Hydroxymethylation of 3-Aroylpropanoic Acids; An Improved Synthesis of 4-Aroyl-2(3*H*)-dihydrofuranones and an Easy Approach to 3-Aroyl-3-butenoic Acids

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For the synthesis of some indeno[1,2-*c*]pyridazinones, recently found active as antiinflammatory agents[1,2], a convenient method for obtaining the starting 4-aroyl-2(3*H*)-dihydrofuranones **2** was desired. Known procedures for obtaining **2a**[3,4] involving hydroxymethylation of 3-benzoylpropanoic acid (**1a**) with formaldehyde and potassium carbonate in water solution at room temperature were unsatisfactory in our hands, especially for large runs, because of the long reaction time and the modest yield (~50%).

The synthesis of **2a** was reported[4] to occur in 72% yield by allowing to stand (20 h, room temperature) an aqueous solution of **1a**, potassium carbonate, and formaldehyde (molar ratio: 1.0:1.0:1.1). However, repetition of this method led, as average of three experiments, to the recovery of 65% of unchanged **1a**. Yields of **2a** reached 48% after 60 h and did not substantially increase on prolonging the reaction time to 120 h. In these cases, T.L.C. and N.M.R. analyses gave evidence of the formation of by-products **3a** and **4a** in amounts proportional to the reaction time.

We wish now to report here that by simply replacing potassium carbonate with 0.5 normal sodium hydroxide and by employing a reagent ratio **1a**/CH_2O/NaOH of 1.0:1.1:1.1, product **2a** was obtained in 81% yield within 1 h at room temperature. In addition to **2a**, 15% of an isomer (m.p. 60–65 °C) was isolated and identified as 3-benzoyl-3-butenoic acid (**3a**) on the basis of I.R. and N.M.R. spectra. The extension of this procedure to **1b** (R = Br) and **1c** ($R=CH_3$) led to 74% and 80% yields of **2b** and **2c**, respectively. In these cases, no by-products were isolated although their presence could be inferred by T.L.C. (silica gel 60 F_{254}, benzene/acetone 7:3 as mobile phase) and N.M.R. analyses of the crude products.

The course of the hydroxymethylation of **1** appeared to be strictly dependent on the reagent ratio. In fact, if sodium

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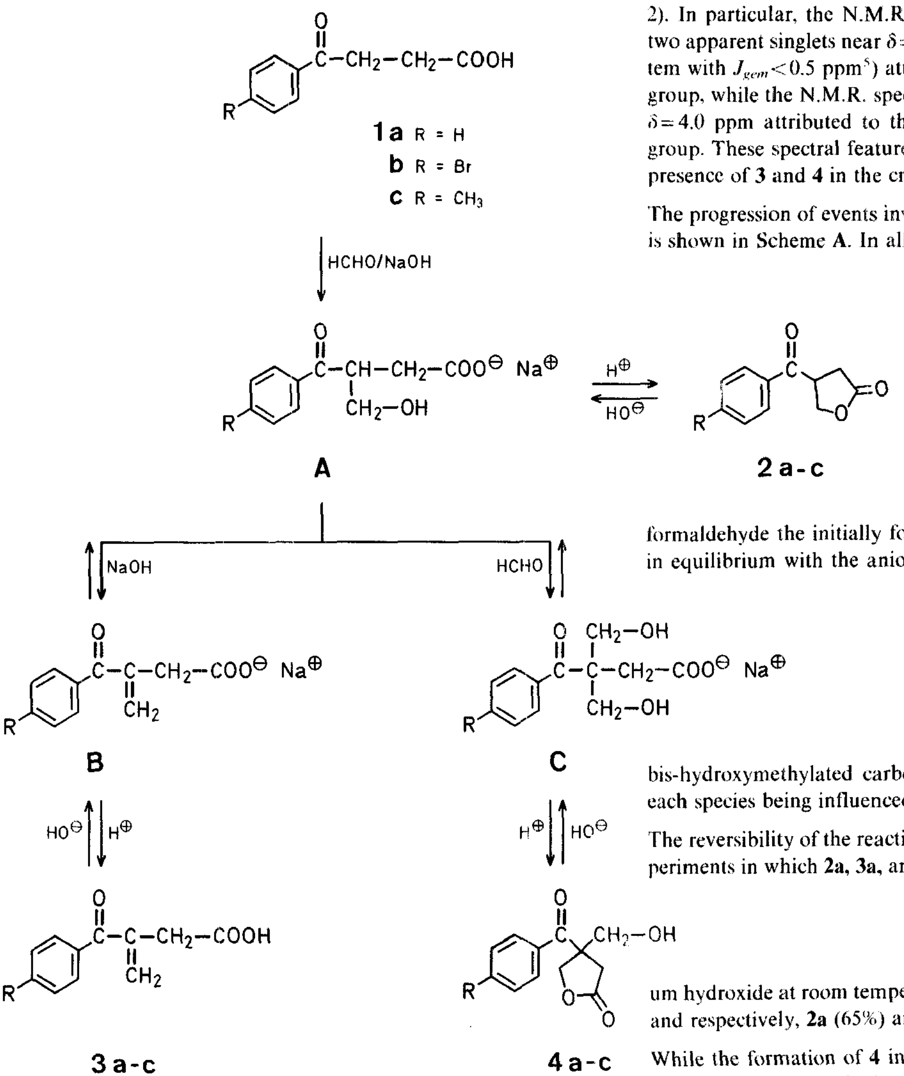
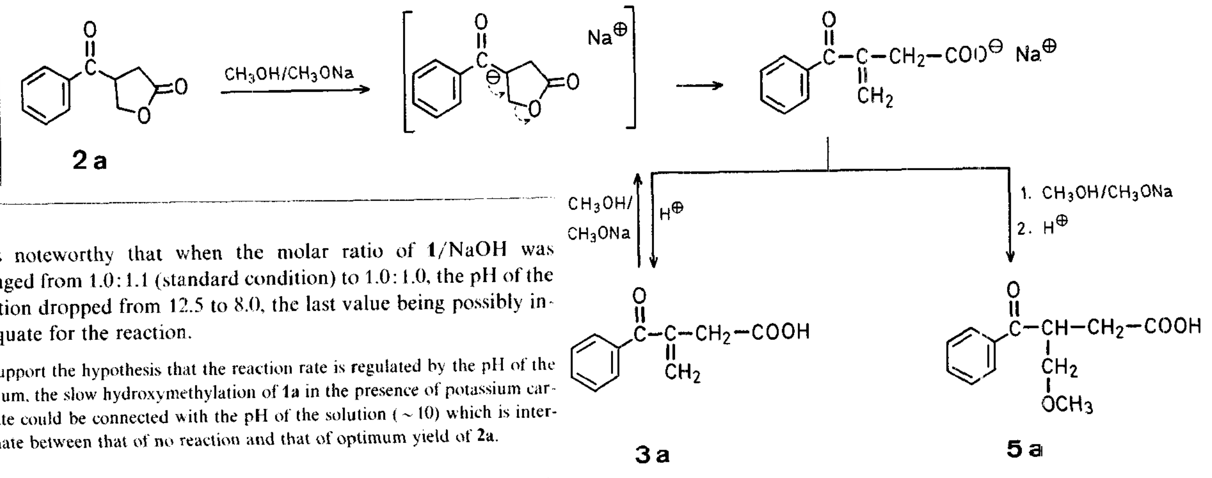


Schema A

hydroxide was used in a stoichiometrical amount, up to 90% of the starting **1** was recovered. On the contrary, if sodium hydroxide or formaldehyde were in a large excess (2.2 mol), 15–30% of 3-aroyl-3-butenoic acids **3**, or 15–20% of 4-aroyl-4-hydroxymethyl-2(3*H*)-dihydrofuranones **4** were formed besides other unidentified, resinous material, thus causing loss of the desired **2** (see Table 1).



Scheme B

It is noteworthy that when the molar ratio of **1**/NaOH was changed from 1.0:1.1 (standard condition) to 1.0:1.0, the pH of the solution dropped from 12.5 to 8.0, the last value being possibly inadequate for the reaction.

To support the hypothesis that the reaction rate is regulated by the pH of the medium, the slow hydroxymethylation of **1a** in the presence of potassium carbonate could be connected with the pH of the solution (~10) which is intermediate between that of no reaction and that of optimum yield of **2a**.

The structure of all compounds isolated was assigned on the basis of analytical and spectroscopic (I.R., N.M.R.) evidences (see Table 2). In particular, the N.M.R. spectrum of **3** was characterized by two apparent singlets near $\delta = 5.7$ and 6.0 ppm (actually an AB system with $J_{gem} < 0.5$ ppm[5]) attributed to the unsaturated methylene group, while the N.M.R. spectrum of **4** exhibited a singlet at about $\delta = 4.0$ ppm attributed to the methylene protons of the CH_2OH group. These spectral features were also taken as indicative of the presence of **3** and **4** in the crude reaction products.

The progression of events involved in the hydroxymethylation of **1** is shown in Scheme **A**. In alkaline medium and in the presence of formaldehyde the initially formed hydroxycarboxylic anion (**A**) is in equilibrium with the anion of **3** (**B**) and with the anion of the bis-hydroxymethylated carboxylic acid (**C**), the concentration of each species being influenced by the molar ratio **1**/CH_2O/NaOH. The reversibility of the reaction $\mathbf{A} \rightleftarrows \mathbf{B}$ and $\mathbf{A} \rightleftarrows \mathbf{C}$ was proved by experiments in which **2a**, **3a**, and respectively, **4a**, in 0.5 normal sodium hydroxide at room temperature for 1 h gave **3a** (35%), **2a** (28%), and respectively, **2a** (65%) and **3a** (15%).

While the formation of **4** in addition to **2** could be regarded as a normal event in the hydroxymethylation of ketocarboxylic acids with excess of formaldehyde[6], the formation of **3** was somewhat unexpected, at least under the mild conditions employed. To our knowledge, the only evidence consistent with our finding was the presence of methacrylophenone, inferred by N.M.R. monitoring, in the products of the hydroxymethylation of propiophenone with formaldehyde and potassium carbonate in methanol[7].

Finally, we report that, on studying the behavior of **2a** in alkaline medium, we succeeded in synthesing the butenoic acid **3a** in up to 60% yield by treating **2a** with 1% methanolic sodium methoxide at room temperature for 15 min, then quenching the reaction by acidification. On increasing the molar ratio CH_3ONa/**2a** to 3:1, the main reaction product was 3-benzoyl-4-methoxybutanoic acid (**5a**), also formed from **3a** and excess methanolic sodium methoxide at room temperature (Scheme **B**).

Hydroxymethylation of 3-Aroylpropanoic Acids 1; Typical Procedure:

37% Formaldehyde (22.3 ml, 0.30 mol) is added to a stirred solution of 3-benzoylpropanoic acid (**1a**; 48.1 g, 0.27 mol) in 0.5 normal sodium hydroxide solution (600 ml, 0.30 mol) (molar ratios of **1**/CH_2O/NaOH = 1.0:1.1:1.1). After 1 h at room temperature, the mixture is is acidified with concentrated hydrochloric acid (~30 ml) and stirred for additional 12 h. The semi-solid product which separates is triturated with ether (250 ml) to give *4-benzoyl-2(3H)-dihydrofuranone* (**2a**); yield: 41.1 g (80%); m.p. 63–65 °C.

The ether-soluble fraction is chromatographed on silica gel, eluting with benzene/acetone (95:5); there are collected in succession **2a**; yield: 0.5 g (1%) and *3-benzoyl-3-butenoic acid* (**3a**); yield: 7.5 g (15%).

The hydroxymethylation of **1** was also carried out with different molar ratios of reagents. The results obtained are summarised in Table 1.

Table 1. Hydroxymethylation of **1** with Formaldehyde in Dilute Sodium Hydroxide Solution (1 h at room temperature)

Substrate No.	R	Molar ratio of **1**/CH_2O/NaOH	Relative Yields [%] of Products **2**	**3**	**4**
1a	H	1:1.1:1.1[a]	81	15	—
		1:1.1:2.2[b]	45	22	—
		1:2.2:1.1	48	trace	19
1b	Br	1:1.1:1.1	74	trace	trace
		1:1.1:2.2	51	29	—
		1:2.2:1.1	65	—	20
1c	CH_3	1:1.1:1.1	80	trace	—
		1:1.1:2.2	75	15	—
		1:2.2:1.1	55	—	19

[a] In 0.5 normal sodium hydroxide solution.

[b] In 1.0 normal sodium hydroxide solution.

Table 2. Characterisation of Products **1–5**

Product	m.p. [°C] (solvent) or b.p./torr	Molecular formula[a] or Lit. m.p. [°C]	I.R. (nujol of film)[b] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS)[c] δ [ppm]
1a	115–119° (water)	111–113°[8]	1700, 1675	10.6 (br.s, 1H, COOH); 8.2–6.9 (m, 5H_{arom}); 3.33 + 2.81 (2 apparent t, 4H, CH_2CH_2)
1b	147–150°	148–149°[9]	1700, 1672	7.69 (apparent q, 4H_{arom}); 7.0 (br.s, 1H, COOH); 3.26 + 2.78 (2 apparent t, 4H, CH_2CH_2)
1c	125–129° (water)	111°[10]	1700, 1670	10.0 (br.s, 1H, COOH); 7.57 (apparent q, 4H_{arom}); 3.30 + 2.81 (2 apparent t, CH_2CH_2); 2.41 (s, 3H, CH_3)
2a	63–65° (ether)	63–65°[1]	1761, 1679	8.2–7.3 (m, 5H_{arom}); 4.8–4.0 (m, 3H, CH, CH_2O); 3.1–2.7 (m, 2H, CH_2CO)
2b	98–100° (methanol)	98–100°[1]	1773, 1678	7.70 (apparent q, 4H_{arom}); 4.7–4.0 (m, 3H, CH, CH_2O); 3.1–2.7 (m, 2H, CH_2CO)
2c	85–87° (ethanol)	$C_{12}H_{12}O_3$ (204.2)	1765, 1672	7.51 (apparent q, 4H_{arom}); 4.8–3.9 (m, 3H, CH, CH_2O); 3.2–2.7 (m, 2H, CH_2CO); 2.41 (s, 3H, CH_3)
3a	60–65° 150–155°/0.5	$C_{11}H_{10}O_3$ (190.2)	1701, 1676, 1648	9.5 (br.s, 1H, COOH); 8.1–7.1 (m, 5H_{arom}); 5.98 + 5.77 (2 apparent s, 2H, $=CH_2$); 3.54 (s, 2H, $C\underline{H}_2COOH$)
3b	82–85°	$C_{11}H_9BrO_3$ (269.1)	1708, 1675, 1649	10.2 (br.s, 1H, COOH); 7.60 (apparent s, 4H_{arom}); 6.01 + 5.75 (2 apparent s, 2H, $=CH_2$); 3.53 (s, 2H, $C\underline{H}_2COOH$)
3c	130–135°/0.5	$C_{12}H_{12}O_3$ (204.2)	1700, 1670, 1645	10.5 (br.s, 1H, COOH); 7.39 (apparent q, 4H_{arom}); 5.95 + 5.75 (2 apparent s, 2H, $=CH_2$), 3.50 (s, 2H, CH_2COOH); 2.38 (s, 3H, CH_3)
4a	75–80° (ether)	$C_{12}H_{12}O_4$ (220.2)	3400, 1750, 1663	8.0–7.3 (m, 5H_{arom}); 4.61 (s, 2H, CH_2O); 3.96 (s, 2H, CH_2OH); 3.00 (d, 2H, CH_2CO)
4b	120–122° (methanol)	$C_{12}H_{11}BrO_4$ (299.1)	3350, 1780, 1665	7.63 (apparent s, 4H_{arom}); 4.61 (s, 2H, CH_2O); 3.97 (s, 2H, CH_2OH); 3.00 (d, 2H, CH_2CO)
4c	109–111° (ethanol)	$C_{13}H_{14}O_4$ (234.2)	3400, 1740, 1662	7.47 (apparent q, 4H_{arom}); 4.62 (apparent s, 2H, CH_2O); 3.99 (s, 2H, CH_2OH); 2.99 (d, 2H, CH_2CO); 2.41 (s, 3H, CH_3)
5a	68–71° 165–170°/0.5	$C_{12}H_{14}O_4$ (222.2)	1700, 1679	8.6 (br.s, 1H, COOH); 8.2–7.3 (m, 5H_{arom}); 4.4–2.4 (m, 5H, CH_2CHCH_2); 3.24 (s, 3H, OCH_3)

[a] The microanalyses were in satisfactory agreement with the calculated values (C ± 0.20, H ± 0.17, Br ± 0.16).

[b] Perkin-Elmer 297 spectrophotometer.

[c] Hitachi Perkin-Elmer R-24A spectrometer.

3-Benzoyl-3-butenoic Acid (3a) and 3-Benzoyl-4-methoxybutanoic Acid (5a) from 2a:

A mixture of **2a** (14.6 g, 76.7 mmol) in 1% methanolic sodium methoxide (176.3 ml, 76.7 mmol) is stirred for 15 min at room temperature and then acidified to pH 3 with dilute hydrochloric acid. The methanol is removed in vacuo without applied heat, and the residual oil is taken up in ether (200 ml), washed with water, and extracted with 5% sodium hydrogen carbonate solution (130 ml). The aqueous layer is acidified to pH 2 and extracted with ether (200 ml) to give, after evaporation of the solvent, an oily residue (12.5 g) consisting of **3a** and a small quantity of **5a**.

Attempts to isolate **3a** by distillation in vacuo (150–160 °C/0.5 torr) result in extensive polymerisation. Better results are obtained by chromatography on silica gel eluting with benzene/acetone (98:2), which gives pure **3a**; yield: 60%.

The reaction repeated under the above conditions but with excess (3:1) of 5% methanolic sodium methoxide gives a crude product roughly composed of 85% **5a** and 15% **3a** (N.M.R. analysis), which is chromatographed on silica gel eluting with benzene/acetone (98:2), to give foreruns consisting of **3a** and **5a** in admixture, followed by pure **5a**; yield: 64%; m.p. 68–71 °C.

Acid **5a** is also obtained in 70% yield by allowing **3a** to react with 5% methanolic sodium methoxide in a molar ratio of 1:3 for 15 min at room temperature.

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