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A facile catalyst-free Knoevenagel condensation of pyridinecarbaldehydes and active methylene compounds

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This paper reports a study of the facile catalyst-free Knoevenagel condensation of pyridinecarbaldehydes and active methylene compounds like malononitrile, cyanoacetamide, ethyl cyanoacetate, and methyl cyanoacetate. The reaction occurs in a H_2O:EtOH mixture at room temperature to give high yields of electron-deficient alkenes with E-selectivity.

Keywords: Active methylene compounds, Catalyst-free, Knoevenagel condensation, Pyridinecarbaldehydes

INTRODUCTION

Catalysts play an important role in organic synthesis. In spite of its importance, at the end of a reaction, the catalyst should be separated from the products. This usually needs an organic solvent. Recently, green chemistry has tried to decrease the use of toxic solvents. With the increasing interest in developing environmentally benign reactions, the atom-economic catalytic processes, along with the use of approximately green solvents, are considered as ideal processes in organic chemistry [1]. There are some reports on catalyst-free reactions in organic synthesis such as the preparation of dithiocarbamates [1], thiosemicarbazones [2], nitrogen heterocycles [3] and vinyl sulfides [4].

Knoevenagel condensation is one of the most useful C=C bond forming reactions in organic synthesis [5,6]. Although other organic reactions, like Heck and Wittig reactions, yield alkenes, Knoevenagel condensation has the advantage of being a simple and easy reaction to perform. This is because water is the only side product and no unstable reactive intermediates are involved. These elements make this reaction environmentally friendly. Furthermore, the products of this reaction are usually E-alkenes. In contrast, Wittig reaction produces a mixture of Z/E-alkenes [5]. Knoevenagel condensation is applied to the synthesis of therapeutic drugs [7], natural products [8], herbicides, insecticides, functional polymers [9], and fine chemicals [10]. It is usually performed in organic solvents in the presence of common bases such as piperidine [11]. However, certain alternative approaches such as aqueous media [7], high pressure [11], microwave [12], and ultrasound [13] have been employed. Also, a wide range of catalysts have been used. They include Lewis acids [14], zeolites [15], solid bases [16], heterogeneous catalysts [17], amines immobilized on polymers [18], ionic liquids [19], and amino acids [20]. The development of facile and environmentally benign methods for Knoevenagel condensation would be of value and is still required for green organic synthesis. In this paper, we report a facile uncatalyzed synthetic approach to prepare a series of new electron-deficient alkenes with operational simplicity, economic viability, and greater E-selectivity *via* Knoevenagel condensation. This condensation reaction was carried out in a H_2O:EtOH mixture at room temperature. The structures of the products were determined by IR, ^{1}H-, and ^{13}C-NMR spectra.

EXPERIMENTAL

Instrumenmts

IR spectra were recorded on a Bruker Eqinox 55 spectrometer. ^{1}H- and ^{13}C-NMR spectra were obtained using a Bruker Avance 500 MHz spectrometer (DRX). The elemental analysis was done on a Costech ECS 4010 CHNS-O analyzer. The melting points were determined on a Büchi melting point B-540 apparatus.

General experimental procedure

At room temperature, active methylene compound (1mmol) was added to a magnetically stirred solution of pyridinecarbaldehyde (1 mmol, 0.1 g) in H_2O:EtOH (5 ml). The progress of the reaction was monitored by TLC using $CHCl_3$: MeOH 90:10 as an eluent. After completion of the

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reaction, the corresponding solid product was filtered off. The sole product was obtained after simple recrystallization in a 50% H_2O:EtOH mixture in excellent yields (90-95%).

Selected spectroscopic data

2-(Pyridin-4-ylmethylene)malononitrile (Table 2, Entry 1): White solid; mp 100-101 ºC; IR: 3023, 2233, 1610, 1590, 1548, 1416, 1403, 1236, 1219, 1067, 947, 933, 819,771, 621. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.69 (d, *J* = 5.3 Hz, 2H, ArH); 7.83 (s, 1H, vinyl H); 8.88 (d, *J* = 5.3 Hz, 2H, ArH). ^{13}C-NMR (125 MHz, $CDCl_3$): 89.0; 111.8; 112.9; 123.1; 137.4; 151.9; 158.0. Anal. calc. for $C_9H_5N_3$: C 69.67, H 3.25, N 27.08; Found: C 69.59, H 3.54, N, 26.96.

2-(Pyridin-3-ylmethylene)malononitrile (Table 2, Entry 2): White solid; mp 81-83 ºC; IR: 3035, 2226, 1589, 1412, 1263, 1234, 1023, 974, 856, 802, 692, 650, 618. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.53 (dd, *J* = 8.2 Hz, *J* = 4.8 Hz, 1H, ArH); 7.86 (s, 1H, vinyl H); 8.48 (d, *J* = 4.8 Hz, 1H, ArH); 8.83 (d, *J* = 4.8 Hz, 1H, ArH); 8.91 (s, 1H, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$): 86.1; 112.5; 113.4; 124.7; 127.4; 136.1; 152.8; 155.1; 156.1. Anal. calc. for $C_9H_5N_3$: C 69.67, H 3.25, N 27.08; Found: C 69.42, H 3.53, N 27.05.

(E)-Methyl-2-cyano-3-(pyridin-4-yl)acrylate (Table 2, Entry 3). White solid, mp 124-125 ºC; IR: 3029, 2227, 1725, 1615, 1596, 1547, 1434, 1418, 1274, 1236, 1197, 1099, 969, 847, 816, 795, 763. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.99 (s, 3H, CH_3); 7.77 (d, *J* = 6.1 Hz, 2H, ArH); 8.22 (s, 1H, vinyl H); 8.83 (d, *J* = 6.3 Hz, 2H, ArH). ^{13}C-NMR (125 MHz, $CDCl_3$): 54.2; 97.3; 114.6; 123.7; 138.4; 151.5; 152.8; 162.2. Anal. calc. for $C_{10}H_8N_2O_2$: C 63.82, H 4.28, N 14.89; Found: C 63.73, H 4.18, N 14.74.

(E)-Methyl-2-cyano-3-(pyridin-3-yl)acrylate (Table 2, Entry 4): White solid; mp 127-128 ºC; IR: 3035, 2226, 1731, 1612, 1584, 1564, 1475, 1429, 1236, 1264, 1196, 1089, 1044, 1023, 937, 814, 793, 757, 703, 626. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.95 (s, 3H, CH_3); 7.52 (dd, *J* = 8.1 Hz, *J* = 4.8 Hz, 1H, ArH); 8.31 (s, 1H, vinyl H); 8.61 (d, *J* = 8.1 Hz, 1 H, ArH); 8.80 (d, *J* = 4.8 Hz, 1H, ArH); 8.96 (s, 1H, ArH). ^{13}C-NMR (125 MHz, $CDCl_3$): 54.1; 95.7; 115.2; 124.5; 127.9; 136.5; 151.9; 153.2; 153.8; 162.6. Anal. calc. for $C_{10}H_8N_2O_2$: C 63.82, H 4.28, N 14.89; Found: C 63.69, H 4.20, N 14.90.

(E)-Ethyl-2-cyano-3-(pyridin-4-yl)acrylate (Table 2, Entry 5): White solid; mp 99-100 ºC; IR: 3032, 2224, 1725, 1618, 1596, 1542, 1416, 1365, 1260, 1236, 1192, 1087, 1014, 853, 830, 764. 1H-NMR (500 MHz, $CDCl_3$): 1.40 (t, *J* = 7.0 Hz, 3H, CH_3); 4.40 (q, *J* = 7.0 Hz, 2H, CH_2); 7.74 (d, *J* = 6.2 Hz, 2H, ArH); 8.19 (s, 1H, vinyl H); 8.81 (d, *J* = 6.2 Hz, 2H, ArH). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.5; 63.7; 98.7; 114.6; 123.6; 138.5; 151.5; 152.5; 161.6. Anal. calc. for $C_{11}H_{10}N_2O_2$: C 65.34, H 4.98, N 13.85; Found: C 65.45, H 4.86, N 13.52.

(E)-Ethyl-2-cyano-3-(pyridin-3-yl)acrylate (Table 2, Entry 6): White solid; mp 78-80 ºC; IR: 3023, 2221, 1728, 1611, 1584, 1419, 1363, 1250, 1225, 1092, 1014, 896, 852, 763, 705, 632. 1H-NMR (500 MHz, $CDCl_3$): 1.43 (t, *J* = 7.1, 3H, CH_3), 4.43 (q, *J* = 7.1, 2H, CH_2), 7.50 (dd, *J* = 8.2, *J* = 4.7, 1H, ArH), 8.28 (s, 1H, vinyl H), 8.59 (d, *J* = 8.2, 1H, ArH), 8.78 (d, *J* = 4.7, 1H, ArH), 8.95 (s, 1H, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$): 14.5; 63.5; 96.1; 115.3; 124.3; 128.0; 136.4; 151.7; 153.3; 153.9; 162.1. Anal. calc. for $C_{11}H_{10}N_2O_2$: C 65.34, H 4.98, N 13.85; Found: C 65.62, H 4.92, N 13.76.

(E)-2-Cyano-3-(pyridin-4-yl)acrylamide (Table 2, Entry 7): White solid; mp 209-211 ºC; IR: 3427, 3325, 3027, 2216, 1697, 1598, 1414, 1360, 1240, 1004, 974, 808, 668. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.76 (d, *J* = 5.9, 2H, ArH); 8.05 (brs, 2H, NH_2); 8.18 (s, 1H, vinyl H); 8.79 (d, *J* = 5.9, 2H, ArH). ^{13}C-NMR (125 MHz, $CDCl_3$): 89.5; 116.3; 123.8; 139.9; 149.1; 151.6; 162.7. Anal. calc. for $C_9H_7N_3O$: C 62.42, H 4.07, N 24.27; Found: C 62.01, H 4.10, N 24.26.

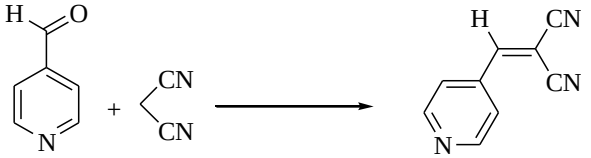
(E)-2-Cyano-3-(pyridin-3-yl)acrylamide (Table 2, Entry 8): White solid; mp 228-231 ºC; IR: 3415, 3331, 3029, 2220, 1687, 1594, 1419, 1380, 1257, 1225, 1029, 803, 693. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.61 (dd, *J* = 7.9, *J* = 4.8, 1H, ArH); 7.98 (brs, 2H, NH_2); 8.24 (s, 1H, vinyl H); 8.37 (d, J = 7.9, 1H, ArH); 8.72 (d, J = 4.8, 1H, ArH); 8.97 (s, 1H, ArH). ^{13}C- NMR (125 MHz, $CDCl_3$): 109.8; 116.9; 125.0; 129.08; 136.83; 148.6; 152.1; 153.2; 163.0. Anal. calc. for $C_9H_7N_3O$: C 62.42, H 4.07, N 24.27; Found: C, 62.31, H, 4.11, N 24.21.

RESULTS AND DISCUSSION

Knoevenagel condensation produced some products that can be regarded as Michael acceptors in Michael or Aza- Michael reaction, as dienophiles in Diels-Alder and hetero Diels-Alder reactions, and as monomers in anionic polymerization. This condensation reaction was also applied to the synthesis of bioactive molecules. In this work, we report an environmentally benign procedure for the synthesis of some new electron-deficient alkenes *via* Knoevenagel condensation of pyridine-carbaldehydes and active methylene compounds.

At first, for the optimization of the reaction conditions, the condensation of 4-pyridine-

Table 1. Condensation of 4-pyridinecarbaldehyde with malononitrile in various conditions [a)]



Entry	Solvent	Temperature. (°C)	Time (h)	Yield (%)[b)]
1	MeCN	r. t.	24	20
2	MeCN	reflux	24	35
3	EtOH	r. t.	24	50
4	EtOH	70	24	65
5	H_2O	r. t.	-	-[c]
6	Solvent-free	r. t.	-	-[c]
7	H_2O:EtOH (25:75)	r. t.	2	92
8	H_2O:EtOH (50:50)	r. t.	0.5	95
9	H_2O:EtOH (75:25)	r. t.	1.5	90
10	H_2O:EtOH (50:50)	70	0.5	94

a) 4-Pyridinecarbaldehyde (1 mmol), malononitrile (1 mmol). [b)] Yield refers to isolated yield. [c)] Black stick.

carbaldehyde with malononitrile was studied as a model reaction in various solvents at room temperature. The reaction in an aprotic solvent such as MeCN and in EtOH, as a protic one, did not proceed well and produced 2-(pyridin-4-ylmethylene)malononitrile with low yield after long reaction time even in refluxing conditions. As environment consciousness imposes the use of water for organic processes from both industrial and academic points of view [21-24], we decided to study the model reaction in pure water. The reactants were consumed promptly and a black sticky mixture was obtained in water. The black stick was also obtained in solvent-free conditions. In order to avoid this problem, the reaction was performed in a H_2O:EtOH mixture, and the ratio of the solvents was optimized. Fortunately, in a 50% H_2O:EtOH solution, this condensation was took place in a short reaction time (30 min) to produce 2-(pyridin-4-ylmethylene)malononitrile with an excellent yield under catalyst-free conditions (Table 1).

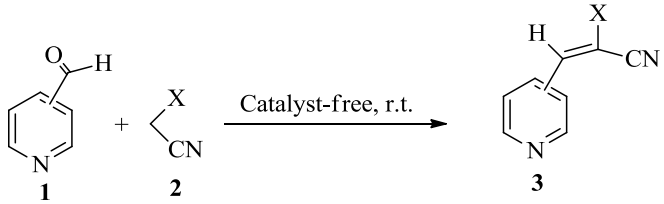
To examine the generality of the procedure, we checked the Knoevenagel condensation of various pyridylcarbaldehydes and active methylene compounds under optimized reaction conditions. The results summarized in Table 2 show that malononitrile is more active than cyanoacetamide, ethyl cyanoacetate, and methyl cyanoacetate due to the electron-withdrawing ability of CN groups. Ethyl and methyl cyanoacetates are more active than cyanoacetamide and readily react with pyridinecarbaldehydes. The Knoevenagel condensation of 4-pyridinecarbaldehyde with active methylene compounds is faster than that of 3-pyridinecarbaldehyde. It is because of the the resonance electron-withdrawing effect. The reaction of 2-pyridincarbaldehyde is also faster than that of 3-pyridincarbaldehyde and 4-pyridincarbaldehyde due to both resonance and induced effects of nitrogen in a pyridine ring.

All aforementioned reactions proceeded well enough and delivered high to excellent yields (Table 2). One of the advantages of this method, as mentioned in the experimental section, is that the product is precipitated, as the reaction proceeds and is isolated by simple filtration after the reactant is consumed. Thus, the reaction can be conducted without using any reaction workup method. Furthermore, we applied this green method for the condensation of malononitrile with an aromatic aldehyde such as benzaldehyde, 4-nitrobenzaldehyde, and 4-cyanobenzaldehyde with a view to compare with pyridinecarbaldehydes (Table 3).

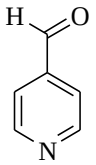
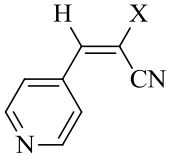
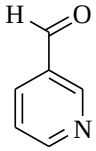
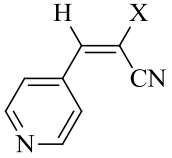
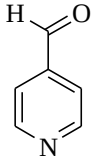
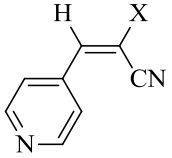
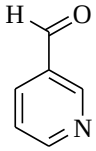
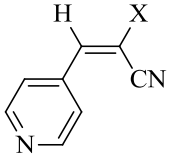
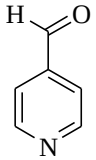
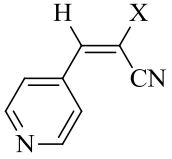
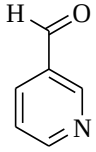
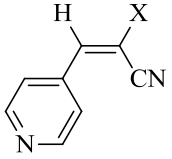
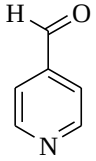
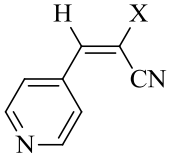
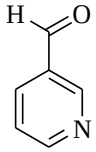
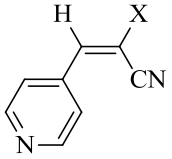
According to the results, the Knoevenagel condensation of pyridinecarbaldehydes with malononitrile is much faster than the condensation of the same active methylene compound with benzaldehyde, 4-nitrobenzaldehyde, 4-cyanobenzaldehyde, and even 4-nitrobenzaldehyde in the presence of pyridine. These results also show that the pyridine ring has dual activity. One is to activate the methylene compounds by attracting the proton from the methylene *via* a non-bonding electron pair of nitrogen in the pyridine ring. The second is to activate the carbonyl group in the fourth position of the pyridine ring. A possible mechanism is denoted in the Scheme 1.

After the catalysts have accelerated the rate of a reaction in many cases, they should be separated at the end of the reaction. Catalyst-free reactions usually occur by reflux, microwave or other energetic methods while, in this work, we perform the catalyst-free reaction at room temperature.

Table 2. Condensation of pyridinecarbaldehydes (**1**) with active methylene compounds (**2**) [a)]



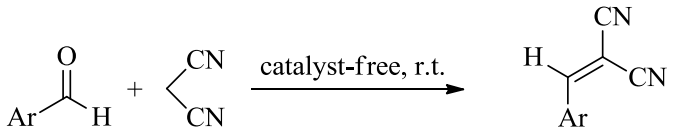
1 **2** **3**

Entry	Pyrdinecarbaldehyde	X	Product	Time(min)	Yield %[b]	Mp (°C)
1		CN		30	95	100-101
2		CN		40	93	81-83
3		CO_2Me		45	92	124-125
4		CO_2Me		55	92	127-128
5		CO_2Et		50	91	99-100
6		CO_2Et		65	93	78-80
7		$CONH_2$		80	90	209-211
8		$CONH_2$		95	92	228-231

[a] Reaction conditions: pyridinecarbaldehyde (1 mmol), active methylene compound (1 mmol), H_2O:EtOH (1:1).

[b] Yields refer to isolated pure products which were characterized by their Mp, IR, ^{1}H- and ^{13}C-NMR spectra and elemental analysis.

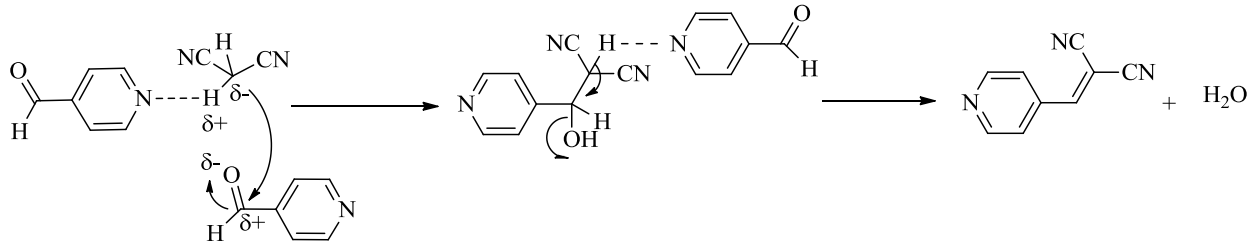
Table 3. Comparison of different arylaldehydes in a catalyst-free Knoevenagel reaction [a)]



Entry	Ar	Time(min)	Yield (%)
1	C_6H_5	240	93
2	4-CN- C_6H_4	160	85
3	4-NO_2- C_6H_4	160	91
4	4-NO_2- C_6H_4 [b)]	110	92
5	2-Pyridyl	Very fast	-
6	3-Pyridyl	40	93
7	4-Pyridyl	30	95

[a)] Reaction conditions: arylaldehyde (1 mmol), malononitrile (1 mmol), H_2O:EtOH (1:1).
[b)] Pyridine was added to the reaction media.

Scheme 1. The proposed mechanism of synthesizing 2-(Pyridin-4-ylmethylene)malononitrile



Scheme 1

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ПРОСТА KNOEVENAGEL'ОВА КОНДЕНЗАЦИЯ НА ПИРИДИН-КАРБАЛДЕХИДИ И АКТИВНИ МЕТИЛЕНОВИ СЪЕДИНЕНИЯ БЕЗ КАТАЛИЗАТОР

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(Резюме)

В статията се съобщава за изследване на една проста Knoevenagel'ова кондензация без катализатор на пиридин-карбалдехиди и активни метиленови съединения, като малонитрил, цианацетамид, етил-цианоацетат и метил-цианоацетат. Реакцията протича в смес от вода и етанол при стайна температура с високи добиви на производни на пиридил-метилиден-малононитрила с Е-селективност.