SUPPORTING INFORMATION

Efficient and green preparation of 2-amino-4H-chromenes by a room temperature Na₂CO₃-catalysed three-component reaction of malononitrile, benzaldehydes and phloroglucinol or resorcinol in aqueous medium

¹Ishmael B Masesane and ²Shetonde O. Mihigo

¹Department of Chemistry, University of Botswana, Private Bag 00704, Gaborone, Botswana. ²Department of chemistry, University of Kinshasa, P. O. Box 190, Kinshasa XI, DR Congo.

Experimental

Materials and methods

Laboratory grade chemicals and solvents were procured from Sigma-Aldrich and used without any further purification. Reactions were monitored by TLC using Merck's TLC Silica gel 60 F254 aluminium sheets. Melting point measurements were determined on a Stuart melting point apparatus and are uncorrected. Infrared spectra were recorded neat on a Perkins Elmer FT-IR spectrophotometer 1000. High resolution mass spectra were recorded on a GCT Premier mass spectrometer (Waters) with an ionization energy of 70 eV. NMR spectra were recorded on a Bruker Avance DPX 300 MHz NMR spectrometer with TMS as an internal standard.

Typical procedure: A mixture of benzaldehyde (0.30 g, 2.8 mmol), malononitrile (0.19 g, 2.8 mmol) and phloroglucinol (0.36 g, 2.8 mmol) was dissolved in methanol (1.0 cm³) in a round bottom flask. A solution of Na₂CO₃ (0.09 g, 0.8 mmol) in water (19.0 cm³) was then added to the round bottom flask and the resulting suspension was stirred at room temperature for 10 hours. The solid formed was filtered off, washed with water followed by cold methanol and dried in an oven at 100 °C to give 2-amino-3-cyano-5,7-dihydroxy-4-phenyl-4H-chromene in 65% yield.

2-Amino-3-cyano-5,7-dihydroxy-4-phenyl-4H-chromene (4): white solid, 65%; mp 162-164 °C; IR (neat) ν : 3331, 3203, 2188, 1654, 1618, 1468 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 4.48 (1H, s, H-4), 5.98 (1H, d, J = 1.5 Hz, H-6), 6.06 (1H, d, J = 1.5 Hz, H-8), 6.78 (2H, s, 2OH), 7.20 (5H, m, ArH), 9.57 (2H, br, NH₂); ¹³C NMR (75 MHz, DMSO-d₆) δ 36.8 (C-4), 58.0 (C-3), 94.2 (C-8), 99.3 (C-6), 102.8 (C-4a), 121.3 (CN), 126.6 (C-4'), 127.5 (C-2' and 6'), 128.6 (C-3' and 5'), 146.8 (C-1'), 150.9 (C-8a), 155.8 (C-7), 157.9 (C-5), 160.9 (C-2); HRMS-EI (m/z) calcd for C₁₆H₁₂N₂O₃: 280.2848; found, 280.2853.

2-amino-3-cyano-5,7-dihydroxy-4-(4'-methoxyphenyl)-4H-chromene (17): yellow solid, 75%; mp 211-212 °C; IR (neat) ν_{max} : 3460, 3226, 2994, 2191, 1648, 1602, 1583, 1409 cm^{-1} ; ^1H NMR (300 MHz, DMSO- d_6) δ 3.71 (3H, s, OCH₃), 4.42 (1H, s, H-4), 5.96 (1H, d, J = 2.4 Hz, H-6), 6.06 (1H, d, J = 2.4 Hz, H-8), 6.80 (2H, dd, J = 8.8 and 2.3 Hz, H-3' and 5'), 7.07 (2H, dd, J = 8.8 and 2.3 Hz, H-2' and 6'), 9.55 (2H, br, NH₂); ^{13}C NMR (75 MHz, DMSO- d_6) δ 35.8 (C-4), 54.3 (OCH₃), 58.5 (C-3), 93.9 (C-8), 98.6 (C-6), 103.3 (C-4a), 113.2 (C-3' and 5'), 120.9 (CN), 128.0 (C-2' and 6'), 138.3 (C-1'), 150.7 (C-8a), 155.5 (C-4'), 157.3 (C-7), 158.2 (C-5), 161.3 (C-2); HRMS-EI (m/z) calcd for C₁₇H₁₄N₂O₄: 310.3012; found, 310.3009.

2-Amino-3-cyano-5,7-dihydroxy-4-(4'-hydroxyphenyl)-4H-chromene (18): yellow solid, 79%; mp 215-216 °C; IR (neat) ν_{max} : 3457, 3448, 2187, 1641, 1609, 1590, 1506, 1413 cm^{-1} ; ^1H NMR (300 MHz, (CD₃)₂CO) δ 4.61 (1H, s, H-4), 6.05 (2H, br, 2OH), 6.13 (1H, d, J = 2.1 Hz, H-6), 6.21 (1H, d, J = 2.1 Hz, H-8), 6.75 (2H, dd, J = 9.3 and 2.7 Hz, H-3' and 5'), 7.06 (2H, dd, J = 9.3 and 2.7 Hz, H-2' and 6'), 8.60 (2H, br, NH₂); ^{13}C NMR (75 MHz, (CD₃)₂CO) δ 35.9 (C-4), 60.1 (C-3), 94.4 (C-8), 99.1 (C-6), 103.7 (C-4a), 114.9 (C-3' and 5'), 120.2 (CN), 128.4 (C-2' and 6'), 137.2 (C-1'), 150.8 (C-4'), 155.4 (C-8a), 155.8 (C-7), 157.8 (C-5), 160.5 (C-2); HRMS-EI (m/z) calcd for C₁₆H₁₂N₂O₄: 296.2837; found, 296.2841.

2-Amino-3-cyano-5,7-dihydroxy-4-(4'-hydroxy-3'-methoxyphenyl)-4H-chromene (19): yellow solid, 70%; mp 239-240 °C; IR (neat) ν_{max} : 3447, 3354, 2194, 1657, 1906, 1506, 1480 cm^{-1} ; ^1H NMR (300 MHz, (CD₃)₂CO) δ 3.76 (3H, s, OCH₃), 4.61 (1H, s, H-4), 6.02 (2H, s, 2OH), 6.11 (1H, d, J = 2.1 Hz, H-6), 6.21 (1H, J = 2.1 Hz, H-8), 6.64 (1H, dd, J = 8.1 and 1.8 Hz, H-6'), 6.73 (1H, d, J = 8.1 Hz, H-5'), 6.86 (1H, d, J = 2.1 Hz, H-2'), 8.56 (2H, br, NH₂); ^{13}C NMR (75 MHz, (CD₃)₂CO) δ 36.3 (C-4), 55.4 (OCH₃), 60.1 (C-3), 94.5 (C-8), 99.1 (C-5), 103.6 (C-2'), 111.2 (C-4a), 114.7 (C-5'), 119.7 (CN), 120.1 (C-6'), 137.7 (C-1'), 145.1 (C-4'), 147.1 (C-3'), 150.9 (C-8a), 155.4 (C-5), 157.4 (C-7), 160.4 (C-2); HRMS-EI (m/z) calcd for C₁₇H₁₄N₂O₅: 326.3003; found, 326.3299.

2-Amino-4-(benzo[d][1,3]dioxol-5-yl)-3-cyano-5,7-dihydroxy-4H-chromene (20): yellow solid, 72%; mp 231-232 °C; IR (neat) ν_{max} : 3463, 3361, 2191, 1657, 1631, 1593, 1487 cm^{-1} ; ^1H NMR (300 MHz, DMSO- d_6) δ 4.49 (1H, s, H-4), 5.95 (2H, s, OCH₂O), 5.97 (1H, d, J = 2.2 Hz, H-6), 6.08 (1H, d, J = 2.2 Hz, H-8), 6.59 (1H, dd, J = 7.8 and 2.1 Hz, H-6'), 6.77 (1H, d, J = 7.8 Hz, H-5'), 6.82 (1H, d, J = 2.1 Hz, H-2'), 9.58 (2H, br, NH₂); ^{13}C NMR (75 MHz, DMSO- d_6) δ 36.5 (C-4), 58.1 (C-3), 94.2 (C-8), 99.3 (C-5), 101.2 (OCH₂O), 107.9 (C-5'), 108.4 (C-2'), 120.4 (C-4a), 121.3 (CN), 140.9 (C-6'), 146.0 (C-1'), 147.5 (C-4'), 150.8 (C-3'), 155.7 (C-8a), 157.9 (C-5 and 7), 160.9 (C-2); HRMS-EI (m/z) calcd for C₁₇H₁₂N₂O₅: 324.2946; found, 324.2948.

2-Amino-3-cyano-5,7-dihydroxy-4-(o-tolyl)-4H-chromene (21): yellow solid, 78%; mp 220-221 °C; IR (neat) ν_{max} : 3454, 3332, 2194, 1661, 1622, 1596, 1465 cm^{-1} ; ^1H NMR (300 MHz, CD₃OD) δ 2.53 (3H, s, CH₃), 4.95 (1H, s, H-4), 6.02 (1H, d, J = 2.1 Hz, H-6), 6.18 (1H, d, J = 2.1 Hz, H-8), 6.94-7.12 (4H, m, ArH); ^{13}C NMR (75 MHz, CD₃OD) δ 18.4 (CH₃), 32.3 (C-4), 58.2 (C-3), 93.9 (C-

8), 98.6 (C-6), 103.4 (C-4a), 121.1 (CN), 125.7 (C-6'), 125.9 (C-4'), 128.0 (C-5'), 129.6 (C-3'), 134.8 (C-2'), 144.7 (C-1'), 150.9 (C-8a), 155.6 (C-7), 157.3 (C-5) 160.8 (C-2); HMRS-EI (m/z) calcd for C₁₇H₁₄N₂O₃: 294.3004; found, 294.3011.

2-Amino-3-cyano-5,7-dihydroxy-4-(m-tolyl)-4H-chromene (22): yellow solid, 83%; mp 181-182 °C; IR (neat) ν_{max} : 3452, 3329, 2192, 1659, 1601, 1459 cm⁻¹; ¹H NMR (300 MHz, CD₃OD) δ 2.29 (3H, s, CH₃), 4.56 (H-4), 6.09 (2H, s, H-6 and 8), 6.95 (3H, m, H-2', 4' and 6'), 7.16 (1H, dd, J = 7.5 and 6.9 Hz, H-5'); ¹³C NMR (75 MHz, CD₃OD) δ 20.2 (CH₃), 36.5 (C-4), 58.3 (C-3), 93.9 (C-8), 98.6 (C-6), 103.0 (C-4a), 121.0 (CN), 124.1 (C-6'), 126.6 (C-4'), 127.6 (C-5'), 127.7 (C-2'), 137.3 (C-3'), 145.9 (C-1'), 150.8 (C-8a), 155.5 (C-7), 157.5 (C-5), 161.1 (C-2); HRMS-EI (m/z) calcd for C₁₇H₁₄N₂O₃: 294.3004; found, 294.2998.

2-amino-3-cyano-5,7-dihydroxy-4-(p-tolyl)-4H-chromene (23): yellow solid, 79%; mp 132-124 °C; IR (neat) ν_{max} : 3449, 3338, 2193, 1660, 1599, 1452 cm⁻¹; ¹H NMR (300 MHz, (CD₃)₂CO) δ 2.27 (3H, s, CH₃), 4.64 (1H, s, H-4), 6.04 (2H, s, 2OH), 6.14 (1H, d, J = 2.1 Hz, H-8), 6.22 (1H, d, J = 2.1 Hz, H-6), 7.08 (4H, m, ArH), 8.64 (2H, br, NH₂); ¹³C NMR (75 MHz, (CD₃)₂CO) δ 20.2 (CH₃), 36.4 (C-4), 60.0 (C-3), 94.4 (C-8), 99.1 (C-6), 103.4 (C-4a), 120.0 (CN), 127.3 (C-3' and 5'), 128.7 (C-2' and 6'), 135.5 (C-4'), 143.2 (C-1'), 150.9 (C-8a), 155.5 (C-7) 157.6 (C-5), 160.4 (C-2); HRMS-EI (m/z) calcd for C₁₇H₁₄N₂O₃: 294.3004; found, 294.3010.

2-Amino-3-cyano-5,7-dihydroxy-4-(4'-nitrophenyl)-4H-chromene (24): yellow solid, 96%; mp 268-270 °C; IR (neat) ν_{max} : 3399, 3180, 2206, 1651, 1587, 1512, 1409 cm⁻¹; ¹H NMR (300 MHz, (CD₃)₂CO) δ 4.82 (1H, s, H-4), 6.16 (1H, d, J = 2.1 Hz, H-8), 6.22 (1H, d, J = 2.1 Hz, H-6), 6.25 (2H, s, 2OH), 7.48 (2H, d, J = 8.7 Hz, H-2' and 6'), 8.18 (2H, d, J = 8.7 Hz, H-3' and 5'), 8.85 (2H, br, NH₂); ¹³C NMR (75 MHz, (CD₃)₂CO) δ 36.9 (C-4), 58.3 (C-3), 94.6 (C-8), 99.1 (C-6), 101.6 (C-4a), 119.4 (CN), 123.4 (C-3' and 5'), 128.5 (C-2' and 6'), 146.6 (C-4'), 150.7 (C-1'), 153.7 (C-8a), 155.6 (C-7), 158.3 (C-5), 160.5 (C-2); HRMS-EI (m/z) calcd for C₁₆H₁₁N₃O₅: 325.2799; found, 325.2802.

2-Amino-4-(4'-chlorophenyl)-3-cyano-5,7-dihydroxy-4H-chromene (25): yellow solid, 73%; mp 142-144 °C, IR (neat) ν_{max} : 3606, 3460, 3301, 2994, 2192, 1649, 1608, 1579 cm⁻¹; ¹H NMR (300 MHz, (CD₃)₂CO) δ 4.65 (1H, s, H-4), 6.11 (3H, m, H-8 and 2OH), 6.19 (1H, d, J = 3.6 Hz, H-6), 7.22 (2H, d, J = 8.7 Hz, H-2' and 6'), 7.32 (2H, d, J = 8.7 Hz, H-3' and 5'), 8.95 (2H, br, NH₂); ¹³C NMR (75 MHz, (CD₃)₂CO) δ 36.3 (C-4), 59.2 (C-3), 94.4 (C-8), 99.1 (C-6), 119.4 (CN), 121.1 (C-4a), 128.1 (C-3' and 5'), 129.1 (C-2' and 6'), 130.9 (C-4'), 145.2 (C-1'), 151.2 (C-8a), 155.5 (C-7), 157.9 (C-5), 160.4 (C-2); HRMS-EI (m/z) calcd for C₁₆H₁₁ClN₂O₃: 314.7214; found, 314.7220.

2-Amino-3-cyano-7-hydroxy-4-(4'-hydroxy-3'-methoxyphenyl)-4H-chromene (30): Yellow solid, 70%, mp 248-249 °C, IR (neat) ν_{max} : 3509, 3419, 3337, 3215, 2198, 1642, 1616, 1556, 1501 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 3.73 (3H, s, OCH₃), 4.53 (1H, s,

H-4), 6.40 (1H, d, J = 2.4 Hz, H-8), 6.49 (1H, dd, J = 7.8 and 2.4 Hz, H-6), 6.55 (1H, dd, J = 7.5 and 2.1 Hz, H-6'), 6.71 (1H, d, J = 7.5 Hz, H-5'), 6.76 (1H d, J = 2.1 Hz, H-2'), 6.85 (1H, d, J = 7.8 Hz, H-5), 8.87 (2H, br, NH₂); ¹³C NMR (75 MHz, DMSO-d₆) δ 40.0 (C-4), 56.09 (OCH₃), 59.8 (C-3), 102.6 (C-8), 112.1 (C-6), 112.7 (C-2'), 113.4 (C-4a), 115.7 (C-5'), 116.0 (C-6'), 120.2 (CN), 130.4 (C-5), 137.2 (C-1'), 147.2 (C-4'), 147.8 (C-3'), 150.1 (C-8a), 156.4 (C-4'), 157.4 (C-7), 160.5 (C-2); HRMS-EI (m/z) for C₁₇H₁₄N₂O₄: 310.3041; found, 310.3050.

2-Amino-3-cyano-7-hydroxy-4-(*o*-tolyl)-4H-chromene (31): Yellow solid, 54%, mp 217-218 °C, IR (neat) ν_{max}: 3488, 3385, 3216, 2195, 1651, 1622, 1589, 1503 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 2.32 (3H, s, CH₃), 3.45 (1H, br, OH), 4.92 (1H, s, H-4), 6.43 (1H, d, J = 2.7 Hz, H-8), 6.47 (1H, dd, J = 8.1 and 2.7 Hz, H-6), 6.98 (1H, d, J = 8.1 Hz, H-5), 7.12 (4H, m, H-3', 4', 5' and 6'), 9.72 (2H, br, NH₂); ¹³C NMR (75 MHz, DMSO-d₆) δ 19.5 (CH₃), 37.3 (C-4), 56.6 (C-3), 102.5 (C-8), 112.9 (C-6), 114.0 (C-4a), 121.0 (CN), 126.9 (C-2'), 127.0 (C-4'), 129.7 (C-3'), 130.2 (C-5), 131.1 (C-6'), 135.5 (C-5'), 144.5 (C-1'), 149.6 (C-8a), 157.5 (C-7), 160.4 (C-2); HRMS-EI (m/z) for C₁₇H₁₄N₂O₂: 278.3053; found, 278.3048.

2-Amino-3-cyano-7-hydroxy-4-(*m*-tolyl)-4H-chromene (32): White solid, 87%, mp 175-176 °C, IR (neat) ν_{max}: 3334, 3200, 2922, 2191, 1648, 1588, 1507 cm⁻¹; ¹H NMR (300 MHz, CD₃OD) δ 2.32 (3H, s, CH₃), 4.58 (1H, s, H-4), 6.48 (1H, d, J = 1.5 Hz, H-8), 6.52 (1H, d, J = 8.1 Hz, H-6), 6.78 (1H, d, J = 8.1 Hz, H-5), 7.01 (3H, m, H-2', 4' and 6'), 7.19 (1H, dd, J = 7.5 and 7.2 Hz, H-5'); ¹³C NMR (75 MHz, CD₃OD) δ 20.1 (CH₃), 40.5 (C-4), 57.2 (C-3), 102.2 (C-8), 112.1 (C-6), 114.1 (C-4a), 120.6 (CN), 124.5 (C-6'), 127.2 (C-4'), 128.0 (C-5'), 128.1 (C-2'), 129.8 (C-5), 138.0 (C-3'), 146.0 (C-1'), 149.3 (C-8a), 157.1 (C-7), 160.8 (C-2); HRMS-EI (m/z) for C₁₇H₁₄N₂O₂: 278.3053; found, 278.3061.

SM1A (Using Benzaldehyde)
PROTON DMSO

9.61
9.52
7.28
7.26
7.24
7.18
7.15
7.11
7.09
6.78
6.07
6.06
5.98
5.97
4.47

SM1A
¹³C NMR DMSO

160.90
 157.90
 155.75
 150.89
 146.78

128.62
 127.46
 126.59
 121.32

102.84
 99.29
 94.17

57.96

36.84

M6-4-Hydroxy
13CPD Acetone

160.45
157.45
155.79
155.43
150.83
137.20
128.35
120.20
114.94
103.71
99.13
94.44
60.07
35.91

0
CPD Acetone

160.43
157.48
155.43
150.90
147.06
145.06
137.74

120.06
119.70
114.71
111.23
103.61
99.14
94.49

60.06
55.40

36.27

SM15
PROTON MeOD

SM15
C13CPD MeOD

160.80
160.78
157.25
155.59
150.85
144.65
134.82
129.58
127.95
125.89
125.65
121.11

103.44
98.57
93.85

58.20

32.27

18.36

SM16
C13CPD MeOD

161.11
157.38
155.49
150.80
145.94
137.33
127.66
127.56
126.57
124.09
121.04

103.00
98.56
93.91

58.33

36.50

20.18

ketone

8.635
7.138
7.110
7.084
7.066
7.058
6.226
6.219
6.147
6.140
6.039
4.644

2.267

13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 ppm

1.84

4.48

0.90

0.91

1.80

1.00

3.04

R2
PD Acetone

160.37
157.60
155.46
150.92
143.22
135.54
128.73
127.25
119.91

103.40
99.07
94.43

59.97

36.38

20.17

SM11
PROTON Acetone

SM11
C13CPD Acetone

160.52
158.25
155.55
153.65
150.73
146.62

128.53
123.41
119.35

101.66
99.13
94.59

58.29

36.86

SM19RB
PROTON Acetone

SM19RB
C13CPD Acetone

160.37
157.91
155.50
145.15

129.09
128.09

99.08
94.43

59.24

36.33

SM15B=2Toluald
PROTON DMSO

9.717
7.171
7.154
7.134
7.117
7.094
7.074
7.000
6.983
6.963
6.821
6.673
6.641
6.495
6.488
6.468
6.458
6.436
6.427
4.920
2.323

SM15B=2Toluald
C13CPD DMSO

SM16B=3Toluald
 PROTON MeOD

7.211
 7.186
 7.162
 7.051
 7.024
 7.003
 6.997
 6.966
 6.798
 6.771
 6.769
 6.525
 6.517
 6.490
 6.485
 4.577
 2.318

SM16B=3Toluald
C13CPD MeOD