Basic ionic liquid [bmIm]OH mediated Gewald reaction as green protocol for the synthesis of 2-aminothiophenes

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Experimental protocols

All the reagents used were as purchased without purification. Solvents used for reactions were dried according to standard methods. Melting points were recorded in open capillaries on Casiaa Siamea (VMP-AM) melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer FT-IR 240-C spectrophotometer using KBr discs. ¹H NMR and ¹³C NMR spectra were recorded on Bruker Avance II (400 MHz and 100 MHz respectively) spectrometer in DMSO-*d*₆ or CDCl₃ using TMS as internal standard. Mass spectra (ESI) were recorded on Waters Micromass Q-TOF Micro. All the reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254 (mesh) (E. Merck, Mumbai) and spots were visualized under UV light (254 nm).

Experimental Data

2-amino-4,5-dimethylthiophene-3-carbonitrile (2a)

White solid; Mp 140 °C (lit.^[22] 89–90 °C); IR (KBr): 3445, 3328, 2196, 1521 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 4.7 (s, 2H), 2.2 (s, 3H), 2.28 (s, 3H).

Ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate (**2b**)

Brown color solid; Mp 90 °C (lit. ^[22] 89–90 °C); IR (KBr): 3345, 3318, 1624 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 5.17 (s, 2H), 4.25 (q, *J* = 6.7 Hz, 2H), 2.2 (s, 3H), 2.28 (s, 3H), 1.33 (t, *J* = 6.7 Hz, 3H).

2-amino-5,6-dihydro-4H-cyclopenta[*b*]thiophene-3-carbonitrile (**2c**)

Brown color solid; Mp 161 °C; IR (KBr): 3414, 3294, 2184, 1287 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 4.73 (s, 2H), 2.80 (m, 2H), 2.74 (m, 2H), 2.36 (m, 2H); MS (ESI): *m/z* = 212.2 (M+H)⁺.

Ethyl 2-Amino-5,6-dihydro-4H-cyclopenta[*b*]thiophene-3-carboxylate (**2d**)

Brown color solid; Mp 90 °C (lit. ^[23] 89–90 °C); IR (KBr): 3414, 3294, 1624, 1287 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 5.83 (s, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 2.85–2.80 (m, 2H), 2.74 (m, 2H), 2.36 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 166.2, 165.8, 142.7, 121.4, 103.0, 59.4, 30.8, 28.9, 27.2, 14.4; MS (ESI): *m/z* = 212.2 (M+H)⁺.

2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (**2e**)

White solid; Mp 145 °C (lit. ^[23] 146–147 °C); IR (KBr): 3445, 3328, 2196, 1521 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 4.71 (s, 2H), 2.48 (m, 4H), 1.79 (m, 4H); ¹³C NMR (100 MHz, CDCl₃): δ = 160.1, 132.3, 120.6, 115.6, 88.5, 24.5, 24.1, 23.4, 22.1; MS (ESI): *m/z* = 178.3 (M+H)⁺.

Ethyl 2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (**2f**)

White solid; Mp 113 °C (lit. ^[23] 115 °C); IR (KBr) 3405, 3299, 1647, 1274 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 6.01 (s, 2H), 4.25 (q, *J* = 7.2 Hz, 2H), 2.71 (m, 2H), 2.48 (m, 2H), 1.75 (m, 4H), 1.33 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 166.6, 161.9, 132.4, 117.5, 105.5, 59.4, 27.0, 24.5, 23.3, 22.9, 14.5. MS (ESI): *m/z* = 225.4 (M+H)⁺.

2-Amino-5,6,7,8-tetrahydro-4H-cyclohepta[*b*]thiophene-3-carbonitrile (**2g**)

White solid; Mp 125 °C (lit. ^[24] 126 °C); IR (KBr): 3443, 3310, 2203 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 4.26 (s, 2H), 2.65 (m, 4H), 1.83 (m, 2H), 1.67 (m, 4H). ¹³C NMR (100 MHz, CDCl₃): δ = 157.7, 136.9, 123.9, 115.9, 92.0, 31.9, 29.4, 29.2, 28.1, 27.2.; MS (ESI): *m/z* = 192.3 (M+H)⁺.

Ethyl 2-Amino-5,6,7,8-tetrahydro-4H-cyclohepta[*b*]thiophene-3-carboxylate (**2h**)

White solid; Mp 87 °C (lit. ^[24] 89 °C); IR (KBr): 3398, 3301, 1651, 1277 cm⁻¹.; ¹H NMR (400 MHz, CDCl₃): δ = 5.74 (s, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.00 (m, 2H), 2.60 (m, 2H), 1.82 (m, 2H), 1.68 (m, 4H), 1.35 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 166.0, 159.7, 137.9, 121.4, 107.6, 59.6, 32.2, 28.7, 28.6, 27.8, 27.0, 14.5.; MS (ESI): *m/z* = 239.4 (M+H)⁺.

2-amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carbonitrile (**2i**)

Red color solid; Mp 89–90 °C; ¹H NMR (400 MHz, CDCl₃): δ = 7.31 (m, 5H), 4.68 (s, 2H), 3.69 (s, 2H), 3.40 (s, 2H), 2.80 (t, *J* = 6.0 Hz, 2H), 2.63 (t, *J* = 6.0 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 160.5, 137.8, 130.9, 129.9, 128.4, 127.3, 117.8, 115.1, 88.2, 61.7, 50.7, 49.5, 24.6. MS (ESI): *m/z* = 270.1 (M+H)⁺.

Ethyl 2-amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylate (**2l**)

Brick red color solid; ¹H NMR (400 MHz, CDCl₃): δ = 7.31 (m, 5H), 5.7 (s, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.69 (s, 2H), 3.40 (s, 2H), 2.81 (t, *J* = 6.0 Hz, 2H), 2.63 (t, *J* = 6.0 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3H); MS (ESI): *m/z* = 316.9 (M+H)⁺.

2-Amino-4-phenyl-3-thiophenecarbonitrile (**5a**)

White solid; Mp 100-102 °C (lit. ^[25] 100–102 °C); ¹H NMR (400 MHz, CDCl₃): δ = 7.48-7.56 (m, 2H), 7.38 (m, 2H), 7.30 (m, 1H), 7.23 (s, 2H), 6.51 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 165.7, 137.9, 133.9, 128.1, 127.3, 126.4, 116.2, 104.7, 82.9.; MS (ESI): *m/z* = 201.0 (M+H)⁺.

2-Amino-4-(4-methoxyphenyl)-3-thiophenecarbonitrile (**5b**)

White solid; Mp 164–166 °C (lit. ^[26] 166 °C). ¹H NMR (400 MHz, CDCl₃): δ = 7.45 (d, *J* = 8.9 Hz, 2H), 7.18 (s, 2H), 6.97 (d, *J* = 8.9 Hz, 2H), 6.39 (s, 1H), 3.77 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 165.6, 158.3, 137.6, 127.6, 126.5, 116.3, 113.6, 103.3, 83.1, 55.1.; MS (ESI): *m/z* = 231 (M+H)⁺.

2-Amino-4,5-diphenyl-3-thiophenecarbonitrile (5c)

Brown color solid; Mp 203–205 °C (lit. ^[26] 205 °C); ¹H NMR (400 MHz, CDCl₃): δ = 7.50 (m, 3H), 7.42 (m, 2H), 7.28 (m, 3H), 7.26 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 163.3, 134.1, 133.7, 132.4, 128.8, 128.1, 127.6, 127.4, 126.4, 118.8, 115.7, 86.6.; MS (ESI): *m/z* = 277.2 (M+H)⁺.

2-Amino-4-(4-bromophenyl)thiophene-3-carbonitrile (5d)

Yellow solid; Mp 190–191 °C (lit. ^[25] 190-192 °C); ¹H NMR (400 MHz, DMSO-d₆): δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.29 (s, 2H), 6.56 (s, 1H), 4.87 (s, 2H); ¹³C NMR (100 MHz, DMSO-d₆): δ 167.0, 137.5, 134.0, 132.0, 129.3, 121.5, 116.9, 106.1, 83.2.

Diethyl 5-amino-3-methylthiophene-2,4-dicarboxylate (5g)

Brown color solid; Mp. 108-109 °C (lit. ¹⁷ 106 °C); IR (KBr): 3408, 3294, 1682, 1660, 1587, 1529, 1232 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 1.33 (t, *J* = 7.1 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 3H), 2.70 (s, 3H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 6.60 (s, 2H).; ¹³C NMR (100 MHz, CDCl₃): δ = 14.5, 14.6, 16.3, 60.2, 60.6, 108.6, 108.7, 148.2, 163.1, 166.3, 166.4.; MS (ESI): *m/z* = 257.0 (M+H)⁺.

2-amino-4-methoxythiophene-3-carbonitrile (8a)

Black colour solid; Mp. 78-79 °C; ¹H NMR (400 MHz, CDCl₃): δ = 5.21 (s, 1H), 4.89 (s, 2H, NH₂), 3.79 (s, 3H, OCH₃). ¹³C NMR (100 MHz, CDCl₃): δ = 160.8, 154.1, 113.9, 82.6, 79.9, 57.0. MS (ESI): *m/z* = 155.02 (M+H)⁺.

2-amino-4-ethoxythiophene-3-carbonitrile (**8b**)

Brown colour solid; Mp 134 °C; IR (KBr): 3439, 3320, 3213, 2972, 2199, 1631, 1557 cm⁻¹.; ¹H NMR (400MHz, CDCl₃): δ = 5.18 (s, 1H), 4.79 (s, 2H, NH₂), 4.01 (q, *J* = 6.8 Hz, 2H), 1.40 (t, *J* = 6.8 Hz, 3H). ¹³C NMR (100MHz, CDCl₃): δ = 160.4, 154.2, 113.9, 82.6, 78.9, 59.0, 15.1; MS (ESI⁺): *m/z* = 169.1 (M+H).

2-amino-4-propoxythiophene-3-carbonitrile (**8c**)

Cream colour solid; Mp 220 °C; IR (KBr): 3436, 3320, 3215, 2934, 2877, 2205, 1632, 1559 cm⁻¹.; ¹H NMR (400 MHz, CDCl₃): δ 5.18 (s, 1H), 4.77 (s, 2H, NH₂), 3.85 (t, *J* = 6.8 Hz, 2H), 1.82 (m, 2H), 1.01 (t, *J* = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 160.4, 153.6, 113.9, 83.1, 78.9, 62.1, 22.1, 17.5.; MS (ESI⁺): *m/z* 182.9 (M+H)⁺

2-amino-4-butoxythiophene-3-carbonitrile (**8d**)

White solid; Mp 84 °C; IR (KBr): 3438, 3339, 3221, 2951, 2867, 2198, 1620, 1555 cm⁻¹.; ¹H NMR (400 MHz, CDCl₃): δ 5.17 (s, 1H), 4.88 (s, 2H, NH₂), 3.92 (t, *J* = 6.4 Hz, 2H), 1.76 (m, 2H), 1.47 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 160.1, 153.3, 113.8, 83.2, 80.3, 74.2, 28.0, 21.1, 12.1.; MS (ESI⁺): *m/z* 197.0 (M+H)⁺.

2-amino-4-isobutoxythiophene-3-carbonitrile (**8e**)

Brown colour solid; Mp 104 °C; IR (KBr): 3433, 3322, 3207, 2958, 2207, 1622, 1557 cm⁻¹.; ¹H NMR (400MHz, CDCl₃): δ = 5.16 (s, 1H), 4.79 (s, 2H, NH₂), 3.67 (d, *J* = 6.4 Hz, 2H), 2.1 (m, 1H), 1.01 (d, *J* = 6.4 Hz, 6H). ¹³C NMR (100MHz, CDCl₃): δ = 160.3, 153.5, 113.8, 83.2, 80.2, 76.25, 28.0, 14.1.; MS (ESI⁺): *m/z* = 197.0 (M+H)⁺.

2-amino-4-(pentyloxy)thiophene-3-carbonitrile (**8f**)

White solid; Mp 78 °C; IR (KBr): 3446, 3347, 3225, 2942, 2864, 2199, 1621, 1554 cm⁻¹.; ¹H NMR (400MHz, CDCl₃): δ = 5.17 (s, 1H), 4.8 (s, 2H, NH₂), 3.91(t, *J* = 6.4 Hz, 2H), 1.80 (m,

2H), 1.43 (m, 4H), 0.94 (t, $J = 6.4$ Hz, 3H). ^{13}C NMR (100MHz, CDCl_3): $\delta = 160.4, 153.4, 113.9, 83.2, 80.2, 70.1, 28.5, 28.0, 22.4, 13.9$.; MS (ESI^+): $m/z = 211.1$ (M+H) $^+$.

2-amino-4-(octyloxy)thiophene-3-carbonitrile (**8g**)

White solid; Mp 82 °C; IR (KBr): 3445, 3320, 3213, 2924, 2852, 2205, 1626, 1558 cm^{-1} .; ^1H NMR (400MHz, CDCl_3): $\delta = 5.17$ (s, 1H), 4.83 (s, 2H, NH_2), 3.91(t, $J = 6.4$ Hz, 2H), 1.78 (m, 2H), 1.46 (m, 2H), 1.32 (m, 8H), 0.88 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR (100MHz, CDCl_3): $\delta = 160.1, 153.4, 113.9, 83.2, 80.2, 64.1, 28.5, 28.0, 22.4, 19.8, 19.3, 19.2, 11.9$.; MS (ESI^+) $m/z = 253.1$ (M+H) $^+$

2-amino-4-(benzyloxy)thiophene-3-carbonitrile (**8h**)

Black colour solid; IR (KBr): 3311, 3172, 2927, 2211, 1646, 1513 cm^{-1} .; ^1H NMR (400MHz, CDCl_3): $\delta = 7.36\text{--}7.25$ (m, 5H), 5.18 (s, 1H), 4.60 (s, 2H, NH_2), 3.69 (s, 2H). ^{13}C NMR (100MHz, CDCl_3): $\delta = 163.0, 153.1, 143.4, 129.2, 124.1, 121.6, 113.9, 83.2, 80.2, 70.1$.; MS (ESI^+) $m/z = 231.0$ (M+H) $^+$

2-(1-morpholinoethylidene)malononitrile (**7i**)

White solid; Mp 92 °C; ^1H NMR (400MHz, $\text{DMSO-}d_6$): $\delta = 3.73$ (m, 8H), 2.2 (s, 3H). ^{13}C NMR (100MHz, $\text{DMSO-}d_6$), δ (ppm): 168.6, 118.5, 117.1, 65.6, 49.9, 48.9, 20.5.

2-amino-4-morpholinothiophene-3-carbonitrile (**8i**)

Brown colour solid; Mp 126 °C; ^1H NMR (400MHz, $\text{DMSO-}d_6$): $\delta = 6.96$ (s, 2H), 5.31 (s, 1H), 3.7 (t, $J = 4.8$ Hz, 4H), 2.9 (t, $J = 4.8$ Hz, 4H). ^{13}C NMR (100MHz, $\text{DMSO-}d_6$): $\delta = 164.8, 148.5, 115.9, 86.2, 79.9, 65.8, 50.9$; MS (ESI^+) $m/z = 210.0$ (M+H) $^+$.