One-Pot Synthesis of Carbazoles and γ-Carboline Derivatives Under Metal-Free Condition

M.Sc. Thesis

By

ISHA

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One-Pot Synthesis of Carbazoles and γ-Carboline Derivatives Under Metal-Free Condition

A THESIS

Submitted in partial fulfillment of the
requirements for the award of the degree
of
Master of Science

by
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DISCIPLINE OF CHEMISTRY
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CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis entitled **One-Pot Synthesis of Carbazoles and γ-Carboline Derivatives Under Metal-Free Condition** in the partial fulfillment of the requirements for the award of the degree of **MASTER OF SCIENCE** and submitted in the **DISCIPLINE OF CHEMISTRY, Indian Institute of Technology Indore**, is an authentic record of my own work carried out during the time period from July 2017 to June 2018 under the supervision of Dr. Sampak Samanta, Associate Professor, IIT Indore.

The matter presented in this thesis has not been submitted by me for the award of any other degree of this or any other institute.

Signature of the student with date
(Isha)

This is to certify that the above statement made by the candidate is correct to the best of my knowledge.

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M.Sc. thesis (with date)
(Dr. Sampak Samanta)

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Convener, DPGC
Date:

Signature of PSPC Member
Dr. Chelvam Venkatesh
Date:

Signature of PSPC Member
Dr. Manavendra N Mahato
Date:

Dedicated to My Parents……..

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ABSTRACT

This thesis describes the detailed investigation towards the synthesis of highly substituted carbazole derivatives and γ-carboline in a metal- free one-pot approach. Initially a general introduction for the synthesis of carbazoles and γ-carboline with historical background has been described. Next, towards our synthetic goals a detailed mechanistic as well as synthetic study has been accomplished for the synthesis of alknyl substituted carbazole derivatives via a Michael-Henry-aromatization sequential reaction of methyl 2-(3-formyl-1*H*-indol-2-yl)acetate with (*E*)-(2-nitrobut-1-en-3-yne-1,4-diyl)dibenzene. An extensive effort led us to the undesired methyl 3-nitro-2-aryl-9*H*-carbazole-1-carboxylate derivatives, instead of formation of alknyl substituted carbazole derivatives. Moreover, this thesis also contains a metal-free one-pot approach for the synthesis of γ- carboline through the reaction of ethyl (*E*)-2-(3-(2-nitrovinyl)-1*H*-indol-2-yl)acetate with benzaldehyde and ammonium acetate.

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ACRONYMS

OLEDs	Organic light emitting diodes
DMSO	Dimethyl sulfoxide
DMF	*N*, *N*-Dimethyl formamide
TMS	Tetramethylsilane
NMR	Nuclear magnetic resonance
SCE	Saturated calomel electrode
$PdCl_2(PPh_3)_2$	Dichlorobis(triphenylphosphine) palladium(II)
PPh_3	Tri-phenylphosphine
DCM	Dichloromethane
NBS	*N*-Bromosuccinimide
DFT	Density functional theory
HRMS	High Resolution Mass
$CDCl_3$	Chloroform-d
CuI	Copper Iodide
Et_3N	Triethyl Amine
THF	Tetrahydrofuran
DBU	1,8- Diazaicyclo [5,4,0]undec-7-ene
^{1}H NMR:	Proton NMR spectroscopy
^{13}C NMR:	Carbon- 13 NMR spectroscopy
Ppm:	Parts per million

NOMENCLATURE

π	pi
λ	Wavelength
δ	Chemical shift
nm	Nanometre
^{o} C	Degree Celsius
mmol	Millimole
mL	Millilitre
RT	Room temperature
δ	Chemical shift

CHAPTER 1

1. INTRODUCTION

This chapter highlights some of the biologically important heterocyclic compounds in the field of organic chemistry.

In the first part, background, synthesis, importance, classification of heterocyclic compounds and biological interesting compounds has been discussed briefly.

1.1 Heterocyclic compounds

A heterocyclic compound is one that contains a ring made up of more than one kind of atom[1-4]. In many of the cyclic compounds that we have studied so far benzene, naphthalene, cyclohexanol, cyclopentadiene the rings are made up of only of carbon atoms; such compounds are called homocyclic compounds. But there are also rings containing, in addition to carbon, other kinds of atoms, most commonly nitrogen, oxygen, or Sulphur; such compounds are called heterocyclic compounds.

Many natural drugs such as papaverine, quinine, atropine, procaine, reserpine, and morphine are heterocycles. Almost all the compounds we known as synthetic drugs are heterocycles. Some dyes (e.g. mauveine), luminophores, (e.g. acridine orange), pesticides (e.g. diazion) and herbicides (e.g. paraquat) are also heterocyclic in nature. Heterocycles containing carbazole moiety also exhibits biological activity [5-11].

In the biological world, heterocyclic compounds are everywhere. Carbohydrates are heterocyclic; so are chlorophyll and heme, which make leaves green and blood red and bring life to plants and animals. Heterocycles form the sites of reaction in many enzymes and coenzymes. Heredity comes down, ultimately, to the particular sequence of attachment of a half-dozen heterocyclic rings to the long chains of nucleic acids.

1.2 Carbazole Compounds

Carbazole is a heterocyclic aromatic organic compound. It has a tricyclic structure, consisting of two six membered benzene rings fused on either side of a five membered nitrogen containing ring. Alternatively, this compound can be considered as extension of indole moiety where one benzene ring is fused onto 2-3 positions of indole ring. Conventionally, the nomenclature has been assigned for carbazoles by denoting tricyclic carbazole ring system as A, B and C, and the numbering starts from ring A as shown in Figure 1. Carbazole was first isolated in 1872, almost 150 years ago, by Graebe and Glaser from the anthracene fraction of coal tar distillate [12-14].

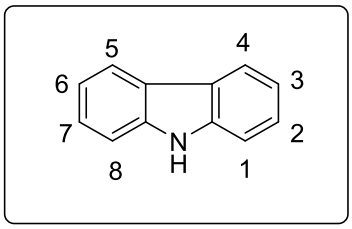


Figure 1. Structure of 9*H*- carbazole

Carbazole is a conjugated unit that has interesting optical and electronic properties such as its photoconductivity and photorefractivity. These moieties also exhibited a broad spectrum of therapeutic activities such as anti-bacterial, anti-fungal, anti-cancer, anti-HIV, anti-diabetes, anti-inflammatory etc. They also have many useful applications in materials science. e.g. in organic light emitting diodes (OLED), photovoltaic cells, field effect transistors.

Carbazoles have been studied for their unique electrical, electrochemical and optical-physical properties in the past decades. This kind of materials are typical hole transporting unit due to the electron donating character and can be easily modified with electron transport units in different position. It is believed that carbazole compounds have great promise as photoelectric functional materials for their photo physical and fluorescent properties in the blue light region.

Some structures of biologically active carbazole compounds.

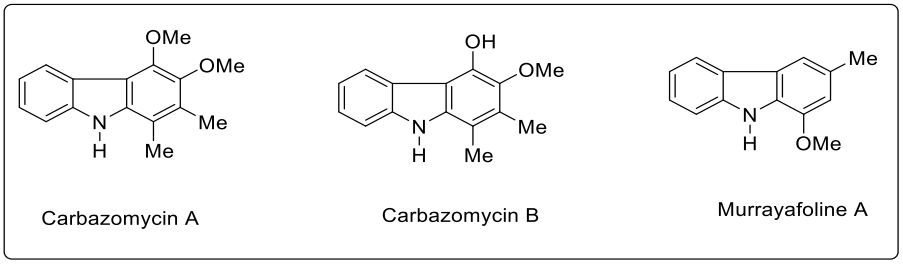


Figure 2. Examples of biologically active carbazole compounds.

Carbazomycins are important class of antibiotics with a carbazole framework. Carbazomycins A and B inhibit the growth of phytopathogenic fungi and have antibacterial and anti-yeast activities and Murrayafoline A, exhibited strong fungicidal activity.

1.3 γ-Carboline

Pyrido[4,3-*b*]indole is tricyclic ring structure consist of pyridine ring that is fused to an indole skeleton with molecular formula $C_{11}H_8N_2$ and commonly known as γ- carboline. The γ-carboline skeleton has been identified as a superior scaffold structure for their potential biological activity, namely as antipsychotic and antitumor agents. Over the years, this tricyclic aza-scaffold has been attracting a considerable interest in medicinal and synthetic organic chemistry due to it's a broad spectrum of biological activities such as anti-cancer, antibiotic, antipsychotic, anti-Alzheimer, antihistamine and anti-inflammatory activity [15-17].

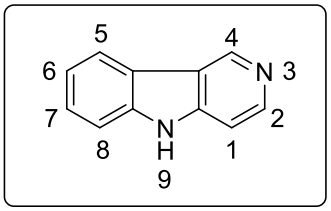
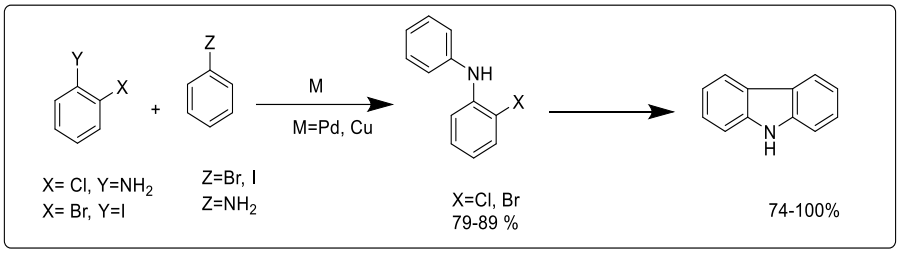


Figure 3. Representative structure of γ-carboline (pyrido[4,3-*b*]indole)

The synthesis of γ-carboline and its derivatives is always a delight for the medicinal chemist due to their indispensable biological importance.

1.4 Review of Past work

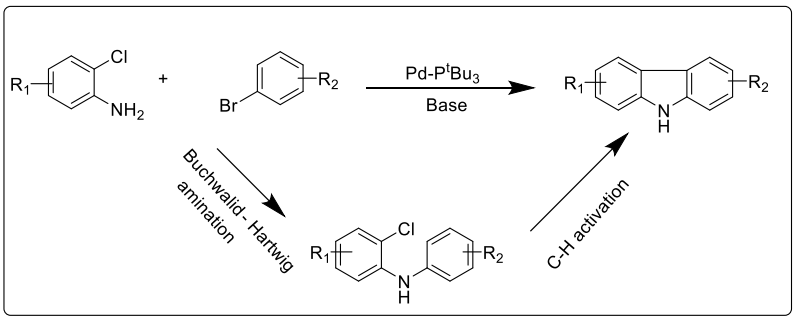
In 2009, Roberto A.Rossi and his coworkers reported synthesis of carbazoles by Intramolecular arylation of diarylamide anions in moderate to very good yields.



Scheme 1. Synthesis of substituted 9*H*- carbazoles

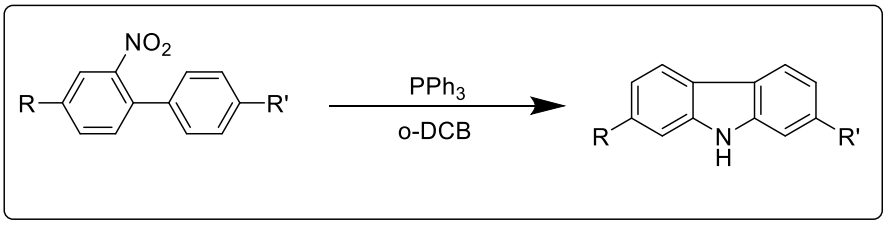
They synthesized substituted 9*H*- carbazoles by the photostimulated substitution reaction with diarylamines.

In 2006, Robin B.Bedford and his coworkers synthesized N-H carbazole from 2-Chloroanilines via consecutive amination and C-H activation [18].



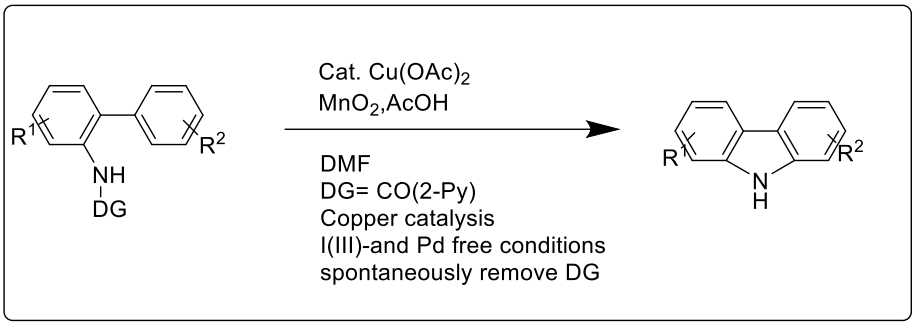
Scheme 2. Synthesis of N-H carbazole

In 2005, Adam W.Freeman coworkers synthesized carbazoles from reductive cyclization of 2- Nitrobiphenyls using triphenyl phosphine [19].



Scheme 3. Synthesis of carbazoles from reductive cyclization of 2-Nitrobiphenyls

In 2016, Masahiro Muira and his coworkers synthesized carbazoles by copper- catalyzed Intramolecular C-H/N-H coupling [20].



Scheme 4. Synthesis of carbazoles by copper- catalyzed intramolecular C-H/N-H coupling

1.5 Objective of the thesis

As we observed in review and past work, different methodologies have been used for the synthesis of substituted carbazoles. Various methods, among them the most common involve the palladium catalyst, intramolecular arylation of diarylamide anions, annulations of arynes with 2-haloacetamides, reductive cyclization of 2- Nitrobiphenyls using triphenyl phosphine, the domino N-H/C-H bond activation reaction of anilines with dihaloarenes, etc. were used for the synthesis of carbazole derivatives [21-25].

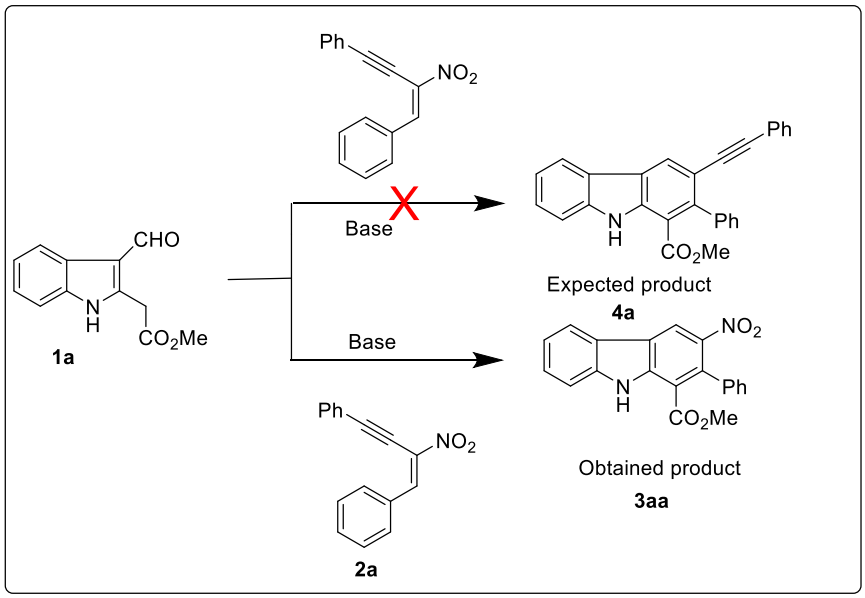
Transition metals (Cu, Pt, Au, Rh etc) were also used for the synthesis of carbazole derivatives.

However, many of these reactions have drawbacks like these reactions involve transition metal catalysis, harsh conditions, harmful side products. So, we developed a metal free methodology for the synthesis of carbazole compounds.

1.6 Present work

This work aims to synthesized compound methyl 2-phenyl-3-(phenylethynyl)-9*H*-carbazole-1-carboxylate (**4a)** via a base catalyzed Michael–Henry–aromatisation sequential processes. Therefore we performed reaction between methyl 2-(3-formyl-1*H*-indol-2-yl)acetate

(**1a**) and (*E*)-(2-nitrobut-1-en-3-yne-1,4-diyl)dibenzene (**2a**) using DABCO. But surprisingly the reaction didn't generate the expected compound methyl 2-phenyl-3-(phenylethynyl)-9*H*-carbazole-1-carboxylate (**4a).** Instead of that, methyl 3-nitro-2-phenyl-9*H*-carbazole-1-carboxylate (**3aa**) compound has been obtained.



Scheme 5. Proposed synthetic route for the synthesis of alknyl substituted carbazoles.

Chapter 2

2. Experimental section

2.1 Materials and Methods

All reactions were carried out under air and monitored by TLC using Merck 60 F_{254} pre coated silica gel plates (0.25 mm thickness) and the products were visualized by UV detection. Flash chromatography was carried out with silica gel (200-300 mesh). FT-IR spectra were recorded on a Bruker Tensor-27 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance (III) 400 MHz spectrometer. Data for ^{1}H NMR are reported as a chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, q = quartet, m = multiplet), coupling constant J (Hz), integration, and assignment, data for ^{13}C are reported as a chemical shift. High resolutions mass spectral analyses (HRMS) were carried out using ESI-TOF-MS. Compounds were named by using Chem Draw Ultra 12.0 and ACD NMR.

2.2 Procedure of starting material: (*E*)-(2-nitrobut-1-en-3-yne-1,4-diyl)dibenzene (1b)

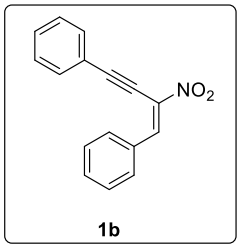
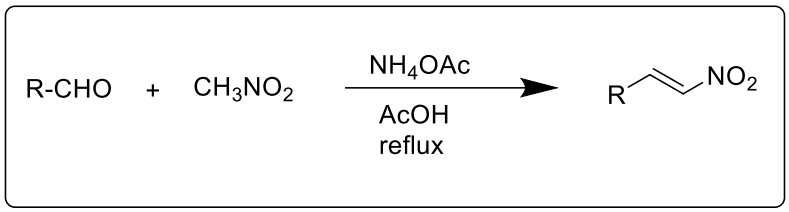


Figure 4. Structure of (*E*)-(2-nitrobut-1-en-3-yne-1,4-diyl)dibenzene.

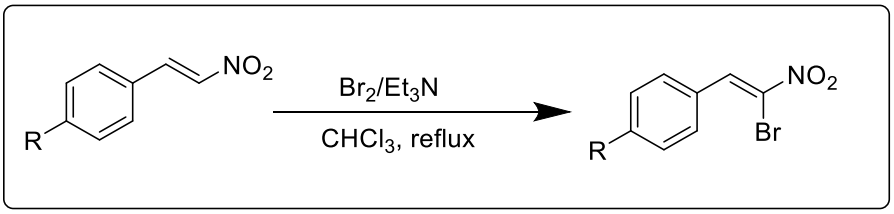
Aldehyde (10.0 mmol), nitromethane (20.0 mmol) and ammonium acetate (6 mmol) were added to 7 mL of glacial acetic acid. The resulting solution was refluxed for 4 h and then poured into ice water and extracted with CH_2Cl_2 (3×20 mL). The extract was washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using ethyl acetate and hexane as eluent.



Scheme 6. Synthesis of nitro styrene

General procedure for the preparation of 1-(2-Bromo -2-nitrovinyl) benzene

To a stirred solution of β- nitrostyrene (2 g, 0.013 mol) in $CHCl_3$ (10 mL) was added a solution of Br_2 (1 mL) in $CHCl_3$ (10 mL) at rt over 5 min; the mixture was refluxed for 35 min. The temperature was decreased to 8 °C and solution of Et_3N (5.6 mL, 0.04 mol) in $CHCl_3$ (50 mL) was added dropwise over 30 min. The mixture was maintained for 15 min and poured into a mixture of $CHCl_3$ (10 mL) and H_2O (400 mL). The organic layer was washed with H_2O (400 mL) and brine (2×250 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was recrystallized (EtOH).

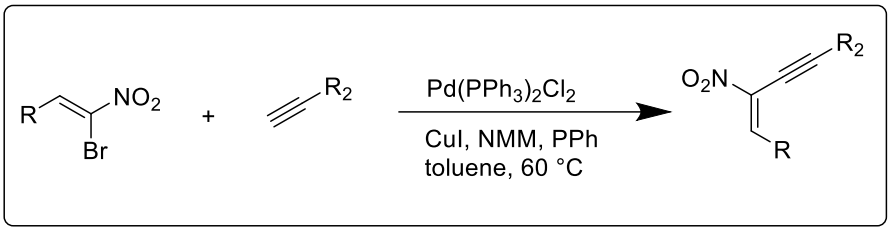


Scheme 7. Synthesis of α-Bromo Nitrostyrene

General procedure for electron deficient conjugated 1,3-enynes

To a solution of alkyne (5.2 mmol) in toluene (2 mL) was added Copper (I) iodide (2.0 mol%) and the reaction mixture was stirred at ambient temperature for 15 min. Meanwhile, a solution of β- bromo- nitro alkene (4.38 mmol) in toluene (2 mL) was added and the reaction mixture was stirred for 15 min. Now $Pd(PPh_3)_2Cl_2$ (2.5 mol%) was added in one portion followed by N-methyl morpholine (17.5 mmol) over 1 min. The reaction mixture was slowly warmed to 50-60 °C and the progress of this reaction was monitored by TLC analysis. It was cooled to ambient

temperature and diluted with CH_2Cl_2 and filtered. The organic layer was concentrated under reduced pressure and crude product was purified by silica gel column chromatography using ethyl acetate and hexane as eluent to give pure electron deficient conjugated 1,3 enynes.



Scheme 8. Synthesis of electron deficient conjugated 1,3-enynes

2.3 Synthesis of methyl 2-(3-formyl-1*H*-indol-2-yl)acetate (2b):

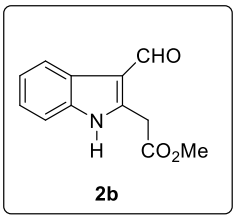
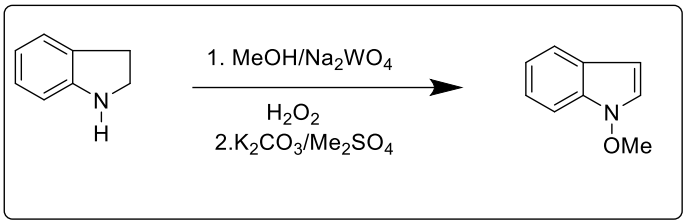


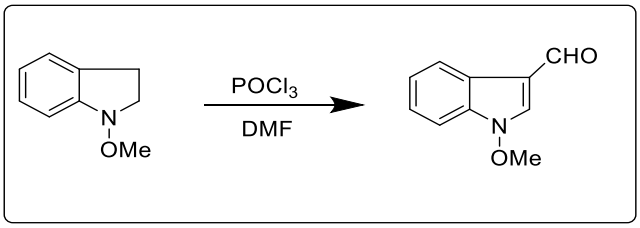
Figure 5. Structure of methyl 2-(3-formyl-1*H*-indol-2-yl)acetate :

Indoline (10.0 mmol) was added to 30-40 mL of methanol at 0 °C. After 10-15 min, Na_2WO_4 (2.0 mmol) was added to the resulting solution followed by the addition of H_2O_2 (~10 mL). The mixture was stirred for 15 min. After that, (30 mmol, 4.0 g) K_2CO_3 was added in the reaction mixture. Again reaction mixture was stirred for 10-15 minutes followed by the addition of dimethyl sulphate (25.0 mmol). The organic layer was washed with H_2O (400 mL) and brine (2×250 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was recrystallized (EtOH). Crude product was purified by silica gel column chromatography using ethyl acetate and hexane as eluent to give pure product.



Scheme 9. Synthesis of 1-methoxy-1*H*-indole

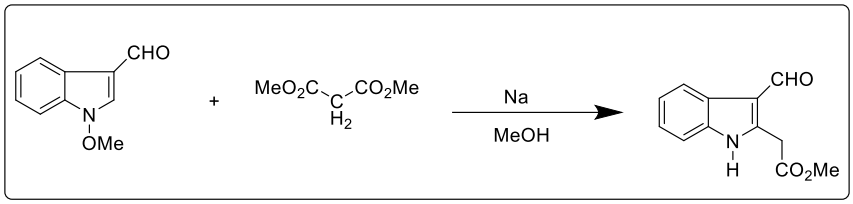
2.5 mL DMF was taken in round bottom flask followed by the addition of $POCl_3$ (12.4 mmol) dropwise. The reaction mixture was stirred for 15-20 minutes. The reaction condition was maintained at 0 °C. After 15-20 minute, 9.52 mmol of 1-methoxy-1*H*-indole was added to the resulting reaction mixture. After completion of the reaction, reaction mixture was neutralized by NaOH (2M) solution. The organic layer was washed with H_2O (400 mL) and brine (2×250 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was recrystallized (EtOH). Crude product was purified by silica gel column chromatography using ethyl acetate and hexane as eluent to give pure product.



Scheme 10. Synthesis of 1-methoxy-1*H*-indole-3-carbaldehyde

Sodium (1.05 g) was dissolved in dry MeOH in argon atmosphere at 0 °C and waited until all the sodium was dissolved. Once it dissolved, dimethyl malonate was added dropwise. The reaction mixture was stirred for 15 min. Then 1-methoxy -1*H*-indole-3-carbaldehyde (3.6 g) was added dropwise dissolving in MeOH. Then after 10-15 min, it was kept for reflux at 80 °C until starting material was fully consumed. After completion of the reaction, methanol was evaporated and the reaction mixture was neutralized by 2N HCl. The organic layer was washed with H_2O (400 mL) and brine (2×250 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was recrystallized (EtOH). Crude product was purified by silica gel column

chromatography using ethyl acetate and hexane as eluent to give pure product.



Scheme 11. Synthesis of methyl 2-(3-formyl-1*H*-indol-2-yl)acetate

2.4 Synthesis of starting material methyl (*E*)-2-(3-(2-nitrovinyl)-1*H*-indol-2-yl)acetate (3b):

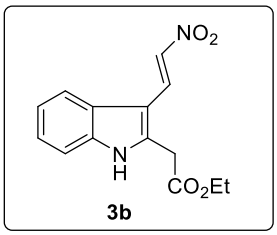
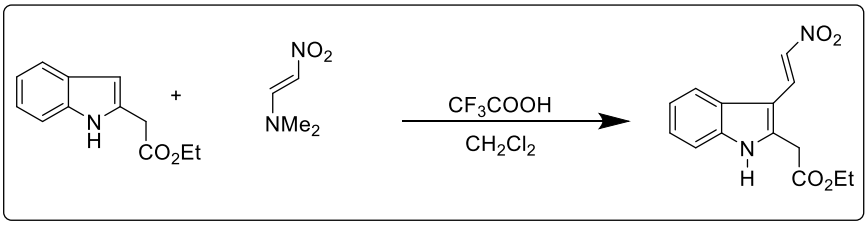


Figure 6. Structure of (*E*)-2-(3-(2-nitrovinyl)-1*H*-indol-2-yl)acetate:

(*E*)-N,N-dimethyl-2-nitroethen-1-amine (2.75 mmol), CH_2Cl_2 (5 mL), DCM (1 mL) were dissolved in round bottom flask and cooled at 0°C. After 10-15 min, 2.5 mmol of ethyl 2-(1*H*-indol-2-yl)acetate was added in the reaction mixture. The reaction mixture was stirred for 1 hr maintaining the reaction condition at 0 °C. The organic layer was washed with H_2O (400 mL) and brine (2×250 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was recrystallized (EtOH). The organic layer was concentrated under reduced pressure and crude product was purified by silica gel column chromatography using ethyl acetate and hexane as eluent to give pure product.

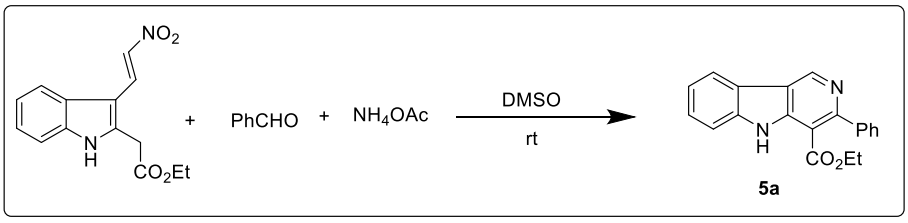


Scheme 12. Synthesis of ethyl (*Z*)-2-(3-(2-nitrovinyl)-1*H*-indol-2-yl)acetate.

2.5 Procedure for synthesis of compound 3aa:

0.1 mmol of methyl 2-(3-formyl-1*H*-indol-2-yl)acetate (**1a**) and 0.12 mmol of (*E*)-(2-nitrobut-1-en-3-yne-1,4-diyl)dibenzene (**2a**) were taken in round bottom flask. Then 0.5 mL THF was added followed by the addition of DABCO (0.3 eq). The reaction condition was maintained at 60 °C. After the completion of the reaction, solvent was evaporated. The organic layer was concentrated under reduced pressure and crude product was purified by silica gel column chromatography using ethyl acetate and hexane (1:9) as eluent to give pure product. Same procedure was followed for the synthesis of following compounds (**3aa-3ag**).

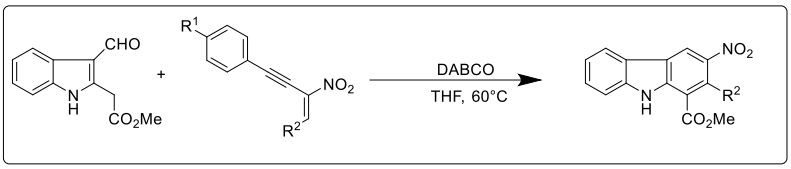
2.6 Procedure for synthesis of ethyl (*E*)-2-(3-(2-nitrovinyl)-1*H*-indol-2-yl)acetate (5a)



Scheme 13. Synthesis of ethyl (*E*)-2-(3-(2-nitrovinyl)-1*H*-indol-2-yl)acetate.

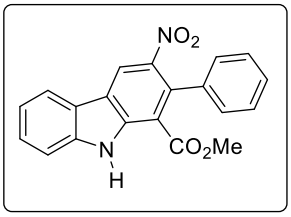
0.1 mmol of ethyl (*E*)-2-(3-(2-nitrovinyl)-1*H*-indol-2-yl)acetate, 0.12 mmol of benzaldehyde, 0.2 mmol of ammonium acetate were added in a round bottom flask. After that 10 mL DMSO was added to the reaction mixture at rt. After the completion of the reaction, brine solution was added to the reaction mixture. The organic layer was washed with H_2O (400 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was recrystallized (EtOH). The organic layer was concentrated under reduced pressure and crude product was purified by silica gel column chromatography using ethyl acetate and hexane as eluent to give pure product.

Scheme 14. Synthesis of carbazole



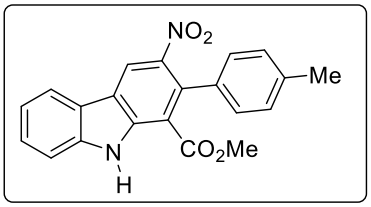
All the products were fully characterized by their corresponding spectroscopic data (^{1}H and ^{13}C NMR and HRMS).

1. Methyl 3-nitro-2-phenyl-9*H*-carbazole-1-carboxylate

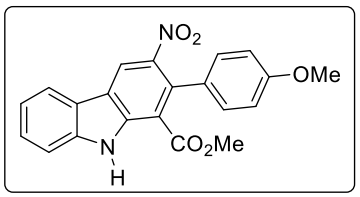


(3aa): light yellow solid; yield 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.0 (s, 1H), 8.72 (s, 1H), 8.12-8.14 (d, J = 7.8 Hz, 1H), 7.56-7.56 (m, 2H), 7.37-7.41 (m, 4H), 7.27-7.29 (m, 2H), 3.55 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 143.7, 141.4, 140.6, 137.0, 135.4, 128.5, 128.2, 127.8, 123.3, 122.2, 121.4, 120.1, 112.7, 111.8, 52.2; HRMS (ESI) m/z calcd for $C_{20}H_{14}N_2O_4[M+H]^+$ 347.1026, found 347.1098.

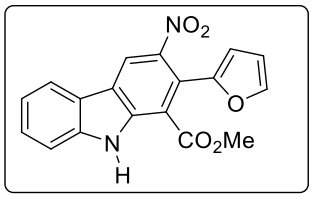
2. Methyl 3-nitro-2-(p-tolyl)-9*H*-carbazole-1-carboxylate



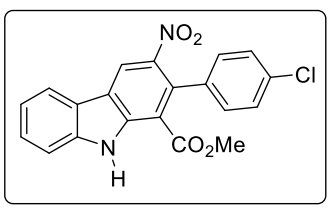
(3ab): light yellow solid; yield 68% ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 8.68 (s, 1H), 8.12 (d, J= 7.52 Hz, 1H) ,7.55(s, 1H), 7.37-7.37 (m, 2H), 7.15-7.22 (m, 5H), 3.59 (s, 3H), 2.42 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 141.4, 140.6, 137.0, 135.4, 128.5, 128.2, 127.7, 123.3, 122.2, 121.4, 121.0, 120.0, 112.7, 111.8, 52.2, 21.3; HRMS (ESI) m/z calcd for $C_{21}H_{16}N_2O_4[M+Na]^+$ 361.1183, 361.1185.

3. Methyl 2-(4-methoxyphenyl)-3-nitro-9*H*-carbazole-1-carboxylate (3ac) : 

light yellow solid; yield 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.0 (s, 1H), 8.71 (s, 1H), 8.13 (d, *J*= 7.76 Hz,1H), 7.57-7.57 (m, 2H), 7.49 (s, 1H), 7.38-7.39 (m, 1H), 7.19 (d, *J*= 8.04 Hz,1H), 6.92-6.94 (m, 1H), 3.96 (s, 3H), 3.64 (s ,3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 141.1, 140.3, 133.2, 128.4, 128.0, 123.2, 121.8, 121.2, 120.7, 119.8, 112.4, 111.5, 110.7, 55.9, 52.1; HRMS (ESI) m/z calcd for $C_{18}H_{12}N_2O_5[M+H]^+$ 337.0819, found 337.0825 .

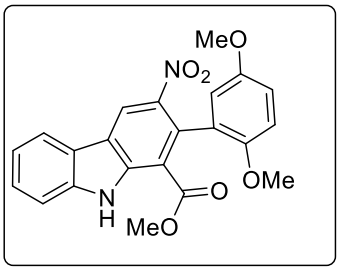
4. Methyl 2-(furan-2-yl)-3-nitro-9*H*-carbazole-1-carboxylate (3ad): 

light yellow solid; yield 74%; ^{1}H NMR (400 MHz, $CDCl_3$)): δ 10.02 (s, 1H), 8.73 (s, 1H), 8.12-8.12 (m, 1H), 7.56-7.59 (m, 3H), 7.38 (s,1H), 6.53-6.53 (m, 1H), 6.43-6.43 (s, 1H), 3.78 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 142.7, 140.9, 140.5, 128.3, 124.1, 123.5, 121.7, 121.3, 120.9, 119.8, 113.1, 111.5, 111.1, 109.7, 52.6 ; HRMS (ESI) m/z calcd for $C_{21}H_{16}N_2O_5[M+H]^+$ 377.1132, found 377.1138 .

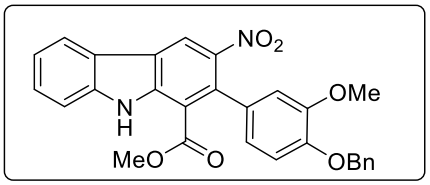
5. Methyl 2-(4-chlorophenyl)-3-nitro-9*H*-carbazole-1-carboxylate (3ae): 

light yellow solid; yield 80%; δ 10.07 (s, 1H), 8.74 (s, 1H), 8.12 (d, *J*= 8 Hz,1H), 7.57-7.58 (m, 2H), 7.36-7.40 (m, 3H), 7.21-7,23 (d, *J*= 8.2 Hz,2H), 3.60 (s, 3H) ppm; ^{13}C

NMR (100 MHz, $CDCl_3$) δ 167.0, 143.2, 141.2, 140.3, 135.2, 133.8, 133.5, 129.6, 128.0, 127.7, 123.2, 121.8, 121.2, 120.7, 119.9, 111.5, 52.0; HRMS (ESI) m/z calcd for $C_{20}H_{14}ClN_2O_4[M+H]^+$ 381.0637, found 381.0644

6. Methyl-2-(2,5-dimethoxyphenyl)-9*H*-carbazole-1-carboxylate (3af) : 

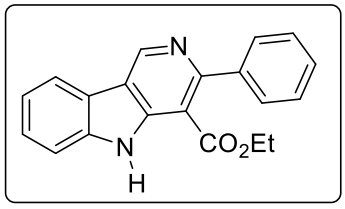
light yellow solid; yield 75%; ^1H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 8.77 (s, 1H), 8.10 (d, *J*= 7.5 Hz, 1H), 7.54-7.54 (s, 2H), 7.35 (s, 1H), 6.90-6.90 (m, 2H), 6.69 (s, 1H), 3.77 (s, 3H), 3.70 (s, 3H), 3.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 153.6, 151.0, 143.5, 141.7, 140.6, 131.9, 128.1, 127.4, 123.3, 122.3, 121.3, 121.0, 120.4, 115.6, 113.8, 111.7, 111.4, 56.3, 55.8, 52.3; HRMS (ESI) m/z calcd for $C_{22}H_{19}NO_4[M+H]^+$ 362.1387, found 362.1392

7. Methyl 2-(4-(benzyloxy)-3-methoxyphenyl)-3-nitro-9*H*-carbazole-1-carboxylate (3ag) : 

light yellow solid; yield 68%; δ 9.94 (s, 1H), 8.65 (s, 1H), 8.10-8.12 (d, *J*= 7.8 Hz ppm), 7.55-7.56 (m, 2H), 7.48 (d, *J*= 7.28 Hz, 2H), 7.35-7.40 (m, 3H), 7.31-7.34 (m, 1H), 5.20 (d, *J*= 6 Hz, 2H), 3.87 (s, 3H), 3.54 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 149.2, 147.9, 144.0, 141.3, 140.6, 137.1, 134.7, 129.9, 128.6, 128.1, 127.9, 127.5, 123.1, 122.2, 121.4, 121.1, 121.0, 119.7, 113.5, 113.0, 112.7,

111.7, 71.1, 56.2, 52.2 ; HRMS (ESI) m/z calcd for $C_{28}H_{20}N_2O_6[M+H]^+$ 483.1551, found 483.1556

8. Ethyl 3-phenyl-5*H*-pyrido[4,3-b]indole-4-carboxylate



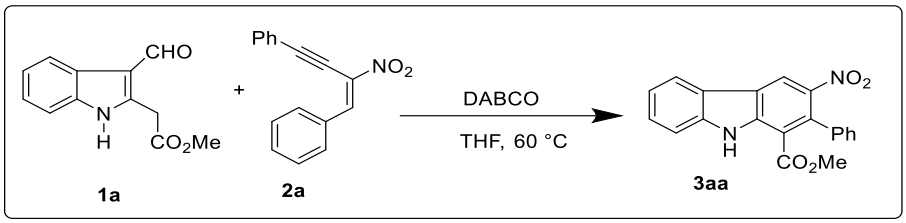
(5a) : light yellow solid; yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.84 (s, 1H), 9.25 (s, 1H), 8.05-8.07 (d, *J*= 7.8 Hz, 1H), 7.43-7.45 (m, 4H), 7.31-7.34 (m, 3H), 7.23-7.28 (m, 2H), 4.6 (q, *J*= 7.28 Hz, 3H) ppm ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 157.1, 145.3, 143.6, 142.1, 140.0, 129.1, 129.0, 127.9, 127.8, 127.5, 121.5, 121.1, 120.9, 119.8, 111.5, 61.1, 13.4 ppm; HRMS (ESI) m/z calcd for $C_{20}H_{16}N_2O_2[M+H]^+$ 317.1285, found 317.1289 .

CHAPTER 3

3. Results and Discussion

Screening of solvent and catalyst

3.1 Initially, we began our study with a model reaction between methyl 2-(3-formyl-1*H*-indol-2-yl)acetate (**1a**) with (*E*)-(2-nitrobut-1-en-3-yne-1,4-diyl)dibenzene (**2a**) for the screening of catalysts and reaction conditions.



Scheme 15. Synthesis of methyl 3-nitro-2-phenyl-9*H*-carbazole-1-carboxylate.

Table 2. Reactions conditions optimization

Entry	Catalyst	Solvent	T/h	Temp (^{0}C)	Yield (%)
1.	DABCO	THF	9	60	76
2.	DABCO	Toluene	9	60	65
3.	DABCO	MeCN	9	60	70
4.	DABCO	MeOH	9	60	68
5.	Et_3N	THF	9	60	62
6.	DBU	THF	9	60	64
7.	Hünig's base	THF	9	60	70

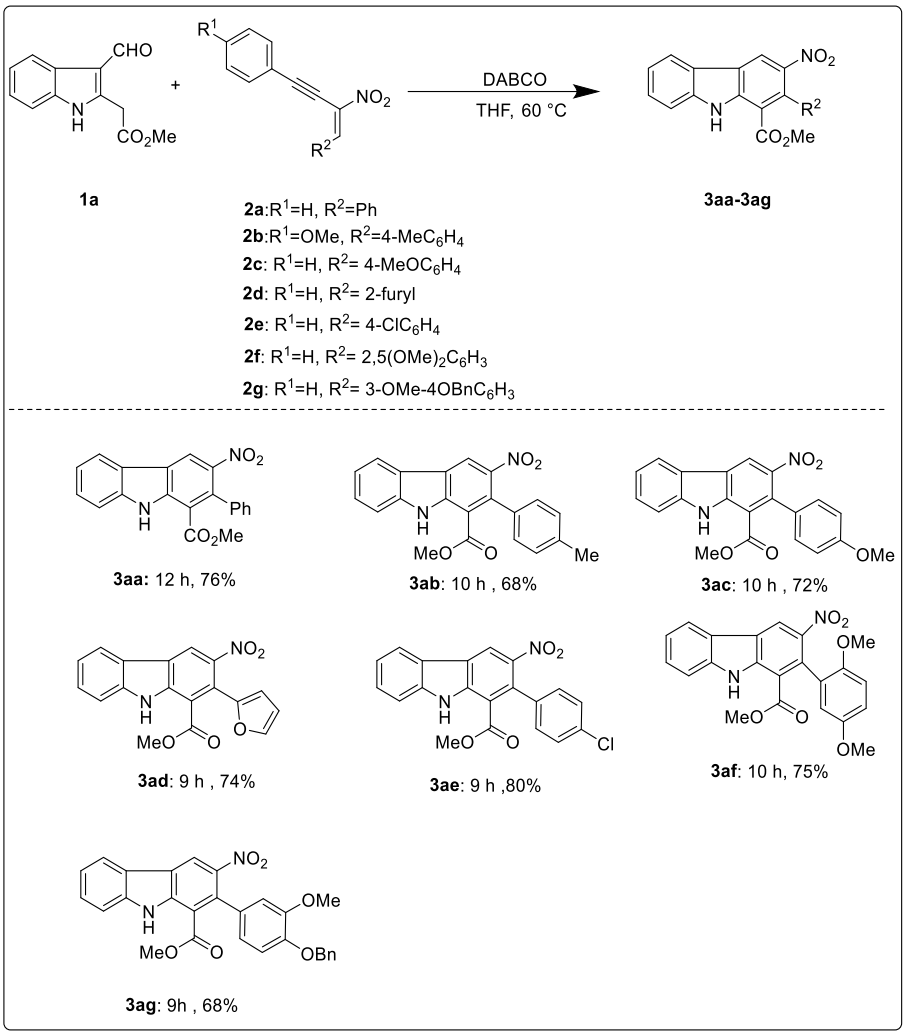
In the beginning, the reaction was performed in THF in the presence of catalyst DABCO for 9 h at 60 °C. In this, we obtained 76% yield of the desired product.

This result motivates us to investigate the above reaction with several organic solvents. Then, we used toluene at 60 °C and stirred for 9h. In this we observed that reaction didn't occur properly and we obtained 65% yield of the desired product. After that, we tried for some other solvents like methanol, acetonitrile, etc. Among all these, we analyzed that THF is the best solvent for the target reaction as we obtained better yield in the case of THF. Moving ahead, we also used different catalyst Et_3N, DBU, Hünig's base. The best result was found in DABCO with THF as solvent, maintaining the reaction conditions at 60 °C for 9h with almost 78% yield.

3.2 Generality of the reaction

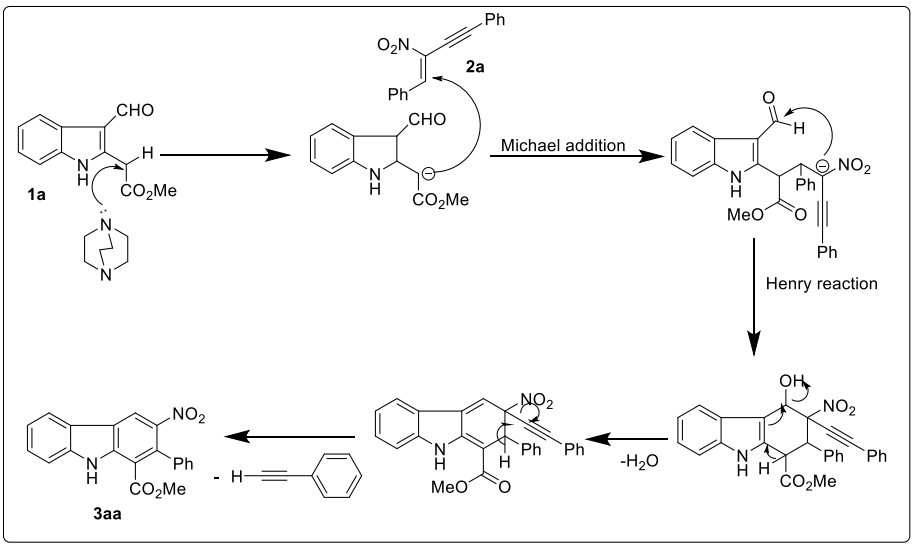
We studied a group of substituted nitro enynes (**2a-2g**) with methyl 2-(3-formyl-1*H*-indol-2-yl)acetates using 30 mol% DABCO as a catalyst under our standard conditions. From the table, we concluded that both the electron donating (Me, OMe, and OBn) and electron withdrawing (Cl, etc.) substituents on aryl ring of nitroenyne reacted smoothly with (**1a),** leading to the formation of substituted carbazoles in moderate to good yields. During our investigations, we had noticed that enyne with electron withdrawing group on aryl ring reacted slightly faster than electron donating group. (**2e**, **2f**) reacted smoothly with substrate (**1a**) providing the desired carbazoles (**3ae**, **3af**) in high yields (75-80%). On the other hand, electron donating group on aryl ring (**2b**, **2g**) of nitro enyne providing the desired carbazoles (**3ab**, **3ag**) in moderate yields (65-68%).

Table 3. Generality of the reaction



3.3 Mechanism of the reaction

On the basis of the above results, we proposed the following probable mechanism for the formation of carbazoles. In the following step, tetrahydrocarbazole is formed via a domino Michael- Henry reaction of (**1a)** with (**2a)** in the presence of DABCO. Next, an intermediate is generated by protonation of secondary hydroxyl group followed by dehydration as depicted in scheme 16. Finally, the carbazole is formed followed by the elimination of phenyl acetylene.



Scheme 16. Mechanism for substituted carbazoles.

CHAPTER 4

4.1 CONCLUSION and SCOPE FOR FUTURE WORK

A new methodology has been presented for the synthesis of alkynl substituted carbazole derivatives via the reaction of methyl 2-(3-formyl-1*H*-indol-2-yl)acetate (**1a**) with (*E*)-(2-nitrobut-1-en-3-yne-1,4-diyl)dibenzene (**2a**) using DABCO in THF. The current protocol provides unexpected methyl 3-nitro-2-phenyl-9*H*-carbazole-1-carboxylate carbazoles with diverse substitution in good yields. In future, this study will help us to design and synthesized new electron deficient enyne system for the synthesis of alkynl substituted carbazole derivative.

SPECTRAL DATA

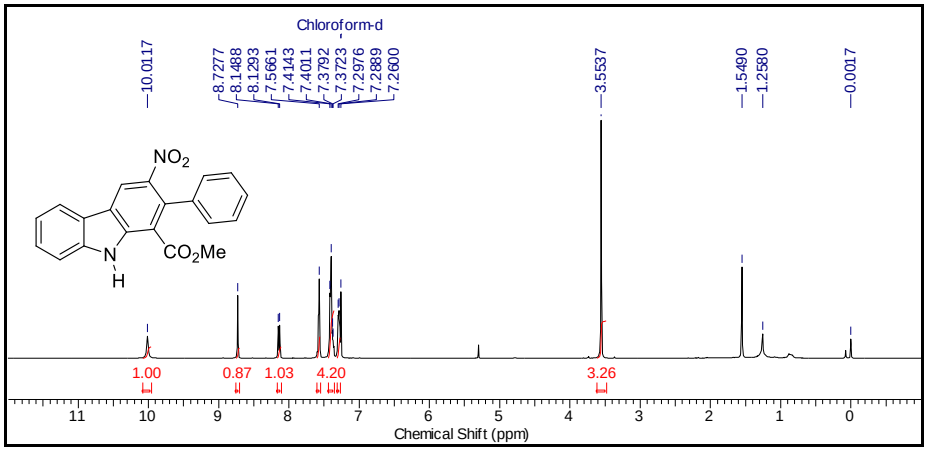


Figure 8. 400 MHz ^{1}H NMR spectrum of **3aa** in $CDCl_3$.

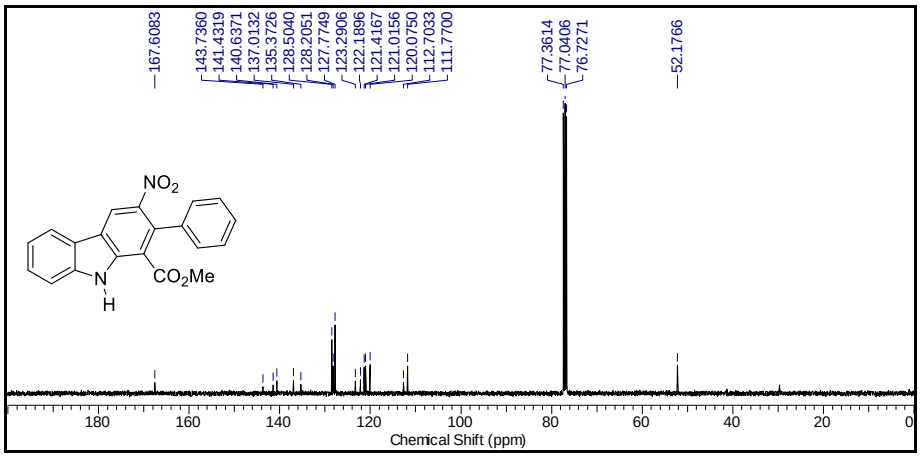


Figure 9. 100 MHz ^{13}C NMR spectrum of **3aa** in $CDCl_3$.

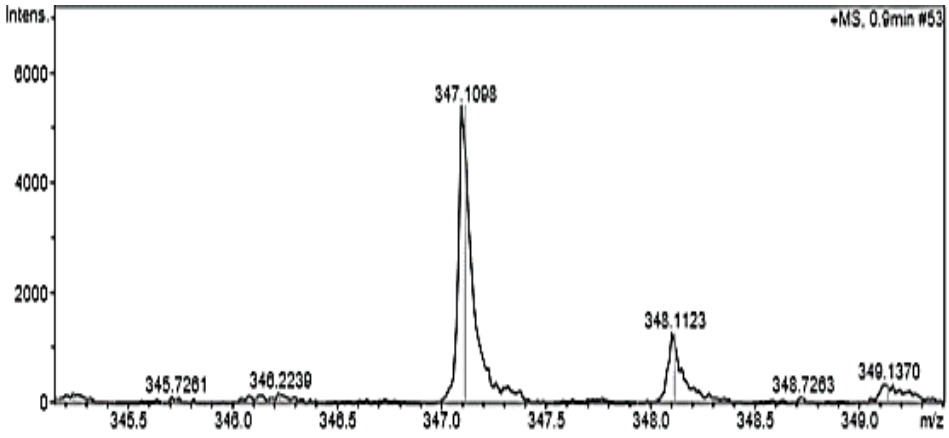


Figure 10. HRMS spectrum of **3aa**

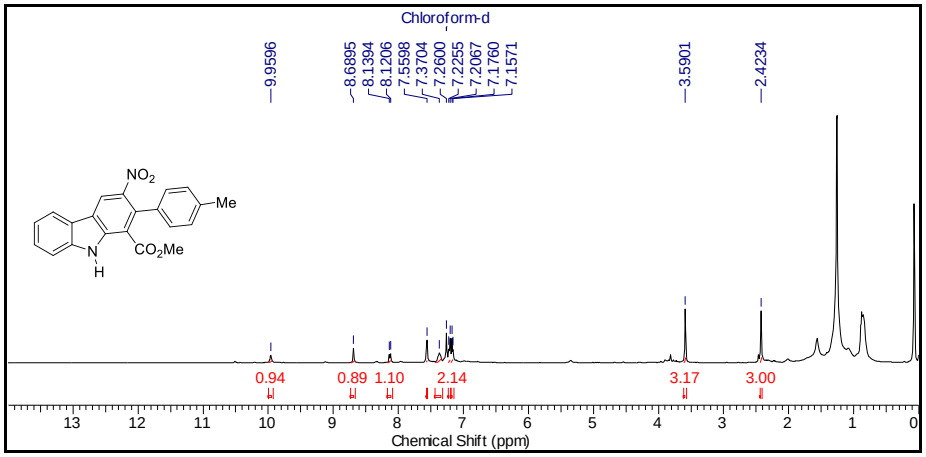


Figure 11. 400 MHz ^{1}H NMR spectrum of **3ab** in $CDCl_3$.

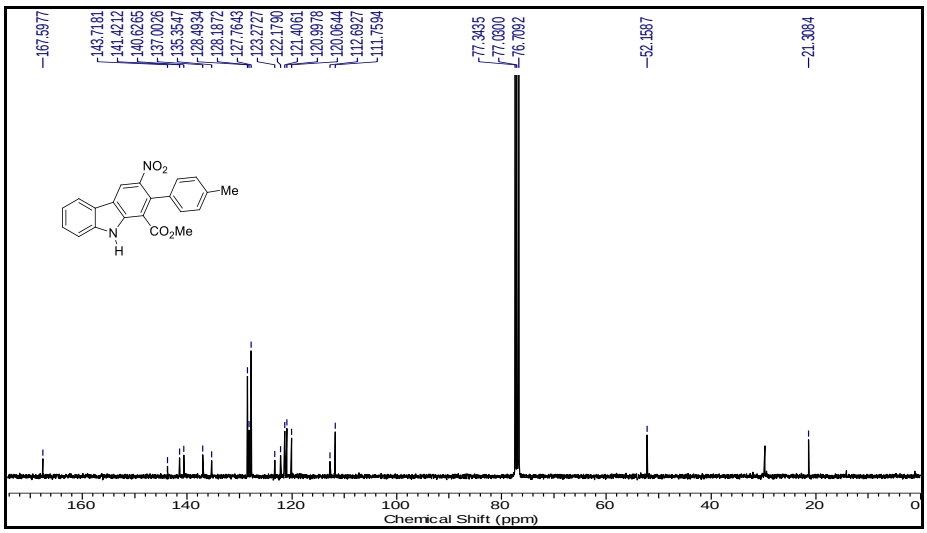


Figure 12. 100 MHz ^{13}C NMR spectrum of **3ab** in $CDCl_3$.

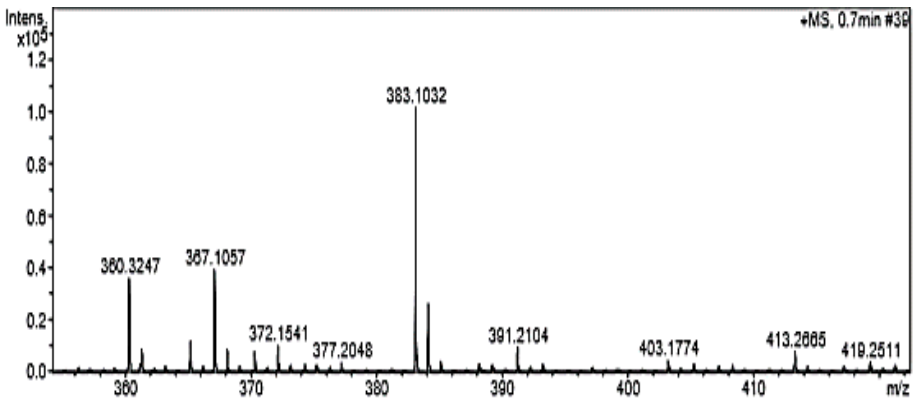


Figure 13. HRMS spectrum of **3ab.**

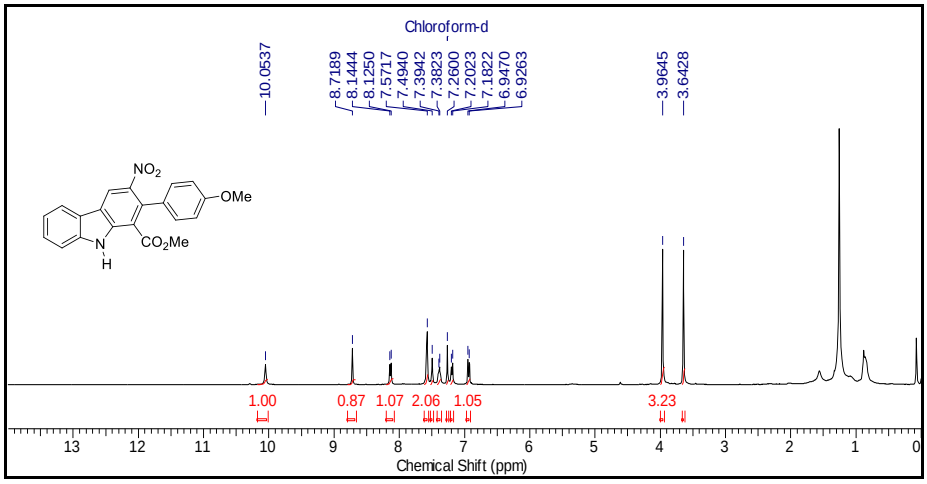


Figure 14. 400 MHz ^{1}H NMR spectrum of **3ac** in $CDCl_3$.

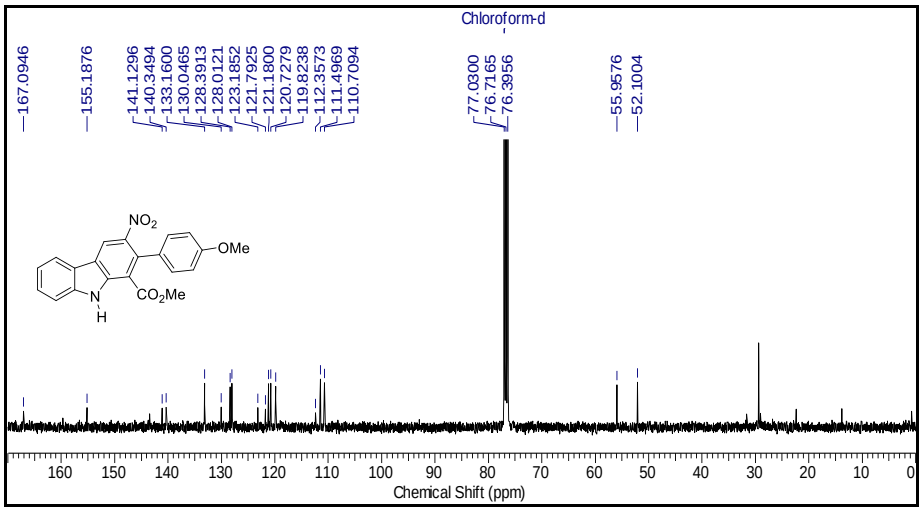


Figure 15. 100 MHz ^{13}C NMR spectrum of **3ac** in $CDCl_3$.

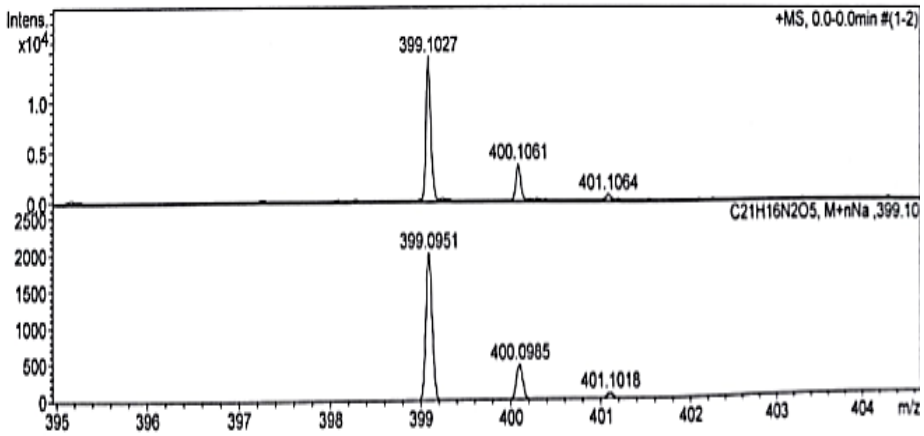


Figure 16. HRMS spectrum of **3ac.**

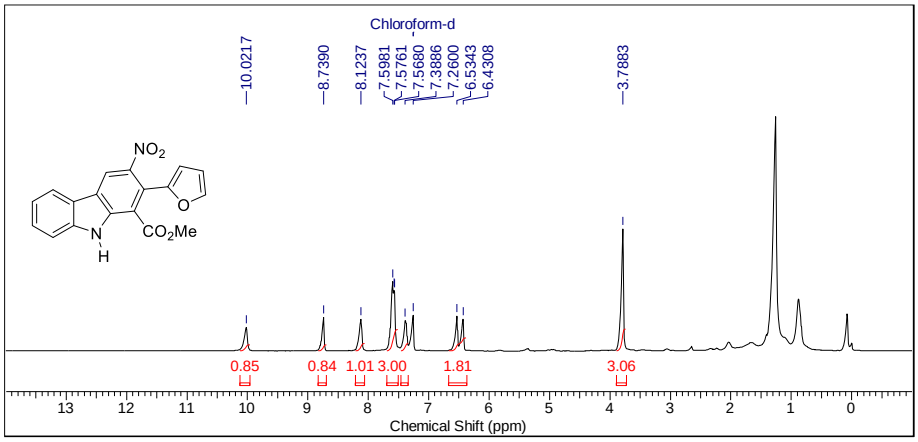


Figure 17. 400 MHz ^{1}H NMR spectrum of **3ad** in $CDCl_3$.

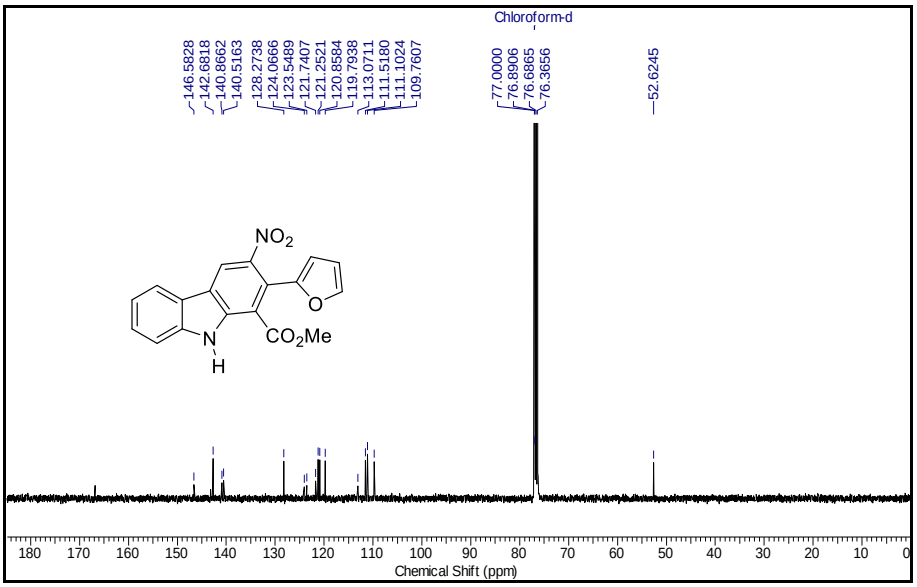


Figure 18. 100 MHz ^{13}C NMR spectrum of **3ad** in $CDCl_3$.

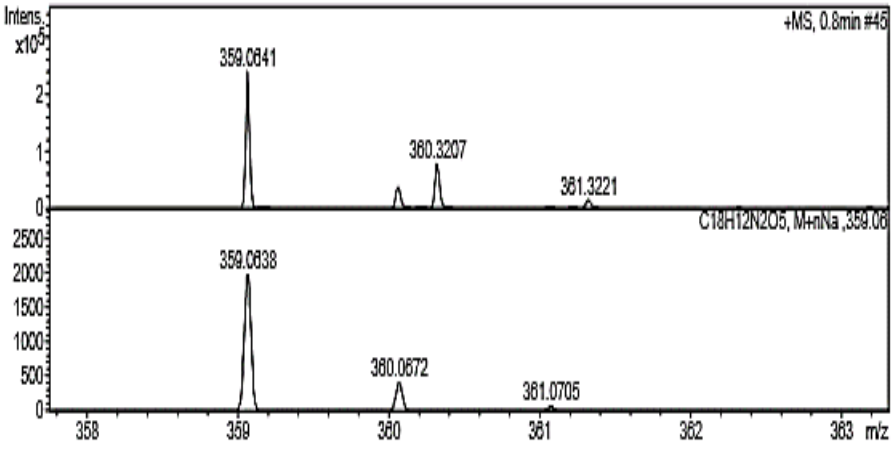


Figure 19. HRMS data of **3ad.**

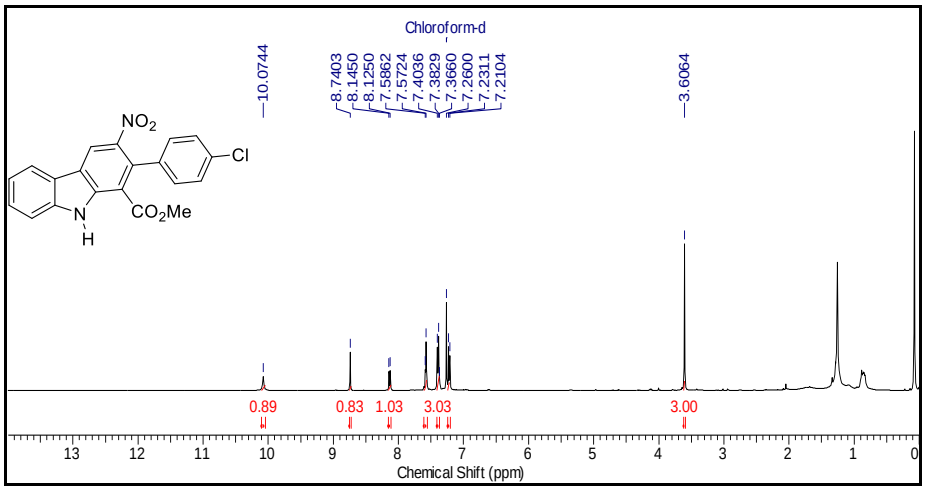


Figure 20. 400 MHz ^{1}H NMR spectrum of **3ae** in $CDCl_3$.

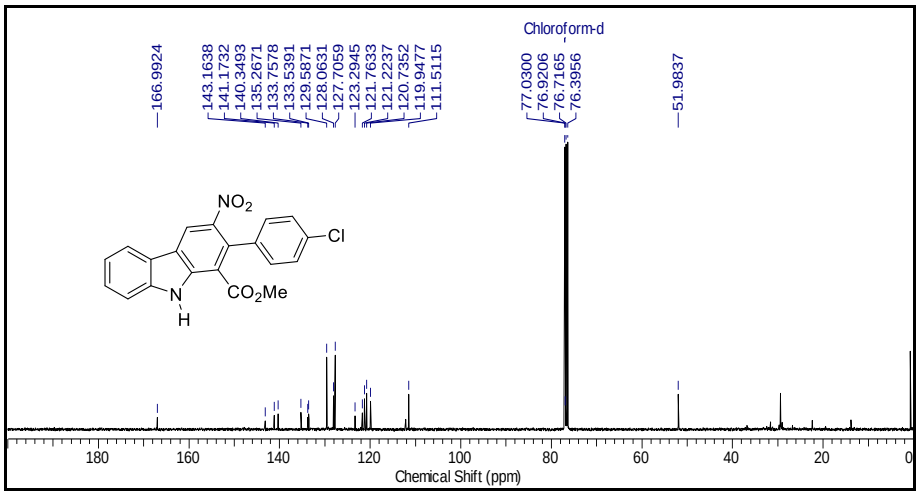


Figure 21. 100 MHz ^{13}C NMR spectrum of **3ae** in $CDCl_3$

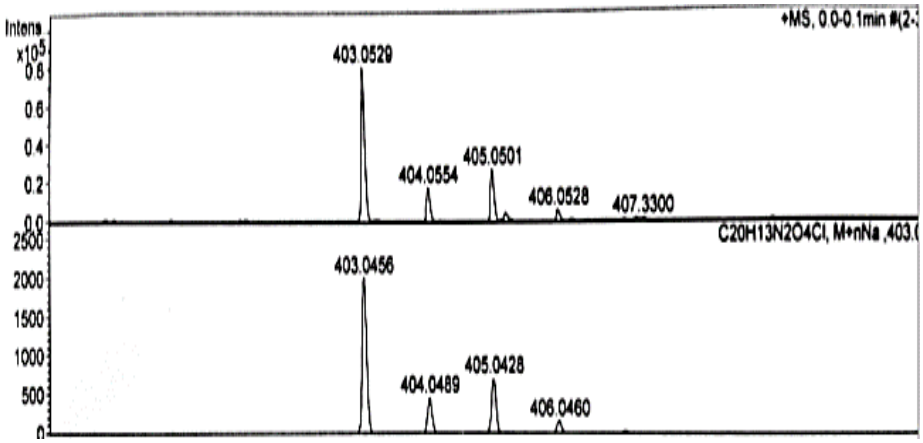


Figure 22. HRMS spectrum of **3ae.**

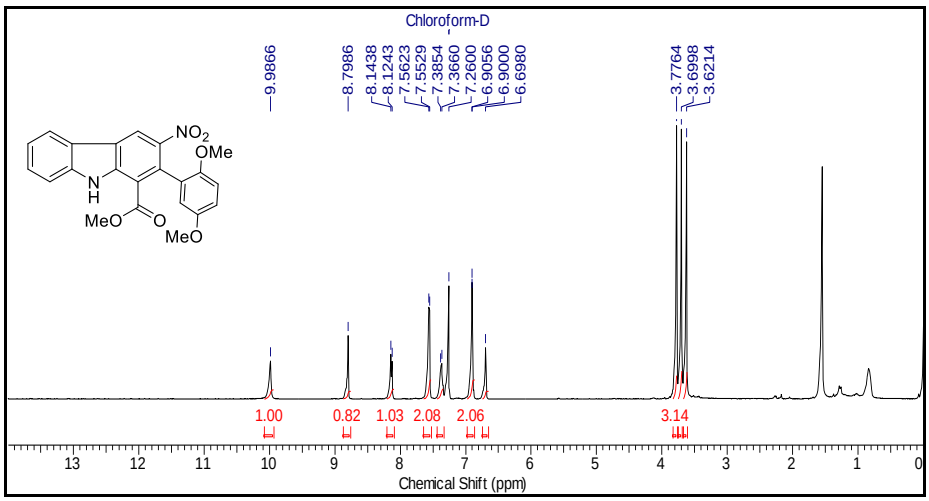


Figure 23. 400 MHz ^{1}H NMR spectrum of **3af** in $CDCl_3$.

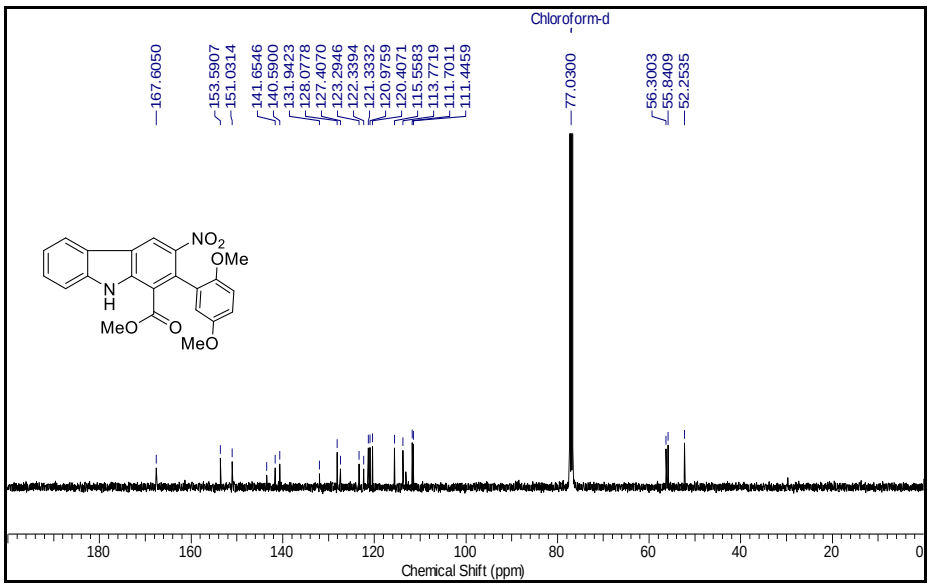


Figure 24. 100 MHz ^{13}C NMR spectrum of **3af** in $CDCl_3$.

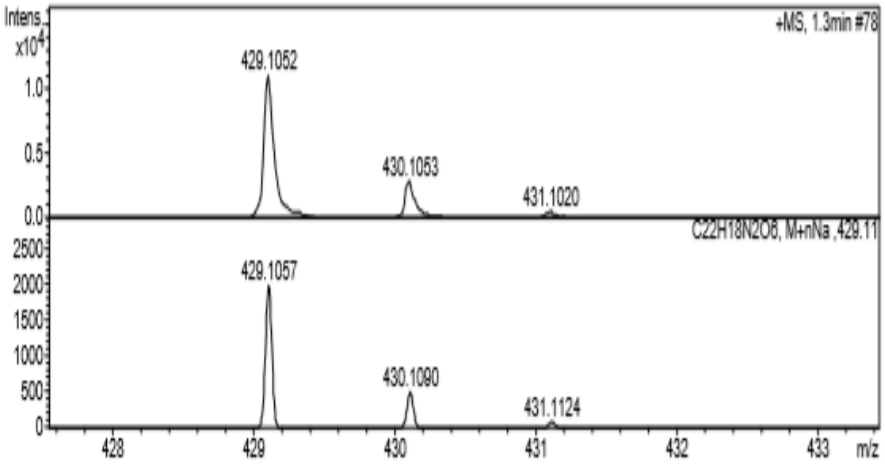


Figure 25. HRMS spectrum of **3af.**

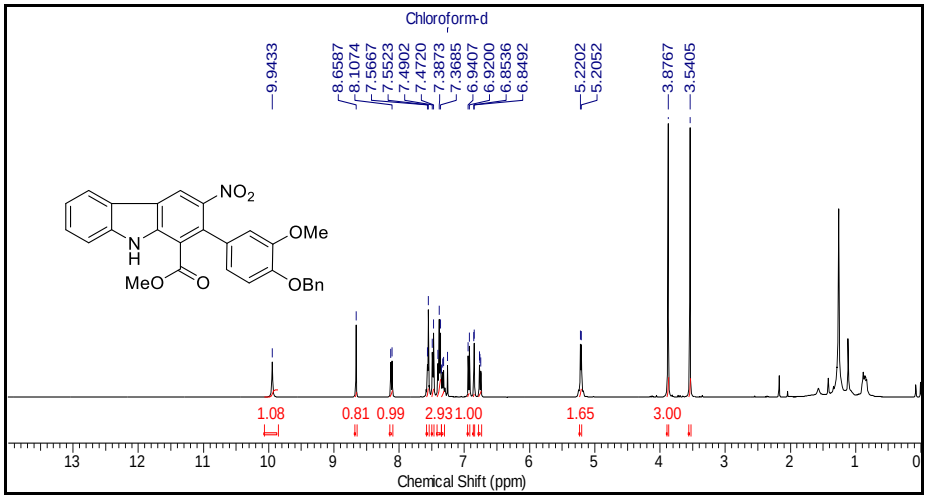


Figure 26. 400 MHz ^{1}H NMR spectrum of **3ag** in $CDCl_3$.

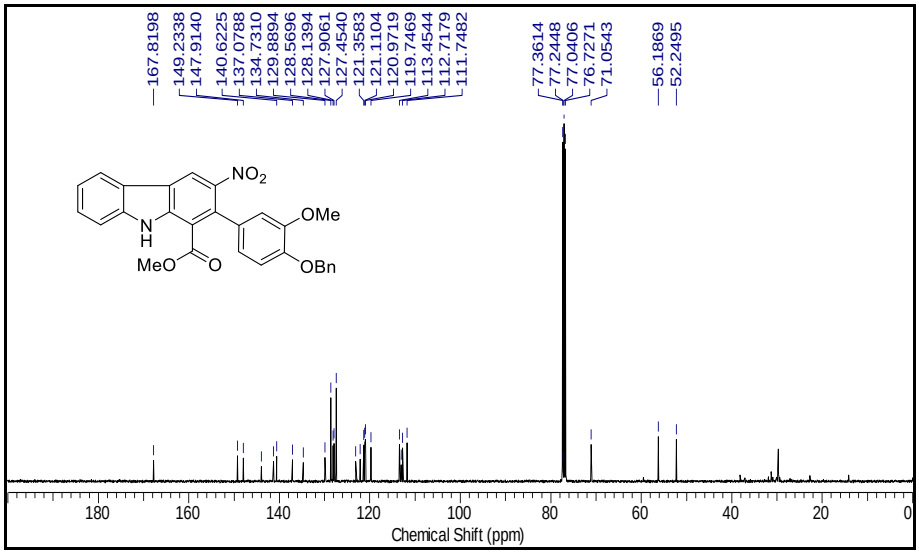


Figure 27. 100 MHz ^{13}C NMR spectrum of **3ag** in $CDCl_3$.

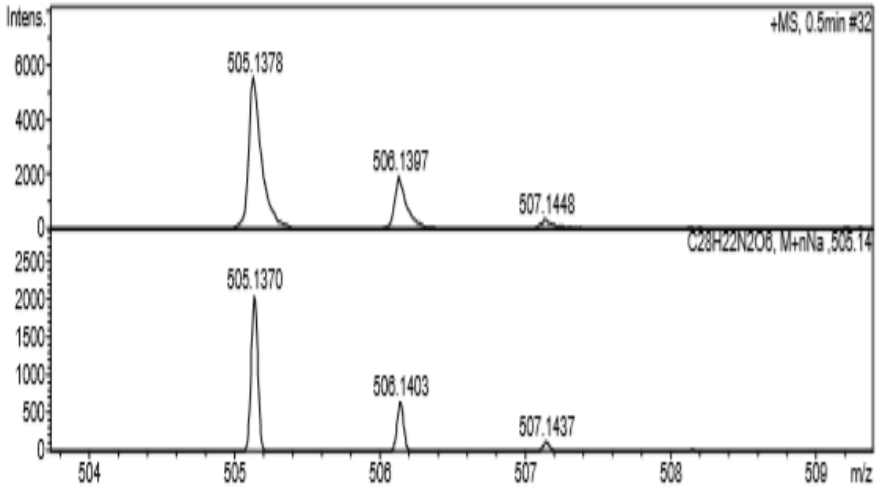


Figure 28. HRMS Spectrum of **3ag**.

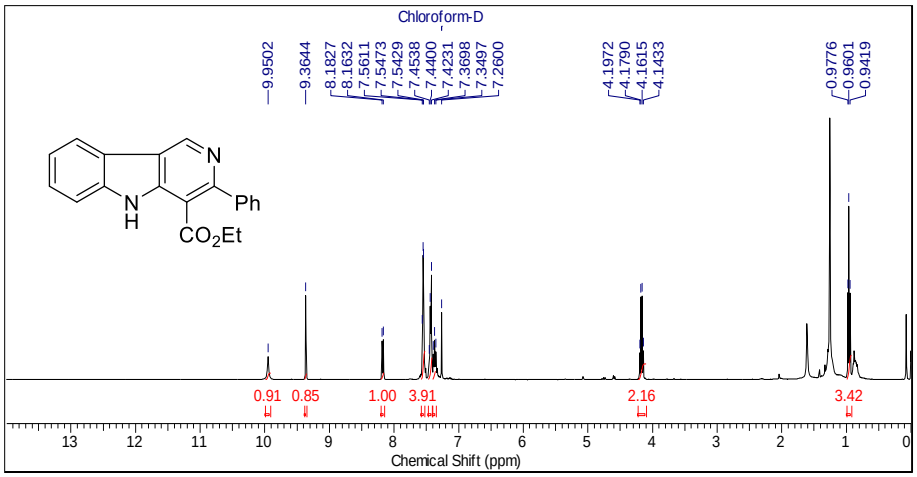


Figure 29. 400 MHz ^{1}H NMR spectrum of **5a** in $CDCl_3$.

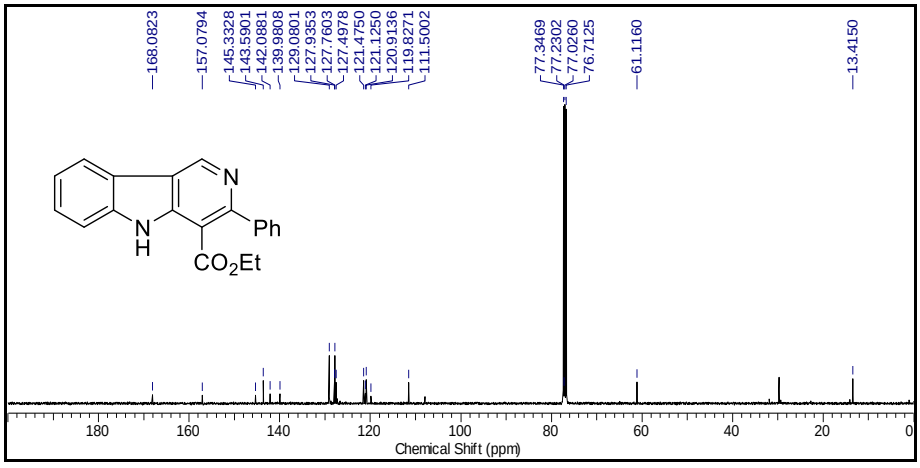


Figure 30. 100 MHz ^{13}C NMR spectrum of **5a** in $CDCl_3$.

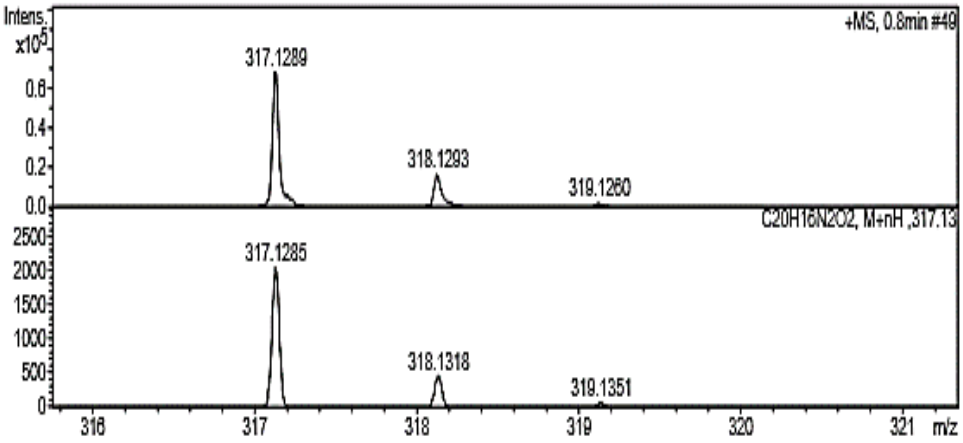


Figure 31. HRMS spectrum of **5a.**

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