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A SHORT SYNTHETIC ROUTE TO A HYBRID MOLECULE BENZOSULTINE-SULFONE VIA [2+2+2] CYCLOTRIMERIZATION USING Mo(CO)$_6$†

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†This paper is dedicated to Professor Dr. Masakatsu Shibasaki on the occasion of his 70th birthday.

Abstract – Here, we report an improved and short synthetic route to benzosultine-sulfone via [2+2+2] cyclotrimerization as a key step, starting with dipropargyl ether and 1,4-dibromo-2-butyne with an overall yield of 16%.

The reactive intermediate *o*-quinodimethane (*o*-QDM), also called as *o*-xylylene (Figure 1, **1a-d**), has attracted much attention of both synthetic and theoretical chemists over the past fifty years.[1] *o*-QDMs have a remarkable reactivity in Diels–Alder (DA) reaction and are often used as key building blocks in the synthesis of polycycles by inter- or intramolecular [4+2] cycloaddition reactions (Scheme 1). To expand the DA reaction,[2] we were interested in generating various *o*-QDM intermediates with the help of sultine derivatives involving rongalite chemistry.[3]

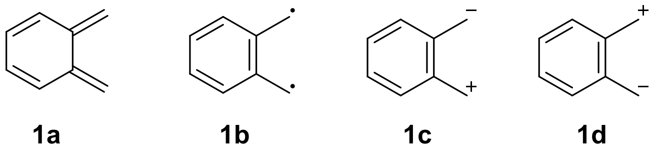
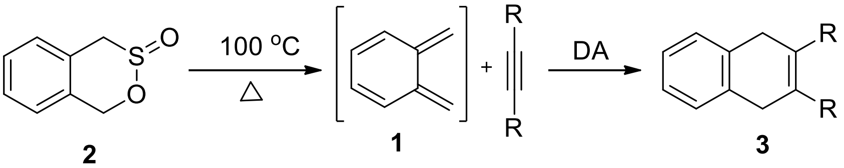
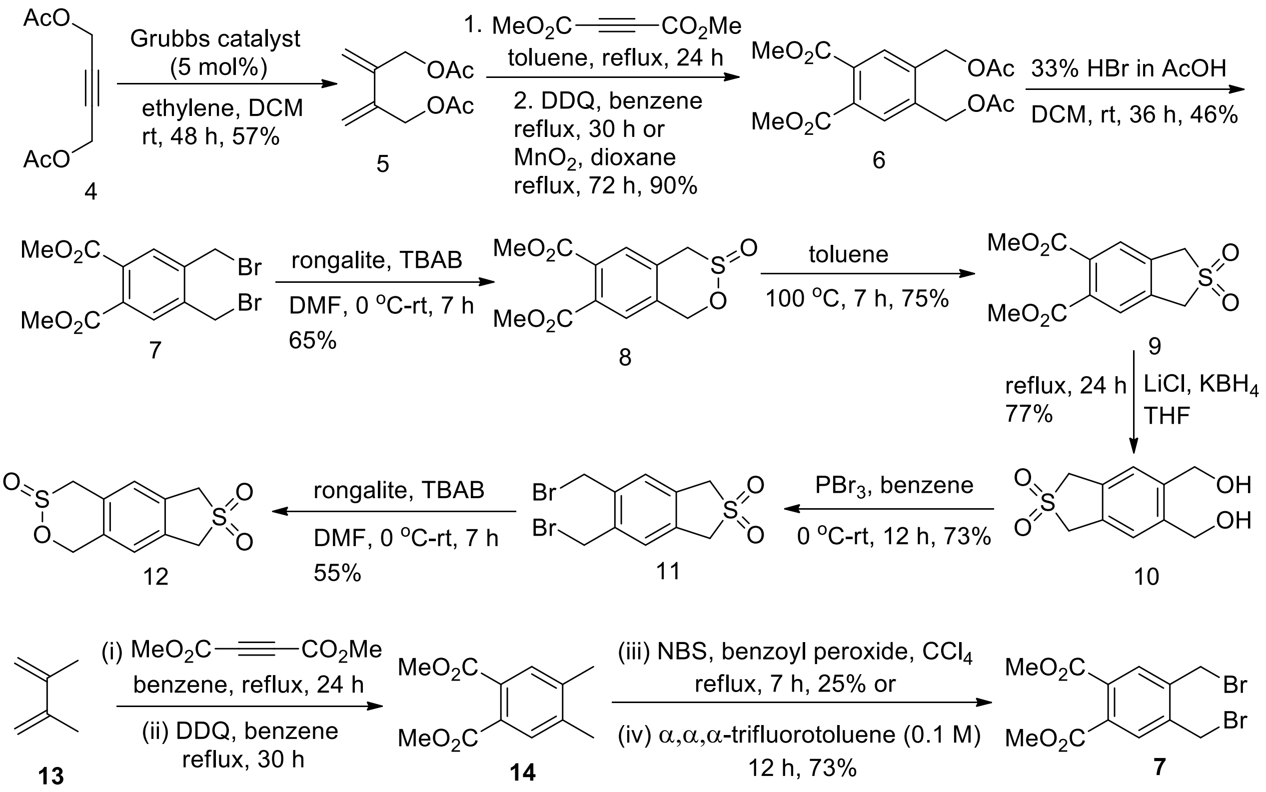


Figure 1. Different structures contributing to *o*-QDM



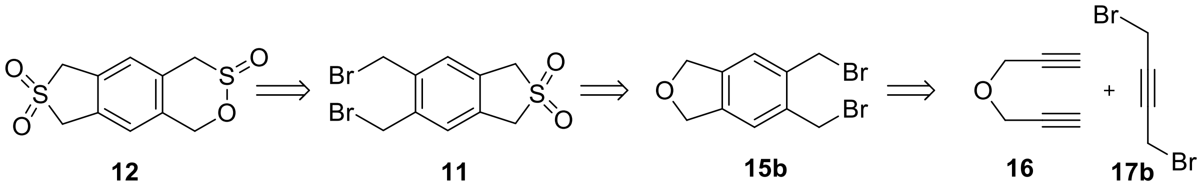
Scheme 1. Generation of *o*-quinodimethane from sultine followed by DA reaction

Recently, we reported a hybrid molecule benzosultine-sulfone,[4] which is a useful building block for the synthesis of functionalized polycycles. This hybrid molecule can participate in DA reaction in a stepwise manner by opening the sultine or the sulfone side at different temperatures and the corresponding *o*-xylylene intermediate can be trapped with different dienophiles. This approach delivers densely functionalized polycyclic compounds. We synthesized benzosultine-sulfone **12**, by using but-2-yne-1,4-diacetate **4** as starting material in eight steps and in another sequence, 2,3-dimethylbutadiene **13** and dimethyl acetylenedicarboxylate (DMAD) as starting materials in seven steps with an overall yield of 7% and 4% respectively (Scheme 2).



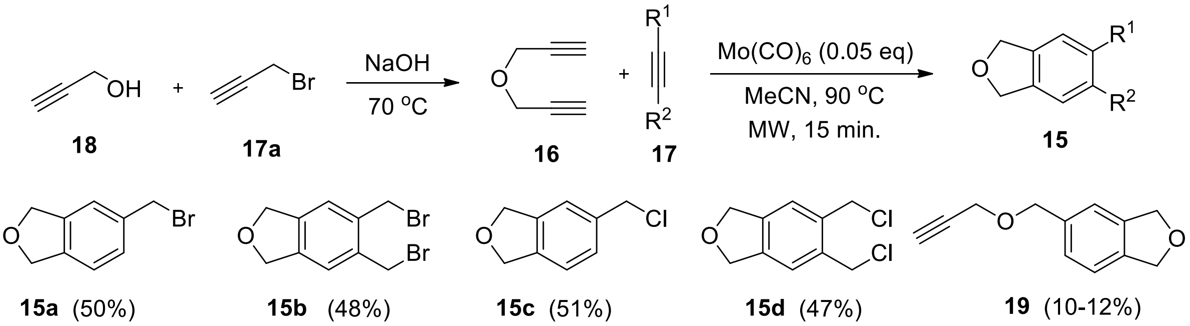
Scheme 2. Synthesis of benezosultine-sulfone via cross-enyne metathesis and DA reactions

Recently, we reported [2+2+2] co-trimerization[5a] of 1,6-diynes with propargyl halides using catalytic amount of molybdenum hexacarbonyl [$Mo(CO)_6$].[5b] Now, we realized that the benzosultine-sulfone **12** can be synthesized from the dibromo derivative **15b** which can be prepared from dipropargyl ether **16** via a [2+2+2] cycloaddition reaction using 1,4-dibromo-2-butyne **17b** as a co-trimerization partner in less number of steps (Scheme 3). To this end, we explored an alternate protocol involving [2+2+2] co-trimerization with the propargyl halides.



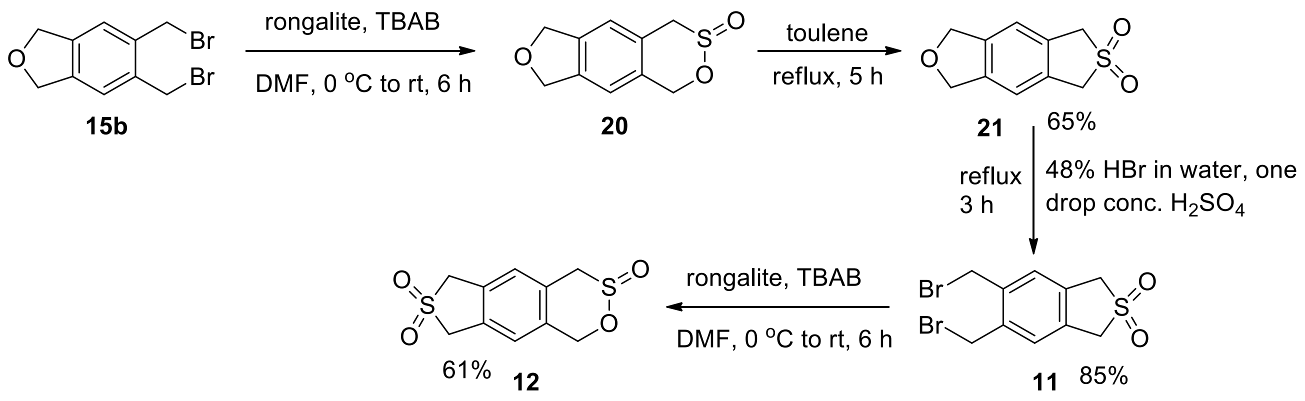
Scheme 3. Retrosynthetic analysis of benezosultine-sulfone

To synthesize 1,3-dihydrobenzofuran derivatives, dipropargyl ether **16** was prepared from propargyl alcohol **18** and propargyl bromide **17a** in the presence of NaOH at 70 ^{o}C.[6] Further, the diyne **16** was treated with proprgyl halides under microwave (MW) irradiation conditions using catalytic amount of Mo(CO)$_6$ to obtain the corresponding halo derivatives **15a-d** in moderate yields along with minor amount of self trimerized product **19**. Since, both the starting materials **18** and **17a** are readily available even 48% yield may be acceptable. We believe that the volatile nature of **16** may be responsible for low yield of **15**.



Scheme 4. Preperation of benzofuran derivatives via [2+2+2] co-trimerization

The dibromobenzofuran **15b** was further utilized towards the synthesis of benzosultine-sulfone **12** which was previously prepared in our laboratory via cross-enyne metathesis and DA reaction as key steps.[4] In this regard, Mo(CO)$_6$ and 1,4-dibromo-2-butyne **17b** with dipropargyl ether **16** gave dibromo derivative **15b**, which was converted into sultine derivative using rongalite. The sultine **20** generated was used for next step without any further purification and it was rearranged in refluxing toluene to give the corresponding sulfone derivative **21**. Later, we propose to cleave the ether linkage to generate the dibromosulfone **11**. Therefore, the sulfone **21** was treated with PBr$_3$ in dichloromethane at room temperature for 6 h. However, we did not realize any change in the starting material and it was recovered. So, we changed the reaction conditions and accordingly, the sulfone derivative **21** was treated with 48% HBr in water and a drop of conc. H$_2$SO$_4$ at reflux conditions for 3 h, to deliver the desired dibromosulfone **11** with good yield. Then, the dibromosulfone **11** was further converted to benzosultine-sulfone **12** in the presence of rongalite and TBAB under standard reaction conditions.[4]



Scheme 5. Synthesis of benzosultine-sulfone from 15b

In conclusion, we have shown that the [2+2+2] cyclotrimerization of propargyl halides with sensitive substrate such as dipropargyl ether **16** and the corresponding 1,3-dihydrobenzofuran derivatives **15a-d** were isolated in a reasonable yield along with the minor amount of self trimerized product **19**. We have also synthesized benzosultine-sulfone **12** in five steps with an overall yield of 16%.

EXPERIMENTAL

All reactions were performed under an argon or nitrogen atmosphere using well-dried reaction flask. All commercially available products were used as received without further purification. All the solvents used as reaction media were dried over predried molecular sieves (4 Å) in oven. Column chromatography was performed with silica gel (100-200 mesh) using mixture of petroleum ether and EtOAc as eluent. ^{1}H and ^{13}C NMR spectral data were recorded on 400 MHz and 100 MHz or 500 MHz and 125 MHz spectrometers using tetramethylsilane (TMS) as an internal standard and chloroform-*d* as a solvent. The high resolution mass spectroscopy (HRMS) was performed using Brucker (Maxis Impact) or Micromass Q-ToF spectrometer. The melting points recorded are uncorrected.

General procedure for [2+2+2] cyclotrimerization of propargyl halides with dipropargyl ether:

To the solution of dipropargyl ether **16** in dry MeCN taken in a microwave 10 mL tube, propargyl halide **17** (2 eqv.) and $Mo(CO)_6$ (5 mol%) were added and kept in microwave (CEM Discover Microwave) at 90 °C for 15 min. After completion of the reaction (TLC monitoring), the solvent was removed at reduced pressure and the crude product was purified by silica gel column chromatography (5% EtOAc-petroleum ether) gave the cyclotrimerization compound **15**.

Compound 15a: Brown denser liquid (yield = 50%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52 (s, 2H), 5.10 (s, 4H), 7.20 (d, J = 7.56 Hz, 1H) 7.27-7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.58, 73.45, 73.54, 121.50, 121.85, 128.46, 137.32, 139.79, 140.19; IR υ_{max} 621, 705, 823, 901, 964, 1047, 1215, 1319, 1365, 1435, 1492, 1766, 2531, 2851 cm^{-1}.

Compound 15b: White solid (yield = 48%); MP 141-143 ºC; ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.68 (s, 4H), 5.08 (s, 4H), 7.26 (s, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 30.23, 73.39, 123.86, 136.19, 140.04; IR υ_{max} 607, 740, 895, 959, 1032, 1068, 1176, 1197, 1218, 1309, 1490, 2528, 2867 cm^{-1}.

Compound 15c: Colourless liquid (yield = 51%); ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.60 (s, 2H), 5.10 (s, 4H), 7.21-7.30 (m, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 46.31, 73.48, 73.53, 121.42, 121.46, 128.05, 137.04, 139.75, 140.15; IR υ_{max} 676, 722, 825, 904, 1047, 1140, 1260, 1276, 1367, 1436, 1446, 1473, 1491, 2854, 2905 cm^{-1}.

Compound 15d: White solid (yield = 47%); MP 128-130 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.78 (s, 4H), 5.10 (s, 4H), 7.28 (s, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 43.44, 73.41, 123.52, 135.81, 128.05, 140.86; IR υ_{max} 683, 754, 894, 1034, 1067, 1176, 1258, 1270, 1371, 1473, 2856 cm^{-1}; HRMS (ESI, Q-ToF) *m/z*: calculated for $C_{10}H_{10}Cl_2KO$ [M+K]+ 254.9740, found: 254.9744.

Compound 19: The spectra of this compound matched with the literature report.[7]

Synthesis of sultine compound 20: To a solution of dibromide **15b** (200 mg, 0.65 mmol) and TBAB (105 mg, 0.33 mmol) in DMF (5 mL) was added rongalite (771 mg, 6.5 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 3 h and at rt for another 3 h. At the conclusion of the reaction (TLC monitoring), the aqueous layer was extracted with EtOAc and the organic layer was washed with water (4-5 times) to remove excess of DMF. The solvent was removed under reduced pressure and the crude product was used for next step without further purification.

Synthesis of sulfone compound 21: The solution of crude sultine compound **20** in toluene (3 mL) was refluxed for 6 h. After completion of the reaction (TLC monitoring), quenched with water and extracted with EtOAc. The solvent was removed under reduced pressure and dried under vacuum, crystalline solid was obtained. The NMR of the crude product was pure, hence used directly for next step. Colourless crystalline solid, yield = 65% (from two steps); MP 196-198 ºC; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.36 (s, 4H), 5.10 (s, 4H), 7.19 (s, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 56.98, 73.37, 119.02, 130.48, 140.44; IR υ_{max} 593, 902, 1039, 1097, 1134, 1162, 1220, 1311, 1364, 1395, 1442, 2857, 2920, 2983 cm^{-1}; HRMS (ESI, Q-ToF) *m/z*: calculated for $C_{10}H_{10}NaO_3S$ [M+Na]+ 233.0243, found: 233.0241.

Synthesis of dibromosulfone compound 11: To the sulfone **21** (50 mg, 0.24 mmol), 48% HBr in water, and a drop of conc. H_2SO_4 were added and refluxed for 3 h. After completion of the reaction (TLC monitoring), water was added and extracted with EtOAc. The solvent was removed under reduced pressure and the crude product was purified by by silica gel column chromatography (30% EtOAc-petroleum ether) to obtain the compound **11** (62 mg, 85% yield).

Synthesis of compound 12: Compound **12** was synthesized from compound **11** as reported in the literature.[4]

11 and 12: The spectra of these compounds matched with the literature reports.[4]

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