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A New Preparative Method of 4-Hydroxybenzofuran-2-carboxylic Acid Derivatives

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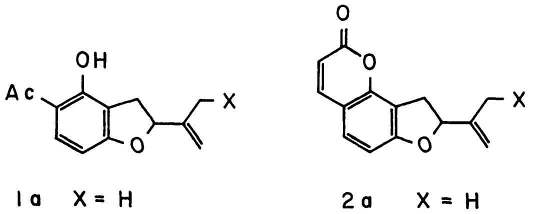
Synopsis. 4-Oxo-4,5,6,7-tetrahydrobenzofuran-2-carboxylic acid was prepared from 1,3-cyclohexanedione and ethyl bromopyruvate. Dehydrogenation of this acid or its methyl ester gave 4-hydroxybenzofuran-2-carboxylic acid derivatives.



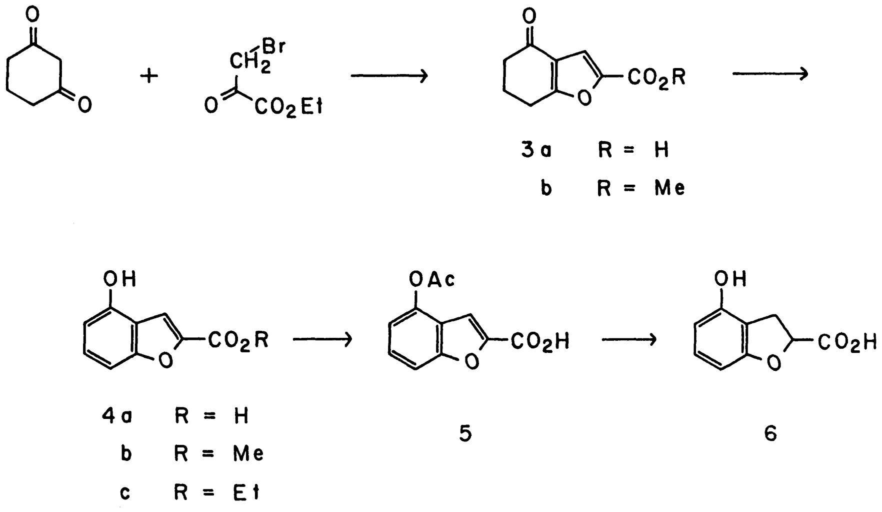
1a X = H
1b X = $OCOCH(CH_3)_2$
1c X = $OCOCH(CH_3)C_2H_5$

2a X = H
2b X = OH

Chart 1.

We reported the synthesis of some natural dihydrobenzofuran derivatives from optically active 2,3-dihydrobenzofuran-2-carboxylic acid.[1] For a similar synthesis of some natural dihydrobenzofuran derivatives having an *O*-functional group at the 4 position, such as **1a**,[2] **1b**, **1c**,[3] **2a**,[4] and **2b**,[5] 4-hydroxy-2,3-dihydrobenzofuran-2-carboxylic acid (**6**) might be a key compound. However, no effective preparation of 4-hydroxybenzofuran-2-carboxylic (**4**) and **6** has been reported. We now describe a new preparative method of **4** and its conversion to **6**.

A methanolic solution of 1,3-cyclohexanedione and ethyl bromopyruvate was refluxed with sodium methoxide; acidification of this mixture gave 4-oxo-4,5,6,7-tetrahydrobenzofuran-2-carboxylic acid (**3a**) in 76% yield. This acid **3a** was readily converted to the corresponding methyl ester **3b** with methanol-*p*-toluenesulfonic acid (76%) or diazomethane (69%).



3a R = H
b R = Me

4a R = H
b R = Me
c R = Et

5

6

Chart 2.

Table 1. Dehydrogenation Reactions of 3a and 3b

Substrate	Reagent[a)]	Conditions Temp/°C	Conditions Time/h	Product	Yield/%
3a	A	250	1	—	0
3b	A	250	3	**4a**	13
3a	B	AcOEt-$CHCl_3$[b)]	1	**4a**	9
3a	B	AcOEt-$CHCl_3$[b)]	5	**4c**	23
3a	B	AcOMe-$CHCl_3$[b)]	5	**4b**	28
3a	B	EtOH[b)]	2	**4c**	38
3a	B	MeOH[b)]	2	**4b**	56
3a	B	THF[b)]	2	**4a**	16
3b	B	MeOH[b)]	2	**4b**	38
3a	C	Benzene[b)]	4	**4a**	5
3b	C	Benzene[b)]	4	**4b**	5

a) A: sulfur, B: copper(II) bromide, C: DDQ. b) Refluxing temp.

Table 2. Some Physical Data and Elemental Analyses of New Benzofuran-2-carboxylic Acid Derivatives

Compound	Mp	IR ν_{CO} /cm^{-1}	UV λ_{max}(log ε) /nm	MS (m/z)	Elemental analyses		
	°C				Found (%)	Calcd (%)	
3a	146—147	1730 1630	264 (3.70)	180 152 136	C 59.70 H 4.72	C 60.00 H 4.48	for $C_9H_8O_4$
3b	108.5—109	1735 1655	256 (3.84)	194 166 163	C 61.71 H 5.22	C 61.85 H 5.19	for $C_{10}H_{10}O_4$
4a	200—202	1695	230 (4.32) 260sh (3.96) 287 (3.79)	178 160 132	C 60.77 H 3.48	C 60.68 H 3.40	for $C_9H_6O_4$
4b	87—89	1675	229 (4.04) 275 (3.50)	192 160 132	C 62.34 H 4.36	C 62.50 H 4.20	for $C_{10}H_8O_4$
4c	67—68	1670	231 (3.75) 275 (3.24)	206 160 132	C 64.15 H 4.97	C 64.07 H 4.89	for $C_{11}H_{10}O_4$
5	202—203	1750 1670	250 (3.82) 278sh (2.90)	220 178 160	C 60.04 H 3.56	C 60.00 H 3.66	for $C_{11}H_8O_5$
6	142—143.5	1700	274 (3.26) 280.5 (3.21)	180 178 160	C 59.94 H 4.49	C 60.00 H 4.48	for $C_9H_8O_4$

Table 3. ^{1}H NMR Data of Benzofuran-2-carboxylic Acid Derivatives

Compound	(solvent)	Chemical shifts data/ppm
3a	($CDCl_3$)	2.4 (2H, m, J=6 Hz) 2.7 (2H, t, J=6 Hz) 3.1 (2H, t, J=6 Hz) 8.3 (1H, s) 13.4 (1H, s)
3b	(CCl_4)	2.2 (2H, m, J=6 Hz) 2.6 (2H, t, J=6 Hz) 2.9 (2H, t, J=6 Hz) 3.9 (3H, s) 7.9 (1H, s)
4a	(acetone-d_6)	6.9 (1H, dd, J=8 and 2 Hz) 7.3 (1H, dd, J=8 and 2 Hz) 7.5 (1H, t, J=8 Hz) 8.7 (1H, s)
4b	(CCl_4)	3.8 (3H, s) 6.7 (1H, dd, J=8 and 2 Hz) 6.9 (1H, dd, J=8 and 2 Hz) 7.2 (1H, t, J=8 Hz) 8.0 (1H, s) 9.7 (1H, s)
4c	(CCl_4)	1.4 (3H, t, J=7 Hz) 4.4 (2H, q, J=7 Hz) 6.7 (1H, dd, J=8 and 2 Hz) 6.8 (1H, dd, J=8 and 2 Hz) 7.1 (1H, t, J=8 Hz) 8.0 (1H, s) 9.8 (1H, s)
5	($CDCl_3$)	2.3 (3H, s) 7.1 (1H, dd, J=6 and 3 Hz) 7.3 (1H, t, J=6 Hz) 7.5 (1H, dd, J=6 and 3 Hz) 7.5 (1H, s) 8.3 (1H, s)
6	($CDCl_3$)	4.5 (1H, dd, J=14 and 8 Hz) 4.7 (1H, dd, J=14 and 7 Hz) 4.9 (1H, dd, J=8 and 7 Hz) 6.4 (2H, d, J=8 Hz) 7.0 (1H, t, J=8 Hz) 9.3 (2H, broad s)

The dehydrogenation of **3a** and **3b** was attempted by the following three methods: A) heating with sulfur,[6] B) bromination with copper(II) bromide followed by dehydrobromination,[7] and C) heating with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[8] (summarized in Table 1). In some cases with copper(II) bromide, trans-esterification or esterification was observed. The dehydrogenation of **3a** was most effective with copper(II) bromide in refluxing methanol for 2 h. Interestingly, esters **4b** and **4c** showed a lower carbonyl band than acid **4a** regarding their IR spectra.

4-Hydroxy-2,3-dihydrobenzofuran-2-carboxylic acid (**6**) was obtained by a sodium amalgam reduction of 4-acetoxybenzofuran-2-carboxylic acid (**5**) in 56% yield, which was prepared from **4a** by acetylation with acetic anhydride.

Experimental

The melting points were uncorrected. The IR spectra were measured on a Hitachi EPI-S2 spectrophotometer in KBr disks, and the UV spectra were taken on a Hitachi 220A spectrophotometer in ethanol. The ^{1}H NMR spectra were recorded on a JEOL PMX-60Si NMR spectrometer in CCl_4, $CDCl_3$, or acetone-d_6 and the mass spectra were recorded on a JEOL JMS-OISG-2 mass spectrometer. The yields, some physical data, and elemental analyses are summarized in Tables 1, 2, and 3.

Preparation of 4-Oxo-4,5,6,7-tetrahydrobenzofuran-2-carboxylic Acid (3a). To a methanolic solution of sodium methoxide, prepared from sodium metal (2.8 g, 122 mmol) and abs. methanol (45 ml), 1,3-cyclohexanedione (14.5 g, 129 mmol) was added. Then, a solution of ethyl bromopyruvate[9] (25.0 g, 128 mmol) in abs. methanol was added to the mixture with stirring. After refluxing for 4 h, the mixture was allowed to stand for 20 h at room temperature. The solvent was removed under reduced pressure, and the residue was diluted with water and acidified with 10% hydrochloric acid. The mixture was allowed to stand for 2 d to complete cyclization and crystallization. The crystals were collected and recrytsallized from ethanol to give 4-oxo-4,5,6,7-tetrahydrobenzofuran-2-carboxylic acid (**3a**) (16.6 g, 76%) as colorless needles. A similar reaction of 1,3-cyclohexanedione and ethyl bromopyruvate with equivalent potassium hydroxide in water-methanol also gave **3a**, but in poorer yield (31%).

Preparation of Methyl 4-Oxo-4,5,6,7-tetrahydrobenzofuran-2-carboxylate (3b). To a solution of **3a** (2.11 g, 11.7 mmol) in methanol (100 ml) was added a small amount of *p*-toluenesulfonic acid; the mixture was refluxed for 24 h. After removing the methanol, the residue was diluted with benzene. The benzene layer was washed with sat. sodium hydrogencarbonate solution and then with sat. sodium chloride solution, and dried over anhydrous sodium sulfate. After removing the solvent, the residue was crystallized from cyclohexane to give methyl 4-oxo-4,5,6,7-tetrahydrobenzofuran-2-carboxylate (**3b**) (1.72 g, 76%) as colorless plates. This methyl ester **3b** was also obtained by esterification of **3a** with an excess of diazomethane ethereal solution in 69%.

Dehydrogenation of 3a or 3b. A) With Sulfur:[6] A mixture of **3b** (903 mg, 4.65 mmol) and sulfur powder (152 mg, 4.74 mmol) was heated at ca. 250 °C on a metal bath for 3 h. After cooling, the mixture was treated with benzene and the benzene solution was extracted with a 5% sodium hydroxide solution. The alkaline aqueous solution was acidified with 10% hydrochloric acid and re-extracted with benzene. The benzene layer was washed with sat. sodium chloride solution and dried over anhydrous sodium sulfate. After removing the solvent, the residue was crystallized from benzene to give 4-hydroxybenzofuran-2-carboxylic acid (**4a**) (105 mg, 13%). A similar heating of acid **3a** with sulfur generated an odour of hydrogen sulfide, but did not give **4a**.[10]

B) With Copper(II) Bromide:[6] To a solution of **3a** (1.93 g, 10.7 mmol) in methanol (50 ml) was added copper(II) bromide (4.60 g, 20.6 mmol), and the mixture was refluxed for 2 h. After cooling, the precipitates of copper(I) bromide were filtered off and washed with benzene. The filtrate and the washings were combined and concentrated at reduced pressure. The residue was diluted again with benzene, and the precipitates of copper(II) bromide were filtered off. After removing the benzene, the residue was crystallized from methanol to give methyl 4-hydroxybenzofuran-2-carboxylate (**4b**) (1.15 g, 56%) as colorless plates. Similar treatments of **3a** or **3b** with copper(II) bromide gave **4a**, **4b**, or **4c**, depending on the solvent used. Ester **4c** was purified by recrystallization from ethanol and obtained as colorless wooly crystals. Acid **4a** was purified by sublimation (150—180 °C at 16 mmHg[11]), followed by recrystallization from benzene, and obtained as colorless wooly crystals. The yields and some physical data are summarized in Tables 1, 2, and 3.

C) With DDQ:[7] To a solution of **3a** (588 mg, 3.27 mmol) in benzene (30 ml) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)(763 mg, 3.36 mmol), and the mixture was refluxed for 4 h. After cooling, the precipitated hydroquinone was filtered off and washed with benzene. The filtrate and the washings were combined and extracted with a sodium hydrogencarbonate solution. The alkaline extract was acidified with 10% hydrochloric acid and re-extracted with benzene. The benzene layer was dried over anhydrous sodium sulfate and concentrated. The residue was sublimed to give **4a** (29 mg, 5%). A similar treatment of **3b** (513 mg, 2.64 mmol) with DDQ (711 mg, 3.13 mmol) in benzene (30 ml) for 4 h gave **4b** (26 mg, 5%) as a sodium hydroxide extract, which was purified by crystallization from methanol.

4-Acetoxybenzofuran-2-carboxylic Acid (5). A solution of **4a** (1.02 g, 5.73 mmol) in acetic anhydride (5 ml) was heated on a water bath for 3 h. After removing the solvent, the residue was treated with water and the precipitates were collected and recrystallized from benzene to give 4-acetoxybenzofuran-2-carboxylic acid (**5**) (0.92 g, 74%) as colorless needles.

4-Hydroxy-2,3-dihydrobenzofuran-2-carboxylic Acid (6). To a solution of **5** (1.01 g, 4.59 mmol) in an aqueous potassium hydroxide solution (containing 0.5 g of potassium hydroxide in 10 ml of water) was added 2% sodium amalgam (0.32 g of sodium metal in 17 g of mercury); the mixture was stirred for one night. The alkaline aqueous layer was acidified with 10% hydrochloric acid and extracted with ether. After removing the solvent, the residue was recrystallized from benzene to give 4-hydroxy-2,3-dihydrobenzofuran-2-carboxylic acid (**6**) (450 mg, 56%) as colorless crystals.

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10) High reaction temperature probably caused decarboxylation and polymerization.

11) 1 mmHg = 133.322 Pa.