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One step N-arylation of amines catalyzed by a non-toxic copper complex

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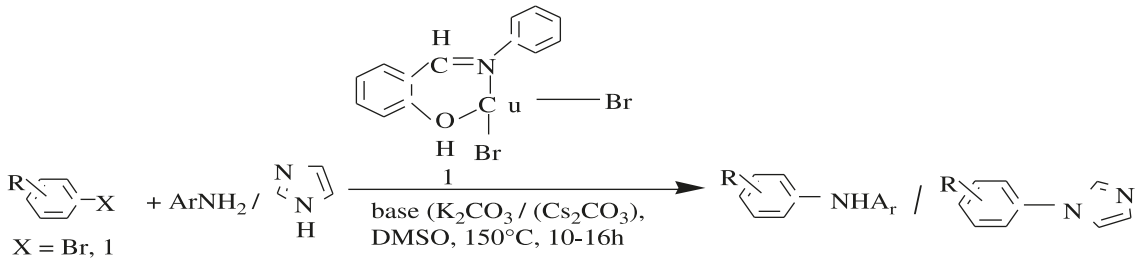
Abstract

A new, simple and efficient copper - catalyzed method has been developed by using a non-toxic copper complex for the preparation of amine derivatives, some of which are biologically active and literary known with high purity. The protocol to prepare the copper complex uses N-salicylidene-N-phenyl amine as the ligand with Cu_2Br_2 in methanol.



Key words: Amination; Non-toxic Copper complex; coupling reaction; catalysis

Introduction

The evolution of organometallic chemistry during the second half of the 20th century has transformed chemical science and technology to a degree and in ways that have rarely been matched throughout the history of chemistry (Halpern, 2001). Since that time, copper salt mediated and much later, copper-catalyzed C-X bond forming reactions (X = C, O, N) have been developed (Koten, 2012). Several copper catalysts are established in the last 10 years.Amination reactions using homogeneous copper catalyst systems are not generally selective and it is also difficult to remove the catalyst from the homogeneous system (Patil *et al.,* 2010). To overcome these difficulties, our efforts were directed towards the development of cheaper heterogeneous catalyst systems, which can be easily removed and handled.

Modern developments in the catalysis field have led to highly effective methods for C-N bond formation. The aryl amines play an important role in medicinal & biological chemistry. The synthesis of various drugs involves the step of N-arylations that has utilized the catalyzed reaction. The Ullmann Coupling (Ullmann and Bielecki, 1901) amination reaction, a new, easy and developed method catalyzed by copper complex, 1 are very efficient and reliable methods for the introduction of new carbon-nitrogen bonds.

Materials and Methods

^{1}H-NMR and ^{13}C-NMR Spectra of some samples were recorded using a Bruker WH 400MZ Spectrometer in the Bangladesh Council of Scientific and Industrial Research (BCSIR) Laboratories, Dhaka, and by using 300 MHz NMR - Spectrometer in Leibniz Institute of Plant Biochemistry, Weinberg-3, D-06120 Halle (Saale), Germany and also by using 400 MHz NMR-Spectrometer in Academia Sinica, Nankang, Taipei, Taiwan, Rebublic of China. The spectra were recorded in CD_3OD, DMSO, and mostly in $CDCl_3$ with TMS as internal standard. The chemical shifts were expressed in δ - values. Mass spectra were recorded on LC-ESI-MS system in Leibniz Institute of Plant Biochemistry, Weinberg-3, D-06120 Halle (Saale), Germany. The thin layer chromatography (TLC) was performed on precoatedaluminium plates (Merck 60 F254 silica gel) and

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detected by UV light and in Iodine chamber. Column chromatography was performed with Merck silica gel 60, 70-230 mesh ASTM. Yields of the products are the isolated yield after column chromatography. All solvents were dried and purified by usual techniques.

General procedure for the preparation of the ligand, N-salicylidene-N-phenyl amine:

2- Hydroxybenzaldehyde, (10 mmol ≃1.22g) was dissolved in 15 mL ethanol (absolute). Four drops of conc. HCl acid were added to it. Then with stirring ethanolic solution of aniline (10.3mmol≅0.96g in 10 mL ethanol) was added. The reaction mixture was refluxed for three hours until completion of the reaction (TLC check up); the reaction mixture was kept for one hour under ice- cooling. It was neutralized with saturated solution of $NaHCO_3$. Some ice was poured into the flask and then it was kept in a refrigerator for overnight. A yellow solid was precipitated out and was collected after filtration and kept in a vaccum desicator for drying. After recrystallization from EtOH, a shiny yellow needle-shaped crystal, mp. 41°C, (170mg, 87%) was obtained.

Complex formation of the ligandwith Cu_2Br_2:

Two separate solutions of cuprous bromide (4mmol≅1.14g) and the ligand (1mmol≅0.197g) were prepared in methanol and then mixed together at room temperature. The reaction was completed after 15 hours of continuous reflux. Then the reaction mixture was kept in room temperature for settling. A green precipitate was found at the bottom of the reaction flask. The solvent was discarded by filtration. On drying in a desicator green solid complex, 1(300 mg, 71%) was obtained having mp. >300°C.

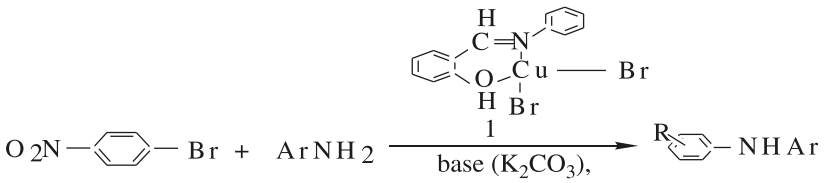
Typical procedure of Amination reaction utilizing the copper complex, 1:

Aryl amine (1.5 mmol), aryl halide (1mmol), catalyst, 1 (optimum amount depending on the substrates), base (K_2CO_3 / Cs_2CO_3, 2 mmol) and DMSO (6 mL) were mixed together. The mixture was refluxed at 150°C for 10-16 hours. The mixture was cooled to room temperature, diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL); any water residual solids present were filtered. The organic phase was dried over anhydrous sodium sulphate and evaporated by a rotary evaporator. The crude product was column chromatographed over a silica gel eluting with $CHCl_3$: $C_2H_5COOCH_3$= (9:1) solvent mixture to obtain pure product.

Results and discussion

For the synthesis of amine derivatives, the copper catalyzed reactions are extremely powerful tools in organic synthesis.

Table I. N - arylation of amines with p-bromonitrobenzene catalyzed by Cu-complex, 1



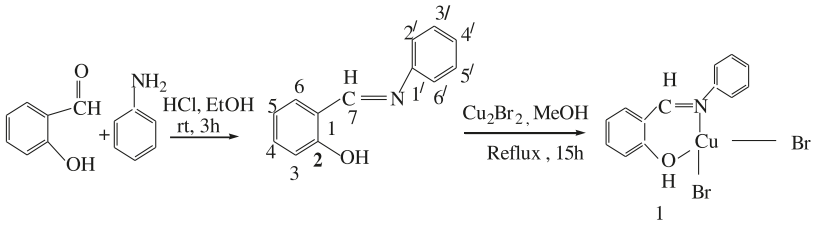
R — x	Amine	Products	Cu-Complex, 1 mmol %	Reacion Time, hrs	Yield %
O2N — Br	H2N — CH3	O2N — N(NO2) — CH3 (2)	10	12	49
O2N — Br	H2N — NO2	O2N — NH — NO2 (3)	10	8	43
O2N — Br	H N O	O2N — N O (4)	10	12	40

Reaction condition: Amines (1.5 mmol), Aryl halide (1.0 mmol), base K_2CO_3 (2 mmol) and the Cu-complex 1 (10 mmol %) in DMSO (6mL), refluxed at 150°C for 8-12 hours.

The mild reaction condition for amination reactions using the Cu-catalyst, 1 was developed in our laboratory to form C-N bond. It offers considerable advantages over classical methods having harsh reaction conditions. The amines used in the reactions were heterocyclic and substituted primary and secondary amines. Important biological compounds such as N-(phenyl)-imidazole (Wolff *et al.,* 1993). 4′-(Imidazol-1-yl) acetophenone (Craven and Rubertis, 1990). 4-(4′-nitrophenyl) morpholine (Wang *et al., 2012).* with high purity were synthesized in a one step process.

Synthesis of Copper complex catalyst, 1:

The following reaction scheme was followed for the preparation of catalyst, 1:



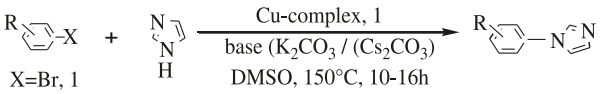
Application of the prepared catalyst, 1:

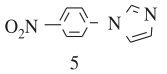
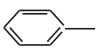
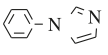
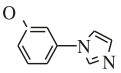
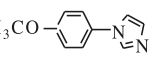
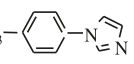
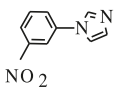
The activity of the Cu-complex, 1 as catalyst was tested in Coupling reaction that is, carbon-nitrogen bond formation reaction. The reactions involve activated/inactivated aryl halides with primary and secondary aryl amines.The reactions are summarized in Table I and Table II:

Optimization of the reaction condition for C-N bond formation regarding the solvent choice:

DMSO was found to be the best solvent of choice, while according to literature (Kwong *et al.,* 2002) Toluene, dioxane and DMF were much less effective. 2-propanol was also used in synthesis of the compound 4-(4-nitro phenyl)

Table II. N-arylation of Imidazole by various substituted phenyls catalyzed by Cu-complex, 1



R—x	Amine	Products	Base	Cu-Complex,1 mmol %	Reacion Time, hrs	Yield %
O_2N—Br		 5	K_2CO_3	10	12	43
		 6	K_2CO_3	20	12	11
H_3O—Br		CH_3O  7	K_2CO_3	80	12	21
H_3CO 		CH_3CO  8	K_2CO_3	100	16	14
CF_3  I		CF_3  9	K_2CO_3	20	10	20
		 10	K_2CO_3	20	10	24

Reaction condition: Imidazole (1.5 mmol), Aryl halide (1.0 mmol), base K_2CO_3/ Cs_2CO_3 (2 mmol) and the Cu-complex 1 (optimum amount) in DMSO (6mL), refluxed at 150°C for 10-16 hours.

morpholine, but the yield of the product is greater in DMSO solvent and also time is shortened compared to that in 2-propanol for completion of the reactions.

Exp. No	Morpholine (mmol)	1-bromo-4 nitrobenzene (mmol)	Base K_2CO_3 (mmol)	Cat.1 (mmol %)	Yield %	Reac. time (hrs)
1	1.5	1	4	10	40	12
2	1.5	1	4	15	20	23

On the basis of the reaction time and yield, it was observed that a convenient and simple one step catalytic method has been developed using newly synthesized air stable and non-toxic copper- complex as pre-catalyst.Various biologically active amine derivatives can be prepared by this method. The catalyst is easy to separate from the reaction mixture; only filtration is needed. A small quantity of complex (10-100 mmo, 1%) is used for completion of the reaction.

Analytical & Spectral Data of the Compounds

N-salicylidene-N-phenyl amine

Melting point: 41°C. Yield: 170 mg (87%). FT-IR (υ): 3448 (OH, broad), 3054(aro. C-H str.), 1616 (C=N, str.), 1589, 1570(C=C), 1357, 1275(C-N, str.), 1185(C-O, str.) cm^{-1}. ^1H - NMR (400 MHz, $CDCl_3$) δ(ppm): 13.26 (1H, s, OH), 8.61 (1H, s, H-7), 7.40 (4H, m, H-2′, 3′, 5′, 6′), 7.28 (3H, m, H- 4, 5, 6), 7.04(1H, d, H-3), 6.95(1H, t, H-4′). ^{13}C - NMR: 162(C-7), 161(C-2), 148(C-1), 148(C-1′), 129(C-3′, 5′), 121(C-2′, 4′). Mass Spectra: 197[M^+], 196 [M-1]$^+$

[Salicylideneaminato- χ^2 N, O]Copper (II) complex, 1

Melting point: >300°C, Yield: 300 mg (71%). FT-IR (υ): 3420(O-H, broad), 1610(C=N, str.), 683 (C-Br, str. strong), 1560, 1545, 1529 (aro. C=C) cm^{-1}. ^1H - NMR (400 MHz, $CDCl_3$) δ (ppm): 12.96 (s, 1H, OH), 8.52(d, 1H, H-3, J=5.6Hz), 7.60(d, 1H, H-6, J=5.2), 7.51(t, 1H, H-4,J=5.6,5.6 Hz), 7.45(dd, H-5, J= 5.2, 5.6 Hz), 7.20-7.40(m, 5H, H- 2′, 3′, 4′, 5′, 6′), 6.96(s, 1H, H-7). Mass Spectra: 427, 429, 231(M^+, 1:2:1, 2-Bromine isotopic pattern, 6%), 412, 414, 416 (M^+-OH, 2-bromine isotopic pattern, 5%), 331, 333(M^+-Br-OH, single bromine isotopic pattern, 10%), 252(M-2Br-OH, 1%), 197(M^+, 100%).

N, N-(Di-4'-nitrophenyl)-4-methylaniline, 2

Obtained by reaction of 4-nitrobromobenzene and 4-methylaniline as orange solid.mp: 135°C, Yield: 112 mg (49%).^1H-NMR (400 MHz, $CDCl_3$) δ(ppm): 8.28 (4H, m), 8.11 (2H,d, *J*=8.1 Hz, H-4', 5'), 7.14 (6H, *m*, H-3, 6), 2.38 (2H, s). ^{13}C-NMR δ(ppm): 160.66 (C-4', 4") 151.89 (C-1',1"), 144.26(C-1)., 142.61 (C-4), 142.16, 137.36 ,131.16, 127.22 , 126.22, 125.45(C-2, 6), 122.03, 119.25, (C-3,5), 21.04 (CH_3). Mass Spectra: *m/z*: 350 [M]$^+$, 260 [M^+- $2NO_2$]

N-(4'-nitrophenyl)-4-nitroaniline, 3

Obtained by reaction of 4-nitrobromobenzene and 4-Nitroniline as orange solid.mp: 210-212°C , Yield: 140mg (54%).^1H-NMR (400 MHz, $CDCl_3$) δ(ppm): 8.22(4H, d, J=9.01 Hz, H-3,5, 3',5'), 7.18 (4H,m, H-4, 5, 4', 5'), 6.61 (1H, s). ^{13}C-NMR δ(ppm): 146.56 (C-4', 4"), 142.39 (C-1',1"), 126(C-3, 5, 3', 5'), 117.37(C-2, 6, 2', 6'). Mass Spectra: m/z: 259 [M]$^+$, 167 [M^+- $2NO_2$]

4-(4-nitro phenyl) morpholine, 4

Obtained by reaction of 1- bromo-4-nitrobenzene and morpholine as yellow solid; mp: 152°C[9].Yield: 84 mg (40%), ^1H - NMR (400 MHz, $CDCl_3$) δ(ppm): 8.11(d, 2H, J=9.1Hz, H-3′, 5′), 6.82 (d, 2H, =9Hz, H-2′, 6′), 3.85(t, 4H, J=4.8Hz, H-3, 5), 3.36 (t, 4H, J=4. 7Hz, H-2, 6).13_C - NMR (100 MHz, $CDCl_3$) δ(ppm):155.0(C-4′), 139.04 (C-1′), 125.86(C-3′, 5′), 112.64 (C-2′, 6′), 66.36 (C-3, 5), 47.16 (C-2, 6). Mass spectra : ESI ($^+$ve): [M+Na]$^+$ = 231.2, [M+H] = 208.8

N-(4'- Nitrophenyl)-imidazole, 5

Obtained by reaction of 4-nitrobromobenzene and imidazole as yellow solid; mp: 170°C, Yield: 82mg (43%).^1H-NMR (400 MHz, $CDCl_3$): δ(ppm): 8.37(2H, d, J= 8 Hz, H-3', 5'), 8.01(1H,s, H-4', 5'), 7.57 (2H, d, J=8.0Hz, H-2', 6'), 7.35(2H, d, H- 5). 13_C-NMR δ(ppm): 146.35 (C-4′), 142 (C-1′) ,135.42 (C-2), 131.75 (C-5), 125.76 , (C-3', 5'), 121.08 (C-2', 6)' , 117.64 (C-4). Mass Spectra: m/z: 189 [M^+].

[N- (phenyl) - imidazole], 6

Obtained by reaction of Iodo benzene and imidazole as yellow liquid. Bp:142ºC[10],Yield: 20.3mg (11%), ^1H - NMR (400 MHz, $CDCl_3$) δ(ppm): 7.97 (1_H, s, H-2), 7.40-7.49 (2H, m, H-4, 5), 7.39-7.47(3H, m, H-3′, 4′, 5′), 7.25-7.47(2H, m, H-2′, 6′).

[N-(3/ -methoxy phenyl) imidazole], 7

Obtained by reaction of 3-bromo anisol and imidazole as yellow liquid. Yield: 91.6mg (21.06%). ^{1}H - NMR (400 MHz, $CDCl_3$) δ(ppm): 7.86 (1H, s, br, H-2), 7.37 (1H, dd, H-2/, J=2Hz, 2Hz), 7.25 (1H, d, H-4, J=12Hz), 7.23 (1H, d, H-5, J=12Hz), 6.85-7.00 (3H, m, H-4/,5/,6/), 3.86 (3H, s, OCH_3).

[1-[4-(1H-imidazol-1-yl) phenyl] ethanone], 8

Obtained by reaction of imidazole and 4-bromoacetophenone as yellow powder, mp: 108-110ºC[11], Yield: 62.9mg (14.3%). FT-IR (υ): 3121, 3106, 3060 (aro. C-H, str.), 2919 (C-H, aliphatic, asym. Str.), 1676 (C=O, strong), 1605, 1519, 1490 (aro. C=C), 1331, 1306 (sym. C-N str.) cm-^{1}. ^{1}H - NMR (400 MHz, $CDCl_3$) δ(ppm): 8.10 (d, 1H, H-5), 8.08 (d, 2H, H-3/, 5/, J=8.4 Hz), 7.96 (s (br), H-2), 7.48 (d, 2H, H-2/, 6/, J=8.4 Hz), 7.48(d, 1H, H-4), 2.6 (s, 3H).

[1-(4- trifluoromethyl phenyl)] imidazole, 9

Obtained by reaction of 4-trifluoromethyliodobenzene and imidazole as white solid, mp: 71ºC[12] Yield: 82.9mg (20%). FT-IR (υ): 3116 (aro. C-H str.), 1530, 1618 (aro. C=C), 1329, 1306 cm^{-1} (C-N sym. str.)cm^{-1}. ^{1}H - NMR (400 MHz, $CDCl_3$) δ(ppm): 7.92 (s, br, 1H, H-2), 7.75 (d, H-2/, 6/, J=7.2), 7.51 (d, H-3/, 5/, J=7.2), 7.33(br., s, H-4), 7.23 (d, H-5, J=4).

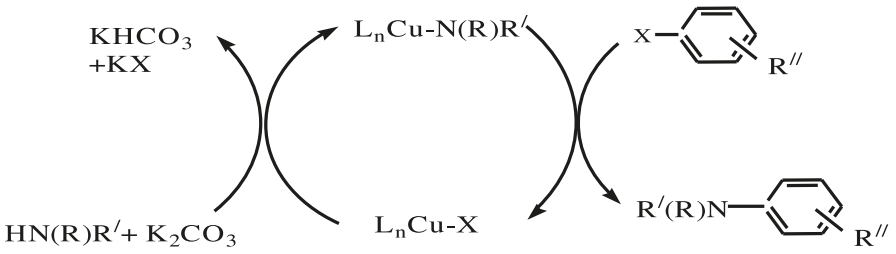
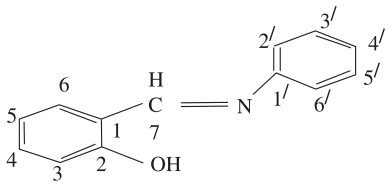


Fig. 1.

Spectra of the ligand & the catalyst



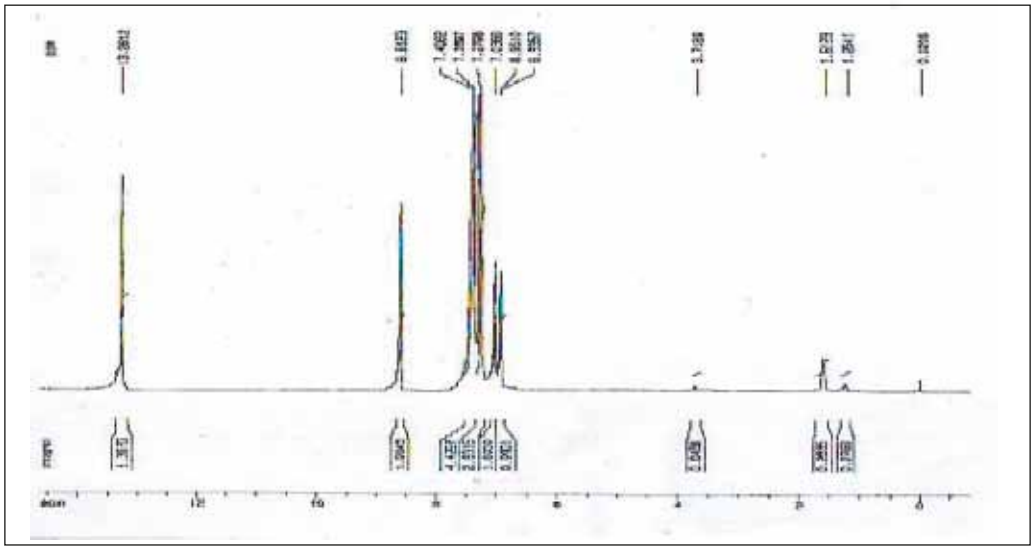


Fig. 2. ^{1}H-NMR of the ligand

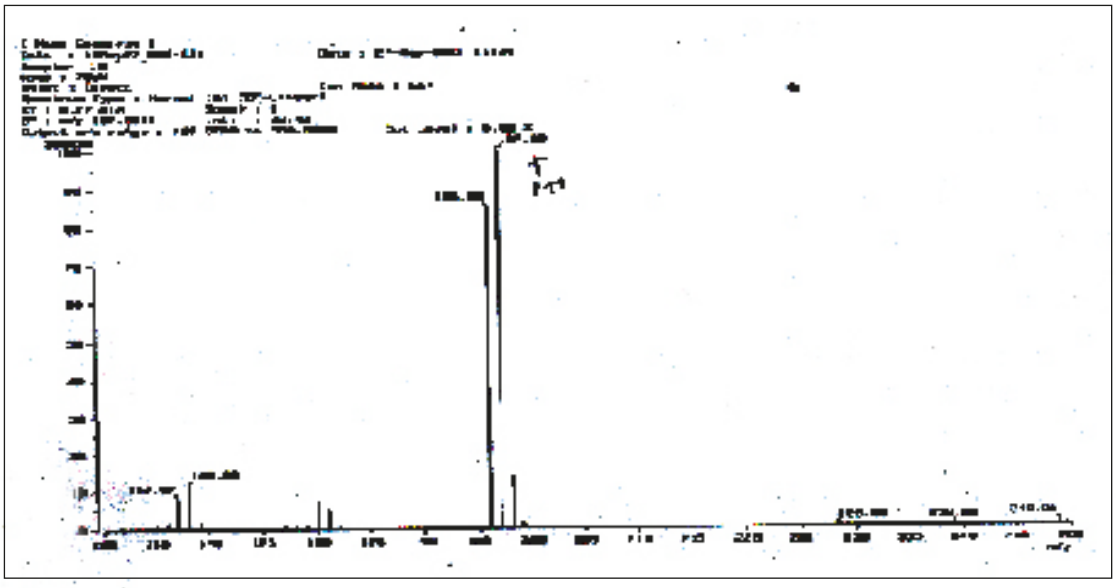


Fig. 3. ^{1}H-NMR of the ligand

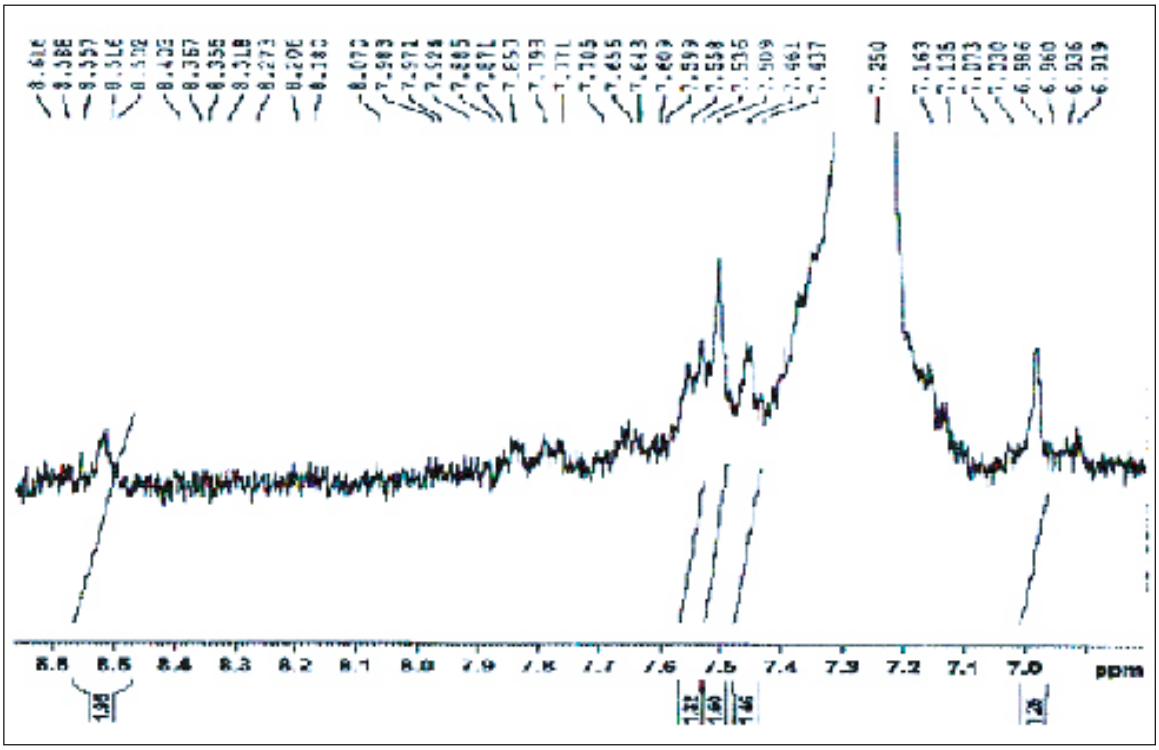


Fig. 4. ^{1}H-NMR of the Cu-catalyst

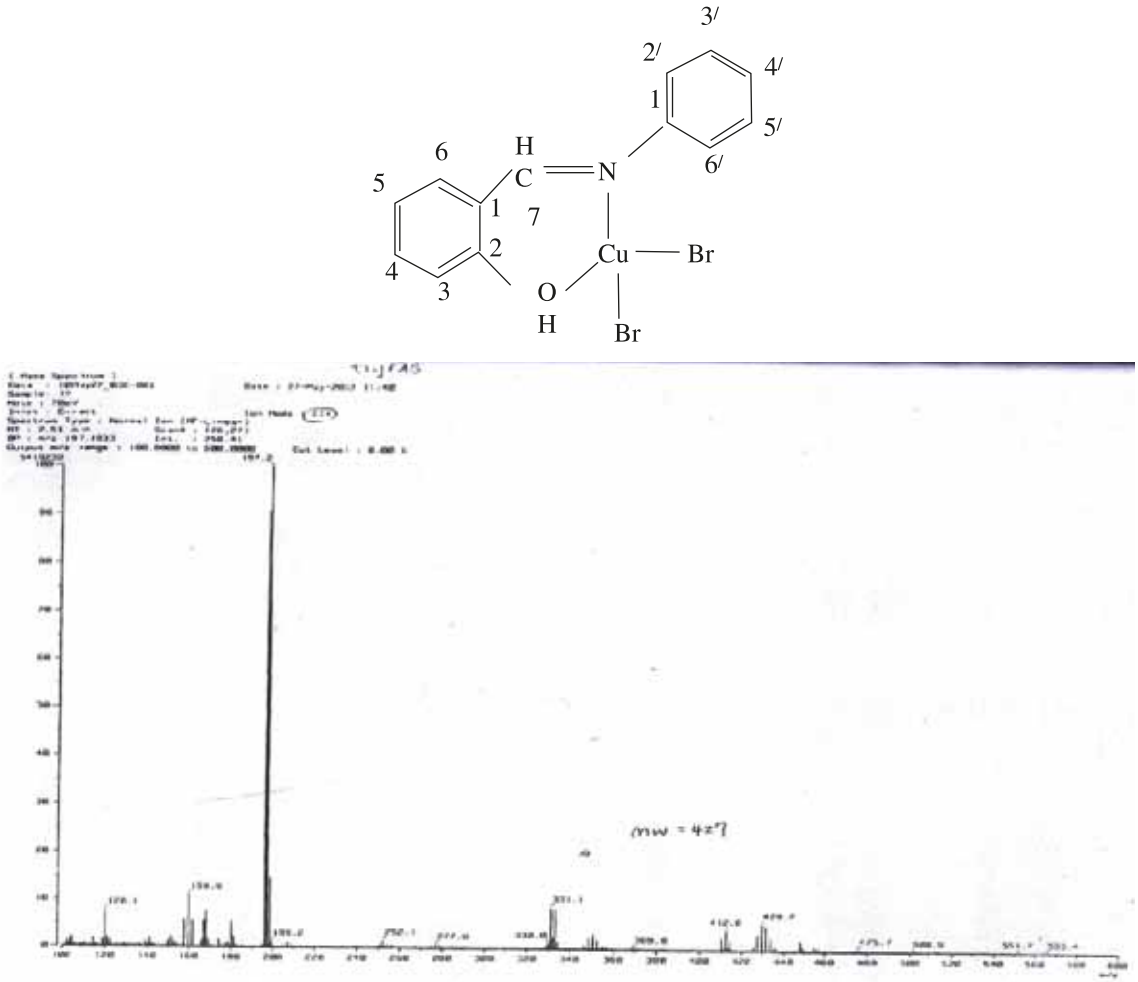


Fig. 5. Mass spectra of the Cu-catalyst

1-(3- nitrophenyl) imidazole, 10

Obtained by reaction of 1- Iodo-3-nitrobenzene and imidazole as yellow solid; mp: 174ºC[13]. Yield: 90.2 mg (24%). FT-IR (υ): 1624 (aro. C=C), 1522 (-NO_2), 1351, 1300 (C-N sym.str.) cm^{-1}. ^1H - NMR (400 MHz, $CDCl_3$) δ(ppm): 7.81 (d, H-2/, J=2.8 Hz), 7.77 (dd, H-4/, J=8.4Hz), 7.68 (s, H-2), 7.39 (t, H-5/),7.34(dd, 1H, H-4, J=8.4Hz), 7.21(d, H-5, J=8.4Hz), 7.14 (dd, H-6/, J= 8, 8, 1.2 Hz).

Possible catalytic mechanism

The general possible reaction mechanism[14] is shown below. The Cu(I)-catalyzed C-N bond-forming reaction between nucleophiles and aryl halides proceeds by a Cu(I)-mediated nucleophilic aromatic substitution type mechanism in which the aryl halide activation and the nucleophile formation occurs in two independent, sequential stages (figure-1). Consistent with this proposal, Cu(I) amidatespromote the kinetically competent stoichiometric N-arylation.

Conclusion

In summary, an efficient, environment friendly, inexpensive and new copper complex1 has been successfully used as pre-catalyst for amination reactions. From synthetic point of view, a new, effective & single step method has been developed to form C-N bond with high purity.

Acknowledgement

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