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ARTICLE

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Application of salicylic acid as an eco-friendly and efficient catalyst for the synthesis of 2,4,6-triaryl pyridine, 2-amino-3-cyanopyridine, and polyhydroquinoline derivatives

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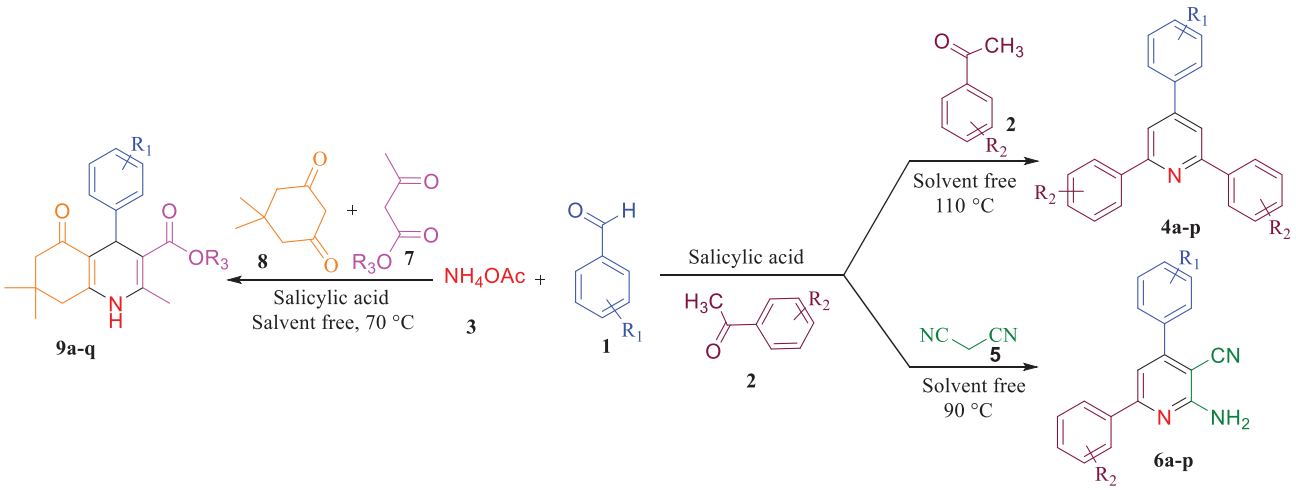
In this study, three eco-friendly, efficient, and convenient protocols have been reported for one-pot synthesis of 2,4,6-triaryl pyridine, 2-amino-3-cyanopyridine, and polyhydroquinoline derivatives using salicylic acid as a catalyst under solvent-free condition. The reported protocols offer several significant advantages such as the application of a nontoxic, neutral, and cheap catalyst, environmentally friendly conditions, the easy isolation of products by filtering, short reaction times, simple methodology, and good yields.

1 | INTRODUCTION

In recent years, the management, development, and design of chemical processes are the most important goals of green chemistry to remove or decrease the generation and use of substances that are hazardous to the environment and health.[1] Green chemistry has been widely used in all industry areas such as agriculture, household products, cosmetic, aerospace, pharmaceutical, electronics, and aerospace for their approach striving to obtain sustainability at the molecular level.[2] Hence, most investigations have focused on the design of synthetic strategies containing environmentally friendly conditions such as using a green catalyst, low temperature, using the green solvents or solvent-free condition.[3–7]

Multicomponent reactions (MCRs) are useful strategies for the preparation of structurally different complex molecules with significant pharmacological and biological properties that at least three components are involved to generate a single product containing all the atoms of the starting materials. Also, multicomponent reactions have ideally exploratory power for the generation of organic molecules because they are step efficient, atom economic, so these reactions have been found to have an important role in drug discovery projects and have received significant attention from industries and academia.[8–12]

In recent years, significant attention has been focused on the synthesis of polyfunctionalized heterocyclic materials because they are essential in the drug production process, and 68% of the produced drugs are heterocyclic.[13,14] The ability to construct various structures is the most important reason for the widespread application of heterocyclic compounds to obtain the desired functions.[15,16] Among the various heterocyclic compounds, nitrogen-bearing heterocyclic molecules such as pyridine and quinoline derivatives are more important because of their various pharmaceutical and biological activities. Among the various pyridine ring, 2-amino-3-cyanopyridines and 2,4,6-triaryl pyridines are famous as Kröhnke pyridine motifs that are individually attractive.[17,18] Furthermore, it has been observed which pyridines be employed as dyes, pesticides, additives, herbicides, fungicides, and medicinally active compounds with properties such as antibacterial, anticonvulsant, antimalarial, antioxidant, and antiparasitic.[19–23] Other valuable nitrogen-containing heterocycles are polyhydroquinoline derivatives with a variety of biological activities.[24] Also, these compounds are well known as one of the most valuable classes of drugs that have a variety of biological properties such as Ca^{2+} channel blockers, antidiabetic agent, antitumor, bronchodilator, hepatoprotective, antiatherosclerotic, geroprotective, and vasodilator.[25,26]



SCHEME 1 Salicylic acid catalyzed one-pot multicomponent reaction of 2,4,6-triaryl pyridine, 2-amino-3-cyanopyridine, and polyhydroquinoline derivatives [Colour figure can be viewed at wileyonlinelibrary.com]

In this research, in continuation of the earlier study,[27–29] three eco-friendly, efficient, and convenient methods have been developed for the one-pot pseudo-four-component synthesis of 2,4,6-triaryl pyridines via various acetophenones **2**, ammonium acetate **3**, and various arylaldehydes **1**, the one-pot four-component synthesis of 2-amino-3-cyanopyridines via various acetophenones **2**, ammonium acetate **3**, various arylaldehydes **1**, and malononitrile **5**, and also the one-pot four-component synthesis of polyhydroquinolines via various arylaldehydes **1**, ammonium acetate **3**, ethyl or methyl acetoacetate **7**, and dimedone **8** in the percent of salicylic acid as a catalyst under solvent-free condition (Scheme 1).

2 | EXPERIMENTAL

2.1 | General

Melting points of pure products were obtained using an Electrothermal melting point apparatus (type 9100). All applied chemicals were prepared from Merck and Aldrich companies in high purity. BRUKER DRX-300 Avance instrument in DMSO at 300 Hz, BRUKER DRX-300 Avance instrument in DMSO at 75.6 MHz, and FT-IR-JASCO-460 plus spectrometer were applied to record ^{1}H NMR, ^{13}C NMR, and FT-IR spectra related to known compounds, respectively.

2.2 | General procedure for the pseudo-four-component synthesis of 2,4,6-triaryl pyridine derivatives

In a vial, a mixture of ammonium acetate (1.5 mmol), acetophenone derivatives (2.0 mmol), arylaldehyde derivatives (1.0 mmol), and 15 mol% of salicylic acid was heated at 110°C under solvent-free condition and the progress of the reaction was controlled by TLC. After a suitable time, the mixture of the reaction was cooled to room temperature and 2 mL of ethanol was added to the reaction mixture, and the corresponding product was filtered by Whatman filter paper. In order to further purify, the corresponding product was recrystallized in hot ethanol.

2.3 | General procedure for the four-component synthesis of 2-amino-3-cyanopyridine derivatives

In a vial, a mixture of ammonium acetate (1.5 mmol), acetophenone derivatives (1.0 mmol), malononitrile (1.0 mmol), arylaldehyde derivatives (1.0 mmol), and 5 mol% of salicylic acid was stirred at 90°C under the solvent-free condition, and the progress of the reaction was controlled by TLC. After enough time, the mixture of the reaction was allowed to cool to room temperature and 2 mL of ethanol was added to the reaction mixture, and the desired product was separated by filtering. Finally, the pure product was obtained by recrystallization from ethanol.

2.4 | General procedure for the four-component synthesis of polyhydroquinoline derivatives

In a vial, a mixture of ammonium acetate (1.5 mmol), ethyl or methyl acetoacetate (1.0 mmol), dimedone (1.0 mmol), arylaldehyde derivatives (1.0 mmol), and 10 mol% of salicylic acid was stirred at 70°C under

solvent-free condition, and the progress of the reaction was controlled by TLC. After an appropriate time, the mixture of the reaction was allowed to cool to room temperature and the desired product was washed by ethanol and separated by filtering. Finally, the product was purified by recrystallization from ethanol.

2.5 | Selected spectra for the products are given as follows

2.5.1 | 2,6-bis(4-chlorophenyl)-4-(4-methoxyphenyl)pyridine (4b)

White solid; IR(KBr): v: 3435, 3070, 2837, 1897, 1601, 1252, 825 cm^{-1}; ^1H NMR (300 MHZ, DMSO) (δ, ppm): 3.86 (s, 3H, OCH_3), 7.11 (d, 2H, J = 8.7 Hz, $H_{aromatic}$), 7.60 (d, 4H, J = 8.7 Hz, $H_{aromatic}$), 8.05 (d, 2H, J = 8.7 Hz, $H_{aromatic}$), 8.21 (s, 2H, $H_{aromatic}$), 8.37 (d, 4H, J = 8.7 Hz, $H_{aromatic}$).

2.5.2 | 2,6-bis(4-methylphenyl)-4-(4-fluorophenyl)pyridine (4c)

Yellow solid; IR (KBr): v: 3424, 2918, 1605, 1507, 818, 555 cm^{-1}; ^1H NMR (300 MHZ, DMSO-d6) (δ, ppm): 2.40 (s, 6H, $2CH_3$), 7.36 (d, 4H, J = 8.1 Hz, $H_{aromatic}$), 7.42 (d, 2H, J = 8.7 Hz, $H_{aromatic}$), 8.10 to 8.15 (m, 4H, $H_{aromatic}$), 8.25 (d, 2H, J = 8.1 Hz, $H_{aromatic}$).

2.5.3 | 2,6-bis(4-bromophenyl)-4-(4-hydroxyphenyl)pyridine (4o)

Yellow solid; IR (KBr): 3129, 1604, 1209, 820 cm^{-1}; ^1H NMR (300 MHz, DMSO-d6) (δ, ppm): 6.96 (d, 2H, J = 8.4 Hz, $H_{aromatic}$), 7.73 (d, 4H, J = 8.4), 7.93 (d, 2H, J = 8.7 Hz, $H_{aromatic}$), 8.16 (s, 2H, $H_{aromatic}$), 8.28 (d, 4H J = 8.4 Hz, $H_{aromatic}$), 9.91 (s, 1H, OH); ^{13}C NMR (300 MHz, DMSO-d6): δ = 159.40, 155.66, 150.11, 138.41, 132.08, 129.41, 129.18, 128.30, 123.30, 116.33. MS (EI, 70 ev): M_Z, M^+ = 479.9.

2.5.4 | 2,6-bis(4-chlorophenyl)-4-(4-hydroxyphenyl)pyridine (4p)

Yellow solid; IR(KBr): v: 3102, 1897, 1601, 1212, 828 cm^{-1}; ^1H NMR (300 MHz, DMSO-d6) (δ, ppm): 6.95 (d, 2H, J = 8.7 Hz, $H_{aromatic}$), 7.60 (d, 4H, J = 8.4 Hz), 7.95 (d, 2H, J = 8.4 Hz $H_{aromatic}$), 8.18 (s, 2H, $H_{aromatic}$), 8.36 (d, 4H, J = 8.4 Hz, $H_{aromatic}$), 9.91 (s, 1H, OH); ^{13}C NMR (300 MHz, DMSO d_6): δ = 159.39, 155.55, 150.08, 138.05, 134.51, 129.16, 128.29, 116.35, 116.29. MS (EI, 70ev): M_Z, M^+ = 391.9.

2.5.5 | 2-amino-4-(4-bromophenyl)-6-(4-chlorophenyl)nicotinonitril (6m)

White solid; IR (KBr): ν: 3499, 3376, 2208, 1545, 1010, 820, 498 cm^{-1}; ^1H-NMR (300 MHz, DMSO-d6) (δ, ppm): 7.12 (s, 2H, NH_2), 7.33 (s, 1H, $H_{aromatic}$), 7.56 to 8.19 (m, 8H, $H_{aromatic}$); ^{13}C NMR (300 MHz, DMSO-d6): (δ, ppm): 161.25, 157.87, 154.35, 136.73, 136.51, 135.50, 132.42, 132.17, 131.02, 129.52, 129.17, 123.77, 117.23, 109.51, 87.21. MS (EI, 70 ev): M_Z, M^+ = 383.9.

2.5.6 | 2-amino-4-(naphthalen-2-yl)-6-(p-tolyl)nicotinonitrile (6n)

Yellow solid; IR (KBr): ν: 3485, 3307, 2206, 3192, 3039 cm^{-1}; ^1H-NMR (300 MHz, DMSO-d6) (δ, ppm): 2.38 (s, 3H, CH_3), 7.04 (s, 2H, NH_2), 7.33 (d, 2H, J = 8.1 Hz, $H_{aromatic}$), 7.39 (s, 1H, $H_{aromatic}$), 7.61 to 7.67 (m, 2H, $H_{aromatic}$), 7.80 (dd, 1H J = 8.4 Hz, J = 1.8 Hz, $H_{aromatic}$), 8.02 to 8.12 (m, 5H, $H_{aromatic}$), 8.27 (s, 1H, $H_{aromatic}$); ^{13}C NMR (300 MHz, DMSO-d6): δ = 161.36, 159.08, 155.26, 140.42, 135.28, 135.00, 133.56, 133.08, 129.74, 128.94, 128.73, 128.39, 128.13, 127.70, 127.24, 126.29, 117.68, 109.65, 86.99, 21.40. MS (EI, 70 ev): M_Z, M^+ = 336.1.

2.5.7 | 2-amino-4-(4-methylphenyl)-6-(4-methoxyphenyl)nicotinonitril (6o)

White solid; IR (KBr): ν: 3499, 3376, 2208 cm^{-1}; ^1H-NMR (300 MHz, DMSO-d6) (δ, ppm): 2.38 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.93 (s, 2H, NH_2), 7.12 (d, 2H, J = 9 Hz, $H_{aromatic}$), 7.23 (s, 1H, $H_{aromatic}$), 7.31 (d, 2H, J = 8.1 Hz, $H_{aromatic}$), 7.66 (dd, 2H, J = 9.1 Hz, J = 1.8 Hz, $H_{aromatic}$), 8.05 (d, 2H, J = 8.1 Hz, $H_{aromatic}$); ^{13}C NMR (300 MHz, DMSO-d6): δ = 161.41, 160.86, 158.89, 154.83, 140.30, 135.34, 130.31, 129.71, 129.62, 127.64, 117.88, 114.62, 109.16, 86.48, 55.83, 21.39; MS (EI, 70 ev); M_Z, M^+ = 316.

2.5.8 | 2-amino-6-(4-chlorophenyl)-4-(naphthalen-2-yl)nicotinonitrile (6q)

White solid; IR (KBr): ν: 3460, 3372, 2209 cm^{-1}; ^1H-NMR (300 MHz, DMSO-d6) (δ, ppm): 7.13 (s, 2H, NH_2), 7.46 (s,

2H, $H_{aromatic}$), 7.58 to 7.66 (m, 4H, $H_{aromatic}$), 7.82 (dd, 1H, $J = 8.4$ Hz, $J = 1.8$ Hz, $H_{aromatic}$), 8.03 to 8.13 (m, 3H, $H_{aromatic}$), 8.22 (d, 2H, $J = 8.4$ Hz, $H_{aromatic}$), 8.29 (s, 1H, $H_{aromatic}$); ^{13}C NMR (62.5 MHz, DMSO-d6): δ = 161.32, 157.76, 155.59, 136.89, 135.46, 134.81, 133.60, 133.06, 129.54, 129.18, 128.95, 128.75, 128.48, 128.14, 127.73, 127.29126.26, 117.47, 109.98, 87.73. MS (EI, 70ev); M_Z, $M^+ = 355.2$.

2.5.9 | Ethyl 2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9a)

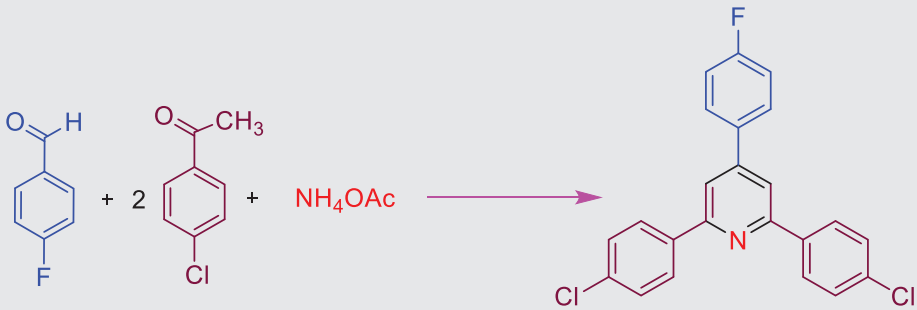
White solid; IR (KBr): ν: 3290, 2963, 1698, 1620, 1484, 1211 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (δ, ppm): 0.86 (s, 3H, CH_3), 1.02 (s,3H, CH_3), 1.14 (t, 3H, $J = 7.2$ Hz, CH_3), 1.96 to 2.33 (m, 4H, CH_2), 2.33 (s, 3H, CH_3), 3.99 (q, 2H,

TABLE 1 Investigation of the synthesis of 2,4,6-triaryl pyridines in the presence of the different catalysts at 110°C

Entry	Catalyst (15 mol%)	Solvent	Time (min)	Isolated yield (%)
1	**Salicylic acid**	**Solvent free**	**25**	**90**
2	DABCO	Solvent free	150	45
3	Lactose	Solvent free	180	35
4	Tannic acid	Solvent free	100	42
5	Benzilic acid	Solvent free	90	65
6	Bismuth chloride	Solvent free	240	48
7	Cobalt (II) nitrate hexahydrate	Solvent free	240	54

Note: Bold indicates optimized conditions.

TABLE 2 Optimization of reaction conditions for the synthesis of 2,4,6-triaryl pyridines [Colour figure can be viewed atwileyonlinelibrary.com]



Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Time (min)	Yield (%)
1	5	Solvent free	110	50	65
2	10	Solvent free	110	35	80
3	**15**	**Solvent free**	**110**	**25**	**90**
4	20	Solvent free	110	25	88
5	25	Solvent free	110	22	83
6	30	Solvent free	110	25	79
7	35	Solvent free	110	25	73
8	15	Solvent free	25	360	Trace
9	15	Solvent free	50	240	20
10	15	Solvent free	60	180	35
11	15	Solvent free	70	100	48
12	15	Solvent free	80	60	54
13	15	Solvent free	90	45	63
14	15	Solvent free	100	35	77
15	15	Solvent free	120	25	87
16	15	Solvent free	130	20	86

Note: Bold indicates optimized conditions.

J = 7.2 Hz, OCH_2), 4.87 (s, 1H, CH), 7.05 to 7.22 (m, 5H, $H_{aromatic}$), 9.07 (s, 1H, NH).

2.5.10 | Methyl 4-(3,4-dimethoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9o)

White solid; IR (KBr): ν: 3276, 3202, 3076, 2945, 1699, 1602, 1380, 1217, cm^{-1}; ^1H NMR (300 MHz, DMSO) (δ, ppm): 0.89 (s, 3H, CH_3), 1.03 (s,3H, CH_3), 1.99 to 2.41 (m, 4H, CH_2-CMe_2-CH_2), 2.30 (s 3H, CH_3-C=), 3.57 (s, 3H, CO_2Me), 3.67 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 4.83 (s, 1H, CH), 6.61 to 6.79 (m, 3H, $H_{aromatic}$), 9.07 (s, 1H, NH); ^{13}C NMR (300 MHZ, DMSO-d6): δ = 194.94, 167.92, 149.92, 148.54, 147.42, 145.41, 140.76, 119.45, 111.93, 103.97, 55.85, 55.75, 51.11, 50.73, 35.41, 32.59, 29.70, 26.85, 18.73; MS (EI, 70 ev): M_Z, M^+ = 386.

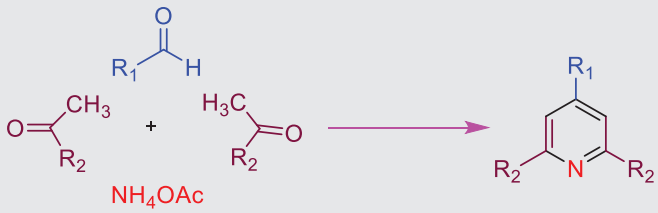
2.5.11 | Methyl4-(2,4-dimethoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9p)

White solid; IR(KBr): ν: 3290, 3082, 2963,1698, 1640, 1484, 1211, cm^{-1}; ^1H NMR (300 MHz, DMSO) (δ, ppm): 0.87 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.89 to 2.53 (m, 4H, CH_2), 2.28 (s, 3H, CH_3-C=), 3.35 (s, 3H, OMe), 3.50 (s, 3H, OMe), 3.70 (s, 3H, OMe), 4.98 (s, 1H, CH), 6.33 to 6.98 (m, 3H, $H_{aromatic}$), 8.94 (s, 1H, NH); ^{13}C NMR (300 MHZ, DMSO-d6): δ = 194.30, 168.34, 159.09, 158.41, 150.25, 144.19, 130.97, 128.26, 109.28, 104.70, 103.67, 98.71, 55.81, 55.41, 50.90, 50.82, 32.46, 32.67, 29.82, 26.75, 18.46, MS(EI, 70 ev): M_Z, M^+ = 386.

2.5.12 | Methyl 2,7,7-trimethyl-5-oxo-4-(3,4,5-trimethoxyphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9q)

White solid; IR (KBr): ν: 3283, 3077, 2960, 2933, 1699, 1648, 1503, 1221 cm^{-1}; ^1H NMR (300 MHz, DMSO) (δ, ppm): 0.95 (s, 3H, CH_3), 1.04 (s,3H, CH_3), 2.02 to 2.53 (m, 4H, CH_2), 2.29 (s, 3H, CH_3-C=), 3.35 (s, 3H, CO_2Me), 3.61 (s, 3H, OCH_3), 3.69 (s, 6H, $2OCH_3$), 4.85 (s, 1H, CH), 6.42 (s, 2H, $H_{aromatic}$), 9.11 (s, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d6): δ = 194.95, 167.89, 152.85, 150.33, 145.52, 143.66, 136.24, 110.08, 104.93, 103.86, 60.35, 56.12, 51.13, 50.73, 36.03, 32.59, 29.74, 26.84, 18.73. MS(EI, 70 ev): M_Z, M^+ = 416.

TABLE 3 Synthesis of 2,4,6-triaryl pyridine derivatives in the presence of salicylic acid (15 mol%) as catalyst under solvent-free condition at 110°C [Colour figure can be viewed atwileyonlinelibrary.com]

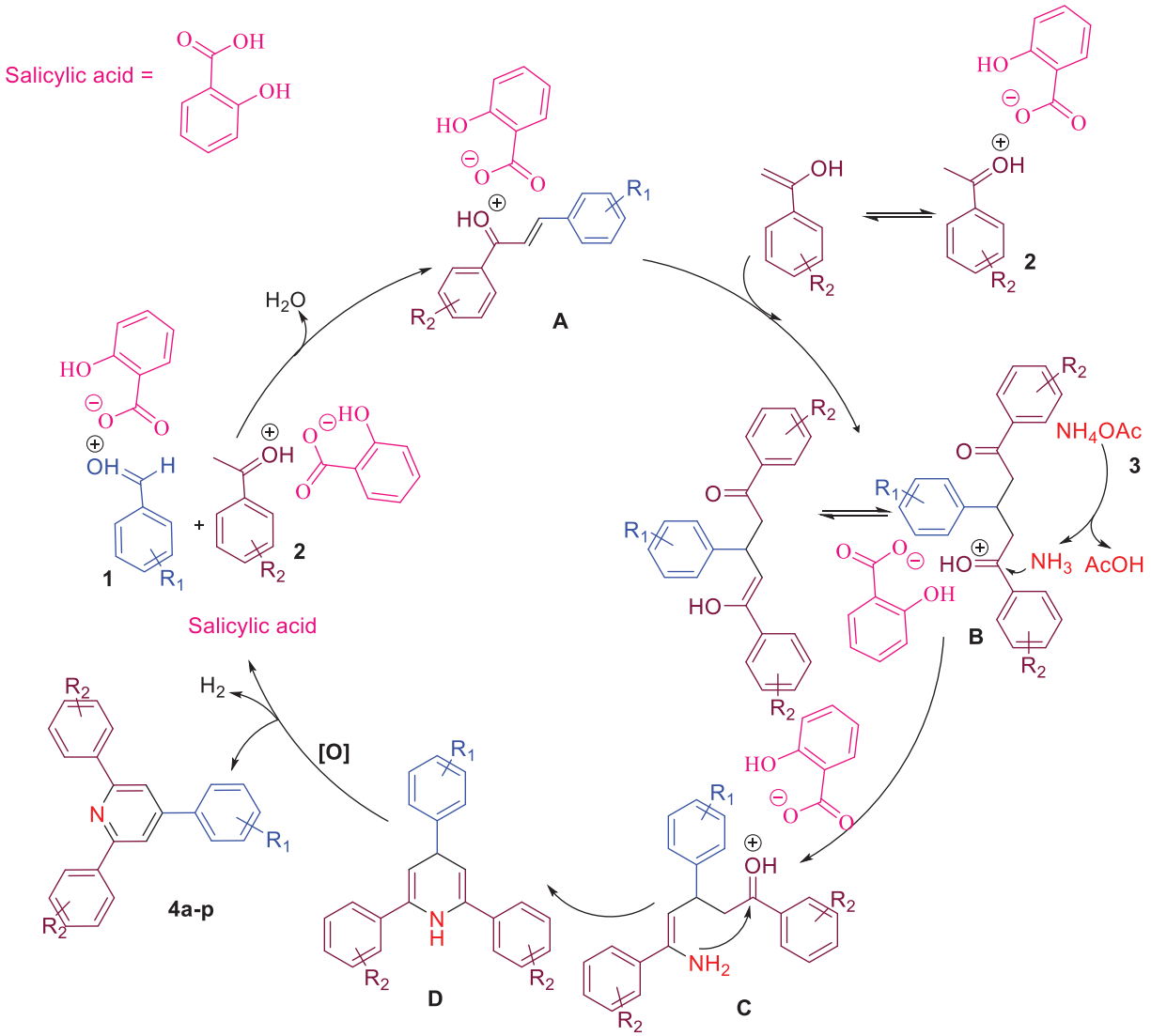


Entry	R_1	R_2	Product	Time (min)	Isolated yield (%)	M.p (°C)	M.p (°C) [References]
1	4-OH-Ph	4-Me-Ph	**4a**	70	86	162-164	164-165 [34]
2	4-OMe-Ph	4-Cl-Ph	**4b**	10	90	191-192	188-190 [30]
3	4-F-Ph	4-Me-Ph	**4c**	30	85	185-186	202-204 [34]
4	4-F-Ph	4-Cl-Ph	**4d**	25	90	243-245	242-244 [34]
5	3-F-Ph	4-Cl-Ph	**4e**	15	95	250-252	250-252 [34]
6	4-NO_2-Ph	4-Cl-Ph	**4f**	45	87	190-191	188-190 [34]
7	3-NO_2-Ph	4-Cl-Ph	**4g**	55	58	227-229	230-232 [30]
8	4-Me-Ph	4-Cl-Ph	**4h**	40	82	202-204	201-203 [31]
9	4-OH-Ph	4-OMe-Ph	**4i**	50	90	235-237	243-245 [31]
10	Ph	4-Cl-Ph	**4j**	25	84	175-177	180-182 [30]
11	4-NO_2-Ph	Ph	**4k**	60	87	200-202	196-198 [35]
12	4-Cl-Ph	4-Me-Ph	**4l**	30	75	197-200	200-202 [35]
13	4-Br-Ph	Ph	**4m**	50	88	113-115	103-105 [35]
14	4-$N(CH_3)_2$-Ph	4-Cl-Ph	**4n**	75	72	147-149	139-140 [32]
15	4-OH-Ph	4-Br-Ph	**4o**	40	82	258-260	This work
16	4-OH-Ph	4-Cl-Ph	**4p**	30	88	263-264	This work

3 | RESULTS AND DISCUSSION

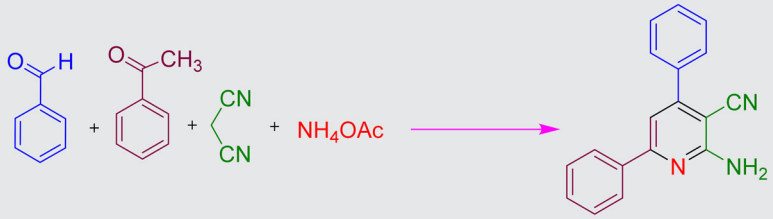
In this article, we describe three practical protocols using salicylic acid as an efficient catalyst. It is noteworthy that according to the previous studies in the literature,[28,30–33] the synthesis of 2,4,6-triaryl pyridines, 2-amino-3-cyanopyridines, and polyhydroquinolines has not progressed well in the presence of solvents such as water, ethanol, and water:ethanol, so the solvent-free condition was chosen as a good and green condition in this study. In the first protocol, to study the optimal performance in the synthesis of 2,4,6-triaryl pyridines, ammonium acetate (1.5 mmol), 4-F-acetophenone (2.0 mmol), and 4-Cl-benzaldehyde (1.0 mmol) were chosen as model substrates. Initially, the different catalysts were tested for the synthesis of 2,4,6-triaryl pyridines at 110°C under solvent-free condition (Table 1). It has been found which salicylic acid is a suitable catalyst for the synthesis of 2,4,6-triaryl pyridines with short reaction times and high yields. Subsequently, the model reaction was investigated using various amounts of salicylic acid and different temperatures under solvent-free condition, and the results are summarized in Table 2. Observably, when the model reaction was performed in the percent of 15 mol% of catalyst at 110°C under solvent-free condition (entire 3), the best yield and time reaction were achieved.

After optimization, optimized reaction conditions were applied for the preparation of 2, 4, 6-triaryl pyridine derivatives using various acetophenones and arylaldehydes with electron-donating or electron-withdrawing groups to investigate the efficiency of this



SCHEME 2 The proposed synthetic pathway for the synthesis of 2,4,6-triaryl pyridine derivatives [Colour figure can be viewed at wileyonlinelibrary.com]

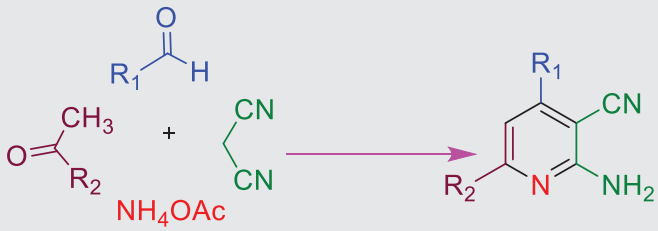
TABLE 4 Optimization of reaction conditions for the synthesis of 2-amino-3-cyanopyridines [Colour figure can be viewed atwileyonlinelibrary.com]



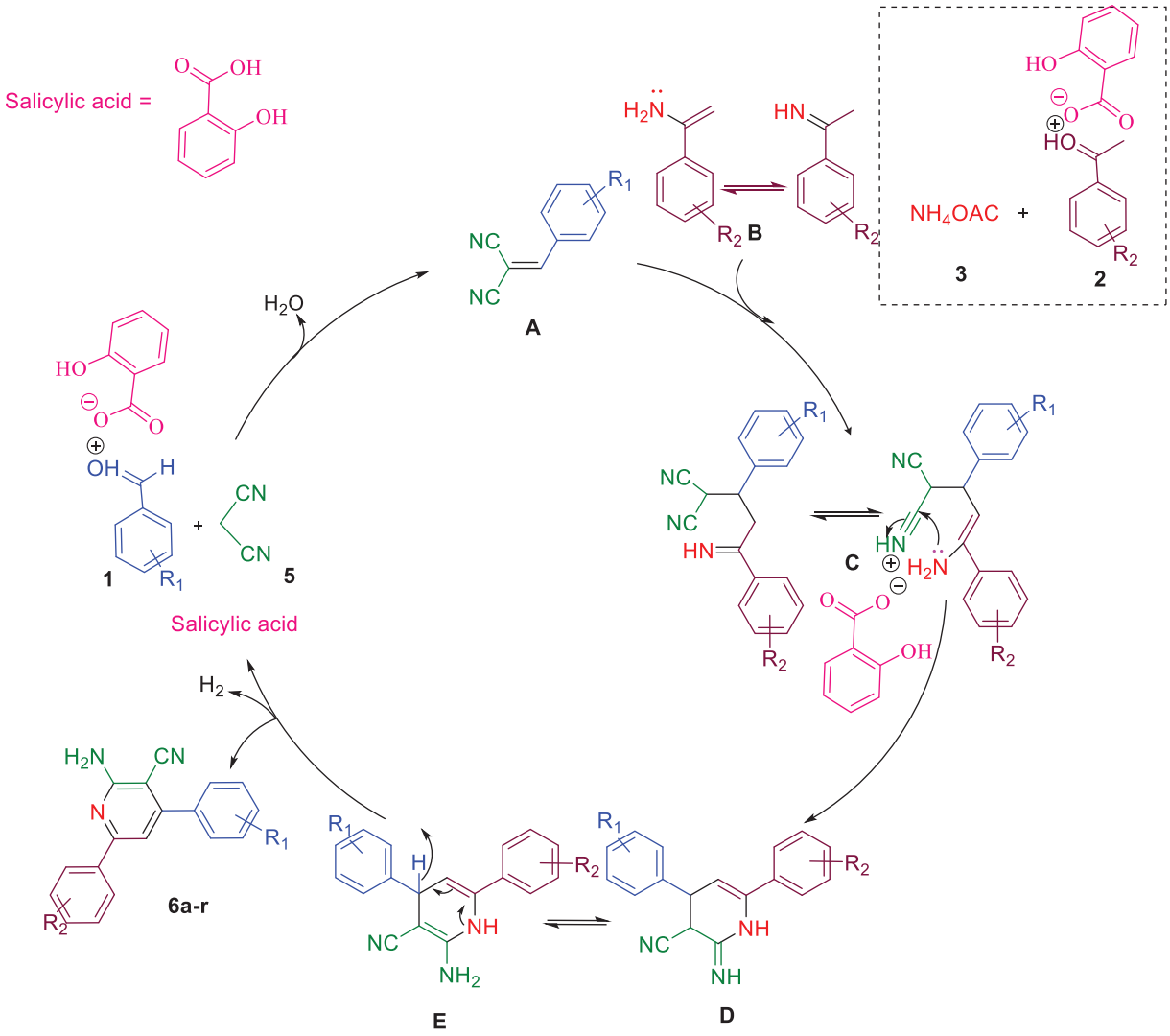
Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Time (min)	Yield (%)
1	**5**	**Solvent free**	**90**	**20**	**92**
2	10	Solvent free	90	20	92
3	15	Solvent free	90	20	90
4	20	Solvent free	90	20	85
5	25	Solvent free	90	20	76
6	30	Solvent free	90	20	72
7	5	Solvent free	25	300	Trace
8	5	Solvent free	50	150	55
9	5	Solvent free	70	85	75
10	5	Solvent free	80	45	82
11	5	Solvent free	100	25	92
12	5	Solvent free	110	20	90
13	5	Solvent free	120	20	88

Note: Bold indicates optimized conditions.

TABLE 5 Synthesis of 2-amino-3-cyanopyridine derivatives in the presence of salicylic acid (5 mol%) as catalyst under solvent-free condition at 90°C [Colour figure can be viewed atwileyonlinelibrary.com]



Entry	R_1	R_2	Product	Time (min)	Isolated yield (%)	M.p (°C)	M.p (°C) [References]
1	Ph	Ph	**6a**	25	92	186-187	186-187 [36]
2	4-OMe-Ph	Ph	**6b**	35	92	173-174	180-182 [36]
3	4-F-Ph	Ph	**6c**	10	95	144-146	148-150 [37]
4	4-Me-Ph	Ph	**6d**	20	90	150-151	173-175 [36]
5	4-NO_2-Ph	Ph	**6e**	50	88	210-212	212-213 [37]
6	4-OMe-Ph	4-Cl-Ph	**6f**	30	80	194-196	205-207 [38]
7	Ph	4-Cl-Ph	**6g**	35	86	237-239	238-240 [37]
8	4-Br-Ph	Ph	**6h**	25	96	198-200	195-197 [37]
9	4-Cl-Ph	Ph	**6i**	15	93	230-232	234-236 [37]
10	Ph	4-Me-Ph	**6j**	20	91	170-172	172-174 [39]
11	2-Cl-Ph	Ph	**6k**	40	80	192-195	194-197 [37]
12	4-F-Ph	4-Cl-Ph	**6l**	20	90	238-240	242-243 [40]
13	4-Br-Ph	4-Cl-Ph	**6m**	20	94	240-242	This work
14	2-Nph	4-Me-Ph	**6n**	60	73	210-212	This work
15	4-OMe-Ph	4-Me-Ph	**6o**	40	80	142-144	This work
16	2-Nph	4-Cl-Ph	**6p**	35	86	210-212	This work



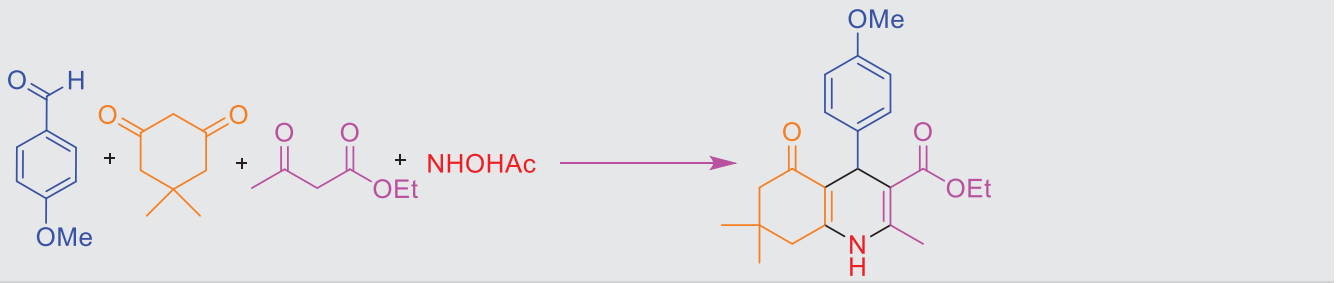
SCHEME 3 The proposed synthetic pathway for the synthesis of 2-amino-3-cyanopyridines [Colour figure can be viewed at wileyonlinelibrary.com]

protocol (Table 3). As expected, all of the 2,4,6-triaryl pyridine derivatives were easily synthesized in excellent to good yields that make this method be useful for the synthesis of 2,4,6-triaryl pyridine.

The mechanism for the synthesis of 2,4,6-triaryl pyridine derivatives is not clear enough. According to previous studies in the literature,[32,35] a catalyzed proposed mechanism with salicylic acid is suggested in Scheme 2. Mechanistically, carbonyl groups of the desired arylaldehyde **1** and acetophenone **2** have been protonated and activated by salicylic acid (a Brønsted acid catalyst) and the reaction has been initially progressed by an aldol condensation to generate a 1,3-diaryl-2-propen-1-one **A**. Then, intermediate **B** has been achieved by Michael addition between another equivalent of activated acetophenone and 1,3-diaryl-2-propen-1-one **A**. Next, NH_3 formed from the destruction of ammonium acetate **3** attacked intermediate B in the presence of salicylic acid as a Brønsted acid catalyst to form intermediate **C**. Finally, The formation of the final desired product (**4a-p**) has been followed by cyclized, dehydrogenated, and tautomerization of intermediate **C** and the generated H^+ of catalyst is released back into the catalytic route.

In the second protocol, the one-pot synthesis of 2-amino-3-cyanopyridins has been developed using salicylic acid as a green catalyst under solvent-free condition. To study the optimal performance in the synthesis of 2-amino-3-cyanopyridines, ammonium acetate (1.5 mmol),

TABLE 6 Optimization of reaction conditions for the synthesis of polyhydroquinolines [Colour figure can be viewed atwileyonlinelibrary.com]



Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Time (min)	Yield (%)
1	**10**	**Solvent free**	**70**	7	**93**
2	15	Solvent free	70	7	93
3	20	Solvent free	70	10	93
4	25	Solvent free	70	20	90
5	30	Solvent free	70	25	85
6	10	Solvent free	25	240	40
7	10	Solvent free	30	180	50
8	10	Solvent free	40	90	65
9	10	Solvent free	50	20	73
10	10	Solvent free	60	15	85
11	10	Solvent free	80	7	94

Note: Bold indicates optimized conditions.

acetophenone (1.0 mmol), benzaldehyde (1.0 mmol), and malononitrile (1.0 mmol) were chosen as model substrates. For this purpose, the different amounts of catalyst and various temperatures were tested in the model reaction under solvent-free condition, and the best result was achieved by 5 mol% of catalyst at 90°C (Table 4, entry 1).

After optimization, in order to check the efficiency of this protocol, optimized reaction conditions were applied for the preparation of 2-amino-3-cyanopyridine derivatives using various acetophenones and arylaldehydes with electron-donating or electron-withdrawing groups. As evident from Table 5, salicylic acid shows high catalytic activity in the synthesis of all derivatives of 2-amino-3-cyanopyridines.

The mechanism for the synthesis of 2-amino-3-cyanopyridin derivatives is not clear enough. According to the literature review,[28,37] a catalyzed proposed mechanism with salicylic acid is suggested in Scheme 3. The acid-base interactions between salicylic acid as a Lewis acid, arylaldehyde, and acetophenone lead to active C═O groups of arylaldehyde **1** and acetophenone **2**. Immediately, malononitrile **5** reacts with activated arylaldehyde via Knoevenagel condensation followed by dehydration to generate intermediate **A**. On the other hand, generated ammonia from ammonium acetate **3** reacts with activated acetophenone to form the enamine intermediate **B**. Afterward, this enamine intermediate **B** reacts with intermediate **A** to give intermediate **C**. Here, the presence of salicylic acid as a catalyst helps to afford the desired products (**6a-p**) after intramolecular cyclization, tautomerization, and aromatization.

Finally, the attractive results achieved in the synthesis of 2,4,6-triaryl pyridines and 2-amino-3-cyanopyridines led us to investigate the ability of salicylic acid in the synthesis of polyhydroquinoline derivatives. Therefore, the reaction between 4-OMe-benzaldehyde, ammonium acetate, ethyl acetoacetate, and dimedone was chosen as a model to study the optimization of the reaction parameters such as temperature and amount of catalyst, and the results are presented in Table 6. According to the results summarized in Table 6, the optimized conditions were obtained to be as follows: 4-OMe-benzaldehyde (1.0 mmol), ammonium acetate (1.5 mmol), ethyl acetoacetate (1.0 mmol), dimedone (1.0 mmol), and salicylic acid (10 mol%) at 70°C under solvent-free condition (Table 6, entry 1).

In an attempt to generalize the utility of this methodology, a series of polyhydroquinolines were synthesized using many types of benzaldehydes containing electron-

TABLE 7 Synthesis of polyhydroquinoline derivatives in the presence of salicylic acid (10 mol%) as catalyst under solvent-free condition at 70°C [Colour figure can be viewed atwileyonlinelibrary.com]

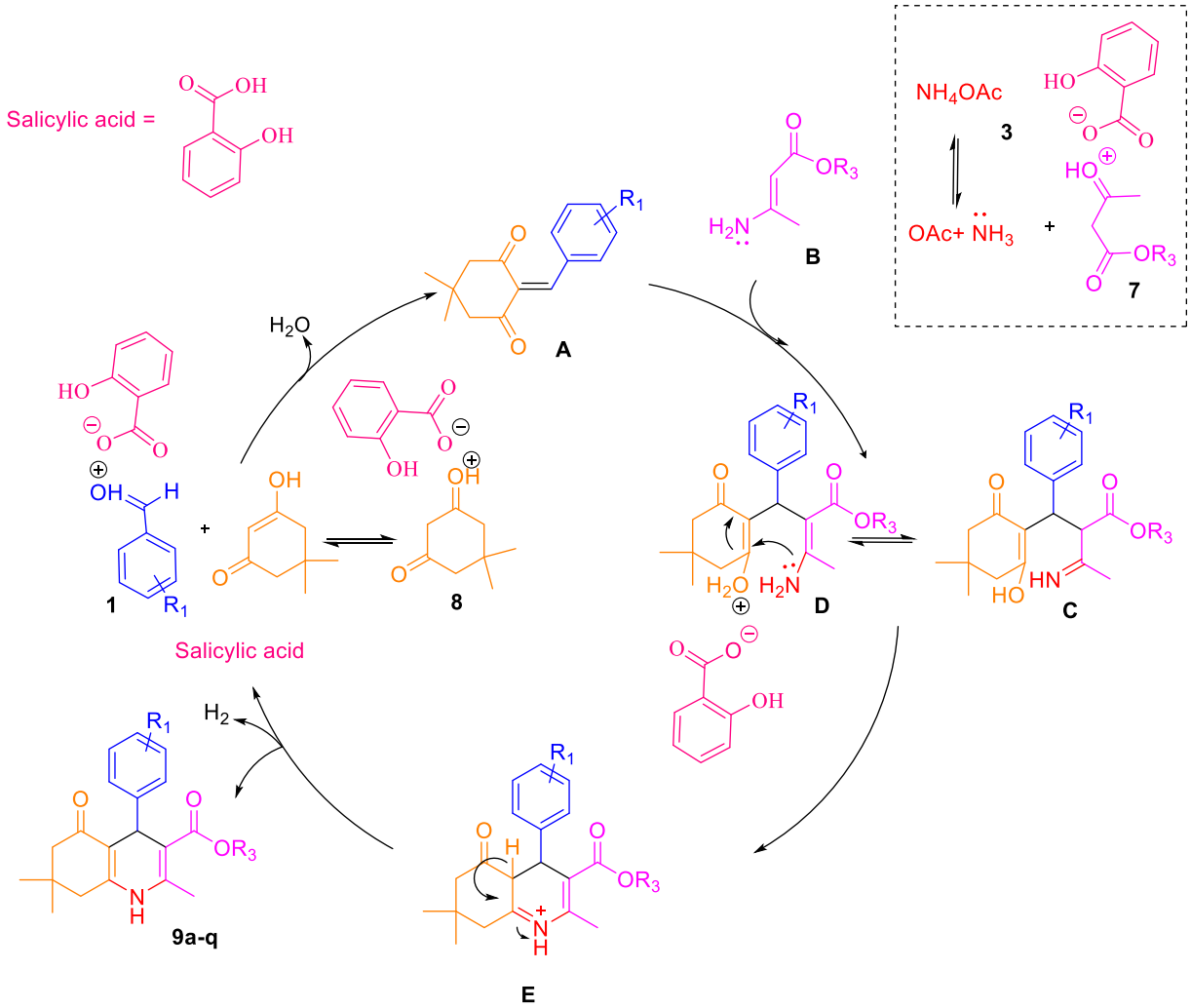
Entry	R_1	R_3	Product	Time (min)	Isolated yield (%)	M.p (°C)	M.p (°C) [References]
1	H	Et	**9a**	7	92	206-208	205-207 [33]
2	3-F	Et	**9b**	8	88	210-212	206-208 [33]
3	4-Cl	Et	**9c**	5	85	247-249	244-246 [33]
4	4-Br	Et	**9d**	5	89	252-254	255-257 [33]
5	4-OH	Et	**9e**	8	80	222-224	234-236 [33]
6	4-NO_2	Et	**9f**	10	88	242-244	242-244 [41]
7	3-NO_2	Et	**9g**	9	92	180-181	175-177 [42]
8	2-NO_2	Et	**9h**	8	85	198-200	207-209 [33]
9	2-Cl	Et	**9i**	6	90	201-203	209-211 [42]
10	4-Me	Et	**9j**	5	90	255-257	259-261 [33]
11	4-OMe	Et	**9k**	7	93	253-256	258-259 [33]
12	4-$N(CH_3)_2$	Et	**9l**	8	90	230-232	231-233 [42]
13	3-OMe-4-OH	Et	**9m**	5	91	210-212	206-208 [41]
14	3-OH	Et	**9n**	7	85	218-220	217-219 [42]
15	3,4-di-OMe	Me	**9o**	8	90	200-202	This work
16	2,4-di-OMe	Me	**9p**	10	80	246-248	This work
17	3,4,5-tri-OMe	Me	**9q**	9	92	262-264	This work

withdrawing and electron-donating moieties. As tabulated in Table 7, all of the polyhydroquinolines derivatives were efficiently synthesized in excellent to good yields and short reaction times that make this methodology useful for the synthesis of polyhydroquinolines.

The mechanism for the synthesis of polyhydroquinoline derivatives is not clear enough. Based on the literature review,[33,41,42] a catalyzed proposed mechanism with salicylic acid is suggested in Scheme 4. Carbonyl groups of the desired arylaldehydes **1**, ethyl or methyl acetoacetate **7**, and dimedone **8** have been protonated and activated by salicylic acid (a Brønsted acid catalyst), and the reaction has been initially progressed by a Knoevenagel condensation between enol form of dimedone with activated arylaldehyde to form a 2-benzylidenedimedone **A**. On the other hand, NH_3 obtained from ammonium acetate **3** linked to activated ethyl or methyl acetoacetate with salicylic acid to generate enamine **B**. Afterward, intermediate **C** has been achieved by Michael addition between enamine **B** and 2-benzylidenedimedone **A**. Then, intermediate **C** has been changed to intermediate **D** by tautomerization. Finally, the presence of salicylic acid as a catalyst helps to afford the desired product (**9a-q**) after intramolecular cyclization, dehydrogenated, and aromatization.

4 | COMPARISON

In order to highlight the importance and efficiency of these protocols, the present results were compared with several reported data. Based on Table 8, our catalytic protocols show a high catalytic activity and are superior in terms of reaction conditions, product yield, and reaction time.



SCHEME 4 The proposed mechanism for the synthesis of polyhydroquinolines [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 8 Comparison of the efficiency of salicylic acid with other catalysts in the literature

Entry	Product	Catalyst	Amount	Condition	Time (min)	Yield (%)	References
1	**4k**	$CoCl_2.6H_2O$	2.5 mol%	Solvent-free, 110°C	—	84	35
		Nanocrystalline $MgAl_2O_4$	5 mol%	AcOH, 90°C	55	98	32
		CMC-Ce^{IV}	4 mol%	Solvent-free, 80°C	89	60	31
		Salicylic acid	15 mol%	Solvent-free, 110°C	25	84	This work
2	**6a**	Cobalt (II) nitrate hexahydrate	20 mol%	Solvent-free, 100°C	20	91	28
		ClO_4/Al-MCM-41	20 mg	Solvent-free, 100°C	20	73	36
		$\{Fe_3O_4@SiO_2@(CH_2)_3Im\}C(CN)_3$	7 mg	Solvent-free, 100°C	40	86	37
		Salicylic acid	5 mol%	Solvent-free, 90°C	25	92	This work
	9a	Chitosan	15 mg	Solvent-free, 60°C	8	91	33
		{[TPPSP]OTf}	0.5 mol%	Solvent-free, r.t	13	95	42
		$Yb(OTf)_3$	5 mol%	EtOH, r.t	300	90	43
		Salicylic acid	10 mol%	Solvent-free, 70°C	7	92	This work

5 | CONCLUSIONS

In brief, we present three versatile and simple protocols for preparing 2,4,6-triaryl pyridine, 2-amino-3-cyanopyridine, and polyhydroquinoline derivatives using mild reaction condition, and salicylic acid as an eco-friendly and efficient catalyst. These synthetic strategies showed some striking advantages such as the absence of solvents, high reaction rate, simple purification and work-up, highly catalytic nature of salicylic acid, cheap and cost-effective methodology, excellent yields, and simple operation.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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