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A catalyst-free and eco-friendly approach to synthesis of 1,8-naphthyridines *via* natural deep eutectic solvents

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Abstract: The use of deep eutectic solvents (DESs) not only promotes the reaction but also aligns with green chemistry principles due to their biodegradability, low toxicity, cost-effectiveness, and recyclability. A green and efficient one-pot, three-component synthesis of 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitrile derivatives has been developed using lactic acid-based DESs. The reaction, involving 2-aminopyridine, aromatic aldehydes, and malononitrile, proceeds under mild conditions in a DES composed of lactic Acid, maltose, and amla (Indian gooseberry) Juice (3:1:3 molar ratio) without the need for any additional catalysts or additives. Among various DESs evaluated, this ternary mixture exhibited the highest catalytic activity, delivering products in good to excellent yields. The methodology offers notable advantages, including high atom economy, reduced reaction time, and elimination of hazardous solvents. The synthesized naphthyridine derivatives were structurally confirmed by FTIR, NMR, and HRMS analyses. This study highlights the potential of natural-product-based DESs as sustainable media for multicomponent heterocycle synthesis, with significant implications for the field of organic synthesis and green chemistry.

Keywords: Multicomponent reactions; deep eutectic solvents (DESs); 1,8-naphthyridine; green synthesis; 2-amino pyridine; lactic acid.

1. Introduction

Heterocyclic compounds play a crucial role in medicinal chemistry because of their diverse biological activities. Therefore, establishing an appropriate method for their synthesis is highly desirable.[1] Among these heterocyclic compounds, 1,8-naphthyridines derivatives have garnered significant attention for their potential applications in pharmaceuticals[2-4] and used in bacteria detection.[5] The 1,8-naphthyridine derivatives can also act as monodentate, bidentate, or binucleating bridging ligands.[6-7] They also exhibit excellent thermally activated delayed fluorescence (TADF) and high photoluminescence quantum yield, which makes them suitable for blue organic light-emitting diodes (OLEDs).[8-9] They were also used as corrosion inhibitors,[10] perovskite solar photovoltaics,[11] self-assembly/host-guest systems,[12] and molecular tweezers.[13] In recent decades, several methods, including the Skraup, Combes, Pfitzinger, Conrad–Limpach, and Friedländer reactions, have been employed to synthesize 1,8-naphthyridine[14-18] of these techniques, the Friedländer reaction is especially favored for its simplicity and relatively high yield.[19-21] However, this method typically relies on hazardous and

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costly acid or base catalysts that are not recyclable, posing considerable challenges for large-scale or industrial use. Besides this methodology, a one-pot, three-component reaction between 2-aminopyridine, benzaldehyde, and malononitrile was reported for the synthesis of 2,3,4-trisubstituted-1,8-naphthyridine.[22-31] These reported methods suffered from demerits such as the hazardous nature of the catalyst, acidic or basic conditions, high energy consumption, and the use of expensive catalysts or reagents. Hence, there is a need to develop a new methodology for the synthesis of 1,8-naphthyridine molecules due to their various bioactivity.

Deep eutectic solvents (DES) have emerged as a promising class of green solvents, offering low toxicity, biodegradability, low volatility, and high availability. Unlike traditional organic solvents and even some ionic liquids, DES is often composed of inexpensive and renewable components, such as choline chloride and natural acids or amides. Their preparation is straightforward, typically involving simple heating and mixing without requiring purification. Due to their unique physicochemical properties, DES are not only effective solvents but can also act as catalysts or reagents in various organic transformations[32-35]. Lactic acid-based DES has been widely used in the extraction process,[36-37] while their application in the organic reaction has been explored less. In this study, we have investigated the synthesis of 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitrile using lactic acid-based DESs as simultaneously the reaction medium and catalyst. We systematically analyzed the effect of different DES on the reaction efficiency and product yield to establish an environmentally sustainable method for synthesizing 1,8-naphthyridine.

2. Experimental

All solvents used were commercial anhydrous grade and did not require further purification. Aluminum sheets measuring 20 x 20 cm, along with Merck grade silica gel 60 F254, were employed for thin-layer chromatography to monitor the progress of the reaction. Column chromatography was performed using silica gel with a particle size of 80-120 mesh. Melting points were determined using an open capillary tube. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 500 MHz spectrometer in $CDCl_3$ solvent. IR spectra were recorded on PerkinElmer Spectrum Version 10.5.3 spectrophotometer. Mass analyses were performed using Bruker Impact HD.

2.1. Preparation of Deep Eutectic Solvents (DESs)

Previously, reported methodologies were applied to synthesize all the DES tested.[38] Lactic acid-based DESs were synthesized by combining lactic acid (as the hydrogen bond donor) with various hydrogen bond acceptors (HBAs), including Maltose, Amla Juice, $SnCl_2$, Aloe vera Juice, and Proline in appropriate molar ratios as shown in Table 1. The mixtures were placed in a round-bottom flask fitted with a magnetic stirrer and sealed, then gently heated in an oil bath at 50-90 °C with continuous stirring. Formation of a homogeneous and transparent liquid indicated successful eutectic interaction, typically achieved within 30-90 minutes, depending on the specific components used.

These DESs are characterized by a substantial depression in melting point compared to their constituents, attributed to strong intermolecular hydrogen bonding, which disrupts regular lattice formation. The prepared solutions are stable, biodegradable, non-volatile, and readily recyclable. Owing to their ease of synthesis, low toxicity, and ability to act as both solvent and catalyst, these DESs present a highly sustainable alternative for liquid-phase organic transformations. Their simplicity and environmental compatibility make them particularly attractive for applications in green and scalable synthetic methodologies.

Table 1. Composition and molar ratios of various Lactic Acid-based DESs prepared using different hydrogen bond acceptors (HBAs) and natural additives[a]

Entry	Eutectic Mixtures	Molar ratio
1	Lactic Acid + Maltose + Amla Juice[b]	3:1:3
2	Lactic Acid + Maltose+ H_2O	3:2:1
3	Lactic Acid + Proline+ $SnCl_2$	3:1:1
4	Lactic Acid + Maltose + Aloe Vera Juice[b]	3:1:3
5	Lactic Acid + L-Proline + Aloe Vera Juice[b]	2:1:2

[a]All DES systems were prepared by mixing Lactic Acid with the listed hydrogen bond acceptors (HBAs) in the molar ratios indicated in parentheses (e.g., 3:1:3). All mixtures were stirred at 50-90 °C until homogeneous liquids were obtained. [b]Aloe Vera Juice and Amla Juice were used in their natural extract forms.

*2.2. General Procedure for Synthesizing 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitrile (**1-27**)*

A mixture of 2-aminopyridine (5 mmol), malononitrile (5 mmol), and the corresponding aromatic aldehyde (5 mmol) was added to a lactic acid-based DES prepared from lactic acid, maltose, and amla Juice (Indian gooseberry Juice) in a 3:1:3 molar ratio. The reaction mixture was stirred at room temperature for the appropriate time, as listed in Table 3. The progress of the reaction was monitored by thin-layer chromatography (TLC) using petroleum ether and ethyl acetate (9:1, *v/v*) as the eluent. Upon completion, the reaction mixture was poured into water to precipitate the product. The solid was collected by filtration, washed thoroughly with water, and dried. The crude product was then recrystallized from a mixture of ethanol (4 mL) and water (0.5 mL) to afford the pure 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitrile.

*2-Amino-4-(phenyl)-1,8- naphthyridine-3-carbonitrile (**4a**):* Yellow Solid; Yield 95%; mp: 154-158 °C. Lit.[39] : 153-155 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 7.54 (dd, *J*= 8.0, 2.1 Hz, 1H), 7.57 (dd, *J* = 8.0 Hz, 2H), 7.63 (dd, *J* = 8.0 Hz, 2H), 7.79 (s, 2H), 7.90 (dd, *J* = 8.0 Hz, 1H), 7.91 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.93 (dd, *J* = 8.0, 2.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 82.5, 112.2, 113.4, 115.8, 123.8, 129.3, 130.4, 134.3, 152.1, 152.7, 159.6, 161.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{15}H_{10}N_4$, 247.0983 found, 247.0963

*2-Amino-4-(3,4-dimethoxyphenyl)-1,8- naphthyridine-3-carbonitrile (**4b**):* Yellow Solid; Yield 85%; mp: 180-182 °C. Lit[39]:170-172 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 3.94 (s, 3H), 3.99 (s, 3 H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.97 (s, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.40 (dd, *J* = 8.0 Hz, 1H), 7.68 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.69 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.65 (S, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 56..3, 56.5, 78.7, 111.0, 111.3, 114.6, 120.5, 124.5, 128.3, 135.6, 149.7, 152.4, 155.0, 159.3, 164.2; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{17}H_{14}N_4O_2$, 307.1195 found, 307.1225

*2-Amino-4-(4-Chlorophenyl)-1,8- naphthyridine-3-carbonitrile (**4c**):* Yellow Solid; Yield 91%; mp: 166-168 °C. Lit[39]: 164-166 °C; ^{1}H NMR (500 MHz, $CDCl_3$) ppm 7.52 (d, *J* = 8.1 Hz, 2H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.74 (s, 2H), 7.85 (dd, *J* = 8.1 Hz, 1H), 7.86 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.87 (dd, *J* = 8.1, 2.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 83.0, 112.0, 113.1, 121.0, 128.9, 129.8, 131.5, 131.8, 140.8, 152.6, 154.7, 158.0, 161.0; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{15}H_9N_4Cl$, 282.0594 found, 282.0486

*2-Amino-4-(3,4-dihydroxyphenyl)-1,8- naphthyridine-3-carbonitrile (**4d**):* Yellow Solid; Yield 70%; mp: 178-180 °C (New); ^{1}H NMR (500 MHz, *DMSO-d*$_6$) d ppm 3.33 (br. s., 2H), 6.92 (s, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.33 (dd, *J* = 2.0 Hz, 1H), 7.54 (dd, *J* = 7.8, 2.0 Hz, 2H), 8.21 (s, 2H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$) ppm 74.8, 114.6, 116.4, 116.6, 116.6, 123.6, 127.4, 132.9, 134.1, 146.4, 146.4, 152.6, 153.6, 160.8, 161.0; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{15}H_{10}N_4O_2$, 279.0882 found, 279.0933

*2-Amino-4-(3-nitrophenyl)-1,8- naphthyridine-3-carbonitrile (**4e**):* Yellow Solid; Yield 94%; mp: 170-172 °C. Lit[39]:171-173 °C ; ^{1}H NMR (500 MHz, $CDCl_3$) 7.79 (dd, *J* = 8.0 Hz, 1H), 7.82 (dd, *J* = 8.0 Hz, 1H), 7.91 (s, 1H), 8.34 (d, *J* = 8.0, 2.0 Hz, 2H), 8.47 (dd, *J* = 8.0, 2.0 Hz, 1H), 8.49 (dd, *J* = 8.0, 2.0 Hz, 1H), 8.67 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 86.2, 112.8, 113.9, 119.0, 120.1, 124.7, 130.9, 137.0, 140.3, 150.0, 152.9, 152.9, 159.6, 162.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{15}H_9N_5O_2$, 292.0834 found, 292.0829

*2-Amino-4-(4-dimethylaminophenyl)-3-crbonitrile (**4f**):* Yellow Solid; Yield 75%; mp: 172-174 °C (New); ^{1}H NMR (500 MHz, $CDCl_3$) 3.15 (s, 6H), 6.69-6.71 (d, *J* = 7.8 Hz, 4H), 7.45 (s, 2H), 7.81-7.82 (dd, *J* = 7.8, 2.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 40.3, 40.3, 72.1, 111.8, 111.8, 115.1, 119.5, 124.7, 129.4, 129.4, 134.0, 152.0, 153.5, 154.4, 158.3, 162.9; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{17}H_{15}N_5$, 290.1405 found, 290.1361

*2-Amino-4-(3-hydroxy-4-methoxy)-1,8-naphthyridine-3-carbonitrile (**4g**):* Yellow Solid; Yield 83%; mp: 170-172 °C (New); ^{1}H NMR (500 MHz, DMSO-d_6) 3.34 (br s, 1H), 3.89 (s, 3H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 7.16 (s, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 2H), 8.21 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) 56.1, 74.5, 111.7, 112.3, 115.4, 116.3, 123.4, 124.5, 126.5, 127.1, 130.0, 146.1, 147.1, 153.4, 154.0, 160.8; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{16}H_{12}N_4O_2$, 293.1038 found, 293.0994

*2-Amino-4-(2,4-dimethoxyphenyl)-3-carbonitrile (**4h**):* Yellow Solid; Yield 74%; mp: 184-186 °C (New); ^{1}H NMR (500 MHz, $CDCl_3$) 3.91 (s, 6H), 6.45 (d, *J* = 2.2 Hz, 2H), 6.62 (dd, *J* = 7.8, 2.2 Hz, 2H), 8.19 (s, 2H), 8.28 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 56.1, 56.2, 88.2, 98.2, 106.9, 114.2, 115.4, 122.3, 130.9, 131.2, 137.3, 152.9, 153.2, 160.1, 161.4, 161.4, 167.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{17}H_{14}N_4O_2$, 307.1195 found, 307.1150

*2-Amino-4-(3-ethoxy-4-hydroxy)-1,8-naphthyridine-3-carbonitrile (**4i**):* Yellow Solid; Yield 78%; mp: 176-178 °C (New); ^{1}H NMR (500 MHz, DMSO-d_6) 1.37 (t, 3H), 3.33 (br. s., 1H), 4.05 (q, 2H), 6.98 (d, J = 8.3 Hz 1H), 7.00 (s, 1H), 7.48 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.50 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 8.27 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) 14.9, 64.3, 75.3, 112.3, 114.5, 116.6, 123.5, 126.2, 128.1, 129.1, 137.0, 142.6, 147.5, 153.6, 154.6, 158.0, 161.0; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{17}H_{14}N_4O_2$, 307.1195 found, 307.1150

*2-Amino-4-(2-methoxyphenyl)-1,8-naphthyridine-3-carbonitrile (**4j**):* Yellow Solid; Yield 67%; mp: 160-162 °C (New); ^{1}H NMR (500 MHz, $CDCl_3$) 3.94 (s, 3H), 6.99 (d, *J* = 7.8, 2.0 Hz, 1H), 7.01 (dd, *J* = 7.8 Hz, 1H), 7.09 (dd, *J* = 7.8 Hz, 1H), 7.59 (dd, *J* = 7.8 Hz, 1H), 7.61 (dd, *J* = 7.8, 2.0 Hz, 1H), 8.18 (dd, *J* = 7.8, 2.0 Hz, 1H), 8.20 (dd, *J* = 7.8, 2.0 Hz, 1H), 8.31 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 56.1, 56.2, 88.2, 98.2, 106.9, 114.2, 115.4, 122.3, 130.9, 131.2, 137.3, 152.9, 153.2, 160.1, 161.4, 167.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{16}H_{12}N_4O$, 277.1089 found, 277.0920

*2-Amino-4-(2,3-dichlorophenyl)-1,8-naphthyridine-3-carbonitrile (**4k**):* Yellow Solid; Yield 81%; mp: 162-166 °C (New); ^{1}H NMR (500 MHz, $CDCl_3$) 7.42 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.43 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.71 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 8.36 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 87.6, 111.6, 113.0, 127.9, 128.3, 131.2, 135.1, 135.36, 140.3, 150.2, 153.4, 156.2, 160.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{15}H_8N_4Cl_2$, 316.0078 found, 316.0097

*2-Amino-4-(4-nitrophenyl)-1,8-naphthyridine-3-carbonitrile (**4l**):* Yellow Solid; Yield 86%; mp: 176-178 °C. Lit[39]: 174-176 °C; ^{1}H NMR (500 MHz, DMSO-d_6) 8.13-8.15 (dd, *J* = 8.0, 2.1 Hz, 3H), 8.43 (d, *J* = 8.0 Hz, 2H), 8.45 (d, *J* = 8.0 Hz, 2H), 8.73 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) 86.2, 112.8, 113.9, 119.0, 120.1, 124.7, 130.9, 137.0, 140.3, 150.0, 152.9, 159.6, 162.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{15}H_9N_5O_2$, 292.0834 found, 292.0831

2-*Amino-4-(4-hydroxyphenyl)-1,8-naphthyridine-3-carbonitrile (**4m**):* Yellow Solid; Yield 63%; mp: 160-162 ℃. Lit[39]:157-159 ℃; ^{1}H NMR (500 MHz, DMSO-d_6) 3.30 (br. s., 1H), 6.97 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 2H), 7.89 (dd, *J* = 8.0 Hz, 1H), 7.90 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.91(dd, *J* = 8.0, 2.1 Hz, 1H), 8.32 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) 75.3, 113.1, 114.5, 116.9, 123.1, 134.2, 152.5, 153.7, 158.5, 160.8, 164.2; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{15}H_{10}N_4O$, 263.0933 found, 263.1590

*2-amino-4-(2-nitrophenyl)-1,8-naphthyridine-3-carbonitrile (**4n**):* Yellow Solid; Yield 60%; mp: 168-170 ℃ (New); ^{1}H NMR (500 MHz, $CDCl_3$) 7.80 (dd , *J* = 8.0 Hz, 1H), 7.81 (dd , *J* = 8.0 Hz, 1H), 7.83 (dd , *J* = 8.0, 2.1 Hz, 1H), 7.89 (dd , *J* = 8.0, 2.1 Hz, 1H), 7.91 (dd , *J* = 8.0, 2.1 Hz, 1H), 8.35 (dd , *J* = 8.0, 2.1 Hz, 1H), 8.37 (dd , J = 8.0, 2.1 Hz, 1H), 8.46 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 88.7, 111.1, 112.4, 122.2, 125.7, 126.0, 126.9, 130.6, 133.6, 135.1, 147.0, 152.7, 154.8, 158.9, 161.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{15}H_9N_5O_2$, 292.0834 found, 292.0790

*2-Amino-4-(4-methylphenyl)-1,8-naphthyridine-3-carbonitrile (**4o**):* Yellow Solid; Yield 87%; mp: 168-170 ℃ (New); ^{1}H NMR (500 MHz, $CDCl_3$) 1.70 (s, 3H), 7.62-7.71 (dd , *J* = 8.0 Hz, 4H), 7.98 (d, *J* = 8.0 Hz, 1H), 8.11 (dd, *J* = 8.0, 2.1 Hz, 1H), 8.29 (dd, *J* = 8.0, 2.1 Hz, 1H), 8.66 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 85.3, 113.5, 114.3, 124.1, 125.7, 127.5, 127.5, 128.3, 128.4, 129.1, 133.3, 134.4, 137.1, 160.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{16}H_{12}N_4$, 261.1140 found, 261.1096

*2-Amino-4-(2-thiophenephenyl)-1,8- naphthyridine-3-carbonitrile (**4p**):* Yellow Solid; Yield 73%; mp: 110-112 ℃ (New); ^{1}H NMR (500 MHz, *DMSO-d_6*) 7.39 (dd, *J* = 4.8, 3.8 Hz, 1H), 7.41 (dd, *J* = 4.8, 3.8 Hz, 1H), 7.95 (dd, *J* = 3.8, 1.0 Hz, 1H), 7.96 (dd, *J* = 4.8, 3.8 Hz, 1H), 8.30 (dd, *J* = 4.8, 1.0 Hz, 1H), 8.31 (dd, *J* = 4.8, 1.0 Hz, 1H), 8.74 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) 76.2, 113.9, 114.6, 129.5, 135.6, 138.9, 140.7, 153.7, 159.8, 160.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{13}H_8N_4S$, 253.0548 found, 253.0503

*2-Amino-4-(2-bromophenyl)-1,8- naphthyridine-3-carbonitrile (*4q*):* Yellow Solid; Yield 68%; mp: 180-182 ℃ (New); ^{1}H NMR (500 MHz, $CDCl_3$) 7.45 (dd, *J* = 7.8, 2.0 Hz, 1H), 7.51 (dd, *J* = 7.8, 2.0 Hz, 1H), 7.52 (dd, *J* = 7.8, 2.0 Hz, 1H), 7.75 (dd, *J* = 7.8, 2.0 Hz, 1H), 7.75 (dd, *J* = 7.8, 2.0 Hz, 1H), 8.13 (dd, *J* = 7.8, 2.0 Hz, 1H), 8.14 (dd, *J* = 7.8, 2.0 Hz, 1H), 8.23 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 83.0, 112.0, 113.1, 121.0, 128.9, 129.8, 131.5, 131.8, 140.8, 152.6, 154.7, 158.0, 161.0; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{15}H_9N_4Br$, 325.0089 found, 325.2183

*2-Amino-4-(2-hydroxyphenyl)-1,8-Naphthyridine-3-carbonitrile (**4r**):* Yellow Solid; Yield 41%; mp: 174-176 ℃ (New); ^{1}H NMR (500 MHz, $CDCl_3$) 1.58 (br. s., 1H), 7.41 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.43 (dd, *J* = 8.1 Hz, 1H), 7.44 (d, *J* = 8.0, 2.1 Hz, 1H), 7.62 (dd, *J* = 8.1 Hz, 1H), 7.63 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.74 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.76 (dd, *J* = 8.0, 2.1 Hz, 1H), 8.28 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 87.3, 102.3, 112.5, 116.1, 116.4, 123.5, 124.7, 128.2, 132.7, 134.5, 150.8, 153.5, 155.4, 159.0, 160.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{15}H_{10}N_4O$, 263.0933 found, 263.0888

*2-amino-4-(4-methoxyphenyl)-1,8-naphthyridine-3-carbonitrile (**4s**)*: Yellow Solid; Yield 83%; mp: 164-166 ℃. Lit[39]: 162-164 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) 3.93 (s, 3H), 7.02 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 7.66 (s, 2H), 7.91-7.93 (dd, *J* = 8.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 55.8, 78.6, 113.3, 114.4, 114.4, 115.1, 119.7, 124.0, 129.2, 133.4, 151.6, 155.7, 158.8, 164.8; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{16}H_{12}N_4O$, 277.1089 found, 277.2150

3. Results and Discussion

A series of lactic acid-based DESs were prepared *via* simple heating and stirring until homogeneous liquids were obtained. These DESs were evaluated for their physicochemical and spectroscopic properties to understand their structural characteristics and suitability for green Synthesis. The results are summarized below.

Amla Juice is a highly beneficial substance rich in natural antioxidants, offering a significant blend of vitamins, flavonoids, and polyphenols. These compounds play a crucial role in combating oxidative stress and enhancing the stability of chemical reactions, highlighting the importance of amla Juice as a natural resource. This Juice contains small quantities of natural enzymes, which, although generally inactivated under extreme chemical processing conditions, have the potential to influence specific biochemical interactions when exposed to milder environments. In addition, the presence of tannins, phenolic acids, and related compounds makes amla Juice a valuable source of powerful reducing agents and stabilizers. These components enhance the Juice's chemical reactivity and protective qualities in various reaction systems. The reducing and antioxidant properties of amla Juice work synergistically to stabilize reactive intermediates and prevent unwanted oxidation. Its inherent acidity can affect reaction pH, potentially improving the kinetics of various processes. Furthermore, amla juice serves as a natural hydrogen bond donor, positioning it as an excellent alternative to synthetic polyols in deep eutectic solvent (DES) formulations.

Lactic Acid–Maltose–Amla Juice (3:1:3): This ternary DES showed a density of 1.1820 g/cm³ and a refractive index of 1.309 at 27 °C, with a pH of 1.37, indicating mild acidity. FTIR spectroscopy revealed characteristic bands at 3378, 1717, 1630, 1453, and 1231 cm^{-1}, associated with O–H/N–H stretching, C=O stretching, and C=C or C–O/C–N vibrations. ^1H NMR spectra showed resonances at δ 7.27, 4.38, 2.18, and 1.49 ppm, confirming the presence of both lactic acid and sugar components. The DES exhibited strong hydrogen bonding and excellent solubilizing power, making it an ideal candidate for promoting multicomponent reactions.

Lactic Acid–Maltose–Water (3:2:1): L2 displayed a higher refractive index (1.401) and density (1.1887 g/cm³) compared to L1, with a moderately acidic pH of 2.48. FTIR peaks appeared at 3389, 1717, 1640, 1455, and 1225 cm^{-1}, consistent with strong hydrogen bonding and carbonyl functionalities. ^1H NMR analysis revealed sugar-associated multiplets and lactic acid signals between δ 5.52 and 1.49 ppm. This DES offers enhanced polarity due to the presence of water, which may improve the solvation of polar reactants.

Lactic Acid–Proline–$SnCl_2$ (3:1:1): This DES exhibited the highest density (1.3412 g/cm³) and refractive index (1.447) among the series, with a pH of 2.56. FTIR analysis identified absorptions at 3362, 1711, 1625, 1453, and 1228 cm^{-1}, indicating complex interactions between the acidic, amino, and chloride species. The ^1H NMR spectrum showed signals ranging from δ 5.24 to 1.50 ppm, confirming the incorporation of proline and its coordination with $SnCl_2$. The high density and index suggest a strong ionic character, suitable for reactions requiring Lewis acidic environments.

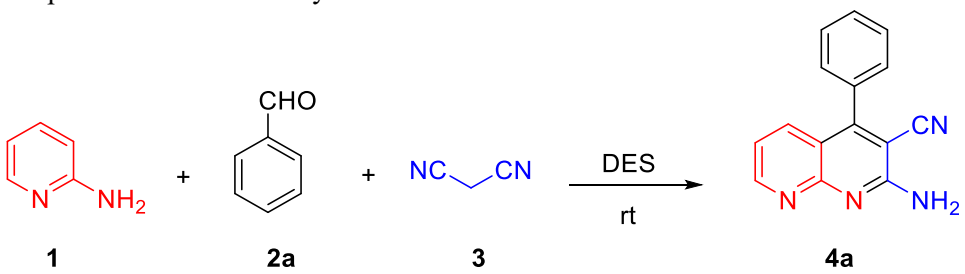
Lactic Acid–Maltose–Aloe Vera Juice (3:1:3): This DES had a density of 1.1693 g/cm³, a refractive index of 1.310, and a pH of 1.39. FTIR bands at 3464, 1718, 1620, 1454, and 1221 cm^{-1} suggest the presence of polysaccharide, polyphenol, and acid functionalities. ^1H NMR data included peaks at δ 5.24, 4.38, 2.18, and 1.50 ppm, typical of hydroxyl-rich matrices. The aloe vera extract introduces additional bioactive groups, enhancing the solvent's hydrogen bonding capacity and natural origin.

Lactic Acid–Proline–Aloe Vera Juice (2:1:2): showed a density of 1.1717 g/cm³ and refractive index of 1.309, with the highest acidity in this group (pH 2.60). FTIR revealed strong bands at 3370, 1718, 1639, 1454, and 1230 cm^{-1}. ^1H NMR peaks at δ 5.25, 4.40, 2.37, and 1.34 ppm confirmed the integration of proline and aloe vera components. This solvent combines amino acid coordination with phytochemical functionality, potentially enhancing both catalytic and solvation properties.

These DESs, derived from biocompatible, non-toxic, and renewable sources, provide a sustainable platform for green organic Synthesis. Their physicochemical and spectroscopic profiles demonstrate their capacity to act as both reaction media and organocatalysts in multicomponent transformations. The present study focuses on the green synthesis of 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitrile molecules using lactic acid-based DESs as reaction media and catalysts (Scheme 1). A variety of DESs were synthesized by combining lactic acid with different hydrogen bond donors (HBDs), as indicated in Table 1. Among them, the ternary eutectic mixture comprising lactic acid, maltose, and amla Juice (2:1:2 molar ratio) emerged as the most efficient, delivering the target compound (**4a**) in 63% yield under ambient conditions without the use of any catalyst or additive.

The screening results revealed a clear dependence of yield on the physicochemical characteristics of DESs. Solvents with natural sugar or polyphenolic content, such as maltose and amla Juice, appeared

to enhance reaction rates, possibly due to better stabilization of transition states *via* hydrogen bonding networks and increased polarity (Table 2). Structural and spectroscopic characterization (FTIR, NMR, MS) of DESs and products confirmed the successful Synthesis and provided insight into the eutectic interactions responsible for their catalytic behaviour.

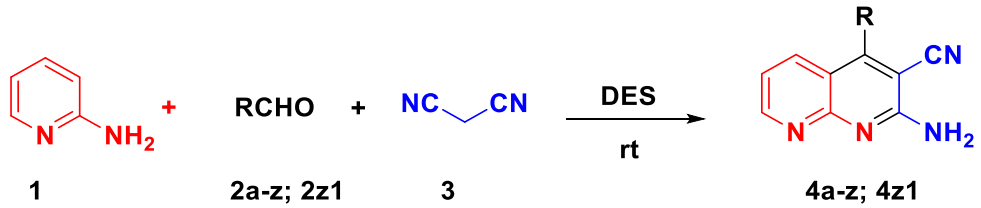


Scheme 1. Model reaction for the optimization of DES and reaction conditions: one-pot three-component synthesis of 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitrile (**4a**) from 2-aminopyridine (**1**), benzaldehyde (**2a**), and malononitrile (**3**)

Table 2. Effect of different lactic acid-based DESs on the yield of 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitrile under catalyst-free conditions[a]

Entry	Solvents	Yield (%)[b]
1	Lactic Acid + Maltose + Amla Juice[b]	95
2	Lactic Acid + Maltose+ H_2O	78
3	Lactic Acid + Proline+ $SnCl_2$	72
4	Lactic Acid + Maltose + Aloe Vera Juice[b]	82
5	Lactic Acid + L-Proline + Aloe Vera Juice[b]	82

[a]Reaction condition: 2-amino pyridine (5 mmol), benzaldehyde (5 mmol) and malononitrile (5 mmol) in 4 mL lactic acid based Deep Eutectic Solvent (DES) at rt; [b]: Isolated yield after purification



Scheme 2. Synthesis of 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitrile (**4a–z1**) *via* a one-pot three-component reaction of 2-aminopyridine (**1**), aromatic aldehydes (**2a–z1**), and malononitrile (**3**) in DES medium

Exploration of substrate scope (Figure 1, Scheme 2) demonstrated broad functional group tolerance across electron-rich and electron-poor aldehydes. Electron-withdrawing groups (e.g., $–NO_2$, –Cl) generally required longer reaction times but afforded good yields, while electron-donating groups (e.g., –OH, $–OCH_3$) facilitated faster conversion. TLC monitored selected reactions, and post-reaction work-up involved simple precipitation and ethanol-water recrystallization, highlighting the simplicity and scalability of the protocol.

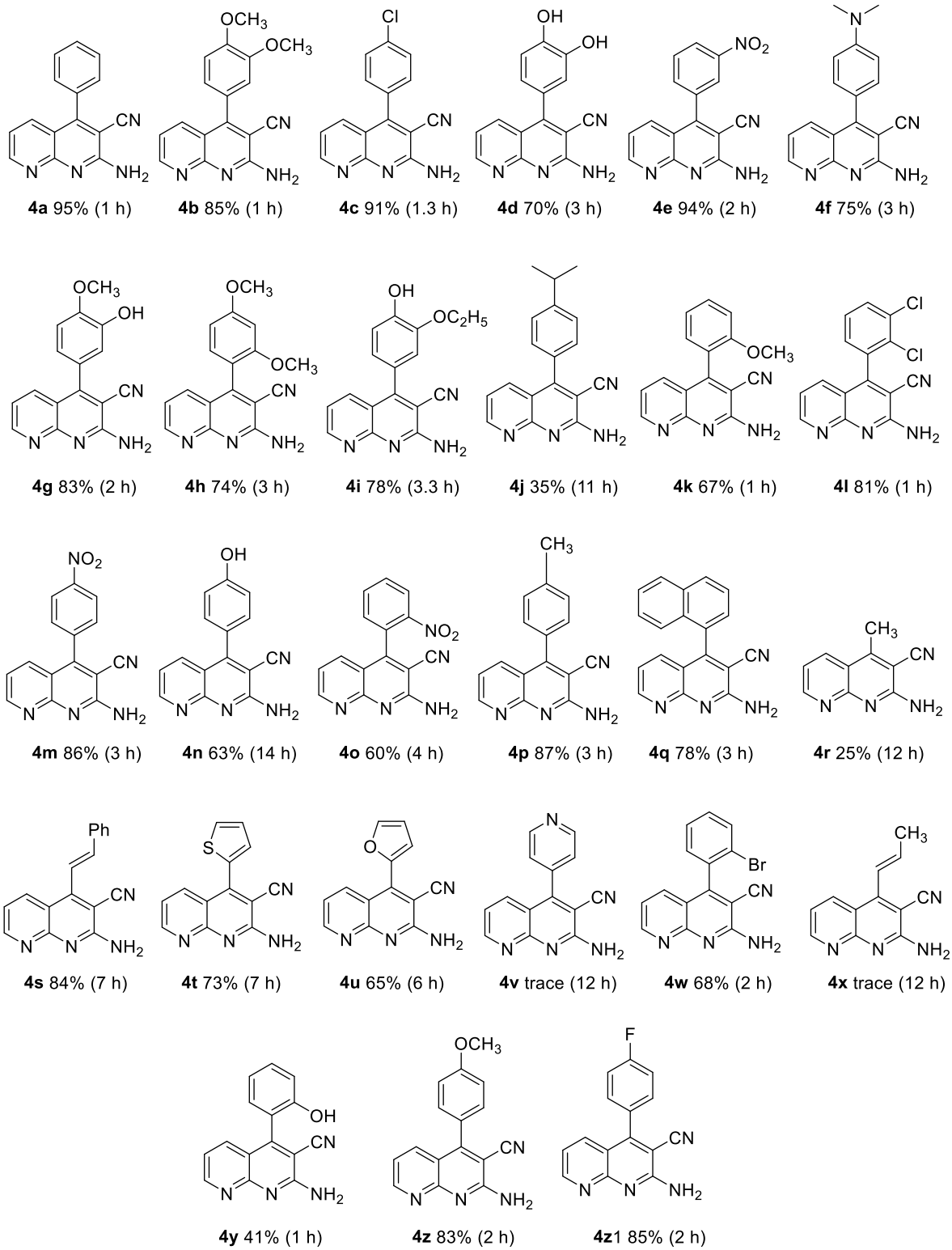


Figure 1. Substrate scope for the synthesis of 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitrile derivatives using Lactic Acid–based DES (Lactic Acid: Maltose: Amla Juice, 3:1:3) under catalyst-free conditions[a,b]

[a]*Reaction conditions:* 2-amino pyridine (5 mmol), substituted aromatic aldehyde (5 mmol) and malononitrile (5 mmol) in 4 ml Lactic acid- Maltose-Amla Juice DES at rt; [b]Isolated yield after purification

Figure 1 illustrates the substrate scope for the synthesis of 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitrile derivatives (**4a–4z1**) using various aromatic aldehydes (**2a–2z1**) under catalyst-free

conditions in a green medium composed of lactic acid–maltose–amla juice (3:1:3 molar ratio) DES. The reactions were performed at room temperature, and the yields of the isolated products varied significantly depending on the electronic nature and steric effects of the substituents on the aromatic aldehydes. Aromatic aldehydes bearing electron-withdrawing groups such as –NO_2 (**4e**, 94%), –Cl (**4c**, 91%), and –CN (**4m**, 86%) generally resulted in high product yields within moderate reaction times. This high yield is significant as it demonstrates the effectiveness of the green synthesis method in accommodating and converting these electron-withdrawing groups. Similarly, substrates containing electron-donating groups such as –OCH_3 (**4b**, 85%; 4z, 83%), –OH (**4d**, 70%; 4y, 41%), and –CH_3 (**4o**, 60%) also underwent smooth conversion, although slightly longer times were often required. Notably, simple benzaldehyde (**2a**) yielded the highest conversion (**4a**, 95%) within just 1 hour. On the other hand, it's important to note that substrates with strong steric hindrance or multiple deactivating groups, such as **2v** and **2x**, led to trace product formation even after prolonged reaction times. This highlights the method's current limitations in accommodating such substrates, underscoring the need for further research in this area. Substrate **2r** also yielded the lowest conversion (**4r**, 25%), possibly due to the electron-donating and bulky nature of the *ortho*-substituted bromophenyl group.

Overall, the data confirm the effectiveness of the DES system in accommodating a broad range of aldehydes, including electron-rich, electron-poor, and heteroaryl varieties. The developed green protocol's robustness and functional group tolerance should reassure the audience about the reliability of the research and its potential for future applications. The environmentally benign nature of DESs, combined with their recyclability and biocompatibility, further supports their suitability as green reaction media. Notably, the **4b** DES system retained substantial activity over three cycles with a negligible decline in product yield (less than 5%).

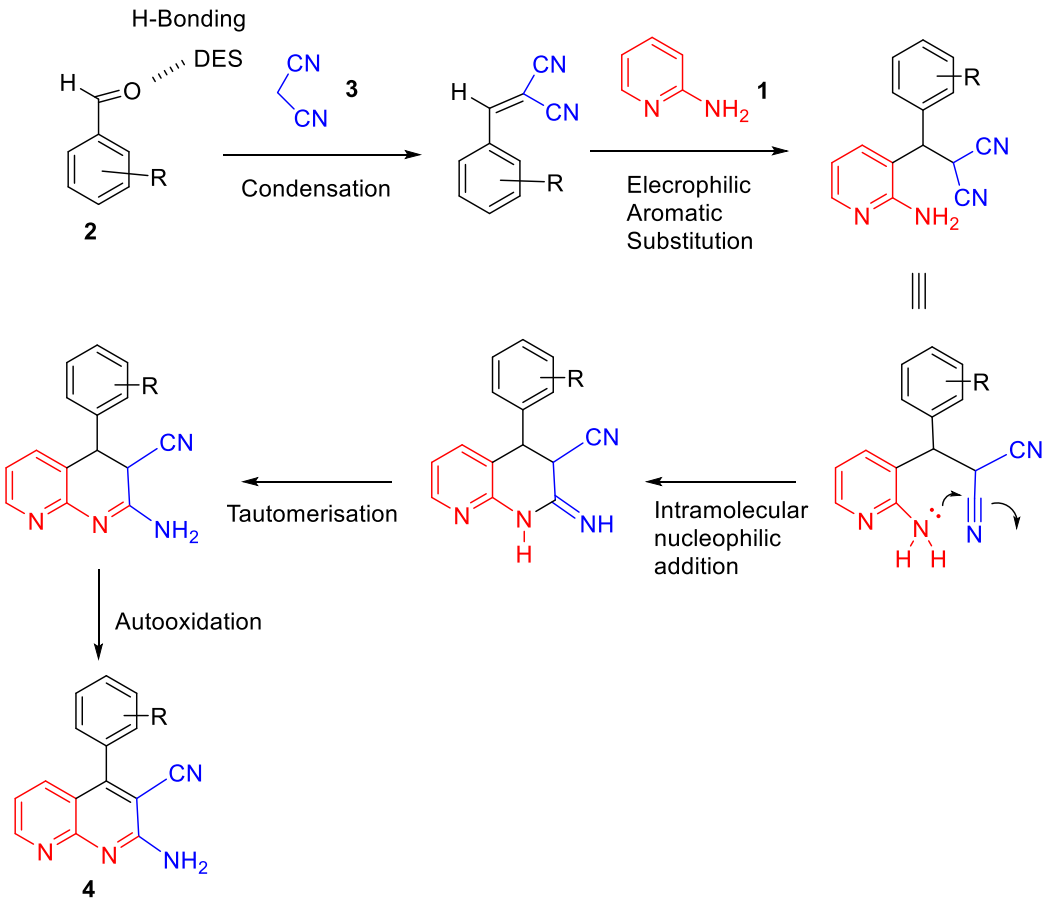


Figure 2. Plausible reaction mechanism for the formation of 1,8-naphthyridines

Mechanistically, the DES components likely facilitate the Knoevenagel condensation and subsequent cyclization through hydrogen bonding and acidic activation of carbonyl groups (Figure 2).

4. Conclusion

We have developed a sustainable, catalyst-free approach for the synthesis of 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitrile derivatives using lactic acid-derived DES. The optimized DES comprising lactic acid, maltose, and amla Juice served a dual role as solvent and organocatalyst, enabling the one-pot, three-component reaction under mild conditions. This protocol offers notable advantages, including operational simplicity, reduced environmental impact, low toxicity, and high product yields without the need for external reagents or harsh conditions. The findings reinforce the potential of natural-product-based DESs in green organic synthesis and suggest broader application of such systems in the field of liquid-phase sustainable chemistry.

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Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/Journal/organic-communications

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