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Synthesis of secondary amides by direct amidation using polymer supported copper(II) complex

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Abstract A new polymer supported Cu(II) complex has been synthesized and characterized by CHN analyses, IR and UV–Vis spectral studies, ESR and thermogravimetric analyses, ICP-OES, surface area measurements. This complex was screened for their catalytic study towards the direct amidation reaction. The effects of solvents, reaction time, temperature and catalyst amount for the direct formation of amides from aldehydes and benzylamine with the aid of heterogeneous copper complex were reported. The polymer supported Cu(II) catalyst could be reused more than five times without appreciable loss of its initial activity. The plausible reaction mechanism has been proposed. The catalytic activity of the unsupported complex was also compared with the polymer supported Cu(II) complex.

Keywords Cu(PS-BBMA)Cl₂, Direct amidation, Heterogeneous catalysis, Benzyl amine

Introduction

Amide functionality is well known due to its stability, high polarity and conformational diversity and constitute the most abundant motif in synthesis and medicinal chemistry [1]. They are found in compounds with anticancer, antihypertensive, antiinflammatory, antiallergic, antimigraine, and antiviral activities [2-4]. Due to the broad application of amides and sulfonamides, finding new, efficient and practical methods for their synthesis is desirable. Amides are produced in enormous amounts every year, thus, environmental friendly and selective methods for their formation are of great importance.

The most prevalent and straight forward approach to amide bond formation is the condensation of an amine with a carboxylic acid derivative [5-7]. On the other hand, due to instability of

activated carboxylic acid derivatives, it confines their universal applications and creates significant challenges [8]. To overcome these challenges, alternative routes like hydrative amide synthesis with terminal alkynes [9], carbonylation of alkynes [10], alkenes and haloarenes [11], direct amidation of aldehydes [12] have been used.

Transition metal-catalyzed reactions have emerged in recent years as more atom-economical and powerful tools for preparing amides. The seminal work in the field oxidative amidation was performed by Milstein and co-workers, who developed a ruthenium pincer complex that produces hydrogen gas as by-product and hence avoids the use of external oxidants [13]. A rhodium complex with hydrogen peroxide as stoichiometric oxidant for the formation of primary and secondary amides has also been reported for the oxidative amide formation from alcohols [14]. Palladium complex as catalyst with stoichiometric amounts of an aryl halide as oxidant also formed amides in good yields [15]. Copper iodide has also been used in catalytic amounts in combination with tert-butyl hydroperoxide (TBHP) for the oxidative amidation of aldehydes [16]. In addition, lanthanide-catalyzed Cannizzaro-type protocols have been reported [17, 18]. Furthermore, organocatalytic protocols employing N-heterocyclic carbenes for oxidative amidation of aldehydes have been developed [19, 20]. In general, formation of imines from alcohol/aldehyde with amine over heterogeneous catalytic systems is possible [21, 22] but the current system gave amides from aldehydes and amines in the presence of polymer supported Cu(II) catalyst.

Direct amidation is the reaction between an aldehyde and an amine, generating the amide product and hydrogen gas as the only by-product. These reactions attracted considerable attention due to the high atom economy and easy availability of substrates [23-29]. Amides are produced in enormous amounts every year, thus, environmentally friendly and selective methods for their formation are of great importance. In contrast to the most common methods for amide formation to date, which involve the use of waste-intensive, expensive and often toxic coupling reagents and also to circumvent the problems of harsh reaction conditions and low atom economy, catalysis is a promising strategy for amide synthesis. A desired scenario for the amide synthesis, the direct reaction between readily available aldehydes and amines, is currently very limited. Herein we describe the direct synthesis of amide compounds from readily accessible

benzylamine and aldehyde surrogates. The present method features a much broad scope on amide synthesis and eliminates the requirement of oxidant. This paper is focused on catalytic amidation using polymer supported copper complex of substituted benzimidazole Cu(PS-BBMA)Cl₂ under mild reaction conditions to produce secondary amides in good yields. To the best of our knowledge, there is still no report on using polymer supported copper complex as catalyst on the direct amidation of aldehydes and alcohols.

Experimental

Materials

Chloromethylated polystyrene divinyl benzene (PS) was obtained as a gift from THERMAX Ltd. India. The CuCl₂.2H₂O, iminodiacetic acid, 1,2-diaminobenzene, and substituted aldehydes were purchased from Merck and used without further purification. Solvents were used after purification by standard methods.

Catalyst preparation

Bis(benzimidazol-2-ylmethyl)amine (BBMA) was synthesized according to the procedure described in the literature [30]. Chloromethylated polystyrene (1.0 g; Cl content 6 mmol) was swelled in DMF for 2 h, and then a solution of BBMA (0.29 g, 0.78 mmol) in DMF (10 mL) was added, followed by triethylamine (4 mL) and ethyl acetate (30 mL). The mixture was heated at 100 °C for 48 h. After cooling, it was filtered, Soxhlet extracted with ethanol, and dried. 1.0 g of functionalized polymer (PS-BBMA) was added to ethanol (10 mL) and kept for 1 h. A solution of CuCl₂.2H₂O (0.23 g; 1 mmol) in ethanol (20 mL) was added to it and the mixture was stirred at 70 °C for 48 h. The resultant bluish green coloured beads were filtered off and washed by Soxhlet extraction and dried at 100 °C (Scheme 1).



Scheme 1. Preparation of the polymer anchored Cu(II) complex, Cu(PS-BBMA)Cl₂. Characterization of Cu(PS-BBMA)Cl₂

Elemental analyses were carried out using an Elementar Vario Micro Cube CHNS analyser. Diffuse reflectance spectra were recorded as $BaSO_4$ disks on a Shimadzu UV-Vis-NIR model-3101P spectrophotometer. Infrared spectra were recorded on Shimadzu 8,400 s FTIR spectrometer in the range of 4000-400 cm⁻¹ using KBr disks. Thermogravimetric analyses was carried out with a TA instrument, SDT analyser model Q600. ESR measurements were carried out in the solid state at room temperature in a standard X band JES - FA200 spectrometer. The percentage of Cu in the supported complex was determined by using AAS, Avanta Pm, GF 3000. Nuclear magnetic resonance spectra were recorded on 300 and 600 MHz Bruker Avance spectrometer using TMS as standard in CDCl₃ solvent. Spin multiplicities are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet) and br s (broad singlet).

General procedure for direct amidation reaction

In a typical reaction 60 mg of Cu(PS-BBMA)Cl₂ was taken in 5 mL acetonitrile, benzaldehyde (1.0 mmol) and benzylamine (1.2 mmol) were added to it. The mixture was stirred at 60 °C for 6 h (monitored by TLC). The catalyst was separated by filtration and the solution was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel with ethyl acetate/petroleum ether (1:8) as elutant to afford the amide product.



Scheme 2. Synthesis of amide (Table 2, entry 8) catalyzed by Cu(PS-BBMA)Cl₂.

Results and Discussion

Catalyst Characterization

CHN and FTIR analyses

The elemental analyses and IR spectral data of polymer support, ligand, functionalized polymer and supported complex are depicted in Table 1. The % of Cu present in the polymer supported complex was 2.3 %.

Table 1

	CHN analyses (%)			IR spectral data					
Compound	С	Ν	Η	Cu	v(CH ₂ -Cl)	v(C-Cl)	v(ArN-H)	v(N-H)	v(C=N)
BBMA	70.1	23.1	6.8	-	-	-	3056	3010	1583
PS	97.8		2.2	-	1267 (s)	829 (s)	-	-	-
PS-BBAMA	90.7	5.2	4.1	-	1267 (w)	829 (w)	2924	-	1580
Cu(PS-	90.1	5.6	4.3	2.3	-	-	2923	-	1508
BBMA)Cl ₂									

Elemental analyses and IR spectral data (cm⁻¹)

s = strong; w = weak band

The BBMA exhibited (ArN-H) v(N-H) and v(C=N) peaks at 3056, 3010 and 1583 cm⁻¹

respectively. The functionalization of polymer beads was confirmed by comparing the IR spectrum of PS-BBMA with polymer beads and BBMA. The PS-BBMA showed a peak at 1580 cm⁻¹ corresponding to v(C=N) which was absent in polymer beads while latter displayed peaks at 1267 and 829 cm⁻¹ ascribed to v(CH₂-Cl), v(C-Cl) respectively decreased in intensity was an evidence for anchoring of BBMA on to polymer and the peak at 3010 cm⁻¹ due to aliphatic N-H in BBMA was absent in PS-BBMA, it confirmed that anchoring of aliphatic nitrogen of BBMA

to the polymer. Cu(PS-BBMA)Cl₂ exhibited a peak at 1508 cm⁻¹ due to v(C=N) which was shifted by 72 cm⁻¹ on complexation indicating the coordination of copper to aliphatic secondary nitrogen of benzimidazole moieties (Table 1).

Electronic spectral studies



Fig. 1. Electronic spectra of (a) PS, (b) PS-BBMA and (c) BBMA



Fig. 2. Electronic spectrum of Cu(PS-BBMA)Cl₂

Electronic spectra of PS, PS-BBMA and its complex are displayed in figures 1 and 2. The bands in the range of 200 to 293 nm were attributed to $\pi \to \pi^*$ and $n \to \pi^*$ transitions and bands at 315-352 nm due to charge transfer. In addition to ligand peaks, polymer supported complex exhibited bands at 431 (${}^{2}E_{g} \to {}^{2}B_{1g}$), 692 (${}^{2}B_{2g} \to {}^{2}B_{1g}$) and 838 nm (${}^{2}A_{1g} \to {}^{2}B_{1g}$) attributed to d \to d transitions (Fig 2) indicating the square pyramidal environment around Cu(II) ion.

ESR spectral and magnetic moment measurements

Room temperature magnetic moment of $Cu(PS-BBP)Cl_2$ was measured using vibrating sample magnetometer (VSM). It exhibited a value of 1.71 BM indicating the presence of one unpaired electron.

X-band ESR spectrum of polymer supported complex at room temperature showed a welldefined hyperfine structure with four line splitting due to interaction of electron with the nuclear spin of copper(II) (I = 3/2) (Fig. 3). ESR of Cu(PS-BBMA)Cl₂ exhibited axial symmetric gtensor parameters with $g_{\parallel} > g_{\perp} > 2.0023$ ($g_{\parallel} = 2.24$, $g_{\perp} = 2.06$, $A_{\parallel} = 19$ mT, $A_{\perp} = 27$ mT) indicating that the copper site has a dx²-y² ground state characteristic of five coordinated square pyramidal stereochemistry.



Fig. 3. X-band ESR spectrum at room temperature for Cu(PS-BBMA)Cl₂

TGA measurements

The polymer support was stable up to 275 °C. Cu(PS-BBMA)Cl₂ complex showed the first stage decomposition in the range 184-216 °C with mass loss of ~2.5 % attributed to the loss of chlorides. In the second stage loss of BBMA ligand occurred in the temperature range 216-310 °C with ~9.3 % weight loss, while the third step (>301 °C) could be attributed to the polymer decomposition (Fig. 4).



Fig. 4. Thermograms of (a) PS and (b) Cu(PS-BBMA)Cl₂ **Catalytic activity studies**

Effect of catalyst free and oxidant free conditions

The synthesized Cu(II) polymer supported complex was used to investigate the optimized reaction conditions. Several parameters such as solvents, reaction temperature, time and catalyst amount were varied by employing benzaldehyde and benzylamine as the model reaction. The amidation reaction was carried out at 60 °C for 6 h in the absence of catalyst wherein only 20 % yield occurred. The reaction performed in presene and absence of oxidant TBHP, the yield obtained was same, and the reaction was performed in O₂ as oxidant to confirm whether the

atmospheric air helps in the amidation, it confirmed that O_2 is not involved in the amide formation. Hence the amidation reactions were carried out in the absence of oxidant.

Effect of solvents

To explore the effect of reaction media on the transformation yield, reaction was carried out in water, thf, methanol, and acetonitrile. Though the reaction proceeded in all the solvents, the yield was maximum in acetonitrile. Hence, it was chosen for the subsequent investigations (Table 2, entry 3).

Effect of temperature

This amidation was found to be sensitive to the reaction temperature. At lower temperatures (RT-40 °C) only low yield was obtained (Table 2, entries 8 and 9; 10-29 % yield). A reaction temperature of 60 °C was found to be optimal for the model reaction to give 90 % yield whereas at higher temperature yield decreased. Therfore 60 °C was considered as optimum temperature.

Effect of catalyst amount

Effect of concentration of catalyst in amidation reaction was evaluated using different amounts of catalyst. On increasing the Cu(PS-BBMA)Cl₂ amount from 30-60 mg, the amide yeild was increased from 40 to 90 % and for 90 mg there was no increase in yield was observed (Table 2, entries 3, 5, 6). As 60 mg of catalyst showed maximum yield it was choosen as optimum concentration.

Thus, the optimized reaction conditions for amidation of benzaldehyde (1 mmol) with benzylamine (1.2 mmol) were the 60 mg of Cu(PS-BBMA)Cl₂ in 4 mL acetonitrile at 60°C for 6 h (entry 3, Table 2).

Comparision of catalutic activity with unsupported Cu(II) complex

The unsupported Cu(II) complex Cu(BBMA)Cl₂ was prepared according to the literature [31]. Under optimized reaction conditions, Cu(BBMA)Cl₂ showed 40 % yield (entry 12). The results indicated that polymer supported Cu(II) complex showed good catalytic activity than the

unsupported complex.

Table 2

Results of screening the reaction conditions^a

No.	Solvents	Catalyst	Oxidant	Temperature	Yeild (%) ^b
		amount (mg)		(°C)	
1	THF	60	-	60	72
2	H_2O	60	-	60	62
3	CH ₃ CN	60	-	60	90
4	CH ₃ OH	60	-	60	42
5	CH ₃ CN	30	-	60	40
6	CH ₃ CN	90	-	60	88
7	CH ₃ CN	60	TBHP	60	90
8	CH ₃ CN	60	-	RT	10
9	CH ₃ CN	60	-	40	29
10	CH ₃ CN	60	-	80	80
11	CH ₃ CN	Blank reaction	-	60	20
12	CH ₃ CN	Cu(BBMA)Cl ₂	F	60	40

^a All the reactions were run with benzaldehyde (1 mmol), benzylamine (1.2 mmol) with catalyst in 4 mL solvent for 6 h. ^b Isolated yield.

Catalytic amidation reaction of aldehyde surrogates

To examine the scope for this heterogeneous copper-catalyzed direct amidation reaction, a series of reactions were carried out by employing a wide range of aromatic, aliphatic and hetero-aromatic aldehydes under the optimized reaction conditions and the results are summarized in Table 3. All the reactions proceeded smoothly and efficiently in acetonitrile to generate the desired product amides in moderate to excellent yields up to 96 %. Diverse functionalities including nitro, methoxy, halo, methyl, and trifluoro methyl groups were tolerated. Remarkably, the coupling of less electrophilic aldehydes also gave the desired products, albeit in low yields.

The results summarized in Table 3 indicated that the electron-withdrawing substituent on aromatic rings of aldehydes had positive effects on the transformation (entries 1-4, 7, 9, 11) and for those with no electron withdrawing substituent(s), poor to moderate yields were obtained (entry 10, Table 3). The aliphatic aldehydes gave good yields (entry 6 and 12).

Table 3



% yield of various benzamides using Cu(PS-BBMA)Cl₂



aldehyde surrogates (1 mmol), benzylamine (1.2 mmol), 60 mg Cu(PS-BBMA)Cl₂, CH₃CN (4 mL), at 60 °C for 6 h.

Plausible reaction mechanism catalyzed by Cu(PS-BBMA)Cl₂

To find out whether reaction followed free radical mechanism or not, radical scavenger BHT (Butylated Hydroxy Toluene) was added to the reaction system wherein there was reaction proceeded in the presence of scavenger showed non free radical mechanism.

The hemi-aminal was formed by nucleophilic addition of amine with aldehyde, undergoes dehydrogenation to give corresponding amide product [32, 33].



Scheme 3. Plausible mechanism for coupling between benzylamine and benzaldehyde catalyzed by Cu(PS-BBMA)Cl₂.

¹H NMR spectral data of amides

1. N-benzyl-4-nitrobenzamide

¹H NMR (300 MHz, CDCl₃): δ 4.72 (d, 2H, J = 6 Hz), δ 6.64 (bs, 1H), δ 7.36 (m, 5H), δ 7.96 (d, 2H, J = 9.0 H), δ 8.28 (d, 2H, J = 9.0 Hz).

2. N-benzyl-4-methoxybenzamide

¹H NMR (300 MHz, CDCl₃): δ 3.90 (s, 3H), δ 4.68 (d, 2H, J = 6 Hz), δ 6.41 (bs, 2H, J = 9.0 Hz), δ 7.28-7.38 (m, 5H), δ .78 (d, 2H, J = 9.0 Hz).

3. N-benzyl-4-fluorobenzamide

¹H NMR (400 MHz, CDCl₃):3 δ 4.65 (d, 2H, J = 6 Hz), δ 6.48 (bs, 1H), δ 7.07-7.14 (m, 2H), δ 7.28- 7.36 (m, 5H), δ 7.78 – 7.85 (m, 2H).

4. N-benzyl-4-chlorobenzamide

¹H NMR (400 MHz, CDCl₃): δ 4.59 (d, 2H, J = 4.0 Hz), δ 6.96 (br s, 1H), δ 7.29-7.36 (m, 5H), δ 7.52 (d, 2H, J = 8.0 Hz), 7.66 (d, 2H, J = 8.0 Hz).

5. N-benzylcyclohexanecarboxamide

¹H NMR (400 MHz, CDCl₃): δ 1.20-1.32 (m, 3H), δ 1.48 (q, 2H, J = 12.0Hz), δ 1.69 (s, 1H), δ 1.79-1.81 (m, 2H), δ 1.87-1.90 (m, 2H), δ 2.13 (t, 1H, J = 12.0Hz), δ 4.42 (d, 2H, J = 8.0Hz), δ 6.04 (br s, 1H), δ 7.25-7.35 (m, 5H).

6. N-benzylpentanamide

¹H-NMR (CDCl₃): δ 0.91 (t, 3H, J = 7.26 Hz), δ 1.62 (m, 2H), δ 1.34 (m, 2H), δ 2.20 (t, 2H, J = 7.52 Hz), δ 4.41 (d, 2H, J = 5.77 Hz), δ 5.97 (bs, 1H), δ 7.22-7.36 (m, 5H).

7. N-benzyl-4-(trifluoromethyl)benzamides

¹H NMR (300 MHz, CDCl₃): δ 4.66 (d, 2H, J = 3 Hz), δ 6.58 (bs, 1H), δ 7.28-7,36 (m, 5H), δ 7.70 (d, 2H, J = 9 Hz), δ 7.91 (d, 2H, J = 6 Hz).

8. N-benzylbenzamide

¹H NMR (300 MHz, CDCl₃): δ 4.65 (d, 2H, J = 6 Hz), δ 6.44 (bs, 1H), δ 7.28-7,36 (m, 5H), δ 7.40-7.45 (m, 2H), δ 7.48-7.52 (m,1H), δ 7.78-7.81 (m, 2H).

9. N-benzyl-4-iodobenzamide

¹H NMR (300 MHz, CDCl₃): δ 4.63 (d, 2H, J = 3 Hz), δ 6.48 (bs, 1H), δ 7.28-7.38 (m, 5H), δ 7.52 (d, 2H, J = 9.0 Hz), δ 7.78 (d, 2H, J = 9.0 Hz).

10. N-benzyl-4-methylbenzamide

¹H NMR (400 MHz, CDCl₃): δ 2.36 (s, 3H), δ 4.58 (d, 2H, J = 4.0Hz), δ 6.74 (br s, 1H), δ 7.17 (d, J = 8.0 Hz, 2H), δ 7.26-7.30 (m, 5H), δ 7.69 (d, 2H, J = 8.0Hz).

11. N-benzyl-3,5-dimethoxybenzamide

¹H NMR (400 MHz, CDCl₃): δ 3.80 (s, 6H), δ 4.61 (d, 2H, J = 4.0 Hz), δ 6.58 (s, 1H), δ 6.75 (br s, 1H), δ 6.95 (s, 2H), δ 7.29-7.34 (m, 5H).

12. N-benzylbutyramide

¹H NMR (400 MHz, CDCl₃): δ 0.91 (t, 3H, J = 8.0 Hz), δ 1.58-1.65 (m, 2H), δ 2.14 (t, 2H, J = 8.0 Hz), δ 4.34 (d, 2H, J = 8.0 Hz), δ 6.81 (br s, 1H), δ 7.21-7.28 (m, 5H).

13. N-benzyl-2-phenylacetamide

¹H-NMR (400 MHz, CDCl₃) δ 3.64 (s, H), δ 4.42 (d, 2H, J = 5.85 Hz), δ 5.66 (bs, 1H), δ 7.15-7.20 (m, 2H), δ 7.22-7.38 (m, 8H).

14. N-benzyl-2-(thiophen-3-yl)acetamide

¹H-NMR (400 MHz, CDCl₃): δ 3.65 (s, 2H), δ 4.42 (d, 2H, J = 5.79 Hz), δ 5.81 (bs, 1H), δ 7.01 (dd, 1H, J = 4.90), δ 7.13-7.16 (m, 1H), δ 7.17-7.22 (m, 2H), δ 7.23-7.36 (m, 4H).

Comparision with literature

Table 4

Comarision of present catalyst Cu(PS-BBMA)Cl₂ with literature methods

No.	Catalyst	Oxidant	Base/Additive	Yield (%)	Reference
1	FeCl ₂	TBHP	-	90	[34]
2	$[(COD)_2Rh]BF_4 + BINAP$	Styrene	CsOAc	76	[35]
3	[RhCl(PPh ₃)(TAC)]	-	NaHCO ₃	95	[36]
5	Present catalyst	-	-	96	

BINAP = 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl; TAC = 2-(2-thiazolylazo)cresol

Catalyst recycling and heterogeniety test

Recycling efficiency of Cu(PS-BBMA)Cl₂ was investigated by carrying out the amidation reaction between benzaldehyde and benzylamine. The catalyst was separated from the reaction mixture after each run by filtration, washed with solvent and dried before using it in the subsequent run. The catalyst showed same activity for three runs and slight decrease was observed in subsequent runs. Esimation of Cu present in the recycled catalyst indicated that no leaching of the metal occurred confirmed by ICP-OES. The IR spectrum of the recycled catalyst (after fourth cycle) was similar to that of fresh catalyst. Catalyst recycling studies is depicted in Fig. 5.

The heterogeneity of the catalyst was established by hot filtration method. For this, one reaction set was quenched after 2 h and product was isolated (25 % yield) at optimized conditions. In the other set, the catalyst was separated after 2 h by filtration and the reaction was allowed to continue for 6 h, which resulted in no appreciable conversion (27 %). The solution was tested for metal content and absence of metal suggested no leaching of the metal complex during the reaction, indicating the heterogeneity of the catalyst.



Fig. 5. Catalyst recycling studies using Cu(PS-BBMA)Cl₂ as catalyst for the amidation **Conclusions**

The polymer-supported bis(benzimidazolylmethyl)amine copper complex was synthesized and characterized successfully and investigated its catalytic activity towards direct amidation reaction. The formation of complex was evidenced from elemental, AAS, and thermogravimetric

analyses, FT-IR, UV-Vis, and ESR spectral techniques and magnetic moment measurement. The yield of the amide was dependent on the various parameters such as solvent, reaction time, Cu(PS-BBMA)Cl₂ concentrataion and reaction temperature. The amidation reactions also proceeded in water with slight lower yield. The electronic effect of the substituents can also perturb the amidation reaction. This procedure provides an efficient and oxidant-free method for direct amidation. The catalyst was recyclable and showed excellent activity. A tentative reaction mechanism was proposed.

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Authors declare 'no conflict of interest'.

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Graphical abstract

