DBU-Catalyzed Three-Component One-Pot Synthesis of Highly Functionalized Pyridines in Aqueous Ethanol

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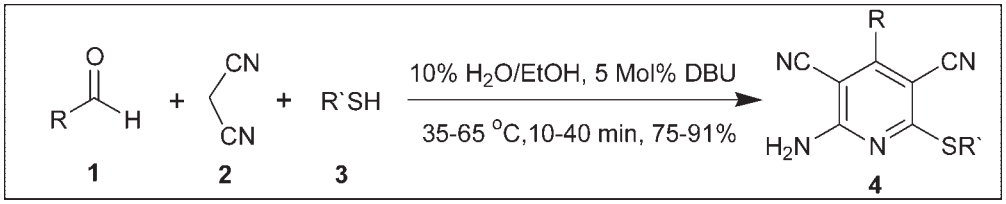

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) efficiently catalyzes three-component one-pot condensations of aldehyde, malononitrile, and thiophenol to produce highly functionalized pyridines in excellent yield in aqueous ethanol.

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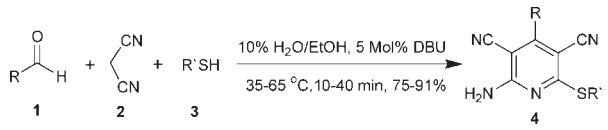
INTRODUCTION

The pyridine scaffold is a key constituent of a wide range of naturally occurring and synthetic bioactive compounds, pharmaceuticals, and functional materials [1–3]. Penta-substituted pyridines are known as medicinally privileged scaffold, inhibit MAPK-activated PK-2 [4] and modulate androgen receptor functions [5]. These compounds are also useful in the treatment of urinary incontinence [6], HBF infections [7], Creutzfeldt-Jacob disease [8], and Parkinson's disease, hypoxia/ischemia, asthma, kidney disease, epilepsy, cancer [9–11] and also exhibit antibacterial, anti-biofilm and anti-infective activities [12]. The importance of this class of compounds can be realized by the number of patents filed in the recent years [4–7,12]. Thus, synthesis of highly functionalized pyridine derivatives, with the aim to develop new drug molecules has been an active area of research [13–15]. Various synthetic protocols have been developed for the synthesis of pyridine-3,5-dicarbonitriles [16–25]. The most interesting synthetic methodology has been three-component condensation of aldehydes, malononitrile, and thiolphenols [17,26,27]. Various bases such as Et_3N, DABCO [17,26,27], and piperidine, morpholine, thiomorpholine, pyrrolidine, N,N-DIPEA, pyridine, 2,4,6-collidine, DMAP, aniline, *N*-methyl-aniline, *N*,*N*-dimethylaniline, and *N*,*N*-diethylaniline [27] have been used. However, the major drawback of these procedures is the formation of various side products [26], thus reducing the yield of the desired product to 20–48% [26,27]. It is important to mention here that Ranu *et al*. [28] have reported a better synthetic protocol for this reaction and immidazolium-based ionic liquid and ethanol have been used as reaction media. Although ionic liquids are considered to be green solvents as the risk of air pollution is significantly reduced due to their nonvolatile nature [29,30] but their toxicity, especially, immidazolium-based ionic liquids and cost has been a matter of concerns [31,32]. So, development of an improved synthetic protocol for the generation of pyridine-3,5-dicarbonitriles for lead optimization is of considerable interest. As a part of our ongoing effort towards the synthesis of biologically active compounds [33–35] and keeping the medicinal values of pyridine-3,5-dicarbonitriles in mind, we considered it necessary to develop an efficient high yielding synthetic protocol for the synthesis of this class of compounds.

RESULTS AND DISCUSSION

Careful literature analyses revealed that a variety of bases with pK_a ranges from 4 to 11 have been used for this multicomponent reaction. We speculated that use of neutral organic base that have high basicity, and can form a stable protonated species, may suppress the formation of enaminonitrile and other side products. 1,8-Diazabicyclo-[5.4.0]undec-7-ene (DBU) fulfills these requirements, and it has been used in many organic transformations in recent years. DBU is commercially available, cheap homogenous catalyst. It is a sterically hindered amidine base and especially useful where side reactions due to the inherent nucleophilicity of a basic nitrogen are a problem [36–40]. DBU is one of the strongest organic neutral base (pK_a = 12) and the +M effect of the adjacent nitrogen stabilizes the protonated species. Inspired with the catalytic potential of DBU, we examined the catalytic role of DBU in the synthesis of pyridine-3,5-dicarbonitriles *via* three component reaction of aldehydes, malononitriles, and thiols. The reaction of

Scheme 1



an aldehyde (**1**), malononitrile (**2**), and thiol (**3**) was carried out in the presence of catalytic amount of DBU (Scheme 1). We were pleased to observe that use of 5 mol % DBU as a catalyst in 10% aqueous ethanol significantly increases the rate of reaction and yield of the product at lower temperatures (Table 1). A wide range of substituted aromatic as well as heteroaromatic aldehydes underwent this three-component condensation with malononitrile and thiols to produce pyridine-3,5-dicarbonitriles (**4**) in high yield. The results are summarized in Table 1. All the utilized functionalities were found to be compatible under the reaction conditions.

For example, three-component reaction of benzaldehyde, malononitrile, and thiophenol lead to the formation of **4a** at 35°C in 15 min in 80% yield, while the same reaction takes 1.5 h to complete at reflux temperature in ethanol, and yield of the product was reported to be 35% when other bases were used [26]. Encouraged by this observation, a series of reactions were carried out under identical reaction conditions, and in all of the cases the product was isolated in very good yield (Table 1). However, reaction temperature was increased up to 65°C in some cases. A library of compounds was synthesized using 5 mol % DBU as base. The same reactions were also carried out in ethanol, but it was observed that the addition of 10% water in the reaction lead to increase in the yield to 8–10%. However, when ethanol-water (1:1) and water was used as a reaction media, no or very low yield was observed even at elevated temperature, due to the insolubility of the starting materials. We have also explored the possibility of using polyethylene glycol (PEG) as a reaction media, but no product formation was observed in PEG. This multicomponent reaction works well for unsubstituted (entry **4a**, **4q**, **4w**), electron poor (entry **4g**, **4h**), electron rich (entry **4b–4e**, **4i–4v**), and

Table 1

DBU catalyzed three-component synthesis of substituted pyridine-3,5-dicarbonitriles *via* Scheme 1.

Compd. No.	R	R′	Temp (°C)	Time (min)	Yield (%)	MP (°C) Found	MP (°C) Reported
4a	Ph	Ph	35	15	80	220–221	218 [26]
4b	4-Cl-Ph	Ph	35	15	87	223	222 [26]
4c	4-OMe-Ph	Ph	50	15	90	241–244	240 [27]
4d	4-OH-Ph	Ph	55	15	89	313	315 [17]
4e	3-Pyridinyl	Ph	50	25	85	<300	305–306 [26]
4f	1-Naphthyl	Ph	65	15	87	258–260	–
4g	3-NO_2-Ph	Ph	55	15	85	219–220	–
4h	2-NO_2-Ph	4-Me-Ph	50	20	83	290–291	–
4i	4-Cl-Ph	Ph	50	15	85	230–231	228–230 [28]
4j	2-Naphthyl	Ph	50	10	89	236	–
4k	4-F-Ph	Ph	50	20	88	248–249	250 [10]
4l	2-OH-Ph	Ph	50	15	88	265–266	–
4m	3-Me-Ph	Ph	55	20	89	278–280	280 [10]
4n	4-Br-Ph	Ph	35	20	90	255–257	–
4o	3-Me-Ph	4-Me-Ph	55	20	91	236	–
4p	4-Cl-Ph	4-Me-Ph	55	15	89	245–246	–
4q	Ph	4-Me-Ph	50	15	86	238	–
4r	4-Me-Ph	2-NH_2-Ph	55	30	80	208–210	207–208 [41]
4s	4-OMe-Ph	2-NH_2-Ph	55	35	85	232	235–236 [41]
4t	4-Cl-Ph	2-NH_2-Ph	60	30	80	233	239–240 [26]
4u	4-OH-Ph	2-NH_2-Ph	60	40	75	175	–
4v	1-Naphthyl	2-NH_2-Ph	55	25	88	220–222	–
4w	Ph		60	40	85	189	–
4x	4-Me-Ph		60	35	80	180–181	–
4y	4-Br-Ph		55	30	79	180–182	–
4z	1-Naphthyl		60	25	83	220–222	–
4aa	2-Naphthyl		60	25	85	248	–
4ab	4-OMe-Ph		60	40	85	198	–
4ac	4-Cl-Ph		55	30	85	193–195	–

heteroaromatic aldehydes (entry **4e**). However, aliphatic aldehydes either gave very poor yield or did not react.

According to the proposed mechanisms, the first step of this reaction is the formation of Knoevenagel product by the condensation of an aldehyde with malononitrile [26,27,41,42]. During this base-catalyzed three-component reaction, formation of many side products such as enaminonitrile, higher adducts, reduced products, and malononitrile self addition products have been noticed [26,41]. We believe that low reaction temperature, higher basicity, and stability of DBU-H^+ species generated in this reaction suppress the formation of these side products and, hence, yield of the product increases. It is important to mention here that use of DABCO has been shown to promote the reaction of hindered aldehydes, with marginal increase of yield of the product [26].

To assess the feasibility of the methodology on higher scale under identical reaction conditions, we carried out the reaction on a 50 gm scale (entry **4b**, **4g**) and it was observed that the reaction proceeded smoothly and the desired product was isolated in 87% and 85% yields, respectively. It is important to mention here that the reaction media can be reused for further reactions. For example, after completion of the reaction, the reaction mixture was cooled, and solid product was collected by filtration (entry 4b). To the filtrate, *p*-chlorobenzaldehyde, malononitrile, and thiophenol were added in the same molar ratio without additional load of DBU. The reaction mixture was stirred for specified time, marginal loss of the yield was observed in first three run (87%, 86%, and 83%), while in fourth and fifth run the yield dropped to 75% and 65%, respectively. Structures of all of the compounds were identified by their mp and spectral data.

CONCLUSION

In conclusion, we have developed a novel synthetic methodology for the synthesis of pyridine-3,5-dicarbonitriles using 5 mol % DBU as a catalyst and 10% aqueous ethanol as the reaction media through a three component condensation of aldehydes, malononitrile and thiols. The short reaction times, high yields, use of commercially inexpensive DBU as a catalyst, and reusability of the reaction media are the main advantages of this process.

EXPERIMENTAL

All of the chemicals used in the synthesis were purchased from Sigma-Aldrich and used as received. Thin-layer chromatography was used to monitor reaction progress. Compounds were purified either by crystallization or over silica gel column. Melting points were determined on a melting point apparatus and are uncorrected. IR (KBr) spectra were recorded using Perkin-Elmer FTIR spectrophotometer and the values are expressed as ν_{max} cm^{-1}. Mass spectral data were recorded on a waters micromass LCT Mass Spectrometer/Data system. The ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Spectrospin spectrometer at 300 MHz and 75.5 MHz, respectively using TMS as an internal standard. The chemical shift values are recorded on δ scale and the coupling constants (*J*) are in Hz. Elemental analysis were performed on a Carlo Erba Model EA-1108 elemental analyzer and data of C, H, and N is within ±0.4% of calculated values.

General procedure for the synthesis of substituted pyridines. To a stirred solution of substituted benzaldehyde (4.71 mmol) in 10% aqueous ethanol (5 mL), DBU (5 mol %) was added followed by dropwise addition of malononitrile (9.43 mmol) at room temperature. To this stirred mixture substituted thiols (4.71 mmol) was added dropwise. The reaction mixture was stirred at 35–65°C as specified in Table 1; reaction progress was monitored by TLC. The crude product was collected by filtration and was purified by crystallization or by SiO_2 column chromatography. Spectral data of all unknown compounds is given later.

2-Amino-4-(1-naphthyl)-6-phenylsulphanylpyridine-3,5-dicarbonitrile (4f). IR: 3437, 3327, 3217, 2219, 1626, 1552, 1462, 1377, 1270, 798, 776, 750, 721 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.53–7.62 (*m*, 5H), 7.66–7.68 (*m*, 5H), 7.91 (brs, 2H), 8.07–8.15 (*m*, 2H); HRMS calc. for $C_{23}H_{14}N_4S$: 378.0939, found: 378.0929; Anal. calc. for $C_{23}H_{14}N_4S$: C, 72.99; H, 3.73; N, 14.80; S, 8.47; found: C, 72.89; H, 3.66; N, 14.88; S, 8.42.

2-Amino-4-(3-nitrophenyl)-6-phenylsulphanylpyridine-3,5-dicarbonitrile (4g). IR: 3400, 3323, 3230, 2213, 1647, 1550, 1526, 1426, 1377, 1260, 1037, 805, 754 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.52–7.61 (*m*, 5H), 7.89–7.94 (*m*, 2H), 8.07 (*d*, $J = 6$ Hz, 1H), 8.45 (*d*, $J = 6$ Hz, 1H), 8.52 (brs, 2H); HRMS calc. for $C_{19}H_{11}N_5O_2S$: 373.0633, found: 373.0631; Anal. calc. for $C_{19}H_{11}N_5O_2S$: C, 61.12; H, 2.97; N, 18.76; S, 8.59; found: C, 61.18; H, 3.01; N, 18.69; S, 8.51.

2-Amino-4-(2-nitrophenyl)-6-(4-tolyl)sulphanylpyridine-3,5-dicarbonitrile (4h). IR: 3395, 3323, 3231, 2211, 1645, 1551, 1523, 1463, 1354, 1258, 1036, 813, 736 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.37 (s, 3H), 7.30 (*d*, $J = 8$ Hz, 2H), 7.50 (*d*, $J = 8$ Hz, 2H), 7.91–7.94 (*m*, 2H), 8.05 (*d*, $J = 6$ Hz, 1H), 8.43 (*d*, $J = 6$Hz, 1H), 8.52 (brs, 2H); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 87.15, 93.22, 114.78, 115.09, 123.36, 123.59, 125.13, 130.18, 130.65, 134.92, 135.21, 135.42, 139.66, 147.66, 156.26, 159.52, 166.64; HRMS calc. for $C_{20}H_{13}N_5O_2S$: 378.0790, found: 378.0799; Anal. calc. for $C_{20}H_{13}N_5O_2S$: C, 62.00; H, 3.38; N, 18.08; S, 8.28; found: C, 61.96; H, 3.42; N, 18.13; S, 8.20.

2-Amino-4-(2-naphthyl)-6-phenylsulphanylpyridine-3,5-dicarbonitrile (4j). IR: 3371, 2209, 1615, 1545, 1458, 1377, 1246, 815, 736 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.50–7.53 (*m*, 5H), 7.63–7.65 (*m*, 5H), 7.89 (brs, 2H), 8.06–8.18 (*m*, 2H); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 87.34, 93.63, 115.06, 115.38, 125.38, 127.03, 127.75, 128.41, 129.46, 129.67, 131.41, 132.25, 133.33, 134.82, 158.66, 159.68, 166.18; HRMS calc. for $C_{23}H_{14}N_4S$: 378.0939, found: 378.0935; Anal. calc. for $C_{23}H_{14}N_4S$: C, 72.99; H, 3.73; N, 14.80; S, 8.47; found: C, 72.93; H, 3.64; N, 14.85; S, 8.42.

2-Amino-4-(2-hydroxyphenyl)-6-phenylsulphanylpyridine-3,5-dicarbonitrile (4l). IR: 3422, 3338, 3208, 2183, 1639, 1614, 1579, 1545, 1460, 1404, 1377, 1263, 1193, 1046, 763, 749 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 6.95–7.15 (*m*,

6H), 7.33 (brs, 1H), 7.50–7.61 (*m*, 5H); HRMS calc. for $C_{19}H_{12}N_4OS$: 344.0732, found: 344.0738; Anal. calc. for $C_{19}H_{12}N_4OS$: C, 66.26; H, 3.51; N, 16.27; S, 9.31; found: C, 66.30; H, 3.55; N, 16.33; S, 9.40.

2-Amino-4-(4-bromophenyl)-6-phenylsulphanylpyridine-3,5-dicarbonitrile (4n). IR: 3441, 3336, 3220, 2219, 1629, 1555, 1529, 1459, 1378, 1312, 1257, 1022, 784, 758 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.52–7.60 (*m*, 5H), 7.80–7.82 (*m*, 4H), 7.88 (brs, 2H); Anal. calc. for $C_{19}H_{11}BrN_4S$: C, 56.03; H, 2.72; N, 13.76; S, 7.87; HRMS calc. for $C_{19}H_{11}BrN_4S$: 405.9888, found: 405.9885; found: C, 56.09; H, 2.78; N, 13.69; S, 7.81.

2-Amino-4-(3-tolyl)-6-(4-tolyl)sulphanylpyridine-3,5-dicarbonitrile (4o). IR: 3487, 3324, 3219, 2215, 1631, 1548, 1460, 1377, 1264, 1243, 1016, 801, 716 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.40 (*s*, 3H), 2.44 (*s*, 3H), 6.89 (brs, 2H), 7.25–7.30 (m, 4H), 7.33–7.36 (m, 1H), 7.40–7.45 (m, 3H); HRMS calc. for $C_{21}H_{16}N_4S$: 356.1096; found: 356.1099; Anal. calc. for $C_{21}H_{16}N_4S$: C, 70.76; H, 4.52; N, 15.72; S, 9.00; found: C, 70.80; H, 4.48; N, 15.77; S, 9.05.

2-Amino-4-(4-chlorophenyl)-6-(4-tolyl)sulphanylpyridine-3,5-dicarbonitrile (4p). IR: 3477, 3346, 3222, 2214, 1635, 1574, 1495, 1457, 1377, 1258, 1092, 836, 805, 795 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.37 (*s*, 3H), 7.30 (*d*, J = 8Hz, 2H), 7.48 (d, J = 8Hz, 2H), 7.58–7.68 (*m*, 4H), 7.83 (brs, 2H); HRMS calc. for $C_{20}H_{13}ClN_4S$: 376.0549, found: 376.0546; Anal. calc. for $C_{20}H_{13}ClN_4S$: C, 63.74; H, 3.48; N, 14.87; S, 8.51; found: C, 63.77; H, 3.51; N, 14.81; S, 8.4.

2-Amino-4-phenyl-6-(4-tolyl)sulphanylpyridine-3,5-dicarbonitrile (4q). IR: 3451, 3323, 3208, 2215, 1618, 1547, 1523, 1458, 1377, 1266, 1015, 897, 810, 755 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.37 (*s*, 3H), 7.30 (*d*, J = 8Hz, 2H), 7.47 (*d*, J = 8Hz, 2H), 7.54–7.56 (*m*, 5H), 7.80 (brs, 2H); HRMS calc. for $C_{20}H_{14}N_4S$: 342.0939; found: 342.0949; Anal. calc. for $C_{20}H_{14}N_4S$: C, 70.15; H, 4.12; N, 16.36; S, 9.36; found: C, 70.20; H, 4.08; N, 16.30; S, 9.30.

2-Amino-4-(4-hydroxyphenyl)-6-(2-aminophenyl)sulphanylpyridine-3,5-dicarbonitrile (4u). IR: 3317, 2197, 1638, 1610, 1542, 1508, 1456, 1410, 1247, 1170, 1023, 845, 760 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 5.50 (brs, 2H), 5.88 (brs, 1H), 6.40–6.46 (*m*, 2H), 6.79–6.86 (*m*, 4H), 7.28–7.31 (*m*, 2H), 7.69 (brs, 2H); HRMS calc. for $C_{19}H_{13}N_5OS$: 359.4056; found: 359.4146; Anal. calc. for $C_{19}H_{13}N_5OS$: C, 63.49; H, 3.65; N, 19.49; S, 8.92; found C, 63.51; H, 3.70; N, 19.41; S, 8.96.

2-Amino-4-(1-naphthyl)-6-(2-aminophenyl)sulphanylpy-ridine-3,5-dicarbonitrile (4v). IR: 3429, 3333, 3219, 2217, 1632, 1611, 1548, 1468, 1310, 1271, 1162, 1022, 996, 797 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 5.50 (brs, 2H), 6.58 (*t*, 1H), 6.81 (*d*, J = 8 Hz, 1H), 7.20 (*t*, 1H), 7.29 (*d*, J = 8 Hz, 1H), 7.55–7.69 (*m*, 4H), 7.77 (brs, 3H), 8.05–8.13 (*m*, 2H); HRMS calc. for $C_{23}H_{15}N_5S$: 393.4649; found: 393.4556; Anal. calc. for $C_{23}H_{15}N_5S$: C, 70.21; H, 3.84; N, 17.80; S, 8.15; found: C, 70.25; H, 3.88; N, 17.88; S, 8.11.

2-((Furan-2-yl)methylthio)-6-amino-4-phenylpyridine-3,5-dicaronitrile (4w). IR: 3470, 3325, 3215, 2210, 1625, 1540, 1419, 1243, 1150, 1010, 930, 780 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.59 (*s*, 2H), 6.40–6.56 (*m*, 2H), 7.54–7.60 (*m*, 6H), 8.16 (brs, 2H); HRMS calc. for $C_{18}H_{12}N_4OS$: 332.3802; found: 332.3781; Anal. calc. for $C_{18}H_{12}N_4OS$: C, 65.04; H, 3.64; N, 16.86; S, 9.65; found: C, 65.09; H, 3.57; N, 16.90; S, 9.69.

2-((Furan-2-yl)methylthio)-6-amino-4-(4-tolyl)pyridine-3,5-dicaronitrile (4x). IR: 3458, 3331, 3225, 2208, 1634, 1543, 1263, 1007, 769, 732 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.38 (*s*, 3H), 4.58 (*s*, 2H), 6.39–6.54 (*m*, 2H), 7.34–7.59 (*m*, 5H), 8.16 (brs, 2H); HRMS calc. for $C_{19}H_{14}N_4OS$: 346.4068; found: 346.4159; Anal. calc. for $C_{19}H_{14}N_4OS$: C, 65.88; H, 4.07; N, 16.17; S, 9.26; found: C, 65.82; H, 4.17; N, 16.21; S, 9.30.

2-((Furan-2-yl)methylthio)-6-amino-4-(4-bromophenyl)pyridine-3,5-dicaronitrile (4y). IR: 3407, 3337, 3245, 2216., 1629, 1573, 1527, 1487, 1373, 1294, 1133, 1090, 1016, 806, 743 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.11 (*s*, 2H), 7.29–7.33 (*m*, 3H), 7.50–7.65 (*m*, 4H), 7.99 (brs, 2H); HRMS calc. for $C_{18}H_{11}BrN_4OS$: 411.2763; found: 411.2753; Anal. calc. for $C_{18}H_{11}BrN_4OS$: C, 52.57; H, 2.70; N, 13.62; S, 7.80; found: C, 52.61; H, 2.71; N, 13.61; S, 7.89.

2-((Furan-2-yl)methylthio)-6-amino-4-(1-naphthyl)pyridine-3,5-dicaronitrile (4z). IR: 3475, 3328, 3220, 3053, 2993, 2214, 1630, 1547, 1503, 1419, 1269, 1245, 1211, 1155, 1040, 1010, 933, 825, 780, 733, 685 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.64 (*s*, 2H), 6.43–6.61 (*m*, 2H), 7.57–7.63 (*m*, 4H), 8.05–8.10 (*m*, 4H), 8.13 (brs, 2H); HRMS calc. for $C_{22}H_{14}N_4OS$: 382.4389; found: 382.4487; Anal. calc. for $C_{22}H_{14}N_4OS$: C, 69.09; H, 3.69; N, 14.65; S, 8.38; found: C, 69.10; H, 3.73; N, 14.61; S, 8.39.

2-((Furan-2-yl)methylthio)-6-amino-4-(2-naphthyl)pyridine-3,5-dicaronitrile (4aa). IR: 3475, 3328, 3220, 2214, 1630, 1547, 1461, 1419, 1269, 1245, 1211, 1155, 1040, 1010, 933, 860, 780, 733 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.60 (*s*, 2H), 6.40–6.56 (*m*, 2H), 7.61–7.63 (*m*, 4H), 8.00–8.09 (*m*, 4H), 8.12 (brs, 2H); Anal. calc. for $C_{22}H_{14}N_4OS$: C, 69.09; H, 3.69; N, 14.65; S, 8.38; found: C, 69.13; H, 3.79; N, 14.66; S, 8.32.

2-((Furan-2-yl)methylthio)-6-amino-4-(4-methoxyphenyl)-pyridine-3,5-dicaronitrile (4ab). IR: 3469, 3326, 3211, 2218, 1616, 1574, 1542, 1455, 1294, 1255, 1177, 1019, 839, 816, 749 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.83 (*s*, 3H), 4.58 (*s*, 2H), 6.40–6.55 (*m*, 2H), 7.09–7.11 (*m*, 2H), 7.48–7.60 (*m*, 3H), 8.12 (brs, 2H); HRMS calc. for $C_{19}H_{14}N_4O_2S$: 362.4062; found: 362.4162; Anal. calc. for $C_{19}H_{14}N_4O_2S$: C, 62.97; H, 3.89; N, 15.46; S, 8.85; found: C, 62.92; H, 3.93; N, 15.40; S, 8.79.

2-((Furan-2-yl)methylthio)-6-amino-4-(4-chlorophenyl)pyridine-3,5-dicaronitrile (4ac). IR: 3455, 3336, 3229, 2211, 1634, 1573, 1544, 1494, 1264, 1092, 929, 805, 742 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.58 (*s*, 2H), 6.39–6.55 (*m*, 2H), 7.56–7.66 (*m*, 5H), 8.20 (brs, 2H); HRMS calc. for $C_{18}H_{11}ClN_4OS$: 366.8250; found: 366.8151; Anal. calc. for $C_{18}H_{11}ClN_4OS$: C, 58.94; H, 3.02; N, 15.27; S, 8.74; found: C, 58.99; H, 3.03; N, 15.29; S, 8.78.

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