Three-Component One-Pot Synthesis of 2,4,6-Triarylpyridines without Catalyst and Solvent

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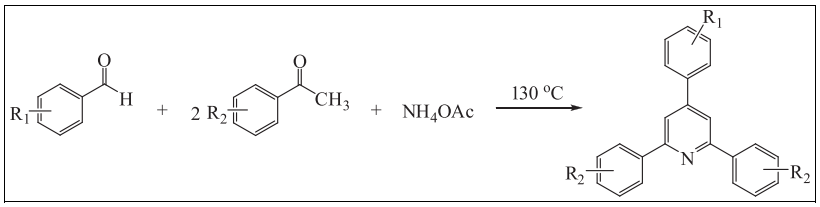

An efficient and green synthesis of 2,4,6-triarylpyridines by a one-pot three-component condensation of aromatic aldehydes, substituted acetophenones, and ammonium acetate without catalyst at 130°C under solvent-free conditions is described. This method offers several advantages such as simple procedure, easy work-up, short reaction time, low cost, environmentally friendly conditions, and moderate to high yields.

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INTRODUCTION

In modern synthetic organic chemistry, multi-component reactions (MCRs) have been regarded as efficient tools because MCRs fulfilled the requirements of environmentally friendly processes by reducing the number of synthetic steps, decreasing energy and resources consumption, and isolating no intermediates. The product purity was improved. Therefore, developing new MCRs and improving existing MCRs are very significant research areas.

Now, pyridines play a key role in biological and chemical systems. They were found in biologically active compounds and natural products such as nicotinamide adenine dinucleotides, vitamin B_6, and pyridine alkaloids [1]. Compounds containing pyridine rings show variable biological activities such as hypoglycemic activity, hypolipidemic activity, fungicidal activity, antimicrobial agent, dopamine transporter inhibitors, and anti-inflammatory agents [2–6]. The pyridine rings also used in agrochemicals such as herbicides [4]. In addition, because of their π-stacking ability, some pyridines are used in supramolecular chemistry [7].

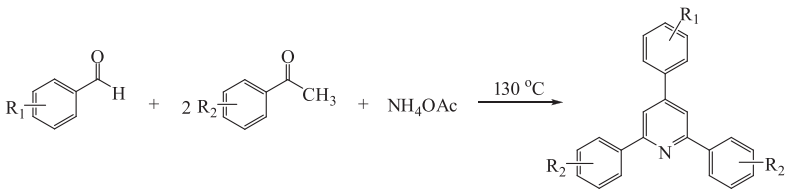
Traditionally, 2,4,6-triarylpyridines (Kröhnke-type pyridine) are synthesized from *N*-phenacylpyridinium salts with *α,β*-unsaturated ketones in the presence of ammonium acetate [8]. However, pyridinium salts and the unsaturated ketones have to be synthesized first, so the method is relative expensive, time consuming, and harmful to the environment. Since then, some new methods for the synthesis of 2,4,6-triarylpyridines have been reported, for example, the reaction of *α*-ketoketene dithioacetals with methyl ketone carbanions and ammonium acetate in hot acetic acid [9], reaction of *N*-(diphenylphosphiny)-1-phenylethanimine with aldehydes [10], solvent-free reaction of chalcones with ammonium acetate [11], three-component reaction of acetophenones, benzaldehydes, and ammonium acetate in the presence of various catalysts such as heteropolyacid [12], supported acids [13,14], solid acids [15,16], ionic liquids [17,18], phase transfer catalysts [19,20], and Lewis acids [21,22] at 120°C or under microwave irradiation. However, many of the established methods are subjected to certain disadvantages including use of costly and toxic catalysts, acidic media, and organic solvents. To avoid such drawbacks, development of more simple, inexpensive, green, and efficient protocols is still in demand.

In this research, we report a simple and green method for the synthesis of 2,4,6-triarylpyridines in moderate to high yields by the three-component condensation of various aromatic aldehydes 1, substituted acetophenones 2 with ammonium acetate at 130°C (Scheme 1). To the best of our knowledge, the synthesis of title compounds without catalyst and solvent under conventional heating conditions has not been reported. Many new products were reported first.

RESULTS AND DISCUSSION

At the onset of our research, we screened different catalysts and reaction conditions using the model reaction of benzaldehyde, acetophenone, and ammonium acetate. The results were summarized in Table 1. It can be seen that the results in the presence of catalysts were almost the same as the results in the absence of catalyst (entries 1–7). That is to say the catalyst did not show distinct catalytic activity on the reaction. Catalyst is not necessary for this conversion. A satisfied result was obtained with 1 : 2 : 1.3 molar ratio of benzaldehyde, acetophenone, and ammonium acetate in the absence of catalyst at 130°C (entry 7). Further increase or decrease of the reaction temperature cannot favor the product

Scheme 1



1 **2** **3**

Table 1

Screening of different catalysts and reaction temperature for the condensation.[a]

Entry	Catalyst (mol%)	Temp. (°C)	Time (h)	Yield (%)
1	$NaHSO_4 \cdot H_2O$ (10)	130	7.5	54
2	CH_3SO_3H (5)	130	6.0	55
3	$Al(NO_3)_3 \cdot 9H_2O$ (10)	130	10.0	57
4	$H_3O_{40}PW_{12} \cdot xH_2O$ (1)	130	6.0	75
5	$Fe_2(SO_4)_3 \cdot 9H_2O$ (10)	130	7.5	78
6	$SnCl_4 \cdot 5H_2O$ (10)	130	7.5	79
7	—	130	5.5	75
8	—	140	5.5	76
9		120	6.0	63
10		110	6.0	44

[a]Benzaldehyde, 4 mmol; acetophenone, 8 mmol; and ammonium acetate, 5.2 mmol.

yields (entries 7–10). In addition, the model reaction was also examined in various solvents at 130°C. The yield of the reaction under solvent-free conditions was the highest, and the reaction time was shortest. No conversion to product was obtained when the reaction was carried out in water (2 mL).

In order to show the generality and scope of this new protocol, we screened various aromatic aldehydes and substituted acetophenones, the results are summarized in Table 2. All reactions proceeded smoothly in the absence of catalyst. It gave the corresponding 2,4,6-triarylpyridines in moderate to high yields. Aromatic aldehydes and ketones carrying either electron-withdrawing group or electron-donating group were all suitable for use with this procedure. Compared with other reported methodologies for the synthesis of 2,4,6-triarylpyridines via one-pot reaction, the present protocol offers suitable conditions with respect to reaction time, yield, cost, and environmental pollution. However, the position of the substituents on the aromatic ring has obvious effects on this conversion. Ortho-substituted aromatic aldehydes such as 2-chlorobenzaldehyde and 2-nitrobenzaldehyde failed to give the desired products.

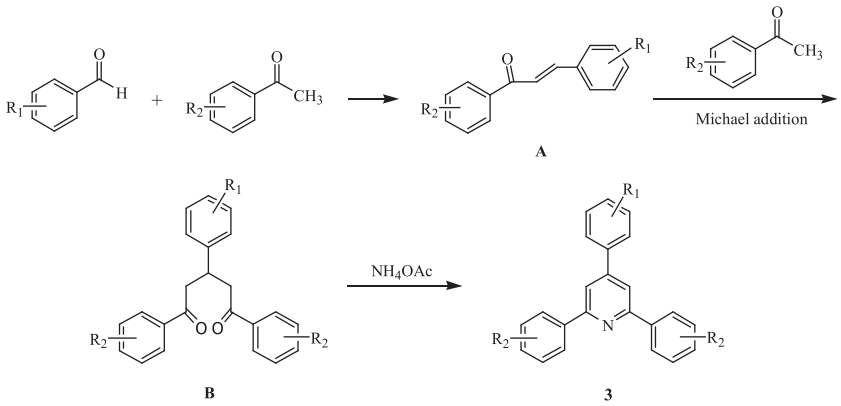
A probable mechanism for the synthesis of highly substituted pyridines has been proposed in Scheme 2. An aromatic aldehyde reacted with a substituted acetophenone

Table 2

Three-component reactions of aromatic aldehydes with substituted acetophenones and ammonium acetate at 130°C.

					mp (°C)	
Entry	R_1	R_2	Time (h)	Yield (%)	Found	Reported
3a	H	H	5.5	75	134–135	130–131 [16]
3b	4-Cl	H	2	81	124–126	120–122 [23]
3c	3-NO_2	H	6	72	126–128	—
3d	4-CH_3	H	1	79	117–118	118–118.5 [12]
3e	4-OCH_3	H	4	82	97–98	99–100 [12]
3f	4-$(CH_3)_2N$	H	2	85	139–140	136–138 [23]
3g	4-OH	H	4	60	264–266	—
3h	4-NO_2	4-NO_2	0.7	86	>300	>300°C [24]
3i	4-$(CH_3)_2N$	4-NO_2	1	79	166–167	—
3j	H	4-Cl	2	68	186–187	—
3k	4-Cl	4-Cl	5	76	269–270	264–265 [21]
3l	3-NO_2	4-Cl	1.5	75	230–232	—
3m	4-CH_3	4-Cl	1	62	221–223	—
3n	4-OCH_3	4-Cl	2.5	69	193–194	—
3o	4-$N(CH_3)_2$	4-Cl	6	77	163–164	—
3p	H	4-OCH_3	2	68	124–125	—
3q	4-CH_3	4-OCH_3	6	74	128–129	—
3r	4-OCH_3	4-OCH_3	6	78	134–135	134–135 [25]
3s	4-$N(CH_3)_2$	4-OCH_3	6	82	149–150	—

Scheme 2



to form a 1,3-diaryl-2-propen-1-one A, which further underwent *in situ* Michael addition with substituted acetophenone to yield an intermediate B. Intermediate B is then cyclized and dehydrogenated to afford the title product 3.

CONCLUSIONS

In conclusion, a novel and environmentally benign method for synthesizing 2,4,6-triarylpyridines was achieved without any catalyst and solvent. The protocol has obvious environmental benefits. In addition, it simplified the overall experimental process. Our work makes a valuable contribution to the synthesis of 2,4,6-triarylpyridines.

EXPERIMENTAL

Melting points were determined using an RY-1 micromelting point apparatus. Infrared spectra were recorded on a Scimitar 2000 series Fourier Transform instrument of VARIAN (Palo Alto, CA). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on an Agilent 400-MR instrument (Santa Clara, CA) in DMSO-d_6 using TMS as an internal standard. Mass spectra were obtained with an Agilent 1100 series LC/MSD VL ESI instrument (Santa Clara, CA). Elemental analyses were carried out on an EA 2400II elemental analyzer (PerkinElmer, Waltham, MA).

General procedure for the synthesis of 2,4,6-triarylpyridines (3). A mixture of an aromatic aldehyde 1 (4 mmol), a substituted acetophenone 2 (8 mmol), and ammonium acetate (5.2 mmol) was magnetically stirred at 130°C in an oil bath and the reaction was monitored by TLC (ethyl acetate/*n*-hexane, 1/4). After completion, the gummy mixture was purified by column chromatography over silica gel using hexane as eluent to obtain pure product. The pure products were identified by mp, IR, ^{1}H-NMR, ^{13}C-NMR, MS, and elemental analysis. The characteristic data of some new 2,4,6-triarylpyridines are given in the succeeding text:

4-(3-nitrophenyl)-2,6-diphenylpyridine (3c). Yellow solid. IR (KBr): 1603, 1526, 1438, 1397, 1350, 775, 740, 690 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.84 (s, 1H), 8.51 (d, 1H, J = 7.5 Hz), 8.38–8.28 (m, 7H), 7.86 (t, 1H, J = 7.9 Hz), 7.64–7.49 (m, 6H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 157.1, 149.0, 147.8, 139.9, 138.9, 134.6, 131.0, 129.8, 129.1, 127.5, 124.3, 122.6, 117.3. MS (ESI): *m*/*z* (%) 353 (M^++H, 100). *Anal*. Calcd for $C_{23}H_{16}N_2O_2$: C, 78.39; H, 4.58; N, 7.95. Found: C, 78.48; H, 4.52; N, 8.01.

4-(4-hydroxyphenyl)-2,6-diphenylpyridine (3g). White solid. IR (KBr): 3197, 1603, 1546, 1519, 1398, 839, 776, 696 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.90 (s, 1H), 8.32 (d, 4H, J = 7.5 Hz), 8.13 (s, 2H), 7.93 (d, 2H, J = 8.1 Hz), 7.57–7.47 (m, 6H), 6.95 (d, 2H, J = 8.1 Hz). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 159.2, 156.7, 149.8, 139.4, 129.5, 129.1, 128.5, 127.3, 116.3, 116.1. MS (ESI): *m*/*z* (%) 324 (M^++H, 100). *Anal*. Calcd for $C_{23}H_{17}NO$: C, 85.42; H, 5.30; N, 4.33. Found: C, 85.51; H, 5.34; N, 4.26.

4-(4-dimethylaminophenyl)-2,6-bis(4-nitrophenyl)pyridine (3i). Reddish brown solid. IR (KBr): 2907, 2361, 1601, 1569, 1522, 1437, 1340, 855, 806 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.37–8.31 (m, 8H), 7.75–7.73 (m, 4H), 6.76 (d, 2H, J = 8.0 Hz), 2.85 (s, 6H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 186.2, 151.1, 148.2, 145.7, 142.2, 130.1, 128.3, 122.6, 120.4, 114.4, 110.5, 43.5. MS (ESI): *m*/*z* (%) 441 (M^++H, 100). *Anal*. Calcd for $C_{25}H_{20}N_4O_4$: C, 68.17; H, 4.58; N, 12.72. Found: C, 68.06; H, 4.63; N, 12.78.

2,6-bis(4-chlorophenyl)-4-phenylpyridine (3j). White solid. IR (KBr): 2361, 1602, 1544, 1492, 1387, 834, 763 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.38 (d, 4H, J = 8.4 Hz), 8.27 (s, 2H), 8.06 (d, 2H, J = 7.3 Hz), 7.61 (d, 4H, J = 8.5 Hz), 7.58–7.53 (m, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 155.7, 150.3, 137.8, 134.6, 129.9, 129.5, 129.2, 127.9, 117.3. MS (ESI): *m*/*z* (%) 377 (M^++H, 100). *Anal*. Calcd for $C_{23}H_{15}NCl_2$: C, 73.42; H, 4.02; N, 3.72. Found: C, 73.53; H, 3.98; N, 3.77.

4-(3-nitrophenyl)-2,6-bis(4-chlorophenyl)pyridine (3l). White solid. IR (KBr): 1600, 1525, 1493, 1350, 830, 738 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.86 (s, 1H), 8.52 (d, 1H, J = 7.6 Hz), 8.41–8.35 (m, 7H), 7.86 (t, 1H, J = 8.0 Hz), 7.61 (d, 4H, J = 8.3 Hz). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 154.2, 147.3, 146.4, 137.9, 135.9, 133.1, 132.9, 129.3, 128.2, 127.6, 122.8, 121.0, 116.0. MS (ESI): *m*/*z* (%) 422 (M^++H, 100). *Anal*. Calcd for $C_{23}H_{14}N_2Cl_2O_2$: C, 65.57; H, 3.35; N, 6.65. Found: C, 65.66; H, 3.31; N, 6.70.

4-(4-methylphenyl)-2,6-bis(4-chlorophenyl)pyridine (3m). White solid. IR (KBr): 3030, 2361, 1602, 1543, 1491, 831, 811 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.37 (d, 4H, J = 8.3 Hz), 8.24 (s, 2H), 7.98 (d, 2H, J = 7.8 Hz), 7.61 (d, 4H, J = 8.3 Hz), 7.38 (d, 2H, J = 7.9 Hz), 2.41 (s, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 155.1, 149.5, 139.1, 137.3, 134.3, 134.0, 129.5, 129.1, 128.6, 127.1, 116.4, 20.7. MS (ESI): *m*/*z* (%) 391

(M^++H, 100). *Anal*. Calcd for $C_{24}H_{17}NCl_2$: C, 73.85; H, 4.39; N, 3.59. Found: C, 73.96; H, 4.32; N, 3.62.

4-(4-methoxyphenyl)-2,6-bis(4-chlorophenyl)pyridine (3n). White solid. IR (KBr): 2836, 2361, 1602, 1545, 1514, 1491, 825, 578 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.37 (d, 4H, J = 8.0 Hz), 8.21 (s, 2H), 8.05 (d, 2H, J = 8.1 Hz), 7.60 (d, 4H, J = 8.0 Hz), 7.11 (d, 2H, J = 8.1 Hz), 3.86 (s, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 160.9, 155.6, 149.7, 137.9, 134.5, 129.9, 129.1, 128.8, 116.6, 114.8, 55.8. MS (ESI): *m/z* (%) 407 (M^++H, 100). *Anal*. Calcd for $C_{24}H_{17}NCl_2O$: C, 70.95; H, 4.22; N, 3.45. Found: C, 71.07; H, 4.16; N, 3.42.

4-(4-dimethylaminophenyl)-2,6-bis(4-chlorophenyl)pyridine (3o). Crocus solid. IR (KBr): 2361, 1600, 1534, 1490, 1435, 831, 807 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.35 (d, 4H, J = 7.6 Hz), 8.16 (s, 2H), 7.95 (d, 2H, J = 7.8 Hz), 7.59 (d, 4H, J = 7.6 Hz), 6.84 (d, 2H, J = 7.9 Hz), 3.01 (s, 6H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 155.4, 151.6, 150.1, 138.1, 134.3, 129.1, 128.4, 124.3, 115.6, 112.6, 110.0, 40.1. MS (ESI): *m/z* (%) 420 (M^++H, 100). *Anal*. Calcd for $C_{25}H_{20}N_2Cl_2$: C, 71.61; H, 4.81; N, 6.68. Found: C, 71.49; H, 4.86; N, 6.73.

2,6-bis(4-methoxyphenyl)-4-phenylpyridine (3p). White solid. IR (KBr): 3065, 2833, 1608, 1545, 1512, 833, 773, 583 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 4H), 8.06–8.02 (m, 4H), 7.57–7.53 (m, 3H), 7.11 (s, 4H), 3.84 (s, 6H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 160.1, 155.9, 149.2, 137.9, 131.3, 129.0, 128.1, 127.2, 114.8, 113.9, 55.1. MS (ESI): *m/z* (%) 368 (M^++H, 100). *Anal*. Calcd for $C_{25}H_{21}NO_2$: C, 81.72; H, 5.76; N, 3.81. Found: C, 81.85; H, 5.66; N, 3.76.

4-(4-methylphenyl)-2,6-bis(4-methoxyphenyl)pyridine (3q). White solid. IR (KBr): 2957, 2361, 1608, 1544, 1514, 1425, 833, 814, 580 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.28 (d, 4H, J = 8.3 Hz), 8.04 (s, 2H), 7.93 (d, 2H, J = 7.6 Hz), 7.37 (d, 2H, J = 7.6 Hz), 7.09 (d, 2H, J = 8.3 Hz), 3.85 (s, 6H), 2.40 (s, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 160.6, 156.4, 149.5, 139.2, 135.4, 131.8, 130.0, 128.7, 127.5, 115.0, 114.4, 55.7, 21.3. MS (ESI): *m/z* (%) 382 (M^++H, 100). *Anal.* Calcd for $C_{26}H_{23}NO_2$: C, 81.86; H, 6.08; N, 3.67. Found: C, 81.95; H, 6.01; N, 3.72.

4-(4-dimethylaminophenyl)-2,6-bis(4-methoxyphenyl)pyridine (3s). Green-yellow solid. IR (KBr): 2931, 1593, 1514, 1438, 1364, 814, 578 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.27 (dd, 4H, J = 8.1, 5.1 Hz), 7.99–7.90 (m, 4H), 7.09 (dd, 4H, J = 8.2, 5.1 Hz), 6.87–6.85 (m, 2H), 3.85 (d, 6H, J = 5.0 Hz), 3.00 (d, 6H, J = 4.9 Hz). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 160.5, 156.2, 151.4, 149.5, 132.1, 128.6, 128.2, 125.0, 114.4, 113.9, 112.7, 55.6, 40.2. MS (ESI): *m/z* (%) 411 (M^++H, 100). *Anal.* Calcd for $C_{27}H_{26}N_2O_2$: C, 79.00; H, 6.38; N, 6.82. Found: C, 78.87; H, 6.29; N, 6.89.

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