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A Facile One-Pot Synthesis of 2,4,6-Triarylpyridine in DMSO

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A facile, efficient and practical method for the one-pot synthesis of 2,4,6-triarylpyridines starting from acetophenones, aryl aldehydes and ammonium acetate by the use of catalytic amounts of 40 % potassium hydroxide in dimethyl sulfoxide is presented. The present methodology offers attractive features such as the ease of workup, short reaction time and good yields of the products and it does not need any complex catalyst.

Keywords: One-pot reaction, Multi-component reaction, 2,4,6-Triaryl pyridine, Dimethyl sulfoxide.

INTRODUCTION

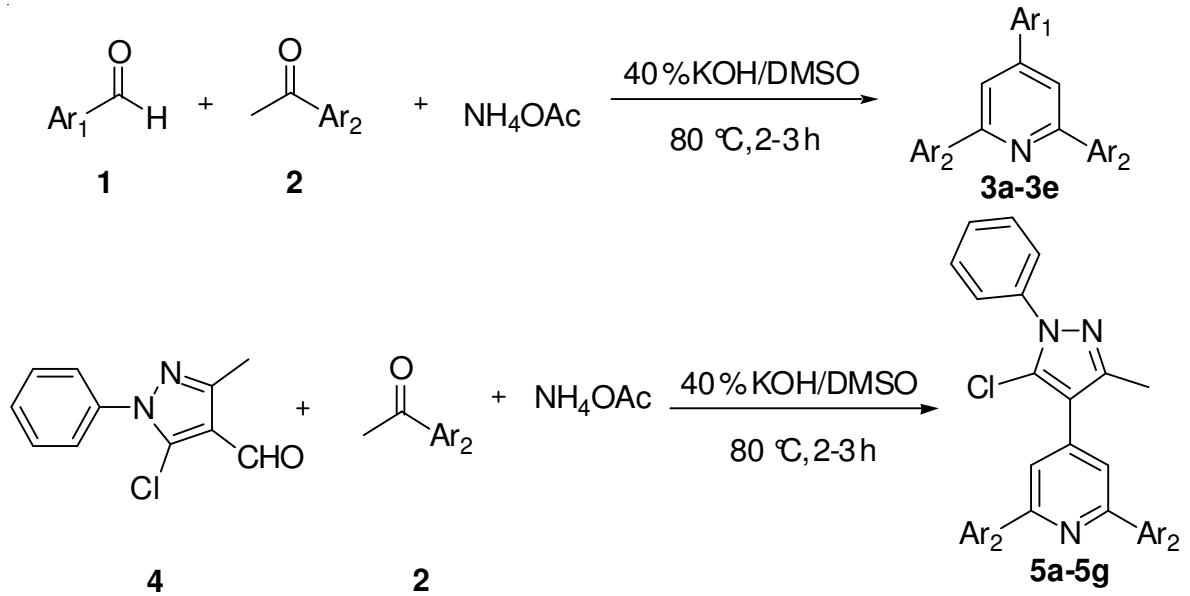
Pyridine ring system, particularly 2,4,6-triarylpyridine, is of considerable interest as it is usually the skeletal moiety in a wide range of important compounds with biological activities such as antimalerial[1] and antitumor[2]. In addition, some of 2,4,6-triaryl pyridines were used as synthons in supramolecular chemistry due to their π-stacking ability along with directional H-bonding capacity[3] and these pyridines have also instigated a growing interest for their use as monomeric building blocks in thin films and organometallic polymers[4]. Therefore, the syntheses of 2,4,6-triarylpyridines have gained significant attentions of chemists and many preparing protocols from different start materials have been proposed[5].

In recent years, one-pot multi-component reactions (MCRs) as well as domino reactions[6] has been widely used to produce many biologically active compounds because of their synthetic efficiency, intrinsic atom economy and procedural simplicity to construct highly complex molecules. A few one-pot multi-component reactions for the syntheses of 2,4,6-triarylpyridines between acetophenones, aryl aldehydes and ammonium acetate have been described. The reaction proceeded under different conditions, such as microwave irradiation[7], ionic liquid mediated synthesis[8], catalyzed by Preyssler type heteropoly acid $H_{14}[NaP_5W_{30}O_{110}]$, bismuth triflate[9]. However, these protocols are having one or more drawbacks such as long reaction time, expensive catalyst and special care in handling. Thus, there is still a need to develop efficient and practical methods for the synthesis of 2,4,6-triaryl pyridine.

In preparation of 2,4,6-triaryl pyridine through the one-pot multi-component reaction, 1,5-diketone is believed to be the key intermediate which is produced by an Aldo condensation of acetophenones with aryl aldehydes to form the corresponding Aldo product, then the product further undergoes a Michael addition reaction with another molecule of acetophenone[10]. Then, the 1,5-diketone with insertion of nitrogen atom is cyclized to dihydropyridine which on aromatization and oxidation leads to pyridine. The highly dipolar aprotic media have a profound rate accelerating on certain aldol reactions and recently dimethyl sulfoxide as a solvent has been reported to improving the reaction rates and yields of the products in some Aldol and Michael addition reactions[11]. This background prompted us to attempt the synthesis of 2,4,6-triaryl pyridine in DMSO. Herein, we would like to report a new, efficient and practical one-pot three-component reaction with a variety of aromatic aldehydes, acetophenones and ammonium acetate in DMSO for the preparation of 2,4,6-triarylpyridines (**Scheme-I**).

EXPERIMENTAL

All reagents were purchased from commercial suppliers and used without further purification. Compound **4** was synthesized according to the literature method[12]. Dimethyl sulfoxide was freshly distilled at reduced pressure from calcium hydride. All melting points were determined on a Mel-TEMP-II melting point apparatus which was uncorrected. IR spectra were recorded on a Bruker VERTEX 70 instruments. Proton magnetic resonance spectra were recorded on a Bruker AV400 instrument. The spectra were recorded in $CDCl_3$ and chemical shifts are reported in parts per million (ppm) down field from tetramethyl silane (TMS) as the internal standard. Mass spectra were recorded on an Agilent 1100 LC/MSD Trap.



Scheme-I: One-pot syntheses of 2,4,6-triarylpyridine

General procedure for preparation of 3a-e and 5a-g: To a solution of benzaldehyde or compound **4** (0.88 g, 4 mmol) dissolved in dimethyl sulfoxide (20 mL) were added acetophenone (**2**) (0.93 mL, 8 mmol) and 40 % KOH solution (0.25 mL). The mixture was stirred at room temperature for 10-30 min. Thereafter, NH_4OAc (2 g, 26 mmol) was added and the solution stirred at 80 °C for 1.8-2.5 h. On completion of the reaction (TLC), the reaction mixture was cooled at room temperature and poured into ice cold water (100 mL). The resultant solid was filtered, washed with ice cold water (50 mL) and recrystallization from ethanol or chromatograph on silica gel to give the corresponding products **3a-e** and **5a-g**.

Spectroscopic data of compounds 3a-e and 5a-g

2,4,6-Triphenylpyridine (3a): IR (KBr, ν_{max}, cm^{-1}): 1592, 1542, 1033, 871; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.23-7.29 (m, 1H, Ar), 7.51-7.55 (m, 2H, ArH), 7.57-7.62 (m, 2H, ArH), 8.04 (d, 2H, *J* = 7.4 Hz, ArH), 8.06-8.10 (m, 4H, ArH), 8.33 (s, 2H, ArH), 8.37 (d, 4H, *J* = 7.6 Hz, ArH); ESI-MS: 308 $[M + H]^+$.

4-(4-Methoxyphenyl)-2,6-diphenylpyridine (3b): IR (KBr, ν_{max}, cm^{-1}): 3035, 2936, 1596, 1037; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.82 (s, 3H, CH_3), 7.1 (d, 2H, *J* = 7.1 Hz, ArH), 7.48 (d, 2H, *J* = 7.3 Hz, ArH), 7.50 (t, 4H, *J* = 6.8 Hz, ArH), 7.61 (t, 4H, *J* = 6.8 Hz, ArH), 8.03 (d, 2H, *J* = 7.1 Hz, ArH), 8.14 (s, 2H, ArH), 8.30 (d, 2H, *J* = 7.3 Hz, ArH), 8.38 (d, 2H, *J* = 7.6 Hz, ArH); ESI-MS: 338 $[M + H]^+$.

4-(4-Nitrophenyl)-2,6-diphenylpyridine (3c): IR (KBr, ν_{max}, cm^{-1}): 1590, 1540,1380, 1100; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.20-7.66 (6H, m, ArH), 7.85 (2H, s, ArH), 7.87 (2H, d, *J* = 9 Hz, ArH), 8.08-8.25 (4H, m, ArH), 8.36 (2H, d, *J* = 9 Hz, ArH). ESI-MS: 351$[M + H]^+$.

4-Phenyl-2,6-di-(4-chlorophenyl)pyridine (3d): IR (KBr, ν_{max}, cm^{-1}): 1598, 1544, 1012, 869; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.50-7.61 (m, 7H, ArH), 8.04 (d, 2H, *J* = 7.7Hz, ArH) 8.23 (s, 2H, ArH), 8.33 (d, 2H, *J* = 7.5Hz, ArH), 8.42 (d, 2H, *J* = 7.6 Hz, ArH); ESI-MS: 377 $[M + H]^+$.

4-Phenyl-2,6-di-(4-methylphenyl)pyridine (3e): IR (KBr, ν_{max}, cm^{-1}): 3063, 1587, 1554, 867; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.35 (s, 6H, $2CH_3$), 7.10 (d, 4H, *J* = 7.7 Hz, ArH), 7.21 (s, 2H, ArH), 7.58 (t, 3H, *J* = 7.5 Hz, ArH), 8.18 (d, 2H, *J* = 7.8 Hz, ArH), 8.36 (d, 4H, *J* = 7.6 Hz, ArH); ESI-MS: 336 $[M + H]^+$.

4-(5-Chloro-3-methyl-1-phenylpyrazole-4-yl)-2,6-diphenylpyridine (5a): IR (KBr, ν_{max}, cm^{-1}): 3030, 1601, 1549, 998; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.50 (s, 3H, CH_3), 7.47 (t, *J* = 6.6 Hz, 3H, ArH), 7.53 (t, *J* = 7.2 Hz, 6H, ArH), 7.62 (d, 2H, *J* = 7.6 Hz, ArH), 7.79 (s, 2H, ArH), 8.18 (d, 4H, *J* = 7.2 Hz, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 157.41, 148.09, 141.02, 139.43, 138.12, 129.19, 129.12, 128.79, 128.48, 127.18, 125.71, 125.22, 118.76, 117.41, 13.74; ESI-MS: 422 $[M + H]^+$.

4-(5-Chloro-3-methyl-1-phenylpyrazole-4-yl)-2,6-di-(4-methylphenyl)pyridine (5b): IR (KBr, ν_{max}, cm^{-1}): 3028, 1598, 1069, 864; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.43 (s, 6H, CH_3), 2.49 (s, 3H, CH_3), 7.31 (d, 4H, *J* = 8 Hz, ArH), 7.44 (t, 1H, *J* = 14.4 Hz, ArH), 7.52 (t, 2H, *J* = 15.2 Hz, ArH), 7.61 (d, 2H, *J* = 8 Hz, ArH), 7.73 (s, 2H, ArH), 8.08 (d, 4H, *J* = 8 Hz, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 153.71, 151.89, 149.48, 148.19, 140.71, 138.12, 129.11, 128.44, 125.63, 125.23, 117.33, 115.80, 110.54, 108.41, 13.98, 13.58; ESI-MS: 450 $[M + H]^+$.

4-(5-Chloro-3-methyl-1-phenylpyrazole-4-yl)-2,6-di-(4-methoxyphenyl)pyridine (5c): IR (KBr, ν_{max}, cm^{-1}): 3032, 1601, 1499, 870; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.48 (s, 3H, CH_3), 3.88 (s, 6H, OCH_3), 7.04 (d, 4H, *J* = 7.2 Hz, ArH), 7.43-7.53 (m, 3H, ArH), 7.62 (d, 2H, *J* = 7.6 Hz, ArH), 7.66 (s, 2H, ArH), 8.14 (d, 4H, *J* = 7.2 Hz, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 160.63, 156.82, 148.14, 140.77, 138.16, 132.23, 129.54, 128.59, 128.47, 128.42, 126.60, 125.56, 125.23, 117.66, 117.43, 114.12, 113.90, 55.40, 13.67; ESI-MS: 482 $[M + H]^+$.

4-(5-Chloro-3-methyl-1-phenylpyrazole-4-yl)-2,6- di-(4-ethoxyphenyl)pyridine (5d): IR (KBr, ν_{max}, cm^{-1}): 3031, 1604, 1492, 874; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.46 (t, 6H, *J* = 10.8 Hz, $OCH_2\underline{CH_3}$), 2.49 (s, 3H, CH_3), 4.11 (q, 4H, *J* = 4 Hz, $OCH_2\underline{CH_3}$), 7.03 (d, 4H, *J* = 8 Hz, ArH), 7.37-7.53 (m,

3H, ArH), 7.62 (d, 2H, *J* = 7.6 Hz, ArH), 7.66 (s, 2H, ArH), 8.12 (d, 4H, *J* = 8 Hz, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 160, 156.81, 148.13, 140.76, 138.15, 131.91, 129.11, 128.45, 128.40, 125.55, 117.77, 117.37, 63.56, 14.85, 13.66; ESI-MS: 510 $[M + H]^+$.

4-(5-Chloro-3-methyl-1-phenylpyrazole-4-yl)-2,6- di-(3,4-dimethylphenyl)pyridine (5e): IR (KBr, ν_{max}, cm^{-1}): 3029, 1602, 1545, 873; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.38 (s, 6H, CH_3Ph), 2.43 (s, 6H, CH_3Ph), 2.52 (s, 3H, CH_3), 7.31 (d, 2H, *J* = 8 Hz, ArH), 7.47-7.57 (m, 3H, ArH), 7.66 (d, 2H, *J* = 7.6 Hz, ArH), 7.74 (s, 2H, ArH), 7.92 (d, 2H, *J* = 7.2 Hz, ArH), 7.99 (s, 2H, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 157.51, 148.15, 140.66, 138.16, 137.74, 137.24, 136.89, 130.03, 129.11, 128.44, 128.37, 125.58, 125.23, 124.61, 118.37, 117.66, 20.02, 19.67, 13.64; ESI-MS: 478 $[M + H]^+$.

4-(5-Chloro-3-methyl-1-phenylpyrazole-4-yl)-2,6-di-(3,4-methylenedioxyphenyl)pyridine (5f): IR (KBr, ν_{max}, cm^{-1}) δ: 3032, 1603, 1498, 875; ^{1}H NMR (400 MHz, $CDCl_3$): 2.48 (s, 3H, CH_3), 6.02 (s, 4H, OCH_2O), 6.93 (d, 2H, *J* = 8 Hz, ArH), 7.45 (t, 1H, *J* = 14.8 Hz, ArH), 7.53 (t, 2H, *J* = 15.6 Hz, ArH), 7.60-7.66 (m, 6H, ArH) 7.72 (d, 2H, *J* = 7.2 Hz, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 156.42, 150.33, 148.62, 147.53, 144.18, 138.78, 129.72, 128.85, 128.36, 126.67, 125.48, 120.79, 120.21, 118.57, 115.36, 112.98, 101.65, 13.61; ESI-MS: 510 $[M + H]^+$.

4-(5-Chloro-3-methyl-1-phenylpyrazole-4-yl)-2,6-di-[2-(5-methyl)furyl]pyridine (5g): IR (KBr, ν_{max}, cm^{-1}): 3030, 1606, 1527, 872; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.42 (s, 6H, furyl-CH_3), 2.47 (s, 3H, pyrazolyl-CH_3), 6.15 (d, 2H, *J* = 2.8 Hz, furyl-H), 7.11 (d, 2H, *J* = 2.8 Hz, furyl-H), 7.44 (t, 1H, *J* = 14.8 Hz, ArH), 7.50-7.55 (m, 4H, ArH), 7.60 (d, 2H, *J* = 8 Hz, ArH); ^{13}C NMR (400 MHz, $CDCl_3$): 153.71, 151.89, 149.48, 148.19, 140.71, 138.12, 129.11, 128.44, 125.63, 125.23, 117.33, 115.80, 110.54, 108.41, 13.98, 13.8; ESI-MS: 430 $[M + H]^+$.

RESULTS AND DISCUSSION

Firstly, benzaldehyde was chosen as a model for the reaction condition optimization and it was treated with 2 equivalents of acetophenone in DMSO as solvent, then a catalytic amount of strong base was added. The mixture was stirred at room temp for a few minutes as monitored by TLC. The reaction was completed in a few minutes depending on the base. In accordance with the aforementioned mechanism, this step involves an Aldo condensation and a Michael addition, the intermediate 1,3,5-triphenylpentane-1,5-dione was isolated and the structure was confirmed.

The reaction was initially performed using NaOH pellet and KOH pellet at room temp. But, even after stirring for 40 min, it was incomplete and only poor yield of intermediate product was obtained. Changing the base to 10 % aq KOH caused some improvement in the yields. When the reaction was carried out under 40 % KOH condition, it proceeded quickly and was completed in 15 min. After that, excess NH_4OAc was added and the solution was stirred at 80 °C for 2 h. To optimize the reaction temperature, a series of reactions were carried out at temperatures ranging from 60 to 110 °C in an increment of 10 °C each time, the better yields are obtained at 80 °C, further increase in temperature was found to have an inhibitory effect on formation of the product.

After establishing the reaction conditions, various aldehydes were treated with acetophenones to investigate the reaction scope. Giving the importance of imidazole in medicinal chemistry, 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**4**) was chosen to take place of benzaldehyde to synthesize a serial of 2,4,6-triarylpyridine bearing imidazole moiety. The results are summarized in Table-1. All the reactions were completed in 2-3 h in good to high yields. The first step was completed in 10-30 min (Time 1 in Table-1) depending on the reactants. The nature of the substituents on the aromatic ring showed obvious effects on this conversion, it would take less time for the electron-withdraw substituent than the electron-donating one (Entry **3c** and **3e**). The reaction time for the second step (Time 2 in Table-1) did not show significant differences. The steric nature of substituents on the aromatic ring of acetophenones affected the yields of the product. As compared with compounds **5a**, **5f** with more steric group was associated with lower yield.

From the environmental point of view, DMSO is not an ideal solvent for the organic syntheses. But, as compared with the method mentioned above, this method doesn't need harsh reaction condition, complexly catalyst and it can shorten reaction time with some other advantages such as the ease of workup and good yields of the products. It provides a practically synthetical way for the exploration of the bioactivities of 2,4,6-triarylpyridine derivatives.

TABLE-1
SYNTHESIS OF 2,4,6-TRIARYLPYRIDINE IN DMSO

Entry	Ar_1	r_2	Time 1 (min)	Time 2 (h)	Yield[a] (%)	m.p. (°C)
3a	Ph	Ph	15	2.0	80	133-134 (130[9a])
3b	4-MeO-Ph	Ph	18	2.2	85	99-100 (98[9a])
3c	4-NO_2-Ph	Ph	10	1.8	70	187(184-186[9a])
3d	Ph	4-Cl-Ph	15	2.0	75	179-181 (175-178[9b])
3e	Ph	4-Me-Ph	20	2.2	82	143-145 (140[9a])
5a	--	Ph	15	2.0	90	141-142
5b	--	4-Me-Ph	22	2.2	92	119-121
5c	--	4-MeO-Ph	20	2.3	89	158-160
5d	--	4-C_2H_5O-Ph	20	2.3	86	143-144
5e	--	3,4-$(CH_3)_2$-Ph	25	2.5	78	150
5f	--	3,4-O-CH_2-O-Ph	30	2.5	63	196-197
5g	--	2-(5-Methyl)furyl	20	2.5	72	166

[a]Isolated yields based on aromatic aldehyde

Conclusion

In summary, a facile, efficient and practical method is demonstrated for the one-pot synthesis of 2,4,6-triarylpyridines between acetophenones, aryl aldehydes and ammonium acetate by the use of catalytic amounts of 40 % potassium hydroxide in dimethyl sulfoxide.

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