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Synthesis of 2-Alkylbenzofurans *via* Acid-catalyzed Cyclization of 1,1-Dimethoxy-2-phenoxyalkanes

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Treatment of 2-phenoxyalkanals **1a–e** with methanol at room temperature under homo- or heterogeneous acid-catalysis conditions leads to formation of diacetal as well as some quantities of appropriate 2-alkylbenzofurans. 2-Alkylbenzofurans **3a–e** were obtained in high yields *via* cyclization of the 1,1-dimethoxy-2-phenoxyalkanes **2a–e** under mild conditions over Amberlyst 15.

Key words: aldehydes, acetals, benzofurans, cyclization

2-Alkylbenzofurans are important intermediates used in pharmaceutical industry [1] as well as in the syntheses of pesticides [2] and dyes [3]. Numerous methods for the synthesis of 2-alkylbenzofurans are described [4–10]. The majority of the syntheses are based on the formation of the furan ring from various phenolic substrates, with the exception of the method starting from benzofuran *via* acylation followed by reduction of the acyl derivative with hydrazine [4]. Commonly used precursors of 2-alkylbenzofurans are 2-formylphenoxy ketones [5] and 2-(2-formylphenoxy)alkanoic acids [6–10], both prepared from salicylaldehyde. The competitive precursors of 2-alkylbenzofurans can be diacetals of 2-phenoxyalkanals, which can be prepared from phenol. Hitherto known 1,1-dialkoxy-2-phenoxyethanes were obtained *via* alkylation of phenols with commercially available 2-bromo-1,1-diethoxyethane in boiling anhydrous N,N-dimethylformamide or absolute dimethylsulfoxide in the presence of such basic as potassium carbonate, sodium alkanolate or potassium hydroxide [11–17]. The application of this method for higher homologs than 1,1-dialkoxy-2-phenoxyethanes is limited because of the unavailability of the appropriate 2-halogeno-1,1-dialkoxyalkanes and require harsh reaction conditions. For example, alkylation of phenol with either 2-bromo-1,1-dimethoxypropane [11] or 2-bromo-1,1-diethoxybutane [18] was performed in ethanol, in the presence of sodium ethylate at 200–210°C or 160°C, respectively.

Cyclization of 1,1-dialkoxy-2-phenoxyethane, as well as of its analogs with their diversely substituted ring was performed with a variety of acid reagents, for example, sulphuric [11] or polyphosphoric acid [13,14], zinc chloride in oxalic or acetic acid [12] and phosphorus pentoxide or acid resin in chlorobenzene [15,16]. These reactions were usually carried out for dozen hours at 100°C upwards and gave the corresponding benzofurans in small or moderate yields only. However, there are no data

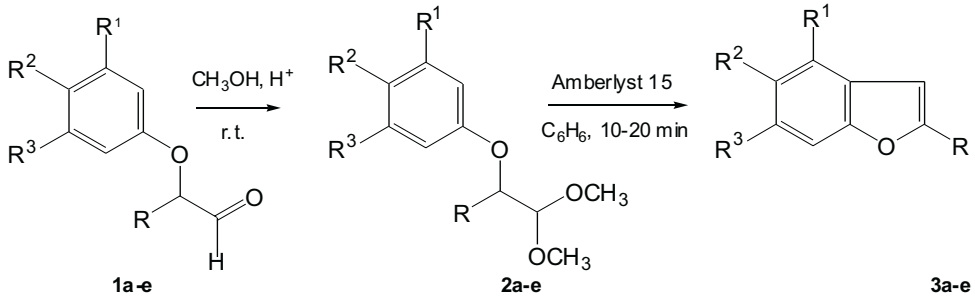
concerning the cyclization of other homologous of 2-phenoxy-1,1-dialkoxyethanes, except for 2-phenoxy-1,1-diethoxypropane [11].

Due to the requirement for a convenient synthesis of 1,1-dialkoxy-2-phenoxyalkanes as a potential precursors of 2-alkylbenzofurans we have investigated the acetalization of the corresponding 2-phenoxyalkanals. The aldehydes can be readily prepared from phenols and methyl 2-bromoalkanoate or 2-bromoalkanoic acids *via* Pd-catalyzed Rosenmund's reduction of the corresponding acids chlorides [19,20].

RESULTS AND DISCUSSION

In order to prepare the acetals of phenoxyalkanals **2a–e**, we have carried out the homo- and heterogeneous acid-catalyzed reaction of these aldehydes with methanol in the presence of sulphuric acid or Amberlyst 15 resin as the catalyst at room temperature (Scheme). The reaction progress was controlled by gas chromatography. Table 1 shows that the best results of the acetalization were achieved when Amberlyst 15 was used as a catalyst.

Scheme



1a-e **2a-e** **3a-e**

1, 2, 3	R	R^1	R^2	R^3
a	C_2H_5	H	H	H
b	C_4H_9	H	H	H
c	C_2H_5	H	OCH_3	H
d	C_2H_5	H	*t*-Bu	H
e	C_2H_5	CH_3	H	CH_3

The acetals were isolated after the filtering off the resin followed by the neutralization of the reaction mixture with sodium carbonate.

Table 1. Synthesis of 2-phenoxy-1,1-dimethoxyalkanes **2a–e**.

Entry	Starting aldehyde		Methanol	H_2SO_4*	Amberlyst 15	Reaction time	Acetal		2-Alkylbenzofuran	
		(mmol)	(ml)	(ml)	(g)	(days)		(%)		(%)
1		6.0	10	–	0.03	6		94		–
2		6.0	10	–	0.06	6		97		–
3	**1a**	6.0	10	–	0.09	6	**2a**	93	**3a**	trace
4		6.0	15	0.04	–	12		74		9
5		3.6	10	0.02	–	12		85		–
6		5.2	10	–	0.06	12		91		2
7	**1b**	5.2	10	0.03	–	12	**2b**	82	**3b**	3
8		3.6	10	0.05	–	12		75		10
9		3.6	10	–	0.05	6		93		–
10	**1c**	5.1	10	0.03	–	8	**2c**	68	**3c**	–
11		10.2	20	0.06	–	17		58		20
12		5.9	12	–	0.06	6		94		–
13	**1d**	5.9	12	0.04	–	12	**2d**	87	**3d**	2
14		3.2	10	0.02	–	17		68		15
15		3.6	12	–	0.04	6		93		–
16	**1e**	3.6	12	0.03	–	12	**2e**	70	**3d**	10
17		3.6	12	0.03	–	17		64		15

*d = 1.84 g cm^{-1}

The structure of acetals was confirmed by ^{1}H NMR. When sulphuric acid was used as a catalyst, a mixture comprising the acetal (64–78%), 2-alkylbenzofuran (2–15%) and the starting aldehyde (3–10%) was obtained after 12 days. When the reaction mixture was left for a period longer than 12 days, or when more than 0.1 equivalent of sulphuric acid per 1.0 equivalent of aldehyde was used, the yield of 2-alkylbenzofuran was increasing considerably, although the decomposition of acetal to the starting phenoxyaldehyde was also increased. The formation of 2-alkylbenzofurans was also observed during the catalyzed by Amberlyst 15 acetalization, yet the process of the cyclization of acetals was markedly slower.

The cyclization of acetals **2a–e** to 2-alkylbenzofurans **3a–e** was investigated in methanol, benzene and toluene, using homogeneous sulphuric acid and heterogeneous Amberlyst 15 resin as catalysts. When the reaction was carried out at room temperature, for several days, the 2-alkylbenzofuran was formed in a moderate yield. The best results (practically quantitative yields of cyclization of acetals) were achieved when the reaction mixture was heated in nonpolar solvent such as benzene or toluene for 10–20 minutes over the Amberlyst 15 (Table 2). The mixtures obtained from such a reaction were colourless, and 2-alkylbenzofuran was sufficiently pure when isola-

ted by simply filtering off the resin, neutralizing the mixture and distilling off the solvent under reduced pressure. When the cyclizations were carried out in methanol, 2-alkylbenzofurans were obtained in lower yields and appropriate 2-phenoxyalkanals were found in the reaction mixture. This is probably due to easy acid catalyzed decomposition of acetals in methanol to 2-phenoxyaldehydes which in turn undergo cyclization harder comparing to the corresponding acetal. When acetals were treated with a larger than catalytic amount of sulphuric acid or when the reactions were performed at higher temperature (120°C) or for a longer time (more than 2 h), the yields of 2-alkylbenzofurans decreased due to the polymerization processes.

Table 2. Cyclization of 1,1-dimethoxy-2-phenoxyalkanes **2a–e** to 2-alkylbenzofurans **3a–e**.

Entry	Starting material		Solvent	Amberlyst 15	H_2SO_4*	Temperature	Reaction time	2-Alkylbenzofuran	
		(mmol)	(ml)	(g)	(ml)	(°C)	(min)		(%)
1		2.4	Toluene (20)	1.2	–	107	10		96
2		3.3	Toluene (20)	2.0	–	107	10	**3a**	97
3	**2a**	2.4	Benzene (20)	1.1	–	82	45		96
4		2.4	Methanol (20)	1.4	–	65	20		25
5		2.4	Methanol (20)	–	0.03	65	180		20
6	**2b**	3.4	Benzene (25)	1.5	–	82	15	**3b**	96
7		1.7	Toluene (20)	1.4	–	107	10		97
8		2.9	Methanol (15)	0.2	–	65	270	**3c**	22
9	**2c**	2.1	Benzene (20)	0.9	–	82	15		97
10		5.0	Benzene (30)	1.5	–	82	15		97
11	**2d**	4.5	Methanol (12)	–	0.04	65	120	**3d**	32
12		2.2	Benzene (20)	1.2	–	82	15		96
13	**2e**	2.1	Benzene (20)	1.0	–	82	20	**3e**	96
14		2.1	Toluene (20)	0.8	–	107	15		94

*d = 1.84 g cm^{-1}

In conclusion, we have developed a mild and simple cyclization of 1,1-dimethoxy-2-phenoxyalkanes to 2-alkylbenzofurans.

EXPERIMENTAL

^{1}H NMR spectra were recorded with TM Bruker DPX 400 spectrometer for solution in $CDCl_3$ with TMS as internal standard. The analyses of a reaction products were carried out on a GC/MS Hewlett-Packard 6890 apparatus equipped with a mass detector HP 5973 and 30 m x 0.2 mm capillary column filled up with a 0.25 mm film of a 5% Me Ph silicate.

Starting materials. Amberlyst 15 was purchased from Fluka. All the remaining reagents and solvents were purchased from Merck or POCh and used without further purification. 2-Phenoxyalkanals **1a** and **1c–e** were prepared from corresponding 2-phenoxyalkanoyl chloride [20] according to procedure described for 2-phenoxyhexanal (**1b**) [9] and were obtained as colourless liquids in 70–75% yields. The following compounds were obtained:

2-Phenoxybutanal (1a): b.p. 68–70°C/6 Torr (lit. [19] 118–119°C/10 Torr).

2-(4-Methoxyphenoxy)butanal (1c): b.p. 105–108°C/3 Torr; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.05 (t, J = 7.4, 3H, CH_3) 1.84–1.91 (m, 2H, CH_2), 3.75 (s, 3H, OCH_3), 4.32 (q, J = 2.3, 1H, CH), 6.82 (s, 4Har), 9.68 (d, J = 2.4, 1H, CHO). Anal. Calcd. for $C_{11}H_{14}O_3$ (194.09): C, 68.02; H, 7.27. Found: C, 67.25; H, 7.35.

2-(4-*t*-Butylphenoxy)butanal (1d): b.p. 115–118°C/4 Torr; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.04 (t, J = 7.4, 3H, CH_3), 1.29 (s, 9H, CH_3), 1.85–1.92 (m, 2H, CH_2), 4.38 (q, J = 2.3, 1H, CH), 6.79–6.83 (m, 2Har), 7.28–7.31 (m, 2Har), 9.68 (d, J = 2.4, 1H, CHO). Anal. Calcd. for $C_{14}H_{20}O_2$ (220.15): C, 76.33; H, 9.15. Found: C, 76.22; H, 9.19.

2-(3,5-Dimethylphenoxy)butanal (1e): b.p. 83–85°C/3 Torr; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.06 (t, J = 7.4, 3H, CH_3), 1.84–1.91 (m, 2H, CH_2), 2.27 (s, 6H, CH_3), 4.37 (q, J = 2.3, 1H, CH), 6.32 (s, 2Har), 6.63 (s, 1Har), 9.67 (d, J = 2.3, 1H, CHO). Anal. Calcd. for $C_{12}H_{16}O_2$ (192.12): C, 74.97; H, 8.39. Found: C, 74.81; H, 8.41.

Typical procedure for synthesis of 1,1-dimethoxy-2-phenoxyalkanes from phenoxyaldehydes. To a solution of 2-phenoxyalkanal (6.0 mmol) in methanol (10 ml) was added Amberlyst 15 (0.06 g) and the mixture was left in a closed flask at room temperature for 6 days. When reaction was completed (gas chromatography control) resin was filltered and solution was concentrated. The residue was neutralized with sodium bicarbonate and extracted with ether. The organic layer was washed with water and dried over $MgSO_4$. Concentration of solution under reduced pressure gave crude acetals which were used in the next step without further purification. The following 1,1-dimethoxy-2-phenoxyalkanes **2a–e** were obtained:

1,1-Dimethoxy-2-phenoxybutane (2a): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.06 (t, J = 7.4, 3H, CH_3), 1.82–1.90 (m, 2H, CH_2), 3.40 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 4.18–4.22 (m, 1H, CH), 4.41 (d, J = 5.0, 1H, CH), 6.80–6.81 (m, 5Har).

1,1-Dimethoxy-2-phenoxyhexane (2b): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.88 (t, J = 7.5, 3H, CH_3), 1.32–1.47 (2m, 4H, CH_2), 1.83–1.85 (m, 2H, CH_2), 3.40 (s, 3H. OCH_3), 3.45 (s. 3H, OCH_3), 4.27 (m, 1H, CH), 4.38 (d, J = 3.5, 1H, CH), 6.08–6.98 (m, 3Har), 7.24–7.27 (m, 2Har).

1,1-Dimethoxy-2-(4-methoxyphenoxy)butane (2c): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.06 (t, J = 7.4, 3H, CH_3), 1.83–1.91 (m, 2H, CH_2), 3.41 (s, 3H, OCH_3), 3.43 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.18–4. 22 (m, 1H, CH), 4.41 (d, J = 5.0, 1H, CH), 6.82 (s, 4Har).

1,1-Dimethoxy-2-(*t*-butylphenoxy)butane (2d): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.98 (t, J = 7.4, 3H, CH_3), 1.29 (s, 9H, CH_3) 1.78–1.80 (m, 2H, CH_2), 3.42 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 4.17–4. 21 (m, 1H, CH), 4.40 (d, J = 5.2, 1H, CH), 6.89–6.91 (m, 2Har), 7.26–7.29 (m, 2Har).

1,1-Dimethoxy-2-(3,5-dimethylphenoxy)butane (2e): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.06 (t, J = 7.4, 3H, CH_3), 1.29 (s, 6H, CH_3), 1.85–1.92 (m, 2H, CH_2), 3.42 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 4.17–4. 21 (m, 1H, CH), 4.40 (d, J = 5.2, 1H, CH), 6.32 (s, 2Har), 6.63 (s, 1Har).

Cyclization of 1,1-dimethoxy-2-phenoxyalkanes 2 to 2-alkylbenzofurans 3. To a solution of crude 1,1-dimethoxy-2-phenoxyalkane **2** (5 mmol) in benzene (30 ml) Amberlyst 15 (1.5 g) was added and the mixture was heated under reflux with stirring for 15 min. The resin was filtered off, the solution was washed with aqueous sodium bicarbonate and with water and dried over $MgSO_4$. The solvent was evaporated and the crude 2-alkylbenzofurans were distilled under reduced pressure. The following compounds were obtained:

2-Ethylbenzofuran (3a): b.p. 53–55°C/2 Torr; lit. [10] b.p. 69°C/5 Torr.

2-Butylbenzofuran (3b): b.p. 80–82°C/3 Torr; lit. [9] b.p. 114–116°C/8 Torr.

2-Ethyl-5-methoxybenzofuran (3c): b.p. 112–114°C/6 Torr; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.29 (t, J = 7.4, 3H, CH_3), 2.75 (q, J = 7.4 , 2H, CH_2), 3.79 (s, 3H, OCH_3), 6.28 (s, 1Har), 6.74–6.78 (dd, J = 8.5, 2.6, 1Har), 6.94 (d, J = 2.6, 1Har), 7.27 (d, J = 8.4); MS, *m/z* (%) = 176 (M^+, 70), 161 (100), 146 (10), 131 (4), 103 (6), 77 (9), 63 (4), 39 (2). Anal. Calcd. for $C_{11}H_{12}O_2$ (176.21): C, 74.98; H, 6.86. Found: C, 74.88; H, 6.87.

2-Ethyl-5-*t*-butylbenzofuran (3d): b.p. 115–116°C/8 Torr; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.30 (t, J = 7.5, 3H, CH_3), 1.36 (s, 9H, CH_3), 2.75 (q, J = 7.5, 2H, CH_2), 6.32 (d, J = 0.6, 1Har), 7.25–7.33 (m, 2Har), 7.47 (d, J = 1.8, 1Har); MS, *m/z* (%) = 202 (M^+, 36), 187 (100), 171 (7), 159 (9), 131 (16), 115 (8), 91 (7), 72 (6), 57 (7), 41 (2), 39 (2). Anal. Calcd. for $C_{14}H_{18}O$ (202.29): C, 83.12; H, 8.97. Found: C, 08.01; H, 8.85.

4,6-Dimethyl-2-ethylbenzofuran (3e): b.p. 99–100°C/10 Torr; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.30 (t, J = 7.5, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.42 (s,3H, CH_3), 2.76 (q, J = 7.5, 2H, CH_2), 6.31 (d, J = 0.7, 1Har), 7.04 (s, 1Har), 7.18 (s, 1Har); MS, *m/z* (%) = 174 (M^+, 50), 159 (100), 144 (5), 128 (8), 115 (12), 91 (6), 72 (2), 51 (2), 39 (2). Anal. Calcd. for $C_{12}H_{14}O$ (174.24): C, 82.72; H, 8.10. Found: C, 82.65; H, 8.15.

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