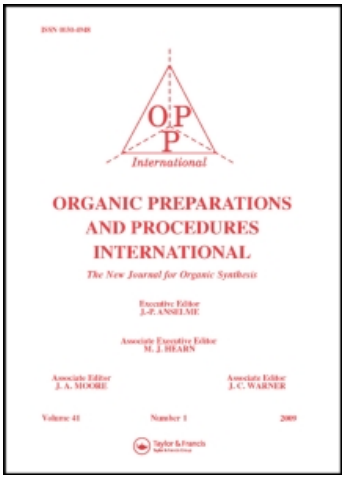


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# A CONVENIENT SYNTHESIS OF 2*H*-PYRAN-2-ONES AND OF 3- AND 5- BROMO-2*H*-PYRAN-2-ONES

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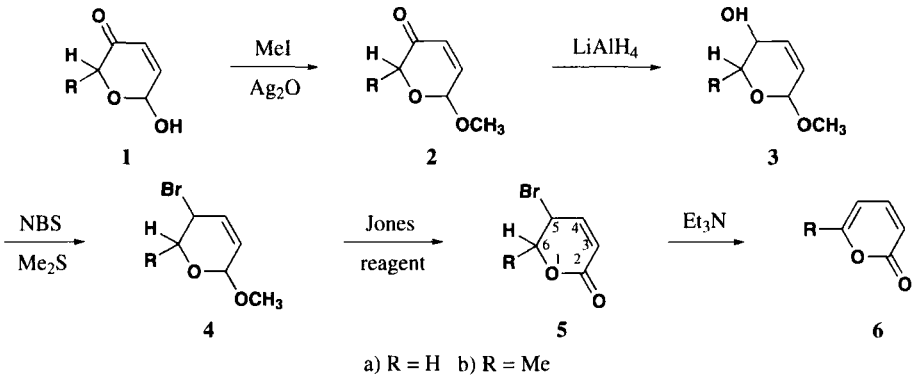
2-Pyrones have attracted much attention as precursors for the synthesis of a variety of biologically important compounds such as solanopyrones,[1] coumarins,[2] pheromones,[3] inhibitors of α-chymotrypsin,[4] elastase[5] and HIV protease,[6] while some of their derivatives display significant biological activities (antifungal, phytotoxic).[7] It is known that volatile compounds and among them 2-pyrones are produced during the Maillard reaction.[8] These pyrones modify the flavor/aroma in food as well as a toasted caramel aroma in the heated oak wood to be used in barrels for aging wine and brandy products.[9] 3- or 5-Bromopyrones are ambiphilic dienes which have been used as chameleon-like precursors to the much more reactive 2-pyrones at the Diels-Alder cycloaddition. These bromopyrones are also key compounds for the total synthesis of vitamin $D_3$ derivatives.[10,11] A variety of approaches has been employed for the preparation of 2-pyrones starting mainly from 3-butenoic acid,[12] 4,5-epoxy-3,4-diphenyl-2-cyclopentene-1-one,[13] decarboxylation of coumalic acid,[14] or *via* cycloaddition of 1-methoxybuta-1,3-diene.[3] Bromopyrones have recently been obtained starting from 2-pyrones.[10,11] This paper reports a procedure for the effective synthesis of 2-pyrones as well as bromopyrones starting with 2-hydroxy-pyran-3(6*H*)-ones.

Our starting materials which are endowed with different functionalities have been used for a multitude of reactions.[15] The reported procedure depending on the experimental conditions, may lead to 2-pyrones or bromopyrones. These products may be used as synthons for additional syntheses.

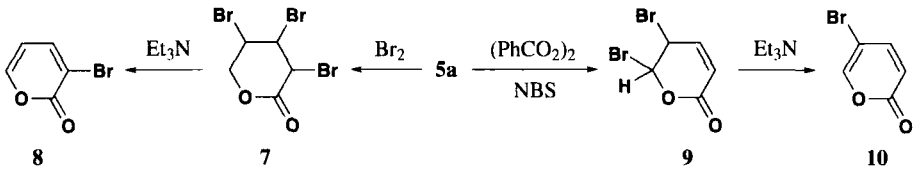
The synthesis of the 2*H*-pyran-2-one (**6a**) and 6-methyl-2*H*-pyran-2-one (**6b**) is depicted in (*Scheme 1*). The starting materials 6-hydroxy-2*H*-pyran-3(6*H*)-one (**1a**) and 6-hydroxy-2-methyl-2*H*-pyran-3(6*H*)-one (**1b**) were easily prepared in 80% yield according to the literature.[16,17]

Compound **5a** was used as a key intermediate to prepare the corresponding bromopyrones **8** and **10** as shown in (*Scheme 2*). The $^1H$-NMR spectrum of **8** is characterized by the absence of *H*-3 and decreased shielding at *H-5* and *H-4* due to the presence of bromine. On the

other hand, the $^1H$-NMR spectrum of **10** is characterized by the absence of *H*-5, while the position of bromine causes protons *H*-6 and *H*-4 to resonate further downfield.




**Scheme 1**




**Scheme 2**

## EXPERIMENTAL SECTION

All reagents were of commercial quality from freshly opened containers and obtained from Aldrich. Reagent quality solvents, purchased from Merck, were used without further purification. $Et_3N$ was purified by treatment with p-toluenesulfonyl chloride and distillation. NBS was recrystallized from benzene. TLC analyses were carried out on silica gel 60 $F_{254}$ pre-coated plates (Merck) and spots were visualized by spraying with a solution $H_2SO_4$/EtOH (8:2), solvent system A (hexane:AcOEt 3:1) and solvent system B (hexan:ether 1:1). Flash column chromatography was performed on silica gel 60 (70-230 mesh) purchased from Merck. Melting points are uncorrected and were determined with a Buchi apparatus. Boiling points refer to air-bath temperatures. IR spectra were recorded on a Perkin Elmer 283B Infrared spectrometer. $^1H$ NMR were recorded with a Varian 360MHz spectrometer for $CDCl_3$ solutions ($\delta$ scale, $Me_4Si$ 0 ppm). MS spectra obtained with a Kratos MS 80 RFA spectrometer . Compounds **1a** and **1b** were prepared as reported previously.[16,17]

**6-Methoxy-2*H*-pyran-3(6*H*)-one (2a)**.- To a solution of **1a** (8g, 70mmol) in anhydrous acetone (100 mL) was added $Ag_2O$ (23g, 102mmol) and MeI (24mL, 380mmol). The mixture was stirred for 24h in the dark at RT and was then filtered through a pad of Celite. The filtrate was evaporated on a rotary evaporator at low pressure and the residue, after flash chromatography on a silica gel column (hexane:AcOEt, 5:1, as eluent), yielded 6.7g (75%) of compound **2a** as a yellowish oil, bp. 76-81°/ 23Torr., *lit.*[20] bp. 76-80° / 23Torr, $R_f$ = 0.50 (system A).

IR ($cm^{-1}$): 2960, 2940 ($CH_3$), 1700 (C=O), 1640 (C=C), 1155, 1030 (C-O-C). $^1$H-NMR (300 MHz, $CDCl_3$): δ 3.50 (s, 3H, $OCH_3$), 4.05 (d, $J_{2e,2a}$ =16.0 Hz, 1H, H-2e, ), 4.30 (d, $J_{2a,2e}$ =16.0 Hz, 1H, H-2a), 5.10 (dd, $J_{6,5}$ =3.0 Hz, $J_{6,4}$ =1.0 Hz, 2H, H-6), 6.05 (dd, $J_{4,5}$ =10.0 Hz, $J_{4,6}$ =1.0 Hz, 1H, H-4), 6.80 (dd, $J_{5,4}$ =10.0 Hz, $J_{5,6}$ =3.0 Hz, 1H, H-5).

**6-Methoxy-2-methyl-2*H*-pyran-3(6*H*)-one (2b)**.- By the same procedure, a mixture of **1b** (5g, 39 mmol) with $Ag_2O$ (13g, 56.8mmol) and MeI (13mL, 210mmol) gave 4.3g (78%) of compound **2b** as a yellowish oil, bp. 82-85°C/ 30Torr., *lit.*[20] bp. 82-84° / 30Torr., $R_f$ = 0.60 (system A). MS/CI (*m/z*, %): 142 (15, $M^{+\cdot}$).

IR ($cm^{-1}$): 2960, 2940, 2815 ($CH_3$), 1700 (C=O), 1630 (C=C), 1140, 1040 (C-O-C). $^1$H-NMR (300 MHz, $CDCl_3$): δ 1.30 (d, *J* =7.0 Hz, 3H, $CH_3$), 3.42 (s, 3H, $OCH_3$), 4.20 (q, *J* =7.0 Hz, 1H, H-2), 5.05 (d, $J_{6,5}$ =3.1 Hz, 1H, H-6), 5.85 (d, $J_{4,5}$ =10.0 Hz, 1H, H-4), 6.60 (dd, $J_{5,4}$ =10.0 Hz, $J_{5,6}$ =3.1 Hz, 1H, H-5).

**6-Methoxy-3,6-dihydro-2*H*-pyran-3-ol (3a)**.- To a solution of **2a** (2.4g, 18.5mmol) in ether (50mL), $LiAlH_4$ (0.7g, 18.5mmol) was added at -60°. After 30min, $H_2O$ (1.5mL) and NaF (3.0g, 71.4mmol) were added and the mixture was stirred vigorously for 1h at RT. The white precipitate was removed by filtration through a pad of Celite with ether (20mL). The filtrate was concentrated, yielding 2.1g (90%) of **3a** as an oil, which was used in the next step synthesis without further purification, bp. 64-65° / 0.5 Torr., *lit.*[21] bp. 63-65° / 0.4Torr., $R_f$ = 0.42 (system A).

IR ($cm^{-1}$): 3500 (OH), 2960, 2940 ($CH_3$), 1645 (C=C), 1120, 1045 (C-O-C). $^1$H-NMR (300 MHz, $CDCl_3$): δ 2.20 (br, 1H, OH), 3.40 (s, 3H, $OCH_3$); 3.50 (m, 1H, H-2e), 3.85 (m, 1H, H-2a), 4.10 (m, 1H, H-3), 4.68 (dd, $J_{6,5}$ =3.1 Hz, $J_{6,4}$ =1.0 Hz, 2H, H-6), 5.65-5.90 (m, 2H, H-4, H-5).

**6-Methoxy-2-methyl-3,6-dihydro-2*H*-pyran-3-ol (3b)**.- By the same procedure, to a solution of **2b** (1.9g, 13.7mmol) in ether (50mL), $LiAlH_4$ (0.5g, 13.7mmol) was added of at -60° yielding 1.8g (90%) of **3b** as an oil, bp. 60-62°/ 0.3Torr., *lit.*[21] bp. 60-61° / 0.3Torr., $R_f$ = 0.36 (system A). MS/CI (*m/z*, %): 145 [55, $(M+H)^+$].

IR ($cm^{-1}$): 3500 (OH), 2990, 2810, 2940 ($CH_3$), 1630 (C=C), 1040, 1010 (C-O-C). $^1$H-NMR (300 MHz, $CDCl_3$): δ 1.20-1.30 (m, 3H, $CH_3$), 2.20 (br, 1H, OH), 3.40 (s, 3H, $OCH_3$), 3.55-3.90 (m, 2H, H-1, H-3), 5.00 (d, $J_{6,5}$ =3.1Hz, 1H, H-6), 5.65-5.80 (m, 2H, H-4, H-5).

**3-Bromo-6-methoxy-3,6-dihydro-2*H*-pyran (4a)**.- To a cold (0°) solution of NBS (2.0g, 11.5mmol) in anhydrous methylene chloride (50mL) under nitrogen, dimethyl sulfide (0.86g, 13.8mmol) was added dropwise with stirring. The mixture was cooled to -20° and **3a** (1.4g, 1.7mmol) in $CH_2Cl_2$ (3mL) was added dropwise over 5min. The mixture was then warmed at 0° and stirred for 1h. After dilution with pentane, the mixture was poured into ice-water. The organic phase was washed with cold brine and dried ($MgSO_4$). The solvent was evaporated on a rotary evaporator at low pressure and gave a residue which was purified by chromatography on a silica gel column (hexane:AcOEt 6:1), yielding 1.1g (72%) of **4a** as a yellow oil, $R_f$ =

0.84 (system B). The product was stored under $N_2$ at 0°. MS/CI (*m/z*, %): 192(5, $M^{+\cdot}$), 194 (5, $M^{+\cdot}$). IR ($cm^{-1}$): 2960, 2940 ($CH_3$), 1640 (C=C), 1120, 1030 (C-O-C), 535 (C-Br). $^1$H-NMR (300 MHz, $CDCl_3$): δ 3.40 (s, 3H, $OCH_3$), 3.00 (m, 1H, H-3), 4.50-4.90 (m, 2H, H-2), 5.00 (d, $J_{6,5}$ =3.1 Hz, 1H, H-6), 5.65-5.90 (m, 2H, H-4, H-5).

*Anal.* Calcd. for $C_6H_9BrO_2$: C, 37.33; H, 4.70. Found: C, 37.51; H, 4.57

**3-Bromo-6-methoxy-2-methyl-3,6-dihydro-2*H*-pyran (4b)**.- To a cold (0°) solution of NBS (3.2g, 18.2mmol) in anhydrous methylene chloride (50mL), dimethyl sulfide (1.4g, 21.8mmol) was added dropwise under nitrogen with stirring. By the same procedure, the mixture was cooled to -20° and **3b** (1.7g, 12.1mmol) in $CH_2Cl_2$ (3mL) was added dropwise over 5min, yielding 1.8g (72%) of **4b** as a yellow oil, $R_f$ = 0.82 (system B). The product is stored under $N_2$ at 0°. MS/CI (*m/z*, %): 206 (8, $M^{+\cdot}$), 208 (8, $M^{+\cdot}$).

IR ($cm^{-1}$): 2960, 2940 ($CH_3$), 1650 (C=C), 1120, 1030 (C-O-C), 530 (C-Br). $^1$H-NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 3H, $CH_3$), (3.40 (s, 3H, $OCH_3$), 3.00 (m, 1H, H-3), 4.50-4.90 (m, 1H, H-2), 5.00 (d, $J_{6,5}$ =3.1 Hz, 1H, H-6), 5.65-5.90 (m, 2H, H-4, H-5).

*Anal.* Calcd. for $C_7H_{11}BrO_2$: C, 40.60; H, 5.35. Found: C, 40.54; H, 5.46

**5-Bromo-5,6-Dihydro-2*H*-pyran-2-one (5a)**.- To an ice cold stirred solution of **4a** (1.1g, 5.5mmol) in acetone (50mL), Jones reagent[22] (2mL) was added dropwise. Subsequently after stirring for 30min, the solid inorganic by-products were eliminated by decantation, the liquid layer was evaporated under reduced pressure and the resulting residue was partitioned in $Et_2O$ and $H_2O$. The organic layer was separated, washed with $H_2O$, dried ($MgSO_4$) and evaporated on a rotary evaporator at low pressure, yielding 0.87g (90%) of **5a** as a yellowish oil, which was stored under $N_2$ at 0°, bp. 106-107.5° / 3Torr., *lit.*[23] bp. 107-107.5° / 3Torr, $R_f$ = 0.54 (system B). MS/CI (*m/z*, %): 176 (40, $M^{+\cdot}$), 178 (40, $M^{+\cdot}$).

IR ($cm^{-1}$): 1720 (C=O), 1680 (C=C), 1120, 1030 (C-O-C), 530 (C-Br). $^1$H-NMR (300 MHz, $CDCl_3$): δ 2.45 (m, 1H, H-5), 4.60-4.85 (m, 2H, H-6), 6.05 (d, $J_{3,4}$ =10.0 Hz, 1H, H-3), 6.80-7.10 (m, 1H, H-4).

*Anal.* Calcd. for $C_5H_5BrO_2$: C, 33.93; H, 2.85. Found: C, 33.80; H, 2.93

**5-Bromo-6-methyl-5,6-dihydro-2*H*-pyran-2-one (5b)**.- By the same procedure, to an ice cold stirred solution of **4b** (1.8g, 8.7mmol) in acetone (50mL), Jones reagent (2.5mL) was added dropwise yielding 1.5g (90%) of **5b** as a yellowish oil, which was stored under $N_2$ at 0°, $R_f$ = 0.53 (system B). MS/CI: (*m/z*, %): 190(2, $M^{+\cdot}$), 192 (2, $M^{+\cdot}$).

IR ($cm^{-1}$): 2960, 2940 ($CH_3$), 1720 (C=O), 1680 (C=C), 1120, 1030 (C-O-C), 535 (C-Br). $^1$H-NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 3H, $CH_3$), 2.45 (m, 1H, H-5), 4.60-4.85 (m, 1H, H-6), 6.05 (d, $J_{3,4}$ =10.0 Hz, 1H, H-3), 6.80-7.10 (m, 1H, H-4).

*Anal.* Calcd. for $C_6H_7BrO_2$: C, 37.73; H, 3.69. Found: C, 37.79; H, 3.73

**2*H*-pyran-2-one (6a)**.- Compound **5a** (0.87g, 4.9mmol) was stirred at RT while $Et_3N$ (15mL) added and the mixture refluxed for 30min. Then the mixture was cooled at RT, the excess of $Et_3N$ was evaporated in vacuum, the residue was dissolved in $H_2O$ and the product was

extracted with benzene. The organic layer was dried ($MgSO_4$) and evaporated affording 0.36g (70%) of **6a** as a liquid oil that discolors on standing at RT, bp. 110° / 26Torr., *lit.*[24] bp. 210-211° / 760Torr, $R_f$ = 0.50 (system B). MS/CI (*m/z*, %): 96 (100, $M^{+\cdot}$).

IR ($cm^{-1}$): 1720 (C=O),1630, 1550 (C=C), 1120, 1045 (C-O-C). $^1$H-NMR (300 MHz, $CDCl_3$): δ 6.25 (dd, $J_{5,4}$ =7.0 Hz, $J_{5,6}$ =5.2 Hz, 1H, H-5), 6.30 (d, $J_{3,4}$ =9.6 Hz, 1H, H-3), 7.30 (ddd, $J_{4,3}$ =9.6 Hz, $J_{4,5}$ =7.0 Hz, $J_{4,6}$ =2.6 Hz, 1H, H-4), 7.52 (d, $J_{6,5}$ =5.2 Hz, 1H, H-6).

*Anal.* Calcd. for $C_5H_4O_2$: C, 62.50; H, 4.20. Found: C, 62.59; H, 4.38

**6-Methyl-2*H*-pyran-2-one (6b)**.- By the same procedure, compound **5b** (1.5g, 7.8mmol) was stirred at RT while $Et_3N$ (16mL) was added and the mixture was refluxed for 30min affording 0.59g (68%) of **6b** as a liquid oil (discolors on standing at RT), $R_f$ = 0.48 (system B). MS/CI (*m/z*, %): 110 (100, $M^{+\cdot}$).

IR ($cm^{-1}$): 1720 (C=O), 1625, 1550 (C=C), 1120, 1030 (C-O-C). $^1$H-NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 3H, $CH_3$), 6.15 (d, $J_{5,4}$ =7.0 Hz, 1H, H-5), 6.35 (d, $J_{3,4}$ =9.6 Hz, 1H, H-3), 7.25 (dd, $J_{4,3}$ =9.6 Hz, $J_{4,5}$ =7.0 Hz, 1H, H-4).

*Anal.* Calcd. for $C_6H_6O_2$: C, 65.45; H, 5.49. Found: C, 65.55; H, 5.54

**3,4,5-Tribromo-3,4,5,6-tetrahydro-2*H*-pyran-2-one (7)**.- In the solution of **5a** (1.1g, 6mmol) in $CHCl_3$ (25mL), $Br_2$ (0.62mL, 12mmol) was added dropwise and the mixture was refluxed for 1h. Then the solvent was evaporated in vacuum and the crude product purified by column chromatography with hexane:$Et_2O$ (4:1) as eluent affording 1.3g (65%) of **7** as a yellow oil, $R_f$ = 0.78 (system B). The product is stable at –20° under $N_2$ for several weeks.

IR ($cm^{-1}$): 1740 (C=O), 1625, 1550 (C=C), 1120, 1030 (C-O-C), 525 (C-Br).

*Anal.* Calcd. for $C_5H_5Br_3O_2$: C, 17.83; H, 1.50. Found: C, 17.99; H, 1.33

**3-Bromo-2*H*-pyran-2-one (8)**.- Compound **7** (0.8g ,2.4mmol) and $Et_3N$ (3mL) were worked on according to the above procedure (that is, in compound **6a**) and afforded 0.4g (90%) of **8** as a white solid, mp. 63-64°, *lit.*[24] mp. 63.5°, $R_f$ = 0.56 (system B). It was observed that this product may gradually decompose when is kept at 25° for several weeks, while is stable at 0° for more than 1 year. MS/CI (*m/z*, %): 174(90, $M^+$), 176 (90, $M^{+\cdot}$).

IR ($cm^{-1}$): 740 (C=O), 1610, 1540 (C=C), 1120, 1045 (C-O-C). $^1$H-NMR (300 MHz, $CDCl_3$): δ 6.17 (dd, $J_{5,4}$ =7.0 Hz, $J_{5,6}$ =5.2 Hz, 1H, H-5), 7.50 (dd, $J_{4,5}$ =7.0 Hz, $J_{4,6}$ =2.6 Hz, 1H, H-4), 7.70 (dd, $J_{6,5}$ =5.2 Hz, $J_{6,4}$ =2.6 Hz, 1H, H-6).

*Anal.* Calcd. for $C_5H_3BrO_2$: C, 34.32; H, 1.73. Found: C, 34.49; H, 1.89

**5,6-Dibromo-5,6-dihydro-2*H*-pyran-2-one (9)**.- A mixture of **5a** (1.1g, 6mmol), NBS (1.1g, 6mmol) and benzoyl peroxide (0.05g, 0.2mmol) in $CCl_4$ (30mL) was refluxed for 4h. After removal of solvent, it was purified by chromatography on silica gel column with hexane:$Et_2O$ (3:1) as eluent, affording 0.99g (65%) of **9** as a yellow oil, which is stable at -20° under $N_2$ for several weeks, $R_f$ = 0.63 (system B). MS/CI (*m/z*, %): 252 (20, $M^{+\cdot}$), 254 (40, $M^{+\cdot}$), 256 (20, $M^{+\cdot}$). IR ($cm^{-1}$): 1720 (C=O), 1670 (C=C), 1120, 1030 (C-O-C), 525 (C-Br).

*Anal.* Calcd. for $C_5H_4Br_2O_2$: C, 23.47; H, 1.58. Found: C, 23.30; H, 1.73

**5-Bromo-2*H*-pyran-2-one (10)**.- Compound **9** (0.82g, 3.2mmol) was worked on according to the above procedure (that is, in compound **6a**) with $Et_3N$ (1mL) and afforded 0.5g (90%) of **10** as a white solid, mp. 60-61°, *lit.*[11] mp. 58-60°, $R_f$ = 0.57 (system B). This product gradually decomposed at 25° after several weeks, while is stable at 0° for more than a year. MS/CI (*m/z*, %): 174 (90, $M^+$), 176 (90, $M^+$).

IR ($cm^{-1}$): 1740 (C=O), 1613, 1533 (C=C), 1120, 1045 (C-O-C). $^1$H-NMR (300 MHz, $CDCl_3$): δ 6.30 (dd, $J_{3,4}$ =9.6 Hz, $J_{3,6}$ =1.1 Hz, 1H, H-3), 7.35 (dd, $J_{4,3}$ =9.6 Hz, $J_{4,6}$ =2.6 Hz, 1H, H-4), 7.60 (dd, $J_{6,3}$ =1.1 Hz, $J_{6,4}$ =2.6 Hz, 1H, H-6).

*Anal.* Calcd. for $C_5H_3BrO_2$: C, 34.32; H, 1.73. Found: C, 34.43; H, 1.85

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