Supplementary Material (ESI) for Lab on a Chip

Supplementary Information.

The use of solid-supported reagents for the multi-step synthesis of analytically pure α,β-unsaturated compounds in miniaturized flow reactors

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Experimental.

Materials. All solvents were purchased as puriss grade (≥99.5%) over molecular sieves (H_2O <0.005%) from Fluka (Gillingham, UK) and unless otherwise stated chemicals were purchased from Sigma-Aldrich (Gillingham, UK) and used as received. Dimethyl acetals were synthesized using a previously reported procedure[15] and the resulting compounds stored at -15 °C in order to prevent degradation. Prior to use, 3-(1-piperazino)propyl-functionalized silica gel **6** (1.7 mmol N g^{-1}), 3-(dimethylamino)propyl-functionalized **11** (1.50 mmol N g^{-1}) and 3-(1,3,4,6,7,8-hexahydro-2*H*-pyrimidino)propyl-functionalized silica gel **12** (2.4 mmol N g^{-1}), were sieved to afford a particle size distribution of 38 to 75 μm (Endcotts, UK). The polymer-supported acid catalysts, Amberlyst-15 **5** (4.2 mmol g^{-1}), polymer-supported *p*-toluenesulfonic acid **9** (2.0-3.5 mmol g^{-1}) and ytterbium polystyryl sulfonate(III) **10** (0.80 mmol g^{-1}) (NovaBiochem, Nottingham, UK), were ground in a pestle and mortar, prior to sieving, to afford 38 to 75 μm particles.

Instrumentation. ^{1}H and ^{13}C NMR spectra were recorded as solutions in deuteriochloroform ($CDCl_3$) using tetramethylsilane (TMS) as an internal standard. The spectra were recorded on a Jeol GX400 spectrometer and the chemical shifts reported in parts per million (ppm) with coupling constants given in Hertz (Hz). The following abbreviations are used to report NMR data; s = singlet, d = doublet, t = triplet, br s = broad singlet, m = multiplet and C_0 = quaternary carbon. Elemental analyses were performed using a Fisons Carlo Erba EA1108 CHN analyzer. Infra-red spectra were recorded (4000 to 600 cm^{-1}) using a Perkin Elmer Paragon 1000 FT-IR spectrometer and peaks reported in wavenumbers (cm^{-1}). Melting points were determined using a Gallenkamp melting point apparatus. Gas Chromatography-Mass Spectrometry (GC-MS) was performed using a Varian GC (CP-3800) coupled to a Varian MS (Saturn 2000) with a CP-Sil 8 column (30 m, Zebron ZB-5, Phenomenex, UK) and ultra high purity helium (99.999%, Energas, UK) carrier gas. Samples were analyzed using the following method; injector temperature 250 °C, 1.0 μl sample volume, helium flow rate 1.0 ml min^{-1}, oven temperature 60 °C for 1 min, then ramped to 270 °C at 25 °C min^{-1} and held at 270 °C for 5 min with a 2.5 min filament delay.

With the exception of 1-dimethoxymethyl-4-methylbenzene, all characterization data was obtained using compounds synthesized within the miniaturized flow reactors described herein; in all cases, no additional product purification was performed.

1-Dimethoxymethyl-4-methyl benzene. Amberlyst-15 5 (0.50 mmol) was added to a stirred solution of *p*-tolylaldehyde (0.600 g, 5.00 mmol) and trimethylorthoformate 13 (1.37 ml, 12.50 mmol) in anhydrous MeCN (50 ml) under N_2. After stirring overnight, the resulting reaction mixture was filtered and concentrated *in vacuo* to afford 1-dimethoxymethyl-4-benzene as a pale yellow oil (0.719 g, 4.330 mmol, 86.60 %); (Found C 71.99; H, 8.39. $C_{10}H_{14}O_2$ requires C, 72.26; H, 8.49 %); υ_{max}/cm^{-1} 701.0, 1055, 1105, 1205, 1355, 1454, 2830 and 2938; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 2.49 (3H, s, CH_3), 3.24 (6H, s, 2 x OCH_3), 5.32 (1H, s, CH), 7.32 (2H, d, J 8.4, Ar) and 7.89 (2H, d, J 8.4, Ar); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 21.5 (CH_3), 46.7 (2 x OCH_3), 101.7 (CH), 128.4 (C_0), 130.4 (2 x CH), 130.8 (2 x CH) and 146.4 (C_0CH_3); m/z (EI) 167 (M^++1, 1 %), 166 (5), 165 (20), 135 (100), 119 (20), 105 (15) and 75 (10); GC-MS retention time R_T 5.40 min.

2-Cyano-3-phenyl acrylic acid ethyl ester (4a).[1] (0.015 g, 0.075 mmol, 99.4 %) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 1.41 (3H, t, J 7.0, CH_2CH_3), 4.39 (2H, q, J 7.0, CH_2CH_3), 7.49-7.55 (3H, m, Ar), 8.00 (2H, m, Ar) and 8.26 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 14.2 (CH_3), 62.8 (CH_2), 103.1 (C_0CN), 115.5 (CN), 129.3 (2 x CH), 131.1 (2 x CH), 131.5 (C_0), 133.3 (CH), 155.1 (CH) and 162.5 (CO); m/z (EI) 202 (M^++1, 70 %), 201 (100), 172 (80), 156 (90), 128 (75), 102 (55), 77 (50) and 51 (50); GC-MS retention time R_T 6.63 min.

3-(4-Bromophenyl)-2-cyano acrylic acid ethyl ester (4b).[2] (0.0338 g, 0.121 mmol, 99.8 %) as a white crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 1.40 (3H, t, J 7.3, CH_2CH_3), 4.39 (2H, q, J 7.3, CH_2CH_3), 7.65 (2H, d, J 8.7, Ar), 7.86 (2H, d, J 8.7, Ar) and 8.19 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 14.2 (CH_3), 62.9 (CH_2), 103.7 (C_0CN), 115.3 (CN), 128.3 (C_0Br), 130.3 (C_0), 132.3 (2xCH), 132.7 (2 x CH), 153.6 (CH) and 162.3 (CO); m/z (EI) 281 (M^++1, 90 %), 280 (45), 279 (100), 251 (25), 200 (20), 154 (10), 127 (25), 100 (20) and 76 (20); GC-MS retention time R_T 10.84 min.

3-(4-Chlorophenyl)-2-cyano acrylic acid ethyl ester (4c).[3] (0.0227 g, 0.096 mmol, 99.6 %) as a white crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 1.44 (3H, t, J 7.0, OCH_2CH_3), 4.43 (2H, q, J 7.0, OCH_2CH_3), 7.52 (2H, d, J 8.7, 2 x Ar), 7.98 (2H, d, J 8.7, 2 x Ar), 8.20 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 13.3 (OCH_2CH_3), 61.1 (OCH_2CH_3), 101.8 (C_0), 113.5 (CN), 127.9 (2 x CH), 128.1 (C_0), 130.4 (2 x CH), 137.8 (C_0), 151.7 (CH) and 160.4 (CO); m/z (EI) 236 (M^++1, 100 %), 235 (30), 191 (25), 127 (20), 100 (15) and 75 (10); GC-MS retention time R_T 8.68 min.

3-(4-Cyanophenyl)-2-cyano acrylic acid ethyl ester (4d).[4] (0.0284 g, 0.126 mmol, 99.7 %) as a white crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 1.42 (3H, t, J 7.0, OCH_2CH_3), 4.41 (2H, q, J 7.0, OCH_2CH_3), 7.81 (2H, d, J 8.4, Ar), 8.08 (2H, d, J 8.4, Ar) and 8.26 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 14.1 (OCH_2CH_3), 53.5 (OCH_2CH_3), 106.8 (C_0), 114.6 (C_0CN), 116.0 (CN), 117.7 (CN), 131.0 (2 x CH), 132.8 (2 x CH), 135.2 (C_0), 152.2 (CH) and 161.5 (CO); m/z (EI) 227 (M^++1, 65 %), 226 (100), 181 (20), 125 (20), 100 (10) and 75 (5); GC-MS retention time R_T 9.10 min.

3-Ethoxy-4-naphthalen-2-yl-2-oxo-but-3-enenitrile (4e).[5] (0.0298 g, 0.119 mmol, 99.8 %) as a beige solid; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 1.43 (3H, t, J 7.3, CH_3), 4.45 (2H, q, J 7.3, OCH_2CH_3), 7.48 (1H, d, J 1.7 and 8.6, Ar), 7.56 (1H, d, J 1.7 and 8.6, Ar), 7.82 (2H, m, Ar), 7.91 (2H, m, Ar), 8.20 (1H, m, Ar) and 8.40 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 14.1 (OCH_2CH_3), 53.5 (OCH_2CH_3), 102.7 (C_0), 115.8 (CN), 125.3 (CH), 127.3 (CH), 127.8 (CH), 127.9 (CH), 129.1 (CH), 129.2 (CH), 129.4 (CH), 129.6 (C_0), 131.1 (C_0), 132.4 (C_0), 154.9 (CH) and 164.5 (CO); m/z (EI) 252 (M^+ +1, 25 %), 251 (100), 207 (10), 178 (11), 152 (12), 127 (10), 101 (10) and 63 (5); GC-MS retention time R_T 10.50 min.

4-(3-Cyano-2-ethoxycarbonyl-vinyl)-benzoic acid methyl ester (4f). (0.0253 g, 0.098 mmol, 99.7 %) as a white solid (Found C 65.05; H, 5.14; N, 5.35. $C_{14}H_{13}O_4N$ requires C, 64.86; H, 5.05; N, 5.40 %); Melting point = 163-164 °C; υ_{max}/cm^{-1} 696, 776, 1206, 1276, 1611, 1712 and 2222; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 1.42 (3H, t, *J* 7.0, OCH_2CH_3), 3.97 (3H, s, OCH_3), 4.42 (2H, q, *J* 7.0, OCH_2CH_3), 8.04 (2H, d, J 8.4, Ar), 8.16 (2H, d, J 8.4, Ar) and 8.28 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 14.2 (OCH_2CH_3), 52.6 (OCH_3), 63.1 (OCH_2CH_3), 105.5 (C_0), 115.0 (CN), 130.3 (2 x CH), 130.8 (2 x CH), 133.8 (C_0), 135.2 (C_0), 153.5 (CH), 162.0 (CO) and 165.9 (CO); m/z (EI) 260 (M^++1, 30 %), 259 (80), 229 (100), 201 (30), 170 (10), 154 (10), 127 (10), 115 (5), 101 (9) and 89 (10); GC-MS retention time R_T = 9.69 min.

3-(4-Benzyloxyphenyl)-2-cyano acrylic acid ethyl ester (4g).[6] (0.0219 g, 0.071 mmol, 99.1 %) as a cream solid; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 1.39 (3H, t, J 7.3, CH_2CH_3), 4.37 (2H, q, J 7.3, CH_2CH_3), 5.15 (2H, s, CH_2), 7.00 (2H, d, J 8.7, Ar), 7.40 (5H, m, Ar), 7.99 (2H, d, J 8.7, Ar) and 8.17 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 14.2 (CH_3), 62.5 (CH_2), 70.4 (C_0CH_2), 99.5 (C_0), 115.6 (2 x CH), 124.6 (CN), 127.5 (2 x CH), 128.4 (CH), 128.8 (2 x CH), 133.7 (2 x CH), 135.8 (C_0), 154.4 (CH), 162.9 (OC_0) and 163.1 (CO); m/z (EI) 308 (M^++1, 5 %), 307 (20), 91 (100) and 65 (20); GC-MS retention time R_T = 12.35 min.

2-Cyano-3-(5-nitro-thiophen-2-yl)-acrylic acid ethyl ester (4h). (0.0284 g, 0.101 mmol, 99.7 %) as a white solid (Found C 47.49; H, 3.18; N, 10.89; S, 12.54. $C_{10}H_8O_4N_2S$ requires C, 47.61; H, 3.20; N, 11.11; S, 12.71 %); Melting point = 126 - 127 °C; υ_{max}/cm^{-1} 1269, 1340, 1526, 1600, 1709 and 2221; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 1.41 (3H, t, J 7.0, OCH_2CH_3), 4.41 (2H, q, J 7.0, OCH_2CH_3), 7.74 (1H, d, J 4.3, CH), 7.95 (1H, d, J 4.3, CH) and 8.25 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 14.1 (CH_3), 63.4 (CH_2), 105.0 (C_0), 114.5 (CN), 128.2 (CH), 134.6 (CH), 140.2 (C_0), 144.9 (C_0NO_2), 156.1 (CH) and 161.2 (CO); m/z (EI) 253 (M^++1, 30 %) 252 (70), 236 (30), 223 (10), 206 (90), 178 (100), 150 (35) and 69 (20); GC-MS retention time R_T = 9.71 min.

2-Cyano-3-(3,5-dimethoxy-phenyl)-acrylic acid ethyl ester (4i).[7] (0.0213 g, 0.082 mmol, 99.5 %) as a white crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 1.40 (3H, t, J 7.0, CH_2CH_3), 3.85 (6H, s, 2 x OCH_3), 4.39 (2H, q, J 7.0, CH_2CH_3), 6.65 (1H, m, Ar), 7.15 (2H, m, Ar) and 8.17 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 14.2 (CH_3), 55.7 (2 x OCH_3), 62.8 (CH_2), 103.4 (C_0CN), 106.2 (CH), 108.6 (2

x CH), 115.6 (CN), 133.1 (C_0), 155.2 (CH), 161.1 (2 x C_0) and 162.5 (CO); m/z (EI) 262 (M^++1, 20 %), 261 (100), 189 (55), 161 (25) and 77 (10); GC-MS retention time R_T = 9.79 min.

2-Cyano-3-*p*-tolyl-acrylic acid ethyl ester (4j). (0.0284 g, 0.132 mmol, 99.3 %) as a white crystalline solid; (Found C, 72.54; H, 6.09; N, 6.51. $C_{13}H_{13}O_2N$ requires C, 72.62; H, 6.31; N, 6.46 %); Melting point = 111 - 112 °C; υ_{max}/cm^{-1} 761, 816, 1273, 1596, 1725 and 2251; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 1.40 (3H, t, J 7.0, CH_2CH_3), 2.44 (3H, s, CH_3), 4.39 (2H, q, J 7.0, CH_2CH_3), 7.30 (2H, d, J 8.1, Ar), 7.90 (2H, d, J 8.1, Ar) and 8.22 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 14.2 (CH_2CH_3), 21.9 (CH_3), 62.6 (OCH_2CH_3), 101.6 (C_0), 115.8 (CN), 128.9 (C_0), 130.0 (2 x CH), 131.3 (2 x CH), 144.7 (C_0), 155.0 (CH) and 162.8 (CO); m/z (EI) 216 (M^++1, 10 %), 215 (100), 200 (5), 170 (35), 142 (15), 115 (40), 89 (10) and 64 (10); GC-MS retention time R_T = 8.51 min.

2-Benzylidene malononitrile (8a).[1] (0.0121 g, 0.079 mmol, 99.4 %) as a pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.55 (2H, m, Ar), 7.64 (1H, m, Ar), 7.79 (1H, s, CH) and 7.91 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 83.0 (C_0), 112.6 (CN), 113.7 (CN), 129.7 (2 x CH), 130.8 (2 x CH),131.0 (C_0), 134.7 (CH) and 159.9 (CH); m/z (EI) 155 (M^++1, 20 %), 154 (100), 127 (20) and 76 (10); GC-MS retention time R_T = 6.71 min.

2-(4-Bromobenzylidene)-malononitrile (8b).[4] (0.0312 g, 0.134 mmol, 99.4 %) as a pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.69 (2H, d, J 8.4, Ar), 7.72 (1H, s, CH) and 7.77 (2H, d, J 8.4, Ar); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 83.6 (C_0), 112.3 (CN), 113.5 (CN), 129.7 (C_0Br), 130.0 (C_0), 131.8 (2 x CH), 133.1 (2 x CH) and 158.4 (CH); m/z (EI) 235 (M^++1, 70 %), 234 (100), 233 (95), 232 (90), 153 (25) and 77 (10); GC-MS retention time R_T = 8.11 min.

2-(4-Chlorobenzylidene)-malononitrile (8c).[8] (0.0179 g, 0.095 mmol, 99.4 %) as a colourless solid; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.53 (2H, d, J 8.7, Ar), 7.74 (1H, s, CH) and 7.87 (2H, d, J 8.7); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 84.2 (C_0), 111.7 (CN), 112.3 (CN), 128.2 (2 x CH), 135.6 (2 x CH), 138.7 (C_0), 144.9 (C_0NO_2) and 159.6 (CH); m/z (EI) 189 (M^++1, 35 %), 188 (100), 153 (30), 126 (15), 100 (10) and 63 (10); GC-MS retention time R_T 7.67 min.

2-(4-Cyanobenzylidene)-malononitrile (8d).[4] (0.0222 g, 0.124 mmol, 99.6 %) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.13 (1H, s, CH), 7.84 (2H, d, J 8.7, Ar) and 8.00 (2H, d, J 8.7, Ar); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 87.0 (C_0), 111.7 (CN), 112.7 (CN), 116.5 (CN), 117.4 (C_0CN), 130.7 (2 x CH), 133.2 (2 x CH), 134.3 (C_0) and 157.3 (CH); m/z (EI) 180 (M^++1, 25 %), 179 (100), 152 (20), 125 (10), 100 (10) and 74 (10); GC-MS retention time R_T = 8.26 min.

2-Naphthalen-2-ylmethylene-malononitrile (8e). [9] (0.0255 g, 0.125 mmol, 99.2 %) as a cream solid; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.61 (1H, dt, J 2.0 and 8.7, Ar), 7.68 (1H, dt, J 2.0 and 8.7, Ar), 7.91 (2H, m, Ar), 7.97 (2H, m, Ar), 8.09 (1H, dd, J 2.0 and 8.7, Ar) and 8.30 (1H, s, CH); ^{13}C NMR (100 MHz,

$CDCl_3$/TMS) δ 82.3 (C_0), 112.9 (CN), 114.0 (CN), 124.2 (CH), 127.7 (CH), 128.0 (CH), 129.2 (2 x CH), 129.6 (C_0), 129.7 (CH), 130.0 (CH), 132.3 (C_0), 134.5 (CH), 135.9 (C_0) and 159.8 (CH); m/z (EI) 205 (M^++1, 100 %), 204 (80), 178 (20), 150 (20), 127 (15), 89 (10) and 63 (15); GC-MS retention time R_T 9.35 min.

4-(2,2-Dicyano-vinyl)-benzoic acid methyl ester (8f).[10] (0.0211 g, 0.100 mmol, 99.5 %) as a white crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 3.97 (3H, s OCH_3), 7.83 (1H, s, CH), 7.97 (2H, d, J 8.6, Ar) and 8.18 (2H, d, J 8.6, Ar); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 52.8 (OCH_3), 85.4 (C_0CN), 112.1 (CN), 113.2 (CN), 130.5 (2 x CH), 130.6 (2 x CH), 134.3 (C_0), 134.9 (C_0), 158.5 (CH) and 165.5 (CO); m/z (EI) 213 (M^++1, 25 %), 212 (50), 181 (100), 153 (20), 126 (10), 100 (5) and 75 (5); GC-MS retention time R_T = 8.55 min.

2-(4-Benzyloxybenzylidene)-malononitrile (8g).[11] (0.0155 g, 0.060 mmol, 99.4 %) as a pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 5.17 (2H, s, CH_2), 7.08 (2H, d, J 9.0, Ar), 7.39 (5H, m, Ar), 7.64 (1H, s, CH) and 7.90 (2H, d, J 9.0, Ar); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 70.6 (CH_2), 78.8 (C_0), 113.3 (CN), 114.4 (CN), 116.0 (2 x CH), 124.2 (C_0), 127.5 (2 x CH), 128.6 (CH), 128.9 (2 x CH), 133.5 (2 x CH), 135.5 (C_0), 158.8 (CH) and 163.9 (OC_0); m/z (EI) 261 (M^++1, 5 %), 260 (5), 114 (10) and 91 (100); GC-MS retention time R_T = 11.97 min.

2-(5-Nitro-thiophen-2-ylmethylene)-malononitrile (8h).[12] (0.0319 g, 0.156 mmol, 100.0 %) as a beige crystalline solid; (Found C, 47.08; H, 1.26; N, 20.76; S, 15.92, $C_8H_3SN_3O_2$ requires C, 46.83; H, 1.47; N, 20.48; S, 15.63 %); ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.74 (1H, d, J 4.5, CH), 7.82 (1H, s, CH) and 7.98 (1H, d, J 4.5, CH); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 84.2 (C_0), 111.7 (CN), 112.3 (CN), 128.2 (CH), 135.6 (CH), 138.7 (C_0), 144.9 (C_0NO_2) and 159.6 (CH); m/z (EI) 206 (M^++1, 25 %), 205 (100), 189 (25), 175 (30), 159 (15), 132 (15), 115 (25), 88 (20), 69 (25) and 45 (20); GC-MS retention time R_T 8.82 min.

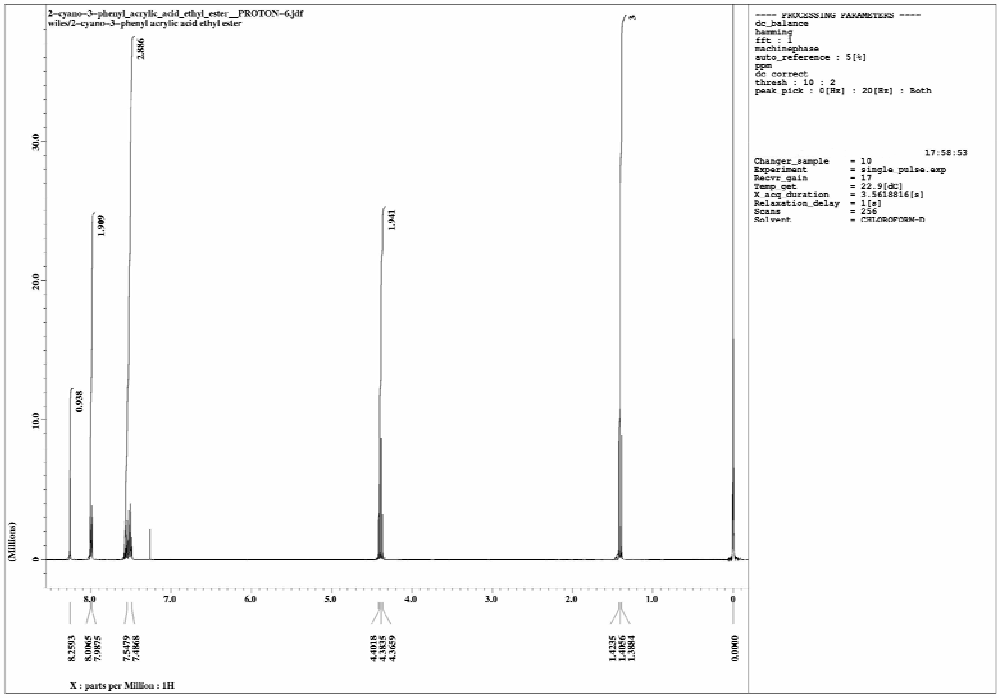
2-(3,5-Dimethoxybenzylidene)-malononitrile (8i).[1] (0.0177 g, 0.083 mmol, 99.7 %) as a yellow crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 3.84 (6H, s, OCH_3), 6.70 (1H, m, Ar), 7.03 (2H, m, Ar) and 7.69 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 55.7 (2 x OCH_3), 83.2 (C_0), 107.3 (CH), 108.3 (2 x CH), 112.7 (CN), 113.7 (CN), 132.4 (C_0), 160.1 (CH) and 161.3 (2 x C_0OCH_3); m/z (EI) 215 (M^++1, 25 %), 214 (100), 186 (55), 171 (20), 155 (20), 142 (15), 114 (10) and 76 (10); GC-MS retention time R_T = 8.69 min.

2-(4-Methyl-benzylidene)-malononitrile (8j). (0.0263 g, 0.157 mmol, 99.6 %) as a white crystalline material; (Found C, 78.53; H, 4.86; N, 16.51. $C_{11}H_8N_2$ requires C, 78.55; H, 4.79; N, 16.51 %); Melting point = 132 - 133 °C; υ_{max}/cm^{-1} 615, 815, 1588, 1606 and 2256; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 2.46 (3H, s, CH_3), 7.34 (2H, d, J 8.1, Ar), 7.72 (1H, s, CH) and 7.81 (2H, d, J 8.1, Ar); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 22.0 (CH_3), 81.3 (C_0), 112.9 (CN), 114.0 (CN), 128.5 (C_0), 130.4 (2 x CH), 130.9 (2 x

CH), 146.4 (C_0CH_3) and 159.8 (CH); m/z (EI) 169 (M^++1, 13 %),168 (100), 141 (65), 114 (30), 89 (10) and 63 (12); GC-MS retention time R_T = 7.45 min.

NMR spectra of 2-cyano-3-phenyl acrylic acid ethyl ester 4a synthesized in a flow reactor.

(a).



(b).

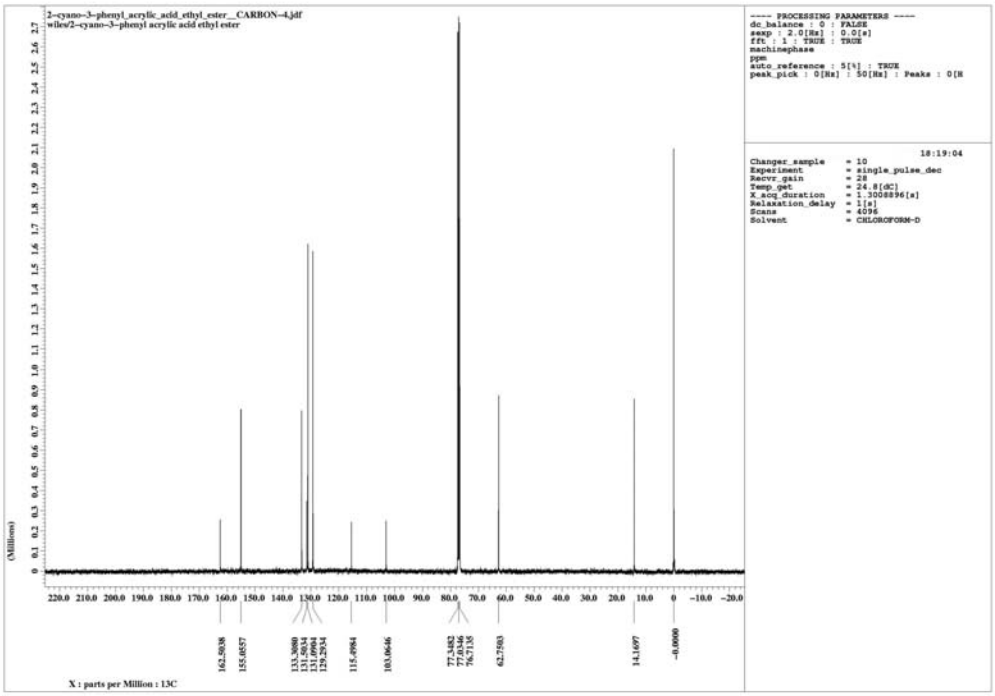


Fig. A (a). ^{1}H NMR and (b). ^{13}C NMR spectra of 2-cyano-3-phenyl acrylic acid ethyl ester **4a** synthesized in a miniaturized flow reactor.

1. B. M. Choudray, M. Lakshmi Kantam, B. Kavita, C. Venkat Reddy and F. Figueras, *Tetrahedron,* 2000, **56**, 9357-9364.

2. Y. Shen and B. Yang, *Synth. Commun.,* 1989, 3069-3074.

3. J. S. Yadav, B. V. Subba-Reddy, A. K. Basak, B. Visali, A. Narsaiah, and K. Nagaiah, *Eur. J. Org. Chem.,* 2004, **3**, 546-551.

4. S. Datta, A. De, S. P. Bhattacharyya, C. Medhi, A. K. Chakravarty, J. S. A. Brunskill, S. Fadoujou and K. Fish, *J. Chem. Soc., Perkin Trans. 2,* 1988, 1599-1606.

5. W. Ertel and K. Friedrich, *Chem. Ber.,* 1977, **110**, 86-95.

6. C. Wiles, P. Watts and S. J. Haswell, *Tetrahedron,* 2004, **60**, 8421-8427.

7. V. P. Arya and S. P. Ghate, *Indian J. Chem.,* 1971, **91**, 1209.

8. J.-Y. Liu, Y.-J. Jang, W.-W. Lin, J.-T. Liu and C.-F. Yao, *J. Org. Chem.,* 2003, **68**, 4030-4038.

9. Y. C. Kim and H. Hart, H. *Tetrahedron,* 1969, **25**, 3869-3877.

10. T. M. Posner and C. D. Hall, C. D. *J. Chem. Soc., Perkin Trans. 2,* 1976, 729-731.

11. A. Cornelis, S. Lambert and P. J. Laszlo, *J. Org. Chem.,* 1977, **42**, 381-382.

12. T. M. Patrick Jnr. and W. S. Emerson, *J. Am. Chem. Soc.,* 1952, **74**, 1356-1357.