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단 신

Medicagol 메톡시벤조푸란의 합성

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A Facile Synthesis of Medicagol Methoxybenzofuran

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7-Hydroxy-11,12-methylenedioxycoumestan (**2**), named medicagol, was isolated from alfalfa,[1] and the basic ring pattern of medicagol is very similar to that of pisatin which is a potent antifungal agent.[2] Because medicagol can successively be degraded by methylative ring opening, hydrolysis, and decarboxylation to medicagol benzofuran (**1**), which has been utilized in elucidating the structure of medicagol mixture.[1,3] As a precursor of 2-(2',4'-dihydroxyphenyl)-5,6-methylenedioxybenzofuran (**3**)[4] isolated from the aerial parts of *Sophora tomentosa* L., medicagol benzofuran (**1**) could also be obtained by the methylation of **3** with diazomethane (Fig. 1).

We have recently reported i) a convenient synthesis of 2-methylbenzofurans by one pot reaction of substituted phenols with 1-chloro-1-(methylthio)acetone in the presence of Lewis acid,[5] and ii) an efficient synthetic method of 2-arylbenzofuran derivatives using substituted phenols with 2-chloro-2-(methylthio)acetophenone or 2-chloro-2-methylthio-(3',4'-methylenedioxy)acetophenone.[6] In the present paper the methods are applied to synthesis of the compound **1**, which is an useful intermediate for structural elucidation of natural products **2** and **3**.

1-(Methylthio)acetyl chloride (**4**) was obtained from (methylthio)acetic acid with thionyl chloride according to the procedure reported by Mooradian *et al.*[7] in 71% yield. Friedel-Crafts acylation of *m*-dimethoxybenzene with **4** in the presence of $SnCl_4$ afforded 2-methylthio-(2',4'-dimethoxy)acetophenone (**5**) in 75% yield. 2-Chloro-2-methylthio-(2',4'-dimethoxy)acetophenone (**6**) was prepared from **5** by chlorination with N-chlorosuccinimide according to the procedure described by Tamura *et al.*[8] in 62% yield.

The treatment of 3,4-methylenedioxyphenol with **6** in the presence of $ZnCl_2$ at 0 °C gave 2-(2',4'-dimethoxyphenyl)-3-methylthio-5,6-methylenedioxybenzofuran (**7**) in 63% yield. The structure of **7** was assigned on the basis of spectroscopic evidence. The elemental analysis and mass spectrum (MS) (M^+ m/z 344) showed the molecular formula to be $C_{18}H_{16}O_4S$. The ^1H NMR spectrum of **7** was readily compared with that of **1** reported in the literature,[4] and exhibited methylthio protons as singlet at 2.28 ppm in place of C_3-proton. Finally, treatment of **7** with Raney nickel in ethanol furnished medicagol benzofuran (**1**) in 87% yield, the data (mp, IR and ^1H NMR) of which were in good agreement with those reported.[4]

In conclusion, we succeeded in the new synthesis of medicagol benzofuran (**1**) by using the reaction of 3,4-methylenedioxyphenol with the chloride **6** under Friedel-Crafts reaction conditions and successive desulfurization of the resulting product **7** as the key steps. Now synthetic applications of this route to the other natural products having 2-arylbenzofuran skeleton are in progress.

EXPERIMENTAL

All melting points were determined by a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR-300E spectrophotometer. ^1H NMR spectra were measured at 60 MHz with a Hitachi R-1500 FT NMR spectrometer using tetrameth-

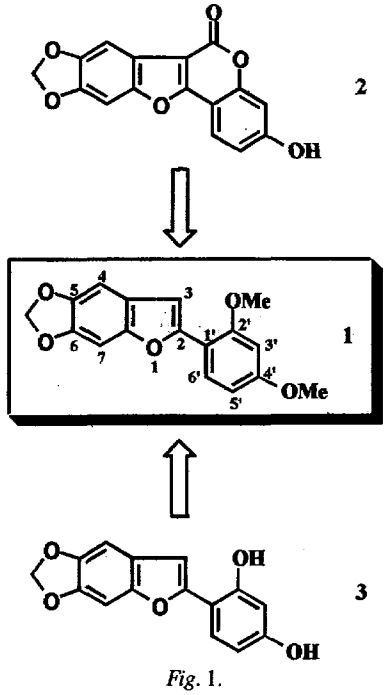
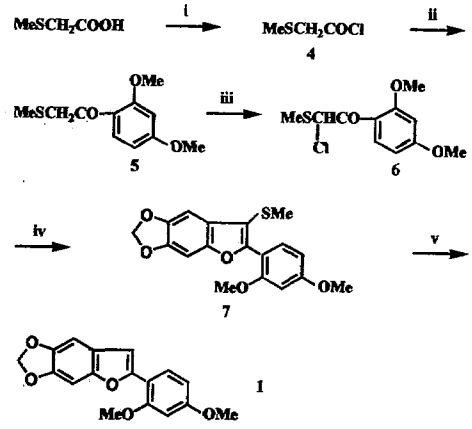


Fig. 1.



Scheme 1. Reagents and conditions: (i) $SOCl_2$, DMF, 50-55 °C, 2h; (ii) *m*-dimethoxybenzene, $SnCl_4$, $ClCH_2CH_2Cl$, 0 °C, 1 h; (iii) N-chlorosuccinimide, CCl_4, rt, 12 h; (iv) 3,4-methylenedioxyphenol $ZnCl_2$, CH_2Cl_2, 0 °C, 1h; (iv) Raney-nickel, EtOH, 60-70 °C, 1 h.

ylsilane as an internal standard. Mass spectra were taken at 70 eV with a Hewlett Packard 5970 GC/MS system by the electron impact (EI) method. Elemental analyses were performed by an Elmentar Vario EL apparatus. Tlc was carried out on a Merck silica gel $60F_{254}$ and silica gel (silica gel 60, 70-230 mesh, E. Merck) was used for column chromatography.

1-(Methylthio)acetyl chloride (4). A mixture of (methylthio) acetic acid (6 g, 56.6 mmol) and N,N-dimethylformamide (2 drops) in thionyl chloride (6 mL) was heated at 50-55 °C for 2 h. The residue was distilled to give **4** (5 g, 71%) as an oil. bp 29-30 °C (7 mmHg), lit.[7] 49-50 °C (14 mmHg); ^{1}H NMR ($CDCl_3$) δ 2.35 (3H, s, SCH_3), 3.64 (2H, s, CH_2).

2-Methylthio-(2',4'-dimethoxy)acetophenone (5). $SnCl_4$ (5.72 g, 22 mmol) was added to a stirred solution of **4** (2.74 g, 22 mmol) and *m*-dimethoxybenzene (2.77 g, 20 mmol) in 1,2-dichloroethane (20 mL) at -10 °C under N_2 atmosphere, and stirring was continued at the same temperature for 1 h. The reaction mixture was quenched by the addition of water and the organic phase was separated. The aqueous phase was extracted with methylene chloride (10 mL). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate=3/1) to give **5** (3.39 g, 75%) as an oil. ^{1}H NMR ($CDCl_3$) δ 2.07 (3H, s, SCH_3), 3.80 (2H, s, -$COCH_2$-), 3.86 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 6.48 (1H, s, Ar-H), 6.61 (1H, d, J=8.2Hz Ar-H), 7.90 (1H, d, J=8.2Hz, Ar-H); IR ($CHCl_3$) 3028, 3012, 2942, 2839, 1727, 1655 (CO), 1601, 1500, 1466, 1419, 1276, 1188, 1165, 1119, 1030 cm^{-1}; MS m/z 226 (M^+), 180, 165 (base peak), 150, 122, 77, 61.

2-Chloro-2-methylthio-(2',4'-dimethoxy)acetophenone (6). N-Chlorosuccinimide (1.34 g, 10 mmol) was added to a stirred solution of **5** (2.26 g, 10 mmol) in carbon tetrachloride (20 mL) at 0 °C and the stirring was continued at room temperature for 12 h. The precipitated succinimide was filtered off and the solvent was removed *in vacuo*. The residual solid was recrystallized from hexane/ethyl acetate (2/1) to give **6** (1.61 g, 62%) as a white solid. mp 79-80 °C; ^{1}H NMR ($CDCl_3$) δ 2.13 (3H, s, SCH_3), 3.87 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 6.38-6.64 (2H, m, Ar-H), 6.67 (1H, s, -COCH-), 7.92 (1H, d, J=8.1Hz, Ar-H); IR (KBr) 3023, 2973, 2922, 2836, 1661 (CO), 1597, 1566, 1499, 1467, 1417, 1273, 1246, 1217, 1176, 1122, 1043 cm^{-1}; MS m/z 262 (M+2), 260 (M^+), 225, 165 (base peak), 122, 107, 92, 63; Anal. Calcd for $C_{11}H_{13}ClO_3S$: C, 50.67; H, 5.03. Found C, 50.92; H, 5.07.

2-(2',4'-Dimethoxyphenyl)-3-methylthio-5,6-methylenedioxybenzofuran (7). $ZnCl_2$ (245 mg, 1.8 mmol)

was added to a stirred solution of 3,4-methylenedioxyphenol (227 mg, 1.64 mmol) and **6** (427 mg, 1.64 mmol) in methylene chloride (10 mL) at 0 °C under N_2 atmosphere, and the stirring was continued at the same temperature for 1 h. The reaction mixture was quenched by the addition of water and the organic phase was separated. The aqueous phase was extracted with methylene chloride (10 mL). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate=2/1) to give **7** (356 mg, 63%) as a white solid. mp 142-143 °C; ^{1}H NMR ($CDCl_3$) δ 2.28 (3H, s, SCH_3), 3.84 (3H, s, C_4-OCH_3), 3.86 (3H, s, C_2-OCH_3), 5.99 (2H, s, -OCH_2O-), 6.51-6.67 (2H, m, $C_{3',5'}$-H), 7.01 (1H, s, C_4-H), 7.06 (1H, s, C_7-H), 7.44 (1H, d, J=9.4Hz, C_6-H); IR (KBr) 2924, 1620, 1574, 1458, 1299, 1203, 1157, 1092, 1030 cm^{-1}; MS m/z 344(M^+, base peak), 298, 271, 172, 127, 121, 69; Anal. Calcd for $C_{18}H_{16}O_4S$: C, 62.78; H, 4.68. Found C, 62.91; H, 4.75.

2-(2',4'-Dimethoxyphenyl)-5,6-methylenedioxybenzofuran (1). Raney nickel (W-2, ca. 3 g) was added to a solution of **7** (300 mg, 0.88 mmol) in ethanol (30 mL), and the mixture was heated at 60-70 °C for 1 h. The Raney nickel was filtered off and the solvent was evaporated off. The residual solid was recrystallized from isopropyl alcohol to give **1** (228 mg, 87%) as a white solid. mp 166-167 (lit.[4] 168-169); IR (KBr) 2999, 2898, 1612, 1581, 1502, 1456, 1371, 1319, 1290, 1211, 1159, 1078, 1036 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.85 (3H, s, C_4-OCH_3), 3.95 (3H, s, C_2-OCH_3), 5.96 (2H, s, -OCH_2O-), 6.51-6.63 (2H, m, $C_{3',5'}$-H), 6.92 (1H, s, C_4-H), 6.99 (1H, s, C_7-H), 7.07 (1H, s, C_3-H), 7.88 (1H, d, J=9.3Hz, C_6-H); these spectral data are in accord with those reported.[4]

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