

# CROSSED ALDOL CONDENSATION IN SUB-CRITICAL WATER

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The Aldol reaction of benzaldehyde with a number of donor ketones occurred rapidly in water at 280°C in 30 min. Effect of the addition of small amounts of NH<sub>3</sub> on the yield was also investigated. It is suggested that the addition of small amounts of NH<sub>3</sub> to sub-critical water (SbCW) can significantly increase the yields for aldol condensation of benzaldehyde by base-catalysis.

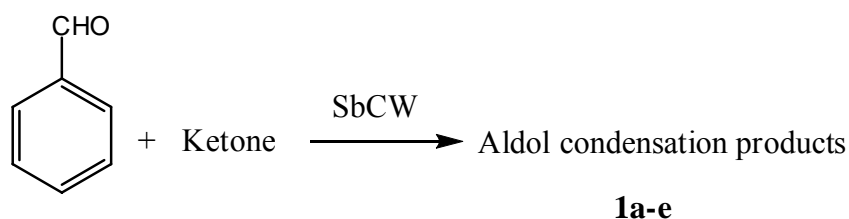
## INTRODUCTION

The aldol reaction is one of the most important methods for construction of carbon-carbon bonds and, usually carried out in protic solvents with base or acid as the catalyst and the post-reaction addition of base or acid to neutralize the solution, is one of the most versatile methods in organic synthesis(1). By application of this reaction a great number of aldols and related compounds have been prepared from various carbonyl compounds. However, because of difficulty in directing the coupling, the conventional method has serious synthetic limitations. This is particularly notable when two different carbonyl compounds are used in a cross-coupling; the reaction is often accompanied by undesirable side reactions such as self-condensation and polycondensation (2). New and powerful variants of these classical reactions have been developed in recent years. Two classes were mainly used for asymmetric induction in these reactions: the use of asymmetric modified enolates or electrophiles and the use of chiral Lewis acids.. A production method that eliminates the need for the base and acid would make this reaction more environmentally benign.

Green and sustainable chemistry, a new concept that arose in the early 1990s, gained wider interest. Green and sustainable chemistry concerns the development of processes and technologies that result in more efficient chemical reactions that generate little waste and fewer environmental emissions than "traditional" chemical reactions do. The use of water as solvent for organic reactions is one of the finest solutions to the problem of solvent toxicity and disposal (3). The chemistry in natural systems (biochemical reactions) is based on water. The use of water as solvent for synthetic chemistry holds great promise for the future in terms of the cheaper and less hazardous production of chemicals. Researchers in this area are discovering that reactions in water may be predisposed to favor transition states that optimize hydrophobic interactions, thereby achieving unusual, unique selectivity in organic reactions (4).

Sub-critical water has many advantages over the usual organic solvents. It is efficiently one of the cheaper solvent and so one of the most economic. It is also safer than the usual organic solvents. From an industrial point of view, the use of a two-phase system allows an easy separation of the products from water. Finally, water is environmentally friendly and could obviously diminish the problems of pollution by organic solvents.

In this study, we propose an alternative, fast and clean method using sub-critical water. First, we found that the reaction of benzaldehyde with acetophenone occurred rapidly in water at 280°C in 30 min.



**Figure 1:** Aldol reaction of benzaldehyde with donor ketones

## MATERIALS AND METHODS

**Materials.** Succinic acid; aniline; 2,5-dichloroaniline; propane-1-amine ; butane-1-amine ; hexane-1-amine are all analytical reagent grade and were obtained from Merck. All materials were used as received.

**Experimental Procedure.** Reactions were typically carried out at 280 C with 1:20 mol ratio of substrat and amine. First, the system was purged with high-purity nitrogen. A certain amount of succinic acid and amine were added to the reactor, together with 10 mL of degassed deionized water. After the temperature inside the reactor had reached the reaction temperature, reactions were carried out for 30 min. The pressure during the reaction depend on the substrats. After the reaction the reactor were removed from heater and cooled down quickly in an ice bath. The reactor contents were extracted with ether ( 6x3mL) and analyzed using Thermo-Finnigan GC-FID and GC-MS.

## Analysis

Reaction products were identified by Finnigan-Trace GC–MS equipped with an auto sampler and quantitative analysis was carried out by Finnigan-Trace GC- FID. One microlitre of sample volume was injected using split method with 50 split ratio. Chromatographic separations were accomplished with a Zebtron ZB-5 capillary column (5% phenyl–95% dimethylpolysiloxane, 0.25mm i.d.×60 m, film thickness 0.25  $\mu$ m). Analysis was carried out using helium as the carrier gas, flow rate 1.0 mL/min. The column temperature was programmed from 50 to 280 °C at 5°C/min with hold 10 min at 280°C. The injection port temperature was 250°C. The ionization voltage applied was 70 eV, mass range  $m/z$  41–400 a.m.u. The separated components were identified tentatively by matching with GC–MS results of National Institute of Standards and Technology (NIST) mass spectral library data because their reference reagent were not available.

## Mass spectral analysis results of products

Calcon **1a**: 208 (M+, 85), 207 (40), 131 (18) , 105 (30), 77 (100) , 51 (40)

1-penten-3-one,1- fenil **1b**: 160 (M+, 65), 131 (100) , 103 ( 90 ) , 77 (75), 51 (45)

3- büten 2 one 3- metil 4 fenil **1c**: 160 (M+,55) , 159 (95) , 145 (30) , 117 (85), 115 (100), 91 (35) , 43 (45)

Benzalpinacolone **1d**: 188 (M+,10), 146 (20), 131 (100), 103 (90) , 77 (85) ,51 (30)

(*E*)-2-benzylidenecyclohexanone **1e**: 186(M+, 100) , 128 (80), 115 ( 55), 91 (40) , 67 (45) , 39 (25)

## RESULTS

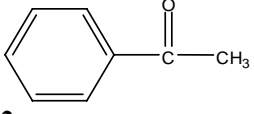
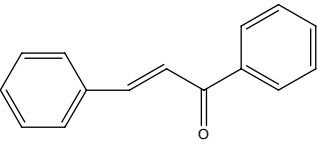
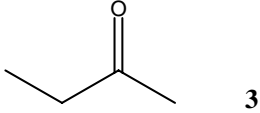
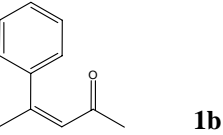
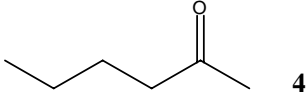
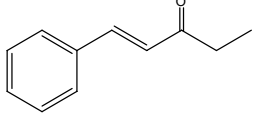
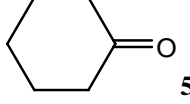
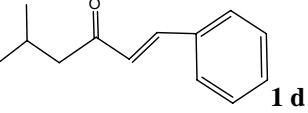
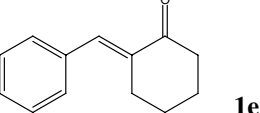
In an initial study, we examined the Aldol reaction (figure 1) among acetophenone and benzaldehyde without using any catalyst in the presence of water at 280 and 250°C. We found out that the reaction of benzaldehyde **1** with acetophenone **2** occurred rapidly in water at 280°C in 30 min with a good yield of calcone (50%). It was also observed that, the reaction was occurred enantioselectively (Table 1, entry 1). After first observations, we try to get more product yield. Since the Aldol reactions are a base catalysed reaction, the effect of the addition of small amounts of NH<sub>3</sub> was investigated. Only one drop NH<sub>3</sub> in 5 ml water was enough to increase the yield of **1a** from 50 to 80%. The optimum amount of water was found as 5 ml affording the product in good yield. The addition of excess water or NH<sub>3</sub> to the reaction mixture does not have any significant effects on the Aldol condensation reaction. Moreover, the reaction carried out with different ratios of substrats. The employment of a large excess of ketone in the reaction also afforded the product in good yield. The optimized conditions were achieved using 1:4 ratios of benzaldehyde to acetophenone. The optimized conditions were extended to a series of ketone donors to explore the generality of this green system and the results are summarized in Table 1.

In most cases, the Aldol products were obtained in good yields and high regioselectivities and enantioselectivities with only trace amounts of other aldol condensation side products. Regioselective enolate formation using kinetic deprotonation of an unsymmetrical ketone is possible using a strong base such as LDA at very low temperatures(5). However, in this study it was smoothly achieved by using SbCW. On the other side, unsymmetrical ketones normally results in a mixture of aldol products. This is not surprising considering the equilibration with the less-substituted enolate, the possible proton abstraction and self-condensation of the aldehyde and potential for enolization and further reaction of the product. In this study, we did not observed any mixed condensation products from the reaction of benzaldehyde with 4-methyl-2-pentanone **4** which is a candidate for two enolates while the aldol reaction of 2-butanone **3** with benzaldehyde gave a mixture of products **1b** and **1c** with the yields of 11% and 41%, respectively. Nevertheless, the major product was obtained from less substituted enolate. Both of 4-methyl-2-pentanone **4** and cyclohexanone **5** gave single isomers **1d** and **1e** with perfect product yields 95% and 99%, respectively.

## CONCLUSIONS

In summary, (1) Aldol condensation reaction of benzaldehyde with donor ketones has been realized with high regioselectivities in the presence of subcritical water with a simple procedure; (2) perfect Aldol condensation product yields were attained for both cyclohexanone and 4-methyl-2-pentanone (3) as a result of regioselectivity single products were obtained for all experiments except for 2-butanone; (4) addition of small amounts of NH<sub>3</sub> into SbCW significantly increased the yields for aldol condensation;(5) reactions must be extended for different donor ketones especially for cyclic ones.

**Table 1.** The results of Aldol condensation reaction of benzaldehyde with donor ketones in SbCW.

Entry	Ketone	Product	Yield (%)
1			80
2			11
3			41
4			95
			99

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