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

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

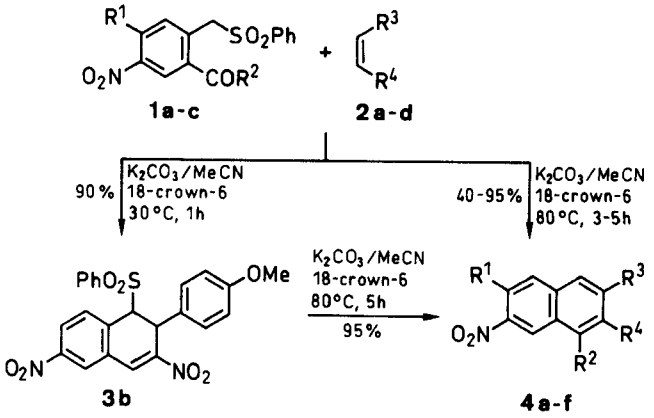
Many substituted naphthalene derivatives have found applications as pharmaceuticals, plant protection agents, dyes etc.[1] There are, however, substantial problems connected with the synthesis of such naphthalene derivatives in which a few substituents occupy well-defined positions. Published general solutions to this synthetic problem namely, 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 nitroarenes with chloromethyl phenyl sulfone carbanion.[2,3] 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.[4]

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 phenylsulfinic acid (Scheme 1).

This approach to benzene ring construction onto a heterocyclic moiety is already reported.[5] The value of our method is due to the facile synthesis of the starting nitrobenzyl phenyl sulfones via the VNS reaction.

Condensation of the nitrobenzylic 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 dihydronaphthalene derivative and subsequent elimination of phenylsulfinic 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



1	R^1	R^2	2	R^3	R^4
a	H	H	a	CO_2Et	CO_2Et
b	Cl	Me	b	4-MeOPh	NO_2
c	MeO	Me	c	H	COMe
			d	SO_2Ph	SO_2Ph

4	R^1	R^2	R^3	R^4
a	H	H	CO_2Et	CO_2Et
b	H	H	4-MeOPh	NO_2
c	H	H	H	COMe
d*	H	H	SO_2Ph	SO_2Ph
e	Cl	Me	CO_2Et	CO_2Et
f	MeO	Me	4-MeOPh	NO_2

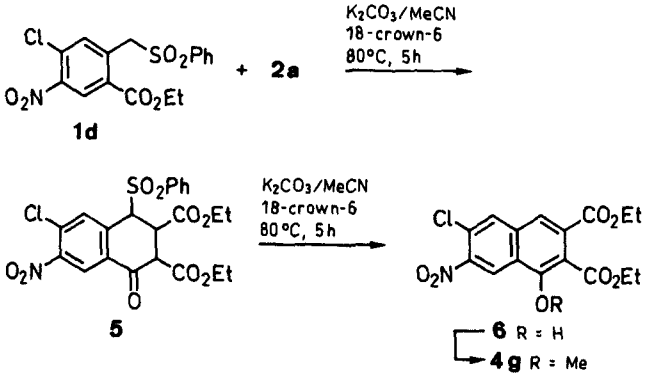
* R^3 in position 1

Scheme 1

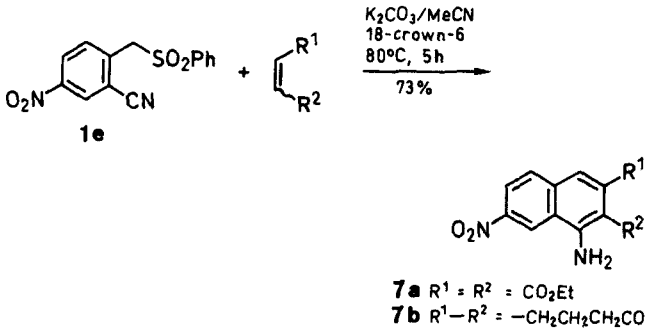
the condensation and elimination processes are sufficient to separate these steps, as shown in the reaction of **1a** with 4-methoxy-ω-nitrostyrene **(2b)** giving **3b** under mild conditions and **4b** when the reaction was carried out at a higher temperature for a longer period. The condensation of **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 phenylsulfinic 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 alkoxycarbonyl 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 benzenesulfinic 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)propyl]benzoic acid (**10**).

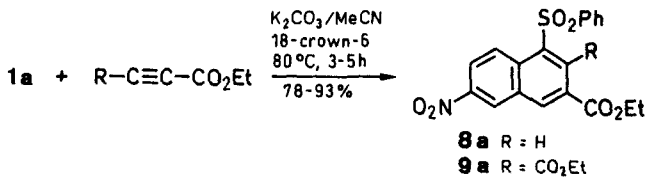


Scheme 2



Scheme 3

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



Scheme 4

Table 1. Nitronaphthalene Derivatives Prepared

Product	Yield[a] (%)	mp (°C) (solvent	IR (KBr) ν (cm^{-1}) NO_2	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
3b	90	214–215 (AcOEt/MeOH)	1531–1331 (AcOEt/MeOH)	3.72 (s, 3H), 4.54 (s, 1H), 5.33 (s, 1H), 5.33 (s, 1H), 6.73 (m, 2H), 6.88 (m, 2H), 7.44–7.62 (m, 7H), 8.24 (dd, J = 9.2, 2.3, 1H), 8.31 (d, J = 2.4, 1H)
4a	76	139–141 (MeOH)	1533, 1348	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 (s, 1H), 8.38 (dd, J = 9.0, 2.2, 1H), 8.46 (s, 1H), 8.88 (d, J = 2.1, 1H)
4b	95	149–151 (AcOEt)	1535, 1354	3.88 (s, 3H), 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)
4c	47	151–152 (EtOH)	1521, 1342	2.77 (s, 3H), 8.03 (d, J = 8.9, 2H), 8.25 (J = dd, J = 8.7, 1.7, 1H), 8.37 (J = dd, J = 9.1, 2.3, 1H), 8.64 (s, 1H), 8.95 (d, J = 1.7, 1H)
4d[c]	85	242–243.5 (AcOH)	1531, 1349	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 = (d, J = 9.5, 1H), 8.95 (s, 1H), 8.96 (J = d, J = 2.4, 1H), 9.00 (d, J = 1.8, 1H)
4e	40	132–133.5 (MeOH)	1535, 1346	1.43 (m, 6H), 2.71 (s, 3H), 4.46 (m, 4H), 8.14 (s, 1H), 8.41 (s, 1H), J = 2.1, 1H), 8.63 (d, J = 2.1, 1H)
4f	79	184–185.5 (MeOH)	1515, 1363	2.66 (s, 3H), 3.86 (s, 3H), 4.07 (s, 3H), 6.97 (m, 2H), 7.34 (m, 2H), 7.34 (m, 2H), 7.38 (s, 1H), 7.66 (s, 1H), 8.54 (s, 1H)
4g	73	117–119 (MeOH)	1534, 1345	1.43 (m, 6H), 4.08 (s, 3H), 4.46 (m, 4H), 8.14 (s, 1H), 8.29 (d, J = 2.1, 1H), 8.63 (d, J = 2.1, 1H)
7a	66	149–151	1522, 1337	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), 7.90 (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)
7b	48	217–218 (*i*-PrOH)	1509, 1319	2.11 (m, 2H), 2.75 (t, J = 6.5, 2H), 3.03 (t, J = 6.0, 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)
8a	78	172.5–174 (AcOH/*i*-PrOH)	1528, 1347	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)
9a	93	205–206.5 (EtOH)	1530, 1331	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)

[a] Yields of isolated product
[b] Satisfactory HRMS values obtained: ± 0.00220 amu
[c] 1,3-Bis(phenylsulfonylmethyl)-6-nitronaphthalene

^{1}H 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 Interctia GmbH Germany). Starting materials were commercial or prepared as described[2,6] and according to procedures given below.

5-Nitro-2-phenylsulfonylmethylbenzaldehyde (1a):
2-(2-Phenylsulfonylmethyl-5-nitrophenyl)-1,3-dioxolane[2] (9.20 g, 26.4 mmol), 10% H_2SO_4 (3.4 mL) and H_2O (8.5 mL) were heated at 100 °C for 1 h. H_2O (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 (NO_2), 1703 (CO).

^{1}H NMR ($CDCl_3$): 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-3-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% H_2SO_4 (8 mL) at 100 °C for 1 h. After the mixture was cooled the precipitate was filtered, washed with H_2O and dried, yield 2.70 g (61%). The product was purified by recrystallization from EtOH mp 185–187 °C.

IR (KBr): ν = 1527, 1361 (NO_2), 1691 (CO).

^{1}H NMR ($CDCl_3$): 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-3-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 (NO_2), 1692 (CO).

^{1}H NMR ($CDCl_3$): 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-dihydronaphthalene (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 CH_3CN (10 mL) was added K_2CO_3 (700 mg) in one portion and the mixture stirred at 30 °C for 1 h. The mixture was filtered and the residue washed with CH_3CN (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 CH_3CN (10 mL) was added K_2CO_3 (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 CH_3CN (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(ethoxycarbonyl)-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 anhydr. K_3CO_3 (700 mg). The suspension was stirred at 80 °C for 6 h, acidified by addition of 50% AcOH and the mixture extracted with $CHCl_3$ (3 × 15 mL). The solvent was evaporated and the residue purified by column chromatography on silica gel CH_2Cl_2/hexane/EtOAc (9:9:1), yield 375 mg (72%); mp 144–145 °C (benzene).

IR (KBr): ν = 1354, 1568 (NO_2), 1677 (CO).

^{1}H NMR ($CDCl_3$): 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).

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