

## Rapid Knoevenagel condensation: unique reactivity of kaolin in aqueous suspension

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**Abstract:** A simple, efficient and environmental friendly route, using kaolin as a green catalyst for the Knoevenagel condensation in refluxing water in excellent yields, is reported.

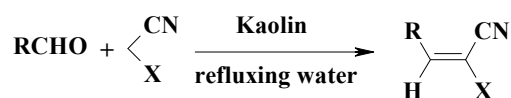
**Keywords:** Knoevenagel; Kaolin; Aqueous media; Reusable catalysts; Rapid reactions

### Introduction

Water is a desirable solvent for chemical reactions for reasons of cost, safety, and environmental concerns and the study of organic reactions in aqueous solvents has an intriguing history [1].

Knoevenagel condensation of carbonyl compounds on molecules containing an active methylene group is an important method for the preparation of substituted alkenes. Several important key products, such as nitriles used in anionic polymerization and  $\alpha,\beta$ -unsaturated ester intermediates employed in the synthesis of several therapeutic drugs, e.g., niphedipine and nitrendipine, etc have been synthesized via this condensation. This reaction has been widely studied under a variety of conditions, solvents and catalysts and is generally catalyzed by a base or a Lewis acid.

The Knoevenagel reaction in heterogeneous media has been carried out in the presence of alumina [2], silica [3], zinc, magnesium oxides [4], resins [5], and other catalysts [6-10]. Most of these reactions need long reaction times, toxic and expensive solvents or reagents. Recently Bigi and his co-workers have reported Knoevenagel condensation in water without catalyst in 1h [11]. However they did not claim the reaction of ethyl acetoesters with carbonyl compounds under the same conditions. In connection with our studies to implement organic reactions in eco-friendly manner [12-15] we explored the Knoevenagel condensation in water using kaolin as an inexpensive, available and eco-friendly catalyst (Scheme 1).



Scheme 1

### Results and Discussion

In recent years considerable emphasis has been placed on improvement in environmental impact of industrial chemical processes. However the toxic and volatile nature of many organic solvents, particularly chlorinated hydrocarbons which are widely used in

organic synthesis have still posed a serious threat to the environment. Recently organic reactions in solvent free system have gained popularity [14,15]. However in most of these reactions in work up procedures organic solvents are still used for extraction and separation.

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Despite such advances, solvents still play a critical role in making the process "liquids" and allowing molecular interactions to be more efficient. In such situations, search for alternative reaction media to replace organic solvents has attracted much attention from academia and industry [16]. Reactivity of organic compounds in aqueous media has been recently under attention and reviewed [17].

It is well recognized that solids can play a significant role in the development of cleaner technologies through their abilities to act as catalysts, support reagents, avoid aqueous work-up and influence product selectivity [18-19]. Aluminosilicate clays are well characterized by their surface acidities, which render them efficient and versatile supports or catalysts [20-22]. While montmorillonite (bentonites) has achieved very wide use, kaolin-based reagents or kaolin assisted reactions appear to be extremely limited [20,21]. Kaolin is a 1:1 layer lattice mineral and consists of successive layers of alumina and silica. It has been used in protection of carbonyl compounds [23], alkylation of benzene [24]

and bromination and chlorination of aromatic compounds [25].

The idea was examined by studying the effect of various solvents on the reaction times and yields in the synthesis of 1,1-dicyano-2-(4-chlorophenyl)ethylene as a model reaction. From the results given in Table 1 it can be concluded that by using kaolin, the solvent of choice for this reaction is water. As can be seen from Table 1 with water as solvent the reaction completed on shorter reaction time. Due to its well known characteristics such as being non-toxic, and its enormous abundance, water is superior to all organic solvents from both environmental and economical points of view. In this protocol, the use of water as solvent also simplified the final treatment of products. It is noteworthy to mention that both the catalyst and the product were not soluble in water so they could be separated as a mixture by simple filtration. Since the Kaolin is not soluble in ethanol the product could be isolated from the mixture by recrystallization from EtOH.

**Table 1:** Effects of different solvents in the model reaction.

Solvent	reaction time (h)	Yield (%) <sup>a</sup>
DMF	1	95
CHCl <sub>3</sub>	8	80
CH <sub>3</sub> CN	1.5	95
H <sub>2</sub> O	0.25	97

<sup>a</sup> Yields refer to isolated products.

Malononitrile and ethylcyanoacetate were used as active methylene sources. With the identification of appropriate reaction condition we investigated the suitability of this approach to a variety of other aldehydes such as benzaldehyde, 2-methyl benzaldehyde (activated), 3-NO<sub>2</sub> benzaldehyde (deactivated), furfural (heterocycle), to establish the generality of this method. The results are summarized in Table 2. It is worthwhile to mention that Knoevenagel condensation with ketones in this condition did not occur. We used acetophenone as an example of ketones which did not react in these conditions even after prolonged reaction time (24h).

Our studies showed, in this reaction kaolin is reusable and could be used for at least 5 runs for the condensation reaction. The results of the first experiment and our subsequent experiments on benzaldehyde were almost consisting in yields (90%, 85%, 83%, 82%, 80%).

## Conclusions

In summary, we have developed a novel, eco-friendly and efficient method for the Knoevenagel condensation using kaolin as an inexpensive, available, green and reusable catalyst in water. The advantages of the present method are the simplicity of work up, the high yields, short reaction times and the recyclability of the catalyst and most important using of water as solvent. We believe that this methodology can find usefulness in organic synthesis and industry. Once again we proved the venerable assumption "*corpora non agunt nisi soluta*" (substances do not interact unless dissolved) can be distinctly counterproductive.

## Experimental Section

All the chemicals were purchased from Merck Company. Melting points were measured by using the capillary tube method with an electro thermal 9200

apparatus.  $^1\text{H-NMR}$  spectra were recorded on a Bruker AQS AVANCE-500 MHz spectrometer using TMS as an internal standard ( $\text{CDCl}_3$  solution). IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. All products were well characterized by their physical

and spectral data. All products were known and characterized by comparison of their physical and spectra data with those of reported [10,26-30].

**Table 2:** Knoevenagel condensation using Kaolin as catalyst in aqueous media

Entry	R	x	Time(min)	Yield (%) <sup>a,b</sup>	m.p. (°C)	
					Found	Reported
1	Ph-	CN	15	90	87	84[26]
2	2-MeO Ph-	CN	5	90	134	114[26]
3	4-Me Ph-	CN	10	87	137-139	135[26]
4	4-Cl Ph-	CN	15	90	169	163[27]
5	4-OH Ph-	CN	15	90	184	Viscous liquid[28]
6	Furyl-	CN	75	89	69-71	72[26]
7	2-NO <sub>2</sub> Ph-	COOEt	90	80	103-104	96[29]
8	3- NO <sub>2</sub> Ph-	COOEt	90	82	136-7	128-132[30]
9	4-Cl Ph-	COOEt	60	83	92-3	86[30]
10	4-MeO Ph-	COOEt	120	83	88	88[30]

<sup>a</sup>All products are well characterized by FT-IR,  $^1\text{H-NMR}$  and melting point.

<sup>b</sup>Yields refer to isolated products.

## General procedure

A mixture of carbonyl compound (1mmol), ethyl cyanoacetate or malononitrile (1mmol) and kaolin (0.1 g) was refluxed in water for indicated time as required to complete the reaction (table2). Upon completion of the reaction, monitored by TLC, the mixture was cooled to room temperature and filtered. The residue recrystallized from absolute EtOH to obtain pure products. Kaolin is not soluble in EtOH and it could be separated in the recrystallization stage, washed with hot EtOH and reused.

## Spectral and physical data for new compounds

2-Cyano-3-(2-nitrophenyl)-2-propenoic acid ethylester [10] (7):  $^1\text{HNMR}$ (500 MHz,  $\text{CDCl}_3$ )  $\delta$ (ppm): 1.46 (t, 3H,  $J=7.1$  Hz), 4.45 (q, 2H,  $J=7.1$  Hz), 7.75 (dt, 1H,  $J=7.8, 1.5$  Hz), 7.84 (dt, 1H,  $J=7.8, 1.1$ Hz), 7.9 (dd, 1H,  $J=7.8, 1.5$  Hz), 8.32 (dd, 1H,  $J=7.8, 1.1$  Hz), 8.76(s, 1H). IR (KBr pellets): 2250, 1730, 1610, 1530  $\text{cm}^{-1}$ .

2-propenoic acid, 2-Cyano-3-(3-nitrophenyl) ethylester [10] (8):  $^1\text{HNMR}$ (500 MHz,  $\text{CDCl}_3$ )  $\delta$ (ppm): 1.46 (t, 3H,  $J=7.1$  Hz), 4.4 (q, 2H,  $J=7.1$  Hz), 7.76(t, 1H,  $J=8.05$  Hz), 8.35 (s, 1H), 8.4 (m, 2H), 8.74 (s, 1H) IR (KBr pellets): 2360, 1718, 1650, 1557  $\text{cm}^{-1}$ .

2-Cyano-3-(4-chlorophenyl)-2-propenoic acid ethylester [10] (9):  $^1\text{HNMR}$ (500 MHz,  $\text{CDCl}_3$ )  $\delta$ (ppm): 1.46 (t, 3H,  $J=6.9$  Hz), 4.45 (q, 2H,  $J=6.9$  Hz), 7.42 (d, 2H,  $J=9.3$  Hz), 7.95(d, 2H,  $J=9.3$ Hz), 8.18(s, 1H); IR (KBr): 2222, 1723, 1612, 1587  $\text{cm}^{-1}$ .

2-Cyano-3-(4-methoxyphenyl)-2-propenoic acid ethylester [10] (10):  $^1\text{HNMR}$  (500 M Hz,  $\text{CDCl}_3$ )  $\delta$ (ppm): 1.42 (t, 3H,  $J=7.15$  Hz), 3.9 (s, 3H), 4.34 (q, 2H,  $J=7.14$  Hz), 7.02 (dd, 2H,  $J=6.9, 2.0$  Hz), 8.03 (dd, 2H,  $J=6.9, 2.0$  Hz), 8.2 (s, 1H); IR (KBr pellets) 2180, 1710, 1560  $\text{cm}^{-1}$ .

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