Regular Article

Reaction of 2a,8b-Dihydrobenzo[b]cyclobutene[d]pyran-3-ones with Dimethylsulfoxonium Methylide

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Using dimethylsulfoxonium methylide as the methylene transfer reagent, 2a,8b-dihydrobenzo[b]cyclobutene[d]pyran-3-ones were converted into 2,2′-biphenol derivatives as major products and dihydrodibenzofurans as minor products. The reaction mechanism was extrapolated from a deuteration experiment with CD$_2$=S(O)(CD$_3$)$_2$.

Key words cyclobutene; ylide; ring opening; 2,2′-biphenol

Small cycloalkanes, such as cyclopropanes and cyclobutanes, play an important role in organic synthesis owing to their molecular instability and high reactivity.1–6 We have been interested in small cycloalkanes and have reported several reactions, including cyclopropane and cyclobutane ring opening reactions.7–15 In a previous study, we found that benzo[b]cyclobutene[d]pyran-3-ones 2, prepared by the [2+2] photocycloaddition reaction of 3-substituted coumarins 1 with monosubstituted alkenes, were stereocconvertently transformed into tetrahydrodibenzofuran derivatives 3 by using more than 2 equiv. of dimethylsulfoxonium methyliide [CH$_2$=S(O)Me$_2$], which is known as Corey’s sulfur ylide and is used as the methylene transfer reagent in the Corey-Chaykovsky cyclopropanation16–20 (Chart 1). The transformation of 2 into 3 was applied to the syntheses of dibenzofurantype natural products.17,18,21–27 In our continuing studies of the reaction of small cycloalkanes with CH$_2$=S(O)Me$_2$, we have examined with much interest the reaction of 2a-substituted 2a,8b-dihydrobenzo[b]cyclobutene[d]pyran-3-ones 4, which are cyclobutene derivatives that have more strain than 2, with CH$_2$=S(O)Me$_2$. However, contrary to our expectation, the main products were not dihydrobenzofuran 5 but 2,2′-biphenols 6. In this paper, we describe a novel skeletal transformation of 4 into 6 using CH$_2$=S(O)Me$_2$.

Benzo[b]cyclobutene[d]pyran-3-ones 4 were prepared by the [2+2] photocycloaddition reaction of 3-substituted coumarins 1 with substituted alkynes23 (Chart 1). When 4a was initially treated with 1.0 equiv. of CH$_2$=S(O)Me$_2$ in N,N-dimethylformamide (DMF) at room temperature (r.t.), dihydrodibenzofuran 5a was obtained in only 8% yield (Table 1, entry 1). When 2.0 equiv. of CH$_2$=S(O)Me$_2$ was used, the yield of 5a was improved to 38%. Unexpectedly, 2,2′-biphenol 6a was obtained in 45% yield (entry 2). When 3.0 equiv. of CH$_2$=S(O)Me$_2$ was used, the yield of 6a was decreased (entry 3). The use of dimethyl sulfoxide (DMSO), tetrahydrofuran (THF), or CH$_3$Cl$_2$ instead of DMF as solvent gave a low or no yield of 5a and 6a (entries 4–6). When the reaction was carried out at 0°C, a similar result to that in entry 2 was obtained (entry 7). Both products were not obtained at 80°C (entry 8). The intermediate (vide infra) of 5a and 6a could be unstable at high temperature. From these results, the conditions shown in entry 2 were selected as the optimum conditions for the skeletal transformation of 4a to give 5a and 6a. The structures and stereochemistries of 5a and 6a were confirmed on the basis of diverse spectral data, including heteronuclear multiple bond connectivity (HMBC), 1H-detected heteronuclear multiple quantum coherence (HMQC), and nuclear Overhauser effect spectroscopy (NOESY) data, and X-ray crystallographic analysis.

Under the optimum conditions, the scope of this reaction was explored. Benzo[b]cyclobutene[d]pyran-3-ones 4b–o were subjected to the optimum reaction conditions and the following results were obtained (Table 2). Cyclobutenes having a phenyl group at the 1-position and an alkyl ketone group at the 2a-position 4b–d were transformed into only 2,2′-biphenols 6b–d in moderate yields (entries 1–3). Compounds 4e and f having a benzyl group at the 2a-position were transformed into 6e and f in 55 and 59% yields together with 5e and f in 19 and 23% yields, respectively (entries 4, 5). The nature of the substituent at the 2a-position would affect the selectivity of the products. In the case of cyclobutenes having an alkyl ketone group, which was a strong electron-withdrawing group, 2,2′-biphenols 6 were obtained. In the case of cyclobutenes with a n-Bu group at the 1-position 4g and phenyl and methyl groups on the cyclobutene ring 4h, corresponding products 6g and h were obtained in 22 and 49% yields, respectively (entries 6, 7). Not only the substituent at the 2a-position but also those at 1-, 1,2-positions could be influenced the selectivity of 5 and 6 (entries 6, 7 vs. entry 2 in Table 1). Substrates 4i–k having a methyl group on the phenyl group of the coumarin ring were transformed into 6i–k in moderate yields without dihydrodibenzofurans 5i–k (entries 8–10). Similar to the methyl group, substrates 4l–o having a trimethylsilyl (TMS) group were also transformed into 6l–o in moderate yields (entries 11–14).

In order to gain further insights into the course of the skeletal transformation reaction, 4a was treated with CD$_2$=S(O)(CD$_3$)$_2$, which was deprotonated predeuterated trimethylsulfoxonium salt.28 Non-deuterated 6a and monodeuterated 5a′ were obtained in 38 and 19% yields, respectively. The deuteration ratio of 5a′ was 86% (Chart 2).

A plausible reaction mechanism is shown in Chart 3. Similar to the previously reported skeletal transformation reaction of benzo[b]cyclobutene[d]pyran-3-ones 2,31 one equivalent of
CH$_2$S(O)Me$_2$ would attack the lactone carbonyl group to initiate ring opening to form 8. The use of one more equivalent of CH$_2$S(O)Me$_2$ as the base would promote the cyclobutene ring opening and re-closure to give intermediate 12. In route A, a C–C bond would be formed between the carbon of the enolate moiety and the carbon of the dimethylsulfoxonium group, and this would be followed by aromatization accompanying cleavage of the cyclopropane ring to give 6. On the
other hand, in route B, a C–O bond would be formed between the oxygen of the enolate moiety and the carbon of the dimethylsulfoxonium group to give 5.

In conclusion, we have found that CH₂=S(O)Me₂ promoted the skeletal transformation of cyclobutene derivatives into 2,2′-biphenols. In contrast to the transformation of 2, structurally similar substrate 4 was transformed into 6 as the major product with or without 5. The reaction proceeded with the cyclopropanation to 13, a cyclopropane ring cleavage, and finally aromatization. These steps were clarified in the deuteration experiment with CD₂=S(O)(CD₃)₂.

**Experimental**

**General** Melting points (mp) were measured with a Yanaco MP micro-melting point apparatus and uncorrected. NMR spectra were measured on JEOL EX-270 (¹H: 270MHz), JEOL AL-300 (¹H: 300MHz; ¹³C: 75.5MHz), and Varian INOVA 400NB (¹H: 400MHz; ¹³C: 100MHz) spectrometers with tetramethylsilane as the internal standard. Chemical shifts are reported in ppm. IR spectra were measured with Shimadzu IR-435 and Shimadzu FTIR-8400 spectrophotometer. A JEOL JMS-GC mate spectrometer was used for low-resolution and high-resolution electron ionizations MS (LR-EI-MS and HR-EI-MS). Silica gel 60 (grade 7734, 60–230 mesh, Merck) and Silica gel 60N (Kanto Chemical Co., Inc.) for column chromatography and Silica gel 60F₂₅₄ plate (0.5 mm and 1 mm in thickness, Merck) for preparative TLC were used.

**Typical Procedure for the Synthesis of 2,2′-Biphenol**

To a suspension of (CH₃)₂S(O)I (91 mg, 0.41 mmol) in DMF (2 mL), NaH (60% in mineral oil, 16 mg, 0.41 mmol) was added with stirring, and the whole was stirred for 30 min at r.t. under N₂ atmosphere. Starting material 4a (70 mg, 0.20 mmol) was added slowly to the reaction mixture, and the stirring was continued overnight. After completion of the reaction, the mixture was acidified with 10% HCl aq. and extracted with ethyl acetate. The combined extracts were washed with water and brine, dried over Na₂SO₄, and evaporated. The residue was purified by silica gel column chromatography (n-hexane:AcOEt=3:1) to yield 5a (30 mg, 45%) and 6a (25 mg, 38%).

Methyl (4aRS,9bSR)-4a,9b-Dihydro-4-hydroxy-1-phenyl dibenzofuran-3-carboxylate (5a)

Pale yellow powder. mp 169.8–171.3°C (AcOEt). ¹H-NMR (400 MHz, CDCl₃) δ: 3.84 (3H, s), 5.03 (1H, d, J=11.8, 0.8 Hz), 5.37 (1H, d, J=11.9Hz), 6.58–6.70 (3H, m), 6.92 (1H, d, J=8.1Hz), 7.07–7.12 (1H, m), 7.31–7.35 (1H, m), 7.39–7.44 (2H, m), 7.49–7.52 (2H, m), 12.36 (1H, s). ¹³C-NMR (100 MHz, CDCl₃) δ: 43.8, 52.2, 80.0, 100.4, 109.7, 115.9, 121.1, 124.8, 126.2, 127.5, 128.0, 128.2, 128.5, 128.7, 139.3, 157.6, 165.5, 170.7. IR (CHCl₃) 1658, 1591 cm⁻¹. LR-EI-MS m/z: 320 (M⁺, 46.8), 289 (23.1), 288 (100.0). HR-EI-MS Calcd for C₂₀H₁₆O₄: M⁺ 320.1048. Found: 320.1046. Anal. Calcd for C₂₀H₁₆O₄: C; 74.89, H; 5.03. Found: C; 74.71, H; 4.92.

(5a')

¹H-NMR (400 MHz, CDCl₃) δ: 3.84 (3H, s), 5.03 (1H, s), 5.73 (0.14H, d, J=11.9Hz), 6.58–6.70 (3H, m), 6.91–6.93 (1H,
m), 7.07–7.12 (1H, m), 7.26–7.35 (1H, m), 7.39–7.44 (2H, m), 7.49–7.52 (2H, m), 12.36 (1H, s). HR-ESI-MS Calcd for C_{12}H_{12}O_{2}: 231.111. Found: 231.1105.

Methyl 2,2'-Dihydroxy-5-phenylbiphenyl-3-carboxylate (6a)

Colorless needles. mp 160.5–161.5°C (AcOEt). 1H-NMR (300 MHz, CDCl3) δ: 4.03 (3H, s), 6.48 (1H, s), 7.02–7.11 (2H, m), 7.32–7.37 (3H, m), 7.42–7.46 (2H, m), 7.57–7.59 (2H, m), 7.81 (1H, d, J=2.4 Hz), 8.16 (1H, d, J=2.4 Hz), 11.99 (1H, s). 13C-NMR (75 MHz, CDCl3) δ: 52.8, 113.0, 118.3, 121.3, 125.3, 126.8, 127.4, 127.9, 128.0, 128.9, 129.8, 131.2, 133.7, 137.1, 139.4, 153.9, 160.7, 171.1. IR (CHCl3): 3331, 3000, 1668, 1599 cm⁻¹. LR-ESI-MS m/z: 320 (M⁺, 491), 288 (100), 271 (43.5). HR-ESI-MS Calcd for C_{18}H_{15}O₃: 320.1048. Found: 320.1041. Anal. Calcd for C_{18}H_{15}O₃: C; 74.99, H; 5.03. Found: C; 74.97, H; 5.31. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated CuKα radiation at 23°C. The structure was solved by SHELX-97 and expanded using Fourier techniques (DIRDIF-99). C_{20}H_{16}O_{4}·CH₂(C₂H₅O₂)·1/2 CH₂(OH); orthorhombic (0.30 mm); space group Pccn (n=56); cell dimension a=33.263(2) Å, b=14.597(4) Å, c=7.228(4) Å, V=3599(3) Å³; Z=8; Dcalcd=1.281 g·cm⁻³; μ(CuKα)=7.367 cm⁻¹; 3134 reflections measured (2θ max 136.3°), unique 320 (Rint=0.030); the final refinement gave R1=0.0543 (I>2.0σ(I)) and wR2=0.1750 (CCDC No. 144037).

1-(2',2'-Dihydroxy-5-phenylbiphenyl-3-yl)-2,2'-dimethylpropan-1-one (6b)

Pale yellow amorphous. 1H-NMR (400 MHz, CDCl3) δ: 1.33 (6H, d, J=7.0 Hz), 3.78 (1H, hept, J=7.0 Hz), 6.70 (1H, s), 7.03–7.11 (2H, m), 7.31–7.53 (5H, m), 7.54–7.58 (2H, m), 7.82 (1H, d, J=2.2 Hz), 8.06 (1H, d, J=2.2 Hz), 13.9 (1H, s). 13C-NMR (100 MHz, CDCl3) δ: 19.4, 35.3, 118.2, 121.4, 125.4, 126.9, 127.5, 128.1, 129.0, 129.1, 132.2, 135.0, 137.8, 137.9, 154.0, 211.9. IR (CHCl3): 3333, 2955, 1630, 1593 cm⁻¹. LR-ESI-MS m/z: 332 (M⁺, 35.4), 289 (100.0). HR-ESI-MS Calcd for C_{12}H_{12}O_{2}: 332.1412. Found: 332.1401. 1-(2',2'-Dihydroxy-5-phenylbiphenyl-3-yl)-2,2'-dimethylpropan-1-one (6c)

Yellow amorphous. 1H-NMR (400 MHz, CDCl3) δ: 1.56 (9H, s), 6.68 (1H, s), 7.04–7.11 (2H, m), 7.31–7.40 (3H, m), 7.46–7.50 (2H, m), 7.54–7.57 (2H, m), 7.79 (1H, d, J=2.3 Hz), 8.34 (1H, d, J=2.3 Hz). 13C-NMR (100 MHz, CDCl3) δ: 29.0, 45.0, 117.6, 118.5, 121.4, 125.8, 126.8, 127.5, 129.1, 129.3, 129.5, 132.1, 132.4, 137.0, 139.9, 154.1, 158.6, 213.3. IR (CHCl₃): 3336, 1621 cm⁻¹. LR-ESI-MS m/z: 346 (M⁺, 11.0), 289 (100.0), 271 (28.8). HR-ESI-MS Calcd for C_{12}H_{11}O_{2}: 346.1569. Found: 346.1566.

Adamantan-1-yl (2',2'-Dihydroxy-5-phenylbiphenyl-3-yl)ketone (6d)

Pale yellow amorphous. 1H-NMR (400 MHz, CDCl3) δ: 1.74–1.94 (9H, br), 2.06–2.22 (9H, br), 2.27 (6H, d, J=2.7 Hz), 6.78 (1H, s), 7.03–7.11 (2H, m), 7.24–7.41 (3H, m), 7.47–7.51 (2H, m), 7.56–7.58 (2H, m), 7.78 (1H, d, J=2.2 Hz), 8.55 (1H, d, J=2.2 Hz). 13C-NMR (100 MHz, CDCl3) δ: 27.8, 28.3, 36.6, 36.6, 39.0, 48.4, 115.3, 118.1, 118.5, 121.3, 121.4, 122.8, 125.9, 126.2, 126.7, 126.9, 127.4, 127.6, 128.0, 128.2, 128.9, 129.1, 129.6, 129.7, 131.1, 132.1, 136.8, 138.4, 140.0, 154.1, 158.5, 212.7. IR (CHCl₃): 2981, 1686 cm⁻¹. LR-ESI-MS m/z: 424 (M⁺, 6.5), 289 (22.6), 55.1 (100.0). HR-ESI-MS Calcd for C_{13}H_{13}O_{2}: 424.2038. Found: 424.2041.
Yellowish oil. \(^{1}H\)-NMR (300 MHz, CDCl\(_3\)) \(\delta\): 1.32 (6H, d, \(J\) = 6.8 Hz), 2.36 (3H, s), 3.79 (1H, hept, \(J\) = 7.5 Hz), 7.14 (1H, dd, \(J\) = 1.3, 7.7 Hz), 7.20–7.24 (1H, m), 7.39–7.57 (5H, m), 7.80 (1H, d, \(J\) = 2.4 Hz), 8.06 (1H, d, \(J\) = 2.2 Hz), 13.9 (1H, s). \(^{13}C\)-NMR (75 MHz, CDCl\(_3\)) \(\delta\): 16.5, 29.0, 45.0, 117.6, 120.8, 125.3, 126.8, 127.1, 127.4, 128.8, 129.0, 129.1, 130.1, 132.3, 137.0, 139.9, 152.2, 158.1, 211.9. IR (CHCl\(_3\)): 3650–3300, 1616 cm\(^{-1}\). LR-ESI-MS \(m/z\): 360 (M\(^+\), 100.0), 343 (M\(^+\)−15, 73.2), 105 (85.5), 77 (57.7). HR-ESI-MS Calcd for C\(_{26}\)H\(_{20}\)O\(_3\): 380.1413. Found: 380.1412.

Yellowish powder. \(^{1}H\)-NMR (300 MHz, CDCl\(_3\)) \(\delta\): 0.39 (9H, s), 1.54 (9H, s), 6.80 (1H, s), 7.05 (1H, t, \(J\) = 7.3 Hz), 7.32–7.39 (2H, m), 7.43–7.48 (3H, m), 7.52–7.56 (2H, m), 7.77 (1H, d, \(J\) = 2.4 Hz), 8.30 (1H, d, \(J\) = 2.2 Hz), 14.0 (1H, s). \(^{13}C\)-NMR (75 MHz, CDCl\(_3\)) \(\delta\): 0.80–28.9, 45.0, 117.5, 121.1, 125.0, 126.7, 126.8, 127.0, 127.5, 127.8, 128.5, 130.1, 132.3, 137.0, 139.9, 152.2, 158.2, 213.2. IR (CHCl\(_3\)): 3650–3300, 1616 cm\(^{-1}\). LR-ESI-MS \(m/z\): 360 (M\(^+\), 13.6), 303 (100.0). HR-ESI-MS Calcd for C\(_{25}\)H\(_{28}\)O\(_3\): 360.1725. Found: 360.1731.

Yellowish crystals (AcOEt/\(n\)-hexane). mp 76.1–78.3°C. \(^{1}H\)-NMR (300 MHz, CDCl\(_3\)) \(\delta\): 2.38 (3H, s), 6.48 (1H, s), 6.97 (1H, t, \(J\) = 7.5 Hz), 7.14 (1H, dd, \(J\) = 1.3, 7.7 Hz), 7.22 (1H, dd, \(J\) = 1.3, 7.7 Hz), 7.20–7.55 (5H, m), 7.70 (1H, d, \(J\) = 2.2 Hz), 8.30 (1H, d, \(J\) = 2.4 Hz), 14.0 (1H, s). \(^{13}C\)-NMR (75 MHz, CDCl\(_3\)) \(\delta\): 6.5, 29.0, 45.0, 117.6, 120.8, 125.3, 126.8, 127.1, 127.4, 128.8, 129.0, 129.1, 130.1, 132.3, 137.0, 139.9, 152.2, 158.2, 213.2. IR (CHCl\(_3\)): 3650–3300, 1723, 1592 cm\(^{-1}\). LR-ESI-MS \(m/z\): 360 (M\(^+\), 100.0), 285 (73.2), 105 (85.5), 77 (57.7). HR-ESI-MS Calcd for C\(_{25}\)H\(_{28}\)O\(_3\): 380.1412. Found: 380.1413.

White powder (AcOEt/\(n\)-hexane). mp 166.5–168.1°C. \(^{1}H\)-NMR (300 MHz, CDCl\(_3\)) \(\delta\): 0.34 (9H, s), 2.74 (3H, s), 6.74 (1H, s), 7.03 (1H, t, \(J\) = 7.3 Hz), 7.31–7.55 (7H, m), 7.80 (1H, d, \(J\) = 2.2 Hz), 7.97 (1H, d, \(J\) = 2.2 Hz), 13.5 (1H, s). \(^{13}C\)-NMR (75 MHz, CDCl\(_3\)) \(\delta\): –0.80, 26.9, 119.8, 121.1, 124.5, 126.8, 127.5, 128.7, 128.8, 129.0, 129.2, 132.5, 133.6, 135.5, 138.2, 139.5, 157.3, 158.6, 205.5. IR (CHCl\(_3\)): 3650–3300, 1594, 1534 cm\(^{-1}\). LR-ESI-MS \(m/z\): 376 (M\(^+\), 63.4), 361 (42.7), 343 (100.0), 164 (40.7). HR-ESI-MS Calcd for C\(_{25}\)H\(_{28}\)O\(_{3}\)Si: 376.1495. Found: 376.1490.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.


