Solvent-free L-proline catalysed condensation of ethyl cyanoacetate with aldehydes

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Solvent-free Knoevenagel condensation of ethyl cyanoacetate with aromatic aldehydes, catalysed by environmentally friendly silica gel supported L-proline under microwave irradiation is studied.

Keywords: Knoevenagel, ethyl cyanoacetate, L-proline, solventless system

The Knoevenagel condensation is an important reaction in organic chemistry.[1] This carbon–carbon bond formation[2,3] reaction has been extensively studied under a variety of conditions, in solvents,[4] with various catalysts,[5] with inorganic solid supports[6] and new techniques exploiting solvent-free microwave assisted conditions.[7] Recently the Knoevenagel reaction has also been carried out in ionic liquids.[8]

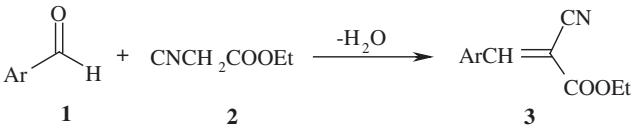
L-proline has been used as a catalyst for one-pot trimolecular condensation of indoles,[9] asymmetric aldol reactions of thiopyran-4-one with aldehydes,[10] Michael additions,[11] and asymmetric synthesis of anti-1,2-diols.[12]

Recently microwave-assisted synthesis in solventless system in organic reactions has been of growing interest as an efficient, economic and clean procedure.[13]

In continuation of our interest in catalytic reactions,[14] Knoevenagel reaction[15] and other organic reactions in solventless system under microwave irradiation,[16] we now report that L-proline supported onto silica gel is a highly efficient catalyst for the condensation of ethyl cyanoacetate with aromatic aldehydes under microwave irradiation in solventless system.

We first examined proline in catalytic amount in Knoevenagle reaction without any support. The reaction was conducted by mixing of aldehyde **1** (1 mmol) and ethyl cyanoacetate **2** in amounts given in Table 1 and catalytic amount of proline in a beaker using spatula. The mixture was placed in microwave oven and the progress of reaction was monitored by TLC. Although TLC showed some conversion, the reaction was sluggish and considerable amounts of starting materials were unchanged and more seriously the starting material adhered to the walls of vessel. Over the past few years, a considerable number of organic transformations have been developed in which inorganic solid supports appeared to be useful in terms of mildness of conditions, yields, rapidity and conveniences.[17] In a manner analogous to our previous experiments[16] we supported the starting materials and catalyst onto silica gel by mixing them and irradiated this mixture with microwaves. By monitoring the progress of reaction, we found that L-proline catalyses the Knoevenagel reaction to yield the product in excellent yield and in short reaction time. To establish the generality of the method various aldehydes were reacted with ethyl cyanoacetate to give the corresponding alkenes (Scheme 1). The resulting alkenes **3**, reaction conditions and yields are shown in Table 1.

In all cases, the products **3a–l**, were identified as the *E* isomers by the comparison of their IR, ^{1}H NMR spectra and literature reported melting points. The absence of the carbonyl group absorption of the aldehydes in IR spectra and appearance of olefinic hydrogens at down field are indication for the completion of the reaction. Cinnamaldehyde reacted with ethyl cyanoacetate to give 1-cyano-1-carboxyethyl-4-phenylbuta-1,3- dione with no Michael addition product (entry **l**). High yields for both aromatic rings carrying electron withdrawing and electron donating groups were achieved (Table1). The electron donating groups (OCH_3, CH_3, and OH) on the aromatic ring did not retard the Knoevenagel condensation under these conditions.



Scheme 1

In summary, we have developed a solvent-free, eco-friendly Knoevenagel condensation using available L-proline under microwave irradiation in very short time and excellent yields.

Experimental

Melting points were taken in open capillary on an electrically heated metal block are uncorrected. The IR spectra were recorded on FT-IR Bruker Tensor 27 spectrometer. ^{1}H NMR spectra were measured in D-chloroform solution on FT-NMR Bruker operating at 500 MHz and reported in δ ppm using tetramethylsilane as the internal standard. The reactions were carried out in a domestic microwave oven, Panasonic Model No.NN-K543WF.

L-Proline catalysed condensation of ethyl cyanoacetate with aldehydes: general procedure

A mixture of the aldehyde (1 mmol), ethyl cyanoacetate, proline (amounts given in Table 1) and silica gel (2 g) were mixed thoroughly using pestle and mortar. This reaction mixture was placed in a beaker and kept over an alumina bath inside a domestic microwave oven and irradiated for the indicated time at high power level (1000 Watt). The progress of reaction was monitored by TLC using petroleum: acetone, 10 : 3 (v/v) as eluent. The product was extracted with $CHCl_3$ (3 ml), and dried over $MgSO_4$. Evaporation of solvent and recrystallisation of the crude gave the pure desired product (Table 1).

2-Cyano-3-phenyl-2-propenoic acid ethylester (**3a**): IR (KBr): 3029–2981, 2222, 1729, 1606, 1367–1572, 1262, 1092, 769, 685 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (3H, t, *J* = 7.1Hz, OCH_2CH_3), 4.42 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 7.5–7.6 (3H, m, 3', 4', 5'H), 8.02 (2H, m, 2', 6'H), 8.08 (1H, s, =CH)

2-Cyano-3-(4-methylphenyl)-2-propenoic acid ethylester (**3b**): IR (KBr): 3020–2922, 2216, 1722, 1596, 1510–1366, 1272, 1208, 1189, 1093, 1018, 849–760 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 2.40 (3H, s, CH3Ar), 4.45 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 7.27 (2H, d, *J* = 8.2 Hz, 3', 5'H), 7.75 (2H, d, *J* = 8.2 Hz, 2', 6'H), 8.21 (1H, s, =CH)

2-Cyano-3-(2-nitrophenyl)-2-propenoic acid ethylester (**3c**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 4.45 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 7.75 (1H, dt, *J* = 7.8, 1.5 Hz, 5'-H), 7.84 (1H, dt, *J* = 7.8, 1.1Hz, 4'H), 7.9 (1H, dd, *J* = 7.8, 1.5 Hz, 3'H), 8.32 (1H, dd, *J* = 7.8, 1.1 Hz, 6'H), 8.76(1H, s, =CH)

2-Cyano-3-(3-nitrophenyl)-2-propenoic acid ethylester (**3d**): IR (KBr): 3020–2987, 2360, 1718, 1650, 1557, 1356, 1267, 1205, 1096–670 cm^{-1}

^{1}H NMR(500MHz, $CDCl_3$) δ 1.46 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 4.4 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 7.76(1H, t, *J* = 8.05 Hz, 5'H), 8.35 (1H, s, =CH), 8.4 (2H, m, 4' H, 6'H), 8.74 (1H, s, 2'H)

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Table 1 Condensation of ethyl cyanoacetate with aromatic aldehydes catalysed by L-proline under microwave irradiation in solventless system.

Entry	Substrate	Ethylcyanoacetate/ mmol	Proline/ mmol	Reaction time/min	Yield/%[a]	M.p[b]/ °C	
						Found	Reported
a	C_6H_5CHO	1.2	0.6	5	100	50–51	52[18]
b	4-$CH_3C_6H_4CHO$	2.6	0.9	5	100	82–84	88[19]
c	2-$NO_2C_6H_4CHO$	1.8	0.7	3	100	94–96	96[20]
d	3-$NO_2C_6H_4CHO$	2.6	0.7	6	100	135–137	135[21]
e	4-$NO_2C_6H_4CHO$	2.6	0.7	6	100	166–170	170[18]
f	4-ClC_6H_4CHO	1.8	0.7	2	100	82–85	87[18]
g	2-$CH_3OC_6H_4CHO$	1.2	0.7	4	100	72–74	69[18]
h	3-$CH_3OC_6H_4CHO$	1.8	0.7	4	88.9	oil	–
i	4-$CH_3OC_6H_4CHO$	1.8	0.7	12	94.7	84–85	86[18]
j	2-pyrrolcarbaldehyde	1.8	0.7	15	92.7	128–130	
k	2-furfural	1.8	0.7	2	100	80–85	84[18]
l	C_6H_5CH=$CHCHO$	1.8	0.7	5	100	111–112	115[22]

[a]Purified product.
[b]Reported melting points are uncorrected.

2-Cyano-3-(4-nitrophenyl)-2-propenoic acid ethylester (**3e**): IR (KBr): 3096–2941, 2224, 1721, 1616, 1593, 1515, 1347, 1267, 858, 790–686 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 4.45 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 8.14 (2H, d, *J* = 9.5 Hz, 2', 6'H), 8.25(1H, s, =CH), 8.35 (2H, d, *J* = 9.5 Hz, 3', 5'H)

2-Cyano-3-(4-chlorophenyl)-2-propenoic acid ethylester (**3f**): IR (KBr): 3020–2800, 2222, 1723, 1612, 1587, 1490–1364, 1265, 1203, 1080, 831–583 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (3H, t, *J* = 6.9 Hz, OCH_2CH_3), 4.45 (2H, q, *J* = 6.9 Hz, OCH_2CH_3), 7.42 (2H, d, *J* = 9.3 Hz, 2', 6'H), 7.95(2H, d, *J* = 9.3Hz, 3', 5'H), 8.18(1H, s, =CH)

2-Cyano-3-(2-methoxyphenyl)-2-propenoic acid ethylester (**3g**): 2983, 2220, 1714, 1613, 1579, 1241, 1073, 751–684 cm^{-1}

^{1}H NMR (500 M Hz, $CDCl_3$) δ 1.4 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 3.9 (3H, s, OCH_3), 4.34 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 7.62 (2H, dd, *J* = 6.5, 2.5 Hz, 3'H, 6'H), 8.03 (2H, dd, *J* = 6.5, 2. 5 Hz, 4'H, 5'H), 8.2(1H, s, =CH)

2-Cyano-3-(3-methoxyphenyl)-2-propenoic acid ethylester (**3h**): IR (NEAT): 3028–2839, 2226, 1727, 1607, 1490–1370, 1247, 1096, 1038–792, 764–684 cm^{-1}

2-Cyano-3-(4-methoxyphenyl)-2-propenoic acid ethylester (**3i**): ^{1}H NMR (500 M Hz, $CDCl_3$) δ 1.42 (3H, t, *J* = 7.15 Hz, OCH_2CH_3), 3.9 (3H, s, OCH_3), 4.34 (2H, q, *J* = 7.14 Hz, OCH_2CH_3), 7.02 (2H, dd, *J* = 6.9, 2.0 Hz, 2'H, 6'H), 8.03 (2H, dd, *J* = 6.9, 2.0 Hz, 3'H, 5'H), 8.2 (1H, s, =CH)

2-Cyano-3-pyrrole-2-propenoic acid ethylester (**3j**): IR (KBr): 3307, 3124–2965, 2209, 1696, 1582, 1427, 1281, 1220, 1146–699 cm^{-1}

^{1}H NMR(500 MHz, $CDCl_3$) δ 1.4 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 4.3(2H, q, *J* = 7.1 Hz, OCH_2CH_3), 6.9(1H, d, *J* = 2.0Hz, 5'H), 7.2(1H, dd, *J* = 3.4, 2.0 Hz, 4'H), 7.3(1H, d, *J* = 3.4Hz, 3'H), 8.05(1H, s, =CH), 10.0 (1H, s, NH)

2-Cyano-3-furyl-2-propenoic acid ethylester (**3k**): IR (KBr): 3128–2938, 2222, 1716, 1620, 1539–1261, 1211, 1091–843, 760 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.4 (3H, t, *J* = 7.1 Hz, OCH2CH3), 4.34 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 6.7(1H, dd, *J* = 3.6, 1.6Hz, 4'H), 7.4 (1H, d, *J* = 3.6 Hz, 3'H), 7.7 (1H, d, *J* = 1.6 Hz, 5'H), 8.05 (1H, s, =CH)

(E-E)-2-Cyano-5-phenyl-2, 4-pentadiene carboxylic acid ethylester (**3l**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.4 (3H, t, *J* = 7.16 Hz, OCH_2CH_3), 4.36(2H, q, *J* = 7.16 Hz, OCH_2CH_3), 7.30(1H, dd, *J* = 5.1, 2.9Hz CH=CH–CH=CN(CO_2Et)), 7.32(1H, dd, *J* = 7.9, 5.1Hz, CH=CH–CH=CN(CO_2Et)), 7.4(1H, dt, *J* = 6.6, 2.5 Hz, 4'H), 7.46 (2H, dt, *J* = 6.6, 1.9 Hz, 3', 5'H), 7.63(2H, dd, *J* = 6.6, 2.5Hz, 2', 6'H), 8.04 (1H, dd, *J* = 7.9, 2.9 Hz, CH=CN(CO_2Et))

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