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One-pot, solvent-free, and efficient synthesis of 2,4,6-triarylpyridines using CoCl₂.6H₂O as a recyclable catalyst

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Abstract: A one-pot, three components coupling of aryl aldehyde, acetophenone, and ammonium acetate was performed to afford the corresponding 2,4,6-triarylpyridines (TAP_{1-17}). The TAP_{1-17} were synthesized in the presence of cobalt(II) chloride hexahydrate (CoCl₂.6H₂O) via an improved Chichibabin pyridine synthesis protocol. This study has shown that CoCl₂.6H₂O promotes this reaction in comparison to other transition metal salt such as with FeCl₃, NiCl₂.6H₂O, CuCl₂.2H₂O, CdCl₂.H₂O, SbCl₃, SnCl₂.2H₂O, and ZnCl₂. This method has several advantages, for example, excellent yields, short reaction times, easy work up, and solvent-free condition. Also, this catalyst was recyclable for four consecutive runs.

Keywords: 2,4,6-triarylpyridine; chichibabin pyridine synthesis; kröhnke pyridines; cobalt(ii) chloride hexahydrate

1. Introduction
Pyridine ring systems are of interest because of their wide range of pharmacological activities such as antimalarial, vasodilator, anesthetic, anticonvulsant, antiepileptic, and agrochemicals such as fungicidal, pesticidal, and herbicidal (Enyedy, Sakamuri, Zaman, Johnson, & Wang, 2003; Kim et al., 2004; Klimesová, Svoboda, Waisserr, Pour, & Kaustová, 1999; Pillai et al., 2003). Recent studies have highlighted the biological activity of triarylpyridines as a pyridine derivative, providing impetus for further studies in utilizing this scaffold in new therapeutic drug classes (Bonse, Richards, Ross, Lowe, & Kraut-Siegel, 2000; Lowe et al., 1999; Zhao et al., 2001, 2004). Due to their π-stacking ability, triarylpyridines are commonly used as building blocks in supramolecular chemistry (Cave, Hardie, Roberts, & Raston, 2001; Constable et al., 2000; Jetti, Nagia, Xue, & Mak, 2001; Watson, Bampos, & Sanders, 1998). Therefore, there has been increasing interest to develop new methods for the synthesis of 2,4,6-triarylpyridines, Kröhnke pyridines. Previously, 2,4,6-triarylpyridines have been
prepared by the condensation of 1,5-diketones with formamide-formic acid (Chubb, Hay, & Sandin, 1953) and by other synthetic procedures including the Chichibabin method (Frank & Seven, 1949; Zecher & Kröhnke, 1961), and reaction of N-phenacylpyridinium salts with α,β-unsaturated ketones in the presence of ammonium acetate (Kröhnke, 1976; Kröhnke & Zecher, 1962). Recently, several new improved methods and procedures for preparation of 2,4,6-triarylpyridines have been reported, for example, the reaction of α-ketoketene dithioacetals with methyl ketones in the presence of NH₄OAc (Potts, Cipullo, Ralli, & Theodoridis, 1981), the reaction of N-phosphinylethanamines with aldehydes (Kobayashi, Kakiuchi, & Kato, 1991), solvent-free reaction of chalcones with ammonium acetate (Adib, Tahermansouri, Koloogani, Mohammadi, & Bijan zadeh, 2006). Also, there are a number of methods reported for synthesis of these compounds using various catalysts, for example, Preyssler-type heteropolyacid (H₄[NaP₅W₃₀O₁₁₀]) (Heravi, Bakhtiari, Daroogheha, & Bamoharram, 2007), HClO₄–SiO₂ (Nagarapu, Peddiraju, & Apuri, 2007), AlPO₄ (Rajput, Subhashini, & Shivaraj, 2010), Bi(OTf)₃ (Shinde, Labade, Gujar, Shingate, & Shingare, 2012), I₂ (Ren & Cai, 2009), ionic liquid ([HO₃S(CH₂)₄MIM][HSO₄]) (Davoodnia, Bakavoli, Moloudi, Tavakoli-Hoseini, & Khashi, 2010), nanoparticles (Safari, Zarnegar, & Borujeni, 2013; Shafiee & Moloudi, 2011), and without catalyst (Tu et al., 2005; Wang, Yang, Song, & Wang, 2015).

Herein, we would like to report an efficient procedure for the preparation of 2,4,6-triarylpyridines through a one-pot condensation reaction including aldehydes, acetophenones, and NH₄OAc in the presence of cobalt(II) chloride hexahydrate (CoCl₂·6H₂O) under solvent-free conditions.

| Catalyst | Isolated yield (%) |
|----------|--------------------|
| FeCl₃    | 10                 |
| CoCl₂·6H₂O | 90             |
| NiCl₂·6H₂O | 38             |
| CuCl₂·2H₂O | 53             |
| ZnCl₂    | 68                 |
| CdCl₂·H₂O | 65                 |
| SnCl₂·2H₂O | 67             |
| SbCl₃    | 56                 |

*Benzaldehyde (1 mmol), acetophenone (2 mmol), NH₄OAc (1.5 mmol), catalyst, 20% mol, Solvent Free, 120°C, 5 h.

| Temperature (°C) of React. | Catalyst (mol%) | CoCl₂·6H₂O as catalyst |
|----------------------------|-----------------|-------------------------|
| 90                         | 20              | 4                       | 35          |
| 100                        | 20              | 4                       | 83          |
| 110                        | 20              | 4                       | 90          |
| 120                        | 20              | 4                       | 90          |
| 110                        | 20              | 5                       | 90          |
| 110                        | 0.5             | 4                       | 55          |
| 110                        | 1               | 4                       | 75          |
| 110                        | 2.5             | 4                       | 89          |
| 110                        | 5               | 4                       | 90          |
| 110                        | 10              | 4                       | 90          |
2. Results and discussion

In order to study the efficiency of new methods, acetophenone (1), benzaldehyde (2), ammonium acetate (3), and a range of different metal salt were investigated and were heated to give 2,4,6-triphenylpyridine (TAP) (Scheme 1), under solvent-free conditions. Initially, the reactions were carried out using different catalysts (CoCl$_2$.6H$_2$O, FeCl$_3$, NiCl$_2$.6H$_2$O, CuCl$_2$.2H$_2$O, CdCl$_2$.H$_2$O, SbCl$_3$, SnCl$_2$.2H$_2$O). CoCl$_2$.6H$_2$O was selected as the best catalyst of those investigated with an initial yield of 90% (Table 1). The reaction was performed at different temperatures, times, and differing amounts of CoCl$_2$.6H$_2$O. The results from this study are presented in Table 2, whereby the best yields were obtained when the temperature was at 110°C with 4 h reaction time and 2.5 mol% of CoCl$_2$.6H$_2$O.

Several activated and deactivated aromatic aldehydes, and acetophenones derivatives underwent the reaction to give the corresponding TAPs in high yields. The results are shown in Table 3. The experimental procedure was very simple, convenient, and had the ability to tolerate a variety of other functional groups such as methoxy, nitro, hydroxyl, and halides under the reaction conditions (Table 3).

Interestingly, the catalyst can be recycled for four consecutive runs without significant loss of activity (Table 4). For this purpose, after completion of the reaction, the reaction mixture was cooled to room temperature, and then, water was added. The precipitated solid was isolated by filtration;

### Table 3. Details 2,4,6-triarylpyridine synthesis

| Entry | Ar   | Ar'  | Product | Isolated yield (%) | mp°C  |
|-------|------|------|---------|--------------------|-------|
|       |      |      |         | Found              | Lit.  |
| 1     | Ph   | Ph   | TAP$_{1}$ | 89                | 135–137 | 134–135$^a$ |
| 2     | Ph   | 4-Cl-Ph | TAP$_{2}$ | 91                | 124–127 | 124–126$^b$ |
| 3     | Ph   | 4-NO$_2$-Ph | TAP$_{3}$ | 92                | 196–198 | 195–197$^b$ |
| 4     | Ph   | 2-Me-Ph  | TAP$_{4}$ | 86                | 122–124 | 120–122$^b$ |
| 5     | Ph   | 4-Me-Ph  | TAP$_{5}$ | 87                | 121–123 | 123–124$^b$ |
| 6     | Ph   | 4-HO-Ph  | TAP$_{6}$ | 89                | 194–196 | 197$^b$      |
| 7     | Ph   | 4-MeO-Ph | TAP$_{7}$ | 90                | 99–101  | 98$^b$       |
| 8     | Ph   | 4-Br-Ph  | TAP$_{8}$ | 92                | 103–105 | 102–104$^b$ |
| 9     | Ph   | 2-Thienyl | TAP$_{9}$ | 84                | 162–164 | 165–166$^b$ |
| 10    | Ph   | 2-Furyl  | TAP$_{10}$ | 83                | 169–170 | 170–171$^b$ |
| 11    | 4-Cl-Ph | Ph      | TAP$_{11}$ | 84                | 177–189 | 188–190$^b$ |
| 12    | 4-Cl-Ph | 2-Cl-Ph | TAP$_{12}$ | 76                | 165–169 | 168–170$^b$ |
| 13    | 4-Me-Ph | Ph      | TAP$_{13}$ | 90                | 159–160 | 159–160$^b$ |
| 14    | 4-Me-Ph | 4-MeO-Ph | TAP$_{14}$ | 86                | 154–156 | 156–157$^b$ |
| 15    | 4-Me-Ph | 4-Me-Ph | TAP$_{15}$ | 89                | 178–179 | 178–180$^b$ |
| 16    | 4-Me-Ph | 4-Cl-Ph | TAP$_{16}$ | 91                | 199–201 | 200–202$^b$ |
| 17    | 4-MeO-Ph | 4-NO$_2$-Ph | TAP$_{17}$ | 92                | 142–144 | 143–144$^b$ |

$^a$Adib et al. (2006); $^b$Ren and Cai (2009); $^c$Herovi et al. (2007); $^d$Shinde et al. (2012); $^e$Kobayashi et al. (1991); $^f$Chiu, Tang, and Ellingboe (1998); $^g$Safari et al. (2013); $^h$maleki et al. (2010); $^i$Kröhnke and Zecher (1962); $^j$Shafiee and Moloudi (2011).
the catalyst was recovered from the filtrate by evaporation of the water at room temperature, and reused for the similar reaction.

3. Experimental
All reactions were carried out in an efficient hood. The starting materials were purchased from Merck and Fluka chemical companies. Melting points were determined with a Branstead Electrothermal model 9200 apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer RX1 Fourier transform infrared spectrometer. The \(^1\)H and \(^13\)C NMR spectra were recorded in DMSO-d\(_6\), on Bruker Avance 300-MHz spectrometers. Elemental analyses were carried out by a Perkin Elmer 2400 series II CHN/O analyzer.

3.1. Synthesis of TAP\(_1\) as general procedure
A mixture of benzaldehyde (0.21 mL, 2 mmol), acetophenone (0.47 mL, 4 mmol), \(\text{NH}_4\text{OAc}\) (0.23 gr, 3 mmol), and \(\text{CoCl}_2\cdot6\text{H}_2\text{O}\) (0.12 gr, 2.5 mol%) was heated on oil bath with stirring at 110°C for 4 h (Tables 1 and 2). After cooling, the reaction mixture was poured in ice water (10 mL) and the precipitated solid was collected by filtration, washed with distilled water (40 mL), and dried. The crude product was recrystallized from 95% ethanol (10 mL) to give the corresponding pure product (TAP\(_1\)). Colorless crystals in 89% yield, mp 135–137°C, IR (KBr) \(\nu\): 3,071, 1,585, 1,583, 1,496, 1,476, 1,384, 1,054, 1,011, 742, 665 cm\(^{-1}\). \(^1\)H NMR (300 MHz, DMSO-d\(_6\)): \(\delta\): 7.40–7.60 (9H, m), 8.03 (d, \(J = 7.6\) Hz, 2H), 8.17 (s, 2H), 8.28 (d, \(J = 7.6\) Hz, 2H), 8.35 (d, \(J = 7.3\) Hz, 2H) ppm. \(^13\)C NMR (75 MHz, DMSO-d\(_6\)): \(\delta\): 117.2, 127.4, 127.7, 128.8, 129.0, 129.4, 129.5, 139.0, 139.5, 150.2 and 157.3 ppm. Anal. Calcd for \(\text{C}_{23}\text{H}_{17}\text{N}\): C, 89.87; H, 5.57; N, 4.56. Found: C, 89.53; H, 5.49; N, 4.89.

4. Conclusion
In conclusion, we have successfully developed a quick, convenient, and efficient method for the synthesis of TAPs under solvent-free conditions. The environmental advantages include omitting organic solvent, generality and simplicity of procedure, shorter reaction time, simple workup, reusable catalyst condition, and pure products in excellent yields.

Table 4. Recycled of CoCl\(_2\cdot6\)H\(_2\)O in the synthesis of TAP\(_1\) reactions

| Catalyst type | Runs | 1  | 2  | 3  | 4  | 5  | 6  |
|---------------|------|----|----|----|----|----|----|
| Product yield (%) |     | 89 | 88 | 86 | 82 | 80 | 75 |

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