

BFA: Bael Fruit Ash as a biogenic, heterogeneous catalyst for the synthesis of 2-amino-3,5-dicarbonitrile-6-thiopyridine and chromeno[2,3-b]pyridine derivatives

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Received mm-dd-yyyy

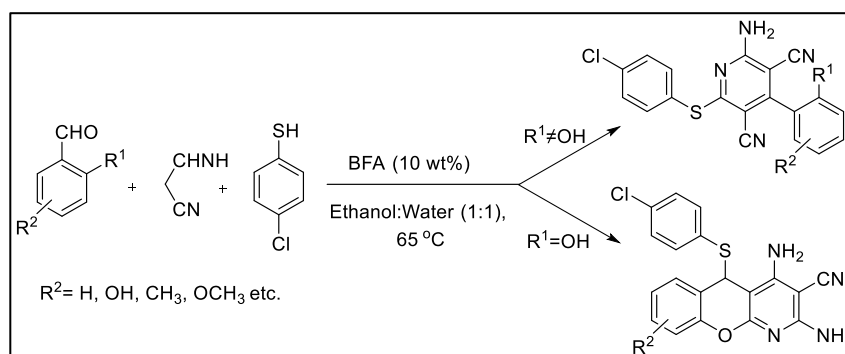
Accepted mm-dd-yyyy

Published on line mm-dd-yyyy

Dates to be inserted by editorial office

Abstract

Bilva Fruit ash (*Aegle marmelos*), also known as Bael Fruit Ash (BFA), is reported as a biogenic, heterogeneous, environmentally friendly basic reagent for the synthesis of 2-amino-3,5-dicarbonitrile-6-thiopyridine and chromeno[2,3-b]pyridine derivatives via a one-pot, multicomponent reaction involving aromatic aldehydes, malononitrile, and thiophenol. The reactions proceed efficiently in an eco-friendly ethanol: water (1:1) solvent mixture at 65 °C under open-air conditions without needing external oxidizing agents. Excellent product yields (85-95%), short reaction times (30-45 min), operational simplicity, and the reusability of the BFA catalyst for multiple consecutive cycles make this protocol a sustainable and green alternative.



Keywords: Bael Fruit Ash (BFA), aldehydes, malononitrile, *p*-chlorothiophenol, 2-amino-3,5-dicarbonitrile-6-thiopyridine, chromeno[2,3-b]pyridines.

Introduction

Apprehensions about environment and the sustainability have made the use of renewable catalysts a crucial strategy in contemporary organic synthesis. Catalysts derived from the biogenic origin are very attractive substitutes for traditional catalysts since they are mostly economical, environmentally friendly and frequently reusable. Their use helps in reducing negative effects on the environment. The synthesis and use of such sustainable catalysts have received more attention in recent years due to their enormous potential in green chemistry practices and as they satisfy the needs of modern research and industrial applications.¹ The pharmaceutical and chemical industries are highly interested in catalytic synthetic methods in organic chemistry that meet ever-tougher environmental regulations.²

Catalysts derived from the biogenic origin have attracted scientific community in recent years, among the various biomass sources reported for the preparation of ash-based catalysts include the use of banana, pomegranate, rice, papaya, mango, onion, muskmelon, pomelo, lemon, and tamarind. These agricultural waste materials are inexpensive, readily available, and environmentally sustainable. As many of them are derived from edible materials, use of such edible biomass may raise concerns regarding competition with their use as food resources. Therefore, bael fruit waste represents a more attractive biomass source for catalyst preparation, as it adds value to agricultural residues while avoiding the use of edible biomass resources.³ *Aegle marmelos* fruit waste, specifically the shell, rind, and other non-edible residues remaining after consumption offer useful biomass for the preparation of the catalyst.

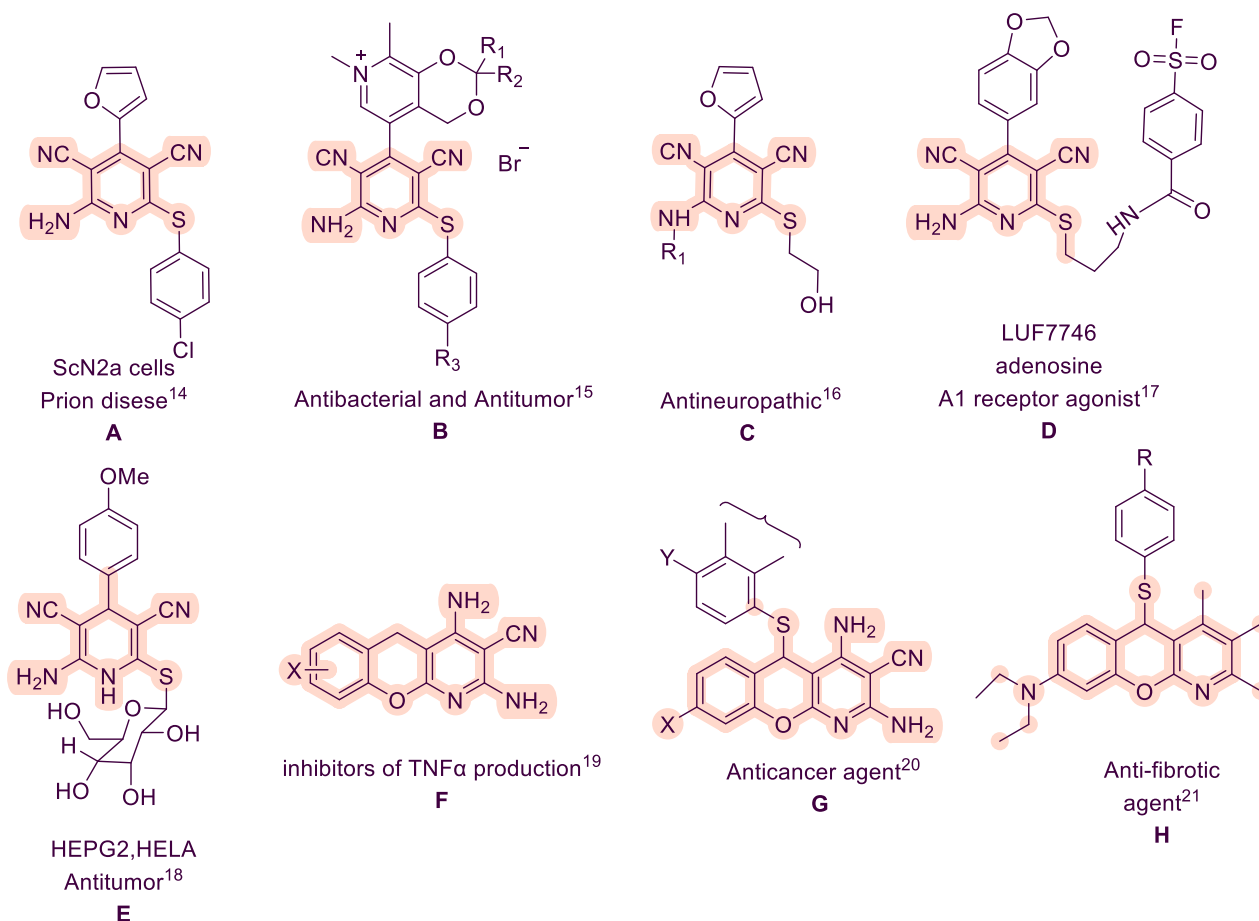


Figure 1. Selected biologically active 2-amino-3,5-dicyanopyridine, dihydropyridine and chromeno[2,3-b]pyridines derivatives

Pyridine and dihydropyridine scaffolds are highly valuable in medicinal chemistry because they enhance the biological activity of many drug molecules. The pyridine ring helps to improve drug stability, solubility, and the ability to interact effectively with biological targets, which increases therapeutic efficiency. According to the U.S. Food and Drug Administration (FDA) database, pyridine or dihydropyridine rings are present in approximately 95 approved medications. This indicates that these classes of molecules are prevalent and crucial for the production of the medicines.⁴

2-amino-3,5-dicarbonitrile-6-thiopyridinesald exhibit properties such as antiviral activity,⁵ A1/A2B partial agonism,⁶ α -glucosidase inhibitors and are useful for treatment of diabetes mellitus.⁷ They act as inhibitors of DNA gyrase (GyrA) of salmonella typhi⁸ and are also used in the treatment of epilepsy.⁹ A novel series of 2-amino-3,5-dicarbonitrile-6-thiopyridine derivatives was reported as selective adenosine receptor ligands such as A1-, A2a-, and A2b-. Owing to their biological activity, they have been proposed as potential therapeutic agents for the treatment of cardiovascular, respiratory, inflammatory, neurodegenerative, diabetic, hepatic, and cancer-related disorders.¹⁰ Their non-medical applications include use in fluorescence quantum¹¹ and for Corrosion protection.¹² Similarly, dihydropyridine derivatives are well known for their strong pharmacological properties, especially nifedipine, nitrendipine, amlodipine and nisoldipine, are the calcium antagonists and reported to be used in the treatment of cardiovascular system.¹³ Overall, these scaffolds contribute to the development of a wide range of biologically active compounds with important medicinal applications.

Figure 1 displays selected structures of biologically active molecules containing 2-amino-3,5-dicarbonitrile-6-sulfanyl pyridine, dihydropyridine and chromeno[2,3-*b*]pyridines motifs. Among these, **A** is used in the treatment of prion disease,¹⁴ **B** exhibits potent antibacterial and antitumor activity,¹⁵ while **C** acts as an antineuropathic.¹⁶ Affinity towards adenosine A1 receptor¹⁷ was observed for structure **D**. Dihydropyridine **E** acts as an antitumor agent;¹⁸ similarly derivatives of 2,4-diamino-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile serve as effective inhibitors of TNF α (**F**),¹⁹ as anticancer agent (**G**),²⁰ and anti-fibrotic agent (**H**).²¹

Many protocols have been developed for the synthesis of 2-amino-3,5-dicarbonitrile-6-thiopyridine and chromeno[2,3-*b*]pyridines derivatives. The most common method involves use of the three-component condensation of aromatic aldehyde, malononitrile, and thiophenol. Brief information on various catalysts reported for the synthesis of 2-amino-3,5-dicarbonitrile-6-thiopyridine and chromeno[2,3-*b*]pyridines derivatives are summarized in Table 1 and Table 2 respectively.

Table 1. Various catalysts used for the synthesis of 2-amino-3,5-dicarbonitrile-6-thiopyridine derivatives.

Entry	Catalyst	Wt. % of catalyst	Solvent	Temp., °C	Time, min	Yield, %	Ref.
1	Et ₃ N	10-20 mol%	EtOH	Reflux	150–180	40-48/96	22
2	Piperidine	10 mol%	EtOH /MWI	Reflux/90	180 / 30	86/97	23
3	Diethylamine	20 mol%	EtOH	RT	270	80	24
4	Imidazole	20 mol%	EtOH	Reflux	30–120	81-91	25
5	K ₂ CO ₃	10 mol%	PEG-400	40	60	92	26
6	(2-HEAA)	0.5mL	-	RT	5	70	27
7	Mont-K10 clay	20 mol%	EtOH	78	45	92	28
8	BFA	5 wt. %	EtOH: Water	65	50	62	Present work
9	BFA	10 wt. %	EtOH: Water	65	30	85–95	Present work

Table 2. Various catalysts used for the synthesis of chromeno[2,3-*b*]pyridines derivatives.

Entry	Catalyst	Wt. % of catalyst	Solvent	Temp., °C	Time,	Yield, %	Ref.
1	Et ₃ N	6.7 mol%	EtOH	Reflux	180-210	75	29
2	K ₂ CO ₃ /KMnO ₄	20 mol%	Water: EtOH	Reflux	180-210	92	30
3	SnO NPs	6 mol%	EtOH	Reflux	54	88	31
4	Porcine pancreas lipase	66-94 wt. %	EtOH	40	1080	79	32
5	BFA	10 wt. %	EtOH: Water	65	30	85–95	Present work

Although numerous catalysts have been reported for this transformation, many require elevated temperatures, prolonged reaction time, or afford only moderate yields. Considering these facts, still there is scope for the development of a new protocol using a biogenic catalyst under mild conditions.

Results and Discussion

With our interest in the development of new synthetic methodology using heterogeneous catalyst for the synthesis of nitrogen-containing heterocyclic molecules, we intended to evaluate the potential application of natural BFA in the synthesis of 2-amino-3,5-dicarbonitrile-6-thiopyridine. The BFA catalyst was prepared by collecting dried fruits of *Aegle marmelos* (Bael) and manually breaking them into small pieces using a mortar and pestle. The resulting material was placed in a silica crucible and calcined in a muffle furnace at 600 °C for 6 hr to obtain a soft white/grayish ash. The basicity of the prepared BFA was evaluated by measuring the pH of an aqueous suspension (5.3 g of BFA in 25 mL of distilled water), which gave a pH value of approximately 12.5, confirming its strongly basic character².

The physical and chemical attributes of the Bael Fruit Ash (BFA) catalyst and its water-extracted residue were characterized using FT-IR, XRD, and SEM-EDX techniques (for full spectra and micrographs, see Supplementary Information). The analytical data confirm that BFA is a complex heterogeneous mixture of inorganic oxides and carbonates, with calcite (CaCO₃) and potassium carbonate (K₂CO₃) serving as the primary active catalytic components. Powder XRD and FT-IR spectra confirm the retention of crystalline calcite ($2\theta = 29.38^\circ$) and silicate phases, while SEM-EDX profiling reveals an aggregated, micro-crystalline structure that becomes porous upon water extraction due to the selective leaching of soluble potassium salts.

Accordingly, a trial reaction was performed by reacting Benzaldehyde (**1a**), malononitrile (**2**), and *p*-chlorothiophenol (**3a**) using Ethanol : water (1:1), as a solvent and BFA catalyst (10 wt. % relative to the weight of aldehyde).

Since BFA is essentially a mixture of inorganic oxides and carbonates, it requires an aqueous phase to facilitate active basic site interactions, while the organic substrates necessitate a water-miscible organic solvent to maintain a sufficiently homogeneous liquid phase for efficient reaction. Considering its free miscibility, non-toxic nature, ready availability, and low cost, ethanol was selected as an organic co-solvent. It was found that BFA efficiently promoted the multi-component reaction to yield 2-amino-3,5-dicarbonitrile-6-thiopyridine and chromeno[2,3-*b*]pyridines derivatives. To improve the yield and to identify the optimal reaction medium, various solvents were screened. (Table 3) The model reaction was investigated using various solvents and temperature conditions and catalytic amount of BFA (10 wt. %). No product formation was observed under water, Methanol, Methanol: water (1:1) and Ethanol: water (1:1) at room temperature. Methanol: water (1:1) under reflux conditions afforded a moderate yield (75 %), whereas Ethanol: water (1:1) at 65 °C with an open-air condenser (no need of external oxidizing agent) provided the best results, delivering the desired products in

excellent yields (85–95 %) within 30 min. It was found that Ethanol: water (1:1) works as the best solvent. The results related to study of effect of solvent and variation in temperature are summarized in Table 3.

Table 3. Effect of solvent and temperature on the synthesis of 2-amino-3,5-dicarbonitrile-6-thiopyridine derivatives catalyzed by BFA.

Entry	Solvent	Temperature, °C	Time, min.	Yield, %
1	Water	RT	120	No product formation
2	Water	Reflux	90	No product formation
3	Methanol	RT	120	No product formation
4	Methanol	Reflux	90	No product formation
5	Methanol: water (1:1)	RT	120	No product formation
6	Methanol: water (1:1) open air condenser	Reflux	60	75
7	Ethanol: water (1:1)	RT	120	No product formation
8	Ethanol: water (1:1), open air condenser	65	30	85-95

Reaction conditions: Benzaldehyde (**1a**) (106 mg, 1 mmol), malononitrile (**2**) (66 mg, 2 mmol), and *p*-chloro thiophenol (**3**) (144 mg, 1 mmol) mixed in the presence of BFA (10 wt. %) in solvent (2 mL).

With the established set of reaction conditions, we decided to evaluate the efficacy of the catalyst using substituted aromatic aldehydes (**1a–1k**) with electron-donating, electron-withdrawing, heterocyclic group. The results are summarized in Table 4. In general, the reaction afforded the desired thiopyridine derivatives in good to excellent yields (85–96%). Electron-donating substituents, particularly methoxy groups (**4e** & **4f**), exhibit enhanced reactivity. Electron-withdrawing substituents were also well tolerated, although the nitro-substituted (**4i**) substrate required a longer reaction time and provided a comparatively lower yield. Heterocyclic aldehyde (**4j**) also gave good yield of the desired product. Notably, *m*-hydroxybenzaldehyde (**4k**) exhibited distinct reactivity compared to other substituted aldehydes. Under the optimized reaction conditions, a mixture of the aromatized pyridine derivative and the corresponding 1,4-dihydropyridine derivative was obtained. Formation of both the products was confirmed by HRMS analyses. The MS spectrum displayed peaks for aromatized product for ^{35}Cl at $m/z = 379.0426$, ^{37}Cl at $m/z = 381.0470$ and for dihydropyridine for ^{35}Cl at $m/z = 381.0586$, ^{37}Cl at $m/z = 383.0695$ respectively. This supports the formation of both products. In contrast with use of other aldehydes accomplishment of aromatization using atmospheric oxygen under open-air reflux was observed, avoiding the need for external chemical oxidizing agents. Use of ethyl cyanoacetate as active methylene compound instead of malononitrile did not furnish the desired product under the optimized reaction conditions. Substituted salicylaldehydes displayed distinct reactivity under the optimized conditions, affording chromeno[2,3-*b*]pyridine derivatives (**5l**, **5m**) instead of the expected thiopyridine products **4**. Electron-donating substituted salicylaldehydes successfully furnished the corresponding chromeno[2,3-*b*]pyridine derivatives, whereas when electron-withdrawing substituted salicylaldehydes (-Br, -Cl, and -NO₂) were employed, no desired product was obtained, indicating the crucial role of electronic effects in the cyclization process.

Reusability of the catalyst is another important aspect of green chemistry. To evaluate the reusability of the catalyst, a model reaction was performed using Benzaldehyde (**1a**), malononitrile (**2**), and *p*-chlorothiophenol (**3**) in ethanol: water (1:1) system and BFA (10 wt. %) as a catalyst. After completion of the reaction (as indicated by TLC), ethanol (20 mL) was added to the reaction mixture, it was stirred for 30 min and

then it was filtered. The residue containing product and catalyst was stirred with ethyl acetate followed by filtration to collect the residue of solid catalyst. This recovered catalyst, after oven drying at 70–80 °C was reused in subsequent reaction cycles. The catalyst retained good catalytic activity over multiple runs, affording product yields of 95 %, 88 %, and 82 % in the first, fifth, and eleventh cycles, respectively. Although a gradual decrease in yield was observed upon reuse there was no substantial loss in catalytic activity and the catalyst remained highly effective, demonstrating its excellent reusability and potential as a sustainable green base catalyst.

To quantitatively evaluate the sustainability and environmental impact of the BFA-catalyzed multicomponent synthesis, key green chemistry metrics were calculated. The reaction demonstrates high step-efficiency with an Atom Economy (AE) of 91.6 %, producing water as the sole environmentally benign by-product. The simple Reaction E-factor was determined to be 0.18, corresponding to a Process Mass Intensity (PMI) of 1.18, which highlights the minimal waste generation of this methodology.

Although the initial preparation of the BFA catalyst involves thermal calcination at 600 °C for 6 hr, this is a single, bulk-scale activation step for a renewable, agricultural waste-derived material. The high recyclability and structural stability of the BFA catalyst across multiple consecutive runs effectively offset this initial energy input, drastically reducing the overall lifecycle thermal footprint per mole of product.

Scheme 1. Synthesis of 2-amino-3,5-dicarbonitrile-6-thiopyridine derivatives **4a–k** and chromeno[2,3-b]pyridines derivatives **5l–m** catalyzed by BFA.

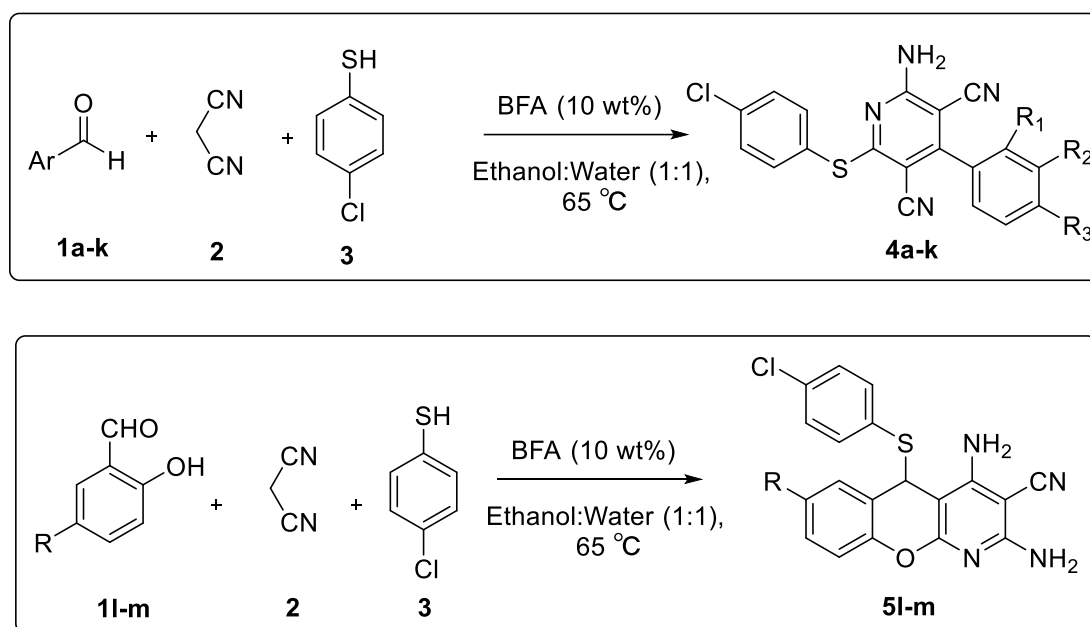


Table 4. Synthesis of 2-amino-3,5-dicarbonitrile-6-thiopyridine derivatives **4a–k** and chromeno[2,3-b] pyridines derivatives **5l–m** catalyzed by BFA.

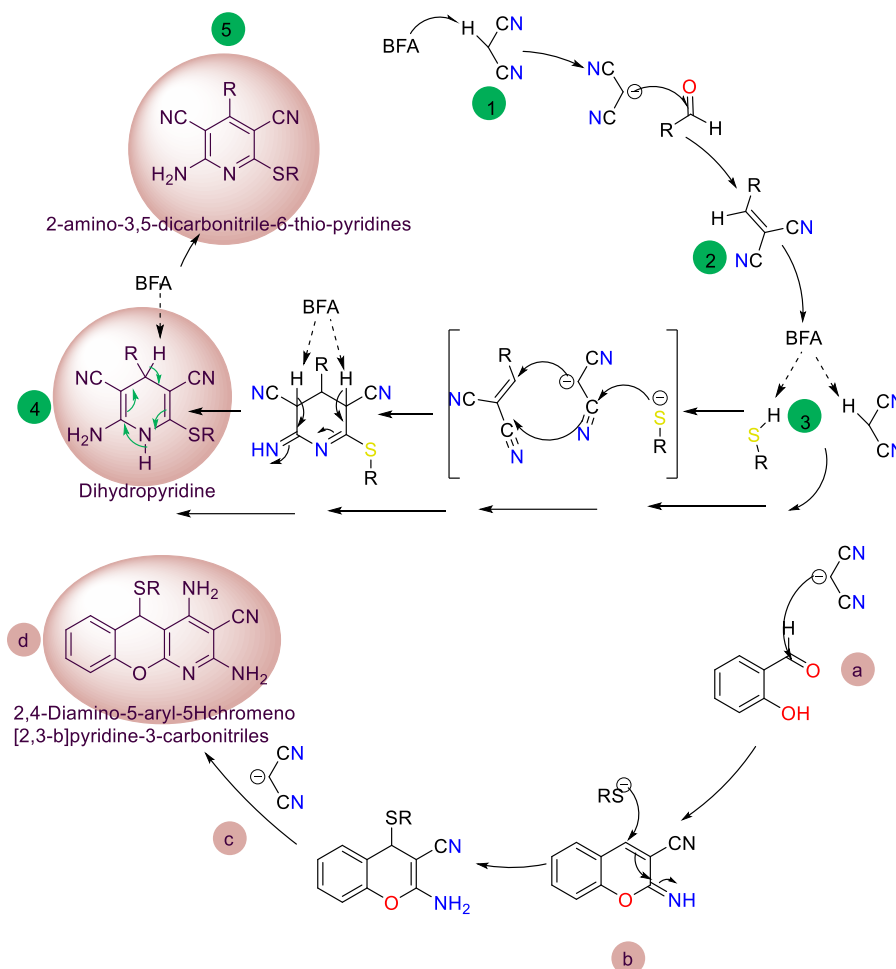
Entry	Ar-	Time, min	Yield, %
4a ³⁰	C ₆ H ₅ -	30	95
4b	4-CH ₃ C ₆ H ₄ -	30	86
4c ²⁴	4(CH ₃) ₂ CH-C ₆ H ₄ -	30	85
4d	4-OCH ₃ C ₆ H ₄ -	30	92

4e	4-OH(3-OCH ₃)-C ₆ H ₃ ⁻	30	96
4f	2,3,4CH ₃ OC ₆ H ₂ ⁻	30	96
4g ³⁰	4-OH-C ₆ H ₄ ⁻	30	89
4h ³³	4-ClC ₆ H ₄ ⁻	30	90
4i	4- NO ₂ C ₆ H ₄ ⁻	45	85
4j	Furyl-	45	95
4k	3-OH-C ₆ H ₄ ⁻	30	90*
5l ³⁰	R=H	30	95
5m	R=CH ₃	30	95

Reaction conditions: (substituted) aldehyde (**1**) (1 mmol), malononitrile (**2**) (2 mmol) and *p*-chlorothiophenol (**3**) (1mmol), BFA (10 wt. %), solvent Ethanol: water (1:1) (2 mL), 65 °C. *Yield refers to the unseparated mixture of fully aromatized pyridine (**4k**) and its 1,4-dihydropyridine precursor (single spot-on TLC), confirmed by NMR and Mass spectrometry.

To elucidate the reaction pathway and confirm the role of ambient oxygen as the terminal oxidant in the dehydrogenative aromatization step, control experiments were performed (for detailed experimental procedures and ¹H NMR spectra, see Supplementary Information, S60-S62). When the model reaction between *p*-anisaldehyde, malononitrile, and *p*-chlorothiophenol was conducted under restricted-oxygen conditions (condenser fitted with a cotton plug), the transformation stalled at the Knoevenagel condensation stage, yielding the 2-(4-methoxybenzylidene)malononitrile intermediate without further conversion. Additionally, introducing Na₂SO₃ as an oxygen scavenger intercepted the oxidation sequence, inhibiting complete aromatization to the pyridine system. These control studies unambiguously validate that atmospheric molecular oxygen is essential to drive the final oxidative dehydrogenation of the dihydropyridine intermediate to afford the desired fully conjugated 2-amino-3,5-dicarbonitrile-6-thiopyridine core.

Based on these observations, a plausible mechanism for the synthesis of 2-amino-3,5-dicarbonitrile-6-thiopyridine can be shown in Scheme 2. Initially, the aromatic aldehyde undergoes Knoevenagel condensation with one molecule of malononitrile (**1**) using BFA as base catalyst to afford benzylidenemalononitrile (**2**). Subsequently, a second molecule of malononitrile (**3**) adds to the Knoevenagel adduct through a Michael-type addition and the thiophenolate ion then attacks the electrophilic carbon of the cyano group, leading to the formation of a sulfur-containing intermediate. Intramolecular cyclization of this intermediate produces the dihydropyridine derivative (**4**). Finally, oxidation and aromatization of the dihydropyridine intermediate by atmospheric oxygen under the reaction conditions furnish the desired 2-amino-3,5-dicarbonitrile-6-thiopyridine derivative (**5**). In case of synthesis of chromeno[2,3-*b*]pyridines initially, salicylaldehyde (**a**) reacts with one equivalent of malononitrile through a Knoevenagel condensation, followed by cyclization to afford iminochromene (**b**). Subsequently, thiophenol adds to the activated double bond of iminochromene, yielding the phenylsulfanylchromene intermediate. This intermediate then reacts with a second equivalent of malononitrile, followed by cyclization and aromatization, to furnish the desired chromeno[2,3-*b*]pyridine derivative (**d**) in good to excellent yield.



Scheme 2. Plausible mechanism of the synthesized compound 2-amino-3,5-dicarbonitrile-6-thiopyridine, dihydropyridine and chromeno[2,3-b]pyridines derivatives.

Conclusions

The Bilva (*Aegle marmelos*) Fruit Ash (BFA) was successfully used as a sustainable, biogenic, reusable, and eco-friendly catalyst for the synthesis of 2-amino-3,5-dicarbonitrile-6-thiopyridines and chromeno[2,3-b]pyridine derivatives. The protocol afforded excellent yields under mild conditions, providing a simple, cost-effective, and environmentally benign approach to these important heterocyclic compounds. Use of aqueous ethanol as a green solvent, BFA as reusable catalyst are noteworthy highlights of the developed protocol.

Experimental Section

General. A Bruker ALPHA II FTIR spectrophotometer was used to record IR spectra. ^1H NMR and ^{13}C spectra were recorded using a Bruker Avance III FT-NMR spectrometer at 400 and 100 MHz, respectively. Internal standard TMS. HRMS was recorded on an Agilent 6540 UHD Q-TOF LCMS instrument using the Mass Hunter software for data acquisition and data processing (mass range 50 to 3000 m/z units). For compounds containing a chlorine atom, all reported HRMS m/z values correspond to the monoisotopic mass calculated using the ^{35}Cl

isotope. Melting points were recorded on a Kumar melting point apparatus KI-11-02(A). Merck Silica gel 60 F254 plates were used for thin-layer chromatography (TLC).

General experimental procedure for the catalyst. Dried fruits of *Aegle marmelos* (Bael) were collected and manually broken (using mortar and pestle) into tiny pieces. This mass was taken into the silica crucible and it was heated in muffle furnace at 600 °C for 6 hr. to get soft white or grayish ash. This BFA acts as base catalyst. The basicity of BFA was evaluated by measuring the pH of its aqueous suspension prepared by mixing 5.3 g of BFA and 25 mL of distilled water. The pH was found to be approximately 12.5, indicating its strong basic nature².

General experimental procedure of 2-Amino-3,5-dicarbonitrile-6-thiopyridine and Chromeno[2,3-*b*]pyridines Derivatives. Aromatic aldehyde (1mmol) and malononitrile (1mmol) were mixed with ethanol: water (1:1, 2 mL) in a 25-mL round bottom flask and BFA catalyst (10 wt. % relative to the weight of aldehyde) was added. The reaction mixture was stirred at room temperature for 1-5 min. The precipitate of intermediate was formed (monitored with TLC). Further malononitrile (1mmol) and thiophenol (1mmol) were added and the mixture was stirred at 65 °C with an open-air condenser till completion of the reaction. The progress of the reaction was monitored by TLC (eluent petroleum ether – ethyl acetate, 3:2). After completion of the reaction, the reaction mixture was cooled to room temperature and subjected to structure-specific workup.

2-Amino-3,5-dicarbonitrile-6-thiopyridines 4. Ethanol (20 mL) was added, and the mixture was stirred for 10 minutes. The resulting solid residue, containing both the product and BFA catalyst, was collected by filtration and washed with ethyl acetate (20 mL). The catalyst remained as insoluble residue. The filtrate containing product was subjected to vacuum distillation to afford the product. The products were found to be pure (TLC) and did not require any further purification

Chromeno[2,3-*b*]pyridines. The crude mixture was dissolved in ethylene glycol (5 mL) under gentle heating at 50-60 °C and filtered to remove the insoluble BFA catalyst. Water (10 mL) was added to the filtrate to precipitate the product, which was obtained by filtration. The solid product was washed with water (50 mL) and dried under vacuum to afford the pure chromeno[2,3-*b*]pyridine derivative.

In both cases, the recovered heterogeneous BFA catalyst was washed thoroughly with ethyl acetate to remove any organic residues, dried, and reused in subsequent reaction cycles.

Gram scale synthesis of 2-amino-6-((4-chlorophenyl)thio)-4-(4-methoxyphenyl)pyridine-3,5-dicarbonitrile (4d). In a 100 mL round-bottom flask, 4-methoxybenzaldehyde (*p*-anisaldehyde) (1.36 g, 10 mmol,) and malononitrile (10 mmol, 0.66 g) were combined with ethanol: water (1:1, 20 mL) containing BFA catalyst (0.136g, 10 wt. % relative to weight of *p*-anisaldehyde). The mixture was stirred at room temperature for 5 min. Additional malononitrile (0.66, 10 mmol g) and *p*-chlorothiophenol (1.45g, 10 mmol) were added, and the reaction mixture was heated at 65 °C with an open-air condenser until completion (monitored by TLC, (eluent petroleum ether - ethyl acetate, 3:2). After cooling to room temperature, ethanol (100 mL) was added and stirred for 10 min. The mixture was filtered, and the residue was extracted with ethyl acetate (100 mL) to separate the insoluble BFA catalyst. Concentration of the organic filtrate under reduced pressure afforded the pure product without requiring further purification (3.60 g, 95 % yield).

2-Amino-6-((4-chlorophenyl)thio)-4-phenylpyridine-3,5-dicarbonitrile (4a)⁽³⁰⁾. White solid, yield 0.344g (95%); mp 228-230 °C (CHCl₃) (230-232 °C (MeOH)³⁰); IR (KBr): 3450.87–3210.72, 2218.05, 1618.61, 1545.80–1525.24, 1475.81–1426.24, 1311.95–1265.76, 1178.12–1012.80, 904.59–706.51, 598.86–409.22 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 5.52(s, 2H, -NH₂), 7.26 (s, 2H, Ar-H), 7.43-7.49 (m, 2H, Ar-H), 7.50-7.57(m, 5H, Ar-H); ¹³C NMR

(100MHz, CDCl₃ + DMSO d₆, 3 :1 v/v): δ = 166.70 (C-NH₂, Pyridine C2), 160.06 (C-S, Pyridine C6), 158.50 (Pyridine C4), 136.89 (Ar-Cq), 135.54 (Ar-Cq), 133.99 (Ar-Cq), 130.62 (Ar-CH), 129.54 (Ar-CH), 128.92 (Ar-CH), 128.59 (Ar-CH), 126.31 (Ar-CH), 115.26 (2 x -C $\equiv$ N), 93.81 (Pyridine C-CN, sp²), 87.41 (Pyridine C-CN, sp²) ppm; **HRMS:** Found, m/z : 363.0510 [M+H]⁺ C₁₉H₁₁ClN₄S. Calculated, m/z 363.0467

2-Amino-6-((4-chlorophenyl)thio)-4-(p-tolyl)pyridine-3,5-dicarbonitrile (4b). White solid, yield 0.324g (86%); mp 250-252 °C (CHCl₃); **IR (KBr):** 3471.43, 3363.27, 3307.73, 3204.38, 2211.42, 1617.84, 1574.27, 1545.27, 1511.52, 1473.88–1418.99, 1387.11, 1309.64–1241.95, 1189.65–1011.16, 956.00, 814.23, 773.89, 674.71, 618.92.cm⁻¹; **¹H NMR (400 MHz, CDCl₃):** δ = 2.44 (s, 3H, -CH₃), 5.52, 7.26 (s, 2H, Ar-H), 7.34-7.48 (m, 4H, Ar-H), 7.50 (s, 2H, Ar-H); **¹³C NMR (100MHz, CDCl₃):** δ = 168.38 (C-NH₂, Pyridine C2), 159.32 (C-S, Pyridine C6), 158.60 (Pyridine C4), 141.54 (Ar-Cq), 137.09 (Ar-Cq), 136.44 (Ar-Cq), 130.15 (Ar-CH), 129.77 (Ar-CH), 129.58 (Ar-CH), 128.40 (Ar-CH), 125.63 (Ar-CH), 115.33 (C $\equiv$ N), 114.88 (C $\equiv$ N), 95.87 (Pyridine C-CN, sp²), 87.54 (Pyridine C-CN, sp²), 21.52 (Ar-CH₃) ppm; **HRMS:** Found, m/z : 377.0689 [M+H]⁺ C₂₀H₁₃ClN₄S. Calculated, m/z : 377.0627

2-Amino-6-((4-chlorophenyl)thio)-4-(4-isopropylphenyl)pyridine-3,5-dicarbonitrile (4c)⁽²⁴⁾. White solid, yield 0.344g (85%); mp 225-228 °C (CHCl₃) (224-226 °C)²⁴; **IR (KBr):** 3397.60, 3316.75, 3207.02, 2962.85, 2932.66, 2874.27, 2216.85, 1625.57, 1570.40, 1539.51, 1510.74, 1472.80–1389.87, 1315.05, 1261.97, 1080.57, 1013.34, 823.00, 781.00, 746.59, 734.84, 681.12 cm⁻¹; **¹H NMR (400 MHz, CDCl₃):** δ = 7.47-7.50 (m, 4H, Ar-H), 7.26-7.44 (m, 4H, Ar-H), 5.52 (s, 2H, -NH₂), 2.95-3.02 (hept, J = 6.8 Hz, 1H, -CH), 1.30 (d, J = 6.8 Hz, 6H, 2-CH₃); **¹³C NMR (100MHz, CDCl₃ + DMSO d₆, 3 :1 v/v):** δ = 166.82 (C-NH₂, Pyridine C2), 160.16 (C-S, Pyridine C6), 158.45 (Pyridine C4), 151.44 (Ar-Cq), 136.90 (Ar-Cq), 135.54 (Ar-Cq), 131.23 (Ar-Cq), 129.52 (Ar-CH), 128.72 (Ar-CH), 126.93 (Ar-CH), 126.36 (Ar-CH), 115.50 (C $\equiv$ N), 115.46 (C $\equiv$ N), 93.80 (Pyridine C-CN, sp²), 87.29 (Pyridine C-CN, sp²), 33.91 (Isopropyl -CH-, SP³), 23.92 (Isopropyl 2 X -CH₃, SP³) ppm; **HRMS:** Found, m/z : 405.1017 [M+H]⁺ C₂₂H₁₇ClN₄S. Calculated, m/z : 405.0940

2-Amino-6-((4-chlorophenyl)thio)-4-(4-methoxyphenyl)pyridine-3,5-dicarbonitrile (4d). White solid, yield 0.361g (92%); mp 230 °C (CHCl₃); **IR (KBr):** 3481.97, 3357.26, 3203.83, 3074.92, 3014.80, 2975.74, 2942.01, 2845.29, 2208.23, 1614.37, 1579.16, 1543.16, 1510.66, 1477.62–1391.02, 1315.02, 1294.58, 1264.28, 1188.49–1011.04, 833.82, 808.72, 776.28, 746.16, 675.49.cm⁻¹; **¹H NMR (400 MHz, CDCl₃):** δ = 7.36-7.46 (m, 4H, Ar-H), 7.26-7.28 (m, 2H, Ar-H), 6.98-7.01 (m, 2H, Ar-H), 6.01 (s, 2H, -NH₂), 3.82-3.83 (s, 3H, -OCH₃); **¹³C NMR (100MHz, CDCl₃ + DMSO d₆, 3 :1 v/v):** δ = 166.80 (C-NH₂, Pyridine C2), 161.33 (C-S, Pyridine C6), 160.15 (Ar-C-OCH₃), 158.22 (Pyridine C4), 136.90 (Ar-C-Cl), 135.55 (Ar-C-S), 130.33 (Ar-CH), 129.54 (Ar-CH), 126.27 (Ar-Cq), 125.78 (Ar-CH), 115.56 (C $\equiv$ N), 114.31 (Ar-CH/ C $\equiv$ N), 93.80 (Pyridine C-CN, C5 sp²), 87.21 (Pyridine C-CN, C3 sp²) 55.54 (-OCH₃, SP³) ppm; **HRMS:** Found, m/z : 393.0645 [M+H]⁺ C₂₀H₁₃ClN₄OS. Calculated, m/z : 393.0577

2-Amino-6-((4-chlorophenyl)thio)-4-(4-hydroxy-3-methoxyphenyl)pyridine-3,5-dicarbonitrile (4e). Pale yellow solid, yield 0.392g (96%); mp 290 °C (CHCl₃); **IR (KBr):** 3425.04, 3338.32, 3222.03, 3030.63, 2218.71, 1640.21, 1550.73, 1512.65, 1426.72, 1288.51, 1265.94, 1214.15, 1180.45–1011.09, 873.88, 851.88, 814.84, 762.93, 701.15, 587.21, 532.74, 457.28–407.78 cm⁻¹; **¹H NMR (400 MHz, CDCl₃):** δ = 8.20-8.33 (br s, 1H, -OH), 7.31-7.38 (m, 4H, Ar-H), 6.85-6.93 (m, 3H, -Ar-H), 6.20 (s, 2H, -NH₂), 3.82 (s, 3H, -OCH₃); **¹³C NMR (100MHz, CDCl₃ + DMSO d₆, 3 :1 v/v):** δ = 166.62 (C-NH₂, Pyridine C2), 160.23 (C-S, Pyridine C6), 158.48 (Pyridine C4), 149.25 (Ar-C-OH), 147.66 (Ar-C-OCH₃), 136.87, 135.43, 129.52, 126.53, 124.47, 122.21, 115.83, 115.76, 112.70 (Ar-C and C $\equiv$ N), 93.80 (Pyridine C-CN, sp²), 87.20 (Pyridine C-CN, sp²), 56.08 (OCH₃, sp³) ppm; **HRMS:** Found, m/z : 409.0607 [M+H]⁺ C₂₀H₁₃ClN₄O₂S. Calculated, m/z : 409.0526

2-Amino-6-((4-chlorophenyl)thio)-4-(2,3,4-trimethoxyphenyl)pyridine-3,5-dicarbonitrile (4f). White solid, yield 0.434g (96%); mp 253-255 °C (CHCl₃); **IR (KBr):** 3487.60, 3401.92, 3326.28, 3228.59, 2939.56, 2223.30, 1648.98, 1624.57, 1593.81, 1554.54, 1527.23, 1497.23, 1473.33–1410.69, 1320.92, 1296.18, 1265.02, 1099.20, 1012.57, 912.74, 818.30, 805.47, 748.73, 682.76, 651.37, 577.36, 554.17 cm⁻¹; **¹H NMR (400 MHz, CDCl₃):** δ =

7.50 (d, $J=8.5$ Hz, 2H, Ar-H), 7.43 (d, $J=8.5$ Hz, 2H, Ar-H), 6.98 (d, $J=8.8$ Hz, 1H, Ar-H), 6.78 (d, $J=8.8$ Hz, 1H, Ar-H), 5.48 (s, 2H, -NH₂), 3.91-3.93 (s, 9H, 3-OCH₃); **¹³C NMR (100MHz, CDCl₃ + DMSO d₆, 3 :1 v/v)**: δ = 166.06 (C-NH₂, Pyridine C2), 159.73 (C-S, Pyridine C6), 156.26 (Pyridine C4), 155.69 (Ar-C-OCH₃), 150.72 (Ar-C-OCH₃), 141.81 (Ar-C-OCH₃), 136.87, 135.59, 129.45, 126.30, 124.24, 120.35, 115.23 (C $\equiv$ N), 115.19 (C $\equiv$ N), 107.39 (Ar-CH), 95.43 (Pyridine C-CN, sp²), 88.88 ((Pyridine C-CN, sp²), 61.57 (OCH₃, sp³) 60.94 (OCH₃, sp³), 56.09 (OCH₃, sp³) ppm; **HRMS**: Found, m/z : 453.0883 [M+H]⁺ C₂₂H₁₇ClN₄O₃S Calculated, m/z : 453.0788

2-Amino-6-((4-chlorophenyl)thio)-4-(4-hydroxyphenyl)pyridine-3,5-dicarbonitrile (4g)⁽³⁰⁾. Pale yellow solid, yield 0.337 g (89%); mp 280-282 °C (CHCl₃) (284-286 °C(MeOH)⁽³⁰⁾); **IR (KBr)**: 3477.02, 3339.88, 3221.37, 2219.85, 1638.95, 1613.13, 1549.93, 1511.88, 1474.49-1415.79, 1287.14, 1263.60, 1235.03, 1178.49-1010.72, 826.11, 775.93, 646.10, 595.65, 570.15 cm⁻¹; **¹H NMR (400 MHz, DMSO d₆)**: δ = 9.80 (s, 1H, -OH), 7.91 (br s, 2H, Ar-H), 7.48 (d, $J=8.5$ Hz, 2H, Ar-H), 7.39 (d, $J=8.5$ Hz, 2H, Ar-H), 7.28 (br s, 2H, -NH₂), 6.87 (d, $J=8.6$ Hz, 2H, Ar-H); **¹³C NMR (100MHz, CDCl₃ + DMSO d₆, 3 :1 v/v)**: δ = 160.22 (C-NH₂, Pyridine C2) 159.98 (Ar-C-OH), 158.59 (C-S, Pyridine C6), 136.86 (Ar-C-Cl), 135.43 (Ar-C-S), 130.36 (Ar-CH), 129.49 (Ar-CH), 129.44 (Ar-CH), 126.51 (Ar-Cq), 124.22 (Ar-CH), 115.84 (C $\equiv$ N), 115.68 (Ar-CH), 93.80 (Pyridine C-CN, C5, sp²), 87.40 (Pyridine C-CN, C3, sp²) ppm; **HRMS**: Found, m/z : 379.0425 [M+H]⁺ C₁₉H₁₁ClN₄OS Calculated, m/z : 379.0417

2-Amino-4-(4-chlorophenyl)-6-((4-chlorophenyl)thio)pyridine-3,5-dicarbonitrile (4h)⁽³³⁾. Pale yellow solid, yield 0.357 g (90%); mp 270-275 °C (CHCl₃) (261-262 °C)⁽³³⁾; **IR (KBr)**: 3480.76-3219.64, 2922.85, 2215.03, 1632.65, 1572.97-1474.94, 1420.43-1388.72, 1303.07-1235.49, 1092.66, 1035.20-1012.96, 822.17-774.25, 674.19, 510.27-429.26 cm⁻¹; **¹H NMR (400 MHz, CDCl₃)**: δ = 7.26-7.44 (m, 8H, Ar-H), 6.31 (s, 2H, -NH₂); **¹³C NMR (100MHz, CDCl₃ + DMSO d₆, 3 :1 v/v)**: δ = 167.95 (C-NH₂, Pyridine C2), 159.62 (C-S, Pyridine C6), 157.13 (Pyridine C4), 137.01 (Ar-Cq), 136.92 (Ar-Cq), 136.10 (Ar-Cq), 131.70 (Ar-Cq), 129.85 (Ar-CH), 129.45 (Ar-CH), 129.25 (Ar-CH), 125.65 (Ar-CH), 115.02 (C $\equiv$ N), 114.76 (C $\equiv$ N), 94.52 (Pyridine C-CN, sp²), 87.15 (Pyridine C-CN, sp²) ppm; **HRMS**: Found, m/z : (³⁵Cl₂) 397.0162, (³⁵Cl₂ ³⁷Cl₂) 399.0137, (³⁷Cl₂) 401.0114 [M+H]⁺ C₁₉H₁₀Cl₂N₄S Calculated, m/z : (³⁵Cl₂) 397.0078, (³⁵Cl₂ ³⁷Cl₂) 399.0048, (³⁷Cl₂) 401.0019

2-Amino-6-((4-chlorophenyl)thio)-4-(4-nitrophenyl)pyridine-3,5-dicarbonitrile (4i). Pale yellow solid, yield 0.346 g (85%); mp 305-310 °C (CHCl₃); **IR (KBr)**: 3433.16-3238.79, 2216.19, 1649.00, 1554.68-1464.77, 1410.52-1350.06, 1257.58-1092.93, 1036.58-1012.81, 852.72-705.60, 651.59, 529.89-412.93 cm⁻¹; **¹H NMR (400 MHz, DMSO d₆)**: δ = 8.39 (d, $J=8.4$ Hz, 2H, Ar-H), 8.14 (s, 2H, -NH₂), 7.80 (d, $J=8.4$ Hz, 2H, Ar-H), 7.56 (d, $J=8.4$ Hz, 2H, Ar-H), 7.48 (d, $J=8.4$ Hz, 2H, Ar-H); **¹³C NMR (100MHz, CDCl₃ + DMSO d₆, 3 :1 v/v)**: δ = 170.05 (C-S, pyridine C6), 163.03 (C-NH₂, Pyridine C2), 159.98 (Pyridine C4), 148.93 (Ar-C-NO₂), 147.48 (Ar-Cq), 143.58 (Ar-C-S), 140.49 (Ar-C-Cl), 136.96 (Ar-CH), 130.39 (Ar-CH), 129.72 (Ar-CH), 124.19 (Ar-CH, ortho to NO₂), 115.16 (C $\equiv$ N), 93.07 (pyridine CN, C5, sp²), 87.38 (pyridine CN, C3, sp²) ppm; **HRMS**: Found, m/z : 408.3769 [M+H]⁺ C₁₉H₁₀ClN₅O₂S Calculated, m/z : 408.0322.

2-Amino-6-((4-chlorophenyl)thio)-4-(furan-2-yl)pyridine-3,5-dicarbonitrile (4j). Yellow solid, yield 0.335 g (95%); mp 228-230 °C; **IR (KBr)**: 3483.45-3214.52, 2213.44, 1628.21, 1572.47-1516.05, 1411.40-1386.37, 1320.36, 1270.12-1092.37, 1035.35-1010.72, 941.54-761.34, 590.84, 515.11-408.21 cm⁻¹; **¹H NMR (400 MHz, DMSO d₆)**: δ = 7.67-7.74 (m, 1H, Ar-H), 7.33-7.45 (m, 5H, Ar-H), 7.00 (b, 2H, -NH₂), 6.59-6.63 (m, 1H, Ar-H); **¹³C NMR (100MHz, CDCl₃ + DMSO d₆, 3 :1 v/v)**: δ = 167.60 (C-NH₂, Pyridine C2), 160.62 (C-S, Pyridine C6), 146.38 (Furan C2), 145.53 (Furan C5, CH), 144.04 (Pyridine C4), 137.00 (Ar-C-Cl), 135.43 (Ar-C-S), 129.62 (Ar-CH), 126.37 (Ar-CH), 116.71 (C $\equiv$ N), 115.88 (C $\equiv$ N), 113.00 (Furan CH), 89.63 (Pyridine C-CN, sp²), 82.91 (Pyridine C-CN, sp²) ppm; **DEPT**: 146.36, 137.01, 129.61, 116.73, 113.00 ppm; **HRMS**: Found, m/z : 353.0346 [M+H]⁺ C₁₇H₉ClN₄OS Calculated, m/z : 353.0260

2-Amino-6-((4-chlorophenyl)thio)-4-(3-hydroxyphenyl)pyridine-3,5-dicarbonitrile (4k). (Note : A mixture of the fully aromatized pyridine **4k** and its 1,4-dihydropyridine intermediate was obtained. The identity was

confirmed by NMR and HRMS analysis of the mixture; only the resolved characteristic signals for the fully aromatized pyridine **4k** are assigned and reported below)

White solid, yield 0.340 g (90%); mp 246-250 °C; **IR (KBr)**: 3482.66, 3456.32, 3380.13, 3312.04, 3214.82, 2218.71, 2188.30, 2170.71, 1625.13, 1596.40, 1553.67, 1520.02, 1474.45, 1330.57–1092.29, 1012.60, 998.89 cm⁻¹; **¹H NMR (400 MHz, DMSO d₆)**: δ = 9.19 (s, 1H, -OH), 7.40-7.38 (m, 4H, Ar-H), 7.31-7.29 (m, 4H, Ar-H), 7.09 (s, 1H, Ar-H), 7.05 (s, 1H, N-H), 6.76-6.68 (m, 1H, Ar-H), 6.63-6.61 (m, 1H, Ar-H), 6.18 (s, 4H, 2NH₂); **¹³C NMR (100MHz, CDCl₃ + DMSO d₆, 3 :1 v/v)**: δ = 157.83 (Ar-C-OH), 151.60 (C-NH₂, Pyridine C2), 140.73 (C-S, Pyridine C6), 136.90 (Pyridine C4), 133.69 (Ar-Cq), 132.94 (Ar-Cq), 130.67 (Ar-CH), 129.56 (Ar-CH), 120.33 (Ar-CH), 118.73 (Ar-CH), 114.95 (C≡N), 114.58 (C≡N), 85.59 (Pyridine C-CN, sp²) ppm; **HRMS**: Found, *m/z*: 379.0426, 381.0586 [M+H]⁺ C₁₉H₁₁ClN₄OS, C₁₉H₁₃ClN₄OS Calculated, *m/z*: 379.0417, 381.0577

2,4-Diamino-5-((4-chlorophenyl)thio)-5H-chromeno[2,3-b]pyridine-3-carbonitrile (5l)³⁰. Pale yellow solid, yield 0.361 g (95%); mp 228-230 °C, (226-228(MeOH)³⁰); **IR (KBr)**: 3419.74, 3348.57, 3251.22, 3167.99, 2206.38, 1649.26, 1627.01, 1601.13, 1571.59, 1473.69, 1454.97, 1407.19, 1316.52, 1260.86, 1217.47, 1197.05, 1175.43, 1121.39, 1088.64, 1072.71, 1011.72, 793.36, 761.74, 703.84, 654.27, 569.72 cm⁻¹; **¹H NMR (400 MHz, DMSO d₆)**: δ = 7.42 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.31 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.21 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.03 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.73 (t, *J* = 7.4 Hz, 1H, Ar-H), 6.66 (d, *J* = 8.0 Hz 1H, Ar-H), 6.64 (br s, 2H, -NH₂), 6.15 (br s, 2H, -NH₂), 5.65 (s, 1H, C5-H); **¹³C NMR (100MHz, CDCl₃ + DMSO d₆, 3 :1 v/v)**: δ = 160.03 (C-NH₂, Pyridine C-2/C-4), 159.71 (C-NH₂, Pyridine C-2/C-4), 156.63 (Ar-C-O), 151.21 (Pyridine C-5a), 138.13 (Ar-C-S), 135.00 (Ar-C-Cl), 134.94 (2x Ar-CH), 133.20 (2x Ar-CH), 129.45 (Ar-CH), 129.33 (Ar-CH), 129.20 (Ar-CH), 128.61 (Ar-CH), 128.33 (Ar-Cq), 124.08 (Ar-Cq), 121.50 (Ar-Cq), 116.76 (C≡N), 116.03 (Pyridine C-4a), 86.90 (Pyridine C-C-3), 43.61 (Pyridine CH-S) ppm; **DEPT**: 138.13, 129.29, 129.19, 128.56, 128.30, 124.06, 116.03, 43.62 ppm; **HRMS**: Found, *m/z*: 381.0657 [M+H]⁺ C₁₉H₁₃ClN₄OS Calculated, *m/z*: 381.0577

2,4-Diamino-5-((4-chlorophenyl)thio)-7-methyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile (5m). **Yellow solid**, yield 0.375g (95%); mp 245-250 °C; **IR (KBr)**: 3430.50-3251.48, 3160.13, 2206.17, 1649.63-1629.34, 1578.48–1472.97, 1404.48-1337.06, 1263.47-1088.62, 1011.03, 815.02–701.62, 665.12, 544.98-407.09 cm⁻¹; **¹H NMR (400 MHz, DMSO d₆)**: δ = 7.03 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.94 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.75 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.68 (s, 1H, Ar-H), 6.63 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.16 (s, 2H, -NH₂), 5.59 (s, 1H, C5-H), 2.25 (s, 3H, -CH₃) ppm; **¹³C NMR (100MHz, CDCl₃ + DMSO d₆, 3 :1 v/v)**: δ = 160.13 (C-NH₂, Pyridine C-4), 159.48 (C-NH₂, Pyridine C-2), 156.52 (Ar-C-O), 149.14 (Pyridine C-5a), 138.15 (Ar-C-S), 133.29 (Ar-CH), 129.35 (Ar-CH), 129.30 (2X Ar-CH), 129.26 (Ar-C-CH₃), 129.16 (Ar-C-Cl), 128.24 (Ar-CH), 115.78 (C≡N), 96.25 (Pyridine C-CN, C3), 87.11 (Pyridine C-CN/Cq), 72.14 (ring junction C4a/C5a), 43.81 (CH-S, C5), 20.78 (Ar-CH₃) ppm; **DEPT**: 138.27, 129.40, 129.36, 129.13, 128.33, 115.80, 43.79, 20.80 ppm; **HRMS**: Found, *m/z*: 395.0828 [M+H]⁺ C₂₀H₁₅ClN₄OS Calculated, *m/z*: 395.0733

Acknowledgements

We are thankful to Dr. Pinak Mohan Chincholkar for his valuable input in designing scheme and contribution for manuscript preparation. MSK is thankful to Govt. of Maharashtra (MJPRF) for a Senior Research Fellowship (2022_1414), PHK is thankful to Govt. of Maharashtra (BARTI) for a Senior Research Fellowship (BARTI/BANRF/2022/750).

Supplementary Material

Supplementary information file containing IR spectra, ^1H , ^{13}C NMR spectra and HRMS spectra of synthesized compounds. Control Experiments and Mechanistic Probing for Pyridine Formation: Detailed experimental procedures, ^1H NMR spectra of isolated intermediates under oxygen-restricted conditions, and scavenger control studies (pages S60–S62). Characterization of Bael Fruit Ash (BFA) Catalyst and Extracted BFA Residue: Comprehensive analytical data including FT-IR spectra, powder XRD patterns, and SEM-EDX surface micrographs/elemental profiles of pristine and water-extracted BFA catalyst (Figures S63–S74).

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