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Highly efficient Cs_2CO_3-catalyzed conjugate hydrocyanation of α, β-unsaturated diesters and enones with acetone cyanohydrin

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ABSTRACT

An efficient conjugate hydrocyanation of a wide range of α,β-unsaturated esters and enones with acetone cyanohydrin has been developed with excellent yields (85-99%) using Cs_2CO_3 as the catalyst. Mild reaction condition, low catalyst loading and short reaction time make this protocol much practical.

KEYWORDS

Acetone cyanohydrin;
1,4-Addition;
Catalysis;
Conjugate hydrocyanation;
Regioselectivity.

INTRODUCTION

The conjugate addition of cyanide to α,β-unsaturated carbonyl compounds is one of the most important C-C bond formation in organic chemistry. In addition, it has been extensively utilized in providing efficient synthetically valuable building blocks[1], and also widely employed in the syntheses of complex natural products[2a] and pharmaceuticals[2b].

The first example was documented by Jacobsen and co-workers[3], who described chiral salen-Al(III) and bimetallic cooperative catalyst systems for the enantioselective 1,4-addition of trimethylsilyl cyanide (TMSCN) to α,β-unsaturated imides. From that time on, 1,4-addition of cyanide to α,β-unsaturated carbonyl compounds gained a mushroom growth. Shibasaki's group firstly reported polymetallic Gd(III) catalysts for the cyanation of α,β-unsaturated *N*-acylpyrroles[4a] and enones[4b,4c]. Then Ru complex was disclosed by Ohkuma's group[5], chiral phase transfer catalysts (PTC) by Deng's group[6], and *cinchona* alkaloid catalysts by Shibata's group[7] for the 1,4-addition of cyanide to enones. Besides, Feng and co-workers[8] described catalytic asymmetric cyanation of diethyl alkylidenemalonate with ethyl cyanoformate by a modular Titanium catalyst. Though these significant achievements have been made, a practical and general regioselective 1,4-addition of cyanide to a broad scope of α,β-unsaturated carbonyl compounds is still highly demanding. Up to now, some attempts have been made[9], but these methods required complicated experimental procedures and resulted in low yields. Furthermore, the substrate scope was narrow.

Previously, we reported CsF and Cs_2CO_3-catalyzed conjugate addition of TMSCN to enones analogues with excellent yields[10]. As extension of these works, a facile and efficient Cs_2CO_3-catalyzed 1,4-addition has been developed with inexpensive and easy to handle cyanation reagent (acetone cyanohydrin) to α,β-unsaturated esters and enones.

EXPERIMENTAL SECTION

General information

NMR spectra were recorded on the Bruker AVIII

400 or Bruker AVIII 500 spectrometers. Chemical shifts were recorded in units of parts per million (ppm) downfield from Me_4Si and relative to the signal of $CDCl_3$. The IR spectra were recorded on a Perkin-Elmer Spectrum One with KBr pellets for solids and as films for liquids. The elemental analyses were performed on an Elementar Vario MICRO CUBE instrument. ESI-HRMS spectra were recorded on a Bruker Apex IV FTMS instrument. All melting points were determined on a XT4A melting point apparatus and uncorrected. Analytical thin layer chromatography (TLC) was performed using F254 precoated silica gel plate. Column chromatography was performed with silica gel (200–300 mesh).

Acetone cyanohydrins and Cs_2CO_3 were commercially available and used directly without further purification. Solvents used in the catalytic reactions were dried under argon prior to use. The α,β-unsaturated diesters **(1a-n)** were prepared by Knoevenagel condensation of corresponding aldehydes and dialkyl malonate[12]. Enones **(4a-y)** were synthesized according to the known literature procedures[13].

CAUTION: Acetone cyanohydrin is poison and should only be used in a well-ventilated hood.

General procedure for synthesis of β-cyanoesters (3) and β-cyanoketones (5)

Cs_2CO_3 (4.9 mg, 0.015 mmol, 5 mol%, or 1.0 mg, 0.003 mmol, 1 mol%), α,β-unsaturated diesters/enones (0.3 mmol) and H_2O (22 μL, 1.2 mmol, 4 equiv) were taken in a dry Schlenk tube, then acetone cyanohydrin (33 μL, 0.45 mmol, 1.5 equiv, or 44 μL, 0.60 mmol, 2 equiv) were added to it. The reaction tube was sealed and subsequently heated at 102 °C in the open air. After completion (monitored by TLC), the reaction mixture was extracted by ethyl acetate (3×15 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude products were purified by silica gel column chromatography (petroleum ether/EtOAc = 10:1, v/v) to afford the corresponding products.

Ethyl 2-carbethoxy-3-cyano-3-phenylpropionate (3a)

Yield: 98%, 81 mg; Oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ_{ppm} 1.08 (t, J = 7.5 Hz, 3H), 1.30 (t, J = 7.5 Hz, 3H), 3.89 (d, J = 9.5 Hz, 1H), 4.02-4.09 (m, J = 7.0, 2.5 Hz, 2H), 4.28 (q, J = 7.0 Hz, 2H), 4.51 (d, J = 9.5 Hz, 1H), 7.34-7.38 (m, 5H).

Ethyl 2-carbethoxy-3-cyano-3-(4-fluorophenyl) propionate (3b)

Yield: 90%, 79 mg; Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 1.12 (t, J = 7.2 Hz, 3H), 1.30 (t, J = 7.2 Hz, 3H), 3.86 (d, J = 9.6 Hz, 1H), 4.04-4.14 (m, 2H), 4.29 (q, J = 7.2 Hz, 2H), 4.52 (d, J = 9.2 Hz, 1H), 7.07 (t, J = 8.4 Hz, 2H), 7.36-7.39 (m, 2H).

Ethyl 2-carbethoxy-3-cyano-3-(4-chlorophenyl) propionate (3c)

Yield: 92%, 86 mg; Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 1.12 (t, J = 7.2 Hz, 3H), 1.30 (t, J = 7.2 Hz, 3H), 3.85 (d, J = 9.6 Hz, 1H), 4.04-4.12 (m, 2H), 4.25-4.31 (m, 2H), 4.50 (d, J = 9.6 Hz, 1H), 7.31-7.37 (m, 4H).

Ethyl 2-carbethoxy-3-cyano-3-(4-bromophenyl) propionate (3d)

Yield: 97%, 103 mg; Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.12 (t, J = 7.2 Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H), 3.84 (d, J = 9.6 Hz, 1H), 4.05-4.12 (m, 2H), 4.25-4.32 (m, 2H), 4.49 (d, J = 9.6 Hz, 1H), 7.25-7.53 (m, 4H).

Ethyl 2-carbethoxy-3-cyano-3-(4-methylphenyl) propionate (3e)

Yield: 92%, 82 mg; Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 1.10 (t, J = 7.2 Hz, 3H), 1.30 (t, J = 7.2 Hz, 3H), 2.33 (s, 3H), 3.87 (d, J = 9.6 Hz, 1H), 4.04-4.10 (m, 2H), 4.28 (q, J = 7.2 Hz, 2H), 4.48 (d, J = 9.6 Hz, 1H), 7.16 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H).

Ethyl 2-carbethoxy-3-cyano-3-(4-methoxyphenyl) propionate (3f)

Yield: 95%, 89 mg; Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 1.11 (t, J = 7.2 Hz, 3H), 1.30 (t, J = 7.2 Hz, 3H), 3.80 (s, J = 9.6 Hz, 3H), 3.85 (d, J = 9.6 Hz, 1H), 4.04-4.11 (m, 2H), 4.28 (q, J = 7.2 Hz, 2H), 4.47 (d, J = 10.0 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H).

Ethyl 2-Carbethoxy-3-cyano-3-(4-biphenyl) propionate (3g)

Yield: 91%, 96 mg; White solid, mp 100-102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 1.10 (t, J = 7.2 Hz, 3H), 1.31 (t, J = 7.2 Hz, J = 9.6 Hz, 3H), 3.93 (d, J =

7.2 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 4.30 (q, J = 7.2 Hz, 2H), 4.57 (d, J = 9.6 Hz, 1H), 7.35-7.39 (m, 1H), 7.43-7.48 (m, 4H), 7.55-7.61 (m, 4H).

Ethyl 2-carbethoxy-3-cyano-3-(3- fluorophenyl) propionate (3h)

Yield: 95%, 83 mg; Oil. ^{1}H NMR (500 MHz, CDCl3) δ_{ppm}: 1.13 (t, J = 7.0 Hz, 3H), 1.30 (t, J = 7.0 Hz, 3H), 3.87 (d, J = 7.0 Hz, 1H), 4.07-4.13 (m, 2H), 4.27-4.31 (m, 2H), 4.53 (d, J = 9.5 Hz, 1H), 7.05-7.13 (m, 2H), 7.18 (d, J = 8.0 Hz, 1H), 7.37-7.39 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 165.2, 165.0, 162.5 (d, $^1J_{C-F}$ = 247.0 Hz), 134.1 (d, $^3J_{C-F}$ = 7.5 Hz), 130.6 (d, $^3J_{C-F}$ = 8.3 Hz), 123.7, 117.8, 115.9 (d, $^2J_{C-F}$ = 20.9 Hz), 115.3 (d, $^2J_{C-F}$ = 22.9 Hz), 62.5, 62.3, 56.0, 36.0, 13.7, 13.5. IR (neat): ν = 1733, 2248 cm^{-1}. HRMS: calcd for $C_{15}H_{16}FNO_4$ [M + H]$^+$ 294.1136, found 294.1144.

Ethyl 2-carbethoxy-3-cyano-3-(3-methoxyphenyl) propionate (3i)

Yield: 98%, 90 mg; Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 1.11 (t, J = 7.2 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 3.81 (s, 3H), 3.88 (d, J = 9.6 Hz, 1H), 4.04-4.14 (m, 2H), 4.29 (q, J = 7.2 Hz, 2H), 4.49 (d, J = 10.0 Hz, 1H), 6.87-6.95 (m, 3H), 7.28-7.30 (m, 1H).

Ethyl 2-carbethoxy-3-cyano-3-(3-phenoxy-phenyl) propionate (3j)

Yield: 93%, 102 mg; Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 1.13 (t, J = 7.2 Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H), 3.86 (d, J = 9.6 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 4.27 (q, J = 7.2 Hz, 2H), 4.48 (d, J = 9.6 Hz, 1H), 6.96-7.01 (m, 4H), 7.09-7.16 (m, 2H), 7.31-7.38 (m, 3H).

Ethyl 2-carbethoxy-3-cyano-3-(2-chlorophenyl) propionate (3k)

Yield: 90%, 84 mg; Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 1.19 (t, J = 7.2 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H), 4.09 (d, J = 7.6 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 4.21-4.31 (m, 2H), 4.96 (d, J = 7.6 Hz, 1H), 7.31-7.35 (m, 2H), 7.41-7.45 (m, 1H), 7.55-7.58 (m, 1H).

Ethyl 2-carbethoxy-3-cyano-3-(2-bromophenyl) propionate (3l)

Yield: 96%, 102 mg; Oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ_{ppm}: 1.21 (t, J = 7.0 Hz, 3H), 1.26 (t, J = 7.0 Hz, 3H), 4.08 (d, J = 8.0 Hz, 1H), 4.18-4.28 (m, 4H), 4.98 (d, J = 8.0 Hz, 1H), 7.23-7.27 (m, 2H), 7.35-7.39 (m, 1H), 7.59-7.61 (m, 1H).

Diethyl 2-(benzo(d)(1,3)dioxol-5-yl(cyano)methyl) malonate (3m)

Yield: 99%, 95 mg; Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 1.14 (t, J = 7.2 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 3.83 (d, J = 10.0 Hz, 1H), 4.06-4.14 (m, 2H), 4.23-4.33 (m, 2H), 4.43 (d, J = 10.0 Hz, 1H), 5.98 (s, 2H), 6.77-6.85 (m, 3H).

Dimethyl 2-carbethoxy-3-cyano-3-phenylpropionate (3n)

Yield: 95%, 71 mg; Oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ_{ppm}: 3.61 (s, 3H), 3.82 (s, 3H), 3.93 (d, J = 9.5 Hz, 1H), 4.53 (d, J = 9.5 Hz, 1H), 7.34-7.40 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_{ppm}: 132.0, 129.3, 129.1, 128.1, 118.5, 56.3, 53.4, 53.2, 36.7. IR (neat): ν cm^{-1} 1735, 2246. HRMS: calcd for $C_{13}H_{13}NO_4$ [M+H]$^+$ 248.0917, found 248.0925.

4-Oxo-2,4-diphenylbutanenitrile (5a)

Yield: 99%, 70 mg; White solid, mp 121-123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 3.52 (dd, J = 18.0, 6.0 Hz, 1H), 3.74 (dd, J = 18.0, 8.0 Hz, 1H), 4.57 (dd, J = 8.0, 6.0 Hz, 1H), 7.34-7.50 (m, 7H), 7.58-7.62 (m, 1H), 7.92-7.94 (m, 2H).

2-(4-Fluorophenyl)-4-oxo-4-phenylbutanenitrile (5b)

Yield: 98%, 74 mg; white solid, mp 99-102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.51 (dd, J = 17.9, 6.5 Hz, 1H), 3.71 (dd, J = 17.9, 7.2 Hz, 1H), 4.57 (t, J = 6.9 Hz, 1H), 7.05-7.11 (m, 2H), 7.39-7.49 (m, 4H), 7.58-7.62 (m, 1H), 7.91-7.93 (m, 2H).

2-(4-Chlorophenyl)-4-oxo-4-phenylbutanenitrile (5c)

Yield: 96%, 78 mg; white solid, m.p. 110-113 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm}: 3.53 (dd, J = 18.0, 4.5 Hz, 1H), 3.68 (dd, J = 18.0, 9.4 Hz, 1H), 4.93 (dd, J = 9.4, 4.5 Hz, 1H), 7.26–7.38 (m, 2H), 7.42-7.50 (m, 3H), 7.58-7.62 (m, 1H), 7.67-7.79 (m, 1H), 7.94-7.96 (m, 2H).

2-(4-Bromophenyl)-4-oxo-4-phenylbutanenitrile (5d)

Yield: 97%, 91 mg; white solid, m.p. 117-118

°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 3.50 (dd, J = 18.0, 6.5 Hz, 1H), 3.71 (dd, J = 18.0, 7.3 Hz, 1H), 4.55 (t, J = 6.9 Hz, 1H), 7.32-7.33 (m, 2H), 7.46-7.53 (m, 4H), 7.59-7.62 (m, 1H), 7.90-7.92 (m, 2H).

2-(4-Methylphenyl)-4-oxo-4-phenylbutanenitrile (5e)

Yield: 97%, 91 mg; White solid, mp 120-123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 2.34 (s, 3H), 3.49 (dd, J = 17.9, 6.1 Hz, 1H), 3.70 (dd, J = 17.9, 7.9 Hz, 1H), 4.53 (dd, J = 7.8, 6.2 Hz, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.44-7.48 (m, 2H), 7.57-7.61 (m, 1H), 7.90-7.93 (m, 2H).

2-(4-Methoxyphenyl)-4-oxo-4-phenylbutanenitrile (5f)

Yield: 99%, 79 mg; white solid, m.p. 112-114 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 3.49 (dd, J = 17.9, 6.3 Hz, 1H), 3.69 (dd, J = 17.9, 7.7 Hz, 1H), 3.80 (s, 3H), 4.52 (dd, J = 7.4, 6.5 Hz, 1H), 6.89-6.91 (m, 2H), 7.33-7.36 (m, 2H), 7.45-7.49 (m, 2H), 7.57-7.61 (m, 1H), 7.91-7.93 (m, 2H).

2-(3-Fluorophenyl)-4-oxo-4-phenylbutanenitrile (5g)

Yield: 93%, 71 mg; white solid, m.p. 99-100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 3.51 (dd, J = 17.9, 6.5 Hz, 1H), 3.71 (dd, J = 17.9, 7.2 Hz, 1H), 4.57 (t, J = 6.9 Hz, 1H), 7.05–7.11 (m, 2H), 7.39-7.49 (m, 4H), 7.58-7.62 (m, 1H), 7.91-7.93 (m, 2H).

2-(3-Methoxyphenyl)-4-oxo-4-phenylbutanenitrile (5h)

Yield: 97%, 77 mg; white solid, m.p. 107-109 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm} 3.48 (dd, J = 17.9, 6.3 Hz, 1H), 3.69 (dd, J = 17.9, 7.7 Hz, 1H), 3.80 (s, 3H), 4.52 (dd, J = 7.4, 6.5 Hz, 1H), 6. 91-6.94 (m, 2H), 7.26-7.44 (m, 5H), 7.89-7.91 (m, 2H).

2-(3-phenoxy-phenyl)-4-oxo-4-phenylbutanenitrile (5i)

Yield: 99%, 97 mg; white solid, m.p. 93-94 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ_{ppm}: 3.49 (dd, J = 18.0, 6.0 Hz, 1H), 3.70 (dd, J = 18.0, 8.0 Hz, 1H), 4.51 (dd, J = 8.0, 6.0 Hz, 1H), 6.92-7.17 (m, 6H), 7.31-7.60 (m, 6H), 7.91 (d, J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_{ppm}: 194.7, 158.4, 156.6, 137.3, 135.9, 134.2, 130.8, 130.1, 129.1, 128.3, 124.1, 122.2, 120.6, 119.5, 118.5, 117.9, 44.5, 32.0. IR (neat): vcm^{-1} 1685, 2244. Anal. calcd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.68; H, 5.25; N 4.28.

2-(2-Chlorophenyl)-4-oxo-4-phenylbutanenitrile (5j)

Yield: 92%, 74 mg; white solid, m.p. 100-102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 3.53 (dd, J = 18.0, 4.5 Hz, 1H), 3.68 (dd, J = 18.0, 9.4 Hz, 1H), 4.93 (dd, J = 9.4, 4.5 Hz, 1H), 7.26-7.38 (m, 2H), 7.42-7.50 (m, 3H), 7.58-7.62 (m, 1H), 7.67-7.79 (m, 1H), 7.94-7.96 (m, 2H).

2-(2,4-Dichlorophenyl)-4-oxo-4-phenylbutanenitrile (5k)

Yield: 90%, 82 mg; white solid, m.p. 89-91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 3.52 (dd, J = 18.0, 4.7 Hz, 1H), 3.67 (dd, J = 18.0, 9.2 Hz, 1H), 4.88 (dd, J = 9.0, 4.7 Hz, 1H), 7.33-7.36 (m, 1H), 7.45-7.50 (m, 3H), 7.59-7.63 (m, 2H), 7.93-7.95 (m, 2H).

2-(2-Bromophenyl)-4-oxo-4-phenylbutanenitrile (5l)

Yield: 99%, 93 mg; white solid, m.p. 95-97 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 3.53 (dd, J = 18.0, 4.5 Hz, 1H), 3.66 (dd, J = 18.0, 9.5 Hz, 1H), 4.92 (dd, J = 9.5, 4.0 Hz, 1H), 7.22-7.26 (m, 1H), 7.39-7.50 (m, 3H), 7.59-7.62 (m, 2H), 7.69-7.71 (m, 1H), 7.94-7.96 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 194.4, 135.6, 134.4, 134.0, 133.6, 130.1, 129.5, 128.9, 128.5, 128.2, 122.9, 119.8, 42.8, 32.5. IR (neat): vcm^{-1} 1685, 2247. Anal. calcd for $C_{16}H_{12}BrNO$: C, 61.17; H, 3.85; N, 4.46. Found: C, 61.48; H, 4.05; N 4.44.

2-(2-Methoxyphenyl)-4-oxo-4-phenylbutanenitrile (5m)

Yield: 90%, 72 mg; white solid, m.p. 84-86 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 3.50 (dd, J = 17.9, 4.9 Hz, 1H), 3.65 (dd, J = 17.9, 9.0 Hz, 1H), 3.87 (s, 3H), 4.78 (dd, J = 9.0, 4.8 Hz, 1H), 6.91-7.02 (m, 2H), 7.31-7.33 (m, 1H), 7.45-7.51 (m, 3H), 7.57-7.61 (m, 1H), 7.93-7.95 m (m, 2H).

4-(4-Fluorophenyl)-4-oxobutanenitrile (5n)

Yield: 98%, 74 mg; white solid, m.p. 97-99 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 3.47 (dd, J = 17.9,

6.0 Hz, 1H), 3.70 (dd, J = 17.9, 8.1 Hz, 1H), 4.55 (dd, J = 8.0, 6.0 Hz, 1H), 7.12-7.16 (m, 2H), 7.32-7.34 (m, 5H), 7.45-7.49 (m, 2H), 7.94-7.98 (m, 2H).

4-(4-Chlorophenyl)-4-oxobutanenitrile (5o)

Yield: 98%, 79 mg; white solid, mp 110-112 °C. ^1H NMR (300 MHz, $CDCl_3$): δ_H 3.46 (dd, J = 17.9, 6.0 Hz, 1H), 3.69 (dd, J = 17.9, 8.0 Hz, 1H), 4.54 (dd, J = 7.8, 6.1 Hz, 1H), 7.26-7.45 (m, 7H), 7.84-7.87 (d, J = 8.7 Hz, 2H).

4-(4-Bromophenyl)-4-oxobutanenitrile (5p)

Yield: 95%, 90 mg; White solid, m.p. 120-123 °C. ^1H NMR (300 MHz, $CDCl_3$) δ_{ppm}: 3.45 (dd, J = 17.9, 5.9 Hz, 1H), 3.680 (dd, J = 17.9, 8.0 Hz, 1H), 4.53(dd, J = 7.9, 6.1 Hz, 1H), 7.25-7.43 (m, 5H), 7.58-7.61 (d, J = 8.4 Hz, 2H), 7.78-7.75 (d, J = 8.4 Hz, 2H).

4-(4-Methylphenyl)-4-oxobutanenitrile (5q)

Yield: 94%, 70 mg; white solid, mp 71-72 °C. ^1H NMR (300 MHz, $CDCl_3$) δ_{ppm}: 3.48 (dd, J = 17.8, 6.0 Hz, 1H), 3.71 (dd, J = 17.8, 7.9 Hz, 1H), 4.58 (t, J = 6.8 Hz, 1H), 7.34-7.49 (m, 7H), 7.98-7.94 (m, 1H).

4-(4-Methoxyphenyl)-4-oxobutanenitrile (5r)

Yield: 99%, 79 mg; white solid, m.p. 79-83 °C. ^1H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 3.45 (dd, J = 17.7, 6.1 Hz, 1H), 3.67 (dd, J = 17.7, 8.0 Hz, 1H), 3.86 (s, 3H), 4.56 (dd, J = 7.9, 6.1 Hz, 1H), 6. 91-6.94 (m, 2H), 7.26-7.44 (m, 5H), 7.89-7.91 (m, 2H).

4-(3-Bromophenyl)-2-(4-methoxyphenyl)-4-oxobutanenitrile (5s)

Yield: 94%, 97 mg; white solid, m.p. 94-97 °C. ^1H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 3.50 (dd, J = 17.9, 4.9 Hz, 1H), 3.65 (dd, J = 17.9, 9.0 Hz, 1H), 3.87 (s, 3H), 4.78 (dd, J = 9.0, 4.8 Hz, 1H), 6.91-7.02 (m, 2H), 7.31-7.33 (m, 1H), 7.45-7.51 (m, 3H), 7.57-7.61 (m, 1H), 7.93-7.95 (m, 2H).

2-Methyl-4-oxo-4-phenylbutanenitrile (5t)

Yield: 96%, 50 mg; Oil. ^1H NMR (500 MHz, $CDCl_3$) δ_{ppm}: 1.43 (d, J = 7.0 Hz, 3H), 3.23 (dd, J = 18.0, 6.5 Hz, 1H), 3.35 (dd, J = 13.5, 6.5 Hz, 1H), 3.42 (dd, J = 17.0, 6.0 Hz, 1H), 7.48-7.51 (m, 2H), 7.60-7.63 (m, 1H), 7.95-7.96 (m, 2H).

2–(1,1-Dimethylethyl)-4-oxo-4-phenylbutanenitrile (5u)

Yield: 86%, 55 mg; white solid, mp 116-118 °C. ^1H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 1.13 (s, 9H), 3.15-3.21 (m, 2H), 3.37 (dd, J = 18.0, 10.0 Hz, 1H), 7.48-7.52(m, 2H), 7.60-7.63(m, 1H), 7.96-7.98 (m, 2H).

2-Cyclohexyl-4-oxo-4-phenylbutanenitrile (5v)

Yield: 85%, 62 mg; white solid, m.p. 138-140 °C. ^1H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 1.22-1.32 (m, 5H), 1.60-1.92(m, 6H), 3.24-3.32(m, 2H), 3.42 (dd, J = 19.2, 9.2 Hz, 1H), 7.46-7.53 (m, 2H), 7.61-7.65 (m, 1H), 7.97-7.99 (m, 2H).

4-Oxo-2-propylbutanenitrile (5w)

Yield: 98%, 37 mg; Oil. ^1H NMR (500 MHz, $CDCl_3$) δ_{ppm}: 0.96 (t, J = 8.0 Hz, 3H), 1.47–1.61 (m, 4H), 2.21 (s, 3H), 2.68 (dd, J = 18.5, 6.5 Hz, 1H), 2.86 (dd, J = 17.6, 5.6 Hz, 1H), 3.05–3.09 (m, 1H).

4-Oxo-2-propylpentanenitrile (5x)

Yield: 99%, 41mg; Oil. ^1H NMR (500 MHz, $CDCl_3$) δ_{ppm}: 0.96 (t, J = 8.0 Hz, 3H), 1.47–1.61 (m, 4H), 2.21 (s, 3H), 2.68 (dd, J = 18.5, 6.5 Hz, 1H), 2.86 (dd, J = 17.6, 7.0 Hz, 1H), 3.05–3.09 (m, 1H).

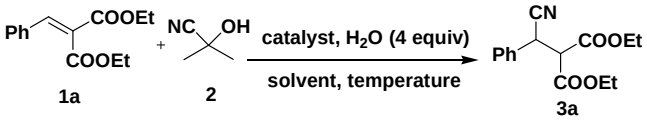
2-(2-Oxopropyl)heptanenitrile (5y)

Yield: 97%, 49 mg; Oil. ^1H NMR (500 MHz, $CDCl_3$) δ_{ppm}: 0.90 (t, J = 7.0 Hz, 3H), 1.31–1.33 (m, 4H), 1.41–1.62 (m, 4H), 2.21 (s, 3 H), 2.68 (dd, J = 18.5, 6.5 Hz, 1H), 2.87 (dd, J = 18.0, 7.5 Hz, 1H), 3.02–3.07 (m, 1H).

RESULTS AND DISCUSSION

Diethyl alkylidenemalonate (**(1a)**, 0.15 mmol) and acetone cyanohydrin (**(2)**, 2 equiv) was selected as a model system with water (4 equiv) as the additive in reflux THF (1 mL). A series of Lewis acids were screened for their capability to catalyze the synthesis of β-cyano esters with results listed in TABLE 1. In the presence of Na_2CO_3 or K_2CO_3, the desired product **(3a)** was obtained, albeit in a low yield (entries 1–2). Fortunately, when the strong alkali Cs_2CO_3 was used, the yield was greatly enhanced to 90% (entry 3). However, other cesium salts such as CsCl and CsF,[11] promoted the reaction in comparatively low yields (entries 4–5). A survey of catalysts revealed Cs_2CO_3 as the

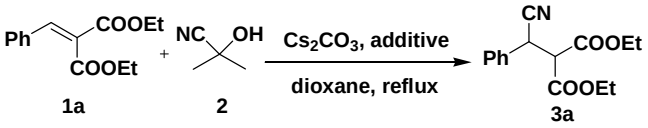
TABLE 1 : Effects of catalyst, solvent and temperature on the conjugate hydrocyanation of (1a) with acetone cyanohydrin



Entry[a]	Catalyst [10 mol%]	Solvent	Temp. [°C]	Yield [%][b]
1	Na_2CO_3	THF	68	17
2	K_2CO_3	THF	68	39
3	Cs_2CO_3	THF	68	90
4	CsCl	THF	68	10
5	CsF	THF	68	71
6	Cs_2CO_3	MTBE	58	NR
7	Cs_2CO_3	dioxane	102	97
8	Cs_2CO_3	toluene	110	trace
9	Cs_2CO_3	DMF	102	85
10	Cs_2CO_3	CH_3CN	102	82
11	Cs_2CO_3	dioxane	40	42
12	Cs_2CO_3	dioxane	80	89
13	Cs_2CO_3	dioxane	120	98

[a]Conditions: 1a (0.15 mmol), 2 (2 equiv), solvent (1 mL), 1 h; [b]Isolated yield; MTBE = methyl *tert*-butyl ether. NR = no reaction

TABLE 2 : Effects of catalyst loading, additive and concentration of (1a) on the conjugate hydrocyanation



Entry[a]	Catalyst [mol%][b]	Additive [equiv] [b]	Concn. [mol·L^{-1}] [c]	Yield [%][d]
1	10	H_2O (4)	0.15	97
2	10	*i*PrOH (4)	0.15	44
3	10	2-*t*BuPhOH (4)	0.15	68
4	10	H_2O (2)	0.15	85
5	10	H_2O (6)	0.15	70
6	10	H_2O (8)	0.15	46
7	1	H_2O (4)	0.075	72
8	1	H_2O (4)	0.15	85
9	1	H_2O (4)	0.30	90
10	1	H_2O (4)	0.60	94
11	5	H_2O (4)	0.60	99
12[e,f]	5	H_2O (4)	0.60	98

[a]Unless otherwise noted, all reactions were performed with 1a (0.15 mmol) and (2) (0.3 mmol, 2 equiv) by Cs_2CO_3 in refluxing dioxane under argon, 4 h; [b]Relative to (1a); [c]Concentration of 1a; [d]Isolated yield; [e]The reaction was conducted with (1a) (0.3 mmol) and (2) (0.45 mmol, 1.5 equiv); [f]The reaction was performed open to air

effective catalyst.

The reaction was found to be strongly solvent dependent. No product was observed in MTBE (TABLE 1, entry 6). Replacement of THF with dioxane enhanced the yield to 97% (entry 7), while toluene, DMF or CH_3CN led to lower yield (entries 8–10). Temperature was also a significant factor for catalyst efficiency. When increasing the reaction temperature from 40 °C to reflux temperature, the yield increased stepwise (entry 7, entries 11–12). However, over-heated dioxane couldn't improve the reaction rate any more (entry 13). Therefore, the optimal reaction medium is in reflux dioxane.

Further, various additives were screened summarizing in TABLE 2. 4 Equivalents of H_2O was found to be better than other alcohols and phenols (entry 1 *vs*. entries 2–3). Neither more nor less amount of water could improve the yield (entries 4–6 *vs*. entry 1). Subsequently, effects of catalyst loading and the concentration of substrate **(1a)** were investigated. As the concentration increasing from 0.075 M to 0.60 M the yield was improved from 72% to 94% at the catalyst loading of 1 mol% of Cs_2CO_3 (entries 7–10). Reasonably, the reaction afforded full conversion at 0.60 M with 5 mol% of Cs_2CO_3 (entry 11) within much shorter 1 h. In addition, excellent yield was also obtained with 1.5 equivalents of acetone cyanohydrin and open to air condition as well (entry 12).

Thus, the optimal conditions are α,β-unsaturated esters (**(1)**, 0.60 M) and acetone cyanohydrin (**(2)**, 1.5 equiv) catalyzed by Cs_2CO_3 (5 mol%) with water (4 equiv) as additive in refluxing dioxane. And substrate scope was evaluated under optimized reaction conditions with data in TABLE 3. High yields were obtained regardless of the nature and the location of substituent on the benzene ring of substrate **(3a-n)**. With halogen substituent at *para*-position, the yield decreases slightly as higher electron-negativity is (entries 2–4). Accordingly, those substrates bearing electron-donating groups gave higher yields (entries 5–7). *Ortho*- and *meta*-substituted substrates were also tolerated with excellent

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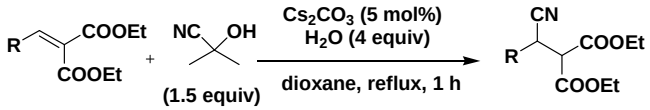
TABLE 3 : Substrate scope of Cs_2CO_3-catalyzed conjugate hydrocyanation of α, β-unsaturated esters



1 2 3

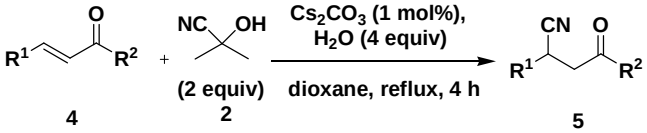
Entry[a]	Product	Yield [%][b]
1	3a, R = Ph	98
2	3b, R = 4-FC_6H_4	90
3	3c, R = 4-ClC_6H_4	92
4	3d, R = 4-BrC_6H_4	97
5	3e, R = 4-MeC_6H_4	91
6	3f, R = 4-$MeOC_6H_4$	98
7	3g, R = 4-PhC_6H_4	91
8	3h, R = 3-FC_6H_4	95
9	3i, R = 3-$MeOC_6H_4$	98
10	3j, R = 3-$PhOC_6H_4$	93
11	3k, R = 2-ClC_6H_4	90
12	3l, R = 2-BrC_6H_4	96
13	3m, R = 3,4-methylenedioxyphenyl	99
14	3n, R = Ph	95

[a]**Reaction conditions: (1) (0.3 mmol), (2) (0.45 mmol, 1.5 equiv), Cs_2CO_3 (0.015 mmol, 5 mol%), H_2O (4 equiv), dioxane (0.5 mL), reflux, 1 h;** [b]**Isolated yield**

yields (entries 8–13). Furthermore, the ester moiety changing from ethyl to methyl didn't affect catalyst efficiency affording β-cyanoester **(3n)** in 95% yield (TABLE 3, entry 14).

Encouraged by the good substrate scope for the above conditions to α,β-unsaturated diesters, we then proceeded to extend this catalyst system to other α,β-unsaturated compounds. As shown in TABLE 4, chalcone **(4a)** was fully consumed with acetone cyanohydrin (2 equiv) by Cs_2CO_3 (1 mol%) with water (4 equiv) as the additive in refluxing dioxane. Electron-rich and electron-deficient substituents on the benzene ring and alkyl groups at the R^1 position on the double bond terminus were well tolerated, providing β-cyanoketones **(5b-5m)** and **(5t-5v)** in high yields (entries 1–13, and 20–22). The substituents at the R^2 position could also be varied without any discernible issue under the optimized reaction conditions (entries 14–19). It's noteworthy that the present protocol can

TABLE 4 : Substrate scope of Cs_2CO_3-catalyzed conjugate hydrocyanation of enones



4 2 5

Entry[a]	Product	R^1	R^2	Yield [%][b]
1	5a	Ph	Ph	99
2	5b	4-FC_6H_4	Ph	98
3	5c	4-ClC_6H_4	Ph	96
4	5d	4-BrC_6H_4	Ph	97
5	5e	4-MeC_6H_4	Ph	97
6	5f	4-$MeOC_6H_4$	Ph	99
7	5g	3-FC_6H_4	Ph	93
8	5h	3-$MeOC_6H_4$	Ph	97
9	5i	3-$PhOC_6H_4$	Ph	99
10	5j	2-ClC_6H_4	Ph	92
11	5k	2,4-$Cl_2C_6H_3$	Ph	90
12	5l	2-BrC_6H_4	Ph	99
13	5m	2-$MeOC_6H_4$	Ph	90
14	5n	Ph	4-FC_6H_4	98
15	5o	Ph	4-ClC_6H_4	98
16	5p	Ph	4-BrC_6H_4	95
17	5q	Ph	4-MeC_6H_4	94
18	5r	Ph	4-$MeOC_6H_4$	99
19	5s	4-$MeOC_6H_4$	3-BrC_6H_4	94
20	5t	Me	Ph	96
21	5u	*t*-Bu	Ph	86
22	5v	*c*-hexanyl	Ph	85
23	5w	Me	Et	98
24	5x	*n*-Pr	Me	99
25	5y	*n*-C_5H_{11}	Me	97

[a]**Conditions: (4) (0.3 mmol), (2) (0.6 mmol, 2 equiv), Cs_2CO_3 (0.003 mmol, 1 mol%), H_2O (4 equiv), dioxane (0.5 mL), reflux, 4 h;** [b]**Isolated yield**

be applied to aliphatic enones with excellent yields (entries 23–25).

CONCLUSIONS

In conclusion, a facile and efficient Cs_2CO_3-catalyzed conjugate hydrocyanation of both α,β-unsaturated esters and enones has been elaborated with ex-

cellent yields and short reaction times. This protocol employed the cheap catalyst and easy to handle cyanation reagents.

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