Supporting Information

Base promoted one pot solvent free version of Ramachary reductive coupling/alkylation reaction for the synthesis of 2,2-disubstituted ethyl cyanoacetates

Guangyou Jianga#, Min Liu#, Dongmei Fangb, Ping Tan, Min Huang, Taiping Zhou, Zhenju Jiang, Zhihong Xua, Zhouyu Wang*
a Department of Chemistry, Xihua University, Chengdu, 610039, China. E-mail: zhongwon27@163.com, xzh1966@163.com
b Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu, 610041, China.
These authors contributed equally to this work and should be considered co-first authors.
Fax: +86-028-8772-3006; Tel: +86-028-8772-9463

General Methods: All starting materials were of the commercially available (analytical grade) and used without further purification. All the solvents are used after redistillation. Reactions were monitored by thin layer chromatography using silica gel HSGF254 plates. Flash chromatography was performed using silica gel HG/T2354-92. Melting points were measured with SGW X-4 melting point apparatus. $^1$H NMR (400 MHz) spectra were recorded in CDCl$_3$ or DMSO. $^1$H NMR chemical shifts are reported in ppm ($\delta$) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard (CDCl$_3$, $\delta$ = 7.26 ppm; DMSO, $\delta$ = 2.50 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, q = quartet, m = multiplet), coupling constants (Hz) and integration.$^{13}$C NMR chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard (CDCl$_3$, 77.0 ppm; DMSO, 39.5 ppm). Chemical yields refer to pure isolated substances. ESIMS spectra were recorded on BioTOF Q. All products were prepared according to the general procedure. Except for 1f and 1i, all the products are unknown compounds.

General experimental procedure for preparing 2, 2-disubstituted ethyl cyanoacetates:
Under solvent-free conditions, the mixture of aldehydes (0.25 mmol), ethyl 2-cyanoacetate (0.30 mmol), benzyl bromide (0.75 mmol), DIEA (0.50 mmol) and Hantzsch esters (0.30 mmol) was stirred at 90 °C for 2 h. After the completion of the K/H/A process and the reaction mixtures were cooled to room temperature. Then the residue was purified through column chromatograph on silica gel to give the pure products.
General experimental procedure for preparing 2, 2-disubstituted 2-(4-nitrophenyl)-acetonitrile: Under solvent-free conditions, the mixture of aldehydes (0.25 mmol), 2-(4-nitrophenyl)-acetonitrile (0.25 mmol), DIEA (0.25 mmol) and Hantzsch esters (0.30 mmol) was stirred at 90 ºC for 2 h. After the completion of the K/H process and the reaction mixtures were cooled to room temperature. Without any work up process, the benzyl bromide (0.75 mmol) with DIEA (0.75 mmol) were added and the stirring was maintained at 90 ºC for 2 h. The reaction mixtures were cooled to room temperature. The residue was purified through column chromatograph (Petroleum ether : EtOAc, 80:1→15:1) onto silica gel to give the crude products. Finally, all the crude products are purified through the silica gel plate (200 mm × 200 mm, Petroleum ether : CH₂Cl₂ = 1: 1).

![Chemical diagram](image)

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<th>Entry</th>
<th>R²</th>
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General experimental procedure for preparing 2, 2-disubstituted malononitrile: Under solvent-free conditions, the mixture of aldehydes (0.25 mmol), malononitrile(0.25 mmol) and Hantzsch esters (0.30 mmol) was stirred at 90 °C for 2 h. After the completion of the self-catalyzed K/H process and the reaction mixtures were cooled to room temperature. Without any work up process, the benzyl bromide (0.75 mmol) with DIEA (0.75 mmol) were added and stirred at 90 °C for 2 h. The reaction mixtures were cooled to room temperature. The residue was purified through column chromatograph (Petroleum ether : EtOAc , 80:1→15:1) onto silica gel to give the crude products. Finally, all the crude products are purified through the silica gel plate (200 mm × 200 mm, Petroleum ether : CH₂Cl₂ = 1: 1).

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ethyl 2-benzyl-3-(4-bromophenyl)-2-cyanopropanoate (1a): The crude mixture was purified by column chromatography using Petroleum ether /EtOAc (60/1→15/1) to yield 1a as yellow liquid with 92% yield. 

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.47 (d, $J = 8.32$ Hz, 2H), 7.32 - 7.34 (m, 5H), 7.20 (d, $J = 8.32$ Hz, 2H), 4.03 (q, $J = 7.12$ Hz, 2H), 3.34, 3.32 (AB system, $J_{AB} = 13.40$ Hz, 2H), 3.13, 3.08 (AB system, $J_{AB} = 13.44$ Hz, 2H), 1.03 (t, $J = 7.12$ Hz, 3H). $^{13}$C NMR (100 MHz, DMSO) $\delta$ 167.9, 149.4, 143.5, 134.9, 130.3, 128.9, 128.2, 118.6, 111.1, 109.4, 62.9, 52.0, 42.2, 35.5, 14.2. ESI HRMS exact mass calcd. for (C$_{19}$H$_{18}$BrNO$_2$ + Na)$^+$ requires m/z 394.04099, found m/z 394.04089.

ethyl 2-benzyl-3-(4-chlorophenyl)-2-cyanopropanoate (1b): The crude mixture was purified by column chromatography using Petroleum ether /EtOAc (60/1→15/1) to yield 1b as yellow oily liquid with 96% yield. 

$^1$H NMR (400 MHz, DMSO) $\delta$ 7.25 - 7.45 (m, 9H), 4.04 (q, $J = 7.12$ Hz, 2H), 3.36, 3.33 (AB system, $J_{AB} = 11.32$ Hz, 2H), 3.27, 3.23 (AB system, $J_{AB} = 13.56$ Hz, 2H), 1.01 (t, $J = 7.12$ Hz, 3H). $^{13}$C NMR (100 MHz, DMSO) $\delta$168.1, 135.1, 135.0, 134.1, 133.0, 132.1, 130.3, 128.9, 128.1, 118.9, 62.8, 54.0, 42.8, 41.8, 14.1. ESI HRMS exact mass calcd. for (C$_{19}$H$_{18}$ClNO$_2$ + Na)$^+$ requires m/z 350.09168, found m/z 350.09172.

ethyl 2-benzyl-2-cyano-3-(4-fluorophenyl)propanoate (1c): The crude mixture was purified by column chromatography using Petroleum ether /EtOAc (60/1→15/1) to yield 1c as yellow liquid with 95% yield. 

$^1$H NMR (400 MHz, DMSO) $\delta$ 7.18 - 7.38 (m, 9H), 4.04 (q, $J = 7.12$ Hz, 2H), 3.37, 3.36 (AB system, $J_{AB} = 11.52$ Hz, 2H), 3.29, 3.25 (AB system, $J_{AB} = 10.96$ Hz, 2H), 1.01 (t, $J = 7.12$ Hz, 3H). $^{13}$C NMR (100 MHz, DMSO) $\delta$168.0, 163.4, 161.0, 135.1, 132.3, 131.3, 130.2, 128.9, 128.1, 118.8, 115.9, 62.8, 54.0, 42.6, 41.8, 14.1. ESI HRMS exact mass calcd. for (C$_{19}$H$_{18}$FNO$_2$ + H)$^+$ requires m/z 312.1394, found m/z 312.1382.

ethyl 2-benzyl-2-cyano-3-p-tolylpropanoate (1d): The crude mixture was purified by column chromatography using Petroleum ether /EtOAc (60/1→15/1) to yield 1d as white colorless liquid 95% yield. 

$^1$H NMR
(400 MHz, DMSO) δ 7.13 - 7.38 (m, 9H), 4.04 (q, J = 7.12 Hz, 2H), 3.18 - 3.35 (m, 4H), 2.29 (s, 3H), 1.03 (t, J = 7.12 Hz, 3H). ^13^C NMR (100 MHz, DMSO) δ 168.1, 137.3, 135.1, 132.0, 130.3, 130.1, 129.5, 128.9, 128.1, 118.9, 62.7, 54.1, 42.8, 42.4, 21.1, 14.2. ESI HRMS exact mass calcd. for (C_{20}H_{21}NO_{2} + H)^+ requires m/z 308.1644, found m/z 308.1647.

**ethyl 2-benzyl-2-cyano-3-(4-methoxyphenyl)propanoate (1e):** The crude mixture was purified by column chromatography using Petroleum ether /EtOAc (60/1→15/1) to yield 1e as colorless liquid with 73% yield. ^1^H NMR (400 MHz, DMSO) δ 7.26-7.36 (m, 5H), 7.20 (d, J = 8.64 Hz, 2H), 6.92 (d, J = 8.64 Hz, 2H), 4.06 (q, J = 7.08 Hz, 2H), 3.75 (s, 3H), 3.35, 3.31 (AB system, J_{AB} = 13.32 Hz, 2H), 3.24, 3.22 (AB system, J_{AB} = 14.00 Hz, 2H), 1.02-1.05 (t, J = 7.12 Hz, 3H). ^13^C NMR (100 MHz, DMSO) δ 168.2, 159.2, 135.2, 131.4, 130.2, 128.9, 128.1, 126.9, 119.0, 114.3, 62.7, 55.5, 54.2, 42.7, 42.1, 14.2. ESI HRMS exact mass calcd. for (C_{20}H_{21}NO_{3} + H)^+ requires m/z 324.1594, found m/z 324.1593.

**ethyl 2-benzyl-2-cyano-3-(4-cyanophenyl)propanoate (1f):** The crude mixture was purified by column chromatography using Petroleum ether /EtOAc (60/1→15/1) to yield 1f as colorless liquid with 24% yield. ^1^H NMR (400 MHz, DMSO) δ 7.31 - 7.39 (m, 5H), 7.25 - 7.31 (m, 4H), 4.03 (q, J = 7.12 Hz, 2H), 3.37, 3.34 (AB system, J_{AB} = 13.56 Hz, 2H), 3.27, 3.24 (AB system, J_{AB} = 13.56 Hz, 2H), 1.01 (t, J = 7.12 Hz, 3H). See reference 16.

**ethyl 2-benzyl-2-cyano-3-(4-nitrophenyl)propanoate (1g):** The crude mixture was purified by column chromatography using Petroleum ether /EtOAc (60/1→15/1) to yield 1g as white solid with 76% yield. ^1^H NMR (400 MHz, CDCl$_3$) δ 8.22 (d, J = 8.72 Hz, 2H), 7.51 (d, J = 8.72 Hz, 2H), 7.31 - 7.40 (m, 5H), 4.03 – 4.08 (m, 2H), 3.48, 3.45 (AB system, J_{AB} = 13.40 Hz, 2H), 3.20, 3.16 (AB system, J_{AB} = 13.48 Hz, 2H), 1.03 (t, J = 7.16 Hz, 3H). ^13^C NMR (100 MHz, DMSO) δ 167.8, 147.6, 143.0, 134.8, 131.7, 130.3, 129.0, 128.2, 124.0, 118.5, 63.1, 53.5, 42.7, 41.8, 14.1. ESI HRMS exact mass calcd. for (C_{19}H_{18}N$_2$O$_4$ + H)^+ requires m/z 338.1194, found m/z 338.1124.
2-benzyl-2-((naphthalen-5-yl)methyl)malononitrile (1h): The crude mixture was purified by column chromatography using Petroleum ether/EtOAc (60/1→15/1) to yield 1h as colorless liquid with 92% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.23 (d, $J=7.84$ Hz, 1H), 7.90 - 7.97 (m, 2H), 7.37 - 7.60 (m, 4H), 7.31 - 7.35 (m, 5H), 3.91 (q, $J= 7.08$ Hz, 2H), 3.87 (s, 2H), 3.52, 3.48 (AB system, $J_{AB} = 13.52$ Hz, 2H), 0.88 (t, $J= 7.12$ Hz, 3H). $^{13}$C NMR (100 MHz, DMSO) $\delta$ 168.3, 135.3, 134.0, 132.3, 131.6, 130.4, 129.0, 128.9, 128.5, 128.1, 126.4, 126.3, 125.7, 124.6, 119.0, 62.8, 53.4, 42.9, 38.4, 13.9. ESI HRMS exact mass calcd. for (C$_{23}$H$_{21}$NO$_2$ + H)$^+$ requires m/z 344.1604, found m/z 344.1602.

ethyl 2-benzyl-2-cyano-3-(thiophen-2-yl)propanoate (1i): The crude mixture was purified by column chromatography using Petroleum ether/EtOAc (60/1→15/1) to yield 1i as yellow liquid with 94% yield. $^1$H NMR (400 MHz, DMSO) $\delta$ 7.47 (d, $J= 1.28$ Hz, 1H), 7.33 - 7.46 (m, 3H), 7.25 - 7.27 (m, 2H), 7.00 - 7.03 (m, 2H), 4.09 (q, $J= 7.12$ Hz, 2H), 3.60, 3.53 (AB system, $J_{AB} = 14.72$ Hz, 2H), 3.35 (s, 2H), 1.07 (t, $J= 7.12$ Hz, 3H).

ethyl 2-benzyl-2-cyano-3-(furan-2-yl)propanoate (1j): The crude mixture was purified by column chromatography using Petroleum ether/EtOAc (60/1→15/1) to yield 1j as colorless liquid with 88% yield. $^1$H NMR (400 MHz, DMSO) $\delta$ 7.61 (d, $J= 1.04$ Hz, 1H), 7.26 - 7.39 (m, 6H), 6.43 (d, $J= 5.0$ Hz, 1H), 6.30 (d, $J= 3.16$ Hz, 1H), 4.12 (q, $J= 7.12$ Hz, 2H), 3.22 - 3.41 (m, 4H), 1.10 (t, $J= 7.12$ Hz, 3H). $^{13}$C NMR (100 MHz, DMSO) $\delta$ 167.8, 149.4, 143.5, 134.9, 130.3, 128.9, 128.2, 118.6, 111.1, 109.4, 62.9, 52.0, 42.2, 35.5, 14.1. ESI HRMS exact mass calcd. for (C$_{17}$H$_{17}$NO$_3$ + H)$^+$ requires m/z 284.1281, found m/z 284.1278.

References


$^1$H and $^{13}$C NMR Spectra:

The $^1$H NMR Spectra of 1a

The $^{13}$C NMR Spectra of 1a
The $^1$H NMR Spectra of 1b

The $^{13}$C NMR Spectra of 1b
The $^1$H NMR Spectra of 1c

The $^{13}$C NMR Spectra of 1c
The $^1$H NMR Spectra of 1d
The $^{13}$C NMR Spectra of 1d

The $^1$H NMR Spectra of 1e

The $^{13}$C NMR Spectra of 1e
The $^1$H NMR Spectra of 1f
The $^1$H NMR Spectra of 1g

The $^{13}$C NMR Spectra of 1g
The $^1$H NMR Spectra of 1h

The $^{13}$C NMR Spectra of 1h
The $^1$H NMR Spectra of 1i
The $^1$H NMR Spectra of 1j

The $^{13}$C NMR Spectra of 1j