Supporting Information

One-Pot Synthesis of Densely Substituted 1,2,3,4-Tetrahydro-1,6-naphthyridine Mediated by Isocyanide-Assisted Reduction of C—C Double Bond

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Materials and Methods

All solvents were dried by standard methods. Column chromatography was performed on silica gel (60-120 mesh) and appropriate mixture of petroleum ether and ethyl acetate were used for elution. The solvents were removed using rotary evaporator. TLC was done on glass sheets pre-coated with silica gel. The ^1H - and ^{13}C -NMR analyses were carried out on Bruker-Advance Digital Instrument in DMSO- d_6 and CDCl_3 with TMS as an internal reference. The chemical shifts were reported as δ values (ppm) relative to TMS. Elemental analyses (C, H, N) were performed using a PerkinElmer 240C elemental analyser. Single crystal X-ray data were collected on a Bruker D8 QUEST diffractometer using the SMART/SAINT software. Electrospray ionization mass spectrometry (ESI-MS) experiments were carried out on a Bruker Daltonics (Esquire 300 Plus ESI model) spectrometer using standard spectroscopic-grade solvents.

General procedure for the synthesis of 1,2,3,4-tetrahydro-1,6-naphthyridine (5). A mixture of ketone **1** (2 mmol), malononitrile **2** (2 mmol), Et_3N catalyst (0.2 mmol) and water (20 mL) were taken in a 50 mL round-bottomed flask fitted with a reflux condenser. The resulting mixture was refluxed at 100 °C for 4 hrs (until the formation of intermediate **B** as evidenced from the TLC) in an oil bath. Then thiol **3** (1 mmol) and $\text{CNCH}_2\text{COOEt}$ **4** (2 mmol) were injected into the reaction mixture and the reaction was further refluxed for 6 h. After completion of the reaction, the reaction mixture was cooled to room temperature (25-30 °C) and the crude product was extracted from water with ethylacetate (2x10 mL) using separating funnel. The solvents were evaporated in a rotary evaporator and the residue was subjected to silica gel column chromatography (60-120 mesh) with ethyl acetate/petroleum ether (60-80 °C) as eluant. The products were characterized by standard analytical techniques such as ^1H & ^{13}C NMR, elemental analysis, melting point determination, X-ray single crystal analysis.

Spectroscopic characterization of 1,2,3,4-tetrahydro-1,6-naphthyridine (5):

5-Amino-7-(3-chloro-phenylsulfanyl)-2-methyl-2,4-diphenyl-1,2,3,4-tetrahydro-

[1,6]naphthyridine-8-carbonitrile (5a): Yield: 55%; Yellowish white solid; mp 150–152 °C (EtOAc/DCM); ¹H NMR (300 MHz, CDCl₃; Me₄Si) δ 7.52 (s, 1H), 7.39–7.36 (m, 1H), 7.26–7.19 (m, 3H), 7.11–6.97 (m, 7H), 6.82–6.80 (m, 2H), 5.24 (s, 1H), 4.22 (s, 2H), 3.78 (t, *J*=6.6 Hz, 1H), 2.43–2.36 (m, 1H), 2.28–2.21 (m, 1H), 1.55 (s, 3H); ¹³C NMR (75 MHz, CDCl₃; Me₄Si) δ 160.0, 157.8, 153.0, 145.1, 141.2, 134.8, 130.4, 129.7, 128.9, 128.8, 128.7, 128.6, 128.4, 127.1, 126.2, 125.5, 124.9, 116.4, 95.0, 84.2, 55.7, 45.8, 37.2, 29.0; Anal. Calcd for C₂₈H₂₃ClN₄S: C, 69.62; H, 4.80; N, 11.60%. Found: C, 69.65; H, 4.81; N, 11.63%.

5-Amino-2-methyl-2,4-diphenyl-7-p-tolylsulfanyl-1,2,3,4-tetrahydro-[1,6]naphthyridine-8-

carbonitrile (5b): Yield: 51%; Yellowish white solid; mp 134–136 °C (EtOAc/DCM); ¹H NMR (300 MHz, DMSO-*d*₆) δ: 7.57–7.51 (m, 3H), 7.47–7.44 (m, 2H), 7.07–7.05 (m, 2H), 7.00–6.93 (m, 3H), 6.874–6.868 (m, 2H), 6.71 (s, 3H), 5.54 (s, 2H), 3.94–3.92 (m, 1H), 2.58–2.57 (m, 1H), 2.26–2.19 (m, 1H), 2.08 (s, 3H), 1.52 (s, 3H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ: 159.4, 158.0, 152.3, 147.4, 145.8, 141.5, 136.6, 135.5, 133.3, 129.5, 129.2, 129.1, 129.0, 127.7, 127.6, 127.5, 125.9, 125.3, 125.2, 116.4, 93.7, 81.9, 55.0, 43.8, 35.5, 30.7, 29.6; Anal. Calcd for C₂₉H₂₆N₄S: C, 75.29; H, 5.66; N, 12.11%. Found: C, 75.31; H, 5.67; N, 12.13%.

5-Amino-2-methyl-2,4-diphenyl-7-phenylsulfanyl-1,2,3,4-tetrahydro-[1,6]naphthyridine-8-

carbonitrile (5c): Yield: 53%; Yellowish white solid; mp 170–172 °C (EtOAc/DCM); ¹H NMR (300 MHz, CDCl₃) δ: 7.51–7.48 (m, 2H), 7.33–7.27 (m, 3H), 7.21–7.19 (m, 2H), 7.12–7.03 (m, 3H), 7.01–6.96 (m, 3H), 6.82–6.79 (m, 2H), 5.21 (s, 1H), 4.14 (s, 2H), 3.78 (t, *J*=6.6 Hz, 1H), 2.43–2.36 (m, 1H), 2.28–2.21 (m, 1H), 1.56 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ: 160.4, 157.7, 152.8, 144.9, 141.2, 134.6, 130.3, 128.8, 128.7, 128.6, 128.5, 128.4, 127.5, 127.4, 127.0, 126.7, 125.0, 124.9, 116.3, 94.6, 84.2, 55.5, 45.7, 37.3, 29.1; Anal. Calcd for C₂₈H₂₄N₄S: C, 74.97; H, 5.39; N, 12.49%. Found: C, 74.99; H, 5.40; N, 12.52%.

5-Amino-7-(3-chloro-phenylsulfanyl)-2-methyl-2,4-di-thiophen-2-yl-1,2,3,4-tetrahydro-

[1,6]naphthyridine-8-carbonitrile (5d): Yield: 61%; White solid; mp 153–155 °C (EtOAc/DCM) ¹H NMR (300 MHz, CDCl₃; Me₄Si) δ 7.60 (s, 1H), 7.48–7.43 (m, 1H), 7.31–7.28 (m, 2H), 7.10–7.07 (m, 2H), 6.80–6.76 (m, 2H), 6.72–6.69 (m, 1H), 6.51 (d, *J*=3.3 Hz, 1H), 5.32 (s, 1H), 4.63 (s, 2H), 4.20 (t, *J*=6.6 Hz, 1H), 2.61–2.59 (m, 1H), 2.48–2.41 (m, 1H), 1.72 (s, 3H); ¹³C NMR (75 MHz, CDCl₃; Me₄Si) δ 160.3, 157.8, 151.8, 150.4, 146.0, 140.3, 134.8, 130.0, 129.6, 129.3, 127.0, 125.8, 125.7, 125.0, 123.9, 123.8, 123.3, 116.0, 94.8, 84.8, 54.1, 46.1, 32.6, 30.4; Anal. Calcd for C₂₄H₁₉ClN₄S₃: C, 58.22; H, 3.87; N, 11.32%. Found: C, 58.26; H, 3.89; N, 11.35%.

5-Amino-2-methyl-7-phenylsulfanyl-2,4-di-thiophen-2-yl-1,2,3,4-tetrahydro-

[1,6]naphthyridine-8-carbonitrile (5e): Yield: 58%; White solid; mp 135–137 °C (EtOAc/DCM); ¹H NMR (300 MHz, CDCl₃) δ: 7.57-7.55 (m, 2H), 7.36-7.26 (m, 3H), 7.05 (d, *J*=3.0 Hz, 2H), 6.76-6.67 (m, 3H), 6.48 (s, 1H), 5.35 (s, 1H), 4.43(s, 2H), 4.17 (t, *J*=6.0 Hz, 1H), 2.62-2.56 (m, 1H), 2.45-2.38 (m, 1H), 1.64 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ: 160.8, 157.9, 151.7, 150.5, 145.4, 142.6, 134.6, 128.9, 128.6, 126.8, 126.7, 125.5, 124.6, 124.4, 123.4, 115.9, 94.7, 84.1, 54.2, 46.9, 32.7, 30.6; Anal. Calcd for C₂₄H₂₀N₄S₃: C, 62.58; H, 4.38; N, 12.16%. Found: C, 62.59; H, 4.39; N, 12.18%; ESI MS (*m/z*): Calcd.460.0850, found 460.0825.

5-Amino-7-(4-bromo-phenylsulfanyl)-2-methyl-2,4-di-thiophen-2-yl-1,2,3,4-tetrahydro-

[1,6]naphthyridine-8-carbonitrile (5f): Yield: 62%; White solid; mp 120–122 °C (EtOAc/DCM); ¹H NMR (300 MHz, CDCl₃) δ: 7.51 (d, *J*=8.4 Hz, 2H), 7.43 (d, *J*=8.4 Hz, 2H), 7.07 (t, *J*=4.8 Hz, 2H), 6.79-6.76 (m, 2H), 6.71-6.68 (m, 1H), 6.50 (d, *J*=3.0 Hz, 1H), 5.38 (s, 1H), 4.45 (s, 2H), 4.19 (t, *J*=6.6 Hz, 1H), 2.65-2.58 (m, 1H), 2.47-2.40 (m, 1H), 1.67 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ: 160.1, 157.8, 151.7, 150.3, 145.2, 136.2, 132.0, 129.1, 126.8, 126.7, 125.5, 124.7, 124.5, 123.4, 123.1, 115.8, 94.8, 84.0, 54.2, 46.8, 32.7, 30.5; Anal. Calcd for C₂₄H₁₉BrN₄S₃: C, 53.43; H, 3.55; N, 10.38%. Found: C, 53.46; H, 3.57; N, 10.39%; Found: C, 62.59; H, 4.39; N, 12.18%; ESI MS (*m/z*): Calcd.537.9952, found 537.9924.

5-Amino-2-methyl-7-(naphthalen-2-ylsulfanyl)-2,4-di-thiophen-2-yl-1,2,3,4-tetrahydro-

[1,6]naphthyridine-8-carbonitrile (5g): Yield: 55%; White solid; mp 141–143 °C (EtOAc/DCM); ¹H NMR (300 MHz, DMSO-*d*₆) δ: 8.11 (s, 1H), 7.90-7.88 (m, 3H), 7.53-7.50 (m, 3H), 7.12 (d, *J*=4.8 Hz, 1H), 7.08 (d, *J*=5.1 Hz, 1H), 7.01-6.95 (m, 2H), 6.78 (s, 1H), 6.67-6.59 (m, 2H), 5.68 (s, 2H), 4.27 (s, 1H), 2.46-2.45 (m, 1H), 2.33-2.26 (m, 1H), 1.60 (s, 3H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ: 160.9, 158.0, 151.8, 150.4, 145.2, 142.6, 134.7, 130.0, 129.1, 128.9, 128.5, 128.0, 126.6, 126.0, 125.9, 125.4, 124.6, 124.5, 123.3, 116.0, 94.8, 84.0, 54.1, 46.8, 32.8, 30.9; Anal. Calcd for C₂₈H₂₂N₄S₃: C, 65.85; H, 4.34; N, 10.97%. Found: C, 65.88; H, 4.35; N, 10.99%.

5-Amino-7-cyclohexylsulfanyl-2-methyl-2,4-di-thiophen-2-yl-1,2,3,4-tetrahydro-

[1,6]naphthyridine-8-carbonitrile (5h): Yield: 60%; White solid; mp 104–106 °C (EtOAc/DCM); ¹H NMR (300 MHz, CDCl₃; Me₄Si) δ 7.16 (t, *J*=7.8 Hz, 2H), 6.87-6.84 (m, 2H), 6.79 (t, *J*=3.9 Hz, 1H), 6.59 (d, *J*=2.4 Hz, 1H), 5.38 (s, 1H), 4.52 (s, 2H), 4.19 (t, *J*=6.3 Hz, 1H), 3.78-3.75 (m, 1H), 2.66-2.59 (m, 1H), 2.48-2.41 (m, 1H), 2.00-1.98 (m, 2H), 1.66 (s, 3H), 1.501-1.500 (m, 2H), 1.28-1.16 (m, 6H); ¹³C NMR (75 MHz, CDCl₃; Me₄Si) δ 160.0, 157.9, 151.8, 150.2, 145.0, 129.2, 128.8, 126.0, 125.2, 123.8, 123.4, 116.0, 94.1, 83.9, 54.1, 46.8, 43.2, 33.4, 33.1, 32.6, 30.2, 26.7, 25.9, 25.7; Anal. Calcd for C₂₄H₂₆N₄S₃: C, 61.77; H, 5.62; N, 12.01%. Found: C, 61.99; H, 5.71; N, 11.95%.

5-Amino-2,4-bis-(4-methoxy-phenyl)-2-methyl-7-phenylsulfanyl-1,2,3,4-tetrahydro-[1,6]naphthyridine-8-carbonitrile (5i): Yield: 41%; Light yellow solid; mp 180–182 °C (EtOAc/ DCM); ¹H NMR (300 MHz, CDCl₃; Me₄Si) δ 7.52-7.49 (m, 2H), 7.31-7.30 (m, 3H), 7.21 (d, *J*=8.4 Hz, 2H), 7.11 (d, *J*=8.4 Hz, 2H), 6.74-6.70 (m, 4H), 5.26 (s, 1H), 4.27 (s, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.73 (t, *J*=6.3 Hz, 1H), 2.46-2.40 (m, 1H), 2.27-2.20 (m, 1H), 1.58 (s, 3H); ¹³C NMR (75 MHz, CDCl₃; Me₄Si) δ 160.8, 159.4, 159.0, 157.8, 152.6, 140.7, 134.8, 130.4, 129.9, 129.5, 129.4, 129.3, 129.1, 128.5, 128.4, 128.1, 126.2, 116.2, 114.1, 113.9, 94.8, 84.4, 55.5, 55.3, 45.9, 37.3, 30.0; Anal. Calcd for C₃₀H₂₈N₄O₂S: C, 70.84; H, 5.55; N, 11.02%. Found: C, 70.92; H, 5.59; N, 11.09%.

5-Amino-7-(4-bromo-phenylsulfanyl)-2,4-bis-(4-chloro-phenyl)-2-methyl-1,2,3,4-tetrahydro-[1,6]naphthyridine-8-carbonitrile (5j): Yield: 65%; Light yellow solid; mp 132–134 °C (EtOAc/DCM); ¹H NMR (300 MHz, CDCl₃; Me₄Si) δ 7.51 (d, *J*=8.1 Hz, 2H), 7.42 (d, *J*=8.1 Hz, 2H), 7.18-7.06 (m, 6H), 6.80 (d, *J*=8.7 Hz, 2H), 5.25 (s, 1H), 4.26 (s, 2H), 3.83 (t, *J*=6.3 Hz, 1H), 2.46-2.40 (m, 1H), 2.27-2.20 (m, 1H), 1.54 (s, 3H); ¹³C NMR (75 MHz, CDCl₃; Me₄Si) δ 160.7, 157.7, 152.7, 145.0, 140.0, 136.4, 134.8, 131.4, 131.1, 129.9, 129.7, 129.5, 129.4, 129.2, 129.1, 129.0, 128.9, 128.4, 126.5, 123.9, 116.3, 94.9, 84.3, 55.5, 45.9, 37.5, 30.2; Anal. Calcd for C₂₈H₂₁BrCl₂N₄S: C, 56.39; H, 3.55; N, 9.39%. Found: 56.44; H, 3.56; N, 9.45%.

^1H and ^{13}C Spectral Data of 1,2,3,4-tetrahydro-1,6-naphthyridine (5):

Representative ESI-MS

Figure S1. ESI-MS of 5e

Figure S2. ESI-MS of 5f

Discussion on structural characterization

A. Detailed analysis data of the X-ray crystal structures of the compounds 5e

Table S1. Descriptions of crystallographic parameters

Crystal descriptions	Compound 5e
Formula	C ₂₄ H ₂₀ N ₄ S ₃
Formula Weight	460.62
Crystal System	Triclinic
Space group	P -1
a [Å]	6.2257(8)
b[Å]	12.5137(17)
c [Å]	14.5356(18)
α [°]	106.221(4)
β[°]	92.191(4)
γ [°]	90.195(4)
V [Å ³]	1086.4(2)
Z	2
D(calc) [g/cm ⁻³]	1.408
Absorption coefficient	0.361
μ [mm ⁻¹]	
Absorption correction	Empirical
F(000)	480.0
Crystal Size [mm]	0.8 x 0.6 x 0.4
Temperature (K)	273

Radiation [Angstrom]	MoK α ($\lambda=0.71073$)
Theta Min-Max [°]	2.92, 27.59
Collection range	$-8 \leq h \leq 8$; $-16 \leq k \leq 16$; $-18 \leq l \leq 18$
Reflections collected	4961
Independent reflections (Rint)	4014 (0.0557)
R, wR2, S	0.0821, 0.2483, 1.679
CCDC number	1878352

B. Discussion on the proton NMR taking compound **5f** as an example.

Figure S3. ¹H NMR spectrum and structure of compound **5f**

In the above ¹H NMR spectrum of compound **5f** the origin of different peaks are explained. The two closely spaced doublets at 7.51 and 7.43 ppm with $J = 8.4$ Hz is due to the para-

disubstitutedbenzene (marked in brown). The splitting is due to the coupling with ortho proton. Again the collection of peaks from 7.09-6.50 ppm is due to the six hydrogens of two thiophene ring protons (marked in black). The broad singlet at 5.38 and 4.45 ppm are due to the –NH and –NH₂ protons respectively. The –CH proton (marked in blue) obtained after the reduction of double bond of 1,2-dihydro-1,6-naphthyridine appears at 4.19 ppm as triplet due to coupling with adjacent –CH₂. The diastereotopic –CH₂protons (marked in red) appear as two closely spaced multiplets between 2.65-2.58 and 2.47-2.40 ppm. Lastly the –CH₃ protons appear at 1.67 ppm as broad singlet.