CONCISE SYNTHESIS OF 7, 8-DIMETHOXYISOCHROMAN-3-ONE: FORMAL SYNTHESIS OF BERBERINE[1]

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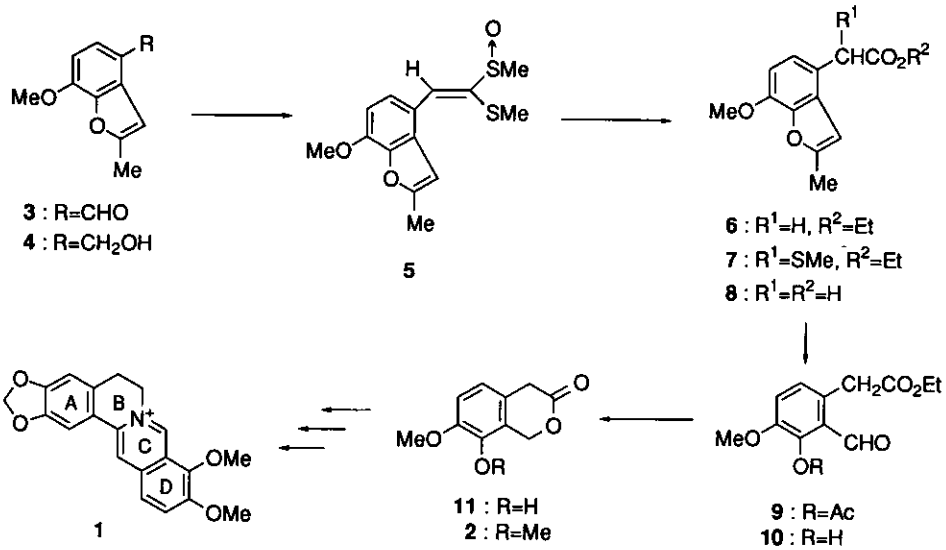
Abstract - 7, 8-Dimethoxyisochroman-3-one (**2**), a synthetic precursor for berberine, was concisely synthesized from 4-formyl-7-methoxy-2-methylbenzo[*b*]furan (**3**), which had been readily available from isovanillin through the CsF-mediated Claisen rearrangement of the corresponding propargyl ether.

Berberine (**1**) is one of the most important natural products for medicinal uses. Thus, though a lot of research groups have focused on the synthesis of it or its tetrahydro derivative, canadine, not so many reports appeared because of difficult construction of the D ring of a 3, 4-disubstituted 1, 2-dimethoxybenzene in **1**. Among the synthetic studies[2] Narasimhan *et al.*[2c] reported the synthesis of canadine using 7, 8-dimethoxyisochroman-3-one (**2**) as a source of the D ring. Recently we succeeded in effective preparation of a salicylaldehyde from a phenol by combination of the cesium fluoride (CsF)-mediated Claisen rearrangement of an aryl propargyl ether and successive cleavage of the furan ring in the exclusively formed 2-methylarylfuran.[3] This method was applied to the syntheses[4] of some natural products with a 3, 4-disubstituted 1, 2-dimethoxybenzene moiety in their molecules. In this paper we present concise preparation of the isochromanone (**2**) from 4-formyl-7-methoxy-2-methylbenzo[*b*]furan (**3**), our common synthetic key intermediate,[4] which had been readily available from isovanillin through the CsF-mediated Claisen rearrangement of the corresponding propargyl ether.

In our synthetic plan elongation of a carbon unit to the aldehyde group in **3** to provide 7-methoxy-2-



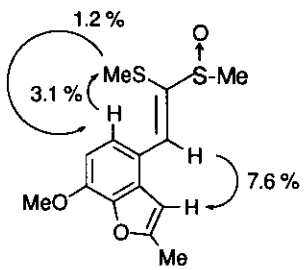


Figure NOE of **5**

methylbenzo[*b*]furan-4-acetic acid derivative (**6** or **8**) should be needed. At first we attempted displacement reactions using a benzyl alcohol (**4**) easily given by reduction of **3**. Unfortunately all trials for introduction of a new carbon unit to the benzylic position in **4** failed.

Ogura *et al.*[5] reported the useful preparation of phenylacetic acid derivatives by condensation of aromatic aldehydes with methyl methylsulfinylmethyl sulfide (formaldehyde dimethyl mercaptal S-oxide: FAMSO) followed by hydrolysis. Application of this condensation reaction to the aldehyde (**3**) in the presence of powdered sodium hydroxide (NaOH) afforded the desired product (**5**) in 83.5 % yield. The geometry of the double bond in **5** was determined as an expected *E* configuration[5] by difference nuclear Overhauser effect (NOE) experiments in the nmr spectroscopy as shown in Figure. Use of Triton B in place of NaOH as a base led to the lower formation (63.5 %) of **5**.

The report[5] mentioned that phenylacetic acids had been given by treatment of condensation products with hydrochloric acid while the corresponding esters by treatment with alcoholic hydrogen chloride. In our case incomplete hydrolysis to an acid (**8**) was observed under the former condition. On the other hand treatment with ethanolic hydrogen chloride afforded a homogeneous product on tlc as a yellow oil. An ester carbonyl absorption band was observed at 1729 cm^{-1} in the ir spectrum of the product. However its nmr spectrum showed a characteristic signal at δ 4.70 as 1Hx3/4 singlet, which was attributable to a benzylic methine

proton of a product (**7**) with a methylthio group on the benzylic position, in addition to a 2H x 1/4 singlet at δ 3.71 due to the benzylic methylene protons of a desired phenylacetate (**6**). The ratio of **6** and **7** was found to be 1 : 3. Heating the inseparable mixture of **6** and **7** in ethanol with Raney nickel under reflux resulted in smooth removal of the methylthio group to give a phenylacetate (**6**) in 79.5 % yield from **5**, which was easily hydrolyzed to produce the corresponding acid (**8**).

Ozonolysis of **6** followed by treatment with dimethyl sulfide quantitatively afforded a cleaved product (**9**). Ethanolysis of **9** gave a salicylaldehyde (**10**), which was subjected to reduction with sodium borohydride ($NaBH_4$) without purification to give a cyclized product (**11**) in 56.0 % yield from **6**. Methylation of it afforded 7, 8-dimethoxyisochromanone (**2**), mp 98.5-101 °C (lit. mp 95 °C[2c]; mp 98-100 °C[6a]; mp 97-99 °C[6b]), as colorless needles. Thus, 7, 8-dimethoxyisochromanone (**2**), a synthetic precursor for berberine (**1**), was concisely prepared from 4-formyl-7-methoxy-2-methylbenzo[*b*]furan (**3**) through 7 steps in 39.6 % overall yield.

EXPERIMENTAL

All melting points were measured on a micro melting-point hot stage (Yanagimoto) and are uncorrected. Ir spectra were recorded for Nujol mulls, unless otherwise stated, on a Hitachi 260-10 or JASCO IR-700 spectrophotometer. Nmr spectra were recorded in $CDCl_3$ with a JEOL GSX-500 (500 MHz) spectrometer with tetramethylsilane (TMS) as an internal reference. Peak multiplicities are quoted in Hz as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Diffused splitting pattern is abbreviated as dif. Mass spectra (Ms) were measured with a JEOL JMS-Automass 20 spectrometer using a direct inlet system. For column silica gel 60 (70-230 mesh ASTM; Merck) was used, while for tlc and preparative tlc (plc), silica gel 60 F_{254} (Art. 5715 and 5717, Merck) were used. Ozone was generated by passing O_2 at a flow rate of 50 l/h at 70 V using Japan Ozone 0-1-2. Raney nickel was perchased from Aldrich Chemical Company Inc.

4-Hydroxymethyl-7-methoxy-2-methylbenzo[*b*]furan (4) To a stirred solution of the aldehyde (**3**)[4] (10.0 g, 0.0526 mol) in methanol (300 ml) was gradually added $NaBH_4$ (2.01 g, 0.0531 mol) at 0 °C and then the mixture was stirred at room temperature for 0.5 h. After work-up recrystallization of the residue with ether-hexane gave the alcohol (**4**) as colorless needles (9.76 g, 96.9 %), mp 75-77 °C. *Anal.* Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.90; H, 6.22. Ir ν_{max}: 3240 cm^{-1}. Nmr δ: 2.49 (3H, d, *J*=1.0 Hz, C_2-Me), 4.00 (3H, s, OMe), 4.79 (2H, s, CH_2OH), 6.51 (1H, dif. d, *J*=1.0 Hz, C_3-H), 6.68 (1H, d, *J*=8.0 Hz, C_6-H), 7.08 (1H, d, *J*=8.0 Hz, C_5-H).

(*E*)-7-Methoxy-2-methyl-4-(2-methylsulfinyl-2-methylthioethylidene)benzo[*b*]furan (5)

(a) In the Presence of NaOH: A mixture of FAMSO (0.11 ml, 1.05 mmol) and powdered NaOH (0.0071 g, 0.18 mmol) was stirred at 70 °C for 0.5 h. To the solution was added the aldehyde (**3**) (0.10 g, 0.53 mmol) and the whole was stirred at the same temperature for 5 h. After work-up the residue was purified by column chromatography using a mixed solvent of benzene : ethyl acetate (3 : 1) to give a yellow oil (0.130 g, 83.5 %). Nmr δ: 2.29 (3H, s, SMe), 2.49 (3H, s, C_2-Me), 2.78 (3H, s, S(O)Me), 4.05 (3H, s, OMe), 6.63 (1H, s, C_3-H), 6.81 (1H, d, *J*=8.5 Hz, C_6-H), 7.81 (1H, s, olefinic H), 8.16 (1H, d, *J*=8.5 Hz, C_5-H). Ms *m/z*: 296 (6.1 %, M^+), 218 (100 %).

(b) In the Presence of Triton B: A solution of the aldehyde (**3**) (0.50 g, 2.63 mmol), FAMSO (0.33 ml, 3.16 mmol), and Triton B (40 % solution in methanol: 0.84 ml, 1.85 mmol) in tetrahydrofuran (10 ml) was refluxed for 7 h. After treated as above the product (**5**) was obtained in 63.5 % yield.

Treatment of the Condensation Product (5) with Ethanolic Hydrogen Chloride A large excess of hydrogen chloride was bubbled into a solution of **5** (0.059 g, 0.20 mmol) in dry ethanol (0.5 ml) at 0 °C and the resulted solution was allowed to stand at room temperature for 21 h. After work-up the residue was purified by plc using a mixed solvent of hexane : ethyl acetate (4 : 1) to give a yellow oil (Rf=0.69, 0.0286 g). Ir ν_{max} (neat): 1729 cm^{-1}. Nmr δ: 1.23 (3Hx1/4, t, *J*=7.2 Hz, $CH_2\underline{CH_3}$ of **6**), 1.24 (3Hx3/4, t, *J*=7.0 Hz, $CH_2\underline{CH_3}$ of **7**), 2.05 (3Hx3/4, s, SMe of **7**), 2.47 (3H, s, C_2-Me of **6** and **7**), 3.71 (2Hx1/4, s, $Ar\underline{CH_2}CO$ of **6**), 3.98 (3Hx1/4, s, OMe of **6**), 3.99 (3Hx3/4, s, OMe of **7**), 4.13-4.22 (2H, m, $O\underline{CH_2}CH_3$ of **6** and **7**), 4.70 (1Hx3/4, s, $Ar\underline{CH}(SMe)CO$ of **7**), 6.43 (1Hx1/4, s, C_3-H of **6**), 6.62 (1Hx3/4, s, C_3-H of **7**), 6.69 (1H, d, *J*=8.1 Hz, C_6-H of **6** and **7**), 6.99 (1Hx1/4, d, *J*=8.1 Hz, C_5-H of **6**), 7.19 (1Hx3/4, d, *J*=8.1 Hz, C_5-H of **7**).

Ethyl 4-(7-Methoxy-2-methylbenzo[*b*]furanyl)acetate (6) A crude product (1.835 g) given by the ethanolysis of **5** (2.503 g, 8.44 mmol) was dissolved in ethanol (60 ml) and the solution was refluxed for 4 h in the presence of Raney nickel (5.0 ml). After removal of the catalyst by decantation the solution was evaporated *in vacuo*. The residue was purified by short column chromatography using chloroform to give a yellow oil (1.666 g, 79.5 % from **5**). Ir ν_{max}(neat): 1734 cm^{-1}. Nmr δ: 1.23 (3H, t, *J*=7.0 Hz, $CH_2\underline{CH_3}$), 2.47 (3H, d, *J*=1.0 Hz, C_2-Me), 3.71 (2H, s, $Ar\underline{CH_2}CO$), 3.99 (3H, s, OMe), 4.14 (2H, q, *J*=7.0 Hz, $O\underline{CH_2}CH_3$), 6.43 (1H, dif. d, *J*=1.0 Hz, C_3-H), 6.68 (1H, d, *J*=8.3 Hz, C_6-H), 6.99 (1H, d, *J*=8.3 Hz, C_5-H). Ms *m/z*: 248 (17.2 %, M^+), 175 (100 %).

4-(7-Methoxy-2-methylbenzo[*b*]furanyl)acetic Acid (8) A solution of the ester (**6**) (0.107 g, 0.43 mnol) in ethanol (1.4 ml) and 17 % aqueous potassium hydroxide solution (0.25 ml) was stirred at room temperature for 0.5 h. After work-up the crude product was recrystallized from ether-hexane to give pale yellow prisms (0.0765 g, 80.5 %), mp 122-123 °C. *Anal.* Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.33; H, 5.41. Ir ν_{max}: 1692 cm^{-1}. Nmr δ: 2.46 (3H, s, C_2-Me), 3.74 (2H, s, $ArCH_2CO$), 3.98 (3H, s, OMe), 6.40 (1H, s, C_3-H), 6.69 (1H, d, *J*=8.0 Hz, C_6-H), 6.99 (1H, d, *J*=8.0 Hz, C_5-H).

8-Hydroxy-7-methoxyisochroman-3-one (11) Ozone was bubbled into a solution of the ester (**6**) (0.514 g, 2.07 mmol) in dry methylene chloride (20 ml) at -70 °C for 10 min. Dimethyl sulfide (15 ml, 0.21 mol) was added to the solution and the mixture was stirred at room temperature for 1 h. Evaporation of the solvent *in vacuo* afforded ethyl 3-acetoxy-2-formyl-4-methoxyphenylacetate (**9**)[7] as a yellow oil quantitatively. A solution of the crude **9** in 0.1 N sodium ethoxide in ethanol (4.1 ml) was stirred at 0 °C for 0.5 h. After work-up the crude ethyl 2-formyl-3-hydroxy-4-methoxyphenylacetate (**10**)[8] (0.392 g) was obtained as a yellow oil. A solution of the crude **10** in ethanol (10 ml) was treated with $NaBH_4$ (0.156 g, 4.11 mmol) at room temperature for 0.5 h. After work-up recrystallization of the product with methylene chloride-hexane gave 8-hydroxy-7-methoxyisochroman-3-one (**11**) as colorless prisms (0.225 g, 56.0 % from **6**), mp 185-186 °C (lit. mp 183-185 °C[6a]; mp 180-183 °C[6b]). *Anal.* Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.16; H, 5.09. Ir ν_{max}: 3356, 1711 cm^{-1}. Nmr δ: 3.56 (2H, s, C_4-H_2), 3.83 (3H, s, OMe), 5.34 (2H, s, C_1-H_2), 5.75 (1H, s, OH, exchangeable), 6.62 (1H, d, *J*=8.0 Hz, C_6-H), 6.75 (1H, d, *J*=8.0 Hz, C_5-H).

7, 8-Dimethoxyisochroman-3-one (2) A mixture of a phenol (**11**) (0.225 g, 1.16 mmol), potassium carbonate (0.482 g, 3.49 mmol), and dimethyl sulfate (0.16 ml, 1.75 mmol) in dimethylformamide (6.0 ml) was stirred at room temperature for 0.5 h. After work-up recrystallization of the crude product with ether-hexane afforded 7, 8-dimethoxyisochroman-3-one (**2**) as colorless fine needles (0.170 g, 70.7 %), mp 98.5-101 °C (lit. mp 95 °C[2c]; mp 98-100 °C[6a]; mp 97-99 °C[6b]). *Anal.* Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.39; H, 5.74. Ir ν_{max}: 1755 cm^{-1}. Nmr δ: 3.63 (2H, s, C_4-H_2), 3.87 (3H, s, OMe), 3.88 (3H, s, OMe), 5.40 (2H, s, C_1-H_2), 6.89 (2H, s, C_5- and C_6-H).

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1. Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday.

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7. Spectral data of **9** [Ir ν_{max} (neat): 1773, 1736, 1694 cm^{-1}. Nmr δ: 1.18 (3H, t, *J*=7.0 Hz, $CH_2\underline{CH_3}$), 2.31 (3H, s, COMe), 3.79 (3H, s, OMe), 3.83 (2H, s, $ArC\underline{H_2}CO$), 4.08 (2H, q, *J*=7.0 Hz, $OC\underline{H_2}CH_3$), 7.03 (1H, d, *J*=8.4 Hz, C_5-H), 7.07 (1H, d, *J*=8.4 Hz, C_6-H), 10.22 (1H, s, $ArC\underline{H}O$)].
8. Spectral data of **10** [Ir ν_{max} ($CHCl_3$): 3534, 1730, 1647 cm^{-1}. Nmr δ: 1.18 (3H, t, *J*=7.0 Hz, $CH_2\underline{CH_3}$), 3.79 (2H, s, $ArC\underline{H_2}CO$), 3.83 (3H, s, OMe), 4.08 (2H, q, *J*=7.0 Hz, $OC\underline{H_2}CH_3$), 6.67 (1H, d, *J*=8.3 Hz, C_5-H), 6.94 (1H, d, *J*=8.3 Hz, C_6-H), 10.18 (1H, s, $ArC\underline{H}O$), 11.97 (1H, s, OH, exchangeable)].

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