A Convenient Route to Heteronaphthacenes

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Heteronaphthacenes **1** were prepared in two steps from 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (**4**) and dienophiles **2** *via* convenient high-temperature Diels-Alder reactions.

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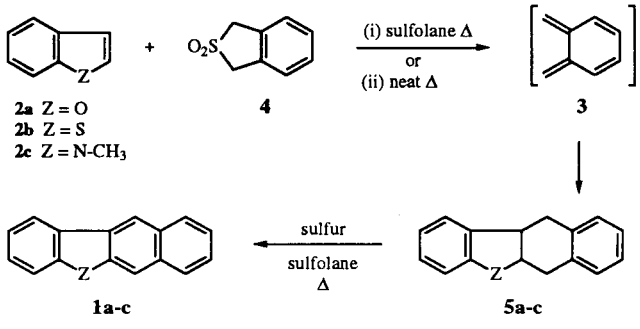
Interest in polycyclic aromatic hydrocarbons (PAH) analogous to naphthacene in which ring B is a π excessive heterocyclic unit **1** stems from their natural occurrence in coal tars, shale oils, and minerals [2-7], their isosteric relationship to carcinogenic PAH [8-11] and antitumor agents [12,13], and their utility in mechanistic [8,14-19] and chemiluminescent [20] studies. Recently, derivatives of **1a** and **1c** in which ring C is a quinone have been reported to be pharmacologically active [21,22]. Despite such wide utility, syntheses of **1** frequently involved severe pyrolytic conditions [8,14-17], unfavorable regioselectivity [14-19], low overall yields [8,12,23-25], and hazardous reagents [9,10].

This paper presents a new route to selected heteronaphthacenes based on the cycloaddition of **2** to *o*-xylylene (**3**). Although compounds such as **2** exhibit low reactivity as dienophiles, they are known to participate in inverse electron demand Diels-Alder reactions with triazines [26] and tetrazines [27,28]. In the present case a highly reactive diene was needed to effect the cycloaddition of **2**. We turned first to the generation of **3** from α,α'-dibromo-*o*-xylene under the mild conditions reported by Mori *et al.* [29]. Next, we sought to produce the dibromo derivative of **3** from α,α,α',α'-tetrabromo-*o*-xylene [30]. In none of these cases did the product mixture from **2b** contain any material corresponding to a cycloadduct. The desired reaction was effected, however, by the thermolysis of 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (**4**) [31-33]. To circumvent the difficulty of product isolation from high-boiling solvents we used water-soluble sulfolane, which was the solvent of choice for other Diels-Alder studies in this laboratory [34]. The process (method A, shown as step i in Scheme I) worked reasonably well for **2a** and **2b**, but was less satisfactory for **2c**. Mindful that others produced **3** without solvent [32,33], we found that such a process (method B, shown as step ii in Scheme I) gave improved yields in all cases.

Adduct **5a** *via* method B was a single compound (m/z 222), which was isolated. The same product mixture *via* method A exhibited two major peaks (both m/z 222) in the ratio of 2:3. The major isomer had the same gc retention time as the single product *via* method B was assigned the *cis* structure. The minor component was considered to be the *trans* structure, arising from partial isomerization at the ring junction. No attempt was made to separate the isomers, since subsequent aromatization gave **1a** exclusively.

Scheme I

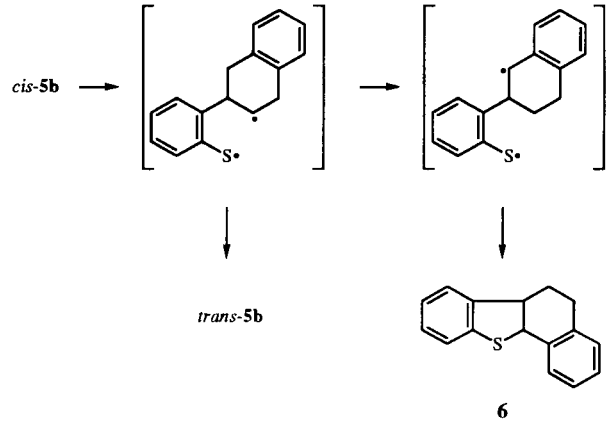


2a Z = O
2b Z = S
2c Z = N-CH$_3$

4 **3** **1a-c** **5a-c**

In the case of **5b**, the product mixture *via* either method exhibited four major peaks (each m/z 238) in the ratios of 5:2:2:1 and 5:2:1:3 from methods A and B, respectively. In addition to *cis*- and *trans*-**5b**, the other components were considered to be *cis- and trans*-tetrahydrobenzo[*b*]naphtho[2,1-*d*]thiophene (**6**), arising from rearrangement of **5b**

Scheme II



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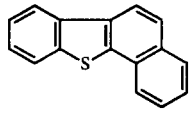
(Scheme II). Precedent for this process was found in the high temperature Elbs reaction of *o*-tolyl benzo[*b*]thien-3-yl ketone [19]. Subsequent aromatization of the **5b/6** mixture gave only **1b** and benzo[*b*]naphtho[2,1-*d*]thiophene (**7**),



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thereby confirming the structure postulated for **6**. In the case of **2c** the existence of **5c** was only inferred because aromatization occurred spontaneously during the Diels-Alder reaction, producing **1c** directly. Optimal conditions were determined for both methods A and B of the Diels-Alder step; the results are summarized in the Table.

Table

Dienophile	Method [a]	Product (%) [b]	Product (%) [b]
2a	A	**5a** (39)	
	B	**5a** (61)	**1a** (84) [c]
2b	A	**5a/6** (35)	
	B	**5a/6** (59)	**1b** (55) [c] + **7** (14) [c]
2c	A		**1c** (13) [d]
	B		**1c** (50) [d]

[a] Method A: sulfolane, reflux 1 hour; method B: neat, 280-285° 1 hour. [b] GC/MS analysis. [c] Yield from **5**. [d] Yield from **2c**.

For the dehydrogenation of **5** to **1** we devised a new, convenient procedure. Treatment of **5** with excess sulfur in refluxing sulfolane gave **1** in good yields. The advantages of this method were threefold: sulfur was insoluble in cold sulfolane and excess reagent was removed by filtration of the product mixture, the water solubility of sulfolane permitted easy extraction of products, and the use of toxic selenium was avoided [9,10,35]. We established that sulfur in refluxing sulfolane did not oxidize the solvent to sulfolene. We also tested palladium on charcoal, chloranil, and dichlorodicyanobenzoquinone as oxidizing agents; but none was as effective as sulfur. As mentioned above, **5a** gave **1a** as the sole product. The mixture of **5b** and **6** gave **1b** and **7** in the ratio of 3.8:1, which represented a much larger fraction of the linear isomer than observed in the Elbs [19] or sulfur-bridging reactions [16,17]. This stability of the linear cycloadducts **5** was in contrast to the Diels-Alder reactions of **2** with 3,6-disubstituted-1,2,4,5-tetrazines in which the initial adducts of **2a** and **2c** (but not **2b**) underwent ring opening to phenol and *N*-methylaniline derivatives, respectively [28]. Optimal conditions were determined for the dehydrogenation by sulfur; the results are summarized in the Table. The unexpected behavior of **5c** led us to attempt one-pot sequences with **2a** and **2b** by adding sulfur to the sulfolane solution after the reflux period for the first step; but complex mixtures were obtained and aromatization was incomplete.

Relative rates for the reactions of **2** with **3** were determined by competitive cycloadditions. One equivalent each of **2a**, **2b**, and **4** were heated in a sealed ampule under standard conditions; direct gc/ms analysis of the crude product mixture showed a ratio for **5b**:**5a** of 1.3. Similarly **2a** and **2c** showed a ratio for (**5c** + **1c**):**5a** of 1.4, and **2b** and **2c** showed a ratio for (**5c** + **1c**):**5b** of 3.0. Thus, toward **3** the relative dienophilicities were **2c** > **2b** > **2a**.

Two other dienophiles were investigated: indole (**2d**, Z = NH) and indene (**2e**, Z = CH_2). With indole the product mixture by gc/ms analysis contained two peaks consistent with **5d** (m/z 221, 12% of total area), one peak consistent with **1d** (m/z 217, 9% of total area), and thirteen other compounds. With indene the product mixture contained one peak consistent with **5e** (m/z 220, 32% of total area) and six other compounds, several of which corresponded to dimers of **2e**. Due to the multiple unidentified products in each case, no further studies with **2d** and **2e** were carried out.

EXPERIMENTAL

Melting points are uncorrected. The gc/ms analyses were performed on a Hewlett-Packard 5890II gas chromatograph with a HP-1 crosslinked methyl silicone gum column (12 m x 200 μm with 33 μm film) and a Hewlett-Packard 5791A mass spectrometer (EI, 70 eV). Liquid chromatography was carried out on short columns of alumina (ICN neutral, Super I, 70-290 mesh) with hexane-benzene as eluent. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Authentic samples of **1a** and **1c** were kindly provided by McNab [15] and White [20], respectively; **1b** and **7** were purchased from Acros and Aldrich, respectively. 1,3-Dihydrobenzo[*c*]thiophene 2,2-dioxide (**4**) was prepared by the reported procedure and obtained as colorless needles (benzene-petroleum ether), mp 151-152.5°, lit [33] mp 150-151°. All other materials were commercially available and were used as received.

General Procedure for Diels-Alder Reactions of 2 with Sulfone 4.

Method A. Sulfolane Solution.

A solution **2** (0.75 mmole) and sulfone **4** (0.042 g, 0.25 mmole) in sulfolane (1 ml) was refluxed 1 hour, cooled, diluted with brine (20 ml), and extracted with diethyl ether (2 x 10 ml). The combined extract was washed with brine (2 x 20 ml), dried (sodium sulfate), concentrated *in vacuo,* and the residual oil analyzed by gc/ms. The yields of **5** were estimated by multiplying the weight of the residual oil by the fractional area of the total gas chromatogram corresponding to peaks with appropriate m/z values. Ratios of **2**:**4** over the range 1:1-3:1 and reflux times of 0.5-2.0 hours were used to set the standard conditions.

Method B. Without Solvent.

To an argon-swept, flat-bottom, 2-ml glass ampule were added **2** (1.25 mmoles) and sulfone **4** (0.042 g, 0.25 mmole). The sealed ampule was heated at 280-285° for 1 hour in a machined aluminum block on a hotplate. The cooled ampule was opened and the product mixture was analyzed as above by gc/ms. Ratios of **2**:**4** over the range 5:1-20:1 and heating times of 1-5 hours were used to set the standard conditions.

Competitive runs were carried out without solvent. To a glass ampule as above were added **2a** (0.127 mmole), **2b** (0.127 mmole), and sulfone **4** (0.125 mmole). The reaction and analysis were the same as above. Other pairings were done similarly.

General Procedure for Aromatization.

A mixture of **5a** or **5b/6** (0.15 mmole), sulfur (0.011 g, 0.34 mmole), and sulfolane (1 ml) was refluxed 1 hour, cooled, and filtered by suction. The filtrate was diluted with diethyl ether (10 ml) and washed with brine (20 ml); the aqueous phase was extracted with ether (10 ml). The combined ether extract was washed with brine (3 x 20 ml), dried (sodium sulfate), concentrated *in vacuo,* and the residual solid analyzed by gc/ms. Product identification was made by coinjection with authentic samples.

5a,6,11,11a-Tetrahydrobenzo[*b*]naphtho[2,3-*d*]furan (**5a**).

By method B **2a** (0.148 g, 1.25 mmoles) gave an orange product mixture, which by gc/ms analysis exhibited only two peaks corresponding to **2a** (m/z 118) and **5a** (m/z 222). Evaporative distillation and vacuum sublimation gave **5a** (0.034 g, 61%) as a pale yellow solid. The analytical sample was obtained by chromatography, mp 103-105°.

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.39; H, 6.12.

Benzo[*b*]naphtho[2,3-*d*]furan (**1a**).

Sulfur treatment of **5a** (0.034 g, 0.15 mmole) gave **1a** (0.028 g, 84%), which by gc/ms analysis exhibited a single peak (m/z 118) identical to an authentic sample, isolated as colorless crystals from 95% ethanol, mp 207.5-209°, lit [36] 209.2-209.8°.

Benzo[*b*]naphtho[2,3-*d*]thiophene (**1b**) and Benzo[*b*]-naphtho[2,1-*d*]thiophene (**7**).

Sulfur treatment of **5b/6** (0.035 g, 0.15 mmole; isolated as a pale yellow oil from the Diels-Alder reaction *via* method B by chromatography with hexane-benzene as eluent) gave a solid (0.030 g), which by gc/ms analysis exhibited two peaks (m/z 234, 79% of total area) corresponding to **1b** and **7** and four peaks (m/z 238, 18% of total area) corresponding to unreacted **5b/6**. The **1b:7** ratio was 3.8:1.

5-Methyl-5*H*-benzo[*b*]carbazole (**1c**).

Cycloaddition of **2c** (0.146 g, 0.125 mmole) with sulfone **4** (0.042 g, 0.25 mmole) *via* method B (2 hours reflux) gave a dark liquid, which by gc/ms analysis gave one peak (m/z 131) for **2c**, one peak (m/z 231, 32% of total area) for **1c**, and one peak (m/z 260) considered to be a **2c** dimer. Chromatography gave **1c** (0.014 g, 24%), identical to an authentic sample.

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