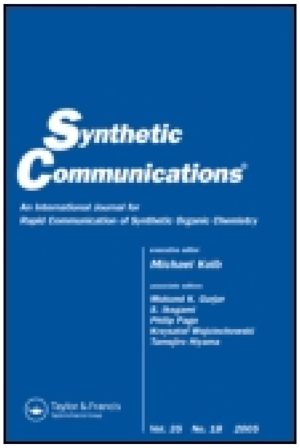

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THE KNOEVENAGEL CONDENSATION REACTION OF AROMATIC ALDEHYDES WITH MALONONITRILE BY GRINDING IN THE ABSENCE OF SOLVENTS AND CATALYSTS

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ABSTRACT

An improved Knoevenagel condensation reaction of aldehydes and malononitrile can be achieved by grinding at room temperature in the absence of solvents and catalysts. This process is simple, efficient, economical, and environmentally benign. Compared to reactions carried out by microwave irradiation, this procedure is completely free from organic solvents during both the reaction and separation of the product.

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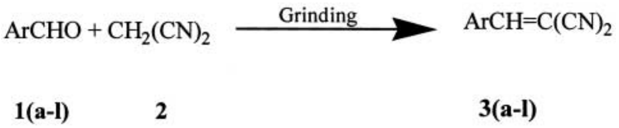
With the increasing public concern over environmental degradation, one of the challenges for chemists is to come up with new approaches that are less hazardous to human health and the environment. The solvents used in organic synthesis are high on the list of environmental pollutants, because they are employed in large amounts and usually are volatile liquids. We are interested in seeking new processes involving solvent-free reactions, for these methods have many advantages such as reduced pollution, lower cost, and simplicity in processing. These factors are beneficial to industry as well as to the environment.[1]

In the conventional view, it is very important for a successful reaction that the molecules move freely and collide with each other at the most suitable orientation. As a result, most of the organic reactions are accomplished in a solvent serving as the medium. In recent years, significant articles have appeared reporting solid-state reactions by grinding, such as Grignard Reaction,[2] Reformatsky Reaction,[3] Aldol Condensation,[4] Dieckhmann Condensation,[5] Phenol Coupling Reaction,[6] Reduciton,[7] and other reactions.[8] These works show the great potential of this methodology, but are just a beginning. Most of the reactions are carried out at room temperature, are absolutely solvent-free and use only a mortar and pestle, and therefore the common merit of these processes is that they are efficient, economical, and environmentally friendly. We focus on developing this novel procedure involving a solid-state reaction performed by grinding.

The Knoevenagel reaction is one of the most common synthetic methods of effecting carbon–carbon bond formation.[9] The reaction is catalyzed by various amines, their corresponding ammonium salts[9] or Lewis acids, such as $TiCl_4$/base,[10] $ZnCl_2$,[11] $BiCl_3$,[12] and CdI_2.[13] Recently, the Knoevenagel reaction carried out by microwave irradiation in the absence of solvents has rapidly increased.[14] Herein, we will report a new process of Knoevenagel reaction at room temperature by grinding in the absence of solvents and catalysts.



Evidence of the condensation and dehydration reaction of aromatic aldehydes with malononitrile performed by grinding is obvious. First, the mixture of aldehydes, either solid or liquid and malononitrile turned into a liquid or a colloid in several minutes. About 15 min later, the mixture became a muddy colloid and the color of the ground substance changed.

After 45 min of grinding with the glass mortar and pestle, the colloid was transformed into powdered solid compounds.

The Knoevenagel reaction is strongly solvent-dependent. The first step the aldol addition, is facilitated in a solvent of high polarity and the second step, 1,2-eliminaiton is inhibited by protic solvents.[9] The result of our experiment indicates that the grinding can cause condensation and a dehydration reaction with a glass mortar and pestle as effectively as with an organic solvent. To our knowledge, this is the first report that the Knoevenagel condensation can occur by grinding at room temperature in the absence of solvents and catalysts.

In order to verify the role of grinding, we have examined the model reaction of 4-methyl-benzaldehyde (**1b**) with malononitrile (**2**) stirred or left standing in the glassware at room temperature for 24 h. The mixture of starting materials was still liquid and the solid product was not obtained. To keep this method economical, we chose a glass mortar and pestle. But when we used a china mortar and pestle to repeat this experiment under the same conditions, it was very surprising that the mixture of 4-methyl-benzaldehyde and malononitrile was still liquid after grinding for 1 h, whereas with a glass mortar and pestle the yield of the condensation reaction of the same starting material was 96%. So far we cannot exactly explain this result, but it will stimulate further research.

This process results in an excellent yield of condensate from liquidaromatic aldehydes, with the exception of benzaldehyde (Table 1). The reason for the low yield from benzaldehyde is that it is volatilized during grinding, as indicated by the fact that the weight of the condensation mixture before separation 72% of the starting material.

In the microwave irradiation process, organic solvents are finally necessary for isolation of the product by extraction. However, the Knoevenagel reaction carried out by grinding is completely free from organic solvents during both the reaction and separation of the product.[14a,14b]

Table 1. Knoevenagel Reaction of **1** and **2** in the Absence of Solvent

Entry	Ar	Yield (%)	Entry	Ar	Yield (%)
3a	C_6H_5	68	**3g**	$3\text{-}CH_3O\text{-}4\text{-}HO\text{-}C_6H_3$	80
3b	$4\text{-}CH_3\text{-}C_6H_4$	96	**3h**	$3,4\text{-}CH_2O_2\text{-}C_6H_3$	80
3c	$4\text{-}CH_3O\text{-}C_6H_4$	94	**3I**	$4\text{-}Cl\text{-}C_6H_4$	85
3d	$2\text{-}Cl\text{-}C_6H_4$	95	**3J**	$3\text{-}NO_2\text{-}C_6H_4$	88
3e	$4\text{-}HO\text{-}C_6H_4$	83	**3k**	$4\text{-}NO_2\text{-}C_6H_4$	91
3f	$3\text{-}HO\text{-}C_6H_4$	87	**3l**	$4\text{-}(CH_3)_2N\text{-}C_6H_4$	92

In conclusion, we have found a simple, efficient, economical, and environmentally benign Knoevenagel reaction by grinding.

EXPERIMENTAL SECTION

General Procedure for the Knoevenagel Reaction in the Absence of Solvents and Catalysts

A mixture of aromatic aldehydes (2.5 mmol) and malononitrile (3 mmol) is ground at room temperature in the glass mortar and pestle for 1 h and the mixture is allowed to stand over night. The reaction product is stirred in 15 mL of water for 15 min collected by suction filtration and dried at room temperature.

3a: M.p. 82.0–83.0°C, (lit.[15a] m.p. 83.5–84.0°C), IR (KBr, ν/cm^{-1}): CN, 2222.

3b: M.p. 134.5–135.0°C, (lit.[15b] m.p. 134.0°C), IR (KBr, ν/cm^{-1}): CN, 2221.

3c: M.p. 113.5–114.0°C, (lit.[15a] m.p. 114.5–115.0°C), IR (KBr, ν/cm^{-1}): CN, 2221.

3d: M.p. 94.0–95.0°C, (lit.[15a] m.p. 95.0–96.0°C), IR (KBr, ν/cm^{-1}): CN, 2224.

3e: M.p. 187.5–188.0°C, (lit.[15a] m.p. 188.0–189.5°C), IR (KBr, ν/cm^{-1}): CN, 2228.

3f: M.p. 155.0–156.0°C, (lit.[15c] m.p. 151.5–153.0°C), IR (KBr, ν/cm^{-1}): CN, 2224.

3g: M.p. 137.0–138.0°C, (lit.[15d] m.p. 136.5–139.0°C), IR (KBr, ν/cm^{-1}): CN, 2227.

3h: M.p. 201.0–202.0°C, (lit.[15a] m.p. 198.0–200.0°C), IR (KBr, ν/cm^{-1}): CN, 2223.

3I: M.p. 162.0–163.0°C, (lit.[15c] m.p. 162.0–163.0°C), IR (KBr, ν/cm^{-1}): CN, 2225.

3j: M.p. 103.0–104.0°C, (lit.[15a] m.p. 104.0–105.0°C), IR (KBr, ν/cm^{-1}): CN, 2253.

3k: M.p. 161.5–162.0°C, (lit.[15c] m.p. 159.0–160.0°C), IR (KBr, ν/cm^{-1}): CN, 2230.

3l: M.p. 180.0–181.0°C, IR (KBr, ν /cm^{-1}): CN, 2220.

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