Synthesis of *cis*- and *trans*-1,2-Diphenoxyethenes and *p,p′*-Disubstituted Diaryloxyethenes

Jingkui Yang and Nathan L. Bauld*

Department of Chemistry and Biochemistry, The University of Texas, Austin, Texas 78712

Received September 8, 1998 (Revised Manuscript Received October 19, 1999)

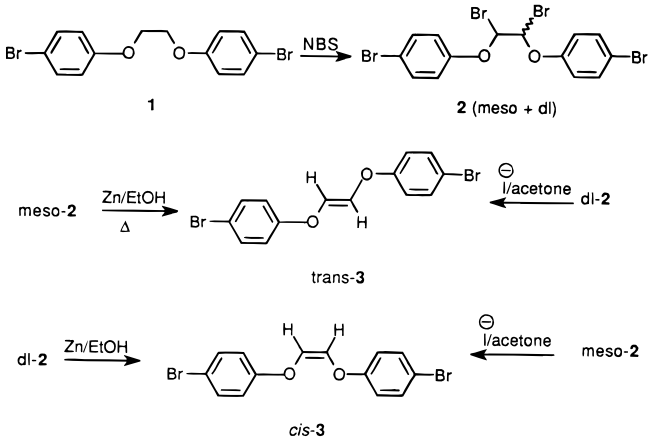
In connection with mechanistic and synthetic studies of the cation radical Diels−Alder reaction,[1,2] the electron-rich alkenes *cis*- and *trans*-1,2-diphenoxyethene (**4**) and their derivatives appeared to be exceptionally attractive dienophiles. Somewhat surprisingly, the synthesis of these compounds had not previously been reported. The presently reported synthesis permits the stereospecific formation of *either cis*- or *trans*-**4** and its *p,p′*-disubstituted derivatives from a common precursor.

Results and Discussion

A potentially straightforward synthesis of **4** from 1,2-diphenoxyethane by NBS bromination/elimination was frustrated by facile electrophilic ring bromination para to the ether functionality. Consequently, the *p,p′*-dibromo derivative **1** (Scheme 1) was prepared by reacting 4-bromophenol with 1,2-dibromoethane. Bromination[3] of **1** then yielded a mixture of *meso*- and *dl*-1,2-dibromo-1,2-bis(4-bromophenoxy)ethane (**2**; Scheme 1; *meso*/*dl* = 71:29), which could be separated chromatographically from each other and smaller amounts of tribromo and tetrabromo derivatives.

The meso isomer of **2** could be converted stereospecifically to either *cis*- or *trans*-**3** (Scheme 1). Zinc debromination[4] occurs with the expected anti stereospecificity to yield pure *trans*-**3**, while iodide ion induced debromination[5] gives *cis*-**3** with net syn stereospecificity. Presumably, the *meso*-dibromide is initially converted, via an invertive S_N2 displacement by iodide ion, to a racemic mixture of (*R,R*)- and (*S,S*)-1-bromo-2-iodo-1,2-bis(4-bromophenoxy)ethane, followed by anti elimination of IBr initiated by the preferential nucleophilic attack of iodide ion upon the iodo substituent. In an analogous manner, *dl*-**2** affords *cis*-**3** via zinc debromination and *trans*-**3** via iodide ion induced dehalogenation. The yields in the iodide ion induced reaction (95−98%) are superior to those obtained in the zinc debrominations (49−60%), and purification is also more facile in the former reaction.

Scheme 1. Preparation of *cis*- and *trans*-1,2-Bis(4-bromophenoxy)ethene



Attempts to isolate the monobromination product of **1** from *N*-bromosuccinimide bromination were unsuccessful, and it appears probable that this substance is unstable toward chromatography.

Treatment of *cis*- and *trans*-**3** with butyllithium, followed by either protonation or methylation, then afforded pure *cis*- and *trans*-1,2-diphenoxyethene (**4**) or the corresponding 4,4′-dimethyl derivative (**5**), respectively (Scheme 2).

Bromine Addition to Diaryloxyethenes. The debromination of *meso*- and *dl*-**2** to give **3** has been found to be highly stereospecific. It was therefore of special interest to determine whether the reverse process, the addition of Br_2 to **3** to yield **2**, would also prove to be stereospecific. Somewhat surprisingly, **3** (either cis or trans) failed to react with bromine in dichloromethane at room temperature. Addition did occur, however, in refluxing chloroform but was only partially stereospecific. Addition to *trans*-**3** gave 70% of *meso*-**2** along with 30% of *dl*-**2** (Scheme 3). Correspondingly, *cis*-**3** gave 87% of *dl*-**2** along with 13% of *meso*-**2**. In both cases, anti addition is prevalent but by no means exclusive. These results are inconsistent with either an epibromonium ion or an open carbocation as an exclusive intermediate in the reaction.[6] They are, however, nicely consistent with a reaction mechanism that proceeds via an epibromonium ion that, at a rate comparable to its reaction with bromide ion, isomerizes to its diastereoisomeric epibromonium ion via an open carbocation. Since this partial equilibration of diastereoisomeric epibromonium ions could be facilitated by the slightly elevated temperature required for the reaction, the analogous addition of bromine to **5**, which occurs at room temperature, was also studied. This reaction proved to be largely nonstereospecific. Thus, *cis*-**5** adds bromine to give a 1:1 mixture of *meso*- and *dl*-dibromides. Evidently, the presence of an aryloxy substituent tends to increase the stability of the open carbocation relative to the epibromonium ion, facilitating opening of the former.

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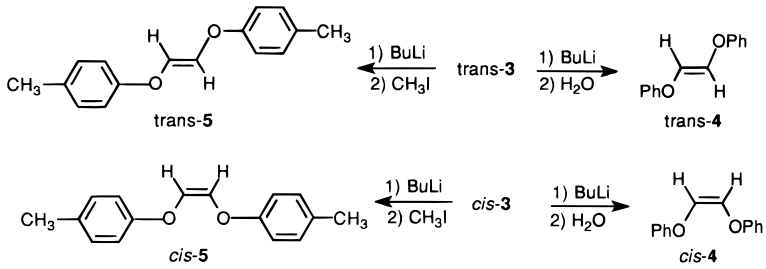
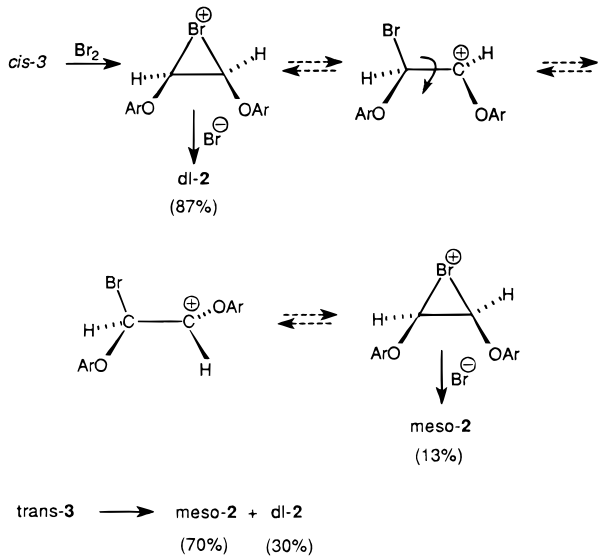
10.1021/jo9812577 CCC: $18.00
Published on Web 11/18/1999

Scheme 2. Preparation of *cis*- and *trans*-1,2-Diphenoxyethene and Their *p,p′*-Dimethyl Derivatives



Scheme 3. Partially Anti Stereospecific Addition of Bromine to 1,2-Diaryloxyethenes



Experimental Section

Analysis. Routine ^{1}H and ^{13}C NMR spectra were recorded as solutions in $CDCl_3$.

Reagents. Organic chemicals used as starting materials in these syntheses were used as received from the Aldrich Co. These included 4-bromophenol, 1,2-dibromoethane, and *N*-bromosuccinimide.

1,2-Bis(4-bromophenoxy)ethane (1). To a solution of sodium hydroxide (12.4 g, 0.31 mol) in water (50 mL) was added 4-bromophenol (51.7 g, 0.3 mol). The mixture was stirred at 60−70 °C for 0.5 h prior to the addition of 1,2-dibromoethane (26.3 g, 0.14 mol). The resulting mixture was then heated at reflux for 6 h. After being cooled to room temperature, the reaction mixture was filtered to obtain a white solid, which was recrystallized from ethanol and dried in vacuo. The yield of pure **1** was 32.7 g (56.7%): mp 130−132 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.25 (s, 4H), 6.81 (d, 4H, J = 6.85 Hz), 7.37 (d, 4H, J = 6.85 Hz); ^{13}C NMR (250 MHz, $CDCl_3$) δ 66.68, 113.41, 116.48, 132.33, 157.45; LRMS *m/e* 370 (M^+), 372, 374, 199, 197, 157, 155; HRMS calcd for $C_{14}H_{13}O_2Br_2$ 370.928 227, found 370.927 493.

***meso*- and *dl*-1,2-Dibromo-1,2-bis(4-bromophenoxy)ethane (*meso*-2 and *dl*-2).** In 50 mL of carbon tetrachloride was dissolved 3.37 g (9.06 mmol) **1**, 3.95 g (22.19 mmol) of *N*-bromosuccinimide, and 0.54 g (2.23 mmol) of benzoyl peroxide. The resulting solution was heated at reflux for 6 h. After being cooled to room temperature, the mixture was filtered and the crude products obtained from the filtrate by evaporating the solvent. Silica gel chromatography (230−400 mesh; 6:1 hexane/dichloromethane) yielded pure *meso*- and *dl*-**2**. The isolated yield of pure *meso*-**2** was 0.82 g (17.1%). *meso*-**2b**: mp 140−142 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.51 (s, 2H, J = 6.2 Hz), 7.08 (dd, 4H, J = 8.95, 1.25 Hz); 7.51 (dd, 4H, J = 8.95, 1.25 Hz); ^{13}C NMR (250 MHz, $CDCl_3$) δ 85.31, 116.97, 118.87, 132.89, 153.72; HRMS calcd for $C_{14}H_{10}O_2Br_4$ 525.741424, found 525.741353.The yield of dl-**2** was 0.62 g (13%): mp 118−120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.48 (s, 2H, J = 1.8), 7.14 (dd, 4H, J = 8.95,1.25), 7.52 (dd, 4H, J = 8.95, 1.25); ^{13}C NMR (250 MHz, $CDCl_3$) δ 84.80, 117.57, 119.16, 132.91, 154.76; HRMS calcd for $C_{14}H_{10}O_2Br_4$ 525.741 424, found 525.740 938.

***cis*-1,2-Bis(4-bromophenoxy)ethene (*cis*-3).** The *dl* diastereoisomer of **2** (0.54 g, 1.02 mmol) was dissolved in 20 mL of acetone. Sodium iodide (0.45 g, 3 mmol) was then added to this solution. The reaction mixture was stirred for 2 h at room temperature, during which time a deep red color developed. After the acetone solvent had been removed by rotary evaporation, water (25 mL) and dichloromethane (100 mL) were added, and a saturated aqueous solution of sodium thiosulfate was added until the solution was colorless. The organic layer was then separated, evaporated, dried, filtered to get a small amount of a solid, and recrystallized ethanol to obtain *cis*-**3** (0.35 g, 95%). Similarly, 0.537 g (1 mmol) of *meso*-**2** was dissolved in ethanol−water (40 mL, 30:10), and 0.072 g (1.1 mmol) of zinc powder was added. The resulting reaction mixture was stirred and refluxed for 3 h. After rotary evaporation of the solvents, *cis*-**3** (0.18 g, 49%) was obtained by silica gel chromatography (hexanes/dichloromethane 10:1): mp 102−104 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.11 (s, 2H, J(HC=CH) = 3.42 Hz), 6.96 (d, 4H, J = 9.04 Hz), 7.42 (d, 4H, J = 9.04 Hz); ^{13}C NMR (250 MHz, $CDCl_3$) δ 115.40, 117.94, 128.46, 132.54, 156.30; LRMS *m/e* 368 (M^+), 370, 372, 198, 196, 155, 153, 118, 76; HRMS calcd for $C_{14}H_{10}O_2Br_2$ 367.904 752, found 367.905 142.

***trans*-1,2-Bis(4-bromophenoxy)ethane (*trans*-3).** In the same manner as described for *cis*-**3**, *trans*-**3** could be obtained by zinc debromination of *meso*-**2** (60% yield) or by the iodide ion induced debromination of *dl*-**2** (98%): mp 113−114 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (s, 2H), 6.90 (d, 4H, J = 8.95 Hz), 7.42 (d, 4H, J = 8.95 Hz, J(HC=CH) = 13.44 Hz); ^{13}C NMR C 250 MHz, $CDCl_3$ δ 115.22, 117.53, 132.59, 134.79, 156.59; LRMS *m/e* 368 (M^+) 0.370, 372, 157, 155, 118, 97, 76; HRMS calcd for $C_{14}H_{10}O_2Br_2$ 367.904 57, found 367.905 698.

***trans*-1,2-Diphenoxyethene (*trans*-4).** A solution of *trans*-**3** (1.22 g, 3.31 mmol) in anhydrous diethyl ether (20 mL) in an atmosphere of nitrogen was cooled to ca. −15 °C. A solution of butyllithium in hexanes (6.62 mL of 1.6 M solution, 10.6 mmol) was then added to the cold solution, and the mixture was stirred for 20 min at that temperature. Water (5 mL) was added, and the organic products were then extracted with dichloromethane. The crude product was chromatographed on silica gel to yield 0.63 g (90%) of pure *trans*-**4**: mp 78−79 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.82 (s, 2H, vinyl protons), 7.00−7.05 (m, 6H), 7.24−7.36 (m, 4H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 115.75, 122.64, 129.67, 134.80, 157.58; LRMS *m/e* 212 (M^+), 155, 153, 118, 91, 77, 65 (w), 51; HRMS calcd for $C_{14}H_{12}O_2$ 212.083 730; found 212.084 289.

***cis*-1,2-Diphenoxyethene (*cis*-4).** This cis isomer was obtained from *cis*-**3** by the same procedure as described above (95% yield): mp 64−66 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.15 (s, 2H, vinyl protons), 7.05−7.11 (m, 6H), 7.29−7.35 (m, 4H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 116.26, 122.85, 128.38, 129.61, 157.01; LRMS *m/e* 212 (M^+), 182, 155, 135, 118, 91, 77, 65 (s), 51; HRMS calcd for $C_{14}H_{12}O_2$ 212.083 730, found 212.084 289.

***trans*-1,2-Bis(4-methylphenoxy)ethene (*trans*-5).** This derivative was obtained in the same manner as *trans*-**4** from *trans*-**3** by quenching the lithio derivatives with excess methyl iodide instead of water (>90% yield): mp 66−68 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.30 (s, 6 H), 6.81 (s, 2H, vinyl protons), 6.91 (m, 2H), 6.93 (m,2H), 7.10 (m, 2H), 7.13 (m, 2H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 20.54, 115.61, 130.07, 131.98, 134.71,

155.55; LRMS *m*/*e* 240 (M^+), 183, 168, 132, 105, 91, 65; HRMS calcd for $C_{16}H_{17}O_2$ (M + 1) 241.122 855, found 241.122 488.

***cis*-1,2-Bis(4-methylphenoxy)ethene (*cis*-5).** This compound was prepared from *cis*-**3** in the same manner as described for *cis*-**4**, except that excess methyl iodide was used to quench the lithio compounds: mp 80−82 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.30 (s, 6H), 6.07 (s, 2H, vinyl protons), 6.96 (m, 2H), 6.99 (m, 2H), 7.09 (m, 2H), 7.12 (m, 2H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 20.57, 116.11, 128.36, 129.98, 132.56, 155.18; LRMS *m*/*e* 240 (M^+), 196, 168, 149, 132, 105, 91, 77, 65; HRMS calcd for $C_{16}H_{17}O_2$ (M + 1) 241.122 855, found 241.121 919.

Acknowledgment. The authors thank the Robert A. Welch Foundation (F-149) for support of this research.

Supporting Information Available: ^{13}C NMR spectra for compounds **1**, *meso*-**2**, *dl*-**2**, *cis*-**3**, *trans*-**3**, *cis*-**4**, *trans*-**4**, *cis*-**5**, and *trans*-**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9812577