An efficient and practical synthesis of β-hydroxyl ketones catalysed by trisodium phosphate under ultrasound

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In the presence of trisodium phosphate, cross-aldol reactions of reactive aldehydes with substituted acetophenone in CH_3OH-water mixed solvent afford β-hydroxyl ketones in good to excellent yields under ultrasound irradiation.

Keywords: aldol condensation, β-hydroxyl ketones, synthesis, trisodium phosphate, ultrasound

The aldol condensation is one of the most important carbon–carbon bond-forming reactions in organic chemistry.[1] Over the past several years, research in the area of aldol type addition reactions has dramatically increased. This is due, in part, to the large number of important natural products containing the β-hydroxyl carbonyl unit.

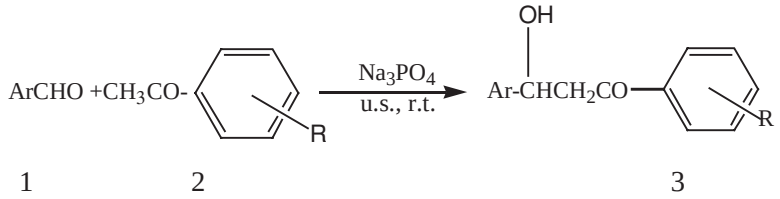
Aldol reaction have been classically conducted in the presence of a strong base or acid.[2] However, under such conditions, the synthesis of the desired aldol product is plagued by the formation of the concomitant α,β-unaturated ketone, Michael addition to the formed enone, and so on. To overcome these problems, various Lewis acids[3] or bases[4] have been employed as alternative catalysts, but in most cases the ketones need to be modified as silyl enol ethers, ketene silyl acetals, *etc*. Meanwhile, aldol reactions can also be carried out in the presence of phase-transfer catalysts such as TBAF[5] and calix [6] arene derivatives[6] or without catalyst[7], but the ketones also need to be modified. In recent years, proline-catalysed aldol reactions in aqueous micelles have been reported.[8] In addition, potassium phosphate was found to catalyse the condensation of nitroalkanes with various aliphatic and aromatic aldehydes to form nitroaldols. Most recently, Na_2CO_3 has been used to promote aldol reactions of unmodified ketones with reactive aldehydes in pure water.[10] However, in spite of their potential utility, some of the reported methods suffer from drawbacks such as longer reaction times and lower yields.

Ultrasound (U.S.) has increasingly been used in organic synthesis in the last three decades. Compared with traditional methods, the procedure is more convenient and easily controlled. A large number of organic reactions can be carried out in higher yields, shorter reaction times or milder conditions under ultrasonic irradiation.[11] Herein we present the highly efficient and practical aldol reactions of unmodified ketones with reactive aldehydes bearing electronic-withdrawing groups in CH_3OH-H_2O catalysed by trisodium phosphate under ultrasound irradiation (Scheme 1**)**

Results and discussion

As shown in Scheme 1 and Table 1, the synthesis of β-hydroxyl ketones was carried out in good to excellent yield for the aldol reaction of reactive aromatic aldehydes with acetophenone catalysed by trisodium phosphate under ultrasound. The dramatic improvement observed is with regard to reaction time. In the reaction catalysed by Na_2CO_3 in water **3a** and **3b** were obtained in 95% and 94% yield by stirring at room temperature for 3 h and 10 h respectively, whereas the present procedure results in 98% and 91% yield respectively within 90 min. It shows that the aldol reaction can be completed with a nearly quantitative yield in a shorter time under ultrasound irradiation.

The amount of catalyst and temperature had a significant effect on the reaction. When using 0.5 mol equivalent trisodium phosphate, the condensation of *m*-nitrobenzaldehyde (**1b**)



Scheme 1

Table 1 Synthesis of β-hydroxyl ketones catalysed by trisodium phosphate under ultrasound

Entry	Ar	R	T/min	Product	Yield[a]/% (lit.)	M.p./°C (lit.)
a	*p*-$NO_2C_6H_4$	H	90	**3a**	98 (95)[10]	111–113(112–114)[10]
b	*m*-$NO_2C_6H_4$	H	90	**3b**	91 (94)[10]	83–85(84–86)[10]
c	*p*-ClC_6H_4	H	150	**3c**	85	97–99(96–96.5)[12]
d	2,4-$Cl_2C_6H_3$	H	210	**3d**	98	89–92
e	*p*-$NO_2C_6H_4$	*m*-NO_2	55	**3e**	96	130–132
f	*m*-$NO_2C_6H_4$	*m*-NO_2	10	**3f**	99	120–122
			120	**3f**	81[b]	120–122
			10	**3f**	92[c]	120–122
			10	**3f**	95[d]	120–122
g	2,4-$Cl_2C_6H_3$	*m*-NO_2	235	**3g**	98	122–124

[a]Isolated yield based on aromatic aldehydes [b] Stirred without ultrasound. [c]With a frequency of 59 kHz.
[d] With a frequency of 40 kHz. e Formally a tentative assignment – see experimental section.

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with acetophenone (**2b**) resulted the chalcone in 92% yield. In fact, using 0.25 mol equivalent trisodium phosphate for the same reaction, the desired product β-hydroxyl ketone (**3b**) was obtained in 91% yield. When the reaction temperature was higher than 42 ˚C, the dehydration of β-hydroxyl ketones formed took place to give chalcones. So the temperature was controlled to under 32 ˚C.

The aromatic aldehydes bearing electron-withdrawing groups could undergo the Na_3PO_4-catalysed aldol reaction at room temperature and give selectively the β-hydroxyl ketones under ultrasound, while benzaldehyde and the aromatic aldehydes bearing electron-donating groups did not react with acetophenone under these condition. When ethyl cyanoacetate was used as the active methylene compound to react with aromatic aldehydes, we could not achieve the desired β-hydroxyl ketones but the dehydration products, ethyl alkylidene α-cyanoacetates were obtained.

In order to verify the effect of ultrasound irradiation, we have performed the reaction of *m*-nitrobenzaldehyde with *m*-nitroacetophenone by stirring for 120 min at room temperature without sonication. The yield of **3f** was 81%. While under ultrasound the reaction can be completed in 10 min in 99% yield. This demonstrates that ultrasound irradiation improved the results. We also observed the effect of different frequencies of ultrasound irradiation on the reaction. When the frequency was 25 kHz, the condensation of *m*-nitrobenzaldehyde to *m*-nitroacetophenone resulted in the desired product **3f** in 99% yield within 10 min. While the frequency was 59 kHz and 40 kHz, the reaction was carried out in 92% and 95% yield respectively within 10 min. It seems that the frequency of irradiation did not have a significant effect on the yield.

In conclusion, we have provided an efficient and practical synthesis of β-hydroxyl ketones catalysed by trisodium phosphate under ultrasound irradiation.

Experimental

Melting points were uncorrected. IR spectra were recorded on a Bruker VECTOR 22. ^{1}H NMR spectra were measured on a Bruker ADVANCE 400 (400 MHz) spectrometer using TMS as internal standard and $CDCl_3$ as solvent. Sonication was performed on a Shanghai Branson-CQX ultrasonic cleaner (with a frequency of 25 kHz and a nominal power of 250 W) and an SK 250 LH ultrasonic cleaner (with a frequency of 59 kHz and 40 kHz and a nominal power of 250 W; Shanghai Kudos Ultrasonic Instrument Co., Ltd.). The reaction flask was located in the maximum energy area in the cleaning bath and addition or removal of water was used to control the temperature of the water bath.

General procedure: To a solution of aromatic aldehyde (**1**, 1 mmol) and acetophenone (**2**, 1.05 mmol) in CH_3OH-H_2O mixture (v/v =1:2) was added trisodium phosphate (0.25 mmol). The mixture was irradiated in a water bath of an ultrasonic cleaner at 25–32 ˚C for the length of time as indicated in Table 1 (Sonication was continued until crystals appeared or the aldehyde had disappeared as indicated by TLC). After the reaction was completed, the aldol product (**3**) was collected by filtration and washed with water. The pure product was obtained by chromatography on silica gel (200–300 mesh) eluted with petroleum ether or a mixture of petroleum ether and acetone. The authenticity was established by comparing their melting points with literature[10,12] and the spectral data of ^{1}H NMR, IR. For **3d–f** the structural assignments are tentative in the absence of full characterisation data and based on the IR and ^{1}H NMR data

3d: ν_{max} (KBr): 3504, 3064, 2911, 2851, 1667, 1588, 1470, 862, 797, 755, 729 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.28–7.99 (m, 8H, Ar–H), 5.64–5.66 (m, 1H, CH), 3.92 (s, 1H, OH), 3.54–3.58 (m, 1H, CH_2), 3.10–3.17 (dd, 1H, *J*=9.6, 17.2 Hz, CH_2) ppm.

3e: ν_{max} (KBr): 3486, 3087, 1672, 1606, 1534, 1436, 1347, 844, 811, 704 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.65–8.88 (m, 8H, Ar–H), 5.53–5.55 (m, 1H, CH), 3.40–3.52 (m, 3H, OH and CH_2) ppm.

3f: ν_{max} (KBr): 3466, 3091, 2916, 1688, 1614, 1581, 1525, 1349, 878, 738, 701 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.59–8.80 (m, 8H, Ar–H), 5.52–5.56 (m, 1H, CH), 3.42–3.55 (m, 3H, OH and CH_2) ppm.

3g: ν_{max} (KBr): 3477, 3086, 2917, 1689, 1612, 1580, 1532, 1342, 864, 829, 745, 680 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.28–8.80 (m, 7H, Ar–H), 5.69–5.72 (m, 1H, CH), 3.52–3.57 (dd, 1H, *J*=2, 17.6 Hz), 3.49–3.50 (m, 1H, OH), 3.22–3.28 (dd, 1H, *J*=5.6, 17.6 Hz, CH_2) ppm.

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