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ORIGINAL PAPER

K_2CO_3 catalyzed green and rapid access to 2-amino-3,5-dicarbonitrile-6-thio-pyridines

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Abstract A series of 2-amino-3,5-dicarbonitrile-6-thio-pyridine derivatives have been synthesized by a simple method via a one-pot, three-component condensation reaction of aromatic aldehydes and malononitrile with substituted thiophenols using potassium carbonate as a green base in polyethylene glycol (PEG-400) as a reusable solvent. This protocol proved to be efficient and environmentally benign in terms of high yields, short reaction times, mild conditions, and reusability of the reaction medium.

Keywords 2-Amino-3,5-dicarbonitrile-6-thio-pyridines · Potassium carbonate · Polyethylene glycol · Multi-component reactions · Green chemistry

Introduction

Multi-component reactions (MCRs) are powerful tools in modern medicinal chemistry, enabling straightforward access to large libraries of structurally related, 'drug-like' compounds and thereby facilitating lead generation. Combined with the use of combinatorial chemistry and high-throughput parallel synthesis, such reactions have constituted an increasingly valuable approach to drug discovery efforts in recent years [1, 2]. The synthesis of privileged medicinal scaffolds is important as these compounds often act as ligands for a number of functionally and structurally diverse biological receptors, and consequently, serve as a platform for developing pharmaceutical agents for diverse applications [3, 4]. One such significant scaffold is the pyridine nucleus which is the key constituent in a range of bioactive compounds, both naturally occurring and synthetic, and often of considerable complexity [5–8]. Among these, 2-amino-3,5-carbonitrile-6-thio-pyridines exhibit various pharmacological activities and are useful as antihepatitis B virus [9], antiprion [10], antibacterial [11], and anticancer [12–14] agents and as potassium channel openers for the treatment of urinary incontinence [15]. Recently, some of these compounds have been recognized as potential targets for the development of new drugs for the treatment of Parkinson's disease, hypoxia, asthma, kidney disease, epilepsy, and Creutzfeldt–Jakob disease [10, 16, 19].

Owing to their vast medicinal utility, numerous methods have been adopted for the synthesis of these compounds employing various catalysts such as Et_3N, 1,4-diazabicyclo[2.2.2]octane (DABCO) [17, 18], piperidine, morpholine, thiomorpholine, pyrrolidine, *N*,*N*-Diisopropylethylamine (*N*,*N*-DIPEA), pyridine, 2,4,6-collidine, 4-Dimethylaminopyridine (DMAP), aniline, *N*-methylaniline, *N*,*N*-dimethylaniline, and *N*,*N*-diethylaniline [19]. Moreover, H_3BO_3 [20], 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) [21], tetrabutylammonium hydroxide (TBAH) [22] and $ZnCl_2$ [23] were also found to be efficient catalysts for the synthesis of such polysubstituted pyridines. Many of these methods, however, required higher temperatures and suffered from the serious limitations such as formation of considerable amounts of side products, use of a toxic and expensive catalyst, and low yields. Subsequently, there stands a demand and scope for the development of an efficient protocol involving a very mild, effective, and an eco-safe catalyst for the synthesis of highly substituted pyridines.

Over the past few decades, the replacement of potentially hazardous solvents and stoichiometric reagents by

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environmentally benign solvents and sustainable reagents has been one of the major issues of green chemistry. In this context, the utilization of reaction media with environmentally acceptable alternatives such as polyethylene glycol (PEG) is an area of tremendous importance in modern organic synthesis. PEG is an inexpensive, thermally stable, recoverable, biologically compatible, and non-toxic reaction medium [24]. In fact, polyethylene glycol has widespread use in organic reactions for a long time [25, 26]. It has previously been suggested that PEGs could be used as complexing solvents for inorganic salts, to enhance the reactivity of the anion with the organic substrate [27–29]. In these systems, the anion could be brought into solution with higher reactivity. Thus, owing to the therapeutic activity of 2-amino-3,5-dicarbonitrile-6-thio-pyridine derivatives and in continuation of our on-going endeavor [30–33] aimed at developing eco-sustainable methodologies, we report the use of PEG-400 as a solvent for the anionic activation of K_2CO_3 which could be used for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridine derivatives.

Experimental section

Materials and methods

Chemicals were purchased from Alfa-Aesar and Sisco Research Laboratories, and were used as such without further purification. All the reactions and the purity of the 2-amino-3,5-dicarbonitrile-6-thio-pyridine derivatives were monitored by thin-layer chromatography (TLC) using aluminum plates coated with silica gel F_{254} plates (Merck) using 40 % ethyl acetate and 60 % hexane as eluent. The spots were detected either under ultra-violet (UV) light or by placing in iodine chamber. Melting points were determined in open capillary tubes using a Thomas Hoover melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer FTIR-1710 spectrophotometer using KBr pellets. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-ECX 400P FT NMR system using tetramethylsilane (TMS) as an internal standard, and the values of chemical shifts are recorded on the δ scale and coupling constant (*J*) values are in hertz (Hz). The temperature of the reaction mixture was measured through a non-contact infrared mini gun thermometer (AZ minigun type, model 8868).

General procedure for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridine derivatives

To a solution of aromatic aldehydes **1(a–k)** (1 mmol) and malononitrile **(2)** (2 mmol) in PEG-400 (2 mL), K_2CO_3 (10 mol%) was added at room temperature. The resulting mixture was then heated to 40 °C and substituted thiophenol **3(a–d)** (1 mmol) was added. The reaction mixture was then stirred for the required time as indicated in Table 5. The progress of the reaction was monitored using TLC. After completion of the reaction, the reaction mixture was allowed to cool to room temperature and distilled water (10 mL) was added and then the product was extracted with ethyl acetate (5 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The solvent was evaporated in vacuo to give the crude product. After extraction with ethyl acetate, the remaining solution of PEG-400 and water was concentrated to recover pure PEG-400 which was then reused for subsequent reactions [33]. The crude products were subjected to purification by recrystallization or column chromatography on silica gel using hexane/ethyl acetate in varying proportions as eluent to afford the pure 2-amino-6-phenylsulfanyl-3,5-dicarbonitrile derivatives **4(a–y)**. All the synthesized products were stable solids and their structures were established on the basis of their spectral analysis (IR, ^{1}H NMR, ^{13}C NMR).

Spectral data for the synthesized compounds, **4(a–y)**

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

Yellow solid, M.Pt. 217–218 °C [39]; IR (KBr, ν_{max}): 3,460, 3,321, 2,214, 1,624, 1,569, 1,552, 1,242, 765, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 5.67 (br s, 2H, NH_2), 7.27–7.36 (m, 5H, Ar–H), 7.48–7.58 (m, 5H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 54.64, 83.51, 85.00, 126.81, 127.03, 128.02, 128.42, 128.69, 130.21, 134.77, 137.16, 160.32, 160.89, 166.14, 179.34 ppm.

*2-Amino-4-(4-methylphenyl)-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile (**4b**)*

Yellow solid, M.Pt. 208–210 °C [39]; IR (KBr, ν_{max}): 3,473, 3,328, 2,213, 1,623, 1,542, 1,261, 1,024, 759 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 2.34 (s, 3H, CH_3), 5.48 (br s, 2H, NH_2), 7.30 (d, J = 7.6 Hz, 2H, Ar–H), 7.36 (d, J = 7.6 Hz, 2H, Ar–H), 7.39–7.47 (m, 5H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 21.39, 87.14, 95.42, 114.96, 115.31, 127.11, 128.28, 129.23, 129.60, 129.80, 130.17, 135.62, 141.28, 159.37, 168.77, 184.23 ppm.

*2-Amino-4-(4-methoxyphenyl)-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile (**4c**)*

Yellow solid, M.Pt. 242–244 °C [21]; IR (KBr, ν_{max}): 3,440, 3,330, 2,214, 1,638, 1,512, 1,259, 836, 754,

687 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 3.86 (s, 3H, OCH_3), 5.42 (br s, 2H, NH_2), 7.28 (d, $J = 7.8$ Hz, 2H, Ar–H) 7.35 (d, $J = 7.8$ Hz, 2H, Ar–H), 7.44–7.55 (m, 5H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 54.94, 94.23, 99.21, 113.84, 115.14, 115.48, 126.75, 126.95, 128.62, 128.78, 129.75, 135.03, 159.37, 160.99, 167.77, 183.78 ppm.

*2-Amino-4-(4-chlorophenyl)-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile (**4d**)*

Yellow solid, M.Pt. 221–222 °C [39]; IR (KBr, ν_{max}): 3,468, 3,340, 2,216, 1,618, 1,581, 1,546, 1,295, 784, 741, 688 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 5.70 (br s, 2H, NH_2), 7.28 (d, $J = 7.8$ Hz, 2H, Ar–H), 7.32 (d, $J = 7.8$ Hz, 2H, Ar–H), 7.46–7.55 (m, 5H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 83.88, 86.72, 114.29, 115.30, 127.11, 129.02, 129.32, 129.82, 130.57, 132.45, 134.23, 136.48, 160.79, 166.64, 187.15 ppm.

*2-Amino-4-(4-bromophenyl)-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile (**4e**)*

Yellow solid, M.Pt. 254–256 °C [21]; IR (KBr, ν_{max}): 3,479, 3,350, 2,213, 1,630, 1,544, 1,259, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 6.10 (br s, 2H, NH_2), 7.28 (d, $J = 7.0$ Hz, 2H, Ar–H), 7.36 (d, $J = 6.8$ Hz, 2H, Ar–H), 7.43–7.58 (m, 5H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 86.76, 94.66, 114.65, 114.92, 123.76, 125.56, 129.12, 129.67, 129.88, 132.10, 132.34, 135.42, 159.34, 168.65, 186.24 ppm.

*2-Amino-4-(4-nitrophenyl)-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile (**4f**)*

Yellow solid, M.Pt. 286–287 °C [40]; IR (KBr, ν_{max}): 3,424, 3,335, 2,213, 1,635, 1,552, 1,261, 848, 750, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 6.74–7.15 (m, 5H, Ar–H), 7.92 (d, $J = 7.8$ Hz, 2H, Ar–H), 8.10 (br s, 2H, NH_2), 8.32 (d, $J = 7.8$ Hz, 2H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 85.69, 93.10, 113.78, 123.98, 126.17, 128.45, 128.91, 129.09, 134.46, 139.67, 147.88, 167.20, 171.69, 188.24 ppm.

*2-Amino-4-(2-furyl)-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile (**4g**)*

Yellow solid, M.Pt. 176–178 °C [20]; IR (KBr, ν_{max}): 3,396, 3,322, 2,214, 1,635, 1,524, 1,259, 846, 754, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 6.86–7.30 (m, 3H, Ar–H), 7.43–7.60 (m, 5H, Ar–H), 7.70 (br s, 2H, NH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 86.17, 92.42, 101.46, 108.30, 114.78, 124.02, 127.56, 129.18, 129.66, 133.76, 139.58, 144.67, 146.69, 166.29, 182.45 ppm.

*2-Amino-4-(2-thienyl)-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile (**4h**)*

Yellow solid, M.Pt. 206–208 °C [20]; IR (KBr, ν_{max}): 3,426, 3,340, 2,210, 1,625, 1,534, 1,256, 846, 734, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 6.88–7.14 (m, 3H, Ar–H), 7.32–7.58 (m, 5H, Ar–H), 7.84 (br s, 2H, NH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 85.25, 91.67, 116.60, 122.33, 123.78, 126.68, 127.16, 129.13, 129.46, 131.42, 141.32, 149.56, 164.13, 183.78 ppm.

*2-Amino-4-phenyl-6-(4-methoxy-phenylsulfanyl)-pyridine-3,5-dicarbonitrile (**4i**)*

Yellow solid, M.Pt. 228–230 °C [41]; IR (KBr, ν_{max}): 3,434, 3,334, 2,209, 1,629, 1,592, 1,248, 1,031, 823, 755 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 3.41 (s, 3H, OCH_3), 6.39 (br s, 2H, NH_2), 6.92–7.06 (m, 5H, Ar–H), 7.07 (d, $J = 6.8$ Hz, 2H, Ar–H), 7.18 (d, $J = 6.8$ Hz, 2H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 54.76, 86.12, 93.76, 114.04, 114.30, 114.63, 124.78, 128.27, 130.05, 131.96, 136.71, 159.30, 160.32, 168.54, 184.03 ppm.

*2-Amino-4-(4-methylphenyl)-6-(4-methoxy-phenylsulfanyl)-pyridine-3,5-dicarbonitrile (**4j**)*

Yellow solid, M.Pt. 260–262 °C; IR (KBr, ν_{max}): 3,386, 3,331, 2,210, 1,618, 1,249, 1,027, 814, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 2.41 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 5.44 (br s, 2H, NH_2), 6.80 (d, $J = 7.6$ Hz, 2H, Ar–H), 6.95 (d, $J = 7.8$ Hz, 2H, Ar–H), 7.29 (d, $J = 7.6$ Hz, 2H, Ar–H), 7.38 (d, $J = 7.8$ Hz, 2H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 21.46, 55.38, 87.09, 95.49, 114.56, 117.56, 128.33, 128.37, 129.60, 129.67, 132.62, 137.39, 158.39, 160.78, 169.78, 187.20 ppm.

*2-Amino-4-(4-chlorophenyl)-6-(4-methoxy-phenylsulfanyl)-pyridine-3,5-dicarbonitrile (**4k**)*

Yellow solid, M.Pt. 234–236 °C; IR (KBr, ν_{max}): 3,480, 3,350, 2,216, 1,624, 1,581, 1,247, 1,092, 828, 784 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 3.78 (s, 3H, OCH_3), 5.71 (br s, 2H, NH_2), 7.36 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.43 (d, $J = 7.8$ Hz, 2H, Ar–H), 7.47 (d, $J = 7.8$ Hz, 2H, Ar–H), 7.52 (d, $J = 7.8$ Hz, 2H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 55.31, 83.83, 86.29, 114.55, 114.91, 115.30, 129.29, 129.81, 132.59, 137.35, 159.43, 160.81, 166.62, 187.48 ppm.

*2-Amino-4-(4-bromophenyl)-6-(4-methoxy-phenylsulfanyl)-pyridine-3,5-dicarbonitrile (**4l**)*

Yellow solid, M.Pt. 162–164 °C; IR (KBr, ν_{max}): 3,469, 3,346, 2,218, 1,624, 1,590, 1,248, 1,025, 828, 798 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 3.78 (s, 3H, OCH_3), 5.48 (br s, 2H, NH_2), 6.80 (d, $J = 7.8$ Hz, 2H, Ar–H), 6.96 (d, $J = 7.8$ Hz, 2H, Ar–H), 7.36 (d, $J = 8.6$ Hz, 2H, Ar–H), 7.46 (d, $J = 8.6$ Hz, 2H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 54.85, 85.95, 93.58, 114.36, 114.69, 116.95, 123.18, 124.63, 129.59, 131.60, 131.99, 136.74, 156.46, 160.50, 168.80, 183.67 ppm.

*2-Amino-4-(3-hydroxyphenyl)-6-(4-methoxy-phenylsulfanyl)-pyridine-3,5-dicarbonitrile (**4m**)*

Yellow solid, M.Pt. 138–142 °C; IR (KBr, ν_{max}): 3,465, 3,328, 2,214, 1,620, 1,551, 1,251, 1,028, 814, 774, 640 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 3.02 (br s, 1H, OH), 3.63 (s, 3H, OCH_3), 6.20 (br s, 2H, NH_2), 6.64 (m, 1H, Ar–H), 6.70–6.75 (m, 3H, Ar–H), 7.04 (d, $J = 7.8$ Hz, 2H, Ar–H), 7.22 (d, $J = 7.8$ Hz, 2H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 54.95, 86.59, 94.03, 114.42, 114.94, 115.01, 117.28, 117.54, 118.74, 124.76, 129.52, 134.17, 136.85, 157.11, 159.24, 160.44, 168.52, 184.78 ppm.

*2-Amino-4-(3-nitrophenyl)-6-(4-methoxy-phenylsulfanyl)-pyridine-3,5-dicarbonitrile (**4n**)*

Yellow solid, M.Pt. 196–200 °C; IR (KBr, ν_{max}): 3,407, 3,330, 2,213, 1,645, 1,551, 1,250, 1,029, 828, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 3.85 (s, 3H, OCH_3), 6.47 (d, $J = 8.0$ Hz, 2H, Ar–H), 6.84 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.56–7.67 (m, 3H, Ar–H), 7.94 (s, 1H, Ar–H), 8.20 (br s, 2H, NH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 55.24, 83.53, 86.60, 92.80, 114.93, 116.91, 123.35, 124.96, 130.51, 134.94, 135.29, 136.86, 147.61, 157.92, 159.47, 161.13, 167.69 ppm.

*2-Amino-4-(2-thienyl)-6-(4-methoxy-phenylsulfanyl)-pyridine-3,5-dicarbonitrile (**4o**)*

Yellow solid, M.Pt. 204–208 °C; IR (KBr, ν_{max}): 3,448, 3,338, 2,209, 1,638, 1,544, 1,286, 1,020, 824, 710 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 3.68 (s, 3H, OCH_3), 6.19 (br s, 2H, NH_2), 6.66–6.79 (m, 3H, Ar–H), 7.38 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.47 (d, $J = 8.0$ Hz, 2H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 55.01, 86.10, 93.64, 114.49, 117.22, 123.03, 124.58, 125.32, 127.37, 127.47, 130.71, 132.52, 136.92, 149.96, 160.55, 161.12, 169.35, 186.06 ppm.

*2-Amino-4-phenyl-6-(4-bromo-phenylsulfanyl)-pyridine-3,5-dicarbonitrile (**4p**)*

Yellow solid, M.Pt. 202–204 °C; IR (KBr, ν_{max}): 3,450, 3,327, 2,217, 1,618, 1,549, 1,263, 1,007, 811, 757, 706 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 5.48 (br s, 2H, NH_2), 7.30–7.35 (m, 5H, Ar–H), 7.38 (d, $J = 8.6$ Hz, 2H, Ar–H), 7.42 (d, $J = 8.6$ Hz, 2H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 87.64, 96.35, 118.32, 121.49, 128.41, 129.05, 131.04, 132.18, 135.68, 137.27, 159.04, 168.25 ppm.

*2-Amino-4-(4-chlorophenyl)-6-(4-bromo-phenylsulfanyl)-pyridine-3,5-dicarbonitrile (**4q**)*

Yellow solid, M.Pt. 184–186 °C; IR (KBr, ν_{max}): 3,481, 3,351, 2,927, 2,214, 1,630, 1,544, 1,257, 1,090, 811 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 6.51 (br s, 2H, NH_2), 7.20 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.36 (d, $J = 8.4$ Hz, 2H, Ar–H), 7.59 (d, $J = 8.4$ Hz, 2H, Ar–H), 7.68 (d, $J = 8.2$ Hz, 2H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 86.58, 93.54, 115.57, 120.85, 125.81, 128.76, 129.41, 131.63, 131.88, 135.06, 136.58, 156.61, 159.23, 167.02 ppm.

*2-Amino-4-(4-methylphenyl)-6-(4-bromo-phenylsulfanyl)-pyridine-3,5-dicarbonitrile (**4r**)*

Yellow solid, M.Pt. 216–218 °C; IR (KBr, ν_{max}): 3,453, 3,274, 2,927, 2,207, 1,646, 1,536, 1,264, 1,084, 821 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 2.31 (s, 3H, CH_3), 6.62 (br s, 2H, NH_2), 6.76 (d, $J = 8.0$ Hz, 2H, Ar–H), 6.93 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.10 (d, $J = 7.8$ Hz, 2H, Ar–H), 7.32 (d, $J = 7.8$ Hz, 2H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 20.76, 88.56, 93.49, 114.55, 118.45, 125.42, 127.72, 128.65, 129.69, 131.41, 133.63, 137.77, 152.58, 164.76, 183.75 ppm.

*2-Amino-4-(4-methoxyphenyl)-6-(4-bromo-phenylsulfanyl)-pyridine-3,5-dicarbonitrile (**4s**)*

Yellow solid, M.Pt. 222–224 °C; IR (KBr, ν_{max}): 3,466, 3,348, 2,920, 2,210, 1,642, 1,544, 1,262, 1,113, 803 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 3.67 (s, 3H, OCH_3), 6.68 (br s, 2H, NH_2), 6.80 (d, $J = 7.4$ Hz, 2H, Ar–H), 6.98 (d, $J = 7.6$ Hz, 2H, Ar–H), 7.13 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.30 (d, $J = 8.0$ Hz, 2H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 55.46, 88.16, 92.42, 113.61, 116.52, 119.23, 126.54, 128.28, 129.65, 130.76, 132.65, 157.33, 160.67, 166.48, 185.43 ppm.

*2-Amino-4-phenyl-6-(2-amino-phenylsulfanyl)-pyridine-3,5-dicarbonitrile (**4t**)*

Yellow solid, M.Pt. 224–226 °C [40]; IR (KBr, ν_{max}): 3,462, 3,358, 2,924, 2,213, 1,609, 1,264, 1,158, 747 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 5.67 (br s, 2H, NH_2), 7.11–7.18 (m, 4H, Ar–H), 7.28–7.48 (m, 5H, Ar–H), 7.51 (br s, 2H, NH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 87.15, 95.68, 115.23, 118.68, 118.80, 120.84, 128.39, 128.98, 130.91, 131.54, 136.73, 148.53, 159.59, 168.15 ppm.

*2-Amino-4-(4-methylphenyl)-6-(2-amino-phenylsulfanyl)-pyridine-3,5-dicarbonitrile (**4u**)*

Yellow solid, M.Pt. 204–206 °C [42]; IR (KBr, ν_{max}): 3,476, 3,380, 2,924, 2,216, 1,614, 1,548, 1,265, 1,024, 739 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 2.31 (s, 3H, CH_3), 4.32 (br s, 2H, NH_2), 5.77 (br s, 2H, NH_2), 6.54 (d, $J = 7.2$ Hz, 2H, Ar–H), 6.69 (d, $J = 7.2$ Hz, 2H, Ar–H), 7.12–7.43 (m, 4H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 21.88, 87.26, 97.78, 110.00, 115.22, 118.17, 118.74, 128.31, 128.92, 129.64, 131.51, 136.67, 137.77, 148.50, 160.82, 168.04, 182.27 ppm.

*2-Amino-4-(3-nitrophenyl)-6-(2-amino-phenylsulfanyl)-pyridine-3,5-dicarbonitrile (**4v**)*

Yellow solid, M.Pt. 242–246 °C; IR (KBr, ν_{max}): 3,476, 3,313, 2,926, 2,208, 1,624, 1,543, 1,253, 1,087, 804, 734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 6.43 (br s, 2H, NH_2), 6.50–7.04 (m, 4H, Ar–H), 7.56–7.68 (m, 3H, Ar–H), 7.76 (s, 1H, Ar–H), 8.29 (br s, 2H, NH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 86.42, 93.83, 114.32, 115.37, 117.29, 117.76, 123.24, 124.84, 129.95, 131.68, 134.11, 137.09, 147.68, 149.64, 155.25, 159.28, 167.77 ppm.

*2-Amino-4-(4-methoxyphenyl)-6-(2-amino-phenylsulfanyl)-pyridine-3,5-dicarbonitrile (**4w**)*

Yellow solid, M.Pt. 230–234 °C [20]; IR (KBr, ν_{max}): 3,461, 3,320, 2,922, 2,214, 1,639, 1,544, 1,263, 1,097, 796 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 3.70 (s, 3H, OCH_3), 6.47 (br s, 2H, NH_2), 6.58 (d, $J = 7.4$ Hz, 2H, Ar–H), 7.05 (d, $J = 7.4$ Hz, 2H, Ar–H), 7.36–7.78 (m, 4H, Ar–H), 8.10 (br s, 2H, NH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 56.15, 89.42, 92.58, 113.76, 115.25, 117.22, 118.59, 120.26, 125.79, 127.32, 130.81, 131.63, 145.77, 152.27, 160.57, 167.45, 184.03 ppm.

*2-Amino-4-(4-chlorophenyl)-6-(2-amino-phenylsulfanyl)-pyridine-3,5-dicarbonitrile (**4x**)*

Yellow solid, M.Pt. 234–236 °C [20]; IR (KBr, ν_{max}): 3,450, 3,284, 2,928, 2,217, 1,642, 1,537, 1,241, 1,078, 821, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 6.54 (br s, 2H, NH_2), 6.68–7.14 (m, 4H, Ar–H), 7.32 (d, $J = 7.6$ Hz, 2H, Ar–H), 7.58 (d, $J = 7.6$ Hz, 2H, Ar–H), 8.16 (br s, 2H, NH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 90.76, 92.67, 115.56, 117.18, 118.82, 120.61, 124.70, 127.21, 128.76, 131.26, 135.47, 137.58, 143.88, 158.79, 164.70, 182.04 ppm.

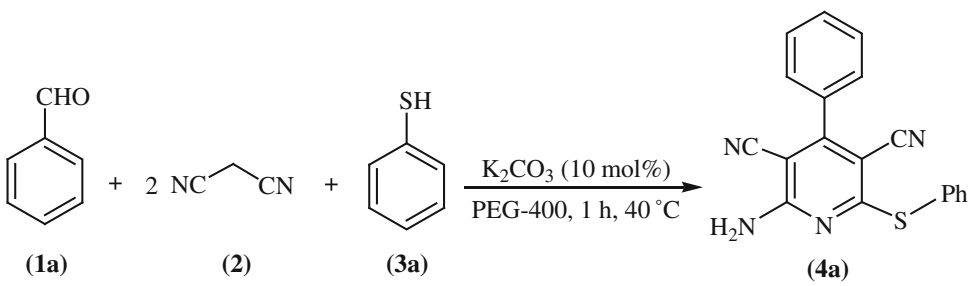
*2-Amino-4-(4-hydroxyphenyl)-6-(2-amino-phenylsulfanyl)-pyridine-3,5-dicarbonitrile (**4y**)*

Yellow solid, M.Pt. 174–178 °C [20]; IR (KBr, ν_{max}): 3,484, 3,296, 2,927, 2,214, 1,632, 1,552, 1,260, 1,075, 814, 747 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 6.38 (br s, 2H, NH_2), 6.72 (d, $J = 7.6$ Hz, 2H, Ar–H), 6.97 (d, $J = 7.6$ Hz, 2H, Ar–H), 7.30–7.62 (m, 4H, Ar–H), 7.84 (br s, 2H, NH_2), 10.45 (br s, 1H, OH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 91.25, 92.76, 114.60, 116.51, 118.90, 119.63, 120.18, 125.37, 127.17, 129.10, 130.79, 143.58, 151.26, 156.48, 164.17, 185.66 ppm.

Results and discussion

We initiated our study by choosing a model reaction involving the MCR of benzaldehyde **(1a)**, malononitrile **(2)** and thiophenol **(3a)** using K_2CO_3 as catalyst in ethanol as a solvent at 40 °C (Scheme 1). The reaction produced 68 % of the desired product **(4a)** in 6 h. In an effort to optimize the reaction conditions, the same reaction was carried out in the presence of PEG-400 as an eco-friendly medium. A remarkable improvement was observed and the yield of product **(4a)** increased up to 92 % after stirring the mixture at 40 °C for only 1 h.

Scheme 1 Model reaction for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines



(1a) **(2)** **(3a)** **(4a)**

Table 1 Optimization of the catalyst concentration

Entry	K_2CO_3 (mol%)	Time (h)	Yield (%)[a]
1	0	20	Nil
2	2	10	54
3	5	4.5	72
4	10	1	92
5	15	1	92
6	20	1	92
7	25	1	92

Reaction conditions: benzaldehyde **(1a)** (1 mmol), malononitrile **(2)** (2 mmol), thiophenol **(3a)** (1 mmol); catalyst: K_2CO_3 (*x* mol%); temp: 40 °C; solvent: PEG-400 (2 mL)

[a] Isolated yields

Table 2 Screening of bases for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines

Entry	Base (mol%)	Time (h)	Yield (%)[a]
1	K_2CO_3	1	92
2	Cs_2CO_3	2	78
3	Na_2CO_3	2	82
4	$NaHCO_3$	4	58
5	KOH	3	68
6	NaOH	3.5	65
7	KOAc	6	54
8	Et_3N	2.5	46

Reaction conditions: benzaldehyde **(1a)** (1 mmol), malononitrile **(2)** (2 mmol), thiophenol **(3a)** (1 mmol); different bases: *x* (10 mol%); temp: 40 °C; solvent: PEG-400 (2 mL)

[a] Isolated yields

Catalyst concentration plays a major role in the optimization of the product yield. In order to determine the appropriate concentration of the K_2CO_3, we investigated the model reaction at different molar ratios (Table 1). By increasing the molar concentration of K_2CO_3 from 10 to 25 mol%, it was observed that yield of the product **4a** was almost the same (Table 1, entries 4–7). But when 2–5 mol% of the catalyst was used, yield of the product **4a** was quite low (Table 1, entries 2, 3). The results indicated that 10 mol% of K_2CO_3 is optimal to carry out the conversion smoothly (Table 1, entry 4). It is noteworthy that there was no reaction without the catalyst even after 20 h, showing the essentiality of the catalyst for this reaction (Table 1, entry 1).

A variety of bases were also tested for their catalytic activities in the model reaction (Scheme 1). The results are presented in Table 2. In this study, K_2CO_3 stood out as the most efficient catalyst, producing the product **(4a)** in 92 % yield in 1 h (Table 2, entry 1).

Table 3 Comparison of the present protocol with the reported methods

Entry	Catalyst (mol%)	Time (h)	Yield (%)[a]
1	Et_3N[b] (10)[12,13]	1.5	35
2	DABCO[b] (10)[12,13]	1.5	20
3	Piperidine[b] (10)[14]	21	43
4	*N*,*N*-DIPEA[b] (10)[14]	3	31
5	DMAP[b] (10)[14]	3	35
6	H_3BO_3[b] (10)[15]	0.6	78
8	TBAH[c] (50)[17]	1	46
9	$ZnCl_2$[b] (20)[18]	2	73

Reaction conditions: benzaldehyde **(1a)** (1 mmol), malononitrile **(2)** (2 mmol), thiophenol **(3a)** (1 mmol); solvent: EtOH

[a] Isolated yields

[b] Reflux

[c] Room temperature

Table 4 Effect of various solvents on the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines

Entry	Solvent (mL)	Time (h)	Yield (%)[a]
1	MeOH	6	72
2	EtOH	6	68
3	CH_3CN	5	71
4	THF	7	55
5	Toluene	8	43
6	Dioxane	8	48
7	DMF	10	64
8	PEG-200	1	90
9	PEG-400	1	92
10	DMSO	4	60

Reaction conditions: benzaldehyde **(1a)** (1 mmol), malononitrile **(2)** (2 mmol), thiophenol **(3a)** (1 mmol); base: K_2CO_3 (10 mol%); temp: 40 °C; different solvents: *y* (2 mL)

[a] Isolated yields

Moreover, the efficiency of the present protocol was also compared with the methods reported in the literature (Table 3). This method proved to be better from the point of view of economical and efficiency considerations. Some of the reported routes for the preparation of 2-amino-3,5-dicarbonitrile-6-thio-pyridines lead to low yields, employed high catalyst loading, prolonged reaction times, and refluxing conditions with usage of harmful organic solvents.

The nature of reaction medium plays an important role in the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridine derivatives in the presence of K_2CO_3 (Table 4). The yields were comparable in MeOH, EtOH, and CH_3CN,

Scheme 2 Synthesis of library of 2-amino-3,5-dicarbonitrile-6-thio-pyridine derivatives

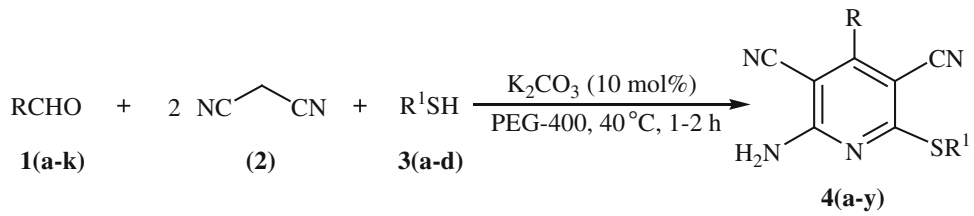


Table 5 K_2CO_3-mediated synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridine derivatives

Entry	R	R^1	Product	Time (h)	Yield (%)[a]
1	C_6H_5	C_6H_5 (**3a**)	**4a**	1.0	92
2	4-Me-C_6H_4	**3a**	**4b**	1.0	92
3	4-MeO-C_6H_4	**3a**	**4c**	1.0	90
4	4-Cl-C_6H_4	**3a**	**4d**	1.5	90
5	4-Br-C_6H_4	**3a**	**4e**	1.0	86
6	4-NO_2-C_6H_4	**3a**	**4f**	2.0	85
7	2-Furyl	**3a**	**4g**	1.75	86
8	2-Thienyl	**3a**	**4h**	2.0	84
9	C_6H_5	4-MeO-C_6H_4 (**3b**)	**4i**	1.0	91
10	4-Me-C_6H_4	**3b**	**4j**	1.0	92
11	4-Cl-C_6H_4	**3b**	**4k**	1.5	90
12	4-Br-C_6H_4	**3b**	**4l**	1.25	88
13	3-HO-C_6H_4	**3b**	**4m**	1.25	87
14	3-NO_2-C_6H_4	**3b**	**4n**	2.0	86
15	2-Thienyl	**3b**	**4o**	1.5	82
16	C_6H_5	4-Br-C_6H_4 (**3c**)	**4p**	1.25	85
17	4-Cl-C_6H_4	**3c**	**4q**	1.5	87
18	4-Me-C_6H_4	**3c**	**4r**	1.5	88
19	4-MeO-C_6H_4	**3c**	**4s**	1.25	90
20	C_6H_5	2-NH_2-C_6H_4 (**3d**)	**4t**	1.0	88
21	4-Me-C_6H_4	**3d**	**4u**	1.0	88
22	3-NO_2-C_6H_4	**3d**	**4v**	1.5	84
23	4-MeO-C_6H_4	**3d**	**4w**	1.5	89
24	4-Cl-C_6H_4	**3d**	**4x**	1.75	86
25	4-HO-C_6H_4	**3d**	**4y**	2.0	85

Reaction conditions: aromatic aldehydes **1(a–k)** (1 mmol), malononitrile **(2)** (2 mmol), substituted thiophenols **3(a–d)** (1 mmol); base: K_2CO_3 (10 mol%); temp: 40 °C; solvent: PEG-400 (2 mL)

[a] Isolated yields

whereas yields were much lower in non-polar solvents like toluene. We also used PEGs of different molecular weights including 200, 400, but PEG-400 gave the best outcome in terms of yield (Table 4, entry 9). A plausible explanation for such an increase in yield could be that "PEGs can be regarded as open-chain crown ethers as they are able to form complexes with alkaline and alkaline-earth cations in protic and aprotic solvents" [34, 35]. "PEG wraps itself around the metal ions forcing the ether oxygens to point inwards and coordinate to metal ions mimicking crown ethers, or coordinated with the metal ions by the terminal OH group. The coordination effect of PEG was even stronger than crown ethers" [36–38].

To assess the versatility of this protocol, a wide range of structurally diverse aldehydes **1(a–k)** were allowed to undergo this three-component coupling reaction with malononitrile **(2)** and different thiophenols **3(a–d)** under the optimized reaction parameters (Scheme 2). Aromatic aldehydes with different substituents and heteroaromatic

Table 6 Recycling studies of the solvent PEG-400

No. of cycles	Native	Run 1	Run 2	Run 3	Run 4
Yield (%)[a]	92	92	92	91	89
Time (h)	1	1	1	1	1

Reaction conditions: benzaldehyde **(1a)** (1 mmol), malononitrile **(2)** (2 mmol), thiophenol **(3a)** (1 mmol); base: K_2CO_3 (10 mol%); temp: 40 °C; solvent: PEG-400 (2 mL)

[a] Isolated yields

aldehydes (thiophene-2-carbaldehyde, furan-2-carbaldehyde) were equally amenable to these conditions (Table 5). Aliphatic aldehydes were also tried for the present reaction, but the yields of products were so low that they were not worth mentioning.

In accordance with the mechanism delineated by Evdokimov et al. [17, 18], the first step of this reaction involves the base-catalyzed Knoevenagel condensation of aldehyde with a first molecule of malononitrile to form 2-(arylidenemalononitrile). Subsequent addition of the thiol to one of the nitrile groups of this adduct which then undergoes reaction with the second molecule of malononitrile and the adduct formed experiences cyclization to afford the corresponding dihydropyridines, which upon aromatization and aerial oxidation under the reaction conditions leads to the desired substituted pyridines.

Recycling experiments were also performed for the model reaction (Scheme 1) to establish the eco-friendly nature and economic viability of solvent PEG-400 (Table 6). After extraction with ethyl acetate, the remaining solution of PEG-400 and water was concentrated to recover pure PEG-400 [33]. The recovered PEG-400 phase was reused in subsequent reactions, which proceeded cleanly showing consistent results up to four consecutive cycles; although a weight loss of approximately 5 % was observed from cycle to cycle due to mechanical loss.

Conclusion

We have demonstrated a clean, facile, and practically convenient protocol for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines via MCR of aromatic aldehydes, malononitrile, and substituted thiophenols using K_2CO_3 as a green base. The use of PEG-400 as a solvent renders this method an environmentally friendly protocol. The advantages of this method include high isolated yields, shorter reaction times, operational simplicity, and wide substrate scope and recyclability of the solvent.

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