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Synthesis and structure of novel sulfur bridged cyclic di- and tetraalkynes

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Abstract—Some novel sulfur bridged 13- to 30-membered cyclic di- and tetraalkynes derived from 1,2-, 1,3- and 1,4-dihydroxybenzene and 1,2-bis(bromomethyl)benzene were synthesized and their structures confirmed by X-ray analysis. The unexpected formation of 2,6-divinyl-1,4-dithiin during Na_2S/alumina induced cyclization was also observed and the reaction mechanism is discussed.

The so-called enediyne antibiotics such as calicheamicin or esperamicin[1] are amongst the most potent antitumor agents known to date. However, due to the toxicity and instability of the enediyne natural products on the one hand, and their difficult synthesis on the other, a great variety of enediyne models have been designed and tested for their biological activity during the last decade. This remarkable activity which resulted in the publication of scores of articles was initiated by K. C. Nikolaou's report on pH-dependent DNA-cleavage by propargylic and allenic sulfones,[2] which, in turn, is based on the cyclization of diallenic sulfones, a reaction discovered by us more than two decades ago and demonstrated to involve a diradical intermediate.[3]

Recently, we have investigated the behavior of some novel acyclic π-conjugated bis-propargylic sulfides, sulfoxides and sulfones.[4] These compounds have been found to undergo facile isomerization to the corresponding diallenes followed by a tandem cyclization and aromatization via a diradical intermediate in the presence of various bases at room temperature.[4] In continuation, we decided to prepare some novel cyclic sulfur bridged di- and tetrapropargylic systems (**1**, **2**) (Fig. 1) and investigate their tandem isomerization and cyclization under basic conditions in order to compare their reactivity with the reactivity of the acyclic sulfur bridged propargylic systems.[4] We expect that the presence of oxygen atoms in the new macrocycles would

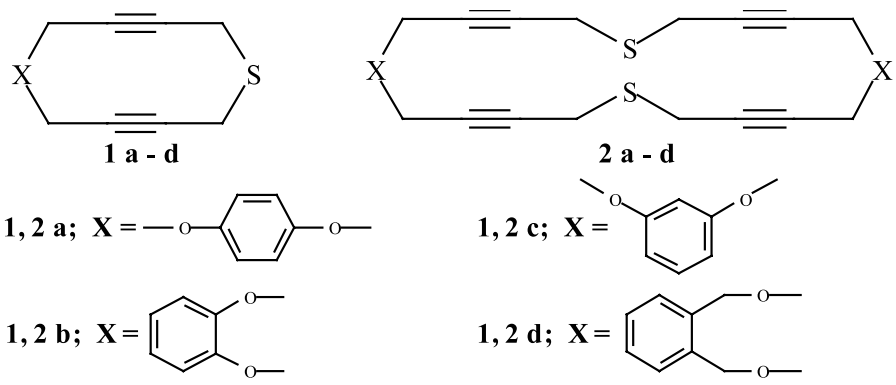

Figure 1.

Keywords: cyclic dipropargylic sulfide; cyclic tetrapropargylic sulfide; 1,4-dithiin.
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provide further enhancement to their chemical and potential biological activity due to the well-known metal-ion acceleration.[5] Furthermore, we wanted to study the effect of the nature of the bridge as well as the cycle size on the reactivity of these macrocycles. Here we wish to report some preliminary results about synthesis and structure of the above-mentioned compounds.

1,4-, 1,3- and 1,2-Bis(4′-bromobut-2′-ynyloxy)benzenes **3a–c** required for the synthesis of the corresponding sulfur-bridged cyclic alkynes **1a–c** and **2a–c** were prepared by two alternative ways 'a' and 'b' according to Scheme 1, starting from 1,4-, 1,3- and 1,2-dihydroxybenzene, respectively.

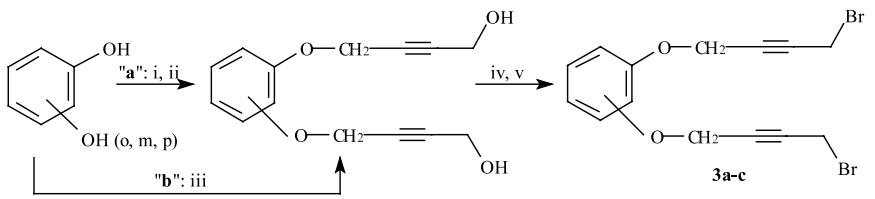
However, during our attempts to prepare the bis-propargylic sulfide **1a**, we found that the reaction of the corresponding dibromide **3a** with an excess of alumina-supported sodium sulfide[6] in boiling THF, resulted in formation of 2,6-divinyl-1,4-dithiin (**4**) instead of the expected product (Scheme 2). Keeping in mind the high reactivity of allenes towards sulfur nucleophiles[7] and the good leaving group ability of phenolate anions, we suggest the mechanism shown in Scheme 2. Following the formation of the cyclic sulfide **1a** and its alumina-catalyzed rearrangement to the corresponding diallenyl sulfide **5**, attack of the sulfide dianion on the latter leads to fragmentation of **1a** and formation of the dithiin **4**.[8] Analogous rearrangement of a cyclic bis-(propargylic)sulfide to the corresponding bis-allene induced by the alumina-supported sodium sulfide reagent was reported by Kerwin.[9]

1,4-Dithiins are well-studied and documented compounds.[10] However, we are not aware of any previously reported 2,6-divinyl-1,4-dithiin derivatives, e.g. (**4**). Vinyl derivatives of 1,4-dithiins, which can potentially act both as dienes as well as dienophiles, may be subjected to various cycloaddition reactions and thus open a route to some new polycyclic systems.

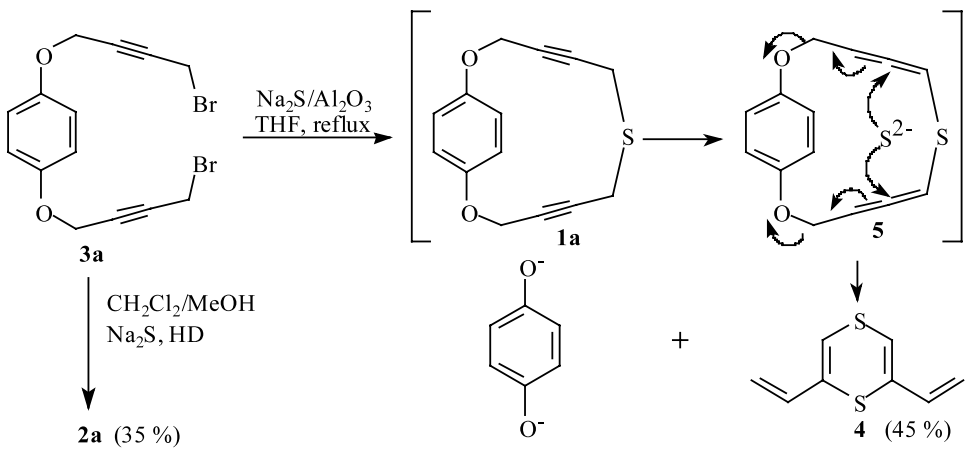
In view of the above results and in order to prevent the alumina-catalyzed propargyl-allenyl isomerization, we ran the reaction of dibromide **3a** with $Na_2S{\cdot}9H_2O$ under high dilution conditions (Scheme 2). These resulted in formation of the 30-membered cyclic tetra-alkyne **2a** (vide supra).

Interestingly, unlike 1,4-derivative **3a**, dibromide **3b** reacts either with $Na_2S{\cdot}Al_2O_3$ or under high dilution with sodium sulfide nonahydrate in an intramolecular fashion with the formation of the dipropargylic 13-membered cyclic sulfide **1b**[11] only. The corresponding 26-membered cyclic tetrapropargylic bis-sulfide **2b** was obtained by the base-induced reaction of bis-thioacetate **7b** with bis-mesylate **6b** (Scheme 3).

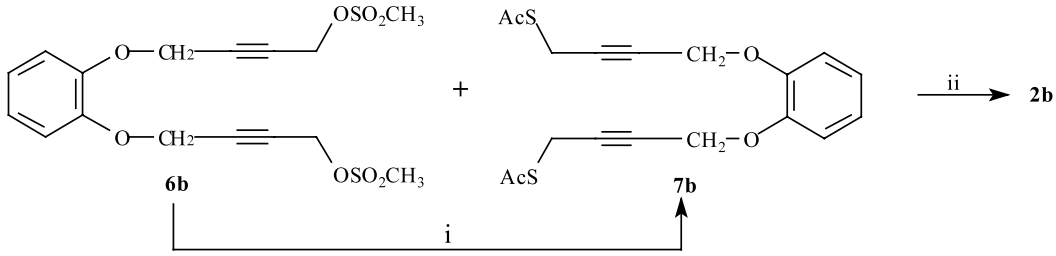
Concerning the resorcinol derivatives **1c** and **2c**, 1,3-bis(4′-bromobut-2′-ynyloxy)benzene **3c**, available only by pathway 'b' (Scheme 1) reacts with $Na_2S{\cdot}9H_2O$ under high dilution with the formation of a mixture of both types of ring systems in the ratio **1c**/**2c** 1:5 and in a total yield of 60%. The products were separated by fractional recrystallization from acetone. Here, we may see the effect of the substitution in the starting dihydroxybenzenes on the competitive intra- versus inter-



Scheme 1. *Reagents and conditions*: (i) propargyl bromide, K_2CO_3, DMF, rt, 48 h, 80–90%; (ii) *n*-BuLi, $(CH_2O)_n$, THF, −78°C, 4 h, 80–85%; (iii) 4-bromobut-2-yn-1-ol, K_2CO_3, DMF, rt, 48 h, 85–90%; (iv) CH_3SO_2Cl, Et_3N, Et_2O, 0°C, 6 h, 70–75%; (v) NaBr, CH_3CN, rt, 48–72 h, 80–85%.



Scheme 2.



Scheme 3. *Reagents and conditions*: (i) AcSK, MeOH, rt, 2 h, 80%; (ii) KOH, MeOH/THF, HD, rt, 1 h, 35%.

molecular cyclization. The instability of **1a** as compared to **1b** and **1c** may be explained in terms of excessive ring strain in the former. Formation of the less strained **1c** as a minor product may serve as indirect evidence for the intermediacy of the macrocycle **1a** in the formation of 2,6-divinyl-1,4-dithiin (**4**). Interestingly, another factor which has an influence on the mode of cyclization is the nature of halogen in the bis(4′-halobut-2′-ynyloxy)benzenes. Since, the reaction of the corresponding dimesylates with NaBr takes 2–3 days (Scheme 1) we used NaI to accelerate the formation of the required dihalogenides. However, when we ran the reaction of the diiodides with $Na_2S{\cdot}9H_2O$ the output of the cyclization changed. For the resorcinol derivatives we found that both rings are formed in a total yield of 90% and a **1c**/**2c** ratio of 1:10. For the catechol derivatives this effect was even more striking. Using 1,2-bis(4′-iodobut-2′-ynyloxy)benzene, we obtained instead of **1b** as the only product, a mixture of **1b** and **2b** in the ratio of 2:1 with the total yield of 75%. We assume that these results reflect the increase in leaving group ability and steric hindrance associated with the substitution of bromine by iodine. In any case, the high yields of cyclization by the use of the latter, especially for the formation of **2c**, are rather remarkable.

1,2 - Bis(4′ - bromobut - 2′ - ynyloxymethyl)benzene, required for the synthesis of products **1d** and **2d**, was obtained according to Scheme 1 (pathway 'a') except that corresponding diol was prepared by the reaction of 1,2-bis(bromomethyl)benzene with propargyl alcohol and NaH in THF. Reaction of 1,2-bis(4′-bromobut-2′-ynyloxymethyl)benzene with $Na_2S{\cdot}9H_2O$ under high dilution gave the dipropargylic cycle **1d** with the yield of 80% (Scheme 1), whereas tetrapropargylic cycle **2d** was obtained by the base induced reaction of the corresponding bis-mesylate with bis-thioacetate (24% yield) according to Scheme 3. All the cyclic sulfides **1b–d** and **2 a–d** obtained[12] were oxidized by MCPBA to the corresponding sulfones.

For the compounds **2a** and **2b** we were able to grow single crystals (recrystallization from chloroform/hexane), so the molecular structure of both compounds

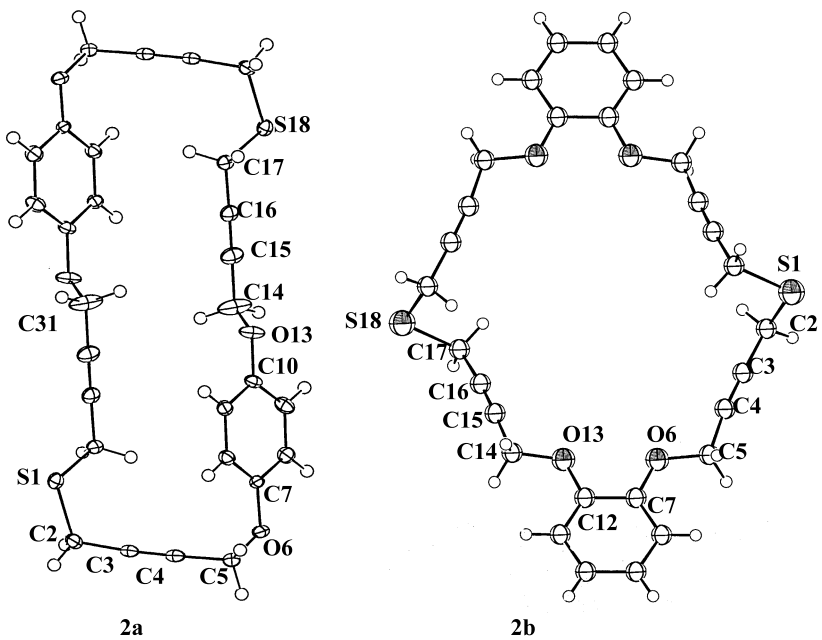


Figure 2. Crystal structure of compounds **2a** and **2b**. Selected bond lengths (Å) and angles (°): **2a**: S1–C2 1.82, C2–C3 1.46, C3–C4 1.19, C5–O6 1.44, O6–C7 1.38; C34–S1–C2 98.18, C3–C2–S1 112.13, C4–C3–C2 175.56, C3–C4–C5 178.36, C7–O6–C5 117.22, O6–C7–C12 124.73, O6–C7–C8 115.43, O6–C5–C4 112.95. **2b**: S1–C2 1.819, C2–C3 1.465, C3–C4 1.189, C4–C5 1.463, C5–O6 1.439, O6–C7 1.372; C17–S1–C2 98.66, C3–C2–S1 112.10, C4–C3–C2 177.3, C3–C4–C5 173.3, C7–O6–C5 115.22, O6–C7–C12 115.39, O6–C7–C8 125.0, O6–C5–C4 108.82.

was unambiguously elucidated by means of X-ray analysis (Fig. 2). In the case of tetrapropargylic cycle **2a** the structure contains two crystallographically independent molecules, each residing on a center of inversion. The two molecules differ slightly in their conformation at atoms C(14) and C(31), which represent the most flexible part of the molecular structure.

Reactivity of the above di- and tetrapropargylic sulfur bridged cycles under basic conditions is now under investigation and the results will be published soon.

Acknowledgements

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8. 2,6-Divinyl-1,4-dithiin (**3**): yellow–orange oil, yield 45% (column chromatography on silica gel with hexane as eluent); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.15 (1H, d, 10), 5.67 (1H, d, 17), 6.31 (1H, d, 0.5), 6.54 (1H, ddd, 0.5, 10, 17); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 115.19 (CH_2), 122.05 (CH), 133.07 (CH), 134.34 (C_q); MS-EI m/z 168 (M^+, 100), 153 (9.71), 141(8.2), 135 (24.9), 124 (22.74); HRMS calcd. for $C_8H_8S_2$ 168.006744; found 168.006321.
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12. All new compounds prepared gave satisfactory analytical and spectral data in accordance with their structures. Selected data are as follows: **2a**: mp 216°C (white crystals, from $CHCl_3$), yield 35% (flash chromatography, CH_2Cl_2/hexane 3:1); ^{1}H NMR (acetone-d_6, 300 MHz) δ 3.37 (4H, t, 2.2), 4.79 (4H, t, 2.2), 6.99 (4H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 18.24 (CH_2S), 56.19 (CH_2O), 78.71 and 82.65 (C≡C), 116.12 (CH_{arom}), 151.57 (C-*ipso*); MS-CI (NH_3) m/z 506 (MNH_4^+, 100), 489 (MH^+, 6.5), 374 (8), 212 (7), 161 (7.2); HRMS calcd for $C_{28}H_{24}O_4S_2$ 488.111603; found 488.111585. **1b**: mp 93–94°C (white crystals, from $CHCl_3$/hexane), yield 30%; ^{1}H NMR (acetone-d_6, 300 MHz) δ 3.39 (4H, t, 2.0), 4.91 (4H, t, 2.0), 7.01 (4H, m); ^{13}C NMR (acetone-d_6, 75 MHz) δ 21.17 (CH_2S), 57.55 (CH_2O), 77.68 and 84.40 (C≡C), 118.62 and 122.59 (CH_{arom}), 148.56 (C-*ipso*); MS-EI: m/z 244 (M^+, 100), 198.08 (27.10), 160.04 (25.61), 136.04 (51.45), 103.05 (35.31), 91.06 (86.02); HRMS for $C_{14}H_{12}O_2S$ calcd 244.055802; found 244.054000; **1d**: yield 80% (flash chromatography on silica gel, eluent CH_2Cl_2/hexane 2:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.61 (4H, t, 2), 4.29 (4H, t, 2), 4.75 (4H, s), 7.36 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.30 (**C**H_2S), 57.63 (O**C**H_2C≡), 68.07 (Ph**C**H_2), 80.24 and 81.94 (**C**≡**C**), 128.17 and 129.36 (CH_{arom}), 136.00 (C-*ipso*); MS-CI(CH_4): m/z 272.1 (M+, 6.76), 225.1 (10.09), 179.1 (18.10), 171.1 (59.29), 153 (17.08), 151 (21.01), 135 (21.28), 119.1 (48.40), 104 (81.52), 91 (100); HRMS calcd. for $C_{16}H_{16}O_2S$ 272.087102; found 272.086319.