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Tetrahedron Letters 45 (2004) 2511–2513
Tetrahedron Letters

An efficient synthesis of substituted anthraquinones and naphthoquinones ☆

David Bailey and Vance E. Williams*

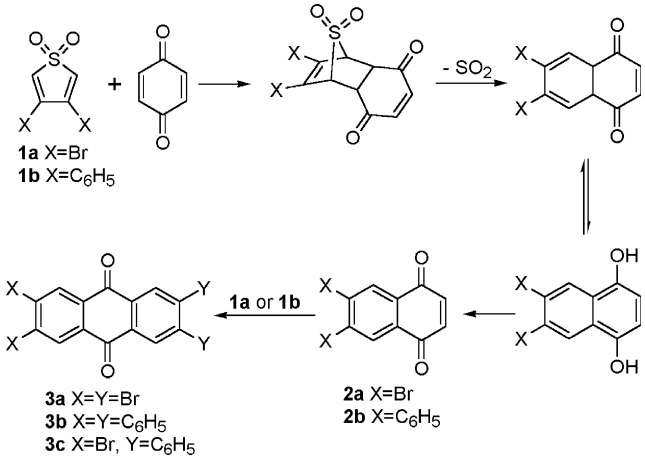
Department of Chemistry, Simon Fraser University, 8888 University Dr., Burnaby, British Columbia, Canada V5A 1S6

Received 12 January 2004; revised 3 February 2004; accepted 4 February 2004

Abstract—An efficient synthesis of 6,7-disubstituted naphthoquinones and 2,3,6,7-tetrasubstituted anthraquinones were developed using the reaction of thiophene dioxides and benzoquinone and naphthoquinone derivatives, respectively.

Anthraquinone derivatives have been employed as dyes,[1] chemical sensors,[2] organogelators,[3] mesogens,[4–9] anticancer agents,[10] and, perhaps most importantly, as precursors of peripherally substituted anthracenes. Although a number of methods exist for the assembly of substituted anthraquinones, these molecules are most commonly obtained via the condensation of appropriately substituted phthalic anhydride and benzene derivatives.[11–14] Unfortunately, this Friedels–Craft approach is often low yielding, cumbersome, and incompatible with many substrates. We therefore decided to explore alternative methods for constructing anthraquinone derivatives substituted at the 2-, 3-, 6-, and 7-positions.

The Diels–Alder condensations between quinones and dienes have been used sporadically to assemble both naphthoquinones and anthraquinones.[15–18] We were interested in developing a general strategy whereby these reactions could be harnessed to synthesize highly functionalized symmetrical and unsymmetrical anthraquinone derivatives. Our general strategy focused on the use of thiophene-1,1-dioxides as dienes in an iterative synthetic approach (Scheme 1). The reaction of substituted thiophene-1,1-dioxides, such as **1a** or **1b**, with benzoquinone, followed by loss of sulfur dioxide and oxidation, is anticipated to afford the corresponding naphthoquinones **2a** or **2b**, respectively. These naphthoquinones could then react with a second thiophene dioxide to yield either symmetrical or unsymmetrical anthraquinone derivatives, **3a**–**c**.



Scheme 1. Proposed synthesis of anthraquinone derivatives.

Our preliminary investigations focused on these two sulfones, the 3,4-dibromothiophene-1,1-dioxide (**1a**) and its 3,4-diphenyl analog, **1b**, because of their potential usefulness in other contexts. The brominated naphthoquinone and anthraquinone compounds derived from **1a** could be further elaborated using Pd- or Ni-catalyzed cross-coupling reactions. Our approach would therefore be compatible with and complementary to the strategy developed by Anthony for the synthesis of linear acenes from *ortho*-dibrominated arenes.[19] These compounds

Keywords: Thiophene-1,1-dioxides; Diels–Alder; Anthraquinones; Naphthoquinones.

☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.02.010

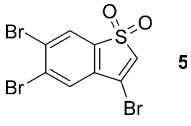
* Corresponding author. Tel.: +1-604-291-3352; fax: +1-604-291-3765; e-mail: vancew@sfu.ca

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.02.010

would also be useful in syntheses wherein *ortho*-dihalides are employed to generate arynes *en route* to extended aromatic structures.[20,21] The diphenylsulfone **1b** is an attractive precursor for a variety of novel polyphenylated naphthalene and anthracene derivatives, which have been the focus of considerable theoretical and practical interest.[22–24]

The choice of 3,4-disubstituted thiophene-1,1-dioxides as our dienes was guided by the combination of their strong tendency to condense with dienophiles and their relative inertness toward homodimerization reactions under ambient conditions. Similarly substituted cyclopentadienones react in a similar manner to thiophene-1,1-dioxides, but are highly unstable and must be generated in situ. In contrast, the sulfone derivatives **1a** and **1b** were sufficiently stable to be isolated and purified, and have been stored for prolonged periods without special precautions. Sulfones **1a** and **1b** were readily prepared by oxidation of the corresponding thiophenes using peroxytrifluoroacetic acid.[25] The precursor for **1b**, 3,4-diphenylthiophene, was obtained via the Suzuki coupling of 3,4-dibromothiophene with phenylboronic acid.

In order to demonstrate the feasibility of preparing anthraquinones from these starting materials, we first examined the reaction of **1a** and **1b** with 1,4-naphthoquinone (Scheme 2). Condensation of the dibromosulfone, **1a**, with 2 equiv naphthoquinone in refluxing acetic acid affords the unsymmetrical anthraquinone derivative, **4a** in 28% yield. The major product for this reaction identified as the sulfone, **5**, which was isolated in 49% yield. The latter product forms as the exclusive product when the sulfone is heated in the absence of benzoquinone, and presumably arises from the homodimerization of **1a**.[15] Formation of this unwanted compound can be suppressed by using a large excess (10 equiv) of naphthoquinone; under these latter conditions the desired anthraquinone **4a** was isolated in 76% yield. In contrast, the diphenylsulfone, **1b** does not undergo homodimer formation to an appreciable extent and reacts with 2 equiv of naphthoquinone to afford the 3,4-diphenylanthraquinone, **4b** in 70% yield.



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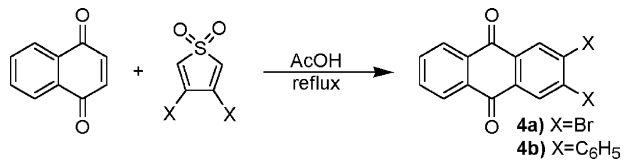
We next turned our attention to the synthesis of the disubstituted naphthoquinones, **2a** and **2b**; the results of these reactions are summarized in Table 1. Condensation of the diphenylthiophene dioxide **1b** with 2 equiv benzoquinone in refluxing acetic acid surprisingly produced 3,4,6,7-tetraphenyl-9,10-anthraquinone, **3b**, in 52% yield. Only when a very large excess of benzoquinone (>10 equiv) was used was the expected naphthoquinone product **2b** observed. Even under these conditions, appreciable quantities of the anthraquinone **3b** were formed. That the double addition product **3b** forms under conditions that one would expect to favor the naphthoquinone strongly suggests that one of the intermediates *en route* to **4c** acts as a much better dienophile than benzoquinone itself. Under such circumstances, addition of a second sulfone would be highly favorable.



Scheme 2. Condensation of thiophene S,S-dioxides with 1,4-naphthoquinone.

The outcome of this condensation was strongly dependent upon the solvent employed. For example, when the reaction was carried out in toluene rather than acetic acid, the naphthoquinone product is formed in much higher ratios (Table 1). Changing the solvent thus provides a convenient method for obtaining either the naphthoquinone or the anthraquinone product, as desired. The reason for this difference is unclear at this time, although a similar solvent effect has been observed for the Diels–Alder reaction of benzoquinone with anthracene.[26]

The reaction of the dibromosulfone **1a** with 1 equiv of benzoquinone yielded the naphthoquinone **2a** in only trace amounts, while the homodimer product **5** was again formed as the major product. Using 2 equiv of benzoquinone gave only slightly better results; it was only when a large excess of this dienophile was added that the naphthoquinone **2a** became the major product. In contrast to the reaction of the diphenyl analog **1b**, we did not isolate any anthraquinone product from the direct reaction of **1a** with benzoquinone.

We next attempted to prepare the tetrabromoanthraquinone, **3a**, by condensing the isolated dibromonaphthoquinone **2a** with the thiophene dioxide. We were able to obtain the desired product, albeit in poor (<20%) yields. Isolation and purification of this compound was difficult owing to its low solubility in most organic solvents.

The final compound in this series, the unsymmetrical anthraquinone **3c** could, in principle, be prepared either via the condensation of the diphenylnaphthoquinone **2b** with the dibromothiophene dioxide, **1a**, or from the complementary reaction of **2a** with **1b**. We found it

Table 1. Condensation of benzoquinone with sulfones **1a** and **1b**

Sulfone (mmol)	Benzoquinone (mmol)	Solvent	Product (mmol)	
1a (1.00)	1.00	AcOH	**2a** (0.03)	**5** (0.36)
1a (1.00)	2.00	AcOH	**2a** (0.12)	**5** (0.30)
1a (1.00)	10.00	AcOH	**2a** (0.56)	**5** (0)
1b (1.00)	2.00	AcOH	**2b** (0.35)	**3b** (0)
1b (1.00)	10.00	AcOH	**2b** (0.35)	**3b** (0.10)
1b (1.00)	2.00	Toluene	**2b** (0.39)	**3b** (0.16)

expedient to employ the latter set of reagents, given the pronounced tendency of **1a** to undergo homodimerization. In this manner, **3c** was obtained in 76% yield.

In conclusion, we have developed an efficient synthesis of peripherally substituted naphthoquinone and anthraquinone derivatives using the Diels–Alder condensation of 3,4-disubstituted thiophene-1,1-dioxides. This route allows for the preparation of a variety of symmetrical and unsymmetrical molecules. Perhaps most remarkable is the observation that the condensation of 3,4-diphenylthiophene 1,1-dioxide leads to the symmetrical anthraquinone, **3b**. If the condensation of quinones and sulfones proceeds according to the mechanism outlined in Scheme 1, as Bluestone has suggested,[27] then this transformation is accomplished by 10 elementary reactions that take place in a one-pot procedure. Further investigations are underway to better understand this reaction and to explore its generality.

Supplementary materials: Synthetic procedures and analytical data are available as supplementary material. The supplementary data is available online with the paper in ScienceDirect.

Acknowledgements

The authors gratefully acknowledge the financial assistance of Simon Fraser University and the Natural Sciences and Engineering Research Council (NSERC).

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