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Conjugate Hydrocyanation of Chalcone Derivatives Using Ethyl Cyanoacetate as an Organic Cyanide Source

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The conjugate hydrocyanation of chalcone derivatives using ethyl cyanoacetate as an organic cyanide source at room temperature under open air and transition metal-free conditions was described. The protocol has advantages of using relatively cheap, less toxic, stable and easy-to-handle cyanating reagent, high yield, and mild reaction condition.

Keywords hydrocyanation, chalcone derivative, ethyl cyanoacetate, organic cyanide source

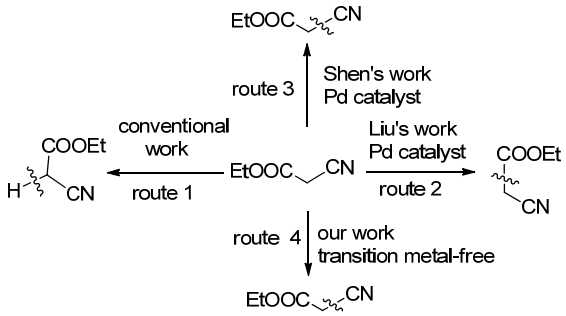
Introduction

Cyanation of organic chemicals is an important way to synthesize various compounds bearing cyano group.[1] Conjugate addition of cyanide to chalcone derivatives has been explored in recent years, which has been demonstrated to be an efficient route to *β*-cyano ketones.[2] *β*-Cyano ketones are valuable synthons for the synthetic organic chemistry, and the cyano group can be easily transformed into a variety of functional groups, such as amides, amines, aldehydes, acids, esters, triazoles, tetrazoles, oxazoles and thiazoles.[3] However, the current existing reactions require the use of various highly toxic cyanide sources, such as HCN,[4] KCN[5] and Et_2AlCN,[6] in super-stoichiometric amounts. Therefore, the discovery of new sources of cyanide generated from simple and readily available reagents is still an extremely attractive challenging goal.

As an important reagent, the conventional reactions of ethyl cyanoacetate are the provision of carbon anion under basic conditions to participate in Knoevenagel condensation *etc*. (Scheme 1, route 1).[7] Liu reported a palladium-catalyzed decarboxylative coupling of ethyl cyanoacetate with aryl halides (triflates),[8] in which ethyl cyanoacetate provided $NCCH_2^-$ through C—C bond cleavage (Scheme 1, route 2). Recently, Shen reported ethyl cyanoacetate could be used as an organic cyanide source to provide CN^- via C—C bond cleavage of NC-CH_2 moiety for the palladium-catalyzed cyanation of aryl halides (Scheme 1, route 3).[9] However, in this reaction the expensive transition metal is required, and the substrate scope only limits to aryl halides.

In this paper, we report the utilization of ethyl cyanoacetate as an organic cyanide source via C—CN bond cleavage at room temperature under transition metal-free and open air conditions to conduct the conjugate hydrocyanation of chalcone derivatives (Scheme 1, route 4). In comparison with other organic cyanide sources reported, such as TMSCN,[10] acetone cyanohydrin,[11] ethyl cyanoformate,[12] acetyl cyanide,[13] NCTS,[14] mandelonitrile,[15] isonitrile,[16] acetonitrile,[17] DMF-ammonia[18] and DMF,[19] ethyl cyanoacetate as a new and alternative organic cyanide source has the distinct advantages of being relatively cheap, less toxic, stable and easy-to-handle.

Scheme 1 The bond cleavage type of ethyl cyanoacetate



Experimental

IR spectra were recorded using KBr pellets on an Alpha Centauri FTIR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Mercury-400BB instrument using $CDCl_3$ as solvent and Me_4Si as internal standard. Melting points were observed in an electrothermal melting point apparatus.

Typical procedure for conjugate hydrocyanation of chalcone derivatives with ethyl cyanoacetate

To a solution of 0.5 mmol of chalcone derivative in 5

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mL of DMF was added 0.55 mmol of ethyl cyanoacetate and 1.0 mmol of potassium hydroxide. The reaction mixture was stirred at room temperature for 8 h under open air. After completion of the reaction, the resulting mixture was poured into water and extracted with EtOAc (3×10 mL). The combined organic phase was washed with water (3×10 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography [silica gel, *V*(petroleum ether)/*V*(ethyl acetate)=20∶1] to give product. The analytical data for products are given below.

4-Oxo-2,4-diphenylbutanenitrile (2a) White solid. M.p. 120—122 ℃ (lit.[20] 120—122 ℃). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.51 (dd, J=5.6, 18.0 Hz, 1H, CHCH_aHCO), 3.74 (dd, J = 7.6, 18.0 Hz, 1H, CHCH_bHCO), 4.58 (dd, J=6.0, 6.4 Hz, 1H, ArCHCH$_2$), 7.26—7.43 (m, 7H, ArH), 7.58—7.62 (m, 1H, ArH), 7.92—7.94 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.9, 44.5, 120.6, 127.5, 128.1, 128.4, 128.8, 129.3, 133.9, 135.2, 135.6 194.6. IR (KBr) v: 1681 (C=O), 2238 (CN) cm^{-1}. Anal. calcd for $C_{16}H_{13}NO$ (235.28): C 81.68, H 5.57, N 5.95; found C 81.59, H 5.56, N 5.97.

4-Oxo-2-phenyl-4-(4-tolyl)butanenitrile (2b) White solid. M.p. 66—68 ℃ (lit.[21] 71—73 ℃). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.34 (s, 3H, CH_3) 3.41 (dd, J=6.4, 17.6 Hz, 1H, CHCH_aHCO), 3.63 (dd, J=8.4, 17.6 Hz, 1H, CHCH_bHCO), 4.49 (dd, J=6.0, 8.0 Hz, 1H, ArCHCH$_2$), 7.18—7.38 (m, 7H, ArH), 7.45 (d, J=8.0 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.7, 31.9, 44.4, 120.7, 127.5, 128.2, 128.3, 129.2, 129.5, 133.2, 135.3, 144.9, 194.2. IR (KBr) v: 1676 (C=O), 2242 (CN) cm^{-1}. Anal. calcd for $C_{17}H_{15}NO$ (249.31): C 81.90, H 6.06, N 5.62; found C 81.99, H 6.05, N 5.64.

4-(4-Methoxyphenyl)-4-oxo-2-phenylbutanenitrile (2c) Oil (lit. Oil).[21] ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.37 (dd, J=6.0, 17.6 Hz, 1H, CHCH_aHCO), 3.60 (dd, J=8.4, 17.6 Hz, 1H, CHCH_bHCO), 3.79 (s, 3H, CH_3), 4.49 (dd, J=6.0, 8.0 Hz, 1H, ArCHCH$_2$), 6.85 (d, J=6.8 Hz, 2H, ArH), 7.23—7.37 (m, 5H, ArH), 7.83 (d, J=6.8 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.9, 44.1, 55.5, 113.9, 120.8, 127.4, 128.3, 128.7, 129.2, 130.4, 135.4, 164.0, 193.0. IR (KBr) v: 1676 (C=O), 2243 (CN) cm^{-1}. Anal. calcd for $C_{17}H_{15}NO_2$ (265.31): C 76.96, H 5.70, N 5.28; found C 76.80, H 5.71, N 5.30.

4-(4-Chlorophenyl)-4-oxo-2-phenylbutanenitrile (2d) White solid. M.p. 112—114 ℃. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.39 (dd, J=5.6, 18.0 Hz, 1H, CHCH_aHCO), 3.63 (dd, J = 8.4, 18.0 Hz, 1H, CHCH_bHCO), 4.47 (dd, J=6.4, 7.6 Hz, 1H, ArCHCH$_2$), 7.25—7.38 (m, 7H, ArH), 7.79 (d, J=8.8 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.9, 44.5, 120.4, 127.4, 128.4, 129.2, 129.3, 129.5, 133.9, 135.0, 140.4, 193.5. IR (KBr) v: 1676 (C=O), 2241 (CN) cm^{-1}. Anal. calcd for $C_{16}H_{12}ClNO$ (269.73): C 71.25, H 4.48, N 5.19; found C 71.37, H 4.50, N 5.21.

4-(4-Nitrophenyl)-4-oxo-2-phenylbutanenitrile (2e) Yellow solid. M.p. 148—150 ℃. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.55 (dd, J=5.6, 18.0 Hz, 1H, CHCH_aHCO), 3.78 (dd, J=7.6, 18.0 Hz, 1H, CHCH_bHCO), 4.56 (dd, J=5.6, 6.8 Hz, 1H, ArCHCH$_2$), 7.38—7.43 (m, 5H, ArH), 8.09 (d, J=8.0 Hz, 2H, ArH), 8.32 (d, J=8.0 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.8, 45.0, 120.1, 124.0, 127.4, 128.6, 129.2, 129.4, 134.6, 139.8, 150.7, 193.3. IR (KBr) v: 1685 (C=O), 2242 (CN) cm^{-1}. Anal. calcd for $C_{16}H_{12}N_2O_3$ (280.28): C 68.56, H 4.32, N 9.99; found C 68.67, H 4.33, N 10.01.

4-Oxo-4-phenyl-2-(4-tolyl)butanenitrile (2f) White solid. M.p. 132—134 ℃ (lit.[20] 129—131 ℃). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.27 (s, 3H, CH_3), 3.42 (dd, J=6.0, 18.0 Hz, 1H, CHCH_aHCO), 3.63 (dd, J=8.0, 18.0 Hz, 1H, CHCH_bHCO), 4.46 (dd, J=6.4, 7.6 Hz, 1H, ArCHCH$_2$), 7.11—7.54 (m, 7H, ArH), 7.85 (d, J=8.4 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.0, 31.5, 44.5, 120.8, 127.3, 128.0, 128.8, 129.9, 132.2, 133.8, 135.6, 138.2, 194.7. IR (KBr) v: 1676 (C=O), 2239 (CN) cm^{-1}. Anal. calcd for $C_{17}H_{15}NO$ (249.31): C 81.90, H 6.06, N 5.62; found C 81.98, H 6.09, N 5.60.

4-Oxo-2,4-di-(4-tolyl)butanenitrile (2g) White solid. M.p. 108—110 ℃. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.27 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.39 (dd, J=6.4, 18.0 Hz, 1H, CHCH_aHCO), 3.61 (dd, J=7.2, 18.0 Hz, 1H, CHCH_bHCO), 4.45 (dd, J = 6.4, 7.6 Hz, 1H, ArCHCH$_2$), 7.12 (d, J=7.6 Hz, 2H, ArH), 7.18—7.26 (m, 4H, ArH), 7.75 (d, J=8.0 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.1, 21.7, 31.5, 44.4, 120.9, 127.3, 128.2, 129.5, 129.9, 132.3, 133.2, 138.2, 144.8, 194.3. IR (KBr) v: 1671 (C=O), 2243 (CN) cm^{-1}. Anal. calcd for $C_{18}H_{17}NO$ (263.33): C 82.10, H 6.51, N 5.32; found C 82.25, H 6.53, N 5.30.

4-(4-Chlorophenyl)-4-oxo-2-(4-tolyl)butanenitrile (2h) White solid. M.p. 90—92 ℃. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.35 (s, 3H, CH_3), 3.45 (dd, J=6.0, 18.0 Hz, 1H, CHCH_aHCO), 3.67 (dd, J=8.4, 18.0 Hz, 1H, CHCH_bHCO), 4.50 (t, J=6.8 Hz, 1H, ArCHCH$_2$), 7.19 (d, J=7.6 Hz, 2H, ArH), 7.31 (d, J=8.0 Hz, 2H, ArH), 7.44 (d, J=7.6 Hz, 2H, ArH), 7.86 (d, J=8.0 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.0, 31.5, 44.5, 120.6, 127.3, 129.1, 129.4, 129.9, 132.0, 133.9, 138.3, 140.4, 193.5. IR (KBr) v: 1676 (C=O), 2241 (CN) cm^{-1}. Anal. calcd for $C_{17}H_{14}ClNO$ (283.75): C 71.96, H 4.97, N 4.94; found C 72.08, H 4.99, N 4.93.

2-(4-Methoxyphenyl)-4-oxo-4-phenylbutanenitrile (2i) White solid. M.p. 112—114 ℃ (lit.[20] 111—113 ℃). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.41 (dd, J=6.4, 18.0 Hz, 1H, CHCH_aHCO), 3.62 (dd, J=7.6, 18.0 Hz, 1H, CHCH_bHCO), 3.74 (s, 3H, CH_3), 4.43 (t, J=6.8 Hz, 1H, ArCHCH$_2$), 6.83 (d, J=9.2 Hz, 2H, ArH), 7.37—7.54 (m, 5H, ArH), 7.84 (d, J=9.2 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.1, 44.5, 55.3, 114.5, 120.9, 127.1, 128.0, 128.6, 128.8, 133.9, 135.6, 159.5, 194.8. IR (KBr) v: 1678 (C=O), 2238 (CN) cm^{-1}. Anal. calcd for $C_{17}H_{15}NO_2$ (265.31): C 76.96, H 5.70, N 5.28; found C 77.05, H 5.68, N 5.30.

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2-(4-Methoxyphenyl)-4-oxo-4-(4-tolyl)butanenitrile(2j) White solid. M.p. 100－102 ℃. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.32 (s, 3H, CH_3), 3.39 (dd, J= 6.4, 18.0 Hz, 1H, CHCH_aHCO), 3.58 (dd, J=8.0, 18.0 Hz, 1H, CHCH_bHCO), 3.72 (s, 3H, CH_3), 4.42 (t, J= 6.8 Hz, 1H, ArCHCH$_2$), 6.83 (d, J=8.8 Hz, 2H, ArH), 7.17 (d, J=8.0 Hz, 2H, ArH), 7.29 (d, J=8.8 Hz, 2H, ArH), 7.73 (d, J=8.0 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.9, 31.4, 44.7, 55.6, 114.8, 121.3, 127.5, 128.4, 128.9, 129.7, 133.5, 145.1, 159.7, 194.6. IR (KBr) v: 1671 (C＝O), 2242 (CN) cm^{-1}. Anal. calcd for $C_{18}H_{17}NO_2$ (279.33): C 77.40, H 6.13, N 5.01; found C 77.33, H 6.11, N 4.99.

2-(4-Chlorophenyl)-4-oxo-4-phenylbutanenitrile (2k) White solid. M.p. 112－114 ℃ (lit.[21] 112－113 ℃). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.41 (dd, J= 6.4, 18.0 Hz, 1H, CHCH_aHCO), 3.61 (dd, J=8.8, 18.0 Hz, 1H, CHCH_bHCO), 4.46 (dd, J=6.4, 7.2 Hz, 1H, ArCHCH$_2$), 7.25－7.52 (m, 7H, ArH), 7.80－7.82 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.3, 44.3, 120.2, 128.1, 128.8, 128.9, 129.4, 133.7, 134.0, 134.4, 135.5, 194.3. IR (KBr) v: 1676 (C＝O), 2242 (CN) cm^{-1}. Anal. calcd for $C_{16}H_{12}ClNO$ (269.73): C 71.25, H 4.48, N 5.19; found C 71.37, H 4.50, N 5.20.

2-(4-Chlorophenyl)-4-oxo-4-(4-tolyl)butanenitrile (2l) White solid. M.p. 102－104 ℃. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.36 (s, 3H, CH_3), 3.43 (dd, J=6.0, 18.0 Hz, 1H, CHCH_aHCO), 3.63 (dd, J=7.6, 18.0 Hz, 1H, CHCH_bHCO), 4.50 (t, J=6.8 Hz, 1H, ArCHCH$_2$), 7.22 (d, J=8.4 Hz, 2H, ArH), 7.29－7.34 (m, 4H, ArH), 7.76 (d, J=8.4 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.7, 31.4, 44.1, 120.3, 128.0, 128.9 129.2, 129.3, 129.5, 133.8, 134.3, 145.0, 193.9. IR (KBr) v: 1669 (C＝O), 2245 (CN) cm^{-1}. Anal. calcd for $C_{17}H_{14}ClNO$ (283.75): C 71.96, H 4.97, N 4.94; found C 71.80, H 4.96, N 4.97.

2,4-Bis-(4-chlorophenyl)-4-oxo-butanenitrile (2m) White solid. M.p. 102－104 ℃. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.41 (dd, J=6.4, 18.0 Hz, 1H, CHCH_aHCO), 3.61 (dd, J=7.2, 18.0 Hz, 1H, CHCH_bHCO), 4.49 (t, J=7.2 Hz, 1H, ArCHCH$_2$), 7.19－7.33 (m, 6H, ArH), 7.74 (d, J=8.4 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.3, 44.2, 120.3, 128.2, 129.0, 129.4, 129.5, 133.1, 133.8, 134.4, 145.1, 193.9. IR (KBr) v: 1670 (C＝O), 2246 (CN) cm^{-1}. Anal. calcd for $C_{16}H_{11}Cl_2NO$ (304.17): C 63.18, H 3.65, N 4.60; found C 63.24, H 3.66, N 4.62.

2-(2,4-Dichlorophenyl)-4-oxo-4-phenylbutanenitrile (2n) White solid. M.p. 88－90 ℃ (lit.[20] 90－91 ℃). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.44 (dd, J=8.4, 18.0 Hz, 1H, CHCH_aHCO), 3.59 (dd, J=9.2, 18.0 Hz, 1H, CHCH_bHCO), 4.80 (dd, J＝4.8, 9.2 Hz, 1H, ArCHCH$_2$), 7.25－7.56 (m, 6H, ArH), 7.86 (d, J=8.0 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 29.6, 42.1, 119.3, 128.0, 128.1, 128.8, 130.0, 130.4, 131.2, 133.4, 133.9, 135.2, 135.3, 194.1. IR (KBr) v: 1670 (C＝O), 2246 (CN) cm^{-1}. Anal. calcd for $C_{16}H_{11}Cl_2NO$ (304.17): C 63.18, H 3.65, N 4.60; found C 63.00, H 3.64, N 4.59.

2-(3-Bromophenyl)-4-oxo-4-phenylbutanenitrile (2o) White solid. M.p. 114－116 ℃. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.52 (dd, J=5.6, 18.0 Hz, 1H, CHCH_aHCO), 3.74 (dd, J=7.6, 18.0 Hz, 1H, CHCH_bHCO), 4.55 (dd, J=5.6, 8.0 Hz, 1H, ArCHCH$_2$), 7.27－7.63 (m, 7H, ArH), 7.93 (d, J=8.4 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.4, 44.2, 120.1, 123.1, 126.3, 128.1, 128.9, 130.6, 130.8, 131.6, 134.1, 135.4, 137.4, 194.2. IR (KBr) v: 1679 (C＝O), 2241 (CN) cm^{-1}. Anal. calcd for $C_{16}H_{12}BrNO$ (314.18): C 61.17, H 3.85, N 4.46; found C 61.09, H 3.85, N 4.45.

2-(4-Nitrophenyl)-4-oxo-4-phenylbutanenitrile (2p) Yellow solid. M.p. 152－154 ℃. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.55 (dd, J=5.6, 18.0 Hz, 1H, CHCH_aHCO) 3.78 (dd, J=8.0, 18.0 Hz, 1H, CHCH_bHCO), 4.55 (dd, J=6.0, 7.6 Hz, 1H, ArCHCH$_2$), 7.36－7.45 (m, 5H, ArH), 8.09 (d, J=8.8 Hz, 2H, ArH), 8.19 (d, J=8.8 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.9, 45.0, 120.1, 124.1, 127.4, 128.6, 129.2, 129.4, 134.6, 139.9, 150.7, 193.3. IR (KBr) v: 1684 (C＝O), 2241 (CN) cm^{-1}. Anal. calcd for $C_{16}H_{12}N_2O_3$ (280.28): C 68.56, H 4.32, N 9.99; found C 68.67, H 4.33, N 9.96.

4-(Furan-2-yl)-4-oxo-2-phenylbutanenitrile (2q) White solid. M.p. 111－113 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.38 (dd, J=17.6, 6.0 Hz, 1H, COCH_aH), 3.59 (dd, J=17.6, 7.6 Hz, 1H, COCHH_b), 4.54 (t, J= 7.6 Hz, 1H, ArCHCH$_2$), 6.56 (s, 1H, ArH), 7.25 (d, J= 11.3 Hz, 1H, ArH), 7.29－7.50 (m, 5H, ArH), 7.59 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.5, 43.9, 112.6, 117.9, 120.3, 127.4, 128.4, 129.2, 135.0, 146.9, 151.9, 183.7. IR (KBr) v: 1662 (C＝O), 2246 (CN) cm^{-1}. Anal. calcd for $C_{14}H_{11}NO_2$ (225.08): C 74.65, H 4.92, N 6.22; found C 74.57, H 4.93, N 6.20.

Results and Discussion

Initially, the model reaction of chalcone (**1a**) with ethyl cyanoacetate was examined under various conditions. It was found that the reaction could be carried out through conjugate hydrocyanation to give **2a** and through Michael addition to give **3a** (Scheme 2). The bases played a key role in the reaction. The reaction in some organic bases like Et_3N, DABCO and piperidine only gave Michael addition product **3a** (Table 1, entries 1－3). The reaction in some inorganic bases like Na_2CO_3 and K_2CO_3 could afford both hydrocyanation product **2a** and Michael addition product **3a** at the same time (Table 1, entries 4, 5). However, the reaction in NaOH and KOH could selectively produce **2a** as a sole product in high yield (Table 1, entries 6, 7). Among them, the best yield was obtained by using KOH as a base (Table 1, entry 7). In addition, when the amount of KOH was decreased from 2 to 1 equiv., the selectivity and yield for **2a** was largely reduced (Table 1, entry 8). Moreover, if the reaction was carried out under nitrogen atmosphere, only by-product **3a** was observed, which implied that air was an indispensable condition for the

hydrocyantion of **1a** (Table 1, entry 9).

Scheme 2 The reaction of **1a** with ethyl cyanoacetate

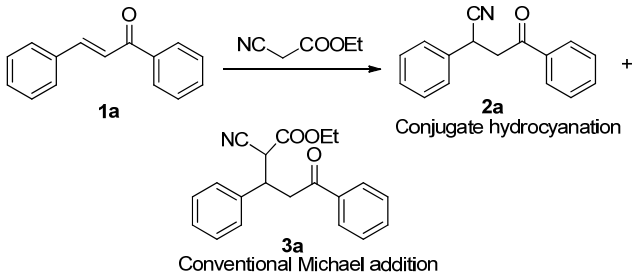


Table 1 The effect of the bases on the yield of **2a**[a]

Entry	Base	Yield of **2a**[b]/%	Yield of **3a**[b]/%
1	Et_3N	—	81
2	DABCO	—	46
3	Piperidine	—	95
4	Na_2CO_3	43	47
5	K_2CO_3	86	9
6	NaOH	81	—
7	KOH	92	—
8[c]	KOH	24	47
9[d]	KOH	0	95

[a] Reaction conditions: **1a** (0.5 mmol), ethyl cyanoacetate (0.55 mmol) and base (1.0 mmol) in DMF (5 mL) at room temperature under air for 8 h. [b] Isolated yields. [c] Using 1 equiv. of KOH. [d] Under N_2 atmosphere.

The solvents also played an important role in the reaction. It was found that the reaction in THF, 1,4-dioxane, MeCN and PhMe only gave by-product **3a** (Table 2, entries 1—4). The reaction in EtOH and DMSO could produce **2a** and **3a** simultaneously in different yield (Table 2, entries 5, 6). However, the reaction in DMF could selectively afford **2a** as a sole product in excellent yield (Table 2, entry 7). These results indicated that the selectivity of reaction was related to the solvent polarity, and high polar solvents were advantageous to the formation of **2a**. In addition, the reaction in DMF under the absence of ethyl cyanoacetate as a cyanating agent could not give any product, which indicated that DMF could not act as a cyanating agent in this reaction as the literature reported (Table 2, entry 8).[19]

Under the optimized condition, a range of chalcone derivatives were examined for the conjugate hydrocyanation by employing ethyl cyanoacetate as an organic cyanide source at room temperature under open air and transition metal-free conditions (Scheme 3, Table 3). All reactions proceeded smoothly to afford the corresponding β-cyanoketones in moderate to excellent yield. Both R^1 and R^2 could be electron-rich or electron-deficient aromatic rings (Table 3, entries 1—16). In addition, for heteroaromatic ring, such as furyl, the corresponding product was also obtained in high yield (Table 3, entry17). However, for the aliphatic enone, such as

Table 2 The effect of solvents on the yield of **2a**[a]

Entry	Solvent	Yield of **2a**[b]/%	Yield of **3a**[b]/%
1	THF	—	19
2	1,4-dioxane	—	33
3	PhMe	—	70
4	MeCN	—	91
5	EtOH	14	86
6	DMSO	77	13
7	DMF	92	—
8[c]	DMF	—	—

[a] Reaction conditions: **1a** (0.5 mmol), ethyl cyanoacetate (0.55 mmol) and KOH (1.0 mmol) in solvent (5 mL) at room temperature under air for 8 h. [b] Isolated yields. [c] Without ethyl cyanoacetate.

Scheme 3 Hydrocyanation of chalcone derivatives with ethyl cyanoacetate

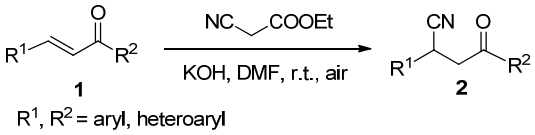
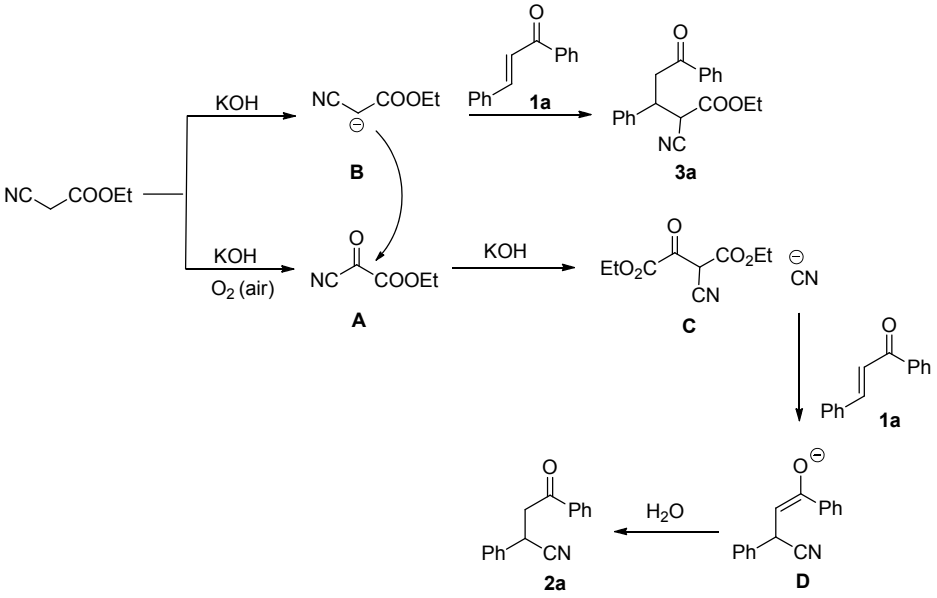


Table 3 The substrate scope for the hydrocyanation of chalcone derivatives with ethyl cyanoacetate[a]

Entry	R^1	R^2	Yield[b]/%
1	C_6H_5	C_6H_5	**2a** 92
2	C_6H_5	4-MeC_6H_4	**2b** 88
3	C_6H_5	4-$MeOC_6H_4$	**2c** 93
4	C_6H_5	4-ClC_6H_4	**2d** 90
5	C_6H_5	4-$O_2NC_6H_4$	**2e** 56[c]
6	4-MeC_6H_4	C_6H_5	**2f** 87
7	4-MeC_6H_4	4-MeC_6H_4	**2g** 85
8	4-MeC_6H_4	4-ClC_6H_4	**2h** 88
9	4-$MeOC_6H_4$	C_6H_5	**2i** 91
10	4-$MeOC_6H_4$	4-MeC_6H_4	**2j** 89
11	4-ClC_6H_4	C_6H_5	**2k** 92
12	4-ClC_6H_4	4-MeC_6H_4	**2l** 91
13	4-ClC_6H_4	4-ClC_6H_4	**2m** 88
14	2,4-$Cl_2C_6H_3$	C_6H_5	**2n** 81
15	3-BrC_6H_4	C_6H_5	**2o** 90
16	4-$O_2NC_6H_4$	C_6H_5	**2p** 55[d]
17	C_6H_5		**2q** 87

[a] Reaction conditions: chalcone derivative (0.5 mmol), ethyl cyanoacetate (0.55 mmol) and KOH (1.0 mmol) in DMF (5 mL) at room temperature under air for 8 h. [b] Isolated yields. [c] Conventional Michael additional product was observed in 26% yield. [d] Conventional Michael additional product was observed in 18% yield.

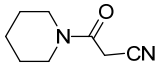
Scheme 4 Proposed mechanism for the conjugate hydrocyanation of **1a** with ethyl cyanoacetate



hex-3-en-2-one, the corresponding cyanation product was not observed, and only conventional Michael additional product was obtained in low yield. For the *β*,*β*-disubstituted enones, such as 1,3,3-triphenylprop-2-en-1-one, no reaction was observed under studied conditions

In addition, we have also compared the similar organic cyanide sources containing R-CH_2CN structures (Table 4). It was found that propanenitrile and chloropropanenitrile as cyanating agents could not give the expected product at all (Table 4, entries 1, 2). 3-Oxo-3-(piperidin-1-yl)propanenitrile could give **2a** in low yield (Table 4, entry 3). Meanwhile, phenylacetonitrile could afford **2a** in moderate yield (Table 4, entry 4). However, manolonitrile was also an excellent cyanating agent and produced **2a** in almost the same yield as ethyl cyanoactate (Table 4, entries 5, 6).

Table 4 The effect of similar organic cyanating agents on the yield of **2a**[a]

Entry	RCH_2CN	Yield of **2a**[b]/%	Yield of **3a**[b]/%
1	CH_3CH_2CN	0	56
2	$ClCH_2CH_2CN$	0	63
3		8	38
4	$PhCH_2CN$	38	49
5	$NCCH_2CN$	91	0
6	$EtOOCCH_2CN$	92	0

[a] Reaction conditions: **1a** (0.5 mmol), cyanating agent (0.55 mmol) and KOH (1.0 mmol) in DMF (5 mL) at room temperature under air for 8 h. [b] Isolated yields.

Based on the similar report,[22] a plausible mechanism for the conjugate hydrocyanation of chalcone derivatives with ethyl cyanoacetate is proposed (Scheme 4). Initially, aerobic C—H oxidation of ethyl cyanoacetate with the assistance of KOH and O_2 provided ethyl 2-cyano-2-oxoacetate (**A**). In addition, ethyl cyanoacetate could also produce anion **B** in the presence of KOH. Nucleophilic attack of the anion **B** on the carbonyl group of **A** generated cyanide anion (CN^-) and **C**. Subsequently, nucleophilic addition of a cyanide anion to chalcone (**1a**) in the presence of KOH resulted in the formation of the key intermediate **D**. **D** was protonated by water to give the final product **2a**. Under a certain condition, anion **B** could also directly attack the chalcone **1a** to afford **3a** as a by-product.

Conclusions

In summary, a new efficient method has been developed for the conjugate hydrocyanation of chalcone derivatives using ethyl cyanoacetate as an organic cyanide source. It is the first report on the utilization of ethyl cyanoacetate as an organic cyanating reagent via C—CN bond cleavage under transition metal-free condition. The new cyanating agent has the distinct advantages of being relatively cheap, less toxic, stable and easy-to-handle.

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