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Synthesis of Some Hydroxymethyl Derivatives of 4*H*-Pyran-4-ones *via* N–O Bond Cleavage

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A new method was developed for the synthesis of hydroxymethyl derivatives of 4*H*-pyran-4-ones from corresponding phthalimidoxymethyl derivatives by reduction of N–O bond with zinc powder and hydrochloric acid. These phthalimidoxymethyl derivatives of 4*H*-pyran-4-ones were synthesized by means of reactions of their bromomethyl derivatives and N-hydroxyphthalimide.

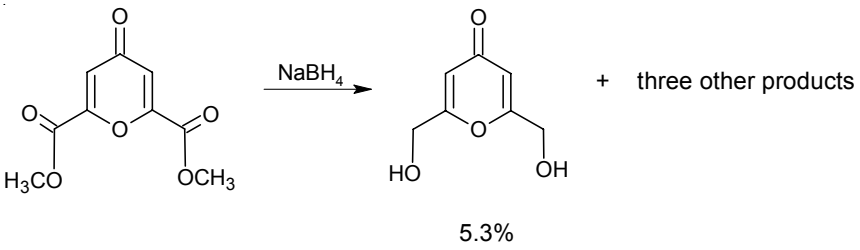
Key Words: 4*H*-Pyran-4-ones, Phthalimidoxymethyl derivatives, Hydroxymethyl.

INTRODUCTION

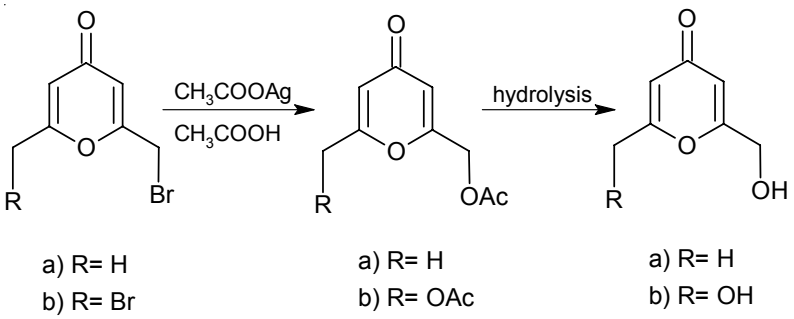
4*H*-Pyran-4-one and corresponding derivatives have been the subject of much research due to their importance in various applications and their widespread biological significance[1-3]. The synthetic utility would still be enhanced if more 4*H*-pyran-4-ones possessing various functional groups could be synthesized. Many reports of new methods for their synthesis have appeared in literature[4-8].

It is an important studies to explore an efficient method for the synthesis of hydroxymethyl derivatives of 4*H*-pyran-4-ones, because these compounds are potentially useful and carry out a wide range of reactions that would make them suitable for the synthesis of a number of 4*H*-pyran-4-one derivatives. For example host macrocycles could be obtained from *bis*-hydroxymethyl derivatives of them.

Some 4*H*-pyran-4-ones containing a hydroxymethyl group may be prepared by fermentation, *e.g.*, kojic acid[9-11], by reduction of dimethyl chelidonate with sodium borohydride (after difficult separation)[12] (**Scheme-I**) and by hydrolysis of the corresponding acetoxymethyl derivatives[5] (**Scheme-II**).

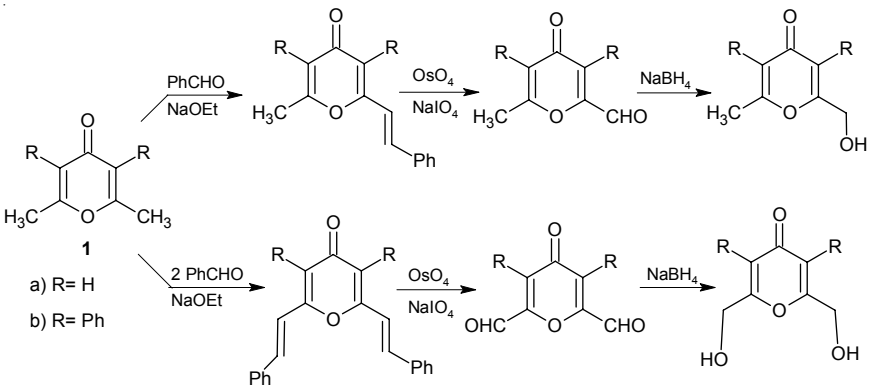


Scheme-I. Reduction of dimethyl chelidonate by $NaBH_4$



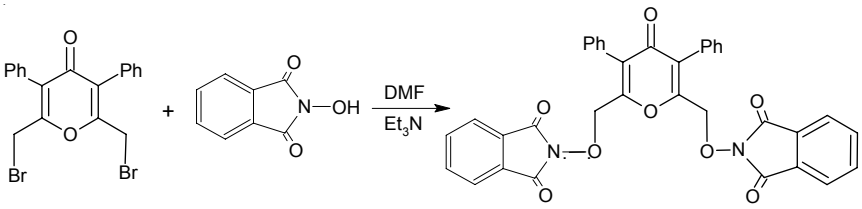
Scheme-II. Preparation and hydrolysis of acetoxymethyl derivatives of 4*H*-pyran-4-ones

Ghandi and coworkers[13] prepared hydroxymethyl substituted at position 2 and 6 of 4*H*-pyran-4-one and 3,5-diphenyl-2,6-dimethyl-4*H*-pyran-4-one derivatives through reduction of corresponding carboxaldehyde derivatives of them with sodium borohydride (**Scheme-III**).



Scheme-III. Preparation and reduction of carboxaldehyde derivatives of 4*H*-pyran-4-ones

Recently, we prepared 2,6-*bis*-phthalimidoxymethyl-3,5-diphenyl-4*H*-pyran-4-one by the reaction of 2,6-bisbromomethyl-3,5-diphenyl-4*H*-pyran-4-one with N-hydroxyphthalimide in DMF and in the presence of triethylamine in 52 % yield[14] (**Scheme-IV**).



Scheme-IV. Synthesis of 2,6-*bis*-phthalimidoxymethyl-3,5-diphenyl-4*H*-pyran-4-one

In continuation of our studies in the chemistry of 4*H*-pyran-4-ones, we have investigated the reduction reaction by zinc powder and hydrochloric acid on some mono and *bis*-phthalimidoxymethyl derivatives of 4*H*-pyran-4-ones. We report here the synthesis of some hydroxymethyl derivatives of 4*H*-pyran-4-ones substituted at position 2 and 6, which have been prepared by a new method from N–O bond cleavage reaction of corresponding phthalimidoxymethyl derivatives of 4*H*-pyran-4-ones with zinc powder and hydrochloric acid.

EXPERIMENTAL

Melting points were determined with an Electrothermal Instrument model 9100 and are uncorrected. Infrared (IR) spectra were run on a Shimadzu FT-IR 4300 Spectrophotometer as KBr disks or as smears between salt plates. The ^{1}H NMR spectra were recorded on a FT-NMR Bruker 300 MHz spectrometer. The ^{13}C NMR spectra were determined on a FT-NMR Bruker 100 MHz spectrometer. Chemical shifts were reported in values in ppm with TMS as internal standard. Mass spectra were taken with a Shimadzu MS-QP 1100 EX mass spectrometer. Elemental analyses were performed on a Heareus, CHN-O-RAPID analyzer.

2-Bromomethyl-6-methyl-4*H*-pyran-4-one (1a): Compound **1a** was prepared according to literature[5] in 73 % yield as beige crystals; m.p. 108 °C (lit.[15], 107°C).

2,6-*Bis*-bromomethyl-4*H*-pyran-4-one (1b): Compound **1b** was synthesized according to literature[5] in 59 % yield as pale brown crystals; m.p. 92°C (lit.[15], 91 °C).

2-Bromomethyl-3,5-diphenyl-6-methyl-4*H*-pyran-4-one (1c): A mixture of 2.5 g (9 mmol) of 2,6-dimethyl-3,5-diphenyl-4*H*-pyran-4-one[16], 1.77 g (10 mmol) of N-bromosuccinimide, 0.03 g of dibenzoyl peroxide and 15 mL of tetrachloromethane was refluxed for 48 h. The reaction

mixture was filtered after cooling. The separated solid was heated at 50-60 °C in 110 mL of aqueous ethanol (5 % EtOH) for 0.5 h. After cooling, the precipitate was filtered, washed with cold ethanol and recrystallized from 95 % ethanol to give white crystals (68 %); m.p. 177 °C. Anal. calcd. % for $C_{19}H_{15}O_2Br$: C, 64.24; H, 4.26. Found %: C, 64.5; H, 4.3. MS: m/z 356/354 (M^+). IR: 1582, 1600, 1630, 2925 and 3005 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.20 (3H, s, -C**H**$_3$), 4.13 (2H, s, -C**H**$_2$Br), 7.15-7.33 (10H, m, Phenyl-**H**). ^{13}C NMR ($CDCl_3$): δ 16.0 (-**C**H_3), 26.0 (-**C**H_2Br), 123.0 (Pyran-**C**-5), 128.0 (Pyran-**C**-3), 128.5-130.0 (m, Phenyl-**C**), 157.0 (Pyran-**C**-6), 159.0 (Pyran-**C**-2), 176.5 (Pyran-**C**-4).

2,6-*Bis*-bromomethyl-3,5-diphenyl-4*H*-pyran-4-one (1d): Compound **1d** was synthesized according to literature[17] in 56 % yield as white crystals; m.p. 215.5-216.8 °C (lit[17], 216-217 °C).

General procedure for synthesis of compounds 2(a-d): A mixture of compounds **1a** or **1c** (5 mmol) or **1b** or **1d** (2.5 mmol), 0.9 g (5.5 mmol) of N-hydroxyphthalimide, 0.84 g (8.3 mmol) of Et_3N and 10 mL of DMF was stirred at 45 ºC for 48 h. After cooling, the reaction mixture was filtered. The filtrate was concentrated under reduced pressure and chloroform (30 mL) was added to the residue. The mixture was washed with several portions of saturated NaCl and then H_2O (3 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting solid was recrystallized from EtOH to give desired product. Specific details are given for each compounds.

6- Methyl-2-phthalimidoxymethyl-4*H*-pyran-4-one (2a): From 1.02 g of **1a**, pale yellow crystals (1.24 g, 87 %) were obtained, m.p. 176.5-177.3 ºC. Anal. calcd. % for $C_{15}H_{11}NO_5$: C, 63.16; H, 3.89; N, 4.91. Found %: C, 62.95; H, 3.78; N, 4.85. MS: m/z 285 (M^+). IR: 695, 755, 1610, 1648, 1730, 1787, 2885, 2920, 2995 and 3048 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.15 (3H, s, -C**H**$_3$), 4.85 (2H, s, -C**H**$_2$O-), 6.15 (2H, s, Pyran-C**H**-3, -5), 7.75 (4H, s, Phenylene-**H**). ^{13}C NMR ($CDCl_3$): δ 20.0 (-**C**H_3), 67.3 (-**C**H_2O-), 113.0 (Pyran-**C**-5), 117.5 (Pyran-**C**-3), 128, 130 and 132 (Phenylene-**C**), 161.0 (Pyran-**C**-6), 163.3 (Phthalimide-**C**O), 165.0 (Pyran-**C**-2), 178.3 (Pyran-**C**-4).

2,6-*Bis*-phthalimidoxymethyl-4*H*-pyran-4-one (2b): From 0.71 g of **1b**, pale yellow crystals (0.80 g, 72 %) were obtained, m.p. 191.3-192.8°C. Anal. calcd. % for $C_{23}H_{14}N_2O_8$: C, 61.89; H, 3.16; N, 6.28. Found %: C, 61.75; H, 3.12; N, 6.19. MS: m/z 446 (M^+). IR: 702, 756, 872, 1127, 1192, 1485, 1571, 1612, 1650, 1735, 1785, 2915, 2989, 3005 and 3055 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.75 (4H, s, -C**H**$_2$O-), 6.20 (2H, s, Pyran-C**H**-3, -5), 7.80 (8H, s, Phenylene-**H**). ^{13}C NMR ($CDCl_3$): δ 68.9 (-**C**H_2O-), 117.8 (Pyran-**C**-3, -5), 128.2, 129.9 and 131.8 (Phenylene-**C**), 160.8 (Pyran-**C**-2, -6), 163.9 (Phthalimide-**C**O), 178.1 (Pyran-**C**-4).

3,5- Diphenyl-6-methyl-2-phthalimidoxymethyl-4*H*-pyran-4-one (2c): From 1.78 g of **1c**, colourless crystals (1.77 g, 81 %) were obtained, m.p. 208.5-209.8 °C. Anal. calcd. % for $C_{27}H_{19}NO_5$: C, 74.13; H, 4.38; N, 3.20. Found %: C, 73.60; H, 4.40; N, 3.12. MS: m/z 437 (M^+). IR: 699, 762, 876, 1500, 1605, 1618, 1657, 1729, 1786, 2853, 2925, 3026 and 3058 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.30 (3H, s, -C**H**$_3$), 5.05 (2H, s, -C**H**$_2$O-), 7.15-7.40 (10H, m, Phenyl-**H**), 7.80 (4H, s, Phenylene-**H**). ^{13}C NMR ($CDCl_3$): δ 19.0 (-**C**H_3), 73.0 (-**C**H_2O-), 124.0 (Pyran-**C**-5), 126.0 (Pyran-**C**-3), 128.0, 128.5, 130.0, 131.0, 132.5 and 135.0 (Phenyl-**C** and Phenylene-**C**), 158.0 (Pyran-**C**-6), 162.5 (Pyran-**C**-2), 163.0 (Phthalimide-**C**O), 178.5 (Pyran-**C**-4).

2,6-*Bis*-phthalimidoxymethyl-3,5-diphenyl-4*H*-pyran-4-one (2d): From 1.09 g of **1d**, colourless crystals (1.17 g, 78 %) were obtained, m.p. 228.5-229.2 °C (lit.[14], 228-229.5 °C). Anal. calcd. % for $C_{35}H_{22}N_2O_8$: C, 70.23; H, 3.70; N, 4.68. Found %: C, 69.80; H, 3.80; N, 4.50. MS: m/z 598 (M^+). IR: 700, 760, 876, 1120, 1185, 1490, 1579, 1620, 1631, 1740, 1790, 2925 and 3094 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.95 (4H, s, -C**H**$_2$O-), 7.20 (10H, s, Phenyl-**H**), 7.70 (8H, s, Phenylene-**H**). ^{13}C NMR ($CDCl_3$): δ 74.0 (-**C**H_2O-), 123.0 (Pyran-**C**-3, -5), 127.5, 130.5 and 135.0 (m, Phenyl-**C** and Phenylene-**C**), 155.0 (Pyran-**C**-2, -6), 162.5 (Phthalimide-**C**O), 177.5 (Pyran-**C**-4).

General procedure for the reduction of compounds 2(a,b)-synthesis of compounds 3(a,b): To a stirred mixture of 1.5 mmol of compounds **2a** or **2b**, 0.5 g zinc powder and 15 mL methanol at -5 ºC and under argon atmosphere was gently added 4 mL of 35 % hydrochloric acid. After stirring at -5ºC for 1 h, the reaction mixture was filtered. The filtrate was cooled and neutralized with addition of saturated aqueous solution of $NaHCO_3$ to pH 7. The mixture was concentrated under reduced pressure and the residue, after complete drying, was extracted with 5 × 7 mL of dry methanol and the combined organic solution was concentrated *in vacuo*. Specific details are given for each compounds.

2-Hydroxymethyl-6-methyl-4*H*-pyran-4-one (3a): From 0.43 g of **2a**, white crystals (0.17 g, 79 %) were obtained, m.p. 134.3-135.8 °C (lit.[5], 135 °C). Anal. calcd. % for $C_7H_8O_3$: C, 60.0; H, 5.75. Found %: C, 59.85; H, 5.87. MS: m/z 140 (M^+). IR: 940, 1103, 1285, 1618, 1675, 2945 and 3395 (broad) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.20 (3H, s, -C**H**$_3$), 3.45 (1H, s, -C**H**$_2$OH), 4.25 (2H, s, -C**H**$_2$OH), 6.0 (1H, s, Pyran-CH-5), 6.13 (1H, s, Pyran-C**H**-3). ^{13}C NMR (DMSO-d_6): δ 17.9 (-**C**H_3), 57.6 (-**C**H_2O-), 123.1 (Pyran-**C**-5), 125.9 (Pyran-**C**-3), 157.2 (Pyran-**C**-6), 158.8 (Pyran-**C**-2), 176.8 (Pyran-**C**-4).

2,6-*Bis*-hydroxymethyl-4*H*-pyran-4-one (3b): From 0.67 g of **2b**, white crystals (0.15 g, 63 %) were obtained, m.p. 110.2-110.9°C (lit.[12], 111 °C). Anal. calcd. % for $C_7H_8O_4$: C, 53.85; H, 5.16. Found %: C, 53.62; H, 5.01. MS: m/z 156 (M^+). IR: 938, 1115, 1285, 1630, 1685, 2950 and

3400 (broad) cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.65 (2H, s, -C**H**$_2$OH), 4.30 (4H, s, -C**H**$_2$OH), 6.15 (2H, s, Pyran-C**H**-3, -5). ^{13}C NMR (DMSO-d_6): δ 58.2 (-**C**H$_2$O-), 125.2 (Pyran-**C**-3, -5), 158.6 (Pyran-**C**-2, -6), 177.1 (Pyran-**C**-4).

General procedure for the reduction of compounds 2(c,d)-Synthesis of compounds 3(c,d): To a stirred mixture of 1.5 mmol of compounds **2c** or **2d**, 0.4 g zinc powder and 10 mL methanol at 0 ºC and under argon atmosphere was gently added 4 mL of 35 % hydrochloric acid. After stirring at 0 ºC for 45 min, the reaction mixture was filtered and concentrated under reduced pressure. 10 mL of H_2O was added to the residue. The mixture was cooled and neutralized with addition of $NaHCO_3$ to pH 7 and then adjusted at pH 10 with addition of sodium carbonate. The mixture was extracted with 5 × 10 mL of chloroform and dried over $MgSO_4$. The solvent was evaporated *in vacuo*. Specific details are given for each compounds.

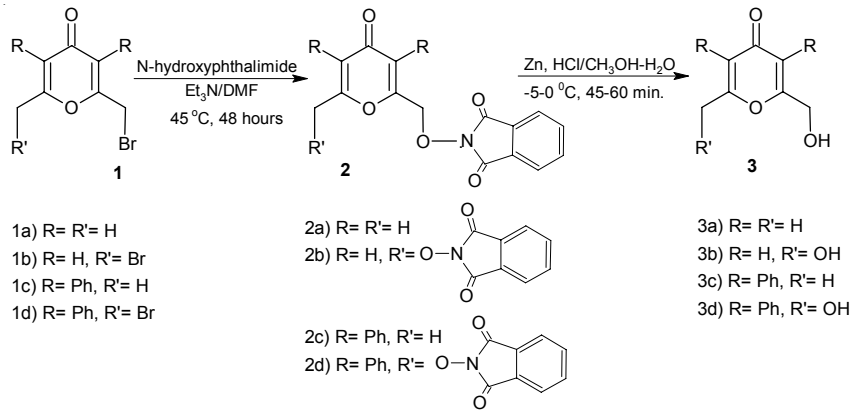
3,5-Diphenyl-2-hydroxymethyl-6-methyl-4*H*-pyran-4-one (3c): From 0.66 g of **2c**, white crystals (0.36 g, 83 %) were obtained, m.p. 217.5-218.9 °C (lit.[13], 217.2-219.0°C). Anal. calcd. % for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found %: C, 78.59; H, 5.62. MS: m/z 292 (M^+). IR: 1590, 1655 and 3360 (broad) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.40 (3H, s, -C**H**$_3$), 2.50 (lH, br, -C**H**$_2$OH), 4.50 (2H, s, -C**H**$_2$OH), 7.48 (10H, s, Phenyl-**H**). ^{13}C NMR ($CDCl_3$): δ 19.8 (-**C**H$_3$), 59.5 (-**C**H$_2$O-), 126.8 (Pyran-**C**-5), 127.8 (Pyran-**C**-3), 128.5, 129, 130.1, 130.7 and 131.9 (Phenyl-**C**), 158.5 (Pyran-**C**-6), 161.9 (Pyran-**C**-2), 176.2 (Pyran-**C**-4).

2,6-*Bis*-hydroxymethyl-3,5-diphenyl-4*H*-pyran-4-one (3d): From 0.9 g of **2d**, white crystals (0.35 g, 75 %) were obtained, m.p. 231 °C (lit.[13], 232.1-232.8°C). Anal. calcd. % for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found %: C, 74.39; H, 5.38. MS: m/z 308 (M^+). IR: 1575, 1655 and 3409 (broad) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.80 (2H, s, -C**H**$_2$OH), 4.30 (4H, s, -C**H**$_2$OH), 7.10-7.50 (10H, m, Phenyl-**H**). ^{13}C NMR ($CDCl_3$): δ 58.5 (-**C**H$_2$O-), 128.5 (Pyran-**C**-3, -5), 128.0-131.0 (m, Phenyl-**C**), 157.0 (Pyran-**C**-2, -6), 176.5 (Pyran-**C**-4).

RESULTS AND DISCUSSION

2-Bromomethyl-6-methyl-4*H*-pyran-4-one (**1a**) and 2,6-*bis*-bromomethyl-4*H*-pyran-4-one (**1b**) were both synthesized according to reported method[5] in 73 and 59 % yields, respectively. 2,6-*Bis*-bromomethyl-3,5-diphenyl-4*H*-pyran-4-one (**1d**) was first prepared in 1990 by Massa and coworkers[17] through bromination of 2,6-dimethyl-3,5-diphenyl-4*H*-pyran-4-one with N-bromosuccinimide in 56 % yield. Recently, the synthesis 2-bromomethyl-3,5-diphenyl-6-methyl-4*H*-pyran-4-one (**1c**) by means of Wohl-Ziegler bromination in 68 % yield have been reported[8].

Treatment of the mono and *bis*-bromomethyl derivatives of 4*H*-pyran-4-ones, compounds **1(a-d)**, with N-hydroxyphthalimide and Et_3N in DMF[14] produced the corresponding phthalimidoxymethyl derivatives, compounds **2(a-d)**, in 87, 72, 81 and 78 % yields, respectively (**Scheme-V**).



Scheme-V: Preparation and reduction of phthalimidoxymethyl derivatives of 4*H*-pyran-4-ones

It is often necessary in organic synthesis to convert alcohols into alkyl halides, but only occasionally it is necessary to achieve the reverse conversion, *i.e.* the hydrolysis of alkyl halides. Hydrolysis of primary alkyl halides is usually achieved by using alkali metal hydroxide. However, the 4*H*-pyran-4-one ring is unstable under aqueous basic conditions and direct substitution of the halide by hydroxyl group is not feasible. Recently, Shahrisa and coworkers[5] have converted bromomethyl derivatives of 4*H*-pyran-4-one to corresponding acetoxymethyl derivatives which afforded the hydroxymethyl derivatives on hydrolysis.

Accordingly, we decided to perform the reductive cleavage of N–O bond in mono and *bis*-phthalimidoxymethyl groups of 4*H*-pyran-4-ones, compounds **2(a-d)**, to the corresponding mono and *bis*-hydroxymethyl groups. Attempted reductive cleavage of N–O bond of compounds **2(a-d)** to the corresponding hydroxymethyl derivatives of 4*H*-pyran-4-ones, compounds **3(a-d)**, with sodium borohydride and some other reducing agents gave no characterizable products. However, reductive cleavage of compounds **2(a-d)** with a mixture of zinc powder and hydrochloric acid in methanol at -5 to 0 ºC gave the corresponding compounds **3(a-d)** in yields of 63 to 83 % (**Scheme-V**).

The data obtained from Mass, IR, ^1H and ^{13}C NMR spectra and elemental analyses are fully consistent with the proposed structures.

In conclusion, we developed a convenient new method for the preparation of mono and *bis*-hydroxymethyl derivatives of 4*H*-pyran-4-ones substituted at position 2 and 6, compounds **3(a-d)**. These compounds can be oxidated to carboxaldehyde derivatives and used as precursor for synthesis of host molecules.

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