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Ruthenium (III) Chloride as a Novel and Efficient Catalyst for the Synthesis of Substituted Pyrroles Under Solvent-Free Conditions

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Abstract Paal-Knorr condensation of 2,5-hexadione with primary amines in the presence of a catalytic amount of $RuCl_3$ under solvent-free conditions has been accomplished with an excellent yield. This method is very easy, rapid, and high yielding reaction for the synthesis *N*-substituted pyrrole derivatives.

Keywords Pyrroles · Paal-Knorr reaction · Ruthenium(III) chloride · Solvent-free conditions

1 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, antiasthamatic, 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], Al_2O_3 [10], $Bi(NO_3)_3$ [11], $Bi(OTf)_3$ [12], $Sc(OTf)_3$ [13], montmorillonite-KSF, [14] and others [15]. No reaction is observed in the absence of catalyst. 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 work-up 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.

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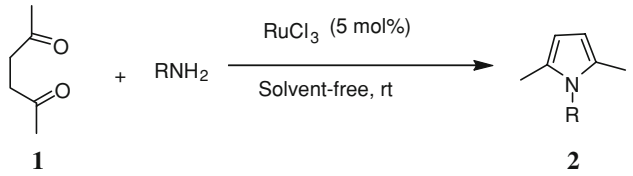
2 Results and Discussion

Recently, there has been growing considerable interest in the use $RuCl_3$ as a catalyst in organic synthesis [16]. However, there are no reports in the use of ruthenium 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 ruthenium(III) chloride under solvent-free conditions. Accordingly, treatment of 2,5-hexadione with aniline in the presence of catalytic amount of ruthenium chloride afforded 2, 5-dimethyl-*N*-phenylpyrrole in 94% yield (Scheme 1). In the same manner, a variety of amines were coupled with a 1,4-diketone in the presence of catalytic amount of ruthenium(III) chloride at room temperature to give the corresponding pyrroles in good to



1 2

Scheme 1

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.

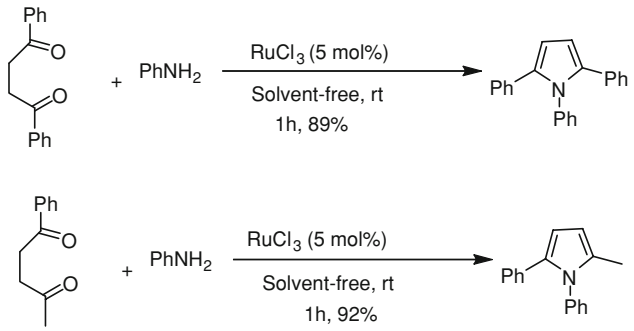
To extend the scope of this reaction, other substituted diketones such as 1,4-diphenylbutane-1,4-dione and 1-phenylpentane-1,4-dione were used. Clean formation of pyrroles was observed under solvent-free conditions (Scheme 2). This method does not require any other additives to promote the reaction. 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 work-up 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, $RuCl_3$ 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, $RuCl_3$ was found to be superior in terms of conversions and reaction times (Table 2). The

Table 1 Synthesis of pyrroles using $RuCl_3$ as a catalyst

Entry	Amine	Product	Time (min)	Yield[a] (%)
1	$C_6H_5NH_2$	**2a**	30	94
2	4-$NO_2C_6H_4NH_2$	**2b**	45	85
3	Furfurylamine	**2c**	40	88
4	4-$CH_3OC_6H_4NH_2$	**2d**	30	91
5	Benzyl amine	**2e**	40	82
6	*n*-Butyl amine	**2f**	50	85
7	2-Aminopyridine	**2g**	60	82
8	4-$ClC_6H_4NH_2$	**2h**	35	92
9	1-aminonaphthalene	**2i**	65	88
10	1-aminoanthracene	**2j**	90	85

[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 anliline 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 [14]
4	$Bi(NO_3)_3$	100	600	96 [11]
5	$Bi(OTf)_3$	5	240 (at 90 °C)	85 [12]
6	$Y(OTf)_3$	5	30	86 [13]
7	$Nd(OTf)_3$	5	30	65
8	$CuCl_2$	5	30	36
9	$RuCl_3$	5	30	94
10	$RuCl_3$	1	120	82

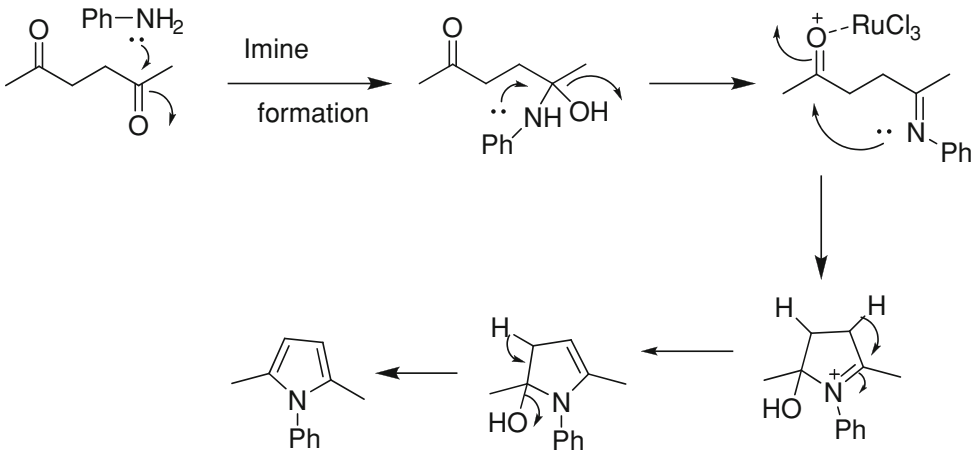
1 mol% catalyst is sufficient to give the desired product in good yield. Interestingly, the present method was applied to less nucleophilic aromatic amines such 1-amino naphthalene and 1-aminoanthracene (entries 9 and 10 in Table 1). The most of the reported methods failed to give the corresponding pyrroles in good yields when applied with less nucleophilic aromatic amines [8–12].

The mechanism of the reaction probably involves an imine formation and then cyclization promoted by $RuCl_3$ as shown in Scheme 3. The $RuCl_3$ behaves as a Lewis acid that promotes imine formation and water elimination of this reaction.

3 Experimental

NMR spectra were recorded on a Bruker ARX 300 (300 MHz) instrument. Low resolution mass spectra (EI, 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 uncorrected. All solvents and reagents were purchased from Aldrich with high quality, and used without any further purification. All yields refer to isolated products.

Scheme 3



3.1 Typical Procedure

A mixture of hexane-2,5-dione (684 mg, 6 mmol), aniline (465 mg, 5 mmol), and ruthenium (III) chloride (52 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 (94%).

2,5-Dimethyl-1-pheny-1*H*-pyrrole (**2a**, entry 1):oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06 (s, 6 H), 5.94 (s, 2 H), 7.20–7.28 (m, 2 H), 7.42–7.54 (m, 3 H), 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, $CDCl_3$) δ 2.04 (s, 6 H), 3.88 (s, 3 H), 5.89 (s, 2 H), 6.92 (m, 2 H), 7.16 (m, 2 H); 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-1*H*-pyrrole (**2e**, entry 5): Mp 43–45 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18 (s, 6 H), 5.04 (s, 2 H), 5.89 (s, 2 H), 6.90–6.95 (m, 2 H), 7.20–7.41 (m, 3 H); 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-1*H*-pyrrole (**2f**, entry 6): oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, $J = 7.2$ Hz, 3 H), 1.38 (m, 2 H), 1.61 (m, 2 H), 2.17 (s, 6 H), 3.71 (t, $J = 7.2$ Hz, 2 H), 5.79 (s, 2 H); 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-1*H*-pyrrol-1yl)-pyridine (**2g**, entry 7): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10 (s, 6 H), 5.92 (s, 2 H), 7.27 (m, 2 H), 7.81 (m, 1 H), 8.61 (m, 1 H); HRMS calcd for $C_{11}H_{12}N_2$ 172.1000, found 172.10002. Anal calcd for $C_{11}H_{12}$ 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)-1*H*-pyrrole (**2i**, entry 9): Mp 120–121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91 (s, 6 H), 6.01 (s, 2 H), 7.15 (d, $J = 8.2$ Hz, 1 H), 7.36–7.59 (m, 4 H), 7.94 (d, $J = 8.2$ Hz, 2 H); 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-1*H*-pyrrole (**2j**, entry 10): Mp 183–184 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.95 (s, 6 H), 6.04 (s, 2 H), 7.35–7.59 (m, 4 H), 7.71 (s, 1 H), 7.92 (d, $J = 8$ Hz, 1 H), 8.02 (d, $J = 7.9$ Hz, 1 H), 8.10 (d, $J = 8.4$ Hz, 1 H), 8.52 (s, 1 H); 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-1*H*-pyrrole (Scheme 2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 3 H), 6.09 (d, $J = 3.6$ Hz, 1 H), 6.32 (d, $J = 3.5$ Hz, 1 H), 7.02–7.40 (m, 10 H); 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.

4 Conclusion

In conclusion, we have demonstrated a mild and efficient procedure for the synthesis of pyrrole derivatives using a catalytic amount of $RuCl_3$. The significant features of this method include (a) operational simplicity, (b) does not need to extensive work up procedure (c) high yields, and (d) short reaction times. In addition, unlike many other methods, no extra energy source such as microwave irradiation or ultrasound is needed for the success of the reaction. This procedure has a great potential for future application.

References

1. (a) Sundberg RA (1984) In: Katritzky A, Rees CW (eds) In comprehensive heterocyclic chemistry, vol. 4. Oxford, Pergamon, p. 329; (b) Lainton J, Hoffman JW, Martin BR, Compton DR (1995) Tetrahedron Lett 36:1401. (c) Rango R, Marshal, GR, Di Santo R, Costi R, Rompei S, Artico M (2000) Bioorg Med Chem 8:1423
2. Manning AR, Davis DJ (2003) Nature Rev Drug Disc 2:554
3. De Leo CY, Ganem B (1997) Tetrahedron 53:7731
4. Gilchrist TL (1998) J Chem Soc Perkin Trans 1 1:615
5. (a) Hantzsch A (1890) Ber Dtsch Chem Ges 23:1474; (b) Trautwein AW, Submuth RD, Jung G (1998) Bioorg Med Chem Lett 8:2381
6. (a) Knorr L (1884) Ber Dtsch Chem Ges 17:1635; (b) Alberola A, Ortega, AG, Sadaba M L, Sanudo C (1999) Tetrahedron 55:6555
7. Katritzky AR, Jiang J, Steel PJ (1994) J Org Chem 59:4551
8. (a) Paal C (1885) Ber Dtsch Chem Ges 18:367; (b) Jones RA, Been RGP (1977) The chemistry of pyrroles, vol 3. Academic Press, New York; (c) Chiu PK, Sammes MP (1990) Tetrahedron 46:3439
9. Yu SX, Quesne PW (1995) Tetrahedron Lett 36:6205
10. Ballini R, Barboni A, Bosica G, Petrini M (2000) Synlett 391
11. Banik BK, Renteria M, Dasgupta SK (2005) Tetraheron Lett 46:2643
12. Yadav JS, Reddy BVS, Eeshwaraiah B, Gupta MK (2004) Tetraheron Lett 45:5873
13. Chen J, Wu H, Zheng Z, Jin C, Zhang X, Su W (2006) Tetrahedron Lett 47:5383
14. Banik BK, Samajdar S, Banik I (2004) Simple synthesis of pyrroles. J Org Chem 69:213
15. (a) Wang B, Gu Y, Luo C, Yang T, Yang L, Suo J (2004) Tetrahedron Lett 45:3417; (b) Curini M, Montanari F, Rosati O, Lioy E, Margarita R (2003) Tetrahedron Lett 44:3923; (c) Das B, Reddy VS, Tehseen F (2006) Indian J Het Chem 16:79; (d) Ranu BC, Ghosh S, Das A (2006) Mandeleev Comm 4:220
16. (a) Lowe JT, Youngsaye W, Panek JS (2006) J Org Chem 71:3639; (b) Kumar S, Saini A, Sandhu JS (2005) Tetrahedron Lett 46:8737; (c) Haddour N, Chauvin J, Gondram C, Cosnier S (2006) J Am Chem Soc 128:9693; (d) De SK (2004) Tetrahedron Lett 45:2919; (e) De SK (2005) Adv Synth Cat 347:673; (f) De SK, Gibbs RA (2004) Tetrahedron Lett 45:8141; (g) Dieltiens N, Moonen K, Stevens CV (2007) Chem Eur J 13:203; (h) Dieltiens N, Stevens CV, Allaert B, Verpoot F (2005) Arkivoc1:92; (i) Dieltiens N, Stevens CV, Devos D, Allaert B, Drozdzak R, Verpoot F (2004) Tetrahedron Lett 45:8995; (j) Moonen K, Dieltiens N, Stevens CV (2006) J Org Chem 71:4006
17. (a) De SK, Gibbs RA (2004) Tetrahedron Lett 45:7404; (b) De SK, Gibbs RA (2005) Tetrahedron Lett 45:1647 (c) De SK, Gibbs RA (2005) Tetrahedron Lett 46:1811–1813; (d) Royer L, De SK, Gibbs RA (2005) Tetrahedron Lett 46:4595