Synthesis of Pyrazole-Functionalized Cyclopropanes via Base Promoted Aza-Michael Addition

M.Sc. Thesis

By

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DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY

INDORE

(2025-2026)

Synthesis of Pyrazole-Functionalized Cyclopropanes via Base Promoted Aza-Michael Addition

A THESIS

Submitted in partial fulfillment of the requirements

for the award of the degree

of

Master of Science

by

MANISH SHARMA



DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY

INDORE

(2025-2026)

INDIAN INSTITUTE OF TECHNOLOGY INDORE

CANDIDATE'S DECLARATION

I hereby declare that the work which is being presented by me in the thesis entitled **"Synthesis of Pyrazole-Functionalized Cyclopropanes via Base Promoted Aza-Michael Addition"** in the partial fulfillment of the requirements for the award of the degree of **MASTER OF SCIENCE** and submitted in the **DEPARTMENT OF CHEMISTRY, Indian Institute of Technology, Indore,** is an authentic record of my own work carried out during the time period from June 2025 to May 2026 under the supervision of **Prof. Sampak Samanta,** 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.

(Manish Sharma)

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

Signature of the Supervisor
(Prof. Sampak Samanta)

MANISH SHARMA has successfully given his M.Sc. Oral Examination held on **21-05-2026.**

Signature of supervisor

(prof. Sampak Samanta)

Date: 21-05-2026

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Manish Sharma

Department of Chemistry

Abstract

Here, we synthesized a series or pattern of N-cyclopropyl pyrazole derivatives with good yield. In the presence of a base under heating conditions, this reaction proceeds via an aza-Michael reaction involving pyrazoles as Michael donors and in situ produced cyclopropanecarboxylates as Michael acceptors. Notably, this approach has a good substrate scope and is straightforward.

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ACRONYMS

ACN	Acetonitrile
$CDCl_3$	Chloroform-D
DMSO	Dimethyl sulfoxide
DCM	Dichloromethane
DBU	1,8- Diazabicylo[5,4,0]undec7-ene
DABCO	1,4- Diazabicyclo[2,2,2]octane
DBN	1,5- Diazabicyclo[4,3,0]non-5-ene
DMF	N, N-diethyl formamide
EtOAc	Ethyl Acetate
HRMS	High-Resolution Mass Spectroscopy
THF	Tetrahydrofuran
M	Molar
NMR	Nuclear Magnetic Resonance
UV	Ultra Visible Spectroscopy
PPM	Parts Per Million

NOMENCLATURE

cm	Centimetre
°C	Degree Celsius
mmol	Milimole
mL	Mililitre
rt	Room temperature
δ	Chemical shift

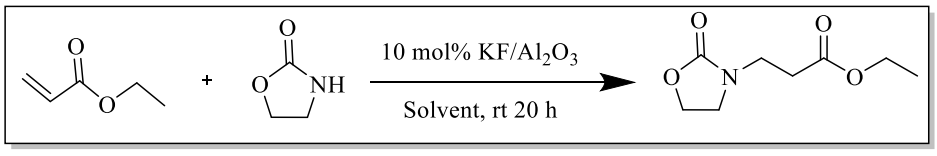
CHAPTER 1: INTRODUCTION

1.1 General Introduction

The chemistry of diazo compounds is very broad and interesting. Diazo compounds are very useful compounds for organic synthesis, especially for the formation of carbene intermediates or also 1,3-dipoles in cycloaddition reaction under thermal conditions. Diazo compounds have more applications in medicinal chemistry and they are very useful to build synthetic building blocks. The heating of vinyl diazo compounds was easily converted into pyrazoles which are very useful heterocyclic compounds for showing biological activities like analgesic, anticancer, antidepressant, etc. 1-Chlorocyclopropanecarboxylates are important activated cyclopropane derivatives widely used in organic synthesis. 1-Chlorocyclopropanecarboxylate generate cyclopropene in the presence of a base, which act as an efficient Michael acceptor that reacts well with in situ generated pyrazoles from vinyl-diazo ketones, an excellent Michael donor, forming aza Michael adduct.

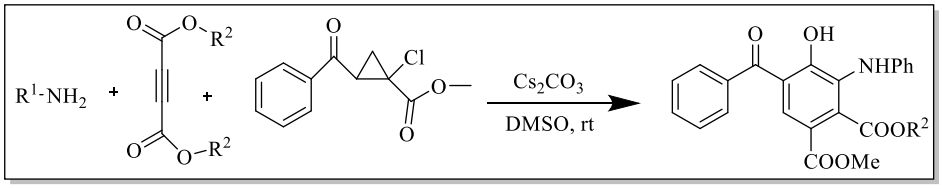
1.2 Review Work

It was in 2005 that Chun-Gu Xia's group developed a simple Michael addition of carbamates to α, β-unsaturated esters to synthesize N-protected β-aminocarbonyl compounds. **(Scheme 1).** [1]



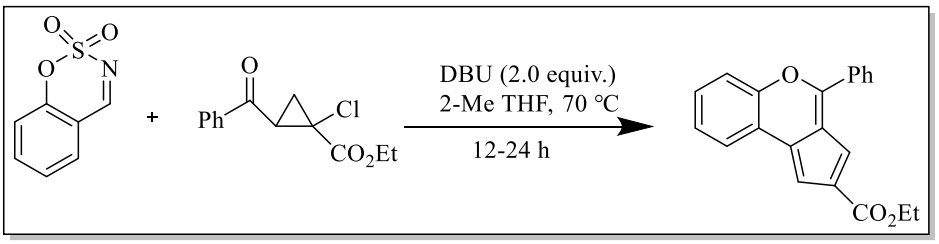
Scheme 1: Conjugate addition of carbamates to α, β-Unsaturated esters derivatives

In 2018, Yoefa Gong's group developed a three-component reaction of 1-chlorocyclopropanecarboxylates, alkyne diesters, and amines promoted by Cs_2CO_3 to synthesize substituted 2-aminophenols in high yields. The process involves [3+3] cycloaddition between enamine and cyclopropane intermediate formed in situ. **(Scheme 2).** [2]



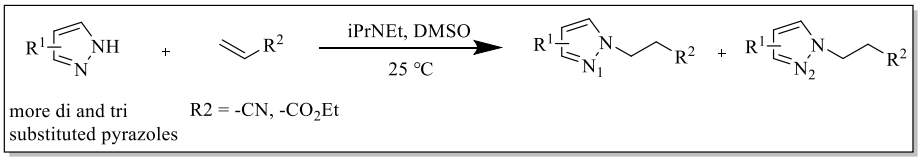
Scheme 2: One pot synthesis of substituted 2- aminophenols

Our group also developed a domino approach of pentafulvene frameworks which is formed by cyclopropane derivatives which act as effective Michael acceptor with N-sulphonyl ketimines in 2021. **(Scheme 3).** [3]



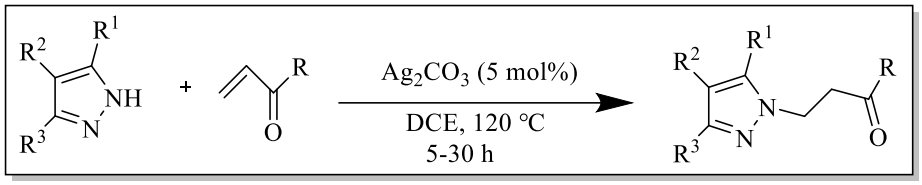
Scheme 3: Domino approach of Pentafulvene

In order to produce N-alkylated pyrazoles with excellent regioselectivities, Adrian Huang's group also performed addition reaction of pyrazoles with alkenes for Michael adduct in 2022. **(Scheme 4).** [4]



Scheme 4: Highly selective N-alkylation of pyrazoles

In 2023, Guang-Bo Che's group performed an Aza-Michael addition using Ag_2CO_3-catalyzed reaction of pyrazole with α, β-unsaturated carbonyl compounds with good regioselectivity and higher yield. **(Scheme 5).** [5]



Scheme 5: Ag_2CO_3 catalyzed aza-Michael addition of pyrazoles to α, β-Unsaturated compounds

1.3 Conclusion of the review work

The literature review revealed that there are many effective methods for formation of aza-Michael addition product under different thermal conditions. However, 1-Chlorocyclopropanecarboxylates and pyrazoles which is generated through in situ from vinyl diazo compounds, do not have an aza Michael reaction. Thus, we create a novel C-N bond forming reaction between in situ generated pyrazole and cyclopropane derivative for the formation of aza-Michael addition product.

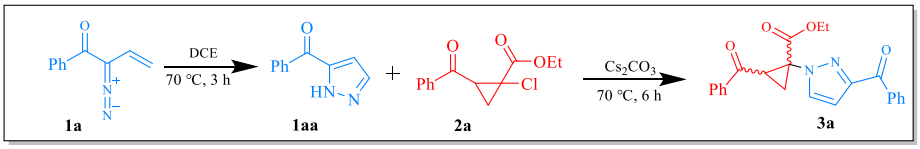
The pyrazole ring containing heterocyclic compounds usually introduced to unique product formation in organic synthesis due to their high reactivity. Here we produce a different and unique approach to produce Michael adduct or complex that is optimize more effectively to our diazo compounds without changing its functionality.

1.4 Objectives of the present work

Due to the importance of its in organic synthesis, the formation of cyclopropane-pyrazole adduct has been very attractive in some recent years. Depending upon the nature of the substrate, pyrazole ring containing heterocyclic compounds are very known as they have a wide pharmalogical or medicinal properties, including anticancer and analgesic effect. For this purpose, here we produce a novel C-N bond-formation reaction between pyrazole and 1-chlorocyclopropanecarboxylate using dichloroethane as solvent under heating conditions using Cs_2CO_3 as a base.

CHAPTER 2: RESULT AND DISCUSSION:

2.1 Reaction Scheme



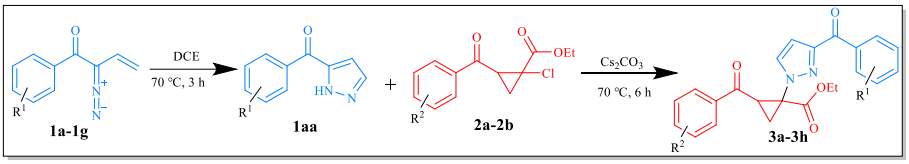
Scheme 6: One pot stepwise synthesis of pyrazole cyclopropanecarboxylate

Pyrazole **1aa** is created in situ from vinyl diazo ketone **1a** (0.11 mmol, 1equiv.) and 2-aroyl-1-chlorocyclopropanecarboxylate **2a** (0.11mmol, 1 equiv.) in a dry dichloroethane (1.5 ml) solvent. Cesium carbonate (2 equiv.) is used as a strong base at 70 °C with good yield. Instead of operating in an inert state, the reaction is carried out in the presence of air. At ambient temperature, the reaction is inactive; however, it becomes active at 50 °C and ends at 70 °C.

2.2 Substrate Scope:

Utilizing the optical characteristics, we elucidated the substrate scope of the reaction by employing diverse pyrazoles generated by in situ from distinct diazo compounds in dichloroethane under heating condition, using cesium carbonate as base under aerobic conditions. **Table 1** contains the results. Under the effect of a base, we discovered that different diazo compounds are transformed into intermediate (pyrazole), which formed the Michael product with cyclopropane derivative. Each reaction produced a moderate yield of the respective N-cyclopropyl pyrazoles.

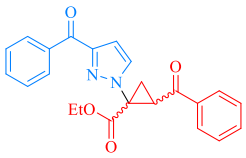
Many functionalities like methyl, F, NO_2, cyclohexyl, Br, napthyl, etc. were achieved for further synthetic manipulation.



R^1 = alkyl, aryl….

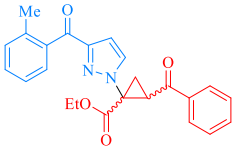
R^2 = alkyl, aryl….

……



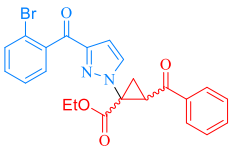
3aa = 40%

dr = 69:31



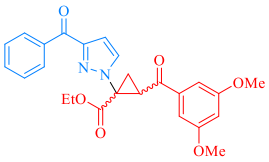
3ab = 38%

dr = 72:28



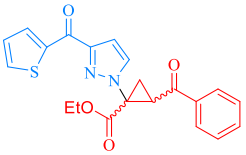
3ac = 41%

dr = 78:22



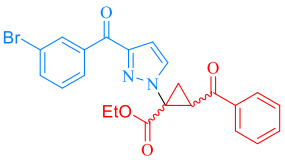
3ad = 30%

dr = 68:32



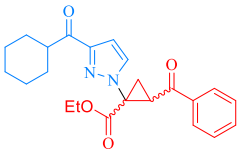
3ae = 47%

dr = 76:24



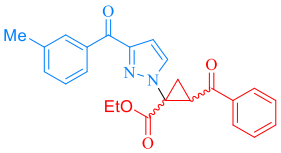
3af = 34%

dr = 73:27



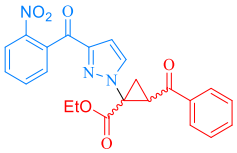
3ag = 49%

dr = 70:30



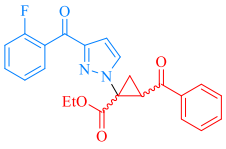
3ah = 52%

dr = 72:28



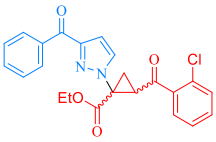
3ai = 31%

dr = 71:29



3aj = 44%

dr = 76:24



3ak = 28%

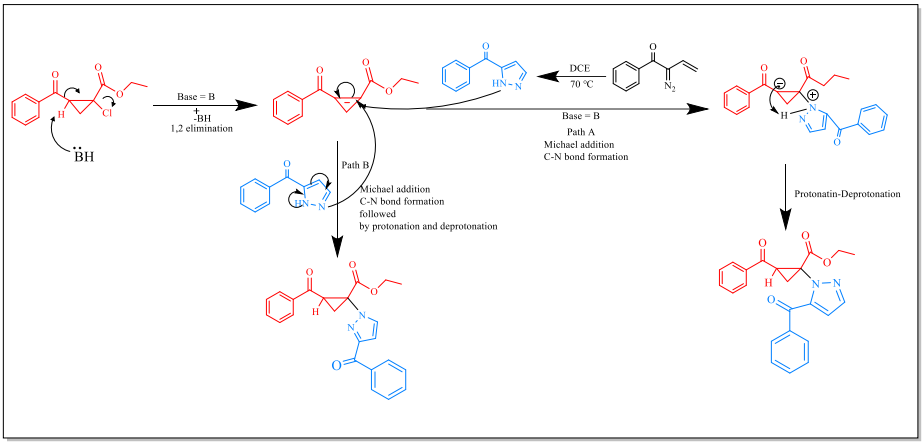
dr = 65:35

……

Table 1: Substrate scope

2.3 Plausible Reaction Mechanism

Based on the literature, a plausible mechanism is drawn in scheme 7. Initially in the presence of base, 1-chlorocyclopropanecaarboxylate undergoes 1,2 elimination and thereby generate cyclopropane intermediate, which then undergoes Michael addition by pyrazole as Michael donor, which generates from vinyl diazo ketones forming pyrazole cyclopropane carboxylate.



Scheme 7: A plausible aza-Michael reaction.

CHAPTER 3: EXPERIMENTAL AND CHARACTERIZATION DETAILS

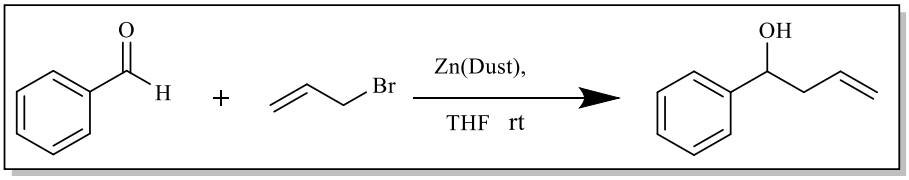
3.1Required Materials and Instrumentation:

Here All required chemicals were brought from Spectrochem, TCI, Sigma Aldrich, Avra. All reactions were carried out in a reaction tube and observed by TLC plate of a Merck 60 pre coated silica gel plate, and the desired product was apprehended by UV detection. For the purification of desired product, silica gel (60-120 mesh) was used for column chromatography. All NMR data ^{1}H NMR (500 MHz) and ^{13}C NMR (125MHz) were taken in Deuterated chloroform ($CDCl_3$) solvent using Bruker advance 500. All NMR data processed by MestReNova.

3.2 Standard Procedure for the synthesis:

3.2.1 Synthesis of Pyrazole

3.2.2 Step 1:

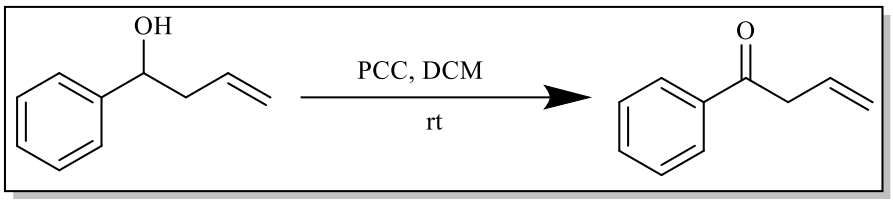


Scheme 8: Synthesis of allylic alcohols.

Procedure: Firstly we added zinc dust (3.67 gm, 56.6 mmol, 2.0 equiv.) in a 250 mL round bottom flask and then degassing was done and then we added allyl bromide (4.89 mL, 56,6 mmol, 2.0 equiv.) in flask using THF as the solvent and then stirred the mixture for two hours at room temperature and then we added benzaldehyde (3.0 mL, 28.3 mmol, 1.0 equiv.) drop by drop at 0 ℃ and then stirred the reaction mixture for whole night at room temperature. Then Check the TLC, after completion of the reaction, evaporate the THF first and then work up with ethyl acetate and water is done. The upper layer is collected and used Na_2SO_4 to dry the filtrate. Evaporation of the filtrate is done by rotation

evaporator and purify the crude mixture using column chromatography.

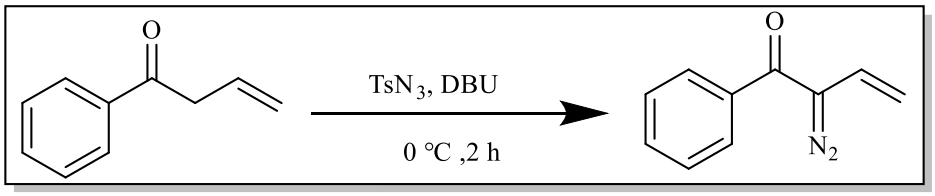
Step 2:



Scheme 9: Synthesis of allyl ketones.

Procedure: In a 100 mL round bottom flask allylic alcohol (3.5 g, 23.6 mmol, 1.0 equiv.) was taken and dissolved in DCM, later Celite was added as a binding agent at rt, after this PCC (7.66 g, 35.4 mmol, 1.5 equiv.) was added. The reaction mixture was stirred for 3 h at rt. After completion of the reaction, no need to do work up of the mixture; got the purified product using column chromatography.

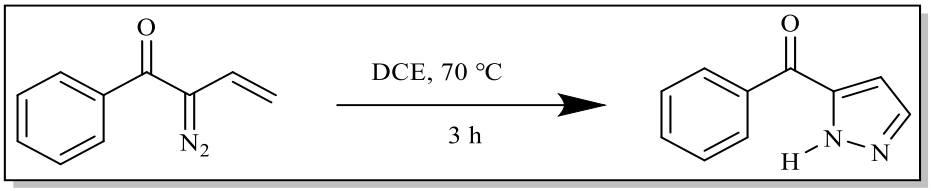
Step 3:



Scheme 10: Synthesis of vinyl diazo ketones

Procedure: Add ketone (2.6g, 17.8 mmol, 1.0 equiv.) in 100 mL round bottom flask and then and mix the compound using ACN as solvent then we added p-toluenesulphonyl azide (3.5g, 17.7 mmol, 1.0 equiv.) slowly and stir the reaction mixture for some time and then add DBU (2.9g, 19.5 mmol, 1.1 equiv.) as a base drop by drop at 0 ℃ and stirred the mixture for 2 h, after completion of the reaction, evaporate the ACN first and then work up with EtOAc and water is done . The upper layer is collected and used Na_2SO_4 to dry the filtrate. Evaporation of the filtrate is done by rotation evaporator and purify the crude mixture using column chromatography.

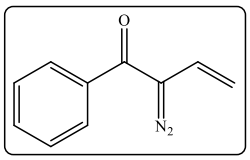
Step 4:



Scheme 11: Synthesis of Pyrazoles.

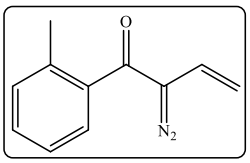
Procedure: Add diazo compound in a reaction tube and dissolve it into dichloroethane as a solvent and heat it under 70 °C for 3 h. After completing the reaction, a work up with ethyl acetate and water is done, the filtrate is dried using Na_2SO_4. Evaporate the filtrate and purify the product using column chromatography.

2-Diazo-1-phenylbut-3-en-1-one (1a): ^{1}H NMR (500 MHz, $CDCl_3$) δ



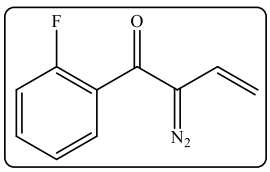
7.59 (d, *J* = 1.4 Hz, 1H), 7.51 – 7.48 (m, 2H), 7.46 – 7.41 (m, 2H), 6.42 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.23 (d, *J* = 10.8 Hz, 1H), 4.93 (d, *J* = 17.3 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 145.1, 137.4, 131.8, 129.2, 128.5, 127.4, 121.2, 108.5 ppm.

2-Diazo-1-(*o*-tolyl)but-3-en-1-one (1a): ^{1}H NMR (500 MHz, $CDCl_3$) δ

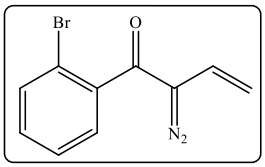


7.24 – 7.20 (m, 1H), 7.14 (dd, *J* = 18.1, 10.4 Hz, 3H), 6.18 (s, 1H), 5.10 (s, 1H), 4.82 (d, *J* = 17.3 Hz, 1H), 2.27 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 137.5, 135., 131.1, 130.4, 126.4, 125.7, 120.6, 108.4, 19.0 ppm.

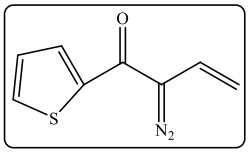
2-Diazo-1-(2-fluorophenyl)but-3-en-1-one (1a): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.43 (m, 2H), 7.23 (td, *J* = 7.5, 1.0 Hz, 1H), 7.14 – 7.08 (m, 1H), 6.35 (s, 1H), 5.23 (d, *J* = 10.8 Hz, 1H), 4.95 (d, *J* = 17.3 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.8, 158.8, 146.0, 169.8 – 126.0, 169.8 – 124.9, 169.8 – 120.9, 169.8 – 116.4, 219.7 – 116.0, 108.7 ppm.



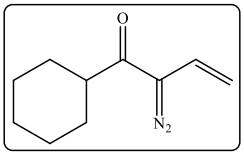
1-(2-bromophenyl)- 2-Diazobut-3-en-1-one (1a): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.58 (m, 1H), 7.35 (dd, *J* = 7.3, 0.9 Hz, 1.43H), 7.29 (dd, *J* = 8.4, 4.3, 2.0 Hz, 2.57H), 6.68 (dd, *J* = 15.7, 6.9 Hz, 1H), 6.45 (dd, *J* = 15.7, 1.6 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 195.1, 148.5, 140.9, 133.2, 131.9, 131.0, 128.8, 127.1, 119.2 ppm.



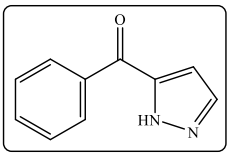
2-Diazo-1-(thiophen-2-yl)but-3-en-1-one (1a): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 1.4 Hz, 1H), 7.50 (s, 1H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.03 (d, *J* = 6.9 Hz, 1H), 6.92 – 6.84 (m, 1H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 190.7, 145.0, 137.8, 132.6, 128.5, 127.5 ppm.



1-cyclohexyl- 2-Diazobut-3-en-1-one (1a): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.28 (dd, *J* = 17.2, 10.9 Hz, 1H), 5.17 (t, *J* = 13.6 Hz, 1H), 4.86 (d, *J* = 17.3 Hz, 1H), 2.55 (td, *J* = 8.2, 4.1 Hz, 1H), 1.48 (d, *J* = 12.1 Hz, 2H), 1.29 – 1.22 (m, 8H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 130.2, 127.5, 120.3, 117.2, 29.9, 28.7, 25.6, 25.4, 22.7 ppm.



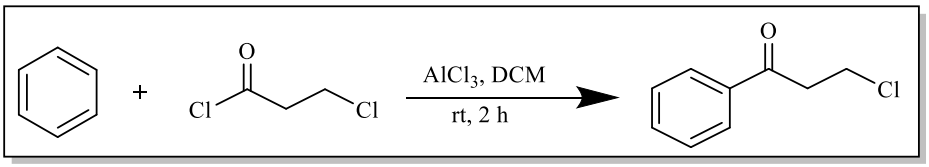
2-Diazo-1-(2-nitrophenyl)but-3-en-1-one (1a): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 28.7, 8.2 Hz, 0.96H), 7.93 (d, *J* = 8.2 Hz, 0.33H), 7.83 (d, *J* = 7.9 Hz, 0.33H), 7.79 – 7.68 (m, 1.05H), 7.63 (dt, *J* = 20.7, 7.8 Hz, 1.40H), 7.42 (t, *J* = 8.3 Hz, 1.37H), 6.43 (dd, 1H), 5.18 (dd, 1H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 193.0, 147.1, 133.9, 132.2, 130.3, 128.7, 128.1, 124.3, 119.1, 113.2 ppm.



phenyl (1H-pyrazolle-5-yl)methanone (1aa): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.4 Hz, 2H), 7.59 (dd, *J* = 15.1, 4.6 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 2H), 6.85 (d, *J* = 2.1 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 188.0, 137.7, 132.9, 129.8, 128.5, 109.3 ppm.

3.2.2 Synthesis of 1-chlorocyclopropane Carboxylates:

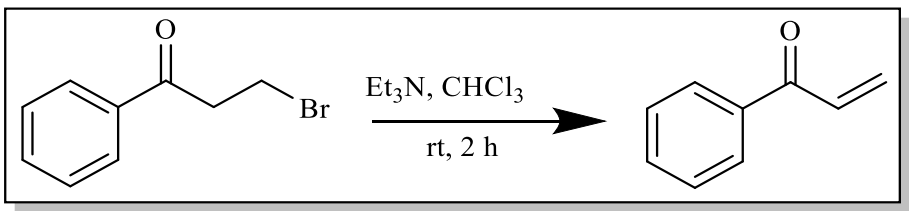
Step 1:



Scheme 12: Synthesis of 3-chloropropiophenones.

Procedure: In a 250 mL round bottom flask attached with an argon-filled balloon, add anhydrous AlCl3 (2.1g, 16 mmol, 1.25 equiv.) and DCM. Next, add 3-chloropropionyl chloride (2.4g, 14.1 mmol, 1.1 equiv.) dropwise over the course of 15 minutes at room temperature and continue for another 15 minutes. Then add Arene (1g, 12.8 mmol, 1.0 equiv.) drop by drop and stirred the mixture for 15 min over 30 min 0 ℃. Then check the reaction using TLC plate after 3h. After completing the reaction, do the work up with DCM and water. Evaporate the crude and purify the crude by column chromatography.

Step 2:

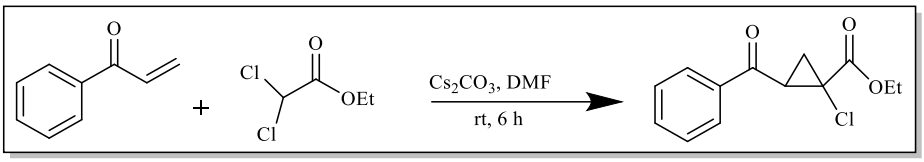


Scheme 13: Synthesis of vinyl ketones

Procedure: In a 100 mL round bottom flask with chloroform, we first added propionyl chloride (3.5g, 16.5 mmol, 1.0 equiv.) and then Et_3N (4.5mL, 33 mmol, 2.0 equiv.). Check the reaction using a TLC plate after three hours. Next, dilute the reaction mixture with water and NH_4Cl. Work up with DCM and water, then filter it. Column chromatography is used to purify the crude product after the filtrate has been dried with

Na_2SO_4 and evaporated.

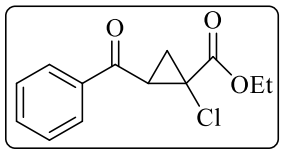
Step 3:



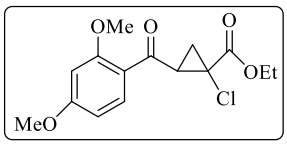
Scheme 14: Synthesis of 1-chlorocyclopropanecarboxylates.

Procedure: Firstly, Degas a 250 mL round-bottom flask after adding Cs_2CO_3 (1.6g, 4.9 mmol, 1.1 equiv.). Next, add DCM and ethyl dichloroacetate (0.7g, 4.5 mmol, 1.0 equiv.). Add arene (1.0 equiv.) after that. TLC was used to track the reaction's progress after six hours. When the reaction is finished, add some ice and stirred for 20 minutes to ensure that all of the DMF is in the water. The bottom layer is then linked, a work-up with DCM is completed, and Na_2SO_4 is used to dry the filtrate. Use column chromatography to purify the crude once the filtrate has evaporated.

Ethyl 2-benzoyl-1-chlorocyclopropane-1-carboxylate(2a): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.2 Hz, 2H), 7.56 – 7.45 (dd, 1H), 7.38 (dd, *J* = 17.7, 10.2 Hz, 2H), 4.23 (dd, *J* = 14.2, 7.1 Hz, 2H), 3.45 (dd, *J* = 8.8, 8.2 Hz, 1H), 2.13 (dd, *J* = 7.7, 5.7 Hz, 1H), 1.96 – 1.84 (dt, 1H), 1.11 (t, 3H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 191.5, 168.7, 137.0, 133.6, 128.8, 77.2, 76.9, 76.90, 63.2, 43.6, 33.4, 31.5, 26.8, 25.2, 22.6, 21.9, 14.1 ppm.

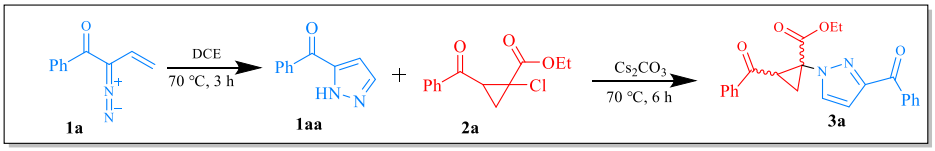


Ethyl 1-chloro-2-(2,4-dimethoxybenzoyl)cyclopropane-1-carboxylate(2a): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.8 Hz, 1H), 6.55 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.45 (d, *J* = 2.2 Hz, 1H), 4.30 (dd, *J* = 0.9 Hz, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.56 (t, 1H), 2.21 (dd, *J* = 8.3, 5.6 Hz, 1H), 1.93 (dd, *J* = 8.9, 5.6 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 190.2, 169., 165.2, 161.5, 133.2, 120.6, 105.6, 98.4, 77.3, 77.0, 76.7, 62.7, 55.6, 43.6, 39.1,



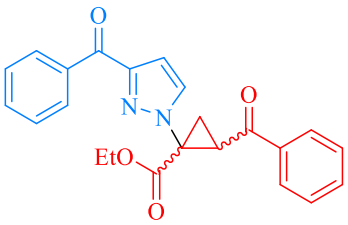
22.3, 14.2 ppm.

3.2.3 One-Pot Two-Step Synthesis of N-Cyclopropyl Pyrazoles



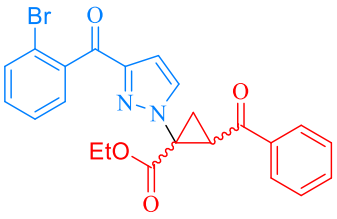
Procedure: firstly, we take diazo compound **(1a)** (0.11 mmol, 1.0 equiv.) in a clean reaction tube and dissolve using Dichloroethane as a solvent and stirred the solution for 3 h at 65-70 °C. Check the reaction using a TLC plate, it converts into pyrazole intermediate then we added Cs_2CO_3 (0.22 mmol,2.0 equiv.) and 1-chlrocyclopropanecarboxylate **(2a)** (0.11 mmol, 1.0 equiv.) and stirred the reaction further for 4-6 h. Monitor the reaction using TLC plate. After completion of the reaction, do the work up of the mixture with EtOAc and water. Dry the crude by Na_2SO_4, and Then, use column chromatography purify the crude. MastReNova is utilized to characterize the product using ^1H and ^{13}C NMR.

The product might have the following structure based on the ^1H and ^{13}C NMR

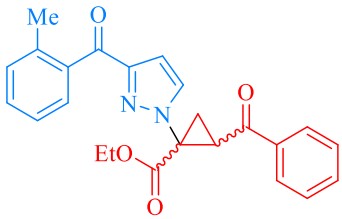


Ethyl 2-benzoyl-1-(3-benzoyl-1*H*-pyrazol-1-yl) cyclopropane-1-carboxylate: White Solid; yield = 40% (dr = 69:31); R_f = 0.31 (EtOAc/hexane = 12:88); **^1H NMR (500 MHz, $CDCl_3$) δ** 8.43 (d, *J* = 7.6 Hz, 1.30H), 8.39 (d, *J* = 7.5 Hz, 1.30H), 8.09 (d, *J* = 7.4 Hz, 0.70H), 7.62 (d, J= 7.7Hz 0.70H), 7.70 (d, *J* = 2.2 Hz, 0.66H), 7.65 (dd, *J* = 14.0, 9.0 Hz, 0.99H), 7.59 (dd, *J* = 13.7, 6.6 Hz, 1.04H),7.56- 7.51 (m, 2.04H), 7.44 (t, *J* = 7.3 Hz, 1.63H), 7.35 (t, *J* = 7.1 Hz, 0.39H), 7.07 (d, J=2.1Hz, 0.68H), 7.00 (t, *J* = 7.7 Hz, 0.57H), 6.92 (d, J= 2.1Hz, 0.32H), 4.28 – 4.13 (m, 0.66H), 3.95

(dd, J = 24.2, 17.0 Hz, 1.68H), 3.61 (t, J = 9.2 Hz, 0.66H), 2.79 (dd, 0.30H), 2.61 (dd, *J* = 8.4, 5.9 Hz, 0.70H), 2.17 (dd, *J* = 8.4, 4.9 Hz, 0.30H), 2.05 (dd, J = 9.7, 5.8 Hz, 0.70H), 1.18 (t, J = 7.1 Hz, 0.94H), 0.92 (t, J = 7.1 Hz, 2.06H) ppm; **^{13}C NMR (125 MHz, $CDCl_3$) δ** 191.3, 187.1, 167.2, 151.2, 137.2, 136.3, 133.8, 132.7, 132.3, 130.7, 129.0, 128.1, 109.8, 62.04, 49.1, 35.5, 19.7, 13.6 ppm. HRMS (ESI-TOF): *m/z* $[M+Na]^+$ calcd for $C_{23}H_{20}N_2O4$ 411.1315, found 411.1318.

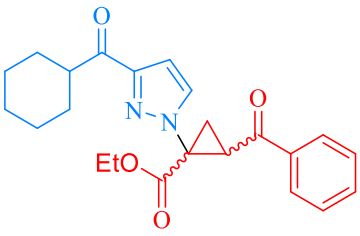


Ethyl 2-benzoyl-1-(3-(2-bromobenzoyl)-1*H*-pyrazol-1-yl) cyclopropane-1-carboxylate: White Solid; yield = 41% (dr = 78:22); R_f = 0.36 (EtOAc/hexane = 12:88); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.26 (d, *J* = 7.3 Hz, 1.70H), 7.94 (d, *J* = 7.3 Hz, 0.30H), 7.69 (dd, *J* = 5.0, 1.7 Hz, 1.85H), 7.61 (dd, *J* = 7.5, 1.6 Hz, 1.14H), 7.52 (dd, *J* = 12.5, 5.1 Hz, 1.22H), 7.46 (td, *J* = 7.5, 1.0 Hz, 1.31H), 7.43 (t, 1.18H), 7.04 (d, *J* = 2.4 Hz, 0.95H), 6.89 (d, *J* = 2.5 Hz, 0.12H), 6.77 (t, *J* = 7.5 Hz, 0.14H), 4.2 (q, 0.41H), 3.93 (q, 2H), 3.53 (t, *J* = 9.2 Hz, 1H), 2.73 (dd, *J* = 7.3, 5.0 Hz, 0.21H), 2.55 (dd, *J* = 8.6, 5.7 Hz, 1H), 2.12 (dd, *J* = 8.6, 5.0 Hz, 0.20H), 1.98 (dd, *J* = 9.8, 5.7 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 0.39H), 0.88 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 191.1, 189.43, 167.0, 150.3, 140.6, 136.1, 133.6, 133.1, 132., 131.2,130.0, 129.0, 128.6, 126.8, 120.2, 108.8, 62.3, 49.0, 35.4, 32.16, 29.71 19.7, 13.5 ppm. HRMS (ESI-TOF): *m/z* $[M+Na]^+$ calcd for $C_{23}H_{19}BrN_2O_4$ 466.0528, found 466.0538.

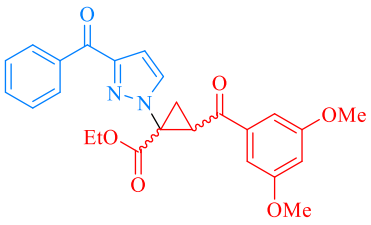


Ethyl 2-benzoyl-1-(3-(2-methylbenzoyl)-1*H*-pyrazol-1-yl) cyclopropane-1-carboxylate: White Solid; yield = 38% (dr = 72:28); R_f = 0.40 (EtOAc/hexane = 12:88); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.26 (d, *J* = 7.6 Hz, 2.14H), 7.94 (d, *J* = 7.5 Hz, 0.35H), 7.72 (d, *J* = 7.4 Hz, 1.31H), 7.62 (d, 1.36H), 7.45 (s, 1.44H), 7.40 (t, *J* = 7.4 Hz, 1.83H), 7.09 (dd, *J* = 15.7, 7.6 Hz, 0.53H), 7.02 (d, *J* = 7.4 Hz, 0.55H), 6.96 (s, 1.48H), 6.81 (s, 0.28H), 6.53 (t, *J* = 7.3 Hz, 0.20H), 4.13 (dt, *J* = 17.6,

10.5 Hz, 0.36H), 3.85 (dd, *J* = 14.9, 7.5 Hz, 2H), 3.47 (t, *J* = 9.0 Hz, 1H), 2.79 (m, 0.20H), 2.45 (m, 0.99H), 2.40 (s, 3H), 2.08 (dd, *J* = 14.3, 10.1 Hz, 0.29H), 1.94 (dd, *J* = 9.4, 5.7 Hz, 0.96H), 1.12 (t, *J* = 7.0 Hz, 0.52H), 0.84 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 191.2, 167.1, 151.6, 138.2, 137.6, 136.1, 133.6, 132.6, 131.0, 130.5, 130.0, 129.0, 128.7, 124.9, 109.0, 62.3, 49.0, 35.5, 21.1, 19.4. 17.7, 13.6 ppm. HRMS (ESI-TOF): *m/z* $[M+Na]^+$ calcd for $C_{24}H_{22}N_2O_4$ 402.1580, found 402.1596.

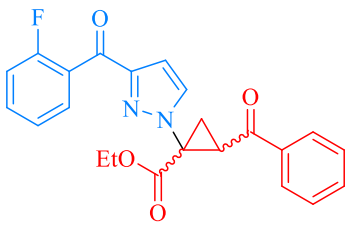


Ethyl 2-benzoyl-1-(3-(cyclohexanecarbonyl)-1*H*-pyrazol-1-yl) cyclopropane-1-carboxylate: White Solid; yield = 49% (dr = 70:30); R_f = 0.30 (EtOAc/hexane = 12:88); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.50 (d, *J* = 7.5 Hz, 2.08H), 8.39 (d, *J* = 7.5 Hz, 0.27H), 8.02 (d, *J* = 7.5 Hz, 0.16H), 7.85 (d, *J* = 8.2 Hz, 0.17H), 7.74 (t, *J* = 7.5 Hz, 0.24H), 7.61 (dd, J = 7.67Hz, 2.06H), 7.57 (t, J = 7.8 Hz, 2.56H), 6.90 (d, *J* = 2.3 Hz, 0.13H), 6.86 (d, *J* = 2.3 Hz, 0.99H), 4.26 (dd, *J* = 7.1 Hz, 0.26H), 3.97 (dd, J = 14.1Hz, 1.98H), 3.62 (t, *J* = 9.2 Hz, 1H), 3.57 (t, J = 9.4 Hz, 0.53H), 2.72 (dd, *J* = 13.7, 6.5 Hz, 0.11H), 2.58 (dd, *J* = 8.5, 5.8 Hz, 1.04H), 2.01 (dd, *J* = 9.8, 5.7 Hz, 1.65H), 1.95 (m, 2.07H), 1.59 (m, 3.03H), 1.50 (m, 3.21H), 1.27 (m, 1.97H), 0.98 (t, *J* = 7.1 Hz, 0.32H), 0.90 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 199.2, 191.3, 167.2, 150.5, 136.4, 133.8, 132.6, 128.9, 107.7, 62.3, 49.0, 46.6, 35.4, 29.0, 28.4, 23.4, 19.7, 13.5 ppm. HRMS (ESI-TOF): *m/z* $[M+Na]^+$ calcd for $C_{23}H_{26}N_2O_4$ 394.1893, found 394.1906.

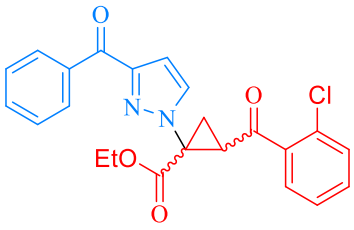


Ethyl 1-(3-benzoyl-1*H*-pyrazol-1-yl)-2-(3,5-dimethoxybenzoyl)cyclopropane-1-carboxylate: White Solid; yield = 30% (dr = 69:31); R_f = 0.26 (EtOAc/hexane = 20:80); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.29 (dd, J = 6.9Hz, 2.03H), 8.16 (dd, *J* = 6.9 Hz, 0.26H), 8.04 (d, J =

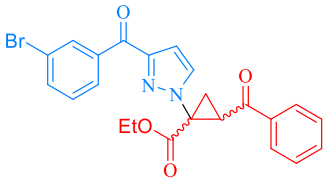
8.7Hz, 0.76H), 7.97 (d, *J* = 8.7 Hz, 1.05H), 7.81 (d, *J* = 2.5 Hz, 1.12H), 7.72 (d, *J* = 9.0 Hz, 0.42H), 7.57 (d, *J* = 7.4 Hz, 1.19H), 7.48 (t, *J* = 7.7 Hz, 3.16H), 7.01 (d, *J* = 2.5 Hz, 1.01H), 6.86 (d, *J* = 2.5 Hz, 0.53H), 6.46 (d, *J* = 2.2 Hz, 1.18H), 4.21 (d, *J* = 7.1 Hz, 0.87H), 4.11 (dd, J = 7.1Hz, 2.08H), 3.96 (dd, *J* = 14.6, 6.3 Hz, 0.44H), 3.86 (s, 3.03H), 3.80 (s, 3H), 3.65 (dd, *J* = 9.8, 8.5 Hz, 1.08H), 2.86 (dd, *J* = 8.0, 5.1 Hz, 0.42H), 2.58 (d, *J* = 2.6 Hz, 1.04H), 2.16 (t, J = 5.7Hz, 1.06H), 1.17 (t, *J* = 7.1 Hz, 0.52H), 1.09 (t, *J* = 7.1 Hz, 3.0H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 190.8, 187.7, 169.5, 167.2, 165.1, 161.2, 150.7, 137.2, 136.0, 132.6, 128.4, 120.6, 109.5, 105.6, 98.6, 62.3, 55.7, 50.4, 38.4, 20.4, 13.9 ppm. HRMS (ESI-TOF): *m/z* $[M+Na]^+$ calcd for $C_{25}H_{24}N_2O_6$ 448.4750, found 448.4763.



Ethyl 2-benzoyl-1-(3-(2-fluorobenzoyl)-1*H*-pyrazol-1-yl) cyclopropane-1-carboxylate: White Solid; yield = 44% (dr = 76:24); R_f = 0.35 (EtOAc/hexane = 12:88); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.26 (d, J = 7.3 Hz, 1.93H), 8.00 (d, *J* = 7.3 Hz, 0.45H), 7.86 (t, J= 7.8Hz, 0.99H), 7.68 (d, *J* = 2.5 Hz, 1.0H), 7.63 (t, *J* = 7.4 Hz, 0.45H), 7.52 (dd, *J* = 13.3 Hz, 1.28H), 7.31 (dd, *J* = 4.2 Hz, 2.73H), 7.19(t, J = 7.2 Hz, 1.14H), 7.04 (d, *J* = 2.5 Hz, 1.01H), 6.88 (dd, *J* = 9.2, 6.2 Hz, 0.46H), 6.64 (t, *J* = 7.5 Hz, 0.24H), 4.14 (m, 0.40H), 3.90 (t, *J* = 7.2 Hz, 2.02H), 3.56 (t, *J* = 9.2 Hz, 1.03H), 2.75 (dd, *J* = 7.3, 5.0 Hz, 0.25H), 2.57 (dd, *J* = 5.8 Hz, 1.01H), 2.19 – 2.09 (dd, J = 5.7 Hz, 0.29H), 2.04 (dd, J = 5.7 Hz, 1.05H), 1.19 (t, *J* = 7.1 Hz, 0.68H), 0.89 (t, *J* = 7.1 Hz, 3.0H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 191.2, 186.5, 167.1, 160.7, 151.0, 136.2, 133.6, 132.9, 132.6, 131.3, 129.6, 127.3, 123.7, 116.2, 108.7, 62.3, 49.1, 35.4, 30.8, 21.0, 19.7, 13.5 ppm. HRMS (ESI-TOF): *m/z* $[M+Na]^+$ calcd for $C_{23}H_{19}FN_2O_4$ 406.1329, found 406.1335.

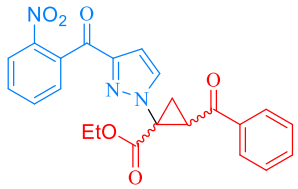


Ethyl 1-(3-benzoyl-1*H*-pyrazol-1-yl)-2-(2-chlorobenzoyl) cyclopropane-1-carboxylate: White Solid; yield = 28% (dr = 65:35); R_f = 0.32 (EtOAc/hexane = 15:85); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.31 (dd, *J* = 8.3 Hz, 1.23H), 8.12 (dd, J = 7.9 Hz, 0.75H), 8.05 (dd, *J* = 8.3 Hz, 2.10H), 7.76 (d, *J* = 2.5 Hz, 0.89H), 7.74 (dd, J = 2.5 Hz, 0.42H), 7.62 (d, *J* = 2.6 Hz, 1.51H), 7.50 (d, *J* = 7.9 Hz, 1.60H), 7.47 (d, *J* = 1.9 Hz, 2.06H), 7.02 (d, *J* = 2.5 Hz, 0.86H), 6.95 (d, *J* = 2.5 Hz, 1.12H), 4.21 (d, *J* = 7.1 Hz, 2.02H), 4.11 (dd, *J* = 7.1 Hz, 1.17H), 3.87 (dd, *J* = 8.5, 7.6 Hz, 1.32H), 3.53 (dt, *J* = 5.2 Hz, 0.93H), 2.81 (dd, *J* = 5.7 Hz, 1.1H), 2.58 (dd, J = 5.8 Hz, 0.73H), 2.27 (dd, *J* = 8.6, 5.0 Hz, 1.07H), 2.21 (dd, *J* = 9.8, 5.9 Hz, 0.81H), 1.12 (t, *J* = 7.1 Hz, 2.75H), 0.88 (t, *J* = 6.9 Hz, 3.0H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 193.3, 193.2, 187.7, 187.4, 168.5, 166.6, 219.7, 130.5, 151.3, 142.8, 133.5, 155.6, 130.9, 133.4, 133.1, 142.8, 131.2, 128.1, 127.8, 127.1, 110.0, 109.5, 62.8, 51.7, 37.4, 36.2, 31.6, 29.6, 22.7, 22.1, 20.8, 14.0, 13.8 ppm. HRMS (ESI-TOF): *m/z* $[M+Na]^+$ calcd for $C_{23}H_{19}ClN_2O_4$ 422.1033, found 422.1042.

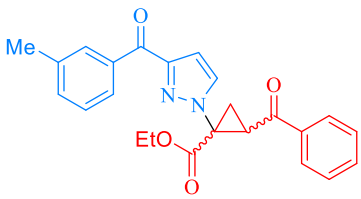


Ethyl 2-benzoyl-1-(3-(3-bromobenzoyl)-1*H*-pyrazol-1-yl) cyclopropane-1-carboxylate: White Solid; yield = 34% (dr = 73:27); R_f = 0.32 (EtOAc/hexane = 12:88); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.46 (t, *J* = 8.3 Hz, 23H), 8.43 – 8.37 (d, J = 8.2 Hz, 2.06H), 8.36 (dd, J = 8.11 Hz, 1.11H), 7.95 (d, *J* = 7.3 Hz, 0.33H), 7.84 (d, *J* = 7.1 Hz, 0.52H), 7.76 (d, *J* = 1.9 Hz, 1.21H), 7.71 (d, *J* = 2.5 Hz, 1.21H), 7.58 (d, *J* = 7.4 Hz, 1.58H), 7.45 (t, *J* = 7.8 Hz, 2.83H), 7.06 (d, *J* = 2.5 Hz, 1.15H), 4.23 (dd, *J* = 7.2 Hz, 0.26H), 3.94 (dd, *J* = 7.1 Hz, 2.05H), 3.60 (dd, *J* = 8.6 Hz, 1.08H), 2.78 (dd, *J* = 5.0 Hz, 0.71H), 2.62 (dd, *J* = 5.8 Hz, 1.02H), 2.19 (dd, J = 5.8 Hz, 0.21H), 2.05 (dd, *J* = 5.8 Hz, 1.12H), 1.20 (t, *J* = 7.1 Hz, 051H), 0.92 (t, *J* = 7.1 Hz, 3.0H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 191.2, 185.9, 167.1, 150.7, 139.0, 135.5, 133.8, 133.5, 132.6, 129.6, 129.3, 128.9, 122.3, 109.9, 62.4, 49.2, 35.4, 29.7, 19.7, 13.6 ppm. HRMS (ESI-TOF): *m/z*

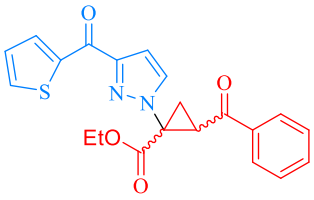
[M+Na]$^+$ calcd for $C_{23}H_{19}BrN_2O_4$ 466.0528, found 466.0541.



Ethyl 2-benzoyl-1-(3-(2-nitrobenzoyl)-1*H*-pyrazol-1-yl) cyclopropane-1-carboxylate: White Solid; yield = 31% (dr = 71:29); R_f = 0.35 (EtOAc/hexane = 12:88); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.16 (d, *J* = 7.6 Hz, 1.92H), 8.11 (d, *J* = 8.0 Hz, 0.98H), 7.98 (d, *J* = 7.7 Hz, 0.15H), 7.82 (t, *J* = 7.4 Hz, 1H), 7.72 (t, *J* = 7.5 Hz, 2H), 7.65 (d, *J* = 2.2 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 1.25H), 7.27 (s, *J* = 7.1 Hz, 0.99H), 7.24 (s, *J* = 7.1 Hz, 0.56H), 7.05 (d, *J* = 2.3 Hz, 0.99H), 3.86 (dd, *J* = 7.1 Hz, 2H), 3.40 (t, *J* = 9.2 Hz, 1H), 2.50 (dd, *J* = 8.4 Hz, 1H), 1.93 (dd, *J* = 9.8, 5.7 Hz, 1H), 0.86 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 191.1, 186.8, 166.9, 150.4, 148.8, 136.1, 135.2, 133.8, 133.6, 133.3, 130.8, 129.9, 128.9, 128.5, 123.5, 108.0, 62.4, 49.0, 35.0, 29.7, 19.7, 13.4 ppm. HRMS (ESI-TOF): *m/z* [M+Na]$^+$ calcd for $C_{23}H_{19}N_3O_6$ 433.1274, found 433.1285.



Ethyl 2-benzoyl-1-(3-(3-methylbenzoyl)-1*H*-pyrazol-1-yl) cyclopropane-1-carboxylate: White Solid; yield = 52% (dr = 72:28); R_f = 0.32 (EtOAc/hexane = 12:88); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.42 (d, *J* = 6.3 Hz, 2.05H), 8.22 (d, *J* = 5.5 Hz, 1H), 8.06 (s, *J* = 7.8 Hz, 1.33H), 7.70 (s, *J* = 7.8 Hz, 1.31H), 7.40 (d, *J* = 7.8 Hz, 3.53H), 7.02 (s, *J* = 7.3 Hz, 1H), 6.88 (s, *J* = 7.3 Hz, 0.21H), 4.24 (dd, *J* = 7.1 Hz, 0.36H), 3.96 (dd, *J* = 7.1 Hz, 2H), 3.59 (t, *J* = 7.7 Hz, 1H), 2.77 (s, 0.23H), 2.57 (d, *J* = 5.2 Hz, 1H), 2.39 (s, 3H), 2.19 (t, *J* = 8.4 Hz, 0.51H), 2.07 (t, *J* = 8.4 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 0.48H), 0.93 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 191.3, 187.7, 167.2, 151.2, 137.9, 136.3, 133.8, 133.6, 132.4, 130.8, 128.9, 128.6, 128.4, 128.0, 109.7, 62.3, 49.1, 35.5, 32.0, 21.5, 19.7, 13.6 ppm. HRMS (ESI-TOF): *m/z* [M+Na]$^+$ calcd for $C_{24}H_{22}BrN_2O_4$ 402.1580, found 466.0541.



Ethyl 2-benzoyl-1-(thiphene-2-carbonyl)-1*H*-pyrazol-1-yl) cyclopropane-1-carboxylate: White Solid; yield = 45% (dr = 76:24); R_f = 0.40 (EtOAc/hexane = 15:85); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.47 – 8.44 (m, 3H), 7.68 (d, *J* = 2.2 Hz, 1H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.03 (dd, *J* = 14.5, 5.5 Hz, 3H), 3.92 (s, 2H), 3.61 (t, *J* = 9.1 Hz, 1H), 2.61 (dd, *J* = 8.4, 5.8 Hz, 1H), 2.05 (dd, *J* = 9.7, 5.7 Hz, 1H), 0.92 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 191.4, 185.7, 167.2, 163.4, 151.5, 136.3, 133.7, 133.1, 132.1, 130.0, 129.0, 128.8, 113.4, 109.8, 62.3, 55.5, 49.1, 35.5, 19.7, 13.6 ppm. HRMS (ESI-TOF): *m/z* $[M+Na]^+$ calcd for $C_{21}H_{18}N_2O_4S$ 394.0987, found 394.1011.

Conclusion

In conclusion, we have developed a simple, one pot sequential synthesis of N-alkylated pyrazole with a cycloprpopane moiety from several in situ generated pyrazoles from vinyl diazo ketones and 1-chlorocyclopropanecarboxylates. The aza-Michael reaction proceeds in the presence of Cs_2CO_3 at 70 °C in DCE solvent. This approach has several of positive characteristics, including good substrate scope, standard optimization, diastereoselectivity, and relative configuration of the Michael adducts, as well as satisfactory yields and the absence of transition metals. There are ongoing efforts to expand the scope of the substrate.

APPENDIX A

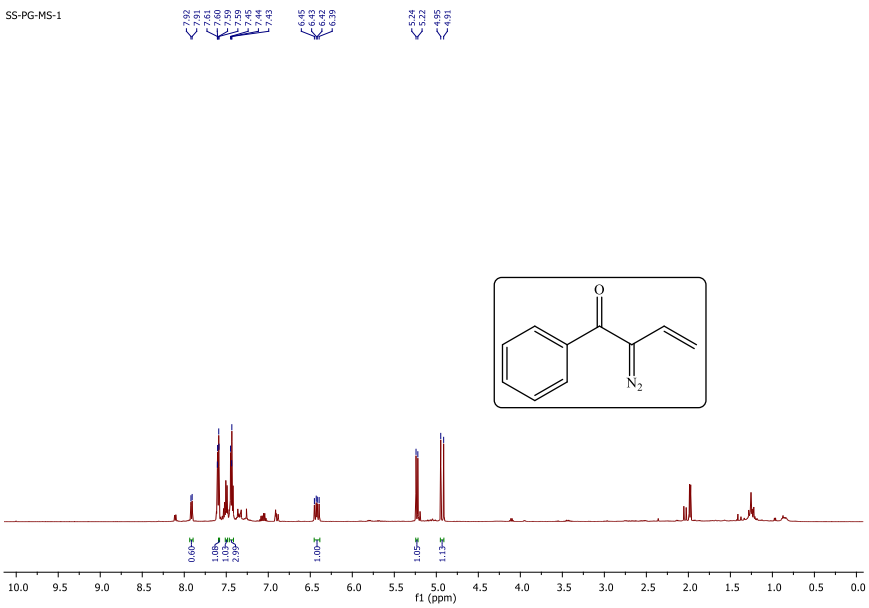


Fig 1: ^{1}H NMR spectrum (500 MHz) of **1a** in $CDCl_3$

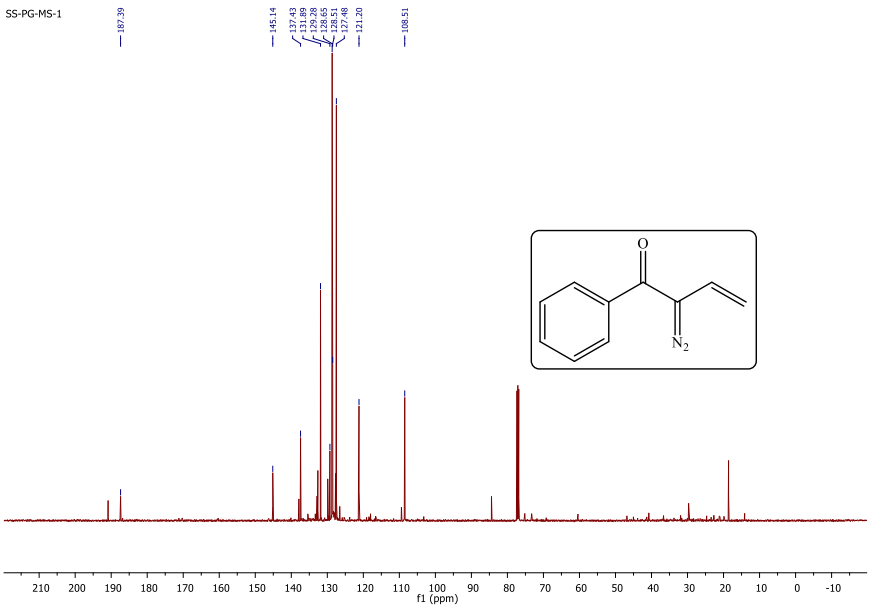


Fig 2: ^{13}C NMR spectrum (125 MHz) of **1a** in $CDCl_3$

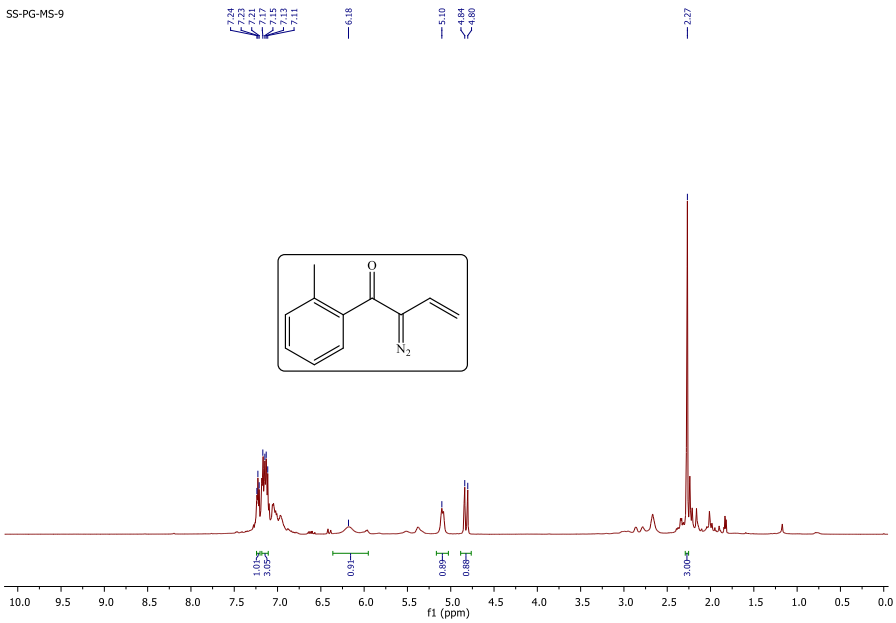


Fig 3: ^{1}H NMR spectrum (500 MHz) of **1b** in $CDCl_3$

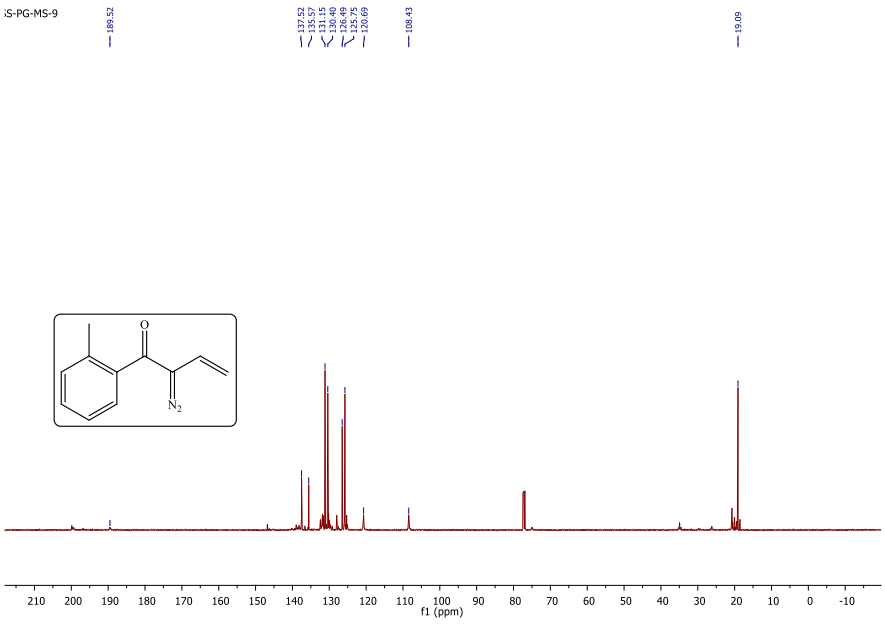


Fig 4: ^{13}C NMR spectrum (125 MHz) of **1b** in $CDCl_3$

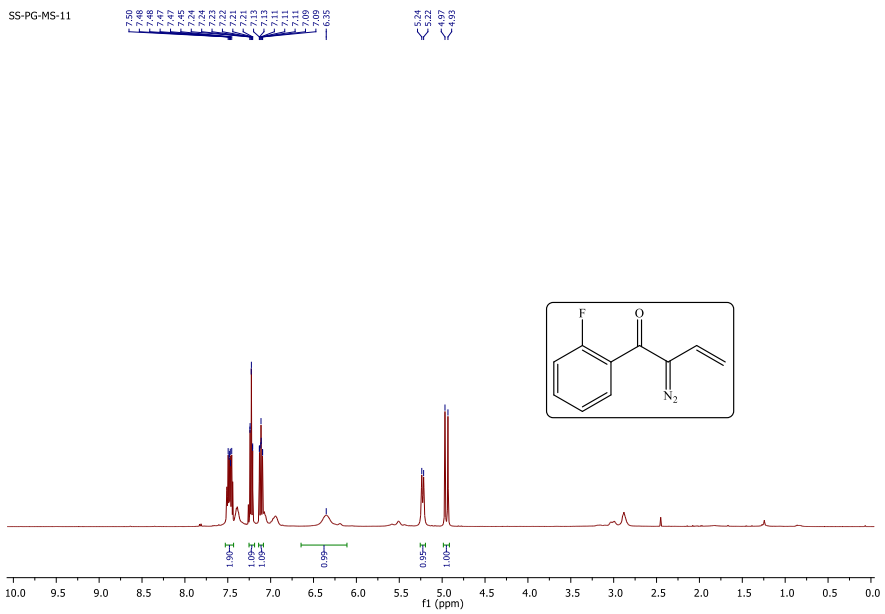


Fig 5: ^{1}H NMR spectrum (500 MHz) of **1c** in $CDCl_3$

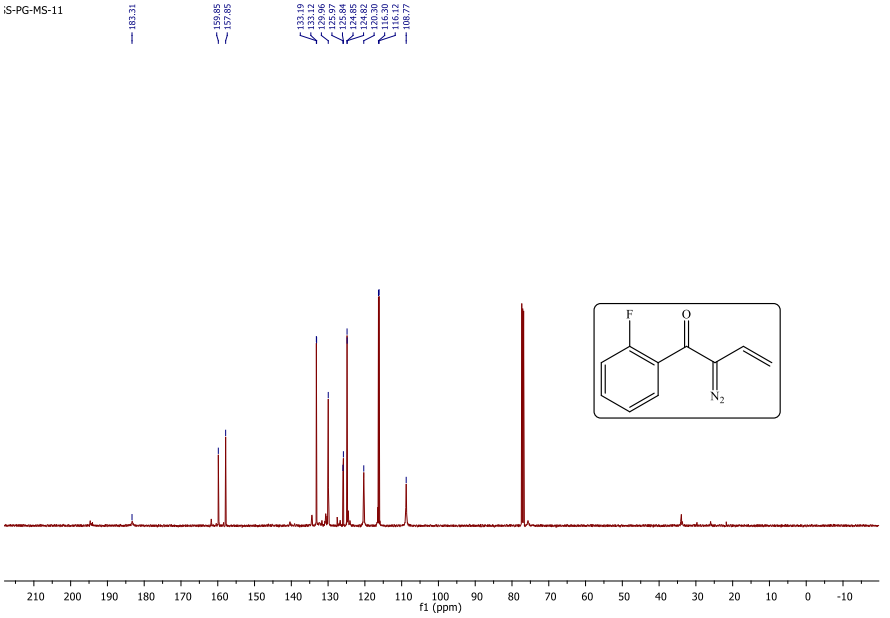


Fig 6: ^{13}C NMR spectrum (125 MHz) of **1c** in $CDCl_3$

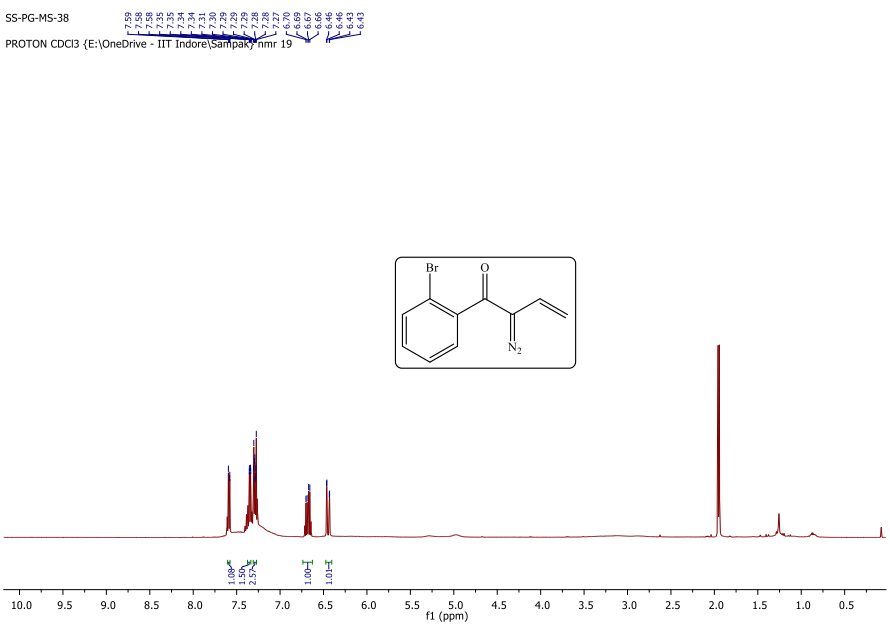


Fig 7: ^{1}H NMR spectrum (500 MHz) of **1d** in $CDCl_3$

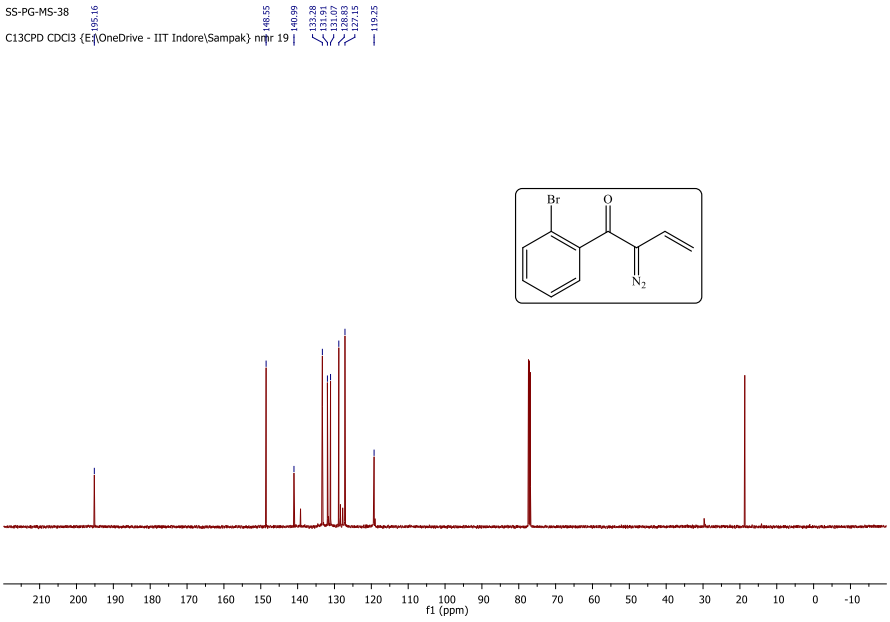


Fig 8: ^{13}C NMR spectrum (125 MHz) of **1d** in $CDCl_3$

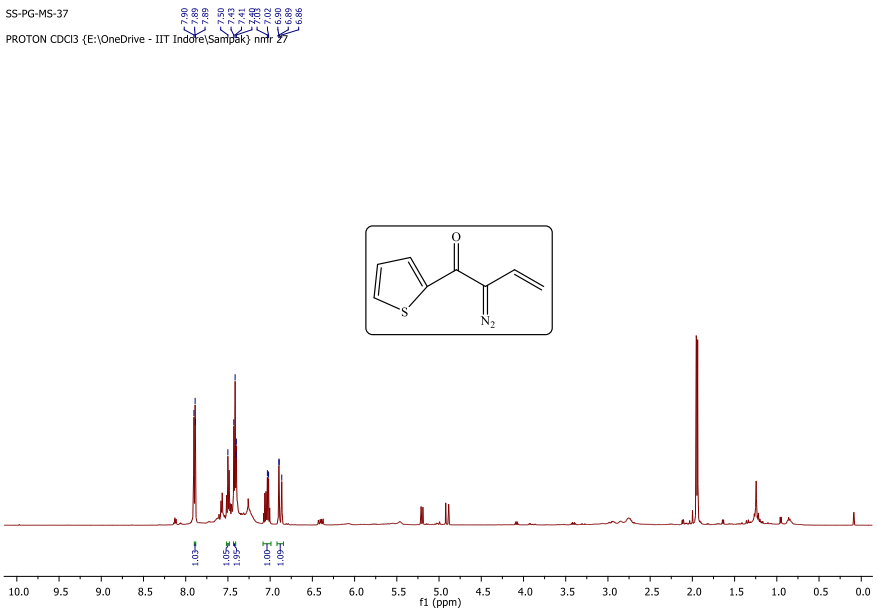


Fig 9: ^{1}H NMR spectrum (500 MHz) of **1e** in $CDCl_3$

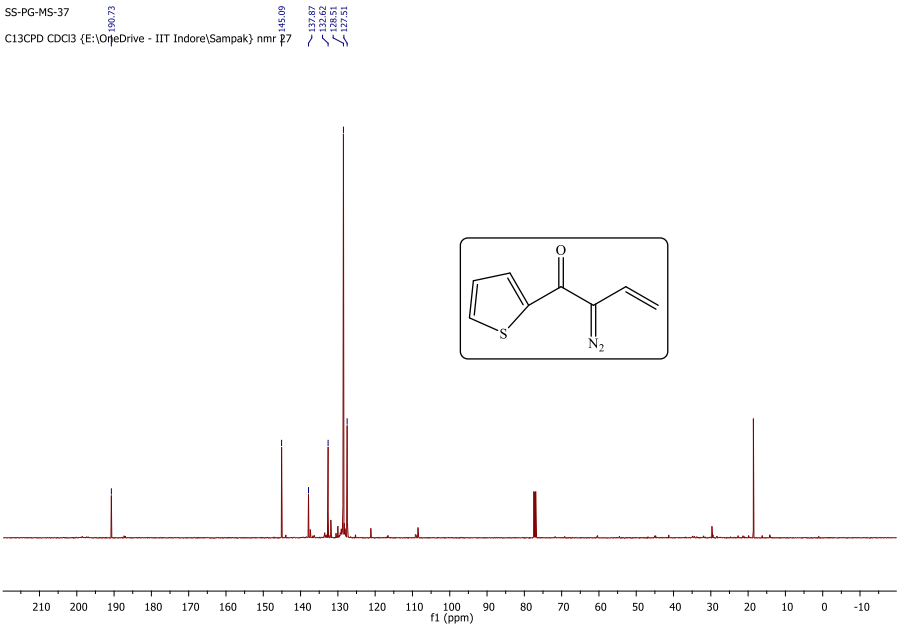


Fig 10: ^{13}C NMR spectrum (125 MHz) of **1e** in $CDCl_3$

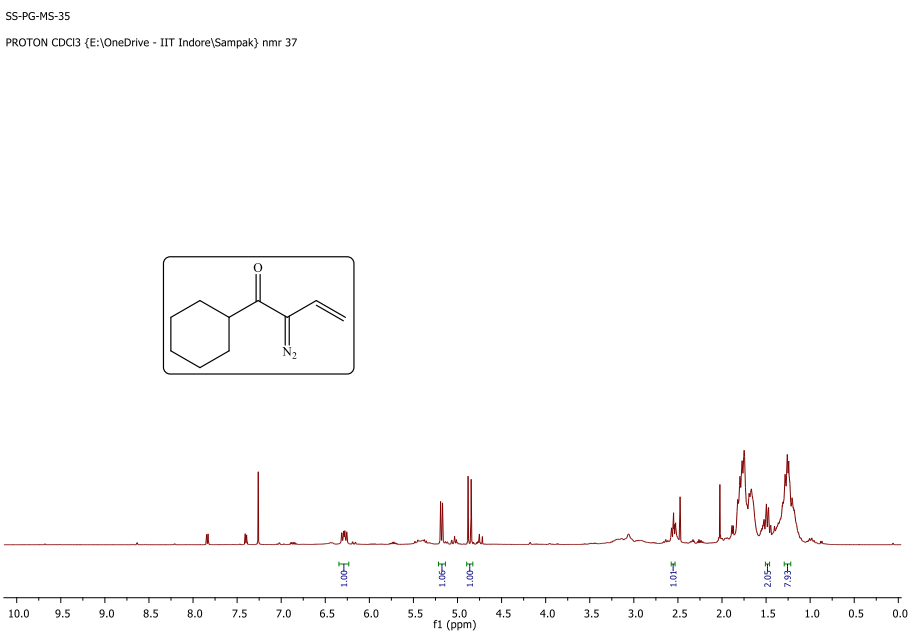


Fig 11: ^{1}H NMR spectrum (500 MHz) of **1f** in $CDCl_3$

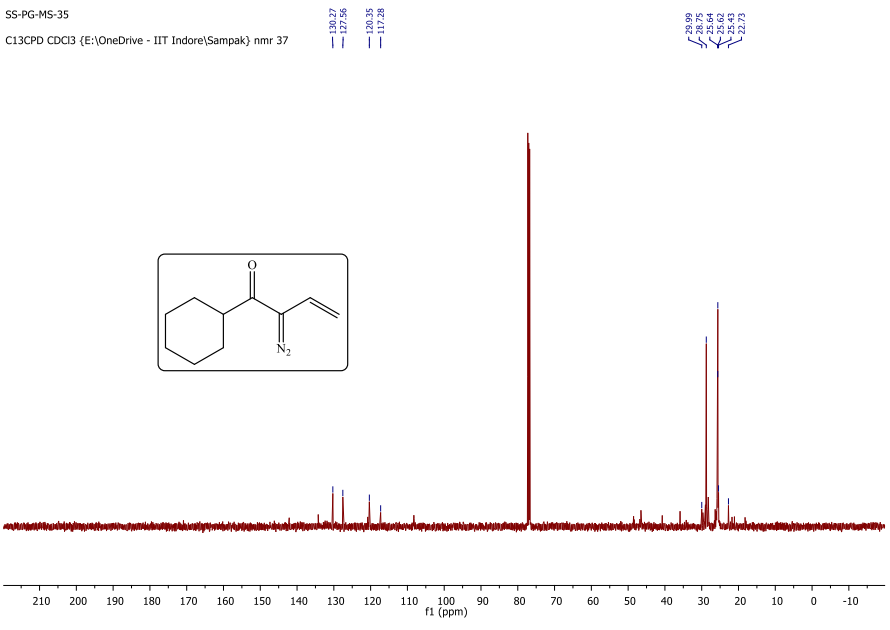


Fig 12: ^{13}C NMR spectrum (125 MHz) of **1f** in $CDCl_3$

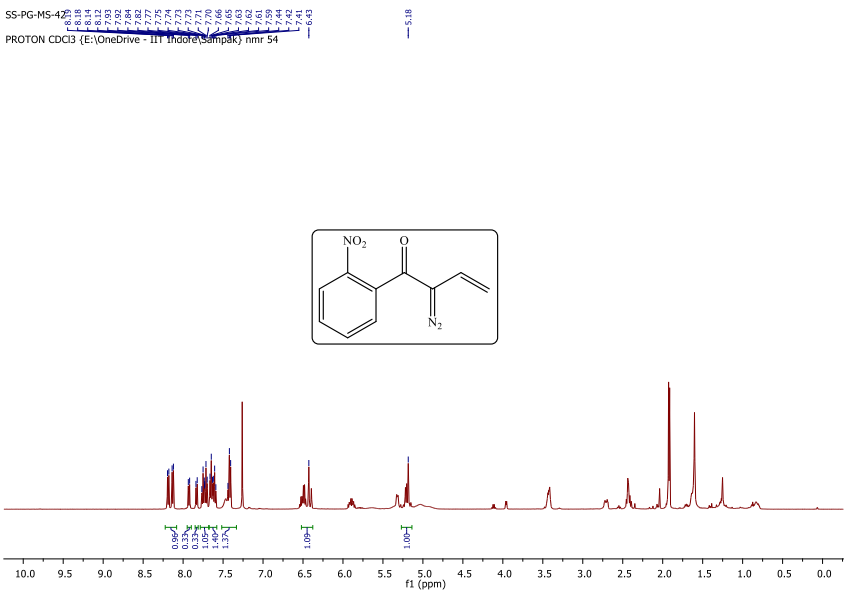


Fig 13: ^{1}H NMR spectrum (500 MHz) of **1g** in $CDCl_3$

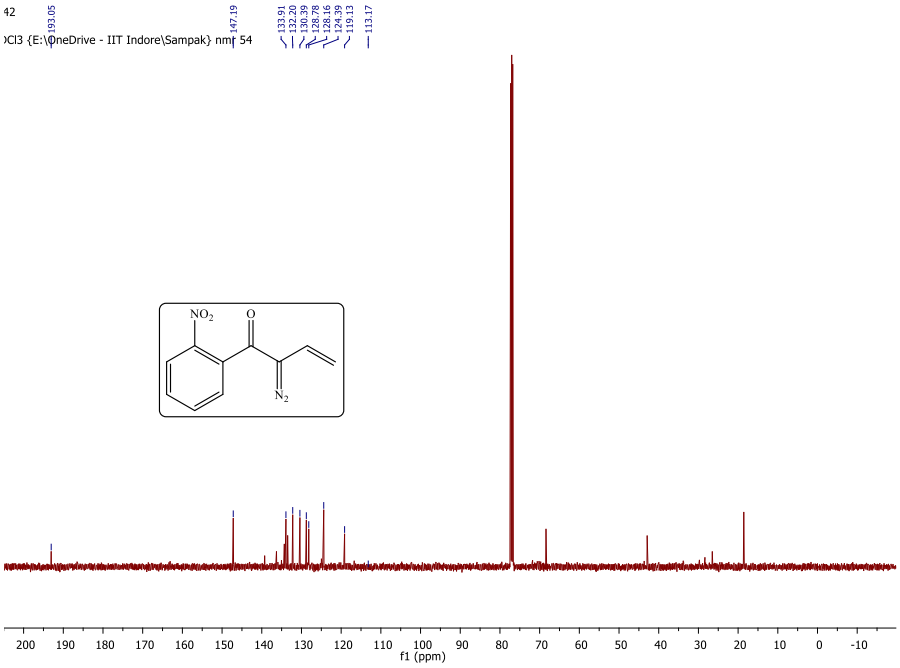


Fig 14: ^{13}C NMR spectrum (125 MHz) of **1g** in $CDCl_3$

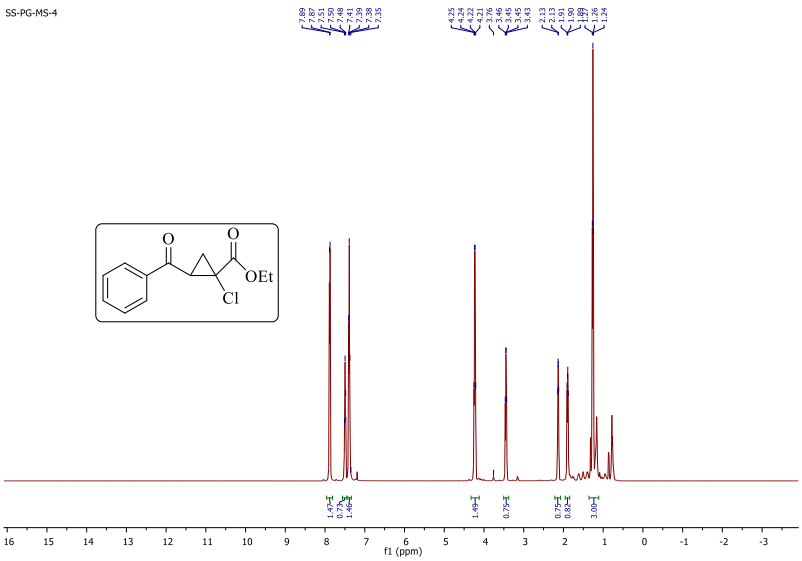


Fig 15: ^{1}H NMR spectrum (500 MHz) of **2a** in $CDCl_3$

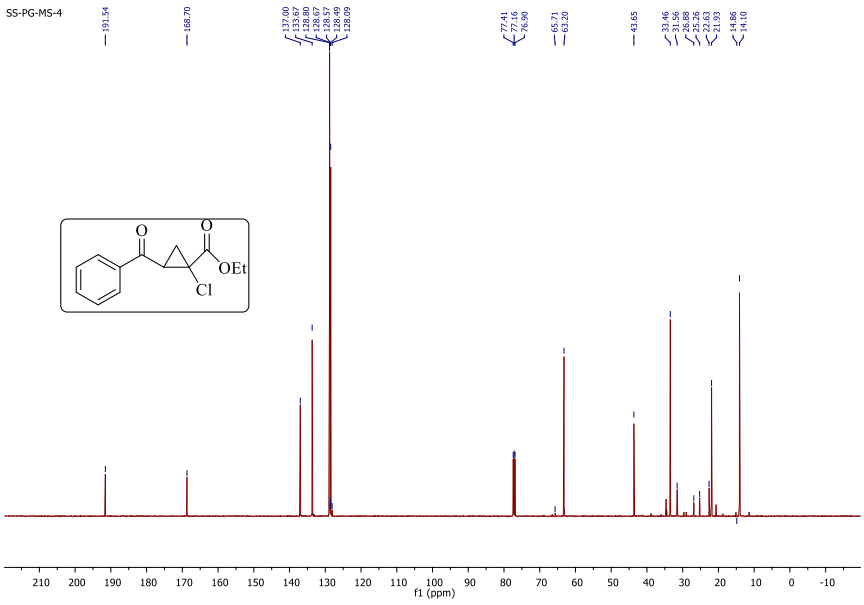


Fig 16: ^{13}C NMR spectrum (125 MHz) of **2a** in $CDCl_3$

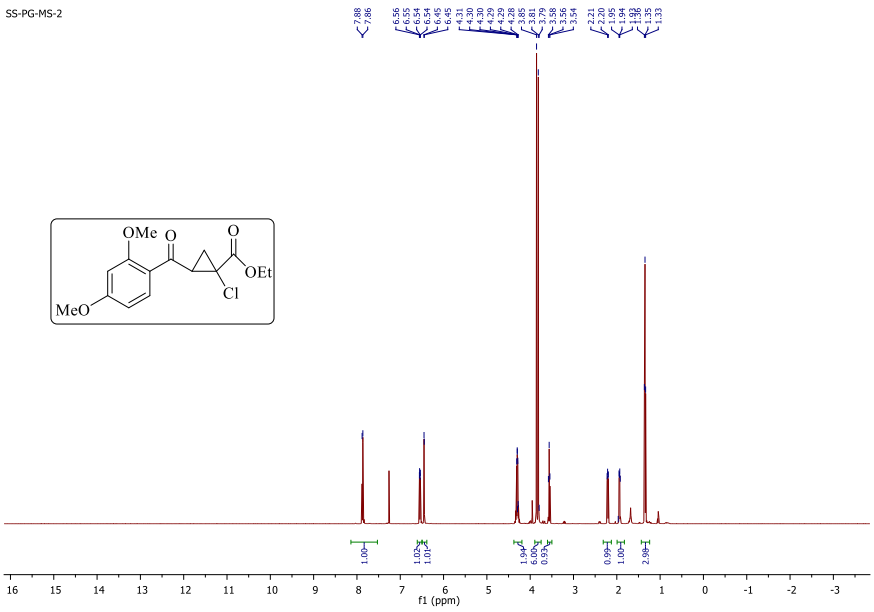


Fig 17: ^{1}H NMR spectrum (500 MHz) of **2b** in $CDCl_3$

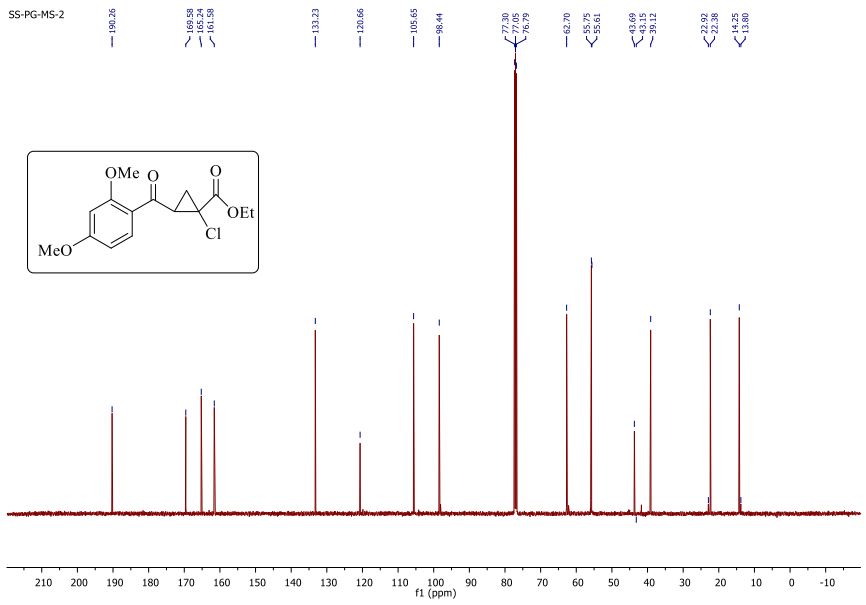


Fig 18: ^{13}C NMR spectrum (125 MHz) of **2b** in $CDCl_3$

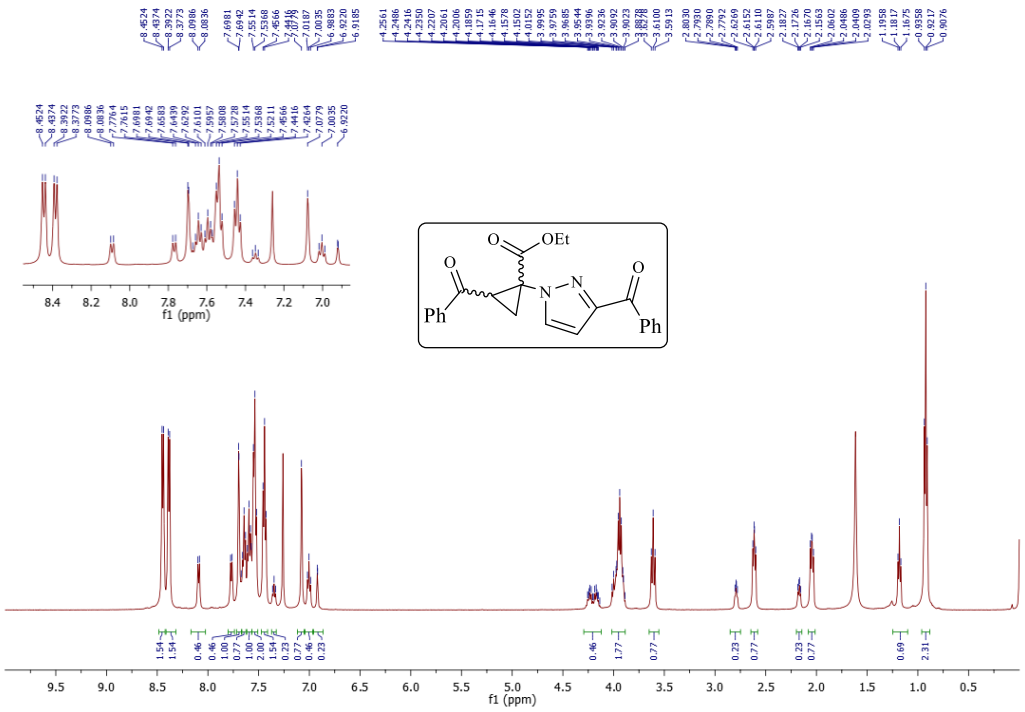


Fig 19: ^{1}H NMR spectrum (500 MHz) of **3a** in $CDCl_3$

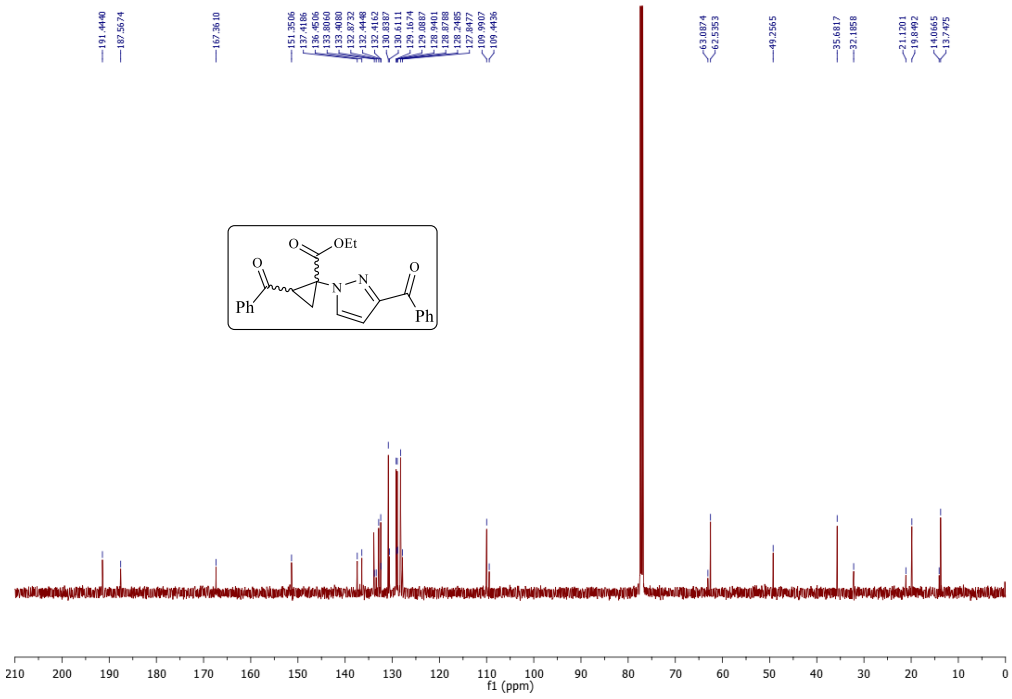


Fig 20: ^{13}C NMR spectrum (125 MHz) of **3a** in $CDCl_3$

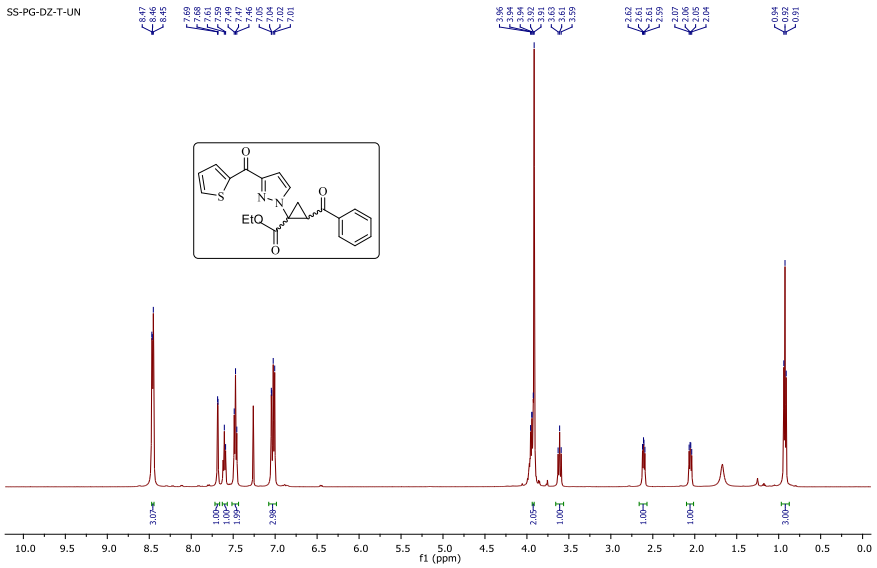


Fig 21: ^{1}H NMR spectrum (500 MHz) of **3ae** in $CDCl_3$

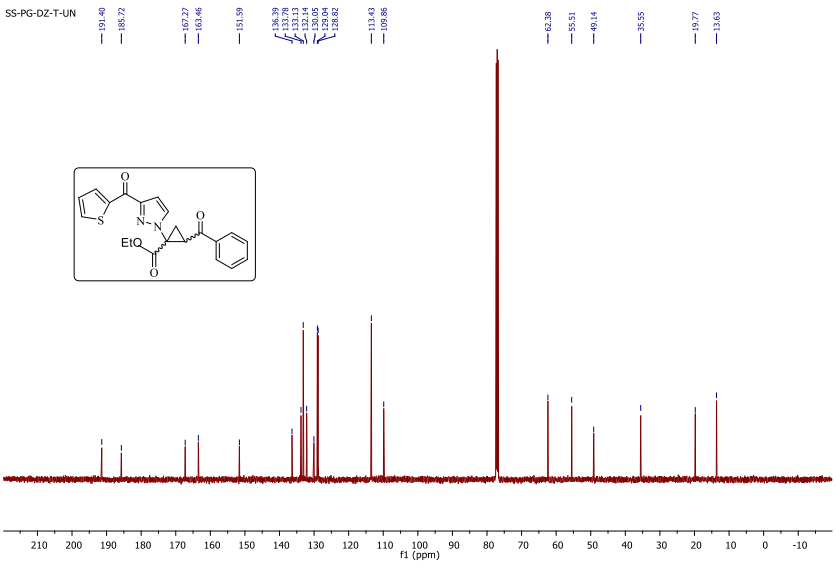


Fig 22: ^{13}C NMR spectrum (125 MHz) of **3ae** in $CDCl_3$

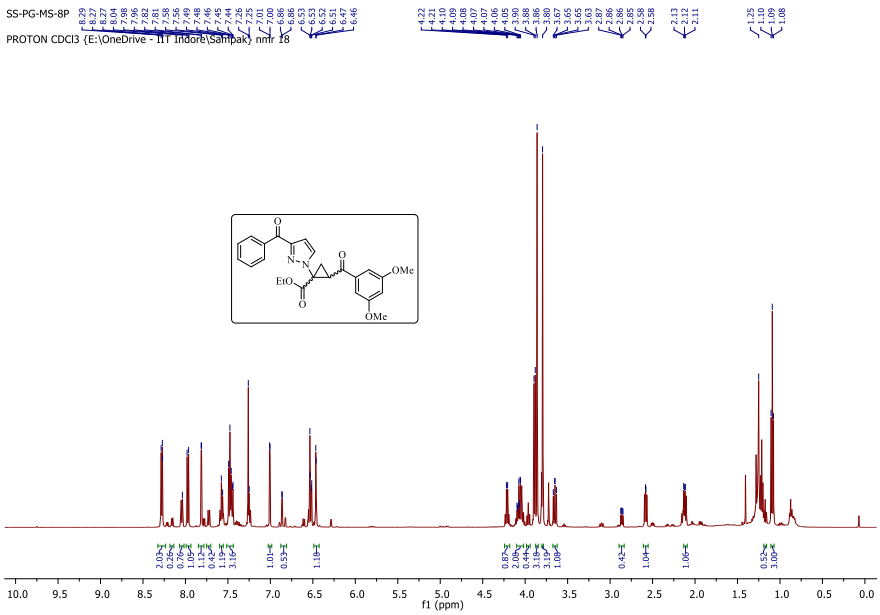


Fig 23: ^{1}H NMR spectrum (500 MHz) of **3ad** in $CDCl_3$

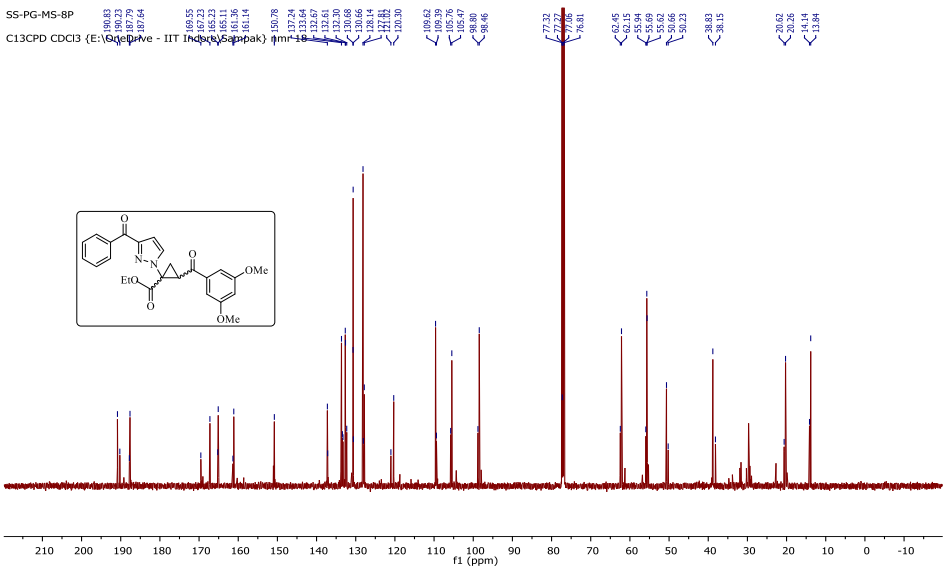


Fig 24: ^{13}C NMR spectrum (125 MHz) of **3ad** in $CDCl_3$

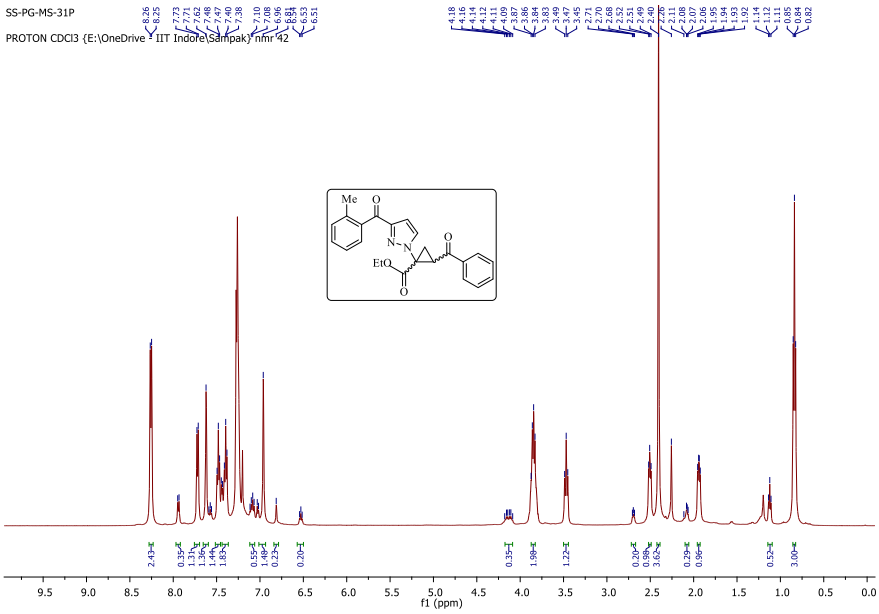


Fig 25: ^{13}C NMR spectrum (125 MHz) of **3ab** in $CDCl_3$

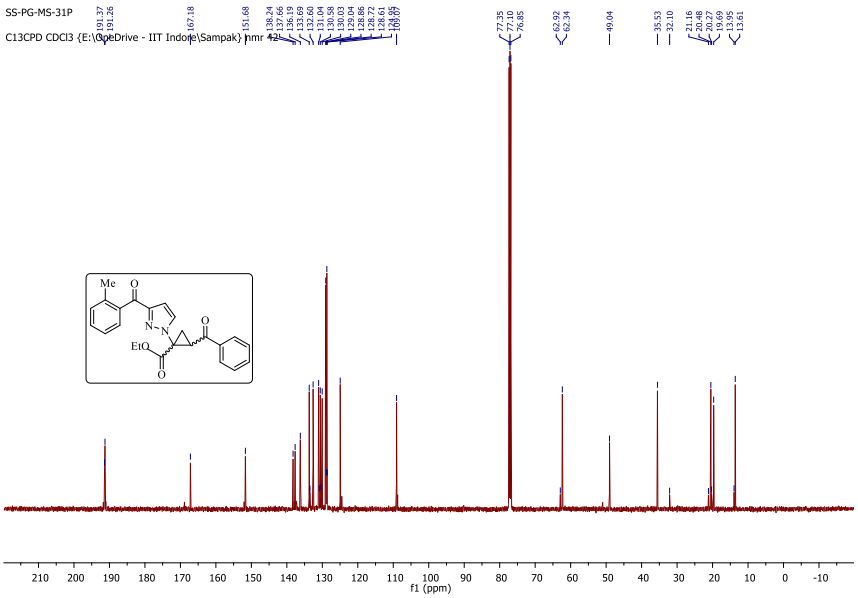


Fig 26: ^{13}C NMR spectrum (125 MHz) of **3ab** in $CDCl_3$

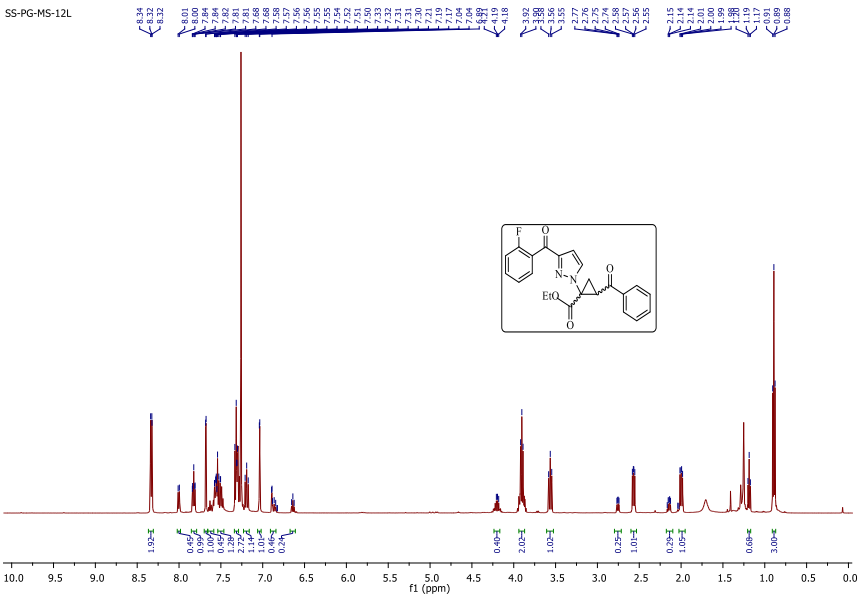


Fig 27: ^{1}H NMR spectrum (500 MHz) of **3aj** in $CDCl_3$

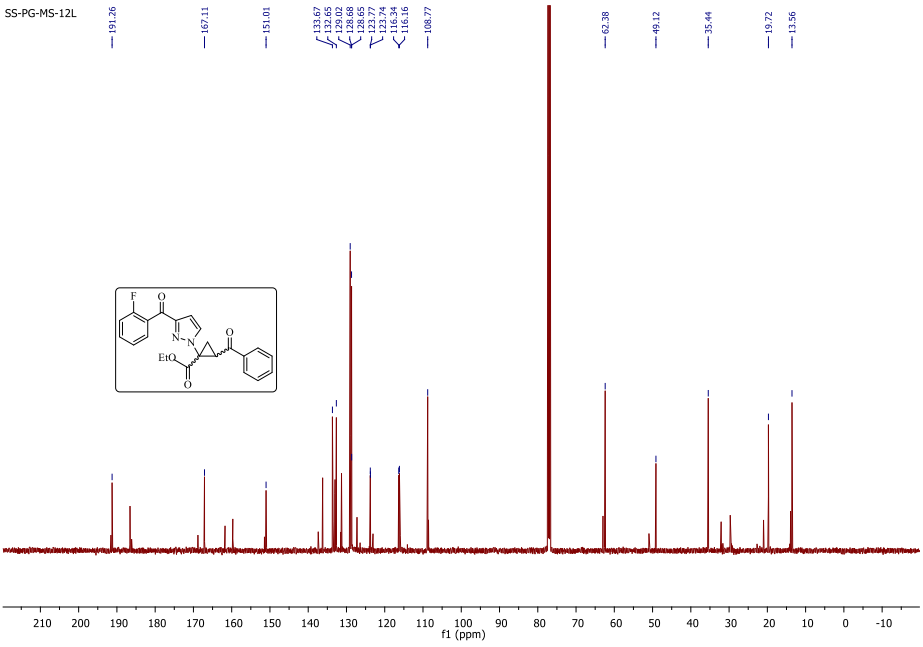


Fig 28: ^{13}C NMR spectrum (125 MHz) of **3aj** in $CDCl_3$

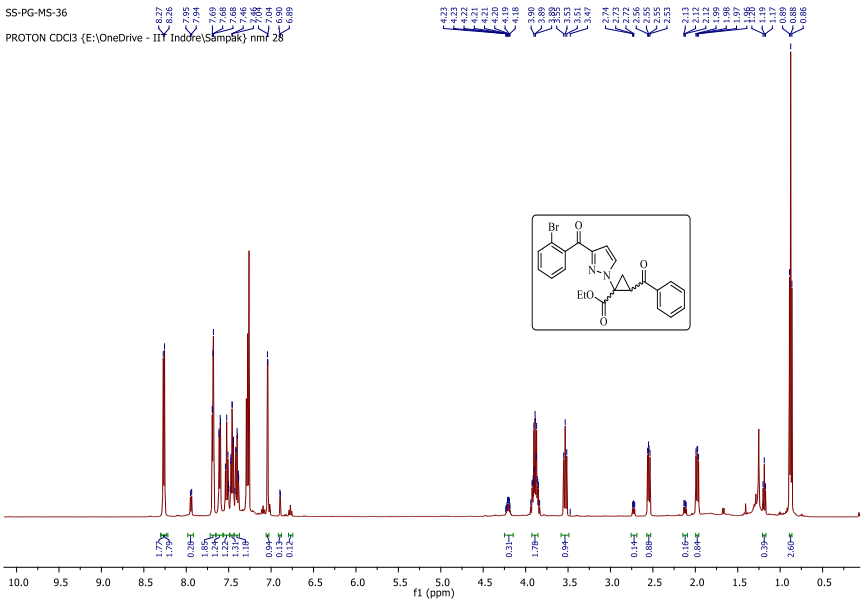


Fig 29: ^{1}H NMR spectrum (500 MHz) of **3ac** in $CDCl_3$

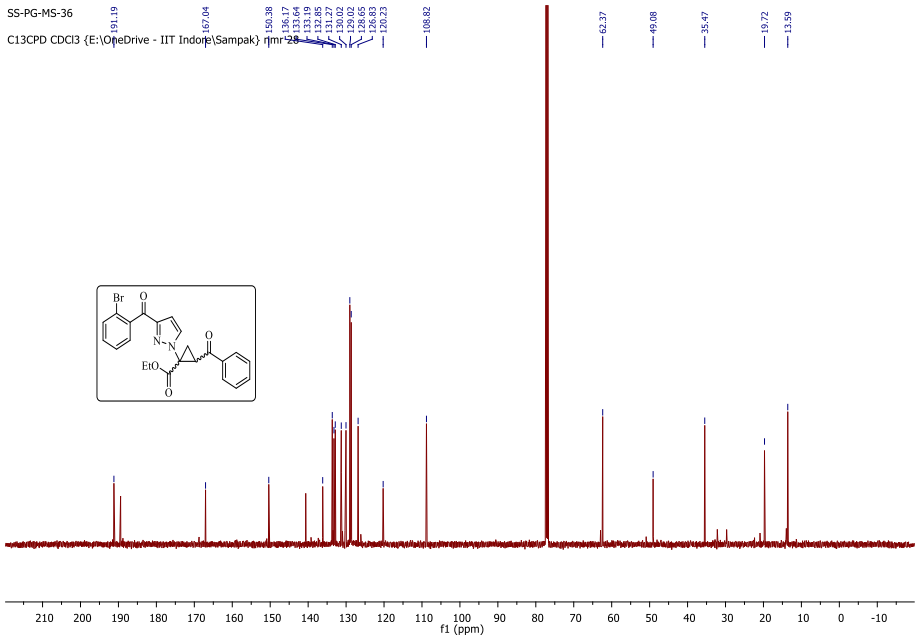


Fig 30: ^{13}C NMR spectrum (125 MHz) of **3ac** in $CDCl_3$

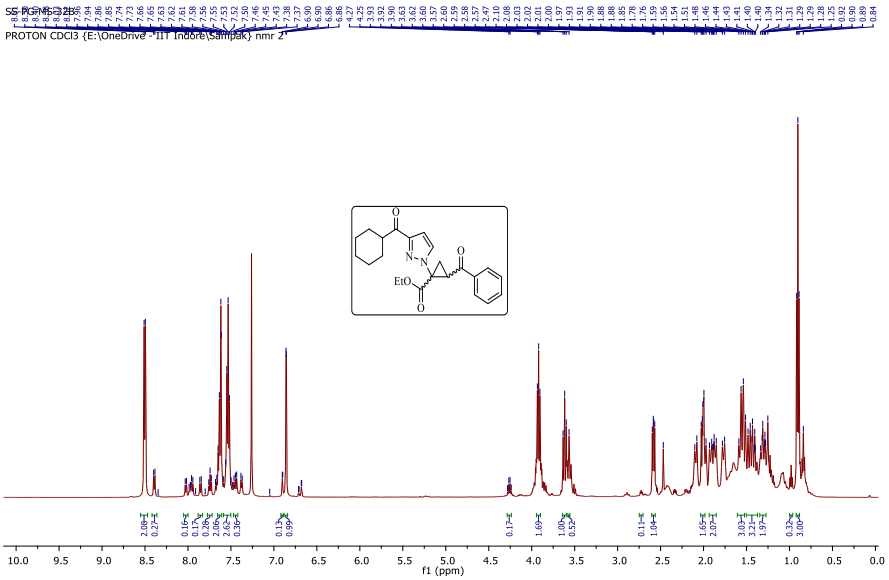


Fig 31: ^{1}H NMR spectrum (500 MHz) of **3ag** in $CDCl_3$

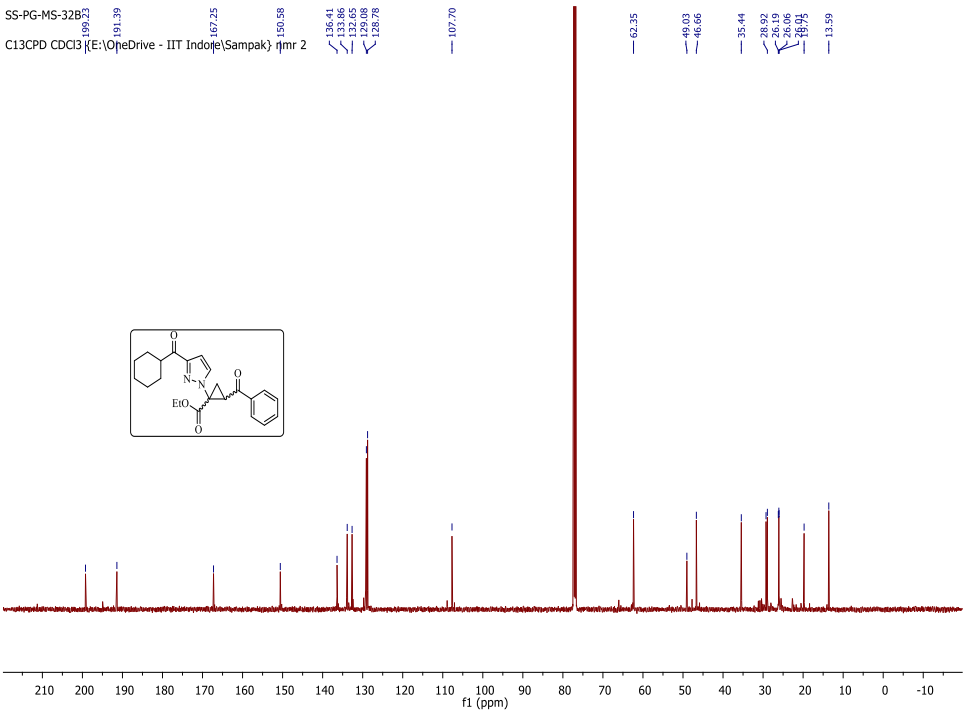


Fig 32: ^{13}C NMR spectrum (125 MHz) of **3ag** in $CDCl_3$

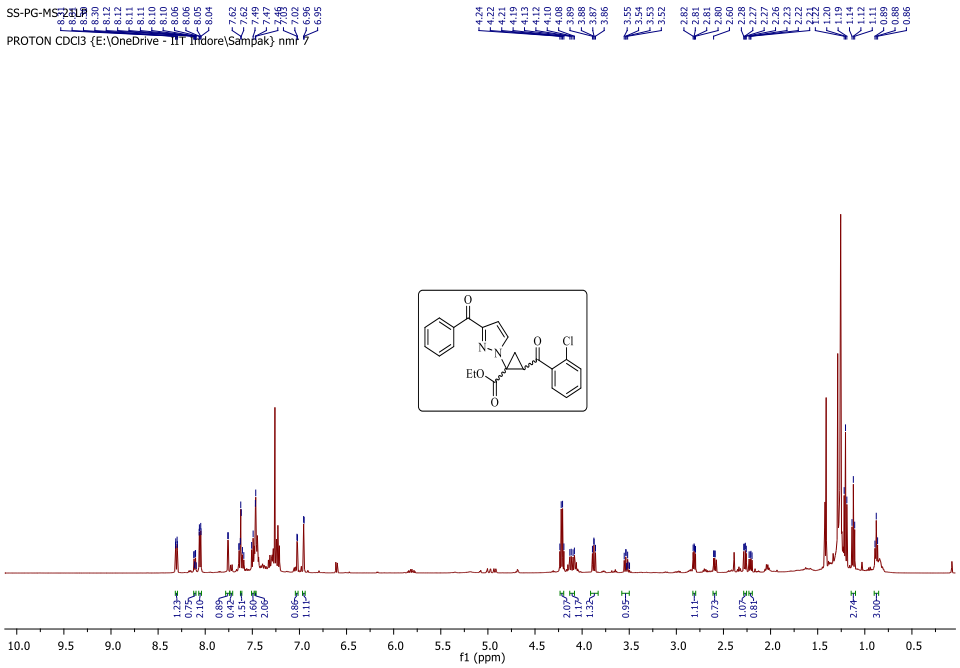


Fig 33: ^{1}H NMR spectrum (500 MHz) of **3ak** in $CDCl_3$

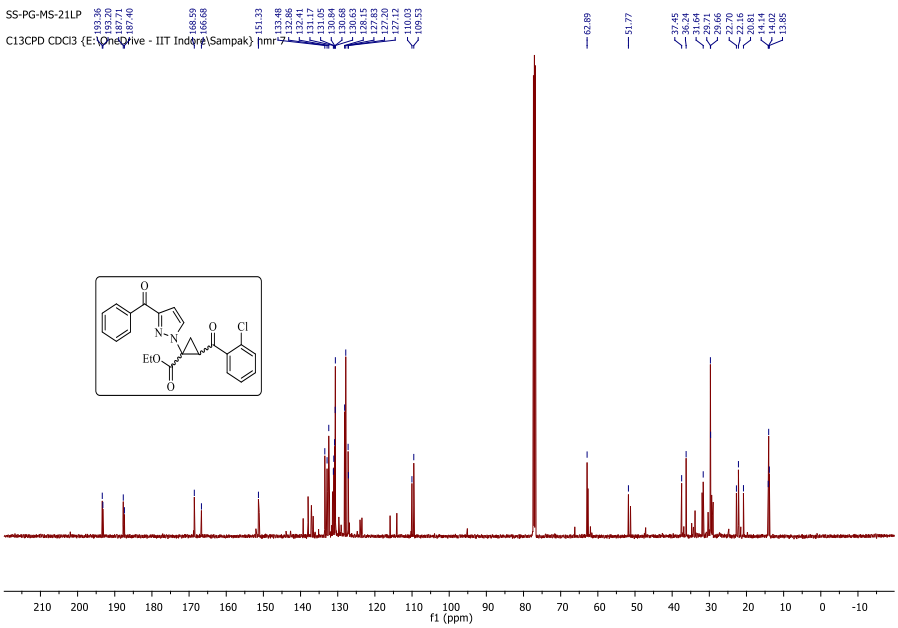


Fig 34: ^{13}C NMR spectrum (125 MHz) of **3ak** in $CDCl_3$

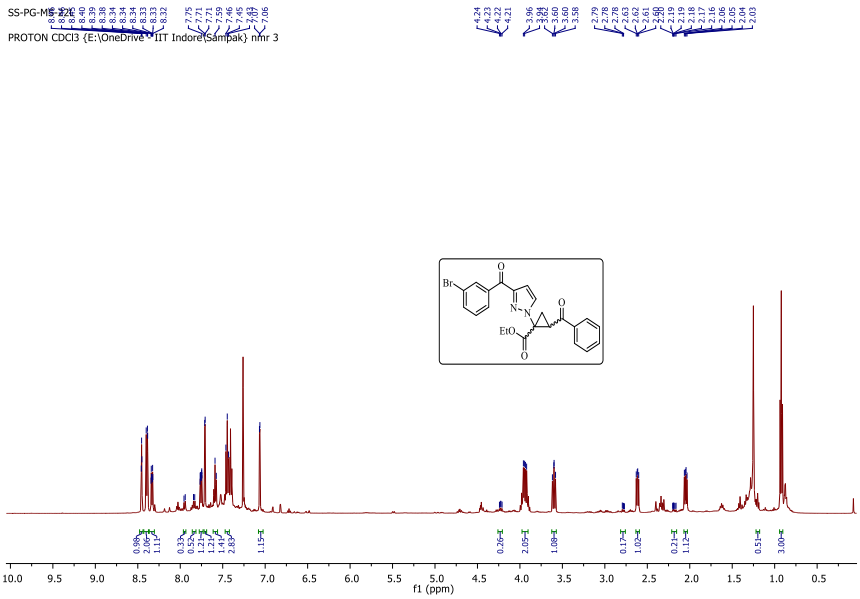


Fig 35: ^{1}H NMR spectrum (500 MHz) of **3af** in $CDCl_3$

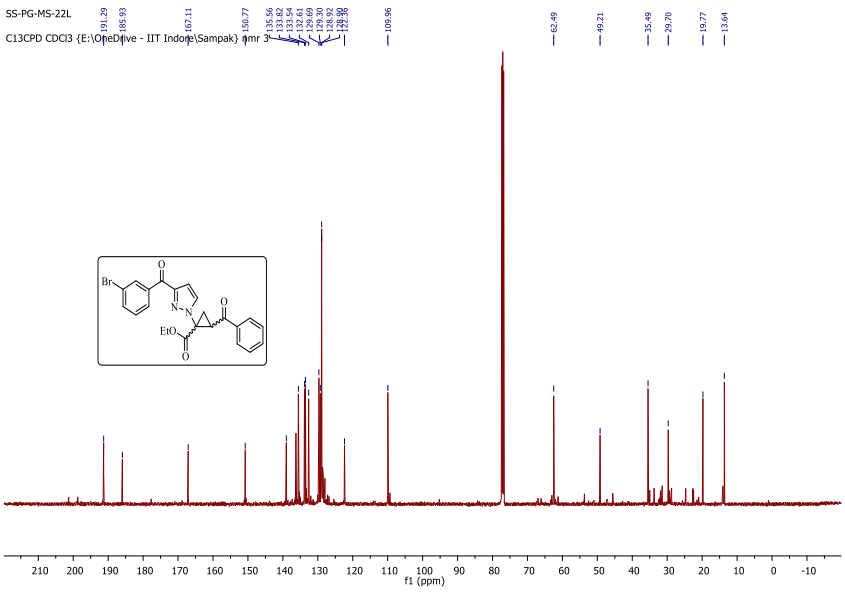


Fig 36: ^{13}C NMR spectrum (125 MHz) of **3af** in $CDCl_3$

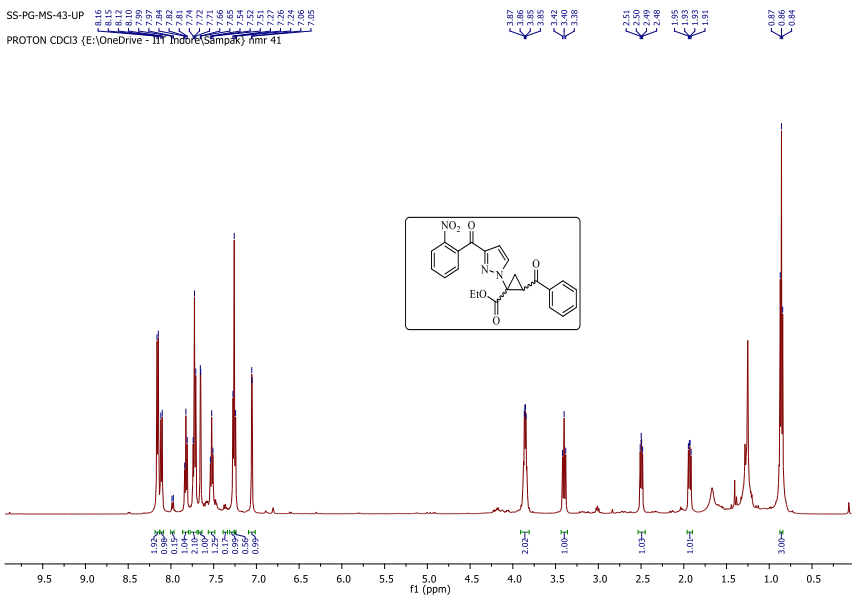


Fig 37: ^{1}H NMR spectrum (500 MHz) of **3ai** in $CDCl_3$

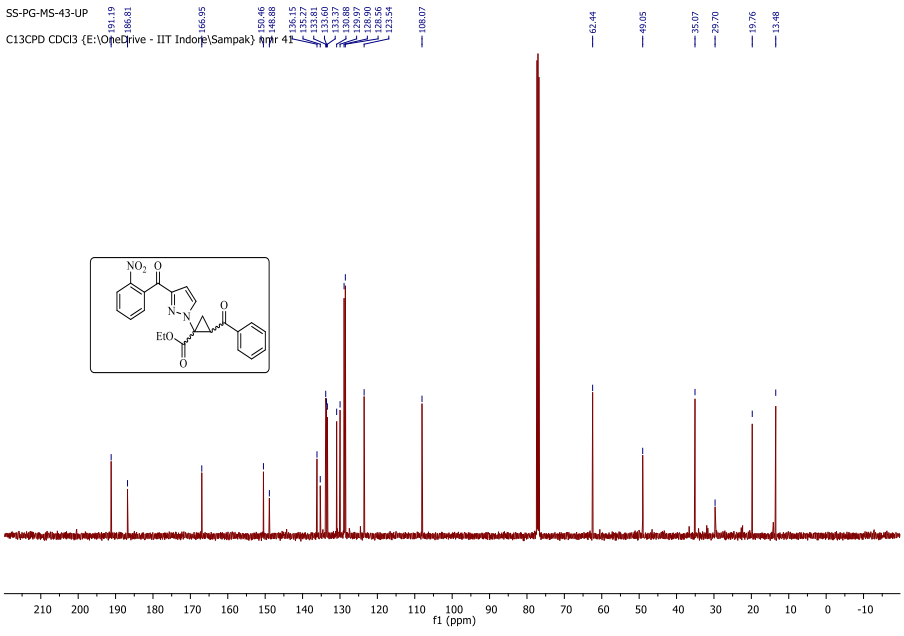


Fig 38: ^{13}C NMR spectrum (125 MHz) of **3ai** in $CDCl_3$

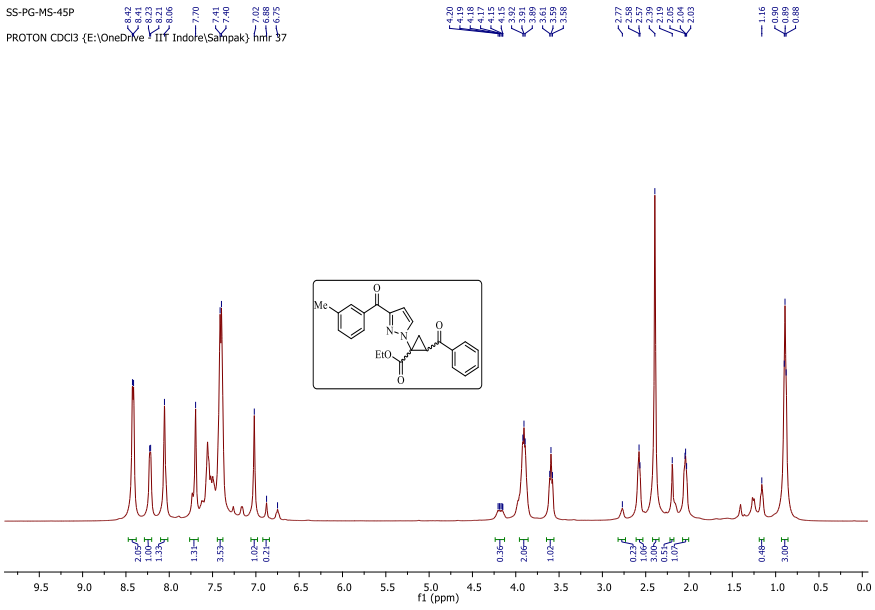


Fig 39: ^{1}H NMR spectrum (500 MHz) of **3ah** in $CDCl_3$

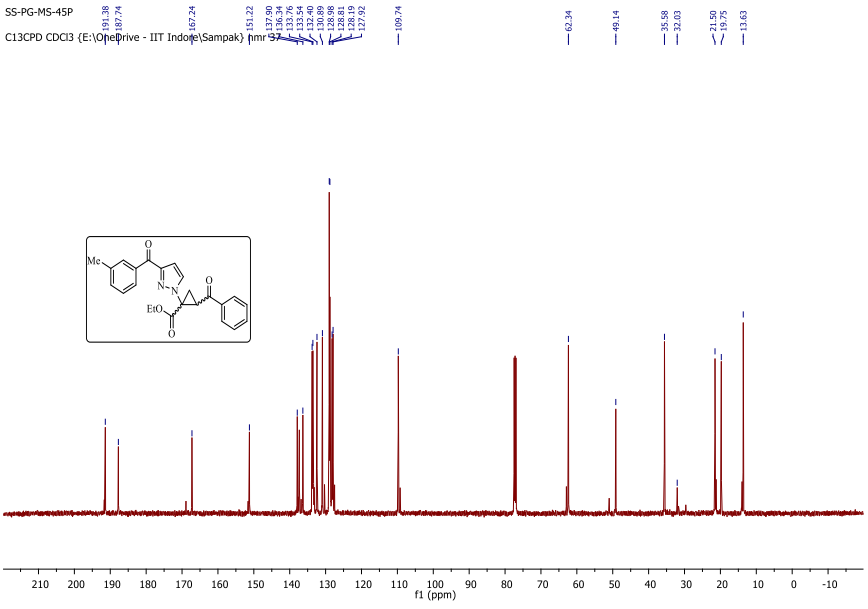


Fig 40: ^{13}C NMR spectrum (125 MHz) of **3ah** in $CDCl_3$

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