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Design and Synthesis of Benzosultine-sulfone as a *o*-Xylylene Precursor via Cross-enyne Metathesis and Rongalite: Further Expansion to Polycyclics via Regioselective Diels−Alder Reaction

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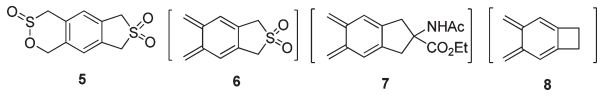
Received April 6, 2010



Benzosultine-sulfone **5** has been prepared as a *o*-xylylene or *o*-quinodimethane precursor by utilization of rongalite. Thermal activation of this hybrid molecule **5** has resulted a new sulfone-based building block **6**. Building block **5** is a suitable precursor for the synthesis of unsymmetrically functionalized polycyclics through Diels−Alder (DA) chemistry. The dibromosulfone **24** and benzosultine-sulfone **5** has also been used for the synthesis of various sulfone based unnatural α-amino acid (AAA) derivatives.

Transient intermediates related to *o*-quinodimethane (*o*-QDM) or *o*-xylylene[1] **1** have expanded the Diels−Alder (DA) strategy.[2] Diverse approaches toward the generation of **1** either by thermal (Figure 1) or photochemical means are available. To expand the DA strategy, we had reported a novel synthetic approach to various new *o*-xylylene (*o*-quinodimethane) intermediates such as **7**[3] and **8**.[4]

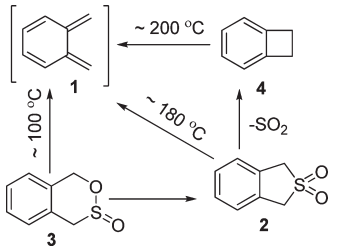


FIGURE 1. Approaches toward the generation of *o*-quinodimethane **1**.

Although the thermal ring opening of benzosulfone[5] **2**, benzosultine[6] **3**, and benzocyclobutene[7] **4** generates the *o*-xylylene **1**, benzosultine **3** opens up at relatively low temperature as compared with the other *o*-xylylene precursors such as **2** and **4**. Dittmer and co-workers had reported the synthesis of the sultine derivative (1,4-dihydro-2,3-benzoxathiin-3-oxide) **3** from *o*-xylylene dibromide in high yield under phase-transfer catalyst (PTC) conditions using rongalite. They had also demonstrated the generation of *o*-xylylene intermediate **1** at relatively low temperature.[8] Generally, sultine derivatives are prepared from the corresponding α,α′-dibromoxylenes via rongalite at low temperature, and the corresponding sulfones are prepared by heating the sultines in the absence of trapping agents in a sealed tube[9] or oxidation of corresponding sulfides.[10] On some occasions it was reported that the pyrolysis of benzosulfone derivatives gave benzocylcobutenes by extrusion of sulfur dioxide.[11] Rongalite (sodium hydroxymethanesulfinate or sodium formaldehyde sulfoxylate) is commercially available material used in the textile industry as a decolorizing agent, and it has also been used in organic synthesis.[12]

In view of our interest in designing polycyclics and unusual α-amino acid (AAA) derivatives via rongalite,[13] we

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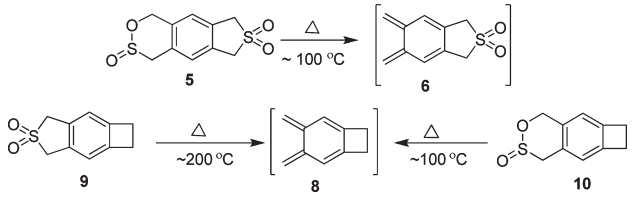
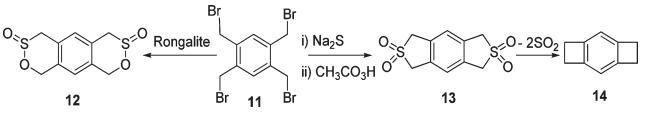
DOI: 10.1021/jo100655c Published on Web 05/24/2010

SCHEME 1. Strategies for New *o*-Xylylene Precursors



SCHEME 2. Symmetrical Bis(*o*-xylylene) Precursors

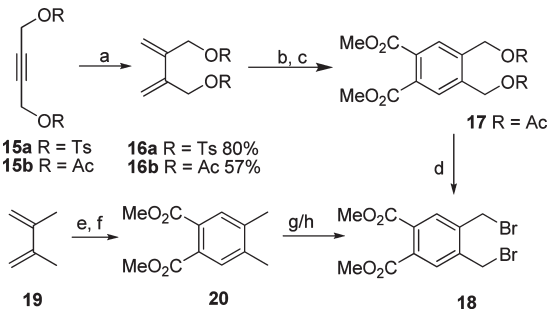


envisioned a hybrid molecule such as benzosultine-sulfone **5** as a useful building block for the synthesis of densely functionalized unsymmetrical polycycles. For example, by opening the sultine and sulfone portion of this hybrid molecule **5** in a stepwise manner at different temperatures and trapping the resulting *o*-xylylene intermediate with appropriate dienophiles, one can generate unsymmetrical polycyclics. It is worth mentioning that here the temperature of the reaction is used as regiocontrol element. In view of these interesting possibilities, *o*-xylylene derivatives **6** and **8** are worthwhile targets. Moreover, these building blocks are also useful to generate a library of sulfone and BCB derivatives respectively. In this regard, recently we have demonstrated that the transient intermediate **8** can be generated either from **9** or from **10**.[4] Herein, we report the synthesis of **5**, a potential precursor for sulfone containing *o*-xylylene moiety **6** (Scheme 1). It is interesting to note that various sulfone derivatives can be alkylated by carbanion chemistry, and then the resulting alkylated sulfones can undergo DA chemistry with appropriate dienophiles to generate complex polycyclics.

Chung and co-workers had reported the synthesis of benzodisultine **12** from the α,α′,α″,α‴-tetrabromo durene **11** via rongalite and explored its DA chemistry with various dienophiles.[14] Cava and co-workers had reported the synthesis of benzodisulfone **13** by the oxidation of corresponding disulfide by cold peracetic acid.[10] The benzodisulfone **13** on thermal extrusion of two molecules of sulfur dioxide gives the benzodicyclobutene **14**[11] (Scheme 2). Generally, thermal activation of the sultine **3** generates the *o*-QDM **1** at around 100 °C and sulfone **2** or cyclobutene **4** derivatives open up at higher temperature (180−200 °C). Subsequently, we realized that the *o*-xylylene intermediate generated from the sultine **3** can be trapped with dienophile containing an AAA moiety (e.g., methyl 2-acetamidoacrylate).

Toward the synthesis of intricate polycycles and unusual AAA derivatives, dibromo derivative **18** was identified as a key intermediate (Scheme 3) that can be assembled by the DA reaction of dimethyl acetylenedicarboxylate (DMAD) and 2,3-dimethylenebutane-1,4-ditosylate **16a**. The required diene **16a** was prepared by cross-enyne metathesis of but-2-yne-1,4-ditosylate[15] **15a** with Grubbs second generation catalyst in 80% yield. Unfortunately, the diene **16a** did not undergo DA reaction with DMAD under a

SCHEME 3. Preparation of Dimethyl 4,5-Bis(bromomethyl)-phthalate 18[a]



[a]Reagents and conditions: (a) Grubbs catalyst (5 mol %), ethylene, DCM, rt, 48 h; (b) DMAD, toluene, reflux, 24 h; (c) DDQ, benzene, reflux, 30 h or MnO_2, dioxane, reflux, 72 h, 90%; (d) 10 equiv 33% HBr in acetic acid, DCM, rt, 36 h, 46%; (e) DMAD, benzene, reflux, 24 h; (f) DDQ, benzene, reflux, 30 h or MnO_2, dioxane, reflux, 60 h, 75%; (g) NBS, benzoyl peroxide, CCl_4, reflux, 7 h, 25%; (h) NBS, benzoyl peroxide, DCE or α,α,α-trifluorotoluene (0.1 M), 12 h, 73%.

variety of reaction conditions (e.g., toluene, reflux; toluene, BF_3-etherate, 0 °C; toluene, hydroquinone, reflux; microwave irradiation). Then, we tried the DA reaction of the diene **16a** with various other dienophiles under different conditions, but none of the dienophiles gave the required DA adduct. Then, we speculated that the bulky tosylate group present in the diene **16a** may be responsible for the failure of the DA reaction. To address this issue, the hydroxyl groups present in but-2-yne-1,4-diol were protected as acetyl groups, and the cross-enyne metathesis of the resulting but-2-yne 1,4-diacetate **15b** by Grubbs first generation catalyst in DCM at rt gave the 2,3-dimethylene butane-1,4-diacetate **16b** in good yield.[16] Later, the DA reaction of **16b** with DMAD in toluene followed by aromatization with MnO_2 in dry dioxane gave the dimethyl 4,5-bis(acetoxymethyl) phthalate **17**. Next, the diacetate **17** was converted to dimethyl 4,5-bis(bromomethyl)phthalate **18** by treating it with 33% HBr in acetic acid at rt in DCM using the known protocol.[17] This reaction gave an acceptable yield in a small scale reaction; however, in large scale, poor yield of the desired product along with 4,5-bis(bromomethyl)phthalic acid as a side product was observed. Later, when the 4,5-bis(bromomethyl)phthalic acid was subjected to acid-catalyzed esterification, dimethyl 4,5-(methoxymethyl) phthalate was obtained.

Alternatively, the dibromo derivative **18** was also prepared by the DA reaction of 2,3-dimethyl butadiene **19** and DMAD in benzene followed by the aromatization of the resulting DA adduct with DDQ in benzene (or with MnO_2 in dry dioxane) to give the dimethyl 4,5-(dimethyl)phthalate **20**.[18] Next, benzylic bromination of **20** mediated by NBS in dry CCl_4 involving a radical mechanism gave the expected dimethyl 4,5-bis(bromomethyl)phthalate **18** in 25% yield.[19] Later, it was found that the bromination yield can be improved by using NBS and benzoyl peroxide as a radical

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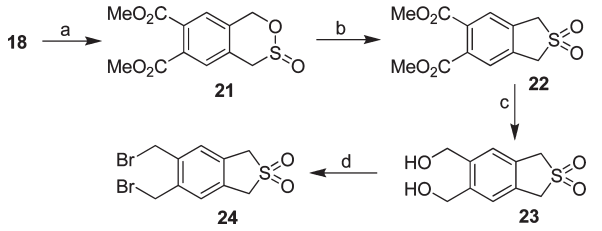
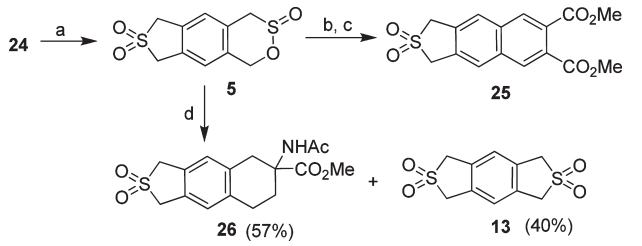
SCHEME 4. Preparation of Dibromosulfone 24[a]



[a]Reagents and conditions: (a) rongalite, TBAB, DMF, 0 °C to rt, 7 h, 65%; (b) toluene, 100 °C, 7 h, 75%; (c) LiCl, KBH_4, THF, reflux, 24 h, 77%; (d) PBr_3, benzene, 0 °C to rt, 12 h, 73%.

SCHEME 5. Preparation of Benezosultine-sulfone and Its Regioselective DA Reaction at the Sultine Terminus[a]



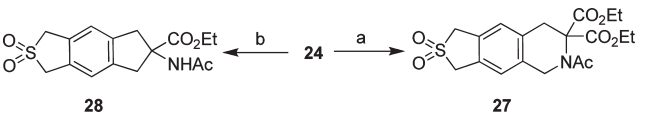
[a]Reagents and conditions: (a) rongalite, TBAB, DMF, 0 °C to rt, 7 h, 55%; (b) DMAD, toluene, reflux, 24 h; (c) MnO_2, dioxane, reflux, 72 h, 90%; (d) methyl 2-acetamidoacrylate, toluene, reflux, 24 h.

initiator in 1,2-dichloroethane (DCE) or α,α,α-trifluorotoluene (0.1 M solution) (Scheme 3).

When the compound **18** was treated with rongalite in the presence of PTC such as tetrabutylammonium bromide (TBAB) in DMF at 0 °C, the sultine derivative **21** was obtained in good yield. Later the compound **21** was converted to the sulfone derivative **22** by heating in toluene at 100 °C for 7 h. Based on Anderson's observation,[20] the reduction of diester containing sulfone **22** was achieved by using KBH_4, LiCl in refluxing THF to generate the corresponding diol **23** in good yield. The dihydroxysulfone **23** was then treated with phosphorus tribromide in benzene at 0 °C to deliver the dibromosulfone **24** in 73% yield (Scheme 4).

Next, the dibromide **24** was converted to the desired benzosultine-sulfone **5** by treatment with rongalite in presence of TBAB in DMF at 0 °C. Having prepared the key building block **5** in 55% yields, next we explored its utility by selective opening of sultine portion and reacting the resulting *o*-xylylene intermediate with DMAD and methyl 2-acetamidoacrylate to generate the corresponding sulfone-based building blocks. When the benzosultine-sulfone **5** was reacted with DMAD in refluxing toluene, the desired DA adduct was obtained in good yield, which was further aromatized with freshly activated MnO_2 in dry dioxane to obtain the sulfone-based diester **25** in 90% yield. Similarly, when the benzosultine-sulfone **5** was reacted with methyl 2-acetamidoacrylate in refluxing toluene, the desired tetraline-based AAA derivative **26** was obtained in a moderate yield (57%) along with rearranged benzodisulfone **13** (40%) as a side product. These sulfone derivatives **25** and **26** can be further utilized to design various polycyclics and unusual AAA derivatives (Scheme 5). Our initial attempts to open up the sulfone side were not successful. We are exploring alternate conditions in this direction.

SCHEME 6. Preparation of Sulfone-Based Unusual AAA Derivatives[a]



[a]Reagents and conditions: (a) diethyl acetamidomalonate, K_2CO_3, MeCN, 12 h, reflux, 62%; (b) (i) ethyl isocyanoacetate, K_2CO_3, TBAHS, MeCN, 20 h, reflux; (ii) 4−5 drops of conc HCl, EtOH, rt, 9 h; (iii) DMAP, acetic anhydride, DCM, rt, 24 h, 52% (overall yield).

Alternatively, the dibromosulfone **24** has also been used for the synthesis of sulfone-based AAA derivatives **27** and **28**.[3] When the dibromosulfone **24** was treated with diethyl acetamidomalonate[13g] in dry acetonitrile in presence of K_2CO_3 as a base, the sulfone based 1, 2, 3, 4-tetrahydroisoquinoline-3-carboxylic acid (Tic) derivative **27** was obtained in good yield. Similarly, treating the dibromosulfone **24** with ethyl isocyanoacetate[21] in dry acetonitrile in the the presence of base such as K_2CO_3, gave the coupling product, which on hydrolysis and protection using acetic anhydride in presence of DMAP gave the indane based AAA derivative **28**. Because some of the isocyanonitrile derivatives are unstable, its isolation and characterization was not attempted. The corresponding AAA derivative **28** was prepared. These sulfone derivatives **27** and **28** serve as advanced building blocks for further synthetic manipulation to design various unusual AAA derivatives (Scheme 6).

A new methodology has been devised for the synthesis of benzosultine-sulfone **5**, as a useful building block suitable for DA strategy. This hybrid molecule **5** contains two latent *o*-QDM intermediates of different reactivity. The selective DA reaction at sultine terminus has delivered the sulfone-based precursors, which may be suitable for the synthesis of various polycyclics and unusual AAA derivatives.

Experimental Section

Prepareation of Benzosultine-sulfone 5. To a suspension of rongalite (2.39 g, 15.5 mmol) in DMF (15 mL) were added TBAB (501 mg, 1.55 mmol) and 4,5-bis(bromomethyl)benzosulfone **24** (550 mg, 1.55 mmol) at 0 °C, and the stirring was continued for 4 h at 0 °C. Then, the reaction mixture was brought to rt, and the stirring was continued for an additional 4 h. After completion of the reaction (TLC monitoring), the reaction mixture was diluted with ethyl acetate and washed with water (3−4 times). The aqueous layer was again extracted with ethyl acetate and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure, and the product was purified by silica gel column chromatography. Elution of the column with 60% ethyl acetate−petroleum ether gave **5** as a white solid (203 mg, 51% yield). R_f = 0.26 (silica gel, 60% EtOAc−petroleum ether). Mp dec at 185−190 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (s, 1H), 7.22 (s, 1H), 5.30 (1/2 ABq, J = 14.0 Hz, 1H), 4.97 (1/2 ABq, J = 14.0 Hz, 1H), 4.38 (s, 4H), 4.35 (d, J = 15.6 Hz, 1H), 3.61 (d, J = 15.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.5, 132.0, 131.4, 127.8, 127.3, 123.6, 62.7, 56.73, 56.71, 56.4. IR (KBr, cm^{-1}): 2924, 2857, 1602, 1314, 1226, 1112, 726. HRMS (Q-Tof) m/z: $[M + Na]^+$ calcd for $C_{10}H_{10}S_2O_4Na$ 280.9918, found 280.9908

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Preparation of 6,7-Bis(carbomethoxy)-2,3-naphthalene-sulfone 25. To a solution of benezosultine-sulfone **5** (42 mg, 0.581 mmol) in toluene (15 mL), DMAD (124 mg, 0.827 mmol) was added under N_2 atmosphere, and the reaction mixture was refluxed for 36 h. After completion of the reaction (TLC monitoring), the reaction mixture was cooled, and the solvent was evaporated under reduced pressure. The crude DA adduct was directly aromatized without any further purification. This crude DA-adduct was dissolved in dry dioxane (25 mL) and treated with 70 equiv of MnO_2 (970 mg). Then the reaction mixture was refluxed for 72 h, and the reaction mixture was filtered through Buchner funnel and washed (2−3 times) with ethyl acetate. The combined organic layer was concentrated under reduced pressure, and the product was purified by silica gel column chromatography.

Elution of the column with 30% ethyl acetate−petroleum ether gave **25** (40 mg, 90% overall yield). R_f = 0.42 (silica gel, 60% EtOAc−petroleum ether). Mp 226−228 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 2H), 7.88 (s, 2H), 4.55 (s, 4H), 3.97 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 133.1, 132.2, 129.9, 129.7, 126.3, 56.5, 53.1. IR (KBr, cm^{-1}): 2956, 1720, 1458, 1317, 1290, 1126. HRMS (Q-Tof) m/z: $[M + Na]^+$ calcd for $C_{16}H_{14}SO_6Na$ 357.0408, found 357.0424

Preparation of Sulfone-Based Tetraline AAA Derivative 26. A solution of benzosultine-sulfone **5** (40 mg, 0.155 mmol) and methyl 2-acetamidoacrylate (33 mg, 0.233 mmol) in toluene (10 mL) was refluxed for 24 h. After completion of the reaction (TLC monitoring), the reaction mixture was brought to rt, and the solvent was removed under reduced pressure. The insoluble material was washed (2−3 times) with DCM. The DCM fraction was concentrated and charged on silica gel column chromatography. Elution of the column with 70% ethyl acetate−petroleum ether gave **26** as a white crystalline product (30 mg, 57% yield). R_f = 0.19 (silica gel, 70% EtOAc−petroleum ether). Mp 238−240 °C. The insoluble material was again washed with ethyl acetate to obtain the pure benzodisulfone **13** (16 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (s, 1H), 7.03 (s, 1H), 5.66 (s, 1H, NH), 4.33 and 4.29 (ABq, J = 16.0 Hz, 4H), 3.76 (s, 3H), 3.35 (1/2 ABq, J = 17.2 Hz, 1H), 3.03 (1/2 ABq, J = 17.2 Hz, 1H), 2.90−2.80 (m, 2H), 2.52−2.48 (m, 1H), 2.18−2.11 (m, 1H), 1.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 170.4, 136.0, 133.8, 129.6, 129.3, 127.0, 126.5, 57.8, 56.8, 52.9, 37.7, 28.5, 25.4, 23.3. IR (KBr, cm^{-1}): 3297, 2925, 1737, 1651, 1542, 1315, 1238, 1127. HRMS (Q-Tof) m/z: $[M + Na]^+$ calcd for $C_{16}H_{19}NSO_5Na$ 360.0881, found 360.0890.

Acknowledgment. We thank CSIR and DST, New Delhi for financial support and SAIF, Mumbai for recording the spectral data. A.C. thanks CSIR, New Delhi for award of the research fellowship.

Supporting Information Available: Detailed experimental procedures and characterization data with copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.