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Room Temperature C-C Coupling Reactions: Ullmann Reaction Catalyzed by Novel Biocatalytic System of *Trapa natans* L./Copper Acetate and its Antidiabetic Activity

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The fibrous root system of *Trapa natans* L. (Hei-kak-yeli) provides a great surface area for adsorption of metals. By taking advantage of phytoremediation ability of *T. natans* L., the biocatalyst was prepared by using *T. natans* L. with copper acetate. The prepared biocatalyst was employed for the greener approach in coupling reaction of derivatives of aryl chloride and aryl bromide (a classic Ullmann reaction). The synthesis of biaryl derivatives using biocatalyst undergoes at room temperature in the presence of DMF as solvent and KOH as base for 15-20 h with 76-92% overall yields. The optimum amount of biocatalyst used is about 20-40 mg (0.128-0.256 mmol of Cu) for complete conversion, thereby representing the lowest amount of catalyst used for a general catalytic Ullmann reaction. Moreover, given that copper complexes exhibit significant potential for antidiabetic properties, a copper-based biocatalyst was synthesized, and its antidiabetic activity was assessed. Promising result of antidiabetic property was obtained and the IC_{50} value was found to be 5.74809 ± 0.5185 µg/mL.

Keywords: Antidiabetic, Ullmann coupling, *Trapa natans* L., Hei-kak-yeli, Biocatalyst, Biaryl derivative.

INTRODUCTION

One of the greener approaches toward catalytic organic synthesis is using a plantmediate catalyst. Plant material having root biomass is favourable for the preparation of Curich ecocatalysts [1]. *T. natans* L. also known as water chestnut was reported to be effective for the removal of different parameters of municipal wastewater by their roots leading to promising high absorption of metals [2]. With the advances in industrial processes, more numbers of biocatalysis applications have extended to a great length [3]. Biocatalysis has many more applications such as the development of artificial metalloenzymes, non-natural reactions catalyzed by enzymes, biocatalysis cascades, enzyme catalyzed protein conjugations, metabolic pathways for chemical biosynthesis and computations and library design strategies for enzyme engineering [4].

In recent years, organic chemistry has focused on eco-friendly processes [5-7]. The development of copper catalyzed formations of C-N, C-O and C-C bonds were also highlighted by Taillefer [8,9]. Among the different chemical methods, the organic synthesis prefers the formation of C-O, C-N and C-S bond. The successful Pd-mediated C-X bond formation provided a powerful tool to access a wide range of pharmaceutical molecules and bioactive natural product [9].

Moreever, due to cost factor as well as air sensitiveness of palladium reagents, organic chemists are recently searching for palladium alternatives. Thus, many scientists start using innovative ideas about metal catalyzed reactions instead of using expensive palladium. In contrast, the use of copper metal seemed to lag behind the trend of development in this area, though the copper catalyzed C-C, C-O and C-N bond formations has been observed at Ullmann couplings [10-13]. Several reviews concerning the Ullmann and Ullmann-type reactions have been reported due to the rapid development of copper-catalyzed coupling reactions [10,14].

Other reviews include applications of the Ullmann reaction in the synthesis of bioactive natural products [15], anticancer agents [16] and alkaloids [17]. Ma *et al*. [18,19] reviewed the developments and applications of amino acid-based ligands in copper-catalyzed coupling reactions. Comparison of copper- and palladium-catalyzed coupling reactions was described by Senra [20] and Koenig [21]. Thus, Ullmann reaction was one

of the main reactions for the formation of C–C bond (aryl–aryl bond). Some of the limitations of Ullmann reaction are due to harsh reaction conditions, high copper catalyst loading, poor functional group tolerance and generally the low yield% of the products. This facilitates the wide applications of the Ullmann reaction to the synthesis of heterocyclic compounds, druglike molecules, natural products, chiral auxiliaries, *etc.* [20,21].

In addition to its many benefits as an Ayurvedic supplement and its volatile and semi-volatile components, *T. natans* L. has been shown to have anti-inflammatory, antioxidant, antibacterial, antibiofilm, pain-relieving, antidiabetic and neuroprotective effects [22]. Ethanol extract isolated from *T. natans* L. roots has shown the presence of flavonoids, carbohydrates, phenols, tannins, sterols, proteins, fats, ferulic, caffeic acid [23-27]. The vegetative part of *Trapa natans* L. has been found to possess a significantly high potential for metal accumulation mainly of heavy metals like copper, zinc, cadmium and lead [28]. Especially the higher content of the metals is found to be accumulated in the roots of *T. natans* L. Furthermore, it can act as a sensitive biomarker in checking the pollution of aquatic life.

The fibrous root system of *Trapa natans* L. (Hei-kak-yeli) provides a great surface area for adsorption of metals [29]. By taking advantage of phytoremediation ability of *T. natans* L., the biocatalyst is prepared by using *T. natans* L. with copper acetate. On account greener catalysis, the usage of plant based and naturally found compounds show great catalytic properties and cost effective [30]. As an extension of our interest in the heterogeneous catalytic activities as stated in Nahakpam *et al.* [31-34] and the idea of plant based catalytic activities towards advancement of greener approach of organic reactions, we have come up with the idea of using a plant-based heterogeneous catalyst in this work. We have used *Trapa natans* L. (Hei-kak-yeli) as plant material, which has great metal absorptivity property by their roots and established a biocatalyst using $Cu(OAc)_2$. Herein, we are reporting the synthesis, characterization and antidiabetic potential of biaryl derivatives using *Trapa natans* L./$Cu(OAc)_2$ as catalyst at room temperature in the presence of DMF as solvent and KOH as base.

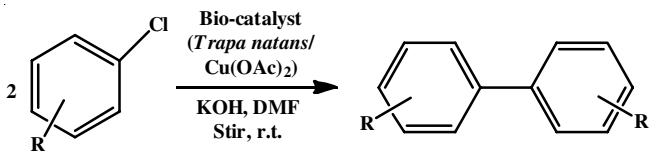
EXPERIMENTAL

All the commercial chemicals and reagents were distilled before use. The EDS was measured using SEMQUANTA 250. XRD was measured using X'Pert PRO PAnalytical X-ray diffractometer. TEM was measured using TEM JEOL (JEM-ARM-200F) instrument. The melting points of the compounds prepared were determined by using a Buchi melting point M-560 machine. IR spectra were recorded using a Shimadzu FT-IR spectrophotometer in the range of 4000 to 200 cm^{-1}. NMR spectra were recorded on a Bruker–ACF-400 spectrometer (^1H at 400 MHz, ^{13}C at 400 MHz) in $CDCl_3$ and TMS as an internal standard. Antidiabetic activity was measured by using Multiskan Skyhigh, Thermo-Scientific Invitrogen instrument.

Preparation of biocatalysis: *Trapa natans* L. also known as water chestnut is a traditionally found floating aquatic plant in Loktak Lake (latitude: 24.5593° N, longitude; 93.8147° E), Manipur, India. The collected plant was then dried under sun for 5 days and then powdered.The sundried powdered material (0.5 g) was mixed with 0.5 g of copper acetate in a mortar. The materials were grounded together properly and then 10 mL of ethanol was added. The mixture was transferred to a 100 mL oven dried round-bottomed flask, stirred at room temperature for 4 h, then filtered and finally the residue was dried .

The fibrous mediated copper acetate was subjected to use as biocatalyst in a classic Ullmann-reaction. Amount of catalyst prepared was 900 mg. The reaction was a heterogeneous system. The catalyst could be recovered after the reaction but the copper content was low and ineffective for further reaction.

Procedure for classic Ullmann reaction: To a mixture of phenyl halide (2.0 mmol) and KOH (2.0 mmol) in DMF (4.0 mL), biocatalyst (40 mg) was added with stirring at room temperature. The completion of the reaction was checked by using thin layer chromatography. After the completion of the reaction, the mixture was filtered, washed with CH_2Cl_2 (2 × 3 mL), dried (Na_2SO_4) and concentrated. Product was isolated without column chromatography after work up with ethyl acetate/H_2O (**Scheme-I**). The organic layer was dried using Na_2SO_4 and filtered. The solid crystals were obtained and recrystallized in ethanol to obtain the desired product.



R = 4-NH_2, 4-CN, 2-NH_2, 2-CN, 2-CHO, 2-NO_2, 4-CH_3, 4-OCH_3

Scheme-I: A classic Ullmann reaction

[1,1′-Biphenyl]-2,2′-dicarbonitrile (3a): White solid, m.p.: 171-173 ºC; IR (KBr, ν_{max}, cm^{-1}): 3094, 3069, 2230, 1591, 1472, 1439, 1057, 758; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.61 (d, 2H, ArH), 7.47 (m, 3H, ArH), 7.31 (m, 3H, ArH); ^{13}C NMR (400 MHz, $CDCl_3$): δ_C 136.9, 134.3, 133.9, 130.3, 127.2, 116.0, 113.5 [35].

[1,1′-Biphenyl]-4-carbonitrile (3b): White solid, m.p.: 85-88 ºC; IR (KBr, ν_{max}, cm^{-1}): 3096, 3067, 2230, 1591, 1439, 1057; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.69 (d, 2H, ArH), 7.69 (d, 3H, ArH), 7.38 (dd, 4H, ArH); ^{13}C NMR (400 MHz, $CDCl_3$): δ_C 140, 134, 133.4, 130, 129, 128.8, 118, 110.9 [36].

[1,1′-Biphenyl]-2-carbonitrile (3c): White solid, m.p.: 37-40 ºC ; IR (KBr, ν_{max}, cm^{-1}): 3096, 3067, 2230, 1591, 1439, 1057, 768, 557; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.70 (d, 2H, ArH), 7.56 (m, 4H, ArH), 7.40 (m, 3H, ArH); ^{13}C NMR (400 MHz, $CDCl_3$): δ_C 137, 134, 133.8, 130, 127, 116, 113.4 [37].

[1,1′-Biphenyl]-2,2′-diamine (3e): White solid, m.p.: 80-82 ºC; IR (KBr, ν_{max}, cm^{-1}): 3466, 3381, 3068, 2930, 1614, 1485, 1022, 742; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.16 (d, 2H, ArH), 6.97 (d, 2H, ArH), 6.64 (m, 4H, ArH), 3.95 (s, 4H, -NH_2); ^{13}C NMR (400 MHz, $CDCl_3$): δ_C 143, 129.4, 127.6, 119.3, 119, 115.8 [38].

[1,1′-Biphenyl]-4,4′-diamine (3f): White solid, m.p.: 190-193 ºC; IR (KBr, ν_{max}, cm^{-1}): 3466, 3381, 3069, 1614, 1485, 1306, 743; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.13 (d, J = 8.4 Hz, 4H, ArH), 6.62 (d, J = 8.4 Hz, 4H, ArH), 3.57 (br s,

4H, NH_2); ^{13}C NMR (400 MHz, $CDCl_3$): δ_C 145.0, 129.1, 123.2, 116.3 [39].

[1,1′-Biphenyl]- 4-amine (3g): White solid, m.p.: 52-54 ºC; IR (KBr, ν_{max}, cm^{-1}): 3466, 3381, 3069, 1614, 1485, 1306, 743; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.17 (d, *J* = 8.4 Hz, 2H, ArH), 7.01 (m, *J* = 8.4 Hz, 5H, ArH), 6.51 (d, 2H, ArH), 3.57 (br s, 4H, NH_2); ^{13}C NMR (400 MHz, $CDCl_3$): δ_C 145.0, 129.1, 123.2, 116.3 [40].

2-Nitro-1,1′-biphenyl (3h): White solid, m.p.: 35-38 ºC; IR (KBr, ν_{max}, cm^{-1}): 3096, 2918, 1530, 1346, 1288, 1055, 853, 735; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.74 (d, *J* = 8.4 Hz, 2H, ArH), 7.45 (d, *J* = 8.4 Hz (1H, ArH); 7.33 (d, *J* = 8.4 Hz, 1H, ArH), 6.91 (m, *J* = 8.4 Hz 5H, ArH); ^{13}C NMR (400 MHz, $CDCl_3$): δ_C 148, 146, 139, 133, 132, 131, 127.6, 126, 125, 118, 117.8 [41].

4′-Methyl-[1,1′-biphenyl]-4-carbonitrile (3i): White solid, m.p.: 109-112 ºC; IR (KBr, ν_{max}, cm^{-1}): 3091, 3068, 3041, 2785, 2225, 1593, 1483, 1087, 1016, 827, 779; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.47 (d, *J* = 8.4 Hz, 2H, ArH), 7.60 (d, *J* = 8.4 Hz (2H, ArH), 7.27 (s, 4H, ArH); ^{13}C NMR (400 MHz, $CDCl_3$): 139.3, 133.4, 129.7, 129, 117.8, 110.7, 29.7 [42].

4′-Methoxy-[1,1′-biphenyl]-4-carbonitrile (3j): White solid, m.p.: 103-105 ºC; IR (KBr, ν_{max}, cm^{-1}): 3091, 3068, 2920, 2783, 2225, 1593, 1483, 1087, 1016, 825, 781; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.59 (d, *J* = 8.4 Hz, 2H, ArH), 7.46 (d, *J* = 8.4 Hz (2H, ArH), 7.28 (s, 4H, ArH), 3.78 (3H, OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$): 139, 135, 133, 129, 128.6, 128, 125.6, 124.4, 113, 64.5 [43].

Antidiabetic activity

***In vitro* α-glucosidase inhibitory assay:** For the preparation of test samples, 1 mg of biocatalyst dissolved in 20 µL of water and then sterile water was added until the volume reached 1000 µL. The α-glucosidase inhibitory assay was performed in a reaction volume of 75 µL using a 96-well microplate. A test sample solution of 25 µL (1 mg/mL) was gently mixed with 25 µL of α-glucosidase enzyme (0.5 U in 0.1 M phosphate buffer, pH 6.8) and preincubated at 37 ± 1 ºC for 10 min. After the pre-incubation, 25 µL of substrate (0.5 mM PNPG) was added to the reaction mixture and again incubated at 37 ± 1 ºC for 30 min. Blank reactions (25 µL enzyme was replaced by 0.1 M phosphate buffer, pH 6.8) were included for all samples. A control reaction containing a mixture of 25 µL buffer, 25 µL of α-glucosidase enzyme and 25 µL of substrate (0.5 mM PNPG) and a reaction of standard α-glucosidase inhibitor drug, acarbose were included. After, 30 min, the reactions were stopped by adding 100 µL of 0.2 M sodium carbonate solution. All reactions were performed in five replicas.

Dose-effect analysis for calculation of 50% effective concentration (EC_{50}) values of antidiabetic activity was performed using *in vitro* α-glucosidase assay in a reaction volume of 75 µL using 96-well microplate. A sample solution of 2, 5, 10, 15, 20 and 25 µL were mixed with 25 µL of α-glucosidase enzyme (0.5 U) and the volume made up the up to 50 µL with assay buffer.

The absorbance of test reactions, controls and standard inhibitor reaction were measured on a 96-well microplate at 405 nm in a UV-visible spectrophotometer. The percentage of α-glucosidase inhibition activity was calculated by using the following formula [44]:

$$\alpha\text{-Glucosidase inhibition (\%)} = \frac{\text{Control OD} - \text{Sample OD}}{\text{Control OD}} \times 100$$

where Control OD = OD of the control reaction – Blank OD; Sample OD = Sample OD – Sample blank OD].

RESULTS AND DISCUSSION

EDS studies of biocatalyst prepared and plant material: In Fig. 1a, the EDS spectrum of the plant material reveal that Cu is absent (0.00%), whereas in Fig. 1b, the spectrum of the prepared biocatalyst reveal that Cu is present (40.76%). No observation of other peaks related to any other impurity clearly inferred that the prepared biocatalyst is pure. Based on the EDS results, it can be concluded that 40 mg of biocatalyst contains 0.256 mmol of copper.

XRD studies: The XRD spectrum of the raw plant material shows no prominent peak of possible metal complexes (Fig. 2a), whereas the prepared biocatalyst shows the prominent peaks correspond to copper diacetohydrate (Fig. 2b). Applying the Debye-Scherrer equation [45,46] to the XRD pattern's distinctive peak value of 2θ and the full width at half maximum (FWHM) value, the average particle size was found to be 38.59 Å.

UV-visible studies: In prepared biocatalyst, the prominent absorption around 710-720 nm is due to Cu^{2+} ion in octahedral coordination with strong tetragonal distortion. Copper in Cu^{2+} ($3d^9$) ions shows a broad optical absorption band around 710-750 nm (Fig. 3), which was assigned to the $^2B_{1g} \rightarrow {}^2B_{2g}$ transition of the Cu^{2+} centers [47,48].

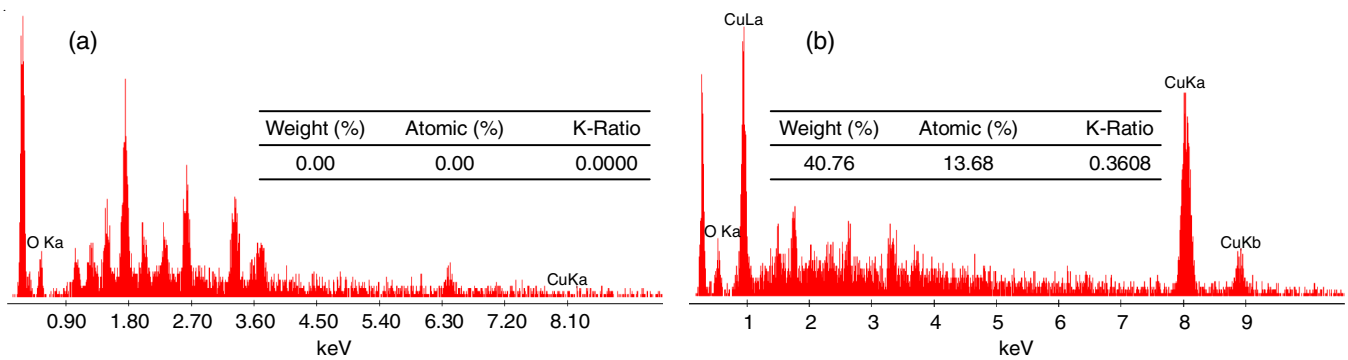


Fig. 1. EDS spectra of (a) plant material and (b) prepared bio-catalyst

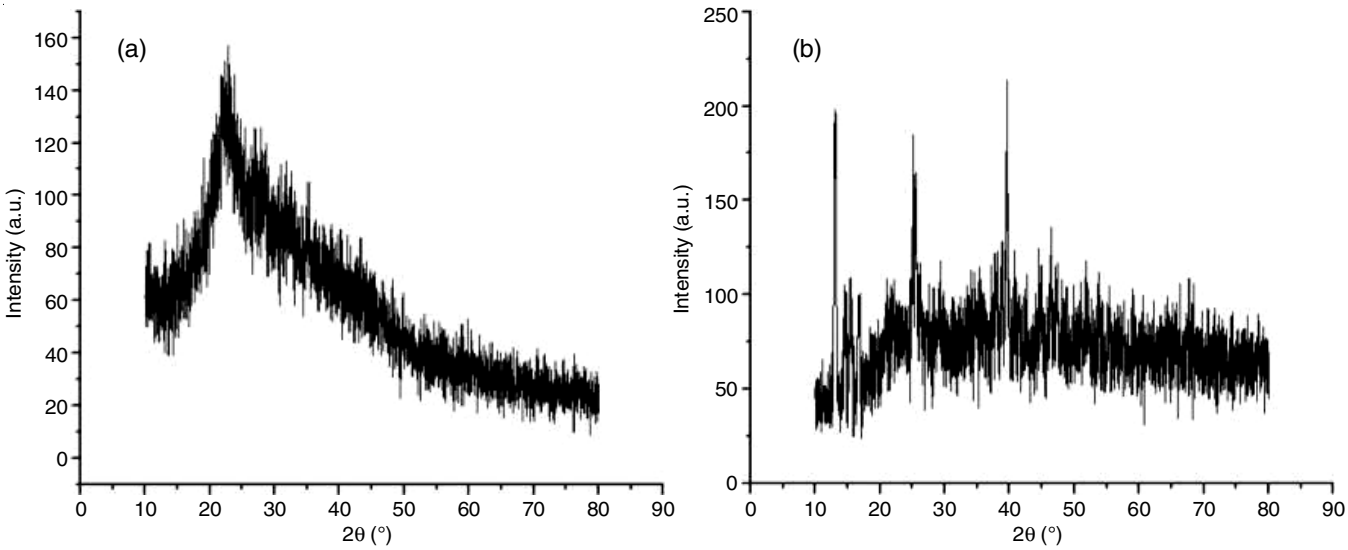


Fig. 2. XRD spectra of (a) plant material before adding copper acetate and (b) biocatalyst prepared using copper acetate

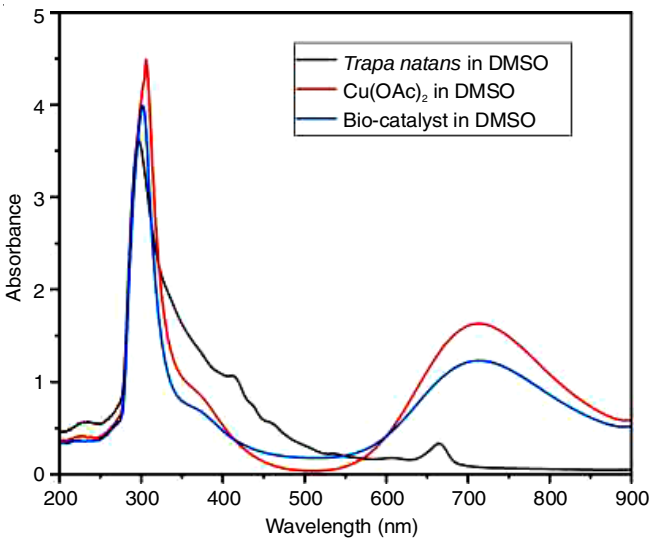


Fig. 3. UV spectra of plant material, $Cu(OAc)_2$ in DMSO and bio-catalyst in DMSO

IR spectral studies: The IR spectra of the prepared bio-catalyst has significant peaks at 3365 and 3272 cm^{-1}, which shift from a singular broad band at 3340 cm^{-1} observed in the IR spectrum of the plant material, displaying the conversion of secondary amine groups to primary NH_2 groups (Fig. 4). The observed downfield shift, going from plant material to metal complex of $Cu(OAc)_2$ suggests neutral ketonic coordination of carbonyl groups to the copper metal. The IR stretching frequency observed in 1420-1442 cm^{-1} region in the prepared biocatalyst has been attributed to the presence of acetate group. Furthermore, the appearance of a peak at 688-626 cm^{-1} indicates the Cu-O stretching frequencies [49].

Optimization of Ullmann reaction: For the optimization of the reaction conditions, the Ullmann reaction of 2-chlorobenzonitrile using *T. natans* L./$Cu(OAc)_2$ as catalyst was opted as a model reaction. In the presence of strong base, the classic Ullmann reaction could be catalyzed by copper. However, no reaction occurred in absence of any copper catalyst (Table-1, entry 1). When $Cu(OAc)_2$ was used as catalyst at different concentrations, the product was formed at reflux condition (Table-1, entries 2 & 3).

However, when CuI and $CuCl_2$ were used as catalysts, product was formed at 25% and 41% yields, respectively (Table-1, entries 4 & 5), whereas using 20% of silica-supported copper(II) catalyst generally completed in DMSO at 130 ºC under stirring for 20 h yielding the product (88%) (Table-1,

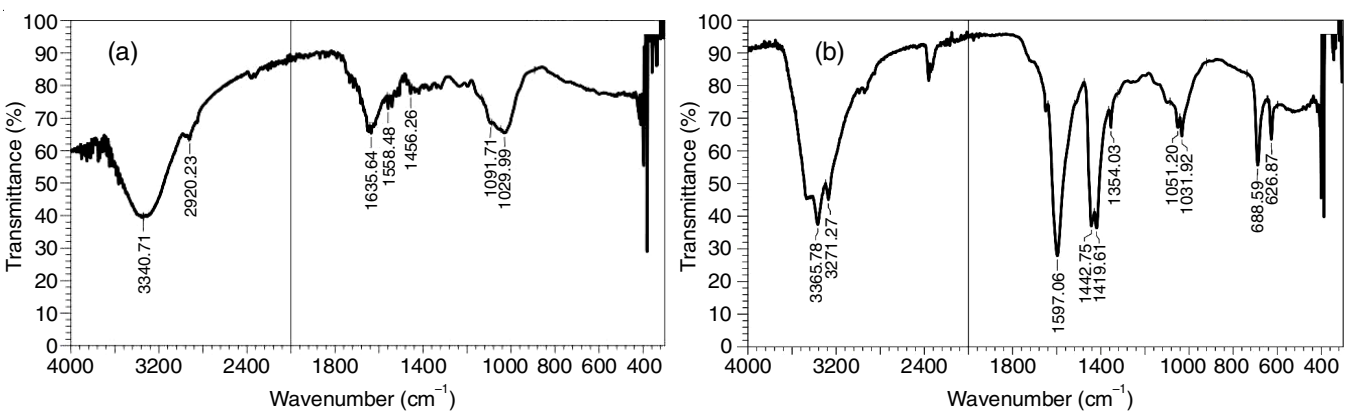
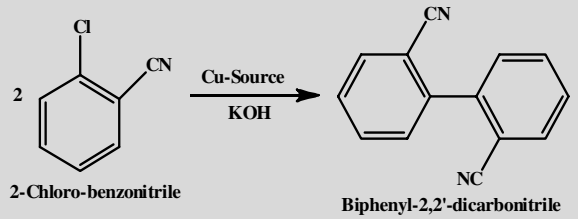


Fig. 4. IR spectrum of (a) plant material and (b) bio-catalyst prepared

TABLE-1
EFFECT OF COPPER SOURCE ON
THE CLASSIC ULLMANN REACTION[a]



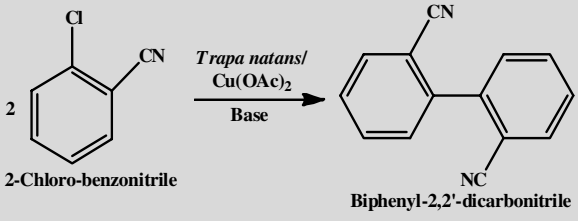
Entry	Copper source (mol%/mmol)	Time	Yield (%)[c]
1[a]	No copper	15 h (r.t.)	0
2[b]	$Cu(OAc)_2$ (10 mol%)	20 h (reflux)	45
3[b]	$Cu(OAc)_2$ (20 mol%)	20 h (reflux)	52
4[b]	CuI (20 mol%)	20 h (reflux)	25
5[b]	$CuCl_2$ (20 mol%)	20 h (reflux)	41
6[b]	Silica supported Cu(II), (0.20 mmol of Cu)	20 h (reflux)	88
7[a]	Bio-cat (0.128 mmol of Cu)	20 h (r.t.)	78
8[a]	Bio-cat (0.192 mmol of Cu)	18 h (r.t.)	82
9[a]	Bio-cat (0.256 mmol of Cu)	15 h (r.t.)	92

[a]2-Chloro benzonitrile (2.0 mmol), bio-catalyst, KOH (2.00 mmol) in DMF (4 mL) at room temperature for 15 h.
[b]2-Chloro benzonitrile (2.0 mmol), silica-supported Cu(II) catalyst (containing 0.20 mmol of Cu), KF (2.0 mmol) in DMSO (4 mL) at 130°C and stirring for 20 h.
[c]Isolated product.

entry 6). It was also observed that the coupling reaction can undergo with biocatalyst in DMF with stirring at room temperature (Table-1, entry 7-9). It was found that coupling reaction can undergo with biocatalyst (40 mg, 0.256 mmol of Cu) in DMF with stirring at room temperature for 15 h yielding the product as 92% (Table-1, entry 9). This may be due to an increase in the surface area of the fibrous biocatalyst used.

Efficiency of different bases was also investigated in DMF solvent. Among the investigated bases, KOH was found to be more prominent than other bases (Table-2). Further investigation was carried out to check the efficiency of different solvents on the coupling reaction. Reaction in DMF was found to get excellent yield (up to 92%) and DMSO gave 82% yield. No desired product was found during the reactions in H_2O, EtOH and THF (Table-3).

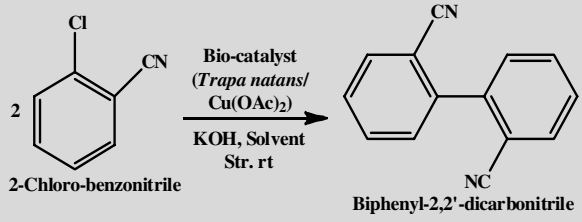
TABLE-2
EFFECT OF BASES ON THE CLASSIC ULLMANN REACTION[a]



Entry[a]	Base	Yield (%)[b]
1	K_2CO_3	74
2	K_3PO_4	58
3	KOAc	64
4	NaOH	78
5	KOH	92
6	Na_2CO_3	62
7	Cs_2CO_3	68

[a]2-Chlorobenzonitrile (2.00 mmol), bio-catalyst containing Cu (40 mg, containing 0.256 mmol of Cu), KOH (2.00 mmol) in DMF (4 mL) at room temperature for 15 h; [b]Isolated product.

TABLE-3
EFFECT OF SOLVENT ON THE
CLASSIC ULLMANN REACTION[a]

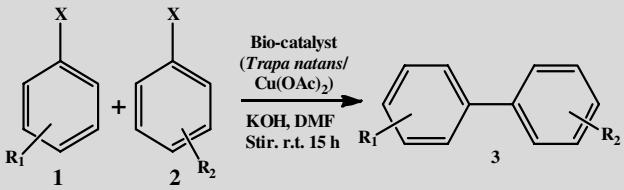


Entry[a]	Solvent/temp. (°C)	Yield (%)[b]
1	H_2O/25	0
2	EtOH/25	0
3	THF/25	0
4	DMSO/25	72
5	DMSO/90	78
6	DMSO/130	82
7	DMF/25	92
8	DMF/90	86
9	DMF/130	78

[a]2-Chloro benzonitrile (2.00 mmol), bio-catalyst containing Cu (40 mg, containing 0.256 mmol of Cu), KOH (2.00 mmol) in DMF (4 mL) at room temperature for 15 h; [b]Isolated product.

Thus, the best optimized conditions for the Ullmann reaction were 40 mg of *T. natans L.*/$Cu(OAc_2)$,0.256 mmol of Cu, 2 mmol of KOH as base and 4 mL of DMF. The mixture was stirred at room temperature for 15 h. Several derivatives of phenyl chlorides and bromides underwent under the optimized reaction condition to yield the biaryl products in the 76-92% range (Table-4) [50-54].

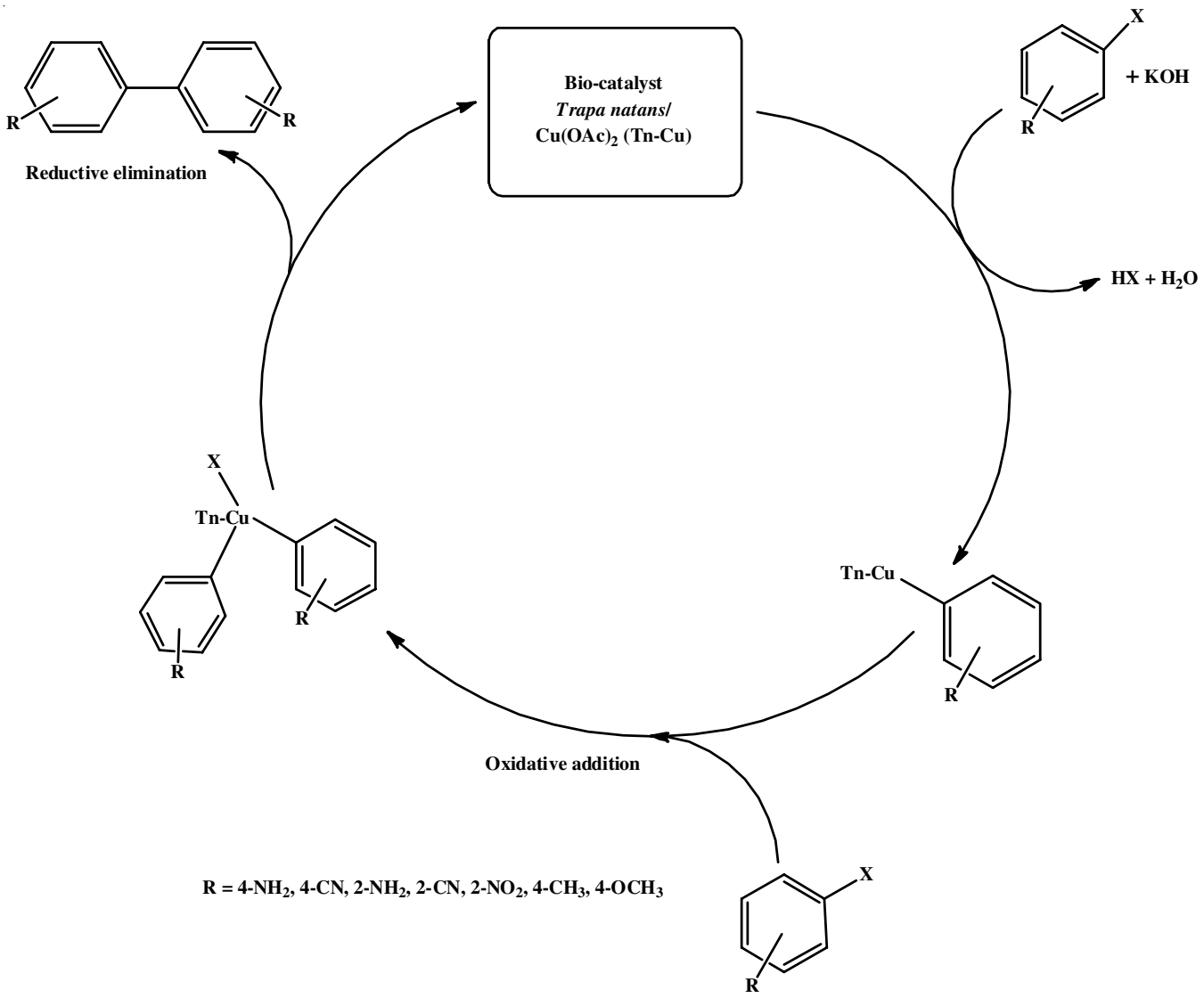
TABLE-4
SYNTHESIS OF BI-ARYL DERIVATIVES[a]



Entry	**1** R_1/X	**2** R_2/X	Product	Yield (%)
1	2-CN/Cl	2-CN/Cl	**3a**	92
2	4-CN/Cl	–/Cl	**3b**	88
3	2-CN/Cl	–/Cl	**3c**	85
4	2-NH_2/Cl	2-NH_2/Cl	**3e**	76
5	4-NH_2/Cl	4-NH_2/Cl	**3f**	84
6	4-NH_2/Cl	–/Cl	**3g**	85
7	2-NO_2/Cl	–/Br	**3h**	87
8	4-CN/Cl	4-CN/CH_3	**3i**	92
9	4-CN/Cl	4-CN/OCH_3	**3j**	88

[a]Phenyl halide (2.00 mmol), bio-catalyst containing Cu (40 mg, containing 0.256 mmol of Cu), KOH (2.00 mmol) in DMF (4 mL) at room temperature for 15 h.

Mechanism: The proposed reaction mechanism is shown in **Scheme-II**. Electron deficient and electron donating aryl chlorides can undergo self-coupling as well as cross-coupling



Scheme-II: Plausible mechanism of the Ullmann reaction

with different substituents producing excellent yield under the optimized conditions [55].

Antidiabetic activity: The inhibition activity on the α-glucosidase enzyme along the standard compound, acarbose (use for antidiabetic treatment) was evaluated with the prepared biocatalyst. Different concentrations of the compound was used and investigated and found its inhibition properties varied from 16.88% (2 µL) to a maximum of 63.12% (10 µL) (Table-5). The compounds were further investigated along with acarbose for the calculation of 50% inhibition concentration IC_{50} against the enzyme inhibition activity. The biocatalyst has an IC_{50} value at 5.74 ± 0.5185 µg mL (Table-6), which indicate effective IC_{50} value as compared to acarbose standard with value of 1.8 ± 2.609.

The Hill coefficient value found at the calculation of IC_{50} of compound is higher than 1.0, which indicates that the compound has some binding to different active sites of the enzyme showing the maximum % inhibition of 59.63 to 63.12. Thus, based on the results, the compounds could be used for *in vivo* antidiabetic investigations. Moreover, the compounds is synthesized in water, it may be useful for antidiabetic therapeutic analysis.

TABLE-5
ANTIDIABETIC ACTIVITY OF BIOCATALYST AT DIFFERENT CONCENTRATION

No. of experiment	Catalyst amount used (µL)	Inhibition (%)	
		Biocatalyst	Acarbose
1	2	16.88	-34.94
2	5	36.13	0.62
3	10	63.12	-9.95
4	15	61.97	-3.23
5	20	59.63	4.91
6	25	59.95	9.39

Conclusion

An efficient and low cost biocatalyst using copper acetate in the fibrous part of *Trapa natans* L., for the classic Ullmann reactions in DMF medium was synthesized and characterized. The formation of homocoupled products were of good to high yields (76-92%). The biaryl compounds synthesized was also

TABLE-6
IC_{50} VALUE FOR BIOCATALYST AND ACARBOSE

No.	Concentration (µL)	Inhibition (%)	
		Biocatalyst	Acarbose
1	2	-0.68	-24.1
2	2	11.16	-28.39
3	2	22.61	-36.86
4	5	21.51	-11.86
5	5	29.97	21.37
6	5	30.89	28.27
7	10	55.32	-6.77
8	10	62.38	-5.83
9	10	65.56	-3.83
10	15	64.21	-4.2
11	15	66.75	1.21
12	15	68.19	3.3
13	20	61.92	4.74
14	20	60.18	7.26
15	20	67.03	8.67
16	25	56.60	10.68
17	25	63.85	12.01
18	25	65.39	16.54

characterized using IR, ^{1}H & ^{13}C NMR spectra and melting point. This work shown the benefit of using Cu-biocatalyst of phenyl halides at room temperature. The antidiabetic activity of synthesized phenyl halides using Cu-biocatalyst was also evaluated. The promising results of antidiabetic property was obtained and the IC_{50} value was found to be 5.74809 ± 0.5185 µg/mL.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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