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A Mild Alternative to the Use of Benzyne in [4+2]-Cycloaddition Reactions

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Abstract: A synthetic protocol to assemble a benzene ring, mimicking the [4+2]-cycloaddition of benzyne is reported. The sequence of reactions is made up of simple and mild steps and overall it furnishes comparable or even better yields with respect to the direct addition of benzyne.

Benzyne is a well-known highly unstable intermediate which exhibits a wide range of reactivity including electrophilic attack,[1] dimerization and/or trimerization,[2] as well as [2+2]- and [4+2]-cycloadditions.[3] Although the reactivity of benzyne in Diels Alder cycloadditions is extraordinarily high,[2-4] it is often desirable to isolate its propensity in cycloaddition rections from other reactivity modes. Indeed, it is often difficult to obtain [4+2]-cycloadducts cleanly and in high yields, while more commonly addition to olefins results in the formation of a complex mixture of products, sometimes derived from carbonium ion rearrangement.[4] In addition, the reaction conditions employed for the generation of benzyne, such as the nature of the precursors, the requirement to use a strong base and its inherent hazard, play a crucial role in the synthetic practice, and today the generation of benzyne under mild conditions is an actual problem.[5]

Here, we report an alternative entry into the benzyne [4+2]-cycloadducts based on the cycloaddition of readily available 2-chloro-1,4-benzodithiin-*S*,*S*'-tetraoxide[6] and further manipulations of the adducts as schematically illustrated in Scheme 1. Although it appears that the synthetic sequence is composed of many steps, they are all straightforward affording high overall yields. Due to the simplicity of operations and to the low cost of reagents all the reactions can be performed on a multigram scale.

Scheme 1

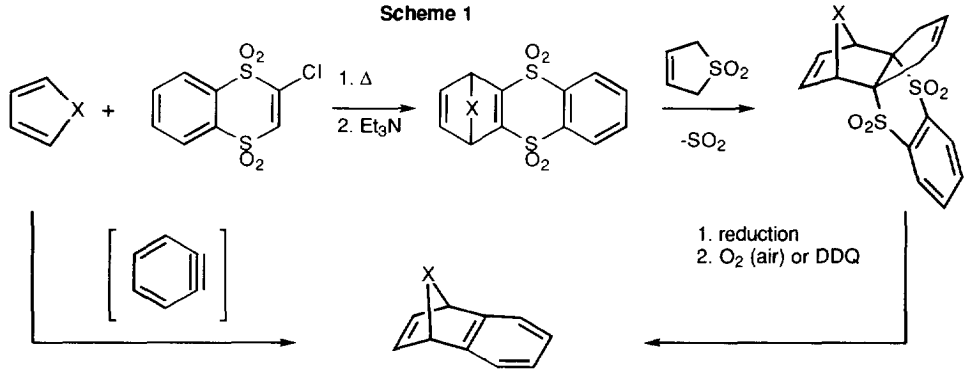
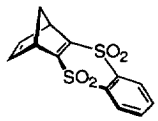
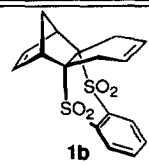
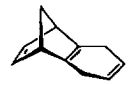
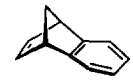
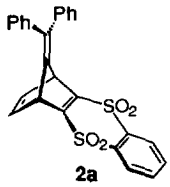
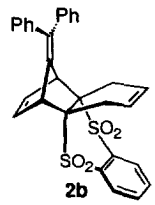
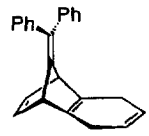
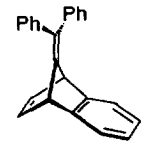
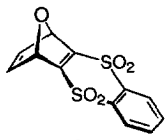
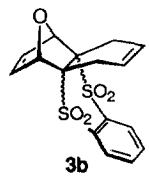
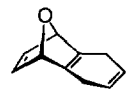
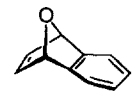
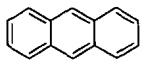
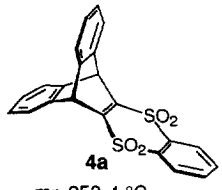
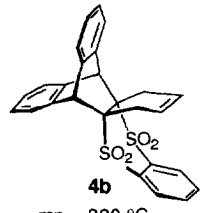
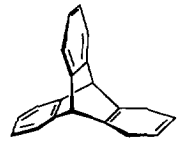
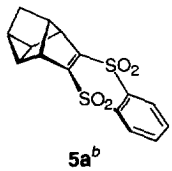
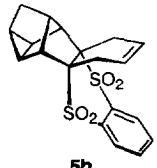
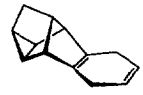
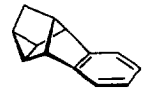
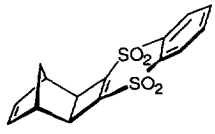
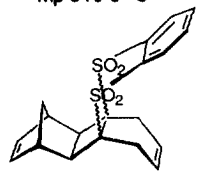
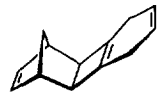
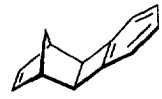


Table 1. Reagents and structures[a] of adducts.

 **1**	 **1a** mp 184-5 °C	 **1b** mp 247-9 °C	 **1c** oil	 **1d**[3]
 **2**	 **2a** mp 235-7 °C	 **2b** mp 205-7 °C	 **2c**	 **2d**[9]
 **3**	 **3a** mp 164-5 °C	 **3b** 1:1 mixture of isomers	 **3c**	 **3d**[3]
 **4**	 **4a** mp 253-4 °C	 **4b** mp > 320 °C	 **4c**	 **4d**[3]
 **5**	 **5a**[b] mp 237-8 °C	 **5b** mp 316-8 °C	 **5c** oil	 **5d**[10]
 **6**	 **6a**[b] mp 173-5 °C	 **6b** 17:2 mixture of isomers	 **6c** oil	 **6d**[10]

a) Determined by NMR spectroscopy.

b) Structure also confirmed by diffractometric analysis.[7,8]

As shown in Table 1, the early intermediates of the sequence are the crystalline compounds **1a-6a** which are obtained in very good overall yields by cycloaddition of the 2-chloro-1,4-benzodithiin-*S*,*S*'-tetraoxide with cyclopentadiene (**1**), diphenylfulvene (**2**), furan (**3**), anthracene (**4**), norbornadiene (**5**), and quadricyclane (**6**), followed by dehydrochlorination with triethylamine.[6] The reaction is usually carried out in one pot without purification of the primary adduct.

Compounds **1a-6a** were in turn reacted at 60 °C with 1,3-butadiene (generated *in situ* by retro-cheletropic reaction from 3-sulfolene) over 48-72 hrs to obtain bis-adducts **1b-6b** (48 to 94% yields).[6] All these compounds showed a high degree of crystallinity which simplified their purification. Their structure has been determined on the basis of NMR spectra including HETCOR (^{1}H and ^{13}C) experiments and NOE measurements. It is worth noting that a single product was obtained in many cases (only **3b** and **6b** were obtained as a mixture of isomers) and that polycyclic hydrocarbons possessing an activated C-C double bond able to react with dienes in a stereochemically controlled fashion are rare.

The reductive desulfonylation of the bis-adducts **1b-6b** has been readly accomplished using sodium amalgam in buffered (KH_2PO_4) methanol[11] or alternatively with SmI_2/HMPA system.[12] After standard work-up polycyclic hydrocarbons **1c-6c** were obtained in remarkable purity in 60 to 90% unoptimized yields. Compounds **1c**, **5c** and **6c** are sufficiently stable at rt and were fully characterised: only after a few days it is possible to observe the formation of the corresponding aromatic derivatives **1d, 5d** and **6d** derived from the spontaneous oxidation of the 1,4-cyclohexadiene ring. Compounds **2c**, **3c** and **4c** were obtained mixed with the corresponding aromatic derivatives **2d**, **3d**, and **4d**. The oxidation process is improved by treating a sample of either one of the cyclohexadienes **1c-6c** with a stoichiometric amount of dichlorodicyanoquinone (DDQ), a well-known oxidizing agent, at rt in chloroformic solution, for 24-48 hr. The reaction furnished **1d-6d** in quantitative yields. The reaction is usually carried out without purification of the desulfonylated adducts.

The utility of the present method of introduction of a benzene ring into a polycyclic structure becomes evident in the comparison of the yield of the direct cycloaddition of benzyne to quadricyclane or to diphenylfulvene (50% *vs* 90% and 19% *vs* 85% respectively overall for the full synthetic sequence). Also compound **5d**, whose trivial name is benzodeltacyclene, cannot be prepared in acceptable yields by direct cycloaddition of benzyne to norbornadiene (it gives mainly the [2+2] cycloadduct[10]) while in our case it could be obtained in 90% overall yield.

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EXPERIMENTAL SECTION

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian VXR 300 spectrometer operating at 300 and 75.4 MHz respectively, with tetramethylsilane as internal standard. NOE measurement were performed on a Varian Unity 400. IR spectra were performed in the range 4000-600 cm^{-1} on a Perkin Elmer 983 or on a Bruker FT-IR spectrophotometers. Microanalytical determinations were performed by a Perkin Elmer 2400 analyser. Known compounds used in this research were either purchased

from standard chemical suppliers or prepared according to literature procedures and purified to match the reported physical and spectral data.

General procedure for the reaction of adducts 1a-6a with 3-sulfolene. Reaction of 1a-6a with 3-sulfolene. A mixture of either **1a-6a** and 3-sulfolene into a 100 mL flask, equipped with condenser was stirred in a oil bath preheated at 60 °C. The reaction was monitored by TLC eluting with dichloromethane. After 24 hr the reaction was completed and the crude reaction mixture was purified by flash-chromatography eluting with gradient of dichloromethane-petrol ether and recrystallized from the indicated solvent.

1b. Starting from **1a** (5 g, 16.9 mmol) and 3-sulfolene (4.0 g, 34.0 mmol) the general procedure previously described was employed.
Colorless prisms (94% yield); mp 247-9 °C (CH_2Cl_2-Et_2O). ^1H NMR (300 MHz, $CDCl_3$), δ, ppm: 1.66 (1 H, dt, 1/2 AB system, J = 10.7, 1.9 Hz), 2.2 (1 H, d, 1/2 AB system, J = 10.7 Hz), 2.32 (2 H, d, 1/2 AB system, J = 16.7 Hz), 3.20 (2 H, t, J = 1.9 Hz), 3.40 (2 H, ddd, 1/2 AB system, J = 16.7, 5.0, 2.4 Hz), 5.65 (2 H, t, J = 1.9 Hz), 6.16-6.26 (2 H, m), 7.69-7.78, 7.98-8.05 (4 H, series of m, Ar). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ, ppm: 29.74, 46.10, 55.70, 78.68, 125.35, 125.93, 133.52, 136.85, 139.50; *Elem. anal.*, found % (calcd for $C_{17}H_{16}O_4S_2$): C, 58.42 (58.60); H, 4.55 (4.63).

2b. Starting from **2a** (2 g, 4.36 mmol) and 3-sulfolene (1.0 g, 8.7 mmol) the general procedure previously described was employed.
Colorless prisms (95% yield); mixture of isomers in 3:1 ratio. ^1H NMR (300 MHz, $CDCl_3$), δ ppm: 3.90-4.27 (8 H, m, 2 isomer), 4.66 (2 H, dd, J = 1.8, 1.5 Hz, minor isomer), 5.05 (2 H, t, J = 2.0 Hz, major isomer), 5.86-6.08 (2 H, m, major isomer), 6.50-6.65 (2 H, m, minor isomer), 6.90-7.45, 7.70-8.25 (32 H, series of m, 2 isomer, 28 Ar and 4 vinylic). ^{13}C NMR (75.4 MHz, $CDCl_3$, mixture of isomers in 3:1 ratio, 2 C atoms omitted), δ, ppm: 47.76, 48.66, 65.46, 66.50, 73.23, 74.50, 77.11, 124.70, 125.48, 125.54, 125.62, 125.89, 126.75, 127.00, 127.18, 127.26, 127.51, 127.64, 127.73, 120.00 (2C), 128.12, 128.22, 128.59, 128.70, 128.83, 128.92, 129.00, 129.30, 129.75, 133.49, 133.56, 133.76 (2C), 133.84 (2C), 134.26, 134.52, 136.68, 137.40, 137.68, 137.87, 137.91, 138.29, 138.32 (2C), 138.67, 138.88, 138.97, 139.33, 140.62, 140.69 (2C), 141.45, 142.81, 143.26, 153.59, 159.24. *Elem. anal.*, found % (calcd for $C_{30}H_{24}O_4S_2$): C, 69.95 (70.29); H, 4.80 (4.72).

3b. Starting from **3a** (2 g, 4.36 mmol) and 3-sulfolene (1.0 g, 8.7 mmol) the general procedure previously described was employed.
Colorless powder (48% yield); mixture of isomers in 1:1 ratio. ^1H NMR (300 MHz, $CDCl_3$), δ, ppm: 8.40-8.00, 7.90-7.70 (8 H, series of m, Ar, 2 isomers), 7.70-6.45 (8 H, series of m, vinylic, 2 isomers), 5.60 (2 H, bs, 1 isomer), 5.40 (2 H, bs, 1 isomer), 4.13-4.05 (4 H, m), 3.50-3.30 (4 H, m). *Elem. anal.*, found % (calcd for $C_{14}H_{14}O_5S_2$): C, 54.59 (54.84); H, 4.23 (4.03).

4b. Starting from **4a** (4 g, 9.8 mmol) and 3-sulfolene (2.3 g, 19.7 mmol) the general procedure previously described was employed.
Colorless prisms (94% yield): mp>320 °C (CH_2Cl_2-Et_2O). ^1H NMR (300 MHz, $CDCl_3$), δ, ppm: 3.14 -3.18 (2 H, m), 3 .20-3.24 (2 H, m), 4.83 (2 H, s), 6.00 (2 H, t, J = 2.7 Hz), 6.60-6.80, 7.03-7.10, 7.18-7.24, 7.32-

7.44, 7.68-7.76 (12 H, series of m, Ar). *Elem. anal.*, found % (calcd for $C_{26}H_{22}O_4S_2$): C, 67.51 (67.80); H, 4.79 (4.91).

5b. Starting from **5a** (3 g, 9.4 mmol) and 3-sulfolene (2.21 g, 18.7 mmol) the general procedure previously described was employed.
Colorless needles (96% yield): mp 316-8 °C (CH_2Cl_2-Et_2O). ^1H NMR (300 MHz, $CDCl_3$), δ , ppm: 0.62 (2 H, dd, J = 5.1, 1.0 Hz), 1.33 (1 H, dt, J = 5.1, 1.2 Hz),1.46 (2 H, t, J = 1.2 Hz), 2.15 (2 H, d, J = 16.2 Hz), 2.45 (3 H, m), 3.26 (2 H, ddd, J = 16.2, 4.2, 2.7 Hz), 6.17 (2 H, m), 7.75-7.81, 8.13-8.20 (4 H, series of m, Ar). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ, ppm: 29.41, 29.61, 39.04, 48.24, 50.86, 53.05, 84.09, 123.59, 133.30, 140.98, 141.15. *Elem. anal.*, found % (calcd for $C_{19}H_{18}O_4S_2$): C, 60.70 (60.94); H, 4.81 (4.85).

6b. Starting from **6a** (3.5 g, 9.24 mmol) and 3-sulfolene (2.58 g, 18.5 mmol) the general procedure previously described was employed.
Colorless needles (95% yield): mixture of isomers in 17:2 ratio. ^1H NMR (300 MHz, $CDCl_3$), δ, ppm: 0.80 (1 H, d, J = 11.1 Hz, minor isomer), 0.95 (1 H, d, J = 11.1 Hz, major isomer), 1.56 (2 H, d, J = 11.1 Hz, 2 isomer), 1.77 (1 H, s, minor isomer), 1.81 (1 H, s, major isomer), 2.72-2.86 (4 H, m, major isomer), 3.00-3.12 (4 H, m, minor isomer), 3.36 (2 H, s, minor isomer), 3.39 (2 H, s, major isomer), 6.01 (2 H, s, major isomer), 6.08 (2 H, s, minor isomer), 6.10-6.20 (2 H, m, major isomer), 6.22-6.35 (2 H, m, minor isomer), 7.76-7.86 (4 H, Ar, 2 isomer), 8.00-8.08 (2 H, Ar, minor isomer), 8.10-8.17 (2 H, Ar, major isomer). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ, ppm: 30.60, 44.16, 44.17, 47.66, 68.86, 126.61, 126.84, 133.72, 138.07, 140.13. *Elem. anal.*, found % (calcd for $C_{19}H_{18}O_4S_2$): C, 60.72 (60.94); H, 4.89 (4.85).

Reductive Desulfonylation of Adducts 1b-6b with Sodium Amalgam in KH_2PO_4/MeOH. Synthesis of 1c-6c. The preparation of **5c** is representative. A mixture of the **5b** (3 g, 8.01 mmol), KH_2PO_4 (1 g, 8.4 mmol) in dry methanol (25 mL) was purged with argon. Under an efficient stirring, sodium amalgam was added in portions (6% *ca.* an 8:1 equivalent ratio sodium to substrate). The reaction mixture was kept stirring at room temperature and monitored by TLC eluting with *n*-hexane. After ca. 12 h. the conversion was complete. Water was added and the reaction mixture was extracted with *n*-pentane (3 x 50 mL). The combined extracts were washed with brine, dried over sodium sulfate and concentrated under reduced pressure furnishing 1.2 g (94% yield) of a colorless oil. The procedure above described was successfully employed for the preparation of **1c-6c**. Compounds **2c** (80% yield), **3c** (60% yield), **4c** (90% yield), were obtained as a mixture with **2d, 3d,** and **4d** respectively and were directly used in the next step without further purifications.
Alternatively, the desulfonylation with SmI_2/HMPA system was succesfull employed.[12]

1c. Colorless oil (93% yield): ^1H NMR (300 MHz, $CDCl_3$), δ, ppm: 1.93 (1 H, dt, J = 6.0 and 3.0 Hz), 1.98 (1 H, dt, J = 6.0 and 3.0 Hz), 2.52-2.70 (2 H, m), 2.85-3.05 (2 H, m), 3.29 (2 H, m), 5.65 (2 H, m), 6.78 (2 H, t, J = 1.8 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ, ppm: 27.51 (t), 52.17 (d), 71.35 (t), 124.78 (d) , 142.54, (d) 144.02 (s).

5c. Colorless oil (94% yield): ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 1.26-1.37 (2 H, m), 2.44 (4 H, bs), 2.53-2.67 (4 H, m), 5.76 (2 H, s), 6.01 (2 H, t, J = 3.0 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$), δ, ppm: 24.43 (t), 38.29 (d), 40.56 (t), 47.54 (d), 125.31 (d), 135.91 (d), 141.58 (s).

6c. Colorless oil (94% yield): ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 1.23-1.27 (2 H, m), 1.44 (2 H, t, J = 1.5 Hz), 1.61 (1 H, m), 1.85 (1 H, s), 2.36 (2 H, bs), 2.62-2.86 (4 H, m), 5.67 (2 H, s). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ, ppm: 22.56 (d), 24.86 (d), 26.52 (t), 32.31 (t), 50.94 (d), 55.04 (d), 125.21 (d), 136.80 (s).

Oxidation of 1c-6c with DDQ. Preparation of 1d-6d. The synthesis of **6d** is representative. A mixture of either **6c** (2 g, 11.74 mmol), DDQ (2.66 g,11.74 mmol) and chloroform (20 mL) was stirred at r.t. After 48 hr the conversion was complete (TLC) and the crude reaction mixture was concentrated and purified by filtration on a short silica gel column eluting with dichloromethane, furnishing quantitatively **6d**. The same methodology was used for the quantitative preparation of **1a-6d** which were recognized by comparison of their spectral data with those reported in the literature.[3,9,10]

REFERENCES

1. For a review of benzyne chemistry: Hart, H. in *The Chemistry of Triple Bonded Functional Group* Supplement C2, ed. S. Patai, Wiley, Chichester, 1994, ch. 18; Gilchrist, T. L. in *The Chemistry of Functional Groups* Supplement C ed. S. Patai, Wiley, Chichester, 1983, ch. 11; Huisgen, R.; Sauer, J. *Angew. Chem.* **1960**, *72*, 91; Simmons, H. E. *J. Org. Chem.* **1960**, *25*, 691; Roberts, J. D.; Semenow, D. A.; Simmons, H. E.; Carlsmith, L. A. *J. Am. Chem. Soc.* **1956**, *78*, 601 and references cited herewith.
2. Wittig, G.; Pohmer, L. *Chem. Ber.* **1956**, *89*, 1334.
3. For a review of benzynes as dienophiles: Hoffmann, R. W. in *Dehydrobenzene and Cycloalkynes* pp. 200-239, Academic Press, New York, 1967.
4. Wittig, G.; Niethammer, K. *Chem. Ber.* **1960**, *93*, 944; Wittig, G.; Behnisch, W. *ibid.* **1958**, *91*, 2358; Wittig, G.; Knauss, E. *ibid.* **1958**, *91*, 893; Wittig, G.; Ludwig, R. *Angew. Chem.* **1956**, *68*, 40.
5. Buxton, P. C.; Fensome, M.; Heaney, H., Mason, K. G. *Tetrahedron* **1995**, *51*, 2959; Kitamura, T.; Yamane, M. *J. Chem. Soc., Chem. Commun.* **1995**, 983 and references cited herewith.
6. Cossu, S.; De Lucchi, O. *J. Chem. Soc., Chem. Commun.* **1992**, 1089.
7. Peters, K.; Peters, E.-M.; Cossu, S.; De Lucchi, O. *Zeit. Krist.* **1996**, *211*, 431.
8. Peters, K.; Peters, E.-M.; Cossu, S.; De Lucchi, O. *Zeit. Krist.* **1996**, *211*, 429.
9. Adam, W.; Lucchini, V.; Peters, E.-M.; Peters, K.; Pasquato, L.; von Schnering, H.; Seguchi, K.; Walter, H.; Will, B. *Chem. Ber.* **1989**, *122*, 133.
10. Simmons, H. E. *J. Am. Chem. Soc.* **1961**, *83*, 1657.
11. De Lucchi, O.; Lucchini, V.; Pasquato, L.; Modena, G. *J. Org. Chem.* **1984**, *49*, 596.
12. Künzer, H.; Stahnke, M.; Sauer, G.; Wiechert, R. *Tetrahedron Lett.* **1991**, *32*, 1949.

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