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Efficient and easy Knoevenagel condensation of arylaldehydes with ethyl cyanocinnamate/thiazolidindione catalyzed by KF–Al$_2$O$_3$

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Abstract: Efficient and easy Knoevenagel condensation of a variety of arylaldehydes with active methylene-containing compounds such as ethyl cyanoacetate, thiazolidindione is reported, under three different conditions including (i) reflux in acetonitrile, (ii) reflux in acetic acid, and (iii) solvent-free conditions. In all conditions, the desired products are obtained in high yields after relatively short reaction times. Nevertheless, the reactions proceed faster, cleaner and in higher yields when they carry out in solvent-free fashion.

Keywords: Knoevenagel condensation, Arylaldehyde, Active methylene-containing compound, Ethyl cyanoacetate, Thiazolidindione.

Introduction

A Knoevenagel condensation is a nucleophilic addition of an active hydrogen compound to a carbonyl group followed by a dehydration reaction in which a molecule of water is eliminated. The product is often an alpha, beta conjugated enone. In this reaction the carbonyl group is an aldehyde or a ketone. The catalyst is usually a weakly basic amine. The active hydrogen component has the form Z–CH2-Z or Z–CHR–Z for instance diethyl malonate, Meldrum's acid, ethyl acetoacetate or malonic acid [1-3]. Knoevenagel condensation has so many applications such as the preparation of a range of substituted alkenes and bioactive molecules and as a key step in natural product synthesis. So many organic bases have been applied for Knoevenagel condensation, include: aliphatic amines, urea, ethylenediamine, piperidine and their corresponding ammonium salts, and also the amino acids such as glycine or β-alanine [4, 5]. The effect of different solvent such as benzene, ethanol, DMF and etc. has been investigated.

Different scientific study focused on application of versatile Lewis bases and acids such as: ZnCl$_2$ [6], CdI$_2$ [7], TiCl$_4$ [8], Al$_2$O$_3$ [9], Ni-SiO$_2$ [10], MgO [11], ZnO [11], and AlPO4–Al2O3 [12], natural phosphate (NP) /KF or NP/NaNO3 [13] and synthetic phosphates (Na$_2$CaP$_2$O$_7$ [14], Ca$_2$P$_2$O$_7$ [15] and K$_2$NiP$_2$O$_7$ [16]). Moreover, modified inorganic solids such as cation-exchanged zeolite [17–18], resins [19], phase-transfer agents [20], ionic liquids [21, 22], LDH-F hydrotalcite [23], or mesoporous materials [24], and MCM-41 [25] can catalyze this transformation. It is notable in some literatures; KF/Al$_2$O$_3$ has been applied for this condensation [26, 27].

In recent years, chemists have paid much attention to the clean synthesis of alkenes by condensation reactions, the necessity to dispose of huge amounts of organic waste due to the formation of undesirable side products resulting from polymerization, bis-addition and self-condensation; in addition to the total dissolved salts formed during the neutralization of the base or acid catalysts. Generally, these condensation reactions are performed in organic solvent such as benzene; ethanol and DMF, most of them are toxic. The need to

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reduce the amount of toxic waste and byproducts arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods. Therefore, development of efficient and new methods for the formation of carbon-carbon double bonds based on green methodology is still in demand. The first is a push towards environmentally friendly processes using safer reagents, generating fewer side products and having decreased solvent requirements.

Having the above points in mind, we wish to report Knoevenagel condensation of a variety of arylaldehydes with active methylene-containing compounds such as ethyl cyanoacetate, thiazolidindione in the presence of catalytic amount of KF–Al_2O_3 in solution (acetonitrile and acetic acid) and solvent-free conditions which gives excellent yields of high purity. It has many other advantages, such as milder reaction conditions, relatively short reaction times, and recyclability of the catalyst by simple re-treated.

Results and discussion

At first, KF–Al_2O_3 catalytic system was produced according to the literature [28]. For this purpose, KF.2H_2O (20 g) was dissolved in water (80 ml), and then basic Al_2O_3 (30 g) was added. The resulting mixture was stirred at 65–75 °C for 1 h. The water was removed under reduced pressure at 100 °C, and the resulting powder was dried at 120 °C for 4h to give active KF–Al_2O_3. The content of KF was found to be about 30% (w/w).

To recognize the efficiency of the catalyst in the Knoevenagel condensation, the reaction of benzaldehydes (1 mmol) with ethyl cyanoacetate (2 mmol) in acetonitrile (15 ml) was selected as a model reaction and its behavior was studied in the presence of different amounts of KF–Al_2O_3. The results are summarized in Table **1**. As Table **1** indicates, the best results were obtained when 150 mg of the prepared KF–Al_2O_3 was applied.

Table 1: Optimization of the catalyst amount.

Entry	Catalyst (mg)	Time (min)	Yield[a] (%)
1	KF–Al_2O_3 (250 mg)	210	98
2	KF–Al_2O_3 (150 mg)	210	98
3	KF–Al_2O_3 (100 mg)	264	75
4	KF–Al_2O_3 (50 mg)	264	65
5	---	420	No reaction

[a]Isolated yield.

Afterward, in order to find the best catalysis, the reaction of benzaldehydes (1 mmol) with ethyl cyanoacetate (2 mmol) in acetonitrile (15 ml) was studied in the presence of different basic catalysts (Table **2**). As it can be seen in Table **2**, KF–Al_2O_3 afforded the best results.

Table 2: Comparison of reaction yield and reaction time of Knoevenagel condensation of aldehydes in the presence of various catalysts.

Entry	Catalyst(mg)	Time (h)	Yield[a] (%)
1	NaHCO$_3$–Al_2O_3	9	38
2	KF–Al_2O_3 (basic)	3.5	98
3	KF–Al_2O_3 (acidic)	5.5	41
4	KF	5.5	45
5	Al_2O_3	7.5	35
6	KH$_2$PO$_4$–Al_2O_3	6	51
7	Na$_2$CO$_3$–Al_2O_3	4	45
8	K$_2$CO$_3$–Al_2O_3	4.5	49
9	K$_2$CO$_3$	6.5	34
10	Na$_2$CO$_3$	6	38
11	NaHCO$_3$	9.5	59
12	NH$_4$OAC	12	25

[a]Isolated yield.

In another study, recyclability of the catalyst was investigated. For this purpose, the reaction of benzaldehydes (1 mmol) with ethyl cyanoacetate (2 mmol) in acetonitrile (15 ml) was performed in the presence of KF–Al_2O_3 several times, and the reaction mixtures were combined. Afterward, the combined mixture was filtered to separate the catalyst (the product is soluble in hot acetonitrile, but KF–Al_2O_3 is not soluble in this solvent), and the remained catalyst was used for the next run of the reaction. Catalytic activity of KF–Al_2O_3 was restored within the limits of the experimental errors for four successive recycle runs Table **3**). Plausible mechanism of typical Knoevenagel is represented in Figure **1**.
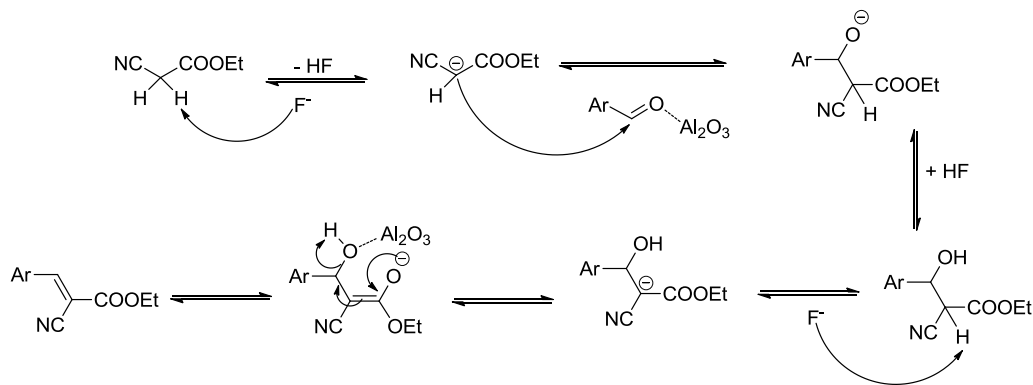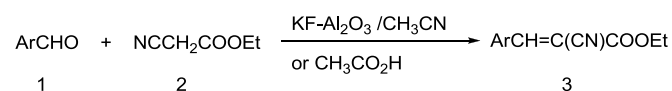
Figure 1: Plausible mechanism of Knoevenagel condensation in the presence of KF–Al$_2$O$_3$.

Table 3: Recycled of Catalyst.

Entry	Catalyst(mg)	Time(min)	Yield^a (%)
1	KF–Al$_2$O$_3$ (150mg)	210	98
2	KF–Al$_2$O$_3$ (150mg)	210	95
3	KF–Al$_2$O$_3$ (150mg)	225	95
4	KF–Al$_2$O$_3$ (150mg)	280	89

^{a}Isolated yield.

Scheme 1: Condensation reaction in room temperature

Aldehyde 1 (1 mmol), ethyl cyanoacetate 2 (1.36 g, 2 mmol), 15 ml acetic acid and catalytic quantity of KF–Al$_2$O$_3$ (150 mg) was added to a 50 ml Pyrex flask. The mixture was stirred at 85 °C in oil bath for a specified time as required till the aldehyde disappeared, as indicated by TLC. After cooling to room temperature, the solvent (After filtrateration) was removed under reduced pressure. The reaction mixture was isolated by separation on a silica gel column with ethyl acetate/n-hexane as the eluent or by recrystallization from ethanol to afford the product of good purity. The pure product for ^{1}H NMR analysis was obtained by recrystallization or column chromatography. Some condensation reactions were carried out at room temperatures (20–25°C) in 15–100 min with no side products. The authenticity of the products was established by comparing their melting points with literature data of IR, MS, ^{13}C NMR and ^{1}H NMR spectra (Scheme 1 and Table 4).

Solvent free is a useful technique because it can enhance the rate of reactions and in many cases improve the product yields compared to traditional heating methods (Scheme 2). We therefore decided to probe this reaction. Thus, there is necessity to develop a more effective and convenient synthetic procedure.
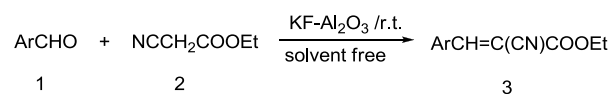
Scheme 2: Condensation reaction in room temperature and solvent free condition
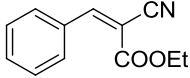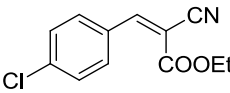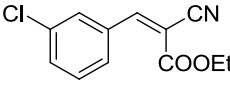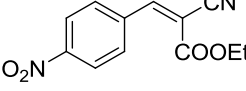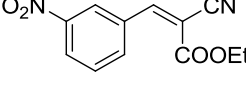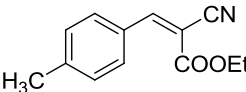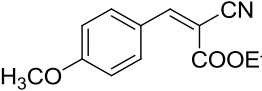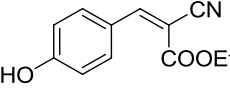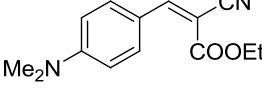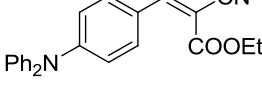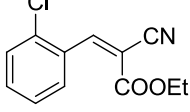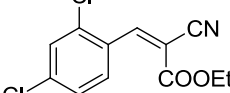
A mixture of Aldehyde 1 (1 mmol), ethyl cyanoacetate 2 (1.36 g, 2 mmol) and catalytic quantity of KF–Al$_2$O$_3$ (150 mg) was vigorously milled at r.t for a specified time to complete the reaction, the formation of the product was indicated by TLC in several cases. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The separated solid was suction filtered. Finally, the crude product was purified by column chromatography with ethyl acetate/n-hexane to afford the product of good purity. The authenticity of the products was established by comparing their melting points with literature data of IR, MS, ^{13}C NMR and ^{1}H NMR spectra (Scheme 2 and Table 4).
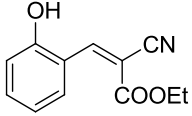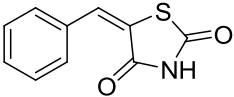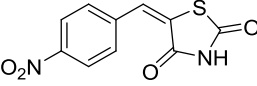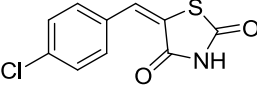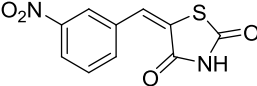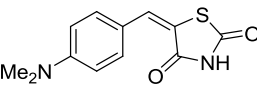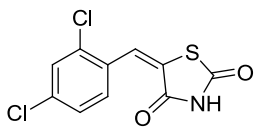
During this study, we decided to investigate the Koevenagel condensations from aryl aldehydes with thiazolidindione (Scheme 3 and Table 4).
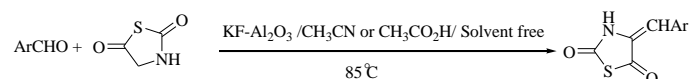
Scheme 3: Condensation reaction of aryl aldehydes with thiazolidindione

Table 4: Reaction of functionalized benzaldehydes with active methylene compounds.

Entry	Product	CH₃CN		CH₃CO₂H		Solvent-free		M.p. °C (Lit.)
		Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	
1		66	2.5	78	2	84	2.5	49-50 (50-51) [30]
2		82	2.15	88	2.5	98	2	93-94 (92-93) [30]
3		86	3.5	87	3	92	3.5	100-102 (102-103) [28]
4		79	3.5	83	3	89	3	172-173 (172-173) [28]
5		85	3	89	3	94	3.5	136-137 (135-137) [28]
6		82	2.5	85	3	85	2	95-97 (94-95) [29]
7		75	3	78	3.15	89	3. 5	83-84 (83-84) [31]
8		82	1.15	79	2	95	2	172-173 (171-172) [31]
9		88	2	85	2.15	98	1	125-127 (126-127) [29]
10		85	2.5	92	2	89	2	94(96) [31]
11		92	3	89	3.5	92	3.5	108-110 (109-111) [30]
12		87	3	84	3	94	2	104-105 (102-103) [29]

No.	Structure							m.p.
13		78	3.5	81	3.5	96	3	169-171 (168-169) [29]
14		92	1.5	98	1	100	1.15	241-243 (241-242) [35]
15		88	1.45	90	1.5	92	1	260-262 (261-263) [36]
16		90	1.5	95	1.5	95	2	225-227 (223-224) [32]
17		89	1.15	98	1.45	98	2	187-188 (185-190)[32]
18		86	2	85	1.5	85	1.5	281-283 (281)[34]
19		92	1.15	98	1.15	100	1.15	213-215 (215) [33]

Conclusion

In summary, we have found a practical Knoevangel condensation procedure for the preparation of ethyl -cyanocinnamates catalyzed by KF–Al$_2$O$_3$, which gives excellent yields of high purity. It has many other advantages, such as milder reaction condition, shorter reaction time, and the catalyst can be recycled several times without loss of catalytic efficiency, and its performance has been compared with that of other heterogeneous base catalysts such as zeolite, potassium exchanged zirconium phosphate, amberlist, modified hydrotalcites. As a result KF–Al$_2$O$_3$ is known to be a useful and interesting solid-supported reagent for base-induced organic reactions.

Experimental

Aldehyde 1 (1 mmol), ethyl cyanoacetate 2 (1.36 g, 2 mmol), 15 ml acetonitril and catalytic quantity of KF–Al$_2$O$_3$ (150 mg) were added to a 50 ml Pyrex flask. The mixture was stirred at 85°C in oil bath for a specified time as required till the aldehyde disappeared, as indicated by TLC. After cooling to room temperature, the solvent (after filtration) was removed under reduced pressure. The reaction mixture was isolated by separation on a silica gel column with ethyl acetate/n-hexane as the eluent or by recrystallization from ethanol to afford the product of good purity. The pure product for ^{1}H NMR analysis was obtained by recrystallization or column chromatography. Some condensation reactions were carried out at room temperatures (20–25°C) in 15–100 min with no side products. The authenticity of the products was established by comparing their melting points with literature data of IR, MS, ^{13}C NMR and ^{1}H NMR spectra (Scheme **1** and Table **4**).

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