

A VERSATILE NOVEL SYNTHESIS OF BENZOFURAN
AND RELATED COMPOUNDS. II.
THE VILSMEIER REACTION OF α -PHENOXYACETOPHENONES

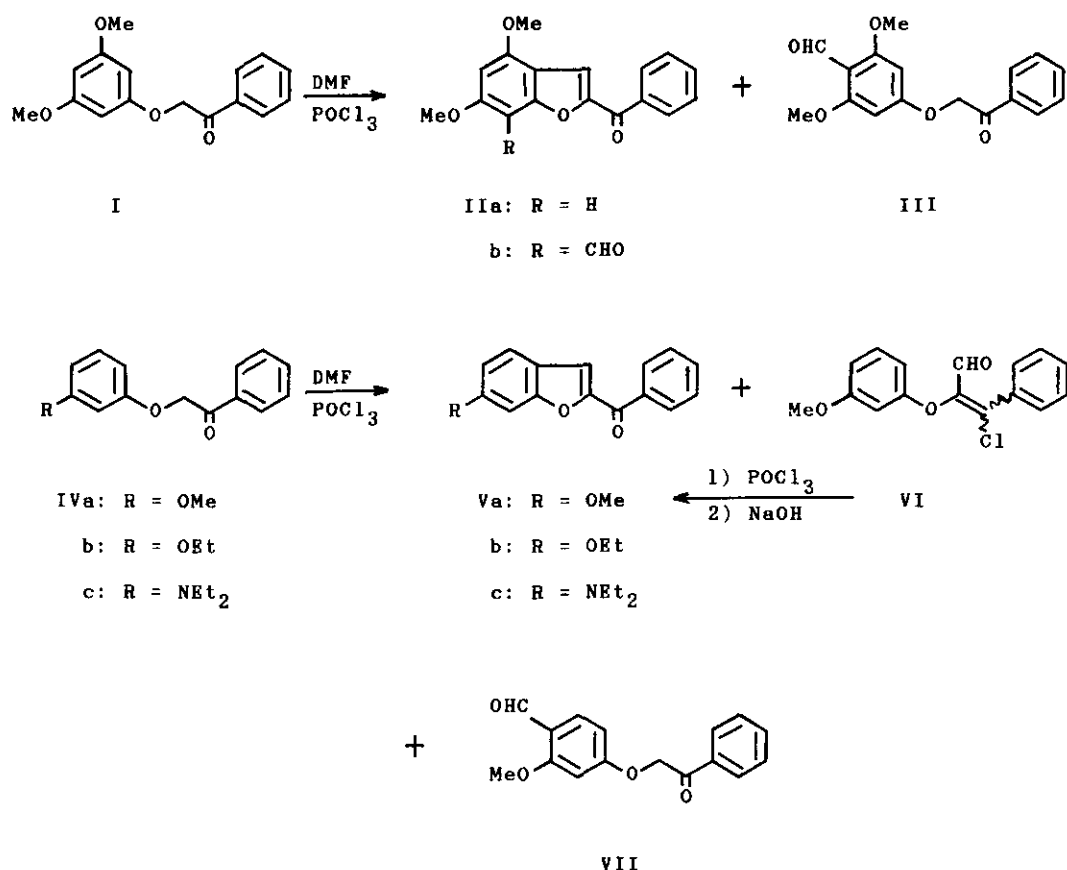
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Abstract - A novel synthesis of 2-benzoylbenzofurans by the
Vilsmeier reaction of α -phenoxyacetophenones are described.

We have recently reported a versatile synthesis of 2-benzofurancarboxylic acid derivatives by the Vilsmeier reaction of phenoxyacetoneitriles¹. In this reaction, 2-cyano group of benzofuran was partly converted to a mixture of amide, imide, and carboxylic acid and this complex mixture made the subsequent purification troublesome. Further development of this synthesis was proceeded by using α -phenoxyacetophenones as substrate, which were easily available by the condensation of corresponding phenols and α -bromoacetophenone in the presence of K_2CO_3 ². As shown in Scheme 1, the Vilsmeier reaction of α -(3,5-dimethoxyphenoxy)acetophenone (I)^{2a} with dimethylformamide (DMF) and $POCl_3$ afforded 2-benzoylbenzofurans (IIa and IIb) and formylated compound (III). Usually, coupling constant ($J_{3,7}$) is observed in ca. 1 Hz in nmr spectra of benzofuran derivatives, however, $J_{3,5}$ does not³. While proton of C-3 coupled with that of C-7 by 0.9 Hz in compound IIa, that of C-3 appeared as sharp singlet in compound IIb. Thus the position of formyl group of IIb was determined at C-7.

Similar reactions were carried out by using α -(3-methoxyphenoxy)- (IVa), α -(3-ethoxyphenoxy)- (IVb), and α -(3-diethylaminophenoxy)acetophenone (IVc). The results are summarized in Scheme 1 and Table I. In the case of the reaction of IVa, chlorovinylformyl derivative (VI) and formylated compound (VII) were



Scheme 1

isolated. Although an analysis of the geometrical isomerism of compound VI was not performed, it seemed to be an intermediate of benzofuran cyclization. Expectedly, compound VI could be converted to benzofuran (Va) by heating with POCl₃, followed by treating with NaOH. The nmr spectrum of VII indicated that the formylated position was situated at C-2 or C-4. If VII is the 2-formylated compound, it should react with K₂CO₃ in DMF and give benzofuran (Va) in good yield¹, however, no reaction occurred. Thus the position of the formyl group was determined at C-4.

Table I Reaction Conditions and Other Data of the Products

Starting Material (React. Condition)	Product No.*	Appearance (Recryst. Solv.)	Mp (°C)	Yield (%)
I (50 °C, 6 h)	IIa	colorless needles (<u>n</u> -hexane)	140-141	39
	IIb	pale yellow plates (benzene-cyclohexane)	210-211	21
	III	colorless scales (benzene-cyclohexane)	157-159	14
IVa (30 °C, 9 h)	Va	colorless needles (benzene- <u>n</u> -hexane)	103-104.5 (lit. ⁴ 105)	25
	VI	pale yellow needles (benzene- <u>n</u> -hexane)	60-61	19
	VII	colorless needles (benzene-cyclohexane)	120-121	8
IVb (60 °C, 2 h)	Vb	pale yellow prisms (benzene- <u>n</u> -hexane)	101-101.5	31
IVc (60 °C, 10 h)	Vc	viscous oil, brownish powder as HCl salt (ethanol)	150-153 as HCl salt	78

* Eluted solvent of silica gel column chromatography; benzene : cyclohexane = 1 : 1 (VI), benzene (IIa, Va, Vb, and Vc), benzene : CH₂Cl₂ = 1 : 1 (IIb and VII), CHCl₃ (III).

EXPERIMENTAL

Mps were recorded on a Yanagimoto micro melting point apparatus and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-2 CHN Corder elemental analyzer. The ir spectra were obtained with a Japan Spectroscopic A-102 diffraction grating infrared spectrophotometer and measured in KBr pellet unless otherwise noted. The nmr spectra were measured on a Hitachi R-22FTS-A FT-NMR spectrometer (90 MHz). The chemical shifts (δ) in ppm are measured relative to tetramethylsilane as an internal standard. The ms spectra were

taken with a Shimadzu LKB-9000 instrument at 70eV. The uv spectra were taken on a Hitachi ESP-2 spectrophotometer in ethanol.

α -Phenoxyacetophenones (I, IVa, Vb, and Vc) were prepared according to the method of Saburi *et al.*^{2b}:

I: mp 87-88 °C (cyclohexane, *lit.*^{2a} 89 °C). Ir ν max: 1710 cm^{-1} ; nmr (CDCl_3): 3.75 (s, 6H), 5.23 (s, 2H), 6.13 (br s, 3H), 7.52 (m, 3H), 7.97 (m, 2H).

IVa: mp 85-87 °C (benzene-cyclohexane, *lit.*^{2b} 88 °C). Ir ν max: 1700 cm^{-1} ; nmr (CDCl_3): 3.79 (s, 3H), 5.27 (s, 2H), 6.55 (m, 3H), 7.20 (t, J = 9 Hz, 1H), 7.55 (m, 3H), 8.00 (m, 2H).

IVb: Recrystallization from benzene-n-hexane gave pale yellow needles (75%), mp 69-70 °C. Anal. Calcd. for $\text{C}_{16}\text{H}_{16}\text{O}_3$: C, 74.98; H, 6.29. Found: C, 74.80; H, 6.23. Ir ν max: 1700 cm^{-1} ; nmr (CDCl_3): 1.38 (t, J = 7 Hz, 3H), 4.02 (q, J = 7 Hz, 2H), 5.25 (s, 2H), 6.54 (m, 3H), 7.19 (br t, J = 8.5 Hz, 1H), 7.54 (m, 3H), 8.02 (m, 2H); ms m/z: 256 (M^+).

IVc: Recrystallization from dil. MeOH gave colorless needles (54%), mp 40-42 °C. Anal. Calcd. for $\text{C}_{18}\text{H}_{21}\text{NO}_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.02; H, 7.38; N, 4.88. Ir ν max: 1700 cm^{-1} ; nmr (CDCl_3): 1.14 (t, J = 7 Hz, 6H), 3.34 (q, J = 7 Hz, 4H), 5.22 (s, 2H), 6.27 (m, 3H), 7.10 (t, J = 8 Hz, 1H), 7.51 (m, 3H), 7.99 (m, 2H).

General Procedure of Vilsmeier Reaction

The Vilsmeier reagent was prepared by stirring of 0.12 M of DMF and 0.36 M of POCl_3 under cooling in an ice bath for 0.5 h. To the reagent, was added 0.1 M of α -phenoxyacetophenone and the mixture was stirred in appropriate condition (Table I) until disappearance of the starting material (tlc check). The reaction mixture was cooled and hydrolyzed with ca. 40 ml of H_2O . The resulting solution was basified with NaHCO_3 and extracted with CHCl_3 . The organic layer was worked up usually and the resulting residue was purified with silica gel column chromatography followed by the recrystallization.

Elemental analyses and instrumental data of the products are as follows:

2-Benzoyl-4,6-dimethoxybenzofuran (IIa)

Anal. Calcd. for $\text{C}_{17}\text{H}_{14}\text{O}_4$: C, 72.33; H, 5.00. Found: C, 72.39; H, 4.95. Ir ν max: 1630 (C=O) cm^{-1} ; nmr (CDCl_3): 3.88, 3.91 (each s, 2 x OMe, each 3H), 6.34 (d, J = 2 Hz, 5-H, 1H), 6.71 (br s, 7-H, 1H), 7.51, 7.97 (each m, benzoyl-H, 3H, 2H), 7.53 (d, J = 0.9 Hz, 3-H, 1H); uv λ max: 251 nm (log ϵ 4.35), 349 (4.42); ms m/z: 282 (M^+).

2-Benzoyl-4,6-dimethoxy-7-benzofurancarbaldehyde (IIb)

Anal. Calcd. for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55. Found: C, 69.72; H, 4.46.

Ir ν max: 1675, 1632 (C=O) cm^{-1} ; nmr ($CDCl_3$): 4.05 (br s, 2 x OMe, 6H), 6.36 (s, 5-H, 1H), 7.49, 8.20 (each m, benzoyl-H, 3H, 2H), 7.62 (s, 3-H, 1H), 10.49 (s, CHO, 1H); uv λ max: 231 nm (log ϵ 3.52), 264 (3.39), 293 (3.64), 344 (3.72); ms m/z: 310 (M^+).

 α -(4-Formyl-3,5-dimethoxyphenoxy)acetophenone (III)

Anal. Calcd. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.81; H, 5.27.

Ir ν max: 1705, 1670 (C=O) cm^{-1} ; nmr ($CDCl_3$): 3.86 (s, 2 x OMe, 6H), 5.33 (s, -OCH₂-, 2H), 6.14 (s, phenoxy-2- and 6-H, 2H), 7.54, 7.98 (each m, benzoyl-H, 3H, 2H), 10.34 (s, CHO, 1H); ms m/z: 300 (M^+).

2-Benzoyl-6-methoxybenzofuran (Va)⁴

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.80. Found: C, 76.19; H, 4.81.

Ir ν max: 1638 (C=O) cm^{-1} ; nmr ($CDCl_3$): 3.91 (s, OMe, 3H), 7.03 (dd, J = 9 Hz, 2 Hz, 5-H, 1H), 7.12 (br s, 7-H, 1H), 7.52, 8.01 (each m, 3-, 4- and benzoyl-H, 7H); uv: λ max 233 (log ϵ 4.19), 254 (4.22), 341 (4.54); ms m/z: 250 (M^+).

3-Chloro-2-(3-methoxyphenoxy)cinnamaldehyde (VI)

Anal. Calcd. for $C_{16}H_{13}ClO_3$: C, 66.55; H, 4.53. Found: C, 66.74; H, 4.57.

Ir ν max: 1685 (C=O) cm^{-1} ; nmr ($CDCl_3$): 3.81 (s, OMe, 3H), 6.60 (m, phenoxy-2-, 4-, and 6-H, 3H), 7.21 (br t, J = 8.5 Hz, phenoxy-5-H, 1H), 7.56 (br s, phenyl-H, 5H), 9.51 (s, CHO, 1H); ms m/z: 288 (M^+) : 290 ($M^+ + 2$) = 3 : 1; Beilstein test: positive.

 α -(4-Formyl-3-methoxyphenoxy)acetophenone (VII)

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.18; H, 5.20.

Ir ν max: 1708, 1680 (C=O) cm^{-1} ; nmr ($CDCl_3$): 3.92 (s, OMe, 3H), 5.38 (s, OCH₂, 2H), 6.52 (dd, J = 8 Hz, 2.5 Hz, phenoxy-6-H, 1H), 6.61 (d, J = 2.5 Hz, phenoxy-2-H, 1H), 7.57, 8.01 (each m, benzoyl-H, 3H, 2H), 7.82 (d, J = 9 Hz, phenoxy-5-H, 1H), 10.34 (s, CHO, 1H); ms m/z: 270 (M^+).

2-Benzoyl-6-ethoxybenzofuran (Vb)

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.68; H, 5.21.

Ir ν max: 1641 (C=O) cm^{-1} ; nmr ($CDCl_3$): 1.47, 4.13 (t, q, J = 7 Hz, CH₃CH₂, 3H, 2H), 6.97 (dd, J = 8.5 Hz, 2 Hz, 5-H, 1H), 7.09 (br s, 7-H, 1H), 7.53, 8.02 (each m, 3-, 4-, and benzoyl-H, 5H, 2H); uv λ max: 232 nm (log ϵ 3.94), 254 (3.93), 342 (4.21); ms m/z: 266 (M^+).

2-Benzoyl-6-diethylaminobenzofuran (Vc)

Anal. Calcd. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.52; N, 4.77. Found: C, 77.58; H, 6.60; N, 4.59 (HCl salt, Calcd. for $C_{19}H_{19}NO_2 \cdot HCl$: C, 69.19; H, 6.11; N, 4.24. Found: C, 69.07; H, 6.05; N, 4.15). Ir ν_{max} (liquid): 1640 (C=O) cm^{-1} ; nmr ($CDCl_3$): 1.23, 3.45 (t, q, J = 7 Hz, 2 x CH_3CH_2 , 6H, 4H), 6.79 (br d, J = 9 Hz, 5-H, 1H), 6.86 (br s, 7-H, 1H), 7.41 (br s, 3-H, 1H), 7.52, 7.99 (each m, 4- and benzoyl-H, 4H, 2H); uv λ_{max} : 260 nm (log ϵ 3.93), 344 (3.79), 414 (3.90); ms m/z: 293 (M^+).

Reaction of VI with $POCl_3$

A mixture of 58 mg (0.2 mM) of VI and 1 ml of $POCl_3$ was refluxed for 1 h. After evaporation of $POCl_3$, ca. 5 ml of H_2O was added. The mixture was basified with NaOH and warmed at 50-60 °C for 0.5 h. The mixture was extracted with $CHCl_3$. The organic layer was worked up as usually. The residue was recrystallized from benzene-n-hexane to give 42 mg (84%) of Va as colorless needles, which was identified with above Va (mixed mp, tlc, and ir).

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