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Solvent-Free Synthesis of Ethyl α -Cyanocinnamates Catalyzed by K₂O-Al₂O₃ Using Grinding Method

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ABSTRACT

 $K_2O-Al_2O_3$ catalyzes the Knoevenagel condensation of ethyl cyanoacetate with aromatic aldehydes, giving ethyl α -cyanocinnamates in 94–98% yield under solvent-free condition by grinding at room temperature.

Key Words: Knoevenagel condensation; Ethyl α -cyanocinnamates; Solvent-free; Cyanoacetate; Grinding method.

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All synthetic chemistry will consume of energy and materials. An environmentally problematic aspect in organic synthetic chemistry is the use of organic solvents. The solvents have to be produced in another chemical process, which again consumes energy and resources. During the reaction the large amount of solvent has to be heated or cooled, and has to be removed after completion of the reaction from the reaction mixture, a further waste of energy.

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Recently, some solvent-free reaction conditions have been developed for oxidation,^[1] reduction,^[2] substitution,^[3] condensation^[4] and the Michael addition.^[5] And in many cases, these reactions are more efficient and selective than those executed in the corresponding solutions.^[6] And some solvent-free reactions could be completed by grinding,^[4] the procedure are milder reaction condition, better yield, and easier work-up compared with the classical heating method.

Ever since its discovery, the Knoevenagel reaction has been widely utilized in organic synthesis. In the last years, there has been a growing interest in the Knoevenagel condensation products, because many of them present significant biological activity.^[7]

Usually ethyl α -cyanocinnamates is prepared via the Knoevenagel condensation of ethyl cyanoacetate with aromatic aldehydes under homogenous conditions. The catalysts are ammonia, organic amines and their salts,^[6] some Lewis acids and bases such as ZnCl₂,^[8] CdI₂,^[9] MgO, and ZnO^[10] have also been used as catalysts.

In recent years, the application of inorganic supported catalysts in organic synthesis has rapidly increased,^[11] because these reactions often involve easier work-up procedures than those needed for homogenous methods.

This prompted us to study the possibility of the Knoevenagel condensation without solvent. In this work, $K_2O-Al_2O_3$, an inexpensive but efficient catalyst, has been employed in the Knoevenagel condensations under solventfree condition at room temperature by grinding.

Most products described herein were previously prepared and described in the literature.^[11–14] As shown in the Sch. 1 and Table 1, the Knoevenagel condensation of ethyl cyanoacetate (2) with aromatic aldehydes (1) produces



Scheme 1.



Solvent-Free Synthesis of Ethyl &-Cyanocinnamates

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Table 1. The condensation of aromatic aldehydes 1a-11 with ethyl cyanoacetate 2. п

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Entry	Ar	time (min)	temperature (°C)	Yield ^a (%)	m.p. (°C) (Lit)
a	C_6H_5	90	23	94	50-51 (49-51 ^[11])
a ^b		90	26	95	
a ^c		90	27	93	
a ^d		120	60	83	
a ^e		90	25	0	
a ^f		90	25	0	
a ^g		90	25	0	
b	$4-ClC_6H_4$	30	27	97	91-92 (90-91 ^[13])
c	$3-ClC_6H_4$	30	26	97	102-103 (100-102.5 ^[13])
d	$3-NO_2C_6H_4$	8	28	98	136–137 (134–136 ^[13])
e	$4-NO_2C_6H_4$	12	21	96	172–173 (172–173 ^[11])
f	$4-CH_3C_6H_4$	25	25	97	94-95 (94-95 ^[11])
g	$4-CH_3OC_6H_4$	50	24	95	83-84 (80-84 ^[12])
h	3,4-(CH ₂ O ₂)C ₆ H ₃	40	20	98	106-107 (106-107 ^[14])
i	3-OCH ₃ -4-HOC ₆ H ₃	180	23	97	$111 - 112 (111 - 112^{[11]})$
j	4-(CH ₃) ₂ NC ₆ H ₄	25	20	97	126–127 (124–126 ^[11])
k	4-HOC ₆ H ₅	188	22	96	171–172 (176–177 ^[11])
l	$C_6H_5CH = CH$	10	27	98	107-108 (116 ^[12])

^aIsolated yield based on the aldehyde.

^bOn 0.1 mol scale, $K_2O-Al_2O_3$ 20 g.

^cRecycled K₂O-Al₂O₃ as catalyst.

^dReaction at 60°C for 2 hr using EtOH as solvent.

^eKNO₃ as catalyst.

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^fAl₂O₃ (neutral) as catalyst.

^gKNO₃ deposit on Al₂O₃ (neutral) as catalyst.

ethyl α -cyanocinnamates (3) in high yield. Some reactions (**b**-**h**, **j** and **l**) are completed in relative short time (8–50 min). The α,β -unsaturated aromatic aldehyde (11) gave the corresponding E-isomer olefin; no Michael-type addition product was obtained. Condensation of aldehydes (1i and 1k) with 2 was slow probably due to the acidity of hydroxyl group in the benzene ring.

The results in Table 1 indicate that $K_2O-Al_2O_3$ is an effective catalyst. The yield of product $3a^{c}$ is excellent by using recycled K₂O-Al₂O₃ (see entry \mathbf{a}^{f}). KNO₃, neutral Al₂O₃, and KNO₃ deposit on neutral Al₂O₃ did not catalyze the reaction (see entries \mathbf{a}^{e} , \mathbf{a}^{f} and \mathbf{a}^{g}).

In summary, we have found a practical Knoevenagel condensation procedure for the synthesis of ethyl α-cyanocinnamates catalyzed by K₂O-Al₂O₃

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in the absence of solvent at room temperature by using a grinding method. Compared with the classical heating method, the main advantages of the procedure are milder reaction condition, better yield, and easier work-up.

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EXPERIMENTAL

Liquid aldehydes 1 were purified by distillation. Melting points were uncorrected. IR spectra were recorded on a Bio-Rad FTS-40 spectrometer (KBr). ¹H NMR spectra were measured on a Bruker AC-80 (80 MHz), TMS used as internal standard and CDCl₃ as solvent.

Preparation and Activation of the Catalyst of K₂O-Al₂O₃

A solution of 13 g KNO₃ in 50 mL water, and 37 g neutral Al_2O_3 (Tianjin No. 3 Chemical Reagent Factory, China, 0.154 mm) was added to a 250 mL flask. The mixture was stirred in presence of air at 50°C for 0.5 hr. Water was evaporated at 50°C under reduced pressure (2.7 kPa) on a rotary evaporator. The resulting free flowing powder was added to a crucible and heated in muffle furnace at 500°C for 3 hr.

General Procedure

Aldehyde 1 (1 mmol), ethyl cyanoacetate 2 (119 mg, 1.05 mmol) and $K_2O-Al_2O_3$ (200 mg) were added to a mortar. The mixture was grounded with a pestle at room temperature for 5 min, and laid up at room temperature till the aldehyde was disappeared (TLC). After completion, 10 mL dichloromethane was added to the reaction mixture; the catalyst was removed by filtration and washed with dichloromethane (3 × 5 mL). Then the solvent was evaporated at 30°C under reduced pressure (27 kPa) on a rotary evaporator to give solid, which was washed with 5% aqueous ethanol. The pure product was obtained by recrystallization from 50% aqueous ethanol. The authenticity of the products was established by comparing their melting points.

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