Aromatization of Benzamide 1,2-Oxide and *N,N*-Dimethylbenzamide 1,2-Oxide

Frank R. Busch and Glenn A. Berchtold*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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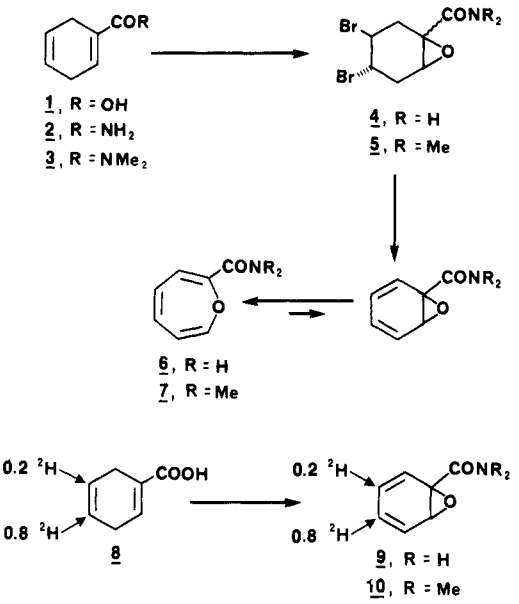
The mechanisms for aromatization of the title compounds have been investigated through product studies and studies with the deuterium-labeled arene oxides. Results from the primary amide **6** show that the relative amounts of C_1–O and C_2–O cleavage under acidic and neutral conditions are similar to those observed previously for the corresponding methyl ester and carboxylic acid derivatives. Aromatization of the cation derived from initial C_2–O cleavage occurred by both substituent loss and substituent migration; substituent loss was the major pathway under acid-catalyzed conditions and the minor pathway under neutral conditions. Substantially more C_1–O cleavage was observed with arene oxide **7**. For the reaction proceeding via C_2–O cleavage of **7**, substituent loss predominated over substituent migration at pH 0.1, but only substituent migration was observed at higher pH (4.0, 7.0).

A common pathway for the oxidative metabolism of aromatic substrates involves monooxygenase-catalyzed formation of arene oxides that subsequently rearrange to phenolic metabolites.[1] Numerous examples of biological hydroxylation reactions of benzene derivatives in which the arene 1,2-oxide or arene 2,3-oxide may be the initial metabolic intermediate are reported in the literature. Because of their importance in understanding biological hydroxylation reactions in addition to a general interest in understanding the effect of substituents, we have been investigating the pathway of aromatization of such arene oxides. Detailed studies of the aromatization of arene 1,2-oxides where the substituent is CH_3,[2] $Si(CH_3)_3$,[3] CO_2H,[4,5] CO_2CH_3,[4,5] CN,[6] CHO,[5] CH_2OH,[5] $CH_2CO_2CH_3$,[7] or *trans*-$CH{=}CHCO_2CH_3$[7] have been reported previously. Reported herein are studies of the aromatization of arene 1,2-oxides where the substituent is $-CONH_2$ or $-CON(CH_3)_2$.

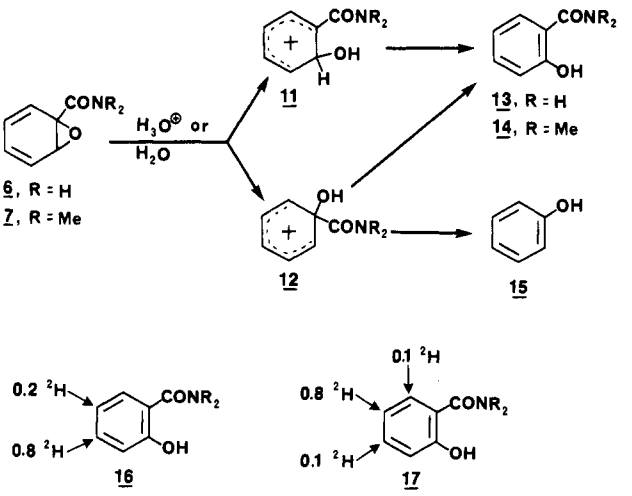
The preparation of benzamide 1,2-oxide (**6**) and *N,N*-dimethylbenzamide 1,2-oxide (**7**) is outlined in Scheme I. Acid **1** was converted to amides **2** and **3** via the acid chloride. Bromination of **2** and **3** followed by epoxidation (CF_3CO_3H) afforded **4** and **5** which were converted to **6** and **7** by dehydrobromination with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN). The deuterium-labeled derivatives of the arene oxides **9** and **10**, which had 80% ^2H at C_4 and 20% ^2H at C_5, were prepared from **8**[5] by the same procedure used to prepare **6** and **7**. Spectral data suggest that **6** and **7** exist predominantly as the oxepin valence tautomer.

The acid- or water-catalyzed aromatization of **6** and **7**, outlined in Scheme II, could occur by initial C_1–O cleavage to cation **11** or by initial C_2–O cleavage to cation **12**. Cation **11** should aromatize by migration of hydrogen (NIH shift)

Scheme I



Scheme II



to either ortho position followed by enolization to **13** (from **6**) or **14** (from **7**). Cation **12** should aromatize by migration of $-CONR_2$ followed by enolization to **13** or **14**. Alternatively, loss of the side chain [H^+ + HNCO or $(CH_3)_2N^+{=}C{=}O$] from **12** would yield phenol. The amount of **13** and

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Table I. Summary of Aromatization Reactions of 6 and 7

arene oxide	conditions[a]	% yield of o-$HOC_6H_4CONR_2$ total	via cation 11[b]	via cation 12[c]	% yield of phenol[d]
6	10% $CF_3CO_2{}^2H$	42			58
	pH 0.1	38	26	12	62
	pH 1.0	39			61
	pH 4.0	62			38
	pH 7.0	66	10	56	34
	pH 10.0	59			41
7	10% $CF_3CO_2{}^2H$	69			31
	pH 0.1	62	45	17	38
	pH 1.0	62			38
	pH 2.5	88			12
	pH 4.0	100	83	17	0
	pH 7.0	100	86	14	0
	pH 10.0	100			0

[a] Reactions were run in 1:1 $C^2H_3O^2H/^2H_2O$ and in 1:1 Me_2SO-$^2H_6/^2H_2O$ with the pH of the aqueous portion as indicated. [b] No migration of $CONR_2$. [c] Migration of $CONR_2$. [d] Via cation 12.

14 formed from initial C_1–O cleavage vs. C_2–O cleavage may be determined from aromatization of deuterium-labeled arene oxides 9 and 10, since reaction proceeding by formation of cation 11 should afford 13 or 14 with the deuterium distribution indicated in 16. The deuterium distribution indicated in 17 would be observed for reaction proceeding through formation of cation 12.

Arene oxides 6 and 7 were aromatized under the conditions indicated in Table I. The yields of ortho-substituted phenols and phenol from loss of substituent were determined from aromatization of the unlabeled arene oxides. The extent of substituent migration (reaction via cation 11 vs. cation 12) was determined from ^1H NMR analysis of ortho-substituted phenol from aromatization of deuterium-labeled arene oxides 9 and 10. Results are summarized in Table I. All reactions were run in duplicate.

The aromatization reactions of 6 and 7 represent the first examples of 1-substituted arene oxides that aromatize by all three pathways indicated in Scheme II. Results from the primary amide derivative (6) show that the relative amounts of C_1–O and C_2–O cleavage (cation 11 vs. cation 12) under acidic and neutral conditions are similar to those observed previously for the corresponding methyl ester and carboxylic acid derivatives. Whereas aromatization via C_2–O cleavage occurred solely by substituent migration in the case of the methyl ester and solely by substituent loss in the case of the carboxylic acid, cation 12 derived from initial C_2–O cleavage of 6 underwent both substituent loss and substituent migration.[8] Substituent loss was the major pathway under acid-catalyzed conditions (pH 0.1) and the minor pathway under neutral conditions.

Substantially more C_1–O cleavage is observed with arene oxide 7 in which the *N,N*-dimethylcarboxamide substituent is less electron withdrawing. For reaction proceeding via C_2–O cleavage, substituent loss predominates over substituent migration at pH 0.1, but only substituent migration is observed at higher pH (4.0, 7.0).

Experimental Section[9]

1,4-Cyclohexadiene-1-carboxamide (2). The acid chloride, prepared from 1,4-cyclohexadiene-1-carboxylic acid[10] and thionyl chloride, reacted with concentrated NH_4OH to give 2 (68%): mp 110–110.5 °C; IR ($CHCl_3$) 3550, 3430, 1690, 1660, 1640, 1590 cm^{-1}. Anal. Calcd for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.22; H, 7.28; N, 11.31.

***N,N*-Dimethyl-1,4-cyclohexadiene-1-carboxamide (3).** The acid chloride used to prepare 2 reacted with dimethylamine to give 3 (54%): bp 65 °C (0.02 mm); IR (neat) 1690, 1630 cm^{-1}. Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.66; N, 9.27. Found: C, 70.87; H, 8.71; N, 9.02.

Benzamide 1,2-Oxide (6). Bromine (24 g, 0.15 mol) was added dropwise over 1 h to a solution of 2 (18.3 g, 0.15 mol) in 250 mL of $CHCl_3$ at −40 °C. The solution was allowed to warm to room temperature, and solvent was removed under reduced pressure to give the crystalline 4,5-dibromo derivative of 2 (100%): mp 110–111 °C ($CHCl_3$); IR ($CHCl_3$) 3540, 3510, 1680, 1650, 1590 cm^{-1}.

The dibromide (10.2 g, 36 mmol) was dissolved in 1 L of CH_2Cl_2, and 100 g of Na_2HPO_4 was added. Trifluoroperoxyacetic acid,[11] prepared from trifluoroacetic anhydride (60 g, 0.28 mol) and 90% H_2O_2 (11.8 g, 0.34 mol), was added dropwise at room temperature. The mixture was heated under reflux for 46 h, cooled, and filtered. The filtrate was washed with 2 M Na_2SO_3 (100 mL) and 2 M Na_2CO_3 (100 mL). The organic layer was dried ($MgSO_4$), and solvent was removed under reduced pressure to give 10 g (92%) of 4: mp 164–166 °C (ethyl acetate/petroleum ether); IR ($CHCl_3$) 3520, 3410, 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 6.5–5.6 (br m, 2 H), 4.4–4.1 (m, 2 H), 3.6–2.4 (br m, 5 H). Anal. Calcd for $C_7H_9Br_2NO_2$: C, 28.12; H, 3.03; Br, 53.46; N, 4.59. Found: C, 27.98; H, 3.11; Br, 53.28; N, 4.53.

A solution of DBN (0.90 g, 7.3 mmol) in tetrahydrofuran (THF, 10 mL) was added dropwise to a solution of 4 (0.66 g, 2.2 mmol) in THF (25 mL) at 0 °C. The ice bath was removed, and the reaction was stirred overnight. The mixture was filtered, and solvent was removed under reduced pressure to obtain crude 6 as a yellow oil. Preparative TLC (silica gel, 2:1 ether/ethyl acetate, R_f 0.6) gave yellow crystals of pure 6 (0.20 g, 68%): mp 91.5–93.0 °C; IR ($CHCl_3$) 3520, 3400, 1690, 1640, 1620, 1570 cm^{-1}; UV (C_2H_5OH) 214 (ε 16 000), 321 nm (1800); ^1H NMR ($CDCl_3$, 60 MHz) δ 6.9–6.7 (m, 1 H), 6.7–5.6 (br m, 2 H, exchange with D_2O), 6.45–6.25 (m, 2 H), 5.8–5.65 (m, 2 H).

A crystalline Diels–Alder adduct of 6 was prepared by reaction with maleic anhydride in ether: mp 238 °C; high-resolution mass spectrum calcd for $C_{11}H_9NO_5$ 235.0481, found 235.0491.

***N,N*-Dimethylbenzamide 1,2-Oxide (7).** Bromination of 3 by the same procedure described above for the bromination of 2 gave the dibromide as a viscous oil (90%): IR (neat) 1630 cm^{-1}. Epoxidation of the dibromide by the same procedure described above for the preparation of 4 gave 5 in 75% yield after purification by column chromatography on silica gel: IR ($CHCl_3$) 1635 cm^{-1}; high-resolution mass spectrum calcd for $C_9H_{13}{}^{79}Br_2NO_2$ 324.9313, found 324.9290. Base-catalyzed elimination by the procedure described above for the preparation of 6 gave crude 7. Preparative TLC (silica gel, 1:1 ether/$CHCl_3$, R_f 0.65–0.45) gave pure 7 as a yellow oil (65%): IR ($CHCl_3$) 1730 cm^{-1}; UV

(8) Migration of the carboxamide group to an electron-deficient center has been observed previously. See, for example; Dahn, H.; Ballenegger, M.; Schlunke, H. *Chimia* **1964**, *18*, 59–60.

(9) High-resolution mass spectra were provided by the facility supported by National Institutes of Health Grant RR00317 (principal investigator Professor K. Biemann) from the Biotechnology Resources Branch, Division of Research Resources. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN. Unless otherwise indicated, ^1H NMR spectra were obtained in $CDCl_3$ at 250 or 270 MHz.

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(C_2H_5OH) 206 (8,800), 260 (sh), 310 nm (1100); ^1H NMR ($CDCl_3$, 60 MHz) δ 6.44 (m, 2 H), 6.31 (m, 1 H), 6.14 (m, 1 H), 5.21 (d, J = 5.3 Hz, 1 H), 3.05 (s, 3 H), 2.97 (s, 3 H).

A crystalline Diels-Alder adduct of **7** was prepared by reaction with maleic anhydride in ether: mp 215.5-216 °C. Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.97; N, 5.32. Found: C, 59.16: H, 5.03; N, 5.30.

Preparation of Deuterium-Labeled Arene Oxides 9 and 10. Hydrolysis of the ester of **8**, prepared as described previously,[5] gave acid **8** with the deuterium distribution as indicated in Scheme I. Arene oxides **9** and **10** were prepared from **8** by the same procedures described above for preparation of arene oxides **6** and **7** from **1**.

Aromatization of Arene Oxides 6 and 7. Aromatization of each arene oxide was studied under the conditions indicated in Table I. Buffer systems used were the same as described previously.[5] The time required for complete reaction at room temperature varied from a few hours under strongly acidic conditions to ~2 months at pH 7 or higher. Yields (Table I) were determined by integration of the aromatic region of the 250-MHz ^1H NMR spectrum of each product mixture.

Aromatization of 9 and 10. The aromatization procedure for the deuterium-labeled arene oxides was the same as described for the unlabeled materials. Deuterium-labeled amide **13** or **14** was isolated from each reaction, and the deuterium distribution was determined by analysis of the 250-MHz ^1H NMR spectrum as described previously.[5] Chemical shift data for the aromatic protons of unlabeled **13** and **14** were as follows: **13** ($CDCl_3$) δ 6.98 (H_5), 7.03 (H_3), 7.49 (H_4), 7.52 (H_6); **14** (CD_3OD) δ 6.97 (H_5), 6.99 (H_3), 7.22 (H_6), 7.34 (H_4).

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Registry No. 1 acid chloride, 95673-76-0; **2**, 95673-77-1; **3**, 95673-78-2; **4**, 95673-79-3; **5**, 95673-80-6; **6**, 95673-81-7; **6**-maleic anhydride Diels-Alder adduct, 95673-86-2; **7**, 95673-82-8; **7**-maleic anhydride Diels-Alder adduct, 95673-85-1; **13**, 65-45-2; **14**, 1778-08-1; 4,5-dibromocyclohex-1-ene-1-carboxamide, 95673-83-9; 4,5-dibromo-*N*,*N*-dimethylcyclohex-1-ene-1-carboxamide, 95673-84-0; maleic anhydride, 108-31-6.

Deconjugative Alkylation of α,β-Acetylenic Esters by Electrogenerated Base

Masao Tokuda* and Osamu Nishio

Division of Organic Synthesis, Department of Chemical Process Engineering, Faculty of Engineering, Hokkaido University, Sapporo 060, Japan

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Electrolysis of ethyl propiolate (**1**) and an excess of methyl iodide at a platinum cathode in hexamethylphosphoric triamide (HMPA) or *N*,*N*-dimethylformamide (DMF) solution containing tetra-*n*-butylammonium salt gave the acetylenic esters **2**, **3**, and **4**. Similar electrochemical reactions of α,β-acetylenic esters **2**, **5**, and **9** with methyl iodide took place in good yields to give the corresponding α,α-dimethyl β,γ-acetylenic esters **3** and **4**, **4**, and **10**, respectively. Electrochemical reactions of **5** with ethyl, butyl, and allyl iodides also gave α,α-dialkyl β,γ-acetylenic esters **6**, **7**, and **8**, respectively. These facile deconjugative alkylations appeared to take place by the action of the electrogenerated base (EGB) which was formed by the electrochemical reduction of alkyl iodides. Alkyl iodides worked as both a probasic compound of the EGB and as an electrophile. Reaction pathways of the present deconjugative alkylations are also discussed.

α,β-Unsaturated esters[1,2] or amides[3] are known to give the corresponding β,γ-unsaturated isomers having an alkyl substituent at the α-position when they are treated with a strong base such as lithium diisopropylamide (LDA) and followed by an addition of alkyl halide. However, when such a deconjugative alkylation was applied to α,β-acetylenic acid, a mixture of conjugated allenic and acetylenic acids having an alkyl substituent at the α- and the γ-position, respectively, has been obtained.[4] It has also been reported that a treatment of methyl but-2-ynoate with lithium isopropylcyclohexylamide followed by a protonation gave methyl buta-2,3-dienoate in a 60% yield.[1] Under basic conditions in protic solvents, α,β-acetylenic acid usually gives an equilibrium mixture of α,β-acetylenic, β,γ-acetylenic, and allenic acids,[5] except several examples.[6] Therefore, it is not necessarily easy to prepare the β,γ-acetylenic ester via a deconjugative alkylation of α,β-acetylenic ester by a conventional method.

In our continuing study on the carbon-carbon bond formation by electrochemical reductions of organic halides,[7] we have studied the electrochemical reaction of acetylenic compounds with alkyl halides. We wish to report here that the β,γ-acetylenic ester having two alkyl substituents at the α-position is prepared by the electrochemical reduction of α,β-acetylenic ester in the presence of alkyl iodide.[8] This electrochemical reaction can be carried out under a mild condition without the use of any strong base and, therefore, provides a convenient method for a synthesis of β,γ-acetylenic esters. Synthetic methods for those compounds that have been reported involve an oxidation of alk-3-yn-1-ols with chromic acid,[6b,9] a reaction of propargylmagnesium halide with carbon dioxide,[10] reactions of alkyl diazoacetate with terminal acetylenes[11] or

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