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Catalytic conjugate addition of indole to α,β-unsaturated ketones by $Co(ClO_4)_2\cdot 6H_2O$/*bis*-Schiff base complexes

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Abstract

$Co(ClO_4)_2\cdot 6H_2O$/*bis*-Schiff base complexes promoted the conjugate addition of indole to α,β-unsaturated ketones under mild conditions, giving the corresponding addition products with high yields. And the complex has been characterized with XRD and IR.

Keywords: Conjugate addition; Indole; α,β-Unsaturated ketone; Schiff base

The development of synthetic methods leading to indole derivatives has received much interest because a number of their derivatives were found in a number of natural products and biologically active molecules [1]. Among them 3-substituted indoles are highly interesting important building blocks for the synthesis of biologically active compounds as well as natural products [2]. Since 3-position in indoles is the preferred site for electrophilic substitution, 3-alkyl or acyl indoles are versatile intermediates for synthesis of a wide range of indole derivatives [3]. Furthermore, 3-substituted indoles are components of drugs and are commonly found in molecules of pharmaceutical interest in variety of the therapeutic areas [4].

Recently, a variety of methods have been reported for the synthesis of 3-substituted indoles [5]. Acid catalyzed electrophilic substitution of indoles requires careful control of acidity to prevent side reactions such as dimerization and polymerization [3]. Other method for the synthesis of 3-alkylated indoles involves the conjugate addition of indoles to α,β-unsaturated ketones in the presence of either protic [6] or Lewis acid [7]. Although several catalytic methods have been known to promote the addition of indoles to α,β-unsaturated ketones, only limited number of different organometallic systems have been reported. Lewis acid catalyzed electrophilic substitution of indoles requires careful control of acidity to prevent side reactions such as dimerization and polymerization. With a good Lewis acidity and high coordination capability, cobalt (Co) shows good analogical actions in organic synthesis and Co complex has been a good development [8]. And in our group, Co complexes have been proven to be efficient in the oxidation of tetrahydrofuran [9]. Based on our previous research, the Schiff bases have been applied to many procedures [10], we envisioned that Co(II) *bis*-Schiff base catalysts could represent readily available candidates as catalytic systems to actively promote the direct addition of indoles to α,β-unsaturated ketones. Therefore, a series of

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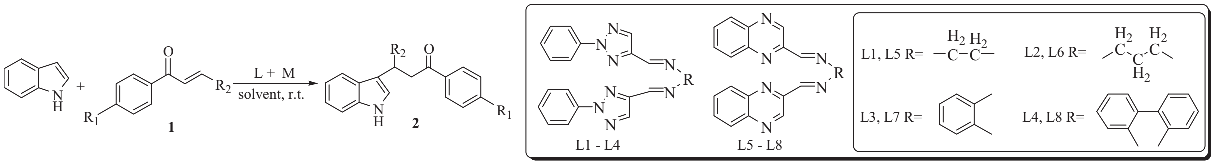


Scheme 1. Ligands used in the conjugate addition of indole to α,β-unsaturated ketones.

bis-Schiff bases (L1–L8) (Scheme 1) were facilely synthesized according to our reported [11]. In this connection we describe the version of this process employing the *bis*-Schiff base Co(II) complex as the catalyst.

1. Results and discussion

Initially, chalcone **1a** and indole were chosen as model reaction to optimize the reaction conditions. A series of *bis*-Schiff bases were examined in the presence of $Co(ClO_4)_2$ as metal salt. When Co(II) was used as the central metal, L2 was found to be the most suitable for this reaction (Table 1, entry 2). However, L2 or $Co(ClO_4)_2{\cdot}6H_2O$ as catalyst showed the worst potential in this reaction, no products were obtained (Table 1, entries 9 and 10).

To further improve the yields, other conditions were investigated. We screened various solvents for the addition indole to α,β-unsaturated ketone **1a**, and CH_3CN gave the best yield at room temperature, 88% yield (Table 1, entry 2). Increasing the catalyst loading from 10 mol% to 15 mol% did not lead to an improvement on the yield (Table 1, entry 16). However, by reducing the catalyst loading to 5 mol%, the reaction activity was not affected, either (Table 1, entry 17). Extensive screening showed that this Friedel–Crafts reaction was well performed using 10 mol% *bis*-Schiff base L2–Co(II) complex in MeCN at room temperature for 10 h.

With optimized conditions established, the substrate scope of the conjugate addition was explored. As shown in Table 2, the electron-donating as well as electron-withdrawing substituents on the aromatic ring R_1 were tolerated under these conditions with good yields of 80–89% (Table 2, entries 1–11). Then we turned our attention to this kind of α,β-unsaturated ketones having triazole substituents, and pleasing results with good-yield were obtained (Table 2, entries 12–20). Notably, the electron-rich substrate was CH_3, **1o** and **1s** gave the best results, and the corresponding products **2o** and **2s** were obtained in 85% and 82% yields (Table 2, entries 15 and 19). When a substituent of R_1 was CH_3O, the yield of the product **2t** decreased to 78%, respectively (Table 2, entry 20). In addition, the R_1 having the electron-withdrawing group halogen proceeded smoothly and gave moderate yields (Table 2, entries 13–14 and 17–18). Notably, when C1 were CH_3, no product was obtained.

To evaluate the complex, we continued spectroscopic analysis of the catalyst. Fig. 1(a) shows the wide-angle XRD patterns, the pattern of L2 sample exhibits several reflections at about 9°, 13°, 14°, 16°, 19°, 26° and 28°, which were

Table 1
Optimization of the reaction conditions.[a]

Entry	L	Solvent	Yield (%)[b]	Entry	L	Solvent	Yield (%)[b]
1	L1	CH_3CN	72	9[c]	L2	CH_3CN	0
2	L2	CH_3CN	88	10[d]	–	CH_3CN	0
3	L3	CH_3CN	78	11	L2	CH_2Cl_2	70
4	L4	CH_3CN	75	13	L2	EtOH	71
5	L5	CH_3CN	63	14	L2	Toluene	67
6	L6	CH_3CN	60	15	L2	THF	30
7	L7	CH_3CN	61	16[e]	L2	MeCN	89
8	L8	CH_3CN	65	17[f]	L2	MeCN	86

[a] Reaction conditions (unless noted otherwise): chalcone **1a** (1 mmol), indole (1 mmol), 10 mol% L and 10 mol% $Co(ClO_4)_2$ in 5 mL CH_3CN at room temperature for 10 h.

[b] Isolated yield.

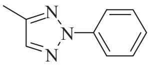
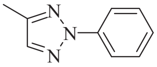
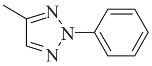
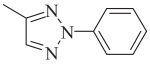
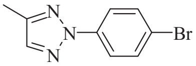
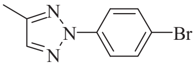
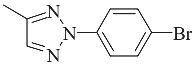
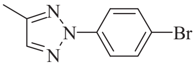
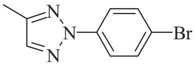
[c] L2 as catalyst for the reaction.

[d] $Co(ClO_4)_2{\cdot}6H_2O$ as catalyst for the reaction.

[e] Use 15 mol% catalyst.

[f] Use 5 mol% catalyst.

Table 2
Conjugated addition of indole with various α,β-unsaturated ketones.[a]

Entry	R_1	R_2	Prod.	Yield[b] (%)	Entry	R_1	R_2	Prod.	Yield [b] (%)
1	H	C_6H_5	**2a**	89	11	H	3-$NO_2C_6H_4$	**2k**	85
2	Cl	C_6H_5	**2b**	81	12	H		**2l**	82
3	Br	C_6H_5	**2c**	80	13	Cl		**2m**	76
4	CH_3	C_6H_5	**2d**	89	14	Br		**2n**	77
5	OCH_3	C_6H_5	**2e**	87	15	CH_3		**2o**	85
6	H	4-$OCH_3C_6H_4$	**2f**	85	16	H		**2p**	80
7	Cl	4-$OCH_3C_6H_4$	**2g**	80	17	Cl		**2q**	75
8	Br	4-$OCH_3C_6H_4$	**2h**	83	18	Br		**2r**	74
9	CH_3	4-$OCH_3C_6H_4$	**2i**	86	19	CH_3		**2s**	82
10	OCH_3	4-$OCH_3C_6H_4$	**2j**	88	20	OCH_3		**2t**	78

[a] Reaction conditions (unless noted otherwise): **1a–1t** (1 mmol), indole (1 mmol) and 10 mol% L2–Co(II) (1:1) complex in CH_3CN (5 mL) at room temperature for 10 h.

[b] Isolated yield.

attributed to functional groups of *bis*-Schiff base. On the other hand, the pattern of L2–$Co(ClO_4)_2 \cdot 6H_2O$ sample exhibits only two reflections at about $2\theta = 17^\circ$ and 25°, the typical peaks suggesting that the cobalt salt had significant effect on the nature of ligand. An FT-IR spectrum of the ligand (L2) and the catalyst L2–Co(II) (Fig. 1(b)) demonstrated successfully coordination of ligand and metal salt, in which relatively absorption bands around 1600 cm^{-1} for ν(C═N) and 450 cm^{-1} for ν(N–Co) were derived from the organometallic cobalt complex [12].

In the light of the above experimental results, we propose a mechanism that involves the deprotonation of indole by L–Co(II) accompanied (Scheme 2). The chalcone coordinates to this catalyst and undergoes the alkylation reaction of

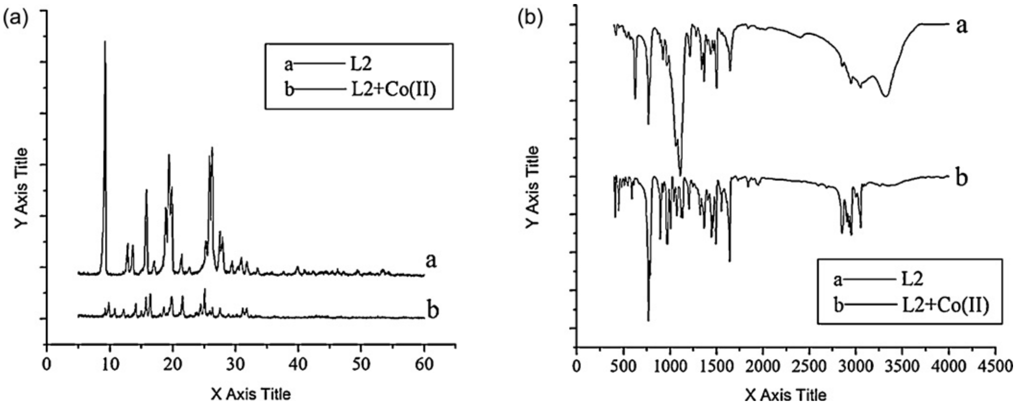
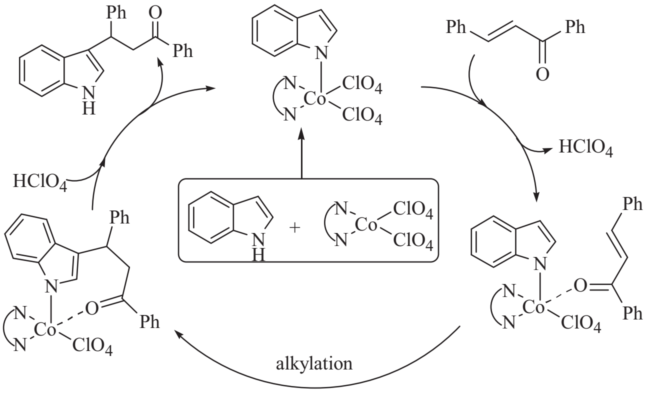


Fig. 1. (a) Wide-angle XRD patterns of L2 and L2 + Co(II). (b) FT-IR spectrum of L2 and L2 + Co(II).



Scheme 2. Proposed catalytic cycle.

indole. The catalytic cycle is in according with the literature [13], which closed by a proton exchange with an incoming indole to release the product and reform the active catalyst.

In conclusion, we have described an efficient $Co(ClO_4)_2$–L2 (*bis*-Schiff base) catalyst, which exhibited good catalytic activities (up to 89%) in the conjugate addition of indole to α,β-unsaturated ketones. And the L2–$Co(ClO_4)_2$ complex has been characterized with XRD and IR. This, we believe that the cobalt salts might be of great applicability in other reactions.

Acknowledgments

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