SHORT PAPER

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A water based method for hydroxymethylation of phenols and phenolic ketones†

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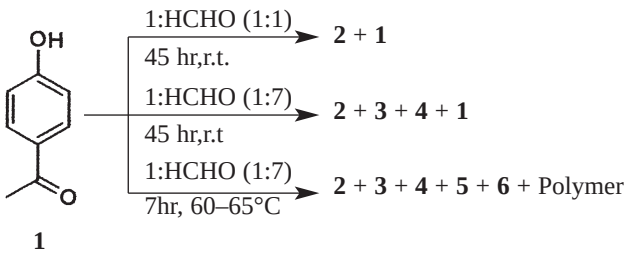
A water based eco-friendly method for the hydroxymethylation of phenols and phenolic ketones has in good yield been developed.

Keywords: hydroxymethylation, phenols, phenolic ketones

Many hydroxymethylated phenols and phenolic ketones find use as intermediates in the preparation of artificial sweetners,[1] antiulceratives,[2] anticonvulsives[3], antiarrhythmatics[4] and pesticides[5] and in different other organic syntheses. The reported methods of hydroxymethylation are not clean and use environmentally unfavourable toxic metal catalysts[6] and solvents, high-pressure[7] reaction conditions and in certain cases the yields[8-11]/are poor.

In connection with our work on the enantioselective synthesis of β-adrenoreceptor agonists[12] we were looking for a green route for the preparation of 3-hydroxymethyl-4-hydroxyacetophenone (2). In this paper we report a method for hydroxymethylation of phenolic ketones. The method uses water as solvent, is easy to operate, safe and environmentally-friendly.

We carried out the hydroxymethylation of 4-hydroxyacetophenone (1) with paraformaldehyde (1:1) in the presence of water, hydrochloric acid and acetic acid (1:1:0.2) keeping the molar concentration of **1** at 0.03 M. The reaction produced **2** at room temperature after 45 hours with low yield (Table 1, entry 1). When the ratio of **1** to paraformaldehyde was raised to 1:7 it produced **2**, 6-acetyl-1,3-benzodioxane **(3)** and 6-acetyl-8-hydroxymethyl-1,3-benzodioxane **(4)** and some of **1** remained unreacted. When the reaction was carried out at 60-65°C for 7 hours **2**, **3**, **4** and 3-chloromethylacetophenone **(5)** were formed with traces of **6** and polymeric material (Scheme 1**)**. The compound **3** was hydrolysed to **2 by** refluxing in dilute hydrochloric acid.



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Scheme 1

Hydroxymethylation of **3** to **4** was prevented when the reaction was carried out in a two-phase solvent system of water and petroleum ether. It was found that the compound remained in the organic phase and did not react with formaldehyde to form **4.**

The compound *m*-hydroxyacetophenone (**7**, entry 2) responded to the reaction poorly forming about 20% of 2-hydroxymethyl-3-hydroxyacetophenone **(8)** and 8% of 5-acetyl-1,3-benzodioxane **(9)** with traces of polymeric product. Phenol **(10)** and formaldehyde (1:3) produced *o*-hydroxy benzyl alcohol (**11**, 7%) and *p*-hydroxy benzyl alcohol (**12**, 68%) and only a small amount of 4H-1,3-benzodioxin **(13)** (3%), when heated for 20 hours under the above conditions. Increase of the amount of formaldehyde facilitates polymerization. The reaction did not proceed with *p*-nitrophenol in agreement with an earlier observation.[13]

The reaction of 2-hydroxy-5-methyl acetophenone **(14)** was interesting (Entry 4). It did not form any 1,3-benzodioxane compound unlike **1** and 4-hydroxy-3-methyl acetophenone **(18)**. The strong H- bonding between the phenolic hydroxyl group and the carbonyl group of 2-hydroxy-3-hydroxymethyl–5-methylacetophenone **(15)** probably prevented the formation of 1,3-benzodioxane compound. The effect of H-bonding is evident as 6-acetyl-8-methyl-1,3-benzodioxane **(20)** was formed as a major product from 4-hydroxy-3-methyl acetophenone **(18)**.

Conclusion

In conclusion we report here a novel method of synthesis of hydroxymethyl acetophenones with water as the sole solvent.

Experimental

Melting points reported were uncorrected. PMR spectra were recorded on a Varian T-60 NMR spectrometer, IR spectra were recorded on a Perkin Elmer 237B spectrometer and mass spectra on an AEI MS Finnigan Mat 50 spectrometer. C, H analyses were carried out on a Perkin-Elmer 2400 instrument.

1a.Preparation of 4-hydroxy-3-hydroxymethylacetophenone **(2)**: 4-hydroxyacetophenone (1) 1.36 g (0.11 mol) was taken in distilled water (150 ml). To it was added hydrochloric acid (150 ml) and acetic acid (30 ml). Paraformaldehyde (2.19) was added at room temperature and stirred at this temperature for 5 hours. The TLC was checked and the mixture was heated at 60–65°C under constant vigorous stirring. The reaction continued for about 7 hours. After that the crude reaction mixture was cooled and filtered. The polymeric material (6%) was removed and the mixture extracted in ethyl acetate (3 × 100 ml). The extract was concentrated by distillation under vacuum and passed through a silica gel column and the products were isolated on eluting with a pet. ether, dichlorormethane and ethyl acetate solvent mixture in the ratio 2.5:1.5:1. The products were identified as: (i) 4-hydroxy-3-hydroxymethylacetophenone (**2**, 0.61 g, 37%); (ii) 6-acetyl-1,3-benzodioxane (**3**, 0.82 g, 46%); (iii) 3-chloromethyl-4-hydroxyacetophenone (**5**, 0.05g, 3–4%,). The spectral data of all these compounds were found to tally with the data reported in the literature;[15,16] (iv) 6-acetyl-8-hydroxymethyl-1, 3-benzodioxane **(4)** (0.10gm, 5%),^{1}H NMR($CDCl_3$): δ ppm 2.36 (s, 3H, $COCH_3$), 4.46(s,2H, CH_2OH), 4.70(s,2H, CH_2–O–C), 5.06(s, 2H,–O–CH_2–O), 7.20, (d, 1H, *J*=2Hz, Ar-5-H), 7.62(d, 1H, *J*=2 Hz, Ar-7-H); IR (KBr) cm^{-1} 3311, 3029, 1696, 1577, 1503, 1400, 850; EIMS 208(M^+); Microanalysis Found C 63.33, H 5.69, $C_{11}H_{12}O_4$ Requires C 63.46, H 5.76%, (v) 3-hydroxymethyl-4-hydroxy-5-(2′-hydroxy-5′-acetyl benzyl)acetophenone **(6)** ^{1}H NMR(CD_3COCD_3):δ ppm 2.06(s, 3H,$COCH_3$), 4.16(d,2H, *J*=10Hz, Ar-CH_2-Ar), 4.40(d, 2H, CH_2OH), 6.33(d, *J*=9Hz, Ar-5′-H), 7.21(d, 2H, *J*=2Hz, Ar-2-H and 6-H),

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table

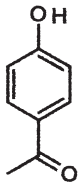
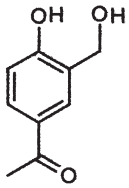
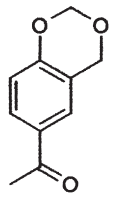
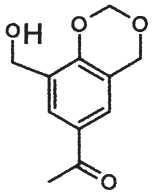
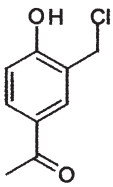
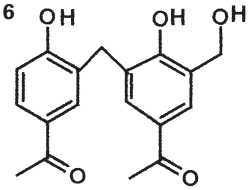
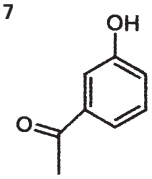
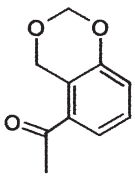
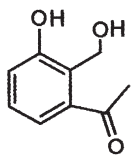
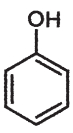
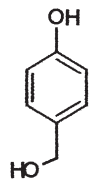
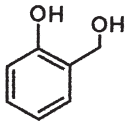
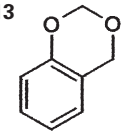
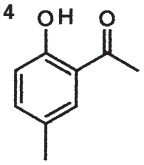
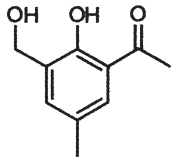
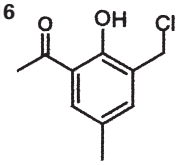
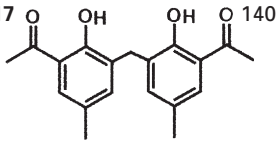
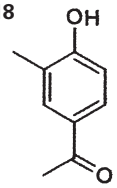
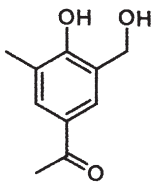
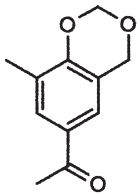
Entry	Substrate (no.)	Substrate: paraformaldehyde	Reaction time /h	Reaction temperature/°C	Catalyst	Product (no.)	M.p./°C ref (lit)
1	**1** 	1:7	7	60–65	Acetic acid	**2** 	116 (116)[15]
						3 	65 (66–67)[18].
						4 	156
						5 	159 (160)[15]
						6 	168
2	**7** 	1:7	7	65	Acetic acid	**8** 	65
						9 	105–107
3	**10** 	1:3	20	65	Acetic acid	**11** 	84 (83–85)[14,20]
						12 	117 (118)[14,20]

Table *continued*

Entry	Substrate (no.)	Substrate: paraformaldehyde	Reaction time /h	Reaction temperature/°C	Catalyst	Product (no.)	M.p./°C ref (lit)
						13 	Oil (12)[19]
3	**14** 	1:9	5	60-70	Acetic acid	**15** 	81 (81)[16,17]
						16 	59 (59–60)[16,17]
						17 	140
4	**18** 	1:12	4	70		**19** 	101
						20 	63

7.36(d, 1H, *J*=9Hz, Ar-3′-H), 7.44 (dd, 1H, *J*=2 and 9hz, Ar-4′-H and 6′-H); IR (KBr) cm^{-1} 3200, 3020, 1750, 1600, 1575, 1503, 1250, 800; EIMS 314(M^+); Microanalysis Found C 68.73, H 5.68, $C_{11}H_{12}O_4$ Requires C 68.79, H 5.73%.

1b. Hydrolysis of 6-acetyl 1,3-benzodioxane **(3)**: 0.80 g of 6-acetyl-1, 3-benzodioxane **(3)** was taken in 10 ml dilute hydrochloric acid and refluxed for 2 hours. After that the reaction mixture was extracted with ethyl acetate which was washed several times with water. Then the extract was dried over anhydrous sodium sulfate and the ethyl acetate was removed under reduced pressure to give 0.59 g (80%) 4-hydroxy-3-hydroxymethyl acetophenone **(2)**. The overall yield of 4-hydroxy-3-hydroxymethyl acetophenone **(2)** in the combined (i) and (ii) was 66.12%.

2a. Hydroxymethylation of 3-hydroxyacetophenone (7): The same procedure was followed as described in 1a. 3-Hydroxy acetophenone (7):1 g, formaldehyde (37%) solution: 4.25 ml, distilled water: 150 ml, hydrochloric acid: 150 ml, acetic acid (catalyst): 0.1 g. The products obtained were: 2-hydroxymethyl-3-hydroxyacetophenone (8,0.24g,20%),:^{1}H NMR ($CDCl_3$ with CD_3COCD_3)): δ ppm 1.83 (s,3H,$COCH_3$), 3.96(s,2H, CH_2OH), 6.06–7.33(m,4H,Ar.-H); IR (KBr)cm^{-1}, 3350, 2975, 1670, 1550, 1340, 850; EIMS: 166 (M^+), Microanalysis Found C 64.87, H 4.89, $C_9H_{10}O_3$ requires C 65.06, H 5.06%; 5-Acetyl-1, 3-benzodioxane (9,0.10gm, 8%): ^{1}H NMR ($CDCl_3$): δ ppm 2.30 (s, 3H, $COCH_3$), 4.56(s, 2H, C–CH_2O–C), 4.92(s, 2H, O–CH_2–O), 6.56–7.30(m, 4H, Ar.-H); IR (KBr) cm^{-1}, 2950, 1730, 1550, 1460, 850; EIMS: 178 (M^+), Microanalysis Found C 67.39, H 5.55, $C_{10}H_{10}O_3$ requires C 67.41, H 5.62%.

2b. Hydrolysis of 5-acetyl 1,3-benzodioxane **(9):** Same as described in **1b.** Yield of 2-hydroxymethyl-3-hydroxyacetophenone **(8)** 0.080 g (82%). Overall yield of 2-hydroxymethyl-3-hydroxy acetophenone **(8)** is 0.32 g(27%).

3a. Hydroxymethylation of phenol **(10):** Same procedure was followed as described in 1a. Phenol**(9)**: 0.93 g, paraformaldehyde: 0.90 g,distilled water: 150 ml, hydrochloric acid: 150 ml, acetic acid: 30 ml. Yield of *p*-hydroxybenzyl alcohol **(11)**: 0.84 g (68%), *o*-hydroxybenzyl alcohol **(12)**: 0.086 g (7%), 4H-1, 3, 2-benzodioxin **(13)**: 0.04 g (3%).

3b. Hydrolysis of 4H-1, 3, 2-benzodioxin **(13):** Same procedure was followed as described in 1b. Yield of *o*-hydroxybenzyl alcohol: 0.029g (80%). Overall yield of *o*-hydroxybenzyl alcohol: 0.115 g (9.20%).

4a.Hydroxymethylation of 2-hydroxy-5-methylacetophenone **(14)**: Same procedure was followed as described in 1a. 2-hydroxy-5-methylacetophenone **(14)**: 1.5 g, paraformaldehyde: 2.7g, distilled water: 150 ml, hydrochloric acid: 150 ml, acetic acid: 30 ml. The products obtained were 2-hydroxy-3-hydroxymethyl-5-methylace-

tophenone(**15**, 1.19g,66%)), 3-chloromethyl-2-hydroxy-5-methyl acetophenone (**16**, 0.05g, 3%) and *bis* (2-hydroxy-3-acetyl-5-methylphenyl) methane (**17,** 0.31g, 10%**).** Compound **15** and **16** were characterised by comparing their physical and spectral data with the values reported in the literature[16,17].

4b. Bis (2-hydroxy-3-acetyl-5-methylphenyl) methane (17): ^{1}H NMR ($CDCl_3$): δ ppm 2.20(s, 6H, aromat $2xCH_3$), 2.55(s, 6H, $2\times COCH_3$), 3.88(s, 2H, Ar-CH_2-Ar) 7.06–7.25(m, 4H, Ar.-H); IR (KBr) cm^{-1} 3207, 3060, 1710, 1580, 1460, 822; EIMS: 312 (M^+), Microanalysis Found C 73.01, H 6.33, $C_{19}H_{20}O_4$ requires C 73.07, H 6.41%.

5a. Hydroxymethylation of 4-hydroxy-3-methylacetophenone **(18):** As above. 4-Hydroxy-3-methylacetophenone **(18)**: 1.5 g, para-formaldehyde: 3.6 g, distilled water: 150 ml, hydrochloric acid: 150 ml, acetic acid: 30 ml. The products obtained were 4-hydroxy-3-hydroxymethyl-5-methylacetophenone (**19**, 0.86g, 20%). and 6-acetyl-8-methyl-1, 3-benzodioxan (**20**, 2.7g, 70%): (i) **19:** ^{1}H NMR($CDCl_3$): δ ppm 2.21(s, 3H, aromat.-CH_3), 3.03(s, 3H, $COCH_3$), 4.20 (s, 2H, CH_2OH), 7.27 (d, *J*=2 Hz, 1H, Ar-2-H), 7.83(d, *J*=2Hz.1H, Ar-6-H), 10.10 (bs, 1H, phenolic –OH); IR (KBr): cm^{-1}, 3250, 3190, 3030, 1665; EIMS: 180 (M^+); Microanalysis Found C 66.48 H 6.51 $C_{10}H_{12}O_3$ requires C 66.66% H 6.66%. (ii) **20**: ^{1}H NMR($CDCl_3$): δ ppm 2.10(s, 3H, Ar–CH_3), 2.30(s, 3H, Ar–$COCH_3$), 4.80(s, 2H, ArCH_2–O–), 5.20(s, 2H,–OCH_2O–), 7.00-7.66(m, 2H, Ar-H); IR (KBr): cm^{-1} 3045, 1680, 1620, 1490, 1100; EIMS: 192(M^+); Microanalysis: Found C 68.65 H 6.11 $C_{11}H_{12}O_3$ requires C 68.75 H 6.25%.

5b. Hydrolysis of 6-acetyl–8-methyl-1,3-benzodioxane **(20):** Same procedure was followed as described in procedure 1b**.** Yield of 4-hydroxy-3-hydroxymethyl-5-methyl acetophenone **(19)**: 1.00 gm (80%). Overall yield of 4-hydroxy-3-hydroxymethyl-5-methyl acetophenone **(19)** in the whole reaction: 1.36 g (75%).

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