Silica Supported Ammonium Acetate: An Efficient and Recyclable Heterogeneous Catalyst for Knoevenagel Condensation between Aldehydes or Ketones and Active Methylene Group in Liquid Phase

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A simple and efficient method has been developed for Knoevenagel condensation between aldehydes or ketones and active methylene group by stirring in methylene chloride at 60 °C under heterogeneous conditions using silica supported ammonium acetate. The products are obtained in excellent yields and are in a state of high purity. The structures of the products were confirmed by IR, ^{1}H NMR and mass spectral data and comparison with authentic samples available commercially.

Key Words: Knoevenagel, Heterogeneous, Recyclable, Aldehyde or ketone, Active methylene group

Introduction

Knoevenagel condensation[1] is one of the basic reactions in organic chemistry known for its synthetic utility in carbon-carbon bond formation.[2] Knoevenagel condensation have numerous applications in the elegant synthesis of fine chemicals,[3] hetero Diels-Alder reactions[4] and in the synthesis of carbocyclic as well as heterocyclic[5] compounds of biological significance. The products of Knoevenagel condensation have found increasing applications in industry, agriculture, medicine and biological science.[3,6] Substituted cinnamic acids possess a wide range of activities such as antiallergic[7] and in the synthesis of substituted styrenes.[8] Numerous reagents have been reported for Knoevenagel condensation in literature such as triethylbenzylammonium chloride (TEBA),[9] NaCl and NH_4OAc-AcOH,[10] zinc acetate,[11] triethylamine and catalytic amount of magnesium bromide diethyl etherate,[12] ammonium acetate in combination with basic alumina,[13] bentonite,[14] lithium perchlorate and lithium bromide,[15] K_2CO_3 and P_2O_5,[16] KF-montmorillonite,[17] water,[18] fluorapatite (FAP)/sodium nitrate,[19] calcium oxide,[20] rhenium complex,[21] chitosan hydrogel,[22] hydrotalcite in ionic liquid,[23] CsNaX-NH_2,[24] polyacrylamide,[25] natural phosphate doped with potassium fluoride,[26] anion-exchange resin,[27] 12-tungstophophoric acid.[28] But most of the reported reagents are associated with certain disadvantages such as tedious work-up, expensive nature of the reagent, toxic nature etc. In order to cumbersome these problems, emphasis has been laid on the use of supported reagents. The major advantage of supported reagent is the reusability of the catalyst which makes the process inexpensive. Moreover, it also contributes towards the area of "Green Chemistry".

Results and Discussion

To optimize the reaction conditions, 4-chlorobenzaldehyde and malononitrile were selected as the model substrates to examine the effects of different solvents (CH_2Cl_2, CH_3CN, DMF and toluene) and molar ratios of the catalyst at different temperatures (r.t., 60 and 80 °C). The reactions were monitored by TLC and all the yields reported in Table 1 and 2 are isolated yields. The effect of different solvents on the course of reaction was studied (Table 1). From the results given in Table 1, it was found that among various solvents tried, methylene chloride was found to give optimum results in term of reaction time and yield. Thus, the optimum conditions for the reaction are: 4-chlorobenzladehyde (1 mmol), malononitrile (1 mmol) and 0.2 g of silica supported ammonium acetate. 60 °C was found to be the optimum reaction temperature as at low temperature, reaction time was longer.

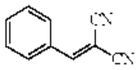
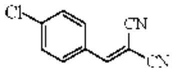
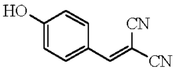
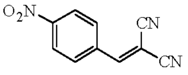
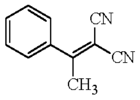
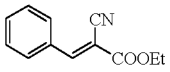
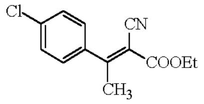
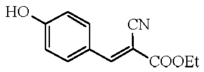
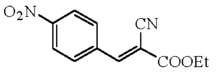
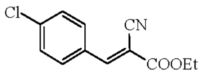
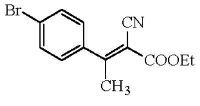
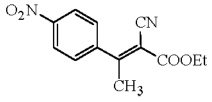
Table 1. Knoevenagel condensation between 4-chlorobenzaldehyde and malononitrile in different solvents under reflux

Solvent	Reaction time (h)	Isolated Yield (%)
DMF	12	64
Toluene	9.5	69
CH_3CN	7	83
CH_2Cl_2	6.5	90

Using the optimized conditions, the reactions of various aromatic substituted aldehydes or ketones and malononitrile or ethyl cyanoacetate were investigated (Scheme 1). It was found that all the reactions proceeded smoothly to give the corresponding Knoevenagel products in high yield (Table 2). The reaction of various aromatic aldehydes containing electron-withdrawing groups (entries **3b**, **3d**, **3g**, **3i**) and electron-releasing groups (**3c** and **3h**) were examined. They all gave the products in goods yields (Table 2). The aldehydes containing electron withdrawing groups gave the products in shorter time as compared to the aldehydes containing electron-donating groups. The catalyst also worked well for ketones (entries **3e**, **3g**, **3k** and **3l**).

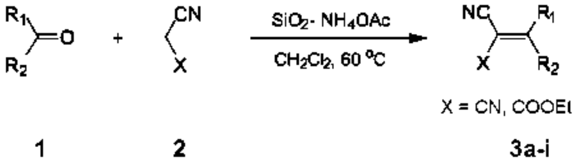
When using heterogeneous catalyst, the important issue is the recyclability. To test this, a series of 3 consecutive runs of the reactions of 4-chlorobenzaldehyde and malononitrile with

Table 2. Silica supported ammonium acetate catalyzed Knoevenagel condensation between aldehydes or ketones and active methylene compounds at 60 °C using dichloromethane as solvent

Entry	Product[a]	Time (h)	Yield[b] (%)	m.pt / lit. m.pt (°C)
3a		7	87	83-84/82-84[30]
3b		6.5	90	158-160/161-163[30]
3c		8	84	187-189/187-188[30]
3d		6	90	158-161/159-160[30]
3e		10	79	90-92/92[29]
3f		8	85	51-53/49-50[31]
3g		7	88	91-92/92-94[30]
3h		9.5	76	171-174/172-173[30]
3i		6.5	87	129-132/129-131[30]
3j		9.5	77	85-88/88[32]
3k		10	75	81-82/84[33]
3l		9	80	140-144/144[34]

[a]All the products were characterized by ^1H NMR, IR and mass data and comparison with authentic samples available commercially or prepared according to reported methods. [b]Yields refer to the isolated yields.

the catalyst were carried out (Ist use: 90% isolated yield after 6.5 h; 2nd use: 83% isolated yield after 8 h; 3rd use: 74% isolated yield after 10.5 h). These results demonstrate that there is decrease in the activity of the catalyst after every use. This may be due to either the deactivation of active centers resulting from complexation with both starting materials and products or by microscopic changes in the structure of the catalyst.



Scheme 1

Preparation of Catalyst

The catalyst was prepared by grinding silica (1 g, K 100) with ammonium acetate (0.5 g) in a pestle and mortor at room temperature. The catalyst was stored in a desiccator.

In this paper, we wish to report Knoevenagel condensation between aldehydes or ketones and active methylene compounds (malononitrile or ethyl cyanoacetate) in the presence of silica supported ammonium acetate by stirring in CH_2Cl_2 at 60 °C under heterogeneous conditions (Scheme 1).

Experimental Section

General. All the melting points were determined on Perfit melting point apparatus and are uncorrected. ^1H NMR spectral data was registered on Bruker DPX-200 NMR spectrometer (200 MHz) in $CDCl_3$ using tetramethylsilane as an internal standard. The IR spectra were recorded using KBr disc on Perkin-Elmer FTIR spectrophotometer. Mass spectral data was recorded on Jeol JMS D-300 mass spectrometer at 70 eV.

General procedure for Knoevenagel condensation between aldehydes or ketones and active methylene group using silica supported ammonium acetate as heterogeneous catalyst in liquid phase. To a mixture of aldehyde or ketone **1** (1 mmol) and active methylene compound (malononitrile or ethyl cyanoacetate) **2** (1 mmol for aldehyde and 1.5 mmol for ketone) in a round-bottomed flask (50 mL) containing methylene chloride (10 mL), catalyst (0.2 g) was added. The reaction mixture was stirred at 60 °C in an oil-bath for the appropriate time (Table 2). After completion of reaction (monitored by TLC), the reaction mixture was filtered off. The product was obtained after removal of solvent under reduced pressure and crystallization from pure ethanol. The catalyst was washed with methylene chloride (2 × 15 mL) and dried for 2 h. It could be reused further for carrying out the reaction.

The structures of all the products were confirmed by ^1H NMR, IR, mass spectral data and comparison with authentic samples prepared according to the literature methods.

Conclusion

In conclusion, we have developed a novel, eco-friendly and efficient method for Knoevenagel condensation. The advantages of the present method are simplicity of work-up, high yields, short reaction times and recyclability of the catalyst.

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