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Sequential Intermediates in the Base-Catalyzed Conversion of Bis(π-conjugated propargyl) Sulfones to 1,3-Dihydrobenzo- and Naphtho[*c*]thiophene-2,2-dioxides

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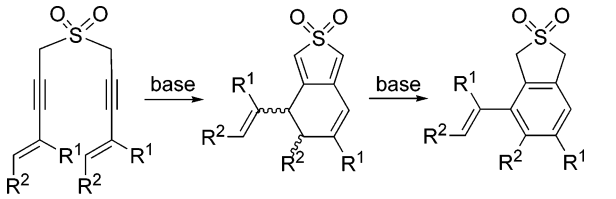
Received August 10, 2005



1a. R^1, R^2 = $(CH{=}CH)_2$
b. R^1 = CH_3 , R^2 = H
c. R^1, R^2 = $(CH_2)_4$

In a recent article, we reported on the base-catalyzed rearrangements of dipropargyl selenides, -sulfides, -sulfoxides, and -sulfones that eventually lead to polycyclic aromatic products. In the present work, we report on the first isolation and characterization of the thiophene dioxide intermediates **5b**,**c** from a mild tandem isomerization/cyclization/aromatization of bis(π-conjugated propargyl) sulfones. Monoallene **2b**,**c** and diallene **3b** intermediates were also identified by NMR. A kinetic study of the rearrangement of **1a**−**c** revealed that the unusual facile tandem process is highly dependent on the nature of γ-substitution.

The cyclization reactions of diallenes or diacetylenes involving free radical species have been the subject of a large number of studies over the past decade.[1] The revival of interest in this type of reaction arises from the prior discovery of the elegant mode of action of the naturally occurring enediynes,[2] whose biological activity involves a diradical cycloaromatization.[3]

Recently we reported on the one-pot, but multistep, DBU-catalyzed conversion of dipropargyl selenides, -sulfides, -sulfoxides, and -sulfones conjugated in their γ-positions to substituted carbon−carbon double bond, to the respective substituted dihydrobenzo- or naphtho-[*c*]-selenophens, -thiophenes, -thiophene-*S*-oxides, and -thiophene-*S*-dioxides (cf. **1** to **6**, Scheme 1, for the case of sulfones).[4−7] Whereas it has been shown in the past that the first step in this type of multistep transformation (as also in the cases of other bridging heteroatoms such as N and O)[8−12] is the base-catalyzed tautomerization of one of the propargyl groups to an allene, yielding an heteroatom bearing both a propargyl and an allenyl group (**2**, Scheme 1), three different possibilities have been considered for the subsequent steps. These are: (1) An intramolecular Diels−Alder (IMDA) reaction between the triple bond on one "arm" and the conjugated allene-ene system of the other "arm", followed by proton transfers (x, Scheme 1). (2) The tautomerization of the second propargyl group to an allene followed by an IMDA between the two allenyl "arms", and subsequent double proton transfer (y, Scheme 1). (3) The tautomerization of the second propargyl group to an allene and bonding between the central carbons of the two allenyl "arms" to yield two allylic (or benzylic) radicals, followed by bond formation between these two radicals leading to a doubly unsaturated five-membered heterocycle condensed in the 3,4-position to a substituted cyclohexene ring (z, Scheme 1). The latter spontaneously aromatizes in the cases of thiophene mono- or dioxides by double proton transfer to the heterocyclic ring.

In our previous report it was noted that the above-mentioned conversion proceeded especially rapidly and in near-quantitative yield in the case of dipropargyl sulfones **1a**−**c**. This could be attributed to the relative acidity of the propargyl hydrogens that are α to the sulfone function, and consequently the base-catalyzed tautomerization to an allenyl system is facilitated.[4,5]

A brief kinetic study using ^{1}H NMR tracking of the reaction of bis(γ-phenylpropargyl) sulfone (**1a**), made feasible by using the weaker base triethylamine in chloroform (rater than DBU in acetonitrile), permitted the identification of only one intermediate, the propargyl allenyl sulfone **2a** (for curve-fitting for this reaction see Figure S3, Supporting Information). This showed that the first tautomerization was the rate-determining step, but yielded no information as to the mechanisms of subsequent steps on the path to the final product dihydrothiophene-2,2-dioxide (**6a**). However, indirect evidence was adduced indicating that the path followed was that

(1) Selected reviews: (a) Nicolaou, K. C.; Smith, A. L. In *Modern Acetylene Chemistry*; Stang, P. J., Diedrich, F., Eds.; VCH: Weinheim, Germany, 1995; Ch. 7. (b) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D. *Tetrahedron* **1996**, *52*, 6453. (c) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207. (d) Maier, M. E. *Synlett* **1995**, 13. (e) Magnus, P. *Tetrahedron* **1994**, *50*, 1397. (f) Nicolaou, K. C.; Dau, W. M.; Tsay, S. C.; Estevez, V. A. *Science* **1992**, *256*, 1172.

(2) For recent reviews, see: (a) Pogozelsky, W. K.; Tullius, T. D. *Chem. Rev.* **1998**, *98*, 1089. (b) Maier, M. E.; Bosse, F.; Niestroj, A. J. *Eur. J. Org. Chem.* **1999**, *1999*, 1. (c) Thorson, J. S.; Shen, B.; Whitwam, R. E.; Liu, W.; Li, Y.; Ahlert, J. *Bioorg. Chem.* **1999**, *27*, 172.

(3) Nicolaou, K. C.; Dai, W. M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1387 and references therein.

(4) Braverman, S.; Zafrani, Y.; Gottlieb, H. E. *Tetrahedron Lett.* **2000**, *41*, 2675.

(5) Braverman, S.; Zafrani, Y.; Gottlieb, H. E. *Tetrahedron* **2001**, *57*, 9177.

(6) Braverman, S.; Zafrani, Y.; Gottlieb, H. E. *J. Org. Chem.* **2002**, *67*, 3277.

(7) Zafrani, Y.; Cherkinsky, M.; Gottlieb, H. E.; Braverman, S. *Tetrahedron* **2003**, *59*, 2641.

(8) Iwai, I.; Ide, J. *Chem. Pharm. Bull. Jpn.* **1964**, *12*, 1094.

(9) Bartlett, A. J.; Laird, T.; Ollis, W. D. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1315.

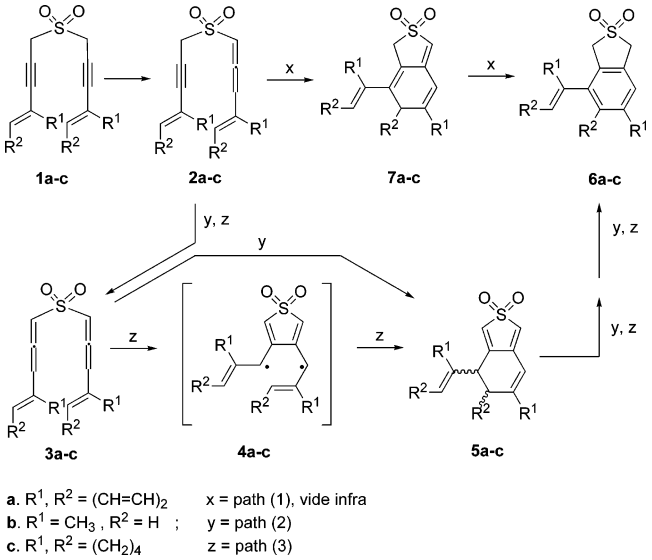
(10) Bartlett, A. J.; Laird, T.; Ollis, W. D. *Chem. Commun.* **1974**, 496.

(11) Garratt, P. J.; Neoh, S. B. *J. Am. Chem. Soc.* **1975**, *97*, 3255.

(12) Garratt, P. J.; Neoh, S. B. *J. Org. Chem.* **1979**, *44*, 2667.

10.1021/jo051692i CCC: $30.25
Published on Web 11/02/2005

SCHEME 1. Tandem Isomerization, Cyclization, and Aromatization of Bridged Propargylic Compounds 1a−c



a. R^1, R^2 = $(CH{=}CH)_2$ x = path (1), vide infra
b. R^1 = CH_3 , R^2 = H ; y = path (2)
c. R^1, R^2 = $(CH_2)_4$ z = path (3)

outlined in (3) above, that is, via a diradical intermediate (z, Scheme 1).[5,11,12] Inter alia it was found that when bis-(γ-phenylpropargyl) sulfone (**1a**) was reacted in the presence of double-stranded supercoiled ΦX174 form I DNA it caused cleavage of the latter. In contrast, this reactivity was not found in the presence of reacting bis-(γ-isopropenylpropargyl) sulfone (**1b**) or bis(γ-cyclohexenylpropargyl) sulfone (**1c**).[5] Since the phenyl substituents in sulfone **1a** would favor diradical formation, but would disfavor a Diels−Alder reaction involving the aromatic π system, it seemed possible that the other two sulfones, **1b**,**c**, lacking an aromatic substituent might proceed to their respective product dihydrothiophene-2,2-dioxides **6b**,**c** by one of the Diels−Alder pathways, (1) or (2).

A brief ^{1}H NMR kinetic study of the reactions of the other two sulfones **1b** and **1c** was undertaken, again using the less basic conditions of triethylamine in chloroform, and its results are reported herewith. The expectations were as follows. If a diallenyl intermediate **3** is formed and in fact detected, it should be formed as a mixture of two diastereoisomers, meso and dl, and with luck their ratio may be available. If, as in pathway (2), the following step is an IMDA reaction, then the stereospecificity of such reaction would preserve the ratio between the stereoisomers in the immediate product, whereas if pathway (3) via a diradical were operative then the isomer ratio in the reactant would probably not be preserved in the immediate product, **5**. The immediate product in which the stereoisomerism of interest may be discernible is the same in pathways (2) and (3), that is, the thiophene dioxides **5b**,**c** before tautomerization to dihydrothiophene dioxides **6b**,**c**.

The results of the kinetic study of the reactions of sulfones **1b** and **1c** are presented in Figures 1 and 2, respectively. It will be noted that in both cases the product obtained in the presence of triethylamine was the respective thiophene dioxide intermediate **5b**,**c**. The latter were tautomerized to the previously obtained

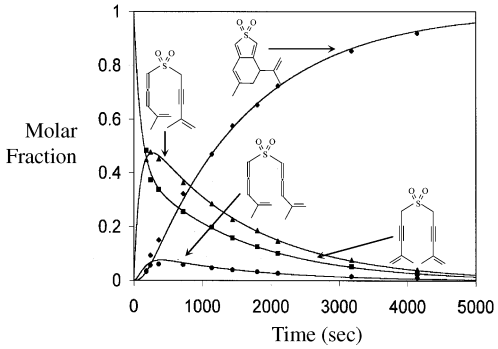


FIGURE 1. Reaction of **1b** with 0.5 equiv of Et_3N.

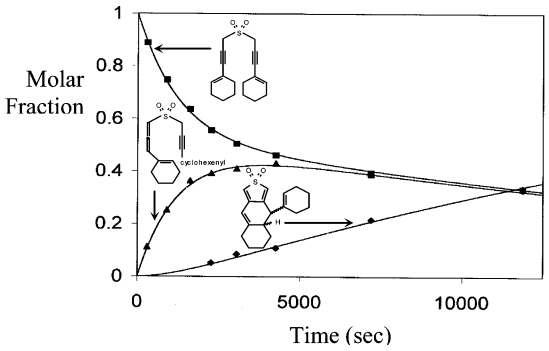


FIGURE 2. Reaction of **1c** with 0.5 equiv of Et_3N.

products **6b**,**c** having a dihydrothiophene dioxide ring fused to a benzenoid system, only upon further treatment with the stronger base, DBU. This contrasts withthe behavior of sulfone **1a**, which yielded only the dihydrothiophene derivative **6a** even in the presence of triethylamine. The difference is easily rationalized in terms of the benzhydrylic and benzylic nature of the hydrogens of **5a** undergoing the facile prototropy.

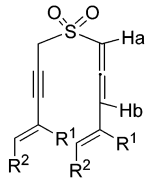
In the reaction of sulfone **1b**, the diallenyl sulfone **3b** was identified as a kinetically competent intermediate (Figure 1, Table 1). Thus, reaction of sulfone **1b** with 0.5 equiv of triethylamine in $CDCl_3$ led to the formation of monoallene **2b** (50%) and diallene **3b** (8%) intermediates, which appeared at maximum concentration near the beginning of the reaction time and then gradually decreased. Curve-fitting led to the following minimal kinetic model:

$$\mathbf{1b} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{2b} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathbf{3b} \xrightarrow{k_p} \mathbf{5b}$$

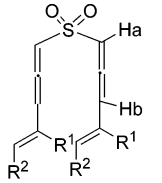
with calculated (pseudo) first-order rate constants having values of $k_1 = 6.5 \times 10^{-3}$ (s^{-1}), $k_{-1} = 4.0 \times 10^{-3}$ (s^{-1}); $k_2 = 2.0 \times 10^{-3}$ (s^{-1}), $k_{-2} = 5.0 \times 10^{-3}$ (s^{-1}); and $k_p = 7.0 \times 10^{-3}$ (s^{-1}).

Unfortunately, the two stereoisomeric diallenes could not be distinguished by ^{1}H NMR. The product obtained under these conditions is in fact, as already noted, the thiophene dioxide **5b**, before aromatization of the cyclohexene ring. However, since it has only one chiral center the stereoisomerism present is of the enantiomeric type (i.e., *a racemate*).

TABLE 1. Experimental ^{1}H NMR Data for Monoallenes 2b,c and Diallene 3b



2b. $R^1 = CH_3$, $R^2 = H$
c. R= R^1, $R^2 = (CH_2)_4$



3b. $R^1 = CH_3$, $R^2 = H$

	Ha	Hb	CH_2-propargyl	R
2b	6.62 (d, J = 5.7 Hz)	6.52 (dm, J = 5.7 Hz)	4.07 (s)	5.37 (m, 1H), 5.33 (quintet, J = 1.5 Hz, 1H), 5.18 (m, 1H), 5.11 (m, 1H), 1.89 (dd, J = 1.5, 1 Hz, 3H), 1.86 (bs, 3H)
3b	6.58 (d, J = 6.0 Hz)	6.46 (d, J = 6.0 Hz)	_	5.18 (m, 1H), 5.11 (m, 1H), 1.84 (bs, 3H)
2c	6.54 (d, J = 5.7 Hz)	6.48 (dm, J = 5.7 Hz)	4.05 (s)	6.18 (m, 1H), 5.93 (m, 1H), 2.11 (m, 8H), 1.61 (m, 8H)

Curve-fitting for the reaction of **1c** led to the following minimal kinetic model:

$$\mathbf{1c} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{2c} \xrightarrow{k_p} \mathbf{5c}$$

with calculated (pseudo) first-order rate constants having values of $k_1 = 4.0 \times 10^{-4}$ (s^{-1}), $k_{-1} = 3.7 \times 10^{-4}$ (s^{-1}); $k_p = 8.0 \times 10^{-5}$ (s^{-1}). In this reaction, the rate-determining step is the first tautomerization of the starting sulfone to the propargyl allenyl sulfone **2c**. The diallenyl sulfone **3c** once formed is consumed too fast to be detected. Its intermediacy is, however, implied by the formation of two diastereoisomers of thiophene dioxide **5c**, cis and trans in the ratio of 7:8.

In summary, the data presented herein confirm the proposed intermediacy of the diallenyl sulfone **3** and of the thiophene dioxide **5** in the previously discovered base-catalyzed conversion of bis(γ-alkenylpropargyl) sulfones **1** to the corresponding dihydrothiophene dioxides **6** and negate mechanism (1) (x, Scheme 1). Moreover, the success in isolation of thiophene dioxides in this facile and high atom-economical tandem isomerization, cyclization, and aromatization offers special opportunity for enhancing efficiency and for construction of complicated aromatic compounds. The slowest step in the multistep process is in every case a propargyl to allenyl tautomerization, in keeping with our previous finding for **1a**. However, the relative rates of all the successive steps in the present cases studied were such that distinction between mechanisms (2) and (3) (vide infra, y, z, Scheme 1) was not possible.

Experimental Section

Experimental data for sulfones **1a**−**c** and products **6a**−**c** of their reaction with DBU were reported previously.[5] The data for new compounds **5b**,**c** are listed below.

4-Isopropenyl-6-methyl-4,5-dihydrobenzo[*c*]thiophene-2′,2′-dioxide (5b) was obtained from **1b** by the general procedure after 1.5 h in 100% yield as white semisolid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.24 (m, 2H), 6.11 (s, 1H), 5.03 (quintet, J = 1.5 Hz, 1H), 4.93 (m, 1H), 3.36 (ddd, J = 9.5, 6.6, 3 Hz, 1H), 2.42 and 2.35 (ABX system, J_{AB} = 16.5, J_{AX} = 9.5, J_{BX} = 6.5 Hz; long-range couplings are also visible, 2H), 2.00 (s, 3H), 1.76 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 150.6 (C), 143.9 (C), 142.3 (C), 136.9 (C), 124.7 (CH), 117.9 (CH), 116.3 (CH), 115.7 (CH_2), 43.1 (CH), 33.8 (CH_2), 24.8 (CH_3), 19.0 (CH_3); IR (neat): 1642, 1435, 1286, 1195, 1137, 1094 cm^{-1}; MS (CI): *m/e* 223 (MH^+, 88.6%), 158 (12.1%), 143 (32.5%); HRMS (elemental composition), calcd ($C_{12}H_{15}O_2S$) 223.0792, obsd 223.0795.

4-(Cyclohex-1-enyl)-4,5,6,7,8,9-hexahydronaphtho[2,3-c]-thiophene-2′,2′-dioxide (5c) was obtained from **1c** by the general procedure after 24 h, as a mixture of cis and trans products in the ratio of 7:8 with 10% of starting material and traces impurities. During attempted separation of this mixture by column chromatography, **5c** was partially isomerized to naphthalenic compound **6c**. Therefore, thiophene dioxide **5c** was identified and characterized only by ^{1}H and ^{13}C NMR data.

trans Isomer: ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.15 (m, 2H), 6.07 (m, 1H), 5.65 (m, 1H), 2.84 (dd, J = 8.5, 3.0 Hz, 1H), 2.53 (m, 1H), 2.28 (m, 1H), 2.24−2.17 (m, 1H), 2.10−2.06 (m, 2H), 1.90−1.83 (m, 4H), 1.70−1.56 (m, 4H), 1.43−1.36 (m, 3H), 1.08 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 156.5 (C), 145.5 (C), 136.7 (C), 133.6 (C), 128.5 (CH), 124.1 (CH), 117.5 (CH), 114.7 (CH), 51.0 (CH), 38.2 (CH), 35.8 (CH_2), 32.8 (CH_2), 28.5 (CH_2), 26.2 (CH_2), 25.3 (CH_2), 24.5 (CH_2), 22.9 (CH_2), 22.2 (CH_2).

cis Isomer: ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.34 (m, 2H), 6.16 (m, 1H), 6.08 (m, 1H), 5.61 (m, 1H), 3.32 (dd, J = 6.5, 2.5 Hz, 1H), 2.51 (m, 1H), 2.46 (m, 1H), other 7×CH_2 have multiplets between 2.24 and 1.02; ^{13}C NMR (151 MHz, $CDCl_3$): δ 158.9 (C), 143.9 (C), 137.3 (C), 134.5 (C), 127.2 (CH), 125.3 (CH), 117.2 (CH), 113.4 (CH), 46.1 (CH), 41.3 (CH), 37.1 (CH_2), 31.9 (CH_2), 28.6 (CH_2), 26.2 (CH_2), 25.4 (CH_2), 25.2 (CH_2), 22.8 (CH_2), 22.0 (CH_2).

Acknowledgment. The financial support of this study by the Israel Science Foundation is gratefully acknowledged.

Supporting Information Available: General procedure for the reaction of dipropargyl sulfones with triethylamine. Curve-fitting for the reaction of **1a** with triethylamine. ^{1}H and ^{13}C NMR spectra of thiophene dioxide **5b** and ^{13}C spectrum of the cis and trans mixture of thiophene dioxide **5c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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