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Cobalt(II) Chloride as a Novel and Efficient Catalyst for the Synthesis of 1,2,5-Trisubstituted Pyrroles under Solvent-Free Conditions

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ABSTRACT: *$CoCl_2$ is used as an efficient catalyst in the Paal–Knorr condensation of 2,5-hexadione with primary amines under solvent-free conditions, leading to the formation of pyrrole derivatives in excellent yield. This method is very easy, rapid, and high yielding reaction for the synthesis N-substituted pyrrole derivatives.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:592–595, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20482

INTRODUCTION

Pyrroles are an important class of heterocyclic compounds having different biological activities [1]. Members of this family have wide applications in medicinal chemistry, being used as antimalarial, antiinflammatory agents, antiasthmatic, antibacterial, antihypertensive, and tyrosine kinase-inhibiting agents [2]. In addition, pyrroles are found in many naturally occurring compounds such as heme, chlorophyll, and vitamin B_{12} [3]. Despite their importance from a pharmacological, industrial, and synthetic point of view, comparatively few methods for their preparation have been reported [4]. Of the current methods such as Hantzsch [5], Knorr [6], and aza-Witting reactions [7], the Paal–Knorr [8] reaction is one of the most simple and straightforward methods for the synthesis of N-substituted pyrroles. Many catalysts have been used to promote the Paal–Knorr reaction such as $Ti(OiPr)_4$ [9], $A1_2O_3$ [10], $Bi(NO_3)_3$ [ll], $Bi(OTf)_3$ [12], $Sc(OTf)_3$ [13], montmorillonite-KSF [14], and others [15]. It should be mentioned that the reaction did not give any good yield at room temperature without any catalyst. At high temperature only gave very low yield without any catalyst for a few cases. No reaction is observed in the absence of catalyst at room temperature [15c]. However, many of these methods have some drawbacks such as low yields of the products [11], long reaction times [11], harsh reactions conditions [10], tedious workup leading to the generation of large amounts of toxic metal-containing waste [9], the requirement for an inert atmosphere or high temperatures [12], and the use of stoichiometric [11] or relatively expensive reagents [9,13]. This reaction is usually carried in polar and toxic solvents such as DMSO, DMF, and other. Therefore, there is a need to develop new methods using less hazardous solvents or even better, those that do not need solvents at all. Therefore, the search continues for a better catalyst for the synthesis of pyrroles in terms of operational simplicity, economic viability, and greater selectivity.

RESULTS AND DISCUSSION

In view of the recent trend on the catalytic processes toward the development of clean and green chemical processes, investigation of new, less hazardous chemical catalyst has become a priority in synthetic organic chemistry. Cobalt(II) chloride is

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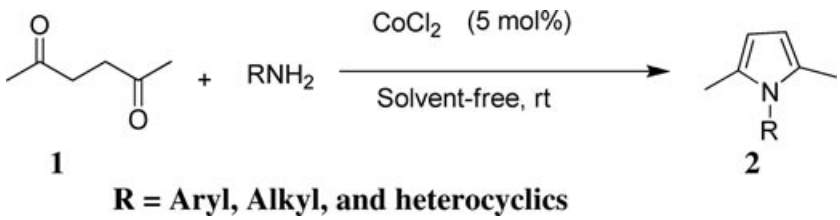


SCHEME 1

an inexpensive, fairy insensitive to small amounts of water, and environmentally benign reagent. Recently, there has been growing considerable interest in the use of $CoCl_2$ as a catalyst in organic synthesis [16]. However, there are no reports in the use of cobalt(II) chloride as a catalyst for the synthesis of pyrroles.

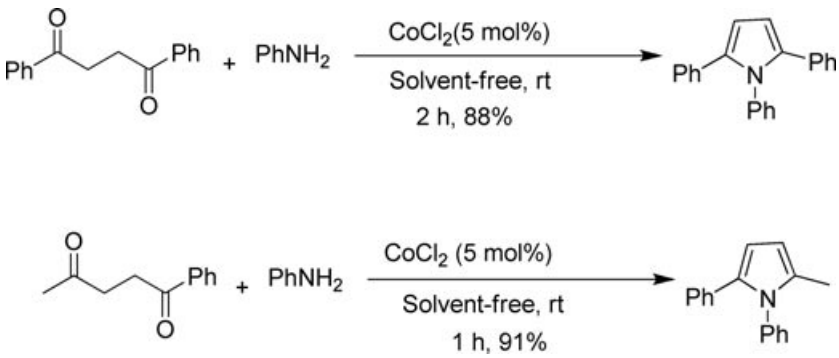
In continuation of our work to develop new synthetic methodologies [17], we report herein a facile method for the synthesis of pyrroles by the condensation of 1,4-diketones with primary amines in the presence of a catalytic amount of cobalt(II) chloride under solvent-free conditions. Accordingly, treatment of 2,5-hexadione with aniline in the presence of a catalytic amount of cobalt(II) chloride afforded 2, 5-dimethyl-*N*-phenylpyrrole in 92% yield (Scheme 1). In the same manner, a variety of amines were coupled with a 1,4-diketone in the presence of a catalytic amount of cobalt(II) chloride at room temperature to give the corresponding pyrroles in good to excellent yields (Table 1). We also observed that the reaction in DCM, methanol, or THF takes longer times than the neat conditions. This acceleration is probably attributable to the concentration effect.

To extend the scope of this reaction, other substituted diketones such as 1,4-diphenylbutane-l,4-dione and l-phenylpentane-l,4-dione were used. Clean formation of pyrroles was observed under solvent-free conditions (Scheme 2). This method

TABLE 1 Synthesis of Pyrroles Using $CoCl_2$ as a Catalyst

Entry	*Amine*	*Product*	*Time (min)*	*Yield (%)*[a]
1	$C_6H_5NH_2$	**2a**	30	92
2	4-$NO_2C_6H_4NH_2$	**2b**	45	86
3	Furfurylamine	**2c**	40	85
4	4-$CH_3OC_6H_4NH_2$	**2d**	30	92
5	Benzyl amine	**2e**	40	83
6	n-butyl amine	**2f**	50	81
7	2-aminopyridine	**2g**	60	80
8	4-$ClC_6H_4NH_2$	**2h**	35	90
9	1-Aminonaphthalene	**2i**	65	84
10	1-Aminoanthracene	**2j**	90	82

[a]Yields refer to pure products and were characterized by comparison of their mp, IR, and ^{1}H NMR spectra with those of authentic samples [9–14].



SCHEME 2

TABLE 2 Comparison of the Effect of Catalysts in the Formation of Pyrrole from Aniline and 2,5-Hexane Dione at Room Temperature

Entry	*Catalyst*	*Catalyst Load (mol%)*	*Time (min)*	*Yield (%)*
1	$Cu(OTf)_2$	5	30	78
2	$Mg(OTf)_2$	5	30	48
3	KSF	excess	600	95 (ref: 14)
4	$Bi(NO_3)_3$	100	600	96(ref: 11)
5	$Bi(OTf)_3$	5	240 (at 90°C)	85 (ref: 12)
6	$Y(OTf)_3$	5	30	86 (ref: 13)
7	$Nd(OTf)_3$	5	30	65
8	$CuCl_2$	5	30	36
9	$CoCl_2$	5	30	92
10	$CoCl_2$	1	150	80

does not require any other additives to promote the reaction. The reaction is fairly general, clean, and efficient. The experimental procedure is very simple. The high yield transformation did not lead to any significant amounts of undesirable side products. Unlike previously reported methods, the present method does not require high temperatures or extensive workup procedures to produce pyrrole derivatives. The results shown in Table 1 clearly indicate the scope and generality of the reactions with respect to various aromatic, aliphatic, and heterocyclic primary amines.

In comparison with other catalysts such as KSF, $Bi(NO_3)_3$, $Bi(OTf)_3$, $Y(OTf)_3$, which are recently reported in the formation of pyrroles, $CoCl_2$ employed here shows a more effective catalytic activity than the others in terms of the amount of catalyst, yields, and the reaction times (Table 2). The efficacy of other Lewis acids such as $Nd(OTf)_3$, $Cu(OTf)_2$, $Mg(OTf)_2$ was studied for this reaction. Among these catalysts, $CoCl_2$ was found to be superior in terms of conversions and reaction times (Table 2). The l mol% catalyst is sufficient to give the desired product in good yield. Interestingly, the present method was successfully applied to less nucleophilic aromatic amines such 1-amino naphthalene and 1-aminoanthracene (entries 9 and 10 in Table 1). The most of the reported methods are failed to give the corresponding pyrroles in good yields when applied with less nucleophilic aromatic amines [8–12].

EXPERIMENTAL

NMR spectra were recorded on a Bruker ARX 300 (300 MHz) instrument. Low resolution mass spectra (El, CI) were recorded on a Finnigan 4000 mass spectrometer. High resolution were recorded (HRMS, ESI) were recorded on Finnigan Mat XL 95 mass spectrometer. Melting points were recorded on Buchi R-535 apparatus and are unconnected. All solvents and reagents were purchased from Aldrich with high quality, and used without any further purification. All yields refer to isolated products.

Typical Procedure

A mixture of hexane-2,5-dione (684 mg, 6 mmol), aniline (465 mg, 5 mmol), and cobalt(II) chloride (32 mg, 5 mol%) was stirred at room temperature under solvent-free conditions for 30 min. After completion of the reaction, as indicated by TLC, the reaction mixture was filtered over short silica gel column (20% ethyl acetate in hexane) to give the desired product (92%). We observed when amines are solids the ketone needed an excess amount to give a good yield.

2,5-Dimethyl-l-pheny-1H-pyrrole (**2a**, entry l): oil, ^{1}H NMR (300 MHz, $CDC1_3$) δ: 2.06 (s, 6H), 5.94 (s, 2H), 7.20–7.28 (m, 2H), 7.42–7.54 (m, 3H): HRMS Calcd for $C_{12}H_{13}N$ 171.1048, found 171.1049. Anal Calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.19; H, 7.71; N, 8.21.

1-(4-Methoxyphenyl)-2,5-dimethyl-1-H-pyrrole (**2d**, entry 4): mp 60–61°C; ^{1}H NMR (300 MHz, $CDC1_3$) δ: 2.04 (s, 6H), 3.88 (s, 3H), 5.89 (s, 2H), 6.92 (m, 2H), 7.16 (m, 2H); HRMS Calcd for $C_{13}H_{15}NO$ 201.1154, found 201.1156. Anal Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.15; N, 6.95. Found: C, 77.52; H, 7.18; N, 6.99.

1-Benzyl-2,5-dimethyl-1H-pyrrole (**2e**, entry 5): mp 43–45°C, ^{1}H NMR (300 MHz, $CDC1_3$) δ: 2.18 (s, 6H), 5.04 (s, 2H), 5.89 (s, 2H), 6.90–6.95 (m, 2H), 7.20–7.41 (m, 3H); HRMS Calcd for $C_{13}H_{15}N$ 185.1205, found 185.1204. Anal Calcd for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.32; H, 8.21; N, 7.61.

1-Butyl-2,5-dimethyl-1H-pyrrole (**2f**, entry 6): oil, ^{1}H NMR (300 MHz, $CDC1_3$) δ: 0.94 (t, $J = 7.2$ Hz, 3H), 1.38 (m, 2H), 1.61 (m, 2H), 2.17 (s, 6H), 3.71 (t, $J = 7.2$ Hz, 2H), 5.79 (s, 2H); HRMS Calcd for $C_{10}H_{17}N$ 151.1361, found 151.1360. Anal Calcd for

$C_{10}H_{17}N$: C, 76.41; H, 11.33; N, 9.26. Found: C, 76.43; H, 11.38; N, 9.30.

2-(2,5-Dimethyl-1H-pyrrol-1yl)-pyridine (**2g**, entry 7): ^{1}H NMR (300 MHz, $CDC1_3$) δ: 2.10 (s, 6H), 5.92 (s, 2H), 7.27 (m, 2H), 7.81 (m, 1H), 8.61 (m, 1H); HRMS Calcd for $C11H_{12}N_2$ 172.1000, found 172.1002. Anal Calcd for $C11H_{12}N$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.76; H, 7.05, N, 16.30.

2,5-Dimethy-1-(naphthalene-1-yl)-1H-pyrrole (**2i**, entry 9): mp 120–121°C; ^{1}H NMR (300 MHz, $CDC1_3$) δ: 1.91 (s, 6H), 6.01 (s, 2H), 7.15 (d, $J = 8.2$ Hz, 1 H), 7.36–7.59 (m, 4H), 7.94 (d, $J = 8.2$ Hz, 2H); HRMS Calcd for $C_{16}H_{15}N$ 221.1204, found 221.1206. Anal Calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.88; H, 6.85; N, 6.31.

1-(Anthracen-1-yl)-2,5-dimethyl-1H-pyrrole (**2j**, entry 10): mp 183–184°C; ^{1}H NMR (300 MHz, $CDC1_3$) δ: 1.95 (s, 6H), 6.04 (s, 2H), 7.35–7.59 (m, 4H), 7.71 (s, 1H), 7.92 (d, $J = 8$ Hz, 1H), 8.02 (d, $J = 7.9$ Hz, 1H), 8.10 (d, $J = 8.4$ Hz, 1H), 8.52 (s, 1H); HRMS Calcd for $C_{20}H_{17}N$ 271.1361, found 271.1362. Anal Calcd for $C_{20}H_{17}N$: C, 88.52; H, 6.31; N, 5.16. Found: C, 88.58; H, 6.37; N, 5.20.

2-Methyl-1,5-dipheny-1H-pyrrole (Scheme 2): ^{1}H NMR (300 MHz, $CDC1_3$) δ: 2.15 (s, 3H), 6.09 (d, $J = 3.6$ Hz, 1H), 6.32 (d, $J = 3.5$ Hz, 1H), 7.02–7.40 (m, 10H); HRMS Calcd for $C_{17}H_{15}N$ 233.1204, found 233.1206. Anal Calcd for $C_{17}H_{17}N$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.58; H, 6.54; N, 6.04.

CONCLUSION

In summary, a very simple and convenient method has been developed for the synthesis of *N*-substituted pyrroles under solvent-free conditions. The method has advantages in terms of yields, short reaction times, ease of operation, and cheap catalyst, and will make a useful and important addition to the present methodologies.

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