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Erin E. Chapman[a]; Richard F. Langler[a]
[a] Department of Chemistry, Mount Allison University, Sackville, NB, Canada

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Selective deprotection of phenolic polysulfonates

Erin E. Chapman and Richard F. Langler*

Department of Chemistry, Mount Allison University, Sackville, NB, Canada E4L 1G8

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Nosylates of phenols can be selectively deprotected by thiocresol anions in DMSO. Successful deprotection can be accomplished in molecules containing aryl-appended halides, ethers, aldehydes, alkanesulfonates or arylsulfonates. Nosylate deprotection is accomplished by the CS bond rupture which is believed to proceed by nucleophilic aromatic substitution.

Keywords: sulfonate deprotection; phenols; CS cleavage of *p*-nitrobenzenesulfonates; nucleophilic aromatic substitutions; single-electron transfer

1. Introduction

Recently, we have taken on the problem of constructing phenol-ether-derived sulfonates to explore their biological activities vis à vis malaria, human skin cancer and breast cancer cells (*1–5*). A common feature of synthetic planning for molecules with repeating functional groups is the use of protecting groups. Given that our target molecules include phenolic-derived sulfonate moieties, it seemed worthwhile to explore the development of a sulfonate protecting group that could be selectively removed in the presence of other sulfonate functionalities.

Well before our current interest in phenolic sulfonate ethers emerged, a report appeared describing smooth CS rupture in reactions between *p*-toluenethiolate anions and *p*-nitrobenzenesulfonates (Scheme 1). The initial report (*6*) has been, subsequently, placed into context in a review of ionic reactions of sulfonic acid esters (*7*, pp 13–24). From the standpoint of mass balance, Scheme 1 and related reactions, described in (*6*), must produce phenols (*e.g.* **4** in Scheme 1), although no phenols were isolated and properly characterized at that time.

2. Results and discussion

2.1. *Deprotections*

The *p*-nitrobenzenesulfonate (nosylate) of 2-naphthol, **6**, was prepared and deprotected to provide 2-naphthol **7** in reasonable yield (Scheme 2).

*Corresponding author. Email: rlangler@mta.ca

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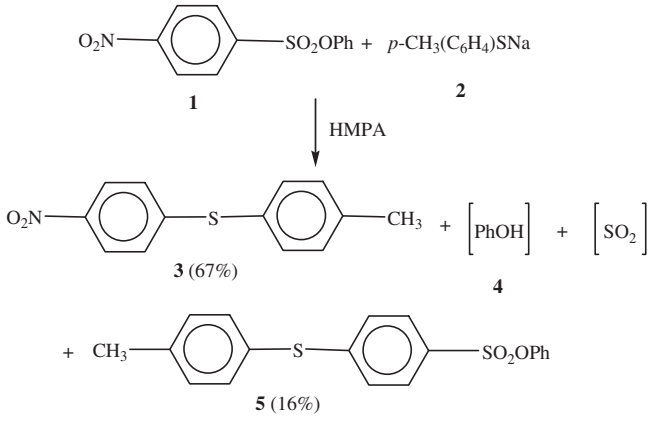
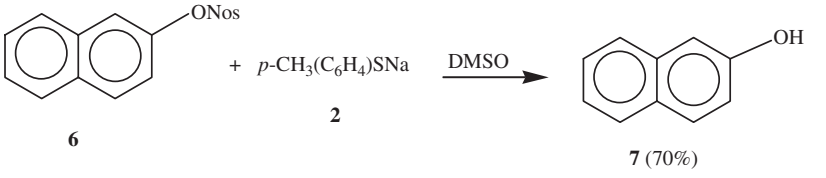


Scheme 1.



Scheme 2.

Under these same conditions, the corresponding *p*-cyanobenzenesulfonate furnished 2-naphthol **7** in 55% yield (*8*), so that further work focussed on nosylate deprotections. Note that yields for both nosylate preparations and deprotections refer to isolated products.

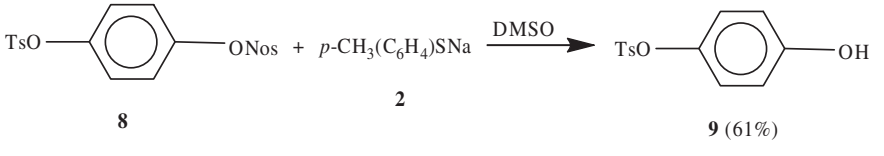
On the basis of Scheme 2 results, we have concluded that nucleophilic aromatic substitutions, by mercaptide anions, resulting in CS cleavage of phenol-derived nosylates showed some promise as a deprotection strategy. Next, the question of selectivity in the deprotection of mixed polysulfonates was tackled. The nosylate tosylate **8**, upon treatment with the arylthiolate **2**/DMSO smoothly removed the nosylate group and left the tosylate group in place (Scheme 3).

Hence, good selectivity and reasonable yields in nosylate deprotections might be expected.

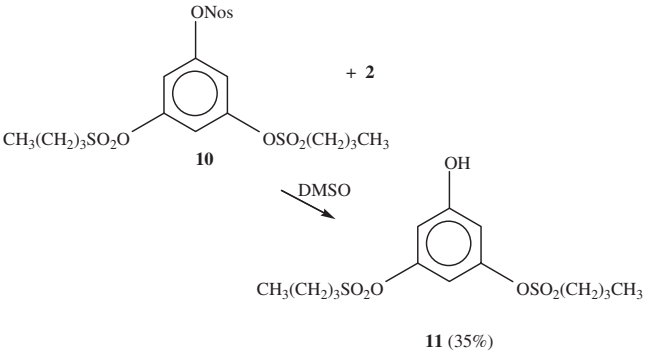
When Scheme 3 reaction was repeated with sodium phenylmethanethiolate in place of **2**, no tosylate phenol **9** and no benzylic sulfide (corresponds to **3** in Scheme 1) were isolated. Further work employed **2** as the reagent of choice.

To explore selectivity in the deprotection of polysulfonates, the di-*n*-butanesulfonate nosylate derived from phloroglucinol, **10**, was subjected to our standardized deprotection conditions (Scheme 4).

Earlier attempts (*3*) to convert symmetrical polyphenolic aromatic rings directly to phenol polysulfonates (*e.g.* preparation of **11**) proved to be rather frustrating, giving bad mixtures with low yields. Therefore, we have briefly examined the preparation of a nosylate phenol by attempted



Scheme 3.



Scheme 4.

monodeprotection of the dinosylate. The *p*-dinosylate of benzene, **12**, was smoothly converted to the nosylate phenol **13** as shown in Scheme 5.

Note that work with polynosylates is complicated by their very poor solubility in common organic solvents.

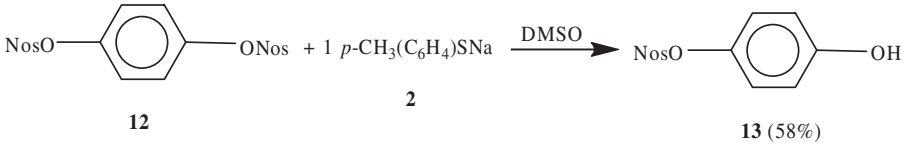
Nosylate deprotection, in the presence of other functionalities, was briefly explored with the results given in Scheme 6.

The *p*-bromo substrate **14** was selected for inclusion in this study because *p*-haloaryl sulfonates appear to undergo complicating single-electron transfer (SET) chemistry in some reactions (*7*, *9*, *10*).

Nonetheless, in this case, deprotection appears to have proceeded by means of a nucleophilic aromatic substitution and gave a reasonable yield.

The vanillin nosylate **14** (Scheme 6) was examined as an exemplary case which provided an assortment of electrophilic sites to compete for mercaptide anion attack. Although the yield of the deprotected phenol, **17**, was not high, no sulfide aldehyde **18** (Figure 1) was formed in the reaction shown in Scheme 6.

Competing formation of **18** was the chief concern prior to undertaking the deprotection of **16**.

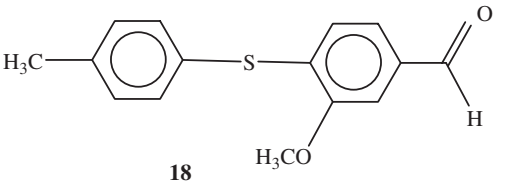


Scheme 5.

14 X = Br; Y = H
16 X = CHO; Y = OCH_3

15 X = Br; Y = H (58%)
17 X = CHO; Y = OCH_3 (40%)

Scheme 6.



18

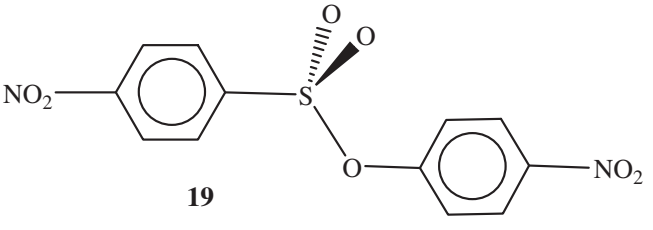
Figure 1. Structure for **18**.

2.2. *Mechanistic considerations*

Earlier, we have explored the mechanism for mercaptide-anion-induced CS bond rupture in aryl nosylates (*6*). By means of model nosylates, we established that *p*-tolyl mercaptide anions would induce a ratio of CS bond rupture to CO bond rupture of 19:1 in the hypothetical reaction with nosylate 19 (Figure 2) in HMPA.

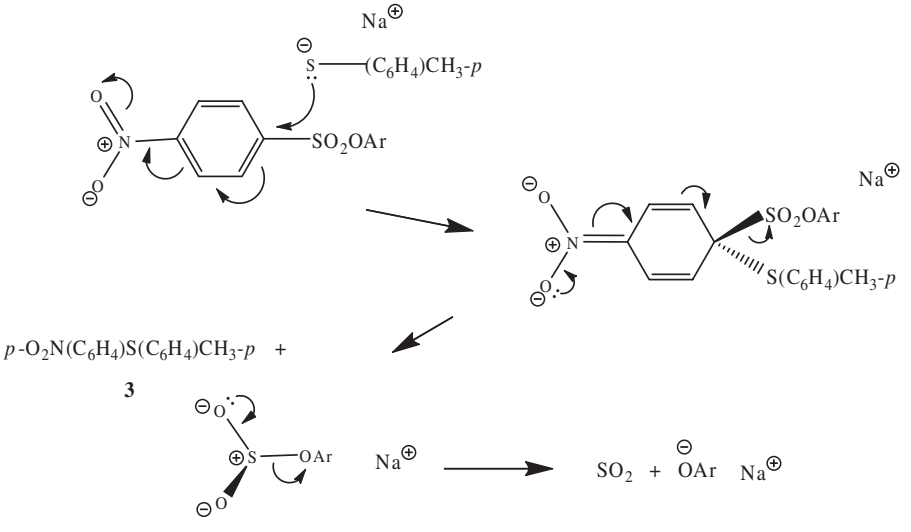
ZINDO molecular orbital calculations (*6*) supported the view that our experimental results were consistent with nucleophilic aromatic substitution (Scheme 7) rather than SET.

In a related study, Bordwell and Hughes (*11*) have shown that *p*-nitrobenzenes, equipped with good leaving groups, react with 9-substituted fluorenides in DMSO through a Meisenheimer complex and that neither benzynes nor SET intervenes. In contrast, Sammes *et al.* (*12*) have shown that the displacement of a nitro group from *p*-dinitrobenzene by substituted phenoxide



19

Figure 2. Structure for **19**.



Scheme 7.

ions in DMSO is inhibited by radical scavengers that may implicate SET in those reactions. Furthermore, Shishlov *et al.* (*13–15*) have reported fascinating results supporting SET steps between arylsulfonates and hydroxide ions in aqueous DMSO or lithium metal in dry DMSO.

Typically, a freshly prepared reaction mixture containing mercaptide anions and *p*-nitroarylsulfonyl substrates in DMSO or HMPA is black and turns orange/red after a brief interval. A black solution is consistent with the presence of a species having a loosely held electron as would be expected for a radical anion. Since our product studies and computational work (*6*) implicated nucleophilic aromatic substitution (Scheme 7) as the principal pathway by which the major products arose, we concluded that SET was, at best, a minor pathway in those reactions.

Reactions described in the current report revealed a new product, *p*-tolyl *p*-nitrophenyl sulfoxide **20** (Figure 3) along with *p*-tolyl disulfide **21**.

In several cases, the sulfoxide was isolated in good purity. Yields ranged from 1 to 10%.

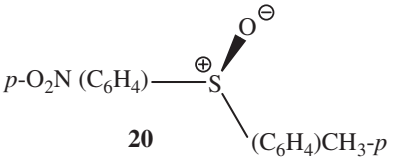
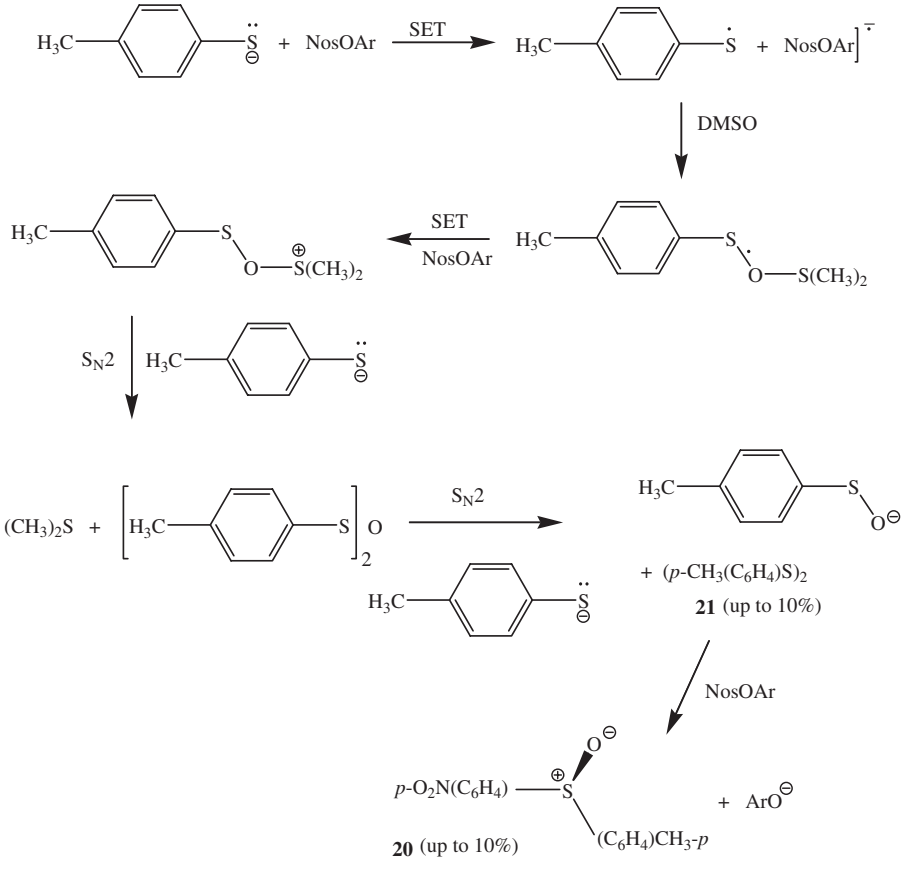


Figure 3. Structure for **20** which is racemic.



Scheme 8.

A straightforward rationale for the observation of the sulfoxide **20** in product mixtures would invoke nucleophilic aromatic substitution arising from nucleophilic attack by *p*-tolyl sulfenate anions on a nosylate (*e.g.* **6** in Scheme 1). The mechanistic proposal in Scheme 8 accounts for the formation of a modest amount of sulfenate anions. A summary of a good array of circumstantial evidence for SET steps in reactions of thiolate anions with aryl sulfonates is available (*7*).

Hence, in our view, the sulfoxide offers intriguing support for SET chemistry as a route to the minor products, **20** and **21**, in these reactions.

3. Conclusions

Phenolic polysulfonates, in which at least one of the sulfonate protecting groups is a nosylate group, will, in the presence of thiocresol anions, undergo selective removal of the nosylate group(s) restoring phenolic hydroxyl groups at those sites. Past evidence suggests that the reactions proceed, principally, by nucleophilic aromatic substitutions (Scheme 7). Current evidence suggests that SET chemistry may account for the formation of a secondary product, the sulfoxide **20** (Scheme 8).

4. Experimental

4.1. *General*

Infrared spectra were recorded on a Thermolet Nicolet 2000 spectrophotometer. ^{1}H NMR (270 MHz) and ^{13}C NMR spectra were obtained on a JEOL JNM-GSX270 Fourier-transform NMR system. Unless otherwise specified, all NMR spectra were obtained in deuterated chloroform using tetramethylsilane as an internal standard. Mass spectra were obtained on a Hewlett-Packard 5988A gas–liquid chromatography mass spectrometer system. Melting point determinations were done with a Gallenkamp MFB-595 capillary melting point apparatus and are uncorrected.

The staring phenols, 2-naphthol, dihydroquinone, *p*-bromophenol and vanillin were obtained from Aldrich Chemicals. The preparation and properties of dibutanesulfonate phenol **11** and tosylate phenol **9** have been described elsewhere (*1*, *3*).

4.2. *Standard nosylate preparation and nosylate properties*

The phenolic starting material (*ca*. 0.5 g) and dry triethylamine (1 equivalent) were added to dry pyridine (*ca*. 50 ml). *p*-Nitrobenzenesulfonyl chloride (1 equivalent) was added slowly over 5 min and the reaction stirred at ambient temperature for 1 week. Chloroform (200 ml) was added and the resultant solution washed with 2.5% hydrochloric acid (100 ml aliquots) until the aqueous pH remained acidic. In the preparation of **6**, **8**, **10**, **14** and **16**, damp homogeneous solutions were obtained. At this point in the preparation of dinosylate **12**, the product had precipitated and was filtered off using impure solid **12** and a damp homogeneous solution.

The damp homogeneous solution was dried ($MgSO_4$), filtered and the solvent evaporated to afford the target molecule **6**, **8**, **10**, **14** or **16** along with unchanged phenol. At this point in the preparation of **12**, the residue obtained from solvent evaporation was, principally, impure nosylate phenol **13** (*ca*. 12% yield).

In each case, except dinosylate **12**, the crude product was dissolved in chloroform (200 ml) and the resultant solution washed with 2.5% sodium hydroxide solution (two 100 ml portions), dried ($MgSO_4$), filtered and the solvent evaporated. Each target nosylate, except **12**, was recrystallized from methanol affording clean product. Solid dinosylate **12** (prepared from dihydroquinone (0.7 g) and *p*-nitrobenzenesulfonyl chloride (2.8 g)) was covered with methanol (1750 ml) and the mixture boiled. The hot mixture was filtered affording clean dinosylate **12** (1.47 g).

The recrystallized nosylate of 2-naphthol, **6**, was obtained in 33% yield (mp 106.0–107.5 °C). $C_{16}H_{11}NO_5S$ requires C, 58.4; H, 3.4. Found C, 58.0; H, 3.2%. **6** had IR 1531, 1403, 1351, 1189 cm^{-1}. ^1H NMR (270 MHz) δ 7.07 (d of d, $J = 8.9$ Hz, $J = 2.5$ Hz, 1H), 7.50 (m, 3H), 7.78 (m, 3H), 8.04 (d, $J = 8.9$ Hz, 2H), 8.34 (d, $J = 8.9$ Hz, 2H). ^{13}C NMR δ 119.8, 120.5, 124.4, 126.9, 127.3, 127.92, 127.96, 130.0, 130.3, 132.1, 133.4, 141.1, 146.7, 151.0. GCMS: 329 ($M^+\cdot$, 13%), 143 (55%), 115 (100%).

The recrystallized nosylate tosylate **8** was obtained in 17% yield (mp 164.5–166.5 °C). $C_{19}H_{15}NO_8S_2$ requires C, 50.8; H, 3.4. Found C, 50.7; H, 3.5%. **8** had IR 1597, 1529, 1406, 1367, 1149 cm^{-1}. ^1H NMR (270 MHz) δ 2.47 (s, 3H), 6.97 (s, 4H), 7.34 (d, $J = 8.2$ Hz, 2H), 7.70 (d, $J = 8.2$ Hz, 2H), 8.30 (d, $J = 8.9$ Hz, 2H), 8.41 (d, $J = 8.9$ Hz, 2H). ^{13}C NMR δ 21.8, 123.4, 124.1, 124.5, 128.5, 129.94, 129.98, 132.0, 140.7, 145.9, 147.3, 148.4, 151.2. GCMS: 449 ($M^+\cdot$, 11%), 419 (46%), 155 (100%), 91 (64%).

The recrystallized nosylate dibutanesulfonate **10** was obtained in 41% yield (mp 106.0–107.0 °C). $C_{20}H_{25}NO_{11}S_3$ requires C, 43.5; H, 4.6. Found C, 43.7; H, 4.6%. **10** had IR 1531, 1377, 1351, 1170 cm^{-1}. ^1H NMR (270 MHz) δ 0.98 (t, 6H), 1.50 (sex, 4H), 1.92 (quin, 4H), 3.25 (t, 4H), 6.90 (d, $J = 2.0$ Hz, 2H), 7.11 (t, $J = 2.0$ Hz, 1H), 8.01 (d, $J = 8.7$ Hz, 2H), 8.39 (d, $J = 8.7$ Hz, 2H). ^{13}C NMR δ 13.4, 21.4, 25.4, 51.1, 115.7, 116.1, 124.8, 130.0, 139.7, 149.3, 149.6, 151.4. GCMS: 551 ($M^+\cdot$, 0.1%), 366 (25%), 246 (65%), 126 (100%).

The dinosylate **12** was obtained in 48% yield. $C_{18}H_{12}N_2O_{10}S_2$ requires C, 45.0; H, 2.5. Found: C, 45.4; H, 2.5%. **12** had IR 1532, 1404, 1348, 1146 cm^{-1}. ^1H NMR (270 MHz, DMSO-d_6) δ 7.11 (s, 4H), 8.11 (d, $J = 8.9$ Hz, 4H), 8.43 (d, $J = 8.9$ Hz, 4H). ^{13}C NMR (DMSO-d_6) δ 124.6, 125.5, 130.6, 139.5, 147.8, 151.7. MS(DIP): 480 ($M^+\cdot$, 16%), 355 (15%), 294 (38%), 186 (100%).

Preparation of dinosylate **12** also furnished the nosylate phenol **13** in 9% yield after recrystallization from 2:1 chloroform:carbon tetrachloride (mp 132.0–134.0 °C). $C_{12}H_9NO_6S$ requires C, 48.8; H, 3.1. Found: C, 49.2; H, 3.4%. **13** had IR 3479, 1525, 1502, 1404, 1361, 1147 cm^{-1}. ^1H NMR (270 MHz) δ 5.24 (s, 1H), 6.71 (d, $J = 9.1$ Hz, 2H), 6.82 (d, $J = 9.1$ Hz, 2H), 8.00 (d, $J = 8.9$ Hz, 2H), 8.35 (d, $J = 8.9$ Hz, 2H). ^{13}C NMR δ 116.4, 123.3, 124.3, 130.0, 140.9, 142.7, 151.0, 154.9. GCMS: 123 (4%), 109 ($M^+\cdot - C_6H_4NO_4S$, 100%), 81 (17%).

The recrystallized bromonosylate **14** was obtained in 39% yield (mp 125.5–126.2 °C). $C_{12}H_8BrNO_5S$ requires C, 40.2; H, 2.3. Found: C, 40.0; H, 2.2%. **14** had IR 1530, 1392, 1348, 1172 cm^{-1}. ^1H NMR (270 MHz) δ 6.89 (d, $J = 8.9$ Hz, 2H), 7.44 (d, $J = 8.9$ Hz, 2H), 8.02 (d. $J = 9.0$ Hz, 2H), 8.38 (d. $J = 9.0$ Hz, 2H). ^{13}C NMR δ 121.4, 123.9, 124.5, 129.9, 133.2, 140.7, 148.1, 151.2. GCMS: 359 ($M^+ \cdot +2$, 14%), 357 ($M^+\cdot$, 13.4%), 186 (32%), 173 (100%), 171 (98.8%).

The recrystallized aldehyde nosylate **16** was obtained in 34% yield (mp 151.0–153.0 °C). $C_{14}H_{11}NO_7S$ requires C, 49.9; H, 3.3. Found: C, 50.1; H, 3.5%. **16** had IR 1705, 1533, 1420, 1348, 1142 cm^{-1}. ^1H NMR (270 MHz) δ 3.62 (s, 3H), 7.38 (d, $J = 1.6$ Hz, 1H), 7.41 (d, $J = 8.0$ Hz, 1H), 7.47 (d of d, $J = 8.0$ Hz, $J = 1.6$ Hz, 1H), 9.93 (s, 1H). ^{13}C NMR δ 55.9, 111.3, 124.1, 124.4, 124.7, 129.9, 136.3, 141.8, 142.3, 151.0, 152.2, 190.5. GCMS: 151 ($M^+\cdot - C_6H_4NO_4S$, 100%), 122 (9%), 95 (36%).

4.3. *Nosylate deprotections*

Nosylate deprotections were carried out in the manner described below for the exemplary case of **6**. Sodium metal (19 mg, 0.83 mmol) was dissolved in methanol (10 ml) and thiocresol (107 mg, 0.86 mmol) added. The solution was stirred for 5 min and the solvent evaporated. DMSO (15 ml) was added and the mixture stirred to dissolve the salt. The nosylate of 2-naphthol, **6**, (251 mg, 0.76 mmol) was added in small portions over 5 min. The reaction mixture was stirred at ambient temperature for 2 h. Water (400 ml) and 10% hydrochloric acid (25 ml) were added and the resultant mixture extracted with diethyl ether (three 100 ml aliquots). The combined ether layers

were evaporated and the residue covered with 2.5% hydrochloric acid (100 ml). The resultant mixture was extracted with diethyl ether (three 100 ml portions). The combined organic layers were dried ($MgSO_4$), filtered and the solvent evaporated to provide crude product (0.288 g).

Chloroform (100 ml) was added and the resultant solution extracted with 2.5% sodium hydroxide (two 50 ml portions). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated to provide impure sulfide **3** (154 mg). The aqueous layers were combined, acidified with concentrated hydrochloric acid (10 ml) and backextracted with chloroform (three 100 ml aliquots). The combined organic layers were dried ($MgSO_4$), filtered and the solvent evaporated furnishing 2-naphthol (77 mg). The 2-naphthol, so obtained, was identical to the authentic material by ^{1}H NMR, ^{13}C NMR and GCMS.

Impure sulfide **3** was chromatographed on silica gel (15 g) employing 6:1 petroleum ether:chloroform (thirty 15 ml fractions), followed by chloroform (thirty 15 ml fractions).

Fraction 2 furnished *p*-tolyl disulfide **21** (15 mg). Fractions 4–8 were combined and concentrated affording clean sulfide **3** (117 mg) which was identical to the previously described material (*6*) by ^{1}H NMR, ^{13}C NMR and GCMS. Fractions 31 and 32 were combined and concentrated to give sulfoxide **20** (20 mg). Although some chemistry of **20** was outlined earlier (*16*), no spectra were described. **20** has ^{1}H NMR (270 MHz) δ 2.35 (s, 3H), 7.26 (d, $J = 8.2$ Hz, 2H), 7.64 (d, $J = 8.2$ Hz, 2H), 7.80 (d, $J = 8.9$ Hz, 2H), 8.28 (d, $J = 8.9$ Hz, 2H). ^{13}C NMR δ 21.5, 124.4. 125.2, 125.3, 130.5, 141.3, 142.9, 149.2, 153.3. GCMS: 261 ($M^+\cdot$, 30%), 245 (93%), 213 (93%), 107 (100%).

The procedure for the deprotection of the dinosylate **12** differed from the representative procedure, outlined above, in three ways. Dissolution of **12** in DMSO required warming to 90 °C and the reaction time was extended to 3 h. Initial extractive work-up with diethyl ether led to precipitation of unchanged starting material (41%) which was filtered off before the second cycle of ether extractions was initiated.

Yields for the deprotections are given in Schemes 2–6.

Acknowledgement

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