



## Sodium ascorbate-catalyzed Knoevenagel condensation under aqueous medium

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### ABSTRACT

An efficient procedure for the Knoevenagel condensation of various aryl aldehydes with active methylene nitrile compounds using sodium ascorbate as an efficient, green, inexpensive, and commercially available catalyst in water is reported. The advantages of this work are clean, easy work-up, high yields, and the use of water as environmentally benign solvent.

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### KEYWORDS

Aryl aldehydes;  
Sodium ascorbate;  
Knoevenagel condensation;  
Aqueous medium;  
Green catalyst.

### INTRODUCTION

The Knoevenagel condensation reaction is a well-known reaction for carbon-carbon bond formation between an aldehyde or ketone and a methylene compound, activated by two electron-withdrawing groups in organic synthesis<sup>[1]</sup>. Compounds are formed in this reaction, a variety of applications including perfumery<sup>[2]</sup>, pharmaceuticals<sup>[3]</sup>, cosmetics<sup>[4]</sup>, agrochemicals<sup>[5]</sup>, biologically active compounds<sup>[6]</sup>, and nonlinear optical application<sup>[7]</sup>. Also, the Knoevenagel condensation reactions could be used to obtain fine chemicals<sup>[8]</sup>, azo dye derivatives<sup>[9]</sup>, coumarins<sup>[10]</sup>, some photochromic compounds<sup>[11]</sup>, hetero Diels-Alder products<sup>[12]</sup>, and materials for organic solar cells<sup>[13]</sup>. Generally, these reactions are catalyzed by weak bases such as Primary, secondary, and tertiary amines and their salts in organic solvents<sup>[14]</sup>. In recent years, there have many methods reported for the Knoevenagel condensation including the use of other catalysts such as leucoemeraldine-base<sup>[15]</sup>,  $\text{ReBr}(\text{CO})_5$ <sup>[16]</sup>, guanidine<sup>[17]</sup>, PEG400 and  $\text{K}_2\text{CO}_3$ <sup>[18]</sup>, cobalt hydroxyapatite<sup>[19]</sup>, sodium silicate<sup>[20]</sup>,

polystyrene-supported poly(amidoamine) (PAMAM) dendrimers<sup>[21]</sup>, imidazolium-based phosphinite ionic liquid<sup>[22]</sup>, 1-methyl-3-(2-(sulfooxy)ethyl)-1*H*-imidazol-3-ium chloride<sup>[23]</sup>, diethyl amine functionalized polyethylene glycol<sup>[24]</sup>, choline chloride<sup>[25]</sup>, proline<sup>[26]</sup>,  $[\text{bmim}]\text{BF}_4$ <sup>[27]</sup>, 1,1,3,3-tetramethylguanidium lactate<sup>[28]</sup>, cellulose sulphuric acid<sup>[29]</sup>, lemon juice<sup>[30]</sup>, nickel nanoparticles<sup>[31]</sup>, ZnO nanoparticle<sup>[32]</sup>, MgO<sup>[33]</sup>, ethyl ammonium nitrate<sup>[34]</sup>, tetra-*n*-butylammonium hydroxide (TBAH)<sup>[35]</sup>, melamine<sup>[36]</sup>, methane sulfonic acid (MSA)/morpholine system<sup>[37]</sup>, sodium benzoate<sup>[38]</sup>, cetyltrimethylammonium bromide (CTMAB)<sup>[39]</sup>, basic alumina<sup>[40]</sup>,  $\text{Na}_2\text{S}/\text{Al}_2\text{O}_3$ <sup>[41]</sup>, sodium carbonate<sup>[42]</sup>, and ammonium sulphamate<sup>[43]</sup>. Each of the these synthetic methods has its own benefit, but suffer from drawbacks such as prolonged reaction time, use of environmentally hazardous catalysts, organic solvents, energy expenses, harsh reaction conditions, and tedious work-up procedures. Also, some of the methods listed require to specific conditions such as laboratory techniques and inert atmospheres, microwave or ultrasound irradiation. Thus, the development of alternative procedures,

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which are lacking some of mentioned drawbacks and ecological green catalysts and solvents, of interest to those who work in this field.

It was found that Knoevenagel condensation could be catalyzed in water<sup>[44]</sup>. Water is one of the solvents used in organic reactions is the highly attention, due to having several advantages including safe, non-toxic, clean, green, non-flammable, low cost, readily available, environmentally friendly properties<sup>[45]</sup>.

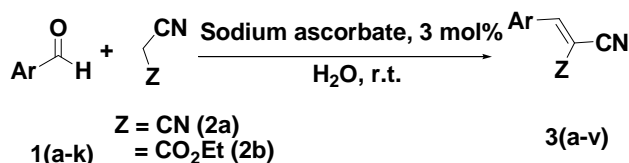
Organocatalysts are small organic molecules that are able to accelerate chemical transformations and have attracted a lot of consideration for application in organic synthesis owing to their efficiency and selectivity. Compared with metallic catalysts, preparation and handling most of the organocatalysts are easier, cheaper, and more stable and are environmental friendly<sup>[46]</sup>.

In consideration of green chemical methodology, we report use of sodium ascorbate as a safe, green, and effective organocatalyst for Knoevenagel condensation of aldehydes with active methylene nitrile compounds in water.

Sodium ascorbate together with copper salts is used to synthesis of triazole ring by “click reaction” strategy<sup>[47]</sup>. Also sodium ascorbate and CuSO<sub>4</sub> pentahydrate in a mixture of *tert*-butanol/water was applied for preparation of substituted isoxazoles *via* 1,3- dipolar cycloaddition<sup>[48]</sup> and three-component reaction<sup>[49]</sup>.

## RESULTS AND DISCUSSION

In the present study, the Knoevenagel reactions between active methylene nitrile compounds [malononitrile (2a) and ethyl cyanoacetate (2b) with aryl aldehydes in the presence of sodium ascorbate as an efficient, green, and commercially available catalyst under aqueous conditions were reported (Scheme 1).



**Scheme 1 :** The Knoevenagel reaction catalyzed by sodium ascorbate

At the beginning, to evaluation the effect of the amounts of catalyst on Knoevenagel condensation, we investigated their effectiveness in the model reaction

between 4-(dimethylamino)benzaldehyde (1f) and malononitrile (2b) in presence of sodium ascorbate ranging from 1- 10 mol% in water at room temperature. The results are listed in TABLE 1.

**TABLE 1:** Effects of solvents and catalyst amount on the Knoevenagel condensation of 4- (Dimethylamino) benzaldehyde (1f) and malononitrile (2a)<sup>a</sup>

Entry	Solvent	Catalyst amount (mol %)	Yield(%) <sup>b</sup>	Time (min)
1	H <sub>2</sub> O	1	85	10
2	H <sub>2</sub> O	2	92	10
3	H <sub>2</sub> O	3	98	10
4	H <sub>2</sub> O	5	95	10
5	H <sub>2</sub> O	10	95	10
6	C <sub>2</sub> H <sub>5</sub> OH	3	90	240
7	THF	3	Trace	600
8	Acetone	3	Trace	600
9	1,4-Dioxane	3	Trace	600
10	CH <sub>3</sub> CN	3	30	600
11	H <sub>2</sub> O/C <sub>2</sub> H <sub>5</sub> OH (1 : 1)	3	90	60
12	Solvent free	3	94	60

<sup>a</sup> Reaction Conditions: 4-(Dimethylamino)benzaldehyde (1 mmol), Sodium ascorbate, and solvent (4 mL), <sup>b</sup> Isolated yields

As illustrated in TABLE 1, the best yield was achieved when the reaction was conducted in the presence of 3 mol% of sodium ascorbate in aqueous media (TABLE 1, entry 3). There was no noticeable rising in the yield of product when further catalyst was added (TABLE 1, entries 4-5). The optimal loading of sodium ascorbate was 3 mol% in which case (1f) obtained 98%. Therefore 3 mol% of catalyst is sufficient for increasing the conversion rate and yield.

In order to examine effects of solvent on the condensation reaction, the model reaction was performed in different solvent such as EtOH, CH<sub>3</sub>CN, THF, acetone, 1,4-dioxane, and mixed solvent of EtOH with H<sub>2</sub>O (1:1, V/V) in presence of 3 mol% catalyst (TABLE 1, entries 6-11). The reaction also proceeded in EtOH in longer reaction time. In the absence of a solvent the product was formed with 94% yield for 60 min (TABLE 1, entry 12). The use of CH<sub>3</sub>CN furnished poor yield (30%), (TABLE 1, entry 10). The other solvents such

as THF, acetone and 1,4-dioxane were ineffective for this reaction. Hence, in terms of reaction time and yield of the product, 3 mol% loading sodium ascorbate and water was considered to be the most conditions for this type reaction.

After optimizing the reaction conditions, aryl aldehydes were reacted with various active methylene nitrile compounds such as malononitrile (**2a**) and ethyl cyanoacetate (**2b**) and the results are summarized in TABLE 2. The results indicated that this sodium ascorbate-catalyzed condensation reaction worked well for a wide range of aryl aldehydes bearing various functional groups including electron-donating and electron-withdrawing substituents on the phenyl ring the reaction

proceeded smoothly in all cases. Therefore, the electronic nature of the functional groups on phenyl ring has no significant effect on the yield of products, however reaction times are affected. Substrates with electron-withdrawing groups (TABLE 2, entries 8-11 and 19-22) reacted rapidly, whereas electron-donating groups (TABLE 2, entries 2-4, 6-7, 13-15 and 17-18) decreased the reactivity, requiring longer reaction time. In addition to the aryl aldehydes, reaction with electron-rich aromatic heterocyclic aldehydes such as furan-2-carbaldehyde was also smoothly developed and high yield is achieved (TABLE 2, entries 5 and 16). It could be found that this reaction involving less reactive ethyl cyanoacetate (TABLE 2, entries 12-22) gave corre-

**TABLE 2: Knoevenagel condensation catalyzed by sodium ascorbate under aqueous medium<sup>a</sup>**

		$\text{Z} = \text{CN (2a)}$ $= \text{CO}_2\text{Et (2b)}$				$\text{3(a-v)}$	
Entry	Ar	Z	Product	Time (min)	Yield (%) <sup>b</sup>	mp (°C)	
						Found	Reported
1	C <sub>6</sub> H <sub>5</sub> 1a	CN	3a	8	95	83-84	80-83 <sup>[42]</sup>
2	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> 1b	CN	3b	10	96	110-114	114 <sup>[42]</sup>
3	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> 1c	CN	3c	20	93	128-129	129-130 <sup>[43]</sup>
4	4-OH-3-CH <sub>3</sub> OC <sub>6</sub> H <sub>3</sub> 1d	CN	3d	15	97	135-136	133-135 <sup>[38]</sup>
5	2-Furyl 1e	CN	3e	14	95	66-67	66-67 <sup>[38]</sup>
6	4-(NMe) <sub>2</sub> C <sub>6</sub> H <sub>4</sub> 1f	CN	3f	10	98, 94, 90, 89, 85 <sup>c</sup>	179-180	180-182 <sup>[36]</sup>
7	4-OHC <sub>6</sub> H <sub>4</sub> 1g	CN	3g	10	98	188-189	187 <sup>[42]</sup>
8	2-ClC <sub>6</sub> H <sub>4</sub> 1h	CN	3h	10	94	94-96	91-92 <sup>[36]</sup>
9	4-ClC <sub>6</sub> H <sub>4</sub> 1i	CN	3i	8	97	163-164	162-163 <sup>[43]</sup>
10	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> 1j	CN	3j	7	97	158-159	159-160 <sup>[43]</sup>
11	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> 1k	CN	3k	8	96	103-104	102-103 <sup>[36]</sup>
12	C <sub>6</sub> H <sub>5</sub> 1a	CO <sub>2</sub> Et	3l	15	90	50-51	52 <sup>[42]</sup>
13	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> 1b	CO <sub>2</sub> Et	3m	20	92	82-83	80-82 <sup>[36]</sup>
14	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> 1c	CO <sub>2</sub> Et	3n	30	89	90-91	90-91 <sup>[43]</sup>
15	4-OH-3-CH <sub>3</sub> OC <sub>6</sub> H <sub>3</sub> 1d	CO <sub>2</sub> Et	3o	22	93	99-101	100 <sup>[43]</sup>
16	2-Furyl 1e	CO <sub>2</sub> Et	3p	18	90	95-96	95 <sup>[43]</sup>
17	4-(NMe) <sub>2</sub> C <sub>6</sub> H <sub>4</sub> 1f	CO <sub>2</sub> Et	3q	15	93	120-122	119-120 <sup>[36]</sup>
18	4-OHC <sub>6</sub> H <sub>4</sub> 1g	CO <sub>2</sub> Et	3r	15	90	169-170	164-167 <sup>[38]</sup>
19	2-ClC <sub>6</sub> H <sub>4</sub> 1h	CO <sub>2</sub> Et	3s	13	89	52-53	53-55 <sup>[36]</sup>
20	4-ClC <sub>6</sub> H <sub>4</sub> 1i	CO <sub>2</sub> Et	3t	12	90	91-92	92-93 <sup>[43]</sup>
21	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> 1j	CO <sub>2</sub> Et	3u	11	92	130-131	131-132 <sup>[36]</sup>
22	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> 1k	CO <sub>2</sub> Et	3v	13	90	166-167	166-168 <sup>[36]</sup>

<sup>a</sup> Conditions: aryl aldehyde 1 (1 mmol), malononitrile (2a) or ethyl cyanoacetate (2b) (1 mmol), sodium ascorbate (3 mol%), H<sub>2</sub>O (4 mL), r.t. All the products are known compounds and were identified by comparison of their melting points and spectral data with those reported. <sup>b</sup> Isolated yields. <sup>c</sup> Catalyst was reused five times

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sponding products in small lower yield and required longer reaction time than malononitrile, which may be attributed to the competency of the cyanide group in stabilizing the reaction intermediates compared to the ester group.

The recoverability and reusability of the catalyst have also been explored, and it could be recycled five times (TABLE 2, entry 6). The catalyst was recovered by evaporation of solvent from filtrated solution after each run.

## EXPERIMENTAL

Melting points were measured on a Buchi 510 melting point apparatus and are uncorrected.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded at ambient temperature on a BRUKER AVANCE DRX-400 MHz using  $\text{CDCl}_3$  as solvent. FT-IR spectra were recorded on a PerkinElmer RXI spectrometer. Chemicals were obtained from Merck, Fluka and Alfa-Aesar. The development of reactions was monitored by thin layer chromatography (TLC) on Merck pre-coated silica gel 60 F<sub>254</sub> aluminum sheets, visualized by UV light.

### General procedure for the synthesis of arylidene nitrile compounds (Knoevenagel condensation)

A mixture of malononitrile (**2a**) (1 mmol) or ethyl cyanoacetate (**2b**) (1 mmol), aryl aldehyde (**1**) (1 mmol) and sodium ascorbate (3 mol%) in 4 mL of distilled water was stirred at room temperature for appropriate time (TABLE 2). When the reaction was completed as indicated by TLC, the precipitate was filtered off, and washed with cold distilled water and dried in air to afford the title pure compounds (**3a-v**). After removal of the water from the filtered solution, the catalyst is recovered and used for the subsequent reaction.

## CONCLUSION

In summary, an efficient, safe, and environmentally benign approach for Knoevenagel condensation of aryl aldehydes with active methylene nitrile compounds using sodium ascorbate as a recyclable, inexpensive, and commercially available catalyst has been developed. Another advantage of this procedure can be pointed to the high yields, mild reaction conditions, simplicity, and

using of water.

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