An Efficient *O*-Methylation of 4-Hydroxy-2-pyrones and 4-Hydroxycoumarin

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O-Methylation of 4-hydroxy-2-pyrones is an important process in the total syntheses of naturally occurring pyrones having 4-methoxy-2-pyrone (α-pyrone) or 2-methoxy-4-pyrone (γ-pyrone) units in their molecules[1].

Two conventional methods are now available. Method A[2,3] consists of refluxing 4-hydroxy-2-pyrones with dimethyl sulfate in 2-butanone in the presence of anhydrous potassium carbonate for several hours and Method B[4] of treatment of 4-hydroxy-2-pyrones with diazomethane in ether under mild conditions which provides exclusively or preferentially α-pyrones along with none or minor γ-pyrones depending upon the reaction conditions employed.

However, application of these methods for the preparation of 3-acetyl-4-methoxy-6-methyl-2-pyrone (**2a**), regarded as a potential precursor of masked β-polyketones[5], from dehydroacetic acid (3-acetyl-4-hydroxy-6-methyl-2-pyrone) (**1a**)[6]

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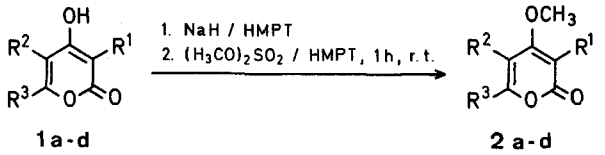
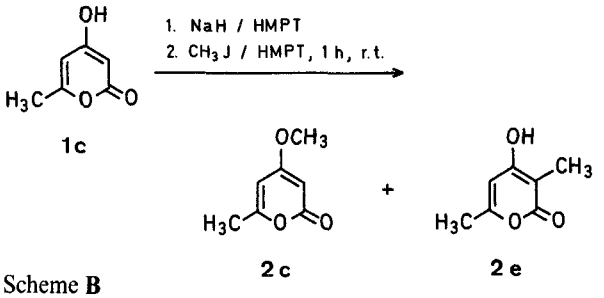
was found to be unsatisfactory[7]. This result prompted us to develop an efficient *O*-methylation method for 4-hydroxy-2-pyrones and 4-hydroxycoumarin to give the corresponding 4-methoxy-2-pyrones and 4-methoxycoumarin. Thus, when a solution of sodium salt of **1a** in anhydrous hexamethylphosphoric triamide is allowed to react with 1.2 equiv of dimethyl sulfate at room temperature for 1 h, the desired 3-acetyl-4-methoxy-6-methyl-2-pyrone (**2a**) is isolated in 51% yield[8]. The structure of the methylated product is proved as **2a** by the spectral data: especially, the α-pyrone structure is evidenced by its U.V. spectrum (methanol), $\lambda_{max}=311$ nm ($\varepsilon=8021$), which is apparently differentiated from that of the isomeric γ-pyrone[9].



Scheme **A**

Further application of this mild method for the *O*-methylation of 3-ethoxycarbonyl-4-hydroxy-6-methyl-2-pyrone (**1b**)[10], 4-hydroxy-6-methyl-2-pyrone (**1c**)[6,11] and 4-hydroxycoumarin (**1d**)[6] furnishes 67–95% yields of the corresponding 4-methoxy-2-pyrones (**2b** and **2c**) and 4-methoxycoumarin (**2d**) as shown in the Table. In these experiments, no appreciable amounts of *C*-alkylated products have been obtained.

However, when compound **1c** is methylated with 4 equiv of methyl iodide, as a soft alkylation reagent in place of dimethyl sulfate, under the same conditions as mentioned above, a partial *C*-methylation is observed to give 3,6-dimethyl-4-hydroxy-2-pyrone (**2e**)[12], a metabolite of *Penicillium stipitatum*, in 16% yield together with the major product (**2c**) (59%) (see Scheme **B**). By comparison of the physical



Scheme **B**

properties, the dimethylpyrone (**2e**) is found to be identical with an authentic sample prepared from the thallium(I) salt of *t*-butyl acetoacetate and methylmalonyl dichloride in two steps[13]. Despite the low yield, this reaction offers a simple and convenient preparation of the metabolite **2e** since the starting material **1c** is readily accessible.

The procedure presented herein has the following advantage over the Method A: Stirring at room temperature for 1 h is sufficient to promote the *O*-methylation; this fact is important for the pyrone rings because they are easily cleaved by bases under harsher conditions.

General Procedure for *O*-Methylation of 4-Hydroxy-2-pyrones (1a–1c) and 4-Hydroxycoumarin (1d) with Dimethyl Sulfate:

To a stirred solution of 4-hydroxy-6-methyl-2-pyrone (**1c**; 120 mg, 1 mmol) in anhydrous hexamethylphosphoric triamide (1 ml), sodium hydride (52.9% in mineral oil, 1 mmol) is added at room temperature under nitrogen atmosphere. After the evolution of gas has ceased, a solution of dimethyl sulfate (151 mg, 1.2 mmol) in HMPT (0.5 ml) is added to the resultant mixture at room temperature. Stirring is continued for 1 h at that temperature. The reaction mixture is diluted with ethyl acetate (10 ml), washed with 5% hydrochloric acid, and brine. The brine washing is extracted with dichloromethane (5 ml). The combined organic layers are dried over sodium sulfate and concentrated to dryness under reduced pressure. The residue is purified by column chromatography on silica gel with dichloromethane/methanol (20:1) as eluent. Evaporation of the solvent affords 4-methoxy-6-methyl-2-

Table. Preparation of 4-Methoxy-2-pyrones (**2a–2c**) and 4-Methoxycoumarin (**2d**)

Product No	R^1	R^2	R^3	Yields [%] this work	Yields [%] Method A	m.p.	Lit. m.p.
2a	H_3C—CO	H	CH_3	51[8]	15[a]	88–89°	—[b]
2b	H	C_2H_5OOC	CH_3	67	37[a]	137–138°	—[c]
2c	H	H	CH_3	95	93	86–87.5°	87–88°[3]
2d	H	—CH=CH—CH=CH—		91	64	124–125°	125–126°[4]

[a] Our experiments.

[b] $C_9H_{10}O_4$ (182.2) calc. C 59.33 H 5.53; found 59.10 5.50

I.R. (nujol): $\nu_{max}=1701, 1655, 1495\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta=2.32$ (broad s, 3H, CH_3-6); 2.40 (s, 3H, $COCH_3$); 3.93 (s, 3H, OCH_3); 6.09 ppm (broad s, 1H, H-5).

U.V. (CH_3OH): $\lambda_{max}=313$ nm ($\varepsilon=8021$).

M.S.: m/e = 182 (M^+).

[c] $C_{10}H_{12}O_5$ (212.2) calc. C 56.60 H 5.70; found 56.53 5.74

I.R. (nujol): $\nu_{max}=1730, 1686, 1639, 1549\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta=1.36$ (t, 3H, $J=7$ Hz, $OCH_2\underline{CH_3}$); 2.34 (broad s, 3H, CH_3-6); 3.98 (s, 3H, OCH_3); 4.30 (q, 2H, $J=7$ Hz, $OC\underline{H_2}CH_3$); and 6.23 ppm (broad s, 1H, H-5).

U.V. (CH_3OH): $\lambda_{max}=311$ nm ($\varepsilon=7037$).

M.S.: $m/e=212$ (M^+).

pyrone (**2c**); yield: 133 mg (95%); m.p. 83–85°; which is recrystallized from benzene to give colorless needles; m.p. 86–87.5° (Lit.[3] m.p. 87–88°). Physical data confirm the structure of **2c**.

Other 4-methoxy-2-pyrones, (**2a**) and (**2b**), and 4-methoxycoumarin (**2d**) are prepared in the similar manner. The physical properties of the compounds (**2a**) and (**2b**) are shown in the Table.

Methylation of 4-Hydroxy-6-methyl-2-pyrone (1c) with Methyl Iodide:

To a stirred solution of **1c** (120 mg, 1 mmol) in anhydrous HMPT (1 ml), sodium hydride (52.9% in mineral oil, 1.2 mmol) is added at room temperature under a nitrogen atmosphere. After evolution of gas has ceased, a solution of methyl iodide (611 mg, 4 mmol) in HMPT (0.5 ml) is added to the resultant mixture at room temperature and stirring is continued for 1 h at that temperature. The usual work-up as described above produces a crude solid which is separated by preparative thin layer chromatography on silica gel with dichloromethane/methanol (20:1) to give the 4-methoxypyrone (**2c**); yield: 82 mg; (59%); m.p. 86–87.5°, and the dimethylpyrone (**2e**); yield: 22 mg; (16%); m.p. 207–208° (Lit.[13] m.p. 207–208°). The physical data of the compounds **2c** and **2e** are identical with those of authentic samples, respectively.

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[1] For examples, 4-methoxy-6-styryl-2-pyrones, luteoreticulin, and citreoviridin are cited for 4-methoxy-2-pyrones, and aureothin, spectinabilin and colletotrichin for 2-methoxy-4-pyrones.

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[6] Commercially available.
[7] Only 15% and 20% yields of **2a** are obtained in our attempts according to the Method A and the Method B, respectively.
[8] Corrected yield based on the consumed starting material **1a**; yield based on **1a** employed in the reaction is 41%.
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