A Modified Synthesis of 4-Chromanones

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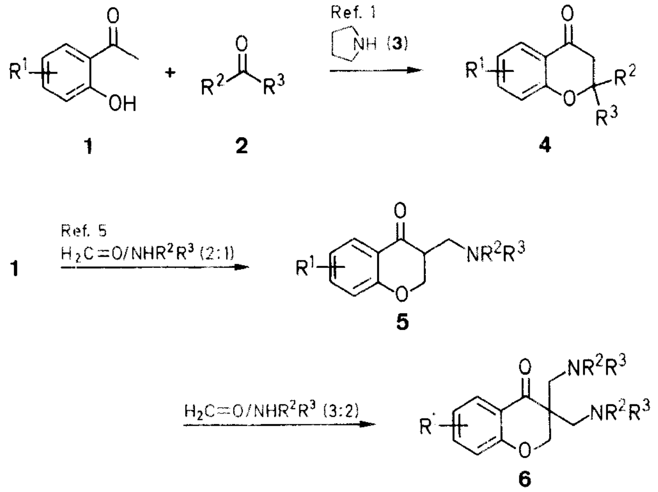
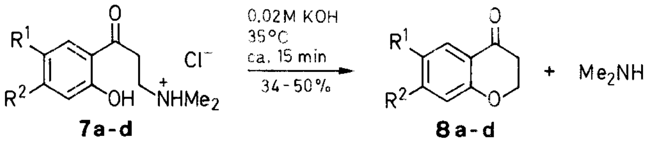
Problems in the synthesis of 4-chromanones by condensation of 2-hydroxyacetophenones with formaldehyde can be avoided by the isolation of the Mannich base hydrochlorides and cyclization by titration with potassium hydroxide.

A very simple and effective route to 4-chromanones involves the base-catalyzed condensation and cyclization of an aldehyde or ketone with 2-hydroxyacetophenone.[1] A limitation of this approach occurs with formaldehyde. The sodium salt of 2-hydroxyacetophenone in aqueous formaldehyde at 50 °C gives only a polymeric material.[2] Interestingly, the sodium salt of 2-hydroxypropiophenone under the same conditions yields 27–50% of 3-methyl-4-chromanone.[2,3] Pyrrolidine is used widely as a basic catalyst in these reactions.[1] Normally a mixture of the appropriate 2-hydroxyacetophenone **1**, aldehyde or ketone **2**, and pyrrolidine **3**, in the ratio of about 1 : 1 : 0.5 in toluene is allowed to stand for a time and then heated to boiling in an apparatus fitted with a water separator.[1]



A mixture of 2-hydroxyacetophenone, aqueous formaldehyde, and pyrrolidine in the ratio of 1 : 1 : 0.5 under these conditions yields no 4-chromanone, but a multi-component mixture of unidentifiable polar/polymeric compounds.[4] Increasing equivalents of aqueous formaldehyde and secondary amine result in the formation of 3-aminomethyl-4-chromanones **5** and 3,3-bis(aminomethyl)-4-chromanones **6**.[5]

We have been able to show that Mannich base hydrochlorides **7a–d**, formed from 2-hydroxyacetophenone by reaction with formaldehyde and dimethylamine under acidic conditions[6] will cyclize to 4-chromanones **8a–d** on titration with potassium hydroxide. If allowance is made for recovered starting material the yield on this final step is good. The 4-chromanones are obtained in pure form very readily since they are non-basic, so that separation from the starting material is very simple.



7, 8	R1	R2
a	H	H
b	Cl	H
c	H	Cl
d	Cl	Cl

2-Hydroxyacetophenones were prepared by the method of Jucker and Vogel[7] from the corresponding phenyl acetates. Phenyl acetates were prepared by *O*-acetylation of commercially available phenols.

Yields quoted are for purified materials. Melting points were obtained on a Kofler hot-stage apparatus, and are corrected. IR spectra were recorded on a Pye Unicam SP3-100 spectrophotometer. ^{1}H-NMR spectra were obtained using a Bruker WP 80 spectrometer. Mass spectra were recorded on a Kratos MS 30 spectrometer equipped with a DS-50 data system.

Table 1. Substituted Mannich Base Hydrochlorides 7 Prepared

Product	Yield (%)	mp (°C) (EtOH)	Molecular Formula[a] or Lit. mp (°C)	IR (KBr) ν (cm^{-1})	^{1}H-NMR (D_2O/DSS[b]) δ	MS (70 eV) m/z (%)
7a	45	154–160	156–157[8]	1650 (C=O)	6.9–8.1 (m, 4H); 3.4–3.8 (m, 4H); 2.7 (s, 6H)	193 (M$^+$, 1.9); 58 (100)
7b	22	195–197	188–189[9]	1645 (C=O)	6.85–7.9 (m, 3H); 3.5–3.6 (m, 4H); 2.85 (s, 6H)	229 (M$^+$, 0.3); 227 (M$^+$, 1.0); 58 (100)
7c	25	179–181	$C_{11}H_{15}Cl_2NO_2$ (264.2)	1650 (C=O)	6.9–7.8 (m, 3H); 3.45–3.55 (m, 4H); 2.85 (s, 6H)	229 (M$^+$, 0.6); 227 (M$^+$, 1.7); 58 (100)
7d	7	185	$C_{11}H_{14}Cl_3NO_2$ (298.6)	1640 (C=O)	7.95 (s, 1H); 7.05 (s, 1H); 3.5–3.6 (m, 4H); 2.85 (s, 6H)	263 (M$^+$, 0.4); 261 (M$^+$, 0.6); 58 (100)

[a] Satisfactory microanalyses obtained: C ± 0.4, H ± 0.2, N ± 0.2.

[b] Internal standard, sodium 2,2-dimethyl-2-silapentane-5-sulfonate.

Table 2. Substituted 4-Chromanones 8 Prepared

Product	Yield (%)	Starting Material Recovered (%)	Conversion (%)	mp (°C)	Lit. mp (°C)	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)	MS (70 eV) m/z (%)
8a	50	32	74	36–37	38.5[10]	1670 (C=O)	6.9–7.95 (m, 4H); 4.45–4.6 (t, 2H, $J = 6.5$); 2.7–2.9 (t, 2H, $J = 6.5$)	148 (M$^+$, 67.3); 120 (100)
8b	38	52	79	101–103	106[11]	1670 (C=O)	6.9–7.9 (m, 3H); 4.5–4.7 (t, 2H, $J = 6.5$); 2.7–2.9 (t, 2H, $J = 6.5$)	184 (M$^+$, 18.4); 182 (M$^+$, 57.2); 154 (100)
8c	35	37	56	65–67	72–74[12]	1670 (C=O)	6.9–7.9 (m, 3H); 4.5–4.7 (t, 2H, $J = 6.5$); 2.7–2.9 (t, 2H, $J = 6.5$)	184 (M$^+$, 19.1); 182 (M$^+$, 59.6); 181 (100)
8d	34	34	52	126–132	131–133[13]	1670 (C=O)	7.95 (s, 1H); 7.15 (s, 1H); 4.45–4.65 (t, 2H, $J = 6.5$); 2.7–2.9 (t, 2H, $J = 6.5$)	220 (M$^+$, 5.9); 218 (M$^+$, 34.7); 216 (M$^+$, 56.0); 188 (100)

Mannich Base Hydrochlorides 7a–d; General Procedure:

A stirred mixture of the 2-hydroxyacetophenone (0.05 mol), paraformaldehyde (3.0 g, 0.1 mol), $Me_2HN \cdot HCl$ (6.08 g, 0.05 mol), 2-propanol (25 mL) and concentrated HCl (0.1 mL) is heated at reflux temperature for 5 h. After this time the mixture is cooled to 0 °C whereupon crystallization occurs. The mixture is triturated with acetone (20 mL) and the crystalline material is filtered off. In each case the product is recrystallized from abs. EtOH. Product **7d**, although crystalline, has a deep-blue coloration which cannot be removed even with repeated recrystallization. The material is therefore dissolved in abs. EtOH (50 mL) and boiled with activated charcoal (1 g) for 10 min. The charcoal is filtered off and EtOH is evaporated off to yield a pale-yellow crystalline solid.

4-Chromanones 8a–d; General Procedure:

The appropriate Mannich base hydrochloride **7a–d** (0.5 mmol) is dissolved in and made up to 25 mL with H_2O. The solution is then titrated with aq. KOH (0.02 M). During the titration the solution is maintained at 35 °C between pH 3·0 and pH 11·0, and the pH is monitored with a pH-meter. The addition rate of KOH is such as to give a total time for titration of approximately 15 min. The titration is stopped when no further increase in pH is observed. After the titration the mixture is cooled to r.t. Any solid that has formed is filtered off and dried. The mixture is shaken with Et_2O (3×50 mL), the ethereal extracts are combined, dried ($MgSO_4$), and the solvent is evaporated. The residue is redissolved in Et_2O (20 mL) and saturated ethereal HCl is added until no further precipitation occurs. The solid material is filtered off and dried, and the ethereal filtrate is evaporated to dryness.

In each case the material precipitated by addition of ethereal HCl is found to be the starting material (Mannich bases **7a–d**). The material obtained from the evaporation of the ethereal filtrate is found to be the corresponding 4-chromanone **8a–d**. The titration of Mannich base **7d** produces crystalline 6,7-dichloro-4-chromanone (**8d**) during the titration.

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