Functionalized 1,3-Dicarbonyls: Synthesis and Their Applications to Access Biaryls, Bis-Indole Substituted Indenes and 1,4-Naphthoquinones

A thesis submitted for the degree of

DOCTOR OF PHILOSOPHY

IN CHEMISTRY

by

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INDIA

……..Dedicated to

Farmers and Indian soldiers

Declaration

I, T Chandrahas hereby state that the matter encapsulated in this thesis is the result of research carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, under the supervision of **Prof. R. Balamurugan**.

In keeping with the general practice of reporting scientific notes, due acknowledgement has been made wherever the work described is based on the findings of other investigators. Any oversight, which might have occurred by misconstruction or fault, is regretted. This work is free from Piracy. I hereby agree that my thesis can be placed in Shodhganga/INFLIBNET.

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Certificate

Certified that the work demonstrated in this thesis entitled **"Functionalized 1,3-Dicarbonyls: Synthesis and Their Applications to Access Biaryls, Bis-Indole Substituted Indenes and 1,4-Naphthoquinones"** has been carried out by **T. CHANDRAHAS** under my supervision, in the School of Chemistry. This thesis is free form plagiarism and the same has not been submitted elsewhere for a degree.

Parts of the thesis have been

A. Published in the following publications

1. **Chandrahas Tarigopula,** Thota, G. K.; Rengarajan Balamurugan. *Eur. J. Org. Chem.* **2016**, 5855-5861 (**Chapter 1**).
2. **Chandrahas Tarigopula,** Seetharaman, Manojveer, Rengarajan Balamurugan. (*J. Org. Chem*. doi.org/10.1021/acs.joc.1c01277) (**Chapter 2**).
3. **Chandrahas Tarigopula,** Rengarajan Balamurugan. (Manuscripts to be communicated) (**Chapter 3**).

B. Presented in the following conferences

1. ICOS21-2016; **2**. ChemFest-2017; **3**. ChemFest-2019

Further the student has passed the following courses towards fulfilment of course work requirement for Ph.D.

Course Code	Name	Credits	Pass/Fail/Grade
CY801	Research Proposal	3	B
CY802	Chemistry Pedagogy CY305: Organic Chemistry Lab	3	A
CY805	Instrumental Method- A	3	C
CY502	Advanced Organic Synthesis	3	B

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T. Chandrahas

TABLE OF CONTENTS

List of acronyms used

Å	Angstrom
Ac	Acetyl
Anal. Calc'd	Analytically calculated
Aq.	Aqueous
Ar	Aryl
BA	Brønsted acid
Bn	Benzyl
br s	Broad singlet (spectral)
t-Bu	tert-Butyl
°C	Degree Celsius
Cacld	Calculated
Cat.	Catalytic
cm^{-1}	Wavenumber(s)
conc.	Concentrated
δ	Chemical shift in parts per million
d	Doublet
DABSO	1,4-Diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct
DABCO. $(SO)_2$	1,4-Diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct
DCE	Dichloroethane
DCM	Dichloromethane
dd	Doublet of doublets (spectral)
DDQ	2,3-Dichloro-5,6-dicyano-p-benzoquinone
DFT	Density functional theory
dil.	Dilute
DMA	N,N-Dimethylacetamide
DMAP	4-Dimethylaminopyridine

DMAD	Dimethyl acetylenedicarboxylate
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
DNB	Dinitrobenzene
dr	Diastereomeric ratio
dt	Doublet of triplets (Spectral)
ee	Enantiomeric excess
EPR	Electron paramagnetic resonance
equiv	Equivalent
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol
FT	Fourier transformation
g	Gram(s)
h	Hour(s)
HRMS	High resolution mass spectrometryv
Hz	Hertz
i-Pr	Isopropyl
IR	Infrared
J	Coupling constant (in NMR Spectroscopy)
K	Kelvin (Temperature)
LA	Lewis acid
Lit.	Literature
M	Molar (Solution concentration)
m	Multiplet (spectral)
Me	Methyl
MeCN	Acetonitrile
mg	Milligram(s)

MHz	Megahertz
min	Minute(s)
mL	Millilitre (s)
mmol	Millimole(s)
mp	Melting point
MS	Molecular sieves
μL	microliter
MTBD	7-methyl-1,5,7-triazabicyclo [4.4.0]dec-5-ene
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
ORTEP	Oak ridge thermal ellipsoid plot
OTf	Trifluoromethanesulfonate
PDC	Pyridinium dichromate
Ph	Phenyl
PMA	Phosphomolybdic acid
PNBB	p-Nitrobenzylbromide
PNBC	p-Nitrobenzylchloride
p-TSA	p-Toluenesulfonic acid
q	Quartet (spectral)
R_f	Retardation factor
RT	Room temperature
s	Singlet (spectral)
SET	Single Electron Transfer
t	Triplet (spectral)
TBAF	Tertiary butyl ammonium Fluoride
TBAI	Tetra-n-butyl ammonium iodide

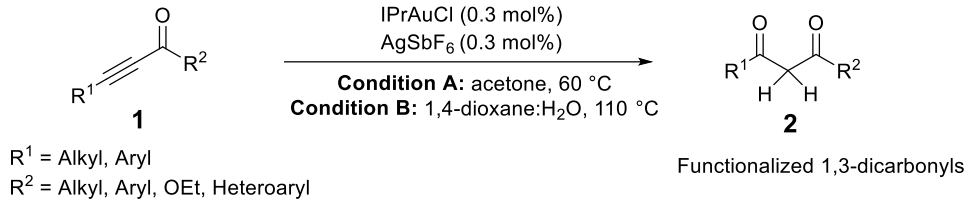
TBDMS	tert-Butyldimethylsilyl ether
TBHP	Tertiary butyl hydro peroxide
TBP	Tributyl phosphate
td	Triplet of doublets(spectral)
TFA	Trifluoroacetic acid
TfOH	Triflic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMOF	Trimethyl orthoformate
TMSCl	Trimethylsilyl chloride
UV	Ultraviolet
XRD	X-Ray Diffraction

Synopsis

This thesis entitled "**Functionalized 1,3-Dicarbonyls: Synthesis and Their Applications to Access Biaryls, Bis-Indole Substituted Indenes and 1,4-Naphthoquinones**" contains three chapters. The first chapter deals with the synthesis of 1,3-dicorbonyls by a gold catalyzed regioselective hydration of alkynyl esters and alkynyl ketones. Chapter 2 deliberates about an one-pot Brønsted acid-promoted synthesis of biaryls by construction of benzene via *in situ* acetals formed from 1,3-diketones/alkynyl methyl ketone and propargylic alcohols. Chapter 3 presents the synthetic utility of bis-alkylidene dihydroisobenzofurans which were synthesized from a class of functionalized 1,3-dicarbonyls. This chapter has two parts. The first Part presents the synthesis of bis-indole substituted indene derivatives from bis-alkylidene dihydroisobenzofurans in acidic medium. In the second part, the synthesis of 1,4-naphthoquinone in the presence of NIS is discussed.

Chapter 1: Access to Functionalized β-Keto Esters and β-Diketones via Gold-Catalyzed Regioselective Hydration of Alkynyl Esters and Alkynyl Ketones

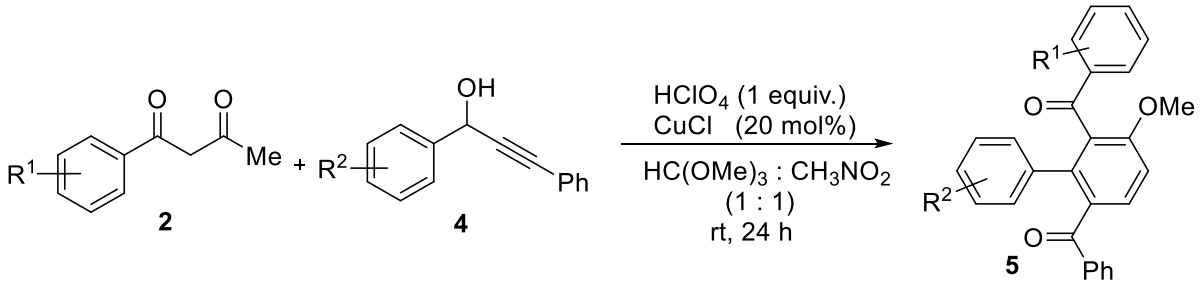
A regioselective hydration of α-alkynyl esters and ketones **1** by using a cationic NHC–Au^{I} catalyst results in β-keto esters and β-diketones **2**, respectively (Scheme 1). In this, we used two different solvent systems for the hydration of α-alkynyl esters and ketones. While acetone is a better solvent for the hydration of 2-alkynoates, 1,4-dioxane/water is more appropriate for the hydration of alkynones. In acetone solvent system, water which generated from acetone by aldol self-condensation in the presence of acid catalyst is responsible for the controlled hydration reaction. This transformation displays significant substrate scope and the details are discussed in this chapter.



Scheme 1. Regioselective hydration of alkynyl esters and alkynyl ketones

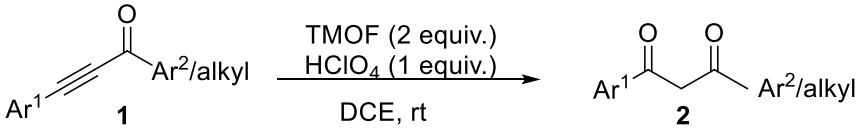
Chapter 2: A Facile Access to Highly Substituted Biaryls by Construction of Benzene Ring via *in situ* Formed Acetals

This chapter presents an interesting method for the synthesis of biaryls **5** by the construction of benzene ring using propargylic alcohols **4** and 1,3-dicarbonyls **2**. This protocol involves three new C-C bond formations via cascade alkylation, formylation, annulation and aromatization to make substituted biaryls (Scheme 2). This one-pot Brønsted acid-promoted protocol utilizes the unique reactivity of acetal formed under the reaction condition.



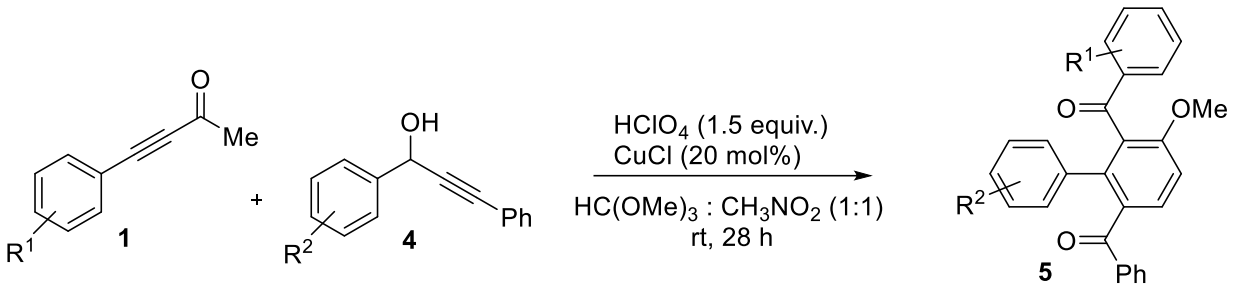
Scheme 2. Synthesis of biaryls from 1,3-diketones and propargylic alcohols

Synthesis of 1,3-dicarbonyls **2**, apart from trivial Claisen condensation, has been achieved by regioselective hydration of alkynones **1** using gold-catalysts is presented in chapter 1. It has been found out that hydration can be carried out on alkynones **1** regioselectively using a Brønsted acid in the presence of trimethyl orthoformate. Perchloric acid promoted hydration of alkynones **1** occurs at room temperature to afford 1,3-dicarbonyls **2** (Scheme 3).



Scheme 3. TMOF-assisted $HClO_4$-promoted conversion of alkynones into 1,3-diketones

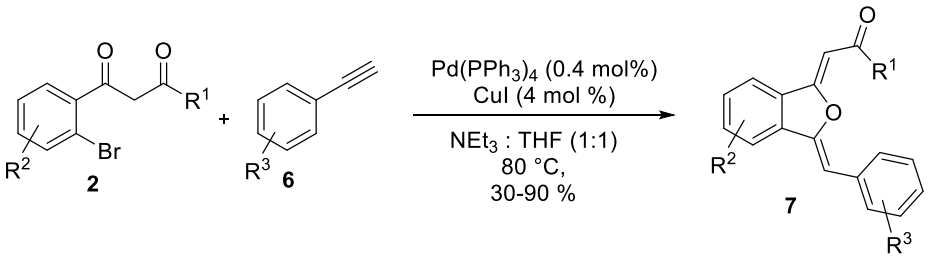
In this regard, alkynyl methyl ketones **1** could also be employed for the synthesis of biaryls in the place of 1,3-dicarbonyls as they get converted into 1,3-dicarbonyls by hydration under the reaction conditions (Scheme 4). This one-pot protocol involving sequential hydration, propargylation, formylation, cyclization and aromatization shows a significant substrate scope for the synthesis of biaryl products **5**.



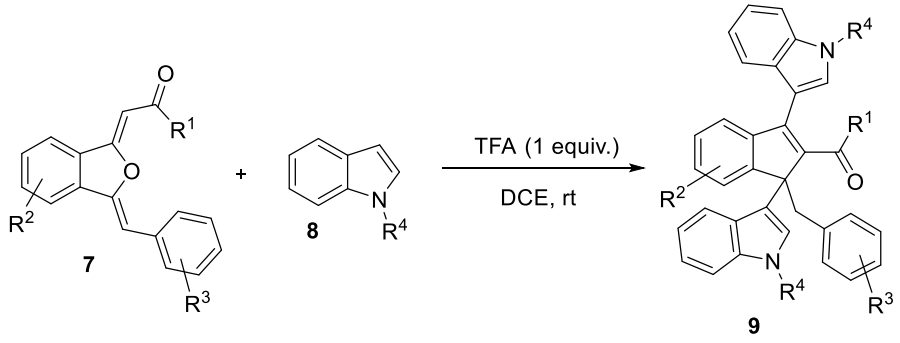
Scheme 4. Synthesis of biaryls from alkynyl methyl ketones and propargyl alcohols

Chapter 3: Synthesis of Bis-Alkylidene Dihydroisobenzofuran from 1,3-Dicarbonyls and its Applications in Organic Synthesis

Palladium catalyzed reaction of 1,3-dicarbonyl derivatives **2** with terminal alkynes **6** results in bis-alkylidene dihydroisobenzofurans **7** (Scheme 5). The initially formed Sonogashira coupled product undergoes palladium-catalyzed cyclization under reaction conditions to give bis-alkylidene dihydroisobenzofuran **7**. A wide variety of bis-alkylidene dihydroisobenzofurans were synthesized and characterized. We explored the synthetic applications of these bis-alkylidene dihydroisobenzofuran derivatives since the bis-alkylidene dihydroisobenzofurans have both electrophilic as well as nucleophilic centres. We have developed reactions using both nucleophile and electrophile. The product bis-indole substituted indenes derivative **9** was observed when bis-alkylidene dihydroisobenzofurans **7** was treated with substituted indoles **8** in the presence of a Lewis/Brønsted acids at ambient temperature. The reaction proceeds through acid mediated ring opening, nucleophilic addition of indole and then ring closing to afford the indene derivative (Scheme 6).

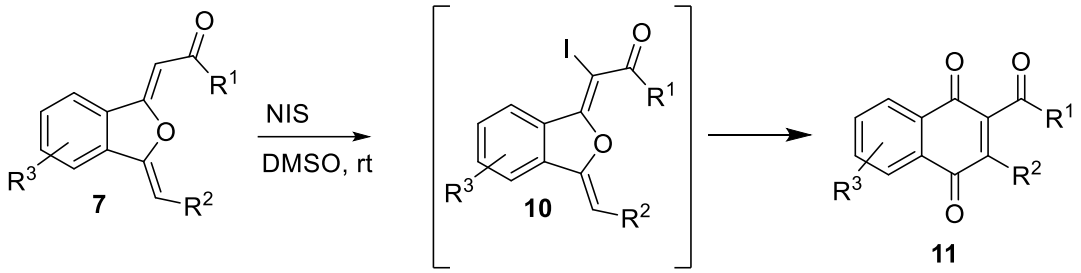


Scheme 5. Synthesis of bis-alkylidene dihydroisobenzofurans from 1,3-dicarbonyl compounds



Scheme 6. Synthesis of bis-indole substituted indene derivatives from bis-alkylidene dihydroisobenzofurans

Secondly, an interesting method for the formation of highly substituted 1,4-naphthoquinones **11** form bis-alkylidene dihydroisobenzofuran **7** in the presence of N-iodosuccinimide has been developed (Scheme 7). In this transformation, initially bis-alkylidene dihydroisobenzofuran undergoes iodination to form the intermediate **10**, followed by ring-opening and cyclization to result in 1,4-NQs. Control experiments were conducted to propose an acceptable mechanism of this transformation.



Scheme 7. Synthesis of 1,4-naphthoqinones from bis-alkylidene dihydroisobenzofurans.

Note: Schemes numbers and compound numbers given in this synopsis are different from those given in chapters 1, 2 and 3.

Chapter 1

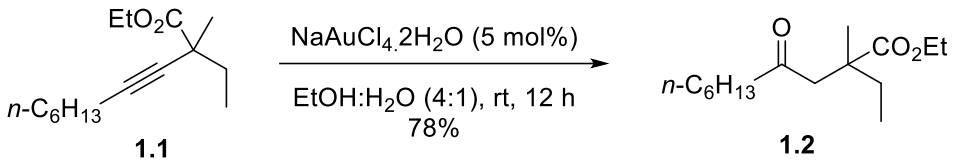
Access to Functionalized β-Keto Esters and β-Diketones via Gold-Catalyzed Regioselective Hydration of Alkynyl Esters and Alkynyl Ketones

1.1 Introduction

β-Keto esters and β-diketones are essential building blocks commonly used in the synthesis of biologically active compounds including heterocycles.[1] In addition, β-diketones exhibit remarkable coordination ability with metal ions to form valuable small metal complexes to single molecular magnetic clusters.[2] Usually they are made by Claisen ester condensation facilitated by bases.[3] In addition, other methods are also available involving different tactics.[4] However, synthesis of functionalized β-keto esters and β-diketones using trivial base-promoted Claisen condensation is tricky. Hence alternate methods are desirable to make such compounds under milder reaction conditions.

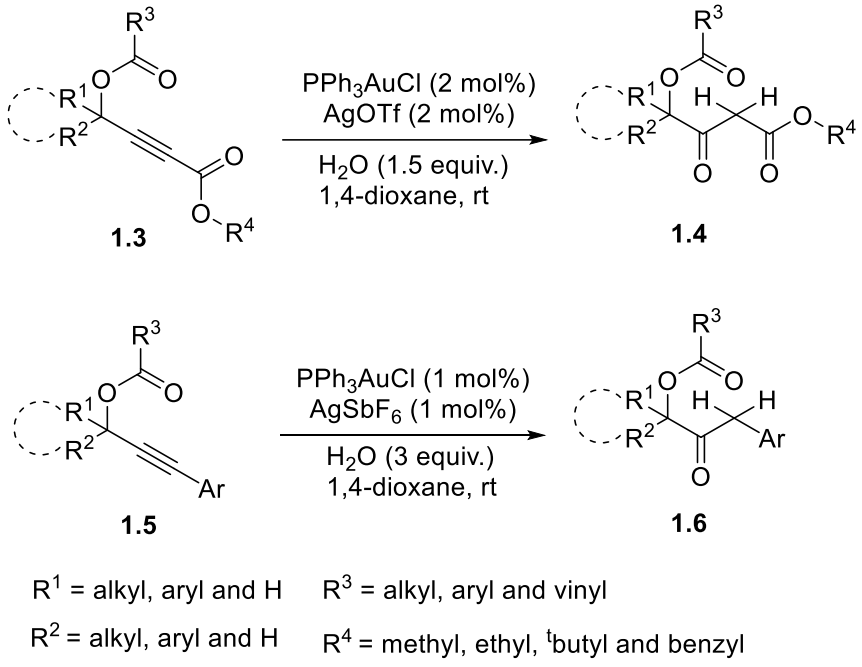
1.1.2 Recent progress on gold-catalyzed hydrolysis of alkynes

Gold catalysts have proved their efficiency to facilitate a range of organic transformations under milder reaction conditions.[5] Among the gold-catalyzed functional group transformations, hydration of alkynes is an important reaction.[6] Controlling the regioselectivity of hydration is a definite issue in this reaction and is generally addressed by making use of neighboring group participation.[6] Hydration of β-alkynyl esters and alkynyl ketones regioselectively at the β-carbon using gold catalysts is a viable approach to synthesize β-keto esters and β-diketones. Hammond and co-workers have employed $NaAuCl_4$ for the ester-assisted regioselective hydration of 3-alkynoates **1.1** to make β-ketoesters **1.2** (Scheme 1.1).[6q, 6r] They have also made a α, β-keto ester from 2-alkynoic ester using the same catalyst. However, they did not elaborate the study to weigh its applicability towards functionalized substrates. Among the gold catalysts, NHC-Au[I] based catalytic systems in dioxane/water have shown their superiority for the hydration of simple alkynes.[6s]



Scheme 1.1. Synthesis of γ-keto esters **1.2** through neighboring carbonyl group-assisted regioselective hydration of 3-Alkynoates **1.1**

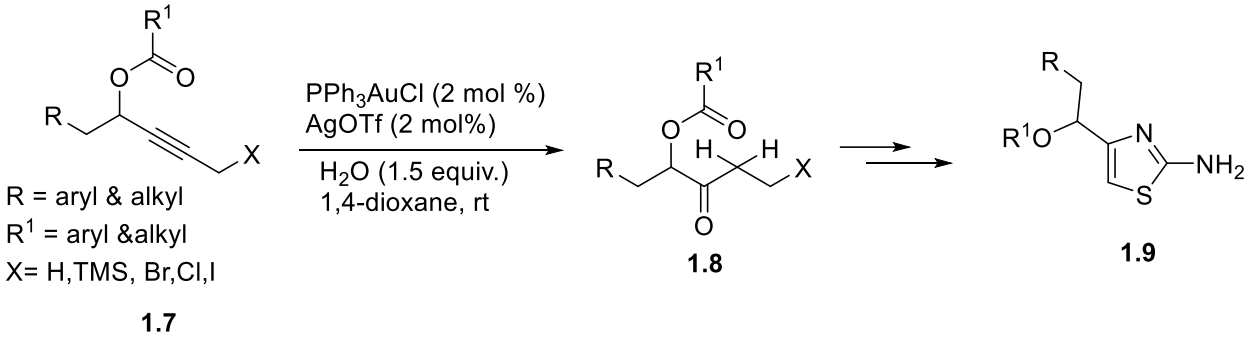
In 2015 and 2019, Mohapatra and co-workers have reported the synthesis of γ-acetoxy β-keto esters **1.4** and γ-acetoxy β-keto alkynyl aryls[6a] **1.6** using Ph_3PAuCl and a silver catalyst.[6g] In this reaction hydration of the γ-acetoxy-α, β-alkynoates **1.3** and unsymmetrical aryl alkynes **1.5** is assisted by the neighboring group participation of the acetoxy group (Scheme 1.2).



Scheme 1.2. Neighboring carbonyl group-assisted hydration of acetoxy alkynoates and unsymmetrical aryl alkynes

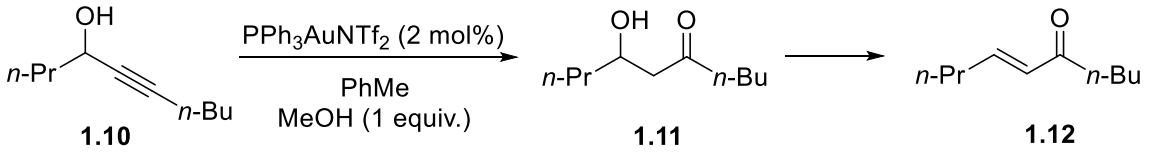
Sahoo and co-workers reported a regioselective hydration of terminal propargyl acetates and terminal halo-substituted propargyl carboxylates under gold catalysis (Scheme 1.3). They have observed that, having an electronegative element like halogen on alkyne terminus improves the

polarization of the C≡C bond and helps the hydration by gold. Also, the hydration products from halo-substituted terminal alkynes have been used for the synthesis of thiazole derivatives.[5b, 6m, 11]



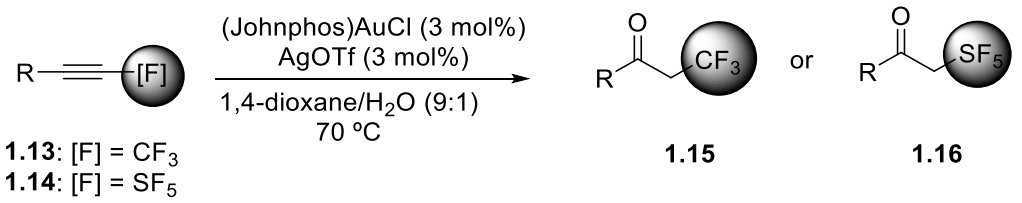
Scheme 1.3. Gold-catalyzed regioselective hydration of propargyl carboxylates

A gold-catalyzed Meyer-Schuster rearrangement of propargylic alcohols **1.10** to offer α, β-unsaturated ketones (**1.12**) through hydration products β-hydroxy ketones **1.11** was developed by Sheppard and co-workers (Scheme 1.4). In this transformation, protic additive (ROH) plays an important role for rapid protodemetallation to give **1.11** followed by water elimination to result in α, β-unsaturated ketones **1.12**.[6d]



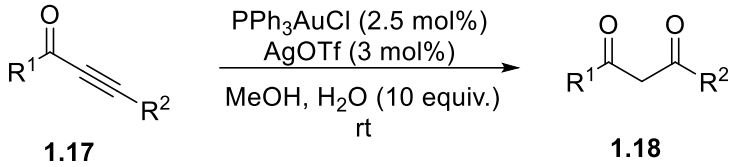
Scheme 1.4. A regioselective hydration of propargyl alcohols via gold-catalyzed Meyer-Schuster rearrangement

Paquin group developed an unprecedented regioselective gold-catalyzed hydration of CF_3 and SF_5 attached alkynes **1.13** and **1.14**. The corresponding trifluoromethylated **1.15** and pentafluorosulfanylated **1.16** carbonyl compounds were obtained as the only one regioisomer. In this conversion CF_3 and SF_5 groups acts as highly efficient directing groups for the transformation of CF_3 and SF_5–alkynes into corresponding ketones (Scheme 1.5).[6b]



Scheme 1.5. CF_3 and SF_5-directed gold-catalyzed hydration

Kuang *et al.* reported the synthesis of 1,3-diketones via a gold-catalyzed regioselective hydration of ynones (Scheme 1.6). This work appeared in literature in the year 2019, years after our publication on gold-catalyzed hydration of alkynones and alkynoates in acetone in 2016.[6e] In this methodology, alkynones **1.17** underwent hydration in the presence of 2.5 mol% of PPh_3AuCl and 3 mol% of AgOTf at room temperature to result in 1,3 diketones **1.18**.[6c]



Scheme 1.6. Access to 1,3-diketones under gold-catalysis

1.2 Background

During our work on the gold-catalyzed synthesis of bicyclic acetals from epoxyalkynes,[7] we had noticed the involvement of solvent acetone, especially with substrates having an ester on the alkyne. It was proposed, from the control experiments using acetone-d_6, that water formed from acetone under the reaction conditions involved in protodemetallation. In our efforts to explore the involvement of acetone in gold-catalyzed reactions, we have found $IPrAuCl/AgSbF_6$ catalyst system in acetone to promote regioselective hydration of 2-alkynoates to result in β-ketoesters in promising yields. As believed, the water which is generated by the aldol self-condensation of acetone under the Lewis acidic condition is involved in the hydration under mild condition. The substrate **1.18a** has intriguing structural features as it has different functionalities in it. For example, it has an active methylene carbon, Michael acceptors, carbonyl, and two different esters. In other words, most of its carbon centers can selectively be functionalized and

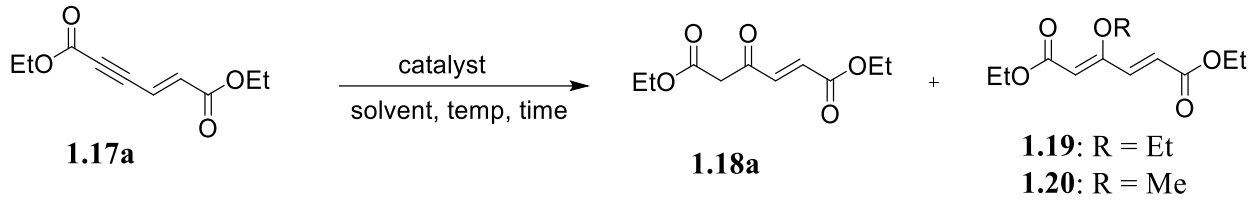
therefore it can serve as a useful intermediate in organic synthesis. This compound has been synthesized in multi-step processes.[8] We envisaged that this compound could easily be made by the hydration of **1.17a** which in turn could be made in quantitative yield from ethyl propiolate using literature method.[9] Applications of the compounds **1.17a** and **1.18a** have been covered in the Ph.D. theses of Sakthivel and Ganesh Kumar Thota.[10]

1.3 Results and discussion

Hydration of substrate **1.17a** was evaluated using different gold catalysts under different conditions. Initial attempts using gold catalysts under known[6q, 6r] conditions were not productive. For example, reactions using EtOH/H_2O and MeOH/H_2O solvent systems resulted in ethanol and methanol added products, respectively, along with unreacted starting material (Table 1, entries 1–8). Heating the reactions at reflux temperature resulted in a complex mixture of products (entries 3 and 8). Using $Ph_3PAuCl/AgSbF_6$ in 1,4-dioxane/$MeNO_2$ (20:1) along with H_2O (3 equiv.),[11] the reaction resulted in trace amounts of the product (entry 9). In our earlier studies on the synthesis of bicyclic acetals and dioxolanes,[7] we found that water generated by gold-catalyzed aldol self-condensation of acetone crucially involved in the reaction. In this regard, hydration was attempted using 2 mol% of $Ph_3PAuCl/AgSbF_6$ in refluxing acetone at 60 °C. To our delight, this reaction resulted in 72% of the desired product **1.18a** (entry 10). The same reaction, when conducted at room temperature, resulted in only 45% yield (entry 11). Use of a cationic NHC–Au(I) catalyst in 1,4-dioxane/water (2:1) at 110 °C resulted in 71% yield (entry 12). With the same catalyst system in acetone at 60 °C, the yield enhanced significantly to 85 % (entry 13). It should be noted that only 0.3 mol% of the NHC–Au(I) catalyst was required. The efficiency of the reaction was relatively lower when 0.1 mol% of the catalyst was used (entry 15). Since it is believed that water involved in the hydration is generated from acetone, a couple of reactions were carried out using 1:1 mixtures of acetone/H_2O and acetone/D_2O (entries 17 and 18). Although both reactions took less time for completion in comparison to that in entry 13, the yields were lower. In the reaction involving D_2O, the corresponding methylene-deuterated product **1.18a-d$_2$** was obtained along with

1.18a in a ratio of 2:1. Based on these results, the substrate scope was evaluated using the optimized reaction conditions given in entry 13 and entry 16 and the efficacies were compared.

Table 1.1. Optimization of reaction conditions for gold-catalyzed hydration



1.17a **1.18a** **1.19**: R = Et **1.20**: R = Me

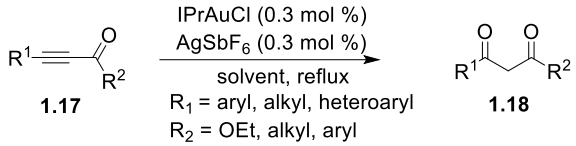
entry	**catalyst (mol%)**	**solvent**	**Temp in ºC**	**hours (h)**	**Yield of 1.18a (%)[a]**
1	$NaAuCl_4.2H_2O$ (2)	EtOH:H_2O (4:1)	rt	24	25[b](42)[e]
2	$NaAuCl_4.2H_2O$ (2)	MeOH:H_2O (4:1)	rt	24	16[c](38)[e]
3	$NaAuCl_4.2H_2O$ (2)	EtOH:H_2O (4:1)	reflux	2	Complex mixture
4	$AuCl_3$ (2)	EtOH:H_2O (4:1)	rt	24	15[b](46) [e]
5	$AuCl_3$/3$AgSbF_6$ (2)	EtOH:H_2O (4:1)	rt	24	16[b](43) [e]
6	$Ph_3PAuCl/AgSbF_6$ (2)	EtOH:H_2O (4:1)	rt	24	34[b](30) [e]
7	Ph_3PAuCl/AgOTf(2)	EtOH:H_2O (4:1)	rt	24	30[b](37) [e]
8	$Ph_3PAuCl/AgSbF_6$ (2)	EtOH:H_2O (4:1)	reflux	3	Complex mixture
9	$Ph_3PAuCl/AgSbF_6$ (2)	1,4-Dioxane/$MeNO_2$ (20:1), H_2O (3 equiv.)	rt	12	Trace
10	$Ph_3PAuCl/AgSbF_6$ (2)	Acetone	60	2	72
11	$Ph_3PAuCl/AgSbF_6$ (2)	Acetone	rt	48	45
12	(IPr)AuCl/$AgSbF_6$ (1)	H_2O:Dioxane (1:2)	110	1.5	71
13	**(IPr)AuCl/$AgSbF_6$ (0.3)**	**Acetone**	**60**	**6**	**86**
14	(IPr)AuCl/$AgSbF_6$ (0.3)	Acetone	rt	72	70
15	(IPr)AuCl/$AgSbF_6$ (0.1)	Acetone	60	11	79

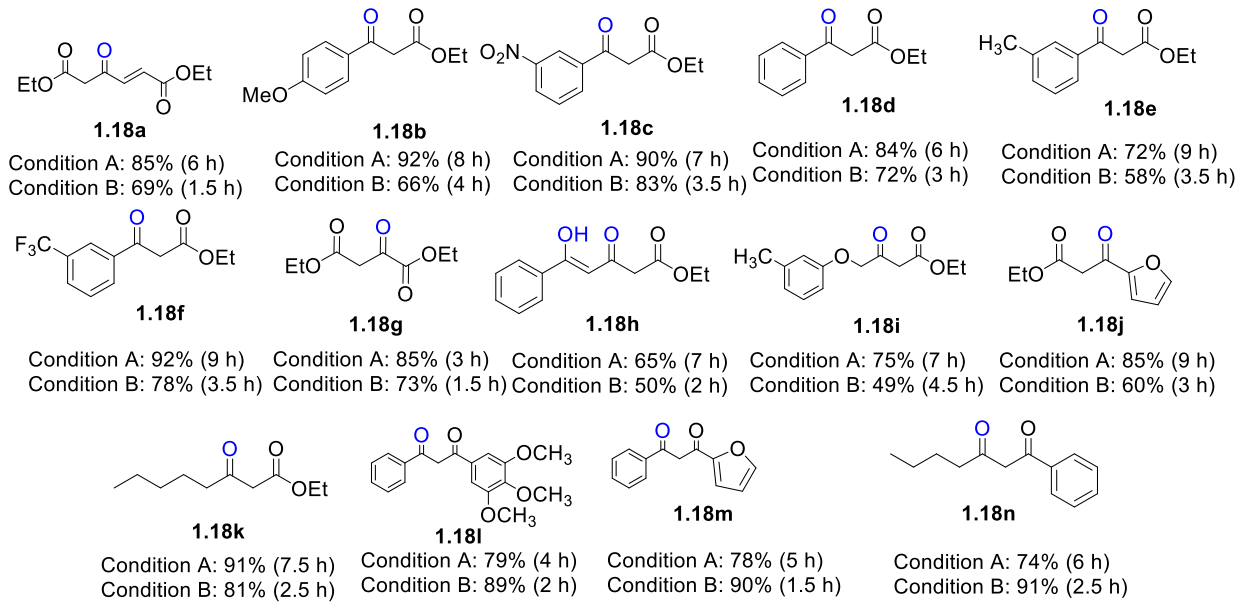
entry	catalyst (mol%)	solvent	Temp in ºC	hours (h)	Yield of 1.18a (%)[a]
16	(IPr)AuCl/$AgSbF_6$ (0.3)	H_2O:Dioxane (1:2)	110	1.5	69
17	(IPr)AuCl/$AgSbF_6$ (0.3)	Acetone/ H_2O	60	4	62
18	(IPr)AuCl/$AgSbF_6$ (0.3)	Acetone/D_2O	60	5	65[d]
19	(IPr)AuCl (0.3)	Acetone	60	48	61
20	$AgSbF_6$ (0.3)	Acetone	60	38	45
21	TfOH (10)	Acetone	60	3	decomposed

[a]Isolated yield. [b]Yield of **1.19**. [c]Yield of **1.20**. [d]1:1.2 mixture of **1.18a** and **1.18a-d$_2$**. [e]Values in parenthesis represent the percentage of recovered starting material.

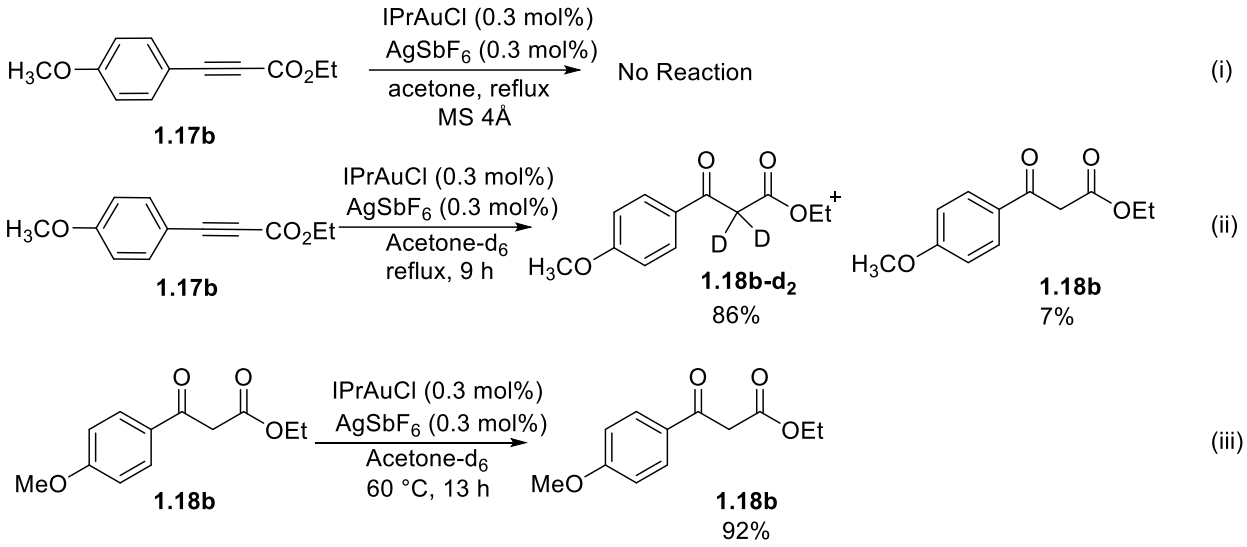
Different 2-alkynoates prepared by trivial synthetic procedures were subjected to NHC–Au(I)-catalyzed hydration. The results are presented in Table 2 (products **1.18a**–**1.18k**). Although the reactions were faster in 1,4-dioxane/water than in acetone, the yields are significantly inferior. Refluxing in 1,4-dioxane/water perhaps facilitates ester hydrolysis, which might have caused dropping of yields. 3-Aryl-2-alkynoates with electron-donating and withdrawing groups on the aryl ring underwent clean hydration to give the respective keto esters (**1.18b, 1.18c, 1.18e, 1.18f**). Hydration of diethyl acetylenedicarboxylate resulted in the product **1.18g**, which is generally prepared by a base-promoted Claisen condensation of ethyl acetate and diethyloxalate or by the reaction of diethyl acetylenedicarboxylate with stoichiometric amounts of methyl hydrazine and sulfuric acid.[12] Interestingly, ethyl 5-phenylpenta-2,4-diynoate resulted in δ-diketo ester **1.18h** by hydration of the conjugated alkyne functionality in a regioselective fashion. A protected γ-hydroxy-α-alkynoate ester could also be hydrated to get **1.18i** in respectable yield. A furan-substituted 2-alkynoate or a β-alkyl-α-alkynoate could be hydrated to give **1.18j** or **1.18k**, respectively. To check whether acetone is generally a better solvent, hydration of different alkynones to β-diketones was attempted. In all these cases, 1,4-dioxane/water was found to be a better solvent system (**1.18l** – **1.18n**). More reactive β-diketones may react with acetone under the reaction conditions, which could have decreased the yields of the β-diketones.

Table 1.2. Substrate scope for gold-catalyzed hydration





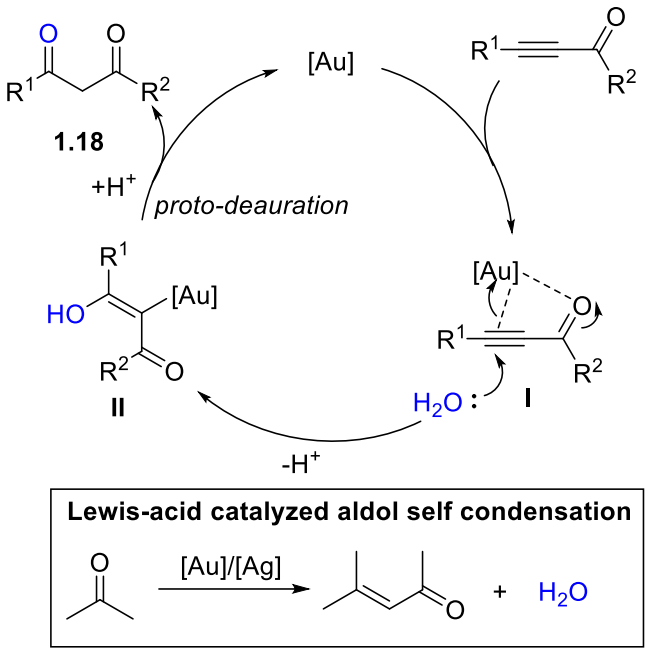
In order to ascertain the role of acetone in this reaction, three control experiments were carried out (Scheme 1.7). There was no reaction when NHC-Au(I)-catalyzed hydration of **1.17b** in acetone was attempted in the presence of molecular sieves 4Å (Scheme 1.7, eqn. i). When the reaction was carried out in acetone-d_6, 86% of the deuterium incorporated product **1.18b-d**$_2$ was obtained in 86% along with 7% of **1.18b** from **1.17b** (Scheme 1.7, eqn. ii). This reaction took more time than that the one conducted in acetone. This obviously shows the involvement of acetone in the protodemetallation step.[7, 13] Considering the results of the above two reactions, it can be claimed that it is the water that is formed from solvent acetone, perhaps by aldol self-condensation of acetone under the Lewis acidic condition is responsible for the hydration. In another control experiment, we refluxed the product **1.18b** in acetone-d_6 along with the gold catalyst in order to ascertain whether deuterium incorporation takes place after the formation of product **1.18b**. However, no deuterium incorporation was observed (Scheme 1.7, eqn. iii).



Scheme 1.7. Control experiments

1.3.1 Mechanism

A tentative mechanism as shown in scheme 1.8 can be proposed for the regioselective hydration of alkynones/alkynyl esters. Au(I) catalyst will coordinate with both the triple bond as well as the carbonyl oxygen through its alkyno and oxophilicities as shown in the intermediate **I**. This makes the β–carbon susceptible to nucleophilic attack. From the control experiments, it is understood that water required for the hydration comes from the solvent acetone (condition A) by aldol self-condensation under the Lewis acidic conditions.[7] Water attacks at the β position of the gold activated alkynones/alkynyl esters to form intermediate **II** which will undergo proto-deauration to result in the 1,3-dicarbonyl compound.



Scheme 1.8. proposed mechanism

1.4 Conclusion

Synthesis of substituted β-keto esters and β-diketones has been efficiently achieved by the hydration of 2-alkynoates and alkynones respectively using a cationic NHC–Au(I) catalyst. While acetone is a better solvent for the hydration of 2-alkynoates, 1,4-dioxane/water is more appropriate for the hydration of alkynones. Water, generated from acetone by aldol self-condensation, is responsible for the hydration in acetone. Using this hydration reaction, structurally interesting 1,3-dicarbonyl compounds could be synthesized.

1.5 Experimental Section

1.5.1 General Information

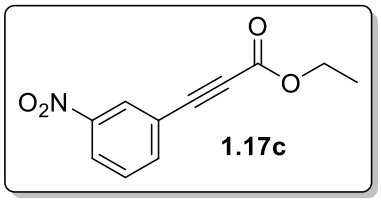
All the reagents were obtained commercially and used without further purification unless otherwise mentioned. For TLC, silica gel plates 60 F254 were used, and the spots were visualized with UV light, Seebach's stain [phosphomolybdic acid (2.5 g), $Ce(SO_4)_2$ (1 g), conc. H_2SO_4 (6 mL), H_2O (94 mL)], and I_2 vapors. Column chromatography was performed on silica gel (100–200 mesh) using mixtures of ethyl acetate and hexanes as eluent. ^1H and ^{13}C NMR spectra of the

synthesized compounds were recorded with an NMR spectrometer (400 MHz) and (500 MHz) by using solutions in $CDCl_3$. The ^1H NMR and ^{13}C NMR signals were referred to TMS and the central line of $CDCl_3$ peaks, respectively. IR spectra were recorded using a FTIR spectrometer. High resolution mass spectra (HRMS) were recorded using the ESI-Q-TOF technique. Synthesis and data of many alkynyl ketones and alkynyl esters employed in this work are already reported in the literature. [14–23]

1.5.2 General procedure for the preparation of enyne diester[10]

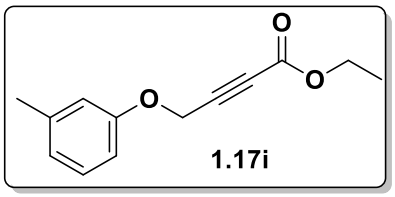
To a solution of alkynoates (1.0 equiv.) in CH_2Cl_2, DABCO (5 mol%) was added at 0 °C. The reaction immediately turned to dark in colour and was allowed to stir for 10-15 min. Then the solvent was removed under reduced pressure in a rotary evaporator. The residue was loaded on a silica gel column. It was eluted with ethyl acetate/hexanes mixture to get the pure enynediester **1.17a**.

1.5.3 Preparation of alkynyl esters



1.17c

Ethyl 3-(3-nitrophenyl)propiolate (1.17c): To a mixture of 1-iodo-3-nitrobenzene (250 mg, 1.0 mmol) and ethyl propiolate (390 mg, 4.016 mmol) in dry THF (10 mL) were added $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol), K_2CO_3 (554 mg, 4.0 mmol) and CuI (7 mg, 0.04 mmol). The reaction mixture was heated to reflux for 3.5 h. After that, the reaction mixture was filtered through celite, and the filtrate was concentrated. The crude product was purified by column chromatography using EtOAc/hexanes as eluent to get pure **1.17c**. Yield (204 mg, 92%); yellow liquid; R_f = 0.51 in EtOAc/hexanes (1:10). ^1H NMR (400 MHz, $CDCl_3$): δ 8.54 (s, 1H), 8.32 (d, J = 7.2 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.61 (t, J = 8.0 Hz, 1 H), 4.34 (q, J = 7.2 Hz, 2 H), 1.39 (t, J = 8.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 148.0, 138.2, 129.8, 127.5, 125.1, 121.5, 82.4, 82.3, 62.4, 13.9; IR (neat): 3084, 2975, 2926, 2849, 1720, 1463, 1353, 1194, 1024, 893, 734, 673 cm^{-1}; HRMS (ESI): calcd. for $C_{11}H_{10}NO_4$ $[M + H]^+$ 220.0610; Found 220.0612.



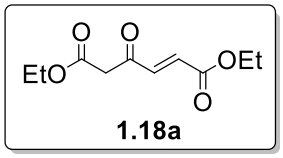
Ethyl 4-(*m*-tolyloxy)but-2-ynoate (1.17i): To a solution of 1-methyl-3-(prop-2-yn-1-yloxy)benzene (200 mg, 1.38 mmol) in dry THF (5 mL) was added *n*-BuLi (0.8 mL, 1.38 mmol) followed by ethyl chloroformate (1.2 mL, 2.07 mmol) at -78 °C. After 1 h, the reaction mixture was allowed to stir at r.t. for 3 h. Then the reaction mixture was extracted with ethyl acetate and the organic layer was concentrated. The crude product was purified by column chromatograph using EtOAc/hexanes as eluent to get pure **1.17i** Yield (246 mg, 82%); colorless liquid; R_f = 0.54 in EtOAc/hexanes (1:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (t, J = 8.0 Hz, 1 H), 6.83 (d, J = 8.0 Hz, 1 H), 6.75 (d, J = 8.0 Hz, 1 H), 6.74 (s, 1 H), 4.78 (s, 2 H), 4.23 (q, J = 7.2 Hz, 2 H), 2.34 (s, 3 H), 1.29 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 152.9, 139.3, 129.3, 122.8, 115.7, 111.6, 81.9, 78.5, 62.2, 55.4, 21.4, 13.9 ppm. IR (neat): 2964, 2925, 2860, 1747, 1490, 1369, 1145, 1030, 761, 615 cm^{-1}; HRMS (ESI): calcd. for $C_{13}H_{14}NaO_3$ $[M + Na]^+$ 241.0841; Found 241.0842.

1.5.4 General procedure for the gold-catalyzed hydration reaction

Condition A: To a stirred solution of alkynyl esters or alkynyl ketones in acetone, IPrAuCl (0.3 mol%) and $AgSbF_6$ (0.3 mol%) were added simultaneously then heated up to 60 °C. The progress of the reaction was monitored by checking the TLC. After completion of the reaction, the reaction mixture was concentrated and directly loaded on a silica gel column. The pure products were obtained by eluting the column with ethyl acetate and hexanes mixture.

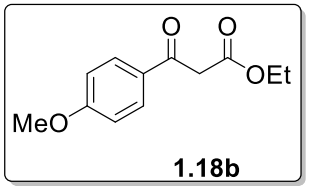
Condition B: To a stirred solution of alkynyl esters or alkynyl ketones in 1,4-dioxane, IPrAuCl (0.3 mol%) and $AgSbF_6$ (0.3 mol%) were added simultaneously. Water (0.5 v/v w.r.t. dioxane) was added and the reaction mixture was heated up to 110 °C and monitored by checking TLC. After completion of the reaction, the reaction mixture was concentrated and directly loaded on a silica gel column. The pure products were obtained by eluting the column with ethyl acetate and hexanes mixture.

(2*Z*, 4*E*)-Diethyl 3-hydroxyhexa-2,4-dienedioate (1.18a):[8]



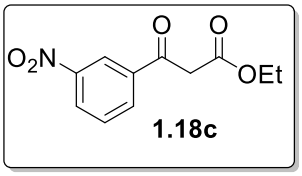
Yield: Condition A (91 mg, 85%) from 100 mg of **1.17a**; Condition B (74 mg, 69%) from 100 mg of **1.17a**. Colorless liquid; R_f = 0.58 in (9:1) EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.66 (s, 1H), 6.92 (d, *J* = 15.6 Hz, 1H), 6.64 (d, *J* = 15.6 Hz, 1H), 5.29 (s, 1H),4.28-4.23 (m, 4H), 1.34-1.30 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 165.9, 165.8, 137.2, 125.7, 96.5, 60.9, 60.7, 14.1.

Ethyl 3-(4-methoxyphenyl)-3-oxopropanoate (1.18b):



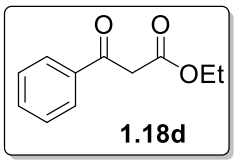
Yield: Condition A (50 mg, 92%) from 50 mg of **1.17b**; Condition B (36 mg, 67%) from 50 mg of **1.17b**. Colorless liquid; R_f = 0.49 in (9:1) EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8 Hz, 2H), 6.94 (d, *J* = 8 Hz, 2H), 4.21 (q, *J* = 8 Hz, 2H), 3.94 (s, 2H), 3.84 (s, 3H), 1.23 (t, *J* = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0, 167.7,164.0, 130.9, 129.1, 127.7, 113.9, 61.4, 55.5, 45.8, 14.1; IR (neat): 2980, 2832, 1736, 1676, 1600, 1512, 1463, 1315, 1249, 1167, 1024, 843 cm^{-1}; HRMS (ESI): calcd for $C_{12}H_{14}O_4$ $[M+Na]^+$ 245.0785; Found 245.0790.

Ethyl 3-(3-nitrophenyl)-3-oxopropanoate (1.18c):



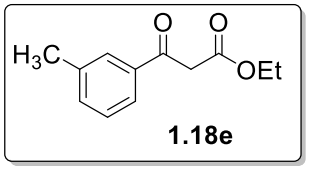
Yield: Condition A (68 mg, 90%) from 70 mg of **1.17c**; Condition B (90 mg, 83%) from 100 mg of **1.17c**. Yellow color solid; 1:7 keto-enol tautomers; R_f = 0.43 in (9:1)EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.63 (s, 1H), 8.78 (s, 1H), 8.62 (s, 1H), 8.46 (d, *J* = 7.6 Hz, 1H), 8.33-8.29 (m, 2H), 8.10 (d, *J* = 7.6 Hz), 7.73 (t, *J* = 16, 8 Hz, 1H), 7.63 (t, *J* = 16, 8 Hz, 1H), 5.78 (s,1H), 4.30 (q, *J* = 7.2 Hz, 2H), 4.23 (q, *J* = 7.2 Hz, 2H), 4.07 (s, 2H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.5, 172.7, 168.2, 166.7, 148.5, 137.2, 135.2, 134.0, 131.6, 130.1, 129.7, 127.9, 125.5, 123.4, 121.0, 89.2, 61.8, 60.8, 45.9, 14.2, 14.0; IR (neat): 2970, 2936, 1621, 1528, 1402, 1030, 915, 728; HRMS (ESI): calcd for $C_{11}H_{11}NO_5$ $[M + Na]^+$ 260.0532; Found 260.0535.

(*Z*)-Ethyl 3-hydroxy-3-phenylacrylate (1.18d):[24]



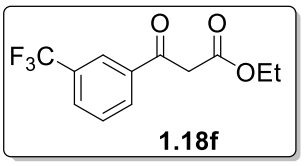
Yield: Condition A (93 mg, 84%) from 100 mg of **1.17d**; Condition B (79 mg, 72%) from 100 mg of **1.17d**. Colorless liquid; 9:1 keto-enol tautomers; R_f = 0.47 in (9:1) EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 7.6 Hz, 2H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 4.22 (q, *J* = 8 Hz, 2H), 3.99 (s, 3H), 1.26 (t, *J* = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.4, 173.1, 171.3, 167.4, 135.9, 133.5, 131.1, 128.6, 128.4, 125.9, 87.2, 61.3, 60.1, 45.8, 14.1, 13.9.

Ethyl 3-oxo-3-(*m*-tolyl)propanoate (1.18e):



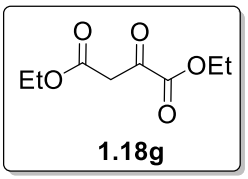
Yield: Condition A (80 mg, 72%) from 100 mg of **1.17e**; Condition B (33 mg, 58%) from 50 mg of **1.17e**. Colorless liquid; 1:0.5 keto-enol form; R_f = 0.43 in (9:1)EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.57 (s, 1H), 7.75-7.71 (m, 4H), 7.40-7.35 (m, 4H), 5.65(s, 1H), 4.24 (q, *J* = 8 Hz, 2H), 4.19 (q, *J* = 8 Hz, 2H), 3.96 (s, 2H), 2.40 (s, 3H), 1.32 (t, *J* = 8 Hz, 3H), 1.22 (t, *J* = 8 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl*$_3$): δ 192.6, 173.1, 171.6, 167.5, 138.5, 136.0, 134.4, 131.9, 128.8, 128.5, 128.3, 126.5, 125.7, 123.1, 87.2, 61.3, 60.2, 45.9, 21.2, 14.2, 14.0; IR (neat): 2969, 2925, 2849, 1742, 1682, 1627, 1462, 1276, 1145, 1030, 794 cm^{-1}; HRMS (ESI): calcd for $C_{12}H_{11}F_3O_3$ $[M + Na]^+$ 229.0840; Found 229.0841.

Ethyl 3-oxo-3-(3-(trifluoromethyl)phenyl)propanoate (1.18f):



Yield: Condition A (98 mg, 92%) from 100 mg of **1.17f**; Condition B (84 mg, 78%) from 100 mg of **1.17f**. Colorless liquid; 1:0.5 keto-enol tautomers; R_f = 0.47 in (9:1)EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.60 (s, 1H), 8.85-7.53 (m, 8H), 5.72 (s, 1H), 4.28 (q, *J* = 5.6 Hz, 2H), 4.22 (q, *J* = 5.6 Hz, 2H), 4.02 (s, 2H), 1.34 (t, *J* = 5.6 Hz, 3H), 1.26 (t, *J* = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.2, 172.8, 169.4, 166.9, 136.5, 134.3, 134.3, 131.8, 131.6, 131.5, 131.4,131.3, 131.0, 131.0, 130.0, 129.4,129.1, 127.6, 127.5, 125.3, 125.3, 124.8, 124.6, 122.9, 122.8, 122.6, 122.4, 88.5, 61.6, 60.5, 45.9, 14.1, 13.9; IR (neat): 2964, 2931, 2865, 1747,1720, 1632, 1463, 1309, 1238, 1095, 942, 849 cm^{-1}; HRMS (ESI): calcd for $C_{12}H_{11}F_3O_3$ $[M + Na]^+$ 283.0556; Found 283.0558.

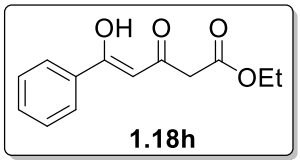
Diethyl 2-hydroxyfumarate (1.18g):



1.18g

Yield: Condition A (70 mg, 85%) from 75 mg of **1.17g**; Condition B (41 mg, 73%) from 50 mg of **1.17g**. Colorless liquid; 0.5:1 keto-enol forms; R_f = 0.46 in (9:1) EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.66 (s, 1H), 6.02 (s, 1H), 4.36 (q, J = 5.6 Hz, 2H), 4.34 (q, J = 5.6 Hz, 2H), 1.38 (t, J = 5.6 Hz, 3H), 1.27 (t, J = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 161.7, 159.3, 96.8, 62.3, 61.2, 14.0, 14.0, 13.9; IR (neat): 1627, 1528, 1473, 1374, 1216, 915, 728 cm^{-1}; HRMS (ESI): calcd for $C_{11}H_{11}NO_5$ [M + Na]$^+$ 211.0577; Found 211.0582.

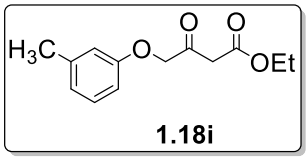
(*Z*)-Ethyl 5-hydroxy-3-oxo-5-phenylpent-4-enoate (1.18h):[25]



1.18h

Yield: Condition A (46 mg, 65%) from 60 mg of **1.17h**; Condition B (35 mg, 50%) from 60 mg of **1.17h**. Yellow color liquid; R_f = 0.34 in (9:1) EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 15.78 (bs, 1H), 7.89-7.87 (m, 2H), 7.54-7.52 (m, 1H), 7.47-7.43 (m, 2H), 6.30 (s, 1H), 4.23 (q, J = 7.2 Hz, 2H), 3.4 (s, 2H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.2, 182.6, 167.5, 134.1, 132.6, 128.8, 127.1, 96.7, 61.5, 45.9, 14.1.

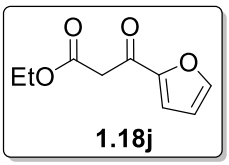
Ethyl 3-oxo-4-(*m*-tolyloxy)butanoate (1.18i):



1.18i

Yield: Condition A (80 mg, 75%) from 100 mg of **1.17i**; Condition B (56 mg, 49%) from 100 mg of **1.17i**. Colorless liquid; 9:1 keto-enol tautomers; R_f = 0.43 in (9:1) EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (t, J = 8 Hz 1H), 6.82 (d, J = 7.2 Hz, 1H), 6.71 (s, 1H), 6.67 (d, J = 8 Hz, 1H), 4.61 (s, 2H), 4.18 (q, J = 8 Hz, 2H), 3.61 (s, 2H), 2.32 (s, 3H), 1.26-1.23 (J = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.7, 172.5, 166.7, 157.4, 139.8, 129.4, 122.7, 115.3, 111.2, 89.1, 72.4, 66.2, 61.4, 60.3, 46.0, 21.4, 14.1, 14.0; IR (neat): 2975, 2920, 2361, 1720, 1583, 1490, 1369, 1260, 1156, 926, 772 cm^{-1}; HRMS (ESI): calcd for $C_{13}H_{16}O_4$ [M+Na] $^+$ 259.0944; Found 259.0946.

Ethyl 3-(furan-2-yl)-3-oxopropanoate (1.18j):

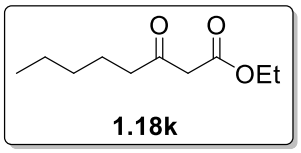


1.18j

Yield: Condition A (153 mg, 85%) from 160 mg of **1.17j**; Condition B (50 mg, 60%) from 75 mg of **1.17j**. Brown color liquid; R_f = 0.41 in (9:1)

EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (dd, J = 1.2, 0.8 Hz, 1H), 7.27 (dd, J = 3.6, 1.2 Hz, 1H),6.57 (dd, J = 3.6, 0.8 Hz, 1H), 4.23 (q, J = 8 Hz, 2H), 3.87 (s, 2H), 1.28 (t, J = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.1, 167.0, 152.0, 147.0, 118.3, 112.7, 61.5, 45.5, 14.0; IR (neat): 2975, 2931, 1742, 1682, 1561, 1463, 1276, 1024, 761 cm^{-1}; HRMS (ESI): calcd for $C_9H_{10}O_4$ $[M + Na]^+$ 205.0475; Found 205.0477

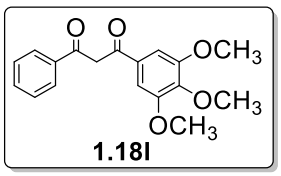
Ethyl 3-oxooctanoate (1.18k):



1.18k

Yield: Condition A (100 mg, 91%) from 100 mg of **1.17k**; Condition B (89 mg, 81%) from 100 mg of **1.17k**. Colorless liquid; R_f = 0.54 in (9:1)EtOAc/hexane; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.19 (q, J = 8 Hz, 2H), 3.42 (s, 2H), 2.53 (t, J = 7.2 Hz, 2H), 1.60 (quintet, J = 7.2 Hz, 2H), 1.30-1.26 (m, 7H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.9, 179.0, 172.7, 167.2, 88.9, 61.2, 59.8, 49.2, 42.9, 34.9, 31.1, 31.1, 25.8, 23.0, 22.3, 14.2, 14.0, 13.8; IR (neat) 1742, 1687, 1627, 1490, 1320, 1248, 1161, 1073, 1035, 805, 767, 690 cm^{-1}; HRMS (ESI): calcd for $C_{10}H_{18}O_3$ $[M + Na]^+$ 209.1156; Found 209.1154.

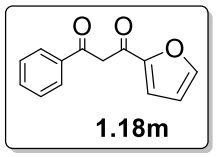
(*Z*)-3-Hydroxy-1-phenyl-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (1.18l):



1.18l

Yield: Condition A (82mg, 79%) from 100 mg of **1.17l**; Condition B (91 mg, 89%) from 100 mg of **1.17l**. Yellow color liquid; enol tautomer; R_f = 0.47 in (9:1) EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 8 Hz, 2H), 7.53 (t, J = 8, 1.2 Hz, 2H),7.47 (t, J = 1.6 Hz, 1H), 7.22 (s, 2H), 6.76 (s, 1H), 3.95 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.2, 184.3, 153.1, 142.0, 135.1, 132.3, 130.9, 128.6, 126.9, 104.6, 92.7, 60.8, 56.2; IR (neat): 2936, 2838, 1556, 1495, 1424, 1331, 1232, 1167, 1002, 953, 854, 767, 695 cm^{-1}; HRMS (ESI): calcd for $C_{18}H_{18}O_5$ $[M + H]^+$ 315.1231; Found 315.1234.

(*Z*)-3-(Furan-2-yl)-3-hydroxy-1-phenylprop-2-en-1-one (1.18m):[26]

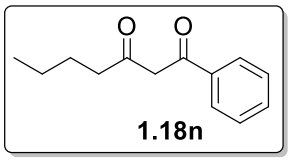


1.18m

Yield: Condition A (85 mg, 78%) from 100 mg of **1.17m**; Condition B (96 mg, 90%) from 100 mg of **1.17m**. Yellow color liquid; R_f = 0.51 in (9:1) EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 16.17 (bs, 1H),7.96-7.94 (m, 2H), 7.60 (dd, J = 1.6, 0.7 Hz, 1H), 7.53-7.44

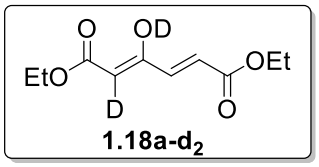
(m, 3H), 7.24 (dd, J = 3.5, 0.7 Hz, 1H), 6.76 (s, 1H), 6.57 (dd, J = 3.5, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.4, 177.6, 151.0, 146.1, 134.6, 132.3, 128.6 (2C), 126.9, 115.8, 112.6, 92.7.

(*Z*)-3-Hydroxy-1-phenylhept-2-en-1-one (1.18n):



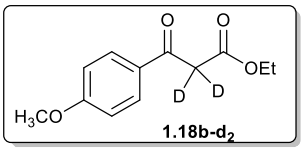
Yield: Condition A (80 mg, 74%) from 100 mg of **1.17n**; Condition B (98 mg, 91%) from 100 mg of **1.17n**. Colorless liquid; R_f = 0.61 in (9:1)EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 7.6, 2H), 7.51 (d, *J* = 7.6 Hz, 1H),7.44 (t, *J* = 8Hz, 2H), 6.18 (s, 1H), 2.43 (t, *J* = 7.6 Hz, 2H), 1.68 (pent, *J* = 7.6 Hz, 2H), 1.41 (sextet, *J* = 7.6 Hz, 2H), 0.95(t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.0, 183.4, 135.0, 132.1, 128.5, 126.9, 96.0, 38.9,27.9, 22.4, 13.8; IR (neat) 2958, 2925, 2871, 1731, 1605, 1462, 1380, 1265, 1172, 1095, 761 cm^{-1}; HRMS (ESI): calcd for $C_{13}H_{16}O_2$ $[M + Na]^+$ 227.1048; Found 227.1042.

(2*Z*, 4*E*)-Diethyl 2-deuterio-3-deuterioxyhexa-2,4-dienedioate (1.18a-d2):



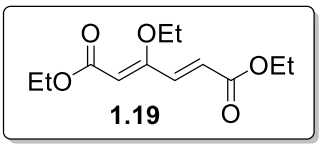
Yield = 35 % colorless liquid; R_f = 0.38 in EtOAc/hexanes (1:10); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.95 (d, *J* = 15.5 Hz, 1H), 6.46 (d, *J* = 15.5 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 4H), 1.29 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.1, 160.6, 134.8, 126.7, 99.8, 61.2, 14.1 ppm. IR (neat): 2926, 1736, 1643, 1583, 1309, 1216, 1073, 882 cm^{-1}; $C_{10}H_{12}D_2O_5$ (216.23): calcd. C 55.55, H 7.46; Found C 55.46, H 7.51.

Ethyl 3-(4-methoxyphenyl)-3-oxopropanoate-d2 (1.18b-d2):



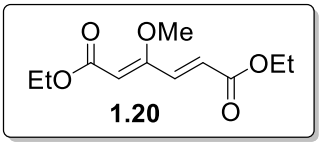
Yield (46 mg, 86 %, from 50 mg of **1.17b**, condition A ([D_6] acetone); colorless liquid; R_f = 0.49 in EtOAc/hexanes (1:9); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 4.10 (q, *J* = 8.0 Hz, 2H), 3.86 (s, 3H), 1.18 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.2, 169.1, 163.6, 130.8, 113.8, 60.9, 55.4, 14.0 ppm. IR (neat): 2975, 2838, 1731, 1671, 1520, 1457, 1309, 1271, 1172, 1024, 838 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{13}D_2O_4$ $[M + H]^+$ 225.1091; Found 225.1095.

(2*Z*,4*E*)-Diethyl 3-ethoxyhexa-2,4-dienedioate (1.19):



Colorless liquid; R_f = 0.61 in EtOAc/hexanes (1:10, triple run); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38 (d, J = 15.6 Hz, 1H), 6.49 (d, J = 15.6 Hz, 1H), 5.25 (s, 1H), 4.22 (q, J = 7.2 Hz, 2H), 4.16 (q, J = 7.2 Hz, 2H), 3.88 (q, J = 6.8 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H), 1.31–1.25 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 166.3, 163.0, 135.1, 124.6, 97.3, 64.1, 60.7, 60.1, 14.3, 14.2, 14.0; HRMS (ESI): calcd. for $C_{12}H_{18}NaO_5$ $[M + Na]^+$ 265.1052; Found 265.1051.

(2*Z*, 4*E*)-Diethyl 3-methoxyhexa-2,4-dienedioate (1.20):



Colorless liquid; R_f = 0.41 in EtOAc/hexanes (1:10); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (d, J = 16.0 Hz, 1H), 6.30 (d, J = 15.6 Hz, 1H), 5.41 (s, 1H), 4.25 (q, J = 7.2 Hz, 2H), 4.20 (q, J = 7.2 Hz, 2H), 3.94 (s, 3H), 1.33–1.29 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 164.5, 140.0, 124.6, 106.9, 61.4, 60.9, 60.3, 14.2, 14.1; HRMS (ESI): calcd. for $C_{11}H_{17}O_5$ $[M + H]^+$ 229.1077; Found 229.1078.

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Chapter 1

1.7 Representative spectra

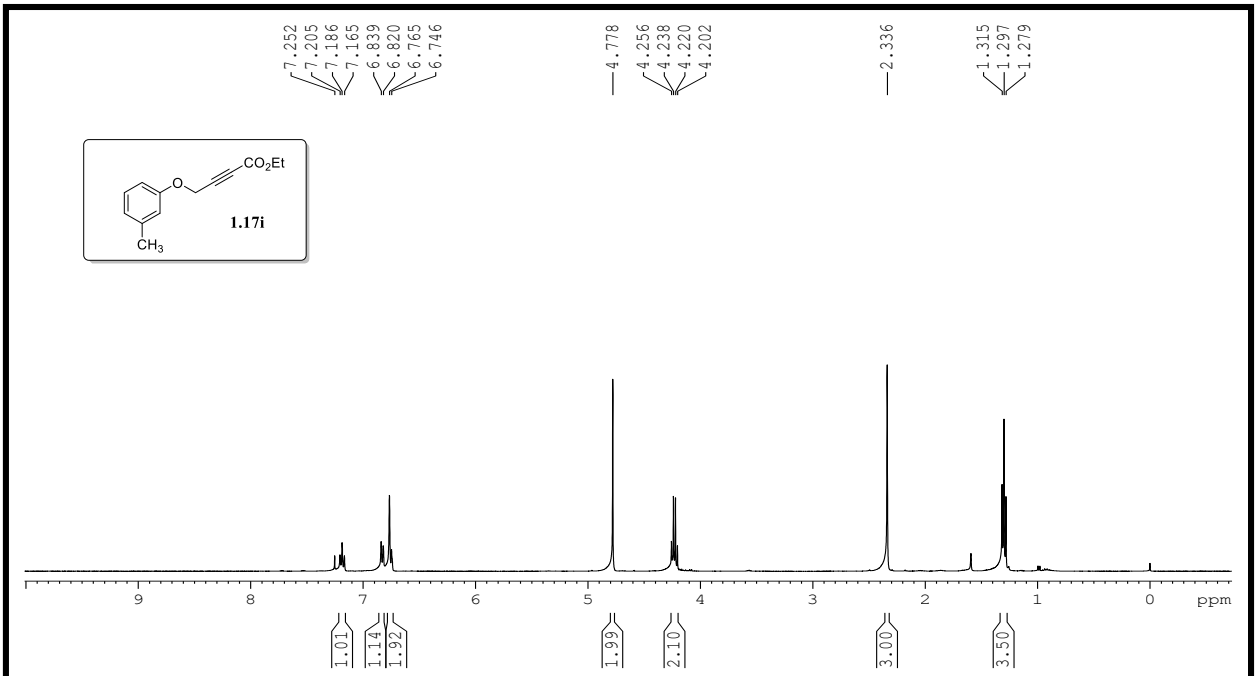


Figure 1.1: ^{1}H NMR spectra of Compound **1.17i**

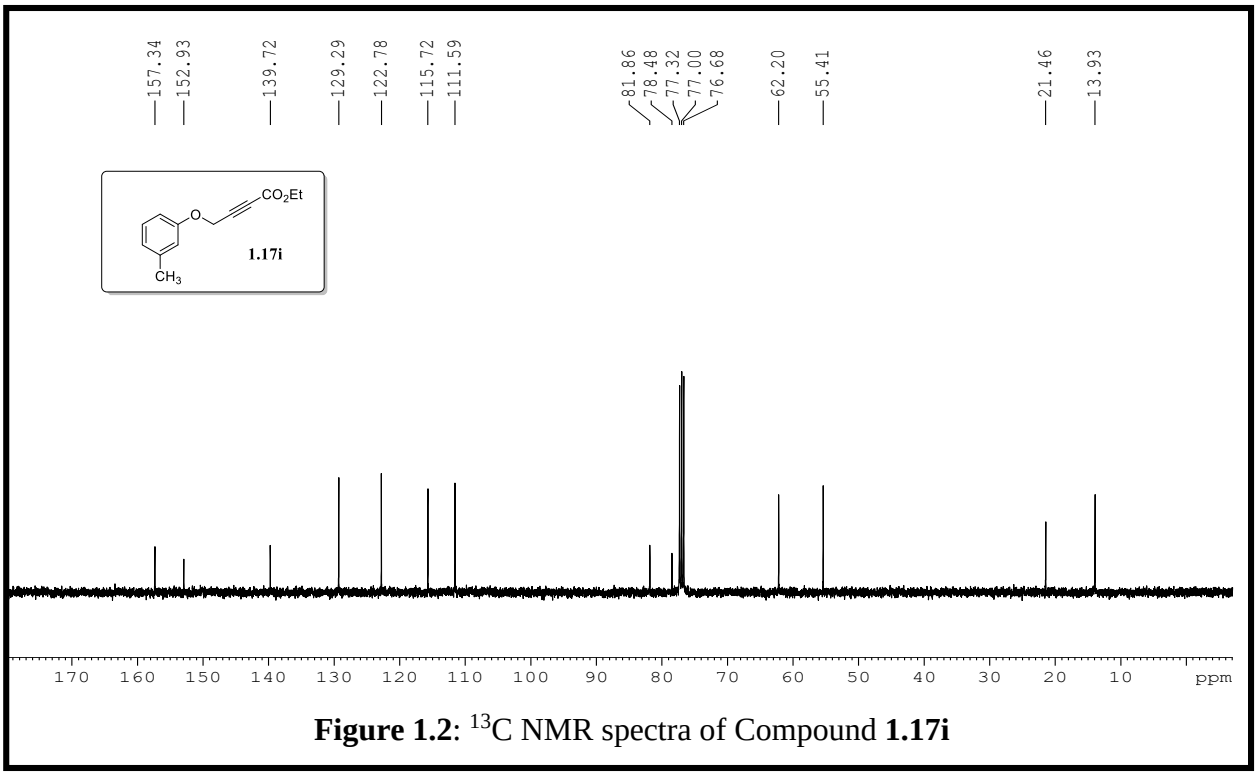


Figure 1.2: ^{13}C NMR spectra of Compound **1.17i**

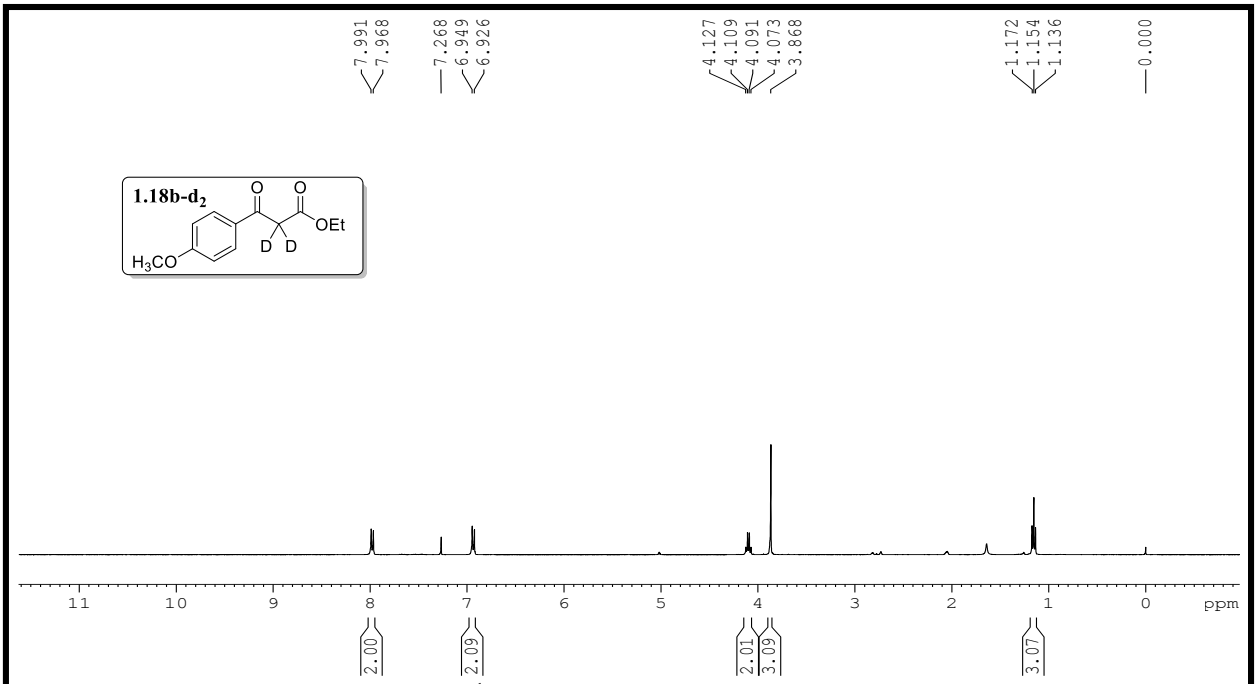


Figure 1.3: ^{1}H NMR spectra of Compound **1.17i**

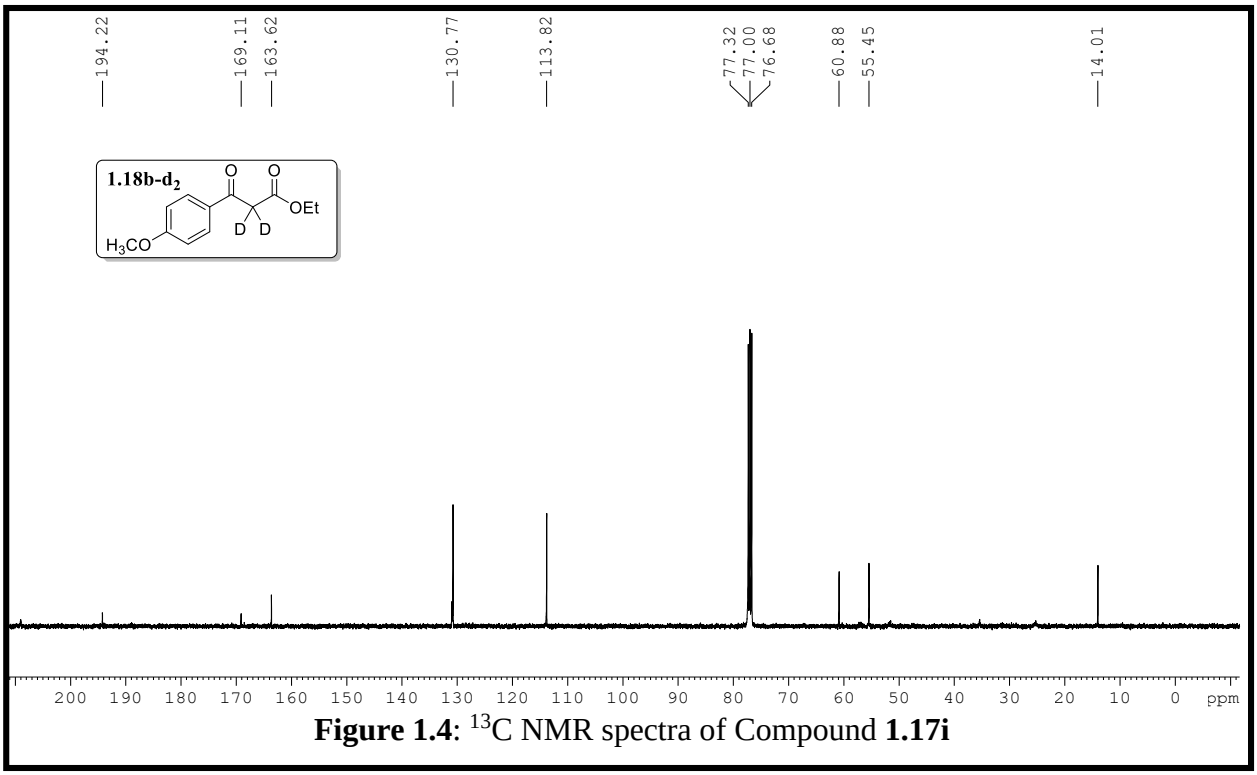


Figure 1.4: ^{13}C NMR spectra of Compound **1.17i**

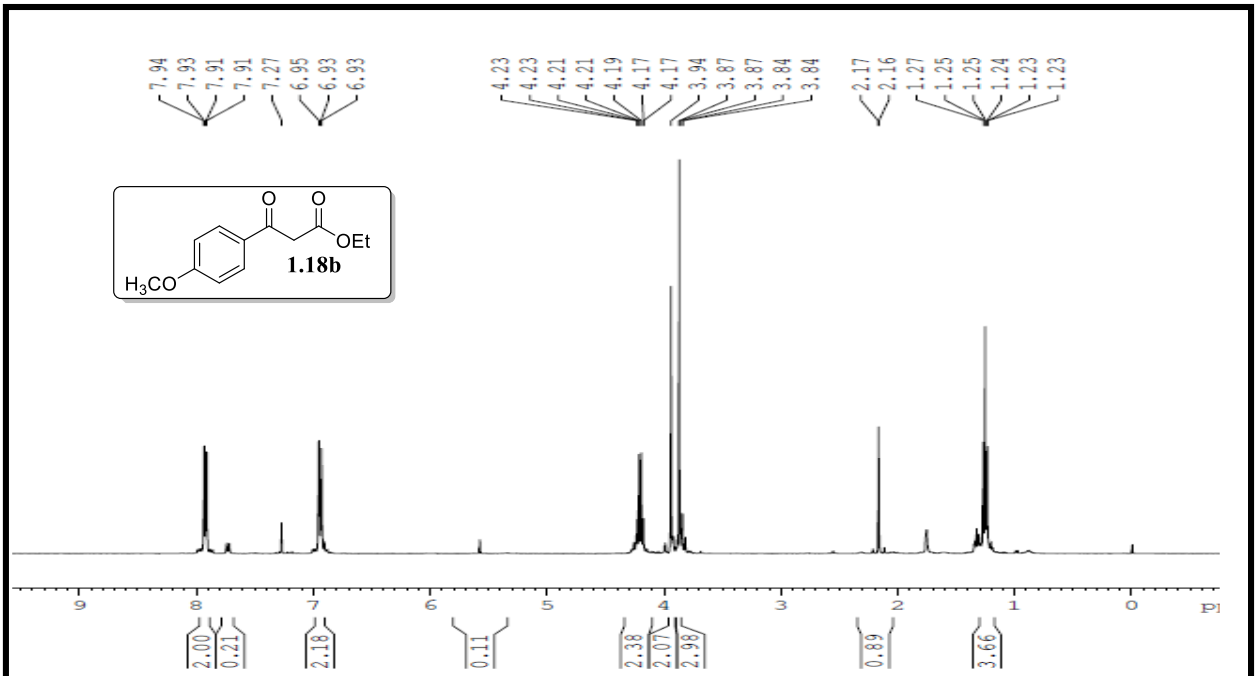


Figure 1.5: ^{1}H NMR spectra of Compound **1.18b**

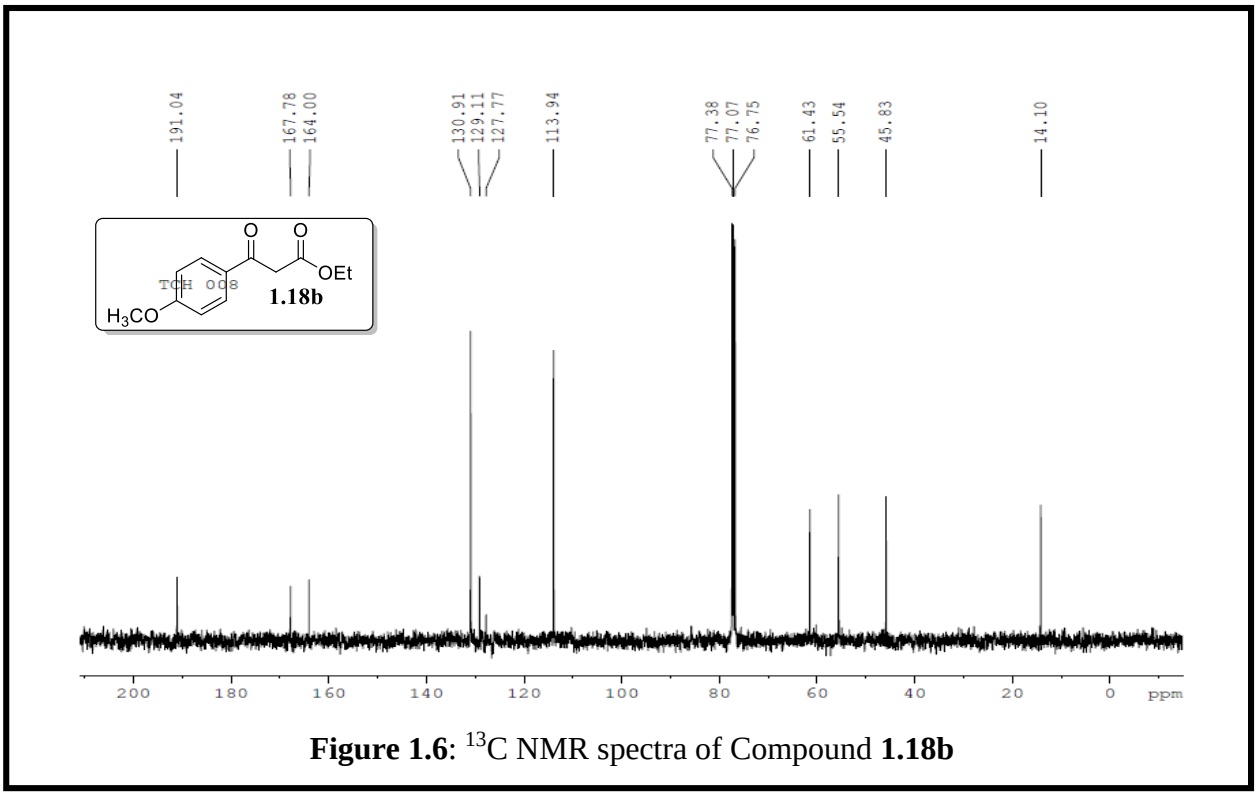


Figure 1.6: ^{13}C NMR spectra of Compound **1.18b**

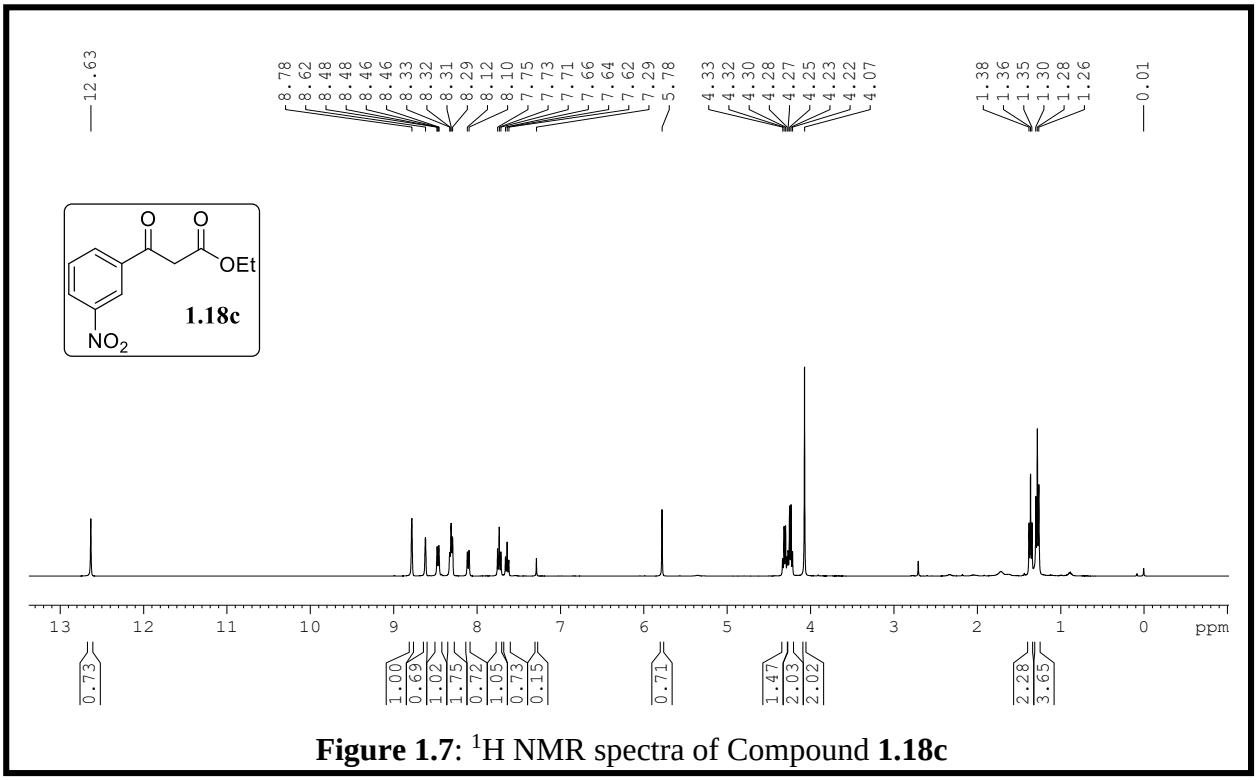


Figure 1.7: ^{1}H NMR spectra of Compound **1.18c**

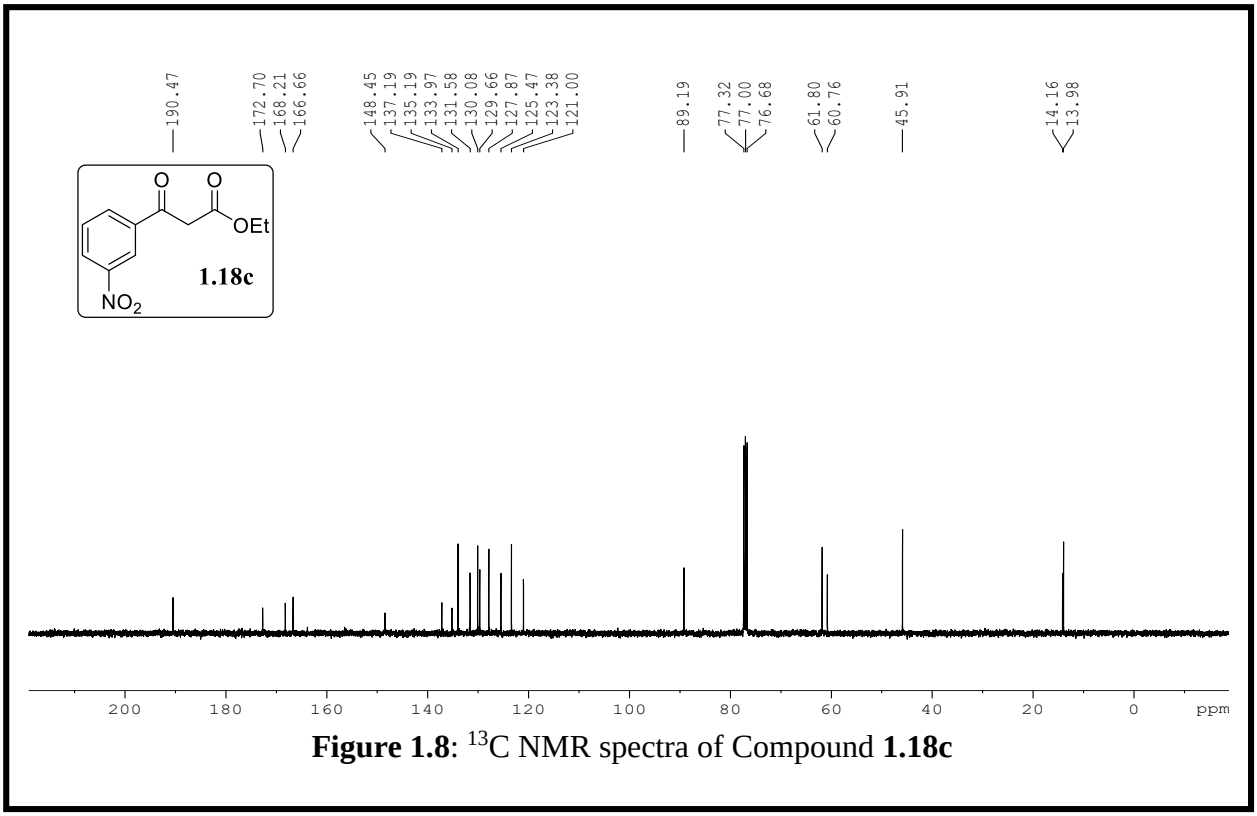


Figure 1.8: ^{13}C NMR spectra of Compound **1.18c**

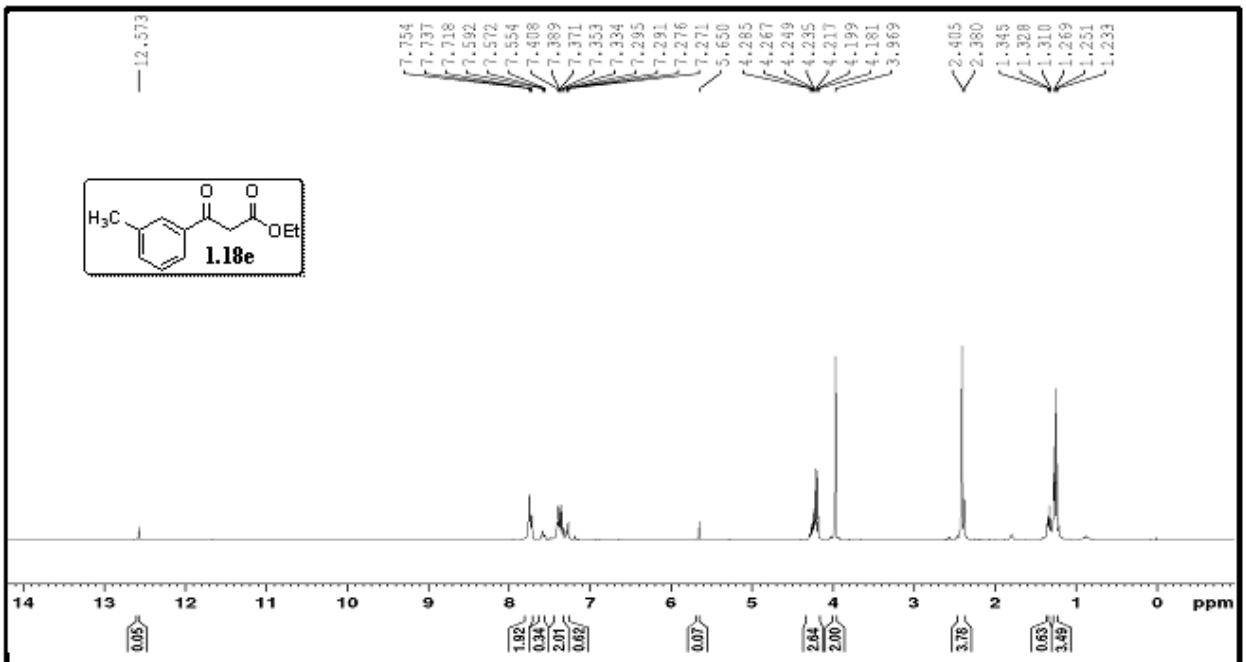


Figure 1.9: ^{1}H NMR spectra of Compound **1.18e**

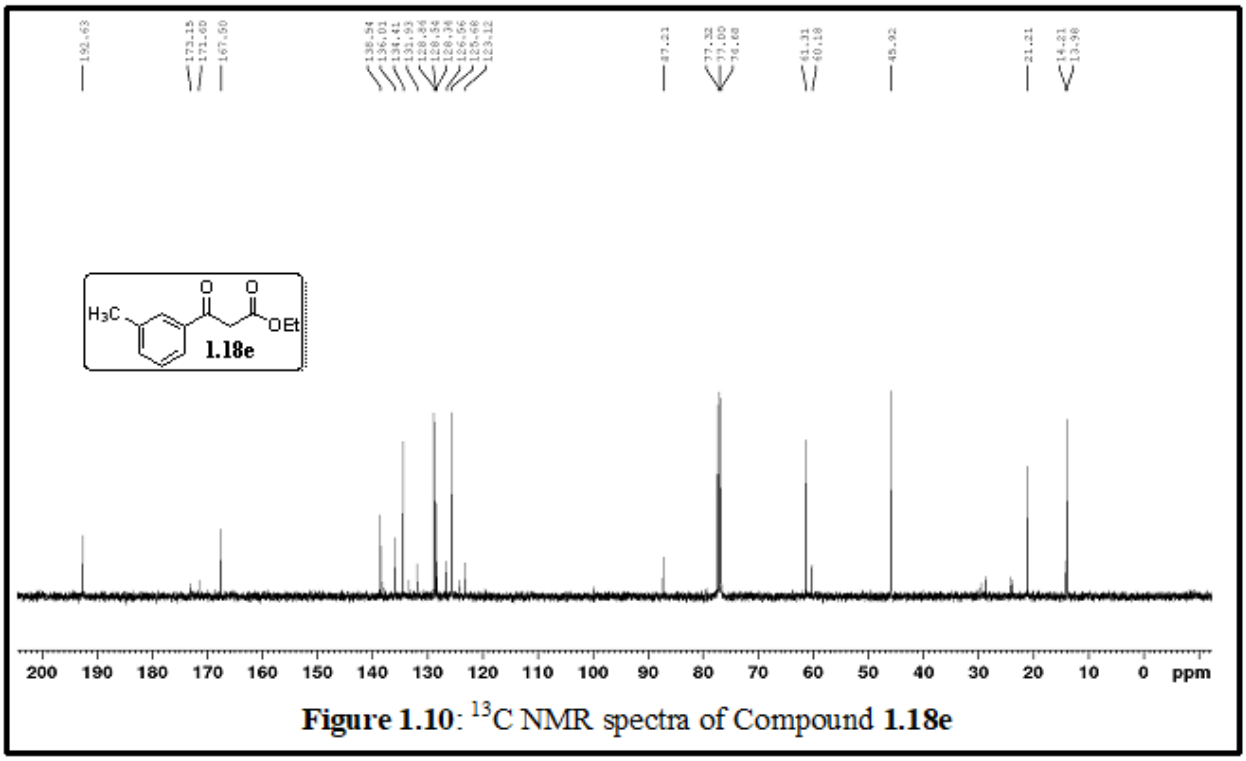


Figure 1.10: ^{13}C NMR spectra of Compound **1.18e**

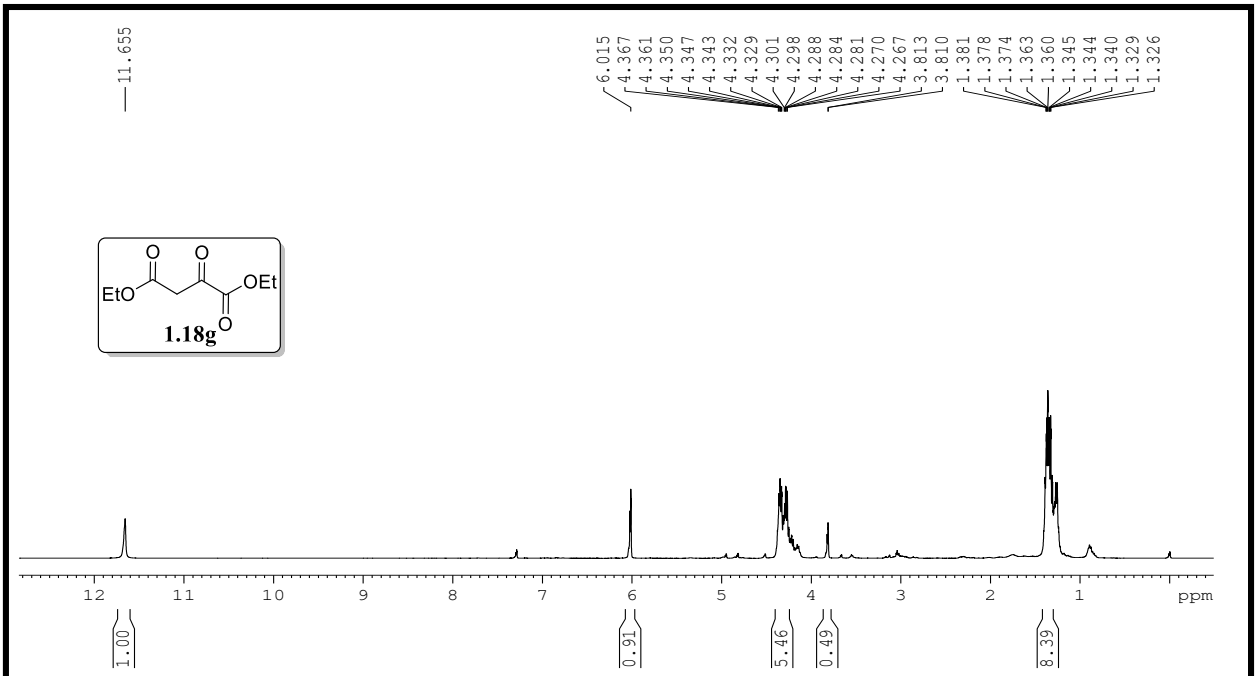


Figure 1.11: ^{1}H NMR spectra of Compound **1.18g**

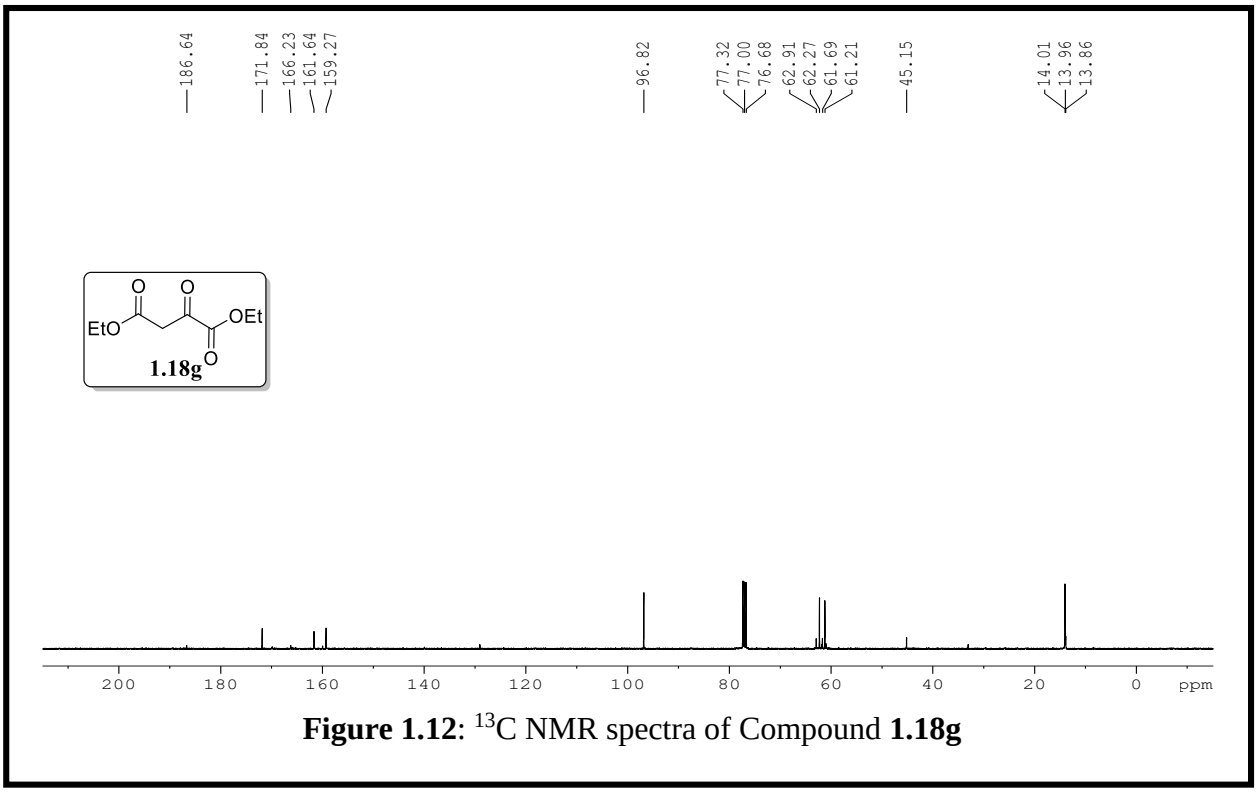


Figure 1.12: ^{13}C NMR spectra of Compound **1.18g**

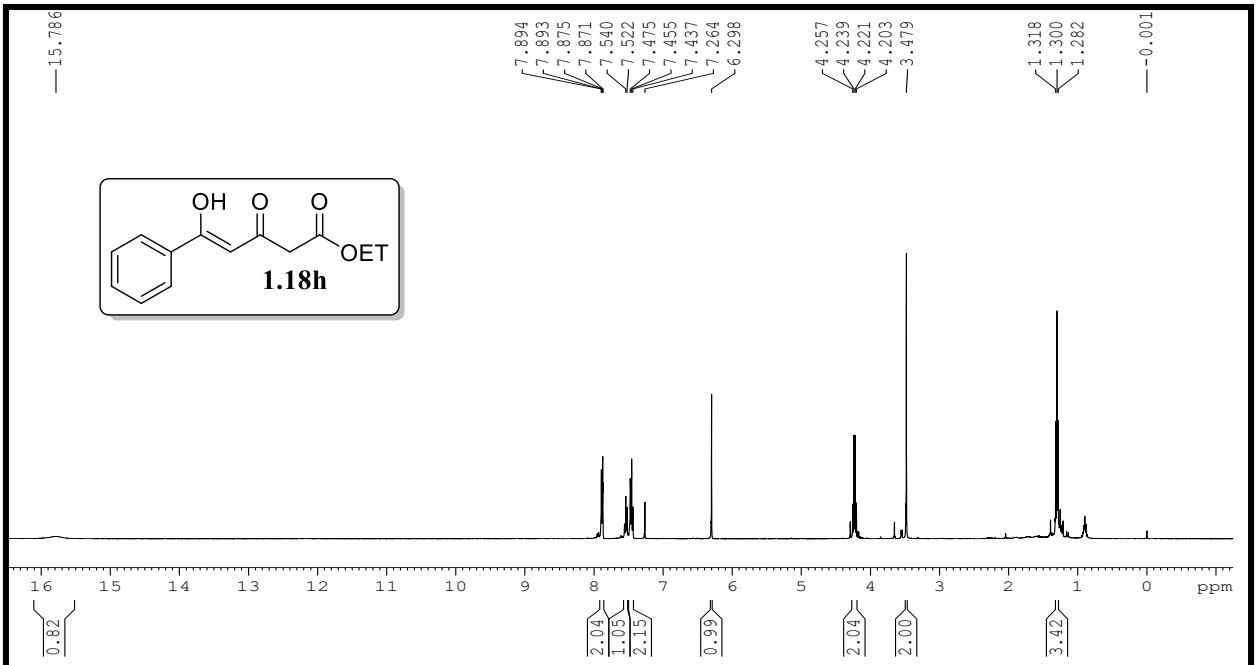


Figure 1.13: ^{1}H NMR spectra of Compound **1.18h**

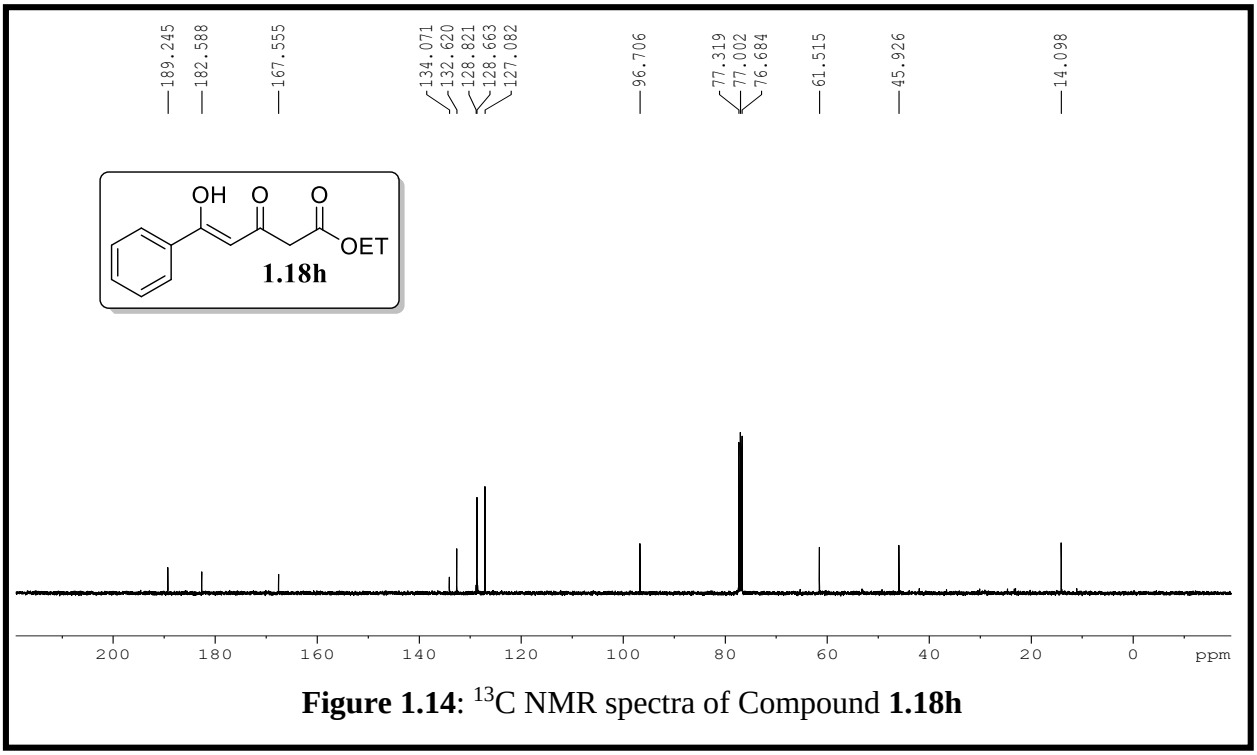


Figure 1.14: ^{13}C NMR spectra of Compound **1.18h**

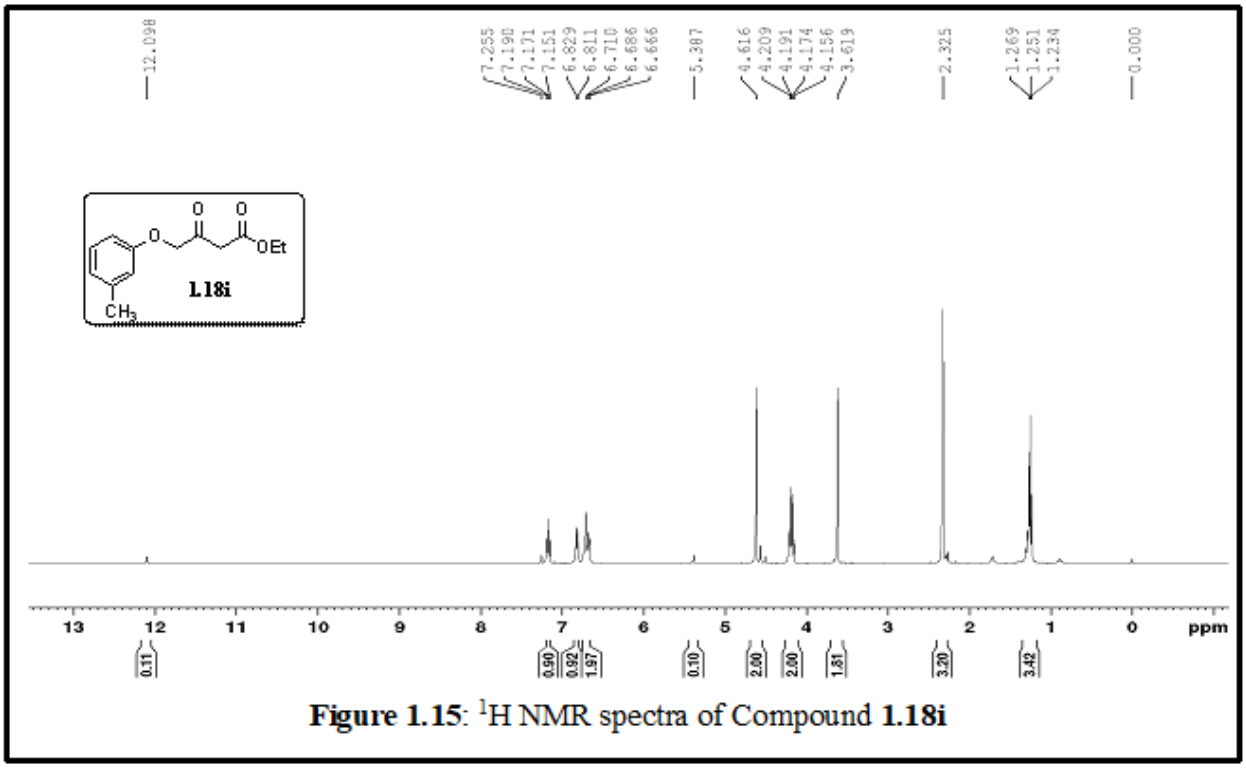


Figure 1.15: ^{1}H NMR spectra of Compound **1.18i**

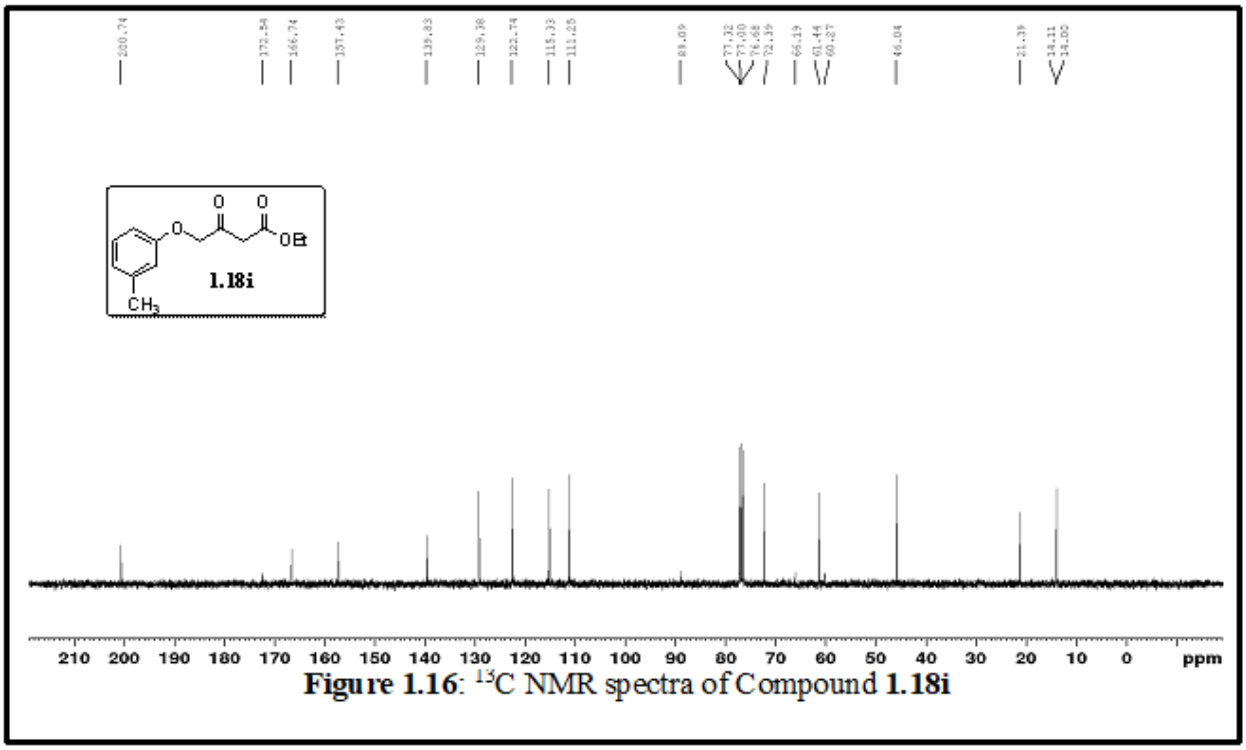


Figure 1.16: ^{13}C NMR spectra of Compound **1.18i**

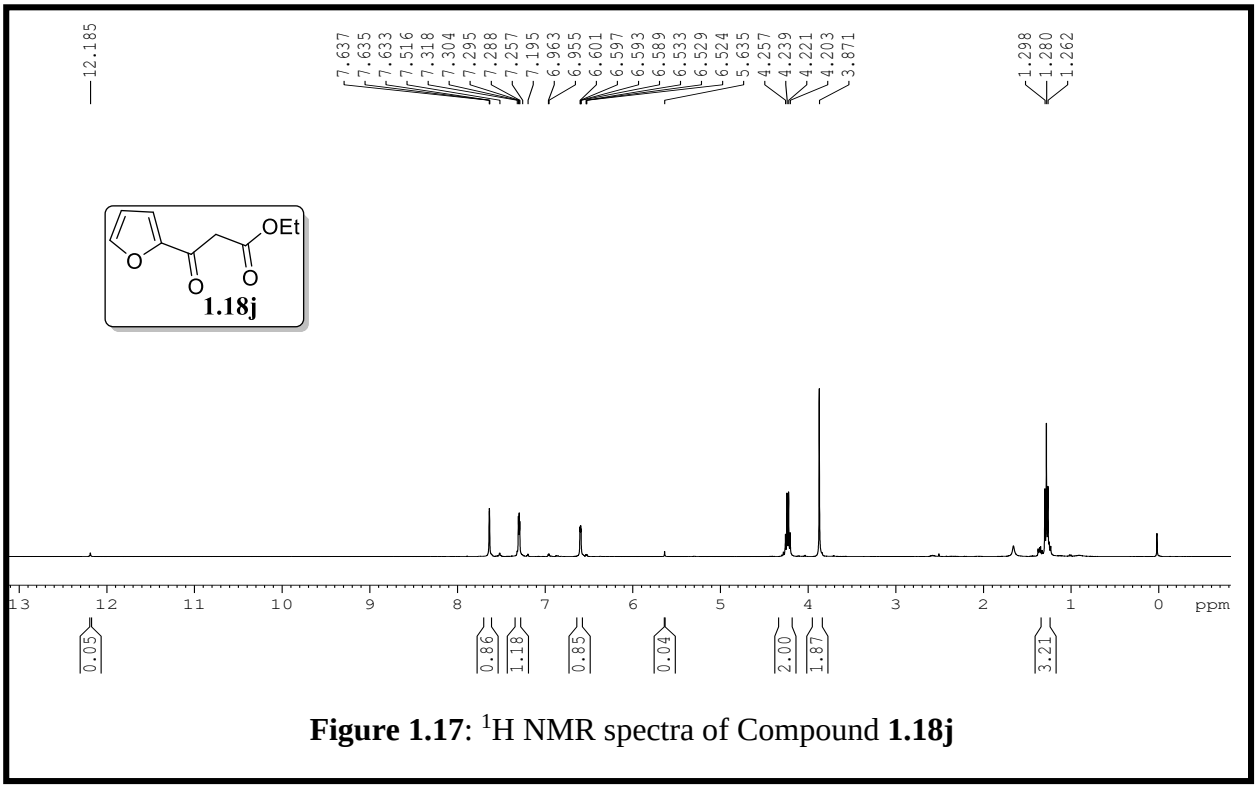


Figure 1.17: ^{1}H NMR spectra of Compound **1.18j**

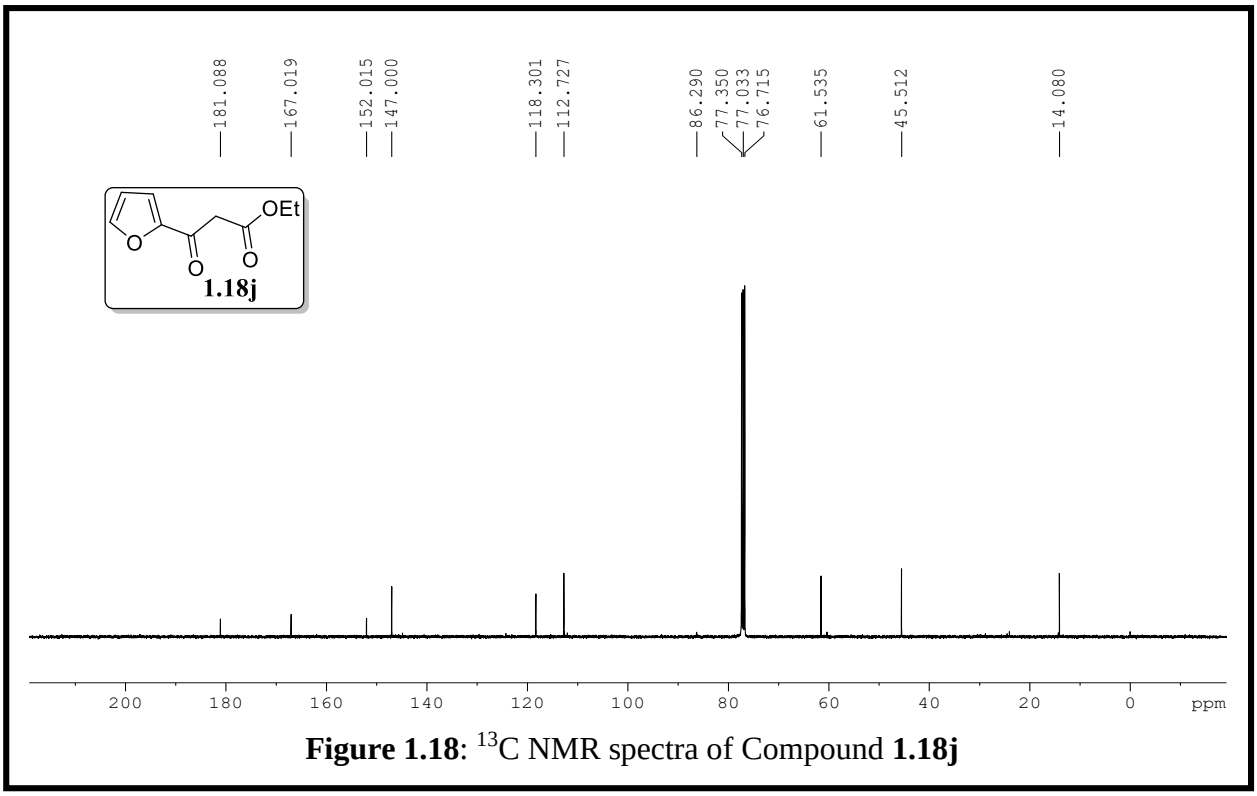


Figure 1.18: ^{13}C NMR spectra of Compound **1.18j**

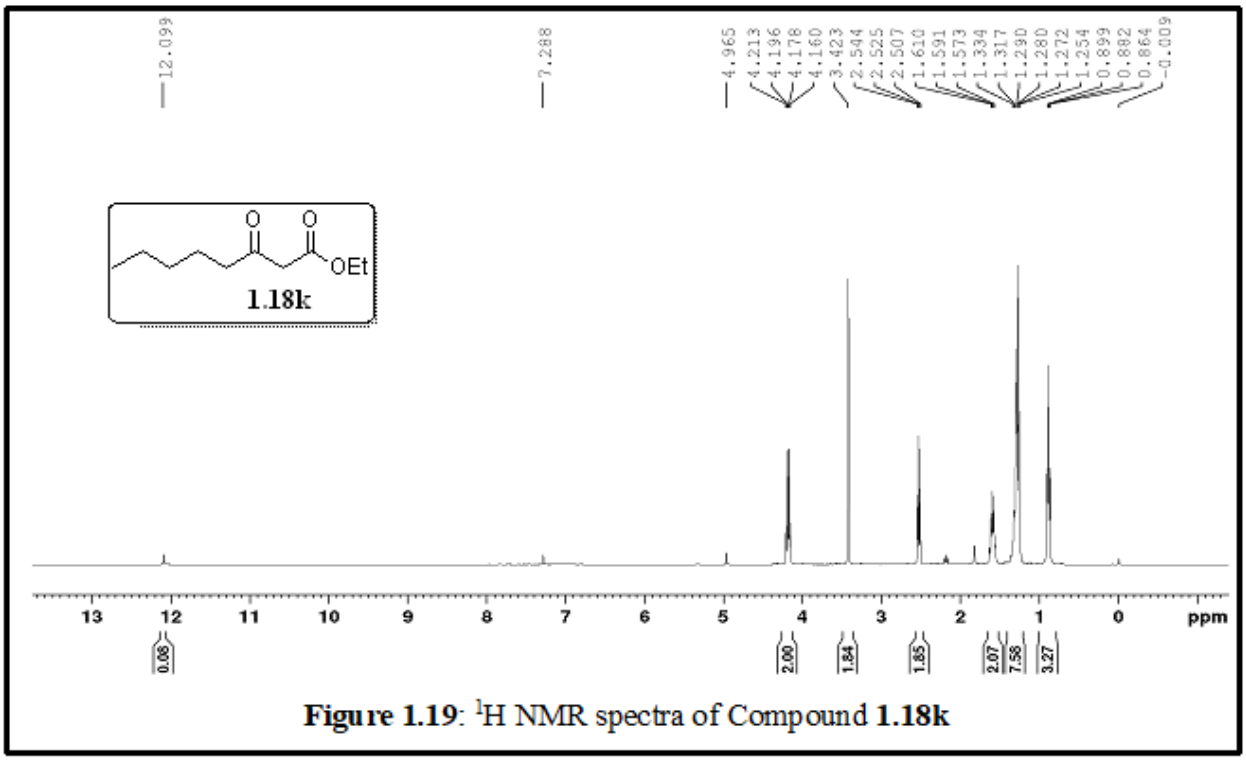


Figure 1.19: ^{1}H NMR spectra of Compound **1.18k**

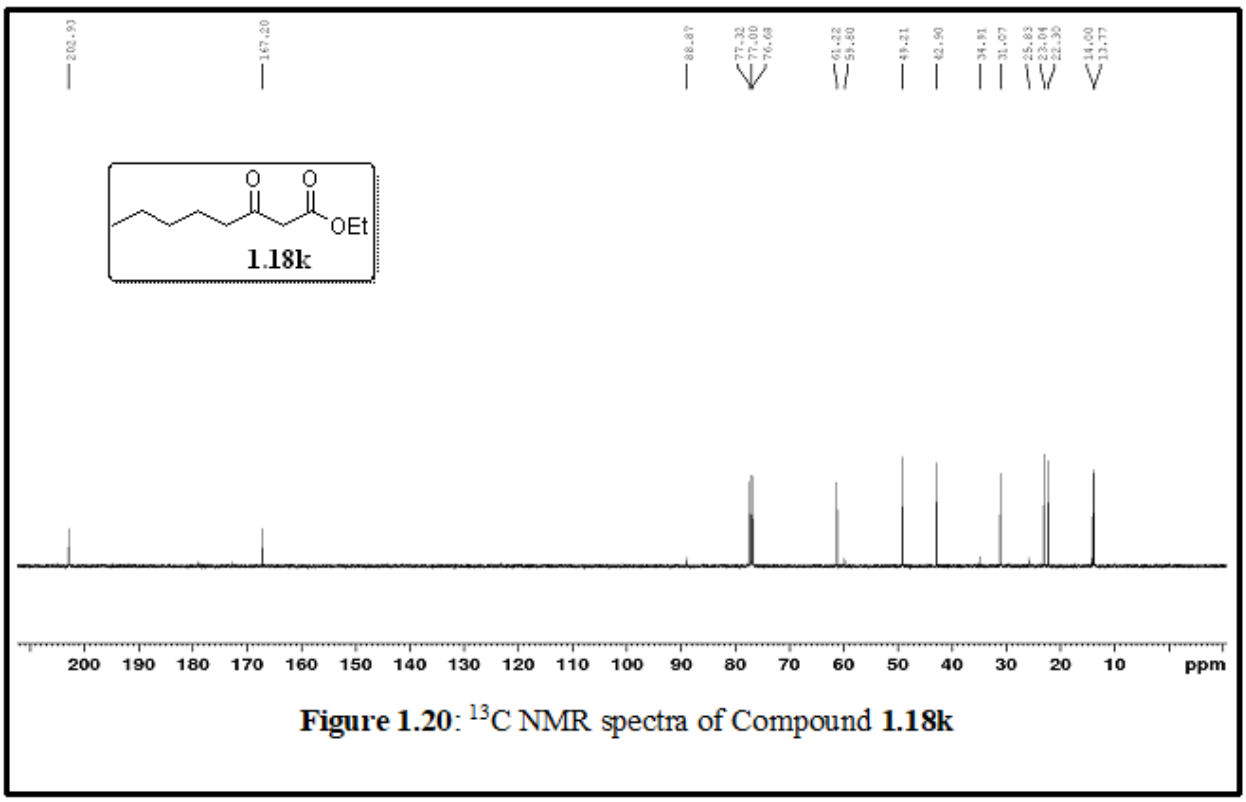


Figure 1.20: ^{13}C NMR spectra of Compound **1.18k**

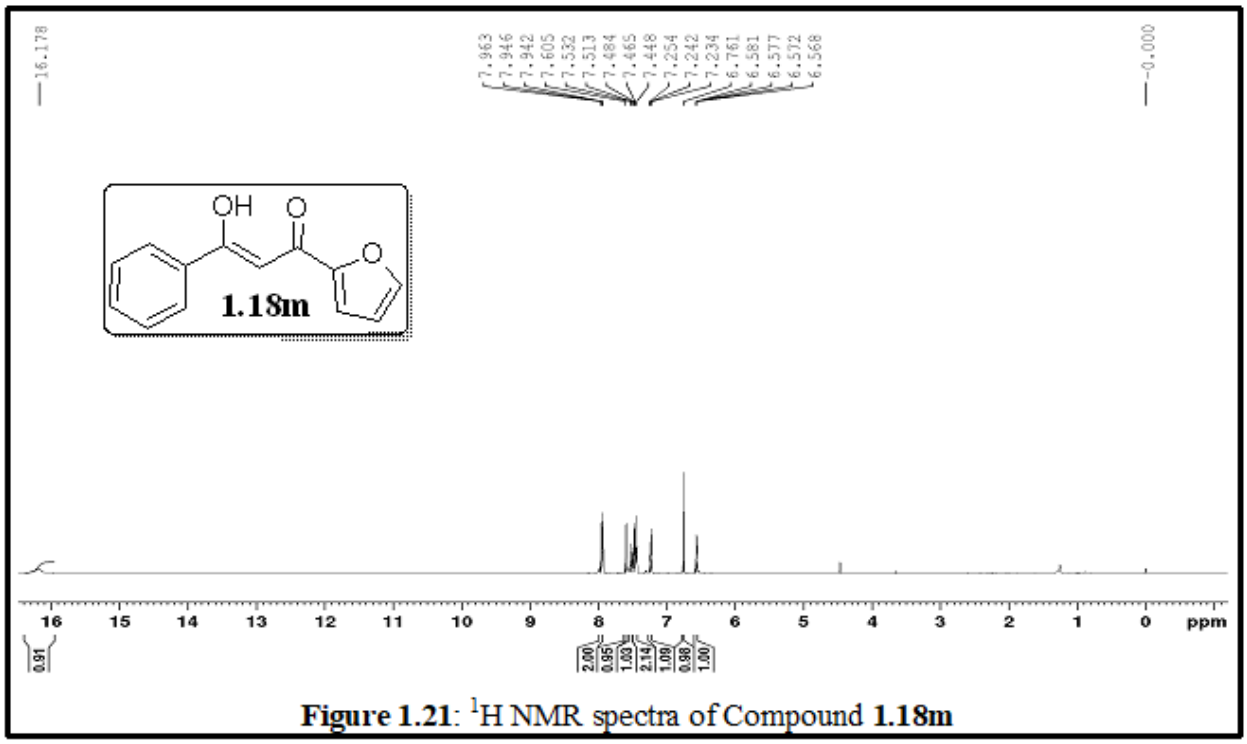


Figure 1.21: ^{1}H NMR spectra of Compound **1.18m**

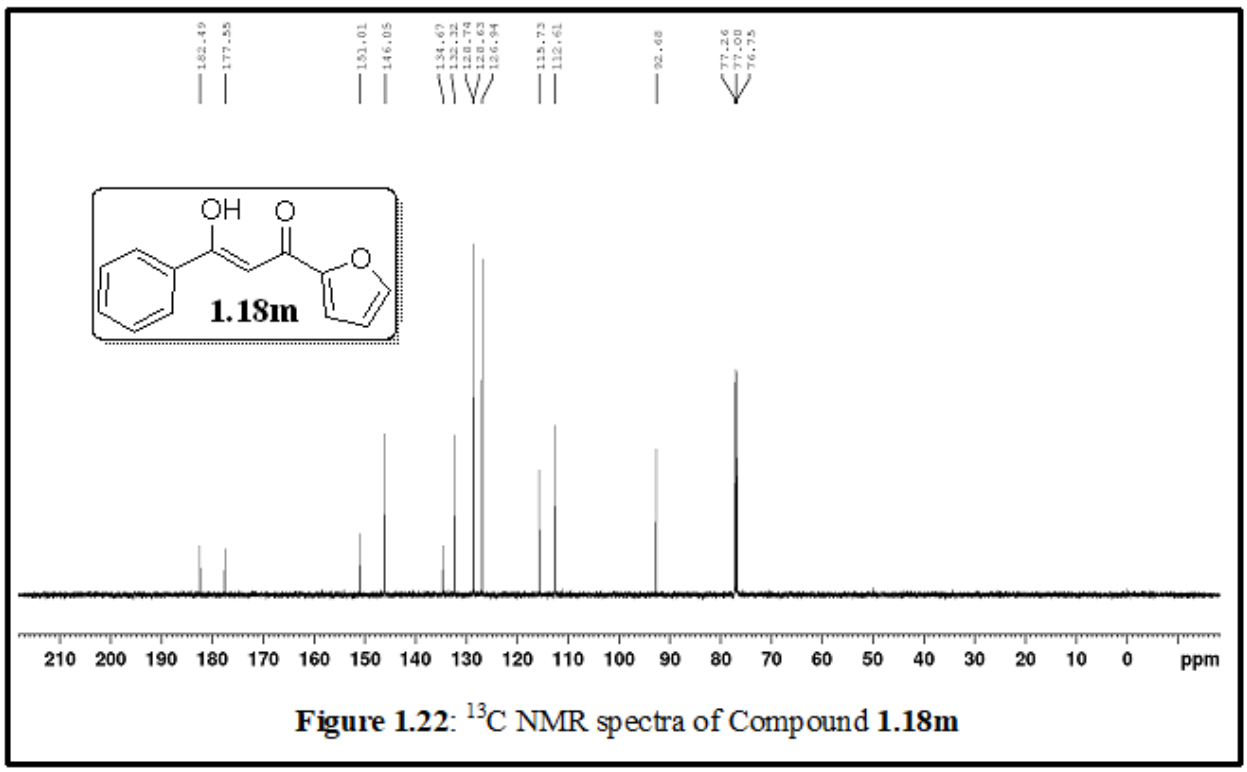


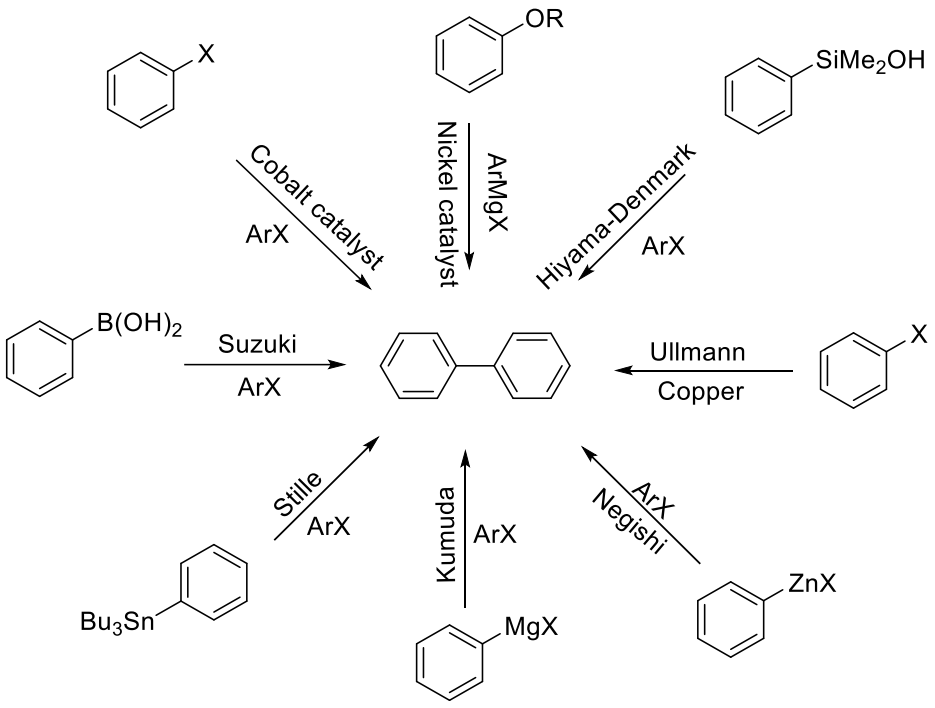
Figure 1.22: ^{13}C NMR spectra of Compound **1.18m**

Chapter 2

Construction of Benzene Ring via *in situ* Formed Acetals: A Facile Access to Highly Substituted Biaryls

2.1 Introduction

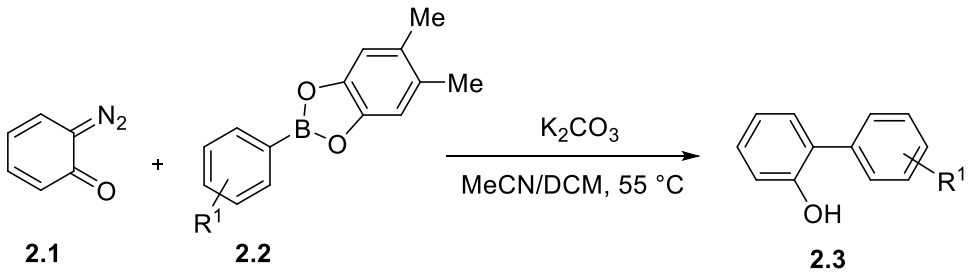
Biaryl is a structural feature present in numerous functional molecules such as natural products,[1] biologically active molecules,[2] materials,[3] pharmaceuticals,[4] catalysts.[5] There has been quite some interest among synthetic chemists towards the synthesis of biaryl systems since last century. Several methods are there for biaryls formation. Especially, the transition metal-catalyzed cross-coupling reaction is a classical approach (Scheme 2.1).[6] Recently, the C-H bond activation based arylation of arenes with haloarenes has been developing as a fast growing area.[7] High cost and toxicity of transition metals encouraged finding of metal-free reactions. In this regard, a base-promoted biaryl formation has been found out.[8] Some of the other approaches towards synthesis of biaryl skeleton bearing complex molecules involve benzannulation, aryne intermediates and ring metathesis strategies.[9] It is of special interest to develop reactions to synthesize biaryls making use of simple starting materials and strategies. In this regard biaryl synthesis via construction of benzene offers good scope for incorporating different functional groups at the required positions.



Scheme 2.1. Diverse approaches for the construction of biaryls through C-C coupling

2.1.1 Biaryl synthesis through benzene construction

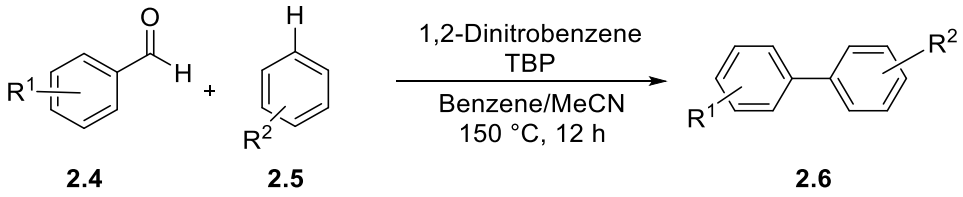
Recently, Che and co-workers developed a transition metal free cross-coupling reaction between diazo compound **2.1** and boronic ester **2.2** in the presence of a base to make biaryl compounds **2.3** under simple conditions (Scheme 2.2).[10] They explained the mechanism using DFT calculations and mechanic studies. The diazo quinones were made from aminophenols.



Scheme 2.2. Transition metal free cross-coupling reaction for biaryl synthesis

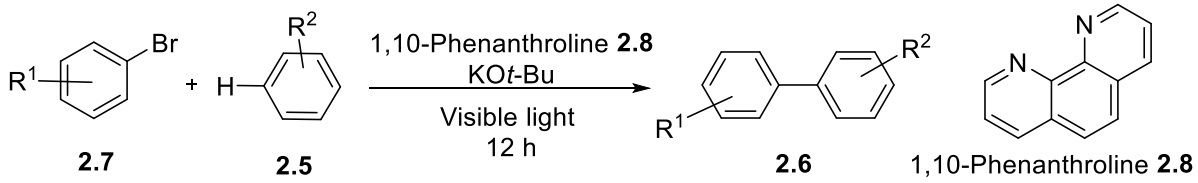
Yang and co-workers described an efficient method for the synthesis of biaryls **2.6** from benzaldehydes **2.4** and aromatic hydrocarbons **2.5** through transition metal free oxidative

decarboxylation reaction in the presence of stoichiometric additive DNB (1,2-dinitrobenzene) and TBP (Scheme 2.3). They have explained mechanism through DFT calculations. DNB was used as an electron transfer agent for the reaction. The advantage of this protocol is that biaryls can be prepared from readily available benzaldehydes and aromatic hydrocarbons.[11]



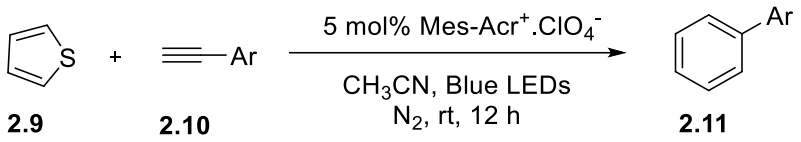
Scheme 2.3. Synthesis of biaryls from aromatic aldehydes and arenes

Yuan and co-workers developed a visible-light photoredox-catalyzed coupling reaction between aryl halides **2.7** and benzene derivatives **2.5** in the presence of N-heterocycles (1,10-phenanthroline **2.8**) under basic medium for the formation of biaryl derivatives **2.6** (Scheme 2.4).[12] In this protocol, under light, N-heterocycle forms radical anion in basic medium *via* SET which was identified by EPR spectra. This plays the leading role for the formation the product. This photoredox-catalyzed reaction can also be employed between aryl halides and pyridine derivatives to form corresponding biaryl products.



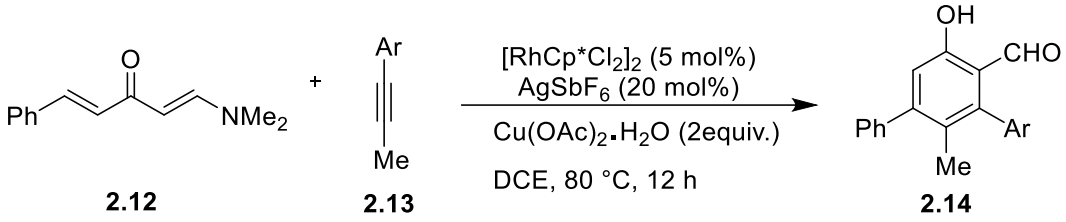
Scheme 2.4. Photoredox synthesis of biaryls from haloarenes and aromatic hydrocarbons

Recently, Lei and co-workers developed a method for the synthesis of benzene derivatives **2.11** from thiophene **2.9** and alkynes **2.10** *via* visible-light influenced [4+2] cycloannulation. This reaction occurs under oxidant-free, metal-free and mild conditions (Scheme 2.5).[13] The high regio and chemo selectivity of benzene derivative formation was explained by DFT calculations.



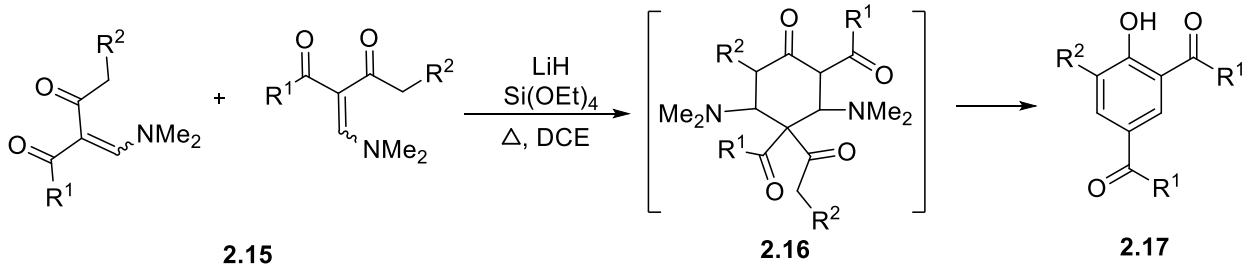
Scheme 2.5. Construction of benzene ring from thiophene and alkynes for biaryl synthesis

Zhu and co-workers reported a Rh(III)-catalyzed C-H activation of enaminone **2.12** and alkyne **2.13** for the formation of highly substituted benzene derivative **2.14** under simple conditions (Scheme 2.6).[14] This reaction is an unique approach for the formation of benzene ring *via* transition metal-catalyzed C-H bond activation.



Scheme 2.6. Synthesis of benzene ring formation via Rh(III) catalysis

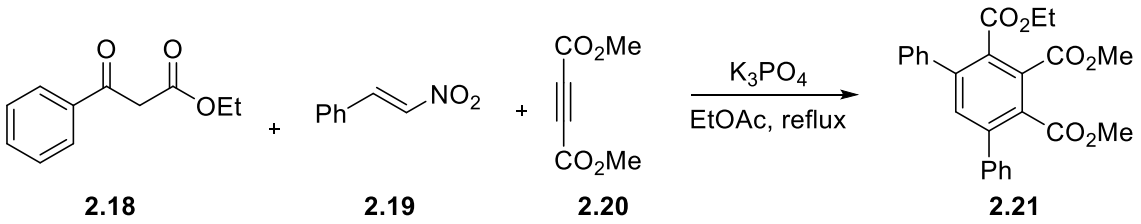
In 2018, Dmitrii and co-workers reported that benzene rings **2.17** could be constructed from enaminodiones **2.15** by self-condensation in the presence of a base (Scheme 2.7).[15] This reaction involves a cascade [4+2] cycloaddition to form cyclohexanone ring **2.16** which subsequently undergoes aromatization as a result of amine elimination. By this method highly functionalized benzene rings can be prepared under mild and simple conditions.



Scheme 2.7. Benzene derivatives formation from enaminodiones

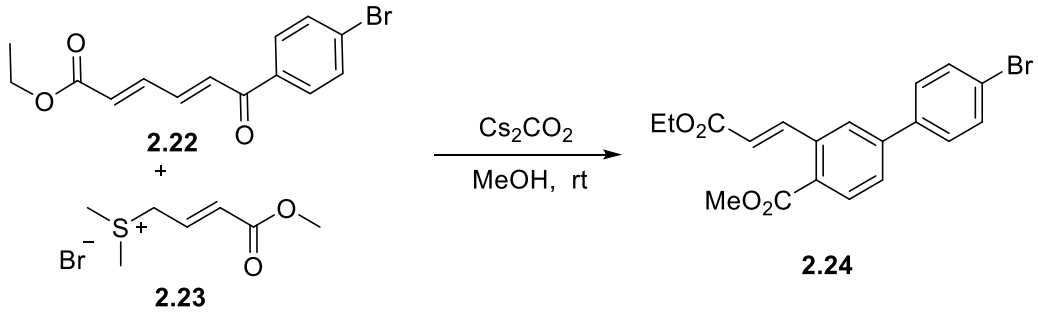
Wu and co-workers developed a benzannulation strategy for the synthesis of highly substituted benzene derivatives **2.21** using a multicomponent reaction of ethyl benzoyl acetate

2.18, β-nitrostyrene **2.19** and DMAD **2.20** under acidic conditions (Scheme 2.8).[16] In this protocol benzene derivatives can be prepared from cheaply available starting materials without the use of transition metal catalysts.



Scheme 2.8. Multicomponent benzannulation towards the synthesis of benzenes

Haung and Gao disclosed a protocol involving a tandem benzannulation between dienoates **2.22** and sulfur ylides **2.23** to offer biaryls *via* benzene construction (Scheme 2.9).[17] In addition to this, alkenylated, alkynylated benzene rings can also be prepared using this method. The proposed mechanism involves initial Michael addition followed by sulfur Wittig type reaction and subsequent aromatization to result in the product **2.24.**

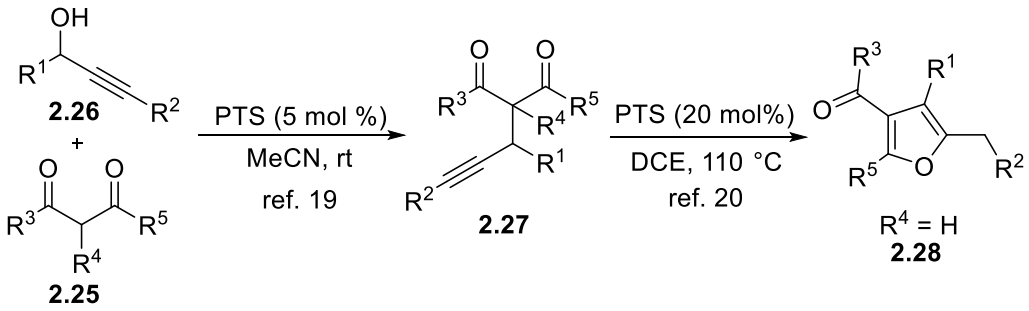


Scheme 2.9. Synthesis of benzene derivatives from sulfur ylides

2.2 Background

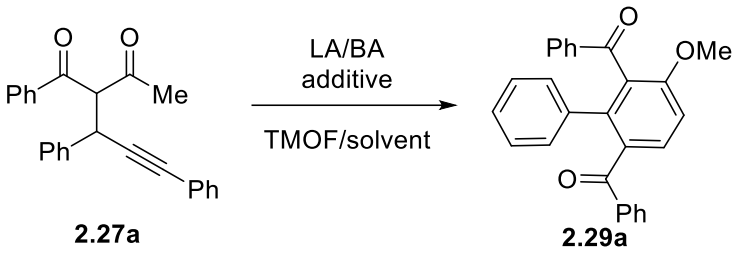
Our group has developed a number of transformations taking advantage of the reactivity of acetals generated *in situ* by reacting their parent carbonyl compounds with trimethyl orthoformate (TMOF) in the presence of a Lewis/Brønsted acid.[18] Thus formed acetals promote certain reactions to happen which are otherwise not possible directly from the parent carbonyl compounds. Unactivated ketones in the presence of trimethyl orthoformate and a Lewis/Brønsted

acid generate enol ethers, which were used as nucleophiles in α-functionalization of unactivated ketones.[18c-18f, 21a] In this context, we were curious to check the reactivity of 1,3-dicarbonyls having a methyl group as it bears both the active methylene and the less reactive α-methyl group in the presence trimethyl orthoformate and an acid catalyst. Specifically, propargyl alcohols were chosen as electrophilic reaction partners as it would lead to propargylated products that can cyclize on the alkyne functionality under the reaction conditions. It is known that 1,3-dicarbonyl compounds undergo propargylation at the active methylene position upon reaction with benzylic propargyl alcohols in the presence of catalytic PTS.[19]



Scheme 2.10. Acid-promoted propargylation of 1,3-dicarbonyls and its subsequent cyclization

In the beginning, we took the propargylated benzoylacetone **2.27a** and attempted its cyclization in the presence of different Brønsted/Lewis acids and trimethyl orthoformate. It has been reported that propargylated benzoylacetone to result in tri-substituted furan derivative in the presence of an acid catalyst.[20] Interestingly, the reaction of propargylated benzoylacetone **2.27a**, in the presence of trimethyl orthoformate and an acid catalyst, gave a substituted biaryl derivative **2.29a** (Scheme 2.11). Among the acids attempted, $HClO_4$ facilitated the formation of biaryl **2.29a** and a maximum yield of 58% was obtained when the reaction was carried out using 2 equivalents each of $HClO_4$ and DDQ in TMOF (Table 2.1). It has to be stated that the reaction became clean only when 2 equivalents of oxidant DDQ was used as an additive in the reaction. It is assumed that the biaryl formation happened via α-formylation,[21] annulation and aromatization. Presence of trimethyl orthoformate makes the reaction to take a different reaction route to result in biaryl compounds involving three new C-C bond formation steps.



2.27a **2.29a**

Scheme 2.11. Formation of biaryl via formylation, cyclization and aromatization sequence

Table 2.1. Optimization of reaction conditions for the biaryl formation

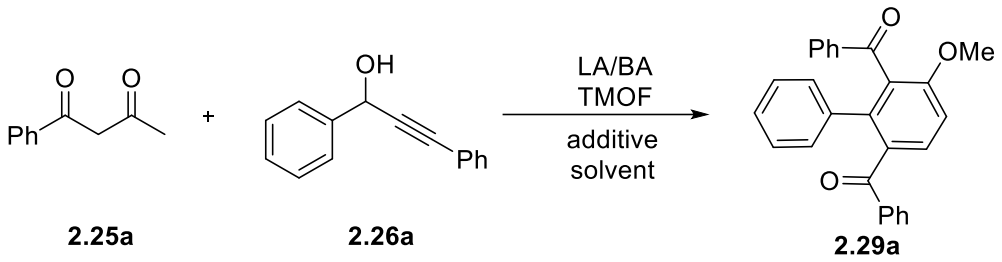
Entry	**LA/BA** (equiv.)	**Additive** (equiv.)	**Solvent**	**Yield in % (24 h)**
1	TfOH (0.2)	-	TMOF	traces
2	TfOH (1.2)	-	TMOF	traces
3	$HClO_4$ (2.1)	-	TMOF	14
4	$HClO_4$ (2.1)	-	TMOF-CH_3NO_2	34
5	$HClO_4$ (2.1)	-	TMOF-CH_2Cl_2	20
6	$HClO_4$ (2.1)	-	TMOF-Dioxane	traces
7	AgOTf (0.1)	-	TMOF	NR
8	$HClO_4$ (2.1)	DDQ (2)	TMOF	40
9	$HClO_4$ (2.1)	DDQ (1)	TMOF	58

2.3 Results and Discussion

2.3.1 One-pot synthesis of biaryls from 1,3-dicarbonyls and propargyl alcohols

Formation of biaryl derivative **2.29a** from **2.27a** prompted us to try and optimize the condition for the formation biaryl product by directly reacting **2.25a** and **2.26a** in one-pot, as the propargylation is possible under the acidic condition. However, it was found that TMOF alone, as solvent, was not suitable to promote the propargylation. Therefore, the $HClO_4$-promoted propargylation was carried out first using nitromethane as solvent and then equal amount of TMOF was added to effect the conversion of the propargylated benzoylacetone **2.27a** into biaryl derivative.

Table 2.2. Optimization of reaction for one-pot biaryl synthesis[a]



2.25a **2.26a** **2.29a**

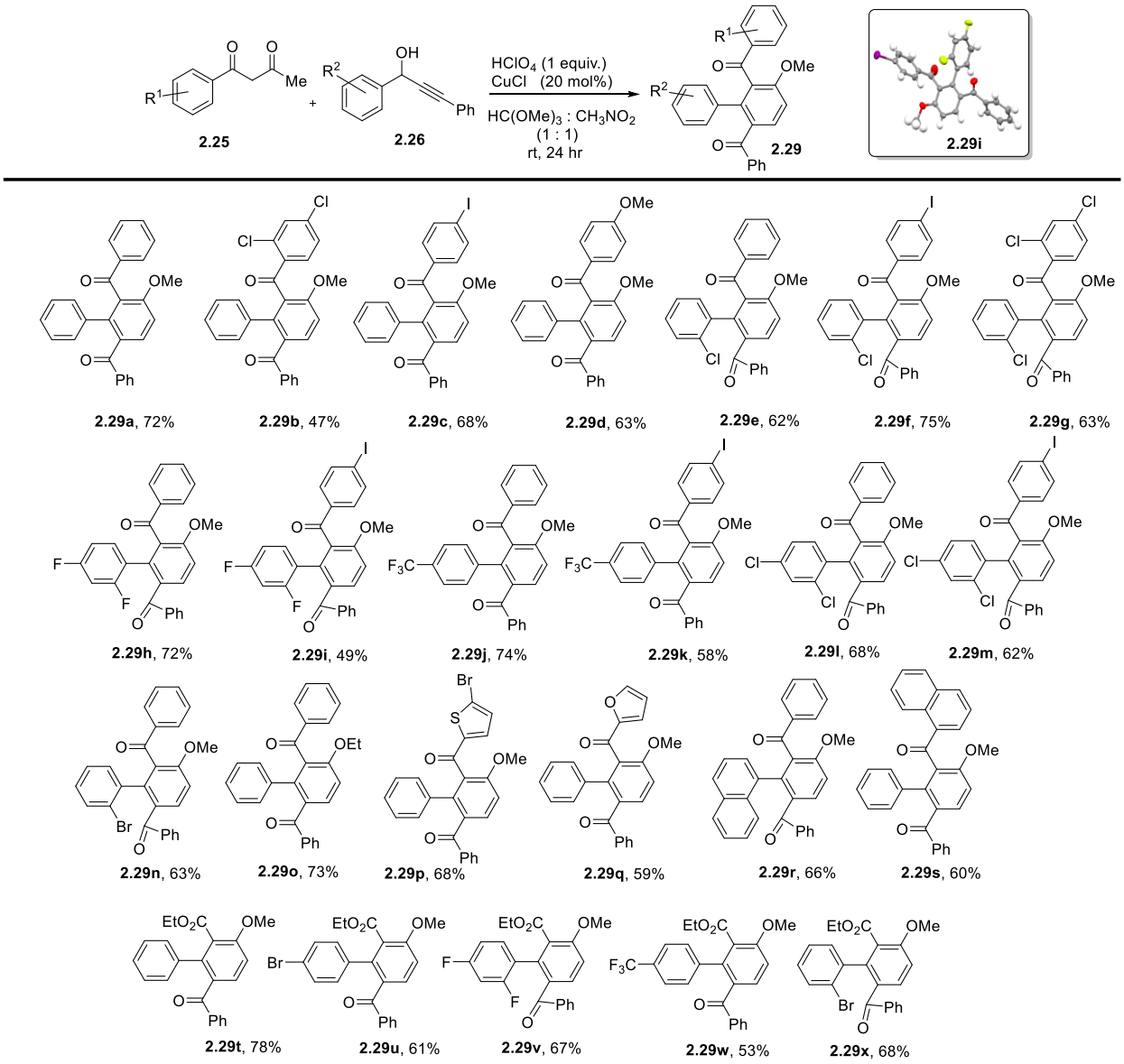
Entry	Acid (equiv.)	Additive (equiv.)	Solvent	Yield in %
1	$HClO_4$ (2)	DDQ (1)	TMOF/CH_3NO_2 (1:1)	48
2	$HClO_4$ (2)	-	TMOF/CH_3NO_2 (1:1)	trace
3	$HClO_4$ (2)	DDQ (1)	TMOF/CH_3NO_2 (1:1)	30
4	$HClO_4$ (2)	DDQ (1)	TMOF/toluene (1:1)	20
5	$HClO_4$ (2)	DDQ (1)	TMOF/CCl_4 (1:1)	25
6	$HClO_4$ (1)	DDQ (1)	TMOF/CH_3NO_2 (1:1)	40
7	$HClO_4$ (2)	DDQ (0.5)	TMOF/CH_3NO_2 (1:1)	30
8	$HClO_4$ (2)	DDQ (1)	TMOF/CH_3NO_2 (1:1)	20
9	$HClO_4$ (2)	$CuCl_2$ (1)	TMOF/CH_3NO_2 (1:1)	[b]
10	$HClO_4$ (2)	CuCl (1)	TMOF/CH_3NO_2 (1:1)	73
11	$HClO_4$ (2)	CuCl (0.2)	TMOF/CH_3NO_2 (1:1)	68
12	$HClO_4$ (2)	CuI (0.2)	TMOF/CH_3NO_2 (1:1)	65
13	$HClO_4$ (1)	CuCl (0.2)	TMOF/CH_3NO_2 (1:1)	73
14	$HClO_4$ (0.5)	CuCl (0.2)	TMOF/CH_3NO_2 (1:1)	72
15	$HNTf_2$ (10 mol %)	CuCl (0.2)	TMOF/CH_3NO_2 (1:1)	[b]
16	*p*TSA (1)	CuCl (0.2)	TMOF/CH_3NO_2 (1:1)	[b]
17	$HClO_4$ (0.5)	CuCl (0.2)	TMOF	NR

[a] All the reactions were conducted using 0.24 mmol of **2.25a** and **2.26a** each for 24 h in 2 mL of solvent mixture. [b]complex mixture

It is anticipated that propargylation at the active methylene carbon followed by formylation[21] at the methyl and cyclization would lead to a cyclohexadiene system which may undergo double bond migrations under acidic condition to effect conjugation of double bonds with the available carbonyl groups. Therefore, it was considered to conduct the reaction in the presence of 1 equivalent of DDQ to aromatize the products to get better yields of the product (Table 2.2, entries 1, 3-8). Interestingly, CuCl, as an additive, assisted smooth aromatization to result in the desired biaryl derivative **2.29a** in good yield (Table 2.2, entries 10, 11, 13-17). Being alkynophilic, CuCl might have favored the alkyne-carbonyl metathesis.[22] Its role in aromatization in the final step might not be ruled out since DDQ was not required in this reaction to furnish the product. $CuCl_2$, as additive, was not effective as it resulted in a complex product mixture (Table 2.2, entry 9). Overall, the formation of biaryl involves propargylation, formylation, cyclization/annulation[22] and aromatization, all in one-pot, as shown in the scheme 2.13.

The condition mentioned in entry 13 of the table 2.2 was used for the evaluation of substrate scope. A number of aryloylacetone derivatives were treated with different aryl propargyl alcohols. The reactions resulted in the expected biaryl products with moderate to good yields (Table 2.3). Aryl groups having substituents such as F, Cl, Br, I, OMe and CF_3 could very well tolerate the reaction conditions. Heterocycles such as furan and thiophene containing 1,3-dicarbonyl reacted smoothly to give the biaryls attached to heterocycles (**2.29p** and **2.29q**). On the other hand, propargyl alcohols having furan or thiophene rings decomposed under the reaction conditions. Sterically bulky naphthalene could be accommodated in both 1,3-dicarbonyl or propargyl alcohol to get their respective biaryl products (**2.29r** and **2.29s**). 1,3-Ketoester such as ethyl acetoacetate could also be employed to get diaryls having an ester substituent (**2.29t-2.29x**). Desired biaryl products were not obtained with dicarbonyl compounds having longer alkyl groups in the place of methyl, non-benzylic and aliphatic propargyl alcohols. 1,3-Ketoamides such as aceto acetamide and N-benzyl-3-oxobutanamide decomposed under the reaction conditions.

Table 2.3. Substrate scope for the synthesis of biaryls from 1,3-dicarbonyls

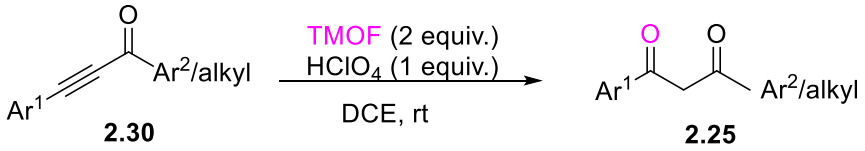


2.3.2 Brønsted acid-promoted regioselective hydration of alkynones

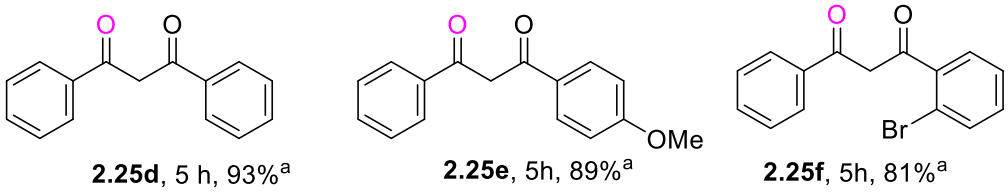
Synthesis of 1,3-dicarbonyls, apart from trivial Claisen condensation, have been achieved by regioselective hydration of alkynones using gold-catalysts.[23] However, efficient Brønsted acid-promoted regioselective hydration of alkynones has not been explored systematically.[23c-d] TfOH-catalyzed regioselective hydration of alkynones occurs at 100 °C and resulted in poor yields of the 1,3-dicarbonyls.[23d] With this background, it was anticipated that treatment of an alkynone with

trimethyl orthoformate in the presence of a $HClO_4$ might lead to regioselective addition of methoxy group at the β-carbon. Hydrolysis of the enol ether might occur under the reaction condition to furnish 1,3-diketone as the $HClO_4$ used is an aqueous solution. Gratifyingly, reaction of 1,3-diphenylprop-2-yn-1-one with trimethyl orthoformate (2 equivalents) in the presence of $HClO_4$ (1 equivalent) in DCE at room temperature resulted in the formation of 1,3-diphenylpropane-1,3-dione in 93% yield. It has to be noted that the conversion does not occur when the reaction was conducted using excess of water in the place of TMOF. Better nucleophilicity of OMe group in TMOF due to the formation of a stabilized carbenium ion after the transfer MeO^- might be a reason for the successful reaction with TMOF. The scope of the reaction was evaluated with a few more alkynones which smoothly transformed into their corresponding 1,3-dicarbonyl compounds (Table 2.4). Thus, this protocol serves as a simple and metal-free transformation of alkynones into 1,3-diketones. Ethyl 3-phenylpropiolate did not undergo hydration under the reaction condition. The success of the hydration of alkynones might be due to the formation of acetal of the carbonyl under the reaction condition facilitating the hydration.

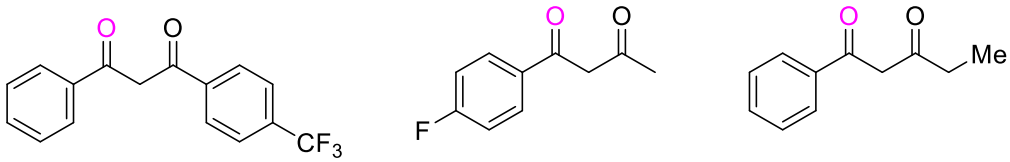
Table 2.4. TMOF-assisted $HClO_4$-promoted conversion of alkynones into 1,3-diketones



2.30 **2.25**



2.25d, 5 h, 93%[a] **2.25e**, 5h, 89%[a] **2.25f**, 5h, 81%[a]



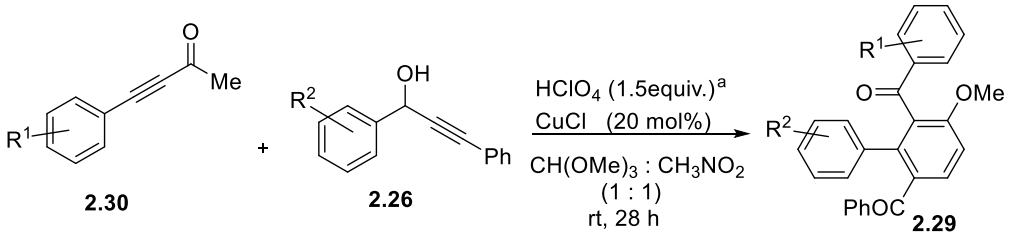
2.25g, 4h, 81%[a] **2.25h**, 4h, 85%[a] **2.25i**, 4h, 80%[a]

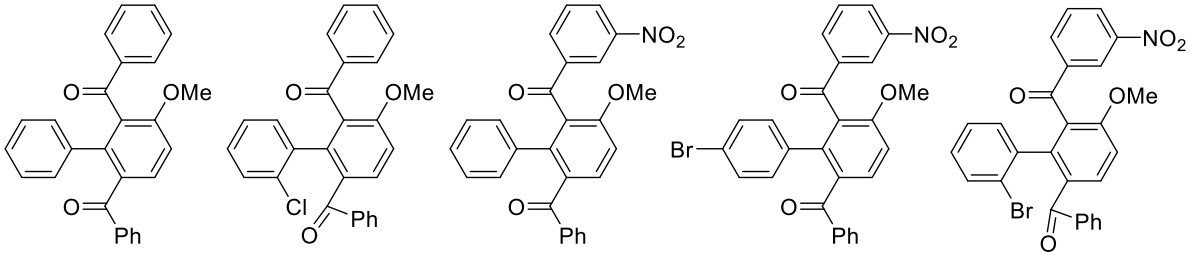
[a]Isolated yield

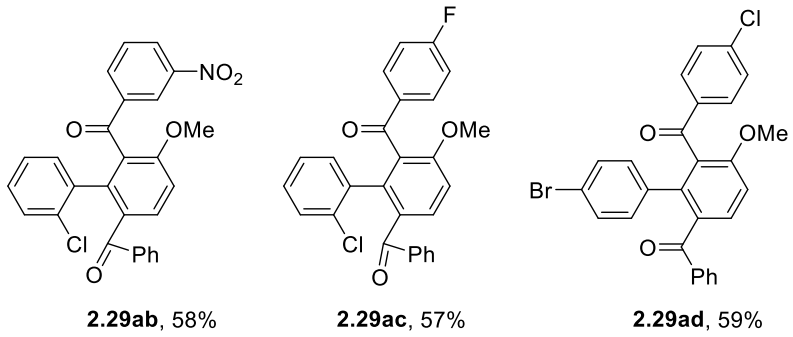
2.3.3 Synthesis of biaryls from alkynyl methyl ketones and propargyl alcohols

The success of hydration of alkynones using $HClO_4$/TMOF prompted us to carry out the hydration of 4-arylbut-3-yn-2-one and the subsequent reaction of the resulting 1,3-diketone with an aryl propargyl alcohol in one-pot. In this regard, alkynone **2.30a** was treated with 1 equivalent of $HClO_4$ and 2 equivalents of TMOF in nitromethane solvent. Smooth completion of hydration was noted within 4 h. Then benzylic propargyl alcohol **2.26a** (0.83 equiv. with respect to **2.30a**) and 0.5 equivalent of $HClO_4$ were added to effect propargylation. Generally, the propargylation is fast and completed in less than 5 minutes. Then TMOF (equal amount by v/v with respect to CH_3NO_2) and 20 mol% of CuCl were added to the reaction mixture and the stirring was continued for another 24 h to ensure the formation of biaryl product **2.29a**. The generality of this reaction was examined by employing a few alkynones. The results of this one-pot sequential hydration, propargylation, formylation, cyclization, aromatization are provided in Table 2.5. Although the yields were slightly less (**2.29a**: 61% vs 72% and **2.29e**: 57% vs 62%) when compared to the reaction of 1,3-diketones, annexation of one more step (hydration) in the reaction of alkynones makes it attractive.

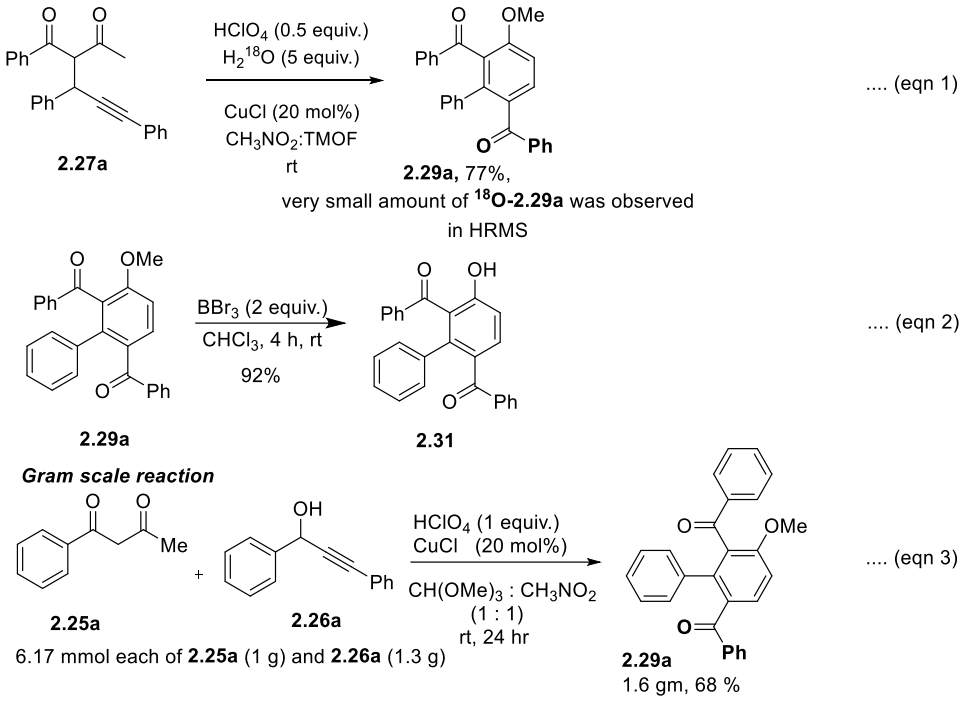
Table 2.5. Synthesis of biaryls from alkynones







[a]1 equiv. of $HClO_4$ and 2 equiv. of TMOF were used for hydration of **2.30** into corresponding 1,3-diketone



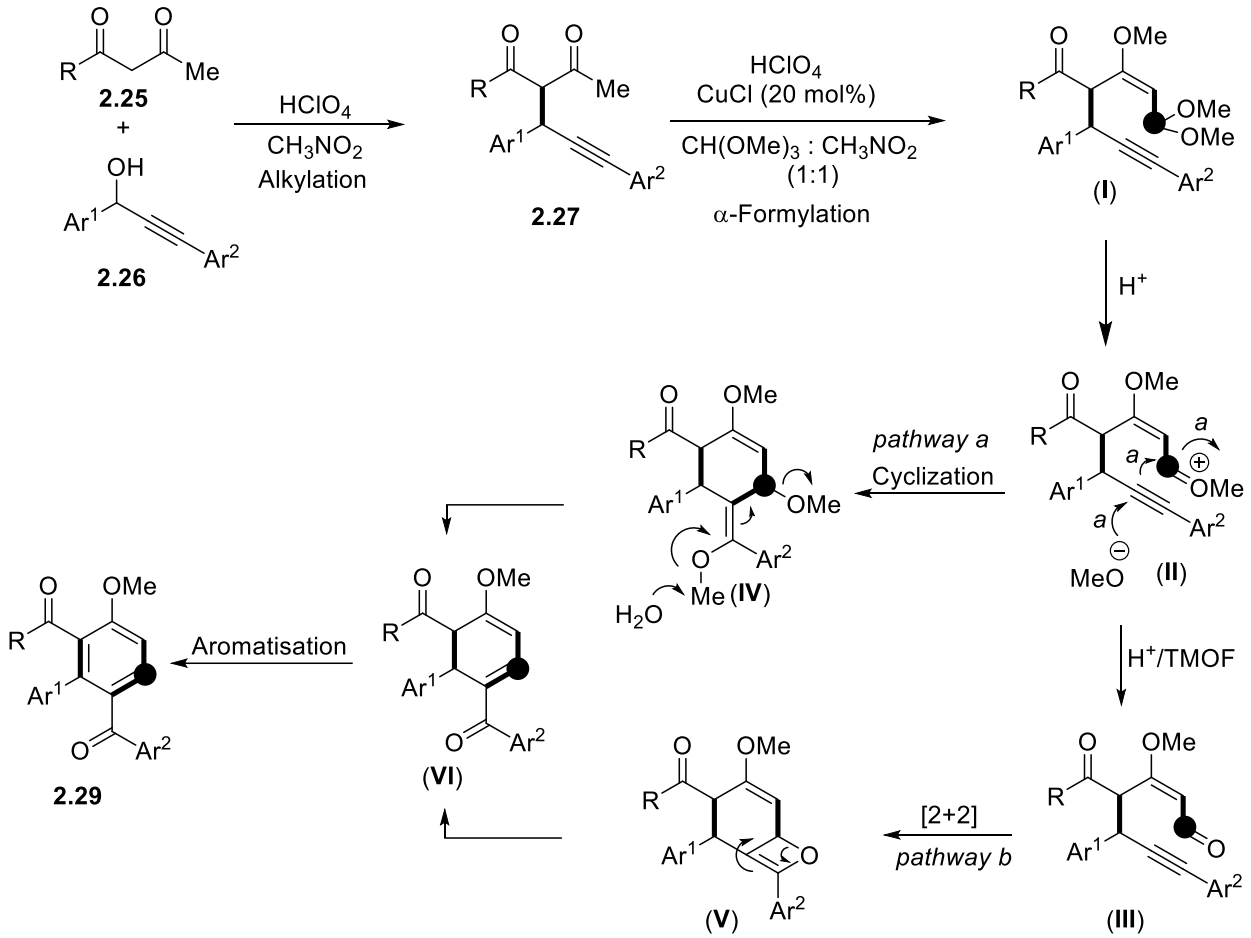
Scheme 2.12. Control experiment and synthesis of substituted phenol

To evaluate the source of oxygen in the product, a reaction was carried out using the substrate **2.27a** in the presence of 5 equivalents of $H_2{}^{18}O$ (Scheme 2.12, eqn 1). HRMS analysis of the product revealed a very little incorporation of ^{18}O in the product suggesting that trimethyl orthoformate as its source. The OMe group can easily be deprotected using BBr_3 to get *o*, *p*-diacyl-*m*-aryl phenols, whose skeleton is present in biologically important compounds.[24] For example, **2.27a**, upon reaction with BBr_3, resulted in 92% of phenol derivative **2.30** (Scheme 2.12, eqn 2).

2.3.4 Mechanism

The reaction of 1,3-dicarbonyls with propargyl alcohols to form substituted biaryls involves alkylation, α-formylation, cyclization and aromatization, all happening in one-pot. Initially, acid-promoted propargylation might take place at the active methylene carbon. Then, formylation occurs at the methyl carbon α- to the carbonyl to give intermediate **I**. In the presence of acid and TMOF, intermediate **I** can result in oxacarbenium ion **II** or the completely deprotected aldehyde **III**. The oxacarbenium ion **III** can undergo cyclization upon attack of MeO^- to result in **IV** and subsequently **VI**. On the other hand, the intermediate **VI** can also be formed from the aldehyde

intermediate **III** via aldehyde alkyne metathesis *via* intermediate **IV**. Finally, the intermediate **VI** results in the biaryl product **2.29** by aromatization.



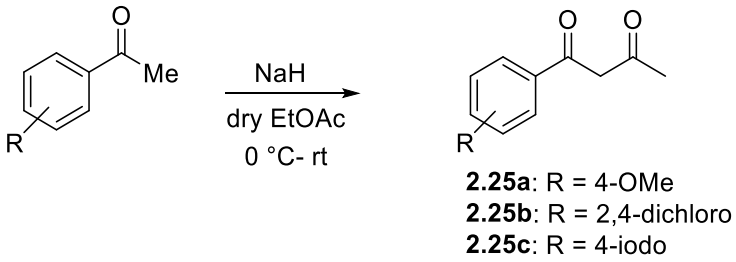
Scheme 2.13. Plausible mechanism for biaryl formation

2.4 Conclusion

In conclusion, we have developed a new method for the synthesis of highly substituted biaryls from propargylic alcohols and 1,3-diketones involving sequential propargylation, formylation, annulation and aromatization by exploiting the unique reactivity of *in situ* formed acetal. Metal-free regioselective hydration of alkynones has been evaluated using perchloric acid and this has been employed in the reaction of alkynones with benzylic propargyl alcohols to make substituted biaryls.

2.5 Experimental section

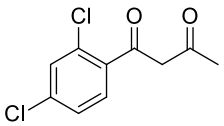
2.5.1 Representative procedure for the synthesis of 1,3-Diketones 2.25a-2.25i



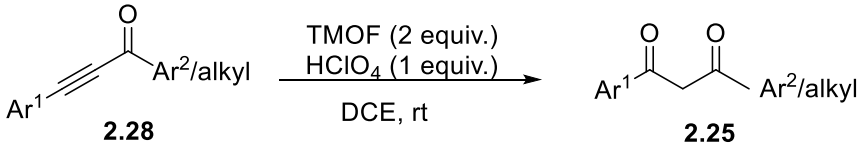
2.25a: R = 4-OMe
2.25b: R = 2,4-dichloro
2.25c: R = 4-iodo

1,3-Dicarbonyl compounds were prepared by Claisen condensation. Acetophenone derivative was dissolved in dry ethyl acetate (1 mL per 100 mg of ketone derivative). To this 60% NaH (1.2 equiv.) was added at 0 °C with constant stirring. The reaction mixture was allowed to stir for 12 - 14 h for completion of the reaction. Then saturated aqueous NH_4Cl solution was added carefully and the reaction mixture was acidified to pH 5 with aqueous HCl solution. The aqueous phase was separated and extracted with ethyl acetate and the combined organic phase was dried over anhydrous sodium sulphate and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography with 5% EtOAc/hexanes to get 1,3-diketone derivatives. The 1,3-diketones **2.25a-c** are already reported in literature.[25]

1-(2, 4-Dichlorophenyl)butane-1,3-dione (2.25b):

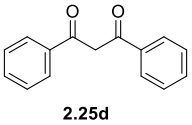


Compound existed in enolic form; Yield 84%; yellow solid (m.p. 40-42 °C); IR (neat): 2952, 1748, 1655, 1216, 1076, 926, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 15.68 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.33 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.05 (s, 1H), 2.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 192.8, 183.3, 137.0, 133.9, 132.6, 130.9, 130.5, 127.3, 101.7, 25.4; HRMS (ESI): Calcd for $C_{10}H_8Cl_2NaO_2$ $[M + Na]^+$ 252.9799; Found 252.9795.



TMOF-assisted and $HClO_4$–promoted hydration of alkynones: Alkynones (1 equiv.), trimethyl orthoformate (2 equiv.) and $HClO_4$ (1 equiv.) were added to DCE in a round bottom flask at room temperature. The progress of the reaction was monitored by TLC. Generally, the reaction took 4-6 h for completion. After completion of the reaction solvent DCE was evaporated and the residue was loaded on a silica gel column and eluted with mixtures of EtOAc/hexanes to get pure 1,3-diketone derivative.

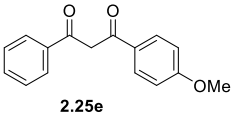
1,3-Diphenyl-1,3-propanedione (2.25d):[25]



2.25d

Yield 93%; yellow solid ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, *J* = 7.2 Hz, 4H) 7.56 (t, *J* = 7.2 Hz, 2H), 7.49(d, *J* = 7.2 Hz, 4H). 6.86 (s, 1H).

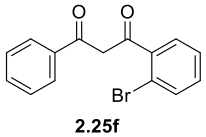
1-(4-Methoxyphenyl)-3-phenylpropane-1,3-dione (2.25e): [25]



2.25e

Yield 89%; white solid ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01-7.98 (m, 4H), 7.57-7.55 (m, 1H), 7.52-7.47 (m, 2H), 7.01-6.99 (m, 2H), 6.82 (s, 1H), 3.91 (s, 3H).

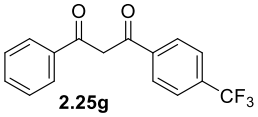
1-(2-Bromophenyl)-3-phenylpropane-1,3-dione (2.25f): [25]



2.25f

Yield 81%; colourless oil, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, *J* = 7.2 Hz, 2H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 1H), 6.67 (s, 1H).

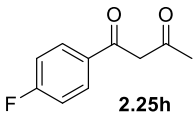
1-Phenyl-3-(4-(trifluoromethyl)phenyl)propane-1,3-dione (2.25g): [25]



2.25g

Yield 81%; white solid, ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, *J* = 7.6 Hz, 2H), 7.99 (d, *J* = 7.4 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.2 Hz, 2H), 6.87 (s, 1H).

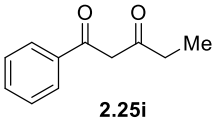
1-(4-Fluorophenyl)butane-1,3-dione (2.25h):[25]



2.25h

Yield 85%; white solid, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91−7.88 (m, 2 H), 7.15−7.11 (m, 2 H), 6.13 (s, 1 H), 2.20 (s, 3 H).

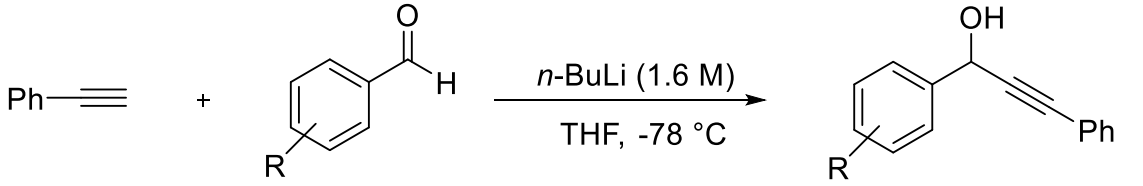
1-Phenylpentane-1,3-dione (2.25i):[25]



2.25i

Yield 80%; brown colour liquid, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 – 7.87 (m, 2H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.46 – 7.43 (m, 2H), 6.18 (s, 1H), 2.47 (q, *J* = 7.5 Hz, 2H), 1.21 (t, *J* = 7.5 Hz, 3H).

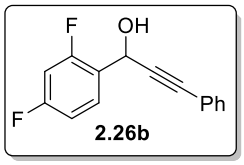
2.5.2 Representative procedure for the synthesis of propargylic alcohols 2.26a-2.26h



2.26a: R = H
2.26b: R = 2,4-difluoro
2.26c: R = 2,4-dichloro
2.26d: R = 4-trifluoromethyl
2.26e: R = 2-chloro
2.26f: R = 2-bromo
2.26g: R = 4-bromo
2.26h: R = 4-chloro

n-BuLi in hexane (1.5 equiv. 1.6 M) was added to a phenyl acetylene (1.2 equiv.) in THF at –78 °C under N_2. The mixture was stirred for 1 h at the same temperature and benzaldehyde (1.0 equiv.) was added. The reaction mixture was warmed to room temperature and stirred for 4 h to overnight depending upon the product formed. The reaction was quenched with a saturated aqueous NH_4Cl solution. The aqueous solution was extracted with EtOAc and the combined organic layers were washed with saturated aqueous brine solution. Organic layer was dried with $NaSO_4$ and the solvents were removed under reduced pressure. The residue was purified using silica gel chromatography with 10% EtOAc/hexanes to get respective propargylic alcohol derivative. Except **2.26b** all the other propargyl alcohols are reported already.[26a-d]

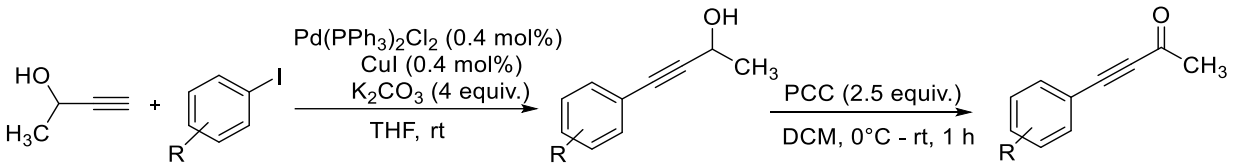
1-(2, 4-Difluorophenyl)-3-phenylprop-2-yn-1-ol (2.26b):



Yield 72%; yellow oil; IR (neat): 3054, 1216, 1076, 876, 694 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73-7.68 (m, 1H), 7.46-7.44 (m, 2H), 7.32-7.30 (m, 3H), 6.92-6.88 (m, 1H), 6.85-6.81 (m, 1H), 5.92 (s, 1H), 2.65 (br s, OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.0, 161.9, 161.3, 159.3, 131.7, 129.5, 128.7, 128.2, 114.4, 104.0, 90.2, 87.2, 86.7, 82.6, 58.9; HRMS (ESI): Calcd. for $C_{15}H_{11}F_2O$ $[M + H]^+$ 245.0778; Found 245.0780.

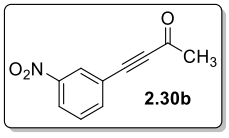
2.5.3 Representative procedure for the synthesis of alkynones 2.30a-c and 2.30h

$Pd(PPh_3)_2Cl_2$ (0.4 mol%), CuI (4 mol%) and K_2CO_3 (4 equiv.) were added sequentially to a solution of propargylic alcohol (1 equiv.) and iodobenzene (1.2 equiv.) in THF. The reaction mixture was stirred for 4 h at rt. After this the reagents were removed by filtering through a celite pad. Evaporation of solvents followed by purification by column chromatography (20% EtOAc/hexanes) resulted in phenyl butynol 90%. The resulting product was oxidized to its corresponding alkynone using standard PCC oxidation conditions**.**



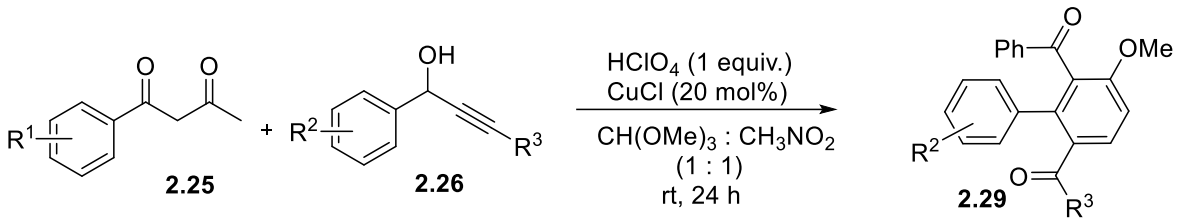
2.30a: R = H
2.30b: R = 3-NO_2
2.30c: R = 4-Cl
2.30h: R = 4-F

4-(3-Nitrophenyl)but-3-yn-2-one (2.30b):



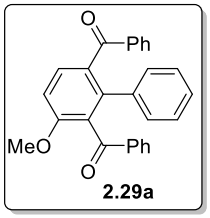
Yield 76%, brown solid; (m.p. 89-91 °C); IR (neat): 3054, 2930, 1717, 1216, 1076, 926, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 8.27 (d, *J* = 7.6 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 2. 47(s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.9, 147.9, 138.2, 129.7, 127.3, 125.0, 121.5, 89.0, 86.2, 32.5; HRMS (ESI): calcd for $C_{10}H_7NO_3$ $[M + H]^+$ 190.0504; Found 190.0505.

2.5.4 Representative procedure for the synthesis of biaryls from propargylic alcohols and 1,3-diketones and analytical data of compounds 2.29a-2.29x



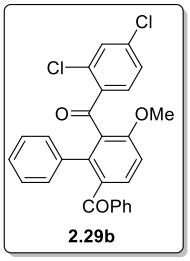
A reaction flask (10 mL) was charged with propargylic alcohol **2.26** (1 equiv.), 1,3-diketone/ethyl acetoacetate **2.25** (1 equiv.), $HClO_4$ (1 equiv.) in nitromethane (1 mL) solvent. After 15 minutes trimethyl orthoformate (1 mL per 0.25 mmol of **2.25**) and CuCl (20 mol%) were added. The reaction mixture was stirred at rt for 24 h. Solvents were evaporated in a rotary evaporator. The residue was diluted with ethyl acetate and washed with water. The aqueous layer was extracted twice with ethyl acetate and the combined organic layers were dried over sodium sulphate. After evaporation of solvents, the crude product was purified by column chromatography (20 % EtOAc/hexanes) to afford respective biaryl product **2.29**.

(3-Methoxy-[1,1'-biphenyl]-2,6-diyl)bis(phenylmethanone) 2.29a:



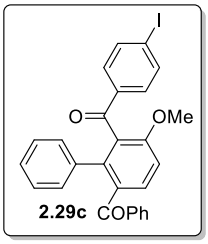
The product was obtained as a brown liquid in 72% yield (68 mg); R_f = 0.54 (in 20% EtOAc/hexanes); IR (neat): 3054, 2930, 1717, 1655, 1216, 1076, 926, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 -7.59 (m, 3H), 7.58-7.53 (m, 2H), 7.43-7.34 (m, 3H), 7.26-7.24 (m, 2H), 7.23-7.16 (m, 3H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.87-6.86 (m, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 196.1, 157.9, 140.2, 137.7, 137.2, 136.5, 133.0, 132.7, 132.4, 131.0, 129.8, 129.5, 129.4, 129.0, 128.1, 127.8, 127.4, 127.3, 109.4, 55.9; HRMS (ESI): Calcd for $C_{27}H_{21}O_3$ $[M + H]^+$ 393.1491; Found 393.1492.

(6-Benzoyl-3-methoxy-[1,1'-biphenyl]-2-yl)(2,4-dichlorophenyl)methanone 2.29b:



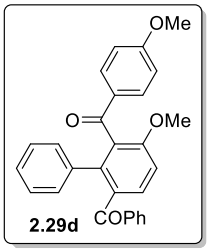
The product was obtained as a brown liquid in 47% yield (51 mg); R_f = 0.56 (20% EtOAc/hexanes); IR (neat): 3059, 2925, 1725, 1670, 1221, 1009, 916, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.5 Hz, 1H), 7.53-7.51 (m, 2H), 7.38-7.30 (m, 1H), 7.27-7.7.19 (m, 3H), 7.21 (d, *J* = 2.0 Hz, 1H) 7.08 (d, *J* = 8.5 Hz, 1H) 7.04-7.01 (m, 1H), 6.94-6.94 (m, 5H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 193.8, 158.3, 140.2, 138.0, 137.8, 136.5, 135.1, 134.0, 132.7, 132.6, 132.5, 131.7, 130.5, 130.1, 129.7, 129.6, 128.0, 127.9, 127.7, 127.6, 126.6, 109.7, 56.1; HRMS (ESI): Calcd for $C_{27}H_{19}Cl_2O_3$ $[M + H]^+$ 461.0711; Found.461.0710.

(6-Benzoyl-3-methoxy-[1,1'-biphenyl]-2-yl)(4-iodophenyl)methanone 2.29c:



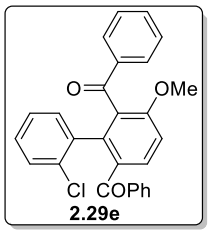
The product was obtained as a brown liquid in 68% yield (84 mg); R_f = 0.45 (20% EtOAc/hexanes); IR (neat): 3054, 2853, 1722, 1665, 1271,1126, 1081, 921, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68-7.65 (m, 3H), 7.58-7.56 (m, 2H), 7.40-7.37 (m, 1H), 7.34-7.32 (m, 2H), 7.28-7.24 (m, 2H), 7.08 (d, *J* = 8.5 Hz, 1H), 6.99-6.94 (m, 5H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 195.4, 157.9, 140.3, 137.8, 137.5, 136.6, 136.4, 133.0, 132.6, 131.3, 130.4, 129.9, 129.6, 128.9, 127.9, 127.7, 127.6, 109.5, 56.0; HRMS (ESI): Calcd for $C_{27}H_{20}IO_3$ $[M + H]^+$ 519.0457; Found 519.0456.

(6-Benzoyl-3-methoxy-[1,1'-biphenyl]-2-yl)(4-methoxyphenyl)methanone 2.29d:



The product was obtained as a brown liquid in 63% yield (62 mg); R_f = 0.51 (20% EtOAc/hexanes); IR (neat): 3059, 2837, 1722, 1660, 1257, 1123, 1019, 916, 766, 601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.5 Hz, 1H), 7.60-7.57 (m, 2H), 7.56-7.54 (m, 2H), 7.36-7.34 (m, 1H), 7.23-7.20 (m, 2H), 7.08 (d, *J* = 8.5 Hz, 1H) 7.07-7.04 (m, 2H), 7.03-6.91 (m, 3H), 6.90-6.73 (m, 2H), 3.83 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.0. 194.6, 163.5, 158.0, 140.1, 138.0, 136.8, 133.0, 132.4, 131.6, 131.0, 130.5, 130.0, 129.7, 129.6, 127.8, 127.5, 127.4, 113.4, 109.4, 56.0, 55.3; HRMS (ESI): Calcd for $C_{28}H_{23}O_4$ $[M + H]^+$ 423.1596; Found 423.1597.

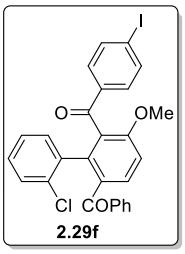
(2'-Chloro-3-methoxy-[1,1'-biphenyl]-2,6-diyl)bis(phenylmethanone) 2.29e:



2.29e

The product was obtained as a brown color liquid in 62% yield (86 mg); R_f = 0.55 (20% EtOAc/hexanes); IR (neat): 3059, 2930, 1732, 1665, 1252,1179, 1066, 916, 771, 622 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.72-7.64 (m, 5H), 7.48-7.42 (m, 2H), 7.36-7.25 (m, 5H), 7.18-7.16 (m, 1H), 7.08 (d, *J* = 8.5 Hz, 1H), 6.98-6.96 (m, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.7, 195.5, 158.6, 138.40, 137.6, 137.0, 135.2, 133.8, 132.6, 132.5, 132.4, 131.8, 130.5, 130.0, 129.1, 128.8, 128.0, 128.9, 125.7, 109.4, 56.0; HRMS (ESI): Calcd for $C_{27}H_{20}{}^{35}ClO_3$ $[M + H]^+$ 427.1101; Found 427.1102.

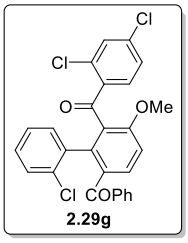
(6-Benzoyl-2'-chloro-3-methoxy-[1,1'-biphenyl]-2-yl)(4-iodophenyl)methanone 2.29f:



2.29f

The product was obtained as a brown liquid in 75% yield (84 mg); R_f = 0.54 (20% EtOAc/hexanes); IR (neat): 3054, 2920, 1722, 1665, 1262,1123, 1061, 911, 756, 627 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.71-7.64 (m, 5H), 7.49-7.45 (m, 1H), 7.38-7.23 (m, 4H), 7.16-7.15 (m, 1H), 7.07-6.98 (m, 4H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.6, 194.7, 158.5, 138.4, 137.6, 137.4, 136.3, 135.1, 132.6, 132.4, 132.0, 130.4, 130.0, 129.8, 129.1, 128.9, 128.0, 125.8, 109.3, 101.5, 56.0; HRMS (ESI): Calcd for $C_{27}H_{19}{}^{35}ClIO_3$ $[M + H]^+$ 553.0067; Found 553.0070.

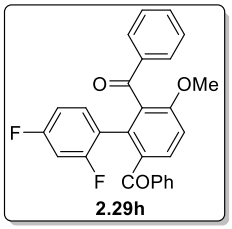
(6-Benzoyl-2'-chloro-3-methoxy-[1,1'-biphenyl]-2-yl)(2,4-dichlorophenyl)methanone 2.29g:



2.29g

The product was obtained as a brown liquid in 63% yield (62 mg); R_f = 0.55 (20% EtOAc/hexanes); IR (neat): 3054, 2925, 1722, 1660, 1262, 1123, 1061, 921, 870, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.67-7.64 (m, 3H), 7.48-7.45 (m, 1H), 7.35-7.32 (m, 2H), 7.26-7.22 (m, 2H), 7.12-7.10 (m, 1H), 7.07-6.97 (m, 5H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.6, 192.6, 159.0, 138.2, 137.8,137.7, 135.5, 135.3, 133.7, 133.0, 132.8, 132.5, 132.3, 132.2, 132.0, 130.8, 130.4, 130.0, 129.1, 128.9, 128.0, 126.6, 126.1, 109.7, 56.2; HRMS (ESI): Calcd for $C_{27}H_{18}{}^{35}Cl_3O_3$ $[M + H]^+$ 495.0322; Found 495.0320.

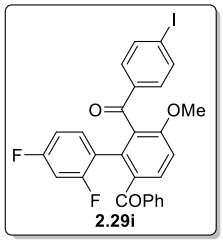
(2',4'-Difluoro-3-methoxy-[1,1'-biphenyl]-2,6-diyl)bis(phenylmethanone) 2.29h:



2.29h

The product was obtained as a brown liquid in 72% yield (63 mg); R_f = 0.52 (20% EtOAc/hexanes); IR (neat): 3054, 2961, 1722, 1660, 1257, 1092, 1004, 962, 797, 622 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.67-7.63 (m, 5H), 7.49-7.46 (m, 2H), 7.36-7.31 (m, 4H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.06-7.02 (m, 1H), 6.57 (dt, *J* = 8.0, 2.0 Hz, 1H) 6.38 (dt, *J* = 8.0, 2.0 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 195.4, 162.3 (dd, *J* = 247.8, 11.8 Hz), 159.7 (dd, *J* = 247.6, 12.3 Hz), 158.1, 137.8, 137.1, 133.8, 133.4, 132.9, 132.7, 132.6, 131.9, 130.8, 129.7, 129.1, 128.3, 128.1, 120.5, (dd, *J* = 16.2, 4.1 Hz), 110.8 (dd, *J* = 21.8, 3.5Hz), 109.9, 103.3 (t, *J* = 25.5 Hz), 56.7; HRMS (ESI): Calcd for $C_{27}H_{19}F_2O_3$ $[M + H]^+$ 429.1302; Found. 429.1295.

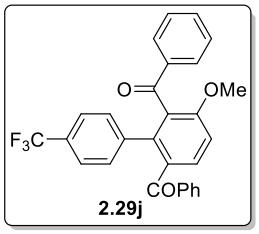
(6-Benzoyl-2',4'-difluoro-3-methoxy-[1,1'-biphenyl]-2-yl)(4-iodophenyl)methanone 2.29i:



2.29i

The product was obtained as a brown liquid in 49% yield (54 mg); R_f = 0.52 (20% EtOAc/hexanes); IR (neat): 3065, 2920, 1722, 1660, 1092, 1004, 965, 730, 616 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.71 -7.65 (m, 5H), 7.48-7.47 (m, 1H), 7.36-7.35 (m, 4H), 7.09-7.01 (m, 2H), 6.61 (s, 1H), 6.41 (m, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.1, 194.6, 162.6 (dd, *J* = 249.1, 11.9 Hz), 159.7 (dd, *J* = 247.8, 11.7 Hz), 158.4, 137.8, 137.7, 136.9, 136.3, 133.8, 132.7, 132.1, 130.3, 130.1, 129.7, 128.1, 120.4 (dd, *J* = 16.1, 3.8 Hz), 110.8 (dd, *J* = 21.3, 3.4 Hz), 109.9, 103.5 (t, *J* = 25.8 Hz), 101.7, 56.0; HRMS (ESI): Calcd for $C_{27}H_{18}F_2IO_3$ $[M + H]^+$ 555.0269; Found 555.0267.

(3-Methoxy-4'-(trifluoromethyl)-[1,1'-biphenyl]-2,6-diyl)bis(phenylmethanone) 2.29j:

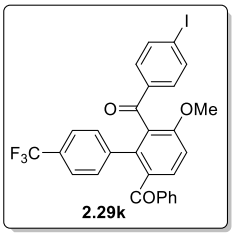


2.29j

The product was obtained as a brown liquid in 74% yield (86 mg); R_f = 0.53 (20% EtOAc/hexanes); IR (neat): 3065, 2920, 1737, 1670, 1272, 1169, 1009, 916, 715, 622 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.0 Hz, 1H), 7.61 (dd, *J* = 7.8, 1.3 Hz, 2H), 7.57 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.48-7.41 (m, 3H), 7.33-7.27 (m, 4H), 7.21-7.18 (m, 2H), 7.12 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.1, 195.7, 158.1, 140.4, 139.2, 138.0, 137.3, 133.4, 132.8, 132.6, 131.5, 130.3, 130.2, 129.8, 129.6, 129.3, 129.1, 128.4, 128.1, 124.4 (q, *J* = 3.6 Hz), 123.7

(q, J = 270.5 Hz), 121.6, 109.8, 56.1; HRMS (ESI): Calcd for $C_{28}H_{20}F_3O_3$ $[M + H]^+$ 461.1365; Found 461.1366.

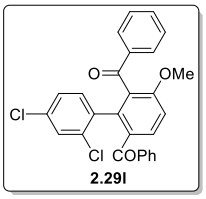
(6-Benzoyl-3-methoxy-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)(4iodophenyl)methanone 2.29k:



2.29k

The product was obtained as a brown liquid in 58% yield (61 mg); R_f = 0.54 (20% EtOAc/hexanes); IR (neat): 3065, 2920, 1732, 1670, 1272, 1164, 1009, 916, 715, 611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.71-7.59 (m, 3H), 7.58-7.47 (m, 2H), 7.47-7.45 (m, 1H), 7.44-7.32 (m, 6H), 7.31-7.12 (m, 3H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7, 195.0, 158.0, 140.3, 139.7, 137.9, 137.8, 136.6, 132.9, 132.8, 131.7, 130.4, 130.2, 129.7, 129.2, 128.1, 124.8 (q, J = 3.5 Hz), 123.8 (q, J = 270.6 Hz) 109.1, 101.9, 56.1; HRMS (ESI): Calcd for $C_{28}H_{19}F_3IO_3$ $[M + H]^+$ 587.0331; Found 587.0330.

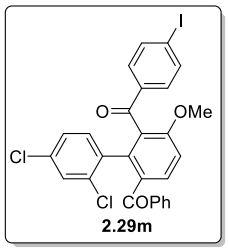
(2',4'-Dichloro-3-methoxy-[1,1'-biphenyl]-2,6-diyl)bis(phenylmethanone) 2.29l:



2.29l

The product was obtained as a brown liquid in 68% yield (54 mg); R_f = 0.54 (20% EtOAc/hexanes); IR (neat): 3059, 2915, 1722, 1665, 1241, 1055, 1009, 916, 704, 622 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.70-7.63 (m, 2H), 7.53-7.50 (m, 3H), 7.48-7.39 (m, 2H), 7.25-7.20 (m, 4H), 7.06-7.68 (m, 4H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.6, 195.3, 158.8, 137.6, 137.5, 137.0, 134.2, 134.0, 133.5, 133.2, 132.7, 132.6, 130.7, 130.1, 129.2, 128.8, 128.3, 128.2, 126.2, 126.1, 109.5, 56.9; HRMS (ESI): Calcd for $C_{27}H_{19}Cl_2O_3$ $[M + H]^+$ 461.0711; Found 461.0709.

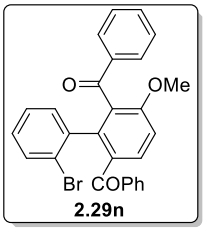
(6-Benzoyl-2',4'-dichloro-3-methoxy-[1,1'-biphenyl]-2-yl)(4-iodophenyl)methanone 2.29m:



2.29m

The product was obtained as a brown liquid in 62% yield (66 mg); R_f = 0.55 (20% EtOAc/hexanes); IR (neat): 3054, 2920, 1732, 1670, 1262, 1179, 1066, 999, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.72-7.69 (m, 4H), 7.66 (d, J = 8.8 Hz, 1H), 7.53 (tt, J = 8.7, 2.0 Hz, 1H), 7.41-7.37 (m, 4H), 7.12-7.02 (m, 4H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.4, 194.5, 158.6, 137.6, 137.5, 137.4, 136.2, 134.3, 133.8, 133.4, 133.2, 132.8, 132.7, 131.9, 130.5, 130.1, 130.0, 128.9, 128.1, 126.3, 109.5, 101.9, 56.0; HRMS (ESI): Calcd for $C_{27}H_{18}{}^{35}Cl_2IO_3$ $[M + H]^+$ 586.9678; Found 586.9679.

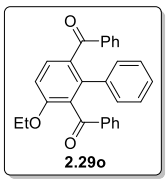
(2'-Bromo-3-methoxy-[1,1'-biphenyl]-2,6-diyl)bis(phenylmethanone) 2.29n:



2.29n

The product was obtained as a brown liquid in 63% yield (74 mg); R_f = 0.52 (20% EtOAc/hexanes); IR (neat): 3054, 2925, 1727, 1665, 1252, 1164, 1055, 911, 709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.1 Hz, 2H), 7.67 (d, *J* = 7.6 Hz, 3H), 7.50-7.44 (m, 2H), 7.38-7.30 (m, 4H), 7.19 (d, *J* = 7.1 Hz, 2H), 7.07-7.04 (m, 2H), 6.90-6.87 (m, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 195.5, 158.6, 140.1, 137.7, 137.1, 133.2, 132.7, 132.6, 132.3, 132.0, 131.6, 130.5, 130.2, 129.2, 129.0, 128.1, 127.9, 126.4, 123.1, 109.2, 56.0; HRMS (ESI): Calcd for $C_{27}H_{20}{}^{79}BrO_3$ $[M + H]^+$ 471.0596; Found 471.0595.

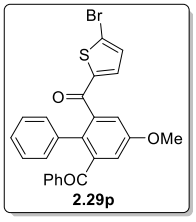
(3-Ethoxy-[1,1'-biphenyl]-2,6-diyl)bis(phenylmethanone) 2.29o:



2.29o

The product was obtained as a brown liquid in 73% yield (68 mg); R_f = 0.58 (20% EtOAc/hexanes); IR (neat): 3411, 3054, 2925, 1722, 1670, 1247, 1045, 946, 808, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.62-7.55 (m, 5H), 7.43-7.37 (m, 1H), 7.35-7.27 (m, 1H), 7.26-7.20 (m, 5H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.99-6.89 (m, 3H), 3.77 (q, *J* = 8.0 Hz, 2H), 1.23 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 196.1, 157.9, 140.2, 137.7, 137.2, 136.5, 133.0, 132.7, 132.4, 131.0, 129.8, 129.5, 129.4, 129.0, 128.1, 127.8, 127.4, 127.3, 110.3, 64.4, 14.3; HRMS (ESI): Calcd for $C_{28}H_{23}O_3$ $[M + H]^+$ 407.1647; Found 407.1648.

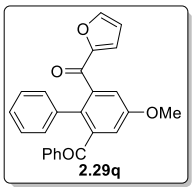
(6-Benzoyl-4-methoxy-[1,1'-biphenyl]-2-yl)(5-bromothiophen-2-yl)methanone 2.29p:



2.29p

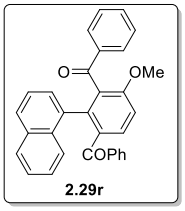
Brown liquid, yield 68% (77 mg); R_f : 0.54 (20% EtOAc/hexanes); IR (neat): 3056, 2839, 1650, 1567, 1406, 1264, 1016, 987, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.6 Hz, 1H), 7.54 (dd, *J* = 9.2, 1.5 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.23 (t, *J* = 8.2 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 3H), 7.00-6.99 (m, 3H), 6.96 (d, *J* = 4.6 Hz, 1H), 6.90 (d, *J* = 4.2 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 186.7, 157.9, 146.0, 140.2, 137.7, 136.4, 134.4, 132.8, 132.5, 131.5, 131.0, 130.0, 129.9, 128.4, 128.3, 127.8, 127.7, 127.6, 123.4, 109.5, 50.8; HRMS (ESI): calcd. for $C_{25}H_{18}{}^{35}BrO_3S$ $(M + H)^+$ 477.0160; Found 477.0163.

(6-Benzoyl-4-methoxy-[1,1'-biphenyl]-2-yl)(furan-2-yl)methanone 2.29q:



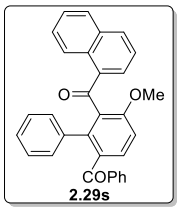
Brown liquid, yield 59% (54 mg); R_f : 0.56 (20% EtOAc/hexanes); IR (neat): 3005, 2915, 1709, 1687, 1564, 1389, 1273, 1017, 942, 823 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.6 Hz, 1H), 7.52 (dd, *J* = 9.2, 1.9 Hz, 2H), 7.41 (d, *J* = 1.2 Hz, 1H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 2H), 7.06 (d, *J* = 8.6 Hz, 3H), 6.95-6.94 (m, 3H), 6.76 (d, *J* = 3.6 Hz, 1H), 6.32 (dd, *J* = 5.2 1.4 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 183.0, 158.1, 153.0, 146.9, 140.5, 137.8, 136.5, 132.7, 132.4, 131.4, 129.8, 129.5, 128.3, 127.8, 127.6, 127.5, 119.7, 112.4, 109.5, 56.0; HRMS (ESI): calcd. for $C_{25}H_{19}O_4$ $(M + H)^+$ 383.1283; Found 383.1288.

(4-Methoxy-2-(naphthalen-1-yl)-1,3-phenylene)bis(phenylmethanone) 2.29r:



Yellow liquid, yield 66% (89 mg); R_f : 0.46 (20% EtOAc/hexanes); IR (neat): 3243, 2925, 1665, 1594, 1385, 1254, 1053, 981, 797 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.6 Hz, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.50-7.46 (m, 3H), 7.38 (d, *J* = 8.6 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 2H), 7.25-7.20 (m, 5H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 2H), 7.06 (t, *J* = 8.0 Hz, 2H), 6.99 (t, *J* = 8.1 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.1, 195.6, 158.4, 138.8, 137.8, 137.1, 133.7, 133.6, 132.8, 132.7, 131.9, 131.7, 131.6, 130.7, 129.0, 128.8, 128.1, 127.8, 127.6, 127.4, 126.3, 125.6, 125.4, 124.0, 109.7, 56.0; HRMS (ESI): calcd. for $C_{31}H_{23}O_3$ $(M + H)^+$: 443.1647; Found 443.1651.

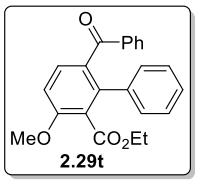
(6-(1-Naphthoyl)-5-methoxy-[1,1'-biphenyl]-2-yl)(phenyl)methanone 2.29s:



Yellow liquid, yield 60% (64 mg); R_f : 0.49 (20% EtOAc/hexanes); IR (neat): 3062, 2928, 1713, 1663, 1464, 1361, 1106, 914, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.85 (d, *J* = 8.3 Hz, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.54 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.49 (tt, *J* = 8.3, 1.2 Hz, 1H), 7.41 (tt, *J* = 8.3, 1.2 Hz, 2H), 7.32 (tt, *J* = 7.4, 1.2 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 7.08 (d, *J* = 8.3 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.75 (t, *J* = 7.5 Hz, 2H), 6.68 (tt, *J* = 7.3, 1.3 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.7, 197.5, 158.0, 140.3, 137.9, 136.8, 134.2, 133.7, 133.5, 132.9, 132.4, 132.0, 131.3, 130.9, 130.4, 129.8, 129.5, 127.9, 127.8, 127.3, 127.0,

126.1, 126.0, 123.9, 109.6, 56.0; HRMS (ESI): calcd. for $C_{31}H_{23}O_3$ $(M + H)^+$ 443.1647; Found 443.1649.

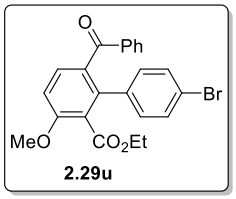
Ethyl 6-benzoyl-3-methoxy-[1,1'-biphenyl]-2-carboxylate 2.29t:



2.29t

The product was obtained as a pale brown liquid in 78% yield (68 mg); R_f = 0.60 (20% EtOAc/hexanes); IR (neat): 3431, 3059, 2977, 1732, 1587, 1272, 1014, 973, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.56-7.54 (m, 3H), 7.40-7.36 (m, 1H), 7.26-7.22 (m, 2H), 7.17-7.11 (m, 5H), 7.02 (d, *J* = 8.0 Hz, 1H), 4.03 (q, *J* = 8.0 Hz, 2H), 3.94 (s, 3H), 0.89 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.2, 166.8, 157.5, 140.4, 137.9, 137.3, 132.5, 132.4, 131.2, 129.6, 129.2, 127.9, 127.7, 127.6, 124.9, 109.4, 61.1, 56.1, 13.5; HRMS (ESI): Calcd for $C_{23}H_{21}O_4$ $[M + H]^+$ 361.1440; Found 361.1441.

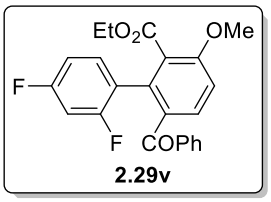
Ethyl 6-benzoyl-4'-bromo-3-methoxy-[1,1'-biphenyl]-2-carboxylate 2.29u:



2.29u

The product was obtained as a yellow liquid in 61% yield (46 mg); R_f = 0.62 (20% EtOAc/hexanes); IR (neat): 3059, 2977, 1732, 1577, 1272, 1097, 978, 828, 709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.58-7.53 (m, 3H), 7.47-7.43 (m, 1H), 7.31-7.27 (m, 4H), 7.06-7.01 (m, 3H), 4.05 (q, *J* = 7.0 Hz, 2H), 3.95 (s, 3H), 0.97 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.8, 166.6, 157.6, 139.2, 137.8, 136.2, 132.8, 132.1, 131.5, 131.0, 130.9, 129.7, 128.1, 125.0. 122.0, 109.6, 61.3, 56.2, 13.7; HRMS (ESI): Calcd for $C_{23}H_{20}BrO_4$ $[M + H]^+$ 439.0545; Found 439.0549.

Ethyl 6-benzoyl-2',4'-difluoro-3-methoxy-[1,1'-biphenyl]-2-carboxylate 2.29v:

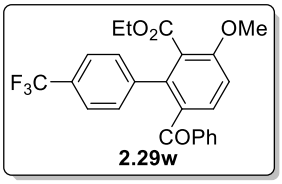


2.29v

The product was obtained as a pale yellow liquid in 67% yield (53 mg); R_f = 0.63 (20% EtOAc/hexanes); IR (neat): 3059, 2977, 1727, 1598, 1267, 1019, 968, 849, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.64-7.62 (m, 2H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.51-7.47 (m, 1H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.23-7.17 (m, 1H), 7.03 (d, *J* = 8.7 Hz, 1H), 6.77 (dt, *J* = 9.0, 2.0 Hz, 1H), 6.64 (dt, *J* = 9.0, 2.0 Hz, 1H), 4.07 (q, *J* = 7.2 Hz, 2H), 3.95 (s, 3H), 0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.0, 166.2, 162.2 (dd, *J* = 249.1, 12.3 Hz), 159.4 (dd, *J* = 253.2, 12.6 Hz), 158.0, 137.7, 133.8, 132.7, 132.2, 132.1, 129.7, 128.9, 128.6, 128.1, 126.0, 121.2 (dd, *J* = 17.0, 4.3 Hz),

110.7 (dd, *J* = 21.4, 3.2 Hz), 110.9, 103.7 (t, *J* = 25.9 Hz), 61.3, 56.1, 13.7; HRMS (ESI): Calcd for $C_{23}H_{19}F_2O_4$ [M + H] $^+$ 397.1251; Found 397.1256.

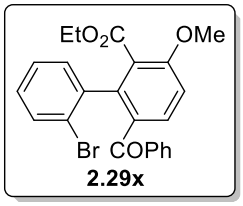
Ethyl 6-benzoyl-3-methoxy-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylate 2.29w:



2.29w

The product was obtained as a yellow color liquid in 53% yield (41 mg); R_f = 0.63 (20% EtOAc/hexanes); IR (neat): 3059, 2977, 1727, 1598, 1267, 1019, 968, 849, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.55 (m, 3H), 7.44-7.41 (m, 3H), 7.31-7.29 (m, 4H), 7.05 (d, *J* = 8.7 Hz, 1H), 4.03 (q, *J* = 7.2 Hz, 2H), 3.96 (s, 3H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.6, 166.4, 157.7, 141.1, 139.2, 137.9, 132.9, 132.0, 131.7, 129.9, 129.7, 128.6, 128.2, 128.0, 125.1, 125.0, 124.6 (q, *J* = 3.6 Hz), 123.9 (q, *J* = 270.6 Hz) 109.9, 61.4, 58.2, 13.5; HRMS (ESI): Calcd for $C_{24}H_{20}F_3O_4$ [M + H] $^+$ 429.1314; Found 429.1316.

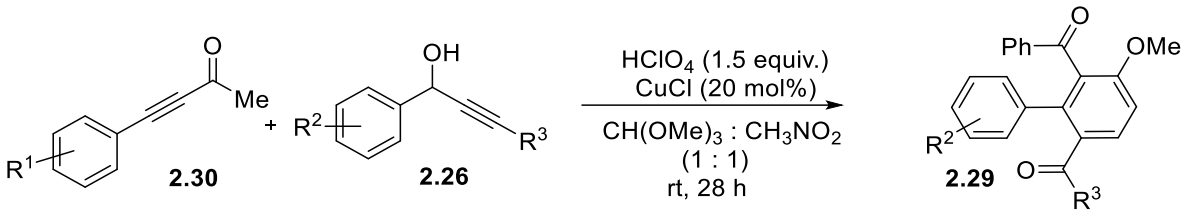
Ethyl 6-benzoyl-2'-bromo-3-methoxy-[1,1'-biphenyl]-2-carboxylate 2.29x:



2.29x

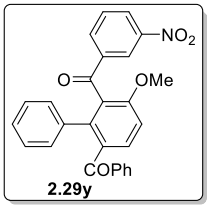
The product was obtained as a pale yellow liquid in 68% yield (51 mg); R_f = 0.62 (20% EtOAc/hexanes); IR (neat): 3416, 2917, 1727, 1577, 1272, 1009, 978, 828, 715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70-7.68 (m, 2H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.51-7.47 (m, 1H), 7.46-7.43 (m, 1H), 7.38-7.34 (m, 2H), 7.31-7.28 (m, 1H), 7.24-7.22 (m, 1H), 7.10 (dt, *J* = 8.2, 2.4 Hz, 1H), 7.01 (d, *J* = 8.6 Hz, 1H), 4.01 (q, *J* = 7.2 Hz, 2H), 3.95 (s, 3H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.4, 166.1, 158.1, 140.4, 138.1, 137.7, 133.0, 132.7, 132.6, 132.3, 132.1, 132.0, 131.7, 131.5, 131.0, 130.2, 130.1, 129.3, 129.0, 128.1, 127.8, 125.4, 123.3, 109.4, 109.1, 61.2, 56.2, 13.6; HRMS (ESI): Calcd for $C_{23}H_{20}{}^{79}BrO_4$ [M + H] $^+$ 439.0545; Found 439.0551.

2.5.5 Representative procedure for the synthesis of biaryls from alkynones and propargylic alcohols and analytical data of compounds 2.29y-2.29ad



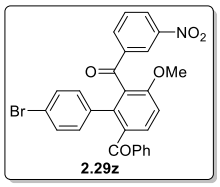
A reaction flask (10 mL) was charged with alkynone **2.30** (1.5 equiv.), TMOF (2 equiv.), $HClO_4$ (1.5 equiv.) in nitromethane solvent (1 mL/0.25 mmol of **2.26**). The reaction mixture was stirred at ambient temperature. The alkynone got converted into its corresponding 1,3- diketone derivative in 4 h. Then, propargylic alcohol derivative **2.26** (1 equiv.) was added to the reaction mixture. After then 15 minutes TMOF (1 mL/0.25 mmol of **2.26**) and CuCl (20 mol %) were added. The reaction mixture was stirred at rt for 24 h. Solvents were evaporated using a rotary evaporator. The resulting residue was diluted with ethyl acetate and washed with water. The aqueous layer extracted twice with ethyl acetate and the collective organic phase was dried over anhydrous sodium sulphate. After evaporation of the solvents, the crude product was purified by column chromatography (20% EtOAc/hexanes) to afford biaryl product **2.29**.

(6-Benzoyl-3-methoxy-[1,1'-biphenyl]-2-yl)(3-nitrophenyl)methanone 2.29y:



The product was obtained as a brown liquid in 58% yield (60 mg); R_f = 0.56 (20% EtOAc/hexanes); IR (neat): 3085, 2943, 1680, 1665, 1283,1123, 1086, 704, 658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.38 (t, *J* = 1.7 Hz, 1H), 8.25 (qt, *J* = 8.0, Hz, 1.7 Hz, 1H), 7.89 (td, *J* = 7.7, 1.7 Hz, 1H), 7.70 (d, *J* = 8.7 Hz, 1H), 7.58-7.56 (m, 2H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.38 (tt, *J* = 1.7, 3.0 Hz, 1H), 7.27-7.23 (m, 2H), 7.14 (d, *J* = 8.7 Hz, 1H), 6.99-6.97 (m, 2H), 6.93-6.90 (m, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.2, 194.0, 158.0, 148.1, 140.5, 138.5, 137.7, 136.3, 134.4, 133.0, 132.6, 132.0, 129.8, 129.6, 129.4, 128.0, 127.9, 127.8, 127.2, 123.8, 109.5, 56.1; HRMS (ESI): Calcd for $C_{27}H_{20}NO_5$ $[M + H]^+$ 438.1341; Found 438.1340.

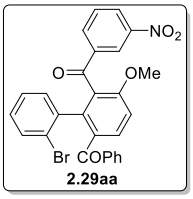
(6-Benzoyl-4'-bromo-3-methoxy-[1,1'-biphenyl]-2-yl)(3-nitrophenyl)methanone 2.29z:



2.29z

The product was obtained as a brown liquid in 57% yield (49 mg); R_f = 0.55 (20 EtOAc/hexanes); IR (neat): 3085, 2961, 1686, 1660, 1273,1173, 1081, 880, 715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.40 (t, *J* = 1.7 Hz, 1H), 8.32-8.30 (m, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.61-7.59 (m, 2H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.49-7.44 (m, 2H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.13 (d, *J* =8.8 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 3.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.8, 193.7, 158.0, 148.3, 139.5, 138.4, 137.7, 135.3, 134.3, 133.6, 133.0, 132.9, 132.1, 131.8, 131.3, 131.0, 130.5, 129.8, 129.6, 128.5, 128.2, 128.1, 128.0, 127.8, 127.5, 123.9, 122.3, 109.9, 56.1; HRMS (ESI): Calcd for $C_{27}H_{19}BrNO_5$ $[M + H]^+$ 516.0447; Found 516.0447.

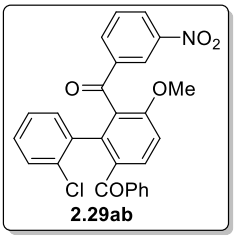
(6-Benzoyl-2'-bromo-3-methoxy-[1,1'-biphenyl]-2-yl)(3-nitrophenyl)methanone 2.29aa:



2.29aa

The product was obtained as brown liquid in 55% yield (47 mg); R_f = 0.54 (20% EtOAc/hexanes); IR (neat): 3085, 2941, 1686, 1660, 1272,1174, 1081, 859, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.46 (t, *J* = 1.7 Hz, 1H), 8.30 (qt, *J* = 8.0, 1.7 Hz, 1H), 7.98-7.96 (m, 1H), 7.73 (t, *J* = 8.0, Hz, 3H), 7.52-7.48 (m, 2H), 7.38 (t, *J* = 8.0, Hz, 2H), 7.21 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.15 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.12-7.09 (m, 2H), 6.92 (dt, *J* = 7.6, 1.7 Hz, 1H), 387 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 193.4, 158.6, 148.0, 140.4, 138.4, 137.5, 136.8, 134.4, 133.4, 132.8, 132.6, 132.2, 132.0, 130.2, 130.1, 129.4, 129.3, 129.1, 128.4, 128.0, 127.3, 126.5, 124.0, 123.0, 109.6, 56.1; HRMS (ESI): Calcd for $C_{27}H_{19}{}^{79}BrNO_5$ $[M + H]^+$ 516.0447; Found 516.0451.

(6-Benzoyl-2'-chloro-3-methoxy-[1,1'-biphenyl]-2-yl)(3-nitrophenyl)methanone 2.29ab:

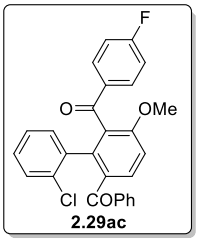


2.29ab

The product was obtained brown liquid in 58% yield (66 mg); R_f = 0.55 (20% EtOAc/hexanes); IR (neat): 3080, 2925, 1727, 1660, 1267, 1174, 1086, 864, 715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.44 (s, 1H), 8.30 (d, *J* = 9.6 Hz, 1H), 7.96 (d, *J* = 8.5 Hz, 1H), 7.72-7.71 (m, 3H), 7.52-7.48 (m, 2H), 7.37 (t, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 9.6 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 7.00-6.94 (m, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.4, 193.3, 158.6, 148.1, 138.8, 138.5, 137.5, 135.0, 134.4, 133.2, 132.6, 132.2, 130.0, 129.3, 129.1, 129.0,

128.5, 128.0, 127.4, 126.0, 123.9, 109.7, 56.1; HRMS (ESI): Calcd for $C_{27}H_{19}{}^{35}ClNO_5$ $[M + H]^+$ 472.0952; Found 472.0952.

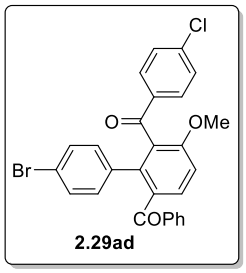
(6-Benzoyl-2'-chloro-3-methoxy-[1,1'-biphenyl]-2-yl)(4-fluorophenyl)methanone 2.29ac:



2.29ac

The product was obtained as a yellow liquid in 57% yield (50 mg); R_f = 0.54 (20% EtOAc/hexanes); IR (neat): 3049, 2920, 1722, 1665, 1262, 1148, 1061, 914, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.72-7.66 (m, 5H), 7.50-7.46 (m, 1H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.17 (d, *J* = 6.5 Hz, 1H), 7.07 (4, *J* = 7.5 Hz, 1H), 7.06-6.95 (m, 5H), 385 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.7, 193.5, 167.5 (d, *J* = 253.8 Hz), 158.5, 138.4, 137.6, 135.1, 133.6, 132.6, 132.5, 132.4, 132.0, 131.9, 131.7, 130.2, 130.0, 129.1, 129.0, 128.0, 125.9, 115.3 (d, *J* = 21.8 Hz), 109.3, 56.4; HRMS (ESI): Calcd for $C_{27}H_{19}{}^{35}ClFO_3$ $[M + H]^+$ 445.1007; Found 445.1006.

(6-Benzoyl-4'-bromo-3-methoxy-[1,1'-biphenyl]-2-yl)(4-chlorophenyl)methanone 2.29ad:



2.29ad

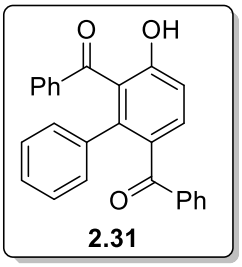
The product was obtained as a yellow liquid in 59% yield (52 mg); R_f = 0.52 (20% EtOAc/hexanes); IR (neat): 3059, 2925, 1722, 1665, 1278, 1174, 1092, 916, 839, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.5 Hz, 1H), 7.58- 7.54 (m, 4H), 7.45-7.42 (m, 1H), 7.30-7.27 (m, 4H), 7.09 (m, 3H), 6.67 (m, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.2, 194.6, 158.0, 140.0, 139.2, 137.7, 135.6, 135.4, 132.9, 132.8, 131.5, 131.4, 130.9, 130.5, 129.7, 129.1, 128.8, 128.1, 122.1, 109.7, 56.1; HRMS (ESI): Calcd for $C_{27}H_{19}{}^{79}BrClO_3$ $[M + H]^+$ 505.0206; Found 505.0209.

2.5.6 Preparation and analytical data of compound 2.31

BBr_3 (1.0 M solution in CH_2Cl_2, 20 μL, 0.28 mmol) was charged to a stirring $CHCl_3$ (1 mL) solution of compound **2.27a** (57 mg, 0.14 mmol) in a 5 mL round bottom flask at ambient temperature. After 4 h, water was added to the reaction mixture and was extracted with chloroform. The organic phase was separated then washed with aqueous NH_4Cl solution and dried over anhydrous Na_2SO_4. Solvents were evaporated under reduced pressure and the resultant residue was

purified by column chromatography with 30% EtOAc/hexanes to afford product **2.31** as a yellow liquid (50 mg, 92%).

(3-hydroxy-[1,1'-biphenyl]-2,6-diyl)bis(phenylmethanone) 2.31:



2.31

R_f = 0.39 (30% EtOAc/hexanes); IR (neat): 3049, 2920, 1722, 1665, 1262, 1148, 1061, 914, 715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.50-8.02 (m, 2H), 7.63-7.59 (m, 1H), 7.58-7.54 (m, 5H), 7.50-7.47 (m, 3H) 7.33 (d, *J* = 9.6 Hz, 1H), 7.23-7.21 (m, 1H), 7.12-7.08 (m, 1H), 6.99-6.97 (m, 2H), 6.19 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.4, 186.3, 154.2, 146.7, 143.3, 136.2, 135.9, 134.4, 134.2, 133.9, 131.7, 130.4, 130.1, 129.8, 129.5, 129.1, 128.9, 128.8, 127.1, 125.3, 124.4; HRMS (ESI): Calcd for $C_{26}H_{18}O_3Na$ $[M + Na]^+$ 401.1154; Found 401.1151.

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Chapter 2

2.7 Representative spectra

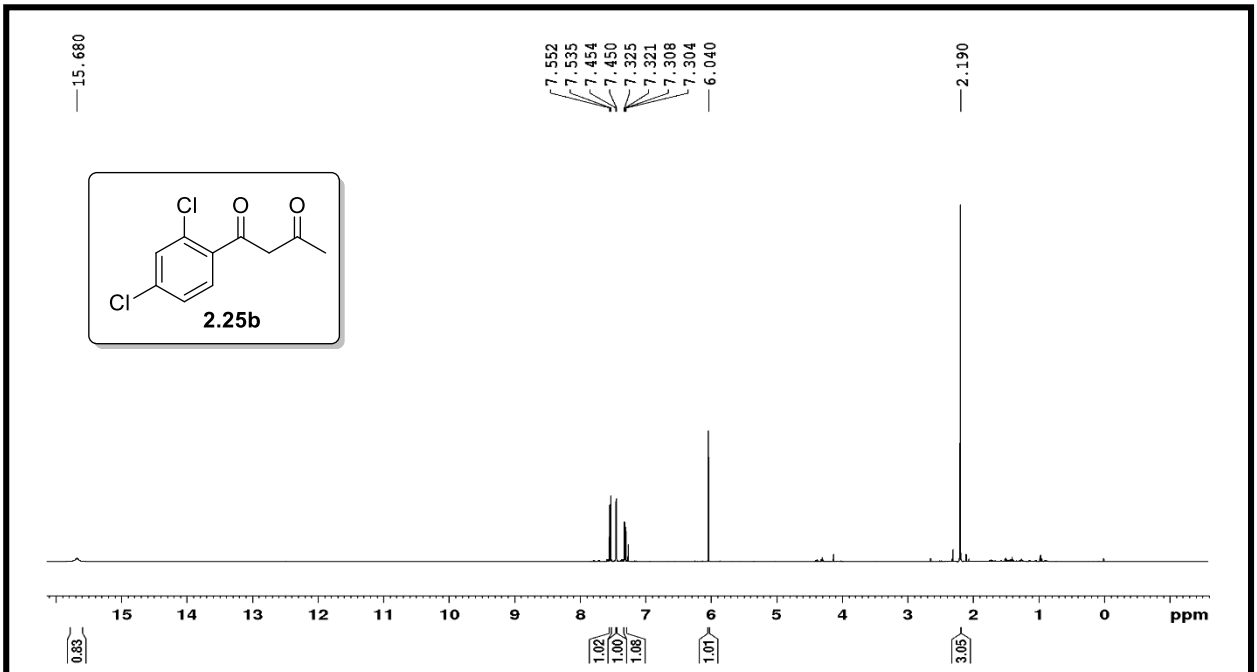


Figure 2.1: ^{1}H NMR spectra of Compound **2.25b**

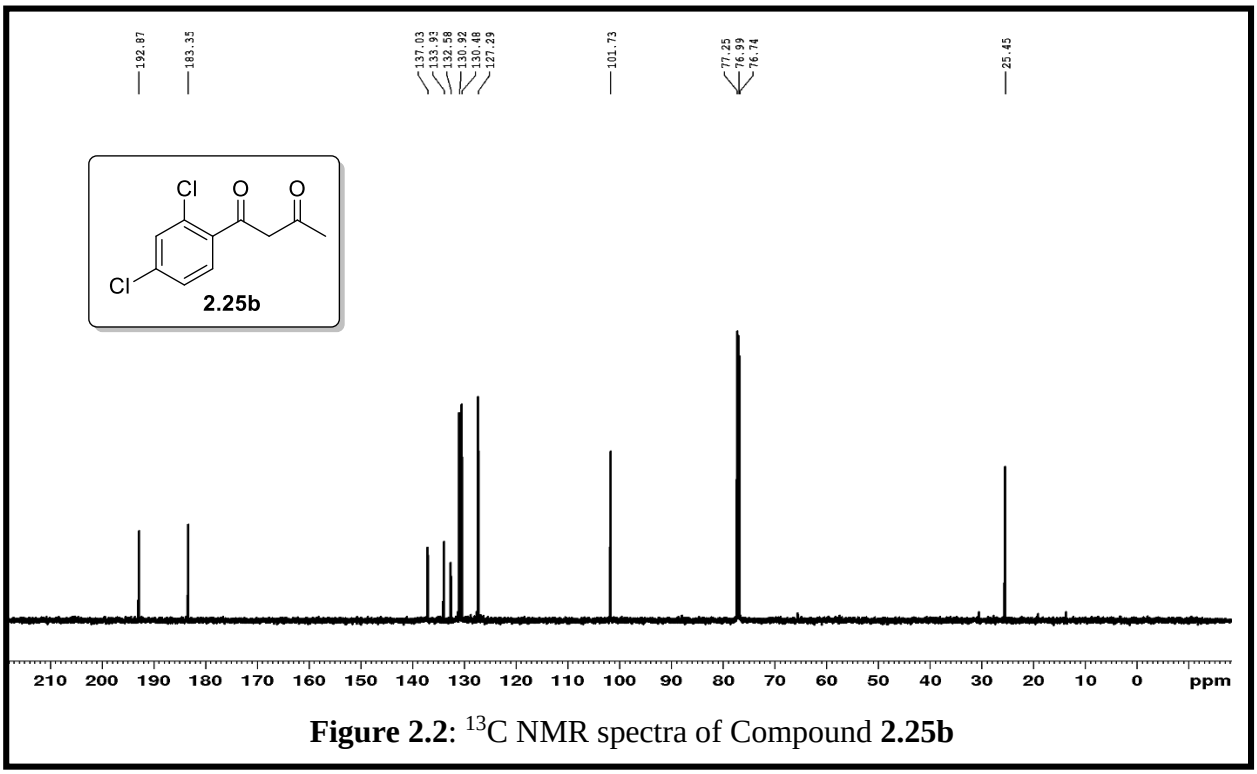


Figure 2.2: ^{13}C NMR spectra of Compound **2.25b**

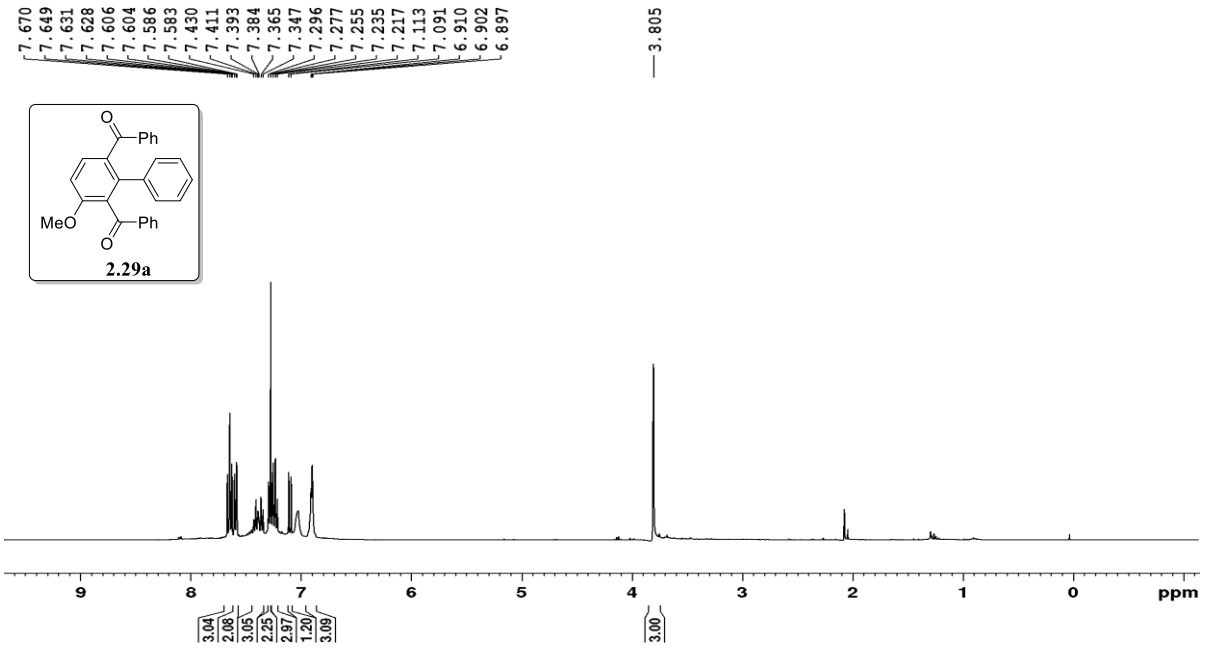


Figure 2.3: ^{1}H NMR spectra of Compound **2.29a**

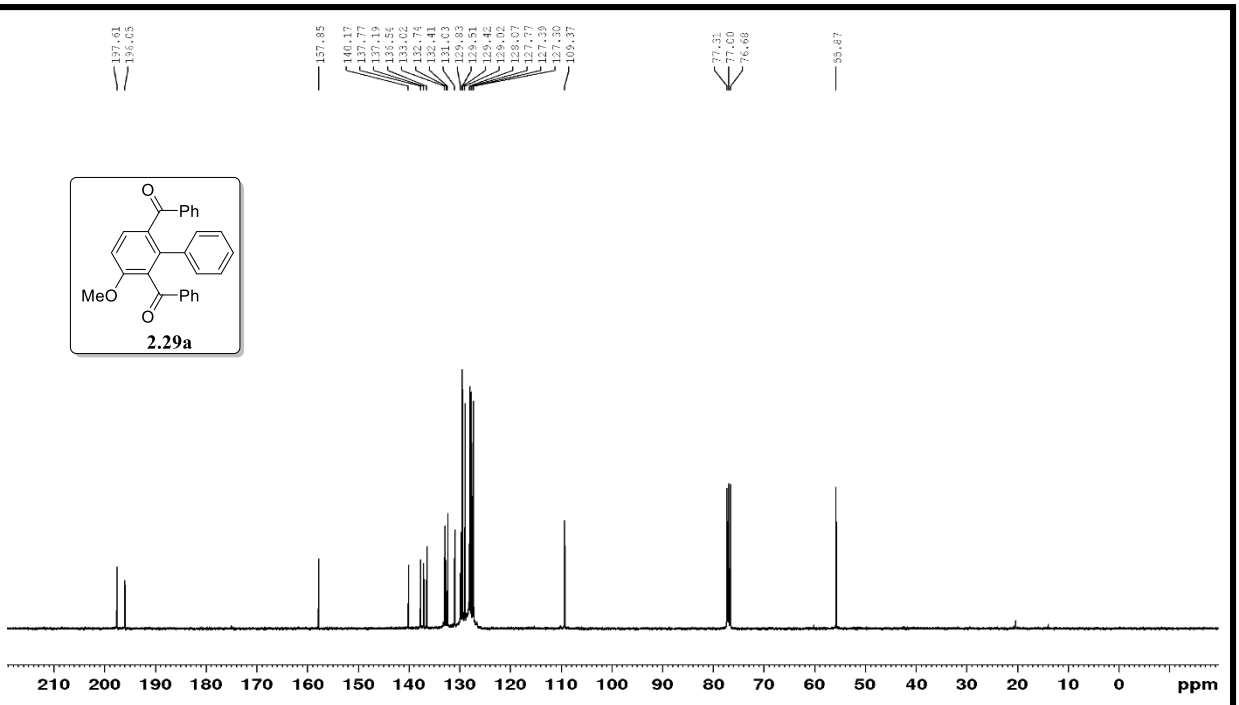


Figure 2.4: ^{13}C NMR spectra of Compound **2.29a**

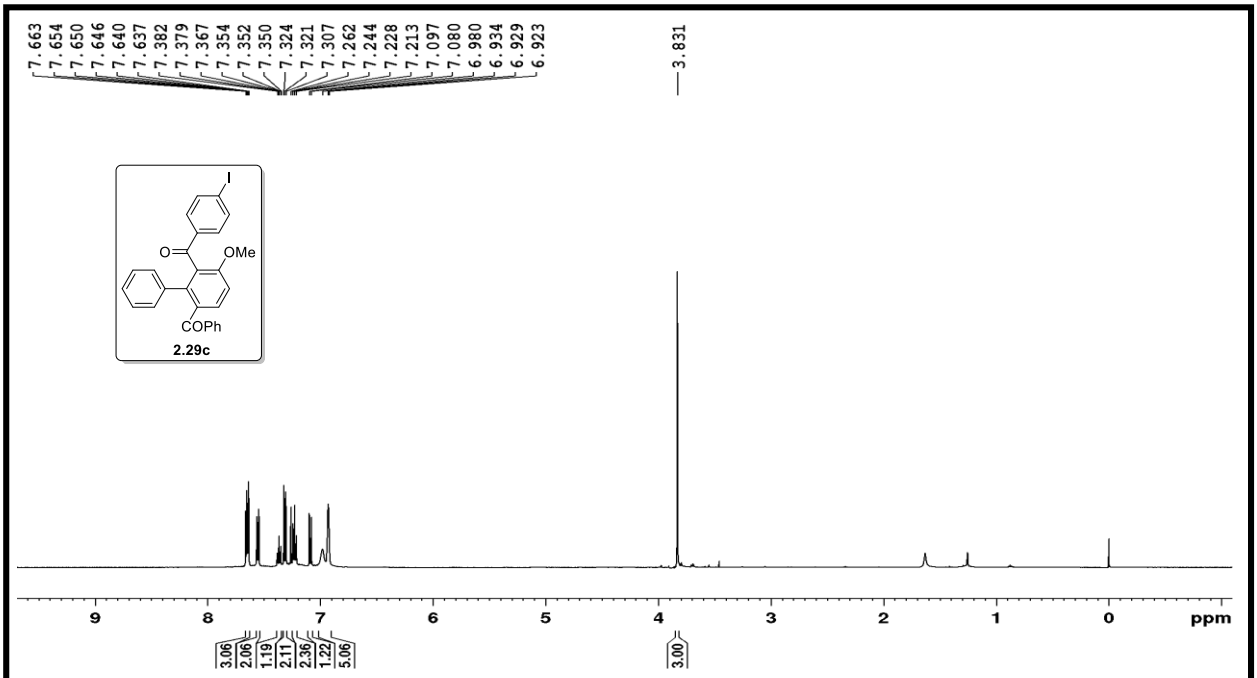


Figure 2.5: ^{1}H NMR spectra of Compound **2.29c**

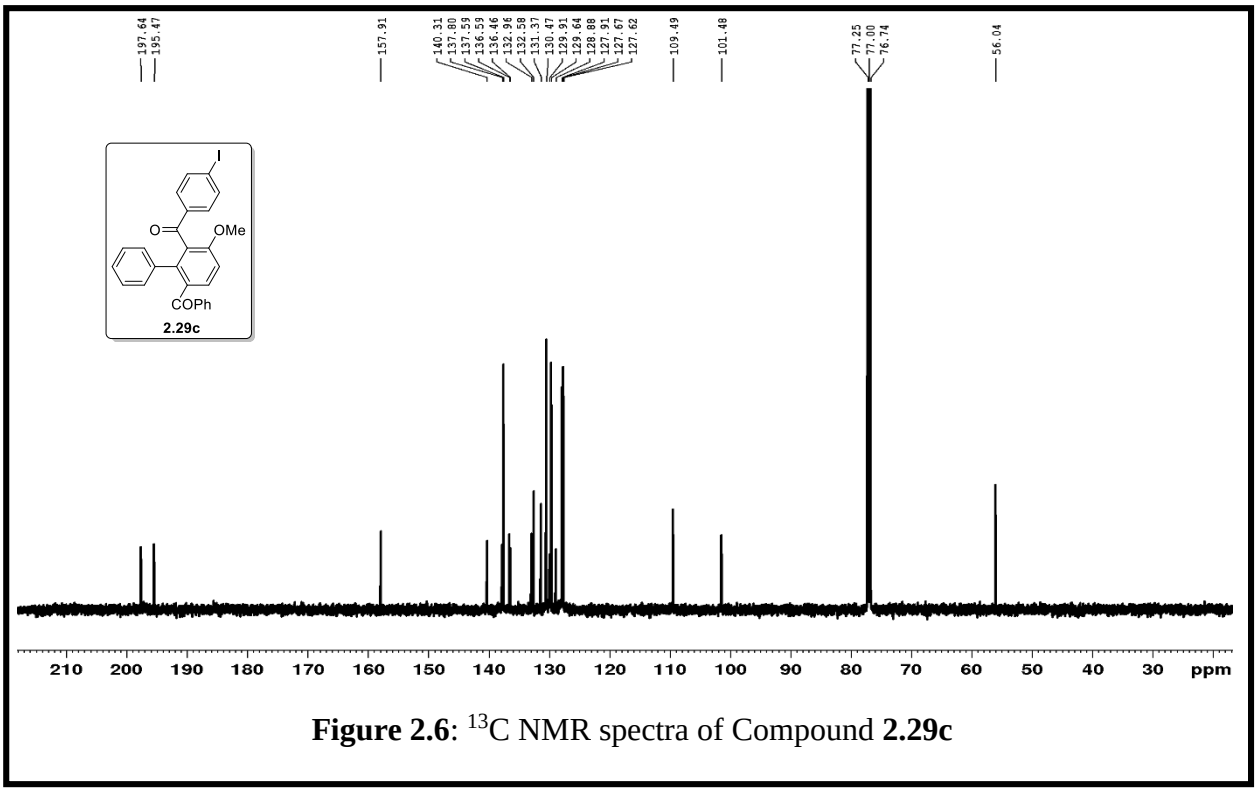


Figure 2.6: ^{13}C NMR spectra of Compound **2.29c**

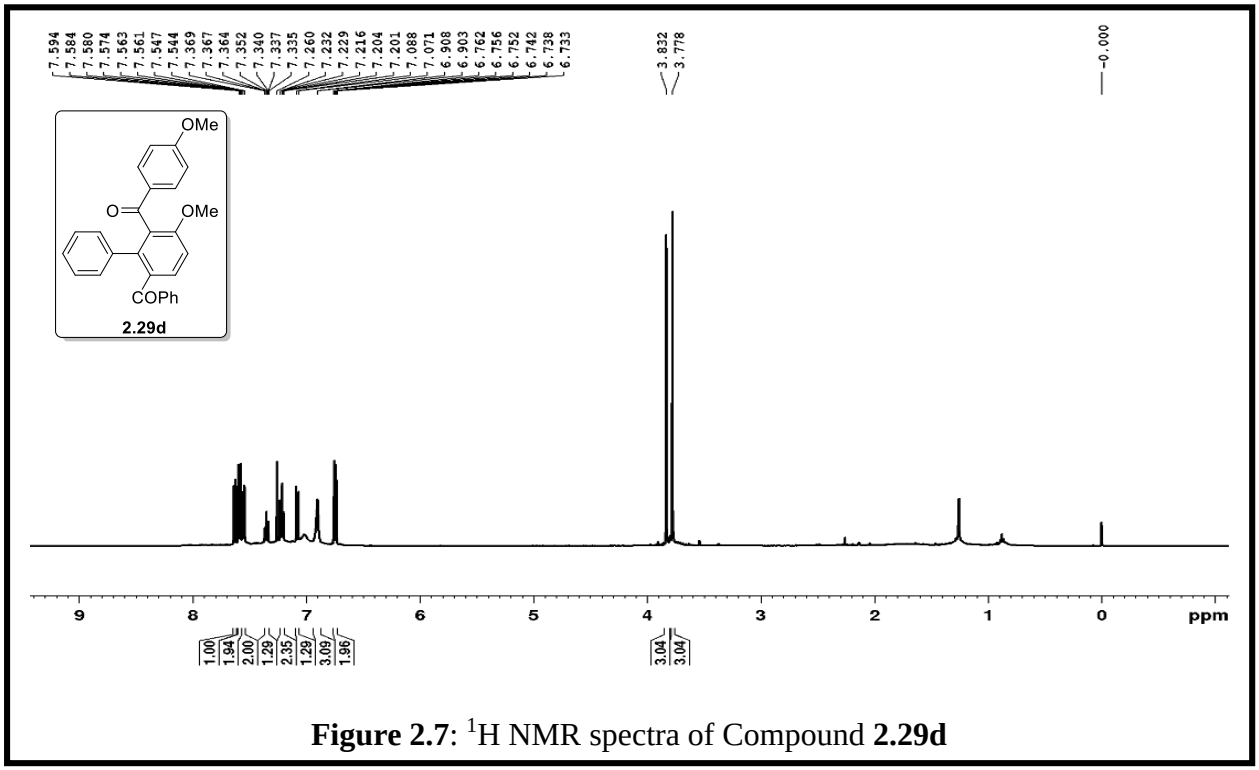


Figure 2.7: ^{1}H NMR spectra of Compound **2.29d**

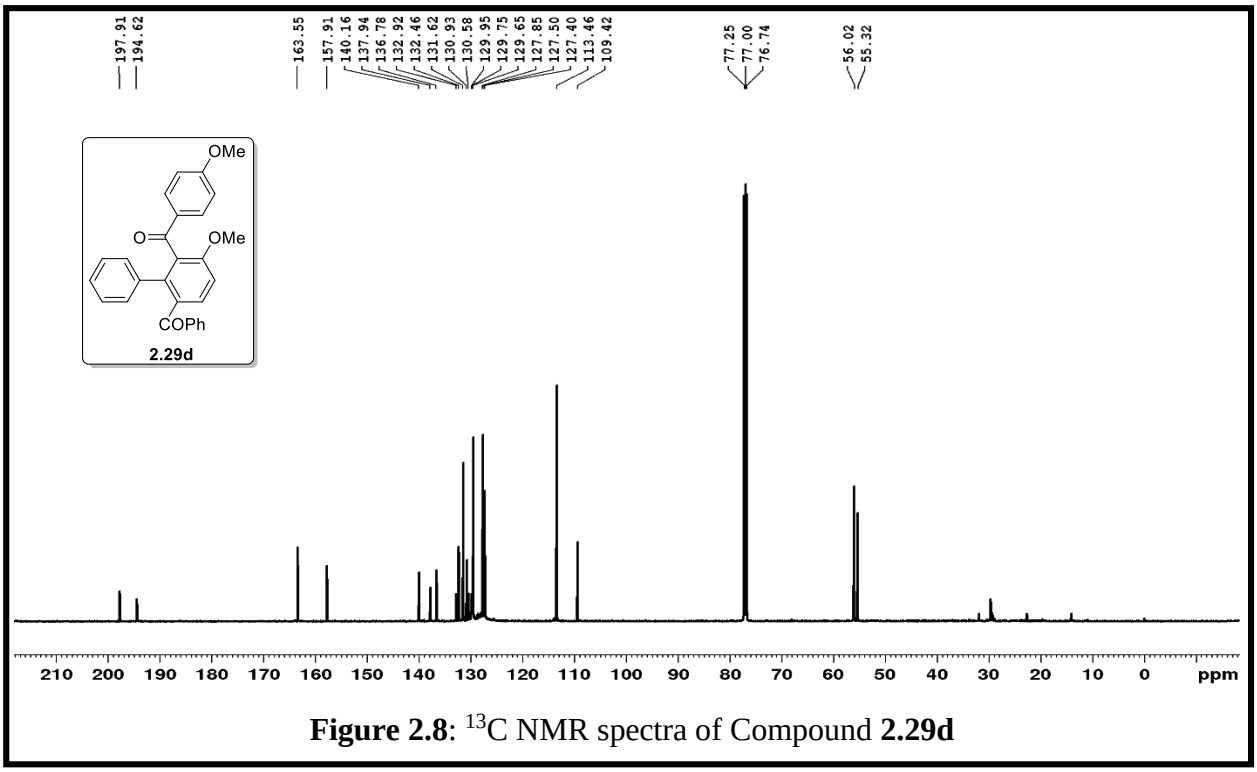


Figure 2.8: ^{13}C NMR spectra of Compound **2.29d**

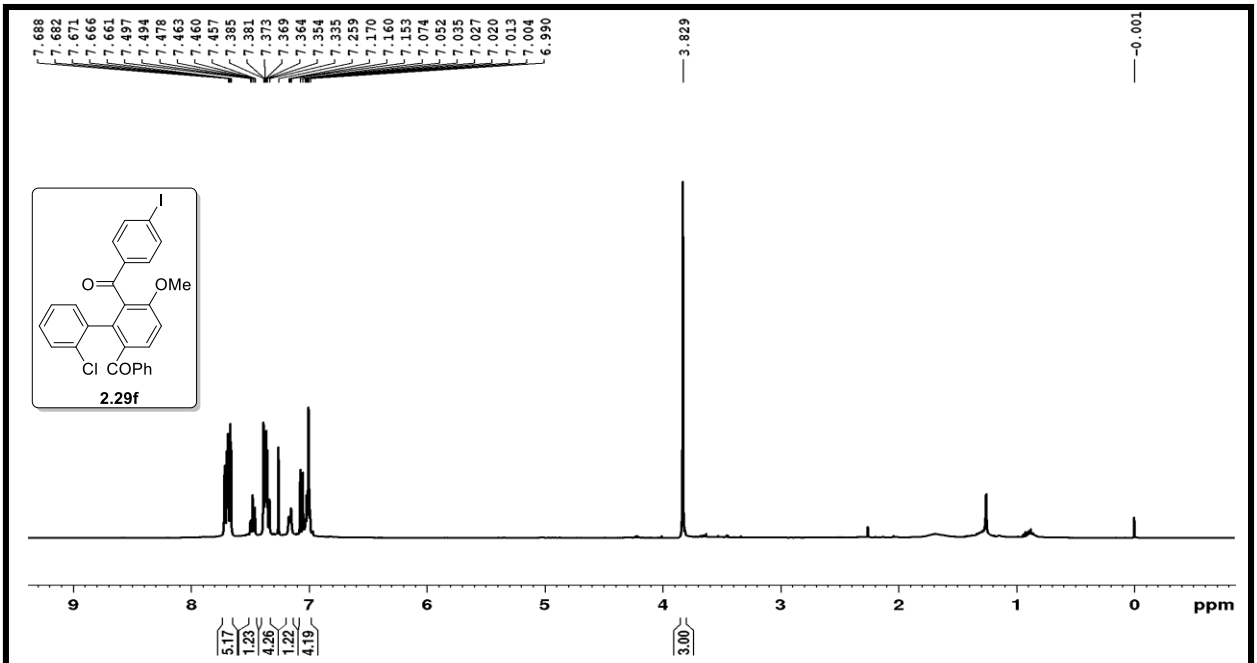


Figure 2.9: ^{1}H NMR spectra of Compound **2.29f**

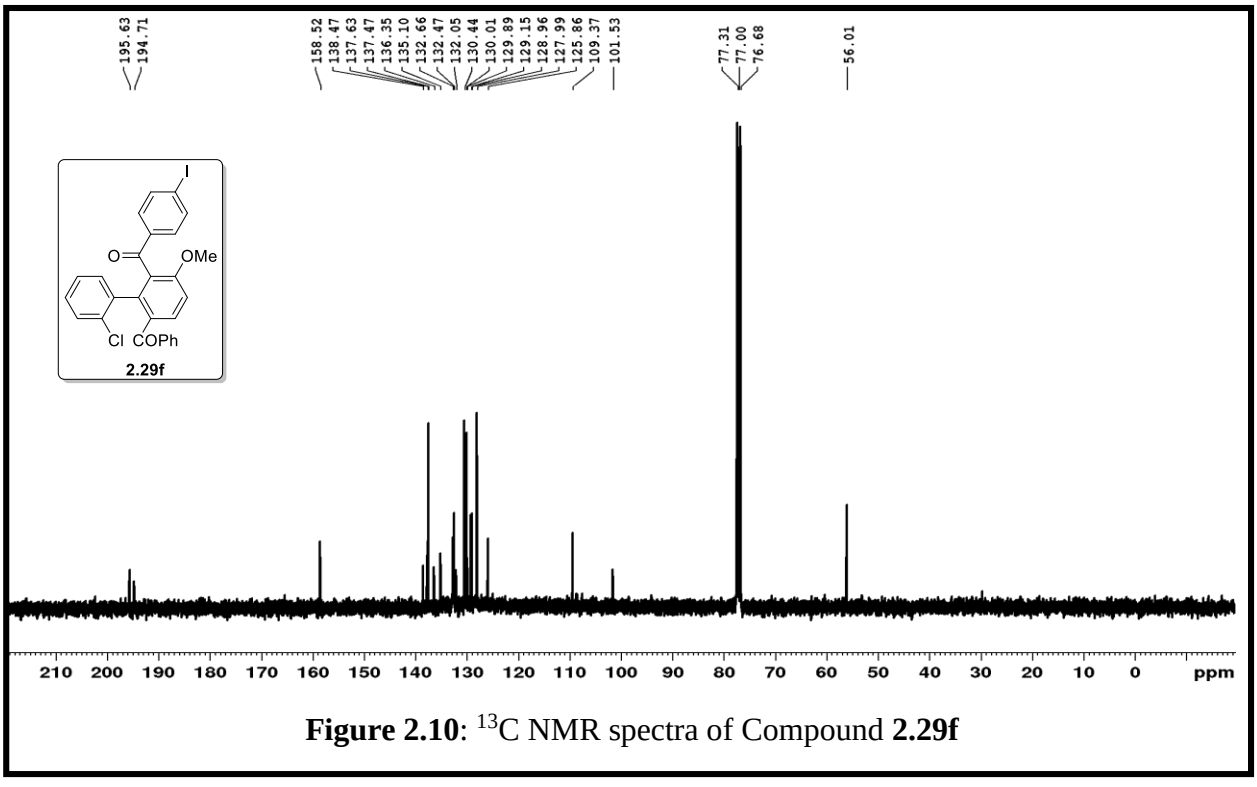


Figure 2.10: ^{13}C NMR spectra of Compound **2.29f**

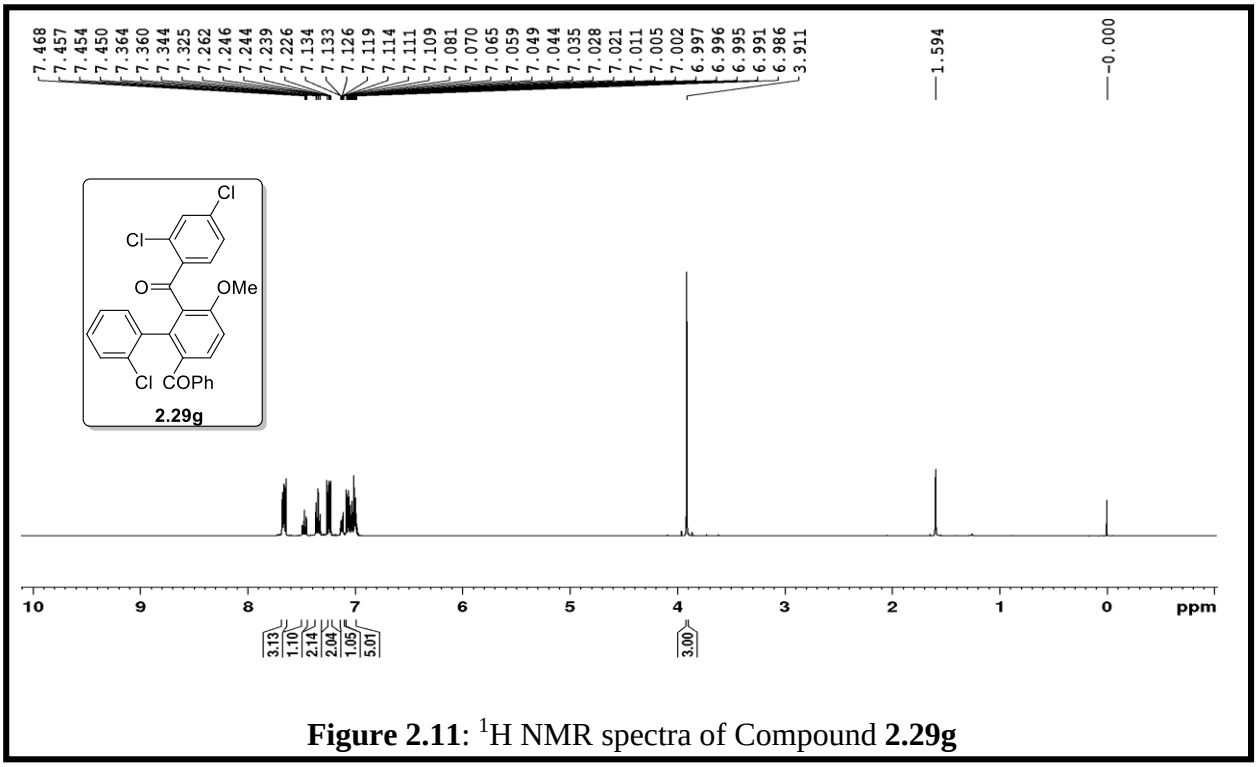


Figure 2.11: ^{1}H NMR spectra of Compound **2.29g**

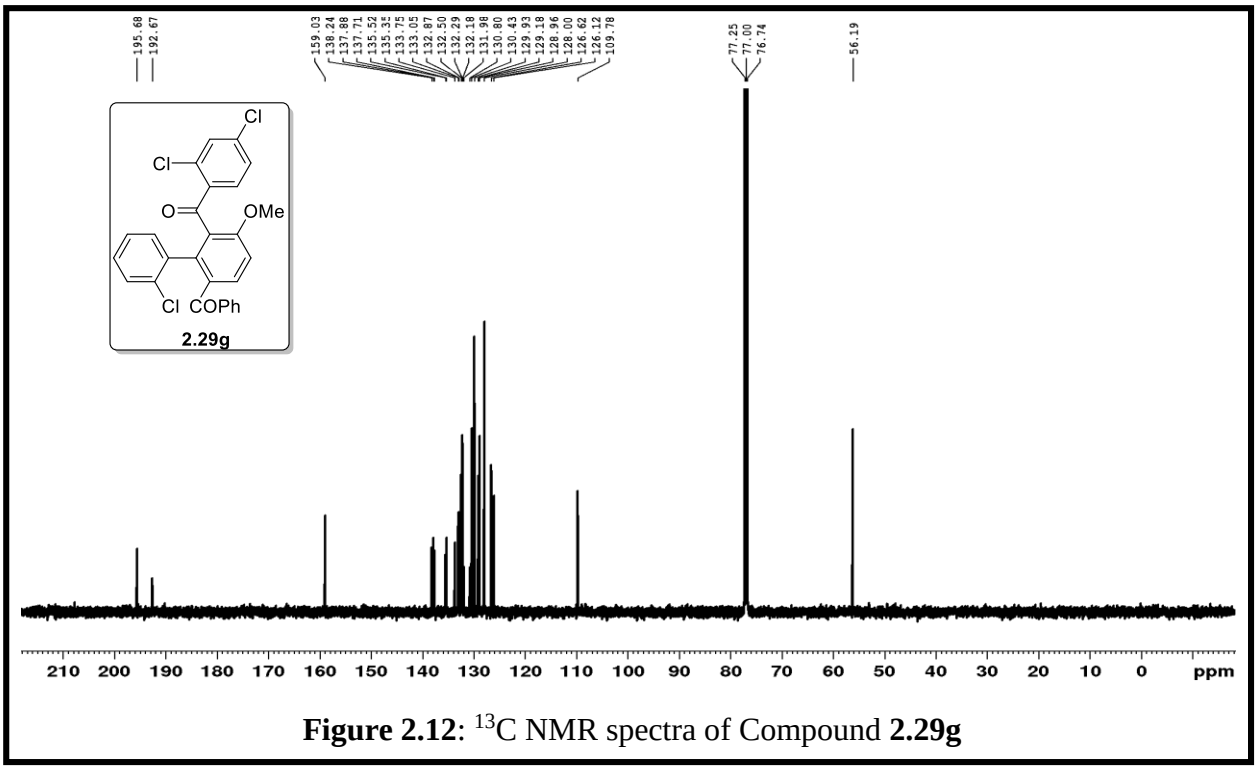


Figure 2.12: ^{13}C NMR spectra of Compound **2.29g**

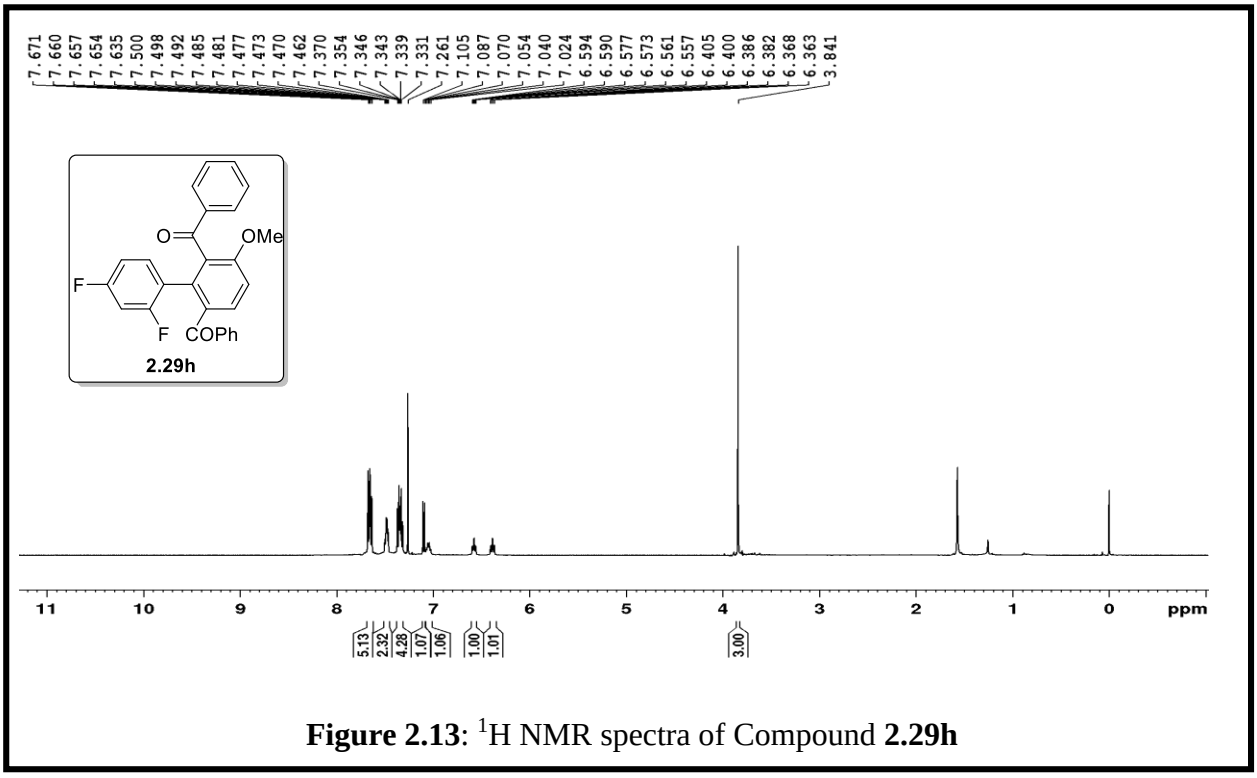


Figure 2.13: ^{1}H NMR spectra of Compound **2.29h**

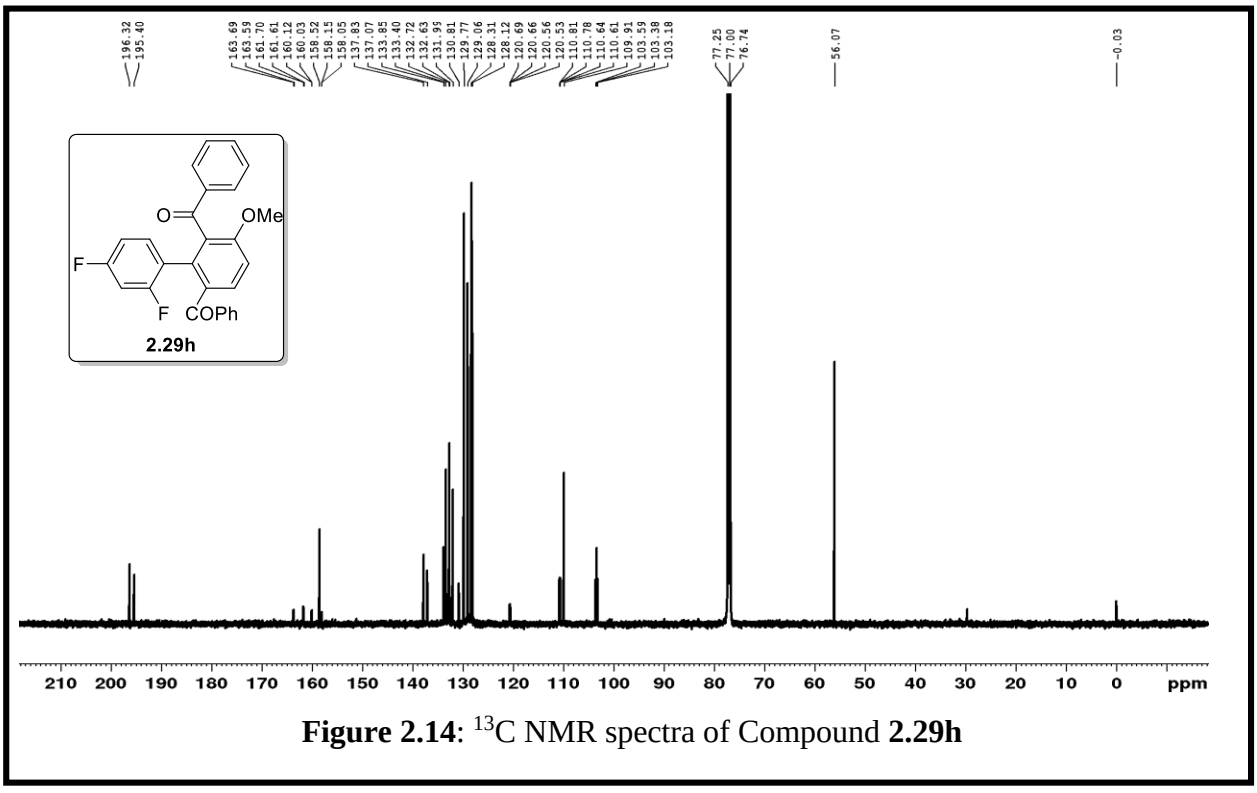


Figure 2.14: ^{13}C NMR spectra of Compound **2.29h**

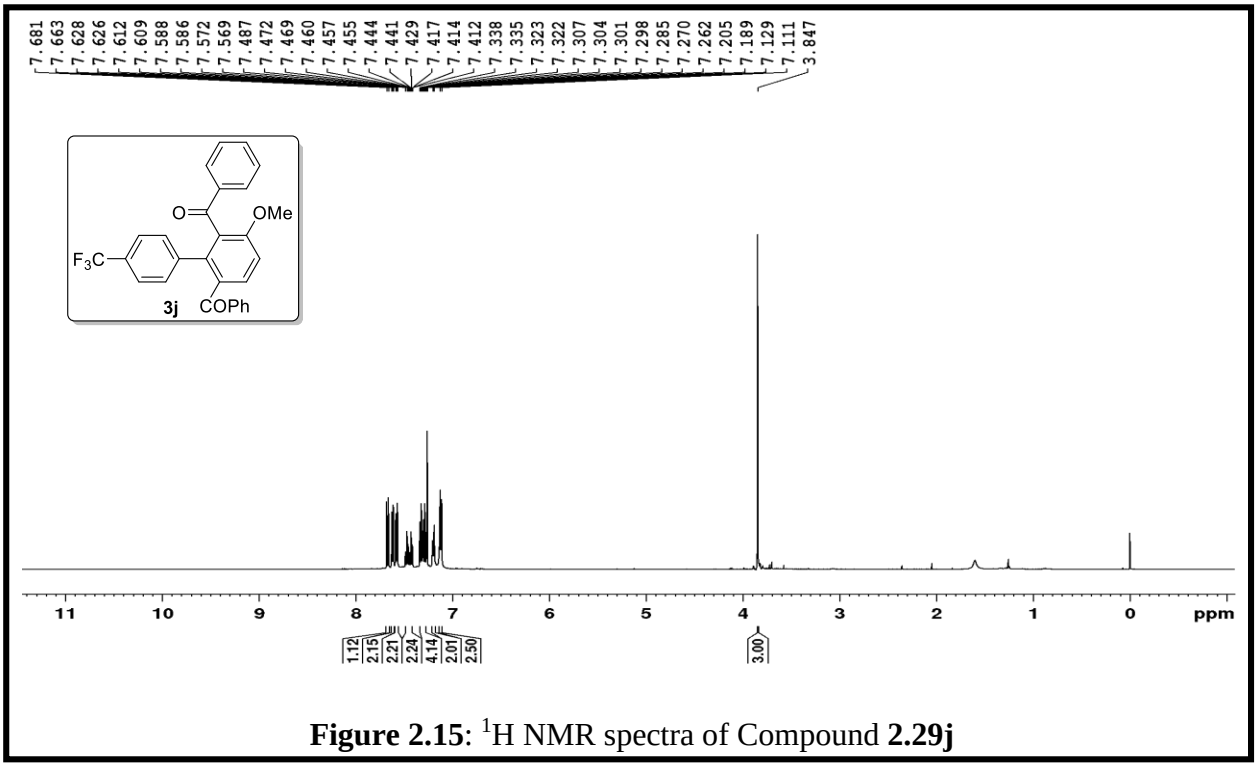


Figure 2.15: ^{1}H NMR spectra of Compound **2.29j**

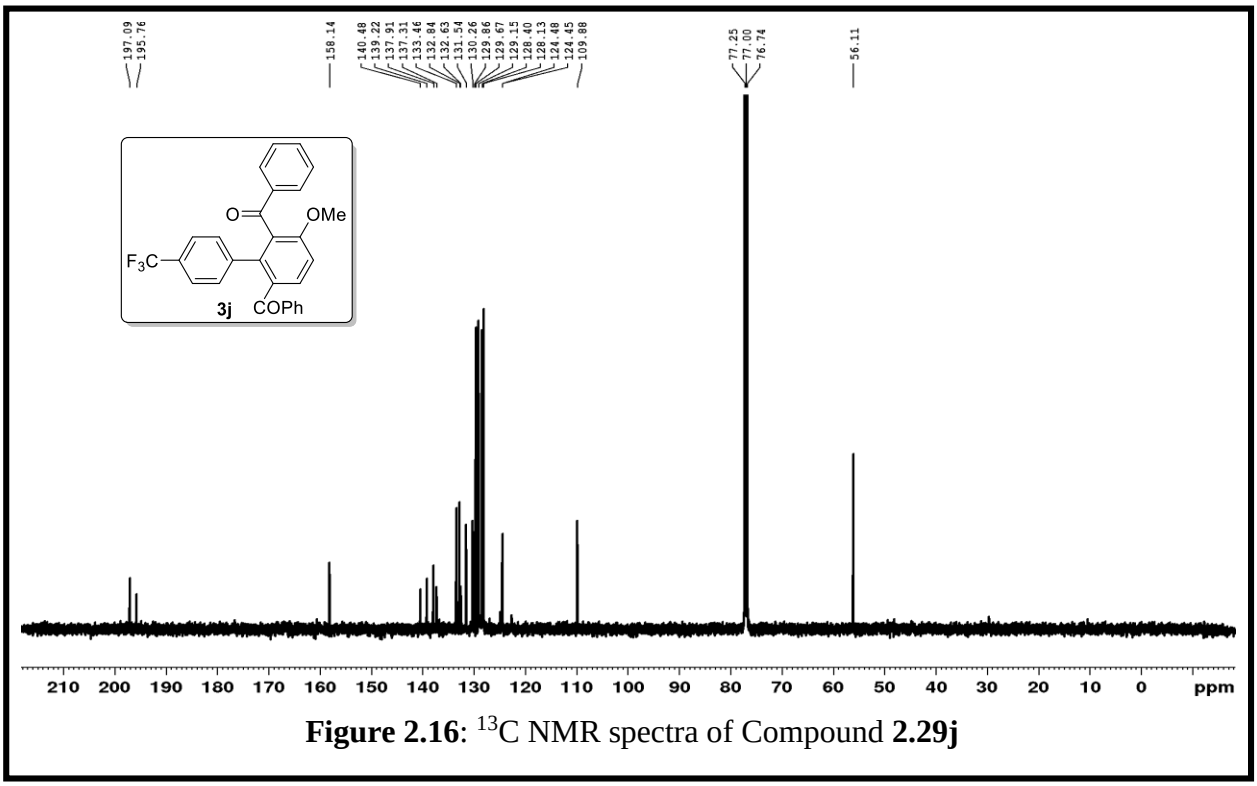


Figure 2.16: ^{13}C NMR spectra of Compound **2.29j**

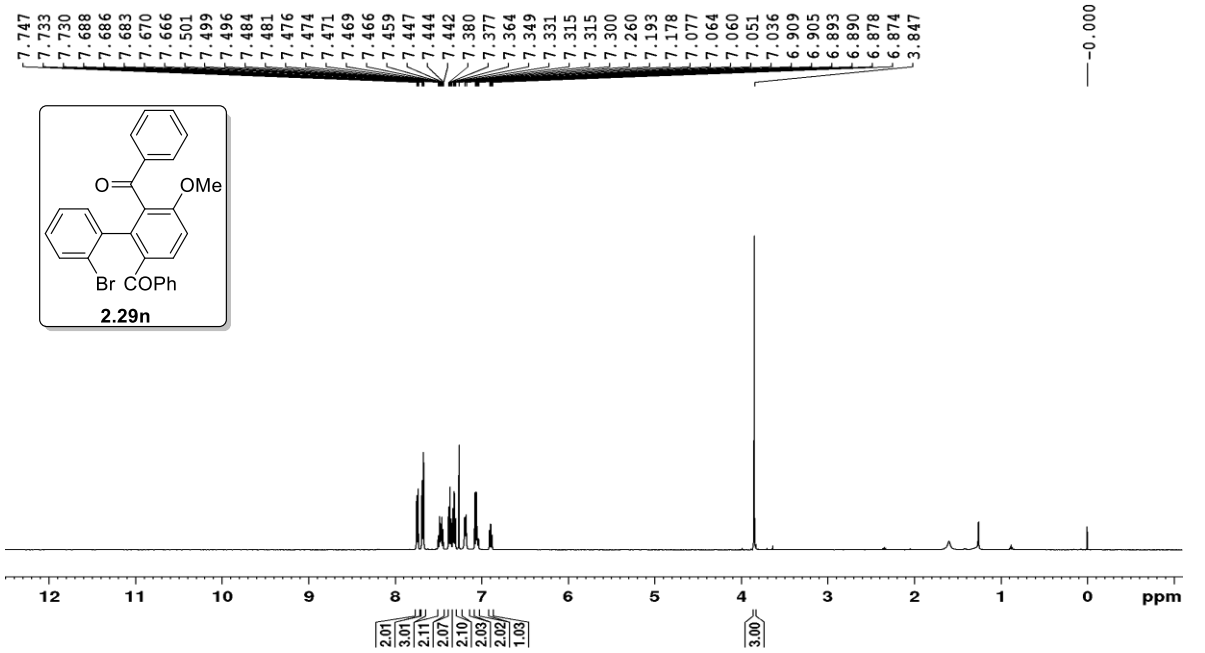


Figure 2.17: ^{1}H NMR spectra of Compound **2.29n**

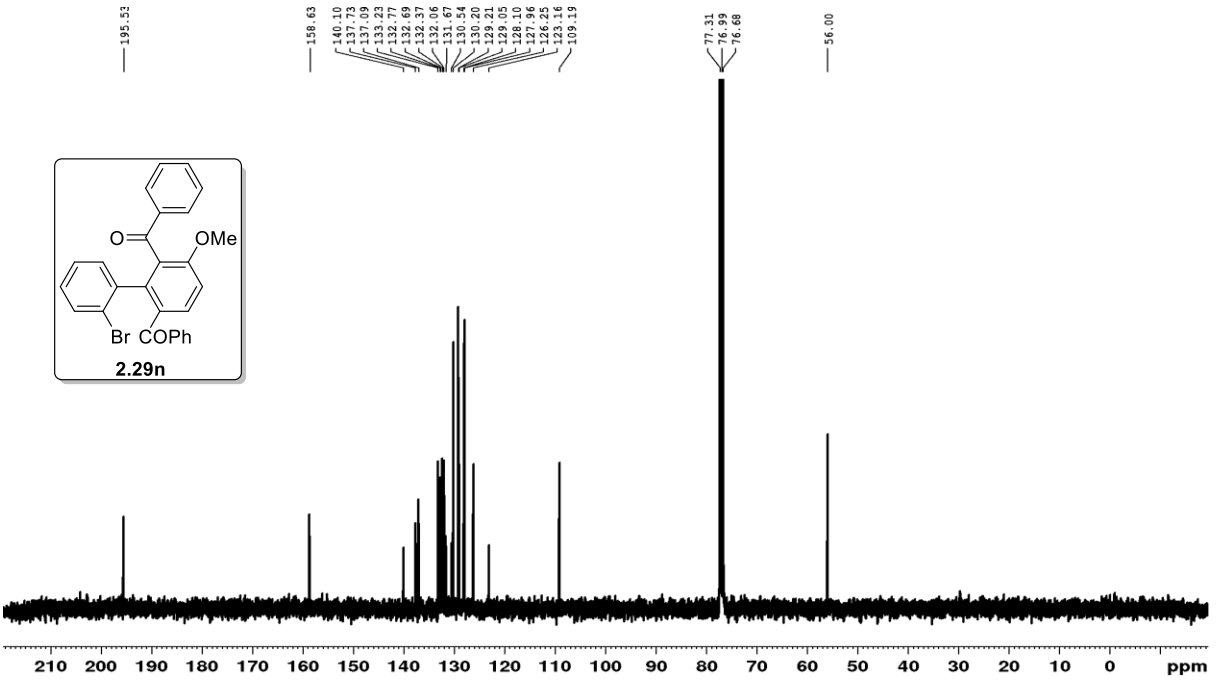


Figure 2.18: ^{13}C NMR spectra of Compound **2.29n**

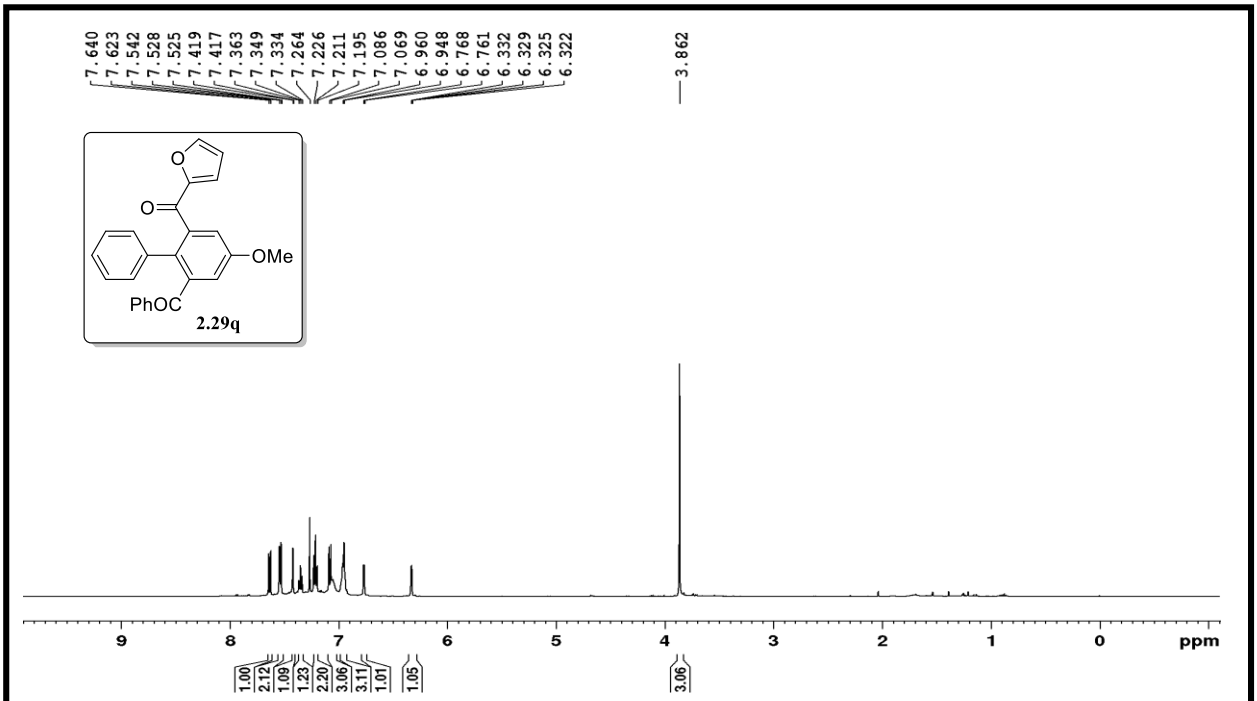


Figure 2.19: ^{1}H NMR spectra of Compound **2.29q**

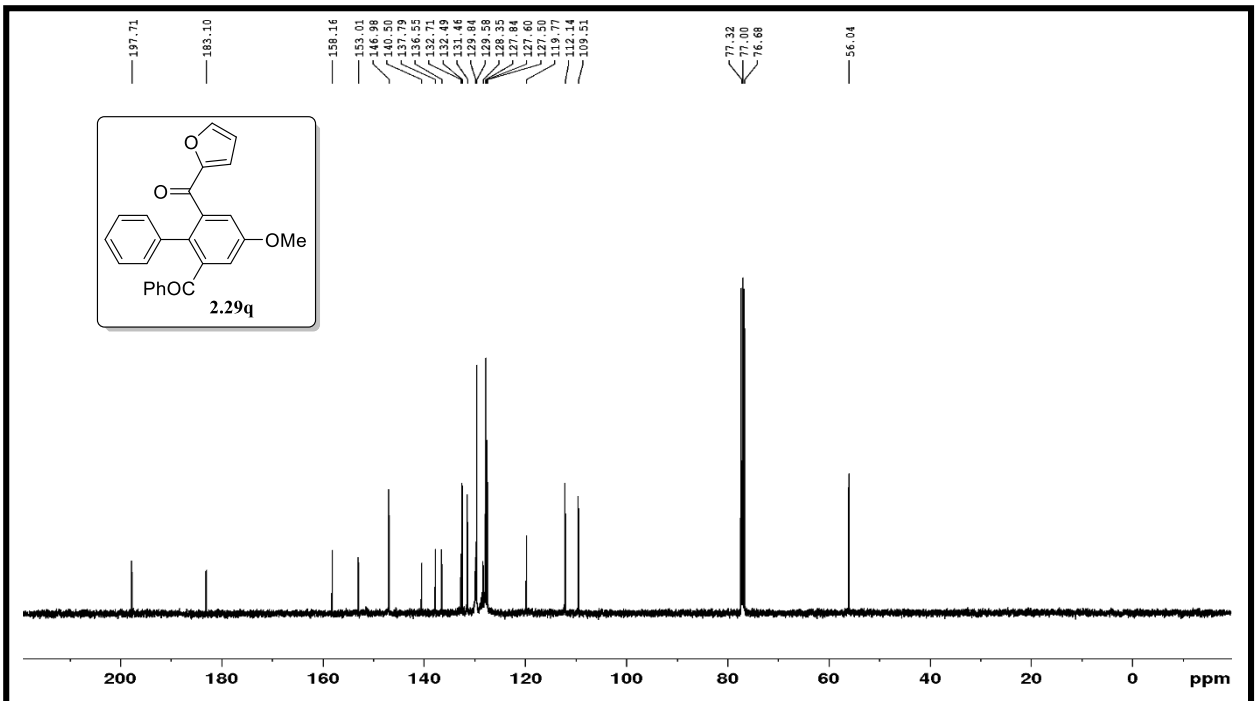


Figure 2.20: ^{13}C NMR spectra of Compound **2.29q**

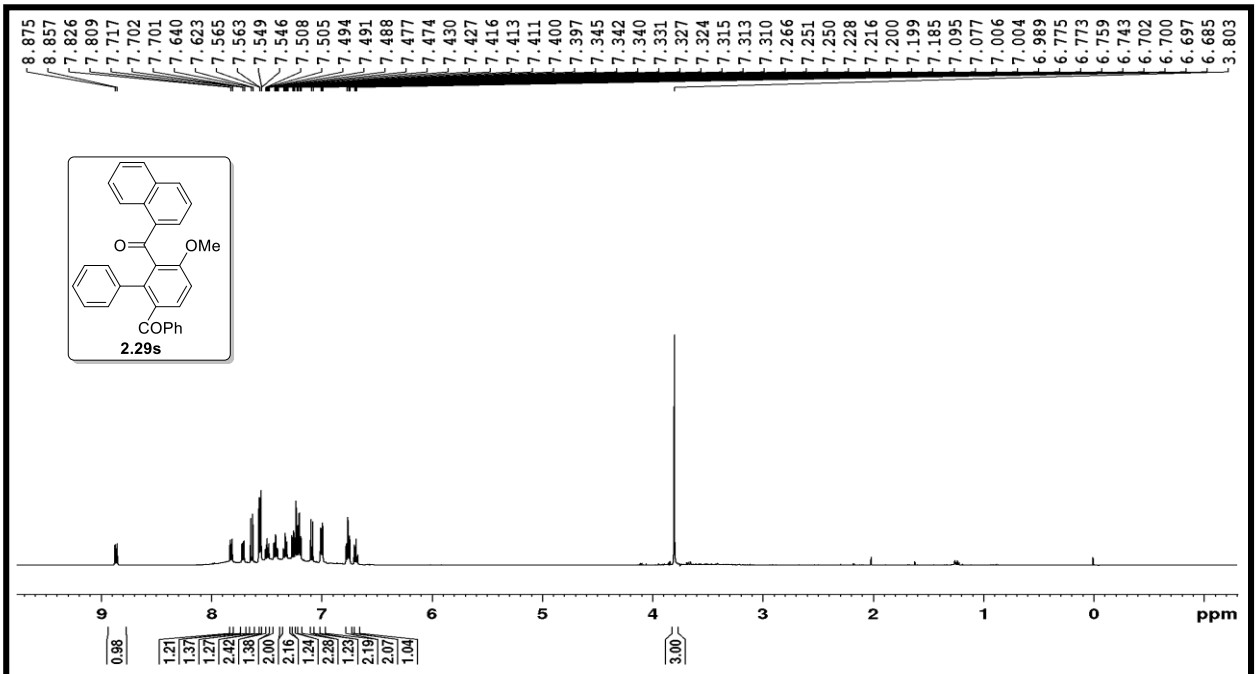


Figure 2.21: ^{1}H NMR spectra of Compound **2.29s**

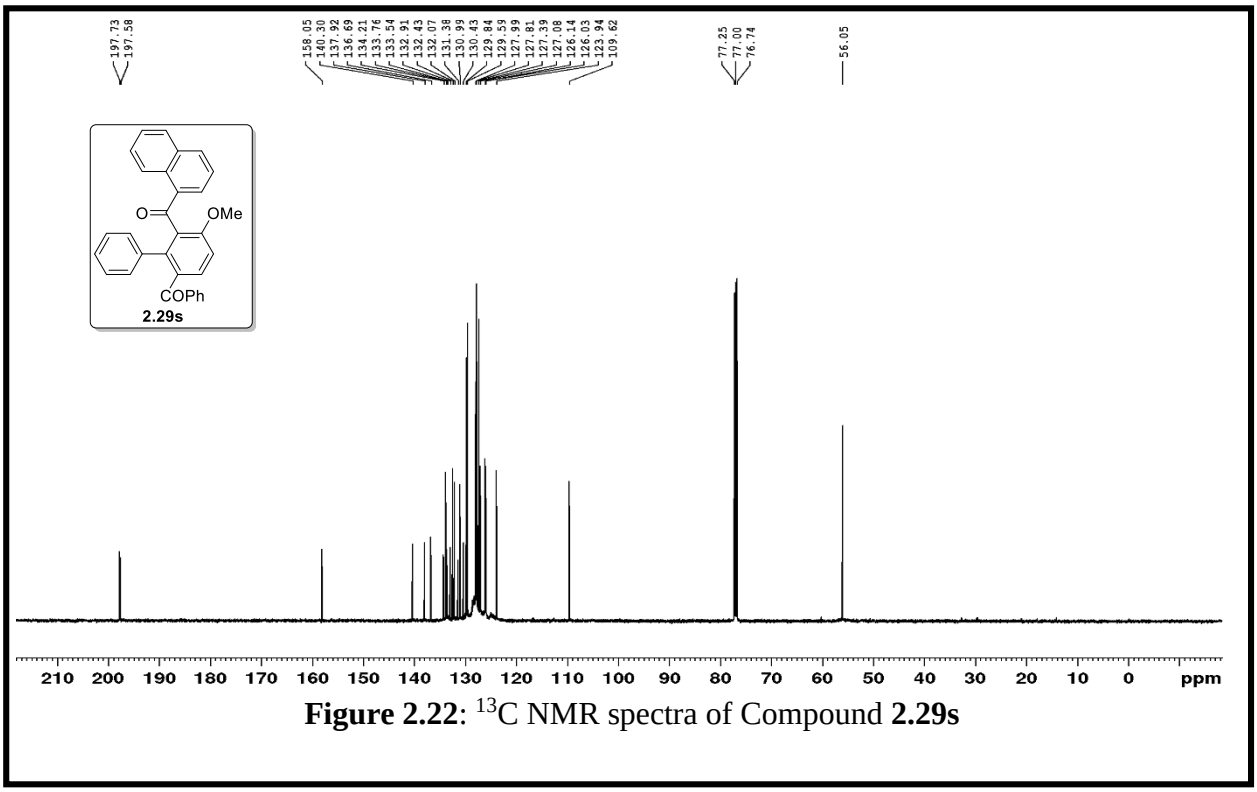


Figure 2.22: ^{13}C NMR spectra of Compound **2.29s**

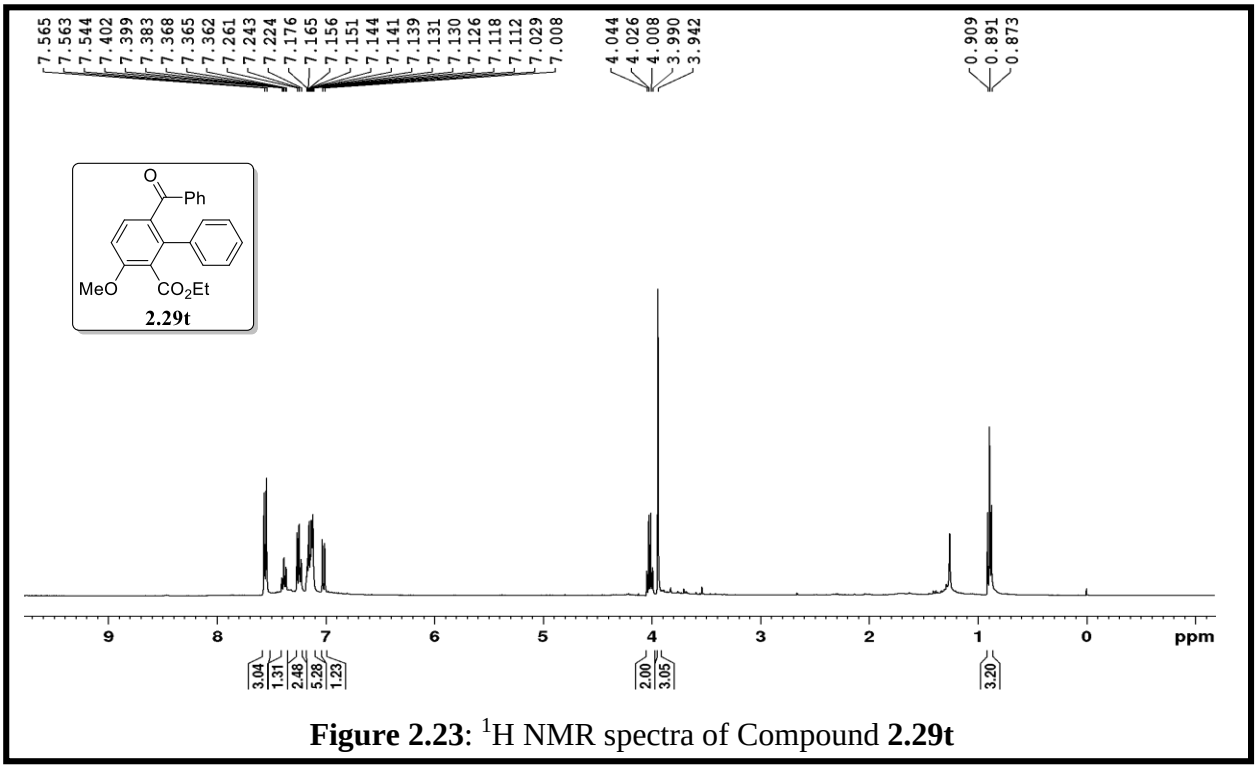


Figure 2.23: ^{1}H NMR spectra of Compound **2.29t**

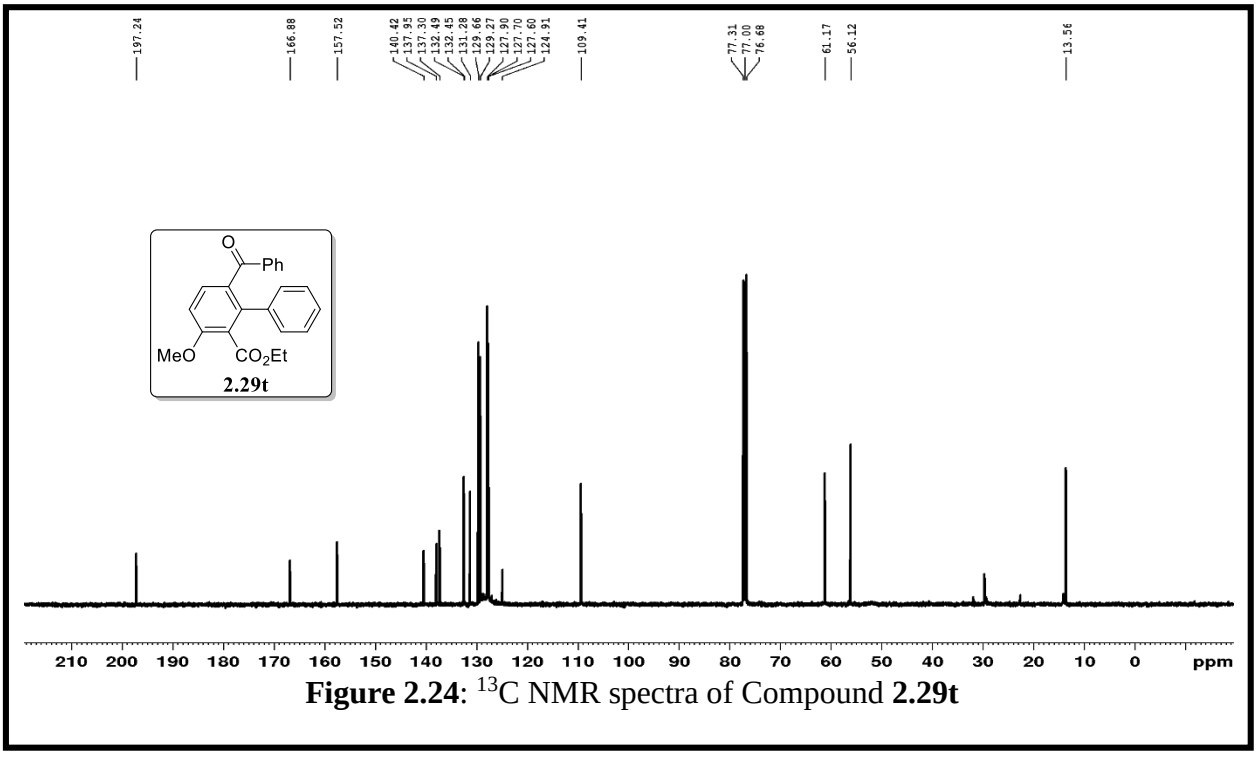


Figure 2.24: ^{13}C NMR spectra of Compound **2.29t**

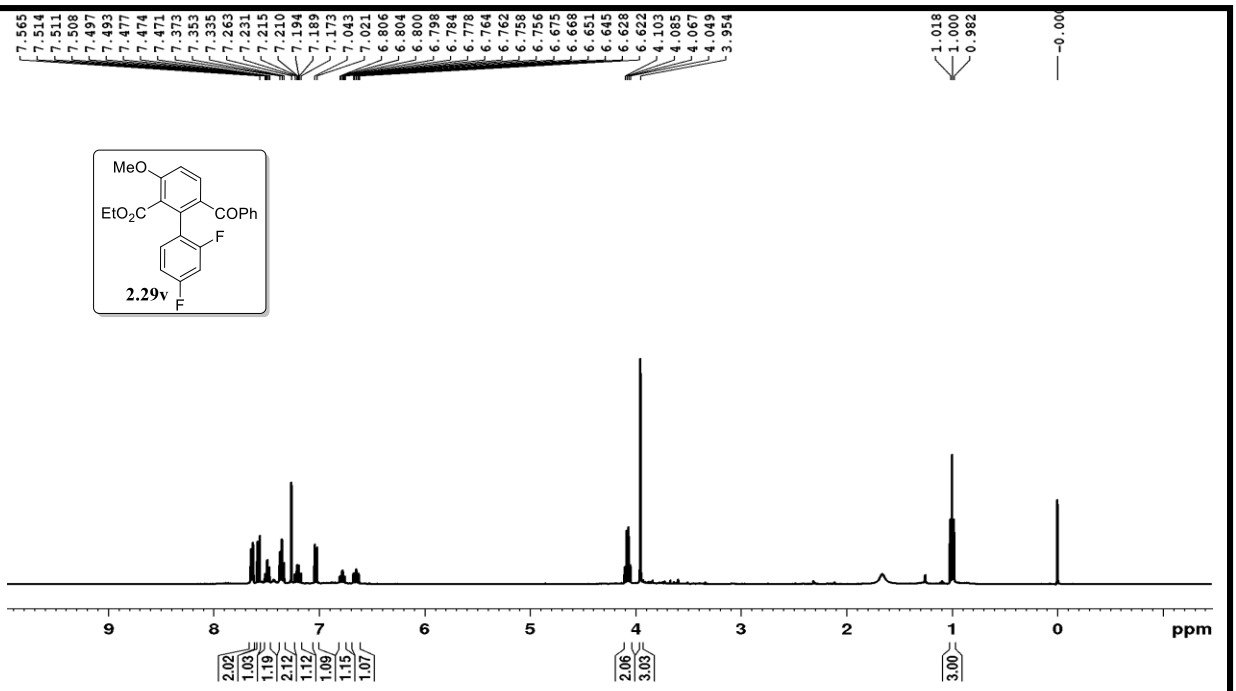


Figure 2.25: ^{1}H NMR spectra of Compound **2.29v**

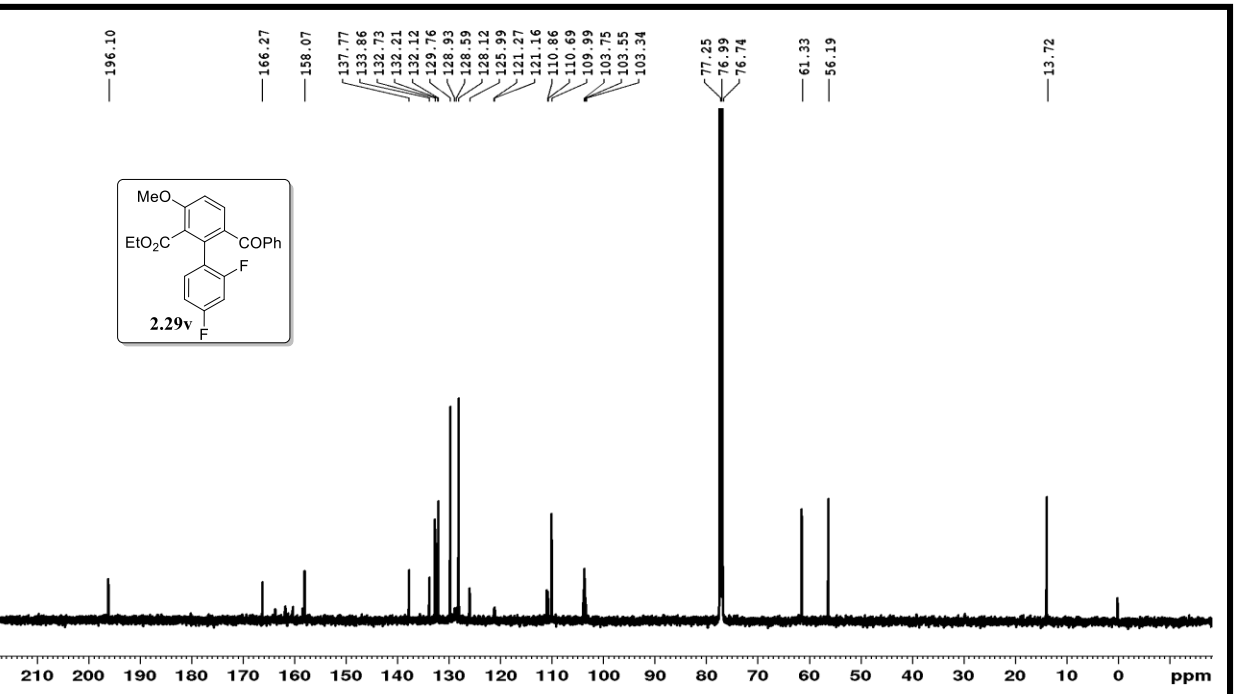


Figure 2.26: ^{13}C NMR spectra of Compound **2.29v**

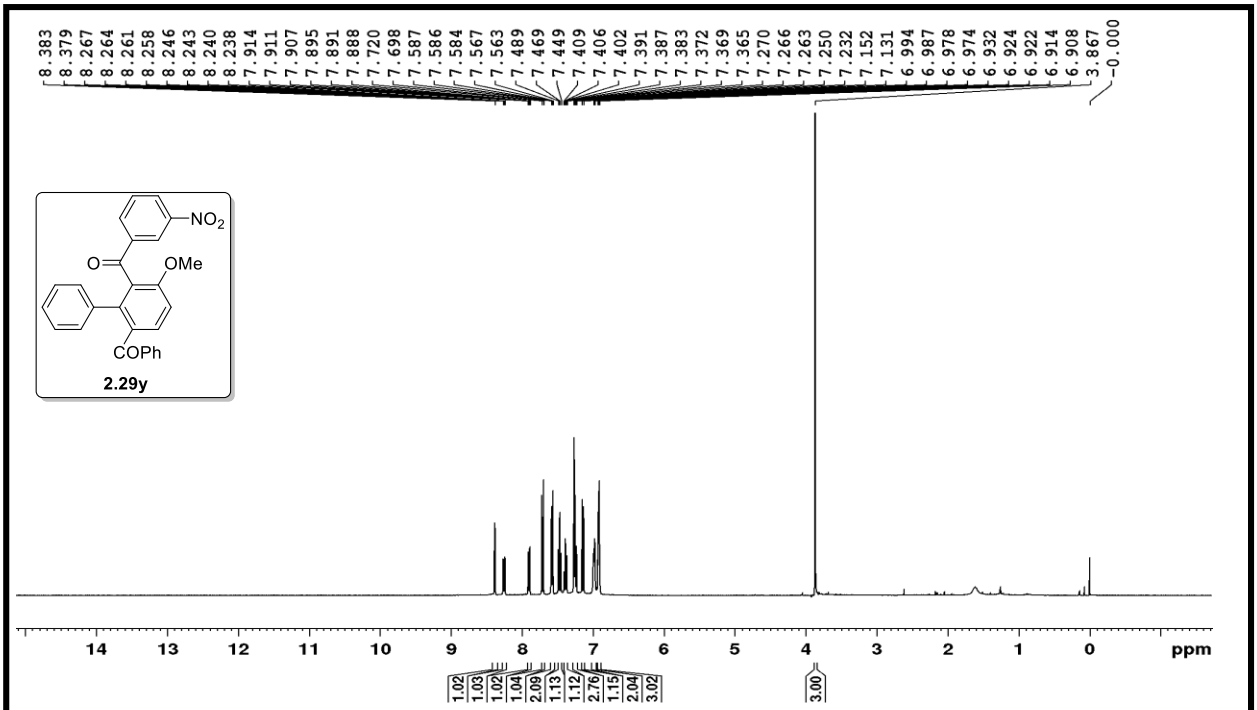


Figure 2.27: ^{1}H NMR spectra of Compound **2.29y**

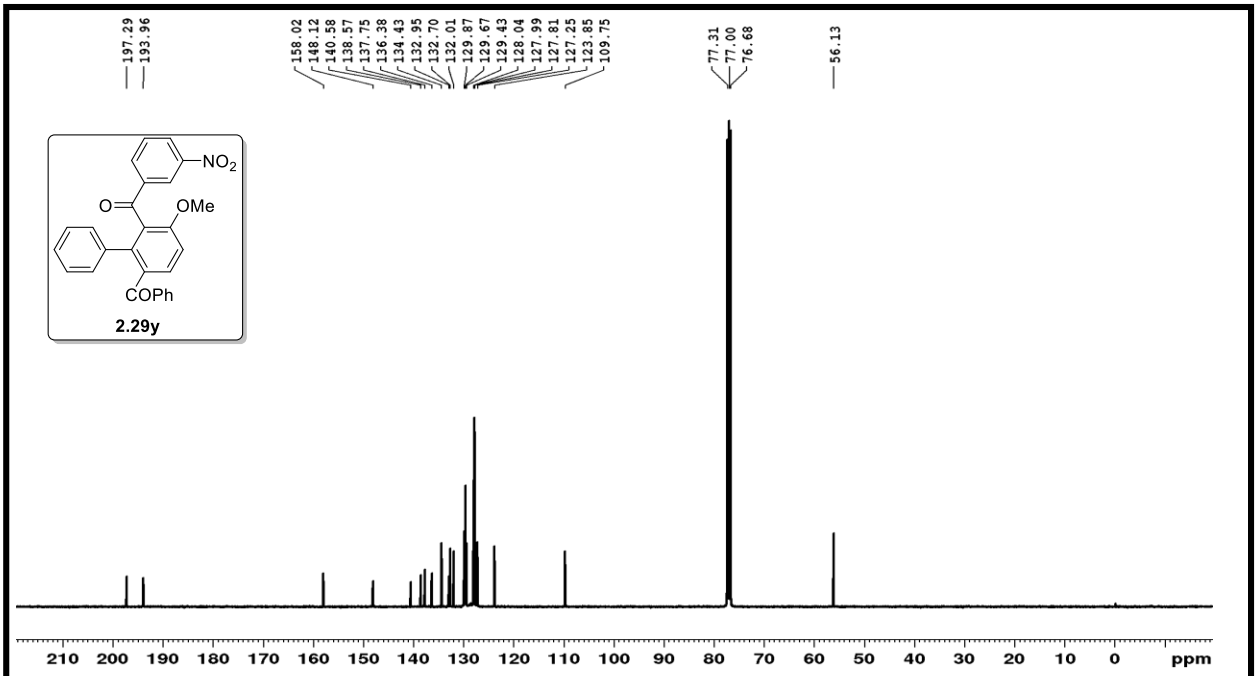


Figure 2.28: ^{13}C NMR spectra of Compound **2.29y**

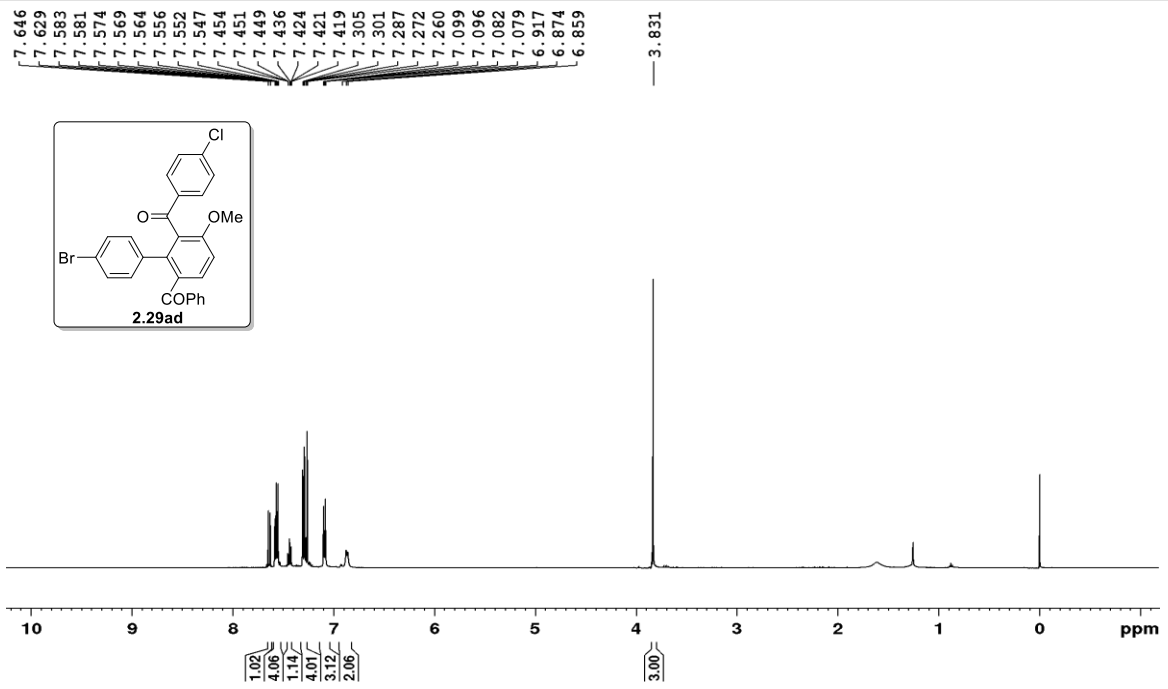


Figure 2.29: ^{1}H NMR spectra of Compound **2.29ad**

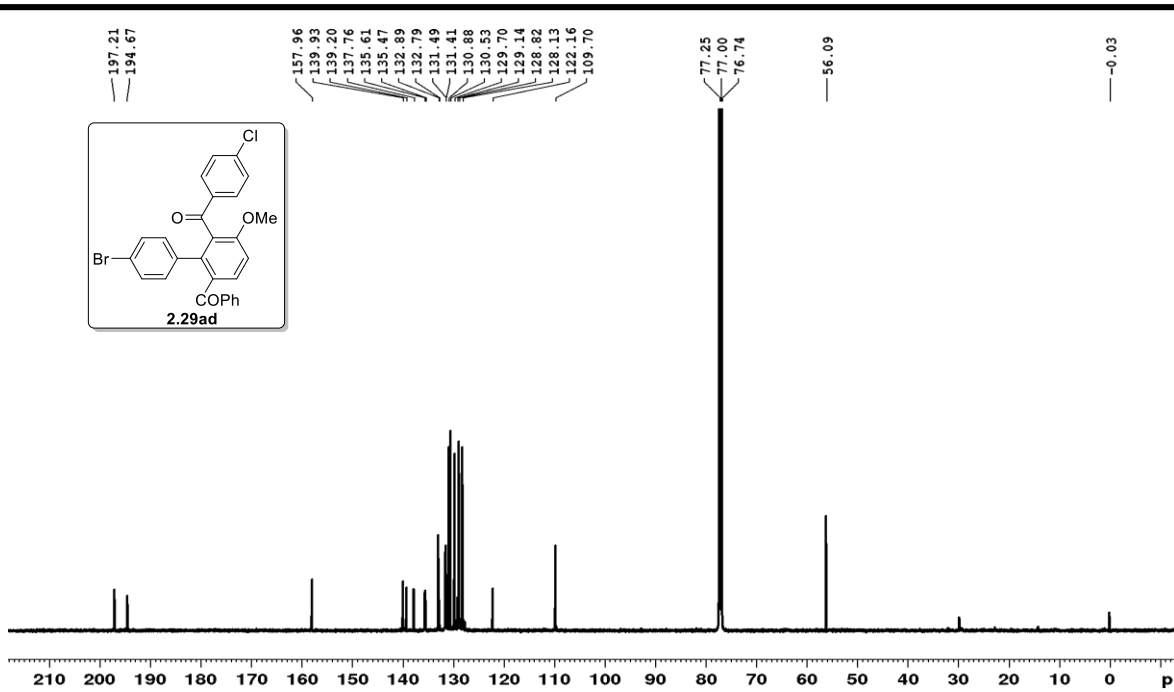


Figure 2.30: ^{13}C NMR spectra of Compound **2.29ad**

Chapter 3

Bis-alkylidene Dihydroisobenzofurans from 1,3-Dicarbonyls and Their Synthetic Applications

This chapter presents our efforts in exploring the synthetic utilities bis-alkylidene dihydroisobenzofurans synthesized using 1,3-dicarbonyls. Two applications have been found out using this interesting structural unit. Part A discusses about the synthesis of bis-indole substituted indene derivatives. Part B presents a novel approach for the synthesis of highly substituted 1,4-naphthaquinones from bis-alkylidene dihydroisobenzofurans.

3.1 Introduction to 1,3-dihydroisobenzofurans

Isobenzofuran is a fused bicyclic motif containing oxygen that widely presents in pharmaceuticals, chemicals, and bioactive natural products as well as active pharmaceutical ingredients.[1] This scaffold acts as key intermediates in the synthesis of natural products and medicinally important products.[2] In particular, bis-alkylidene dihydroisobenzofurans have interesting structure (Figure 3.1). The synthesis of 1,3-substituted bis-alkylidene dihydroisobenzofurans has been achieved by many ways.[3] These compounds having cyclic bis-vinyl ethers might have interesting reactivity pattern. However, the synthetic applications alkylidene dihydroisobenzofurans are less explored as not many applications are known from these units.

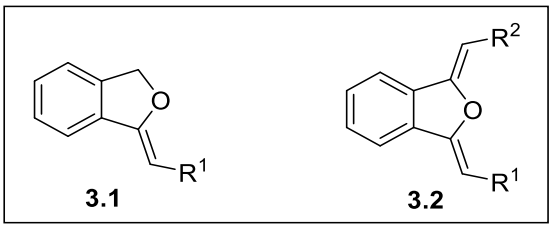
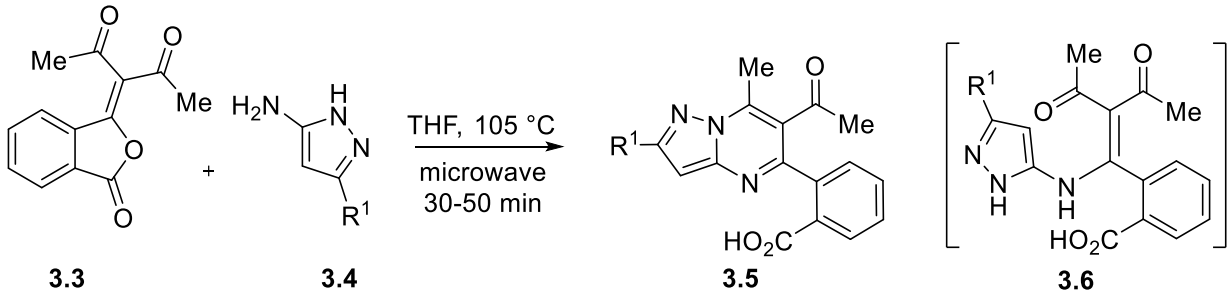


Figure 3.1. Structures of alkylidene dihydroisobenzofurans

3.2 Recent literature on the utility of 1,3-dihydroisobenzofurans

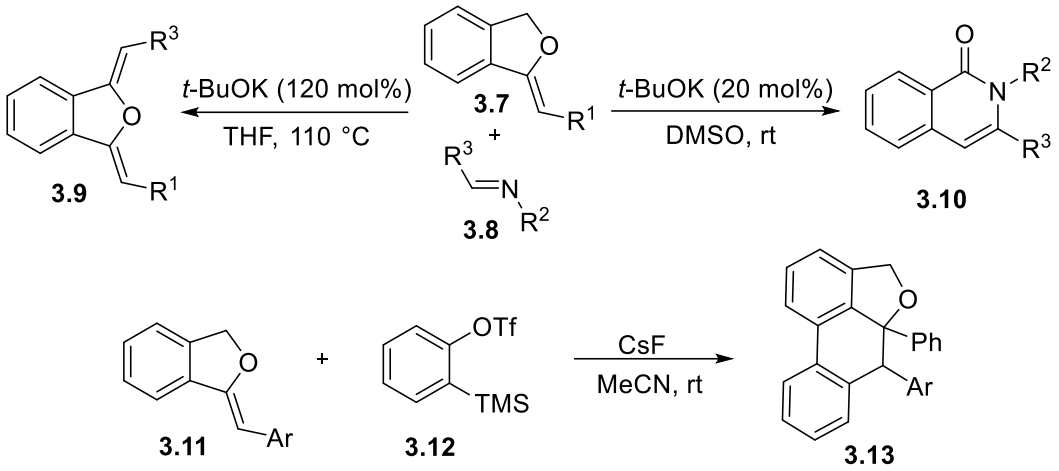
Jaime and co-workers described the synthesis of highly substituted pyrazolo(3,4-*b*) pyrimidine derivatives **3.5** from isobenzofuranone **3.3** and protected pyrazole substrates **3.4** in an one pot in synthesis (Scheme 3.1).[4] Isolation of intermediate **3.6** suggested that the reaction proceeds primarily through the ring-opening of **3.3** after Michael addition of **3.4**. Then the intermediate **3.6** undergo cyclization followed by water elimination to result in **3.5**. The starting isobenzofuranone derivatives **3.3** were prepared from 1,3-pentadione and phthalic anhydride by Knoevenagel condensation.



3.3 **3.4** **3.5** **3.6**

Scheme 3.1. Synthesis of functionalized pyrazolo[3,4-b]pyrimidines from isobenzofuranone

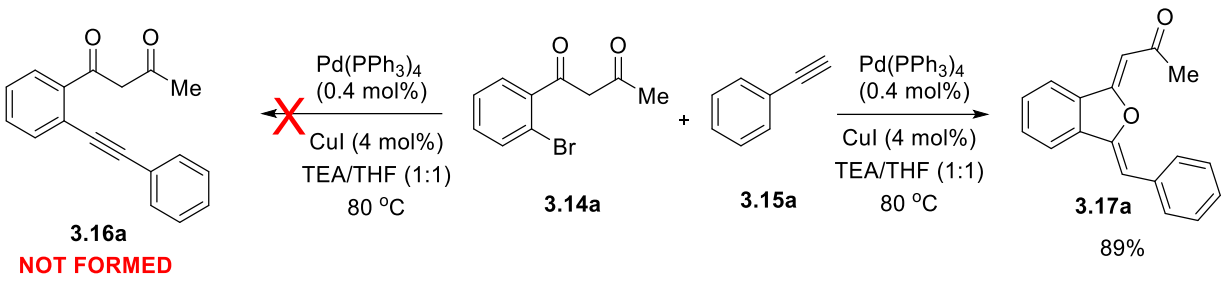
In 2013, Liu group has disclosed an intermolecular benzylic methylene functionalization of alkylidene dihydroisobenzofuran **3.7** using imines **3.8** in the presence of *t*-BuOK as catalyst (Scheme 3.2).[5] This reaction that was conducted in DMSO involves domino addition/ring-opening/cyclization sequence in delivering the isoquinolinone products **3.10** in high yields. The reaction between **3.7** and **3.8** is solvent dependent in nature. In THF, with 1.2 equivalents of *t*-BuOK, an addition/elimination sequence of exocyclic enol ethers with imines provided the bis-alkylidene dihydroisobenzofuran derivatives **3.9** in good yields. In 2014, the same group has developed a cascade reaction of benzyne **3.12** with isobenzofuran **3.11** for the synthesis of phenanthrofurans **3.13** in the presence of a fluoride source (Scheme 3.2).[6] In this protocol the reaction involves a Diels−Alder reaction between **3.11** and the benzyne intermediate followed by the addition of another molecule of benzyne to give the product **3.13**.



Scheme 3.2. Applications of alkylidene dihydroisobenzofurans

3.3 Background

While working on the biaryl synthesis using in situ formed acetals (Chapter 2), we wished to make the substrate **3.16a** to employ it in the reaction expecting the *o*-alkynyl group to participate in the reaction. However, when we subjected the *o*-alkynylbenzaldehyde **3.14** to Sonogashira reaction with phenylacetylene under the condition mentioned in scheme 3.3., the bis-alkylidene dihydroisobenzofuran derivative **3.17a** was obtained in 89% yield. Our attempts to make **3.16a** by modifying the reaction conditions such as changing the Pd catalyst were not successful. It was believed that, in the presence of Pd catalyst, initially formed Sonogashira coupling product cyclized through the enolic oxygen of the *o*-1,3-dicarbonyl moiety. It was later found that similar reaction pattern to form bis-alkylidene dihydroisobenzofurans has been observed by Kobayoshi and co-workers using the reaction condition {$PdCl_2(PPh_3)_2$ (3.5 mol%), CuI (13 mol%), Et_3N (2 equiv.), DMF, r.t.}.[3k] In that report by Kobayoshi, the substrate scope was evaluated only with 1,3-ketoesters, 1,3-ketonitriles and 1,3-ketoamides. The yields were moderate in most of the cases and the ketoamides did not take part in the reaction. Also, the corresponding 1,3-diketone derivatives were not studied. In this regard, we explored the substrate scope of the reaction using various 1,3-diketones under the conditions we used for the preparation of **3.17a**. The results of the bis-alkylidene dihydroisobenzofuran synthesis is presented in Table 3.1.

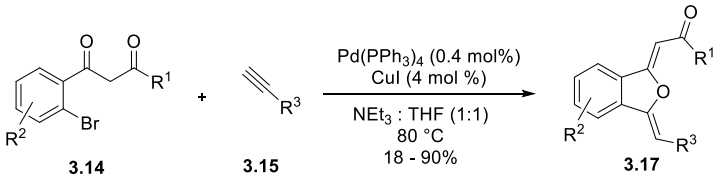


Scheme 3.3. Synthesis of bis-alkylidene dihydroisobenzofuran

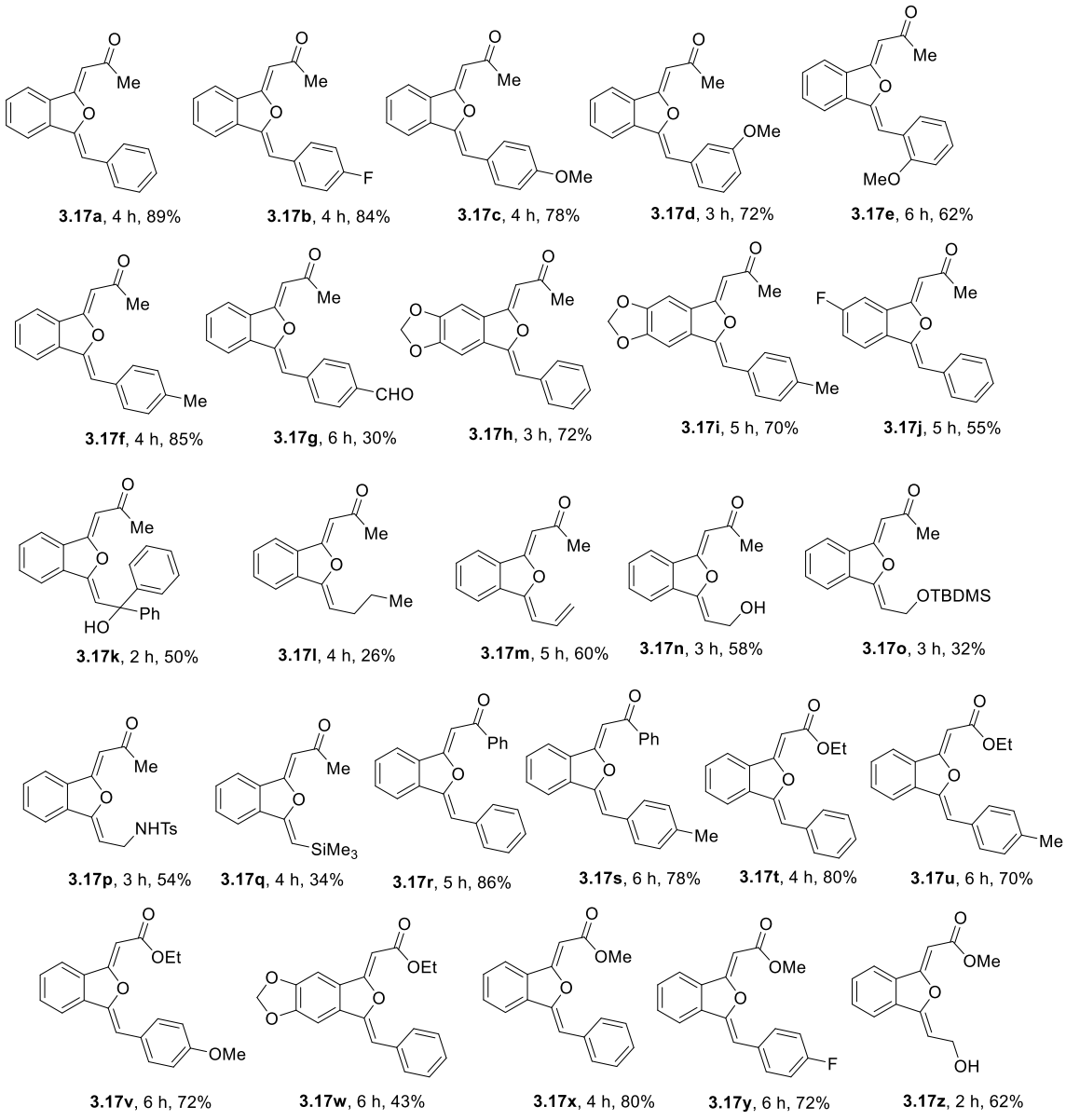
3.3.1 Substrate scope for bis-alkylidene dihydroisobenzofuran synthesis

A variety of starting substrates **3.14** having 1,3-diketone and β-ketoester were subjected to Sonogashira reaction. The reaction resulted in good yields of the products (**3.17a** – **3.17j**, **3.17r** and **3.17s**) when arylalkynes and 1,3-diketones were used as reaction partners. When terminal alkynes have alkyl substituents, the yields were moderate to poor. Terminal alkynes based on propargyl alcohol, propargyl amine and trimethylsilylacetylene could also be employed. The propargyl alcohol based substrates provided moderate yields of the product (**3.17k** and **3.17n**). TBDMS protected propargyl alcohol and trimethylsilylacetylene resulted in poor yield of the products (**3.17o** and **3.17q**). It has to be mentioned that 4-bromobut-1-yne resulted in the product **3.17m** by eliminating a molecule of HBr under the reaction conditions. β-keto ester based substrates were also employed to get their corresponding bis-alkylidene dihydroisobenzofuran derivatives (**3.17t** and **3.17z**).

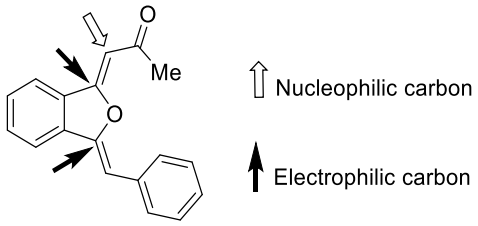
Table 3.1. Synthesis of bis-alkylidene dihydroisobenzofuran derivatives



3.14 + **3.15** → **3.17**



We then explored the synthetic applications of these bis-alkylidene dihydroisobenzofuran derivatives. Since the bis-alkylidene dihydroisobenzofurans have both electrophilic as well as nucleophilic centers, we have developed reactions by reacting them with both nucleophiles and electrophiles.



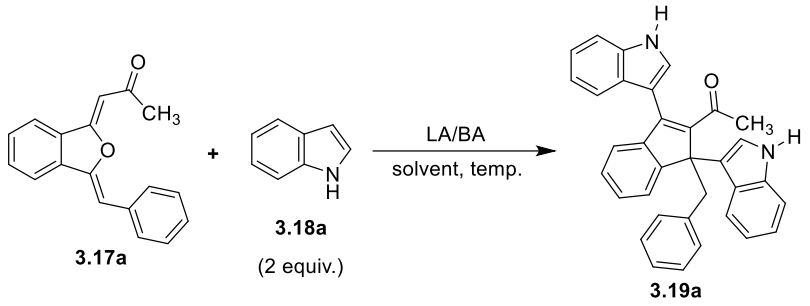
3.4 Synthesis of bis-indole substituted indenes

At the outset, we started our investigations on this title substrate by reacting them with indoles. It was expected to add at either one of the electrophilic carbons. The β-carbon of the enone moiety has more propensity for its attack.

3.4.1 Optimization of reaction conditions

Different Lewis and Brønsted acids were attempted to activate the carbonyl moiety for promoting the nucleophilic attack of indole. Though Lewis acid $Sc(OTf)_3$ resulted in trace amount of the product (bis-indole substituted indole), Lewis acids such as $AgSbF_6$ and $BF_3{\cdot}OEt_2$ provided promising yields of the bis-indole substituted indole **3.19a** (Table 3.2, entries 4 and 5). The reaction worked much better when Brønsted acids such as TFA, *p*-TSA were used as a promotor (Table 3.2, entries 7 and 8). However, the reaction did not occur when acetic acid (in stoichiometric amount or even as solvent) was used. Reducing the amount of TFA, however, did not maintain the efficiency of the reaction (Table 3.2, entries 12 and 13). There was no reaction in the absence of indole with TFA alone (Entry 15).

Table 3.2. Optimization of reaction conditions for the formation of bis-indole-substituted indene derivative **3.19a**.



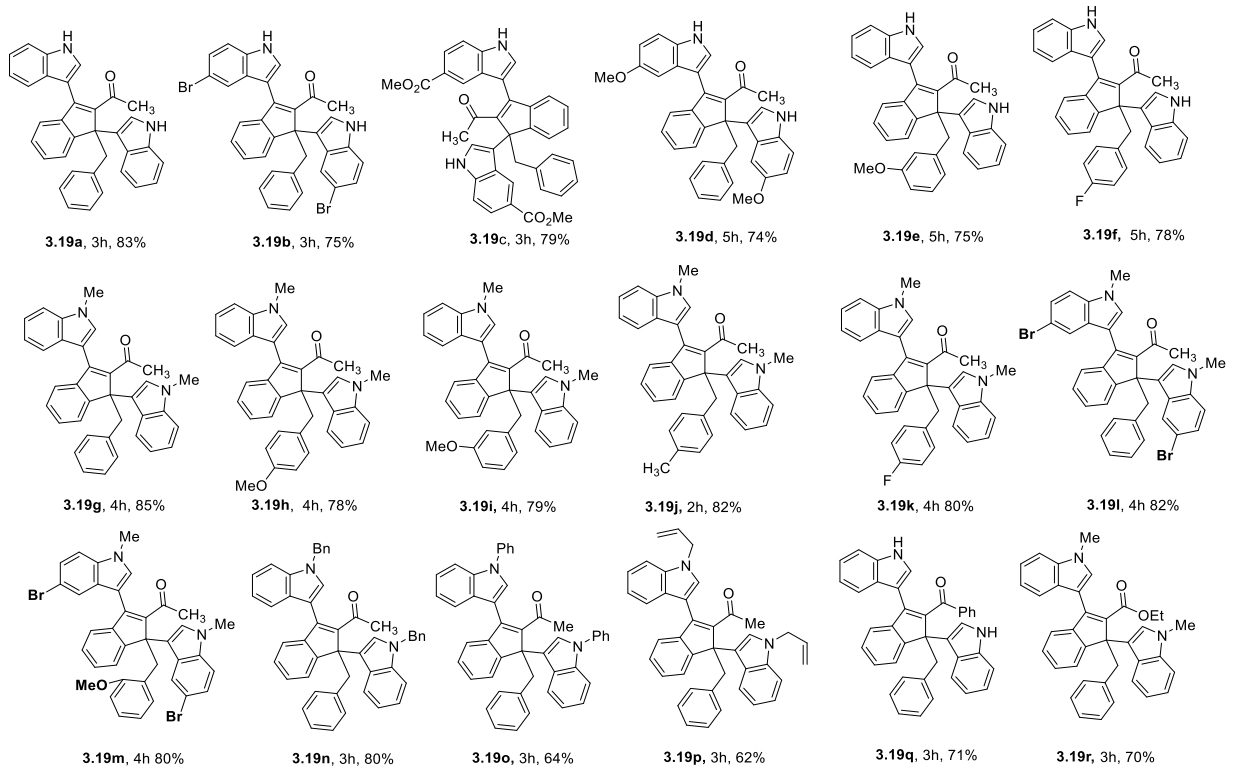
Entry	LA/BA (equiv.)	Solvent	Time	Temp	Yield in % [a]
1	$Sc(OTf)_3$ (0.1)	Toluene	4 h	110° C	trace
2	$Sc(OTf)_3$ (0.1)	Toluene	24 h	rt	trace
3	$Sc(OTf)_3$ (0.1)	DCE	24 h	rt	trace
4	$AgSbF_6$ (0.1)	DCE	4 h	rt	63
5	$BF_3.OEt_2$ (0.1)	DCE	4 h	rt	67
6	TfOH (0.1)	CH_2Cl_2	1 h	rt	Side product
7	**TFA (1)**[b]	**DCE**	**4 h**	**rt**	**85**
8	*p*-TSA (1)	DCE	6 h	rt	76
9	CH_3COOH (2)	DCE			No Reaction
10	-	CH_3COOH	24 h	rt/110 °C	No Reaction
11	$HClO_4$ (1)	DCE	3 h	rt	61
12	TFA (5 mol%)[b]	DCE	48 h	rt	30 (25)[d]
13	TFA (0.5)[b]	DCE	12 h	rt	52
14	-	DCE	48 h	rt	No Reaction
15	TFA (1) [b & c]	DCE	48 h	rt	No reaction
16	TFA (1)[e]	DCE	4 h	rt	41 (32)

[a]Isolated yield, [b]a stock solution of TFA in DCE was used. [c]reaction was carried without indole. [d]the value in parenthesis correspond to amount of unreacted **3.17a.** [e] reaction was carried out with 0.20 mmol (1 equiv.) of indole. All the reaction were carried out with 0.20 mmol of **3.17a** and 0.40 mmol of indole **3.18a**.

3.4.2 Evaluation of substrate scope

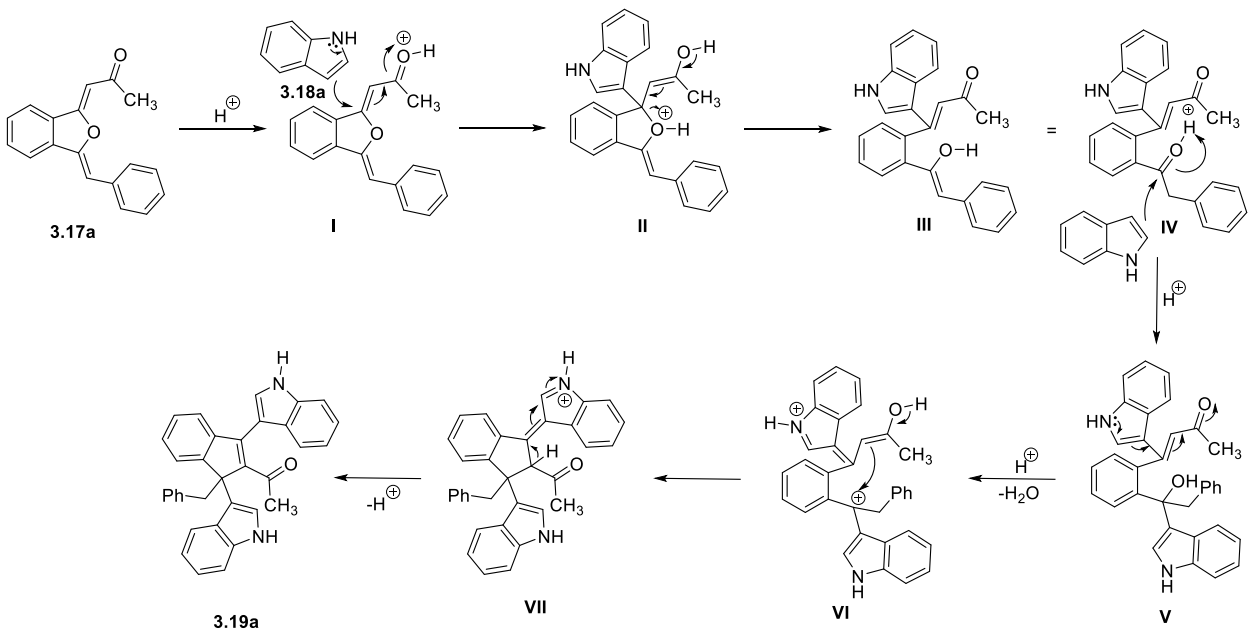
Having the optimized reaction condition in hand, we proceeded to evaluate the substrate scope. A library of bis-indole attached indene derivatives **3.19a** – **3.19r** were synthesized by reacting different bis-alkylidene dihydroisobenzofurans with a range of indoles in the presence of TFA. The structures of the products along with the reaction times and yields are provided in the Table 3.3. Initially, different substituted indoles were investigated. Electron donating groups such as OMe, electron withdrawing groups such as ester, and halides in indole were evaluated. They gave good yields of the products. Next, some reactions were carried out using differently N-protected indoles. The N-Ph and N-allyl protected indoles resulted in slightly lesser yields. Bis-alkylidene dihydroisobenzofurans having different substituents on the hanging aryl ring were also subjected to the reaction condition to get the corresponding bis-indole substituted indene derivatives.

Table 3.3. Substrate scope



3.4.3 Mechanism

A mechanism as depicted in Scheme 3.4 is proposed for the formation of bis-indole substituted indene derivative. Initially, indole will attack on the electrophilic β-carbon of the activated carbonyl followed by ring-opening of the isobenzofuran to result in the intermediate **III** which will go to its keto form **IV**. One more molecule of indole will attack on the ketone activated by acid to give a tertiary alcohol which will form a stable carbocation as in intermediate **VI**. Now indole nitrogen assisted cyclization of the enol on the carbocation will form the indane ring as in **VII**. Deprotonation to neutralize the charge on the indole nitrogen will result in the final product.



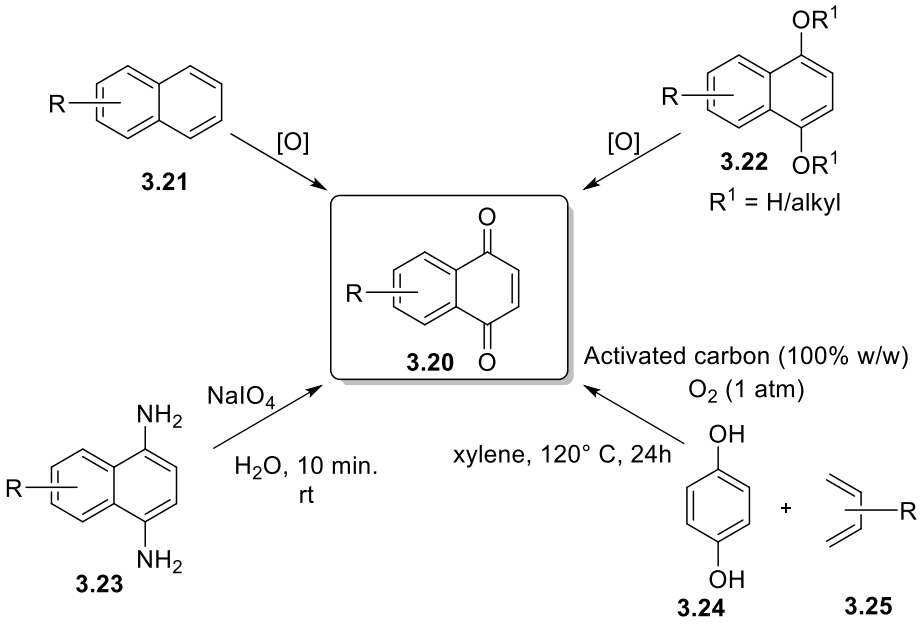
Scheme 3.4. Plausible mechanism for indene formation

3.5 Synthesis of highly substituted 1,4-naphthoquinone from bis-alkylidene dihydroisobenzofuran

3.5.1 Introduction to 1,4-naphthoquinones

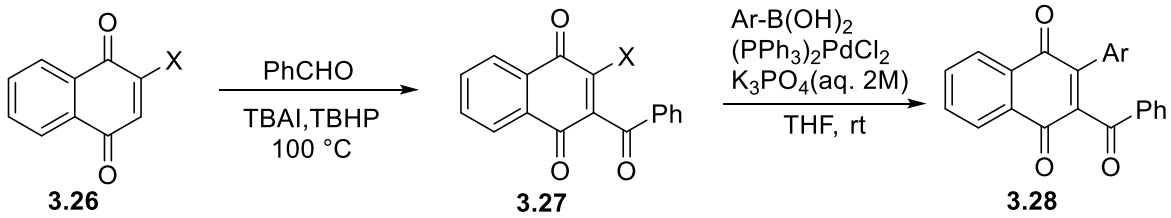
1,4-Naphthoquinones (1,4-NQs) are important scaffold present in various materials, pharmaceuticals, biologically active compounds and intermediates in many natural product synthesis.[7] Several horticultural plants which produce 1,4-NQs have been used as medicinal plants and thus serve as starting point for developing drugs.[8] Hydroxy, acyloxy and alkoxy substituted 1,4-NQs are classified as antiplasmodial agents against *plasmodium falciparum* which is responsible for malaria disease.[9] Acyl 1,4-NQs have notable reactivity feature towards nucleophiles to result in a variety of valuable synthetic organic compounds.[10] Due to these intriguing factors of naphthoquinones (1,4-NQs), their synthesis is in demand consistently. The conventional synthesis of 1,4-NQs **3.20** involves oxidation of naphthalenes **3.21**/naphthols **3.22/** naphtha-1,4-diamines **3.23** (Scheme 3.5).[11] Carbon nanotube-rhodium/gold nanohybrid catalyst systems have been found to be effective for the mild and selective oxidation of naphthols **3.22** for the synthesis of 1,4-NQ.[12a,b] An activated carbon in the presence of O_2 promotes dehydrogenation

of hydroquinone **3.24** followed by Diels-Alder reaction with 1,3-diene **3.25** to afford 1,4-NQs **3.20**.[12c]



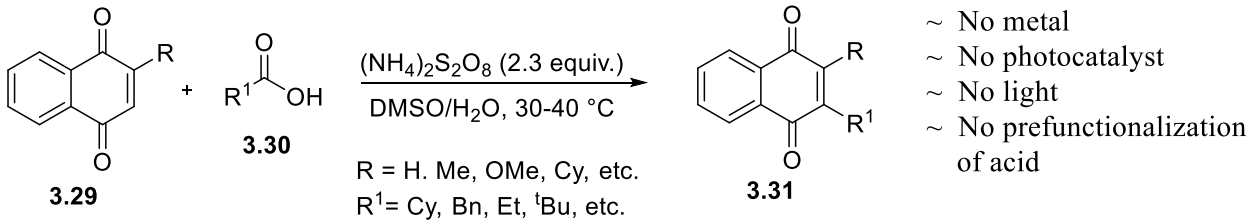
Scheme 3.5. Conventional protocols for the synthesis of 1,4-naphthoquinones

Functionalization of 1,4-naphtoquinones offers ways to make highly substituted analogues. Some methods have been developed and reported in this regard. C-H activation of 1,4-NQs in the presence of oxidant afforded highly substituted naphthoquinones by the reaction with aldehydes or carboxylic acids under mild conditions. Gogoi and co-workers described a method for the synthesis of 2,3-disubstituted 1,4-NQs **3.28** from simple 1,4-NQs **3.26** (Scheme 3.6).[13] Here, benzaldehydes/benzyl alcohols were used for the generation of benzoyl radicals in the presence of TBAI and TBHP in the first stage to afford the product **3.27** which on Suzuki cross-coupling resulted in 2,3-disubstituted 1,4-NQs **3.28**.



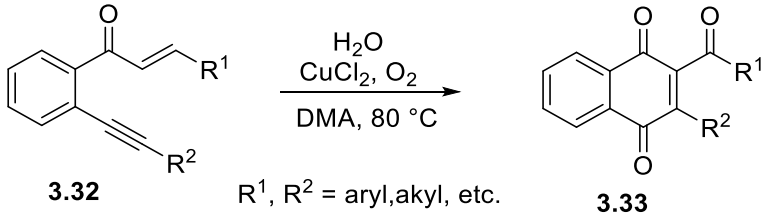
Scheme 3.6. Synthesis of 2,3-disubstituted 1,4-NQs

Recently, Lee and co-workers reported the alkylation of benzoquinones **3.29** with alkylcarboxylic acids **3.30** without the requirement of a metal or a photocatalyst or light or prefunctionalization of acid to make substituted 1,4-naphthoquinones **3.31** (Scheme 3.7).[14] It should be noted that DMSO is very important, probably, to allow the decomposition of persulfates which are byproducts under the reaction conditions in the absence of catalyst or light.



Scheme 3.7. C-H alkylation of 1,4-naphthoquinones using carboxylic acids

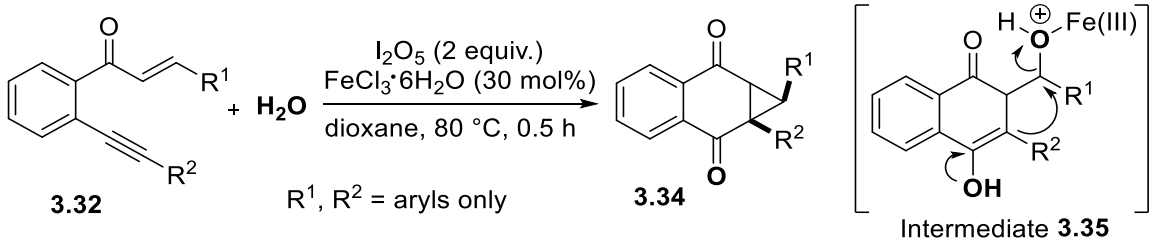
Li group described a protocol for the synthesis of 2,3-disubstituted 1,4-NQs **3.33** from (*E*)-3-aryl-1-(2-(arylethylene)aryl)prop-2-en--ones **3.32**. The reaction involves an intramolecular oxidative 6-*exo-trig* cyclization of 1,6-enyne **3.32** effected by copper catalyst in the presence of water and O_2 (Scheme 3.8).[15] Based on ^{18}O labeling experiments, the source of oxygen was established.



Scheme 3.8. Copper-catalyzed synthesis of 1,4-NQs from 1,6-enynes

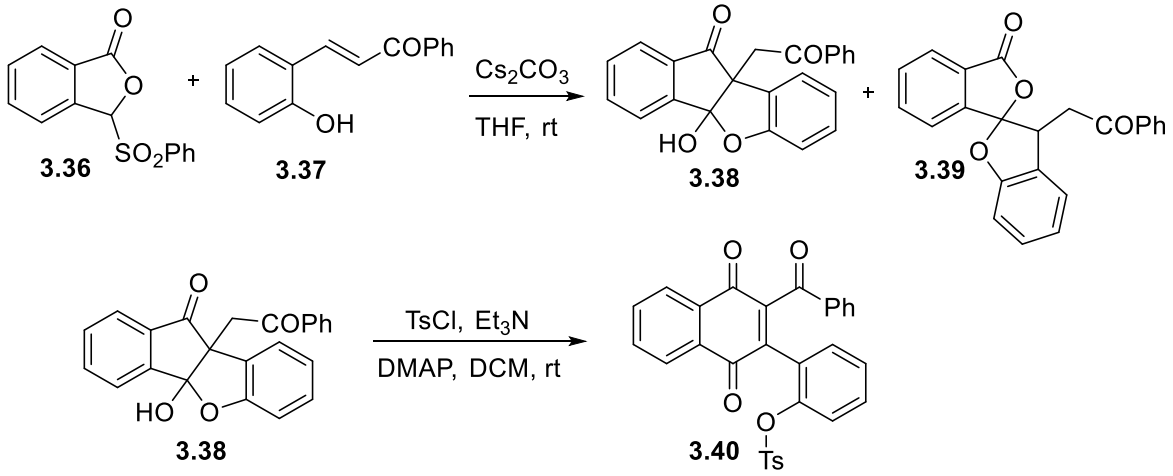
Recently, Liu group developed a method using 1,6-enynes **3.32** to access of highly substituted 1*H*-cyclopropa[*b*]naphthalene-2,7-diones **3.34** in the presence of an iron catalyst and I_2O_5 in dioxane solvent at 80 °C (Scheme 3.9).[16] Here, the iron catalyst, $FeCl_3 \cdot 6H_2O$ goes to high valent (IV or V) in the presence of water and I_2O_5. Addition to 1,6-enyne **3.32** forms intermediate **3.35** and eventually under oxidative conditions offered the final product. Another mechanism involving radical process was also proposed. Initially, I_2O_5 hydrolyze and oxidize water to produce OH radical and I_2. Michael addition of OH radical to **3.32** followed by intramolecular cyclization

could deliver the intermediate **3.35** which transformed into **3.34.** To evaluate the importance of water, ^{18}O labeling experiments were performed.



Scheme 3.9. Domino cyclization of 1,6-enyne towards 1H-cyclopropa[*b*]naphthalene-2,7-diones

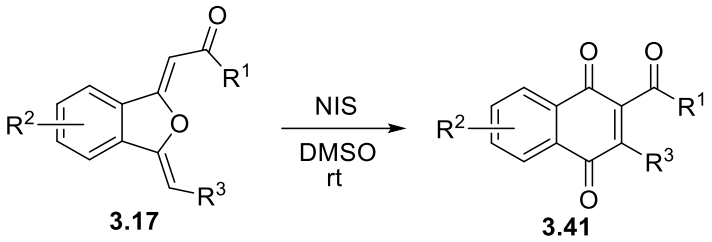
Namboothiri and co-workers reported the synthesis of spiro heterocycles **3.38/3.39** from sulfonylphthalides **3.36** and *o*-hydroxychalcones **3.37** (Scheme 3.10).[17] This method involves cascade of steps to furnish the product. Plausible mechanism involves Michael addition, [4+4] annulation, Dieckmann cyclization, elimination of SO_2Ph and rearrangement to offer fused and spiro heterocycles. It was observed that the fused heterocycle **3.38** converted into 1,4-NQs **3.40** under ambient conditions in the presence of Et_3N and DMAP in DCM.



Scheme 3.10. Multi-cascade process for the synthesis of 1,4-NQs

3.5.2 Background

In the previous section, we had presented the reaction of bis-alkylidene dihydroisobenzofurans with nucleophilic indoles to make bis-indole substituted indane derivatives. We then wished to check the reactivity of bis-alkylidene dihydroisobenzofurans with electrophiles. For this purpose, we reacted them with N-iodosuccinimide (NIS). Interestingly, this reaction led to the formation of substituted 1,4-naphthoquinones (Scheme 3.11). Since 1,4-naphtoquinones are important structural motif in several biologically important compounds (Figure 3.2), we pursued the scope of the transformation and the details are described in the following sections.



Scheme 3.11. Synthesis of 1,4-naphthoquinones from bis-alkylidene dihydroisobenzofurans

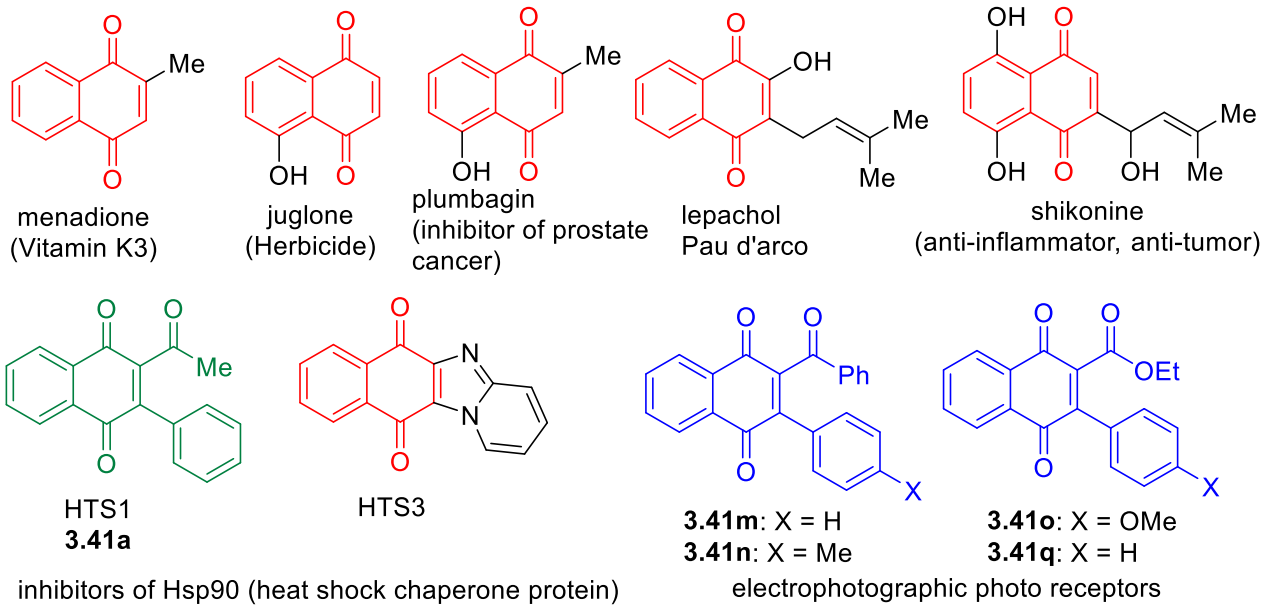
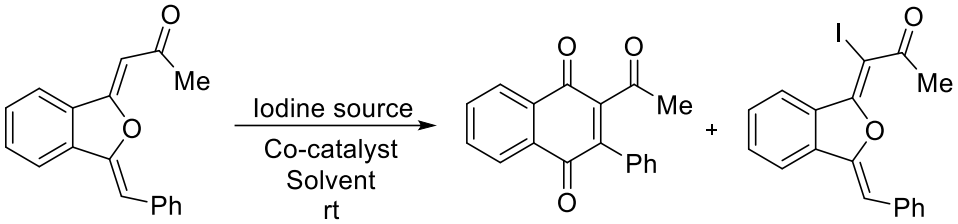


Figure 3.2. Natural products containing 1,4-naphthaquinone structure

3.5.3 Optimization of reaction condition for 1,4-naphthoquinone synthesis

Reaction of bis-alkylidene dihydroisobenzofuran derivative **3.17a** with 5 equivalents of NIS in DCE resulted in two products, 1,4-naphthoquinone derivative **3.41a** and iodinated bis-alkylidene dihydroisobenzofuran **3.42a** in 38% and 29% respectively (Table 3.4, entry 1). This encouraged us to find an appropriate condition that will exclusively yield **3.17a**. In this regard, reactions were tried in the presence of radical initiators and oxidants as additives since the product has one oxygen more than that of the starting bis-alkylidene dihydroisobenzofuran (entries 2-7). However, these attempts were less fruitful as they resulted in either poor yields of the expected product or decomposition. In the presence of $K_2S_2O_8$, the reaction resulted in iodinated bis-alkylidene dihydroisobenzofuran **3.42a** (entry 8). Additives such as H_2O, O_2 (balloon), $Ce(SO_4)_2 \cdot 4H_2O$ did improve the yield moderately (entries 9-11). I_2 in the place of NIS resulted in decomposition (entry 12). We then conducted the reaction in different solvents. Chlorinated solvents such as $CHCl_3$ and CH_2Cl_2 were not effective as they resulted in both **3.41a** and **3.42a** (entries 13-14). Gratifyingly, polar solvents such as DMSO and DMF afforded high yield of the product (entries 15-17), even with 2 equivalents of NIS. Both ethanol and trifluoroethanol were good but not as effective as DMSO/DMF (entries 18 and 19).

Table 3.4 Optimization of reaction condition for 1,4-naphthoquinone formation



3.17a **3.41a** **3.42a**

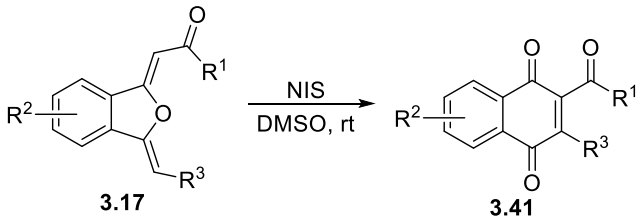
Entry	Iodine source (equiv.)	Additive (equiv.)	Solvent	Time in h	Yield in %	
					3.41a	**3.42a**
1	NIS (5)	-	DCE	4	38	29
2	NIS (5)	AIBN (1.2)	DCE	7	40	30
3	NIS (2)	AIBN (1.2)	DCE	7	45	24
4	NIS (1)	TEMPO (1)	DCE	4	<5	-
5	NIS (1)	AIBN/TEMPO (1)	DCE	5	<5	30
6	NIS (1)	*m*-CPBA (1)	DCE	1	-[a]	-
7	NIS (1)	PhI(OAc) (1)	DCE	3	-[a]	-
8	NIS (1)	$K_2S_2O_8$ (1)	DCE	6	-	52
9	NIS (2)	H_2O (1)	DCE	7	59	trace
10	NIS (2)	O_2 (balloon)	DCE	7	51	trace
11	NIS (2)	$Ce(SO_4)_2 \cdot 4H_2O$	DCE	7	64	trace
12	I_2 (1)	-	DCE	4	-[a]	-
13	NIS (5)	-	$CHCl_3$	5	25	54
14	NIS (5)	-	DCM	5	18	58
15	NIS (5)	-	DMSO	1	83	-
16	**NIS (2)**	-	**DMSO**	**8**	**82**	-
17	NIS (2)	-	DMF	7	78	-
18	NIS (2)	-	EtOH	8	68	-
19	NIS (2)		CF_3CH_2OH	12	61	-
20	NIS (1)	-	DMSO	24	10	48

[a]decomposition of **3.17a** was noted.

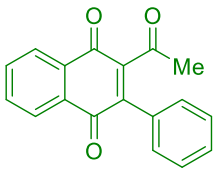
3.5.4 Evaluation of substrate scope

Having a library of bis-alkylidene dihydroisobenzofuran derivatives prepared as described in section 3.3.1, we checked the substrate scope by reacting them with 2 equivalents of NIS in DMSO at room temperature. The results are summarized in Table 3.5. All the attempted reactions completed in 4-8 h resulting the products with yields ranging in 52-92%. bis-Alkylidene dihydroisobenzofuran derivatives having both alkyl and aryl substituents as R^1 and R^2 were tested for the feasibility of product formation. The transformation occurred with all such substituents and resulted in the expected products. Substituents such as 4-F, 2-OMe, 3-OMe, 4-OMe, 4-Me, 4-CHO, on the R^2 aryl group could tolerate the reaction conditions and the correspondingly substituted 1,4-naphthoquinone derivatives could be obtained in good to excellent yields. A highest yield of 92% was noted when the substrate containing 4-F-Ph as R^2 was used (**3.41b**) Remarkably, a CHO group containing 1,4-naphthoquinone derivative **3.41g** was obtained in 74% yield. Simple alkyl and OTBDMS containing alkyl as R^2 group were also employed to get their respective 1,4-naphthoquinone derivatives **3.41k** and **3.41l** in moderate yields. Ester groups attached 1,4-naphthoquinone derivatives (**3.41o - 3.41t**) could also be accessed using this methodology. Finally, substrates having $–OCH_2O-$ and F on the aryl part of isobenzofuran ring were also employed to get the corresponding 1,4-naphthoquinone derivatives (**3.41h**, **3.41j** and **3.41r**) in decent yields. The reaction did not work with substrates such as **3.17k**, **3.17p** and **3.17q** to form the desired products.

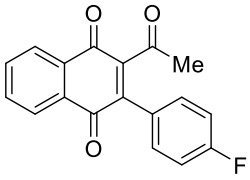
Table 3.5 Substrate scope for 1,4-NQ synthesis



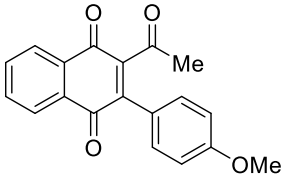
3.17 **3.41**



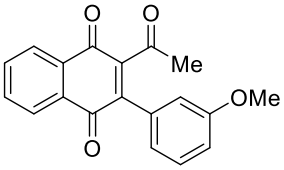
3.41a, 8 h, 82%



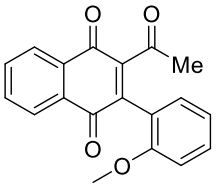
3.41b, 4 h, 92%



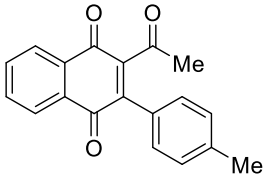
3.41c, 5 h, 72%



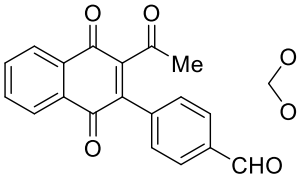
3.41d, 5 h, 79%



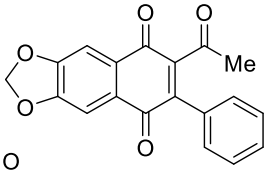
3.41e, 4 h, 68%



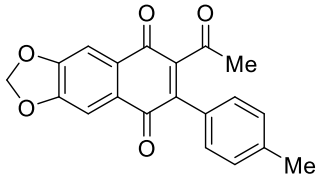
3.41f, 8 h, 90%



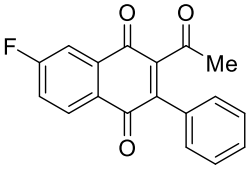
3.41g, 5 h, 74%



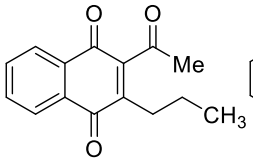
3.41h, 5 h, 78%



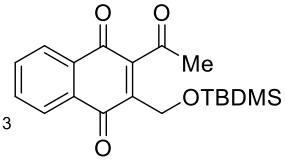
3.41i, 7 h, 58%



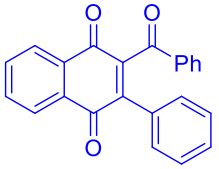
3.41j, 6 h, 60%



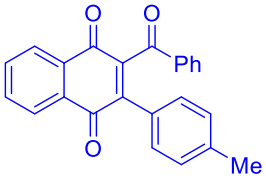
3.41k, 8 h, 59%



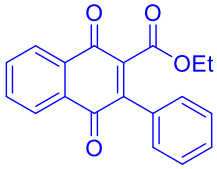
3.41l, 4 h, 68%



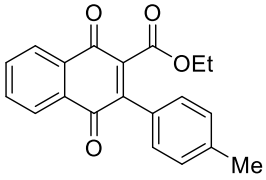
3.41m, 6 h, 72%



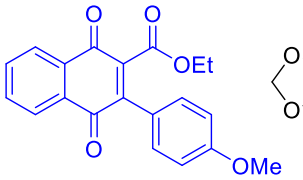
3.41n, 6 h, 70%



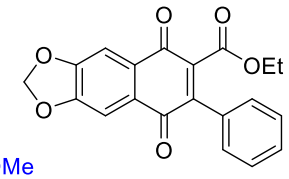
3.41o, 7 h, 70%



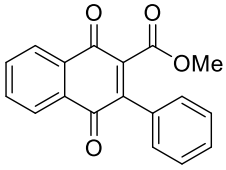
3.41p, 5 h, 68%



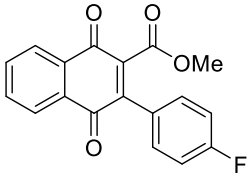
3.41q, 4 h, 56%



3.41r, 4 h, 52%

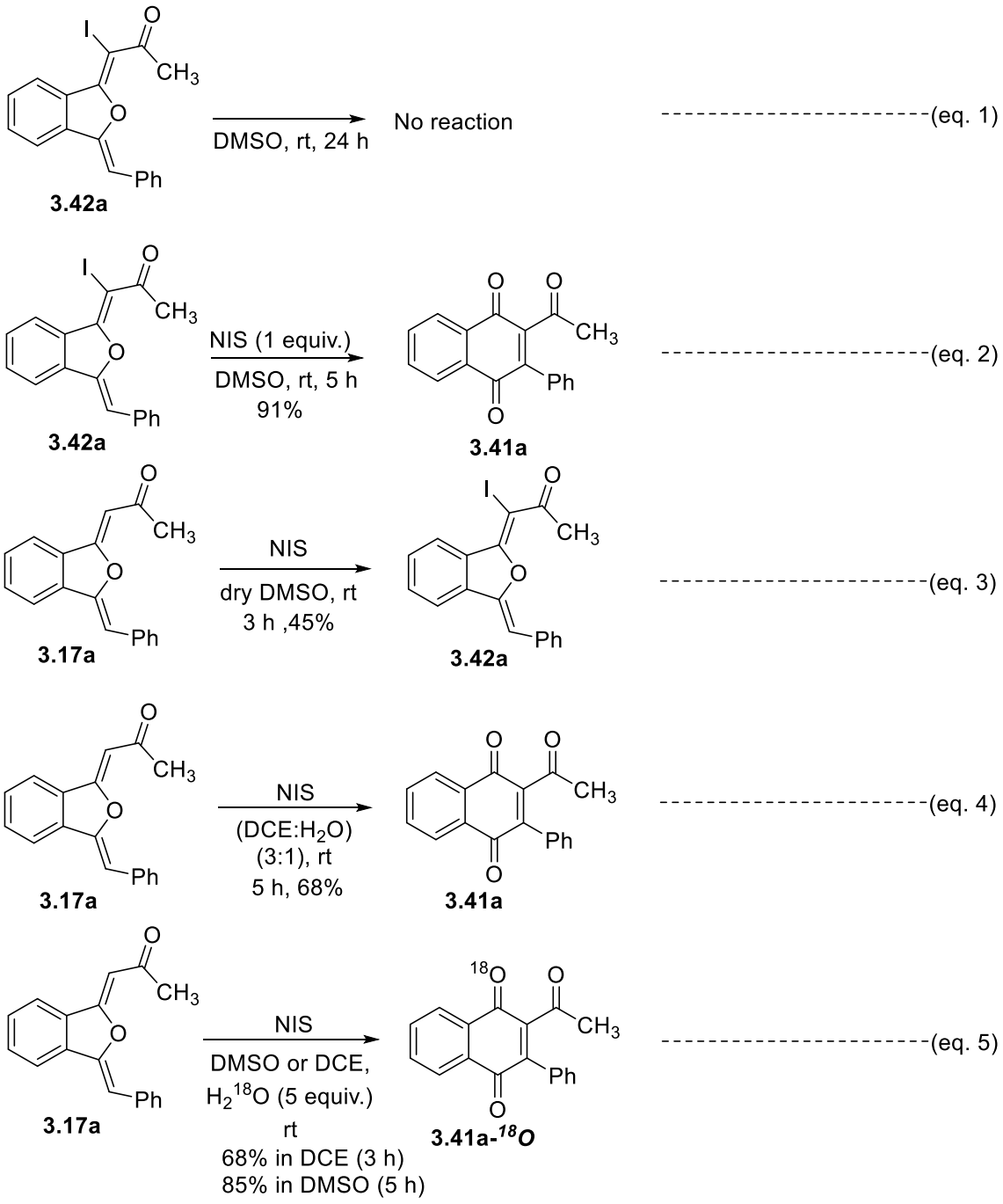


3.41s, 4 h, 75%



3.41t, 5 h, 71%

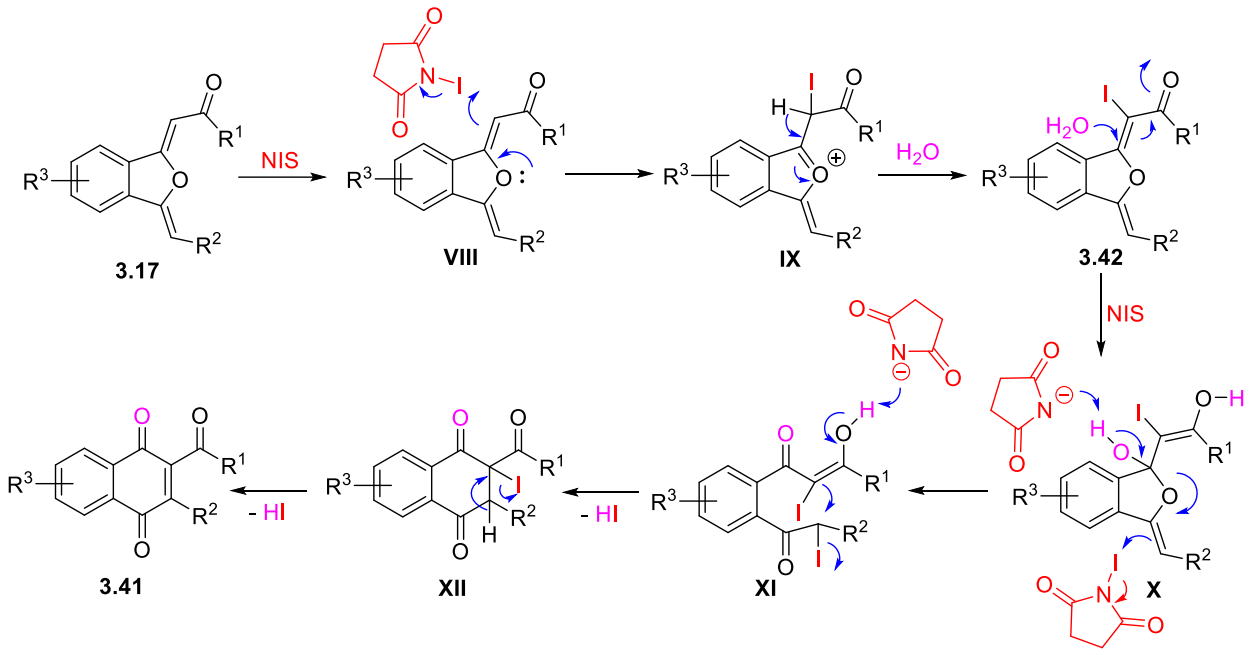
To get insight into the mechanism of this transformation, some control experiments were performed (Scheme 3.12). Stirring the side product **3.42a** at room temperature did not give any product (eq. 1). On the other hand, in the presence of 1 equivalent of NIS, it resulted in 91% yield of **3.41a**, suggesting that compound **3.42a** could be an intermediate (eq. 2). To know the source of oxygen in the reaction, a reaction of **3.41a** with NIS was carried out in dry DMSO. Not surprisingly, the reaction resulted only in the formation of **3.42a** (eq. 3). The reaction of **3.41a** with NIS in DCE/H_2O mixture (3:1) did improve the yield of **3.42a** to 68%. These experiments show that water is, perhaps, the source of oxygen in the product. To confirm this a couple of reactions of **3.41a** with NIS were carried out in the presence of 5 equivalents of $H_2{}^{18}O$ separately in dry DMSO and DCE (eq. 5). In both the cases, the product **3.42a** had one ^{18}O incorporation as revealed by the HRMS analysis. In the product obtained in the reaction conducted in DMSO, some amount of product without ^{18}O incorporation was also there. This may be use to the adventitious water present in DMSO.



Scheme 3.12. Control experiments

3.5.5 Mechanism

Based on the results of control experiments, a mechanism as depicted in Scheme 3.13 could be proposed to explain the product formation. In the presence of NIS, compound **3.17** will undergo iodination at the α-carbon of the enone part assisted by the isobenzofuran oxygen to give intermediate **3.42**. Then a molecule of water can attack at the β-carbon of the α,β-unsaturated carbonyl to give the intermediate which, in the presence of succinamide ion and NIS, will provide the diiodide intermediate **XI**. This intermediate will readily undergo alkylation to form the cyclized fused bicycle **XII**. Elimination of HI could happen instantly to result in the final product **3.41**.



Scheme 3.13. Plausible mechanism

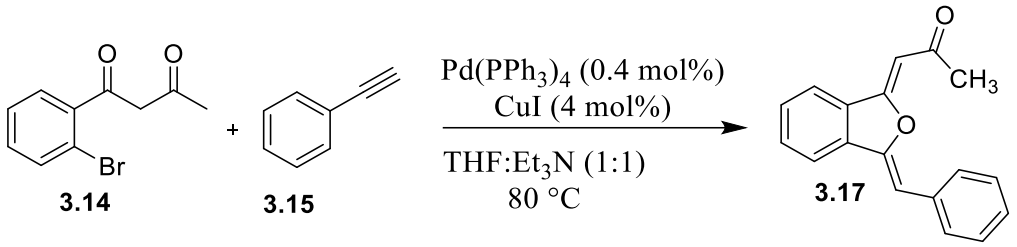
3.6 Conclusions

We have presented the synthesis of bis-alkylidene dihydroisobenzofurans using a palladium catalyzed tandem reaction. These compounds have interesting structural features which we have exploited to react with a nucleophile and an electrophile separately to develop new organic transformations. In both the cases two equivalents of nucleophile/electrophile were used. Reaction with nucleophilic indole gave an access to bis-indole substituted indane derivatives. On the other

hand, electrophilic NIS resulted in 1,4-naphtoquinones when reacted with bis-alkylidene dihydroisobenzofurans. Both the reactions occurred at room temperature and showed very good substrate scope. Based on control experiments, a plausible mechanism for each transformation has been proposed. These bis-alkylidene dihydroisobenzofurans seems to have very good potential to develop new organic transformations to access a wide variety of molecular skeletons.

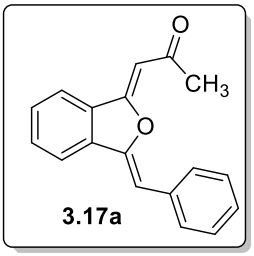
3.7 Experimental section

3.7.1 General Experimental Procedure for isobenzofuran and analytical data



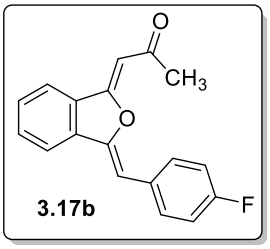
To a stirred solution mixture of 1,3-dikeone **3.14** (1 equiv.) and phenyl acetylene **3.15** (2 equiv.) in THF: Et_3N (1:1) were added $Pd(PPh_3)_4$ (0.4 mol%) and CuI (4 mol %). Then the reaction mixture warmed to 80 °C and allowed until the reaction is completed. It is then concentrated by using rotary evaporator and the crude residue was purified by silica gel column chromatography (EtOAc/hexanes) to afford isobenzofuran **3.17** as yields 26-89%.

(*Z*)-1-((*Z*)-3-Benzylideneisobenzofuran-1(3H)-ylidene) propan-2-one (3.17a):



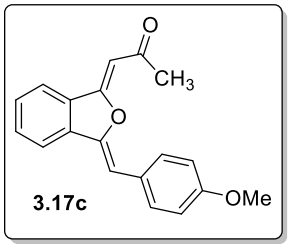
Yellow solid, yield 89%, mp 101-103 °C; R_f = 0.14 (10% EtOAc/hexanes); IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, *J* = 7.4 Hz, 2H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.59 (td, *J* = 7.6, 1.0 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 1H), 6.38 (s, 1H), 5.97 (s, 1H), 2.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.9, 160.9, 150.6, 135.3, 133.7, 132.0, 131.8, 129.6, 129.2, 128.7, 127.7, 121.5, 119.9, 104.1, 99.3, 31.3; HRMS (ESI): calcd. for $C_{18}H_{15}O_2$ $[M + H]^+$ 263.1072; Found 263.1072.

(*Z*)-1-((*Z*)-3-(4-Fluorobenzylidene)isobenzofuran-1(3H)-ylidene)propan-2-one (3.17b):



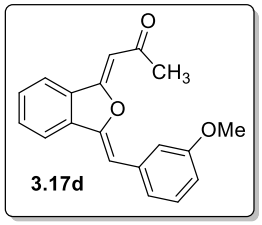
Yellow solid, yield 84%, mp 112-114 °C; R_f = 0.15 (10% EtOAc/hexanes); IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ:7.91-7.88 (m, 2H), 7.69-7.64 (m, 2H), 7.57 (t, *J* = 7.2, Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.13 (td, *J* = 7.2, 1.6 Hz, 2H), 6.32 (s, 1H), 5.98 (s, 1H), 2.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.4, 162.9 (d, *J* = 250.7 Hz), 160.6, 150.1, 135.7, 131.7, 130.8 (d, *J* = 8.0 Hz) , 129.8, 129.5, 121.4, 119.7, 115.7 (d, *J* = 21.0 Hz), 102.8, 98.8, 31.1; HRMS (ESI): calcd. for $C_{18}H_{14}FO_2$ $[M + H]^+$ 281.0978; Found 281.0975.

(*Z*)-1-((*Z*)-3-(4-Methoxybenzylidene)isobenzofuran-1(3H)-ylidene)propan-2-one (3.17c):



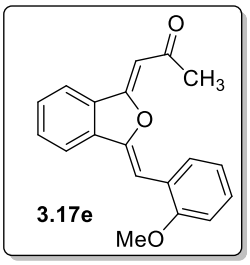
Yellow solid, yield 78%, mp 120-124 °C; R_f = 0.12 (10% EtOAc/hexanes); IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.8 Hz, 2H), 7.62 (dt, *J* = 7.4, 3.6 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.96 (s, 1H), 5.92 (s, 1H), 3.84 (m, 3H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.7, 161.1, 159.2, 149.1, 135.4, 131.7, 131.5, 130.6, 129.0, 126.3, 121.4, 119.5, 114.2, 103.9, 98.6, 55.2, 31.2; HRMS (ESI): calcd. for $C_{19}H_{17}O_3$ $[M + H]^+$ 293.1178; Found 293.1174.

(*Z*)-1-((*Z*)-3-(3-Methoxybenzylidene)isobenzofuran-1(3H)-ylidene)propan-2-one (3.17d):



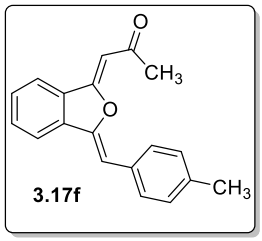
Yellow solid, yield 72%, mp 108-110 °C; R_f = 0.12 (10% EtOAc/hexanes); IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (dd, *J* = 10.0, 7.3 Hz, 2H), 7.56-7.54 (m, 2H), 7.46-7.25 (m, 3H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.31 (s, 1H), 5.95 (s, 1H), 3.91 (m, 3H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.5, 160.6, 159.9, 150.6, 135.3, 134.9, 131.9, 131.7, 129.5, 122.0, 121.4, 119.9, 114.1, 114.0, 104.0, 99.0, 55.4, 31.3; HRMS (ESI): calcd. for $C_{19}H_{17}O_3$ $[M + H]^+$ 293.1178; Found 293.1181.

1-((*Z*)-3-((*Z*)-2-Methoxybenzylidene)isobenzofuran-1(3H)-ylidene)propan-2-one (3.17e):



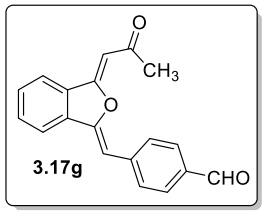
Yellow solid, yield 62%, mp 130-132 °C; R_f = 0.12 (10% EtOAc/hexanes); IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.34 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H) 7.55 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.29-7.26 (m, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.86 (s, 1H), 5.92 (s, 1H), 3.91 (m, 3H), 2.63 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.9, 161.1, 156.7, 150.6, 135.6, 131.8, 131.6, 130.0, 129.3, 129.0, 122.6, 121.4, 120.9, 120.1, 110.5, 99.2, 97.7, 55.5, 31.1; HRMS (ESI): calcd. for $C_{19}H_{17}O_3$ $[M + H]^+$ 293.1178; Found 293.1178.

(*Z*)-1-((*Z*)-3-(4-Methylbenzylidene)isobenzofuran-1(3H)-ylidene)propan-2-one (3.17f):



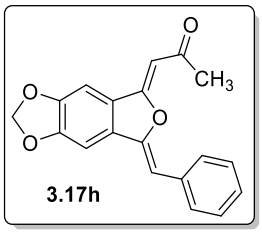
Yellow solid, yield 85%, mp 98-100 °C; R_f = 0.14 (10% EtOAc/hexanes); IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.2 Hz, 2H), 7.65-7.59 (m, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 7.2, Hz, 2H), 6.30 (s, 1H), 5.91 (s, 1H), 2.62 (m, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 161.0, 150.0, 137.8, 135.3, 131.8, 131.7, 130.8, 129.5, 129.3, 129.2, 121.5, 119.7, 104.1, 99.2, 31.2, 21.3; HRMS (ESI): calcd. for $C_{19}H_{17}O_2$ $[M + H]^+$ 277.1229; Found 277.1229.

4-((*Z*)-((*Z*)-3-(2-Oxopropylidene)isobenzofuran-1(3H)-ylidene)methyl)benzaldehyde (3.17g):



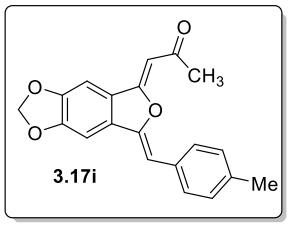
Yellow solid, yield 30%, mp 190-192 °C; R_f = 0.16 (10% EtOAc/hexanes); IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 10.06 (s, 1H), 8.06 (d, *J* = 8.3 Hz, 2H), 7.93 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.61 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.53 (dt, *J* = 7.6, 1.0 Hz, 1H), 6.40 (s, 1H), 6.03 (s, 1H), 2.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.4, 191.5, 160.1, 152.8, 139.9, 134.8, 134.7, 132.3, 132.0, 130.3, 130.1, 129.4, 121.5, 120.3, 102.6, 99.7, 31.3; HRMS (ESI): calcd. for $C_{19}H_{15}O_3$ $[M + H]^+$ 291.1021; Found 291.1019.

(*Z*)-1-(7-((*Z*)-Benzylidene)-[1,3]dioxolo[4,5-f]isobenzofuran-5(7H)-ylidene)propan-2-one (3.17h):



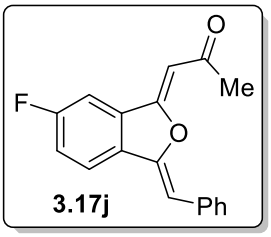
Brown solid, yield 72%, mp 122-124 °C; R_f = 0.11 (10% EtOAc/hexanes); IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, *J* = 7.3 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.00 (s, 1H), 6.92 (s, 1H), 6.14 (s, 1H), 6.09 (s, 2H), 5.74 (s, 1H), 2.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.6, 160.8, 152.0, 150.4, 150.1, 133.7, 131.1, 129.0, 128.6, 127.5, 126.6, 103.0, 102.5, 100.2, 99.7, 98.2, 31.0; HRMS (ESI): calcd. for $C_{19}H_{15}O_4$ $[M + H]^+$ 307.0970; Found 307.0940.

(*Z*)-1-(7-((*Z*)-4-Methylbenzylidene)-[1,3]dioxolo[4,5-f]isobenzofuran-5(7H)-ylidene)propan-2-one (3.17i):



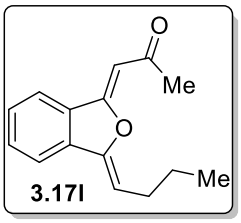
Brown solid, yield 70%, mp 130-132 °C; R_f = 0.14 (10% EtOAc/hexanes); IR (neat): 3041, 2901, 1611, 1257, 1037, 564 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.8 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 2H), 6.97 (s, 1H), 6.90 (s, 1H), 6.11 (s, 1H), 6.08 (s, 2H), 5.72 (s, 1H), 2.60 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.6, 160.1, 152.0, 149.9, 149.8, 137.6, 131.2, 130.8, 129.4, 128.9, 126.4, 103.1, 102.5, 100.1, 98.9, 98.0, 31.0, 21.3; HRMS (ESI): calcd. for $C_{20}H_{17}O_4$ $[M + H]^+$ 321.1127; Found 321.1129.

1-((*Z*)-3-((*Z*)-Benzylidene)-6-fluoroisobenzofuran-1(3H)-ylidene)propan-2-one (3.17j):



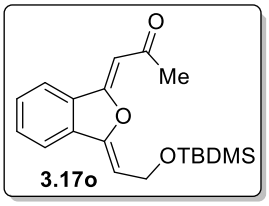
Yellow solid, yield 55%, mp 114-116 °C; R_f = 0.14 (10% EtOAc/hexanes); IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.86 (d, *J* = 7.5 Hz, 2H), 7.67 (q, *J* = 4.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.32-7.27 (m, 3H), 6.30 (s, 1H), 5.89 (s, 1H), 2.63 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.6, 164.4 (d, *J* = 252.7 Hz), 159.7, 159.6, 149.8, 133.8, 133.7, 133.4, 131.4, 131.3, 129.1, 128.7, 127.8, 121.8 (d, *J* = 9.7 Hz), 120.3, 120.1, 107.7 (d, *J* = 25.5 Hz), 103.9, 103.8, 99.7, 31.3; HRMS (ESI) for $C_{18}H_{14}FO_2$ $[M + H]^+$: calcd. 281.0978, Found 281.0975.

1-((1*Z*,3*Z*)-3-Butylideneisobenzofuran-1(3H)-ylidene)propan-2-one (3.17l):



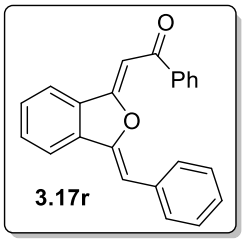
Yellow oil, yield 26%; R_f = 0.18 (10% EtOAc/hexanes); IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.60-7.56 (m, 2H), 7.51 (dt, *J* = 7.4, 1.0 Hz, 1H), 7.42 (dt, *J* = 7.2, 1.5 Hz, 1H), 5.80 (s, 1H), 5.51 (t, *J* = 7.8 Hz, 1H), 2.60 (s, 3H), 2.47 (q, *J* = 7.8 Hz, 2H), 1.58 (sextet, *J* = 7 Hz, 2H), 1.01 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.9, 161.3, 151.7, 134.2, 132.5, 129.1, 121.5, 119.7, 105.3 98.8, 30.9, 27.9, 22.6, 13.8; HRMS (ESI): calcd. for $C_{15}H_{17}O_2$ $[M + H]^+$ 229.1229; Found 229.1234.

11-((1*Z*,3*Z*)-3-(2-((Tert-butyldimethylsilyl)oxy)ethylidene)isobenzofuran-1(3H): ylidene)propan-2-one (3.17o):



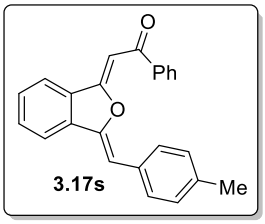
Yellow oil, yield 32%; R_f = 0.11 (10% EtOAc/hexanes); IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.62-7.59 (m, 2H), 7.54 (td, *J* = 7.5, 1.0 Hz, 1H), 7.46 (td, *J* = 7.5, 1.2 Hz, 1H), 5.82 (s, 1H), 5.62 (t, *J* = 6.8 Hz, 1H), 4.66 (d, *J* = 6.8 Hz, 2H); 2.58 (s, 3H), 0.94 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.6, 160.7, 151.1, 133.8, 132.9, 131.7, 129.8, 121.5, 120.2, 104.0, 99.4, 57.9, 30.9, 25.9, 18.3, -5.2; HRMS (ESI): calcd. for $C_{19}H_{26}NaO_3Si$ $[M + Na]^+$ 353.1549; Found 353.1548.

2-((*Z*)-3-((*Z*)-Benzylidene)isobenzofuran-1(3H)-ylidene)-1-phenylethan-1-one (3.17r):



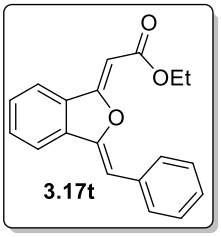
Yellow solid, yield 86%, mp 180-182 °C; R_f = 0.16 (10% EtOAc/hexanes); IR (neat): 2921, 1680, 1450, 1178, 859, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.04-8.02 (m, 2H), 7.94 (d, *J* = 7.2 Hz, 2H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.57-7.41 (m, 7H), 7.29-7.25 (m, 1H), 6.68 (s, 1H), 6.35 (s. 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.2, 162.0, 150.5, 139.9, 135.6, 133.7, 133.5, 132.0, 131.9, 131.0, 129.4, 129.2, 128.7, 128.4, 128.3, 127.9, 127.6, 121.3, 119.8, 104.8, 93.7; HRMS (ESI): calcd. for $C_{23}H_{17}O_2$ $[M + H]^+$ 325.1229; Found 325.1228.

2-((*Z*)-3-((*Z*)-4-Methylbenzylidene)isobenzofuran-1(3H)-ylidene)-1-phenylethan-1-one(3.17s):



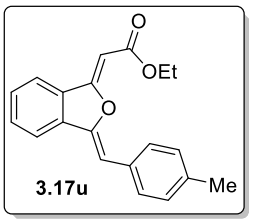
Yellow solid, yield 78%, mp 158-160 °C; R_f = 0.14 (10% EtOAc/hexanes); IR (neat): 2921, 1680, 1450, 1178, 859, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.2 Hz, 2H), 7.84 (d, *J* = 7.6 Hz, 2H), 7.70 (d, *J* = 7.2 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 7.52-7.44 (m, 4H), 7.40-7.36 (m, 2H), 7.23-7.21 (m, 1H), 6.63 (s, 1H), 6.28 (s. 1H), 2.34 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.4, 162.0, 149.9, 139.9, 137.6, 135.6, 131.8, 131.7, 131.6, 130.9, 129.4, 129.3, 128.9, 128.3, 127.8, 121.2, 119.6, 104.9, 93.3, 21.3; HRMS (ESI): for calcd. $C_{24}H_{19}O_2$ $[M + H]^+$ 339.1385; Found 339.1389.

(*Z*)-Ethyl 2-((*Z*)-3-benzylideneisobenzofuran-1(3H)-ylidene)acetate (3.17t)[3k]:



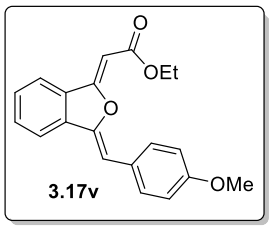
Brown solid, yield 80%, mp 78-80 °C; R_f = 0.16 (10% EtOAc/hexanes); IR (Neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (400 M Hz, $CDCl_3$): δ 7.98 (d, *J* = 7.4 Hz, 2H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.48-7.35 (m, 4H), 7.26 (m, 1H), 6.24 (s, 1H), 5.62 (s, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 M Hz, $CDCl_3$): δ 165.4, 161.5, 150.5, 135.2, 133.9, 131.7, 131.3, 129.2, 129.1, 128.5, 127.3, 121.0, 119.7, 103.6, 88.6, 60.0, 14.4; HRMS (ESI): calcd. for $C_{19}H_{17}O_3$ $[M + H]^+$ 293.1178; Found 293.1168.

(*Z*)-Ethyl 2-((*Z*)-3-(4-methylbenzylidene)isobenzofuran-1(3H)-ylidene)acetate (3.17u):



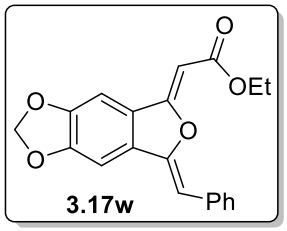
Brown solid, yield 70%, mp 92-94 °C; R_f = 0.16 (10% EtOAc/hexanes); IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.2 Hz, 2H), 7.63 (dd, *J* = 7.6, 10.1 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 2H), 6.28 (s, 1H), 5.65 (s, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 2.37 (s, 3H), 1.44 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 161.7 150.1, 137.5, 135.5, 131.8, 131.4, 131.2, 129.4, 129.3, 129.0, 121.2, 119.7, 103.8, 88.5, 60.0, 21.3, 14.6; HRMS (ESI): calcd. for $C_{20}H_{19}O_3$ $[M + H]^+$ 307.1334; Found 307.1335.

Ethyl 2-((*Z*)-3-((*Z*)-4-methoxybenzylidene)isobenzofuran-1(3H)-ylidene)acetate (3.17v):



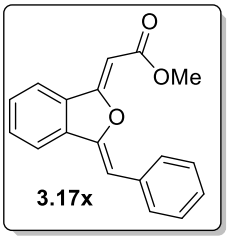
Yellow solid, yield 72%, mp 100-102 °C; R_f = 0.15 (10% EtOAc/hexanes); IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.8 Hz, 2H), 7.64 (dd, *J* = 7.4, 5.2 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.28 (s, 1H), 5.66 (s, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.6, 161.9, 159.1, 149.3, 135.6, 131.6, 131.4, 130.8, 128.8, 126.9, 121.2, 119.5, 114.2, 103.6, 88.2, 60.0, 55.2, 14.6; HRMS (ESI): calcd. for $C_{20}H_{19}O_4$ $[M + H]^+$ 323.1283; Found 323.1276.

Ethyl (*Z*)-2-(7-((*Z*)-benzylidene)-[1,3]dioxolo[4,5-f]isobenzofuran-5(7H)-ylidene)acetate (3.17w):



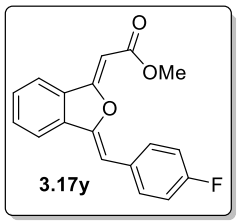
Yellow solid, yield 43%, mp 124-126 °C; R_f = 0.12 (10% EtOAc/hexanes); IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.25 (t, *J* = 7.6 Hz, 1H), 6.95 (s, 1H), 6.88 (s, 1H), 6.06 (s, 1H), 6.04 (s, 2H), 5.42 (s, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 161.5, 151.7, 150.5, 149.9, 134.0, 131.1, 129.1, 128.6, 127.2, 126.5, 102.6, 102.4, 100.0, 99.0, 87.4, 60.0, 14.5; HRMS (ESI): calcd. for $C_{20}H_{17}O_5$ $[M + H]^+$ 337.1076; Found 337.1079.

(*Z*)-Methyl 2-((*Z*)-3-benzylideneisobenzofuran-1(3H)-ylidene)acetate (3.17x)[30]:



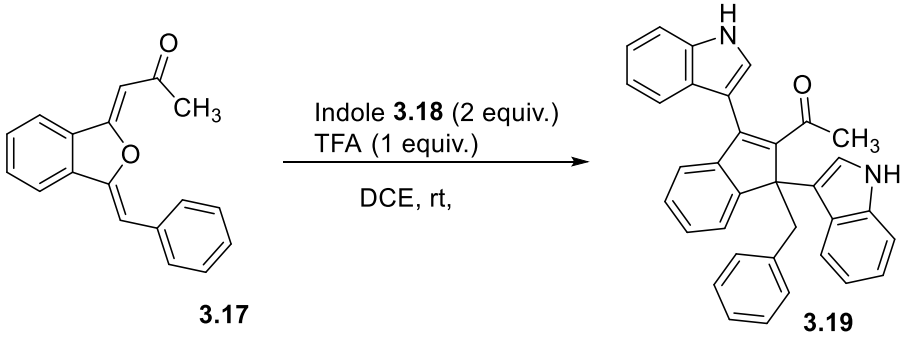
Yellow solid, yield 80%, mp 96-98 °C; R_f = 0.16 (10% EtOAc/hexanes); IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.45-7.39 (m, 3H), 7.35-7.30 (m, 1H), 7.27-7.23 (m, 1H), 6.22 (s, 1H), 5.60 (s, 1H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.6, 161.8, 150.5, 135.2, 133.9, 131.6, 131.3, 129.3, 129.1, 128.5, 127.3, 121.1, 119.7, 103.7, 88.1, 51.2; HRMS (ESI): calcd. for $C_{18}H_{15}O_3$ $[M + H]^+$ 279.1021; Found 279.1021.

Methyl 2-((*Z*)-3-((*Z*)-4-fluorobenzylidene)isobenzofuran-1(3H)-ylidene)acetate (3.17y)[3m,] :



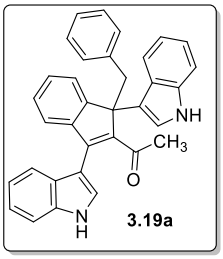
Yellow solid, yield 72%, mp 104-106 °C; R_f = 0.15 (10% EtOAc/hexanes); IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.98 (dd, *J* = 8.8, 5.6 Hz, 2H), 7.62 (dd, *J* = 7.6, 4.0 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 2H), 6.23 (s, 1H), 5.65 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 163.2 (d, *J* = 249.3 Hz), 160.7, 150.2, 150.1, 135.2, 131.6, 131.5, 131.1, 131.0, 130.2 (d, *J* = 6.8 Hz), 129.3, 122.2, 119.7, 115.6 (d, *J* = 25.0 Hz), 102.6, 88.2, 51.3; HRMS (ESI): calcd. for $C_{18}H_{14}FO_3$ $[M + H]^+$ 297.0921; Found 297.0923.

3.7.2 General Experimental Procedure for bisindole indens and analytical data



To a stirred solution of isobenzofuran **3.17** (1 equiv.) and indole **3.18** (2 equiv.) in DCE was added TFA (1 equiv.) at ambient temperature and allowed until the reaction is completed. It is then concentrated by using rotary evaporator and the crude residue was purified by silica gel column chromatography (EtOAc/hexanes) to afford product **3.19** as yields 62-85%

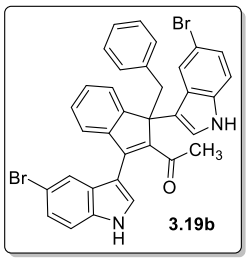
1-(1-Benzyl-1,3-di(1H-indol-3-yl)-1H-inden-2-yl)ethanone 3.19a:



Brown solid, 83%, mp 150-152 °C; R_f = 0.16 (20% EtOAc/hexanes); IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (400 MHz, DMSO-D_6): δ 11.62 (s, 1H), 11.01 (s, 1H), 7.74 (s, 1H), 7.46-7.12 (m, 9H), 7.01-9.89 (m, 6H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.67-6.63 (m, 3H), 4.33 (d, *J* = 12.0 Hz, 1H), 3.88 (d, *J* = 12.0 Hz, 1H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, DMSO-D_6): δ 198.5, 152.5, 145.7, 145.5, 143.9, 137.3, 137.1, 136.7, 129.9 128.6, 127.5, 127.4, 126.9, 126.4, 125.8, 125.5,

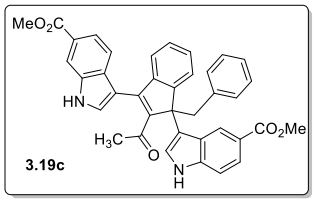
123.9, 123.8, 122.9, 122.2, 121.0, 120.1, 119.8, 119.2, 118.6, 115.9, 112.4, 111.9, 108.9, 79.7, 58.8, 42.5, 30.0; HRMS (ESI): calcd. for $C_{34}H_{27}N_2O$ $[M + H]^+$ 479.2123; Found 479.2123.

1-(1-Benzyl-1,3-bis(5-bromo-1H-indol-3-yl)-1H-inden-2-yl)ethan-1-one 3.19b:



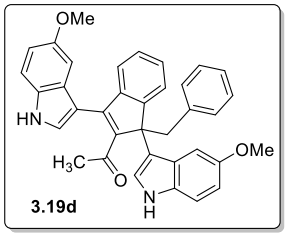
Brown solid, 75%, mp 160-162 °C; R_f = 0.15 (20% EtOAc/hexanes); IR (neat) 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (500 MHz, DMSO-D_6): δ 11.73 (s, 1H), 11.14 (s, 1H), 7.78 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.33-7.19 m, 6H), 7.03-6.85 (m, 6H), 6.59 (d, *J* = 7.0 Hz, 2H), 4.22 (d, *J* = 12.0 Hz, 2H), 1.58 (s, 3H); ^{13}C NMR (125 MHz, DMSO-D_6): δ 197.9, 152.0, 145.9, 143.3, 136.7, 135.5, 135.3, 129.7, 129.2, 128.3, 127.9, 127.4, 127.0, 126.7, 125.3, 125.1, 123.9, 123.5,122.8, 121.4, 121.2, 114.6, 114.0, 112.9, 111.1, 108.4, 58.5, 42.0, 29.8; HRMS (ESI): calcd. for $C_{34}H_{25}$ Br_2N_2O $[M + H]^+$ 635.0334; Found 635.0335.

Methyl3-(2-acetyl-1-benzyl-3-(6-(methoxycarbonyl)-1H-indol-3-yl)-1H-inden-1-yl)-1H-indole-5-carboxylate 3.19c:



Yellow solid, 79%, mp 176-178 °C; R_f = 0.14 (10% EtOAc/hexanes); IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (400 MHz, DMSO-D_6): δ 12.09 (s, 1H), 11.46 (s, 1H), 7.94 (d, *J* = 2.3Hz, 1H), 7.82 (dd, *J* = 1.5 Hz, 8Hz, 1H), 7.74 (s, 1H), 7.60 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.45-7.31 (m, 4H), 7.21 (t, *J* = 7.0 Hz, 1H), 7.07-7.04 (m, 1H), 7.02-6.91 (m, 3H), 6.72 (s, 2H), 4.28 (d, *J* = 12.0 Hz, 1H), 3.92(d, *J* = 12.0 Hz, 1H), 3.42 (s, 6H), 1.68 (s, 3H); ^{13}C NMR (100MHz, DMSO-D_6): δ 197.7, 167.5, 152.2, 146.2, 145.9, 143.6, 139.6, 136.7, 129.8, 128.9, 127.8, 127.4, 126.5, 125.4, 125.0, 123.9, 123.3, 123.0, 122.4, 122.2, 122.1, 121.9, 120.0, 117.8, 112.5, 111.8, 110.4, 58.8, 52.1, 51.8, 30.0; HRMS (ESI): calcd. for $C_{38}H_{31}N_2O_5$ $[M + H]^+$ 595.2233; Found 595.2235.

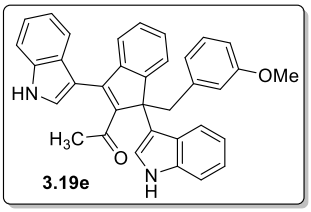
1-(1-Benzyl-1-(5-methoxy-1H-indol-3-yl)-3-(6-methoxy-1H-indol-3-yl)-1H-inden-2-yl)ethan-1-one 3.19d:



Yellow solid, 74%, mp 176-178 °C; R_f = 0.14 (20% EtOAc/hexanes); dr: 1.0:0.34; IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (400 MHz, DMSO-D_6): δ 11.46 (s, 1H), 10.84 (s, 1H), 10.84 (s, 1H), 8.23 (s, 1H), 7.87 (d, *J* = 2.0 Hz, 1H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.57-7.8 (m, 1H),

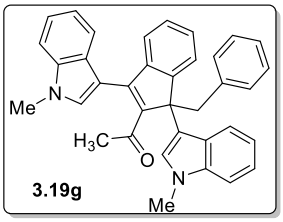
7.39-7.18 (m, 9H), 6.96-6.81 (m, 5H), 6.72-6.58 (m, 4H), 6.21 (s, 1H), 5.08 (s, 1H), 4.31 (d, *J* = 12.0 Hz, 1H), 3.80 (d, *J* = 12.0 Hz, 1H), 3.68 (s, 3H), 3.19 (s, 3H), 3.39 (d, *J* = 12.0 Hz, 1H), 2.80 (d, *J* = 12.0 Hz, 1H), 1.60 (s. 3H); ^{13}C NMR (100 MHz, DMSO-D_6): δ 206.6, 202.3, 198.2, 156.7, 154.3, 152.9, 155.2, 143.6, 137.6, 137.2, 135.8, 134.9, 132.9, 132.2, 131.8, 130.7, 130.3, 129.9, 128.5, 128.2, 128.0, 127.4, 127.2, 127.1, 126.4, 126.3, 125.7, 124.7, 124.5, 124.0, 122.8, 122.5, 118.3, 115.5, 113.0, 112.6, 112.4, 111.0, 110.3, 108.8, 101.4, 64.4, 58.8, 55.8, 49.3, 31.0, 30.1; HRMS (ESI): calcd. for $C_{36}H_{31}N_2O_3$ $[M + H]^+$ 539.2335; Found 539.2338.

1-(1,3-Di(1H-indol-3-yl)-1-(3-methoxybenzyl)-1H-inden-2-yl)ethan-1-one 3.19e:



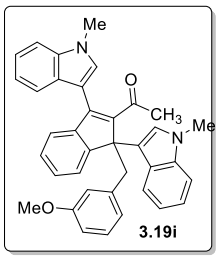
Yellow solid, 75%, mp 160-162 °C; R_f = 0.12 (20% EtOAc/hexanes); dr: 1.0:0.15; IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-D_6): δ 11.59 (s, 1H), 10.97 (s, 1H), 7.72 (s, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.38-7.23 (m,5H), 7.16-7.12 (m, 2H), 6.97-6.87 (m, 4H), 6.77 (d, *J* = 7.5 Hz, 1H), 6.66 (t, *J* = 7.0 Hz, 1H), 6.54 (d, *J* = 7.5 Hz, 1H), 6.30 (d, *J* = 7.5 Hz, 1H), 6.13 (s, 1H), 4.30 (d, *J* = 12.0 Hz, 1H), 3.80 (d, *J* = 12.0 Hz, 1H), 3.42 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (125 MHz, DMSO-D_6): δ 198.2, 158.5, 152.6, 145.5, 144.0, 138.8, 137.0, 136.7, 128.5, 128.3, 127.4, 125.6, 125.4, 123.8, 123.7, 122.9, 122.4, 122.1,121.0, 119.9, 119.7, 119.2, 118.5, 115.8, 115.2, 112.3, 112.0, 111.8, 108.9, 58.8, 54.9, 29.9; HRMS (ESI): calcd. for $C_{35}H_{29}N_2O_2$ $[M + H]^+$ 509.2229; Found 509.2227.

1-(1-Benzyl-1,3-bis(1-methyl-1H-indol-3-yl)-1H-inden-2-yl)ethan-1-one 3.19g:



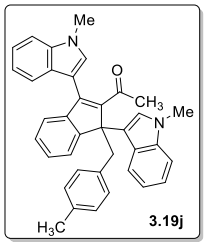
Brown solid, 85%, mp 160-162 °C; R_f = 0.18 (10% EtOAc/hexanes); IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.37-7.15 (m, 9H), 6.75-6.70 (m, 5H), 6.75-6.70 (m, 4H), 4.51 (d, *J* = 12.0 Hz, 1H), 3.83 (s, 6H), 3.71 (d, *J* = 12.0 Hz, 1H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.3, 152.2, 146.2, 145.2, 144.1, 137.3, 136.8, 129.8, 128.3, 128.2, 127.4, 127.3, 127.0, 126.9, 126.1, 126.0, 123.6, 122.9, 122.3, 121.0, 120.6, 119.9, 119.6, 118.4, 115.7, 109.4, 109.2, 109.0, 58.7, 42.8, 33.0, 32.9, 30.2; HRMS (ESI): calcd. for $C_{36}H_{31}N_2O$ $[M + H]^+$ 507.2436; Found 507.2431.

1-(1-(3-Methoxybenzyl)-1,3-bis(1-methyl-1H-indol-3-yl)-1H-inden-2-yl)ethan-1-one 3.19i:



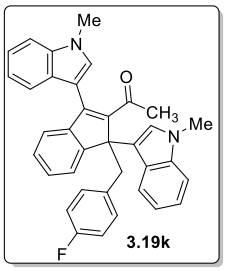
Brown solid, 79%, mp 154-156 °C; R_f = 0.14 (10% EtOAc/hexanes); IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.47 (s, 1H), 7.37-7.16 (m, 8H), 7.08-7.04 (m, 2H), 6.91 (t, *J* = 7.5 Hz, 1H), 6.75 (d, *J* = 7.5Hz, 2H), 6.57 (dd, *J* = 7.5, 2.0 Hz, 1H), 6.41 (d, *J* = 7.5Hz, 1H), 6.14 (s, 1H), 4.48 (d, *J* = 12Hz, 2H), 3.83 (s, 6H), 3.71 (d, *J* = 12Hz, 1H), 3.45 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.2, 158.3, 152.3, 146.2, 145.1, 144.3, 138.3, 137.2, 136.9, 128.3, 128.2, 127.8, 127.4, 127.0, 126.0, 123.6, 123.0, 122.5, 122.0, 121.0, 120.6, 120.0, 119.6, 118.4, 115.1, 114.5, 112.4, 109.3, 109.2, 109.0, 58.7, 54.8, 42.8, 33.0, 32.9, 30.2; HRMS (ESI): calcd. for $C_{37}H_{33}N_2O_2$ $[M + H]^+$ 537.2542; Found 537.2542.

1-(1,3-Bis(1-methyl-1H-indol-3-yl)-1-(4-methylbenzyl)-1H-inden-2-yl)ethan-1-one 3.19j:



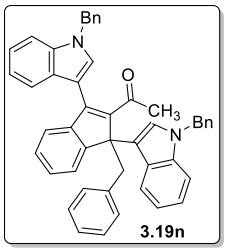
Yellow solid, 82%, mp 142-144 °C; R_f = 0.16 (10% EtOAc/hexanes); IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (s, 1H), 7.41-7.18 (m, 9H), 7.09 (t, *J* = 7.4 Hz, 2H), 6.83-6.78 (m, 4H), 6.62 (d, *J* = 7.4 Hz, 2H), 4.49 (d, *J* = 12.0 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.75 (d, *J* = 12.0 Hz, 1H), 2.22 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.0, 152.4, 146.2, 145.3, 144.2, 137.2, 136.9, 135.4, 133.7, 129.6, 128.4, 127.7, 127.4, 126.9, 126.0, 123.6, 122.2, 120.9, 120.6, 119.8, 119.6, 118.3, 115.3, 109.3, 109.2, 109.0, 58.6, 42.3, 32.9, 32.8, 30.2, 20.9; HRMS (ESI): calcd. for $C_{37}H_{33}N_2O$ $[M + H]^+$ 521.2593; Found 521.2591.

1-(1-(4-Fluorobenzyl)-1,3-bis(1-methyl-1H-indol-3-yl)-1H-inden-2-yl)ethan-1-one 3.19k:



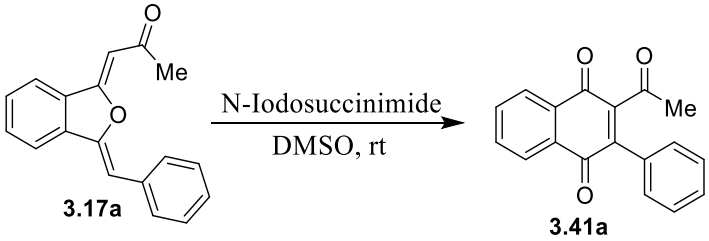
Yellow solid, 80%, mp 158-160 °C; R_f = 0.16 (10% EtOAc/hexanes); IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.44 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.30-7.26 (m, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.77-6.622 (m, 7H), 4.47 (d, *J* = 12.0 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.68 (d, *J* = 12.0 Hz, 1H), 1.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.8, 161.5 (d, *J* = 246.0 Hz), 152.0, 145.1, 114.0, 137.3, 137.0, 132.5, 131.2, 131.0, 128.4, 128.2, 127.3, 127.1, 126.0, 119.6, 118.5, 114.9, 113.7, 113.5, 109.5, 109.0, 58.7, 41.9, 33.0, 32.9, 30.2; HRMS (ESI): calcd. for $C_{36}H_{30}FN_2O$ $[M + H]^+$ 525.2342; Found 525.2339.

1-(1-Benzyl-1,3-bis(1-benzyl-1H-indol-3-yl)-1H-inden-2-yl)ethan-1-one 3.19n:



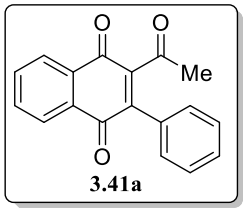
Yellow solid, 80%, mp 196-198 °C; R_f = 0.19 (10% EtOAc/hexanes); IR (neat): 3056, 2909, 1667, 1254, 1205 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.36 (d, *J* = 7.5 Hz, 2H), 7.32-7.05 (m, 18H), 6.98-6.90 (m, 5H), 6.77-6.66 (m, 4H), 5.37-5.22 (m, 4H), 4.47 (d, *J* = 12.0 Hz, 1H), 3.71 (d, *J* = 12.0 Hz, 1H), 1.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.8, 152.0, 146.3, 145.4, 144.0, 137.8, 136.9, 136.8, 136.7, 136.5, 129.7,128.8, 128.6, 128.4, 127.8, 127.4, 127.1, 127.0, 126.8, 126.7, 126.5, 126.3, 125.9, 123.5, 122.9, 122.4, 121.2, 120.6, 120.1, 119.6, 118.7, 115.8, 109.9, 109.8, 109.6, 58.6, 50.1, 50.0, 42.7, 30.1; HRMS (ESI): calcd. for $C_{48}H_{38}NaN_2O$ $[M + Na]^+$ 681.2882; Found 681.2885.

3.7.3 General experimental procedure for 1,4-napthaquinone from isobenzofuran and analytical data of 3a-3t



To the stirred solution of isobenzofuran **3.17** (1 equiv.) in dimethyl sulfoxide (2ML per 100 mg) was added N-iodosuccinimide (2 equiv.) at room temperature. Reaction once completed the reaction mixture diluted with water and extracted with ethyl acetate. The organic phase concentrated by using rotary evaporator and the crude residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford 1,4-napthaqunone derivatives **3.41** yields as 52-94%.

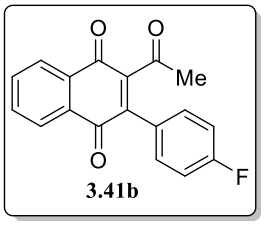
2-Acetyl-3-phenylnaphthalene-1,4-dione (3.41a):



Yellow solid, yield 83%, mp 148-150 °C; R_f = 0.34 (10% EtOAc/hexanes); IR (neat): 2920, 1698, 1668, 1598, 1267, 1205, 792, 718 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.18-8.16 (m, 1H), 8.15-8.12 (m, 1H), 7.83-7.80 (m, 2H), 7.47-7.43 (m, 3H), 7.32-7.30 (m, 2H), 2.12 (s, 3H); ^{13}C NMR (125 MHz,

$CDCl_3$): δ 200.3, 184.3, 183.3, 145.6, 145.2, 134.4, 131.6, 131.5, 130.8, 129.9, 129.7, 128.4, 126.9, 126.3, 31.4; HRMS (ESI): calcd. for $C_{18}H_{13}O_3$ $[M + H]^+$ 277.0865; Found 277.0864.

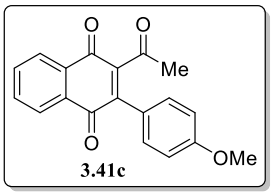
2-Acetyl-3-(4-fluorophenyl) naphthalene-1,4-dione (3.41b):



3.41b

Brown solid, yield 92%, mp 159-161 °C; R_f = 0.32 (10% EtOAc/hexanes); IR (neat): 2921, 1696, 1669, 1559, 1207, 793, 719 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.17 (dq, *J* = 14.0 3.0 Hz, 2H), 7.82 (dd, *J* = 5.0, 3.0 Hz, 2H), 7.31 (dd, *J* = 5.0, 3.0 Hz, 2H), 7.14 (t, *J* = 15 Hz, 2H), 2.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.2, 184.2, 183.2, 163.6 (d, *J* = 257.2 Hz), 145.4, 141.6, 134.4, 134.3, 132.0, 131.9, 131.4 (d, *J* = 4 Hz), 127.0, 126.8, 126.4 (d, *J* = 4.8 Hz), 126.3, 115.6 (d, *J* = 25.6 Hz), 31.4; HRMS (ESI): calcd. for $C_{18}H_{11}FNaO_3$ $[M + Na]^+$ 317.0590; Found 317.0592.

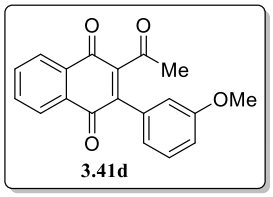
2-acetyl-3-(4-methoxyphenyl) naphthalene-1,4-dione (3.41c):



3.41c

Yellow solid, yield 72%, mp 196-198 °C; R_f = 0.33 (10% EtOAc/hexanes); IR (neat): 2921, 1696, 1669, 1559, 1207, 793, 719 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): δ 8.17-8.11 (m, 2H), 7.82-7.80 (m, 2H), 7.35 (t, *J* = 8Hz, 1H), 7.00 (dq, *J* = 2Hz, 4Hz, 1H), 6.87 (dq, *J* = 2Hz, 4Hz, 1H), 6.85 (dq, *J* = 2Hz, 4Hz, 1H), 3.82 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$): δ 200.2, 184.2, 183.3, 159.3, 145.2, 142.6, 134.6, 134.2, 132.0, 131.6, 131.5, 129.5, 126.9, 126.2, 122.0, 115.8, 115.1, 55.3, 31.4; HRMS (ESI): calcd. for $C_{19}H_{15}O_4$ $[M + H]^+$ 307.0970; Found 307. 0958.

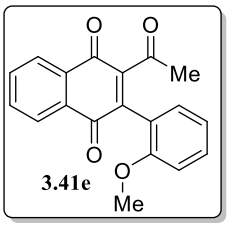
2-Acetyl-3-(3-methoxyphenyl) naphthalene-1,4-dione (3.41d):



3.41d

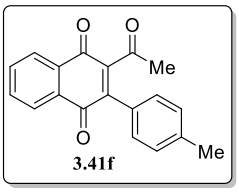
Yellow solid, yield 79%, mp 150-152 °C; R_f = 0.31 (10% EtOAc/hexanes); IR (neat): 2921, 1696, 1669, 1559, 1207, 793, 719 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.17-8.11 (m, 2H), 7.82-7.80 (m, 2H), 7.35 (t, *J* = 8 Hz, 1H), 7.00 (dq, *J* = 4.0, 2.0 Hz, 1H), 6.87 (dq, *J* = 4.0, 2.0 Hz, 1H), 6.85 (dq, *J* = 4.0, 2.0 Hz, 1H), 3.82 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.2, 184.2, 183.3, 159.3, 145.2, 142.6, 134.6, 134.2, 132.0, 131.6, 131.5, 129.5, 126.9, 126.2, 122.0, 115.8, 115.1, 55.3, 31.4; HRMS (ESI): calcd. for $C_{19}H_{14}NaO_4$ $[M + Na]^+$ 329.0790; Found 329.0795.

2-Acetyl-3-(2-methoxyphenyl) naphthalene-1,4-dione (3.41e):



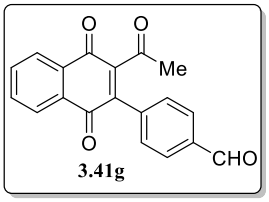
Yellow solid, yield 68%, mp 161-163 °C; R_f = 0.31 (10% EtOAc/hexanes); IR (neat): 2891, 1703, 1669, 1579, 1307, 843, 720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.17-8.15 (m, 2H), 7.82-7.80 (m, 2H), 7.48-7.42 (m, 1H), 7.14 (m, 1H), 7.05-6.98 (m, 2H), 3.80 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.8, 183.4, 183.3, 156.5, 145.8, 142.3, 134.2, 134.0, 131.9, 131.6, 131.3, 130.7, 126.9, 126.2, 120.7, 120.5, 111.0, 55.6, 30.9; HRMS (ESI): calcd. for $C_{19}H_{15}O_4$ $[M + H]^+$ 307.0970; Found 307.0974.

2-Acetyl-3-(p-tolyl)naphthalene-1,4-dione (3.41f):



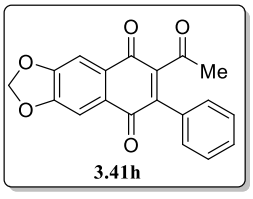
Yellow solid, yield 90%, mp 150-152 °C; R_f = 0.33 (10% EtOAc/hexanes); IR (neat): 2850, 1698, 1668, 1598, 1287, 823, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.17-8.11 (m, 2H), 7.82-7.80 (m, 2H), 7.26-7.20 (m, 4H), 2.40 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.5, 184.4, 183.3, 144.9, 142.7, 140.3, 134.3, 134.2, 131.6, 131.5, 129.7, 129.1, 128.4, 127.9, 127.2, 126.6, 126.2, 116.3, 31.4, 21.4; HRMS (ESI): calcd. for $C_{19}H_{15}O_3$ $[M + H]^+$ 291.1021; Found 291.1018.

4-(3-Acetyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)benzaldehyde (3.41g):



Brown solid, yield 74%, mp 160-162 °C; R_f = 0.35 (10% EtOAc/hexanes); IR (neat): 2921, 2851, 1713, 1665, 1594, 1444, 1355, 1288, 1125, 1069, 974 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 10.08 (s, 1H), 8.18-8.14 (m, 2H), 7.96 (d, *J* = 8.3 Hz, 2H), 7.85-7.83 (m, 2H), 7.49 (d, *J* = 8.2 Hz, 2H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.7, 191.7, 183.7, 183.1, 145.8, 141.6, 136.9, 136.8, 134.6, 134.5, 133.0, 131.4, 130.4, 129.5, 129.4, 127.0, 126.4, 31.6; HRMS (ESI): calcd. for $C_{19}H_{12}O_4Na$ $[M + Na]^+$ 327.0633; Found 327.0633.

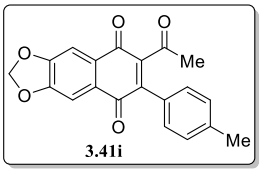
6-Acetyl-7-phenylnaphtho[2,3-d][1,3]dioxole-5,8-dione (3.41h):



Yellow solid, yield 78%, mp 180-182 °C; R_f = 0.31 (10% EtOAc/hexanes); IR (neat): 2919, 1708, 1657, 1592, 1480, 1355, 1218, 1186, 1032, 928 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.47 (s, 1H), 7.45-7.41 (m, 3H),

7.30-7.28 (m, 2H), 6.17 (s, 2H), 2.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.3, 183.2, 182.2, 152.8, 152.6, 144.8, 142.2, 130.9, 129.8, 129.7, 128.7, 128.6, 128.3, 106.3, 105.5, 102.7, 31.4; HRMS (ESI): calcd. for $C_{19}H_{13}O_5$ $[M + H]^+$ 321.0763; Found 321.0764.

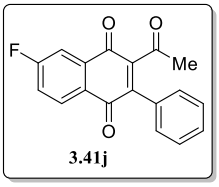
6-Acetyl-7-(p-tolyl)naphtho[2,3-d][1,3]dioxole-5,8-dione (3.41i):



3.41i

Yellow solid, yield 58%, mp 185-187 °C; R_f = 0.32 (10% EtOAc/hexanes); IR (neat): 2920, 1760, 1662, 1594, 1480, 1302, 1218, 1186, 1082, 914 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.47 (s, 1H), 7.24-723 (m, 2H), 7.19-7.18 (m, 2H), 6.17 (s, 2H), 2.39 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.6, 183.3, 182.2, 152.7, 152.6, 144.4, 142.2, 140.2, 129.7, 129.1, 128.7, 128.6, 128.0, 106.3, 105.5, 102.7, 31.4, 21.4; HRMS (ESI): calcd. for $C_{20}H_{15}O_5$ $[M + H]^+$ 335.0919; Found 335.0918.

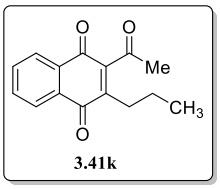
3-Acetyl-6-fluoro-2-phenylnaphthalene-1,4-dione (3.41j):



3.41j

Yellow solid, yield 60%, mp 148-150 °C; R_f = 0.28 (10% EtOAc/hexanes); IR (neat): 2890, 1718, 1652, 1564, 1420, 1332, 1218, 1186, 1052, 898 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23-8.20 (m, 1H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.48-7.43 (m, 4H), 7.31 (d, *J* = 7.2 Hz, 2H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.8, 183.0, 182.2, 167.3 (d, *J* = 257.0 Hz), 145.3, 142.9, 134.1 (d, *J* = 8.4 Hz), 130.6, 130.4, 130.3, 130.1, 129.7, 128.4, 128.2, 121.7, 121.5, 113.9 (d, *J* = 24.8 Hz), 31.3; HRMS (ESI): calcd. for $C_{18}H_{12}FO_3$ $[M + H]^+$ 295.0770; Found 295.0774.

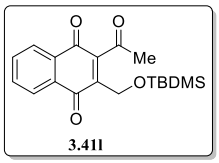
2-Acetyl-3-propylnaphthalene-1,4-dione (3.41k)[18]:



3.41k

Yellow oil, yield 59%; R_f = 0.34 (10% EtOAc/hexanes); IR (neat): 2922, 1713, 1665, 1594, 1444, 1355, 1268, 1125, 1070, 974 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12-8.05 (m, 2H), 7.78-7.74 (m, 2H), 2.50 (s, 3H), 2.45(t, *J* = 7.8 Hz, 2H), 1.55-1.51 (m, 2H), 0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.3, 184.4, 183.7, 146.2, 145.4, 134.1, 134.0, 131.8, 131.4, 126.6, 126.0, 31.9, 29.6, 23.2, 14.4; HRMS (ESI): calcd. for $C_{15}H_{15}O_3$ $[M + H]^+$ 243.1021; Found 243.1023.

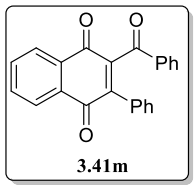
2-Acetyl-3-(((tert-butyldimethylsilyl)oxy)methyl)naphthalene-1,4-dione (3.41l):



3.41l

Yellow oil, yield 68%; R_f = 0.25 (10% EtOAc/hexanes); IR (neat): 2921, 1698, 1669, 1598, 1461, 1358, 1207, 1163, 1016, 908 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.94-7.92 (m, 2H), 7.63-7.61 (m, 2H), 4.67 (s, 2H), 2.35 (s, 3H), 0.79 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.5, 184.9, 183.9, 144.4, 143.1, 134.2, 131.4, 131.3, 126.2, 59.4, 32.6, 25.9, 18.7, -5.8; HRMS (ESI): calcd. for $C_{19}H_{25}O_4Si$ $[M + H]^+$ 345.1522; Found 345.1521.

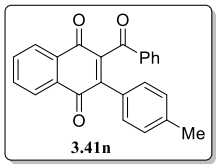
2-Benzoyl-3-phenylnaphthalene-1,4-dione (3.41m)[15]:



3.41m

White solid, yield 72%; R_f = 0.27 (10% EtOAc/hexanes); IR (neat): 2922, 1713, 1665, 1595, 1444, 1322, 1268, 1157, 1070 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.22-8.21 (m, 1H), 8.15-8.13 (m,1H), 7.84-7.82 (m, 2H), 7.78-7.76 (m, 2H), 7.51-7.46 (m, 1H), 7.37-7.33 (m, 3H), 7.27-7.26 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.9, 184.2, 183.8, 144.7, 143.9, 135.8, 134.4, 134.2, 133.9, 131.9, 131.7, 131.0, 129.8, 129.6, 129.0, 128.6, 128.0, 127.0, 126.4; HRMS (ESI): calcd. for $C_{23}H_{15}O_3$ $[M + H]^+$ 339.1021, Found 339.1023.

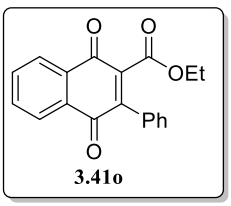
2-Benzoyl-3-(p-tolyl)naphthalene-1,4-dione (3.41n)[15]:



3.41n

White solid, yield 70%; R_f = 0.29 (10% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$): δ 8.23-8.21 (m, 1H), 8.14-8.12 (m, 1H), 7.83-7.78 (m, 4H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.1, 184.3, 183.8, 144.8, 143.6, 139.9, 135.9, 134.3, 134.2, 133.9, 132.0, 131.7, 129.8, 129.2, 129.1, 128.8, 128.7, 128.3, 128.1, 127.0, 126.4, 21.3.

Ethyl 1,4-dioxo-3-phenyl-1,4-dihydronaphthalene-2-carboxylate (3.41o)[19]:

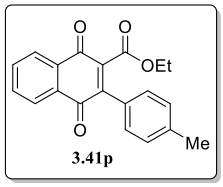


3.41o

Yellow solid, yield 70%, mp 138-140 °C; R_f = 0.16 (10% EtOAc/hexanes); IR (neat): 2924, 1716, 1662, 1563, 1413, 1323, 1288, 1114, 1034, 908 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.19-8.16 (m, 2H) , 7.84-7.80 (m, 2H), 7.47-7.42 (m, 3H), 7.41-7.39 (m, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.07 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 184.0, 181.9, 164.0, 144.4, 139.4, 134.3 134.2, 131.6, 131.4,

131.3, 129.7, 129.2, 128.0, 126.9, 126.4, 61.9, 13.7; HRMS (ESI): calcd. for $C_{19}H_{15}O_4$ $[M + H]^+$ 307.0970; Found 307.0966.

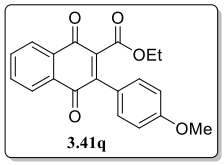
Ethyl 1,4-dioxo-3-(p-tolyl)-1,4-dihydronaphthalene-2-carboxylate (3.41p):



3.41p

Yeloow solid, yield 68%, mp 153-155 °C; R_f = 0.16 (10% EtOAc/hexanes); IR (neat): 2923, 1716, 1678, 1593, 1463, 1324, 1289, 1115, 909 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.16-8.14 (m, 2H), 7.81-7.77 (m, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 1.11 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.2, 182.0, 164.2, 144.2, 144.0, 139.1, 134.2, 134.1, 131.7, 131.4, 129.2, 128.8, 128.4, 126.9, 126.3, 61.8, 21.4, 13.8; HRMS (ESI): calcd. for $C_{20}H_{17}O_4$ $[M + H]^+$ 321.1127; Found 321.1129.

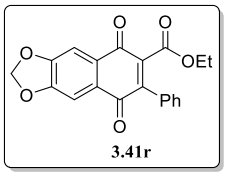
Ethyl 3-(4-methoxyphenyl)-1,4-dioxo-1,4-dihydronaphthalene-2-carboxylate (3.41q):



3.41q

White solid, yield 56%, mp 171-173 °C; R_f = 0.15 (10% EtOAc/hexanes); IR (neat): 2923, 1736, 1653, 1583, 1423, 1224, 1189, 1015, 954 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.16-8.13 (m, 2H), 7.80-7.78 (m, 2H), 7.37 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.58 (s, 3H), 1.14 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 184.4, 182.0, 164.4, 161.0, 144.0, 138.7, 134.2, 131.7, 131.5, 131.2, 127.0, 126.3, 123.6, 113.7, 61.9, 55.3, 13.9; HRMS (ESI): calcd. for $C_{20}H_{17}O_5$ $[M + H]^+$ 337.1076; Found 337.1032.

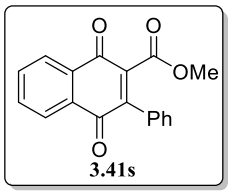
Ethyl 5,8-dioxo-7-phenyl-5,8-dihydronaphtho[2,3-d][1,3]dioxole-6-carboxylate (3.41r):



3.41r

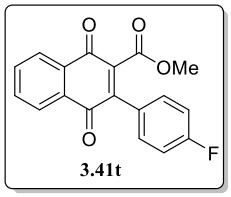
White solid, yield 52%, mp 185-187 °C; R_f = 0.12 (10% EtOAc/hexanes); IR (neat): 2920, 1734, 1667, 1510, 1461, 1290, 1178, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.50 (s, 1H), 7.43-7.41 (m, 3H), 7.37-7.35 (m, 2H), 6.16 (s, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 1.04 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.9, 180.9, 164.0. 152.7, 152.6, 144.0, 138.9, 131.4, 129.7, 129.3, 128.7, 128.5, 128.0, 106.3, 105.6, 102.7, 61.8, 13.7; HRMS (ESI): calcd. for $C_{20}H_{15}O_6$ $[M + H]^+$ 351.0869; Found 351.0818.

Methyl 1,4-dioxo-3-phenyl-1,4-dihydronaphthalene-2-carboxylate (3.41s):



White solid, yield 75%, mp 140-142 °C; R_f = 0.15 (10% EtOAc/hexanes); IR (neat): 2922, 1617, 1592, 1561, 1289, 1133, 908 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.17-8.15 (m, 2H), 7.82-7.80 (m, 2H), 7.45-7.44 (m, 3H), 7.39-7.37 (m, 2H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.9, 181.9, 164.2, 144.5, 139.2, 134.3, 134.2, 131.6, 131.4, 131.3, 129.9, 129.1, 128.1, 127.0, 126.4, 52.6; HRMS (ESI): calcd. for $C_{18}H_{13}O_4$ $[M + H]^+$ 293.0814; Found 293.0815.

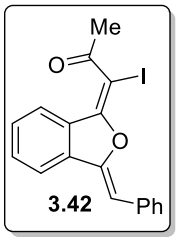
Methyl 3-(4-fluorophenyl)-1,4-dioxo-1,4-dihydronaphthalene-2-carboxylate (3.41t):



White solid, yield 71%, mp 149-151 °C; R_f = 0.15 (10% EtOAc/hexanes); IR (neat): 2922, 1754, 1617, 1592, 1561, 1289, 1133, 908 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.16-8.14 (m, 2H), 7.82-7.80 (m, 2H), 7.38 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.14 (t, *J* = 8.6 Hz, 2H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.8, 181.7, 164.5, 163.6 (d, *J* = 251.5 Hz), 143.4, 139.4, 134.4 (d, *J* = 8.8 Hz), 131.4 (q, *J* = 8.5 Hz), 127.3, 127.2, 127.0, 126.4, 115.(d, *J* = 22.8 Hz), 52.6; HRMS (ESI): calcd. for $C_{18}H_{12}FO_4$ $[M + H]^+$ 311.0720; Found 311.0693.

3.7.4 Analytical data of compound 3.42

1-((Z)-3-((Z)-benzylidene)isobenzofuran-1(3H)-ylidene)-1-iodopropan-2-one (3.42):



Yellow solid, mp 120-122 °C; R_f = 0.61 (10% EtOAc/hexanes); IR (neat): 2922, 1754, 1617, 1592, 1561, 1289, 1133, 908 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.59 (d, *J* = 8.1 Hz, 1H), 7.97 (d, *J* = 7.5Hz, 2H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.55 (dt, *J* = 7.5, 0.8 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 3H), 7.30 (t, *J* = 7.5 Hz, 1H), 6.38 (s, 1H), 2.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.6, 162.4, 148.8, 138.2, 131.7, 129.7, 129.4, 128.7, 128.6, 127.6, 126.3, 119.3, 103.8, 72.6, 31.9; HRMS (ESI): calcd. for $C_{18}H_{14}IO_2$ $[M + H]^+$ 389.0038; Found 389.0036.

3.8 Reference

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Chapter 3

3.9 Representative spectra

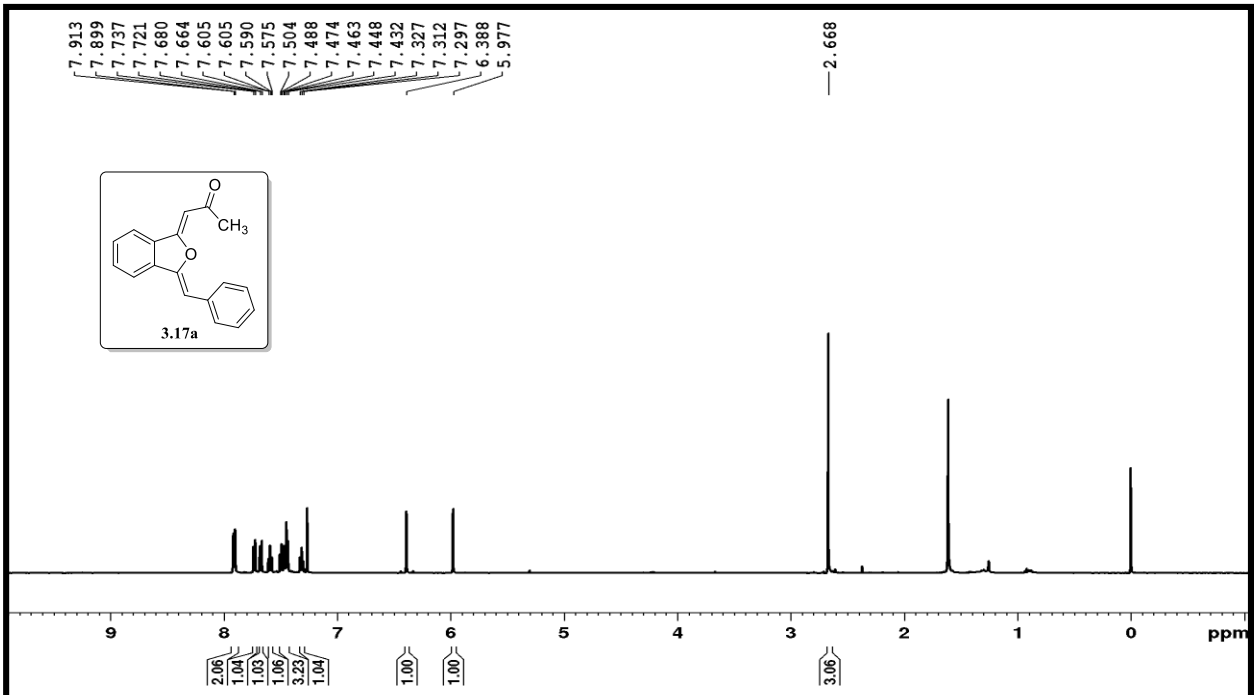

Figure 3.3: ^{1}H NMR spectra of Compound **3.17a**

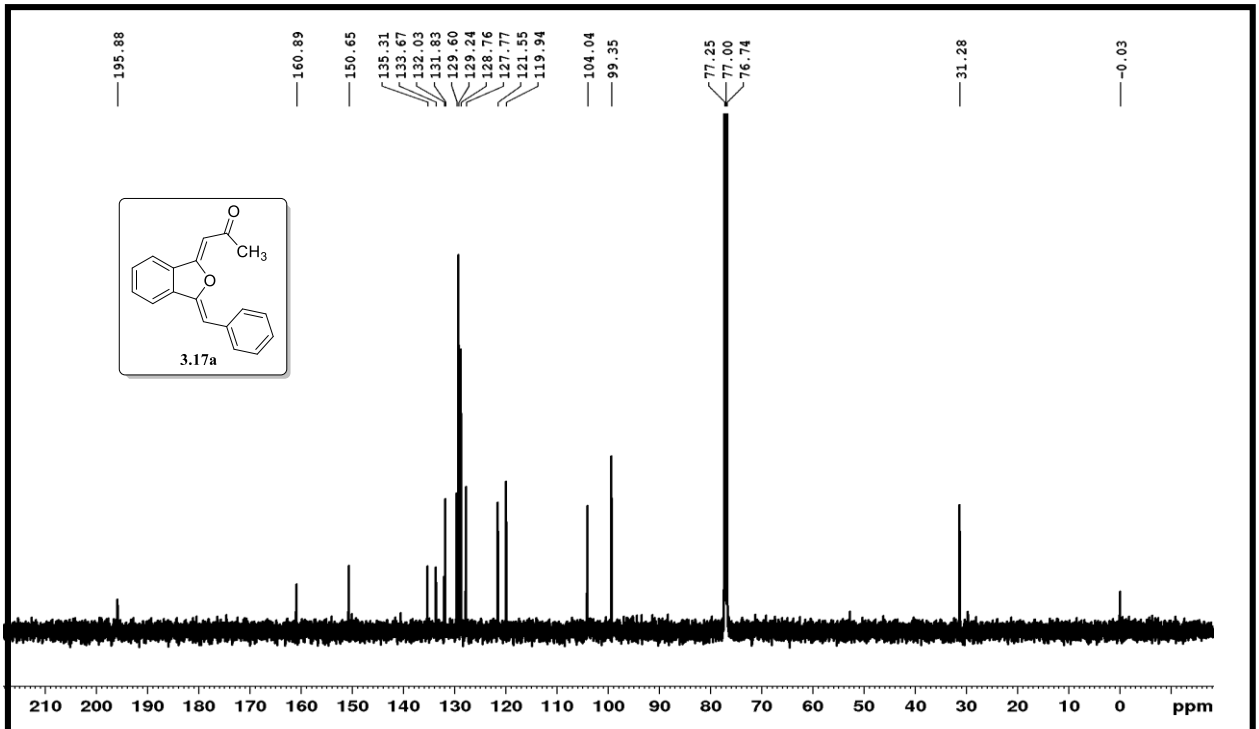

Figure 3.4: ^{13}C NMR spectra of Compound **3.17a**

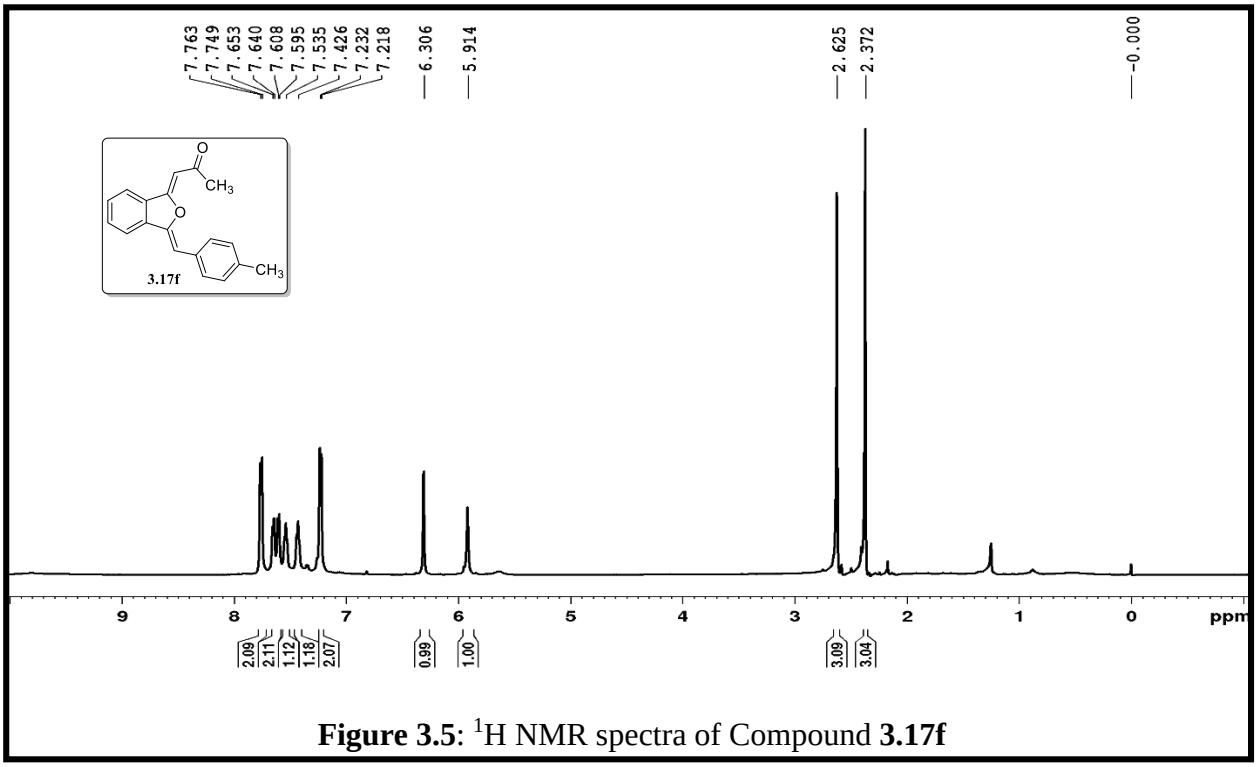

Figure 3.5: ^{1}H NMR spectra of Compound **3.17f**

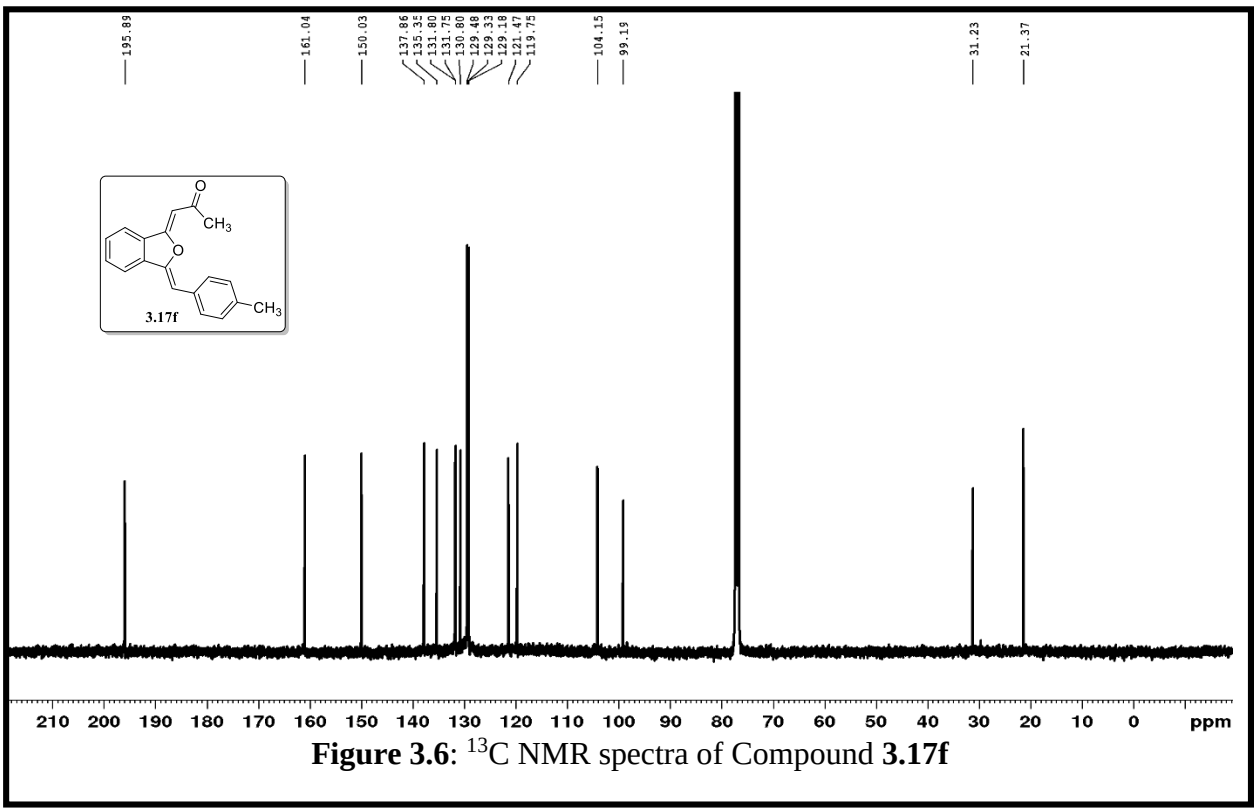

Figure 3.6: ^{13}C NMR spectra of Compound **3.17f**

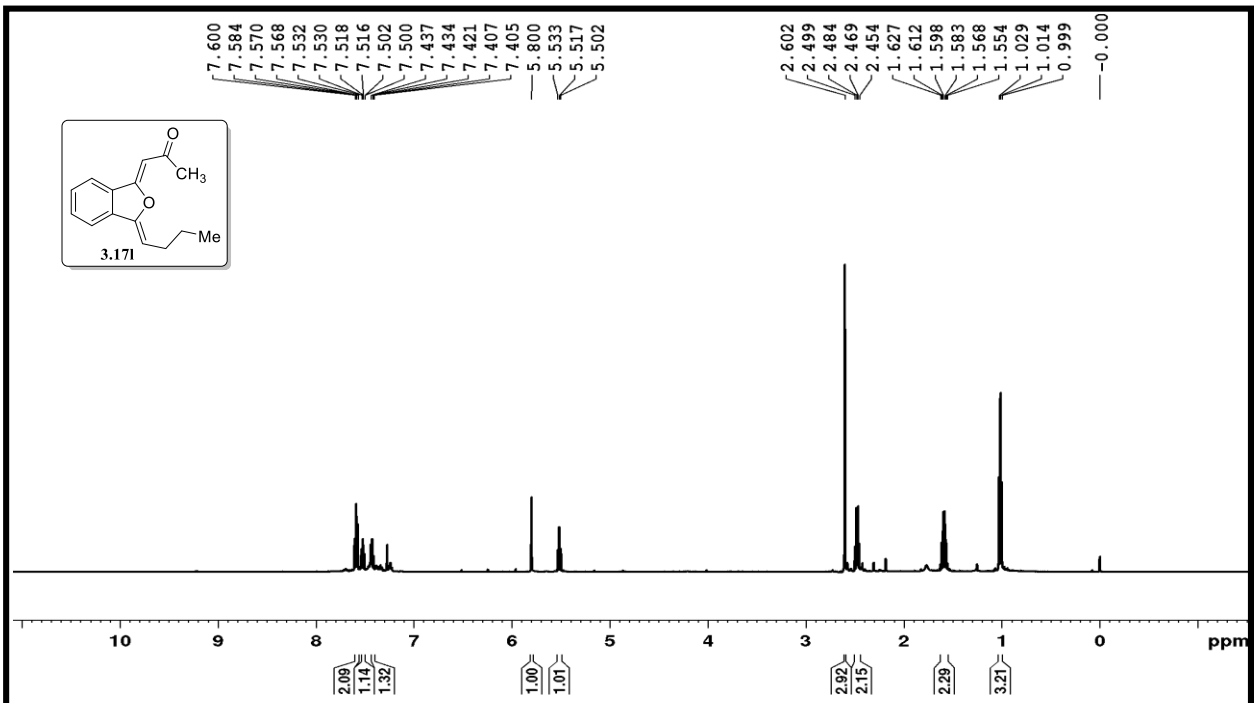

Figure 3.7: ^{1}H NMR spectra of Compound **3.17l**

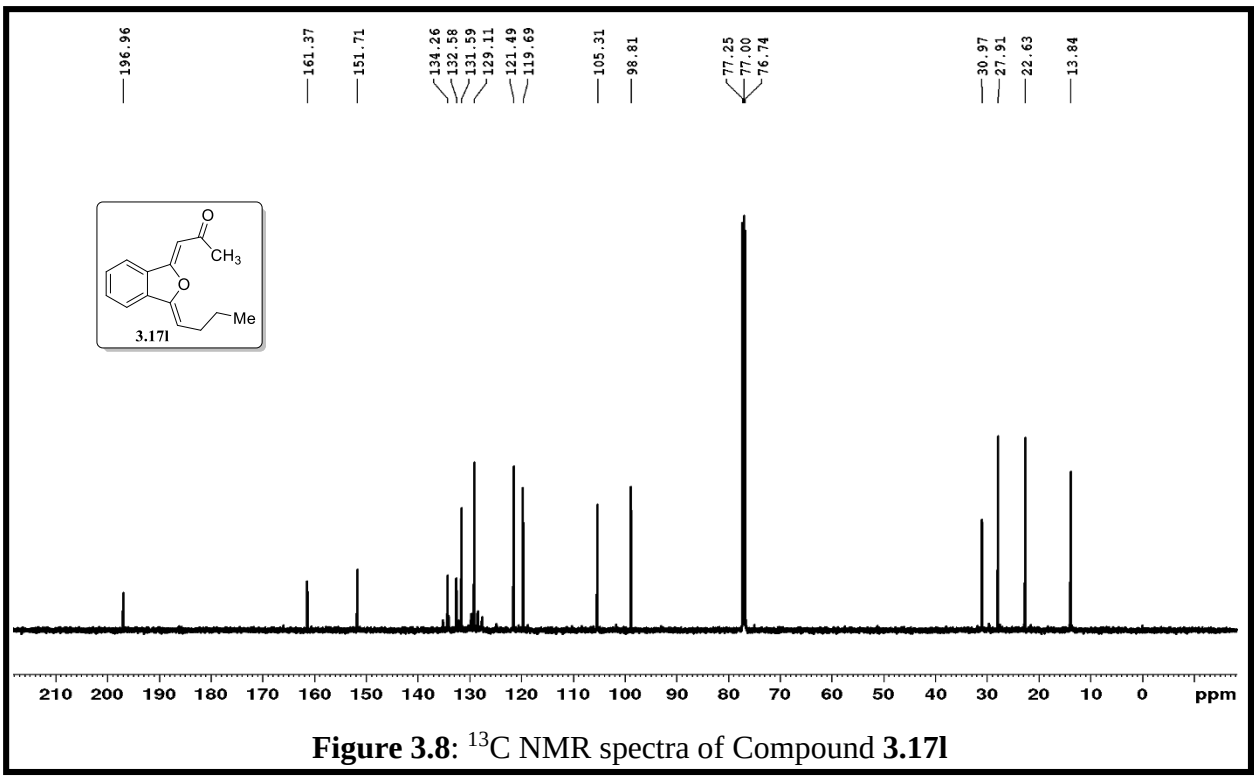

Figure 3.8: ^{13}C NMR spectra of Compound **3.17l**

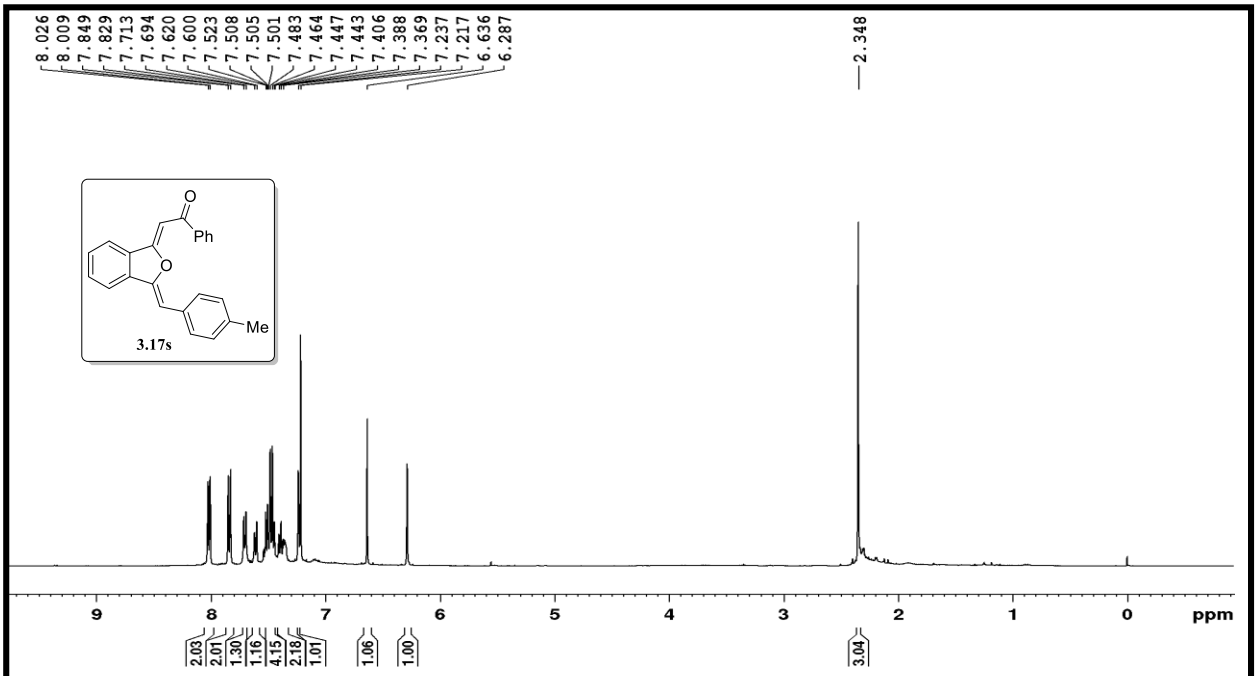

Figure 3.9: ^{1}H NMR spectra of Compound **3.17s**

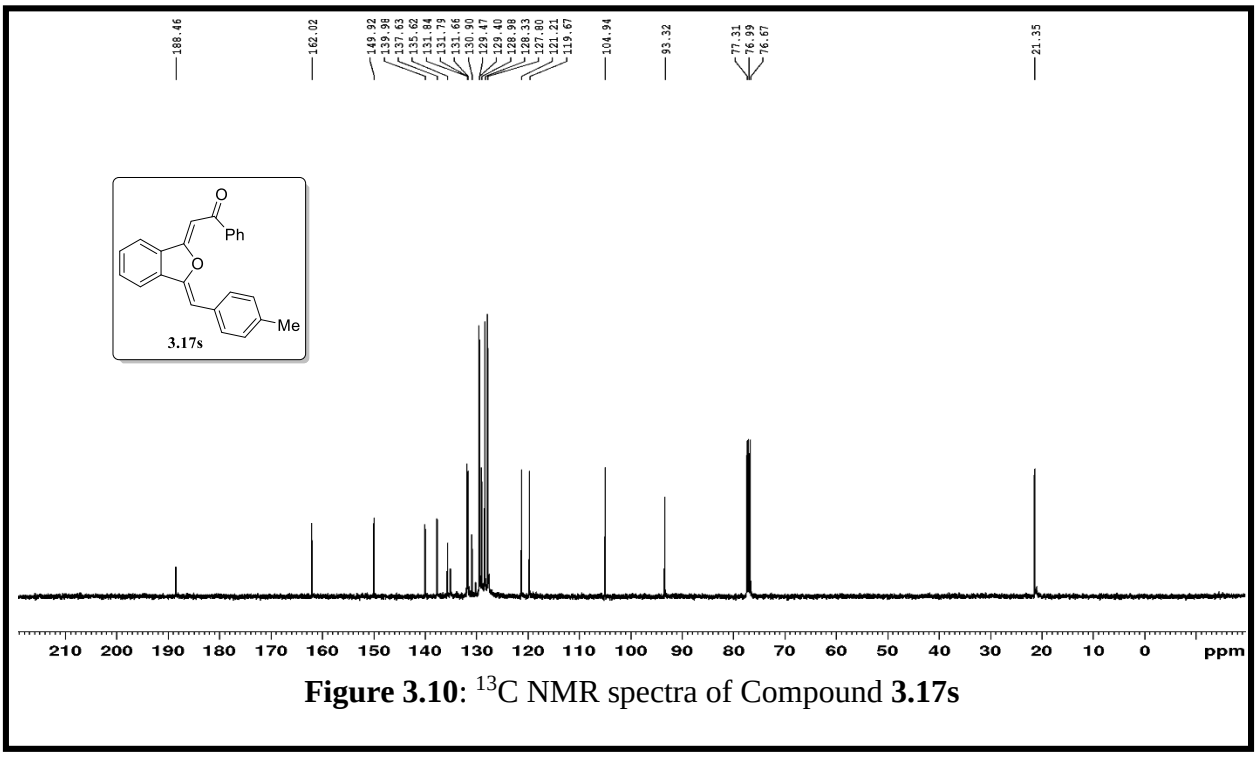

Figure 3.10: ^{13}C NMR spectra of Compound **3.17s**

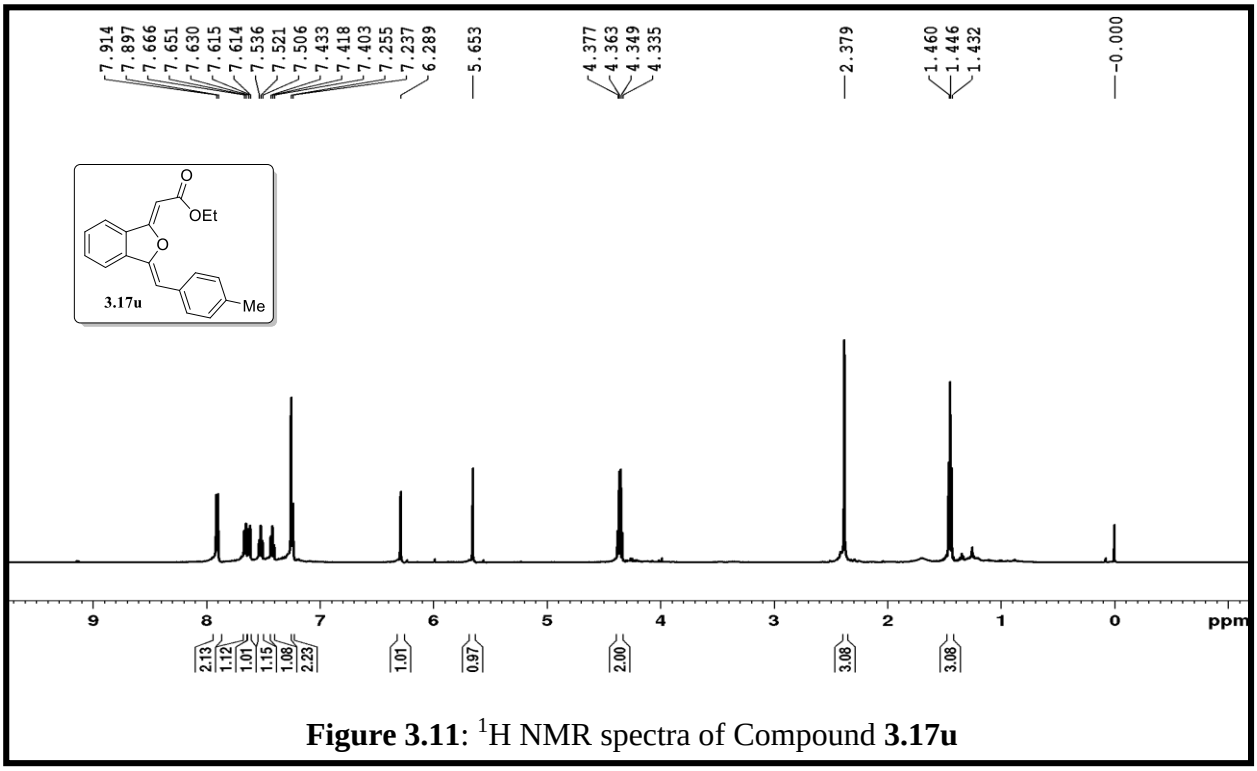

Figure 3.11: ^{1}H NMR spectra of Compound **3.17u**

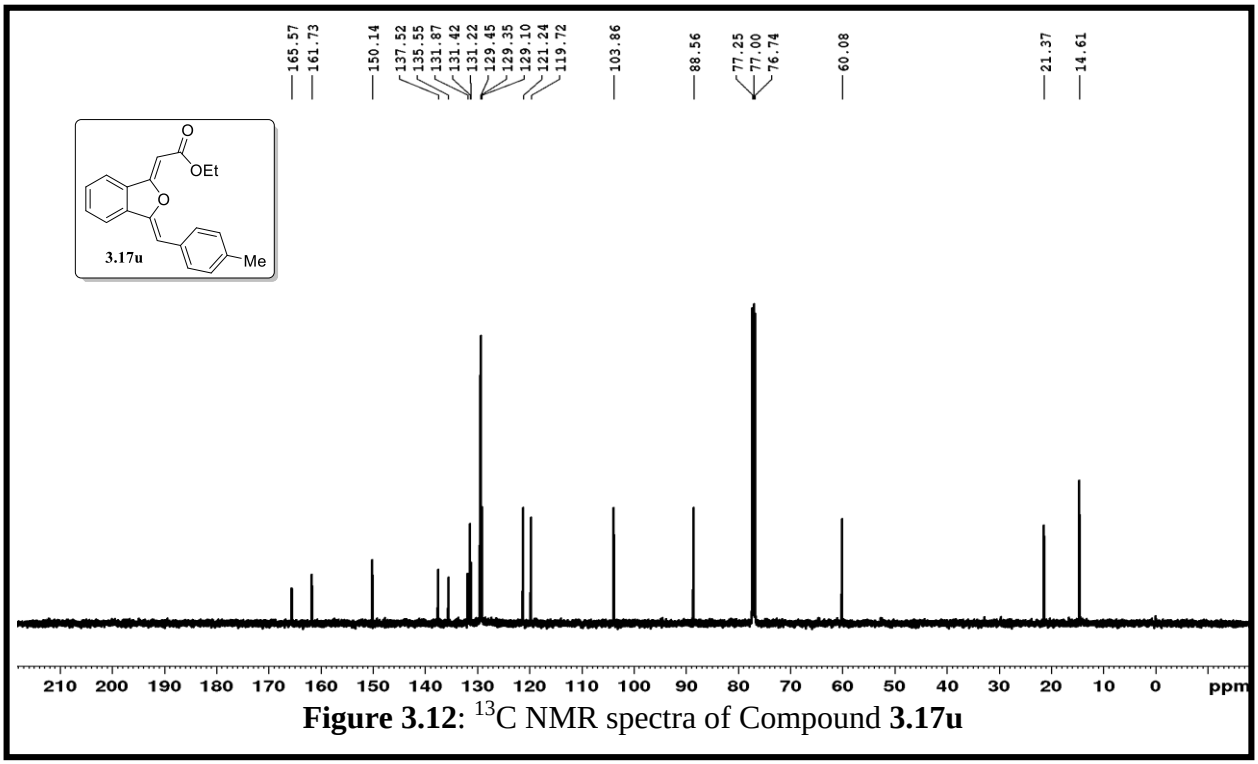

Figure 3.12: ^{13}C NMR spectra of Compound **3.17u**

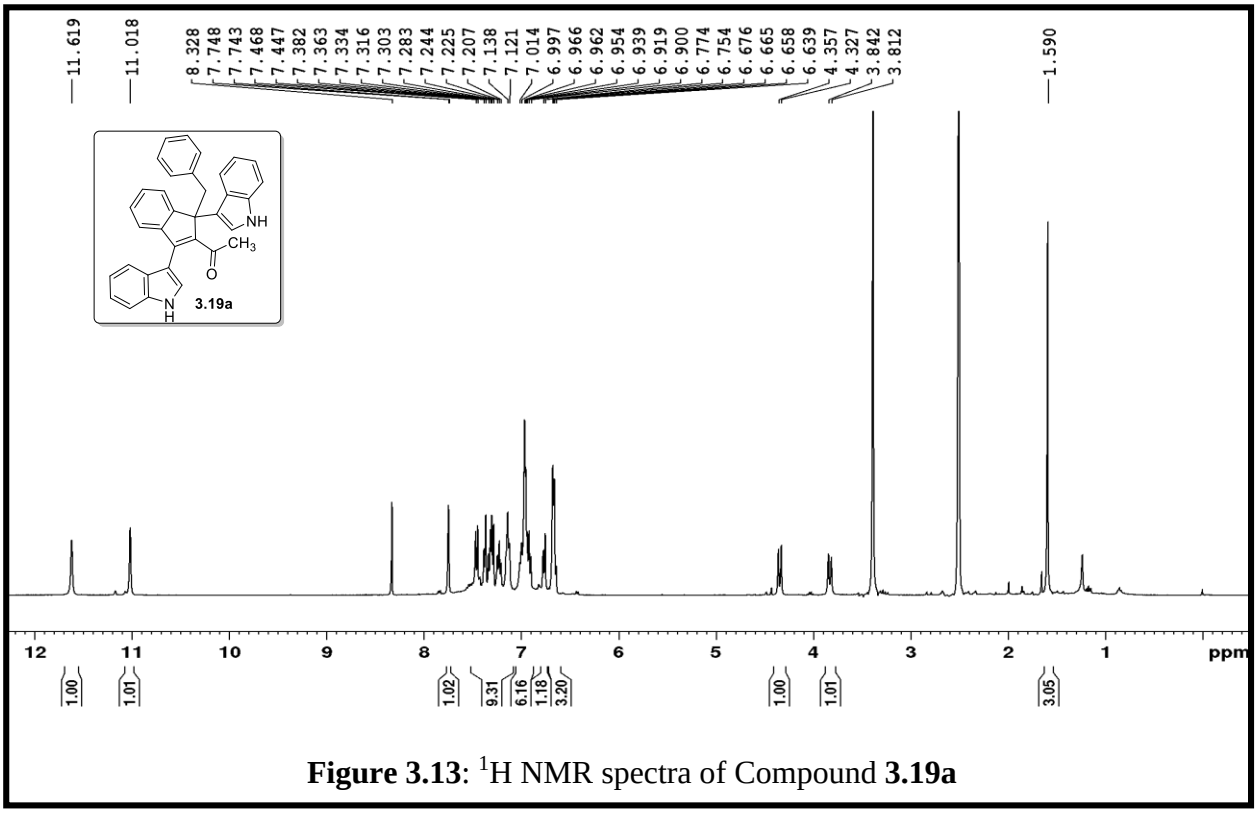

Figure 3.13: ^{1}H NMR spectra of Compound **3.19a**

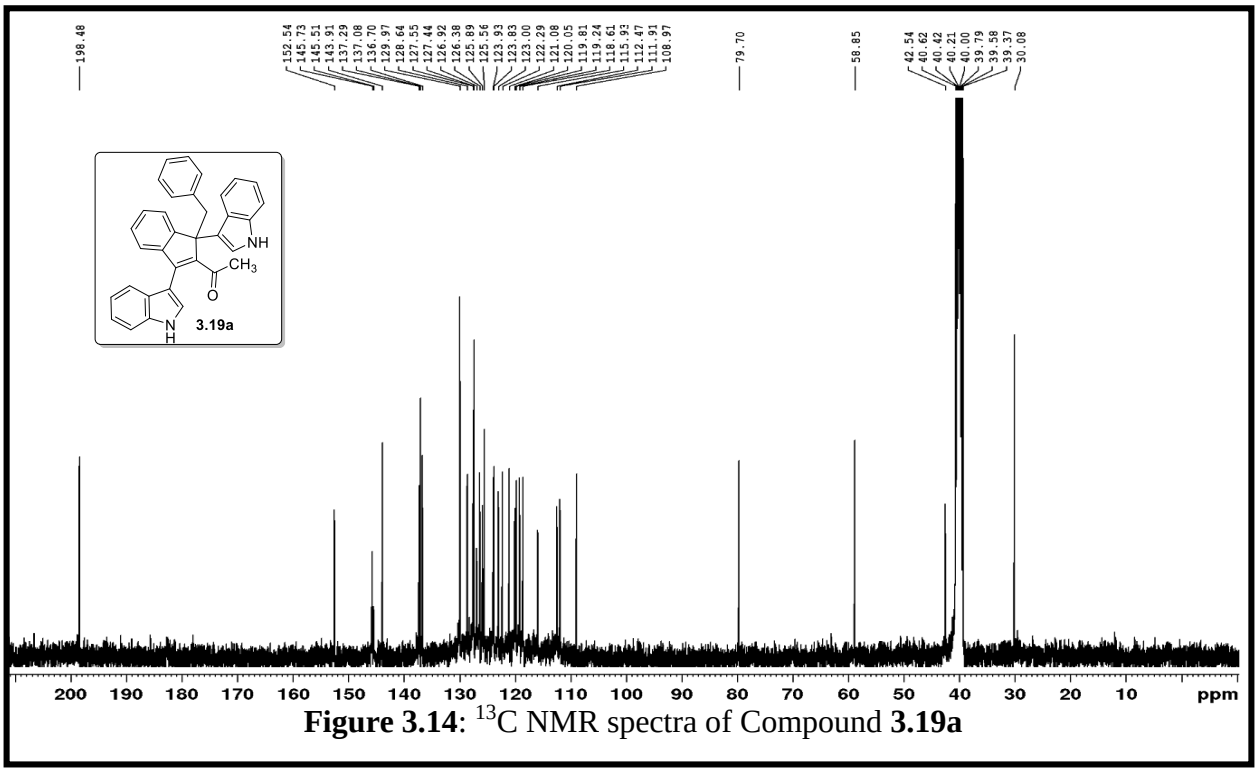

Figure 3.14: ^{13}C NMR spectra of Compound **3.19a**

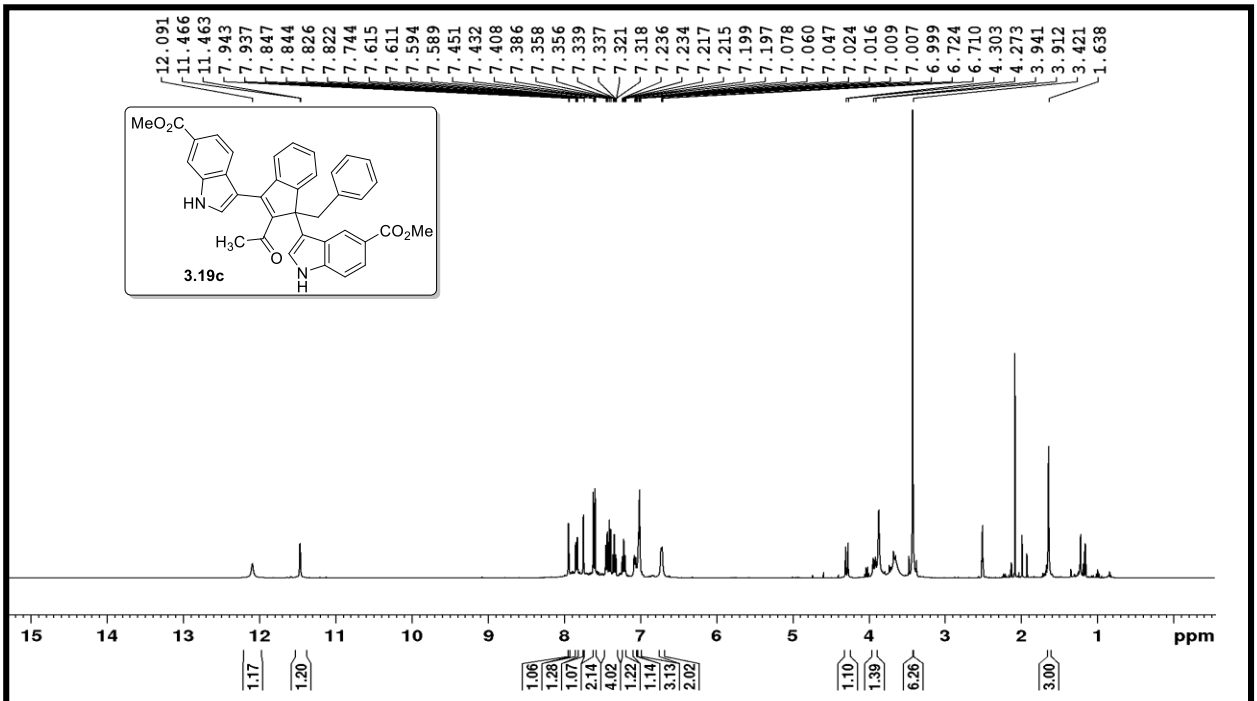

Figure 3.15: ^{1}H NMR spectra of Compound **3.19c**

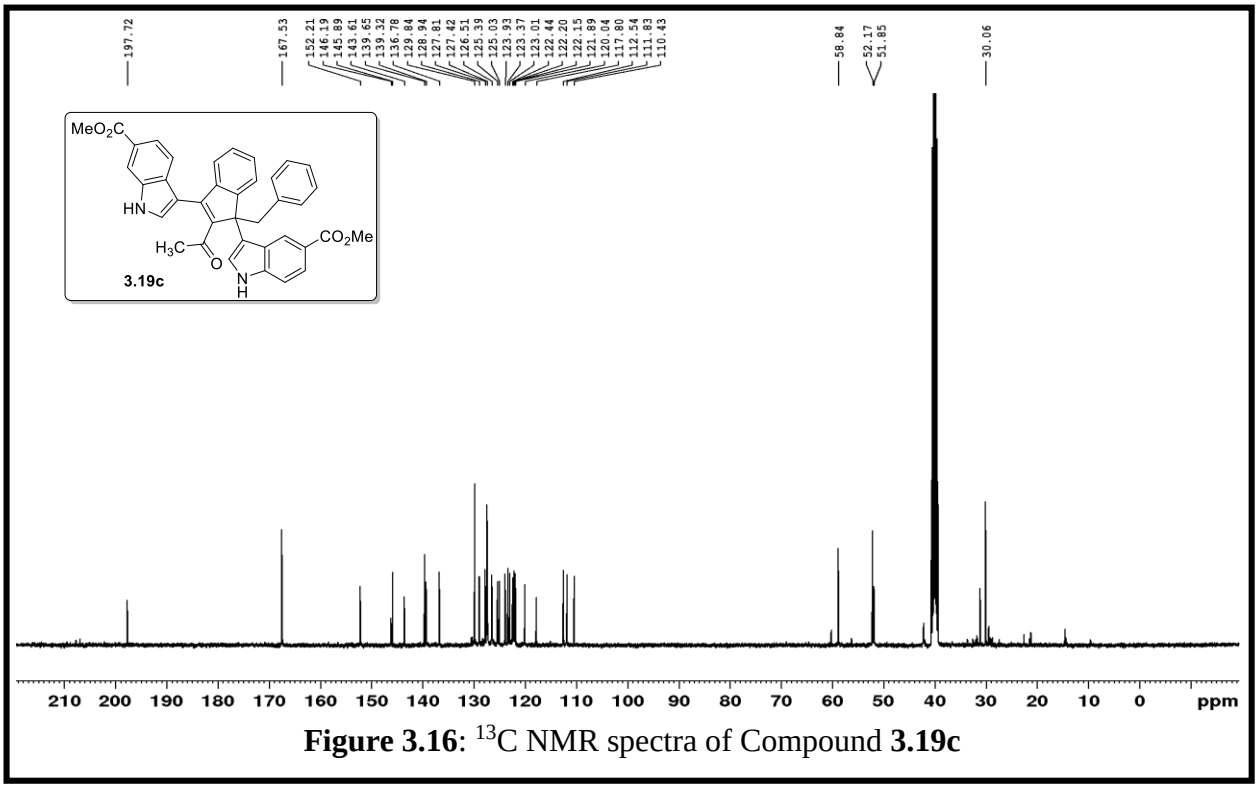

Figure 3.16: ^{13}C NMR spectra of Compound **3.19c**

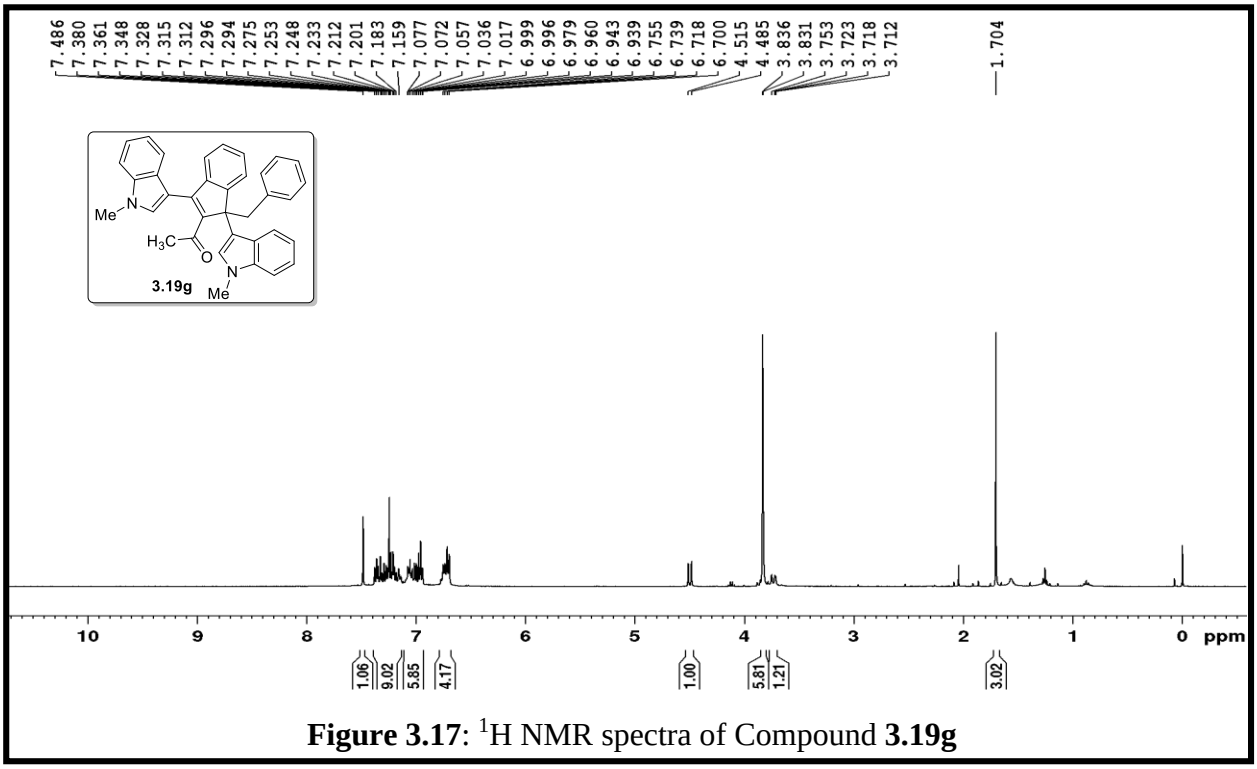

Figure 3.17: ^{1}H NMR spectra of Compound **3.19g**

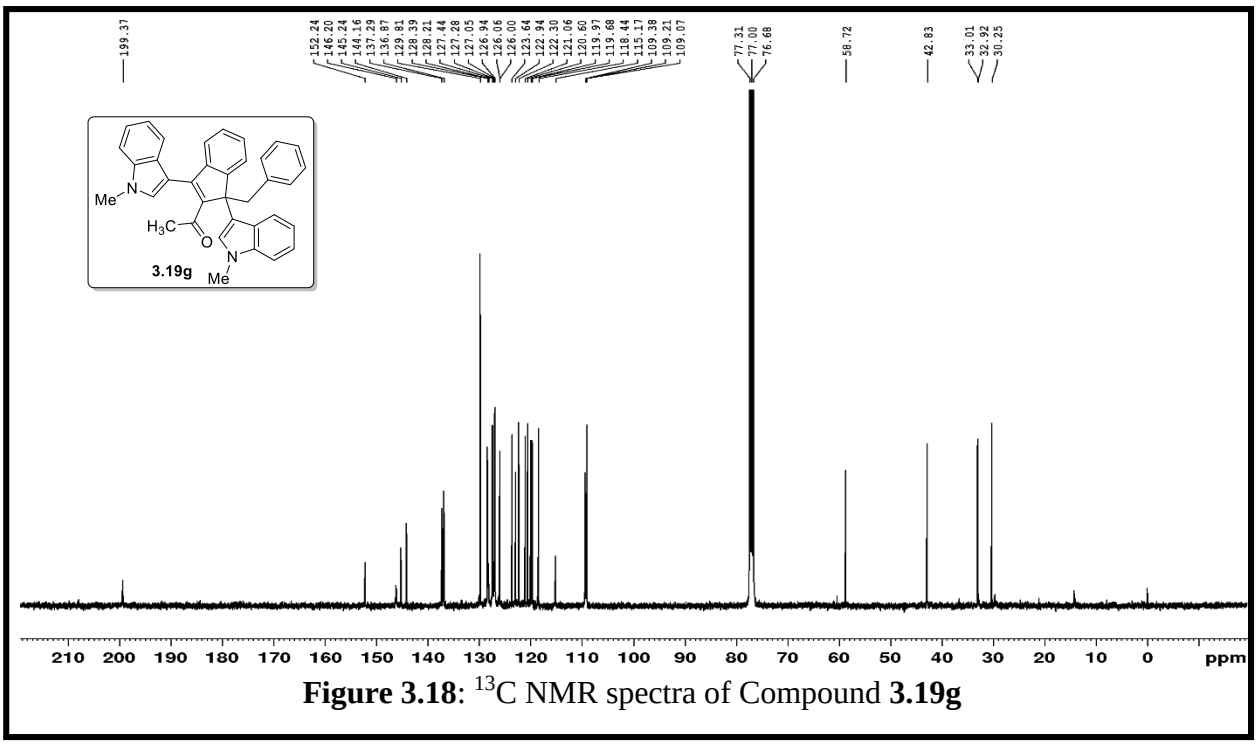

Figure 3.18: ^{13}C NMR spectra of Compound **3.19g**

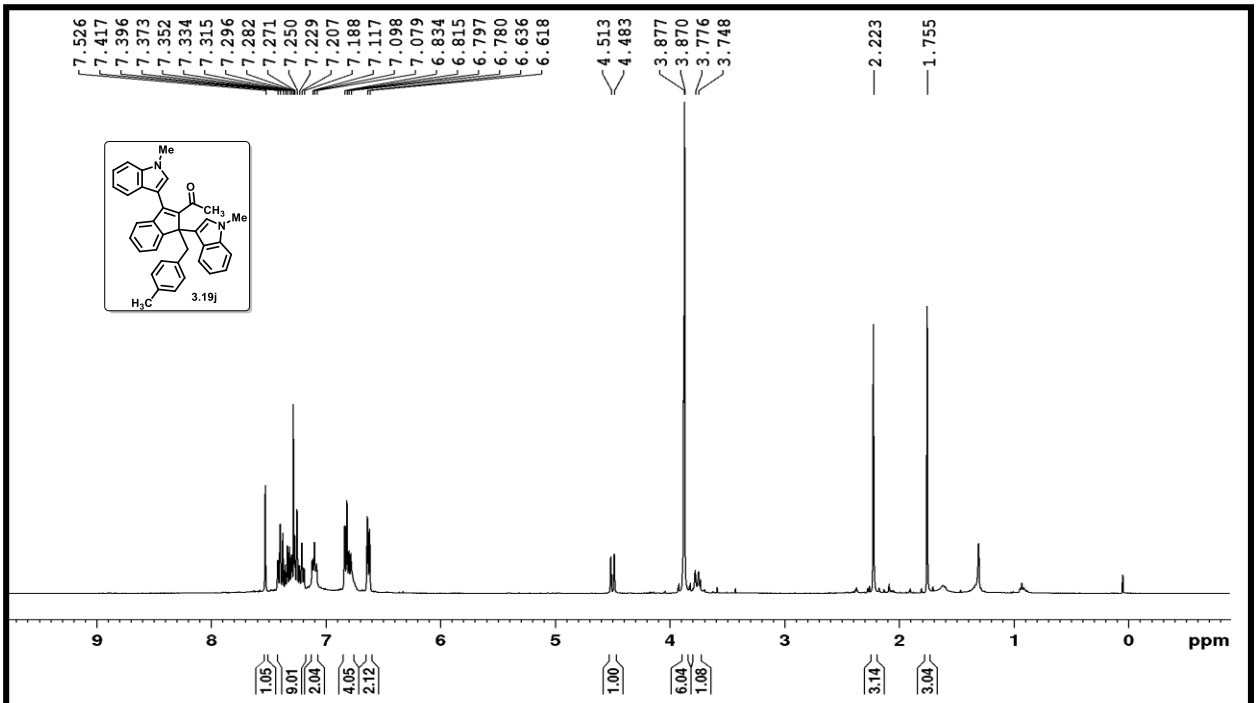

Figure 3.19: ^{1}H NMR spectra of Compound **3.19j**

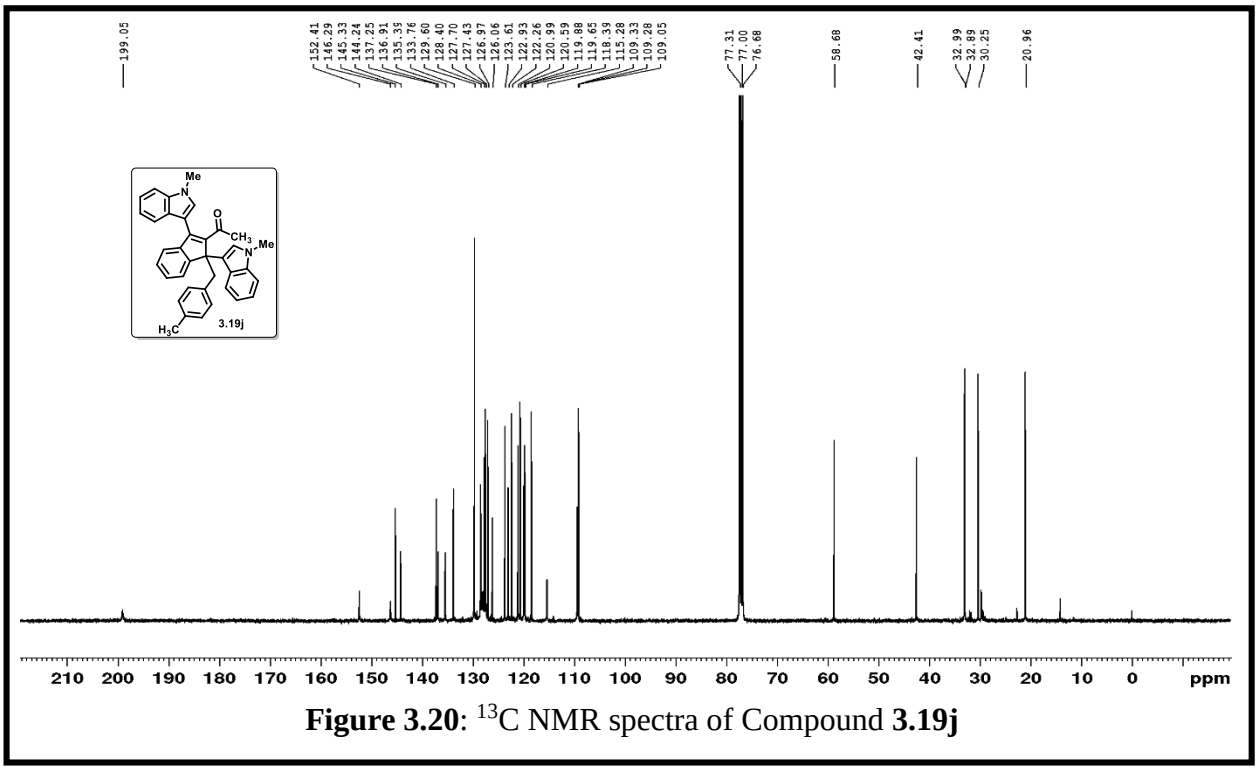

Figure 3.20: ^{13}C NMR spectra of Compound **3.19j**

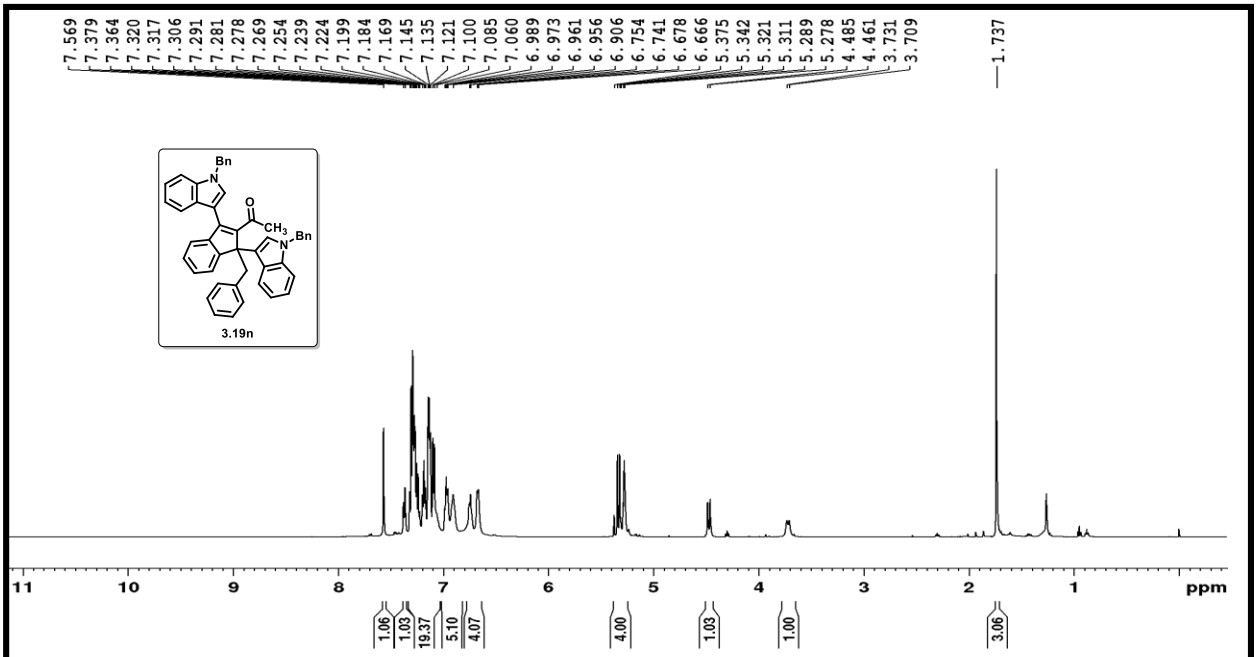

Figure 3.21: ^{1}H NMR spectra of Compound **3.19n**

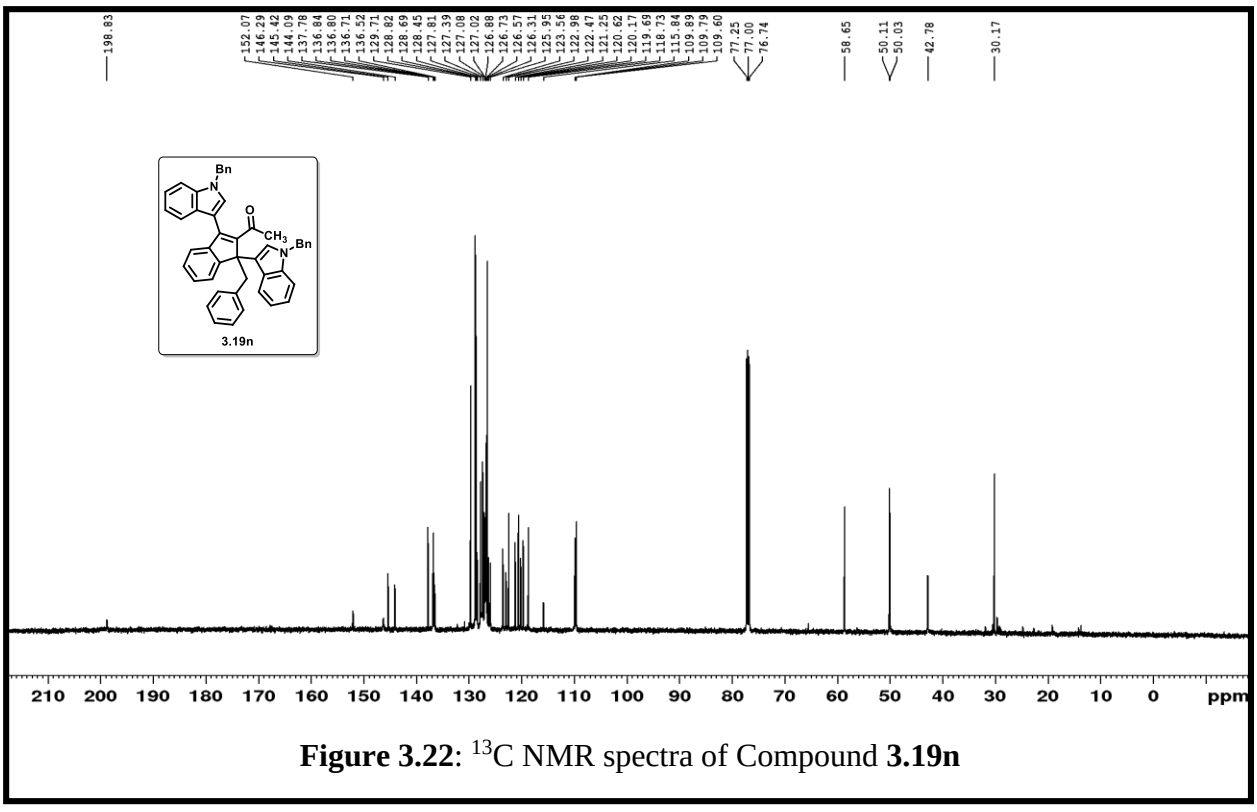

Figure 3.22: ^{13}C NMR spectra of Compound **3.19n**

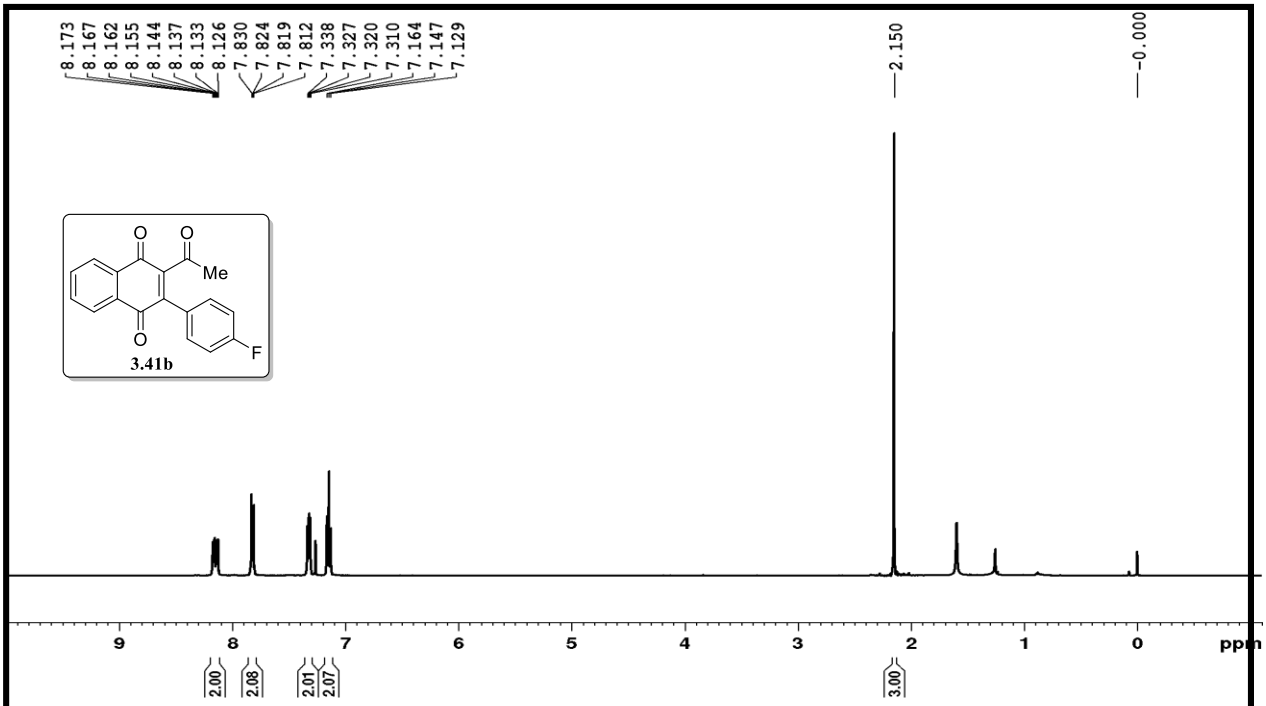

Figure 3.23: ^{1}H NMR spectra of Compound **3.41b**

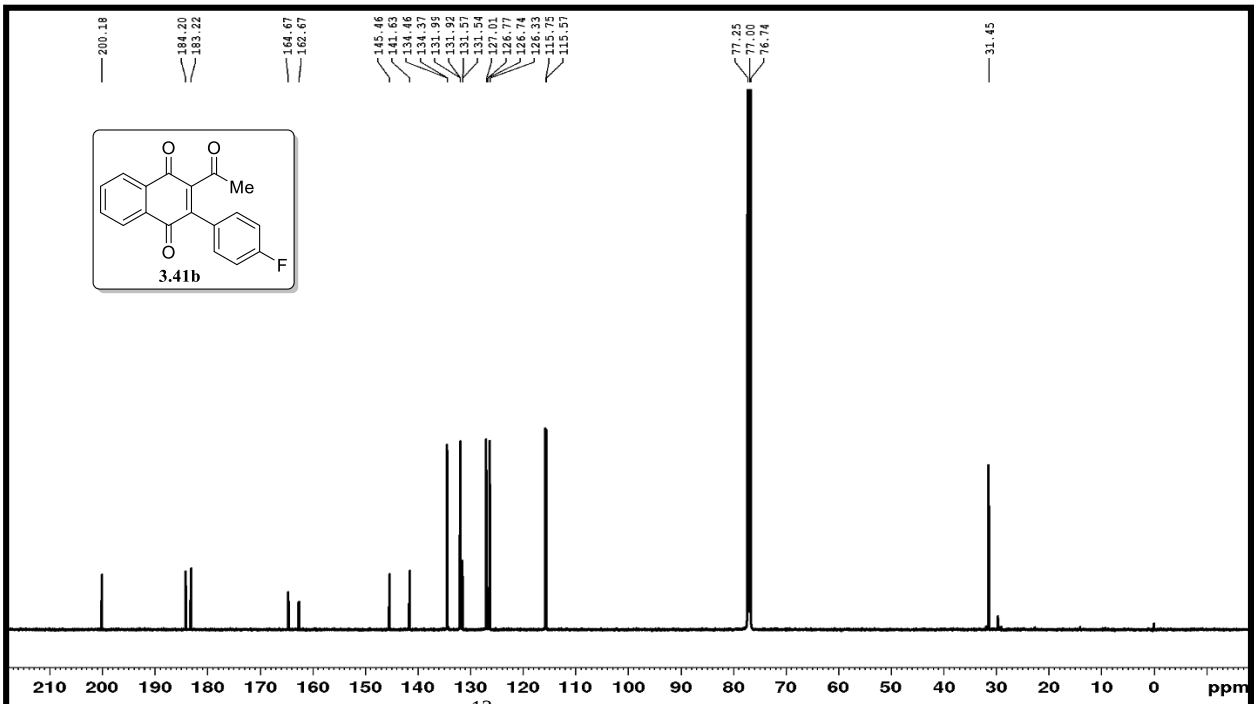

Figure 3.24: ^{13}C NMR spectra of Compound **3.41b**

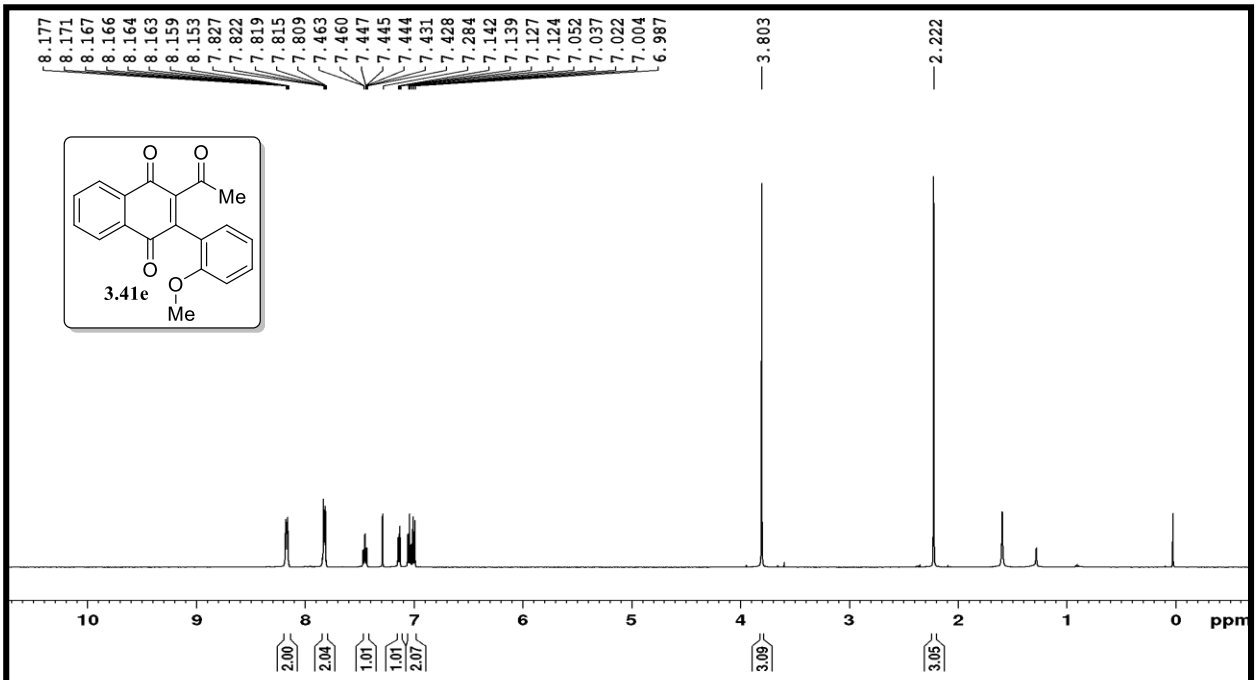

Figure 3.25: ^{1}H NMR spectra of Compound **3.41e**

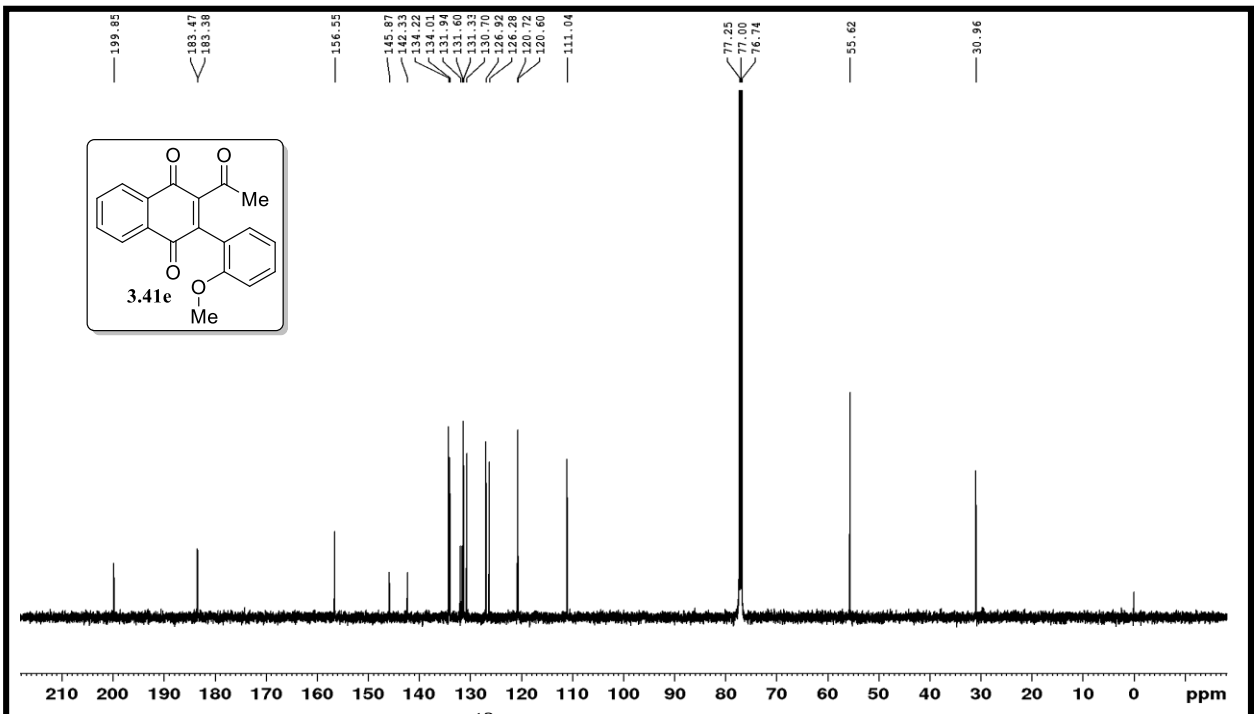

Figure 3.26: ^{13}C NMR spectra of Compound **3.41e**

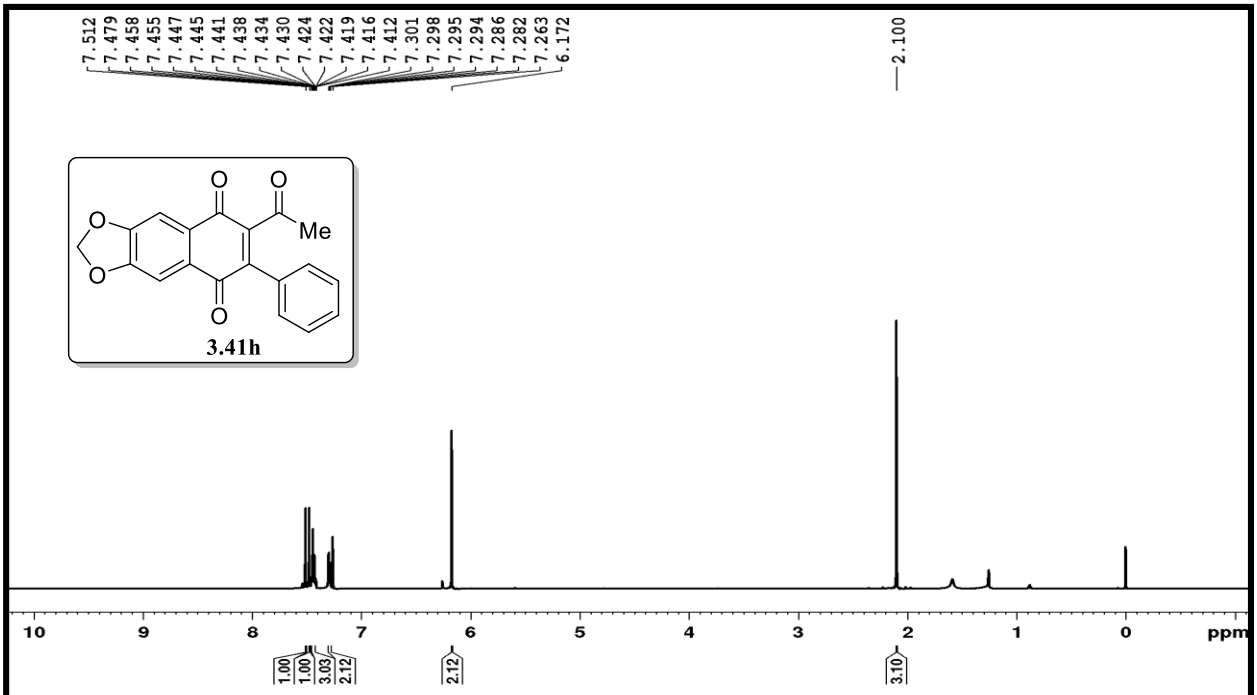

Figure 3.27: ^{1}H NMR spectra of Compound **3.41h**

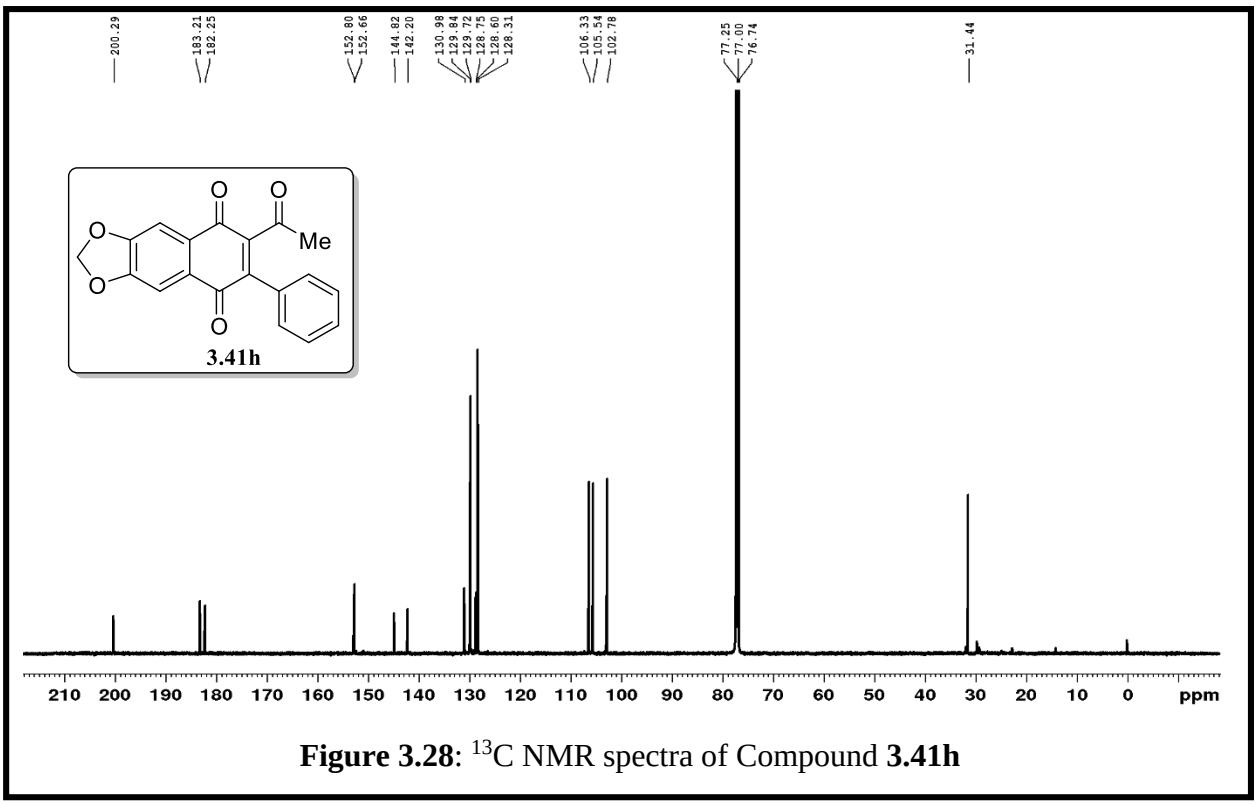

Figure 3.28: ^{13}C NMR spectra of Compound **3.41h**

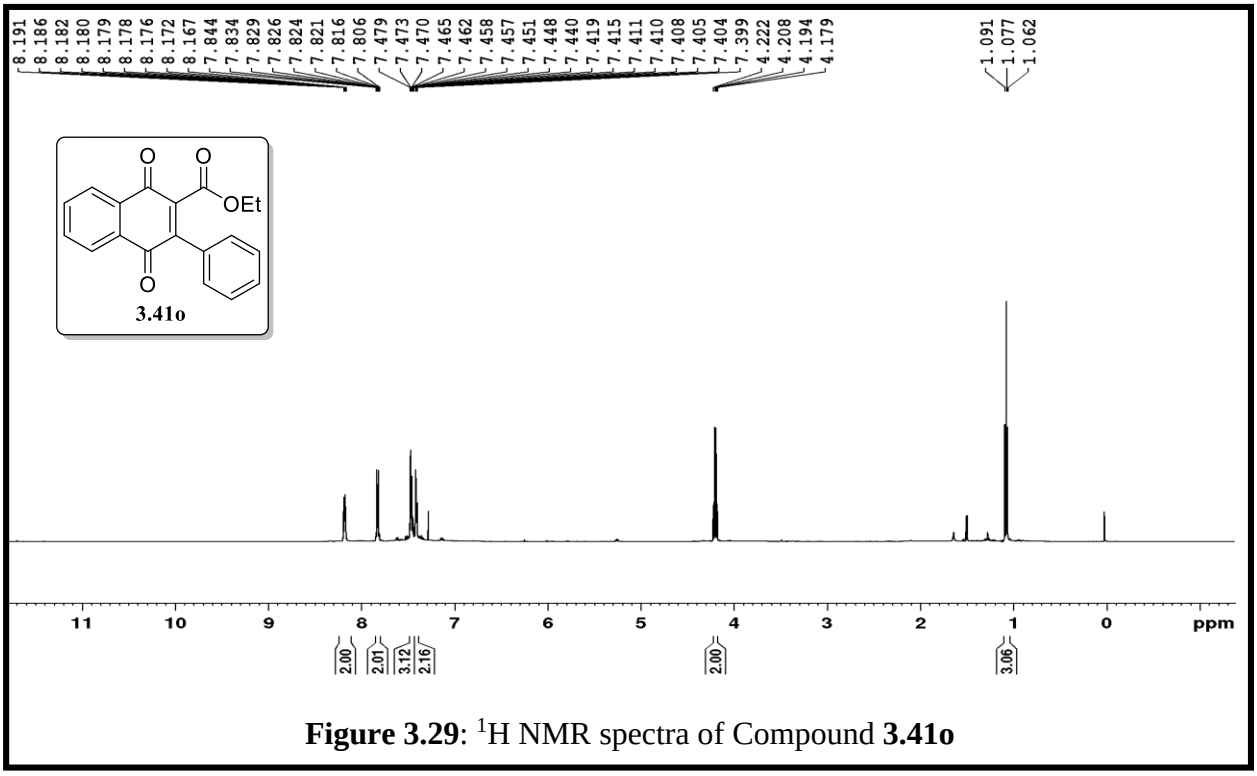

Figure 3.29: ^{1}H NMR spectra of Compound **3.41o**

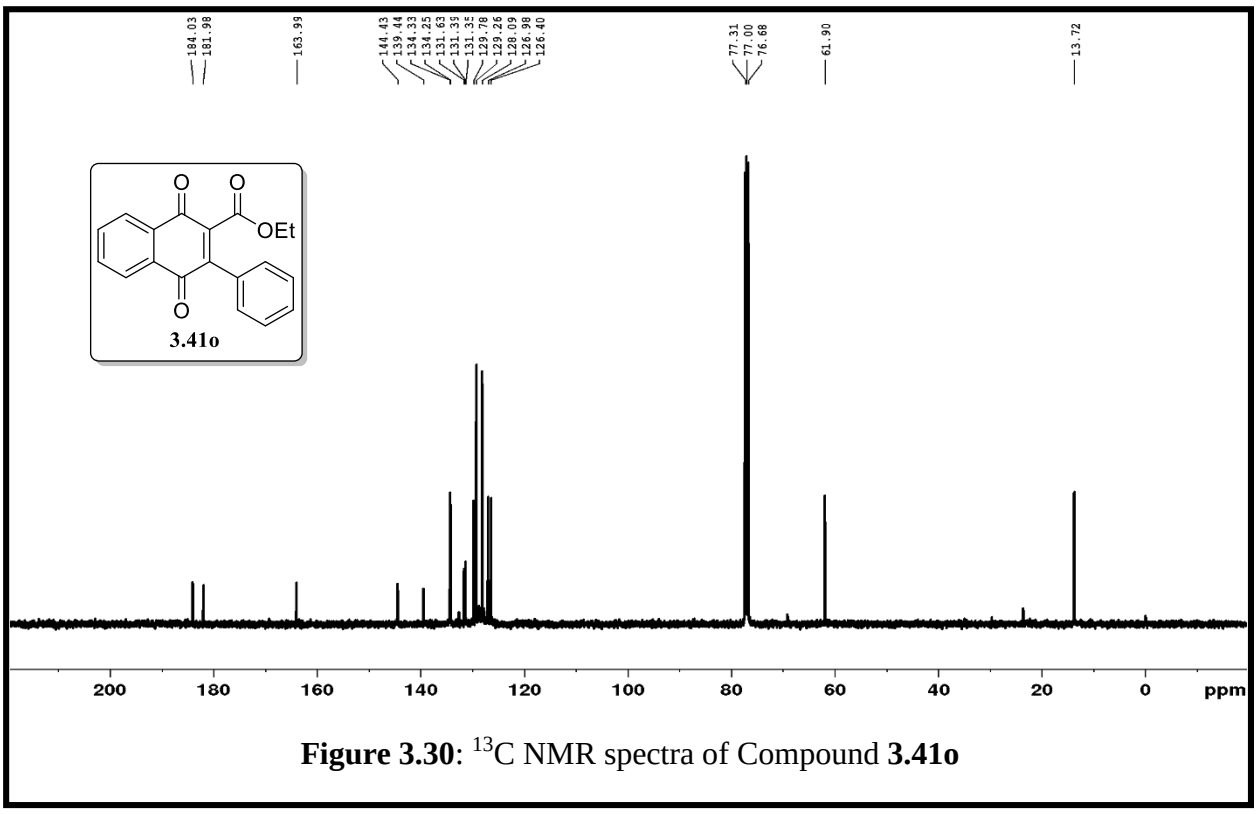

Figure 3.30: ^{13}C NMR spectra of Compound **3.41o**

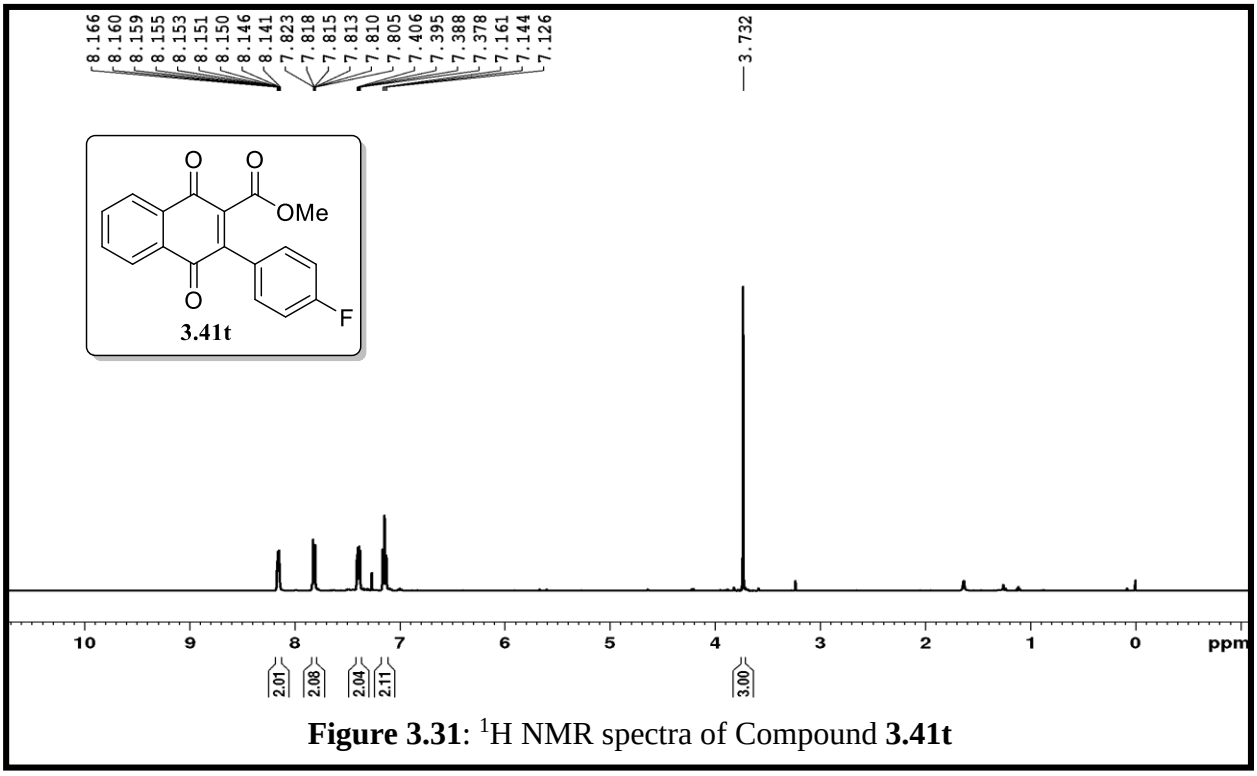

Figure 3.31: ^{1}H NMR spectra of Compound **3.41t**

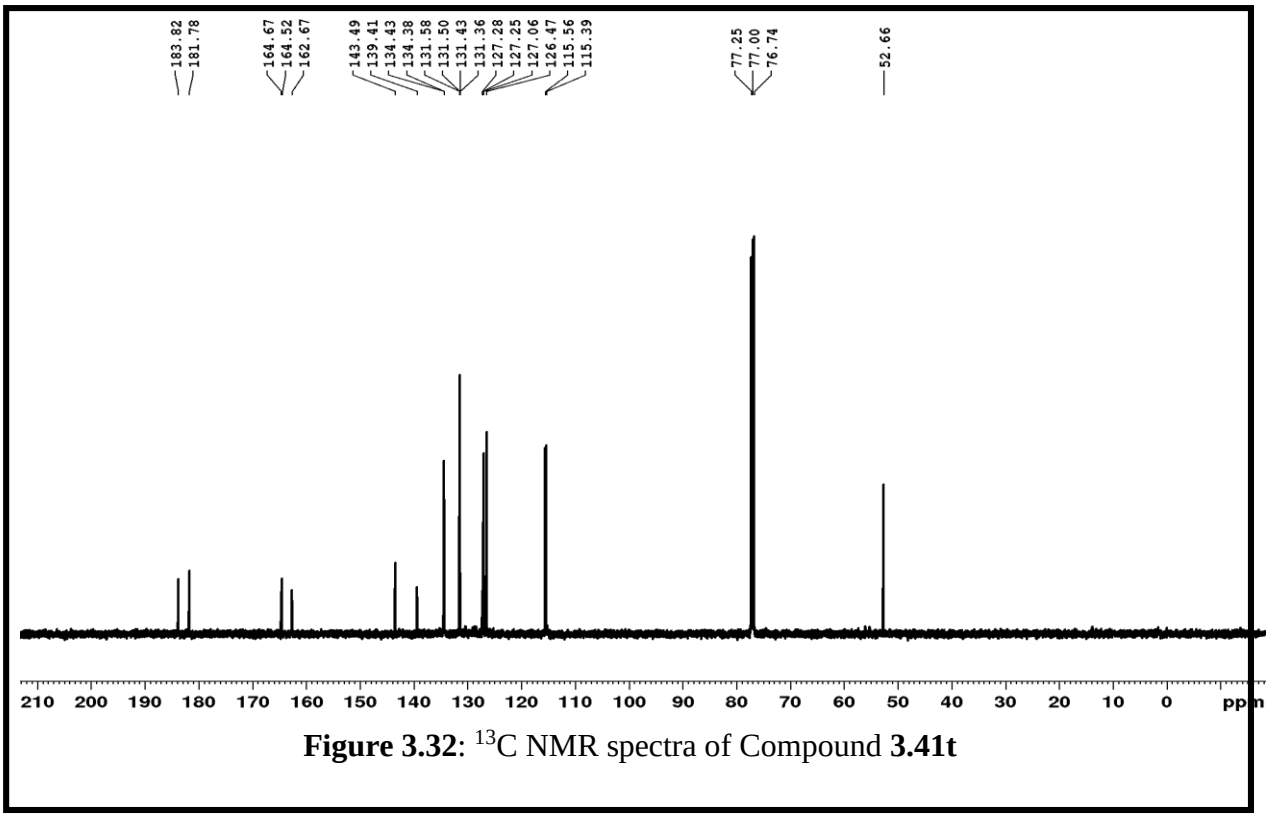

Figure 3.32: ^{13}C NMR spectra of Compound **3.41t**

Appendix

Table 1. Crystal data and structural refinement for compound **2.29i**

Identification code	**2.29i**	
Empirical formula	$C_{27}\ H_{17}\ F_2\ I\ O_3$	
Formula weight	554.31	
Temperature	298 K	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 10.5912(12) Å	α = 64.512(4)°.
	b = 11.2244(13) Å	β = 63.622(4)°.
	c = 11.8078(14) Å	γ = 72.550(4)°.
Volume	1124.9(2) $Å^3$	
Z =	2	
Density (calculated)	1.637 Mg/m^3	
Absorption coefficient	1.467mm^{-1}	
F(000)	1078	
Crystal size	0.30 x0.20 x0.15 mm^3	
Theta range for data collection	2.3 to 25.1°.	
Index ranges	-12<=h<=12, -13<=k<=13, -14<=l<=14	
Reflections collected	38188	
Independent reflections	3953 [R(int) = 0.043	

Completeness to theta = 25.076°	0.988%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3953 / 0 / 299
Goodness-of-fit on F2	1.01
Final R indices [I>2sigma(I)]	R1 = 0.039, wR2 = 0.134
R indices (all data)	R1 = 0.0385, wR2 = 0.1338
Largest diff. peak and hole	1.95 and −1.00 e.$Å^{-3}$
CCDC	**2031090**

List of publication

1. Thota, G. K.; Tarigopula, C.; Balamurugan, R. Tandem activation by gold: synthesis of dioxolanes by intermolecular reaction of epoxides and alkynes in acetone; *Tetrahedron* **2015**, *71*, 2280-2289.

2. Tarigopula, C.; Thota, G. K.; Balamurugan, R. Efficient Synthesis of Functionalized β-Keto Esters and β-Diketones through Regioselective Hydration of Alkynyl Esters and Alkynyl Ketones by Use of a Cationic NHC–AuI Catalyst; *Eur. J. Org. Chem.*, **2016**, 5855-5861.

3. Tarigopula, C.; Manojveer, S.; Balamurugan, R. A Facile Access to Highly Substituted Biaryls by Construction of Benzene Ring via in situ Formed Acetals. (to be communicated)

4. Tarigopula, C.; Balamurugan, R. Bis-alkylidene Dihydroisobenzofurans from 1,3-Dicarbonyls and Their Synthetic Applications: facile access to bis-indole substituted indene derivatives and highly substituted 1,4-Naphthoquinones (to be submitted)

Posters and oral presentation

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4. Poster Presentation: 21st ICOS (International Conference on Organic Synthesis 2016), IIT-Bombay, Mumbai, India.

5. Participation: 1st Indo-Taiwan Symposium on “Recent Trends in Chemical Sciences”, November 2014, University of Hyderabad, INDIA. (Organizer: Academica Sinica, Taiwan and School of Chemistry, University of Hyderabad)

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