One-Pot Synthesis of 2,3-Disubstituted Naphtho[2,3-*b*]thiophene-4,9-diones from a 2-Sulfenyl-1,4-naphthoquinone and Enamines

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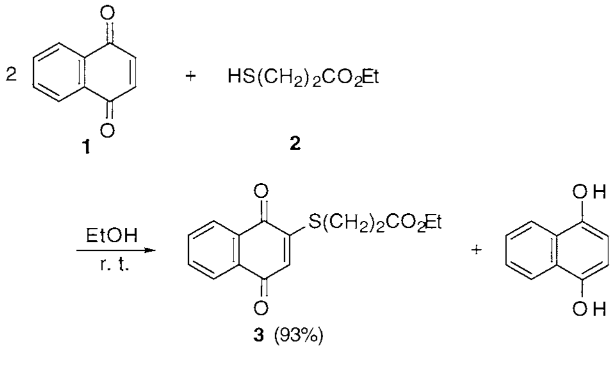
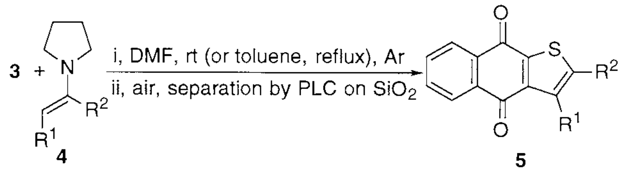
The title naphthothiophenequinone derivatives were generally synthesized in one-pot using a tandem conjugate addition–cyclization sequence between 2-[2-(ethoxycarbonyl)-ethyl]thio-1,4-naphthoquinone and enamines, derived from cyclic and acyclic ketones.

As a part of our program aimed at developing new methods for the preparation of heterocycle-fused quinone derivatives,[1] we have recently described[2] the direct one-pot preparation of 2,3-disubstituted naphtho[2,3-*b*]furan-4,9-diones from 2-hydroxy-1,4-naphthoquinones and enamines, derived from cyclic and acyclic ketones.[3] We interested in investigating the possibility of developing a procedure for the general preparation of naphtho[2,3-*b*]thiophene-4,9-diones using 2-mercapto-1,4-naphthoquinone derivatives as an extension of this work. In this paper we wish to describe the preliminary results of our investigation, which offer a simple and efficient route leading to 2,3-disubstituted naphtho[2,3-*b*]thiophene-4,9-diones **5**. The compounds based on this thiophenequinone skeleton have received considerable attention because of their synthetic,[4] biological,[5] and industrial utilities.[6] There have been reported several methods for the construction of this class of molecules.[7] Most of them, however, involve multi–step conversions and incomplete generality.



Scheme 1.



4a, **5a** $R^1R^2=(CH_2)_3$; **4b**, **5b** $R^1R^2=(CH_2)_4$
4c, **5c** $R^1R^2=(CH_2)_5$; **4d**, **5d** $R^1R^2=(CH_2)_6$
4e, **5e** R^1=Me, R^2=Et; **4f**, **5f** R^1=Et, R^2=Pr^n

Scheme 2.

Table 1. Preparation of naphtho[2,3-*b*]thiophene-4,9-diones **5**

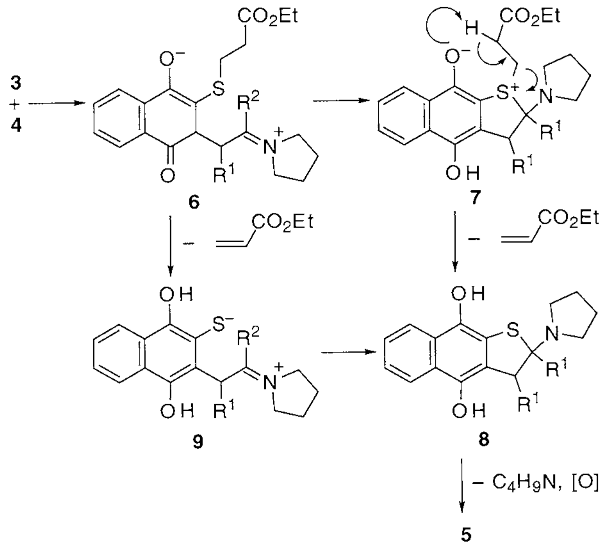
Entry	4	Solvent	Temp	Time/h	5 (Yield/%)[a]
1	**4a**[b]	toluene	reflux	6	**5a** (72)
2	**4b**[b]	toluene	reflux	30	**5b** (30)
3	**4b**[c]	DMF	r. t.	20	**5b** (69)
4	**4c**[c]	DMF	r. t.	23	**5c** (71)
5	**4d**[c]	DMF	r. t.	17	**5d** (71)
6	**4e**[c,d]	toluene	reflux	22	**5e** (31)
7	**4e**[c,d]	DMF	r. t.	16	**5e** (56)
8	**4f**[c,d]	DMF	r. t.	17	**5f** (59)

[a]Isolated yields after separation by preparative TLC on silica gel. [b]Commercially available. [c]Ref. 11. [d]A mixture of stereoisomers was used.

As 2-mercapto-1,4-naphthoquinone was presumed to be too unstable to isolate,[8] we planed to use it or its equivalent under in situ generation conditions.[9] We chose 2-[2-(ethoxycarbonyl)-ethyl]thio-1,4-naphthoquinone (**3**)[10] as the starting substrate, in expectation of the generation of 2-mercapto-1,4-naphthoquinone through elimination of ethyl propenoate. The sulfenyl quinone **3** was easily prepared in high yield according to Scheme 1. The treatment of 1,4-naphthoquinone (**1**) with ethyl 3-mercaptopropanoate (**2**) (2:1 molar ratio) in EtOH at room temperature followed by recrystallization of the resulting precipitate from EtOH afforded **3** as yellow needles (mp 112–114 °C).

The synthesis of 2,3-disubstituted naphtho[2,3-*b*]thiophene-4,9-diones **5** is outlined in Scheme 2 and the yields and reaction conditions are summarized in Table 1. The reactions of **3** with enamines **4** (2 molar amounts)[12] were first conducted in toluene. The sequence proceeded to an appreciable extent at reflux temperature to afford, after usual aqueous workup and subsequent purification by preparative TLC on silica gel, the expected naphthothiophenequinones **5a**, **b**, and **e** (entries 1, 2, and 6). However, the satisfactory yield was achieved only in the case of using 1-pyrrolidino-cyclopentene (**4a**) (entry 1). Later, the reaction sequence was found to proceed smoothly in DMF at room temperature to afford the corresponding naphthothiophenequinones **5b**–**f** in much improved yields (entries 3–5, 7, and 8).[13]

The production of the naphthothiophenequinones **5** may be interpreted as illustrated in Scheme 3. The first step is formation of the intermediate adduct **6** by the addition of an enamine to the sulfenyl quinone **3** at the 3-position in a 1,4-addition manner. There are two possibilities for the route from this intermediate to the products. It could cyclize by the attack of the sulfur to the imminium carbon to give the sulfonium ion intermediate **7**. The elimination of ethyl propenoate affords the hydroquinone intermediate **8**. Oxidation followed by elimination of pyrrolidine (or in reverse order) presumably during the workup and/or separation procedures gives rise to **5**. Alternatively, the elimination of ethyl propenoate from the adduct **6** might first take place to give the thiolate intermediate **9**, cyclization of which gave the hydroquinone intermediate **8**.



Scheme 3.

The results described above provides a simple procedure for the construction of 2,3-disubstituted naphtho[2,3-*b*]thiophene-4,9-diones, which might otherwise be quite troublesome to prepare. Although the yields of the products were not so high, the method may be of value in organic synthesis because of the ease of operation as well as the readily availability of the starting materials. We are continuing to investigate the possibilities of applying the present method to the synthesis of related sulfur-containing heterocycle-fused quinone derivatives.

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12 The reactions with equimolar amount of the enamines gave the products in somewhat diminished yields.

13 All new compounds gave satisfactory spectral [IR (KBr; cm^{-1}), ^1H NMR (270 MHz, $CDCl_3$, *J* values are given in Hz), and LR-MS] and analytical data. Spectral data for the products **5** follow. **5a**: ν_{max} 1664, 1646; δ_H 2.57 (2H, quint, *J* 7.4), 3.00 (2H, t, *J* 7.4), 3.10 (2H, t, *J* 7.4), 7.7–7.8 (2H, m), 8.2–8.25 (2H, m); *m/z* 254 (M^+, 100). **5b**: ν_{max} 1660, 1650; δ_H 1.85–1.9 (4H, m), 2.85–2.95 (2H, m), 3.05–3.1 (2H, m), 7.65–7.75 (2H, m), 8.15–8.25 (2H, m); *m/z* 268 (M^+, 100). **5c**: ν_{max} 1660, 1645; δ_H 1.65–1.8 (4H, m), 1.9–2.0 (2H, m), 2.9–3.0 (2H, m), 3.35–3.45 (2H, m), 7.65–7.75 (2H, m), 8.15–8.2 (2H, m); *m/z* 282 (M^+, 100). **5d**: ν_{max} 1661, 1647 (sh); δ_H 1.3–1.8 (8H, m), 2.98 (2H, t, *J* 6.1), 3.18 (2H, t, *J* 6.4), 7.65–7.75 (2H, m), 8.15–8.25 (2H, m); *m/z* 296 (M^+, 50), 267 (100). **5e**: ν_{max} 1666, 1648; δ_H 1.36 (3H, t, *J* 7.3), 2.53 (3H, s), 2.89 (2H, q, *J* 7.3), 7.7–7.75 (2H, m), 8.15–8.25 (2H, m); *m/z* 256 (M^+, 54), 241 (100). **5f**: ν_{max} 1660; δ_H 1.05 (3H, t, *J* 7.3), 1.20 (3H, t, *J* 7.3), 1.77 (2H, sext, *J* 7.3), 2.84 (2H, t, *J* 7.3), 3.01 (2H, q, *J* 7.3), 7.7–7.75 (2H, m), 8.15–8.2 (2H, m); *m/z* 284 (M^+, 46), 255 (100).