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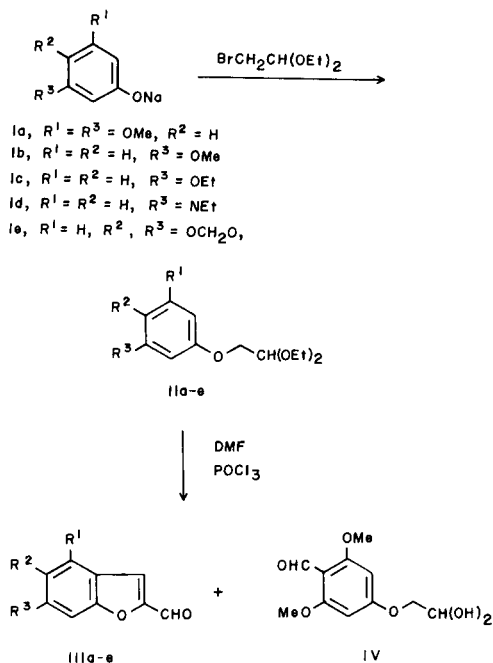
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Received May 5, 1986

A novel synthesis of 2-benzofurancarbaldehydes by the Vilsmeier reaction of phenoxyacetaldehyde diethyl acetals is described.

J. Heterocyclic Chem., **23**, 1715 (1986).

We have recently reported the synthesis of 2-benzofurancarboxylic acid derivatives and 2-benzoylbenzofurans by the Vilsmeier reaction (dimethylformamide (DMF)-phosphoryl chloride) of phenoxyacetoneitriles [1] and α -phenoxyacetophenones [2], respectively. In the course of the studies of this series, phenoxyacetaldehydes were chosen as substrate of the Vilsmeier reaction to obtain 2-benzofurancarbaldehydes. At first, synthesis of phenoxyacetaldehydes was designed by acid-catalyzed hydrolysis of phenoxyacetaldehyde diethyl acetals [3]. However, polymeric compound was yielded as major product during the hydrolysis of acetal. Subsequently, the yield of phenoxyacetaldehyde was very low. So the Vilsmeier reaction was directly carried out to phenoxyacetaldehyde diethyl acetals IIa-e. In addition, Makin and Pomugaev [4] reported that α -methylene group of acetals was active for Vilsmeier reagent.

Scheme 1



As shown in Scheme 1, acetals II were prepared from corresponding sodium phenolate Ia-e and bromoacetaldehyde diethyl acetal in dimethylsulfoxide. Some data are

Table I

Phenoxyacetaldehyde Diethyl Acetals II

Compound No.	Reaction condition	Yield	Formula	Analysis (%)	
				Calcd. C	(Found) H
IIa	50°	65%	$\text{C}_{14}\text{H}_{22}\text{O}_5$	62.20	8.20
	10 hours			(61.99)	(8.28)
IIb	60-70°	74%	$\text{C}_{13}\text{H}_{20}\text{O}_4$	64.98	8.39
	1 day			(64.70)	(8.21)
IIc	100°	84%	$\text{C}_{14}\text{H}_{22}\text{O}_4$	66.11	8.72
	1 day			(65.93)	(8.81)
IId	60-70°	91%	$\text{C}_{16}\text{H}_{27}\text{NO}_3$	68.29	9.67
	2 days			(68.10)	(9.82)
				N, 4.98	(4.86)
IIe	80°	84%	$\text{C}_{13}\text{H}_{18}\text{O}_5$	61.40	7.14
	1.5 days			(61.13)	(7.08)

listed in Table I. The Vilsmeier reaction of II afforded 2-benzofurancarbaldehydes IIIa-e in all cases. The results are shown in Scheme 1 and Table II. A rare geminidol compound IV could be isolated in the reaction for IIa. A similar compound was reported by acid-catalyzed hydrolysis of 2-methoxy-4-methylphenoxyacetaldehyde diethyl acetal [5].

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Analyses were performed on a Yanagimoto MT-2 CHN Corder elemental analyzer. The mass spectra were taken with a Shimadzu LKB-9000 spectrometer (70 eV). The ir spectra were obtained with a Nihon Bunko A-102 spectrometer and the frequencies are expressed in cm^{-1} . The pmr spectra were measured with R-22FTS instrument (90 MHz) in deuteriochloroform unless otherwise stated. Tetramethylsilane was used as an internal standard (δ), and the signals are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The uv spectra were recorded on a Hitachi ESP-2 spectrophotometer, using spectrograde ethanol. The results are expressed as λ max in nanometer (nm) and $\log \epsilon$ in parentheses.

Phenoxyacetaldehyde Diethyl Acetals IIa-e.

Compounds IIa-e were prepared by modifying the method of Kondo *et al.* [6]. Phenol (0.1 mole, Ia-e) was dissolved in an equimolecular amount of 1N sodium hydroxide and the solution was evaporated to dryness. Bromoacetaldehyde diethyl acetal (0.15 mole) was added to the residue in 10 ml of dimethylsulfoxide. The mixture was stirred in an appropriate

Table II
 2-Benzofurancarbaldehydes III

Compound No.	Reaction condition	mp (yield)	Appearance (Recrystallization Solvent)	Formula	Analysis (%)	
					Calcd. C	(Found) H
IIIa	60° 3 hours	132-134° (58%)	pale yellow needles (benzene-cyclohexane)	C ₁₁ H ₁₀ O ₄	64.07 (63.97)	4.89 (4.94)
IIIb	50° 4 hours	74-74.5° (27%)	colorless needles (benzene- <i>n</i> -hexane)	C ₁₀ H ₈ O ₃	68.18 (68.03)	4.58 (4.42)
IIIc	60° 1.5 hours	66-67.5° (29%)	pale yellow granules (cyclohexane)	C ₁₁ H ₁₀ O ₃	69.46 (69.28)	5.30 (5.16)
IIId (as HCl salt)	70° 3 hours	138-139° (33%)	brown granules (ethyl acetate)	C ₁₃ H ₁₅ NO ₂ ·HCl	61.54 (61.45) N, 5.52	6.36 (6.28) (5.33)
IIIe	70° 3 hours	153-155° (15%)	pale brown needles (benzene-cyclohexane)	C ₁₀ H ₆ O ₄	63.16 (63.20)	3.18 (3.17)

condition under nitrogen stream (Table I). After addition of large excess of water to the reaction mixture, the solution was extracted with benzene. The organic layer was shaken with 1*N* sodium hydroxide, washed with water, dried over sodium sulfate, and evaporated. The residue was distilled or chromatographed on silica gel with benzene to give a colorless oil. The ms and pmr are as follows: IIa, ms: *m/z* 270 (M⁺); pmr: 1.25 (6H, t, J = 7 Hz), 3.66 and 3.68 (each 2H, q, J = 7 Hz), 3.73 (6H, s), 3.99 (2H, d, J = 5 Hz), 4.83 (1H, t, J = 5 Hz), 6.12 (3H, br s); IIb, ms: *m/z* 240 (M⁺); pmr: 1.25 (6H, t, J = 7.5 Hz), 3.67 (4H, m), 3.79 (3H, s), 4.00 (2H, d, J = 5 Hz), 4.84 (1H, t, J = 5 Hz), 6.52 (3H, m), 7.18 (1H, br t, J = 9 Hz). IIc [7], ms: *m/z* 254 (M⁺); pmr: 1.25 (6H, t, J = 7.5 Hz), 1.40 (3H, t, J = 7 Hz), 3.68 and 3.74 (each 2H, q, J = 7.5 Hz), 4.00 (2H, d, J = 5 Hz), 4.02 (2H, q, J = 7 Hz), 4.85 (1H, t, J = 5 Hz), 6.49 (3H, m), 7.17 (1H, t, J = 9 Hz); II d, ms: *m/z* 281 (M⁺); pmr: 1.15 (6H, t, J = 8 Hz), 1.25 (6H, t, J = 7 Hz), 3.34 (4H, q, J = 8 Hz), 3.66 and 3.68 (each 2H, q, J = 7 Hz), 4.01 (2H, d, J = 5 Hz), 4.85 (1H, t, J = 5 Hz), 6.25 (3H, m), 7.10 (1H, t, J = 8.5 Hz); IIe, ms: *m/z* 254 (M⁺); pmr: 1.24 (6H, t, J = 7.5 Hz), 3.65 and 3.68 (each 2H, q, J = 7.5 Hz), 3.94 (2H, d, J = 5.5 Hz), 4.82 (1H, t, J = 5.5 Hz), 5.93 (2H, s), 6.35 (1H, dd, J = 9 Hz, 2.5 Hz), 6.55 (1H, d, J = 2.5 Hz), 6.72 (1H, d, J = 9 Hz).

General Procedure of the Vilsmeier Reaction for IIa-e.

To a Vilsmeier reagent prepared from 12 mmoles of DMF and 36 mmoles of phosphoryl chloride, 10 mmoles of II was added and the mixture was stirred under appropriate condition (Table II). After cooling, ca. 40 ml of water was added to the reaction mixture. The mixture was basified with sodium hydrogen carbonate and extracted with chloroform. The organic layer was washed with brine, dried over sodium sulfate, and evaporated. The residue was recrystallized from appropriate solvent (Table II). In the case of IIId, the residue was chromatographed on silica gel with benzene. After elution of benzene, benzene-dichloromethane (1:1) eluate was collected to give a yellowish oil, which was characterized as hydrochloride.

4,6-Dimethoxy-2-benzofurancarbaldehyde (IIIa) [8].

This compound had ms: *m/z* 206 (M⁺); ir (potassium bromide): 1685 (C=O); pmr: 3.88 and 3.95 (each 3H, s, 2 x OMe), 6.35 (1H, d, J = 1 Hz, 5-H), 6.67 (1H, br s, 7-H), 7.58 (1H, br s, 3-H), 9.69 (1H, s, CHO); uv: 249 (3.57), 330 (3.78).

2(4-Formyl-3,5-dimethoxyphenoxy)-1,1-ethanediol (IV).

The aqueous layer of the chloroform extraction in the reaction of IIa was allowed to stand at room temperature for several days. The precipitated solid was collected on a filter and recrystallized from aqueous acetic acid to give IV (4%) as white powder, mp 113-113.5°; ms: *m/z* 224 (M-H₂O); ir (potassium bromide): 3360 (O-H), 1680 (C=O); pmr (DMSO-d₆): 3.82 (6H, s, 2 x OMe), 3.94 (2H, d, J = 5.5 Hz, OCH₂), 5.10 (1H, br quintet, J = 5.5 Hz, CH₂CH), changed to triplet with deuterium oxide), 6.15 (2H, d, J = 5.5 Hz, 2 x OH, exchanged with deuterium oxide), 6.26

(2H, s, Ar-H), 10.24 (1H, s, CHO).

Anal. Calcd. for C₁₁H₁₄O₄: C, 54.54; H, 5.83. Found: C, 54.27; H, 5.82.

6-Methoxy-2-benzofurancarbaldehyde (IIIb) [8].

This compound had ms: *m/z* 176 (M⁺); ir (potassium bromide): 1682 (C=O); pmr: 3.90 (3H, s, OMe), 6.97 (1H, br d, J = 8.5 Hz, 5-H), 7.04 (1H, br s, 7-H), 7.50 (1H, br s, 3-H), 7.61 (1H, d, J = 8.5 Hz, 4-H), 9.77 (1H, s, CHO); uv: 247 (3.10), 325 (3.45).

6-Ethoxy-2-benzofurancarbaldehyde (IIIc) [8].

This compound had ms: *m/z* 190 (M⁺); ir (potassium bromide): 1685 (C=O); pmr: 1.47 (3H, t, J = 7 Hz, CH₃), 4.12 (2H, q, J = 7 Hz, CH₂), 6.97 (1H, dd, J = 9 Hz, 2 Hz, 5-H), 7.03 (1H, br s, 7-H), 7.49 (1H, br s, 3-H), 7.60 (1H, d, J = 9 Hz, 4-H), 9.76 (1H, s, CHO); uv: 247 (3.55), 328 (3.91).

6-Diethylamino-2-benzofurancarbaldehyde (IIId).

This compound had ms: *m/z* 217 (M⁺); ir (liquid film): 1670 (C=O); pmr: 1.22 (6H, t, J = 7 Hz, 2 x CH₃), 3.45 (4H, q, J = 7 Hz, 2 x CH₂), 6.72 (1H, br s, 7-H), 6.76 (1H, br d, J = 8.5 Hz, 5-H), 7.40 (1H, br s, 3-H), 7.51 (1H, d, J = 8.5 Hz, 4-H), 9.63 (1H, s, CHO); uv: 245 (4.21), 300 (3.54), 311 (3.51), 395 (4.37).

5,6-Methlenedioxy-2-benzofurancarbaldehyde (IIIe).

This compound had ms: *m/z* 190 (M⁺); ir (potassium bromide): 1660 (C=O); pmr: 6.09 (2H, s, CH₂), 7.05 (2H, br s, 4 and 7-H), 7.47 (1H, br s, 3-H), 9.73 (1H, s, CHO); uv: 255 (3.43), 266 (3.45), 293 (3.57), 344 (3.69).

Acknowledgement.

The authors are grateful to Mr. A. Iwadoh for mass spectral measurements and to Mrs. M. Aiki for elemental analyses.

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