Double Elimination Protocol for Synthesis of 5,6,11,12-Tetradehydrodibenzo[a,e]cyclooctene

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Abstract: A new method for constructing 5,6,11,12-tetradehydrodibenzo[a,e]-cyclooctene is described on the basis of one-pot double elimination protocol. The target molecule, which is the smallest cyclophane with alternate arylene–ethynylene linkage, is synthesized in 61% yield through oxidative dimerization of ortho-(phenylsulfonylmethyl)benzaldehyde. The initial carbon–carbon bond formation between sp³ carbons followed by stepwise conversion to sp² and finally sp carbons bypasses the difficulty encountered in direct coupling of the sp carbon in the terminal acetylene. The mechanism of this process is discussed. The Wittig–Horner-type coupling is a key reaction employed for the carbon–carbon bond formation. Generation of (E)-vinylsulfone moiety in the first coupling between α-sulfonyl anion and aldehyde functions is crucial for the effective second coupling to complete the cyclization. The syn-elimination of the (E)-vinylsulfone moieties in the cyclized intermediate furnishes the acetylenic bonds.

Keywords: alkynes · C–C coupling · cyclization · elimination · sulfones

Introduction

5,6,11,12-Tetradehydrodibenzo[a,e]cyclooctene (1) is the smallest cyclophane with alternate arylene–ethynylene linkage. As expected, this compound was found to possess highly bent acetylenic bonds (155.7°) on the basis of X-ray analysis.[1] Quite naturally, such acetylenic bonds are highly reactive. They work as a dienophile in Diels–Alder reaction[2] and also undergo cyclopropanation upon treatment with diazoalkanes.[3] In addition, reactions with Pt⁰ complex and orthobis(dimethylsilylethynyl)benzene afforded platinacycloprenes and benzodisilahexene rings, respectively.[4] The synthesis of 1 was first achieved by Sondheimer et al.[5] Bromination of sym-dibenzocyclooctatetraene under irradiation (≈75% yield) followed by dehydrobromination of the resulting tetrabromide with tBuOK (48% yield) furnished 1. Besides a relatively low overall yield (36%) of this process, two procedures for preparing sym-dibenzocyclooctatetraene with recourse to Wittig[6] and Knoevenagel[7] condensations were reported to result in less than 20% yield starting from orthophthalaldehyde. As such, the Sondheimer process is not efficient.[8] More recently, Youngs et al. invoked Sonogashira coupling to dimerize an ortho-ethynyl iodobenzene derivative with bulky substituents at ortho-positions, yet only a 10% yield of the desired cyclophane was obtained.[9] The low yield was ascribed to the highly reactive acetylenic bonds of the product under the reaction conditions. It is apparent, therefore, that the direct C–C bond formation at terminal acetylenes is not easy to generate cyclic acetylenes on account of the propensity of the sp carbon to adopt the linear disposition. Such drawback is particularly conspicuous with small rings such as 1.[10]

In earlier works we presented the double elimination methodology for creating an acetylenic bond (Scheme 1).[11, 12] Aldolates resulting from treatment of α-sulfonyl carbanions with aldehyde are transformed to β-substituted sulfones which, then, undergo double elimination to give acetylenes.[11] Notably, a sequence of these reactions can be integrated into one pot, thus establishing an extremely convenient process.[12] In this pathway, the initial carbon–carbon bond is formed between sp³ carbons and the successive eliminations follow giving rise to sp² and finally sp carbons in a stepwise manner. Accordingly, it is reasonable to assume that involvement of
bent sp³ or sp² carbons allows this protocol to construct arylene–ethylenylene cyclophane skeletons more easily than the terminal acetylene coupling modes. We report herein that this is indeed the case through efficient synthesis of 1.

**Results and Discussion**

Our procedure is quite simple [Scheme 2, Eq. (1)]. A mixture of ortho-(phenylsulfonylmethyl)benzaldehyde (2) and (EtO)₂P(O)Cl was treated with LiHMDS at –78 °C to afford 1 in 61 % yield. Notably, all operations were performed in one pot. Also, the selection of the above combination of bases turned out to be rather crucial. The starting material 2 could be readily obtained from commercially available tolunitrile (see Experimental Section).

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Scheme 2. i) ClP(O)(OEt)₂, LiHMDS, THF, –78 °C → RT, 2 h; ii) LDA, –78 °C, 2 h.
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A plausible reaction pathway is shown in Scheme 3. Initially, 2 undergoes phosphonation and subsequent intermolecular Wittig–Horner reaction to afford mono(vinylsulfonyl) intermediate 3 that probably consists of (E)- and (Z)-isomers. Only the (E)-isomer can undergo the second intramolecular Wittig–Horner reaction to arrive at bis(vinylsulfone) 4 while the (Z)-counterpart presumably oligomerizes as a result of intermolecular condensations. In fact, when the reaction was quenched before addition of LDA, 4 was isolated in 65 % yield after column chromatography [Scheme 2, Eq. (2)]. TLC monitoring of the reaction exhibited highly polar material presumably due to the oligomers derived from (Z)-3. X-ray diffraction study confirmed the (E,E)-structure for 4 (Figure 1). Apparently, the E-geometry of 3 is crucial for arriving at 4 so that the second formyl and sulfonylmethyl groups could get close to each other whereas no effective interaction between these two groups are feasible with Z-geometry. The failure of all attempts to isolate 3 suggests that this intermediate was consumed as soon as it had been generated. Obviously, the rigid E-geometry is responsible for the acceleration of the second Wittig–Horner reaction.

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Scheme 3. Possible reaction pathway.
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Actually, when benzoyl chloride derivatives were employed in place of (EtO)₂P(O)Cl, monoaldolates 5 were obtained in reasonable yields (Scheme 5). However, treatment of 5a with LiHMDS (3 equiv) or LDA (3 equiv) in the presence of (EtO)₂P(O)Cl furnished 4 only in 21 or 25 % yield. Apparently, the flexible conformation resulting from the sp³–sp³ carbon bond in 5 disfavors the intramolecular aldol-type reaction. Thus, the double bond formation by Wittig–Horner

![Figure 1. ORTEP drawing of (E,E)-4.](image)

![Scheme 4. Possible aldol-reaction-type pathway.](image)
condensation prior to the second carbon–carbon bond formation is crucial for the effective cyclization.

The generation of (E,E)-4 can be accounted for on the basis of the equilibration as shown in Scheme 6. The intermediate 3 is converted to 6 through consecutive lithiation, phosphona-
tion, and a second lithiation. The anion 6 undergoes intra-
molecular carbon–carbon bond formation to give 7. The diastereomer 7a is readily transformed to (E,E)-4 through syn-elimination via a four-membered intermediate while the analogous elimination is not allowed for 7b due to the conformational rigidity arising from the pre-existing (E)-sulfonyl alkene linkage. Since 7a and 7b are involved in an equilibrium via 6 due to the well-recognized fluttering of α-
sulfonylbenzylanion[15] as well as rotation of the aryl–formyl bond, the equilibrium is biased in favor of 7a.

The elimination of 4, upon treatment with LDA (4 equiv), proceeded completely to give 1 even at −78 °C (Scheme 7). Such facile reaction has never been encountered since the elimination of vinyl sulfones usually demands higher reaction temperatures (rt → 60 °C) and the yield is not as high as in the present case.[11] Furthermore, the progress of the reaction itself is counter-intuitive in terms of the increase in the ring strain as the elimination advances. The uphill variation is apparent from the heats of formation calculated by PM3[16] for relevant species (Figure 2).[17] Hence, the high reactivity should be accounted for on the kinetic ground. Probably, the facile syn-elimination[18] as depicted in Scheme 7 is responsible. It should be noted that the difference of the heat of formation (ΔΔHf) is larger in the first elimination than in the second one (Figure 2).[19] This is in accord with experimental results that no mono(vinylsul-
fone) species was detected even by use of lesser amounts of LDA indicating much faster second elimination than the first one.

In conclusion, the concise, high-yielding process for 1 has been established according to the reaction pathway given in Scheme 3. It is reasonable to assume that the initial Wittig–Horner reaction provides mono-
(sulfone) intermediate 3 that is composed of (E)- and (Z)-isomers in about 60:40 to 70:30 ratio.[14] Of these two isomers, only the (E)-isomer is capable of undergoing cyclization to furnish 4. Provided that the second Wittig–Horner re-
actions proceeded quantitative-
ly, then the isolated yield of 4 (65 %) in Equation (2) is understand-
able. As it has been dis-
closed that the final elimination took place completely (Scheme 7), the yield in the one-pot process [61% in Scheme 1, Eq. (1)] is recognized as being reminiscent of the yields of the respective steps.

Now, we are in a position to obtain enough amount of I and thus synthetic utilization of this compound is undertaken in our laboratories.

Experimental Section

General: All reactions were carried out under an atmosphere of nitrogen with freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. A THF solution of LiHMDS was purchased from Aldrich and used without titration. A hexane solution of BuLi was purchased from Aldrich and titrated before use by Gilman method.25 A THF/hexane solution of LDA was prepared from disopropylamine and a hexane solution of BuLi. Silica gel (Daisy gel IR-60) was used for column chromatography. NMR spectra were recorded at 25 °C on Varian Gemini-300, JEOL Lambda 300 and JEOL Lambda 500 instruments and calibrated with tetramethylsilane (TMS) as an internal reference. Mass spectra were recorded on JEOL MSStation JMS-700 Shimadzu/Kratos MALDI 4 and Platform II single quadrupole (Micro-mass, Altrincham, UK) mass spectrometers. Elemental analyses were performed by the Perkin–Elmer PE2400.

Synthesis of 5a: A 100 mL flask was charged with (256 mg, 82%, 7:3 anti/syn stereoisomer), and LiHMDS (1.0 mmol in THF, 2.0 mL, 2.0 mmol) was added at −78 °C. After the mixture had been stirred at −78 °C for 30 min and, then, at room temperature for 1.5 h, the reaction mixture was poured into aqueous NH4Cl. The solvent was evaporated in vacuo, and the residue was purified by chromatography (CH2Cl2/hexane 2:3) to give I (61 mg, 61%) as a yellow solid.1 H NMR (300 MHz, CDCl3); δ = 6.71−6.77 (m, 4H), 6.90−6.96 (m, 4H); 13C NMR (75 MHz, CDCl3); δ = 109.28, 126.68, 129.01, 132.83.

Synthesis of 4: A 100 mL flask was charged with (260 mg, 1.0 mmol), CIP(O)(OEt)2 (0.17 mL, 1.2 mmol) and THF (30 mL), and LiHMDS (1.0 mmol in THF, 2.0 mL, 2.0 mmol) was added at −78 °C. After the mixture had been stirred at −78 °C for 30 min and, then, at room temperature for 1.5 h, the reaction mixture was poured into aqueous NH4Cl. The residue was purified by chromatography (AcOEt/hexane 3:7) to give 4 (157 mg, 65%) as a pale yellow foam.1 H NMR (300 MHz, CDCl3); δ = 6.97−6.99 (m, 2H), 7.22−7.30 (m, 4H), 7.36−7.50 (m, 12H), 7.61−7.66 (m, 2H); 13C NMR (75 MHz, CDCl3); δ = 126.69, 128.03, 128.28, 128.82, 129.92, 130.56, 133.83, 135.55, 138.79, 144.64; elemental analysis calcd (%) for C28H20O4S2: C 69.40, H 4.16; found: C 69.22, H 4.14.

Synthesis of 5a: A 100 mL flask was charged with (260 mg, 1.0 mmol), PhCOCl (0.14 mL, 1.2 mmol) and THF (30 mL), and LiHMDS (1.0 mmol in THF, 2.0 mL, 2.0 mmol) was added at −78 °C. After the mixture had been stirred at −78 °C for 30 min and, then, at room temperature for 1.5 h, the reaction mixture was poured into aqueous NH4Cl. After usual work-up with water and AcOEt, the solvent was evaporated in vacuo, and the residue was purified by chromatography (AcOEt/hexane 2:3) to give I (219 mg, 99%) as a yellow solid.

Synthesis of 5b: A 100 mL flask was charged with (2485 mg, 1.0 mmol), THF (30 mL), and LDA (1.0 mmol in THF/hexane, 4.0 mL, 4.0 mmol) was added at −78 °C. The reaction mixture was stirred at this temperature for 2 h, and aqueous NH4Cl was poured into the mixture. After usual work-up with water and AcOEt, the solvent was evaporated in vacuo, and the residue was purified by chromatography (CH2Cl2/hexane 2:3) to give I (199 mg, 99%) as a yellow solid.

Synthesis of 5a: A 100 mL flask was charged with (260 mg, 1.0 mmol), PhCOCl (0.14 mL, 1.2 mmol) and THF (30 mL), and LiHMDS (1.0 mmol in THF, 1.0 mL, 1.0 mmol) was added at −78 °C. After the mixture had been stirred at −78 °C for 30 min and, then, at room temperature for 1.5 h, aqueous NH4Cl was added. After usual work-up with water and AcOEt, the solvent was evaporated in vacuo, and the residue was purified by chromatography (CH2Cl2/hexane 2:3) to give I (219 mg, 99%) as a yellow solid.

Synthesis of 5b: A 100 mL flask was charged with (2485 mg, 1.0 mmol), THF (30 mL), and LDA (1.0 mmol in THF/hexane, 4.0 mL, 4.0 mmol) was added at −78 °C. The reaction mixture was stirred at this temperature for 2 h, and aqueous NH4Cl was poured into the mixture. After usual work-up with water and AcOEt, the solvent was evaporated in vacuo, and the residue was purified by chromatography (CH2Cl2/hexane 2:3) to give I (199 mg, 99%) as a yellow solid.
aqueous NH₄Cl was added. After usual work-up with water and AcOEt, the solvent was evaporated in vacuo, and the residue was purified by chromatography (AcOEt/hexane 3:7) to give an inseparable mixture of 4 (25%) and 5a (69%).

[8] This procedure was further applied to naphtho and phenanthro analogues, respectively: Y.-M. Man, T. C. W. Mak, H. N. C. Wong, J. Org. Chem. 1999, 64, 2947.
[12] an intermolecular version under the same reaction conditions as shown below failed to effect cyclization [Eq. (3)].
[16] The heat of formation was calculated after geometry optimization by PM3 semiempirical molecular orbital method (MOPAC 2000, Fujitsu Ltd., Tokyo, Japan). All the calculations were carried out by interface of CS Chem3D Ultra V. 6.0 (CambridgeSoft Corporation, 100 CambridgePark Dr. Cambridge, MA 02140-2317, USA).
[17] Of course, the overall enthalpy balance may be compensated by the formation of Li₂SO₄ and Et₃NH.
[19] Although relative reaction rates of elimination giving rise to mono- (vinylsulfone) and bis(vinylsulfone) should be discussed on the basis of their activation energies, we concluded that the second elimination proceeds quite faster than the first because of remarkable difference of ΔH₂ (ΔΔH₂; 30 kcalmol⁻¹).

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