Simple Synthesis of 2-Nitronaphthalene Derivatives from Substituted p-Nitrobenzyl Sulfones

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Condensation of p-nitrobenzyl sulfones containing carbonyl or cyclic substituents ortho to the methylsulfonyl group with electrophilic alkenes or alkynes as Michael acceptors provides facile and efficient access to substituted 2-nitronaphthalene derivatives.

Many substituted naphthalene derivatives have found applications as pharmaceuticals, plant protection agents, dyes etc. There are, however, substantial problems connected with the synthesis of such naphthalene derivatives in which a few substituents occupy well-defined positions. Published general solutions to this synthetic problem have mainly been stepwise introduction of substituents into the naphthalene ring or ring closure via Friedel–Crafts or cycloadDITION reactions, do not always give satisfactory results. The former approach is often complicated because formation of isomeric products necessitates laborious separation. An additional complication is the determination of positions of substituents in naphthalene rings using spectral methods. Synthesis of 2-nitronaphthalene derivatives is particularly difficult.

We would like to report a general method for the synthesis of 2-nitronaphthalene derivatives containing a variety of substituents in both aromatic rings starting from substituted p-nitrobenzyl phenyl sulfones 1 which, in turn, can be easily prepared via the vicarious nucleophilic substitution of hydrogen (VNS) in substituted nitroaranes with chloromethyl phenyl sulfone carbanion.\(^1\)\(^,\)\(^2\) We have already reported the synthesis of quinoline derivatives via a similar condensation between substituted o-nitrobenzyl phenyl sulfones and diethyl maleate, or fumarate, in which the annulation process engaged the ortho nitro group.\(^3\)

The synthesis of 2-nitronaphthalenes consists of base-catalyzed condensation of sulfones 1 containing an electrophilic functional group ortho to the sulfonylmethyl substituent with the Michael-type acceptors 2. The condensation is a multistep process involving Michael addition of the nitrobenzylic sulfone carbanion to the electrophilic alkene, followed by addition of the resulting carbanion to the electrophilic substituent and subsequent elimination of phenylsulfonic acid (Scheme 1).

This approach to benzene ring construction onto a heterocyclic moiety is already reported.\(^4\) The value of our method is due to the facile synthesis of the starting nitrobenzyl phenyl sulfones via the VNS reaction.

Condensation of the nitrobenzyl sulfones with electrophilic alkenes was carried out in the presence of anhydrous potassium carbonate and a catalytic amount of 18-crown-6 in acetonitrile. The reaction usually proceeds in two well-defined steps involving initial formation of the dihydronapththalene derivative and subsequent elimination of phenylsulfonic acid to form the final products. Usually, both these processes were carried out as a one-pot reaction simply by elevating the temperature of the reacting mixture. Nevertheless, differences in the rate of the condensation and elimination processes are sufficient to separate these steps, as shown in the reaction of 1a with 4-methoxy-o-nitrostyrene (2b) giving 3b under mild conditions and 4b when the reaction was carried out at a higher temperature for a longer period. The condensation of 1a with 1,2-bis(phenylsulfonyl)ethylene (2d) resulted in the formation of intermediate 1,2,3-tri(phenylsulfonyl)-1,2-dihydro-6-nitronaphthalene. Because of the effect of the nitroaryl group, elimination of phenylsulfonic acid occurs from the 2-position giving 1,2-bis(phenylsulfonylmethyl)-6-nitronaphthalene 4d instead of the 2,3-isomer.

Complications were observed when the alkoxy carbonyl group participated in the reaction as in the case of 1d, because the resulting β-keto ester 5 is immediately deprotonated and in its enolate anion the β-elimination of benzensulfonic acid is somewhat hindered. In addition, chromatographic separation of the naphthol and the tetrahydro derivative 5 proved very difficult. Nevertheless, elimination proceeded satisfactorily upon prolongation of reaction time. Isolation and purification of the naphthol was achieved by methylation of the naphthol func-
tion giving the corresponding methyl ether 4g as the final product (Scheme 2). On the other hand, condensation involving the cyano group proceeded without difficulty producing the corresponding aminonaphthalene derivatives 7a, 7b (Scheme 3). As one would expect a carboxylic acid group, which is deprotonated under the reaction conditions, does not enter the condensation, and reaction with diethyl fumarate stops at the Michael addition step giving 4-chloro-5-nitro-2-[1-phenylsulfonyl]-2,3-di(ethoxycarbonyl)propylbenzoic acid (10).

Scheme 3

Finally, a similar process takes place between nitrobenzyl sulfone (1a) and electrophilic acetylene derivatives such as esters of propionic and acetylenedicarboxylic acids. In these cases the aromatic ring is produced directly in the addition process without elimination of benzenesulfonic acid giving the corresponding substituted naphthalene sulfones as the final products (Scheme 4).

Table 1. Nitronaphthalene Derivatives Prepared

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (a) (%)</th>
<th>mp (°C) (solvent)</th>
<th>IR (KBr) ν (cm⁻¹) NO₂</th>
<th>¹H NMR (CDCl₃/TMS) δ, J (Hz)</th>
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<tbody>
<tr>
<td>3b</td>
<td>90</td>
<td>214-215 (AcOEt/MeOH)</td>
<td>1531-1531</td>
<td>3.72 (s, 3H), 2.64 (s, 3H), 2.21 (s, 3H), 6.73 (m, 2H), 6.88 (m, 2H), 7.74 (m, 2H), 8.24 (dd, J = 9.2, 2.3, 1H), 8.31 (d, J = 2.4, 1H)</td>
</tr>
<tr>
<td>4a</td>
<td>76</td>
<td>139-141 (MeOH)</td>
<td>1533, 1348</td>
<td>1.42 (t, J = 7.1, 3H), 1.43 (t, J = 7.1, 3H), 4.56 (q, J = 7.1, 4H), 8.08 (d, J = 9.2, 1H), 8.31 (d, 1H), 8.38 (dd, J = 9.0, 2.2, 1H), 8.46 (s, 1H), 8.86 (d, J = 2.1, 1H)</td>
</tr>
<tr>
<td>4b</td>
<td>95</td>
<td>149-151 (AcOEt)</td>
<td>1535, 1354</td>
<td>3.88 (s, 1H), 7.01 (m, 2H), 7.36 (m, 2H), 8.00 (s, 1H), 8.06, (d, J = 9.2, 1H), 8.40 (dd, J = 9.0, 2.2, 1H), 8.53 (s, 1H), 8.94 (d, J = 2.2, 1H)</td>
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<tr>
<td>4c</td>
<td>47</td>
<td>151-152 (EtOH)</td>
<td>1521, 1342</td>
<td>2.77 (s, 2H), 8.03 (d, J = 8.9, 2H), 8.25 (d, J = 8.7, 1.7, 1H), 8.37 (J = dd, J = 9.1, 2.3, 1H), 8.64 (s, 1H), 8.95 (dd, J = 1.7, 1H)</td>
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<tr>
<td>4d</td>
<td>85</td>
<td>242-243.5 (AcOH)</td>
<td>1531, 1349</td>
<td>7.54 (m, 2H), 7.61 (m, 3H), 7.67 (m, 1H), 7.95 (d, J = 8.4, 2H), 8.06 (d, J = 8.4, 2H), 8.46 (dd, J = 9.5, 2.4, 1H), 8.85 (j, J = 8.9, 1H), 8.96 (J = d, J = 2.4, 1H), 9.00 (d, J = 1.8, 1H)</td>
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<td>4e</td>
<td>40</td>
<td>132-133.5 (MeOH)</td>
<td>1535, 1346</td>
<td>1.43 (m, 6H), 2.71 (s, 3H), 4.46 (m, 4H), 8.16 (s, 1H), 8.41 (s, 1H), 2.1 (J = 1.1, 1H)</td>
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<td>4f</td>
<td>79</td>
<td>184-185.5 (MeOH)</td>
<td>1515, 1363</td>
<td>2.66 (s, 3H), 3.86 (s, 3H), 4.07 (s, 3H), 6.97 (m, 2H), 7.34 (m, 2H), 7.34 (m, 2H), 7.48 (s, 1H), 7.66 (s, 1H), 8.54 (s, 1H)</td>
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<tr>
<td>4g</td>
<td>73</td>
<td>117-119 (MeOH)</td>
<td>1534, 1345</td>
<td>1.43 (m, 6H), 4.08 (s, 3H), 4.46 (m, 4H), 8.16 (s, 1H), 8.29 (d, J = 2.1, 1H), 8.63 (d, J = 2.1, 1H)</td>
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<tr>
<td>7a</td>
<td>66</td>
<td>149-151 (MeOH)</td>
<td>1532, 1337</td>
<td>1.39 (q, J = 7.1, 6H), 4.36 (q, J = 7.1, 2H), 4.38 (q, J = 7.1, 2H), 6.68 (s, 2H), 7.36 (s, 1H), 7.91 (d, J = 8.9, 1H), 8.34 (dd, J = 8.9, 1H), 8.34 (dd, J = 8.9, 2.1, 1H), 8.88 (d, J = 2.1, 1H)</td>
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<tr>
<td>7b</td>
<td>48</td>
<td>217-218 (i-ProOH)</td>
<td>1509, 1319</td>
<td>2.11 (m, 2H), 2.75 (m, J = 0.6, 2H), 6.91 (s, 1H), 7.70 (d, J = 8.9, 1H), 8.08 (br, 2H), 8.26 (dd, J = 9.0, 2.1, 1H), 8.88 (d, J = 2.1, 1H)</td>
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<td>8a</td>
<td>78</td>
<td>172.5-174 (AcOH/i-ProOH)</td>
<td>1528, 1347</td>
<td>1.50 (t, J = 7.1, 3H), 4.54 (q, J = 7.1, 2H), 7.48-7.61 (m, 3H), 8.00 (m, 2H), 8.44 (dd, J = 9.4, 2.4, 1H), 8.89 (s, 1H), 8.95 (d, J = 2.7, 1H), 9.00 (s, 1H), 9.22 (d, J = 1.7, 1H)</td>
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<tr>
<td>9a</td>
<td>93</td>
<td>205-206.5 (EtOH)</td>
<td>1530, 1331</td>
<td>4.03 (s, 3H), 4.14 (s, 3H), 7.56 (m, 3H), 8.18 (m, 2H), 8.43 (dd, J = 9.7, 2.4, 1H), 9.05 (d, J = 8.9, 2H)</td>
</tr>
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</table>

*Yields of isolated product

(b) Satisfactory HRMS values obtained: ± 0.00220 amu

(c) 1,3-Bis(phenylsulfonylmethyl)-6-nitronaphthalene
1H NMR spectra were recorded on a Varian Gemini at 200 MHz, IR spectra on an Acculab (Beckman), and mass spectra were measured on an AMD-604 (AMD Interctica GmbH Germany). Starting materials were commercial or prepared as described and according to procedures given below.

5-Nitro-2-phenylsulfonylmethylbenzaldehyde (1a): 2-(2-Phenylsulfonylmethyl-5-nitrophenyl)-1,3-dioxolane2 (9.20 g, 26.4 mmol), 10% H2SO4 (3.4 mL) and H2O (8.5 mL) were heated at 100°C for 1 h. H2O (8.5 mL) was added, the mixture cooled to 20°C and the solid filtered. The product was dried and purified by recrystallization from EtOH, yield 7.4 g (92%), mp 177–179°C.

IR (KBr): ν = 1523, 1351 (NO2), 1703 (CO).

1H NMR (CDCl3): δ = 5.09 (s, 2 H), 7.48–7.76 (m, 6 H), 8.41 (dd, J = 8.4, 2.4, 1 H), 8.63 (d, J = 2.4, 1 H), 9.96 (s, 1 H).

4-Chloro-5-nitro-2-phenylsulfonylmethylacetophenone (1b): To a stirred suspension of powdered NaOH (3.7 g, 90 mmol) in DMSO (7.5 mL) a solution of 2-methyl-2-(4-chloro-5-nitrophenyl)-1,3-dioxolane (3.05 g, 12.5 mmol) and chloromethyl phenyl sulfone (2.10 g, 12.6 mmol) in DMSO (17.5 mL) was added dropwise while the temperature was kept ca. 50°C. The reaction was continued for 2 h after addition was complete and then the mixture poured onto ice (100 g), acidified with AcOH (5 mL) and extracted with EtOAc (3 × 30 mL). The solvent was evaporated, the solid residue purified by recrystallization from MeOH, yield 3.53 g (71%). This product was hydrolyzed by heating with 2% H2SO4 (8 mL) at 100°C for 1 h. After the mixture was cooled the precipitate was filtered, washed with H2O and dried, yield 2.70 g (61%). The product was purified by recrystallization from EtOH mp 185–187°C.

IR (KBr): ν = 1527, 1361 (NO2), 1691 (CO).

1H NMR (CDCl3): δ = 4.05 (s, 3 H), 5.10 (s, 2 H), 7.12 (s, 1 H), 7.49–7.70 (m, 5 H), 8.25 (s, 1 H).

4-Methoxy-5-nitro-2-Phenylsulfonylmethylacetophenone (1c): Method as for (1b). Yield, from 2-methyl-2-(4-methoxy-5-nitrophenyl)-1,3-dioxolane (3 g, 12.5 mmol) 1c was obtained, yield 2.8 g (46%), mp 203–205°C.

IR (KBr): ν = 1526, 1362 (NO2), 1692 (CO).

1H NMR (CDCl3): δ = 2.42 (s, 3 H), 4.02 (s, 3 H), 5.08 (s, 2 H), 7.11 (s, 1 H), 7.50–7.75 (m, 5 H), 8.27 (s, 1 H).

3,6-Dinitro-2-(4-methoxyphenyl)-1-phenylsulphonyl-1,2-dihydropyridazine (3b): To a stirred solution of 5-nitro-2-phenylsulfonylmethylbenzaldehyde (1a) (305 mg, 1 mmol), 4-methoxy-ω-nitrostyrene (2b) (200 mg, 1.12 mmol) and 18-crown-6 (13 mg, 0.05 mmol) in CH2Cl2 (10 mL) was added K2CO3 (700 mg) in one portion and the mixture stirred at 30°C for 1 h. The mixture was filtered and the residue washed with CH2Cl2 (15 mL). The solvent was evaporated and the residue purified by column chromatography on silica gel using EtOAc/hexane (3:7) as eluent, yield 420 mg (90%) (Table 1).

3-(4-Methoxyphenyl)-2,7-dinitronaphthalene (4b): Typical Procedure:
To a stirred solution of 5-nitro-2-phenylsulfonylmethylbenzaldehyde (1a) (305 mg, 1 mmol), 4-methoxy-ω-nitrostyrene (2b) (200 mg, 1.12 mmol) and 18-crown-6 (13 mg, 0.05 mmol) in CH2Cl2 (10 mL) was added K2CO3 (700 mg) in one portion. The mixture was stirred at 30°C for 1 h and at 80°C for 5 h. The solid was separated and washed with CH2Cl2 (15 mL). The solvent was evaporated and the residue purified by column chromatography on silica gel using EtOAc/hexane (3:7) as eluent, yield 295 mg (95%) (Table 1).

4-Chloro-5-nitro-2-[1-phenylsulfonyl-2,3-bis(ethoxy carbonyl)propyl]-benzoic Acid (10):
To a stirred solution of 4-chloro-5-nitro-2-phenylsulfonylmethylbenzoic acid (356 mg, 1.0 mmol), diethyl fumarate (258 mg, 1.5 mmol) and 18-crown-6 (13 mg) in MeCN (5 mL) was added powdered anhyd K2CO3 (700 mg). The suspension was stirred at 80°C for 6 h, acidified by addition of 50% AcOH and the mixture extracted with CHCl3 (3 × 15 mL). The solvent was evaporated and the residue purified by column chromatography on silica gel CH2Cl2/hexane/EtOAc (9:9:1), yield 375 mg (72%), mp 144–145°C (benzene).

IR (KBr): ν = 1354, 1568 (NO2), 1677 (CO).

1H NMR (CDCl3): δ = 1.22 (t, J = 7.1, 3 H), 1.34 (t, J = 7.1, 3 H), 2.44 (dd, J = 16.4, 3.9, 1 H), 2.78 (dd, J = 16.4, 10.0, 1 H), 3.52 (br s, 1 H), 3.84 (td, J = 10.0, 3.5, 1 H), 4.08 (q, J = 7.1, 2 H), 4.22 (q, J = 7.1, 2 H), 6.58 (d, J = 10.0, 1 H), 7.40–7.70 (m, 5 H), 7.99 (s, 1 H), 8.37 (s, 1 H).