HETEROCYCLES, Vol. 54, No. 2, pp. 825-831, Received, 15th June, 2000

SUBSTITUTION *vs* ADDITION. REGIOSELECTIVE ELECTRO-BROMINATION OF BENZOFURAN

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Abstract - Regioselective electro-bromination of benzofuran (**2**) was achieved successfully by an adequate choice of solvents and bromide salts to afford 5-bromobenzofuran (**1**), 5,7-dibromobenzofuran (**3**), and 2,3-dibromo-2,3-dihydrobenzofuran (**4**), respectively. Upon electrolysis of benzofuran (**2**) in AcOH/H_2O (100/1) containing NH_4Br, substitution at the C(5)-position of benzofuran (**2**) proceeded smoothly to afford 5-bromobenzofuran (**1**). After passage of totally 4 F/mol of electricity in a similar medium, 5,7-dibromobenzofuran (**3**) was obtained as a sole product. On the other hand, electrolysis of benzofuran (**2**) in CH_2Cl_2/H_2O (1/1) and/or AcOH/H_2O (10/1) in the presence of either NaBr or NH_4Br afforded 2,3-dibromo-2,3-dihydrobenzofuran (**4**), exclusively.

5-Bromobenzofuran (**1**), a potent intermediate for synthesis of benzofuran family of bioactive natural products, has been prepared by multi-step transformation of salicylaldehyde.[1] The most straightforward route to 5-bromobenzofuran (**1**) must be bromination of benzofuran (**2**), but has not yet been realized so far, presumably due to lack of suitable reagents for regioselective bromination of benzofuran (**2**). Electrochemical bromination has been well recognized to be a promising procedure for the preparation of bromo-substituted aromatic compounds, *e.g.*, *N*-acetyl-4-bromoaniline[2] and *N*-acetyl-5-bromoindoline.[3] We investigated electro-bromination of benzofuran (**2**) as an alternative

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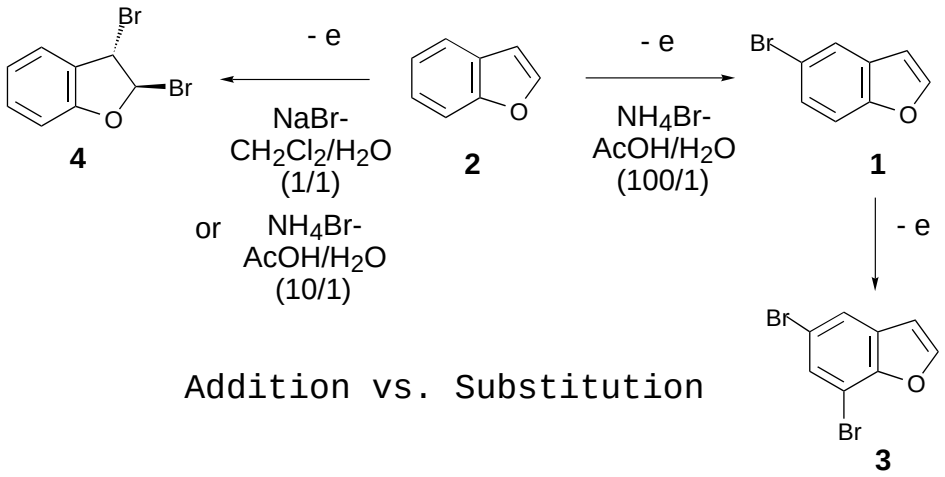
Dedicated to Professor Sho Ito on the occasion of his 77th birthday.

access to 5-bromobenzofuran (**1**). Herein, we describe regioselective electro-bromination of benzofuran (**2**) leading to either 5-bromobenzofuran (**1**), 5,7-dibromobenzofuran (**3**), or 2,3-dibromo-2,3-dihydrobenzofuran (**4**), respectively, depending on the choice of electrolysis media (Scheme 1).



Scheme 1

The electro-bromination of benzofuran (**2**) was carried out under a constant current density (10 mA/cm^2) in an undivided cell fitted with two platinum foil electrodes (1.5 x 1 cm$_2$). The representative results are shown in Table 1. Electrolysis of benzofuran (**2**) (1 mmol) in a CH_2Cl_2/H_2O (1/1) two phase solution (10 mL) in the presence of NaBr (2.1~4.2 equiv.) afforded 2,3-dibromo-2,3-dihydrobenzofuran (**4**) (77~84%) after passage of 2.2~4.4 F/mol of electricity (Entries 1 and 2). A similar bromine addition reaction was performed by use of NH_4Br in place of NaBr (Entry 3). In these experiments, any detectable amounts of the substitution products (**1**) and (**3**) were not obtained.

Electro-bromination of benzofuran (**2**) in AcOH/H_2O (10/1) proceeded in a similar fashion to afford the addition product (**4**) though the yields of **4** were slightly less than those above (Entries 4 and 5). Dramatic change of the products was observed when the amount of water in the electrolysis media was reduced to 1% (Entries 6~8). Thus, upon electrolysis of benzofuran (**2**) in AcOH/H_2O (100/1) in the presence of NH_4Br (2.0 equiv.), regioselective bromination at the C(5)-position of benzofuran (**2**) took place to afford 5-bromobenzofuran (**1**) (48%) together with 5,7-dibromobenzofuran (**3**) (6%) after passage of 2.2 F/mol ofelectricity (Entry 6). Continuing electrolysis of benzofuran (**2**) under same conditions (totally 4.0 F/mol) resulted in the formation of considerable amounts of tarry materials without detectable amounts of **1** and **3** (Entry 7). The 5,7-dibromobenzofuran (**3**) was obtained as a sole product (47%) by the electrolysis (4.0 F/mol) with 4.1 equiv. of NH_4Br (Entry 8).

Table 1. Electro-bromination of Benzofuran (**2**)

Entry	Br^- Salt (equiv.)	Solvent	F/mol	Conv.[a] (%)	Yield(%)[b] **1**	**3**	**4**
1	NaBr (2.1)	CH_2Cl_2/H_2O (1/1)	2.2	81	-	-	77
2	NaBr (4.2)	CH_2Cl_2/H_2O (1/1)	4.4	100	-	-	84[c]
3	NH_4Br (2.1)	CH_2Cl_2/H_2O (1/1)	2.2	78	-	-	69
4	NaBr (2.0)	$AcOH/H_2O$ (10/1)	2.2	60	-	-	70
5	NH_4Br (2.0)	$AcOH/H_2O$ (10/1)	2.2	80	-	-	48
6	NH_4Br (2.0)	$AcOH/H_2O$ (100/1)	2.2	100	48[d]	6	-
7	NH_4Br (2.1)	$AcOH/H_2O$ (100/1)	4.0	100[e]	-	-	-
8	NH_4Br (4.1)	$AcOH/H_2O$ (100/1)	4.0	100	-	47	-

[a] Based on recovered **2** after column chromatography. [b] Isolated yields after column chromatography. [c] Current yield: 38%. [d] Current yield: 38%. [e] A considerable amount of tarry materials was obtained.

The time course of the electrolysis of benzofuran (**2**) in an $AcOH/H_2O$ (100/1)-NH_4Br (4.1 equiv.) system (Entry 8) was monitored by HPLC (Figure 1). In the initial stage of the reaction, bromination at the C(5)-position of benzofuran (**2**) took place efficiently; thus, when 1 F/mol of electricity was passed, 50% of the starting material (**2**) was consumed and almost quantitative yield of 5-bromobenzofuran (**1**) was formed. Then, the yield of 5-bromobenzofuran (**1**) slightly increased but gradually decreased after passage of electricity more than 2 F/mol, affording 5,7-dibromobenzofuran (**3**). After passage of totally 4 F/mol of electricity, 47% yield of 5,7-dibromobenzofuran (**3**) was obtained. Further electrolysis resulted in the decomposition of the dibromide (**3**) leading to mess tarry materials.

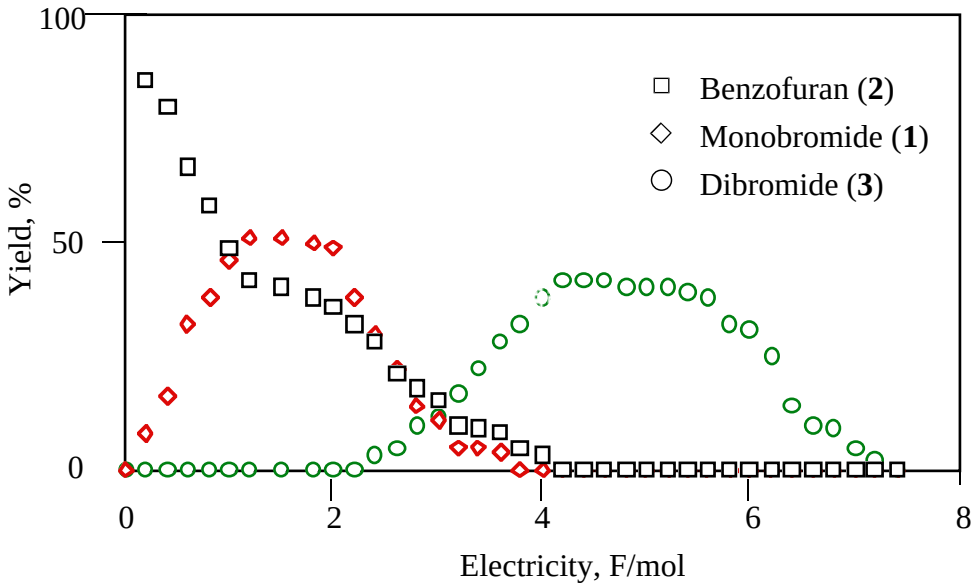
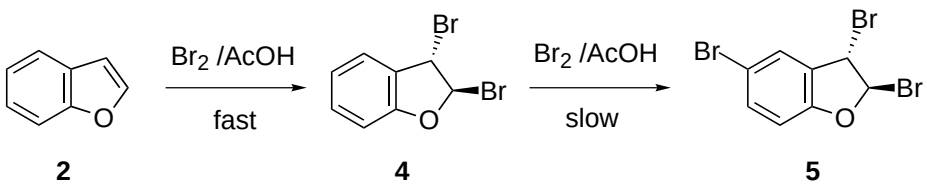


Figure 1

The remarkable change of the products depending on the electrolysis media would be ascribable to generation of different bromine species in each of the electrolysis systems. In this connection, it is interesting to note that bromination of benzofuran (**2**) with Br_2 (3.4 equiv.) in AcOH at room temperature afforded a mixture of 2,3-dibromo-2,3-dihydrobenzofuran (**4**) (42%) and 2,3,5-tribromo-2,3-dihydro-benzofuran (**5**) (28%) after 1 h, and the latter **5** was obtained as an only isolable product (56%) after 3 h. This fact suggests that Br_2 undergoes addition to the C(2)–C(3) double bond of benzofuran (**2**), more efficiently than substitution at the C(5)-position.



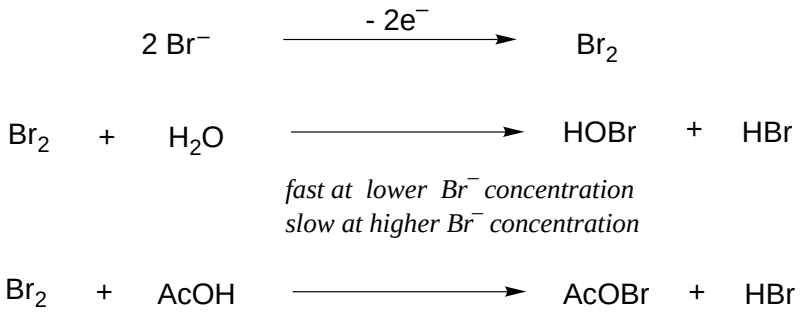
2 **4** **5**

Scheme 2

The difference between the electrolysis media promoting regioselective addition and substitution is the concentration of water (*e.g.*, Entries 5 and 6). In AcOH/H_2O (100/1), only a small part (1 mg/mL) of NH_4Br was dissolved in the media and most of NH_4Br remained as solids. On the other hand, much

more NH_4Br (20 mg/mL) was dissolved in AcOH/H_2O (10/1). The difference in concentration of the bromide salts in each of the electrolysis media would significantly change the bromine species generated by electrooxidation of bromide ion.

In a previous paper,[4] we reported that either electro-bromination or hydroxybromination of olefins could be performed successfully by tuning the bromide concentration in aqueous electrolysis media; indeed, at high concentration of bromide ion (>100 mg/mL), 1, 2-dibromides were exclusively formed, probably *via* addition of electrogenerated Br_2, while at low concentration of bromide ion (~2 mg/mL), bromohydrines were obtained as a sole isolable product, presumably *via* addition of electrogenerated HOBr. The present regioselective bromination of benzofuran (**2**) would be explained in a silimar way by assuming electrochemical generation of different bromine species, *e.g.*, Br_2, HOBr, and AcOBr (Scheme 3) . Thus, upon the electrolysis in an NH_4Br-AcOH/H_2O (10/1) system (higher Br^- concentration), Br_2 generated *via* two electron oxidation of bromide ion would attack mainly at the C(2)–C(3) double bond of benzofuran (**2**) leading to the addition product (**4**). On the other hand, in an NH_4Br-AcOH/H_2O (100/1) system (lower Br^- concentration), the electrogenerated Br_2 would smoothly be hydrolyzed to afford HOBr (and/or AcOBr),[5] which would, in turn, react with benzofuran (**2**), affording the substitution products **1** and **3**.



Scheme 3

In conclusion, regioselective bromination of benzofuran (**2**) leading to addition product (**4**) and substitution products (**1**) and (**3**) was performed by a proper choice of electrolysis media, *e.g.*, NaBr-CH_2Cl_2/H_2O (1/1), NH_4Br-AcOH/H_2O(10/1), and NH_4Br-AcOH/H_2O(100/1). The product selectivity can be reasonably explained by assuming the formation of different active bromine species, *e.g.*, Br_2, HOBr, and AcOBr, depending on the bromide ion concentration of each of the electrolysis media.

EXPERIMENTAL

^{1}H NMR spectra were determined at 200 MHz with a Varian Gemini-200 instrument. IR spectra were obtained with a JASCO FT-IR-VALOR-III spectrometer. High performance liquid chromatography (HPLC) was executed with Shimadzu HPLC instrument equipped with LC-10AT LC pump, SPD-10A UV detector, and C-R6A integrator. All chemicals and solvents were used as supplied without further purification.

General Procedure. Electrolysis was carried out in a beaker type undivided cell fitted with a magnetic stirring bar and two platinum foil electrodes (1.0 x 1.5 cm^2) and regurated dc power was supplied by a Metronix 543B instrument. The reaction was monitored by HPLC analysis under the conditions: column YMC-Pack AM-312 ODS (6.0 mm ϕ x 150 mm), mobile phase CH_3CN/H_2O 65:35, flow rate 1.0 mL/min.

Electrolytic Bromine Addition of Benzofuran (2) in an NaBr–CH_2Cl_2/H_2O (1/1) System. Into the electrolysis cell were added sodium bromide (468 mg, 4.55 mmol), benzofurane (**2**) (128 mg, 1.08 mmol), dichloromethane (4 mL), and water (4 mL). The mixture was electrolyzed under a constant current of 10 mA/cm^2 (applied voltage: 1.5 V) at rt. After passage of 4.4 F/mol of electricities (8.5 h), the mixture was extracted with CH_2Cl_2. The extracts were combined, washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (hexane/AcOEt: 30/1) to afford 2,3-dibromo-2,3-dihydrobenzofuran (**4**) (252 mg, 84%)[6]: ^{1}H NMR (200 MHz, $CDCl_3$-Me_4Si) δ 5.76 (s, 1H), 6.92 (s, 1H), 7.03 (d, J = 7.5 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 7.52 (d, J = 7.5 Hz, 1H); IR (KBr) 3036, 1614, 1601, 1466, 1326, 1314, 1095, 1021, 955 cm^{-1}.

Electrolytic Bromine Substituion of Benzofuran (2) in an NH_4Br–AcOH/H_2O (100/1) System. Into an electrolysis cell were placed ammonium bromide (232 mg, 2.37 mmol), benzofuran (**2**) (142 mg, 1.20 mmol), AcOH (10 mL), and water (0.1 mL). The electrolysis was carried out under a constant current of 10 mA/cm^2 (applied voltage: 2.0 V) at rt. After passage of 2.2 F/mol of electricities (4.7 h), the mixture was poured into aqueous saturated $NaHCO_3$ and extracted with ethyl acetate. The extracts were combined, washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (hexane/AcOEt: 30/1) to afford 5-bromobenzofuran (**1**) (114 mg, 48%) and 5,7-dibromobenzofuran (**3**) (20 mg, 6%).

5-Bromobenzofuran (**1**)[1]: ^{1}H NMR (200 MHz, $CDCl_3$-Me_4Si) δ 6.70 (d, J = 2.2 Hz, 1H), 7.36 (s, 2H),

7.62 (d, J = 2.2 Hz, 1H), 7.74 (s, 1H); IR (KBr) 3022 1612, 1604, 1453, 1336, 1308, 1011 cm^{-1}.

5,7-dibromobenzofuran (**3**)[7]: ^1H NMR (200 MHz, $CDCl_3$-Me_4Si) d 6.81 (d, J = 2.0 Hz, 1H), 7.61 (d, J = 2.0 Hz, 2H), 7.69 (br s, 2H); IR (KBr) 3022 1611, 1609, 1432, 1313, 1307, 1068 cm^{-1}.

Bromination of Benzofuran (2) with Bromine in AcOH. To a solution of benzofuran (**2**) (124 mg, 1.05 mmol) in AcOH (1 mL) (124 mg, 1.05 mmol) was added dropwise a solution of bromine (0.18 mL, 3.60 mmol) in AcOH (2 mL) at 0~5 °C. After being stirred at 0~5 °C for 3 h, the reaction mixture was poured into aqueous saturated Na_2SO_3 and extracted with ethyl acetate. The extracts were combined, washed with aqueous suturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (hexane/AcOEt: 30/1) to afford 2,3,5-tribromo-2,3-dihydrobenzofuran (**5**) (209 mg, 0.58 mmol, 56 %): ^1H NMR (200 MHz, $CDCl_3$-Me_4Si) δ 5.70 (s, 1H), 6.87 (s, 1H), 7.55 (s, 1H), 7.64 (s, 1H); IR (KBr) 3042, 1611, 1599, 1452, 1326, 1322, 1085 cm^{-1}

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