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CONCISE AND EFFICIENT SYNTHESIS OF 4-HYDROXY-2-PYRONES FROM PENTANE-2,4-DIONES[‡]

Masahiro Yoshida,* Hironobu Takai, Chika Mitsuhashi, and Kozo Shishido*

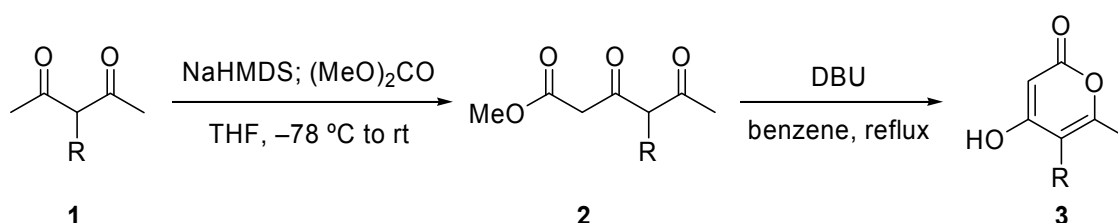
Graduate School of Pharmaceutical Sciences, The University of Tokushima,
 1-78-1 Sho-machi, Tokushima 770-8505, Japan

E-mail: yoshida@ph.tokushima-u.ac.jp, shishido@ph.tokushima-u.ac.jp

Abstract – A concise method for the synthesis of 4-hydroxy-2-pyrones has been developed. Various 5-substituted 4-hydroxy-2-pyrones were efficiently prepared in two steps from 3-substituted pentane-2,4-diones.

2-Pyrones are an important class of heteroaromatic molecules which are components in a variety of biologically active compounds.¹ They are also extensively utilized in organic synthesis as dienes in Diels–Alder reactions² and as precursors to other carbo- and heterocyclic systems.³ For these reasons, considerable effort has been devoted toward finding an efficient synthesis of substituted 2-pyrones.⁴ For example, 4-hydroxy-2-pyrones were prepared via the intramolecular cyclization of β,δ -diketo esters under basic conditions.⁵ Although this method is useful for the synthesis of various 4-hydroxy-2-pyrones, there are problems with the low yields of the products and the lack of reproducibility. We report herein an improved method for the synthesis of 4-hydroxy-2-pyrones, in which various 5-substituted derivatives were efficiently prepared in two steps from 3-substituted pentane-2,4-diones.⁶

Scheme 1. Procedure for 5-substituted 4-hydroxy-2-pyrones **3**

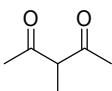
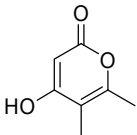
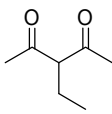
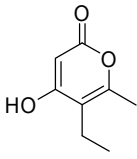
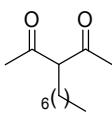
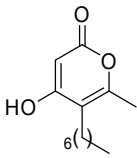
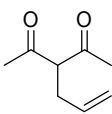
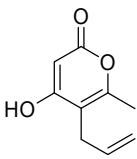
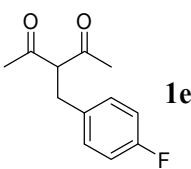
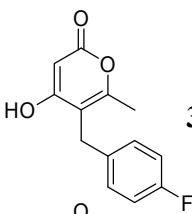
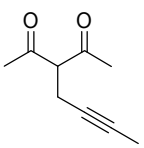
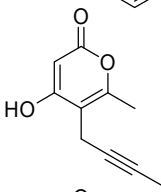
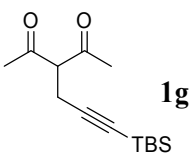
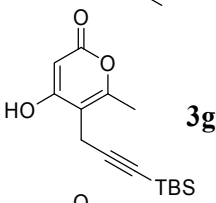
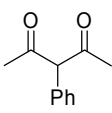
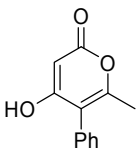
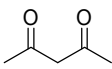
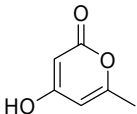


Our procedure for the synthesis of 4-hydroxy-2-pyrones is described in Scheme 1. Thus, methoxycarbonylation of the pentane-2,4-diones **1** in the presence of sodium bis(trimethylsilyl)amide

[‡] This paper is dedicated to Prof. Dr. Albert Eschenmoser on the occasion of his 85th birthday.

(NaHMDS) gives β,δ -diketo esters **2**. Subsequent cyclization of **2** by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing benzene produces 4-hydroxy-2-pyrones **3**.

Table 1. Synthesis of various 4-hydroxy-2-pyrones **3a–3i** from pentane-2,4-diones **1a–1i**

Entry	Substrate	Product	Yield (%) ^b
1	 1a	 3a	68
2	 1b	 3b	62
3	 1c	 3c	89
4	 1d	 3d	56
5	 1e	 3e	40
6	 1f	 3f	68
7	 1g	 3g	79
8	 1h	 3h	43
9	 1i	 3i	62

^a All the reactions were carried out as shown in Scheme 1.

^b The yields were determined in two steps from **1**.

The results of the reactions using various pentane-2,4-diones **1a–1i** are summarized in Table 1. When 3-methylpentane-2,4-dione (**1a**) was subjected to the reaction, the 4-hydroxy-5,6-dimethyl-2-pyrone (**3a**) was obtained in two steps in 68% overall yield (entry 1). The reactions of the 3-ethyl- and 3-heptylpentane-2,4-diones (**1b** and **1c**) uneventfully afforded the corresponding products **3b** and **3c** in 62% and 89% overall yields, respectively (entries 2 and 3). The allyl- and *p*-fluorobenzyl-substituted substrates **1d** and **1e** also reacted to deliver the 4-hydroxy-2-pyrones **3d** and **3e** in moderate yields, respectively (entries 4 and 5). The pentane-2,4-diones **1f** and **1g** having a propargylic substituent at the 3-position were successfully transformed to the 4-hydroxy-2-pyrones **3f** and **3g**, respectively, in good yields (entries 6 and 7). When 3-phenylpentane-2,4-dione (**1h**) was subjected to the reaction, the phenyl-substituted product (**3h**) was produced in 43% overall yield (entry 8). The reactions of the parent pentane-2,4-dione (**1i**) also afforded the corresponding non-substituted product **3i** in 62% overall yield (entry 9).

Thus, we have developed a practical methodology for the synthesis of 5-substituted 4-hydroxy-2-pyrones. The reaction afforded a variety of substituted 4-hydroxy-2-pyrones, and the process provided an efficient and convenient protocol for the preparation of these derivatives.⁷

EXPERIMENTAL

Solvents were dried and distilled according to standard protocols. The phrase ‘residue upon workup’ refers to the residue obtained when the organic layer was separated and dried over anhydrous MgSO₄ and the solvent was evaporated under reduced pressure.

General procedure for the synthesis of 4-hydroxy-2-pyrones **3**

Synthesis of **3c** (Table 1, entry 3): To a stirred solution of 1.06 M solution of NaHMDS in THF (14.3 mL, 15.1 mmol) was added dropwise 3-heptylpentane-2,4-dione (**1c**) (1.00 g, 5.04 mmol) in THF (30 mL) at –78 °C. Stirring was continued for 2 h at rt, and dimethyl carbonate (0.42 mL, 5.04 mmol) was added dropwise to the reaction mixture at –78 °C; stirring continued for another 10 h at rt. The reaction mixture was quenched with 10% HCl and extracted with AcOEt. The combined extracts were washed with brine, and the residue upon workup was chromatographed on a small amount of silica gel with hexane-AcOEt (30:70 v/v) as eluent to give the corresponding β,δ -diketo ester as a yellow oil. To a stirred solution of this β,δ -diketo ester in benzene (25 mL) was added DBU (1.51 mL, 10.08 mmol) at rt, and stirring was continued for 2.5 h under refluxing conditions. The reaction mixture was quenched with 10% HCl and extracted with AcOEt. The combined extracts were washed with brine, and the residue upon workup was chromatographed on silica gel with hexane-AcOEt (60:40 v/v) as eluent to give the 4-hydroxy-2-pyrone **3c** (1.00 g, 89%, 2 steps) as a colorless solid.

5-Methyl-4-hydroxy-6-methylpyran-2-one (3a)⁷

Colorless powder; mp 204.5–206.8 °C (recrystallized from MeOH); IR (KBr) 3355, 2938, 1680, 1625 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.94 (3H, s), 2.26 (3H, s), 5.62 (1H, s); $^{13}\text{C-NMR}$ (100 MHz, DMSO-d_6) δ 9.2 (CH_3), 17.1 (CH_3), 88.3 (CH), 106.4 (Cq), 158.5 (Cq), 163.2 (Cq), 170.2 (Cq); HRMS (ESI) m/z calcd for $\text{C}_7\text{H}_8\text{O}_3$ $[\text{M}+\text{Na}]^+$ 163.0371, found 163.0373.

5-Ethyl-4-hydroxy-6-methylpyran-2-one (3b)

Colorless powder; mp 140.0–141.6 °C (recrystallized from MeOH- H_2O); IR (KBr) 3370, 2976, 2606, 1683, 1605 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.09 (3H, t, $J = 7.6$ Hz), 2.26 (3H, s), 2.41 (2H, q, $J = 7.6$ Hz), 5.62 (1H, s); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 13.4 (CH_3), 17.0 (CH_3), 17.7 (CH_2), 90.1 (CH), 114.9 (Cq), 159.3 (Cq), 167.5 (Cq), 172.5 (Cq); HRMS (ESI) m/z calcd for $\text{C}_8\text{H}_{10}\text{O}_3$ $[\text{M}+\text{Na}]^+$ 177.0528, found 177.0532.

5-Heptyl-4-hydroxy-6-methylpyran-2-one (3c)⁸

Colorless plates; mp 88.8–90.0 °C (recrystallized from MeOH- H_2O); IR (KBr) 3394, 2924, 2360, 1732, 1654 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 0.88 (3H, t, $J = 7.6$ Hz), 1.28–1.46 (10H, m), 2.26 (3H, s), 2.36 (2H, t, $J = 7.6$ Hz), 5.63 (1H, s); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 14.0 (CH_3), 17.2 (CH_3), 22.6 (CH_2), 24.3 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 29.4 (CH_2), 31.8 (CH_2), 90.0 (CH), 113.7 (Cq), 159.4 (Cq), 167.5 (Cq), 172.6 (Cq); HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{20}\text{O}_3$ $[\text{M}+\text{Na}]^+$ 247.1310, found 247.1306.

5-Allyl-4-hydroxy-6-methylpyran-2-one (3d)⁹

Colorless plates; mp 128.0–129.1 °C (recrystallized from MeOH- H_2O); IR (KBr) 3446, 2928, 2742, 1714, 1698, 1645, 1620 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 2.25 (3H, s), 3.16 (2H, d, $J = 6.0$ Hz), 5.01–5.07 (2H, m), 5.65 (1H, s), 5.79–5.89 (1H, m); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 17.2 (CH_3), 28.0 (CH_2), 90.0 (CH), 111.0 (Cq), 115.6 (CH_2), 134.1 (CH), 160.6 (Cq), 167.3 (Cq), 172.1 (Cq); HRMS (ESI) m/z calcd for $\text{C}_9\text{H}_{10}\text{O}_3$ $[\text{M}+\text{Na}]^+$ 189.0528, found 189.0531.

5-(4-Fluorobenzyl)-4-hydroxy-6-methylpyran-2-one (3e)

Colorless powder; mp 195.9–197.4 °C (recrystallized from MeOH- H_2O); IR (KBr) 3447, 2946, 2577, 2531, 1689, 1643, 1613 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 2.29 (3H, s), 3.73 (2H, s), 5.58 (1H, s), 6.98 (2H, d, $J = 8.8$ Hz), 7.29 (2H, d, $J = 8.8$ Hz); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 17.2 (CH_3), 28.2 (CH_2), 88.7 (CH), 110.0 (Cq $\times$ 2), 115.0 (CH, d, $J = 11.5$ Hz), 129.5 (CH, d, $J = 7.4$ Hz), 135.6 (Cq), 160.3 (Cq), 163.0 (Cq), 169.8 (Cq); HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{11}\text{FO}_3$ $[\text{M}+\text{Na}]^+$ 257.0590, found 257.0588.

5-But-2-ynyl-4-hydroxy-6-methylpyran-2-one (3f)

Colorless needles; mp 196.8–199.1 °C (recrystallized from MeOH-H₂O); IR (KBr) 3385, 3107, 2926, 2738, 2672, 2615, 1700, 1652, 1622 cm⁻¹; ¹H-NMR (400 MHz, DMSO-*d*₆) δ 1.70 (3H, s), 2.20 (3H, s), 3.16 (2H, s), 3.33 (2H, s), 5.29 (1H, s); ¹³C-NMR (100 MHz, DMSO-*d*₆) δ 3.0 (CH₃), 13.2 (CH₂), 17.0 (CH₃), 75.4 (Cq), 76.1 (Cq), 88.4 (CH), 107.9 (Cq), 160.1 (Cq), 162.8 (Cq), 169.1 (Cq); HRMS (ESI) *m/z* calcd for C₁₀H₁₀O₃ [M+Na]⁺ 201.0528, found 201.0527.

5-[3-(*tert*-Butyldimethylsilanyl)prop-2-ynyl]-4-hydroxy-6-methylpyran-2-one (3g)

Colorless powder; mp 173.0–174.9 °C (recrystallized from MeOH-H₂O); IR (KBr) 3393, 2930, 2858, 2177, 1715, 1644 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 0.07 (6H, s), 0.94 (9H, s), 2.37 (3H, s), 3.39 (2H, s), 5.70 (1H, s); ¹³C-NMR (100 MHz, CDCl₃) δ -4.6 (CH₃), 14.8 (CH₂), 16.5 (Cq), 17.7 (CH₃), 26.0 (CH₃), 83.9 (Cq), 90.2 (CH), 102.5 (Cq), 109.2 (Cq), 161.4 (Cq), 166.9 (Cq), 170.9 (Cq); HRMS (ESI) *m/z* calcd for C₁₅H₂₂O₃Si [M+H]⁺ 279.1416, found 279.1417.

5-Phenyl-4-hydroxy-6-methylpyran-2-one (3h)¹⁰

Colorless powder; mp 189.1–191.4 °C (recrystallized from MeOH-H₂O); IR (KBr) 3363, 2927, 2683, 2625, 2595, 1658 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 2.13 (3H, s), 5.68 (1H, s), 7.26–7.29 (2H, m), 7.45–7.53 (3H, m); ¹³C-NMR (100 MHz, CDCl₃) δ 18.1 (CH₃), 88.4 (CH), 113.8 (Cq), 127.6 (CH), 128.1 (CH), 130.5 (CH), 132.2 (Cq), 160.2 (Cq), 162.8 (Cq), 169.4 (Cq); HRMS (ESI) *m/z* calcd for C₁₂H₁₀O₃ [M+Na]⁺ 225.0528, found 225.0524.

4-Hydroxy-6-methylpyran-2-one (3i)¹¹

Colorless needles; mp 187.3–188.9 °C (recrystallized from MeOH-H₂O); IR (KBr) 3382, 2926, 2735, 2622, 1715, 1660, 1625 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 2.25 (3H, s), 5.48 (1H, s), 5.88 (1H, s); ¹³C-NMR (100 MHz, DMSO-*d*₆) δ 19.4 (CH₃), 88.1 (CH), 100.2 (CH), 163.3 (Cq), 163.9 (Cq), 170.5 (Cq); HRMS (ESI) *m/z* calcd for C₆H₆O₃ [M+H]⁺ 127.0395, found 127.0395.

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