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Preparation of Mannich Bases from 6-Methoxy-2*H*-pyran-3(6*H*)-one and Its Epoxide

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Synopsis. 4-Morpholinomethyl-2*H*-pyran-3(6*H*)-ones **3** and **8** were prepared directly from 6-methoxy-2*H*-pyran-3(6*H*)-one (**1**) and its epoxide **4** by treatment with morpholine and aqueous 37% formalin in methanol in 70—88% yield. The mechanisms of the reaction have been discussed on the basis of the intermediates 5,6-dimethoxytetrahydropyran-3-one (**2**), 2,6-dimethoxy-5-hydroxytetrahydropyran-3-one (**5**), 2,6-dimethoxy-2*H*-pyran-3(6*H*)-one (**6**), and 2,5,6-trimethoxytetrahydropyran-3-one (**7**).

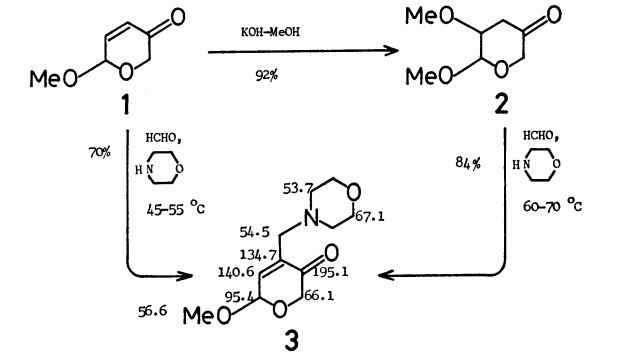
Potential biological activities of Mannich bases along with their very reactive properties have aroused great interest.[1] In connection with our interest in the chemistry of 2*H*-pyran-3(6*H*)-ones[2] we report here our studies on 6-methoxy-2*H*-pyran-3(6*H*)-one (**1**) and its epoxide **4**, functionalized with morpholinomethyl group as a Mannich base.

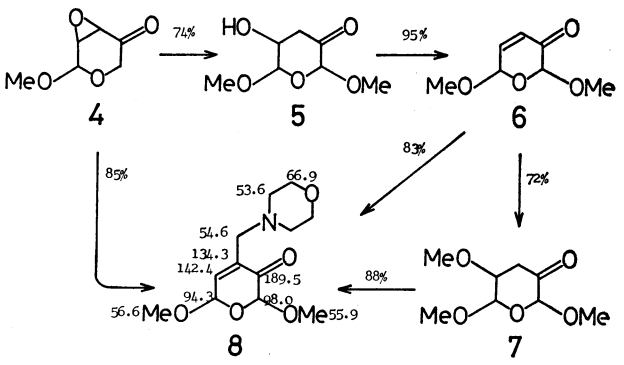
Various studies have been made on Mannich synthesis, but investigations of the reaction at the α position of α,β-unsaturated carbonyl compounds are very limited.[3] No report seems to have appeared on the reaction with α,β-epoxy carbonyl compounds.

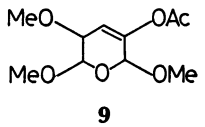
The Mannich products **3** and **8** were synthesized directly from the reactive intermediates **1** and **4**.[2] The 4-morpholinomethyl derivatives **3** and **8** could be prepared in several steps *via* 5-methoxytetrahydropyran-3-ones **2** and **7**. The latter case in particular reveals the fact that introduction of methoxyl function as well as the morpholinomethyl group could be achieved at C-2 and C-4 positions of **4**, respectively.

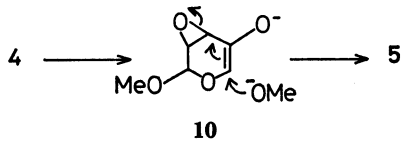
Conversion of 1 and 2 into 3. Stirring **1** in methanol with potassium hydroxide below 5 °C gave **2** in 92% yield.[4] Both **1** and **2** could be converted into the Mannich adduct **3** in 70—84% yields by treatment with morpholine and aqueous formalin in methanol at 45—70 °C for 4—6 h. Under the reaction conditions proton abstraction from C-4 position of **2** followed by nucleophilic attack to formaldehyde would give the Mannich adduct **3**. A possible mechanism for the direct conversion of **1** into **3** can be also rationalized by considering the formation of the intermediate **2**.

Conversion of 4, 6, and 7 into 8. Treatment of **4** in methanol with potassium hydroxide at 15—20 °C for 3 h gave **5** in 74% yield together with a small amount of **7**. Addition of the excess base increased the formation of **7**. The treatment of **5** with a mixture of acetic anhydride and pyridine at room temperature for 6 h gave the enone **6**, whereas a similar treatment of **7** afforded the acetate **9** in 97% yield. The transformation of **4**, **6**, and **7** into **8** in 83—88% yields was carried out by heating with morpholine and aqueous 37% formalin in methanol at 40—65 °C for 3—4 h. A plausible mechanism for the formation of the Mannich adduct **8** directly from **4** can be formulated as follows.









In the presence of morpholine as a base, methoxide ion would be able to react with **10** at C-2 position to give **5**. Subsequent dehydration in the medium would afford **6** smoothly. The assignments of carbon 13 NMR spectra of **3** and **8** are shown on the structural formula.

Experimental

Boiling points are uncorrected. IR spectra were determined with a JASCO IRA-I infrared recording spectrophotometer fitted with a grating. PMR spectra were determined at 60 MHz with a Hitachi R-24 spectrometer. The chemical

shift values are expressed in δ values (ppm) relative to a Me_4Si internal standard. CMR spectra were taken at 25.05 MHz in the Fourier mode with a JEOL FX-100 spectrometer. Samples were dissolved in $CDCl_3$ containing Me_4Si as an internal standard. The mass spectra were obtained with a JEOL Model JMS-OIBM-2, ionizing voltage 75 eV.

5,6-Dimethoxytetrahydropyran-3-one (2). To a mixture of KOH (20 mg) in MeOH (4 ml) was added dropwise a solution of **1**[2] (200 mg, 1.56 mmol) in MeOH (1 ml) at 0—5 °C. The mixture was stirred below 5 °C for 10 min and quenched with 5% aqueous tartaric acid. The mixture was poured into ice water, extracted with AcOEt, washed with brine, and dried ($MgSO_4$). Removal of the solvent gave **2** (239 mg, 92%): bp 61—64 °C/2 Torr; IR (neat) 1732 cm^{-1} (C=O); PMR ($CDCl_3$) δ 2.70 (m, 2, CH_2), 3.39 (s, 3, CH_3O), 3.50 (s, 3, CH_3O), 3.67 (m, 1, CHO), 4.00 (s, 2, CH_2O), 4.77 (d, 1, J=2 Hz, OCHO).

6-Methoxy-4-morpholinomethyl-2H-pyran-3(6H)-one (3). To a solution of **2** (116 mg, 0.72 mmol) and morpholine (73 mg, 0.86 mmol) in MeOH (2 ml) was added dropwise aqueous 37% formalin (67 mg, 0.83 mmol) at room temp. The mixture was stirred at 60—70 °C for 4 h. After removal of the solvent, the residue was chromatographed (SiO_2, benzene–AcOEt/3: 1) to give **3** (137 mg, 84%) as a pale yellow oil: bp 91—96 °C/0.005 Torr; IR (neat) 1688 cm^{-1} (C=O); PMR ($CDCl_3$) δ 2.44 (m, 4, CH_2N), 3.15 (t, 2, J=1 Hz, CH_2N), 3.51 (s, 3, CH_3O), 3.69 (m, 4, CH_2O), 4.10 (d, 1, J=16 Hz, CH_2O), 4.40 (d, 1, J=16 Hz, CH_2O), 5.15 (d, 1, J=4 Hz, CHO), 6.86 (m, 1, HC=C). Found: C, 57.91; H, 7.53%. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54%.

Morpholinomethyl Derivative 3 from 1. To a solution of **1** (136 mg, 1.06 mmol) in MeOH (3 ml) was added dropwise morpholine (130 mg, 1.50 mmol) and aqueous 37% formalin (119 mg, 1.50 mmol). The mixture was stirred at 45—55 °C for 6 h and concentrated. The residue was chromatographed (SiO_2, benzene–AcOEt/3: 1) to give **2** (167 mg, 70%) as a pale yellow viscous oil, whose IR and PMR spectral data were identical with those given above.

2,6-Dimethoxy-5-hydroxytetrahydropyran-3-one (5). To a solution of **4** (287 mg, 1.99 mmol) in MeOH (3 ml) was added dropwise a 0.2 M KOH–MeOH solution (2 ml) at 5—10 °C. The mixture was stirred for 3 h at 15—20 °C and then neutralized with aqueous 5% tartaric acid. After removal of the solvent, the residue was taken up in AcOEt, washed with brine, and dried (Na_2SO_4). Removal of the solvent gave **5** (258 mg, 74%) as a yellow oil, after being chromatographed (SiO_2, benzene–AcOEt/3: 1): IR (neat) 3420 (OH), 1742 cm^{-1} (C=O); PMR ($CDCl_3$) δ 2.73 (d, 1, J=7 Hz, CH_2), 2.75 (d, 1, J=6 Hz, CH_2), 3.14 (broad, 1, OH), 3.53 (s, 3, CH_3O), 3.56 (s, 3, CH_3O), 3.90 (m, 1, CHO), 4.65 (s, 1, CHO), 4.83 (d, 1, J=6 Hz, OCHO). Found: C, 47.73; H, 6.85%. Calcd for $C_7H_{12}O_5$: C, 47.73; H, 6.87%.

2,6-Dimethoxy-2H-pyran-3(6H)-one (6). A mixture of **5**(122 mg, 0.69 mmol), pyridine (0.5 ml) and Ac_2O (0.5 ml) was stirred at room temp for 6 h. The mixture was poured into 2 M HCl. The organic phase was extracted with AcOEt, washed with aqueous $NaHCO_3$, and dried (Na_2SO_4). Removal of the solvent gave **6** (104 mg, 95%) as a pale yellow oil: bp 61—64 °C/1 Torr; IR (neat) 1708 (C=O), 1632 cm^{-1} (C=C); PMR ($CDCl_3$) δ 3.46 (s, 3, CH_3O), 3.52 (s, 3, CH_3O), 4.76 (s, 1, CHO), 5.35 (m, 1, CHO), 6.04 (dd, 1, J=2 Hz, J=11 Hz, HC=C), 6.78 (dd, 1, J=2 Hz, J=11Hz, HC=C); MS *m/e* (rel intensity, %) 158 (M^+, 22), 144 (12), 127 (31), 116 (100), 98 (57), 55 (15), 43 (58). Found: C, 53.31; H, 6.13%. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37%.

2,5,6-Trimethoxytetrahydropyran-3-one (7). To a solution of **6** (218 mg, 1.38 mmol) in MeOH (3 ml) was added dropwise a MeOH–KOH solution (0.2 M, 2 ml) at 0—5 °C. After being stirred at 0—5 °C for 30 min, the mixture was neutralized with aqueous 5% tartaric acid. The mixture was poured into brine and extracted with AcOEt. The extracts were washed with brine, dried (Na_2SO_4), and concentrated, giving **7** (188 mg, 72%) as a pale yellow oil: bp 64—67 °C/1 Torr; IR (neat) 1742 cm^{-1} (C=O); PMR ($CDCl_3$) δ 2.73 (d, 1, J=9 Hz, CH_2), 2.75 (d, 1, J=5 Hz, CH_2), 3.42, 3.53, 3.58 (s, 9, CH_3O), 3.60 (m, 1, CHO), 4.71 (s, 1, CHC=O), 4.88 (d, 1, J=5 Hz, CHO). Found: C, 50.36; H, 7.64%. Calcd for $C_8H_{14}O_5$: C, 50.52; H, 7.42%.

2,6-Dimethoxy-4-morpholinomethyl-2H-pyran-3(6H)-one (8) from 7. A mixture of **7** (116 mg, 0.61 mmol), aqueous 37% formalin (67 mg, 0.82 mmol), and morpholine (75 mg, 0.89 mmol) in MeOH (2 ml) was stirred at 55—65 °C for 4 h. After removal of the solvent, the residue was chromatographed (SiO_2, benzene–AcOEt/3: 1) to give **8** (137 mg, 88%) as a pale yellow oil: bp 81—84 °C/0.04 Torr; IR (neat) 1700 cm^{-1} (C=O); PMR ($CDCl_3$) δ 2.42 (m, 4, CH_2N), 3.14 (t, 2, J=2 Hz, CH_2N), 3.52, 3.54 (s, 6, CH_3O), 3.65 (m, 4, CH_2O), 4.92 (s, 1, CHC=O), 5.47 (m, 1, CHO), 6.84 (m, 1, HC=C); MS *m/e* (rel intensity, %) 257 (M^+, 53), 225 (76), 196 (70), 121 (27), 100 (100), 83 (31), 56 (27), Found: C, 55.99; H, 7.37%. Calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44%.

Morpholinomethyl Derivative 8 from 6. A mixture of **6** (158 mg, 1.00 mmol), aqueous 37% formalin (97 mg, 1.16 mmol) and morpholine (104 mg, 1.20 mmol), in MeOH (3 ml) was heated for 4 h at 45—55 °C. After work-up in a similar way to that described above, **8** (213 mg, 83%) was obtained.

Morpholinomethyl Derivative 8 from 4. To a solution of **4** (590 mg, 4.09 mmol) and morpholine (460 mg, 5.48 mmol) in MeOH (5 ml) was added dropwise aqueous 37% formalin (443 mg, 5.47 mmol) at room temp and the mixture was heated at 55—65 °C for 4 h. After work-up in a similar way to that above, **8** (892 mg, 85%) was obtained.

3-Acetyl-2,5,6-trimethoxy-5,6-dihydro-2H-pyran (9). A solution of **7** (101 mg, 0.53 mmol) in a mixed solution of pyridine (0.5 ml) and Ac_2O (0.5 ml) was stirred at room temp for 12 h. After work-up in a similar way to that above, **9** (120 mg, 97%) was obtained as a colorless oil: bp 93—97 °C/1 Torr; IR (neat 1764 cm^{-1} (AcO); PMR ($CDCl_3$) δ 2.17 (s, 3, CH_3CO), 3.45, 3.50, 3.57 (s, 9, CH_3O), 3.88 (m, 1, CHO), 4.77 (d, 1, J=6 Hz, HC=C), 5.09 (s, 1, HCC=O), 5.68 (d, 1, J=3 Hz, CHO). Found: C, 51.70; H, 6.86%. Calcd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94%.

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