Synthesis of Highly Substituted Pyridines via One-Pot Three-Component Cascade Reaction of Malononitrile with Aldehydes and S-Alkyl-isothiouuronium salts in Water

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General Methods

Melting points were determined on X4 microscope and were uncorrected. $^1$H and $^{13}$C NMR spectra was performed on a VXR300 instrument at 300 MHz, chemical shifts are reported in ppm relative to the internal standard of TMS. TLC was carried out on GF$_{254}$ silica gel plates. All the aldehydes, $S$-alkyl-isothiouronium salts and malononitrile were obtained from commercial suppliers and used without further purification.

Typical Procedure for the Synthesis of Compounds 3a

A mixture of benzaldehyde (106 mg, 1 mmol), malononitrile (132 mg, 2 mmol), the base NaOH (120 mg, 3 mmol) and the catalyst sodium dodecyl sulfate (SDS) (29 mg, 0.1 mmol) in 10 ml water was stirred for 10 minutes at room temperature. And then, the $S$-methylisothiouronium sulfate (139 mg, 1 mmol) was added. The reaction mixture was stirred for another 50 minutes (TLC) until the completion of the reaction. The reaction mixture was filtered and washed with water to give the crude solid which was recrystallized from acetonitrile to furnish the crystals of 2-amino-4-phenyl-6-methylsulfanyl-pyridine-3,5-dicarbonitrile (238 mg, 89%).

This procedure was followed for all the reactions listed in Table 1. The unknown compounds were properly characterized by their spectroscopic ($^1$H NMR, $^{13}$C NMR) data and the elemental analysis, and the known compounds were confirmed by $^1$H NMR and mp’s which were consistent with the reported literatures.

Characterization Data

2-Amino-4-phenyl-6-(methlsulfanyl)-pyridine-3,5-dicarbonitrile (3a)

89%; mp 295-296 °C (CH$_3$CN); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 2.59 (s, 3 H, SCH$_3$), 5.67 (bs, 2 H, NH$_2$), 7.50-7.55 (m, 5 H, Ph); $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta$ = 12.79, 85.55, 93.49, 115.31, 115.46, 128.42, 128.71, 130.33, 133.98, 158.17, 159.72, 167.53; Anal. Caled for C$_{14}$H$_{10}$N$_4$S: C, 63.14; H, 3.78; N, 21.04. Found: C, 63.13; H, 3.96; N, 21.24.

2-Amino-4-phenyl-6-(ethylsulfanyl)-pyridine-3,5-dicarbonitrile (3b)

81%; mp 235-236 °C (CH$_3$CN); which is consistent with the reported reference. ($^1$H NMR, $^{13}$C NMR) 3 a, 93); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.40 (t, 3 H, J = 7.5 Hz), 3.22 (q, 4 H, J = 7.5 Hz, SCH$_2$), 5.65 (bs, 2 H, NH$_2$), 7.50-7.55 (m, 5 H, Ph).

2-Amino-4-phenyl-6-(n-butylsulfanyl)-pyridine-3,5-dicarbonitrile (3c)
76%; mp 182-183 °C(C2H5OH); 1H NMR (300 MHz, CDCl3): δ = 0.97 (t, 3 H, J = 7.2Hz, CH3), 1.47-1.57 (m, 2H, CH2), 1.67-1.76 (m, 2H, CH2), 3.21(t, 2H, J = 7.2 Hz, SCH2), 5.64 (bs, 2H, NH2), 7.50-7.55 (m, 5H, C6H5). 13C NMR (75 MHz, CDCl3): δ = 13.54, 21.36, 29.26, 30.76, 85.64, 93.58, 115.30, 115.43, 128.41, 128.63, 130.30, 134.02, 158.27, 159.65, 167.19. Anal. Calced for C17H16N4S: C, 66.21; H, 5.23; N, 18.17. Found: C, 66.29; H, 5.33; N, 18.25.

2-Amino-6-[(2-[6-amino-3,5-dicyano-4-phenyl-2-pyridinyl]sulfanyl)ethyl] sulfanyl]-4-phenyl-3,5-pyridinedicarbonitrile (3d)

71%; mp 279-282°C(CH3CN); which is consistent with the reported reference. (lit: mp >260°C, J. Org. Chem. 2007, 72, 3443); 1H NMR (300 MHz, CDCl3): δ =3.07 (t, 2 H, J = 7.5Hz, SCH2), 3.56 (t, 2 H, J = 7.5Hz, SCH2) 5.75 (bs, 4H, NH2), 7.50-7.55 (m, 10H, C6H5); Anal. Calced for C28H18N8S2: C, 63.38; H, 3.42; N, 21.12. Found: C, 63.29; H, 3.53; N, 21.23.

2-Amino-4- phenyl-6-(cyclopentylsulfanyl)-pyridine-3,5-dicarbonitrile (3e)

83%; mp 215-216 °C(CH3CN); 1H NMR (300 MHz, CDCl3): δ =1.68-1.77 (m, 6H, CH2), 2.21-2.24 (m, 2H, CH2), 4.10 (t, 1 H, J = 6.6 Hz,CH, CH), 5.64 (bs, 2H, NH2), 7.50-7.55 (m, 5H, C6H5); 13C NMR (75 MHz, DMSO-d6): δ = 24.51, 32.68, 43.10, 85.51, 93.31, 115.31, 115.44, 128.40,128.67, 130.27, 134.02, 158.10, 159.69, 167.89 Anal. Calced for C18H16N4S: C, 67.47; H, 5.03; N, 17.49. Found: C, 67.20; H, 4.96; N, 17.57.

2-Amino-4- phenyl-6-(benzylsulfanyl)-pyridine-3,5-dicarbonitrile (3f)

87%; mp 210-212 °C(CH3CN); (lit: mp 212-214 °C, J. Org. Chem. 2007, 72, 3152); 1H NMR (300 MHz, CDCl3): δ =4.46 (s, 2H, SCH2), 5.67 (bs, 2H, NH2), 7.53-7.56 (m, 5H, C6H5); Anal. Calced for C20H14N4S: C, 70.15; H,4.12; N, 16.36. Found: C,70.20; H, 4.52; N, 16.83.

2-Amino-4- phenyl-6-(allylsulfanyl)-pyridine-3,5-dicarbonitrile (3g)

85%; mp 219-220 °C(CH3CN); 1H NMR (300 MHz, DMSO-d6): δ = 3.92 (d, 2 H, J = 6.9Hz, SCH2), 5.15 (m, 1H, =CH2), 5.43 (m, 1H, =CH2), 5.91(m, 1H, CH), 4.48 (s, 2H, SCH2), 7.52-7.58 (m, 5H, C6H5); 13C NMR (75 MHz, DMSO-d6): δ =12.79, 85.55, 93.50, 115.43, 115.45, 128.41, 128.53, 130.31, 133.97, 158.14, 159.71, 167.54. Anal. Calced for C16H12N4S: C, 65.73; H, 4.14; N, 19.16. Found: C, 65.67; H, 4.27; N, 19.04.

2-Amino-6-(methylsulfanyl)-pyridine-3,5-dicarbonitrile (3h)
51%; mp 259-261 °C(C₂H₅OH); which is consistent with the reported reference. (lit: mp 259-261 °C(C₂H₅OH) Zh. Org. Khim. Ru. 1988, 24, 854); ¹H NMR (300 MHz, DMSO-d₆): δ = 2.55 (s, 3H, SCH₃), 8.00 (bs, 2H, NH₂); 8.27 (s, 1H, CH).

2-Amino-4-methyl-6-(methylsulfanyl)-pyridine-3,5-dicarbonitrile (3i)

75%; mp 239-241 °C(C₂H₅OH); ¹H NMR (300 MHz, DMSO-d₆): δ = 2.41 (s, 3 H, CH₃), 2.54 (s, 3H, SCH₃), 7.90 (bs, 2H, NH₂); ¹³C NMR (75 MHz, DMSO-d₆): δ = 12.57, 19.28, 85.98, 94.00, 115.09, 115.27, 156.73, 159.47, 166.86; Anal. Calcd for C₉H₈N₄S: C, 52.92; H, 3.95; N, 27.43. Found: C, 53.01; H, 4.16; N, 27.61.

2-Amino-4-(4-nitrophenyl)-6-(methylsulfanyl)-3,5-pyridinedicarbonitrile (3j)

79%; mp 279-281 °C(C₂H₅OH); ¹H NMR (300 MHz, DMSO-d₆): δ = 2.41 (s, 3 H, CH₃), 7.86 (d, 2H, J = 9.0Hz), 8.17 (bs, 2H, NH₂); 8.42 (d, 2H, J = 9.0Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ = 12.80, 29.04, 85.37, 93.15, 114.93, 115.10, 123.87, 130.25, 140.30, 148.56, 156.24, 159.50, 167.64; Anal. Calcd for C₁₄H₉N₅O₂S: C, 54.01; H, 2.91; N, 22.50. Found: C, 54.13; H, 3.12; N, 22.57.

2-Amino-4-[3-hydroxy-(4-methoxyphenyl)]-6-(methylsulfanyl)-3,5-pyridinedicarbonitrile (3k)

82%; mp 301-303 °C(C₂H₅OH); ¹H NMR (300 MHz, DMSO-d₆): δ = 2.57 (s, 3H, SCH₃), 3.85 (s, 3H, OCH₃), 6.93 (d, 2H, J = 7.5Hz), 7.08 (d, 1H, J = 7.5Hz); 7.96 (bs, 2H, NH₂), 9.45(s, 1H, OH); ¹³C NMR (75 MHz, DMSO-d₆): δ = 12.78, 55.59, 85.30, 93.44, 111.88, 115.50, 115.55, 115.68, 119.96, 126.11, 146.31, 149.39, 157.94, 159.83, 167.48; Anal. Calcd for C₁₅H₁₂N₄O₂S: C, 57.68; H, 3.87; N, 17.94. Found: C, 57.81; H, 3.92; N, 17.84.

2-Amino-4-(2,4-dimethoxyphenyl)-6-(methylsulfanyl)-3,5-pyridinedicarbonitrile (3l)

87%; mp 200-202 °C(C₂H₅OH); ¹H NMR (300 MHz, DMSO-d₆): δ = 2.57 (s, 3H, SCH₃), 3.80 (s, 3H, OCH₃), 3.85 (s, 3H, OCH₃), 6.66 (dd, 1H, J = 8.4, 2.1Hz), 6.72 (d, 1H, J = 2.1Hz); 7.24(d, 1H, J = 8.4Hz), 7.92(bs, 2H,
2-Amino-4-(2,4-dimethoxyphenyl)-6-(methylsulfanyl)-3,5-pyridinedicarbonitrile (3m)

\[
\begin{array}{c}
\text{H}_2\text{N} & \text{N} & \text{CN} & \text{SMe} & \text{H}_2\text{N} & \text{NC} \\
\end{array}
\]

91%; mp 268-270°C (C₂H₅OH); ¹H NMR (300 MHz, DMSO-d₆): δ = 2.58 (s, 3H, SCH₃), 3.80 (s, 3H, OCH₃), 7.06-7.56 (m, 4H), 7.99 (bs, 2H, NH₂); ¹³C NMR (75 MHz, DMSO-d₆): δ =12.74, 55.73, 55.78, 86.58, 93.66, 101.81, 108.52, 108.92, 115.42, 115.55, 122.99, 127.38, 147.33, 148.92, 157.72, 159.73, 159.59, 167.43; Anal. Calcd for C₁₅H₁₀N₄O₂S: C, 58.05; H, 3.25; N, 18.05. Found: C, 57.80; H, 3.50; N, 17.79.

2-Amino-4-(2-thienyl)-6-(methylsulfanyl)-3,5-pyridinedicarbonitrile (3o)

\[
\begin{array}{c}
\text{H}_2\text{N} & \text{N} & \text{CN} & \text{SMe} & \text{H}_2\text{N} & \text{NC} \\
\end{array}
\]

92%; mp 159-161°C (C₂H₅OH); ¹H NMR (300 MHz, DMSO-d₆): δ = 2.58 (s, 3H, SCH₃), 7.28 (dd, 1H, J = 3.9Hz), 7.57 (dd, 1H, J = 1.2Hz), 7.95 (dd, 1H, J = 3.9Hz, J = 1.2Hz), 8.08 (bs, 2H, NH₂); ¹³C NMR (75 MHz, DMSO-d₆): δ =12.95, 85.29, 93.29, 115.50, 115.55, 122.99, 127.88, 130.69, 131.23, 132.83, 150.31, 159.90, 168.13; Anal. Calcd for C₁₂H₉N₂S₂: C, 52.92; H, 2.92; N, 20.57. Found: C, 52.74 H, 3.22; N, 20.67.
80%; mp 286-288°C(CH$_3$CN); which is consistent with the reported reference (lit: Journal of Chemical Research. synopses. 2001, 124-126, 0411. mp 278-280°C). ¹H NMR (300 MHz, DMSO-d$_6$); $\delta$ = 2.57 (s, 3H, CH$_3$), 6.91 (d, 2H, $J = 8.7$Hz), 7.36 (d, 2H, $J = 8.7$Hz), 7.96 (bs, 2H, NH$_2$); 10.07 (s, 1H, OH).
$^1$H NMR and $^{13}$C NMR spectra of all compounds

Compound 3a
Compound 3b

Compound 3c
Compound 3c

Compound 3d
Compound 3e
Compound 3f

Compound 3g
Compound 3g

Compound 3h
Compound 3i
Compound 3j

Compound 3k
Compound 3k

Compound 3l
Compound 3l

Compound 3m
Compound 3m

Compound 3n
Compound 3n

Compound 3o
Compound 3o

$^{13}$C NMR

DMSO-$d_6$
75 MHz

Compound 3p

$^1$H NMR

DMSO-$d_6$
300 MHz