Facile Synthesis of 3-Methylbenzene Oxide and 1-Methylbenzene Oxide, and ^{1}H-NMR Data for Diels–Alder Adducts of Three Methylbenzene Oxides with 4-Phenyl-1,2,4-triazoline-3,5-dione

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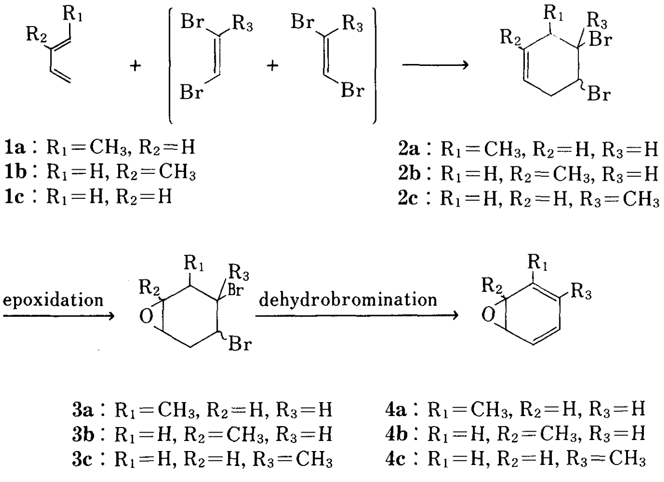
Diels–Alder reaction of methyl-substituted 1,3-butadienes (1) with 1,2-dibromoethylene gave dibromomethylcyclohexenes (2), which were subjected to epoxidation, followed by dehydrobromination of the resultant dibromo oxides (3) to afford 3-methylbenzene oxide (4a) and 1-methylbenzene oxide (4b). However, 4-methylbenzene oxide (4c) could not be obtained in this way.

Keywords 1-methylbenzene oxide; 3-methylbenzene oxide; 4-methylbenzene oxide; toluene oxide; arene oxide

Arene oxides have been postulated as intermediates in the oxidative metabolism of aromatic substrates.1) In this connection, the synthesis of arene oxides has already been reported by Vogel *et al.*2) and Jerina *et al.*3) They utilized dihydroaromatic hydrocarbons obtained through Birch reduction as starting materials: the hydrocarbons are first subjected to bromination (or epoxidation), followed by epoxidation (or bromination), and then dehydrobromination to give the corresponding arene oxides. However, for the synthesis of 3-methylbenzene oxide, several careful steps are needed, including the use of $LiAlH_4$, to obtain 1,4-dihydrotoluene as the starting material. Therefore, we examined a brief synthesis of 3-methylbenzene oxide (**4a**) through Diels–Alder reaction of methyl-substituted 1,3-butadiene (*trans*-1,3-pentadiene (**1a**)) with 1,2-dibromoethylene. The same concept is applicable to the synthesis of 1-methylbenzene oxide (**4b**) using isoprene (**1b**) and 1,2-dibromoethylene, but not to the systhesis of 4-methylbenzene oxide (**4c**) using 1,3-butadiene (**1c**) and 1,2-dibromopropene. The synthetic route based on this concept is shown in Chart 1.

In order to obtain evidence of formation of the unstable methylbenzene oxides, Diels–Alder reactions of the two methylbenzene oxides with 4-phenyl-1,2,4-triazoline-3,5-dione,4) leading to stable adducts, were adopted. The ^{1}H-NMR spectra of the products were compared with those of the corresponding 4-phenyl-1,2,4-triazoline-3,5-dione adducts of the three methylbenzene oxide isomers synthesized according to the conventional method reported by Vogel *et al.*2c,d) and Jerina *et al.*3a–c)



1a : $R_1=CH_3$, $R_2=H$
1b : $R_1=H$, $R_2=CH_3$
1c : $R_1=H$, $R_2=H$

2a : $R_1=CH_3$, $R_2=H$, $R_3=H$
2b : $R_1=H$, $R_2=CH_3$, $R_3=H$
2c : $R_1=H$, $R_2=H$, $R_3=CH_3$

3a : $R_1=CH_3$, $R_2=H$, $R_3=H$
3b : $R_1=H$, $R_2=CH_3$, $R_3=H$
3c : $R_1=H$, $R_2=H$, $R_3=CH_3$

4a : $R_1=CH_3$, $R_2=H$, $R_3=H$
4b : $R_1=H$, $R_2=CH_3$, $R_3=H$
4c : $R_1=H$, $R_2=H$, $R_3=CH_3$

Chart 1

Results and Discussion

Diels–Alder reaction of *trans*-1,3-pentadiene (**1a**) with *cis*, *trans*-dibromoethylene gave the dibromide **2a**, which was oxidized with *m*-chloroperoxybenzoic acid to give the dibromo oxide **3a**. The heaviest ions in the mass spectrum (MS) of **3a** appeared at *m/z* 189 and *m/z* 191, the intensity ratio of which was consistent with the abundance of ^{79}Br and ^{81}Br. These ions (189 and 191, $C_7H_{10}BrO^+$) were due to loss of a bromine. The spectrum was identical with that of **3a** obtained through the procedure reported by Jerina *et al.*3a) The dibromo oxide **3a**, consisting of stereoisomers, was obtained as an oil.

The dibromo oxide **3a** was dehydrobrominated to 3-methylbenzene oxide (**4a**) with potassium *tert*-butoxide. All operations were conducted in glassware which had previously been washed with alkali to prevent acid-catalyzed isomerization to cresol. Methylbenzene oxide is known to be much more unstable than benzene oxide.3a) As reported by Jerina *et al.*,3a) maleic anhydride was used in order to convert the unstable oxide **4a** into a stable adduct, but a good result was not obtained.

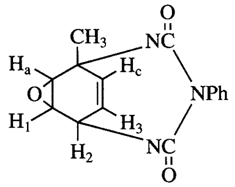
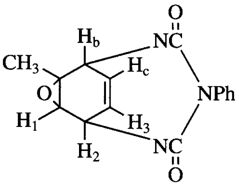
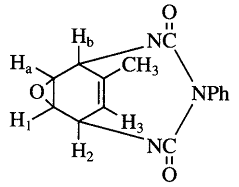
Therefore, the structure of the oxide **4a** was confirmed by formation of the Diels–Alder adduct with 4-phenyl-1,2,4-triazoline-3,5-dione (mp 167—169 °C (dec.); 31% yield based on **3a**; *m/z* 283). The spectra (IR, MS and ^{1}H-NMR) of the adduct **5a** were identical with those of **5a** derived from **4a** obtained by the method of Jerina *et al.*3b,c) ^{1}H-NMR data for **5a** are given in Table I.

On the other hand, Diels–Alder reaction of isoprene (**1b**) with *cis*, *trans*-dibromoethylene gave the dibromide **2b**, which was oxidized with *m*-chloroperoxybenzoic acid to give the dibromo oxide **3b**. The MS of **3b** was similar to that of **3a**. Similarly, the dibromo oxide **3b** was obtained not as crystals, but as an oil, consisting of stereoisomers.

The dibromo oxide **3b** was dehydrobrominated to 1-methylbenzene oxide (**4b**) with sodium methoxide. The same procedures as mentioned above were adopted to prevent acid-catalyzed isomerization to cresol.

The structure of the oxide **4b** was confirmed by formation of the Diels–Alder adduct with 4-phenyl-1,2,4-triazoline-3,5-dione (mp 174—175 °C; 41% yield based on **3b**; *m/z*

TABLE I. ^{1}H-NMR Spectral Data for Adducts of Methylbenzene Oxides and 4-Phenyl-1,2,4-triazoline-3,5-dione (270 MHz, $CDCl_3$, Shifts are δ Values)

Adduct		H_1 H_a	H_2 H_b	H_3 H_c	CH_3	Ph
5a		3.72 3.37	5.31 —	6.13 6.03	2.10	7.40
5b		3.48 —	5.29 4.96	6.24 6.13	1.68	7.40
5c		3.68 3.68	5.23 5.09	5.76 —	1.93	7.40

283). The spectra (IR, MS and ^{1}H-NMR) of the adduct **5b** were identical with those of **5b** derived from **4b** obtained by the method of Vogel *et al.*[2c,d] ^{1}H-NMR data for **5b** are given in Table I.

Although facile syntheses of 3-methylbenzene oxide (**4a**) and 1-methylbenzene oxide (**4b**) were achieved by employing the Diels–Alder reaction of methyl-substituted 1,3-butadienes with 1,2-dibromoethylene, this approach to 4-methylbenzene oxide (**4c**) utilizing 1,3-butadiene and 1,2-dibromopropene was not successful. 1,2-Dibromopropene might be too unstable (due to having bromine attached to quaternary carbon) under the conditions of the Diels–Alder reaction or might have low reactivity owing to the electronic effect of the methyl group.

To confirm the synthesis of **4a** and **4b**, **4c** was synthesized from 1-methyl-1,4-cyclohexadiene according to the method reported by Jerina *et al.*[3a-c] The oxide **4c** was also converted into stable adduct **5c** through Diels–Alder reaction with 4-phenyl-1,2,4-triazoline-3,5-dione. The adduct **5c** was obtained as colorless prisms (mp 175—176 °C; *m*/*z* 283).

^{1}H-NMR data for these adducts (**5a**, **5b**, **5c**) are given in Table I. By comparison of the ^{1}H-NMR spectra of **5a**, **5b** and **5c**, and from the chemical shifts of the methyl, the methine, the vinyl and phenyl protons based on reference data,[5,6] the signals in each spectrum were assigned as shown in Table I.

Experimental

Melting points were determined on a Yamato melting point apparatus using a capillary tube and are uncorrected. IR spectra were measured on a Jasco FT/IR-5300 IR spectrophotometer in KBr disks for solids and as liquid films for oils. Electron impact mass spectra (EI-MS) were taken on a JEOL DX-300 spectrometer. ^{1}H-NMR spectra were recorded on a JEOL GX 270 FT spectrometer. Chemical shifts were recorded in ppm downfield from an internal standard (tetramethylsilane). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Column chromatography was performed on Kieselgel 60 (Merck, 70—230 mesh) or Kieselgel 60 silanisiert (Merck, 70—230 mesh). Thin-layer chromatography (TLC) was carried out with pre-coated Kieselgel 60 plates (Merck) or pre-coated Kieselgel 60 silanisiert plates (Merck).

Adduct (5a) of 3-Methylbenzene Oxide (4a) with 4-Phenyl-1,2,4-triazoline-3,5-dione Method A: 1,4-Dihydrotoluene,[3c] obtained from 1,4-dihydrobenzoic acid[7] *via* several steps,[3c,8] was treated with bromine, followed by epoxidation according to the method described by Jerina *et al.* to give 4,5-dibromo-3-methylcyclohexene oxide (**3a**) (16% yield based on benzoic acid), EI-MS *m*/*z* (%): 189 (M^+ − Br, 43). Treatment of **3a** (675 mg, 2.5 mmol) with potassium *tert*-butoxide by the procedure of Jerina *et al.*[3c] gave 3-methylbenzene oxide (**4a**) as a yellow oil. A solution of 4-phenyl-1,2,4-triazoline-3,5-dione in benzene was added to a stirred solution of **4a** in benzene (10 ml) at 5—10 °C until a red color appeared in the reaction mixture. The resulting solution was allowed to stand for 20 h at 5 °C, followed by concentration under reduced pressure and purification by column chromatography (Kieselgel 60 silanisiert, 50 g; benzene: *n*-hexane = 1 : 1). The eluate was evaporated to afford a crystalline residue, which was recrystallized from ethanol to give the adduct **5a** as colorless prisms (340 mg, 48% yield based on **3a**), mp 167—169 °C (dec.). EI-MS *m*/*z* (%): 283 (M^+, 31), 108 (M^+ − 175, 100). IR (KBr): 1760, 1710, 1490, 1400, 1250 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, s), 3.37 (1H, dd), 3.72 (1H, dt), 5.31 (1H, ddd), 6.03 (1H, dt), 6.13 (1H, dd), 7.40 (5H, m). *Anal.* Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found; C, 63.64; H, 4.63; N, 14.82.

Method B: A mixture of *trans*-1,3-pentadiene (**1a**) (2 g, 0.029 mol) and *cis*, *trans*-dibromoethylene (2.7 g, 0.015 mol) was sealed in a glass tube and heated for 22 h at 160 °C. After removal of unreacted volatile components under reduced pressure, an oily residue (2.3 g) was obtained. The residue was dissolved in benzene (10 ml), and this solution was added to a solution of *m*-chloroperoxybenzoic acid (6.2 g, 0.036 mol) in benzene (50 ml) cooled with ice-water. The resulting solution was allowed to stand for 2 d at room temperature, then filtered. The filtrate was washed with water (100 ml) containing Na_2CO_3 (10 g) and $NaHSO_3$ (3 g). The resulting organic layer was washed with water until the washings were neutral, then dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave the residue (2.6 g), which was purified by column chromatograhy (Kieselgel 60, 90 g; benzene) to afford 4,5-dibromo-3-methylcyclohexene oxide (**3a**) as a colorless oil (1.2 g, 15% yield based on **1a**), EI-MS *m*/*z* (%): 189 (M^+ − Br, 18). A solution of **3a** (810 mg, 3 mmol) in ether (10 ml) was added to a stirred solution of potassium *tert*-butoxide (1.4 g, 12 mmol) in ether (30 ml) at −75 °C over a 15 min period, and stirring was continued for an additional 5 min before adding 10% water–ethanol (5 ml). The ether layer was separated from the aqueous phase, washed with water (30 ml × 2) and dried over anhydrous Na_2CO_3. Removal of the ether gave 3-methylbenzene oxide (**4a**) as a yellow oil.

The oxide **4a** was treated with 4-phenyl-1,2,4-triazoline-3,5-dione according to method A mentioned above. The resulting solution was allowed to stand for 20 h at 5 °C, then concentrated under reduced pressure, and purified by column chromatography (Kieselgel 60 silanisiert, 50 g; benzene : *n*-hexane = 1 : 1). The eluate was evaporated to afford a crystalline residue, which was recrystallized from ethanol to give the adduct **5a** as colorless prisms (260 mg, 31% yield based on **3a**), mp 167—169 °C (dec.). The spectra (MS, IR and ^{1}H-NMR) of the adduct **5a** were identical with those of **5a** obtained by method A mentioned above. *Anal.* Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.68; H, 4.75; N, 14.71.

Adduct 5b of 1-Methylbenzene Oxide (4b) with 4-Phenyl-1,2,4-triazoline-3,5-dione Method A: According to the method described by Vogel *et al.*,[2c,d] 1-methyl-1,4-cyclohexadiene was treated with *m*-chloroperoxybenzoic acid, followed by bromination to give 4,5-dibromo-1-methylcyclohexene oxide (**3b**) as a colorless oil, EI-MS *m*/*z* (%): 189 (M^+ − Br, 100). Treatment of **3b** (680 mg, 2.5 mmol) with sodium methoxide according to the method described by Vogel *et al.*[2c,d] gave 1-methylbenzene oxide (**4b**) as a yellow oil.

The oxide **4b** was treated with 4-phenyl-1,2,4-triazoline-3,5-dione according to method A mentioned earlier. The resulting solution was allowed to stand for 5 d at 5 °C, then the precipitate was collected by filtration and crystallized from ethanol to give the adduct **5b** as colorless needles (350 mg, 49% yield based on **3b**), mp 174—175 °C. EI-MS *m*/*z* (%): 283 (M^+, 34), 240 (M^+ −43, 100). IR (KBr): 1775, 1725, 1490, 1400, 1260, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.68 (3H, s), 3.48 (1H, dd), 4.96 (1H, dd), 5.29 (1H, ddd), 6.13 (1H, m), 6.24 (1H, m), 7.40 (5H, m). *Anal.* Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.69; H, 4.68; N, 14.99.

Method B: A mixture of isoprene (**1b**) (2 g, 0.029 mol) and *cis*, *trans*-dibromoethylene (2.7 g, 0.015 mol) was sealed in a glass tube and heated for 21 h at 150 °C. The tube was opened and after removal of unreacted volatile components under reduced pressure, an oily residue (2.3 g) was obtained. The residue was dissolved in benzene (10 ml), and this solution was added to a solution of *m*-chloroperoxybenzoic acid (6.2 g, 0.036 mol) in benzene (50 ml) cooled with ice-water. The resulting solution was allowed to stand for 2 d at room tempeature, then filtered, and the filtrate was washed with water (100 ml) containing Na_2CO_3 (10 g) and $NaHSO_3$ (3 g). The resulting organic layer was washed with water until the washings were neutral, then dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave the residue (2.7 g), which was purified by column chromatography (Kieselgel 60, 90 g; benzene) to afford 4,5-dibromo-1-methylcyclohexene oxide (**3b**) as a colorless oil (0.75 g, 9.6% yield based on **1b**), EI-MS *m*/*z* (%): 189 ($M^+ - Br$, 100). A solution of **3b** (650 mg, 2.4 mmol) in ether (10 ml) was added to a stirred solution of sodium methoxide (0.59 g, 11 mmol) in ether (10 ml) at 35 °C over a 15-min period, and stirring was continued for an additional 5 min before adding ice-water (20 ml). The ether layer was separated from the aqueous phase, washed with water (30 ml × 2) and dried over anhydrous Na_2CO_3. Removal of the ether gave 1-methylbenzene oxide (**4b**) as a yellow oil.

Treatment of the oxide **4b** with 4-phenyl-1,2,4-triazoline-3,5-dione according to method A mentioned above afforded a precipitate, which was crystallized from ethanol to give the adduct **5b** as colorless needles (280 mg, 41% yield based on **3b**), mp 174—175 °C. The spectra (MS, IR and ^{1}H-NMR) of the adduct **5b** were identical with those of **5b** obtained by method A metioned above. *Anal.* Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.82; H, 4.75; N, 14.93.

Adduct 5c of 4-Methylbenzene Oxide (4c) with 4-Phenyl-1,2,4-triazoline-3,5-dione 1-Methyl-1,4-cyclohexadiene was treated with bromine, followed by epoxidation, according to the method described by Jerina *et al.*$^{3a-c)}$ to give 4,5-dibromo-4-methylcyclohexene oxide (**3c**) as colorless crystals, mp 54—57 °C (lit.$^{3a)}$ 56—62 °C), EI-MS *m*/*z* (%): 189 ($M^+ - Br$, 9.5). Treatment of **3c** (710 mg, 2.6 mmol) with sodium methoxide according to the method described by Vogel *et al.* gave 4-methylbenzene oxide (**4c**) as a yellow oil. The oxide **4c** was treated with 4-phenyl-1,2,4-triazoline-3,5-dione according to the method described above. The resulting solution was allowed to stand for 2 d at 5 °C, then evaporated to dryness under reduced pressure to afford a crystalline residue, which was recrystallized from ethanol to give the adduct **5c** as colorless plates (380 mg, 45% yield based on **3c**), mp 175—176 °C. EI-MS *m*/*z* (%): 283 (M^+, 47), 108 ($M^+ - 175$, 100). IR (KBr): 1765, 1715, 1495, 1410, 1260, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.93 (3H, s), 3.68 (2H, m), 5.09 (1H, m), 5.23 (1H, m), 5.76 (1H, m), 7.40 (5H, m). *Anal.* Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.83; H, 4.75; N, 15.03.

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