

Sodium acetate catalyzed multicomponent approach to medicinally privileged 2-amino-4*H*-chromene scaffold from salicylaldehydes, malononitrile and cyanoacetates

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Methyl (2-amino-3-cyano-4*H*-chromen-4-yl)cyanoacetate (3a)

White solid; yield 0.78 g (95%); diastereoisomers ratio 2:1; mp 127–129°C (lit. mp¹ 128–129 °C). *Major diastereoisomer*: ¹H NMR (300 MHz, [D₆]DMSO): δ 3.79 (s, 3H; OCH₃), 4.42 (d, ³J(H,H)=3.4 Hz, 1H; CH), 4.59 (d, ³J(H,H)=3.4 Hz, 1H; CH), 7.07–7.46 ppm (m, 6H; Ar, NH₂); ¹³C NMR (75 MHz, [D₆]DMSO): δ 37.2, 47.9, 48.9, 53.8, 115.8, 116.3, 119.1, 119.5, 124.8, 128.5, 129.3, 149.4, 162.7, 164.6 ppm. *Minor diastereoisomer*: ¹H NMR (300 MHz, [D₆]DMSO, 25°C): δ 3.75 (s, 3H; OCH₃), 4.33 (d, ³J(H,H)=3.9 Hz, 1H; CH), 4.45 (d, ³J(H,H)=3.9 Hz, 1H; CH), 7.07–7.46 ppm (m, 6H; Ar, NH₂); ¹³C NMR (75 MHz, [D₆]DMSO, 25°C): δ 37.4, 46.9, 50.5, 53.7, 115.7, 116.4, 118.8, 119.6, 124.6, 128.1, 129.4, 149.7, 162.8, 164.8 ppm.

Ethyl (2-amino-3-cyano-4*H*-chromen-4-yl)cyanoacetate (3b)

White solid; yield 0.77 g (89%); diastereoisomers ratio 4:3; mp 125–127°C. *Major diastereoisomer*: ¹H NMR (300 MHz, [D₆]DMSO): δ 1.28 (t, ³J(H,H)=7.0 Hz, 3H; CH₃), 4.23 (q, ³J(H,H)=7.0 Hz, 2H; OCH₂), 4.31 (d, ³J(H,H)=3.5 Hz, 1H; CH), 4.40 (d, ³J(H,H)=3.5 Hz, 1H; CH), 7.05–7.44 ppm (m, 6H; Ar, NH₂); ¹³C NMR (75 MHz, [D₆]DMSO): δ 13.6, 37.2, 47.9, 48.9, 62.6, 115.8, 116.2, 119.3, 119.5, 125.0, 128.6, 129.4, 149.6, 162.9, 164.5 ppm. *Minor diastereoisomer*: ¹H NMR (300 MHz, [D₆]DMSO): δ 1.21 (t, ³J(H,H)=7.0 Hz, 3H; CH₃), 4.18 (q, ³J(H,H)=7.0 Hz, 2H; OCH₂), 4.37 (d, ³J(H,H)=3.8 Hz, 1H; CH), 4.55 (d, ³J(H,H)=3.8 Hz, 1H; CH), 7.05–7.44 ppm (m, 6H; Ar, NH₂); ¹³C NMR (75 MHz, [D₆]DMSO): δ 13.7, 37.4, 47.0, 50.5, 62.4, 115.7, 116.3, 118.9, 119.6, 124.8, 129.6, 128.0, 149.8, 162.8, 164.7 ppm.

Methyl (2-Amino-3-cyano-6-methyl-4*H*-chromen-4-yl)cyanoacetate (3c)

White solid; yield 0.82 g (96%); diastereoisomers ratio 4:3; mp 126–128 °C. IR ν_{max} (KBr): 3406, 3322, 3207, 2197, 1744, 1653, 1578, 1488, 1426, 1214 cm⁻¹; MS (70 eV, EI): *m/z* (%): 283 (0.3) [M⁺], 239 (4), 185 (100), 157 (33), 129 (16), 115 (5), 102 (17), 76 (19), 59 (29), 39 (24); elemental analysis calcd (%) for C₁₅H₁₃N₃O₃ (283.3): C 63.60, H 4.63, N 14.83; found (%): C

63.34, H 4.51, N 14.75. *Major diastereoisomer*: ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$): δ 2.29 (s 3H, CH_3), 3.78 (s, 3H; OCH_3), 4.36 (d, $^3J(\text{H,H})=3.3$ Hz, 1H; CH), 4.60 (d, $^3J(\text{H,H})=3.3$ Hz, 1H; CH), 6.95–7.35 ppm (m, 5H; Ar, NH_2); ^{13}C NMR (75 MHz, $[\text{D}_6]\text{DMSO}$): δ 20.3, 37.4, 47.0, 47.9, 53.3, 115.7, 116.0, 118.7, 119.6, 127.9, 130.0, 130.1, 147.5, 162.9, 165.1 ppm. *Minor diastereoisomer*: ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$, 25°C): δ 2.26 (s 3H, CH_3), 3.74 (s, 3H; OCH_3), 4.26 (d, $^3J(\text{H,H})=3.8$ Hz, 1H; CH), 4.42 (d, $^3J(\text{H,H})=3.8$ Hz, 1H; CH), 6.95–7.35 ppm (m, 5H; Ar, NH_2); ^{13}C NMR (75 MHz, $[\text{D}_6]\text{DMSO}$, 25°C): δ 20.1; 37.6, 48.6, 50.4, 53.2, 115.9, 116.4, 118.8, 119.8, 124.6, 128.0, 129.9, 147.7, 162.8, 165.2 ppm.

Methyl (2-Amino-6-chloro-3-cyano-4H-chromen-4-yl)cianoacetate (3d)

White solid; yield 0.85g (93%); diastereoisomers ratio 3:1; mp 122–124 $^\circ\text{C}$. IR ν_{max} (KBr): 3408, 3322, 3210, 2197, 1745, 1651, 15786, 1502, 1425, 1223 cm^{-1} ; MS (70 eV, EI): m/z (%): 305 (0.2) $[\text{M}^+]$, 303 (0.1) $[\text{M}^+]$, 204 (100), 177 (94), 149 (12), 114 (58), 87 (26), 68 (39), 40 (46); elemental analysis calcd (%) for $\text{C}_{14}\text{H}_{10}\text{ClN}_3\text{O}_3$ (303.7): C 55.37, H 3.32, Cl 11.67, N 13.84; found (%): C 55.24, H 3.41, Cl 11.59, N 13.73. *Major diastereoisomer*: ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$): δ 3.79 (s, 3H; OCH_3), 4.47 (d, $^3J(\text{H,H})=3.5$ Hz, 1H; CH), 4.69 (d, $^3J(\text{H,H})=3.5$ Hz, 1H; CH), 7.08–7.55 ppm (m, 5H; Ar, NH_2); ^{13}C NMR (75 MHz, $[\text{D}_6]\text{DMSO}$): δ 37.0, 47.5, 48.2, 53.3, 115.6, 116.4, 118.1, 119.2, 121.2, 127.7, 129.4, 148.4, 162.7, 164.8 ppm. *Minor diastereoisomer*: ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$, 25°C): 3.72 (s, 3H; OCH_3), 4.37 (d, $^3J(\text{H,H})=3.8$ Hz, 1H; CH), 4.61 (d, $^3J(\text{H,H})=3.8$ Hz, 1H; CH), 7.08–7.55 ppm (m, 5H; Ar, NH_2); ^{13}C NMR (75 MHz, $[\text{D}_6]\text{DMSO}$, 25°C): δ 36.8, 48.5, 50.5, 53.3, 115.8, 116.2, 117.9, 119.1, 121.1, 128.2, 130.0, 148.7, 163.2, 165.1 ppm.

Methyl (2-amino-6-bromo-3-cyano-4H-chromen-4-yl)cianoacetate (3e)

Yellowish solid; Yield 0.95 g (91%); diastereoisomers ratio 2:1; mp 129–130 $^\circ\text{C}$ (lit. mp¹ 129–130 $^\circ\text{C}$). *Major diastereoisomer*: ^1H NMR (200 MHz, $[\text{D}_6]\text{DMSO}$): δ 3.79 (s, 3H; OCH_3), 4.48 (d, $^3J(\text{H,H})=3.6$ Hz, 1H; CH), 4.70 (d, $^3J(\text{H,H})=3.6$ Hz, 1H; CH), 7.06 (d, $^3J(\text{H,H})=8.8$ Hz, 1H; Ar), 7.39 (s, 2H; NH_2), 7.56 (d, $^3J(\text{H,H})=8.8$ Hz, 1H; Ar), 7.71 ppm (s, 1H; Ar); ^{13}C NMR (75 MHz, $[\text{D}_6]\text{DMSO}$): δ 37.4, 48.0, 49.0, 53.8, 116.1, 116.9, 119.0, 119.6, 122.1, 131.8, 132.8, 149.4, 163.2, 165.3 ppm. *Minor diastereoisomer*: ^1H NMR (200 MHz, $[\text{D}_6]\text{DMSO}$): δ 3.73 (s, 3H; OCH_3), 4.37 (d, $^3J(\text{H,H})=3.7$ Hz, 1H; CH), 4.46 (d, $^3J(\text{H,H})=3.7$ Hz, 1H; CH), 7.08 (d, $^3J(\text{H,H})=8.8$ Hz, 1H; Ar), 7.41 (s, 2H; NH_2), 7.54 (d, $^3J(\text{H,H})=8.8$ Hz, 1H; Ar), 7.73 ppm (s, 1H; Ar); ^{13}C NMR (75 MHz, $[\text{D}_6]\text{DMSO}$): δ 37.5, 46.9, 50.5, 53.7, 116.0, 116.5, 118.9, 119.7, 121.9, 131.0, 132.7, 149.6, 163.1, 165.5 ppm.

Methyl (2-amino-3-cyano-8-methoxy-4*H*-chromen-4-yl)cianoacetate (3f)

White solid; Yield 0.79 g (88%); diastereoisomers ratio 2:1; mp 130–131°C (lit. mp¹ 131–132 °C). *Major diastereoisomer*: ¹H NMR (200 MHz, [D₆]DMSO): δ 3.78 (s, 3H; OCH₃), 3.83 (s, 3H; OCH₃), 4.39 (d, ³*J*(H,H)=3.4 Hz, 1H; CH), 4.58 (d, ³*J*(H,H)=3.4 Hz, 1H; CH), 6.95–7.20 (m, 3H; Ar), 7.32 ppm (s, 2H; NH₂); ¹³C NMR (50 MHz, [D₆]DMSO): δ 37.5, 47.7, 48.6, 53.2, 55.7, 112.0, 115.5, 118.7, 119.4, 119.9, 124.8, 139.0, 147.0, 162.8, 164.9 ppm. *Minor diastereoisomer*: ¹H NMR (200 MHz, [D₆]DMSO): δ 3.74 (s, 3H; OCH₃), 3.82 (s, 3H; OCH₃), 4.29 (d, ³*J*(H,H)=3.8 Hz, 1H; CH), 4.43 (d, ³*J*(H,H)=3.8 Hz, 1H; CH), 6.95–7.20 (m, 3H; Ar), 7.35 ppm (s, 2H; NH₂); ¹³C NMR (50 MHz, [D₆]DMSO): δ 37.6, 46.9, 50.5, 53.1, 56.0, 112.3, 115.6, 118.6, 119.5, 119.6, 124.7, 139.1, 147.2, 162.7, 165.1 ppm.

Methyl (2-amino-6-bromo-3-cyano-8-methoxy-4*H*-chromen-4-yl)cianoacetate (3g)

Brownish solid; Yield 1.07 g (94%); diastereoisomers ratio 2:1; mp 149–150°C (lit. mp¹ 149–150 °C). *Major diastereoisomer*: ¹H NMR (200 MHz, [D₆]DMSO): δ 3.78 (s, 3H; OCH₃), 3.86 (s, 3H; OCH₃), 4.42 (d, ³*J*(H,H)=3.4 Hz, 1H; CH), 4.67 (d, ³*J*(H,H)=3.4 Hz, 1H; CH), 7.25 (s, 1H; Ar), 7.26 (s, 2H; NH₂) 7.39 ppm (s, 1H; Ar); ¹³C NMR (75 MHz, [D₆]DMSO): δ 37.5, 47.9, 49.0, 53.8, 56.7, 115.6, 116.0, 116.7, 119.6, 121.8, 122.4, 138.9, 148.5, 163.0, 165.2 ppm. *Minor diastereoisomer*: ¹H NMR (200 MHz, [D₆]DMSO): δ 3.72 (s, 3H; OCH₃), 3.85 (s, 3H; OCH₃), 4.33 (d, ³*J*(H,H)=4.0 Hz, 1H; CH), 4.46 (d, ³*J*(H,H)=4.0 Hz, 1H; CH), 6.84 (s, 1H; Ar), 7.27 (s, 2H; NH₂) 7.42 ppm (s, 1H; Ar); ¹³C NMR (75 MHz, [D₆]DMSO): δ 37.6, 47.0, 50.6, 53.7, 56.8, 115.7, 115.8, 116.4, 119.7, 121.9, 122.2, 139.1, 148.6, 162.9, 165.5 ppm.

References

1. M. N. Elinson, A. S. Dorofeev, F. M. Miloserdov, A. I. Ilovaisky, S. K. Feducovich, P. A. Belyakov and G. I. Nikishin, *Adv. Synth. Catal.*, 2008, **350**, 591.