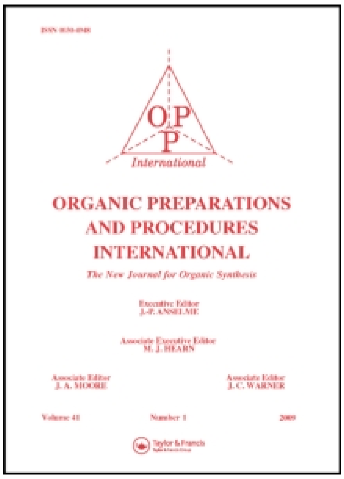

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article Ghandi, M. , Bayat, Y. and Teimuri-Mofrad, R.(2002) 'A NOVEL METHOD FOR THE SYNTHESIS OF FORMYL AND HYDROXYMETHYL DERIVATIVES OF 4*H*-PYRAN-4-ONE', Organic Preparations and Procedures International, 34: 5, 525 — 530

To link to this Article: DOI: 10.1080/00304940209355774

URL: http://dx.doi.org/10.1080/00304940209355774

A NOVEL METHOD FOR THE SYNTHESIS OF FORMYL AND HYDROXYMETHYL DERIVATIVES OF 4*H*-PYRAN-4-ONE

Submitted by (11/14/01)
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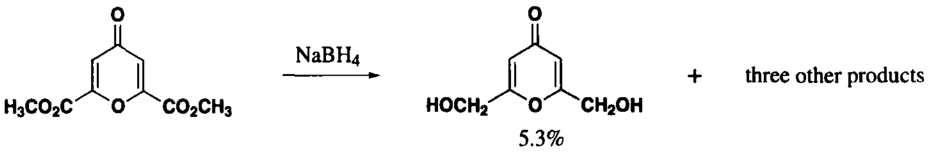
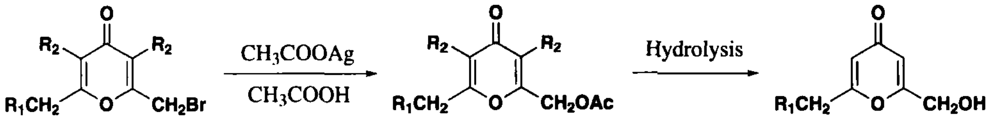
Monocyclic pyrones, particularly the 4*H*-pyran-4-ones, are useful as flavoring agents, food preservatives, fungicides and herbicides.[1-4] Many recent reports of new methods for their synthesis have appeared.[5-7] Some 4*H*-pyran-4-ones containing a hydroxymethyl group may be prepared by fermentation, *e.g.* kojic acid,[8] by reduction of dimethyl chelidonate with sodium borohydride (after a difficult separation,[9] *Scheme 1*) and by hydrolysis of the corresponding acetoxymethyl derivatives[6] (*Scheme 2*).



Scheme 1

Previous syntheses of formyl-substituted 4*H*-pyran-4-one involve the oxidation of hydroxymethyl group in derivatives of kojic acid[10-12] and formylation of pyrones in the presence of trifluoroacetic acid.[13] Many of the methods employed for the synthesis of formyl and hydroxymethyl derivatives of 4*H*-pyran-4-ones substituted at positions 2 and 6 involve multistep-procedures affording low



a) $R_1 = Br, R_2 = H$
b) $R_1 = R_2 = H$
c) $R_1 = Br, R_2 = CO_2CH_3$
d) $R_1 = H, R_2 = CO_2CH_3$
e) $R_1 = Br, R_2 = CO_2C_2H_5$
f) $R_1 = H, R_2 = CO_2C_2H_5$

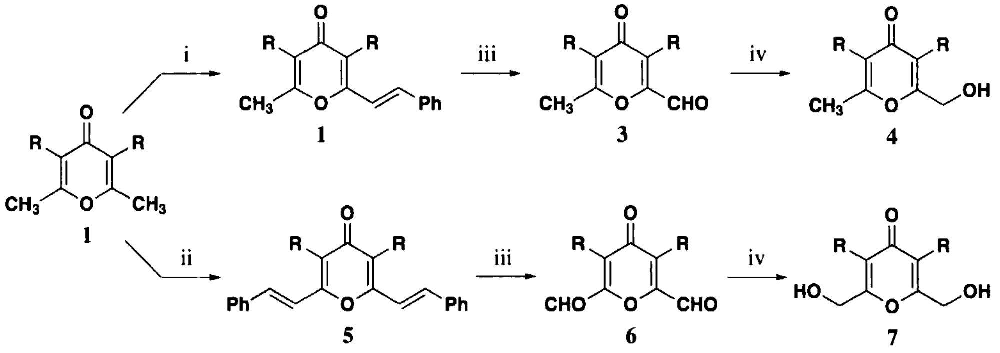
a) $R_1 = OAc, R_2 = H$
b) $R_1 = R_2 = H$
c) $R_1 = OAc, R_2 = CO_2CH_3$
d) $R_1 = H, R_2 = CO_2CH_3$
e) $R_1 = OAc, R_2 = CO_2C_2H_5$
f) $R_1 = H, R_2 = CO_2C_2H_5$

a) $R_1 = H$
b) $R_1 = OH$

Scheme 2

overall yields. Consequently, we undertook a search for a new method to produce these compounds requiring fewer steps with resultant higher yields.

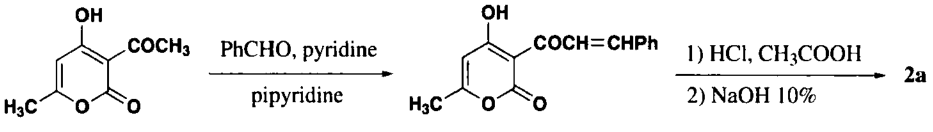
2,6-Dimethyl-4*H*-pyran-4-one (**1a**) and 2,6-dimethyl-3,5-diphenyl-4*H*-pyran-4-one (**1b**) were both synthesized according to the literature in 85% and 50% yields, respectively.[6,16] The mono-styryl (**2b**) and distyryl (**5a,5b**) derivatives of 4*H*-pyran-4-one (**1a** and **1b**) were obtained in 40%, 75% and 82% yields respectively by condensation of **1a,b** with benzaldehyde in the presence of alcoholic sodium ethoxide in a mixture of dioxane-absolute ethanol (*Scheme 3*).[14,15]



i) PhCHO, NaOEt ii) 2PhCHO, 2NaOEt iii) OsO_4, $NaIO_4$ iv) $NaBH_4$

Scheme 3

Since **2a** was obtained only in poor yields by the condensation of **1a** with one equivalent of benzaldehyde, it was prepared according to the literature[17] by condensation of dehydroacetic acid with benzaldehyde to afford 3-cinnamoyl-4-hydroxy-6-methyl-2*H*-pyran-2-one followed by rearrangement and decarboxylation leading to 6-methyl-2-styryl-4*H*-pyran-4-one (**2a**) in 67% overall yields (*Scheme 4*).



Scheme 4

Attempted oxidative cleavage of compounds **5a,b** to the corresponding formyl derivatives (**6a,b**) with a mixture of potassium permanganate and sodium periodate gave no characterizable products; however oxidative cleavage of compounds **2a**, **2b**, **5a** and **5b** with a mixture of osmium tetroxide and sodium periodate in water-dioxane gave the corresponding compounds **3a**, **3b**, **6a** and **6b** in yields of 85% to 100% (*Scheme 3*).

Hydrolysis of primary alkyl halides is usually achieved by using alkali metal hydroxide; however, the 4*H*-pyran-4-one ring is unstable under basic conditions and direct substitution of the halide by hydroxyl group is not feasible. Recently Shahrisa and co-workers have converted bromomethyl derivatives of 4*H*-pyran-4-ones to corresponding acetoxymethyl derivatives which on hydrolysis afforded the hydroxymethyl derivatives.[6] Accordingly, we decided to reduce the mono and diformyls, **3a**, **3b**, **6a** and **6b** to the corresponding hydroxymethyl groups with sodium borohydride in methanol at 0-5°. **4a**, **4b**, **7a** and **7b** were obtained in 70%, 76%, 65% and 69% yield, respectively. Data obtained from mass spectra, IR, ^{1}H and ^{13}C NMR spectra and elemental analyses are fully consistent with the proposed structures.

EXPERIMENTAL SECTION

Melting points were determined with an Electrothermal Instrument model 9100 and are uncorrected. Infrared (FT-IR) spectra were run on a Shimadzu 8010 M Spectrophtometer as KBr disks or as smears between salt plates. The ^{1}H NMR spectra were recorded on a Varian-EM 390 spectrometer. The ^{13}C NMR spectra were determined on an FT-NMR Brucker 100 MHz spectrometer. Chemical shifts are reported in δ (ppm) with TMS as internal standard. Mass spectra were taken with a Shimadzu MS-QP 1100 EX mass spectrometer. Elemental analysis were performed on a Heareus CHN-O-RAPID analyzer. Starting materials were purchased from commercial sources.

2,6-Dimethyl-4*H*-pyran-4-one (1a).- white crystals (water), mp. 131.8-132.1°, *lit.*[6] 132° was synthesized according to the literature.[6]

2,6-Dimethyl-3,5-diphenyl-4*H*-pyran-4-one (1b).- pale brown crystals (toluene-cyclohexane), mp. 203.2-203.9°, *lit.*[16] 204° was prepared according to the literature.[16]

6-Methyl-2-styryl-4*H*-pyran-4-one (2a).- pale brown crystals (ethanol), mp. 124.5-124.8°, *lit.*[17] 125° was synthesized according to the literature.[17]

3,5-Diphenyl-6-methyl-2-styryl-4*H*-pyran-4-one (2b).- To a mixture of 2.76 g of **lb** (0.01 mole) and 1.06 g (0.01 mole) of benzaldehyde in 15 mL of dioxane-ethanol (3:2) was added a solution of 0.01 mole sodium ethoxide in 15 mL of absolute ethanol with cooling. After being stirred for 6 hr at room temperature, the mixture was acidified with dilute hydrochloric acid. The precipitate was collected and purified by column chromatography on silica gel using ethyl acetate-petroleum ether (4:1) as eluent to give **2b** (1.64 g, 45%) as pale yellow crystals, mp. 175.0-175.4° (ethanol). IR (KBr): 3025, 2960, 1630, 1520, 960 and 720 cm^{-1}. ^{1}H NMR (acetone-d$_6$): δ 2.37 (s, 3H,-C**H**$_3$), 6.80 (d, 1H, PhCH=CH-), 7.34 (m, 15H, phenyl-**H**), 7.46 (d, 1H, PhCH=C**H**-). ^{13}C NMR (acetone-d$_6$): δ 19.8 (-CH$_3$), 119.2 (PhCH=CH-), 124.8 (pyran-**C**-5), 126.9 (pyran-**C**-3), 128.1 (PhCH=CH-), 128.5, 129.0, 129.4, 131.3, 132.5, 136.1 and 137.0 (phenyl-**C**), 155.2 (pyran-**C**-6), 157.7 (pyran-**C**-2), 178.3 (pyran-**C**-4). MS (EI, 70 eV): 364 (M$^+$).

Anal. Calcd for $C_{26}H_{20}O_2$: C , 85.69; H, 5.53. Found: C, 85.85; H, 5.39

General Procedure for the Synthesis of 5a,b.- To a cold solution of **1a** or **1b** (0.01mole) and 2.12 g (0.02 mole) of benzaldehyde (freshly distilled in a stream of dry carbon dioxide) in 15 mL of suitable solvent was added a cold solution of sodium ethoxide (0.02 mole) in 15 mL of absolute ethanol. The mixture was kept overnight at room temperature and then acidified with dilute hydrochloric acid to give **5a** and **5b** as solids, which were then crystallized from ethanol. Specific details for each compound are given below:

2,6-Distyryl-4*H*-pyran-4-one (5a).- Using ethanol as solvent, from 1.24 g of **1a**, 2.25 g (75%) of orange crystals, mp. 166.2-166.9°, *lit.*[15] 167° were obtained. IR (KBr): 1650, 1623, 1400, 970, 690 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.11 (s, 2H, pyran-**CH**-3,-5), 6.56 (d, 2H, J=16Hz, PhCH=**CH**-), 7.21-7.44 (m, 12H, Ph-**CH**=CH-, phenyl-**H**), MS (EI, 70 eV): 300 (M^+).

3,5-Diphenyl-2,6-distyryl-4*H*-pyran-4-one (5b).- Using dioxane-ethanol (3:2) as solvent, from 2.76 g of **1b**, 3.70 g (82%) of pale yellow crystals, mp. 228-229° were obtained. IR (KBr): 3040, 1630, 1500, 1450, 1400, 1160, 980 and 750 cm^{-1}. ^1H NMR (acetone-d_6): δ 6.87 (d, 2H, PhCH=**CH**-), 7.38 (m, 20H, phenyl-**H**), 7.57 (d, 2H, Ph**CH**=CH-). ^{13}C NMR (acetone-d_6): δ 119.6 (PhCH=**C**H-), 126.2 (pyran-**C**-3,-5), 127.6 (Ph**C**H=CH-), 128.1, 128.9, 129.5, 131.1, 131.8, 135.6 and 135.9 (phenyl-**C**), 156.9 (pyran-**C**-2,-6), 177.2 (pyran-**C**-4). MS (EI, 70 eV): 452 (M^+).

Anal. Calcd for $C_{33}H_{24}O_2$: C, 87.58; H, 5.35. Found: C, 87.45; H, 5.28

General Procedure for the Synthesis of 3b and 6b.- A mixture of 3 mmol of compounds **2b** or **5b**, 15 mg of osmium tetroxide and 75 mL of dioxane-water (6:1) was stirred for 15 min at 25°. To the dark brown mixture was added 7.4 g of sodium periodate in small portions over a period of 30 min. After being stirred at 25° for an additional 10 hr, the precipitate was collected and washed several times with dioxane. The combined dioxane-water solution was concentrated under reduced pressure. The residue was extracted with 4 x 30 mL of EtOAc and the solvent removed by distillation and residue washed with petroleum ether to give pale yellow solid. Specific details are given for each compound:

3,5-Diphenyl-2-formyl-6-methyl-4*H*-pyran-4-one (3b).- From 1.09 g of **2b**, 0.79 g (91%) of pale yellow crystals, mp. 189.0-189.6° (ethyl acetate-petroleum ether) were obtained. IR (KBr): 3010, 2920, 2820, 1700, 1641, 1260, 980 and 800 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.40 (s, 3H, -$\mathbf{CH_3}$), 7.40 (m, 10H, phenyl-**H**), 9.80 s, 1H,-**CHO**). ^{13}C NMR ($CDCl_3$): δ 21.1 (-**C**H_3), 128.4, 128.8, 130.1, 131.9 and 134.0 (phenyl-**C**), 127.6 (pyran-**C**-5), 130.6 (pyran-**C**-3), 149.1 (pyran-**C**-6), 152.8 (pyran-**C**-2), 183.6 (pyran-**C**-4) , 201.8 (-**C**HO). MS (EI, 70 eV): 290 (M^+).

*Anal.*Calcd for $C_{19}H_{14}O_3$: C, 78.61; H, 4.86. Found: C, 78.41; H, 4.90

2,6-Diformyl-3,5-diphenyl-4*H*-pyran-4-one (6b).- From 1.36 g of **5b**, 0.91 g (100%) of pale yellow crystals, mp. 196.3-196.9° (ethyl acetate-petroleum ether) were obtained. IR (KBr): 3031, 2879, 1708 and 1648 cm^{-1}. ^1H NMR (acetone-d_6): δ 7.40 (s, 10H, phenyl-**H**), 9.69 (s, 2H,-**CHO**). ^{13}C NMR (acetone-d_6): δ 128.4, 128.8, 130.1, 131.9 and 134.0 (phenyl-**C**), 136.1 (pyran-**C**-3,-5), 152.1 (pyran-**C**-2,-6), 185.0 (pyran-**C**-4) , 206.2 (-**C**HO). MS (EI, 70 eV): 304 (M^+).

Anal. Calcd for $C_{19}H_{12}O_4$: C, 74.99; H, 3.98. Found: C, 75.10; H, 4.10

General Procedure for the Synthesis of 3a and 6a.- To the mixture of 5 mmol of compounds **2a** or **5a** and 50 mL of dioxane-water (3:1) was added 0.01 g osmium tetroxide with stirring for 10 min. To the dark mixture was added 4.5 g of sodium periodate in small portions over a period of 30 min. After stirring at 25° for an additional 2 hr, the precipitate was collected and washed with a small amount of dioxane. The combined dioxane-water solution was concentrated under reduced pressure. The residue, after addition of 4 mL H_2O, was extracted with 3 x 10 mL dichloromethane (to remove benzaldehyde and impurities). The aqueous layer was concentrated under reduced pressure and the residue, after complete drying, was extracted with 3 x 10 mL acetone. The combined organic solution, after drying over Na_2SO_4, was concentrated *in vacuo*. Specific details are given for each compound:

2-Formyl-6-methyl-4*H*-pyran-4-one (3a).- From 1.06 g of **2a**, 0.64 g (93%) of white crystals, mp. 117.8-118.4° (ethyl acetate-hexane) were obtained. IR (KBr): 3050, 1710, 1640, 1560, 1280 and 930 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.37 (s , 3H, -CH_3), 6.26 (s, 1H, pyran-CH-3), 6.62 (s, 1H, pyran-CH-5), 9.65 (s, 1H, -CHO). ^{13}C NMR ($CDCl_3$): δ 20.0 (-CH_3) , 118.3 (pyran-C-5), 121.0 (pyran-C-3), 157.0 (pyran-C-6), 167.0 (pyran-C-2), 179.0 (pyran-C-4), 185.0 (-CHO). MS (EI, 70 eV): 138 (M^+).

*Anal.*Calcd for $C_7H_6O_3$: C, 60.87; H, 4.38. Found: C, 60.80; H, 4.50

2,6-Diformyl-4*H*-pyran-4-one (6a).- From 1.5 g of **5a**, 0.53 g (70%) of yellow oil was obtained. IR (KBr): 3010, 1720, 1670, 1610, 1420, 1285 and 1100 cm^{-1}. ^1H NMR (acetone-d_6): δ 7.01 (s, 2H, pyran-CH-3,-5), 9.7(s, 2H, -CHO). ^{13}C NMR (acetone-d_6): δ 123.3 (pyran-C-3,-5), 168.5 (pyran-C-2,-6), 180.5 (pyran-C-4), 187.8 (-CHO). MS (EI, 70 eV): 152 (M^+).

Anal. Calcd for $C_7H_4O_4$: C, 55.28; H, 2.65. Found: C, 55.30; H, 2.70

General Procedure for the Synthesis of 4a, 4b, 7a and 7b.- The compounds **3a**, **3b**, **6a** or **6b** (1 mmol) was dissolved in the minimum volume of dry methanol. Sodium borohydride (molar ratio $NaBH_4$ to formyl 0.275:1) was added in small portions to the stirred solution at 0-5°. The reduction was followed to completion by TLC. The solvent was removed *in vacuo* and the residue was extracted with seveval portions of $CHCl_3$. The combined organic layers were concentrated under reduced pressure. Specific details are given for each compound.

2-Hydroxymethyl-6-methyl-4*H*-pyran-4-one (4a).- From 0.14 g of **3a**, 0.10 g (70%) of a white solid, mp. 134.9-135.3°, *lit.*[6] 135° was obtained. IR (KBr): 3390 (broad), 2940, 1678, 1615, 1280, 1100 and 938 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.20 (s, 3H,-CH_3), 3.45 (s, 1H,-CH_2OH), 4.25 (s, 2H,-CH_2OH), 6.0 (s, 1H, pyran-CH-5), 6.13 (s, 1H, pyran-CH-3).

3,5-Diphenyl-2-hydroxymethyl-6-methyl-4*H*-pyran-4-one (4b).- From 0.29 g of **3b**, 0.22 g (76%) of white crystals, mp. 218.4-218.9° were obtained. IR (KBr): 3362 (broad), 1657 and 1588 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.40 (s, 3H,-CH_3), 2.45 (br, 1H,-CH_2OH), 4.50 (s, 2H, -CH_2OH), 7.48 (s, 10H, phenyl-H). MS (EI, 70 eV): 292 (M^+).

Anal. Calcd for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 78.22; H, 5.68

2,6-*bis*(Hydroxymethyl)-4*H*-pyran-4-one (7a).- From 0.15 g of **6a**, 0.10 g (65%) of a white solid, mp. 110.1-110.8°, *lit.*[6] 111° was obtained. IR (KBr): 3385 (broad), 2938, 1680, 1625, 1779, 1109 and 932 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.63 (s, 2H, -CH_2OH), 4.29 (s, 4H, -CH_2OH), 6.17 (s, 2H, pyran-CH-3,-5).

2,6-*bis*(Hydroxymethyl)-3,5-diphenyl-4*H*-pyran-4-one (7b).- From 0.30 g of **6b**, 0.21 g (69%) of a white solid, mp. 232.1-232.8° was obtained. IR (KBr): 3400 (broad), 1650 and 1580 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.83 (s, 2H, -CH_2OH), 4.30 (s, 4H, -CH_2OH), 7.10-7.50 (m, 10H, phenyl-H). MS (EI, 70 eV): 308 (M^+).

Anal. Calcd for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found: C, 74.16; H, 5.35

Acknowledgment.- Financial support for this work by the Research Council of Malek-ashtar University is gratefully acknowledged.

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