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Ammonium chloride catalyzed Knoevenagel condensation in PEG-400 as ecofriendly solvent

Smita R Waghmare
Center for Advanced Studies, Department of Chemistry, Savitribai Phule Pune University, Pune 411 007, India
E-mail: smitaw23@gmail.com

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A simple and selective green methodology has been successfully developed for Knoevenagel condensation in polyethylene glycol-400 using 10 mol % ammonium chloride as catalyst. The method is applicable to a wide range of aromatic, heteroaromatic and α,β-unsaturated aldehydes. The reactions have been found to be clean and free from the formation of the Michael adduct.

Keywords: Knoevenagel condensation, PEG-400, catalyst, ammonium chloride, α,β-unsaturated alkenes

The Knoevenagel condensation discovered by E. Knoevenagel in 1894 is a venerable and straightforward method to produce α,β-unsaturated alkenes by condensation of aldehyde/ ketone having acidic (C-H) methylene group/compounds in either acidic, basic or neutral medium[1-5]. In recent time there has been a growing interest in Knoevenagel products[1,8] because many of them have significant biological activity such as anti-fouling agents, fungicides, insecticide[7], tyrophostins and α-cynothiocinnamide are known to inhibit autophosphorylation of the EGF receptor and to possing antiproliferative effects on human keratinocytes[8,9]. Moreover Knoevenagel compounds are useful intermediates for many pharmaceutical and biomedical industries. Arylidene malononitriles were primarily used in the preparation of fine chemicals in agriculture and medicine fields as precursors of bioactive heterocycles[10-12]. Morever ethylcyanoacetate and aryl aldehyde derivatives were used in the synthesis of biologically active antimetabolites[13,14]. α,β-Unsaturated acid derivatives can be synthesized by Knoevenagel condensation have major applications in many fields such as in medicine as anticancer[15], antituberculosis agents[16] and in industries as plasticizers, perfumes, aroma compounds[16] and as lubricants, *etc*. In fact, recently they have been used in the synthesis of antibacterial drug Reutericylin[16].

In recent years, a wide array of catalyst were used for Knovenagel condensation like modified hydrotalcites[1], amines[2], K_2CO_3 [17], Lewis-acid catalysts[4] and ionic liquids[5], *etc*. have been employed to catalyze this reaction. Each affording variables yields of Knoevenagel condensation compounds in solution or under solvent free conditions. In contrast, there are only a few acid catalysts that are known to promote this reaction[18].

It was observed that although there are various reports present on Knoevenagel reaction and were simple at laboratory scale but at large scale i.e. at industrial level it faced some critical problems like uneven and vigorous generation of CO_2 gas due to unreacted acid derivatives and also during the subsequent decarboxylation of product, is one of the difficult problems. The presence of volatile solvents and bases such as piperidine and pyridine make the system even more unsafe. The sudden increase in pressure or temperature due to excess of gas along with the volatile solvents is also a critical problem. Besides this present reported methods also serves some limitations as not easily available and inexpensive catalyst, use of high power microwave, long reaction time with high temperature, use of toxic and environmentally unfriendly solvents and reagents such as benzene, piperidine, pyridine, sodium cyanide, potassium cyanide, chloroacetic acid, acetic acid, triphenylphosphine, etc.[17-19]. Hence it is highly desirable to develop a safe, inexpensive and efficient method for the Knoevenagel condensation.

Nowadays there is an urgent need to develop green chemistry processes, where nontoxic substances are used and the generation of waste can be avoided. Recently, Polyethylene glycol (PEG) has been found to be an interesting green solvent system[20]. The use of PEG as an environmental benign protocol has proved to have many applications[22-26]. Particularly, in substitution, oxidation, addition and reduction reactions. A number of recent reviews have also covered PEG chemistry and its applications in biotechnology and medicine[27,28].

Similarly, in recent years, ammonium chloride has also received considerable attention as an inexpensive, non-toxic, readily available catalyst for various organic transformations such as in Ullmann coupling, thia-Michael addition, Claisen rearrangement, Biginelli reaction, Groebke condensation reaction, Multicomponent reaction, Ugi reaction, crossed-aldol condensation, condensation of carbonyl compounds and indoles, reduction of aromatic nitro and azides, reductive cleavage of aza compounds and in oxidation of alcohols[29-31]. Besides this ammonium chloride is readily available, inexpensive, non-toxic and can be easily removed from reaction mixture makes reaction operationally simple therefore enhances ammonium chloride applications in organic synthesis at mild and convenient conditions.

As a part of a continuing effort in our laboratory to study the organic transformations by using ammonium chloride and use of ecofriendly solvents in organic synthesis. We were interested in developing a novel and efficient method to synthesized substituted alkene by Knoevenagel condensation reaction. Herein, we first time report ammonium chloride as a novel, inexpensive, mild and efficient acid catalyst for the title reaction and its effective application to the Knoevenagel condensation with different aromatic, heteroaromatic, α,β-unsaturated aldehydes and ethylcyanoacetate or malononitrile or cynoamide by using in PEG-400 as solvent at room temperature (Scheme I).

Results and Discussion

In this report we wish to highlight our finding on the ammonium chloride catalyzed condensation of active methylene compounds with aromatic and hetroaromatic aldehydes. The Knoevenagel reaction of benzaldehyde with ethylcyanoacetate was chosen as a model system to determine the optimum reaction condition and the results are summarized in Table I. The initial study was conducted by examining the suitable ammonium salts for the model reaction. First the model reaction proceeded in the presence of NH_4OAc and generated the desired product in 88% yield (Table I, entry1). Further, other ammonium salts such as $(NH_4)_2(CO_2)_2$, $(NH_4)_2SO_4$ and $(NH_4)_2Fe(SO_4)_2.6H_2O$ showed less reactivity than NH_4Cl (Table I, entry 2-5), which gave the greatest yield (98%).Next, we investigated the effect of the amount of NH_4Cl reaction. Reducing the catalyst loading from 10 to 7 and 5 mol % lowered the conversion from 98 to 83 and 70%, respectively (Table I, entries 5–7). In the absence of the catalyst, the trace product was observed after a long reaction time (6 h) (Table I, entry 8). It is evident that the amount of catalyst has remarkable effect on this reaction. The effect of temperature has also been investigated. The ammonium salt dissociates in following way and results different pK_a value of dissociated acid

$$NH_4OAc \rightleftharpoons NH_3 + AcOH$$

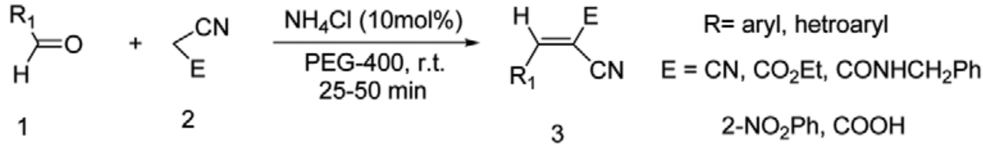
$$NH_4Cl \rightleftharpoons NH_3 + HCl$$

$$(NH_4)_2(CO_2)_2 \rightleftharpoons NH_3 + HCOOH$$

$$(NH_4)_2SO_4 \rightleftharpoons NH_3 + H_2SO_4$$

Table I — Effect of catalyst on the Knoevenagel reaction

Entry	Catalyst	Amount of catalyst (mol %)	Temperature (°C)	Time (min)	Yield (%)
1	NH_4OAc	10	R.T	60	88
2	$(NH_4)_2(CO_2)_2$	10	R.T	60	25
3	$(NH_4)_2SO_4$	10	R.T	60	33
4	$(NH_4)2Fe(SO_4)_2.6H_2O$	10	R.T	60	10
5	NH_4Cl	10	R.T	60	98
6	NH_4Cl	07	R.T	60	83
7	NH_4Cl	05	R.T	60	70
8	Catalyst Free	--	R.T	60	05
9	NH_4Cl	10	60	60	67
10	NH_4Cl	10	80	60	54
11	NH_4Cl	10	R.T	40	81
12	NH_4Cl	10	R.T	20	60



Scheme I — Ammonium chloride catalyzed Knoevenagel Condensation Reaction

The reaction could proceed smoothly at room temperature. However, increasing the temperature from R.T to 60 and 800 °C significantly reduces the conversion of title compound from 98 to 67 and 54% (Table I, entries 9 and 10). We have tried to shorten the reaction time from 60 to 40 and 30 min, but the conversion was obviously lowered from 98 to 81 and 60%, respectively (Table I, entries 11 and 12).

It was observed that the Knoevenagel condensation is strongly solvent dependant[25,26]. In addition, the use of aqueous and highly protic solvents is currently of great importance since it avoids problems of self-condensation, 1,2-elimination and retro-Knoevenagel reactions. Then, we turned to examine the effect of solvent for the Knoevenagel condensation compounds. Initially reaction was carried out in solvent free condition. It was observed that when reaction carried out under solvent free conditions mixture solidified as soon as the catalyst was added. The yield was not so high, because the reaction mixture could not stir well enough (Table II, entry 1).

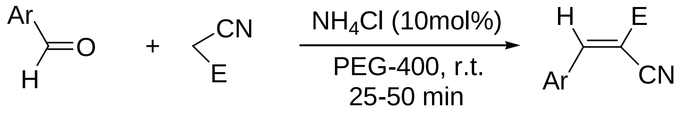
In order to establish the best reaction mixture medium, we performed the reaction using various Environment friendly solvents such as water, ethanol and polyethylene glycol at room temperature; the results are summarized in Table II. Using water as a solvent gave 78% of Knoevenagel condensation product after 20 h (Table II, Entry 4), in ethanol solvent gave 85% yield in 8 h. Surprisingly in PEG-400 reaction completed within 30 min with 94% yield (Table II, Entry 8). To understand the role of PEG as a reaction medium we also performed the Knoevenagel reaction of the same substrate in Ethylene glycol, Triethylene glycol and other glycols such as PEG-600, PEG-4000, PEG-6000 and PEG-8000 (Table II). In ethylene glycol and triethylene glycol the product was observed in low yield (28-24%). However, as the molecular weight of PEGs increases (Table II, entry 10-13), the viscosity increases because of this we raised the temperature up to 70 °C to liquefy the PEG. Even so, No other co-solvents are used. It was also observed that as we increase in the temperature, the reaction time decrease accordingly but the yield is also decreases because it leads to the other side reaction (Table II, Entry 3,5,9). The formation of product 35b was confirmed by IR at 2225 and 1739 shows CN and COOR functional group. In ^{1}HNMR at 1.38δ for three proton of CH_3, quartet at 4.38δ for CH_2 group and deshilded proton of olefinic CH at 8.18δ peak and four aromatic proton clearly indicate formation of Knoevengel product.

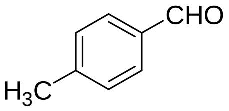
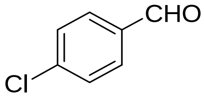
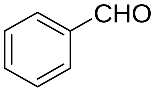
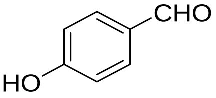
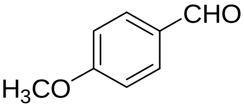
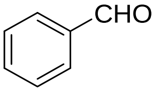
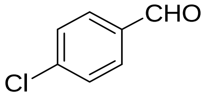
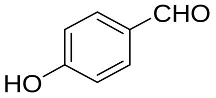
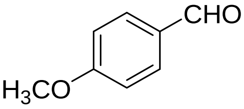
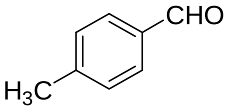
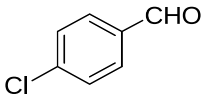
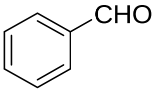
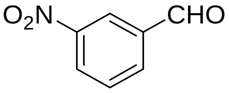
Table II — Effect of solvent and temperature on Knoevenagel reaction

Entry	Solvent	Time	Temperature	Yield (%)
1	Neat	30 min	RT	68
2	EtOH	8 h	RT	85
3	EtOH	2 h	Reflux	76
4	H_2O	20 h	RT	78
5	H_2O	1.5 h	Reflux	69
6	Ethylene glycol	17 h	RT	28
7	Triethylene glycol	18 h	RT	24
8	PEG-400	30 min	RT	94
9	PEG-400	10 min	600°C	64
10	PEG-600	50 min	RT	82
11	PEG-4000	1.5 h	RT	80
12	PEG-6000	2 h	RT	87
13	PEG-8000	2.5 h	RT	70

We next turned to study the Knoevenagel condensation reaction of various aldehydes including aromatic, hetroaromatic and α,β-unsaturated aldehydes with active methylene compounds such as malononitrile, ethyl cynoacetate, cynoacetic acid, benzyl cynoamide and 2-nitro benzyl cyanidewere also examined. In all cases, the reaction proceeds smoothly with 10 mol % NH_4Cl in Water, Ethanol and PEG-400 solvent, NH_4Cl acts as a mild Bronsted acid to induce the reaction. The reaction is highly stereoselective, affording α-β ethylenic compounds in excellent yields with *E*-geometry. Furthermore, the treatment of aldehydes with ethylcyanoacetate, cynoacetic acid, malononitrile, benzyl cyanoacetamide and also gave olefinic compounds under similar reaction condition (Scheme I). Both electron rich and electron deficient aldehydes worked well, giving high yields to products. It was shown that the condensation of aldehydes with electron withdrawing groups such as –Cl and $–NO_2$ in the aromatic ring, with active methylene compounds can be carried out in relatively less time than with electron donating groups such as $–CH_3$ and $–OCH_3$ (Table III). Heterocyclic aldehydes such as furfural, pyrrole 2- carboxaldehyde and indole 3-carboxaldehyde gave comparatively higher yields than aryl aldehydes (Table III). Compared to the Knoevenagel reaction of malanonitrile with aromatic aldehyde, the reactions of ethyl cyanoacetate, cyanoacetamide and cyanoacetic acid with same aromatic aldehydes needed more time. Because the electron withdrawing ability of the -CN group is stronger than that of the carbonyl or carboxylic group, the methylene group of malononitrile is more activated than ethylcyanoacetate and readily reacts with aromatic

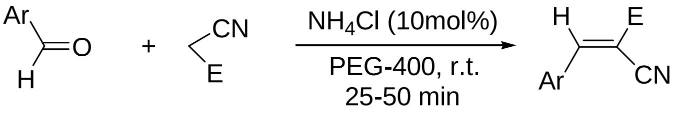
Table III — Knoevenagel condensation catalyzed by ammonium chloride

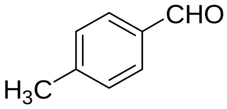
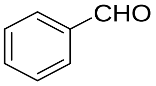
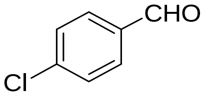
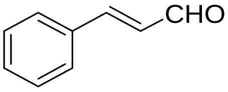
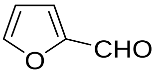
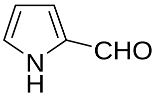
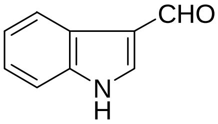
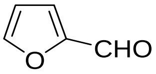
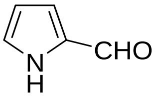
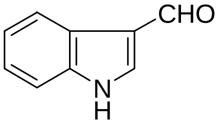
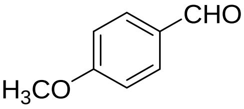


S. No.	Aldehyde	E	Compd	Time (min)	Yield (%)
1		CO_2Et	**3a**	35	89
2		CO_2Et	**3b**	25	92
3		CO_2Et	**3c**	35	90
4		CO_2Et	**3d**	38	90
5		CO_2Et	**3e**	40	85
6		$CONHCH_2Ph$	**3f**	40	92
7		$CONHCH_2Ph$	**3g**	30	95
8		$CONHCH_2Ph$	**3h**	45	90
9		$CONHCH_2Ph$	**3i**	55	90
10		$CONHCH_2Ph$	**3j**	45	92
11		CN	**3k**	25	90
12		CN	**3l**	30	94
13		CN	**3m**	45	89

(*Contd.*)

Table III — Knoevenagel condensation catalyzed by ammonium chloride (*Contd.*)



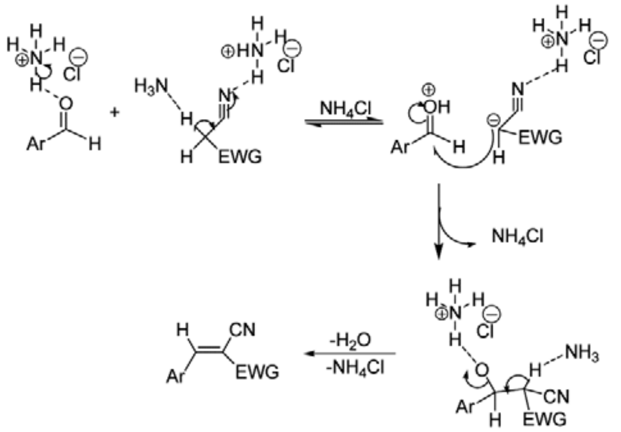
S. No.	Aldehyde	E	Compd	Time (min)	Yield (%)
14		CN	**3n**	30	89
15		2-NO$_2$Ph	**3o**	35	87
16		2-NO$_2$Ph	**3p**	35	95
17		CO$_2$Et	**3q**	30	92
18		CO$_2$Et	**3r**	30	95
19		CO$_2$Et	**3s**	40	90
20		CO$_2$Et	**3t**	50	86
21		CN	**3u**	25	95
22		CN	**3v**	30	91
23		CN	**3w**	30	89
24		COOH	**3x**	30	88

aldehyde. It was also observed that as the acidity of the active methylene compounds decreases from malanonitrile to cyanoamide, the yield is also decreases accordingly (Table III).

It was also noted that, if the reaction of aldehydes with ethyl cyanoacetate were carried out in ethanol at reflux condition the Knoevenagel condensation reactions could proceed very fast. It was noteworthy that the reaction do not required further purification. Commercial application of some of the compounds formed are listed in the Table IV. The mechanism of Knoevenagel condensation by using ammonium

Table IV — Commercial application of selected Knoevenagel products

S. No.	Compd	Commercial application
4	(E)-2-cyano-3-(4-hydroxyphenyl) acrylate	Intermediate of High value matrix substances in MALDI MS
18	(E)-2-cyano-3-(furan-2-yl) acrylate	Intermediate for animal food preservative
17	(2E,4E)-2-cyano-5-phenylpenta-2,4-dienoic acid	Intermediate for agrochemicals



Scheme II — Plausible reaction mechanism for NH4Cl catalyzed Knoevenagel condensation in PEG-400 solvent

chloride was not very clear, the proposed plausible mechanism of ammonium chloride-PEG-400 mediated Knoevenagel condensation could be explained by the initially formation of hydrogen bonding of ammonium chloride with the reactants (Scheme II). This facilitates the nucleophilic attack on carbonyl compounds, and subsequent dehydration leads to the product. Simultaneous removal of water during the reaction is not required presumably because the generated water molecules are involved in strong hydrogen bonding with the ionic liquid. We have developed an improved process which offered several advantages over this procedure. In this process, the filtered product did not need to be purified. Study of solvent reveal that the Knoevenagel condensation reaction preceded smoothly in the presence of ammonium catalyst in a variety of green solvents such as water, ethanol and PEG-400. Among all the tested solvent PEG-400 was considered to be the best solvent in the reaction made the process very cheap and green.

Conclusion

(i) We have successfully developed a simple and selective green method for the Knoevenagel condensation reaction by using 10 mol % ammonium chloride catalyst in polyethylene glycol-400 as a green reaction solvent.

(ii) This method is applicable to a wide range of aromatic, hetroaromatic and α,β-unsaturated aldehyde. In general, the reactions were clean and free from the formation of the Michael adduct.

(iii) Advantages of this protocol include easy of work-up, readily available, inexpensive catalyst, high yields and purity. Moreover, this is a simple route to large scale synthesis of substituted electrophilic alkenes.

(iv) We believe that this attractive feature of NH_4Cl catalyst could help reduce disposal costs and greatly contribute to environmentally greener and safer processes.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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References

1 Choudary B M, Lakshmi Kantam M, Kavita B, Venkat Reddy C & Figueras F, *Tetrahedron*, 56 (2000) 9357.
2 Balalaie S & Nemati N, *Synth Commun*, 30 (2000) 869.
3 CaoY Q, Dai Z, Zhang R & Chen B H, *Synth Commun*, 34 (2004) 2965.
4 Khan R H, Mathur R K & Ghosh A C, *Synth Commun*, 26 (1996) 683.
5 Fan X, Hu X, Zhang X & Wang J, *Aust J Chem*, 57 (2004) 1067.
6 Mase N & Horibe T, *Org Lett*, 15 (2013) 1854.
7 Bigi F, Conforti M L, Maggi R, Piccinno A & Sartori G, *Green Chem*, 2 (2000) 101.
8 Lyall R, Zilberstein A, Gazit A, Gilon C, Levitzki A & Schlessinger J, *J Biol Chem*, 264 (1989) 14503.
9 Shiraishi T, Owada M K, Tatsuki M, Yamashita Y & Kaunaga T, *Cancer Res*, 49 (1989) 2374.
10 Tietze L F, *Chem Rev*, 96 (1996) 115.
11 Oskooie H A, Heravi M M, Derikvand F, Khorasani M & Bamoharram F F, *Synth Commun*, 36 (2006) 2819.
12 Quiroga J, Alvarado M, Insuasty B, Moreno R & Ravina E, *J Heterocycl Chem*, 36 (1999) 1311.
13 Wiener C, Schoeder C H & Link K P, *J Am Chem Soc*, 79 (1957) 5301.
14 Ulbricht T L V, Okuda T & Prince C C, in *Organic Syntheses* (John Wiley & Sons, New York) (1963).
15 De P, Baltas M & Bedos-Belval F, *Curr Med Chem*, 18 (2011) 1672.

16 De P, Koumba Yoya G, Constant P, Bedos-Belval F, Duran H, Saffon N, Daffé M & Baltas M, *J Med Chem*, 54 (2011) 1449.

17 Cao Y Q, Dai Z, Zhang R & Chen B H, *Synth Commun*, 34 (2004) 2965.

18 Rao P S & Venkataratnam R V, *Tetrahedron Lett*, 32 (1991) 5821.

19 Prajapati D, Lekhok K C, Sandhu J S & Ghosh A C, *J Chem Soc*, *Perkin Trans 1*, 959 (1996).

20 Yanlong G, *Green Chem*, 14 (2012) 2091.

21 Chen J, Spear S K, Huddleston J G & Rogers R D, *Green Chem*, 7 (2005) 64.

22 Dawane B S, Konda S G, Khandare N T, Chobe S S, Shaikh B M, Bodade R G & Joshi V D, *Org Commun*, 3 (2010) 22.

23 Dawane B S, Konda S G, Mandawad G G & Shaikh B M, *Eur J Med Chem*, 45 (2010) 387.

24 Jorapur Y R, Rajagopal G, Saikia P J & Pal R R, *Tetrahedron Lett*, 49 (2008) 1495.

25 Das B, Krishnaiah M, Balasubramanyam P, Veeranjaneyulu B & Nandankumar D, *Tetrahedron Lett*, 49 (2008) 2225.

26 Kouznetsov V V, Merchan Arenas D R & Romero Bohorquez A R, *Tetrahedron Lett*, 49 (2008) 3097.

27 *Polyethylene Glycol Chemistry*: *Biotechnical and Biomedicinal Applications*, edited by Harris J M (Plenum Press, New York) (1992).

28 *Polyethylene glycol Chemistry and Biological Applications*, edited by Harris J M & Zalipsky S (ACS Symposium Series 680, American Chemical Society, Washington DC) (1997).

29 Janvier P, Sun X, Bienayme H & Zhu J, *J Am Chem Soc*, 124 (2002) 2560.

30 Bonne D, Dekhane M & Zhu J, *Org Lett*, 6 (2004) 4771.

31 Pirali T, Tron G C, Masson G & Zhu J, *Org Lett*, 9 (2007) 5275.