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One-pot, solvent-free, and efficient synthesis of 2,4,6-triarylpyridines using $CoCl_2.6H_2O$ 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 (**$CoCl_2.6H_2O$**) via an improved Chichibabin pyridine synthesis protocol. This study has shown that $CoCl_2.6H_2O$ promotes this reaction in comparison to other transition metal salt such as with $FeCl_3$, $NiCl_2.6H_2O$, $CuCl_2.2H_2O$, $CdCl_2.H_2O$, $SbCl_3$, $SnCl_2.2H_2O$, and $ZnCl_2$. 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.

Subjects: Chemistry; Environmental Chemistry; Organic Chemistry; Physical Sciences

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 pharmalogical 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, Waisser, 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

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PUBLIC INTEREST STATEMENT

Pyridine ring systems, such as triarylpyridines, Kröhnke pyridines, are of interest because of their wide range of pharmaceutical activities. Also due to their π-stacking ability, triarylpyridines are used building blockers in supramolecular chemistry. Therefore, their synthesis has attracted continuous interest to develop methods for the synthesis of 2,4,6-triarylpyridines. The current work reports an efficient new catalyst (**$CoCl_2.6H_2O$**) and its comparison with some other metal chlorides as catalysts in the preparation of such products.

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 NH_4OAc (Potts, Cipullo, Ralli, & Theodoridis, 1981), the reaction of *N*-phosphinylethanimines with aldehydes (Kobayashi, Kakiuchi, & Kato, 1991), solvent-free reaction of chalcones with ammonium acetate (Adib, Tahermansouri, Koloogani, Mohammadi, & Bijanzadeh, 2006). Also, there are a number of methods reported for synthesis of these compounds using various catalysts, for example, Preyssler-type heteropolyacid ($H_{14}[NaP_5W_{30}O_{110}]$) (Heravi, Bakhtiari, Daroogheha, & Bamoharram, 2007), $HClO_4$-SiO_2 (Nagarapu, Peddiraju, & Apuri, 2007), $AlPO_4$ (Rajput, Subhashini, & Shivaraj, 2010), $Bi(OTf)_3$ (Shinde, Labade, Gujar, Shingate, & Shingare, 2012), I_2 (Ren & Cai, 2009), ionic liquid ($[HO_3S(CH_2)_4MIM][HSO_4]$) (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 NH_4OAc in the presence of cobalt(II) chloride hexahydrate (**$CoCl_2.6H_2O$**) under solvent-free conditions.

Table 1. Synthesis of TAP_1 by different catalysts, under condition reaction[a]

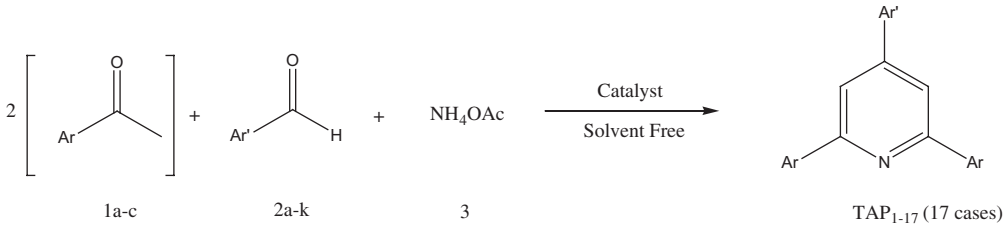
Catalyst	Isolated yield (%)
–	10
$FeCl_3$	–
$CoCl_2.6H_2O$	**90**
$NiCl_2.6H_2O$	38
$CuCl_2.2H_2O$	53
$ZnCl_2$	68
$CdCl_2.H_2O$	65
$SnCl_2.2H_2O$	67
$SbCl_3$	56

[a]Benzaldehyde (1 mmol), acetophenone (2 mmol), NH_4OAc (1.5 mmol), catalyst, 20% mol, Solvent Free, 120°C, 5 h.

Table 2. Synthesis of TAP_1 under different conditions for optimization of reactions by $CoCl_2.6H_2O$ as catalyst

Temperature (°C) of React.	Catalyst (mol%)	$CoCl_2.6H_2O$ as catalyst	
		Time (h)	Isolated yield (%)
90	20	4	35
100	20	4	83
110	20	4	90
120	20	4	90
110	20	5	90
110	20	3	78
110	0.5	4	55
110	1	4	75
110	**2.5**	**4**	**89**
110	5	4	90
110	10	4	90

Scheme 1. Synthesis of 2,4,6-triarylpyridine (TAP[1–17]).



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$_1$**) (Scheme 1), under solvent-free conditions. Initially, the reactions were carried out using different catalysts ($CoCl_2.6H_2O$, $FeCl_3$, $NiCl_2.6H_2O$, $CuCl_2.2H_2O$, $CdCl_2.H_2O$, $SbCl_3$, $SnCl_2.2H_2O$). **$CoCl_2.6H_2O$** 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 **$CoCl_2.6H_2O$**. 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 **$CoCl_2.6H_2O$**.

Several activated and deactivated aromatic aldehydes, and acetophenones derivatives underwent the reaction to give the corresponding **TAP**s 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[a]
5	Ph	4-Me-Ph	TAP_5	87	121–123	123–124[a]
6	Ph	4-HO-Ph	TAP_6	89	194–196	197[c]
7	Ph	4-MeO-Ph	TAP_7	90	99–101	98[c]
8	Ph	4-Br-Ph	TAP_8	92	103–105	102–104[d]
9	Ph	2-Thienyl	TAP_9	84	162–164	165–166[e]
10	Ph	2-Furyl	TAP_{10}	83	169–170	170–171[a]
11	4-Cl-Ph	Ph	TAP_{11}	84	177–189	188–190[f]
12	4-Cl-Ph	2-Cl-Ph	TAP_{12}	76	165–169	168–170[g]
13	4-Me-Ph	Ph	TAP_{13}	90	159–160	159–160[h]
14	4-Me-Ph	4-MeO-Ph	TAP_{14}	86	154–156	156–157[h]
15	4-Me-Ph	4-Me-Ph	TAP_{15}	89	178–179	178–180[h]
16	4-Me-Ph	4-Cl-Ph	TAP_{16}	91	199–201	200–202[i]
17	4-MeO-Ph	4-NO_2-Ph	TAP_{17}	92	142–144	143–144[j]

[a]Adib et al. (2006); [b]Ren and Cai (2009); [c]Heravi 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).

Table 4. Recycled of $CoCl_2.6H_2O$ in the synthesis of TAP_1 reactions

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

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 ^1H 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), NH_4OAc (0.23 gr, 3 mmol), and **$CoCl_2.6H_2O$** (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) ν: 3,071, 1,585, 1,583, 1,496, 1,476, 1,384, 1,054, 1,011, 742, 665 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ: 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): δ: 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 $C_{23}H_{17}N$: 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 **TAP**s 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.

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