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SYNTHESIS OF HIGHLY SUBSTITUTED PYRIDINE VIA SILICA-SUPPORTED PIPERAZINE

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ABSTRACT
A green, novel, and electrochemically driven synthetic approach has been established for the construction of substituted pyridines through a one-pot condensation involving multicomponent reaction of structurally varied aldehydes, various thiols, and malononitrile using silica-supported piperazine. The catalyst silica-supported piperazine is recyclable, non-toxic and aligns with green chemistry principles. The method is time-efficient, cost-effective and scalable, making it suitable for pharmaceutical and industrial applications.
Keywords: Three Component Reaction, Substituted Pyridine, Malononitrile, Condensation Reaction, Silica Supported Piperazine, Green Synthesis.
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INTRODUCTION

Heterocyclic compounds are essential building blocks that play a vital role in various aspects of daily life, thanks to their versatility and widespread applications.[1] The most common heterocyclic structures typically feature five- or six-membered rings that contain heteroatoms like nitrogen, oxygen, or sulfur. Notably, nitrogen-based heterocycles have garnered significant attention due to their prominent presence in pharmaceuticals, natural products, and cutting-edge functional materials.[2] Moreover, certain nitrogen-substituted heterocyclic compounds are pivotal in genetic information transmission, as they form crucial components of nucleic acids, including DNA and RNA, which rely heavily on nitrogenous heterocycles such as purines and pyrimidines as fundamental structural elements. The pyridine moiety is a prominent structural feature in numerous bioactive compounds, both synthetic and naturally occurring, and has received substantial attention in recent years. The incorporation of organo-sulfur groups into pyridine-containing heterocycles can enhance their biological properties. The medicinal importance of substituted pyridine derivatives is highlighted by a substantial number of patents, which demonstrate their potential therapeutic applications. Some compounds in this class have been shown to act as potassium channel openers, offering potential treatments for conditions such as urinary incontinence, as well as exhibiting antibacterial and antibiofilm activities.[3] Additionally, pyridine-based molecules have been extensively studied for their potential in treating various diseases[4], including Alzheimer's disease, asthma, epilepsy, hypoxia, Parkinson's disease, renal disorders, and certain types of cancer. Over the past few decades, numerous innovative synthetic approaches have been introduced, including Vilsmeier reactions[5], Diels–Alder[6] cycloadditions, and nickel- or ruthenium-catalysed cycloadditions involving alkynes and nitriles.[7] Several alternative approaches have been reported for synthesizing substituted pyridines. These include cycloaddition reactions involving oximinosulfonates[8], interactions between imines and with enamines or carbonyl compounds[9], and condensations of thiols[10] with α,β-unsaturated esters or nitriles. Another route involves transforming ketene dithioacetals into pyridine derivatives.[11] Moreover, a variety of catalytic systems, such as ionic liquids[12], containing nanocrystalline magnesium oxide[13], acids, bases, microwave-assisted techniques, and nanoscale metal oxides have been explored under different reaction conditions. Furthermore, various multicomponent reaction (MCR) procedures have been established, the majority of which use the condensation of aldehydes, malononitrile, and thiols in the presence of suitable base catalysts to provide a wide range of substituted pyridines. Developing gentle, efficient, and environmentally acceptable techniques for the synthesis of highly substituted sulfur-containing pyridine derivatives remains a key priority in organic chemistry.

For ongoing and future research, emphasising both reaction efficiency and mild conditions is crucial for advancing innovative synthetic methodologies. In the context of sustainable development, silica-supported piperazine (KG-60-piperazine) facilitated multi-component reactions may significantly contribute to the synthesis of a diverse array of both naturally occurring and manufactured bioactive substituted pyridine molecules. Silica-supported piperazine[14] mediated method facilitates the quick and direct synthesis of complex compounds without the need for purification and isolation of intermediates, thereby reducing waste, effort, time and labour costs from available starting materials through the utilisation of greener and sustainable technologies.

EXPERIMENTAL

General Information

All chemical reagents used in this study were of high purity and obtained from reputable commercial suppliers, including Sigma-Aldrich, Merck, Spectrochem, Alfa Aesar and Qualigens. These materials were used as supplied, without any additional purification. The progress of reactions was tracked using thin-layer chromatography (TLC) on pre-coated aluminium-backed silica gel plates (Merck 60 F-254, 0.25 mm) containing a UV indicator at 254 nm. Structural characterization of the synthesized compounds was carried out using various spectroscopic methods. Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance-II 400FT spectrometer, operating at 300 or 500 MHz for ^{1}H NMR and at 75 MHz or 125 MHz for ^{13}C NMR. Samples were prepared in deuterated solvents such as DMSO-d_6 or $CDCl_3$, with tetramethylsilane (TMS) as the internal standard. Mass spectra were obtained using a Waters UPLC-TQD mass spectrometer equipped with an Electrospray Ionisation (ESI) source. Infrared (IR) spectra were collected on a Thermo Scientific Nicolet iS5 FT-IR spectrometer to provide insights into molecular functional groups. Elemental analysis (CHN) was performed using a Thermo Scientific FLASH 2000 Elemental Analyzer. Melting points of the synthesized compounds were determined using the open capillary method and are reported without correction.

General Procedure for the Preparation of Silica-supported Piperazine

A heterogeneous reaction involving 5.0 g of chloro-propyl functionalised silica gel and 0.69 g (8.0 mmol) of piperazine in 20.0 ml of freshly distilled anhydrous xylene was used to modify the surface of silica gel with piperazine molecules. For forty hours, the mixture was continually mixed and exposed to reflux in xylene. Following the reaction, a number of solvents, such as xylene, ethanol, deionised water, and acetone, were used to thoroughly wash the resultant silica-supported piperazine material in order to eliminate any unreacted species. The intended silica-immobilised piperazine derivative was obtained by drying the finished product for 12 hours at 403 K under decreased pressure.

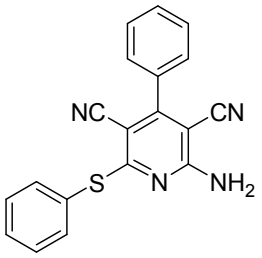
General Procedure for the Synthesis of Highly Substituted Pyridine Through Silica-Supported Piperazine

Benzaldehyde 1 (11.0 mmol) and malononitrile 2 (22.0 mmol) were combined with silica-supported piperazine (KG-60-piperazine / Catalyst 1, 1.0 mmol) to start the reaction. Chromatographic examination verified that the mixture was agitated for around half an hour, or until all of the benzaldehyde had been consumed. Following the addition of thiophenol 3 (1.0 mmol), the reaction was continuously stirred until it was finished, as determined by TLC. Following completion, the residue was extracted using ethyl acetate (50 mL) and quenched with water (10 mL) after the solvent was removed under reduced pressure. The mixed organic extracts were filtered, concentrated under low pressure, and dried over anhydrous sodium sulphate (Na_2SO_4). Analytically pure derivatives (4a–o) were obtained by purifying the crude product using silica gel column chromatography with a hexane–ethyl acetate eluent.

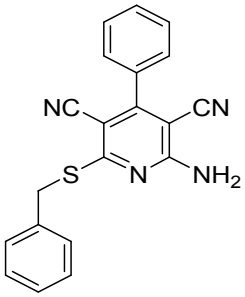
2-amino-4-phenyl-6-(phenylthio) pyridine-3,5-dicarbonitrile (4a)

Compound 4a: The compound was isolated as a colorless solid, with a melting point range of 217-219°C. The ^{1}H NMR spectrum, recorded at 300 MHz in DMSO-d_6, displayed resonances at δ 7.47-7.39 (m, 10H) and 7.25 (br s, 2H). The ^{13}C NMR spectrum, acquired at 75 MHz, exhibited signals at δ 167.4, 160.0, 158.1, 135.1 (2C), 134.0, 130.5 (2C), 130.0, 129.5, 129.0 (2C), 128.5 (2C), 127.5, 114.2 (2C), 93.9, and 87.3. The IR spectrum, obtained using KBr pellets, showed characteristic absorption bands at 3480, 3351,

3215, 2220, 1623, 1581, 1550, 1522, 1263, 760, and 700 cm^{-1}. The mass spectrum, recorded using electrospray ionization (ESI), displayed a molecular ion peak at m/z 351, corresponding to the $[M + Na]^+$ion.

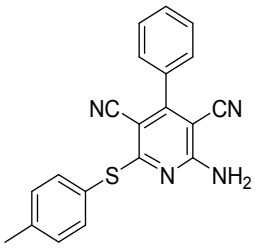


2-Amino-6-benzylsulfanyl-4-phenyl-pyridine-3,5-dicarbonitrile (4b)



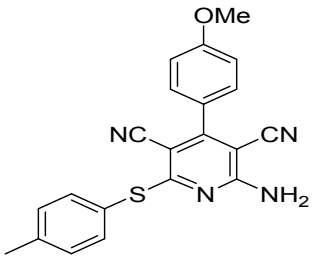
Compound 4b: The compound was isolated as a solid and characterized using various spectroscopic techniques. The ^1H NMR spectrum, recorded at 300 MHz in DMSO-d_6 , exhibited resonances at δ 8.19 (br s, 2H, NH_2), 7.59-7.50 (m, 7H, Ar-H), and 7.31-7.28 (m, 3H, Ar-H), along with a singlet at δ 4.51 (s, 2H, CH_2). The ^{13}C NMR spectrum, acquired at 75 MHz, displayed signals at δ 166.3, 159.5, 159.3, 137.5, 129.9, 128.4, 128.3, 127.1, 117.5, 115.1, 93.0, 85.9, and 33.3 ppm. The IR spectrum, obtained using KBr pellets, showed characteristic absorption bands at 3436, 3321, 3216, 2221, 2205, 1624, 1535, 1519, 1494, 1263, 1237, 1024, 809, 772, 751, 694, and 673 cm^{-1}. The electrospray ionization mass spectrum (ESI-MS) displayed a molecular ion peak at m/z 365, corresponding to the sodium adduct [M + Na].

2-Amino-4-(4-cyanophenyl)-6-(4-methylphenylsulfanyl)-3,5-pyridinedicarbonitrile: (4c)



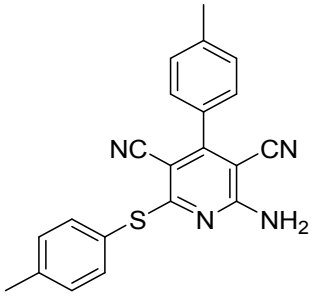
Compound 4c: The compound was obtained as a white solid, with a melting point of 272°C. The ^1H NMR spectrum, recorded at 400 MHz in $CDCl_3$, exhibited resonances at δ 7.73-7.70 (d, J = 8 Hz, 2H, Ar-H), 7.50-7.40 (m, 4H, Ar-H), and 7.30-7.28 (d, J = 8 Hz, 2H, Ar-H), along with singlets at δ 5.49 (s, 2H, NH_2) and δ 2.40 (s, 3H, CH_3). The ^{13}C NMR spectrum, acquired at 100 MHz in $CDCl_3$, displayed signals at δ 165.0, 156.2, 155.4, 136.5, 135.5, 134.5, 134.0, 133.9, 131.4, 130.3, 128.0, 115.8, 115.0, 94.5, and 87.2. Elemental analysis calculated for $C_{21}H_{13}N_5S$: C, 68.65; H, 3.57; N, 19.06%. The experimental values were found to be C, 68.78; H, 3.44; N, 18.95%. The IR spectrum, obtained using KBr pellets, showed characteristic absorption bands at 3479, 3352, 3215, 2218, 1634, 1551, 1498, and 1256 cm^{-1}. The ESI mass spectrum displayed a molecular ion peak at m/z 365, corresponding to the sodium adduct $[M + Na]^+$.

2-(p-tolylthio)-6-amino-4-(4-methoxyphenyl) pyridine-3,5-dicarbonitrile: (4d)



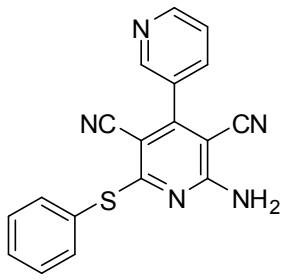
Compound 4d: The compound was isolated as a pale yellow solid, with a melting point range of 230-233°C. The ^{1}H NMR spectrum, recorded at 200 MHz in DMSO-d_6 , exhibited resonances at δ 7.43 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 7.5 Hz, 2H), 7.19 (d, J = 8.2 Hz, 2H), and 7.0 (d, J = 7.5 Hz, 2H), along with a broad singlet at δ 6.74 (br s, 2H) and two singlets at δ 3.85 (s, 3H) and δ 2.38 (s, 3H). The ^{13}C NMR spectrum, acquired at 75 MHz in DMSO-d_6 , displayed signals at δ 166.5, 160.8, 159.5, 158.1, 139.3, 135.0, 131.3, 130.2, 129.9, 128.0, 125.8, 123.5, 115.5, 115.3, 114.0, 113.8, 93.1, 86.8, 55.3, and 21.0. The ESI mass spectrum showed a molecular ion peak at m/z 395, corresponding to the sodium adduct $[M + Na]^{+}$. The IR spectrum, obtained using KBr pellets, exhibited characteristic absorption bands at 3463, 1632, 1603, 1545, 1508, 3323, 3215, 2221, 1258, 1179, 1028, and 811 cm^{-1}.

2-(p-tolylthio)-6-amino-4-p-tolylpyridine-3,5-dicarbonitrile: (4e)



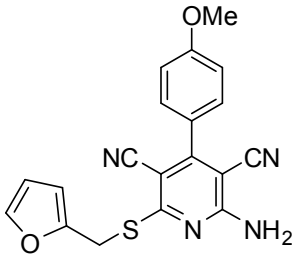
Compound 4e: The compound was obtained as a colorless solid, with a melting point of 222°C. The ^{1}H NMR spectrum, recorded at 400 MHz in $CDCl_3$, exhibited resonances at δ 7.59-7.41 (m, 4H, Ar-H) and 7.36-7.25 (m, 4H, Ar-H), along with singlets at δ 5.44 (s, 2H, NH_2), δ 2.41 (s, 3H, CH_3), and δ 2.11 (s, 3H, CH_3). The ^{13}C NMR spectrum, acquired at 100 MHz in $CDCl_3$, displayed signals at δ 167.6, 160.0, 156.2, 136.1, 135.2, 134.6, 131.8, 131.4, 130.0, 129.7, 129.2, 128.9, 126.6, 115.5, 114.2, 96.3, 86.1, 17.1, and 15.7. The calculated elemental composition for $C_{21}H_{16}N_4S$ was C, 70.76; H, 4.52; N, 15.72%. The experimental values were C, 70.52; H, 4.65; N, 15.84%. The IR spectrum, obtained using KBr pellets, showed characteristic absorption bands at,2211, 1616, 1572, 1533, 3442, 3357, 3198, 1481,and 1252 cm^{-1}.

2-amino-6-(phenylthio)-4-(pyridin-3-yl) pyridine-3,5-dicarbonitrile: (4f)



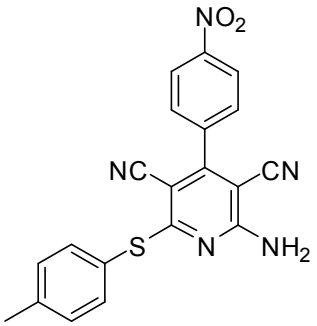
Compound 4f: The compound was isolated as a light-yellow solid, with a melting point range of 305-306°C. The ^{1}H NMR spectrum, recorded in DMSO-d_6 , exhibited resonances at δ 8.77 (dd, J = 1.83 Hz, J = 4.78 Hz, 1H), 8.76 (dd, J = 1.53 Hz, J = 4.88 Hz, 1H), 8.03 (dd, J = 1.53 Hz, J = 7.93 Hz, 1H), 7.80 (br s, 2H), 7.62 (dd, J = 4.88 Hz, J = 7.93 Hz, 1H), and 7.60-7.51 (m, 5H). The ^{13}C NMR spectrum, acquired at 75 MHz, displayed signals at δ 168.2, 160.5, 159.3, 148.9, 147.3, 137.5, 128.5, 128.3, 127.1, 117.5, 115.0, 93.0, and 85.9 ppm. The IR spectrum, obtained using KBr pellets, showed characteristic absorption bands at 2212, 1708, 1656, 1646, 1582, 1550, 3376, 3248, 3152, 2218, 1520, 1420, 1268, 1072, 1054, 1028, 810, 756, and 728 cm^{-1}. The calculated elemental composition for $C_{18}H_{11}N_5S$ (329.387) was C, 65.63; H, 3.37; N, 21.27; S, 9.73%. The experimental values were found to be C, 65.80; H, 3.35; N, 21.20; S, 9.62%.

2-((furan-2-yl) methylthio)-6-amino-4-(4-methoxyphenyl) pyridine-3,5-dicarbonitrile: (4g)



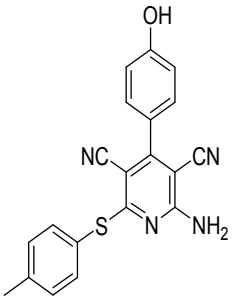
Compound 4g: The compound was isolated as a pale yellow solid with a melting point of 217–218 °C. The ^{1}H NMR spectrum (200 MHz, DMSO-d_6) displayed multiplets at δ 7.62–7.37 (5H), a doublet at δ 7.04 (J = 8.8 Hz, 2H), a doublet at δ 6.44 (J = 2.9 Hz, 1H), and a triplet at δ 6.29 (J = 2.2, 2.9 Hz, 1H), along with singlets at δ 4.51 (2H) and δ 3.88 (3H). The ^{13}C NMR spectrum (75 MHz, DMSO-d_6) exhibited resonances at δ 165.4, 160.7, 159.6, 158.1, 149.8, 142.7, 130.1, 125.7, 115.3, 114.0, 113.6, 110.7, 108.9, 93.4, 85.9, 55.2, and 25.9. The ESI mass spectrum showed a peak at m/z 369 corresponding to the sodium adduct $[M+Na]^+$. HRMS calculated for $C_{19}H_{14}N_4O_2NaS$ was 369.0786, and the observed value was 369.0776. The IR spectrum (KBr) revealed characteristic absorptions at 3459, 3324, 3209, 2363, 2214, 1616, 1541, 1506, 1459, 1247, 1170, 1016, 826, and 743 cm^{-1}.

2-Amino-4-(4-nitrophenyl)-6-(4-methylphenylsulfanyl)-3, 5-pyridinedicarbonitrile: (4h)



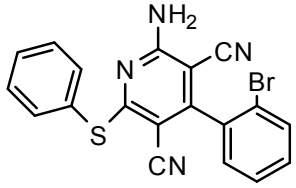
Compound 4h: The compound was obtained as a yellow solid, with a melting point of 301°C. The ^{1}H NMR spectrum, recorded at 400 MHz in $CDCl_3$, exhibited resonances at δ 8.41-8.39 (d, J = 8 Hz, 2H), 7.68-7.66 (d, J = 7.8 Hz, 2H), 7.45-7.43 (d, J = 8 Hz, 2H), and 7.28-7.26 (d, J = 7.8 Hz, 2H), along with singlets at δ 5.50 (s, 2H) and δ 2.40 (s, 3H). The ^{13}C NMR spectrum, acquired at 100 MHz in $CDCl_3$, displayed signals at δ165.1, 158.2, 156.1, 137.3, 136.2, 135.5, 134.9, 134.1, 132.9, 131.3, 125.3, 116.9, 115.1, 96.2, 86.8, and 18.9. The calculated elemental composition for $C_{20}H_{13}N_5O_2S$ was C, 62.01; H, 3.38; N, 18.08%. The experimental values were found to be C, 61.85; H, 3.26; N, 18.16%. The IR spectrum, obtained using KBr pellets, showed characteristic absorption bands at 3218, 2215, 1626, 3472, 3332, 1541, 1509, 1344, and 1262 cm^{-1}.

2-Amino-4-(4-methylphenyl)-6-(4-methylphenylsulfanyl)- 3,5-pyridinedicarbonitrile: (4i)



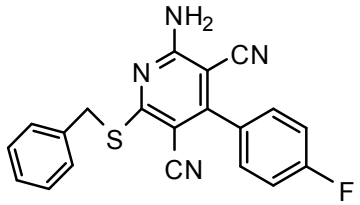
Compound 4i: The compound was isolated as a colorless solid, with a melting point of 222°C. The ^{1}H NMR spectrum, recorded at 400 MHz in $CDCl_3$, exhibited resonances at δ 7.59-7.41 (m, 4H, Ar-H) and 7.36-7.25 (m, 4H, Ar-H), along with singlets at δ 5.44 (s, 2H, NH_2), δ 2.41 (s, 3H, CH_3), and δ 2.11 (s, 3H, CH_3). The ^{13}C NMR spectrum, acquired at 100 MHz in $CDCl_3$, displayed signals at δ 167.6, 158.9, 156.2, 136.1, 135.2, 134.6, 131.8, 131.4, 130.1, 129.7, 129.2, 129.1, 126.6, 115.5, 114.2, 96.3, 86.1, 17.1, and 15.7. The calculated elemental composition for $C_{21}H_{16}N_4S$ was C, 70.76; H, 4.52; N, 15.72%. The experimental values were found to be C, 70.52; H, 4.65; N, 15.84%. The IR spectrum, obtained using KBr pellets, showed characteristic absorption bands at 3442, 3357, 3198, 2211, 1616, 1572, 1533, 1481, and 1252 cm^{-1}.

2-Amino-4-(2-bromo-phenyl)-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile: (4j)



Compound 4j: The compound was obtained as a colorless solid, with a melting point range of 242-244°C, after recrystallization from CH_3 CN. The ^{1}H NMR spectrum, recorded at 300 MHz in DMSO-d_6, exhibited resonances at δ 7.91 (br s, 2H), 7.80 (d, J = 7.8 Hz, 1H), and 7.60-7.43 (m, 8H). The ^{13}C NMR spectrum, acquired at 75 MHz, displayed signals at δ 166.4, 159.8, 158.4, 135.5, 135.3 (2C), 133.3, 132.4, 130.5, 130.2, 129.9, 128.8, 127.2, 121.1, 114.9, 114.6, 94.2, and 88.2. The high-resolution mass spectrometry (HRMS) calculated for $C_{19}H_{11}BrN_4S$ was $[M + H]^+$, 406.9966, and the experimental value was found to be 406.9961. The IR spectrum, obtained using KBr pellets, showed characteristic absorption bands at 3440, 3336, 3217, 2214, 1627, 1596, 1542, 1263, and 758 cm^{-1}.

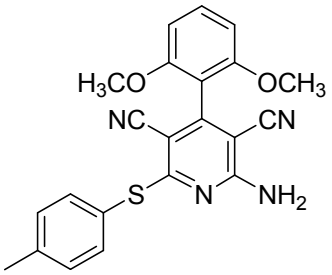
2-Amino-6-benzylsulfanyl-4-(4-fluoro-phenyl)-pyridine-3,5-dicarbonitrile: (4k)



Compound 4k: The ^{1}H NMR spectrum (250 MHz, DMSO-d_6) showed resonances at δ 8.16 (br s, 2H, NH_2), 7.64-7.58 (m, 2H, Ar-H), 7.52 (d, J = 6.4 Hz, 2H, Ar-H), and 7.44-7.25 (m, 5H, Ar-H), as well as a singlet at δ 4.51 (s, 2H). The ^{13}C NMR spectrum (75 MHz, DMSO-d_6) exhibited signals at δ 166.2, 165.1, 159.5, 157.5, 137.6, 131.0, 130.3, 129.4, 128.4, 127.3, 115.8, 115.2, 113.9, 93.3, 86.1, and 33.2. The IR

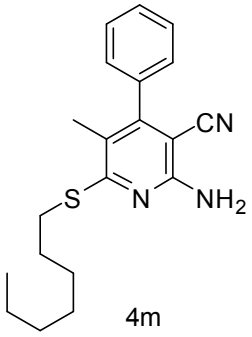
spectrum (KBr) displayed absorption bands at 3439, 3334, 3211, 3069, 2210, 1621, 1606, 1544, 1506, 1462, 1427, 1027, 822, 694, 1321, 1262, 1233, 1165 and 671 cm^{-1}.

2-(p-tolylthio)-6-amino-4-(2,6-dimethoxyphenyl)pyridine-3,5-dicarbonitrile: (4l)



Compound 4l: The compound was obtained as a colorless solid, with a melting point range of 202-203°C. The ^{1}H NMR spectrum, recorded at 200 MHz in DMSO-d_6, exhibited resonances at δ 7.66 (s, 1H), 7.45 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), and 6.7 (d, J = 8.8 Hz, 2H), along with a broad singlet at δ 6.62 (br s, 2H) and singlets at δ 3.85 (s, 6H) and δ 2.42 (s, 3H). The ^{13}C NMR spectrum, acquired at 75 MHz in DMSO-d_6, displayed signals at δ 165.8, 159.5, 156.6, 153.9, 139.5, 135.0, 132.2, 130.0, 123.2, 114.9, 114.7, 110.8, 104.5, 94.8, 88.8, 56.0, and 20.8. The ESI mass spectrum showed a molecular ion peak at m/z 425, corresponding to the sodium adduct $[M + Na]^+$. The high-resolution mass spectrometry (HRMS) calculated for $C_{22}H_{18}N_4O_2NaS$ was 425.1048, and the experimental value was found to be 425.1037. The IR spectrum, obtained using KBr pellets, showed characteristic absorption bands at 3440, 3343, 3220, 2212, 2180, 1630, 1593, 1541, 1465, 1253, 1106, 1021, and 768 cm^{-1}.

2-Amino-6-(Heptylthio)-4-phenylpyridine-3,5-dicarbonitrile: (4m)

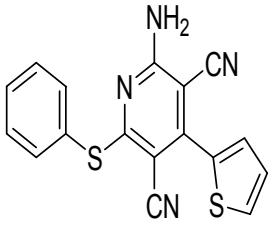


4m

Compound 4m: The compound was isolated as a white crystal, with a melting point of 148°C. The ^{1}H NMR spectrum, recorded at 400 MHz in $CDCl_3$, exhibited resonances at δ 7.73-7.37 (m, 5H), 5.63 (s, 2H), 3.20 (t, J = 7.3 Hz, 2H), 1.73 (t, J = 7.5 Hz, 2H), 1.45 (t, J = 7.5 Hz, 2H), and 1.40-1.21 (m, 6H), along with a triplet at δ 0.89 (t, J = 7.5 Hz, 3H). The low-resolution mass spectrum (LRMS) calculated for $C_{20}H_{22}N_4S$ was $[M + H]^+$, 351.

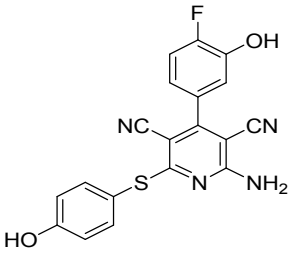
3-Amino-6-(phenylsulfanyl)-4-(3-thienyl)-3,5-pyridinedicarbonitrile: (4n)

Compound 4n: The white solid compound, recrystallized from CH_3CN, had a melting point range of 235-236°C. The ^{1}H NMR spectrum (DMSO-d_6) showed resonances at δ 8.04 (dd, J=1.22 Hz and 3.05 Hz, 1H), δ 7.65 (broad singlet, 2H), δ 7.60 (multiplet, 2H), δ 7.50 (multiplet, 3H), δ 7.39 (dd, J=1.22 Hz and 4.89 Hz, 1H), and 7.00 (dd, J=1.22 and 3.05 Hz, 1H). The ^{13}C NMR spectrum exhibited signals at δ 168.4, 162.7, 160.6, 158.1, 149.8, 142.7, 130.1, 128.7, 116.3, 114.0, 113.6, 111.7, 110.9, 97.4, and 88.9 ppm.



Elemental analysis for $C_{17}H_{10}N_4S_2$ gave calculated values of C, 61.05; H, 3.02; N, 16.76; S, 19.17%, which were in close agreement with the experimental values of C, 60.90; H, 2.98; N, 16.83; S, 19.31%. The IR spectrum (KBr) displayed absorption bands at, 3216, 2216, 1476, 1440, 1366, 1306, 1262, 1024, 1624, 1550, 1512 830, 790, 692, 772, 756, 708, 3472 and 3352 cm^{-1}.

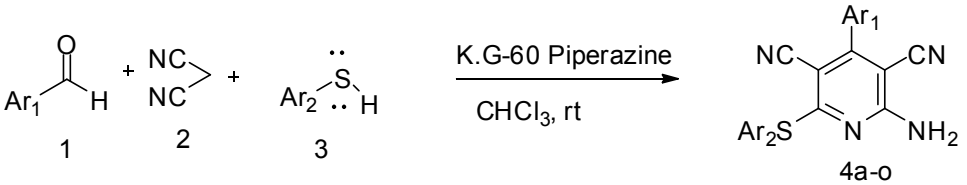
2-Amino-4-(3-fluoro-4-hydroxy-phenyl)-6-(4-hydroxy-phenylsulfanyl)-pyridine3,5-dicarbonitrile: (4o)



Compound 4o: The ^{1}H NMR spectrum (250 MHz, DMSO-d_6) showed resonances at δ 10.57 (s, 1H, OH), 10.00 (s, 1H, OH), 7.74 (br s, 2H, NH_2), 7.44 (bd, J = 11.9 Hz, 1H, Ar-H), 7.37 (d, J = 8.5 Hz, 2H, Ar-H), 7.06-7.22 (m, 2H, Ar-H), and 6.87 (d, J = 8.5 Hz, 2H, Ar-H). The ^{13}C NMR spectrum (75 MHz, DMSO-d_6) exhibited signals at δ 167.5, 159.6, 159.1, 157.2, 151.3, 146.7, 137.1, 125.5, 117.7, 116.9, 116.7, 116.4, 115.4, 115.2, 114.9, 92.8, and 86.6 ppm. The IR spectrum (KBr) displayed absorption bands at 3492, 3432, 3378, 3328, 3230, 2216, 1703, 1548, 1511, 1496, 1470, 1440, 1374, 1269, 1248, 1192, 1170, 1116, 1032, 946, 833, 760, and 685 cm^{-1}. The ESI-MS calculated for $C_{19}H_{11}FN_4O_2S$ was $[M + Na]^+ = 401$.

RESULTS AND DISCUSSION

This study commenced with an analysis of the reaction between benzaldehyde 1 (1.1 mmol), malononitrile 2 (2.2 mmol), and thiophenol 3 (1 mmol) to optimize conditions using two catalysts: piperazine hydrate and silica-supported piperazine (KG-60-piperazine). Notably, KG-60-piperazine yielded higher product formation under similar conditions (Table-1, entries 1-4). The reaction mixture was initially tested at 0°C, resulting in 20% product formation with piperazine (Table-1, entry 1) and 50% with KG-60-piperazine (Table-1, entry 3). When the reaction was warmed to room temperature, the product yield increased to 60% with piperazine (Table-1, entry 2) and 92% with KG-60-piperazine. Increasing the reaction time or temperature did not significantly affect the yield (Table-1, entries 5, 6). However, decreasing the catalyst loading to below 10 mol% resulted in a significant decrease in yield (Table-1, entries 7). Further increases in catalyst loading beyond 10 mol% did not yield additional improvements (Table-1, entry 8). The reaction conditions, including catalyst amount and solvent, played a crucial role in determining the yield, as evident from the results presented in Table-1 (entries 1-13). Among the solvents tested, $CHCl_3$ yielded the best results, likely due to its relatively low polarity (Table-1, entries 4, 9-13).



Scheme-1: Silica-Supported Piperazine (KG-60-piperazine) Mediated Synthesis of Highly Substituted Pyridine

Table-1: Optimization of the Synthesis of 2-amino-4-phenyl-6-(phenylthio) Pyridine-3,5-dicarbonitrile (4a)

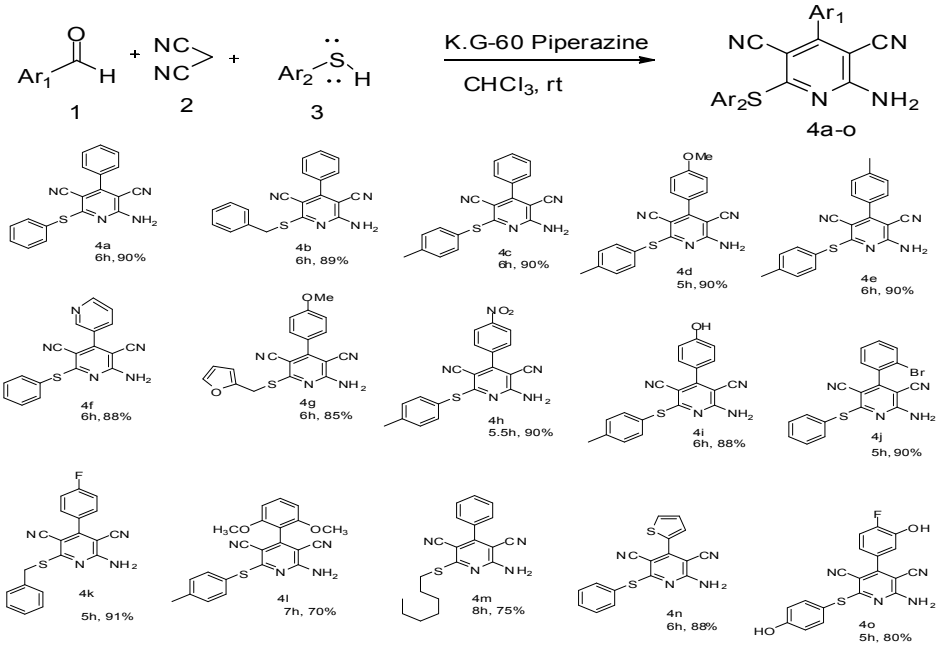
Entry	Solvent	Time (h)	Temp (c)	Catalyst (Mole)	Catalyst	Yield %
1	$CHCl_3$	4h	0°	0.10	Piperazine	20
2	$CHCl_3$	4h	rt	0.10	Piperazine	60
3	$CHCl_3$	4h	0°	0.10	KG-60-piperazine	50
4	$CHCl_3$	4h	rt	0.10	KG-60-piperazine	92
5	$CHCl_3$	7h	rt	0.10	KG-60-piperazine	92
6	$CHCl_3$	7h	reflux	0.10	KG-60-piperazine	92
7	$CHCl_3$	7h	rt	0.05	KG-60-piperazine	48
8	$CHCl_3$	7h	rt	0.20	KG-60-piperazine	92
9	CH_2Cl_2	4h	rt	0.10	Piperazine	no rxn
10	CH_2Cl_2	7h	rt	0.10	Piperazine	40
11	CH_3CN	6h	rt	0.10	KG-60-piperazine	90
12	*i*PrOH	10h	rt	0.10	KG-60-piperazine	90
13	EtOH	10h	rt	0.10	KG-60-piperazine	70

(a.) Optimised Conditions: Benzaldehyde 1 (1.1 mmol), malononitrile 2 (2.2 mmol), thiophenol 3 (1.0 mmol), silica-supported piperazine/ KG-60-piperazine (0.1 mmol), solvent (5 mL).

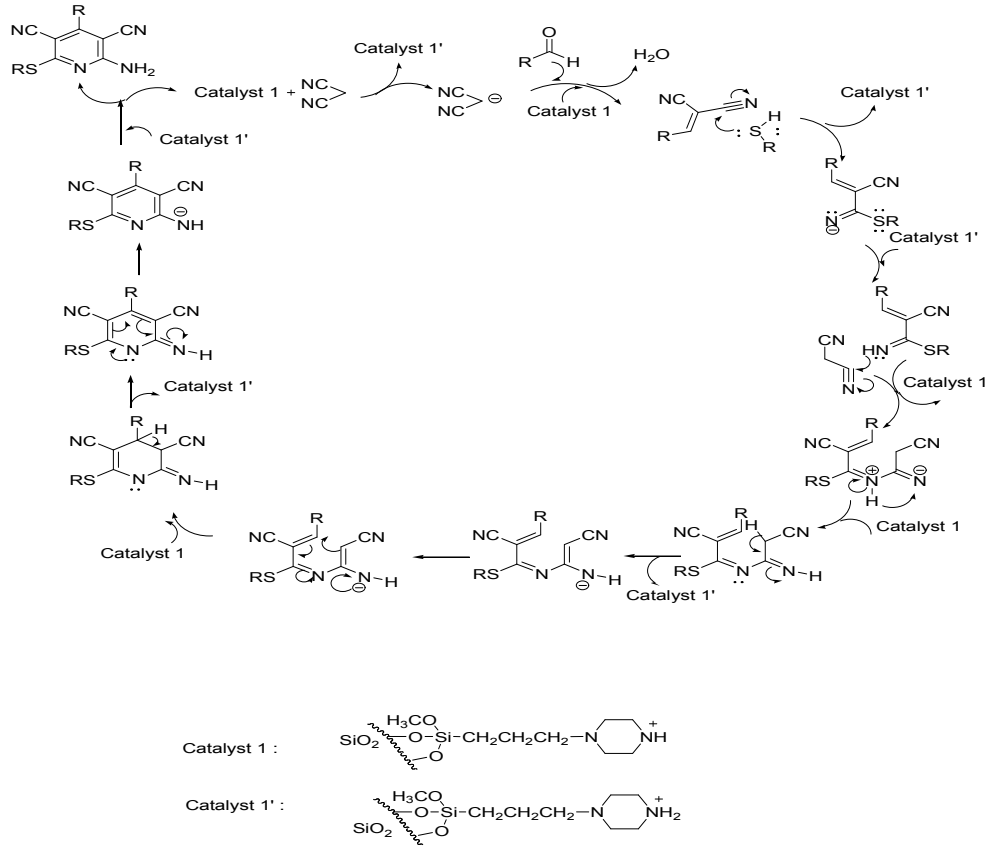
(b.) Isolated Yield of Product 4a-o

A variety of substituted aromatic and heteroaromatic aldehydes were investigated in reactions with different thiophenols and malononitrile, leading to the successful synthesis of 2-amino-3,5-dicyano-6-sulfanyl pyridines under the optimised conditions. The results showed that using heptane thiol instead of thiophenol resulted in a lower yield (Table-2, entry 4m). Additionally, aliphatic aldehydes did not produce identifiable products, indicating that the reaction conditions are particularly effective for aromatic aldehydes. The reaction times were influenced by the electronic properties of the substituents on the aromatic ring, with electron-withdrawing groups (such as -NO_2, -F, and -Br) generally reacting faster (Table-2, entries 4i, 4j, 4k and 4o) than electron-donating groups (such as -OCH_3 and -CH_3) (Table-2, entries 4d, 4e, 4g, and 4l). However, the final product yields were relatively unaffected by the electronic nature of the substituents.

Table-2: Silica-Supported Piperazine (KG-60-piperazine) Mediated Synthesis of Highly Substituted Pyridine Derivatives Under Optimized Conditions



A new silica-supported piperazine-catalysed method for the effective synthesis of highly substituted pyridine compounds is depicted in Scheme-2, which presents a proposed silica-supported piperazine-catalysed mechanism for producing these derivatives.



Scheme-2: Plausible Silica-Supported Piperazine Catalyzed Pathway for the Synthesis of Highly Substituted Pyridine Derivatives

CONCLUSION

A new three-component, one-pot synthetic strategy has been developed for synthesising substituted pyridines, following the principles of green chemistry. This method features environmentally friendly conditions, mild reaction parameters, high atom economy, and the use of a non-toxic catalyst, making it an appealing approach for constructing N-heterocyclic compounds with a pyridine core. The absence of base or ligand requirements adds to the simplicity and attractiveness of this method. This development marks a significant progress in modern synthetic organic chemistry, offering a novel route for the synthesis of highly substituted pyridine derivatives that can be utilized in various applications.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work supports *SDG-4: Quality Education*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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REFERENCES

1. D. L. Boger and S. Nakahara, *Journal of Organic Chemi*stry, **56**, 880 (1991), https://doi.org/10.1021/jo00002a077; (b) D. L. Boger and A. M. Kasper, *Journal of American Chemical Society,* **111**, 1517(1989), https://doi.org/10.1021/ja00186a067; (c) T. Y. Zhang, J. R. Stout, J. G. Keay, E. F. V. Scriven, J. E.Toomey and G. L. Goe, *Tetrahedron* **51**,13177 (1995), https://doi.org/10.1016/0040-4039(96)01909-0; (d) X. Ma and D. R. Gang, *Natural Products Report* , 21, 752 (2004), https://doi.org/**10.1039/B409720N**
2. (a) S. W. Schneller, Thiochromanones and Related Compounds, *In Advances in Heterocyclic Chemistry*, A. R. Katritzky, A. J. Boulton, Eds.; *Academic Press*, **18**, 59(1975), https://doi.org/**10.1016/S0065-2725(08)60128-2**; (b) P.Chauhan, S. Mahajan, D. Enders,*Chemical. Reviews,* **114**, 8807 (2014), https://doi.org/10.1021/cr500235v; (c) K. C. Majumdar, S. Ponra, T. Ghosh, *RSC Advances*, **2**, 1144 (2012), https://doi.org/10.1039/C5RA27069C
3. (a) D. R. Anderson, N. W. Stehle, S. A. Kolodziej, E. J. Reinhard, *PCT Int. Appl., WO* 2004055015 A1 20040701, (2004); (b) A. A. Nirschl, L. G. Hamann, US *Pat. Appl. Publ.* US 2005182105 A1 20050818, (2005); (c) H. Harada, S. Watanuki, T. Takuwa, K. Kawaguchi, T. Okazaki, Y. Hirano, C. Saitoh, *PCT Int. Appl.* WO 2002006237 A1 20020124, (2002); (d) Chen H, Zhang W, Tam R, Raney A K, *PCT Int. Appl.* WO 2005058315 A1 20050630, (2005); (e) S.B. Levy, M. N. Alekshun, B. L.Podlogar , K. Ohemeng, A. K. Verma, T. Warchol, B. Bhatia, T. Bowser, M. Grier, *US Pat. Appl.* Publ. US 2005124678 A1 20050609, (2005)
4. (a) B. B. Fredholm, A. P. Ijzerman, K. A. Jacobson, K. N. Klotz, and J. Linden, *Journal of Pharmacol Rev*, **53**, 527 (2001); (b) A. Samadi, J. Marco-Contelles, E. Soriano, M. Alvarez-Perez, M. Chioua, A. Romero, L. Gonzalez-Lafuente, L. Gandia, J. M. Roda, M. G. Lopez, M. Villarroya, A. G. Garcia & C. Rios, *Bioorganic&Medicinal Chemistry*, **18,** 5861(2010), https://doi.org/10.1016/j.bmc.2010.06.095; (c) X. Zhang, Y. Qiu, X Li, S. Bhattacharjee, M. Woods, P. Kraft, S. G. Lundeen, Z. Sui, *Bioorganic & Medicinal Chemistry*, **17**, 855(2009), https://doi.org/10.1016/j.bmc.2008.11.055; (d) M. W. Beukers, L. C. W. Chang, J. K. Kunzel, T. Mulder-Krieger, R. F. Span-jersberg, J. Brussee and A. P. Ijzerman, *Journal of Medicinal Chemistry*, **47,** 3707 (2004), https://doi.org/10.1021/jm049947s.
5. (a) A. D. Thomas and C. V. Asokan, *Journal of Chemical Society, Perkin Trans*, **1**, 2583 (2001), https://doi.org/10.1039/B105634B; (b) A. D. Thomas and C. V. Asokan, *Tetrahedron Letters*, **43**, 2273 (2002), https://doi.org/10.1016/S0040-4039(02)00174-0
6. (a) M. D. Fletcher, T. E. Hurst, T. J. Miles and J. Moody, *Tetrathedron*, **62**, 5454 (2006), https://doi.org/10.1016/j.tet.2006.03.051; (b) L. Meerpoel, G. Deroover, K. V. Aken, G. Lux and G. Hoornaert, *Synthesis*, **1991(9)**, 765 (1991), https://doi.org/10.1055/s-1991-26570
7. (a) M. M. Mc Cormick, H. A. Duong, G. Zuo and J. Louie, *Journal of American Chemical Society*, **127**, 5030(2005), https://doi.org/10.1021/ja0508931; (b) J. A. Varela, L. Castedo and C. Saa, *Journal of Organic Chemistry*, **68**, 8595(2003), https://doi.org/10.1021/jo035050b

8. (a) A. R. Renslo and R. L. Danheiser, *Journal of Organic Chemistry*, **63,** 7840(1998), https://doi.org/10.1021/jo026258k; (b) S. H. Mashraqui and M. A. Karnik, *Tetrahedron Letters*, **39**,4895(1998), https://doi.org/10.1016/S0040-4039(98)00889-2
9. (a) M. Komatsu, H. Ohgishi, S. Takamatsu, Y. Ohshiro and T. Agawa, *Angewandte Chemie International*, **21**, 213(1982), https://doi.org/10.1002/anie.198202131**;** (b) R. J. Vijin, H. J. Arts, R. Green R and A. M. Castelijns, *Synthesis,* **1994(5)**, 583 (1994), https://doi.org/10.1055/s-1994-25508
10. (a) S. Kambe and K. Saito, A. Sakurai, H. Midorikawa, *Synthesis*, **1981(7)**, 531,(1981), https://doi.org/10.1055/s-1981-29513; (b) S. Kambe, K. Saito, H. Kishi, T. Hayashi & A. Sakurai, *Synthesis*, **1977(12)**, 839 (1977), https://doi.org/10.1055/s-1977-24595
11. (a) E. R. Anabha, K. N. Nirmala, A. Thomas and C. V. Asokan, *Synthesis*, **2007(3)**, 428(2007) https://doi.org/10.1055/s-2006-958964; (b) E. R. Anabha and C. V. Asokan, *Synthesis*, **2006(1)**, 151(2006), https://doi.org/10.1055/s-2005-918491
12. B. C. Ranu, R. Jana and S. Sowmiah, *Journal of Organic Chemistry*, **72**, 3152(2007), https://doi.org/10.1021/jo070015g
13. M. L. Kantam, M. Koosam and S. Bhargava, *Journal of Chemical Sciences*, **122**, 63(2010), https://doi.org/10.1007/s12039-010-0007-x
14. (a) M. G. Fonseca, J. G. P. Espınola, S. F. Oliveira, A. G. Souza, C. Airoldi C, *Colloids and Surfaces* A, **133(3)**, 205(1998), https://doi.org/10.1016/S0927-7757(97)00198-2 ; (b) M. R. M. C. Santos, C. Airoldi, *The Journal of Colloid and Interface Science*, **183**,416(1996), https://doi.org/10.1006/jcis.1996.0564; (c) O. L. Casagrande, J. K. Tomita, A. E. Mauro, D, R. Vallet, *Polyhedron,* **15,** 4179 (1996), https://doi.org/10.1016/0277-5387(96)00174-X

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