TOWARDS DEVELOPMENT OF NOVEL METHODOLOGIES FOR SYNTHESIS OF IND-2-ENONE, PIPERIDINE-2,6-DIONE AND 1H-PYRROLE-2,5-DIONE FRAMEWORKS USING BAYLIS-HILLMAN ADDUCTS

A THESIS SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

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INDIA

AUGUST, 2010

To

My Family

&

Teachers

CONTENTS

STATEMENT

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I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, under the supervision of **Professor D. Basavaiah**.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

August, 2010 **Dandamudi V Lenin**

CERTIFICATE

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Certified that the work embodied in this thesis entitled "**TOWARDS DEVELOPMENT OF NOVEL METHODOLOGIES FOR SYNTHESIS OF IND-2-ENONE, PIPERIDINE-2,6-DIONE AND 1H-PYRROLE-2,5-DIONE FRAMEWORKS USING BAYLIS-HILLMAN ADDUCTS**" has been carried out by **Mr. DANDAMUDI V LENIN**, under my supervision and the same has not been submitted elsewhere for a degree.

Professor D. BASAVAIAH
(THESIS SUPERVISOR)

DEAN
SCHOOL OF CHEMISTRY

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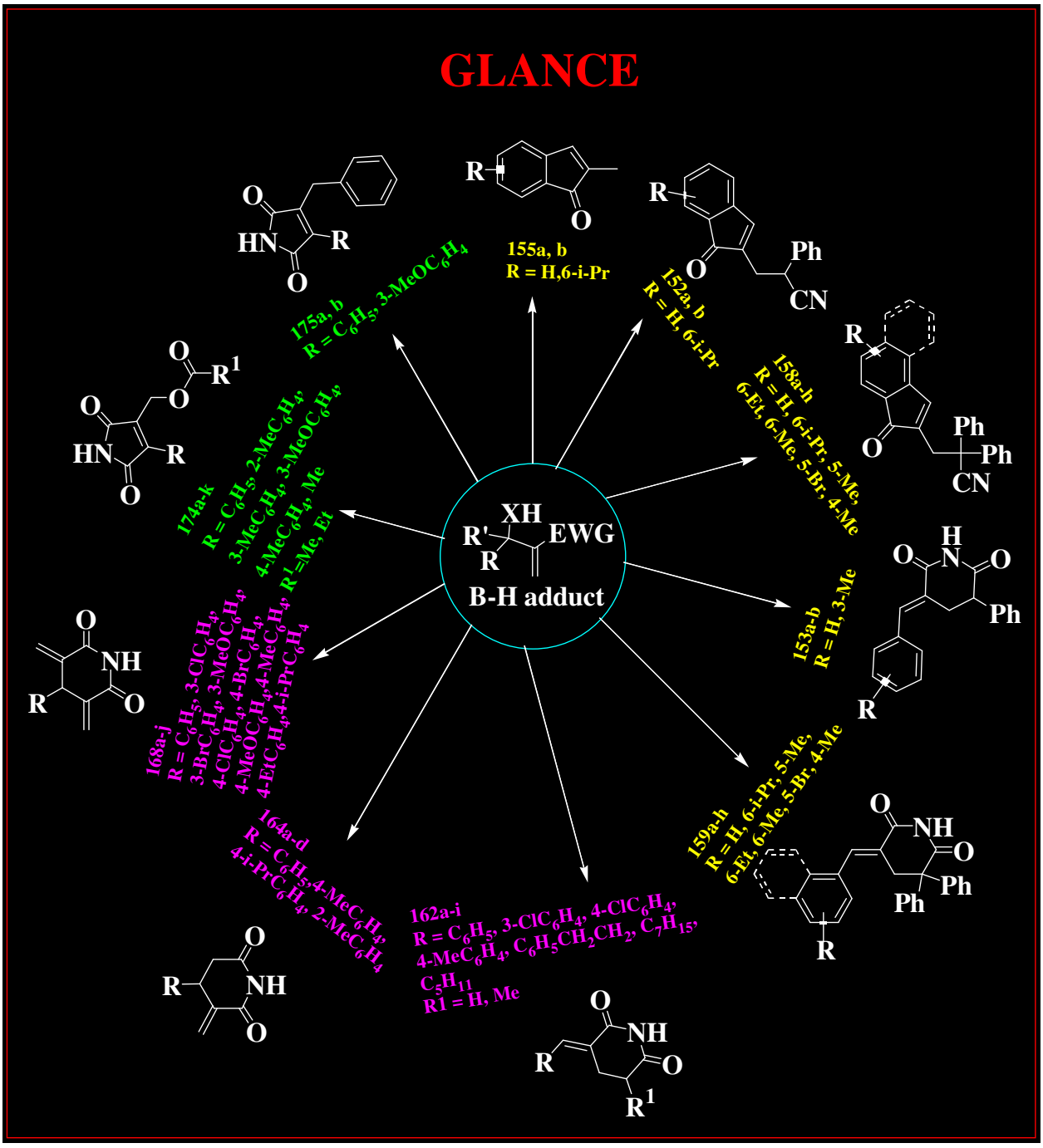
Dandamudi V Lenin

ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
AIBN	azobisisobutyronitrile
aq.	aqueous
Ar	aryl
BINOL	1,1′-bi-2-naphthol
Boc	*tert*-butoxycarbonyl
Bp	boiling point
t-Bu or Bu^t	*tertiar*y butyl
cat.	catalyst
Cbz	benzyloxycarbonyl
*m*CPBA	*meta*-chloroperbenzoic acid
Cy	cymene
DABCO	1,4-diazabicyclo(2.2.2)octane
DBAD	di-*tert*-butyl azodicarboxylate
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCE	1,2-dichloroethane
DEAD	diethyl azodicarboxylate
dec.	decompose
DEPO	diethylphosphine oxide
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DME	ethylene glycol dimethyl ether
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane

DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
dppp	bis(diphenylphosphanyl)propane
dr	diastereomeric ratio
de	diastereomeric excess
DYKAT	dynamic kinetic asymmetric transformation
Eq.	equation
equiv	equivalent(s)
Et	ethyl
EWG	electron withdrawing group
Hex	hexyl
HMT	hexamethylenetetramine
3-HQD	3-hydroxyquinuclidine
IBX	2-iodoxybenzoic acid
β-ICPD	*β*-isocupreidine
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
Me	methyl
Mp	melting point
MsCl	mesyl chloride
MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbene
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine oxide
PAP	polymer bound 4-(*N*-benzyl-*N*-methylamino)pyridine
Ph	phenyl

PMP	*para*-methoxyphenyl
i-pr/pr^i	isopropyl
PTA	1,3,5-triaza-7-phosphaadamantane
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TES-Cl	chlorotriethylsilane
TFA	trifluroacetic acid
TFAA	trifluoroacetic anhydride
TfOH	trifluoromethanesulfonic acid
Tf_2O	trifluoromethanesulfonic anhydride
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
TMG	1,1,3,3-tetramethylguanidine
TMPDA	1,1,3,3-tetramethylpropane-1,3-diamine
TMS	tetramethylsilane
TMSI	trimethylsilyl iodide
Ts	tosyl
TsOH	*para*-toluenesulfonic acid
Troc	2,2,2-trichloroethoxy carbonyl
TTMPP	tris(2,4,6-trimethoxyphenyl)phosphine
UV	ultraviolet


GLANCE
155a, b
R = H,6-i-Pr
175a, b
R = C6H5, 3-MeOC6H4
152a, b
R = H, 6-i-Pr
158a-h
R = H, 6-i-Pr, 5-Me,
6-Et, 6-Me, 5-Br, 4-Me
174a-k
R = C6H5, 2-MeC6H4,
3-MeC6H4, 3-MeOC6H4,
4-MeC6H4, Me
R1=Me, Et
XH
R'
EWG
R
B-H adduct
153a-b
R = H, 3-Me
168a-j
R = C6H5, 3-ClC6H4,
3-BrC6H4, 3-MeOC6H4,
4-ClC6H4, 4-BrC6H4,
4-MeOC6H4, 4-MeC6H4,
4-EtC6H4, 4-i-PrC6H4
159a-h
R = H, 6-i-Pr, 5-Me,
6-Et, 6-Me, 5-Br, 4-Me
164a-d
R = C6H5, 4-MeC6H4,
4-i-PrC6H4, 2-MeC6H4
162a-i
R = C6H5, 3-ClC6H4, 4-ClC6H4,
4-MeC6H4, C6H5CH2CH2, C7H15,
C5H11
R1 = H, Me

ABSTRACT

The Baylis-Hillman reaction is an atom-economical three component carbon-carbon bond forming reaction between α-position of activated alkene and electrophile in the presence of catalyst or catalytic system, providing diverse classes of multifunctional molecule which are usually referred as the Baylis-Hillman (B-H) adducts. Our research group has been working on various aspects of this reaction for the last several years. This thesis deals with applications of Baylis-Hillman adducts in the synthesis of carbocyclic and heterocyclic molecules and consists of three chapters 1) Introduction 2) Objectives, Results & Discussion and 3) Experimental. The first chapter, that is, introduction presents a brief account of literature on the developments in the Baylis–Hillman reaction and also on the important applications of the Baylis–Hillman adducts in synthetic organic chemistry.

The second chapter, that is, Objectives, Results & Discussion, deals with the development of simple methodologies for the synthesis of indenone, piperidine-2,6-dione and maleimide derivatives using the Baylis-Hillman adducts with the following objectives.

Objectives:

1] To develop a facile methodology for transformation of the Baylis-Hillman acetates i.e. *tert*-butyl 3-acetoxy-2-methylene-3-arylpropanoates

into indenone derivatives, (*E*)-3-arylmethylidene-5-phenylpiperidine-2,6-dione and (*E*)-3-arylmethylidene-5,5-diphenylpiperidine-2,6-dione frameworks.

2] To develop a convenient one-pot methodology for transformation of

i) Baylis-Hillman alcohols i.e. 3-hydroxy-2-methylene-3-aryl/alkylpropanoates into (*E*)-3-aryl(alkyl)methylidenepiperidine-2,6-dione derivatives.

ii) Rearranged Baylis-Hillman alcohols i.e. (2*Z*)-2-cyano-3-arylprop-2-en-1-ols into 3-methylidene-4-arylpiperidene-2,6-diones.

iii) Baylis-Hillman compounds i.e. 4-cyano-2-methoxycarbonyl-3-arylpenta-1,4-dienes into 4-aryl-3,5-dimethylidenepiperidene-2,6-dione derivatives.

3] To develop a simple methodology for synthesis of 3, 4-disubstituted-1H-pyrrole-2, 5-dione derivatives (maleimide derivatives) from the Baylis-Hillman alcohols *i.e.* 3-ethoxycarbonyl-3-hydroxy-3-aryl-2-methylenepropanenitriles (or 3-ethoxycarbonyl-3-hydroxy-2-methylenealkanenitriles) in one-pot operation.

Development of a facile methodology for synthesis of substituted indenones and piperidine-2, 6-diones from the Baylis-Hillman acetates.

Ind-2-en-1-one framework represents an important class of carbocyclic molecules because these derivatives are found in important natural products. Some of indenone derivatives are also known to be peroxisome proliferator-activated receptor γ (PPAR γ, drug to type-2 diabetes) agonists, estrogen receptor binding agents, cyclooxygenase-2 inhibitors and potent reversible inhibitors of 3CP. Piperidine-2, 6-dione framework is yet another medicinally important skeleton present in several biologically active and natural products such as alonimid (sedative and hypnotic activity), thalidomide (drug to prevent morning sickness of pregnant women), streptimidone (antibiotic), migrastatin (antitumor agent), lactimidomycin (antibiotic) and sesbanimide (antitumor). Therefore development of facile strategies for the synthesis of these frameworks has become a challenging task in synthetic organic chemistry. We have developed a two-step methodology for the synthesis of ind-2-en-1-ones frameworks (**152a,b; 155a,b; 158a-h**, Eq. 26, 28, 30, Tables 3, 5, 7, Scheme 38) via starting from the Baylis-Hillman acetates (**149a-h,** Table 1). This transformation proceeds through an unusual conversion of *trans* cinnamic esters into ind-2-en-1-one frameworks. The yields of the indenone derivatives depend on the steric bulk of substitution at α-position of ester group of *trans*-cinnamic esters.

We have also developed a simple two-step strategy for transformation of the B-H acetates (**149a-h,** Table 1) into substituted piperidine-2,6-dione derivatives (**153a, b; 159a-h**, Eq. 31, 32 Tables 8, 9).

To develop a simple protocol for the synthesis of a piperidine-2,6-dione frameworks from Baylis-Hillman adducts.

Today science of synthesis demands the development of operationally simple one-pot processes for obtaining important molecules of medicinal relevance. We have therefore, directed our attention towards the development of one-pot process for synthesis of piperidine-2,6-dione derivatives starting from the Baylis-Hillman alcohols derived from acrylonitrile and aldehydes. Accordingly we have developed simple and one-pot methodology for the preparation of (*E*)-3-arylidene(alkylidene)piperidine-2, 6-diones (**162a-i**, Table 12) via Jhonson-Claisen rearrangement of the Baylis-Hillman alcohols (**161a-g,** Table 11) followed by partial hydrolysis of cyano group, cyclization and isomerization using $FeCl_3$/acetic acid.

A simple and one-pot methodology for the preparation of 3-methylidene-4-arylpiperidine-2,6-diones derivatives (**164a-d,** Eq. 36; Table 14) via Jhonson-Claisen rearrangement, partial hydrolysis of cyano group, and cyclization using $FeCl_3$/acetic acid starting from Baylis-Hillman rearranged alcohols (**163a-d,** Table 13**)** has been developed.

The Baylis-Hillman products (**167a-j,** Table 15) has been conveniently transformed into 4-aryl-3,5-dimethylidenepiperidine-2,6-dione derivatives (**168a-j**, Eq. 39; Table 16) via partial hydrolysis of cyano group, and cyclization using $FeCl_3$/acetic acid.

Development of one-pot synthesis of substituted maleimide derivatives using the Baylis-Hillman alcohols.

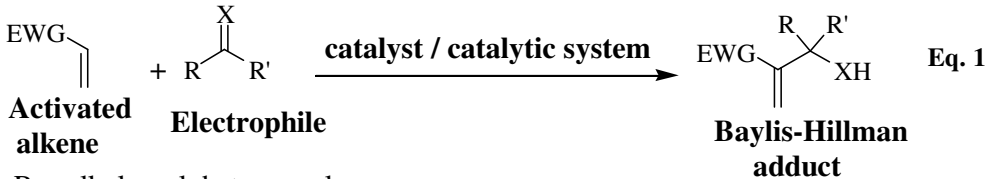
3,4-Disubstituted maleimide framework represents an interesting structural organization in heterocyclic chemistry as this skeleton is present in a number of natural products such as himanimides A-D, polycitrins A & B, and arcyriarubins A & B. Also certain compounds having this framework have been known to exhibit various biological activities such as protein kinase C inhibitors (PKC), inhibitor of calmodulin dependant protien kinase (CaMKIIδ), cell death inhibitor, vascular endothelial cell proliferation, angiogenesis inhibitor and cytotoxicity. We have developed a facile one-pot methodoloy for the synthesis of maleimide dearivatives (**174a-k**, Eq.45; Table 18) starting from the Baylis-Hillman alcocols (**173a-f,** Table 17) via treatment of $FeCl_3/RCO_2H$ (R = Me, Et). Two of such maleimide derivatives (**174a, d**) were further subjected to Friedel-Crafts reaction with benzene in the presence of CH_3SO_3H providing 3-benzyl-4-aryl-1H-pyrrole-2,5-diones (**175a-b**, Table 19).

The third chapter deals with detailed experimental procedures, IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectral data (LCMS), elemental analysis and physical constants (Mp & bp).

INTRODUCTION

The present day synthetic chemistry demands development of novel carbon-carbon bond forming reactions based on the concept of environmental protection. Synthetic chemists have been working in this direction for the last several years. The Baylis-Hillman reaction[1-11] is one such reaction developed in recent years, on the basis of concepts of atom economy and organocatalysis, that are most important components of environmental protection.

The Baylis-Hillman reaction originates from a German patent[1] filed in the year 1972 by two American chemists A. B. Baylis and M. E. D. Hillman. They had also an U.S patent[2] in the year 1973 on this reaction. This is essentially three component reaction involving the coupling at α-position of activated alkenes with electrophiles in the presence of a catalyst or catalytic system, providing interesting classes of densely functionalized molecules which are usually referred to as the Baylis-Hillman (B-H) adducts (Eq. 1).



Activated alkene + **Electrophile** → **Baylis-Hillman adduct** **Eq. 1**

R = alkyl, aryl, hetero-aryl, *etc.*
R' = H, COOR, alkyl, *etc.*
X = O, *N*-Ts, *N*-CO_2R, *N*-$PO(R)_2$, *etc.*
catalyst / catalytic system = *tert*-amines, phosphines, Lewis acids, *etc.*
EWG (Electron Withdrawing Group) = COOR, COR, CHO, CN, $PO(OEt)_2$, SO_2Ph, SO_3Ph, SOPh, *etc.*

During the last several years this reaction has grown exponentially with respect to all the three essential compounds (electrophiles, activated alkenes and catalysts or catalytic systems). Also significant developments have been made in asymmetric version and intramolecular version. This chapter briefly presents the recent developments in the Baylis-Hillman reaction and applications of the Baylis-Hillman adducts.

ACTIVATED ALKENES:

Several activated alkenes[12-37] (Figures 1 & 2) have been successfully employed for coupling with various electrophiles to provide diverse classes of multifunctional molecules. Representative examples are given in Equations 2-5 and Schemes 1, 2.

Figure 1

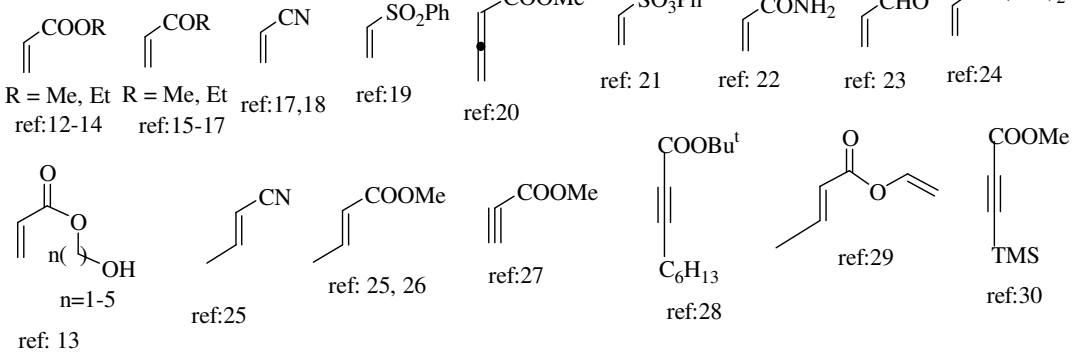
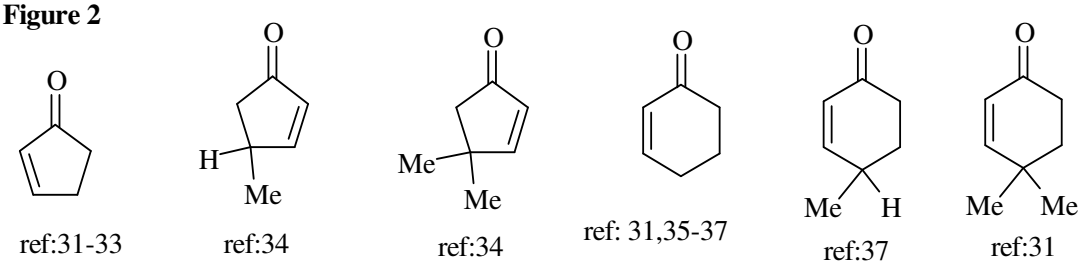
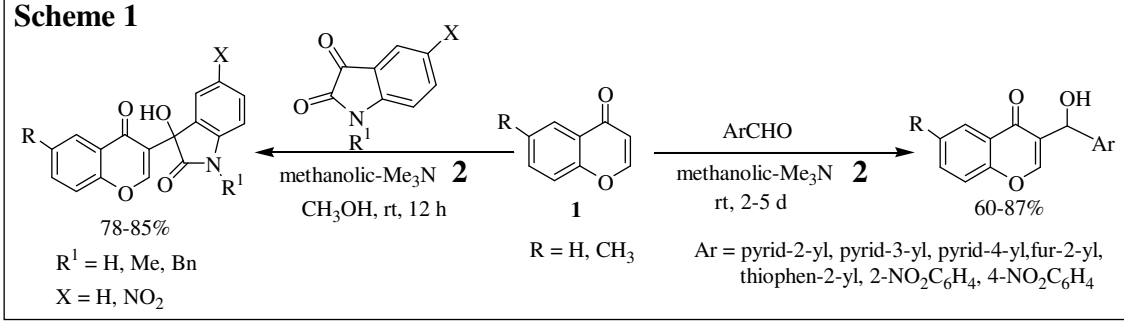


Figure 2

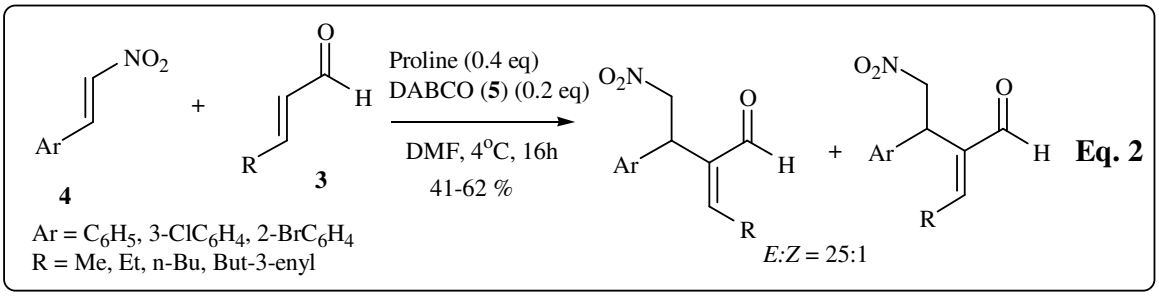


Our research group[38] used 1-benzopyran-4(4*H*)-one derivatives (**1**), as activated alkenes in the Baylis-Hillman reaction with various electrophiles such as hetero-aromatic aldehydes, nitrobezaldehydes and isatin derivatives under the influence of methanolic-Me_3N (**2**) to provide the corresponding adducts in high yields (Scheme 1).

Scheme 1



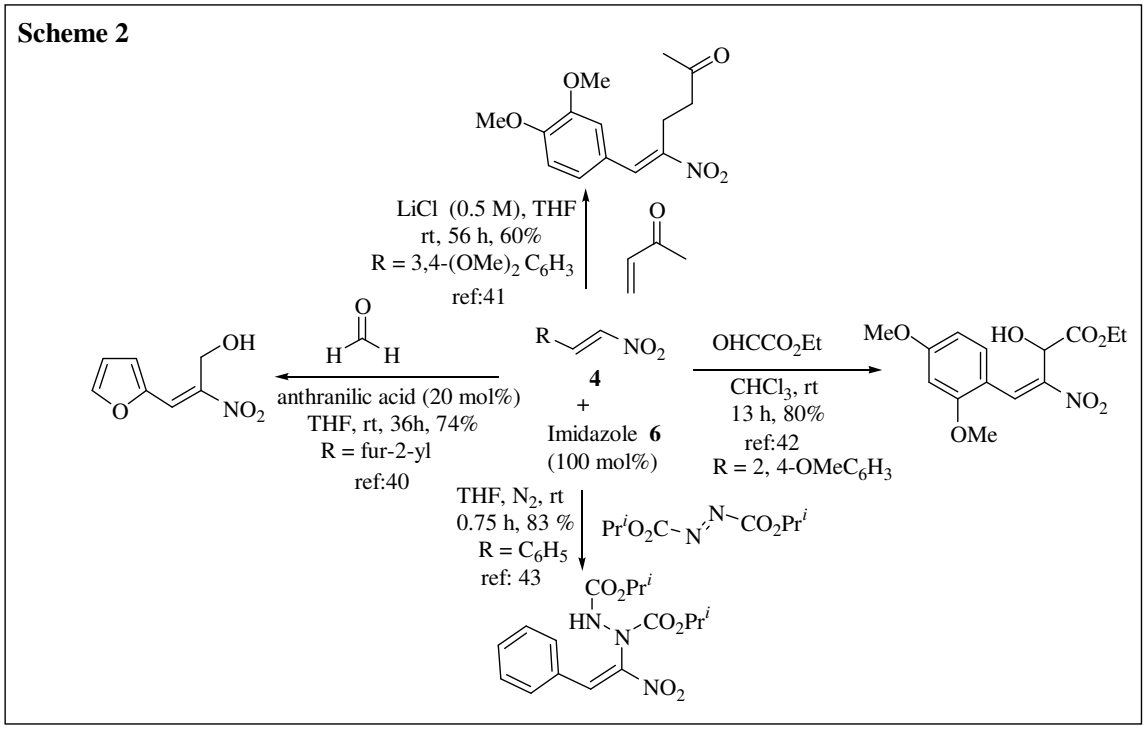
Cordova and co-workers[39] reported an interesting coupling between nitrostyrene derivatives (**4**) as electrophiles and α,β-unsaturated aldehydes (**3**) as activated alkenes in the presence of DABCO (**5**) and proline to provide β-substituted Baylis-Hillman adducts (Eq.2).



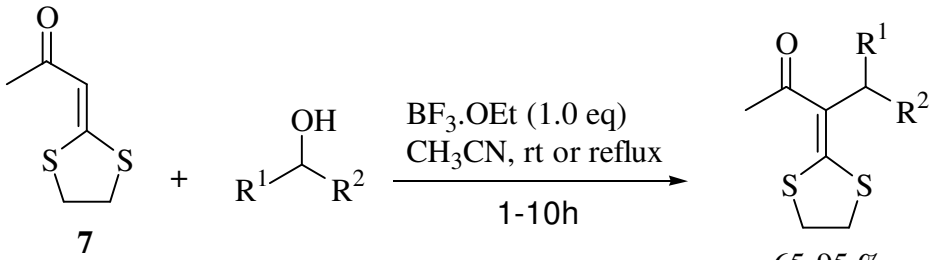
Eq. 2

Namboothiri and co-workers[40-43] successfully applied the conjugated nitroalkenes (**4**) as activated alkenes in the Baylis-Hillman reaction with representative electrophiles under the influence of imidazole (**6**) at room temperature. Representative examples are presented in Scheme 2**.**

Scheme 2



Zhang and Co-workers[44] reported the reaction of α-oxakeleten-S,S-acetals (**7**) with aryl alky cabinols in the presence of $BF_3.OEt_2$ providing the α-alkylated products in excellent yields (Eq. 3).

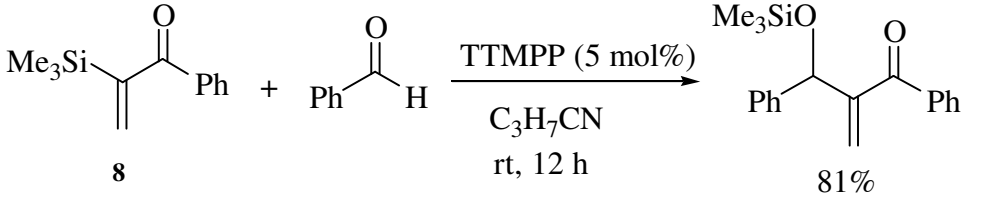


Eq. 3

R^1 = C_6H_5, 4-(OMe)C_6H_4, 4-ClC_6H_4, 3,4(OCH_2O)C_6H_3, 4-(Me_2N)C_6H_4, 4-(Me)C_6H_4CH=CH, Cinnamyl

R^2 = H, Me,Cinnamyl

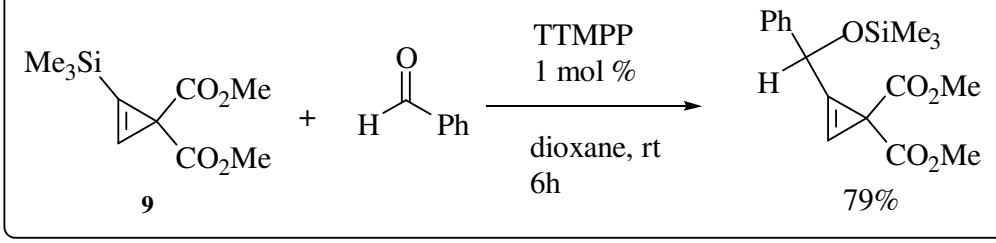
Gevorgyan and Trofimov[45] have reported the Baylis-Hillman type reaction between α-silylvinylaryl ketones (**8**) with aryl aldehydes under the catalytic influence of tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP) to produce silylated adducts *via* a 1,3-Brook rearrangement/elimination cascade. One example is given in Eq. 4.



Eq. 4

TTMPP = Tris(2,4,6-trimethoxyphenyl)phosphine

Subsequently they have also extended the same strategy to the reaction between 1-silylcylopropanes[46] (**9**) with aldehydes to provide Baylis-Hillman type products. One representative example is presented in Eq. 5.

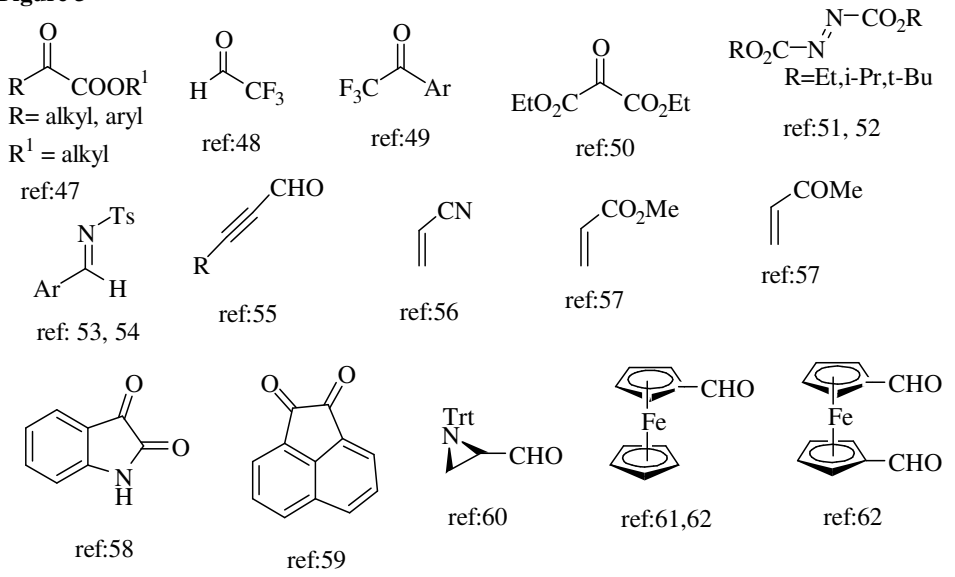


Eq. 5

ELECTROPHILES:

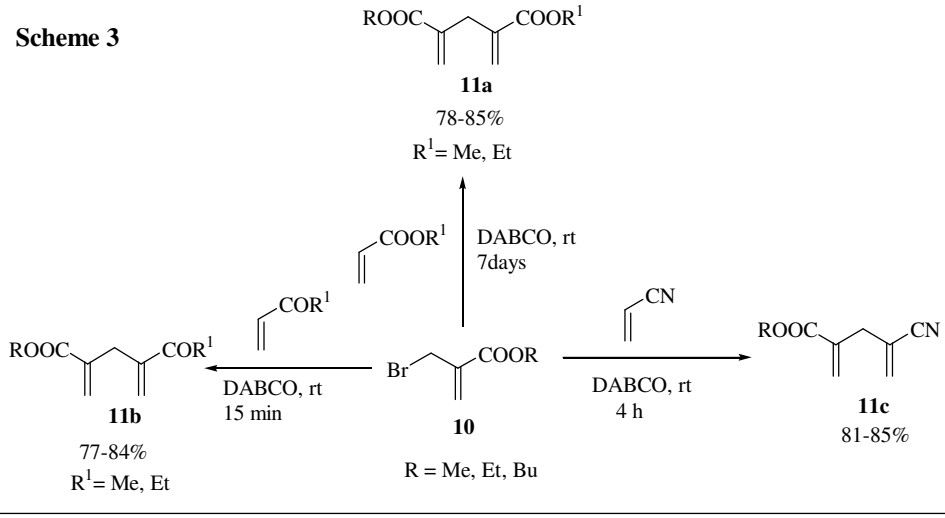
A verity of electrophiles[47-62] (Figure 3), in addition to aldehydes, have been employed for coupling with activated alkenes providing different classes of multifunctional molecules. Selected examples are shown in Schemes 3-5.

Figure 3



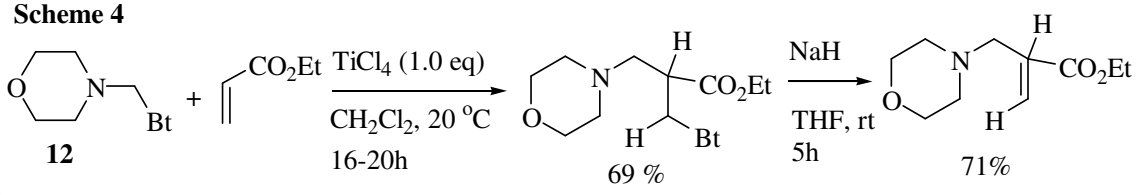
Our research group[63] employed, for the first time, allyl bromides (**10**), prepared from Baylis-Hillman adducts, as electrophiles in the coupling reaction with activated alkenes under the influence of excess amount of DABCO, leading to the synthesis of substituted 1,4-pentadienes (**11a-c**) (Scheme 3).

Scheme 3



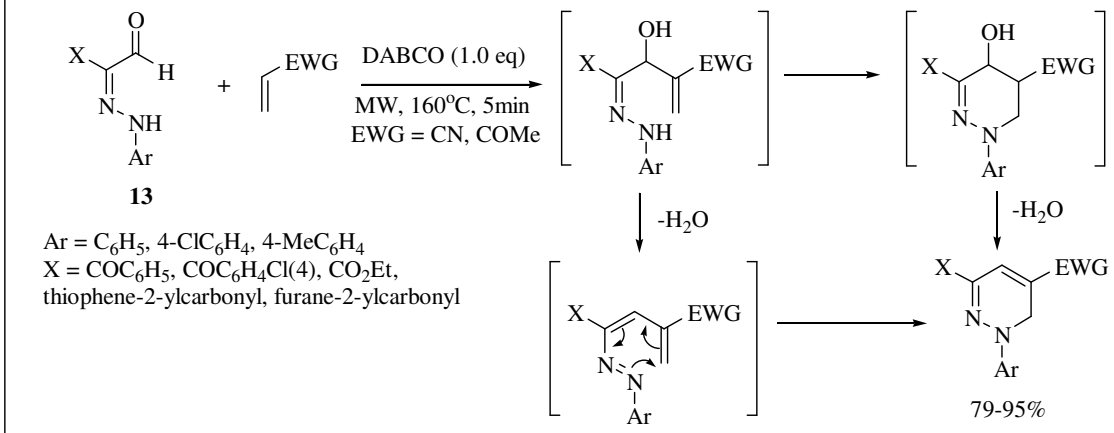
Katrizky and co-workers[64] reported, aminomethybenzotriazoles (**12**) as electrophiles for the coupling with various activated alkenes under the influence of $TiCl_4$ followed by treatment with NaH to provide Baylis-Hillman adducts according to the reaction sequence as shown in Scheme 4 (One example is presented).

Scheme 4



Recently Awadi and co-workers[65] have used arylhydrazonals (**13**) as electrophiles for the Baylis-Hillman coupling with acrylonitrile and MVK to provide pyridazines (Scheme 5).

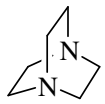
Scheme 5



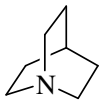
CATALYSTS / CATALYTIC SYSTEMS:

In addition to DABCO (**5**) several tertiary amine catalysts / catalytic systems[59,66-70] (Figure 4) and non-amine catalysts/catalytic systems[71-78] (Figure 5) have been successfully employed for catalyzing or promoting the Baylis-Hillman coupling between various activated alkenes and elecrophiles providing a verity of multifunctional molecules. Due to its high versatility DABCO has been the most commonly used catalyst for the Baylis-Hillman reaction. Representative examples of B-H reactions using various catalysts are presented in the Equations 6-9 and Schemes 6-7.

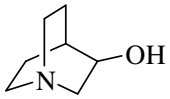
Figure 4



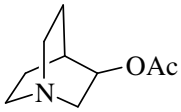
DABCO **5** ref:8



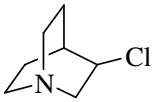
QD **14** ref:66



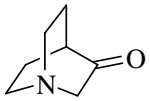
3-HQD **15** ref:66



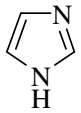
16 ref:66



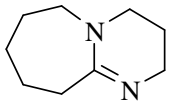
17 ref:66



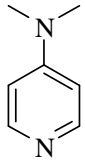
18 ref:66



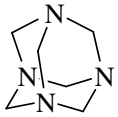
Imidazole **6** ref:67



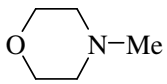
DBU **19** ref:68



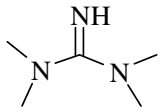
DMAP **20** re:8



Urotropine (HMT)**21** ref:69



NMM **22** ref:69



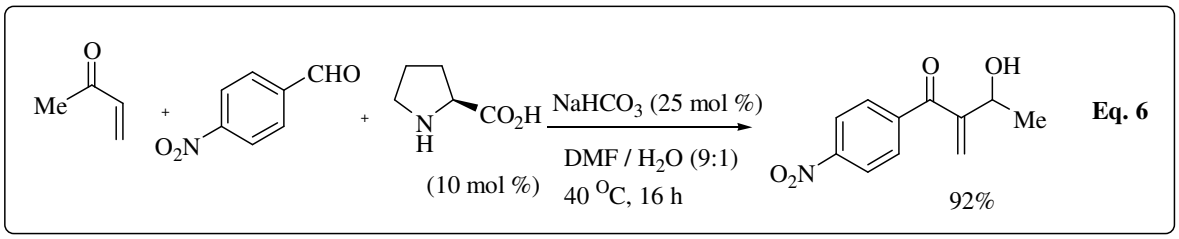
TMG **23** ref:70

Et_3N (aq / MeOH) **2** ref:59

Figure 5

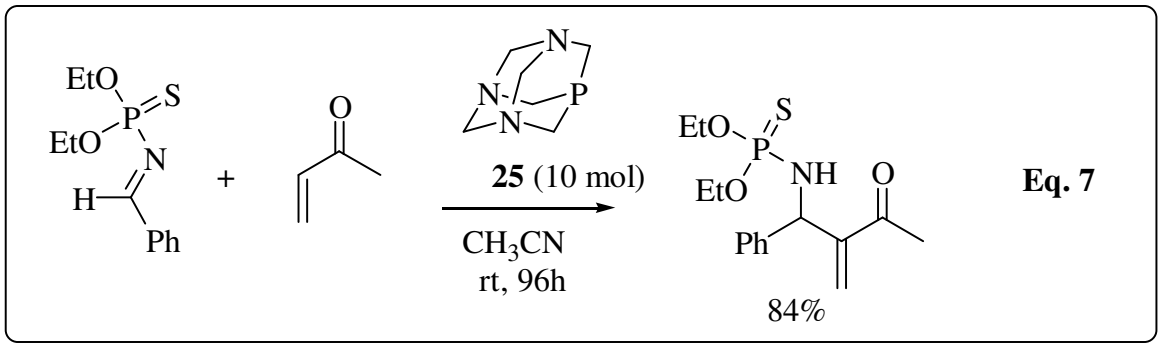
R_2S-$TiCl_4$	$TiCl_4$-R_4NX X = halogen	$TiCl_4$-R_3N	$TiCl_4$	TBDMSOTf & 	Et_2AlI **24**
ref:71,72	ref:72-74, 77	ref:75	ref:76	ref:77	ref:78

Recently Gruttadauria and co-workers[79] have successfully employed *L*-proline as a catalyst in the presence of sodium hydrogen carbonate for the Baylis-Hillman reaction between MVK / EVK and aryl aldehydes (Eq. 6) (one such example is presented).



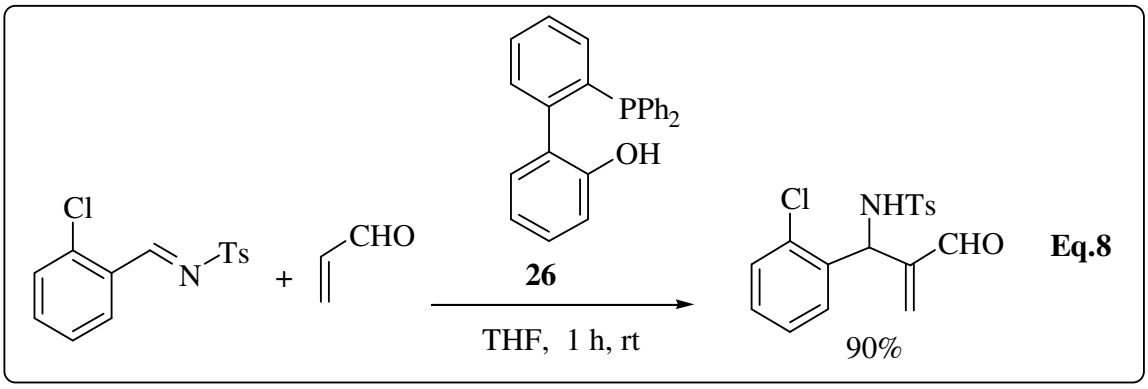
Eq. 6

1,3,5-Triaza-7-phosphaadamantane[80] (PTA) (**25**) has been elegantly used as a catalyst in the Baylis-Hillman reaction between MVK and imines by Zhou and co-workers. One example is presented in Eq. 7



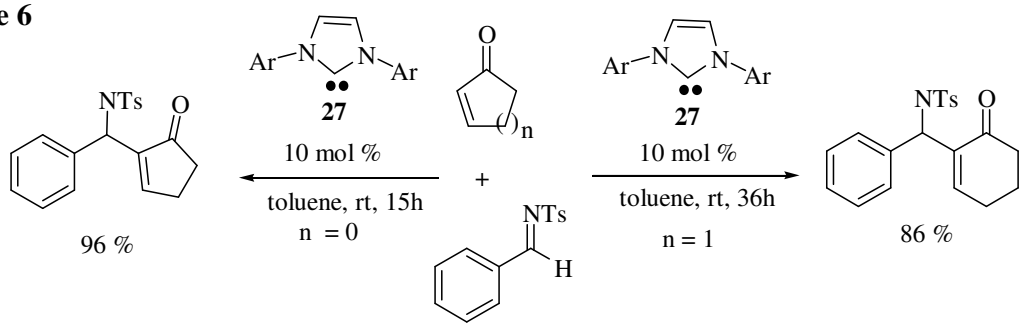
Eq. 7

Recently Huang and co-workers[81] used bifuctional catalyst (**26**) for Baylis-Hillman reaction of N-sulfonated imines with acroline (in Eq. 8, one representative example is given).



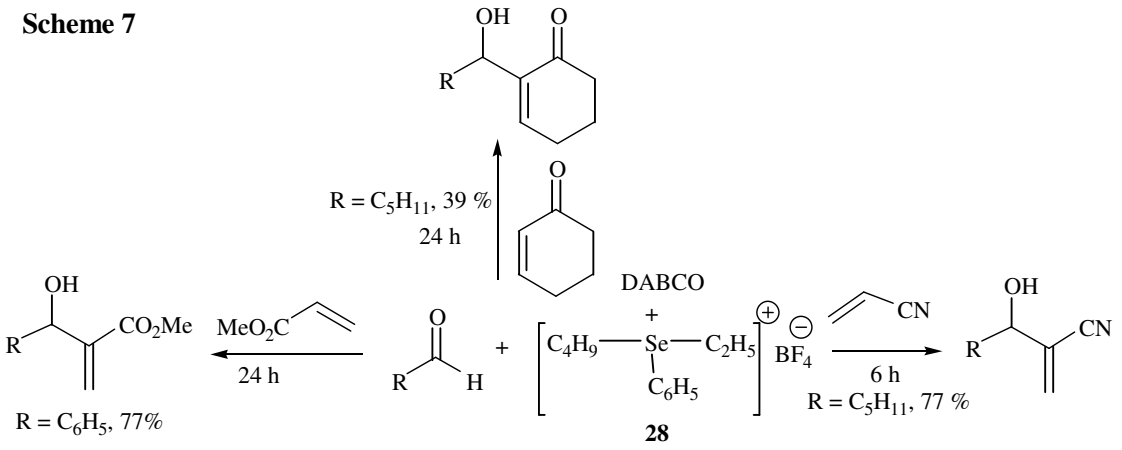
N-Heterocyclic carbenes (**27**) have been recently used as a catalysts for Baylis-Hillman reaction between cyclic enones and N-tosylarylamines by Ye and co-workers[82] (Scheme 6).

Scheme 6

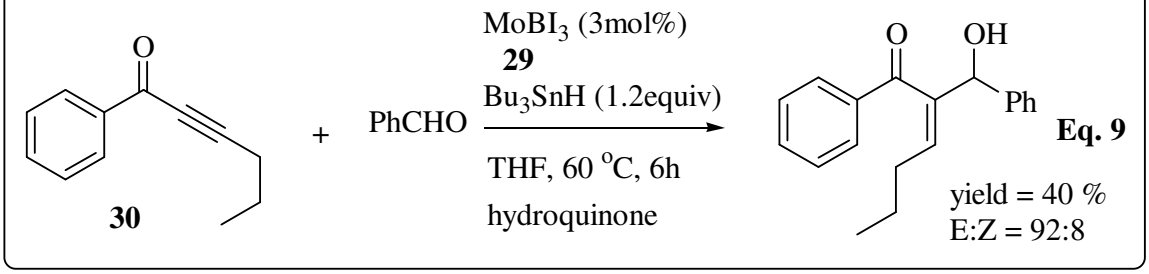


Very recently Lenardao and co-workers[83] have used selenium tetraflurobarate (**28**) as a co-catalyst along with DABCO for performing Baylis-Hillman reaction between activated alkenes and various aldehydes. Representative examples are given in Scheme 7.

Scheme 7



Molybdenum-catalyzed (**29**) Baylis-Hillman reaction between acetylenic ketone (**30**) and aldehyde providing β-substituted Baylis-Hillman adducts was reported by Kazmaier and Lakshmi,[84] following the reaction sequence shown in Eq. 9. (One representative example presented)**.**



Eq. 9

ASYMMETRIC BAYLIS-HILLMAN REACTION:

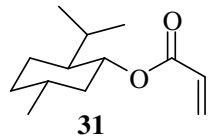
If electrophile is prochiral, there is a possibility of achieving chiral induction in the Baylis-Hillman reaction. Asymmetric version can be performed, in principle, in four different ways 1) having chirality in activated alkene system, 2) having chirality in electrophile

component, 3) using a chiral catalyst and 4) employing chiral additive or medium. Chiral chemists have been working for last several years and in fact, made significant progress in all these aspects.

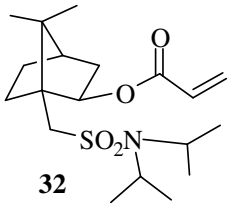
CHIRAL ACTIVATED ALKENES:

Various chiral acrylates and acrylamides[85-88] (Figure 6) have been designed, prepared and employed for coupling with electrophiles to provide the resulting the adducts in low to high diastereoselectivities. Selected examples are shown in Equations 10-11 and Scheme 8.

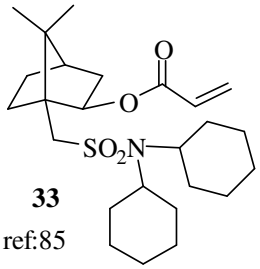
Figure 6



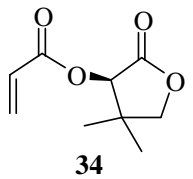
31
ref:85



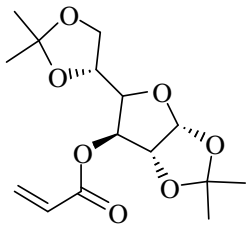
32
ref:85



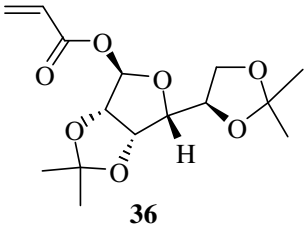
33
ref:85



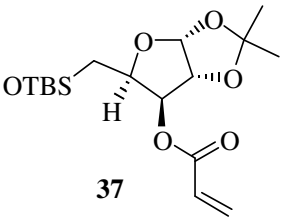
34
ref:86



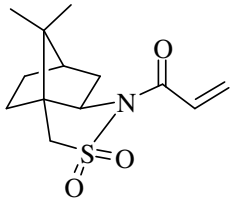
35
ref:87



36
ref:87

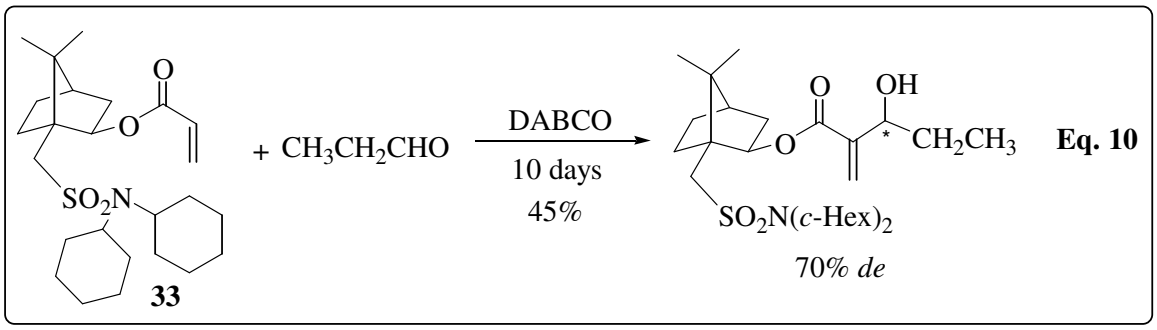


37
ref:87

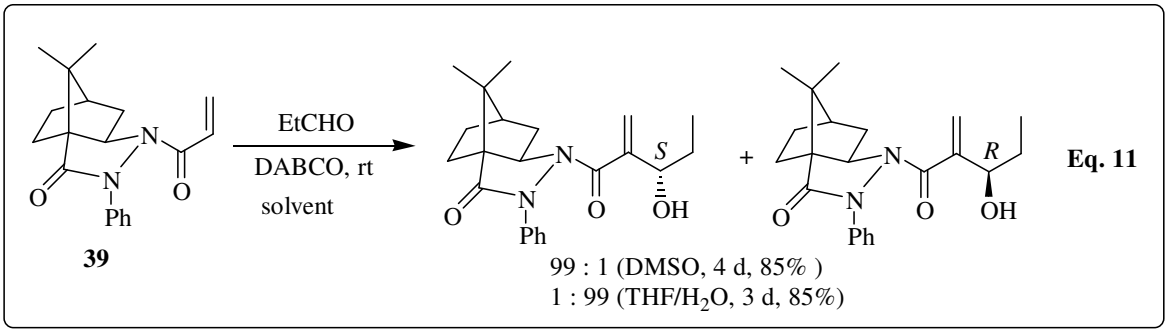


38
ref:88

Our research group[85] has employed chiral acrylate (**33**) as activated alkene for diastereoselective Baylis-Hillaman reaction with different aldehydes to provide the resulting adducts in low to moderate selectivity. One example is presented in Eq. 10.

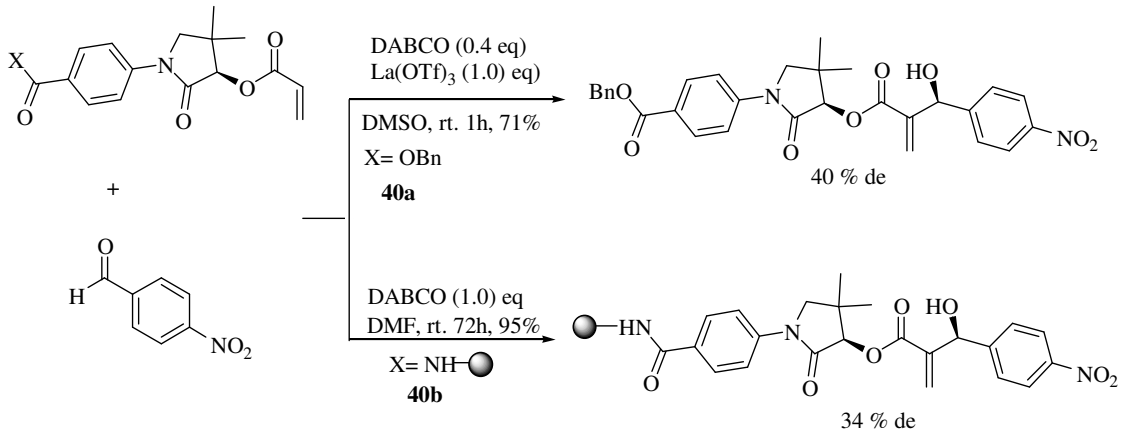


Yang and Chen[89] have used enantiopure acryloylhydrazide (**39**) as activated alkene in Baylis-Hillman reaction with aldehydes. An interesting reversal of diastereoselectivity has been observed by changing the solvent from DMSO to THF / H_2O in this reaction. One such example is presented in the Eq. 11.



Calmes and co-workers[90] have recently prepared chiral arylate (**40a**) and polymer bound chiral acrylate (**40b**) and examined their application in Baylis-Hillman reaction with various aldehydes. The resulting adducts were obtained in high yields and moderate selectivities (Scheme 8).

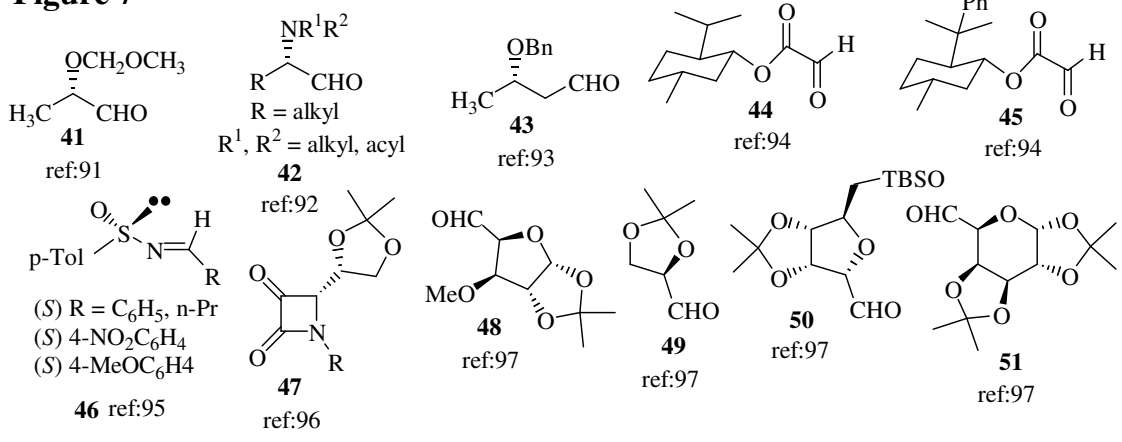
Scheme 8



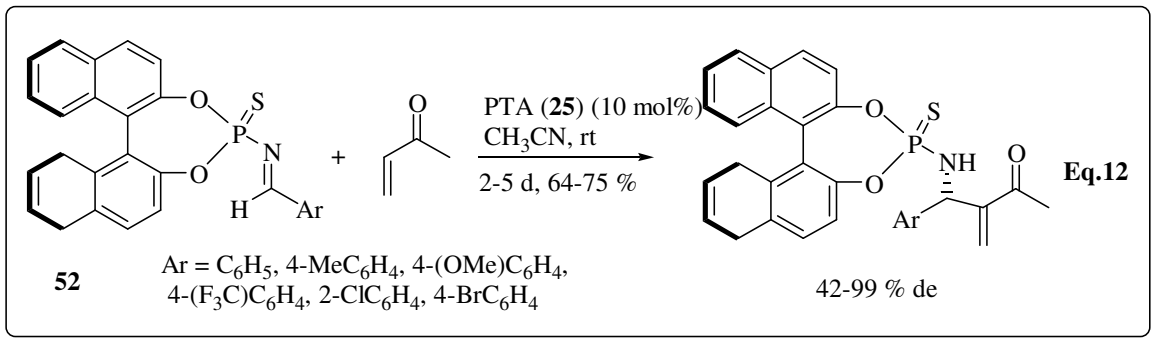
CHIRAL ELECTROPHILES:

Several efforts have been made to use a number of chiral electrophiles[91-97] (Figure 7) for reaction with activated alkenes under the influence of representative catalytic systems to provide the resulting multifunctional Baylis-Hillman adducts in poor to high diastereoselectivities.

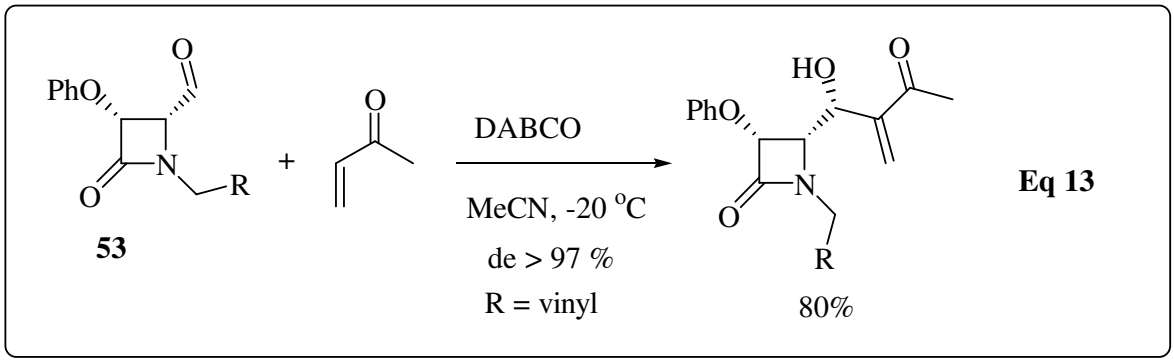
Figure 7



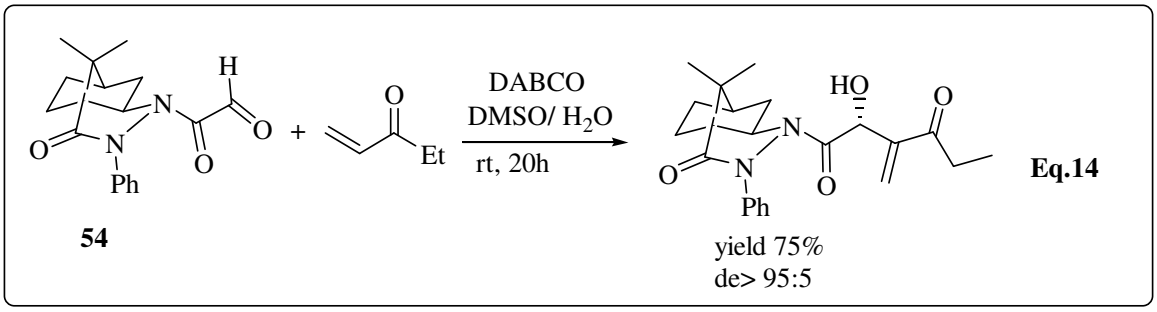
Chiral thiophosphorylimines (**52**) (as chiral elecrtrophile) derived from (S) binapthol[98] have been employed in the Baylis-Hillman reaction with MVK under the influence of PTA (**25**) as a catalyst by Zhou and co-workers to provide the resulting adducts in moderate to excellent diastereoselectivities (Eq.12).



Alcaide and co-workers[99] examined the potential of 4-oxoazetidine-2-caboxaldehydes (**53**) as electrophiles for coupling with MVK under the catalytic influence of DABCO to provide the desired Baylis–Hillman adducts in high diastereoselectivities. One example is presented in Eq.13.



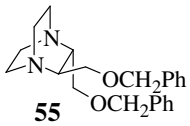
Chen and Pan[100] have employed N-glyoxyloyl camphorpyrazolidinone (**54**) as chiral electrophile for coupling with various activated alkenes for the diastereoselective Baylis-Hillman reaction (Eq.14) (one such example is described).



CHIRAL CATALYSTS / CATALYTIC SYSTEMS:

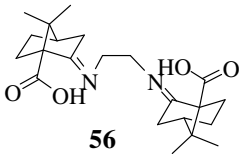
The real challenge in achieving asymmetric version of Baylis-Hillman reaction lies in the development of appropriate chiral catalysts. Efforts have been made by various research groups throughout the world and in fact considerable progress have been achieved in this direction. Representative chiral amine catalysts[101-105] examples are presented in Figure 8. Phosphines and thiourea catalysts[106-114] (Figure 9) have been prepared and their applications have been systematically studied. Some of the Baylis-Hillman adducts prepared in this way have been used as synthons for the synthesis of biologically active and natural products.

Figure 8



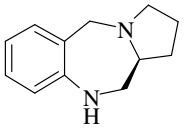
55

ref;101



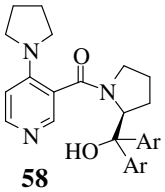
56

ref;102



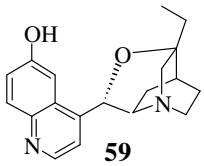
57

ref;103



58

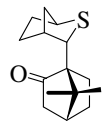
ref;104



59

ref;105

Figure 9



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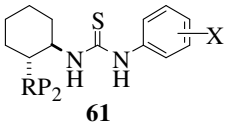
ref:106



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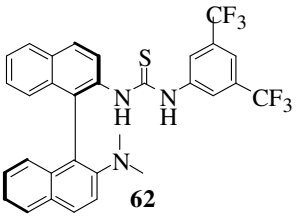
ref:107



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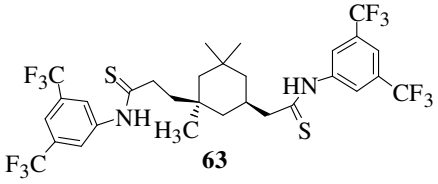
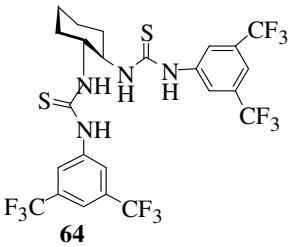
ref:108



63

ref:109



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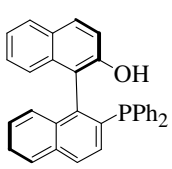

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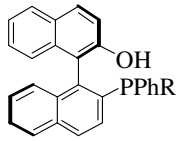
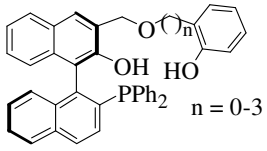
ref:111



R = H, Et, i-Pr
Bu, Cy, i-Bu, Ph, Br

66

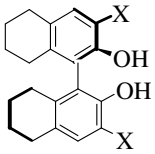
ref:112



n = 0-3

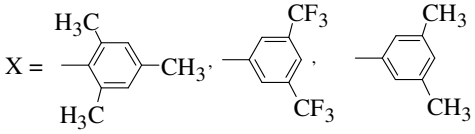
67

ref:113

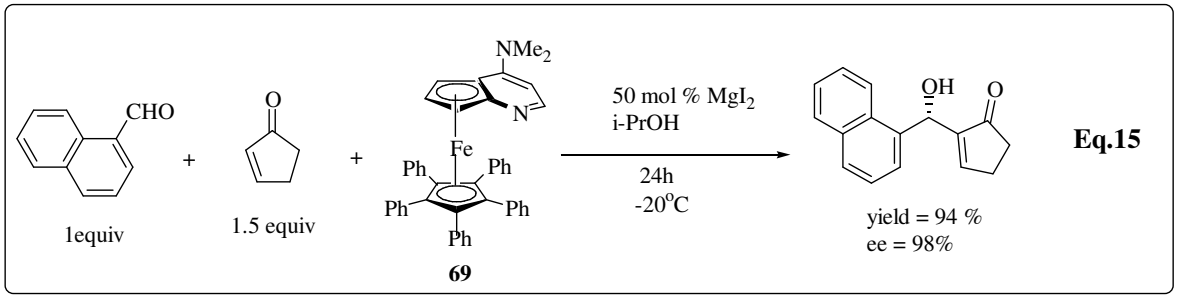


68

ref:114

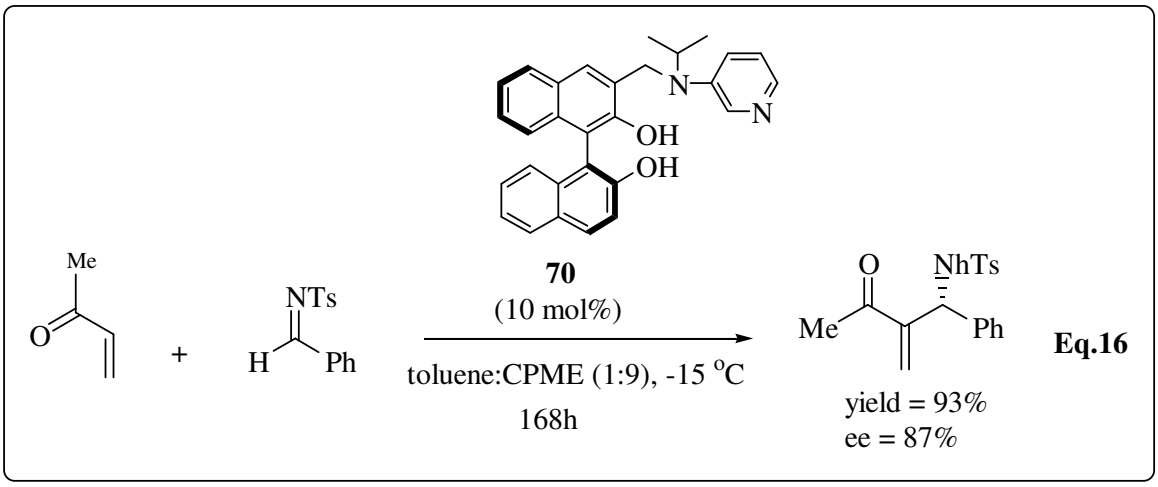


Connel and co-workers[115] have reported MgI_2 accelerated highly enatioselective Baylis-Hillman reaction between cyclopentenone and aldehydes using ferrocine based chiral catalyst **(69).** One representative example shown in Eq. 15.



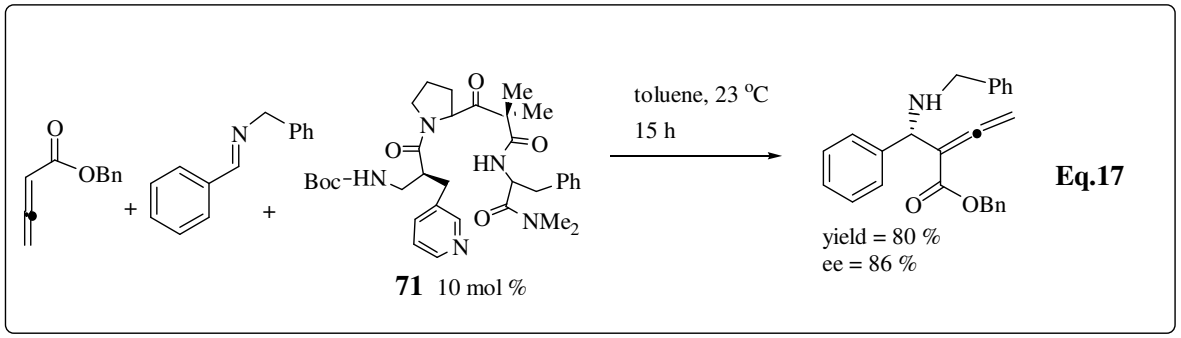
Eq.15

Sasai and co-workers[116] described an enantioselective Baylis-Hillman reaction of alkyl vinyl ketone with various N-tosylimimes under the influence of chiral bifuctional organocatalyst (**70**) (Eq.16). The resulting adducts were obtained in high enatiomeric purity (One example is presented).



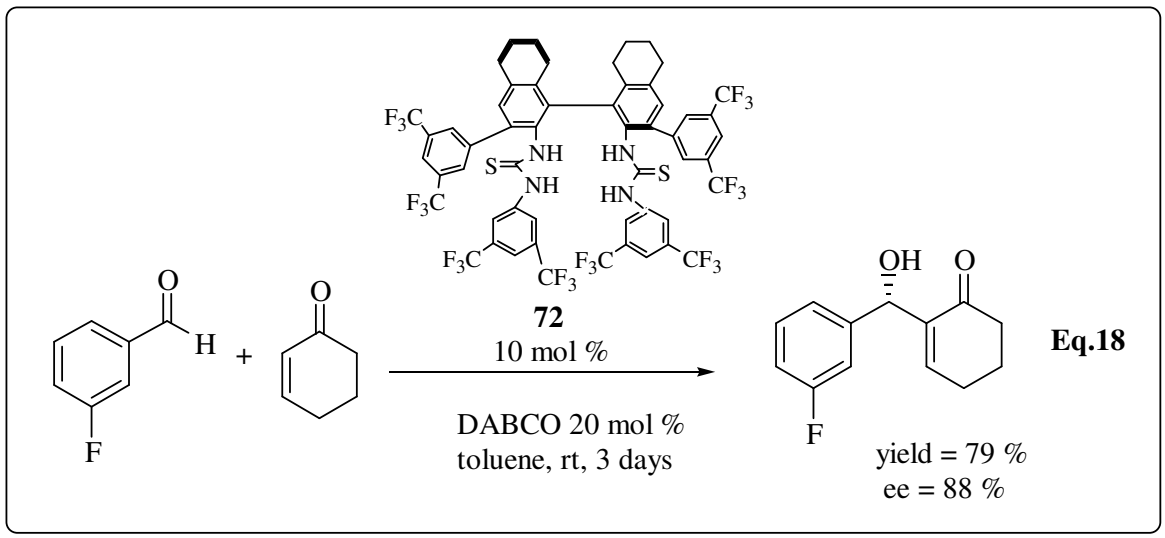
Eq.16

Miller and co-workers[117] have reported a highly enatioselective Baylis-Hillman reaction of allenic ester with imines under the catalytic influence of proline based chiral catalyst (**71**). One representative example is presented in Eq. 17.



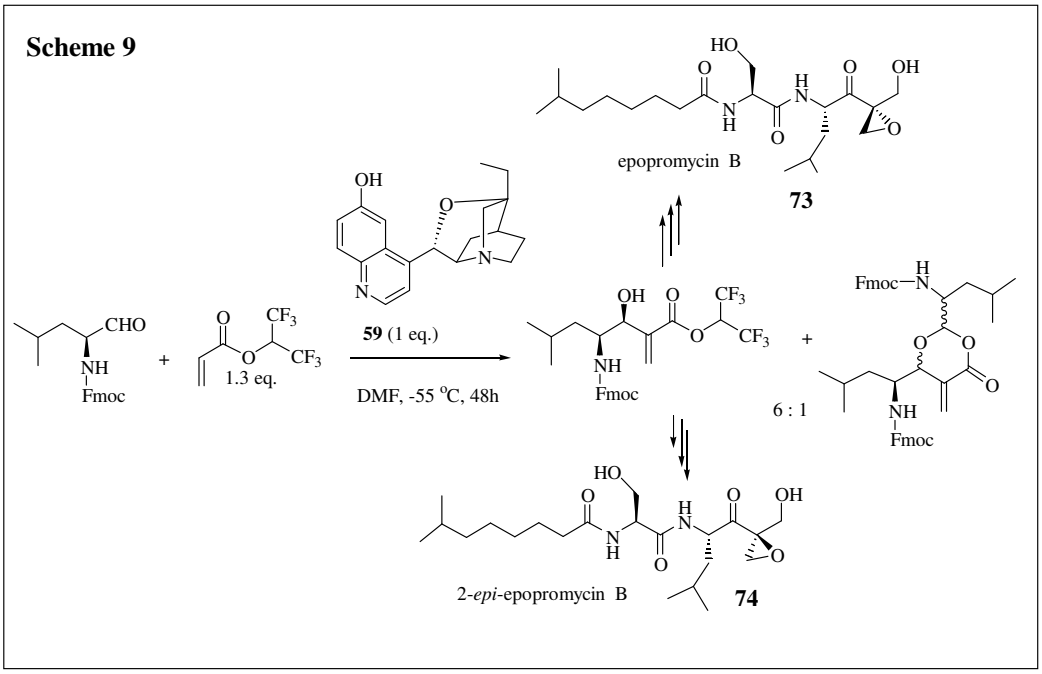
Eq.17

Shi and Liu[118] have reported an interesting asymmetric Baylis-Hillman coupling of cyclohexe-1-one with aryl aldehydes in the presence of bis-thiourea chiral catalyst (**72**). One such example is presented in the Eq. 18



Eq.18

Hatakeyama and co-workers[119] developed an elegant bifunctional catalyst (**59**) for the asymmetric Baylis-Hillman reaction and subsequently this strategy has been applied for synthesis of important biologically active molecules epopromycin B (**73**) and 2-*epi*-epopromycin B (**74**) following the reaction sequence as described in Scheme 9.

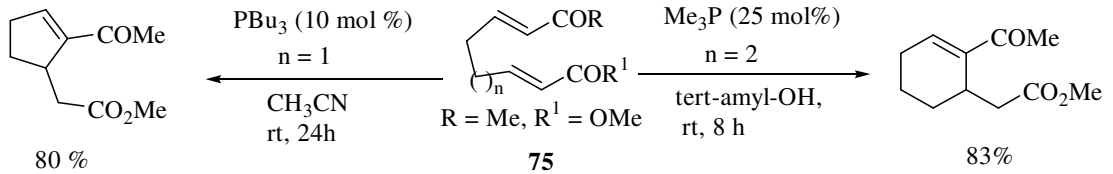


INTRAMOLECULAR BAYLIS-HILLMAN REACTION:

If the substrates contain both the activated alkene and electrophile components in appropriate position there is possibility for performing intramolecular version of Baylis-Hillman reaction providing cyclic adducts. Although the Baylis-Hillman reaction has grown to high popularity, intramolecular version has not grown in that proportion. However during the last few years this aspect has received considerable attention from synthetic chemists. Some of the recent developments are described in this direction.

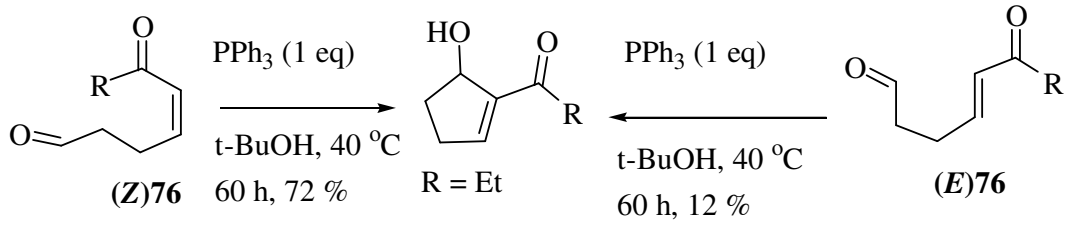
Roush and co-workers[120] reported an intramolecular Baylis-Hillman ring closing reaction of diactivated alkenes (**75**) to provide a convenient method for synthesis of functionalized cyclopentene / cyclohexene derivatives using trialkylphosphines as catalysts (Scheme 10).

Scheme 10



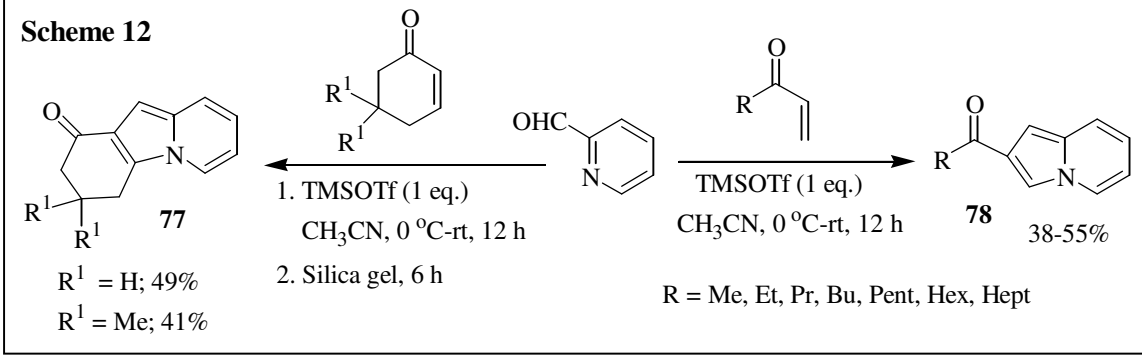
Shi and co-workers[121] have reported phosphine catalyzed intramoleclar Baylis-Billman reaction of the enone aldehyde substrate (**76**) according to Scheme 11.

Scheme 11

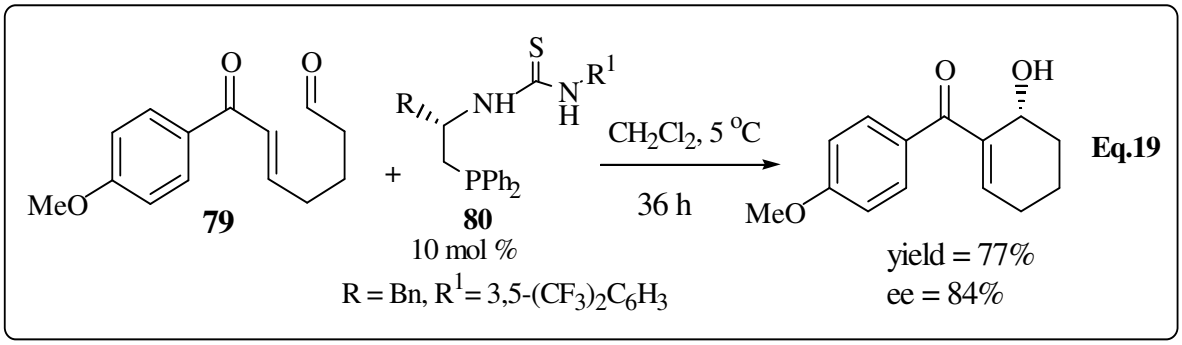


Our research group[122] described an electrophile induced Baylis–Hillman reaction between activated alkenes and pyridine-2-carboxldehyde under the influence of trimethylsilyl trifluoromethanesulfonate (TMSOTf), leading to a novel synthesis of indolizine derivatives (**77, 78**) in one-pot operation (Scheme 12).

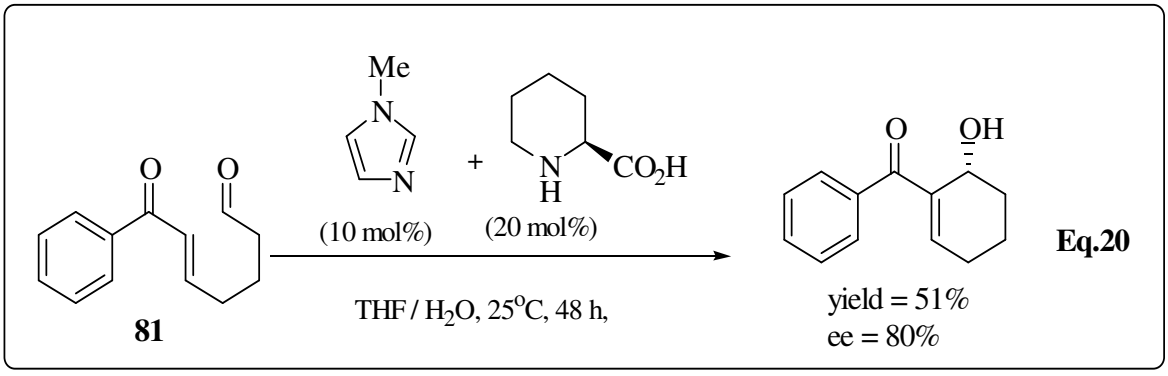
Scheme 12



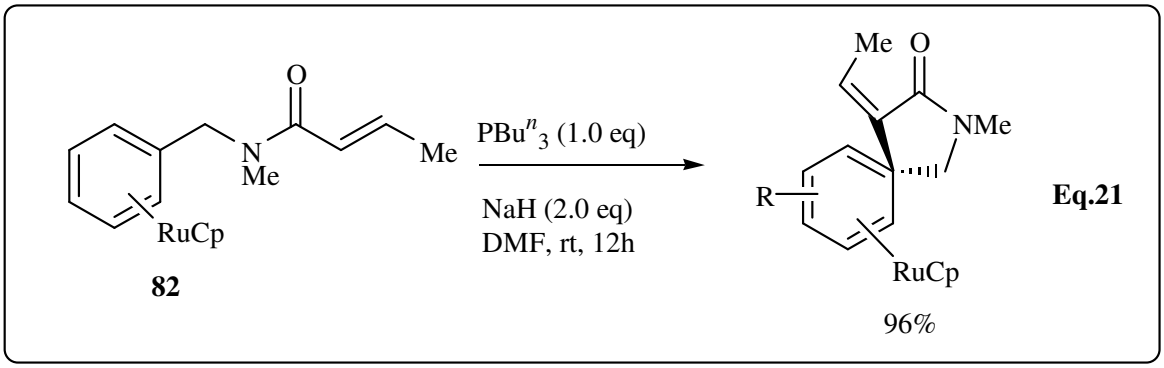
Wu co-workers[123] reported an interesting intramolecular asymmetric Baylis-Hillman ring closing reaction of enone-aldehyde substrate (**79**) using chiral amino acid derived phosinothiourea as a catalyst (**80**) (Eq. 19).



Miller and co-workers[124] reported (*S*)-2-pipecolinic acid catalyzed asymmetric intramolecular Baylis-Hillman reaction of enone-aldehyde substrates (**81**) according to the Eq. 20 (one example is given).



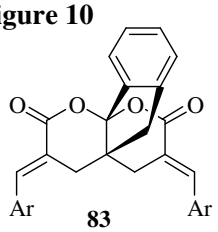
Pigge and co-workers[125] reported an interesting organometallic intramolecular Baylis-Hillman reaction. In this reaction ruthenium-arene complex (**82**) is employed as an electrophile to provide the resulting spiro adduct with 100% diastereoselectivity (Eq. 21).



APPLICATIONS OF THE BAYLIS–HILLMAN ADDUCTS:

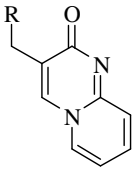
Because of the presence of many fictional groups in proximity the Baylis-Hillman adducts have become important substrates for a number of name and un-named reactions. Thus these substrates have been used in various organic reactions like Friedel-Crafts reaction, Diels-Alder reaction, Heck reaction, Claisen rearrangements, isomerization, hydrogenation, and photochemical reactions[3-11] *etc.* These adducts have also been elegantly employed as valuable synthons in the synthesis of important natural products, biologically active molecules and hetero / carbocycles. Some of the important and recent molecules[126-174] synthesized using Baylis-Hillman adducts are presented in Figures 10-13.

Figure 10



83

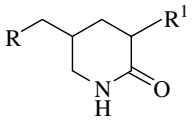
ref:126



84

ref:127

R = alkyl, aryl

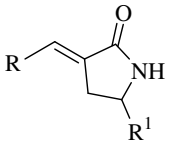


85

R = alkyl, aryl

R^1= H,Me

ref:128

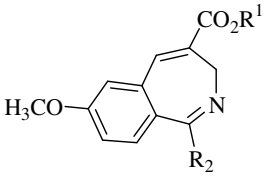


85

ref:129

R = alkyl, aryl

R^1= H,Me

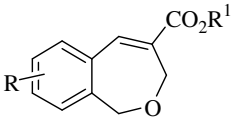


87

ref:130

R^1 = Me, Et

R^2= Me, Et

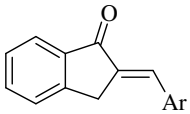


88

ref:131

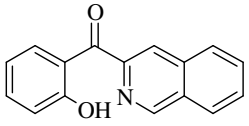
R = alkyl

R^1= Me, Et



89

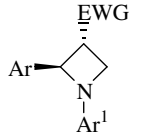
ref:132



90

ref:133

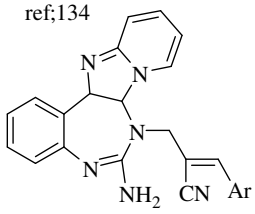
Figure 11



EWG = CN, CO_2Me

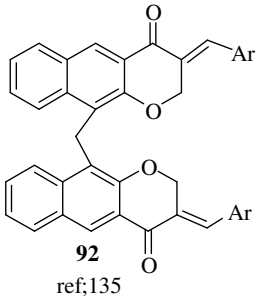
91

ref;134



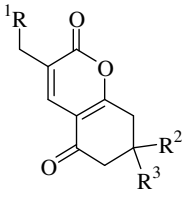
95

ref;138



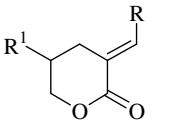
92

ref;135



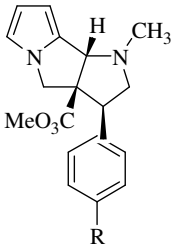
96 ref;139

R^1 = aryl, R^2= R^3= Me



93 ref;136

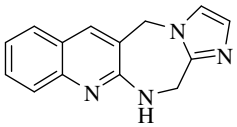
R^1 = H, aryl, R= aryl



R = H, Cl, Br

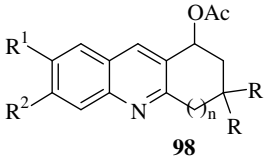
97

ref;140



94

ref;137



98

ref;141

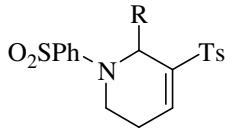
R = Me

R^1 = H, OMe, OEt

R^2 = H, OMe,Cl

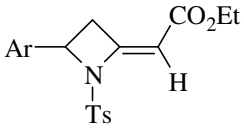
n = 0,1

Figure 12

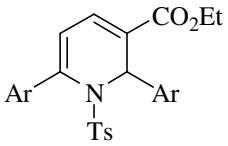


99

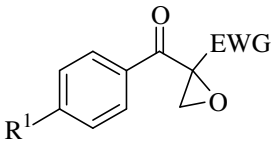
R = C_6H_5, *p*-ClC_6H_5, *p*-NCC_6H_5 ref:142



100 ref:143



101 ref:143

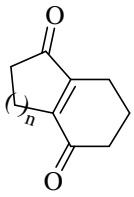


102

EWG = CN, CO_2Et

R^1= H, Cl,OMe

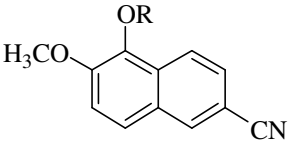
ref:144



103

n = 0-3

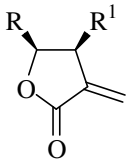
ref:145



104

R= H, alkyl

ref:146

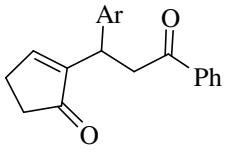


105

R = C_6H_5, 4-$NO_2C_6H_4$,4-$OMeC_6H_4$

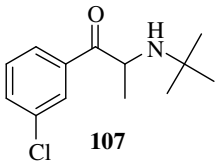
R^1 = C_6H_5, naphyl, tolyl,4-$OMeC_6H_4$

ref:147



106 ref:148

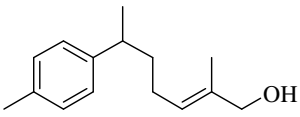
Figure 13



107

(±) -Bupropion

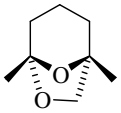
ref;149



(±) -Nuciferol

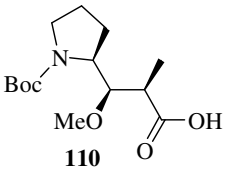
108

ref;150



(±) -Frontalin

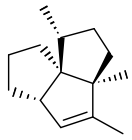
109 ref;151



110

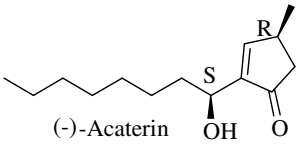
N-Boc-dolaproine(DAP)

ref;152



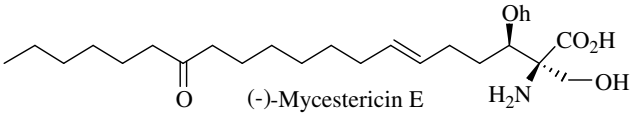
(+)-Arnicenone

111 ref;153



(-)-Acaterin

112 ref;154

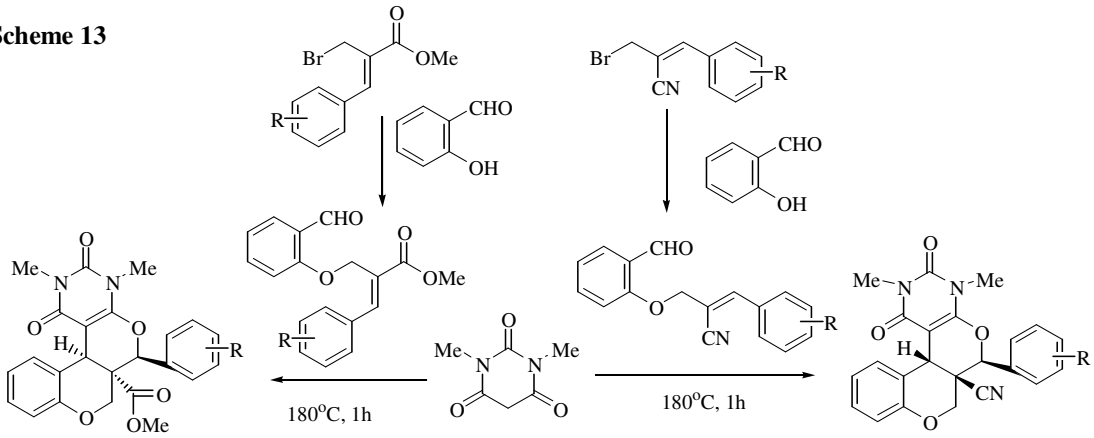


(-)-Mycestericin E

113 ref;155

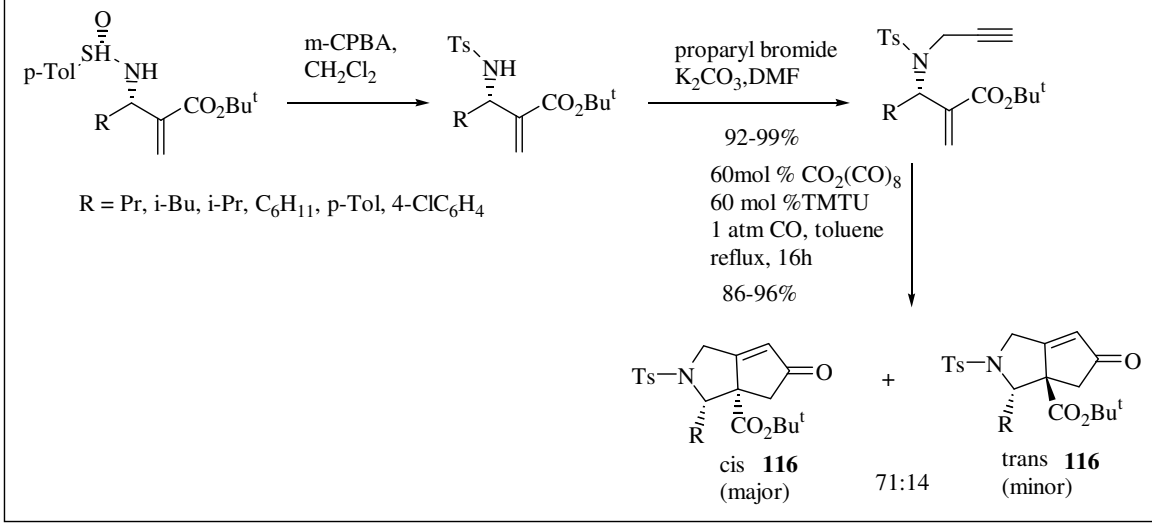
Bakthadoss and co-workers[156] reported a facile synthesis of highly fused tetracyclic chromenopyran pyrimidones (**114, 115**) using Baylis-Hillman bromides according to Scheme 13.

Scheme 13

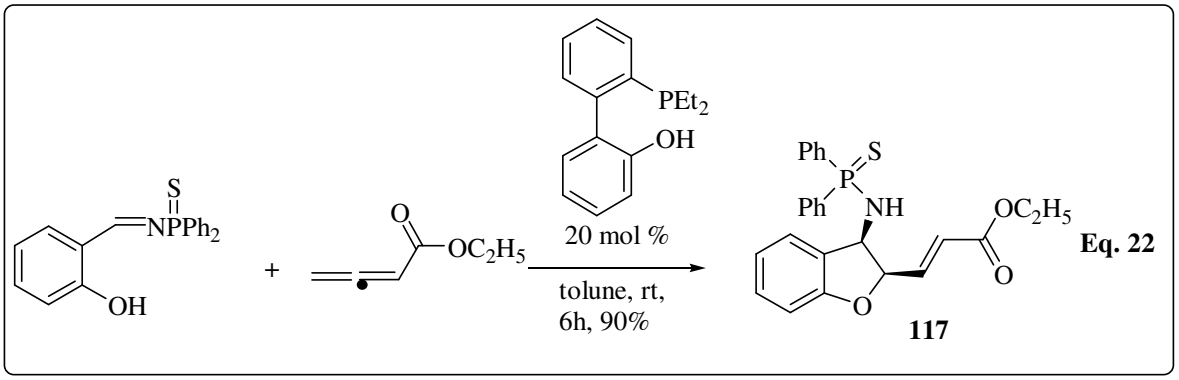


An interesting synthesis of *cis* and *trans* pyrrolidines (**116**) fused with cyclopentenones from Baylis-Hillman adducts, was reported by Kamimura and co-workers[157] following the reaction sequence shown in Scheme 14.

Scheme 14

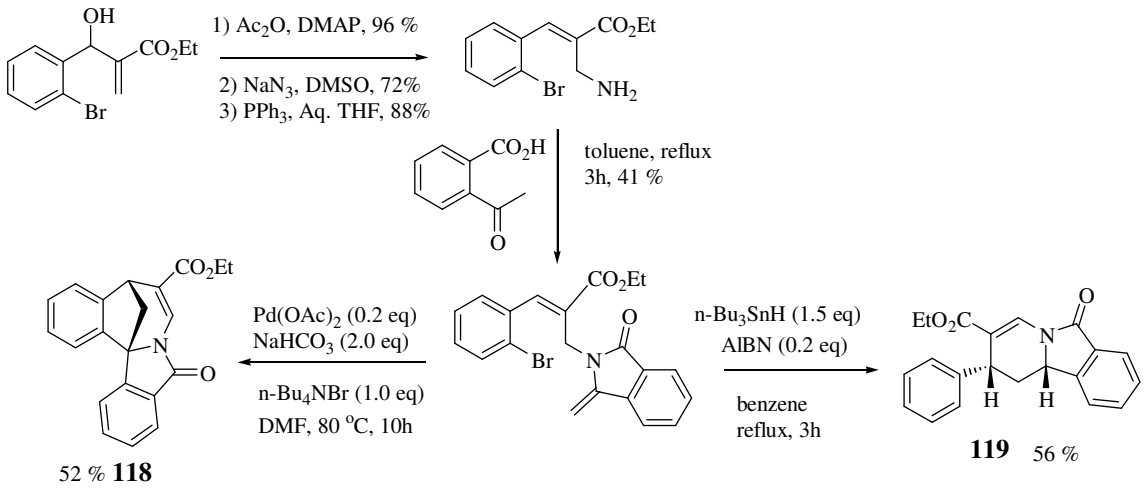


An highly sterereoselective Baylis-Hillman protocol for synthesis of cis-2,3-dihydrobenzofurans (**117**) has been reported by Chen and co-workers[158] (Eq. 22).



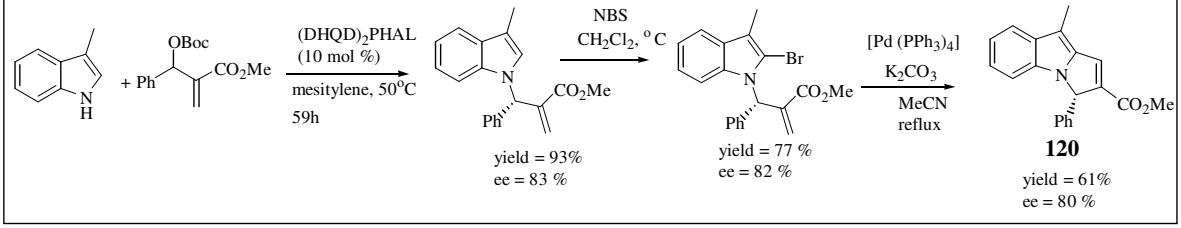
Kim and co-workers[159,160] reported a simple methodology for the synthesis of benzoazepino[2,1-a]isoindoles (**118**) and dihydropyrido[2,1-a]isoindolone (**119**) starting from Baylis-Hillman alcohols. One example each is shown in Scheme 15.

Scheme 15



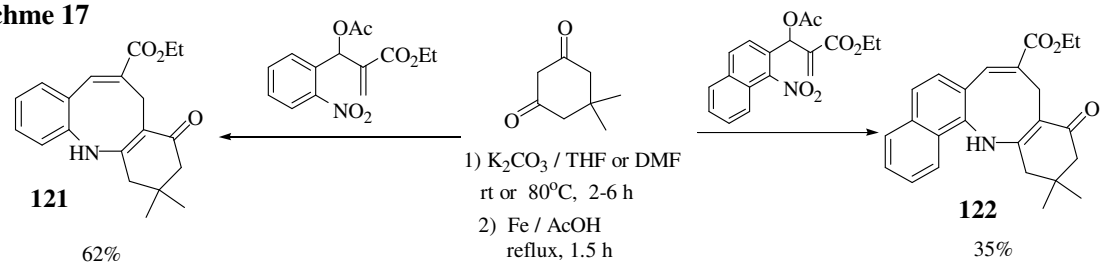
Very recently Chen and co-workers[161] reported a simple synthesis of pyrrolo [1,2-a]indole frameworks (**120**) using Baylis-Hillman adducts through intramolecular Heck reaction using [$Pd(PPh_3)_4$] as a catalyst. One example is presented in Scheme 16.

Scheme 16



An interesting methodology for facile transformation of the Baylis-Hillman acetates into functionalized tri / tetracyclic frameworks (**121, 122**) containing an important azocine moiety was reported by our research group[162] in an operationally simple one-pot procedure (Scheme 17).

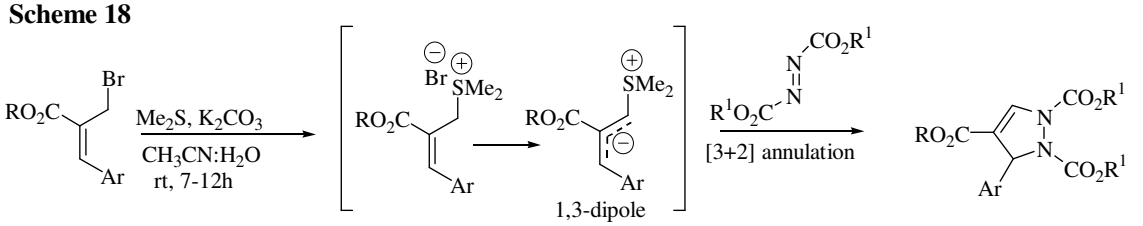
Schme 17



Very recently, our research group[163] developed a facile procedure for synthesis of functionalized dihydropyrazole derivatives (**123**), in an operationally simple one-pot methodology *via* [3+2] annulation strategy, using Baylis-Hillman bromides (as dipole)

and dialkyl azodicarboxylates (dipolarophiles) following the reaction sequence as shown in Scheme 18.

Scheme 18



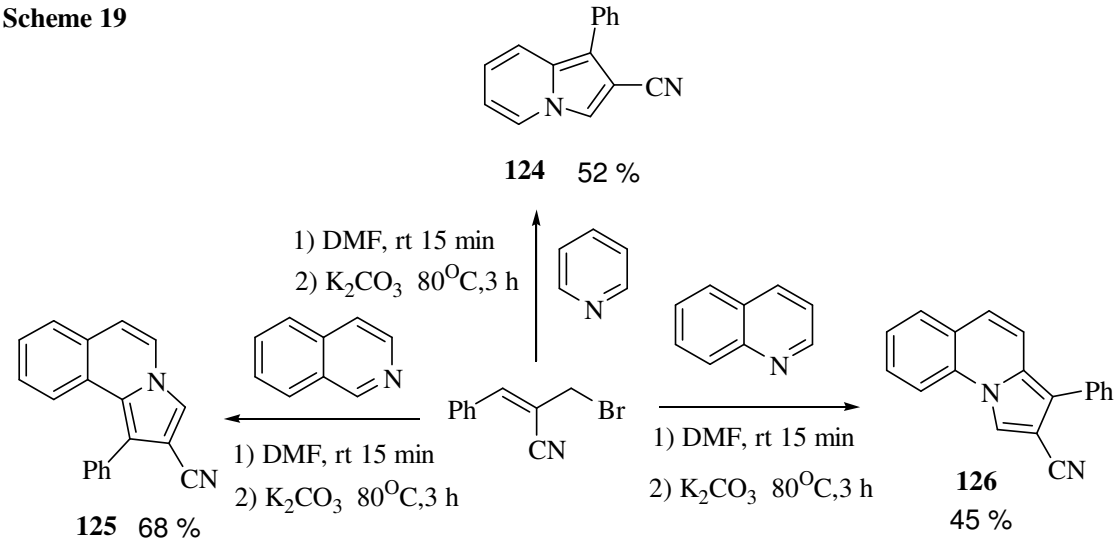
Ar = C_6H_5, 4-MeC_6H_4, 3-ClC_6H_5, 4-ClC_6H_4, 4-BrC_6H_5

R = Me, Et, Bu, Bu^t, R^1= Et, Pr^i

123 64-79%

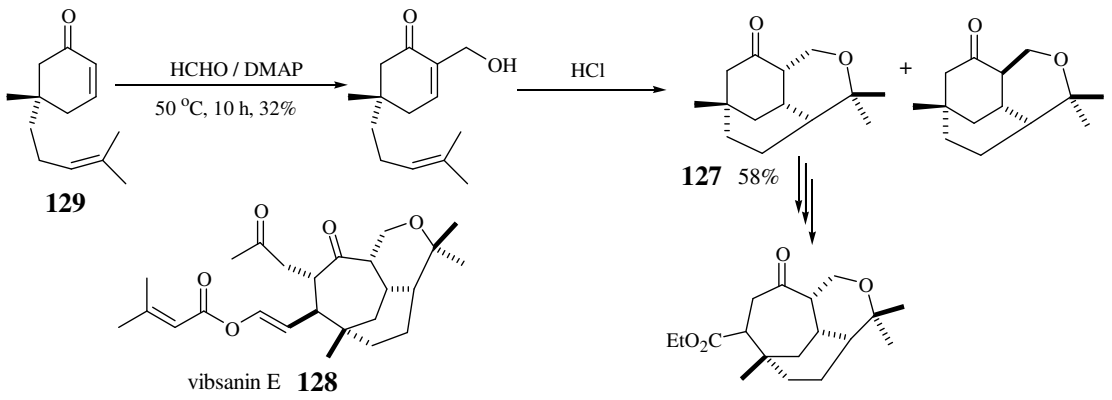
Our research group[164] reported an interesting indolizine (**124**) and bezofused indolizine frameworks (**125, 126**) from Baylis-Hillman bromides following the reaction sequence shown in Scheme 19.

Scheme 19



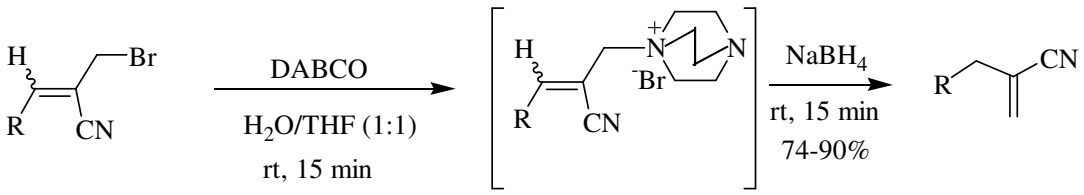
Williams *et. al.* reported a facile synthesis of tricyclic system (**127**) [which was transformed subsequently in to the core framework of vibsanin E (**128**)] starting from Baylis-Hillman adduct, obtained via the coupling of cyclohexenone derivative (**129**) with formaldehyde, following reaction sequence shown in Scheme 20[165]

Scheme 20



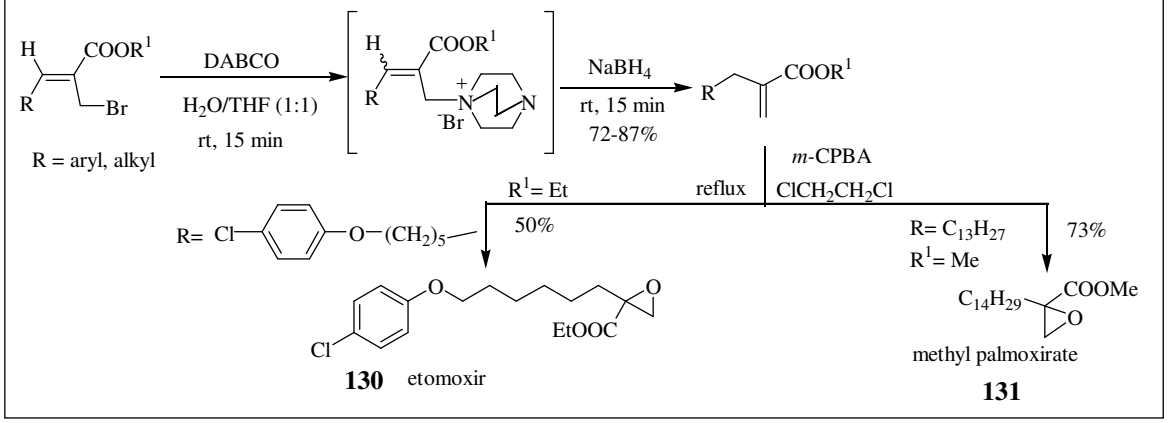
Our research group has developed a convenient and efficient synthesis of 2-methylene alknoates and alkanenitriles from Baylis-Hillman bromides [2(*Z*)-2-(bromomethyl)alk-2-enoates and 2-(bromomethyl)alk-2-enenitriles] according to Scheme 21. Subsequently two hypoglycemic agents, etomoxir (**130**) & methyl palmoxirate (**131**)[166] have been synthesized using this methodology (Scheme 22).

Scheme 21



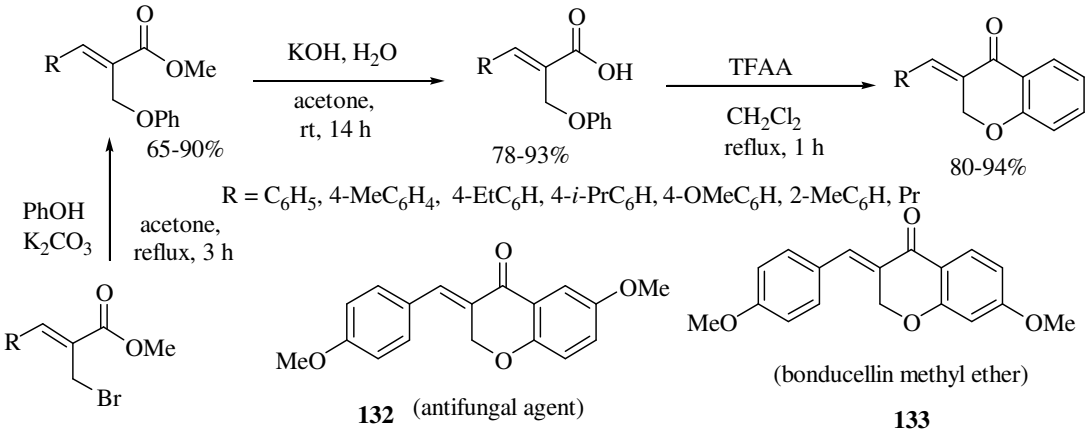
R= C_6H_5, 4-ClC_6H_4, 4-MeC_6H_4, 2-ClC_6H_4, 2-MeC_6H_4, pent, tridecyl

Scheme 22



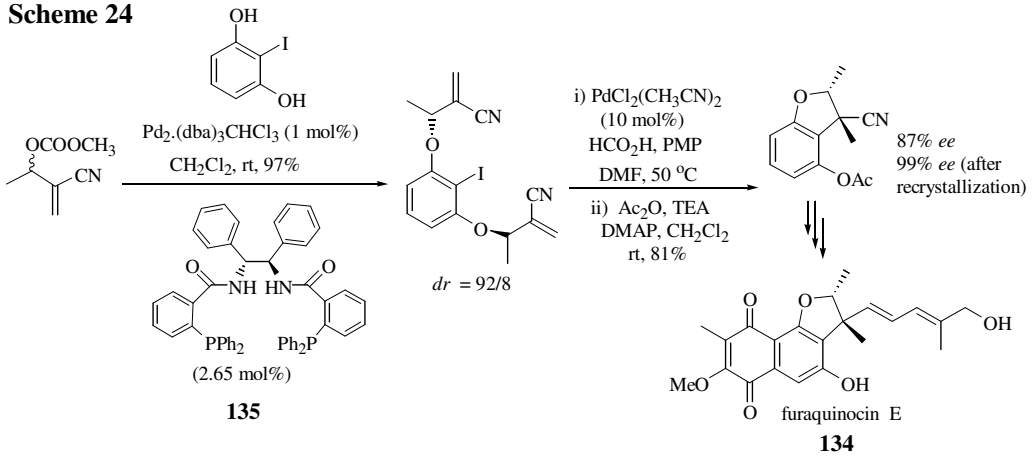
A facile synthesis of 3-arylidene(alkylidene)chroman-4-ones from Baylis-Hillman bromides following the reaction sequence described in Scheme 23 was developed by our research group.[167] This strategy has been conveniently extended to the synthesis of representative natural products such as antifungal agent (**132**), bonducellin methyl ether (**133**).

Scheme 23



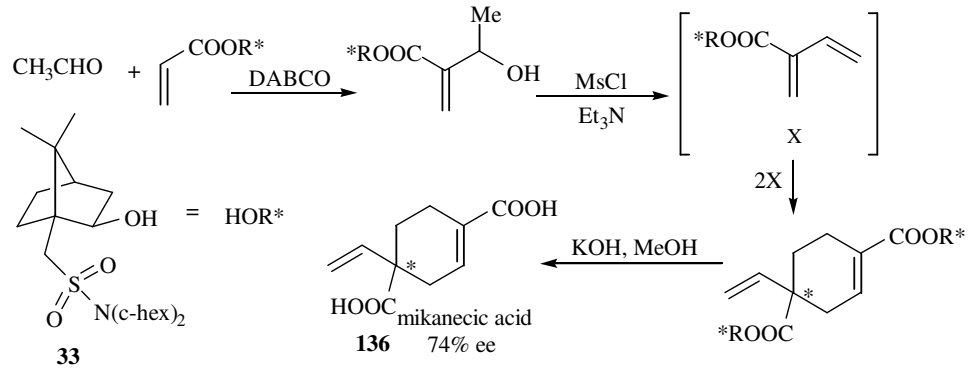
Trost and coworkers[168] have reported an elegant synthesis of furaquinocin E (**134**) biologically active compound strarting from Baylis-Hillman adducts following the reaction sequence using the chiral catalyst (**135**) as a chiral director as shown in Scheme 24.

Scheme 24



A simple synthesis of enantiomerically enriched mikanecic acid (**136**), a terpene dicarboxylic acid containing vinylic quarternary chiral center was developed by our research group[169] starting from the Baylis-Hillman adduct, derived from chiral acrylate (**33**) following the reaction sequence as described in Scheme 25.

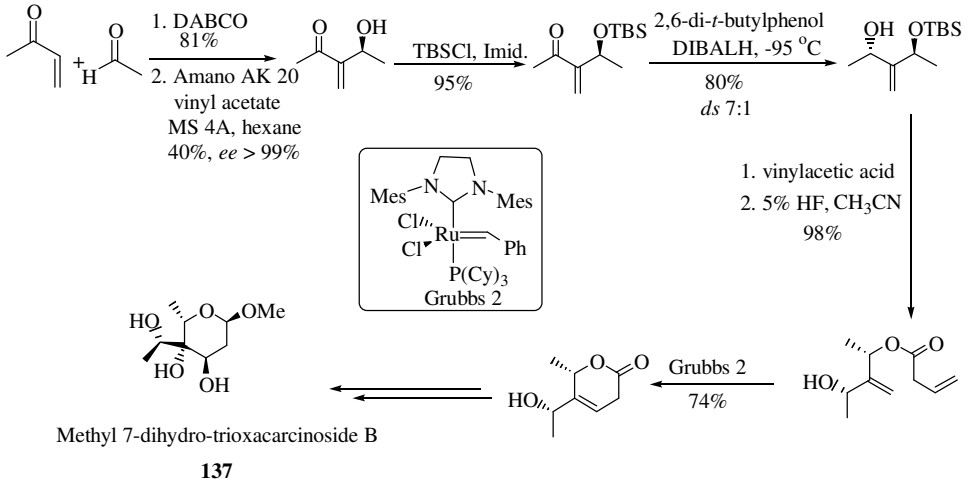
Scheme 25



(92%ee) (hydrolysis after crystalization of the diester)

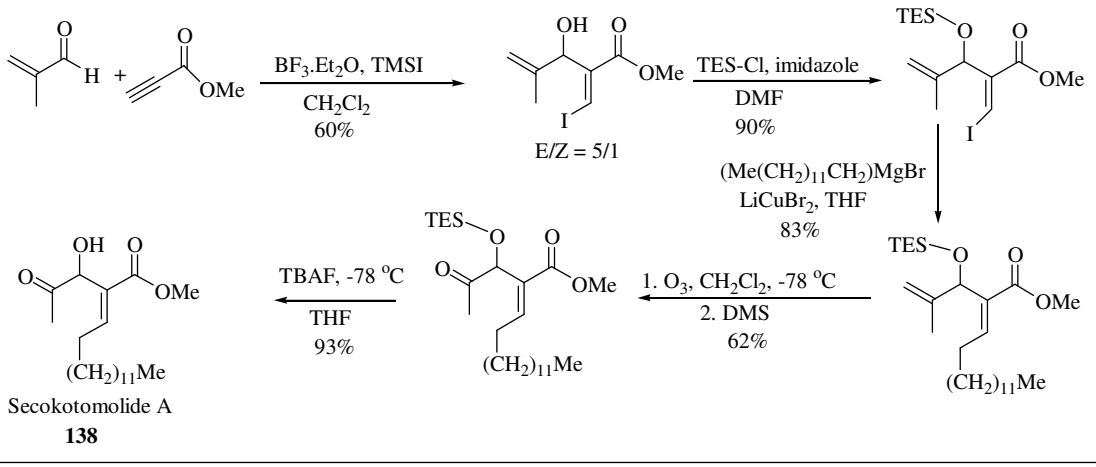
Koert and coworkers[170] have reported a stereoselective synthesis of methyl 7-dihydro-trioxacarcinoside B (**137**) starting from the Baylis-Hillman adduct, derived from acetaldehyde and MVK, according to Scheme 26.

Scheme 26



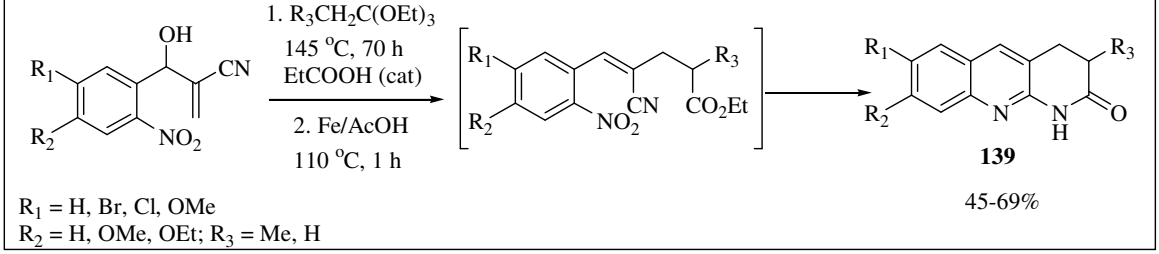
Ryu and coworkers[171] have decribed an interesting synthesis of secokotomolide A (**138**) an important bioactive compound following Baylis-Hillman protocol following reaction sequence (Scheme 27).

Scheme 27



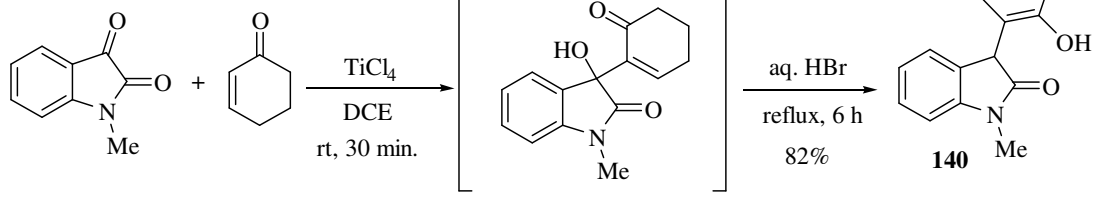
Our research group[172] has developed a simple, facile and one-pot procedure for the synthesis of tricyclic heterocyclic systems containing [1,8]naphthyridin-2-one framework (**139**) from the Baylis–Hillman alcohols following the reaction sequence as presented in Scheme 28.

Scheme 28



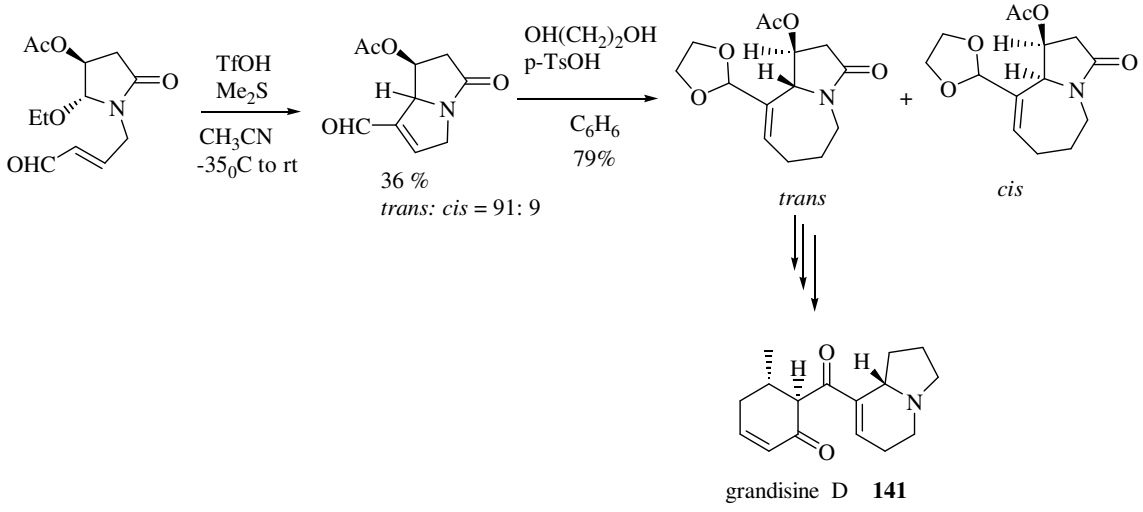
Our research group has reported a simple synthesis of 3-(2-hydroxyphenyl)indolin-2-ones[173] (**140**) via reaction of isatine derivatives with cyclohex-2-ene-1-one according to the reaction sequence shown in Scheme 29 (one example is presented).

Scheme 29



Tamura and co-workers[174] developed a simple procedure for synthesis of grandisine D (**141**) an important bioactive compound following Baylis-Hillman protocol as shown in Scheme 30.

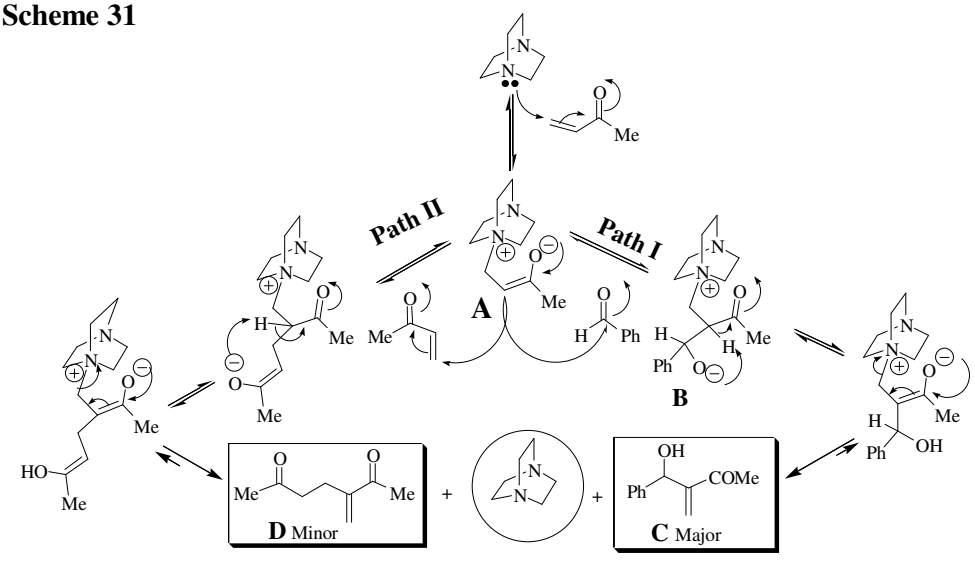
Scheme 30



MECHANISM OF THE BAYLIS-HILLMAN REACTION:

Due to large variations of parameters with respect all three essential components, the exact mechanism is not yet clearly understood. However a pluasible mechanism[8,175-180] of the Baylis-Hillman reaction is illustrated in the Scheme 31 taking the reaction between benzaldehyde (*as an electrophile*) and methyl viny ketone (*as an activated olefin*) under the catalytic influence of DABCO, as a model case. The first step is believed to involve Michel addition of DABCO to methyl viny ketone leading to the formation of zwitterionic enolate **A**. This enolate will then react with aldehyde in aldol fashion to generate zwitterionic species **B** which then releases the catalyst after proton migration to provide the desired multifunctional molecule (**C**) (Scheme 31**; Path I**). In addition to the major product, side product (**D**) is also formed in the case of reactive activated alkenes such as methylvinyl ketone because they themselves act as electrophiles (Scheme 31; **Path II**).

Scheme 31



OBJECTIVES, RESULTS AND DISCUSSION

Objectives

From the previous chapter it is quite clear that the Baylis-Hillman adducts have been widely used in various organic transformation methodologies and in the synthesis of several natural products and bioactive compounds. With a view to expand further the scope of these adducts in organic synthesis and in continuation of our on-going research program on this inspiring reaction, we have undertaken the thesis work with following objectives.

I. To develop a facile methodology for transformation of the Baylis-Hillman acetates i.e. *tert*-butyl 3-acetoxy-2-methylene-3-arylpropanoates into indenone derivatives, (*E*)-3-arylmethylidene-5-phenylpiperidine-2,6-dione and (*E*)-3-arylmethylidene-5,5-diphenylpiperidine-2,6-dione frameworks.

II. To develop a convenient one-pot methodology for transformation of

   a) Baylis-Hillman alcohols i.e. 3-hydroxy-2-methylene-3-aryl/alkylpropanoates into (*E*)-3-aryl(alkyl)methylidenepiperidine-2,6-dione derivatives.

   b) Rearranged Baylis-Hillman alcohols i.e. (2*Z*)-2-cyano-3-arylprop-2-en-1-ols into 3-methylidene-4-arylpiperidene-2,6-diones.

   c) Baylis-Hillman compounds i.e. 4-cyano-2-methoxycarbonyl-3-arylpenta-1,4-dienes into 4-aryl-3,5-dimethylidenepiperidene-2,6-dione derivatives.

III. To develop a simple methodology for synthesis of 3, 4-disubstituted-1H-pyrrole-2, 5-dione derivatives (maleimide derivatives) from the Baylis-Hillman alcohols *i.e.* 3-ethoxycarbonyl-3-hydroxy-3-aryl-2-methylenepropanenitriles (or 3-ethoxycarbonyl-3-hydroxy-2-methylenealkanenitriles) in one-pot operation.

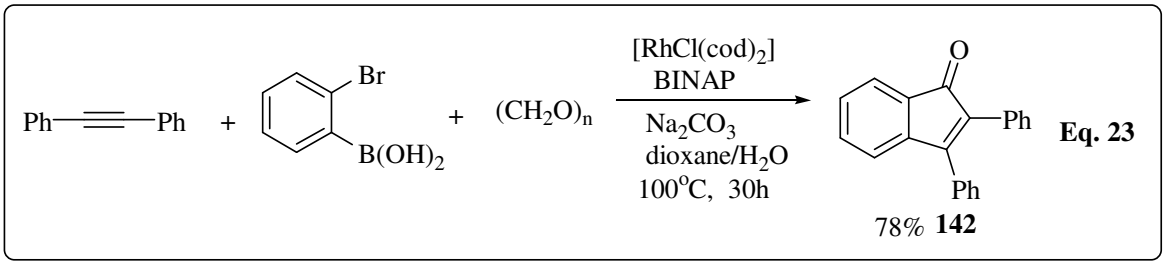
Results and Discussion

I. A Facile Synthesis of Substituted Indenones and Piperidine-2, 6-diones from the Baylis-Hillman Acetates.

Ind-2-en-1-one framework represents an important class of carbocyclic molecules because these derivatives are found in important natural products.[181,182] Some of indenone derivatives are also known to be peroxisome proliferator-activated receptor γ (PPAR γ, drug to type-2 diabetes) agonists,[183,184] estrogen receptor binding agents,[185,186] cyclooxygenase-2 inhibitors[187] and potent reversible inhibitors of 3CP.[188] Due to their significant medicinal importance, development of facile strategies for obtaining such frameworks has become an attractive endeavor in synthetic organic and medicinal chemistry. Piperidine-2, 6-dione framework is yet another medicinally important skeleton present in several biologically active and natural products such as alonimid[189, 190] (sedative and hypnotic activity), thalidomide[191] (drug to prevent morning sickness of pregnant women), streptimidone[192] (antibiotic), migrastatin[193-195] (antitumor agent),

lactimidomycin[196,197] (antibiotic) and sesbanimide[198,199] (antitumor). Therefore development of facile strategies for the synthesis of these frameworks has become a challenging task in synthetic organic chemistry. In fact, several methodologies have been reported for the synthesis of indenone and piperidine-2, 6-dione derivatives in recent years. Some of the recent and imported synthetic strategies are presented in the Equations 23, 24 and Schemes 32-35.

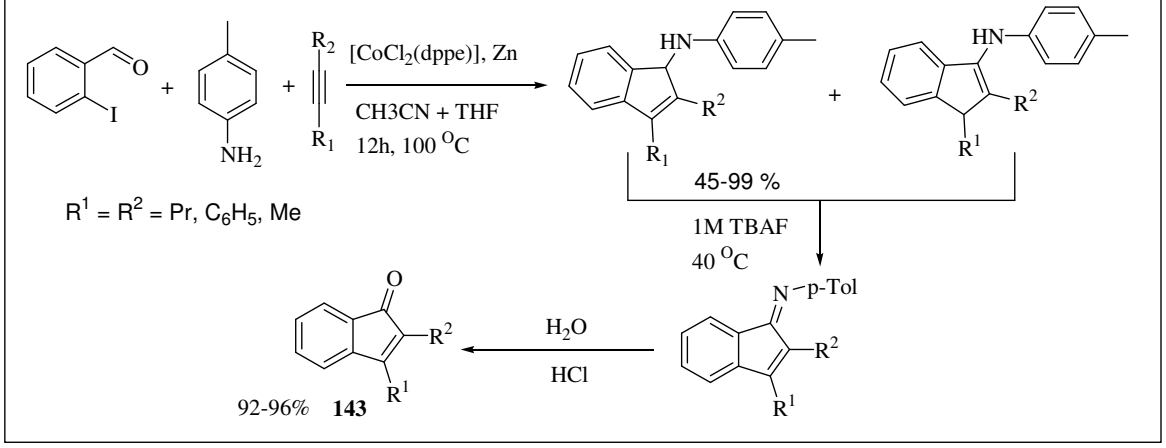
Chatani and co-workers[200] reported an interesting rhodium(I) catalyzed reaction of alkynes with 2-bromophenylboronic acids in the presence of paraformaldehyde for obtaining indenone derivatives (**142**). One such example is shown in Eq. 23.



Eq. 23

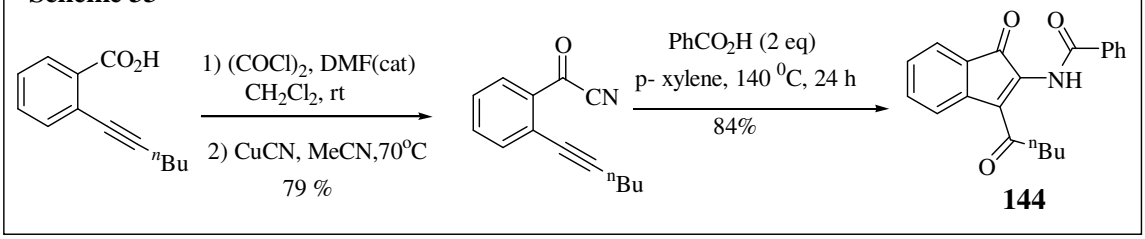
Cheng and co-workers[201] reported a facile methodology for synthesis of indenone derivatives (**143**) via the reaction between 2-iodobenzaldehyde, aniline and alkynes following the reaction sequence shown in Scheme 32.

Scheme 32



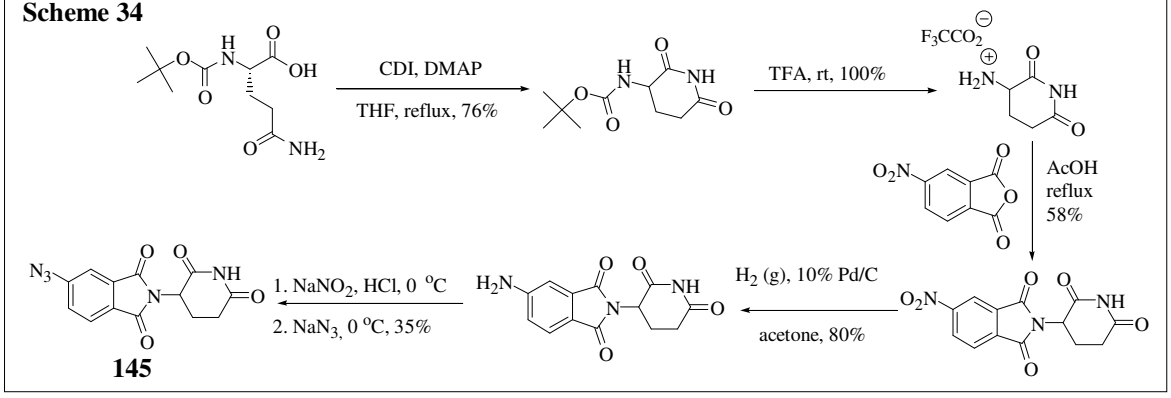
A simple protocol for obtaining indenone derivatives (**144**) starting from 2-(1-hex-1-ynyl-benzoic acids was reported by Murakami and Hiroshi[202] (Scheme 33).

Scheme 33



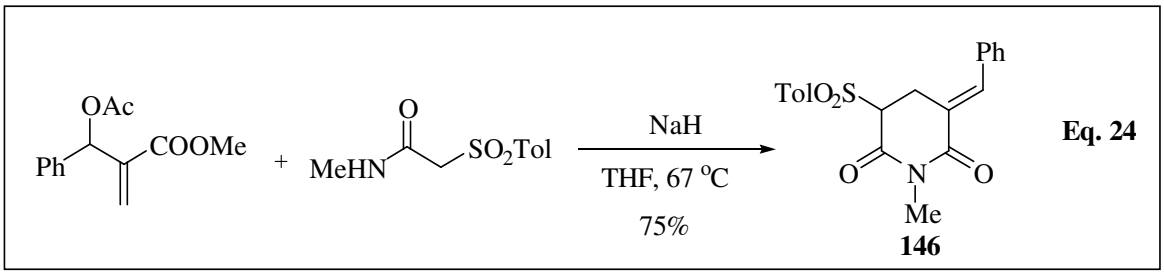
Brown and co-workers[191] reported an elegant synthesis of azidothalidomide (**145**) analogue following the reaction sequence as described in Scheme 34.

Scheme 34



145

Chang and coworkers[203] have described a one-pot conversion of Baylis-Hillman adducts into *N*-alkyl-3(*E*)-arylidene/alkylidene-5-substituted (sulfonyl) piperidine-2, 6-diones (**146**). One example is shown in Eq. 24.

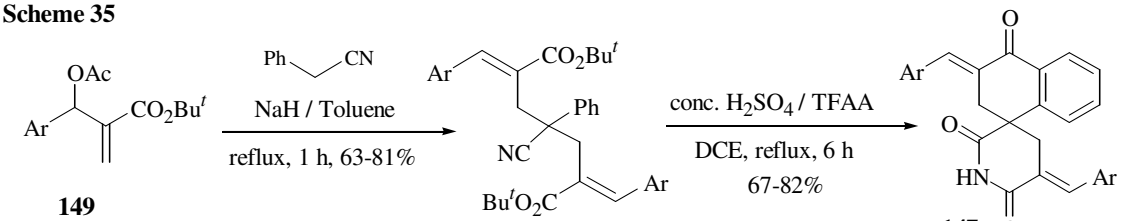


146

Eq. 24

Very recently we have reported a facile two-step protocol for transformation of acetates (**149**) of the Baylis-Hillman (B-H) adducts (**148**) (obtained from aryl aldehydes and *tert*-butyl acrylate) into bis(*E*)-benzylidene-tetralone-spiro-glutarimides[204] (**147**). This strategy proceeds through bis alkylation of benzyl cyanide with B-H acetates (**149**) followed by biscyclization involving tandem intramolecular Friedel-Crafts reaction and imide formation (Scheme 35).

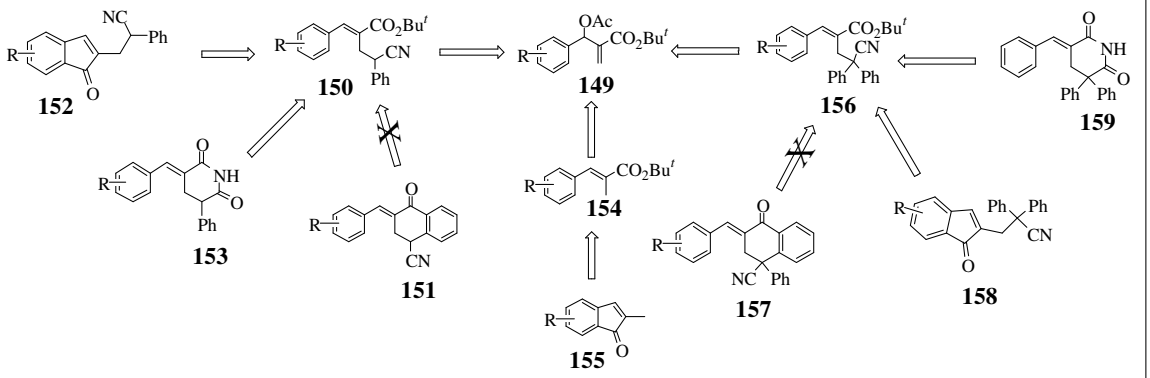
Scheme 35



Ar = C_6H_5, 2-ClC_6H_4, 2-MeC_6H_4, 3-ClC_6H_4, 4-ClC_6H_5, 4-MeC_6H_4, 4-EtC_6H_4

From this experience, it occurred to us that it is possible to synthesize 2-arylmethylidene-4-cyanotetralone derivatives **(151)** via the monoalkylation of benzyl cyanide with B-H acetates (**149**), followed by intramolecular Friedel-Crafts cyclization of the resulting (*E*)-alkylated products (**150)** according to retro-synthetic strategy as shown in Scheme 36. Similarly the (*E*)-alkylated products (**150)** would be transformed into 3-arylmethylidene-5-phenylpiperidine-2, 6-diones (**153)**© *via* partial hydrolysis and cyclization according to the retro-synthetic strategy (Scheme 36).

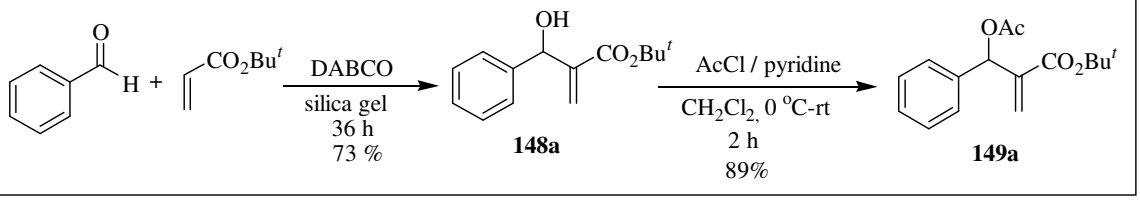
Scheme 36



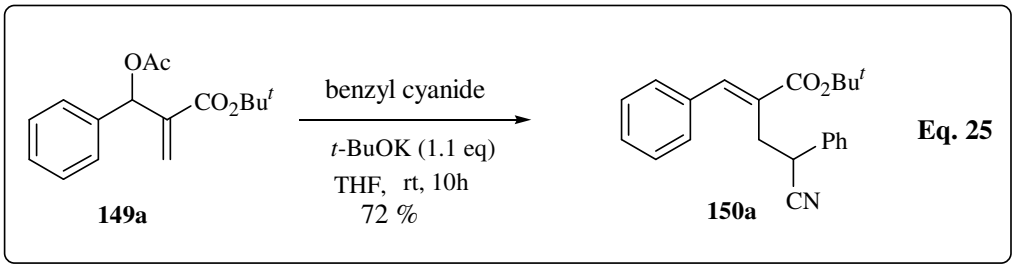
© For easy understanding and convenience, 2-methylind-2-en-1-one**,** 2-(2-phenyl-2-cyano)ethylind-2-en-1-one and 2-(2,2-diphenyl-2-cyano)ethylind-2-en-1-one derivatives are numbered as **155**, **152** and **158** respectively. The 3-arylmethylidene-5-phenylpiperidine-2,6-diones, 3-arylmethylidene-5,5-diphenylpiperidine-2,6-diones are numbered as **153** and 1**59** respectively. The 4-cyanotetralone and 4-cyano-4-phenyltetralone derivatives are numbered as **151** and**157** respectively. *tert*-Butyl 2-methylcinnamic esters are numbered as**154**.

We have first selected *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**149a**) for monoalkylation with benzylcyanide. The required Baylis-Hillman acetate (**149a**) was prepared from the Baylis-Hillman alcohol (**148a**), which was obtained *via* the coupling of benzaldehyde with *tert*-butyl acrylate in the presence of DABCO (Scheme 37).

Scheme 37

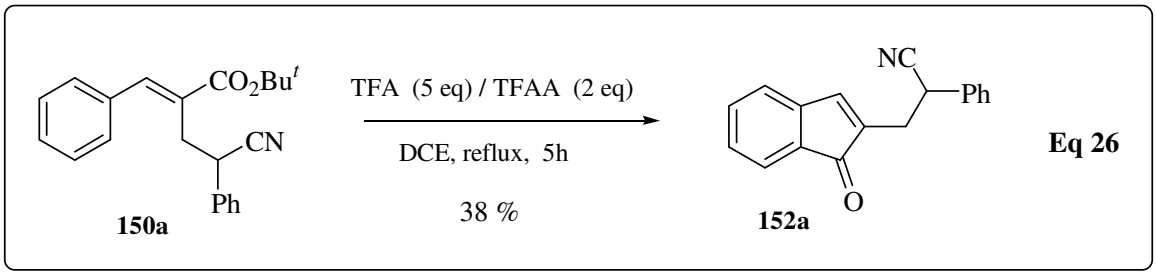


We have then performed the monoalkylation of benzyl cyanide with *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**149a**) in the presence of *t*-BuOK. Thus, treatment of benzyl cyanide (5 mmol) with **149a** (5 mmol) in the presence of *t*-BuOK (5.5 mmol) in THF at room temperature for 10 hours provided the required mono alkylated product, (*E*)-*tert*-butyl 2-benzylidene-4-cyano-4-phenylbutanoate (**150a**)[@], in 72 % isolated yield (Eq. 25). Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 1), ^{13}C NMR (Spectrum 2) and mass (LCMS) spectral data analysis.



@ Chemical shifts of β-vinyl protons *cis* to the carbonyl goup (ketone, ester, acid and amide) are well differentiated from that of corresponding β-vinyl protons *trans* to the carbonyl group in the ^{1}H NMR-spectrum of trisustituted alkenes. The vinylic β-protons *cis* to the carbonyl group appear downfield in comparision with that of protons *trans* to the carbonyl group [see: ref; L. M. Jackman, S. Sternhell, *Applications of nuclear magnetic resonance spectroscopy in organic chemistry*, second edition, Pergamon, Oxford, **1969**, *vol* 5.; S. W. Tobey, *J. Org. Chem*, **1969**, *34*, 1281.

Then we have performed the intramolecular Friedel-Crafts reaction of **150a** with trifluoroacetic acid (TFA) / trifluoroacetic anhydride (TFAA). To our surprise, we did not obtain the expected tetralone derivative **151.** However, we were pleased to see the formation of unexpected indenone derivative **152a** [2-(2-phenyl-2-cyano)ethylind-2-en-1-one]. Thus treatment of **150a** (0.5 mmol) with TFA (2.5 mmol) / TFAA (1 mmol) in dichloroethane (DCE) (3 mL) at reflux temperature for 5 hours provided 2-(2-phenyl-2-cyano)ethylind-2-en-1-one **(152a)** in 38% isolated yield (Eq. 26). Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 3), ^{13}C NMR (Spectrum 4), mass (LCMS) spectral data and elemental analysis.

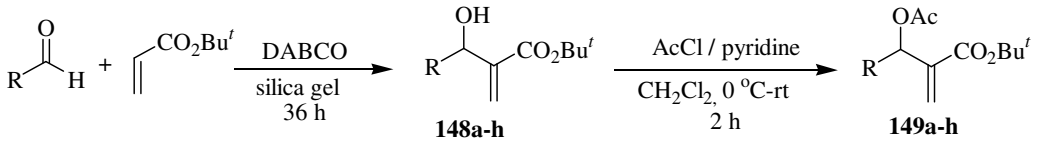


Although the yields are not that encouraging, this reaction is interesting in the sense that tetralone derivative **151,** which in fact was expected to form easily, did not form. But the indenone derivative **152a,** which was not expected to form easily, due to the *trans* orientation of ester group and aryl group (*trans* cinnamic ester derivative), was obtained in reasonably good yield.

To understand the generality of this strategy we have transformed another Baylis-Hillman acetate, *tert*-butyl 3-acetoxy-2-methylene-3-(4-isopropylphenyl)propanoate (**149b**) (Table

1, Entry 2) into (*E*)-*tert*-butyl 2-(4-isopropylbenzylidene)-4-cyano-4-phenylbutanoate (**150b**) (Table 2, Entry 2). Treatment of **150b** with TFA / TFAA provided the desired ind-2-en-1-one (**152b**) in 40 % isolated yield (Table 3, Entry 2). The required Baylis-Hillman acetate **149b** was obtained from corresponding B-H alcohol **148b** which in turn was prepared from 4-isopropylbenzaldehyde and *t*-butyl acrylate in the presence of DABCO (Table 1, Entry 2).

Table 1: Preparation of the Baylis-Hillman adducts and acetates

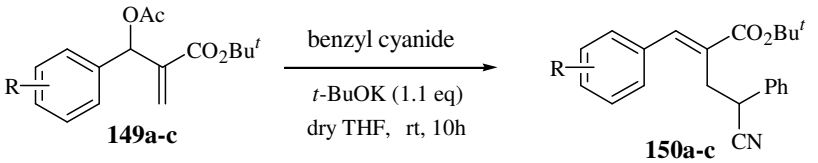


Entry	R	B-H alcohol[a] (148a-h)	Yield[b] %	B-H acetate[c] (149a-h)	Yield[d] (%)
1	C_6H_5	**148a**	73	**149a**	87
2	4-i-PrC_6H_4	**148b**	59	**149b**	86
3	3-MeC_6H_4	**148c**	60	**149c**	84
4	4-EtC_6H_4	**148d**	69	**149d**	80
5	4-MeC_6H_4	**148e**	68	**149e**	87
6	3-BrC_6H_4	**148f**	65	**149f**	75
7	2-MeC_6H_4	**148g**	57	**149g**	88
8	naphth-1-yl	**148h**	51	**149h**	74

a) All reactions were carried out on 100 mmol scale of aryl aldehydes.
b) Isolated yields of the pure products based on the aryl aldehydes.
c) All reaction were carried out on 75 mmol scale of B-H alcohols **(148a-h)**
d) Isolated yields of the pure products based on the B-H alcohols **(148a-h).**

Although these reactions are quite interesting due to the unexpected transformation of *trans* cinnamic esters into ind-2-en-1-one derivatives, low yields of the products have disappointed us. From these results it occurred to us that it should be, in principle, possible to transform *trans* cinnamic acids / esters into indenone derivatives using TFA / TFAA.

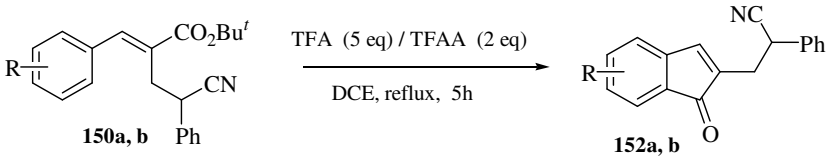
Table 2: Synthesis of (*E*)-*tert*-butyl 2-arylmethylidene-4-cyano-4-phenylbutanoates (**150a-c**)[a]



Entry	B-H acetate **(149a-c)**	R	Product[b] **(150a-c)**	Yield[c] [%]
1	**149a**	H	**150a**	72
2	**149b**	4-i-Pr	**150b**	80
3	**149c**	3-Me	**150c**	73

a) Reactions were carried out on a 5 mmol scale of B-H acetates **(149a-c).**
b) The compounds **(150a-c)** were obtained as colorless viscous liquids and well characterized.
c) Isolated yields based on B-H acetaes **(149a-c).**

Table 3: Synthesis of 2-(2-phenyl-2-cyano)ethylind-2-en-1-ones (**152a, b**)[a]

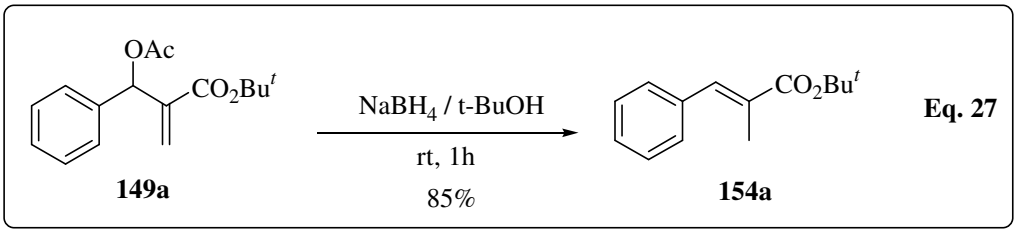


Entry	Substrate **(150a, b)**	R	Product[b] **(152a, b)**	R	Yield[c] [%]
1	**150a**	H	**152a**	H	38
2	**150b**	4-i-Pr	**152b**	6-i-Pr	40

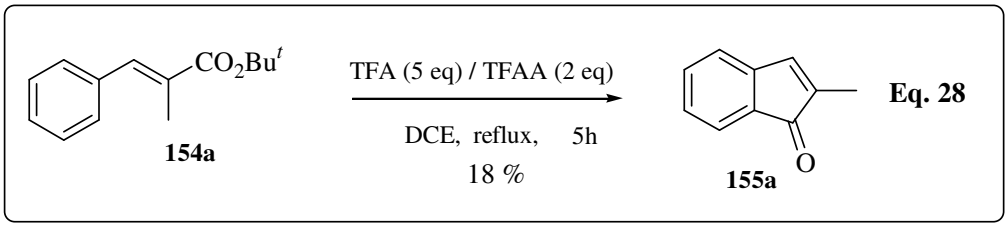
a) Reactions were carried out on a 0.5 mmol scale of (**150a, b**).
b) The compounds (**152a, b)** were obtained as yellow solids and well characterized.
c) Isolated yields based on substrates (**150a, b**).

Accordingly we have directed our attention to examine the conversion of (2*E*)-*tert*-butyl 3-phenyl-2-methylprop-2-enoates **(154a)** into 2-methylind-2-en-1-ones **(155a)** via the

treatment with TFA / TFAA. The required **154a** was prepared via the treatment of *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**149a**) with sodium borohydride following the procedure developed in our laboratory.[205] (Eq. 27)



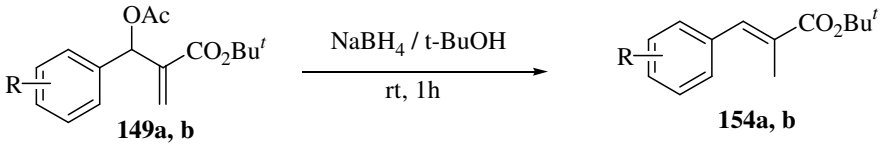
Then we examined the possible Friedel-Crafts cyclization of (2*E*)-*tert*-butyl 3-phenyl-2-methylprop-2-enoate (**154a**) into 2-methylind-2-en-1-one **(155a)** using TFA / TFAA. The best results were obtained when (2*E*)-*tert*-butyl 3-phenyl-2-methylprop-2-enoate (**154a**) (1.0 mmol) was heated under reflux for 5 h in DCE (3 mL) in the presence of TFA (5 mmol) and TFAA (2 mmol) thus providing the expected 2-methylind-2-en-1-one **(155a)** in 18 % isolated yield (Eq. 28). Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 5), ^{13}C NMR (Spectrum 6), mass (LCMS) spectral data and elemental analysis.



In order to understand the general nature of this reaction strategy, we extended this methodology to another B-H acetate, *tert*-butyl 3-acetoxy-2-methylene-3-(4-isopropyl-

phenyl)propanoate (**149b**). Treatment of **149b** with $NaBH_4$ following the known methodology[205] gave the *trans* cinnamic ester **154b** (Table 4, Entry 2) in 80% isolated yield. Subsequent treatment of **154b** with TFA / TFAA provided the desired 6-isopropyl-2-methylind-2-en-1-one (**155b**) in 20% isolated yield (Table 5, Entry 2).

Table 4: Synthesis of (2*E*)-*tert*-butyl 3-aryl-2-methylprop-2-enoate (**154a, b**)[a]

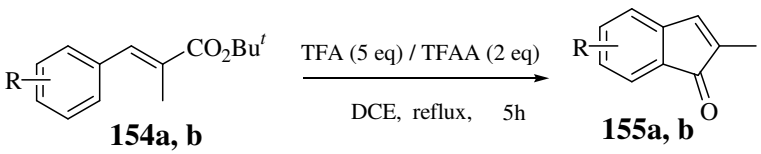


149a, b **154a, b**

Entry	B-H acetate (**149a, b**)	R	Product[b] (**154a, b**)	Yield[c] [%]
1	**149a**	H	**154a**	85
2	**149b**	4-i-Pr	**154b**	80

a) Reactions were carried out on a 2 mmol scale of B-H acetates (**149a, b**).
b) The compounds (**154a, b**) were obtained as colorless liquids and well characterized.
c) Isolated yields based on of B-H acetates (**149a, b**).

Table 5: Synthesis of 2-methylind-2-en-1-ones (**155a, b**)[a]



154a, b **155a, b**

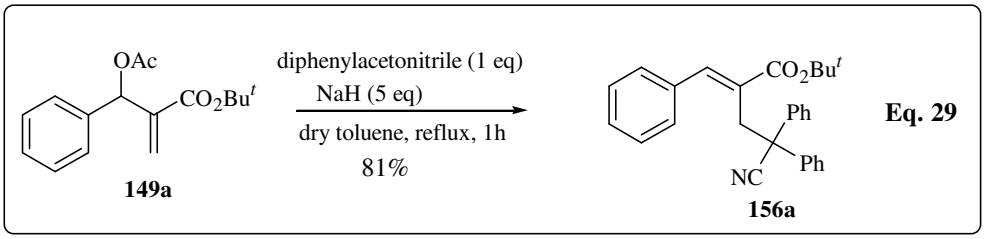
Entry	Substrate (**154a, b**)	R	Product[b] (**155a, b**)	R	Yield[c] [%]
1	**154a**	H	**155a**	H	18
2	**154b**	4-i-Pr	**155b**	6-i-Pr	20

a) Reactions were carried out on a 1 mmol scale of substrates (**154a, b**).
b) The compounds (**155a, b**) were obtained as yellow viscous liquids and well characterized.
c) Isolated yields based on substrates (**154a, b**).

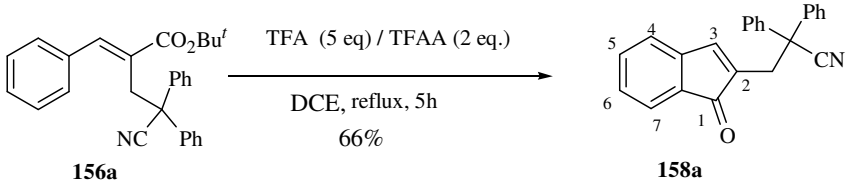
A careful comparison of yields in the cases of **152a** and **152b** (38 and 40%) (Table 3) and in the cases of **155a** and **155b** (18 and 20 %) (Table 5) clearly indicates that *trans* cinnamic esters **152a** and **152b**, containing sterically bulky phenylcyanomethyl group at α-

position provided better yields of indenone derivatives in comparison with that of **155a** and **155b** containing simple methyl group at α-position.

With a view to further understand the influence of steric factors in the formation of ind-2-en-1-one derivatives, we have selected (*E*)-*tert*-butyl 2-benzylidene-4-cyano-4,4-diphenylbutanoate (**156a**) as a substrate for intramolecular Friedel-Crafts cylization. The required *trans* cinnamic ester **156a** was obtatined via treatment of **149a** (2 mmol) with diphenylacetonitrile (2 mmol) in dry toluene (5 mL) in the presence of NaH (5 mmol), in 81 % isolated yield (Eq. 29). Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 7), ^{13}C NMR (Spectrum 8), mass (LCMS) spectral data and elemental analysis.



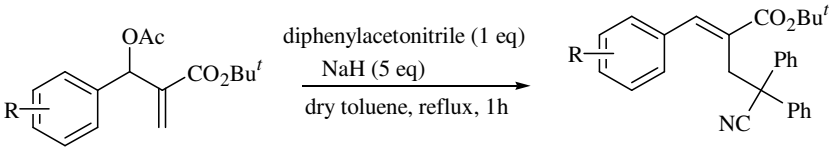
The Friedel-Crafts cyclization of **156a** was performed with TFA / TFAA in DCE for 5h under reflux to provide 2-(2,2-diphenyl-2-cyano)ethylind-2-en-1-one (**158a)** in 66% isolated yield (Eq. 30). Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 9), ^{13}C NMR (Spectrum 10) and mass (LCMS) spectral data analysis.



156a **158a** **Eq. 30**

This result has fascinated us because *trans* cinnamic ester **156a,** containing sterically more hindered diphenylcyanomethyl group, provided superior yields of the indenone derivative **158a**. In order to understand the generality of this methodology we have selected representative class of B-H acetates **149b-g** (Table 1, Entry 2-7). These acetetes were transformed into required cinnamic esters **156b-g** (Table 6, Entry 2-7) via the reaction with diphenylacetonitrile in the presence of NaH. The resulting cinnamic esters **156b-g** were obtained in 75-83% (Table 6, Entry 2-7) isolated yields which on intramolecular Friedel-Crafts reaction using TFA / TFAA furnished the required indenone derivatives, 2-(2,2-diphenyl-2-cyano)ethylind-2-en-1-ones (**158b-g**), in 60-70% (Table 7, Entry 2-7) isolated yields. Structures of these molecules were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass (LCMS) spectral data and elemental analysis. The structure of the compound **156d** (see Figure A for ORTEP diagram, Table I) and **158a** (see Figure B for ORTEP diagram, Table II) were further confirmed by single crystal X-ray data analysis..

Table 6: Synthesis of (*E*)-*tert*-butyl 2-arylmethylidene-4-cyano-4,4-diphenylbutanoates (**156a-g**)[a]

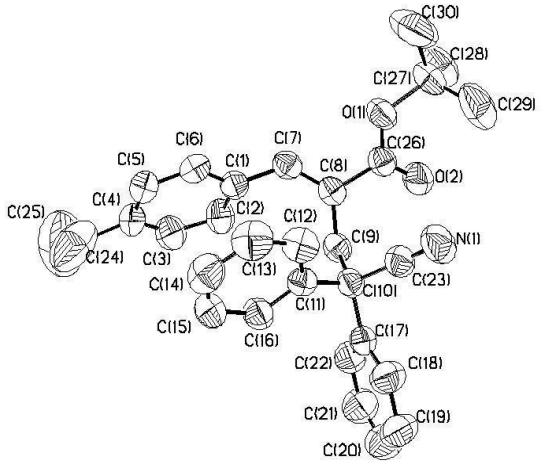


149a-g **156a-g**

Entry	B-H acetate (**149a-g**)	R	Product[b] (**156a-g**)	Yield[c] [%]
1	**149a**	H	**156a**	81
2	**149b**	4-i-Pr	**156b**	83
3	**149c**	3-Me	**156c**	78
4	**149d**	4-Et	**156d**[d]	79
5	**149e**	4-Me	**156e**	75
6	**149f**	3-Br	**156f**	80
7	**149g**	2-Me	**156g**	77

a) All reactions were carried out on a 2 mmol scale of B-H acetates (**149a-g**).
b) All compounds (**156a-g**) were obtained as colorless solids and well characterized.
c) Isolated yields based on B-H acetates (**149a-g**).
d) Structure of this molecule was further confirmed by single-crystal X-ray data analysis.

Figure A

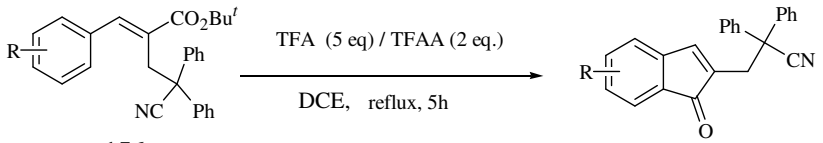


ORTEP diaram of compound **156d**
(hydrogen atoms were omitted for clarity)

Table I. Crystal data and structure refinement for **156d**

Empirical formula	$C_{30}H_{31}NO_2$
Formula weight	437.56
Temperature	298(2) K
Wavelength	0.71073 A
Crystal system	Monoclinic
Space group	P 2 (1)/c
Unit cell dimensions	a = 10.7663(9) A, α = 90 deg.
	b = 19.0208(16) A, β = 102.5600(10) deg.
	c = 12.7679(11) A, γ = 90 deg.
Volume	2552.1(4) A^3
Z, Calculated density	4, 1.139 Mg/m^3
Absorption coefficient	0.070 mm^{-1}
F(000)	936
Crystal size	0.38x 0.32 x 0.22 mm
Theta range for data collection	1.95 to 25.96 deg.
Limiting indices	-13 h≤13, -23≤k≤23, -15≤l≤15
Reflections collected / unique	26140 / 4987 [R(int) = 0.0401]
Completeness to theta = 25.96	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9958 and 0.9724
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4987 / 0 / 302
Goodness-of-fit on F^2	1.029
Final R indices [I>2sigma(I)]	R1 = 0.0401, wR2 = 0.1848
R indices (all data)	R1 = 0.1110, wR2 = 0.2056
Largest diff. peak and hole	0.380 and -0.217 $e.A^{-3}$

Table 7: Synthesis of 2-(2,2-diphenyl-2-cyano)ethylind-2-en-1-ones (**158a-g**)[a]

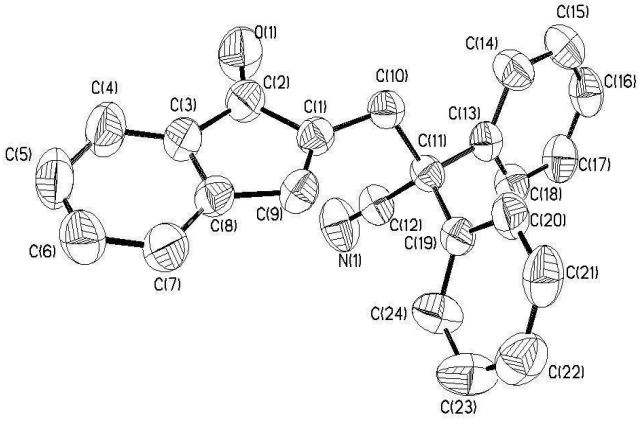


156a-g **158a-g**

Entry	Substrate (**156a-g**)	R	Product[b] (**158a-g**)	R	Yield[c] [%]
1	**156a**	H	**158a**[d]	H	66
2	**156b**	4-i-Pr	**158b**	6-i-Pr	63
3	**156c**	3-Me	**158c**	5-Me	64
4	**156d**	4-Et	**158d**	6-Et	70
5	**156e**	4-Me	**158e**	6-Me	60
6	**156f**	3-Br	**158f**	5-Br	66
7	**156g**	2-Me	**158g**	4-Me	62

a) All reactions were carried out on a 0.5 mmol scale of substrates (**156a-g).**
b) All compounds (**158a-g)** were obtained as yellow solids and well characterized.
c) Isolated yields based on substrates (**156a-g**).
d) Structure of this molecule was also confirmed by single-crystal X-ray data analysis.

Figure B



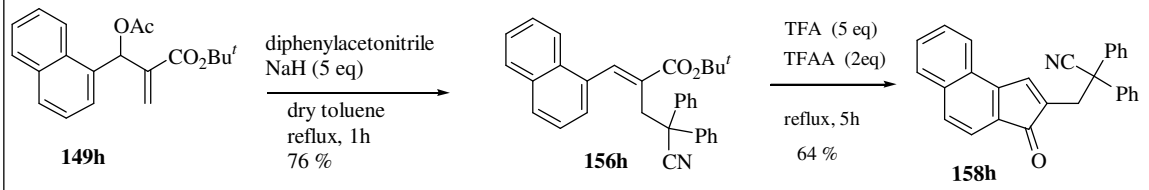
ORTEP diagram of compound **158a**
(hydrogen atoms were omitted for clarity)

Table II. Crystal data and structure refinement for **158a**

Empirical formula	C_{24} H_{17} NO
Formula weight	335.39
Temperature	298(2) K
Wavelength	0.71073 A
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 9.3189(11) A, α = 95.696(2) deg.
	b = 10.0476(12) A, β = 107.552(2) deg.
	c = 10.1708(12) A, γ = 92.075(2) deg.
Volume	901.30(18) A^3
Z, Calculated density	2, 1.236 Mg/m^3
Absorption coefficient	0.075 mm^{-1}
F(000)	352
Crystal size	0.36 x 0.24 x 0.18 mm
Theta range for data collection	2.04 to 26.01 deg.
Limiting indices	-11≤h≤11, -12≤k≤12, -12≤l≤12
Reflections collected / unique	9392 / 3530 [R(int) = 0.0383]
Completeness to theta = 26.01	99.1 %
Max. and min. transmission	0.9866 and 0.9734
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3530 / 0 / 235
Goodness-of-fit on F^2	1.252
Final R indices [I>2sigma(I)]	R1 = 0.0716, wR2 = 0.1525
R indices (all data)	R1 = 0.0844, wR2 = 0.1586
Largest diff. peak and hole	0.149 and -0.259 $e.A^{-3}$

To understand the applicability of this strategy to naphthalene framework, we have prepared (*E*)-*tert*-butyl 4-cyano-2-(naphth-1-ylmethylidene)-4,4-diphenylbutanoate (**156h**) from *tert*-butyl 3-acetoxy-2-methylene-3-(naphth-1-yl)-propanoate (**149h**, Table 1, Entry 8) in 76% yield *via* the reaction with diphenylacetonitrile in the prersence of NaH (Scheme 38). Subsequent treatment of **156h** with TFA / TFAA gave the expected indenone derivative, 12-(2,2-diphenyl-2-cyano)ethyltricyclo[8.3.0.0^{2,7}]trideca-1(10),2(7),3,5,8,12-hexaene-11-one (**158h**) in 64% isolated yield (Scheme 38). Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 11), ^{13}C NMR (Spectrum 12), mass (LCMS) spectral data and elemental analysis.

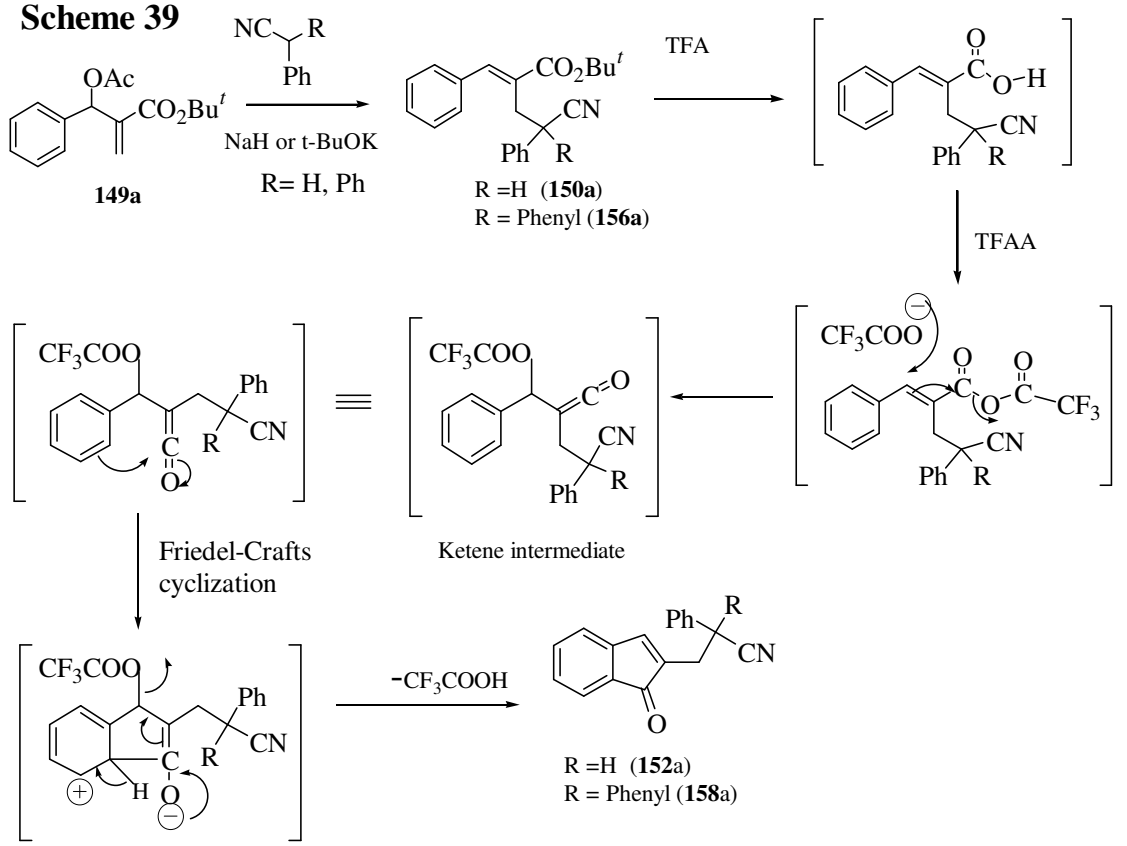
Scheme 38 Synthesis of 12-(2,2-diphenyl-2-cyano)ethyl tricyclo[8.3.0.0^{2,7}] trideca-1(10),2(7), 3, 5, 8, 12-hexaen-11-one (**158h**)



These results, to some extent, suggest that reaction pathway may not proceed through isomerization of *trans* cinnamic esters into *cis* derivatives and probably involve the reorganization of the *trans* double bond so that the five membered ring formation providing indenone derivatives (**152a, b**; **155a,b**; **158a-h**) becomes easier (which is otherwise difficult to form) than the formation of six membered ring (providing the tetralone derivatives **151** and **157**). On this basis a plausible mechanism involving

formation of ketene type transition state via the Michael addition of trifluoroacetoxide anion onto the *trans* cinnamic ester derivative is presented in Scheme 39.

Scheme 39

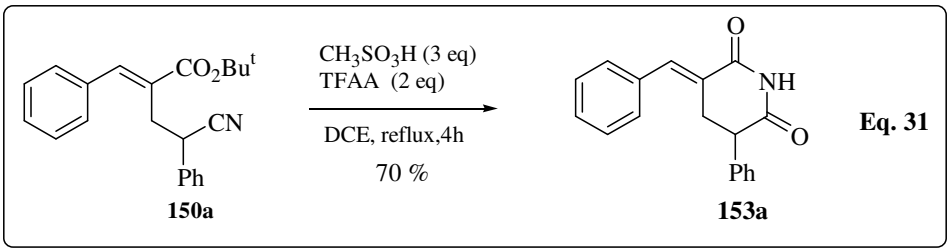


Plausible mechanism for the formation of substituted ind-2-en-1-ones

Synthesis of (*E*)-3-arylmethylidene-5-phenylpiperidine-2,6-diones:

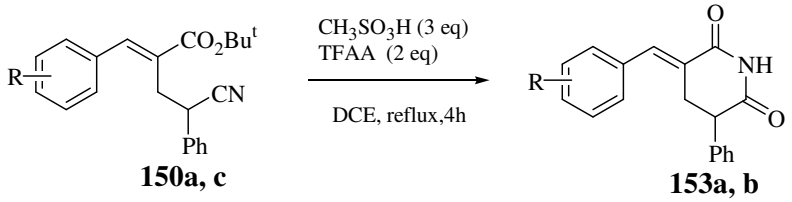
Next we have turned our attention towards synthesis of piperidine-2,6-dione frameworks (**153**) from the *trans* esters, (*E*)-*tert*-butyl 2-arylmethylidene-4-cyano-4-phenylbutanoates (**150**). We have first selected (*E*)-*tert*-butyl 2-phenylmethylidene-4-cyano-4-

phenylbutanoate (**150a**) as a substrate. The best results in this direction were obtained when **150a** (0.5 mmol) was treated with methanesulfonic acid (CH_3SO_3H) (1.5 mmol) / TFAA (1 mmol) in DCE at reflux temperature for four hours thus providing the desired (*E*)-3-arylmethylidene-5-phenylpiperidine-2,6-dione **(153a)** in 70 % isolated yield (Eq. 31). Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 13), ^{13}C NMR (Spectrum 14), mass (LCMS) spectral data and elemental analysis.



Then we have transformed (*E*)-*tert*-butyl 2-(3-methylphenylmethylidene)-4-cyano-4-phenylbutanoate **(150c)** (Table 2, Entry 3) into piperidine-2,6-dione derivative (**153b**) in 75% isolated yield (Table 8, Entry 2) via treatment with CH_3SO_3H/TFAA.

Table 8: (*E*)-3-Arylmethylidene-5-phenylpiperidine-2,6-diones (**153a,b**)[a]

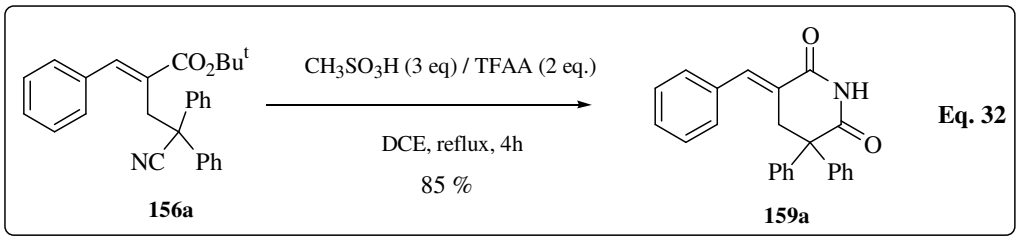


Entry	Substrate (**150a, c**)	R	Product[b] (**153a,b**)	Yield[c] [%]
1	**150a**	H	**153a**	70
2	**150c**	3-Me	**153b**	75

a) Reactions were carried out on a 0.5 mmol scale of substrates (**150a, c**).
b) The compounds (**153a, b**) were obtained as colorless solids and well characterized.
c) Isolated yields based on substrates (**150a, c**).

Synthesis of (*E*)-3-arylmethylidene-5,5-diphenylpiperidine-2,6-diones:

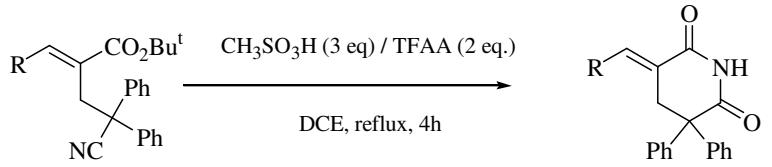
Encouraged by the above mentioned results we have extended the same strategy to the more hindered *trans* ester, (*E*)-*t*-butyl 2-phenylmethylidene-4-cyano-4,4-diphenylbutanoate (**156a).** In this case also treatment of **156a** (0.5 mmol) with CH_3SO_3H (1.5 mmol) / TFAA (1 mmol) in DCE at reflux temperature for four hours furnished (*E*)-3-benzylidene-5,5-diphenylpiperidine-2,6-dione **159a** in 85% isolated yield (Eq. 32). Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 15), ^{13}C NMR (Spectrum 16), mass (LCMS) spectral data and elemental analysis. The structure of this compound was further confirmed by single crystal X-ray data analysis (see Figure C for ORTEP diagram, Table III).



156a **159a** **Eq. 32**

To understand the generality of this methodology we have successfully transformed *trans* cinnamic esters **156b-h** into the corresponding piperidine-2,6-dione derivatives **159b-h** in 75-86% yields (Table 9, Entry 2-8) via the treatment with CH_3SO_3H / TFAA. Structures of these molecules were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass (LCMS) spectral data and elemental analysis. A plausible mechanism for the transformation of trans esters (**150a, c** and **156a-h)** into piperidine-2,6-diones (**153a, b** and **159a-h)** is presented in the Scheme 40.

Table 9: Synthesis of (*E*)-3-arylmethylidene-5,5-diphenylpiperidine-2,6-diones (**159a-h**)[a]

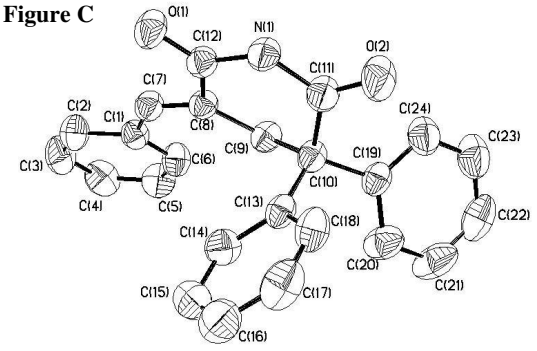


156a-h **159a-h**

Entry	Substrate (**156a-h**)	R	Product[b] (**159a-h**)	Yield[c] [%]
1	**156a**	C_6H_5	**159a**[d]	85
2	**156b**	4-i-PrC_6H_4	**159b**	86
3	**156c**	3-MeC_6H_4	**159c**	81
4	**156d**	4-EtC_6H_4	**159d**	77
5	**156e**	4-MeC_6H_4	**159e**	80
6	**156f**	3-BrC_6H_4	**159f**	82
7	**156g**	2-MeC_6H_4	**159g**	75
8	**156h**	naphth-1-yl	**159h**	79

a) All reactions were carried out on a 0.5 mmol scale of substrates (**156a-h**).
b) All the compounds (**159a-h)** were obtained as colorless solids and well characterized.
c) Isolated yields based on substrates (**156a-h**).
d) Structure of this compound was also confirmed by single-crystal X-ray data analysis.

Figure C

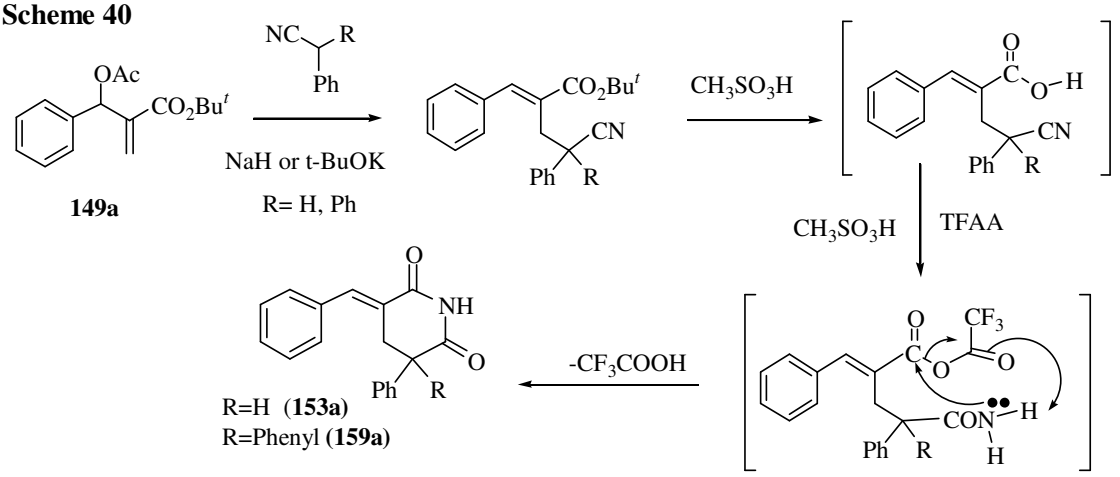


ORTEP diagram of compound **159a**
(hydrogen atoms were omitted for clarity)

Table III. Crystal data and structure refinement for **159a**

Empirical formula	$C_{24}H_{19}NO_2$
Formula weight	353.40
Temperature	298(2) K
Wavelength	0.71073 A
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 7.2161(6) A, α = 90 deg.
	b = 18.4306(16) A, β= 98.373(2) deg.
	c = 13.8854(12) A, α = 90 deg.
Volume	1827.0(3) A^3
Z, Calculated density	4, 1.285 Mg/m^3
Absorption coefficient	0.082 mm^{-1}
F(000)	744
Crystal size	0.28 x 0.20 x 0.18 mm
Theta range for data collection	1.85 to 25.94 deg.
Limiting indices	-8≤h≤8, -22≤k<=22, -17≤l≤17
Reflections collected / unique	18658 / 3563 [R(int) = 0.0534]
Completeness to theta = 25.94	99.9 %
Absorption correction	Empirical
Max. and min. transmission	0.9855 and 0.9675
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3563 / 0 / 244
Goodness-of-fit on F^2	0.846
Final R indices [I>2sigma(I)]	R1 = 0.0404, wR2 = 0.0774
R indices (all data)	R1 = 0.0780, wR2 = 0.0859
Largest diff. peak and hole	0.147 and -0.139 $e.A^{-3}$

Scheme 40



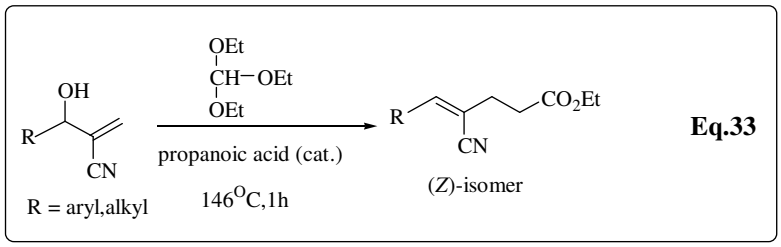
Plausible mechanism for the formation of piperidine-2,6-dione derivatives

Thus we have transformed the B-H acetates into 2-substituted ind-2-en-1-one derivatives in a two-step protocol. This transformation proceeds through an unusual conversion of *trans* cinnamic esters into ind-2-en-1-one frameworks. The yields of the indenone derivatives depend on the steric bulk of substitution at α-position of ester group of *trans*-cinnamic esters. We have also developed a simple two-step strategy for transformation of the B-H acetates into substituted piperidine-2,6-dione derivatives.

II. A Simple One-Pot Protocol for Synthesis of a Piperidine-2,6-dione Frameworks from Baylis-Hillman adducts

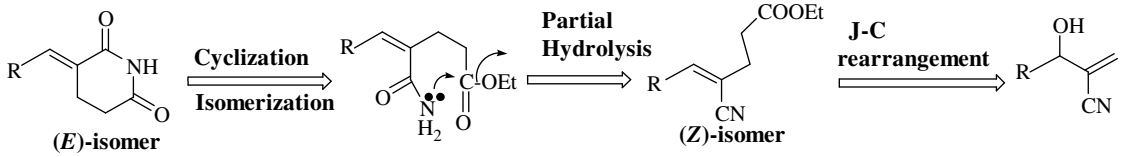
A few years ago we reported an interesting methodology for synthesis of functionalized alkenes *i.e.* ethyl (4*Z*)-4-cyanoalk-4-enoates [with exclusive (*Z*)-selectivity] via the

Jhonson-Claisen rearrangement[206] of 2-methylene-3-hydroxyalkanenitriles, the Baylis-Hillman alcohols derived from various aldehydes and acrylonitriles (Eq. 33).



We felt that the presence of two interesting functionalities (ester and nitrile) in appropriate positions in ethyl (4*Z*)-4-cyanoalk-4-enoates would make these derivatives as attractive synthons for obtaining piperidine-2,6-dione derivatives via the partial hydrolysis of cyano group into amide group followed by cyclization. Today science of synthesis demands the development of operationally simple one-pot processes for obtaining important molecules of medicinal relevance. We have therefore, directed our attention towards the development of one-pot process for synthesis of piperidine-2,6-dione derivatives starting from the Baylis-Hillman alcohols derived from acrylonitrile and aldehydes (see retro-synthetic strategy: Scheme 41).

Scheme 41

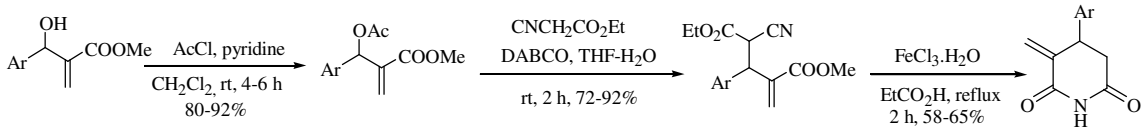


Retro-synthetic strategy

In this direction our real task would be selection of appropriate reagent to transform the nitrile group into the amide group, then leading to cyclization. Literature[207,208] survey reveals that a combination of $FeCl_3$ / carboxylic acid has been used for the preparation of cyclic amides from keto nitriles and imides from the compounds containing the ester and nitrile moieties in appropriate positions.

Batra and coworkers[207] used the combination of $FeCl_3$ / propanonic acid for the conversion of 2-methylidene-3-(cyanoethoxycarbonyl)methyl-3-arylpropanoates, derived from the corresponding Baylis-Hillman acetates, into 3-methylidene-2,6-piperidinedione derivatives in two steps (Scheme 42).

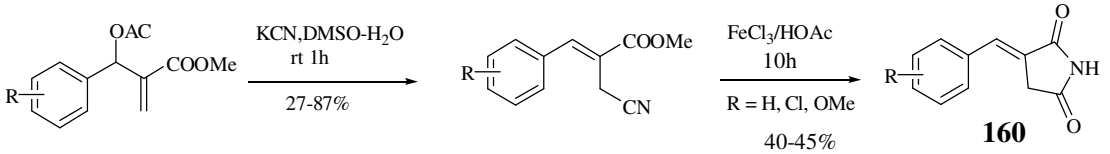
Scheme 42



Ar = C_6H_5, 2-ClC_6H_4, 2-FC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4

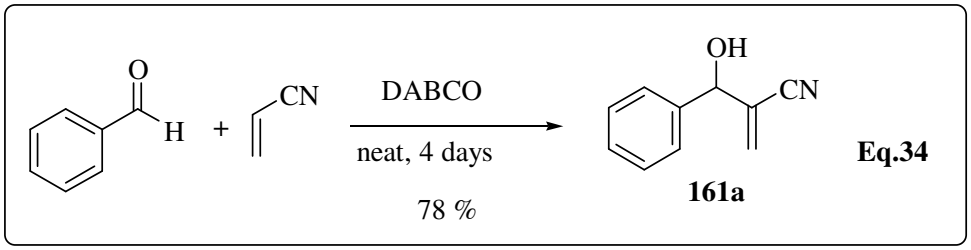
Kim and coworkers[208] used $FeCl_3$ / acetic acid for the synthesis of benzylidenesuccinimides (**160**) from the corresponding Baylis-Hillman acetates as shown in Scheme 43.

Sheme 43



Therefore it occurred to us that $FeCl_3$ / acetic acid, would serve as an appropriate reagent for transformation of the ethyl (4*Z*)-4-cyanoalk-4-enoates into 3-benzylidenepiperidine-2,6-dione framework via selective hydrolysis and cyclization, in one-pot process.

We have accordingly first selected 3-hydroxy-2-methylene-3-phenylpropanoate (**161a**) the Baylis-Hillman alcohol obtained via the coupling of acrylonitrile and benzaldehyde (Eq. 34) as substrate for this purpose. In this direction we have treated Baylis-Hillman alcohol **161a** (1 mmol) with triethyl orthoacetate (1 mL) at 146 ^{o}C in the presence of propanoic acid (3 drops) for 2 h and the excess orthoester and propanoic acid were removed under reduced pressure. The crude product as such, was treated with anhydrous $FeCl_3$ (1 mmol) in acetic acid (5 mL) at reflux temperature for 10 h, to provide 3-benzylidenepiperidine-2,6-dione (**162a**) as a mixture of *E:Z* (78:22) isomers as a colorless solid in 44 % isolated yield, after work-up and purification by column chromatography (Table 10, Entry 1).

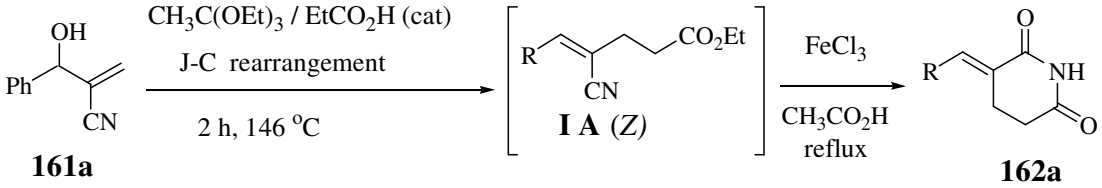


It is indeed interesting to note that the (*Z*)-stereochemistry in the key intermediate (**IA**) has been converted into (*E*)-stereochemistry in the final (major) product. It occurred to us that increasing the amounts of $FeCl_3$ might result in total isomerization of (*Z*)-double bond of the key intermediate into (*E*)-double bond in the product. We have therefore conducted a

number of experiments with increasing quantities of $FeCl_3$ to understand this aspect (Table 10, Entry 1-9). From the Table 10 it is, indeed, quite clear that amount of $FeCl_3$ directs the fate of the stereochemistry of the product and we were pleased to note that $FeCl_3$ (5 mmol) (for 1 mmol of the Baylis-Hillman alcohol) provided 100% (*E*)-stereoselectivity. Structure of this molecule was confirmed by IR, ^1H NMR (Spectrum 17), ^{13}C NMR (Spectrum 18), mass (LCMS) spectral data and elemental analysis. Another interesting point in this strategy is that four steps (orthoester rearrangement, partial hydrolysis of cyano group, cyclization and isomerization) were performed in an operationally simple one-pot to produce 3-benzylidenepiperidine-2,6-dione derivative with (*E*)-selectivity in good yields.

With a view to understand the generality of this reaction, we subjected representative Baylis-Hillman alcohols **161b-g** (Table 11, Entry 2-7), obtained via the reaction of acrylonitrile with various aldehydes, to this reaction strategy to provide (*E*)-3-arylidene (or alkylidene)piperidine-2,6-diones (**162b-g**) in 67-81% isolated yields (Table 12, Entry 2-7). Structures of these molecules were confirmed by IR, ^1H NMR (Spectrum 19 for compound **162e,** Spectrum 21 for compound **162f**), ^{13}C NMR (Spectrum 20 for compound **162e,** Spectrum 22 for compound **162f**), mass (LCMS) spectral data and elemental analysis.

Table 10: Optimization of reaction conditions[a]

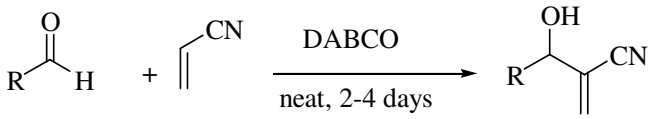


Entry	$FeCl_3$ mmol	Time h	162a[b] (*E:Z*)[@]	Yield[c] of 162a %
1	1	10	78: 22	44
2	2	10	81:18	80
3	3	10	91:09	82
4	4	10	96:04	81
5	5	02	65:35	45
6	5	04	88:12	60
7	5	06	92:08	70
8	5	08	96:04	82
9	**5**	**10**	**100:0**	**84**

a) All reactions were carried out on a 1 mmol scale of B-H alcohol (**161a**).
b) The compound **162a** was obtained as colorless solid and well characterized.
c) Isolated yields based on B-H alcohol (**161a**).

@It has been well known in the literature that in the ^{1}H NMR spectrum of the trisubstituted alkenes the chemical shifts of the vinylic β-protons cis to the carbonyl (ketone, ester, acid, and amide) group and those of the corresponding vinylic β-protons trans to the carbonyl group are well differentiated. The vinylic β-protons cis to the carbonyl group appear downfield in comparison with that of trans β-protons. [see Ref: (a) Jackman, L. M.; Sternhell, S. Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, 2nd ed., Pergamon: Oxford, **1969**; Vol. 5. (b) Tobey, S. W. J. Org. Chem. **1969**, *34*, 1281]. In the case of compound **162a** (R = Phenyl) the *E:Z* ratio was determined by the integration values of the singlets at δ 7.90 [vinylic β-protons cis to the carbonyl group (E-alkene) and δ 6.97 [vinylic β-protons trans to the carbonyl group (Z-alkene)]. In the case of **162a–d** (R = aryl) vinylic β-protons appeared at δ ≈ 7.86 (as a singlet) while in the case of **162e–g** (R = alkyl or 2-phenylethyl) vinylic β-protons appeared at δ ≈ 7.01 (as triplets).

Table 11: Preparation of Baylis-Hillman adducts **(161a-g)**[a]



161a-g

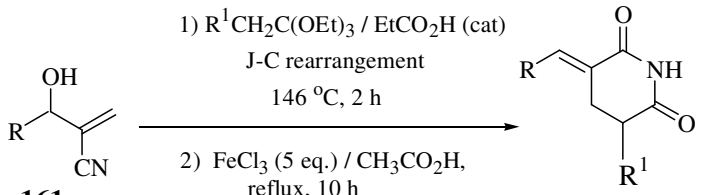
Entry	R	B-H alcohol (161a-g)	Yield[b] %
1	C_6H_5	**161a**	78
2	3-ClC_6H_4	**161b**	75
3	4-ClC_6H_4	**161c**	71
4	4-MeC_6H_4	**161d**	73
5	$C_6H_4CH_2CH_2$	**161e**	65
6	C_7H_{15}	**161f**	69
7	C_5H_{11}	**161g**	74

a) All reactions were carried out on 100 mmol scale of aryl aldehydes
b) All the compounds **(161a-g)** were obtained as colorless liquids
c) Isolated yields of the pure products based on the aryl aldehydes

In order to extend the possibility of this strategy for obtaining more substituted imide derivatives we performed the J-C rearrangement of the Baylis-Hillman alcohols **161a** (Table 11, Entry 1) and **161e** (Table 11, Entry 5) with triethyl orthopropanoate and then treated the *in situ* generated products with $FeCl_3$ / acetic acid for 10 h under reflux to provide the desired compounds (*E*)-3-benzylidene-5-methylpiperidine-2,6-dione (**162h**) (Table 12, Entry 8) and (*E*)-3-(3-phenylpropylidene)-5-methylpiperidine-2,6-dione (**162i**) (Table 12, Entry 9) in 76% and 67% isolated yields respectively. Structures of these molecules were confirmed by IR, ^{1}H NMR (Spectrum 23 for compound **162h**), ^{13}C NMR (Spectrum 24 for compound **162h**), mass (LCMS) spectral data and elemental analysis. The structures of the compounds **162b** (see Figure D for ORTEP diagram, Table IV) and

162c (see Figure E for ORTEP diagram, Table V) were further confirmed by single crystal X-ray data.

Table 12: One-pot multi-step synthesis of (*E*)-3-arylidene(alkylidene)piperidine-2, 6-diones **(162a-i)** from Baylis-Hillman alcohols **(161a-g)**[a]



161 a-g (*E*) **162a-i**

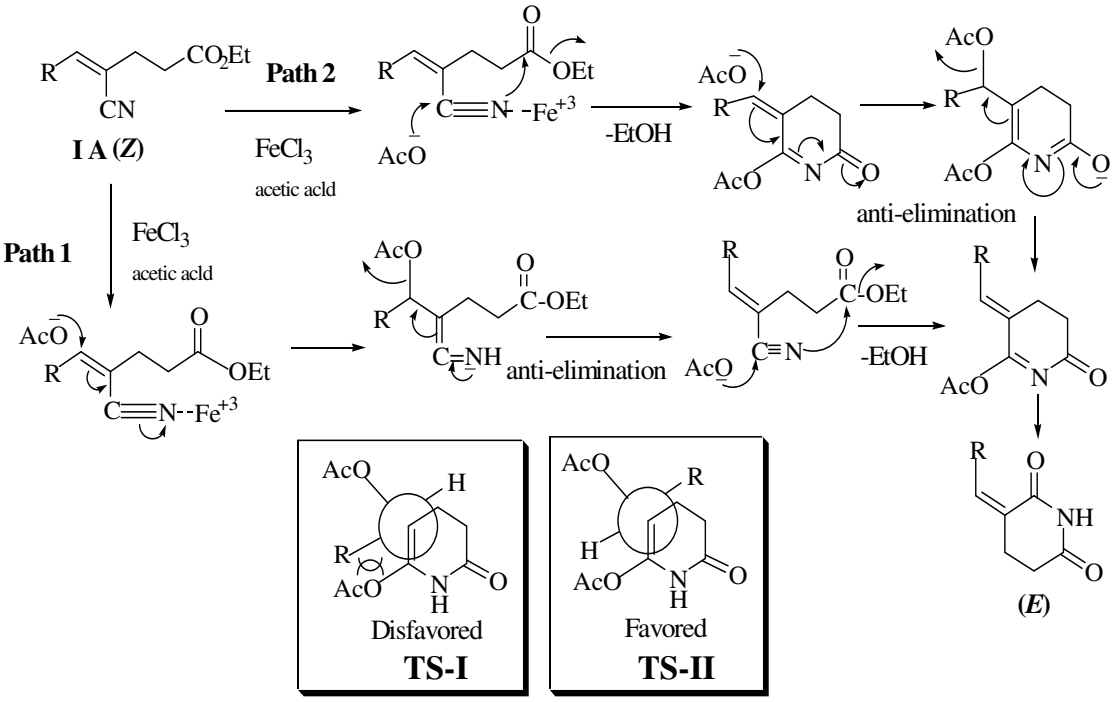
S.NO	B-H alcohol (161a-g)	R	R^1	Product[b] (162a-i)	Yield[c] %
1	**161a**	C_6H_5	H	**162a**	84
2	**161b**	3-ClC_6H_4	H	**162b**[d]	67
3	**161c**	4-ClC_6H_4	H	**162c**[d]	71
4	**161d**	4-MeC_6H_4	H	**162d**	77
5	**161e**	$C_6H_4CH_2CH_2$	H	**162e**	73
6	**161f**	C_7H_{15}	H	**162f**	75
7	**161g**	C_5H_{11}	H	**162g**	81
8	**161a**	C_6H_5	CH_3	**162h**	76
9	**161e**	$C_6H_4CH_2CH_2$	CH_3	**162i**	67

a) All reactions were carried out on a 1 mmol scale of B-H alcohols (**161a-g**).
b) All the compounds (**162a-i**) were obtained as colorless solids and well characterized and the (*E*)-stereochemistry was assigned on the basis of ^{1}H NMR spectral analysis
c) Isolated yields based on B-H alcohols (**161a-g**).
d) Structures of these molecules were also confirmed by the single crystal X-ray data

It is interesting to note that the (*Z*)-stereochemistry in the key intermediate (**I**) has become (*E*)-sterteochemistry in the final product. A possible mechanism for this interesting stereochemical reversal is presented in Scheme 44. $FeCl_3$ might first coordinate with

nitrogen of nitrile group thus making its carbon more electrophilic. Then acetate ion might add on to the ene-nitrile via the 1,4-fashion first and then 1,2-fashion (**Path 1**) leading to the formation of imide ring and subsequent anti-elimination of the acetate might give (*E*)-imide. Alternatively acetate ion might add first in 1,2-fashion on to the ene-nitrile leading to the formation of (*Z*)-imide and then 1,4 addition of acetate ion on the (Z)-imide (**Path 2**) followed by subsequent anti-elimination might provide (*E*)-imide.

Scheme 44

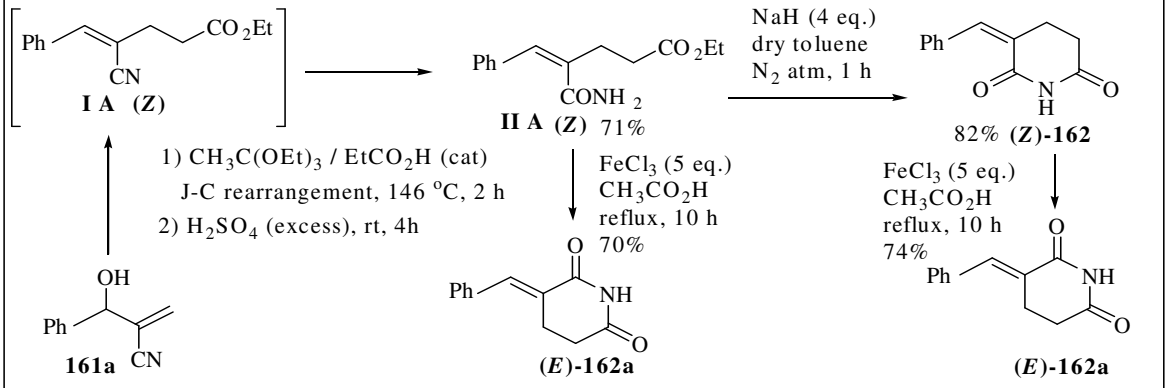


A plausible mechanism for the formation of (*E*)-3-arylidene(alkylidene)piperidine-2,6-dione frame-work

In order to understand the possibility of (*Z*)-imide [(***Z*)-162**] converting into (*E*)-imide we have prepared (*Z*)-3-benzylidenepiperidine-2,6-dione [**(*Z*)-162** imide, structure of [**(*Z*)-162** imide was confirmed by IR, ^{1}H NMR (Spectrum 25), ^{13}C NMR (Spectrum 26), mass

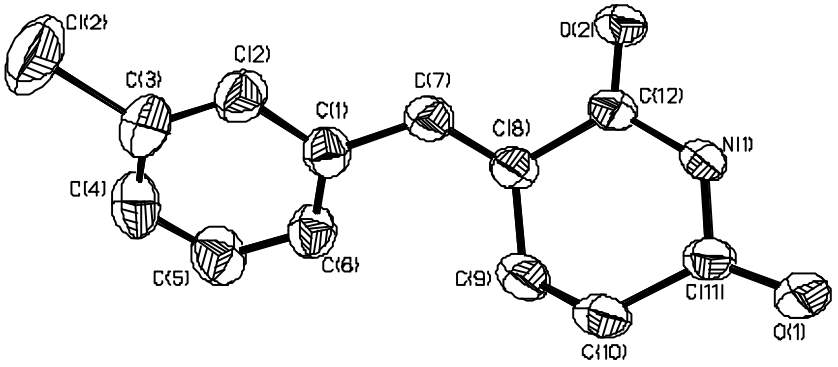
(LCMS) spectral data] via the treatment of the *in situ* generated (4*Z*)-4-cyano-5-phenylpent-4-enoate (**IA**) (the J-C rearrangement product) with H_2SO_4 [to provide-**IIA** amide (isolated), structure of **IIA** amide was confirmed by IR, ^{1}H NMR (Spectrum 27), ^{13}C NMR (Spectrum 28), mass (LCMS) spectral data.] followed by subsequent cyclization using NaH. Treatment of **(*Z*)-162 (**imide) with $FeCl_3$ / acetic acid under reflux for 10 h, provided (*E*)-3-benzylidenepiperidine-2,6-dione [**(*E*)-162**] (Scheme 45). We have also observed that the reaction of (4*Z*)-4-aminocarbonyl-5-phenylpent-4-enoate (**IIA**) with $FeCl_3$/acetic acid at reflux temperature for 10h, directly provided (*E*)-3-benzylidenepiperidine-2,6-dione [**(*E*)-162**] (Scheme 45). These experiments to some extent demonstrate that the change of (*Z*)-stereochemistry into (*E*)-stereochemistry might be either due to Michael addition of acetate ion onto the (Z)-ene-imide or onto the (Z)-ene-nitrile or onto *in situ* formed (Z)-ene-amide followed by anti-elimination (Scheme 44, Transition state models: **TS-I** and **TS-II**).

Scheme 45



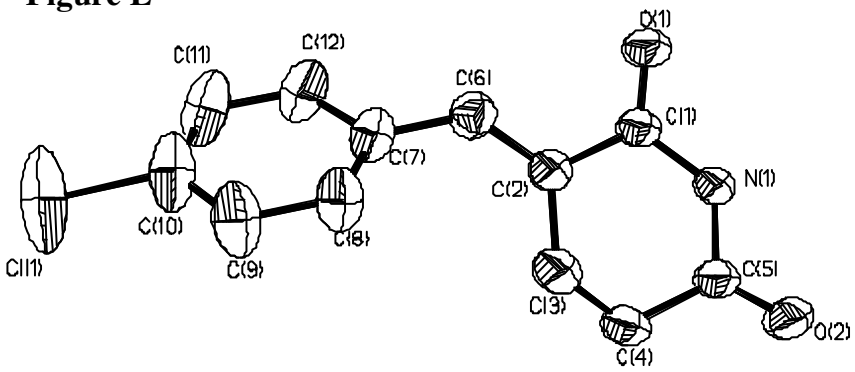
Conversion of (Z)-imide into (E)-imide and (Z)-amide into (E)-imide using FeCl3 / CH_3CO_2H

Figure D



ORTEP diagram of compound **162b**
(hydrogen atoms were omitted for clarity)

Figure E



ORTEP diagram of compound **162C**
(hydrogen atoms were omitted for clarity)

Table IV. Crystal data and structure refinement for **162b**

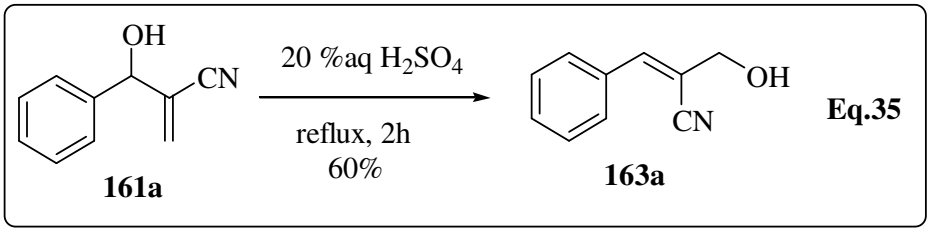
Empirical formula	$C_{12}H_{10}ClNO_2$
Formula weight	235.66
Temperature	273(2) K
Wavelength	0.71073 A
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 21.124(3) A, α = 90 deg.
	b = 7.0062(10) A, β = 97.281(2) deg.
	c = 7.6668(11) A, γ= 90 deg.
Volume	1125.5(3) A^3
Z, Calculated density	4, 1.391 Mg/m^3
Absorption coefficient	0.322 mm^{-1}
F(000)	488
Crystal size	0.42 x 0.22 x 0.22 mm
Theta range for data collection	1.94 to 26.07 deg.
Limiting indices	-26≤h≤20, -8≤k≤8, -9≤l≤9
Reflections collected / unique	6106 / 2217 [R(int) = 0.0186]
Completeness to theta = 26.07	99.6 %
Max. and min. transmission	0.9325 and 0.8765
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2217 / 0 / 149
Goodness-of-fit on F^2	1.046
Final R indices [I>2sigma(I)]	R1 = 0.0569, wR2 = 0.1495
R indices (all data)	R1 = 0.0672, wR2 = 0.1586
Largest diff. peak and hole	0.650 and -0.423 $e.A^{-3}$

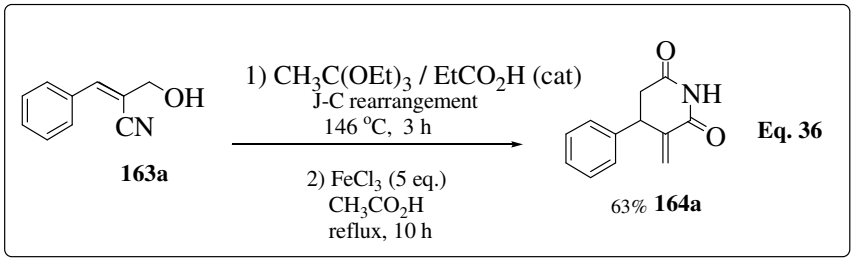
Table V. Crystal data and structure refinement for **162c**

Empirical formula	$C_{12}H_{10}ClNO_2$
Formula weight	235.66
Temperature	273(2) K
Wavelength	0.71073 A
Crystal system	monoclinic
Space group	'P2(1)/c'
Unit cell dimensions	a = 21.531(2) A; α= 90 deg.
	b = 7.1350(7) A; β = 97.930(2) deg.
	c = 7.4685(7) A; δ = 90 deg.
Volume	1136.39(19) A^3
Z, Calculated density	4, 1.377 Mg/m^3
Absorption coefficient	0.319 mm^{-1}
F(000)	488
Crystal size	0.43 x 0.36 x 0.06 mm
Theta range for data collection	1.91 to 26.00 deg.
Limiting indices	-26≤h≤26, -8≤k≤8, -9≤l≤9
Reflections collected / unique	6997 / 2235 [R(int) = 0.0256]
Completeness to theta = 26.00	100.0 %
Max. and min. transmission	0.9811 and 0.8749
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2235 / 0 / 149
Goodness-of-fit on F^2	1.055
Final R indices [I>2sigma(I)]	R1 = 0.0578, wR2 = 0.1572
R indices (all data)	R1 = 0.0719, wR2 = 0.1667
Largest diff. peak and hole	0.626 and -0.321 $e.A^{-3}$

Synthesis of 3-methylidene-4-arylpiperidine-2,6-diones:

In order to understand the generality of this strategy for obtaining 4-aryl-3-methylidenepiperidine-2,6-dione derivatives from rearranged B-H alcohols (the J-C rearrangement followed by partial hydrolysis and cyclization), we have first selected (2*E*)-2-cyano-3-phenylprop-2-en-1-ol[209] (**163a**) as a substrate. This alcohol was obtained from 3-hydroxy-2-methylene-3-arylpropionitrile (**161a**) via the treatment with 20% aq H_2SO_4 at reflux temperature for 2 h (Eq. 35). We have thus performed the J-C rearrangement of the rearranged Baylis-Hillman alcohol **163a,** with triethyl orthoacitate and then treated the in situ generated products with $FeCl_3$/acetic acid for 10 h under reflux to provide 4-phenyl-3-methylidenepiperidine-2,6-dione (**164a**) in 63% isolated yield (Eq. 36). Structure of this molecule was confirmed by IR, ^{1}H NMR (Spectrum 29,), ^{13}C NMR (Spectrum 30), mass (LCMS) spectral data and elemental analysis.





With a view to understand the generality of this reaction, we subjected representative rerranged Baylis-Hillman alcohols **163b-d** (Table 13, Entry 2-4), to this reaction strategy to provide 4-aryl-3-methylidenepiperidine-2,6-diones (**164b-d**) 64-70% isolated yield (Table 14, Entry 2-4). The desired B-H rearranged alcohols **164b-d** were prepared from the B-H alcohols **161a, d, h, i** via treatment with 20 % aq. H_2SO_4. Baylis-Hillman alcohols **161h, i** were prepared via the treatment of 4-isoprophyl benzaldehyde and 2-methyl benzaldehyde respectively with acrylonitrile (Eq.37).

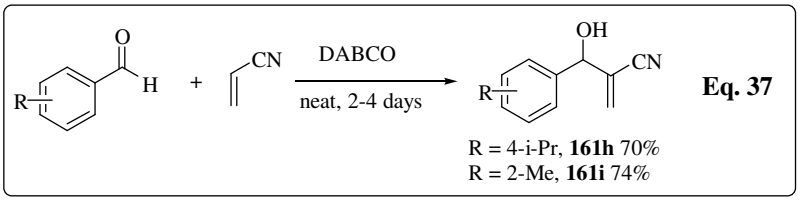
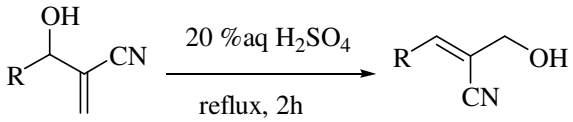


Table 13: Preparation of Baylis-Hillman rearranged adducts **(163a-d)**[a]



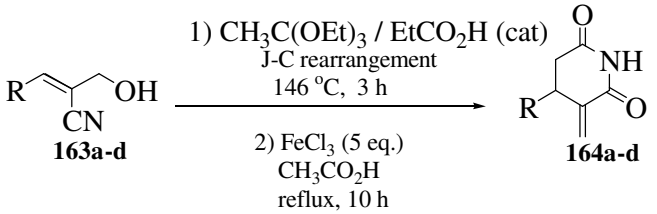
161a, d, h, i **163a-d**

Entry	B-H alcohol (**161a, d, h,i**)	R	B-H rearrange alcohol (**163a-d**)	Yield[b] [%]
1	**161a**	**C_6H_5**	**163a**	60
2	**161d**	4-MeC_6H_4	**163b**	67
3	**161h**	4-i-pr C_6H_4	**163c®**	64
4	**161i**	2-Me C_6H_4	**163d®**	65

a) All reaction carried out on 10 mmol scale of B-H alcohols
b) All the compounds (**163a-d**) were obtained as colorless liquids
c) Isolated yields of the pure products based on the B-H alcohols (**161a,d.h,i**)

® In order to have continuity and better understanding the rearranged alcohols derived from **161h** and **161i** are numbered as **163c** and **163d** respectively

Table 14: One-pot multi-step synthesis of 3-methylidene-4-arylpiperidine-2,6-diones **(164a-d)** from rearranged Baylis-Hillman alcohols **(163a-d)**[a]



S.No	B-H rearranged alcohols (163a-d)	R	Product[b] (164a-d)	Yield[c] %
1	**163a**	C_6H_5	**164a**	63
2	**163b**	4-MeC_6H_4	**164b**	67
3	**163c**	4-$^{i}PrC_6H_4$	**164c**	64
4	**163d**	2-MeC_6H_4	**164d**	70

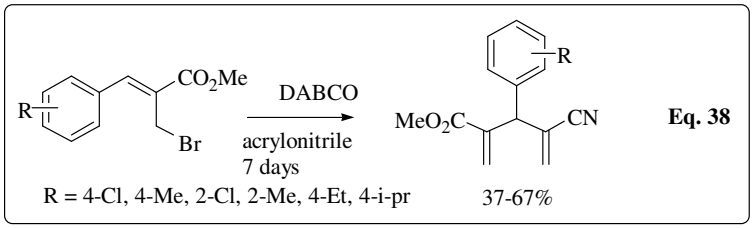
a) All reactions were carried out on a 1 mmol scale of rearranged B-H alcohols (**163a-d**)
b) All the compounds (**164a-d**) were obtained as colorless solids and well characterized.
c) Isolated yields based on rearranged B-H alcohlols (**163a-d**).

Synthesis of 4-aryl-3,5-dimethylidenepiperidine-2,6-diones:

After successfully developing a convenient methodology for the synthesis of (*E*)-3-arylidene(alkylidene)peridine-2, 6-diones and 3-methylidene-4-arylpiperidine-2,6-diones from the Baylis-Hillman adducts, we have focused our attention towards synthesis of the more substituted peridine-2, 6-diones frameworks .

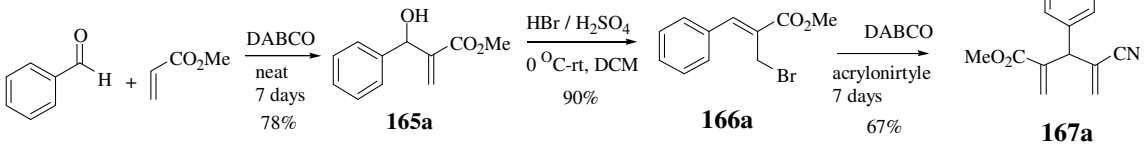
We have recently developed a simple methodology for the preparation of 4-cyano-2-methoxycarbonyl-3-arylpenta-1,4-dienes[210] *via* the reaction of the Baylis-Hillman allyl bromides that is, methyl (2*Z*)-2-(bromomethyl)-3-arylprop-2-enoates with acrylonitrile in the presence of DABCO (Eq.38). It occurred to us that these molecules might serve as

appropriate starting materials for obtaining 4-aryl-3,5-dimethylidenepiperidine-2,6-dione derivatives.



We have first selected 2-cyano-4-methoxycarbonyl-3-phenyl-1,4-pentadiene (**167a**) as a substrate. The required **167a** was obtained via the treatment of (2*Z*)-2-(bromoethyl)-3-phenylprop-2-enoates **(166a)** with acrylonitrile in the presence of DABCO following the known procedure developed in our laborotary[210]. The required allyl bromide **166a** was prepared via the treatment of Baylis-Hillman alohol **165a** with HBr / H_2SO_4. The Baylis-Hillman alohol **165a** was obtained via the reaction between methyl acrylate and benzaldehyde in the presence of DABCO (Scheme 46).

Scheme 46



We have then subjected the Baylis-Hillman compound 4-cyano-2-methoxycarbonyl-3-phenylpenta-1,4-dienes (**167a**) to the reaction with $FeCl_3$ / acetic acid to provide 4-phenyl-3,5-dimethylidenepiperidine-2,6-dione (**168a**) in 81% isolated yields (Eq. 39). Structure of this compound was confirmed by IR, ^{1}H NMR (Spectrum 31), ^{13}C NMR (Spectrum 32), mass (LCMS) spectral data and elemental analysis. The structure of this compound (see

Figure F for ORTEP diagram, Table VI) was further confirmed by single crystal X-ray data analysis.

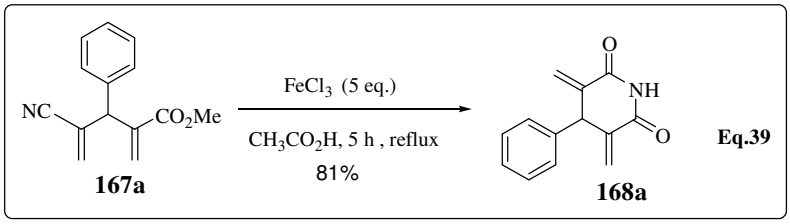
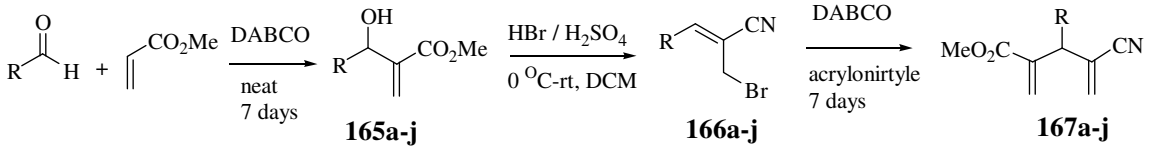


Table 15: Preparation of the Baylis-Hillman compounds (**167a-j**)

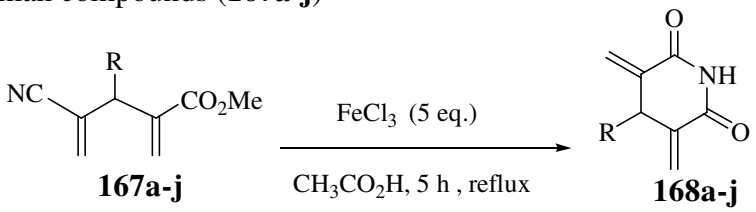


Entry	R	B-H alcohol[a] (165a-j)	Yield[b] %	Allyl bromide[c] (166a-j)	Yield[d] %	B-H compoud[e] (167a-j)	Yield[f] %
1	C_6H_5	**165a**	78	**166a**	91	**167a**	67
2	3-ClC_6H_4	**165b**	65	**166b**	80	**167b**	61
3	3-BrC_6H_4	**165c**	70	**166c**	86	**167c**	60
4	3-$OMeC_6H_4$	**165d**	63	**166d**	87	**167d**	65
5	4-ClC_6H_4	**165e**	76	**166e**	82	**167e**	67
6	4-BrC_6H_4	**165f**	71	**166f**	78	**167f**	60
7	4-$OMeC_6H_4$	**165g**	72	**166g**	75	**167g**	62
8	4-MeC_6H_4	**165h**	76	**166h**	79	**167h**	69
9	4-EtC_6H_4	**165i**	67	**166i**	83	**167i**	66
10	4-i-PrC_6H_4	**165j**	70	**166j**	81	**167j**	68

a) All reactions were carried out on 200 mmol scale of aryl aldehydes.
b) Isolated yields of the pure products based on the aryl aldehydes and well characterized
c) All reaction carried out on 20 mmol scale of B-H alcohols (**165a-j**)
d) Isolated yields of the pure products based on the B-H alcohols (**165a-j**).
e) All reaction carried out on 4 mmol scale of B-H bromides (**166a-j**)
f) Isolated yields of the pure products based on the B-H bromides (**166a-j**) and well characterized

In order to understand the generality of this stratagy we have subjected a representative class of Baylis-Hillman products, 4-cyano-2-methoxycarbonyl-3-arylpenta-1,4-dienes (**167b-j**) (Table 15, Entry 2-10) to this reaction strategy to provide 4-aryl-3,5-dimethylidenepiperidine-2,6-dione derivatives (**168b-j**) in 61-86% isolated yields (Table16, Entry 2-10). Structures of all the compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass (LCMS) spectral data and elemental analysis.

Table 16: Synthesis of 4-aryl-3,5-dimethylidenepiperidine-2,6-dione (**168a-j**) from Baylis-Hillman compounds (**167a-j**) [a]



167a-j **168a-j**

S.NO	B-H compound (167a-j)	R	Product[b] (168a-j)	Yield[c] %
1	**167a**	C_6H_5	**168a**[d]	82
2	**167b**	3-ClC_6H_4	**168b**	80
3	**167c**	3-BrC_6H_4	**168c**	86
4	**167d**	3-$OMeC_6H_4$	**168d**	61
5	**167e**	4-ClC_6H_4	**168e**	75
6	**167f**	4-BrC_6H_4	**168f**	76
7	**167g**	4-$OMeC_6H_4$	**168g**	63
8	**167h**	4-MeC_6H_4	**168h**	85
9	**167i**	4-EtC_6H_4	**168i**	70
10	**167j**	4-i-PrC_6H_4	**168j**	84

a) All reactions were carried out on a 1 mmol scale of B-H compounds (**167a-j**).

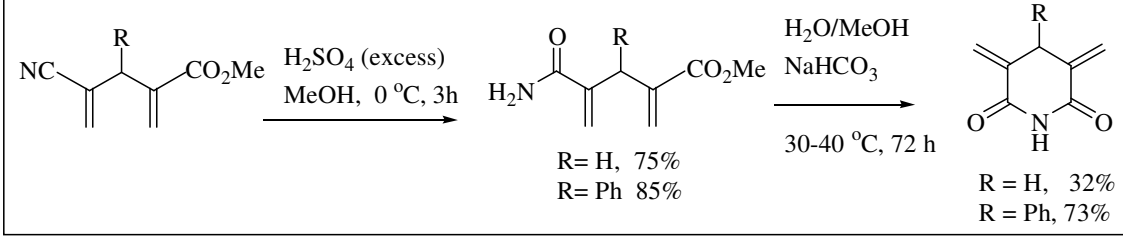
b) All the products (**168a-j**) were obtained as colorless solids and well characterized.

c) Isolated yields based on B-H products (**167a-j**).

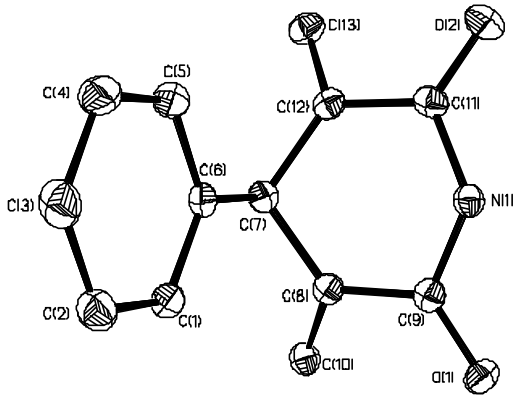
d) The structure of this molecule was also confirmed by single crystal X-ray data

It is worth mentioning here that Kim and coworkers[211] reported the synthesis of 3,5-dimethylidene-4-phenylpiperidine-2,6-dione and 3,5-dimethylidenepiperidine-2,6-dione (two examples) from the corresponding Baylis-Hillman products in two steps (via the treatment with sulfuric acid followed by the treatment of the resulting amides with sodium bicarbonate in aqueous methanol) (Scheme 47). Our results clearly indicated that our one-pot procedure using $FeCl_3$ / acetic acid offers better results than the above mentioned two step process.

Scheme 47



Fiure F



ORTEP diagram of compound **168a**
(hydrogen atoms were omitted for clarity)

Table VI. Crystal data and structure refinement for **168a**

Empirical formula	$C_{13}\ H_{11}\ N\ O_2$
Formula weight	213.23
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system	Orthorhombic
Space group	Pca2(1)
Unit cell dimensions	a = 29.656(2) A, α = 90 deg.
	b = 5.1027(4) A, β = 90 deg.
	c = 13.5642(9) A, γ = 90 deg.
Volume	2052.6(3) A^3
Z, Calculated density	4, 1.380 Mg/m^3
Absorption coefficient	0.094 mm^{-1}
F(000)	896
Crystal size	0.42 x 0.20 x 0.08 mm
Theta range for data collection	1.37 to 25.97 deg.
Limiting indices	$-36\leq h\leq 36$, $-6\leq k\leq 6$, $-16\leq l\leq 16$
Reflections collected / unique	19689 / 2099 [R(int) = 0.0344]
Completeness to theta = 25.97	99.7 %
Max. and min. transmission	0.9925 and 0.9616
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2099 / 1 / 297
Goodness-of-fit on F^2	1.093
Final R indices [I>2sigma(I)]	R1 = 0.0377, wR2 = 0.0947
R indices (all data)	R1 = 0.0394, wR2 = 0.0958
Absolute structure parameter	0(10)
Largest diff. peak and hole	0.269 and -0.174 $e.A^{-3}$

We have in conclusion developed convenient and simple one-pot multi-step procedure for synthesis of (1) (*E)*-3-arylidene / alkylidenepiperidine-2,6-diones using the Baylis-Hillman alcohols, (2) 4-aryl-3-methylidenepiperidine-2,6-diones using the Baylis-Hillman rearranged alcohols and (3) 4-aryl-3,5-dimethylidenepiperidine-2,6-dione using the Baylis-Hillman compounds (derived from the Baylis-Hillman bromides) thus demonstrating the importance of Baylis-Hillman adducts in heterocyclic synthesis.

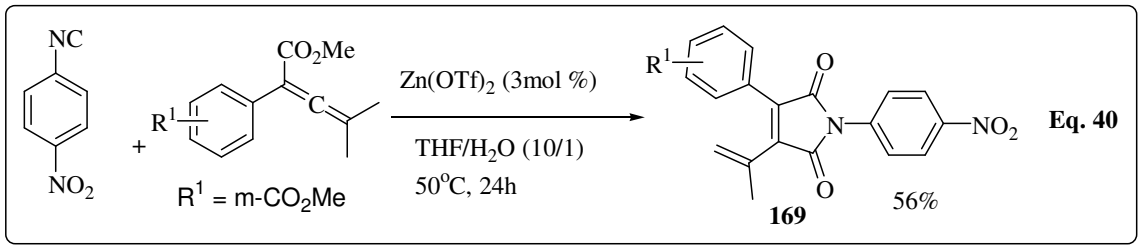
III. Simple Synthesis of Substituted Maleimide Derivatives using the Baylis-Hillman Adducts

After developing a symple methodology for synthesis of 3-arylmethylidene (or alkylidene)piperidine-2,6-diones from the Baylis-Hillman alcohols (derived from aldehydes and acrylonitrile) in a facile one-pot procedure involving Johnson-Claisen (J-C) rearrangement followed by partial hydrolysis of nitrile into amide, and cyclization using $FeCl_3$ / CH_3CO_2H, we have directed our studies towards the development of simple methodology for synthesis of disubstituted maleimide framework. 3,4-Disubstituted maleimide framework represents an interesting structural organization in heterocyclic chemistry as this skeleton is present in a number of natural products such as himanimides A-D,[212] polycitrins A & B,[213,214] and arcyriarubins A & B.[215] Also certain compounds having this framework have been known to exhibit various biological activities such as protein kinase C inhibitors (PKC),[216,217] inhibitor of calmodulin dependant protien kinase

(CaMKIIδ),[218] cell death inhibitor,[219,220] vascular endothelial cell proliferation,[221] angiogenesis inhibitor,[222] and cytotoxicity.[223]

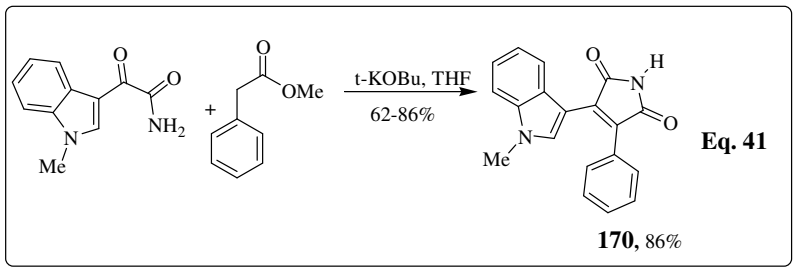
Synthetic chemists developed various methodologies for the synthesis of maleimide derivatives due to their medicinal importance. Some important strategies are presented in Eq. 40-42.

Wang and co-workers[224] reported a facile synthesis of maleimde derivatives (**169**) via $Zn(OTf)_2$ catalyzed reaction between of isonitriles and allenic esters. One example is shown in Eq. 40.



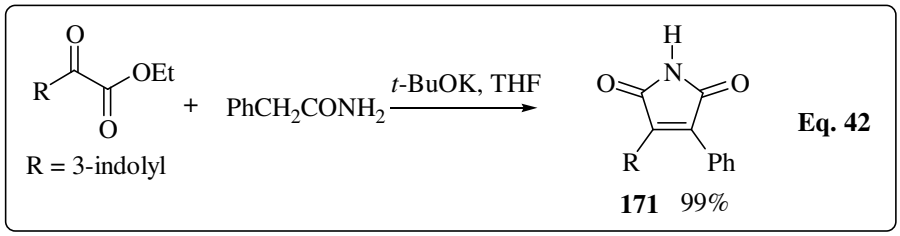
Eq. 40

Gribble and co-workers[225] reported a convenient synthesis of indolylaryl and indolylheteroarylmaleimides (**170**) via treatment of N-methylindole-3-glyoxylamide with methyl arylaetates in the presence of t-KOBu (Eq.41).

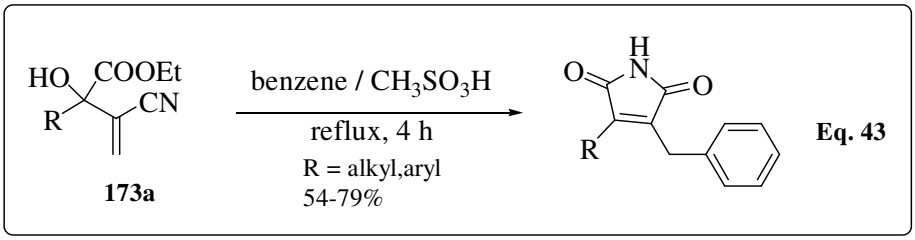


Eq. 41

Faul and co-workers[217] reported one-pot synthesis of maleimides (**171**) via the reaction of glyoxylates esters with acetamides following reaction sequence shown in Eq. 42



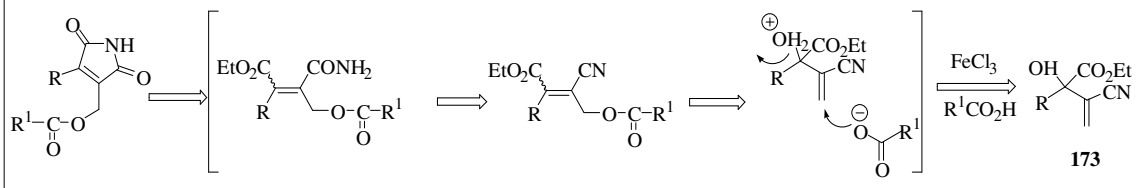
Recently we have reported a facile one-pot methanesulfonic acid mediated transformation of the B-H adducts, 3-ethoxycarbonyl-3-hydroxy-3-aryl(alkyl)-2-methylenepropanenitriles (**173) (**obtained from α-keto esters (**172**) and acrylonitrile) into unsymmetrical maleimides in the presence of benzene (Eq. 43).[226] This strategy involves Friedel-Crafts reaction of benzene with B-H adducts (**173)** (as electrophile), partial hydrolysis of nitrile into amide and then imide formation.



On the basis of the above mentioned observation, it occurred to us that the B-H adducts **173** (Table 17), derived from α-keto esters **172** (Table 17) and acrylonitrile, should in principle, be easily transformed into the desired 3-alkylcarbonyloxymethyl-4-aryl(or

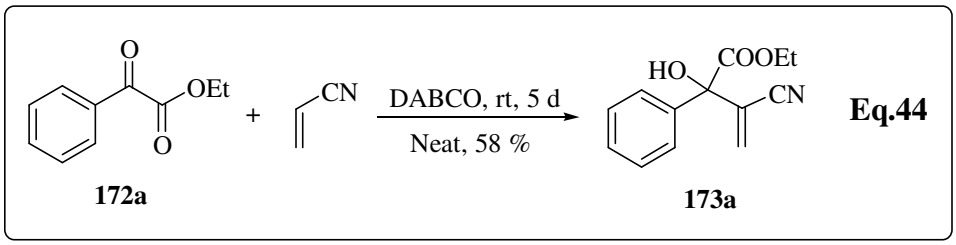
alkyl) maleimide derivatives via the treatment with $FeCl_3$ in the presence of appropriate carboxylic acid (Retrosynthetic strategy see: Scheme 48).

Scheme 48

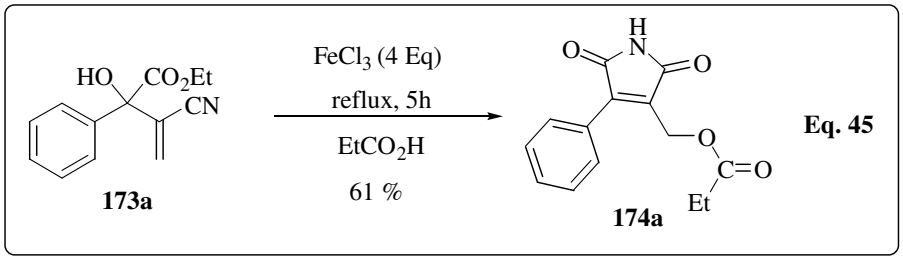


Retrosynthetic strategy for the synthesis of 3,4- disubstituted pyrrole-2,5-diones

Accordingly we have first selected 3-ethoxycarbonyl-3-hydroxy-3-phenyl-2-methylenepropanenitrile (**173a)** as a substrate**.** The required B-H alcohol **173a** was prepared via treatment phenylglyoxylate (**172a**) and acrylonitrile in the presence of DABCO following the known procedure[227] (Eq 44).



The best results were obtained when **174a** was treated with anhydrous $FeCl_3$ (4 mmol) in propanoic acid (5 mL) at reflux temperature for 5 h, thus providing the desired 3-(ethylcarbonyloxy)methyl-4-phenyl-1H-pyrrole-2,5-dione **(174a)** in 61% isolated yield (Eq. 45). Structure of this molecule was confirmed by IR, ^1H NMR (Spectrum 33), ^{13}C NMR (Spectrum 34), mass (LCMS) spectral data and elemental analysis.

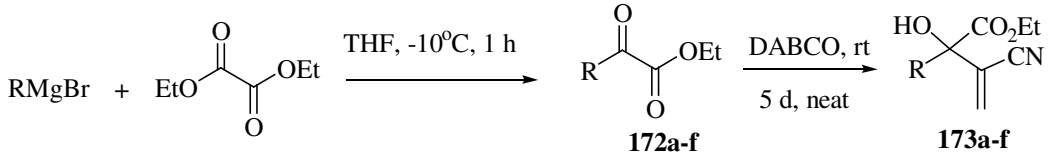


To understand the generality of this strategy we have prepared representative Baylis-Hillman alcohols **172b-e** via the treatment of α-keto esters with acrylonitrile (Table 17, Entry 2-5). The required α-keto esters were prepared via the reaction of diethyloxalate with appropriate Grignard reagent following the known procedure[229] (Table 17). Then Baylis-Hillman alcohols **173b-e** (Table 17, Entry 2-5)**,** were subjected to this strategy (treatment with $FeCl_3$ in the presence of propanoic acid) to provide the desired 3-(ethylcarbonyloxy)methyl-4-aryl-1H-pyrrole-2,5-diones **174b-e** (Table 18, Enrty 2-5) in 54-63 % isolated yields.

With a view to understand the applicability of this strategy to other carboxylic acids, we have also used acetic acid. Thus the treatment of representative Baylis-Hillman alcohols **173a, c-e** (Table 17, Entry 1, 3-5) with $FeCl_3$ in the presence of acetic acid at reflux temperature for 5h provided the expected 3-(methylcarbonyloxy)methyl-4-aryl-1H-pyrrole-2,5-diones **174g-j** in 50-65% isolated yields (Table 18, Entry 7-10). Structures of these compounds were confirmed by IR, ^{1}H NMR (Spectrum 35 for the compound **174g**), ^{13}C NMR (Spectrum 36 for the compound **174g**), mass (LCMS) spectral data and

elemental analysis. The structures of the compounds **174c** (see Figure G for ORTEP diagram, Table VII) and **174h** (see Figure H for ORTEP diagram, Table VIII) were further confirmed by single crystal X-ray data analysis.

Table 17. Preparation of the Baylis-Hillman adducts



172a-f **173a-f**

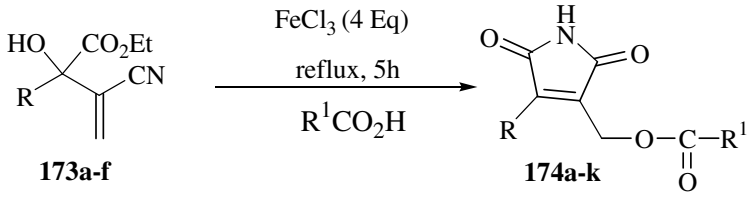
Entry	R	α-Ketoester[a] (172a-e)	Yield %	B-H adduct[b] (173a-f)	Yield[c] %
1	C_6H_5	**172a**	41	**173a**	58
2	2-MeC_6H_4	**172b**	47	**173b**	45
3	3-MeC_6H_4	**172c**	63	**173c**	47
4	3-$MeOC_6H_4$	**172d**	60	**173d**	62
5	4-MeC_6H_4	**172e**	62	**173e**	65
6	Methyl	**-**	-	**173f**	35

a) All reactions were carried out on 250 mmol scale of diethyl oxalate with alkylmagnesium bromide (100 mmol).
b) All reaction carried out on 10 mmol scales of α-keto esters (**172a-f**) with acrylonitrile (20 mmol) under the catalytically influence of DABCO
c) Isolated yields of the pure products based on the α-keto esters.

We have then extended this methodology to Baylis-Hilman adduct **173f** (Table 17, Entry 6) *i.e.* 3-ethoxycarbonyl-3-hydroxy-2-methylenebutanenitrile (obtained from ethyl pyruvate and acrylonitrile). Thus, the reaction between **173f** and $FeCl_3$ in the presence of propanoic acid and acetic acid under similar conditions furnished 3-(ethylcarbonyloxy)-methyl-4-methyl-1H-pyrrole-2,5-dione (**174f**) (Table 18, Entry 6) and 3-(methylcarbonyloxy)methyl-4-methyl-1H-pyrrole-2,5-dione (**174k**) (Table 18, Entry 11)

in 63% and 59% yields respectively. Structures of these molecules were confirmed by IR, ^{1}H NMR (Spectrum 37 for compound **174k**), ^{13}C NMR (Spectrum 38 for compound **174k**), mass (LCMS) spectral data and elemental analysis.

Table 18: Synthesis of 3,5-disubstituted 1H-pyrrole-2,5-diones (**174a-k**)

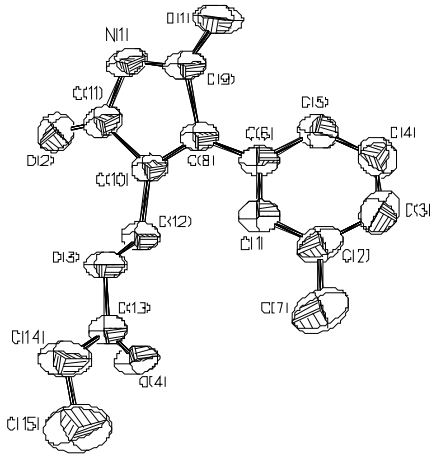


173a-f **174a-k**

S.NO	B-H alcohol (173a-f)	R	R^1	Product[b] (174a-k)	Yield[c] %
1	**173a**	C_6H_5	Et	**174a**	61
2	**173b**	2-MeC_6H_4	Et	**174b**	54
3	**173c**	3-MeC_6H_4	Et	**174c**[d]	60
4	**173d**	3-OMeC_6H_4	Et	**174d**	61
5	**173e**	4-MeC_6H_4	Et	**174e**	55
6	**173f**	Me	Et	**174f**	63
7	**173a**	C_6H_5	Me	**174g**	60
8	**173c**	3-MeC_6H_4	Me	**174h**[d]	65
9	**173d**	3-OMeC_6H_4	Me	**174i**	52
10	**173e**	4-MeC_6H_4	Me	**174j**	61
11	**173f**	Me	Me	**174k**	59

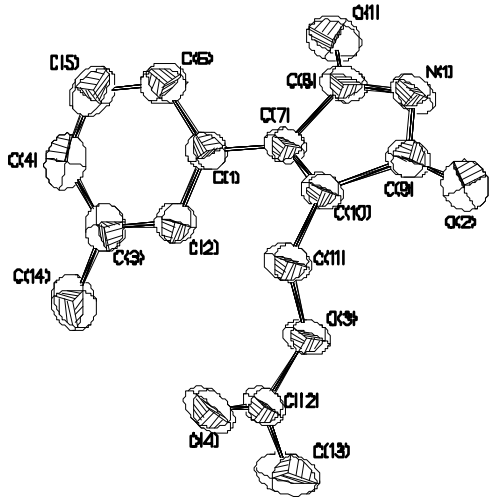
a) All reactions were carried out on a 1 mmol scale of B-H alcohols (**173a-f**)
b) All the compounds (**174a-k**) were obtained as light yellow solids and well characterized.
c) Isolated yields based on B-H alcohols.
d) Structures of these molecules were also confirmed by single crystal X-ray data analysis.

Figure G



ORTEP diagram of compound 174c
(Hydrogen atoms were omitted for clarity)

Figure H



ORTEP diagram of compound 174h
(Hydrogen atoms were omitted for clarity)

Table VII. Crystal data and structure refinement for **174c**

Empirical formula	$C_{15}\,H_{15}\,NO_4$
Formula weight	273.28
Temperature	298(2) K
Wavelength	0.71073 A
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 9.061(6) A, α = 109.574(11) deg.
	b = 9.274(6) A, β = 100.030(11) deg.
	c = 9.397(7) A, γ = 102.505(11) deg.
Volume	699.8(8) A^3
Z, Calculated density	2, 1.297 Mg/m^3
Absorption coefficient	0.095 mm^{-1}
F(000)	288
Crystal size	0.40 x 0.24 x 0.22 mm
Theta range for data collection	2.39 to 28.40 deg.
Limiting indices	$-11\le h\le 11$, $-11\le k\le 12$, $-12\le l\le 12$
Reflections collected / unique	8004 / 3229 [R(int) = 0.0488]
Completeness to theta = 25.00	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.981 and 0.936
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3229 / 0 / 185
Goodness-of-fit on F^2	0.993
Final R indices [I>2sigma(I)]	R1 = 0.0609, wR2 = 0.1616
R indices (all data)	R1 = 0.0932, wR2 = 0.1782
Largest diff. peak and hole	0.308 and -0.333 $e.A^{-3}$

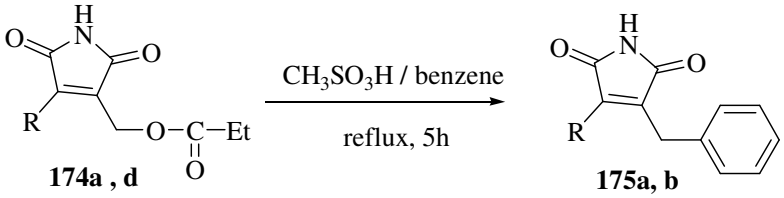
Table VIII. Crystal data and structure refinement for **174h**

Empirical formula	$C_{14}\,H_{13}\,NO_4$
Formula weight	259.25
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system	triclinic
Space group	P -1
Unit cell dimensions	a = 9.0234(18) A, α= 108.58(3) deg.
	b = 9.1464(18) A, β = 103.82(3) deg.
	c = 9.2160(18) A, γ = 103.81(3) deg.
Volume	657.9(2) A^3
Z, Calculated density	2, 1.309 Mg/m^3
Absorption coefficient	0.097 mm^{-1}
F(000)	272
Crystal size	0.40 x 0.32 x 0.28 mm
Theta range for data collection	2.47 to 27.96 deg.
Limiting indices	-11≤h≤11, -11≤k≤11, -12≤l≤12
Reflections collected / unique	7656 / 3033 [R(int) = 0.0365]
Completeness to theta = 27.96	96.2 %
Max. and min. transmission	0.9734 and 0.9623
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3033 / 0 / 174
Goodness-of-fit on F^2	0.960
Final R indices [I>2sigma(I)]	R1 = 0.0470, wR2 = 0.1209
R indices (all data)	R1 = 0.0728, wR2 = 0.1317
Largest diff. peak and hole	0.161 and -0.176 $e.A^{-3}$

Synthesis of 3-benzyl-4-aryl-1H-pyrrole-2,5-diones:

In order to understand the applicability of these maleimides as electrophiles in the Friedel-Crafts reaction, we have performed the reaction between 3-(ethylcarbonyloxy)methyl-4-phenyl-1H-pyrrole-2,5-dione (**174a)** and benzene in the presence of methanesulfonic acid. We were pleased to note that the expected Friedel-Crafts product, 3-benzyl-4-phenyl-1H-pyrrole-2,5-dione (**175a)** was obtained in 81% isolated yield (Table 19, Entry 1). With a view to understand the general nature of this reaction we have also subjected 3-(ethylcarbonyloxy)methyl-4-(3-methoxyphenyl)-1H-pyrrole-2,5-dione **174d,** to the Friedel-Crafts reaction with benzene in the presence of methanesulfonic acid which provided 3-benzyl-4-(3-methoxyphenyl)-1*H*-pyrrole-2,5-dione (**175b)** in 77% isolated yield (Table 19, Entry 2).

Table 19: Synthesis of 3-benzyl 4-aryl-1H-pyrrole-2,5-diones (**175a,b**)[a]



174a , d **175a, b**

Entry	Compound	R	Product[b]	Yield[c] [%]
1	**174a**	C_6H_5	**175a**[#]	81
2	**174d**	3-$MeOC_6H_4$	**175b**[#]	77

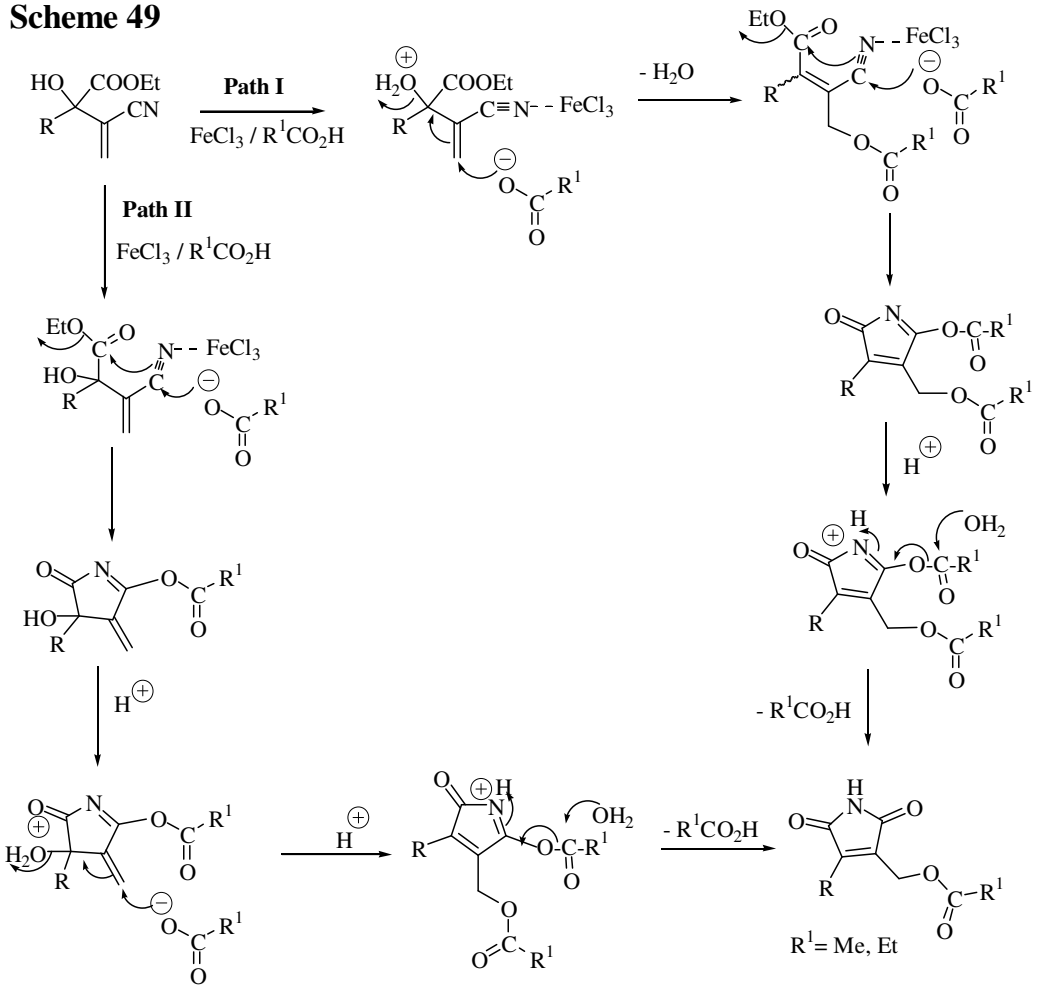
a) Reactions were carried out on a 1 mmol scale of compounds **174a, d**.
b) The compounds (**175a, b)** were obtained as light yellow solids and well characterized.
c) Isolated yields based on the compounds **174a, d**.

Structures of these molecules were confirmed by IR, ^{1}H NMR (Spectrum 39 for compound **175a)**, ^{13}C NMR (Spectrum 40 for compound **175a)** and mass (LCMS) spectral data.

[#] These compounds are known in the literature (synthesized in our laboratory by a different procedure).[226] The present pectral data are in complete agreement with that of reported data.

A plausible mechanism for the formation of 3,4-disubstituted maleimide derivatives (**174a-k**) from B-H adducts (**173a-f)** is shown in Scheme 49.

Scheme 49



A plausible mechanism for the formation of 3,4-disubstituted maleimides

Although the yields of maleimide derivatives are not very high, this study presents a facile and convenient strategy for one-pot synthesis of 3,4-disubstituted maleimide derivatives from the Baylis-Hillman alcohols, obtained from acrylonitrile and α-keto esters.

Conclusions

As we mentioned in the beginning of this section, we have achieved resonable success in our objectives on the applications of Baylis-Hillman adducts for the synthesis of carbocyclic and heterocyclic olecules.

We have transformed the B-H acetates (**149a-h**) into 2-substituted ind-2-en-1-one derivatives (**152a,b; 155a,b; 158a-h**) in a two-step protocol. This transformation proceeds through an unusual conversion of *trans* cinnamic esters into ind-2-en-1-one frameworks. The yields of the indenone derivatives depend on the steric bulk of substitution at α-position of ester group of *trans* cinnamic esters. We have also developed a simple two-step strategy for transformation of the B-H acetates (**149a-h**) into substituted piperidine-2,6-dione derivatives (**153a,b; 159a-h**).

We have developed convenient and simple one-pot multi-step procedure for synthesis of (*E)*-3-arylidene / alkylidenepiperidine-2,6-diones (**162a-i**), and 4-aryl-3-methylidenepiperidine-2,6-diones (**164a-d**) from the Baylis-Hillman adducts (**161a-g;** and rearranged BH-alcohols **163a-d**). This strategy involves Johnson-Claisen rearrangement followed by partial hydrolysis of cyano group leading to formation of pipedine-2,6-dione derivatives. We extended this methodology for the synthesis of 4-aryl-3,5-dimethylidenepiperidine-2,6-diones (**168a-j**) from Baylis-Hillman compounds (**167a-j**).

We have developed simple one-pot synthesis of 3,5-disubstituted 1H-pyrrole-2,5-diones (**174a-k**) starting from Baylis-Hillman adducts 3-ethoxycarbonyl-3-hydroxy-3-aryl/alkyl-2-methylenepropanenitriles (**173a-f**) via treatment with $FeCl_3$ in the presence of RCO_2H (R = Me, Et). Two of these derivatives (**174a, d**) were further converted into 3-benzyl-4-phenyl-1H-pyrrole-2,5-dione (**175a,b**) via Friedel-Crafts reaction with benzene.

EXPERIMENTAL

Melting Points: All melting points were recorded on a Superfit (India) capillary melting point apparatus and are uncorrected.

Boiling Points: Boiling points refer to the temperature measured using short path distillation units and are uncorrected.

Infrared Spectra: Infrared spectra were recorded on a JASCO FT / IR-5300 spectrophotometer. All the spectra were calibrated against polystyrene absorption at 1601 cm^{-1}. Solid samples were recorded as KBr wafers and liquid samples as thin film between NaCl plates or solution spectra in CH_2Cl_2.

Nuclear Magnetic Resonance Spectra: Proton magnetic resonance spectra and carbon-13 magnetic resonance spectra were recorded on a BRUKER-AC-200 and BRUKER-AVANCE-400 spectrometers. ^1H NMR (400 MHz) spectra for all the samples were measured in chloroform-d, unless otherwise mentioned (δ = 2.50 ppm for ^1H NMR in the case of DMSO-d_6), with TMS (δ = 0 ppm) as an internal standard. ^{13}C NMR (50 MHz / 100 MHz) spectra for all the samples were measured in chloroform-*d*, unless otherwise mentioned (in the case of DMSO-d_6, δ = 39.70 ppm its middle peak of the septet), with its middle peak of the triplet (δ = 77.10 ppm) as an internal standard. Spectral assignments are as follows: (1) chemical shifts on the δ scale, (2) standard abbreviation for multiplicity,

that is, s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, dd = doublet of doublet, td = triplet of doublet, dt = doublet of triplet, bs = broad singlet, dABq = doublet of AB quartet, (3) number of hydrogens integrated for the signal, (4) coupling constant *J* in Hertz.

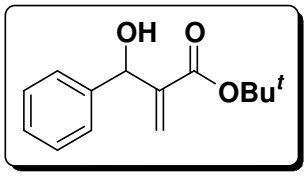
Mass Spectral Analysis: Shimadzu LCMS 2010A mass spectrometer.

Elemental Analysis: Elemental analyses were performed on a Thermo Finnigan Flash EA 1112-CHN analyzer.

X-ray Crystallography: The X-ray diffraction measurements were carried out at 293 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-K_α fine-focus sealed tube (λ = 0.71073 A^o) operated at 1500 W power (50 kV, 30 mA). The detector was placed at a distance of 4.995 cm from the crystal. The frames were integrated with the Bruker SAINT Software package using a narrow-frame algorithm. Data were corrected for absorption effects using the multi-scan technique (SADABS). The structure was solved and refined using the Bruker SHELXTL (Version 6.1) Software package.

General: All the solvents were dried and distilled using suitable drying agents before use. Moisture sensitive reactions were carried out using standard syringe-septum techniques under nitrogen atmosphere. All reactions were monitored using Thin Layer Chromatography (TLC).

***tert*-Butyl 3-hydroxy-2-methylene-3-phenylpropanoate (148a):** This compound was prepared following the procedure developed in our laboratory.[228] Bezaldehyde (150 mmol, 15.9 g, 15.0 mL), *tert*-butyl acrylate (225 mmol, 28.8 g, 33.0 mL) and DABCO (22.5 mmol, 5.04 g) in silica gel (>200 mesh, 45.0 g) were thoroughly and uniformly mixed and this mixture was kept at room temperature for 36 h. Ethyl acetate (150 mL) was added to the reaction mixture and stirred thoroughly and filtered. The solid silica gel was washed with ethyl acetate (2 X 35 mL). The filtrates and washings were combined and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure. Residue, thus obtained was purified by column chromatography (6 % of ethyl acetate / hexanes) to afford *tert*-butyl 3-hydroxy-2-methylene-3-phenylpropanoate (**148a**) in 73 % (25.5 g) as a colorless liquid.



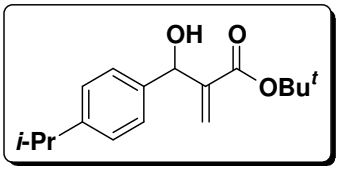
IR (Neat): ν 3441, 1714, 1631 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 9H), 3.12 (bs, 1H), 5.49 (s, 1H), 5. 71 (s, 1H), 6.24 (s, 1H), 7.23-7. 39 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 27.87, 73.21, 81.45, 124.90, 126.60, 127.56, 128.23, 141.70, 143.56, 165.57.

***tert*-Butyl 3-hydroxy-2-methylene-3-(4-isopropylphenyl)propanoate (148b):** Treatment of 4-isopropylbenzaldehyde with *tert*-butyl acrylate in the presence of DABCO (cat.), following similar procedure as described for the compound *tert*-butyl 3-hydroxy-2-

methylene-3-phenylpropanoate (**148a**) provided the title compound as a colorless solid after crystallization from 10 % ethyl acetate in hexanes at ^{o}C.



Reaction time: 18 d

Yield: 59 %

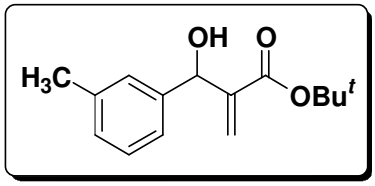
Mp: 44-46 ^{o}C (Lit.[228] 43-45 ^{o}C)

IR (KBr): ν 3460, 1712, 1631 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (d, 6H, J = 7.2 Hz), 1.39 (s, 9H), 2.89 (sept, 1H, J = 6.8 Hz), 3.00 (bs, 1H), 5.48 (s 1H), 5.72 (s, 1H), 6.23 (s, 1H), 7.19 (d, 2H, J = 8.0 Hz), 7.27 (d, 2H, J = 8.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.02, 27.97, 33.84, 73.30, 81.53, 124.94, 126.40, 126.62, 139.11, 143.70, 148.37, 165.79.

***tert*-Butyl 3-hydroxy-2-methylene-3-(3-methylphenyl)propanoate (148c):** This alcohol was obtained as a viscous liquid *via* the coupling of 3-methylbenzaldehyde with *tert*-butyl acrylate under the catalytic influence of DABCO, following similar procedure as described for the compound *tert*-butyl 3-hydroxy-2-methylene-3-phenylpropanoate (**148a**).



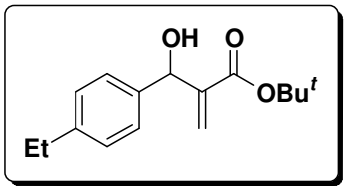
Yield: 60%

IR (Neat): ν 3464, 1714, 1631 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 9H), 2.32 (s, 3H), 3.20 (bs, 1H), 5.45 (s, 1H), 5.73 (s, 1H), 6.23 (s, 1H), 7.04-7.28 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.42, 27.94, 73.37, 81.53, 123.71, 125.03, 127.29, 128.21, 128.38, 137.89, 141.60, 143.58, 165.72.

***tert*-Butyl 3-(4-ethylphenyl)-3-hydroxy-2-methylenepropanoate (148d):** This allylic alcohol prepared *via* the reaction between 4-ethylbenzaldehyde and *tert*-butyl acrylate catalyzed by DABCO, as a colorless solid [after crystallization from 10 % ethyl acetate in hexanes at 0 ^{o}C], following similar procedure as described for the molecule *tert*-butyl 3-hydroxy-2-methylene-3-phenylpropanoate (**148a**).



Reaction time: 16 d

Yield: 69 %

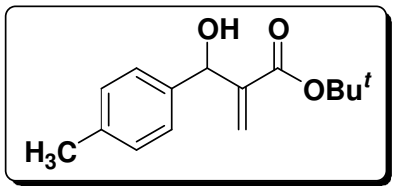
Mp: 45-47 ^{o}C (Lit.[227] 46-48 ^{o}C)

IR (KBr): ν 3310, 1714, 1635 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, 3H, J = 7.6 Hz), 1.39 (s, 9H), 2.61 (q, 2H, J = 7.6 Hz), 3.04 (bs, 1H), 5.47 (s, 1H), 5.72 (s, 1H), 6.23 (s, 1H), 7.16 (d, 2H, J = 8.0 Hz), 7.26 (d, 2H, J = 8.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 15.49, 27.79, 28.42, 72.85, 81.21, 124.47, 126.60, 127.63, 138.96, 143.45, 143.69, 165.57.

***tert*-Butyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate (148e):** Coupling of 4-methylbenzaldehyde with *tert*-butyl acrylate under the catalytic influence of DABCO, following similar procedure as described for the compound *tert*-butyl 3-hydroxy-2-methylene-3-phenylpropanoate (**148a**) provided the title compound **148e** as a colorless solid.



Reaction time: 12 d

Yield: 68 %

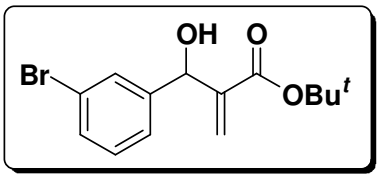
Mp: 40-42 ^{o}C (Lit.[228] 41-43 ^{o}C)

IR (KBr): ν 3337, 1714, 1635 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 9H), 2.33 (s, 3H), 3.05 (bs, 1H), 5.47 (s, 1H), 5.71 (s, 1H), 6.23 (s, 1H), 7.14 (d, 2H, J = 7.6 Hz), 7.25 (d, 2H, J = 8.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.09, 27.93, 73.16, 81.46, 124.85, 126.53, 128.97, 137.22, 138.72, 143.63, 165.70.

***tert*-Butyl 3-hydroxy-2-methylene-3-(3-bromophenyl)propanoate (148f):** This alcohol was obtained as a colorless solid *via* the reaction of 3-bromobenzaldehyde with *tert*-butyl acrylate under the catalytic influence of DABCO, following similar procedure as described for the compound *tert*-butyl 3-hydroxy-2-methylene-3-phenylpropanoate (**148a**).



Mp: 60-62 ^{o}C (Lit.[228] 61-63 ^{o}C)

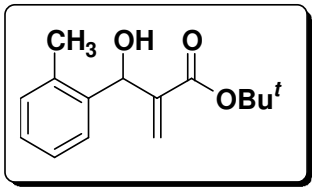
Yield: 65 %

IR (KBr): ν 3437, 1705, 1630 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 1.41 (s, 9H), 3.30 (bs, 1H), 5.44 (s, 1H), 5.73 (s, 1H), 6.26 (s, 1H), 7.15-7.36 (m, 2H), 7.40 (d, 1H, J = 7.6 Hz), 7.52 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 28.01, 72.94, 82.02, 122.48, 125.21, 125.83, 129.72, 129.94, 130.73, 142.90, 144.11, 165.47.

***tert*-Butyl 3-hydroxy-2-methylene-3-(2-methylphenyl)propanoate (148g):** This compound was obtained as a colorless viscous liquid *via* the reaction between 2-methylbenzaldehyde and *tert*-butyl acrylate catalyzed by DABCO, following simlar procedure as described for the compound *tert*-butyl 3-hydroxy-2-methylene-3-phenylpropanoate (**148a**).



Reaction time: 12 d

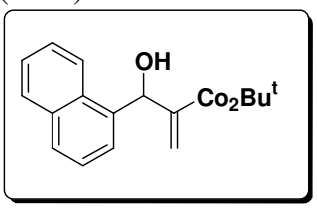
Yield: 57 %

IR (Neat): ν 3395, 1716, 1635 cm^{-1}

^1H NMR (400 MHz. $CDCl_3$): δ 1.39 (s, 9H), 2.32 (s, 3H), 2.92 (bs, 1H), 5.52 (s, 1H), 5.73 (s, 1H), 6.23 (s, 1H), 7.11-7.23 (m, 3H), 7.37-7.45 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 18.91, 27.74, 69.03, 81.12, 124.58, 125.90, 126.12, 127.50, 130.19, 135.63, 139.23, 143.42, 165.78.

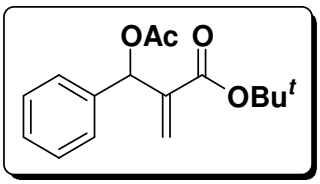
***tert*-Butyl 3-hydroxy-2-methylene-3-(1-naphthyl)propanoate (148h):** This allylic alcohol was prepared as a colorless solid [after crystallization from 10 % ethyl acetate in hexanes at 0 ^{o}C], *via* the Baylis-Hillman reaction of 1-naphaldehyde with *tert*-butyl acrylate in the presence of DABCO (cat.), following similar procedure as described for the compound *tert*-butyl 3-hydroxy-2-methylene-3-phenylpropanoate (**148a**)



Reaction time:	18 d
Yield:	51 %
Mp:	80-82 ^{o}C (Lit.[228] 80-82 ^{o}C)
IR (KBr):	ν 3312, 1714, 1639 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$):	δ 1.40 (s, 9H), 3.15 (d, 1H, J = 4.0 Hz)), 5.50 (s, 1H), 6.25, (s, 1H), 6.31 (d, 1H, J = 4.0 Hz), 7.42-7.54 (m, 3H), 7.60 (d, 1H, J = 8.0 Hz), 7.80 (d, 1H, J = 8.0 Hz), 7.83-7.88 (m, 1H), 8.02 (d, 1H, J = 8.0 Hz)
^{13}C NMR (100 MHz, $CDCl_3$):	δ 27.92, 69.29, 81.52, 123.79, 124.36, 125.32, 125.56, 125.77, 126.13, 128.46, 128.68, 130.95, 133.78, 136.91, 143.50, 166.08.

***tert*-Butyl 3-acetoxy-2-methylene-3-phenylpropanoate (149a):** To a stirred solution of *tert*-butyl 3-hydroxy-2-methylene-3-phenylpropanoate (**148a**) (100 mmol, 34.4 g), pyridine (150 mmol, 11.86 g, 12.1 mL) in dichloromethane (100 mL) at 0 ^{o}C was added acetyl chloride (150 mmol, 11.7 g, 10.7 mL) and stirring continued at room temperature

for 2 h. Reaction mixture was diluted with ether (100 mL) and washed with water. Organic layer was dried over anhydrous Na_2SO_4. Solvent was removed and the residue thus obtained was purified by column chromatography (silica gel, 4 % EtOAc in hexanes) to provide the pure *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**149a**) as a colorless liquid in 87 % (24.05 g) yield.

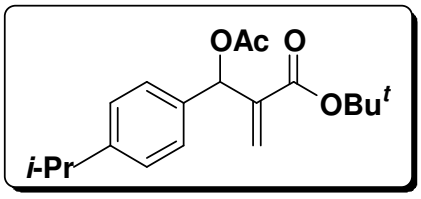


IR (Neat): ν 1745, 1716, 1635 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 1.36 (s, 9H), 2.09 (s, 3H), 5.72 (d, 1H, J = 1.2 Hz), 6.31 (s, 1H), 6.63 (s, 1H), 7.24-7.40 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.04, 27.85, 73.35, 81.39, 124.64, 127.82, 128.26, 128.32, 138.07, 141.16, 164.16, 169.35.

***tert*-Butyl 3-acetoxy-2-methylene-3-(4-isoprophylphenyl)propanoate (149b):** This allyl acetete was obtained as a colorless viscous liquid, *via* the reaction of *tert*-butyl 3-hydroxy-2-methylene-3-(4-isoprophylphenyl)propanoate (**148b**) with acetyl chloride in the presence of pyridine, following a similar procedure as described for the compound *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**149a**).



Reaction time: 2 h

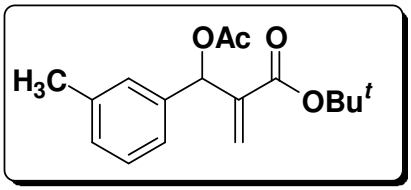
Yield: 86 %

IR (Neat): ν 1747, 1716, 1635 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (d, 6H, J = 6.8 Hz), 1.36 (s, 9H), 2.08 (s, 3H), 2.88 (sept, 1H, J = 6.8 Hz), 5.70 (s, 1H), 6.29 (s, 1H), 6.61 (s, 1H), 7.18 (d, 2H, J = 8.0 Hz), 7.27 (d, 2H, J = 8.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.08, 23.89, 27.85, 33.81, 73.24, 81.30, 124.38, 126.36, 127.82, 135.38, 141.37, 148.95, 164.28, 169.41.

***tert*-Butyl 3-acetoxy-2-methylene-3-(3-methylphenyl)propanoate (149c):** This compound was obtained as a colorless viscous liquid, *via* the reaction of *tert*-butyl 3-hydroxy-2-methylene-3-(3-methylphenyl)propanoate (**148c**) with acetyl chloride in the presence of pyridine, following a similar procedure as described for the compound *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**149a**).



Reaction time: 2 h

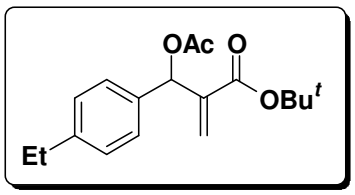
Yield: 84 %

IR (Neat): ν 1747, 1716, 1635 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 9H), 2.08 (s, 3H), 2.32 (s, 3H), 5.71 (s, 1H), 6.30 (s, 1H), 6.60 (s, 1H), 7.06-7.23m (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): 21.08, 21.34, 27.87, 73.40, 81.36, 124.58, 124.88, 128.24, 128.52, 129.03, 137.91, 137.95, 141.25, 164.24, 169.40.

***tert*-Butyl 3-acetoxy-2-methylene-3-(4-ethylphenyl)propanoate (149d):** Reaction of *tert*-butyl 3-hydroxy-2-methylene-3-(4-ethyllphenyl)propanoate (**148d**) with acetyl chloride in the presence of pyridine, following a similar procedure as described for the compound *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**149a**) provided the title compound **149d** as a colorless liquid.



Reaction time: 2 h

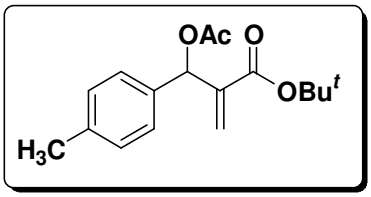
Yield: 80 %

IR (Neat): ν 1745, 1720, 1635 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, 3H, J = 7.6 Hz), 1.37 (s, 9H), 2.08 (s, 3H), 2.65 (q, 2H, J = 7.6 Hz), 5.71 (s, 1H), 6.30 (s, 1H), 6.61 (s, 1H), 7.16 (d, 2H, J = 8.0 Hz), 7.26 (d, 2H, J = 8.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 15.52, 21.22, 27.96, 28.62, 73.36, 81.47, 124.54, 127.92, 135.33, 141.37, 144.48, 164.39, 169.58.

***tert*-Butyl 3-acetoxy-2-methylene-3-(4-methylphenyl)propanoate (149e):** This compound was obtained as a colorless viscous liquid, *via* the reaction of *tert*-butyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate (**148e**) with acetyl chloride in the presence of pyridine, following a similar procedure as described for the compound *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**149a**).



Reaction time: 2 h

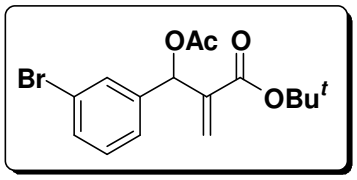
Yield: 87 %

IR (Neat): ν 1745, 1722, 1633 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 9H), 2.08 (s, 3H), 2.33 (s, 3H), 5.71 (s, 1H), 6.30 (s, 1H), 6.59 (s, 1H), 7.13 (d, 2H, J = 8.0 Hz), 7.24 (d, 2H, J = 8.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.10, 21.14, 27.87, 73.25, 81.35, 124.43, 127.79, 129.02, 135.07, 138.04, 141.25, 164.25, 169.43.

***tert*-Butyl 3-acetoxy-2-methylene-3-(3-bromophenyl)propanoate (149f):** This compound was obtained as a colorless viscous liquid, *via* the reaction of *tert*-butyl 3-hydroxy-2-methylene-3-(3-bromophenyl)propanoate (**148f**) with acetyl chloride in the presence of pyridine, following a similar procedure as described for the compound *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**149a**).



Reaction time: 2 h

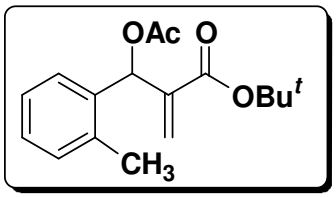
IR (Neat): ν 1747, 1714, 1635 cm^{-1}

Yield: 75 %

^1H NMR (400 MHz, $CDCl_3$): δ 1.38 (s, 9H), 2.10 (s, 3H), 5.76 (s, 1H), 6.33 (s, 1H), 6.57 (s, 1H), 7.15-7.25 (m, 1H), 7.30 (d, 1H, J = 7.6 Hz), 7.43 (d, 1H, J = 7.6 Hz), 7.50 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.09, 27.96, 72.63, 81.78, 122.40, 125.22, 126.55, 129.98, 130.86, 131.41, 140.53, 140.64, 163.93, 169.31.

***tert*-Butyl 3-acetoxy-2-methylene-3-(2-methylphenyl)propanoate (149g):** This compound was obtained as a colorless viscous liquid, *via* the treatment of *tert*-butyl 3-hydroxy-2-methylene-3-(2-methylphenyl)propanoate (**148g**) with acetyl chloride in the presence of pyridine, following a similar procedure as described for the compound *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**149a**).



Reaction time: 2 h

Yield: 88 %

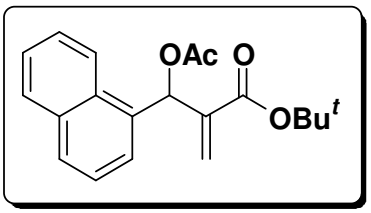
IR (Neat): ν 1745, 1712, 1635 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (s, 9H), 2.10 (s, 3H), 2.38 (s, 3H), 5.52 (s, 1H), 6.32 (s, 1H), 6.85 (s, 1H), 7.09-7.28 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 19.15, 20.93, 27.87, 70.36, 81.37, 125.46, 126.00, 127.10, 128.26, 130.50, 136.02, 136.40, 140.78, 164.43, 169.44.

***tert*-Butyl 3-acetoxy-2-methylene-3-(1-naphthyl)propanoate (149h):** This acetete was obtained as a colorless viscous liquid, *via* the reaction of *tert*-butyl 3-hydroxy-2-methylene-3-(1-naphtyl)propanoate (**148h**) with acetyl chloride in the presence of pyridine,

following the similar procedure as described for the compound *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**149a**).



Reaction time: 2 h

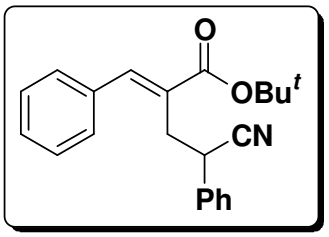
Yield: 74 %

IR (Neat): ν 1743, 1714, 1635 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 1.25 (s, 9H), 2.06 (s, 3H), 5.54 (s, 1H), 6.34 (s, 1H), 7.34-7.50 (m, 5H), 7.74-7.83 (m, 2H), 8.06 (d, 1H, J = 8.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.89, 27.83, 69.88, 81.37, 123.56, 125.06, 125.35, 125.76, 125.80, 126.45, 128.64, 129.06, 131.00, 133.77, 140.94, 164.34, 169.44.

(*E*)-*tert*-Butyl 2-benzylidene-4-cyano-4-phenylbutanoate (150a): To a stirred solution of benzyl cyanide (5 mmol, 0.577 mL) and *tert*-BuOK (5.5 mmol, 0.616 g) in dry THF (10 mL) was added *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate **149a** (5 mmol, 1.380 g) slowly at room temperature. After stirring for 10 h at room temperature, the reaction mixture was diluted with diethyl ether (5 mL) and washed with water (2 X 5 mL). Aqueous layer was extracted with diethyl ether (3 X 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue thus obtained was purified by column chromatography (silica gel, 3 % EtOAc in



hexanes) to provide **150a** as colorless viscous liquid in 72 % (1.20 g) isolated yield.

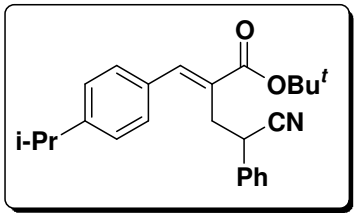
IR (Neat): ν 2245, 1714, 1631 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 1.57 (s, 9H), 2.95 & 3.15 [dABq, 2H, J = 13.6, 7.2 (8.8) Hz], 4.26 (t, 1H, J = 8.4 Hz), 7.18-7.42 (m, 10H), 7.81 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 28.13, 33.70, 36.19, 81.51, 120.42, 127.33, 128.08, 128.50, 128.61, 128.98, 129.52, 135.02, 135.39, 142.75, 166.27.

LCMS (*m/z*): 334 $(M+H)^+$.

(*E*)-*tert*-Butyl 2-(4-isopropylbenzylidene)-4-cyano-4-phenylbutanoate (150b): This compound was obtained as a colorless viscous liquid, *via* the treatment of *tert*-butyl 3-acetoxy-2-methylene-3-(4-isoprophylphenyl)propanoate (**149b**) with benzyl cyanide in the presence *tert*-BuOK in dry THF, following a similar procedure as described for (*E*)-*tert*-butyl 2-benzylidene-4-cyano-4-phenylbutanoate (**150a**).



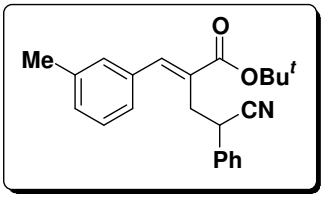
Yield: 80 %.

IR (Neat): ν 2241, 1712, 1631 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 1.25 (d, 6H, J = 6.8 Hz), 1.56 (s, 9H), 2.84-3.03 (m, 2H), 3.12-3.24 (m, 1H), 4.26 (t, 1H, J = 8.0 Hz), 7.04-7.42 (m, 9H), 7.78 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 23.90, 28.20, 33.79, 33.97, 36.28, 81.42, 120.58, 126.71, 127.43, 128.15, 128.97, 129.04, 132.49,135.54, 142.82, 149.67, 166.53.

(*E*)-*tert*-Butyl 2-(3-methylbenzylidene)-4-cyano-4-phenylbutanoate (150c): This *trans* ester was obtained as a colorless viscous liquid, *via* the reaction between *tert*-butyl 3-acetoxy-2-methylene-3-(3-methylphenyl)propanoate (**149c**) and benzyl cyanide in the presence *tert*-BuOK in dry THF, following a similar procedure as described for (*E*)-*tert*-butyl 2-benzylidene-4-cyano-4-phenylbutanoate (**150a**).



Yield : 73 %

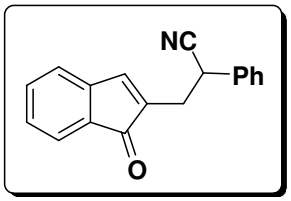
IR (Neat): ν 2241, 1695, 1631 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ1.57 (s, 9H), 2.33 (s, 3H); 2.95 & 3.15 [dABq, 2H, J = 13.6 & 7.6 (8.8) Hz], 4.26 (t, 1H, J = 8.0 Hz), 6.94 (s,1H), 7.00 (d, 1H, J = 7.6 Hz), 7.12 (d, 1H, J = 7.6 Hz), 7.20-7.40 (m, 6H), 7.77 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.37, 28.16, 33.80, 36.21, 81.47, 120.51, 125.66, 127.41, 128.06, 128.41, 128.99, 129.30, 134.99, 135.47, 138.13, 142.97, 166.38.

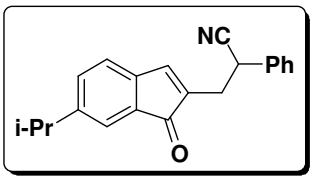
LCMS (*m/z*): 348 $(M+H)^+$.

2-(2-Cyano-2-phenyl)ethylind-2-en-1-one (152a): To a stirred solution (*E*)-*tert*-butyl 2-benzylidene-4-cyano-4-phenylbutanoate **150a** (0.5 mmol, 0.167 g) in 1,2-dichloroethane (DCE, 3 mL) were added trifluroacetic acid (TFA) (2.5 mmol, 0.285 g, 0.19 mL) and tirfluoroacetic anhydride (TFAA, 1 mmol, 0.210 g, 0.139 mL) at room temperature. The reaction mixture was heated under reflux for 5 h and then was allowed to cool to room temperature. Reaction mixture was poured into aqueous K_2CO_3 solution and extracted with diethyl ether (2 X 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue, thus obtained was purified by column chromatography (5 % ethyl acetate in hexanes) to provide **152a** as yellow solid in 38 % (0.049g) yield.



Mp:	116-117 ^{o}C.
IR (KBr):	ν 2237, 1711, 1651, 1604 cm^{-1}.
^{1}HNMR (400 MHz, $CDCl_3$):	δ 2.86 (d, 2H, J = 7.6 Hz), 4.13 (t, 1H, J = 7.6 Hz), 7.01 (d, 1H, J = 7.2 Hz), 7.16-7.22 (m, 1H), 7.30-7.48 (m, 8H).
^{13}CNMR (100 MHz, $CDCl_3$):	δ31.65, 36.70, 120.31, 122.31, 123.08, 127.35, 128.46, 128.89, 129.26, 130.38, 134.23, 134.39, 135.08, 143.99, 146.34, 197.49.
LCMS (*m/z*):	260 $(M+H)^{+}$.
Anal. Calcd. for $C_{18}H_{13}NO$:	C, 83.37; H, 5.05; N, 5.40.
Found:	C, 83.45; H, 5.11; N, 5.51.

2-(2-Cyano-2-phenyl)ethyl-6-isopropylind-2-en-1-one (152b): This ind-2-en-1-one was obtained as yellow solid, *via* treatment of (*E*)-*tert*-butyl 2-(4-isopropylbenzylidene)-4-cyano-4-phenylbutanoate (**150b**) with trifluroacetic acid and tirfluoroacetic anhydride in 1,2-dichloroethane, following a similar procedure as described for 2-(2-phenyl-2-cyano)ethylind-2-en-1-one (**152a**):



Yield: 40 %.

Mp: 66-68 ^{o}C.

IR (KBr): ν 2241, 1705, 1606 cm^{-1}.

^{1}HNMR (400 MHz, $CDCl_3$): δ 1.22 (d, 6H, J = 6.4 Hz), 2.75-2.95 (m, 3H), 4.12 (t, 1H, J = 7.2 Hz), 6.90 (d, 1H, J = 7.2 Hz), 7.09-7.48 (m, 8H).

^{13}CNMR (100 MHz, $CDCl_3$): δ 23.71, 31.66, 34.13, 36.73, 120.34, 121.71, 122.17, 127.35, 128.40, 129.22, 130.80, 131.72, 133.85, 135.13, 141.51, 146.55, 150.32, 197.87.

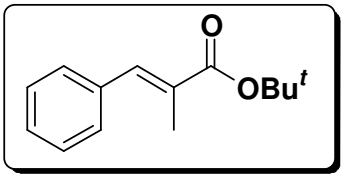
LCMS (*m/z*): 302 $(M+H)^{+}$.

Anal. Calcd. for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65.

Found: C, 83.65; H, 6.39; N, 4.77.

(2*E*)-*tert*-Butyl 3-phenyl-2-methylprop-2-enoates (154a): To a stirred solution of *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**149a)** (1.370 g) in *t*-BuOH (5 mL) was added $NaBH_4$ (0.190 g) at room temperature. After stirring for 1h, *tert*-butyl alcohol was

removed under reduced pressure; the reaction mixture was diluted ether (20 mL) and washed with water. Aqueous layer was extracted with ether (3 X 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was removed and the residue thus obtained was purified by column chromatography (silicagel, 1 % EtOAc in hexanes) to provide (2*E*)-*tert*-butyl 3-phenyl-2-methylprop-2-enoates (**154a**) as colorless liquid in 85 % (0.965 g) isolated yield.

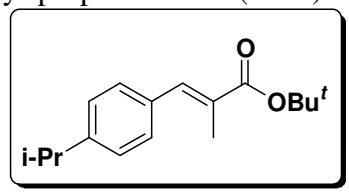


IR (Neat): ν 1703, 1631 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 1.54 (s, 9H), 2.06 (s, 3H), 7.20-7.34 (m, 1H), 7.35-7.45 (m, 4H), 7.59 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.06, 28.15, 80.48, 128.02, 128.30, 129.55, 130.16, 136.22, 137.80, 167.89.

(2*E*)-*tert*-Butyl 3-(4-isopropylpheny)-2-methylprop-2-enoates (154b): This compound was obtained as a colorless liquid, *via* the reaction of *tert*-butyl 3-acetoxy-2-methylene-3-(4-isopropylphenyl)propanoate (**149b**) with $NaBH_4$, following the similar procedure as described for the compound (2*E*)-*tert*-butyl 3-(4-isopropyl)phenyl-prop-2-enoates (**154a**).



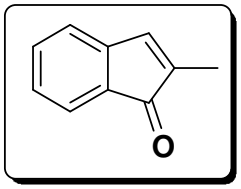
Yield: 80 %

IR (Neat): ν 1703, 1633 cm^{-1}

^1H NMR® (400 MHz, $CDCl_3$): δ 1.25 (d, 6H, J = 6.8 Hz), 1.54 (s, 9H), 2.07 (s, 3H), 2.91 (sept, 1H), 7.01-7.40 (m 4H), 7.57 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.15, 23.89, 28.18, 33.96, 80.38, 126.42, 129.06, 129.29, 129.65, 129.76, 137.85, 168.10.

2-Methylind-2-en-1-one (155a): To a stirred solution of (2*E*)-*tert*-butyl 3-phenyl-2-methylprop-2-enoate (**154a**) (1.0 mmol, 0.218 g) in 1,2-dichloroethane (DCE, 3 mL) was added trifluroacetic acid (TFA) (5 mmol, 0.578 g, 0.38 mL) and tirfluoroacetic anhydride (TFAA, 2 mmol, 0.420 g, 0.28 mL) at room temperature. The reaction mixture was heated under reflux for 5 h and then was allowed to cool to room temperature. Reaction mixture was poured into aqueous K_2CO_3 solution and extracted with diethyl ether (2 X 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue, thus obtained was purified by column chromatography (2 % ethyl acetate in hexanes) to provide **155a** as yellow viscous liquid in 18 % (0.026 g) yield.



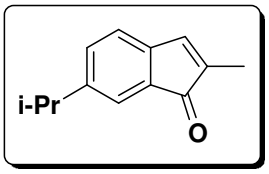
IR (Neat): ν 1712, 1606 cm^{-1}

^{1}HNMR (400 MHz, $CDCl_3$): δ 1.86 (s, 3H), 6.92 (d, 1H, J = 7.2 Hz), 7.08-7.19 (m, 2H), 7.22-7.30 (m, 1H), 7.36 (d, 1H, J = 6.8 Hz).

^{13}CNMR (100 MHz, $CDCl_3$): 10.07, 121.14, 122.62, 127.88, 130.79, 133.84, 136.24, 143.35, 144.95, 198.81.

LCMS (*m/z*): 145 $(M+H)^+$.

6-Isopropyl-2-methylind-2-en-1-one (155b): This compound was obtained as yellow liquid, *via* treatment of (2*E*)-*tert*-butyl 3-(4-isopropylphenyl)-2-methylprop-2-enoate (**154b**) with trifluroacetic acid and tirfluoroacetic anhydride in 1,2-dichloroethane, following a similar procedure as described for 2-methylind-2-en-1-one (**155a**).



Yield: 20 %.

IR (Neat) ©: ν 1712, 1616 cm^{-1}

^{1}HNMR (400 MHz, $CDCl_3$): δ 1.21 (d, 6H, J = 7.2 Hz), 1.85 (s, 3H), 2.85 (sept, 1H, J = 7.2 Hz), 6.83 (d, 1H, J = 7.2 Hz), 7.08-7.15 (m, 2H)®.

^{13}CNMR (100 MHz, $CDCl_3$): δ10.06, 23.76, 34.07, 120.97, 121.29, 131.23, 131.30, 135.76, 142.48, 143.50, 149.17, 199.20.

LCMS (*m/z*): 187 $(M+H)^+$.

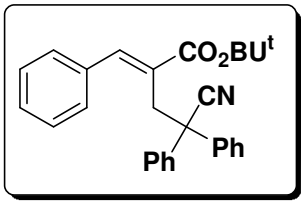
Anal. Calcd. for $C_{13}H_{14}O$: C, 83.83; H, 7.58.

Found: C, 83.75; H, 7.65.

(*E*)-*tert*-Butyl 2-benzylidene-4-cyano-4,4-diphenylbutanoate (156a): To a stirred suspension of oil free NaH (5 mmol, 0.120 g) in anhydrous toluene (5mL) were added successively diphenylacetonitrile (2 mmol, 0.386 g) and *tert*-butyl 3-acetoxy-2-methylene-3-phenylpropanoate (**149a**) (2 mmol, 0.552 g) at room temperature. Then the reaction mixture was heated at reflux for 1h under N_2 atmosphere. Then the reaction mixture was

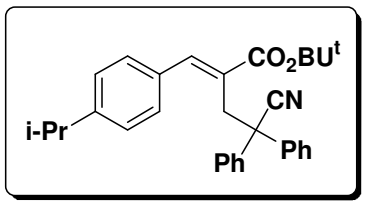
©Literature reports that it is a low melting solid (44-46 ^oC). Since yields of this compound is very low we did not attempt to obtain this as solid. 1) Murray, R. J.; Cromwell, N. H. *J. Org. Chem.* **1976**, *41*, 3540.
®It contain a doublet at δ7.10 (1H, J = 7.2 Hz) and singlet at δ7.09 (1H)], 7.28 (s, 1H).

allowed to cool to 0 ^{o}C and excess NaH was carefully quenched with slow addition of water. Reaction mixture was extracted with diethyl ether (2 X 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was removed and the residue thus obtained was subjected to column chromatography (5 % ethyl acetate in hexanes) to provide a solid which was crystallized from 3 % ethyl acetate in hexanes at 0 ^{o}C to afford **156a** as a colorless crystalline solid, in 81 % (0.660 g) yield.



Mp:	78-80 ^{o}C
IR (KBr):	ν 2243, 1705, 1631 cm^{-1}
^{1}HNMR (400 MHz, $CDCl_3$):	δ 1.44 (s, 9H), 3.82 (s, 2H), 6.97-7.05 (m, 2H), 7.15-7.32 (m, 13 H), 7.67 (s, 1H).
^{13}CNMR (100 MHz, $CDCl_3$):	δ 28.02, 34.81, 51.21, 81.46, 121.70, 127.39, 127.79, 127.88, 128.32, 128.52, 128.62, 129.73, 135.34, 139.99, 142.40, 166.94.
LCMS (*m/z*):	410 $(M+H)^{+}$.

(*E*)-*tert*-Butyl 2-(4-isopropylbenzylidene)-4-cyano-4,4-diphenylbutanoate (156b): This compound was obtained as a colorless solid, *via* the reaction of *tert*-butyl 3-acetoxy-2-methylene-3-(4-isopropylphenyl)propanoate (**149b**) with diphenylacetonitrile, following the similar procedure as described for the compound (*E*)-*tert*-butyl 2-benzylidene-4-cyano-4,4-diphenylbutanoate (**156a**)



Yield: 83 %.

Mp: 90-92 ^{o}C

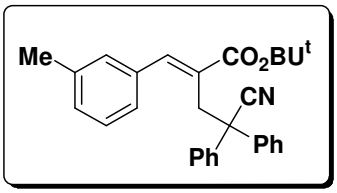
IR (KBr): ν 2237, 1701, 1622 cm^{-1}

^{1}HNMR (400 MHz, $CDCl_3$): δ 1.21 (d, 6H, *J* = 6.8 Hz), 1.44 (s, 9H), 2.85 (sept, 1H, *J* = 6.8 Hz), 3.83 (s, 2H), 6.94 (d, 2H, *J* = 8.0 Hz), 7.03 (d, 2H, *J* = 8.0 Hz), 7.15-7.32 (m, 10H), 7.64 (s, 1H).

^{13}CNMR (100 MHz, $CDCl_3$): δ 23.89, 28.03, 33.88, 34.90, 51.27, 81.32, 121.74, 126.40, 127.42, 127.77, 128.48, 128.79, 132.75, 140.11, 142.55, 148.83, 167.12.

LCMS (*m/z*): 452 $(M+H)^{+}$.

(*E*)-*tert*-Butyl 2-(3-methylbenzylidene)-4-cyano-4,4-diphenylbutano-ate (156c): This *trans* ester was obtained as a colorless solid, via the reaction between *tert*-butyl 3-acetoxy-2-methylene-3-(3-methylphenyl)propanoate (**149c**) and diphenylacetonitrile, in the presence of NaH, following the similar procedure as described for the compound (*E*)-*tert*-butyl 2-benzylidene-4-cyano-4,4-diphenylbutanoate (**156a**).



Yield: 78 %

Mp: 82-84 ^{o}C

IR (KBr): ν 2245, 1703, 1601 cm^{-1}

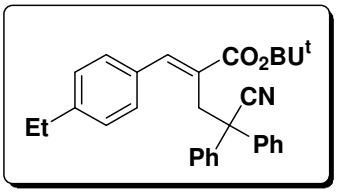
^{1}HNMR (400 MHz, $CDCl_3$): δ 1.45 (s, 9H), 2.22 (s, 3H), 3.81 (s, 2H), 6.68 (s,

1H), 6.84 (d, 1H, *J* = 7.6 Hz), 6.98 (d, 1H, *J* = 7.6 Hz), 7.05-7.12 (m, 1H), 7.17-7.31 (m, 10H), 7.64 (s, 1H).

^{13}CNMR (100 MHz, $CDCl_3$): δ 21.28, 27.98, 34.85, 51.15, 81.37, 121.68, 125.34, 127.33, 127.62, 128.09, 128.41, 128.63, 129.33, 129.44, 135.18, 137.74, 139.99, 142.59, 166.95.

LCMS (*m/z*): 422 $(M-H)^+$

(*E*)-*tert*-Butyl 2-(4-ethylbenzylidene)-4-cyano-4,4-diphenylbutanoate (156d): This alkene-ester was obtained as a colorless solid, via treatment of *tert*-butyl 3-acetoxy-2-methylene-3-(4-ethylphenyl)propanoate (**149d**) with diphenylacetonitrile, following the similar procedure as described for the compound (*E*)-*tert*-butyl 2-benzylidene-4-cyano-4,4-diphenylbutanoate (**156a**)



Yield: 79 %.

Mp: 84-86 °C

IR (KBr): ν 2224, 1699, 1624 cm^{-1}

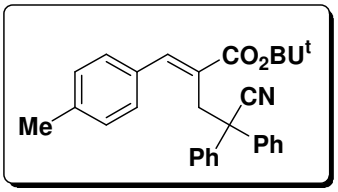
^{1}HNMR (400 MHz, $CDCl_3$): δ 1.18 (t, 3H, *J* = 7.6 Hz), 1.43 (s, 9H), 2.57 (q, 2H, *J* = 7.6 Hz), 3.83 (s, 2H), 6.95 (d, 2H, *J* = 8.0 Hz), 7.01 (d, 2H, *J* = 8.0 Hz), 7.15-7.36 (m, 10H), 7.66 (s, 1H).

^{13}CNMR (100 MHz, $CDCl_3$): δ 15.47, 28.00, 28.62, 34.85, 51.25, 81.29, 121.76,

127.40, 127.77, 127.84, 128.49, 128.81, 132.60, 140.08, 142.57, 144.28, 167.10.

LCMS (*m/z*): 438 $(M+H)^+$.

(*E*)-*tert*-Butyl 2-(4-methylbenzylidene)-4-cyano-4,4-diphenylbutanoate (156e): This compound was obtained via reaction between of *tert*-butyl 3-acetoxy-2-methylene-3-(4-methylphenyl)propanoate (**149e**) and diphenylacetonitrile as a colorless solid, following the similar procedure as described for the compound (*E*)-*tert*-butyl 2-benzylidene-4-cyano-4,4-diphenylbutanoate (**156a**).



Yield: 75 %.

Mp: 112-114 ^oC

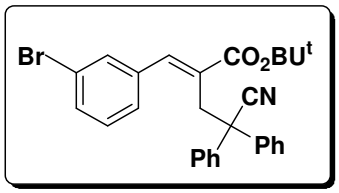
IR (KBr): ν 2233, 1701, 1639 cm^{-1}

^{1}HNMR (400 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.29 (s, 3H), 3.82 (s, 2H), 6.95 (d, 2H, *J* = 8.0 Hz), 7.01 (d, 2H, *J* = 8.0 Hz), 7.18-7.40 (m, 10H), 7.64 (s, 1H).

^{13}CNMR (100 MHz, $CDCl_3$): δ21.22, 27.98, 34.90, 51.27, 81.22, 121.75, 127.39, 127.74, 128.48, 128.76, 128.92, 129.02, 132.38, 137.96, 140.10, 142.47, 167.04.

LCMS (*m/z*): 422 $(M-H)^+$.

(*E*)-*tert*-Butyl 2-(3-bromobenzylidene)-4-cyano-4,4-diphenylbutanoate (156f): This compound obtained as a colorless solid via reaction between *tert*-butyl 3-acetoxy-2-methylene-3-(3-bromophenyl)propanoate (**149f**) and diphenyl acetonitrile in the presence of NaH, following the similar procedure as described for the compound (*E*)-*tert*-butyl 2-benzylidene-4-cyano-4,4-diphenylbutanoate (**156a**).



Yield: 80 %.

Mp: 121-122 ^{o}C

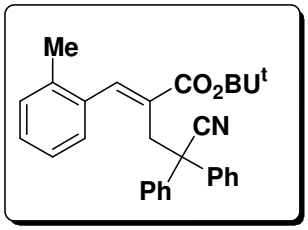
IR (KBr): ν 2235, 1701, 1635 cm^{-1}

^{1}HNMR (400 MHz, $CDCl_3$): δ 1.49 (s, 9H), 3.77 (s, 2H), 6.83-6.98 (m, 2H), 7.00-7.09 (m, 1H), 7.10-7.35 (m, 11H), 7.56 (s, 1H).

^{13}CNMR (100 MHz, $CDCl_3$): δ 28.07, 34.80, 51.08, 81.96, 121.52, 122.57, 126.74, 127.40, 127.95, 128.56, 129.77, 130.74, 131.02, 131.34, 137.45, 139.75, 140.66, 166.56.

LCMS (*m/z*): 488 $(M+H)^+$, 490 $(M+2+H)^+$.

(*E*)-*tert*-Butyl 2-(2-methylbenzylidene)-4-cyano-4,4-diphenylbutanoate (156g): This compound was obtained as a colorless solid by the reaction between *tert*-butyl 3-acetoxy-2-methylene-3-(2-methylphenyl)propanoate (**149g**) and diphenylacetonitrile in the presence of NaH, following the similar procedure as described for the compound (*E*)-*tert*-butyl 2-benzylidene-4-cyano-4,4-diphenylbutanoate (**156a**).



Yield: 77 %.

Mp: 108-110 ^{o}C

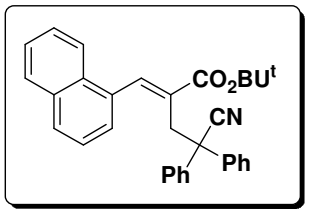
IR (KBr): ν 2239, 1709, 1599 cm^{-1}

^{1}HNMR (400 MHz, $CDCl_3$): δ 1.48 (s, 9H), 1.94 (s, 3H), 3.80 (s, 2H), 6.97-7.27 (m, 14H), 7.67 (s,1H).

^{13}CNMR (100 MHz, $CDCl_3$): δ 19.83, 28.01, 34.32, 51.20, 81.42, 121.44, 125.48, 127.15, 127.63, 127.74, 128.05, 128.45, 129.92, 130.16, 134.63, 137.35, 139.82, 141.85, 166.87.

LCMS (*m/z*): 422 $(M-H)^{+}$.

(*E*)-*tert*-Butyl 4-cyano-2-(naphth-1-ylmethylidene)-4,4-diphenylbutanoate (156h): This *trans* ester was obtained as a colorless solid, via treatment of *tert*-butyl 3-acetoxy-2-methylene-3-(naphth-1-ylmethylidene)propanoate (**149h**) with diphenylacetonitrile, following the similar procedure as described for the compound (*E*)-*tert*-butyl 2-benzylidene-4-cyano-4,4-diphenylbutanoate (**156a**).



Yield: 76%.

Mp: 116-118 ^{o}C

IR (KBr): ν 2229, 1699, 1631 cm^{-1}

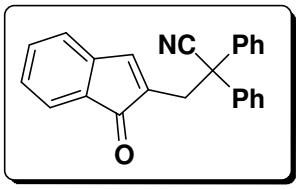
^{1}HNMR (400 MHz, $CDCl_3$): δ 1.57 (s, 9H), 3.82 (s, 2H), 6.82-7.19 (m, 11H),

7.22-7.49 (m, 3H), 7.54 (d, 1H, J = 8.0 Hz), 7.69 (d, 1H, J = 8.0 Hz), 7.74 (d, 1H, J = 8.0 Hz), 8.11 (s, 1H).

^{13}CNMR (100 MHz, $CDCl_3$): δ 28.15, 35.19, 51.08, 81.85, 121.53, 125.04, 125.42, 126.05, 127.01, 127.29, 128.12, 128.28, 128.49, 131.23, 131.48, 132.76, 133.39, 139.71, 141.03, 166.90.

LCMS (*m/z*): 460 $(M+H)^+$.

2-(2,2-Diphenyl-2-cyano)ethylind-2-en-1-one (158a): To a stirred solution of (*E*)-*tert*-butyl 2-benzylidene-4-cyano-4,4-diphenylbutanoate (**156a)** (0.5 mmol, 0.205 g) in DCE (3 mL) were added trifluroacetic acid (TFA) (2.5 mmol, 0.285 g, 0.19 mL) and tirfluoroacetic anhydride (TFAA, 1 mmol, 0.210 g, 0.139 mL) at room temperature. The reaction mixture was heated under reflux for 5 h and then was allowed to cool to room temperature. Reaction mixture was poured into aqueous K_2CO_3 solution and extracted with diethyl ether (2 X 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue, thus obtained was purified by column chromatography (5 % ethyl acetate in hexanes) to provide **158a** as yellow solid in 66 % (0.110 g) yield.

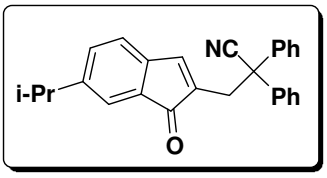


Mp: 148-150 ^{o}C

IR (KBr): ν 2235, 1709, 1599 cm^{-1}

^{1}HNMR (400 MHz, $CDCl_3$):	δ 3.82 (d, 2H, *J* = 0.8 Hz), 6.95 (d, 1H, *J* = 7.2 Hz), 7.10-7.18 (m, 1H), 7.23-7.48 (m, 13H).
^{13}CNMR (100 MHz, $CDCl_3$):	δ 33.57, 51.44, 122.25, 122.40, 123.01, 127.08, 128.22, 128.70, 128.97, 129.84, 133.62, 134.00, 139.35, 144.24, 146.48, 196.85.
LCMS (*m/z*):	336 $(M+H)^+$, 334 $(M-H)^+$.
Anal. Calcd. for $C_{24}H_{17}NO$:	C, 85.94; H, 5.11; N, 4.18
Found:	C, 85.79; H, 5.06; N, 4.05.

2-(2,2-Diphenyl-2-cyano)ethyl-6-isopropylind-2-en-1-one (158b): This compound was obtained as yellow solid, *via* treatment of (*E*)-*tert*-butyl 2-(4-isopropylbenzylidene)-4-cyano-4,4-diphenylbutanoate (**156b**) with trifluroacetic acid and tirfluoroacetic anhydride in 1,2-dichloroethane, following the similar procedure as for described 2-(2,2-diphenyl-2-cyano)ethylind-2-en-1-one **(158a)**.



Yield:	63 %
Mp:	146-148 ^oC
IR (KBr):	*v* 2220, 1705, 1614 cm^{-1}
^{1}HNMR (400 MHz, $CDCl_3$):	δ 1.19 (d, 6H, *J* = 6.8 Hz), 2.85 (sept, 1H, *J* = 6.8 Hz), 3.36 (d, 2H, *J* = 1.6 Hz), 6.85 (d, 1H, *J* = 7.2 Hz), 7.08-7.13 (m, 1H), 7.23-7.39 (m, 8H), 7.40-7.47 (m, 4H).

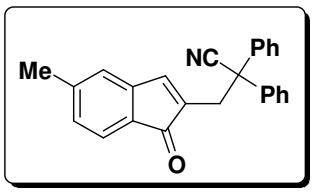
^{13}CNMR (100 MHz, $CDCl_3$): δ 23.67, 33.55, 34.06, 51.46, 121.62, 122.09, 122.39, 127.05, 128.15, 128.92, 130.25, 131.51, 133.05, 139.40, 141.77, 146.71, 150.09, 197.26.

LCMS (*m/z*): 378 $(M+H)^+$.

Anal. Calcd. for $C_{27}H_{23}NO$: C, 85.91; H, 6.14; N, 3.71

Found: C, 85.87; H, 6.09; N, 3.78.

2-(2,2-Diphenyl-2-cyano)ethyl-5-methylind-2-en-1-one (158c): This indenone derivative was obtained as yellow solid *via* treatment of (*E*)-*tert*-butyl 2-(3-methylbenzylidene)-4-cyano-4,4-diphenylbutanoate (**156c**) with trifluroacetic acid and tirfluoroacetic anhydride in 1,2-dichloroethane, following the similar procedure as described for the compound 2-(2,2-diphenyl-2-cyano)ethylind-2-en-1-one **(158a)**.



Yield: 64 %

Mp: 138-140 ^oC

IR (KBr): *v* 2220, 1701, 1620 cm^{-1}

^{1}HNMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.36 (s, 2H), 6.76 (d, 1H, *J* = 7.2 Hz), 6.90 (d, 1H, *J* = 8.0 Hz), 7.10-7.16 (m, 1H), 7.20 (s, 1H), 7.23-7.38 (m, 6H), 7.39-7.48 (m, 4H).

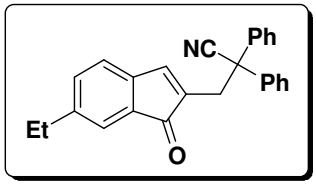
^{13}CNMR (100 MHz, $CDCl_3$): δ 17.13, 33.45, 51.31, 120.07, 122.40, 126.36, 127.04, 128.12, 128.91, 131.85, 133.21, 133.37, 137.80, 139.40, 144.52, 145.26, 197.81.

LCMS (*m/z*): 350 $(M+H)^+$.

Anal. Calcd. for $C_{25}H_{19}NO$: C, 85.93; H, 5.48; N, 4.01

Found: C, 86.10; H, 5.51; N, 4.07.

2-(2,2-Diphenyl-2-cyano)ethyl-6-ethylind-2-en-1-one (158d): This ind-2-en-1-one was obtained as yellow solid, via the treatment of (*E*)-*tert*-butyl 2-(4-ethylbenzylidene)-4-cyano-4,4-diphenylbutanoate (**156d**) with trifluroacetic acid and tirfluoroacetic anhydride in 1,2-dichloroethane, following the similar procedure as described for the compound 2-(2,2-diphenyl-2-cyano)ethylind-2-en-1-one **(158a)**.



Yield: 70 %

Mp: 122-124 ^oC

IR (KBr): ν 2220, 1709, 1604 cm^{-1}

^{1}HNMR (400 MHz, $CDCl_3$): δ 1.18 (t, 3H, *J* = 7.6 Hz), 2.57 (q, 2H, *J* = 7.6 Hz), 3.36 (s, 2H), 6.84 (d, 1H, *J* = 7.2 Hz), 7.08 (d, 1H, *J* = 7.6 Hz), 7.19 (s, 1H), 7.23-7.38 (m, 7H), 7.39-7.48 (m, 4H).

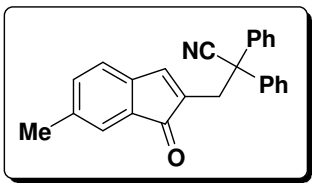
^{13}CNMR (100 MHz, $CDCl_3$): δ 15.26. 28.68, 33.46, 51.42, 122.06, 122.36, 122.99, 127.01, 128.12, 128.88, 130.17, 132.73, 132.88, 139.33, 141.57, 145.31, 146.71, 197.17.

LCMS (*m/z*): 364 $(M+H)^+$.

Anal. Calcd. for $C_{26}H_{21}NO$: C, 85.92; H, 5.82; N, 3.85

Found: C, 85.96; H, 5.79; N, 3.71.

2-(2,2-Diphenyl-2-cyano)ethyl-6-methylind-2-en-1-one (158e): This molecule was obtained as yellow solid, via treatment of (*E*)-*tert*-butyl 2-(4-methylbenzylidene)-4-cyano-4,4-diphenylbutanoate (**156e**) with trifluroacetic acid and tirfluoroacetic anhydride, following the similar procedure as described for the compound 2-(2,2-diphenyl-2-cyano)ethylind-2-en-1-one **(158a)**.



Yield: 60%

Mp: 141-142 ^{o}C

IR (KBr): *v* 2220, 1705, 1620 cm^{-1}

^{1}HNMR (400 MHz, $CDCl_3$): δ 2.28 (s, 3H), 3.36 (d, 2H, *J* = 1.2 Hz), 6.83 (d, 1H, *J* = 7.2 Hz), 7.03-7.09 (m, 1H), 7.15 (s, 1H), 7.27-7.38 (m, 7H), 7.40-7.46 (m, 4H).

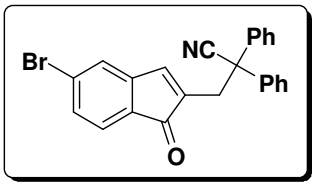
^{13}CNMR (100 MHz, $CDCl_3$): δ 21.32, 33.51, 51.48, 122.00, 122.41, 124.15, 127.07, 128.15, 128.91, 130.16, 132.84, 133.79, 138.89, 139.38, 141.39, 146.71, 197.14.

LCMS (*m/z*): 350 $(M+H)^{+}$, 382 $(M+H+MeOH)^{+}$.

Anal. Calcd. for $C_{25}H_{19}NO$: C, 85.93; H, 5.48; N, 4.01

Found: C, 85.97; H, 5.39; N, 4.07.

2-(2,2-Diphenyl-2-cyano)ethyl-5-bromoind-2-en-1-one (158f): This **i**nd-2-en-1-one derivative was obtained as yellow solid via the treatment of (*E*)-*tert*-butyl 2-(3-bromobenzylidene)-4-cyano-4,4-diphenylbutanoate (**156f**) with trifluroacetic acid and tirfluoroacetic anhydride with following the similar procedure as described for 2-(2,2-diphenyl-2-cyano)ethylind-2-en-1-one **(158a)**.



Yield: 66 %

Mp: 168-170 ^{o}C

IR (KBr): ν 2220, 1714, 1601cm^{-1}

^{1}HNMR (400 MHz, $CDCl_3$): δ 3.39 (s, 2H), 7.11 (s, 1H), 7.18 (1H, d, J = 7.6 Hz), 7.25-7.46 (m, 12H).

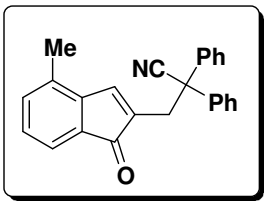
^{13}CNMR (100 MHz, $CDCl_3$): δ 33.65, 51.41, 122.28, 124.14, 125.76, 127.08, 128.35, 128.40, 128.81, 129.06, 131.41, 135.09, 139.20, 145.12, 146.11, 195.46.

LCMS (*m/z*): 414 $(M+H)^+$, 416 $(M+2+H)^+$.

Anal. Calcd. for $C_{24}H_{16}BrNO$: C, 69.58; H, 3.89; N, 3.38

Found: C, 69.48; H, 3.82, N, 3.45.

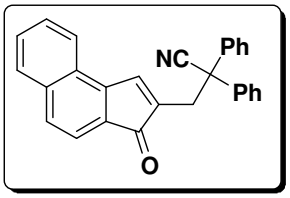
2-(2,2-Diphenyl-2-cyano)ethyl-4-methylind-2-en-1-one (158g): This indenone was obtained as yellow solid via reaction of (*E*)-*tert*-butyl 2-(2-methylbenzylidene)-4-cyano-4,4-diphenylbutanoate (**156g**) with TFA/TFAA following the similar procedure as described for the



compound 2-(2,2-diphenyl-2-cyano)ethylind-2-en-1-one (**158a**).

Yield:	62 %
Mp:	116-119 ^{o}C
IR (KBr):	ν 2239, 1703, 1621 cm^{-1}
^{1}HNMR (400 MHz, $CDCl_3$):	δ 2.18 (s, 3H), 3.37 (s, 2H), 6.98-7.04 (m, 1H), 7.06 (d, 1H, J = 7.6 Hz), 7.15 (d, 1H, J = 6.8 Hz), 7.21-7.46 (m, 11H).
^{13}CNMR (100 MHz, $CDCl_3$):	δ 16.95, 33.53, 51.56, 120.70, 122.41, 127.12, 128.18, 128.57, 128.91, 129.75, 131.53, 132.82, 135.85, 139.39, 142.09, 144.90, 197.15.
LCMS (*m/z*):	350 $(M+H)^{+}$.
Anal. Calcd. for $C_{25}H_{19}NO$:	C, 85.93; H, 5.48; N, 4.01
Found:	C, 85.96; H, 5.41; N, 4.10.

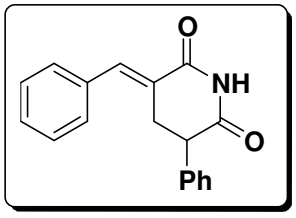
12-(2,2-Diphenyl-2-cyano)ethyltricyclo[8.3.0.0^{2,7}]trideca-1(10),2(7),3, 5, 8, 12-hexaen-11-one (158h): This indenone compound was obtained as red solid via the treatment of (*E*)-*tert*-butyl 4-cyano-2-(naphth-1-ylmethylidene)-4,4-diphenylbutanoate (**156h**) with TFA/TFAA following the similar procedure as described for the compound 2-(2,2-diphenyl-2-cyano)ethylind-2-en-1-one (**158a**).



Yield:	64 %
Mp:	184-186 ^{o}C

IR (KBr):	ν 2220, 1712, 1620 cm^{-1}.
^{1}HNMR (400 MHz, $CDCl_3$):	δ 3.45 (s, 2H), 7.27-7.41 (m, 6H), 7.42-7.53 (m, 7H), 7.65 (d, 1H, J = 8.0 Hz), 7.73-7.82 (m, 3H).
^{13}CNMR (100 MHz, $CDCl_3$):	δ 33.55, 51.58, 119.25, 122.46, 123.21, 125.38, 126.65, 127.12, 127.17, 128.22, 128.25, 128.47, 128.80, 128.94, 132.08, 137.37, 139.33, 142.48, 143.48, 197.76.
LCMS (*m/z*):	386 $(M+H)^+$.
Anal. Calcd. for $C_{28}H_{19}NO$:	C, 87.25; H, 4.97; N, 3.63
Found:	C, 87.16; H, 5.02; N, 3.71.

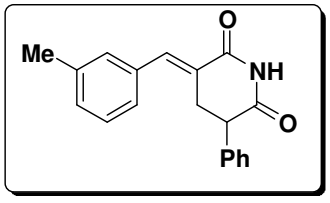
(*E*)-3-Benzylidene-5-phenylpiperidine-2,6-dione (153a): To a stirred solution of (*E*)-*tert*-butyl 2-benzylidene-4-cyano-4-phenylbutanoate (**150a**) (0.5 mmol, 0.167 g) in 1,2-dichloroethane (DCE, 3 mL), methanesulfonic acid (CH_3SO_3H, 1.5 mmol, 0.144 g, 0.098 mL) and tirfluoroacetic anhydride (TFAA, 1 mmol, 0.210 g, 0.14 mL) were added at room temperature. The reaction mixture was heated under reflux for 4 h and then allowed to cool to room temperature. Reaction mixture was poured into aqueous K_2CO_3 solution and extracted with EtOAc (2 X 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4.



Solvent was evaporated and the residue, thus obtained was purified by column chromatography (25 % ethyl acetate in hexanes) to provide, (*E*)-3-benzylidene-5-phenylpiperidine-2,6-dione (**153a**) as a colorless solid in 70 % (0.098 g) yield.

Mp:	172-174 ^{o}C
IR (KBr):	*v* 3150-2900 (multiple bands), 1714, 1687, 1616 cm^{-1}
^{1}HNMR (400 MHz, $CDCl_3$):	δ 3.15-3.27 (m, 1H), 3.30-3.42 (m, 1H), 3.80-3.92 (m, 1H), 7.21 (d, 2H, *J* = 6.8 Hz), 7.28-7.48 (m, 8H), 7.96 (s,1H), 8.09 (s, 1H).
^{13}CNMR (100 MHz, $CDCl_3$):	δ 30.62, 47.68, 125.87, 127.87, 128.15, 128.73, 128.91, 129.45, 129.83, 134.40, 136.85, 140.97, 166.67, 172.64.
LCMS (*m/z*):	278 $(M+H)^+$, 310 $(M+H+MeOH)^+$.
Anal. Calcd. for $C_{18}H_{15}NO_2$:	C, 77.96; H, 5.45; N, 5.05
Found:	C, 77.85; H, 5.41; N, 5.14.

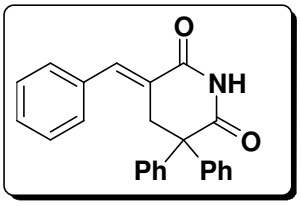
(*E*)-3-(3-Methylbenzylidene)-5-phenylpiperidine-2,6-dione (153b): This piperidine-2,6-dione compound was obtained as colorless solid via treatment of (*E*)-*tert*-butyl 2-benzylidene-4-cyano-4-(3-methylphenyl)butanoate (**150c**) with methanesulfonic acid and tirfluoroacetic anhydride, following the similar procedure described for the compound



(*E*)-3-benzylidene-5-phenylpiperidine-2,6-dione (**153a**).

Yield:	75 %
Mp:	162-164 ^{o}C
IR (KBr):	*v* 3200-2900 (multiple bands), 1720, 1697, 1626 cm^{-1}
^{1}HNMR (400 MHz, $CDCl_3$):	δ 2.35 (s, 3H), 3.14-3.26 (m, 1H), 3.28-3.42 (m, 1H), 3.80-3.90 (m, 1H), 7.08-7.42 (m, 9H), 7.93 (s,1H), 8.10 (s, 1H).
^{13}CNMR (100 MHz, $CDCl_3$):	δ 21.49, 30.66, 47.79, 125.65, 126.88, 127.92, 128.20, 128.65, 128.97, 130.34, 130.55, 134.41, 136.95, 138.53, 141.32, 166.66, 172.69.
LCMS (*m/z*):	292 $(M+H)^+$, 324 $(M+H+MeOH)^+$.
Anal. Calcd. for $C_{19}H_{17}NO_2$:	C, 78.33; H, 5.88; N, 4.81
Found:	C, 78.45; H, 5.93; N, 4.76

(*E*)-3-Benzylidene-5,5-diphenylpiperidine-2,6-dione (159a): To a stirred solution of (*E*)-*tert*-butyl 2-benzylidene-4-cyano-4,4-diphenylbutanoate (**156a**) (0.5 mmol, 0.205 g) in 1,2-dichloroethane (DCE, 3 mL) methanesulfonic acid (CH_3SO_3H) (1.5 mmol, 0.144 g, 0.098 mL) and tirfluoroacetic anhydride (TFAA, 1 mmol, 0.210 g, 0.14 mL) were added at room temperature. The reaction mixture was heated under reflux for 4 h and then allowed

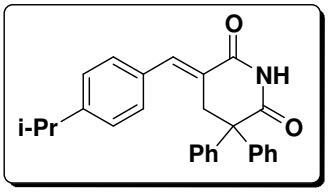


to cool to room temperature. Reaction mixture was poured into aqueous K_2CO_3 solution and extracted with EtOAc (2 X 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue, thus obtained was purified by column chromatography (25 % ethyl acetate in hexanes) to provide, (*E*)-3-benzylidene-5,5-diphenylpiperidine-2,6-dione (**159a**) as a colorless solid in 85 % (0.150 g) yield.

Mp:	218-221 ^{o}C
IR (KBr):	*v* 3150-2900 (multiple bands), 1714, 1685, 1608 cm^{-1}
^{1}HNMR (400 MHz, $CDCl_3$):	δ3.64 (s, 2H), 6.95-7.08 (m, 4H), 7.19-7.52 (m, 11H), 7.85 (s, 1H), 8.32 (bs, 1H).
^{13}CNMR (100 MHz, 50% DMSO-d_6 in $CDCl_3$):	δ34.34, 55.59, 125.84, 126.51, 126.69, 127.23, 127.66, 127.90, 133.02, 137.66, 139.16, 164.76, 172.80.
LCMS (*m/z*):	354 $(M+H)^+$.
Anal. Calcd. for $C_{24}H_{19}NO_2$:	C, 81.56; H, 5.42; N, 3.96
Found:	C, 81.48; H, 5.48; N, 4.05.

(*E*)-3-(4-Isopropylbenzylidene)-5,5-diphenylpiperidine-2,6-dione (159b): This piperidine-2,6-dione was obtained as colorless solid via the reaction of (*E*)-*tert*-butyl 2-(4-isopropylbenzylidene)-4-cyano-4,4-diphenylbutanoate (**156b**) with methanesulfonic acid

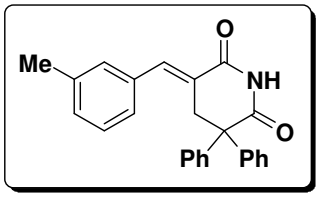
and tirfluoroacetic anhydride following the similar procedure as described for the compound (*E*)-3-benzylidene-5,5-diphenylpiperidine-2,6-dione (**159a**).



Yield:	86 %
Mp:	207-208 ^{o}C
IR (KBr):	*v* 3150-2920 (multiple bands), 1710, 1685, 1624 cm^{-1}
^{1}HNMR (400 MHz, $CDCl_3$):	δ 1.28 (d, 6H, *J* = 6.8 Hz), 2.95 (sept, 1H, *J* = 6.8 Hz), 3.66 (d, 2H, *J* = 1.2 Hz), 7.00-7.10 (m, 4H), 7.22-7.37 (m, 10H), 7.83 (s, 1H), 8.18 (bs, 1H).
^{13}CNMR (100 MHz, $CDCl_3$):	δ 23.78, 34.04, 36.54, 57.44, 125.38, 126.95, 127.66, 128.23, 128.45, 129.90, 132.02, 140.27, 141.29, 150.65, 166.40, 174.15.
LCMS (*m/z*):	396 $(M+H)^{+}$.
Anal. Calcd. for $C_{27}H_{25}NO_2$:	C, 82.00; H, 6.37; N, 3.54
Found:	C, 82.15; H, 6.30; N, 3.61

(*E*)-3-(3-Methylbenzylidene)-5,5-diphenylpiperidine-2,6-dione (159c): This compound was obtained as colorless solid via treatment of (*E*)-*tert*-butyl 2-(3-methylbenzylidene)-4-cyano-4,4-diphenylbutanoate (**156c**) with CH_3SO_3H/TFAA following the similar

procedure as described for the compound (*E*)-3-benzylidene-5,5-diphenylpiperidine-2,6-dione (**159a**)



Yield: 81 %

Mp: 207-208 ^{o}C

IR (KBr): *v* 3150-2925 (multiple bands), 1699, 1685, 1618 cm^{-1}

^{1}HNMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 3.63 (d, 2H, *J* = 1.6 Hz), 6.98-7.18 (m, 4H), 7.11-7.38 (m, 10H), 7.81 (s, 1H), 8.27 (bs, 1H).

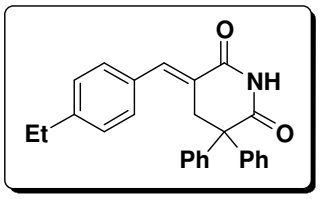
^{13}CNMR (100 MHz, $CDCl_3$): δ 21.50, 36.39, 57.55, 126.09, 126.57, 127.72, 128.23, 128.48, 128.70, 130.27, 130.33, 134.52, 138.56, 140.15, 141.55, 166.29, 174.14.

LCMS (*m/z*): 368 $(M+H)^{+}$.

Anal. Calcd. for $C_{25}H_{21}NO_2$: C, 81.72; H, 5.76; N, 3.81

Found: C, 81.65; H, 5.71; N, 3.92.

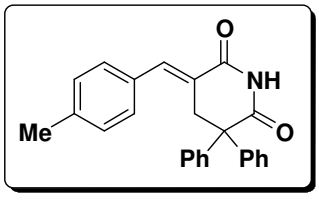
(*E*)-3-(4-Ethylbenzylidene)-5,5-diphenylpiperidine-2,6-dione (159d): This piperidine-2,6-dione was obtained as colorless solid via treatment of (*E*)-*tert*-butyl 2-(4-ethylbenzylidene)-4-cyano-4,4-diphenylbutanoate (**156d**) with methanesulfonic acid and tirfluoroacetic anhydride, following similar procedure as described for the compound (*E*)-3-



benzylidene-5,5-diphenylpiperidine-2,6-dione (**159a**)

Yield:	77 %
Mp:	186-188 ^{o}C
IR (KBr):	ν 3140-2915 (multiple bands), 1716, 1682, 1620 cm^{-1}
^{1}HNMR (400 MHz, $CDCl_3$):	δ 1.27 (t, 3H, J = 7.2 Hz), 2.68 (q, 2H, J = 7.2 Hz), 3.65 (s, 2H), 6.98-7.07 (m, 4H), 7.22-7.37 (m, 10H), 7.83 (s, 1H), 8.13 (bs, 1H).
^{13}CNMR (100 MHz, $CDCl_3$):	δ 15.17, 28.71, 36.50, 57.39, 125.41, 127.58, 128.17, 128.30, 128.38, 129.83, 131.88, 140.26, 141.20, 145.98, 166.50, 174.16.
LCMS (*m/z*):	382 $(M+H)^{+}$.
Anal. Calcd. for $C_{26}H_{23}NO_2$:	C, 81.86; H, 6.08; N, 3.67
Found:	C, 81.92; H, 6.13; N, 3.58

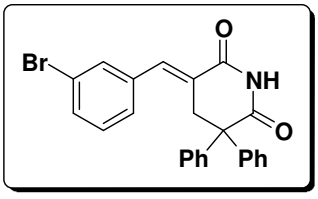
(*E*)-3-(4-Methylbenzylidene)-5,5-diphenylpiperidine-2,6-dione (159e): This piperide-2,6-dione compound was obtained via treatment of (*E*)-*tert*-butyl 2-(4-methylbenzylidene)-4-cyano-4,4-diphenylbutanoate (**156e**) with CH_3SO_3H/TFAA as colorless solid following the similar procedure as described for the compound (*E*)-3-benzylidene-5,5-diphenylpiperidine-2,6-dione (**159a**).



Yield: 80 %

Mp:	228-230 ^{o}C
IR (KBr):	*v* 3150-2925 (multiple bands), 1712, 1682, 1625 cm^{-1}
^{1}HNMR (400 MHz, $CDCl_3$):	δ 2.40 (s, 3H), 3.65 (s, 2H), 6.98-7.07 (m, 4H), 7.22-7.35 (m, 10H), 7.82 (s, 1H), 8.06 (bs, 1H).
^{13}CNMR (100 MHz, 50% DMSO-d_6 in $CDCl_3$):	δ 19.81, 34.48, 55.51, 124.74, 124.98, 125.84, 126.55, 126.70, 127.99, 128.07, 130.12, 137.74, 139.25, 164.81, 172.80.
LCMS (*m/z*):	368 $(M+H)^+$
Anal. Calcd. for $C_{25}H_{21}NO_2$:	C, 81.72; H, 5.76; N, 3.81
Found:	C, 81.57; H, 5.82; N, 3.76.

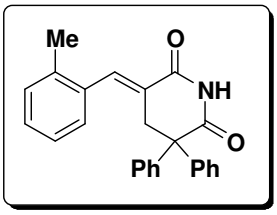
(*E*)-3-(3-Bromobenzylidene)-5,5-diphenylpiperidine-2,6-dione (159f): This compound was obtained as colorless solid via treatment of (*E*)-*tert*-butyl 2-(3-bromobenzylidene)-4-cyano-4,4-diphenylbutanoate (**156f**) with methanesulfonic acid and tirfluoroacetic anhydride, following similar procedure as described for the compound (*E*)-3-benzylidene-5,5-diphenylpiperidine-2,6-dione (**159a**).



Yield:	82 %
Mp:	138-140 ^{o}C
IR (KBr):	*v* 3150-2945 (multiple bands), 1715, 1690, 1614 cm^{-1}

^{1}HNMR (400 MHz, $CDCl_3$):	δ3.58 (s, 2H), 6.97-7.05 (m, 4H), 7.20-7.32 (m, 8H), 7.41 (s, 1H), 7.51 (d, 1H, *J* = 7.6 Hz), 7.73 (s, 1H), 8.61 (bs, 1H).
^{13}CNMR (100 MHz, $CDCl_3$):	δ 36.14, 57.57, 122.92, 127.77, 127.81, 127.85, 128.15, 128.56, 130.35, 132.12, 132.34, 136.59, 139.43, 139.94, 165.85, 173.89.
LCMS (*m/z*):	432 $(M+H)^+$, 434 $(M+2+H)^+$.
Anal. Calcd. for $C_{24}H_{18}BrNO_2$:	C, 66.68; H, 4.20; N, 3.24
Found:	C, 66.57; H, 4.26; N, 3.29.

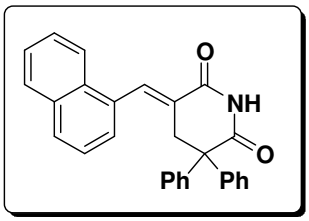
(*E*)-3-(2-Methylbenzylidene)-5,5-diphenylpiperidine-2,6-dione (159g): This molecule was obtained via treatment of (*E*)-*tert*-butyl 2-(2-methylbenzylidene)-4-cyano-4,4-diphenylbutanoate (**156g**) with CH_3SO_3H/TFAA as colorless solid, following the similar procedure as described for the compound (*E*)-3-benzylidene-5,5-diphenylpiperidine-2,6-dione (**159a**)



Yield:	75 %
Mp:	182-184 ^oC
IR (KBr):	*v*3150-2925 (multiple bands), 1716, 1682, 1622 cm^{-1}
^{1}HNMR (400 MHz, $CDCl_3$):	δ 2.14, (s, 3H), 3.52 (d, 2H, *J* = 1.6 Hz), 6.94-7.01 (m, 4H), 7.13 (d, 1H, *J* = 7.6 Hz), 7.18-7.38 (m, 9H), 7.86 (s, 1H), 8.18 (bs, 1H)

^{13}CNMR (100 MHz, $CDCl_3$):	δ 19.80, 36.30, 57.68, 125.86, 126.84, 127.69, 128.12, 128.47, 128.86, 129.40, 130.44, 133.59, 137.64, 140.06, 140.80, 166.27, 174.17
LCMS (*m/z*):	368 $(M+H)^+$
Anal. Calcd. for $C_{25}H_{21}NO_2$:	C, 81.72; H, 5.76; N, 3.81
Found:	C, 81.65; H, 5.81; N, 3.88

(*E*)-3-(Naphth-1-ylmethylidene)-5,5-diphenylpiperidine-2,6-dione (159h): This piperide-2,6-dione was obtained as colorless solid via treatment of (*E*)-*tert*-butyl 2-(napth-1-ylmethylidene)-4-cyano-4,4-diphenylbutanoate (**156h**) with CH_3SO_3H/TFAA, following similar procedure as described for the compound (*E*)-3-benzylidene-5,5-diphenylpiperidine-2,6-dione (**159a**).



Yield:	79 %
Mp:	158-160 ^oC
IR (KBr):	*v* 3150-2920 (multiple bands), 1722, 1685, 1624 cm^{-1}
^{1}HNMR (400 MHz, $CDCl_3$):	δ3.54 (s, 2H), 6.92 (d, 4H, *J* = 7.6 Hz), 7.08-7.61 (m,10H), 7.71 (d, 1H, *J* = 8.4 Hz), 7.86-7.98 (m, 2H), 8.13 (bs, 1H), 8.35 (s, 1H).
^{13}CNMR (100 MHz, $CDCl_3$):	δ36.85, 57.59, 124.70, 125.13, 126.61, 126.83,

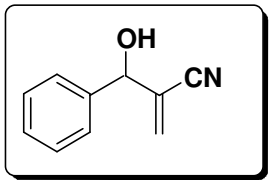
126.99, 127.66, 128.16, 128.34, 128.47, 128.67, 129.84, 131.44, 131.69, 133.57, 139.90, 140.03, 166.02, 174.22.

LCMS (*m/z*): 404 $(M+H)^+$

Anal. Calcd. for $C_{28}H_{21}NO_2$: C, 83.35; H, 5.25; N, 3.47

Found: C, 83.24; H, 5.31; N, 3.55

3-Hydroxy-2-methylene-3-phenylpropanenitrile (161a): This compound was prepared according to the known procedure.[228] A mixture of DABCO (cat.) (30 mmol % 15 mmol, 1.64 g), benzaldehyde (100 mmol, 10.612) in acrylonitrile (150 mmol, 7.958) was kept to react at room temperature for 2 days. Reaction mixture was monitored by TLC (After 2 days benzaldehyde disappeared from the reaction mixture). Reaction mixture was diluted with 100 mL ether and washed successively with 2N HCl (20 mL) solution, water and aqueous $NaHCO_3$ solution. Oranic layer was dried with anhydrous Na_2SO_4 and concentrated, the crude product thus obtained was distilled under reduced pressure to afford **161a** s a colorless liquid.



Yield: 78 %

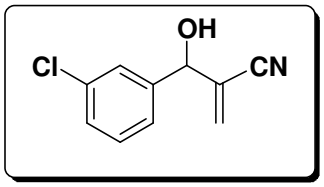
bp: 123-126°C/2.4 mm {Lit[228] 110 °C/0.95 mm}

IR (Neat): 3449, 2229, 1622 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) : δ 2.61 (bs, 1H), 5.28 (s, 1H), 6.02 (s,1H), 6.10 (s, 1H), 7.30-7.48 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 73.76, 116.96, 126.01, 126.43, 128.68, 128.72, 130.13, 139.06.

3-Hydroxy-2-methylene-3-(3-chlorophenyl)propanenitrile (161b): This product was obtained via the treatment of 3-chlorobenzaldehyde with acrylonitrile in the presence of catalytic amount of DABCO, following similar procedure described for the molecule 3-hydroxy-2-methylene-3-phenylpropanenitrile (**161a**).



Reaction time: 2 days

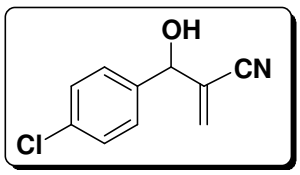
Yield: 75 %

IR (Neat): 3458, 2229, 1620 cm^{-1}

^{1}H NMR(400 MHz, $CDCl_3$): δ 3.10 (bs, 1H), 5.27 (s, 1H), 6.05 (s, 1H), 6.12 (s,1H), 7.23-7.40 (m, 4H).

^{13}C NMR (50MHz, $CDCl_3$): δ 69.75, 116.03, 124.49, 125.39, 126.29, 128.52, 129.90, 130.73, 134.25, 141.09.

3-(4-Chlorophenyl)-3-hydroxy-2-methylenepropanenitrile (161c): Title compound **161c** obtained via treatment of 4-chlorobenzaldehyde in the presence of DABCO (cat.) with acrylonitrile, following similar procedure described for the molecule 3-hydroxy-2-methylene-3-phenylpropanenitrile (**161a**).



Reaction time: 2 days

Yield: 71 %

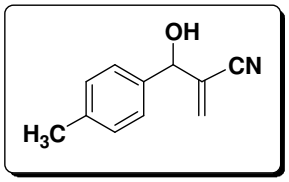
bp: 139-141 ^{o}C/ 0.9 mm

IR (Neat): 3495, 2231, 1618 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.66 (bs, 1H), 5.27 (s, 1H), 6.03 (s, 1H), 6.10 (s, 1H), 7.30-7.40 (m, 4H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 73.21, 116.73, 125.85, 127.84, 128.91, 130.41, 134.51, 137.67

3-Hydroxy-2-methylene-3-(4-methylphenyl)propanenitrile (161d): This alcohol was obtained as colorless liquid via the reaction between 4-methylbenzaldehyde and acrylonitrile in the presence of DABCO, following the similar procedure described for the molecule 3-hydroxy-2-methylene-3-phenylpropanenitrile (**161a**).



Reaction time: 2 days

Yield: 73%

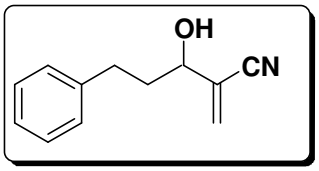
bp: 125-126 ^{o}C/0.8 mm

IR (Neat): 3452, 2229, 1614 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 5,26 (s 1H)), 6.02 (s, 1H), 6.10 (s, 1H), 7.20 (d, 2H, *J* = 8.0 Hz), 7.27 (d, 2H, *J* = 8.0 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.02, 73.58, 117.02, 126.16, 126.37, 129.36, 129.76, 136.14, 138.46.

3-Hydroxy-2-methylene-5-phenylpentanenitrile (161e): This allylic alcohol was prepared via the reaction of hydrocinnamaldehyde with acrylonitrile in the presence of DABCO (cat.), following the similar procedure described for the molecule 3-hydroxy-2-methylene-3-phenylpropanenitrile (**161a**)



Reaction time: 2 days

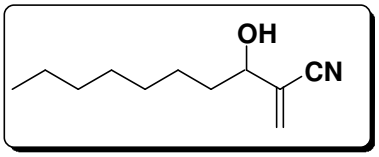
Yield: 65 %

IR (Neat): 3462, 2226, 1620 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.90-2.10 (m, 3H), 2.71-2.91 (m, 2H), 4.25 (bs, 1H), 6.00 (s, 2H), 7.18-7.43 (m, 5H).

^{13}C NMR (50MHz, $CDCl_3$) : δ 31.08, 36.88, 71.13, 116.97, 126.00, 126.56, 128.28, 128.37, 130.22, 140.67.

3-Hydroxy-2-methylene-3-decanenitrile (161f): This compound was obtained as colorless liquid via reaction of octanaldehyde with acrylonitrile in the presence of DABCO (cat.) following the similar procedure described for the compound 3-hydroxy-2-methylene-3-phenylpropanenitrile (**161a**).



Reaction time: 2 days

Yield: 69 %

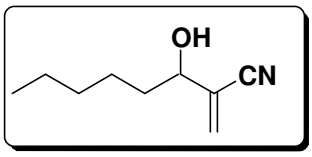
IR (Neat): 3445, 2227, 1626 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) : δ 0.86 (t, 3H, *J* = 6.4 Hz), 1.20-1.52 (m, 10H), 1.60-1.80 (m, 2H), 2.18 (bs, 1H), 4.24 (t, 1H, *J* = 6.4 Hz), 5.97 (s, 1H), 5.99 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.00, 22.55, 25.05, 29.09, 29.18, 31.69, 35.53, 72.18, 117.11, 126.95, 129.93

3-Hydroxy-2-methylene-3-octanenitrile (161g): The reaction between hexanaldehyde and acrylonitrile in the presence of DABCO (cat.), provided the title molecule **161g** as colorless liquid, following the similar procedure described for the molecule 3-hydroxy-2-methylene-3-phenylpropanenitrile (**161a**).

Reaction time: 2 days



Yield: 74 %

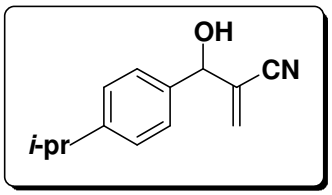
IR (Neat): 3429, 2229, 1624cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 5.6 Hz), 1.25-1.51 (m, 6H), 1.59-1.82 (m, 2H), 2.10 (b, s 1H), 4.21 (t, 1H, *J* = 5.6 Hz), 5.98 (s, 1H), 5.99 (s, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.75, 22.29, 24.56, 31.23, 35.25, 71.92, 117.00, 126.74, 130.00

3-Hydroxy-2-methylene-3-(4-isopropylphenyl)propanenitrile (161h): This molecule was prepared as colorless liquid by the reaction of 4-isopropylbenzaldehyde with

acrylonitrile in the presence of DABCO (cat.), following the similar procedure described for the molecule 3-hydroxy-2-methylene-3-phenylpropanenitrile (**161a**).



Reaction time: 2 days

Yield: 70 %

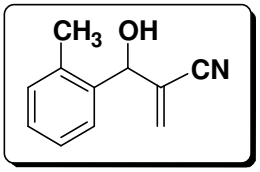
bp: 125-126 ^{o}C/2.4 mm^{-1}

IR (Neat): 3456, 2229, 1614 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.25 (d, 6H, *J* = 6.8 Hz), 2.38 (s, 1H) 2.89 (sept, 1H, *J* = 6.8 Hz), 5.27 (s, 1H), 6.02 (d, 1H, *J* = 1.6 Hz), 6.11 (d, 1H, *J* = 1.6 Hz) 7.22 (d, 2H, *J* = 8.0 Hz), 7.31 (d, 2H, *J* = 8.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 23.84, 33.77, 73.79, 117.08, 126.26, 126.51, 126.87, 129.74, 136.55. 149.55.

3-Hydroxy-2-methylene-3-(2-methylphenyl)propanenitrile (161i): This molecule was prepared as colorless liquid, by the reaction of 2-methylbenzaldehyde with acrylonitrile in the presence of catalytic amount of DABCO, following the similar procedure described for the molecule 3-hydroxy-2-methylene-3-phenylpropanenitrile (**161a**).



Reaction time: 2 days

Yield: 74 %

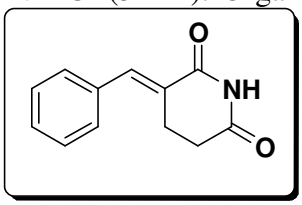
bp: 125-126 ^{o}C/0.8 mm

IR (Neat): 3445, 2228, 1622 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 2.26 (d, 1H, *J* = 4.0 Hz), 2.37 (s, 3H), , 5.53 (d, 1H, *J* = 4.0 Hz), 6.02 (s, 1H), 6.06 (s, 1H) 7.16-7.29 (m, 3H), 7.40-7.46 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 18.98, 70.51, 117.12, 125.36, 126.30, 126.53, 128.64, 130.35, 130.76, 135.58, 136.91.

(E)-3-Benzylidenepiperidine-2, 6-dione (**162a**): To a stirred solution of 3-hydroxy-2-methylene-3-phenylpropanenitrile (**161a**) (1 mmol, 0.159 g) in triethyl orthoacetate (1 mL), propanoic acid (3 drops) was added and the reaction mixture was heated at 146 ^oC for 2 h. Reaction mixture was cooled to room temperature and excess orthoester and propanoic acid were distilled off under reduced pressure. Residue, thus obtained, was dissolved in acetic acid (5 mL). Anhydrous FeCl3 (5 mmol, 0.812 g) was added and the reaction mixture was heated under reflux for 10 h. Then the reaction mixture was cooled to room temperature and acetic acid was removed under reduced pressure. The residue was dissolved in dichloromethane (5 mL) and poured into aqueous 4N HCl (5 mL). Organic layer was separated and aqueous layer was extracted with dichloromethane (2 X 10 mL). The combined organic layer was washed successively with saturated NaHCO3 solution, water



and dried over anhydrous Na2SO4. Solvent was removed and the residue was purified by column chromatography (silica gel, 35% ethyl acetate in hexanes) to provide (*E*)-3-benzylidenepiperidine-2, 6-dione (**162a**) as a colorless solid (0.169 g) in 84 % yield.

Mp: 198-200 ºC, (Lit.€ 209-210 ^{0}C)

IR (KBr): ν 3200-2900 (multiple bands), 1730, 1691, 1624 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.64 (t, 2H, *J* = 6.8 Hz), 2.98-3.06 (m, 2H)*, 7.37-7.50 (m, 5H), 7.90 (s, 1H), 8.03 (bs, 1H).

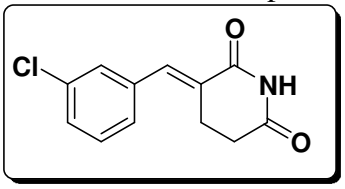
LCMS (*m/z*): 200 $(M-H)^+$

^{13}C NMR (100 MHz, 20% DMSO-d_6 in $CDCl_3$): δ 21.30, 30.29, 126.21, 127.43, 127.86, 128.55, 133.53, 137.26, 166.00, 171.37.

Analysis Calc'd. for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96;

Found: C, 71.69; H, 5.56; N, 6.92.

(*E*)-3-(3-Chlorobenzylidene)piperidine-2, 6-dione (162b): This molecule was obtained as colorless solid *via* the Johnson-Claisen rearrangement of 3-hydroxy-2-methylene-3-(3-chlorophenyle)propanenitrile (**161b**) with triethyle orthoacetate and subsequent treatment with anhydrous $FeCl_3$ / AcOH following similar procedure described for the compound (*E*)-3-benzylidenepiperidine-2, 6-dione (**162a**).



Yield: 67 %

Mp: 192-194 ºC

€ Warner, M. J.; Koomen, G. J. *Synthesis* **1988**, 325

* This multiplet almost looks like an unresolved dd

IR (KBr): ν 3200-2850 (multiple bands), 1732, 1691, 1624 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 2.65 (t, 2H, *J* = 6.8 Hz), 2.98 (t, 2H *J* = 6.8 Hz), 7.26 (s, 1H),* 7.36 (bs, 3H), 7.83 (bs, 1H), 8.12 (bs, 1H)

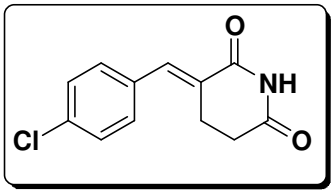
^{13}C NMR (100 MHz, 20% DMSO-d_6 in $CDCl_3$): δ 21.50, 30.42, 126.97, 127.74, 127.95, 128.35, 129.10, 133.29, 135.62, 135.98, 165.91, 171.47

LCMS (m/z): 236 $(M+H)^+$, 238 $(M+2+H)^+$

Analysis Calc'd. for $C_{12}H_{10}ClNO_2$: C, 61.16; H, 4.28; N, 5.94

Found: C, 61.20; H, 4.30; N, 5.77.

(*E*)-3-(4-Chlorobenzylidene)piperidine-2, 6-dione (162c): The Johnson-Claisen rearrangement of 3-hydroxy-2-methylene-3-(4-chlorophenyle)propanenitrile (**161c**) with triethyl orthoacetate and subsequent reaction with anhydrous $FeCl_3$ / AcOH provided the desired compound **162c** as colorless solid, following similar procedure described for the compound (*E*)-3-benzylidenepiperidine-2, 6-dione (**162a**).



Yield: 71 %

Mp: 226-228°C

IR (KBr): ν 3195-2860 (multiple bands), 1728, 1689, 1618 cm^{-1}

* This peak merges with $CHCl_3$ peak

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.64 (t, 2H, *J* = 6.4 Hz), 2.97 (t, 2H *J* = 6.4 Hz), 7.32 (d, 2H, *J* = 8.4 Hz), 7.41 (d, 2H, *J* = 8.4 Hz), 7.84 (s, 1H), 8.12 (bs, 1H).

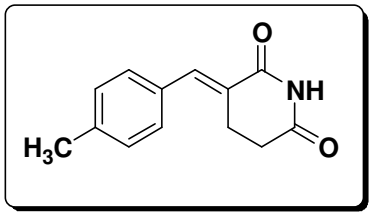
^{13}C NMR (100 MHz, 20% DMSO-d_6 in $CDCl_3$): δ 21.28, 30.19, 126.86, 127.61, 130.01, 132.16, 133.39, 135.90, 165.78. 171.26.

LCMS (m/z): 236 $(M+H)^+$, 238$(M+2+H)^+$

Analysis Calc'd. for $C_{12}H_{10}ClNO_2$: C, 61.16; H, 4.28; N, 5.94

Found. C, 61.09; H, 4.30; N, 6.06.

(*E*)-3-(4-Methylbenzylidene)piperidine-2, 6-dione (162d) : This compound was obtained as colorless solid *via* the treatment of 3-hydroxy-2-methylene-3-(4-methylephenyle) propanenitrile (**161d**) with triethyl orthoacetate and subsequent reaction with anhydrous $FeCl_3$ / AcOH following similar procedure described for the compound (*E*)-3-benzylidenepiperidine-2, 6-dione (**162a**).



Yield: 77 %

Mp: 200-202ºC

IR (KBr): ν 3200-2890 (multiple bands), 1728, 1689, 1622 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 2.63 (t, 2H, *J* = 6.8 Hz)), 3.01 (t, 2H, *J* = 6.8 Hz), 7.24 (d, 2H, *J* = 7.6 Hz), 7.30 (d, 2H, *J* = 7.6 Hz), 7.87 (s, 1H), 8.05 (bs, 1H)

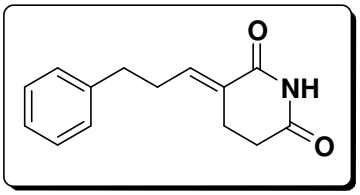
^{13}C NMR (100 MHz, 20% DMSO-d_6 in $CDCl_3$): δ 20.16, 21.31, 30.24, 125.23, 128.11, 128.64, 130.67, 137.35, 137.96, 166.08, 171.37

LCMS (m/z): 216 $(M+H)^+$.

Analysis Calc'd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51

Found: C, 72.56; H, 6.07; N, 6.59.

(*E*)-3-(3-Phenylpropylidene)piperidine-2, 6-dione (163e): The title compound was obtained as colorless solid via the Johnson-Claisen rearrangement of of 3-hydroxy-2-methylene-5-phenylpentanenitrile (**161e**) with triethyl orthoacetate and subsequent treatment with anhydrous $FeCl_3$ / AcOH following similar procedure described for for the compound (*E*)-3-benzylidenepiperidine-2, 6-dione (**162a**).



Yield: 73 %

Mp: 134-136^{o}C

IR (KBr): ν 3190-2850 (multiple bands), 1716, 1691, 1639 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34-2.46 (m, 4H), 2.52-2.61 (m, 2H), 2.80 (t, 2H, *J* = 6.8 Hz), 7.01 (t, 1H, *J* = 8.0 Hz), 7.13-7.36 (m, 5H), 8.20 (bs, 1H)

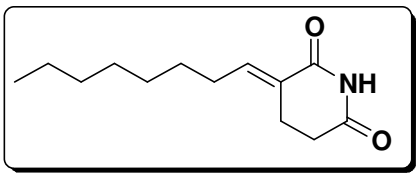
^{13}C NMR (100 MHz, $CDCl_3$): δ 20.94, 30.36, 31.26, 34.56, 126.41, 127.04, 128.56, 140.56, 142.33, 166.22, 172.37

LCMS (m/z): 230 $(M+H)^+$, 262 $(M+CH_3OH)^+$

Analysis Calc'd.for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11

Found: C, 73.40; H, 6.58; N, 6.15.

(*E*)-3-Octylidenepiperidine-2, 6-dione (162f) : This molecule was obtained as colorless solid *via* the Johnson-Claisen rearrangement of 3-hydroxy-2-methylene-3-decanenitrile (**161f**) with triethyl orthoacetate and subsequent reaction with anhydrous $FeCl_3$ / AcOH following similar procedure described for for the compound (*E*)-3-benzylidenepiperidine-2, 6-dione (**162a**).



Yield: 75 %

Mp: 80-82 ^{o}C

IR (KBr): ν 3200-2860 (multiple bands), 1734, 1697, 1643 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 6.0 Hz), 1.22-1.40 (m, 8H), 1.42-1.56 (m, 2H), 2.20-2.31 (m, 2H), 2.58-2.73 (m, 4H), 7.01 (t, 1H, *J* = 7.2 Hz), 7.98 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.09. 20.96, 22.64, 28.46, 28.48, 29.07, 29.33, 31.50, 31.76, 125.95, 144.41, 166.45, 172.52.

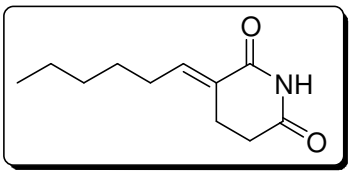
LCMS (m/z): 224 $(M+H)^{+}$

Analysis Calc'd. for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27.

Found: C, 69.82; H, 9.46; N, 6.33.

(*E*)-3-Hexylidenepiperidine-2, 6-dione (162g): The Johnson-Claisen rearrangement of of 3-hydroxy-2-methylene-3-octanenitrile (**161g**) with triethyl orthoacetate and subsequent

treatment with anhydrous $FeCl_3$ / AcOH following similar procedure described for for the compound (*E*)-3-benzylidenepiperidine-2, 6-dione (**162a**) provided the title compound.



Yield: 81%

Mp: 78-80 ^{o}C

IR (KBr): ν 3240-2860 (multiple bands), 1734, 1699, 1643 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, 3H, *J* = 6.8 Hz), 1.26-1.38 (m, 4H), 1.45-1.56 (m, 2H), 2.19-2.28 (m, 2H), 2.58-2.72 (m, 4H), 7.01 (t, 1H, *J* = 7.6 Hz), 8.42 (bs, 1H).

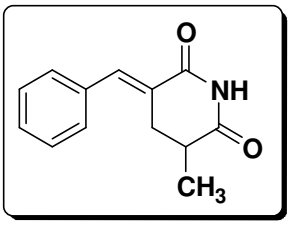
^{13}C NMR (100 MHz, $CDCl_3$): δ 13.98, 20.94, 22.45, 28.15, 28.40, 31.50, 125.95, 144.38, 166.46, 172.53.

LCMS (m/z): 196 $(M+H)^+$ 228 $(M+CH_3OH)^+$

Analysis Calc'd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17

Found. C, 67.74; H, 8.80; N, 7.15.

(*E*)-3-Benzylidene-5-methylpiperidine-2, 6-dione (162h): The Johnson-Claisen rearrangement of 3-hydroxy-2-methylene-3-phenylepropanenitrile (**161a**) with triethyl orthopropanoate followed by the reaction with anhydrous $FeCl_3$ / AcOH provided the title compound as colorless solid following similar procedure described for for the compound (*E*)-3-benzylidenepiperidine-2, 6-dione (**162a**).



Yield: 76 %

Mp: 136-138 ^{o}C

IR (KBr): ν 3170-2870 (multiple bands), 1716, 1684, 1624 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (d, 3H, *J* = 6.0 Hz), 2.59-2.71 (m, 2H), 3.10-3.21 (m, 1H), 7.35-7.48 (m, 5H), 7.91 (s, 1H), 8.20 (bs, 1H).

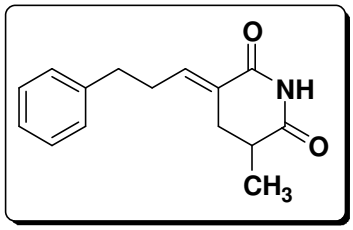
^{13}C NMR (100 MHz, 20% DMSO-d_6 in $CDCl_3$): δ 14.40, 29.49, 34.93, 126.30, 127.47, 127.87, 128.57, 133.56, 137.49, 165.98, 174.13.

LCMS (m/z): 216 $(M+H)^+$

Analysis Calc'd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51

Found: C, 72.56; H, 6.05; N, 6.58.

(*E*)-3-(3-Phenylpropylidene)-5-methylpiperidine-2, 6-dione (162i): This compound was obtained as colorless solid *via* the Johnson-Claisen rearrangement of 3-hydroxy-2-methylene-5-phenylpentanenitrile (**161e**) with triethyl orthoacetate and then reactioin with anhydrous $FeCl_3$ / AcOH following similar procedure described for the compound (*E*)-3-benzylidenepiperidine-2, 6-dione (**162a**).



Yield: 67%;

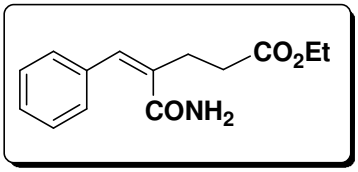
Mp: 108-110 ^oC

IR (KBr): ν 3195-2850 (multiple bands), 1716, 1691, 1641 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (d, 3H, *J* = 7.2 Hz), 2.07-2.20. (m, 1H), 2.25-2.39 (m, 1H), 2.50-2.66 (m, 3H), 2.73-2.90 (m, 2H),

	7.02 (t, 1H, *J* = 8.0 Hz), 7.14-7.22 (m, 3H), 7.25-7.32 (m, 2H), 8.02 (bs 1H).
^{13}C NMR (100 MHz, $CDCl_3$):	δ 15.43. 29.13, 30.33, 34.57, 36.11, 126.35, 127.17, 128.53, 140.59, 142.39, 166.36, 175.26.
MS (m/z):	244 $(M+H)^+$
Analysis Calc'd. for $C_{15}H_{17}NO_2$:	C, 74.05; H, 7.04; N, 5.76
Found:	C, 74.01; H, 7.09; N, 5.72.

(4*Z*)-4-Aminocarbonyl-5-phenylpent-4-enoate [II A (*Z*)]: To a stirred solution of 3-hydroxy-2-methylene-3-phenylpropanenitrile (**161a**) (1 mmol, 0.159 g) in triethyl orthoacetate (1 mL), propanoic acid (3 drops) was added and the reaction mixture was heated at 146 ^oC for 2 h. Reaction mixture was cooled to room temperature and excess orthoester and propanoic acid were distilled off under reduced pressure. The residue was diluted with dichloromethane (5 mL). Then conc. H_2SO_4 (1.5 mL) was added to this solution with stirring at 0 ºC and stirring continued for 4 h at room temperature. Reaction mixture was diluted with ice cold water (5 mL) and neutralized with aqueous K_2CO_3 solution slowly. The organic layer was separated and the aqueous layer was extracted with ether (2 X 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue, thus obtained was purified by column chromatography (silica gel, 40% ethyl acetate in hexanes) to provide (4*Z*)-4-aminocarbonyl-5-phenylpent-4-enoate [**II A (*Z*)**], 0.175 g) in 71 % yield.



Mp: 80-82 ºC.

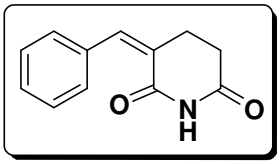
IR (KBr): ν 3350-2800 (multiple bands), 1728, 1651, 1631 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, 3H, *J* = 7.2 Hz), 2.59 (t, 3H, *J* = 7.2 Hz), 2.74 (t, 3H, *J* = 7.2 Hz), 4.15 (q, 2H, *J* = 7.2 Hz), 5.67 (d, 2H, *J* = 4.0 Hz), 6.57 (s, 1H), 7.20-7.40 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.33, 31.11, 33.05, 60.58, 128.07, 128.32, 128.57, 130.39, 135.36, 136.47, 172.00, 172.81.

LCMS (*m/z*): 248 $(M-H)^-$.

(*Z*)-3-Benzylidenepiperidine-2, 6-dione [(*Z*)-162]: To a stirred solution of (4*Z*)-4-aminocarbonyl-5-phenylpent-4-enoate [**IIA-(*Z*)**] (1 mmol, 0.247 g) in dry toluene (5 mL), NaH (4 mmol, 0.092 g) was added and the reaction mixture was stirred for 1 h under N_2 atmosphere. Then excess NaH was carefully quenched with very slow addition of ice cold water at 0 ºC. Organic layer was separated and aqueous layer was extracted with dichloromethane (2 X 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was removed and the residue was purified by column chromatography (silica gel, 35% ethyl acetate in hexanes) to provide (Z)-3-benzylidenepiperidine-2, 6-dione [**(*Z*)-162**] as a colorless solid in (0.165 g) 82 % yield.



Mp: 118-120 ºC

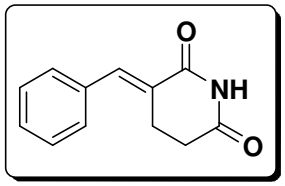
IR (KBr): ν 3200-2600 (multiple bands), 1714, 1684, 1645 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 2.70-2.78 (m, 4H), 6.97 (s, 1H), 7.27-7.40 (m, 3H), 7.51-7.55 (m, 2H), 8.40 (bs, 1H).

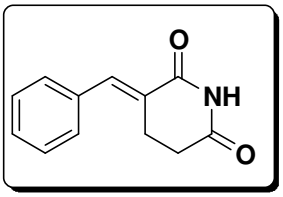
^{13}C NMR (100 MHz, $CDCl_3$): δ 30.45, 32.83, 125.89, 128.11, 129.13, 129.80, 134.27, 141.55, 165.07, 172.29.

LCMS (*m/z*): 202 $(M+H)^+$.

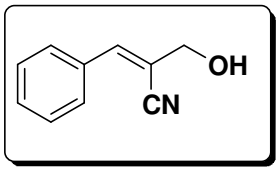
(*E*)-3-Benzylidenepiperidine-2,6-dione [(*E*)-162a] from (4*Z*)-4-aminocarbonyl-5-phenylpent-4-enoate [IIA (Z)]: To a stirred solution of (4*Z*)-4-aminocarbonyl-5-phenylpent-4-enoate [**II A (Z)],** 1 mmol, 0.247 g) in acetic acid (5 mL), was added anhydrous $FeCl_3$ (5 mmol, 0.812 g), and the reaction mixture was heated under reflux for 10 h. Reaction mixture was cooled to room temperature and acetic acid was removed under reduced pressure. The residue was dissolved in dichloromethane (5 mL) and poured into aqueous 4N HCl (5 mL). Organic layer was separated and aqueous layer extracted with dichloromethane (2 X 10 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution and water, and dried over anhydrous Na_2SO_4. Solvent was removed and the residue was purified by column chromatography (silica gel, 35 % ethyl acetate in hexanes) to provide (*E*)-3-benzylidenepiperidine-2,6-dione as a colorless solid (0. 141 g) in 70 % yield. Spectral data and melting point are in complete agreement with that of **(*E*)-162a** prepared from **161a**



(*E*)-3-Benzylidenepiperidine-2, 6-dione [(*E*)-162a] from (*Z*)-3-benzylidenepiperidine-2, 6-dione [(*Z*)-162]: To a stirred solution of (*Z*)-3-benzylidenepiperidine-2, 6-dione [**(*Z*)-162**] (1 mmol, 0.201 g) in acetic acid (5 mL), was added anhydrous $FeCl_3$ (5 mmol, 0.812 g), and the reaction mixture was heated under reflux for 10 h. Reaction mixture was cooled to room temperature and acetic acid was removed under reduced pressure. The residue was dissolved in dichloromethane (5 mL) and poured into aqueous 4N HCl (5 mL). Organic layer was separated and aqueous layer was extracted with dichloromethane (2 X 10 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution and water and dried over anhydrous Na_2SO_4. Solvent was removed and the residue was purified by column chromatography (silica gel, 35% ethyl acetate in hexanes) to provide 3-benzylidenepiperidine-2, 6-dione **[(*E*)-162a]** as a colorless solid (0.151g) in 74 % isolated yield. Spectral data and melting point are in complete agreement with that of **[(*E*)-162a]** prepared from **161a**.



(2*Z*)-2-Cyano-3-phenylprop-2-en-1-ol (163a): This compound was prepared according to the known procedure.[209] Aqueous sulfuric acid (20 %, 20 mL) was added with stirring to 3-hydroxy-2-methylene-3-phenylpropanenitrile (**161a**) (10 mmol, 1.59 g) at room temperature and the reaction mixture was heated under reflux for 2h. Then the reaction mixture was cooled to room temperature. Diethyl ether (20 mL) was added and the reaction mixture was washed



successively with aqueous saturated K_2CO_3 solution and water. Orainic layer was dried over anhydrous $NaHCO_3$. Solvent was evaporated and the residue thus obtained was purified purified by column chromatography (silicagel, 5 % ethyl acetate in hexanes) to furnish (2Z)-2-cyano-3-phenylprop-2-en-1-ol (**163a**) as colorless liquid in 60 % (0.954 g) isolated yield.

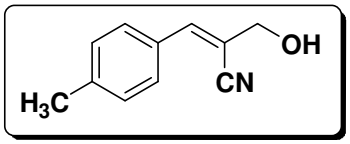
IR (Neat): ν 3396, 2216, 1626 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 2.82 (bs, 1H), 4.39 (s, 2H), 7.19(s, 1H), 7.37-7.44 (m, 3H), 7.71-7.77 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 64.19, 110.62, 117.82, 128.86, 130.51, 133.01, 143.95.

(2Z)-2-Cyano-3-(4-methylphenyl)prop-2-en-1-ol (163b) : This compound was obtained as a colorless liquid *via* the treatment of 3-hydroxy-2-methylene-3-(4-methylphenyl)propanenitrile (**161d**) with aqueous sulfuric acid at relux temperature, following the similar procedure described for the compound (2Z)-2-cyano-3-phenylprop-2-en-1-ol (**163a**)

Yield: 67 %

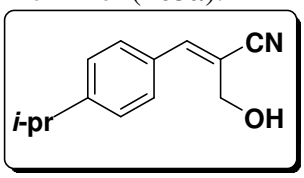


IR (Neat): ν 3406, 2214, 1608 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 2.42 (bs, 1H), 4.37 (s, 2H), 7.14 (s, 1H), 7.21 (d, 2H, J = 8.0 Hz), 7.65 (m, 2H, J = 8.0 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.35, 64.24, 109.19, 118.07, 128.86, 129.49, 130.27, 140.99, 144.02.

(2Z)-2-Cyano-3-(4-isopropyllphenyl)prop-2-en-1-ol (163c): Treatment of 3-hydroxy-2-methylene-3-(4-isopropylphenyl)propanenitrile (**161h**) with aqueous sulfuric acid at reflux temperature provided the rearranged alcohol **163c** a colorless liquid, following the similar procedure described for the compound (2Z)-2-cyano-3-phenylprop-2-en-1-ol (**163a**).



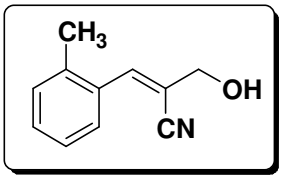
Yield: 64 %

IR (Neat): ν 3445, 2214, 1626 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (d, 6H, *J* = 6.4 Hz), 2.36 (t, 1H, *J* = 5.6 Hz), 2.90 (sept, 1H, *J* = 6.0 Hz), 4.39 (d, 2H, *J* = 7.0 Hz),7.16 (s, 1H), 7.27 (d, 2H, *J* = 8.0 Hz), 7.70 (d, 2H, *J* = 8.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 23.67, 34.05, 64.37, 109.33, 118.15, 126.98, 129.08, 130.68, 144.02, 151.90.

(2Z)-2-Cyano-3-(2-methylphenyl)prop-2-en-1-ol (163d): This rearranged alcohol was obtained as colorless liquid *via* the treatment of 3-hydroxy-2-methylene-3-(2-methylphenyl)propanenitrile (**161i**) with aqueous sulfuric acid following the similar procedure described for the compound (2Z)-2-cyano-3-phenylprop-2-en-1-ol (**163a**)



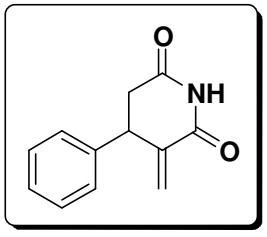
Yield: 65 %

IR (Neat): ν 3447, 2218, 1602 cm^{-1}

^{1}H NMR(400 MHz, $CDCl_3$): δ 2.33 (s, 3H), 2.44 (t, 1H, *J* = 6.0 Hz), 4.42 (d, 2H, *J* = 6.4 Hz), 7.18-7.47 (m, 3H), 7.44 (s, 1H), 7.80 (d, 1H, *J* = 7.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): 19.56, 63.75, 112.71, 117.61, 126.17, 127.65, 130.07, 130.35, 132.30, 137.05, 142.80.

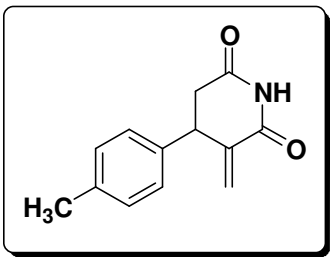
3-Methylidene-4-phenylpiperidine-2, 6-dione (164a): To a stirred solution of (2*Z*)-2-cyano-3-phenylprop-2-en-1-ol (**163a)** (1 mmol, 0.159 g) in triethyl orthoacetate (1 mL), propanoic acid (3 drops) was added and the reaction mixture was heated at 146 ^oC for 3 h. Reaction mixture was cooled to room temperature and excess orthoester and propanoic acid were distilled off under reduced pressure. Residue, thus obtained, was dissolved in acetic acid (5 mL). Anhydrous $FeCl_3$ (5 mmol, 0.812 g) was added and the reaction mixture was heated under reflux for 10 h. Then the reaction mixture was cooled to room temperature and acetic acid was removed under reduced pressure. The residue was dissolved in dichloromethane (5 mL) and poured into aqueous 4N HCl (5 mL). Organic layer was separated and aqueous layer was extracted with dichloromethane (2 X 10 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution and water and dried over anhydrous Na_2SO_4. Solvent was removed and the residue was purified by



column chromatography (silica gel, 35% ethyl acetate in hexanes) to provide 3-methylidene-4-phenylpiperidine-2, 6-dione (**164a**) as a colorless solid (0.127g) in 63 % yield.

Mp:	122-124 ^{o}C
IR (KBr):	ν 3185-2870 (multiple bands), 1739, 1699, 1635 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$):	δ 2.95 & 3.04 [dABq, 2H, *J* = 5.2 (8.8) Hz, and 16.8 Hz], 4.03-4.11 (m, 1H), 5.39 (s, 1H), 6.49 (s, 1H), 7.18-7.45 (m, 5H), 8.09 (bs, 1H).
^{13}C NMR (100 MHz, $CDCl_3$):	δ 38.15, 42.14, 127.35, 127.54, 127.81, 129.10, 138.64, 138.91, 165.70, 171.55.
LCMS (m/z):	200 $(M-H)^{-}$
Analysis: Calc'd. for $C_{12}H_{11}NO_2$:	C, 71.63; H, 5.51; N, 6.96
Found:	C, 71.52; H, 5.50; N, 6.99.

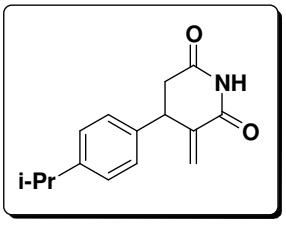
3-Methylidene-4-(4-methylphenyl)piperidine-2, 6-dione (164b): This molecule was obtained as colorless solid *via* the Johnson-Claisen rearrangement of (2*E*)-2-cyano-3-(4-methylphenyl)-prop-2-en-1-ol (**163b**) with triethyle orthoacetate followed by reaction with anhydrous $FeCl_3$ / AcOH following similar procedure described for for the compound 3-methylidene-4-phenylpiperidine-2, 6-dione (**164a**).



Yield: 67 %

Mp:	148-150 ^{o}C (Lit.[207] 152-154 ^{o}C).
IR (KBr):	ν 3185-2855 (multiple bands), 1728, 1697, 1628 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$):	δ 2.34 (s, 3H), 2.92 & 3.02 [dABq, 2H, *J* = 5.6 (9.2) Hz and 16.8 Hz], 4.00-4.12 (m, 1H), 5.38 (s, 1H), 6.47 (s, 1H), 7.08 (d, 2H, *J* = 8.0 Hz), 7.18, (d, 2H, *J* = 8.0 Hz), 8.17 (bs, 1H).
^{13}C NMR (100 MHz, $CDCl_3$):	δ 21.09, 38.32, 41.88, 127.33, 127.42, 129.84, 135.55, 137.66, 139.08, 165.45, 171.23.
LCMS (m/z):	214 $(M-H)^-$
Analysis Calc'd. for $C_{13}H_{13}NO_2$:	C, 72.54; H, 6.09; N, 6.51
Found:	C, 72.49; H, 6.06; N, 6.59.

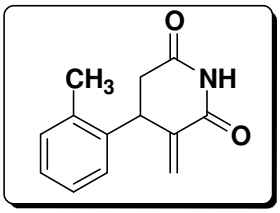
3-Methylidene-4-(4-isopropylphenyl)piperidine-2, 6-dione (164c): Johnson-Claisen rearrangement of (2*E*)-2-cyano-3-(4-isopropylphenyl)-prop-2-en-1-ol (**163c**) with triethyle orthoacetate and subsequent treatment with anhydrous $FeCl_3$ / AcOH gave the title compound as colorless silid, following similar procedure described for for the compound 3-methylidene-4-phenylpiperidine-2, 6-dione (**164a**).



Yield:	64 %
Mp:	128-130 ^{o}C
IR (KBr):	ν 3195-2875 (multiple bands), 1738, 1682, 1633 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$):	δ 1.24 (d, 6H, *J* = 7.2 Hz), 2.85-3.10 (m, 3H), 4.00-4.09 (m, 1H), 5.40 (s, 1H), 6.47 (s, 1H), 7.12 (d, 2H, *J* = 8.0 Hz), 7.22, (d, 2H, *J* = 8.0 Hz), 8.29 (bs, 1H).
^{13}C NMR (100 MHz, $CDCl_3$):	δ 23.93, 33.72, 38.19, 41.78, 127.11, 127.25, 127.42, 135.91, 139.03, 148.44, 165.87, 171.79.
LCMS (m/z):	244 $(M+H)^+$
Analysis Clac'd. for $C_{15}H_{17}NO_2$:	C, 74.05; H, 7.04; N, 5.76
Found:	C, 74.07; H, 7.06; N, 5.67.

3-Methylidene-4-(2-methylphenyl)piperidine-2, 6-dione (164d): This compound was obtained as colorless solid *via* the Johnson-Claisen rearrangement of (2*E*)-2-cyano-3-(2-methylphenyl)-prop-2-en-1-ol (**163d**) with triethyl orthoacetate followed by the treamnt with anhydrous $FeCl_3$ / AcOH following similar procedure described for for the compound 3-methylidene-4-phenylpiperidine-2, 6-dione (**164a**).



Yield:	70 %
Mp:	181-183 ^oC
IR (KBr):	ν 3190-2865 (multiple bands), 1724, 1699, 1631 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$):	δ 2.31 (s, 3H), 2.89 & 3.01 [dABq, 2H, *J* = 4.8 (12.0) Hz and 16.4 Hz], 4.18-4.28 (m, 1H), 5.11 (s, 1H), 6.43 (s, 1H), 7.00-7.31, (m, 4H), 8.31 (bs, 1H).

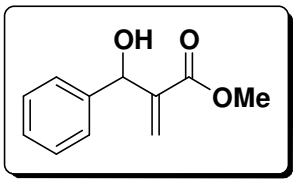
^{13}C NMR (100 MHz, $CDCl_3$): δ 19.42, 37.82, 38.19, 126.29, 126.87, 126.97, 127.75, 131.08, 136.47, 136.57, 138.50, 166.01, 171.81.

LCMS (m/z): 216 $(M+H)^+$

Analysis Calc'd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51

Found: C, 72.42; H, 6.11; N, 6.47.

Methyl 3-hydroxy-2-methylene-3-phenylpropanoate (165a): A mixture of DABCO (15 mol %, 30 mmol, 3.364 g), benzaldehyde (200 mmol, 21.224 g) and methyl acrylate (300 mmol, 25.824 g) was kept at room temperature for 7 days. (Reaction mixture was monitored by TLC). Reaction mixture was diluted with ether (100 mL) and washed successively with 2N HCl, aqueous $NaHCO_3$ solution and water. Organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue was distilled under reduced pressure to provide the methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**165a**) as colorless liquid in 78 % (15 g) yield.



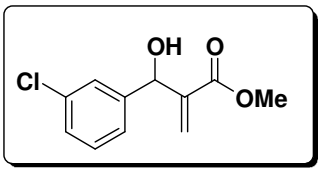
bp: 135-137 ^oC / 4.9mm

IR (Neat): ν 3410, 1714, 1630 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.99 (d, 1H, *J* = 5.8 Hz), 3.72 (s, 3H), 5.56 (d, 1H, *J* = 4.8 Hz), 5.83 (s, 1H), 6.34 (s, 1H), 7.27-7.45 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 51.43, 72.22, 125.17, 126.51, 127.38, 128.01, 141.33, 142.10, 166.34.

Methyl 3-(3-chlorophenyl)-3-hydroxy-2-methylenepropanoate (165b): This molecule was obtained as a colorless viscous liquid *via* the Baylis-Hillman reaction between 3-chlorobenzaldehyde and methyl acrylate catalyzed by DABCO following the similar procedure described for the molecule methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**165a**).



Reaction time: 8 days

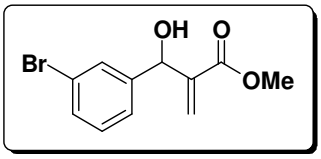
Yield: 65 %

IR (Neat): ν 3464, 1703, 1630 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 3.21 (d, 1H, J = 5.8 Hz), 3.73 (s, 3H), 5.50 (d, 1H, J = 5.8 Hz), 5.84 (s, 1H), 6.35 (s, 1H), 7.21-7.44 (m, 3H), 7.46-7.49 (m, 1H).

^{13}C NM (50 MHz, $CDCl_3$): δ 51.75, 71.83, 124.76, 126.00, 126.65, 127.65, 129.44, 133.98, 141.47, 143.46, 166.26.

Methyl 3-(3-bromophenyl)-3-hydroxy-2-methylenepropanoate (165c): This compound was obtained as colorless viscuss liquid *via* the reaction between 3-bromobenzaldehyde and methyl acrylate in the presence of DABCO (cat.), following the similar procedure described for the molecule methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**165a**).



Reaction time: 8 days

Yield: 70 %

IR (Neat): ν 3466, 1697, 1631 cm^{-1}

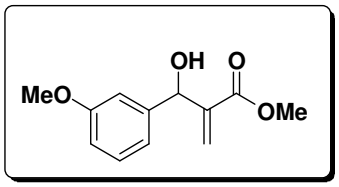
^1H NMR (400 MHz, $CDCl_3$): δ 3.22 (d, 1H, *J* = 5.8 Hz), 3.72 (s, 3H), 5.49 (d, 1H, *J* = 5.8 Hz), 5.84 (s, 1H), 6.35 (s, 1H), 7.15-7.30 (m, 2H), 7.35-7.41 (s, 1H), 7.48-7.52 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 51.72, 71.64, 122.14, 125.20, 125.97, 129.49, 129.68, 130.51, 141.35, 143.63, 166.12.

3-Methyl-3-(3-methoxyphenyl)-3-hydroxy-2-methylenepropanoate (165d): This alcohol was obtained as colorless liquid *via* the reaction between 3-methoxybenzaldehyde and methyl acrylate, catalyzed by DABCO following the similar procedure described for the molecule methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**165a**).

Reaction time: 12 days

Yield: 63 %

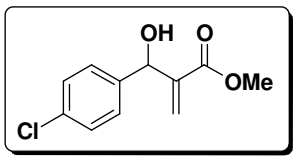


IR (Neat): ν 3464, 1720, 1601 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 3.09 (d, 1H, *J* = 5.8 Hz), 3.73 (s, 3H), 3.80 (s, 3H), 5.43 (d, 1H, *J* = 5.8 Hz), 5.83 (s, 1H), 6.33 (s, 1H), 6.78-6.87 (m, 1H), 6.91-6.98 (m, 2H), 7.20-7.26 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 51.75, 55.02, 72.63, 112.10, 113.17, 118.89, 125.78, 129.25, 141.96, 143.00, 159.52, 166.60.

Methyl 3-(4-chlorophenyl)-3-hydroxy-2-methylenepropanoate (165e): This molecule was prepared as a colorless solid *via* the DABCO catalyzed Baylis-Hillman reaction betwee 4-chlorobenzaldehyde and methyl acrylate following the similar procedure described for the molecule methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**165a**).



Reaction time: 7 days

Yield: 76 %

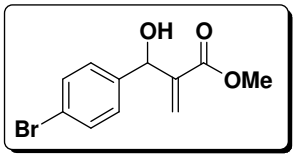
Mp: 46-48 ^{o}C

IR (KBr): ν 3464, 1716, 1630 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.16 (d, 1H, *J* = 4.6 Hz), 3.72 (s, 3H), 5.51 (d, 1H, *J* = 5.8 Hz), 5.83 (s, 1H), 6.33 (s, 1H), 7.29-7.33 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 51.65, 71.66, 125.59, 127.96, 128.20, 133.15, 139.87, 141.72, 166.24.

Methyl 3-(4-bromophenyl)-3-hydroxy-2-methylenepropanoate (165f): This molecule was obtained as a colorless solid via DABCO catalyzed Baylis-Hillman reaction between 4-bromobenzaldehyde and methyl acrylate following the similar procedure described for the molecule methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**165a**).



Reaction time: 7 days

Yield: 71 %

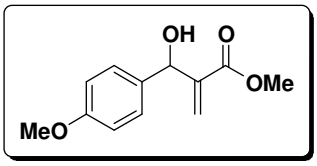
Mp: 48-50 ^{o}C

IR (KBr): ν 3335, 1718, 1633 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 3.13 (d, 1H, *J* = 5.6 Hz), 3.72 (s, 3H), 5.50 (d, 1H, *J* = 4.8 Hz), 5.82 (s, 1H), 6.34 (s, 1H), 7.25 (d, 2H, *J* = 8.0 Hz), 7.46 (d, 2H, *J* = 8.0 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 52.06, 72.60, 121.76, 126.33, 128.38, 131.53, 140.41, 141.65, 166.62.

Methyl 3-(4-methoxyphenyl)-3-hydroxy-2-methylenepropanoate (165g): This compound was prepared as a colorless solid, *via* the reaction between 4-methoxybenzaldehyde and methyl acrylate under the influence of DABCO as a catalyst, following the similar procedure described for the molecule methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**165a**).



Reaction time: 10 days

Yield: 72 %

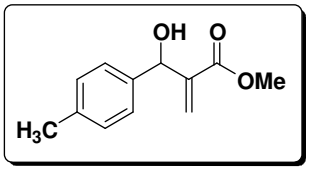
Mp: 60-62 °C

IR (KBr): ν 3346, 1716, 1610 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 3.06 (d, 1H, *J* = 4.8 Hz), 3.69 (s, 3H), 3.77 (s, 3H), 5.49 (d, 1H, *J* = 4.0 Hz), 5.85 (s, 1H), 6.30 (s, 1H), 6.85 (d, 2H, *J* = 8.8 Hz), 7.26 (d, 2H, *J* = 8.8 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 51.89, 55.26, 72.75, 113.87, 125.54, 127.94, 133.57, 142.32, 159.28, 166.82.

Methyl 3-(4-methylphenyl)-3-hydroxy-2-methylenepropanoate (165h): This molecule was obtained as a colorless solid *via* the reaction between 4-methylbenzaldehyde and methyl acrylate, in the presence of DABCO (cat.) following the similar procedure described for the molecule methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**165a**)



Reaction time: 8 days

Yield: 76 %

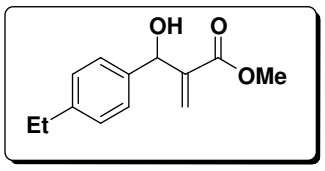
Mp: 44-46 ^{o}C

IR (KBr): ν 3437, 1720, 1630 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 3H), 2.94 (d, 1H, *J* = 6.0 Hz), 3.71 (s, 3H), 5.52 (d, 1H, *J* = 6.0 Hz), 5.84 (s, 1H), 6.32 (s, 1H), 7.15 (d, 2H, *J* = 8.0 Hz), 7.24 (d, 2H, *J* = 8.0 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.84, 51.55, 72.29, 125.10, 126.48, 128.81, 137.11, 138.39, 142.20, 166.48.

Methyl 3-hydroxy-3-(4-ethylphenyl)-2-methylenepropanoate (165i): This compound was prepared as a colorless viscous liquid *via* the treatment of 4-ethylbenzaldehyde with methyl acrylate in the presence of DABCO (cat.) following the similar procedure described for the molecule methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**165a**)



Reaction time: 8 days

Yield: 67 %

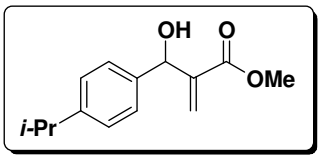
bp: 163-165 ^{o}C / 3.6 mm

IR (Neat): ν 3466, 1716, 1631 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, 3H, *J* = 7.6 Hz), 2.61 (q, 2H, *J* = 7.6 Hz), 3.03 (bs, 1H) 3.70 (s, 3H), 5.52 (s, 1H), 5.85 (s, 1H), 6.31 (s, 1H), 7.16 (d, 2H, *J* = 8.0 Hz), 7.27 (d, 2H, *J* = 8.0 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 15.38, 28.44, 51.72, 72.70, 125.44, 126.60, 127.79, 138.68, 142.23, 143.68, 166.68.

Methyl 3-hydroxy-3-(4-isopropylphenyl)-2-methylenepropanoate (165j): Treatment of 4-isopropylbenzaldehyde with methyl acrylate in the presence of DABCO (cat.), following a similar procedure described for the molecule methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**165a**) provided the title compound **165j** as a colorless viscous liquid.



Reaction time: 8 days

Yield: 70 %

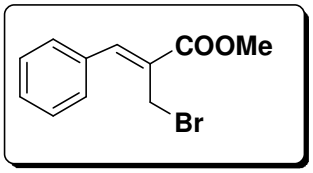
bp: 163-165 ^{o}C / 3.6 mm

IR (neat): ν 3466, 1716, 1631 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (d, 6H, *J* = 6.8 Hz), 2.84 (sept, 1H, *J* = 6.8 Hz), 2.94 (bs, 1H) 3.71 (s, 3H), 5.53 (s, 1H), 5.85 (s, 1H), 6.32 (s, 1H), 7.19 (d, 2H, *J* = 8.0 Hz), 7.28 (d, 2H, *J* = 8.0 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 23.75, 33.60, 51.58, 72.39, 125.20, 126.22, 126.56, 138.73, 142.20, 148.10, 166.53.

Methyl (2*Z*)-2-(bromoethyl)-3-phenylprop-2-enoate (166a): Hydrobromic acid (48 %, 3.3mL) was added to a stirred solution of methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**165a**) (20 mmol, 3.84 g) in dichloromethane (30 mL) followed by a dropwise addition of concentrated sulfuric acid (2.9 mL) at 0 °C. Then the reaction mixture was stirred for 12h at room temperature. The reaction mixture was poured into ice cold water. Organic layer was separated and the aqueous layer was extracted with ether (3 × 30 mL). Combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue thus obtained was purified by column chromatography (3 % EtOAc in hexanes) to provide methyl (2*Z*)-2-(bromoethyl)-3-phenylprop-2-enoate (**166a**) in 91 % (3.7 g) yield as colorless oil.



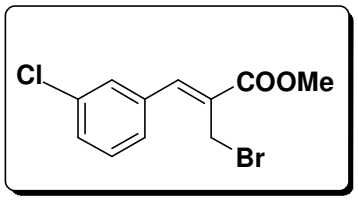
IR (Neat): ν 1720, 1626 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3H), 4.40 (s, 2H), 7.37-7.52 (m, 3H), 7.52-7.63 (m, 2H), 7.82 (s, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.52, 52.01, 128.37, 128.57, 129.32, 134.22, 142.47, 166.05.

Methyl (2*Z*)-2-(bromoethyl)-3-(3-chlorophenyl)prop-2-enoate (166b) : This compound was obtained by the reaction of methyl 3-hydroxy-2-methylene-3-(3-

chlorophenyl)propanoate (**165b**) with 48 % hydrobromic acid in the presence of concentrated sulfuric acid following similar procedure described for the molecule methyl (2*Z*)-2-(bromoethyl)-3-phenylprop-2-enoate (**166a**).



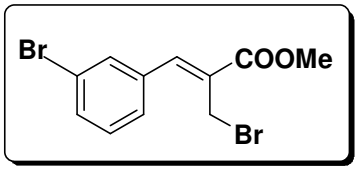
Yield: 80 %

IR (Neat): ν 1716, 1624 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.88 (s, 3H), 4.34 (s, 2H), 7.34-7.55 (m, 4H), 7.74 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.91, 52.43, 127.33, 129.25, 129.39, 129.90, 130.05, 134.68, 135.80,140.92, 165.97.

Methyl (2*Z*)-2-(bromoethyl)-3-(3-bromophenyl)prop-2-enoate (166c): This allylbromide was obtained via the reaction of methyl 3-hydroxy-2-methylene-3-(3-bromophenyl)propanoate (**165c**) with of HBr/H_2SO_4 following similar procedure described for the molecule methyl (2*Z*)-2-(bromoethyl)-3-phenylprop-2-enoate (**166a**).



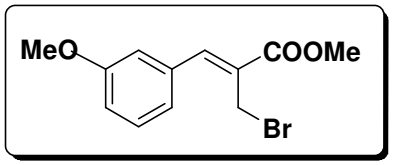
Yield: 86 %

IR (Neat): ν 1716, 1626 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.88 (s, 3H), 4.34 (s, 2H), 7.30-7.38 (m, 1H), 7.48-7.57 (m, 2H), 7.69 (s, 1H), 7.73 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.91, 52.47, 122.82, 127.74, 129.98, 130.29, 132.21, 132.33, 136.11, 140.87, 166.00.

Methyl (2*Z*)-2-(bromoethyl)-3-(3-methoxyphenyl)prop-2-enoate (166d) :This molecule was obtained as colorless liquid via reaction of methyl 3-hydroxy-2-methylene-3-(3-methoxyphenyl)propanoate (**165d**) with HBr/H_2SO_4 following similar procedure described for the molecule methyl (2*Z*)-2-(bromoethyl)-3-phenylprop-2-enoate (**166a**).



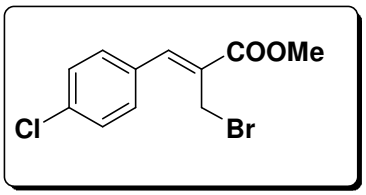
Yield: 87 %

IR (Neat): ν 1716, 1626 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 2.85 (s, 3H), 3.88 (s, 3H), 4. 40 (s, 2H), 6.92-7.02 (m, 1H), 7.10-7.19 (m, 2H), 7.31-7.40 (m, 1H), 7.80 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.76, 52.18, 55.09, 114.06, 115.59, 121.87, 128.59, 129.68, 135.24, 142.69, 159.59, 166.19.

Methyl (2*Z*)-2-(bromoethyl)-3-(4-chlorophenyl)prop-2-enoate (166e) : This allyl bromide was obtained as colorless liquid via reaction of methyl 3-hydroxy-2-methylene-3-(4-chlorophenyl)propanoate (**165e**) with 48 % hydrobromic acid in the presence of concentrated sulfuric acid following similar procedure described for the molecule methyl (2*Z*)-2-(bromoethyl)-3-phenylprop-2-enoate (**166a**).



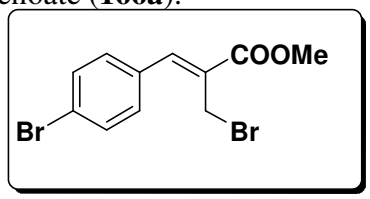
Yield: 82 %

IR (Neat): ν 1720, 1628 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3H), 4.35 (s, 2H), 7.42 (d, 2H, J = 6.8 Hz), 7.50 (d, 2H, J = 6.8 Hz), 7.76 (s, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.23, 52.40, 129.03, 130.82, 132.47, 135.58, 141.28, 166.12.

Methyl (2*Z*)-2-(bromoethyl)-3-(4-bromophenyl)prop-2-enoate (166f) : This compound was prepared via the reaction of methyl 3-hydroxy-2-methylene-3-(4-bromophenyl)propanoate (**165f**) with HBr/H_2SO_4, following similar procedure described for the molecule methyl (2*Z*)-2-(bromoethyl)-3-phenylprop-2-enoate (**166a**).



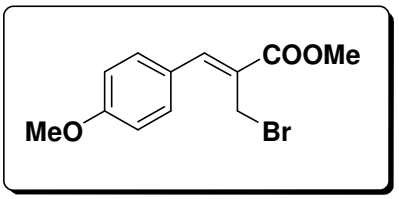
Yield: 78 %

IR (Neat): ν 1712, 1614 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3H), 4.34 (s, 2H), 7.44 (d, 2H, *J* = 8.4 Hz), 7.60 (d, 2H, *J* = 8.4 Hz), 7.74 (s, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 26.30, 52.59, 124.10, 129.21, 131.09, 132.14, 133.01, 141.54, 166.31.

Methyl (2*Z*)-2-(bromoethyl)-3-(4-methoxyphenyl)prop-2-enoate (166g): This allyl bromide was obtained as colorless liquid by the treatment of methyl 3-hydroxy-2-methylene-3-(4-methoxyphenyl)propanoate (**165g**) with HBr/H_2SO_4, following similar procedure described for the molecule methyl (2*Z*)-2-(bromoethyl)-3-phenylprop-2-enoate (**166a**).



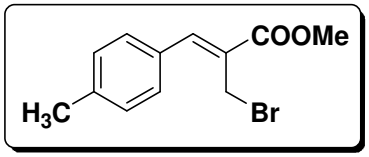
Yield: 75 %

IR (Neat): ν 1701, 1626 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.85 (s, 3H), 3.86 (s, 3H), 4. 44 (s, 2H), 6.98 (d, 2H, *J* = 8.0 Hz), 7.57 (d, 2H, *J* = 8.0 Hz), 7.78 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 27.39, 52.06, 55.12, 114.21, 125.83, 126.43, 131.80, 142.61, 160.66, 166.56.

Methyl (2*Z*)-2-(bromoethyl)-3-(4-methylphenyl)prop-2-enoate (166h) : This compound was prepared via reaction of methyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate (**165h**) with hydrobromic acid and concentrated sulfuric acid following similar procedure described for the molecule methyl (2*Z*)-2-(bromoethyl)-3-phenylprop-2-enoate (**166a**)



Yield: 79 %

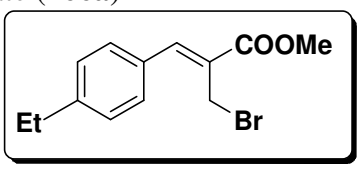
IR (Neat): ν 1718, 1626 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 3.87 (s, 3H), 4.41 (s, 2H), 7.29 (d, 2H, *J* = 7.6 Hz)), 7.46 (m, 2H, *J* = 7.6 Hz), 7.80 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.96, 26.74, 51.82, 127.21, 129.20, 129.49, 130.29, 139.58, 142.49, 166.02.

Methyl (2*Z*)-2-(bromoethyl)-3-(4-ethylphenyl)prop-2-enoate (166i): This molecule was obtained as colorless liquid by the reaction of methyl 3-hydroxy-2-methylene-3-(4-

ethylphenyl)propanoate (**165i**) with HBr/H_2SO_4, following similar procedure described for the molecule methyl (2*Z*)-2-(bromoethyl)-3-phenylprop-2-enoate (**166a**)



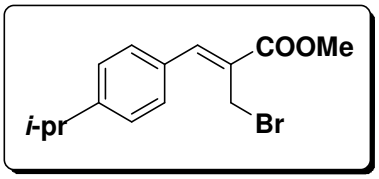
Yield: 83 %

IR (Neat): ν 1716, 1624 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 1.22 (d, 3H, *J* = 7.6 Hz) 2.65 (q, 2H, *J* = 7.6 Hz), 3.85 (s, 3H), 4.41 (s, 2H), 7.27 (d, 2H, *J* = 8.0 Hz)), 7.50 (m, 2H, *J* = 8.08 Hz), 7.79 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 15.19, 27.05, 28.70, 52.28, 127.65, 128.37, 129.93, 131.58, 143.03, 146.28, 166.65.

Methyl (2*Z*)-2-(bromoethyl)-3-(4-isopropylphenyl)prop-2-enoate (166j) : Treatment of methyl 3-hydroxy-2-methylene-3-(4-isopropylphenyl)propanoate (**165j**) with HBr/H_2SO_4 provided the title compound **166j** as colorless liquid following similar procedure described for the molecule methyl (2*Z*)-2-(bromoethyl)-3-phenylprop-2-enoate (**166a**).



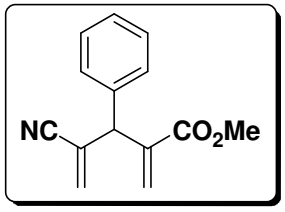
Yield: 81%

IR (neat): ν 1716, 1624 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (d, 6H, J = 6.8 Hz) 2.92 (sept, 1H, *J* = 6.8 Hz), 3.87 (s, 3H), 4.43 (s, 2H), 7.32 (d, 2H, *J* = 8.0 Hz)), 7.53 (d, 2H, *J* = 8.0 Hz), 7.82 (s, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 23.54, 26.93, 33.84, 52.09, 126.82, 127.53, 129.85, 131.58, 142.78, 150.67, 166.41.

4-Cyano-2-methoxycarbonyl-3-phenylpenta-1,4-diene (167a): A mixture of DABCO (8 mmol, 0.896 g), (2*Z*)- 2-(bromomethyl)-3-phenylprop-2-enoate (**166a**) (4 mmol, 1.02 g) in acrylonitrile (4 mL) was kept at room temperature for 7 days. (Reaction mixture was monitored by TLC). Then the reaction mixture was diluted with ether (30 mL) and washed successively with 2N solution, water and aqueous $NaHCO_3$ solution. The Organic layer was dried over anhydrous Na_2SO_4. Solvent was removed and the residue thus obtained was purified by column chromatography (4 % ethylacetate in hexanes) to give 4-cyano-2-methoxycarbonyl-3-phenylpenta-1,4-diene (**167a**) as a colorless viscous liquid in 68 % (0.608 g) yield.



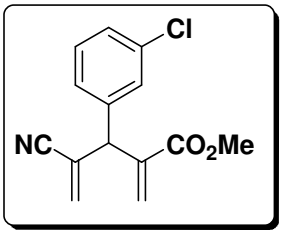
IR (Neat): 2224, 1724, 1630 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.73 (s, 3H), 4.94 (s, 1H), 5.60 (d, 1H, *J* = 1.6 Hz), 5.63 (d, 1H, *J* = 1.6 Hz), 6.08 (d, 1H, *J* = 0.8 Hz), 6.56 (s, 1H), 7.16-7.41 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 50.32, 51.96, 117.94, 124.15, 127.65, 128.30, 128.47, 128.67, 132.40, 136.60, 139.12, 165.83.

3-(3-Chlorophenyl)-4-cyano-2-methoxycarbonylpenta-1,4-diene (167b) : This molecule was obtained *via* the treatment of (2*Z*)-2-(bromomethyl)-3-(3-chlorophenyl)prop-2-enoate

(**166b**) with acrylonitrile under the influence of DABCO following the similar procedure described for the molecule 4-cyano-2-methoxycarbonyl-3-phenylpenta-1,4-diene (**167a**) as a colorless viscous liquid.



Reaction time: 7 days

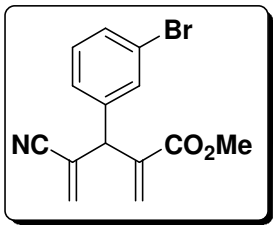
Yield: 61 %

IR (Neat): 2226, 1724, 1631 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.74 (s, 3H), 4.92 (s, 1H), 5.62 (s, 1H), 5.66 (s, 1H), 6.11 (s, 1H), 6.59 (s, 1H), 7.06-7.36 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 50.19, 52.28, 117.80, 123.96 126.90, 128.18, 128.81, 130.17, 133.08, 134.85, 138.88, 139.02, 165.85.

3-(3-Bromophenyl)-4-cyano-2-methoxycarbonylpenta-1,4-diene (167c) : This 1,4-pentadiene was obtained as colorless liquid *via* the treatment of (2*Z*)-2-(bromomethyl)-3-(3-bromophenyl)prop-2-enoate (**166c**) with acrylonitrile, catalysed by DABCO, following the similar procedure described for the molecule 4-cyano-2-methoxycarbonyl-3-phenylpenta-1,4-diene (**167a**) as a colorless viscous liquid.



Reaction time: 7 days

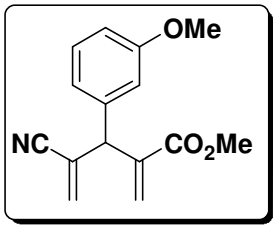
Yield: 60 %

IR (Neat): 2224, 1720, 1631 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75 (s, 3H), 4.91 (s, 1H), 5.62 (s, 1H), 5.66 (s, 1H), 6.12 (s, 1H), 6.60 (s, 1H), 7.12-7.18 (m, 1H), 7.20-7.28 (m, 1H), 7.33(s, 1H), 7.43(d, 1H, *J* = 8.0 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 50.10, 52.40, 117.87, 123.01, 123.89, 127.36, 129.05, 130.49, 131.16, 131.72, 133.08, 138.73, 139.17, 165.88.

3-(3-Methoxyphenyl)-4-cyano-2-methoxycarbonylpenta-1,4-diene (167d): This molecule was obtained via treatment of (2Z)-2-(bromomethyl)-3-(3-methoxyphenyl)prop-2-enoate (**166d**) with acrylonitrile under the influence of DABCO, following the similar procedure described for the molecule 4-cyano-2-methoxycarbonyl-3-phenylpenta-1,4-diene (**167a**) as a colorless viscous liquid.



Reaction time: 7 days

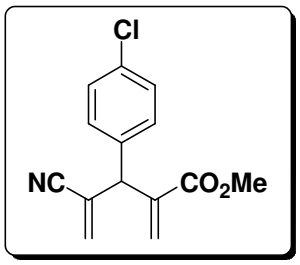
Yield: 65 %

IR (Neat): 2224, 1724, 1631 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.73 (s, 3H), 3.78 (s, 3H), 4.91 (s, 1H), 5.61 (d, 1H, *J* = 1.6 Hz), 5.64 (d, 1H, *J* = 1.6 Hz), 6.07 (s, 1H), 6.55 (s, 1H), 6.70-6.86 (m, 3H), 7.24-7.30 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 50.44, 52.28, 55.19, 113.04, 114.72, 118.19, 120.98, 124.28, 128.64, 129.88, 132.69, 138.25, 139.12, 159.96, 166.12

3-(4-Chlorophenyl)-4-cyano-2-methoxycarbonylpenta-1,4-diene (167e): This molecule was obtained via the reaction between (2*Z*)-2-(bromomethyl)-3-(4-chlorophenyl)prop-2-enoate (**166e**) and acrylonitrile in the presence of DABCO following the similar procedure described for the molecule 4-cyano-2-methoxycarbonyl-3-phenylpenta-1,4-diene (**167a**) as a colorless viscous liquid.



Reaction time: 7 days

Yield: 67 %

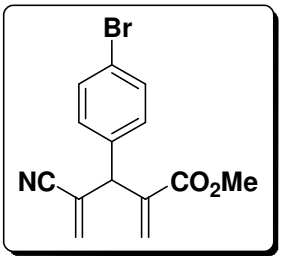
IR (Neat): 2226, 1724, 1631 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.73 (s, 3H), 4.91 (s, 1H), 5.61 (d, 1H, *J* = 1.6 Hz), 5.65 (d, 1H, *J* = 1.6 Hz), 6.10 (d, 1H, *J* = 0.8 Hz), 6.57 (s, 1H), 7.14 (d, 2H, *J* = 6.0 Hz), 7.33 (d, 2H, *J* = 6.0 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 50.00, 52.38, 117.94, 124.13, 128.76, 129.18, 130.07, 132.91, 133.95, 135.41, 139.02. 165.97

3-(4-Bromophenyl)-4-cyano-2-methoxycarbonylpenta-1,4-diene (167f): This compound was obtained as colorless liquid *via* the reaction between (2*Z*)-2-

(bromomethyl)-3-(4-bromophenyl)prop-2-enoate (**166f**) and acrylonitrile under the influence of DABCO following the procedure described for the molecule 4-cyano-2-methoxycarbonyl-3-phenylpenta-1,4-diene (**167a**) as a colorless viscous liquid.



Reaction time: 7 days

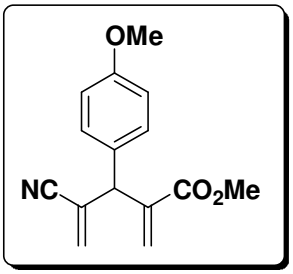
Yield: 60 %

IR (Neat): 2224, 1722, 1631 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 3.73 (s, 3H), 4.90 (s, 1H), 5.61 (s, 1H), 5.65 (s, 1H), 6.10 (s, 1H), 6.57 (s, 1H), 7.08 (d, 2H, *J* = 8.4 Hz), 7.46 (d, 2H, *J* = 8.4 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 50.02, 52.38, 117.92, 122.04, 123.98, 128.79, 130.39, 132.11, 132.96, 135.89, 138.90. 165.92

3-(4-Methoxylphenyl)-4-cyano-2-methoxycarbonylpenta-1,4-diene (167g): Reaction between (2*Z*)-2-(bromomethyl)-3-(4-methoxylphenyl)prop-2-enoate (**166g**) and acrylonitrile catalyzed by DABCO, gave this compound as a colorless viscous liquid, following the similar procedure described for the molecule 4-cyano-2-methoxycarbonyl-3-phenylepenta-1,4-diene (**167a**).



Reaction time: 7 days

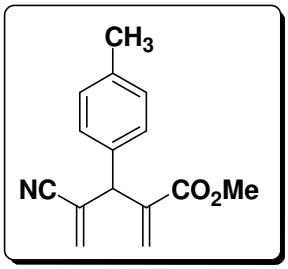
Yield: 62 %

IR (Neat): 2224, 1724, 1612 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.73, (s, 3H), 3.79 (s, 3H), 4.88 (s, 1H), 5.59 (s, 1H), 5.62 (s, 1H), 6.04 (s, 1H), 6.53 (s, 1H), 6.88 (d, 2H, *J* = 8.8 Hz), 7.10 (d, 2H, *J* = 8.8 Hz)

^{13}C NMR (50 MHz, $CDCl_3$): δ 49.98, 52.18, 55.29, 114.43, 118.26, 125.00, 128.13, 128.76, 129.81, 132.16, 139.78, 159.35, 165.24.

3-(4-Methylpylphenyl)-4-cyano-2-methoxycarbonylpenta-1,4-diene (167h): DABCO catalyzed reaction between (2*Z*)-2-(bromomethyl)-3-(4-methylphenyl)prop-2-enoate (**166h**) and acrylonitrile, provided the title compound **167h** as colorless liquid, following the similar procedure described for the molecule 4-cyano-2-methoxycarbonyl-3-phenylepenta-1,4-diene (**167a**).



Reaction time: 7 days

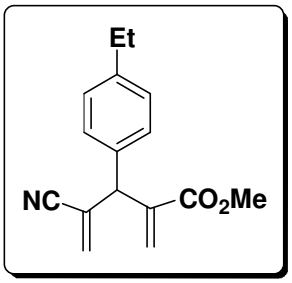
Yield: 69 %

IR (Neat): 2224, 1724, 1631 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33, (s, 3H), 3.73 (s, 3H), 4.90 (s, 1H), 5.59 (s, 1H), 5.63 (s, 1H), 6.06 (s, 1H), 6.54 (s, 1H), 7.07 (d, 2H, *J* = 8.0 Hz), 7.15 (d, 2H, *J* = 8.0 Hz)

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.89, 50.12, 52.09, 118.14, 124.54, 128.25, 128.47, 129.49, 132.30, 133.61, 137.47, 139.39, 166.07.

3-(4-Ethylphenyl)-4-cyano-2-methoxycarbonylpenta-1,4-diene (167i): This 1,4-pentadiene was prepared *via* the reaction between (2*Z*)-2-(bromomethyl)-3-(4-ethylphenyl)prop-2-enoate (**166i**) and acrylonitrile in the presence of DABCO following the similar procedure described for the molecule 4-cyano-2-methoxycarbonyl-3-phenylepenta-1,4-diene (**167a**) as a colorless viscous liquid.



Reaction time: 7 days

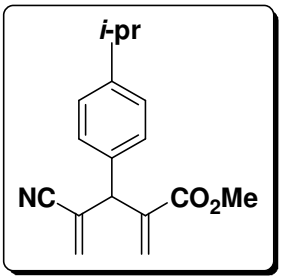
Yield: 66 %

IR (Neat): 2224, 1724, 1631 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, 3H, *J* = 7.6 Hz), 2.61 (q, 2H, *J* = 7.6 Hz), 3.72 (s, 3H), 4.91 (s, 1H), 5.60 (s, 1H), 5.63 (s, 1H), 6.05 (s, 1H), 6.54 (s, 1H), 7.10 (d, 2H, *J* = 8.0 Hz), 7.20 (d, 2H, *J* = 8.0 Hz)

^{13}C NMR (50 MHz, $CDCl_3$): δ 15.29, 28.39, 50.19, 52.23, 118.28, 124.66, 128.37, 128.62, 132.45, 133.86, 139.46, 143.88, 166.22

3-(4-Isopropylphenyl)-4-cyano-2-methoxycarbonylpenta-1,4-diene (167j): This molecule was obtained via the reaction of (2*Z*)-2-(bromomethyl)-3-(4-isopropylphenyl) prop-2-enoate (**166j**) with acrylonitrile in the presence of DABCO (cat.), following the similar procedure described for the molecule 4-cyano-2-methoxycarbonyl-3-phenylepenta-1,4-diene (**167a**) as a colorless viscous liquid.



Reaction time: 7 days

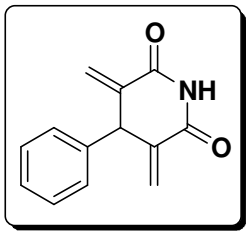
Yield: 68 %

IR (Neat): 2224, 1726, 1631 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 1.25 (d, 6H, *J* = 7.2 Hz), 2.88 (sept, 1H, *J* = 7.2 Hz), 3.73 (s, 3H), 4.91 (s, 1H), 5.60 (s, 1H), 5.63 (s, 1H), 6.06 (s, 1H), 6.54 (s, 1H), 7.10 (d, 2H, *J* = 7.6 Hz), 7.20 (d, 2H, *J* = 7.6 Hz)

^{13}C NMR (50 MHz, $CDCl_3$): δ 23.85, 33.70, 50.29, 52.16, 118.26, 124.83, 126.94, 128.35, 128.62, 132.28, 134.10 139.65, 148.51 166.24

3, 5-Dimethylidene-4-phenylpiperidine-2, 6-dione (168a): To a stirred solution of 4-cyano-2-methoxycarbonyl-3-phenylpenta-1,4-diene (**167a**) (1 mmol, 0.227 g) in acetic acid (5 mL), anhydrous $FeCl_3$ (5 mmol, 0.812 g) was added and the reaction mixture was heated under reflux for 5 h. Then the reaction mixture was cooled to room temperature and acetic acid was removed under reduced pressure. The residue was dissolved in dichloromethane (5 mL) and poured into aqueous 4N HCl (5 mL). Organic layer was separated and aqueous layer was extracted with dichloromethane (2 X 10 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution and water, and dried over anhydrous Na_2SO_4. Solvent was removed and the residue was purified by column chromatography



(silica gel, 35 % ethyl acetate in hexanes) to provide 3, 5-dimethylidene-4-phenylpiperidine-2, 6-dione (**168a**) as a colorless solid (0.175 g) in 82 % yield.

Mp: 178-180 ^{o}C (Lit[211] 177-178 ^{o}C).

IR (KBr): ν 3195-2885 (multiple bands), 1716, 1697, 1639 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.74 (s, 1H), 5.68 (s, 2H), 6.49 (s, 2H), 7.15-7.40 (m, 5H), 7.98 (bs, 1 H).

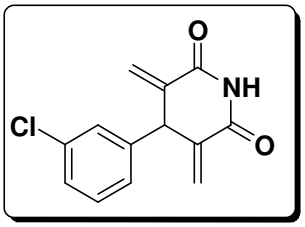
^{13}C NMR (100 MHz, 20% DMSO-d_6 in $CDCl_3$): δ 48.47, 124.42, 125.99, 126.19, 127.59, 136.81, 137.70, 164.43.

LCMS m/z): 214 $(M+H)^{+}$

Analysis Calc'd. for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57

Found: C, 73.32; H, 5.21; N, 6.63.

3, 5-Dimethylidene-4-(3-chlorophenyl)piperidine-2, 6-dione (168b): This molecule was obtained as colorless solid by the reaction of 4-cyano-2-methoxycarbonyl-3-(3-chlorophenyl)penta-1,4-diene (**167b**) with $FeCl_3$ / AcOH following similar procedure described for 3, 5-dimethylidene-4-phenylpiperidine-2, 6-dione (**168a**).



Yield: 80 %

Mp: 176-178 ^{o}C

IR (KBr): ν 3190-2855 (multiple bands), 1701, 1637 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.72 (s, 1H), 5.71 (s, 2H), 6.52 (s, 2H), 7.03-7.12

(m, 1H), 7.18 (s, 1H), 7.23-7.33 (m, 2H), 8.06 (bs, 1 H)

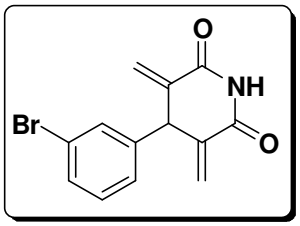
^{13}C NMR (100 MHz, 20% DMSO-d_6 in $CDCl_3$): δ 48.45, 124.66, 125.49, 126.42, 126.72, 129.34, 133.57, 136.37, 140.09, 164.49

LCMS (m/z): 246 $(M-H)^-$, 248 $(M+2-H)^-$

Analysis Calc'd. for $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; N, 5.66

Found: C, 63.01; H, 4.11; N, 5.68.

3, 5-Dimethylidene-4-(3-bromophenyl)piperidine-2, 6-dione (168c): This compound was prepared by the reaction of 4-cyano-2-methoxycarbonyl-3-(3-bromolphenyl)penta-1,4-diene (**167c**) with $FeCl_3$ / AcOH, as colorless solid following similar procedure described for 3,5-dimethylidene-4-phenylpiperidine-2, 6-dione (**168a**).



Yield: 86 %

Mp: 192-194 ^oC

IR (KBr): ν 3195-2850 (multiple bands), 1699, 1639 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.72 (s, 1H), 5.71 (s, 2H), 6.52 (s, 2H), 7.12 (d, 1H, *J* = 7.6 Hz), 7.20-7.25 (m, 1H), 7.33 (s, 1H), 7.43 (d, 1H, *J* = 8.0 Hz), 7.99 (bs, 1 H).

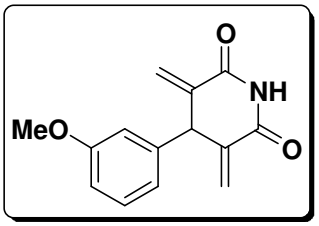
^{13}C NMR (100 MHz, 20% DMSO-d_6 in $CDCl_3$): δ 47.99, 121.52, 124.83, 125.19, 128.96, 129.33, 129.39, 136.14, 140.30, 164.19;

LCMS (m/z): 292 $(M-H)^-$, 294 $(M+2-H)^-$

Analysis Calc'd. for $C_{13}H_{10}BrNO_2$: C, 53.45; H, 3.45; N, 4.79

Found: C, 53.42; H, 3.48; N, 4.73.

3, 5-Dimethylidene-4-(3-methoxyphenyl)piperidine-2, 6-dione (168d): This piperidine-2, 6-dione derivative was obtained as colorless solid via the reaction of 4-cyano-2-methoxycarbonyl-3-(3-methoxyphenyl)penta-1,4-diene (**167d**) with $FeCl_3$ / AcOH following similar procedure described for 3, 5-dimethylidene-4-phenylpiperidine-2, 6-dione (**168a**).



Yield: 61 %

Mp: 192-194 ^oC

IR (KBr): ν 3195-2845 (multiple bands), 1716, 1635, 1602 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 3H), 4.70 (s, 1H), 5.68 (s, 2H), 6.48 (s, 2H), 6.71-6.84 (m, 3H), 7.23-7.32 (m, 1H), 7.95 (bs, 1H)

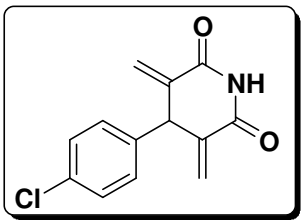
^{13}C NMR (100 MHz, 20% DMSO-d_6 in $CDCl_3$): δ 48.79, 54.15, 111.43, 112.51, 118.48, 124.75, 128.89, 136.91, 139.38, 158.87, 164.66.

LCMS (m/z): 244 $(M+H)^+$

Analysis Calc'd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76

Found: C, 69.20; H, 5.37; N, 5.67.

3, 5-Dimethylidene-4-(4-chlorophenyl)piperidine-2, 6-dione (168e): This compound was obtained by the reaction of 4-cyano-2-methoxycarbonyl-3-(4-chlorophenyl)penta-1,4-diene (**167e**) with $FeCl_3$ / AcOH, as colorless solid following similar procedure described for 3, 5-dimethylidene-4-phenylpiperidine-2, 6-dione (**168a**)



Yield: 75 %

Mp: 166-168 ^{o}C

IR (KBr): ν 3150-2860 (multiple bands), 1705, 1635 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.71 (s, 1H), 5.68 (s, 2H), 6.50 (s, 2H), 7.13 (d, 2H, *J* = 8.0 Hz), 7.32 (d, 2H, *J* = 8.0 Hz), 8.17 (bs, 1 H)

^{13}C NMR (100 MHz, 20% DMSO-d_6 in $CDCl_3$): δ 48.41, 125.35, 128.08, 132.41, 136.54, 136.76, 164.62.

LCMS (m/z): 248 $(M+H)^+$, 250 $(M+2+H)^+$

Analysis Calc'd. for $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; N, 5.66

Found: C, 63.01; H, 4.00; N, 5.61

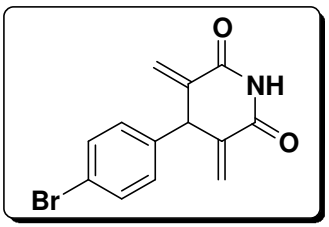
3, 5-Dimethylidene-4-(4-bromophenyl)piperidine-2, 6-dione (168f): This molecule was prepared as colorless solid via the reaction of 4-cyano-2-methoxycarbonyl-3-(4-bromolphenyl)penta-1,4-diene (**167f**) with $FeCl_3$ / AcOH following similar procedure described for 3, 5-dimethylidene-4-phenylpiperidine-2, 6-dione (**168a**)

Yield: 76%

Mp: 200-202 ^{o}C

IR (KBr): ν 3190-2865 (multiple bands), 1699, 1635 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 4.69 (s, 1H), 5.67 (s, 2H), 6.50 (s, 2H), 7.07 (d, 2H, *J* = 8.4 Hz), 7.47 (d, 2H, *J* = 8.4 Hz), 8.07 (bs, 1 H)



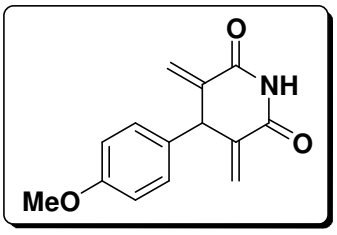
^{13}C NMR (100 MHz, 20% DMSO-d_6 in $CDCl_3$): δ 48.01, 120.16, 124.96, 128.11, 130.69, 136.44, 136.98, 164.27

LCMS (m/z): 292 $(M+H)^+$, 294 $(M+2+H)^+$

Analysis Calc'd. for $C_{13}H_{10}BrNO_2$: C, 53.45; H, 3.45; N, 4.79;

Found: C, 53.54; H, 3.48; N, 4.74.

3, 5-Dimethylidene-4-(4-methoxyphenyl)piperidine-2, 6-dione (168g): The title compound was obtained as colorless solid by the reaction of 4-cyano-2-methoxycarbonyl-3-(4-methoxyphenyl)penta-1,4-diene (**167g**) with $FeCl_3$ / AcOH following similar procedure described for 3, 5-dimethylidene-4-phenylpiperidine-2, 6-dione (**168a**).



Yield: 63 %

Mp: 192-194 ^oC

IR (KBr): ν 3190-2860 (multiple bands), 1714, 1639 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 3H), 4.68 (s, 1H), 5.65 (s, 2H), 6.46 (s, 2H), 6.87 (d, 2H, *J* = 8.8 Hz), 7.10 (d, 2H, *J* = 8.8 Hz), 7.98 (bs, 1H).

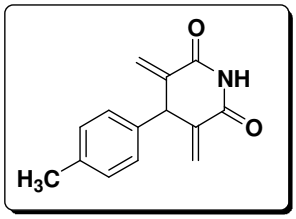
^{13}C NMR (100 MHz, 20% DMSO-d_6 in $CDCl_3$): δ 48.17, 54.25, 113.23, 124.45, 127.49, 129.51, 137.29, 157.86, 164.80.

LCMS (m/z): 242 $(M-H)^-$

Analysis Calc'd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76

Found: C, 69.01; H, 5.38; N, 5.82

3, 5-Dimethylidene-4-(4-methylphenyl)piperidine-2, 6-dione (168h): The reaction of 4-cyano-2-methoxycarbonyl-3-(4-methylphenyl)penta-1,4-diene (**167h**) with $FeCl_3$ / AcOH provided the title compound as colorless solid, following similar procedure described for 3, 5-dimethylidene-4-phenylpiperidine-2, 6-dione (**168a**).



Yield: 85%

Mp: 200-202 ^oC

IR (KBr): ν 3190-2845 (multiple bands), 1720, 1701, 1639 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H), 4.70 (s, 1H), 5.66 (s, 2H), 6.47 (s, 2H), 7.07 (d, 2H, *J* = 8.0 Hz), 7.15 (d, 2H, *J* = 8.0 Hz), 7.90 (bs, 1 H).

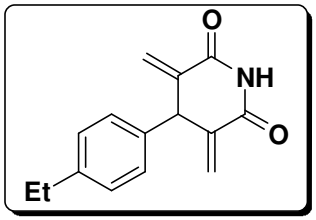
^{13}C NMR (100 MHz, 20% DMSO-d_6 in $CDCl_3$): δ 20.00, 48.67, 124.65, 126.29, 128.59, 134.78, 136.14, 137.24, 164.86.

LCMS (m/z): 226 $(M-H)^-$

Analysis Calc'd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16.

Found: C, 73.85; H, 5.78; N, 6.26.

3, 5-Dimethylidene-4-(4-ethylphenyl)piperidine-2, 6-dione (168i): Treatment of 4-cyano-2-methoxycarbonyl-3-(4-ethylphenyl)penta-1,4-diene (**167i**) with $FeCl_3$ / AcOH furnished the title compound as colorless solid, following similar procedure described for 3, 5-dimethylidene-4-phenylpiperidine-2, 6-dione (**168a**)



Yield: 70 %

Mp: 178-180 ^oC

IR (KBr): ν 3190-2845 (multiple bands), 1716, 1701, 1637 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, 3H, *J* = 7.6 Hz), 2.62 (q, 2H, *J* = 7.6 Hz), 4.71 (s, 1H), 5.67 (s, 2H), 6.47 (s, 2H), 7.09 (d, 2H, *J* = 8.4 Hz), 7.17 (d, 2H, *J* = 8.4 Hz), 7.96 (bs, 1 H).

^{13}C NMR (100 MHz, 20% DMSO-d_6 in $CDCl_3$): δ 14.46, 27.11, 48.45, 124.40, 126.11, 127.20, 134.92, 137.09, 142.26, 164.69.

LCMS (m/z): 242 $(M+H)^+$

Analysis Calc'd. for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81.

Found: C, 74.60; H, 6.23; N, 5.78.

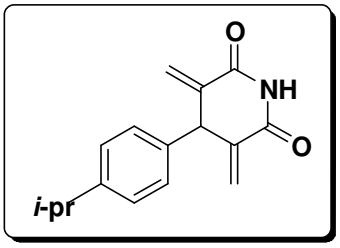
3, 5-Dimethylidene-4-(4-isopropylphenyl)piperidine-2, 6-dione (168j): This compound was pepared as colorless solid via the reaction of 4-cyano-2-methoxycarbonyl-3-(4-isopropyphenyl)penta-1,4-diene (**167j**) with $FeCl_3$ / AcOH, following similar procedure described for 3, 5-dimethylidene-4-phenylpiperidine-2, 6-dione (**168a**)

Yield: 84 %

Mp: 152-154^oC

IR (KBr): 3184-2865 (multiple bands), 1711, 1639 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 1.22 (d, 6H, *J* = 7.2 Hz), 2.88 (sept, 1H, *J* = 7.2 Hz), 4.71 (s, 1H), 5.68 (s, 2H), 6.47 (s, 2H), 7.10 (d, 2H, *J* = 8.0 Hz), 7.19 (d, 2H, *J* = 8.0 Hz), 8.15 (bs, 1 H).



^{13}C NMR(100 MHz, 20% DMSO-d_6 in $CDCl_3$): δ 22.95, 32.51, 48.60, 124.55, 125.85, 126.19, 135.07, 137.13, 147.00, 164.82,

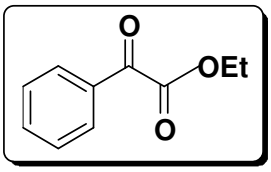
LCMS (m/z): 254 $(M-H)^-$

Analysis Calc'd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49.

Found: C, 75.19; H, 6.76; N, 5.51.

Ethyl phenylglyoxylate (172a): This compound was prepared according to the literature procedure.[229] A solution of phenylmagnesium bromide in THF (200 mmol) [prepared from

bromobenzene (200 mmol, 31.40 g, 21 mL) and magnesium turnings (200 mmol, 4.8 g)] was added to diethyl oxalate (500 mmol, 73 g, 67.7 mL) in THF (200 mL) slowly at –10 ^{o}C over a period of 1 h. Then the reaction mixture was quenched immediately with 2N HCl solution to a pH of 4.0 and extracted with ether (3 × 200 mL). The combined organic layer was dried over anhydrous sodium sulfate. Solvent was evaporated and the residue thus obtained was subjected to fractional distillation to furnish the pure ethyl phenylglyoxylate (**172a**) in 41 % (14.6 g) yield, as a colorless liquid.



IR (Neat): ν 1736, 1687, 1597 cm^{-1}

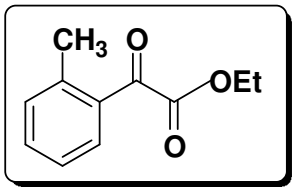
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (t, 3H, *J* = 7.2 Hz), 4.45 (q, 2H, *J* = 7.2 Hz), 7.48-7.54 (m, 2H), 7.62-7.69 (m, 1H), 8.00 (dd, 2H, *J* = 0.8, 8.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.93, 62.17, 128.77, 129.82, 132.31, 134.78, 163.76, 186.36.

Ethyl (2-methylphenyl)glyoxylate (172b): This compound was prepared as a colorless liquid *via* the treatment of 2-(methylphenyl)magnesium bromide with diethyl oxalate in THF, following the similar procedure described for the molecule ethyl phenylglyoxylate (**172a**).

Reaction time: 1h

Yield: 47 %

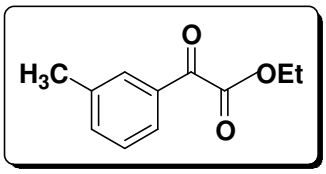


IR (Neat): ν 1736, 1684, 1601 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (t, 3H, *J* = 7.2 HZ), 2.60 (s, 3H), 4.43 (q, 2H, *J* = 7.2 Hz), 7.20-7.34 (m, 2H), 7.45-7.53 (m, 1H), 7.69 (d, 1H, *J* = 8.0 Hz).

^{13}C NMR (400 MHz, $CDCl_3$): δ 14.00, 21.35, 62.16, 125.87, 131.17, 132.20, 132.29, 133.62, 141.20, 164.59, 188.75.

Ethyl (3-methylphenyl)glyoxylate (172c): This compound was obtained as a colorless liquid *via* the reaction between 3-(methylphenyl)magnesium bromide and diethyl oxalate in THF, following the similar procedure described for the molecule ethyl phenylglyoxylate (**172a**).



Reaction time: 1h

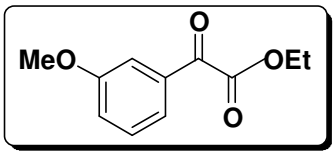
Yield: 63 %

IR (Neat): ν 1738, 1687, 1602 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (t, 3H, *J* = 6.8 Hz), 2.42 (s, 3H), 4.45 (q, 2H, *J* = 6.8 Hz), 7.35-7.43 (m,1H), 7.44-7.50 (m, 1H), 7.75-7.83 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.15, 21.30, 62.30, 127.39, 128.82, 130.32, 132.51, 135.80, 138.89, 164.07, 186.73.

Ethyl (3-methoxyphenyl)glyoxylate (172d): This molecule was obtained as a colorless liquid *via* the treatment of 3-(methoxyphenyl)magnesium bromide with diethyl oxalate in THF, following the similar procedure described for the molecule ethyl phenylglyoxylate (**172a**).



Reaction time: 1h

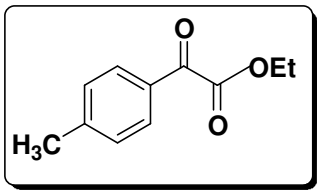
Yield: 60 %

IR (Neat): ν 1736, 1687, 1599 cm^{-1}

^{1}H NMR(400 MHz, $CDCl_3$): δ 1.42 (t, 3H, *J* = 7.2 HZ), 3.86 (s, 3H), 4.45 (q, 2H, *J* = 7.2 Hz), 7.17-7.23 (m, 1H), 7.37-7.45 (m, 1H), 7.51-7.60 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.06, 55.44, 62.29, 133.28, 121.73, 123.01, 129.89, 133.65, 159.91, 163.84, 186.30.

Ethyl (4-methylphenyl)glyoxylate (172e): Treatment of 4-(methylphenyl)magnesium bromide with diethyl oxalate in THF, following the similar procedure described for the molecule ethyl phenylglyoxylate (**172a**) provided the title compound **172e** as a colorless liquid.



Reaction time: 1h

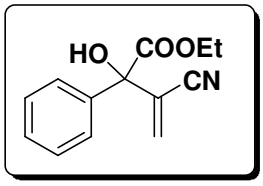
Yield: 62 %

IR (Neat): ν 1720, 1682, 1606 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (t, 3H, *J* = 7.6 Hz), 2.44 (s, 3H), 4.42 (q, 2H, *J* = 6.8 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 7.90 (d, 2H, *J* = 8.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.11, 21.89, 62.23, 130.03, 131.15, 146.25, 164.05, 186.12

3-Ethoxycarbonyl-3-hydroxy-3-phenyl-2-methylenepropanenitrile (173a): This compound was prepared following the procedure described in the literature.[230] A mixture of ethyl phenylglyoxylate (**172a**) (40 mmol, 7.12 g), acrylonitrile (80 mmol, 4.24 g, 5.2 mL) and DABCO (30 mol %, 13.44 g) was kept at room temperature. After 5 days water (20 mL) was added to the reaction mixture and extracted with ether (3 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue thus obtained, was subjected to column chromatography (silica gel, 5 % EtOAc in hexanes) to furnish the pure compound 3-ethoxycarbonyl-3-hydroxy-3-phenyl-2-methylenepropanenitrile (**173a**) in 58 % (5.36 g), as a colorless liquid.

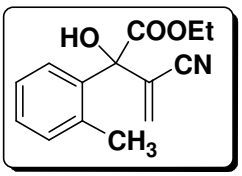


IR (Neat): ν 3479, 2229, 1736, 1616 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (t, 3H, *J* = 7.2 Hz), 4.19 (bs, 1H), 4.33-4.48 (m, 2H), 6.14 (s, 1H), 6.19 (s, 1H), 7.33-7.43 (m, 3H), 7.52 (d, 2H, *J* = 6.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.90, 63.89, 78.60, 116.87, 125.24, 126.32, 128.63, 129.07, 132.92, 137.54, 171.61.

3-Ethoxycarbonyl-3-hydroxy-3-(2-methylphenyl)-2-methylenepropanenitrile (173b):



Baylis-Hillman reaction between ethyl (2-methylphenyl)glyoxylate (**172b**) and acrylonitrile under the influence of DABCO, following the similar procedure described for the molecule 3-ethoxycarbonyl-3-hydroxy-3-phenyl-2-methylenepropanenitrile (**173a**) provided the title compound **173b** as a colorless liquid.

Reaction time: 5d

Yield: 45 %

IR (Neat): ν 3423, 2235, 1743, 1608 cm^{-1}

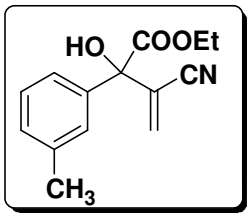
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (t, 3H, *J* = 7.2 Hz), 2.34 (s, 3H), 4.07 (s, 1H), 4.30-4.56 (m, 2H), 6.32 (s, 1H), 6.36 (s, 1H), 7.15-7.32 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.95, 20.40, 63.98, 80.09, 116.79, 125.07, 125.96, 127.62, 129.32, 132.67, 133.65, 135.86, 137.65, 172.77.

3-Ethoxycarbonyl-3-hydroxy-3-(3-methylphenyl)-2-methylenepropanenitrile (173c):

This alcohol was obtained as a colorless liquid *via* the Baylis-Hillman reaction between

ethyl (3-methylphenyl)glyoxylate (**172c**) and acrylonitrile under the influence of DABCO, following the similar procedure described for the molecule 3-ethoxycarbonyl-3-hydroxy-3-phenyl-2-methylenepropanenitrile (**173a**).



Reaction time: 5d

Yield: 47 %

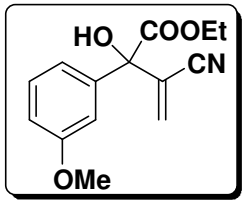
IR (Neat): ν 3476, 2229, 1738, 1606 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (t, 3H, *J* = 7.2 Hz), 2.37 (s, 3H), 4.12 (s, 1H), 4.35-4.49 (m, 2H), 6.16 (s, 1H), 6.19 (s, 1H), 7.17-7.34 (m, 4H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.87, 21.46, 63.75, 78.61, 116.89.123.38, 125.21, 126.82, 128.45, 129.78, 132.87, 137.48, 138.39, 171.63.

3-Ethoxycarbonyl-3-hydroxy-3-(3-methoxyphenyl)-2-methylenepropanenitrile(173d):

This adduct was obtained as a colorless liquid *via* the reaction between ethyl (3-methoxyphenyl)glyoxylate (**172d**) and acrylonitrile under the influence of DABCO, following the similar procedure described for the molecule 3-ethoxycarbonyl-3-hydroxy-3-phenyl-2-methylenepropanenitrile (**173a**)



Reaction time: 5d

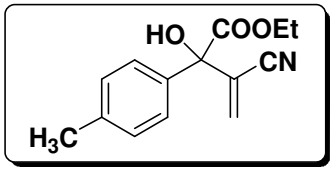
Yield: 62 %

IR (Neat): ν 3410, 2233, 1732, 1608 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (t, 3H, *J* = 7.2 Hz), 3.81 (s, 3H), 4.17 (s, 1H), 4.36-4.46 (m, 2H), 6.14 (s, 1H), 6.19 (s, 1H), 6.88-6.94 (m, 1H), 7.08-7.12 (m, 2H), 7.28-7.34 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.91, 55.24, 63.86, 78.48, 112.16, 114.48, 116.86, 118.56, 125.11, 129.63, 132.95, 138.96, 159.71, 171.47.

3-Ethoxycarbonyl-3-hydroxy-3-(4-methylphenyl)-2-methylenepropanenitrile (173e): This product was prepared *via* the reaction between ethyl (4-methylphenyl)glyoxylate (**172e**) and acrylonitrile under the influence of DABCO as a colorless liquid, following the similar procedure described for the molecule 3-ethoxycarbonyl-3-hydroxy-3-phenyl-2-methylenepropanenitrile (**173a**).



Reaction time: 5d

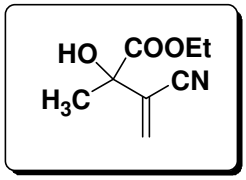
Yield: 65 %

IR (Neat): ν 3443, 2237, 1732, 1612 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (t, 3H, *J* = 7.2 Hz), 2.36 (s, 3H), 4.14 (s, 1H), 4.34-4.47 (m, 2H), 6.15 (s,1H), 6.18 (s, 1H), 7.20 (d, 2H, *J* = 7.6 Hz), 7.40 (d, 2H, *J* = 7.6 Hz).

^{13}C NMR: δ 13.83, 20.96, 63.67, 78.46, 116.88, 125.27, 126.15, 129.23, 132.70, 134.61, 138.87, 171.64.

3-Ethoxycarbonyl-3-hydroxy-2-methylenebutanenitrile (173f): This molecule was obtained as a colorless liquid *via* the Baylis-Hillman coupling of acrylonitrile with ethyl pyruvate under the influence of DABCO, following the similar procedure described for the molecule 3-ethoxycarbonyl-3-hydroxy-3-phenyl-2-methylenebutanenitrile (**173a**).



Reaction Time: 5d

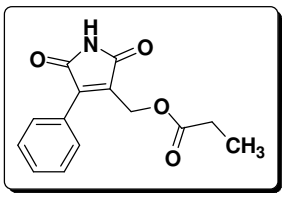
Yield: 35 %

IR (Neat): ν 3466, 2229, 1738, 1624 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 1.35 (t, 3H, *J* = 7.2 Hz), 1.66 (s, 3H), 3.88 (bs, 1H), 4.30-4.35 (m, 2H), 6.10 (s, 1H), 6.28 (s, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.96, 24.74, 63.47, 74.02, 116.62, 125.68, 131.52, 173.13.

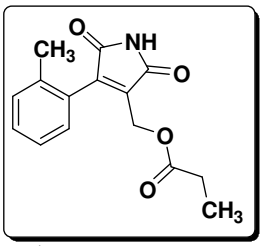
3-(Ethylcarbonyloxy)methyl-4-phenyl-1H-pyrrole-2,5-dione (174a): To a stirred solution of 3-ethoxycarbonyl-3-hydroxy-3-phenyl-2-methylenepropanenitrile (**173a)** (1 mmol, 0.231 g) in propanoic acid (5 mL) was added anhydrous $FeCl_3$ (4 mmol, 0.649 g) and heated under reflux for 5 h. Reaction mixture was cooled to room temperature and the reaction mixture was diluted with aqueous 4N HCl (5 mL) and extracted with dichloromethane (3 X 10 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution and water, and dried over anhydrous Na_2SO_4. Solvent was removed and the residue thus obtained was purified by column chromatography (silica gel, 20 % EtOAc in hexanes) to



provide 3-(ethylcarbonyloxy)methyl-4-phenyl-1H-pyrrole-2,5-dione **(174a)** as a light yellow solid in 61 % (0.157g) yield.

Mp:	78-80 ºC
IR (KBr):	ν 3460, 1768, 1730, 1714, 1633 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$):	δ 1.09 (t, 3H, *J* = 7.6 Hz), 2.29 (q, 2H, *J* = 7.6 Hz), 5.05 (s, 2H), 7.42-7.64 (m, 5H), 8.17 (s, 1H)
^{13}C NMR (100 MHz, $CDCl_3$):	δ 8.88, 27.22, 55.16, 127.61, 128.71, 129.84, 130.70, 133.28, 142.42, 170.24, 173.79.
LCMS (*m/z*):	260 $(M+H)^+$
Analysis:Calcd. for $C_{14}H_{13}NO_4$:	C, 64.86; H, 5.05; N, 5.40
Found:	C, 64.67; H, 5.09; N, 5.45.

3-(Ethylcarbonyloxy)methyl-4-(2-methylphenyl)-1H-pyrrole-2,5-dione (174b): This molecule wsa prepared as yellow sold *via* the treatment of 3-ethoxycarbonyl-3-hydroxy-3-(2-methylphenyl)-2-methylenepropanenitrile (**173b**) with anhydrous $FeCl_3$ in propanoic acid following the similar procedure described for the compound 3-(ethylcarbonyloxy)methyl-4-phenyl-1H-pyrrole 2, 5-dione (**174a**).



Yield:	54 % .
Mp:	74-75 ºC.
IR (KBr):	ν 3229, 1768, 1728, 1716, 1645 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$):	δ 0.94 (t, 3H, *J* = 7.2 Hz), 1.90-2.09 (m, 2H), 2.23

(s, 3H), 4.90 (s, 1H)[#], 4.99 (s, 1H)[#], 7.06-7.56 (m, 4H), 8.01 (bs, 1H)

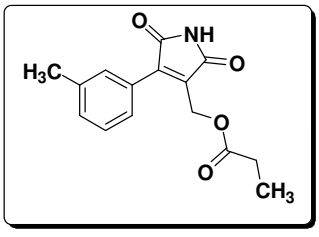
^{13}C NMR (100 MHz, $CDCl_3$): δ 8.68, 20.10, 26.72, 56.16, 125.74, 127.36, 129.50, 130.03, 130.48, 136.65, 136.94, 143.53, 169.80, 169.86, 173.55

LCMS (*m/z*): 272 $(M-H)^+$

Analysis: Calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13

Found: C, 66.03; H, 5.56; N, 5.18

3-(Ethylcarbonyloxy)methyl-4-(3-methylphenyl)-1H-pyrrole-2, 5-dione (174c): Treatment of 3-ethoxycarbonyl-3-hydroxy-3-(3-methylphenyl)-2-methylenepropanenitrile (**173c**) with anhydrous $FeCl_3$ in propanoic acid provided the title compound as light yellow solid, following the similar procedure described for the molecule 3-(ethylcarbonyloxy)methyl-4-phenyl-1H-pyrrole 2, 5-dione (**174a**).



Yield: 60 %

Mp: 78-79 ºC

IR (KBr): ν 3232, 1774, 1714, 1710, 1645 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (t, 3H, *J* = 7.6 Hz), 2.30 (q, 2H, *J* = 7.6 Hz), 2.40 (s, 3H), 5.04 (s, 2H), 7.27-7.42 (m, 4H), 7.76

[#] These two singlets for allyl methyl protons arise due to 2-methyl substitution on phenyl ring

(bs, 1H)

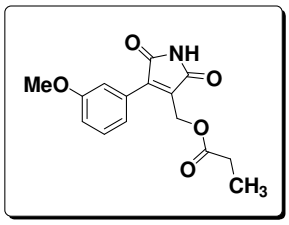
^{13}C NMR (100 MHz, $CDCl_3$): δ 8.94, 21.43, 27.26, 55.12, 126.97, 127.51, 128.64, 130.35, 131.57, 133.07, 138.49, 142.77, 170.26, 173.78.

LCMS (*m/z*): 272 $(M-H)^+$

Analysis: Calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13

Found: C, 66.12; H, 5.48; N, 5.20

3-(Ethylcarbonyloxy)methyl-4-(3-methoxyphenyl)-1H-pyrrole-2,5-dione (174d): The reaction of 3-ethoxycarbonyl-3-hydroxy-3-(3-methoxyphenyl)-2-methylenepropanenitrile (**173d**) with anhydrous $FeCl_3$ / propanoic acid, following similar procedure described for the molecule 3-(ethylcarbonyloxy)methyl-4-phenyl-1H-pyrrole 2, 5-dione (**173a**) provided the title compound **174d** as yellow solid.



Yield: 61 %

Mp: 96-98 ºC

IR (KBr): ν 3256, 1778, 1721, 1705, 1640 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (t, 3H, *J* = 7.6 Hz), 2.31 (q, 2H, *J* = 7.6 Hz), 3.84 (s, 3H), 5.05 (s, 2H), 7.03 (dd, 1H, *J* = 8.0, 2.0 Hz), 7.09-7.18 (m, 2H), 7.36-7.44 (m, 1H), 7.66 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 8.95, 27.29, 55.09, 55.40, 115.11, 116.73, 122.28,

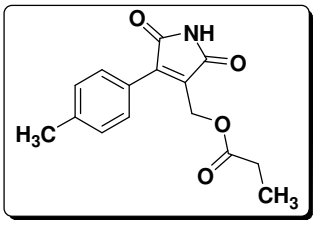
128.74, 129.88, 133.46, 142.49, 159.64, 169.95, 170.00, 173.78.

LCMS (*m/z*): 290 $(M+H)^+$

Analysis: Calcd. for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23. N, 4.84

Found: C, 62.38; H, 5.25; N, 4.58

3-(Ethylcarbonyloxy)methyl-4-(4-methylphenyl)-1H-pyrrole-2,5-dione (174e): This compound was prepared as yellow sold via the treatment of 3-ethoxycarbonyl-3-hydroxy-3-(4-methylphenyl)-2-methylenepropanenitrile (**173e**) with anhydrous $FeCl_3$ in propanoic acid following the similar procedure described for the molecule 3-(ethylcarbonyloxy)methyl-4-phenyl-1H-pyrrole 2, 5-dione (**174a**).



Yield: 55 %

Mp: 91-93 ºC

IR (KBr): ν 3232, 1739, 1714, 1708, 1635 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 1.11 (t, 3H, *J* = 7.6 Hz), 2.32 (q, 2H, *J* = 7.6 Hz), 2.41 (s, 3H), 5.04 (s, 2H), 7.29 (d, 2H, *J* = 8.0 Hz), 7.48 (d, 2H, *J* = 8.0 Hz), 7.69 (bs, 1H)

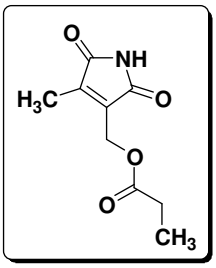
^{13}C NMR (100 MHz, $CDCl_3$): δ 8.95, 21.55, 27.30, 55.12, 124.83, 129.54, 129.86, 132.21, 141.41, 142.65, 170.35, 173.84

LCMS (*m/z*): 274$(M+H)^+$

Analysis: Calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13

Found: C, 65.84; H, 5.58; N, 5.33

3-(Ethylcarbonyloxy)methyl-4-methyl-1H-pyrrole-2,5-dione (174f): This compound was obtained as light yellow sold, via the treatment of 3-ethoxycarbonyl-3-hydroxy-4-methylenebutanenitrile (**173f**) with anhydrous $FeCl_3$ / propanoic acid following the similar procedure described for the molecule 3-(ethylcarbonyloxy)methyl-4-phenyl-1H-pyrrole 2, 5-dione (**174a**).



Yield: 63 %

Mp: 56-57 ºC

IR (KBr): ν 3468, 1765, 1743, 1703 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (t, 3H, *J* = 7.6 Hz), 2.10 (s, 3H), 2.39 (q, 2H, *J* = 7.6 Hz), 4.93 (s, 2H), 7.67 (bs, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 8.98, 9.04, 27.26, 54.88, 134.70, 142.97, 170.49, 171.32, 173.97

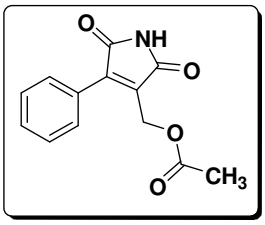
LCMS (*m/z*): 198 $(M+H)^+$

Analysis: Calcd. for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10

Found: C, 54.65; H, 5.63; N, 7.08

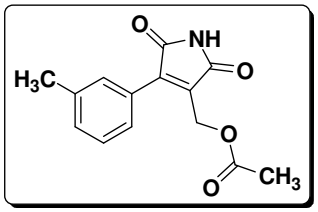
3-(Methylcarbonyloxy)methyl-4-phenyl-1H-pyrrole-2,5-dione (174g): To a stirred solution of 3-ethoxycarbonyl-3-hydroxy-3-phenyl-2-methylenepropanenitrile (**173a**) (1

mmol, 0.231g) in acetic acid (5 mL) was added anhydrous $FeCl_3$ (4 mmol, 0.649 g) and heated under reflux for 5 h. Reaction mixture was cooled to room temperature and acetic acid was removed under reduced pressure. Reaction mixture was diluted with 4N HCl (5 mL) and the organic layer was extracted with dichloromethane (3 X 10 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution and water and dried over anhydrous $NaSO_4$. Solvent was removed and the residue thus obtained was purified by column chromatography (silica gel, 20% ethyl acetate in hexanes) to provide 3-(methylcarbonyloxy)methyl-4-phenyl-1H-pyrrole 2, 5-dione (**174g**) as a colorless solid in 50 % yield (0. 123g).



Yield:	50 %.
Mp:	106-108 ºC.
IR (KBr):	ν 3200, 1770, 1736, 1714, 1641 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$):	δ 2.03 (s, 3H), 5.04 (s, 2H), 7.44-7.62 (m, 5H), 7.97 (bs, 1H)
^{13}C NMR (100 MHz, $CDCl_3$):	δ 20.62, 55.27, 127.57, 128.84, 129.91, 130.87, 133.20, 142.72, 169.87, 170.32
LCMS (*m/z*):	246 $(M+H)^+$
Analysis:Calcd. for $C_{13}H_{11}NO_4$:	C, 63.67; H, 4.52; N, 5.71
Found:	C, 63.73; H, 4.60; N, 5.87

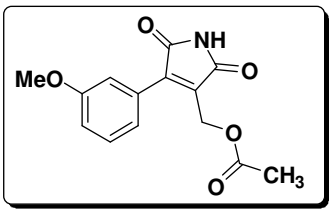
3-(Methylcarbonyloxy)methyl-4-(3-methylphenyl)-1H-pyrrole-2,5-dione (174h): This molecule was obtained as yellow solid, *via* the reaction of 3-ethoxycarbonyl-3-hydroxy-3-(3-methylphenyl)-2-methylenepropanenitrile (**173c**) with $FeCl_3$ / acetic acid following the similar procedure described for the molecule 3-(methylcarbonyloxy)methyl-4-phenyl-1H-pyrrole 2, 5-dione (**174g**).



Yield:	65 %
Mp:	92-94 ºC
IR (KBr):	ν 3205, 1770, 1714, 1705, 1645 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$):	δ 2.03 (s, 3H), 2.41 (s, 3H), 5.03 (s, 2H), 7.29-7.45 (m, 4H), 7.99 (bs, 1H)
^{13}C NMR (100 MHz, $CDCl_3$):	δ 20.55, 21.41, 55.21, 126.95, 127.45, 128.64, 130.34, 131.57, 132.88, 138.48, 142.85, 170.25, 170.31, 170.38
LCMS (*m/z*):	260 $(M+H)^+$
Analysis:Calcd. for $C_{14}H_{13}NO_4$:	C, 64.86; H, 5.05; N, 5.40
Found:	C, 64.82; H, 5.04; N, 5.57

3-(Methylcarbonyloxy)methyl-4-(3-methoxyphenyl)-1H-pyrrole-2,5-dione (174i): Treatment of 3-ethoxycarbonyl-3-hydroxy-3-(3-methoxyphenyl)-2-methylenepropanenitrile (**173d**) with $FeCl_3$ / acetic acid provided the title compound as **174i** as yellow solid,

following the similar procedure described for the molecule 3-(methylcarbonyloxy)methyl-4-phenyl-1H-pyrrole 2, 5-dione (**174g**).



Yield: 52 %

Mp: 81-82 ºC

IR (KBr): ν 3271, 1778, 1749, 1712, 1640 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 (s, 3H), 3.84 (s, 3H), 5.04 (s, 2H), 7.04 (d, 1H, *J* = 8.4 Hz), 7.09-7.19 (m, 2H), 7.34-7.44 (m, 1H), 7.95 (bs, 1H)

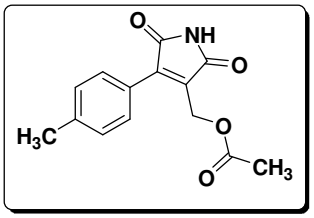
^{13}C NMR (100 MHz, $CDCl_3$): δ 20.55, 55.17, 55.34, 115.08, 116.69, 122.26, 128.69, 129.84, 133.24, 142.54, 159.59, 170.06, 170.17, 170.38.

LCMS (*m/z*): 274 $(M-H)^-$

Analysis: Calcd. for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09

Found: C, 61.00; H, 4.47; N, 5.22

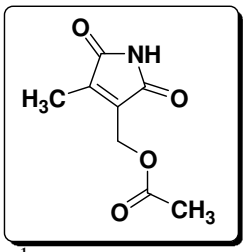
3-(Methylcarbonyloxy)methyl-4-(4-methylphenyl)-1H-pyrrole-2,5-dione (174j): This molecule was obtained as yellow solid via the reaction of 3-ethoxycarbonyl-3-hydroxy-3-(4-methylphenyl)-2-methylenepropanenitrile (**173e**) with $FeCl_3$ / acetic acid, following the similar procedure described for the molecule 3-(methylcarbonyloxy)methyl-4-phenyl-1H-pyrrole 2, 5-dione (**174g**).



Yield: 61 %

Mp:	132-134 ºC
IR (KBr):	ν 3227, 1768, 1745, 1714, 1640 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$):	δ 2.05 (s, 3H), 2.41 (s, 3H), 5.02 (s, 2H) , 7.29 (d, 2H, *J* = 8.0 Hz), 7.48 (d, 2H, *J* = 8.0 Hz), 7.81 (bs, 1H)
^{13}C NMR (100 MHz, $CDCl_3$):	δ 20.66, 21.58, 55.23, 124.79, 129.58, 129.87, 132.07, 141.47, 142.81, 170.26, 170.29, 170.41.
LCMS (*m/z*):	258 $(M-H)^+$
Analysis: Calcd. for $C_{14}H_{13}NO_4$:	C, 64.86; H, 5.05; N, 5.40
Found:	C, 64.75; H, 5.00; N, 5.48

3-(Methylcarbonyloxy)methyl-4-methyl-1H-pyrrole-2,5-dione (174k): This product was prepared as yellow solid *via* the reaction of 3-ethoxycarbonyl-3-hydroxy-4-methylenebutanenitrile (**173f**) with anhydrous $FeCl_3$ in acetic acid following the similar procedure described for the molecule 3-(methylcarbonyloxy)methyl-4-phenyl-1H-pyrrole 2, 5-dione (**174g**).



Yield:	59 %
Mp:	84-86 ºC
IR (KBr):	ν 3470, 1770, 1741, 1699, 1640 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$):	δ 2.10 (s, 6H), 4.92 (s, 2H), 7.59 (bs, 1H)
^{13}C NMR (100 MHz, $CDCl_3$):	δ 9.03, 20.61, 54.90, 134.55, 143.10, 170.44,

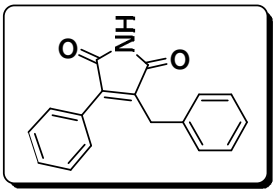
170.51, 171.23

LCMS (*m/z*): 184 $(M+H)^+$

Analysis: Calcd. for $C_8H_9NO_4$: C, 52.46; H, 4.95; N, 7.65

Found: C, 52.50; H, 4.90; N, 7.60

3-Benzyl-4-phenyl-1*H*-pyrrole-2,5-dione (175a): To a stirred solution of 3-(ethylcarbonyloxy)methyl-4-phenyl-1H-pyrrole-2,5-dione (**174a)** (0.5 mmol, 129.5 mg), in benzene (3 mL) was added methanesulfonic acid (1.5 mmol, 0.144 g, 0.1 mL) and heated under reflux for 5 h. Then the reaction mixture was allowed to cool to room temperature. Then aqueous K_2CO_3 solution was added slowly to neutralize the acid and extracted with EtOAc (3 X10 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue thus obtained was purified by column chromatography (silica gel 20% EtOAc in hexanes) to furnish the compound 3-benzyl-4-phenyl-1*H*-pyrrole-2,5-dione (**175a**) as a colorless solid in 81% (0.106g) isolated yield.



Mp: 118-120 ºC (Lit.[226] 118-120)

IR (KBr): ν 3236, 1772, 1699, 1650 cm^{-1}

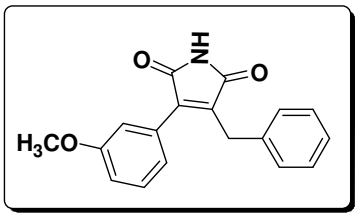
^1H NMR (400 MHz, $CDCl_3$): δ 3.94 (s, 2H), 7.15-7.32 (m, 5H), 7.41-7.47 (m, 3H), 7.49-7.55 (m, 2H), 7.73 (bs, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 29.75, 126.91, 128.41, 128.48, 128.74, 128.90,

129.47, 130.06, 136.98, 139.30, 139.55, 171.03, 171.62

LCMS (*m/z*): 264 $(M+H)^+$

3-Benzyl-4-(3-methoxyphenyl)-1*H*-pyrrole-2,5-dione (175b): This product was obtained as a colorless solid *via* the treatment of 3-(ethycarbonyloxy)methyl-4-(3-methoxyphenyl)-1H-pyrrole 2, 5-dione (**174d**) with benzene in the presence of CH_3SO_3H (cat.) following the similar procedure described for the molecule 3-benzyl-4-phenyl-1*H*-pyrrole-2,5-dione (**175a**).



Yield: 77 %

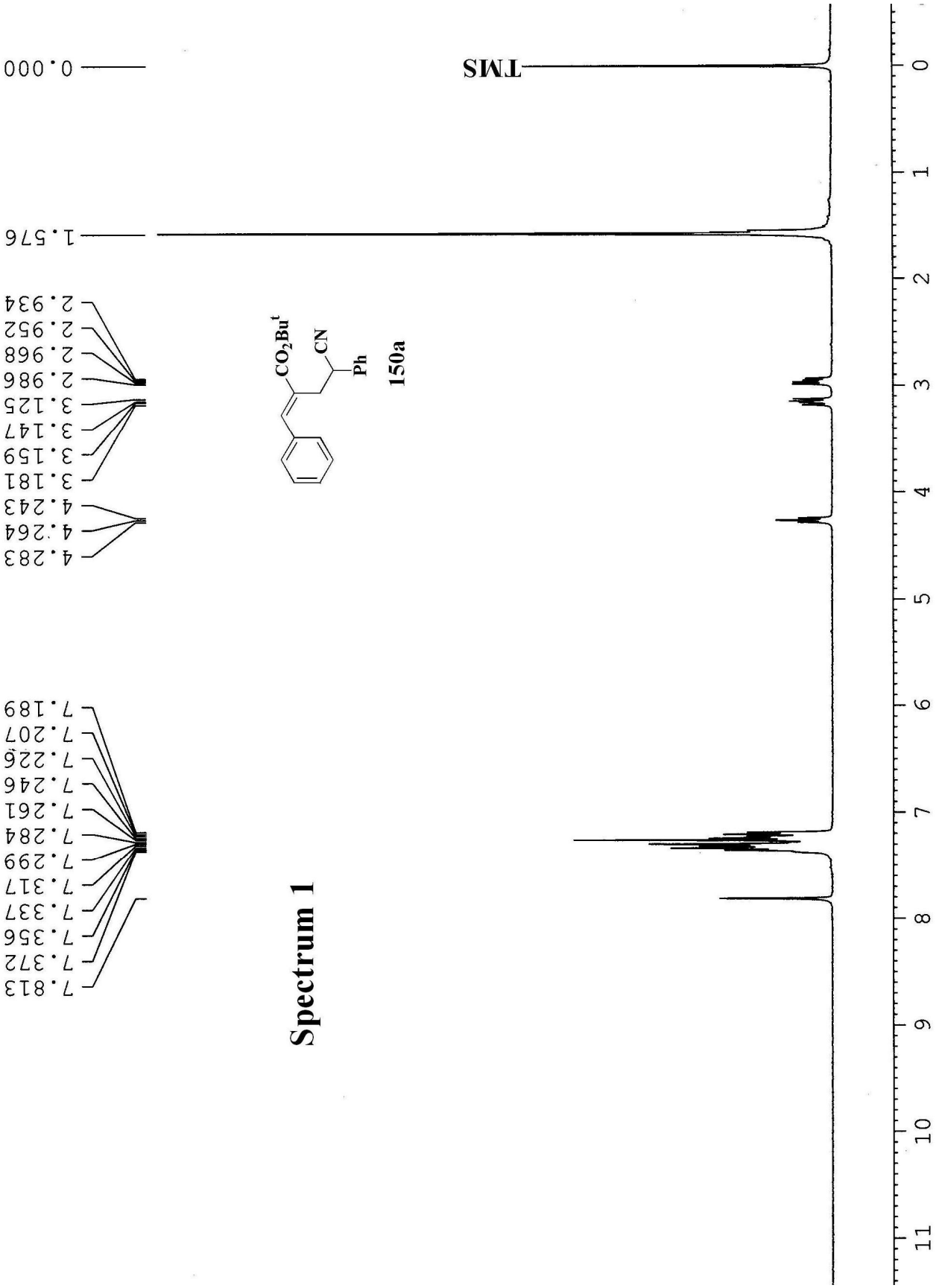
Mp: 104-106 ºC (Lit.[226] 103-105)

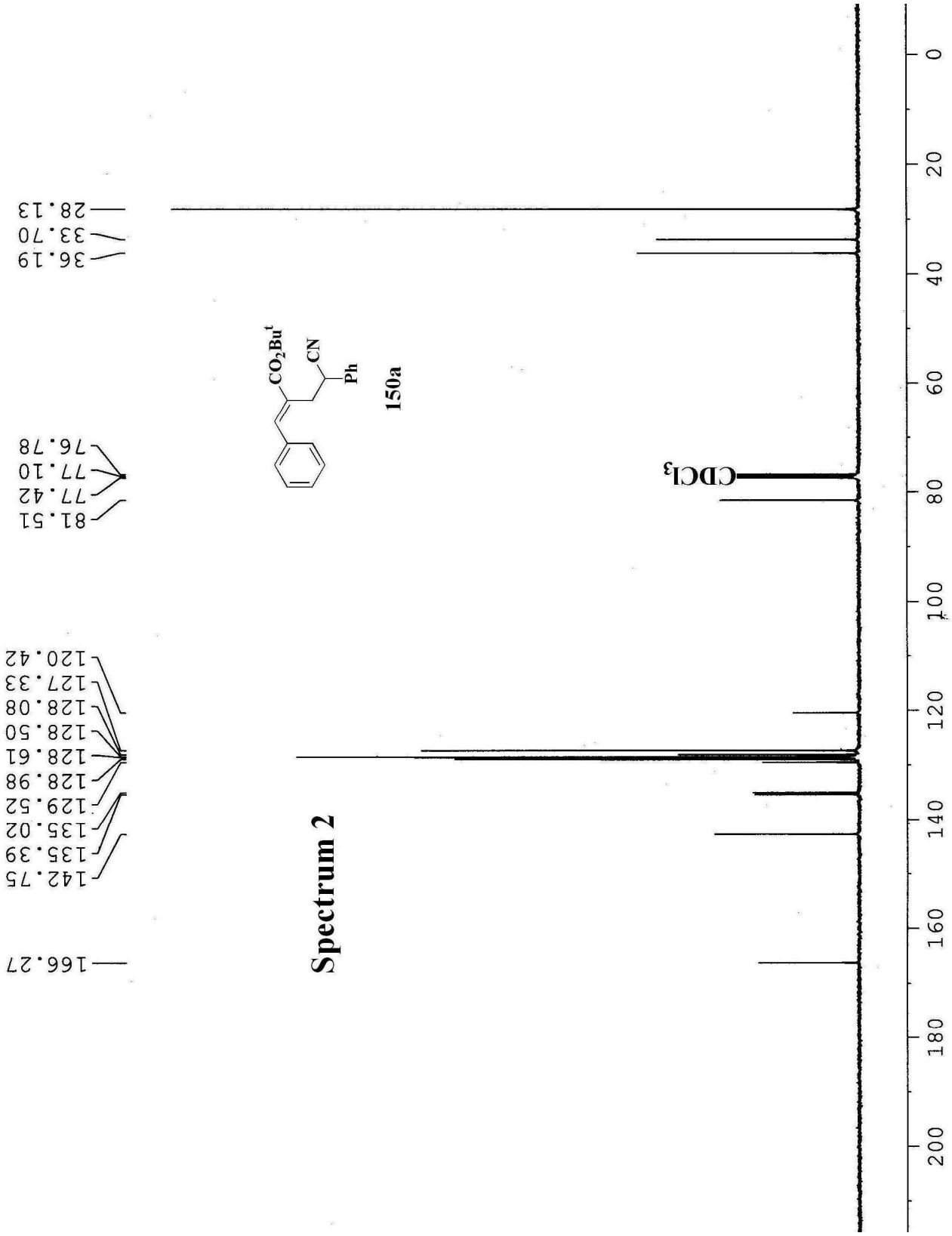
IR (KBr): ν 3219, 1768, 1716, 1640 cm^{-1}

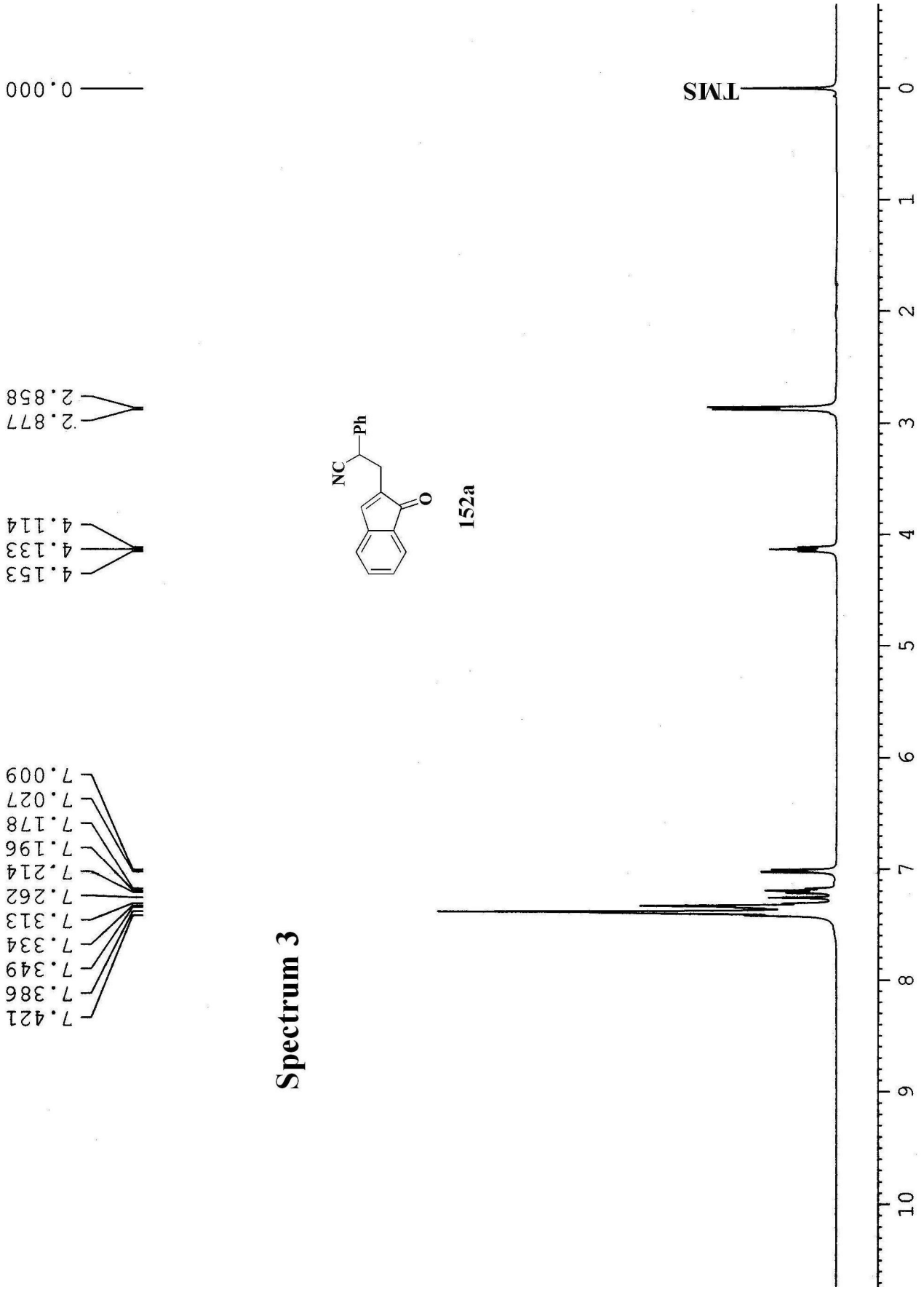
^1H NMR (400 MHz, $CDCl_3$): δ 3.75 (s, 3H), 3.94 (s, 2H), 6.96-7.04 (m, 2H), 7.11 (d, 1H, *J* = 8.0 Hz), 7.16-7.41 (m, 6H), 7.66 (bs, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 29.75, 55.31, 114.65, 116.13, 121.87, 126.92, 128.48, 128.91, 129.57, 129.83, 137.03, 139.42, 139.45, 159.63, 170.91, 171.58

LCMS (*m/z*): 294 $(M+H)^+$.

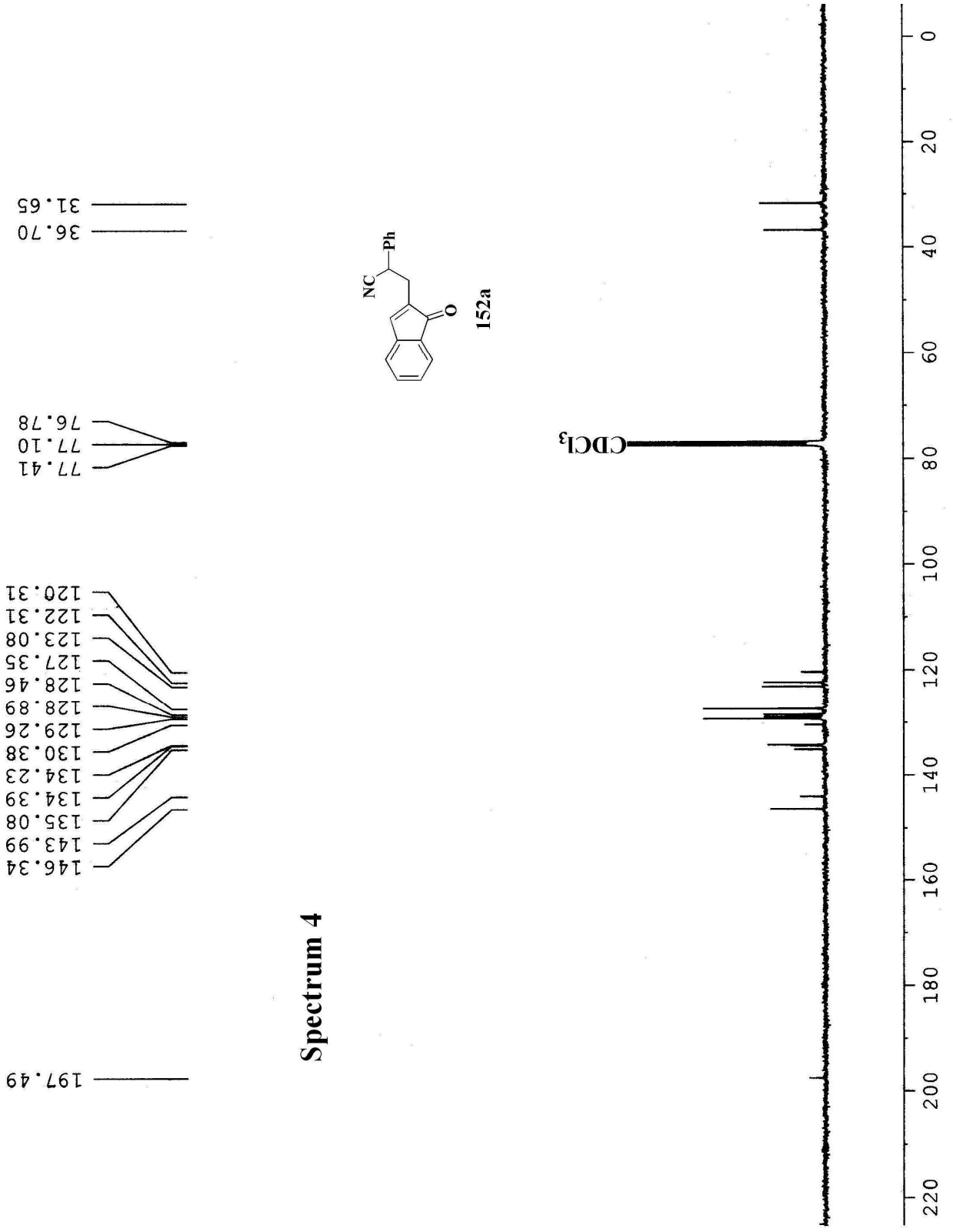

TMS
0.000
1.576
2.934
2.952
2.968
2.986
3.125
3.147
3.159
3.181
4.243
4.264
4.283
7.189
7.207
7.226
7.246
7.261
7.284
7.299
7.317
7.337
7.356
7.372
7.813
CO2But
CN
Ph
150a
Spectrum 1
0
1
2
3
4
5
6
7
8
9
10
11


Spectrum 2
150a
CO2But
CN
Ph
CDCl3
28.13
33.70
36.19
76.78
77.10
77.42
81.51
120.42
127.33
128.08
128.50
128.61
128.98
129.52
135.02
135.39
142.75
166.27
0
20
40
60
80
100
120
140
160
180
200



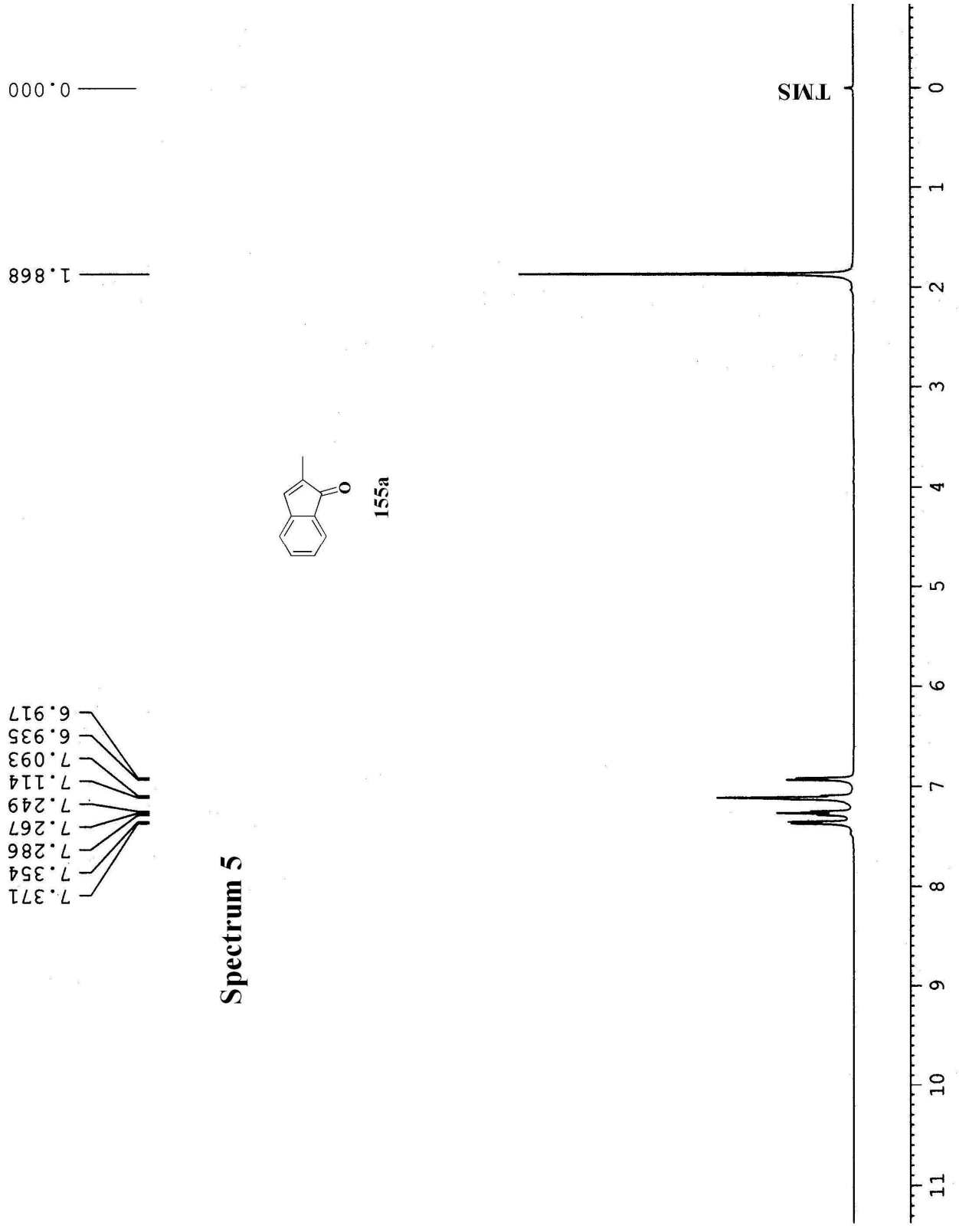
Spectrum 3

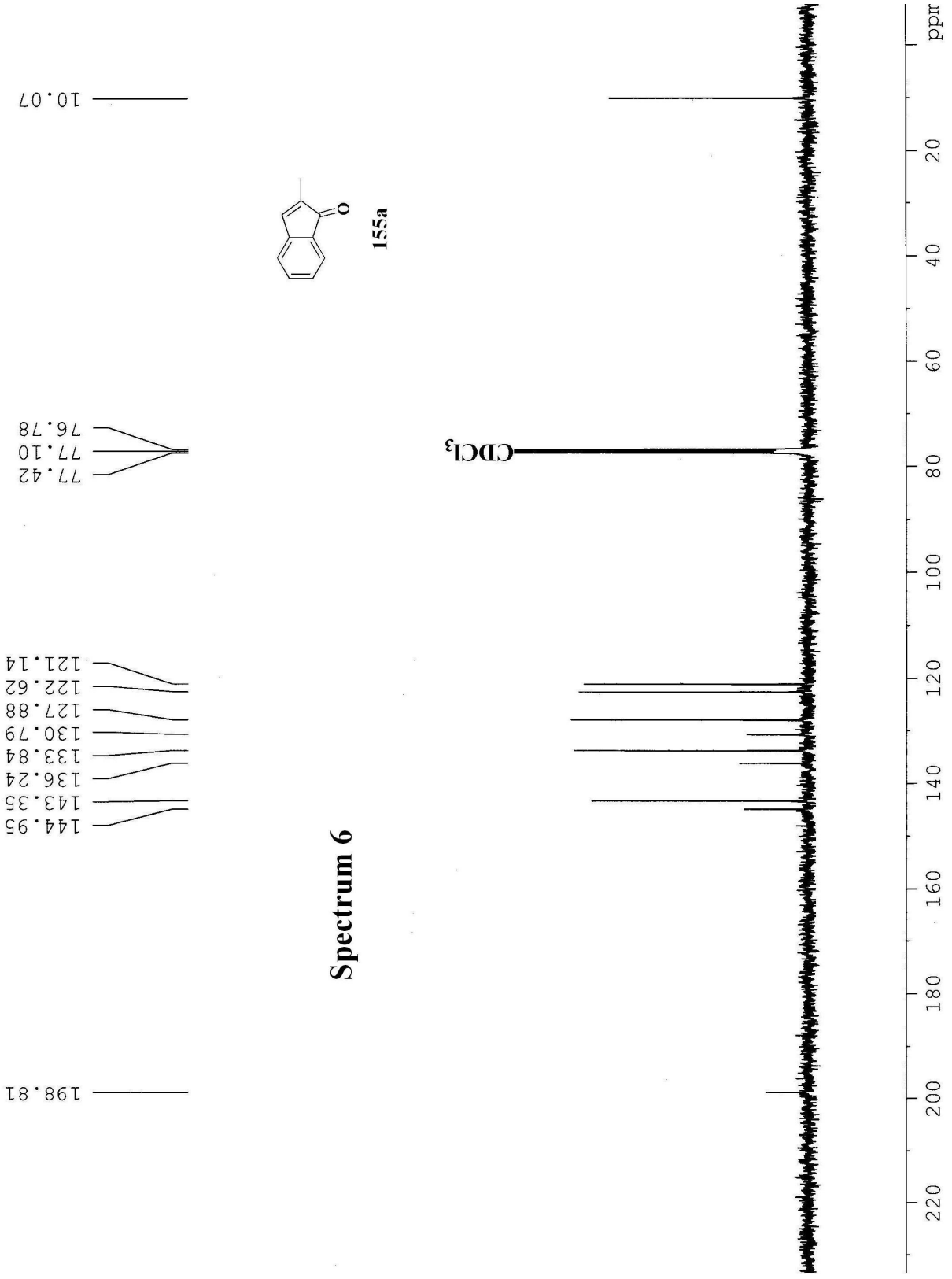
152a

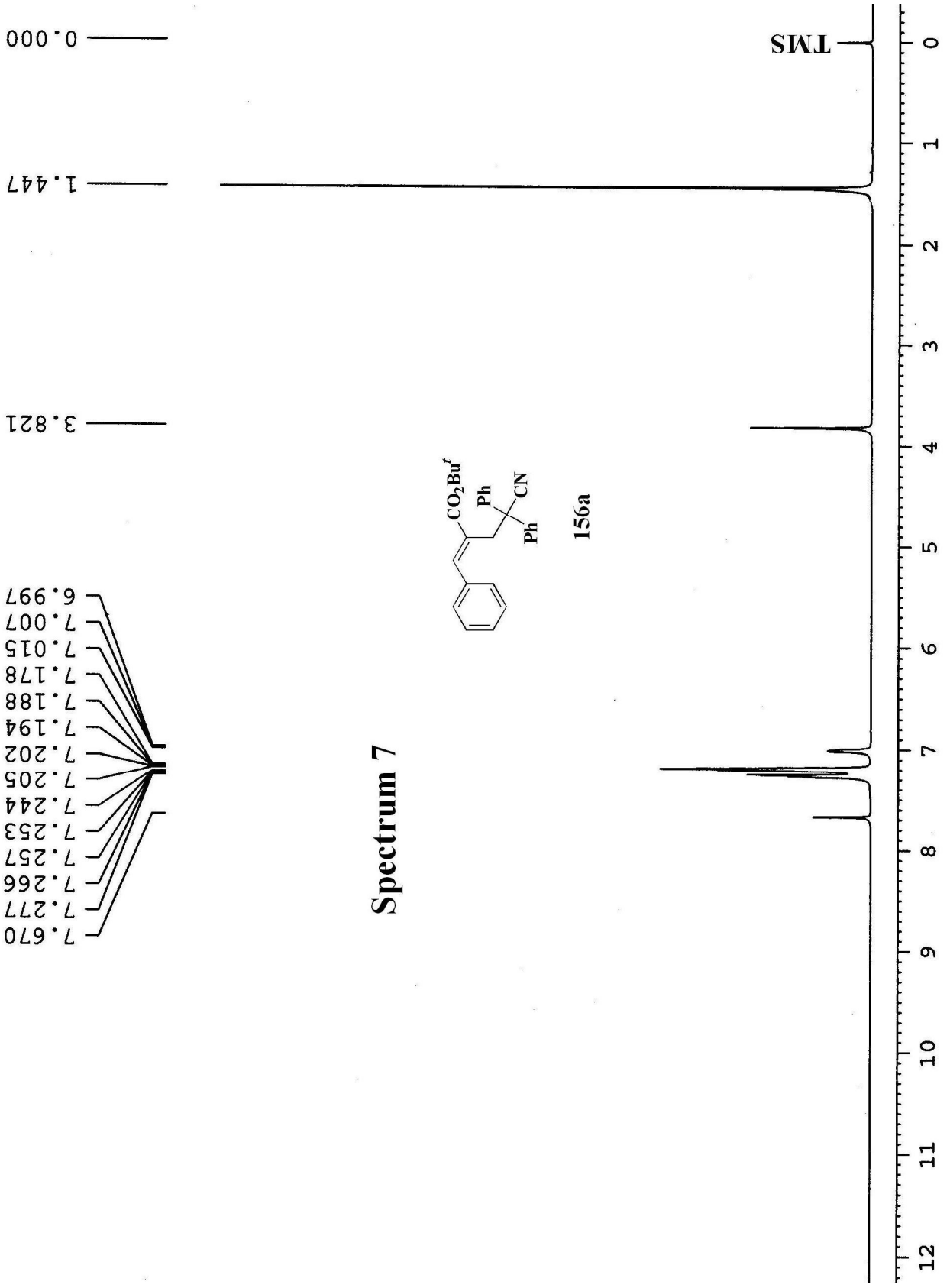


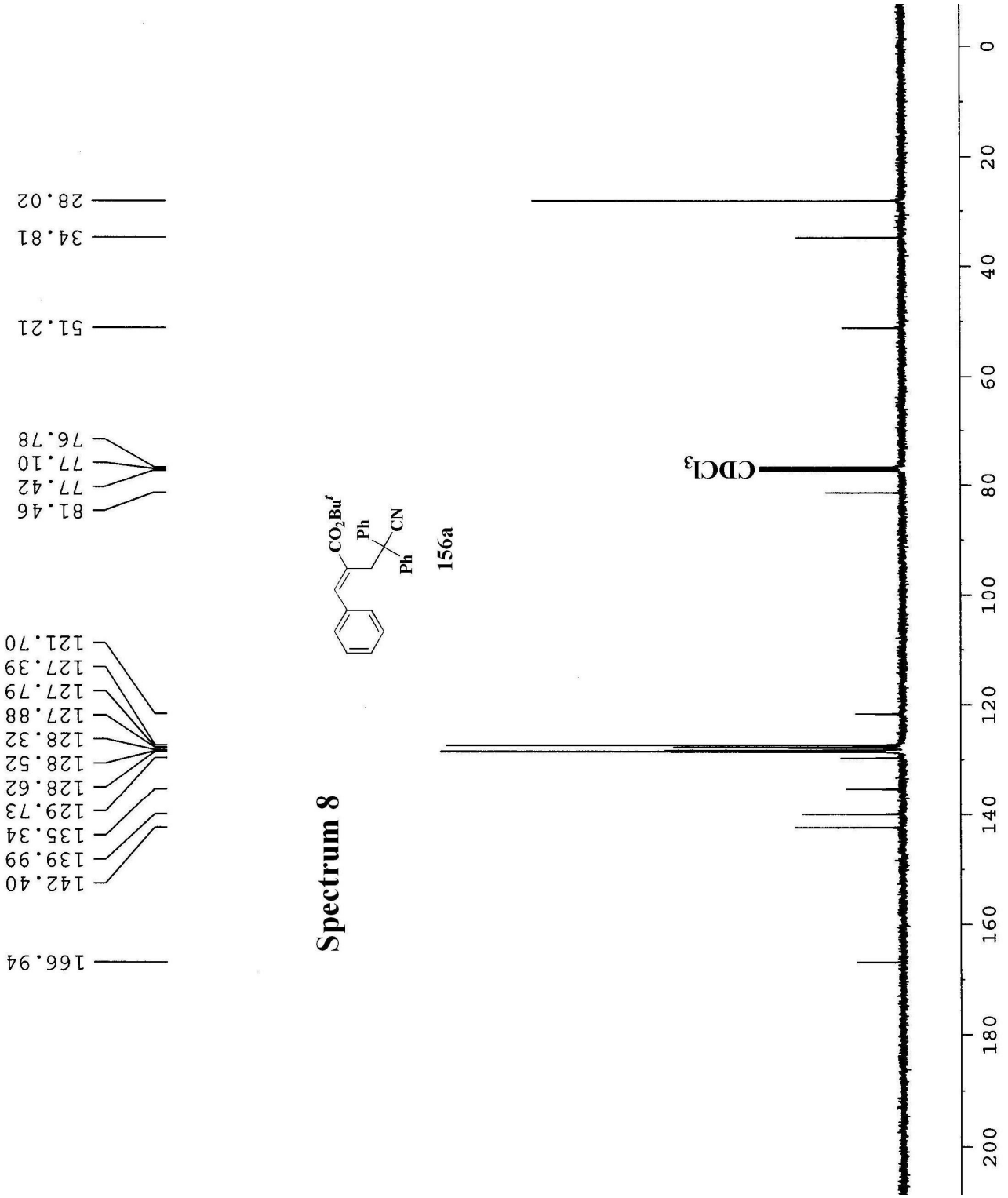
Spectrum 4

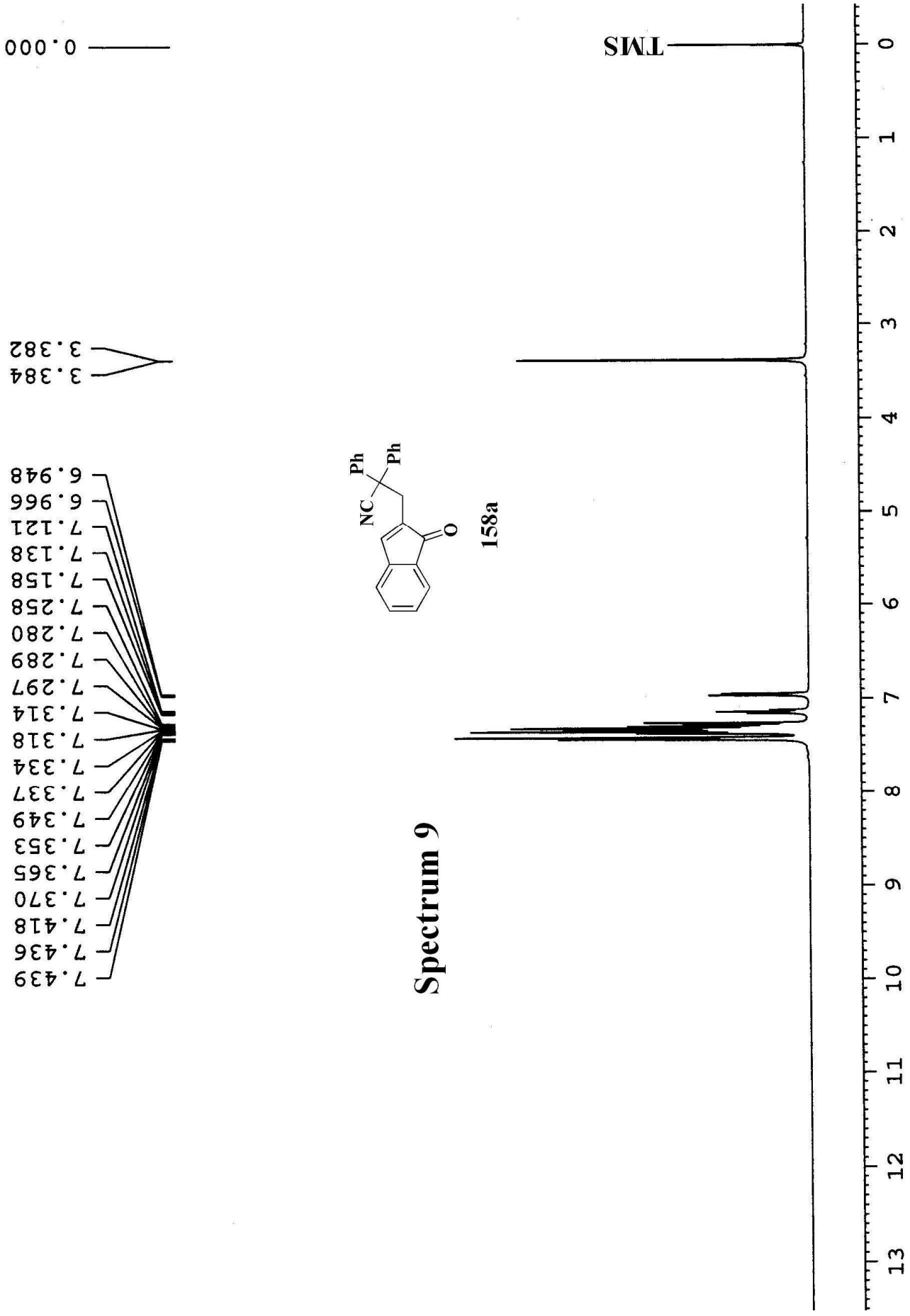
152a

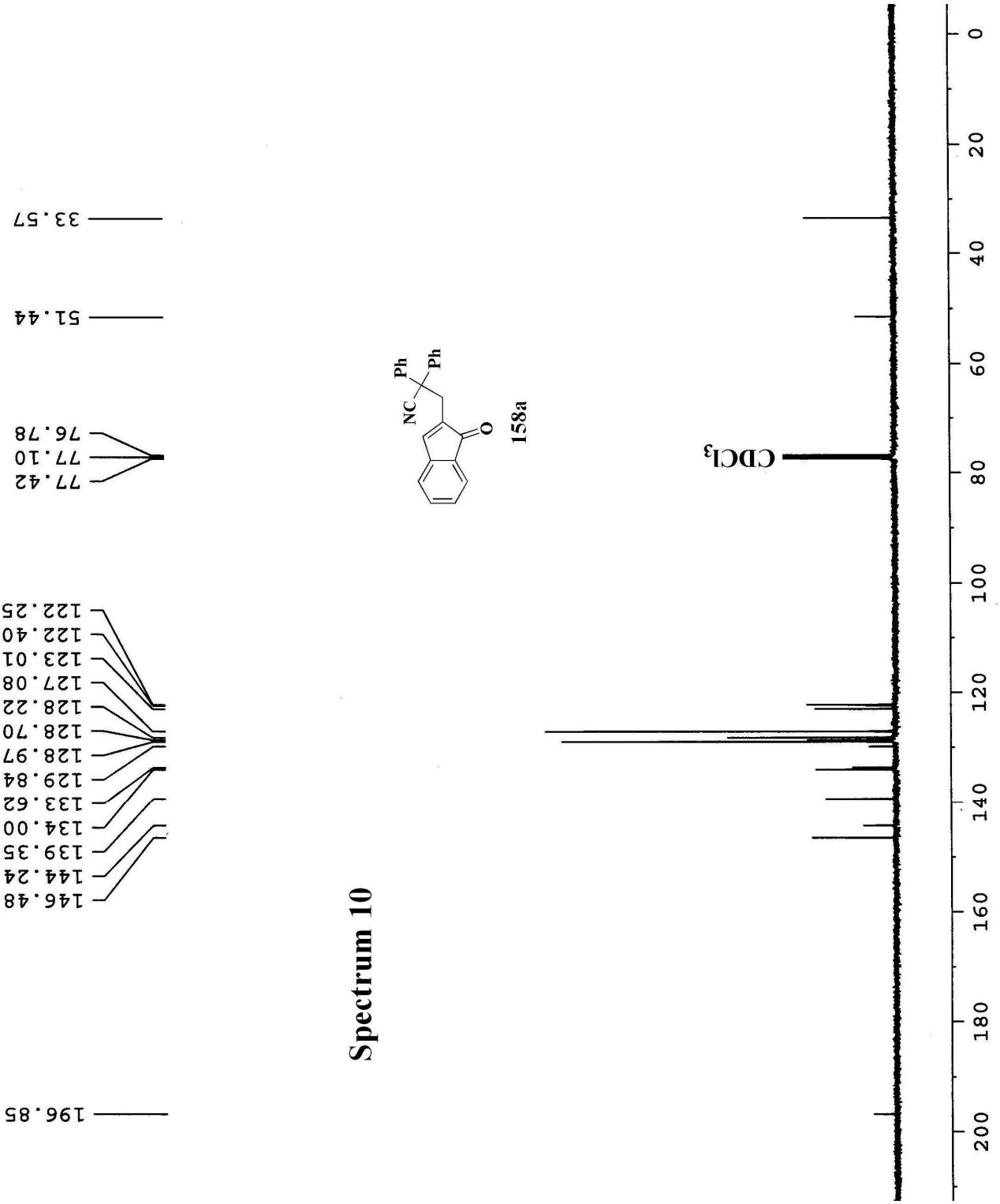

TMS
0.000
1.868
7.371
7.354
7.286
7.267
7.249
7.114
7.093
6.935
6.917
155a
Spectrum 5

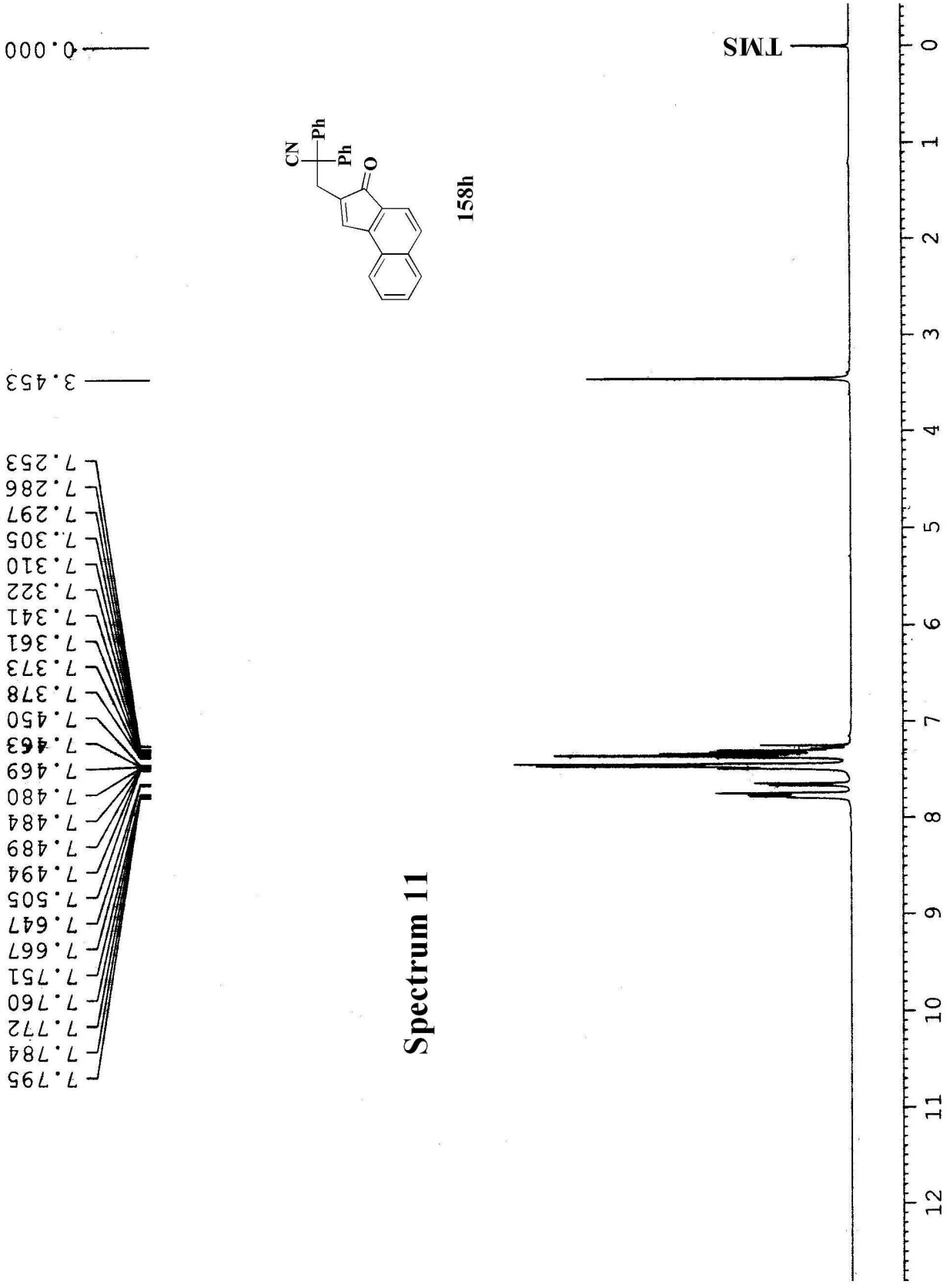

Spectrum 6
155a
CDCl3
198.81
144.95
143.35
136.24
133.84
130.79
127.88
122.62
121.14
77.42
77.10
76.78
10.07
ppm
220
200
180
160
140
120
100
80
60
40
20

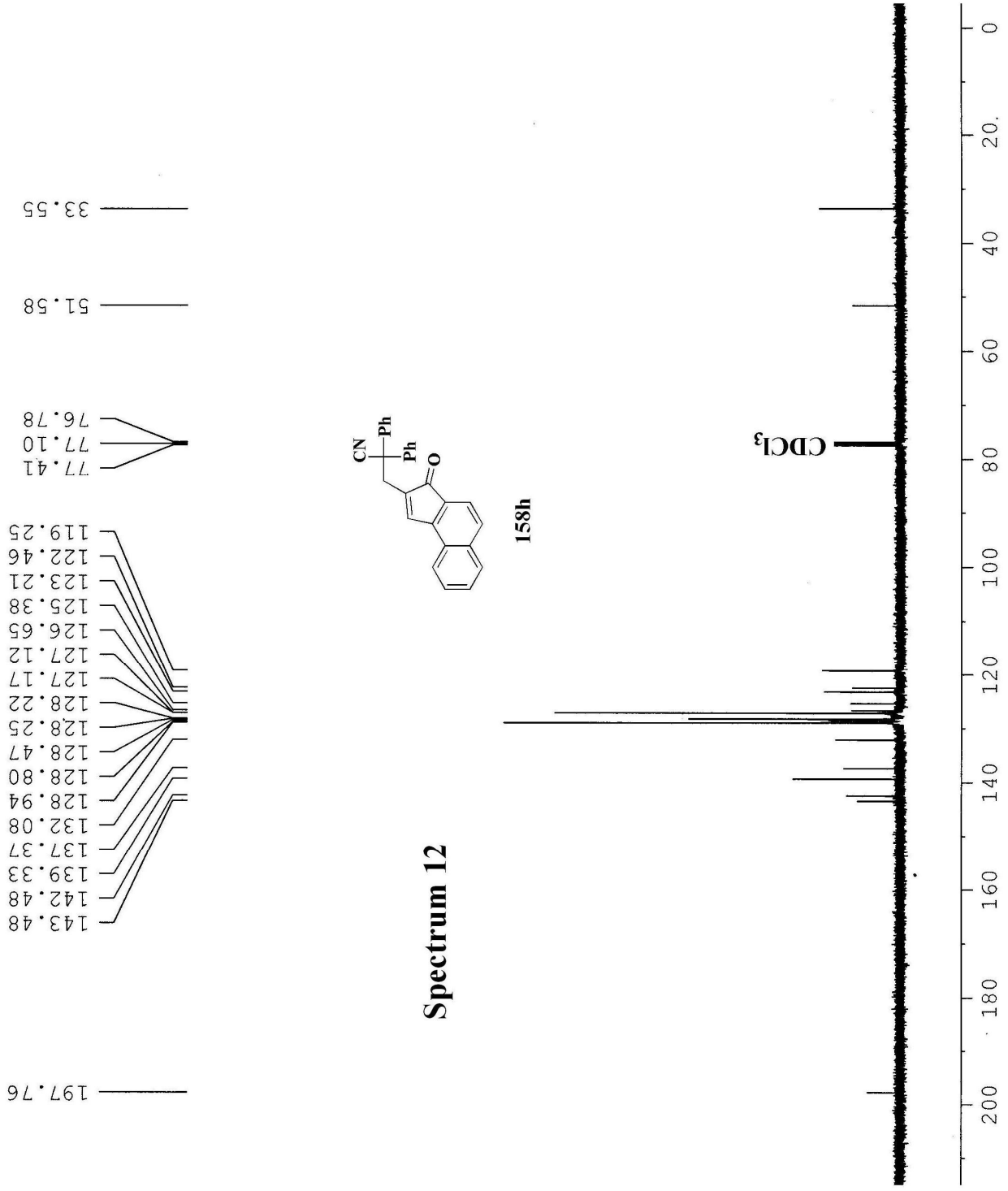

TMS
0.000
1.447
3.821
6.997
7.007
7.015
7.178
7.188
7.194
7.202
7.205
7.244
7.253
7.257
7.266
7.277
7.670
Spectrum 7
CO2But
Ph
CN
Ph
156a
0
1
2
3
4
5
6
7
8
9
10
11
12

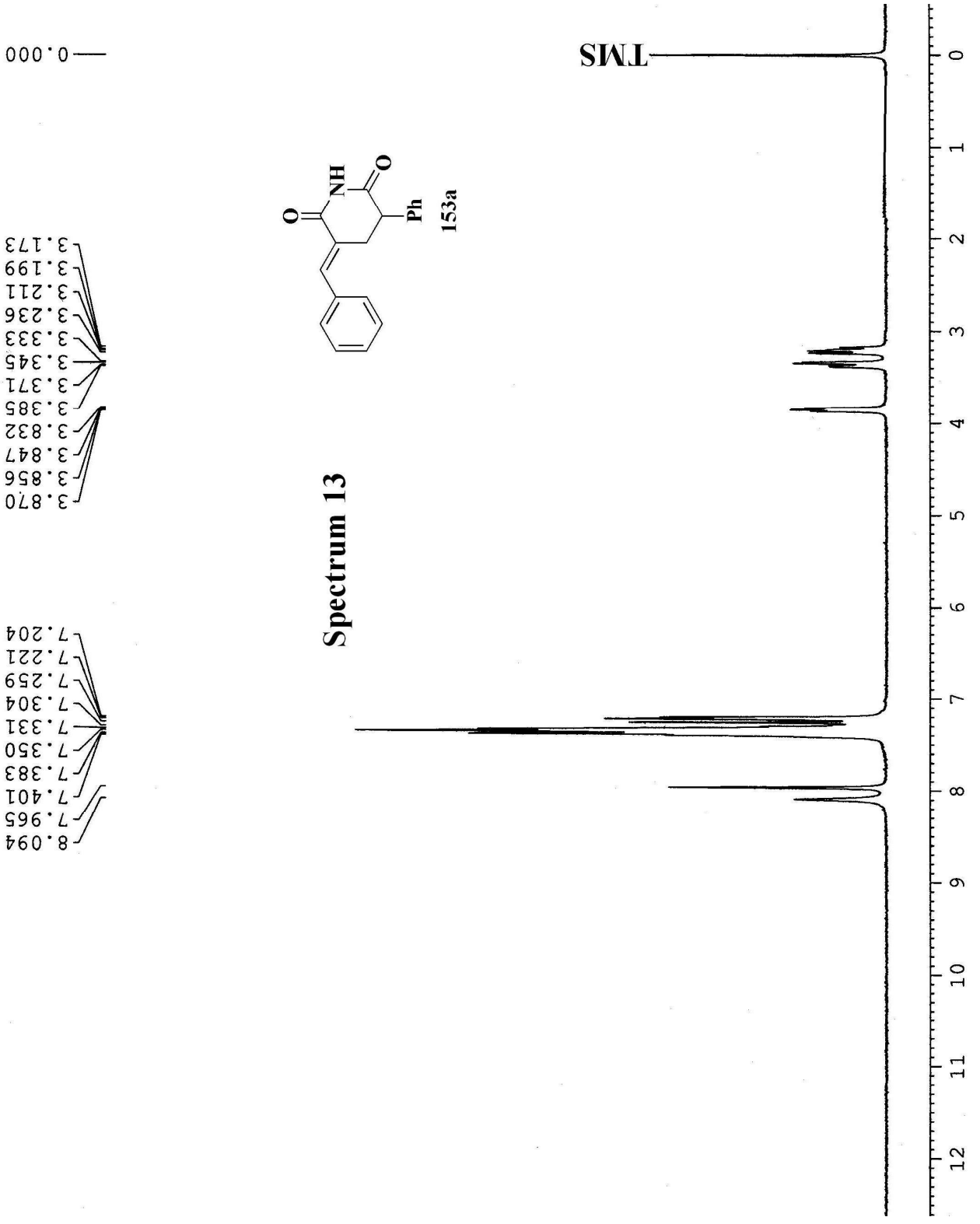

Spectrum 8
156a
CO2But
Ph
CN
Ph
CDCl3
28.02
34.81
51.21
76.78
77.10
77.42
81.46
121.70
127.39
127.79
127.88
128.32
128.52
128.62
129.73
135.34
139.99
142.40
166.94
0
20
40
60
80
100
120
140
160
180
200


Spectrum 9
158a
Ph
Ph
NC
O
TMS
0.000
3.382
3.384
6.948
6.966
7.121
7.138
7.158
7.258
7.280
7.289
7.297
7.314
7.318
7.334
7.337
7.349
7.353
7.365
7.370
7.418
7.436
7.439
0
1
2
3
4
5
6
7
8
9
10
11
12
13


Spectrum 10
158a
Ph
Ph
NC
O
CDCl3
0
20
40
60
80
100
120
140
160
180
200
33.57
51.44
76.78
77.10
77.42
122.25
122.40
123.01
127.08
128.22
128.70
128.97
129.84
133.62
134.00
139.35
144.24
146.48
196.85


0.000
3.453
7.253
7.286
7.297
7.305
7.310
7.322
7.341
7.361
7.373
7.378
7.450
7.463
7.469
7.480
7.484
7.489
7.494
7.505
7.647
7.667
7.751
7.760
7.772
7.784
7.795
TMS
CN
Ph
Ph
O
158h
Spectrum 11
0
1
2
3
4
5
6
7
8
9
10
11
12


Spectrum 12
158h
CN
Ph
Ph
O
CDCl3
0
20
40
60
80
100
120
140
160
180
200
33.55
51.58
76.78
77.10
77.41
119.25
122.46
123.21
125.38
126.65
127.12
127.17
128.22
128.25
128.47
128.80
128.94
132.08
137.37
139.33
142.48
143.48
197.76


Spectrum 13
153a
Ph
NH
O
O
TMS
0.000
3.173
3.199
3.211
3.236
3.333
3.345
3.371
3.385
3.832
3.847
3.856
3.870
7.204
7.221
7.259
7.304
7.331
7.350
7.383
7.401
7.965
8.094
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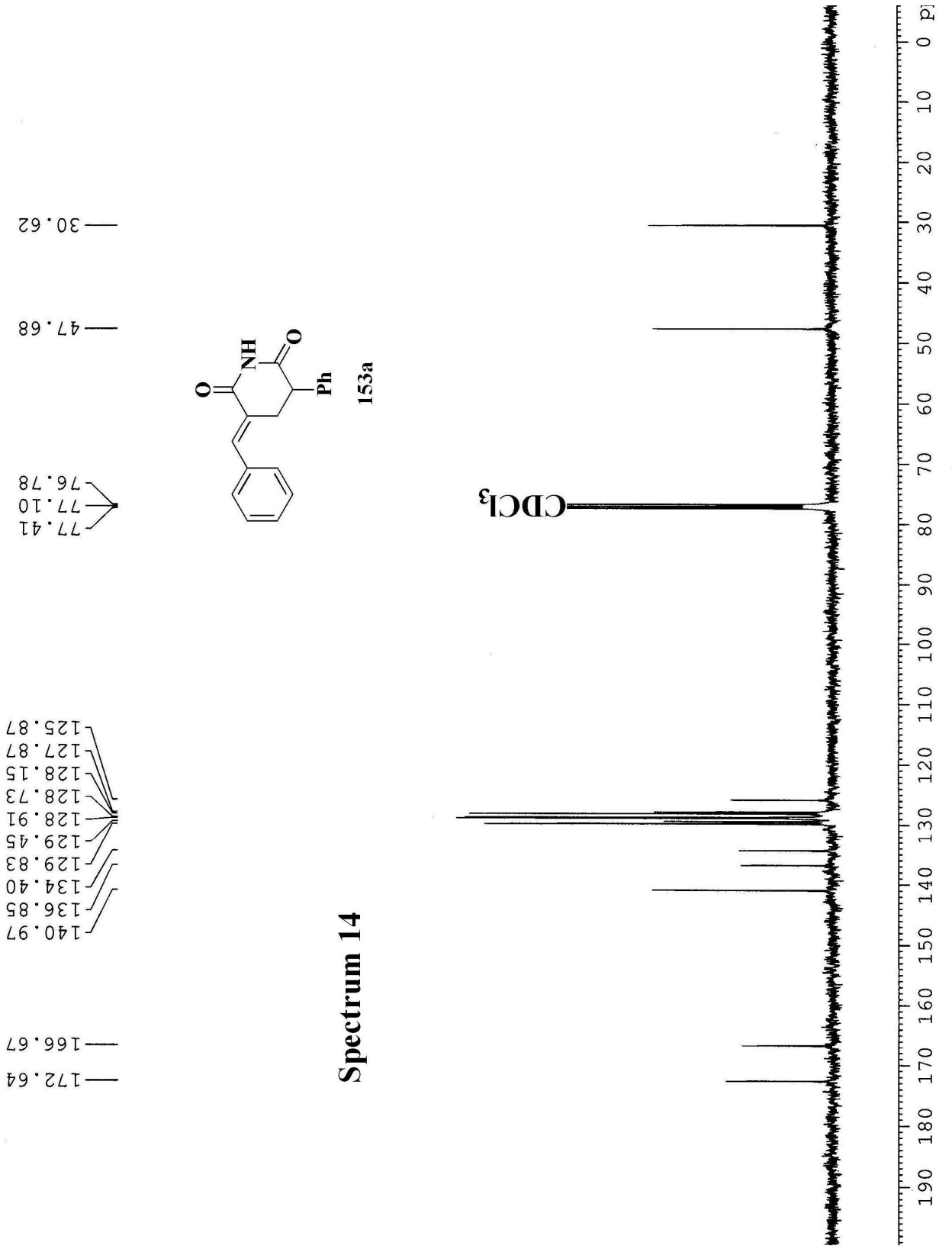
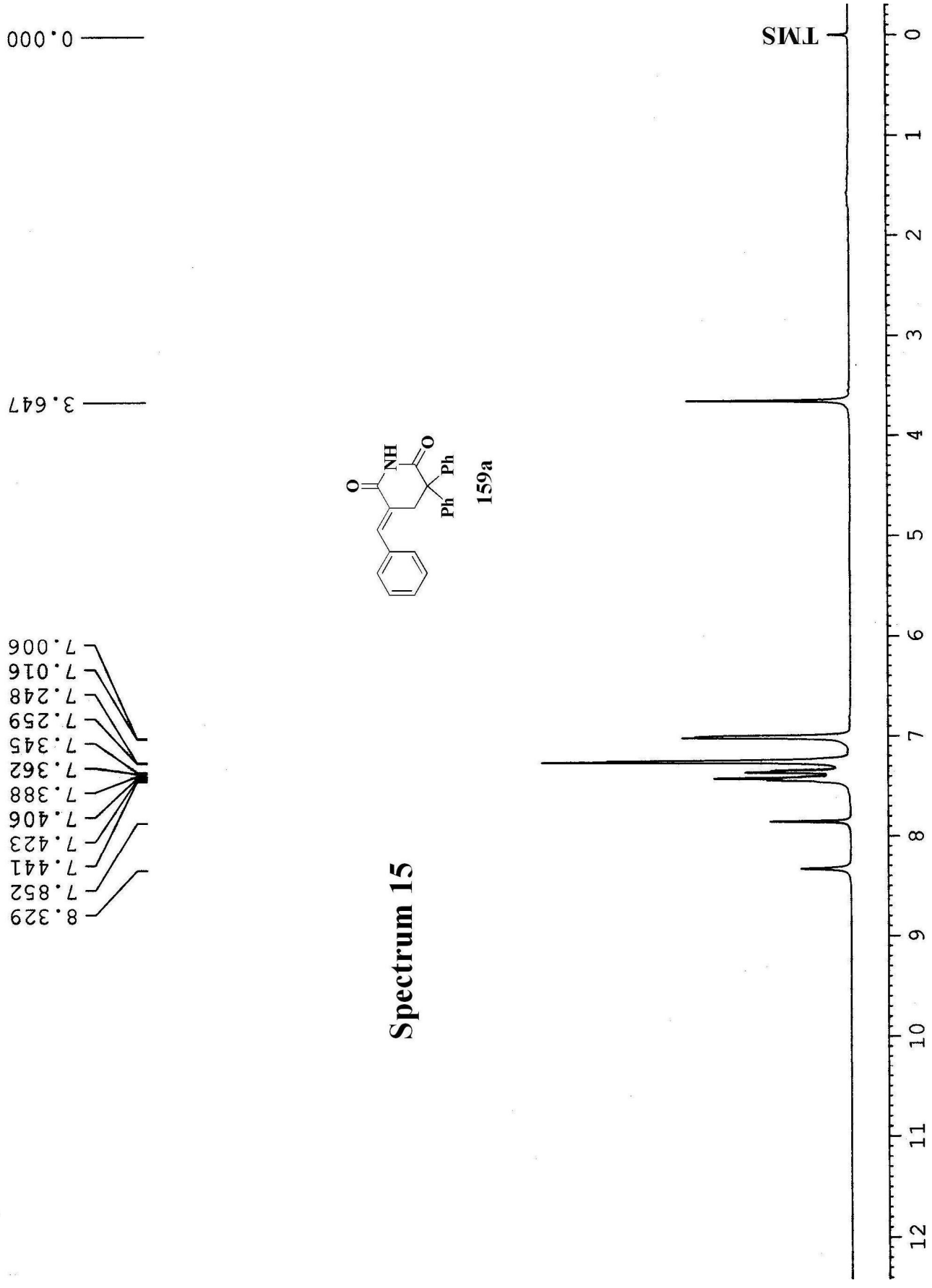
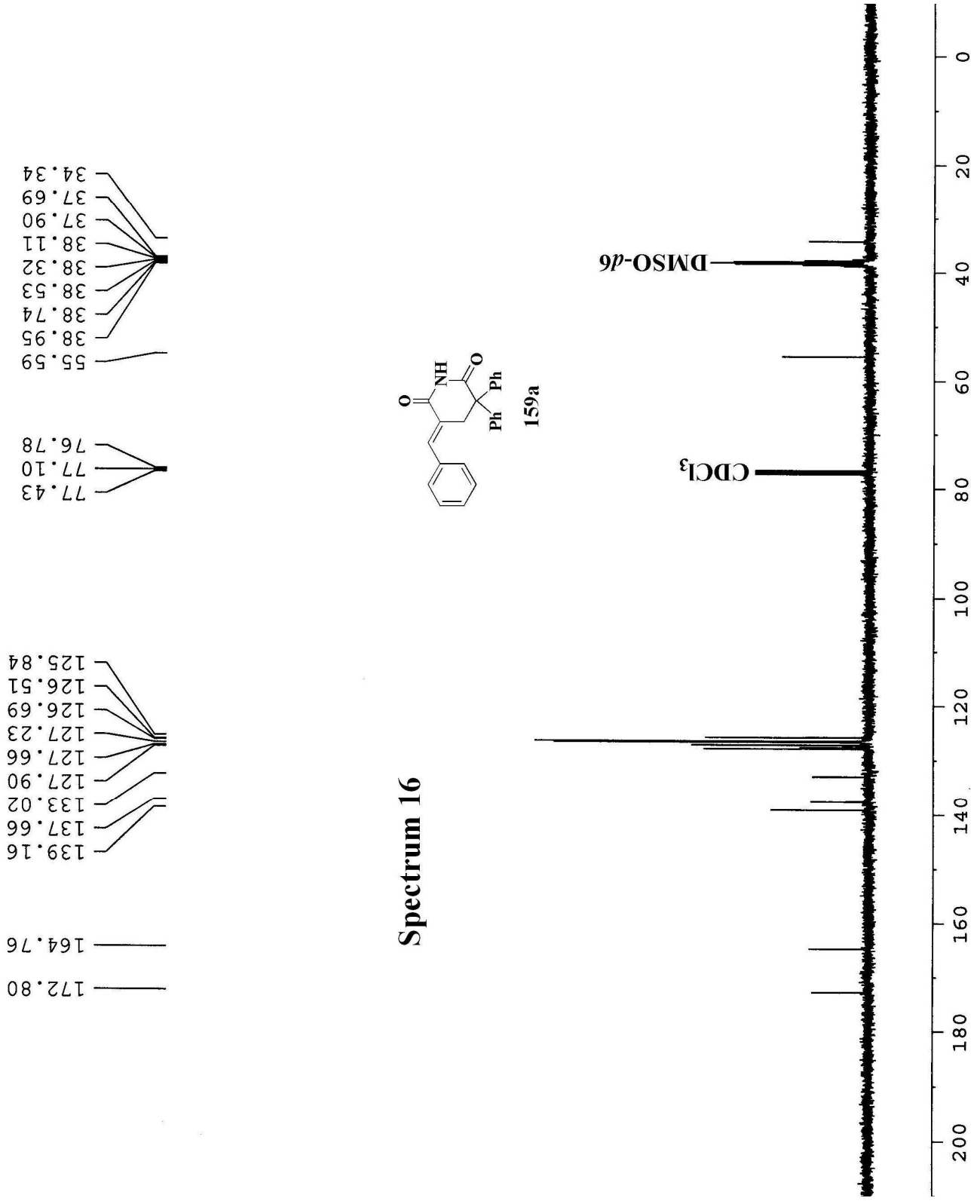
3
4
5
6
7
8
9
10
11
12

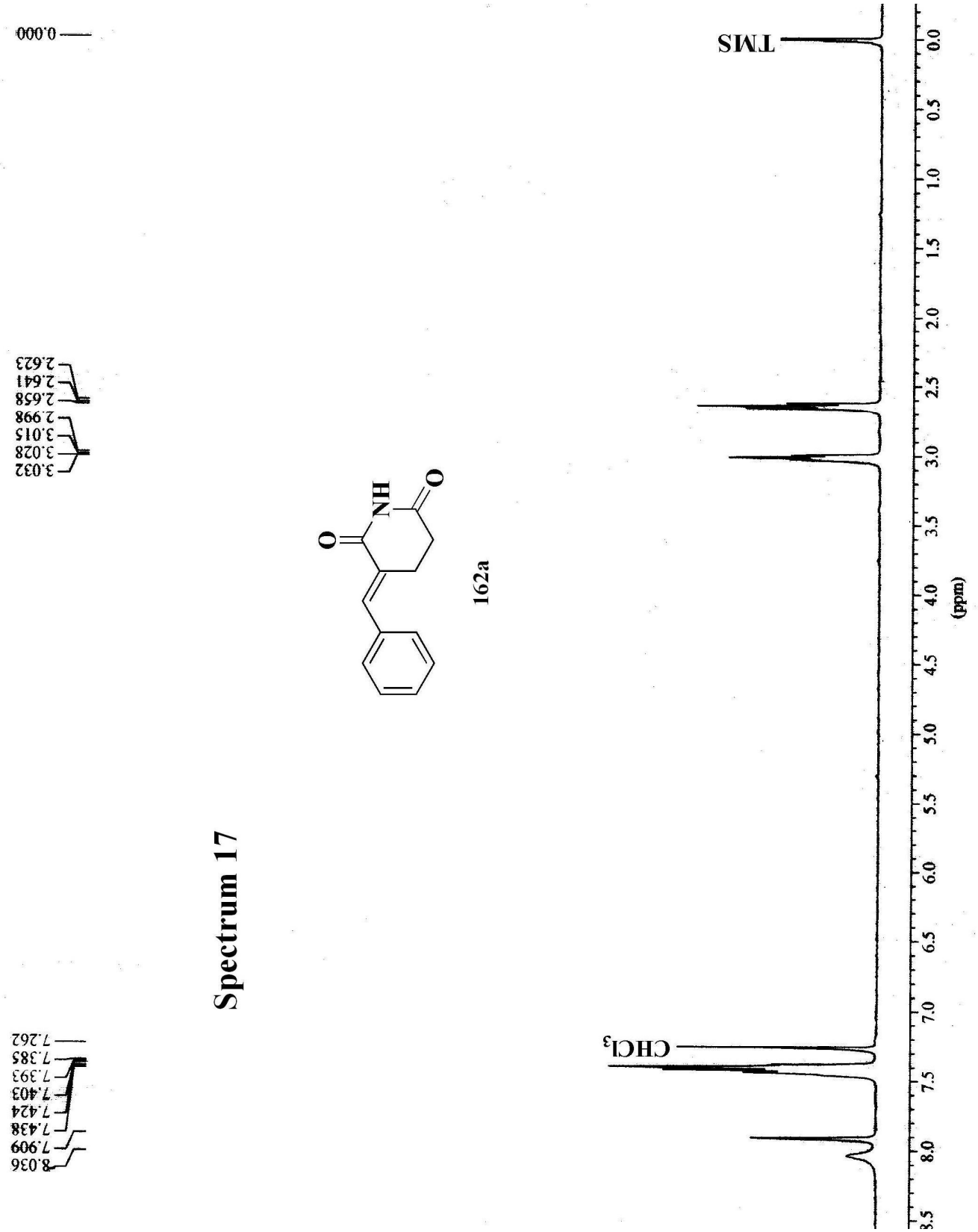

CDCl3
77.41
77.10
76.78
47.68
30.62
172.64
166.67
140.97
136.85
134.40
129.83
129.45
128.91
128.73
128.15
127.87
125.87
O
NH
O
Ph
153a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

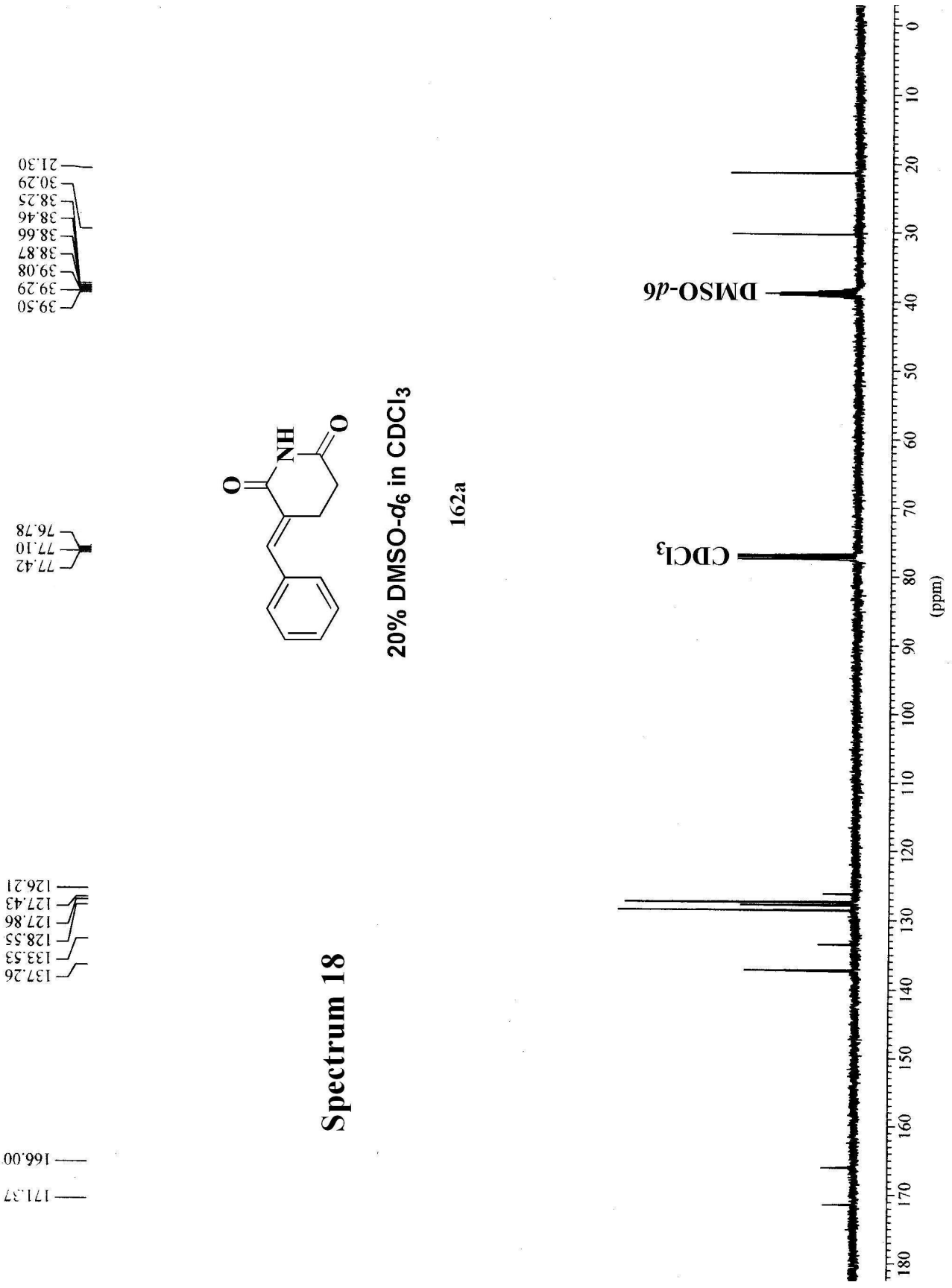
Spectrum 14

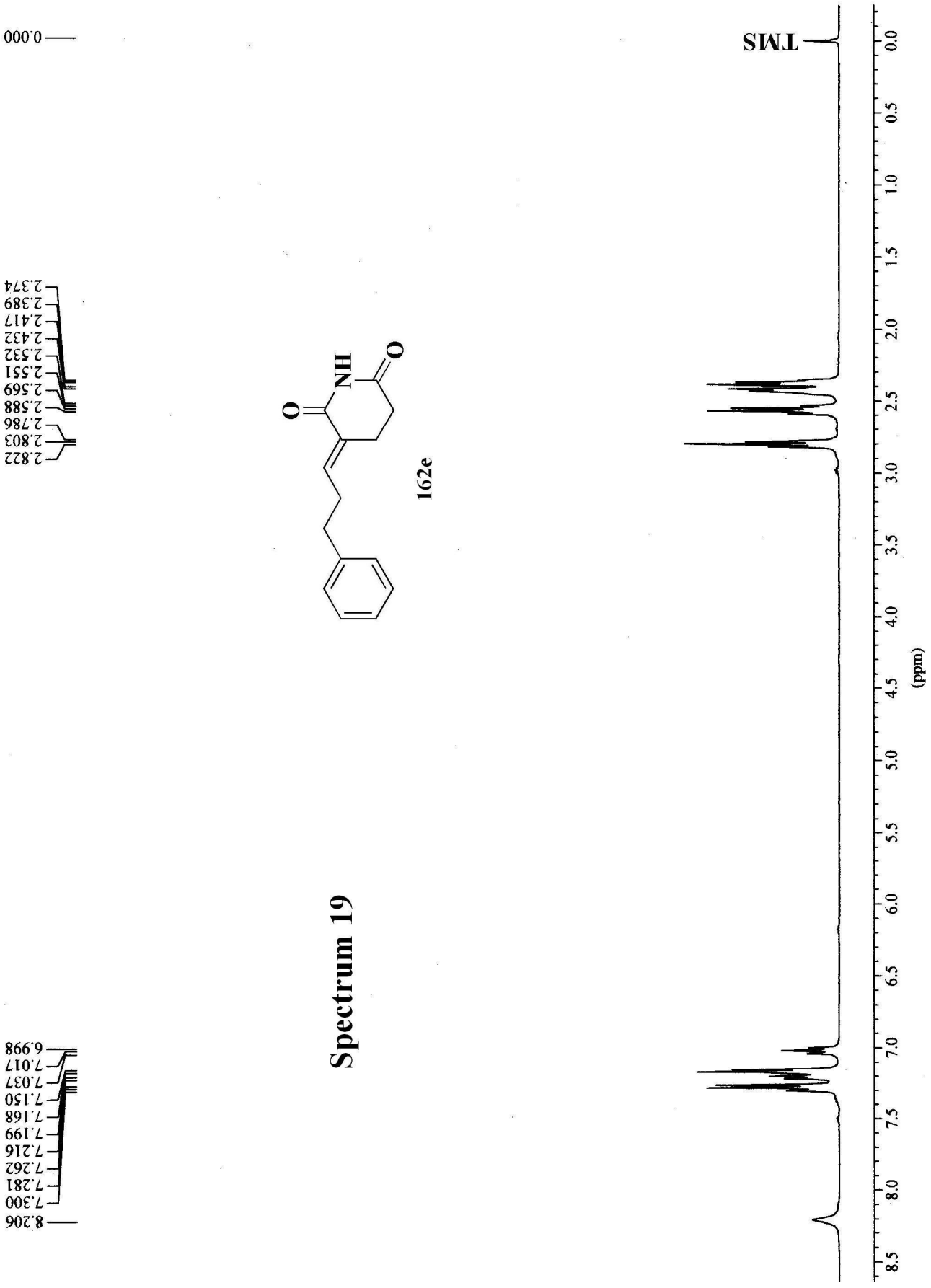

TMS
0.000
3.647
8.329
7.852
7.441
7.423
7.406
7.388
7.362
7.345
7.259
7.248
7.016
7.006
NH
O
O
Ph
Ph
159a
0
1
2
3
4
5
6
7
8
9
10
11
12

Spectrum 15


Spectrum 16
159a
NH
O
O
Ph
Ph
DMSO-d6
CDCl3
0
20
40
60
80
100
120
140
160
180
200
34.34
37.69
37.90
38.11
38.32
38.53
38.74
38.95
55.59
76.78
77.10
77.43
125.84
126.51
126.69
127.23
127.66
127.90
133.02
137.66
139.16
164.76
172.80

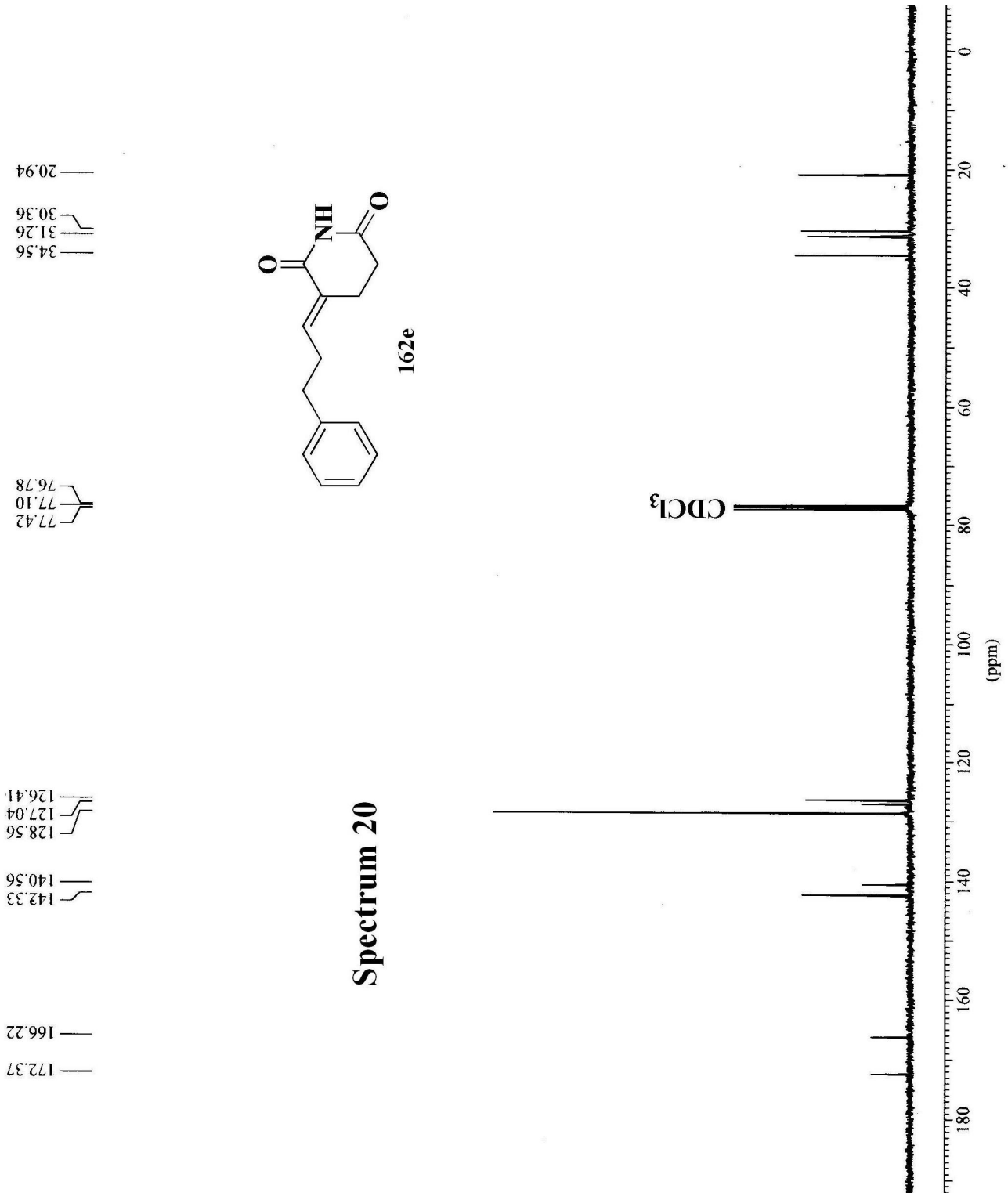

Spectrum 17
162a
TMS
CHCl3
(ppm)
0.000
2.623
2.641
2.658
2.998
3.015
3.028
3.032
7.262
7.385
7.393
7.403
7.424
7.438
7.909
8.036

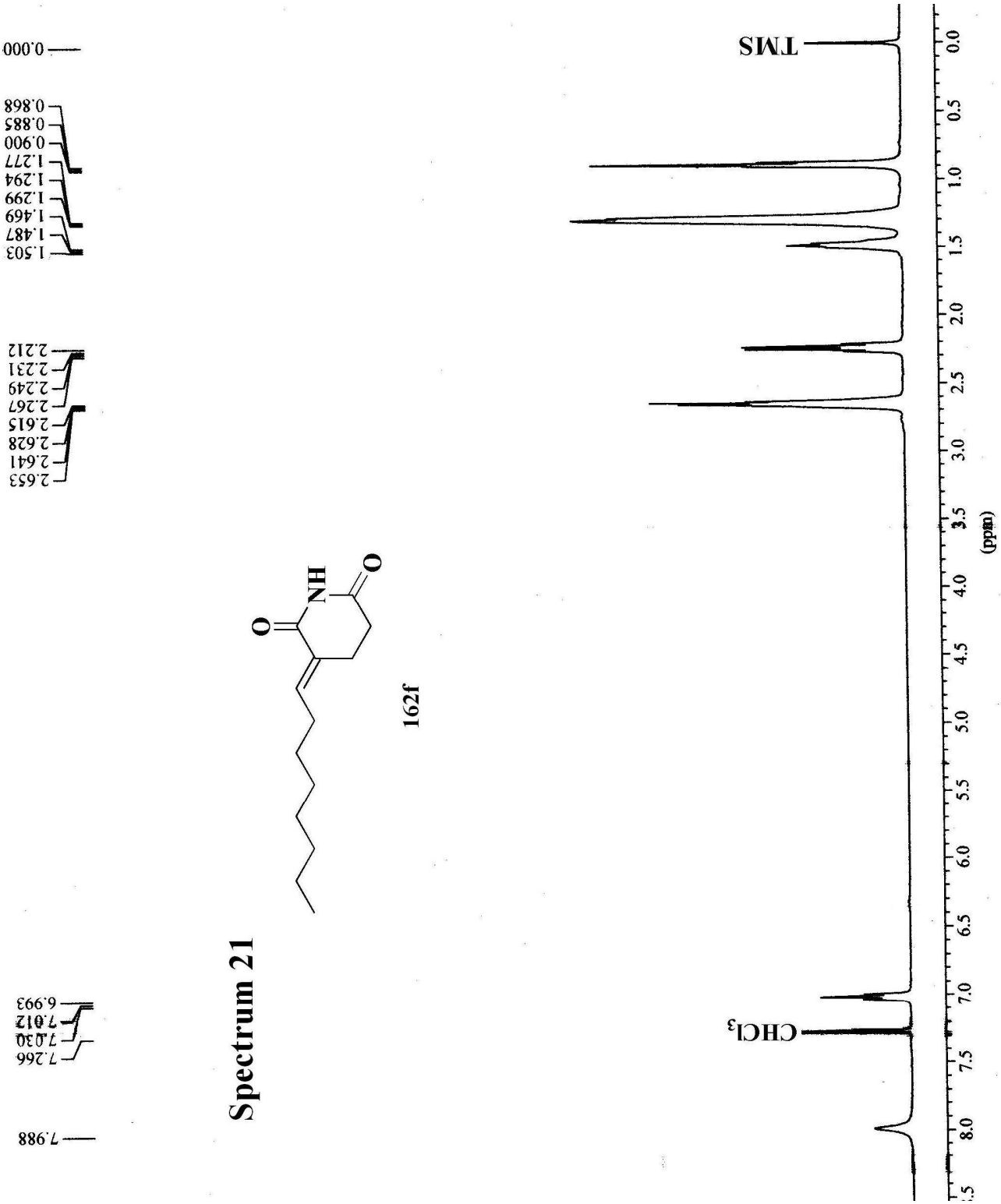

Spectrum 18
20% DMSO-d_6 in $CDCl_3$
162a
O
NH
O
DMSO-d6
CDCl3
(ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
21.30
30.29
38.25
38.46
38.66
38.87
39.08
39.29
39.50
76.78
77.10
77.42
126.21
127.43
127.86
128.55
133.53
137.26
166.00
171.37

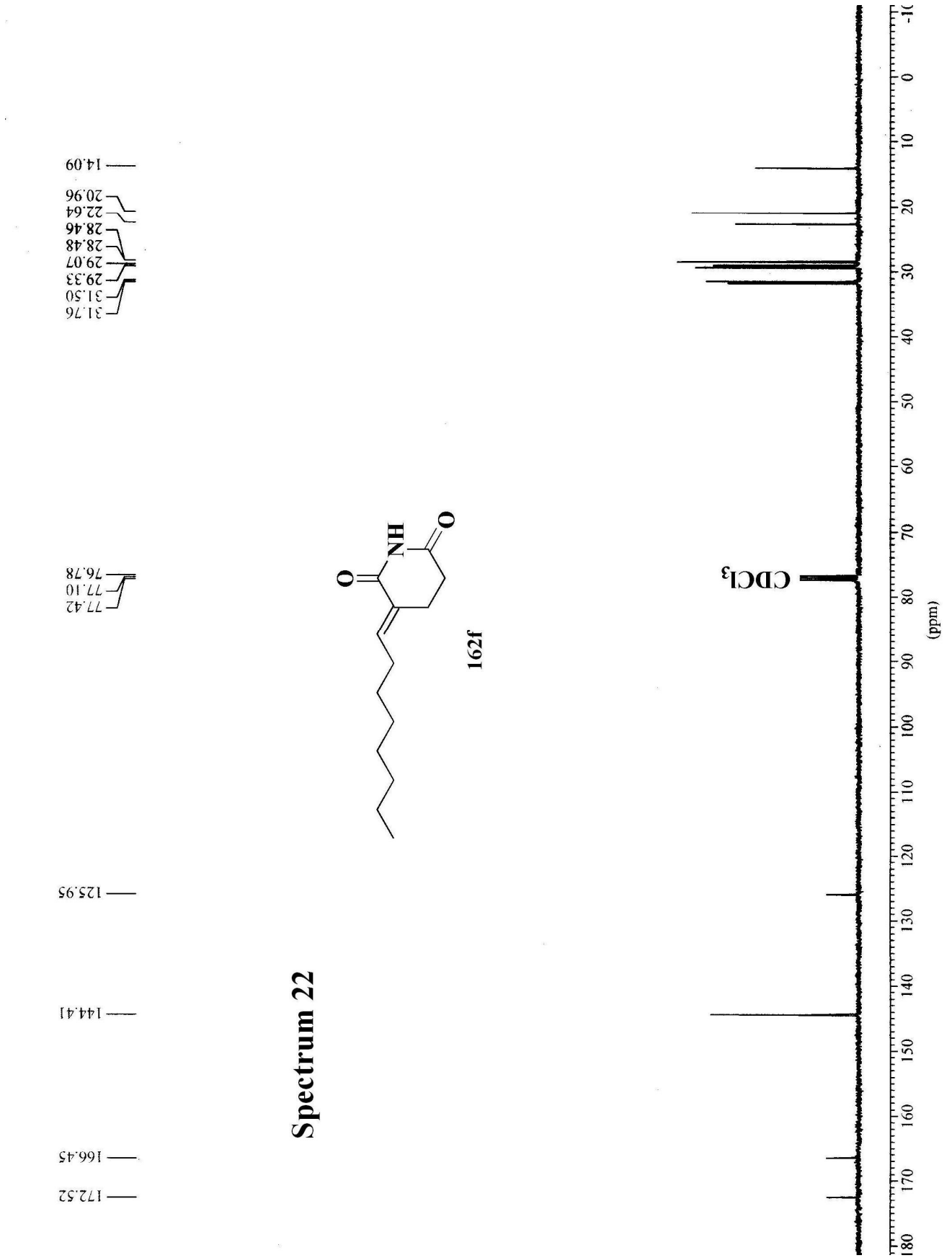


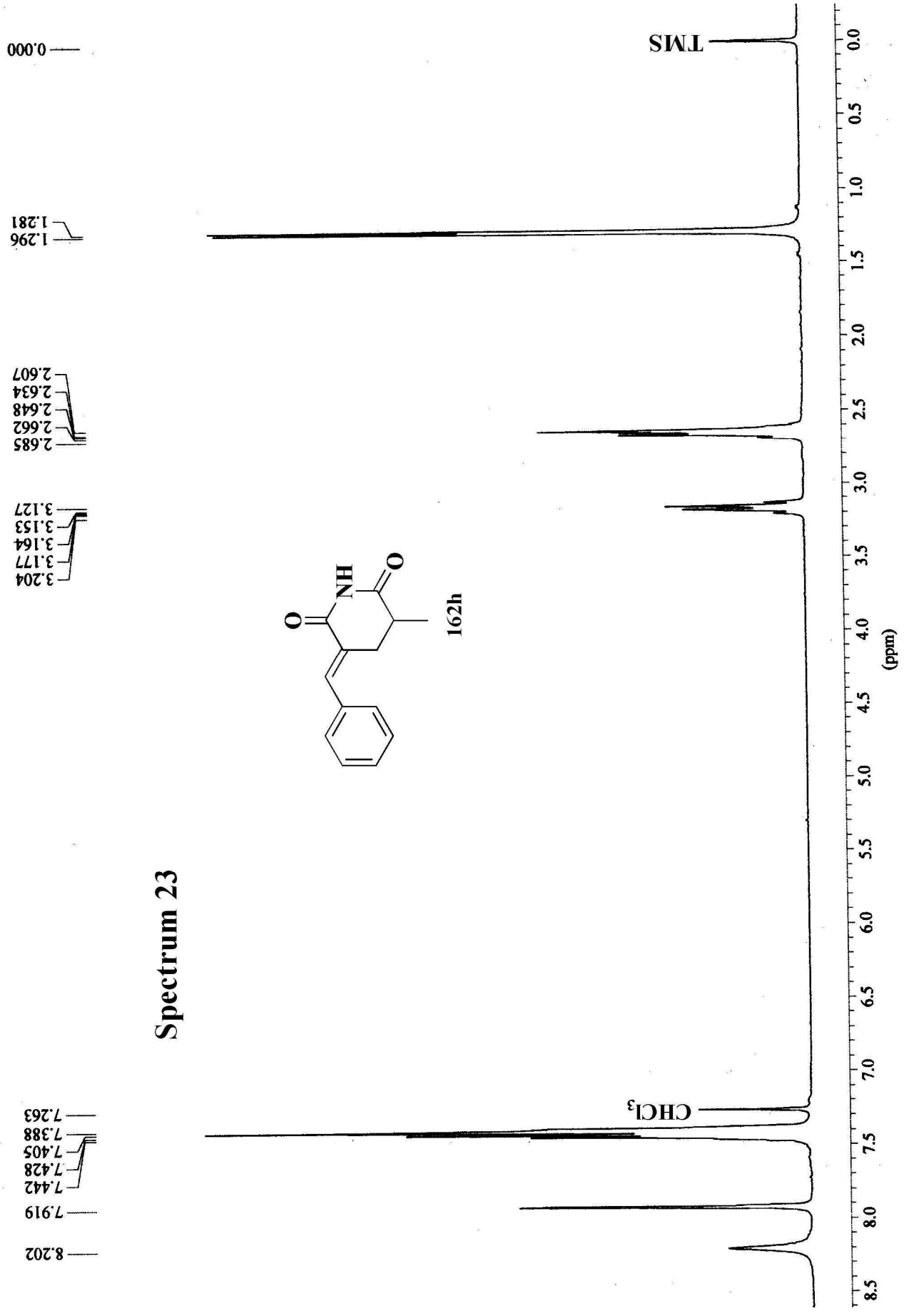
Spectrum 19

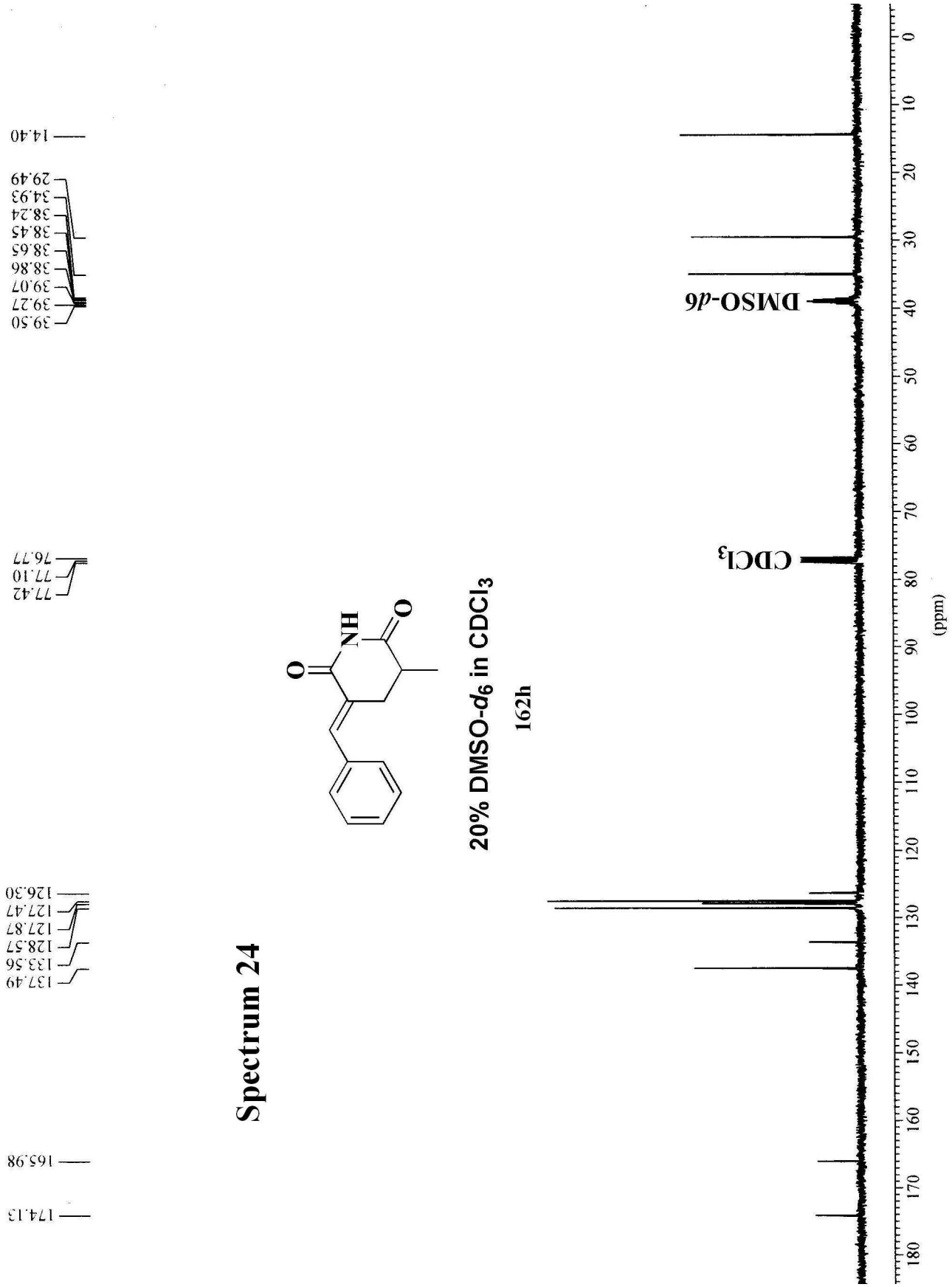
162e

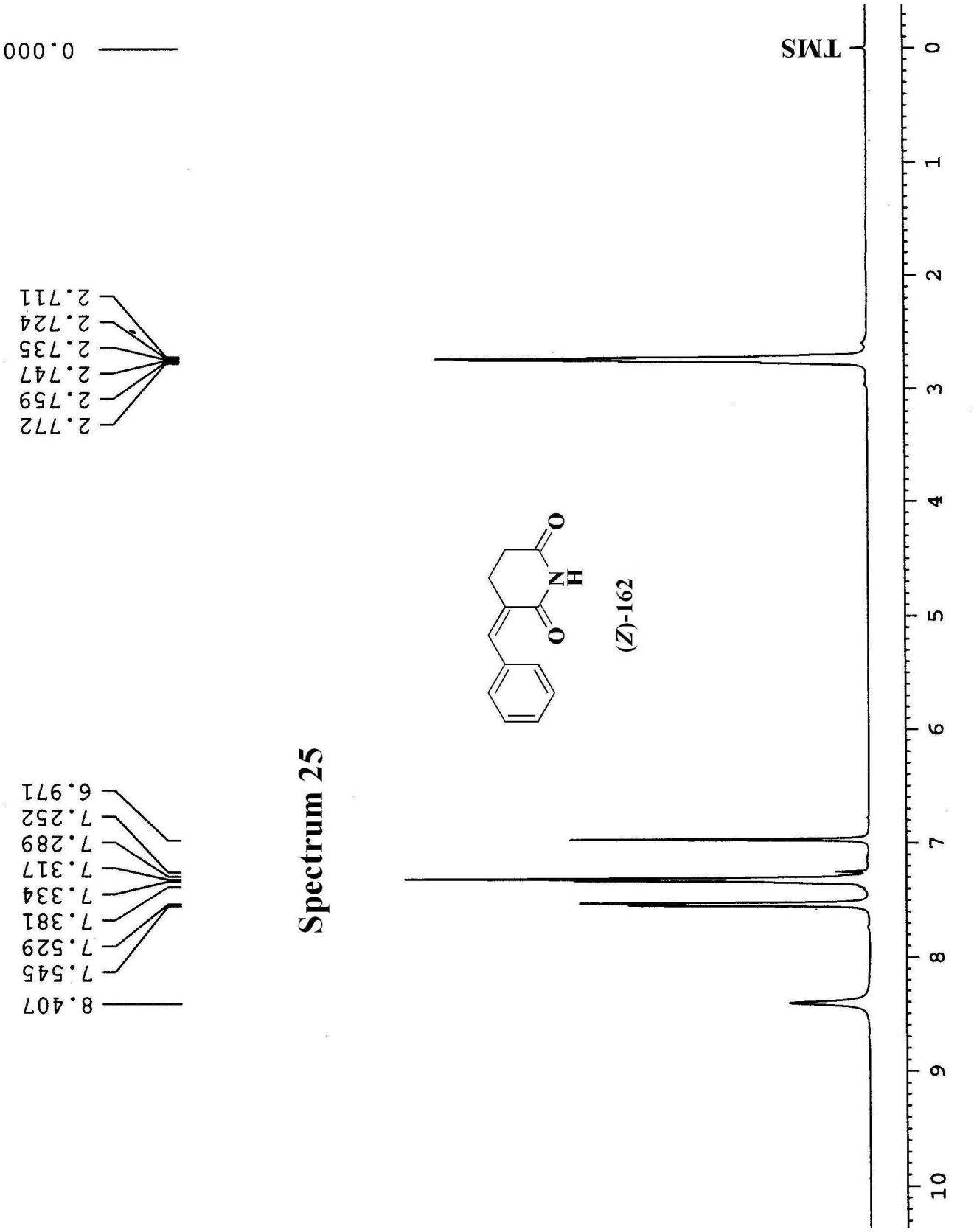

Spectrum 20
162e
CDCl3
20.94
30.36
31.26
34.56
77.42
77.10
76.78
126.41
127.04
128.56
140.56
142.33
166.22
172.37
(ppm)


Spectrum 21
162f
O
NH
O
TMS
CHCl3
(ppm)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
0.000
0.868
0.885
0.900
1.277
1.294
1.299
1.469
1.487
1.503
2.212
2.231
2.249
2.267
2.615
2.628
2.641
2.653
6.993
7.012
7.030
7.266
7.988

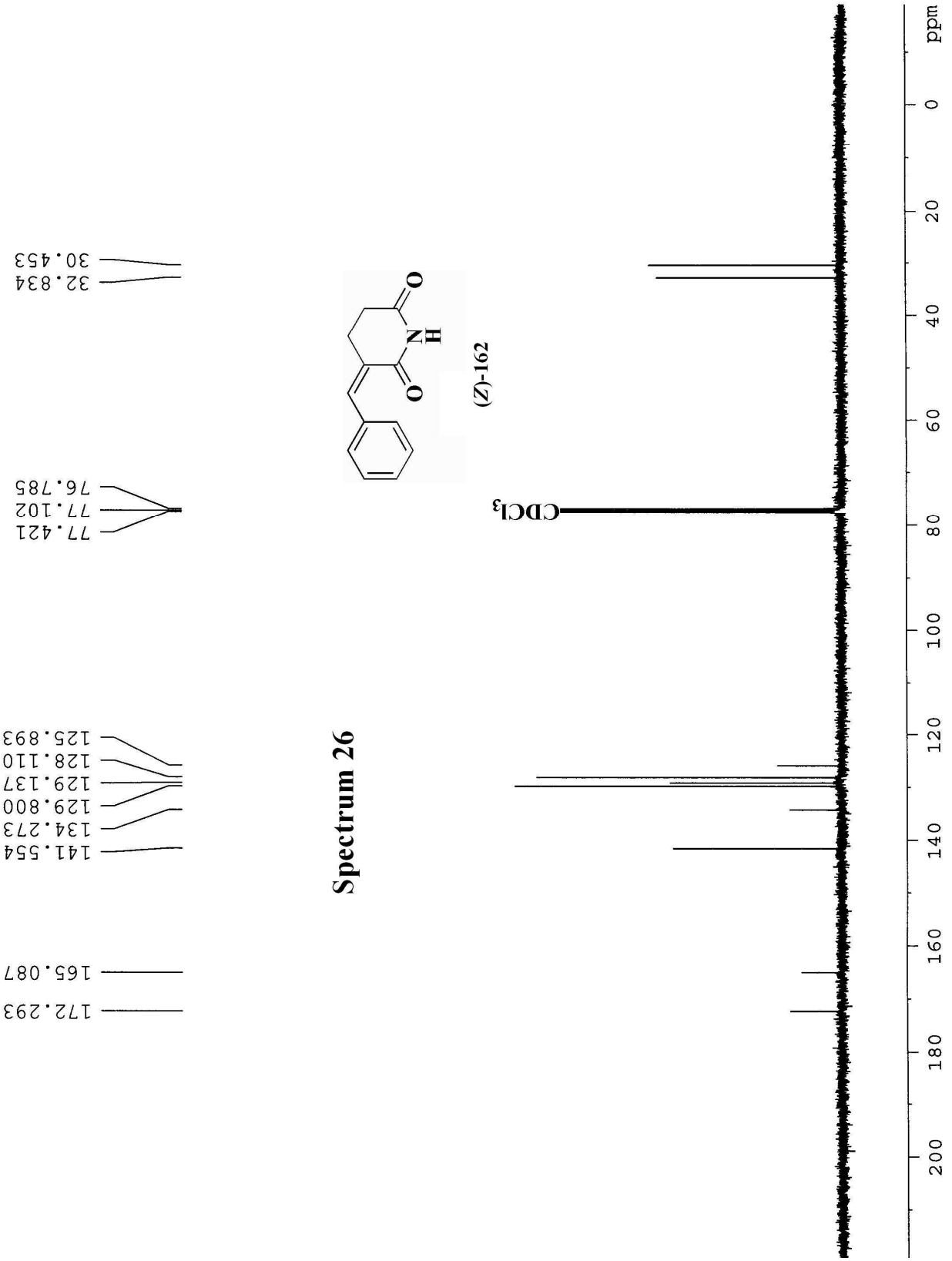

Spectrum 22
162f
CDCl3
(ppm)
172.52
166.45
144.41
125.95
77.42
77.10
76.78
31.76
31.50
29.33
29.07
28.48
28.46
22.64
20.96
14.09


Spectrum 23
TMS
CHCl3
0.000
1.281
1.296
2.607
2.634
2.648
2.662
2.685
3.127
3.153
3.164
3.177
3.204
7.263
7.388
7.405
7.428
7.442
7.919
8.202
NH
O
O
162h
(ppm)


Spectrum 24
20% DMSO-d_6 in $CDCl_3$
162h
$CDCl_3$
DMSO-$d6$
(ppm)
14.40
29.49
34.93
38.24
38.45
38.65
38.86
39.07
39.27
39.50
76.77
77.10
77.42
126.30
127.47
127.87
128.57
133.56
137.49
165.98
174.13

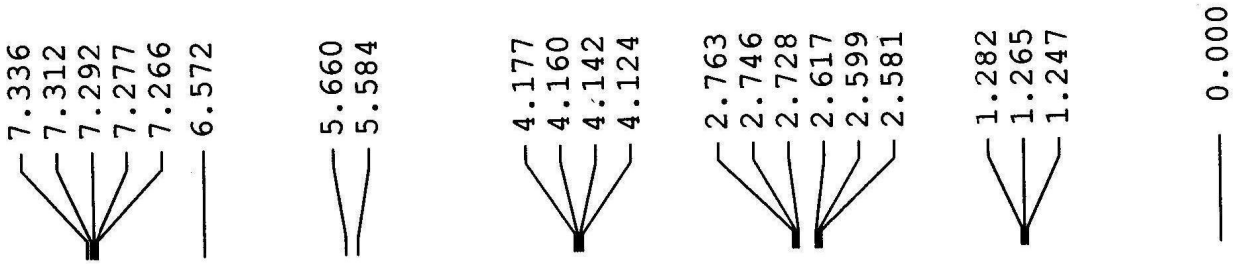

0.000
2.772
2.759
2.747
2.735
2.724
2.711
8.407
7.545
7.529
7.381
7.334
7.317
7.289
7.252
6.971
TMS
0
1
2
3
4
5
6
7
8
9
10
O
N
H
O
(Z)-162

Spectrum 25

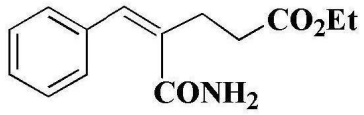


Spectrum 26

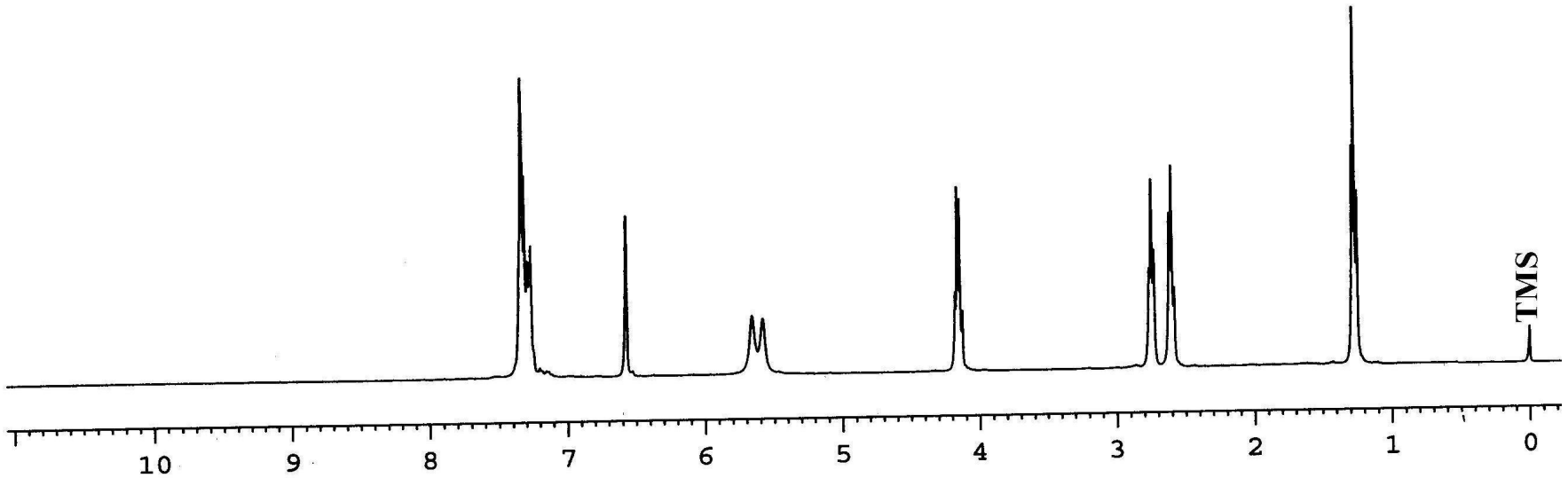
(Z)-162

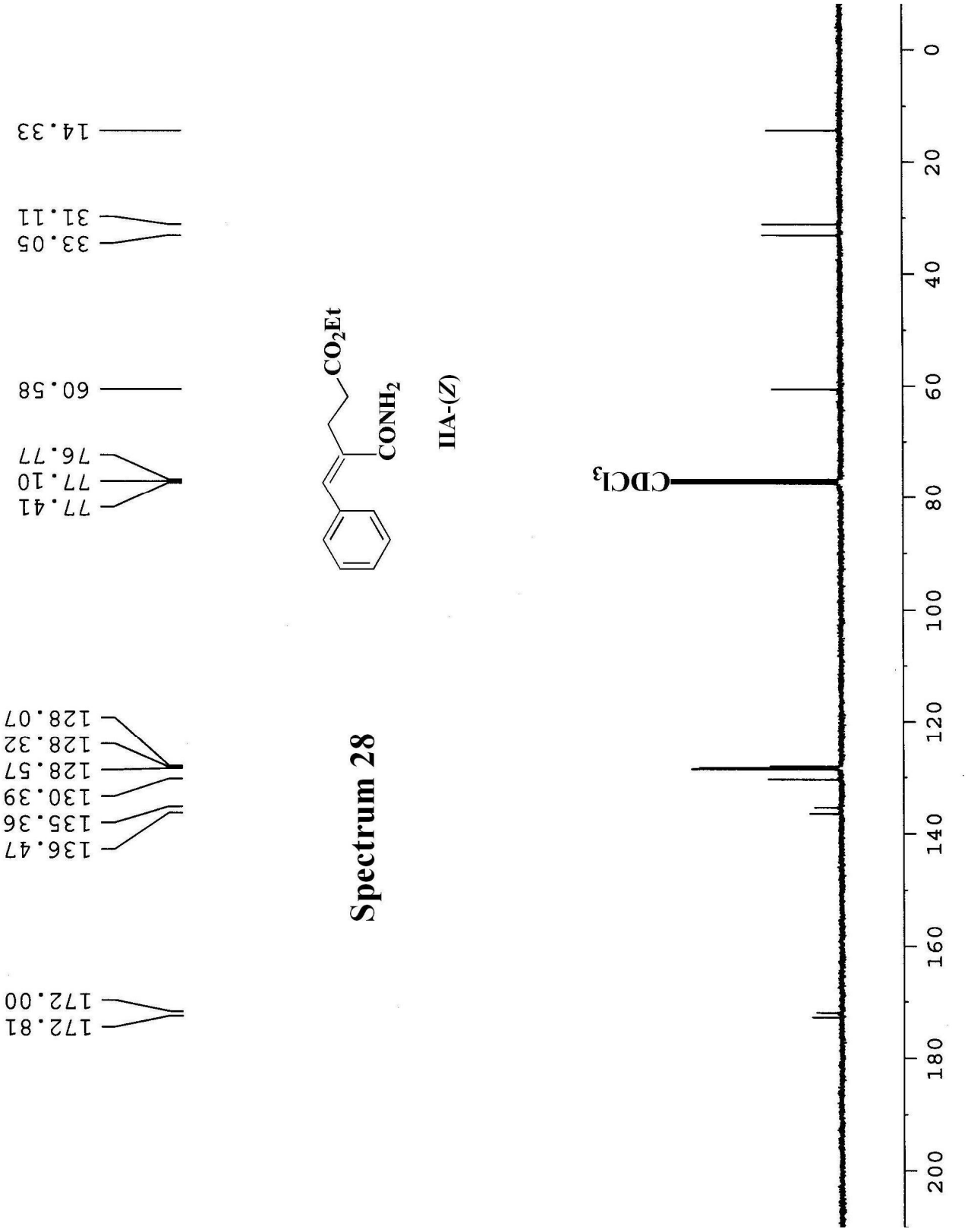


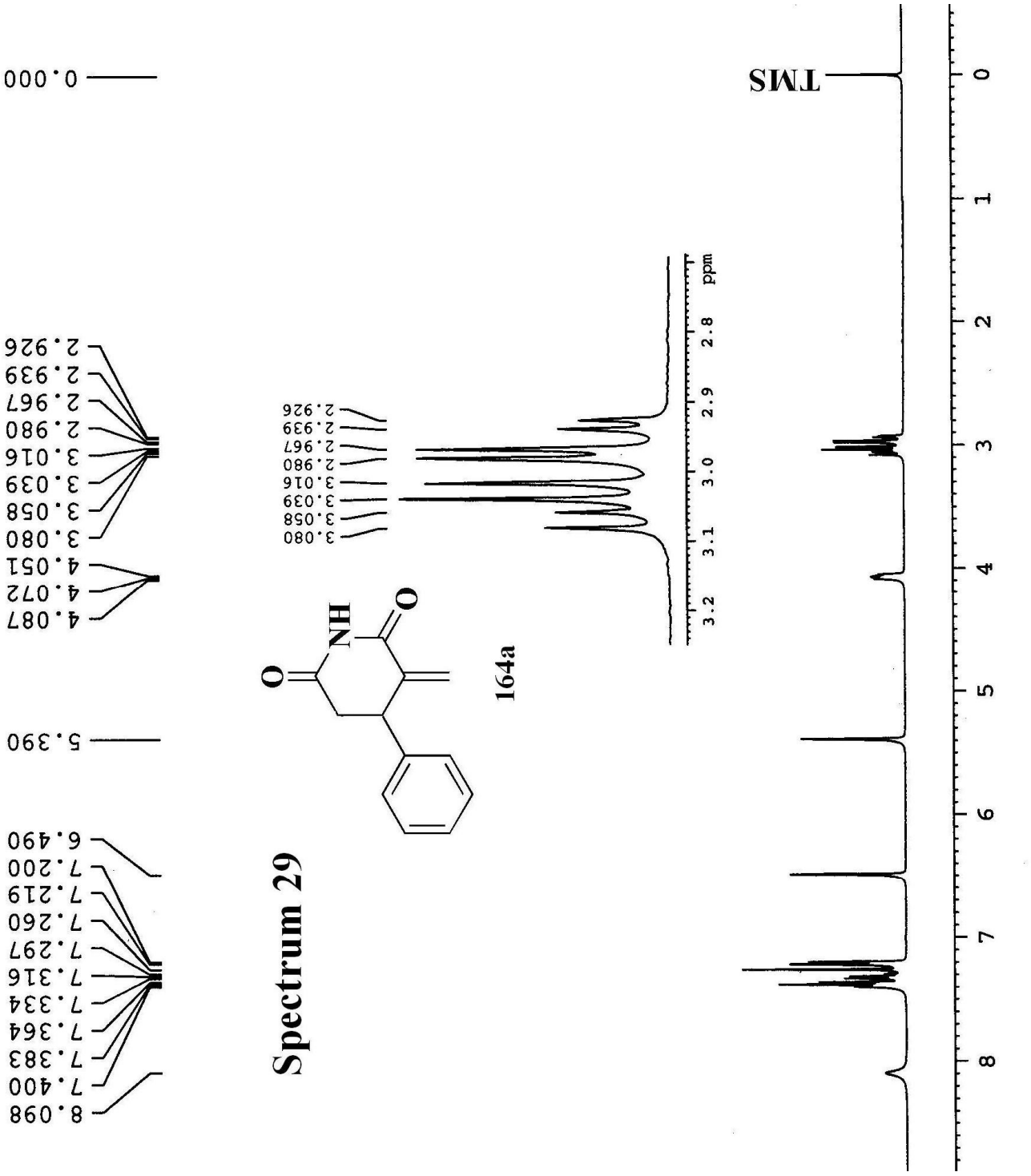
Spectrum 27

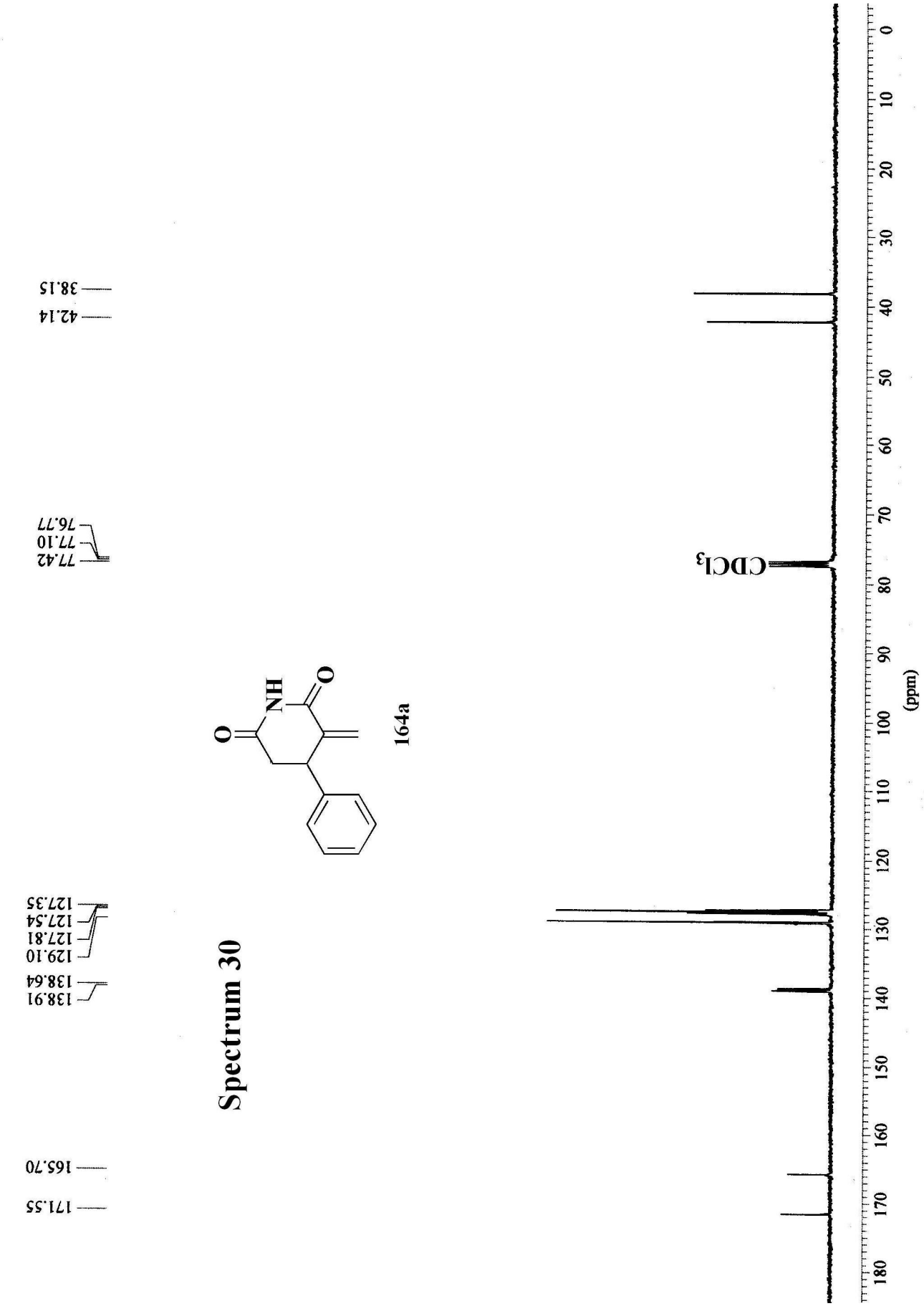


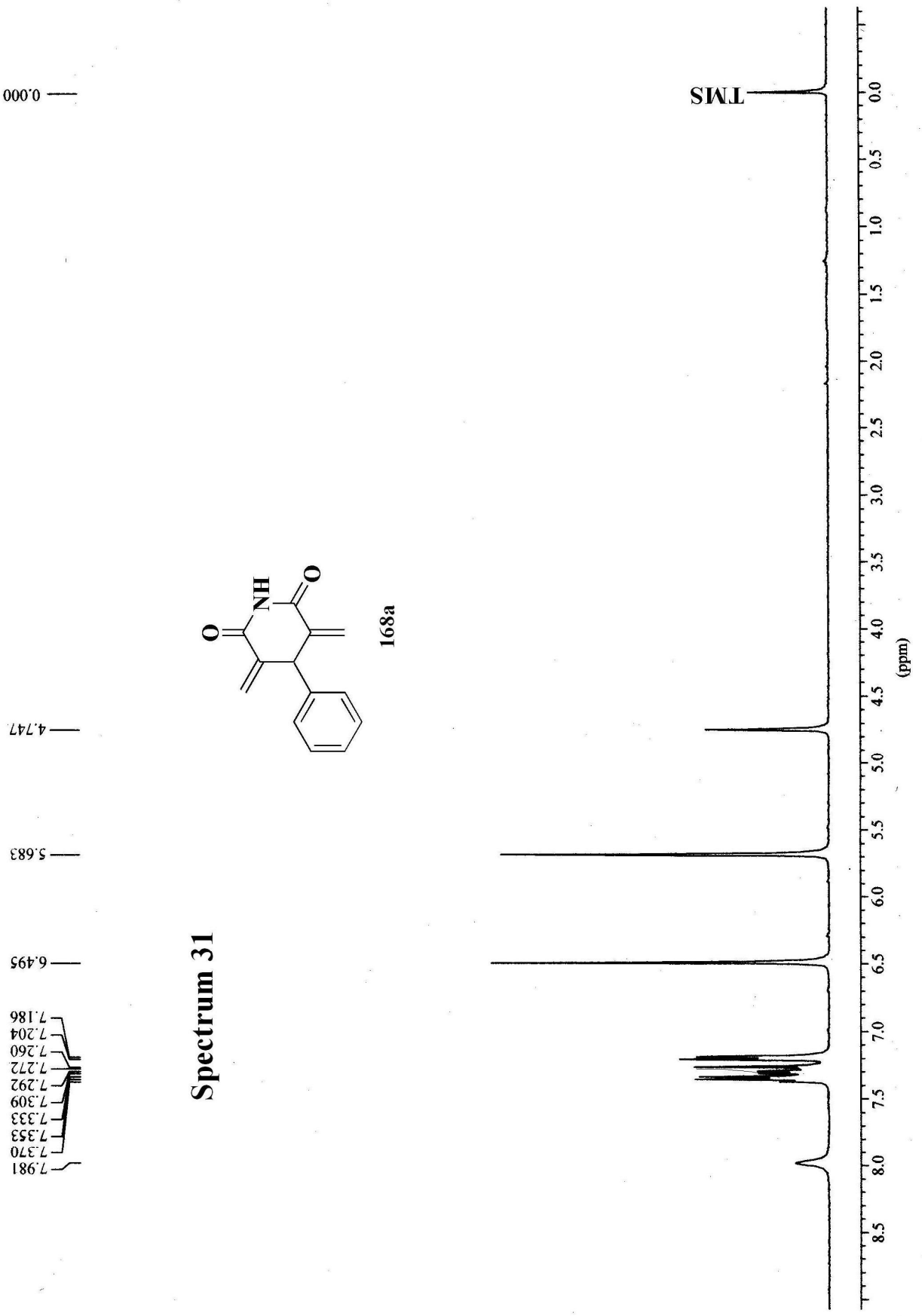
IIA-(*Z*)

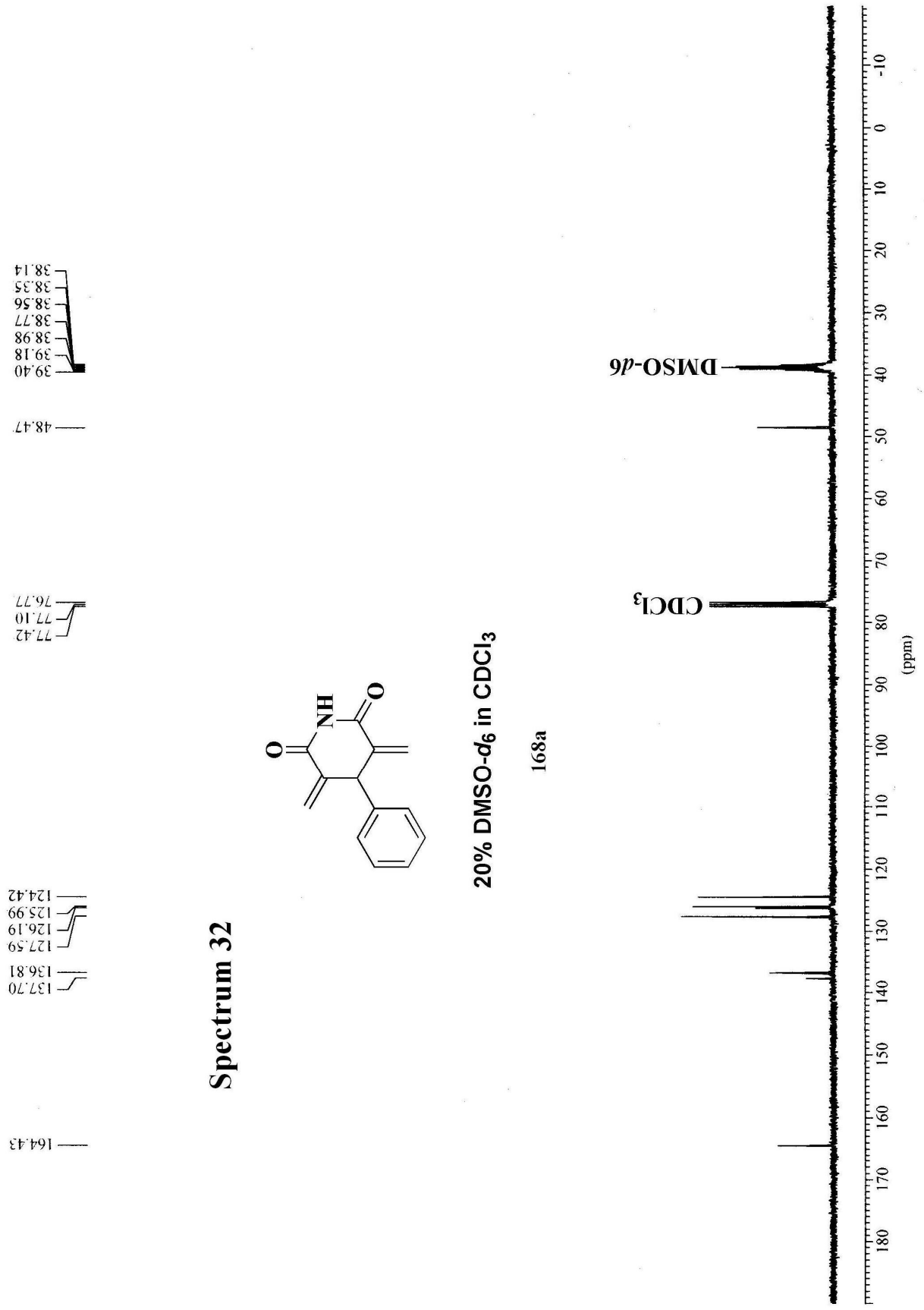


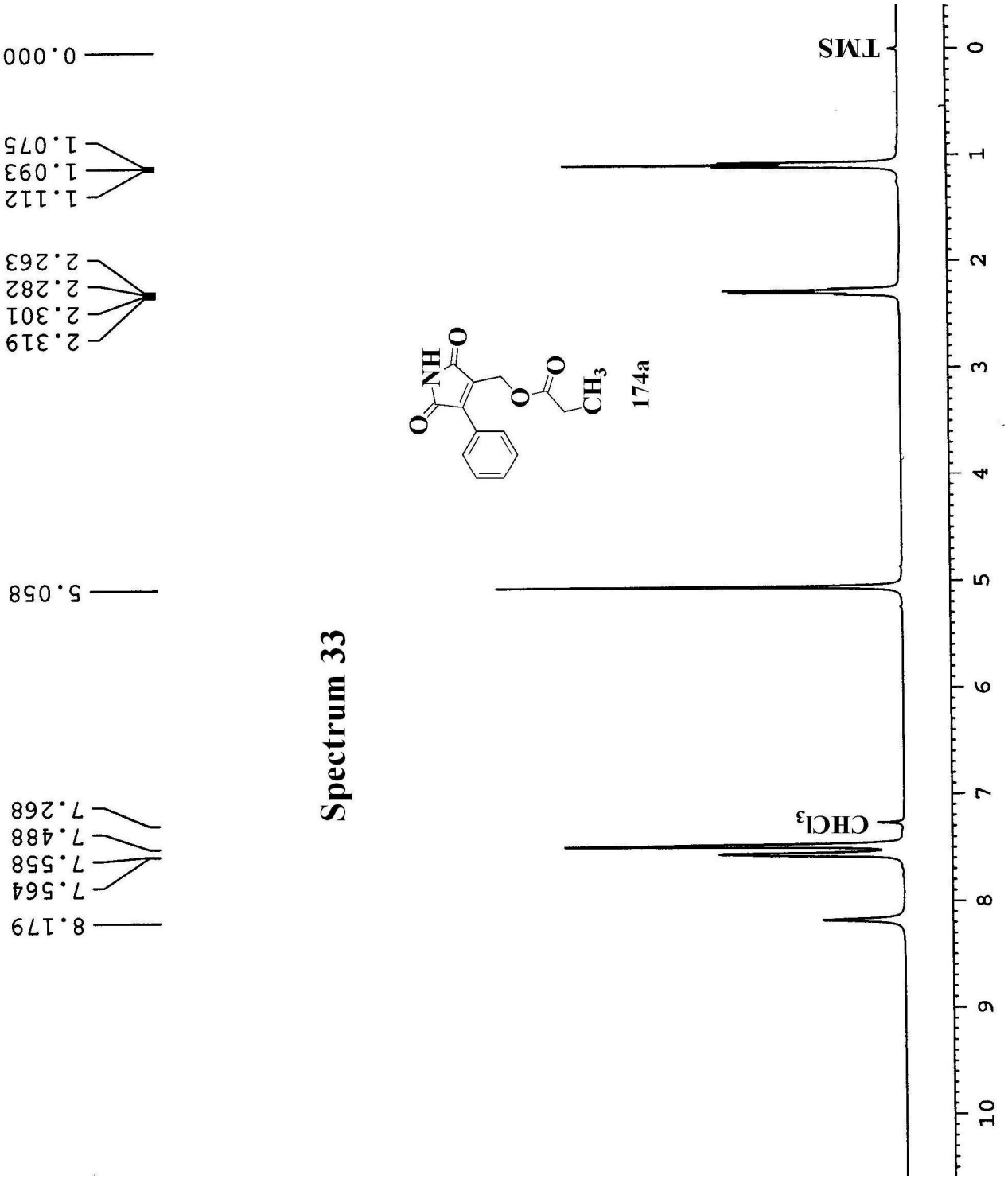

Spectrum 28
IIA-(Z)
CO2Et
CONH2
CDCl3
172.81
172.00
136.47
135.36
130.39
128.57
128.32
128.07
77.41
77.10
76.77
60.58
33.05
31.11
14.33
0
20
40
60
80
100
120
140
160
180
200


Spectrum 29
164a
TMS
0.000
2.926
2.939
2.967
2.980
3.016
3.039
3.058
3.080
4.051
4.072
4.087
5.390
6.490
7.200
7.219
7.260
7.297
7.316
7.334
7.364
7.383
7.400
8.098
ppm

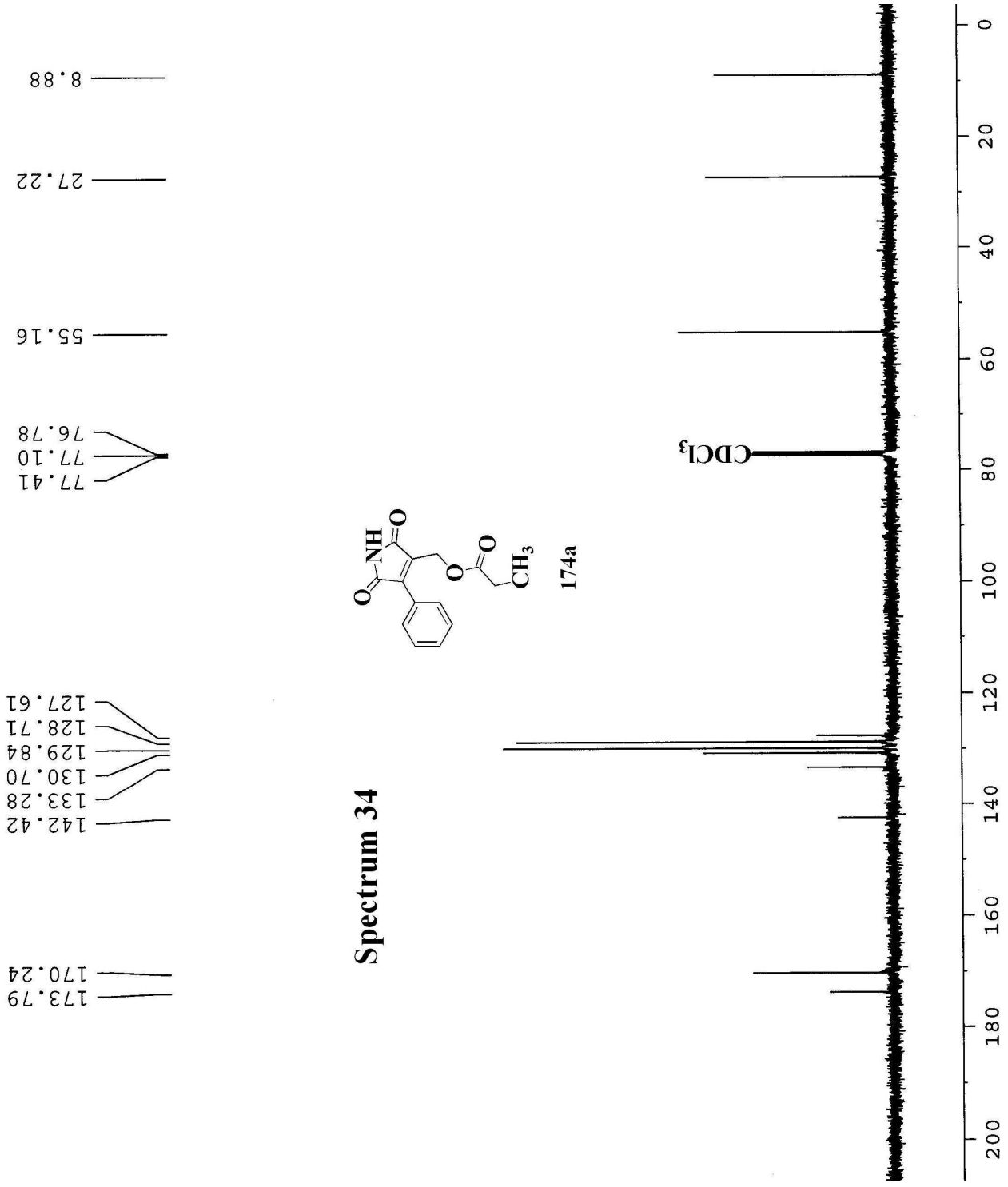

Spectrum 30
164a
CDCl3
(ppm)
171.55
165.70
138.91
138.64
129.10
127.81
127.54
127.35
77.42
77.10
76.77
42.14
38.15

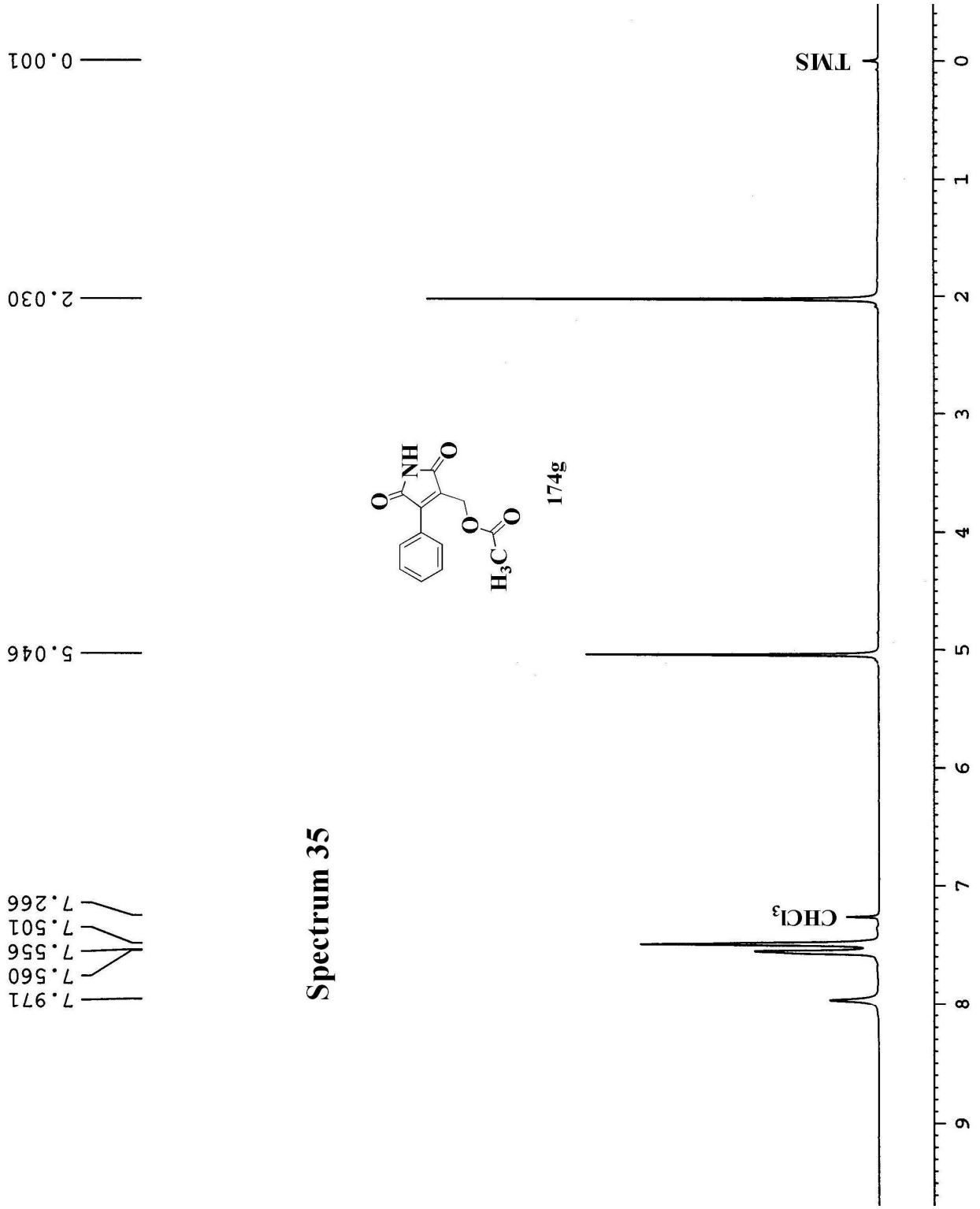

Spectrum 31
168a
TMS
(ppm)
0.000
4.747
5.683
6.495
7.186
7.204
7.260
7.272
7.292
7.309
7.333
7.353
7.370
7.981

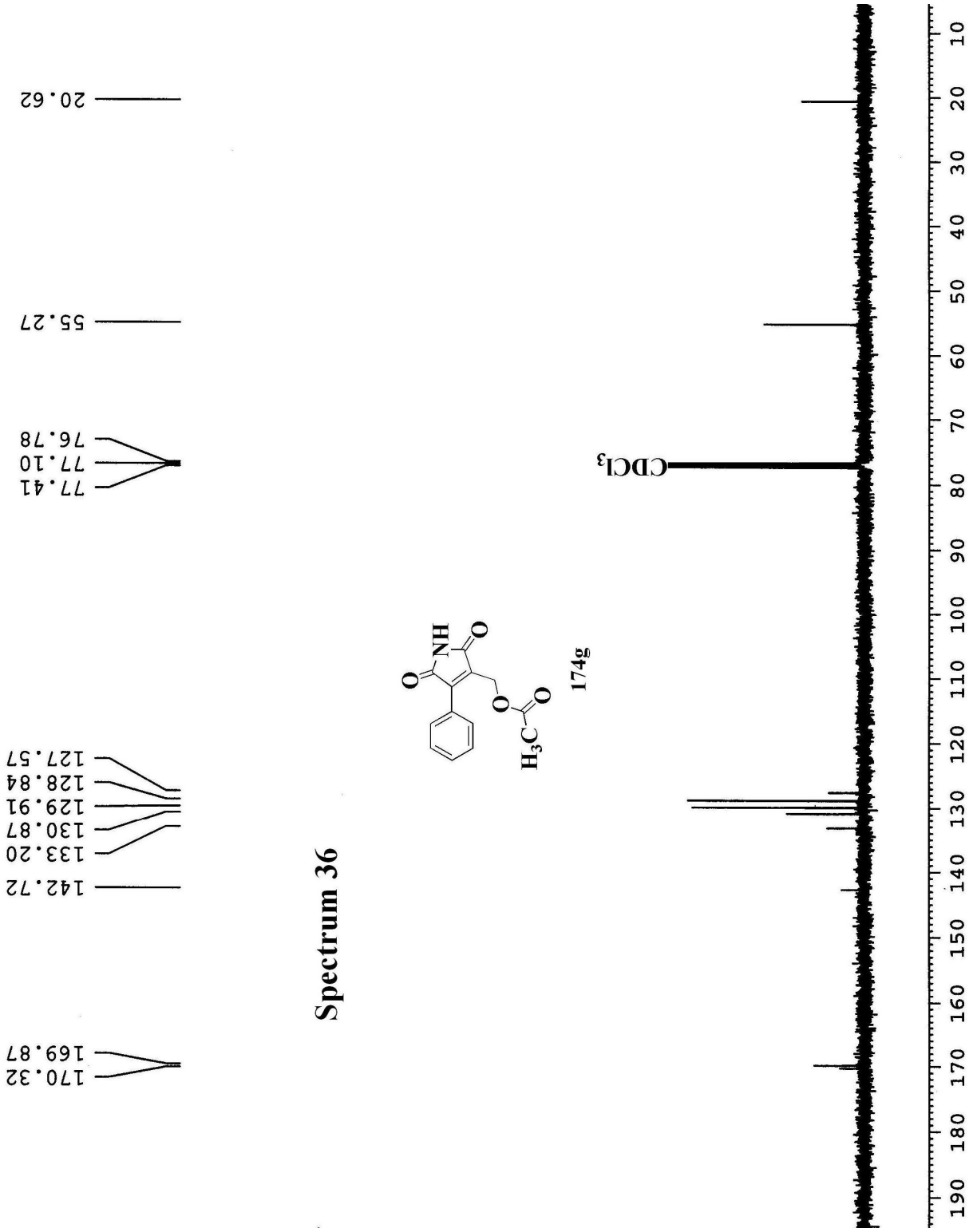

Spectrum 32
20% DMSO-d_6 in $CDCl_3$
168a
$CDCl_3$
DMSO-$d6$
(ppm)
164.43
137.70
136.81
127.59
126.19
125.99
124.42
77.42
77.10
76.77
48.47
39.40
39.18
38.98
38.77
38.56
38.35
38.14

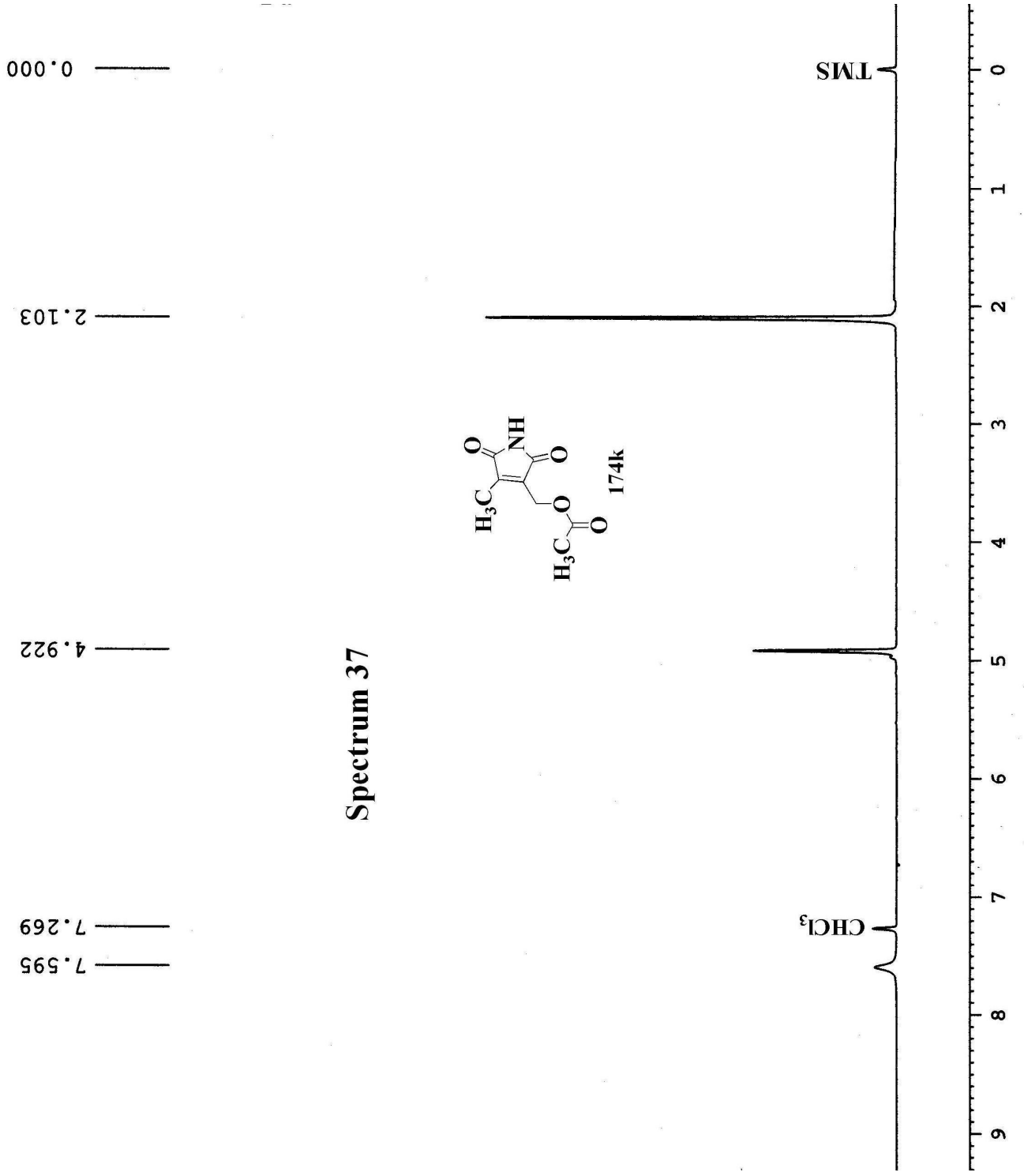

TMS
CHCl3
0.000
1.075
1.093
1.112
2.263
2.282
2.301
2.319
5.058
8.179
7.564
7.558
7.488
7.268
NH
O
O
O
O
CH3
174a

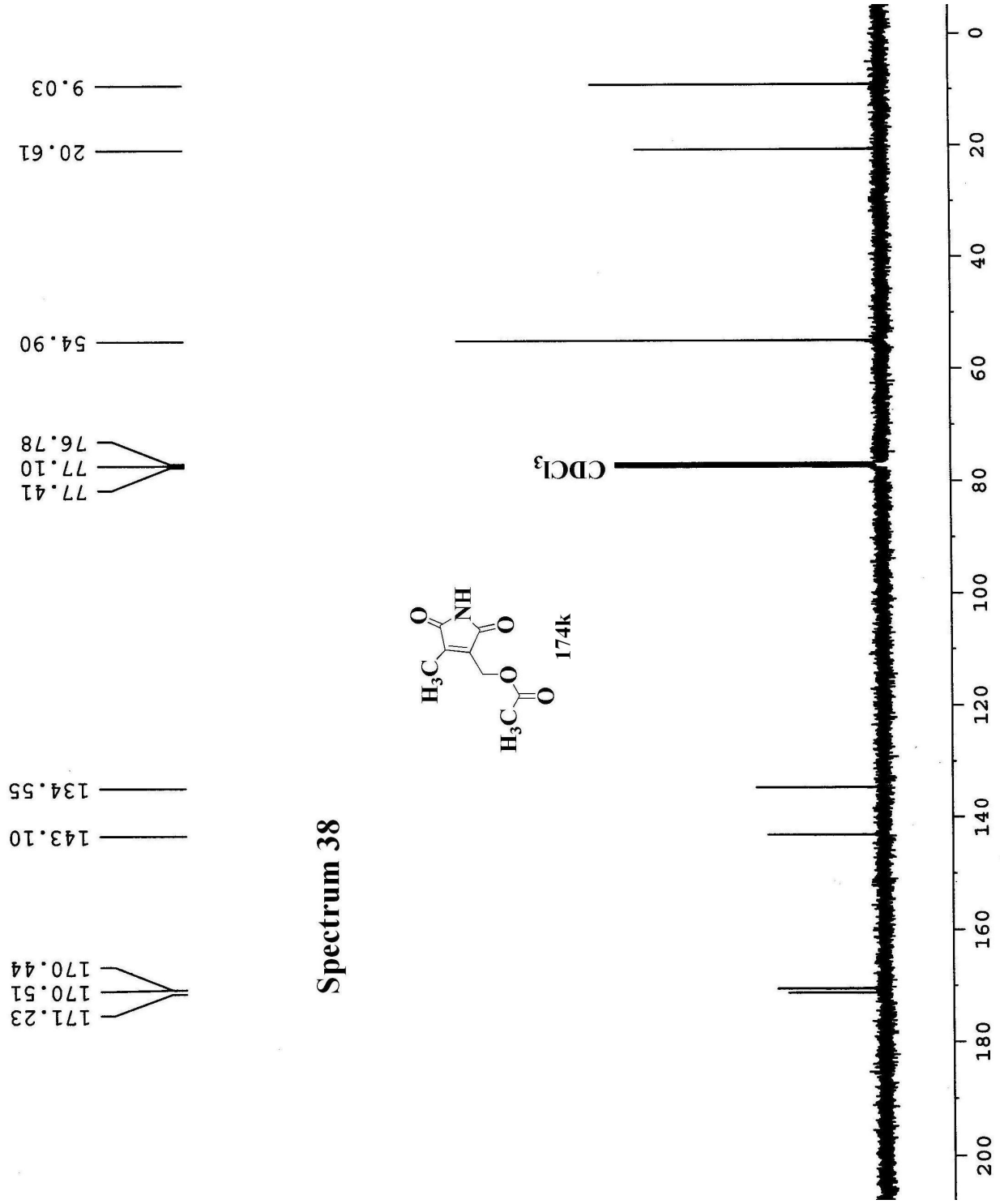
Spectrum 33

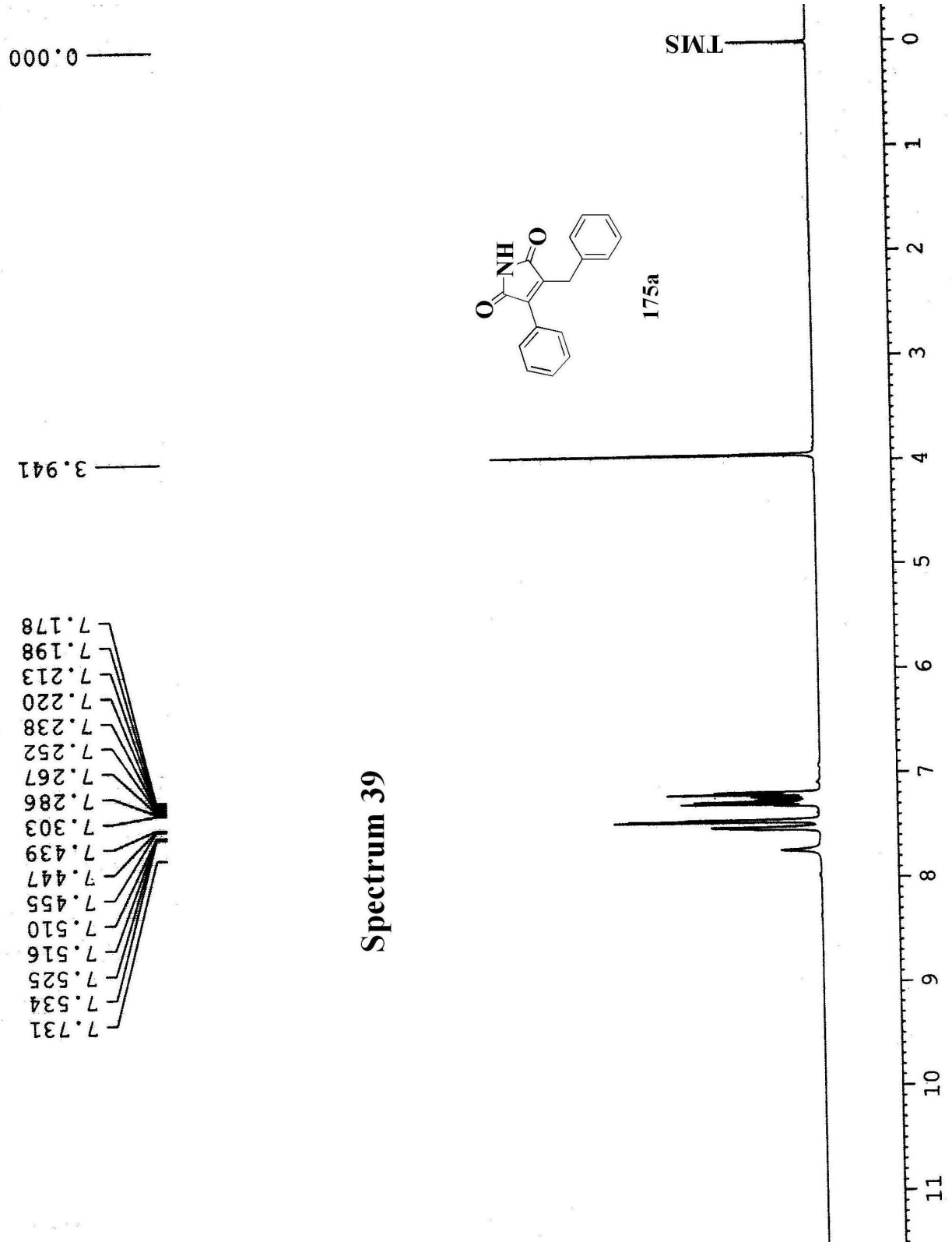

Spectrum 34
174a
CDCl3
8.88
27.22
55.16
76.78
77.10
77.41
127.61
128.71
129.84
130.70
133.28
142.42
170.24
173.79
0
20
40
60
80
100
120
140
160
180
200


Spectrum 35
174g
TMS
CHCl3
0.001
2.030
5.046
7.266
7.501
7.556
7.560
7.971

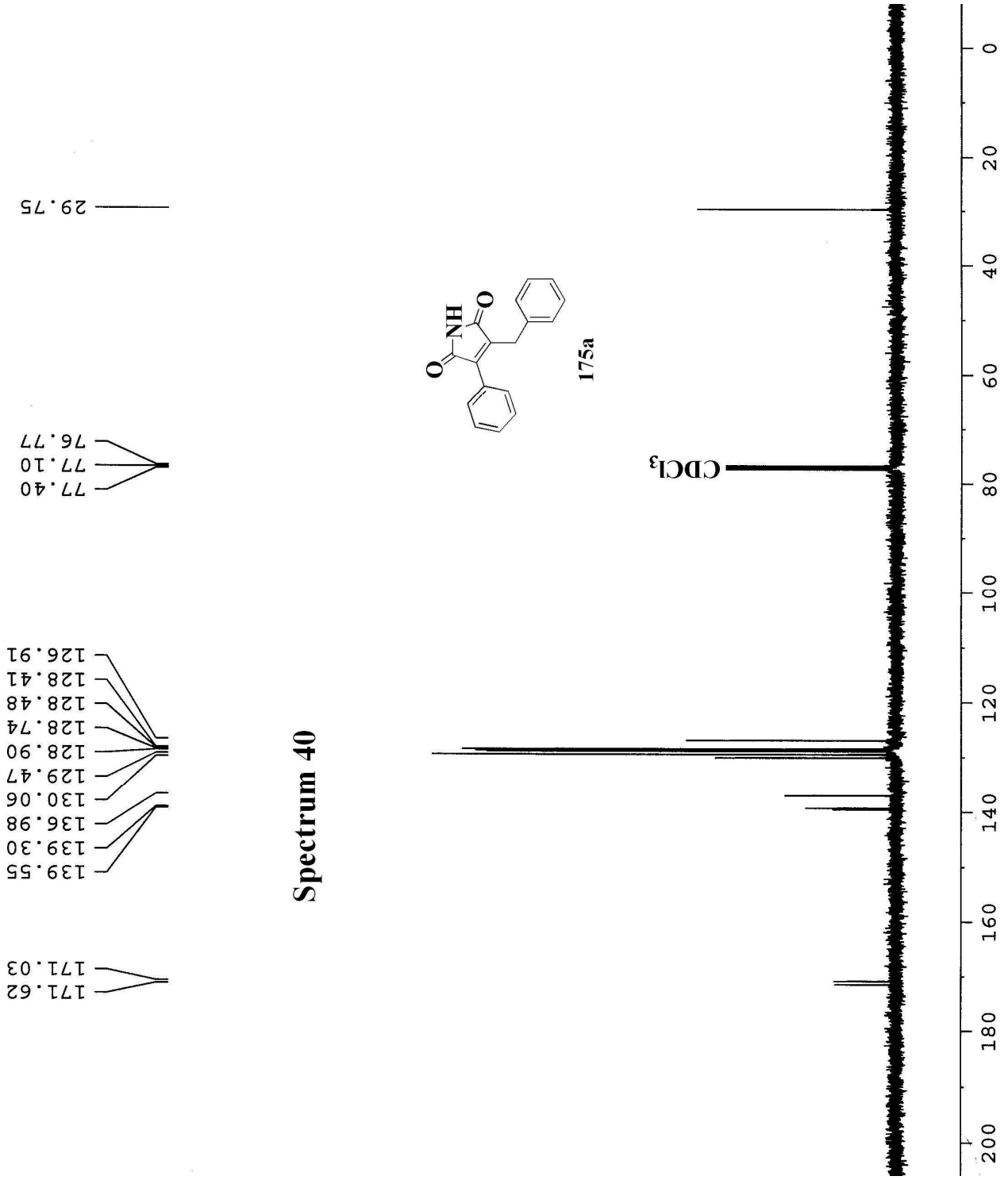

Spectrum 36
174g
CDCl3
20.62
55.27
76.78
77.10
77.41
127.57
128.84
129.91
130.87
133.20
142.72
169.87
170.32


Spectrum 37
174k
TMS
CHCl3
0.000
2.103
4.922
7.269
7.595


Spectrum 38
174k
CDCl3
9.03
20.61
54.90
76.78
77.10
77.41
134.55
143.10
170.44
170.51
171.23
0
20
40
60
80
100
120
140
160
180
200


TMS
0.000
3.941
7.731
7.534
7.525
7.516
7.510
7.455
7.447
7.439
7.303
7.286
7.267
7.252
7.238
7.220
7.213
7.198
7.178
NH
O
O
175a
0
1
2
3
4
5
6
7
8
9
10
11

Spectrum 39


Spectrum 40
175a
CDCl3
171.62
171.03
139.55
139.30
136.98
130.06
129.47
128.90
128.74
128.48
128.41
126.91
77.40
77.10
76.77
29.75
0
20
40
60
80
100
120
140
160
180
200

APPENDIX

X-RAY CRYSRALLORAPHIC DATA

Table I. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **158a**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
C(1)	2035(2)	2225(2)	7236(2)	43(1)
C(2)	4314(2)	3037(2)	6642(2)	46(1)
C(4)	2627(2)	2589(2)	6054(2)	44(1)
O(1)	228(2)	3525(2)	2206(2)	83(1)
C(6)	76(2)	3194(2)	4477(2)	45(1)
C(7)	-2454(2)	2448(2)	3708(2)	48(1)
C(8)	-497(3)	3197(2)	2939(2)	53(1)
C(9)	4849(3)	4360(2)	6779(3)	60(1)
C(10)	-1067(3)	2759(2)	4891(2)	51(1)
C(11)	1672(2)	3661(2)	5267(2)	49(1)
C(12)	2033(3)	3224(3)	8274(2)	58(1)
C(13)	5344(3)	2092(2)	7080(2)	55(1)
C(14)	-2121(3)	2722(2)	2516(2)	53(1)
C(15)	1483(3)	2947(3)	9341(3)	71(1)
C(17)	6862(3)	2457(3)	7623(3)	65(1)
C(18)	-3883(3)	1970(3)	3623(3)	62(1)
C(19)	7375(3)	3775(3)	7758(3)	65(1)
C(20)	1493(3)	959(3)	7302(3)	68(1)
C(21)	6373(3)	4724(3)	7337(3)	68(1)
C(22)	-3194(3)	2524(3)	1239(3)	75(1)
C(23)	958(3)	1681(4)	9404(3)	79(1)
C(24)	-4964(3)	1765(3)	2329(3)	74(1)
C(25)	-4633(3)	2028(3)	1158(3)	81(1)

C(26)	960(4)	694(3)	8384(4)	88(1)
N(2)	2384(3)	542(2)	4180(3)	79(1)
C(27)	2476(3)	1406(2)	5009(3)	52(1)

Table II. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **156d**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
C(1)	5912(3)	2337(1)	3541(2)	58(1)
C(2)	4784(3)	2503(2)	2842(2)	72(1)
C(3)	4777(4)	2946(2)	1979(3)	87(1)
C(4)	5892(4)	3237(2)	1805(3)	92(1)
C(5)	7005(4)	3057(2)	2481(3)	83(1)
C(6)	7021(3)	2608(2)	3324(2)	70(1)
C(7)	5971(3)	1862(1)	4463(2)	56(1)
C(8)	5235(2)	1848(1)	5180(2)	51(1)
C(9)	4198(2)	2361(1)	5248(2)	55(1)
C(10)	4617(2)	2964(1)	6080(2)	53(1)
C(11)	5616(2)	3423(1)	5708(2)	50(1)
C(12)	6894(3)	3313(2)	6087(2)	68(1)
C(13)	7775(3)	3689(2)	5690(3)	83(1)
C(14)	7394(3)	4182(2)	4913(3)	82(1)
C(15)	6124(3)	4302(2)	4528(3)	76(1)
C(16)	5238(3)	3924(2)	4930(2)	65(1)
C(17)	3465(3)	3407(1)	6219(2)	62(1)
C(18)	3604(4)	3860(2)	7076(3)	84(1)
C(19)	2566(5)	4275(2)	7209(4)	106(1)
C(20)	1432(4)	4227(2)	6480(4)	108(1)

C(21)	1307(4)	3790(2)	5635(4)	102(1)
C(22)	2301(3)	3380(2)	5503(3)	78(1)
C(23)	5190(3)	2655(2)	7132(2)	65(1)
C(24)	5991(5)	3878(4)	957(4)	172(3)
C(25)	5245(9)	3677(4)	104(7)	230(4)
C(26)	5356(3)	1256(1)	5968(2)	56(1)
C(27)	6761(3)	348(2)	6916(3)	73(1)
C(28)	5917(4)	-263(2)	6521(3)	99(1)
C(29)	6643(5)	595(2)	8015(3)	115(2)
C(30)	8134(4)	195(3)	6930(4)	139(2)
N(1)	5657(3)	2431(2)	7946(2)	96(1)
O(1)	6480(2)	941(1)	6147(2)	66(1)
O(2)	4493(2)	1085(1)	6368(2)	83(1)

Table III. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **159a**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
O(1)	2957(2)	4944(1)	5537(1)	52(1)
N(1)	4157(2)	5968(1)	5014(1)	45(1)
O(2)	5452(2)	6929(1)	4385(1)	69(1)
C(4)	1318(2)	6043(1)	5764(1)	37(1)
C(5)	1381(2)	6841(1)	5572(1)	41(1)
C(6)	105(2)	5683(1)	6235(1)	42(1)
C(7)	2810(2)	5602(1)	5429(1)	40(1)
C(8)	-1472(2)	5917(1)	6711(1)	41(1)
C(9)	2418(2)	7880(1)	4656(1)	43(1)
C(10)	1053(2)	6769(1)	3712(1)	39(1)
C(11)	2224(2)	7051(1)	4655(1)	39(1)

C(12)	4104(2)	6670(1)	4687(1)	47(1)
C(13)	1802(3)	6782(1)	2843(1)	53(1)
C(14)	3935(3)	8230(1)	5175(1)	60(1)
C(15)	-2590(2)	5373(1)	7019(1)	53(1)
C(16)	-1916(2)	6630(1)	6914(1)	49(1)
C(17)	-736(2)	6498(1)	3682(1)	51(1)
C(18)	800(3)	6521(1)	1997(1)	65(1)
C(19)	-4090(3)	5536(1)	7493(1)	65(1)
C(20)	-3419(2)	6789(1)	7387(1)	60(1)
C(21)	-1741(3)	6246(1)	2827(2)	64(1)
C(22)	3979(3)	8974(1)	5251(2)	75(1)
C(23)	-4509(3)	6243(1)	7676(1)	65(1)
C(24)	968(3)	8301(1)	4214(1)	61(1)
C(25)	-974(3)	6254(1)	1985(2)	70(1)
C(26)	2530(4)	9382(1)	4810(2)	76(1)
C(27)	1023(3)	9052(1)	4288(2)	77(1)

Table IV. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for the compound **162b.** U(eq) is defined as one third of the trace of the orthogonalized

Uij tensor.

Atom	x	y	z	U(eq)
C(1)	4594(2)	4794(3)	2623(2)	57(1)
C(2)	5677(3)	6078(3)	2588(3)	65(1)
C(3)	5151(3)	6832(3)	1631(3)	73(1)
C(4)	3630(3)	6338(3)	763(3)	73(1)
C(5)	2559(3)	5077(3)	813(3)	65(1)
C(6)	3038(2)	4264(2)	1739(2)	53(1)
C(7)	7351(3)	6611(3)	3525(3)	92(1)

C(8)	1942(2)	2894(2)	1782(2)	50(1)
C(9)	276(2)	2839(3)	1845(2)	61(1)
C(10)	2140(2)	1507(2)	1799(2)	50(1)
C(11)	647(2)	506(3)	1867(2)	59(1)
C(12)	3514(2)	894(3)	1655(2)	54(1)
C(13)	5949(2)	1260(2)	3338(2)	54(1)
C(14)	6820(3)	1704(4)	5005(3)	90(1)
C(15)	8466(4)	2153(6)	5372(4)	140(2)
N(1)	-400(2)	1376(3)	1873(2)	64(1)
O(1)	-356(2)	3862(2)	1877(2)	86(1)
O(2)	383(2)	-825(2)	1880(2)	80(1)
O(3)	4481(2)	1330(2)	3223(2)	61(1)
O(4)	6446(2)	856(2)	2213(2)	66(1)

Table V. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for the compound **162c.** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
O(1)	5170(2)	7909(2)	6038(2)	84(1)
O(2)	4529(2)	7986(2)	10793(2)	71(1)
O(3)	276(1)	6608(1)	8590(1)	55(1)
O(4)	-1578(1)	7705(2)	9081(2)	68(1)
N(1)	5277(2)	7958(2)	8560(2)	61(1)
C(10)	2741(2)	8073(2)	8422(2)	46(1)
C(7)	2917(2)	8081(2)	7030(2)	48(1)
C(11)	1377(2)	8240(2)	9029(2)	51(1)
C(1)	1809(2)	8165(2)	5637(2)	51(1)
C(12)	-1191(2)	6513(2)	8672(2)	50(1)
C(9)	4243(2)	7991(2)	9451(2)	53(1)

C(2)	157(2)	7266(2)	5063(2)	54(1)
C(8)	4578(2)	7980(2)	7083(2)	57(1)
C(6)	2387(2)	9166(2)	4878(2)	63(1)
C(3)	-922(2)	7365(2)	3782(2)	61(1)
C(5)	1314(3)	9277(2)	3610(2)	71(1)
C(13)	-2233(3)	4809(3)	8225(3)	92(1)
C(4)	-307(3)	8383(2)	3077(2)	71(1)
C(14)	-2714(2)	6412(2)	3200(3)	89(1)

Table VI. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound the compound **168a.** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
C(1)	2823(1)	833(4)	7296(3)	46(1)
C(2)	3426(1)	1364(4)	7013(4)	57(1)
C(3)	3938(1)	328(5)	7773(5)	68(1)
C(4)	3874(2)	-1188(5)	8845(5)	73(1)
C(5)	3287(2)	-1693(5)	9163(4)	69(1)
C(6)	2761(1)	-704(4)	8396(4)	54(1)
C(7)	2297(1)	969(3)	6456(3)	43(1)
C(8)	1720(1)	1435(3)	5764(3)	38(1)
C(9)	1451(1)	-523(3)	5752(4)	53(1)
C(10)	994(1)	-915(3)	4100(4)	50(1)
C(11)	537(1)	605(3)	3558(3)	41(1)
C(12)	1289(1)	2950(3)	4996(3)	35(1)
Cl(2)	4677(1)	983(2)	7332(2)	120(1)
N(1)	725(1)	2392(3)	4043(3)	40(1)
O(1)	27(1)	370(2)	2669(3)	59(1)
O(2)	1401(1)	4611(2)	5181(2)	46(1)

Table VII Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for the compound **174c.** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
C(1)	1317(1)	1953(3)	4951(3)	40(1)
C(2)	1746(1)	3508(3)	5708(3)	41(1)
C(3)	1471(1)	5492(3)	5652(4)	55(1)
C(4)	1008(1)	5871(3)	4051(4)	56(1)
C(5)	545(1)	4306(3)	3549(3)	45(1)
C(6)	2327(1)	2973(3)	6435(3)	47(1)
C(7)	2857(1)	4133(4)	7250(3)	51(1)
C(8)	2791(1)	5800(4)	8175(3)	58(1)
C(9)	3316(1)	6861(5)	8865(4)	71(1)
C(10)	3912(1)	6242(6)	8628(4)	75(1)
C(11)	4003(1)	4577(6)	7793(4)	80(1)
C(12)	3475(1)	3517(5)	7103(4)	68(1)
Cl(1)	4574(1)	7629(2)	9407(1)	118(1)
N(1)	742(1)	2498(3)	4023(3)	44(1)
O(1)	440(1)	263(2)	5126(2)	51(1)
O(2)	26(1)	4525(2)	2696(3)	66(1)

Table VIII. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for the compound **174h .**U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
C(1)	2124(1)	10214(5)	5855(2)	18(1)
C(2)	1769(1)	11998(5)	5818(2)	23(1)
C(3)	1596(1)	12764(5)	4912(2)	25(1)
C(4)	1772(1)	11724(6)	4054(2)	24(1)

C(5)	2128(1)	9954(5)	4095(2)	21(1)
C(6)	2309(1)	9187(4)	5000(2)	16(1)
C(7)	2689(1)	7137(4)	5036(2)	16(1)
C(8)	2987(1)	7533(5)	5925(2)	16(1)
C(9)	3309(1)	9766(5)	5873(2)	16(1)
C(10)	2978(1)	6049(5)	6726(2)	19(1)
C(11)	3301(1)	9498(5)	4057(2)	17(1)
C(12)	2977(1)	7266(5)	4120(2)	16(1)
C(13)	2962(1)	5575(5)	3380(2)	21(1)
C(14)	5421(1)	6030(5)	7427(2)	20(1)
C(15)	5764(1)	4175(6)	7472(2)	23(1)
C(16)	5895(1)	2858(5)	6634(2)	21(1)
C(17)	5689(1)	3419(5)	5743(2)	20(1)
C(18)	5347(1)	5290(5)	5692(2)	17(1)
C(19)	5207(1)	6594(5)	6539(2)	16(1)
C(20)	4838(1)	8720(5)	6502(2)	16(1)
C(21)	4549(1)	8705(5)	7419(2)	17(1)
C(22)	4216(1)	6524(5)	7491(2)	17(1)
C(23)	4567(1)	10489(5)	8130(2)	19(1)
C(24)	4201(1)	6191(5)	5681(2)	16(1)
C(25)	4535(1)	8381(5)	5621(2)	17(1)
C(26)	4541(1)	9884(5)	4824(2)	18(1)
N(1)	3397(1)	10742(4)	4944(2)	16(1)
N(2)	4114(1)	5255(4)	6612(2)	16(1)
O(1)	3495(1)	10700(3)	6597(1)	20(1)
O(2)	3473(1)	10259(4)	3303(1)	23(1)
O(3)	4013(1)	5258(3)	4965(2)	19(1)
O(4)	4038(1)	5829(4)	8254(1)	23(1)

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LIST OF PUBLICATIONS

[1] A Simple Protocol for Synthesis of Piperidine-2,6-dione Framework from the Baylis-Hillman Adducts: Basavaiah, D,; **Lenin, D. V**. Devendar, B. *Tetrahedron Lett.* **2009**, *50,* 3538-3542

[2] The Baylis-Hillman Bromides as Versatile Synthons: A Facile One-Pot Synthesis of Indolizine and Benzofused Indolizine Frameworks: Basavaiah, D,; Devendar, B,; **Lenin, D. V**,; Satyanarayana, T. *Synlett*, **2009**, 411-416

[3] The Baylis-Hillman Adducts as Valuable Source for One-Pot Multi-Step Synthesis: A Facile Synthesis of Substituted 2-Piperidones: Basavaiah, D,; Reddy, R. J,; **Lenin, D. V**. *Helv. Chimica. Acta* **2010**, *93*, 1180-1186

[4] Simple Synthesis of Indenone Frameworks using Baylis-Hillman Acetates Basavaiah, D,; **Lenin, D. V**. (in press, *Eur. J. Org. Chem.*)

[5] Simple Synthesis of Substituted Maleimide Derivatives using the Baylis-Hillman Adducts: Basavaiah, D.; Lenin, D. V.; Veeraraghavaiah, G. (Communicated)

SYNOPSIS OF THE THESIS ENTITLED

TOWARDS DEVELOPMENT OF NOVEL METHODOLOGIES FOR SYNTHESIS OF IND-2-ENONE, PIPERIDINE-2,6-DIONE AND 1H-PYRROLE-2,5-DIONE FRAMEWORKS USING BAYLIS-HILLMAN ADDUCTS

A THESIS SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

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INDIA

The Baylis-Hillman reaction is an atom-economical three component carbon-carbon bond forming reaction involving the coupling between α-position of activated alkenes and electrophiles in the presence of catalyst or catalytic system, providing diverse classes of multifunctional molecules which are usually referred as the Baylis-Hillman (B-H) adducts. Our research group has been working on various aspects of this reaction for the last several years. This thesis deals with applications of Baylis-Hillman adducts in the synthesis of carbocyclic and heterocyclic molecules and consists of three chapters 1) Introduction 2) Objectives, Results & Discussion and 3) Experimental. The first chapter, that is, introduction presents a brief account of literature on the developments in the Baylis–Hillman reaction and also on the important applications of the Baylis–Hillman adducts in synthetic organic chemistry.

The second chapter, that is, Objectives, Results & Discussion, deals with the development of simple methodologies for the synthesis of indenone, piperidine-2,6-dione and maleimide derivatives using the Baylis-Hillman adducts with the following objectives.

Objectives:

1] To develop a facile methodologies for transformation of the Baylis-Hillman acetates i.e. *tert*-butyl 3-acetoxy-2-methylene-3-arylpropanoates into indenone derivatives, (*E*)-3-arylmethylidene-5-phenylpiperidine-2,6-dione and (*E*)-3-arylmethylidene-5,5-diphenylpiperidine-2,6-dione frameworks.

2] To develop a convenient one-pot methodologies for transformation of

i) Baylis-Hillman alcohols i.e. 3-hydroxy-2-methylene-3-aryl(alkyl)propanoates into (*E*)-3-aryl(alkyl)methylidenepiperidine-2,6-dione derivatives.

ii) Rearranged Baylis-Hillman alcohols i.e. (2*Z*)-2-cyano-3-arylprop-2-en-1-ols into 3-methylidene-4-arylpiperidene-2,6-diones.

iii) Baylis-Hillman compounds i.e. 4-cyano-2-methoxycarbonyl-3-arylpenta-1,4-dienes into 4-aryl-3,5-dimethylidenepiperidene-2,6-dione derivatives.

3] To develop a simple methodology for synthesis of 3, 4-disubstituted-1H-pyrrole-2, 5-dione derivatives (maleimide derivatives) from the Baylis-Hillman alcohols *i.e.* 3-ethoxycarbonyl-3-hydroxy-3-aryl-2-methylenepropanenitriles (or 3-ethoxycarbonyl-3-hydroxy-2-methylenealkanenitriles) in one-pot operation.

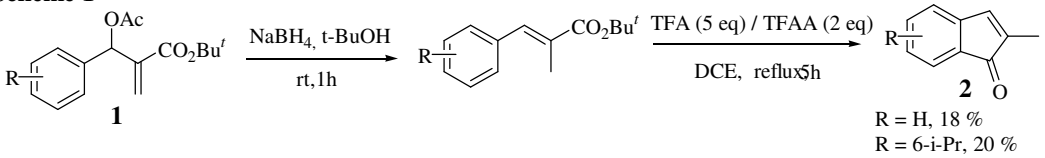
Development of a facile methodologies for synthesis of substituted indenones and piperidine-2, 6-diones from the Baylis-Hillman acetates.

Ind-2-en-1-one framework represents an important class of carbocyclic molecules because these derivatives are found in important natural products. Some of indenone derivatives are also known to be peroxisome proliferator-activated receptor γ (PPAR γ, drug to type-2 diabetes) agonists, estrogen receptor binding agents, cyclooxygenase-2 inhibitors and potent reversible inhibitors of 3CP. Piperidine-2, 6-dione framework is yet another

medicinally important skeleton present in several biologically active and natural products such as alonimid (sedative and hypnotic activity), thalidomide (drug to prevent morning sickness of pregnant women), streptimidone (antibiotic), migrastatin (antitumor agent), lactimidomycin (antibiotic) and sesbanimide (antitumor). Therefore development of facile strategies for the synthesis of these frameworks has become a challenging task in synthetic organic chemistry. We have developed a two-step methodology for the synthesis of ind-2-en-1-ones frameworks (**2**, **3** & **5**) starting from the Baylis-Hillman acetates (**1**) following the reaction sequence as shown in Scheme 1, Scheme 2 (**Path A1**) and Scheme 2 (**Path A2**). This transformation proceeds through an unusual conversion of *trans* cinnamic esters into ind-2-en-1-one frameworks. The yields of the indenone derivatives depend on the steric bulk of substitution at α-position of ester group *trans*-cinnamic esters.

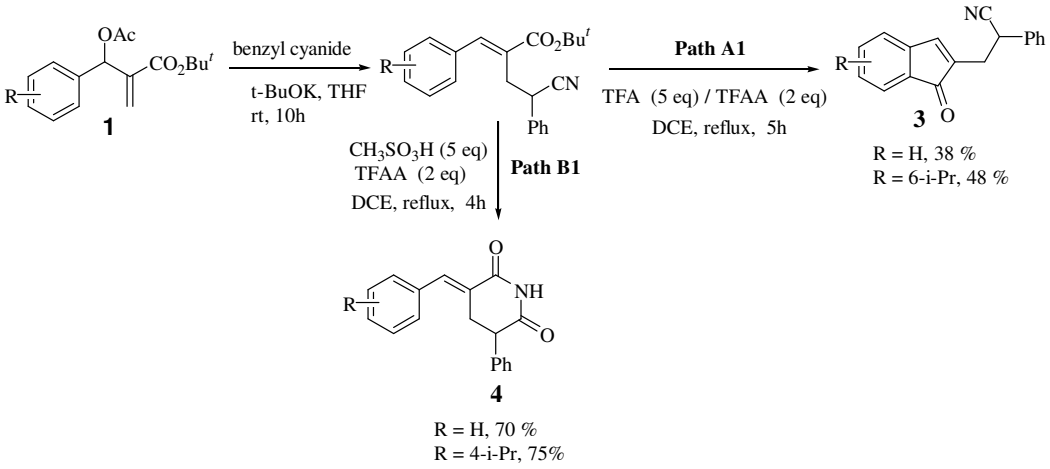
We have also developed a simple two-step strategy for transformation of the B-H acetates (**1**) into substituted piperidine-2,6-dione derivatives (**4** & **6**) following the reaction sequence shown in Scheme 2 (**Path B1**) and Scheme 3 (**Path B2**).

Scheme 1

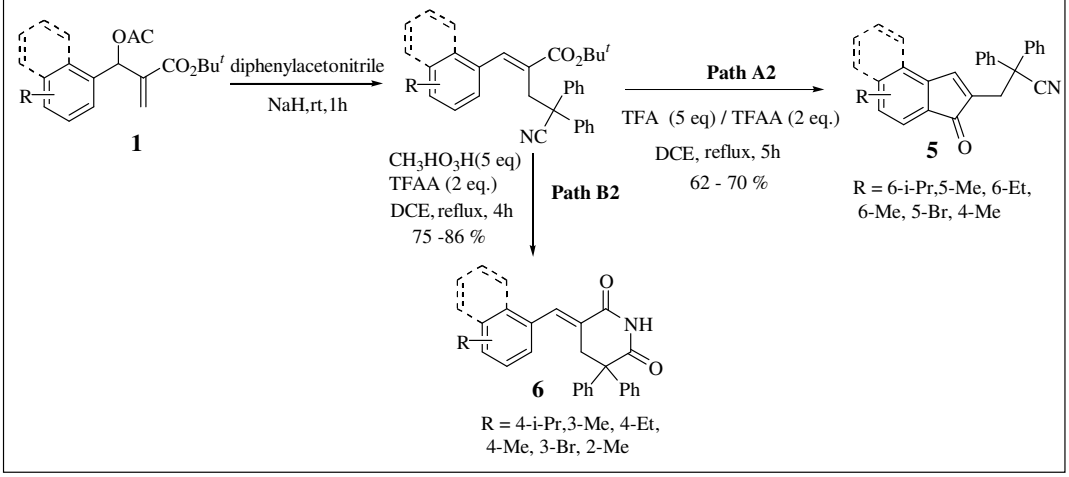


R = H, 18 %
R = 6-i-Pr, 20 %

Scheme 2



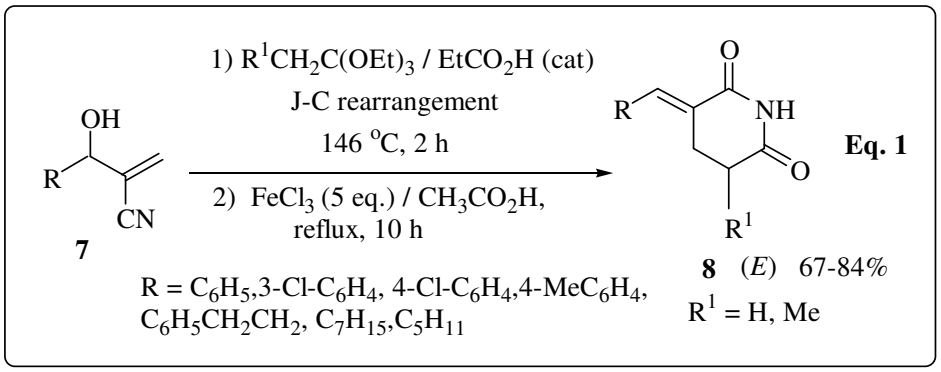
Scheme 3



Development of one-pot protocol for the synthesis of a piperidine-2,6-dione frameworks from Baylis-Hillman adducts

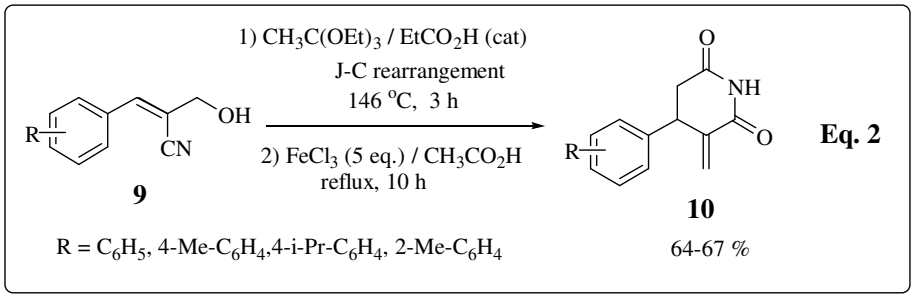
Today science of synthesis demands the development of operationally simple one-pot processes for obtaining important molecules of medicinal relevance. We have therefore,

directed our attention towards the development of one-pot process for synthesis of piperidine-2,6-dione derivatives starting from the Baylis-Hillman alcohols derived from acrylonitrile and aldehydes. Accordingly, we have developed simple and one-pot methodology for the preparation of (*E*)-3-arylidene(alkylidene)piperidine-2, 6-diones (**8**) from the Baylis-Hillman alcohols (**7**) via the Jhonson-Claisen rearrangement followed by partial hydrolysis of cyano group, cyclization and isomerization using $FeCl_3$/acetic acid (Eq1).



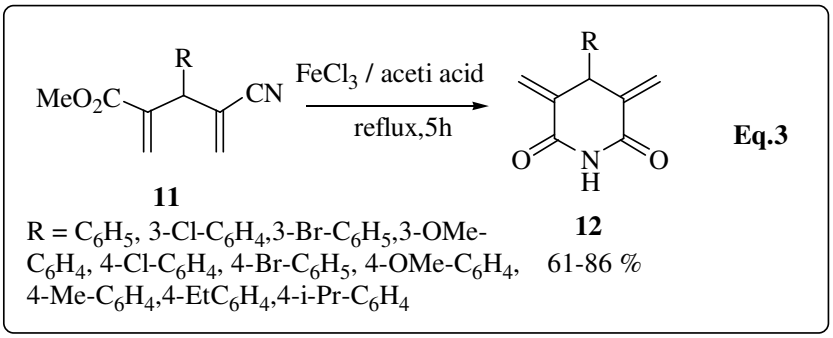
Eq. 1

A simple and one-pot methodology for the preparation of 3-methylidene-4-arylpiperidine-2,6-diones derivatives (**10**) from rearranged Baylis-Hillman alcohols (**9**) via the Jhonson-Claisen rearrangement, partial hydrolysis of cyano group and cyclization using $FeCl_3$/acetic acid has been described (Eq.2).



Eq. 2

The Baylis-Hillman products (**11**) have been conveniently transformed into 4-aryl-3,5-dimethylidenepiperidine-2,6-dione derivatives (**12**) via partial hydrolysis of cyano group, and cyclization using $FeCl_3$/acetic acid (Eq. 3).



11

R = C_6H_5, 3-Cl-C_6H_4,3-Br-C_6H_5,3-OMe-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_5, 4-OMe-C_6H_4, 4-Me-C_6H_4,4-EtC_6H_4,4-i-Pr-C_6H_4

12

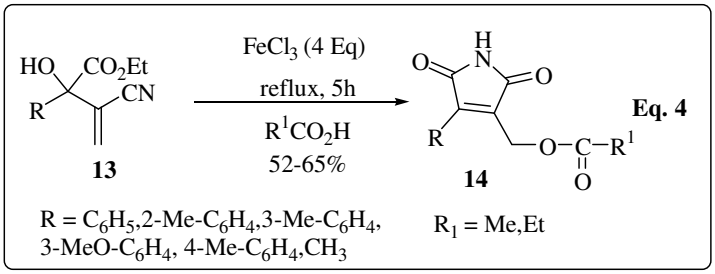
61-86 %

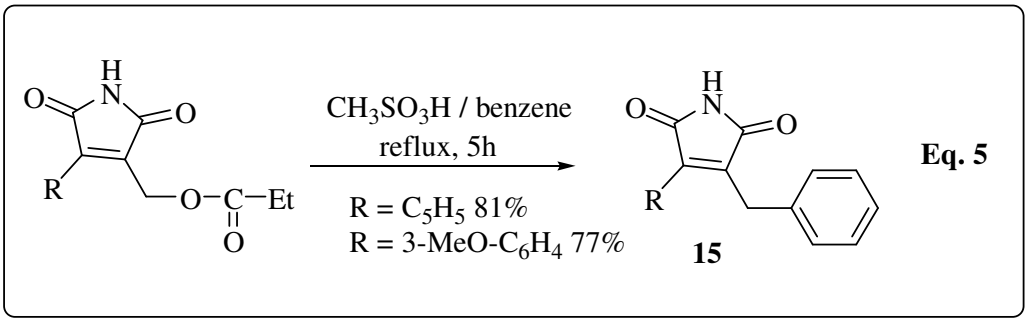
Eq.3

Development of one-pot synthesis of substituted maleimide derivatives using the Baylis-Hillman alcohols.

3,4-Disubstituted maleimide framework represents an interesting structural organization in heterocyclic chemistry as this skeleton is present in a number of natural products such as himanimides A-D, polycitrins A & B, and arcyriarubins A & B. Also certain compounds having this framework have been known to exhibit various biological activities such as protein kinase C inhibitors (PKC), inhibitor of calmodulin dependant protien kinase (CaMKIIδ), cell death inhibitor, vascular endothelial cell proliferation, angiogenesis inhibitor and cytotoxicity. We have developed a facile one-pot methodoloy for the synthesis of maleimide dearivatives (**14**) starting from the Baylis-Hillman alcocols (**13**) derived from acrylonitrile and α-keto esters via treatment with $FeCl_3/RCO_2H$ (R = Me, Et)

according to Eq.4. Two of such maleimide derivatives were further subjected to Friedel-Crafts reaction with benzene in the presence of CH_3SO_3H providing 3-benzyl-4-aryl-1H-pyrrole-2,5-diones (**15)** (Eq.5).





The third chapter provides detailed experimental procedures, physical constants like boiling point, melting point, IR, ^{1}H & ^{13}CNMR mass (LCMS) spectral data and elemental analyses.