Efficient and Clean Aldol Condensation Catalyzed by Sodium Carbonate in Water

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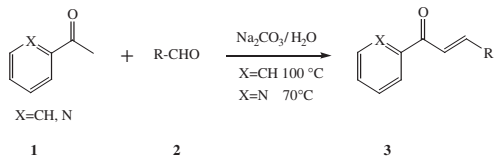
Efficient and environmentally friendly synthesis of chalcone and azachalcone was performed by aldol condensation of aldehydes with ketones in pure water catalyzed by sodium carbonate. In this convenient methodology, side reactions were avoided and thus high yields were achieved.

Based on their crucial role as intermediates in organic synthesis[1] and their chemical flexibility as synthons for the production of five- or six-membered-ring compounds,[2] the synthesis of chalcones and azachalcones has been extensively investigated over the past decades. Traditionally, the synthesis of these compounds is achieved from aromatic aldehyde and ketone with NaOH or KOH as the base in hydroalcoholic medium,[2–7] or strong bases in organic solvents.[8] Under these conditions, the aldol reactions give mixtures of ketols and α,β-unsaturated ketones,[5] and by-products from Michael addition, Cannizzaro reaction, and other side reactions are often formed.[4,7] It should be noted that Toda et al. reported the first example of aldol condensation in the absence of solvent.[5] For the stringent and growing environmental regulations, organic chemists are requested to develop clean, economical, and environmental safer methodologies. One of the most promising approaches is to utilize water as reaction medium. In recent years there has been increasing recognition that water is an attractive medium for many organic reactions.[9] The formation of chalcones from the reactions of aromatic ketones and cyclohexanone with aromatic aldehydes in water catalysed by NaOH has been reported.[10] However, in these reactions ketols were obtained and were even the main products in some cases. More recently, Kourouli et al.[11] reported the synthesis of α,β-unsaturated ketones by aldol condensation of liquid aldehydes with β-ketoacids in pure water with KOH as the base. Nevertheless, this protocol has the disadvantages of relatively low yield and tedious preparation of ketoacid from ketoester. To the best of our knowledge, there has been no report on the synthesis of chalcone and azachalcone by aldol condensation of aromatic aldehydes with ketones catalyzed by sodium carbonate in pure water.

The aldol condensations of ketones **1** with aldehydes **2** in water catalyzed by sodium carbonate were found to afford α,β-unsaturated ketones **3** in high yields (Scheme 1).

This protocol does not require the use of any organic solvent and only 25% molar equivalent of Na_2CO_3 is enough for this aldol condensation. In fact, the products were isolated in practically pure form simply by Büchner filtration of the final aqueous reaction mixture after cooling to room temperature.[12] In spite of the extremely low aqueous solubility of both ketones and aldehydes used, the reaction can still be carried out efficiently. The yields and reaction conditions for the aldol reactions of acetophenone and 2-acetylpyridine with various aromatic aldehydes are summarized in Table 1.



1 2 3

Scheme 1.

Noticeably, the aldol reaction of acetophenone can be carried out in refluxing condition without the occurrence of any side reaction in most cases. But for the aldol reaction of 2-acetylpyridine, it is not the case. To avoid the side reaction, it is necessary to control the temperature at 70 °C or below.

To investigate the effect of applied base on this aldol reaction, we performed the reaction of 4-nitrobenzaldehyde with 2-acetylpyridine in EtOH–H_2O systems catalyzed by sodium carbonate and sodium hydroxide, respectively (Table 2).

From Table 2, it can be seen that Na_2CO_3 is a superior base to NaOH in all EtOH–H_2O media and that this reaction is favoured in pure water although it involves the elimination of a molecule of water. Side reactions were obviously avoided in water compared in EtOH and EtOH–H_2O (1:1).

In conclusion, we have found that chalcone and azachal-

Table 1. Aldol condensations of ketones with aldehydes catalyzed by 25 mol% Na_2CO_3 in water

Product (**3**)[a]	R	X	Temp. /°C	Time /h	Yield[b] /%
3a	4-$NO_2C_6H_4$	CH	100	1	98
3b	3-$NO_2C_6H_4$	CH	100	7	97
3c	4-NCC_6H_4	CH	60[c]	6	97
3d	3,4-ClC_6H_4	CH	100	3	98
3e	4-ClC_6H_4	CH	100	8	84
3f	3,4-$CH_2O_2C_6H_3$	CH	100	10	88
3g[d]	2-pyridine	CH	70[c]	4	92
3h[d]	Ph	CH	100	32	61
3i	4-$NO_2C_6H_4$	N	70	0.5	98
3j	3-$NO_2C_6H_4$	N	70	1.5	98
3k	4-NCC_6H_4	N	60[c]	5	95
3l	3,4-ClC_6H_4	N	70	4	98
3m	4-ClC_6H_4	N	70	28	87
3n	3,4-$CH_2O_2C_6H_3$	N	70	10	89
3o[d]	2-pyridine	N	70	1	94
3p[e]	Ph	N	25[c]	25	68

[a]Products were properly characterized by mp, IR, ^{1}H NMR and ^{13}C NMR. [b]Isolated yield. [c]Higher temperature leads to obvious side reaction. [d]It is necessary to let the final reaction mixture stand overnight due to the relatively low melting point of the product. [e]Isolated by column chromatography on silica gel along with 21% of 3-phenyl-3-hydroxy-1-(2-pyridyl)-1-propanone. A black mixture was obtained due to side reactions under heating conditions.

Table 2. Aldol condensation of 4-nitrobenzaldehyde with 2-acetylpyridine catalyzed by sodium carbonate and sodium hydroxide in EtOH–H_2O media

Entry	Solv.	Catalyst (25 mol%)	Temp. /°C	Time /h	Yield /%
1	H_2O	Na_2CO_3	70	0.5	98
2	H_2O	NaOH	70	0.5	94
3	EtOH–H_2O	Na_2CO_3	Reflux	1	90
4	EtOH–H_2O	NaOH	Reflux	1	82
5	EtOH	Na_2CO_3	Reflux	1	87
6	EtOH	NaOH	Reflux	1	68

cone can be synthesized in good yields from aldehydes and ketones with catalytic amount of Na_2CO_3 in pure water. The use of water as reaction media and cheap Na_2CO_3 as catalyst, and the facile separation of the products by simple Büchner filtration make this protocol convenient, effective and environmentally friendly for the synthesis of α,β-unsaturated ketones.

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12 General procedure for the synthesis of unsaturated compounds **3**: A mixture of the selected aldehyde (1 mmol) and ketone (1.05 mmol) in 15-mL water was stirred vigorously in a preheated oil bath. Then a solution containing 0.25 mmol sodium carbonate in 5-mL water was added to the reaction mixture and allowed to react at the desired temperature. When the reaction was completed (followed by TLC), the reaction mixture was cooled to room temperature. The solid product was collected by Büchner filtration, washed with H_2O and dried in desiccator. Recrystallization from EtOH gave higher purity of the product.

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