

Reactions of Nitroarylmethyl Phenyl Sulfones with Diethyl Maleate and Fumarate. A New, Simple Synthesis of Quinoline-2,3-dicarboxylic Acid Derivatives¹

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Dedicated to Professor Lars Skattebøl on the occasion of his 65th birthday.

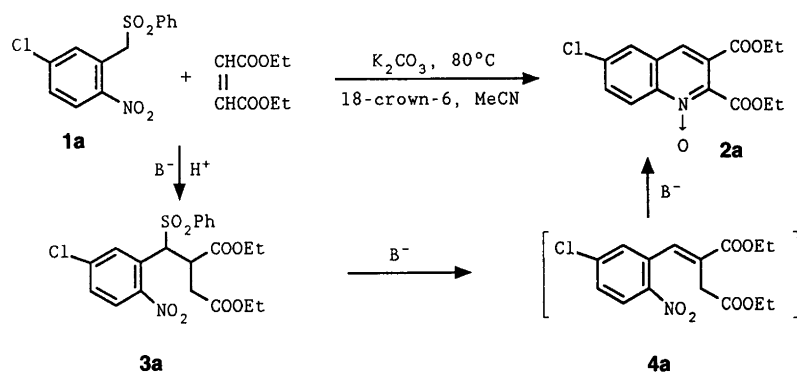
Known methods of synthesis of quinoline-2,3-dicarboxylic acid derivatives are based on condensation of *o*-aminoarylaldehydes with diethyl oxaloacetate² or acetylenedicarboxylates.³ These methods are inconvenient and of limited applicability because the amino aldehydes are unstable and difficult to prepare. Some years ago a novel approach to the synthesis of these compounds was reported involving the Wittig–Horner reaction of *o*-nitroarylaldehydes with diethyl (diethoxyphosphinyl)succinate under basic conditions, which gave directly *N*-oxides of the desired quinoline derivatives.⁴

Here we would like to report a much simpler and versatile method of synthesis of these compounds starting from *o*-nitroarylmethyl phenyl sulfones **1**. These sulfones are readily available because they can be synthesized directly from nitroarenes via vicarious nucleophilic substitution of hydrogen with chloromethyl phenyl sulfone.⁵ This type of reaction also proceeds with nitro derivatives of aromatic heterocycles, thus the corresponding heteroarylmethyl aryl sulfones are also readily available.⁶ The usefulness of these

nitroarylmethyl phenyl sulfones in organic synthesis has already been shown.^{6,7}

Treatment of 5-chloro-2-nitrobenzyl phenyl sulfone with diethyl maleate in the presence of a base resulted in the direct formation of diethyl 6-chloroquinoline-2,3-dicarboxylate *N*-oxide in good yield. Of the base–solvent systems tested for this process, anhydrous K₂CO₃ in acetonitrile and a crown ether catalyst (the so-called solid–liquid phase-transfer catalysis)⁸ was most efficient.

The reaction apparently proceeds via the Michael addition of the sulfone carbanion to the unsaturated ester followed by β-elimination of phenylsulfinate anion from the adduct **3a**. The resulting cinnamic acid derivative **4a** is then deprotonated to generate an ambident allylic carbanion which in turn reacts with the *ortho* nitro group to give the quinoline *N*-oxide as the ultimate product. The last step is identical with that described previously.⁴ One of the postulated intermediates, the Michael adduct **3a**, can be isolated under carefully controlled conditions, however, because of fast deprotonation of **4a** and further reaction of the result-



Scheme 1.

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Table 1. Quinoline derivatives obtained in reaction (1).

(1)

A	Product	Yield ^a (%)	M.p./°C ^b	Molecular ^c formula	IR ν/cm ⁻¹	¹ H NMR (CDCl ₃ /Me ₄ Si)
	2a	60	121–123	C ₁₅ H ₁₄ ClNO ₅	1280	1.41 (t, 3 H), 1.48 (t, 3 H), 4.45 (q, 2 H), 4.59 (q, 2 H), 7.81 (dd, 1 H), 7.89 (d, 1 H), 8.34 (s, 1 H), 8.70 (d, 1 H).
	2b	65	116–117	C ₁₈ H ₁₉ NO ₇	1300	1.42 (t, 3 H), 1.49 (t, 3 H), 4.13 (m, 4 H), 4.45 (q, 2 H), 4.60 (q, 2 H), 6.05 (s, 1 H), 7.86 (dd, 1 H), 8.02 (d, 1 H), 8.44 (s, 1 H), 8.85 (s, 1 H).
	2c	69	131–133	C ₁₆ H ₁₇ NO ₆	1292	1.41 (t, 3 H), 1.48 (t, 3 H), 3.97 (s, 3 H), 4.43 (q, 2 H), 4.58 (q, 2 H), 7.21 (d, 1 H), 1.49 (dd, 1 H), 8.34 (s, 1 H), 8.65 (d, 1 H).
	2d	68	164–165	C ₁₆ H ₁₄ NO ₆	1290	1.43 (m, 6 H), 4.44 (q, 2 H), 4.57 (q, 2 H), 8.00 (dd, 1 H), 8.36 (s, 1 H), 8.43 (s, 1 H), 8.84 (d, 1 H).
	2e	38	115–116	C ₁₃ H ₁₃ N ₂ O ₅	1280	1.41 (t, 3 H), 1.48 (t, 3 H), 4.43 (q, 2 H), 4.58 (q, 2 H), 7.43 (d, 1 H), 7.68 (d, 1 H), 8.41 (s, 1 H).
	2f	35	110–112	C ₁₆ H ₁₇ NO ₈	1280	1.39 (t, 3 H), 1.46 (t, 3 H), 4.14 (m, 4 H), 4.41 (q, 2 H), 4.56 (q, 2 H), 6.13 (s, 1 H), 6.96 (s, 1 H), 8.19 (s, 1 H).

^aYield of isolated products **2** based on **1**. ^bFrom isopropyl alcohol. ^cSatisfactory microanalyses obtained: C±0.25, H±0.22, N±0.22.

ing allylic carbanion with the nitro group, the intermediate **4a** was not isolated. Nevertheless, the presence of **4a** as a mixture of stereo- and regio-isomers was monitored by ¹H NMR spectroscopy and TLC. The overall result of the first two steps is analogous to vicarious substitution in aliphatic systems.⁹

Since the reaction proceeds via addition, elimination and deprotonation, none of the geometry of the original unsaturated ester is retained, therefore identical results were obtained when diethyl fumarate was used.

This process is of general interest as nitroarylmethyl sulfones can carry a variety of substituents in the nitroaromatic ring, so that the corresponding derivatives of substituted quinolines, e.g. **2b–d**, can be produced. Some nitro-substituted heterocyclic sulfones also undergo this reaction to give derivatives of thienopyridine and furo-pyridine. Examples of this reaction are given in Table 1.

Taking into account the facile one-step synthesis of the starting *o*-nitrobenzyl sulfones, via the VNS reaction, and the simple, direct, one-pot conversion of these sulfones

into quinoline derivatives as shown in Scheme 1, the method reported here may be of substantial value in organic synthesis.

Experimental

Melting points are uncorrected. IR spectra were taken in KBr with an Aculab 1 spectrophotometer and, ¹H NMR spectra on a Varian Gemini 200 spectrometer in CDCl₃ with Me₄Si as the internal standard. *o*-Nitroarylmethyl phenyl sulfones were prepared as described earlier (**1a,c,d**,^{5b} **1b**,¹⁰ **1e**,¹¹ **1f**¹²). Other starting materials were commercial.

Diethyl 6-chloroquinoline-2,3-dicarboxylate N-oxide (2a). *General procedure.* To a solution of 5-chloro-2-nitrobenzyl phenyl sulfone **1a** (1.56 g, 5 mmol), diethyl maleate (or fumarate) (0.95 g, 5.5 mmol) and 18-crown-6 (66 mg) in acetonitrile (30 ml) was added anhydrous potassium carbonate (2.76 g, 20 mmol) and the mixture was stirred at

80°C for 4 h. The cooled mixture was filtered through Celite, the precipitate washed with acetonitrile (2 × 15 ml) and the solvent was evaporated off. The residue was chromatographed on silica gel (eluent benzene–ethyl acetate 85:15) to give **2a**, yield 0.97 g (60 %).

Diethyl 2-(5-chloro-2-nitro- α -phenylsulfonylbenzyl)succinate (3a). The reaction was carried out as above at 20°C for 20 h. Chromatographic separation of the crude product gave **3a** (1.0 g) and starting **1a** (0.63 g). The yield of **3a** calculated on consumed **1a** was 70 %, m.p. 50–51°C (from ethanol). Anal. C₂₁H₂₂ClNO₈S: C, H, N. ¹H NMR δ 1.18–1.33 (m, 6 H), 2.68–2.73 (m, 2 H), 3.84–4.0 (m, 1 H), 4.06–4.20 (m, 4 H), 5.77 (d, 1 H), 7.44–7.90 (m, 8 H). IR: 1525, 1355 (NO₂) cm⁻¹.

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