related to the present study. In THF, the only product found was 3-(phenylsulfonyl)-1,2-benzenediol. In water, the only product found was 4-(phenylsulfonyl)-1,2-benzenediol. We have not attempted to repeat this chemistry, but we have studied the addition of benzenesulfinic acid to 2-methyl-1,4-benzoquinone with a select group of anhydrous aprotic solvents.

A careful study of the influence of acidity and solvent composition should provide a better understanding of this reaction along with useful means of preparing the two isomeric sulfones. We have examined the addition of

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[†] Dedicated to Dr. B. Stuart Hurlbert, who by example taught the beauty of research.

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TABLE 1. Benzenesulfinic Acid and 2-Methyl-1,4-benzoquinone: Product Distribution at Various Acidities

pH[a]	2,5-adduct (**1**) (%)	2,6-adduct (**2**) (%)	total yield (%)
1	20	80	85
2	41	59	90
4.5	60	40	92
5.5	39	61	91

[a] Ambient temperature.

TABLE 2. Benzenesulfinic Acid and 2-Methyl-1,4-benzoquinone: Product Distribution in Unbuffered, Acidic Solvent Systems

solvent[a]	pH	2,5-adduct (**1**) (%)	2,6-adduct (**2**) (%)	total yield (%)
$CH_2Cl_2/H_2O/F_3CCO_2H$	1	26	74	91[b]
HOAc/1 M HCl	1	20	80	84
$HOAc/H_2O$	2.5	42	58	86

[a] Ambient temperature. [b] Bruce and Lloyd−Williams:[10] 94% total yield, 25% yield of **1,** and 75% yield of **2**.

TABLE 3. Benzenesulfinic Acid and 2-Methyl-1,4-benzoquinone: Product Distribution in Alcohol Water Mixtures

% ROH[a]	$E_{\mathrm{T}}^{\mathrm{N}}$[b]	2,5-adduct (**1**) (%)	2,6-adduct (**2**) (%)	total yield (%)
12.5 (EtOH)	0.96	40	60	90
43 (EtOH)	0.85	27	73	82
99 (EtOH)	0.66	10	90	81
99 (MeOH)	0.76	9	91	80

[a] Ambient temperature. [b] Lewis acidity parameter.[12,13]

TABLE 4. Benzenesulfinic Acid and 2-Methyl-1,4-benzoquinone: Product Distribution in Anhydrous Aprotic Solvents

solvent[a]	$E_{\mathrm{T}}^{\mathrm{N}}$	2,5-adduct (**1**) (%)	2,6-adduct (**2**) (%)	total yield (%)
2,4-pentanedione	0.54	14	86	92
acetonitrile	0.46	15	85	96
acetone	0.36	17	83	83
tetrahydrofuran	0.18	14	86	87

[a] Ambient temperature.

benzenesulfinic acid to 2-methyl-1,4-benzoquinone using all of the solvent systems that have been reported for this and similar Michael addition reactions.

Tables 1−4 report the total yield obtained as an average of at least three individual runs. We also report the relative yields of the two isomeric sulfones. The yields of individual runs under each set of conditions agree to within ±4%.

The data in Tables 1−4 and the product ratios summarized in Table 6 show that solvent and acidity can markedly influence the product distribution obtained. In five of the solvent systems studied, we obtained an average of 41 ± 1% yield of compound **1**. In seven solvent systems studied, an 84 ± 3% yield of compound **2** was obtained. There are two additional experimental conditions giving product distributions that are clearly different from one another and from the other twelve. When the reaction shown in Scheme 1 was carried out in aqueous solution at pH 4.5, compound **1** was obtained in 60% yield. When the same reaction was carried out in 43% ethanol/water, compound **2** was obtained in 73% yield. These results have been verified by replication as previously indicated.

The optimum synthetic conditions are acetate buffer (pH 4.5), which gave a 92% average yield in a 3:2 ratio of compounds **1**:**2**, and acetonitrile, which gave a 96% average yield in a 1:6 ratio of compounds **1**:**2**.

These results strongly suggest that the mechanistic details of this chemistry are more complex and interesting than previously appreciated.

On the basis of these findings, we re-examined the work of Bruce and Lloyd−Williams. Our results, presented in Table 2, show excellent agreement with the published values in overall yield and isomer distribution.

We attempted to reproduce the product distribution reported by Spinner et al. for the reaction of 4-(2-bromoethyl)benzenesulfinic acid and 2-methyl-1,4-benzoquinone (Scheme 2).[8] We improved the overall yield and the yield of the 2,6-adduct (**4**) but failed to produce the excess of 2,5-adduct (**3**) they reported. The greatest amount of compound **3** we have obtained was produced using the acetic acid/water solvent[3]. These results, along with comparable results for benzenesulfinic acid, are presented in Table 5.

Bruce and Lloyd-Williams cite the study by Houk et al.[7] that shows when reaction takes place on the quinone ring the 2,5-adduct (**1**) is favored. They argued that in strongly acidic media, a methyl group introduces sufficient steric hindrance to favor protonation of the 4-carbonyl group, which leads to the formation of the 2,6-adduct (**2**). Carrying out the same reaction with 2-*tert*-butyl-1,4-benzoquinone led to a 12 to 1 ratio of 2,6-adduct to 2,5-adduct and makes the argument of the protonated quinone as the reactive species very convincing.

Our results are consistent with the notion of selective protonation in strongly acidic solution. We found that the proportion of the 2,5-adduct is increased at acidities up to pH 4.5, which suggests that the unprotonated quinone plays an increasingly significant role. At higher acidities, we observed the proportion of 2,5-adduct to decrease. If this maximum is shown to be real, it may be related to a change in rate-determining step from addition to aromatization. Such a change was shown to occur at exactly this pH by Ogata and his collaborators.[14]

The observations in aqueous ethanol are also instructive. The results found at 12.5% EtOH are identical to those at pH 5.5. Furthermore the proportion of compound **1** changes linearly with Reichardt's Lewis acidity parameter.[12−13]

All of these findings suggest the importance of selective hydrogen bonding and are consistent with selective stabilization of nonidentical quinonoid species.

In conclusion, we offer optimal conditions for the synthesis of the 2,5-adduct or the 2,6-adduct shown in

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TABLE 5. Comparison of Arylsulfinic Acids Added to 2-Methyl-1,4-benzoquinone in Different Solvent Systems

	4-(2-bromoethyl)benzenesulfinic acid			benzenesulfinic acid		
solvent[a]	2,5-adduct (**4**) (%)	2,6-adduct (**5**) (%)	total yield (%)	2,5-adduct (**1**) (%)	2,6-adduct (**2**) (%)	total yield (%)
$HOAc/H_2O$[3]	49	51	95	42	58	86
$EtOH/H_2O$[8]	35	65	87	27	73	82

[a] Ambient temperature.

TABLE 6. Reaction Conditions for Benzenesulfinic Acid and 2-Methyl-1,4-benzoquinone

solvent[a]					
sulfinic acid	quinone	stirring time (h)	crude yield (%)[b]	**1**:**2** ratio (%)[c]	reference
1 M $HClO_4$ (100 mL)	solid	1	85	20:80	14
1 M HOAc (15 mL)	1 M HOAc (15 mL)	1	90	41:59	14
HOAc/NaOAc 1:1[d] (40 mL)	1 M HOAc (40 mL)	1	92	60:40	14
HOAc/NaOAc 1:8 (20 mL)	HOAc/NaOAc 1:8 (20 mL)	1	91	39:61	14
MeOH or EtOH (4 mL)	MeOH or EtOH (4 mL)	3	83	10:90	5
30% $EtOH/H_2O$ (62 mL)	EtOH (10 mL)	3	82	27:73	8
H_2O (45 mL)	50% $EtOH/H_2O$ (15 mL)	1	90	40:60	15
1 M HCl H_2O (6 and 4 mL)	H_2O (25 mL)	1.25[e]	87	43:57	16
H_2O (15 mL)	HOAc (15 mL)	1.25[f]	86	42:58	3
2 M HCl (10 mL)	HOAc (12 mL)	0.5	84	20:80	9
THF[g] (5 mL)	THF (5 mL)	3[f]	87	14:86	5

[a] Volume in mL. [b] Average of at least three determinations. [c] Relative areas ofNMR absorptions at δ 6.9 + 7.5 (**1**) and 6.9 + 7.0 (**2**). [d] Molar ratios ([AH]:[A^-]). [e] Steam bath. [f] Ice bath. [g] Also for acetone, acetonitrile, and 2,4-pentanedione.

Scheme 1. Complete resolution of mechanistic considerations must await detailed kinetic studies in a variety of solvents.

Experimental Section

General. NMR spectra (^1H) were recorded in acetone-d_6 solution using a 300 MHz spectrometer. Chemical shifts (δ) are measured from the acetone absorption at 2.05 ppm. Yields of the isomeric product (**1/2** and **3/4**) were determined from the areas of the hydroquinone protons as described by Gates et al.[5] Melting points are uncorrected. Thin-layer chromatography was carried out on silica gel developed with ethyl acetate/hexane (1:1 v/v). 2-Methyl-1,4-benzoquinone was recrystallized from hexane or sublimed before use. Benzenesulfinic acid was used immediately after acidifying its sodium salt. Table 6 presents the experimental conditions under which each of the 14 different solvent systems were studied.

Addition Reaction: Standard Procedure. In a typical run, benzenesulfinic acid (1.66 g, 10.1 mmol) was added to the solvent being studied, followed by 1.0 g (8.2 mmol) of quinone. The reaction was stirred, usually at room temperature, for various times as reported for the specific solvent system employed (see Table 6). No effort was made to exclude air from the reaction. Except for the aprotic solvents, a precipitate formed shortly after mixing. Successive crops of product were collected by suction filtration and washed with hexane. NMR spectra for each crop were taken, and thin−layer chromatography showed only the presence of compounds **1** and **2**.

Product Determination. Samples chosen from the most favorable runs were recrystallized from toluene to constant melting points. Compound **1** (2-methyl-5-(phenylsulfonyl)hydroquinone): mp 177.9−179.8 °C (lit.[10] 158−164 °C, sample contaminated with **2**). Compound **2** (2-methyl-6-(phenylsulfonyl)-hydroquinone): mp 186.5−187.3 °C (lit.[2] 189−191 °C; lit.[10] 183−186 °C).

Addition of 4-(2-Bromoethyl)benzenesulfinic Acid to 2-Methyl-1,4-benzoquinone: Aqueous Ethanol.[8] A solution of 2-methyl-1,4-benzoquinone (1.2 g, 10 mmol) in 95% ethanol (20 mL) was added dropwise to a stirred suspension of 4-(2-bromoethyl)benzenesulfinic acid (3.0 g, 12 mmol) in 30% aqueous ethanol (100 mL). As the quinone color faded, a solid precipitate appeared and was filtrered under vacuum. The filtrate was diluted with 300 mL of ice−water, and a second crop was obtained. After the mixture was allowed to stand overnight, a third crop was present. Each of the three fractions was a mixture of two sulfones (**3** and **4**) as shown by TLC and NMR. A representative total crude yield was 11 g, 87%. Recrystallization from aqueous ethanol yielded compound (**3**) 2-[[4′-(2-bromoethyl)phenyl] sulfonyl]-5-methylhydroquinone, mp 119−121 °C (lit.[8] 121−122 °C). **Aqueous Acetic Acid.**[3] A solution of 2-methyl-1,4-benzoquinone (410 mg, 3.4 mmol) in 10 mL of glacial acetic acid was added, in one portion, to a stirred suspension of 4-(2-bromoethyl)benzenesulfinic acid (1.2 g, 4.8 mmol) in 10 mL of water. The quinone color disappeared along with the sulfinic acid. After stirring for 0.5 h, the light tan solid was suction filtered. After an additional 1 h of stirring, more tan solid was filtered. The reaction mixture was diluted with 200 mL of ice−water, and a third crop was obtained. Each of the three fractions was a mixture of compounds **3** and **4** as shown by TLC and NMR. A representative total crude yield was 1.2 g, 91%. Recrystallization from aqueous ethanol yielded compound **4** 2-[[4′-(2-bromoethyl)phenyl] sulfonyl]-6-methylhydroquinone mp 145−146 °C (lit.[8] 146−147 °C).

Regiospecificity in the Synthesis of Diarylsulfones. Compound 1: δ_H[300 MHz; $(CD_3)_2CO$] 7.96 (d, 2′-H and 6′-H), 7.60 (m, 3′-H, 4′ and 5′-H), 7.30 (s, 6-H), 6.75 (s, 3-H), and 2.15 (s, Me). The previously reported value of 7.14 for the m, 3′-H, 4′ and 5′-H is almost certainly a typographical error.[10] **Compound 2:** δ_H[300 MHz; $(CD_3)_2CO$] 8.00 (d, 2′-H and 6′-H), 7.70 (m, 3′-H, 4′ and 5′-H), 7.08 (d *J* 3.0 Hz, 5-H), 6.96 (d *J* 3.0 Hz, 3-H), and 2.15 (s, Me). **Compound 3:** ^1H NMR [300 MHz; $(CD_3)_2CO$] 7.90 (d, 2′-H and 6′-H), 7.50 (d, 3′-H and 5′-H), 7.28 (s, 6-H), 6.73 (s, 3-H), 3.71 (t, β-CH_2), 3.25 (t, α-CH_2), and 2.14 (s, Me). **Compound 4:** ^1H NMR [300 MHz; $(CD_3)_2CO$] 7.90 (m, 2′-H and 6′-H), 7.50 (m, 3′-H and 5′-H), 7.02 (d *J* 3.0 Hz, 5-H), 6.90 (d *J* 3.0 Hz, 3-H), 3.68 (t, β-CH_2), 3.24 (t, α-CH_2), and 2.11 (s, Me).

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Supporting Information Available: ^1H spectra for compounds **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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