Zirconium tetrachloride-SiO_2 catalyzed Knoevenagel condensation: a simple and efficient protocol for the synthesis of substituted electrophilic alkenes

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Abstract
A facile method for Knoevenagel condensation has been developed by using $ZrCl_4$-SiO_2 to afford the corresponding substituted electrophilic alkenes in excellent yields. This method is applicable to a wide range of aldehydes and active methylene compounds. The solid supported catalyst system was reused in further reactions and all the reactions were carried out at 80-85 ^oC in acetonitrile.

Keywords: Lewis acid, silica gel, malonates, aldehydes, substituted alkenes, Knoevenagel reaction

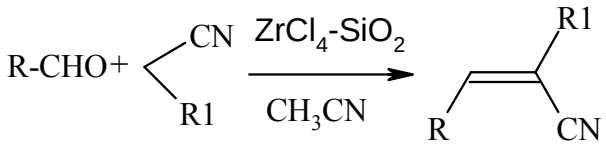
Introduction

Knoevenagel condensation is one of the most important reactions in organic synthesis for carbon-carbon bond formation.[1] This reaction has been used widely for the preparation of coumarins and coumarin derivatives, which are very important intermediates in cosmetics, perfumes and pharmaceuticals industry.[2] There has been a growing interest in Knoevenagel condensation products, because many of them have significant biological activity. Among them, tyrophostins, such as α-cyanothiocinnamide were shown to inhibit autophosphorylation of the EGF-receptor, in addition to possessing antiproliferative effects on human keratinocytes. Generally, Knoevenagel condensation is carried out in homogenous conditions catalyzed by weak bases such as ethylenediamine, piperidine[3] or corresponding ammonium salts, DMAP or amino acids such as glycine, alanine and L-proline[4] and also reported with potassium fluoride, ionic liquids, calcite,[5] triphenylphosphine, natural phosphate, resin[6] and montmorillonite KSF.[7] However, it can also be performed in heterogeneous media, using solid support[8] catalysts. In addition to these methods, in recent years, Lewis acid catalysts[9] are also being used successfully for this transformation. However, many of the methods involve the use of expensive and

stoichiometric amounts of reagents, suffer from generality and also require extended reaction times. Therefore, the development of a new and efficient protocol for this transformation under mild and more convenient conditions is still needed. To our knowledge, there are no reports for Knoevenagel condensation using zirconium tetrachloride adsorbed on silica gel.

Results and Discussion

Herein, we report the use of zirconium tetrachloride adsorbed on silica gel ($ZrCl_4$-SiO_2)[10] as a novel and efficient catalyst for the carbon-carbon bond formation reactions under mild reaction conditions. To optimize the reaction conditions, equimolar amounts of benzaldehyde and ethyl cyanomalonate (Scheme 1) were reacted in presence of $ZrCl_4$-SiO_2 catalyst system (entry **a**) at 80-85 ^oC in acetonitrile solvent. The reaction was completed with in 3.0 h to obtain the corresponding ethyl (*E*)-2-cyano-3-phenyl propionate in excellent yield (90%).



1 **2** **3**

Scheme 1

The same reaction was complete at room temperature after 11.0 h. This experiment clearly indicates the effect of temperature on rate of reaction. In another experiment, equimolar amounts of benzaldehyde and dicyanomalonate were treated in presence of $ZrCl_4$-SiO_2 catalyst at 80-85 ^oC to obtain the corresponding 2-(2-phenylmethylene) malononitrile in 92% yield (entry **b**) within 2.5 h. The observation shows that dicyanomalonate reacts a little faster than ethylcyanomalonate. Encouraged by these results, we have applied this method to a variety of aldehydes such as aliphatic (entry **g**, **h**), alicyclic (entry **k**, **l**), heterocyclic (entry **i**, **j**) and α, β-unsaturated (entry **m**, **n**) aldehydes to obtain the corresponding olefin derivatives. Aromatic aldehydes, containing electron-withdrawing groups (entry **e**, **f**) as well as electron- donating groups (entry **c**, **d**) reacted smoothly with active methylene compounds of dicyanomalonate and ethylcyanomalonate to afford the corresponding substituted alkene products in excellent yields. The particulars of reaction time, yield and the stereochemistry of the products are mentioned in Table 1. All the reactions were carried out at 80-85 ^oC of reaction temperature in acetonitrile solvent, while using the catalyst in catalytic amount (10% mol). In general, the aromatic aldehydes react faster comparatively with aliphatic and alicyclic systems. In a similar manner, the active methylene carbon of dicyanomalonate reacts faster when compared with ethylcyano malonate. The heterocyclic aldehyde, furfural (entry **i**, **j**) reacted very smoothly with both the

malonates to obtain the corresponding derivatives in excellent yields. In all the cases, the reactions were completed within 2-4 hours of reaction time. In the absence of $ZrCl_4$-SiO_2 catalyst, the reaction does not proceed under similar reaction conditions, even after a long reaction time (15 h). Furthermore, after the reaction, the catalyst was filtered off and washed with solvent, dried and reused for further reactions up to three times without any problem. The first reaction of benzaldehyde with ethylcyanomalonate was completed within 3.0 h. The second reaction with the same reactants was completed within 3.5 h and the third reaction with the same reactants was completed in 5.0 h. It clearly shows that the catalyst system is reusable and economic point of view, encouraging for organic synthesis. This method does not require anhydrous reaction conditions or any special precautions.

Conclusions

In conclusion, $ZrCl_4$-SiO_2 catalyst has been employed as an efficient solid support catalyst for carbon-carbon bond formation reactions between aldehydes and active methylene compounds to obtain olefin derivatives. This method is applicable to a wide range of aldehydes including aliphatic, aromatic, heterocyclic and α, β-unsaturated substrates. The attractive features of this procedure are mild reaction conditions, high conversions, reusability of the catalyst, easy isolation of products and operational simplicity, making it a useful procedure for the synthesis of substituted olefins in very good yields.

Table 1. $ZrCl_4$-SiO_2 catalyzed Knoevenagel condensation

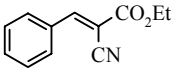
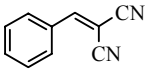
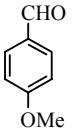
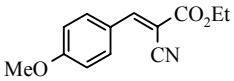
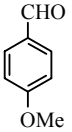
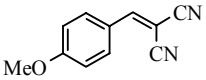
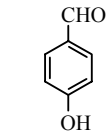
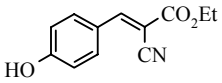
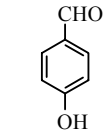
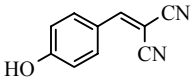
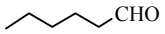
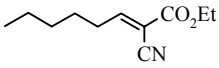
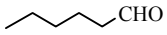
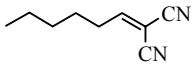
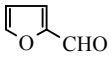
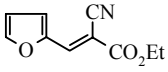
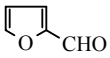
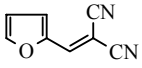
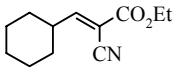
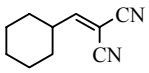
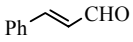
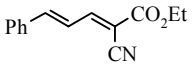
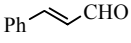
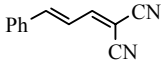
S. No	Substrate	R_1	Product	Reaction Time (h)	Yield (%)
a		CO_2Et		3.0	90
b		CN		2.5	92
c		CO_2Et		3.5	89
d		CN		3.0	90

Table 1. Continued

S. No	Substrate	R_1	Product	Reaction Time (h)	Yield (%)
e		CO_2Et		3.5	86
f		CN		3.0	89
g		CO_2Et		4.0	82
h		CN		3.5	85
i		CO_2Et		2.5	90
j		CN		2.0	93
k		CO_2Et		4.0	83
l		CN		3.5	86
m		CO_2Et		3.5	83
n		CN		3.0	85

Experimental Section

General Procedures. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer. ^{1}H NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer

operating at 70eV. All the products physical and spectroscopic data were compared with those reported in the literature.

General synthetic procedure

To a mixture of aldehyde (2 mmol) and active methylene compound (2.2 mmol) in acetonitrile solvent (5 mL) was added the catalyst (0.2 mmol). The resulting reaction mixture was stirred at 80-85 ^{o}C for appropriate time (Table 1). The progress of the reaction was monitored by thin layer chromatography (TLC). After complete conversion of the starting material as indicated by TLC, the reaction mixture was filtered and the catalyst was washed with solvent (2x2 mL). The combined filtrates were adsorbed on silica gel (60-120 mesh) and eluted with ethyl acetate and hexane mixture to afford the pure products. All the products were confirmed by their ^{1}H NMR, IR and mass spectroscopy data and compared with literature reports[3a,6a].

Ethyl (*E*)-2-cyano-3-phenyl-2-propenoate (3a). Solid, M P. 48-49 ^{o}C. IR (KBr): υ 3057, 2936, 2849, 2225, 1720, 1684, 1605, 1592, 1524, 1469, 1328, 1255, 1210, 1179, 1109, 1095, 952, 861, 749 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$). δ 1.38 (t, 3H, *J* = 6.8 Hz), 4.32 (q, 2H, *J* = 6.8 Hz), 7.40-7.55 (m, 3H), 7.88-7.97 (m, 2H), 8.20 (s, 1H). EIMS *m/z* (%). 201 (m^{+} 28), 172 (15), 128 (100), 102 (56), 77 (68), 51 (40), 43 (20).

2-(Phenylmethylene) Malononitrile (3b). Solid, M P. 101-102 ^{0}C. IR (KBr): υ 3061, 2949, 2852, 2232, 1718, 1685, 1610, 1593, 1517, 1472, 1320, 1210, 1149, 1087, 946, 838, 743 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$). δ 7.35-7.55 (m, 3H), 7.68 (s, 1H), 7.85-7.95 (m, 2H). EIMS *m/z* (%). 154 (m^{+} 20), 127 (35), 102 (100), 76 (18), 51 (20).

Ethyl (*E*)-2-cyano-3-phenyl-2-propenoate (3c). Solid, M P. 80-81 ^{o}C. IR (KBr): υ 3285, 3021, 2972, 2851, 2445, 2360, 1741, 1610, 1532, 1464, 1308, 1232, 1129, 1055, 941, 770 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$). δ 1.36 (t, 3H, *J* = 7.0 Hz), 3.90 (s, 3H), 4.35 (q, 2H, *J* = 7.0 Hz), 6.98 (d, 2H, *J* = 8.0 Hz), 7.97 (d, 2H, *J* = 8.0 Hz), 8.18 (s, 1H). EIMS *m/z* (%). 231 (m^{+} 32), 202 (20), 158 (100), 143 (50), 127 (18), 101 (35), 76 (20), 51 (22).

2-(4-Methoxyphenylmethylene) Malononitrile (3d). Solid M P. 114-116 ^{o}C. IR (KBr): υ 3115, 3072, 2937, 2849, 2230, 1605, 1560, 1462, 1375, 1218, 1139, 1027, 950, 826, 733 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$). δ 3.90 (s, 3H), 7.05 (d, 2H, *J* = 8.0 Hz), 7.66 (s, 1H), 7.90 (d, 2H, *J* = 8.0 Hz). EIMS *m/z* (%). 184 (m^{+} 100), 141 (25), 114 (40), 76 (22), 51 (15).

Ethyl (*E*)-2-cyano-3-(-hydroxyphenyl)-2-propenoate (3e). Solid, M P. 168-169 ^{o}C. IR (KBr): υ 3655, 3173, 3041, 2966, 2845, 2228, 1710, 1602, 1592, 1512, 1449, 1378, 1259, 1208, 1179, 1104, 1045, 972, 831, 739 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$). δ 1.39 (t, 3H, *J* = 7.0 Hz), 4.38 (q, 2H, *J* = 7.0 Hz), 7.02 (d, 2H, *J* = 8.0 Hz), 7.94 (d, 2H, *J* = 8.0 Hz), 8.18 (s, 1H). EIMS *m/z* (%). 217 (m^{+} 100), 189 (45), 172 (70), 145 (26), 117 (20), 93 (12), 89 (22), 76 (10), 51 (20).

2-(4-Hydroxyphenylmethylene) Malononitrile (3f). Solid, M P. 172-173 ^{0}C. IR (KBr): υ 3650, 3170, 3062, 2957, 2838, 2230, 1712, 1674, 1605, 1590, 1510, 1459, 1367, 1278, 1218, 1161, 1105, 1049, 962, 835, 731 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$). δ 2.40 (brs, 1H, OH), 7.05 (d, 2H, *J* = 8.0 Hz), 7.90 (d, 2H, *J* = 8.0 Hz), 8.15 (s, 1H). EIMS *m/z* (%). 170 (m^{+} 15), 144 (25), 118 (100), 101 (46), 76 (30), 51 (22).

Ethyl (*E*)-2-cyano-2-octenoate (3g). Liquid. IR (neat): υ 2960, 2859, 2253, 1718, 1679, 1608, 1583, 1514, 1458, 1410, 1335, 1278, 1208, 1182, 1115, 1093, 1012, 950, 932, 857, 734 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$). δ 0.90 (t, 3H, *J* = 6.5 Hz), 1.21 (t, 3H, J= 6.5 Hz), 1.28- 1.38 (m, 6H), 1.45-1.55 (m, 4H), 2.50-2.60 (m, 2H), 4.28 (q, 2H, *J* = 6.5 Hz), 7.65 (t, 1H, *J* = 10.0 Hz). EIMS *m/z* (%). 195 (m^+ 35), 166 (10), 151 (56), 125 (100), 96 (25), 75 (18), 69 (15), 57 (32), 43 (22).

2-Octylidenemalononitrile (3h). Liquid. IR (neat): υ 2951, 2846, 2249, 1715, 1682, 1618, 1584, 1524, 1479, 1408, 1365, 1231, 1205, 1182, 1115, 1095, 1011, 947, 922, 852, 736 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$). δ 0.95 (t, 3H, *J* = 6.5 Hz), 1.25-1.35 (m, 6H), 1.40-1.50 (m, 4H), 2.52-2.65 (m, 2H), 7.66 (t, 1H, *J* = 10.0 Hz). EIMS *m/z* (%). 176 (m^+ 20), 150 (36), 124 (100), 99 (20), 71 (12), 43 (20).

Ethyl (*E*)-2-cyano-3-(2-furyl)-2-propenoate (3i). Solid, M P. 88-99 °C. IR (KBr): υ 3037, 2951, 2827, 2215, 1755, 1672, 1610, 1534, 1467, 1390, 1346, 1269, 1214, 1173, 1094, 965, 876, 739 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$). δ 1.36 (t, 3H, *J* = 7.0 Hz), 4.33 (q, 2H, *J* = 7.0 Hz), 6.69 (dd, 1H, *J* = 1.5, 4.2 Hz), 7.45 (d, 1H, *J* = 4.2 Hz), 7.80 (d, 1H, *J* = 2.0 Hz), 8.02 (s, 1H). EIMS *m/z* (%). 191 (m^+ 100), 172 (10), 163 (25), 146 (20), 135 (30), 128 (60), 119 (15), 102 (36), 92 (20), 77 (18), 63 (12), 49 (20).

2-(Furylmethylene) malononitrile (3j). Solid, M P. 69-70 °C. IR (KBr): υ 3125, 3042, 2957, 2839, 2225, 1608, 1525, 1452, 1395, 1298, 1109, 1021, 932, 822, 763 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$). δ 6.70 (dd, 1H, *J* = 4.0, 1.8 Hz), 7.45 (d, 1H, *J* = 4.0 Hz), 7.56 (d, 1H, *J*= 4.0 Hz), 7.80 (s, 1H). EIMS *m/z* (%). 144 (m^+ 100), 141 (75), 115 (20), 89 (12), 69 (15), 62 (15), 43 (20).

Ethyl (*E*)-2-cyano-3-cyclohexyl-2-propenoate (3k). Solid. M P. 89-90 °C. IR (neat): υ 2985, 2256, 1725, 1682, 1610, 1588, 1512, 1466, 1349, 1312, 1260, 1215, 1162, 1105, 1087, 1010, 956, 912, 887, 821, 763, 741 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$). δ 1.22-1.35 (m, 9H), 1.68-1.78 (m, 4H), 2.65-2.72 (m, 1H), 4.25 (q, 2H, *J* = 6.9 Hz), 7.48 (d, 1H, *J* = 10.0 Hz). EIMS *m/z* (%). 207 (m^+ 25), 178 (10), 162 (78), 134 (100), 108 (20), 83 (15), 56 (25).

2-(Cyclohexylmethylene) malononitrile (3l). Solid. M P. 101-102 °C. IR (neat): υ 2982, 2846, 2254, 1720, 1686, 1615, 1589, 1510, 1469, 1329, 1318, 1260, 1225, 1160, 1108, 1083, 1012, 957, 910, 889, 820, 765, 739 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$). δ 1.25-1.36 (m, 6H), 1.70-1.80 (m, 4H), 2.65-2.75 (m, 1H), 7.50 (d, 1H, *J* = 10.0 Hz). EIMS *m/z* (%). 160 (m^+ 20), 134 (15), 108 (100), 83 (12), 48 (20).

Ethyl (*2E, 4E*)-2-cyano-5-phenyl-2, 4-pentadienoate (3m). Solid, M P. 116-117 °C. IR (KBr): υ 3087, 2971, 2853, 2245, 1730, 1642, 1524, 1417, 1320, 1263, 1115, 1092, 925, 836, 729 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$). δ 1.42 (t, 3H, *J* = 7.0 Hz), 4.30 (q, 2H, *J* = 7.0 Hz), 7.22-7.30 (m, 2H), 7.38-7.43 (m, 3H), 7.50-7.63 (m, 2H), 8.10 (d, 1H, *J* = 10.0 Hz). EIMS *m/z* (%). 227 (m^+ 20), 198 (30), 154 (100), 128 (50), 103 (30), 77 (20), 51 (22).

2-((*E*)-3-Phenylallylidene) malononitrile (3n). Solid, M P. 132-133 °C. IR (KBr): υ 3082, 2956, 2847, 2241, 1728, 1640, 1571, 1512, 1437, 1322, 1265, 1135, 1068, 973, 841, 734 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$). δ 7.20-7.30 (m, 2H), 7.40-7.45 (m, 3H), 7.50-7.60 (m, 2H), 8.10 (d, 1H, *J* = 10.0 Hz). EIMS *m/z* (%). 180 (m^+ 32), 154 (22), 128(100), 103 (18), 77 (25), 52 (12).

References and Notes

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10. *Catalyst preparation*. A mixture of zirconium tetrachloride (1 gm) and silica gel (10 gm) in methylene dichloride was stirred well for 30 minutes and the solvent was removed under reduced pressure. The obtained powder was dried and used for reactions.