

## Efficient Protocol for Knoevenagel Condensation in Presence of the Diazabicyclo[5.4.0]undec-7-ene-Water Complex

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A simple and efficient protocol for Knoevenagel condensation has been developed in the presence of diazabicyclo[5.4.0]undec-7-ene (DBU)/water complex. A widely range of carbonyl compounds (aliphatic and aromatic aldehydes, ketones) could react smoothly with methylene active ingredients (malononitrile, ethyl cyanoacetate, diethyl malonate and acetylacetone), which can not proceed by conventional catalyst. Other significant features of this method include readily work-up, good recyclability of catalytic system and short reaction time.

**Key Words:** Knoevenagel condensation, Green chemistry, Diazabicyclo[5.4.0]undec-7-ene, Recyclability.

### INTRODUCTION

The Knoevenagel condensation is a well-known organic reaction largely employed in the formation of carbon-carbon bond to produce important intermediated and end products for perfumes and polymers<sup>1</sup>. This reaction is usually performed in organic solvents in the presence of homogeneous basic catalysts, like amines, pyridine, piperidine and guanidine<sup>1b,2</sup>. Recently, some Lewis catalysts, including MgF<sub>2</sub><sup>3a</sup>, MgO/ZrO<sub>2</sub><sup>3b</sup>, Mg(ClO<sub>4</sub>)<sub>2</sub><sup>3c</sup>, NbCl<sub>5</sub><sup>3d</sup> have been developed for the Knoevenagel condensation. However, many of these catalysts are water-sensitive and can not be reused because the Knoevenagel condensation would produce water itself. Thus, some novel catalysts with excellent recyclability like ionic liquid functionalized SBA-15 mesoporous material<sup>4a</sup>, magnetic nanoparticles functionalized with basic ionic liquids<sup>4b,4c</sup>, PEG-supported piperazine<sup>5</sup> and task-specific ionic liquids<sup>6</sup> have been successfully utilized in Knoevenagel condensation. Although PEG-immobilized amines or task-specific ionic liquids can solve the problem of recyclability of catalyst, these novel catalysts were substrate-selective. It is very difficult to react the relatively inert ketones with aliphatic and aromatic aldehydes in the presence of these catalysts. Thus, the establishment of a protocol with highly efficiency, widely scope of substrate, good recyclability, readily work-up is still highly desirable.

Because of its non-nucleophilic, strong tertiary amine base, diazabicyclo[5.4.0]undec-7-ene (DBU) has been widely used in S-N type Smiles rearrangement<sup>7a</sup>, selective deprotection of TMS group<sup>7b</sup>, Baylis-Hillman reaction<sup>7c</sup> and aza-Michael

addition<sup>7d</sup>. Recently, Medina *et al.*<sup>8</sup>, reported that DBU can react with water to obtain a Brønsted type basic catalyst (Fig. 1), showing high catalytic activity for aldol reaction. With the increase in the mole ratio of DBU/H<sub>2</sub>O, the reaction time for the reaction decreased. Considering the potential of the Brønsted basic catalyst **1** for the industrial scale application, the mole ratio of 1:25 was selected for the formation of the Brønsted catalyst **1** with the corresponding time<sup>8</sup> of 3 h. Herein, we wish the Brønsted catalyst **1** in water could be used as an efficient reaction system for Knoevenagel condensation.

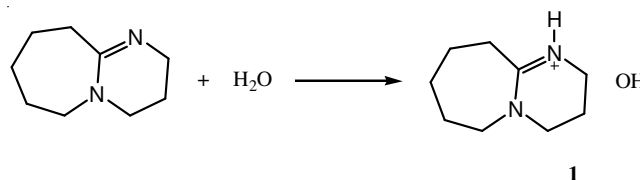


Fig. 1. Preparation of diazabicyclo[5.4.0]undec-7-ene-derived Brønsted base

### EXPERIMENTAL

**General procedure for Knoevenagel condensation:** A 10 mL bottomed flask was charged with DBU (1 mmol) and water (25 mmol). The mixture was stirred at room temperature for 3 h to converse completely DBU to its corresponding Brønsted base as reported by Medina *et al.*<sup>8</sup>. Then 1 mmol carbonyl compounds and methylene active ingredients were added and stirred continuously to form the desired products monitored by TLC. After completion of the reaction, products

were isolated *via* readily filtration and dried under vacuum without further purification, while the filtrate containing DBU/water complex was reused directly in subsequent reactions. All condensation products were characterized by NMR analysis and melting points.

### Selected spectral data

**Ethyl (E)-2-cyano-3-(4-methylphenyl)-2-propenoate (entry 2, Table-2):** White solid; m.p. 92-93 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (ppm): 8.22 (s, 1H, C=CH), 7.90 (d, 2H, *J* = 8 Hz, ArH), 7.30 (d, 2H, *J* = 8 Hz, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) (ppm): 162.7, 155.0, 144.6, 131.2, 130.0, 128.8, 115.7, 101.4, 62.5, 21.8, 14.1.

**Ethyl (E)-2-cyano-3-(4-N,N-dimethylphenyl)-2-propenoate (entry 5, Table-2):** Yellow solid; m.p. 124-125 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (ppm): 8.07 (s, 1H, C=CH), 7.93 (d, 1H, *J* = 8.8 Hz, ArH), 6.69 (d, 2H, *J* = 8.8 Hz, ArH), 4.33 (q, 2H, *J* = 7.2 Hz, CH<sub>2</sub>), 3.11 (s, 6H, N(CH<sub>3</sub>)<sub>2</sub>), 1.37 (t, 3H, *J* = 7.2 Hz, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) (ppm): 164.3, 154.4, 153.4, 133.9, 119.2, 117.5, 111.3, 93.7, 61.7, 39.9, 14.2.

**Ethyl (E)-2-cyano-3-(2-furyl)-2-propenoate (entry 7, Table-2):** White solid; m.p. 91-92 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (ppm): 8.02 (s, 1H, C=CH), 7.76 (d, 1H, *J* = 1.2 Hz, furyl), 7.40 (d, 1H, *J* = 3.6 Hz, furyl), 6.67-6.66 (m, 1H, furyl), 4.36 (q, 2H, *J* = 7.2 Hz, CH<sub>2</sub>), 1.38 (t, 3H, *J* = 7.2 Hz, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) (ppm): 157.5, 143.6, 143.2, 134.4, 116.7, 110.2, 108.8, 93.5, 57.5, 9.1.

**2-(3-Pyridylmethylene)malononitrile (entry 10, Table-2):** White solid; m.p. 84-85 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (ppm): 8.89 (d, 1H, *J* = 2 Hz, pyridyl), 8.83 (d, 1H, *J* = 3.6 Hz, pyridyl), 8.49-8.47 (m, 1H, pyridyl), 7.55-7.52 (m, 1H, pyridyl); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) (ppm): 158.5, 154.6, 152.3, 135.6, 126.9, 124.2, 112.9, 111.9, 85.5.

**2-(Phenylmethylene)malononitrile (Entry 14, Table-2):** White solid; m.p. 79-80 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (ppm): 7.91 (d, 2H, *J* = 7.6 Hz, ArH), 7.79 (s, 1H, C=CH), 7.64 (t, 1H, *J* = 7.6 Hz, ArH), 7.27 (t, 2H, *J* = 7.6 Hz, ArH), 7.27 (t, 2H, *J* = 7.6 Hz, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) (ppm): 160.0, 134.6, 130.9, 130.7, 129.6, 113.7, 112.5, 82.7.

**3-Benzylidene-2,4-pentanedione (entry 16, Table-2):** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (ppm): 7.47 (s, 1H, C=CH), 7.37 (m, 5H, ArH), 2.40 (s, 3H, CH<sub>3</sub>), 2.26 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) (ppm): 200.6, 191.5, 137.8, 134.8, 127.8, 125.6, 124.6, 123.9, 26.6, 21.4.

## RESULTS AND DISCUSSION

After DBU reacted completely with water to form the catalyst **1** within 3 h (DBU: 1 mmol, H<sub>2</sub>O: 25 mmol), benzaldehyde (1 mmol) and ethyl cyanoacetate (1 mmol) were added. To our surprise, the Knoevenagel of benzaldehyde with ethyl cyanoacetate proceeded smoothly and 96 % yield was achieved within just 20 min (entry 3, Table-1). Then we increased the amount of benzaldehyde and lower yield was obtained within the same reaction period (entries 1-2, Table-1), which can be explained by solidification of reaction mixture and the start material can not completely disappear (TLC) when water content in reaction solution decreased. When the amount of benzaldehyde was reduced to 0.2 mmol, 0.1 mmol, respectively,

TABLE-1  
INFLUENCE OF THE MOLE RATIO OF BENZALDEHYDE, DBU AND WATER ON THE KNOEVENAGEL CONDENSATION OF BENZALDEHYDE AND ETHYL CYANOACETATE\*

Entry	Mole ratio of benzaldehyde, DBU and water	Reaction time (min)	Yield (%)**
1	5:1:25	20	83
2	3:1:25	20	85
3	1:1:25	20	96
4	0.2:1:25	60	86
5	0.1:1:25	60	79
6	1:1:0	50	86
7	1:0:25	120	17

\*Reaction conditions: DBU (1 mmol), mole ratio of benzaldehyde and ethyl cyanoacetate = 1:1, at room temperature. \*\*Isolated yields.

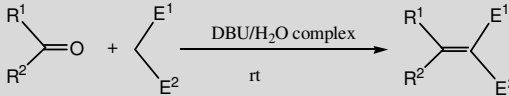
the isolated yields decreased slightly (entries 4-5, Table-1). This behaviour can be explained by the fact that high concentration of water in reaction mixture would partly dissolve the final product. We also investigated performance of the model reaction conducted in absence of water (entry 6, Table-1). Compared with entry 3 and entry 6 of Table-1, Brønsted base DBU/H<sub>2</sub>O complex performed better than Lewis base DBU to catalyze the Knoevenagel condensation. Moreover, a blank experiment was tested and 17 % yield was obtained after 2 h (entry 7, Table-1), demonstrating high catalytic activity of Brønsted base DBU/H<sub>2</sub>O for the model reaction. Thus, we selected the mole ratio of substrate/DBU/water of 1:1:25 for further investigations.

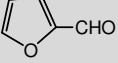
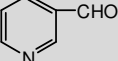
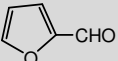
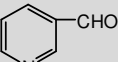
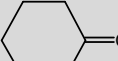
Subsequently, the scope of the Knoevenagel condensation of other aldehydes and ketones with various active methylene compounds in the presence of DBU/water mixture was examined (Table-2). As shown in Table-2, the products were isolated in excellent yields when aromatic aldehydes, including hetero aromatic aldehydes such as 2-furaldehyde and 3-pyridinecarboxaldehyde were exploited to react with malononitrile or ethyl cyanoacetate (entries 1-6 and 7-14, Table-2). Ketones like cyclohexanone and acetone, which were usually sluggish for Knoevenagel condensation, also underwent smoothly with active methylene compounds at room temperature (entries 19-21, Table-2), showing the excellent catalytic activity of DBU/water mixture for Knoevenagel condensation.

Compared to the Knoevenagel reactions of malononitrile with benzaldehyde, the reactions of ethyl cyanoacetate and diethyl malonate with benzaldehyde required more time (Entries 1 and 14-16, Table-2). The order for nucleophilicity of these active methylene compounds is as follows: malononitrile > ethyl cyanoacetate > diethyl malonate ≈ acetylacetone. The reason is that the electron-withdrawing ability of the CN group is stronger than that of carbonyl or carboxylic group. It is worth to note that all the products obtained are E-geometry exclusively and no subsequent Michael adduct is detected.

In order to demonstrate the industrial applicability of this methodology, the Knoevenagel condensation of benzaldehyde and ethyl cyanoacetate was carried out on a larger scale (100 mmol). The reaction was completed in 0.5 h. The excellent yield of 98 % for the condensation product achieved. On the

TABLE-2  
KNOEVENAGEL CONDENSATION PROMOTED  
BY DBU/H<sub>2</sub>O COMPLEX\*



Entry	R <sup>1</sup>	R <sup>2</sup>	E <sup>1</sup>	E <sup>2</sup>	Time (min)	Yield (%)**
1	Ph	H	CN	CO <sub>2</sub> Et	20	96
2	4-Me-Ph	H	CN	CO <sub>2</sub> Et	50	98
3	4-MeO-Ph	H	CN	CO <sub>2</sub> Et	50	100
4	2-MeO-Ph	H	CN	CO <sub>2</sub> Et	50	95
5	4-(N,N)-dimethyl-Ph	H	CN	CO <sub>2</sub> Et	60	100
6	2-NO <sub>2</sub> -Ph	H	CN	CO <sub>2</sub> Et	10	93
7			CN	CO <sub>2</sub> Et	10	95
8			CN	CO <sub>2</sub> Et	60	83
9			CN	CN	1	93
10			CN	CN	10	85
11	4-MeO-Ph	H	CN	CN	5	96
12	4-(Me) <sub>2</sub> N-Ph	H	CN	CN	20	98
13	2-NO <sub>2</sub> -Ph	H	CN	CN	1	89
14	Ph	H	CN	CN	5	95
15	Ph	H	CO <sub>2</sub> Et	CO <sub>2</sub> Et	30	91
16	Ph	H	COMe	COMe	30	95
17	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	H	CN	CN	20	93
18	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	H	CN	CN	20	94
19	Me	Me	CN	CN	5	95
20	Me	Me	CN	CO <sub>2</sub> Et	30	96
21			CN	CN	30	95

\*Reaction conditions: carbonyl compound (1 mmol), active methylene compound (1 mmol), DBU/H<sub>2</sub>O complex formed by reaction of 1 mmol DBU with 25 mmol H<sub>2</sub>O after 3 h as given in ref. 8, room temperature; \*\*Isolated yield.

same scale, the recyclability of catalytic system was investigated using the same reaction as model reaction. Upon the completion of the reaction, the product was isolated *via* readily filtration and dried under vacuum without further purification, while the filtrate containing DBU/water complex was reused directly in subsequent reactions. As shown in Fig. 2, the DBU/

water complex can be reused at least ten times without any loss of the catalytic activity of the DBU-derived Brønsted base **1**.

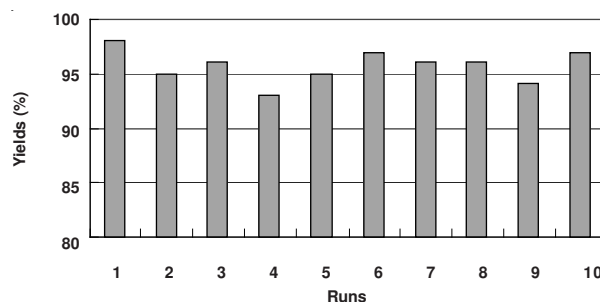


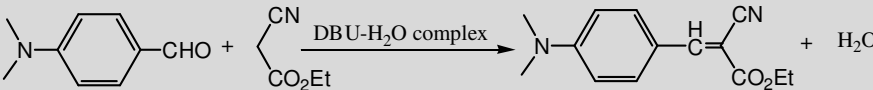
Fig. 2. Reuse of catalytic system for Knoevenagel condensation between benzaldehyde and ethyl cyanoacetate

For the purpose of comparison with other published methodologies about the catalytic efficiency, we carried out the reaction of inert substrate 4-(N,N)-dimethylamino benzaldehyde with ethyl cyanoacetate. As shown in Table-3, only reaction in guanidinium lactate provided the comparable yield (97.2 %) while it required 2.5 equiv amount of ionic liquid, which would limit its large scale application (Entries 4-5, Table-3). There was a problem about recyclability of catalytic system in the condensation reaction promoted by phase-transfer catalyst TEBA (Entry 3, Table-3). Other methods suffered from the longer reaction times as well as lower yields of products (Entries 1-2, Table-3). All the results show the present catalytic system is very efficient and economic for Knoevenagel condensation (Entry 5, Table-3). As for the mechanism of DBU/water complex, we speculated that the hydroxyl of Brønsted base **1** in water absorb the hydrogen of methylene compounds to greatly improve their nucleophilicities and efficiently catalyze the Knoevenagel reaction.

## Conclusion

In summary, a highly efficient, green and facile protocol for Knoevenagel condensation using DBU-derived Brønsted base as promoter in water was established. This method is applicable to a wide range of carbonyl compounds (aliphatic and aromatic aldehydes, ketones) and methylene active ingredients (malononitrile, ethyl cyanoacetate, diethyl malonate and acetylacetone). The advantages of the methodology include readily work-up, excellent recyclability and high product yield, and make us believe that this simple and efficient procedure would be a practical alternative to the existing methods.

TABLE-3  
COMPARISON OF THE PRESENT CATALYTIC SYSTEM WITH OTHER REPORTED PROTOCOLS IN THE MODEL REACTION BETWEEN 4-(DIMETHYLAMINO) BENZALDEHYDE WITH ETHYL CYANOACETATE



Entry	Reaction conditions	Yields (%)*	Ref.
1	Perfluoroalkylated pyridine catalyzed in <i>n</i> -octane, at 80 °C for 10 h.	78.0	9a
2	PEG as solvent, catalyzed by L-proline, reaction time: 210 min	81.2	9b
3	Catalyst: TEBA, reaction time: 15 min	86.0	9c
4	2.5 equiv amount of cyclic guanidinium lactate as solvent, reaction time: 3 min	97.2	–
5	1 h for reaction, DBU/H <sub>2</sub> O complex as promoter	100.0	–

\*Isolated yield.

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