

A reusable zirconium(IV) Schiff base complex catalyzes highly efficient synthesis of quinoxalines under mild conditions

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Abstract A zirconium(IV) complex of a bidentate Schiff base (ZrL_2Cl_2) has been synthesized by the reaction of (z)-N-benzylidene-2-hydroxypropane-1-amine (HL) and $ZrCl_4$. Spectroscopic data and elemental analyses are consistent with a monomeric complex with a ligand:Zr ratio of 2:1. The catalytic activity of ZrL_2Cl_2 has been investigated for the efficient synthesis of a wide variety of quinoxaline derivatives under mild conditions. The employment of ethanol as an environmentally benign solvent in this high yield method, along with high turnover numbers and reusability of the catalyst providing ready scalability, makes it appropriate for practical applications.

Introduction

Quinoxalines play an important role as a basic skeleton for the design of a number of antibiotics such as echinomycin, actinomycin and leromycin [1]. Quinoxaline derivatives have also found applications in dyes [2], organic semiconductors [3], DNA cleaving agents [4–6] and as useful rigid subunits in macrocyclic receptors and molecular recognition [7]. Despite remarkable efforts made in the last decade, the development of an effective and general method for synthesis of the quinoxaline ring is still an important challenge [8].

Zirconium(IV), with a high charge-to-size ratio (Z^2/r is $22.22 \text{ e}^2 \text{ m}^{-10}$) [9], has a strong coordinating ability with oxygen- and nitrogen-containing ligands. This has led to the development of zirconium Schiff base complexes which are efficient catalysts both in homogeneous and heterogeneous reactions. The activity of these complexes varies markedly with the type of ligands and coordination sites [10–16].

In continuation of our ongoing research on the development of new eco-friendly organic synthesis, particularly by mediation of zirconium salts [17–26], in this paper, we introduce (ZrL_2Cl_2) [26] (Scheme 1) as a new and efficient catalyst for the condensation of aryl 1,2-diamines with 1,2-dicarbonyl compounds in ethanol under mild conditions in good to high yields (Scheme 2).

Experimental

Materials and methods

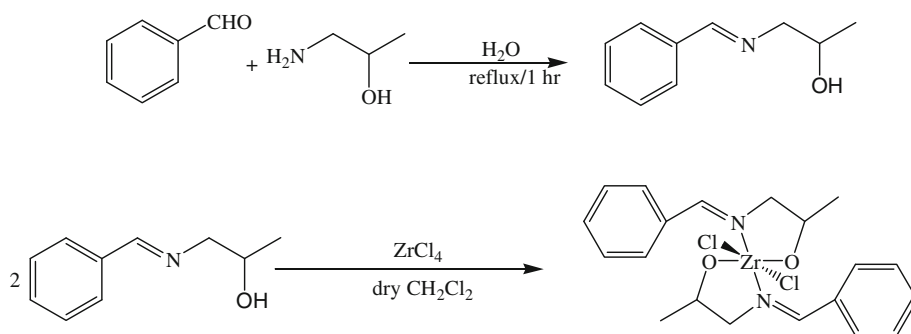
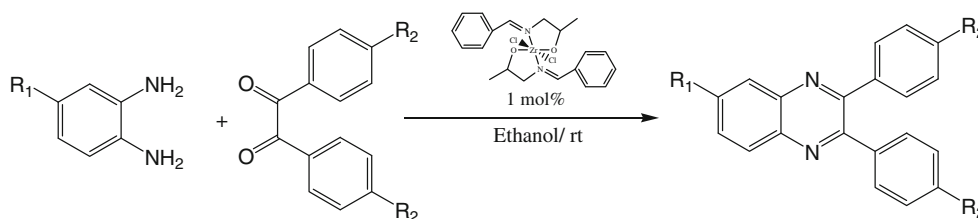
All chemicals were purchased from Merck or Fluka. The progress of the reaction was monitored by TLC using silica gel SIL G/UV 254 plates and also by GC–FID on a Shimadzu GC-16A chromatograph using a 25-m CBP1-S25 (0.32 mm ID, 0.5 μm coating) capillary column. NMR spectra were recorded on Bruker Avance DPX 250 MHz and 400 MHz spectrometers. Mass spectra were recorded on a Shimadzu GC–MS–QP 5050A instrument.

Preparation of the Schiff base

Benzaldehyde (0.1 ml, 1 mmol) was added to a solution of 1-amino-2-propanol (0.17 ml, 1.5 mmol) in distilled water (0.2 ml). The mixture was refluxed for 1 h. The product

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Scheme 1 Synthesis of ZrL_2Cl_2 **Scheme 2** Synthesis of quinoxaline derivatives in the presence of ZrL_2Cl_2 (1 mol %) in ethanol at room temperature

which was precipitated after cooling the reaction mixture, was filtered off and washed with cold water. The Schiff base was purified by recrystallization from n-hexane.

HL^1 ; M.P: 73–75 °C; IR (KBr.): (C=N) 1,638 cm^{-1} ; 1H NMR (250 MHz, $CDCl_3$) δ (ppm) = 1.33 (d, 3H, J = 6.25 Hz), 2.69 (s, 1H, OH), 3.43–3.51(m, 1H), 3.66–3.72 (m, 1H), 4.04–4.11 (m, 1H), 7.40–7.74 (m, 5H, Ar), 8.3 (s, 1H, CH=N); ^{13}C NMR ($CDCl_3$, 63 MHz) δ (ppm) = 20.6, 67.47, 68.59, 128.18, 128.62, 130.88, 135.85, 162.77; Anal. Calcd for ($C_{10}H_{13}NO$): C, 73.6; H, 8; N, 8.6. Found: C, 73.6; H, 8.1; N, 8.6; MS (m/e) = 163 [M] $^+$.

Preparation of the complex

Zirconium(IV) chloride (0.233 g, 1 mmol) was added to a solution of HL (0.326 g, 2 mmol) in dry CH_2Cl_2 (10 ml). The reaction mixture was stirred under N_2 for 2 h at room temperature. The precipitated product was filtered off, washed with cold dry CH_2Cl_2 and then dry n-hexane. The complex was dried under reduced pressure as a deep yellow powder and obtained in 80 % yield. M.P: 143 °C; IR (KBr.): (C=N) 1,665 cm^{-1} ; 1H NMR (400 MHz, d_6 -DMSO) δ (ppm) = 1.17 (d, 6H, J = 6.4 Hz), 3.58–3.88 (m, 4H, CH_2), 4.26 (m, 2H), 7.49–7.62 (m, 10H, Ar), 9.05(s, 2H, CH=N). ^{13}C NMR(100.64 MHz, d_6 -DMSO): 21.31, 63.46, 64.16, 128.21, 129.03, 130.06, 137.07, 171.72; Anal. Calcd for ($C_{20}H_{24}N_2O_2ZrCl_2$): C, 49.4; H, 5; N, 5.8. Found: C, 49.4; H, 5; N, 5.7. MS (m/e) = 484 [M] $^+$.

General procedure for synthesis of quinoxalines

The appropriate 1,2-diamine (1.2 mmol) was added to a solution of the 1,2-dicarbonyl compound (1 mmol) and the complex (0.0048 g, 0.01 mmol) in ethanol (1 ml). The

reaction mixture was stirred at room temperature for an appropriate time, as monitored by TLC (Table 1). When the reaction was complete, the precipitate was filtered off and washed with ethanol. The remaining product in the filtrate was isolated from excess 1,2-diamine by plate chromatography, eluted with n-hexane/EtOAc (10/2). Structural assignment of each product was based on its 1H NMR, ^{13}C NMR and MS spectra.

Results and discussion

Characterization of the complex

The Schiff base ligand HL (Scheme 1) was prepared by the condensation of 1-amino-2-propanol with benzaldehyde in water. Reaction of HL with $ZrCl_4$ in CH_2Cl_2 gave the expected complex, ZrL_2Cl_2 , as a yellow powder.

Analytical and spectroscopic data for the complex are given in the experimental section. The spectroscopic data and elemental analyses are consistent with a monomeric complex with a ligand:Zr ratio of 2:1. When the synthesis was repeated using three equivalents of HL, the same product was obtained as with two equivalents. The characteristic imine band of the Schiff base (1,638 cm^{-1}) is shifted to higher wave number after coordination of the azomethine nitrogen to the Zr center, appearing at 1,665 cm^{-1} for the complex. A sharp singlet at 8.3 ppm in the 1H NMR spectrum of the free Schiff base, assigned to the azomethine proton is shifted downfield after complexation, appearing at 9.05 ppm due to coordination of the azomethine nitrogen. The absence of a broad singlet at ~ 2.75 ppm in the spectrum of the zirconium complex

Table 1 Synthesis of quinoxaline derivatives catalyzed by ZrL_2Cl_2


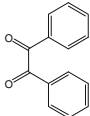
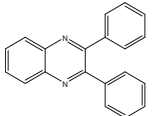
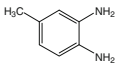
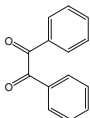
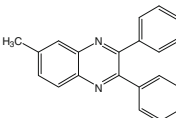
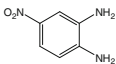
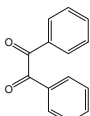
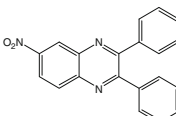

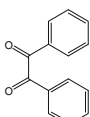
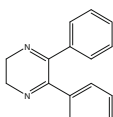

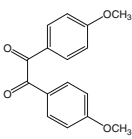
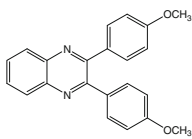
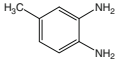
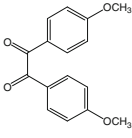
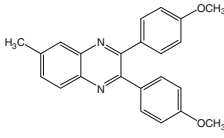
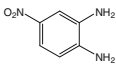
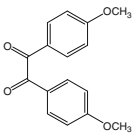
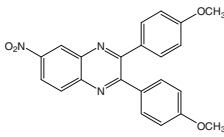


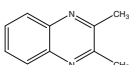
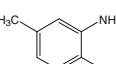

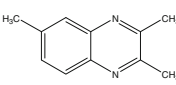
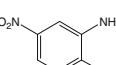

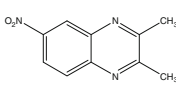




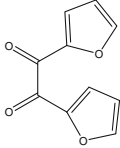
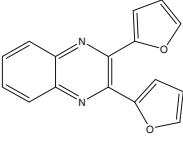
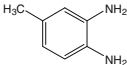
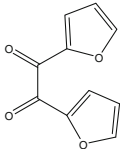
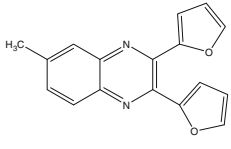
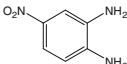
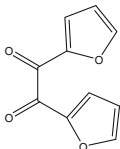
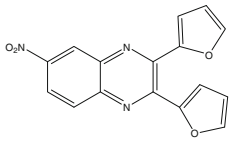
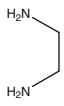
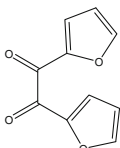
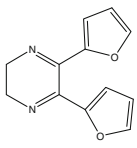
Entry	Diamine	1,2-diketone	Product ^a	Time (min.)	Isolated yield (%)
1				<1	95
2				<1	94
3 ^b				90	96
4				180	97
5				35	97
6 ^c				50	94
7				180	<10
8				2	95
9				<1	94
10				7	95
11				10	95

Table 1 continued

Entry	Diamine	1,2-diketone	Product ^a	Time (min.)	Isolated yield (%)
12				5	97
13				3	97
14				30	64
15				80	95

The reactions were run at room temperature in 1 ml ethanol and the molar ratio of 1,2-dicarbonyl/1,2-diamine/catalyst was 100:120:1

^a All products were identified by their spectroscopic data [22, 24]

^b The molar ratio of 1,2-dicarbonyl/1,2-diamine/catalyst was 100:120:5

^c Reaction was carried out in 2 ml ethanol

compared to the free Schiff base indicates the deprotonation and coordination of the hydroxyl group [14–16, 26].

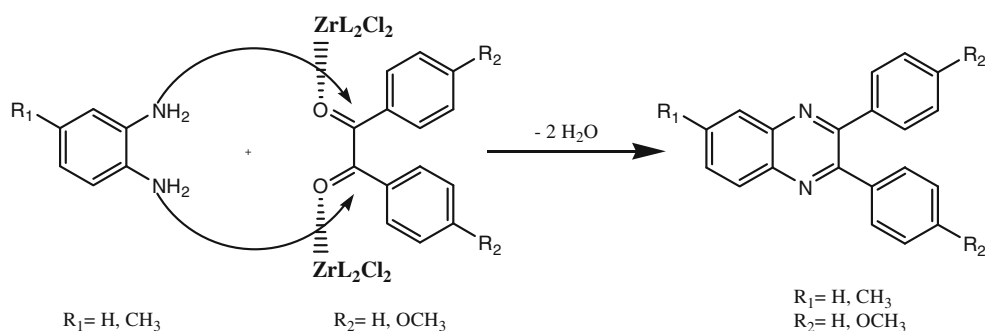
Catalytic activity

Our preliminary studies were addressed to the condensation of *o*-phenylenediamine with 4,4'-dimethoxybenzil as a model reaction under neat conditions, which gave 40–50 % yield by NMR after 7 h. Next, the influence of solvent on the reaction at room temperature in the absence of catalyst

was investigated. From these experiments, ethanol, which is a standard green solvent, was found to be the best choice in terms of both yield and selectivity; however, the desired product was formed in only 58 % yield after 3 h [24].

Next, the reaction conditions were investigated using a reaction of *o*-phenylenediamine and 4,4'-dimethoxybenzil (1.2:1), with respect to temperature, time and the molar ratio of ZrL_2Cl_2 to the reactants in ethanol (1 ml). We found that 1 mol % of ZrL_2Cl_2 was sufficient to obtain the desired quinoxaline in 97 % yield within 35 min at room

Scheme 3 Plausible mechanism for the synthesis of quinoxalines in the presence of ZrL_2Cl_2 complex (1 mol %)



temperature. It should be mentioned here that the employment of an equimolar ratio of 1,2-dicarbonyl and 1,2-diamine in this system, decreased the yield.

These optimized reaction conditions were then applied for various 1,2-diamines and 1,2-dicarbonyl compounds. The yields of products were highly dependent on the electronic demands of the reactants. For instance, the condensations of diamines bearing a strongly electron-withdrawing groups (Table 1, entries 3,7,10 and 14) or dicarbonyl compounds with a strongly electron-donating substituents proceeded slowly (Table 1, entries 5–7).

Based on these observations, a mechanism may be suggested for this reaction (Scheme 3). The Zr(IV) Schiff base complex acts as a Lewis acid, leading to its interaction with the carbonyl oxygen atom of the 1,2-diketone, thereby increasing the polarization of carbonyl moiety and promoting the condensation reaction.

The high yields of condensation products obtained by this catalytic system within short reaction times indicate the high efficiency of this Zr(IV) Schiff base complex as a catalyst. This is further supported by high turnover numbers obtained for the catalyst in the condensation of *o*-phenylenediamine and 4,4'-dimethoxybenzil (6,000/24 h) under mild conditions using a 12,000:10,000:1 molar ratio of *o*-phenylenediamine/4,4'- dimethoxybenzil/catalyst.

The possibility of reuse of the catalyst was examined. For these experiments, the condensation of *o*-phenylenediamine (1.2) and 2,2'-difuril (1 mmol) in ethanol (1 ml) at room temperature in the presence of ZrL₂Cl₂ (1 mol %) was chosen. When the reaction was complete, the precipitated solid was filtered off and washed with ethanol. The filtrate was evaporated under vacuum to afford the complex and excess diamine that was saved for the next reaction. To this mixture was added ethanol (1 ml), 2,2'-difuril

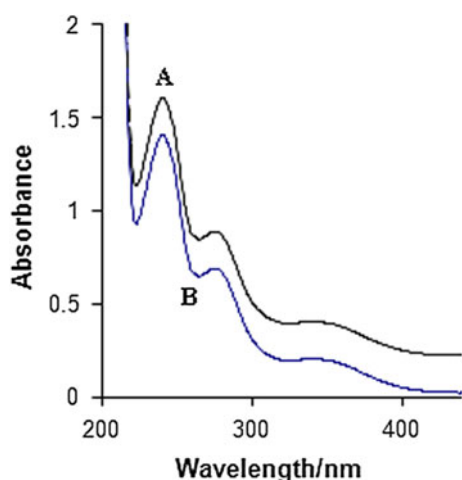


Fig. 1 UV–Vis spectra of fresh ZrL₂Cl₂ complex (a) and after 5 times reuses (b) in the condensation of *o*-phenylenediamine and 2,2'-difuril in ethanol

Table 2 Catalytic activity of ZrL₂Cl₂ in comparison with other catalysts used for *o*-phenylenediamine and benzil

Entry	Catalyst	Catalyst (mol %)	Time (min)	Yield (%)	Ref.
1	ZrL ₂ Cl ₂ /ethanol	1	<1	95	– ^a
2	ZrOCl ₂ ·8H ₂ O	10	2	97	[24]
3	ZrCl ₄ /methanol	5	5	100	[27]
4	Zr(DS) ₄ /H ₂ O	2.5	30	94	[28]
5	Zr–CAP–SG/ethanol	10 wt%	90	92	[29]
6	CuSO ₄ ·5H ₂ O/H ₂ O	10	15	96	[30]
7	Zn[(L)proline], HOAc	10	10	95	[31]
8	Mont K-10, H ₂ O	10	150	100	[32]
9	[Hbim]BF ₄	2 mL	20	96	[33]

^a This work

(1 mmol) and *o*-phenylenediamine (1 mmol), and the resulting mixture was stirred at room temperature. The desired quinoxaline was produced after 5 min in 95 % yield. The recovered catalyst (according to above-mentioned procedure) could be directly reused five times without any treatment and no appreciable loss in its catalytic activity. The comparison of electronic spectra of fresh and reused catalyst demonstrated a durability of 88 % during the five runs, according to intensity of the characteristic absorption bands [$\lambda = 240$ nm, Abs. = 1.6 (A: UV–Vis spectra of fresh complex) and 1.4 (B: UV–Vis spectra of complex after 5 times reuses)], providing more evidence for stability of the title catalyst under the reaction conditions (Fig. 1).

This high yielding condensation method offered ready scalability. In the condensation of *o*-phenylenediamine and benzil as substrates in a semi-scale-up procedure (20-fold), the related product was secured in 95 % yield.

In Table 2, we have also shown the merit of this operationally simple catalytic protocol for condensation of *o*-phenylenediamine and benzil in comparison with some other known catalysts in terms of conversion rate, catalyst loading and media.

Conclusion

In this study, we have introduced an eco-friendly synthesis for a wide variety of quinoxaline derivatives in the presence of a reusable Zr(IV) Schiff base complex catalyst under mild conditions. The employment of ethanol as an environmentally benign solvent in this high yielding method, along with high turnover numbers and reusability of the catalyst providing ready scalability, makes it appropriate for practical applications.

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