Hydroxymethylation of Propiophenones in Aqueous Medium: A New Route to 1-Aryl-2-methyl-2-propen-1-ones

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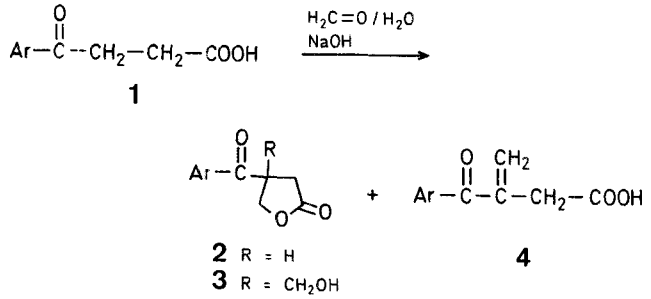
We have recently reported[1] that 3-aroylpropanoic acids **1** react smoothly at room temperature with aqueous formaldehyde in dilute sodium hydroxide solution in a reagent ratio of 1 : 1.1 : 1.1 to give high yields of 3-aroyl-4-hydroxybutanoic acids, as the lactones **2**, besides small amounts of 4-aroyl-4-hydroxymethyl-2(3*H*)-furanones **3** and/or 3-aroyl-3-butenoic acids **4**. Yields of **3** or **4** increased when formaldehyde or sodium hydroxide, were employed, respectively, in 100% excess.



In order to verify the course of the reaction with aromatic ketones lacking the ω-carboxylic group on the side chain, we have now submitted propiophenone **(5a)** and some phenyl-substituted propiophenones **5b–e** to the action of aqueous formaldehyde and sodium hydroxide under the conditions employed for **1**.

Hydroxymethylation of **5a** was first described in 1938[2]. The authors claimed to have isolated 3-hydroxy-2-methyl-1-phenyl-1-propanone **(6a)** by keeping a mixture of **5a**, paraformaldehyde, and potassium carbonate in methanol for six days at room temperature. This report has been questioned in more recent years and it was demonstrated[3] that this method actually led to 3-methoxy-2-methyl-1-phenyl-1-propanone **(8)** as the main product. A poor conversion of **5a** to **6a** was, however, described to occur using paraformaldehyde and sodium hydrogen carbonate as catalyst (1 : 30) in methanol at 50 °C for 24 h[4], as well as aqueous formaldehyde and sodium hydroxide as catalyst (1 : 4) in water at room temperature for 13 h[5].

Our experiments carried out at room temperature for 15 h with a suspension of **5a**, 37% formaldehyde, and 0.5 normal sodium hydroxide solution in a molar ratio 1 : 1.1 : 1.1 (A), 1 : 1.1 : 2.2 (B), and respectively, 1 : 2.2 : 1.1 (C), gave somewhat unexpected results as compared to literature reports[4,5] (Table 1). H.P.L.C. analyses of the crude reaction products revealed in fact that, independent of the reagent ratio, **6a** was present in less than 10%, the main component being identified as 2-methyl-1-phenyl-2-propen-1-one **(7a)**. In particular, working under conditions B, we isolated by column chromatography 61% of **7a**, besides 2% of **6a** and 20% of starting **5a**. However, if methanol was added to the initial reaction mixture to obtain a homogeneous phase, the methoxymethyl derivative **8a**[6] was obtained in about 60% yield. Under conditions C, unidentified polymeric materials were formed[7], which depressed the conversion of **5a** to **7a**.

The described route to **7a**, because of the convenient, mild conditions, and use of inexpensive reagents, offers advantages over the known synthetic approaches to **7** which, but for two exceptions[8,9], all require anhydrous conditions and multistep procedures through Mannich bases[10], α-bromoisobutyrophenones[11], 2-methoxymethyl-[12] and 2-phenylthiomethylpropiophenones[13].

On extending the investigation to propiophenones, **5b–e**, it was observed that, contrary to **1**, the course of the reaction with aqueous formaldehyde and sodium hydroxide was more affected by the phenyl substituent than by the reagent ratio. The most evident example was given by the *p*-hydroxy derivative **5b** which afforded under conditions A–C 70–85% of **6b** and traces of **7b**, thus reverting the **6 : 7** ratio found for **5a**.

p-Methoxy- **(5c)** and *p*-methylpropiophenone **(5d)** gave almost equal amounts (30–40%) of the corresponding **6c, d** and **7c, d** while the **6e : 7e** ratio was about 4 : 1 starting from the *p*-bromo derivative **5e**. Conditions B were, however, unfavourable for the conversion of **5d** and **5e**, about 70% and 50% of starting material being present in the reaction products, respectively (Table 1). When ethanol was added to increase the solubility in one experiment carried out with **5c**, the corresponding ethoxymethyl derivative **9** was isolated as the main product. Under the reaction conditions used, **5** did not give any isolable amount of bis-hydroxymethylated compounds as in the case of **1**. All compounds prepared were

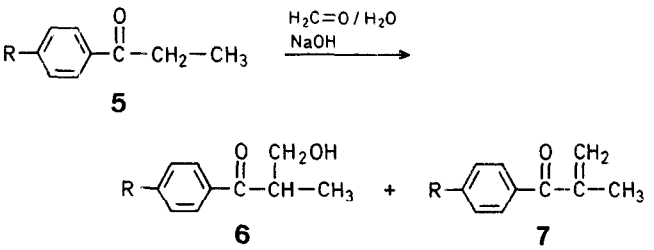


Table 1. Hydroxymethylation of **5** with Formaldehyde to give **6** and **7**

Substrate	R	Reaction conditions[a]	Yield of products [%][b]			H.P.L.C.[c] eluents (Flow)	Elution time [h] (compound **5** = 1)	
			6	**7**	**5** Recovered		**6**	**7**
5a	H	A	5	56	28	H_2O/CH_3CN	0.4	1.3
		B	3(2)	65(61)	22(18)	60:40		
		C	9	31	4	(1.5 ml/min)		
5b	4-HO	A	69	1	26	$H_2O/CH_3CN/CH_3OH$	0.48	1.29
		B	85(80)	1(traces)	10(8)	50:25:25		
		C	79	1	8	(1.5 ml/min)		
5c	4-H_3CO	A	35(25)	25(22)	28(20)	$H_2O/CH_3CN/CH_3OH$	0.5	1.27
		B	26	35	27	50:25:25		
		C	28	30	8	(1.5 ml/min)		
5d	4-H_3C	A	30	31	36	$H_2O/CH_3CN/CH_3OH$	0.4	1.27
		B	13	11	67	40:30:30		
		C	42(35)	31(28)	21(15)	(1 ml/min)		
5e	4-Br	A	41	12	10	H_2O/CH_3CN	0.45	1.18
		B	11	20	49	40:60		
		C	44(38)	13(10)	8	(1 ml/min)		

[a] Molar ratio **5**/HCHO/NaOH: (A) 1:1.1:1.1; (B) 1:1.1:2.2; (C) 1:2.2:1.1

[b] Yields from H.P.L.C. peak intensity, yields in brackets from pure product isolated by chromatography on silica gel. In both cases yields are referred to the starting **5**.

[c] Performed with a Perkin-Elmer Series 3 apparatus, equipped with an integrator Σ10 and an U.V. detector at 254 nm model LC 65 T. Columns: Lichrosorb RP18 (Merck) 250 × 4 mm (internal diameter), size 7 μ and Microbondapack C18 (Water's) 300 × 4 mm (internal diameter) size 10 μ.

Table 2. Characterisation of the Products **6–10**

Product[a]	b.p. [°C]/torr or m.p. [°C] (solvent)	Molecular formula[b] or Lit. data	^{1}H-N.M.R. ($CDCl_3$/TMS)[c] δ [ppm]
6a	130–132°/2	116–117°/1.5[4]	–[4]
6b	114–115° (ethanol)	$C_{10}H_{12}O_3$ (180.2)	1.2 (d, 3H, J = 6 Hz); 3.5–3.9 (m, 4H); 6.9 (d, 2H, J = 9 Hz); 7.9 (d, 2H, J = 9 Hz); 9.15 (br.s, 1H)[d]
6c	154°/0.4[e]	$C_{11}H_{14}O_3$ (194.2)	1.2 (d, 3H, J = 6 Hz); 2.9 (br.s, 1H); 3.5–4.0 (m, 6H); 7.0 (d, 2H, J = 9 Hz); 7.0 (d, 2H, J = 9 Hz)[d]
6d	145°/0.4[e]	$C_{11}H_{14}O_2$ (178.2)	1.2 (d, 3H, J = 6 Hz); 2.4 (s, 3H); 3.5–4.0 (m, 4H); 7.3 (d, 2H, J = 9 Hz); 7.9 (d, 2H, J = 9 Hz)[d]
6e	–[g]	$C_{10}H_{11}BrO_2$ (243.1)	1.15 (d, 3H, J = 6 Hz); 3.2–4.2 (m, 4H); 7.5–8.0 (m, 4H)[d]
7a	50–52°/1[e]	80–90°/0.7[8]	–[8]
7b	59–62° (diisopropyl ether/ *n*-heptane)	120–130°/2[14]	2.1 (s, 3H); 5.55 (s, 1H); 5.9 (s, 1H); 6.75 (br.s, 1H); 6.95 (d, 2H, J = 9 Hz); 7.9 (d, 2H, J = 9 Hz)[f]
7c	–[g]	125°/7[15]	2.1 (s, 3H); 3.9 (s, 3H); 5.55 (s, 1H); 5.8 (s, 1H); 6.95 (d, 2H, J = 9 Hz); 7.85 (d, 2H, J = 9 Hz)[f]
7d	–[g]	101°/5[15]	2.0 (s, 3H); 2.4 (s, 3H); 5.5 (s, 1H); 5.9 (s, 1H); 7.1 (d, 2H, J = 9 Hz); 7.8 (d, 2H, J = 9 Hz)[f]
7e	48° (*n*-hexane)	50–51°[16]	2.1 (s, 3H); 5.6 (s, 1H); 5.95 (s, 1H); 7.6 (s, 4H)[f]
8a	–[g]	75°/0.1[3]	–[3]
8b	150–155°/0.1	$C_{11}H_{14}O_3$ (194.2)	1.7 (d, 3H, J = 6 Hz); 3.38 (s, 3H); 3.45–3.9 (m, 3H); 6.8–7.9 (m, 5H)
9	150°/0.5	$C_{13}H_{18}O_3$ (222.3)	1.0–1.3 (m, 6H); 3.3–4.0 (m, 8H); 7.0 (d, 2H, J = 9 Hz); 8.1 (d, 2H, J = 9 Hz)
10	105° (chloroform)	$C_{10}H_{11}ClO_2$ (198.6)	1.25 (d, 3H, J = 6 Hz); 3.35–4.3 (m, 3H); 6.4 (br.s, 1H); 6.75 (d, 2H, J = 9 Hz); 8.2 (d, 2H, J = 9 Hz)

[a] **6**; I.R. (Nujol or film): ν = 1660 ± 10 cm^{-1} (C=O). **7**; I.R. (Nujol or film): ν = 3400 (OH), 1660 ± 10 cm^{-1} (C=O).

[b] Satisfactory microanalyses obtained: C ± 0.28, H ± 0.30, Br − 0.30, Cl − 0.29 (exceptions: **6e**, C − 0.44; **6c**, H + 0.36).

[c] Recorded on a Hitachi-Perkin Elmer R 600 FT spectrometer at 60 MHz.

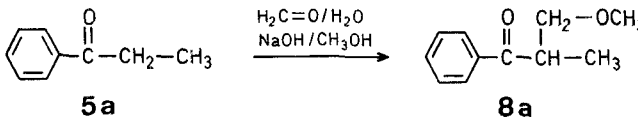
[d] δ = 1.15–1.2 ppm (CH_3—CH); δ = 3–4 ppm (CH—CH_2—OH).

[e] Bath temperature (Kugelrohr distillation).

[f] δ = 2.0–2.1 ppm (=C—CH_3); δ = 5.5–5.6, 5.8–5.95 ppm (—C=CH_2).

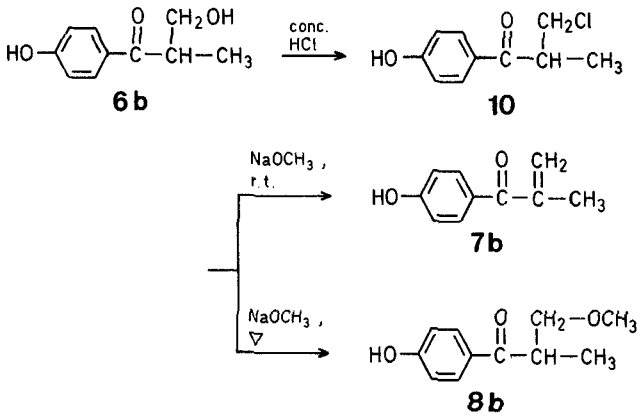
[g] Purified by chromatography on silica gel eluting with cyclohexane/ethyl acetate (from 98:2 to 70:30).

characterised by I.R., ^{1}H-N.M.R. spectral data and microanalyses (Table 2).



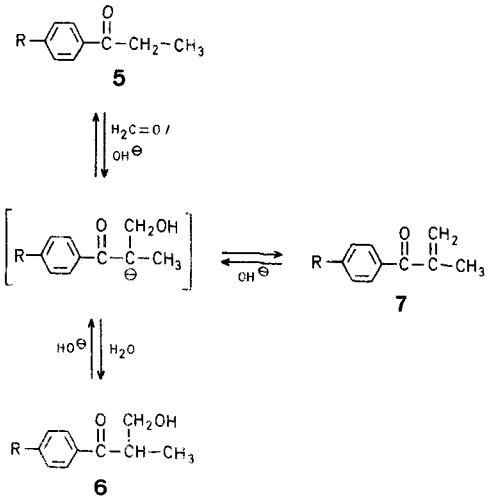
5a **8a**

Compound **7b**, which was isolated only in traces by hydroxymethylation of **5b**, was synthesised efficiently starting from **6b**. The latter was transformed with concentrated hydrochloric acid into the chloro derivative **10** which underwent a rapid dehydrohalogenation with methanolic sodium methoxide at room temperature to **7b**. If the basic solution was heated, a considerable amount of 1-(*p*-hydroxyphenyl)-3-methoxy-2-methyl-1-propanone **(8b)** was formed as by-product.



6b **10** **7b** **8b**

The progression of events involved in the reaction of **5** with formaldehyde and sodium hydroxide in aqueous medium seems to be controlled by the equilibria depicted below. Reasonably, alkali induces deprotonation of the initially formed **6**, which in turn could lose either $OH^{\ominus}$ to give **7**, or formaldehyde to give back **5**. The *reversibility of the reaction* **6** ⇆ **7** was proved by experiments carried out on **6c** and **7c**, which were found (H.P.L.C analysis) to equilibrate in 0.5 normal sodium hydroxide. Thus, the starting ratio 1 : 1.5 of **6c** and **7c** was changed to 2 : 1 after equilibration. The presence of **5c** (5–10%) in the mixture after equilibration also suggests the reversibility of the reaction **5** ⇄ **6**.



5 **7** **6**

Finally, further evidence of the influence of the *p*-substituent in the phenyl group on the conversion of **5** have been found by carrying out the hydroxymethylation of **5a** (R = H) and **5c** (R = OCH_3) with formaldehyde and sodium hydrogen carbonate in methanol at 50 °C, according to a known procedure[4]. While **5a** was transformed into 65% of **6a**, less than 30% of **6c** could be isolated from **5c**.

Hydroxymethylation of Propiophenones 5; General and Typical Procedures:

In aqueous medium: A suspension of **5** (a solution, in the case of **5b**) (0.03 mol), 37% formaldehyde, and 0.5 normal sodium hydroxide, in the reagent ratios given in Table 1, is stirred at room temperature for 15 h. The mixture is acidified to pH 4–5 with concentrated hydrochloric acid and extracted with ether (2 × 50 ml). The organic layer is separated, dried with sodium sulfate, and the solvent is evaporated. The residue is chromatographed on silica gel eluting with cyclohexane/ethyl acetate (98 : 2) collecting in succession **7** and starting **5**; afterwards, the column is eluted with cyclohexane/ethyl acetate (70 : 30) to obtain **6**. If necessary, the fractions isolated could be further purified by crystallisation or distillation in vacuo (Kugelrohr).

In aqueous alcoholic medium: 3-Ethoxy-1-(p-methoxyphenyl)-2-methyl-1-propanone **(9)**: A mixture of *p*-methoxypropiophenone (**5c**; 4.92 g, 0.03 mol), 37% formaldehyde (2.5 ml, 0.033 mol), 0.5 normal sodium hydroxide solution (66 ml, 0.033 mol), and ethanol (10 ml) is stirred 15 h at room temperature. After standard work up (see above), the crude reaction product is chromatographed on silica gel eluting with cyclohexane/ethyl acetate (95 : 5), collecting in succession **7c**; yield: 0.58 g (11%); starting material **5c**; yield: 0.9 g; and **9**; yield: 3.53 g (52%). Subsequent elution with cyclohexane/ethyl acetate (70 : 30) separates **6c**; yield: 0.52 g (9%).

A similar reaction carried out with **5a** by diluting with methanol instead of ethanol affords **8a**; yield: 58%.

In methanol: 3-Hydroxy-2-methyl-1-phenyl-1-propanone **(6a)**; *Modified Procedure*[4]: A solution of propiophenone (**5a**; 4.02 g, 0.03 mol), 37% formaldehyde (4.5 ml, 0.06 mol), and sodium hydrogen carbonate (0.1 g, 0.12 mmol) in methanol (20 ml) is heated at 50 °C for 24 h. After standard work-up (see above), the crude reaction product is chromatographed on silica gel eluting in succession with cyclohexane/ethyl acetate in the ratio of 98 : 2 and then 70 : 30 to give first unreacted **5a** (0.8 g) and then **6a**; yield: 3.15 g (64%); (Ref.[4]; 34% based on starting propiophenone).

Similarly *p*-methoxypropiophenone (**5c**; 4.92 g, 0.03 mol) gives **6c**; yield: 1.63 g (28%) besides recovered **5c** (2.5 g).

3-Chloro-1-(*p*-hydroxyphenyl)-2-methyl-1-propanone (10):
A suspension of **6b** (15 g, 0.083 mol) in concentrated hydrochloric acid (150 ml) is stirred at 80–90 °C for 0.5 h. After cooling, the solid separated is filtered, thoroughly washed with water, and dried at 70 °C in vacuo, to give crude **10** (16 g). Crystallisation from chloroform affords pure **10**; yield: 15.2 g (92%); m.p. 105 °C.

2-(*p*-Hydroxyphenyl)-2-methyl-2-propen-1-one (7b) and 1-(*p*-Hydroxyphenyl)-3-methoxy-2-methyl-1-propanone (8b):
To a solution of sodium methoxide (5.4 g, 0.1 mol) in anhydrous methanol (100 ml) is added **10** (10 g, 0.05 mol) and the mixture is stirred at room temperature for 1 h. After acidification to pH 4 with 5 normal hydrochloric acid and concentration in vacuo, the residue is shaken with ether (50 ml) and water (50 ml). The organic layer is separated, dried with sodium sulfate, and the solvent is evaporated. The semisolid residue is chromatographed on silica gel eluting with benzene, then with benzene/acetone 95 : 5, collecting in the order **7b**: yield: 7.75 g (95%) and **8b**; yield: 0.38 g (4%).

If the reaction mixture is heated at reflux for 1 h, **7b** and **8b** are isolated in 65% and 32% yields, respectively.

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