A Rapid Synthesis of Substituted 4-Hydroxymethyl-3-Chromene from 2'-Hydroxyacetophenone and Phenyl Vinyl Sulfoxide

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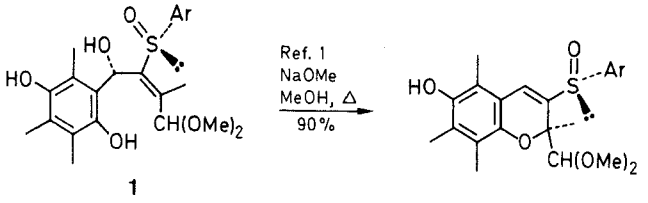
A two-step synthesis of 6-alkyl-4-hydroxymethyl-3-chromene (6-alkyl-4-hydroxymethyl-2*H*-1-benzopyran) from addition of phenyl vinyl sulfoxide carbanion to 5'-alkyl-2'-hydroxyacetophenone is described. Application to the synthesis of 4-methyl-3-chromene (4-methyl-2*H*-1-benzopyran) and 4,4-dimethylchroman (3,4-dihydro-4,4-dimethyl-2*H*-1-benzopyran) is also presented.

A few years ago we reported[1] an asymmetric synthesis of chiral 2,2-disubstituted 3-sulfinyl-3-chromene based on the stereoselective cyclization of the vinylic sulfoxide **1** in basic medium (Scheme **1**). This result was applied to the synthesis of vitamin E.



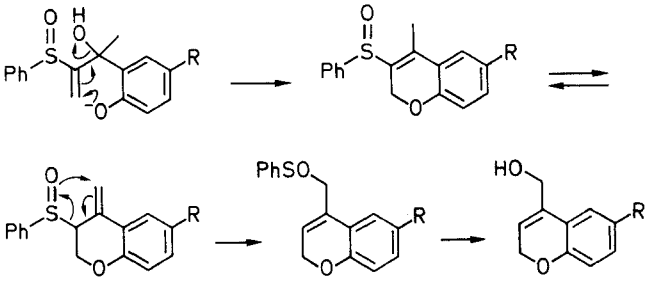
Scheme **1**

We report now an extension of this method to the synthesis of 4-hydroxymethyl-3-chromene **4** in two-steps from 2'-hydroxyacetophenones and commercially available phenyl vinyl sulfoxide (Scheme **2**).

2'-Hydroxyacetophenones **2** are readily prepared in high yield from phenols by acetylation followed by a Fries rearrangement (Scheme **2**).

Addition of the carbanion of phenyl vinyl sulfoxide to the carbonyl function of **2** gave the corresponding β-hydroxy sulfoxide **3** in 90% yield, which was cyclized with sodium ethoxide in refluxing ethanol in 90% yield to the corresponding 4-hydroxymethyl-3-chromene **4** (Scheme **2**).

The formation of compound **4** can be explained by cyclization of the β-hydroxy sulfoxide **3** to the corresponding 3-sulfinyl-3-chromene by a S_N2' type mechanism as shown before,[1] followed by an isomerization of the vinyl sulfoxide to the allylic isomer[2] which undergoes a sigmatropic sulfoxide–sulfenate rearrangement,[3] the resulting sulfenate being hydrolyzed in the basic reaction mixture (Scheme **3**).



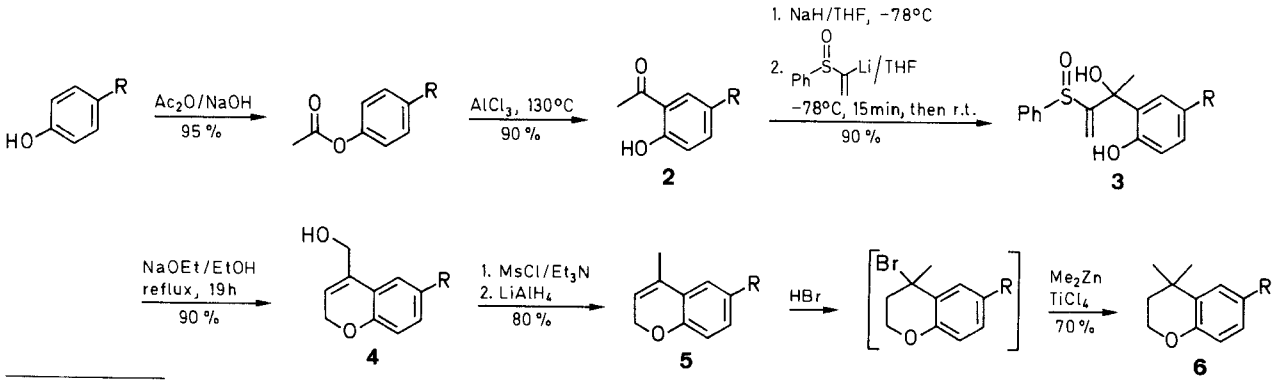
Scheme **3**

Adducts **4** can be easily transformed into 4-methyl-3-chromene **5** by reduction of the corresponding mesylate or to 4,4-dimethylchroman **6** by addition of hydrogen bromide on the double bond[4] followed by methylation with dimethylzinc in presence of titanium tetrachloride[5] (Scheme **2**).

6-Alkyl-4-hydroxymethyl-3-chromene (6-Alkyl-4-hydroxymethyl-2*H*-1-benzopyran, 4); General Procedure:

4-Alkyl-2-(1-hydroxy-1-methyl-2-phenylsulfinyl-2-propenyl)phenol (**3**):

LDA (0.03 mol) in THF (100 mL) is slowly added to commercially available phenyl vinyl sulfoxide (0.03 mol) in THF (20 mL) at −78 °C. Ten minutes after the end of the addition, a suspension of sodium 2-acetyl-4-alkylphenolate [0.03 mol, made with NaH (0.72 g, 1 equiv) in THF (20 mL)] was slowly added at −78 °C and



2-6	a	b
R	Me	Et

Scheme **2**

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the mixture is maintained at this temperature for 15 min and allowed to reach r.t. Then H_2O (80 mL) is added and the THF evaporated, the product is extracted with Et_2O (2 × 80 mL). The resulting solid is very rapidly filtrated over silica gel (eluent: Et_2O/hexane/CH_2Cl_2: 80:10:10), to give a solid, which is not very stable and must be used very quickly and without further purification in the next step.

6-Alkyl-4-hydroxymethyl-3-chromene **(4)**:
The preceeding hydroxy sulfoxide **3** (0.047 mol) in EtOH (200 mL) is treated with NaOEt (0.1 mol) and refluxed for 5 h. Then more NaOEt (0.1 mol) is added and the reflux continued for 14 h. After evaporating the solvent, water (100 mL) is added and the pH adjusted to 4 with 5% aq H_2SO_4. Extraction with CH_2Cl_2 (2 × 100 mL) and purification by flash chromatography (eluent: Et_2O) afforded **4** in 90% yield.

4-Hydroxymethyl-6-methyl-3-chromene **(4a)**: yield 90%; mp 110–113°C.

$C_{11}H_{12}O_2$ (176.2) calc. C 74.97 H 6.86 found 74.88 6.92

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.25 (s, 3H, CH_3), 4.55 (d, 2H, J = 4 Hz, $C\underline{H}_2OH$), 4.8 (d, 2H, J = 5 Hz, $C\underline{H}_2CH$=), 5.9 (m, 1H, HC=), 6.85–7.2 (m, 3 H_{arom}).

6-Ethyl-4-hydroxymethyl-3-chromene **(4b)**: yield: 90%; mp 122°C.

$C_{12}H_4O_2$ (190.2) calc. C 75.76 H 7.42 found 75.65 7.28

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.3 (t, 3H, J = 7 Hz, $CH_2C\underline{H}_3$), 2.7 (q, 2H, J = 7 Hz, $C\underline{H}_2CH_3$), 3.6 (m, 1H, OH), 4.2 (m, 2H, $C\underline{H}_2OH$), 4.6 (d, 2H, J = 7 Hz, OCH_2), 5.6 (t, 1H, J = 7 Hz, HC=), 6.7–7.2 (m, 3 H_{arom}).

6-Alkyl-4-methyl-3-chromene (6-Alkyl-3-methyl-2*H*-1-benzopyran) 5:
According to usual procedures: mesyl chloride/Et_3N/THF/−20°C[6807a]; $LiAlH_4$/Et_2O/r.t.[6b].

4,6-Dimethyl-3-chromene **(5a)**: yield: 80%; liquid.

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.08 (s, 3H, 3-CH_3), 2.29 (s, 3H, 6-CH_3), 4.75 (d, 2H, J = 4 Hz, OCH_2), 5.72 (t, 1H, J = 4 Hz, vinylic H), 6.70–6.77 (m, 3 H_{arom}).

6-Ethyl-4-methyl-3-chromene **(5b)**: yield: 80%; liquid

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.6 (t, 3H, J = 7 Hz, $CH_2C\underline{H}_3$), 2.9 (q, 2H, J = 7 Hz, $C\underline{H}_2CH_3$), 5.0 (d, 2H, J = 6 Hz, OCH_2), 6.0 (t, 1H, vinylic H, J = 6 Hz), 7.3–7.7 (m, 3 H_{arom}).

6-Alkyl-4,4-dimethylchroman (6-Alkyl-4,4-dimethyl-3,4-dihydroxy-2*H*-1-benzopyran) 6:
According to described procedures[4,5] for related molecules.

4,4,6-Trimethylchroman **(6a)**: yield: 70%; bp 93°C/3.5 Torr.

$C_{12}H_{16}O$ (176.3) calc. C 81.77 H 9.15 found 81.61 9.25

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.25 (s, 6H, CH_3), 1.72 (t, 2H, J = 5 Hz, CH_2), 2.2 (s, 3H, CH_3), 4.07 (t, 2H, J = 5 Hz, OCH_2), 6.81 (AB, 2H, J_{AB} = 8.2 Hz, $\Delta\nu$ = 36.8 Hz. A part splitted by J = 2.1 Hz, H-7 and H-8), 7.07 (d, 1H, J = 2.1 Hz, H-5).

6-Ethyl-4,4-dimethylchroman **(6b)**: yield: 80%; bp 104°C/3.5 Torr.

$C_{13}H_{18}O$ (190.3) calc. C 82.11 H 9.47 found 82.33 9.61

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.22 (t, 3H, J = 7.6 Hz, CH_3), 1.35 (s, 6H, $2CH_3$), 1.81–1.87 (m, 4H, $C\underline{H}_2CH_3$ and CH_2), 4.15–4.21 (m, 2H, OCH_2), 7.58 (AB, 2H, J = 8.3 Hz, $\Delta\nu$ = 37.7 Hz, H-7 and H-8, H-7 splitted by J = 2 Hz), 7.08 (d, 1H, J = 2 Hz, H-5).

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(1) Solladié, G.; Moine, G. *J. Am. Chem. Soc.* **1984**, *106*, 6097.
(2) Hoffmann, R.W.; Maak, N. *Tetrahedron Lett.* **1976**, 2237
Hoffmann, R.W.; Gerlach, R.; Goldmann, S. *Tetrahedron Lett.* **1976**, 2599.
(3) Evans, D.A.; Andrews, G.C. *Acc. Chem. Res.* **1974**, *7*, 147.
(4) Walling, C.; Kharasch, M.S.; Mayo, F.R. *J. Am. Chem. Soc.* **1939**, *61*, 2693.
(5) Reetz, M.T.; Westermann, J.; Steinbach, R. *Angew. Chem.* **1980**, *92*, 933; *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 901.
(6) Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis*, Vol. 1, J. Wiley, 1967: a) p. 662, b) p. 587.

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