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One-step synthesis of 5,6-diaryl pyridine-2(1*H*)-thiones from isoflavones†

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Juanjuan Wang, Zunting Zhang,* Wenli Wang and Fangfang Liu

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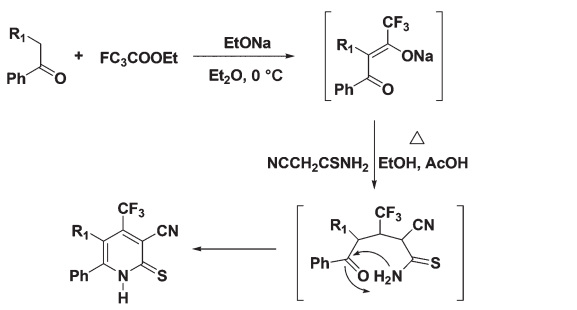
The one-step cyclocondensation of substituted isoflavones with cyanothioacetamide in the presence of sodium hydroxide gave an array of 3-cyano-5,6-diaryl pyridine-2(1*H*)-thiones in good yields. The procedure involves base-mediated ring opening of the isoflavones and subsequent Knoevenagel condensation between the 1,3-dicarbonyl intermediate generated from the isoflavones and cyanothioacetamide, followed by ring closure and dehydration.

Introduction

Pyridine-2(1*H*)-thiones are the principal core structures present in a variety of natural products and have acquired significance. Substituted pyridine-2(1*H*)-thiones are known for their antimicrobial,[1] antidepressant,[2] anticancer,[3] and antischizophrenic activities.[4,5] Palladium(II) complexes with pyridine-2(1*H*)-thiones and triphenylphosphine (PPh_3) were screened for antitumor, brine shrimps lethality bioassay and antibacterial effects activity. These complexes showed significant activities in most of the cases against the tested bacteria as compared to that of a standard drug. Their antitumor activity against prostate cancer cells (PC3) is comparable with doxorubicin, together with no cytotoxic effects in brine shrimps lethality bioassay study.[6] And pyridine-2(1*H*)-thiones can be used for synthesis of pyrido-thieno-pyrimidines. These analogs are potent and selective inhibitors of Cdc7/Dbf4 kinase *in vitro*. The representative compounds from these series can penetrate cultured cancer cells, inhibit MCM2 phosphorylation and show a moderate antiproliferative effect in cancer cells.[7] The most common synthetic route to pyridine-2-(1*H*)-thiones involve the cyclocondensation of α,β-unsaturated carbonyl or 1,3-dicarbonyl substrate such as malonaldehyde, β-carbonyl aldehyde, ethenyl aldehyde with cyanothioacetamide.[8,9] Another synthetic route to pyridine-2(1*H*)-thiones involves substitution reaction of 2-chloropyridine or 2-bromopyridine with sodium hydrosulfide at 160 °C in BuOH.[10,11] However, the preparation of 6-phenyl pyridine-2(1*H*)-thiones requires multistep synthesis and harsher reaction conditions (Scheme 1).[12]

It is known that the chromone fragment present in isoflavones can generate a 1,3-dicarbonyl equivalent in the presence of alkali, which readily reacts with amidines,[13] guanidine,[14] hydrazine,[15] to form the corresponding 2-substituted pyrimidines and diarylpyrazoles. Recently we have reported that 2-aminobenzimidazole,[16] triazole,[17] and 3-amino-5-hydroxypyrazole,[18] condensed with isoflavones yielding pyrimido[1,2-*a*]-benzimidazoles, triazolopyrimidines, pyrazolo[3,4-*b*]pyridines, respectively. These heterocyclic compounds are usually constructed by condensation of isoflavones with substrates containing two nitrogen atoms such as amidines, guanidines, hydrazines, aminoazoles among others. We now report a mild and efficient one-pot strategy for the synthesis of novel 5,6-diaryl pyridine-2(1*H*)-thiones involving the cyclocondensation reactions of isoflavones with an active methylene carbon atom and nitrogen, sulfur atoms of cyanothioacetamide. To the best of our knowledge there are no reports on the synthesis of 5,6-diaryl pyridine-2(1*H*)-thiones.

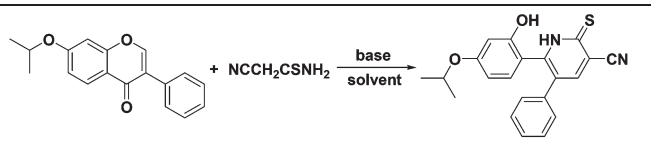


Scheme 1 Method for the synthesis of 3-cyano-6-phenyl pyridine-2(1*H*)-thiones.

Key Laboratory of the Ministry of Education for Medicinal Resources and Natural Pharmaceutical Chemistry, National Engineering Laboratory for Resource Development of Endangered Crude Drugs in Northwest of China, and School of Chemistry and Chemical Engineering, Shaanxi Normal University, Xi'an 710062, P. R. China. E-mail: zhangzt@snnu.edu.cn

†Electronic supplementary information (ESI) available: Copies of ^1H and ^{13}C NMR spectra of all compounds; crystal and structure refinement data for **3a**. CCDC 921360. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob27247h

Table 1 Optimization of cyclocondensation of isoflavone **1a** with cyanothioacetamide **2**[a]



1a 2 3a

Entry	Solvent[b]	Base	Molar ratios 1a : 2 : base	Yield 3a[c] (%)
1	EtOH	NaOH	1 : 1 : 1	35
2	CH_3CN	NaOH	1 : 1 : 1	12
3	DMF	NaOH	1 : 1 : 1	58[d]
4	DMSO	NaOH	1 : 1 : 1	55
5	DMF	KOH	1 : 1 : 1	49
6	DMF	K_2CO_3	1 : 1 : 1	Trace
7	DMF	*t*-BuOK	1 : 1 : 1	8
8	DMF	NaOH	1 : 1 : 3	63
9	DMF	NaOH	1 : 1 : 3.5	65[e]
10	DMF	NaOH	1 : 2 : 3.5	73[f]
11	DMF	NaOH	1 : 2 : 3.5	30[g]

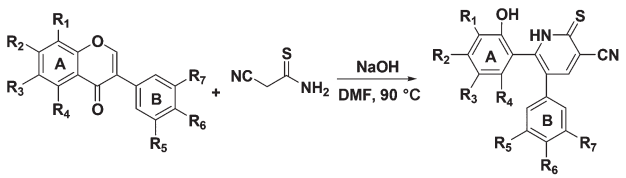
[a] All reactions were carried out on 1 mmol scale of **1a** in the indicated solvent (10 mL) until complete disappearance of **1a**. [b] Reactions at reflux in EtOH and CH_3CN, at 90 °C in DMF and DMSO. [c] Isolated yields. [d] Reactions at 80, 90, or 100 °C in DMF gave **3a** in 38, 58 and 52% yields, respectively. [e] Reactions with 1.5, 2.5, or 4 equiv. of NaOH gave **3a** in 58, 60 and 68% yields, respectively. [f] Reactions with 1.5 and 2.5 equiv. of **2** gave **3a** in 67 and 74% yields, respectively. [g] Reactions with 3.5 equiv. of 3.0 mol L^{-1} sodium hydroxide solution.

Results and discussion

Initially, the reaction between the commercially available 7-isopropoxyisoflavone **1a** and cyanothio-acetamide **2** was optimized by varying the bases and solvents. The reaction results are summarized in Table 1. DMF was the solvent of choice, although condensation in DMSO afforded **3a** in comparable yield (entries 1–4). Solid NaOH was found to be the most effective of the four bases examined for the preparation of pyridine-2(1*H*)-thione **3a** (entries 3, 5–7). Varying the molecular ratios of **1a**, **2**, and NaOH in DMF revealed that the condensation yield was improved to 68% by using 3.5 equiv. of NaOH (entry 9). The yield was further improved to 73% when a 100% excess of **2** was utilized (entry 10).

The optimized conditions were applied to the cyclocondensation of the substituted isoflavones **1a–u** with cyanothioacetamide **2** [**1–2**–NaOH (1 : 2 : 3.5)/DMF/5–7 h/90 °C]. A structurally divergent range of 3-cyano-5,6-diaryl pyridine-2(1*H*)-thiones **3a–u** were produced in good yields (39–81%, Table 2). The highest yields of the appropriate pyridine-2(1*H*)-thiones **3a–u** were obtained when a fluorine or bromine EWG was present on the ring A (76%–81%; entries 7, 9, 12 and 15). Yields were slightly lower when the substituents on the isoflavones **1a–u** had electron-donating character, especially when a hydroxyl group was present on the ring A (entries 3, 4 and 18). It seems

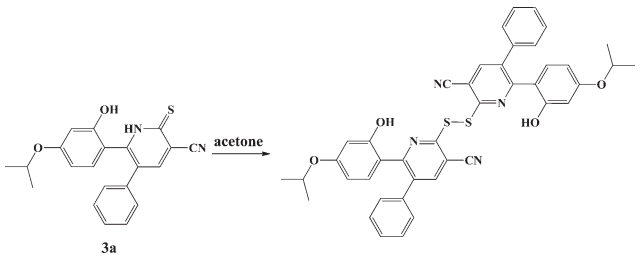
Table 2 Synthesis of 3-cyano-5,6-diaryl pyridine-2(1*H*)-thiones **3a–u** by the cyclocondensation of various isoflavones **1a–u** with cyanothioacetamide **2** in DMF[a]



1 2 3

Entry	Substrate	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Product	Time (h)	Yield[b] (%)
1	**1a**	H	i-OPr	H	H	H	H	H	**3a**	5	79
2	**1b**	H	OMe	H	H	H	OMe	H	**3b**	5.5	73
3	**1c**	H	OH	H	H	H	OMe	H	**3c**	6.5	52
4	**1d**	H	OMe	H	OH	H	OMe	H	**3d**	6.5	51
5	**1e**	H	OMe	H	Me	H	H	H	**3e**	5	76
6	**1f**	H	OMe	H	H	H	H	H	**3f**	5	78
7	**1g**	H	H	F	H	H	Me	H	**3g**	5.5	81
8	**1h**	H	H	H	H	H	Cl	H	**3h**	6	69
9	**1i**	H	H	Br	H	H	Me	H	**3i**	5.5	76
10	**1j**	H	i-OPr	H	H	H	Me	H	**3j**	5	70
11	**1k**	H	H	H	H	H	OMe	H	**3k**	5.5	68
12	**1l**	H	H	Br	H	H	H	H	**3l**	5	78
13	**1m**	Br	i-Opr	H	H	H	OMe	H	**3m**	5.5	76
14	**1n**	H	Obn	H	H	H	OH	H	**3n**	7	60
15	**1o**	H	F	H	H	H	H	H	**3o**	5	78
16	**1p**	H	OMe	OMe	OMe	H	OMe	H	**3p**	6.5	59
17	**1q**	H	OBn	H	H	H	OBn	H	**3q**	5.5	57
18	**1r**	H	OH	H	H	H	OH	H	**3r**	5.0	39
19	**1s**	H	H	H	H	H	Me	H	**3s**	5.0	60
20	**1t**	H	OMe	H	H	H	OH	H	**3t**	6.0	55
21	**1u**	H	H	H	H	H	H	H	**3u**	6.5	63

[a] All reactions were carried out on 1 mmol scale of **1a–u** [**1–2**–NaOH (1 : 2 : 3.5)] at 90 °C in DMF (10 mL) until the substrates **1a–u** had completely disappeared. [b] Isolated yields.



Scheme 2 Formation of the dimer **3a**.

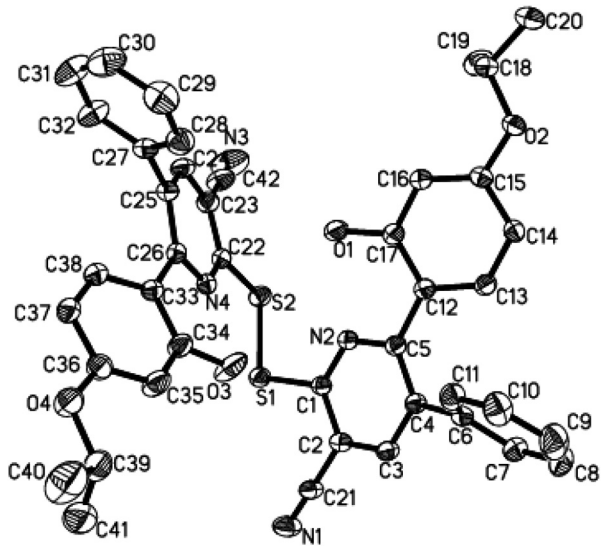
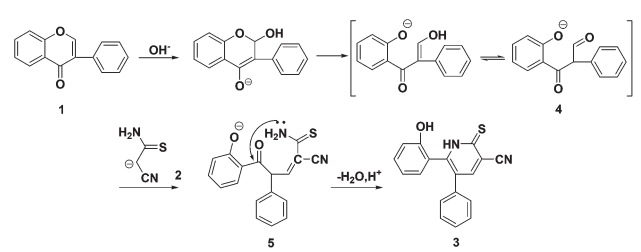


Fig. 1 X-ray crystal structure of **3a** dimer (crystallized from acetone).

plausible that phenolate ions generated under basic conditions from the hydroxyl group present in isoflavones might have a greater electron-donating ability of the hydroxyisoflavones than the corresponding alkoxy and benzoxyisoflavones, thereby affecting the mechanism (see Scheme 2, *vide infra*). The substituents on the ring B had a limited effect on the efficiency of the condensation reactions, although a methoxy substituent (EDG) consistently gave slightly lower yields. All products were characterized by ^{1}H, ^{13}C NMR and HRMS spectra. Single crystal X-ray diffraction analysis of **3a** unequivocally established the postulated structures (Fig. 1). The molecular structure is a dimer of **3a** and is linked by disulfide bonds. Acetone with an oxidizing agent can oxidize thiophenol into a disulfide bond dimer (Scheme 2).[19]



Scheme 3 Proposed mechanism for the formation of **3**.

A plausible mechanism for the formation of pyridine-2(1*H*)-thiones **3** is shown in Scheme 3. In brief, base-mediated ring opening of the isoflavones[20] should lead to the formation of the 1,3-dicarbonyl intermediate **4**. Knoevenagel condensation between aldehyde group in **4** and cyanothioacetamide **2** would generate **5**, and subsequent ring closure and dehydration yields substituted pyridine-2(1*H*)-thiones **3**.

Conclusion

In summary, we have developed a convenient one-pot procedure for the synthesis of substituted 3-cyano-5,6-diaryl pyridine-2(1*H*)-thiones under mild conditions in encouraging yields, through the condensation of the substituted isoflavones with cyanothioacetamide in the presence of NaOH in DMF. The procedure involves base-mediated ring opening of the isoflavones and subsequent Knoevenagel condensation between the 1,3-dicarbonyl intermediate generated from the isoflavones and cyanothioacetamide, followed by ring closure and dehydration.

Experimental procedures

General procedure for the synthesis of 3-cyano-5,6-diaryl pyridine-2(1*H*)-thiones (3a–u)

The corresponding isoflavone **1a–u** (1 mmol), cyanothioacetamide **2** (200 mg, 2 mmol), and solid NaOH (140 mg, 3.5 mmol) were reacted in DMF at 90 °C (10 mL) for 5–7 h. The progress of the reaction was monitored by TLC till the disappearance of **1a–u**. The reaction mixture was poured into water (40 mL) and acidified with 2% HCl/H_2O to the neutral pH. The precipitated yellow solid was filtered off and was purified on silica gel column ($CHCl_3$–MeOH, 100 : 1) to give the corresponding products **3a–u** as colorless amorphous powders.

3-Cyano-6-(2-hydroxy-4-isopropoxyphenyl)-5-phenylpyridine-2-(1*H*)-thione (3a). Mp 253–254 °C; ^{1}H NMR δ 1.21 (d, J = 5.4 Hz, 6H), 4.51 (septet, J = 5.7 Hz, 1H), 6.28 (t, J = 14.4, 7.9 Hz, 2H), 6.78 (d, J = 8.2 Hz, 1H), 7.08 (s, 2H), 7.19 (s, 3H), 8.18 (s, 1H), 10.00 (s, 1H), 12.50 (s, 1H); ^{1}H NMR (DMSO-d_6 + D_2O) δ 1.22 (d, J = 6.0 Hz, 6H), 4.49 (s septet, J = 6.0 Hz, 1H), 6.28 (s, 1H), 6.35 (m, 1H), 6.77 (d, J = 8.5 Hz, 1H), 7.07 (s, 2H), 7.19 (s, 3H), 8.17 (s, 1H); ^{13}C NMR (DMSO-d_6 + D_2O) δ 21.7, 69.2, 102.3, 104.9, 106.6, 115.3, 117.5, 127.6, 128.2, 131.8, 134.9, 137.8, 143.1, 154.7, 156.1, 158.8, 159.7; IR ν (cm^{-1}) 3224, 3081, 2967, 2223, 1621, 1574, 1403, 1260, 1109, 992, 694; HRMS m/z calcd for $[C_{21}H_{18}N_2O_2S + Na]^+$ 385.0987, found 385.0984.

3-Cyano-6-(2-hydroxy-4-methoxyphenyl)-5-(4-methoxyphenyl)-pyridine-2(1*H*)-thione (3b). Mp 221–222 °C; ^{1}H NMR δ 3.69 (s, 6H), 6.52–6.26 (m, 2H), 6.80 (dd, J = 20.1, 8.4 Hz, 3H), 6.98 (d, J = 8.4 Hz, 2H), 8.13 (s, 1H), 10.02 (s, 1H), 12.46 (s, 3H); ^{13}C NMR δ 55.0, 101.2, 104.8, 113.1, 113.5, 116.6, 118.9, 128.9, 129.8, 131.5, 145.0, 150.2, 156.4, 158.1, 159. 9, 161.5; IR ν (cm^{-1}) 3292, 2945, 2841, 2223, 1648, 1609, 1436, 1297,

1129, 957, 736; HRMS *m*/*z* calcd for $[C_{20}H_{16}N_2O_3S + Na]^+$ 387.0780, found 387.0778.

3-Cyano-6-(2,4-dihydroxylphenyl)-5-(4-methoxyphenyl)pyridine-2(1*H*)-thione (3c). Mp 273–274 °C; ^{1}H NMR δ 3.69 (s, 3H), 6.11 (d, J = 8.3 Hz, 1H), 6.28 (s, 1H), 6.68 (d, J = 8.3 Hz, 1H), 6.74 (d, J = 8.3 Hz, 2H), 6.98 (d, J = 8.3 Hz, 2H), 8.12 (s, 1H), 9.63 (s, 1H), 9.8 8 (s, 1H), 12.42 (s, 1H); ^{13}C NMR δ 55.0, 101.3, 104.5, 112.7, 116.9, 118.8, 126.7, 128.1, 12 8.8, 131.5, 137.2, 149.9, 150.1, 157.6, 160.3, 161.6; IR ν (cm^{-1}) 3274, 2989, 2225, 1676, 162 5, 1517, 1320, 1165, 1027, 983; HRMS *m*/*z* calcd for $[C_{19}H_{14}N_2O_3S + Na]^+$ 373.0623, found 373.0619.

3-Cyano-6-(4-methoxy-2,6-dihydroxyphenyl)-5-(4-methoxyphenyl)pyridine-2(1*H*)-thione (3d). Mp 327–328 °C; ^{1}H NMR δ 3.61 (s, 3H), 3.68 (s, 3H), 5.84 (s, 2H), 6.76 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 8.11 (s, 1H), 9.63 (s, 2H), 12.39 (s, 1H); ^{13}C NMR δ 55.0, 92.3, 101.2, 102.1, 113.3, 114.2, 116.8, 120.2, 129.1, 147.1, 149.8, 156.7, 158.1, 160.2, 161.5; IR ν (cm^{-1}) 3295, 3184, 2843, 2224, 1643, 1563, 1267, 1109, 982, 843; HRMS *m*/*z* calcd for $[C_{20}H_{16}N_2O_4S + Na]^+$ 403.0729, found 403.0728.

3-Cyano-6-(4-methoxy-6-methyl-2-hydroxyphenyl)-5-phenylpyridine-2(1*H*)-thione (3e). Mp 268–269 °C; ^{1}H NMR δ 1.81 (s, 3H), 3.67 (s, 3H), 6.18 (s, 1H), 6.25 (s, 1H), 7.11 (s, 2H), 7.29 (s, 3H), 8.23 (s, 1H), 9.88 (s, 1H), 12.57 (s, 1H); ^{13}C NMR δ 19.8, 55.5, 99.0, 102.5, 106.5, 113.7, 117.0, 120.3, 127.5, 128.5, 136.8, 138.1, 149.3, 150.6, 156.9, 160.7, 161.3; IR ν (cm^{-1}) 3436, 3073, 2996, 2228, 1652, 1606, 1257, 1176, 1029, 945, 868; HRMS *m*/*z* calcd for $[C_{20}H_{16}N_2O_2S + Na]^+$ 371.0830, found 371.0828.

3-Cyano-6-(2-hydroxy-4-methoxyphenyl)-5-phenylpyridine-2-(1*H*)-thione (3f). Mp 214–215 °C; ^{1}H NMR δ 3.71 (s, 3H), 6.13 (d, J = 8.2 Hz, 1H), 6.29 (s, 1H), 7.13–6.60 (m, 4H), 7.00 (d, J = 8.4 Hz, 2H), 8.13 (s, 1H), 9.63 (s, 1H), 12.43 (s, 1H); ^{13}C NMR δ 54.9, 100.9, 102.6, 106.6, 111.4, 113.5, 116.7, 118.8, 129.1, 129.8, 131.4, 149.5, 150.2, 156.3, 158.0, 159.9; IR ν (cm^{-1}) 3298, 3136, 2887, 2229, 1650, 1608, 1291, 1172, 1028, 981, 864; HRMS *m*/*z* calcd for $[C_{19}H_{14}N_2O_2S + Na]^+$ 357.0674, found 354.0673.

3-Cyano-6-(5-fluoro-2-hydroxylphenyl)-5-(4-methylphenyl)-pyridine-2(1*H*)-thione (3g). Mp 275–276 °C; ^{1}H NMR δ 2.22 (s, 3H), 6.77–7.04 (m, 7H), 8.20 (s, 1H), 10.20 (s, 1H), 12.40 (s, 1H); ^{13}C NMR δ 21.1, 102.7, 116.9, 117.2, 117.4, 118.0, 118.3, 119.7, 121.4, 129.2, 133.6, 136.8, 148.0, 150.8, 152.0, 153.4, 156.5, 160.3; IR ν (cm^{-1}) 3230, 3029, 2854, 2222, 1650, 1607, 1215, 1197, 1030, 918, 875; HRMS *m*/*z* calcd for $[C_{19}H_{13}FN_2OS + Na]^+$ 359.0631, found 359.0626.

3-Cyano-6-(2-hydroxylphenyl)-5-(4-chlorophenyl)pyridine-2(1*H*)-thione (3h). Mp 300–304 °C; ^{1}H NMR δ 6.75 (t, J = 7.2 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 7.00 (d, J = 7.2 Hz, 1H), 7.10 (d, J = 8.0 Hz, 2H), 7.23 (t, J = 7.9 Hz, 3H), 8.18 (s, 1H), 11.14 (s, 2H); ^{13}C NMR δ 102.4, 116.3, 116.9, 118.4, 119.3, 120.4, 128.5, 130.9, 131.0, 131.9, 132.2, 135.9, 149.9, 150.6, 155.4, 160.4; IR ν (cm^{-1}) 3268, 3092, 2889, 2226, 1647, 1604, 1273, 1150, 1090, 951, 860; HRMS *m*/*z* calcd for $[C_{19}H_{13}FN_2OS + Na]^+$ 361.0179, found 361.0176.

3-Cyano-6-(5-bromo-2-hydroxylphenyl)-5-(4-methylphenyl)-pyridine-2(1*H*)-thione (3i). Mp 302–303 °C; ^{1}H NMR δ 2.25 (s, 3H), 6.79 (d, J = 8.6 Hz, 1H), 7.03 (m, 4H), 7.20 (s, 1H), 7.34 (d, J = 6.8 Hz, 1H), 8.12 (s, 1H), 11.29 (s, 2H); ^{13}C NMR δ 21.1, 102.8, 109.8, 116.9, 118.4, 119.8, 122.9, 128.9, 129.2, 133.2, 133.7, 134.1, 136.8, 147.8, 150.8, 154.9, 160.3; IR ν (cm^{-1}) 3290, 3089, 2908, 2226, 1649, 1600, 1283, 1183, 1083, 985, 859; HRMS *m*/*z* calcd for $[C_{19}H_{13}FN_2OS + Na]^+$ 418.9830, found 418.9825.

3-Cyano-6-(2-hydroxy-4-isopropoxyphenyl)-5-(4-methylphenyl)-pyridine-2(1*H*)-thione (3j). Mp 264–265 °C; ^{1}H NMR δ 1.26 (s, 6H), 2.24 (s, 3H), 4.58–4.45 (m, 1H), 6.29 (d, J = 8.4 Hz, 1H), 6.37 (s, 1H), 6.82 (d, J = 8.3 Hz, 1H), 7.00 (d, J = 2.9 Hz, 4H), 8.08 (s, 1H), 11.55 (s, 2H); ^{13}C NMR δ 21.1, 22.2, 69.7, 103.1, 106.6, 113.1, 117.1, 129.0, 129.1, 132.0, 134.3, 136.4, 137.6, 149.6, 150.7, 156.9, 160.2, 160.4; IR ν (cm^{-1}) 3275, 2979, 2228, 1656, 1612, 1296, 1121, 994, 948, 858; HRMS *m*/*z* calcd for $[C_{22}H_{20}N_2O_2S + Na]^+$ 399.1143, found 399.1143.

3-Cyano-6-(2-hydroxyphenyl)-5-(4-methoxyphenyl)pyridine-2(1*H*)-thione (3k). Mp 254–255 °C; ^{1}H NMR δ 3.70 (s, 3H), 6.80–6.69 (m, 3H), 6.85 (d, J = 8.1 Hz, 1H), 6.99 (dd, J = 17.7, 8.0 Hz, 3H), 7.20 (t, J = 7.1 Hz, 1H), 8.12 (s, 1H), 11.07 (s, 2H); ^{13}C NMR δ 55.5, 102.2, 113.9, 116.2, 117.1, 119.1, 120.7, 129.0, 130.3, 130.9, 131.6, 149.4, 150.9, 155.5, 158.6, 160.3; IR ν (cm^{-1}) 3268, 2956, 2227, 1655, 1609, 1297, 1150, 1081, 990, 861; HRMS *m*/*z* calcd for $[C_{19}H_{14}N_2O_2S + Na]^+$ 357.0674, found 357.0669.

3-Cyano-6-(5-bromo-2-hydroxylphenyl)-5-phenylpyridine-2(1*H*)-thione (3l). Mp 300–304 °C; ^{1}H NMR δ 6.79 (d, J = 8.6 Hz, 1H), 7.52–7.05 (m, 7H), 8.17 (s, 1H), 11.34 (s, 2H); ^{13}C NMR δ 102.8, 109.8, 116.9, 118.3, 119.8, 122.8, 127.6, 128.6, 129.2, 133.2, 134.2, 136.6, 150.7, 155.0, 160.3; IR ν (cm^{-1}) 3299, 3066, 2909, 2230, 1662, 1558, 1278, 1081, 989, 861; HRMS *m*/*z* calcd for $[C_{18}H_{11}BrN_2OS + Na]^+$ 404.9673, found 404.9670.

3-Cyano-6-(3-bromo-2-hydroxy-4-isopropoxyphenyl)-5-phenylpyridine-2(1*H*)-thione (3m). Mp 267–268 °C; ^{1}H NMR δ 1.22 (s, 6H), 4.55–4.22 (m, 1H), 6.31 (s, 1H), 6.89 (s, 1H), 7.27 (d, J = 21.2 Hz, 5H), 8.27 (s, 1H), 9.72 (s, 1H), 12.58 (s, 1H); ^{13}C NMR δ 22.0, 71.6, 101.2, 102.7, 105.1, 115.8, 119.6, 128.2, 128.7, 134.6, 135.4, 138.1, 143.9, 151.9, 154.5, 155.8, 157.5; IR ν (cm^{-1}) 3245, 3128, 2887, 2227, 1615, 1575, 1265, 1132, 1069, 954, 865; HRMS *m*/*z* calcd for $[C_{21}H_{17}BrN_2O_2S + Na]^+$ 463.0092, found 463.0089.

3-Cyano-6-(4-benzyloxy-2-hydroxylphenyl)-5-(4-hydroxyphenyl)-pyridine-2(1*H*)-thione (3n). Mp 266–267 °C; ^{1}H NMR δ 5.03 (s, 2H), 6.44–6.38 (m, 2H), 6.57 (d, J = 8.2, 2H), 6.88–6.80 (m, 3H), 7.41–7.33 (m, 5H), 8.11 (s, 1H), 9.39 (s, 1H), 9.98 (s, 1 H), 12.54 (s, 1H); ^{13}C NMR δ 69.1, 101.2, 102.0, 105.5, 113.3, 114.9, 116.7, 119.3, 127.2, 127.9, 128.4, 129.8, 131.5, 136.8, 148.8, 150.3, 156.2, 156.3, 159.8, 160.4; IR ν (cm^{-1}) 3291, 3098, 2890, 2222, 1647, 1619, 1373, 1150, 1070, 954, 862; HRMS *m*/*z* calcd for $[C_{25}H_{18}N_2O_3S + Na]^+$ 449.0936, found 449.0933.

3-Cyano-6-(5-fluoro-2-hydroxylphenyl)-5-phenylpyridine-2(1*H*)-thione (3o). Mp 266–267 °C; ^{1}H NMR δ 6.78–7.22 (m, 8H), 8.24 (s, 1H), 9.93 (s, 1H), 12.71 (s, 1H); ^{13}C NMR δ 116.8, 117.1, 117.2, 117.3, 117.4, 118.0, 118.2, 127.5, 128.5, 129.1, 136.5, 150.6, 152.0, 153.4, 156.4, 160.1; IR ν (cm^{-1}) 3289, 3143, 2913, 2220, 1645, 1606, 1296, 1170, 1131, 991, 843; HRMS *m*/*z* calcd for $[C_{18}H_{11}FN_2OS + Na]^+$ 345.0474, found 345.0469.

3-Cyano-6-(4,5,6-trimethoxy-2-hydroxyphenyl)-5-(4-methoxyphenyl)pyridine-2(1*H*)-thione (3p). Mp 279–281 °C; ^{1}H NMR δ 3.35–3.73 (m, 12H), 6.22 (s, 1H), 6.77 (s, 2H), 7.06 (s, 2H), 8.18 (s, 1H), 9.74 (s, 1H), 12.54 (s, 1H); ^{13}C NMR δ 55.5, 56.0, 60.9, 95.6, 102.2, 107.1, 113.9, 117.1, 120.5, 129.8, 134.2, 146.5, 150.4, 151.9, 155.4, 158.8, 160.4; IR ν (cm^{-1}) 3436, 3079, 2901, 2224, 1665, 1610, 1253, 1106, 1090, 995, 885; HRMS *m*/*z* calcd for $[C_{22}H_{20}N_2O_5S + Na]^+$ 447.0991, found 447.0889.

3-Cyano-6-(4-benzyloxy-2-hydroxylphenyl)-5-(4-benzyloxyphenyl)-pyridine-2(1*H*)-thione (3q). Mp 268–270 °C; ^{1}H NMR δ 5.04 (s, 4H), 6.43 (s, 2H), 6.84 (s, 2H), 6.99 (s, 3H), 7.40 (s, 10H), 8.15 (s, 1H), 9.99 (s, 1H), 12.48 (s, 1H); ^{13}C NMR δ 69.6, 102.5, 106.0, 114.7, 117.1, 128.3, 128.9, 130.3, 132.0, 137.3, 150.7, 156.8, 157.7, 160.3, 161.1; IR ν (cm^{-1}) 3299, 3108, 2877, 2229, 1656, 1614, 1265, 1170, 979, 858; HRMS *m*/*z* calcd for $[C_{31}H_{22}N_2O_3S + Na]^+$ 525.1249, found 525.1249.

3-Cyano-6-(2,4-dihydroxylphenyl)-5-(4-hydroxyphenyl)pyridine-2(1*H*)-thione (3r). Mp 280–282 °C; ^{1}H NMR δ 6.13 (d, J = 8.3 Hz, 1H), 6.29 (s, 1H), 6.60 (d, J = 8.3 Hz, 2H), 6.67 (d, J = 8.3 Hz, 1H), 6.85 (d, J = 8.3 Hz, 2H), 8.10 (s, 1H), 9.38 (s, 1H), 9.62 (s, 1H), 12.38 (s, 1H); ^{13}C NMR δ 102.5, 106.5, 111.5, 114.9, 116.7, 119.1, 127.3, 129.8, 131.4, 149.3, 150.1, 156.1, 159.9; IR ν (cm^{-1}) 3209, 2999, 2223, 1645, 1613, 1512, 1195, 1078, 943, 828; HRMS *m*/*z* calcd for $[C_{18}H_{12}N_2O_3S + Na]^+$ 359.0467, found 359.0466.

3-Cyano-6-(2-hydroxylphenyl)-5-(4-methylphenyl)pyridine-2-(1*H*)-thione (3s). Mp 280–282 °C; ^{1}H NMR δ 2.22 (s, 3H), 7.23–6.82 (m, 8H), 8.24 (s, 1H), 10.16 (s, 1H), 12.55 (s, 1H); ^{13}C NMR δ 20.6, 102.3, 116.3, 116.7, 116.9, 117.5, 117.8, 127.1, 128.0, 128.5, 128.7, 136.3, 150.2, 151.5, 153.0, 156.1, 159.8; IR ν (cm^{-1}) 3259, 2899, 2225, 1647, 1605, 1209, 1143, 946, 856; HRMS *m*/*z* calcd for $[C_{19}H_{14}N_2OS + Na]^+$ 341.0725, found 341.0720.

3-Cyano-6-(4-methoxy-2-hydroxyphenyl)-5-(4-hydroxyphenyl)-pyridine-2(1*H*)-thione (3t). Mp 262–264 °C; ^{1}H NMR δ 3.71 (s, 3H), 6.50–5.99 (m, 2H), 6.75 (dd, J = 23.2, 8.4 Hz, 3H), 7.00 (d, J = 8.4 Hz, 2H), 8.13 (s, 1H), 9.63 (s, 2H), 12.43 (s, 1H); ^{13}C NMR δ 54.9, 100.9, 102.6, 106.6, 111.4, 113.5, 116.7, 118.7, 129.1, 129.8, 131.4, 149.5, 150.2, 156.3, 158.0, 159.9; IR ν (cm^{-1}) 3424, 3265, 2946, 2223, 1645, 1603, 1532, 1209, 1038, 932, 886; HRMS *m*/*z* calcd for $[C_{19}H_{14}N_2O_3S + Na]^+$ 373.0623, found 373.0620.

3-Cyano-6-(2-hydroxylphenyl)-5-phenylpyridine-2(1*H*)-thione (3u). Mp 287–288 °C; ^{1}H NMR δ 6.70–7.18 (m, 9H), 8.23 (s, 1H), 10.03 (s, 1H), 12.70 (s, 1H); ^{13}C NMR δ 116.1, 117.0, 119.1, 127.3, 128.7, 129.2, 131.1, 131.6, 136.9, 151.2, 155.6, 160.3; IR ν (cm^{-1}) 3237, 3012, 2826, 2223, 1635, 1586, 1204, 1116, 950, 856; HRMS *m*/*z* calcd for $[C_{18}H_{12}N_2OS + Na]^+$ 327.0568, found 327.0565.

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