N-ARYLATION OF INDOLE CATALYZED BY COPPER-DIIMINE COMPLEXES AND COPPER NANOPARTICLES

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ABSTRACT

N-arylation of indoles are an important class of compounds because of the significant pharmacological, biological, and chemical activities and their presence in bioactive natural products. Beside their biological activity, they are also used as synthetic intermediates for the preparation of other biologically active compounds. The example of indole derivative is indole-3-carbinol extracted from broccoli or cabbage. Indole-3-carbinol is used for chemo preventive, anticancer such as breast cancer, and antitumor. Much attention has been focused on these heterocycles and various synthetic strategies have been developed for the *N*- arylation of indoles and other heterocycles. Herein, studied the *N*-arylation of indole is catalyzed by using CuI/diimine (**1**–**6**) as a catalyst and iodobenzene as substrate. The results exhibited good catalytic activity with %yield of C–N coupling, %yield of this reaction of appoximately 40–80%. In addition, the ratio of indole: iodobenzene of 1:1.5 gave good rate of reaction and yield. Moreover, the study of different substituents revealed that the methoxy group as donating group has higher rate of reaction and %yield of C–N coupling than the nitro group as withdrawing group. The position of substituent had the similar trend where both methoxy and nitro group gave *-ortho* > *-meta* > *-para*. Moreover, copper nanoparticles was used as a catalyst in *N*-arylation of indole. The copper nanoparticles was more efficient than CuI/diimine system.

KEY WORDS: *N*-ARYLATION/ INDOLE/ DIIMINE LIGANDS/ COPPER NANOPARTICLES

88 pages

ปฏิกิริยา เอ็น-แอริลเลชัน ของอินโดล ที่เร่งปฏิกิริยาโดยสารเชิงซ้อนระหว่าง คอปเปอร์กับไดอิมมีนลิแกนด์และอนุภาคนาโนของคอปเปอร์

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บทคัดย่อ

ปฏิกิริยา เอ็น-แอริลเลชัน ของอินโดล เป็นปฏิกิริยาที่มีความสำคัญและถูกนำไปใช้ในหลากหลายด้าน เช่น ด้านเภสัชกรรม ด้านชีวภาพและเคมีรวมไปถึงด้านผลผลิตที่ได้จากธรรมชาติ ตัวอย่างอนุพันธ์ของอินโดลที่สำคัญเช่น อินโดล-3-คาร์บินอล เป็นสารอนุพันธ์ของอินโดลที่สกัดได้จากบลอคคอรีหรือกะหล่ำปลี ซึ่งสารอินโดล-3-คาร์บินอลนี้ถูกนำไปใช้เป็นสารต้านการเกิดเนื้องอก ต้านการเกิดมะเร็ง โดยเฉพาะมะเร็งเต้านม เป็นต้น นอกจากนี้ ปฏิกิริยา เอ็น-แอริลเลชัน ของอินโดลยังเป็นวิธีสังเคราะห์สารตัวกลางเพื่อเตรียมเป็นสารตั้งต้นของสารประกอบทางชีวภาพ อื่น ๆ ได้อีกด้วย การทดลองเบื้องต้นพบว่าไดอิมมีนลิแกนด์(1—6)สามารถเร่งปฏิกิริยาการเข้าคู่ของคาร์บอนและไนโตรเจนได้ โดยร้อยละผลผลิตอยู่ในช่วง 40—80 โดยศึกษาอัตราส่วนระหว่างอินโดลต่อไอโอโดเบนซีน พบว่า อัตราส่วน 1:1.5 เป็นอัตราส่วนที่เหมาะสมต่อการทำปฏิกิริยา จึงใช้อัตราส่วนนี้ในการศึกษาในงานวิจัยนี้ นอกจากนี้ยังได้ศึกษาความแตกต่างของตำแหน่งและหมู่แทนที่พบว่าหมู่แทนที่ที่เป็นหมู่ให้อิเลคตรอน (กลุ่มเมทอกซี) ให้ร้อยละผลผลิตและอัตราการเกิดปฏิกิริยาที่ดีกว่าหมู่ดึงอิเลคตรอน (กลุ่มไนโตร) และพบว่าตำแหน่งของหมู่แทนที่ทั้งหมู่ให้อิเลคตรอนและหมู่ดึงอิเลคตรอนมีแนวโน้มเดียวกัน *-ortho* > *-meta* > *-para* นอกจากนี้ยังพบว่าอนุภาคนาโนของคอปเปอร์ก็สามารถใช้เป็นตัวเร่งปฏิกิริยาการเข้าคู่ของคาร์บอนและไนโตเจนได้ โดยอนุภาคนาโนของคอปเปอร์มีประสิทธิภาพสูงกว่าสารประกอบคอปเปอร์ไดอิมมีน

88 หน้า

CONTENTS

CONTENTS (cont.)

CONTENTS (cont.)

CONTENTS (cont.)

LIST OF TABLES

LIST OF FIGURES

Figure **Page**

LIST OF FIGURES (cont.)

Figure **Page**

LIST OF FIGURES (cont.)

Figure **Page**

LIST OF SCHEMES

LIST OF ABBREVIATIONS

%	Percentage
λ	Wavelength
ν	Wavenumber
°C	Degree Celsius
θ	Theta
β	Beta
μL	Microliter, 10^{-6} L
μm	Micrometer, 10^{-6} m
acac	Acetyl acetonate
ACN	Acetonitrile
Cu	Copper
CuI	Copper (I)iodide
CuNPs	Copper nanoparticles
cm^{-1}	Reciprocal centimeters
d	Doublet (spectral)
DI	De-ionized water
EG	Ethylene glycol
EtOAc	Ethyl acetate
EDG	Electron donating group
en	Ethylene diamine
EWG	Electron withdrawing group
FAAS	Flam Atomic Absorption Spectrometry
FCC	Face Center Cubic
g	Gram
h	Hour
kV	Kilovolt, 10^3 V

LIST OF ABBREVIATIONS (cont.)

L	Liter
m	Meter
M	Molarity (mol/L)
m	Multiplet (spectral)
m-	Meta position (1,3-disubstituted on benzene ring)
mg	Milligram, 10^{-3} g
mA	Milliampare, 10^{-3} A
MHz	Megahertz
min	Minute
mL	Milliliter, 10^{-3} L
mm	Millimeter, 10^{-3} m
mmol	Millimol, 10^{-3} mol
mol	Mole
mV	Millivolt, 10^{-3} V
nm	Nanometer, 10^{-9} m
NMR	Nuclear magnetic resonance spectroscopy
NPs	Nanoparticles
o-	Ortho position (1,2-disubstituted on benzene ring)
OAc	Acetate
p-	Para position (1,4-disubstituted on benzene ring)
ppm	Part per million, (1/1,000,000) or chemical shift unit
Rt, RT	Room temperature
s	Singlet (spectral)
sec, s	Second
t	Unit time
TOF	Turnover frequency
TON	Turnover number
V	Volt

LIST OF ABBREVIATIONS (cont.)

v/v	Volume per volume
XRD	X-ray powder diffraction
w	Watt
δ	Chemical shift

THE RELEVANCE OF THE RESEARCH WORK TO THAILAND

Indole and indole derivatives have been widely used for pharmaceuticals, new chemotherapeutic agents targeting the human immunodeficiency virus (HIV), antitumor, anticancer, and natural products. Indole and indole derivatives can be synthesize from many conditions and methodologies such as Ullmann reaction, Goldberg reaction, Leimgruber-Batcho reaction, and Fischer reaction. Consequently, a variety of synthetic methods are necessary for the synthesis of desirable structure of indole derivatives.

In term of this work, the Ullmann reaction is alternative method to synthesize indole derivatives in mild condition. Also the ligands for the synthesis of indole derivatives are easily prepared and cheap. Moreover, this research has been used copper nanoparticles (CuNPs) as a catalyst. Such CuNPs were simply carried out in a short of time and also they have excellent efficiency for catalysis. For those reasons, knowledge of this research should become high valuably for other researchers in chemistry and related study.

CHAPTER I
INTRODUCTION

This chapter introduces about background of catalysis and indole. In the first past, overview of catalysis. The second part involves indole and derivatives of indole and their application. The last past about coupling reaction involve of *N*-arylation reaction are describe in this chapter.

1.1Catalysis

In chemistry, catalysis is the change in the rate of chemical reactions or their excitation in the presence of substances catalysts which participate in reaction, effecting intermediate chemical interaction with the reagents, but which restore their chemical composition after the completion of the catalytic activation.

A catalyst usually effects such interaction many times, changing the chemical reaction rate for a long time and forming reaction products, whose weight may be greater than the weight of the catalyst itself by thousands and even millions of times. However, a catalyst cannot serve endlessly: in some industrial processes, it is used continuously for several years, and in others, only for several minutes. Catalysis may be upset by a change in the composition or structure of a catalyst due to secondary chemical reactions or mechanical and temperature influences. When branched chain reaction, particularly reactions leading to an explosion, are excited, a catalyst may in principle also take part once in a chemical reaction.

Catalyst was to be positive if the reaction rate increase. Negative catalysis implies a decrease in the chemical conversion rate due to catalyst actions; it is connected as a rule with a ratarded conversion in to an intermediate.

Positive catalysis occurs when the rate of the formation of intermediate compounds of a catalyst with the reagents and their further conversation into a product is greater than the rate of production with no catalyst. Catalyst is practically produced only for positive catalysis, which is examined in this monograph and called simply catalysis. The free energy of a catalyst before the catalytic act and after it is invariable. Therefore, in reversible reactions, a catalyst accelerate the attainment of equilibrium, but does not displace it[1].

The reaction order decreases because, in the presence of a catalyst, the reaction proceeds through several elementary stages, whose order may be smaller than that of uncatalyzed reactions. The different effect of the rate of elementary stages on the overall rate of a catalytic reaction often leads to its fractional order.

For instance, in the presence of a catalyst, the synthesis reaction may pass through the following elementary stages showed in Scheme 1.1.

$$A + [Cat] \rightarrow A^*[Cat] \qquad \ldots(1)$$

$$B + A^*[Cat] \rightarrow AB^*[Cat] \qquad \ldots(2)$$

$$AB^*[Cat] \rightarrow AB^* + [Cat] \qquad \ldots(3)$$

Where; A and B = reactant

AB* = product

[Cat] = catalyst

Scheme 1.1 The mechanism of catalysis. Catalysts generally react with one or more reactants to form intermediates that subsequently give the final reaction product, in the process regenerating the catalyst.

The energy change of the reacting system for the given reaction. If E is the activation energy of uncatalyzed reaction, E_c is the activation energy of the catalytic reaction, and e_1 and e_2 are the activation energies of intermediate stages (a) and (b), then, when $E_c < E$, catalysis is positive showed in Figure 1.1.

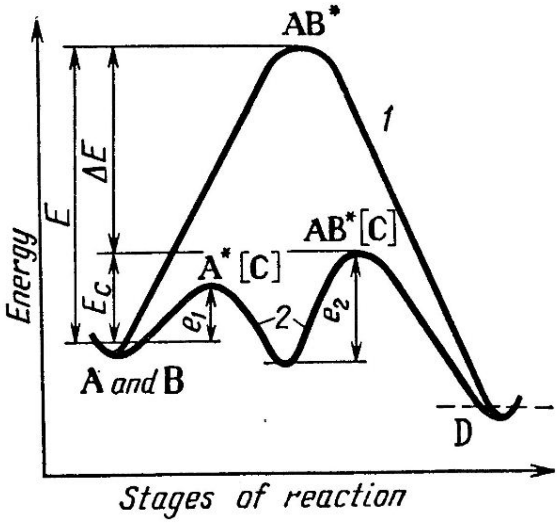


Figure 1.1 Energy change of the reacting system in uncatalyzed (curve 1) and catalytic (curve 2) reactions.

Hence, catalyst activity may be described as the activation energy of catalytic reaction. However, such a standard is inconvenient owing to the exponential and inverse dependencies of the reaction rate on the activation energy. As a standard of catalyst activity (A_1), use is made of the difference in the rate of chemical reactions in the presence of a catalyst u_c and without a catalyst u with due regard to the share of the volume of reaction space φ_c which is occupied by a catalyst and is inaccessible for the reactants[1] showed in equation 4.

$$A_1 = u_c - u\,(1 - \varphi_c) \qquad \ldots(4)$$

The catalytic activity and catalytic efficiency can be described by the turnover number (TON) and the turnover frequency (TOF), respectively, using the following equations:

$$TON = \left(\frac{mole\ of\ product}{mole\ of\ catalyst}\right) \qquad \ldots(1.1)$$

$$TOF = \frac{TON}{t} \qquad ...(1.2)$$

where t is the unit time (usually measured in sec, min, or hour).

The higher TONs and TOFs refer to the catalysts that are more effective in the catalytic reactions.

1.1.1Types of catalyst and examples

Catalysis can be categorized into two main types: heterogeneous and homogeneous. In heterogeneous catalysis, the catalyst is in one phase while the reactants and products are in a different phase or, for some cases, two different phases. In homogeneous catalysis, the catalyst is in the same phase as the reactants and the products.

1.1.1.1 Homogeneous catalyst

Homogeneous catalysis is such a catalysis where the catalyst remains as in the same state as that of all the reactants involved in the chemical process-this is just opposite situation of heterogeneous catalysis process, where catalyst is in the different state from the reactants. Examples of the homogeneous catalyst are: (i) Persulphate ions are extremely strong oxidizing agents and Iodine ions has the property of oxidized easily. Despite the mentioned fact when both the types of ions start reacting in water the reaction process is too slow (Scheme 1.2A), (ii) ion H^+ (aq) in esterification, as well as in the reverse reaction which is hydrolysis of esters (Scheme 1.2B).

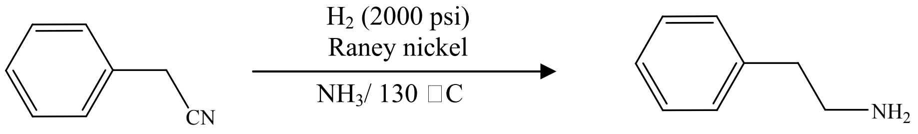
$$S_2O_8^{2} + 2I^{-} \longrightarrow 2SO_4^{2-} + I^{2} \qquad ...(A)$$

$$CH_3OH + CH_3COOH \xrightleftharpoons[H_2O]{H^+} CH_3COOCH_3 \quad ...(B)$$

Scheme 1.2 Examples of homogeneous catalyst.

1.1.1.2 Heterogeneous catalyst

Heterogeneous catalysis is crucial to chemical technology. Innumerable chemical reactions are facilitated by catalysts. Chemical bonds are broken and new chemical bonds are formed during the catalytic process. These events occur repeatedly, usually without a significant change of the catalyst. In the absence of the catalysts, this chemical transformation would either not occur or would take place with lower efficiencies or slower rates. Examples of heterogeneous catalyst are: (i) reduction of nitriles for instance in a synthesis of phenethylamine with Raney nickel and ammonia [2] (Scheme1.3). (ii) hydrogenation of an unsaturated compound such as ethane (C_2H_4) by metal catalysts such as Pt or Ni [3] (Scheme 1.4)



Scheme 1.3 Reduction of nitriles using Raney nickel-catalyzed

$$H_2C{=}CH_2 + H_2 \xrightarrow{\text{Ni or Pt}} H_3C{-}CH_3$$

Scheme 1.4 Hydrogenation of ethane using palladium-catalyzed

Table 1.1 The comparison of homogeneous and heterogeneous catalysts

	Homogeneous	Heterogeneous
Catalyst form	Metal complexes	Metal or metal oxide
Mode of use	Dissolve in reaction medium	Fixed bed or slurry
Solvent	Usually require - can be product or by product	Usually not require
Selectivity	Can be turned	Usually poor
Stability	Often decompose < 100 °C	Stable to high temperature
Recyclability	Can be very difficult	Easy
Special reaction	Hydroformylation of alkene, methanol carbonylation, asymmetric synthesis etc.	Haber process, exhaust clean up etc.

1.2 Indole and derivatives

Indole is an aromatic heterocyclic organic compound. It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring (Figure 1.3). Indole is a famous component of fragrances, the precursor to many pharmaceuticals, biologically active, and chemical activities.

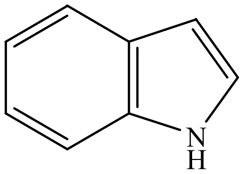


Figure 1.3 Structure of indole

Indole derivatives occur widespread in many natural products. Indole has been obtained, usually in small amounts by extraction from naturally occurring materials by methods which suggest that the indole so obtained is in many cases the result of breakdown of its derivatives. Several of plants have yield of indole contain in plant such as the jasmines, certain citrus plants, and orange blossoms[4]. Indole is also found after putrefactive processes have taken place. It is found in the animal organism and in the liver and pancreas, the brain , and the bile[4]. It is formed in the decay of milk, decay of blood fibrin, decay of albumin, and possibly of vegetable protein. The formation of indole is presumably the result of the decomposition of tryptophan in this case of decay of protein material (Figure 1.4).

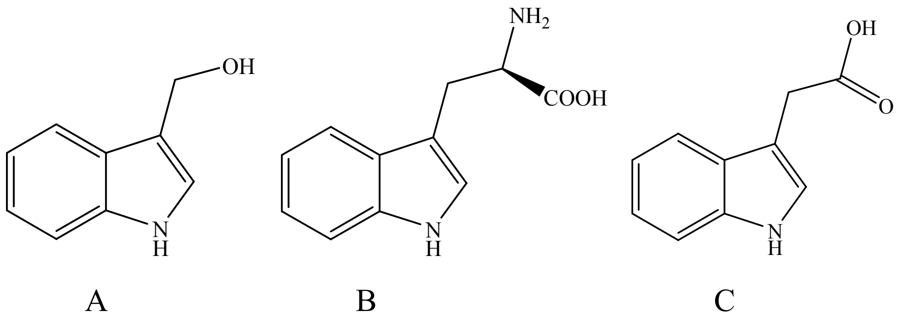


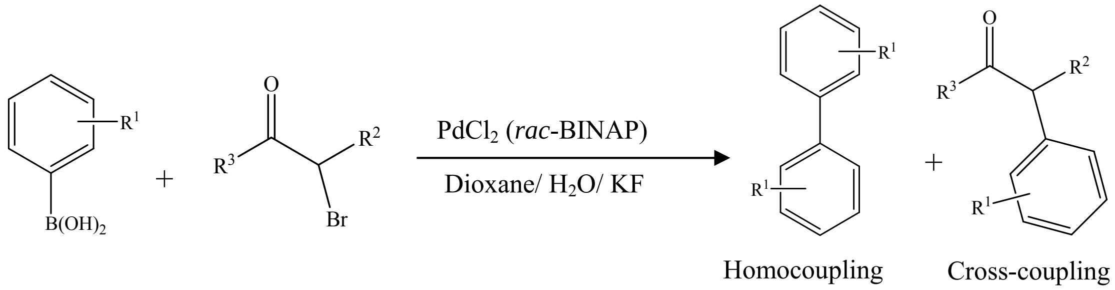
Figure 1.4 Examples of indole derivative (A) indole-3-carbinol extract from broccoli or cabbage and its use for chemopreventive, anticancer and antitumor treatment. (B) tryptophan is one of the 20 standard amino acids in the human. It is an essential amino acid as demonstrated by its growth effects. (C) indole-3-acetic acid or IAA one of plant hormone in Auxin family.

1.3 Coupling reaction

A coupling reaction is a catch-all for a range of reactions in organometallic chemistry where two hydrocarbon fragments are coupled with the aid of a metal catalyst supported by suitable ligands. The most popular metal in laboratory synthetic chemistry is palladium, but industrial processes often use cheaper, but less effective substitutes such as nickel and copper. Normally, there are two types of coupling reactions: cross couplings and homocouplings. Cross couplings involve reaction between two chemically distinct partners, allowing control over both halves of the resulting molecule. Homocoupling couples a molecule to itself, often in a reductive or oxidative reaction.

1.3.1 Homocoupling reaction

The homocoupling reaction, also called Suzuki-type self-coupling reaction, is the formation of a new molecule via a C–C bond coupling of the same reactant. Examples of homocoupling are (i) Palladium-catalyzed homocoupling reaction of aryl boronic acids has been developed using a protocol similar to the well-documented crosscoupling reaction. α-Halocarbonyl compounds are applied to initiate the reaction via oxidative addition to a palladium(0) species. The resulting palladium enolate halide can promote the double transmetallation. Reductive elimination generates the desire homocoupling product (Scheme 1.5).



Scheme 1.5 Palladium-catalyzed coupling reactions of aryl boronic acids

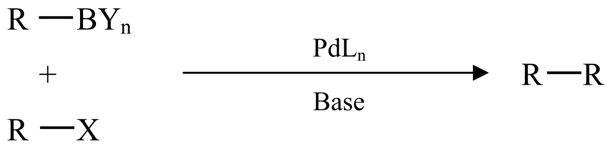
(ii) The homocoupling reaction of the arylboronic acids proceeded smoothly in a mixture of water and ionic liquids in the presence of ethyl bromoacetate ester using $Pd(OAc)_2$ as catalyst in high yield at 60 °C for 3 h (Scheme 1.6).

$$2ArB(OH)_2 \xrightarrow[K_2CO_3/\ BrCH_2COOEt]{Pd(OAc)_2/\ 60\ ^\circ C} Ar\text{–}Ar$$

Scheme 1.6 The homocoupling reaction of arylboronic acids

1.3.2 Cross coupling reaction

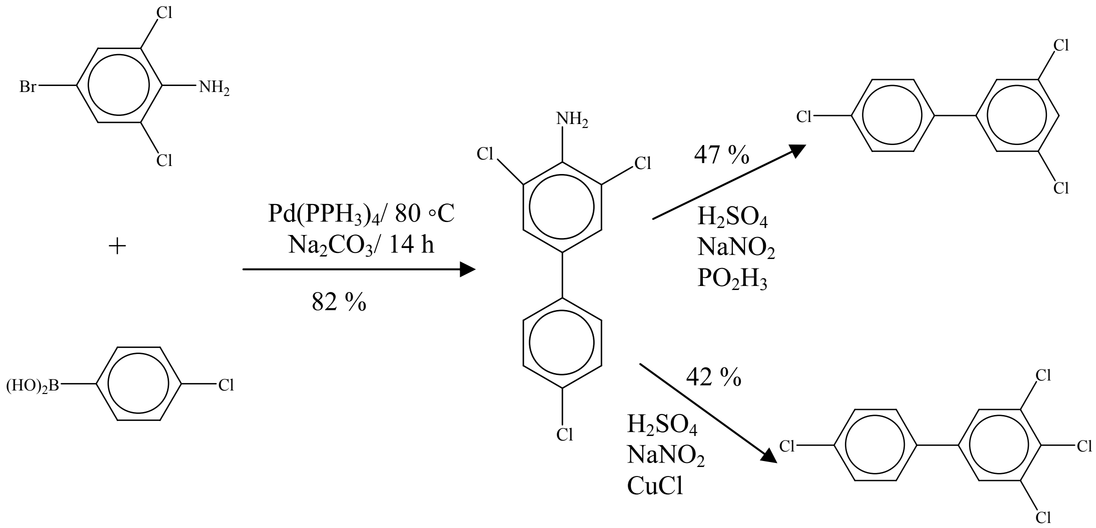
Cross-coupling reaction requires two different molecules to react and form a new molecule (Scheme 1.7). For example, synthesis of polycholorinated biphenyls (PCBs) utilizing a palladium-catalyzed cross coupling reaction. The coupling of (chlorinated) aryl boronic acid with bromochlorobenzenes using the standard conditions of the Suzuki-coupling gave the desired yield (Scheme1.8).



where : Yn = $(OH)_2$, $(OR)_2$, F_3^-, R_2

X = halide, OTf, N_2^+

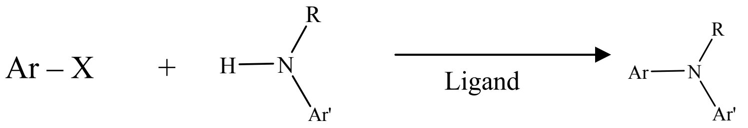
Scheme 1.7 The Suzuki cross coupling reaction



Scheme 1.8 Synthesis of 3,4′,5-trichloro and 3,4,4′,5-tetrachorobiphenyl by using Suzuki-coupling[6].

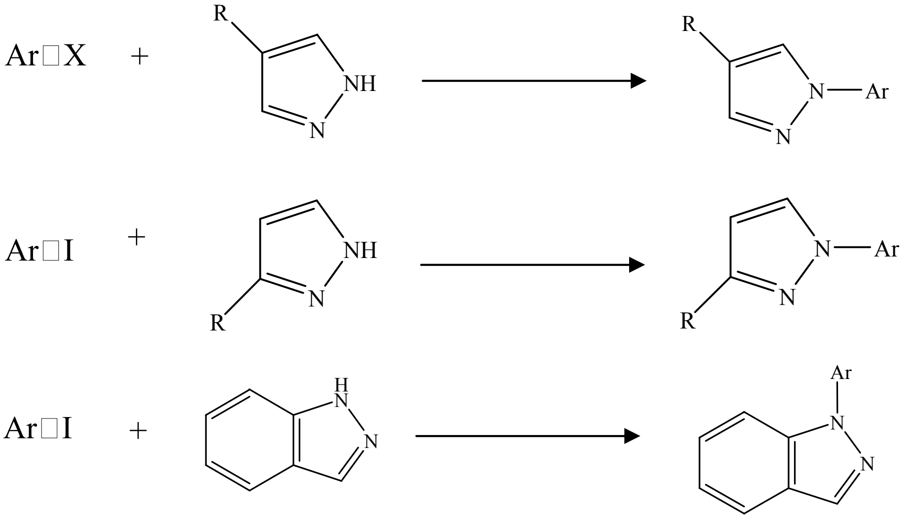
1.4 *N*-arylation reaction

N-arylation reaction is one of C–N bond coupling. Functionalized aromatic and heteroaromatic amines are $Cu_{cat.}$ g blocks for the synthesis of pharmaceuticals, polymers, or materials. In recognition of their widespread importance, many synthetic methods have emerged over the years for the formation of C–N bonds, trying to overcome the shortcomings of the original Ullmann and Goldberg procedures. [7,8] (Scheme 1.9)



Scheme 1.9 Copper-mediated arylation of aromatic amine

Example of *N*-arylation reaction is unsymmetrical heterocycles proceeds with synthetically useful levels of regioselectivity: pyrazoles and imidazoles give products in which the less hindered nitrogen is selectively arylated, whereas indazoles are selectively arylated at *N*-1, provided that aryl iodides (Scheme 1.10).



Scheme 1.10 Regioselectivity of the arylation of unsymmetrical *N*-heterocycles

CHAPTER II

OBJECTIVES

Carbon–nitrogen bond formations or coupling reactions are both academically and industrially interesting. As the coupling reactions provide a new molecule, they were included in the synthetic methodology for making new compounds while catalyst developments for coupling reactions are simultaneously progressing.

To enhance catalyst activity for cross-coupling reactions, this research aims to study an efficiency of catalyst as shown by these studies below:

(i) synthesize of diimine ligands and copper nanoparticles

(ii) the effect of substituents of diimine ligands on the catalytic activities of copper complexes in the *N*-arylation of indole.

(iii) the catalytic activity of copper nanoparticles in the *N*-arylation of indole with the copper complex catalysts.

CHAPTER III

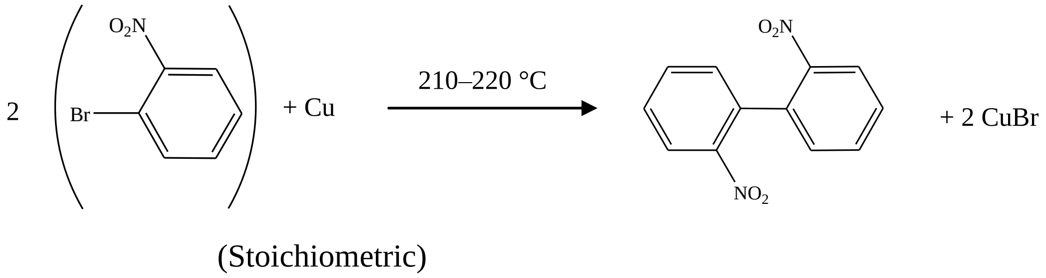
LITERATURE REVIEWS

Literature survey focuses on copper-mediated coupling reaction inclouding C–C, C–O, and C–N bond. In addition, catalytic of C–C, C–O, and C–N Ullmann-type coupling reactions are reviewed.

Natural product synthesis is a highly demanding field in constant need of efficient transformations that allow either straightforward, scalable, and high-yielding preparation of starting materials or especially tolerant reactions that can be used in end game strategies on complex substrates to install a certain functional group with the utmost delicacy and surgical precision. Although many chemical transformations do perform well when applied to relatively simple, commercially available molecules, only a few of them can be used for the preparation of complex natural products in which they are clearly challenged and pushed way beyond their limits. The complex structures and functionalities of these targets ensure that only robust and selective methods come through such a trial. When successful, however, such reactions can enter the “hall of fame” of efficient procedures, and the use of reactions such as olefin metathesis, asymmetric hydrogenations, or oxidations in the context of natural product synthesis clearly helped demonstrate their efficiency, reliability, and generality. Until the beginning of the 21st century, this was certainly not the case for copper-mediated C–N, C–O, and C–C bond formation reactions, a hundred years ago in the pioneering and remarkable work of Ullmann and Goldberg. Even if these conceptual publications clearly are the basis of today’s developments of copper-mediated reactions, and even if they found numerous industrial and academic applications, harsh reaction conditions and low substrate scope hampered their use in natural product synthesis. Using such reactions on complex substrates was a strategic decision that bore way too much risk, and even seemed somewhat counterintuitive palladium-catalyzed transformations were preferred in most cases, and only smart adaptations of the classical reaction conditions or activation of the aryl halide were reported from time to time for the synthesis of complex targets. This situation has come to an end with the development, in the past 10 years or so, of highly efficient catalytic systems that allow reactions to be conducted in milder conditions and with dramatically enhanced yields compared to classical procedures. The keys to the success of these improved conditions were the observation that simple organic derivatives could speed up cross-couplings and the introduction of new reaction partners such as organoboranes. This has allowed for the use of a wide range of substrates and mild reaction conditions together with the extension of these coupling reactions to the introduction of vinyl and alkyne functional groups. The synthetic potential of these transformations is now quite obvious, even if the golden age of copper-mediated cross-coupling reactions is probably just beginning. Their application in natural product synthesis has flourished recently: an array of copper-mediated procedures has been successfully employed to assemble many complex targets with new and efficient bond disconnections.

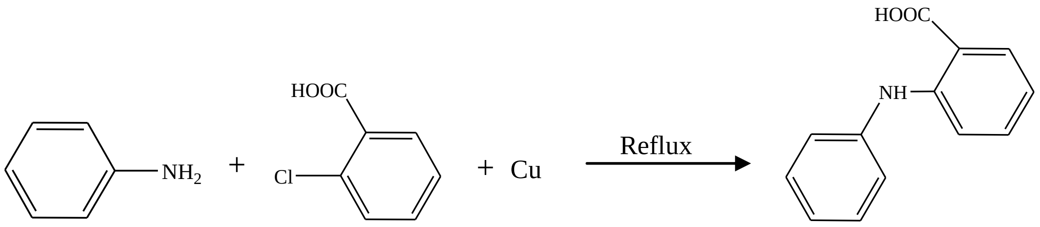
3.1 Overview of copper-mediated coupling reactions

The foundations of modern copper-mediated chemistry lie in the pioneering and remarkable work of Fritz Ullmann and Irma Goldberg. It all started in 1901 when Ullmann reported Two molecules of *o*-bromonitrobenzene could be coupled in the presence of metallic copper to give the corresponding biaryl: the Ullmann reaction was born (Scheme 3.1).

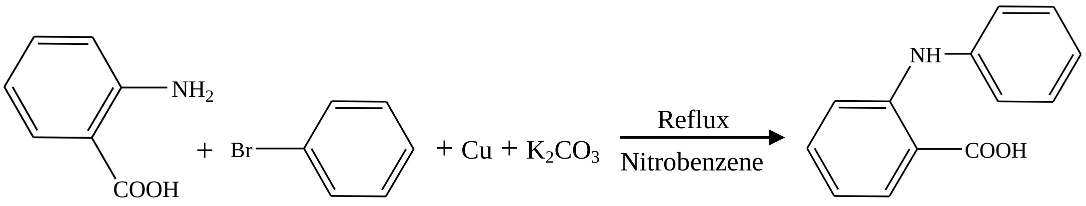


Scheme 3.1 Ullmann reaction: synthesis of biaryls.

In 1093, Ullmann reported that aniline reacted with 2-chlorobenzoic acid in the presence of 1 equiv of copper to give 2-phenylaminobenzoic acid[7], a reaction that was shown to be catalytic by Goldberg in 1906 starting from the potassium salt of 2-aminobenzoic acid (Scheme 3.2).



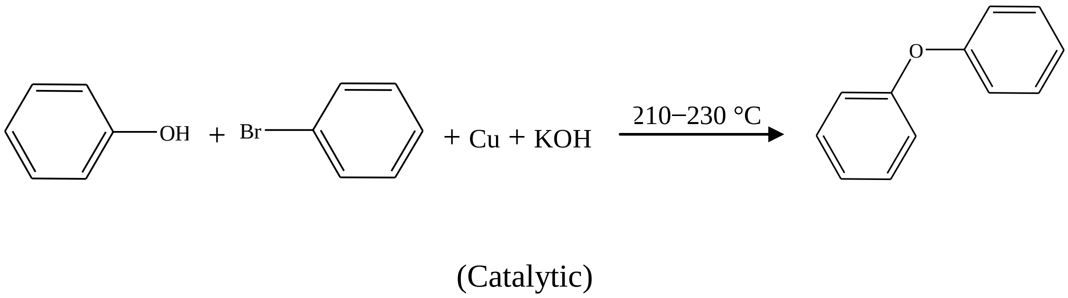
(Stoichiometric)



(Catalytic)

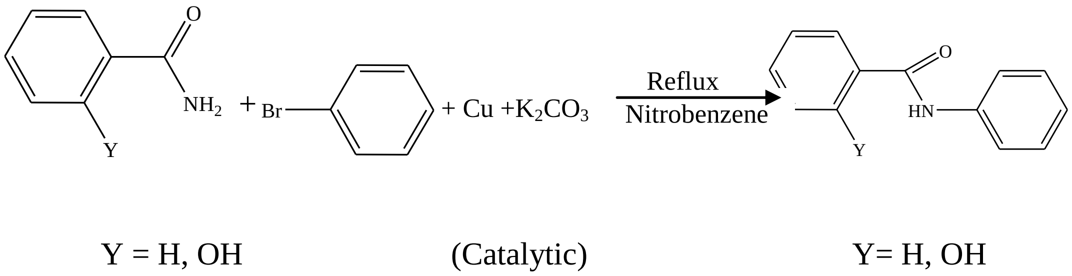
Scheme 3.2 Ullmann condensation reaction: synthesis of diarylamines.

Ullmann next extended the reaction to the preparation of diphenyl ether by reaction of potassium phenoxide and bromobenzene and demonstrated the considerable effect of catalytic amounts of copper on the rate of the reaction (Scheme 3.3)[9].



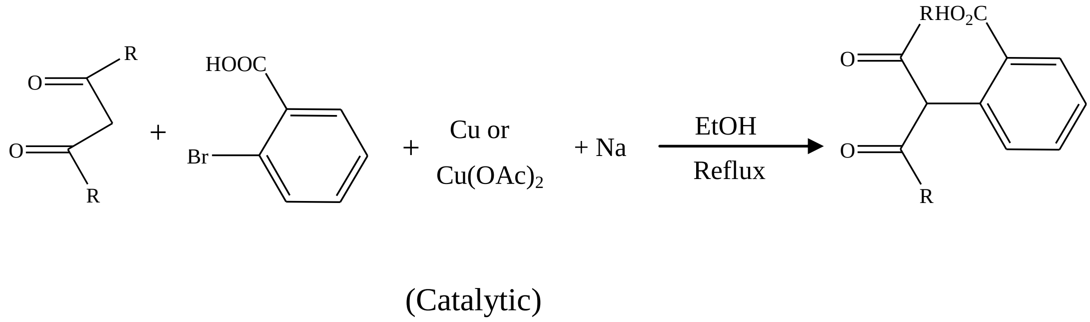
Scheme 3.3 Ullmann condensation reaction: synthesis of diarylethers.

One year later, the first copper-catalyzed arylation of amides was successfully reported by Goldberg, who managed to condense bromobenzene with benzamide and salicylamide (Scheme 3.4)[8].



Scheme 3.4 Goldberg condensation reaction: synthesis of arylamides.

Some 20 years later, another exceptional contribution was reported by William R. H. Hurtley: under the catalytic influence of copper-bronze or copper acetate, the halogen atom in *o*-bromobenzoic acid is easily substituted by sodium salts of diketones and malonates (Scheme 3.5)[10].



Scheme 3.5 Hurtley reaction: arylation of CH-acid derivatives.

3.2 Overview of Ullmann-type coupling reaction

Copper-catalyzed Ullmann condensations are key reactions for the formation of carbon–heteroatom and carbon–carbon bonds in organic synthesis. These reactions can lead to structural moieties that are prevalent in building blocks of active molecules in the life sciences and in many material precursors. An increasing number of publications have appeared concerning Ullmann-type intermolecular reactions for the coupling of aryl and vinyl halides with N, O, and C nucleophiles.

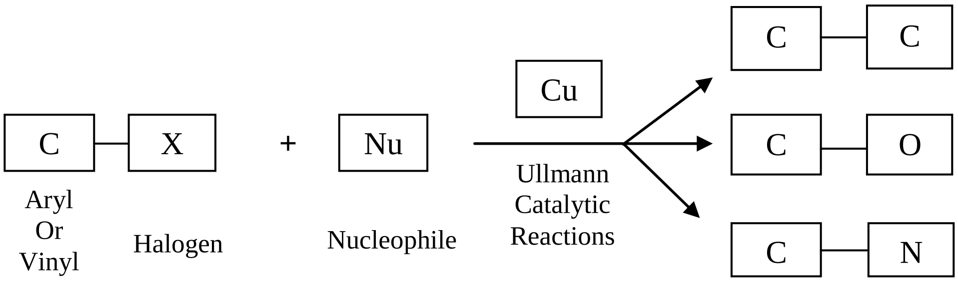


Figure 3.1 Ullmann-type reaction.

Mechanism of the Ullmann reaction

Ullmann-type reactions proceed through a catalytic cycle, and in one mechanism the copper is postulated to undergo oxidation to Cu (III) showed in Figure 3.2. As some Cu (III) salts have been prepared, the suggestion for the mechanism is intriguing.

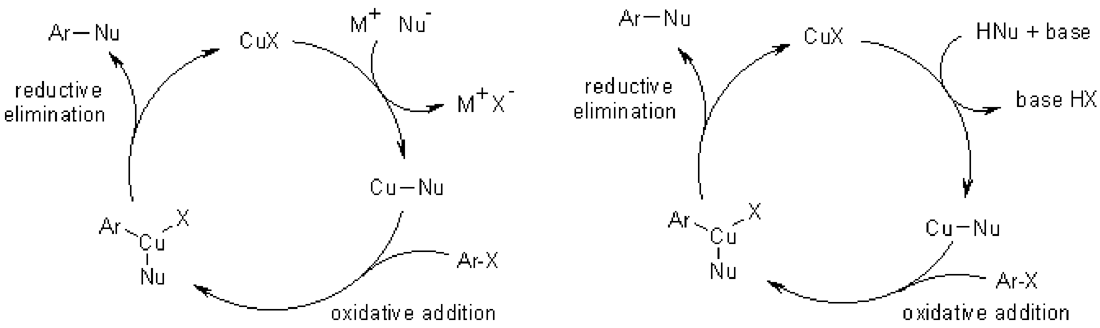


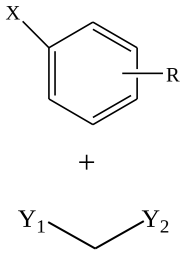
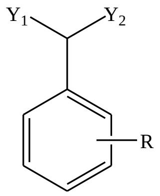
Figure 3.2 Mechanisms of Ullmann reaction

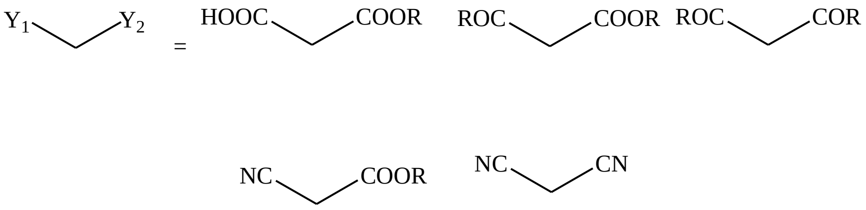
3.2.1 C–C bond formation by Ullmann–Hurtley Condensations

In a recent year, Kwong and co-workers described a mild catalytic system which allows the arylation of diethyl malonate by a wide range of aryl iodides at 25 °C in the presence of 2-picolinic acid as the supporting ligand (Table 3.1, entry 1)[11]. A higher temperature is needed (70°C) for reactions with other 1,3-dicarbonyl derivatives (dimethyl malonate, β-ketoesters), and an even higher one when the reaction is performed with aryl bromides (110°C).

L-Proline also appears to be an excellent ligand for reaction, as reported by Ma and co-workers[12] Condensations of aryl halides (ArI and ArBr) with activated methylene compounds (dialkyl malonate and β-ketoesters) are performed at 40–50 °C (Table 3.1, entry 2). Jiang et al. reported a very similar system, but it is restricted to expensive aryl iodides and a higher temperature (90 °C) for the arylation of β-diketone, ethyl cyanoacetate, or malonitrile (Table 3.1, entry 3)[13].

Table 3.1 Arylation of activated methylene compounds

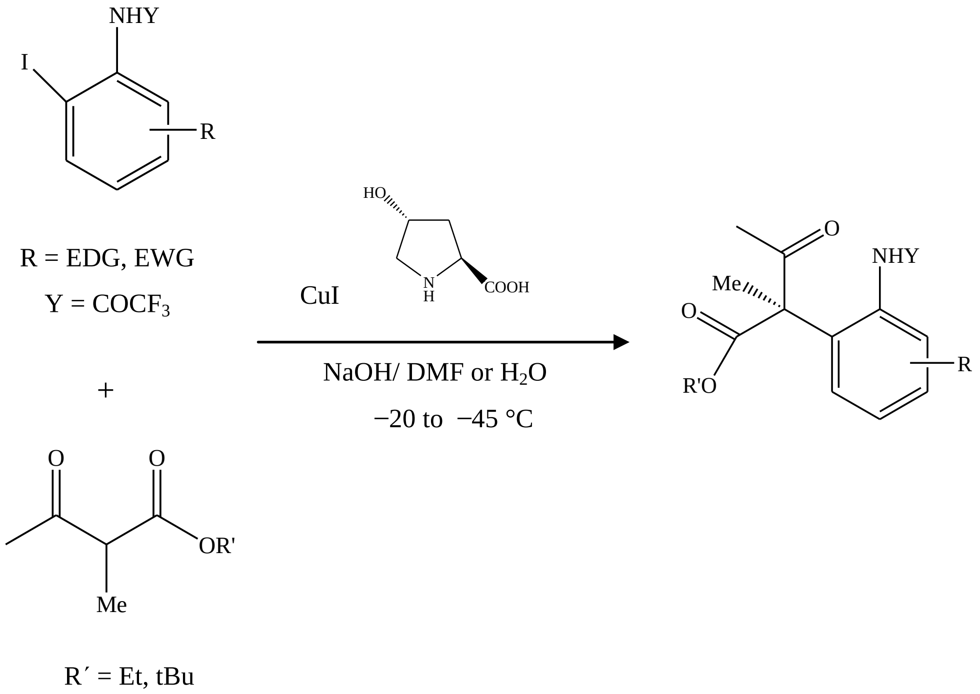
Entry	Substances	Halide (X)	catalyzed	Temperature (°C)	Product
1	 R = EWG, EDG	Br,I	CuI (5 mol%)	RT–110	
2		Br,I	CuI (20 mol%)	40-50	
3		I	CuI (10 mol%)	90	
4		I	CuI (10 mol%)	50–70	

where: 

A year earlier F. Monnier and M. Taillefer presented a general method for the arylation of several malonic acid derivatives by aryl iodides (Table 3.1, entry 4). The use of the Schiff base as the ligand allowed the reactions to be performed under very mild conditions (50–70 °C) in the presence of molecular sieves.

The first enantioselective Ullmann–Hurtley condensation was reported in coupling (at −20/ −45 °C) of various 2-iodotrifluoroacetanilides with 2-methyl acetoacetates by using (2*S*,4*R*)-4-hydroxyproline as the supporting ligand and chiral source (Scheme 3.6). Although the application of this method is limited by the necessary presence of chelating substituents in the -*ortho* position, this method undoubtedly represents an interesting advance in terms of the enantioselectivity[15].

The application of the same system to the arylation of non-carbon-substituted β-keto esters leads to a simple and convenient method for preparing a wide range of 2-(trifluoromethyl)indoles[16]. It is also noteworthy that in the presence of a very large excess of ethyl acetoacetate (this β-ketoester probably also plays the role of supporting ligand) the coppercatalyzed arylation leads to the deacylated product. This interesting result suffers, however, from poor chemoselectivity formation of arylated acetoacetate)[17]. Proline was also used in the only example reported for the copper catalyzed functionalization of activated methylene compounds by vinyl halides ((2-bromovinyl)benzenes)[16].



Scheme 3.6 Copper-catalyzed asymmetric coupling of 2-iodotrifluoroacetanilides with 2-methyl acetoacetates.

3.2.2 C–O bond formation

The synthesis of diaryl ethers and related derivatives by classic Ullmann methods has been well-known for a long time[18]. Despite the recent renaissance of the catalytic Ullmann method, fewer publications have appeared for C–O than for the related C–N coupling reactions.

3.2.2.1 Coupling reactions of aryl halide with phenol

Ma et al., after further development of a system reported earlier,[19] described an efficient catalytic C–O coupling reaction at ambient temperature[20]. Thus, by using the amino acid as a supporting ligand with 30%copper loading, they could couple 2-bromotrifluoroacetanilide and L-tyrosine derivatives in high yields at 25 °C (Table 3.2, entry 1).

A particular advantage of the ambient-temperature conditions used with this system is that the coupling can occur without any accompanying racemization of the tyrosine derivatives. A drawback to this procedure remains the rather high copper and ligand loadings. It also appears that an *ortho*-amide substituent on the aryl halide is required as a directing group. The additional stabilization of the Cu (I) center provided by O coordination of this chelating -*ortho* group was proposed to be a key factor for the success of these reactions.

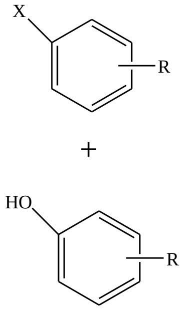
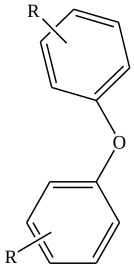
The catalytic system of Lv and Bao described above for the formation of C–N bonds is also efficient for the copper catalyzed arylation of phenol derivatives. The use of the same β-keto ester as a supporting ligand affords the corresponding diaryl ethers from aryl bromides at mild temperatures (Table 3.2, entry 2)[21].

Similarly, the Schiff bases ligand, which we developed for other types of coupling reactions, are also very efficient at promoting the synthesis of diaryl ethers (Table 3.2, entry 3)[22]. In combination with 10%CuI and the inexpensive base K_3PO_4 these ligands allow the coupling of a large range of aryl bromides with phenols under mild conditions. It is worth noting that very low copper and ligand loadings are apparently able to promote some of these reactions[23].

The coupling of phenols with aryl iodides or bromides is also possible with pyrrolidine-2-phosphonic acid phenyl monoester at higher temperatures

(Table 3.2, entry 4)[24] or with 1,10-phenanthroline as the supporting ligand. The latter was used in association with a KF/Al_2O_3 system as the base[25] or in the presence of copper impregnated into charcoal under microwave irradiation (Table3.2, entry 5)[26].

Table 3.2 Systems for the generation of diaryl ethers from ArI or ArBr

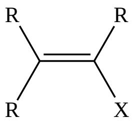
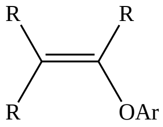
Entry	Substance	Catalyzed	Temperature (°C)	Product
1		CuI (30 mol%)	25	
2		CuBr (10 mol%)	60–80	
3		CuI (0.05−10 mol%)	60–80	
4		CuI (10 mol%)	110	
5	R = EWG, EDG X = Br, I	Cu/C (15 mol%)	MW, Δ	

where: MW = Microwave

3.2.2.2 Coupling reactions of vinyl halides with phenol derivatives

The coupling of vinyl halides with phenol derivatives is possible by Ullmann-type reactions. The corresponding vinyl aryl ethers are an important class of building blocks in organic synthesis as well as synthetic targets for the polymer and life science industries. However, this methodology has not been developed nearly as much as the variant using aryl halides. Since 2004, Ma et al.,[27] Bao et al.,[28] and F. Monnier and M. Taillefer[29] (Table 3.3, entry 1–3) have observed that some of the systems presented above for arylation by aromatic halides are also very efficient with vinyl halide substrates. These procedures, which take place under very mild temperatures, have been applied for the total synthesis of abyssenine A, a compound which displays considerable biological activity[30].

Table 3.3 Efficient systems for the generation of aryl vinyl ethers

Entry	Substance	Catalyzed	Temperature (°C)	Product
1	 + ArOH X = Br, I	CuI (10 mol%)	60–90	
2		CuI (30 mol%)	60	
3		CuI (5 mol%)	50	

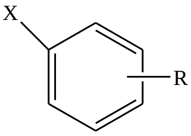
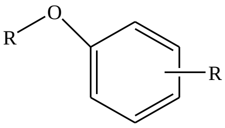
3.2.2.3 Coupling reactions of aryl halides with alcohol derivatives

There are only a few known catalytic copper systems that facilitate the coupling of aryl halides with aliphatic alcohols. In 2008, the Buchwald research group, in a comprehensive study of an earlier system,[31,32] used a highly efficient phenanthroline ligand, which enables this reaction to be carried out with aryl iodides under mild conditions[33]. Their method is particularly noteworthy for not needing a large excess of alcohol and for being remarkably selective for *O*-arylation when amino alcohols are involved (Table 3.4, entry 1).

The coupling of alcohols with aryl iodides has also been realized by Hosseinzadeh et al., who used phenanthroline or its derivatives as the ligand[25] with KF/Al_2O_3 as the base , and by Evano and co-workers in the first total synthesis of paliurine F.[34] Amino acids[35] and also the 1,1′-binaphthyl-2,2′-

diamine (binam) ligand[36] give interesting results, but here the problem of having the nucleophile in excess remains (Table 3.4, entry 2–3)[37].

Table 3.4 Efficient systems for the generation of alkyl aryl ethers

Entry	Substances	Halide (X)	catalyzed	Temperature (°C)	Product
1		I	CuI (5 mol%)	60–110	
2		I	CuI (20 mol%)	110	
3	R = EWG, EDG	Br, I	CuI (10 mol%)	110	

3.2.3 C–N bond formation

The copper-mediated coupling of aryl and vinyl halides to aromatic nitrogen heterocycles or amines and amides the Ullmann[7] and the Goldberg[8] condensations respectively have been well-known for more than a century. By far the greatest number of reports on the modern catalytic Ullmann-type reactions have been concerned with the creation of $C(sp^2)$–N bonds by ipso substitution.

3.2.3.1 Coupling reaction of aryl halides with *N*-heterocycles

a) Overview of supporting ligands

Some years ago we developed polydentate ligands of the Schiff base and oxime type (Figure 3.3). The use of a ligand with at least one imine group and oxygen or nitrogen coordination sites facilitates the coupling of numerous azole and amide derivatives (Figure 3.5) with aryl bromides at mild temperatures

(Table 3.5, entry 1)[38]. Some reactions with aryl iodides were even performed at 25 °C, and a turnover of about 1500 was possible in the presence of pyrazole at 80 °C [38]. This application is one of the rare examples to have already been adopted industrially.

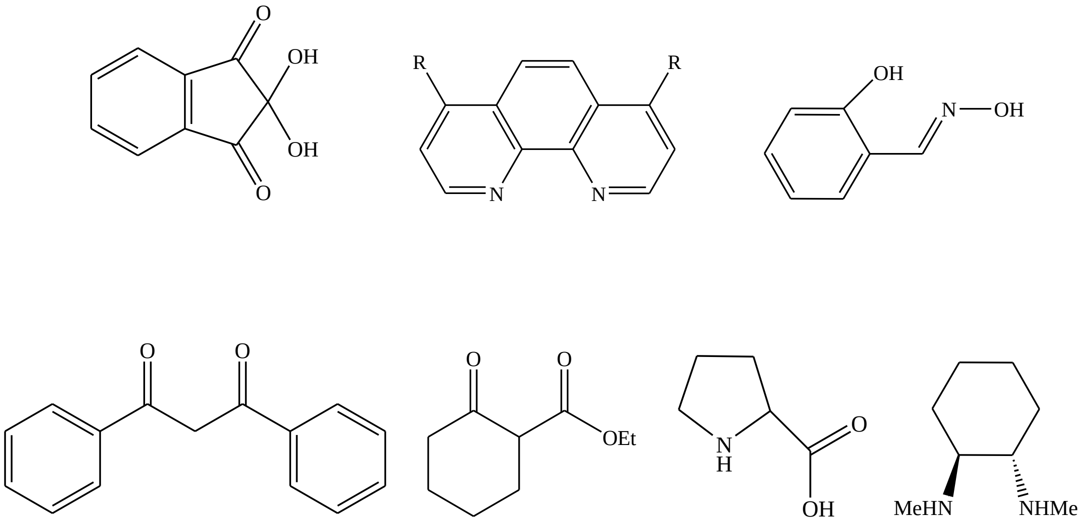


Figure 3.3 Ligands for the coupling of aryl bromides and iodides to nitrogen heterocycles.

Another effective catalytic system was recently developed by Lv and Bao, who used the β-ketoester ligand (Table 3.5, entry 2)[21]. The coupling of different aromatic *N*-heterocycles could be performed at mild temperatures, and reactions of aryl iodides with pyrrolidinone could even be conducted at room temperature.

Ma and co-workers showed that amino acids were excellent bidentate ligands for copper-catalyzed Ullmann type reactions[39]. L-proline and *N*,*N*-dimethylglycine were particularly effective and led to the successful coupling of numerous aryl bromides with various azoles, often at mild temperatures (Table 3.5, entry 4). The low cost of naturally occurring amino acids and their ready availability give this system real economic advantage.

Chen and co-workers reported that 1,3-diketone combined with CuI is an efficient catalytic system for the coupling of aryl bromides with nitrogen heterocycles (Table 3.5, entry 6)[40]. Although the reaction conditions are harsher than in the previous examples, some interesting results for the arylation of imidazole by activated chloropyridine derivatives were obtained.

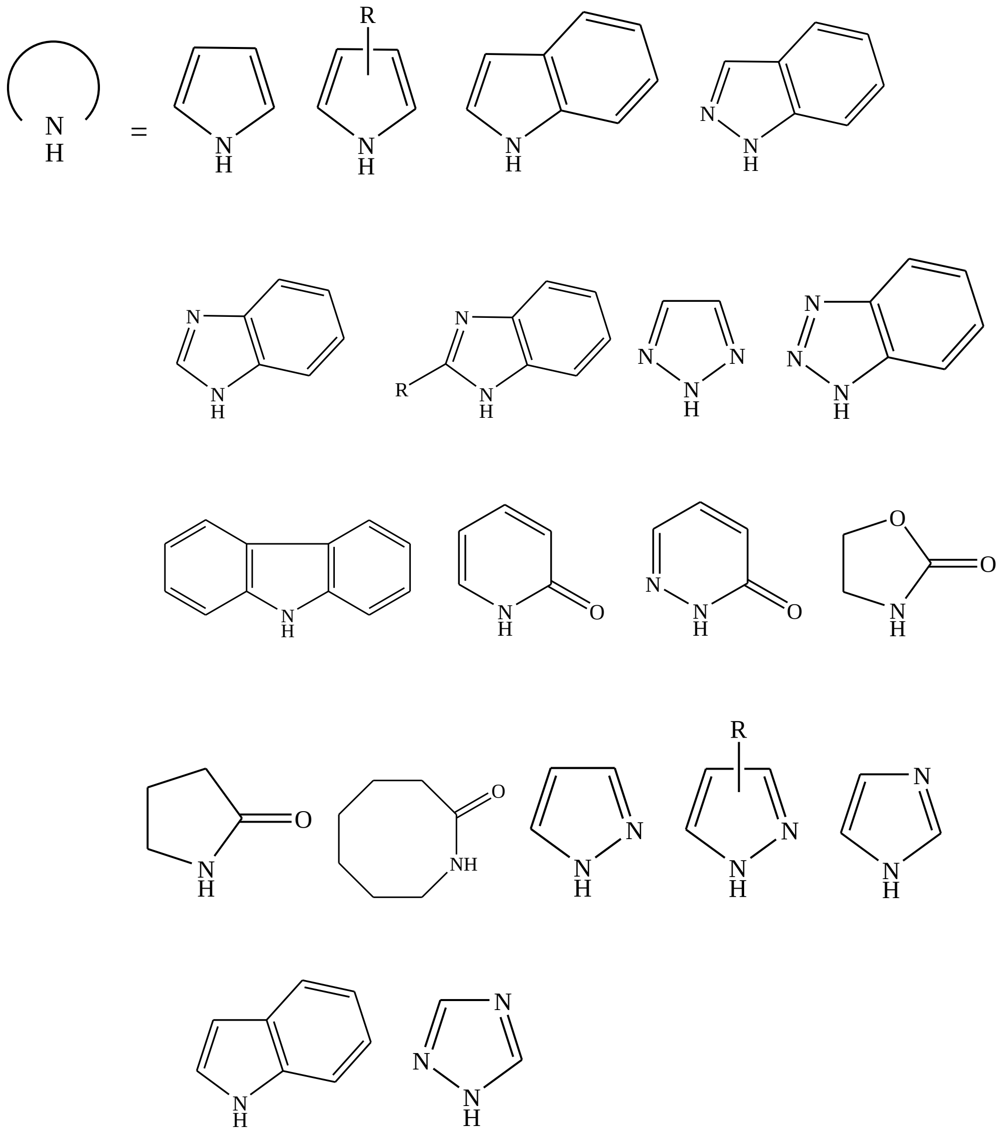
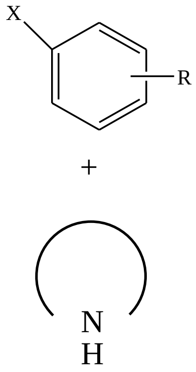
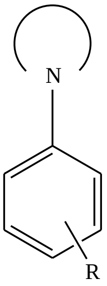
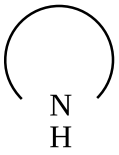


Figure 3.4 Example of aromatic nitrogen heterocycles and cyclic amides.

Table 3.5 The generation of C–N bonds, and the products obtained. When EDG = electron-donating group, EWG = electron-withdrawing group, acac = acetyl acetonate

Entry	Substances	catalyzed	Temperature (°C)	Product
1	 R = EWG, EDG X= Br, I	Cu_2O (0.05–5 mol%)	25–82	
2		CuBr (10 mol%)	25–75	
3		CuO[Fe(acac)$_3$] (10–30 mol%)	90	
4		CuI (10–20 mol%)	75–110	
5		Cu_2O (7−20 mol%)	80–150	
6		CuI (10 mol%)	110	
7		CuI (20 mol%)	110	
8		Cu_2O (20 mol%)	110–150	

where:  = Aromatic nitrogen heterocycles

Buchwald and co-workers[41,42] demonstrated the high efficiency of 1,2-diamine for the coupling of aryl bromides with various types of nitrogen nucleophiles (Table 3.5, entry 7). More recently, the same research group also developed a copper/ 4,7-dimethoxy-1,10-phenanthroline system[43] (Table 3.5, entry5) which allows the *N*-arylation of a wide range of imidazole derivatives, for which no generally useful palladium-based catalysts have been reported. The use of poly(ethylene glycol) (PEG) as a solid–liquid phase-transfer catalyst and a 2000 times turnover achieved at 110°C in one case are additional features of this system.

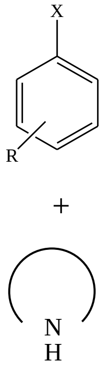
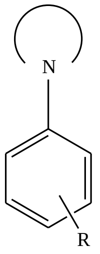
Xu and co-workers reported in 2008 a system based on the use of commercial ninhydrin as the ligand and, although the performance is poorer than the systems mentioned previously (most of the cases concern pyrazole), interestingly, unactivated chlorobenzenes take part in the reactions [albeit at the relatively high temperature of 150 °C and with modest yields (Table 3.5, entry 8)[44].

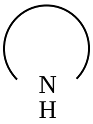
The last example to be discussed relates to a system based on the condensation of numerous nitrogen heterocycles with various aryl bromides at 90°C in the presence of the iron–copper cooperative catalyst CuO–[Fe(acac)$_3$] (Table 3.5, entry 3)[45,46]. This represents a very economically competitive alternative to the usual copper/ligand combination, and an encouraging example involving the coupling of an activated chloride.

b) Overview of ligand free condition

Recently, several ligand-free systems have emerged for the *N*-arylation of aromatic *N*-heterocycles catalyzed by copper compounds. The earliest preliminary results were reported in a 2005 patent (Table 3.6, entry 1)[47]. Arylation using iodo- and bromobenzene was performed under ligand free conditions with 5–10%of a copper source such as CuI in the presence of Cs_2CO_3 as a base in CH_3CN. A similar system was reported three years later by Hu and co-workers, but 20% of the copper source was used in addition to one equivalent of KI for aryl bromides to permit Br/I exchange (Table 3.6, entry 2)[48]. Bolm et al.[49] and Yasutsugu and Mayumi [50] also proposed a “ligand-free-like” system in which 10% Cu_2O (for ArI and ArBr) or CuI (for ArI) were used in DMF (Table 3.6, entry 3). In a similar system, Guo and co-workers[51] used K_3PO_4 as a base, and postulated that the phosphate group could also chelate CuI ions and thus facilitate oxidative addition to the copper center, a proposal already made by Choudary et al. (Table 3.6, entry 4)[52].

Table 3.6 Examples of “ligand-free-like” catalytic system

Entry	Substances	Base/solvent	catalyzed	Temperature (°C)	Product
1		Cs_2CO_3/CH_3CN	CuI (5–10 mol%)	82	
2		Cs_2CO_3/CH_3CN	CuI (20 mol%)	82–120	
3		Cs_2CO_3/DMF	CuI or Cu_2O (10–20 mol%)	100–120	
4	X= I, Br	K_3PO_4/DMF	CuI (5–10 mol%)	110	R= EDG or EWG

where:  = Aromatic nitrogen heterocycles

It seems likely that the solvent and/or base act as ligands for the copper center in all the ligand free systems, although with less efficiency than the chelating organic ligands discussed earlier. Our experience has shown us that under our conditions (aromatic bromide substrates, 10% copper loading at 82 °C) a good performance is not always reproducible for ligand-free systems when the reactions are conducted on an industrial scale. The reproducibility can be improved by using a copper loading [Cu] of 20% and/or higher temperatures, but reactions conducted on an industrial scale under such conditions are questionable in regard to residual toxicity, and are more expensive. This highlights the fact-often overlooked-that supporting ligands not only accelerate the reactions but also make them more reproducible and inherently safer in terms of the operating conditions and residual toxicity.

3.2.3.2 Coupling reactions of aryl halides with alkyl amines, amides, and anilines

Recent progress in modern catalytic Ullmann coupling reactions has also led to the emergence of numerous methods to condense aryl halides (mainly iodides and bromides) with aliphatic amines, amino alcohols, hydrazines, amides, anilines, and other derivatives (Figure 3.5).

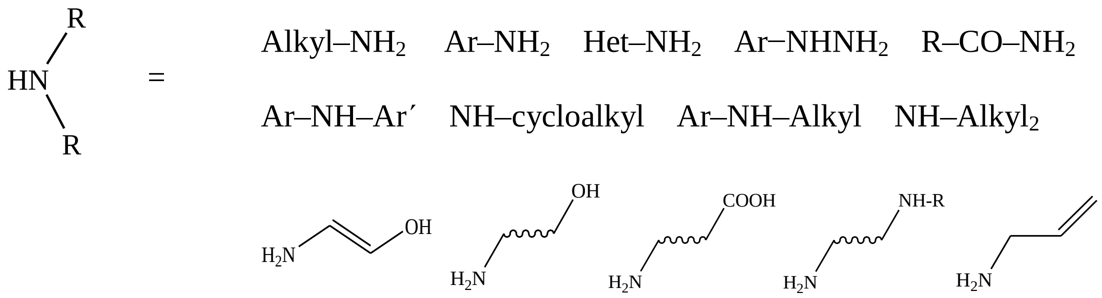
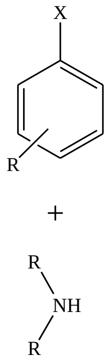
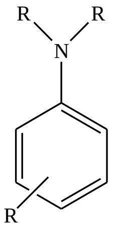


Figure 3.5 Ligands used and the range of N substrates that can be used in the copper-catalyzed coupling with aryl halides.

In 2006, one of the first examples of a room-temperature condensation was reported by Buchwald and coworkers (Table 3.7, entry 1)[32,53]. The use of 1,3-diketone (Alk = i*Pr*) in combination with CuI (5%) enabled the condensation of aryl iodides with primary or secondary alkyl amines[53] as well as amino alcohols[32] to be performed in excellent yields at 25 °C. This system, based on the inexpensive 1,3-diketone is also efficient under harsher conditions (90 °C) with aryl bromides. It nicely complements the related palladium-based methods for the *N*-arylation of aliphatic amines.

Table 3.7 Examples of copper/ligand systems for the formation of C–N bonds

Entry	Substances	Halide (X)	catalyzed	Temperature (°C)	Product
1		Br, I	CuI (5 mol%)	25–90	
2		I	CuI (10 mol%)	30	
3		Br, I	CuI (10 mol%)	40–90	
4		I	Cu_2O (5 mol%)	80	
5	R = EDG, EWG	Cl, Br, I	CuI (2 mol%)	100	

In a similar fashion, Fu and co-workers published two interesting room-temperature systems based on rac-1,1′-bi-2- naphthyl (rac-binol) and *N*-phenylhydrazone ligands (Table 3.7, entry 2)[54]. These ligands in association with 10% CuI or CuBr resulted in high reactivities for the *N*-arylation of aliphatic amines and/or amino acids with aryl iodides.

In 2005 Ma and co-workers showed that the amino acid L-proline and glycine derivative are highly efficient ligands with CuI for the coupling of alkyl amines and aniline derivatives over a temperature range of 40 to 90 °C (Table 3.7, entry 3). These ligands, which probably chelate the copper ion through the carboxy and amino groups, could make the catalytic CuI species more reactive toward an eventual first oxidative addition or coordination of the aryl halide[39,55].

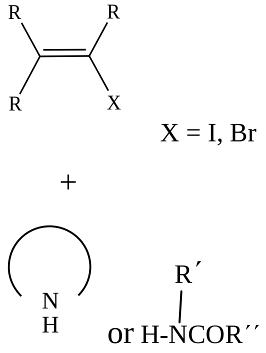
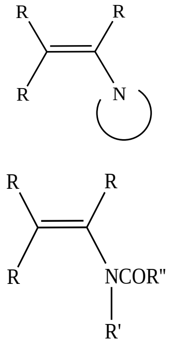
Phosphine-oxime also proved to be a good ligand for the *N*-arylation of alkylamines and *N*-heterocycles by aryl iodides (Table 3.7, entry 4) [56]. Although product formation takes place at higher temperatures (80°C) than in other cited examples, the replacement of N by P in ligand phosphine-oxime constitutes an interesting feature for mechanistic studies.

The last system selected for discussion, developed in 2005 by Yoshifuji and co-workers, also involves a phosphorus containing ligand[57]. Although the ligand is rather complex, it enables the remarkable coupling of aniline and morpholine with non-activated aryl chlorides at a moderate temperature (Table 3.7, entry 5).

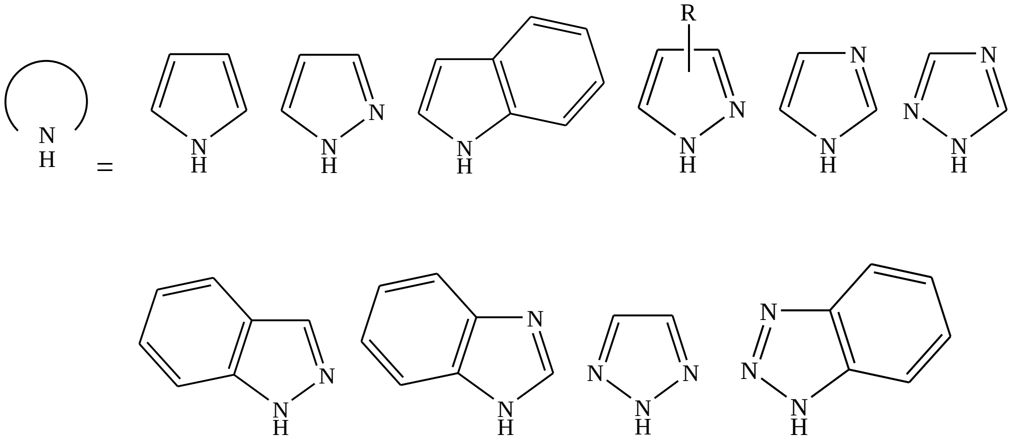
3.2.3.3 Coupling reaction of vinyl halides with *N*-nucleophite

Ligand-assisted copper catalysis recently led to the development of modern versions of the Ullmann and Goldberg reactions of vinyl halides[58]. Ma and co-workers demonstrated that they could generate a wide array of enamides under mild conditions by using amino acid (Table 3.8, entry 1)[59]. Porco and co-workers reported the copper/ phenanthroline-mediated coupling of amides with biodo-acrylates and acrylamides to prepare *N*-acyl vinylogous carbamates and ureas.[60] Our research group also showed that the synthesis of various *N*-vinylazoles occurs very efficiently in the presence of CuI and Schiff base[19] (Table 3.8, entry 2). Finally, Bao et al. were able to couple pyrazole and indazole with vinyl halides (X=Br, I) at 60–80°C in the presence of β-diketone (Table 3.7, entry 3)[18].

Table 3.8 Examples of copper/ligand systems for the formation of C–N bond

Entry	Substances	catalyzed	Temperature (°C)	Product
1		CuI (10 mol%)	RT–60	
2		CuI (10 mol%)	25–80	
3		CuI (15 mol%)	60–80	

where:



CHAPTER IV

MATERIALS AND METHODS

This chapter includes synthetic methods for diimine ligands, preparation of copper nanoparticles, characterization techniques, and procedure for *N*-arylation of indole.

4.1 Materials and Chemicals

The chemicals and solvents used in this experiment were analytical reagent grade. Chemicals and solvents are listed below.

Table 4.1 List of chemicals

Chemicals	**Chemical formula or Abbreviation**	**Company**
2-methoxybenzaldehyde	$C_8H_8O_2$	Acros
3-methoxybenzaldehyde	$C_8H_8O_2$	Acros
4-methoxybenzaldehyde	$C_8H_8O_2$	Merck
2-nitrobenzaldehyde	$C_7H_5NO_3$	Aldrich
3-nitrobenzaldehyde	$C_7H_5NO_3$	Aldrich
4-nitrobenzaldehyde	$C_7H_5NO_3$	Aldrich
Acetronitile	C_2H_3N	Lab Scan
Copper (I)iodide	CuI	Fisher
Copper (II)sulphate pentahydrate	$CuSO_4{\cdot}5H_2O$	Merck
Ethanol	C_2H_6O, EtOH	Lab Scan
Ethylenediamine	$C_2H_8N_2$, en	Carlo Erba
Ethylene glycol	$C_2H_6O_2$	Fuka

Table 4.1 List of chemicals (cont.)

Chemicals	**Chemical formula or Abbreviation**	**Company**
Hydrazine	N_2H_2	Fuka
Indole	C_8H_7N	Fuka
Iodobenzene	C_6H_5I	TCI
Methanol	CH_3OH, MeOH	Lab Scan
Potassium carbonate	K_2CO_3	Aldrich
Toluene	C_7H_8	Lab Scan

4.2 Instrument and Apparatus

^1H NMR was analyzed by 300 MHz Bruker Avance NMR spectrometers at room temperature or 50 ºC in chloroform-*d*. Mass spectrometry was obtained by micro-TOF-LC Bruker mass spectrometer.

Powder X-Ray diffraction measurements were carried out on a Bruker D8 ADVANCE diffractometer using a high-power CuK_α source operating at 40 kV and 40 mA. The diffraction pattern over the range of 10–90°, 2ϴ were recorded at a scan rate of 5 s/step.

Atomic absorption spectrometry was carried out using a Thermo SCIENCTIFIC with iCE 3000 series model with GBC copper hallow cathode lamp, lamp current 100% at wavelength 324.8 nm and band pass 0.5 nm under D_2 background mode, continuous signal type. Flam parameters were using air-C_2H_2 type, rate of fuel flow 0.9 L/min. The nebulizer uptake 4 sec, burner height 10.2 mm.

Zetasizer spectrometry was carried out using a Malvern zetasizer using at 25 ºC. The duration used was 150 s, Count rated was 69.7 kcps. Measured position at 4.65 mm and used disposable sizing cuvette.

Microwave oven was carried out using a SUMSUNG M181 GN model at 850 w.

4.3 Experimental Section

This section was divided into three parts. The first part was the synthesis of diimine ligands. The second part was the synthesis of copper nanoparticles. And the third part was the *N*-arylation of indole.

4.3.1 Method of diimine ligand syntheses

Two types substituent of diimine ligands, electron withdrawing group (**1**–**3**) and electron donating group (**4**–**6**), were targeted as shown in Figure 4.1.

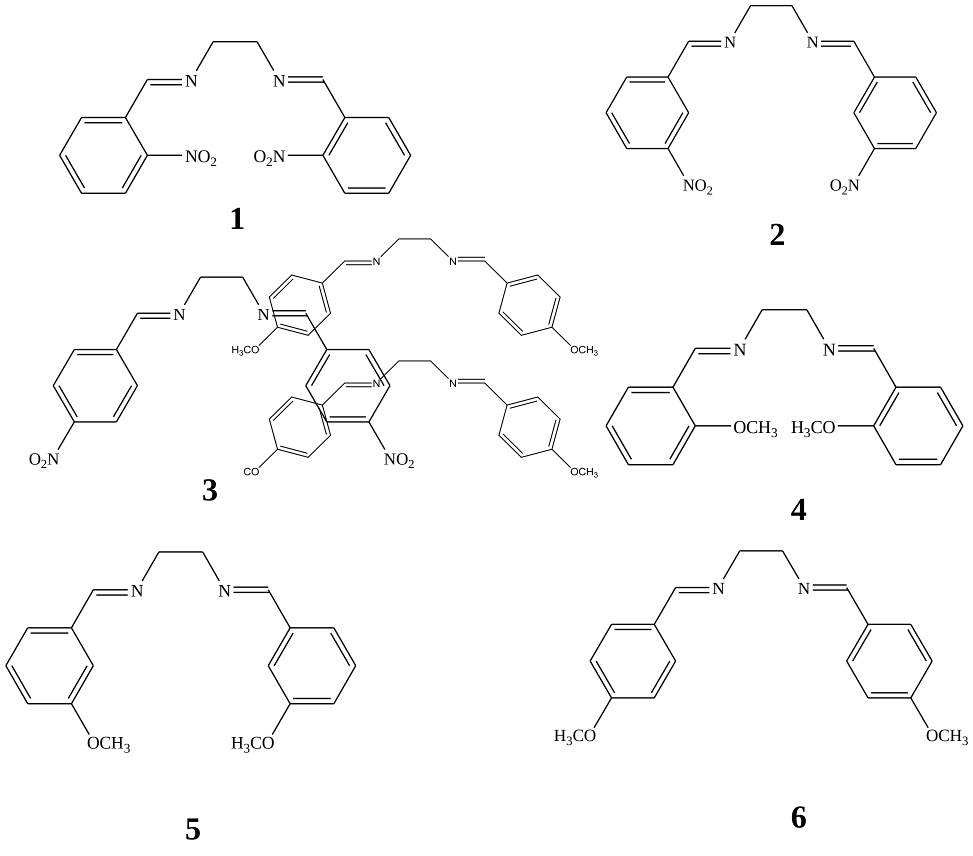
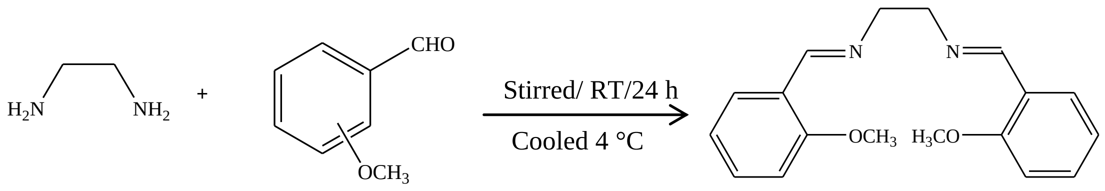


Figure 4.1 Structures of diimine ligands (**1**–**6**).

Synthetic methods for compounds **1** [61], **2** [62], **3** [61], **5** [62] and **6** [63] were previously reported while the synthetic procedure of ligand **4** was described below.



4

Scheme 4.1 The synthetic procedure for diimine ligand **4**.

4.3.1.1 *N,N-bis*(2-nitrobenzylidene)ethylenediamine (1)

Ligand **1** was synthesized as reported [61]. To a solid mixture of *2*-nitrobenzaldehyde (1.5 g, 10 mmol) and ethylenediamine (0.3 g, 5 mmol). The reaction mixture was left stirring at room temperature for 24 h. The product was washed with cool methanol (10 mL × 3) and dried under the reduced pressure to afford *N,N-bis*(2-nitrobenzylidene)ethylenediamine **1** (85 %Yield) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C):δ (ppm) 8.73 (*s*, 2H, ***H***C = N), 8.06 (*d*, 4H, $–C_6\boldsymbol{H}_4$), 7.97 (*d*, 4H, – $C_6\boldsymbol{H}_4$), 7.66 (*t*, 4H, – $C_6\boldsymbol{H}_4$)**,** 7.54 (*t*, 4H, – $C_6\boldsymbol{H}_4$)**,** and 4.08 (*s*, 2H, $–C\boldsymbol{H}_2–$)

4.3.1.2 *N,N-bis*(3-nitrobenzylidene)ethylenediamine (2)

Ligand **2** was prepared according to the same procedure as **1** using 3-nitrobenzaldehyde (1.5 g, 10 mmol) and ethylenediamine (0.3 g, 5 mmol). The bright yellow solid (70 %Yield) was washed with cool methanol (10 mL × 3) and dried under reduced pressure giving ligand **2**.

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm) 8.56 (*s*, 2H, $–C_6H_4$), 8.38 (*s*, 2H, *H*C=N), 8.24 (*d*, 4H, $–C_6\boldsymbol{H}_4$), 8.02 (*d*, 4H, $–C_6H_4$)**,** 7.55 (*m*, 2H, $–C_6H_4$)**,** and 4.06 (*s*, 2H, $–CH_2–$)

4.3.1.3 *N,N-bis*(4-nitrobenzylidene)ethylenediamine (3)

Ligand **3** was prepared according to the same procedure as **1** using 4-nitrobenzaldehyde (1.5 g, 10 mmol) and ethylenediamine (0.3 g, 5 mmol). The yellow (80 %Yield) was washed with cool methanol (10 mL × 3) and dried under reduced pressure giving ligand **3**.

^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ (ppm) 8.56 (*s*, 2H, – C_6*H_4*), 8.31 (*s*, 2H, *H*C=N), 8.16 (*d*, 4H, – C_6*H_4*)**,** 7.78 (*m*, 4H, –C_6*H_4*)**,** and 4.00 (*s*, 4H, –C*H_2*–)

4.3.1.4 *N,N-bis*(2-methoxybenzylidene)ethylenediamine (4)

To a solid mixture of 2-methoxybenzaldehyde (1.5 g, 10 mmol) and ethylenediamine (0.3 g, 5 mmol). The reaction mixture was left stirring at room temperature for 24 h. After that ligand **4** was cooled at 4 °C. The product was washed with cool methanol (10 mL × 3) and dried under reduced pressure giving a white solid as ligand **4** (62 %Yield).

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm) 8.70 (*s*, 2H, *H*C=N), 7.92 (*d*, 2H, – C_6*H_4*), 7.32 (*d*, 4H, –C_6*H_4*)**,** 6.90 (*m*, 4H, –C_6*H_4*)**,** 6.79 (*d*, 2H, –C_6*H_4*)**,** 3.99 (*s*, 4H, –C*H_2*–)**,** and 3.72 (s, 6H, –OC*H_3*)

4.3.1.5 *N,N-bis*(3-methoxybenzylidene)ethylenediamine (5)

Ligand **5** was prepared according to the same procedure as **1** using 3-methoxybenzaldehyde (1.4 g, 10 mmol) and ethylenediamine (0.3 g, 5 mmol). The light yellow solid (76 %Yield) was washed with cool methanol (10 mL × 3) and dried under reduced pressure giving ligand **5**.

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm) 8.26 (*s*, 2H, *H*C=N), 7.19 (*m*, 6H, –C_6*H_4*), 6.94 (*d*, 4H, – C_6*H_4*)**,** 3.95 (*s*, 4H, –C*H_2*–)**,** and 3.79 (s, 6H, –OC*H_3*)

4.3.1.6 *N,N-bis*(4-methoxybenzylidene)ethylenediamine (6)

Ligand **6** was prepared according to the same procedure as **1** using 4-methoxybenzaldehyde (1.4 g, 10 mmol) and ethylenediamine (0.3 g, 5 mmol). The white solid (85 %Yield) was washed with cool methanol (10 mL × 3) and dried under reduced pressure giving ligand **6**.

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm) 8.20 (*s*, 2H, *H*C=N), 8.25 (*d*, 4H, –C_6*H_4*), 6.87 (*d*, 4H, –C_6*H_4*)**,** 3.90 (*s*, 4H, –C*H_2*–)**,** and 3.81 (*s*, 6H, –OC*H_3*)

4.3.2 Method of copper nanoparticles Syntheses

Copper nanoparticles were prepared using the method from Haitao Zhu *et al*. In a conical flask, 20 mL ethylene glycol (EG) solution (0.1M) of copper sulphate pentahydrate ($CuSO_4{\cdot}5H_2O$) was mixed with 20 mL EG mixed solution of sodium hydroxide (NaOH) and hydrazine monohydrate ($N_2H_4{\cdot}H_2O$) under magnetic stirring. The molar ratio of $N_2H_4{\cdot}H_2O$/ $CuSO_4$ was 1.5 and molar ratio of NaOH/ $CuSO_4$ was 0.05. The mixture solution was placed in a microwave oven (SAMSUNG M181GN, Triple Distribution System) and reacted under medium power (750 W, working cycle of 18s and 12 s off) for 3 min. upon irradiating for about 30s, the mixture turned form light blue to black; at about 90s, the mixture boiled at about 195 °C. Then the mixture was irradiated for another 2 min to keep the mixture boiling. After that cooling to room temperature. Copper nanoparticles were obtained by centrifuging and washing with ethanol several times [64].

4.3.3 Method of measurement copper in copper nanoparticles

Determine of percentage of copper loading in copper nanoparticles using Flame Atomic Absorption Spectrometry (FAAS). The calibration was performed for standard solutions of 1.0, 2.0, 4.0, and 6.0 ppm in 2% of Nitric acid (HNO_3)

4.3.3.1 Prepare reagent use in FAAS experiment

a) Stock Standard copper Solution 100 ppm

An accurate amount of copper(II)sulphate pentahydrate (0.0861 g) was dissolved in 2% of nitric acid (10 mL). The solution was made up to exactly 100 mL with deionized water (DI water) to obtain a standard copper concentration 100 ppm.

b) Nitric Acid (2% v/v)

Nitric acid (10 mL) was diluted to 500 mL using deionized water to obtain nitric acid concentration of 2% v/v.

c) Standard Copper Solution 10 ppm

Copper standard solution of 10 ppm was prepared from 100 ppm stock standard copper solution by diluting in 2% v/v $HNO_{3.}$

d) Standard Copper Solution 6 ppm

Copper standard solution of 6 ppm was prepared from 10 ppm stock standard copper solution by diluting in 2% v/v $HNO_{3.}$

e) Standard Copper Solution 4 ppm

Copper standard solution of 4 ppm was prepared from 10 ppm stock standard copper solution by diluting in 2% v/v $HNO_{3.}$

f) Standard Copper Solution 2 ppm

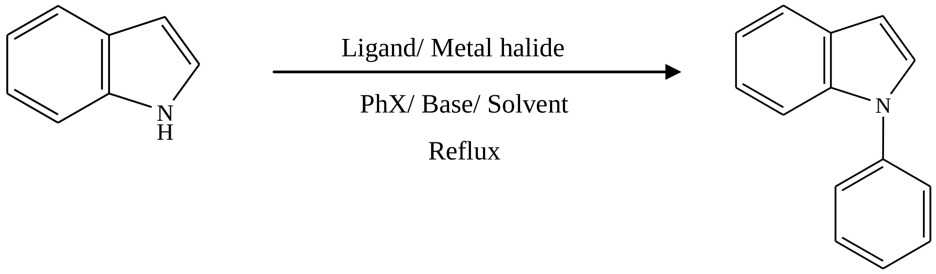
Copper standard solution of 2 ppm was prepared from 10 ppm stock standard copper solution by diluting in 2% v/v $HNO_{3.}$

g) Standard Copper Solution 1 ppm

Copper standard solution of 1 ppm was prepared from 10 ppm stock standard copper solution by diluting in 2% v/v $HNO_{3.}$

4.3.4 Method of *N*-arylation of Indole

General procedure for *N*-arylation of indole was described in Scheme 4.2.



Scheme 4.2 General procedure of *N*-arylation of indole.

In a 100 mL round-bottomed flask equipped with a reflux condenser were placed *N*,*N′*-dibenzylidene ethylenediamine (12 mg, 0.05 mmol), CuI (10 mg, 0.05 mmol), K_3PO_4 (215 mg, 1.0 mmol), indole (60 mg, 0.5 mmol), and toluene (2 mL). To this solution was added PhI (310 mg, 1.5 mmol) then the mixture was heated at 120 °C under reflux for 24 h. The reaction mixture was cooled and filtered through a small silica gel column and washed with EtOAc. The filtrate was evaporated and the product was purified by column chromatography (Silica, hexane/EtOAc) 99.5/0.5.

4.3.4.1 Effect of ratio of indole to iodobenzene

Effect of ratio of indole to iodobenzene in *N*-arylation of indole was studied by varying the ratio of indole to iodobenzene at fixed CuI, diimine ligands, K_3PO_4, and toluene solvent. The ratio of indole to iodobenzene were studied 1:0.5, 1:1, and 1:1.5.

4.3.4.2 Effect of different substituents in the *N*-arylation of indole

Effect of different substituents diimine ligands in *N*-arylation of indole was studied by varying diimine ligands (**1**–**6**) at fixed CuI, K_3PO_4, toluene solvent, and ratio of indole to iodobenzene was used 1:1.5. Sampling sample at 1, 3, 6, 9, 12, and 24 h, respectively.

4.3.4.3 Effect of diimine ligands and copper nanoparticles in *N*-arylation of indole

Effect of diimine ligands and copper nanoparticles in *N*-arylation of indole was studied by using copper nanoparticles replace to diimine ligands in *N*-arylation of indole at fixed CuI, K_3PO_4, toluene solvent, and ratio of indole to iodobenzene was used 1:1.5. Sampling sample at 1, 3, 6, 9, 12, and 24 h, respectively.

CHAPTER V
RESULTS AND DISCUSSION

5.1 Synthesis of diimine ligands

5.1.1 *N,N-bis*(2-nitrobenzylidene)ethylenediamine, *N,N-bis*(3-nitrobenzylidene)ethylenediamine, *N,N-bis*(4-nitrobenzylidene)ethylenediamine, *N,N-bis*(2-methoxybenzylidene)ethylenediamine, *N,N-bis*(3-methoxybenzylidene) ethylenediamine and *N,N-bis*(4-methoxybenzylidene)ethylenediamine

Two series of nitro- and methoxy substituents on benzylidene group of *N,N-bis*(benzylidene)ethylenediamine (**1**–**6**) were obtained by Schiff base condensation of benzaldehyde (2 equiv.) and ethylenediamine (1 equiv.). The characterization of diimine ligands by ^{1}H NMR is shown in Table 5.1, showing the yield and colours of diimine ligands. The structres of diimine ligands are shown in Figure 5.1

Table 5.1 The %yield of diimine ligands (**1**–**6**)

Diimine ligands	%Yield
N,N-bis(2-nitrobenzylidene)ethylenediamine (**1**)	85
N,N-bis(3-nitrobenzylidene)ethylenediamine (**2**)	70
N,N-bis(4-nitrobenzylidene)ethylenediamine (**3**)	80
N,N-bis(2-methoxybenzylidene)ethylenediamine (**4**)	62
N,N-bis(3-methoxybenzylidene)ethylenediamine (**5**)	76
N,N-bis(4-methoxybenzylidene)ethylenediamine (**6**)	85

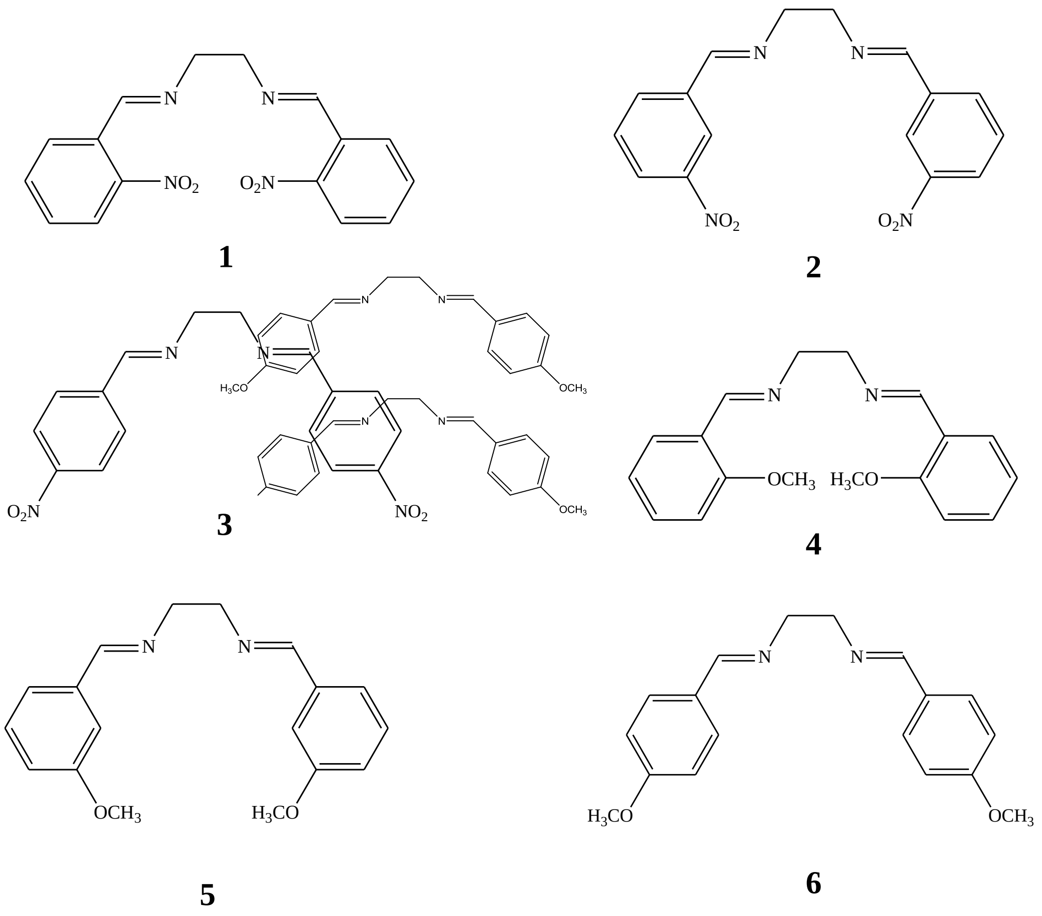


Figure 5.1 Structures of diimine ligands (**1**–**6**)

5.2 Characterization of copper nanoparticles (CuNPs)

Copper nanoparticles (CuNPs) were prepared in three stages: stage 1 involves the dissolution of copper precursor; stage 2 involves the reduction of Cu (II) species by N_2H_2 in solution; stage 3 is the nucleation and growth of metal Cu particles. Afterwards, these copper nanoparticles were characterized using the following techniques.

5.2.1 X-ray diffraction technique

The XRD pattern of the copper nanoparticles (CuNPs) is shown in Figure 5.2. All the peaks on the XRD pattern can be indexed to that of pure FCC copper metal according to JCPDS, File No. 04-0836 as indicated in Figure 5.2. These peaks corresponded to the (111), (200), (220), and (311) plans, respectively.

5.5.2 Zetasizer distribution technique

The particles size distribution of the typical powder is shown in Figure 5.3. The particles were essentially very fine and monodispersed with average diameter of 36.53 nm.

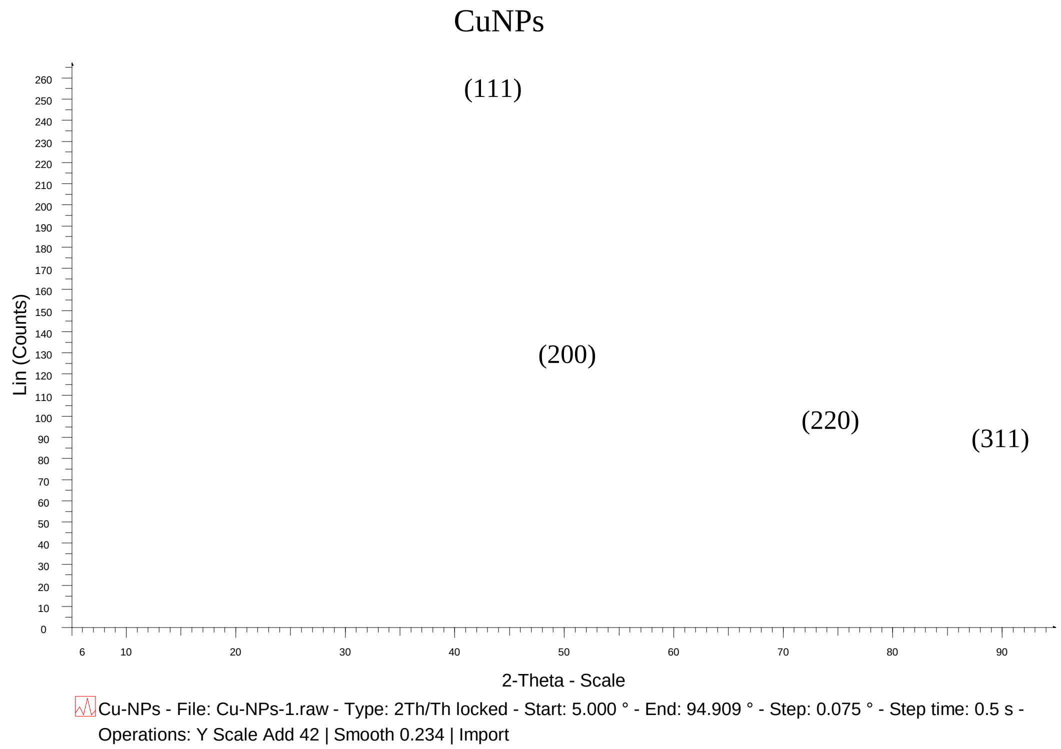


Figure 5.2 XRD patterns of copper nanoparticles (CuNPs) in this reaction.

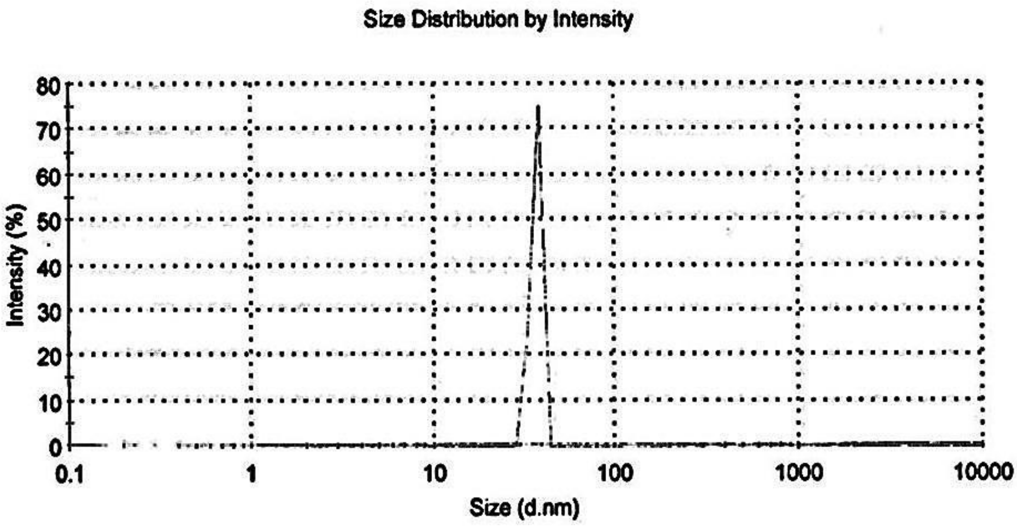


Figure 5.3 The particle size distribution of copper nanoparticles (CuNPs)

5.5.3 Flame Atomic absorption spectrometry (FAAS)

The percentage of copper in copper nanoparticles (CuNPs) is 14.22%. Calculate from calibration curve of copper standard solution of 1.0, 2.0, 4.0, and 6.0 ppm is shown in Figure 5.4.

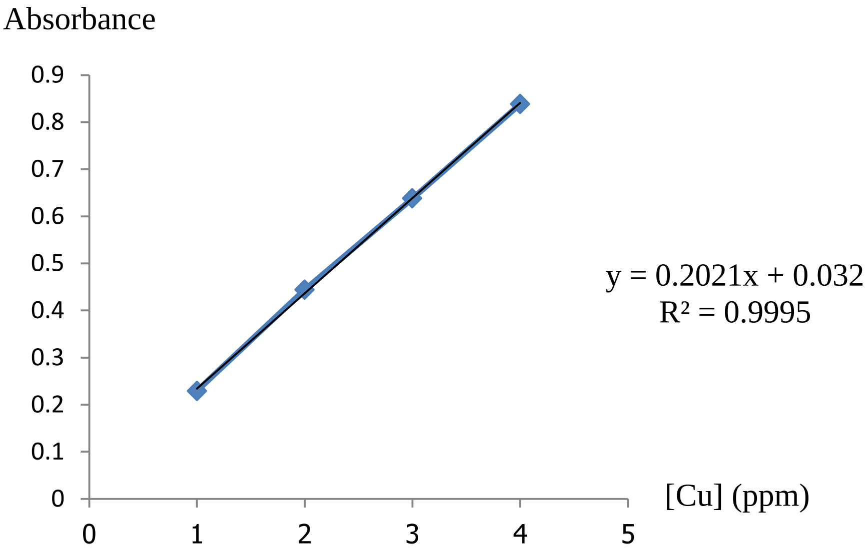


Figure 5.4 The calibration curve of copper at 1, 2, 4, and 6 ppm

5.3 *N*-arylation of indole

5.3.1 Effect of the ratio of indole to iodobenzene in *N*-arylation of indole

In order to investigate the effect of the ratio of indole to iodobenzene, the reactions were carried out using 10%mol of CuI, and 10%mol of diimine ligand (**3**) in the presence of 20 mmol K_3PO_4 in toluene at 110 °C for 24 h. Different ratios of indole to iodobenzene were studied, namely 1:0.5, 1:1, and 1:1.5. Figure 5.5 shows the yield against reaction rate for these different ratios. It can be seen that while the ratios of 1:0.5 and 1:1 gave approximately the same yield, the 1:1 ratio had a much better rate of reaction. Even though the ratio of 1:1 had comparable rate of reaction with the ratio of 1:1.5, the latter had higher yield. Consequently, the ratio of indole to iodobenzene of 1:1.5 was selected for further studies.

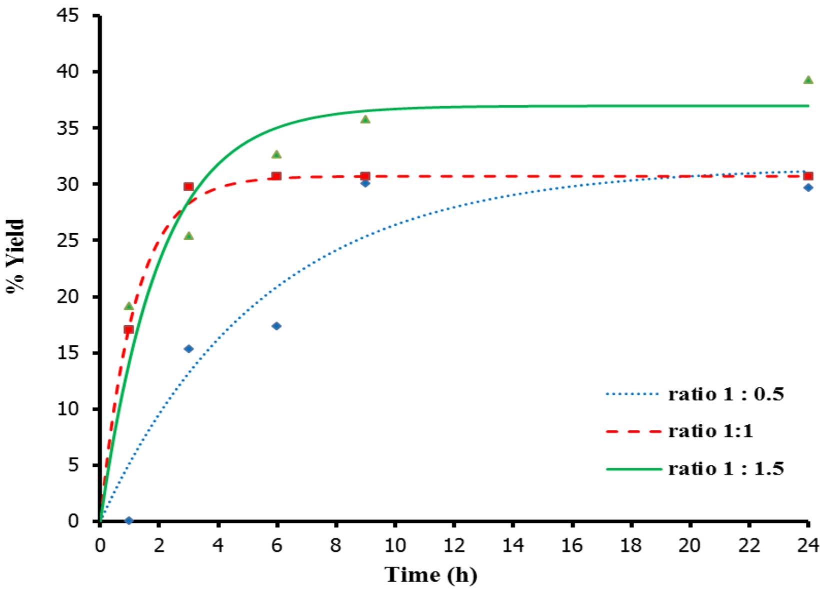


Figure 5.5 The yield and reaction time of *N*-arylation reaction with different ratios of indole to iodobenzene were (……) 1:0.5, (– –) 1:1, (——) 1:1.5. All the reactions were carried out with 1.5 mmol of diimine (**3**), 1.5 mmol of CuI, 15 mmol of indole, and 22.5 mmol of iodobenzene in toluene (60 mL). %Yield was identified using ^{1}H NMR.

5.3.2 Effect of different substituents on diimine ligands in the *N*-arylation of indole

The investigation on the effect of electron withdrawing substituent on diimine ligands in the *N*-arylation of indole was carried out using 1.5 mmol of diimine ligands (**1**–**3**), 1.5 mmol of CuI, 15 mmol of indole, and 22.5 mmol of iodobenzene in toluene (60 mL). Nitro group was used as the withdrawing substituent. The yield was studied using ^{1}H NMR. The results in Figure 5.6 show that the position of the withdrawing substituent affected the yield, with the highest yield when the nitro group was in the -*ortho* position. This is due to the resonance effect of nitro group at –*ortho* position, giving rise to its electron-rich oxygen atom. This had the effect of stabilizing and chelating with copper metal. On the other hand, the nitro group in the –*meta* position did not have the resonance effect but only the inductive effect. Even though the nitro group in the -*para* position could have the resonance effect but, due to its distance to the copper metal, it had limited stabilizing and chelating effect. Furthermore, the nitrogen atom in the diimine were electron deficient making them more positive and, as a result, hindered the chelating of copper metal. This is evident in the lowest yield. The effectiveness of the position of the nitro group withdrawing substituent could be summarized as follows; -*ortho* > -*meta* > -*para*.

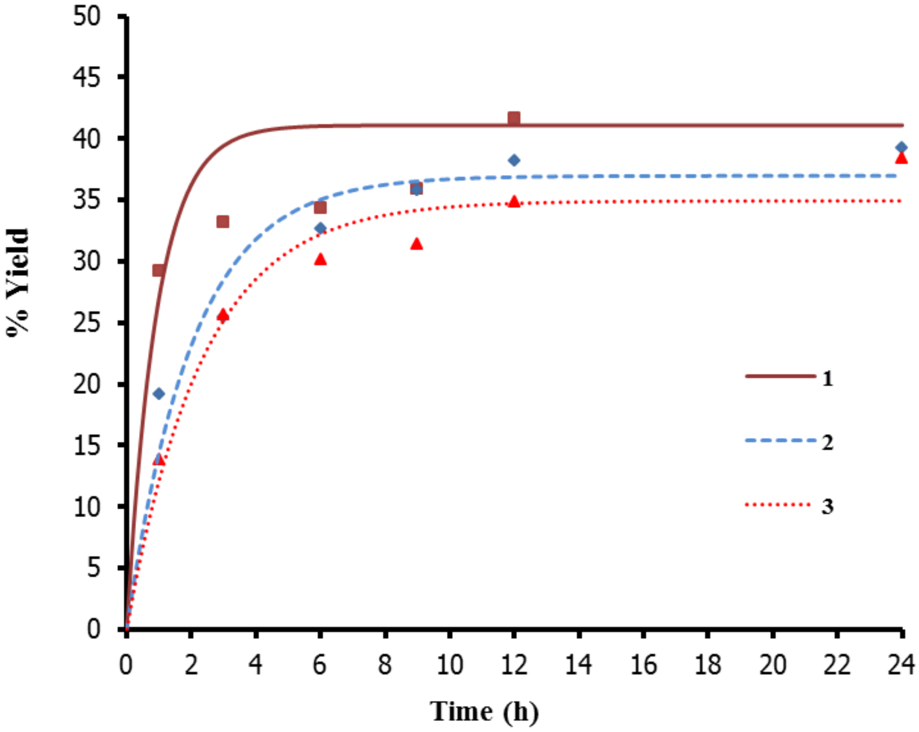


Figure 5.6 The yield and reaction time of *N*-arylation reaction with withdrawing substituent on diimine ligands were studied diimine ligands (——) **1**, (– –) **2**, and (……) **3**. All the reactions were carried out with 1.5 mmol of diimine (**1**–**3**), 1.5 mmol of CuI, 15 mmol of indole, and 22.5 mmol of iodobenzene in toluene (60 mL). %Yield was identified using ^{1}H NMR.

The investigation on the effect of donating substituent on diimine ligands in the *N*-arylation of indole was carried out using 1.5 mmol of diimine ligands (**4**–**6**), 1.5 mmol of CuI, 15 mmol of indole, and 22.5 mmol of iodobenzene in toluene (60 mL). Methoxy group was used as the donating substituent. The yield was studied using ^{1}H NMR. The results in Figure 5.7 show that the position of the donating substituent affected the yield, with the highest yield when the methoxy group was in the -*ortho* position. This is due to the resonance effect and inductive effect of methoxy group at -*ortho* position, giving rise to its electron-rich nitrogen atom in diimine. This had the effect of chelating with copper metal. On the other hand, the nitro group in the -*meta* position did not have the resonance effect but only the inductive effect. Even though the methoxy group in the -*para* position could have the resonance effect but, due to its distance to the copper metal, it had limited stabilizing and chelating effect. The effectiveness of the position of the methoxy group donating substituent could be summarized as follows; *-ortho* > *-meta* > *-para*.

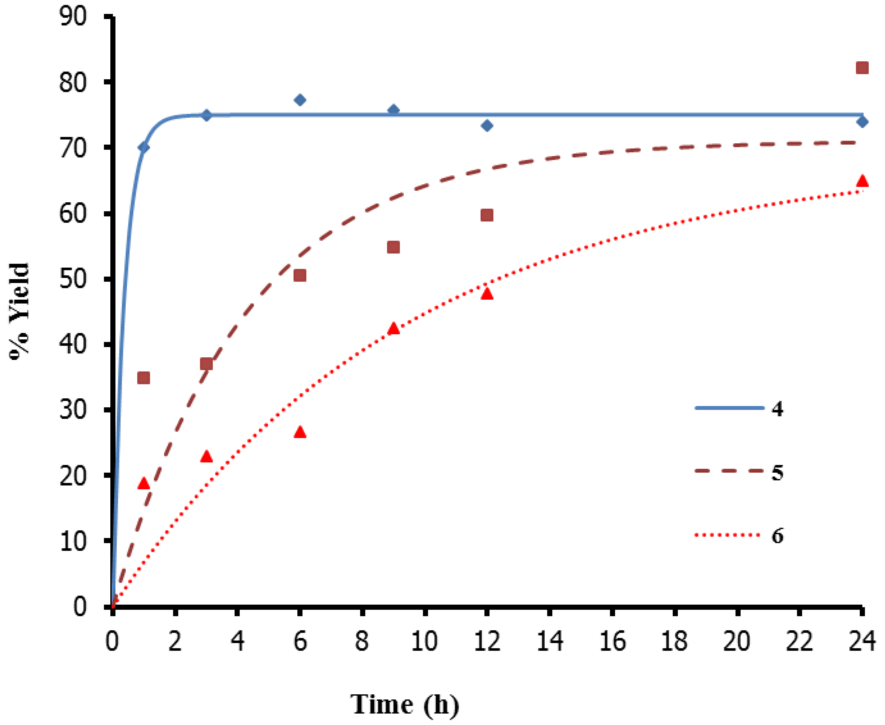


Figure 5.7 The yield and reaction time of *N*-arylation reaction with donating substituent on diimine ligands were studied diimine ligands (——) **4**, (– –) **5**, and (......) **6**. All the reactions were carried out with 1.5 mmol of diimine (**4**–**6**), 1.5 mmol of CuI, 15 mmol of indole, and 22.5 mmol of iodobenzene in toluene (60 mL). %Yield was identified using ^{1}H NMR.

The comparision between the effect of the nitro group and that of the methoxy group as withdrawing substituent and donating substituents is shown in Figure 5.8. It can be seen that the methoxy group substituent had higher rate constant (K_{obs}) and yield, than the nitro group substituent. This is summarized in Table 5.2. The higher rate of reaction and yield for the reaction with methoxy group substituent was due to the methoxy group could have both the resonance effects and inductive effects.

This resulted in more electron-rich nitrogen atom in diimine which, in turn, chelated better with copper metal.

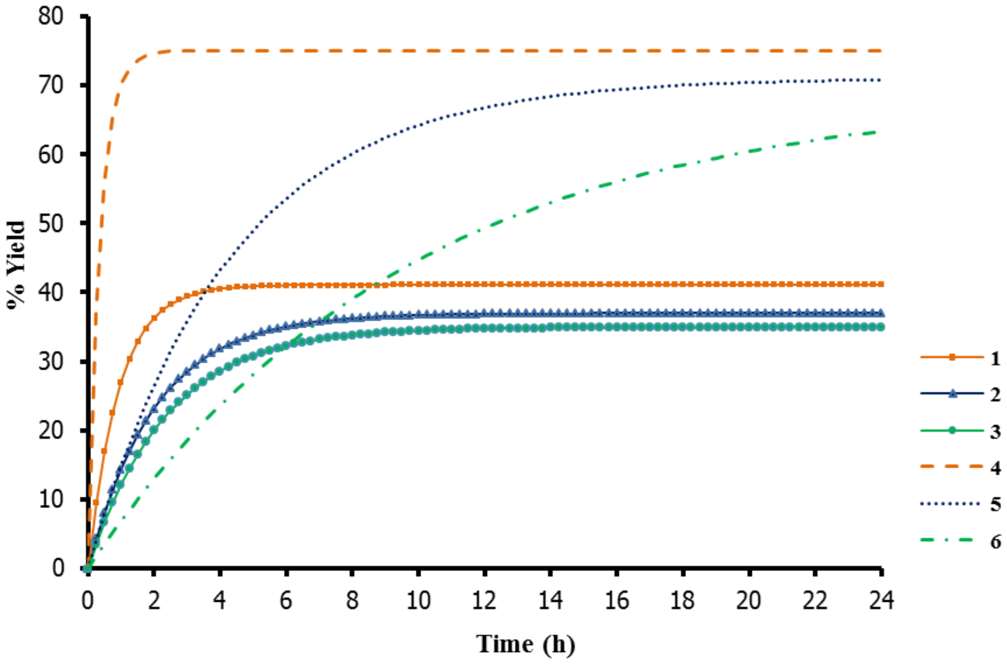
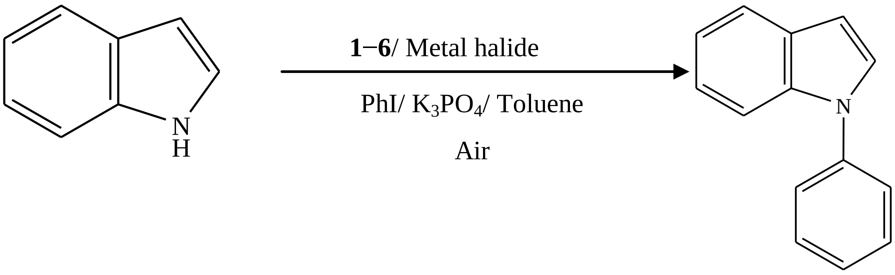


Figure 5.8 The comparison of the effect of withdrawing and donating substituents on diimine ligands were studied (—■—) **1**, (—▲—) **2**, (—●—) **3,** (– –) **4**, (……) **5**, and (– · –) **6**. All the reactions were carried out with 1.5 mmol of diimine (**1**–**6**), 1.5 mmol of CuI, 15 mmol of indole, and 22.5 mmol of iodobenzene in toluene (60 mL). %Yield was identified using ^{1}H NMR.

Table 5.2 Rate of reaction and yield of diimine/CuI-Catalyzed *N*-arylation of indole with iodobenzene and K_3PO_4

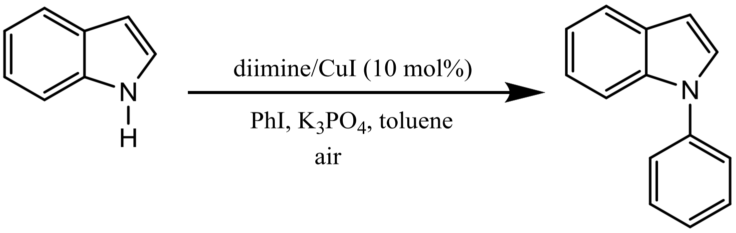


Diimine ligands	K_{obs}	%Yield
N,N-bis(2-nitrobenzylidene)ethylenediamine (**1**)	1.0648	41.10
N,N-bis(3-nitrobenzylidene)ethylenediamine (**2**)	0.4919	36.98
N,N-bis(4-nitrobenzylidene)ethylenediamine (**3**)	0.4254	34.93
N,N-bis(2-methoxybenzylidene)ethylenediamine (**4**)	2.713	75.00
N,N-bis(3-methoxybenzylidene)ethylenediamine (**5**)	0.2338	63.36
N,N-bis(4-methoxybenzylidene)ethylenediamine (**6**)	0.1047	70.80

5.3.3 Effect of diimine ligands and copper nanoparticles (CuNPs) in the *N*-arylation of indole

The catalysis effect of diimine ligands in the *N*-arylation of indole was carried out using 0.5 mmol of diimine ligands (**1**–**3**), 0.5 mmol of CuI, 5 mmol of indole, and 7.5 mmol of iodobenzene in toluene (20 mL). The results were then compared with the same condition but utilizing copper nanoparticles (CuNPs) of 0.23 mmol as a catalyst instead. The yield of the indole and iodobenzene coupling reaction using diimine ligands (**1**–**3**) and CuI as catalysts are 85.64%, 76.08%, and 79.19% for diimines ligands **1**, **2**, and **3**, respectively, as shown in Table 5.3. When the copper nanoparticles (CuNPs) replaced the diimine ligands and CuI catalyst the yield of the same reaction was found to be 32.57%. This is significantly less than using diimine ligands and CuI as catalyst. One of the reasons for this is the lower effective copper loading in copper nanoparticles (CuNPs) catalyst compared with the diimine ligands and CuI as catalyst. The effective mole of catalyst for each catalyst are shown in Table 5.3. It can be seen in Table 5.3 that the effective mole of catalyst of copper nanoparticles (CuNPs) were approximately half that of diimine ligands and CuI as catalyst.

Table 5.3 *N*-arylation of indole with PhI and K_3PO_4 catalyzed by diimine/CuI and CuNPs



Catalyst	Mole of catalyst (mmol)	%Yield	TON
[a]*N,N-bis*(2-nitrobenzylidene)ethylenediamine (**1**)	0.5	85.64	8.56
[a]*N,N-bis*(3-nitrobenzylidene)ethylenediamine (**2**)	0.5	76.08	7.61
[a]*N,N-bis*(4-nitrobenzylidene)ethylenediamine (**3**)	0.5	79.19	7.92
[b]Copper nanoparticles (CuNPs)	0.2	32.57	12.18

[a] All the reactions were carried out with 0.5 mmol of diimine, 0.5 mmol of CuI, 5 mmol of indole, and 7.5 mmol of PhI in toluene (20 mL). % Yield was identified using ^1H NMR.

[b] The reaction was carried out with 2 mmol of CuNPs replace diimine and CuI, 7.5 mmol of indole, and 11.25 mmol of PhI in toluene (20 mL). %Yield was identified using ^1H NMR.

The catalytic efficiency can be described by the turnover number (TON) using the following equation 5.1.

$$TON = \left(\frac{mole\ of\ product}{mole\ of\ catalyst}\right) \qquad ...(5.1)$$

The TON of diimine/CuI complexes were found to be 8.56, 7.61, and 7.92, respectively as shown in Table 5.3 and Figure 5.9. The TON of copper nanoparticles (CuNPs) was found to be 12.18 as shown in Table 5.3 and Figure 5.9. It is clear from this result that the TON of copper nanoparticles (CuNPs) was higher than the TON of diimine/CuI complexes, indicating that the copper nanoparticles (CuNPs) had higher catalytic efficiency than the diimine/CuI complexes although copper nanoparticles (CuNPs) had lower effective copper loading. This could be the consequence of higher effective surface area for copper nanoparticles (CuNPs) than that of the diimine/CuI complexes.

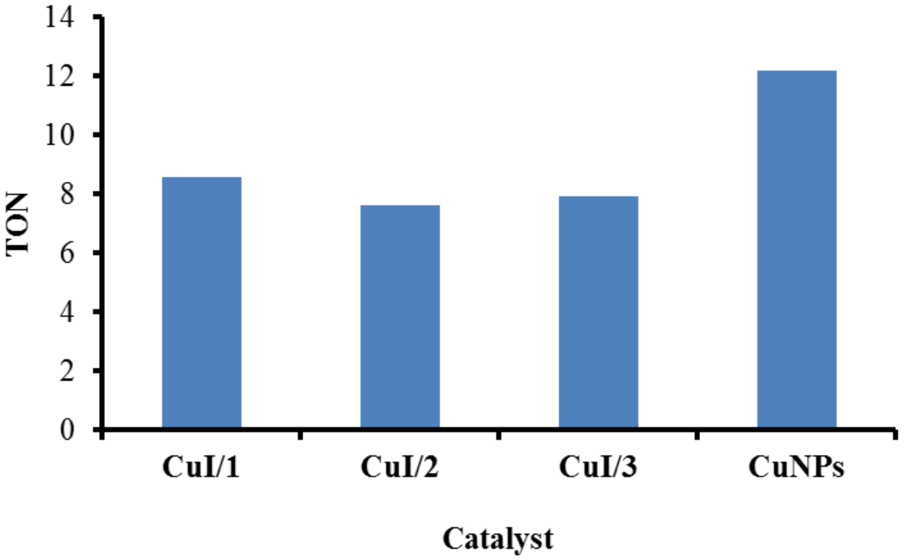


Figure 5.9 Turnover number (TON) of CuI/diimine ligands (**1**–**3**) and copper nanoparticles (CuNPs).

CHAPTER VI

CONCLUSIONS

Diimine ligands (**1**–**6**) were successfully synthesized under mild conditions and without the use of solvent. Then, diimine ligands were used to further form complexes with CuI. The CuI/diimine complexes were used as catalysts in *N*-arylation of indole (C–N coupling reaction). On the other hand, copper nanoparticles (CuNPs) were simply synthesized by using microwave irradiation method with the average particle sizes of 36.53 nm and these CuNPs were also used as a catalyst in the same reaction described above. The ratio of indole to iodobenzene, the effect of substituent group on diimine ligands, and the catalytic activity of copper nanoparticles and copper complex are studied.

Different ratios of indole to iodobenzene were studied for the *N*-arylation of indole which were performed under the conditions of 10% mol of CuI with 10% mol of diimine ligand (**3**) and 20 mmol K_3PO_4 in toluene and then refluxed at 110 °C for 24 h. The fastest rate of reaction and the highest yield was observed for the ratio of indole to iodobenzene of 1:1.5. Therefore, the ratio 1:1.5 was chosen to study the effect of substituent group on diimine ligands, and the catalytic efficiency of copper nanoparticles and copper complex.

The effectiveness of the position of the substituent groups showed the similar trends for both the withdrawing group and donating group with the *-ortho* position having the highest yield and rate of reaction followed by the *-meta* and *-para* positions, respectively.

In addition, copper nanoparticles (CuNPs) were a more efficiency catalyst thand diimine/ CuI complexes for the *N*-arylation of indole as evidently shown in higher turnover number (TON).

Overall, this research suggested the effectiveness of diimine/ CuI complexes catalyst could be varied by the type and the position of the substituent groups. Further studies need to be performed for other types of substituent groups.

Moreover, to better measure the catalytic activity. The control of the effective copper loading for copper nanoparticles (CuNPs) and diimin/CuI complexes is essential.

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APPENDIX

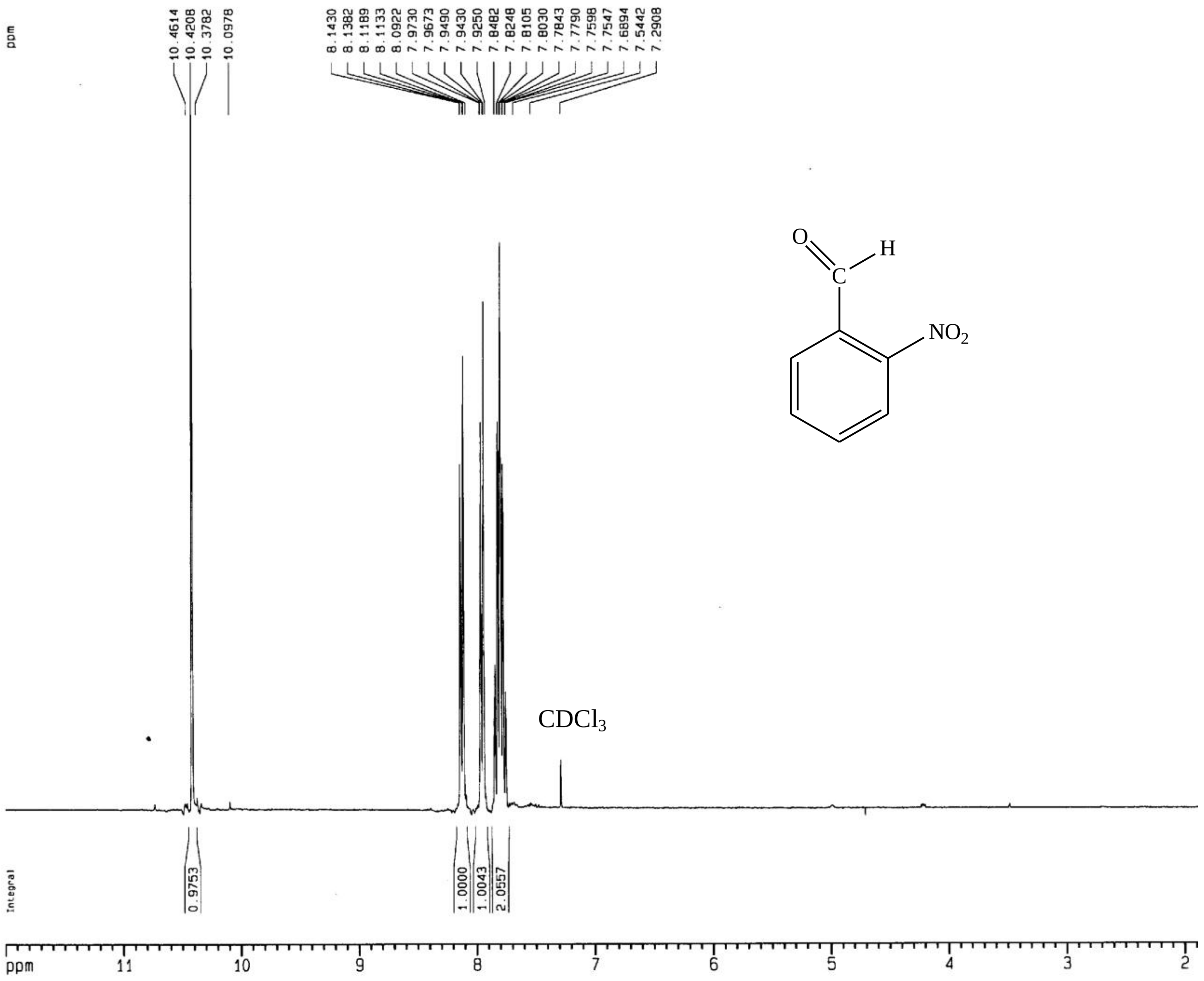

Figure A1 300 MHz 1D ^{1}H NMR spectrum of 2-nitrobenzaldehyde in $CDCl_3$

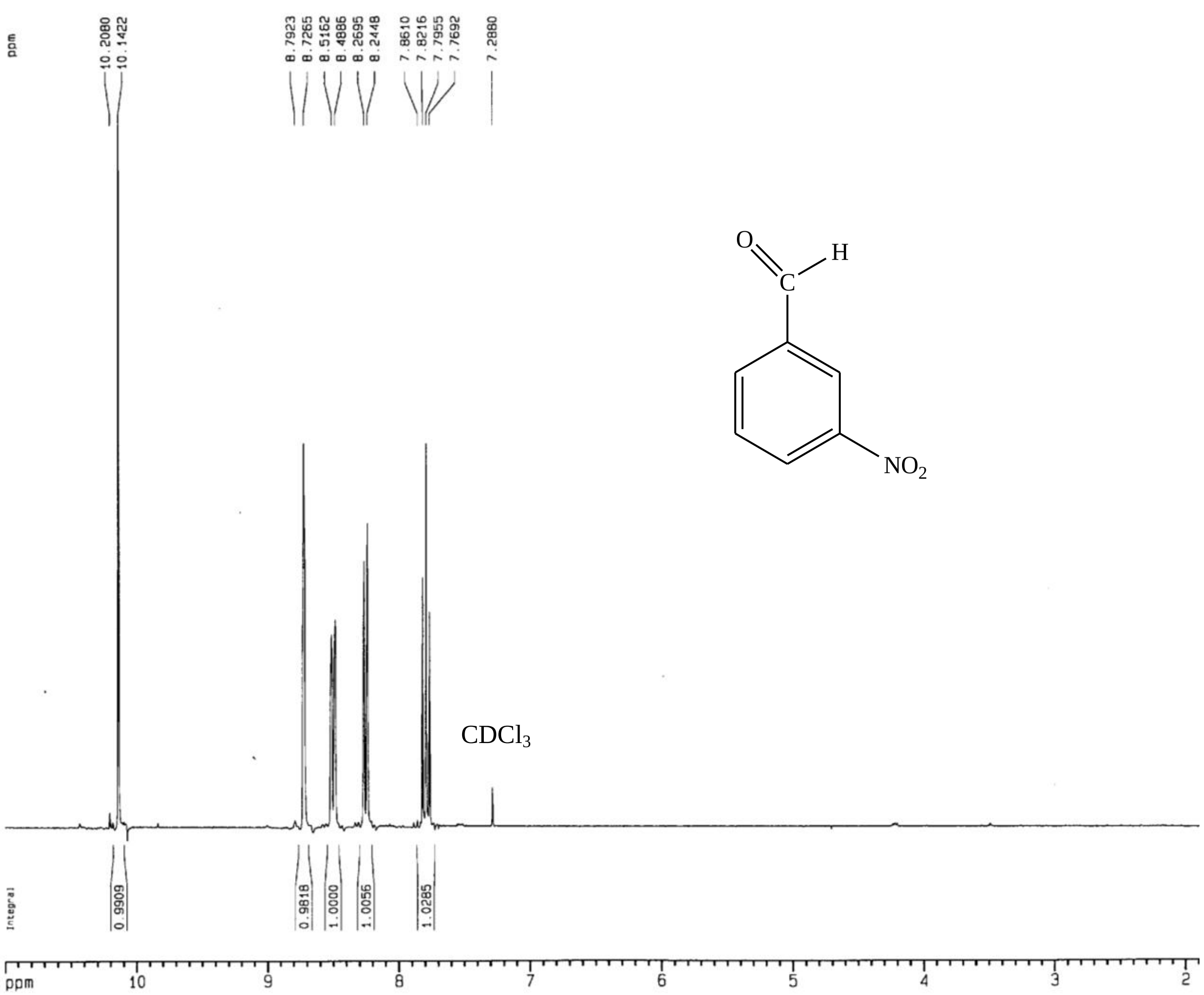

Figure A2 300 MHz 1D ^{1}H NMR spectrum of 3-nitrobenzaldehyde in CDCl$_3$

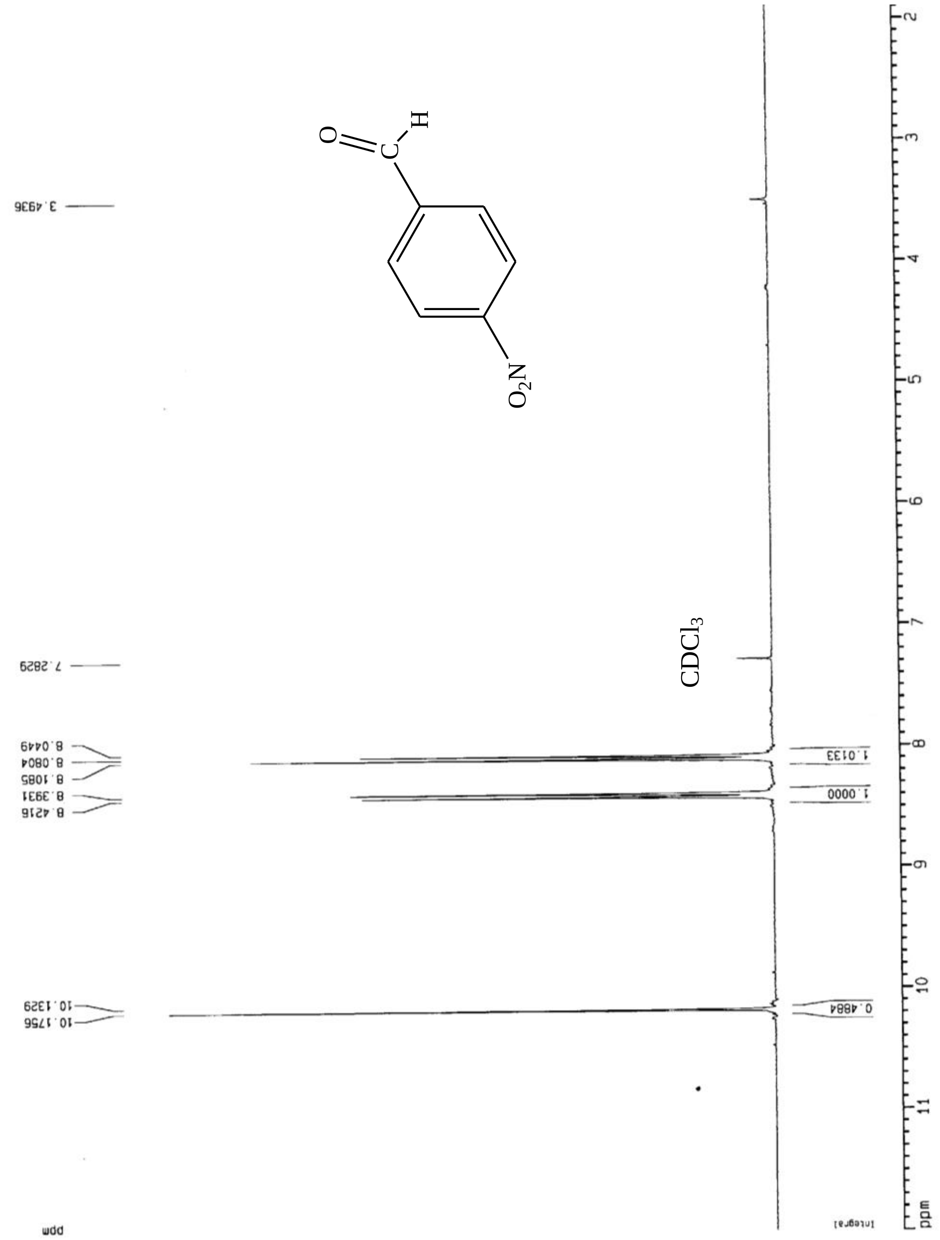

Figure A3 300 MHz 1D ^{1}H NMR spectrum of 4-nitrobenzaldehyde in $CDCl_3$

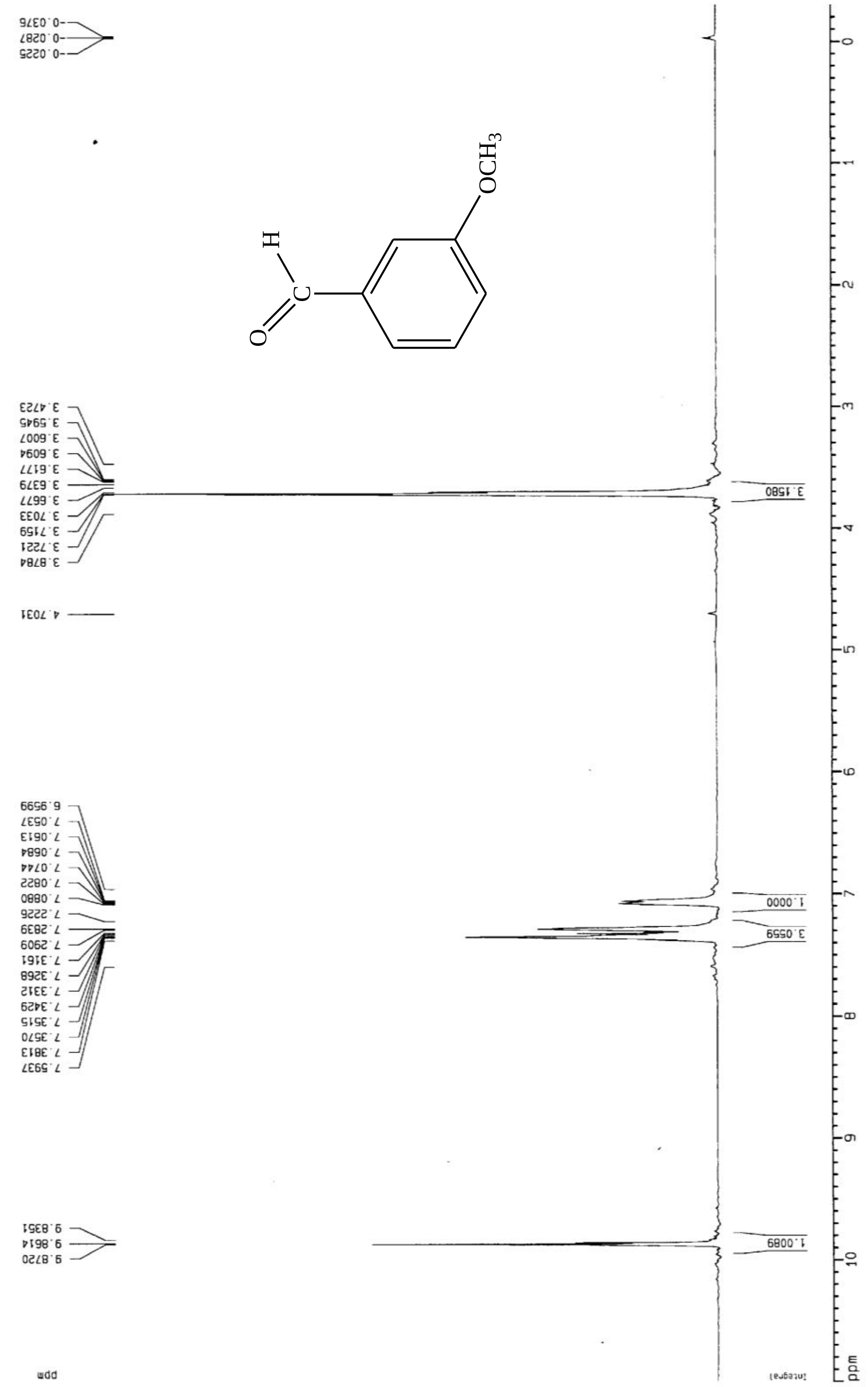

Figure A4 300 MHz 1D ^{1}H NMR spectrum of 3-methoxybenzaldehyde in $CDCl_3$

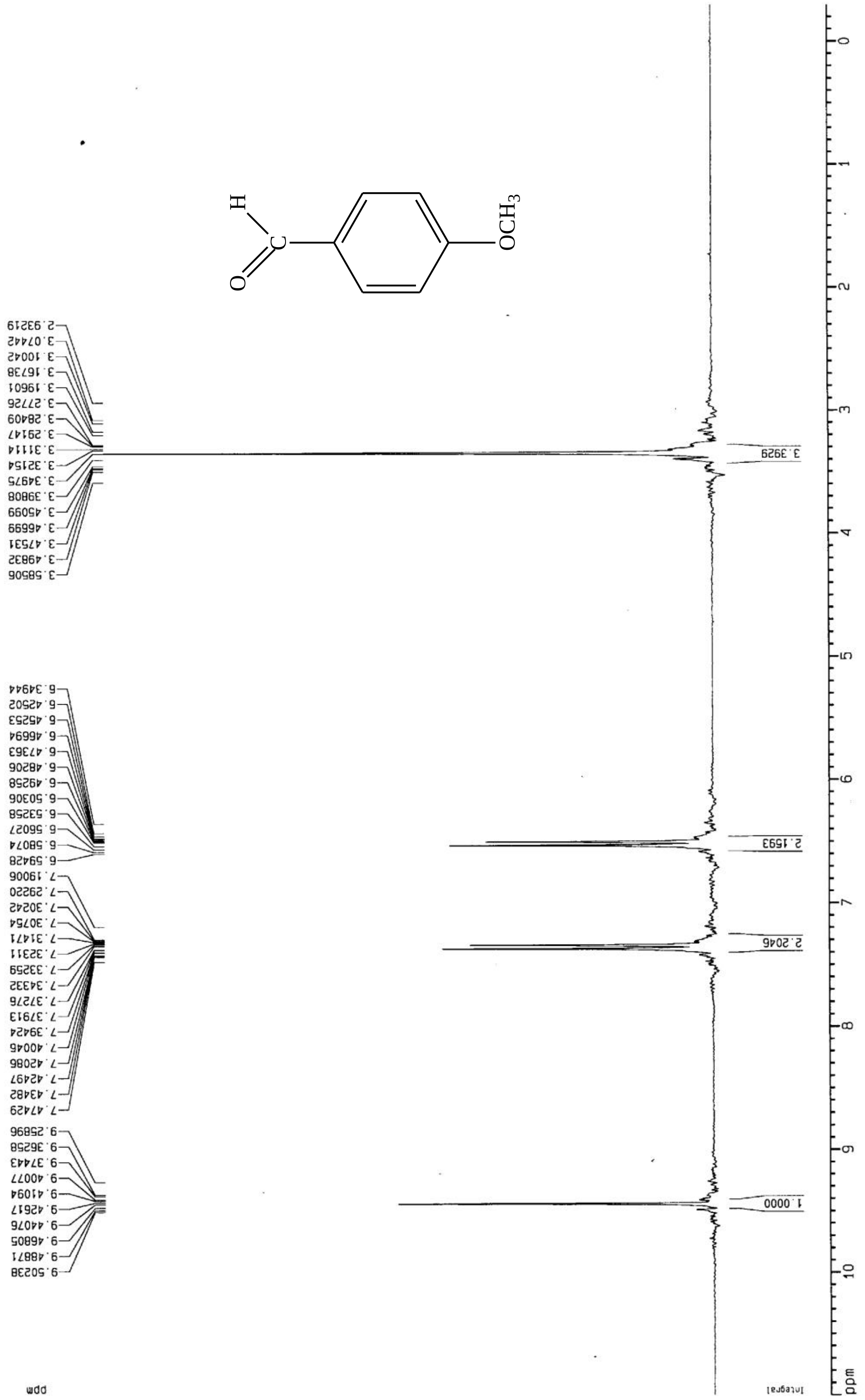

Figure A5 300 MHz 1D ^{1}H NMR spectrum of 4-methoxybenzaldehyde in $CDCl_3$

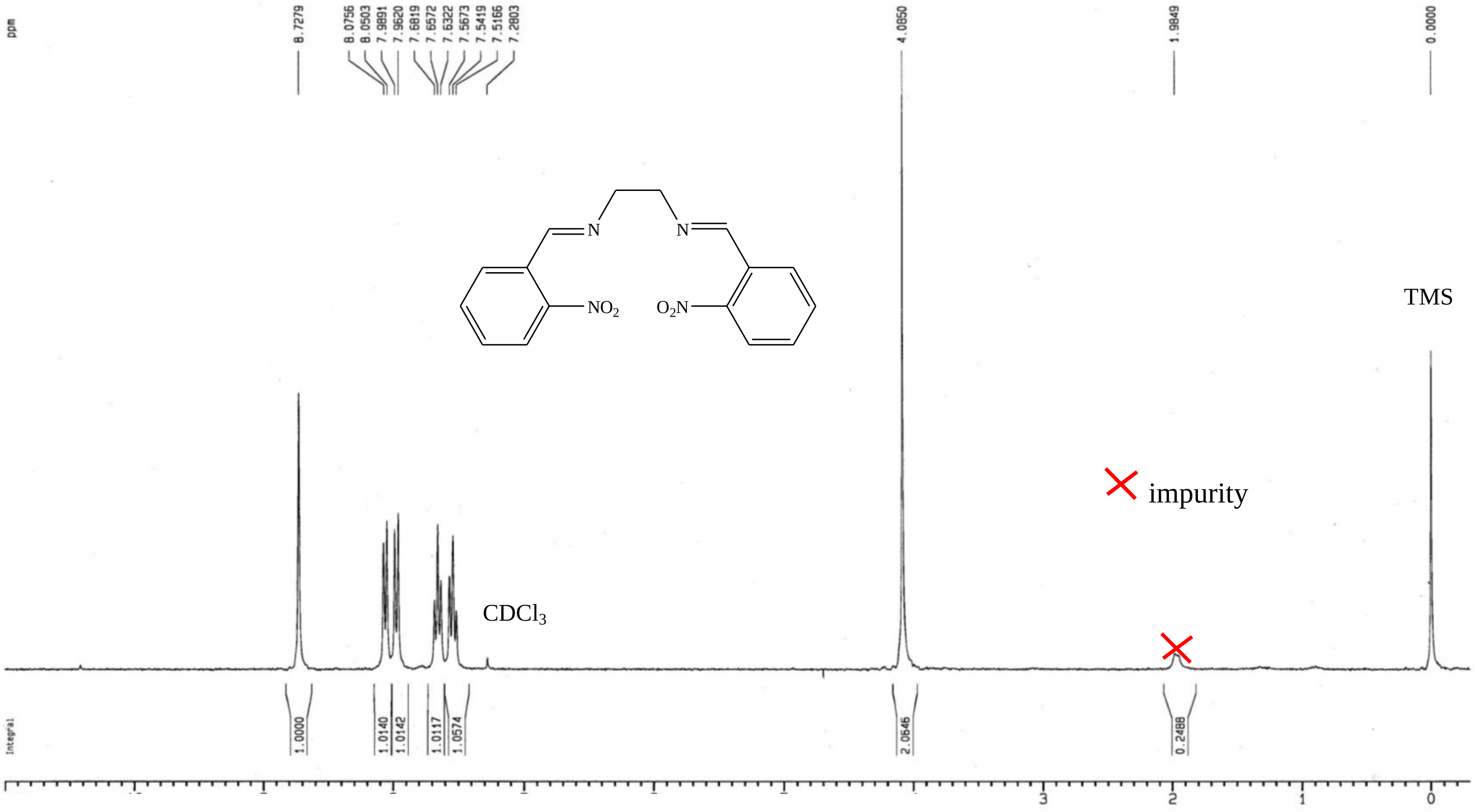

Figure A6 300 MHz 1D ^{1}H NMR spectrum of *N*,*N*-*bis*(2-nitrobenzylidene)ethylenediamine (**1**) in $CDCl_3$

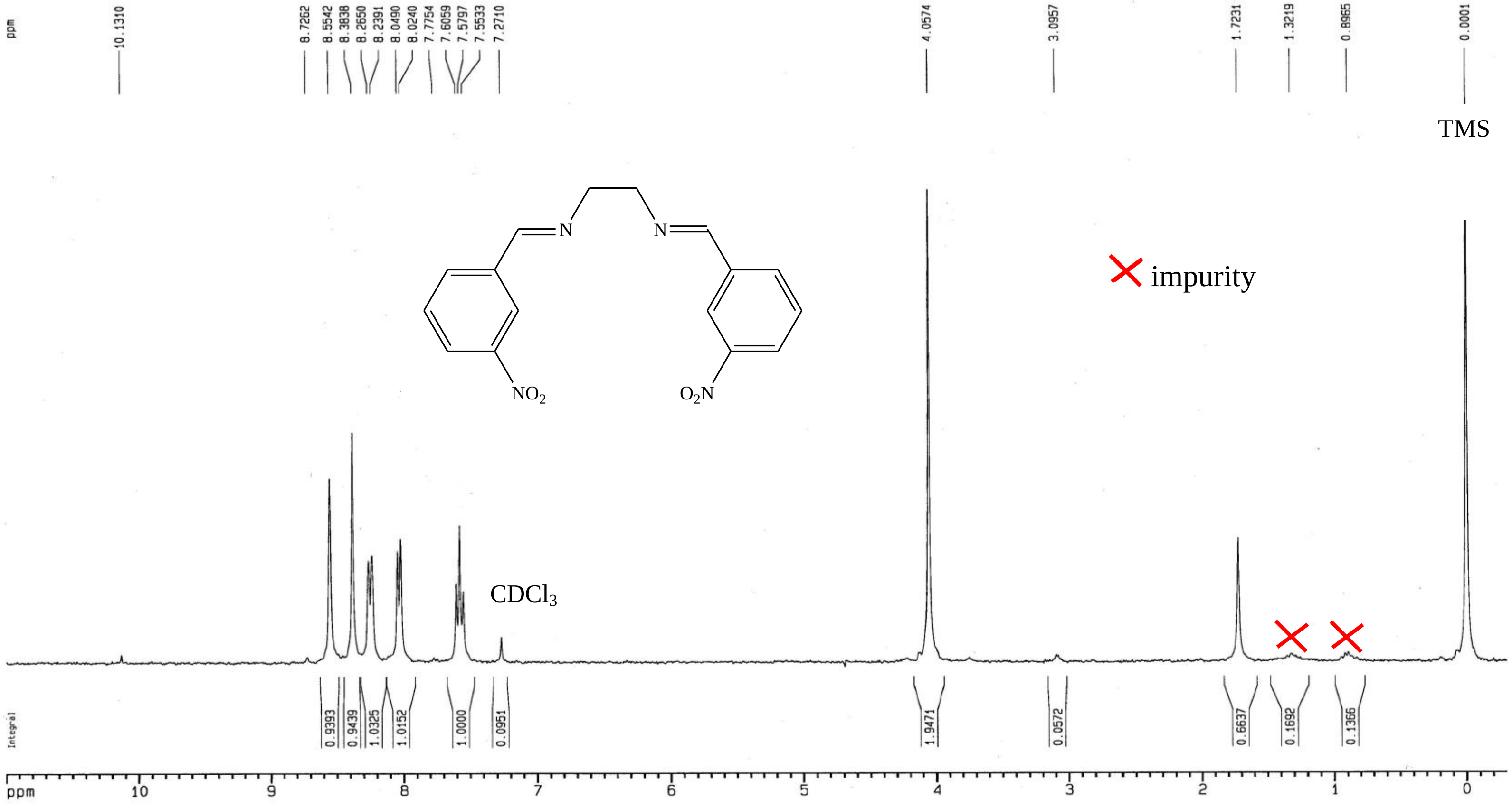

Figure A7 300 MHz 1D ^{1}H NMR spectrum of *N*,*N*-*bis*(3-nitrobenzylidene)ethylenediamine (**2**) in $CDCl_3$

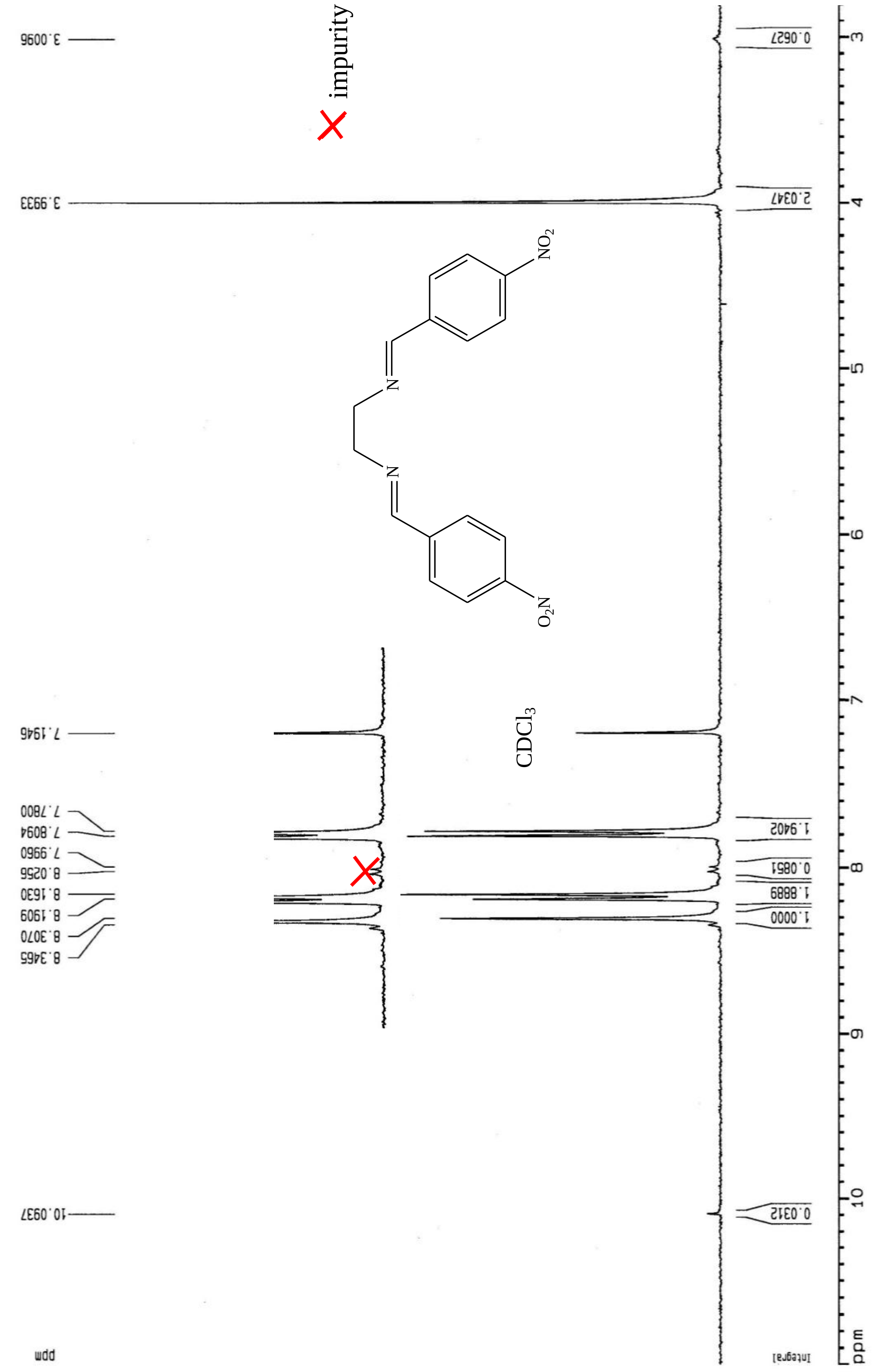

Figure A8 300 MHz 1D ^{1}H NMR spectrum of *N*,*N*-*bis*(4-nitrobenzylidene)ethylenediamine (**3**) in CDCl$_3$

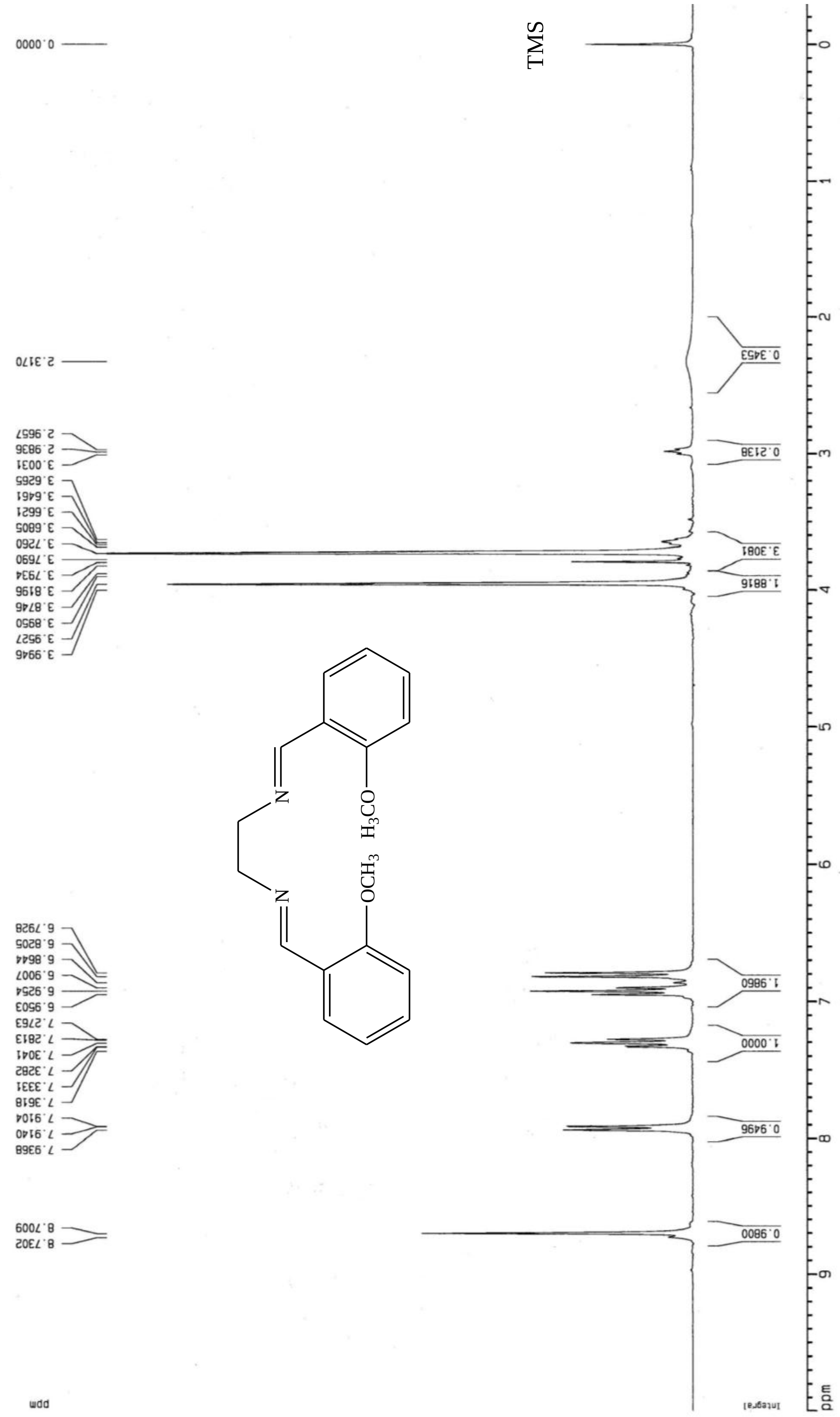

Figure A9 300 MHz 1D ^{1}H NMR spectrum of *N,N-bis*(2-methoxybenzylidene)ethylenediamine (**4**) in $CDCl_3$

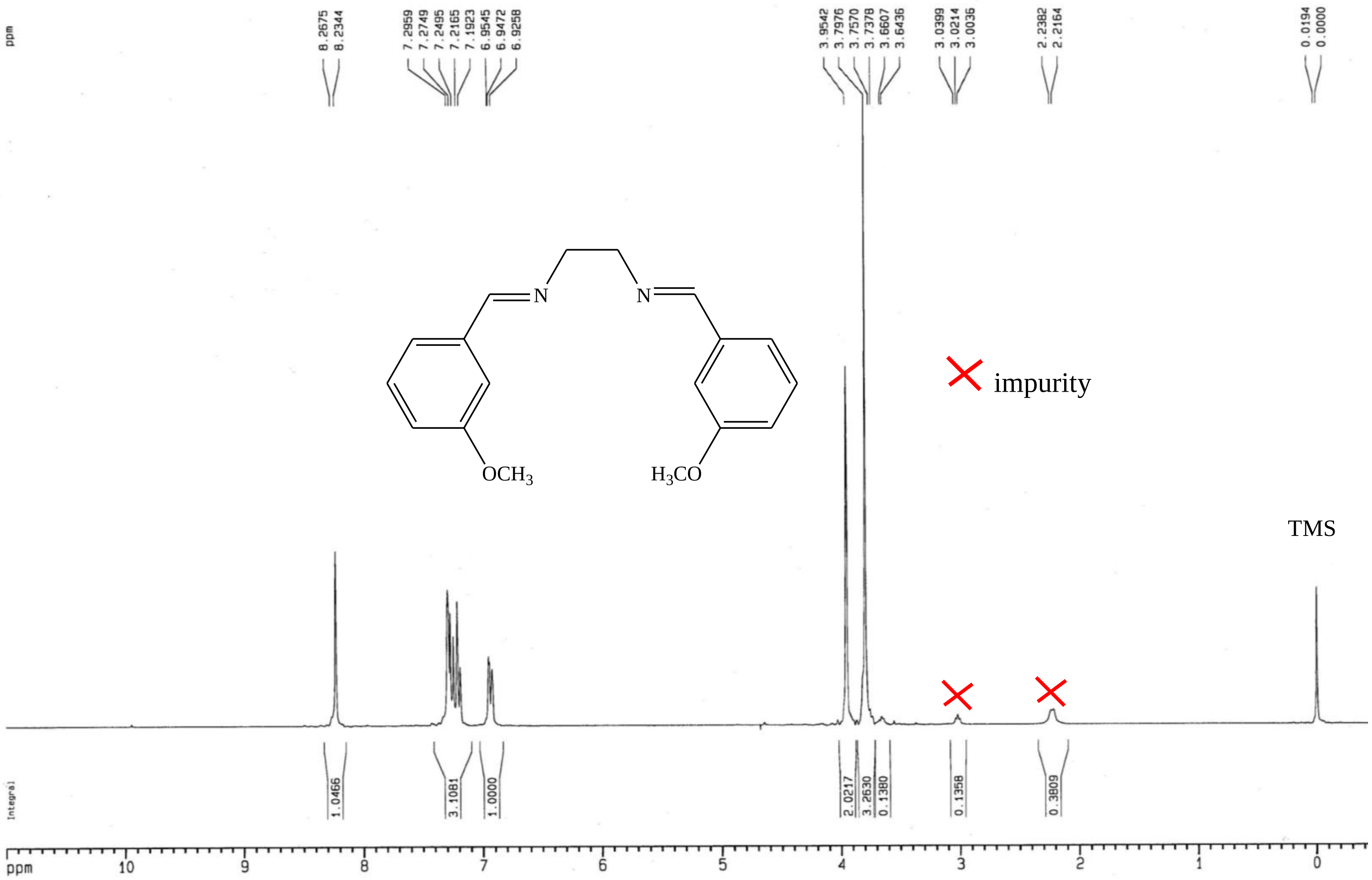

Figure A10 300 MHz 1D ^{1}H NMR spectrum of *N,N-bis*(3-methoxybenzylidene)ethylenediamine (**5**) in $CDCl_3$

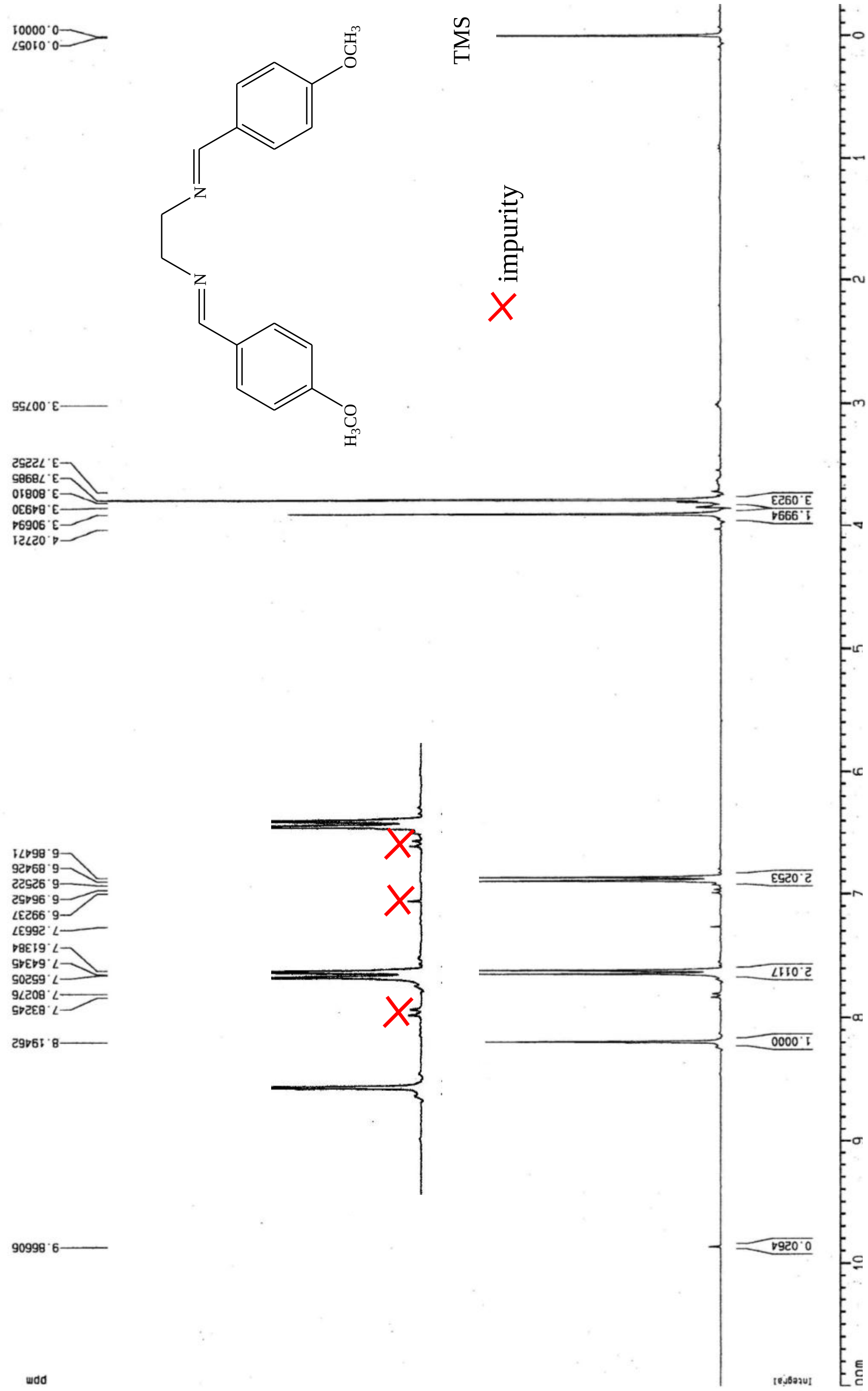

Figure A11 300 MHz 1D ^{1}H NMR spectrum of *N*,*N*-*bis*(4-methoxybenzylidene)ethylenediamine **(6)** in $CDCl_3$

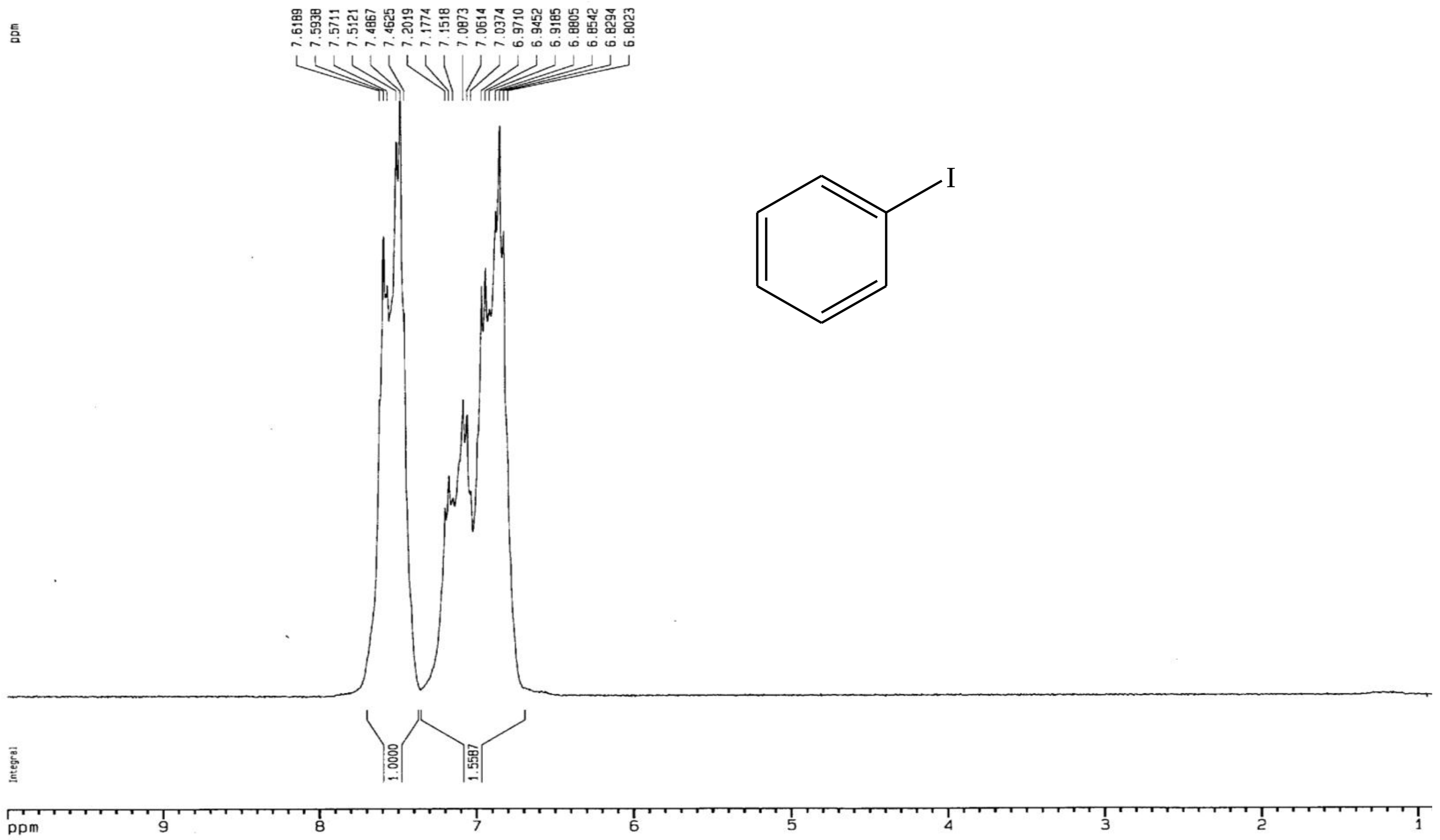

Figure A12 300 MHz 1D ^{1}H NMR spectrum of iodobenzene in $CDCl_3$

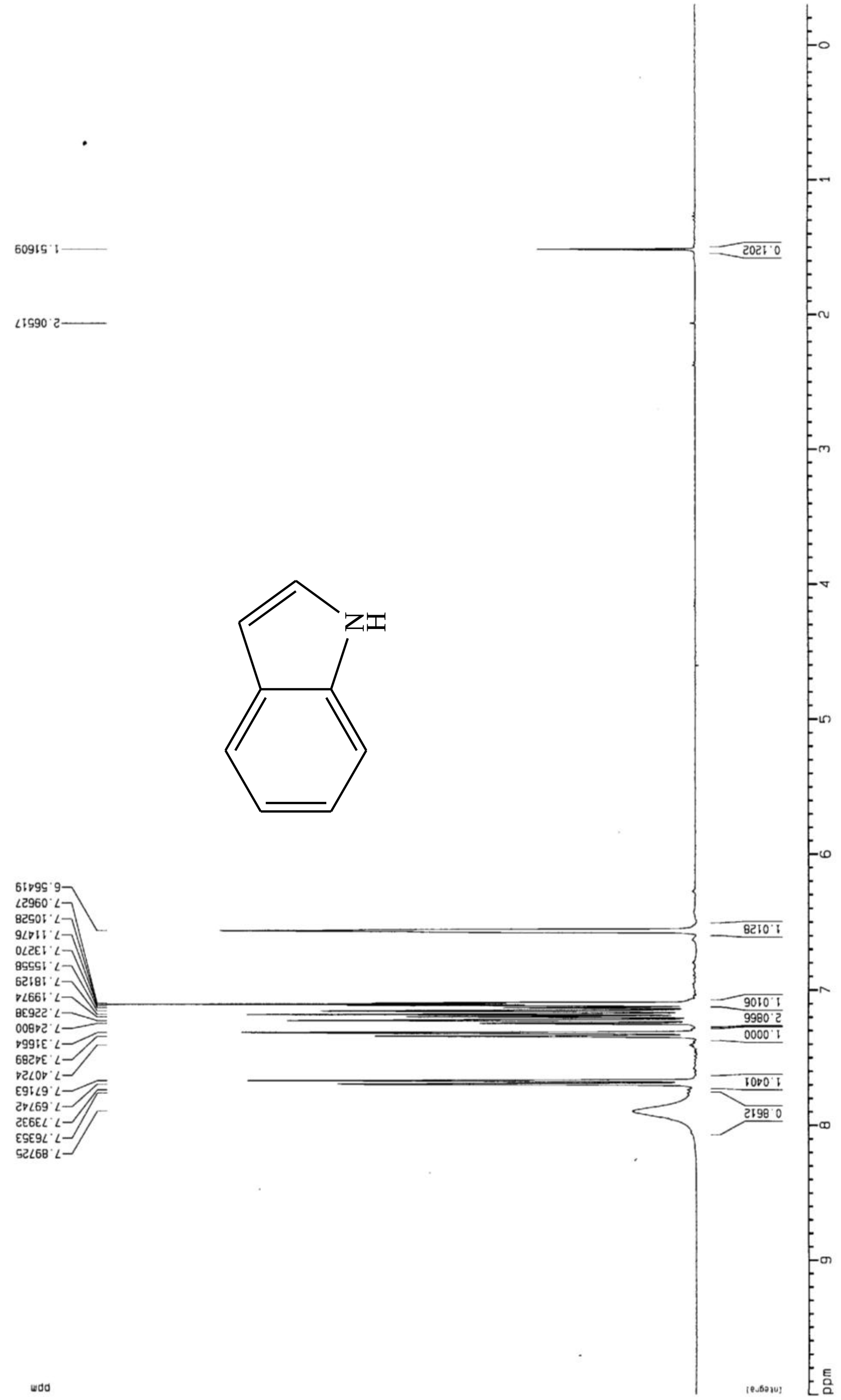

Figure A13 300 MHz 1D ^{1}H NMR spectrum of indole in $CDCl_3$

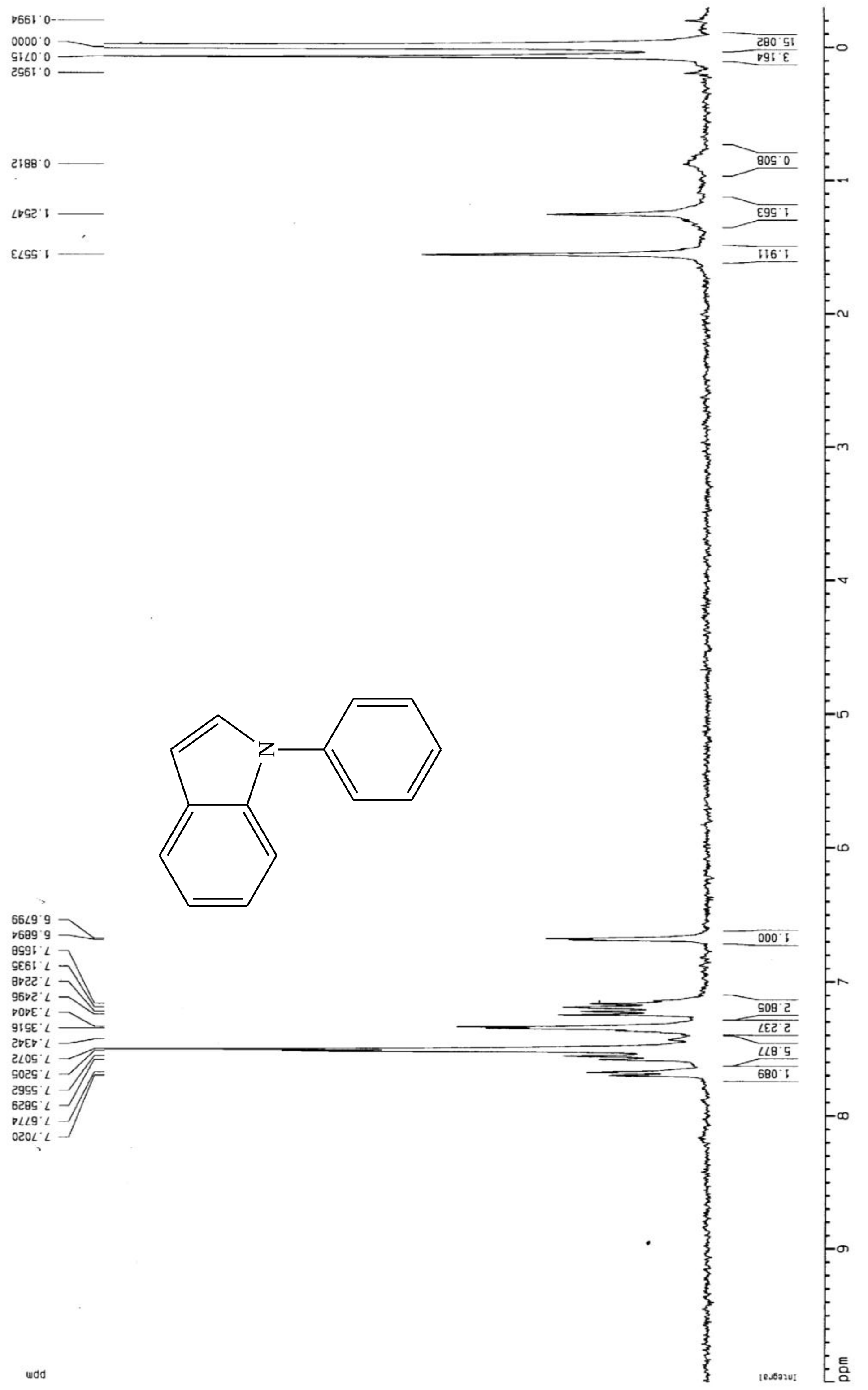

Figure A14 300 MHz 1D ^{1}H NMR spectrum of 1-phenyl-1*H*-indole in $CDCl_3$

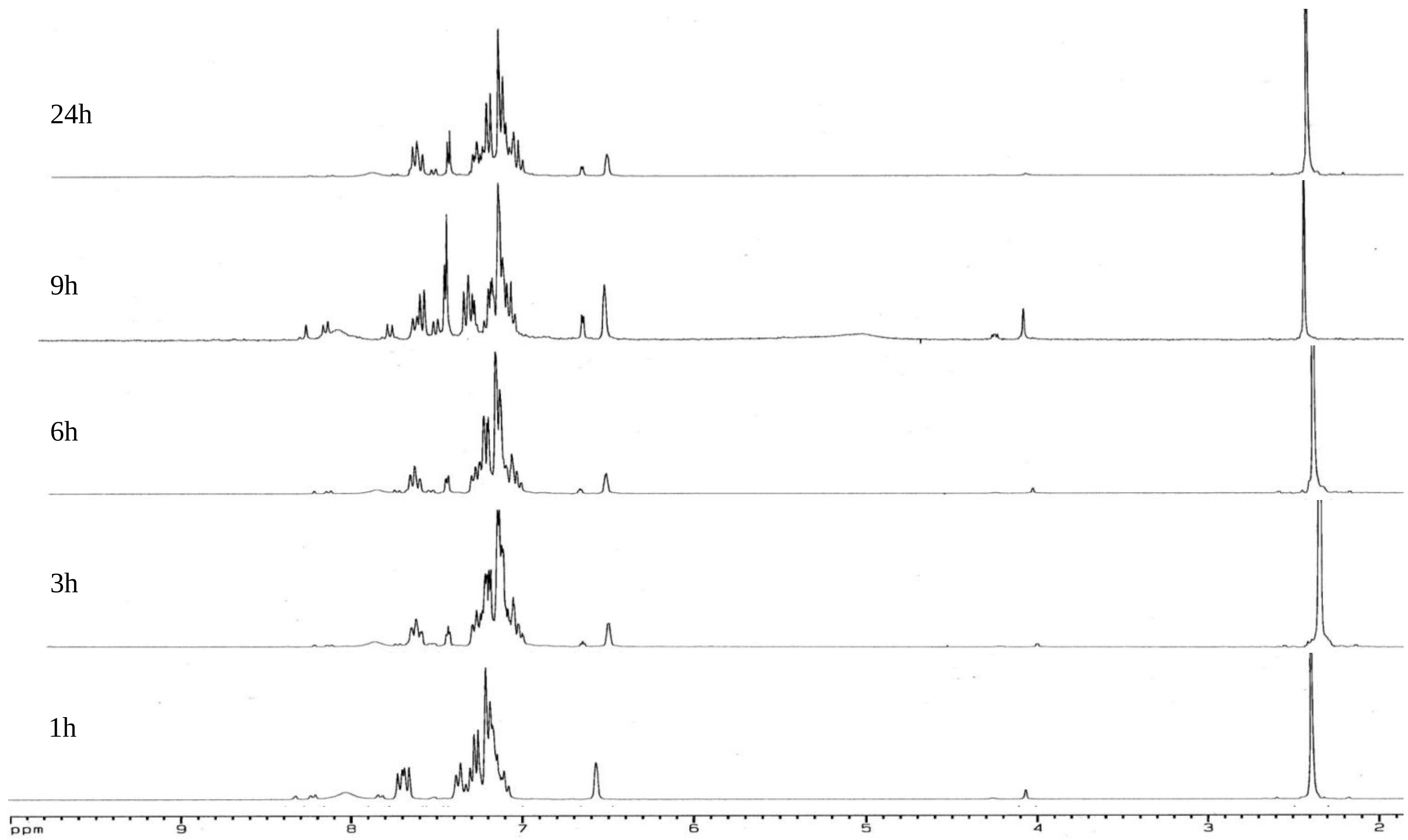

Figure A15 300 MHz 1D ^{1}H NMR overlay spectra in CDCl$_3$ of kinetic *N*-arylation of indole using 10 mol% CuI/**3** (1:0.5) as catalyst.

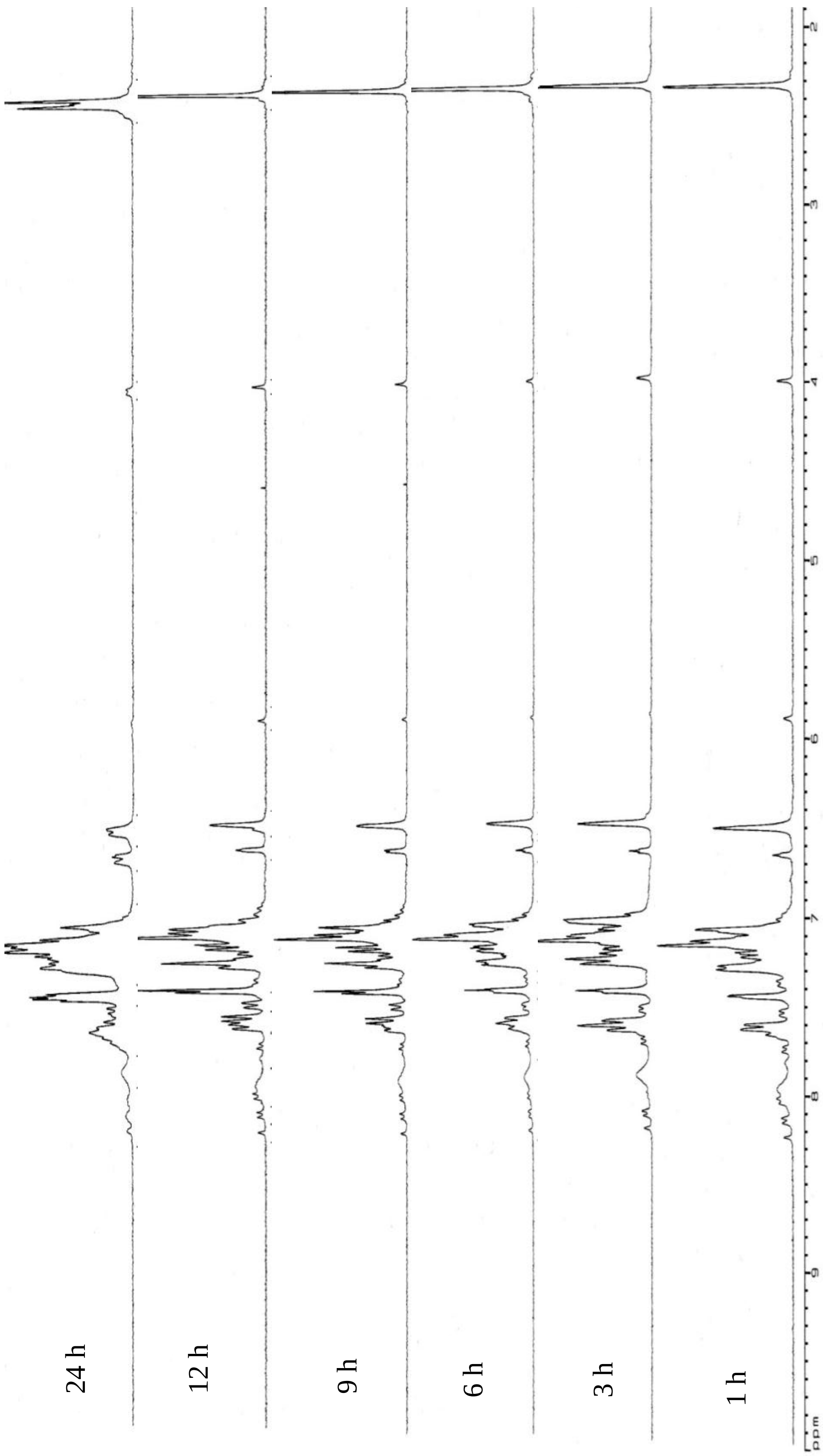

Figure A16 300 MHz 1D ^{1}H NMR overlay spectra in $CDCl_3$ of kinetic *N*-arylation of indole using 10 mol% CuI/**3** (1:1) as catalyst.

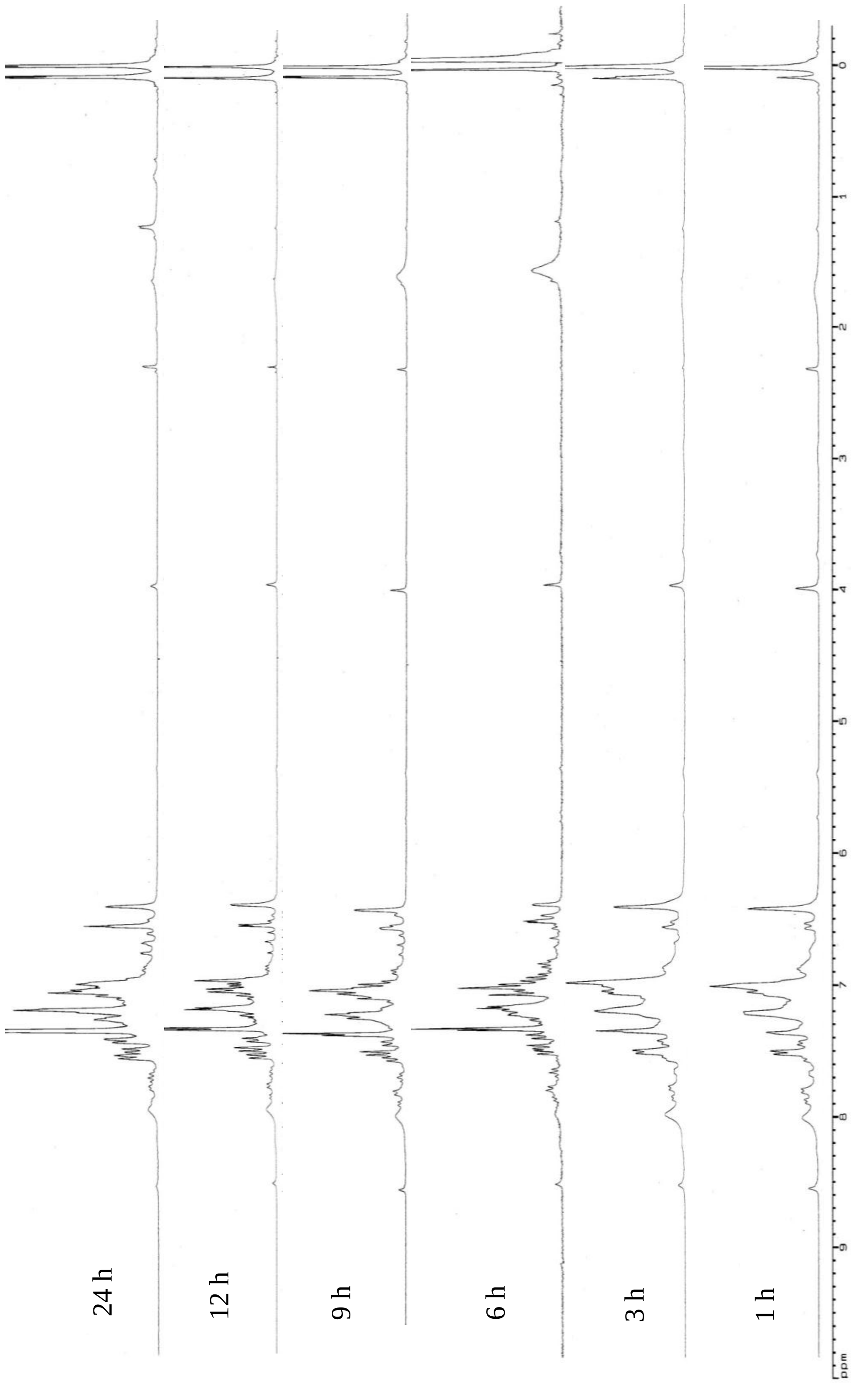

Figure A17 300 MHz 1D ^{1}H NMR overlay spectra in CDCl$_3$ of kinetic *N*-arylation of indole using 10 mol% CuI/**1** (1:1.5) as catalyst.

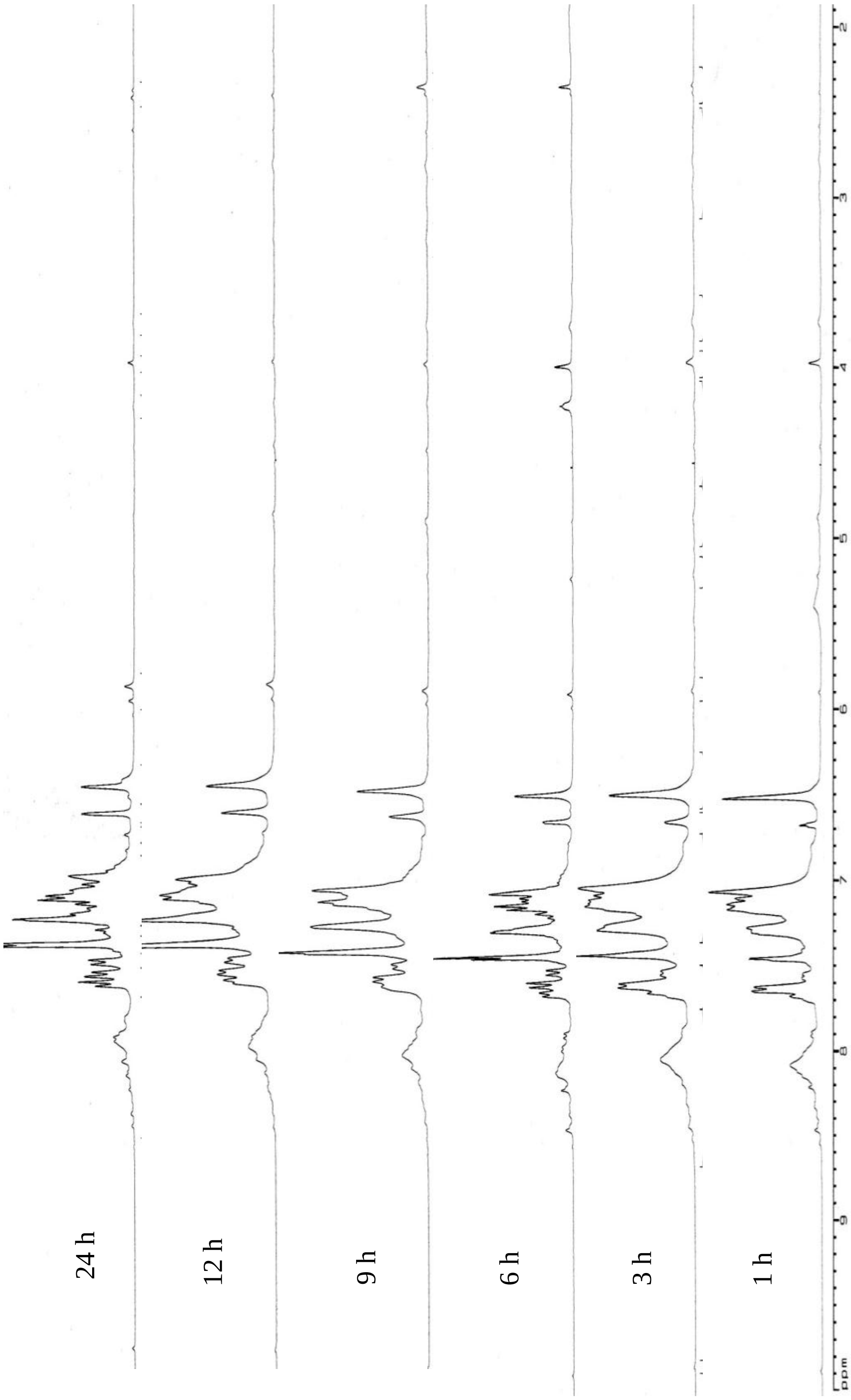

Figure A18 300 MHz 1D ^{1}H NMR overlay spectra in $CDCl_3$ of kinetic *N*-arylation of indole using 10 mol% CuI/**2** (1:1.5) as catalyst.

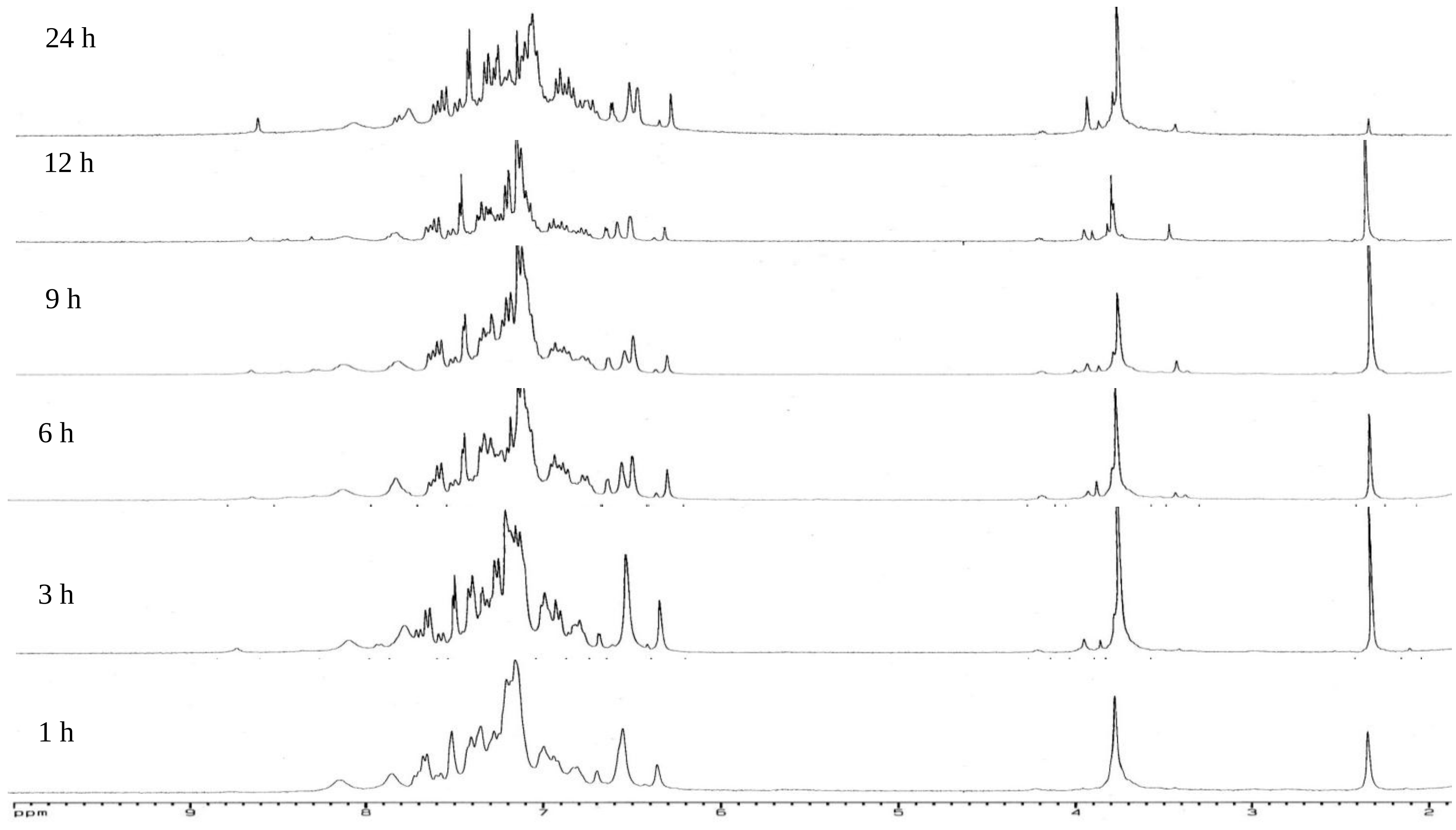

Figure A19 300 MHz 1D ^{1}H NMR overlay spectra in $CDCl_3$ of kinetic *N*-arylation of indole using 10 mol% CuI/**4** (1:1.5) as catalyst**.**

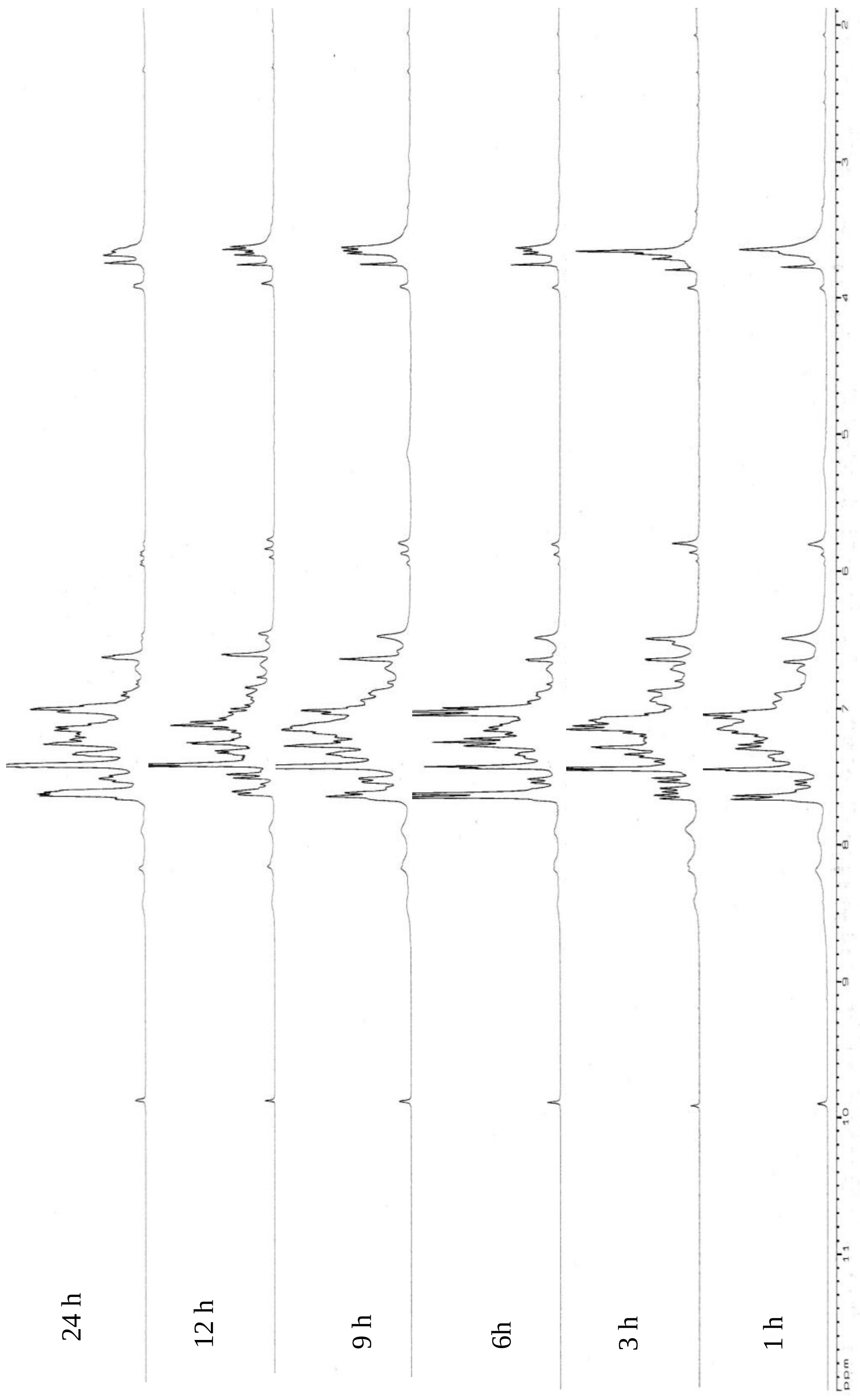

Figure A20 300 MHz 1D ^{1}H NMR overlay spectra in $CDCl_3$ of kinetic *N*-arylation of indole using 10 mol% CuI/**5** (1:1.5) as catalyst.

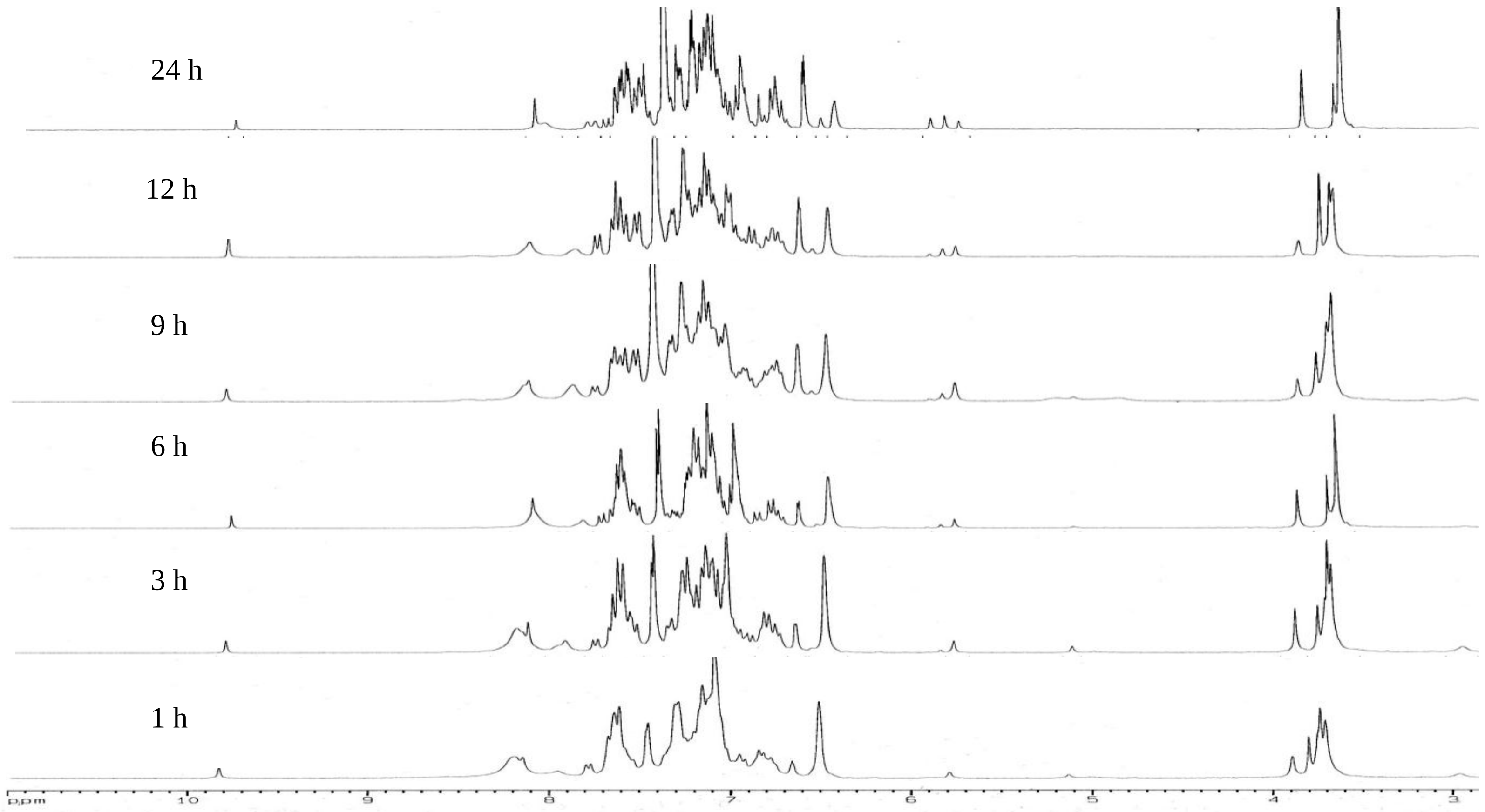

Figure A21 300 MHz 1D ^{1}H NMR overlay spectra in $CDCl_3$ of kinetic *N*-arylation of indole using 10 mol% CuI/**6** (1:1.5) as catalyst.

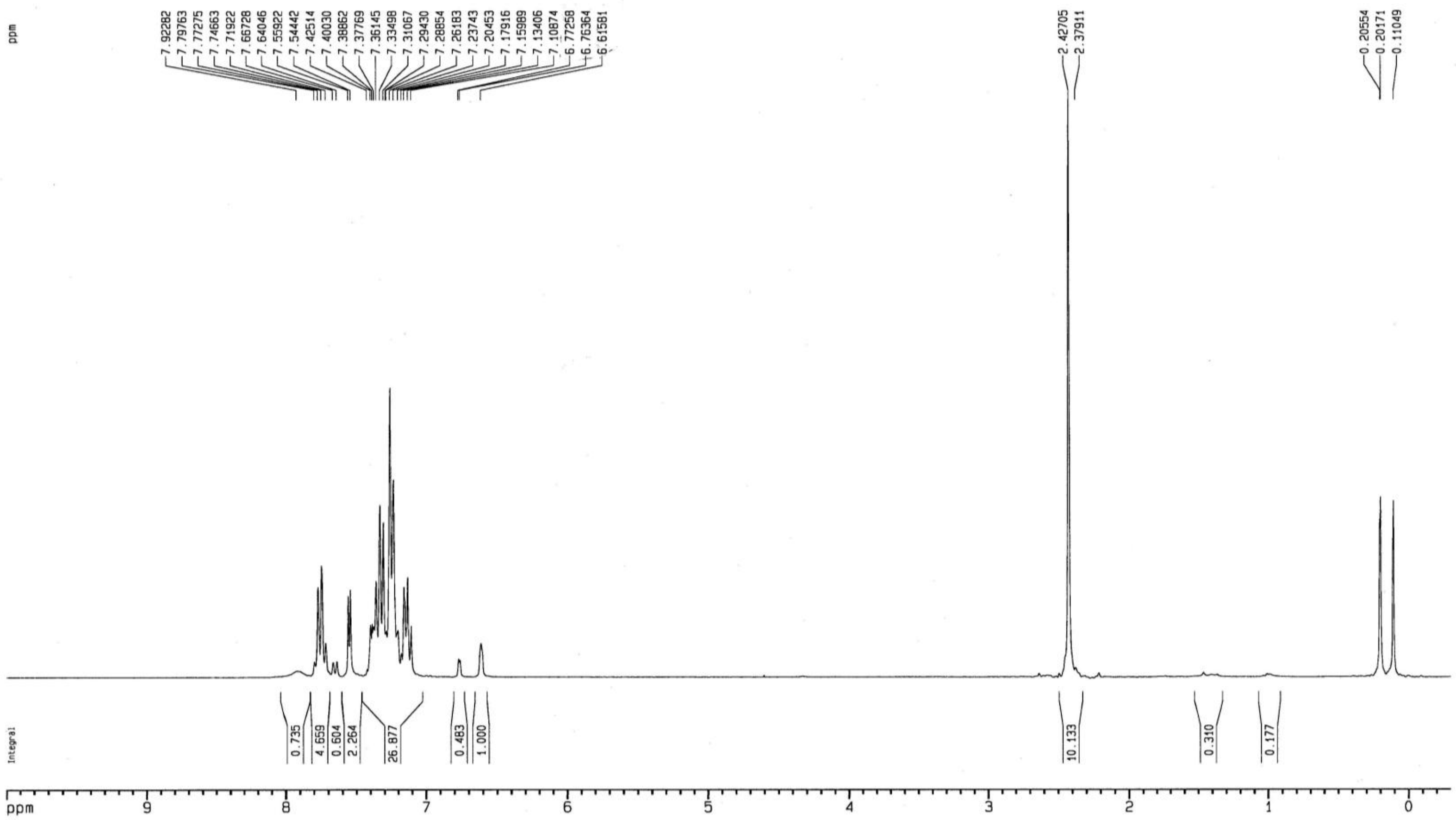

Figure A22 300 MHz 1D ^{1}H NMR spectrum in $CDCl_3$ of *N*-arylation of indole for 24h using CuNPs as catalyst.

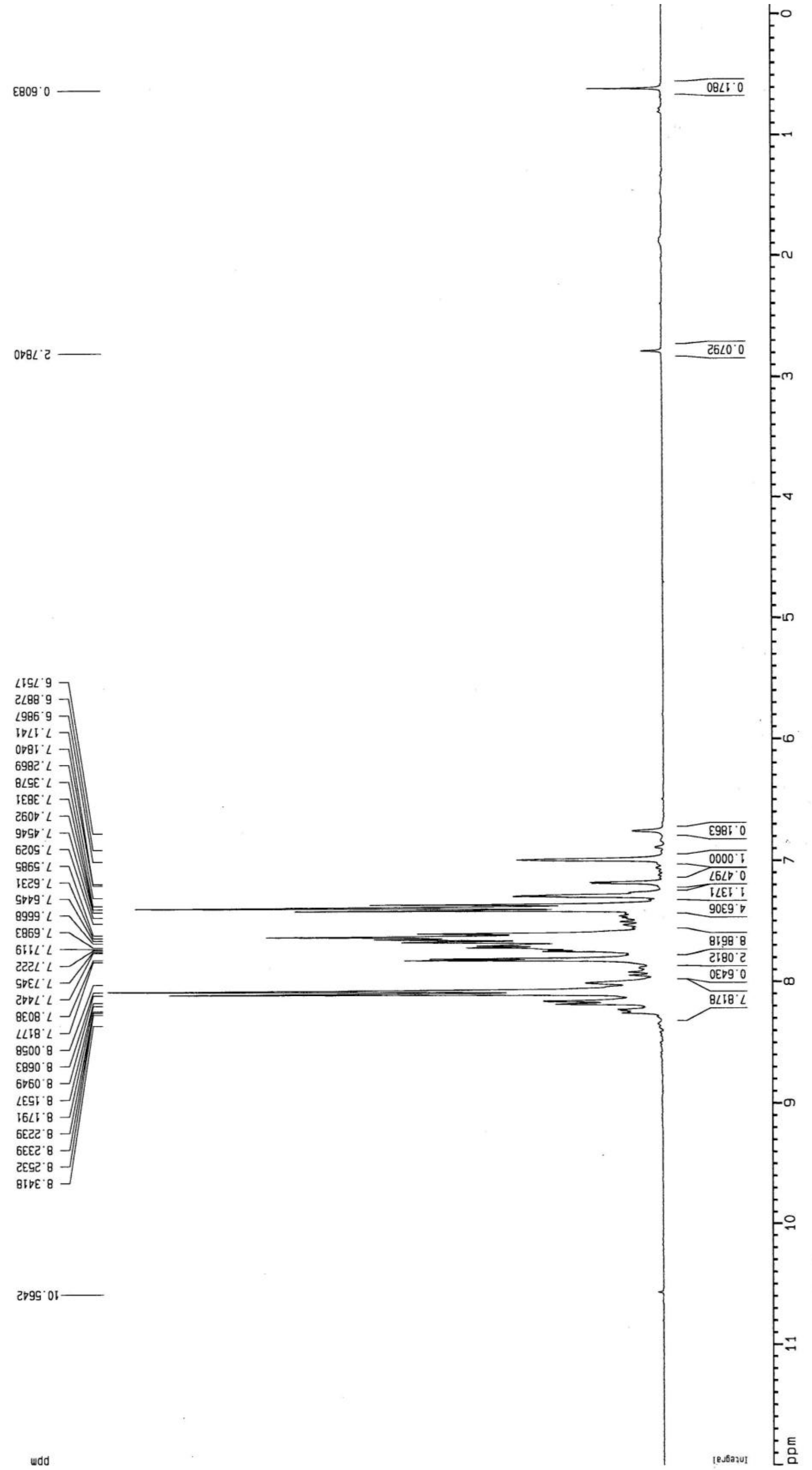

Figure A23 300 MHz 1D ^{1}H NMR spectrum in $CDCl_3$ of *N*-arylation of indole for 24h using CuI/**1** as catalyst.

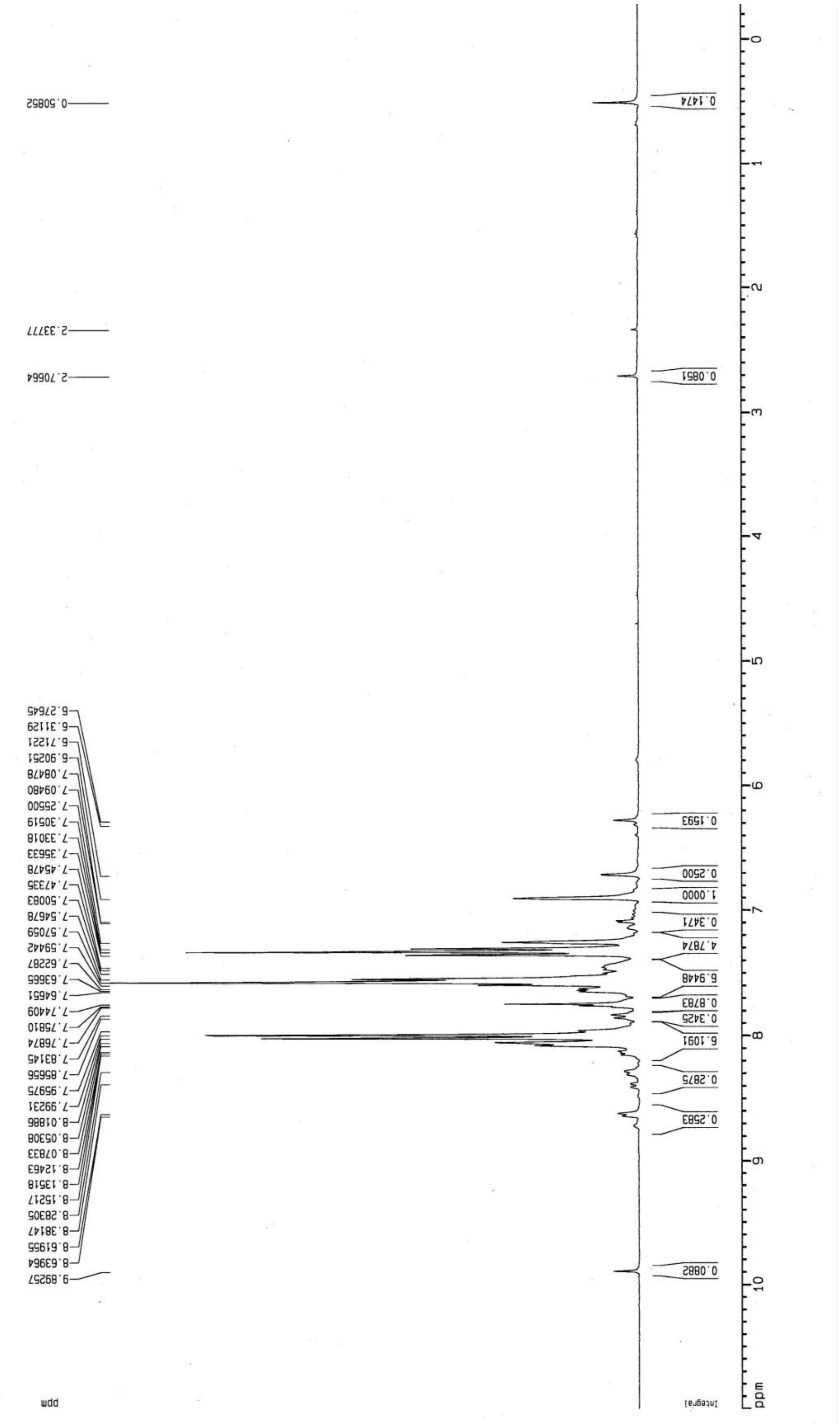

Figure A24 300 MHz 1D ^{1}H NMR spectrum in $CDCl_3$ of *N*-arylation of indole for 24h using CuI/**2** as catalyst.

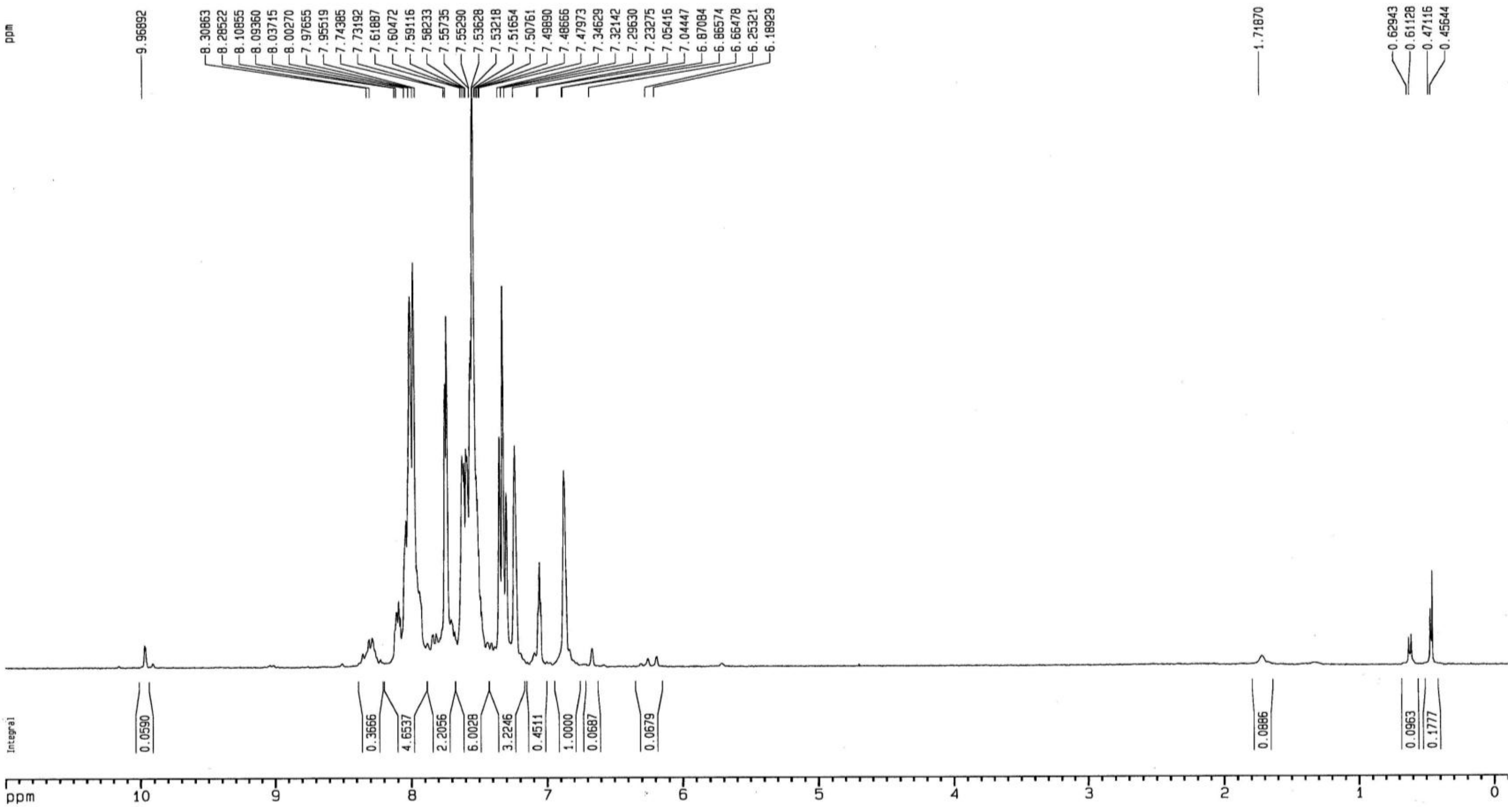

Figure A25 300 MHz 1D ^{1}H NMR spectrum in $CDCl_3$ of *N*-arylation of indole for 24h using CuI/**3** as catalyst.

BIOGRAPHY

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