

Anionotropic Shift of the 3-Substituent in the Reaction of 2-Methoxy-2,3-dihydro-3-benzofuranols with Boron Trifluoride

Luisa Garanti and Gaetano Zecchi

Istituto di Chimica Industriale dell' Università', Centro del C.N.R. per la Sintesi
e Stereochimica di Speciali Sistemi Organici, Via Golgi 19, 20133 Milano, Italy

and

Ugo M. Pagnoni

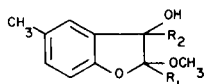
Istituto di Chimica Organica dell' Università', Via Campi 183, 41100 Modena, Italy

Received December 20, 1976

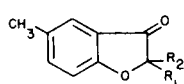
The reaction of 2,3-dihydro-3-benzofuranols **1a,c,d,f** with boron trifluoride in boiling xylene gave 3-(2*H*)benzofuranones **2a,c,d,f** in 40-85% yield. This reaction was not observed in the case of **1b,e**.

J. Heterocyclic Chem., **14**, 445 (1977).

The formation of a positive charge on a carbon atom often results in isomerization by a hydride, alkyl, or aryl 1,2-shift (1). In the benzofuran series, it has been found that 3-phenylbenzofurans rearrange under acidic conditions to the corresponding 2-substituted isomers *via* protonation and subsequent phenyl shift (2). We now wish to describe the anionotropic migration of the 3-substituent which occurs upon acidic treatment of 2-methoxy-2,3-dihydro-3-benzofuranols of type **1**.

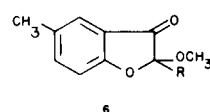
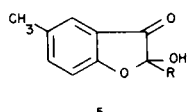
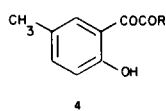
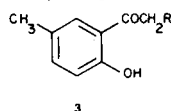


1a, 2a: R₁ = C₆H₅; R₂ = CH₂C₆H₅
1b: R₁ = C₆H₅; R₂ = CH₃
1c, 2c: R₁ = C₆H₅; R₂ = H



1d, 2d: R₁ = CH₃; R₂ = CH₂C₆H₅
1e: R₁ = R₂ = CH₃
1f, 2f: R₁ = CH₃; R₂ = H

Compounds **1a-f** were synthesized as follows. The reaction of phenols **3** with selenium dioxide led to mixtures of the isomeric compounds **4** and **5** (3). The products ratio was 1:4 in the case of **3a** and 9:1 in the case of **3b**. However, the treatment of these mixtures with anhydrous hydrogen chloride in methanol afforded the de-

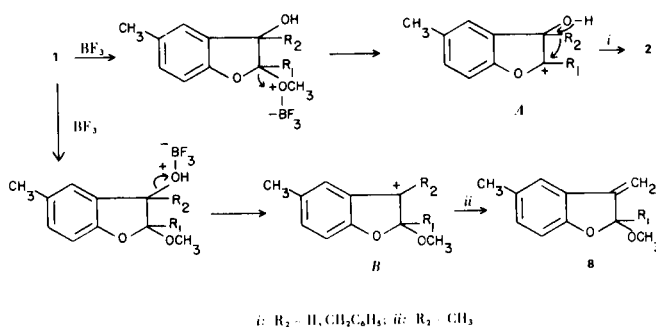


a: R = C₆H₅; b: R = CH₃

sired benzofuran derivatives **6** in satisfactory yields. The reactions of **6a** with benzylmagnesium chloride and methylmagnesium iodide gave **1a** and **1b** respectively, while its reduction with sodium borohydride afforded **1c**. Analogous reactions starting from **6b** provided **1d,e,f**. Compounds **1a,c,d,e,f** were obtained as one isomer of undetermined stereochemistry, while both the possible stereoisomers were isolated in the case of **1b**. Benzofuranols **1a-f** were refluxed in xylene in the presence of boron trifluoride for the time necessary for their complete disappearance (tlc analyses). In the case of **1a,c,d,f**, the reaction resulted in a single product, *i.e.* **2a,c,d,f**, respectively, in a yield ranging from 40 to 85% (see Table). However, only polymeric material was obtained starting from **1b,e**. A reasonable pathway leading to **2a,c,d,f** is illustrated in the Scheme.

The loss of the methoxy group is probably facilitated by the adjacent oxygen atom which stabilizes the resulting

Scheme 1



Table

Compound 2	Yield %	M.p. °C	Ir, cm ⁻¹ nujol	Nmr (Deuteriochloroform): δ	Formula	Anal.	
						Calcd.: C, H	Found: C, H
a	85	95 methanol	1710	1.75 (3H, s, ArCH ₃); 3.35-3.55 (2H, AB type, J = 14 Hz, ArCH ₂), 6.7-8.0 (13H, m, Ar)	C ₂₂ H ₁₈ O ₂	84.05 84.25	5.77 5.82
c	80	230 (4)	1725	2.25 (3H, s, ArCH ₃); 6.7-7.6 (8H, m, Ar)			
d	55	84 methanol	1710	1.28 (3H, s, CH ₃), 2.2-2.6 (5H, m, ArCH ₃ and ArCH ₂), 6.7-7.5 (8H, m, Ar)	C ₁₇ H ₁₆ O ₂	80.92 80.75	6.39 6.45
f	40	61 (5)	1715	1.50 (3H, d, CHCH ₃); 2.32 (3H, s, ArCH ₃); 4.55 (1H, q, CHCH ₃), 6.8-7.5 (3H, m, Ar)			

carbonium ion *A*. The subsequent evolution of this intermediate is closely related to the well known mechanism of the pinacol-pinacolone rearrangement (6). It may also be postulated that loss of the hydroxyl group could lead to carbonium ion species *B*. This pathway, if really present, would be reversible in the case of **1a,c,d,f**. Only when R₂ = CH₃ could proton elimination from *B* and subsequent acid-promoted polymerization occur, thus accounting for the observed behaviour of **1b,e**. In fact, it was ascertained that compound **8** (R₁ = C₆H₅), obtained from **1b** by treatment with phosphorus tribromide and pyridine, polymerizes easily in acid medium. Somewhat similar results were obtained by refluxing the benzofuranols **1** in formic acid.

EXPERIMENTAL

All melting points are uncorrected. Nmr spectra were recorded on a Varian A-60 A instrument in deuteriochloroform solution with tetramethylsilane as internal standard. Ir spectra were obtained with a Perkin-Elmer Model 377 spectrophotometer.

Reaction of **3a** with Selenium Dioxide.

A mixture of **3a** (36 g.) and selenium dioxide (57 g.) in acetic acid (150 ml.) was refluxed under stirring for 60 hours. After cooling, the mixture was filtered through celite and charcoal and the solution was evaporated to dryness. The crystallization of the crude product from methanol gave 1-(2-hydroxy-5-methylphenyl)-2-phenylethandione (**4a**) (22 g.), m.p. 88-90°; ir (nujol): 3320 (OH) and 1720 (CO) cm⁻¹; nmr: δ 2.21 (3H, s, CH₃), 6.9-8.2 (8H, m, Ar), 11.25 (1H, s, OH).

Anal. Calcd. for C₁₅H₁₂O₃: C, 74.99; H, 5.03. Found: C, 75.29; H, 5.15.

The methanolic solution was evaporated and the residue was distilled *in vacuo* to give a 1:1 mixture of **4a** and **5a** (5 g.), b.p. 110-115°/0.1 mm. From the nmr spectrum of this mixture, the following signals were inferred for **5a**: δ 2.15 (3H, s, CH₃), 4.65 (1H, broad s, OH), 6.9-8.2 (8H, m, Ar).

Reaction of **3b** with Selenium Dioxide.

Compound **3b** (22.6 g.) was treated with selenium dioxide (23 g.) as described in the above preparation, for 20 hours. The crude product was crystallized from diisopropyl ether to afford 2,5-dimethyl-2-hydroxy-3(2H)benzofuranone (**5b**) (8.8 g.), m.p. 104°; ir (nujol): 3400 (OH) and 1700 (CO) cm⁻¹; nmr: δ 1.60 (3H, s, CH₃), 2.30 (3H, s, CH₃), 4.4 (1H, broad s, OH), 6.8-7.6 (3H, m, Ar).

Anal. Calcd. for C₁₀H₁₀O₃: C, 67.40; H, 5.66. Found: C, 67.15; H, 5.70.

The mother liquor was evaporated and the residue was distilled *in vacuo* to give a 3:2 mixture of **5b** and **4b** (7.4 g.), b.p. 100-105°/0.5 mm. From the nmr spectrum of this mixture, the following signals were inferred for **4b**: δ 2.05 (3H, s, CH₃), 2.25 (3H, s, ArCH₃), 6.7-7.5 (3H, m, Ar), 11.17 (1H, s, OH).

2-Methoxy-5-methyl-2-phenyl-3(2H)benzofuranone (**6a**).

Dry hydrogen chloride was bubbled into a solution of **4a** + **5a** (25 g.) in methanol (400 ml.) at 0°. After 2 hours, about an half of the solvent was removed, methanol was added, and dry hydrogen chloride was newly bubbled at 0°. After 2 hours, the operation was repeated, then the solvent was entirely removed under reduced pressure and the residue was chromatographed on silica gel column (*n*-hexane-diethyl ether 9/1) to give **6a** (15.5 g.), m.p. 52°; ir (nujol): 1700 cm⁻¹ (CO); nmr: δ 2.35 (3H, s, CH₃), 3.42 (3H, s, OCH₃), 7.0-7.8 (8H, m, Ar).

Anal. Calcd. for C₁₆H₁₄O₃: C, 75.57; H, 5.55. Found: C, 76.02; H, 5.61.

2-Methoxy-2,5-dimethyl-3(2H)benzofuranone (**6b**).

A mixture of **4b** and **5b** (15 g.) was treated with dry hydrogen chloride as described for **4a**. The crude product was distilled *in vacuo* to afford **6b** (12.5 g.), b.p. 95-100°/0.1 mm; ir (nujol): 1725 cm⁻¹ (CO); nmr: δ 1.54 (3H, s, CH₃), 2.35 (3H, s, ArCH₃), 3.23 (3H, s, OCH₃), 6.8-7.6 (3H, m, Ar).

Anal. Calcd. for C₁₁H₁₂O₃: C, 68.73; H, 6.29. Found: C, 68.42; H, 6.35.

3-Benzyl-3-hydroxy-2-methoxy-5-methyl-2-phenyl-2,3-dihydrobenzofuran (**1a**).

A solution of **6a** (7.5 g.) in anhydrous ether (100 ml.) was slowly added to a solution of benzyl magnesium chloride prepared from 2.25 g. of magnesium and 10 g. of benzyl chloride in 200 ml. of anhydrous ether. The mixture was refluxed for 5 hours. After cooling, a saturated solution of ammonium chloride was added, and the organic layer was separated, dried on sodium sulfate, and evaporated. Silica gel column chromatography of the residue (*n*-hexane-diethyl ether 9/1) gave, beside some starting material and 1,2-diphenylethane, compound **1a** (3.9 g.), m.p. 105-106°; ir (nujol): 3600 cm⁻¹ (OH); nmr: δ 2.10 (3H, s, CH₃), 2.25, 2.42 (2H, AB type, J = 14 Hz, CH₂), 3.18 (3H, s, OCH₃), 3.3 (1H, broad s, OH), 6.1 (1H, m, Ar), 6.7-7.9 (12H, m, Ar).

Anal. Calcd. for C₂₃H₂₀O₃: C, 80.21; H, 5.85. Found: C, 79.99; H, 5.94.

3,5-Dimethyl-3-hydroxy-2-methoxy-2-phenyl-2,3-dihydrobenzofuran (**1b**).

A solution of **6a** (8.0 g.) in anhydrous ether (50 ml.) was

slowly added to a solution of methyl magnesium iodide prepared from 0.76 g. of magnesium and 1.6 ml. of methyl iodide in 100 ml. of anhydrous ether. The mixture was refluxed for 2 hours and handled as in the previous preparation. Silica gel column chromatography (*n*-hexane-diethyl ether 9/1) of the crude product allowed separation of two isomers of formula **1b**.

The *cis* isomer was 2.0 g., m.p. 110°; ir (Nujol): 3520 cm⁻¹ (OH); nmr: δ 0.95 (3H, s, CH₃), 2.31 (3H, s, Ar-CH₃), 3.18 (3H, s, OCH₃), 3.6 (1H, s, OH), 6.7-7.8 (8H, m, Ar).

Anal. Calcd. for C₁₇H₁₈O₃: C, 75.53; H, 6.71. Found: C, 75.13; H, 6.95.

The *trans* isomer was 3.1 g., m.p. 73°, ir (Nujol): 3350 cm⁻¹ (OH); nmr: δ 1.29 (1H, s, OH), 1.65 (3H, s, CH₃), 2.31 (3H, s, Ar-CH₃), 3.18 (3H, s, OCH₃), 6.7-7.7 (8H, m, Ar).

Anal. Calcd. for C₁₇H₁₈O₃: C, 75.53; H, 6.71. Found: C, 76.02; H, 6.55.

3-Benzyl-2,5-dimethyl-3-hydroxy-2-methoxy-2,3-dihydrobenzofuran (**1d**).

A solution of **6b** (2.7 g.) in anhydrous ether (20 ml.) was slowly added to a solution of benzyl magnesium chloride prepared from 0.75 g. of magnesium and 3.3 g. of benzyl chloride in 70 ml. of anhydrous ether. After 2 hours refluxing, the mixture was handled as above. Column chromatography (petroleum ether-diethyl ether 9/1) gave **1d** (1.8 g.), m.p. 51-53°; ir (Nujol): 3550 cm⁻¹ (OH); nmr: δ 1.58 (3H, s, CH₃), 2.00 (3H, s, ArCH₃), 2.58 (1H, dd, J = 11 and 3 Hz, one proton of the methylene group), 3.10 (1H, d, J = 11 Hz, one proton of the methylene group), 3.25 (3H, s, OCH₃), 3.30 (1H, d, J = 3 Hz, OH), 6.00 (1H, m, Ar), 6.4-7.2 (7H, m, Ar). The signal at 3.30 δ disappeared by shaking with deuterium oxide while the signal at 2.58 δ became a doublet with J = 11 Hz.

Anal. Calcd. for C₁₈H₂₀O₃: C, 76.03; H, 7.09. Found: C, 75.88; H, 6.89.

3-Hydroxy-2-methoxy-2,3,5-trimethyl-2,3-dihydrobenzofuran (**1e**).

A solution of **6b** (3.8 g.) in anhydrous ether (20 ml.) was added dropwise to a solution of methyl magnesium iodide prepared from 0.49 g. of magnesium and 2.9 g. of methyl iodide in 50 ml. of anhydrous ether. The mixture was refluxed for 2 hours and worked up as above. The crude product was chromatographed on silica gel column (*n*-hexane-diethyl ether 4/1) to yield **1e** (2.1 g., ca. 95% purity) as a viscous oil; ir (Nujol): 3500 cm⁻¹; nmr: δ 1.40 (3H, s, CH₃), 1.51 (3H, s, CH₃), 2.30 (3H, s, ArCH₃), 3.35 (3H, s, OCH₃), 3.3 (1H, broad s, OH), 6.5-7.2 (3H, m, Ar).

3-Hydroxy-2-methoxy-5-methyl-2-phenyl-2,3-dihydrobenzofuran (**1c**).

A solution of **6a** (0.5 g.) and sodium borohydride (0.05 g.) in methanol (50 ml.) was stirred at room temperature for 1 hour. The solvent was evaporated and the residue was taken up with water and extracted with ether. The residue from the distillation of the ether was purified by column chromatography on silica gel (benzene-petroleum ether 1/1) to give **1c** (0.20 g.), m.p. 54-55°; ir (Nujol): 3410 cm⁻¹ (OH); nmr: δ 2.30 (3H, s, CH₃), 3.15 (1H, d, J = 10 Hz, CHOH), 3.25 (3H, s, OCH₃), 5.15 (1H, d, J = 10 Hz, CHOH), 6.6-7.7 (8H, m, Ar).

Anal. Calcd. for C₁₆H₁₆O₃: C, 74.98; H, 6.29. Found: C, 75.15; H, 6.53.

2,5-Dimethyl-3-hydroxy-2-methoxy-2,3-dihydrobenzofuran (**1f**).

A solution of **6b** (0.6 g.) and sodium borohydride (0.06 g.) in methanol (60 ml.) was stirred at room temperature for 1 hour. The solvent was partly removed under reduced pressure and the

residue was treated with water and extracted with ether. The residue from the ethereal solution was chromatographed on silica gel column (benzene-*n*-pentane 1/1) to yield **1f** (0.35 g.) as a viscous oil of purity better than 95%; ir (Nujol): 3420 cm⁻¹ (OH); nmr: δ 1.58 (3H, s, CH₃), 2.22 (3H, s, ArCH₃), 3.20 (1H, d, J = 10 Hz, CHOH), 3.34 (3H, s, OCH₃), 4.87 (1H, d, J = 10 Hz, CHOH), 6.4-7.1 (3H, m, Ar).

Treatment of **1a-f** with Boron Trifluoride.

A solution of **1** (1 mmole) and boron trifluoride (0.2 ml.) in xylene (10 ml.) was refluxed for 2 hours. The solvent was evaporated *in vacuo* and the residue was crystallized from the proper solvent (See Table).

3-Acetoxy-5-methyl-2-phenylbenzofuran (**7**).

Benzofuranone **2c** (0.5 g.) was treated with acetic anhydride according to the procedure described for similar compounds (**4**), to give **7** (0.23 g.), m.p. 146°; ir (Nujol): 1760 cm⁻¹ (CO); nmr: δ 2.20 (3H, s, CH₃), 2.40 (3H, s, COCH₃), 6.8-7.8 (8H, m, Ar).

Anal. Calcd. for C₁₇H₁₄O₃: C, 76.67; H, 5.30. Found: C, 76.51; H, 5.38.

Reaction of **2c** with Benzyl Chloride in the Presence of Sodium Amide.

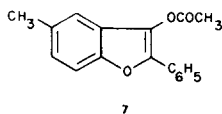
Benzyl chloride (1.3 g.) was added dropwise to a stirred suspension of **2c** (2.24 g.) and sodium amide (1.0 g.) in anhydrous dioxane (100 ml.). The mixture was refluxed for 24 hours. The solvent was partly removed and the residue was poured into cold water, neutralized with hydrochloric acid and extracted with ether. The organic solution was dried over magnesium sulfate and evaporated. The residue was chromatographed on silica gel column (*n*-hexane-diethyl ether 9/1) to give **2a** (1.2 g.).

2-Methoxy-5-methyl-3-methylidene-2-phenyl-2H-benzofuran (**8**, R₁ = C₆H₅).

Phosphorus tribromide (3.5 g.) was slowly added to a solution of **1b** (3.5 g.) and pyridine (3 ml.) in anhydrous ether (100 ml.). The mixture was refluxed for 12 hours, then poured into cold water. The organic layer was dried over sodium sulfate and evaporated. The column chromatography on silica gel of the residue gave **8** (R₁ = C₆H₅) as a viscous oil (3.0 g.); nmr: δ 2.30 (3H, s, CH₃), 3.32 (3H, s, OCH₃), 5.10, 5.68 (2H, two s, CH₂=), 6.7-7.7 (8H, m, Ar). Attempted distillation *in vacuo* caused decomposition.

REFERENCES AND NOTES

- (1) S. P. McManus and C. U. Pittman, Jr., "Organic Reactive Intermediates," S. P. McManus, Ed., Academic Press, New York, N. Y., 1973, p. 287.
- (2) A. Mustafa, "Benzofurans," Wiley Interscience, New York, N. Y., 1974, p. 16.
- (3) An analogous result was reported for the selenium dioxide oxidation of 2-hydroxyacetophenone [R. Howe, B. S. Rao, and H. Heyneker, *J. Chem. Soc. (C)*, 2510 (1967)].
- (4) Compound **1c** afforded a crystalline product identical to that obtained by reacting 2-bromo-1-(2-hydroxy-5-methylphenyl)-2-phenylethanone with sodium acetate [K. von Auwers, *Ber.*, 53B, 2271 (1920)]. Since the signal of the furan proton could not be found in the nmr spectrum, there are some doubts about the assignment of structure **2c**. However, treatment with acetic anhydride gave the enol acetate **7**; also, the reaction with benzyl chloride in the presence of sodium amide led to **2a**.



This behaviour somewhat resembles that reported for 3-phenyl-2(3*H*)benzofuranones [A. Mustafa and A. M. Islam, *J. Chem. Soc.*, 1616 (1951)]. On the other hand, in a recent paper on 2-aryl-3-(2*H*)benzofuranones, nmr data have been given only for the corresponding enol acetates [C. Katamna, *Bull. Chim. Soc. France*, 2309 (1970)].

(5) K. von Auwers, *Ber.*, 45, 991 (1912).

(6) See reference (1), p. 293.