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Synthesis of 2-Alkyl-5-nitrobenzofurans *via* 2-(2-Formyl-4-nitrophenoxy)alkanoic Acids

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An efficient synthesis of 2-alkyl-5-nitrobenzofurans from 5-nitrosalicylaldehyde and 2-bromoesters *via* 2-(2-formyl-4-nitrophenoxy)alkanoic acids is described.

Key words: 2-(2-formyl-4-nitrophenoxy)alkanoic acids, 2-alkyl-5-nitrobenzofurans, hydrolysis, cyclization

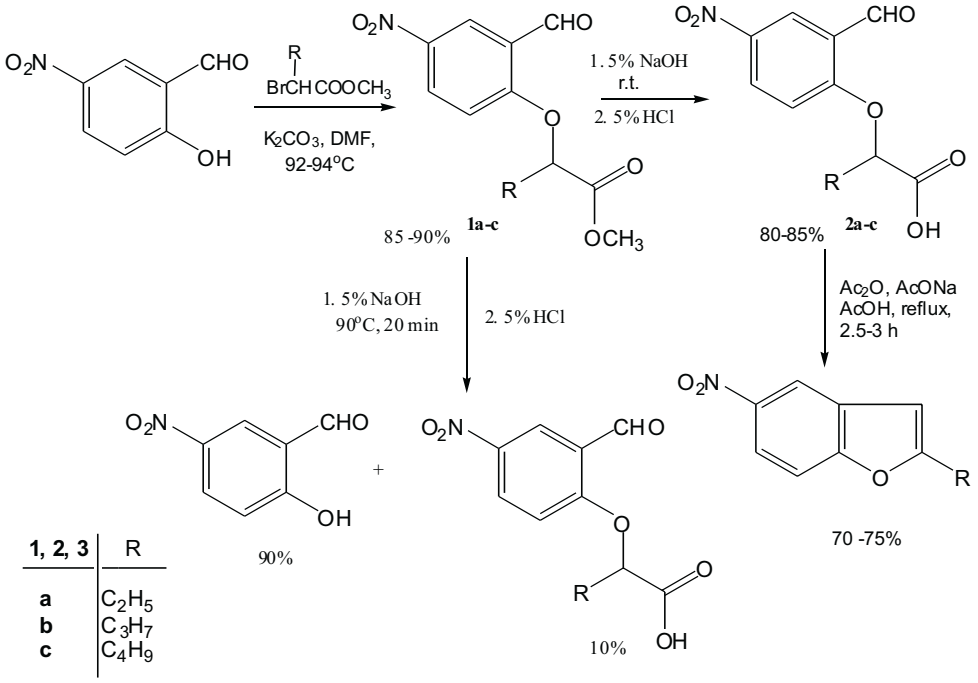
2-Alkyl-5-nitrobenzofurans are intermediates in the production of therapeutic agents for treatment of pathological syndroms of the cardiovascular system, such as of angina pectoris, hypertension and arrhythmias [1]. Several nitrobenzofurans, as well as aminobenzofurans, have exhibited significant pharmacological profiles as potential antibacterial and antifungal agents [2–5]. Nitrobenzofuran structure is a building block in the synthesis of an oxa analogue of the highly cytotoxic natural product duocarmycin SA [6].

Only a few methods for preparation of nitrobenzofurans are available in literature and most of them deal with unsubstituted in 2 position 5-nitrobenzofurans. They are usually prepared by cyclization of available 2-formyl-5-nitrophenoxyacetic acid to 5-nitro-2-benzfurancarboxylic acid, followed by decarboxylation [7–11]. The 2-formyl-5-nitrophenoxyacetic acid was obtained by nitration of 2-formylphenoxyacetic acid [12,13] or by condensation of 5-nitrosalicylaldehyde with haloacetic acids or their esters [14,15]. 2-Methyl-5-nitrobenzofuran was prepared by cyclization either, 2-hydroxy-5-nitrophenylacetone [16,17] or 4-nitrophenyl-2-propynyl ether [18,19]. 2-Alkyl-5-nitrobenzofurans were produced by reaction of 2-hydroxy-5-nitrobenzyltriphenyl-phosphonium bromides with pentanoyl chloride in the presence of pyridine [5] or by cyclization of O-(4-nitrophenyl)-2-ketooximes [20,21]. Recently, propynylnitrophenol acetates were utilized as intermediates in the synthesis of 2-propylnitrobenzofurans [22], whereas 2-(2-formyl-4-nitrophenylphenoxy)hexanoic acid was used in preparation of 2-butyl-5-nitrobenzofuran [23,24].

RESULTS AND DISCUSSION

Continuing our research direct for novel phenylacetyl derivatives of benzofuran, since several hundred grams of 5-nitro-2-alkylbenzofurans were needed, we required a convenient method of synthesis for 2-(2-formyl-4-nitrophenoxy)alkanoic acids [25]. Accordingly, we decided to develop the method we had employed so far [26,27], starting now from 5-nitrosalicylaldehyde and 2-bromoesters. The reaction of 5-nitrosalicylaldehyde with methyl 2-bromoalkanoates was carried out in the presence of potassium bicarbonate in DMF solution under heating for 4 hours and the corresponding esters **1a**–**c** were obtained with 85–90% yields (Scheme 1).

Scheme 1



A basic hydrolysis of 2-(2-formyl-4-nitrophenoxy)alkanoates **2a**–**c**, with 5% sodium or potassium hydroxide under heating, resulted predominantly in a cleavage of the ethereal bond and formation of only small amounts of the desired acids **2a-c** (Table 1). We have found, that the hydrolysis can be conveniently performed with 5% sodium hydroxide at ambient temperature for 3–4 hours and the acids **2a**–**c** were obtained in high yields (Table 1). Heating of the acids with acetic anhydride in acetic acid in presence of sodium acetate afforded benzofurans **3a**–**c** in high yields.

Table 1. Optimization of the conditions of hydrolysis of esters **1a**–**c** into acids **2a**–**c**.

Entry	Ester [mole]	5% NaOH [ml]	Temp. [°C]	Time [h]		Yield*	
						Acid [%]	5-Nitrosalicylaldehyde [%]
1	**1a** / 0.01	40	90	0.5	**2a**	10	90
2	**1a** / 0.01	40	50	2	**2a**	25	75
3	**1a** / 0.01	60	22	4	**2a**	95	5
4	**1a** / 0.01	80	22	3.5	**2a**	100	–
5	**1b** / 0.01	60	50	2	**2b**	10	90
6	**1b** / 0.01	80	22	3.5	**2b**	100	–
7	**1c** / 0.01	80	22	4	**2c**	100	–

*Percentage part of individual compounds in crude product was determined with ^{1}H NMR spectra.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded with TM Bruker DPX 4000 spectrometer for solution $CDCl_3$ (TMS as an internal standard). Mass spectra were obtained with a Hawlett-Packard 6890 apparatus, equipped with a mass detector HP 5973 and 30 m × 0.2 mm capillary column filled up with a 0.25μm film of a 5% Me Ph silicate. Melting points were determined with a Boetius apparatus and are uncorrected.

Starting materials. 5-Nitrosalicylaldehyde was prepared by nitration of salicylaldehyde with nitric acid in acetic acid solution according to [28], although it is commercially available. Methyl 2-bromoalkanoate: -butanoate, -pentanoate and hexanoate were obtained according to [29].

General procedures. Synthesis of methyl 2-(2-formyl-5-nitrophenoxy)alkanoate 1a–c. A mixture of 5-nitrosalicylaldehyde (0.2 mole), methyl 2-bromoalkanoate (0.2 mole), anhydrous potassium carbonate (0.2 mole) and dry DMF (400 ml) was heated at 92–94°C with stirring for 3.5 h. Then the solution was poured into ice-water, the precipitate was filtered off, washed with water and dried in the air. The following compounds were obtained:

Methyl 2-(2-formyl-4-nitrophenoxy)butanoate (**1a**): Yield 90%, m.p. 68–69°C (methanol); ^{1}H NMR, δ ppm: 10.55 (s, 1H, CHO), 8.72 (d, J = 2.9, 1H, Ar), 8.38 (dd, J_1 = 2.9, J_2 = 9.2, 1H, Ar), 6.93 (d, J = 9.2, 1H, Ar), 4.88 (t, J = 5.6, 1H, CH), 3.80 (s, 3H, OCH_3), 2.19–2.12 (m, 2H, CH_2), 1.14 (t, J = 7.4, 3H, CH_3). Anal. Calcd. for $C_{12}H_{13}NO_6$ (267.23): C, 53.93; H, 4.90; N, 5.24. Found: C, 53.75; H, 5.01; N, 5.12.

Methyl 2-(2-formyl-4-nitrophenoxy)pentanoate (**1b**): Yield 85%, m.p. 53–55°C; ^{1}H NMR, δ ppm: 10.54 (s, 1H, CHO), 8.72 (d, J = 2.8, 1H, Ar), 8.38 (dd, J_1 = 2.9, J_2 = 9.2, 1H, Ar), 6.93 (d, J = 9.2, 1H, Ar), 4.92 (q, J_1 = 4.9, J_2 = 2.4 1H, CH), 3.82 (s, 3H, OCH_3), 2.16–2.02 (m, 2H, CH_2), 1.64–1.53 (m, 2H, CH_2), 1.02 (t, J = 7.4, 3H, CH_3). Anal. Calcd. for $C_{13}H_{15}NO_6$ (281.26): C, 55.51; H, 5.38; N, 4.98. Found: C, 55.35; H, 5.47; N, 5.10.

Methyl 2-(2-formyl-4-nitrophenoxy)hexanoate (**1c**): Yield 87%, m.p. 62–63°C, ^{1}H NMR, δ ppm: 10.56 (s, 1H, CHO), 8.67 (d, J = 2.9, 1H, Ar), 8.38 (dd, J_1 = 2.9, J_2 = 9.2, 1H, Ar), 6.94 (d, J = 9.2, 1H, Ar), 4.92 (t, J = 5.9, 1H, CH), 3.79 (s, 3H, OCH_3), 2.13–2.09 (m, 2H, CH_2), 1.54–1.51 (m, 2H, CH_2), 1.45–1.35 (m, 2H, CH_2), 0.95 (t, J = 7.4, 3H, CH_3). Anal. Calcd. for $C_{14}H_{17}NO_6$ (295.29): C, 56.94; H, 5.80; N, 4.74. Found: C, 56.72; H, 5.92; N, 4.70.

Synthesis of 2-(2-formyl-5-nitrophenoxy)alkanoic acids 2a–c. The ether **1a**–**c** (0.1 mole) was added to a solution of 5% sodium hydroxide (700–800 ml) and reaction mixture was stirred and heated at steam bath for 1–2 minutes and next was stirred for an additional 3–4 h at room temperature until the solid was dissolved. The mixture was then filtered, hydrochloric acid (10%) was added to the filtrate and the precipitate was separated, washed with water and dried. The crude acid was recrystallized from methanol. The following compounds were obtained:

2-(2-Formyl-4-nitrophenoxy)butanoic acid (**2a**): Yield 85%, m.p. 145–147°C; ^{1}H NMR, δ ppm: 10.55 (s, 1H, CHO), 8.72 (d, J = 2.9, 1H, Ar), 8.38 (dd, J_1 = 2.9, J_2 = 9.3, 1H Ar), 8.0 (broad band, 1H, COOH), 7.03 (d, J = 9.3, 1H, Ar), 4.84 (q, J = 5.4, J_2 = 1.1, 1H, CH), 2.22–2.11 (m., 2H, CH_2), 1.59 (t, J = 7.4, 3H, CH_3). Anal. Calcd. for $C_{10}H_{11}NO_6$ (253.21): C, 52.18; H, 4.38; N, 5.53. Found: C, 52.03; H, 4.52; N, 5.50.

2-(2-Formyl-4-nitrophenoxy)pentanoic acid (**2b**): Yield 84%, m.p. 126–127°C; ^{1}H NMR, δ ppm: 10.54 (s, 1H, CHO), 8.68 (d, J = 2.8, 1H, Ar), 8.38 (dd, J_1 = 2.8, J_2 =9.3, 1H Ar), 8.05 (broad band, 1H, COOH), 7.02 (d, J = 9.3, 1H, Ar), 4.88 (t, J = 5.4, 1H, CH), 2.13–2.08 (m., 2H, CH_2), 165–1.56 (m., 2H, CH_2), 1.02 (t, J= 7.4, 3H, CH_3). Anal. Calcd. for $C_{12}H_{13}NO_6$ (267.23): C, 53.93; H, 4.90; N, 5.24. Found: C, 53.79; H, 5.02; N, 5.18.

2-(2-Formyl-4-nitrophenoxy)hexanoic acid (**2c**): Yield 80%, m.p. 112–113°C; ^{1}H NMR, δ ppm: 10.50 (s, 1H, CHO), 8.71 (d, J = 2.8, 1H, Ar), 8.38 (dd, J_1 = 2.9, J_2 = 9.3, 1H, Ar), 8.0 (broad band 1H, COOH), 6.98 (d, J = 9.3, 1H, Ar), 4.96 (t, J = 5.4, 1H, CH), 2.17–2.12 (m., 2H, CH_2), 1.57–1.51 (m, 2H, CH_2); 1.44–1.39 (m, 2H, CH_2), 0.95 (t, J = 7.4, 3H, CH_3). Anal. Calcd. for $C_{13}H_{15}NO_6$ (281.26): C, 55.51; H, 5.38; N, 4.98. Found: C, 55.23; H, 5.44; N, 4.90.

Cyclization of acid 2a–c to 2-alkyl-5-nitrobenzofurans. A mixture of acid **2a**–**c** (0.2 mole), acetic anhydride (350 ml), anhydrous sodium acetate (2.0 mole) and glacial acetic acid (300 ml) was heated at reflux until the solution changes colour from slight yellow to slight brown (2.5–3 h). The solution was poured into ice-water, the precipitate was filtered off, washed with water and dried in the air. The crude solid was recrystallized from methanol. The following compounds were obtained:

2-Ethyl-5-nitrobenzofuran (**3a**): pale yellow needles (methanol), m.p. 86°C, lit. [3] 85°C. GC/MS, MS m/z (%) = 191 (M^+, 85), 176 (100), 130 (48), 115 (25), 145 (20), 102 (12), 91 (9), 144 (73), 76 (6), 89 (6), 76 (6), 63 (6), 116 (5), 131 (5), 51 (4). Anal. Calcd. for $C_{10}H_9NO_3$ (191.18): C, 62.82; H, 4.74; N, 7.33. Found: C, 62.68; H, 4.82; N, 7.22.

5-Nitro-2-propylbenzofuran (**3b**): m.p. 34–35°C, pale brown needles (methanol), ^{1}H NMR, δ ppm: 8.40 (d, J = 2.2, 1H, Ar), 8.14 (dd, J_1 = 2.3, J_2 = 9.0, 1H, Ar), 7.46 (d, J = 9.0, 1H, Ar), 6.52 (s, 1H, Ar), 2.78 (t, J = 7.4, 2H, CH_2), 1.84–1.75 (m., 2H, CH_2), 1.03 (t, J= 7.4, 3H, CH_3). GC/MS, MS m/z (%) = 205 (M^+, 63), 176 (100), 130 (60), 177 (27), 102 (16), 131 (8), 76 (7), 159 (7), 115 (6), 118 (5), 89 (4), 63 (4). Anal. Calcd. for $C_{11}H_{11}NO_3$ (205.21): C, .64.38; H, 5.40; N, 6.83. Found: C, 64.13; H, 5.54; N, 6.80.

2-Butyl-5-nitrobenzofuran (**3c**): pale brown needles, m.p. 29–30°C, ^{1}H NMR, δ ppm: 8.29 (s, 1H, Ar), 8.03 (d, J = 8.5, 1H, Ar), 7.35 (d, J = 8.5, 1H, Ar), 6.41 (s, 1H, Ar), 2.72 (t, J = 6.5, 2H, CH_2), 1.67–1.64 (m, 2H, CH_2), 1.35–1.33 (m, 2H, CH_2), 0.87 (t, J= 6.4, 3H, CH_3). GC/MS, MS m/z (%) = 219 (M^+, 49), 176 (100), 177 (90), 130 (58), 102 (17), 60 (12), 115 (10), 178 (10), 76 (8), 144 (7), 118 (5), 89 (5), 63 (4). Anal. Calcd. for $C_{12}H_{13}NO_3$ (219.24): C, 65.74; H, 5.98; N, 6.39. Found: C, 65.66; H, 6.04; N, 6.25.

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