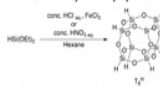


Environmentally friendly synthesis



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To cite this article: Alireza Allahi & Batool Akhlaghinia (2021) WEB (water extract of banana): An efficient natural base for one-pot multi-component synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines, *Phosphorus, Sulfur, and Silicon and the Related Elements*, 196:3, 328-336, DOI: [10.1080/10426507.2020.1835905](https://doi.org/10.1080/10426507.2020.1835905)

To link to this article: <https://doi.org/10.1080/10426507.2020.1835905>



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WEB (water extract of banana): An efficient natural base for one-pot multi-component synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines

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ABSTRACT

One-pot multi-component synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines derivatives using WEB (water extract of banana peels ash) as a green catalyst is described. A variety of aromatic aldehydes (with electron-donating and electron-withdrawing groups) in conjunction with aromatic and aliphatic thiols are known to tolerate this reaction condition using WEB. The reaction has simple work up procedure without using toxic solvents.

GRAPHICAL ABSTRACT



ARTICLE HISTORY

Received 27 July 2020
Accepted 8 October 2020

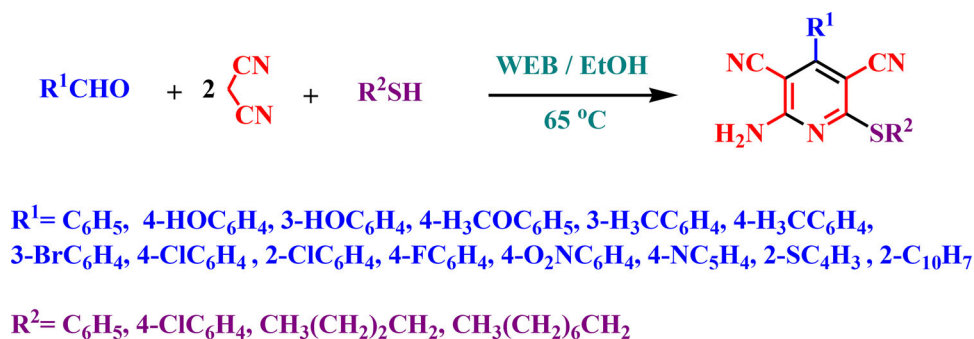
KEYWORDS

2-amino-3,5-dicarbonitrile-6-thio-pyridines; aldehydes; malononitrile; one-pot multi-component reaction; thiophenol; WEB (Water Extract of Banana)

Introduction

Among the nitrogen containing heterocycles, the pyridine nucleus as a key structural subunit in a range of bioactive compounds, both naturally occurring and synthetic is of considerable interest.^[1] Substituted pyridine derivatives particularly 2-amino-3,5-dicarbonitrile-6-thio-pyridines, are among the most promising candidates for demonstrating biological activity, and are also considered as medicinally 'privileged scaffold'^[2] for developing pharmaceutical agents due to their potential therapeutic applications.^[2–11] These pyridine skeletons were reported to inhibit PrP^{Sc} accumulation in scrapie-infected mouse neuroblastoma cells (ScN2a),^[8] MAPK-activated PK-2,^[3] IKK-2 for treating HBV infection,^[4] and modulate androgen receptor function.^[5] Additionally, these compounds are often used as

anti-prion,^[2,7,8] anti-hepatitis B virus,^[4] anti-bacterial,^[9] and anti-cancer^[3] agents and as potassium channel openers for the treatment of urinary incontinence.^[6] Also, the importance of this class of compounds can be recognized as potential targets for the development of new drugs for the treatment of Parkinson's disease, hypoxia, asthma, kidney disease, epilepsy, cancer,^[10] and Creutzfeldt-Jacob disease.^[7,8,11] Therefore, with the aim of developing new drug molecules, the synthesis or structure modifications of highly functionalized pyridine derivatives have attracted huge attention from both synthetic and medicinal chemists.^[10] Recently several scientists have used the multi-component reaction (MCR) strategy as one of the most prominent existing procedure to synthesize 2-amino-3,5-dicarbonitrile-6-thio-pyridines via the cyclocondensation of aldehyde,



Scheme 1. Synthesis of structurally different 2-amino-3,5-dicarbonitrile-6-thio-pyridines using WEB.

malononitrile and thiol. Much attention has been paid to one-pot multicomponent reactions particularly for the development of the library heterocyclic compounds^[12–17] due to atom economy, green conditions, procedural simplicity, and cost-effectiveness over conventional multistep synthesis. Various synthetic methods with their own merits and demerits have been developed for the construction of these compounds following this route with intervention of different basic (KOH,^[18] K₂CO₃,^[19,20] DBU,^[21] Na₂SiO₃,^[22] TBAB/Cs₂CO₃,^[23] MgO,^[24] Et₃N,^[25] DABCO,^[25] ZrOCl₂/NaNH₂,^[26] piperidine,^[11] silica-bonded *N*-propyldiethylenetriamine,^[27] TBAF,^[28] CH₃COONa,^[29] 2-HEAA,^[30] KF/Al₂O₃,^[31] molecular sieves 4 Å,^[32] [bmIm]OH,^[33] [bmim][Br],^[34] CaO NPs^[35] as well as acidic catalysts (γ-Fe₂O₃-2-HEAS,^[36] Sc(OTf)₃,^[37] silica NPs,^[38] CuI NPs,^[39] boric acid,^[40] Zn(II) and Cd(II) MOFs,^[41] phosphotungstic acid/CTAB,^[42] ZnCl₂,^[43] *o*-iodoxybenzoic acid^[44]).

Nevertheless, some of the previously reported methods suffer from one or more drawbacks such as using toxic or expensive catalyst and reagent^[21,23] and exotic reaction conditions (use of microwave irradiation or an ionic liquid).^[29,33,34] Therefore, continuing interest in developing an environmentally safer, green and practical synthetic route using a readily available and inexpensive catalyst for the synthesis of the pyridine derivatives has remained a significant challenge. With respect to the role of green chemistry to reduce or eliminate the use or generation of hazardous substances, significant awareness has been increased to using natural feedstocks as available, nontoxic, and metal-free reagents in greener catalytic processes under mild and convenient reaction conditions.^[45–51]

In the past few years, Sonogashira and Suzuki-Miyaura cross-coupling reactions have been reported using Pd(OAc)₂ and 'Water Extract of Banana' (WEB).^[52,53] Moreover, greener Dakin oxidation under metal catalyst, base and solvent free reaction conditions has been performed employing H₂O₂-WEB system.^[54]

Based on the previous reports^[52–54] and in continuation of our recent studies,^[55–84] with the aim of reducing the environmental impacts, this is the first report for the one-pot multicomponent synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines employing WEB as a natural feedstock without the help of any toxic reagent, external base, transition metal catalyst, external additives, and organic solvent (Scheme 1). In this study, the water extract of banana has been prepared by an aqueous extract of banana peels. It is

believed that various chemical processes could be catalyzed using banana peels (WEB) (based on their basic behavior upon the presence of sodium carbonate and potassium carbonate), which supplied long-term economic and environmental impacts in the near future.

Results and discussion

From the economic and environmental points of view, the use of an inexpensive and environmentally friendly natural feedstock extract without purification or characterization is very appealing and has been an active area of research. In this research, a one-pot multi component reaction of aldehydes, malononitrile and thiols was conducted using WEB as internal base to produce 2-amino-3,5-dicarbonitrile-6-thio-pyridines. In search for the best experimental reaction conditions, benzaldehyde (0.25 mmol), malonitrile (0.5 mmol) and thiophenol (0.25 mmol) in refluxing EtOH were adopted as the model substrates for investigating the multi-component synthesis of 2-amino-3,5-dicarbonitrile-4-phenyl-6-(phenylthio)pyridine using WEB under different reaction conditions. The results of the optimizations are summarized in Table 1. It was found that in the absence of WEB, only Knoevenagel adduct (I) (see Scheme 2) was obtained alongside a trace amount of product after 24 h (Table 1, entry 1). But when the reaction was conducted in the presence of WEB (0.5 mL) the reaction was completed (yielding 90%) in 20 min (Table 1, entry 2). Increasing the amount of WEB up to 1 mL afforded the desired product as the same as using 0.5 mL of WEB (Table 1, entry 3), but lower amount of WEB (0.4 mL) produced 2-amino-3,5-dicarbonitrile-4-phenyl-6-(phenylthio)pyridine in a lower yield (80%) even after 60 min (Table 1, entry 4). To verify the effect of temperature, by applying 0.5 and 0.4 mL of WEB, in two separate flasks the model reaction was performed at 65 °C (Table 1, entries 5–6). It was evident from Table 1 that using 0.4 mL of WEB at 65 °C afforded lower yield of the desired product. Additionally, the effect of other temperatures (55 and 60 °C) was also screened on the model reaction (Table 1, entries 7–8). It was found that the reaction prolonged with very poor yields at 55 and 60 °C. Based on the obtained results, reaction proceeds smoothly toward completion in excellent yield (90%) using 0.5 mL of WEB at 65 °C. After finalizing the amount of catalyst and temperature for this reaction, the next target was to choose proper

solvent. Various solvents like CH₃CN, CH₃OH, THF, CHCl₃ and toluene have been tested and compared their results with EtOH mediated reaction (Table 1, entries 10–14). Prior to using solvents, the reaction was examined under neat conditions, but reaction failed to afford more than 60% yield in 60 min (Table 1, entry 9). Comparatively, in all tested solvents, reaction was carried out but afforded lower yields. Reaction in CH₃CN proceeded smoothly in agreement with EtOH, but because of safety and economic considerations, EtOH was chosen for further experiments. The toxicity and the hazardous nature of CH₃CN confined its use for this one-pot multi component reaction.



After optimization the reaction conditions, we turned our attention to investigate the scope and general applicability of this methodology by carrying out the one-pot multi component reaction of variety of electronically divergent aldehydes with respect to thiols using WEB (Table 2). As is evident from the results shown in Table 2, aryl aldehydes as well as heteroaryl aldehydes (pyridine-4-carbaldehyde and thiophene-2-carbaldehyde) were found to be highly compatible with the optimized reaction conditions and gave the desired products in excellent yields (Table 2, entries 12–13). A variety of electron-donating or electron-withdrawing groups, such as OH, OMe, CH₃, Br, Cl, F and NO₂ groups were used to obtain the corresponding products with excellent yield.^[24,26] The results shown that, aromatic aldehydes bearing electron-donating or electron-withdrawing groups condensed with malononitrile and thiols very smoothly and produced the corresponding 2-amino-3,5-dicyano-6-thio-pyridines in short reaction times (Table 2, entries 7–11 vs entries 2–6).

Surprisingly it was found that 2-naphthaldehyde, as a bulky aldehyde, was suitable to obtain the corresponding pyridine derivative in the present one-pot multicomponent reaction (Table 2, entry 14). Thereafter, various thiols were tested under the optimized reaction conditions. As given in Table 2, both aromatic and aliphatic thiols can undergo the

Table 1. Reaction condition optimizations for preparation of 2-amino-3,5-dicyanonitrile-4-phenyl-6-(phenylthio)pyridine.

Entry	Catalyst (mL)	Solvent	Temperature (°C)	Time (min)	Isolated yield (%)
1	–	EtOH	Reflux	24 (h)	Trace
2	0.5	EtOH	Reflux	20/60	90/90
3	1	EtOH	Reflux	20/60	90/90
4	0.4	EtOH	Reflux	20/60	60/80
5	0.5	EtOH	65	20/60	90/90
6	0.4	EtOH	65	20/60	40/60
7	0.5	EtOH	55	20/60	50/65
8	0.5	EtOH	60	20/60	60/80
9	0.5	–	65	20/60	30/60
10	0.5	CH ₃ CN	65	20/60	50/70
11	0.5	CH ₃ OH	65	20/60	40/50
12	0.5	THF	65	20/60	30/40
13	0.5	CHCl ₃	65	20/60	40/60
14	0.5	Toluene	65	20/60	30/40

present one-pot multicomponent condensation reaction with satisfactory yields.



Most of the synthesized molecules are known (a–h & j–p) and were characterized by ¹H NMR, ¹³C NMR, and mass spectrometry and comparison of their melting points with known compounds. Novel compounds (i & q) were fully characterized with the help of the usual spectroscopic techniques including FT-IR, ¹H NMR, ¹³C NMR, mass spectroscopies and elemental analysis.

The HPLC trace and LC-MS method have high sensitivity, good linearity, and feasibility, which are used to confirmed the structure of compounds as well. For this purpose, the structure of two selected products (g & h) were recorded by LC-MS analysis and also, the purity of another two derivatives (a & f) were determined by high performance liquid chromatography (HPLC). The results can be seen in the Supplemental Materials file.

FT-IR spectroscopy of the purified products revealed two absorption bands at 3465–3453 and 3328–3322 cm⁻¹ due to N–H stretching vibrations and also one absorption band at 2218 cm⁻¹ for –C≡N stretching. An absorption band about 757 cm⁻¹ is mainly attributed to thioether linkage. In addition, the disappearance of the band at about 1720 cm⁻¹ attributed to the carbonyl group is evidence for the product formations. In the ¹H-NMR spectra (in DMSO) of the products, the NH₂ protons were observed downfield as a *singlet* (2H) at about δ = 8 ppm and protons of the aromatic ring were appeared as *multiplet* at δ = 7.5–7.7 ppm.^[25,32,40] All the aromatic carbon atoms of compounds exhibited signals at δ = 115–166 ppm in the ¹³C NMR spectra. The C-3 and C-5 carbon atoms of the pyridine ring, attached to the nitrile group, exhibited signals at δ = 88 and 94 ppm, respectively. The mass spectra detected the expected

Table 2. One-pot multi-component synthesis of 2-amino-3,5-dicyanonitrile-6-thio-pyridines using WEB.

Entry	R ¹	R ²	Product	Time (min)	Isolated yield (%)	Ref.
1	C ₆ H ₅	–C ₆ H ₅	A	20	90	20
2	4-HOC ₆ H ₄	–C ₆ H ₅	B	45	80	86
3	3-HOC ₆ H ₄	–C ₆ H ₅	C	40	85	39
4	4-H ₃ COC ₆ H ₄	–C ₆ H ₅	D	35	80	87
5	3-H ₃ CC ₆ H ₄	–C ₆ H ₅	E	40	85	39
6	4-H ₃ CC ₆ H ₄	–C ₆ H ₅	F	40	90	30
7	3-BrC ₆ H ₄	–C ₆ H ₅	G	25	85	37
8	4-ClC ₆ H ₄	–C ₆ H ₅	H	25	90	86
9	2-ClC ₆ H ₄	–C ₆ H ₅	I	25	85	Novel
10	4-FC ₆ H ₄	–C ₆ H ₅	J	20	85	86
11	4-O ₂ NC ₆ H ₄	–C ₆ H ₅	K	10	90	88
12	4-NC ₅ H ₄	–C ₆ H ₅	L	20	90	89
13	2-SC ₆ H ₃	–C ₆ H ₅	M	25	85	19
14	2-C ₁₀ H ₇	–C ₆ H ₅	N	30	80	30
15	C ₆ H ₅	4-ClC ₆ H ₄	O	20	90	20
16	C ₆ H ₅	CH ₃ (CH ₂) ₂ CH ₂	P	30	85	30
17	C ₆ H ₅	CH ₃ (CH ₂) ₆ CH ₂	Q	35	80	Novel

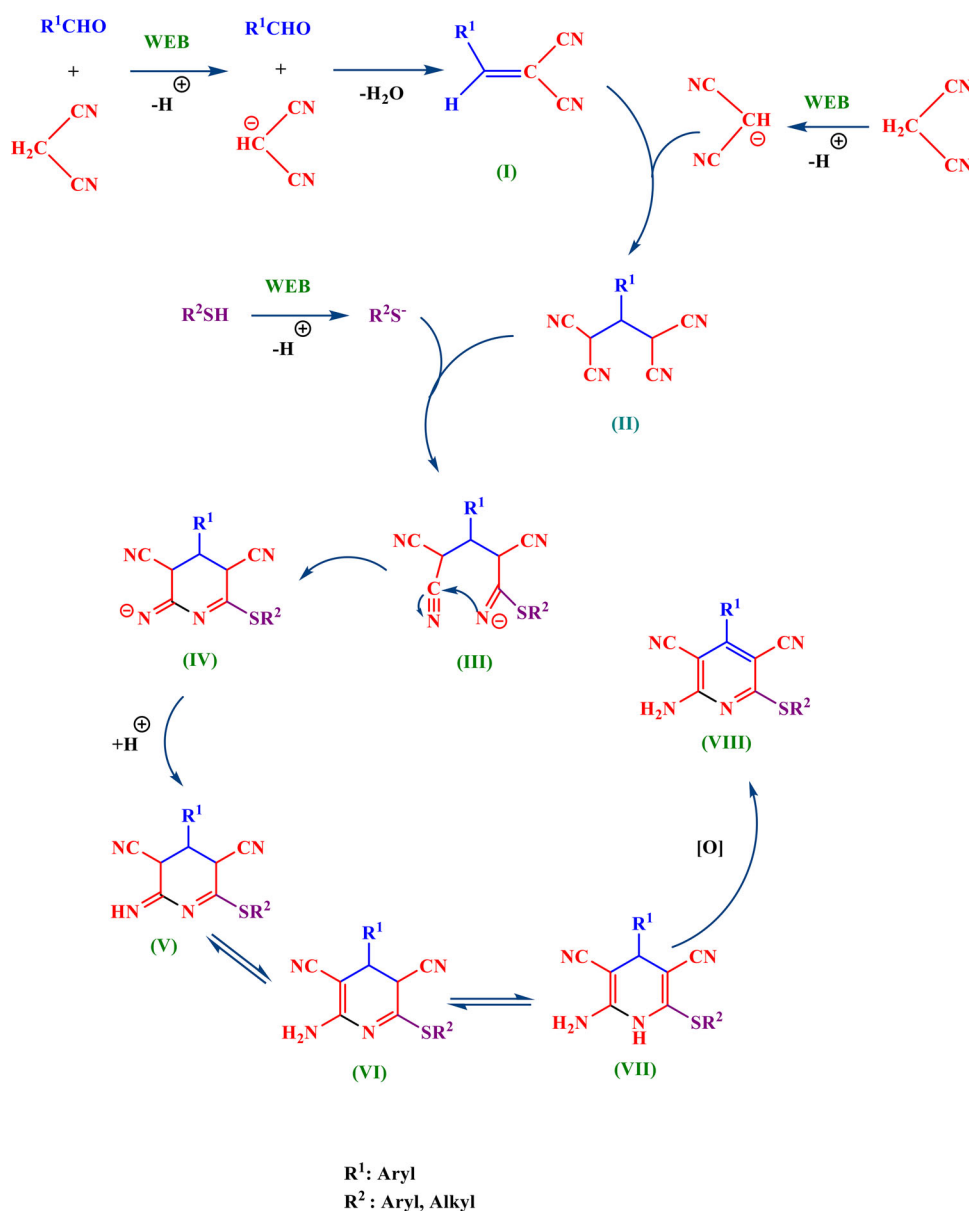
molecular ion signals corresponding to the respective molecular formula of the synthesized compounds.

Based on a literature report^[32] a proposed mechanism for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines using WEB is depicted in Scheme 2.

Previously, it was found that potassium carbonate, sodium carbonate, potassium chloride, and sodium chloride are the major constituents of WEB along with a host of other trace elements.^[85] The mechanistic approach involves the Knoevenagel condensation of aldehyde with malononitrile in basic media forming Knoevenagel adduct (I). In the following steps, the Michael addition of the second molecule of malonitrile on Knoevenagel adduct (I) and subsequent nucleophilic addition of thiolate to CN afforded intermediates II and III respectively. Thereafter, intramolecular cyclization lead to formation of dihydropyridine (VII) as the

most stable tautomeric form (IV, V, VI). Finally, 2-amino-3,5-dicarbonitrile-6-thio-pyridine (VIII) was obtained upon air oxidative aromatization.

In another variation, the catalytic ability of WEB in a one-pot multicomponent preparation of 2-amino-3,5-dicarbonitrile-6-thio-pyridine derivatives is compared with that of catalysts reported by others previously. We have tabulated the results of some commonly basic and acidic catalysts in the literature for the same transformation in Table 3. As Table 3 indicates, despite the merits of most of the previously reported methods, the newly developed catalytic system acts better rather than other ones from the aspect of economic and environmental factors.^[52-54] The current study is much superior to almost all of them in terms of the reaction time (entries 2, 4-11, 13-14), solvent (entry 5) as well as price and toxicity.



Scheme 2. Proposed mechanism for the WEB mediated preparation of 2-amino-3,5-dicarbonitrile-6-thio-pyridines.

Table 3. Comparison of the catalytic activity of WEB with some literature precedents using other catalysts for synthesis of 2-amino-3,5-dicarbonitrile-4-phenyl-6-(phenylthio)pyridine.

Entry	Catalyst	Substrates and reagents	Explanations	Time (min)	Yield (%)
1	–	KOH, EtOH (solvent), reflux ^[18]	Low yield, using 10 mol% base	30	86
2	–	K ₂ CO ₃ , PEG-400 (solvent), 40 °C ^[19]	Long reaction time, using 10 mol% base	60	92
3 ^a	–	DBU, 10% aqueous ethanol (solvent), 35 °C ^[21]	Low yield, expensive base (DBU)	15	80
4	Na ₂ SiO ₃	EtOH (solvent), r.t. ^[22]	Long reaction time, using toxic base, low yield	60	78
5 ^b	TBAB/Cs ₂ CO ₃	MeOH (solvent), r.t. ^[23]	Long reaction time, expensive reagents	3 h	92
6	MgO NPs	EtOH (solvent), reflux ^[24]	Long reaction time, low yield	5 h	78
7	–	Et ₃ N, EtOH (solvent), reflux ^[25]	Long reaction time, low yield	2.5 h	35
8 ^c	–	DABCO, EtOH (solvent), reflux ^[25]	Long reaction time, low yield	2.5 h	45
9	–	Piperidine, EtOH (solvent), reflux ^[11]	Long reaction time, using toxic reagent	27 h	43
10 ^d	–	TBAF, H ₂ O (solvent), 80 °C ^[28]	Corrosive and highly flammable liquid and vapor reagent	50	92
11	[bmlm]OH	EtOH (solvent), r.t. ^[33]	Long reaction time, using ionic base	1.1 h	92
12	Sc(OTf) ₃	EtOH (solvent), reflux ^[37]	Low yield, expensive catalyst	15	85
13	Silica NPs	EtOH (solvent), reflux ^[38]	Long reaction time, low yield	3 h	70
14	CuI NPs	EtOH/H ₂ O (solvent), reflux ^[39]	Long reaction time	100	90
15	Zn(II) and Cd(II) MOFs	Solvent-free, 100 °C ^[41]	High temperature, using expensive catalyst	30	86
16	WEB	EtOH (solvent), 65 °C	Excellent yield, short reaction time, using feedstock, mild reaction conditions, easy work-up	20	90

^a1,8-Diazabicyclo[5.4.0]undec-7-ene.^bTetrabutylammonium bromide.^c1,4-Diazabicyclo[2.2.2]octane.^dTetra-*n*-butyl ammonium fluoride.

Conclusion

We have reported an efficient synthetic method for 2-amino-3,5-dicarbonitrile-6-thio-pyridine derivatives by successive one-pot multi-component reactions of various aldehydes and thiols with malononitrile using WEB as a green catalyst. The WEB as a natural feedstock has a basic nature which helps the reaction proceed under the mild reaction conditions. The scope of using WEB is broad with respect to a range of aromatic/and hetero aromatic aldehydes with electron-donating and electron-withdrawing groups in conjunction with aromatic as well as aliphatic thiols. It has also been shown that the yields are high and reaction completion time is within 10–45 min. Short reaction times, good to excellent yields, safe process and simple work-up (without using toxic solvents) make this method an attractive and useful contribution to the present organic synthesis for the preparation of 2-amino-3,5-dicarbonitrile-6-thio-pyridine derivatives.

Experimental

General

The purity determinations of the products and the progress of the reactions were accomplished by TLC on silica gel polygram STL G/UV 254 plates (Merck, Germany). The melting points of products were determined with an Electrothermal Type 9100 melting point apparatus (UK). The Fourier transform infrared (FT-IR) spectra were recorded on an Avatar 370 FT-IR Thermo Nicolet spectrometer (USA). Elemental analyses were performed using a Thermofinnigan Flash EA1112 CHNO-S Series analyzer and agreed with the calculated values.

The nuclear magnetic resonance (NMR) spectra were provided on Bruker Avance 300 MHz instruments in DMSO-*d*₆ (Germany). Chemical shifts are given in δ relative

to TMS. Coupling constants *J* are given in Hz. Abbreviations used for ¹H-NMR signals are: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra were recorded with a CH7A Varianmat Bremem instrument at 70 eV electron impact ionization, in *m/z* (rel %) (Germany). Chromatographic separation was conducted on a HPLC system (Waters 600, USA). The HPLC instrument consisted of an In-line degasser AF, a smart line pump 600, with a 50- μ L loop and with a 2487 Dual λ Absorbance Detector. Chromatographic separations were carried out using a Thermo-C18 column (USA) packed with octadecyl bonded silica with Column Dimensions 4.6 \times 250 mm and 175 Å pore size at 30 °C. Mobile phase was in isocratic elution mode with a mixture of acetonitrile/water (80:20, v/v), flow rate of 1.0 mL/min. The sample injection volume was 50 μ L and analytes were monitored at 365 nm. The samples were filtered through 0.45 μ m, 13 mm cellulose acetate syringe filters prior to injection. The LC/MS experiments were also performed on the Agilent 6410 triple quadrupole LC/MS system with the Agilent 1200 series (Column: Agilent Eclipse XDB-C18, 4.6 \times 150 mm, 5 μ m). All yields refer to isolated products after purification by recrystallization from EtOH. The Supplemental Materials contains sample ¹H, ¹³C NMR and mass spectra of the products **a–q** (Figures S1–S41).

Preparation of WEB (water extract of banana)

WEB (Water Extract of Banana) (scientific name: *Musa balbisiana* Colla; family: Musaceae; species: *Musa balbisiana*) was obtained according the method reported previously.^[52] Firstly, banana peels ash was obtained by drying the banana peels followed by burning it into ash. Afterwards, the obtained ash (5 g) was suspended in of distilled H₂O (100 mL), magnetically stirred for 10 min at room

temperature and then filtered through sintered glass crucible. The filtrate is termed WEB.

Typical procedure for preparation of 2-amino-3,5-dicarbonitrile-4-phenyl-6-(phenylthio)pyridine using WEB

To a magnetically stirred solution of benzaldehyde (0.25 mmol, 0.0265 g), malononitrile (0.5 mmol, 0.0330 g), and thiophenol (0.25 mmol, 0.025 mL) in EtOH (2 mL), WEB (0.5 mL) was added. The reaction mixture was stirred at 65 °C for 20 min in the open air. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was gradually cooled to room temperature and diluted with distilled water (5 mL). Afterwards, the resulting solid product was collected by simple filtration and washed several times with distilled water and dried. Pure product was then obtained from the resulting solid by recrystallization from EtOH (90% yield, 0.295 g).

Funding

The authors gratefully acknowledge the partial support of this study by Ferdowsi University of Mashhad Research Council (Grant no. p/3/50460).

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