# A NOVEL SYNTHESIS OF BENZOFURAN AND RELATED COMPOUNDS. IV. THE VILSMEIER REACTION OF 3,5-DIMETHOXYPHENYLTHIOMETHYL COMPOUNDS

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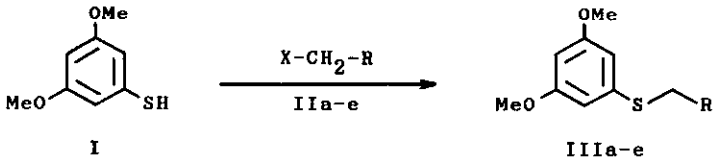
Abstract - A novel synthesis of 2-substituted 4,6-dimethoxybenzothiophenes by the Vilsmeier reaction of 3,5-dimethoxyphenylthiomethyl derivatives is described.

In the previous papers, we have reported a novel synthesis of benzofuran by the Vilsmeier reaction of phenoxymethyl derivatives, that is, phenoxyacetonitriles[1], phenoxyacetophenones[2], and phenoxyacetaldehyde diethyl acetals[3]. In the course of our work, we were interested in an attempt to use this novel synthetic method of benzofuran skeleton for phenylthiomethyl compounds to obtain benzothiophene derivatives.



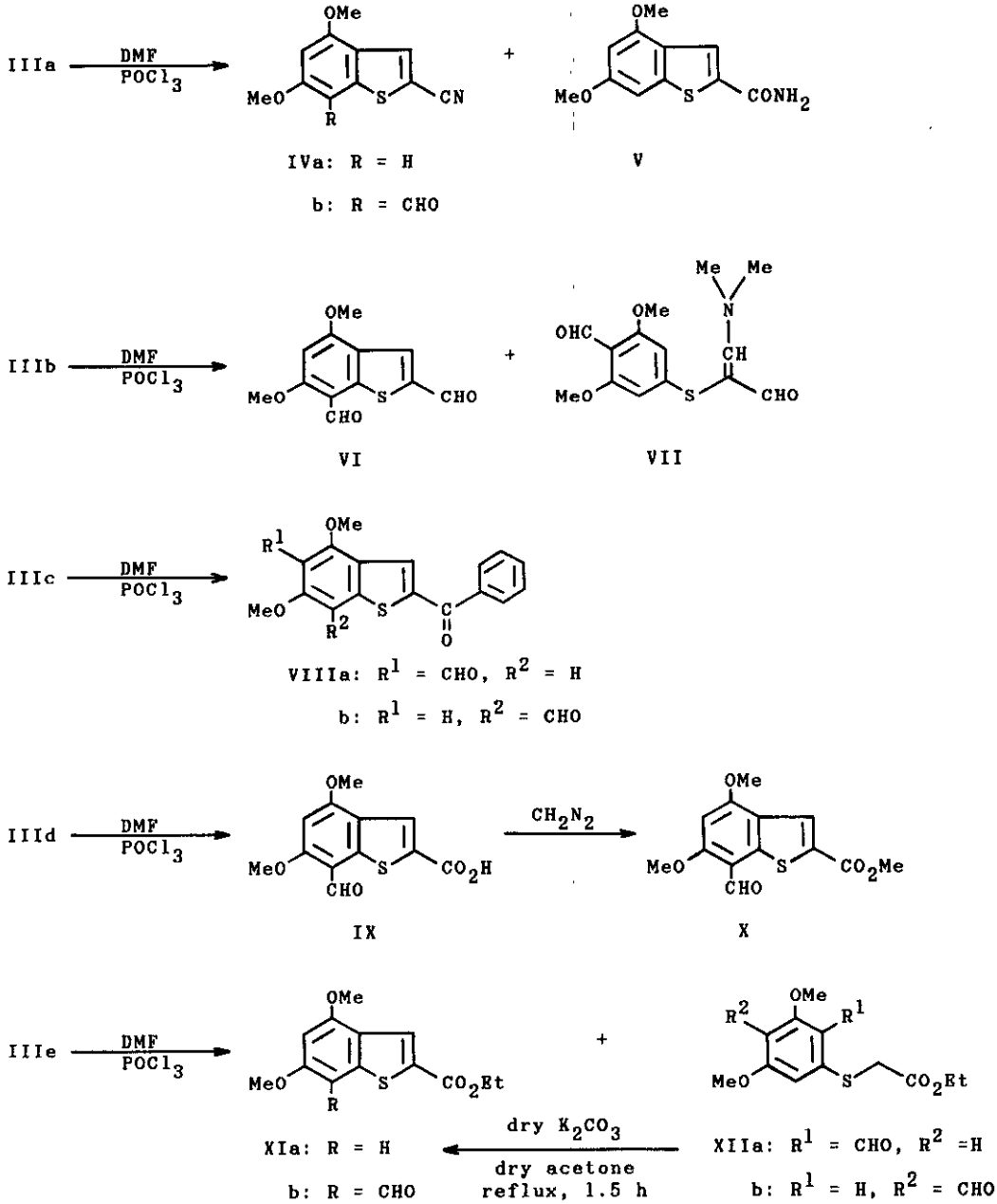

I IIIa-e

IIa: X = Cl, R = CN
b: X = Br, R = $CH(OEt)_2$
c: X = Cl, R = CO-C6H5
d: X = Cl, R = $CO_2H$
e: X = Br, R = $CO_2Et$

Scheme 1

As shown in Scheme 1, phenylthiomethyl derivatives (IIIa-e) were prepared by the condensation of 3,5-dimethoxythiophenol (I)[4] with chloroacetonitrile (IIa),

bromoacetaldehyde diethyl acetal (IIb), α-chloroacetophenone (IIc), chloroacetic acid (IId), or ethyl bromoacetate (IIe) by a similar method for the preparation of phenoxyacetonitrile previously reported[1].




Scheme 2

Table I Reaction Times, Eluting Solvents, Appearances, Melting Points, and Yields of IIIa-e

| Compd. | React. Time (h) | Eluting Solvent[a)] | Appearance (Recryst. Solv.) | Mp (°C) | Yield (%) |
|---|---|---|---|---|---|
| IIIa | 1.5 | b) | colorless oil | ——— | 94 |
| IIIb | 2 | benzene | colorless oil | ——— | 83 |
| IIIc | 0.5 | benzene | colorless prisms (cyclohexane) | 39-42 | 76 |
| IIId | 0.5 | b) | white powder (not recrystallized) | 82-84 | 79 |
| IIIe | 0.5 | $CH_2Cl_2$ | colorless oil | ——— | 77 |

a) Solvent for elution on silica gel column chromatography.
b) Not chromatographed; See in the text.

As shown in Scheme 2, The Vilsmeier reaction of the resulting phenylthiomethyl derivatives with dimethylformamide (DMF) and $POCl_3$ afforded desired benzothiophens (IV, V, VI, VIII, IX, and XI), dimethylaminoacrylaldehyde derivative (VII), and formylated compounds (XII) of the starting material. Physical data of these products (III - XII) are listed in Tables I - IV.
In nmr spectra of benzothiophenes, the coupling constants (0.84 ± 0.01 Hz) between protons of C-3 and C-7 and that (0.05 ± 0.01 Hz) between protons of C-3 and C-5 were reported[5]. In the compound VIIIa, proton of C-3 coupled with that of C-7 by ca. 1.0 Hz. Accordingly, the position of formyl group of VIIIa was determined at C-5. On the other hand, nearly sharp singlet proton of C-3 of compounds IVb, VI, VIIIb, IX, X and XIb supported that the position of formyl group was at C-7. Furthermore, obvious difference was recognized in the chemical shifts of protons of C-5 and C-7 between VIIIa and other benzothiophene derivatives. That is, proton of C-7 of VIIIa was observed at 7.18 ppm in $CDCl_3$, while proton of C-5 of compounds IVb, VI, VIIIb, and XIb appeared at 6.42 - 6.47 ppm. Accordingly, it seemed that the position of formyl group was also able to be detected by considering the chemical shifts of protons of C-5 and C-7. In the case of IX, the nmr spectrum was measured in DMSO-$d_6$ owing to its unsolubility for $CDCl_3$ and benzene ring proton was observed at 6.86 ppm. In order to

Table II Reaction Conditions, Eluting Solvents, Appearances, Melting Points, and Yields of IV - XII

| Compd. | React. Condition | | Eluting Solvent[a] | Appearance | Mp | Yield |
|---|---|---|---|---|---|---|
| | Temp.(°C) | Time(h) | (Ratio, v/v) | (Recryst. Solv.) | (°C) | (%) |
| IVa | 80 | 2 | benzene (only) | colorless needles (benzene) | 172-174 | 12 |
| IVb | | | benzene-$CHCl_3$ (1 : 1) | white powder (benzene) | 199-201 | 3 |
| V | | | benzene-$CHCl_3$ (1 : 1) | white powder (acetone) | 245(dec.) | 22 |
| VI | 50 | 2 | benzene-$CHCl_3$ (1 : 1) | pale yellow plates (acetone) | 224-227 | 18 |
| VII | | | $CHCl_3$-acetone (1 : 1) | yellow needles (benzene-cyclohexane) | 126-128 | 12 |
| VIIIa | 80 | 2 | benzene-$CHCl_3$ (9 : 1) | white powder (cyclohexane) | 189-192 | 2 |
| VIIIb | | | benzene-$CHCl_3$ (4 : 1) | yellow powder (benzene) | 225-227 | 52 |
| IX | 60 | 1.5 | b) | colorless needles (acetone) | 260 (sublim.) | 56 |
| X | | | b) | colorless needles (ether) | 234-236 | c) |
| XIa | 70 | 1 | benzene-$CH_2Cl_2$ (9 : 1) | colorless powder (ethanol) | 104-105 | 4 |
| XIb | | | benzene-$CH_2Cl_2$ (9 : 1) | colorless powder (acetone-ether) | 198-201 | 16 |
| XIIa | | | benzene-$CH_2Cl_2$ (9 : 1) | colorless needles (acetone-ether) | 220-221 | 35 |
| XIIb | | | acetone (only) | colorless needles (diluted ethanol) | 95-98 | 25 |

a) Solvent for elution on silica gel column chromatography. b) Not chromatographed; See in the text. c) Almost quantitatively.

avoid the solvent effect, IX was esterified to X with diazomethane to increase the solubility for $CDCl_3$ and the nmr spectrum of resulting X was measured in $CDCl_3$. Benzene ring proton of X was observed as sharp one proton singlet at 6.44 ppm and coupling with proton of C-3 could not be detected. Accordingly, the position of formyl group of X (and IX) was recognized to be at C-7.

In nmr spectra of compounds VII and XIIb, phenyl protons appeared at 6.35 ppm

and 6.56 ppm as each two proton singlet, respectively. Therefore, the position of formyl group was determined to be at C-4 in both compounds.

In the case of the reaction of IIIe, formylated compounds (XIIa,b) could be isolated in company with cyclized products (XIa,b). In the course of this reaction, it was observed on TLC that the spot of 2-formylated compound (XIIa) decreased with the progress of the reaction and, on the other hand, that of benzothiophene (XIa) increased. Furthermore, XIIa could be converted to XIa with $K_2CO_3$ in refluxing acetone. Therefore, XIIa was considered as an intermediate of cyclization of IIIe to benzothiophene, XIa.

Table III Elemental Analyses and Ms and Ir Spectral Data of III - XII

| Compd. | Formula | Analysis (%); Calcd (Found) | | | Ms (m/z)[a] | Ir[b] |
|---|---|---|---|---|---|---|
| | | C | H | N | $M^+$ | ($cm^{-1}$) |
| IIIa | $C_{10}H_{11}NO_2S$ | 57.39 | 5.29 | 6.69 | 209 | 2250 |
| | | (57.26 | 5.41 | 6.73) | | |
| IIIb | $C_{14}H_{22}O_4S$ | 58.71 | 7.74 | | 286 | —— |
| | | (58.56 | 7.82) | | | |
| IIIc | $C_{16}H_{16}O_3S$ | 66.64 | 5.59 | | 288 | 1680 |
| | | (66.85 | 5.69) | | | |
| IIId | $C_{10}H_{12}O_4S$ | 52.61 | 5.29 | | 228 | 3070,1700 |
| | | (52.42 | 5.48) | | | |
| IIIe | $C_{12}H_{16}O_4S$ | 56.23 | 6.29 | | 256 | 1725 |
| | | (56.15 | 6.47) | | | |
| IVa | $C_{11}H_9NO_2S$ | 60.25 | 4.13 | 6.38 | 219 | 2220 |
| | | (59.99 | 4.07 | 6.39) | | |
| IVb | $C_{12}H_9NO_3S$ | 58.28 | 3.66 | 5.66 | 247 | 2220,1640 |
| | | (58.31 | 3.72 | 5.62) | | |
| V | $C_{11}H_{11}NO_3S$ | 55.68 | 4.67 | 5.90 | 237 | 3430,3350,1650 |
| | | (55.48 | 4.69 | 5.82) | | |
| VI | $C_{12}H_{10}O_4S$ | 57.58 | 4.02 | | 250 | 1660,1650 |
| | | (57.68 | 3.94) | | | |
| VII | $C_{14}H_{17}NO_4S$ | 56.93 | 5.80 | 4.74 | 295 | 1667,1658 |
| | | (56.85 | 5.77 | 4.64) | | |
| VIIIa | $C_{18}H_{14}O_4S$ | 66.24 | 4.32 | | 326 | 1685,1630 |
| | | (66.46 | 4.31) | | | |
| VIIIb | $C_{18}H_{14}O_4S$ | 66.24 | 4.32 | | 326 | 1660,1640 |
| | | (65.96 | 4.20) | | | |
| IX | $C_{12}H_{10}O_5S$ | 54.12 | 3.78 | | 266 | 3420,1700 |
| | | (54.23 | 3.96) | | | |
| X | $C_{13}H_{12}O_5S$ | 55.70 | 4.31 | | 280 | 1690,1650 |
| | | (55.62 | 4.43) | | | |

Table III (continued)

| Compd. | Formula | Analysis (%); Calcd (Found) C | H | N | Ms (m/z)[a] $M^+$ | Ir[b] ($cm^{-1}$) |
|---|---|---|---|---|---|---|
| XIa | $C_{13}H_{14}O_4S$ | 58.63 (58.86 | 5.29 5.22) | | 266 | 1705 |
| XIb | $C_{14}H_{14}O_5S$ | 57.13 (57.11 | 4.79 4.65) | | 294 | 1690,1650 |
| XIIa | $C_{13}H_{16}O_5S$ | 54.91 (54.85 | 5.67 5.75) | | 284 | 1728,1660 |
| XIIb | $C_{13}H_{16}O_5S$ | 54.91 (54.82 | 5.67 5.75) | | 284 | 1730,1665 |

a) The base peak is the molecular ion peak except for IIIb (m/z 195) and XIIa (m/z 197). b) Absorption bands due to N-H, O-H, C≡N, and/or C=O; Measured in KBr disks except for IIIa, IIIb, and IIIe ($CHCl_3$).

## EXPERIMENTAL

Mps were determined 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. The nmr spectra were measured on a Hitachi R-22FTS FT-NMR spectrometer (90 MHz). The chemical shifts ($\delta$) in ppm were measured relative to tetramethylsilane as an internal standard. The ms spectra were taken with a Shimadzu LKB-9000 instrument at 70 eV.

### General Procedure for Preparation of Phenylthiomethyl Derivatives

To a suspension of 828 mg (6 mM) of dry pulverized $K_2CO_3$ and 20 mg of KI in 7 ml of dry dimethylsulfoxide (DMSO), was added 527 mg (3 mM) of 3,5-dimethoxythiophenol (I) and the mixture was stirred at room temperature for 30 min under $N_2$ stream. To the resulting mixture, was added 4.5 mM of bromo or chloro derivatives (IIa-e) and the mixture was stirred at room temperature for appropriate period (Table I). After filtration of the mixture, 70 ml of $H_2O$ was added to the filtrate and the mixture was extracted with benzene. The organic layer was washed with diluted NaOH, $H_2O$, and saturated brine, successively, dried over anhydrous $Na_2SO_4$, and evaporated. Unless otherwise stated, the residue was

Table IV Nmr Spectral Data of III - XII

| Compd.[a] | Nmr δ (J in Hz)[b] |
|---|---|
| IIIa | 3.69[c] (s), 3.77[d], 6.35[e] (t, J = 2.3), 6.57[f] (d, J = 2.3) |
| IIIb | 1.19 (6H, t, J = 7.2, 2 x $OCH_2\underline{Me}$), 2.95[c] (d, J = 5.5), 3.60 (4H, q, J = 7.2, 2 x $OCH_2$), 3.81[d], 4.66 (1H, t, J = 5.5, OCH), 6.31[e] (t, J = 2.0), 6.73[f] (d, J = 2.0) |
| IIIc | 3.76[d], 4.30[c] (s), 6.31[e] (t, J = 2.3), 6.54[f] (d, J = 2.3), 7.47 and 7.92 (3H, 2H, each m, benzoyl-H) |
| IIId | 3.69[c] (s), 3.77[d], 6.35[e] (t, J = 2.3), 6.57[f] (d, J = 2.3) |
| IIIe | 1.24 (3H, t, J = 7.3, $CH_2\underline{Me}$), 3.66[c] (s), 3.79[d], 4.20 (2H, q, J = 7.3, $OCH_2$), 6.32[e] (t, J = 2.3), 6.56[f] (d, J = 2.3) |
| IVa | 3.90 and 3.95[g], 6.45[h] (d, J = 2.5), 6.85[i] (br d, J = 2.5), 7.93[j] (br s) |
| IVb | 4.10[d], 6.47[h] (s), 7.92[j] (s), 10.45[k] |
| V | 3.83 and 3.90[g], 6.53[h] (d, J = 2.5), 7.0 - 7.5 (2H, br, $D_2O$ exchangeable, $NH_2$), 7.10[i] (dd, J = 2.5, 0.8), 8.05[j] (d, J = 0.8) |
| VI | 4.09 and 4.12[g], 6.47[h] (s), 8.09[j] (s), 10.05 and 10.51 (each 1H, each s, 2 x CHO) |
| VII | 3.32 (6H, br s, $NMe_2$), 3.86[d], 6.35[f] (s), 7.67 (1H, br s, N-CH=), 9.21 (1H, s, S-$\overset{\|}{C}$-CHO), 10.38 (1H, s, 4-CHO) |
| VIIIa | 4.04 and 4.07[g], 7.18[i] (d, J = 1.0), 7.57 and 7.90 (3H, 2H, each m, benzoyl-H), 7.96[j] (d, J = 1.0), 10.56[k] |
| VIIIb | 4.07[d], 6.44[h] (s), 7.55 and 7.89 (3H, 2H, each m, benzoyl-H), 7.92[j] (s), 10.50[k] |
| IX | 4.12 and 4.14[g], 6.86[h] (s), 7.94[j] (s), 10.38[k], 13.10 (1H, br, $D_2O$ exchangeable, $CO_2H$) |
| X | 3.93 (3H, s, $CO_2Me$), 4.06 and 4.08[g] (ring-OMe), 6.44[h] (s), 8.15[j] (s), 10.49[k] |
| XIa | 1.39 (3H, t, J = 7.3, $CH_2\underline{Me}$), 3.89 and 3.94[g], 4.39 (2H, q, J = 7.3, $OCH_2$), 6.40[h] (d, J = 2.0), 6.86[i] (dd, J = 2.0, 0.8), 8.11[j] (d, J = 0.8) |
| XIb | 1.40 (3H, t, J = 7.3, $CH_2\underline{Me}$), 4.05 and 4.07[g], 4.39 (2H, q, J = 7.3, $OCH_2$), 6.42[h] (s), 8.13[j] (s), 10.48[k] |
| XIIa | 1.26 (3H, t, J = 7.3, $CH_2\underline{Me}$), 3.66[c] (s), 3.92[d], 4.23 (2H, q, J = 7.3, $OCH_2$), 6.27[e] (d, J = 2.0), 6.60 (1H, d, J = 2.0, 6-H), 10.41[k] |
| XIIb | 1.26 (3H, t, J = 7.3, $CH_2\underline{Me}$), 3.73[c] (s), 3.92[d], 4.23 (2H, q, J = 7.3, $OCH_2$), 6.56[f] (s), 10.37[k] |

a) Measured in $CDCl_3$ except for V and IX (DMSO-$d_6$). b) Abbreviations: br s, broad singlet; br d, broad doublet; d, doublet; dd, double doublet; m, multiplet; q, quartet; s, singlet; t, triplet. c) 2H, $SCH_2$. d) 6H, s, 2 x OMe. e) 1H, 4-H. f) 2H, 2 and 6-H. g) each 3H, each s, 2 x OMe. h) 1H, 5-H. i) 1H, 7-H. j) 1H, 3-H. k) 1H, s, CHO.

chromatographed on silica gel to afford desired product (Table I).

3,5-Dimethoxyphenylthioacetonitrile (IIIa)

After extraction with benzene, obtained residue was dissolved in hot n-hexane and soluble fraction gave desired product.

3,5-Dimethoxyphenylthioacetic Acid (IIId)

After stirring of the reaction mixture, 70 ml of $H_2O$ was added to the mixture. The resulting mixture was acidified with diluted HCl and extracted with AcOEt. The organic layer was washed with $H_2O$ to remove chloroacetic acid (IId) and was extracted with saturated $NaHCO_3$. The latter aqueous layer was acidified with diluted HCl and extracted with $CH_2Cl_2$. The organic layer was worked up usually to afford the desired product.

General Procedure of Vilsmeier Reaction

The Vilsmeier reagent was prepared by stirring of 0.15 M of DMF and 0.45 M of $POCl_3$ under cooling in an ice bath for 0.5 h. To the reagent, was added 0.1 M of 3,5-dimethoxyphenylthiomethyl derivative (IIIa-e) and the mixture was stirred in an appropriate condition (Table II) until disappearance of the starting material on TLC. Unless otherwise stated, the reaction mixture was cooled and hydrolized with ca. 50 ml of $H_2O$. The resulting suspension was extracted with $CHCl_3$. The organic layer was worked up usually and the resulting residue was purified with column chromatography on silica gel followed by the recrystallization (Table II).

7-Formyl-4,6-dimethoxy-2-benzothiophenecarboxylic Acid (IX)

After addition of $H_2O$ to the reaction mixture, the resulting mixture was allowed to stand overnight at room temperature. The precipitated solid was collected on a filter and washed with acetone and $CHCl_3$, successively. The obtained solid was submitted as an analytical sample after recrystallization from acetone.

Methyl 7-Formyl-4,6-dimethoxy-2-benzothiophenecarboxylate (X)

To a suspension of IX in MeOH was added a solution of diazomethane in ether. The resulting suspension changed to a clear solution and then the solid precipitated. The solvent was evaporated in vacuo and the resulting residue was recrystallized from ether to give titled compound almost quantitatively.

Ethyl 4,6-Dimethoxy-2-benzothiophenecarboxylate (XIa) from Ethyl 2-Formyl-3,5-dimethoxyphenylthioacetate (XIIa)

A mixture of 115 mg (0.40 mM) of XIIa, 170 mg (1.2 mM) of dry pulverized $K_2CO_3$,

and 5 ml of dry acetone was refluxed for 1.5 h. After cooling of the reaction mixture, the suspension was filtered and the solid was washed with acetone. The combined filtrate and washing was evaporated to dryness. The obtained residue was purified with short column chromatography on silica gel to give 82 mg (78%) of XIa.

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