Enabling Non-Conventional Pathway for Organic Synthesis

By

Tapas Kumar Achar

CHEM11201004010

National Institute of Science Education and Research Bhubaneswar, Odisha – 752050

A thesis submitted to the
Board of Studies in Chemical Sciences
In partial fulfillment of requirements
for the Degree of

DOCTOR OF PHILOSOPHY

of

HOMI BHABHA NATIONAL INSTITUTE

June, 2016

Homi Bhabha National Institute[1]

Recommendations of the Viva Voce Committee

As members of the Viva Voce Committee, we certify that we have read the dissertation prepared by **Tapas Kumar Achar** entitled **"Enabling Non-Conventional Pathway for Organic Synthesis"** and recommend that it may be accepted as fulfilling the thesis requirement for the award of Degree of Doctor of Philosophy.

Chairman -	Prof. A. Srinivasan	Date: 29.11.'16
Guide / Convener -	Dr. Prasenjit Mal	Date: 29.11.16
Examiner -	Prof. Bhisma Kumar Patel, (IIT Guwahati)	Date: 29/11/2016
Member 1-	Dr. Sudip Barman	Date: 29.11.16
Member 2-	Dr. Arindam Ghosh	Date: 29.11.16

Final approval and acceptance of this thesis is contingent upon the candidate's submission of the final copies of the thesis to HBNI.

I/We hereby certify that I/we have read this thesis prepared under my/our direction and recommend that it may be accepted as fulfilling the thesis requirement.

Date: 29/11/2016

Place: Bhubaneswar

(Dr. Prasenjit Mal)

Guide

[1] This page is to be included only for final submission after successful completion of viva voce.

STATEMENT BY AUTHOR

This dissertation has been submitted in partial fulfillment of requirements for an advanced degree at Homi Bhabha National Institute (HBNI) and is deposited in the Library to be made available to borrowers under rules of the HBNI.

Brief quotations from this dissertation are allowable without special permission, provided that accurate acknowledgement of source is made. Requests for permission for extended quotation from or reproduction of this manuscript in whole or in part may be granted by the Competent Authority of HBNI when in his or her judgment the proposed use of the material is in the interests of scholarship. In all other instances, however, permission must be obtained from the author.

Tapas Kumar Achar

DECLARATION

I, hereby declare that the investigation presented in the thesis has been carried out by me. The work is original and has not been submitted earlier as a whole or in part for a degree / diploma at this or any other Institution / University.

Tapas Kumar Achar

List of Publications arising from the thesis

Journal Published

1. **Achar, T. K.**; Maiti, S.; Mal, P. PIDA-I2 mediated direct vicinal difunctionalization of olefins: iodoazidation, iodoetherification and iodoacyloxylation. *Org. Biomol. Chem.* **2016**, *14*, 4654-4663.

2.[#] **Achar, T. K.**; Mal, P. Transformation of Contact-Explosives Primary Amines and Iodine(III) into a Successful Chemical Reaction under Solvent-Free Ball Milling Conditions. *Adv. Synth. Catal.* **2015**, *357*, 3977-3985.

3.[#] **Achar, T. K.**; Mal, P. Radical-Induced Metal and Solvent-Free Cross-Coupling Using TBAI–TBHP: Oxidative Amidation of Aldehydes and Alcohols with N-Chloramines via C–H Activation. *J. Org. Chem.* **2015**, *80*, 666-672.

4.[#] **Achar, T. K.**; Maiti, S.; Mal, P. IBX works efficiently under solvent free conditions in ball milling. *RSC Adv.* **2014**, *4*, 12834-12839.

5. **Achar, T. K.**; Prakash, V.; Biswal, H. S.; Mal, P. An isoquinoline as cation assisted ON–OFF–ON fluorescence switch with methionine and fluoride ion. *Tetrahedron Lett.* **2013**, *54*, 1067-1070.

Communicated

6.[#] **Achar, T. K.**; Maji, R.; Bhattacharjee, J.; Mal, P. Small Benzocyclobutenols as Smart Mechanophores.

[#] pertaining to the thesis

Under Preparation

7. **Achar, T. K.**; Kumar, N.; Mal, P. Sonochemical Reductive Dehalogenation of Aryl Halides.

Conferences and Presentation

1. **Oral Presentation:** X J-NOST Conference for Research Scholar, 2014 at IIT Madras, Chennai, India on 4^{th} – 6^{th} December, 2014
2. **Poster Presentation:** Indo French Symposium On Functional Metal-Organics: Applications in Materials and Catalysis at NISER, Bhubaneswar on 24^{th} – 26^{th} February, 2014
3. Science Academies' Lecture Workshop on "Organic and Inorganic Assembly", February 21 – 22, 2015 at Department of Chemistry, Kalinga Institute of Industrial Technology (KIIT), Bhubaneswar, India
4. Indo-European Symposium on Frontiers of Chemistry, November 10 - 12, 2011 at NISER, Bhubaneswar
5. 13th CRSI National Symposium in Chemistry & 5th CRSI-RSC Symposium in Chemistry, February 4 – 6, 2011, conducted at Kalinga Institute of Industrial Technology (KIIT) and NISER, Bhubaneswar, India
6. National Seminar on frontiers in chemistry, November 11-14, 2010, conducted at School of Chemical Sciences, National Institute of Science Education and Research (NISER), Bhubaneswar, India

Tapas Kumar Achar

To my Parents and Brothers

ACKNOWLEDGEMENTS

This work might not have been possible without the copious contributions from others. First, I would like to thank my research advisor, Dr. Prasenjit Mal for his valuable guidance, continuous support, helpful discussions and providing space for free thinking throughout the last six years.

I am thankful to Prof. T. K. Chandrashekar, founder Director-NISER and Prof. V. Chandrashekhar, Director-NISER for the laboratory facilities and obviously University Grant Commission (UGC), India for financial support (fellowship).

I would like to recognize my thesis monitoring committee (TMC) members Prof. Alagar Srinivasan, Dr. Sudip Barman and Dr. Arindam Ghosh; chairperson-SCS, Dr. Moloy Sarkar and all other faculty members in SCS for their support and useful suggestions.

I remember Dr. Himansu Sekhar Biswal, Dr. Joydeep Bhattacharjee and his group member Rita for their prompt support in theoretical calculations and also thankful to Dr. Chandra Shekhar Purohit, Milan, Pardha and Subbu for useful discussion and support in crystallography study.

I extend my thanks to Dr. Kalyan Senapati (Asst. Prof. Mahatma Gandhi College, Purulia, West Bengal) for his worth suggestions and directions.

I am extremely fortunate to have lab mates like Saikat, Prasit, Anima, Khokan, Toufique, Ankita, Tuhin and Sunny. Their cheerful accompany, traceless discussion, generous cooperation have provided a thought-provoking and friendly environment which helps this journey smooth. Also, I do remember wonderful and memorable stay with my ex-lab mates Ved Prakash and Nitesh Kumar.

I thank all of my NISER friends, especially Milan, Giri, Manoj, Pardha, Ashim, Antara, Sudhir, Basujit, Mriganka, Tanmay, Manas, Sourav and Arindam for the memorable moments.

Most importantly, I would like to thank my parents, friends and family who were a witness to every step of the way and provided me support and confidence whenever I needed it the most. Thank you all so much for your unconditional love and unwavering support.

…Tapas Kumar Achar

SYNOPSIS

1.	**Name of the Student**	**:**	Tapas Kumar Achar
2.	**Name of the Constituent Institution :**		National Institute of Science Education and Research (NISER)
3.	**Enrolment No**	**:**	CHEM07201004010
4.	**Title of the Thesis**	**:**	Enabling Non-Conventional Pathway for Organic Synthesis
5.	**Board of Studies**	**:**	Chemical Science

Introduction

In recent times, chemists have put sincere efforts to develop methods to use alternative energy as a source of energy-input for chemical transformations. The solution based traditional synthesis is extremely useful, however they are associated with certain disadvantages. For example, generation of waste by-products due to overheating, uses of large quantity of solvents which causes environmental hazard.[1] To triumphs over these issues, chemists have mainly focused to develop environmentally benign and energy-efficient technologies to ensure that the next generation of synthetic protocols for chemical synthesis are more sustainable and greener.[2] Therefore, non-conventional energy sources, such as microwave, ultrasound, mechanical grinding and visible light are becoming popular.[3] In addition, minimizing waste and developing recyclable methodology is an important aspect for doing chemical synthesis in a greener fashion.

Scope and Organization of the Present Thesis

In this thesis, attempts have been made to introduce sustainable methods by implementing the following: targeting atom economy, enabling less hazardous and safer methodologies, facilitating

energy efficient approaches, etc. Our efforts to develop more viable and efficient synthetic protocols using ball milling and ultrasound is mainly described here in addition to historical and mechanistic perspective of mechanochemistry. The present thesis has been organized in five chapters and the contents of each chapter have been summarized as follows:

CHAPTER 1: Historical Development and Mechanistic Insight of Mechanochemistry

This chapter mainly focuses on brief introduction of mechanochemistry and its green chemistry aspects. Basically it consists of two different parts; (1) solvent-free synthesis using ball milling and (2) ultrasound-triggered chemical reactions. The summarizing details of history and development of both approaches have been highlighted. Apart from this, details mechanistic insight of mechanochemistry is documented that is, how low energy excitation can cause chemical reactions which in general requires very high energy. Also, we have made an attempt to present some of the important published articles as a comprehensive review on chemical reactions using nonconventional energy sources. Finally this chapter concludes with conferring the aim of present thesis.

CHAPTER 2: IBX Works Efficiently under Solvent free Conditions in Ball Milling

(Ref: T. K. Achar, S. Maiti and P. Mal, *RSC Adv.* **2014**, *4*, 12834-12839)

This chapter represents the efficiency and synthetic utility of 2-iodoxybenzoic acid (IBX) under solvent free milling conditions.[4] IBX (2-iodoxybenzoic acid), discovered in 1893 by Hartmann and Meyer[5], is metal free, mild and non-toxic organo-oxidant in synthetic chemistry whose extensive use is impeded by its explosiveness at high temperature and poor solubility in common organic solvents except dimethyl sulfoxide (DMSO). Since the discovery of Dess-Martin

Periodinane[6] in 1983, IBX has experienced several modifications to be useful to chemists. On the contrary, these modified IBXs are most often complicated due to involvement of tedious synthetic procedure in non-economical way.[7] Therefore the modification approach has not been converged and is still in demand for better methods. However, under ball milling condition, IBX turned out to be compatible with various organic functionalities at ambient temperature and under solvent free conditions. Also, the waste IBA (2-iodosobenzoic acid) produced from the reactions was *in situ* oxidized to IBX in following step using oxone and thus reused for multiple cycles by conserving its efficiency (only ~6% loss after 15 cycles). In this work, we have demonstrated an outline of a highly economical synthetic methodology which overcomes the problems of using IBX for large scale (gram scale) synthesis in a non-explosive way.

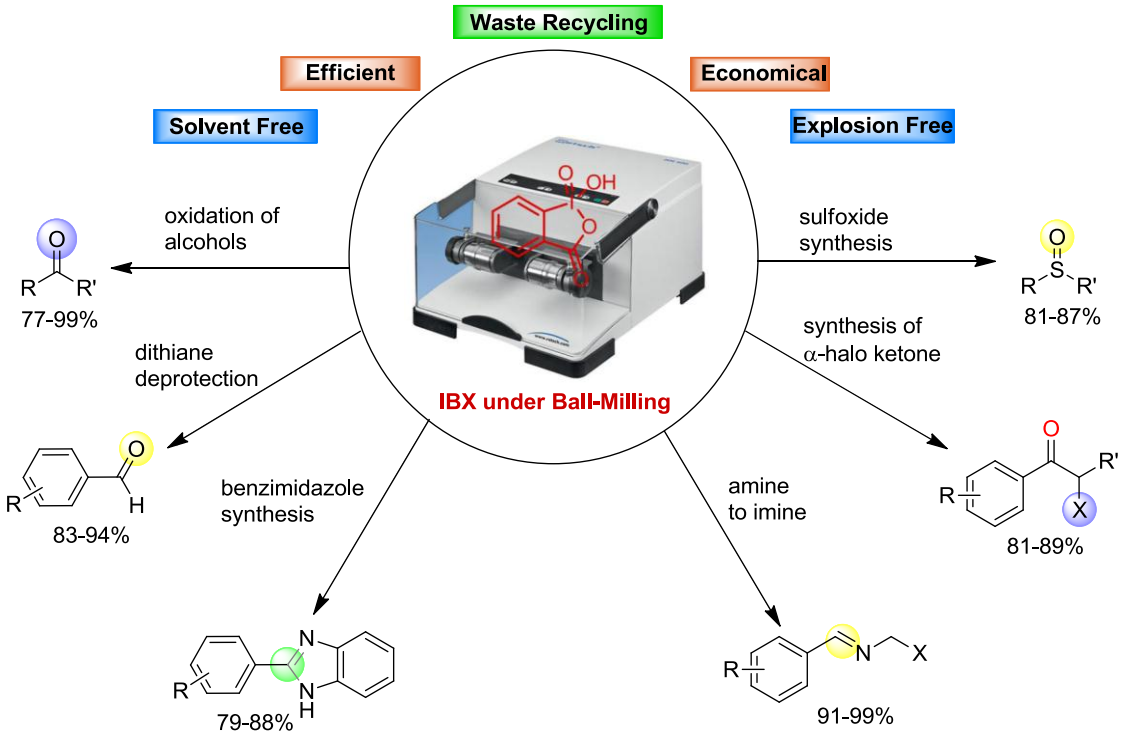


Figure 1. Scope of reactions with IBX under solvent free milling conditions

CHAPTER 3: An Organocatalytic Solvent free Cross Coupling using TBAI-TBHP: Oxidative Amidation of Aldehydes and Alcohols with *N*-Chloramines via C-H Activation

(Ref: T. K. Achar and P. Mal, *J. Org. Chem.* **2015**, *80*, 666-672)

A solvent and metal free cross-coupling method for oxidative amidation of aldehydes and alcohols *via* radical pathway has been demonstrated in Chapter 3. This methodology using TBAI-TBHP combination works efficiently to do metal free C-H activation of aldehydes under neat (50 °C) or ball milling (room temperature, 21 Hz) condition.[8] This TBAI (tetrabutylammonium iodide) – TBHP (*tert*-butyl hydroperoxide) combination is mild, non-toxic and produces the amide

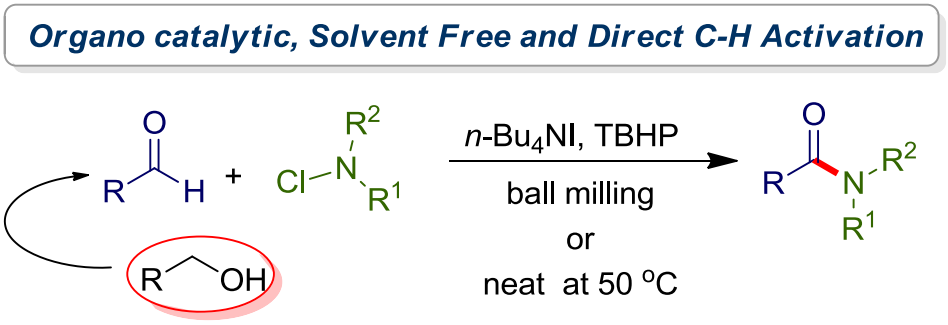


Figure 2. Oxidative amidations of aldehydes and alcohols with *N*-chloramines.

derivative in very good yield. Generally, TBHP has been extensively used for amidation in presence of various metals like Cu, Fe, Ag, Zn etc. To avoid the expensive metal leaching process and to introduce environmental friendly reagents[9], we have used organocatalyst, TBAI for the amidation reactions. This cross coupling reaction of the aldehydes and *N*-chloramine was confirmed to proceed via radical pathway by trapping acyl radical with 2,2,6,6-Tetramethyl-1-piperidinyloxy (**TEMPO**) and established for an example of metal free C-H activation.

CHAPTER 4. Transformation of Contact-Explosives Primary Amines and Iodine(III) into a Successful Chemical Reaction

(Ref: T. K. Achar and P. Mal, *Adv. Synth. Catal.* **2015**, *357*, 3977-3985)

This Chapter describes a method to transform an explosive mixture into a productive chemical reaction for synthesis of organic compounds at maximum contacts of the reactants. Generally, any synthetic transformation using contact-explosives primary amines and hypervalent iodine(III) (phenyliodine diacetate) in a constrained media is practically impossible. Here the presented method describes the diverting of explosive mixture into a successful cross dehydrogenative coupling (CDC) reaction for C-N bond amidation of aldehydes via C-H activation.[10] An acid-salt sodium bisulphate was used to control contact-explosive primary

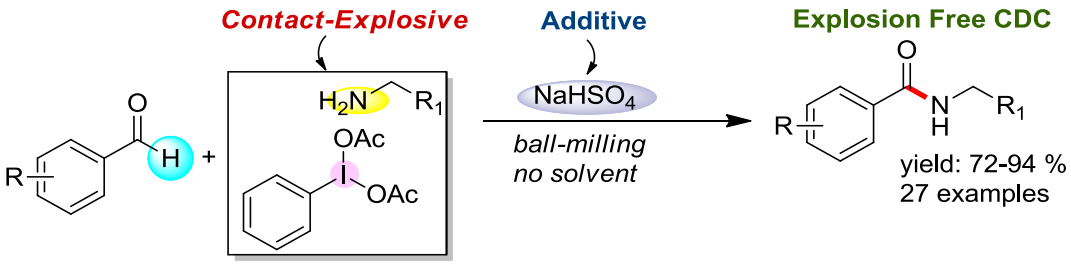


Figure 3. $NaHSO_4$ mediated explosion free cross dehydrogenative coupling for amide synthesis.

amines-phenyliodine diacetate for a successful mechanochemical cross dehydrogenative coupling (CDC). Probable mechanistic pathway has been proposed with the account of several control experiments. An isothermal titration calorimetric (ITC) study was carried out to understand the role of $NaHSO_4$ by determining the enthalpy changes during the reactions before and after addition of $NaHSO_4$.

CHAPTER 5. Input Controlled Mechano-Responsive C-C Bond Scission on Benzocyclobutenols

(Ref: T. K. Achar, R. Maji, J. Bhattacharjee and P. Mal, *Submitted*)

In this section we have demonstrated the possibility for small molecules to host the exotic mechano-responsive bonds that are amenable to scission upon low-energy mechanical excitation like sonication at ultrasonic frequencies, a mechanism well-known to be active only in polymers.[11] Centrally, we report sonication induced C-C bond scission in benzocyclo butenols (**CB**) of low molecular weight (Mw: 198). We have shown that the observed mechano-response is a direct consequence of a close contest between covalent interaction, and a plausible

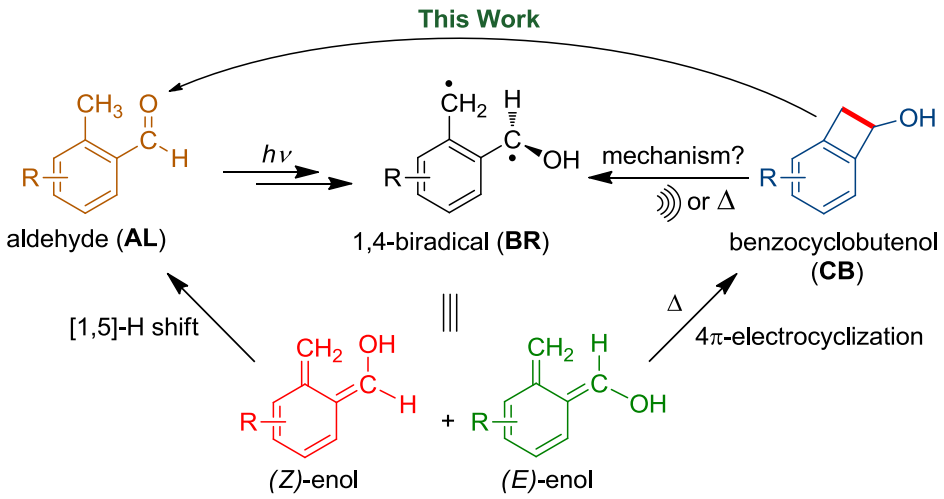


Figure 5. Photo-initiated transformation (left to right) of *o*-alkyl aromatic aldehydes (**AL)** to the corresponding **CB**s *via* 1,4-biradical (**BR**) and followed by (*E*)-enol.[12] In turning around (**CB** to **AL** conversion as conventionally expected).[13]

combination of intermolecular hydrogen bonding interactions facilitated intermolecularly. The observed mechano-responsivity, can be switched through intra-molecular control like suitable

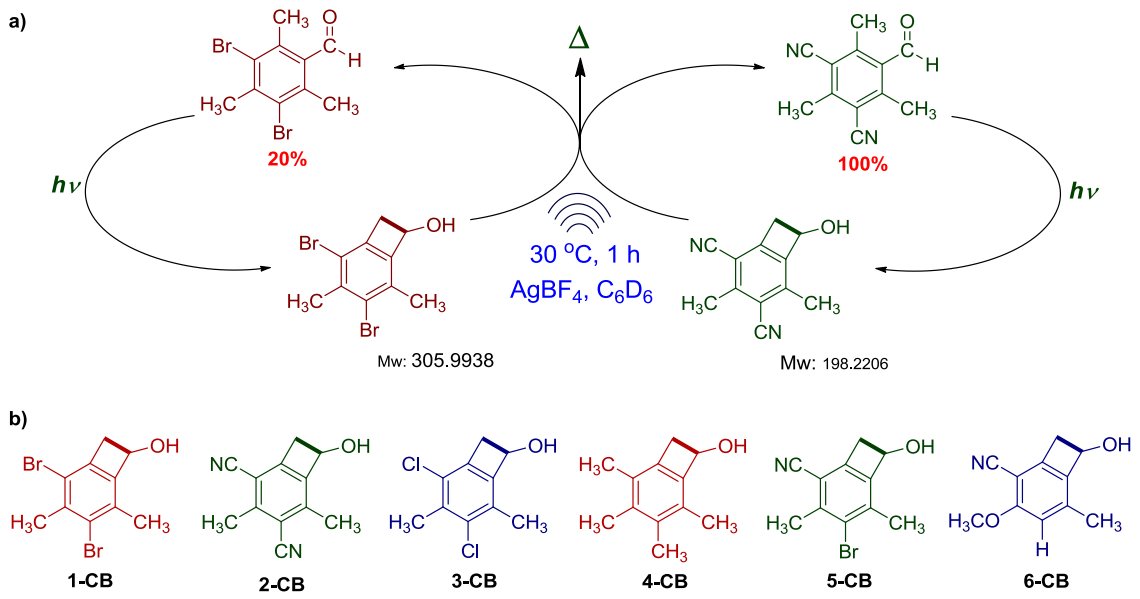


Figure 6. a) Sonochemical conversion of CBs to ALs with release of heat energy; b) CBs used for present study.

substituents and intermolecular effects like solvent polarity and supramolecular interactions. It was established that intermolecular hydrogen bonding interaction between multiple adjacent molecules bring down the dissociation barrier of the non-aromatic C-C bond for effective low energy mechanical excitation. We have also confirmed that C-C bond scission is not due to overheating caused during sonication. Cleavage of such C-C bonds lead to release of energy which may initiate further ring opening of other molecules, *i.e.* triggers the possible chain reaction. Details UV-Vis, IR, NMR and DFT studies were carried out to derive mechanistic understanding of the effects of substituents, solvents or additives which will enable designing new chemical reactions in micro-environment.

References

1. Sheldon, R. A., *Green Chem.* **2005,** *7*, 267.
2. (a) James, S. L.; Adams, C. J.; Bolm, C.; Braga, D.; Collier, P.; Friscic, T.; Grepioni, F.; Harris, K. D. M.; Hyett, G.; Jones, W.; Krebs, A.; Mack, J.; Maini, L.; Orpen, A. G.; Parkin, I. P.; Shearouse, W. C.; Steed, J. W.; Waddell, D. C., *Chem. Soc. Rev.* **2012,** *41*, 413; (b)Stolle, A.; Szuppa, T.; Leonhardt, S. E. S.; Ondruschka, B., *Chem. Soc. Rev.* **2011,** *40*, 2317.
3. Baig, R. B. N.; Varma, R. S., *Chem. Soc. Rev.* **2012,** *41*, 1559.
4. Achar, T. K.; Maiti, S.; Mal, P., *RSC Adv.* **2014,** *4*, 12834.
5. Hartmann, C.; Meyer, V., *Ber. Dtsch. Chem. Ges.* **1893,** *26*, 1727.
6. Dess, D. B.; Martin, J. C., *J. Org. Chem.* **1983,** *48*, 4155.
7. Seth, S.; Jhulki, S.; Moorthy, J. N., *Eur. J. Org. Chem.* **2013**, 2445.
8. Achar, T. K.; Mal, P., *J. Org. Chem.* **2015,** *80*, 666.
9. (a) Garrett, C. E.; Prasad, K., *Adv. Synth. Catal.* **2004,** *346*, 889; (b)Welch, C. J.; Albaneze-Walker, J.; Leonard, W. R.; Biba, M.; DaSilva, J.; Henderson, D.; Laing, B.; Mathre, D. J.; Spencer, S.; Bu, X.; Wang, T., *Org. Process Res. Dev.* **2005,** *9*, 198.
10. Achar, T. K.; Mal, P., *Adv. Synth. Catal.* **2015,** *357*, 3977.
11. Wiggins, K. M.; Brantley, J. N.; Bielawski, C. W., *Chem. Soc. Rev.* **2013,** *42*, 7130.
12. Moorthy, J. N.; Mal, P.; Natarajan, R.; Venugopalan, P., *J. Org. Chem.* **2001,** *66*, 7013.
13. Netto-Ferreira, J. C.; Scaiano, J. C., *J. Am. Chem. Soc.* **1991,** *113*, 5800.

List of Schemes

List of Figures

Page No

List of Tables

List of Abbreviations Used

Å	Angstrom
AcOH	Acetic Acid
Anal.	Analytically
Anhyd	Anhydrous
aq	Aqueous
BM	Ball Milling
bp	Boiling Point
BPO	Benzoyl Peroxide
br	Broad
ºC	Degree Celcius
Calcd	Calculated
cm	Centimeter
Conc	Concentrated
conv	Conversion
d	Doublet, Days
DCE	Dichloroethane
DCM	Dichloromethane
dd	Doublet of a Doublet
DIBALH	Diisobutylaluminium Hydride
dil	Dilute
DMF	*N*,*N*-Dimethyl Formamide
DMSO	Dimethyl Sulfoxide
eq	Equation
equiv	Equivalent
Et	Ethyl
EtOAC	Ethyl Acetate
FAB	Fast Atom Bombardment
g	Grams
h	Hours

HRMS	High-resolution Mass Spectrometry
hv	Irradiation, Photochemical Reaction
i	Iso
ITC	Isothermal Titration Calorimetry
IR	Infrared
K	Kelvin
kcal	Kilo calories
lit	Liter
m	Multiplet
M	Molar
MeCN	Acetonitrile
mp	Melting point
Me	Methyl
MHz	Mega Hertz
Min	Minutes
mL	Milliliter
mM	Millimolar
mmol	Millimole
mol	Mole
MS	Mass Spectra
N	Normal
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
nm	Nanometer
NMR	Nuclear Magnetic Resonance
ns	Nanosecond
pet.ether	Petroleum ether
PM	Planetary Milling
ppm	Parts per Million
rt	Room Temperature
s	Singlet, Seconds

TFE	Trifluoroethanol
TLC	Thin Layer Chromatography
tw	Twisted
TFA	Trifluoroacetic acid
US	Ultrasound
UV	Ultraviolet
Vis	Visible
vs	Versus
XRD	X-Ray Diffraction

Table of Contents

CHAPTER 1

Mechanochemistry: Fundamentals and Application in Synthesis

1.1 ABASTRACT

This section mainly focuses on approach of sustainable synthesis *via* mechanochemistry and collection of significant literature reports. Mainly it consists of two different parts; (1) solvent-free synthesis using ball mill and (2) ultrasound-triggered chemical reactions. Also, details mechanistic insight of mechanochemistry is discussed to understand how low energy excitation can cause chemical reactions which in general requires very high energy. In addition, we have made an attempt to uncover the relevancy of chemical reactions using nonconventional energy sources. Finally this chapter concludes with conferring the aim of present thesis.

1.2 INTRODUCTION

Recently, the field of organic synthesis have experienced significant changes towards achieving the goal of more efficient and sustainable processes. Thus a new branch of chemistry termed as "Green Chemistry" have become a part of research interest by the Chemists. Green chemistry covers a wide range of research area and generally deals with 12 principles like mainly preventing the use of volatile and toxic solvents, reducing the quantity of catalyst and reagents, using environmentally benign chemicals, atom-economical synthesis, minimizing chemical-waste/energy, etc.[1]

Nonconventional energy sources for chemical reactions such as microwave, mechanical mixing, visible-light and ultrasound are becoming surge of interest to the chemist as an alternative energy sources in laboratories. By imposing these techniques innumerable chemical transformations have been achieved and thereby developing many existing protocols with superior results are further expected.

The commonly used techniques in mechanochemistry are mainly traditional hand grinding, mechanical milling or ultrasonication. Hand grinding is usually performed in a mortar and pestle, while mechanical milling is generally conducted in a vibration mill or planetary mill at frequency of 5 – 60 Hz. Mechanochemically, formation of carbon–carbon,[2] carbon–heteroatom,[3] metal–ligand coordination bonds,[4] non-covalent interactions[5] such as hydrogen bonds or π--π arene stacking interactions are reported in literature. A comprehensive review on mechano-milling as synthetic tool in organic synthesis have been presented.

1.3 MECHANOCHEMISTRY

Mechanochemical methods deals with the chemical transformation induced by mechanical energy, such as compression, shear, or friction.[6] According to IUPAC, mechano-chemical reaction is a 'Chemical reaction that is induced by the direct absorption of mechanical energy' with a note that 'Shearing, stretching, and grinding are typical methods for the mechano-chemical generation of reactive sites, usually macroradicals, in polymer chains that undergo mechano-chemical reactions'.[7] In the past decade, mechanochemical reactions have been developed on the methodologies into different areas of chemistry for example, from supramolecular chemistry and organic synthesis to metal–organic frameworks and nanoparticle synthesis. In addition,

mechanochemistry could be subdivided into four different areas, *e.g.* tribochemistry (the chemistry of surfaces in contact), trituration (chemistry induced by grinding and milling), macromolecular mechanochemistry (from breakage of polymer chains to molecular motors and biological motion), and sonochemistry (the chemistry generated from the mechanical consequences of sound). There are several advantages of mechanochemistry, over solution-based methods[8] and thus receiving significant attention in Chemical methods and process development.

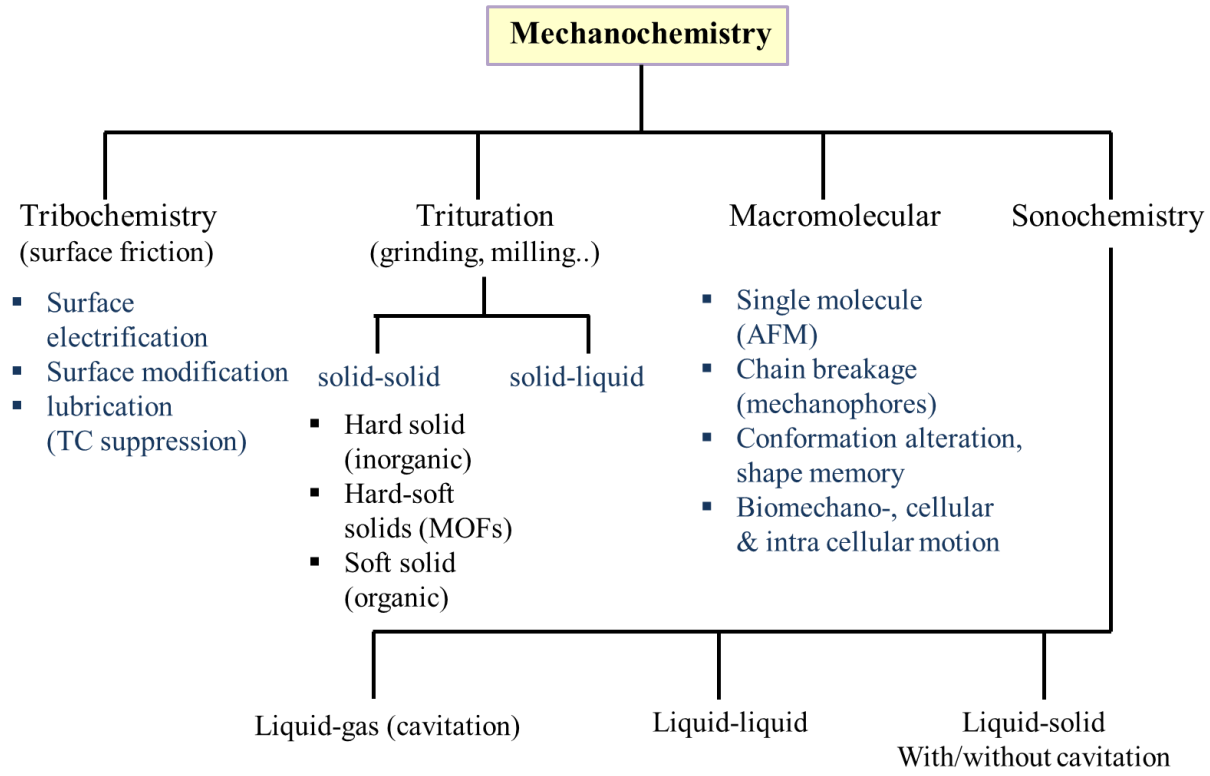
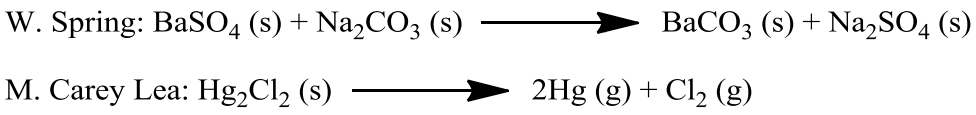


Figure 1.1 An overview of different areas in mechanochemistry.

1.3.1 Mechanochemistry: A Historical Overview

Wilhelm Ostwald, a Russian-German chemist who received the Nobel Prize in 1909, mentioned the term "mechanochemistry" as a branch of physical chemistry like thermochemistry, photochemistry and electrochemistry. According to Ostwald "Mechanochemistry is a branch of

chemistry which is concerned with chemical and physico-chemical changes of substances of all states of aggregation due to the influence of mechanical energy".[9] However, the chemical application of mechanical activation can be traced back to prehistoric times. Theophrastus of Eresus, Aristotle's student and successor at the helm of the Lyceum, wrote a short booklet titled ''On Stones'' in 315 B.C.,[10] in which he mentioned the reduction of cinnabar to mercury by grinding in a copper mortar with a copper pestle. Probably that was the first time in human history that a metal in the elemental form was extracted from a chemical compound under the area of mechanochemical reaction. Despite of this early finding, development of mechanochemistry was very slow. Following, in 1820, Faraday described the reduction of silver chloride by grinding with zinc, tin, iron and copper in a mortar.[11] He termed the technique as the "dry way" of inducing reactions. However, W. Spring in 1880s from Belgium and American scientist M. Carey Lea from Philadelphia, Pennsylvania in 1890s independently carried out the first extensive investigation of mechanochemical reactions. Spring's metathesis reaction (Scheme 1.1) induced by repeated compression and pulverization was the first large scale mechanochemical synthesis.[12] Lea's systematical investigation on decomposition of mercury and silver halides to their elements revealed that mechanochemical reactions could lead to different outcome than thermal ones.[13]



Scheme 1.1 Mechanochemical reactions discovered by W. Spring and M. Carey Lea.

In 1893, Ling and Baker reported first solvent-free organic mechanochemical reaction, probably a cocrystallization reaction.[14] Application of mechanochemistry to inorganic materials (e.g., minerals and metals) has been known since ancient times.[15] Contrastingly, organic

mechanochemistry has remained undeveloped until the pioneering explorations by Toda[16] and Kaupp in 1980s.[17]

1.4 Ball Milling

The simplest technique of mechanochemical synthesis is traditional grinding using a mortar and pestle. Although this technique has been extensively used but having limitations in controlling reaction conditions for air and moisture sensitive substances.[18] In contrast, programmed electrical milling system facilitate mechanochemical reactions within a sealed vessel which is agitated in a controlled manner. The sealed vessel (milling jar) can be either very fine metal or ceramic particles, allowing for thorough mixing and high frictional heating.[19] The milling balls can be made of different materials for example, stainless steel, tungsten carbide, zirconia, agate etc.

1.4.1 Mechanistic Aspects

Mechanistic understanding of mechanochemistry is still unclear. A single idea could not be conceived due to the diversity of reaction types, reaction conditions and reactive materials. In conventional chemical synthesis at solution phase, the energy dispersion and the transport of chemicals are well assured. However, under solvent free system in traditional hand grinding, the mass and energy transport are imbalanced. Contrastingly, the efficient mixing process in ball mills overcome these problems to initiate effective solid phase reactions.[2-3, 16a, 20] There are several processes take place during mechanical grinding of solids such as:[21,2, 6, 22]

- Comminution of the particles to a very small size, resulted large surface area
- With formation of point defects and dislocations in the crystalline structure, helps to transform phase in polymorphic materials
- Decomposition, oxidation–reduction, complex and adduct formation etc. of chemicals

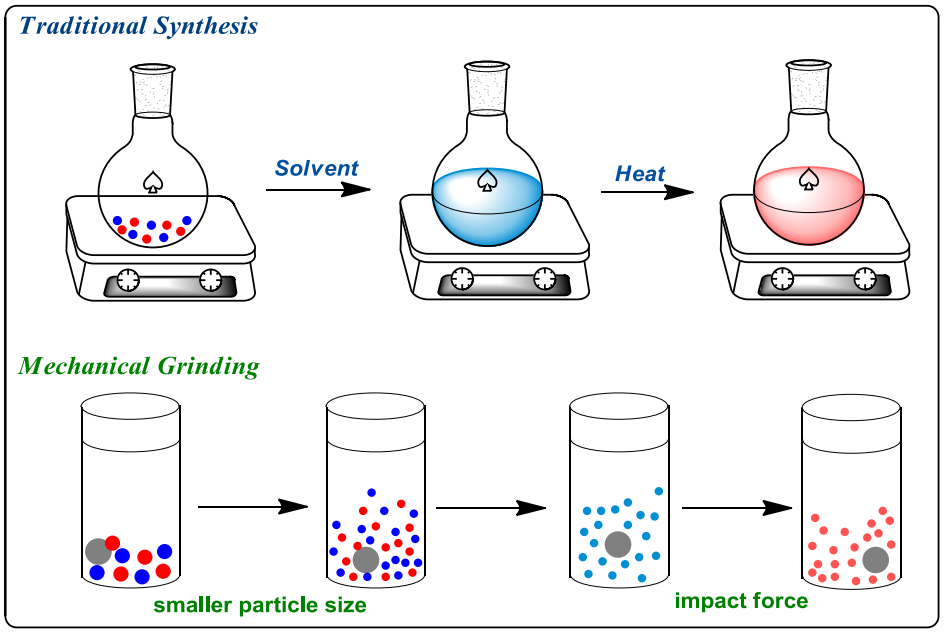


Figure 1.2 Mechanochemical versus traditional solution phase synthesis

Based on the observations discussed above, several models have been proposed[23] and among them hot spot and "magma – plasma model" are the most preferred ones.

Hot spot theory: Hot spot theory developed upon considering frictional processes between two surfaces sliding against each other, proposed by Bowden, Tabor and Yoffe.[24] Small swellings cause plastic distortions associated with intense raising of local (within ca. 1 μm^2) temperatures to above 1000 °C within short periods (10^{-3}-10^{-4} s). More brittle (less plastic) materials would be disposed to crack under strain.[25] However, in brittle materials, hot spots can also be expected at the tips of propagating cracks.

Magma – Plasma Model: The "magma- plasma model", was introduced by Thiessen in 1967.[26] In magma – plasma model, the mechanical impact upon grinding releases a large quantity of energy (local temperatures greater than 10^4 °C) which helps the formation of a transient plasmatic state and also facilitate to eject energetic species including free electrons.

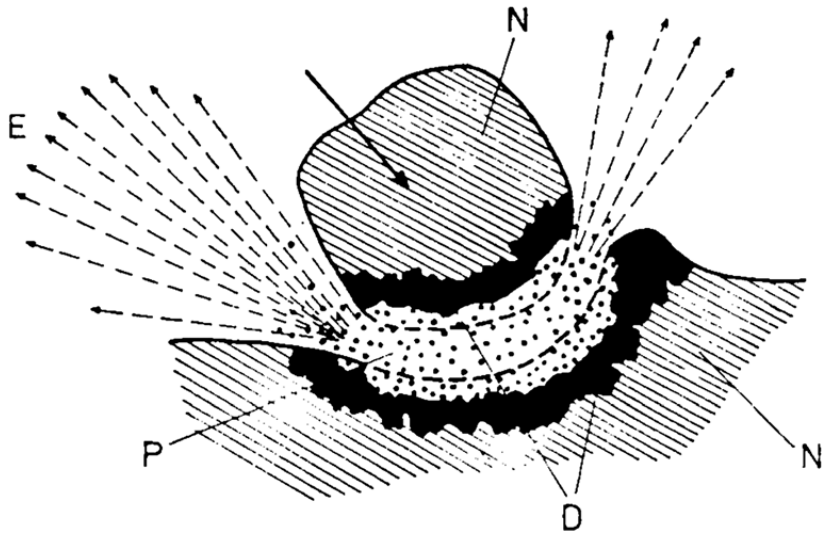
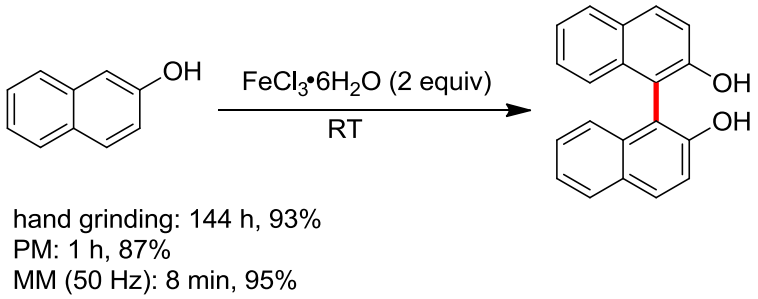


Figure 1.3 Magma-plasma model: E – exo-electrons, N – undeformed solid, D – highly deformed surface layer, P – plasma. (Adopted from *Chem. Soc. Rev.* **2013**, *42*, 7571 with permission of The Royal Society of Chemistry)

Other models like *spherical model*,[28] *dislocation and phonon theory*,[29] *short-live-active center theory*,[30] *kinetic and impulse model*[31] are also proposed. Nevertheless, due to the complex and diversified nature of mechanochemical reactions, this subject is still challenging and seek more attention to both experimental and theoretical chemists.

1.4.2 Ball Milling in Organic Synthesis

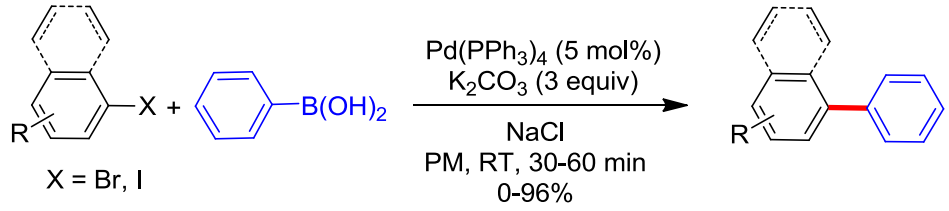
In mechanochemical synthesis using ball milling, pioneering works were reported by the groups of Toda[16a, 32] and Kaupp[17]. They have reported comprehensive work on the stoichiometric conversion of organic compounds in solid state reaction. Basically ball milling technique has been applied to influence efficient mixing of two solid reagents under solvent-free condition.[33]



Scheme 1.2 Oxidative homocoupling of 2-naphthol

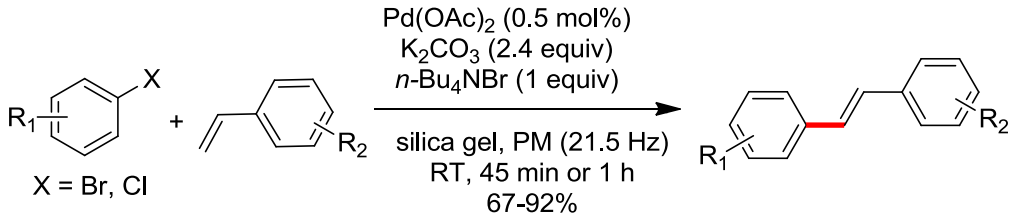
Toda and coworkers reported the oxidative homocoupling of 2-naphthol to 1,1′-bi-2-naphthol in presence of $FeCl_3 \cdot 6H_2O$ under solvent free conditions (Scheme 1.2).[32] While doing the reaction traditionally using an agate mortar and pestle, 93% of binaphthol was isolated after 144 h at room temperature. However, the reaction time could be reduced to 1 h using Planetary Milling (PM) at ambient temperature (yield was 87%)[34] and to 8 min using high-speed vibration mill (MM) at speed of 3000 rpm (50 Hz) (yield 95%).[35]

Palladium catalyzed coupling reactions. The palladium-catalyzed Suzuki coupling reaction is one of the most extensively investigated metal catalyzed reaction.[36] In 2000, Peters and coworkers first reported the palladium catalyzed Suzuki coupling reaction under ball-milling condition.[37] In this reaction, by milling the mixtures of aryl halide (1equiv), phenylboronic acid (2 equiv), K_2CO_3 (3 equiv) and $Pd(PPh_3)_4$ (5 mol%) in a Fritsch Planetary Micro Mill Pulverisette for 30-60 min afforded the desired coupled products in up to 96% yield (Scheme 1.3). The NaCl was used as additives to make the reaction mixture sufficiently powdery for uniform mixing.



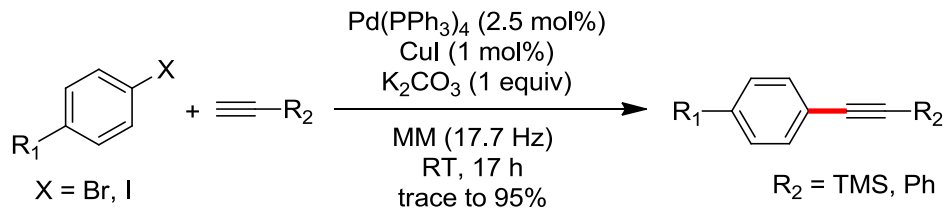
Scheme 1.3 Mechanochemical Suzuki reaction.

Frejd and co-workers first applied the ball milling technique to perform Heck reaction.[38] (E)-Stillbene derivatives were synthesized by the Heck reaction of styrenes with aryl bromides or aryl chlorides by Su and coworkers (Scheme 1.4).[39]



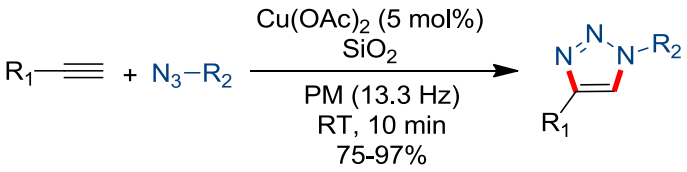
Scheme 1.4 Mechanochemical Heck reaction

The Pd-catalyzed Sonogashira coupling were reported by Mack and co-workers (Scheme 1.5), in which aryl halides were coupled with phenylacetylene or trimethylsilylacetylene in the presence of CuI-K_2CO_3 at 17.7 Hz for 17 h under aerobic conditions to afford the product in excellent yields.[40]



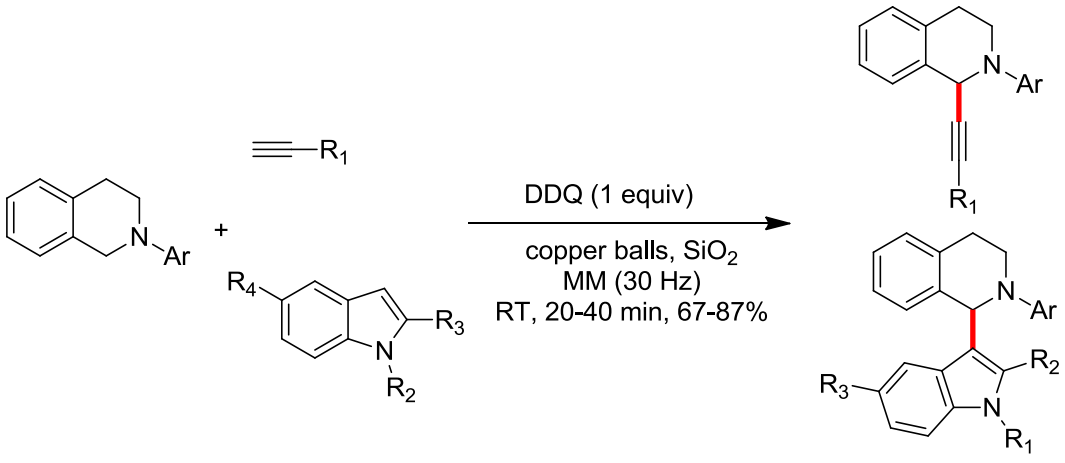
Scheme 1.5 Sonogashira coupling under milling conditions

Cu-catalyzed mechanochemical reactions. Stolle and co-workers developed ligand and solvent free methods for the Huisgen 1,3-dipolar cycloaddition (*click reaction*) reactions of alkynes with azides catalyzed by $Cu(OAc)_2$ using planetary ball mill at 800 rpm for 10 min (Scheme 1.6).[41] This technique was also successfully applied to carry out a *click* polymerization under milling conditions.



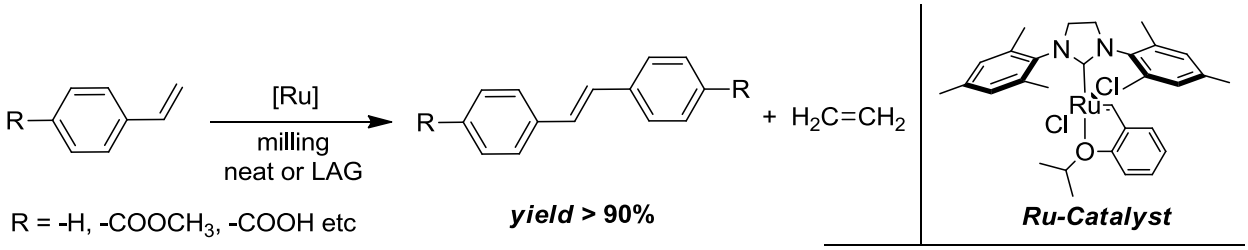
Scheme 1.6 Mechanochemical *click* reaction

Copper has proved to be highly active in oxidative cross-dehydrogenative coupling (CDC) reactions and 2,3-dichloro-5,6-dicyanoquinone (DDQ) has been investigated as an efficient oxidative agent for oxidative carbon-carbon bond formation reactions. Recently, Su and co-workers reported the mechanochemical CDC reaction of tetrahydroisoquinolines with alkynes and indoles using copper balls (Scheme 1.7).[42]



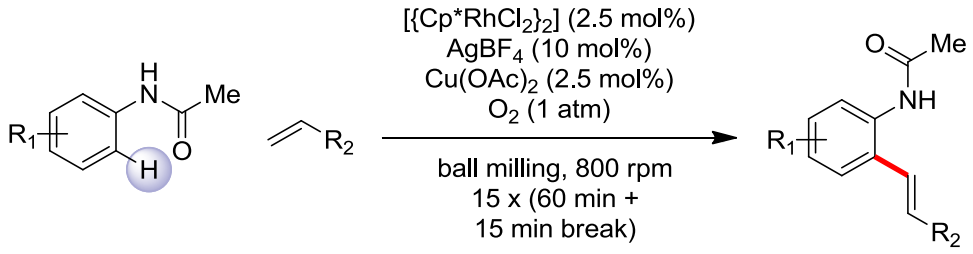
Scheme 1.7 Copper catalyzed cross-dehydrogenative coupling (CDC) reaction under mechano-milling

Ruthenium-catalyzed mechanochemical reaction. Solvent free olefin metathesis was first observed by the Wagner group in which sprinkling solid ruthenium-based catalyst onto polystyrene led to slow liquefaction of the solid polymer.[43] Recently, Friščić and co-workers reported an efficient mechanochemical approach using Ru-based Hoveyda-Grubbs catalyzed olefin metathesis including cross-metathesis and ring-closing metathesis reactions (Scheme 1.8).[44] Advantageously this methodology was applicable for both solid and liquid olefins.



Scheme 1.8 Mechanochemical ruthenium-catalyzed olefin metathesis reaction.

Rhodium-catalysed C–H bond functionalization. Recently, Bolm and co-workers have reported rhodium(III)-catalyzed directing group assisted selective C–H bond functionalization under mechanomilling conditions (Scheme 1.9).[45]

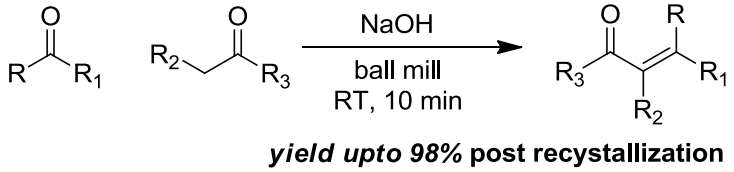


Scheme 1.9 Rhodium(III)-catalyzed C – H bond functionalization under mechanochemical conditions.

In presence of catalytic amount of $Cu(OAc)_2$, the mechanochemical activation led to formation of an active rhodium species that enabled oxidative Heck-type of cross-coupling where molecular

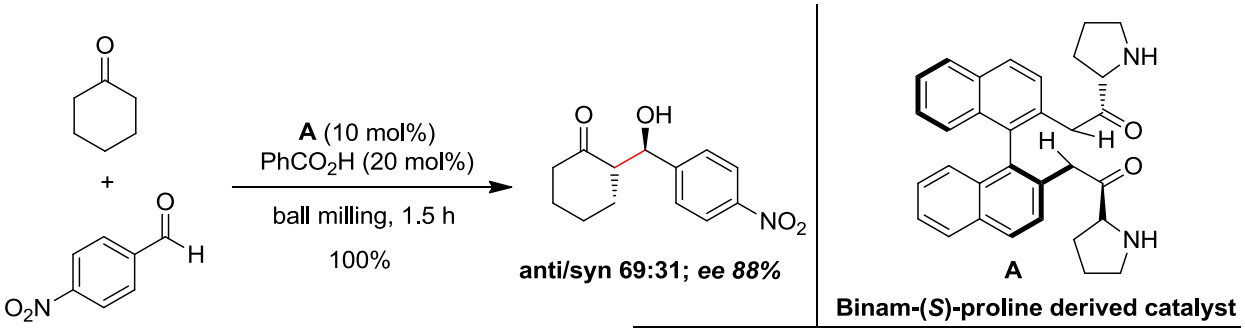
oxygen was the terminal oxidant. This simple protocol resulted in a powerful and environmentally sustainable alternative to the common solution based protocol by avoiding organic solvent and high reaction temperature.

Aldol reaction. In 2000, Raston and co-workers first reported the aldol condensation reaction using veratraldehyde, 4-phenylcyclohexanone and 1-indanone in the presence of NaOH in a vibrating ball mill for 10 min (Scheme 1.10).[46] Single cross aldol condensation products were isolated in high yield (up to 98%) and ruled out for the formation of any other possible product.



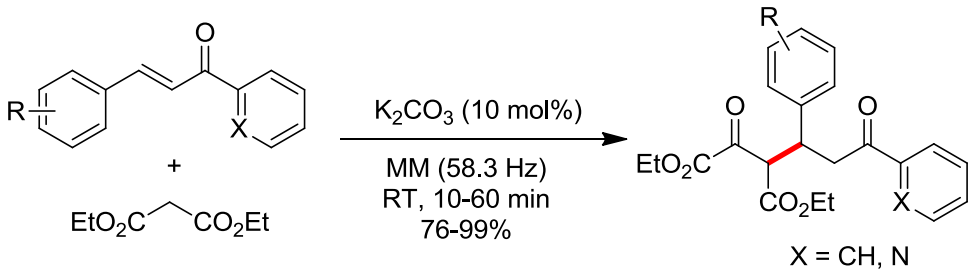
Scheme 1.10 Mechanochemical aldol condensation reactions.

Guillena, N´ajera and co-workers studied the asymmetric version of aldol condensation reaction. Reaction between various ketones and aldehydes under solvent free condition were performed using the combination of (S)-binam-L-Pro (**A**, 5 mol%) and benzoic acid (10 mol%) as a organocatalyst (Scheme 1.11).[47]



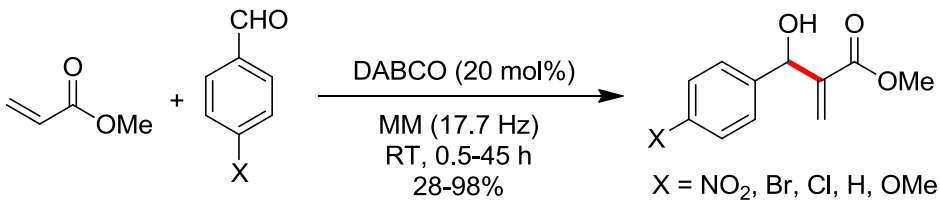
Scheme 1.11 Enantioselective organocatalyzed aldol reactions under mechano milling.

Michael addition. Michael addition of 1,3-dicarbonyl compounds to *α,β*-unsaturated ketones are usually done in organic solvents using strong bases such as NaOH, KOH, $Ba(OH)_2$ and NaOEt as catalyst. Wang and coworkers first reported mechanochemical Michael reaction in 2004 for the addition of 1,3-dicarbonyl compounds to chalcones and azachalcones catalyzed by weak base K_2CO_3 (Scheme 1.12). Upon high-speed vibration mill (HSVM) at a rate of 58.3 Hz for 10-60 min, Michael adducts were isolated in 76-99% yields in the presence of 10 mol% K_2CO_3.



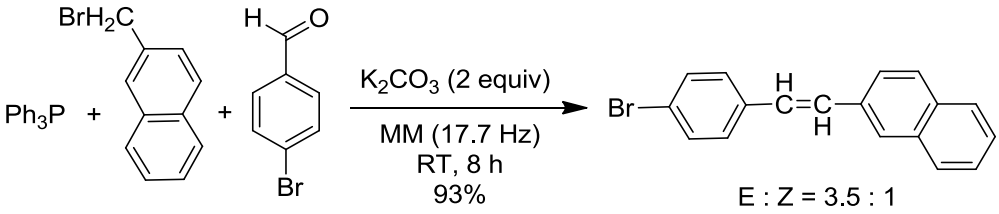
Scheme 1.12 Mechanochemical Michael reaction

Morita-Baylis-Hillman reaction. The Morita-Baylis-Hillman reaction (MBH) employs an electron-deficient olefin, a tertiary amine catalyst and an electrophile like aldehyde to produce a multifunctional product. Generally, MBH reaction is very slow, takes days to weeks to afford the products in moderate yields. Mack *et al.* found a significant rate enhancement of the MBH reaction by ball milling (scheme 1.13).[48] The reaction of methyl acrylate with different *p*-substituted aryl aldehydes in the presence of 20% 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyst in a Spex CertiPrep 8000 M mixer mill for 0.5-45 h yielded the MBH products in 28-98%.



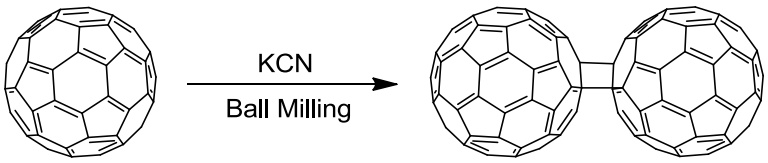
Scheme 1.13 Mechanochemical Morita-Baylis-Hillman (MBH) reaction.

Wittig Reaction. Pecharsky and coworkers reported the solvent-free mechanochemical synthesis of phosphonium salts[49] and also synthesized phosphorus ylides[50] in the presence of weak base K_2CO_3 in the solid state. They utilized this mechanochemical preparation of phosphorus ylide to solvent-free Wittig reaction in one-pot process starting with triphenylphosphine, an organic halide and an aldehyde or ketone in the presence of K_2CO_3 (Scheme 1.14).[50]



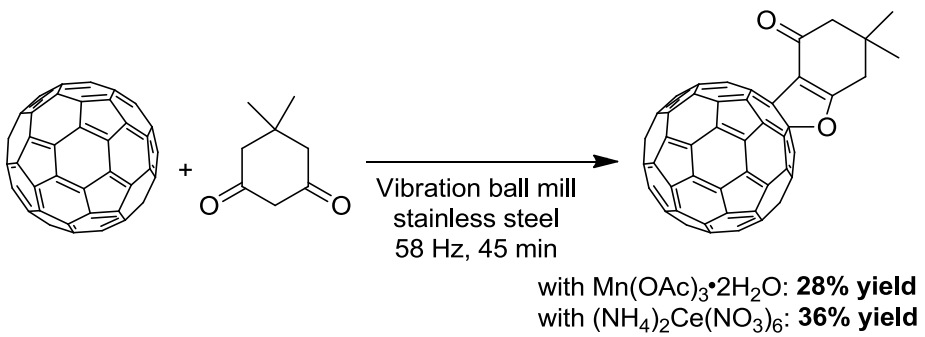
Scheme 1.14 Mechanochemical Wittig reactions.

Buckybowl Chemistry. Komatsu *et al.* found that a C_{120} [2 + 2] –adduct was formed when C_{60} fullerene was ball milled with KCN under solvent-free conditions (Scheme 1.15).[51]



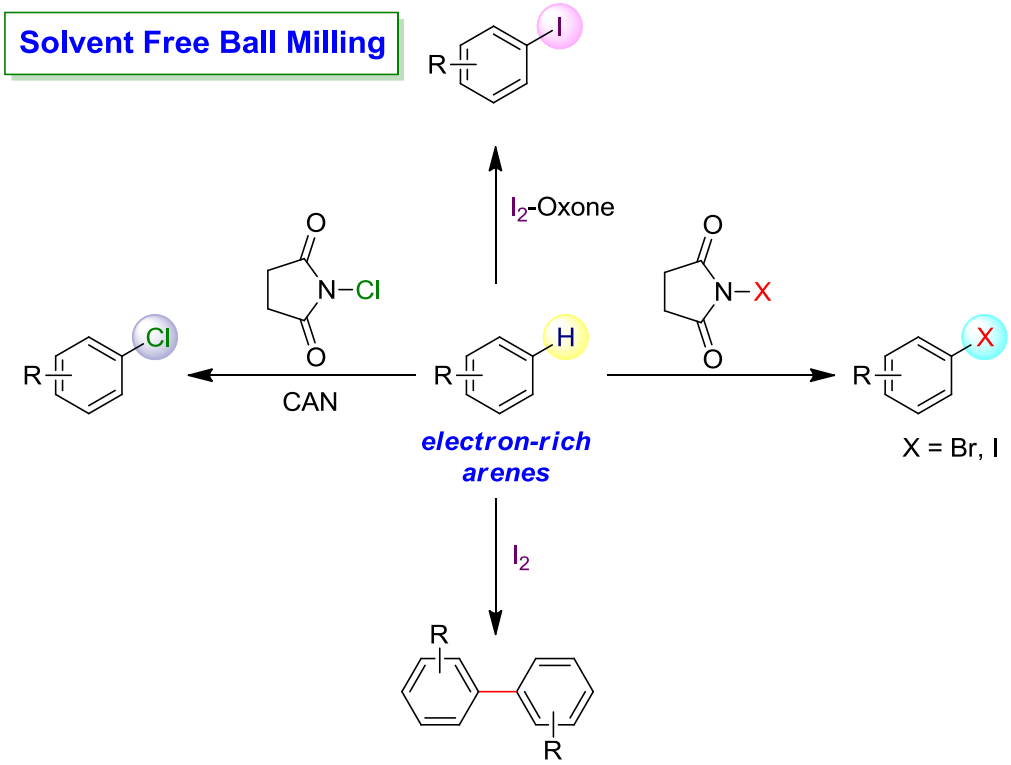
Scheme 1.15 KCN promoted synthesis of C_{120} [2 + 2] adduct of C_{60} under ball milling.

Recently, Cheng *et al.*, described the oxidative addition of 1,3-dicarbonyls to C_{60} to obtain dihydrofurane-fused derivatives (Scheme 1.16).[52] Ceric ammonium nitrate, as an oxidant, is more prone to selective formation of heterocyclic over $Mn(OAc)_3$.



Scheme 1.16 Oxidative addition of 1,3-dicarbonyl to C_{60}

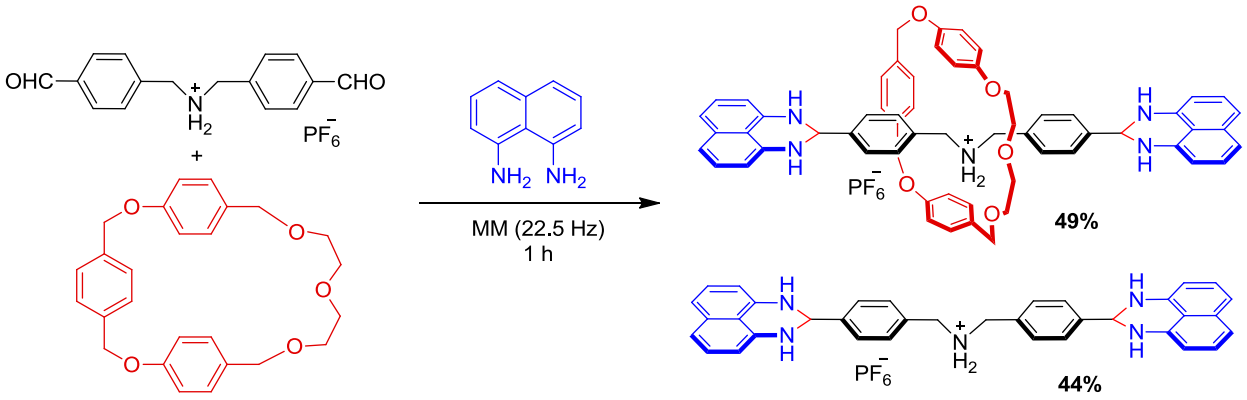
Electrophilic Halogenation of Arenes. A straightforward and efficient protocol of chemo- and regio-selective aryl halogenations were encountered by our group, using respective *N*-halosuccinamides under solvent-free ball milling conditions[53]. Electrophilic aryl-iodination of electron-rich arenes were carried out using I_2-Oxone mixture under milling conditions at room temperature[54]. It was also shown that electron-rich arenes could couple to biaryl in presence of I_2 (Scheme 1.17).



Scheme 1.17 Electrophilic aryl halogenations under mechano-milling

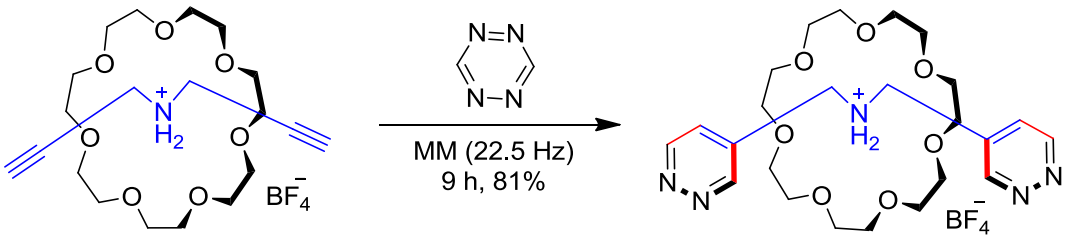
1.4.3 Ball Milling in Supramolecular Chemistry

Synthesis of rotaxanes and cage compounds. Chiu and coworkers reported a mechanochemical reaction for the synthesis of both [2]- and [4]rotaxanes in high yields under solvent-free conditions (Scheme 1.18).[55] Using 1,8-diaminonaphthalene as building blocks [2]- and [4]rotaxanes were prepared.



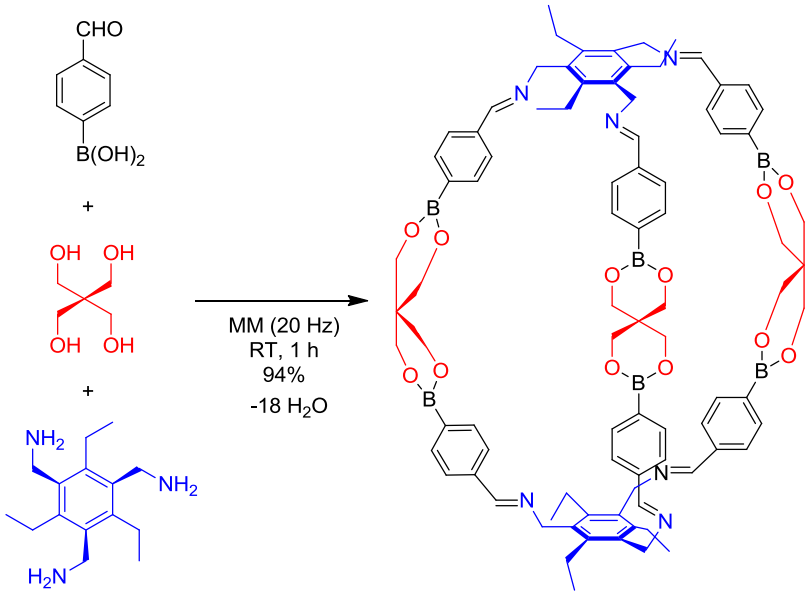
Scheme 1.18 Synthesis of rotaxane

In addition, Chiu group described the mechanochemical synthesis of the smallest rotaxane. They utilized the Diels-Alder reaction of 1,2,4,5-tetrazine with the terminal alkyne unit of a 21-crown-7 (21C7)-based [2]pseudorotaxane to produce pyridazine end groups as stoppers in a 21C7-containing [2]rotaxane in 81% yield (Scheme 1.19).[56]



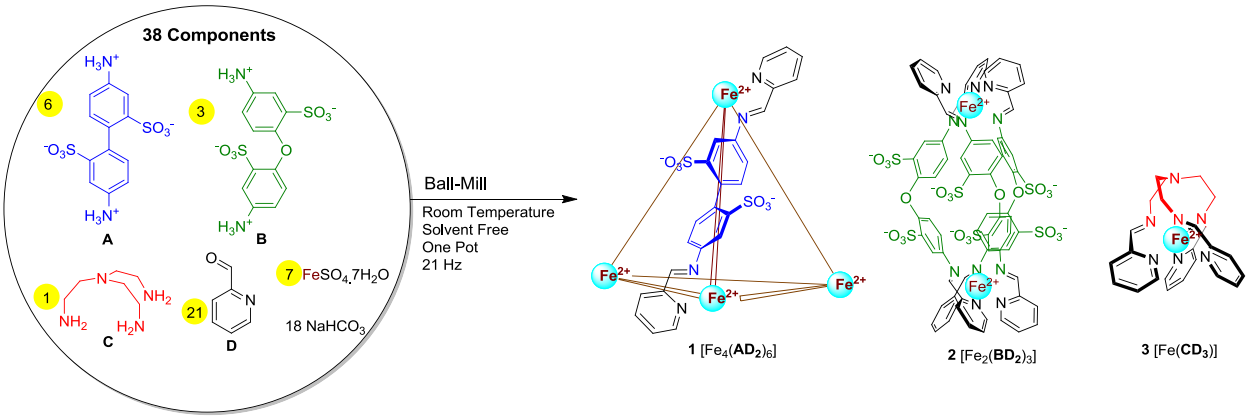
Scheme 1.19 Mechanochemical synthesis of smallest rotaxane

Molecular nanostructures by multicomponent condensation reactions were encountered in ball milling by Severin and co-workers. Upon milling of 4-formylphenylboronic acid with pentaerythritol and 1,3,5-trisaminomethyl-2,4,6-triethylbenzene for 1 h at 20 Hz, 94% of the cage compound was obtained (Scheme 1.20).[57]



Scheme 1.20 Mechanochemical synthesis of molecular nanostructure.

Recently, subcomponent synthesis of metallosupramolecular complexes have been conveyed under solvent-free ball milling conditions by our group (Scheme 1.21)[58]. 38 different components have been self-sorted to three distinct iron(II) complexes in one pot at room temperature. Furthermore, they have demonstrated that the complexes could be transformed to their more stable counterparts upon subcomponent substitution based on the thermodynamic stability of the complexes.

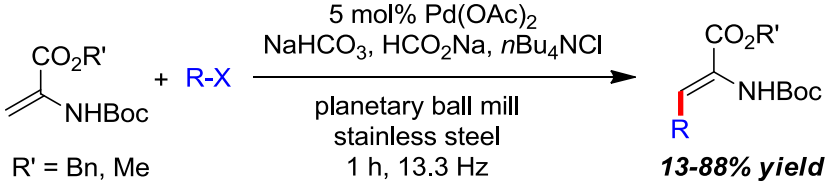


Scheme 1.21 Solvent-free subcomponent synthesis

1.4.4 Advantages over other methods

The most obvious thing to do is to compare the method of ball milling with conventional synthesis. Accomplishment of any reaction in ball mill is more advantageous over solution based synthesis with respect to reproducibility, efficiency, economical and safer handling of reagents etc.[38a, 59]

Tullberg *et al.* investigated the Mizoroki–Heck reaction between iodobenzene and the methyl ester of *N*-Boc-protected aminoacylate under different conditions of energy entry (Scheme 1.20 and Table 1).[38a] Experiments opened that each thermal, pressure or refinement processes alone do not account for the yield found in the ball milling experiment. Rather a cooperative effect of these and further strains are responsible for the observed results. Scheme 1.22 and Table 1 represent how different mode of activation (technique) can alter the efficiency of a reaction.



Scheme 1.22 Mizoroki–Heck reaction of aminoacrylates with aryl halide in a ball mill

Table 1.1 Effect of mode of activation on the Mizoroki–Heck reactiona between iodobenzene and the methyl ester of *N*-Boc-protected aminoacrylate (Scheme 1.22) in a planetary ball mill.[38a] (Reproduce from *Chem. Soc. Rev.* **2011**, *40***,** 2317 with permission of The Royal Society of Chemistry.)

Technique	Yield (%)
Planetary ball mill (stainless steel, 13.3 Hz)	77
Heating in a test tube (80 °C)	18
Heating and stirring in a test tube (80 °C)	33
Hydraulic press with preheated anvil (80 °C, 19.6 MPa)	13

[a] 5 mol%$Pd(OAc)_2$, 2.5 equivalents $NaHCO_3$, 0.2 equivalents HCO_2Na, 1.2 equivalents $n Bu_4NCl$, NaCl; reaction time = 60 min.

1.4.5 Limitation of Ball Milling system

Despite the advantages of ball milling in chemical synthesis still there are some disadvantages over solution phase systems. Two of the most important parameters in synthetic chemistry like temperature and pressure cannot be regulated using ball mill. Handling low boiling liquids, doing the reactions in heterogeneous systems are also disadvantageous in ball milling systems.

1.5 SONOCHEMISTRY

Another important area under mechanochemical systems is Sonochemistry. In general, activation energy for a chemical reaction is gained from conventional heating. Quite often overheating causes damaging of certain substances. Therefore low energy excitation of the compounds are always in demand to promote non-conventional techniques such as mechanical grinding, ultrasound etc. These non-conventional techniques proved to be better in terms of reaction time, selectivity and operational simplicity. Many reactions can be carried out at ambient condition by applying ultrasound irradiation and characteristic of ultrasonic energies are now discussed in Figure 1.4.

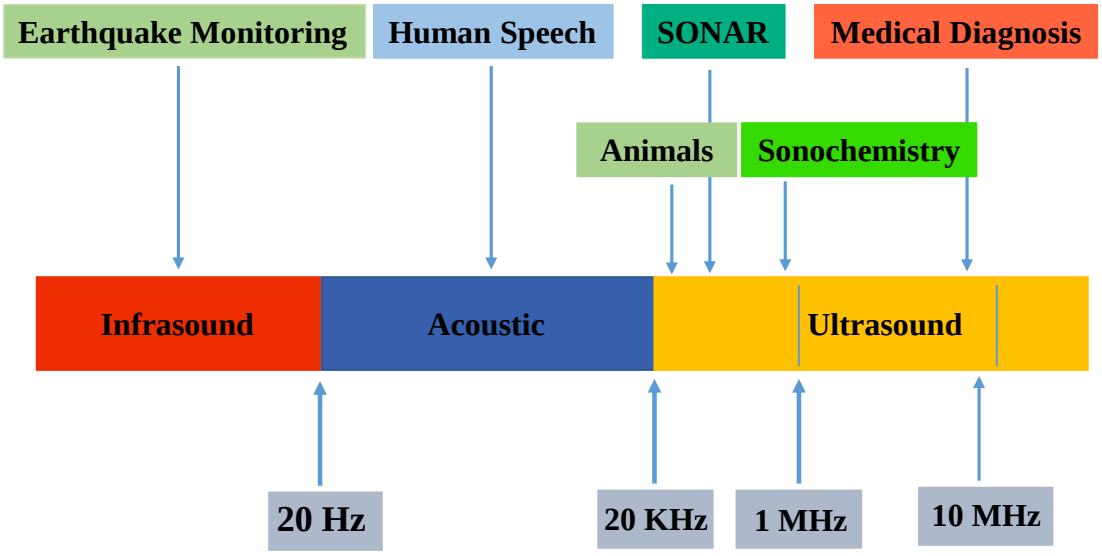


Figure 1.4 Ultrasound range diagram (Reproduced from *Chem. Soc. Rev.* **2012,** *41*, 1559 with permission of The Royal Society of Chemistry.).

Ultrasound can be subdivided into three main regions: (1) low frequency-high power ultrasound (20–100 kHz) (2) high frequency-medium power ultrasound (100 kHz–1 MHz) and (3) high frequency-low power ultrasound (1–10 MHz). The frequency range from 20 kHz to ~1 MHz is used in sonochemistry and in medical or diagnostic applications frequencies ranges are above 1 MHz. The study of sonochemistry is concerned with the understanding the effect of sonic waves and wave properties on chemical systems.[60] As proposed by Suslick and Price, chemical effects of ultrasound can be defined into three different categories like homogeneous sonochemistry of liquids, heterogeneous sonochemistry of liquid-solid systems and sonocatalysis which make an overlap between the first two.[61]

1.5.1 The sonochemical-mechanochemical connection

Sonochemistry is outcome of mechanical effects of sound on liquids which generally develops from acoustic cavitation bubbles in liquids (Figure 1.5).[62] During collapsing of bubble creates

strong compressional heating within the bubble and creates extreme transient conditions in the resultant hot spots that may create a temperature up to 5000 K with pressures exceeding 1000 atmospheres. This process is popularly known as hot spot theory.[63] These conditions are entirely different from the conventional synthetic techniques *e.g.* photochemistry, wet chemistry or hydrothermal synthesis. However, the physical effects of sonochemistry can be considered as an example of mechanochemistry and similar effects like ball milling may be observed.

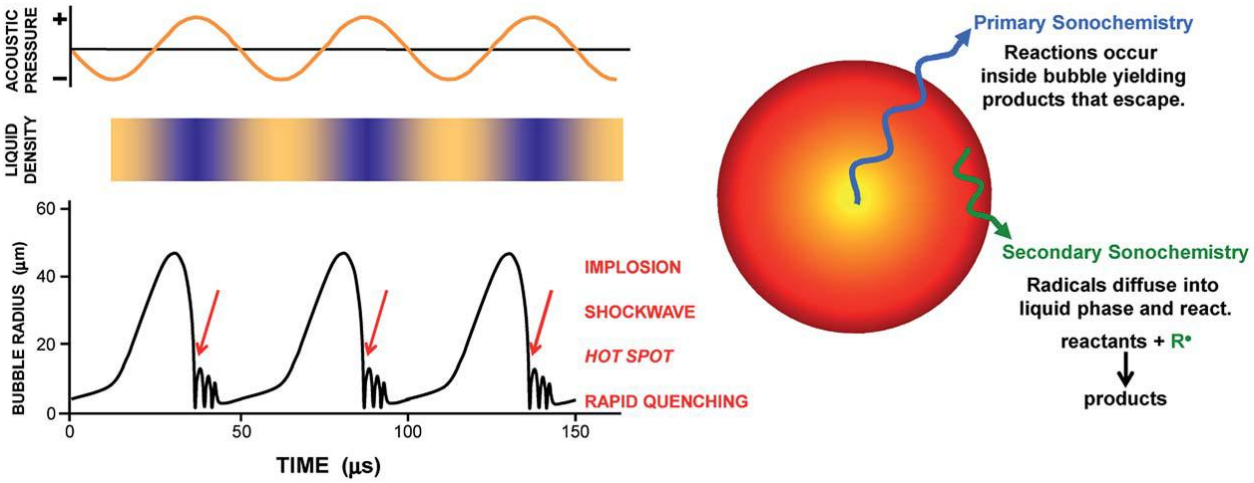
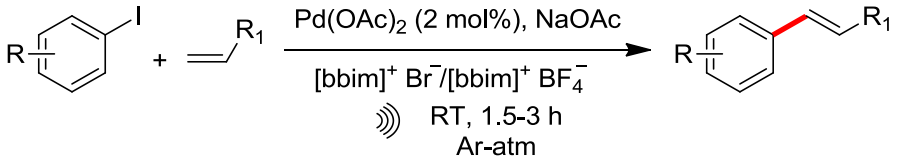


Figure 1.5 Schematic design of the development of acoustic cavitation (Adopted from *Faraday Discuss.* **2014**, *170*, 411 with permission of The Royal Society of Chemistry.)

1.5.2 Ultrasound-assisted organic Synthesis

1.5.2.1 Coupling Reactions:

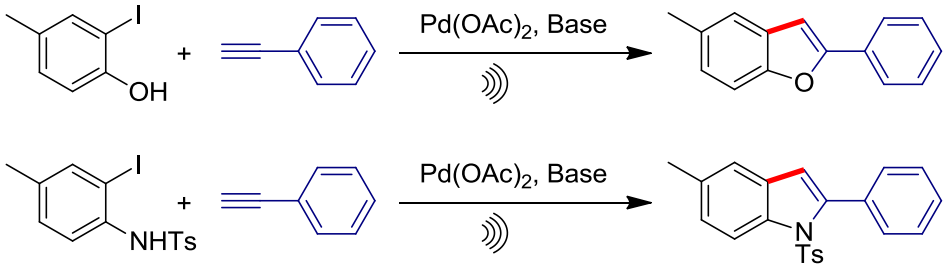
Heck Reaction. Srinivasan and co-workers first reported the Heck reaction which was carried out at room temperature in ionic liquids (IL) under ultrasound irradiation. Aryl iodides were coupled with alkenes in good yields, less reaction time and high selectivity. They also showed that the sound wave activation was essential as no conversion of the starting materials was observed in absence of sonication (Scheme 1.23).[65]



Scheme 1.23 Sonochemical Heck reaction

Later on, Samant and co-workers have demonstrated that Pd/C can be used as recyclable catalyst for Heck reaction using ultrasonic irradiation.[66]

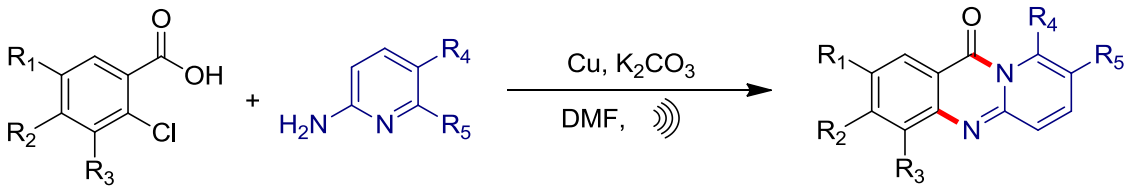
Sonogashira coupling. Ultrasound-mediated Pd nanoparticle-catalyzed cross-coupling reaction between aryl iodides or bromides and terminal acetylenes was reported by Srinivasan and coworkers.[67] They have also reported a copper-ligand free one-pot synthesis of benzo[b]furans *via* palladium acetate catalyzed tandem Sonogashira coupling towards 5-endo-dig cyclization under ultrasonic irradiation at ambient temperature.[68] By using the same protocol 2-substituted indoles were synthesized *via* Sonogashira coupling and 5-endo-dig cyclization (Scheme 1.24).[69]



Scheme 1.24 Ultrasound-assisted one-pot Sonogashira coupling and 5-endo-dig cyclization

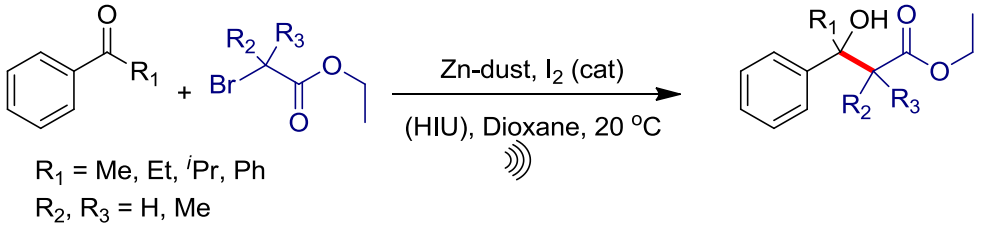
Ullmann coupling. Condensation of 2-chlorobenzoic acid and 2-aminopyridine derivatives in *N*,*N*-dimethylformamide (DMF) using ultrasound has been reported for the synthesis of 11*H* – pyrido[2,1-b]quinazolin-11-one and derivatives. The reaction was carried out in the presence of

anhydrous potassium carbonate and copper powder. The derivatives were prepared in good yield and in short reaction time (ca. 20 min).[70]



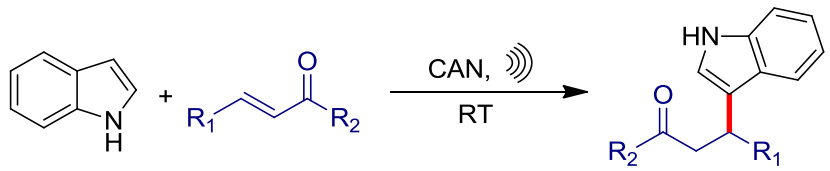
Scheme 1.25 Ultrasound-assisted Ullmann coupling reaction

Reformatsky reaction. The zinc-induced *β*-hydroxyesters synthesis from α-haloesters and aldehydes or ketones is known as the Reformatsky reaction. Due to low reactivity of zinc dust, it is necessary to activate the zinc dust for reaction initiation. Ross and Bartsch have reported the synthesis of *β*-hydroxyesters *via* the ultrasound promoted Reformatsky reaction using 'non-activated' zinc dust and a catalytic amount of iodine (Scheme 1.26).[71]



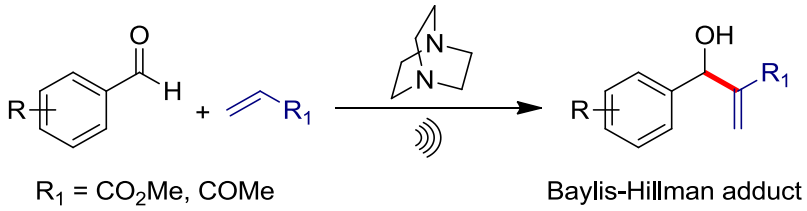
Scheme 1.26 Sonochemical Reformatsky reaction using 'unactivated' zinc dust

Michael addition reaction. S-J, Li and co-workers have reported ceric ammonium nitrate (CAN) catalyzed Michael addition of indole to *α,β*-unsaturated carbonyl ketones for alkylation of indole under ultrasonic irradiation. The corresponding adducts were achieved in excellent yields (Scheme 1.27) with selective substitution on the indole ring exclusively at the 3-position and no *N*-alkylation products were obtained.[72]



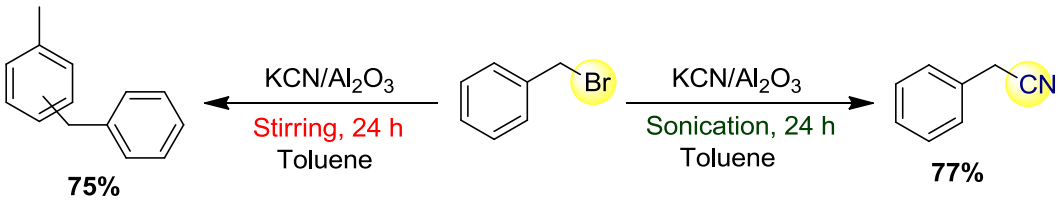
Scheme 1.27 Ultrasound-assisted Michael addition reaction

Baylis–Hillman reactions. Fernando and coworkers have studied the ultrasound mediated 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyzed Baylis–Hillman reaction of several aldehydes (aromatics and aliphatics) and different *α,β*-unsaturated reactants (Scheme 1.28).[73]



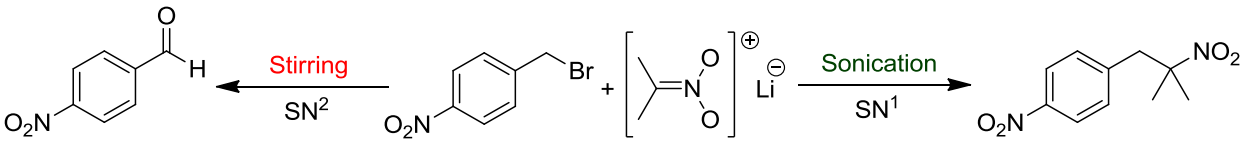
Scheme1.28 DABCO catalyzed Baylis-Hillman reactions

Sonochemical Switching' Reaction. Ando and Kimura showed a unique example under ultrasound chemistry. Their aim was to produce benzyl cyanide by nucleophilic displacement of the bromine by supported cyanide.[74] When the suspension of benzyl bromide and alumina-supported potassium cyanide in toluene was stirred, the reaction provided diphenylmethane products *via* a Friedel–Crafts reaction. In contrast, sonication of the same constituents produced only the substitution product *i.e.* benzyl cyanide (Scheme 1.29).



Scheme 1.29 Reaction of benzyl bromide with alumina-supported potassium cyanide.

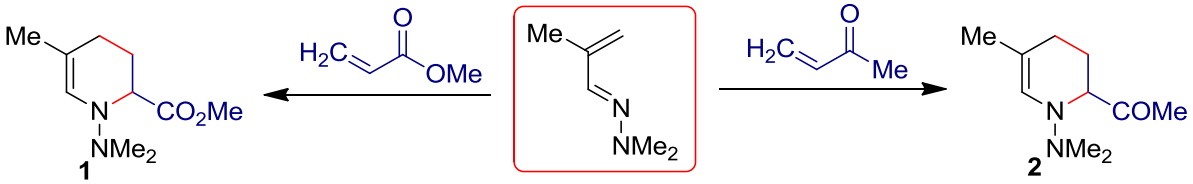
Dickens and Luche described that 4-nitrobenzyl bromide reacts with 2-lithio-2-nitro-propane *via* a polar mechanism to give 4-nitrobenzaldehyde as a final product. However, sonication changes the normal course of the reaction and gave preferentially dinitro compound (Scheme 1.30).[75]



Scheme 1.30 Reaction of 4-nitrobenzyl bromide with 2-lithio-2-nitropropane.

1.5.3 Advantages over other Methods

Villacampa and coworkers perceived that the ultrasound irradiation accelerates hetero Diels–Alder reactions between 1-dimethylamino-1-azadienes and electron-deficient dienophiles (Scheme 1.31).[76] In addition to the shorter reaction times and increased yields, the sonicated reactions decrease the side reactions.



Scheme 1.31 Diels-Alder cycloaddition reactions

Table 1.2 Comparison of ultrasound-assisted Diels-Alder reactions (scheme 1.31) with that of the conventional approach

Product	Ultrasound		Heating	
	Conditions	Yield (%)	Conditions	Yield (%)
1	Neat, 50 °C, 37 h	87	Benzene, 100 °C, 264 h	68
2	Neat, 50 °C, 50 h	56	Acetonitrile, 100 °C, 211 h (sealed tube)	70

1.6 Conclusions and Future Prospects

Mechanochemistry has made significant advancement during the last decade owing to their improvement of environmentally sustainable and more selective processes. Here, mainly we have summarized historical background, available theoretical mechanistic consideration, in addition to the application of mechanochemistry in organic synthesis. Further, there is still a long way to go to realize the elucidation of the mechanism of the reactions, scale-up developments of mechanochemistry especially in the field of nanomaterial and to achieve sustainable goals.

1.7 Notes and References

1. Baig, R. B. N.; Varma, R. S., *Chem. Soc. Rev.* **2012,** *41*, 1559.
2. Rodríguez, B.; Bruckmann, A.; Rantanen, T.; Bolm, C., *Adv. Synth. Catal.* **2007,** *349*, 2213.
3. Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Buriol, L.; Machado, P., *Chem. Rev.* **2009,** *109*, 4140.
4. Garay, A. L.; Pichon, A.; James, S. L., *Chem. Soc. Rev.* **2007,** *36*, 846.
5. Friščić, T.; Jones, W., *Cryst. Growth Des.* **2009,** *9*, 1621.
6. James, S. L.; Adams, C. J.; Bolm, C.; Braga, D.; Collier, P.; Friscic, T.; Grepioni, F.; Harris, K. D. M.; Hyett, G.; Jones, W.; Krebs, A.; Mack, J.; Maini, L.; Orpen, A. G.; Parkin, I. P.; Shearouse, W. C.; Steed, J. W.; Waddell, D. C., *Chem. Soc. Rev.* **2012,** *41*, 413.
7. IUPAC Compendium of Chemical Terminology, 2nd ed. (the ‘‘Gold Book’’). Compiled by A. D. McNaught and A. Wilkinson. Blackwell Scientific Publications, Oxford (1997). XML on-line corrected version: http://goldbook.iupac.org (2006-) created by M. Nic, J.

Jirat, B. Kosata; updates compiled by A. Jenkins. ISBN 0-9678550-9-8. doi:10.1351/goldbook, http://goldbook.iupac.org/MT07141.html.

8. (a) Constable, D. J. C.; Jimenez-Gonzalez, C.; Henderson, R. K., *Org. Process Res. Develop.* **2007,** *11***,** 133; (b) Walsh, P. J.; Li, H.; de Parrodi, C. A., *Chem. Rev.* **2007,** *107*, 2503; (c)Sheldon, R. A., *Green Chem.* **2005,** *7***,** 267.
9. W. Ostwald, Die chemische Literatur und die Organisation derWissenschaft, in Handbuch der allgemeinen Chemie, ed. W. Ostwald and C. Drucker, Akademische Verlagsgesellschaft. m. b. H. Leipzig, 1919, pp. 70 and 77.
10. L. Takacs, *J. Mineral Met. Mater. Soc.* **2000**, *52*, 12.
11. (a) M. Faraday, Q. *J. Sci., Lit., Arts*, **1820**, *8*, 374. ; (b) L. Takacs, *J. Therm. Anal. Calorim.*, **2007**, *90*, 81.
12. W. Spring, *Bull. Soc. Chim. Fr.* **1885**, *44*, 166.
13. (a) M. C. Lea, *Am. J. Sci.* **1893**, *46*, 413.; (b) L. Takacs, *J. Mater. Sci.*, **2004**, 4987.
14. Ling, A. R.; Baker, J. L., *J. Chem. Soc., Trans.* **1893**, *63***,** 1314.
15. Takacs, L., *Chem. Soc. Rev.* **2013**, *42***,** 7649.
16. (a)Tanaka, K.; Toda, F., *Chem. Rev.* **2000**, *100***,** 1025*;* (b) Toda, F., *Acc. Chem. Res.* **1995**, *28***,** 480.
17. Kaupp, G., *Top. Curr. Chem.* **2005**, *254***,** 95.
18. Cincic, D.; Brekalo, I.; Kaitner, B., *Chem. Commun.* **2012**, *48***,** 116*83*.
19. Fang, Y.; Salame, N.; Woo, S.; Bohle, D. S.; Friscic, T.; Cuccia, L. A., *CrystEngComm* **2014**, *16*, 7180.
20. Kaupp, G., *CrystEngComm* **2009**, *11***,** 388.

21. (a) G. Heinicke, Tribochemistry, Akademic-Verlag, Berlin, 1984.; (b) K. Tkacova, Mechanical Activation of Minerals, Elsevier, Amsterdam,1989.

22. (a) Boldyrev, V. V., *Solid State Ionics* **1993**, *537*, 63–65**,;** (b) Kaupp, G., *J. Phys. Org. Chem.* **2008**, *21*, 630*;* (c) Stolle, A.; Szuppa, T.; Leonhardt, S. E. S.; Ondruschka, B., *Chem. Soc. Rev.* **2011**, *40***,** 2317.

23. (a) P. Bala´ zˇ , *Mechanochemistry in Nanoscience and Minerals Engineering, Springer-Verlag, Berlin Heidelberg*, **2008**; (b) P. G. Fox, *J. Mater. Sci.*, **1975**, *10*, 340.

24. (a)F. P. Bowden and A. Yoffe, *Cambridge University Press, Cambridge*, **1952***; (*b) F**.** P. Bowden and A. Yoffe, *Butterworths, London* **1958***;* (c) Tabor, F. P. B. a. D., *Clarendon Press, Oxford* **1958**.

*2***5.** **P**. G. Fox, *J. Mater. Sci.*, **1975**, *10*, 340.

26. P. A. Thiessen, K. M. a. G. H., *Akademie-Verlag, Berlin* **1967**.

*2***7.** Balaz, P.; Achimovicova, M.; Balaz, M.; Billik, P.; Cherkezova-Zheleva, Z.; Criado, J. M.; Delogu, F.; Dutkova, E.; Gaffet, E.; Gotor, F. J.; Kumar, R.; Mitov, I.; Rojac, T.; Senna, M.; Streletskii, A.; Wieczorek-Ciurowa, K., *Chem. Soc. Rev.* **2013**, *42*, 7571.

28. Butyagin, P. Y., *Usp. Khim.* **1971**, 40**.**

29. *(*a) Gutman, E. M., *Metallurgiya, Moscow (in Russian)* **1974***; (*b)Razumovskaya, G. M. B. a. I. V., *Fiz. Chim. Mech. Mater.* **1969,** *5***,** 60**.**

*3*0. Butyagin, P. Y., *Vses. Chim. obsˇcˇ. D. Mendelejeva,* **1973**, *18***,** 90.

*3*1. (a) Boldyrev, V. V., *Kinet. Catal.* **1972**, *13***,** 1411*;* (b) Lyachov, N. Z., *Folia Montana* **1984**, 40**; (**c) Boldyrev, V. V., *Proc. Indian Natl. Sci. Acad., Part A* **1986**, *52***,** 400.

32. Toda, F.; Tanaka, K.; Iwata, S., *J. Mater. Chem.* **1989**, *54*, 3007.

33. (a) Kaupp, G., *CrystEngComm* **2003**, *5***,** 117; (b) Rothenberg, G.; Downie, A. P.; Raston, C. L.; Scott, J. L., *J. Am. Chem. Soc.* **2001**, *123***,** 8701.

34. Rasmussen, M. O.; Axelsson∗, O.; Tanner, D., *Synth. Commun.* **1997**, *27*, 4027.

35. K. Shayesteh, J. M., M. Haghighi and; H. Eskandari, *Asian J. Chem.* **2010**, *22***,** 2106.

36. Alonso, F.; Beletskaya, I. P.; Yus, M., *Tetrahedron* **2008**, *64***,** 3047.

37. Nielsen, S. F.; Peters, D.; Axelsson, O., *Synth. Commun.* **2000**, *30***,** 3501.

38. (a) Tullberg, E.; Peters, D.; Frejd, T., *J. Organomet. Chem. 2004*, *689***,** 3778*;* (b) Tullberg, E.; Schacher, F.; Peters, D.; Frejd, T., *Synthesis* **2006**, 1183.

39. Zhu, X.; Liu, J.; Chen, T.; Su, W., *Appl. Organomet. Chem.* **2012**, *26*, 145.

40. Fulmer, D. A.; Shearouse, W. C.; Medonza, S. T.; Mack, J., *Green Chem.* **2009**, *11***,** 1821.

41. Thorwirth, R.; Stolle, A.; Ondruschka, B.; Wild, A.; Schubert, U. S., *Chem. Commun.* **2011**, *47*, 4370.

42. Su, W.; Yu, J.; Li, Z.; Jiang, Z., *J. Org. Chem.* **2011**, *76*, 9144.

43. Watson, M. D.; Wagener, K. B., *Macromolecules* **2000**, *33*, 1494.

44. Do, J.-L.; Mottillo, C.; Tan, D.; Štrukil, V.; Friščić, T., *J. Am. Chem. Soc.* **2015**, *137***,** 2476.

45. Hermann, G. N.; Becker, P.; Bolm, C., *Angew. Chem. Int. Ed.* **2015**, *54*, 7414.

46. Raston, C. L.; Scott, J. L., *Green Chem.* **2000**, *2*, 49**.**

47. (a) Guillena, G.; del Carmen Hita, M.; Nájera, C.; Viózquez, S. F., *Tetrahedron: Asymmetry* **2007**, *18*, 2300*;* (b) Guillena, G.; Hita, M. d. C.; Nájera, C.; Viózquez, S. F., *J. Org. Chem.* **2008**, *73*, 5933.

48. Mack, J.; Shumba, M., *Green Chem.* **2007**, *9*, 328.

49. Balema, V. P.; Wiench, J. W.; Pruski, M.; Pecharsky, V. K., *Chem. Commun.* **2002**, 724**.**

50. Balema, V. P.; Wiench, J. W.; Pruski, M.; Pecharsky, V. K., *J. Am. Chem. Soc.* **2002**, *124*, 6244.

51. Wang, G.-W.; Komatsu, K.; Murata, Y.; Shiro, M., *Nature* **1997**, 387, 583.

52. Cheng X., W. G.-W., Murata Y. Komatsu K. , *Chin. Chem. Lett.* **2005**, *16*, 1327.

53. Bose, A.; Mal, P., *Tetrahedron Lett.* **2014**, *55*, 2154.

54. Maiti, S.; Mal, P., *Synth. Commun.* **2014**, *44*, 3461.

55. Hsueh, S.-Y.; Cheng, K.-W.; Lai, C.-C.; Chiu, S.-H., *Angew. Chem. Int. Ed.* **2008**, *47*, 4436.

56. Hsu, C.-C.; Chen, N.-C.; Lai, C.-C.; Liu, Y.-H.; Peng, S.-M.; Chiu, S.-H., *Angew. Chem. Int. Ed.* **2008**, *47*, 7475.

57. Içli, B.; Christinat, N.; Tönnemann, J.; Schüttler, C.; Scopelliti, R.; Severin, K., *J. Am. Chem. Soc.* **2009**, *131*, 3154.

58. Giri, C.; Sahoo, P. K.; Puttreddy, R.; Rissanen, K.; Mal, P., *Chem. Eur. J.* **2015**, *21*, 6390.

59. (a) Trotzki, R.; Hoffmann, M. M.; Ondruschka, B., *Green Chem.* **2008**, *10*, 767*;* (b) Achar, T. K.; Maiti, S.; Mal, P., *RSC Adv.* **2014**, *4***,** 12834.

60. (a) Luque de Castro, M. D.; Priego-Capote, F., *Talanta* **2007**, *72*, 321; (b) Davidson, R. S.; Safdar, A.; Spencer, J. D.; Robinson, B., *Ultrasonics* **1987**, *25*, 35; *(*c) Mason T. J., L. J. P., *Wiley-VCH Verlag Gmbh, Weinheim* **2002**.

*6***1.** **S**uslick, K. S.; Price, G. J., Annu. *Rev. Mater. Sci.* **1999**, *29*, 295.

62. (a) Xu, H.; Zeiger, B. W.; Suslick, K. S., *Chem. Soc. Rev.* **2013**, *42*, 2555*;* (b) Suslick, K. S., *Science* **1990**, *247*, 1439.

63. (a) Flannigan, D. J.; Suslick, K. S., *Nature* **2005**, *434*, 52; (b) Flannigan, D. J.; Suslick, K. S., *Nature Phys.* **2010**, *6*, 598; (c) McNamara, W. B.; Didenko, Y. T.; Suslick, K. S., *Nature* **1999**, *401*, 772; (d) Didenko, Y. T.; Suslick, K. S., *Nature* **2002**, *418*, 394.

64. Suslick, K. S., *Faraday Discuss.* **2014**, *170*, 411.

65. Deshmukh, R. R.; Rajagopal, R.; Srinivasan, K. V., *Chem. Commun.* **2001**, *1544.*

66. Ambulgekar, G. V.; Bhanage, B. M.; Samant, S. D., *Tetrahedron Lett.* **2005**, *46*, 2483.

67. Gholap, A. R.; Venkatesan, K.; Pasricha, R.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V., *J. Org. Chem.* **2005**, *70*, 4869.

68. Palimkar, S. S.; Harish Kumar, P.; Lahoti, R. J.; Srinivasan, K. V., *Tetrahedron* **2006**, *62*, 5109.

69. Palimkar, S. S.; More, V. S.; Srinivasan, K. V., *Ultrason. Sonochem.* **2008**, *15*, 853.

70. Docampo Palacios, M. L.; Pellón Comdom, R. F., *Synth. Commun.* **2003**, *33*, 1777.

71. Ross, N. A.; Bartsch, R. A., *J. Org. Chem.* **2003**, *68*, 360.

72. Ji, S.-J.; Wang, S.-Y., *Synlett* **2003**, 2074.

73. Coelho, F.; Almeida, W. P.; Veronese, D.; Mateus, C. R.; Silva Lopes, E. C.; Rossi, R. C.; Silveira, G. P. C.; Pavam, C. H., *Tetrahedron* **2002**, *58*, 7437.

74. T. Ando and T. Kimura, Ultrasonic organic synthesis involving nonmetal solids, Advances in Sonochemistry, *JAI Press, London*, **1991**, *vol. 2*, p. 211.

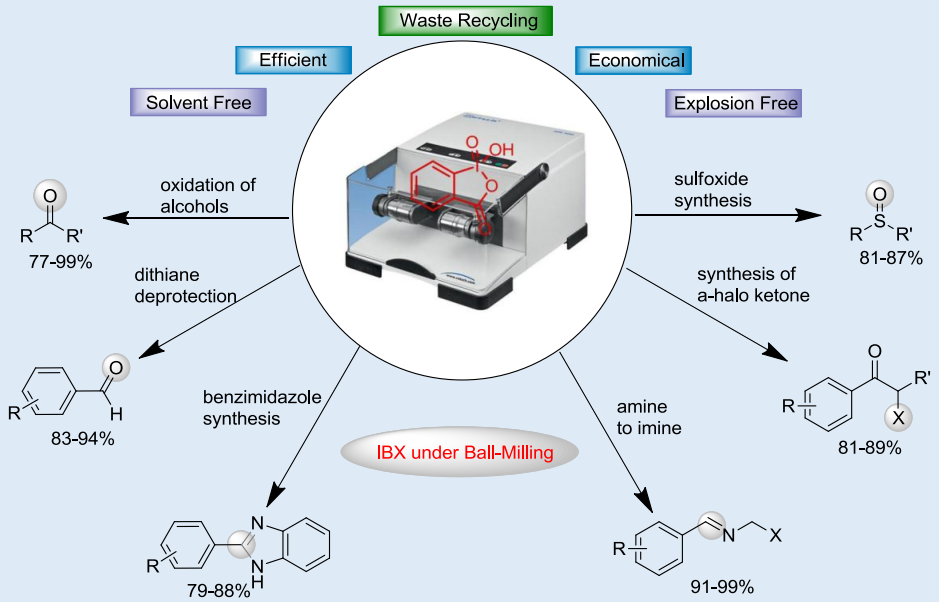
75. Dickens, M. J.; Luche, J.-L., *Tetrahedron Lett.* **1991**, *32*, 4709.

76. Villacampa, M.; Pérez, J. M.; Avendaño, C.; Menéndez, J. C., *Tetrahedron* **1994**, *50*, 10047.

CHAPTER 2

IBX Works Efficiently under Solvent free Conditions in Ball Milling

2.1 ABSTRACT



IBX (2-iodoxybenzoic acid), discovered in 1893, is metal free, mild and non-toxic organo-oxidant in synthetic chemistry whose extensive use is impeded by its explosiveness at high temperature and poor solubility in common organic solvents except DMSO. Since the discovery of Dess-Martin Periodinane in 1983, IBX has experienced several modifications to be useful to chemists. However, under ball milling condition, IBX works perfectly with various organic functionalities at ambient temperature under solvent free conditions. Also, the waste IBA (2-iodosobenzoic acid) produced from the reactions was *in situ* oxidized to IBX in following step using oxone and thus reused for multiple cycles by conserving its efficiency (only ~6% loss after 15 cycles). This work describes an overview of a highly economical synthetic methodology which overcomes the use of commercially available IBX efficiently in gram scale and *via* non-explosive way.

2.2 INTRODUCTION

With rising public concern over renewable energy and global warming, it is important to trim down the usage of chemicals, eliminate waste, and possibly recycle them to obtain better results in greener fashion compared to routine chemical synthesis.[1] The metal free reagents are very popular in pharmaceutical industries to avoid metal contamination in drugs which cause side effects.[2] Generally, IBX (2-iodoxybenzoic acid) is a mild, easy accessible hypervalent iodine(V) reagent, has been preferred for metal free oxidative transformations[3] in synthesis. This intensifying interest in hypervalent iodine reagents is due to the mild and chemoselective oxidizing properties of the organo-iodine reagents, combined with their benign environmental nature and commercial easy accessibility. Although journey of IBX started in 1893 by Hartmann and Meyer[4] but its industrial/laboratory scale use was restricted due to explosiveness at higher temperature[5] and poor solubility in common organic solvents except DMSO.[6] In solvent DMSO, the large scale (gram quantities) syntheses using IBX have practical difficulties in isolation and purification. The limited solubility and explosive nature of IBX has encouraged many investigators to reach more practical experimental conditions, addition to modified-IBX. After the first report on modified IBX *i.e.*, Dess-Martin Periodinane[7] in 1983 (DMP), several modified IBX (Figure 2.1)[8] which include pseudo-IBX[9], solid-supported IBX[10] are reported in literature to overcome the constraint of using IBX as utile oxidant.

2.3 RESULTS AND DISCUSSIONS

These modified IBXs are most often complicated due to involvement of tedious synthetic procedure in non-economical way.[8g] Therefore the modification approach has not been converged and is still in demand for better methods *via* recyclable methodology.[12] We envisioned that mechano-milling (ball-milling) methodology[13] may possibly be used not only to make IBX

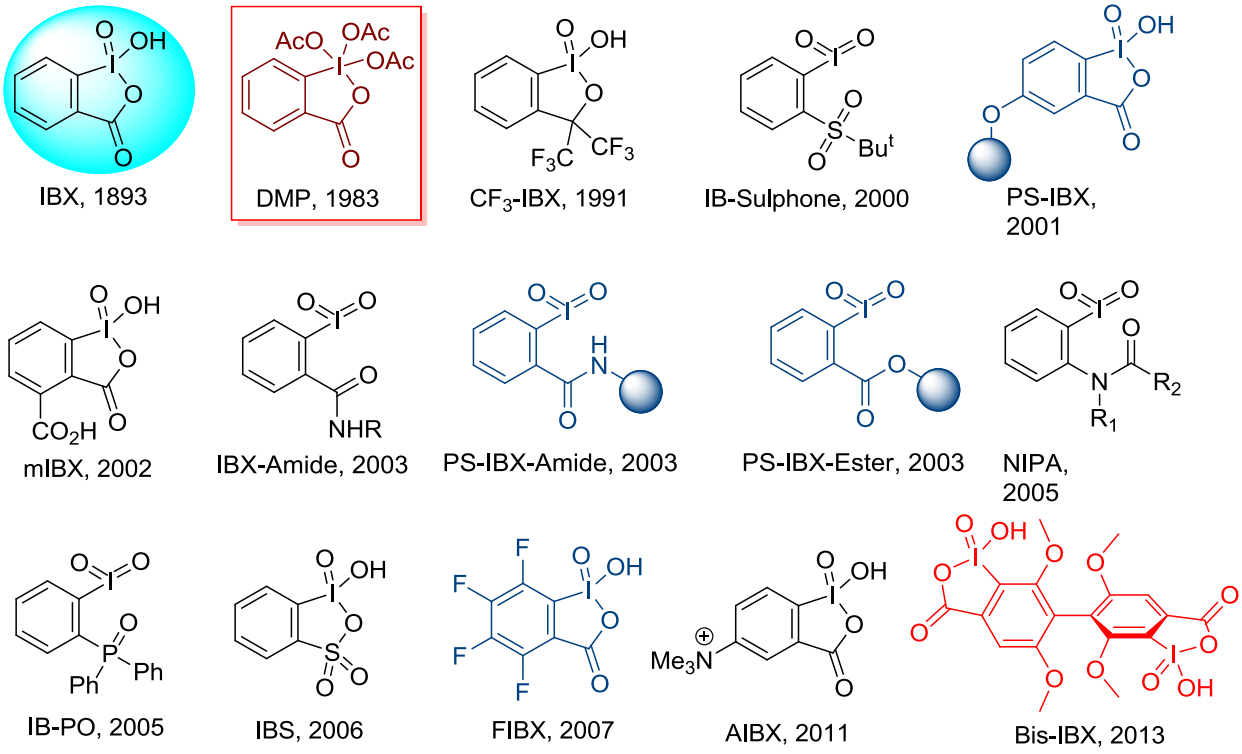


Figure 2.1. Selected and updated information on modified-IBX from 1893, and the abbreviated names are from the references shown in bracket.

compatible with various organic functionalities but also leading to discovery of a Green-Organo-Oxidant. In this context we are revisiting the potential use of IBX[14] under solvent free, milling condition at room temperature to the following reactions: mainly oxidation of primary/secondary alcohols to corresponding carbonyl compounds,[15] amine to imine,[16] conversion of olefins to α-bromo/iodoketones,[17] sulfide to sulfoxide,[18] dithianes deprotection[16] and synthesis of benzimidazoles from primary alcohols[19] etc. Advantageously, this methodology has long-range working window of 10 mg to 2.5 grams[20], the waste 2-iodosobenzoic acid (IBA) was recyclable to multiple cycles by *in situ* oxidative regeneration of IBX[21], survives under non-aqueous workup,

avoids chromatographic purification and can be highly cost effective to be successfully used in pharmaceutical/chemical industry.

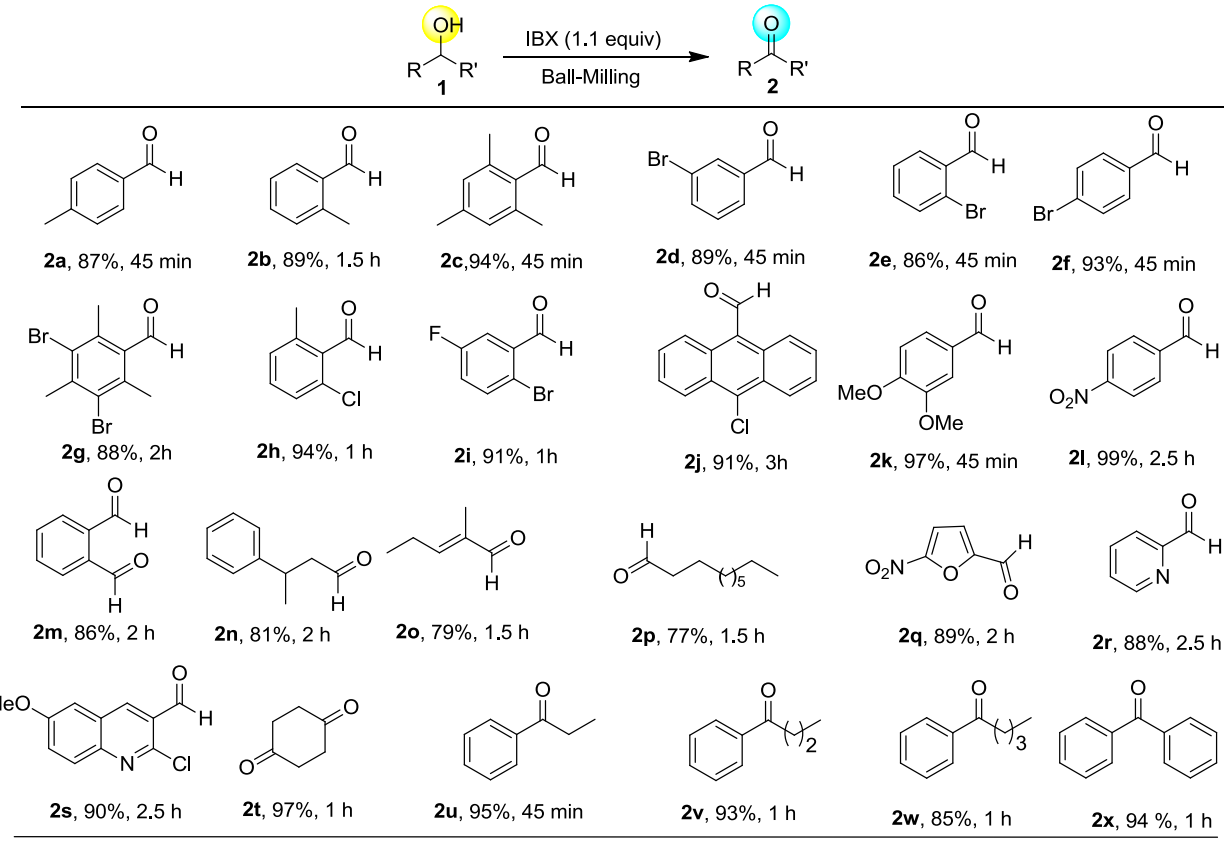


Figure 2.2. Oxidation of alcohols to carbonyls

In Figure 2.1, selective examples of modified IBXs are shown. Now, we are highlighting few shortcomings of these modified systems. The Dess-Martin Periodinane is soluble in common organic solvents but seeks anhydrous condition for storing the reagent.[7] Besides, CF_3-IBX[8a] undergoes rapid ligand exchange with water-acetonitrile solution, water soluble mIBX[8b] is non-reactive towards non-allylic/benzylic alcohols, FIBX[8d] have influence on acid sensitive reactions and, AIBX[8e] and Bis-IBX[8g] are synthetically challenging, obtained via multistep synthesis. Polymer supported IBX[10] which can work under heterogeneous media, easily separable by

filtration, are generally expensive.[22] However, IBX is also known to works in ionic liquids,[23] in aqueous medium with *β*-cyclodextrin (*β*-CD) as catalyst through the formation of host-guest complexes[24] and in solid state at elevated temperature (70-90 ºC) which associated with explosiveness, uncontrollable over-oxidation of primary alcohols to acids.[25]

Primarily, we have tested our methodology on oxidation of alcohols to carbonyls[26] and the results are depicted in Figure 2.2. The oxidized products of primary, secondary and aliphatic alcohols were obtained in very good to excellent yield in relatively smaller time. Comparing our method, as representative examples, **2e** (Figure 2.2) was prepared in 45 min using IBX under ball-milling than 8 h using IBX-CH_3CN-AcOH (traditional) method.[26] Furthermore, with Bis-IBX (Figure 2.1), **2w** (Figure 2.2) was prepared in 11.5 h in MeCN/H_2O[8g] and under milling it is done in 1 h. The supramolecular system like cucurbit[8]uril catalyzed oxidation of alkyl alcohols **2p** to corresponding aldehyde with IBX in aqueous solvent is reported to be < 5%,[27] however our methods resulted the same aldehyde in 77% yield. Thus, primary alcohols are efficiently and selectively converted to the corresponding aldehydes and not leading to over oxidized side

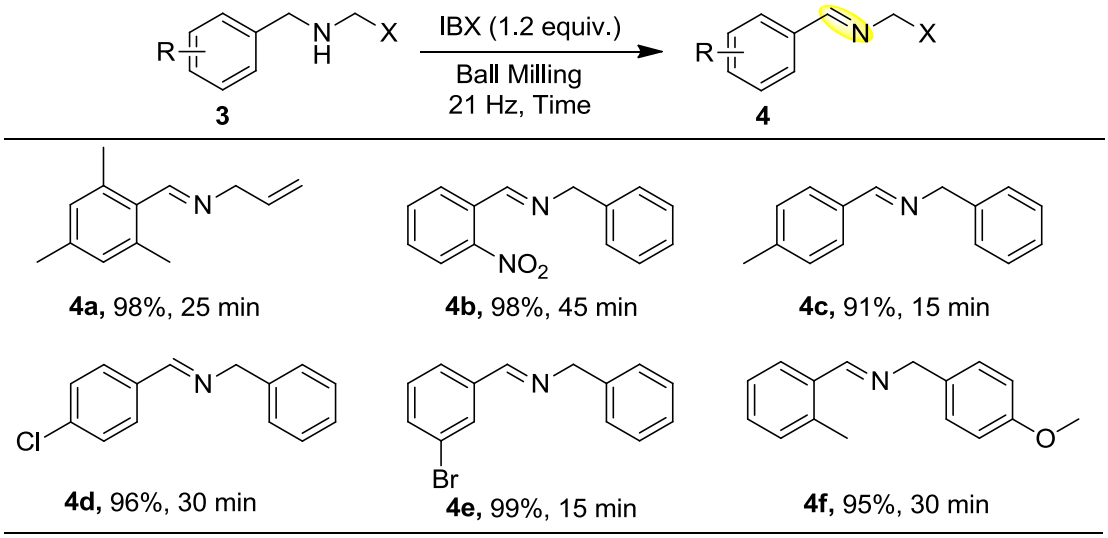


Figure 2.3. Oxidation of amine to imine

products. The results shown in Figure 2.2 are the product of a significantly improved methodology by ball-milling process compared to literature known systems. This fact clearly establishes that the disadvantages associated with poor solubility of IBX are now overcome.

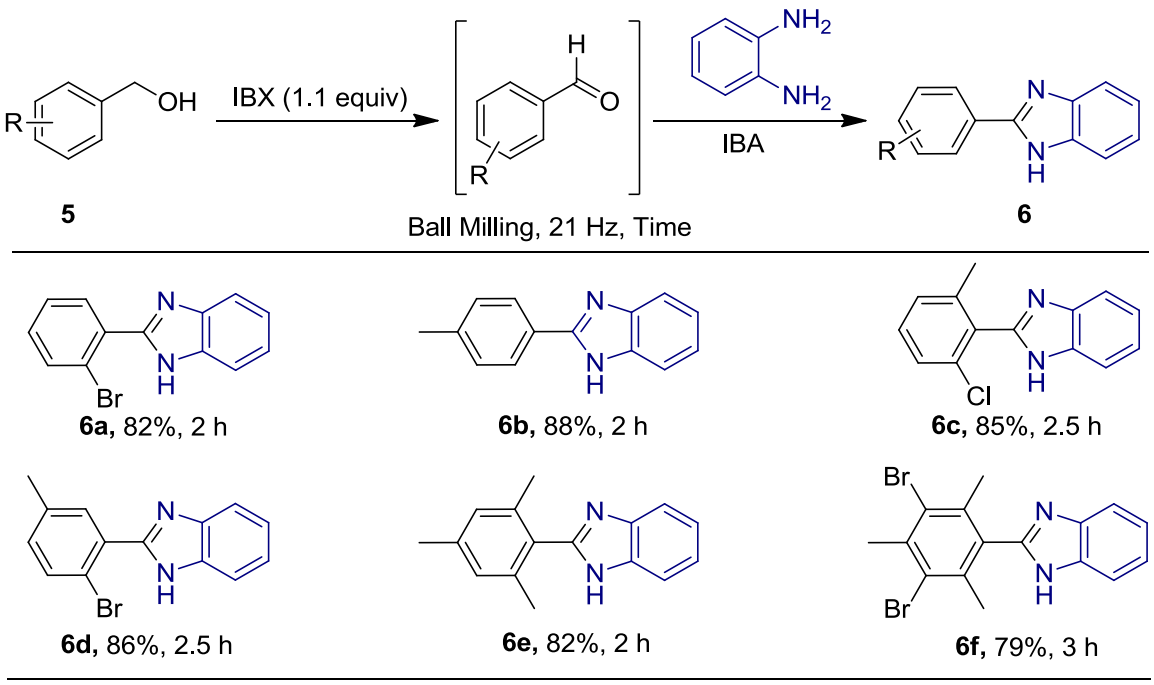


Figure 2.4. Synthesis of benzimidazole

The efficiency and convenience of this methodology on alcohol oxidations have also encouraged us to further explore the scope to verify other IBX-mediated literature reported reaction systems. As described in Figure 2.3 – 2.5, these examples are amine to imine (Figure 2.3),[16] conversion of olefins to α-bromo/iodoketones (Figure 2.5a),[17] sulfide to sulfoxide (Figure 2.5c),[18] dithianes deprotection (Figure 2.5b)[16] and synthesis of benzimidazoles from primary alcohols (Figure 2.4)[19].

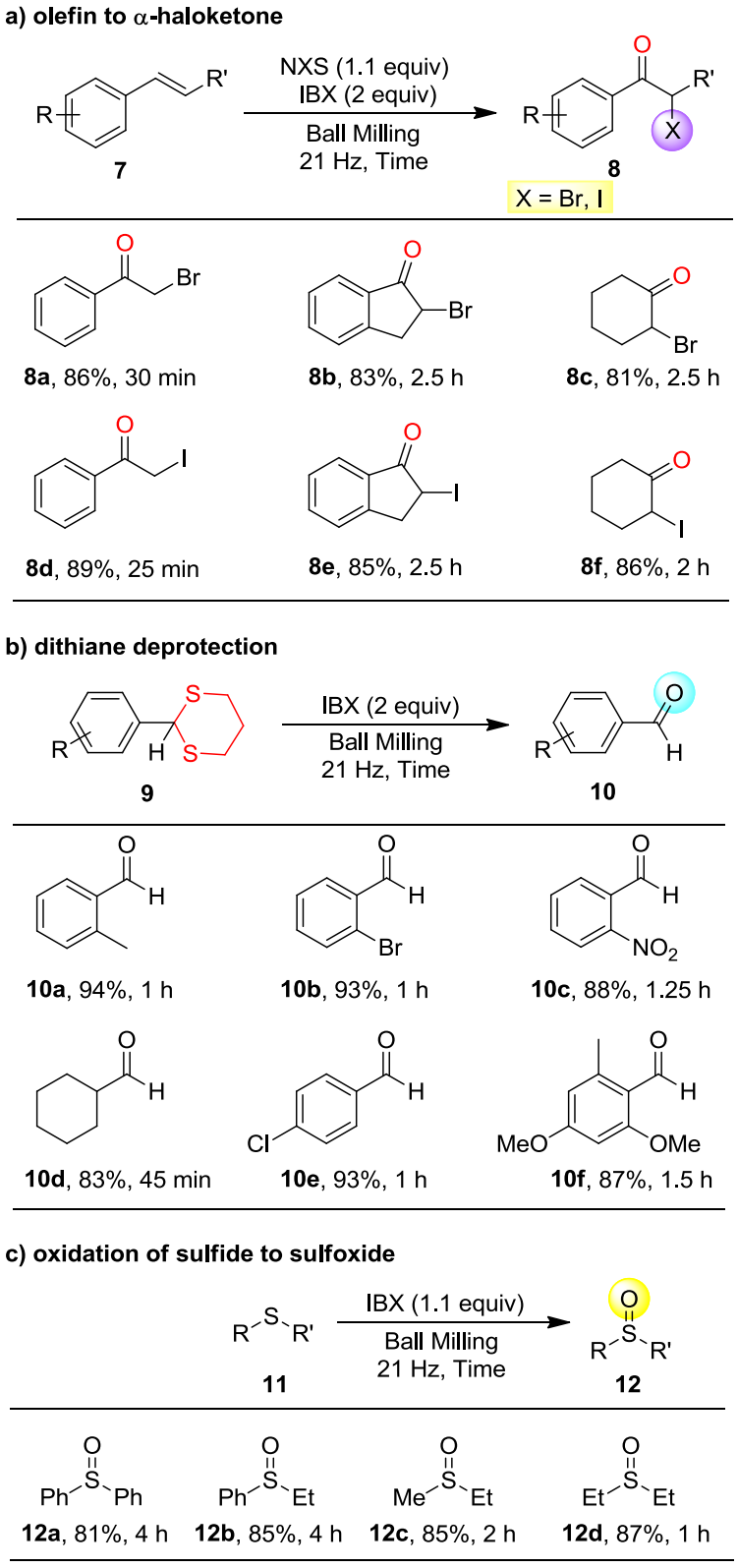


Figure 2.5. (a–c) Methods tested on different reaction schemes; only isolated yields are shown.

Figure 2.6 represents the efficiency and recycling ability of this methodology. Waste IBA *i.e.*, the reduced product of IBX after reaction, was isolated by paper filtration and subsequently *in situ* oxidized to IBX[21] with inexpensive oxone in following recycling step. Importantly, towards waste management *via* recycling, in oxidation of benzhydrol to benzophenone (yield 94%, 1 h), after 15 cycles no significant loss (~ 6%) of IBA was observed. However, oxone in absence of IBA could not efficiently oxidize benzhydrol (conversion < 15%, 5 h) under milling condition (Figure 2.7). On the other hand, oxidized products were isolated after filtration, did not demand any chromatographic purification, and were found to be sufficiently pure to be used for synthetic applications.

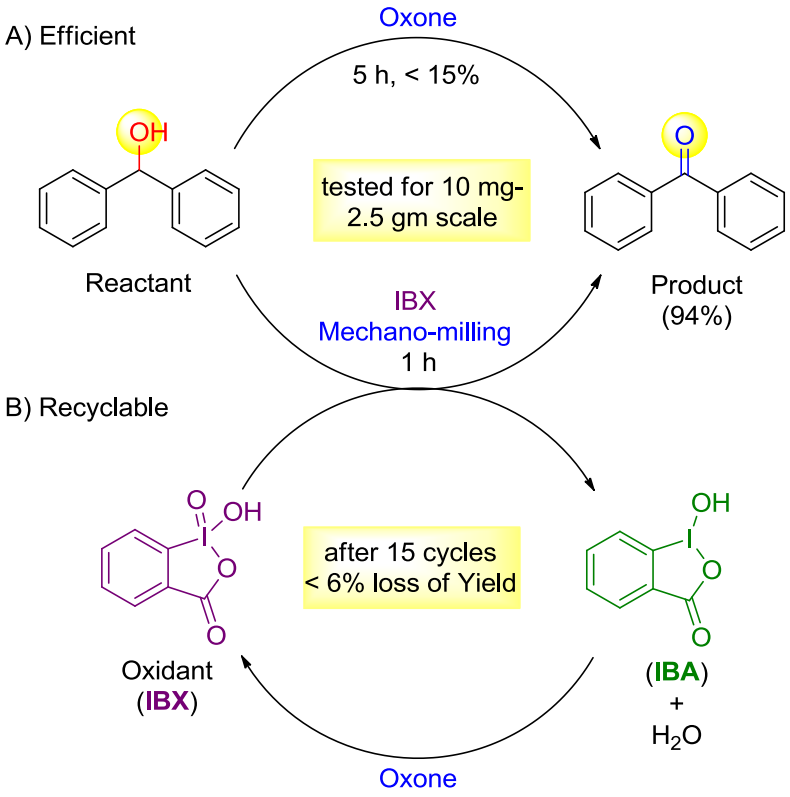


Figure 2.6. a) Efficiency: the methodology is efficient for the transformation of benzhydrol to benzophenone, up to 1 g substrate was successfully oxidized in 1 h. b) Cost effectiveness: overview of recycling performance conducted on the following step using waste IBA and oxone.

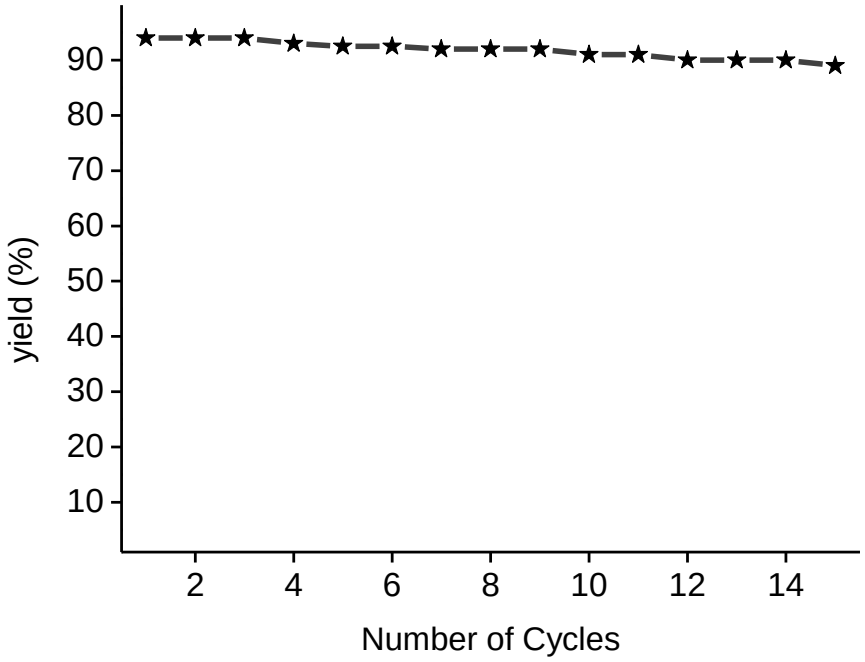
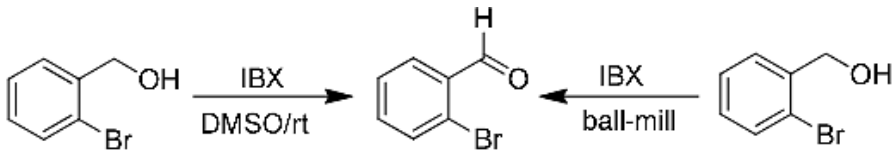


Figure 2.7. Waste management via recycling of in situ generated IBX from IBA with Oxone



estimated for 1 g scale

methods	traditional	milling
reagents	IBX (1.5 equiv); 2.3 gm, $75	IBX (1.1 equiv) 1.7 gm, $55
solvents	DMSO (reaction), 50 mL, $10, DCM (extraction), 300 mL, $3.5	--
purification	chromatography pet. ether, 1.2 L, $11; ethyl acetate, 400 mL, $4; silica gel, 60 g, $4.5	filtration DCM 120 mL $1.4
time	2 h	45 min
yield	82%	87%
total cost	$108	$56.4

*in one recycle with IBA and oxone additional $33.5 was saved

Figure 2.8. Comparative statement on economic benefit may be obtained from our methodology over traditional one. Using 25 mL of ZrO_2 jar, 2.5 g of (2-bromophenyl)methanolwas successfully oxidized

The reaction shown in Figure 2.8 is truly advantageous in terms of cost effectiveness. Per gram synthesis of 2-bromo benzaldehyde from (2-bromophenyl)methanol using IBX, in a single step using ball-milling, we could save nearly 48% of the estimated cost (Figure 2.8, electricity, manpower costs are excluded). However in recycling the same reaction with IBA and oxone, additional 31% could be saved after one recycle (Figure 2.8).

2.4 CONCLUSIONS

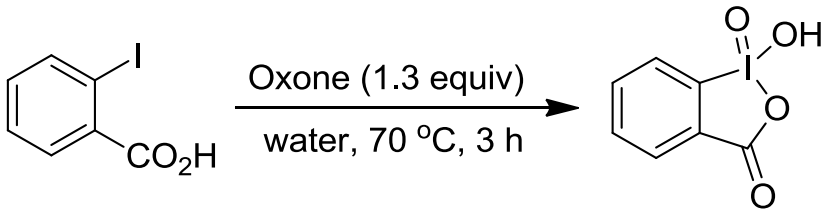
In summary, we anticipate that a broad range of substrates is compatible with this operationally simple organo-oxidant IBX which works under solvent free condition, at room temperature, non-explosive way and also avoids aqueous workup. This methodology adapts in to milder reaction condition and is highly economical, time saving and reducing waste through smarter recycling. Therefore, this methodology may serve as an important addition not only to the synthetic field but also to industries. Thus, after 120 years of its discovery IBX may quench the thrust of Modified-IBX and has a huge potential in solving a long-standing problem of organic chemistry. Our study will certainly be of interest to other researchers working not only on the development of hypervalent iodine mediated oxidation methodologies but also to chemists looking for better methodologies under the research area of organic mechanochemistry.[28]

2.5 EXPERIMENTAL SECTION

All milling experiments were performed in Retsch MM 200 high speed vibration milling instrument (21 Hz), NMR spectra were recorded on Bruker AV 400 MHz instrument and high-resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF-Q II, ESI TOF (time of

flight) mass spectrometer. The compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR and HRMS analysis. Purity of the compounds was determined using ^{1}H NMR. NMR are reported in parts per million (ppm) with respect to residual chloroform (7.26 ppm for ^{1}H and 77.16 for ^{13}C) in the deuterated solvent, unless otherwise stated. Melting points of the compounds were determined by using a WISWO digital melting point apparatus and are uncorrected.

Preparation of 2-iodoxybenzoic acid (IBX)[14]



2-Iodobenzoic acid (6.0 g, 24.2 mmol) and oxone (19.9 g, 31.5 mmol) were taken in a 500 mL round bottom flask and deionized water (200 mL) was added. The suspension was placed on a preheated oil-bath (70 ºC) for 3 h, cooled to room temperature and filtered through sintered-glass funnel followed by repeatedly washing with water. After vacuum drying 5.42 g (80%) white solid was obtained.

Procedure for (2-bromophenyl)methanol oxidation under ball-milling

(2-Bromophenyl)methanol (100 mg, 0.53 mmol) and IBX (162 mg, 0.58 mmol) were transferred into a ball milling ZrO_2 jar (10 mL) and followed by one 15 mm diameter ZrO_2 grinding ball was placed. The progress of the reaction under milling condition was monitored by thin layer chromatography (TLC) and ^{1}H NMR spectroscopy. After completion of the reaction, the reaction mixture was then transferred into 30 mL of dichloromethane (DCM), followed by product was isolated as filtrate upon paper filtration and waste IBA as precipitate. The resulting filtrate were

concentrated *invacuo* to isolate 85 mg (yield: 87%) of 2-bromobenzaldehyde (**2e**) as colorless liquid.

Optimization of gram scale reaction under ball-milling with (2-bromophenyl)methanol

(2-Bromophenyl)methanol (2.5 g, 13.4 mmol) and IBX (4.12 g, 14.7 mmol) were transferred to a milling 25 mL ZrO_2 jar containing one 15 mm diameter ZrO_2 grinding ball. After completion of reaction at 1 h, the product 2-bromobenzaldehyde isolated by following the procedure as presented above (2.10 g, yield: 85%).

Spectral Data of the Compounds

4-Methylbenzaldehyde (2a)[29]**:**Yield: 87%;^{1}H NMR (400 MHz, $CDCl_3$): δ 9.95 (s, 1H), 7.77-7.75 (m, 2H), 7.33-7.31 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.12, 145.66, 134.31, 129.96, 129.82, 21.97.

2-Methylbenzaldehyde (2b, 10a)[2]**:**Yield: 89%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.25 (s, 1H), 7.79-7.77 (m, 1H), 7.48-7.44 (m, 1H), 7.36-7.33 (m, 1H), 7.25-7.24 (m, 1H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.88, 140.68, 134.24, 133.72, 132.12, 131.85, 126.40, 19.64.

2,4,6-Trimethylbenzaldehyde (2c)[30]**:**Yield: 94%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.55 (s, 1H), 6.89 (s, 2H), 2.57 (s, 6H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.10, 143.94, 141.59, 130.61, 130.02, 21.56, 20.60.

3-Bromobenzaldehyde (2d)[31]**:** Yield: 89%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.94 (s, 1H), 7.99 (d, *J* = 0.4 Hz, 1H), 7.81-7.73 (m, 2H), 7.43-7.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.90, 138.05, 137.42, 132.44, 130.74, 128.50, 123.46.

2-Bromobenzaldehyde (2e, 10b)[32]**:** Yield: 87%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.24 (s, 1H), 7.80-7.78 (m, 1H), 7.54-7.52 (m, 1H), 7.36-7.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.85, 135.32, 133.83, 133.39, 129.78, 127.88, 127.03.

4-Bromobenzaldehyde (2f)[2]**:** Yield: 93%; mp 54-56 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 7.75-7.72 (m, 2H), 7.68-7.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.23, 135.14, 132.54, 131.08, 129.89.

3,5-Dibromo-2,4,6-trimethylbenzaldehyde (2g): Yield: 88%; mp 193-196 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.46 (s, 1H), 2.73 (s, 3H), 2.55 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.12, 142.54, 137.70, 135.07, 127.72, 26.92, 20.42.

2-Chloro-6-methylbenzaldehyde (2h): Yield: 94%; mp 37-39 ºC;^{1}H NMR (400 MHz, $CDCl_3$): δ 10.68 (s, 1H), 7.41-7.33 (m, 2H), 7.21-7.19 (m, 1H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.53, 142.52, 139.05, 133.54, 130.70, 128.30, 126.92, 21.25.

2-Bromo-5-fluorobenzaldehyde (2i)[33]**:** Yield: 91%; mp 53-55 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): 10.31 (d, *J* = 2.9 Hz, 1H), 7.61-7.66 (m, 2H), 7.18-7.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.76, 162.15, 135.32, 134.82, 122.73, 121.17, 116.34.

10-Chloroanthracene-9-carbaldehyde (2j): Yield: 91%; mp 213-216 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.45 (s, 1H), 8.91 (d, *J* = 8.8 Hz, 2H), 8.62-8.60 (m, 2H), 7.72-7.63 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.06, 137.16, 132.13, 129.23, 128.56, 127.14, 125.87, 124.70, 123.92.

3,4-Dimethoxybenzaldehyde (2k)[34]**:** Yield: 97%; mp 40-42 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.85 (s, 1H), 7.47-7.45 (m, 1H), 7.41 (d, *J* = 1.6 Hz, 1H), 6.98 (d, *J* = 9.6 Hz, 1H), 3.97 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.09, 154.66, 149.79, 130.29, 127.04, 110.54, 109.11, 56.33, 56.16.

4-Nitrobenzaldehyde (2l)[35]**:** Yield: 99%; mp 104-106 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.15 (s, 1H), 8.36 (d, *J* = 8.4 Hz, 2H), 8.07 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.43, 151.26, 140.17, 130.60, 124.43.

Phthalaldehyde (2m)[36]**:** Yield: 86%; mp 53-56 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.52 (s, 1H), 10.51 (s, 1H), 7.98-7.94 (m, 2H), 7.78-7.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.46, 136.51, 133.87, 131.21.

3-Phenylbutaraldehyde (2n)[37]**:** Yield: 81%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 7.34-7.31 (m, 2H), 7.25-7.20 (m, 3H), 3.42-3.33 (m, 1H), 2.79-2.63 (m, 2H), 1.33 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.98, 145.52, 128.74, 126.82, 126.60, 51.77, 34.33, 22.23.

2-Methylpent-2-enal (2o)[38]**:** Yield: 79%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.34 (s, 1H), 6.45-6.41 (m, 1H), 2.35-2.28 (m, 2H), 1.68 (s, 3H), 1.08-1.04 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.50, 156.40, 138.82, 22.36, 12.85, 9.05.

Decanal (2p)[39]**:** Yield: 77%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (t, *J* = 1.8 Hz, 1H), 2.46-2.35 (m, 2H), 1.65-1.58 (m, 2H), 1.37-1.24 (m, 12H), 0.90 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.16, 101.83, 34.54, 32.02, 29.65, 29.50, 29.44, 23.70, 22.81, 14.23.

5-Nitrofuran-2-carbaldehyde (2q)[40]**:** Yield: 89%; mp 38-40 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.82 (s, 1H), 7.41 (d, *J* = 4 Hz, 1H), 7.34 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.45, 151.09, 118.92, 111.86.

Pyridine-2-carbaldehyde (2r)[41]**:** Yield: 88%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.01 (s, 1H), 8.74-8.72 (m, 1H), 7.92-7.89 (m, 1H), 7.84-7.83 (m, 1H), 7.82-7.80 (m, 1H), 7.49-7.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.46, 152.79, 150.24, 137.13, 127.94, 121.75.

2-Chloro-6-methoxyquinoline-3-carbaldehyde (2s)[42]**:** Yield: 90%; mp 150-152 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.54 (s, 1H), 8.63 (s, 1H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.52-7.49 (m, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.36, 158.80, 147.63, 145.75, 138.66, 129.86, 127.76, 126.59, 126.40, 106.42, 55.77.

Propiophenone (2t)[43]**:** Yield: 95%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94-7.91 (m, 2H), 7.53-7.48 (m, 1H), 7.43-7.39 (m, 2H), 2.95 (q, J_1 = J_2 = 7.2 Hz, 2H), 1.19 (t, J_1 = J_2 = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.79, 136.90, 132.86, 128.54, 127.95, 31.75, 8.22.

1-Phenylbutan-1-one (2u)[44]**:** Yield: 93%;^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94-7.92 (m, 2H), 7.53-7.49 (m, 1H), 7.44-7.39 (m, 2H), 2.93-2.89 (m, 2H), 1.79-1.70 (m, 2H), 1.00-0.96 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.34, 137.12, 132.85, 128.54, 128.02, 40.48, 17.76, 13.88.

1-Phenylpentan-1-one (2v)[45]**:** Yield: 85%;^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97-7.94 (m, 2H), 7.56-7.52 (m, 1H), 7.47-7.43 (m, 2H), 2.96 (t, $J_1 = J_2 = 7.2$ Hz, 2H), 1.75-1.68 (m, 2H), 1.45-1.36 (m, 2H), 0.95 (t, $J_1 = J_2 = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.74, 137.22, 132.97, 128.66, 128.17, 38.45, 26.61, 22.60, 14.05.

Benzophenone (2w)[8]**:** Yield: 94%; mp 48-50 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81-7.79 (m, 2H), 7.60-7.56 (m, 1H), 7.50-7.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.89, 137.72, 132.53, 130.17, 128.39.

Cyclohexane-1,4-dione (2x)[46]**:** Yield: 97%; mp 75-77 ^{o}C; 1H NMR (400 MHz, $CDCl_3$): δ 2.67 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.51, 36.73.

***N*-(2,4,6-trimethylbenzylidene)prop-2-en-1-amine (4a):**Yield: 98%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (s, 1H), 6.88 (s, 2H), 6.17-6.07 (m, 1H), 5.30-5.16 (m, 2H), 4.30-4.29 (m, 2H), 2,42 (s, 6H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 162.08, 138.75, 137.49, 136.47, 131.23, 129.38, 115.68, 64.82, 21.18, 20.68.

***N*-(2-nitrobenzylidene)-1-phenylmethanamine (4b)**[47]**:**Yield: 98%; mp 45-46^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (s, 1H), 8.12-8.10 (m, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.67-7.63 (m, 1H), 7.58-7.54 (m, 1H), 7.38-7.30 (m, 4H), 7.29-7.27 (m, 1H), 4.89 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.71, 148.84, 138.44, 133.43, 131.15, 130.69, 129.82, 128.56, 128.08, 127.19, 124.25, 65.20.

***N*-(4-methylbenzylidene)-1-phenylmethanamine (4c)[48]:** Yield: 91%; mp ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H), 7.71 (d, *J* = 8 Hz, 2H), 7.37-7.24 (m, 7H), 4.83 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.04, 141.12, 139.52, 133.64, 129.42, 128.56, 128.37, 128.06, 127.02, 65.08, 21.60

(E)-N-(4-chlorobenzylidene)-1-phenylmethanamine (4d): Yield: 96%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.79 (d, *J* = 8 Hz, 2H), 7.54-7.24 (m, 7H), 4.89 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.45, 139.01, 136.60, 134.55, 129.42, 128.79, 128.49, 127.94, 127.04, 64.84.

***N*-(3-bromobenzylidene)-1-phenylmethanamine (4e):** Yield: 99%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 8.01 (d, *J* = 1.6 Hz, 1H), 7.69-7.67 (m, 1H), 7.57-7.55 (m, 1H), 7.41-7.38 (m, 4H), 7.32-7.27 (m, 2H), 4.85 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.11, 138.82, 138.06, 133.49, 130.74, 130.01, 128.46, 127.91, 127.03, 126.96, 122.82, 64.85.

1-(4-methoxyphenyl)-*N*-(2-methylbenzylidene)methanamine (4f):Yield: 95%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (s, 1H), 7.96-7.94 (m, 1H), 7.35-7.20 (m, 5H), 6.94-6.90 (m, 2H), 4.81 (s, 2H), 3.82 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.33, 158.74, 137.71, 134.25, 130.87, 130.37, 129.18, 127.71, 126.27, 114.06, 114.00, 65.09, 55.37, 19.43.

2-(2-bromophenyl)-1*H*-benzo[*d*]imidazole (6a)[49]:Yield: 82%; mp 142-143 ^{o}C; 1H NMR (400 MHz, $CDCl_3$): δ 8.07-8.04 (m, 2H), 8.02-7.99 (m, 2H), 7.46-7.42 (m, 2H), 7.22-7.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 170.26, 142.07, 133.60, 133.43, 132.12, 128.17, 94.83; HRMS observed 273.0021 (required for $C_{13}H_9BrN_2$ $[M + H]^+$ 273.0022)

2-(*p*-tolyl)-1*H*-benzo[*d*]imidazole (6b)[50]**:** Yield: 88%; mp 275 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.51 (s, 1H), 8.03 (d, J = 8 Hz, 1H), 7.98 (dd, J_1= J_2= 0.8 Hz, 1H), 7.88 (dd, J_1= J_2= 1.6 Hz, 1H), 7.50-7.39 (m, 2H), 7.14-7.08 (m, 2H), 6.942 (d, J = 8 Hz, 1H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.28, 148.84, 143.36, 141.18, 137.74, 132.21, 130.91, 130.05, 128.08, 125.02, 119.70, 114.35, 94.14, 21.76; HRMS observed 209.1074 (required for $C_{14}H_{12}N_2$ $[M + H]^+$ 209.1073).

2-(2-chloro-6-methylphenyl)-1*H*-benzo[*d*]imidazole (6c): Yield: 85%; mp 247-248 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.47 (m, 2H), 7.27-7.11 (m, 4H), 7.11-7.09 (m, 1H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.05, 140.94, 138.17, 134.56, 130.75, 129.98, 128.67, 127.03, 122.86, 115.36, 20.32; HRMS observed 243.0672 (required for $C_{14}H_{11}ClN_2$ $[M + H]^+$ 243.0684).

2-(2-bromo-5-fluorophenyl)-1H-benzo[d]imidazole (6d): Yield: 86%; mp 139-143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, J = 9.5, 3.1 Hz, 1H), 7.71 – 7.68 (m, 2H), 7.63 (dd, J = 8.8, 5.2 Hz, 1H), 7.37 – 7.30 (m, 2H), 7.04 (ddd, J = 8.8, 7.3, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1 (d, $^{1}J_{CF}$ = 247 Hz), 148.6, 148.6, 135.6, 135.5, 132.3 (d, $^{3}J_{CF}$ = 8 Hz), 123.69, 119.79, 119.54, 118.6 (d, $^{2}J_{CF}$ = 22 HZ), 114.4 (d, $^{4}J_{CF}$ = 3 Hz); HRMS observed 290.9960 (required for $C_{13}H_8BrFN_2$ $[M + H]^+$ 290.9928).

2-Mesityl-1*H*-benzo[*d*]imidazole (6e)[51]**:**Yield: 82%; mp 208 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.58 (m, 2H), 7.20-7.22 (m, 2H), 6.87 (s, 2H), 2.28 (s, 3H), 2.06 (s, 6H); HRMS observed 237.1383 (required for $C_{16}H_{16}N_2$ $[M + H]^+$ 237.1386).

2-(3,5-dibromo-2,4,6-trimethylphenyl)-1*H*-benzo[*d*]imidazole (6f): Yield: 79%; mp 290-292 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (s, 1H), 7.32-7.28 (m, 4H), 2.74 (s, 3H), 2.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.92, 139.78, 137.29, 130.63, 125.86, 123.15, 26.30, 22.28; HRMS observed 392.9604 (required for $C_{16}H_{14}Br_2N_2$ $[M + H]^+$ 392.9597).

2-Bromo-1-phenylethanone (8a)[52]**:** White solid, Yield: 86%; mp: 48-50 ^{o}C ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8 Hz, 2H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 4.46 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.42, 134.17, 129.08, 129.00, 31.11.

2-Bromo-2,3-dihydro-1*H*-inden-1-one (8b)[53]**:** Yield: 83%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84-7.81 (m, 1H), 7.69-7.64 (m, 1H), 7.46-7.40 (m, 2H), 4.65 (dd, J_1 = 7.5 Hz, J_2 = 3.2 Hz, 1H), 3.84 (dd, J_1 = 18.1 Hz, J_2 = 7.5 Hz, 1H), 3.42 (dd, *J*1 = 18.1 Hz, *J*2 = 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.51, 151.16, 135.92, 133.57, 128.24, 126.48, 125.00, 44.08, 37.91.

2-Bromocyclohexanone (8c)[54]**:** Yield: 81%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.49-4.39 (m, 1H), 3.33-2.90 (m, 1H), 2.41-2.12 (m, 3H), 2.11-1.61 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.52, 53.47, 37.91, 36.72, 27.66, 22.18.

2-Iodo-1-phenylethanone (8d)[55]**:** Yield: 89%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00-7.91 (m, 2H), 7.59-7.43 (m, 3H), 4.31 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.81, 133.72, 133.48, 130.02, 128.81, 1.68.

2-Iodo-2,3-dihydro-1*H*-inden-1-one (8e)[56]**:** Yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (m, 4H), 4.92 (dd, J_1 = 7.5 Hz, J_2 = 3 Hz, 1H), 3.90 (dd, J_1 = 18 Hz, J_2 = 7.5 Hz, 1H), 3.45 (dd, J_1 = 18 Hz, J_2 = 3 Hz, 1H).

2-Iodocyclohexanone (8f)[27]**:** Yield: 86%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.67-4.49 (m, 1H), 3.33-3.17 (m, 1H), 2.36-2.14 (m, 2H), 2.11-1.91 (m, 4H), 1.82-1.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.51, 37.48, 36. 41, 32.82, 26.66, 22.63.

2-Nitrobenzaldehyde (10c)[5]: Yield: 88%; mp 42-44 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.41 (s, 1H), 8.12-8.10 (m, 1H), 7.95-7.93 (m, 1H), 7.81-7.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 188.31, 149.69, 134.22, 133.84, 131.45, 129.75, 124.62.

Cyclohexanecarbaldehyde (10d)[5]: Yield: 83%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.59 (s, 1H), 2.24-2.19 (m, 1H), 1.90-1.20 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): 205.17, 50.07, 26.08, 26.02, 25.12.

4-Chlorobenzaldehyde (10e)[2]: Yield: 93%; mp 46-48ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 7.82 (d, *J* = 8.4, 2H), 7.51 (d, *J* = 8.4, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 191.04, 141.13, 134.85, 131.70, 131.06, 129.61, 129.03.

2,4-Dimethoxy-6-methylbenzaldehyde (10f)[57]**:**Yield: 87%; mp 67-69 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.47 (s, 1H), 6.63 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.68, 165.30, 164.55, 144.85, 117.45, 108.87, 95.88, 55.87, 55.56, 22.46.

Sulfinyldibenzene (12a)[58]**:** Yield: 81%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.3 Hz, 4H), 7.35-7.30 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.11, 130.48, 128.76, 124.05.

(Ethylsulfinyl)benzene (12b)[30]**:**Yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 7.2 Hz, 2H), 7.51-7.49 (m, 3H), 2.95-2.86 (m, 1H), 2.80-2.71 (m, 1H), 1.18 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.94, 130.62, 128.84, 123.82, 49.90, 5.62.

(Methylsulfinyl)ethane (12c)[59]**:**Yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.79-2.66 (m, 2H), 2.53 (s, 3H), 1.23 (t, *J* = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.96, 36.83, 6.53.

(Ethylsulfinyl)ethane (12d)[30]: Yield: 87%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.74-2.67 (m, 4H), 1.34 (t, *J* = 7.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.82, 6.74.

2.6 NOTES AND REFERENCES

1. Nonappa; Ahonen, K.; Lahtinen, M.; Kolehmainen, E., *Green Chemistry* **2011,** *13*, 1203.
2. Valko, M.; Morris, H.; Cronin, M. T. D., *Curr. Med. Chem.* **2005,** *12*, 1161.
3. (a) Charest, M. G.; Lerner, C. D.; Brubaker, J. D.; Siegel, D. R.; Myers, A. G., *Science* **2005,** *308*, 395; (b)Zhang, S. L.; Xie, H. X.; Zhu, J.; Li, H.; Zhang, X. S.; Li, J.; Wang, W., *Nature Commun.* **2011,** *2*, 211; (c)Zhdankin, V. V., *J. Org. Chem.* **2011,** *76*, 1185.
4. Hartmann, C.; Meyer, V., *Ber. Dtsch. Chem. Ges.* **1893,** *26*, 1727.
5. Nicolaou, K. C.; Mathison, C. J.; Montagnon, T., *J. Am. Chem. Soc.* **2004,** *126*, 5192.
6. Duschek, A.; Kirsch, S. F., *Angew. Chem. Int. Ed.* **2011,** *50*, 1524.
7. Dess, D. B.; Martin, J. C., *J. Org. Chem.* **1983,** *48*, 4155.
8. (a) Dess, D. B.; Martin, J. C., *J. Am. Chem. Soc.* **1991,** *113*, 7277; (b)Thottumkara, A. P.; Vinod, T. K., *Tetrahedron Lett.* **2002,** *43*, 569; (c)Koposov, A. Y.; Litvinov, D. N.; Zhdankin, V. V.; Ferguson, M. J.; McDonald, R.; Tykwinski, R. R., *Eur. J. Org. Chem.*

2006, 4791; (d)Richardson, R. D.; Zayed, J. M.; Altermann, S.; Smith, D.; Wirth, T., *Angew. Chem., Int. Ed.* **2007,** *46*, 6529; (e)Cui, L.-Q.; Dong, Z.-L.; Liu, K.; Zhang, C., *Org. Lett.* **2011,** *13*, 6488; (f)Moorthy, J. N.; Senapati, K.; Parida, K. N.; Jhulki, S.; Sooraj, K.; Nair, N. N., *J. Org. Chem.* **2011,** *76*, 9593; (g)Seth, S.; Jhulki, S.; Moorthy, J. N., *Eur. J. Org. Chem.* **2013,** *2013*, 2445.

9. Ladziata, U.; Koposov, A. Y.; Lo, K. Y.; Willging, J.; Nemykin, V. N.; Zhdankin, V. V., *Angew. Chem. Int. Ed.* **2005,** *44*, 7127.
10. Mülbaier, M.; Giannis, A., *Angew. Chem. Int. Ed.* **2001,** *40*, 4393.
11. (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y. L.; Barluenga, S.; Hunt, K. W.; Kranich, R.; Vega, J. A., *J. Am. Chem. Soc.* **2002,** *124*, 2233; (b)Nicolaou, K. C.; Baran, P. S.; Zhong, Y. L.; Sugita, K., *J. Am. Chem. Soc.* **2002,** *124*, 2212; (c)Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y. L., *J. Am. Chem. Soc.* **2002,** *124*, 2245; (d)Nicolaou, K. C.; Sugita, K.; Baran, P. S.; Zhong, Y. L., *J. Am. Chem. Soc.* **2002,** *124*, 2221.
12. Hirose, D.; Taniguchi, T.; Ishibashi, H., *Angew. Chem. Int. Ed.* **2013**.
13. (a) Stolle, A.; Szuppa, T.; Leonhardt, S. E. S.; Ondruschka, B., *Chem. Soc. Rev.* **2011,** *40*, 2317; (b)Wang, G.-W., *Chem. Soc. Rev.* **2013,** *42*, 7668.
14. Frigerio, M.; Santagostino, M.; Sputore, S., *J. Org. Chem.* **1999,** *64*, 4537.
15. Uyanik, M.; Akakura, M.; Ishihara, K., *J. Am. Chem. Soc.* **2009,** *131*, 251.
16. Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T., *J. Am. Chem. Soc.* **2004,** *126*, 5192.
17. Moorthy, J. N.; Senapati, K.; Singhal, N., *Tetrahedron Lett.* **2009,** *50*, 2493.
18. Shukla, V. G.; Salgaonkar, P. D.; Akamanchi, K. G., *J. Org. Chem.* **2003,** *68*, 5422.
19. Moorthy, J. N.; Neogi, I., *Tetrahedron Lett.* **2011,** *52*, 3868.

20. Using 25 mL of milling jar we could successfully perform the reactions on 2.5 gram scale and scaled down to 10 mg with a smaller jar (10 mL). In all the cases one ball with 15 mm diameter was used and also followed recommended maximum loading 1/3 volume of the jar capacity.

21. Thottumkara, A. P.; Bowsher, M. S.; Vinod, T. K., *Org. Lett.* **2005,** *7*, 2933.

22. Sorg, G.; Mengei, A.; Jung, G.; Rademann, J., *Angew. Chem., Int. Ed.* **2001,** *40*, 4395.

23. Liu, Z.; Chen, Z.-C.; Zheng, Q.-G., *Org. Lett.* **2003,** *5*, 3321.

24. Surendra, K.; Krishnaveni, N. S.; Reddy, M. A.; Nageswar, Y. V. D.; Rao, K. R., *J. Org. Chem.* **2003,** *68*, 2058.

25. Moorthy, J. N.; Singhal, N.; Venkatakrishnan, P., *Tetrahedron Lett.* **2004,** *45*, 5419.

26. Uyanik, M.; Ishihara, K., *Chem. Commun.* **2009**, 2086.

27. Wang, Y.-H.; Cong, H.; Zhao, F.-F.; Xue, S.-F.; Tao, Z.; Zhu, Q.-J.; Wei, G., *Catal. Commun.* **2011,** *12*, 1127.

28. James, S. L.; Adams, C. J.; Bolm, C.; Braga, D.; Collier, P.; Friscic, T.; Grepioni, F.; Harris, K. D. M.; Hyett, G.; Jones, W.; Krebs, A.; Mack, J.; Maini, L.; Orpen, A. G.; Parkin, I. P.; Shearouse, W. C.; Steed, J. W.; Waddell, D. C., *Chem. Soc. Rev.* **2012,** *41*, 413.

29. Bézier, D.; Park, S.; Brookhart, M., *Org. Lett.* **2013,** *15*, 496.

30. Fergus, S.; Eustace, S. J.; Hegarty, A. F., *J. Org. Chem.* **2004,** *69*, 4663.

31. Olson, M. E.; Carolan, J. P.; Chiodo, M. V.; Lazzara, P. R.; Mohan, R. S., *Tetrahedron Lett.* **2010,** *51*, 3969.

32. Lin, C.-K.; Lu, T.-J., *Tetrahedron* **2010,** *66*, 9688.

33. Dubost, E.; Fossey, C.; Cailly, T.; Rault, S.; Fabis, F., *J. Org. Chem.* **2011,** *76*, 6414.

34. Jeena, V.; Robinson, R. S., *Chem. Commun.* **2012,** *48*, 299.

35. Narasimha Moorthy, J.; Singhal, N.; Venkatakrishnan, P., *Tetrahedron Lett.* **2004,** *45*, 5419.

36. Eikawa, M.; Sakaguchi, S.; Ishii, Y., *J. Org. Chem.* **1999,** *64*, 4676.

37. Denmark, S. E.; Amishiro, N., *J. Org. Chem.* **2003,** *68*, 6997.

38. Hauske, J. R.; Guadliana, M.; Desai, K., *J. Org. Chem.* **1982,** *47*, 5019.

39. Wang, Y.-H.; Cong, H.; Zhao, F.-F.; Xue, S.-F.; Tao, Z.; Zhu, Q.-J.; Wei, G., *Catalysis Commun.* **2011,** *12*, 1127.

40. Tucker-Schwartz, A. K.; Garrell, R. L., *Chem. Eur. J.* **2010,** *16*, 12718.

41. Hanson, S. K.; Wu, R.; Silks, L. A. P., *Org. Lett.* **2011,** *13*, 1908.

42. Shelar, D. P.; Birari, D. R.; Rote, R. V.; Patil, S. R.; Toche, R. B.; Jachak, M. N., *J. Phys. Org. Chem.* **2011,** *24*, 203.

43. Havare, N.; Plattner, D. A., *Org. Lett.* **2012,** *14*, 5078.

44. Yin, L.; Wu, J.; Xiao, J.; Cao, S., *Tetrahedron Lett.* **2012,** *53*, 4418.

45. Seth, S.; Jhulki, S.; Moorthy, J. N., *Eur. J. Org. Chem.* **2013**, 2445.

46. Li, W.; Li, J.; Wu, Y.; Fuller, N.; Markus, M. A., *J. Org. Chem.* **2010,** *75*, 1077.

47. Chen, C.-W.; Tseng, M.-C.; Hsiao, S.-K.; Chen, W.-H.; Chu, Y.-H., *Org. Biomol. Chem.* **2011,** *9*, 4188.

48. Soule, J.-F.; Miyamura, H.; Kobayashi, S., *Chem. Commun.* **2013,** *49*, 355.

49. Chung, K. H.; So, C. M.; Wong, S. M.; Luk, C. H.; Zhou, Z.; Lau, C. P.; Kwong, F. Y., *Chem. Commun.* **2012,** *48*, 1967.

50. Inamdar, S. M.; More, V. K.; Mandal, S. K., *Tetrahedron Lett.* **2013,** *54*, 579.

51. Moorthy, J. N.; Neogi, I., *Tetrahedron Letters* **2011,** *52*, 3868.

52. Prebil, R.; Laali, K. K.; Stavber, S., *Org. Lett.* **2013,** *15*, 2108.

53. Podgorsek, A.; Stavber, S.; Zupan, M.; Iskra, J., *Green Chem.* **2007,** *9*, 1212.

54. Maji, T.; Karmakar, A.; Reiser, O., *J. Org. Chem.* **2010,** *76*, 736.

55. Marri, M. R.; Macharla, A. K.; Peraka, S.; Nama, N., *Tetrahedron Lett.* **2011,** *52*, 6554.

56. Scaron; ket, B.; Zupan, M., *Bull. Chem. Soc. Jpn.* **1987,** *60*, 4489.

57. Foti, M. C.; Daquino, C.; Mackie, I. D.; DiLabio, G. A.; Ingold, K. U., *J. Org. Chem.* **2008,** *73*, 9270.

58. Gu, X.; Li, X.; Chai, Y.; Yang, Q.; Li, P.; Yao, Y., *Green Chem.* **2013,** *15*, 357.

59. Maiti, S. K.; Banerjee, S.; Mukherjee, A. K.; Abdul Malik, K. M.; Bhattacharyya, R., *New J. Chem.* **2005,** *29*, 554.

^{1}H and ^{13}C NMR Spectra of newly synthesized compounds

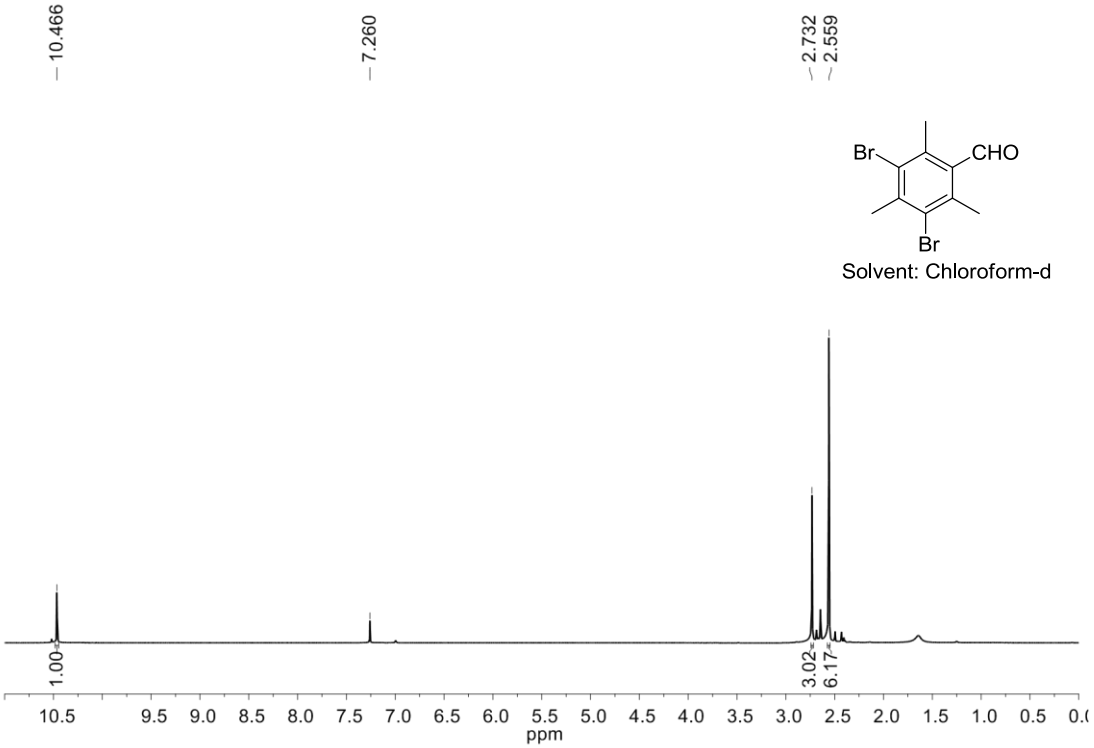


Figure 2.9 ^{1}H NMR spectrum of 3,5-Dibromo-2,4,6-trimethylbenzaldehyde (**2g**).

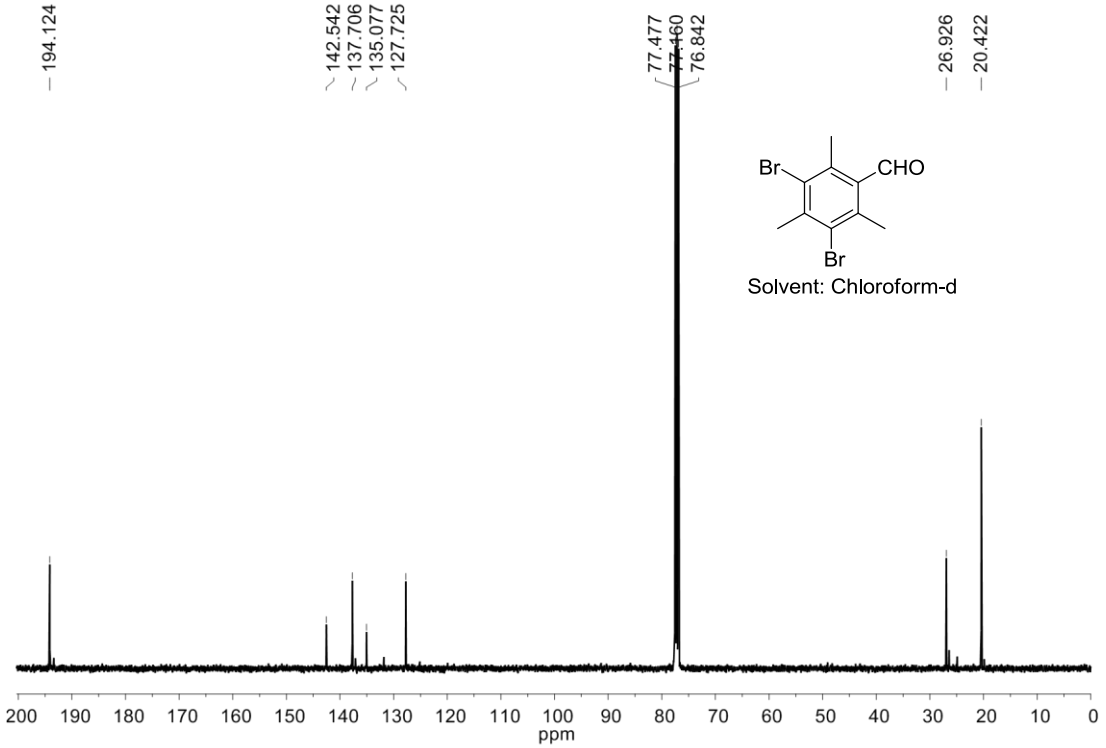


Figure 2.10 ^{13}C NMR spectrum of 3,5-Dibromo-2,4,6-trimethylbenzaldehyde (**2g**).

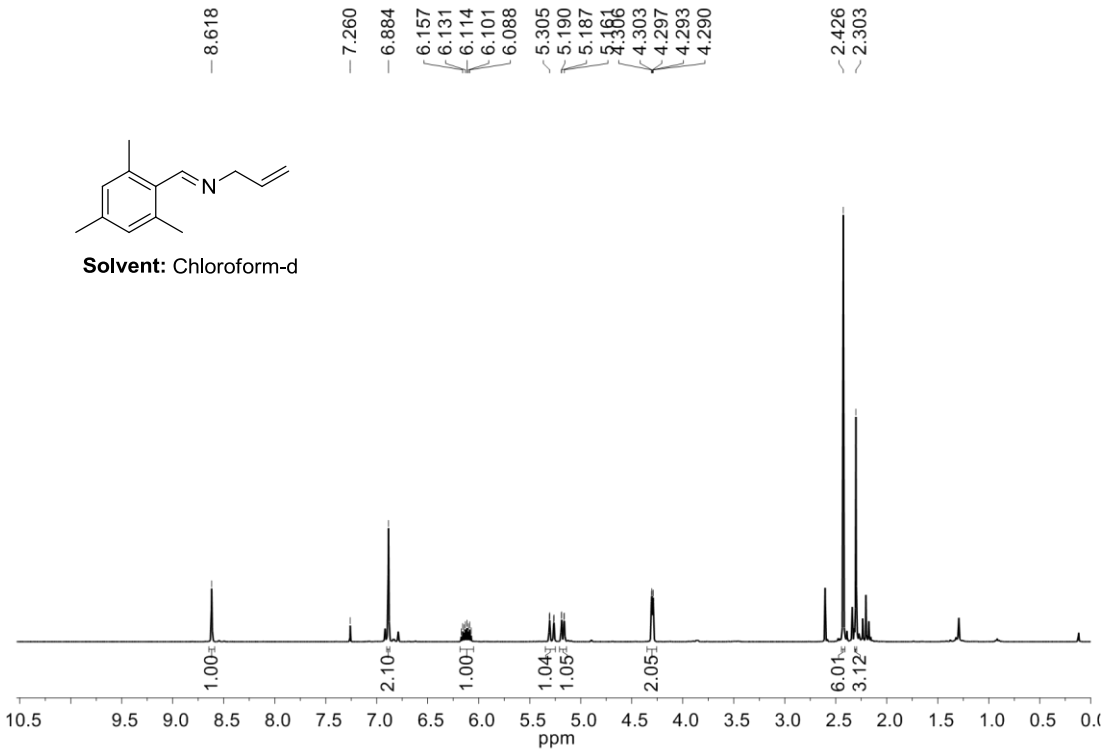


Figure 2.11 ^{1}H NMR spectrum of *N*-(2,4,6-trimethylbenzylidene)prop-2-en-1-amine (**4a**).

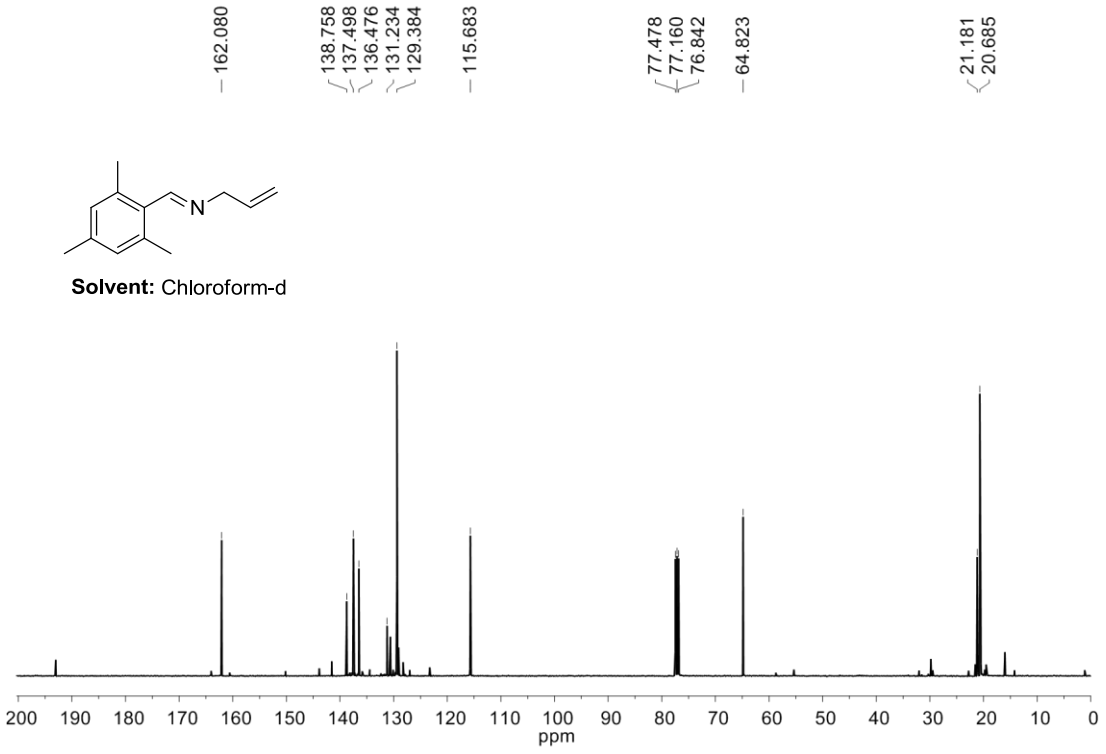


Figure 2.12 ^{13}C NMR spectrum of *N*-(2,4,6-trimethylbenzylidene)prop-2-en-1-amine (**4a**).

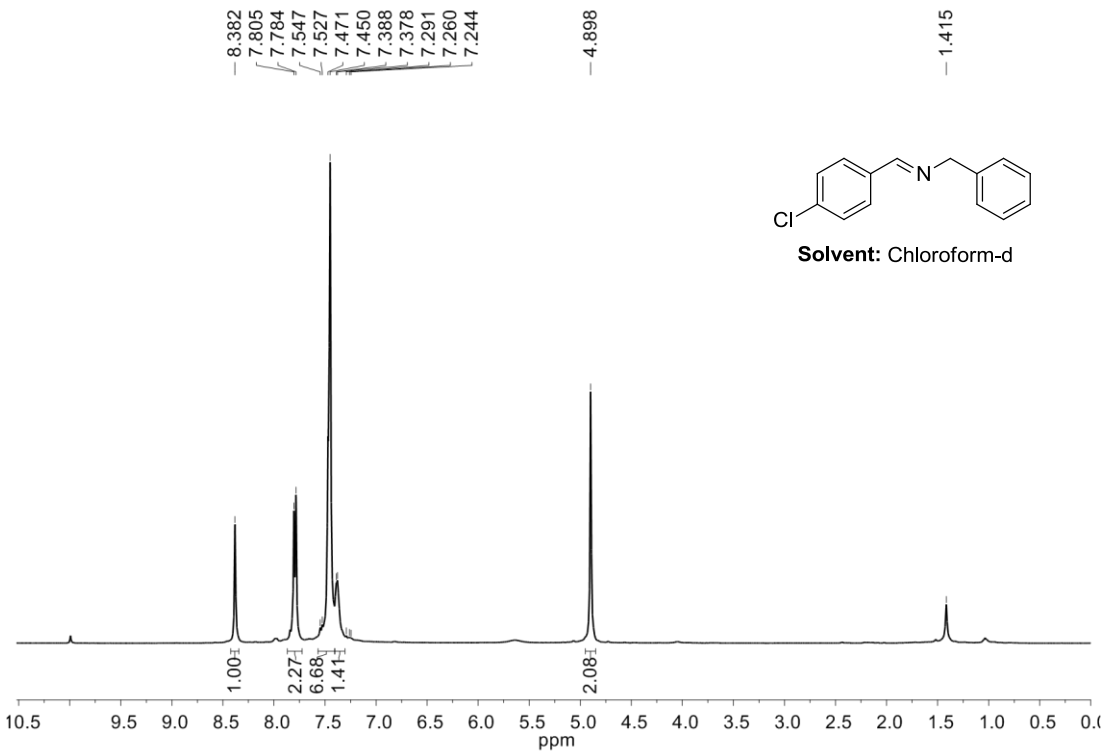


Figure 2.13 ^{1}H NMR spectrum of (E)-N-(4-chlorobenzylidene)-1-phenylmethanamine (**4d**).

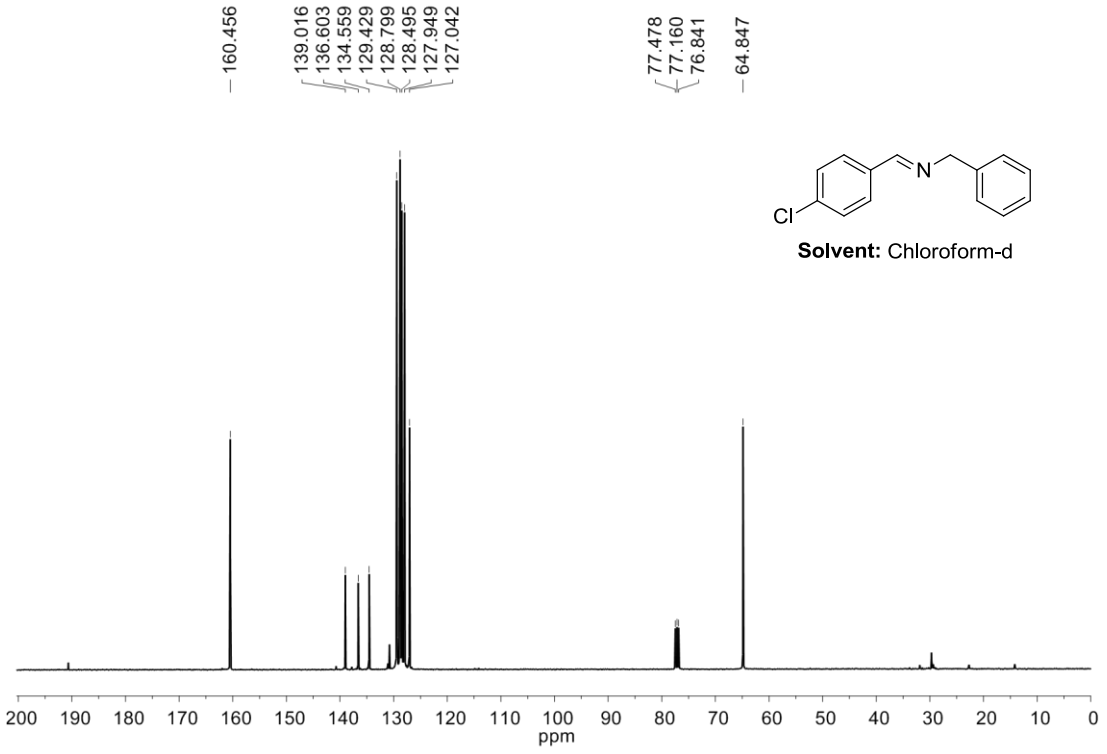


Figure 2.14 ^{13}C NMR spectrum of (E)-N-(4-chlorobenzylidene)-1-phenylmethanamine (**4d**).

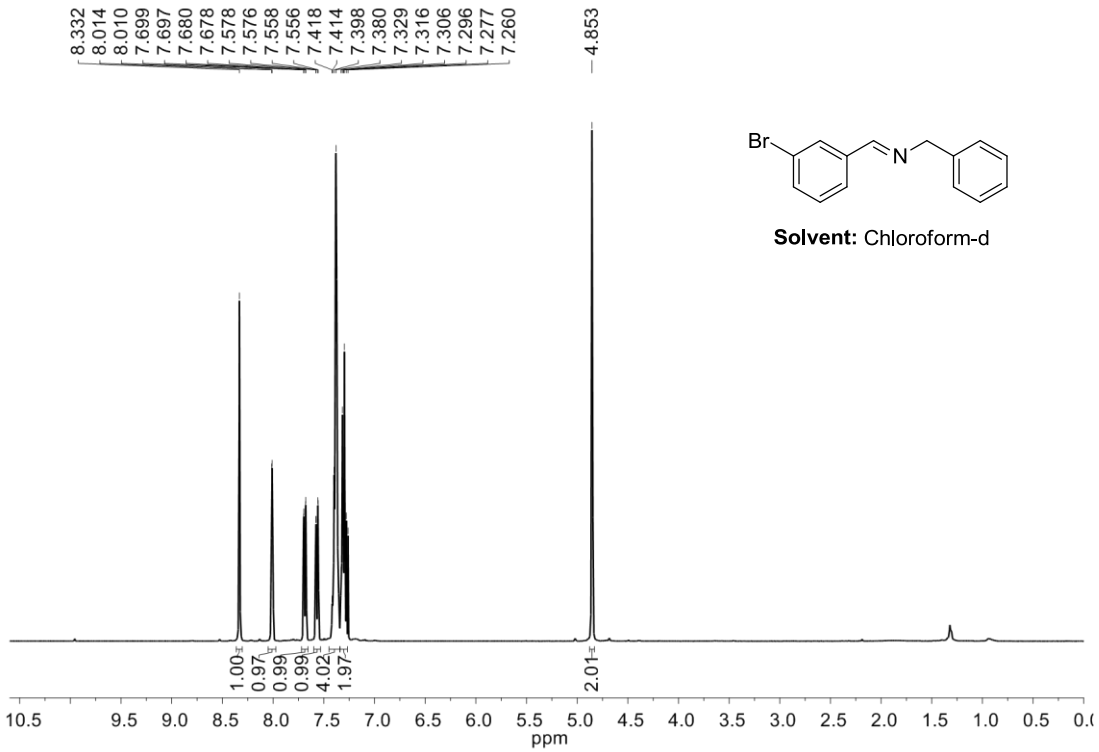


Figure 2.15 ^{1}H NMR spectrum of *N*-(3-bromobenzylidene)-1-phenylmethanamine (**4e**).

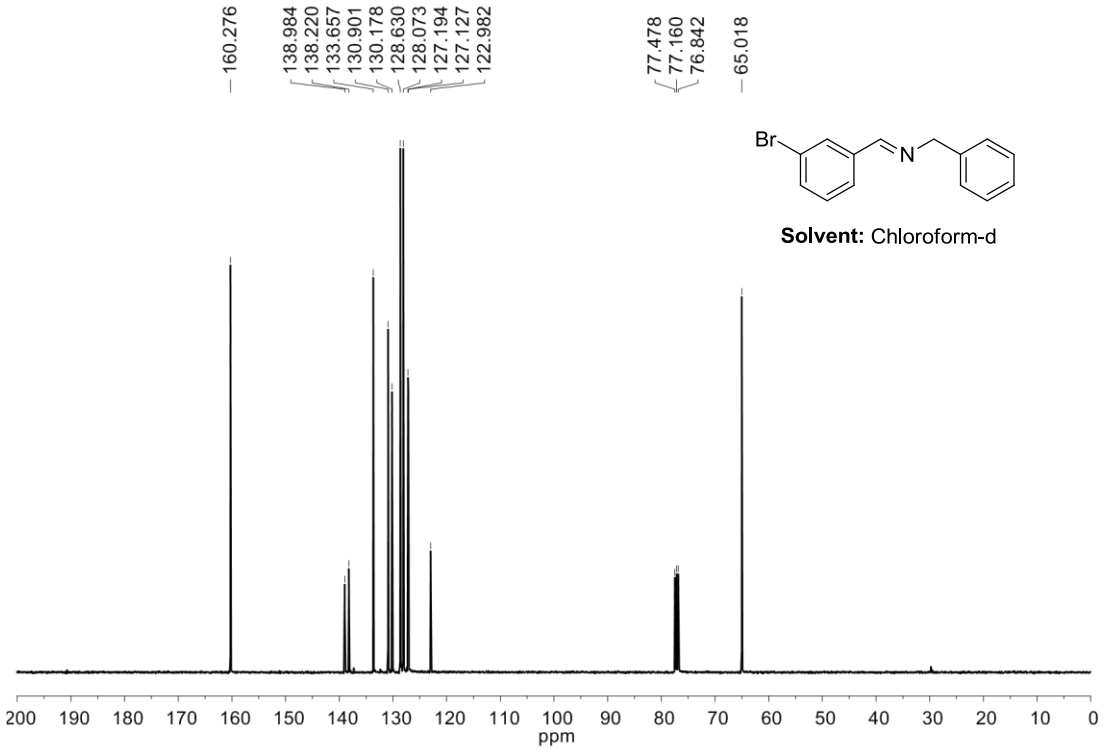


Figure 2.16 ^{13}C NMR spectrum of *N*-(3-bromobenzylidene)-1-phenylmethanamine (**4e**).

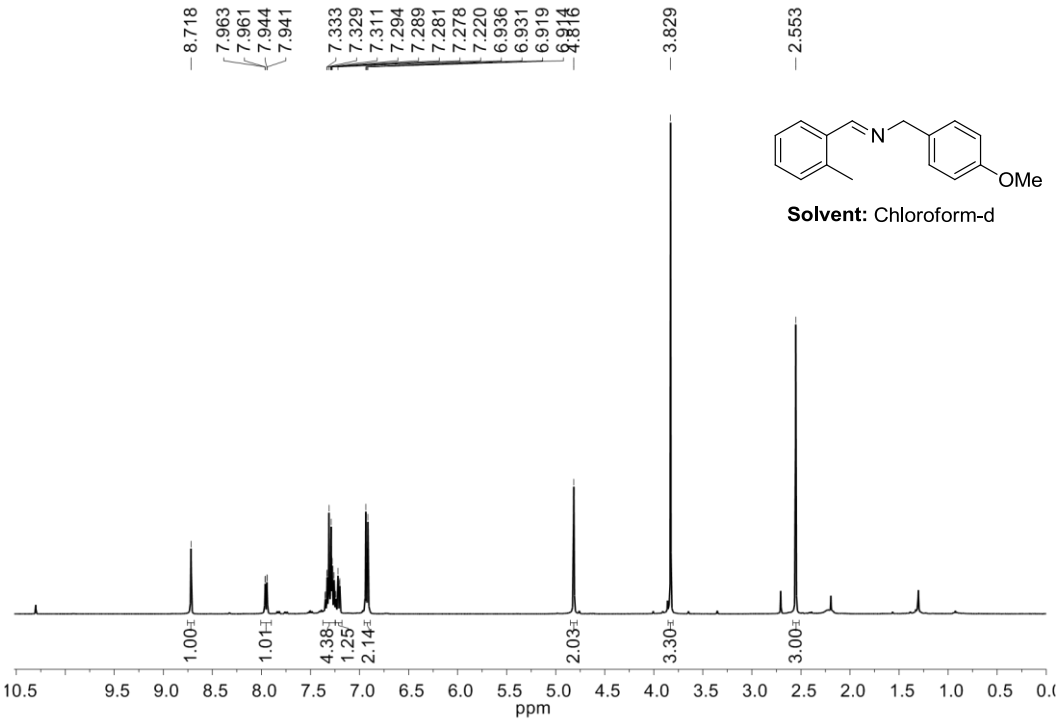


Figure 2.17 ^{1}H NMR spectrum of 1-(4-methoxyphenyl)-*N*-(2-methylbenzylidene)methanamine (**4f**).

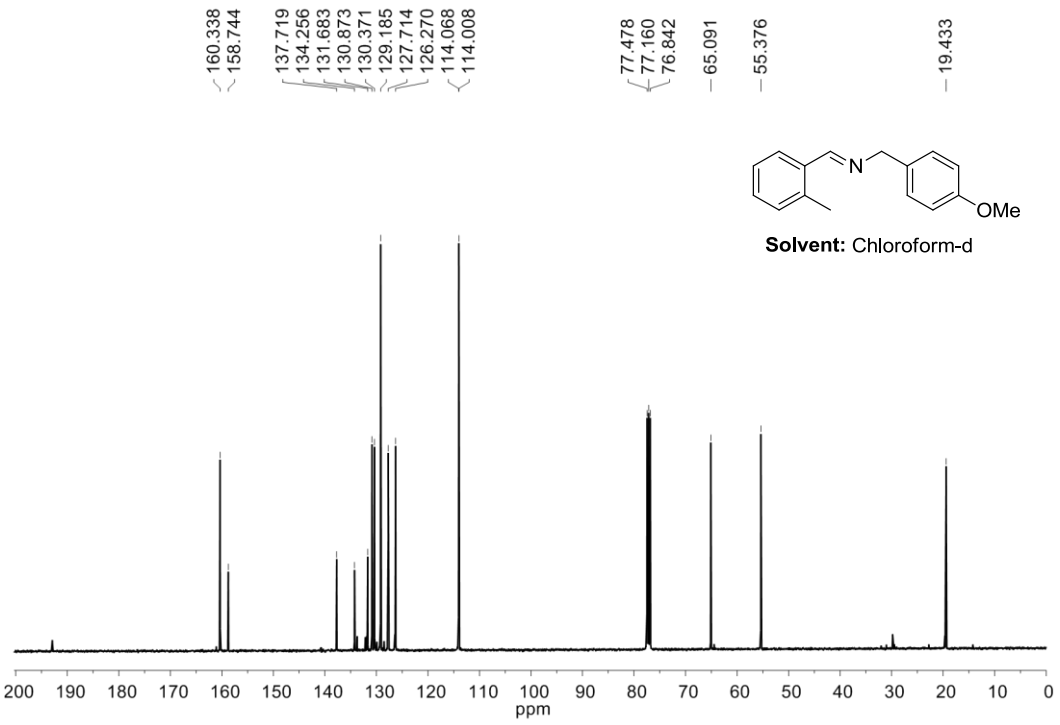


Figure 2.18 ^{1}H NMR spectrum of 1-(4-methoxyphenyl)-*N*-(2-methylbenzylidene)methanamine (**4f**).

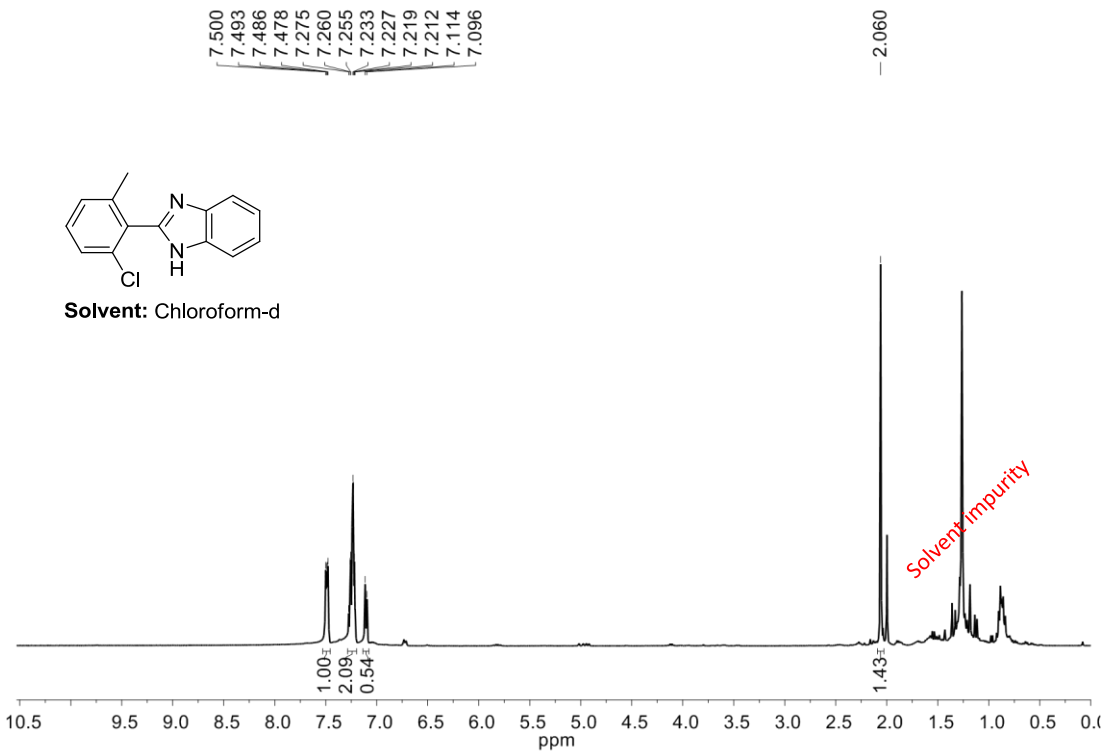


Figure 2.19 ^{1}H NMR spectrum of 2-(2-chloro-6-methylphenyl)-1*H*-benzo[*d*]imidazole (**6c**).

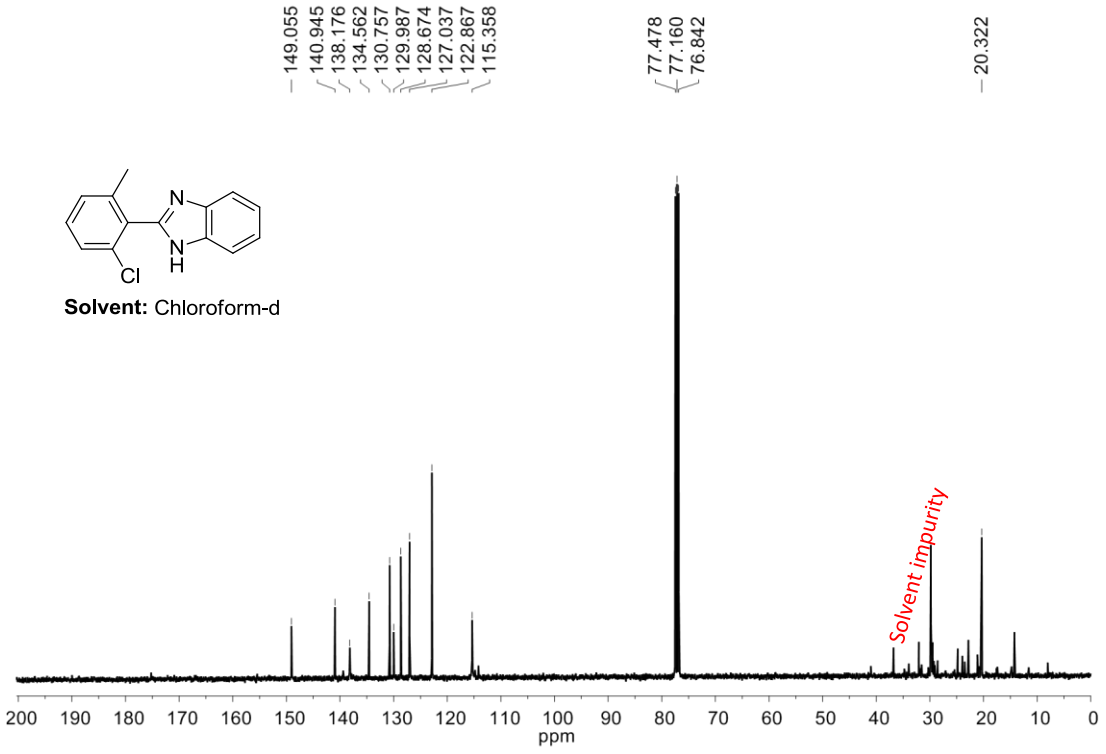


Figure 2.20 ^{13}C NMR spectrum of 2-(2-chloro-6-methylphenyl)-1*H*-benzo[*d*]imidazole (**6c**).

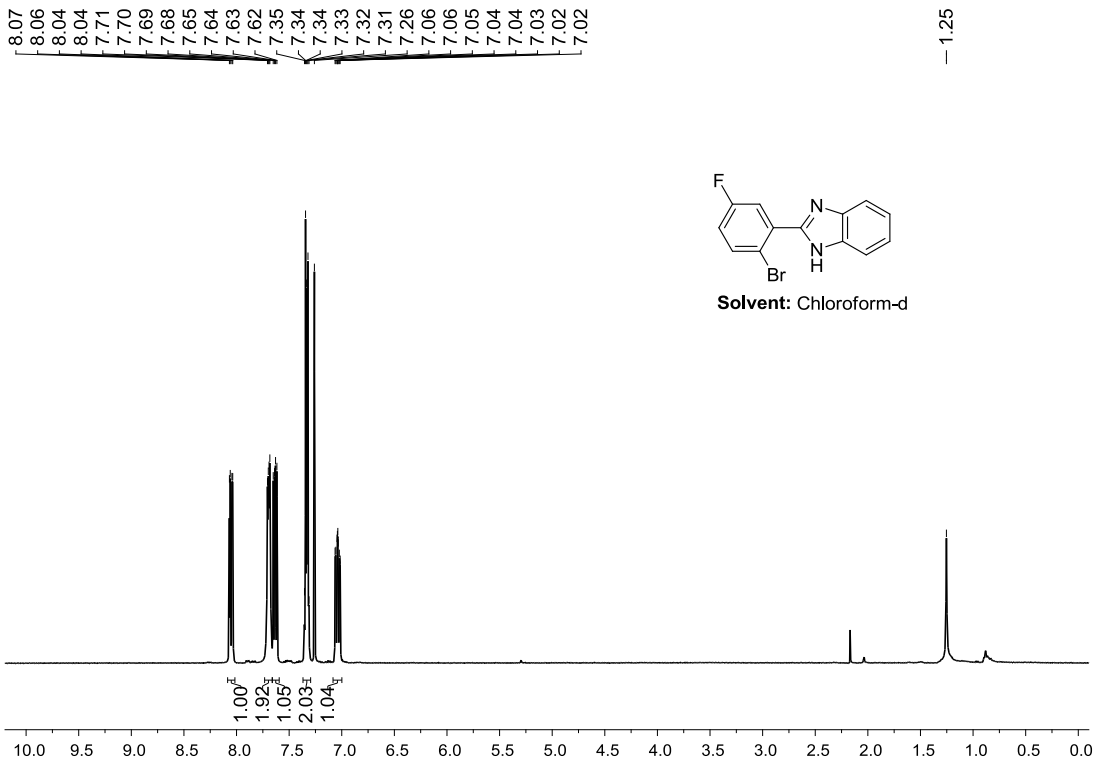


Figure 2.21 ^{1}H NMR spectrum of 2-(2-bromo-5-fluorophenyl)-1*H*-benzo[*d*]imidazole (**6d**).

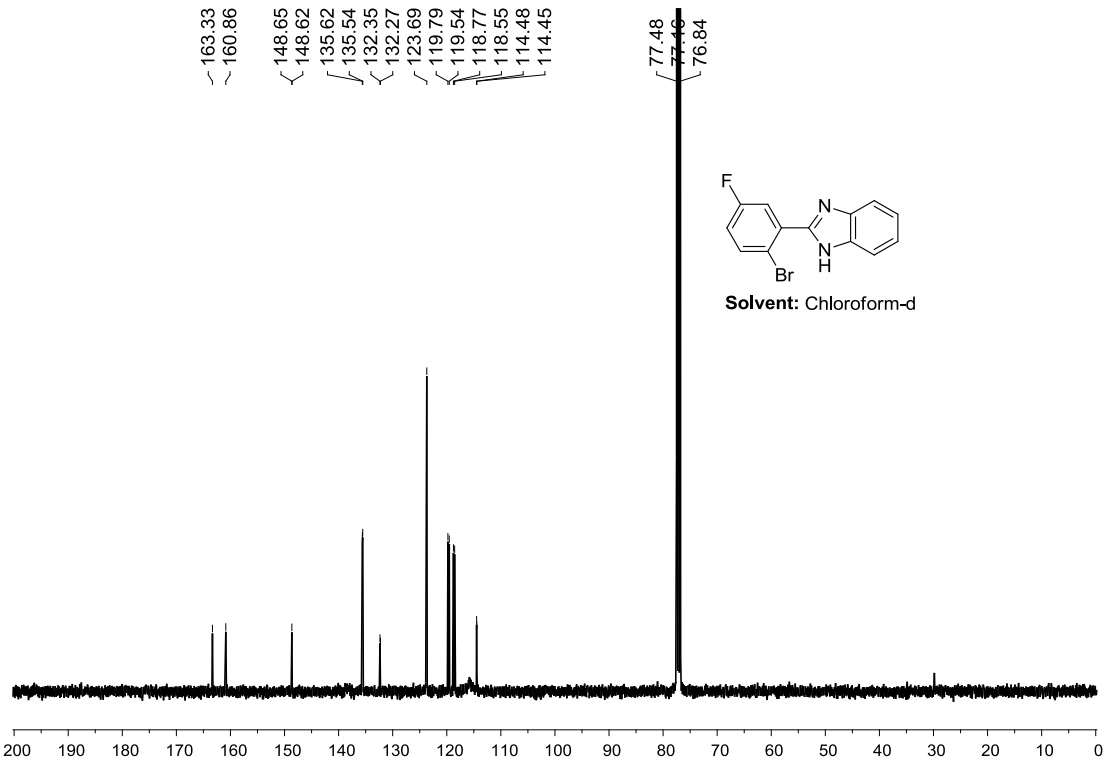


Figure 2.22 ^{13}C NMR spectrum of 2-(2-bromo-5-fluorophenyl)-1*H*-benzo[*d*]imidazole (**6d**).

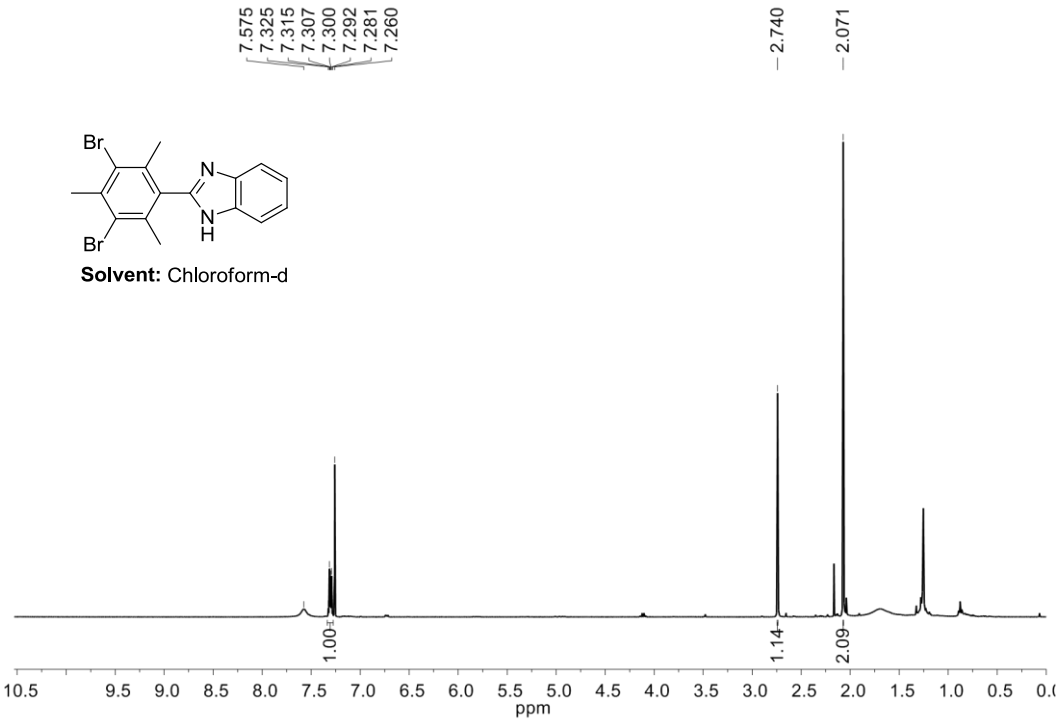


Figure 2.23 ^{1}H NMR spectrum of 2-(3,5-dibromo-2,4,6-trimethylphenyl)-1*H*-benzo[*d*]imidazole (**6f**).

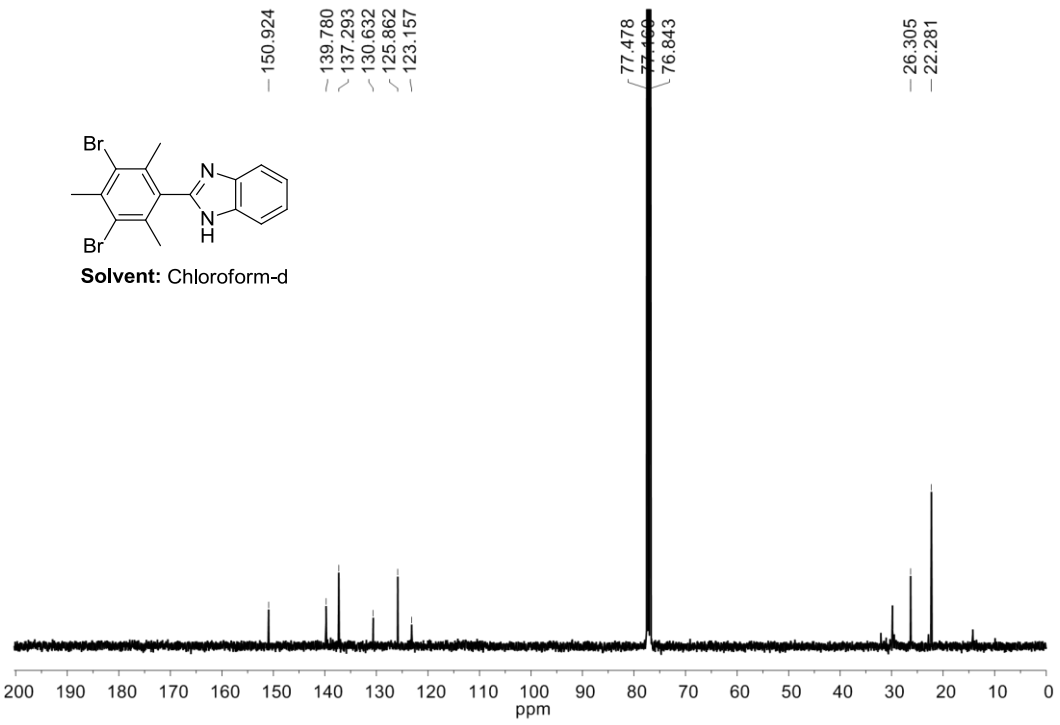
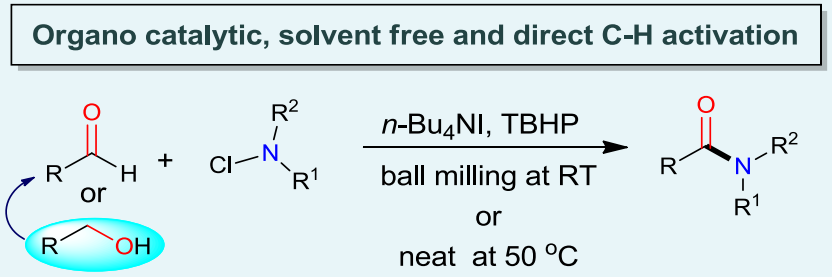


Figure 2.24 ^{13}C NMR spectrum of 2-(3,5-dibromo-2,4,6-trimethylphenyl)-1*H*-benzo[*d*]imidazole (**6f**).

CHAPTER 3

Radical-Induced Metal and Solvent-Free Cross-Coupling Using TBAI−TBHP: Oxidative Amidation of Aldehydes and Alcohols with *N*-Chloramines *via* C−H Activation

3.1 ABSTRACT



A solvent-free cross-coupling method for oxidative amidation of aldehydes and alcohols via a metal-free radial pathway has been demonstrated. The proposed methodology uses the TBAI-TBHP combination which efficiently induces metal-free C−H activation of aldehydes under neat conditions at 50 °C or ball-milling conditions at room temperature.

3.2 INTRODUCTION

Amide functionality is well known in peptides and proteins. During protein synthesis in living systems most amide bonds are created by the complex molecular machine like ribosomes. Due to stability, high polarity and conformational diversity, the amide bond became one of the most abundant motifs in biologically active naturally occurring compounds, pharmaceutically active small molecules, agrochemicals and polymers etc.[1] Few examples of medicinally important amide containing bio-active molecules are shown in Figure 3.1. In 2007 the American Chemical Society

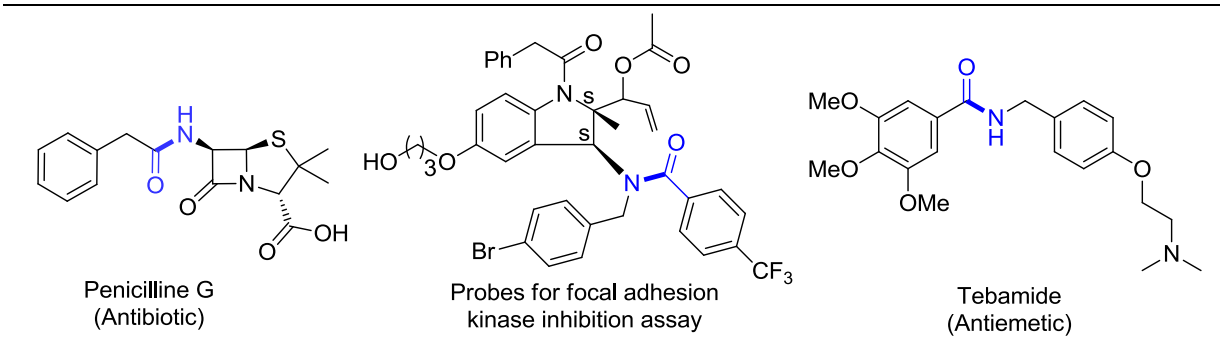
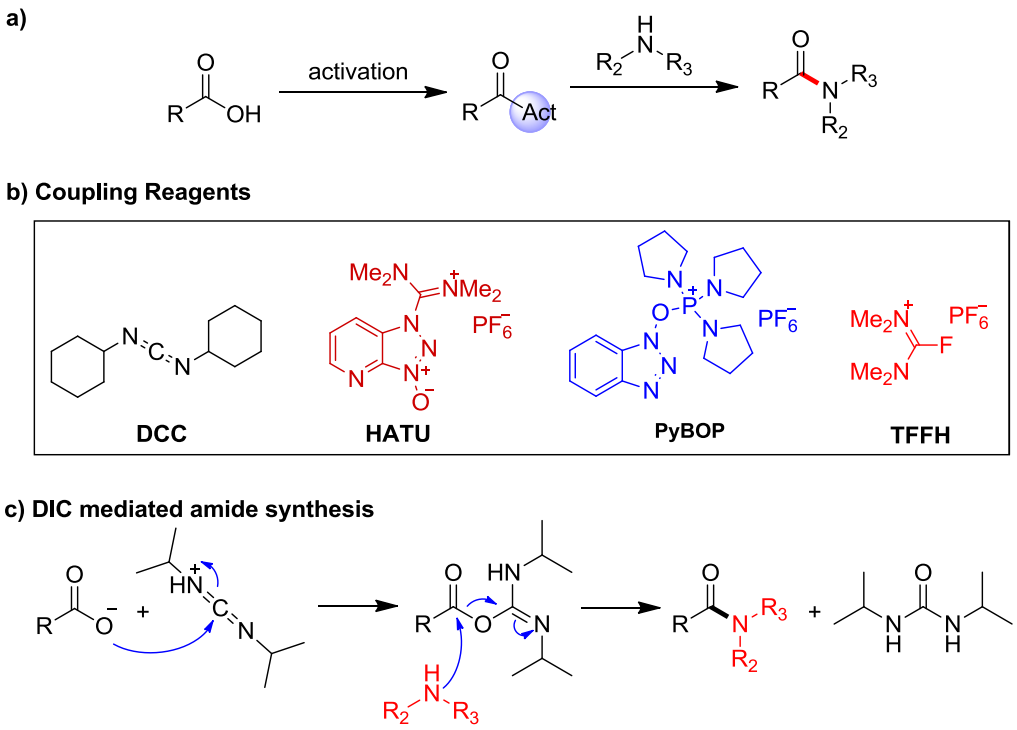


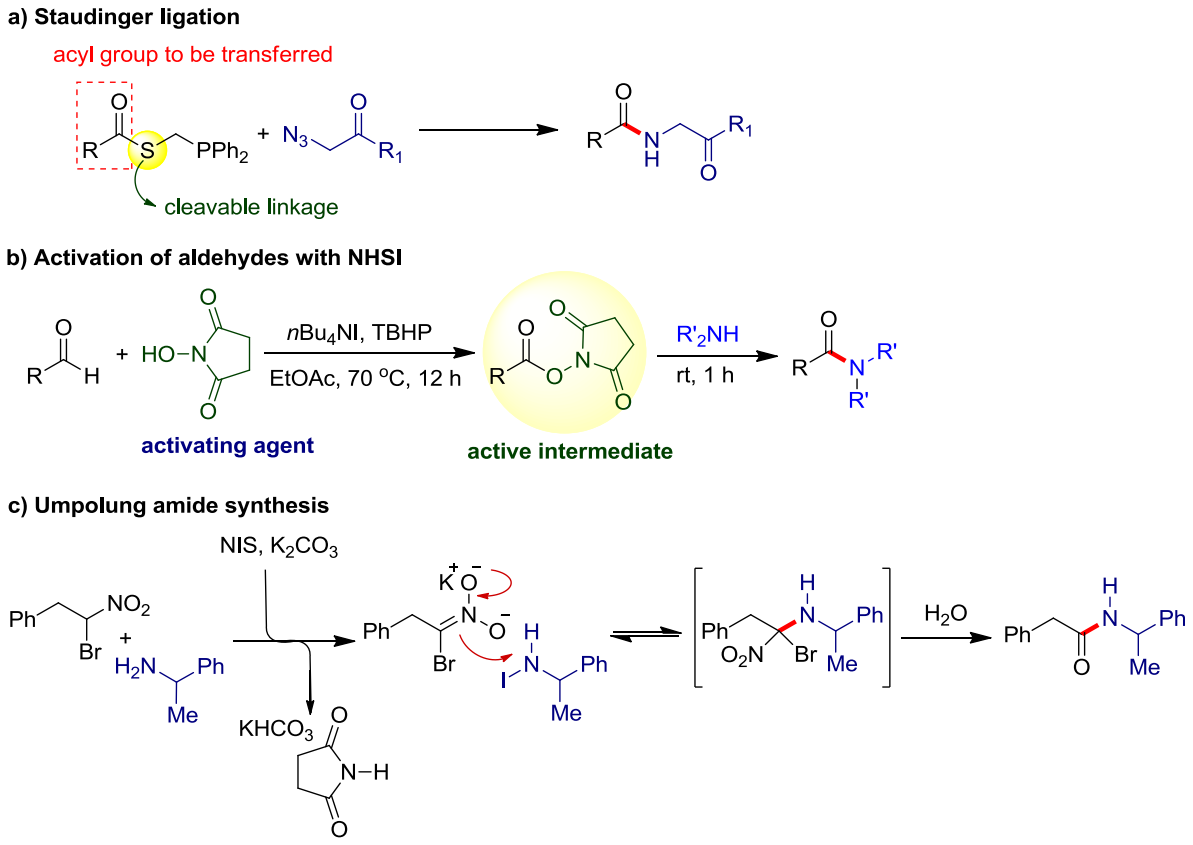
Figure 3.1 Medicinally important molecules containing amide linkage (highlighted in blue color).

(ACS), Green Chemistry Institute (GCI) including several pharmaceutical corporations developed the ACS GCI Pharmaceutical Roundtable who voted 'amide formation avoiding poor atom economy reagents' as the top challenge for organic chemistry.[2] Consequently the development of facile and expedient methodology for amide functionality under catalytic, metal free, waste free and chemoselective condition are in great demand. The most common methods



Scheme 3.1 Amide synthesis; (a) conventionally amide synthesis from carboxylic acid with amine, (b) activating agents and (c) *N*,*N*'-Diisopropylcarbodiimide (DIC) mediated amide synthesis

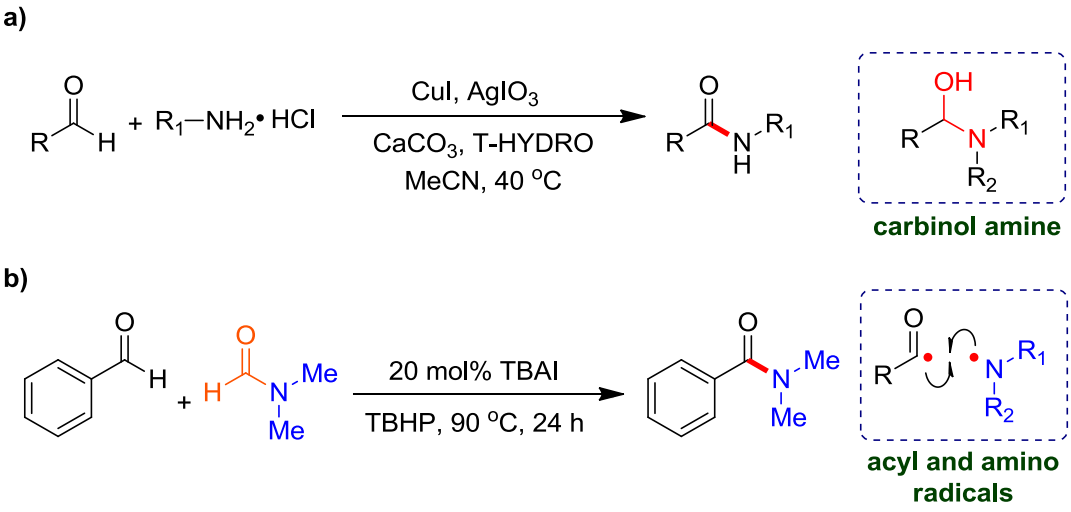
for the synthesis of amide include either the coupling of carboxylic acids and amines in presence of a coupling agent[3,4] or acylation of amines with activated carboxylic acid derivatives (Scheme 3.1).[5,6] These strategies has been shown to be efficient for synthesis of small molecules but unpopular due to usage of very hazardous reagents, unavailability of activated acid derivatives and poor atom economy.[4] Therefore handful of alternatives have been reported such as Staudinger reaction,[7,8] Schmidt reaction,[9] Beckmann rearrangement,[10,11] aminocarbonylation of haloarenes,[12,13] direct synthesis from alcohols with amines[14] and oxidative amidation of aldehydes[15-23] etc. (few examples have been shown in Scheme 3.2). Among other popularly known methods, direct oxidative amidation of aldehyde is an advantageous approach. Recently, transition metal catalyzed aldehyde amidation *via* oxidation of intermediate carbinolamines have been



Scheme 3.2 Alternative approaches for amide synthesis

reported (Scheme 3.3a).[18,24-26] Instead, *N*-heterocyclic carbenes (NHC)[27,28] NHPI[29] and NHSI[30] have also been efficiently used as catalyst for the amidation of aldehydes through formation of active esters.

In addition to the above mentioned methods, the radical pathways where acyl- and nitrogen-centered radicals couple to construct amide have recently become very popular (Scheme 3.3b).[15,22] Lidia de Luca and co-workers have reported Cu(II) and Fe(II) catalyzed synthesis of amide starting from aldehyde and *N*-chloramines *via* radical reaction.[15,17] In addition, the metal free reagents are very popular in pharmaceutical or medicinal industries in order to minimize toxic metal contamination in drugs, to avoid the expensive metal leaching process and also to introduce environmental friendly reagents.[31,32]



Scheme 3.3 Synthesis of amide from aldehyde (a) through carbinol amine intermediate and (b) through radical (acyl and amino) pathway

Herein we present an organcatalytic solvent free cross coupling reaction for oxidative amidation of alcohols and aldehydes with *N*-chloramines under either neat or ball milling condition. In neat condition, the substrates were mixed and the reactions were executed at elevated temperature (50

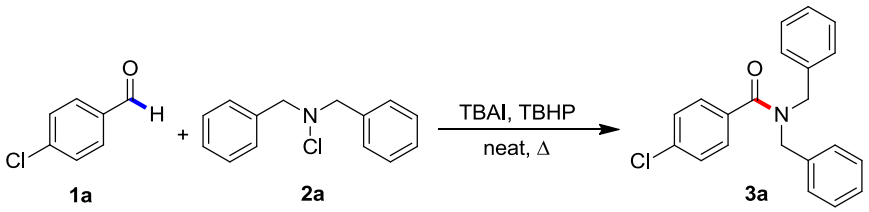
°C) but under ball milling (frequency 21 Hz) the working temperature was 27 °C (room temperature). Thus we demonstrate an unprecedented example of TBAI (tetrabutyl ammonium iodide)-TBHP (*tert*-butyl hydroperoxide)[22, 33] mediated C–H activation[34] of aldehydes.

3.3 RESULTS AND DISCUSSIONS

We have performed the reactions on 4-chlorobenzaldehyde, *N*-benzyl-*N*-chloro-1-phenylmethanamine in presence of TBAI (catalyst), TBHP (oxidant) under solvent free condition (neat) at 50 ºC. After which as a product, the *N*,*N*-dibenzyl-4-chlorobenzamide was isolated in 68% yield (Table 3.1, entry 1). To optimize the condition, we have done screening of the same reaction in presence of various catalysts and the results are shown in Table 3.1. First of all, oxidants like H_2O_2 (hydrogen peroxide), oxone, PIDA (phenyliodine diacetate), $AgNO_3$ (silver nitrate), $(NH_4)_2S_2O_8$ (ammonium persulfate) etc. are found to be less efficient compare to TBHP (Table 3.1, entry 1-6). Secondly, in absence of either catalyst or oxidant no expected product was identified (entry 7, 11). We have also established the role of counter ions by comparing TBAI with different catalyst. KI (potassium iodide), tetrabutyl ammonium bromide (*n*-Bu_4NBr) were used to understand the role of anions and NIS (N-iodosuccinimide) for cation. It is found that with KI, NIS (Table 3.1, entry 12, 15) and *n*-Bu_4NBr (Table 3.1, entry 13) the reaction did not lead the expected product in reasonably good yields. Similarly changing solvent (entry 20, 21), varying temperature (entry 22) and introducing other reagents like I_2 (entry 14), KI/I_2 (entry 16) were also not showing any encouraging improvements.

Under optimized condition, aldehydes (1.0 equivalent), *N*-chloramine (2 equivalent), TBAI (20 mol%) and TBHP (2 equivalent) worked efficiently to produce best results under neat

Table 3.1 Optimization for reaction conditions



Entry	Cat. (mol%)	Oxidant (equiv)	Yield (%)[a]
1	TBAI (25)	TBHP (1.5)	68
2	TBAI (25)	H_2O_2 (1.5)	Trace
3	TBAI (25)	Oxone (1.5)	---
4	TBAI (25)	PIDA (1.5)	Trace
5	TBAI (25)	$AgNO_3$ (1.5)	---
6	TBAI (25)	$(NH_4)_2S_2O_8$ (2)	---
7	TBAI (25)	----	---
8	TBAI (25)	TBHP (1)	59
9	TBAI (25)	TBHP (2)	77
10	TBAI (25)	TBHP (2.5)	75
11	----	TBHP (2)	---
12	KI (25)	TBHP (2)	53
13	TBAB (25)	TBHP (2)	Trace
14	I_2 (25)	TBHP (2)	23
15	NIS (25)	TBHP (2)	38
16	KI/I_2	TBHP (2)	45
17	TBAI (10)	TBHP (2)	64
18	TBAI (15)	TBHP (2)	73
19	TBAI (20)	TBHP (2)	78
20[b]	TBAI (20)	TBHP (2)	56
21[c]	TBAI (20)	TBHP (2)	62
22[d]	TBAI (20)	TBHP (2)	41

Unless specified the reactions were carried out at 50 °C; [a]isolated yield; [b]solvent THF [c]solvent acetonitrile; [d]neat at 30 °C

(solvent free) condition at 50 °C. Synthesis of various amide derivatives in reasonably good yields was achieved and the results are depicted in Figure 3.2. This methodology is efficient and amide derivatives were obtained in good yields with aldehydes having electron donating (**3b**, **3e**), electron withdrawing like nitro (**3m**), trifluoromethyl (**3d**), chloro (**3a**, **3i**), bromo (**3g**) and fluoro (**3o**) substituents etc. Furthermore, this methodology was also working well with hetero aromatic aldehyde (**3f**), aliphatic aldehydes (**3q**) and thus proved to be an important synthetic methods in the amide synthesis. On the other hand, various *N*-chloramines systems *e.g.*, primary (*N*-chloro-1-phenylmethanamine) and secondary (*N*-chloro-*N*-methyl-1-phenylmethanamine, *N*-benzyl-*N*-chloro-1-phenylmethanamine) derivatives were also affording good yields in amide synthesis.

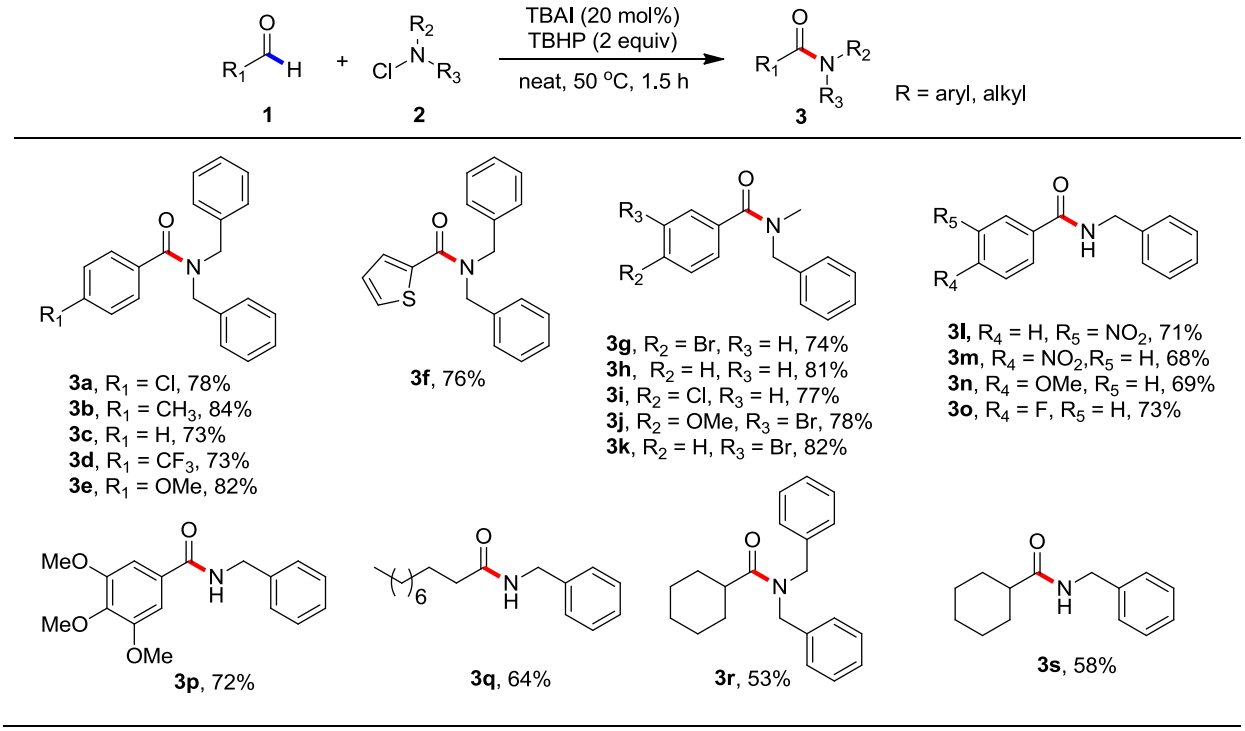
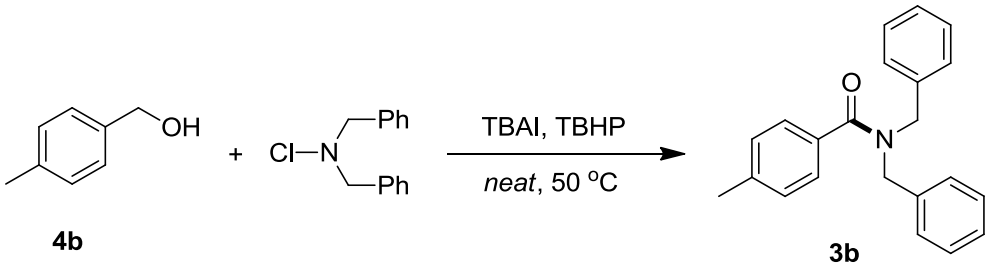


Figure 3.2 Results of amidation of aldehydes with *N*-chloramines under neat conditions.

The efficiency and convenience of this methodology have also encouraged us to further explore the scope of multistep organic synthesis.[35] The oxidative amidation of primary alcohols with *N*-chloramines in presence of TBHP (3 equivalent) and TBAI (2 equivalent) under neat condition was performed (Table 3.2, Figure 3.3). The products were isolated in relatively good yields after the two step process. In this reaction we assumed that, out of three equivalents of TBHP, one equivalent was consumed to do oxidation of alcohol to the aldehyde.

Table 3.2 Optimization for oxidative amidation of alcohols with *N*-chloramine



Entry	TBAI (mol%)	TBHP (equiv)	Time (h)	Yield[a] (%)
1	20	2	1.5	36
2	20	3	1.5	46
3	15	3	1.5	41
4	25	3	1.5	43
5	20	3	2.5	59
6	20	3	3	58

[a]isolated yield.

After the successful execution of the solvent free synthesis under neat condition, we have also explored ball milling condition. The ball milling (mechanochemical) synthesis[36-39] has drawn a significant interest due to its advantages over traditional solution-based method.[40,41] Major benefit of this process is solvent free condition and avoids any traditional workup.[41,42] This process has high impact on ecology, proved to be time saving and economical. Higher conversion of reaction,

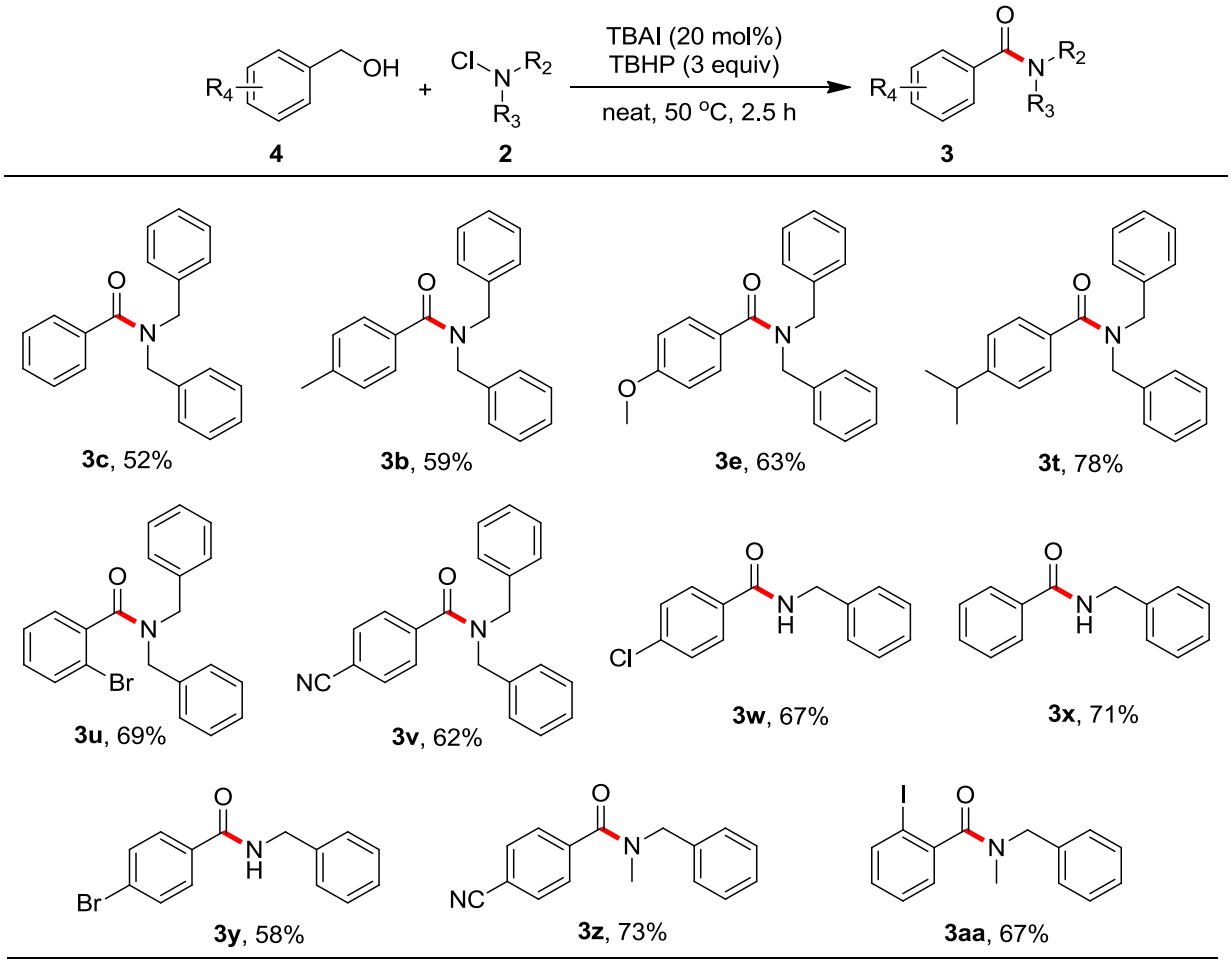


Figure 3.3 Metal-free oxidative amidation of alcohols and *N*-chloramines.

less by products and minimum/no purification bring extra importance to this procedure.[43,44] Under ball milling the reactions were done at solvent free and room temperature condition. The progresses of the reactions were monitored either by TLC or ^{1}H NMR study. The products were isolated by dissolving the reaction mixture in ethyl acetate or dichloromethane and purified by chromatographic methods. It is shown in Table 3.3 that our methodology worked well under ball milling condition and equally efficient like neat condition (Figure 3.2).

Table 3.3 Results for Amidation Aldehyde and *N*-Chloramines under Ball-Milling Conditions

entry	product	yield (%)	entry	product	yield (%)
1	**3c**	72	6	**3i**	75
2	**3e**	75	7	**3k**	69
3	**3f**	63	8	**3o**	62
4	**3u**	66	9	**3z**	71
5	**3v**	64	10	**3aa**	68

The X-ray crystal structure of the core (**3p**) of a potential antiemetic drug Tebamide (Figure 3.1) and compound **3c** is shown in Figure 3.4. These compounds were synthesized using our method.

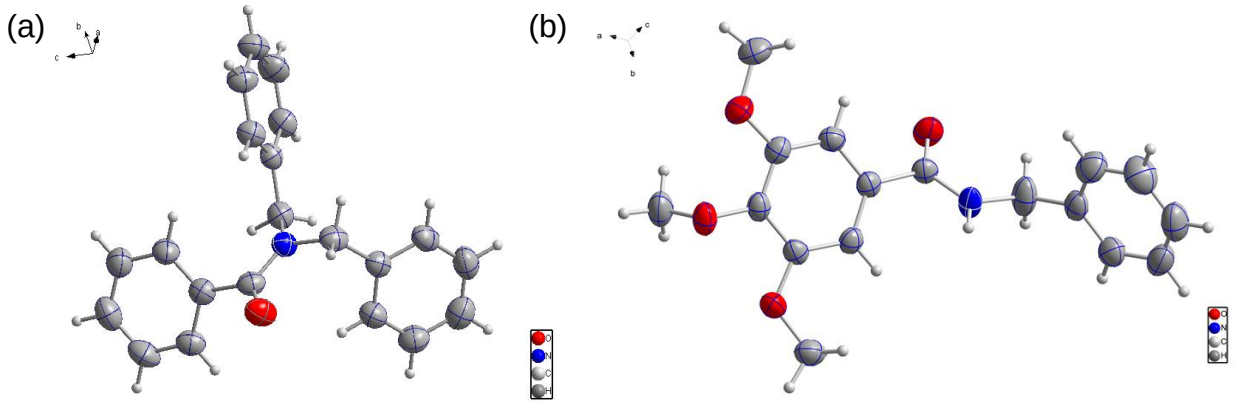
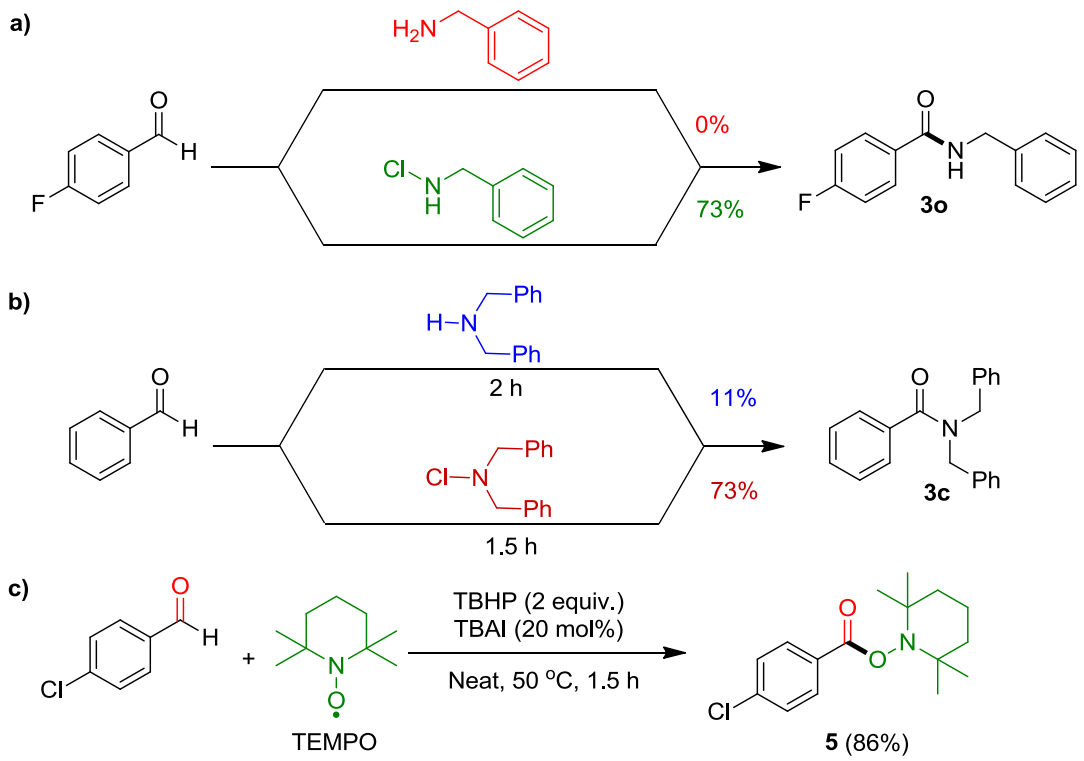


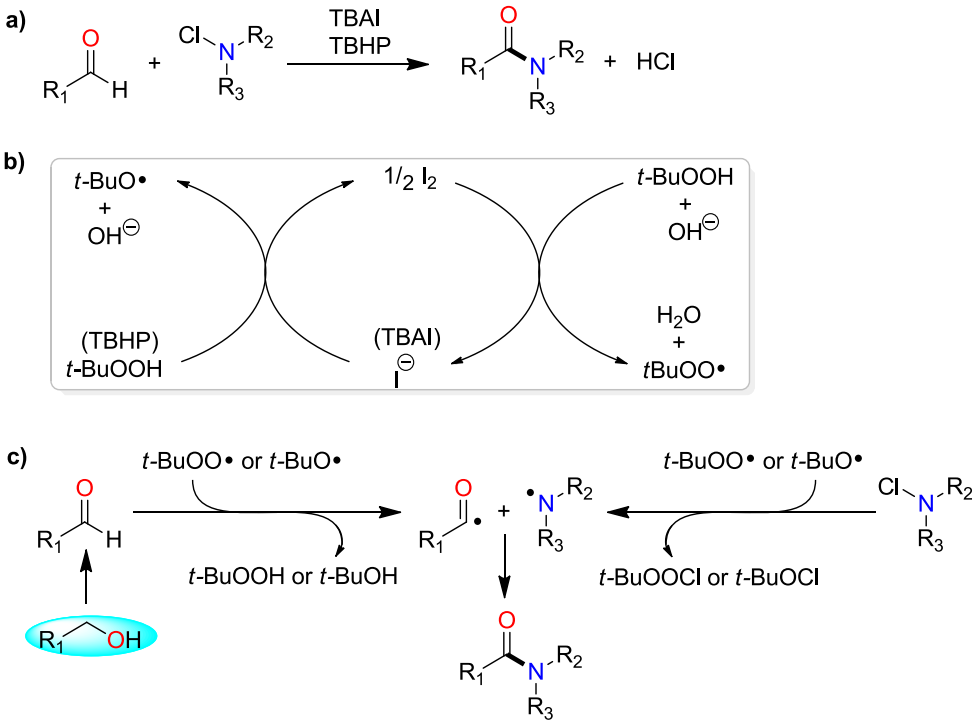
Figure 3.4 X-ray structure of (a) **3c** (CCDC 1013915) and (b) **3p** (CCDC 1016504).

To understand the mechanism of the amidation reaction, we have performed some control experiments (Scheme 3.4). Under neat reaction condition when benzylamine was used as an alternative of *N*-chloramine, no amide was obtained (Scheme 3.4a) due to the formation of imine. However, secondary amine led to only 11% of amide formation (Scheme 3.4b). As shown in Scheme 3.4c, TBAI, TBHP, benzaldehyde and TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxy radical) led to the TEMPO adduct. These results clearly indicate that the reaction proceeds *via* radical pathway.



Scheme 3.4 (a,b) *N*-Chloramine Established To Be Essential for This Reaction and (c) Formation of a TEMPO Adduct with an Aldehyde Radical

Based on the results shown in Scheme 3.4, we have proposed a plausible mechanism (Scheme 3.5) for oxidative amidation reaction (Scheme 3.5a). It has been established that the reaction goes *via* radical pathway (Scheme 3.4c). In the first step, TBAI and TBHP could generate active radicals like *tert*-butoxyl and *tert*-butylhydroperoxide (Scheme 3.5b). These radicals subsequently generate acyl radical[17,22] and amino radicals[45] from the aldehyde and *N*-chloramine, respectively. Finally, these radicals combine to lead the amide (Scheme 3.5c).



Scheme 3.5 (a) Amidation Reaction, (b) Generation of *tert*-Butoxyl and *tert*-Butylhydroperoxide Radicals, and (c) Formation of Acyl Radical and Amino Radical Followed by Recombination to the Final Product

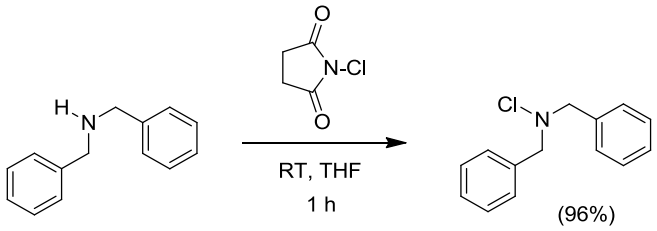
3.4 CONCLUSIONS

In summary, we have developed a mild, efficient and economical organocatalytic method for the synthesis of amides from alcohols and aldehydes using TBHP-TBAI combination under solvent free conditions. The cross coupling reaction of the aldehydes and *N*-chloramine could be demonstrated as an example of metal free C–H activation. Furthermore, this methodology shows good functional group compatibility which also uses cheap and widely accessible starting materials. Performing the reactions under ball milling condition may be considered an important addition in mechanochemical synthesis. Hence, we foresee that our study may draw significant attention to the chemists working not only on the development of synthetic methodologies but also to researchers considering for better methods under the area of organic mechanochemistry.[46]

3.5 EXPERIMENTAL SECTION

General Methods. The ball milling (21 Hz) experiments were executed under open atmosphere. Normal phase column chromatography was performed using silica-gel (mesh 100-200) and hexane-ethylacetate mixture as eluent unless otherwise specified. NMR spectra were recorded on 400 MHz instrument at 25 °C. The chemical shift values are reported in parts per million (ppm) with respect to residual chloroform (7.26 ppm for ^{1}H and 77.16 for ^{13}C). High-resolution mass spectra (HRMS) were recorded on ESI-TOF (time of flight) mass spectrometer. Infrared spectral data are reported in wave number (cm^{-1}). Melting points of the compounds were determined using digital melting point apparatus and are uncorrected.

Preparation of *N*-Chloramine (*Caution!!)* derivatives:[15]



In a representative procedure, dibenzylamine (10.4 mmol) was added to 10 mL of tetrahydrofuran followed by addition of *N*-chlorosuccinimide (11.4 mmol). The reaction mixture was allowed to stir at room temperature for 1 h. After that tetrahydrofuran was evaporated under reduced pressure and compound was extracted with 50 mL of dichloromethane after successively washed with water. The organic phase was dried over anhydrous Na_2SO_4 and solvent was evaporated under reduced pressure to isolate the desired product *N*-benzyl-*N*-chloro-1-phenylmethanamine (2.3 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.34 (m, 10H), 4.19 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 129.2, 128.5, 127.9, 67.2.

Safety issues (*Caution!!*):

***N*-chloramine.** A number of *N*-chloramines have been conveyed to be explosive.[47] However, none of the *N*-chloramine used in this paper showed any of these properties. PPEs (personal protective equipment's) should be used during preparation and use of *N*-chloramines. *N*-chloramines were stable up to few weeks when stored at -20 °C without sign of decomposition.

TBHP. As TBHP is a potential shock sensitive chemical, precautions like PPEs should be used during handling and reactions under ball milling. Herein, the TBHP was used as 70% in water and the reaction was continued for 3 h (additional 1.5 h after completion) for synthesis of 0.96 g of **3e**. Notably, we did not observe any explosion or decomposition of the materials during the reaction.

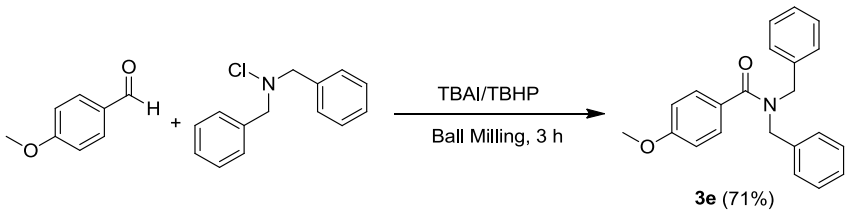
Procedure for preparation of amides under neat condition. In a typical experimental procedure, *N*-benzyl-*N*-chloro-1-phenylmethanamine (0.7 mmol) was added to a 25 mL round bottom flask charged with magnetic stirring bar and 4-chlorobenzaldehyde (0.35 mmol). TBAI (*n*-Bu_4NI, 20 mol%) and TBHP (70% in water, 0.7 mmol) were added to the mixture and the round bottom flask was kept at 50 °C (preheated oil bath). The reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the mass was dissolved in dichloromethane and purified by column chromatography to obtain *N,N*-dibenzyl-4-chlorobenzamide[48] (93 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.29 (m, 12H), 7.14 (br s, 2H), 4.71 (br s, 2H), 4.40 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 135.9, 134.6, 129.7, 128.9, 128.6, 128.3, 127.8, 126.8, 51.6, 47.2.

Procedure for the preparation of amides under ball milling. Benzaldehyde (0.29 mmol), *N*-benzyl-*N*-chloro-1-phenylmethanamine (0.59 mmol), TBAI (20 mol%), TBHP (70% in water, 0.59 mmol) and one grinding ball (15 mm diameter, ZrO_2) were placed in a 10 mL ZrO_2 milling jar. Progress of the reaction under milling condition was checked by thin layer chromatography (TLC)

or ^{1}H NMR. After which the reaction was started and this operation time was excluded from the reported reaction time. Once the reaction was completed, the mixture was dissolved in ethyl acetate or dichloromethane and compound (*N,N*-dibenzylbenzamide, yield 72%) was purified by column chromatography.

Trapping of acyl radical by TEMPO. TEMPO (0.54 mmol) was added to a 25 mL round bottom flask charged with magnetic stirring bar and 4-chlorobenzaldehyde (0.36 mmol). TBAI (*n*-Bu_4NI, 20 mol%) and TBHP (70% in water, 0.72 mmol) were added to the mixture and the round bottom flask was kept at 50 °C. The reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the mass was dissolved in dichloromethane and purified by column chromatography to obtain 2,2,6,6-tetramethylpiperidin-1-yl 4-chlorobenzoate (**5**). yield: 86% (91 mg); R_f = 0.40 (diethyl ether/hexane = 0.25:4.75); Reddish white solid; mp. 80-82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8 Hz, 2H), 7.47 (d, *J* = 8 Hz, 2H), 1.85-1.45 (m, 6H), 1.30 (s, 6H), 1.15 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 138.6, 130.2, 128.1, 127.4, 59.7, 38.3, 31.2, 20.1, 16.2; IR (KBr) $\tilde{\nu}$ 3457 (w), 2973 (s), 2935 (s), 1746 (m), 1633 (m), 1252 (m), 1071 (m), 754 (s) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{16}H_{23}ClNO_2$ (M + H^+) 296.1412, found 296.1432.

Procedure for large scale use of TBHP (*Caution!!*) under ball milling



3e (71%)

In a typical procedure, 4-methoxy benzaldehyde (0.5 mL, 4.1 mmol), *N*-benzyl-*N*-chloro-1-phenylmethanamine (1.9 g, 8.2 mmol), TBAI (0.3 g, 20 mol%), TBHP (70% in water, 1.1 mL, 8.2 mmol) and one grinding ball (15 mm diameter, ZrO_2) were placed in a 25 mL ZrO_2 milling jar.

After continuous milling of 3 h, the mass was dissolved in dichloromethane and compound (*N*,*N*-dibenzyl-4-methoxybenzamide, yield 71%) was purified by chromatography. Spectral data matches with the characterization data provided for 3e.

Compound characterization data

N,N-dibenzyl-4-chlorobenzamide (3a). R_f = 0.17 (ethyl acetate/hexane = 0.25:4.75); White solid; yield: 78% (93 mg); mp. 102-104 °C (lit.[48] 103-104 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.42 (m, 2H), 7.39-7.29 (m, 10H), 7.14 (br s, 2H), 4.70 (br s, 2H), 4.39 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 135.9, 134.6, 129.0, 128.9, 128.6, 128.4, 127.8, 127.0, 51.6, 47.3; IR (KBr) $\tilde{\nu}$ 3459 (w), 3030 (w), 2925 (w), 1637(s), 1450 (m), 1420 (m), 1258 (m), 1089 (m), 750 (m), 700 (m) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{21}H_{19}ClNO$ ($M + H^+$) 336.1150, found 336.1182.

N,N-dibenzyl-4-methylbenzamide (3b.)[49] R_f = 0.20 (ethyl acetate/hexane = 0.25:4.75); White solid; yield: 84% (112 mg); mp. 87-90 °C (no literature report on melting points); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.28 (m, 10H), 7.19 (d, *J* = 8 Hz, 4H), 4.71 (br s, 2H), 4.44 (br s, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 144.3, 139.9, 133.2, 130.2, 129.2, 128.8, 127.6, 126.9, 51.7, 47.0, 21.4; IR (KBr) $\tilde{\nu}$ 3440 (w), 3028 (w), 2923 (w), 1633 (s), 1449 (m), 1419 (m), 1259 (m), 751 (m) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{22}H_{22}NO$ ($M + H^+$) 316.1696, found 316.1716.

N,N-dibenzylbenzamide (3c). R_f = 0.20 (ethyl acetate/hexane = 0.25:4.75); White solid; yield: 73% (108 mg); mp. 113-115 °C (lit.[50] 114-115 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.31 (m, 13H), 7.16 (br s, 2H), 4.72 (br s, 2H), 4.42 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 136.2,

129.7, 128.9, 128.8, 128.7, 128.6, 128.5, 128.5, 127.7, 127.6, 127.1, 126.8, 51.6, 46.9; IR (KBr) $\tilde{\nu}$ 3442 (w), 1633 (s), 1494 (m), 1451(m), 1261 (m), 697 (s) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{21}H_{20}NO$ ($M + H^+$) 302.1539, found 302.1532.

N,N-dibenzyl-4-(trifluoromethyl)benzamide (3d).[49] R_f = 0.35 (ethyl acetate/hexane = 0.5:4.5); White solid; yield: 73% (99 mg); mp. 88-91 °C (no literature report on melting points); ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.53 (m, 4H), 7.33-7.20 (m, 8H), 7.08 (br s, 2H), 4.67 (br s, 2H), 4.30 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 139.8, 136.7, 136.0, 131.8 (q, $^2J_{FC}$ = 65.1 Hz), 129.1, 128.9, 128.6, 128.0, 127.9, 127.2, 127.0, 125.8 (q, $^3J_{FC}$ = 7.4 Hz), 123.8 (d, $^1J_{FC}$ = 271 Hz), 51.5, 47.2; IR (KBr) $\tilde{\nu}$ 3473 (w), 3063 (m), 3031 (m), 2927 (m), 1640 (s), 1451 (m), 1425 (m), 1326 (s), 1261 (m), 1167 (s), 1128 (m), 1065 (s), 850 (s), 747 (m) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{22}H_{19}F_3NO$ ($M + H^+$) 370.1413, found 370.1440.

N,N-dibenzyl-4-methoxybenzamide (3e) R_f = 0.30 (ethyl acetate/hexane = 1:4); White solid; yield: 82% (112 mg); mp. 118-120 °C (lit.[15] 120-122 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8 Hz, 2H), 7.38-7.23 (m, 10H), 6.88 (d, J = 8 Hz, 2H), 4.66 (br s, 2H), 4.49 (br s, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 160.8, 137.0, 128.8, 128.7, 128.3, 127.6, 113.9, 55.4, 51.8, 47.2; IR (KBr) $\tilde{\nu}$ 3440 (w), 2054 (w), 1632 (s), 1451 (m), 1420 (m), 1249 (s), 1029 (m), 992 (m), 839 (m), 699 (m) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{22}H_{22}NO_2$ ($M + H^+$) 332.1645, found 332.1665.

N,N-dibenzylthiophene-2-carboxamide (3f) R_f = 0.24 (ethyl acetate/hexane = 0.5:4.5); White solid; yield: 76% (125 mg); mp. 46-47 °C (lit.[50] 48-50 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d,

J = 8 Hz, 1H), 7.39-7.27 (m, 11H), 6.96 (dd, $J_1 = J_2$ = 4 Hz, 1H), 4.73 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 137.8, 136.7, 129.5, 128.9, 128.7, 127.7, 127.0, 126.8, 51.7, 49.2; IR (KBr) $\tilde{\nu}$ 3444 (w), 2880 (m), 1620 (s), 1615 (s), 1452 (m), 1427 (m), 1252 (m), 975 (s), 735 (m) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{19}H_{18}NOS$ ($M + H^+$) 308.1109, found 308.1093.

N-benzyl-4-bromo-N-methylbenzamide (3g).[51] R_f = 0.22 (ethyl acetate/hexane = 0.5:4.5); Colorless oil; yield: 74% (61 mg); 1:1 mixture of rotamers ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.44 (m, 4H), 7.39-7.30 (m, 12H), 7.16 (br s, 2H), 4.74, 4.50 (two singlets for two rotamers, 4H), 3.03, 2.86 (two singlets for two rotamers, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 133.5, 131.8, 130.2, 128.9, 128.5, 128.3, 127.8, 124.1, 55.3, 51.0, 37.1, 33.5; IR (KBr) $\tilde{\nu}$ 3466 (w), 3062 (m), 3030 (m), 2924 (s), 2854 (s), 1714 (s), 1633 (m), 1453 (m), 1402 (s), 1264 (s), 1073 (s), 1012 (s), 836 (s), 734 (m), 699 (m) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{15}H_{15}BrNO$ ($M + H^+$) 304.0332, found 304.0358.

N-benzyl-N-methylbenzamide (3h).[52] R_f = 0.27 (ethyl acetate/hexane = 1:4); Colorless oil; yield: 81% (180 mg); 1:1 mixture of rotamers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.27 (m, 18H), 7.17 (br s, 2H), 4.77, 4.51 (two singlets for two rotamers, 4H), 3.04, 2.86 (two singlets for two rotamers, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 171.7, 137.0, 136.5, 136.1, 133.0, 130.2, 130.0, 129.7, 128.8, 128.4, 128.3, 128.2, 127.6, 127.0, 126.8, 55.2, 50.8, 37.0, 33.2; IR (KBr) $\tilde{\nu}$ 3468 (w), 3060 (m), 3029 (m), 2923 (m), 1631 (s), 1450 (m), 1401 (s), 1264 (m), 1070 (s), 717 (m), 698 (m) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{15}H_{16}NO$ ($M + H^+$) 226.1226, found 226.1223.

N-benzyl-4-chloro-N-methylbenzamide (3i)[52] R_f = 0.38 (ethyl acetate/hexane = 1:4); Colorless oil; yield: 77% (70 mg); 1:1 mixture of rotamers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.29 (m, 16H), 7.17 (br s, 2H), 4.76, 4.51 (two singlets for two rotamers, 4H), 3.03, 2.86 (two singlets for two rotamers, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 171.7, 137.0, 136.6, 136.2, 135.7, 131.3, 129.7, 128.7, 128.6, 128.5, 128.2, 127.9, 127.6, 127.1, 127.0, 126.8, 126.6, 55.2, 50.9, 37.0, 33.2; IR (KBr) $\tilde{\nu}$ 3449 (w), 3062 (m), 3029 (m), 2925 (s), 2855 (m), 1717 (m), 1632 (s), 1478 (m), 1451 (m), 1401 (s), 1263 (m), 1090 (s), 1069 (s), 734 (m), 700 (s) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{15}H_{14}ClNNaO$ ($M + Na^+$) 282.0656, found 282.0687.

N-benzyl-3-bromo-4-methoxy-N-methylbenzamide (3j). R_f = 0.20 (ethyl acetate/hexane = 1:4); Colorless oil; yield: 78% (60 mg); 1:1 mixture of rotamers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.42-7.18 (m, 6H), 6.89 (br s, 1H), 4.69, 4.58 (two singlets for two rotamers, 2H), 3.90 (s, 3H), 2.94 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 157.0, 136.8, 132.6, 129.6, 128.9, 128.2, 128.0, 128.0, 127.7, 111.6, 111.4, 56.4, 55.4, 51.1, 37.2, 33.6; IR (KBr) $\tilde{\nu}$ 3459 (w), 2924 (s), 2853 (s), 1632 (m), 1600 (s), 1454 (m), 1402 (m), 1293 (s), 1262 (m), 1052 (m), 816 (m), 730 (m), 698 (m) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{16}H_{17}BrNO_2$ ($M + H^+$) 334.0437, found 334.0453.

N-benzyl-3-bromo-N-methylbenzamide (3k).[53] R_f = 0.40 (ethyl acetate/hexane = 1:4); Colorless oil; yield: 82% (107 mg); 1:1 mixture of rotamers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.52 (m, 4H), 7.45-7.28 (m, 12H), 7.23-7.15 (m, 2H), 4.74, 4.49 (two singlets for two rotamers, 4H), 3.02, 2.85 (two singlets for two rotamers, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.9, 138.1, 136.6, 136.1, 133.2, 132.7, 130.1, 130.0, 128.9, 128.8, 128.3, 128.2, 127.7, 126.7, 125.6, 125.2,

122.6, 55.2, 50.9, 37.0, 33.3; IR (KBr) $\tilde{\nu}$ 3459 (w), 3063 (m), 3030 (m), 2925 (m), 1713 (m), 1633 (s), 1562 (m), 1495 (m), 1452 (m), 1400 (m), 1255 (m), 1077 (m), 735 (m), 699 (m) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{15}H_{15}BrNO$ ($M + H^+$) 304.0332, found 304.0363.

N-benzyl-3-nitrobenzamide (3l). R_f = 0.20 (ethyl acetate/hexane = 1:4); White solid; yield: 71% (60 mg); mp. 100-103 °C (lit.[54] 100-101 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.36-8.33 (m, 1H), 8.18-8.16 (m, 1H), 7.63 (t, *J* = 8 Hz, 1H), 7.38-7.28 (m, 5H), 6.73 (br s, 1H), 4.655 (d, *J* = 4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 148.3, 137.6, 136.0, 133.4, 130.0, 129.0, 128.1, 128.0, 126.2, 121.9, 44.6; IR (KBr) $\tilde{\nu}$ 3322 (w), 3087 (m), 1720 (m), 1644 (s), 1528 (s), 1350 (s), 1322 (m), 1080 (m), 911 (m), 815 (m), 719 (m) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{14}H_{13}N_2O_3$ ($M + H^+$) 257.0921, found 257.0948.

N-benzyl-4-nitrobenzamide (3m). R_f = 0.25 (ethyl acetate/hexane = 1:4); White solid; yield: 68% (58 mg); mp. 134-137 °C (lit.[55] 136-137 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8 Hz, 2H), 7.95 (d, *J* = 8 Hz, 2H), 7.39-7.37 (m, 5H), 6.46 (br s, 1H), 4.67 (d, *J* = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 149.8, 140.0, 137.5, 129.1, 128.3, 128.2, 128.1, 124.0, 44.6; IR (KBr) $\tilde{\nu}$ 3449 (w), 2923 (s), 2848 (s), 1638 (m), 1344 (s), 1018 (s), 703 (s) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{14}H_{13}N_2O_3$ ($M + H^+$) 257.0926, found 257.0912.

N-benzyl-4-methoxybenzamide (3n). R_f = 0.20 (ethyl acetate/hexane = 1:4); White solid; yield: 69% (61 mg); mp. 128-131 °C (lit.[56] 129-130 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8 Hz, 2H), 7.36-7.28 (m, 5H), 6.92 (d, *J* = 8 Hz, 2H), 6.33 (br s, 1H), 4.635 (d, *J* = 4 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 162.3, 138.5, 128.9, 128.9, 128.0, 127.7, 126.7,

113.9, 55.5, 44.2; IR (KBr) $\tilde{\nu}$ 3521 (w), 3294 (m), 1633 (s), 1538 (m), 1505 (s), 1255 (s), 1180 (m), 846 (m), 726 (m), 696 (m) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{15}H_{16}NO_2$ ($M + H^+$) 242.1176, found 242.1189.

N-benzyl-4-fluorobenzamide (3o). R_f = 0.30 (ethyl acetate/hexane = 1:4); Off white solid; yield: 73% (79 mg); mp. 140-141 °C (lit.[57] 143-144 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8 Hz, 2H), 7.33 (br s, 5H), 7.08 (d, J = 8 Hz, 2H), 6.59 (br s, 1H), 4.61 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 164.8 (d, $^1J_{FC}$ = 250.4 Hz), 138.2, 130.6 (d, $^4J_{FC}$ = 3.1 Hz), 129.5 (d, $^3J_{FC}$ = 8.8 Hz), 128.9, 128.0, 127.7, 115.7 (d, $^2J_{FC}$ = 21.8 Hz), 44.3; IR (KBr) $\tilde{\nu}$ 3323 (m), 3068 (s), 2927 (s), 2848 (s), 1639 (m), 1544 (s), 1421 (s), 1360 (s), 1255 (s), 1057 (s), 854 (s), 723 (s) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{14}H_{13}FNO$ ($M + H^+$) 230.0981, found 230.0954.

N-benzyl-3,4,5-trimethoxybenzamide (3p). R_f = 0.20 (ethyl acetate/hexane = 1:4); White solid; yield: 72% (55 mg); mp. 139-140 °C (lit.[58] 141 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5H), 7.02 (s, 2H), 6.38 (br s, 1H), 4.645 (d, J = 4 Hz, 2H), 3.89 (s, 6H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 153.3, 141.1, 138.3, 129.9, 128.9, 128.1, 127.8, 104.5, 61.0, 56.5, 44.4; IR (KBr) $\tilde{\nu}$ 3321 (w), 2941 (m), 2838 (m), 1697 (m), 1644 (s), 1585 (s), 1500 (s), 1463 (m), 1415 (s), 1334 (s), 1232 (s), 1127 (s), 1002 (s), 764 (m), 699 (m) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{17}H_{20}NO_4$ ($M + H^+$) 302.1392, found 302.1407.

N-benzyldecanamide (3q). R_f = 0.33 (ethyl acetate/hexane = 1:4); White solid; yield: 64% (75 mg); mp. 60-61 °C (lit.[59] 60-62 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.28 (m, 5H), 5.74 (br s, 1H), 4.445 (d, J = 4 Hz, 2H), 2.21 (t, $J_1 = J_2$ = 8 Hz, 2H), 1.67-1.64 (m, 2H), 1.29-1.26 (m, 12H),

0.88 (t, $J_1 = J_2 = 8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 138.4, 128.8, 128.0, 127.6, 43.8, 37.0, 32.0, 29.5, 29.4, 29.4, 29.4, 25.9, 22.8, 14.2; IR (KBr) $\tilde{\nu}$ 3438 (w), 2919 (m), 2850 (m), 1633 (m), 695 (w) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{17}H_{28}NO$ ($M + H^+$) 262.2165, found 262.2189.

N,N-dibenzylcyclohexanecarboxamide (3r). R_f = 0.34 (ethyl acetate/hexane = 1:4); White solid; yield: 53% ; mp. 118-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 6H), 7.25 – 7.15 (m, 4H), 4.58 (s, 2H), 4.46 (s, 2H), 2.58 – 2.52 (m, 1H), 1.81-1.63 (m, 7H), 1.30 – 1.19 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 137.7, 137.0, 129.0, 128.6, 128.1, 127.7, 127.3, 126.5, 77.4, 77.1, 76.8, 49.7, 47.8, 40.9, 29.8, 25.8; IR (KBr) $\tilde{\nu}$ 3059 (s), 3029 (s), 2927 (m), 2854 (m), 1643 (m), 1494 (s), 1450 (m), 1359 (s), 1244 (s), 1205 (m), 1176 (s), 1079 (s), 1028 (s), 948 (s), 731 (s) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{21}H_{26}NO$ ($M + H^+$) 308.2009, found 308.2026.

N-benzylcyclohexanecarboxamide (3s). R_f = 0.30 (ethyl acetate/hexane = 1:4); White solid; yield: 58%; mp. 110-114 °C (lit.[60] 113 °C); 1 : 4 mixture of rotamers (data for major isomer); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, 10H), 7.25 (s, 1H), 5.73 (br s, 1H), 4.43 (d, J = 4 Hz, 2H); 2.18-2.05 (m, 1H), 1.99-1.85 (m, 2H), 1.84-1.75 (m, 2H), 1.73-1.61 (m, 2H), 1.54-1.39 (m, 2H), 1.35-1.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 138.6, 128.8, 127.8, 127.5, 45.7, 44.3, 43.5, 29.8, 25.8; IR (KBr) $\tilde{\nu}$ 3286 (m), 3085 (s), 3028 (s), 2927 (m), 2851 (s), 1639 (m), 1543 (m), 1492 (s), 1449 (s), 1311 (s), 1258 (s), 1219 (s), 1140 (s), 1079 (s), 991 (s) cm-1; HRMS (ESI-TOF) calculated for $C_{14}H_{20}NO$ ($M + H^+$) 218.1539, found 218.1545.

N,N-dibenzyl-4-isopropylbenzamide (3t). R_f = 0.30 (ethyl acetate/hexane = 0.5:4.5); White solid; yield: 78% (89 mg); mp. 80-83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8 Hz, 2H), 7.34-7.28 (m, 4H), 7.24-7.18 (m, 6H), 7.13 (br s, 2H), 4.66 (br s, 2H), 4.40 (br s, 2H), 2.95-2.78 (m, 1H), 1.19 (d, *J* = 8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 150.8, 137.1, 136.7, 133.6, 128.9, 128.8, 128.5, 127.7, 127.5, 127.1, 127.0, 126.7, 51.7, 46.9, 34.1, 23.9; IR (KBr) $\tilde{\nu}$ 3442 (w), 3031 (m), 2961 (m), 1633 (m), 1452 (m), 1417 (m), 1258 (m), 1148 (m), 993 (m), 842 (s), 733 (m), 699 (s) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{24}H_{26}NO$ (M + H$^+$) 344.2009, found 344.2042.

N,N-dibenzyl-2-bromobenzamide (3u).[61] R_f = 0.30 (ethyl acetate/hexane = 0.5:4.5); White solid; yield: 69% (70 mg); mp. 130-134 °C (no literature report on melting points); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.51 (m, 2H), 7.40-7.30 (m, 10H), 7.17 (br s, 2H), 4.73 (s, 2H), 4.42 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 136.2, 129.7, 128.9, 128.7, 128.6, 128.4, 127.7, 127.6, 127.1, 126.7, 51.6, 46.9; IR (KBr) $\tilde{\nu}$ 3436 (w), 3081 (s), 3059 (s), 3028 (s), 2923 (s), 1637 (m), 1420 (m), 1248 (m), 1144 (s), 1027 (s), 990 (s),732 (m) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{21}H_{19}BrNO$ (M + H$^+$) 380.0650, found 380.0629.

N,N-dibenzyl-4-cyanobenzamide (3v). R_f = 0.40 (ethyl acetate/hexane = 1:4); White solid; yield: 62% (76 mg); mp. 115-117 °C (lit.[50] 114-116 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.675 (d, *J* = 12 Hz, 2H), 7.57 (d, *J* = 8 Hz, 2H), 7.39-7.30 (m, 8H), 7.11 (br s, 2H), 4.72 (br s, 2H), 4.34 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 140.6, 136.5, 135.8, 132.5, 129.2, 128.9, 128.6, 128.1, 127.9, 127.5, 126.9, 118.1, 113.6, 51.5, 47.4; IR (KBr) $\tilde{\nu}$ 3442 (w), 2927 (s), 2229 (s), 1638 (m),

1425 (s),1261 (s), 1077 (s), 991 (s), 847 (s), 750 (s) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{22}H_{19}N_2O$ ($M + H^+$) 327.1497, found 327.1482.

N-benzyl-4-chlorobenzamide (3w). R_f = 0.27 (ethyl acetate/hexane = 1:4); White solid; yield: 67% (58 mg); mp. 158-160 °C (lit.[62] 162 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8 Hz, 2H), 7.39 (d, *J* = 8 Hz, 2H), 7.36-7.30 (m, 5H), 6.46 (br s, 1H), 4.625 (d, *J* = 4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 138.0, 137.9, 132.8, 131.6, 128.9, 128.5, 128.0, 127.8, 44.3; IR (KBr) $\tilde{\nu}$ 3317 (w), 1634 (m), 1416 (m), 1093 (s), 849 (s), 711 (m) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{14}H_{13}ClNO$ ($M + H^+$) 246.0686, found 246.0672.

N-benzylbenzamide (3x). R_f = 0.3 (ethyl acetate/hexane = 1:4); White solid; yield: 71% (69 mg); mp. 105-107 °C (lit.[52] 106 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8 Hz, 2H), 7.52-7.27 (m, 8H), 6.49 (br s, 1H), 4.645 (d, *J* = 4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 138.3, 134.5, 131.6, 128.9, 128.7, 128.0, 127.7, 127.0, 44.2; IR (KBr) $\tilde{\nu}$ 3329 (w), 1641 (s), 1577 (m), 1547 (m), 1418 (m), 1258 (m), 727 (m), 692 (m) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{14}H_{14}NO$ ($M + H^+$) 212.1070, found 212.1065.

N-benzyl-4-bromobenzamide (3y). R_f = 0.40 (ethyl acetate/hexane = 1:4); White solid; yield: 58% (45 mg); mp. 157-160 °C (lit.[63] 160-162 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8 Hz, 2H), 7.56 (d, *J* = 8 Hz, 2H), 7.38-7.29 (m, 5H), 6.37 (br s, 1H), 4.635 (d, *J* = 4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 138.0, 133.3, 131.9, 129.0, 128.7, 128.1, 127.9, 126.4, 44.4; IR (KBr) $\tilde{\nu}$ 3437 (w), 2918 (s), 1634 (m), 1550 (m), 1257 (s), 846 (s), 731 (s), 701 (s) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{14}H_{13}BrNO$ ($M + H^+$) 290.0181, found 290.0164.

N-benzyl-4-cyano-N-methylbenzamide (3z).[64] R_f = 0.20 (ethyl acetate/hexane = 1:4); Colorless oil; yield: 73% (67 mg); 1:1 mixture of rotamers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.64 (m, 4H), 7.54 (d, *J* = 8 Hz, 4H), 7.38-7.28 (m, 8H), 7.12 (d, *J* = 8 Hz, 2H), 4.74, 4.44 (two singlets for two rotamers, 4H), 3.05, 2.82 (two singlets for two rotamers, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 169.6, 136.4, 132.4, 129.1, 128.9, 128.8, 128.2, 128.0, 127.8, 127.7, 127.5, 126.5, 118.1, 113.4, 55.0, 50.9, 36.8, 36.4; IR (KBr) $\widetilde{\nu}$ 3454 (w), 3085 (s), 3063 (s), 3028 (s), 2925 (m), 2230 (m), 1633 (m), 1451 (m), 1402 (m), 1264 (m), 1070 (s), 850 (s), 702 (s) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{16}H_{15}N_2O$ ($M + H^+$) 251.1184, found 251.1201.

N-benzyl-2-iodo-N-methylbenzamide (3aa).[65] R_f = 0.40 (ethyl acetate/hexane = 1:4); Colorless oil; yield: 67% (60 mg); 1:1 mixture of rotamers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.29 (m, 16H), 7.18 (br s, 2H), 4.77, 4.52 (two singlets for two rotamers, 4H), 3.03, 2.86 (two singlets for two rotamers, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 171.7, 139.3, 137.1, 136.7, 136.2, 133.2, 130.1, 129.7, 128.9, 128.7, 128.5, 128.4, 128.3, 127.9, 127.6, 127.3, 127.1, 126.9, 55.3, 50.9, 37.1, 33.3; IR (KBr) $\widetilde{\nu}$ 3459 (w), 3061 (m), 3029 (m), 2923 (m), 1631 (s), 1479 (m), 1450 (m), 1400 (m), 1264 (m), 1069 (s), 718 (m), 698 (s) cm^{-1}; HRMS (ESI-TOF) calculated for $C_{15}H_{15}INO$ ($M + H^+$) 352.0193, found 352.0165.

3.6 NOTES AND REFERENCES

1. Roy, S.; Roy, S.; Gribble, G. W., *Tetrahedron* **2012,** *68*, 9867-9923.
2. Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y., *Green Chem.* **2007,** *9*, 411-420.
3. Montalbetti, C. A. G. N.; Falque, V., *Tetrahedron* **2005,** *61*, 10827-10852.
4. Valeur, E.; Bradley, M., *Chem. Soc. Rev.* **2009,** *38*, 606-631.
5. Ishihara, K.; Ohara, S.; Yamamoto, H., *J. Org. Chem.* **1996,** *61*, 4196-4197.
6. Allen, C. L.; Chhatwal, A. R.; Williams, J. M. J., *Chem. Commun.* **2012,** *48*, 666-668.
7. Saxon, E.; Bertozzi, C. R., *Science* **2000,** *287*, 2007-2010.
8. Nilsson, B. L.; Kiessling, L. L.; Raines, R. T., *Org. Lett.* **2000,** *2*, 1939-1941.
9. Ribelin, T.; Katz, C. E.; English, D. G.; Smith, S.; Manukyan, A. K.; Day, V. W.; Neuenswander, B.; Poutsma, J. L.; Aubé, J., *Angew. Chem. Int. Ed.* **2008,** *47*, 6233-6235.
10. Owston, N. A.; Parker, A. J.; Williams, J. M. J., *Org. Lett.* **2007,** *9*, 3599-3601.
11. Hashimoto, M.; Obora, Y.; Sakaguchi, S.; Ishii, Y., *J. Org. Chem.* **2008,** *73*, 2894-2897.
12. Brennführer, A.; Neumann, H.; Beller, M., *Angew. Chem. Int. Ed.* **2009,** *48*, 4114-4133.
13. Dang, T. T.; Zhu, Y.; Ghosh, S. C.; Chen, A.; Chai, C. L. L.; Seayad, A. M., *Chem. Commun.* **2012,** *48*, 1805-1807.
14. Gunanathan, C.; Ben-David, Y.; Milstein, D., *Science* **2007,** *317*, 790-792.
15. Cadoni, R.; Porcheddu, A.; Giacomelli, G.; De Luca, L., *Org. Lett.* **2012,** *14*, 5014-5017.
16. Ghosh, S. C.; Ngiam, J. S. Y.; Seayad, A. M.; Tuan, D. T.; Chai, C. L. L.; Chen, A., *J. Org. Chem.* **2012,** *77*, 8007-8015.
17. Porcheddu, A.; Luca, L. D., *Adv. Synth. Catal.* **2012,** *354*, 2949-2953.

18. Ghosh, S. C.; Ngiam, J. S. Y.; Chai, C. L. L.; Seayad, A. M.; Dang, T. T.; Chen, A., *Adv. Synth. Catal.* **2012,** *354*, 1407-1412.

19. Vanjari, R.; Guntreddi, T.; Singh, K. N., *Green Chem.* **2014,** *16*, 351-356.

20. Zhang, M.; Wu, X.-F., *Tetrahedron Lett.* **2013,** *54*, 1059-1062.

21. Seo, S.; Marks, T. J., *Org. Lett.* **2008,** *10*, 317-319.

22. Liu, Z.; Zhang, J.; Chen, S.; Shi, E.; Xu, Y.; Wan, X., *Angew. Chem. Int. Ed.* **2012,** *51*, 3231-3235.

23. Tillack, A.; Rudloff, I.; Beller, M., *Eur. J. Org. Chem.* **2001,** *2001*, 523-528.

24. Allen, C. L.; Williams, J. M. J., *Chem. Soc. Rev.* **2011,** *40*, 3405-3415.

25. Pattabiraman, V. R.; Bode, J. W., *Nature* **2011,** *480*, 471-479.

26. Yoo, W.-J.; Li, C.-J., *J. Am. Chem. Soc.* **2006,** *128*, 13064-13065.

27. Vora, H. U.; Rovis, T., *J. Am. Chem. Soc.* **2007,** *129*, 13796-13797.

28. Bode, J. W.; Sohn, S. S., *J. Am. Chem. Soc.* **2007,** *129*, 13798-13799.

29. Tan, B.; Toda, N.; Barbas, C. F., *Angew. Chem. Int. Ed.* **2012,** *51*, 12538-12541.

30. Yao, H.; Tang, Y.; Yamamoto, K., *Tetrahedron Lett.* **2012,** *53*, 5094-5098.

31. Garrett, C. E.; Prasad, K., *Adv. Synth. Catal.* **2004,** *346*, 889-900.

32. Welch, C. J.; Albaneze-Walker, J.; Leonard, W. R.; Biba, M.; DaSilva, J.; Henderson, D.; Laing, B.; Mathre, D. J.; Spencer, S.; Bu, X.; Wang, T., *Org. Process Res. Dev.* **2005,** *9*, 198-205.

33. Wu, X. F.; Gong, J. L.; Qi, X., *Org. Biomol. Chem.* **2014,** *12*, 5807-5817.

34. Wang, J.; Liu, C.; Yuan, J.; Lei, A., *Chem. Commun.* **2014,** *50*, 4736-4739.

35. Wessjohann, L. A.; Rivera, D. G.; Vercillo, O. E., *Chem. Rev.* **2009,** *109*, 796-814.

36. Varma, R. S., *Green Chem.* **2014,** *16*, 2027-2041.

37. Baig, R. B. N.; Varma, R. S., *Chem. Soc. Rev.* **2012,** *41*, 1559-1584.

38. Stolle, A.; Szuppa, T.; Leonhardt, S. E. S.; Ondruschka, B., *Chem. Soc. Rev.* **2011,** *40*, 2317-2329.

39. Wang, G.-W., *Chem. Soc. Rev.* **2013,** *42*, 7668-7700.

40. Ley, S.; O'Brien, M.; *Synthesis* **2011**, 1157-1192.

41. Achar, T. K.; Maiti, S.; Mal, P., *RSC Adv.* **2014,** *4*, 12834-12839.

42. Bose, A.; Mal, P., *Tetrahedron Lett.* **2014,** *55*, 2154-2156.

43. Beyer, M. K.; *Chem. Rev.* **2005,** *105*, 2921-2948.

44. Tanaka, K.; Toda, F., *Chem. Rev.* **2000,** *100*, 1025-1074.

45. Minisci, F., *Synthesis* **1973,** *1973*, 1-24.

46. James, S. L.; Adams, C. J.; Bolm, C.; Braga, D.; Collier, P.; Friscic, T.; Grepioni, F.; Harris, K. D. M.; Hyett, G.; Jones, W.; Krebs, A.; Mack, J.; Maini, L.; Orpen, A. G.; Parkin, I. P.; Shearouse, W. C.; Steed, J. W.; Waddell, D. C., *Chem. Soc. Rev.* **2012,** *41*, 413-447.

47. Guillemin, J. C.; Denis, J. M., *Synthesis* **1985,** *1985*, 1131-1133.

48. Barbe, G.; Charette, A. B., *J. Am. Chem. Soc.* **2008,** *130*, 18-9.

49. Zhou, S.; Junge, K.; Addis, D.; Das, S.; Beller, M., *Angew. Chem. Int. Ed.* **2009,** *48*, 9507-9510.

50. Porcheddu, A.; Luca, L. D., *Adv. Synth. Catal.* **2012,** *354*, 2949-2953.

51. Li, H.; Xie, J.; Xue, Q.; Cheng, Y.; Zhu, C., *Tetrahedron Lett.* **2012,** *53*, 6479-6482.

52. Wang, J.; Li, J.; Xu, F.; Shen, Q., *Adv. Synth. Catal.* **2009,** *351*, 1363-1370.

53. Dubois, N.; Glynn, D.; McInally, T.; Rhodes, B.; Woodward, S.; Irvine, D. J.; Dodds, C., *Tetrahedron* **2013,** *69*, 9890-9897.

54. Agwada, V. C., *J. Chem. Eng. Data* **1982,** *27*, 479-481.

55. Katritzky, A. R.; Cai, C.; Singh, S. K., *J. Org. Chem.* **2006,** *71*, 3375-3380.

56. Martinelli, J. R.; Clark, T. P.; Watson, D. A.; Munday, R. H.; Buchwald, S. L., *Angew. Chem. Int. Ed.* **2007,** *46*, 8460-8463.

57. Mamat, C.; Flemming, A.; Köckerling, M.; Steinbach, J.; Wuest, F. R., *Synthesis* **2009**, 3311-3321.

58. Baker, W.; Glockling, F., *J. Chem. Soc.* **1950**, 2759-64.

59. Perreux, L.; Loupy, A.; Volatron, F., *Tetrahedron* **2002,** *58*, 2155-2162.

60. Maki, T.; Ishihara, K.; Yamamoto, H., *Org. Lett.* **2006,** *8*, 1431-1434.

61. Hiroi, K.; Suzuki, Y.; Abe, I.; Hasegawa, Y.; Suzuki, K., *Tetrahedron: Asymmetry* **1998,** *9*, 3797-3817.

62. Cui, X.; Zhang, Y.; Shi, F.; Deng, Y., *Chem. Eur. J.* **2011,** *17*, 1021-1028.

63. Petricci, E.; Mugnaini, C.; Radi, M.; Corelli, F.; Botta, M., *J. Org. Chem.* **2004,** *69*, 7880-7887.

64. Ekoue-Kovi, K.; Wolf, C., *Org. Lett.* **2007,** *9*, 3429-3432.

65. Matsumoto, S.; Takada, D.; Kageyama, H.; Akazome, M., *Tetrahedron Lett.* **2014,** *55*, 1082-1085.

^{1}H and ^{13}C NMR Spectra

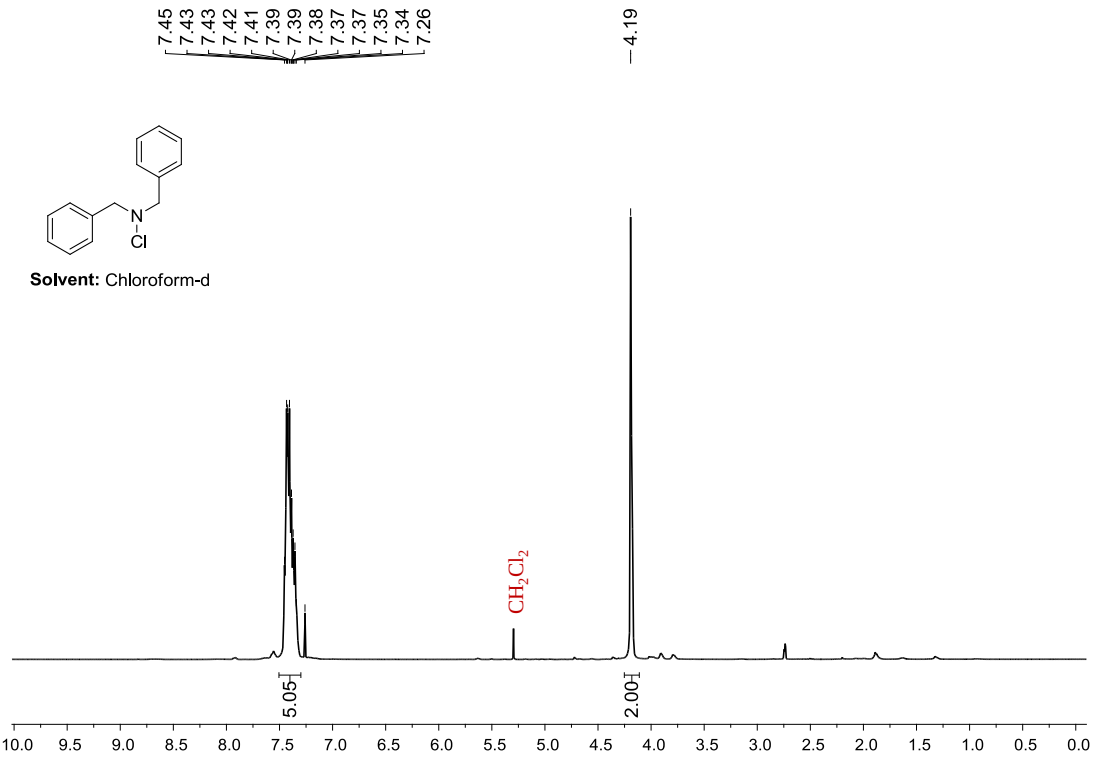


Figure 3.5 ^{1}H NMR spectrum of *N*-benzyl-*N*-chloro-1-phenylmethanamine

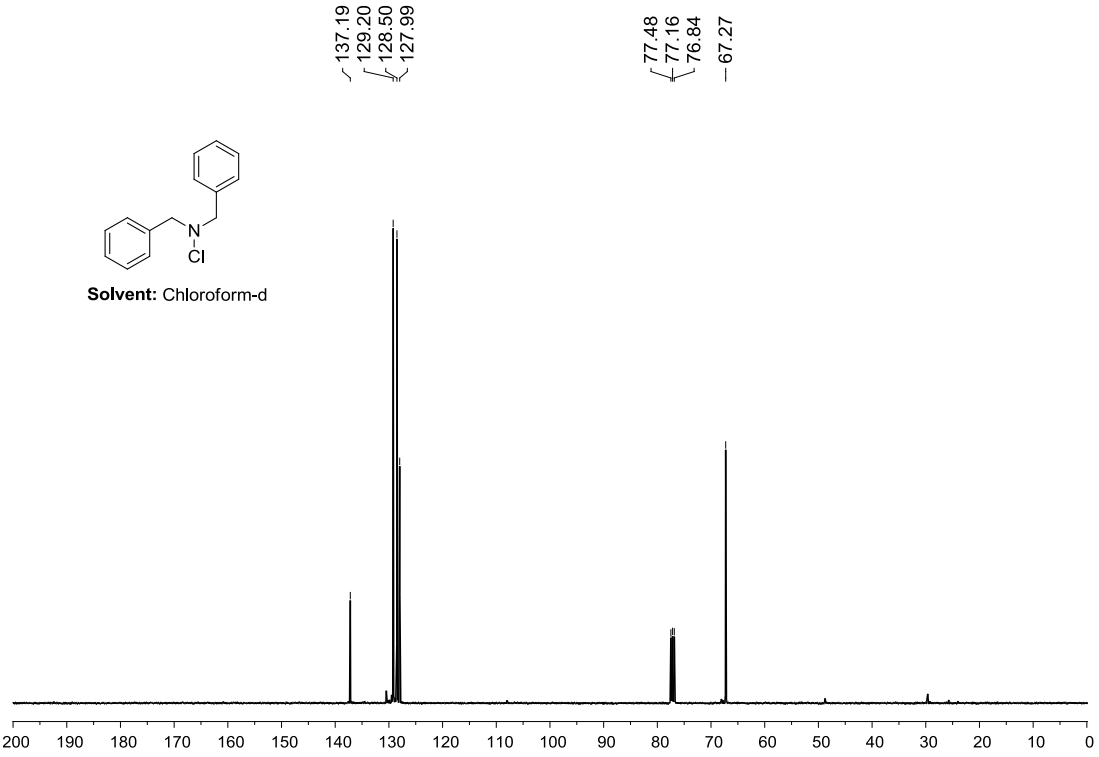


Figure 3.6 ^{13}C NMR spectrum of *N*-benzyl-*N*-chloro-1-phenylmethanamine

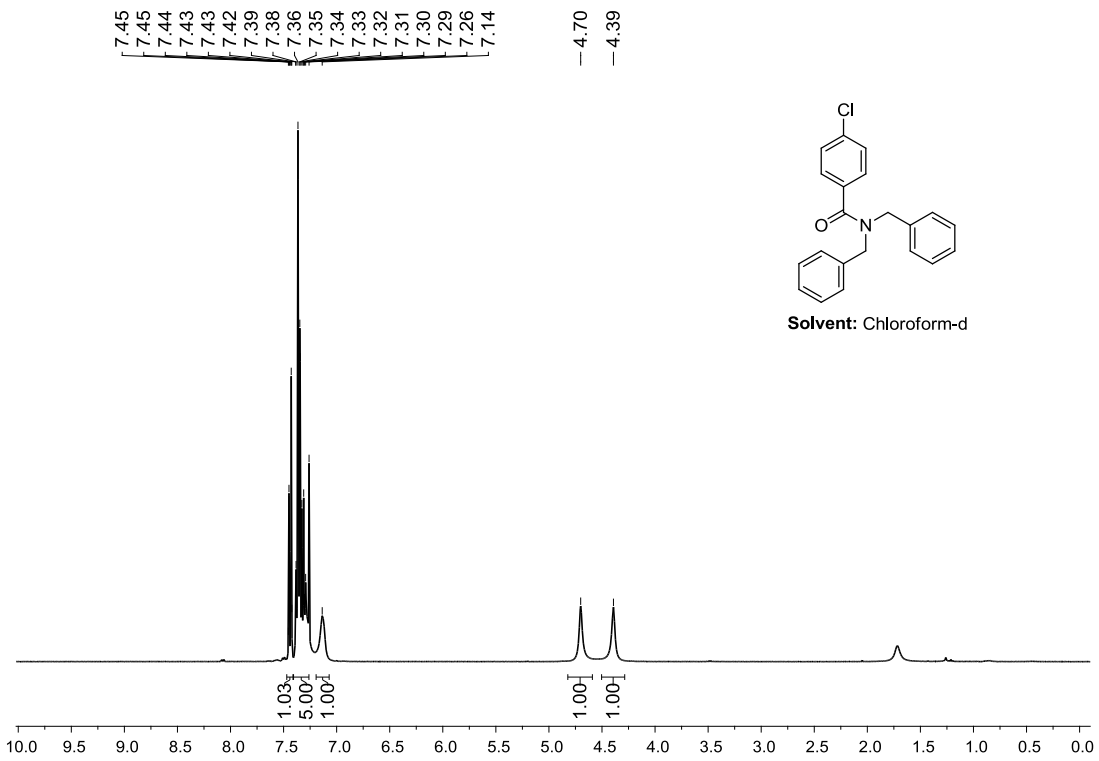


Figure 3.7 ^{1}H NMR spectrum of *N*,*N*-dibenzyl-4-chlorobenzamide (**3a**).

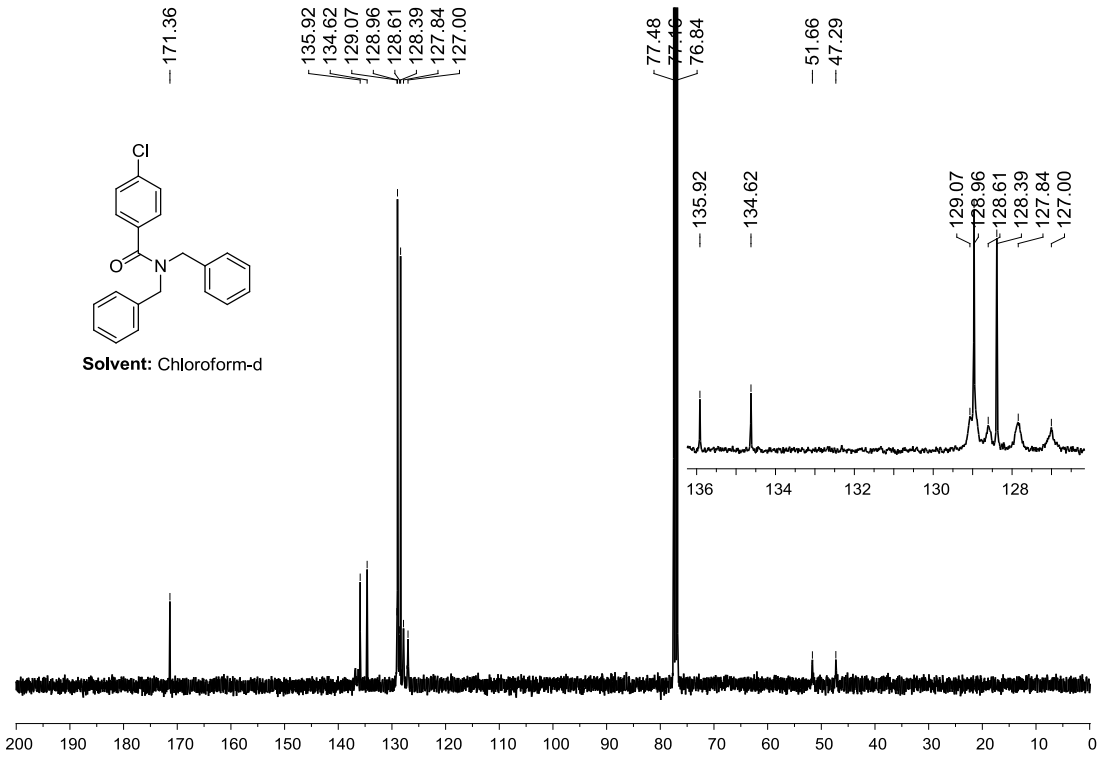


Figure 3.8 ^{13}C NMR spectrum of *N*,*N*-dibenzyl-4-chlorobenzamide (**3a**).

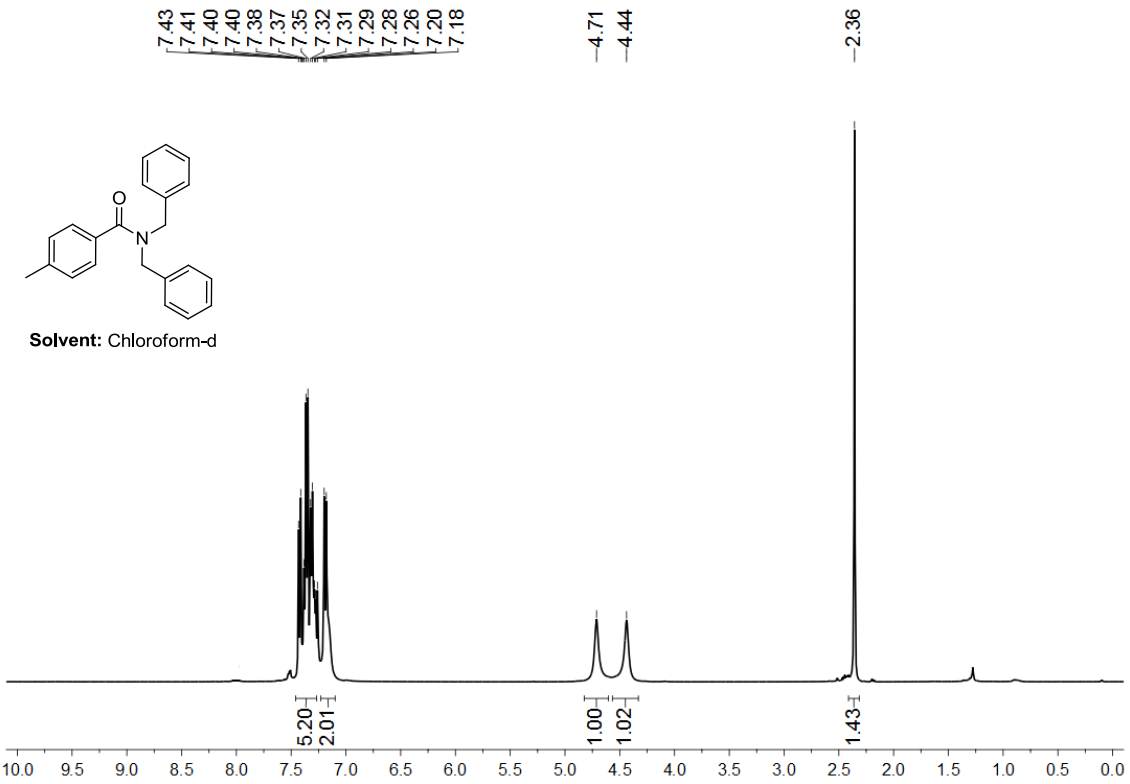


Figure 3.9 ^{1}H NMR spectrum of *N*,*N*-dibenzyl-4-methylbenzamide (**3b**).

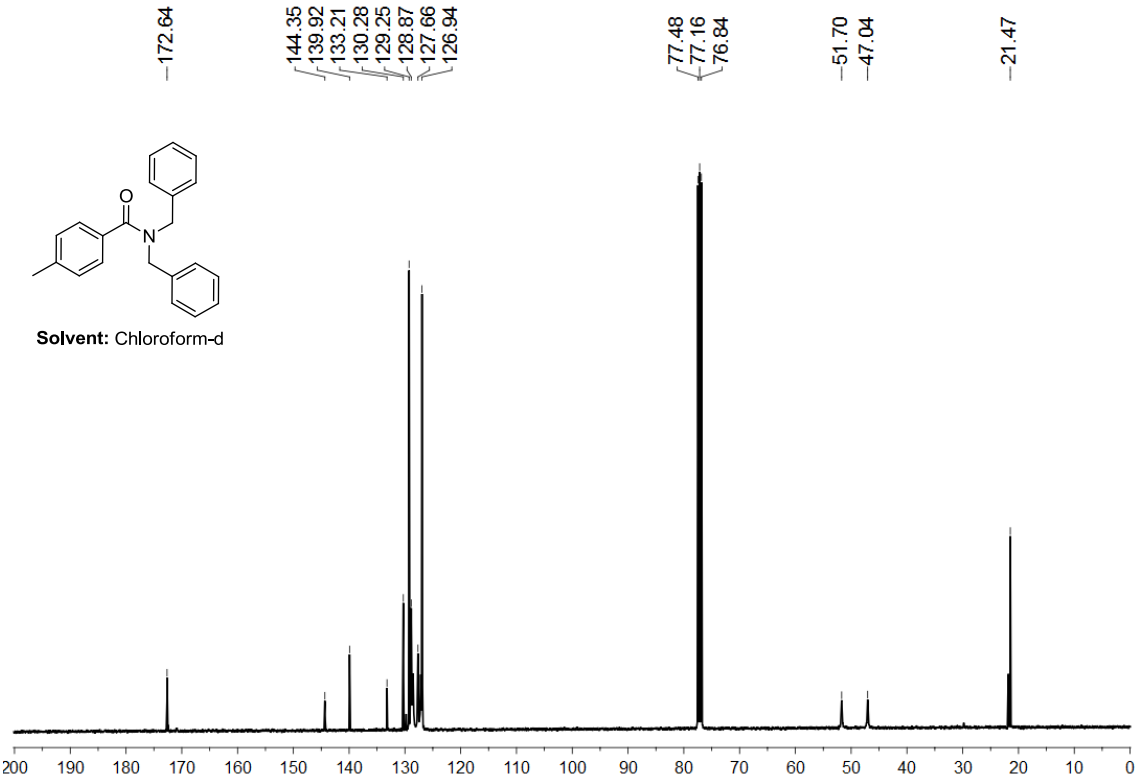


Figure 3.10 ^{13}C NMR spectrum of *N*,*N*-dibenzyl-4-methylbenzamide (**3b**).

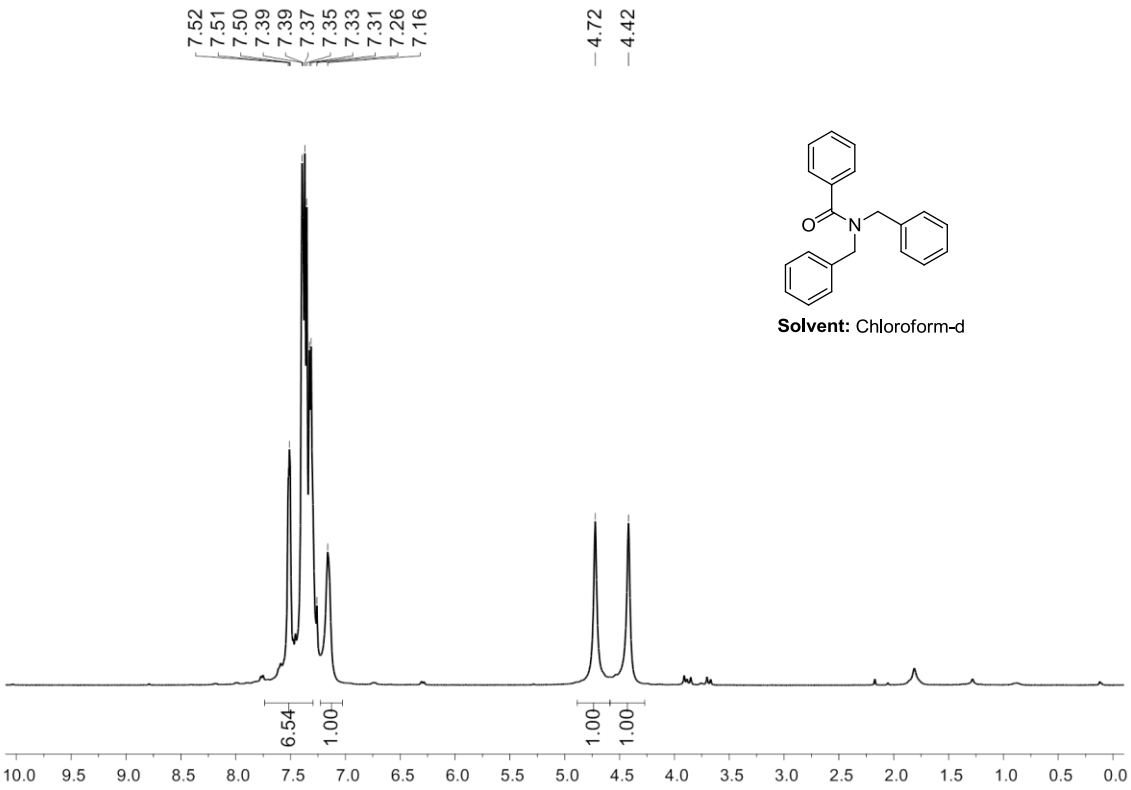


Figure 3.11 ^{1}H NMR spectrum of *N*,*N*-dibenzylbenzamide (**3c**).

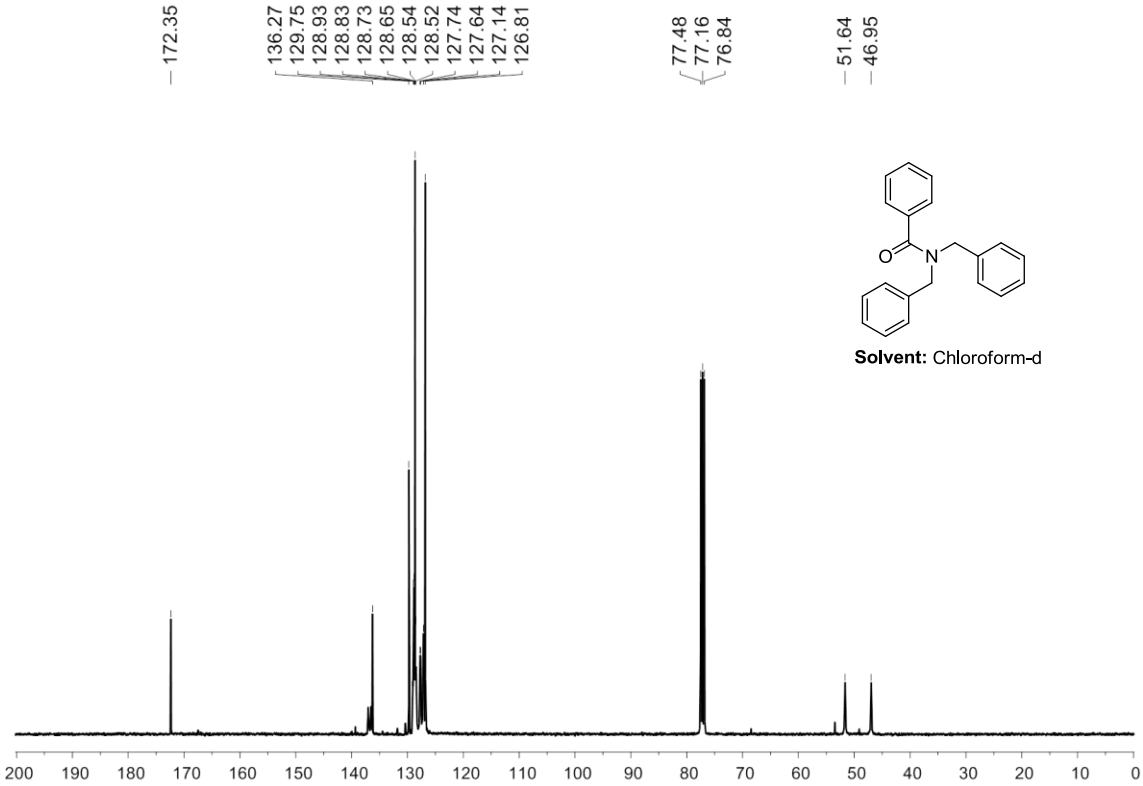


Figure 3.12 ^{13}C NMR spectrum of *N*,*N*-dibenzylbenzamide (**3c**).

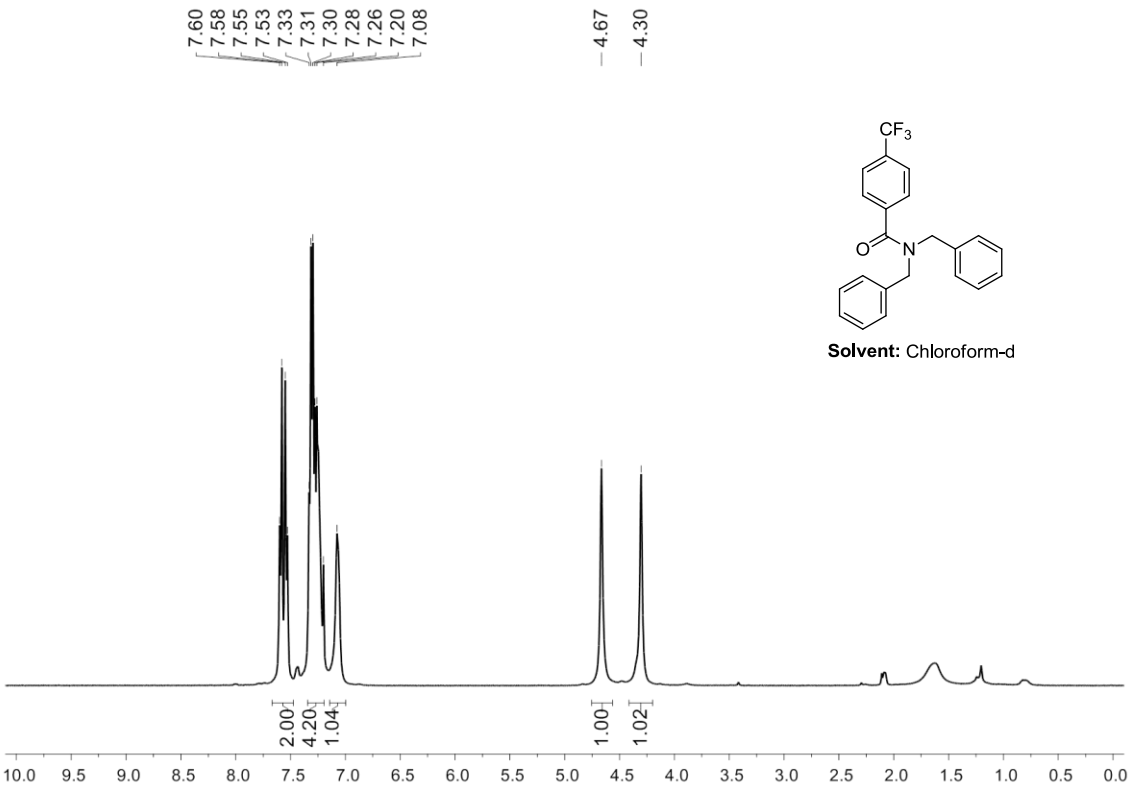


Figure 3.13 ^{1}H NMR spectrum of *N*,*N*-dibenzyl-4-(trifluoromethyl)benzamide (**3d**).

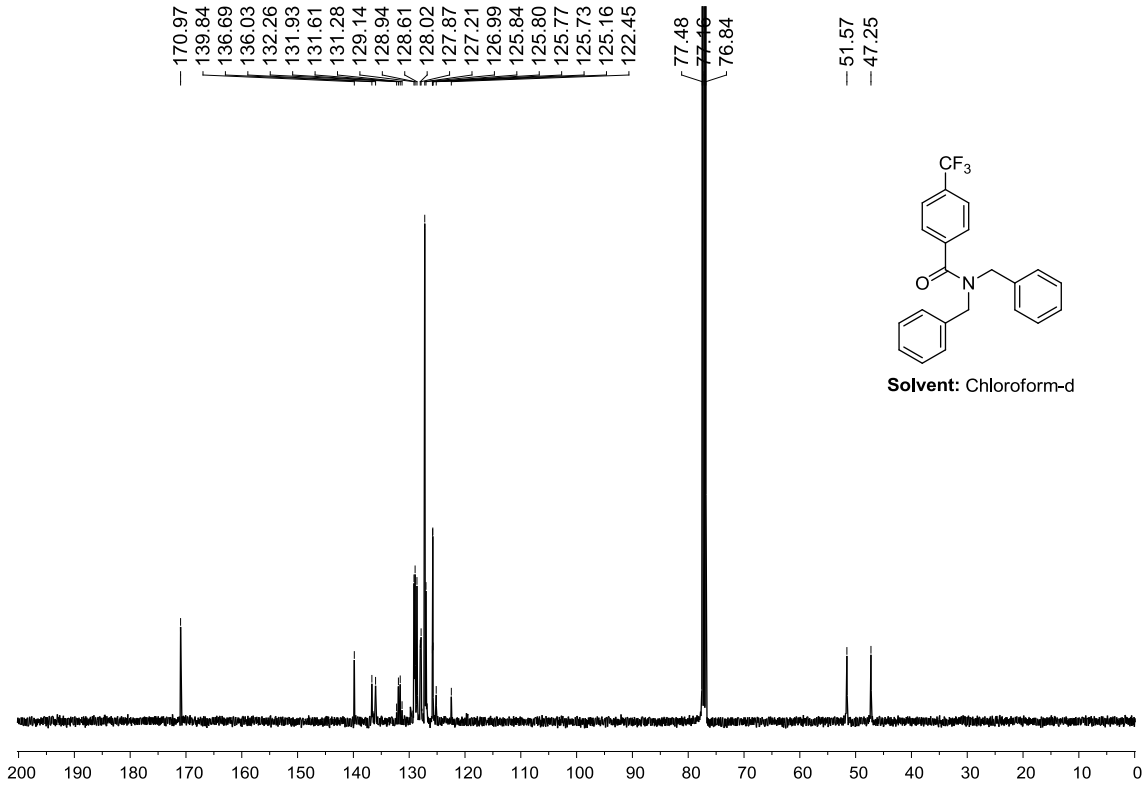


Figure 3.14 ^{13}C NMR spectrum of *N*,*N*-dibenzyl-4-(trifluoromethyl)benzamide (**3d**).

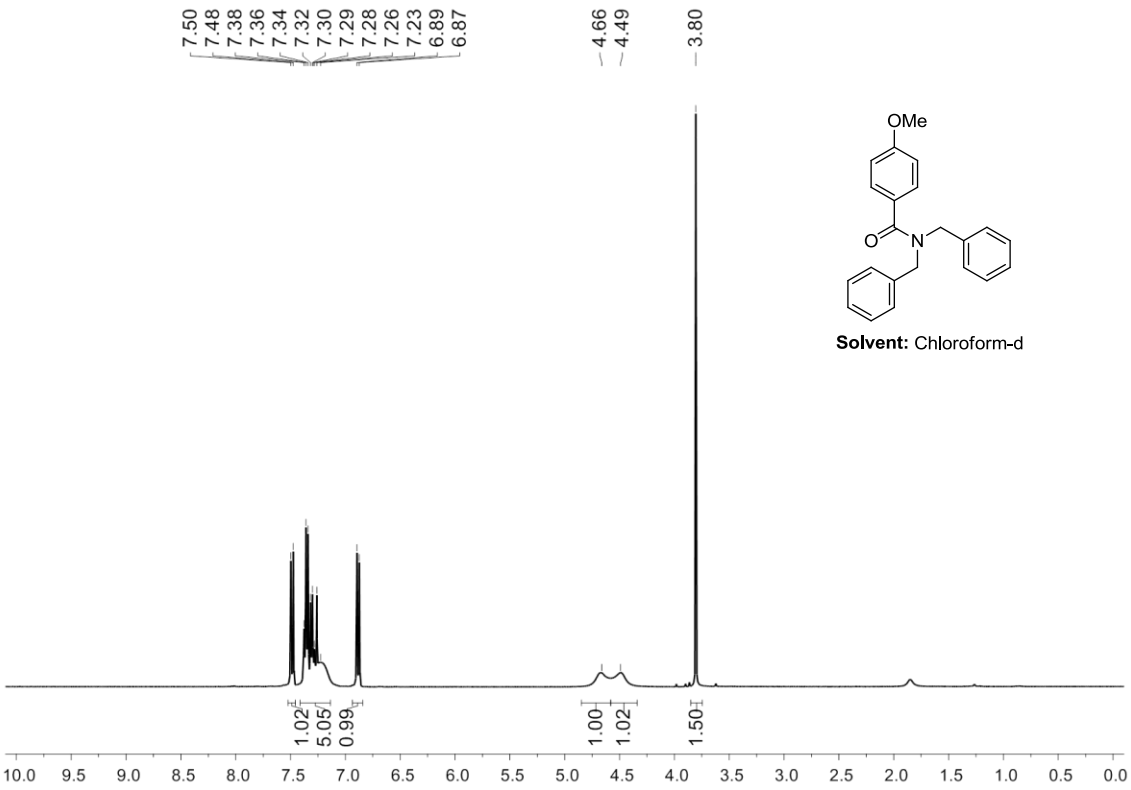


Figure 3.15 ^{1}H NMR spectrum of *N*,*N*-dibenzyl-4-methoxybenzamide (**3e**).

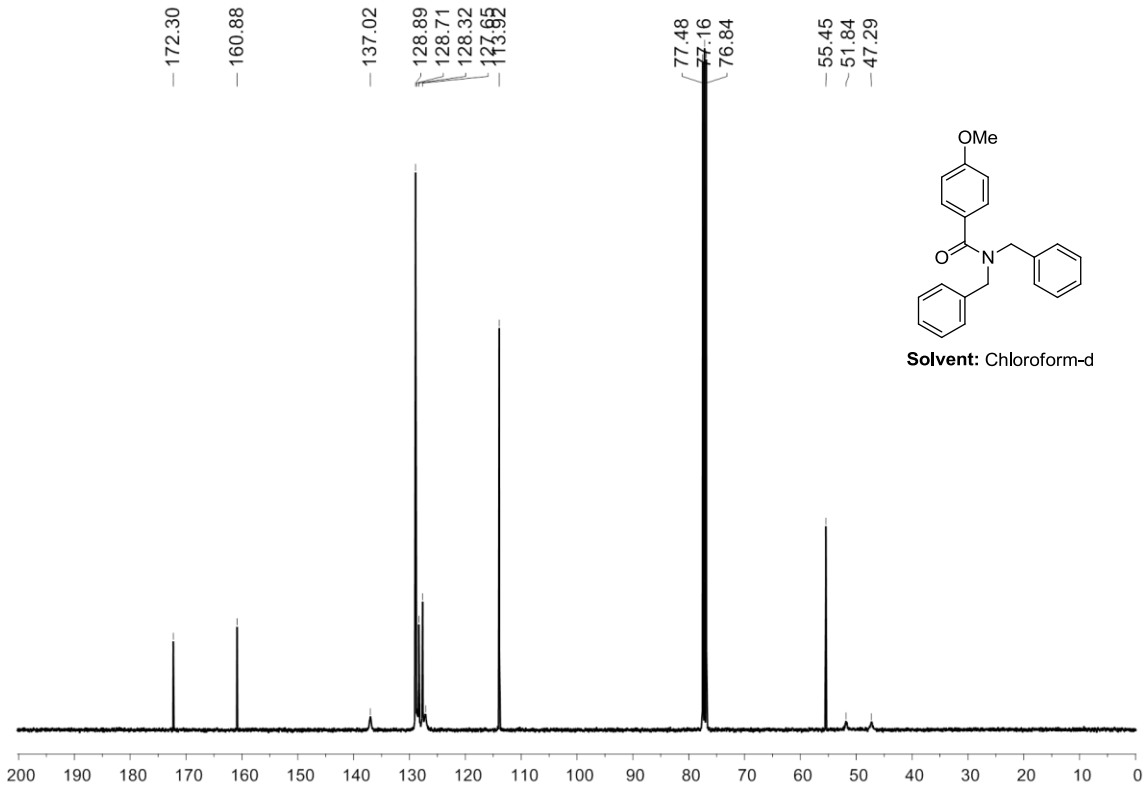


Figure 3.16 ^{13}C NMR spectrum of *N*,*N*-dibenzyl-4-methoxybenzamide (**3e**).

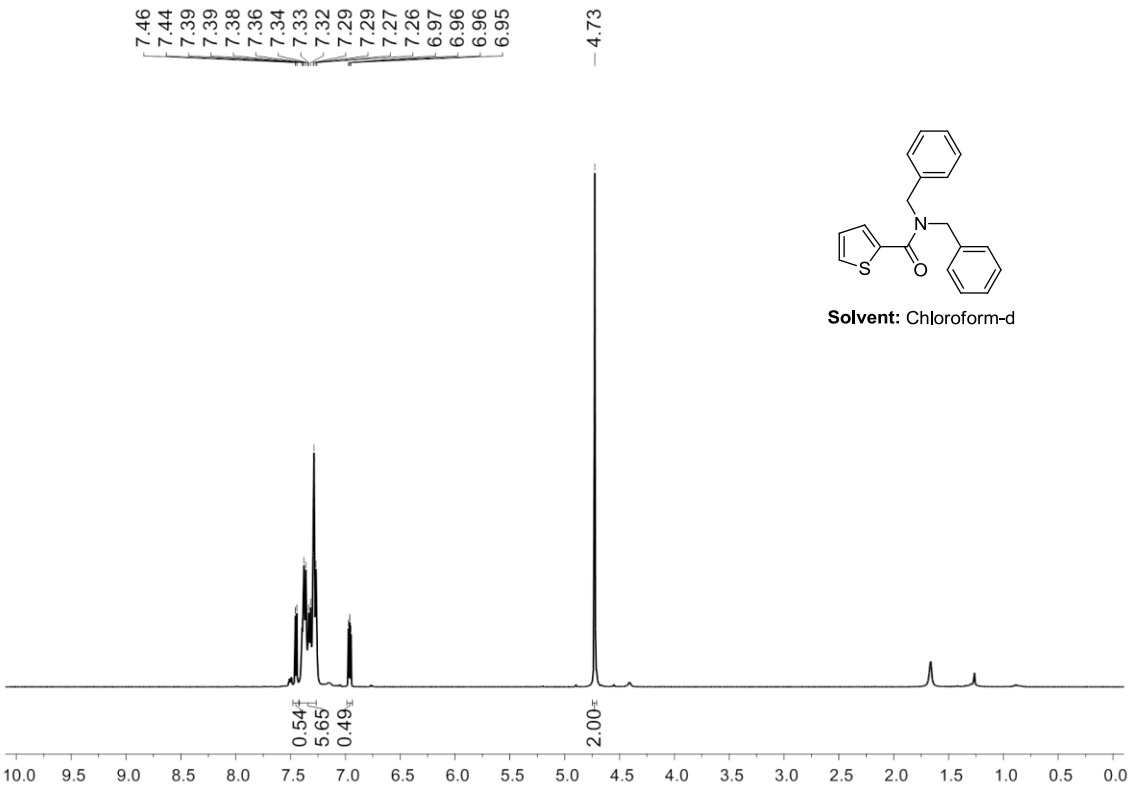


Figure 3.17 ^{1}H NMR spectrum of *N*,*N*-dibenzylthiophene-2-carboxamide (**3f**).

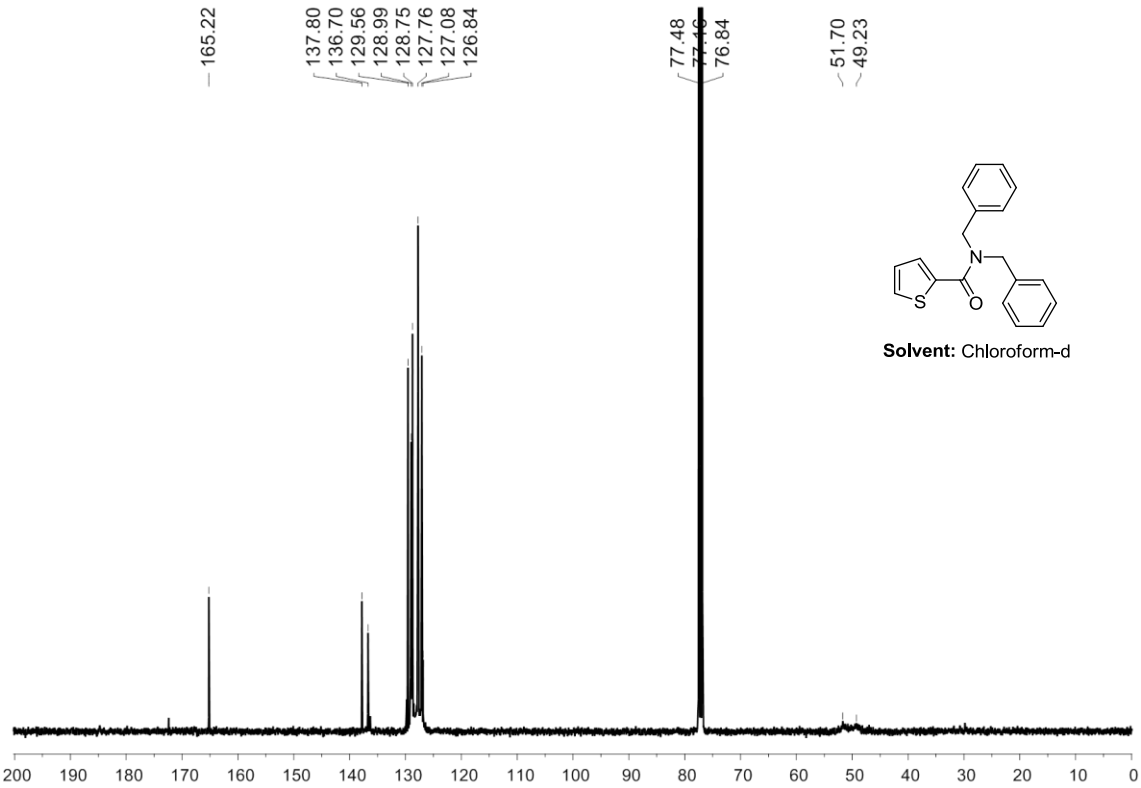


Figure 3.18 ^{13}C NMR spectrum of *N*,*N*-dibenzylthiophene-2-carboxamide (**3f**).

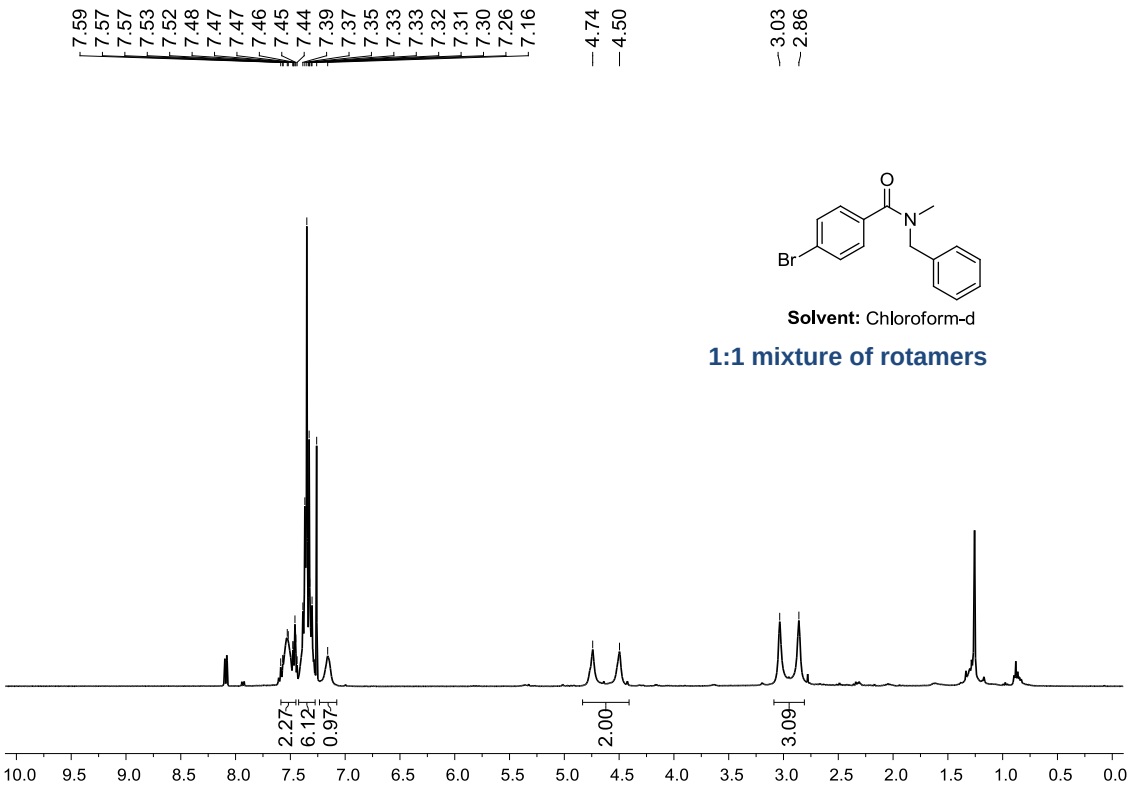


Figure 3.19 ^{1}H NMR spectrum of *N*-benzyl-4-bromo-*N*-methylbenzamide (**3g**).

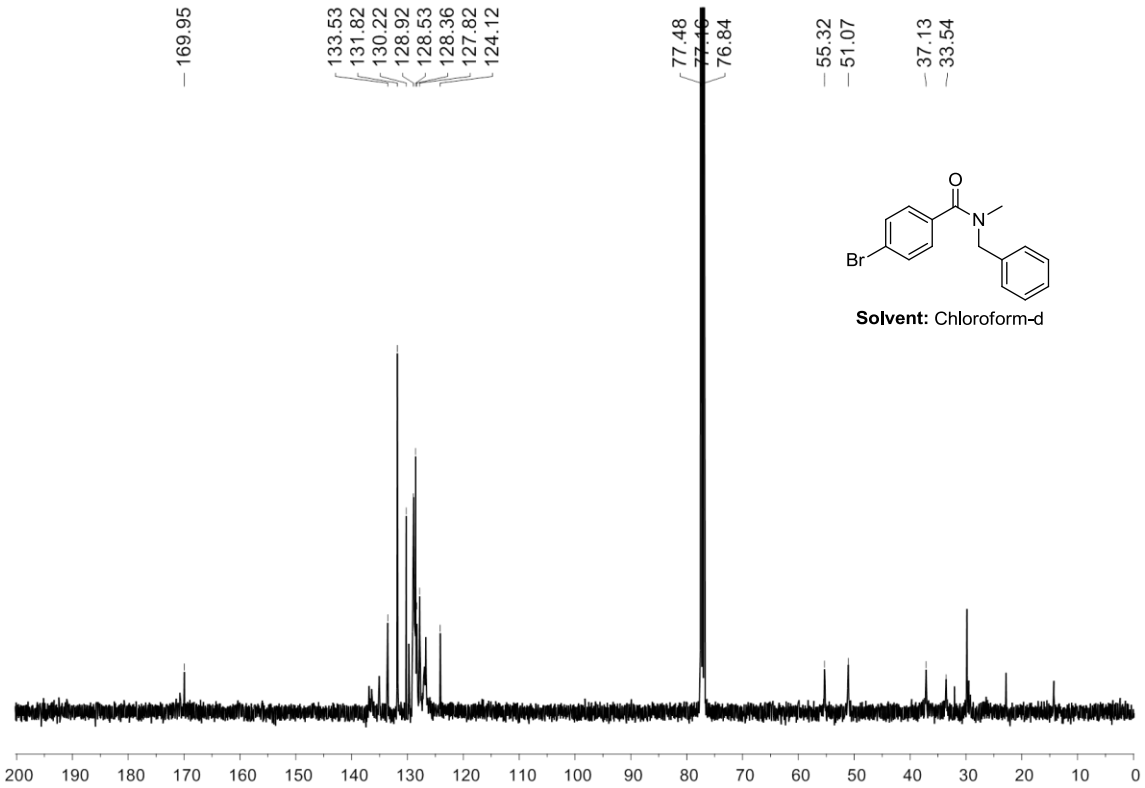


Figure 3.20 ^{13}C NMR spectrum of *N*-benzyl-4-bromo-*N*-methylbenzamide (**3g**).

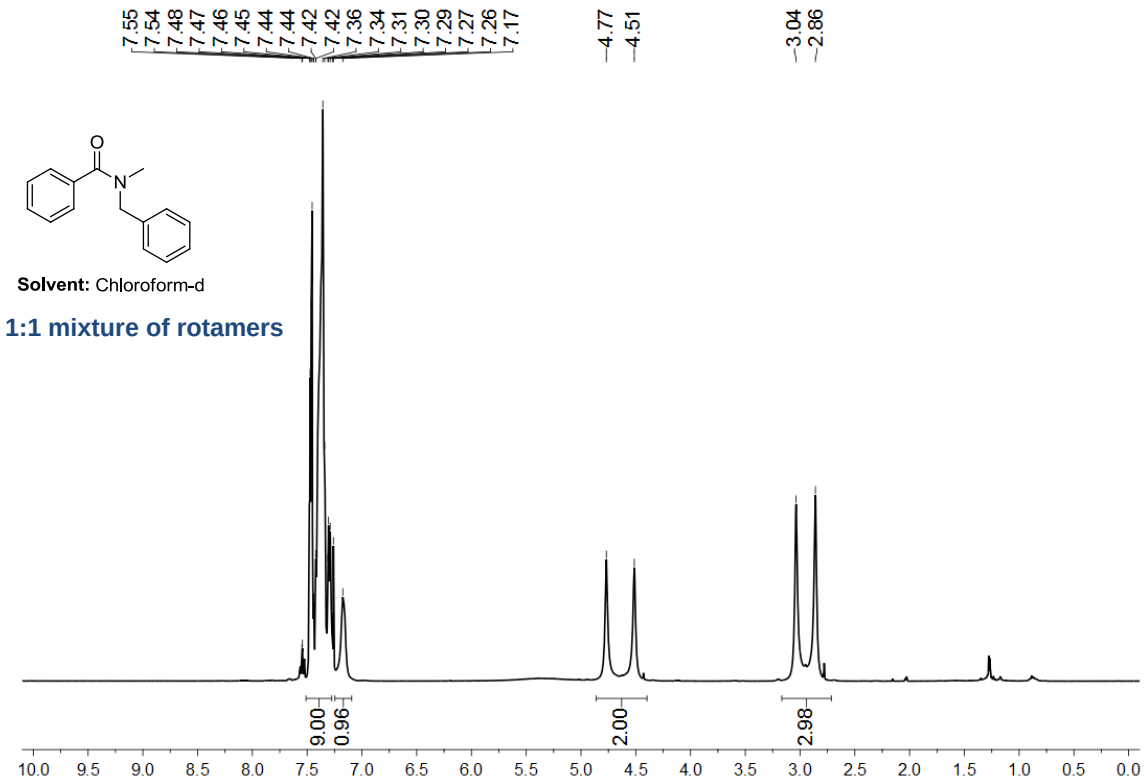


Figure 3.21 ^{1}H NMR spectrum of *N*-benzyl-*N*-methylbenzamide (**3h**).

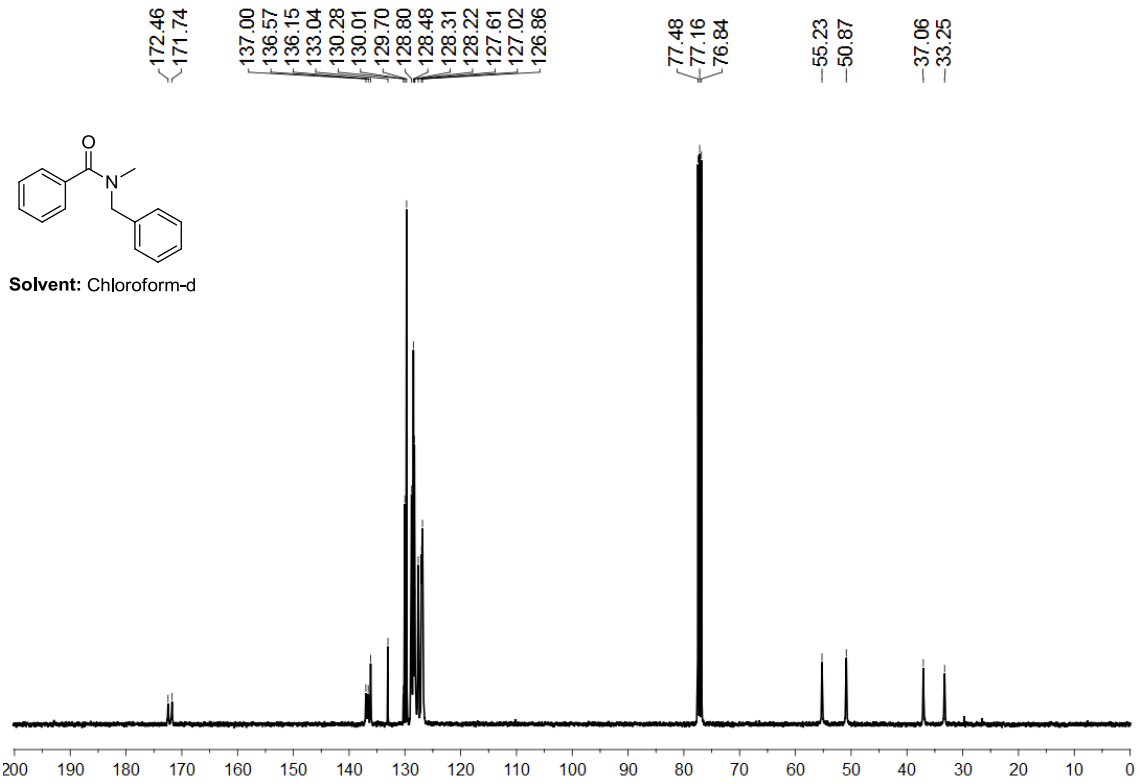


Figure 3.22 ^{13}C NMR spectrum of *N*-benzyl-*N*-methylbenzamide (**3h**).

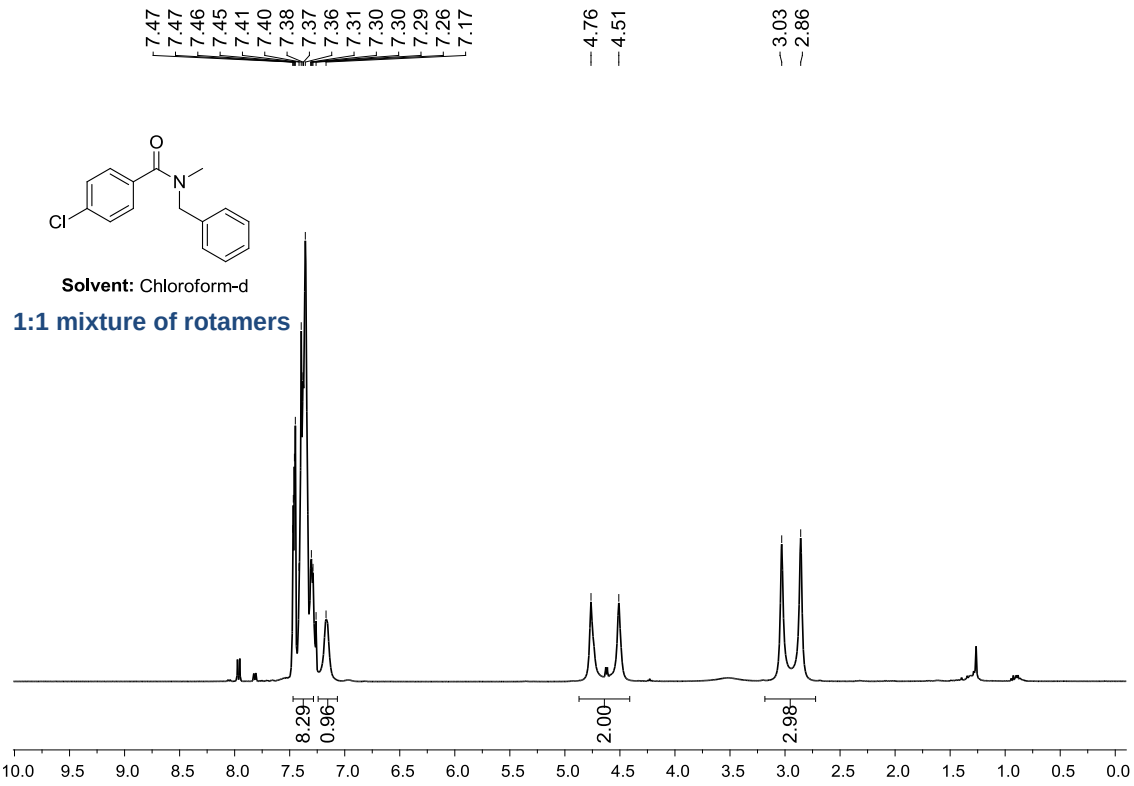


Figure 3.23 ^{1}H NMR spectrum of *N*-benzyl-4-chloro-*N*-methylbenzamide (**3i**).

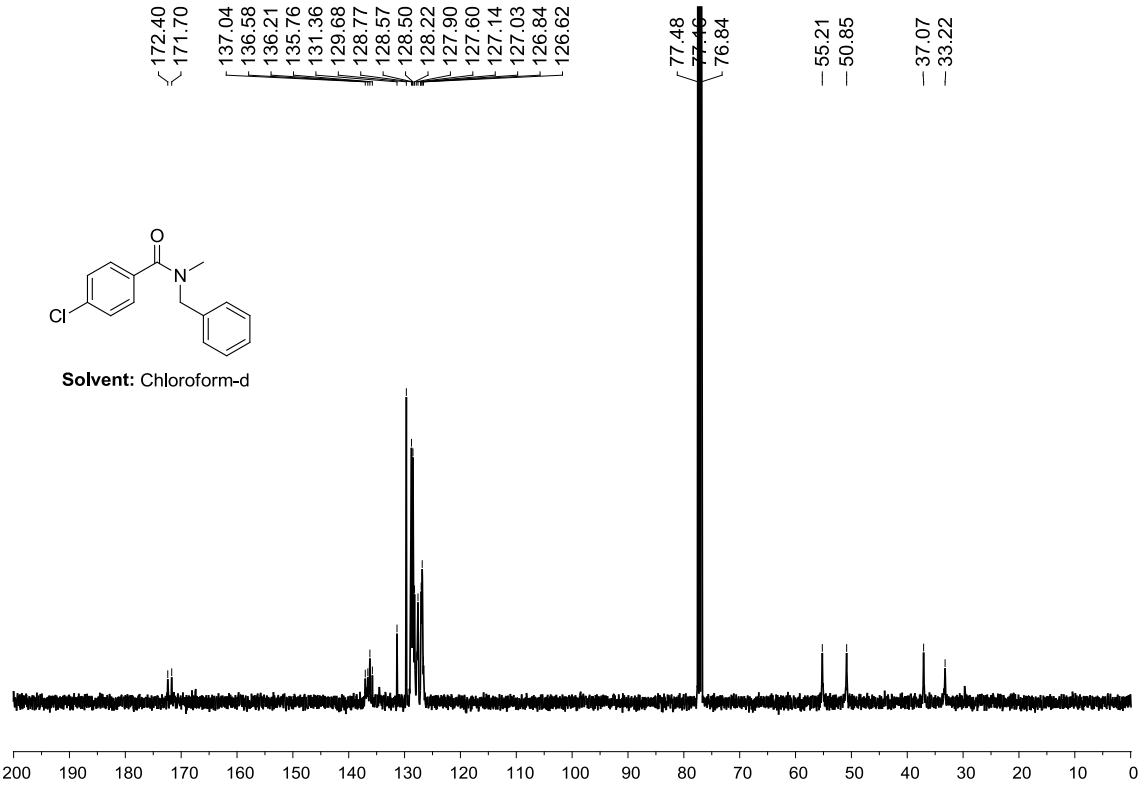


Figure 3.24 ^{13}C NMR spectrum of *N*-benzyl-4-chloro-*N*-methylbenzamide (**3i**).

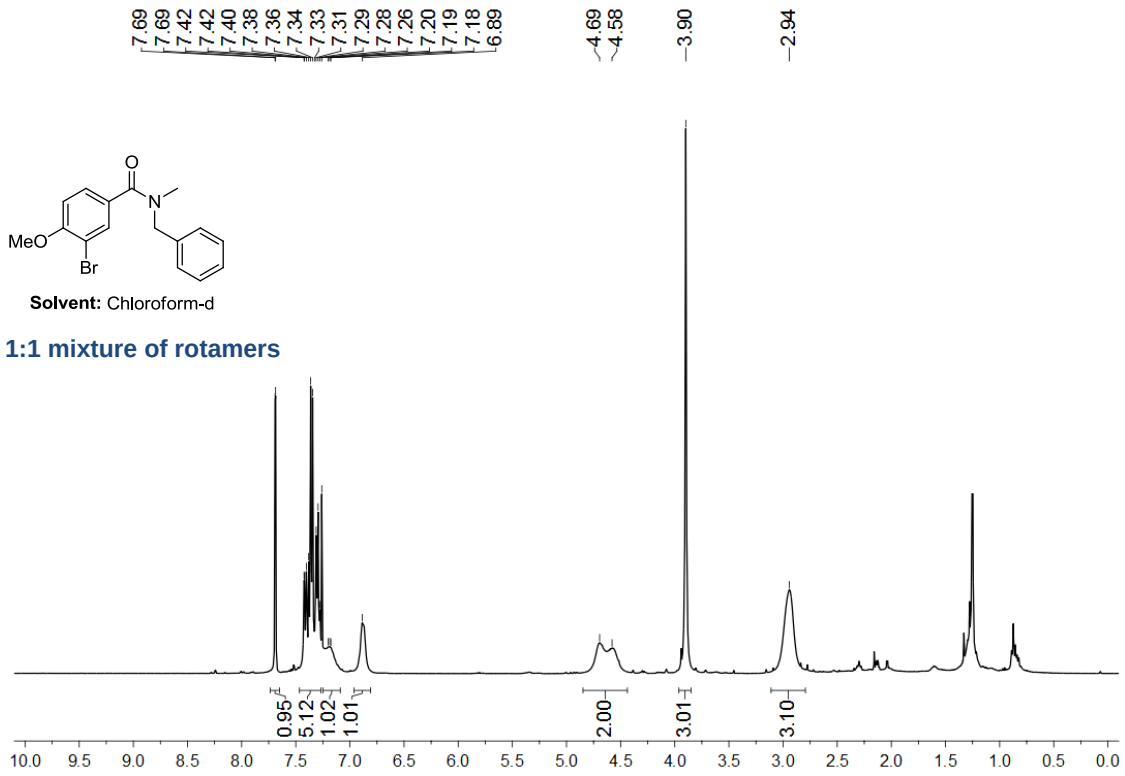


Figure 3.25 ^{1}H NMR spectrum of *N*-benzyl-3-bromo-4-methoxy-*N*-methylbenzamide (**3j**).

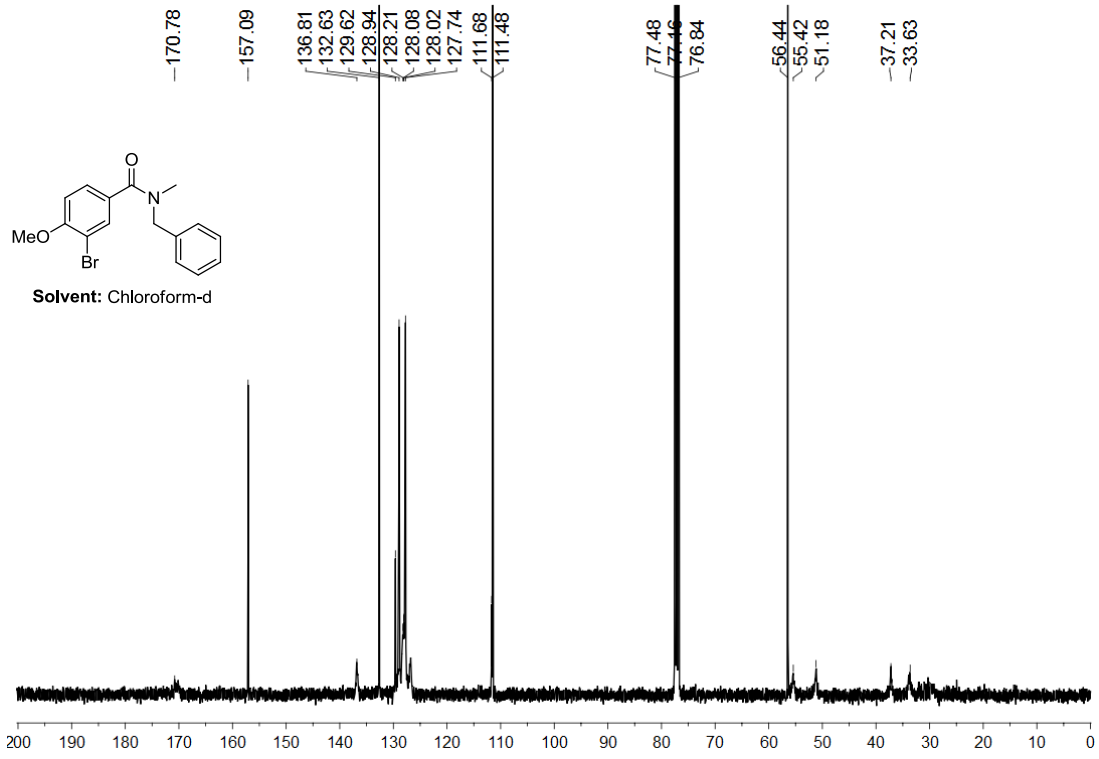


Figure 3.26 ^{13}C NMR spectrum of *N*-benzyl-3-bromo-4-methoxy-*N*-methylbenzamide (**3j**).

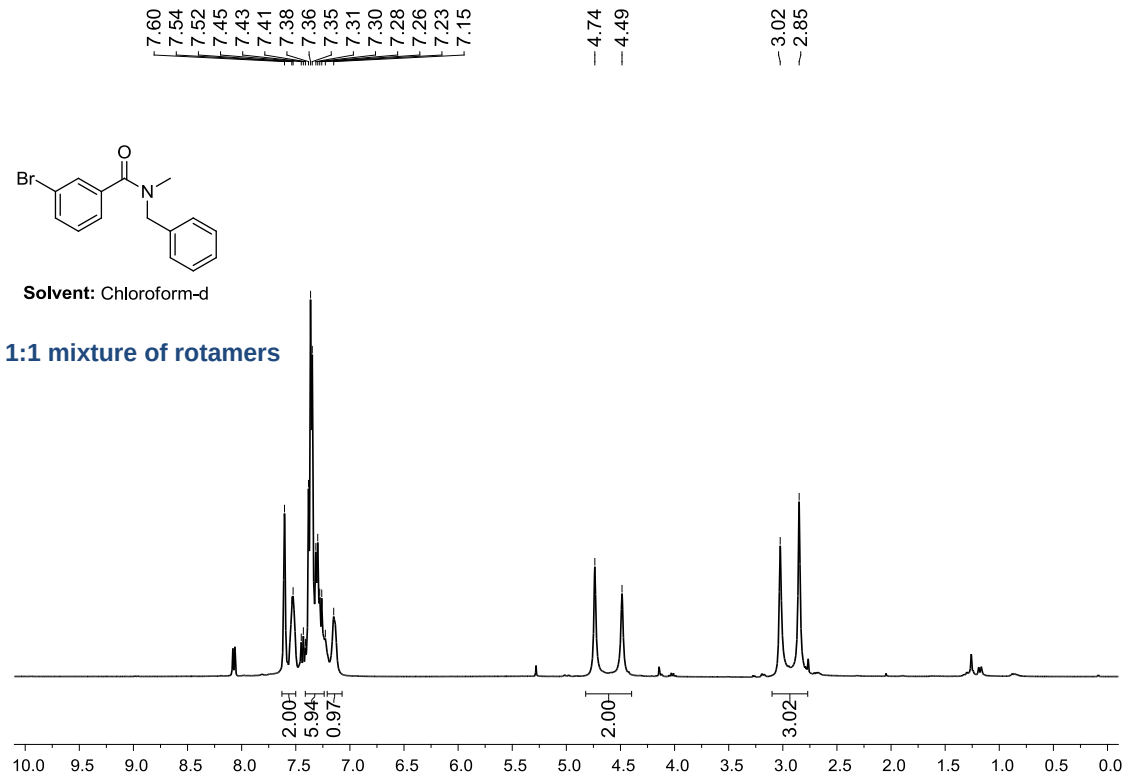


Figure 3.27 ^{1}H NMR spectrum of *N*-benzyl-3-bromo-*N*-methylbenzamide (**3k**).

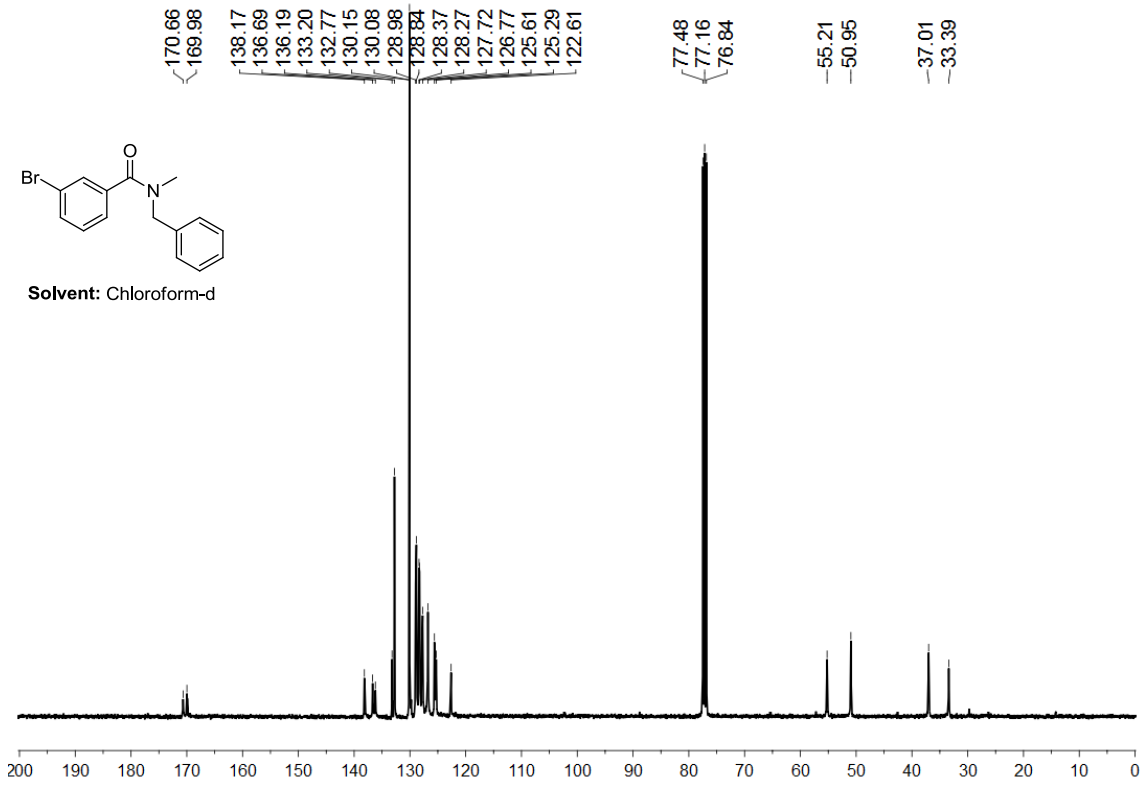


Figure 3.28 ^{13}C NMR spectrum of *N*-benzyl-3-bromo-*N*-methylbenzamide (**3k**).

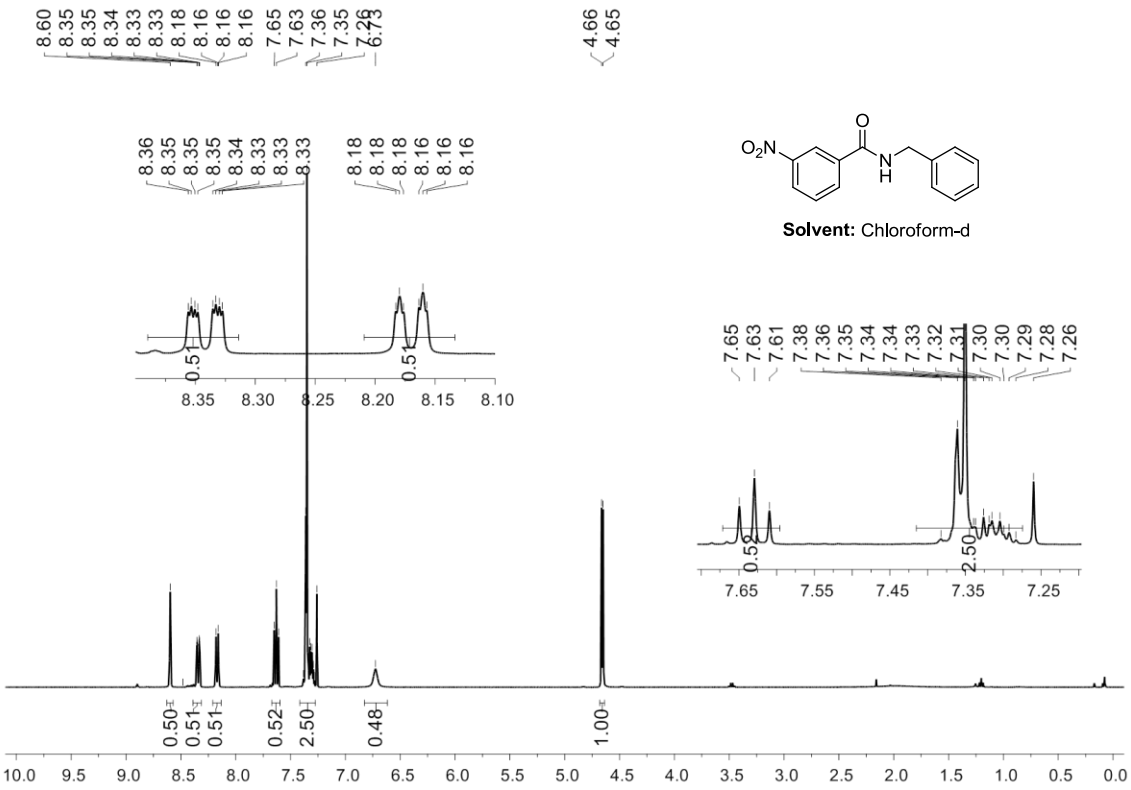


Figure 3.29 ^{1}H NMR spectrum of *N*-benzyl-3-nitrobenzamide (**3l**).

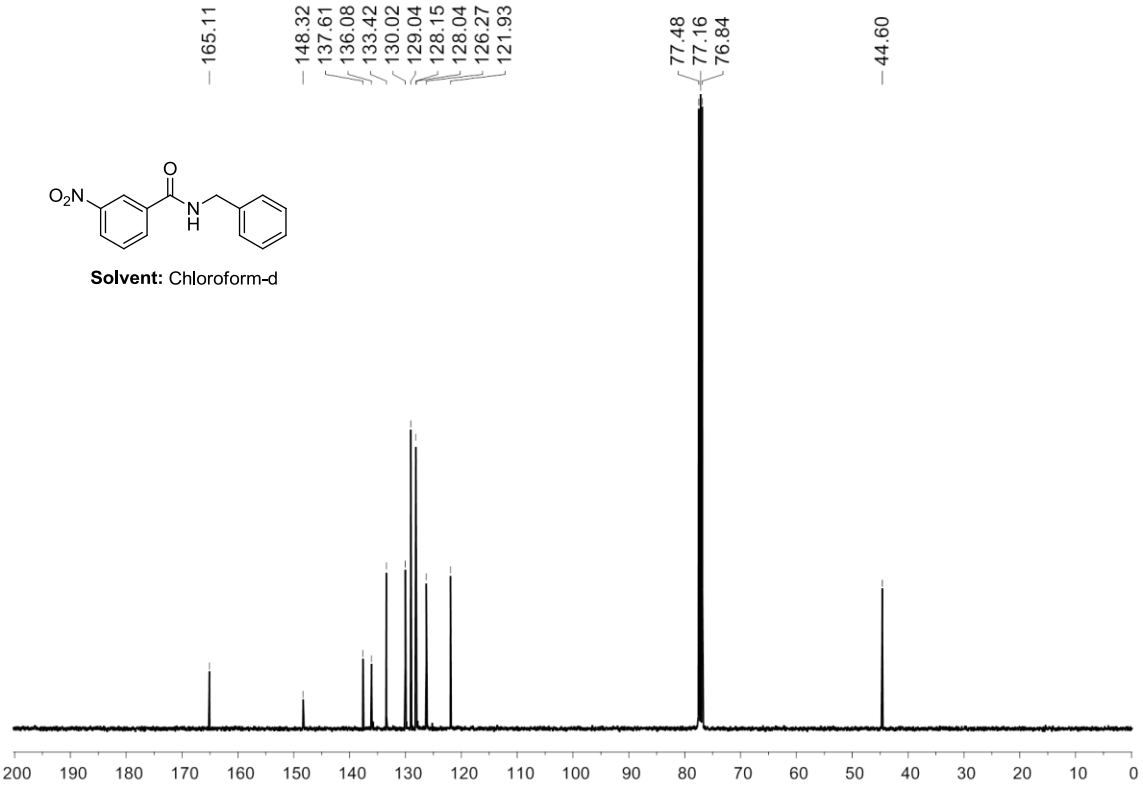


Figure 3.30 ^{13}C NMR spectrum of *N*-benzyl-3-nitrobenzamide (**3l**).

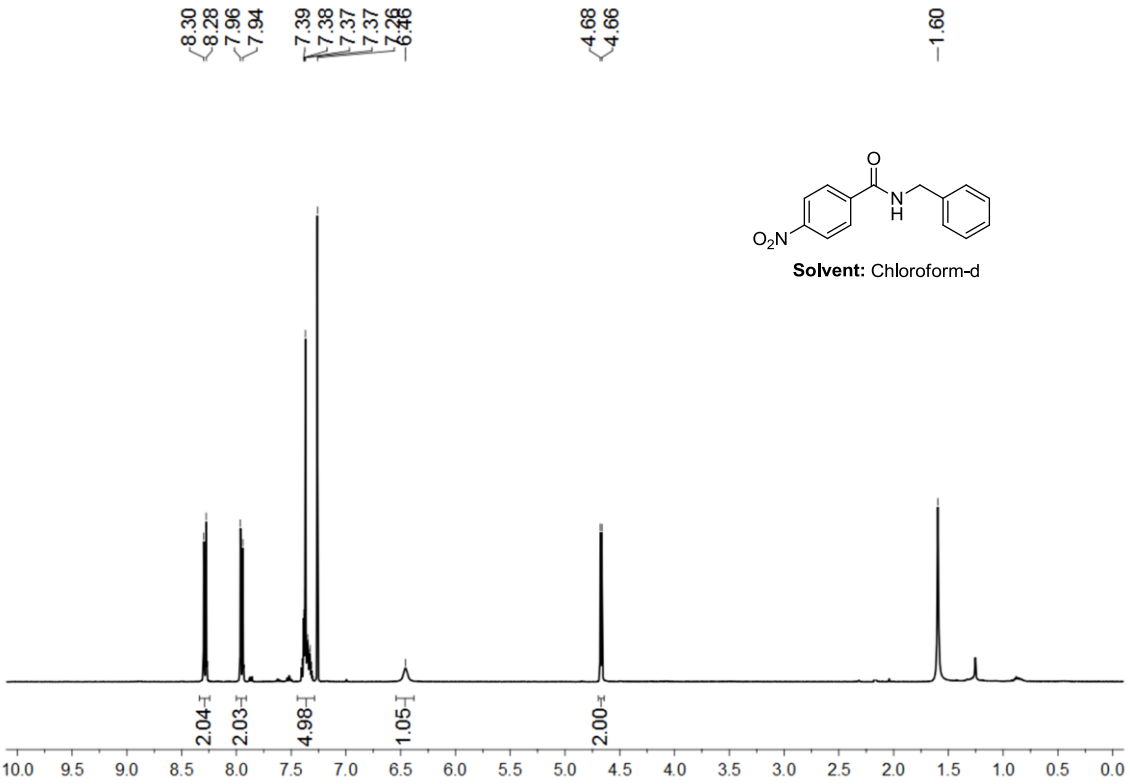


Figure 3.31 ^{1}H NMR spectrum of *N*-benzyl-4-nitrobenzamide (**3m**).

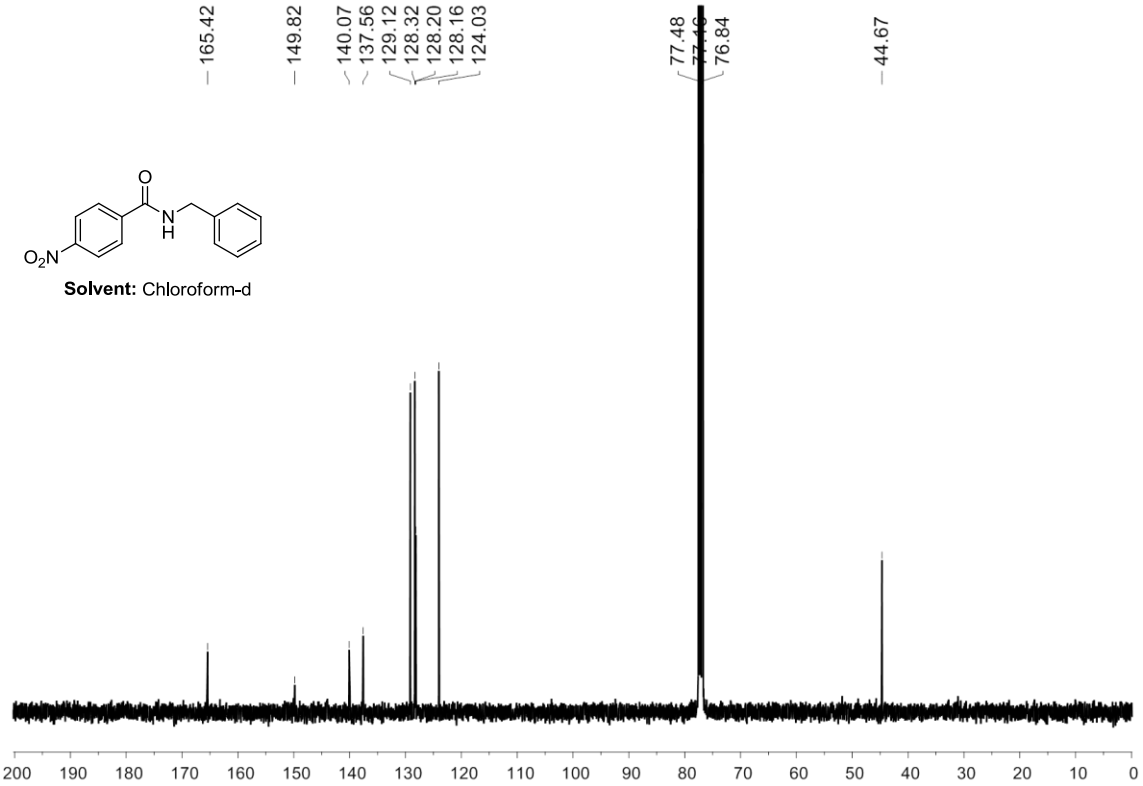


Figure 3.32 ^{13}C NMR spectrum of *N*-benzyl-4-nitrobenzamide (**3m**).

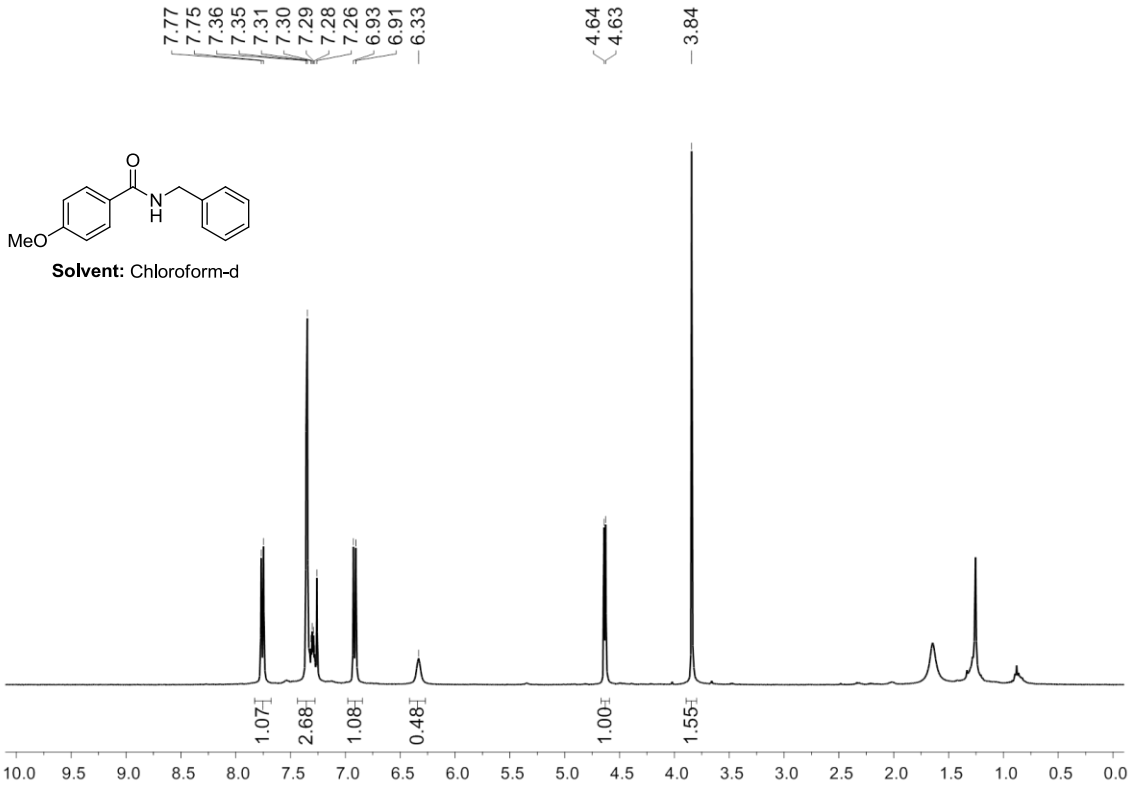


Figure 3.33 ^{1}H NMR spectrum of *N*-benzyl-4-methoxybenzamide (**3n**).

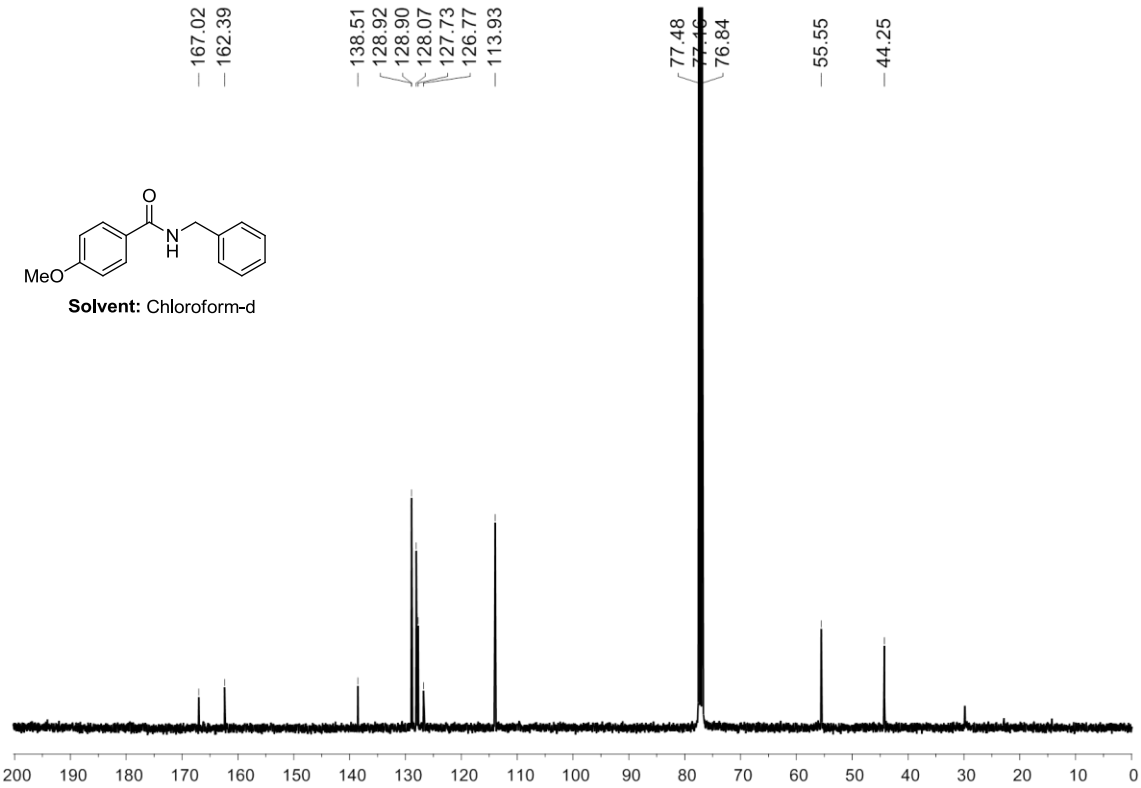


Figure 3.34 ^{13}C NMR spectrum of *N*-benzyl-4-methoxybenzamide (**3n**).

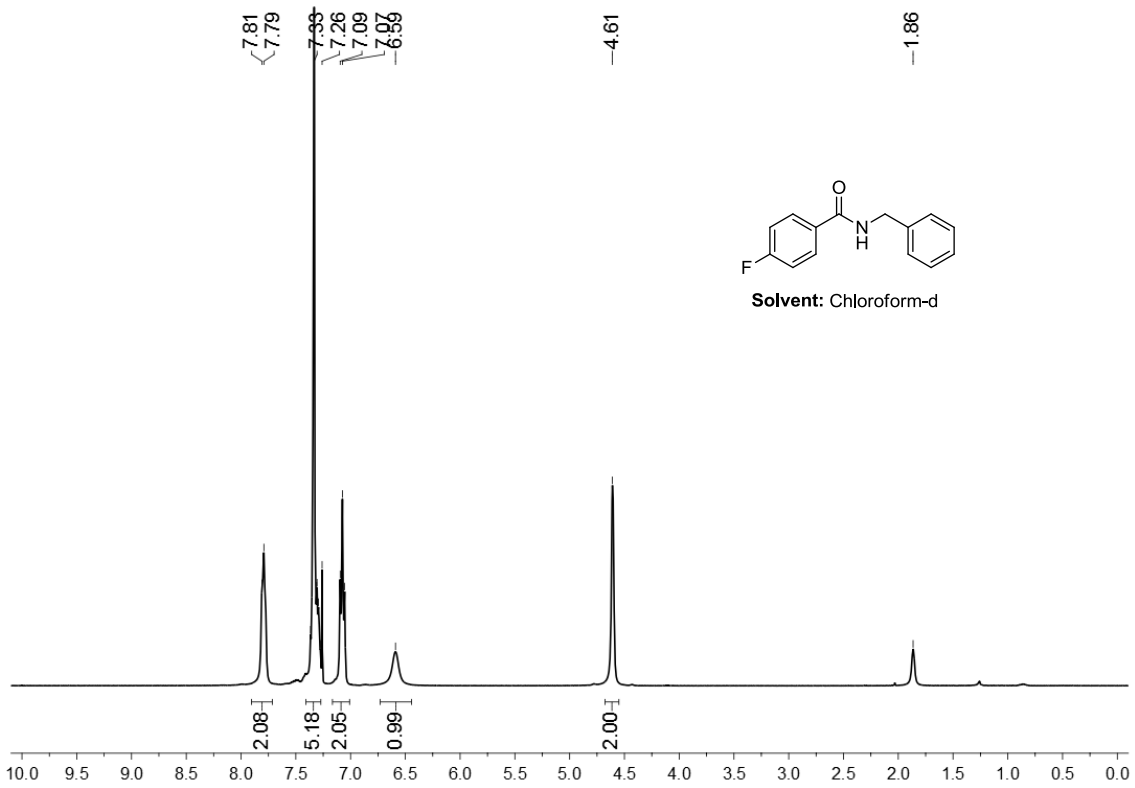


Figure 3.35 ^{1}H NMR spectrum of *N*-benzyl-4-fluorobenzamide (**3o**)

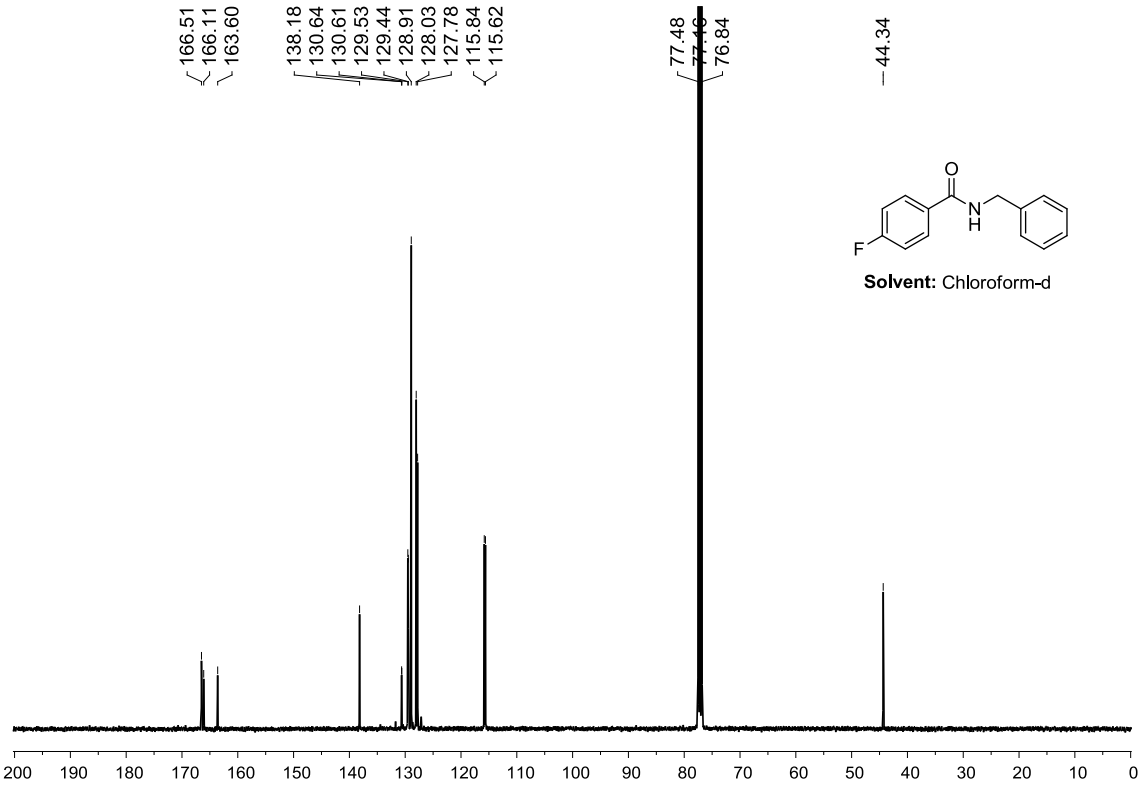


Figure 3.36 ^{13}C NMR spectrum of *N*-benzyl-4-fluorobenzamide (**3o**)

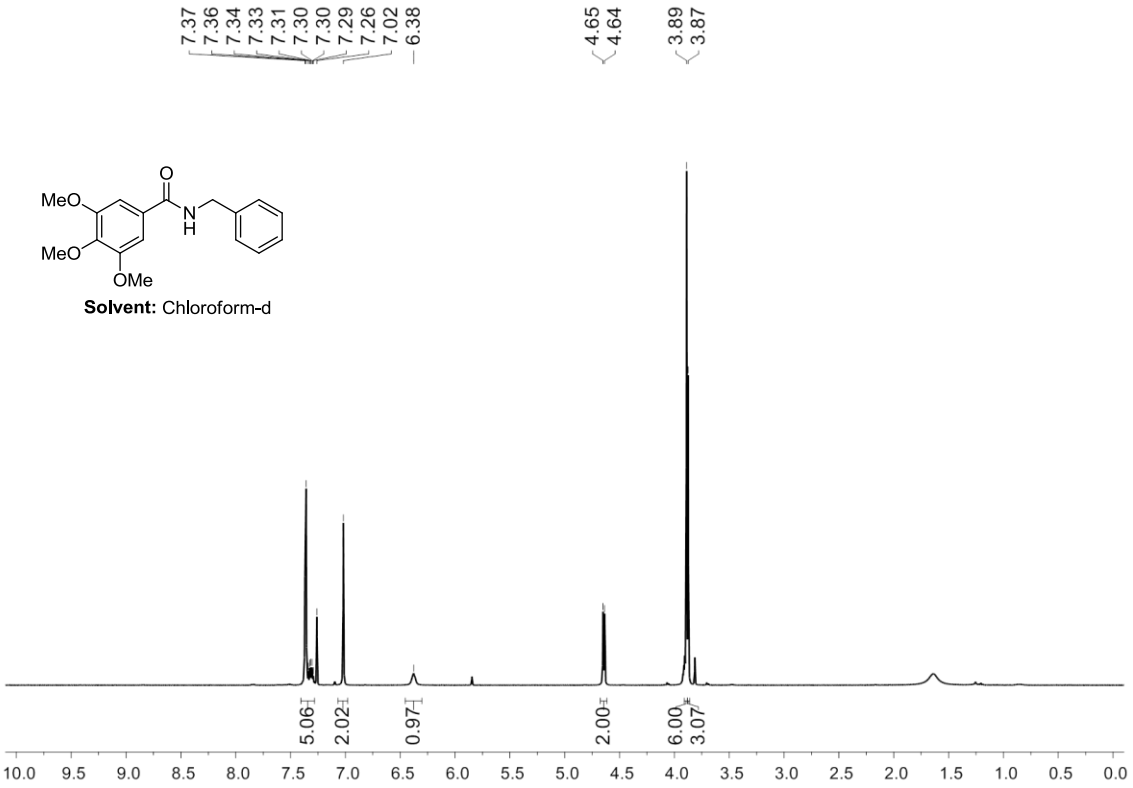


Figure 3.37 ^{1}H NMR spectrum of *N*-benzyl-3,4,5-trimethoxybenzamide (**3p**).

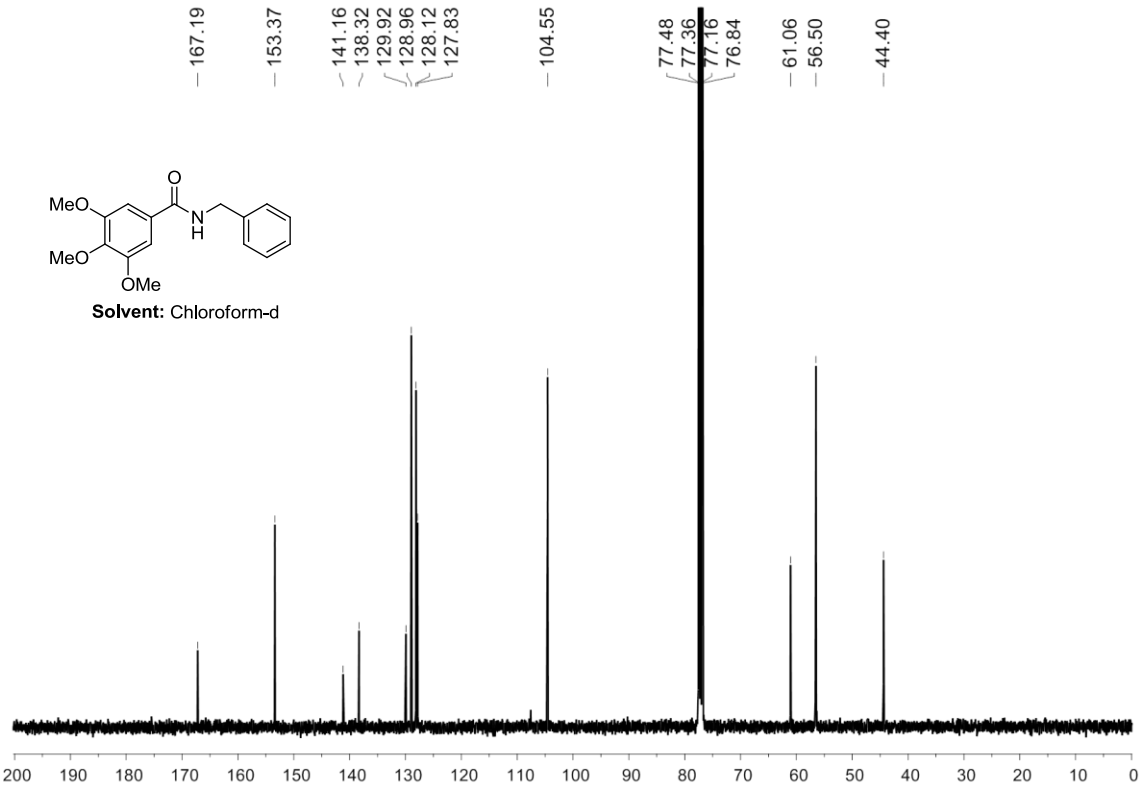


Figure 3.38 ^{13}C NMR spectrum of *N*-benzyl-3,4,5-trimethoxybenzamide (**3p**).

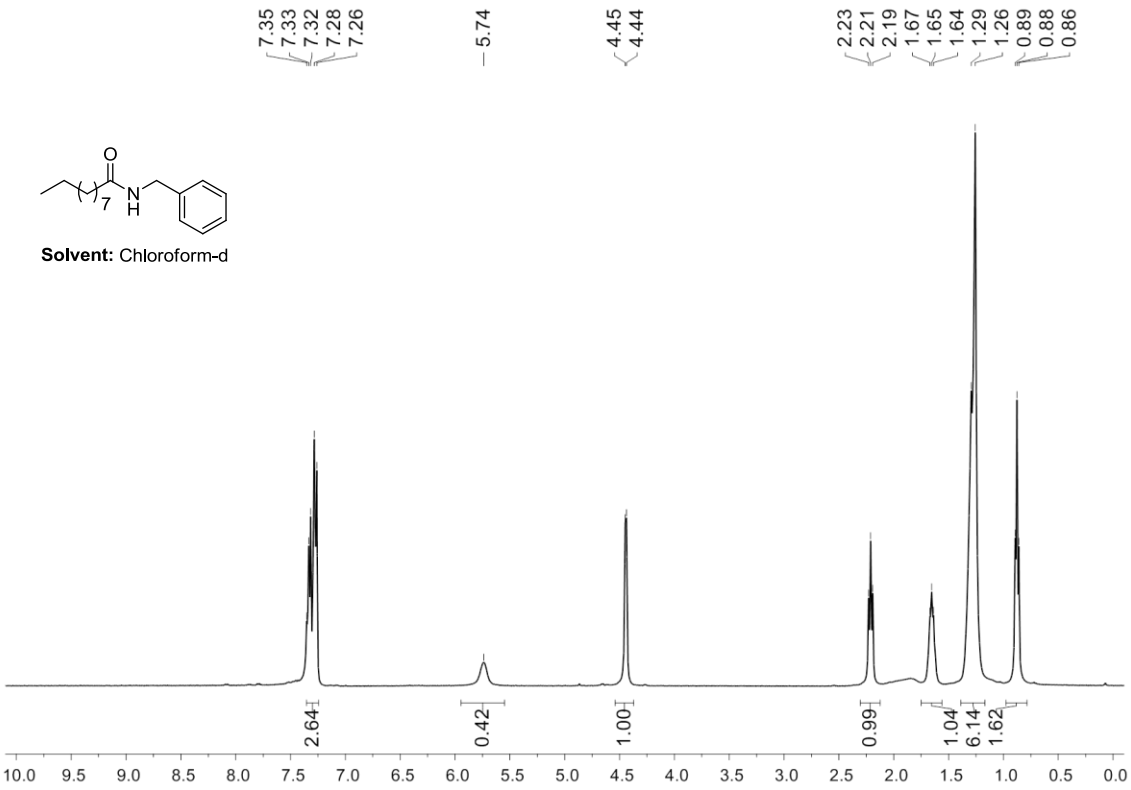


Figure 3.39 ^{1}H NMR spectrum of *N*-benzyldecanamide (**3q**).

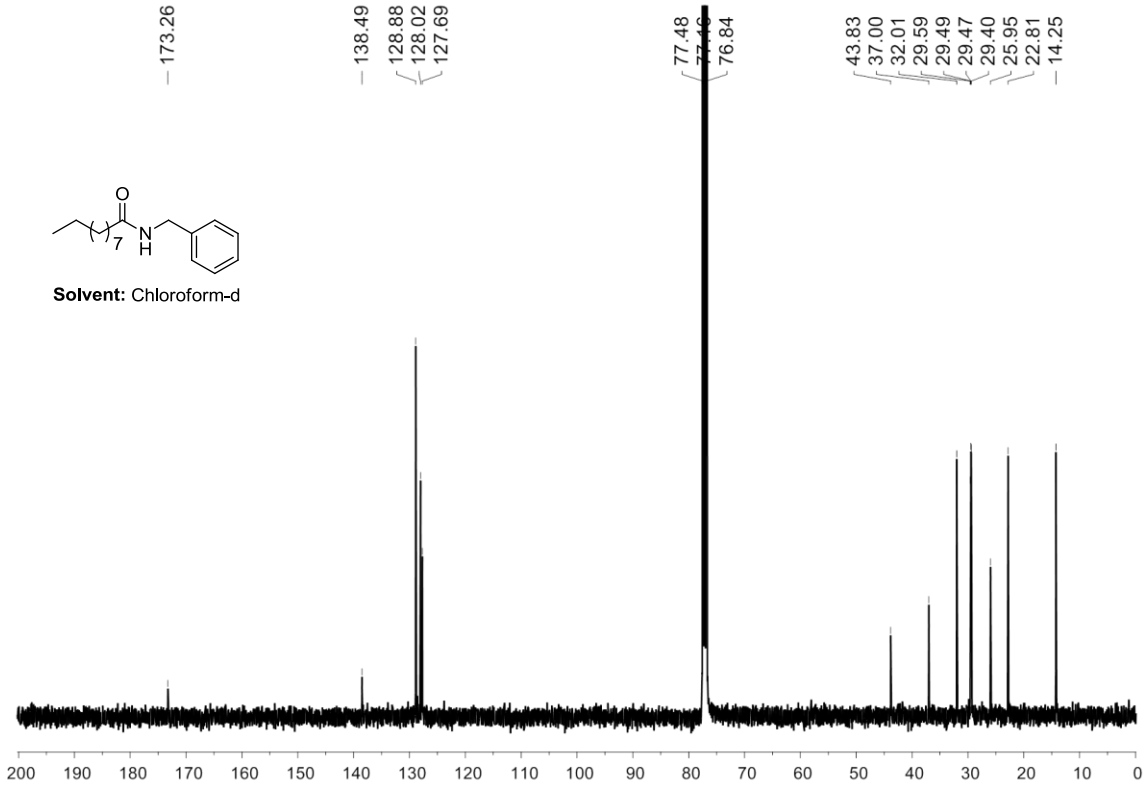


Figure 3.39 ^{13}C NMR spectrum of *N*-benzyldecanamide (**3q**).

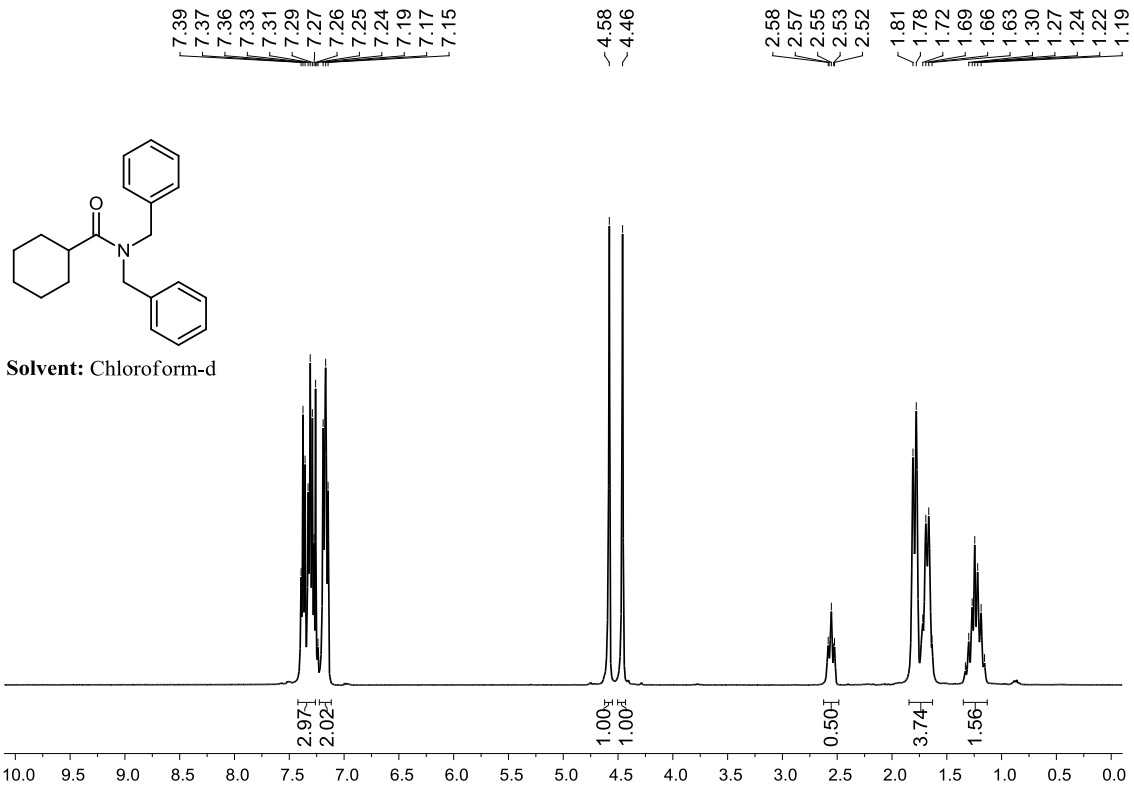


Figure 3.39 ^{1}H NMR spectrum of *N*,*N*-dibenzylcyclohexanecarboxamide (**3r**).

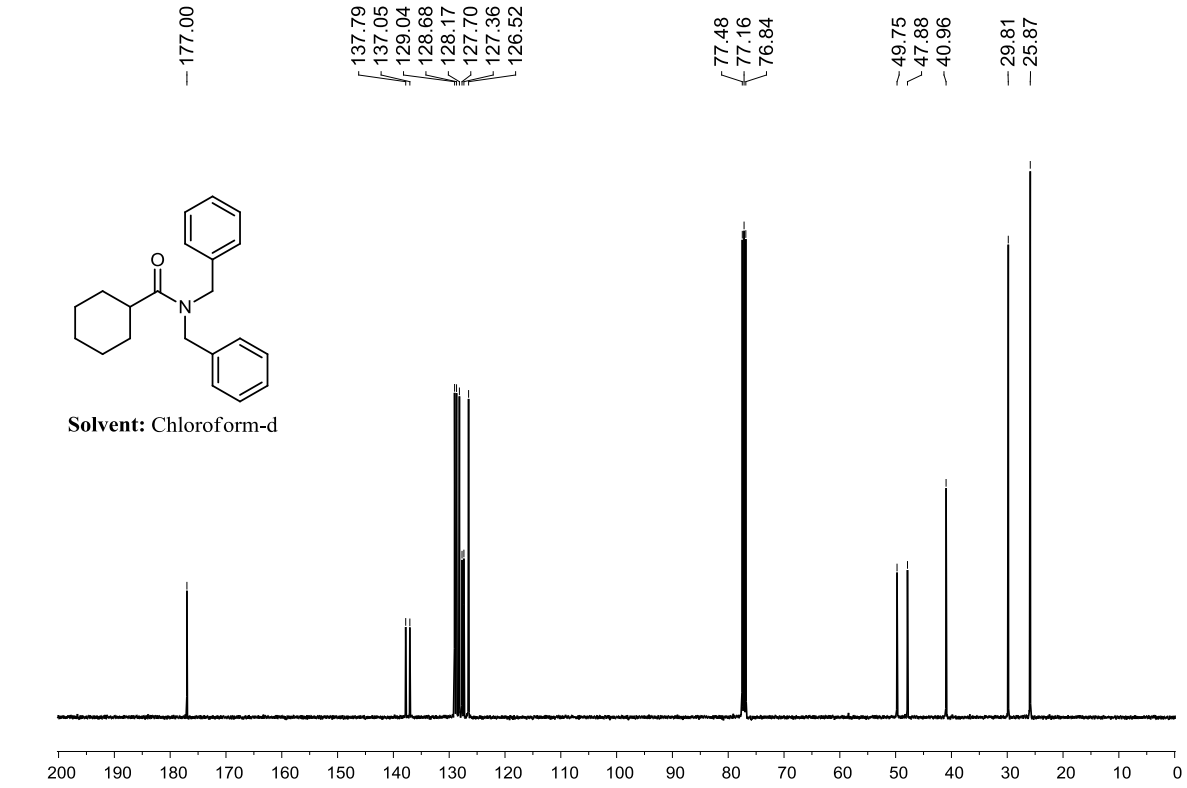


Figure 3.40 ^{13}C NMR spectrum of *N*,*N*-dibenzylcyclohexanecarboxamide (**3r**).

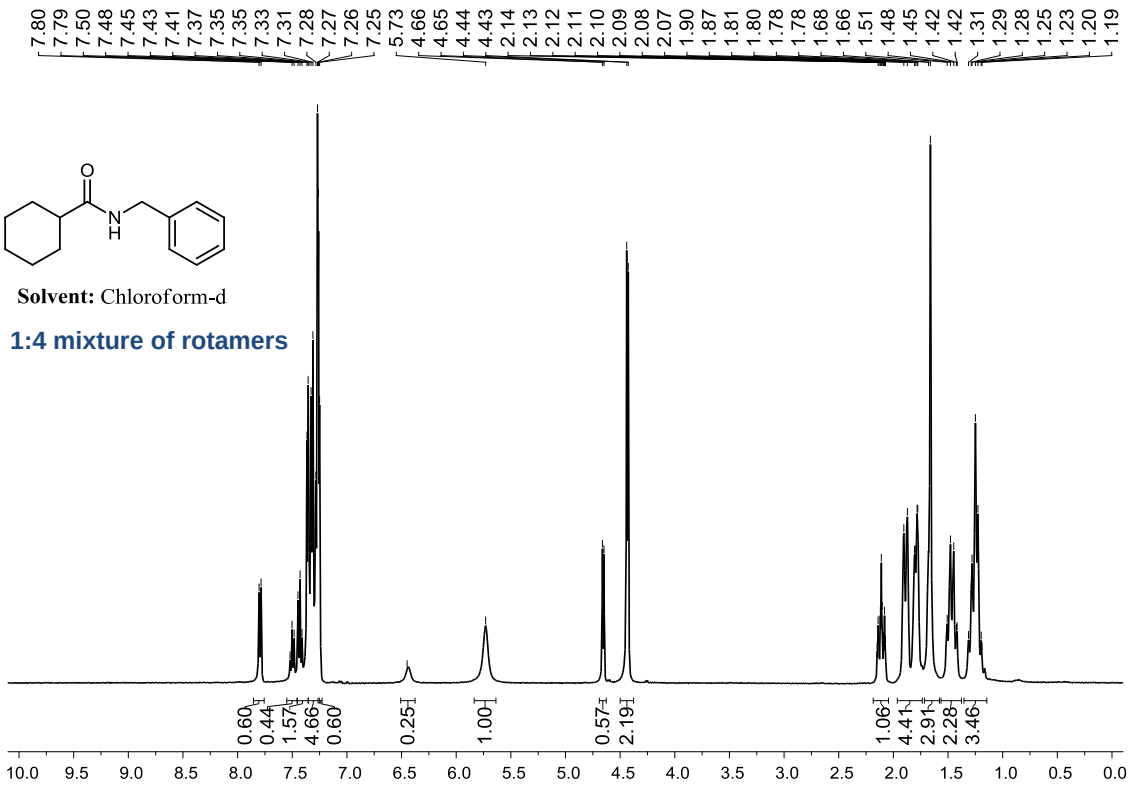


Figure 3.41 ^{1}H NMR spectrum of *N*-benzylcyclohexanecarboxamide (**3s**).

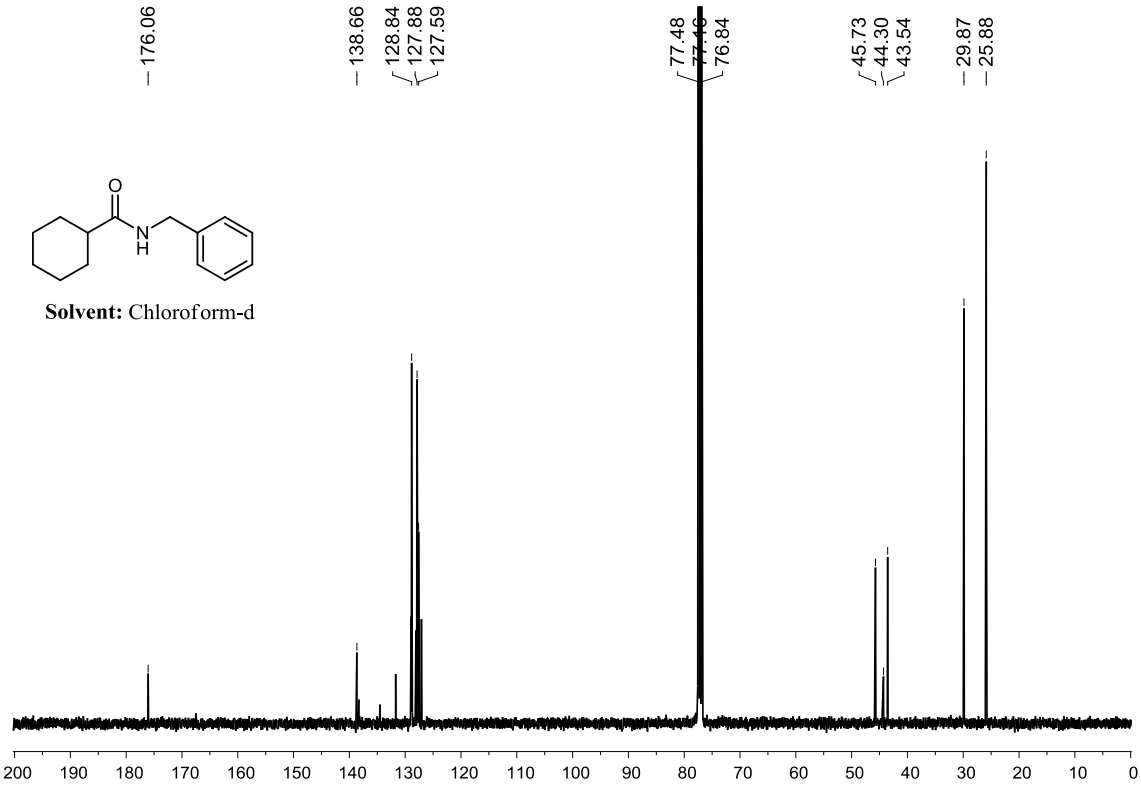


Figure 3.42 ^{13}C NMR spectrum of *N*- benzylcyclohexanecarboxamide (**3s**).

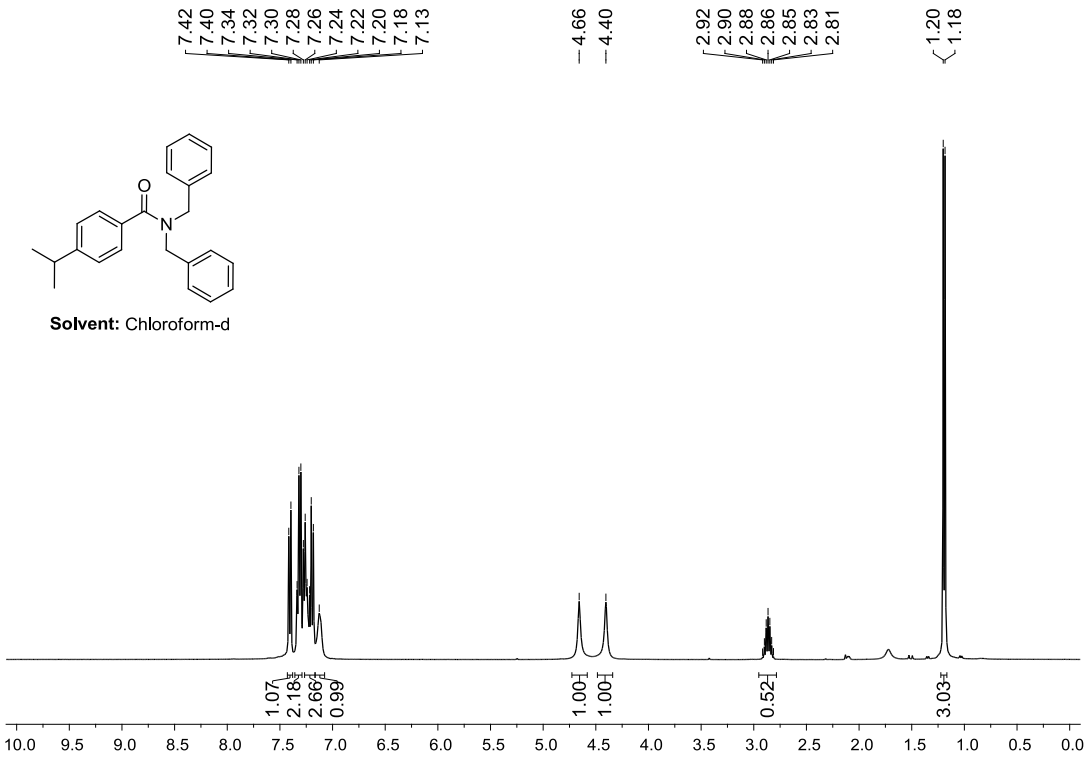


Figure 3.43 ^{1}H NMR spectrum of *N*,*N*-dibenzyl-4-isopropylbenzamide (**3t**).

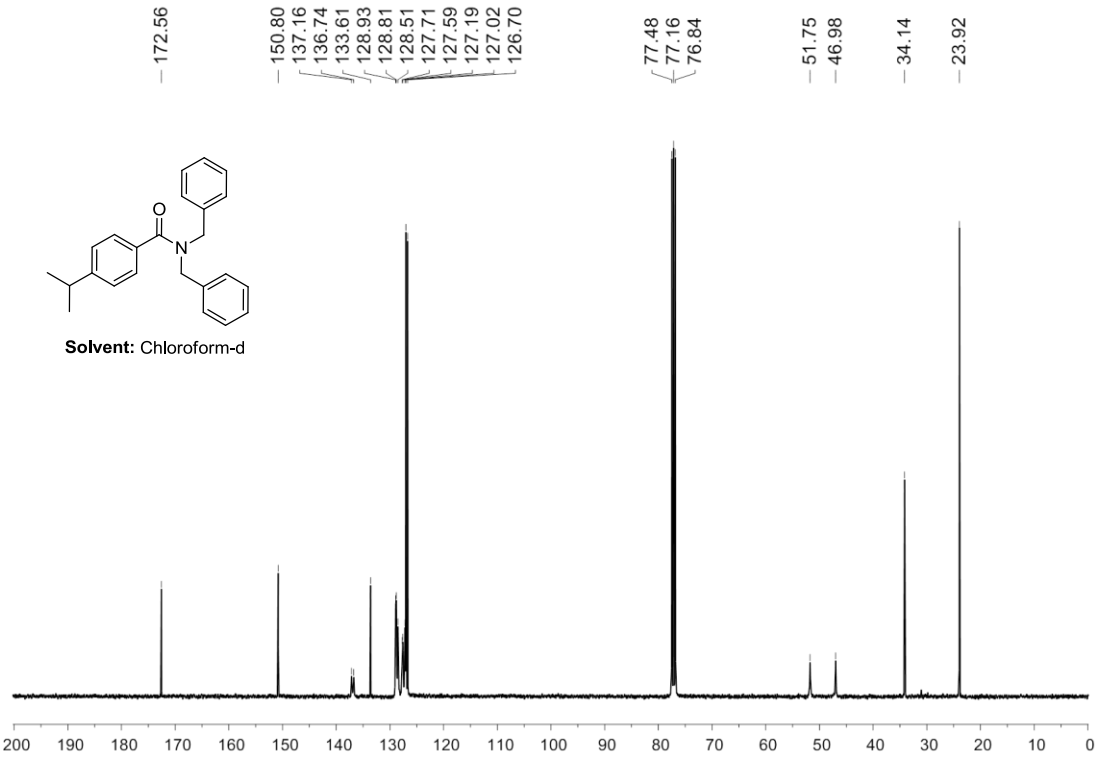


Figure 3.44 ^{13}C NMR spectrum of *N*,*N*-dibenzyl-4-isopropylbenzamide (**3t**).

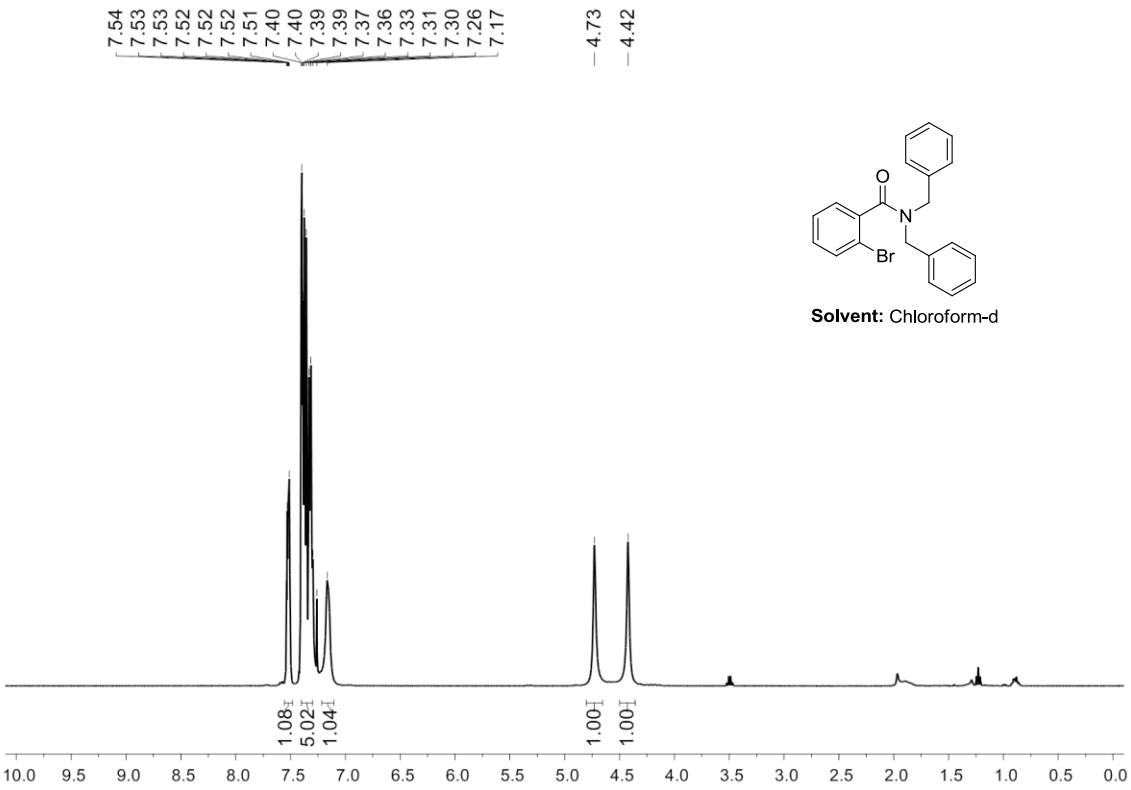


Figure 3.45 ^{1}H NMR spectrum of *N*,*N*-dibenzyl-2-bromobenzamide (**3u**).

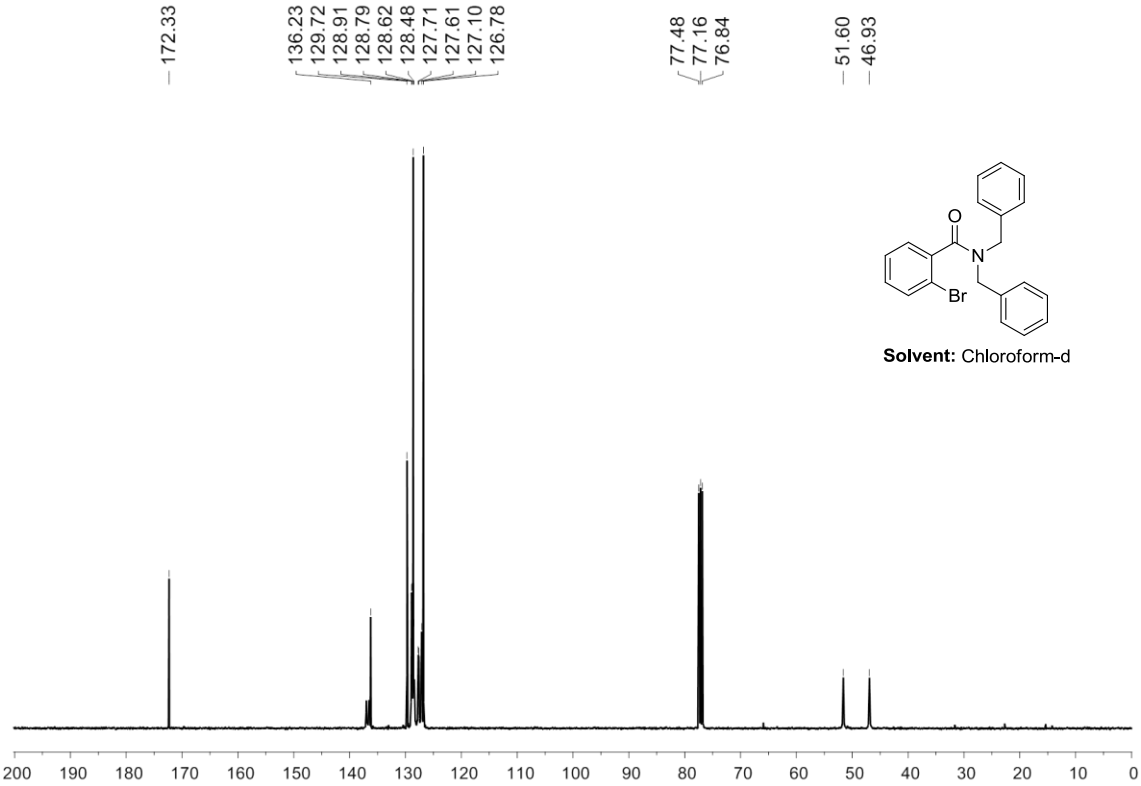


Figure 3.46 ^{13}C NMR spectrum of *N*,*N*-dibenzyl-2-bromobenzamide (**3u**).

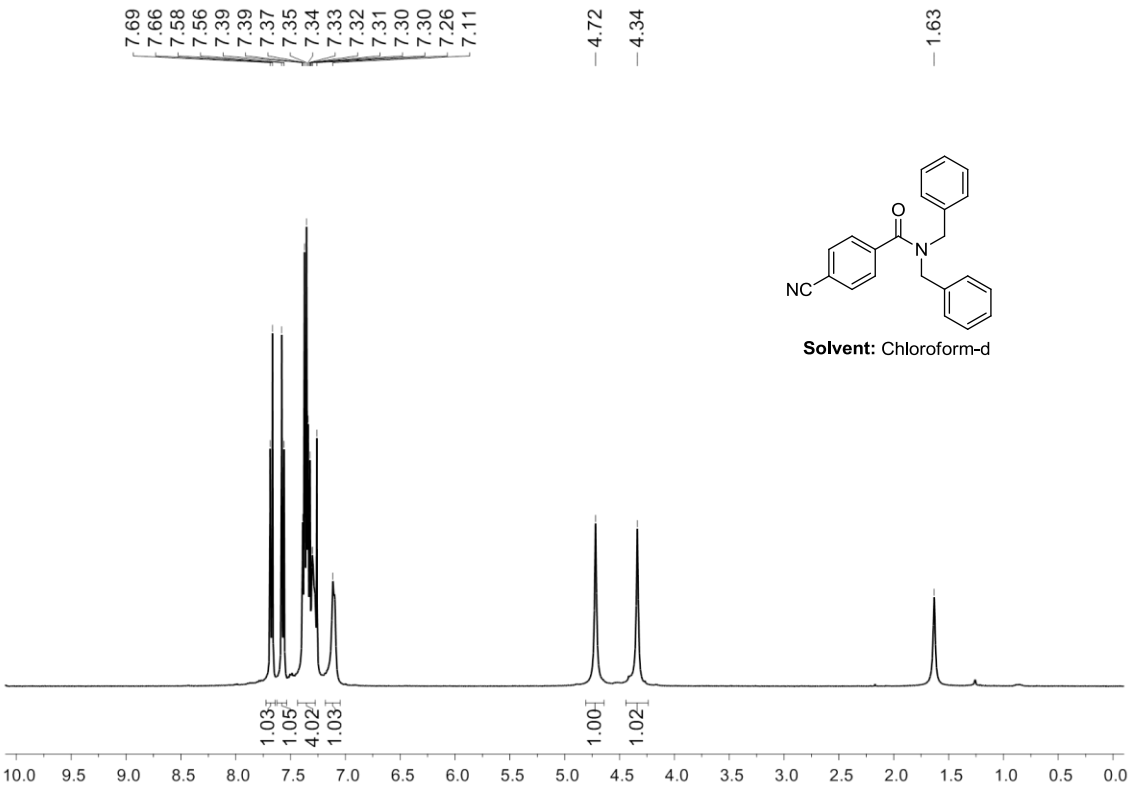


Figure 3.47 ^{1}H NMR spectrum of *N*,*N*-dibenzyl-4-cyanobenzamide (**3v**).

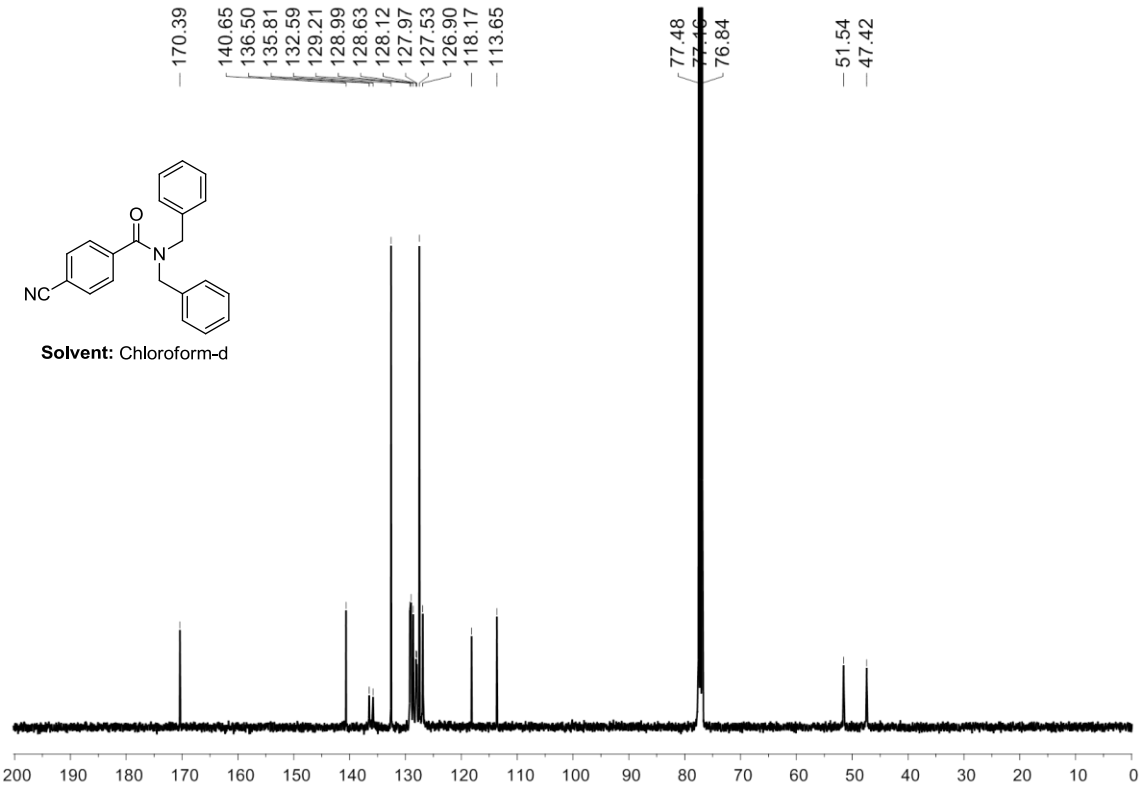


Figure 3.48 ^{13}C NMR spectrum of *N*,*N*-dibenzyl-4-cyanobenzamide (**3v**).

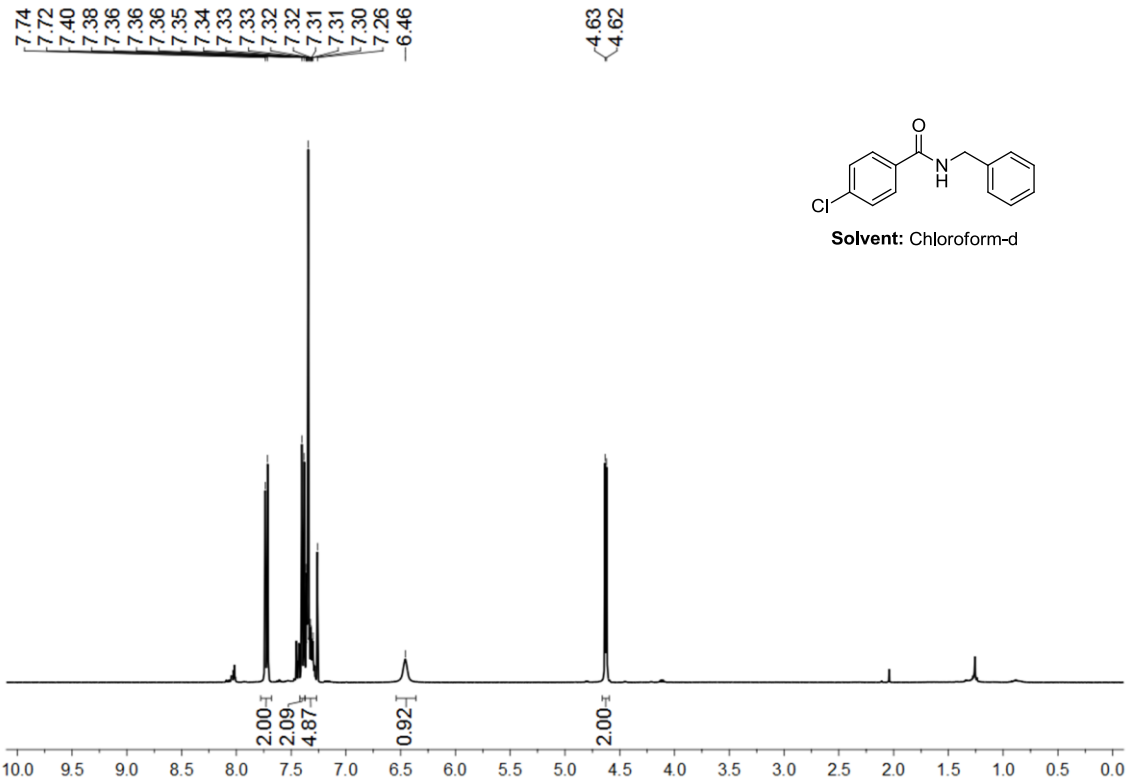


Figure 3.49 ^{1}H NMR spectrum of *N*-benzyl-4-chlorobenzamide (**3w**)

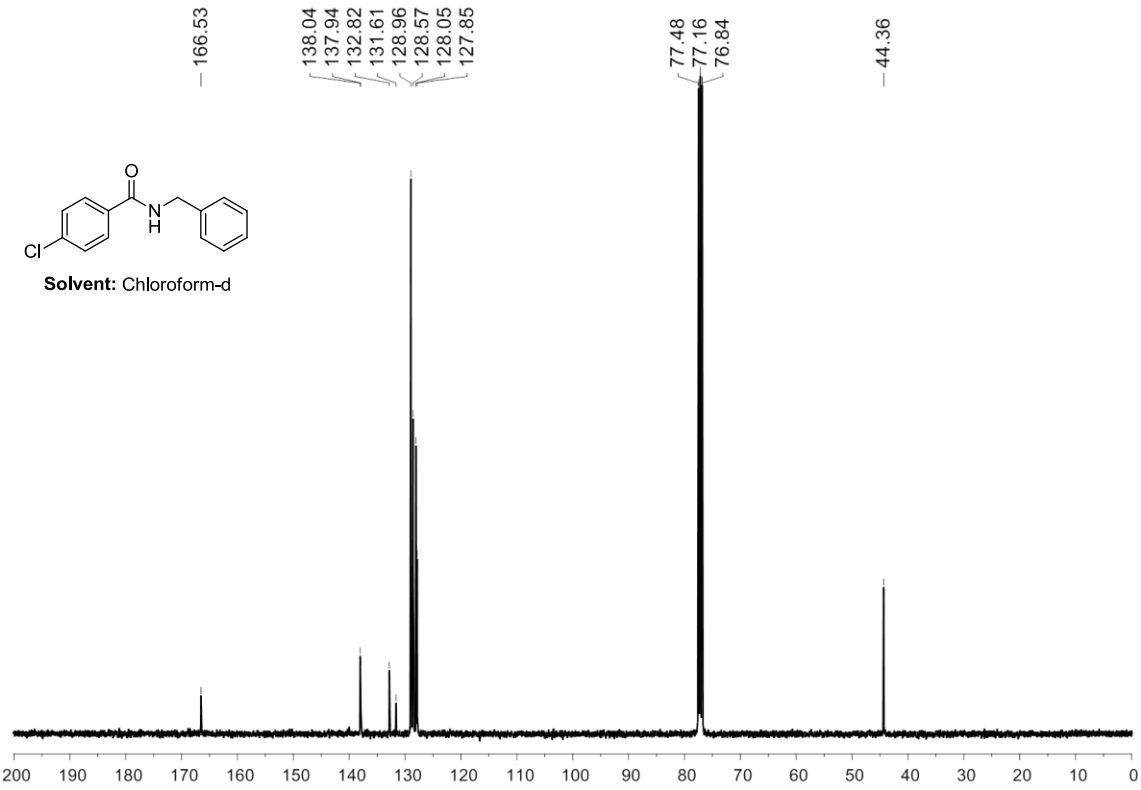


Figure 3.50 ^{13}C NMR spectrum of *N*-benzyl-4-chlorobenzamide (**3w**)

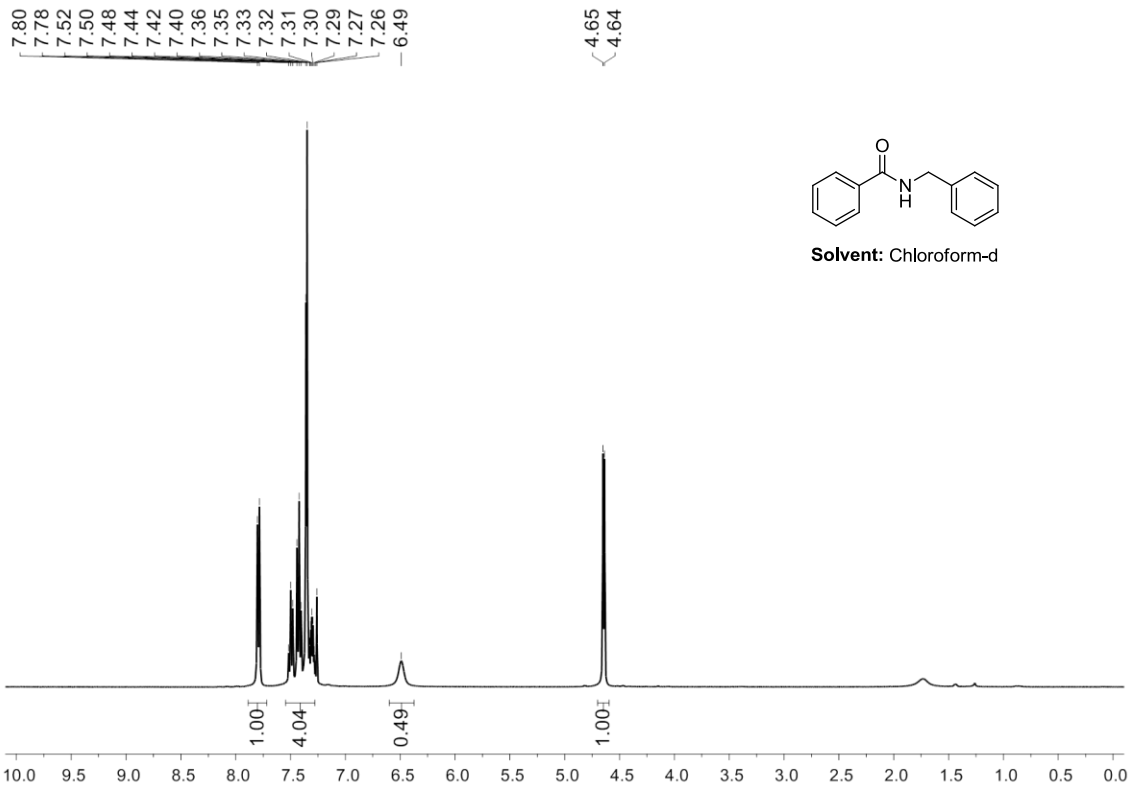


Figure 3.51 ^{1}H NMR spectrum of *N*-benzylbenzamide (**3x**).

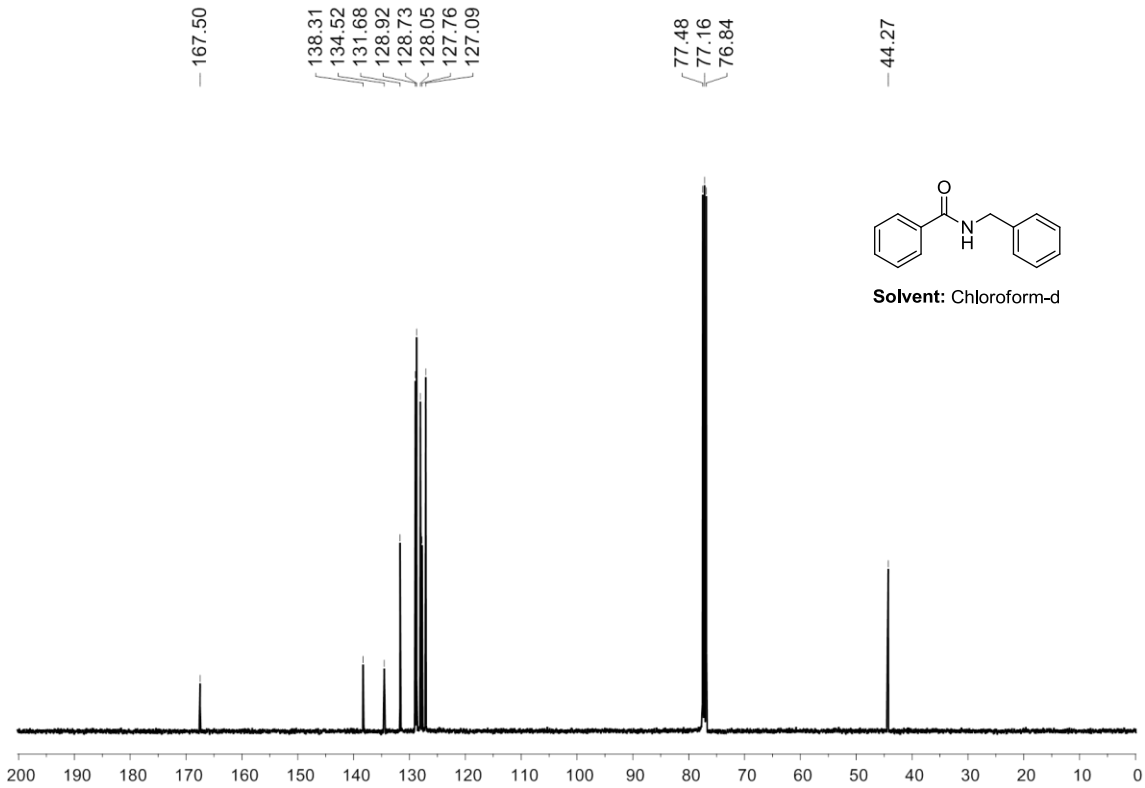


Figure 3.52 ^{13}C NMR spectrum of *N*-benzylbenzamide (**3x**).

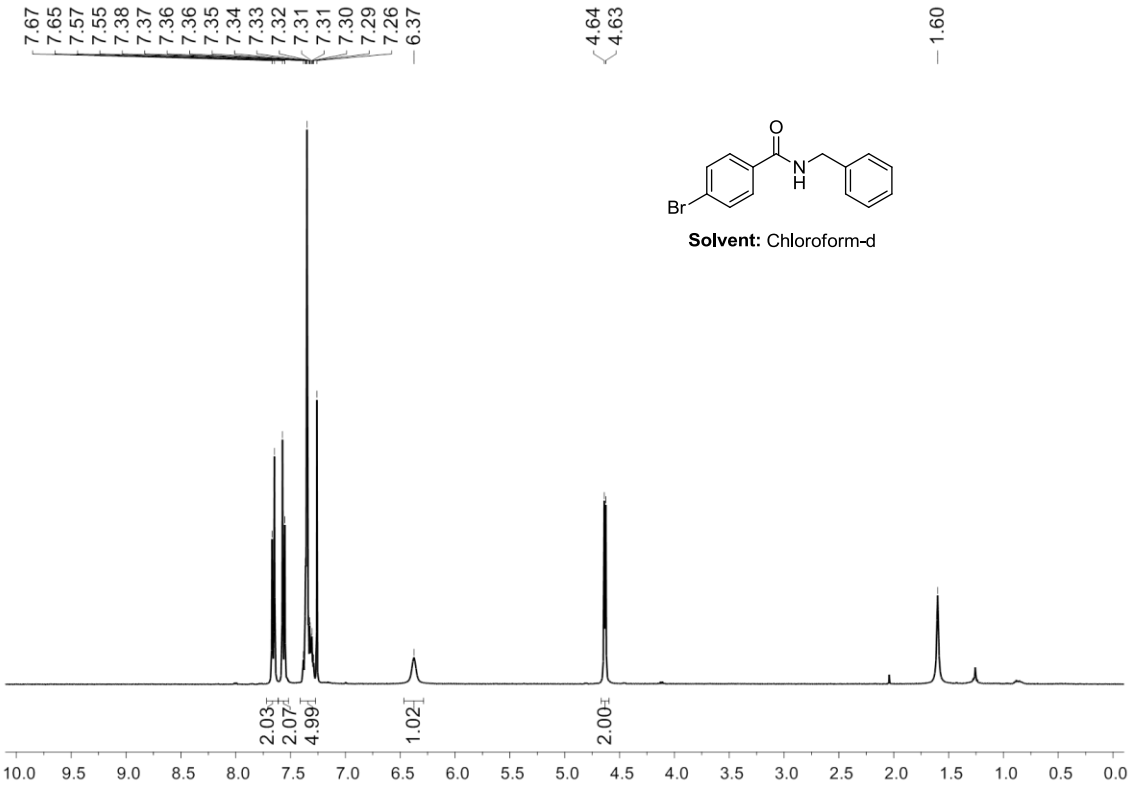


Figure 3.53 ^{1}H NMR spectrum of *N*-benzyl-4-bromobenzamide (**3y**).

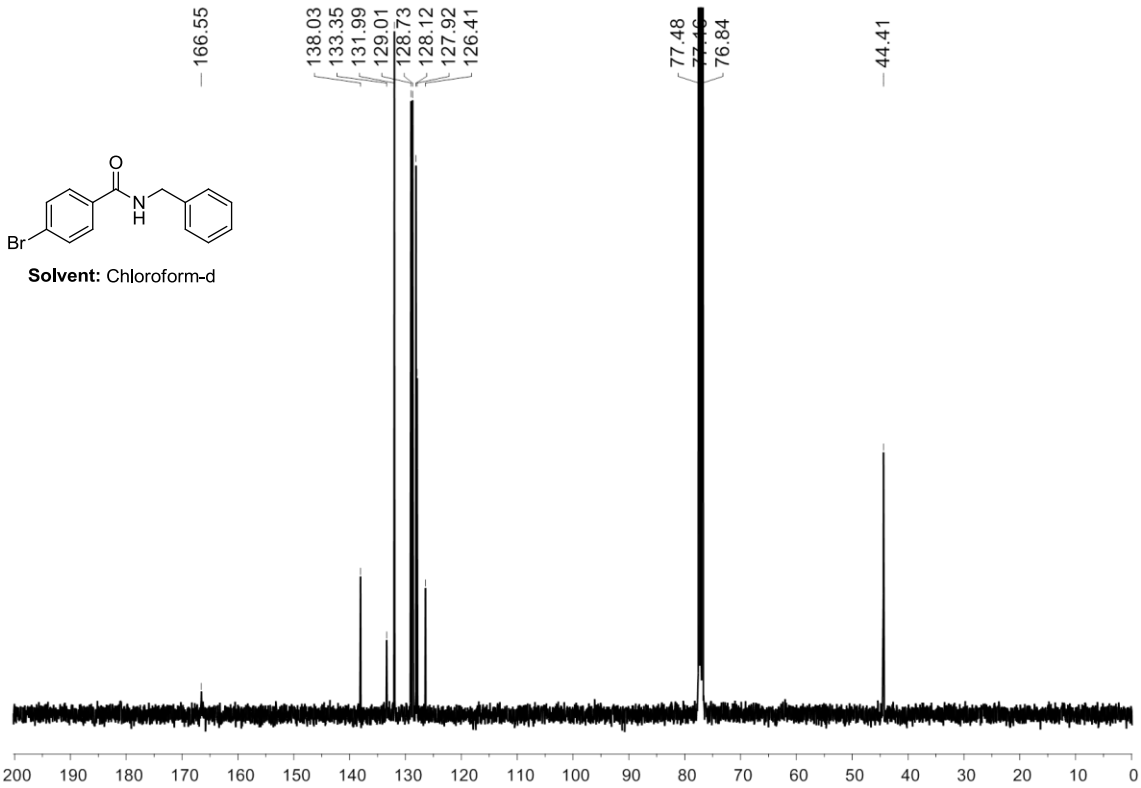


Figure 3.54 ^{13}C NMR spectrum of *N*-benzyl-4-bromobenzamide (**3y**).

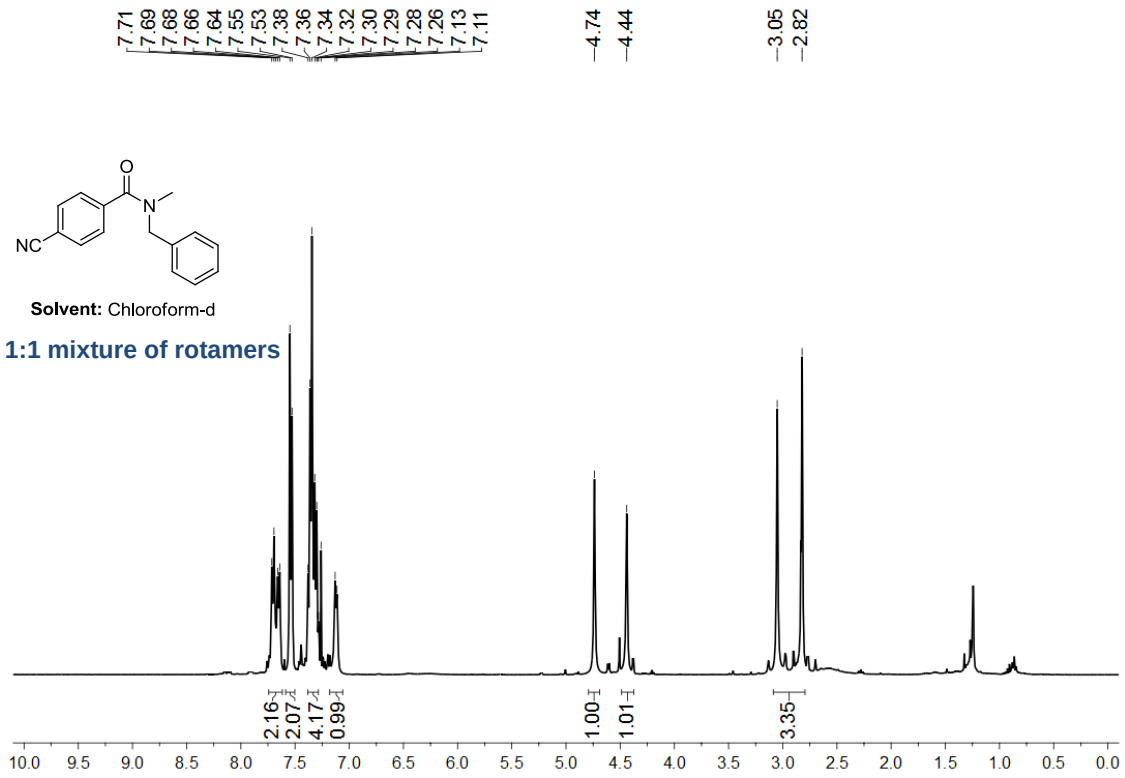


Figure 3.55 ^{1}H NMR spectrum of *N*-benzyl-4-cyano-*N*-methylbenzamide (**3z**).

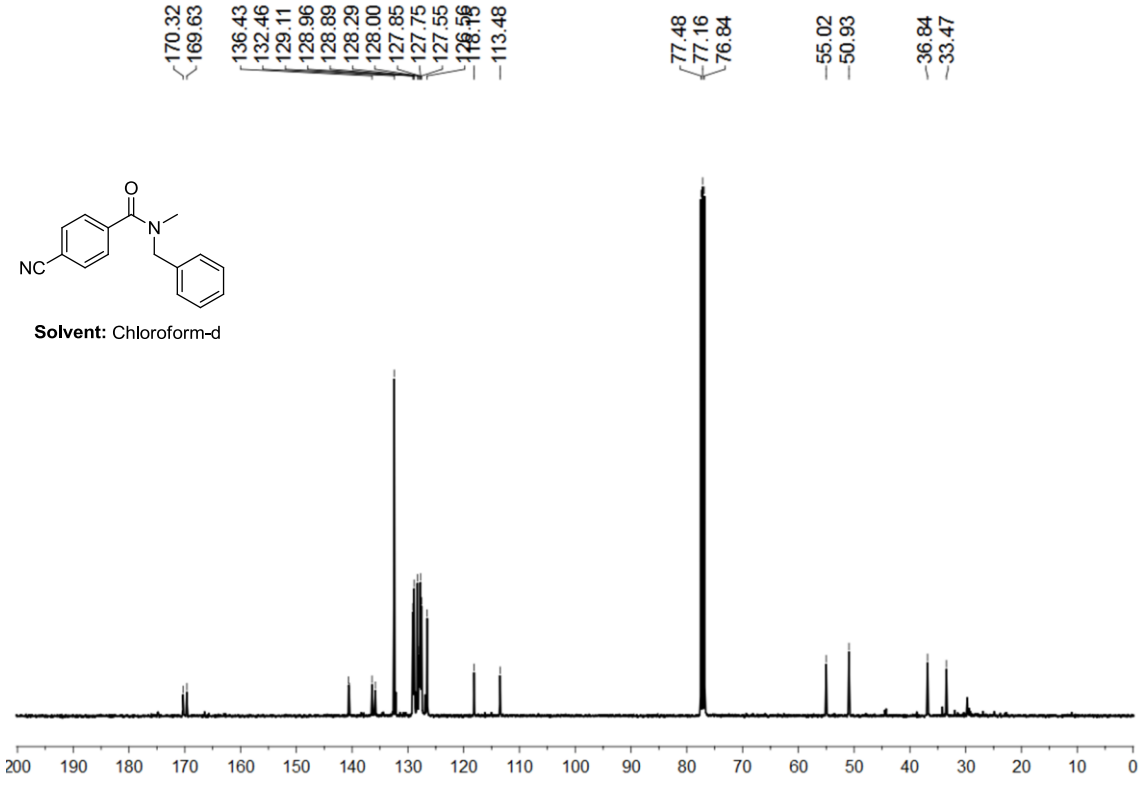


Figure 3.56 ^{13}C NMR spectrum of *N*-benzyl-4-cyano-*N*-methylbenzamide (**3z**).

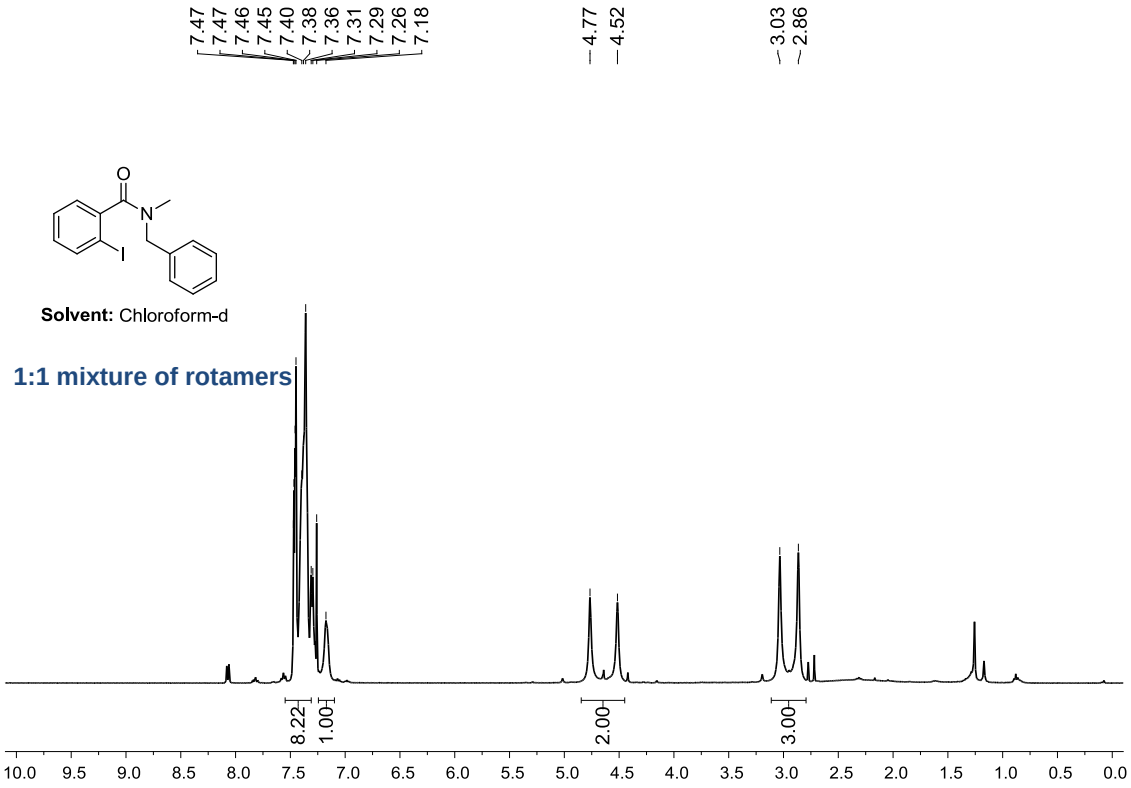


Figure 3.57 ^{1}H NMR spectrum of *N*-benzyl-2-iodo-*N*-methylbenzamide (**3aa**).

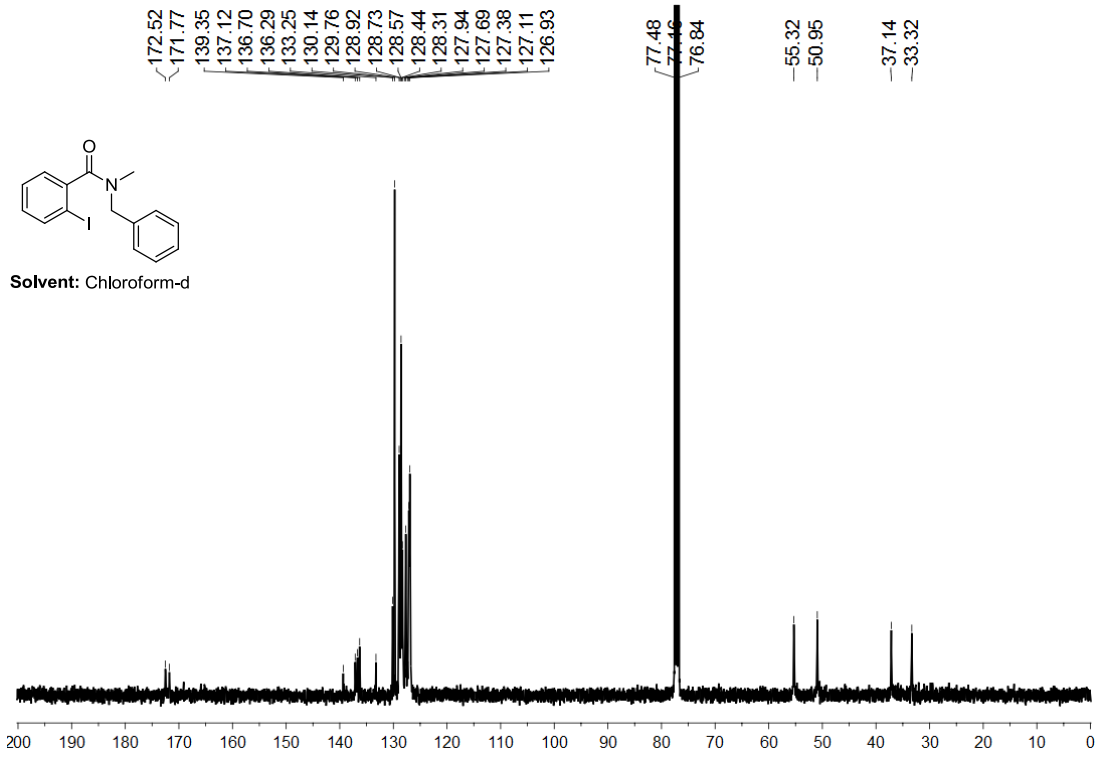


Figure 3.58 ^{13}C NMR spectrum of *N*-benzyl-2-iodo-*N*-methylbenzamide (**3aa**).

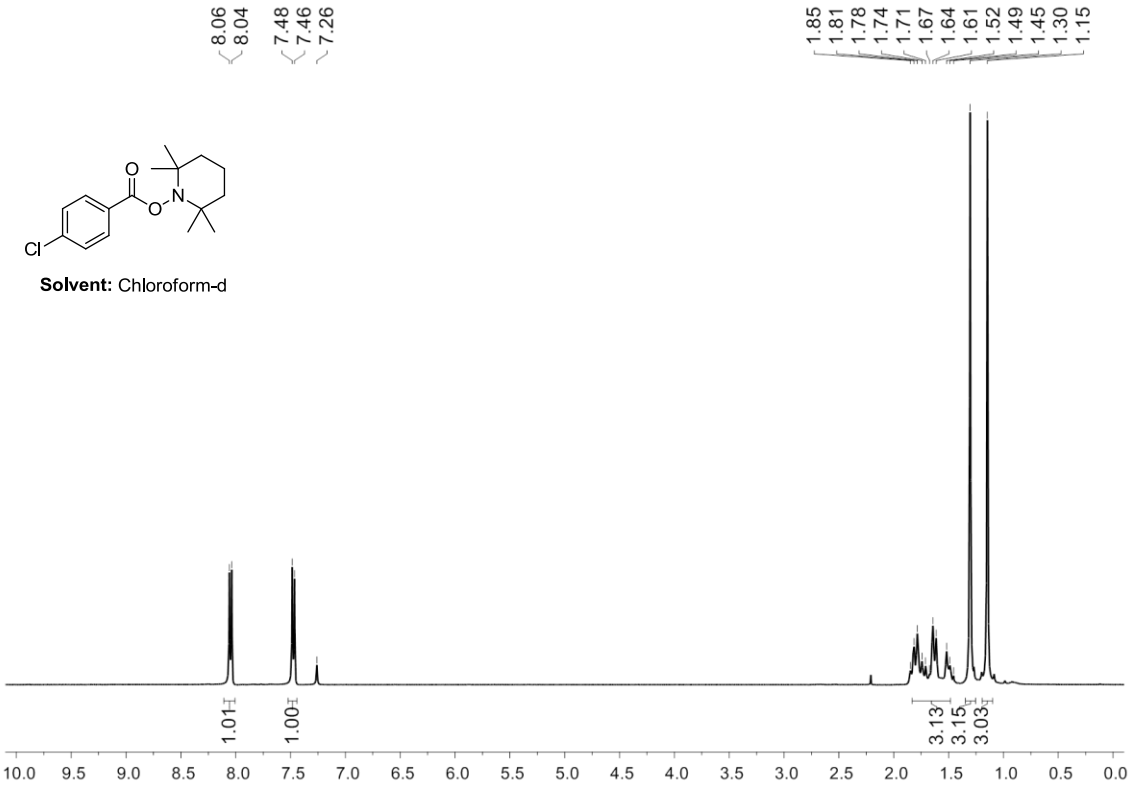


Figure 3.59 ^{1}H NMR spectrum of 2,2,6,6-tetramethylpiperidin-1-yl 4-chlorobenzoate (**5**).

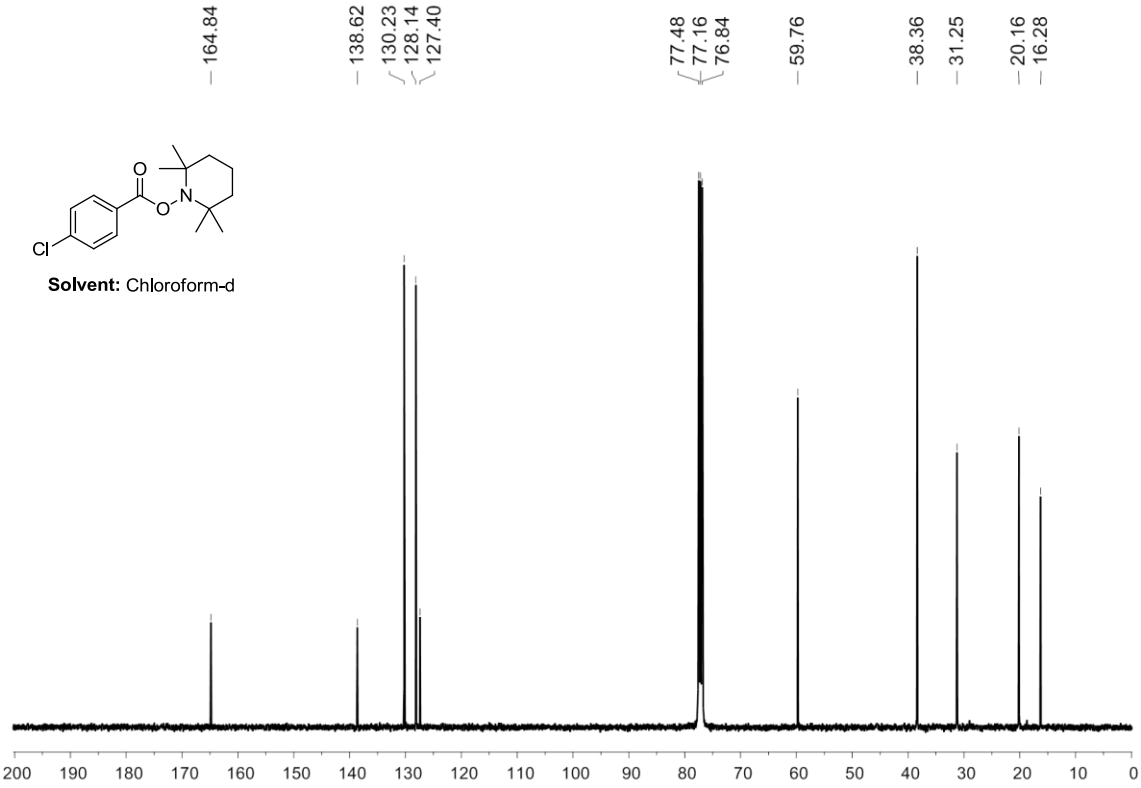
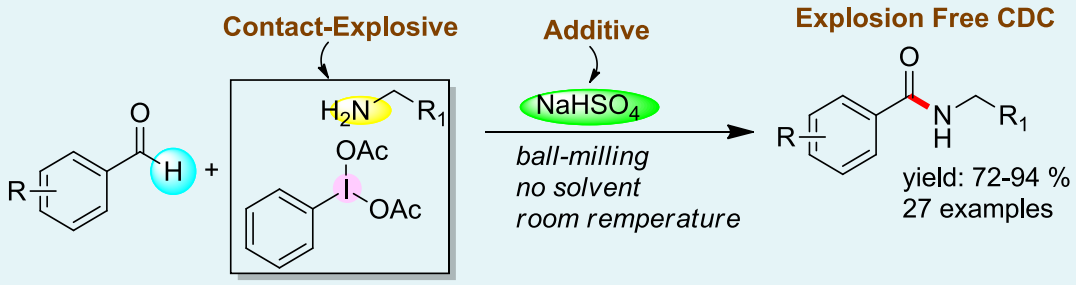


Figure 3.60 ^{13}C NMR spectrum of 2,2,6,6-tetramethylpiperidin-1-yl 4-chlorobenzoate (**5**).

CHAPTER 4

Transformation of Contact-Explosives Primary Amines and Iodine(III) into a Successful Chemical Reaction

4.1 ABSTRACT



Any synthetic transformation using contact-explosives primary amines and hypervalent iodine(III) (phenyliodine diacetate) in constrained media (extreme condition) is practically impossible. Herein, we report a method of controlling the explosion into a successful chemical reaction using acid-salt $NaHSO_4$. As a proof-of-concept, we considered mechanochemical (ball-milling) cross dehydrogenative coupling (CDC) reaction for amidation of aldehydes *via* C–H activation. The isothermal titration calorimetric (ITC) study was helpful to understand enthalpy changes during the reactions before and after addition of $NaHSO_4$.

4.2 INTRODUCTION

The behavior of chemical systems is known to be controlled by environment. In 1867, to reduce safety problems of transporting nitroglycerine, Alfred Nobel mixed absorbent clay 'Kieselguhr' with nitroglycerine to diminish the sensitivity.[1] Encapsulation within a cavity of a container molecule, known to stabilize of reactive species like cyclotrisiloxane[2], benzyne[3], cyclobutadiene[4] or 1,2,4,6-cycloheptatetraene[5] (Figure 4.1a). Also, we reported with Nitschke that white phosphorus was air-stable upon incarceration within tetrahedral metallo-supramolecular capsule

(Figure 4.1b).[6] Not only stabilization of reactive intermediates, also microenvironment could lead to direct the reaction pathway, *e.g.*, highly selective [2 + 2] cross-photodimerization of olefins was observed in crystalline encapsulated state (Figure 4.1c)[7]; on the contrary selectivity in the uncapsulated solution state was very poor. Rebek and coworkers tailored a molecular receptor which could stabilize the energetically unfavorable hemiaminal for minutes to an hour (Figure 4.1d)[8]. Iodine-ammonia combination is known as *contact explosive*[9] in constrained media. Similarly, hypervalent iodines as oxidizer[10] form charge transfer complex with fuel-amines[11] and

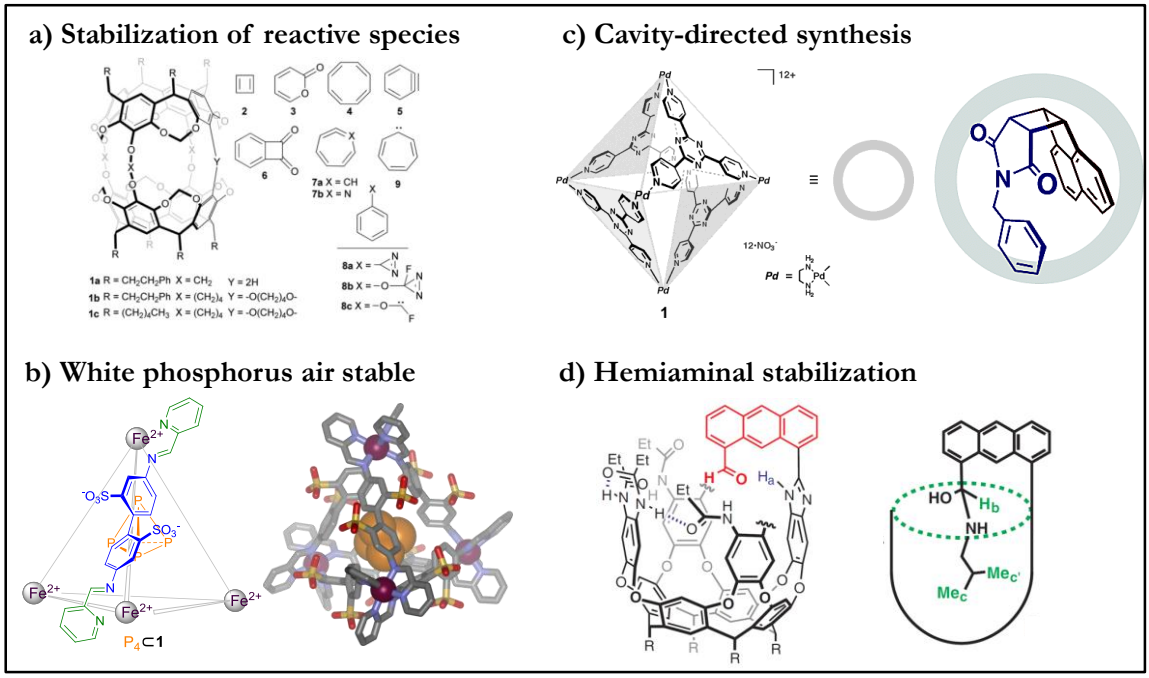


Figure 4.1. Controlling the chemical behaviour by micro-environment. Original artworks from the corresponding references with permissions from corresponding publishers.

cause highly exothermic reactions. Under solvent free condition (constrained media) reactants experience maximum possible contacts among themselves and create an extreme situation for contact-explosives. Therefore, violent exothermic reaction takes place for hypervalent iodine(III) reagents and electron rich amines under solvent free condition. To the best of our knowledge, no

synthetic applications using hypervalent iodine(III) reagents and primary amines in a constrained media is reported, if any.

Recently, ball-milling mechanochemistry,[12-14] has gained significant interest as an alternative technologies in organic synthesis.[15-17] This mechanochemical methodology has huge significance to green processes, time efficient, environmentally benign and shown to be economical. Towards quantitative conversion, less by products and minimum purification bring extra importance to this method.[18-21] The mechanochemical syntheses of small organic molecules,[16, 20] including hypervalent iodine mediated synthesis[22, 23] are well explored.

4.3 Results and Discussions:

We report here a mechanochemical cross dehydrogenative coupling (CDC)[24-30] for oxidative amidation[31-33] of aryl aldehydes *via* C–H activation[34-39] using phenyliodine diacetate (PIDA)[40-42] and benzyl amines. An acid-salt sodium bisulphate ($NaHSO_4$) was used to control the reactivity of contact-explosive (Figure 4.2).

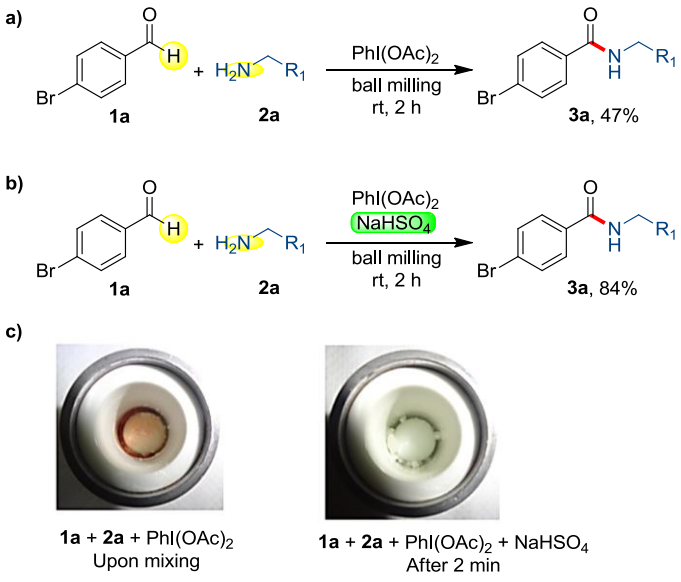


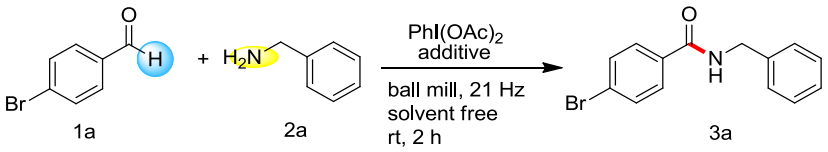
Figure 4.2. Mechanochemical cross dehydrogenative coupling (CDC); (a) Uncontrollable reaction in absence of $NaHSO_4$. (b) $NaHSO_4$ mediated explosion free and successful reaction. (c) Photographs of reaction mixture after explosion (left) and subsequent to making explosion free (right).

The CDC reaction has proven to be a powerful and atom-economic approach for C-N bond construction. Making C–N bond is an important transformation in organic synthesis as it constitutes the structural backbone of proteins and peptides through amide linkage. Common methods for oxidative amidation involve: coupling of carboxylic acids and amines in presence of a coupling agent,[43] acylation of amines with activated carboxylic acids etc.[44] We have also reported metal and solvent free oxidative amidation of aldehydes with *N*-chloramines *via* C–H activation under neat and ball-milling condition using TBAI (tetra-butyl ammonium iodide)-TBHP (*tert*-butyl hydroperoxide) combinations.[45]

For C–N bond constructions, hypervalent iodines are also considered as useful reagents.[46, 47] However, immediate explosion was observed and reaction mixture became brownish during mixing of benzaldehydes, benzyl amines and PIDA under solvent free ball-milling (*Caution!!*, see Caution paragraph in Experimental Section) (Figure 4.2c, left). Consequently, acetic acid generated (from PIDA) could control the reactivity of the amine through protonation and 47% of the amide was obtained (Figure 4.2a). The same reaction was found to be explosion free in presence of externally added acetic acid (yield 41%, Table 1). Likewise, an acid-salt $NaHSO_4$ (Figure 4.2b) as additive yielded 84% of **3a**.

Table 4.1 represents the optimization of reaction condition. Mechanochemical CDC for synthesis of *N*-benzyl-4-bromobenzamide (**3a**) was done successfully using 4-bromobenzaldehyde (1.0 equiv, **1a**), benzyl amine (1.1 equiv, **2a**), PIDA (2.0 equiv) and $NaHSO_4$ (2.0 equiv). During optimization, progress of the reaction was monitored using thin layer chromatography (TLC) or ^{1}H NMR spectroscopy.

Table 4.1. Optimization of reaction condition for synthesis of **3a**.



entry	PIDA (equiv)	Additiuve (equiv)	Yield (%)[b]
1	1.1	$NaHSO_4$ (1)	44
2	2.0	$NaHSO_4$ (2)	84 (67)
3	1.1	NaH_2PO_4 (1)	15
4	1.1	NaCl (1)	Trace
5	1.1	$NaHCO_3$ (1.2)	23
6	2	KH_2PO_4 (2)	19
7	2	AcOH (2)	41
8	2	H_2SO_4 (2)	11
9	2	PTSA (2)	< 5
10	2	TBAHS (2)	~ 5

[a]Reactions were performed with 1.0 equiv of **1a** and 1.1 equiv of **2a**. [b]Isolated yields (based on recovered aldehydes after chromatographic purification) are shown.

Amide derivatives were obtained in good to excellent yields (Figure 4.3) under optimized condition. Higher yields of amides were observed with the aromatic aldehydes containing electron withdrawing (**3a-3c**, **3f-3o**, **3q-3s**, **3u-3x**, **3z** and **3aa**) than electron donating groups (**3d**, **3e**, **3t**, **3y**). Amides from halogen substituted benzaldehydes (**3a**, **3f**, **3h**, **3j**, **3n**, **3o**, **3r** and **3w**) were also isolated in convincing yields. Accordingly, various amines like benzyl amine (**3a-h**, **3o**,**p**), 4-fluorobenzyl amine (**3i-k** and **3aa**), 2-phenylethanamine (**3q-u**), 2-chlorobenzyl amine (**3l-n**) and (3,5-bis(trifluoromethyl)phenyl)methanamine (**3v-z**) derivatives also facilitated excellent yields. In addition, reactions were performed under solvent free condition and therefore highly volatile aliphatic amines were not considered for this study.

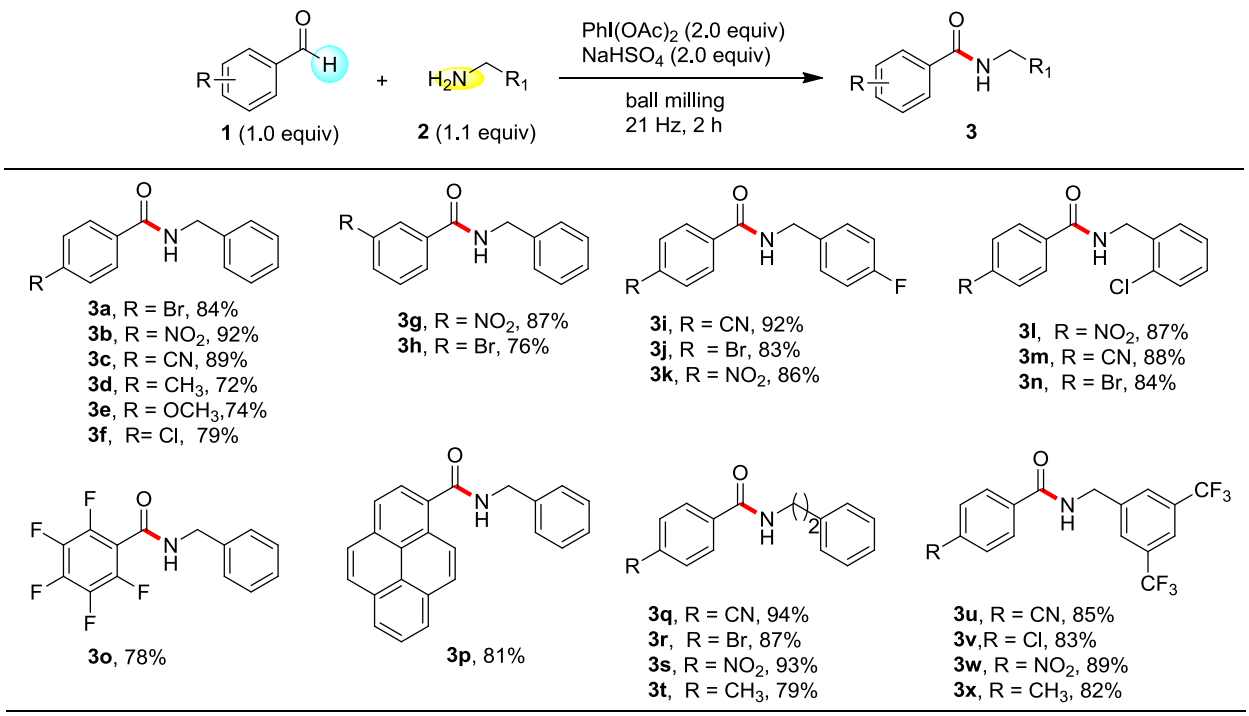


Figure 4.3. Compounds identification number and isolated yields are shown for the synthesized compounds.

Control experiments (Figure 4.4) were performed to shed some light on mechanism of the reaction. Reaction of 4-nitrobenzaldehyde (**1b**) with secondary amine (dibenzyl amine, **4**) led to corresponding amide in 13% yield (Figure 4.4a) and majority of aldehydes remained unreacted. More reactive secondary amine possibly destroyed PIDA and the reaction became uncontrollable using $NaHSO_4$. Oligomeric iodosyl benzene sulfate **6** $[(PhIO)_3SO_3)]_n$[48] is known to be synthesized from grinding of PIDA and $NaHSO_4$.[49] Mechanochemical milling of **6** and imine **5** (synthesized separately from **1a** and **2a**) did not results any amide (Figure 4.4b). Separately, **1a**, **2a** and **6** under ball-milling also led to explosion (*Caution!!*) (Figure 4.4d). More examples of unsuccessful one pot milling reactions were: (a) imine **5**, PIDA, $NaHSO_4$ and K_2CO_3 (14%, Figure 4.4c) (b) imine **5** and PIDA (0%, Figure 4.4e), because PIDA was unable to perform oxo transfer reactions (c) **5**, $NaHSO_4$ and PIDA (5%, Figure 4.4f). From these observations, it was rationalized that the

iodosylbenzene sulfate **6** $[(PhIO)_3SO_3)]_n$ was not the active reagent and imine **5** was not the intermediate[50] for this transformation. Expectedly, the oxidative amidation proceeded *via* hemiaminal intermediate (Figure 4.5a).[51]

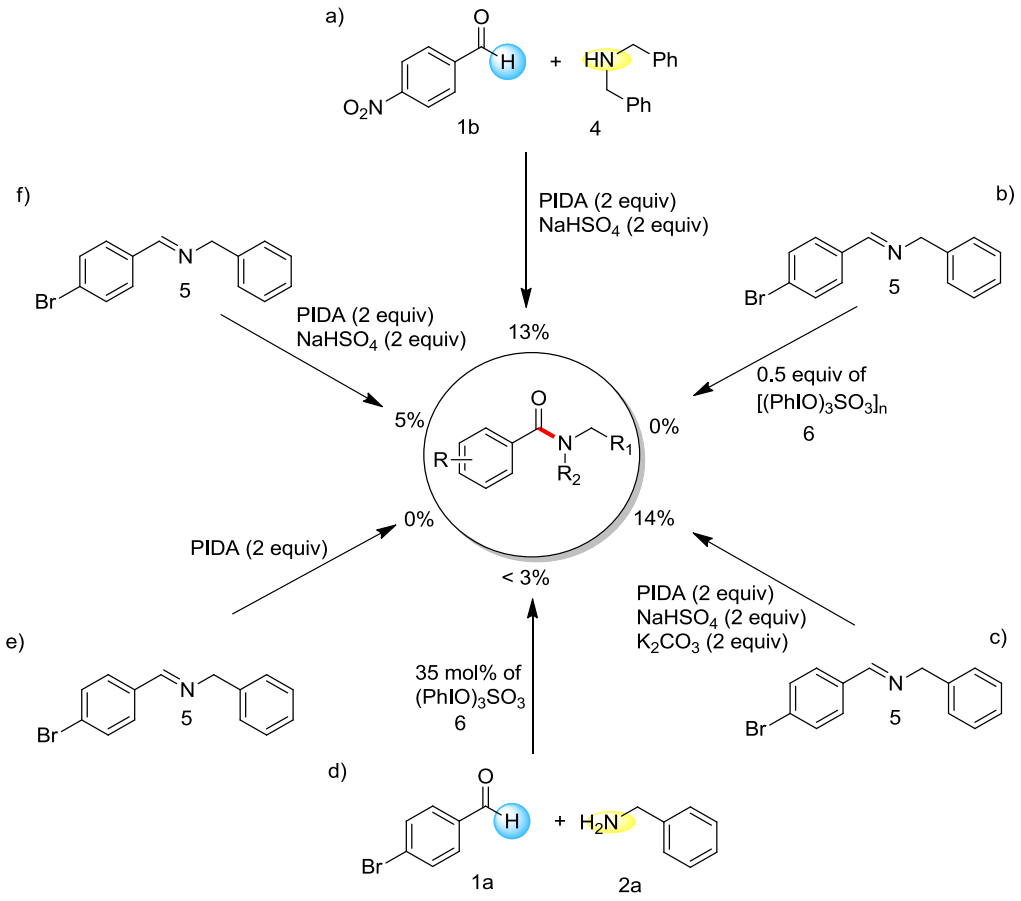


Figure 4.4. (a) – (f) Controlled experiments to understand the mechanism of the reaction.

The role of $NaHSO_4$ towards successful and explosion free mechanochemical CDC reactions was understood. The acid-salt $NaHSO_4$ is widely used in the poultry industry to decrease basic-ammonia and bacterial levels in litter[52]. In aqueous solution, $NaHSO_4$ acts as a medium-strong acid. A solution of 1.0 M $NaHSO_4$ in water shows pH < 1.0 and the bisulphate anion has pKa ~ 1.99. The pKa of benzyl amine is 9.38 (through dissociation of $-NH^+$) and that of comparable to ammonia (9.21)[53]. Ammonia generally reacts with $NaHSO_4$ to form salts ($2NaHSO_4 + 2NH_4OH$

→ $(NH_4)_2SO_4 + Na_2SO_4 + 2H_2O$).[52] Similarly, $NaHSO_4$ may form acid-base complex with basic amines to make explosion free oxidative amidation. Also, in presence of conc. H_2SO_4, benzyl amine did not react with either aldehyde or PIDA. Stronger protic acid H_2SO_4 (pKa -10) could completely deactivated the amine upon -NH^+ protonation. However, using weaker organic acid *p*-toluenesulfonic acid (pKa -2.8), the amide (**3a**) was isolated in < 5% yield. Pyrrolidine (pK_a 11.27 of conjugate acid in water) or 4-methoxy benzyl amines are stronger base than benzyl amine and the explosion could not be controlled using $NaHSO_4$. Following, no amidation products were isolated using pyrrolidine or 4-methoxy benzylamine (**3ab**-**3af**, Figure 4.5b). Also, gram scale synthesis of amide was done successfully using the proposed methodology.

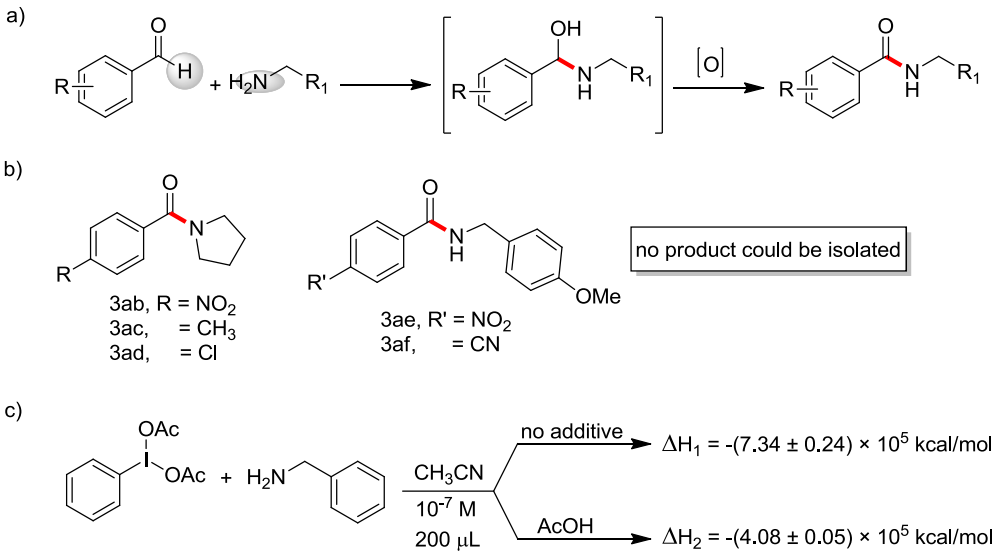


Figure 4.5. (a) Plausible mechanism for the CDC reaction. (b) Unsuccessful amidation under optimized condition. (c) Determination of enthalpy changes from the reaction of benzyl amine and PIDA, both in absence and presence of acetic acid (AcOH)

Isothermal titration calorimetric (ITC) analysis were performed to estimate the enthalpy of reaction (ΔH) from the reaction of PIDA and benzylamine in acetonitrile both in absence (ΔH_1) and

presence (ΔH_2) of acetic acid (Figure 4.5c, 4.6). The acetic acid could control the reaction and $\Delta\Delta H$ (ΔH_1 - ΔH_2) of the reaction was 3.26×10^5 kcal/mol.

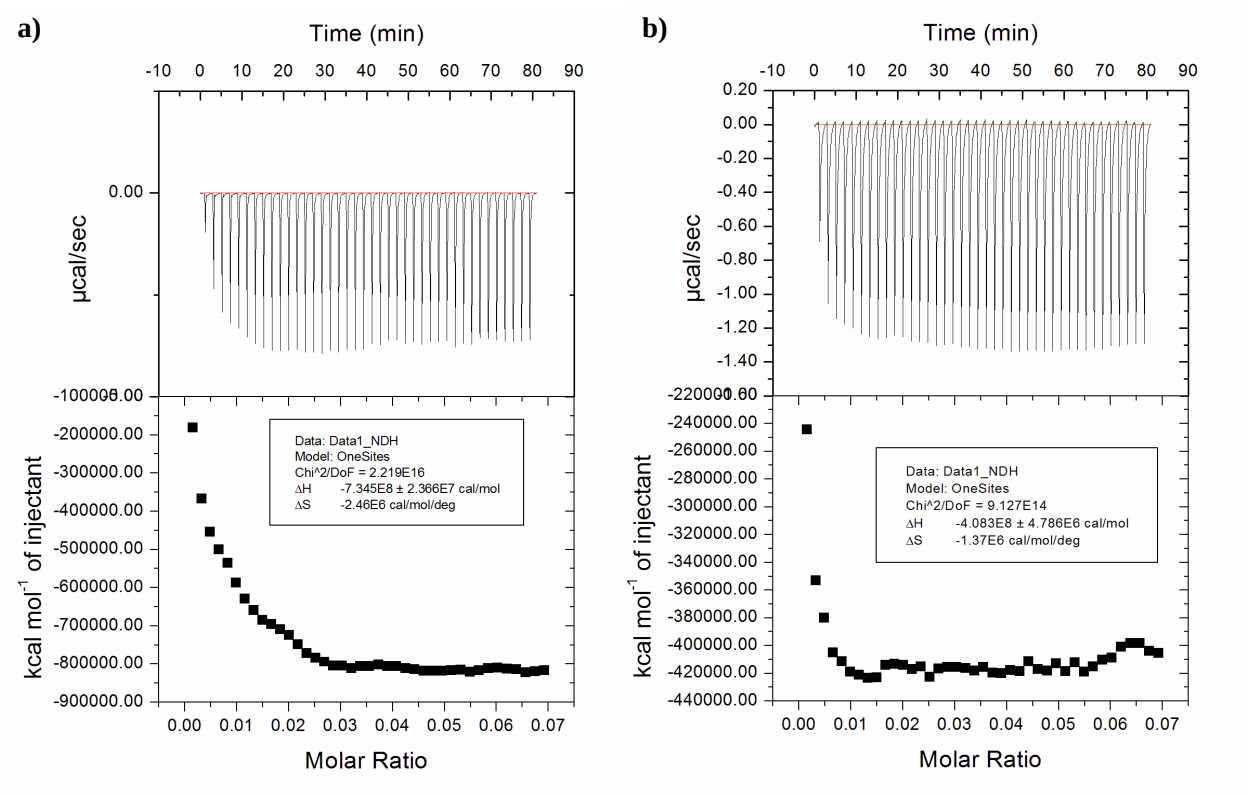


Figure 4.6. 2.08×10^{-7} M of benzylamine was titrated with 1.36×10^{-7} M of PIDA. (a) without any acid; (b) benzylamine was mixed with 2.08×10^{-7} M of acetic acid and then titrated with PIDA.

Amidation reactions using primary-amine and iodine(III) reported by Tiwari and co-workers were done in ionic liquid[50]. Higher concentration of primary-amine destroyed PIDA during fast addition and that resulted in poor yield of amides. Two-fold increase in yield of amide was achieved upon drop-wise addition of amine with constant stirring to PIDA solution in ionic liquids. High polarity of ionic liquids and high-dilution effect, cooperatively could stop the immediate explosion of primary amines and iodine(III). However, in this work under solvent-free ball-milling condition maximum possible concentration putting the system under high stress and thus it could

lead to uncontrollable oxidation more easily. As a result the explosion was observed immediately in absence of $NaHSO_4$.

4.4 CONCLUSIONS

In summary, the presented work is an unprecedented approach in which either an acid or acid-salt ($NaHSO_4$) could transform an explosive reaction mixture into a successful chemical reaction. A concept is proposed in which, by selecting an appropriate condition it is now possible to perform a highly exothermic reaction at ambient laboratory atmosphere. We anticipate that stopping an explosion of contact-explosives primary amines-phenyliodine diacetate and the safety benefits of using them are substantial: (a) a new research area can be initiated using this concept; (b) this approach could be used directly to diffuse dangerous chemical weapons; (c) environment can be protected through the sequestration of hazardous substances. This study also highlights the progress of C–H bond activation chemistry for the formation of amides and should find wide application in the context of both natural product synthesis and pharmaceuticals using mechanochemistry.

4.5 EXPERIMENTAL SECTIONS

General Methods. The ball milling (21 Hz) experiments were performed at open atmosphere. Column chromatographic purifications of compounds were done using silica-gel (mesh 100-200) and hexane-ethylacetate mixture as eluent, unless otherwise mentioned. NMR spectra were recorded on 400 MHz instrument at 25 °C. The chemical shift values are reported in parts per million (ppm) and referred to the residual chloroform (7.26 ppm for ^{1}H and 77.16 for ^{13}C) and deuterium oxide (4.79 ppm for ^{1}H). High-resolution mass spectrometry (HRMS) was conducted

on ESI-TOF (time of flight) mass spectrometer. Isothermal titration calorimetric (ITC) experiment was performed in MicroCal iTC200 isothermal titration calorimeter. Infrared spectral data are reported in wavenumber (cm^{-1}). Melting points of the compounds were determined using digital melting point apparatus and are uncorrected.

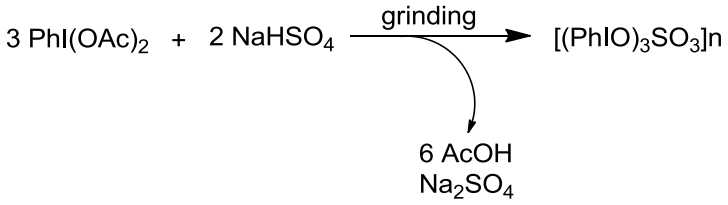
Caution: When PIDA and primary amines were mixed under solvent free condition, immediate explosion was observed. In presence of $NaHSO_4$, no explosion was observed under similar condition. Still, general safety concern at laboratory should be carefully exercised and highly recommended that all reactions should be carried out in a well-ventilated fume hood behind a blast shield.

Large scale synthesis: Recommended loading of the reactant materials should be less than one third of jar volume. In a 25 mL stainless steel milling jar two balls (15 mm dia), PIDA (1.74 gm, 5.4 mmol), $NaHSO_4$ (746 mg, 5.4 mmol), 4-bromobenzaldehyde (500 mg, 2.7 mmol) and benzylamine (324 µL, 2.9 mmol) added sequentially and milled 2 h. Workup and followed by purification (SI) led to 167 mg of 4-bromobenzaldehyde (1a) and product 3a (406 mg, yield 78%).

Isothermal Titration Calorimetric (ITC) study: In a typical procedure, 200 µL of 2.08×10^{-7} M of benzylamine and 40 µL of 1.36×10^{-7} M of PIDA in acetonitrile solution were taken into cell and syringe, respectively. Then benzylamine was titrated with PIDA by following the bellow specified experimental design.

Cell temperature 25 ºC; Initial delay 60 Sec; Stirring speed 600 rpm; Injection volume 0.5 µL (40 times); Duration of injection 3 Sec; Spacing between two injection 120 Sec.

Synthesis of oligomeric iodosylbenzene sulfate $[(PhIO)_3SO_3]_n$ (6):[54]



Phenyliodine diacetate (400 mg, 1.24 mmol) was added to $NaHSO_4 \cdot H_2O$ (176 mg, 1.03 mmol) in an agate mortar. Then the mixture was grinded for 10 min and the resulting mass was transferred to a beaker and dissolved in 5 mL of water. After 5 min, clear yellow solution was formed and allowed to settle for 2 h. After that yellow precipitate was filtered off and washed with cold water and dried to afford yellow crystalline compound (135 mg). The filtrate kept for slow evaporation and an additional 92 mg of compound was isolated. Total 227 mg (74%) of **6** was isolated. ^{1}H NMR (400 MHz, D_2O) δ 8.09 (d, *J* = 8 Hz, 2H), 7.71 (t, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 2H).^{13}C NMR (100 MHz, D_2O) δ 134.3, 133.1, 131.5, 123.5.

General procedure for the preparation of amides under ball-milling: In a 10 mL stainless steel milling jar, benzylamine (65 µL, 0.59 mmol) was added to the mixture of 4-bromobenzaldehyde (100 mg, 0.54 mmol), PIDA (348 mg, 1 mmol), $NaHSO_4$ (149 mg, 1 mmol) and one grinding ball (15 mm diameter, Stainless Steel). The progress of the reaction under milling condition was monitored by thin layer chromatography (TLC) or ^{1}H NMR. After complete the reaction, the mixture was dissolved in dichloromethane and compound (*N*-Benzyl-4-bromobenzamide) was purified by column chromatography. Isolated materials: 20 mg of 4-Bromobenzaldehyde (**1a**) was recovered as unreacted material and **3a** (105 mg, yield 84% based on recovered **1a**).

Compound characterization data.

The isolated yields (after column chromatography) were calculated based on recovered starting material. However, in parenthesis the yields are calculated based on aldehydes used for the reaction.

***N*-Benzyl-4-bromobenzamide (3a):** R_f = 0.30 (ethyl acetate/hexane = 1:4); white solid; yield 84% (73 mg, 67 %); mp 155−159 °C (lit.[55] 160−162 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8 Hz, 2H), 7.56 (d, *J* = 8 Hz, 2H), 7.35-7.31 (m, 5H), 6.42 (br s, 1H), 4.63 (d, *J* = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 138.0, 133.3, 131.9, 129.0, 128.7, 128.1, 127.9, 126.4, 44.4; IR (KBr) $\tilde{\nu}$ 3308 (m), 3081 (s), 2919 (s), 2848 (s), 1640 (m), 1548 (m), 1416 (s), 1256 (s), 847 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{13}BrNO$ ($M + H^+$) 290.0175, found 290.0176.

***N*-Benzyl-4-nitrobenzamide (3b):** R_f = 0.32 (ethyl acetate/hexane = 1:4); white solid; yield 92% (87 mg, 73%); mp 141−144 °C (lit.[56] 142 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8 Hz, 2H), 7.94 (d, *J* = 8 Hz, 2H), 7.37 – 7.34 (m, 5H), 6.60 (br s, 1H), 4.65 (d, *J* = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 149.7, 140.0, 137.5, 129.0, 128.3, 128.1, 128.1, 123.9, 44.6; IR (KBr) $\tilde{\nu}$ 3280 (m), 2922 (m), 2839 (s), 1633 (m), 1597 (m), 1515 (m), 1345 (m), 1105 (s), 870 (s), 697 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{13}N_2O_3$ ($M + H^+$) 257.0921, found 257.0924.

***N*-Benzyl-4-cyanobenzamide (3c):** R_f = 0.32 (ethyl acetate/hexane = 1:4); white solid; yield 89% (89 mg, 71%); mp 154−156 °C (lit.[57] 150−151 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8 Hz, 2H), 7.69 (d, *J* = 8 Hz, 2H), 7.37 – 7.29 (m, 5H), 6.67 (br s, 1H), 4.62 (d, *J* = 4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 138.3, 137.6, 132.5, 129.0, 128.0, 128.0, 127.8, 118.0, 115.2, 44.4; IR (KBr) $\tilde{\nu}$ 3316 (w), 2923 (s), 2218 (s), 1643 (m), 1550 (s), 1422 (s), 1311 (s), 864 (s), 721 (s) cm^{-1}; IR (KBr) $\tilde{\nu}$ 3315 (w), 3090 (s), 3064 (s), 3028 (s), 2923 (s), 2231 (s), 1644 (s), 1547 (m),

1496 (m), 1286 (m), 857 (m), 697 (m) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{13}N_2O$ ($M + H^+$) 237.1022, found 237.1041.

***N*-benzyl-4-methylbenzamide (3d):** R_f = 0.40 (ethyl acetate/hexane = 1:4); white solid; yield 72% (77 mg, 59%); mp 133−136 °C (lit.[55] 131−134 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.1 Hz, 6H), 7.37 – 7.27 (m, 16H), 7.21 (d, *J* = 8.0 Hz, 6H), 6.58 (s, 3H), 4.61 (d, *J* = 5.6 Hz, 7H), 2.39 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.43, 142.02, 138.47, 131.63, 129.31, 128.83, 128.65, 127.97, 127.65, 127.61, 127.10, 77.48, 77.16, 76.84, 44.12, 21.53; IR (KBr) $\tilde{\nu}$ 3311 (m), 3085 (s), 3054 (s), 3028 (s), 1639 (m), 1546 (m), 1420 (s), 1323 (s), 1058 (s), 841 (s), 721 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{16}NO$ ($M + H^+$) 226.1226, found 226.1247.

***N*-Benzyl-4-methoxybenzamide (3e):** R_f = 0.20 (ethyl acetate/hexane = 1:4); white solid; yield 74% (69 mg, 56%); mp 118−121 °C (lit.[58] 124−126 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8 Hz, 2H), 7.40 – 7.28 (m, 5H), 6.92 (d, *J* = 8 Hz, 2H), 6.31 (br s, 1H), 4.64 (d, *J* = 8 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 162.3, 138.5, 128.9, 128.9, 128.0, 127.7, 126.7, 113.9, 55.5, 44.2; IR (KBr) $\tilde{\nu}$ 3521 (w), 3295 (m), 3054 (s), 1633 (m), 1537 (m), 1505 (s), 1256 (s), 846 (m), 726 (m) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{16}NO_2$ ($M + H^+$) 242.1176, found 242.1198.

***N*-Benzyl-4-chlorobenzamide (3f):** R_f = 0.25 (ethyl acetate/hexane = 1:4); white solid; yield 79% (76 mg, 62%); mp 157−162 °C (lit.[55] 163−166 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8 Hz, 2H), 7.43 (d, *J* = 8 Hz, 2H), 7.37 – 7.27 (m, 5H), 6.51 (br s, 1H), 4.645 (d, *J* = 4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 138.2, 134.4, 131.6, 128.9, 128.7, 128.0, 127.7, 127.1, 44.2; IR (KBr) $\tilde{\nu}$ 3324 (m), 3059 (s), 3030 (s), 2928 (s), 1643 (s), 1603 (s), 1576 (s), 1542 (m), 1452 (s), 1418 (s), 1312 (s), 1259 (s), 1028 (s), 727 (s), 694 (m), 666 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{13}ClNO$ ($M + H^+$) 246.0686, found 246.0672.

***N*-Benzyl-3-nitrobenzamide (3g):** R_f = 0.17 (ethyl acetate/hexane = 1:4); white solid; yield 87% (81 mg, 68%); mp 99−102 °C (lit.[59] 95−96 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.34 (d, *J* = 8 Hz, 1H), 8.17 (d, *J* = 8 Hz, 1H), 7.63 (dt, *J* = 11.7, 6.0 Hz, 1H), 7.36 – 7.31 (m, 5H), 6.75, 6.65 (br s, 1H), 4.655 (d, *J* = 4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 148.3, 137.6, 136.1, 133.4, 130.0, 129.0, 128.1, 128.0, 126.2, 121.9, 44.6; IR (KBr) $\tilde{\nu}$ 3301 (w), 3086 (s), 2926 (s), 1642 (m), 1528 (m), 1349 (m), 1159 (s), 1081 (s), 909 (s), 814 (s), 699 (m) cm−1; HRMS (ESI-TOF) calcd for $C_{14}H_{13}N_2O_3$ ($M + H^+$) 257.0921, found 257.0931.

***N*-Benzyl-3-bromobenzamide (3h):**[60] R_f = 0.30 (ethyl acetate/hexane = 1:4); white solid; yield 76% (69 mg, 63%); mp 112−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.71 (d, *J* = 8 Hz, 1H), 7.62 (d, *J* = 8 Hz, 1H), 7.38 – 7.27 (m, 6H), 6.43 br (s, 1H), 4.635 (d, *J* = 4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 137.9, 136.4, 134.6, 130.3, 130.3, 129.0, 128.1, 127.9, 125.7, 122.9, 44.4; IR (KBr) $\tilde{\nu}$ 3320 (m), 3063 (s), 3028 (s), 2925 (s), 1638 (m), 1562 (m), 1542 (m), 1471 (s), 1454 (s), 1315 (s), 1071 (s), 996 (s), 894 (s), 744 (m), 698 (m) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{13}BrNO$ ($M + H^+$) 290.0175, found 290.0189.

4-Cyano-*N*-(4-fluorobenzyl)benzamide (3i): R_f = 0.20 (ethyl acetate/hexane = 1:4); white solid; yield 92% (100 mg, 74%); mp 109−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8 Hz, 2H), 7.72 (d, *J* = 8 Hz, 2H), 7.31 (dd, *J* = 10, 6 Hz, 2H), 7.03 (dd, *J* = 12, 5 Hz, 2H), 6.59 (br s, 1H), 4.60 (d, *J* = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 162.5 (d, $^1J_{CF}$ = 245 Hz), 138.2, 133.5 (d, $^4J_{CF}$ = 3 Hz), 132.6, 129.8 (d, $^3J_{CF}$ = 8 Hz), 127.8, 118.0, 115.9 (d, $^2J_{CF}$ = 21 Hz), 115.3, 43.7; IR (KBr) $\tilde{\nu}$ 3265 9m), 3094 (m), 2922 (m), 2852 (s), 2230 (m), 1633 (m), 1556 (m), 1512 (m), 1428 (s), 1251 (s), 1220 (m), 1154 (s), 1059 (s), 861 (m), 840 (m), 807 (m), 731 (s), cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{12}FN_2O$ ($M + H^+$) 255.0928, found 255.0925.

4-Bromo-*N*-(4-fluorobenzyl)benzamide (3j): R_f = 0.35 (ethyl acetate/hexane = 1:4); white solid; yield 83% (80 mg, 69%); mp 128−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.28 (dd, *J* = 8.3, 5.5 Hz, 2H), 7.01 (t, *J* = 8.6 Hz, 2H), 6.65 (br s, 1H), 4.55 (d, *J* = 5.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 162.4 (d, $^1J_{CF}$ = 244 Hz), 133.9 (d, $^4J_{CF}$ = 3 Hz), 133.1, 131.9, 129.7 (d, $^3J_{CF}$ = 8 Hz), 128.7, 126.4, 115.7 (d, $^2J_{CF}$ = 21 Hz), 43.5; IR (KBr) $\tilde{\nu}$ 3315 (m), 3081 (s), 1638 (m), 1548 (m), 1227 (s), 841 (s), 801 (s), 711 (s) cm−1; HRMS (ESI-TOF) calcd for $C_{14}H_{12}BrFNO$ ($M + H^+$) 308.0081, found 308.0099.

***N*-(4-fluorobenzyl)-4-nitrobenzamide (3k):** R_f = 0.30 (ethyl acetate/hexane = 1:4); white solid; yield 86% (85 mg, 67%); mp 129−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8 Hz, 2H), 7.94 (d, *J* = 8 Hz, 2H), 7.33 (s, 2H), 7.04 (t, *J* = 8.1 Hz, 2H), 6.57 (br s, 1H), 4.625 (d, *J* = 4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 162.5 (d, $^1J_{CF}$ = 245 Hz), 149.8, 139.9, 133.4 (d, $^4J_{CF}$ = 3 Hz), 129.9 (d, $^3J_{CF}$ = 9 Hz), 128.3, 124.0, 115.9 (d, $^2J_{CF}$ = 22 Hz), 43.8; IR (KBr) $\tilde{\nu}$ 3271 (m), 3077 (s), 2923 (m), 2853 (m), 1644 (m), 1600 (m), 1548 (m), 1510 (m), 1349 (m), 1219 (m), 1156 (s), 1064 (s), 981 (s), 824 (m), 723 (m) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{12}FN_2O_3$ ($M + H^+$) 275.0826, found 275.0829.

***N*-(2-chlorobenzyl)-4-nitrobenzamide (3l):** R_f = 0.45 (ethyl acetate/hexane = 1:4); white solid; yield 87% (93 mg, 69%); mp 163−166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8 Hz, 2H), 7.93 (d, *J* = 8 Hz, 2H), 7.48 – 7.38 (m, 2H), 7.29-7.25 (m, 2H), 6.69 (br s, 1H), 4.745 (d, *J* = 4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 149.6, 139.8, 134.9, 133.8, 130.8, 129.7, 129.5, 128.2, 127.3, 123.8, 42.5; IR (KBr) $\tilde{\nu}$ 3331 (m), 3063 (s), 2920 (m), 2857 (s), 1644 (m), 1598 (m), 1523 (m), 1345 (m), 1300 (m), 1015 (s), 752 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{12}ClN_2O_3$ ($M + H^+$) 291.0531, found 291.0537.

***N*-(2-chlorobenzyl)-4-cyanobenzamide (3m):** R_f = 0.30 (ethyl acetate/hexane = 1:4); white solid; yield 88% (92 mg, 64%); mp 132−135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.51 – 7.43 (m, 1H), 7.43 – 7.36 (m, 1H), 7.30 – 7.25 (m, 2H), 6.70 (s, 1H), 4.73 (d, *J* = 5.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.67, 138.29, 135.10, 133.94, 132.61, 130.83, 129.86, 129.55, 127.86, 127.43, 118.09, 115.36, 77.48, 77.16, 76.84, 42.54; IR (KBr) $\tilde{\nu}$ 3415 (w), 2923 (s), 2848 (s), 2230 (s), 1648 (m), 1543 (s), 1288 (s), 858(s), 750 (m) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{12}ClN_2O$ (M + H$^+$) 271.0632, found 271.0640.

4-Bromo-*N*-(2-chlorobenzyl)benzamide (3n): R_f = 0.37 (ethyl acetate/hexane = 1:4); white solid; yield 84% (83 mg, 68%); mp 138−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8 Hz, 2H), 7.56 (d, *J* = 8 Hz, 2H), 7.46 (dd, *J* = 6, 4 Hz, 1H), 7.39 (dd, *J* = 8, 4 Hz, 1H), 7.27 – 7.24 (m, 2H), 6.56 (br s, 1H), 4.72 (d, *J* = 8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 135.4, 133.9, 133.2, 132.0, 130.7, 129.8, 129.3, 128.7, 127.4, 126.4, 42.3; IR (KBr) $\tilde{\nu}$ 3320 (m), 3068 (s), 1633 (m), 1590 (s), 1539 (m), 1482 (m), 1318 (m), 1070 (s), 1009 (s), 847 (s), 749 (m) cm−1; HRMS (ESI-TOF) calcd for $C_{14}H_{12}BrClNO$ (M + H$^+$) 323.9785, found 323.9794.

***N*-Benzyl-2,3,4,5,6-pentafluorobenzamide (3o):** R_f = 0.45 (ethyl acetate/hexane = 1:4); white solid; yield 78% (63 mg, 59%); mp 215 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 5H), 6.42 (br s, 1H), 4.61 (d, *J* = 8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 145.7–145.4 (m), 143.9–143.5 (m), 143.2–142.9 (m), 141.3–141.0, 139.2–138.8 (m), 136.7–136.3 (m), 129.0, 128.1, 127.8, 111.7–111.3 (m), 44.5; IR (KBr) $\tilde{\nu}$ 3235 (m), 3068 (m), 2953 (m), 1652 (m), 1566 (s), 1494 (m), 1059 (s), 988 (m), 875 (s), 746 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_9F_5NO$ (M + H$^+$) 302.0599, found 302.0588.

***N*-benzylpyrene-1-carboxamide (3p):** R_f = 0.32 (ethyl acetate/hexane = 1:4); white solid; yield 81% (49 mg, 48%); mp 105 °C; 4:3 mixture of rotamers;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (dd,

J = 9.2, 3.5 Hz, 1H), 8.28 – 8.16 (m, 2H), 8.16 – 7.93 (m, 6H), 7.84 – 7.71 (m, 3H), 7.52 – 7.37 (m, 8H), 7.37 – 7.27 (m, 8H), 6.60 (s, 1H), 6.49 (s, 1H), 4.87 – 4.73 (m, 2H), 4.71 – 4.54 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 167.4, 138.3, 138.3, 134.4, 132.6, 131.6, 131.2, 130.8, 130.8, 128.9, 128.9, 128.8, 128.7, 128.6, 128.1, 128.0, 127. 8, 127.7, 127.2, 127.1, 126.4, 125.9, 125.8, 124.8, 124.6, 124.5, 124.4, 77.9, 77.2, 76.8, 44.8, 44.2; IR (KBr) $\tilde{\nu}$ 3288 (m), 3063 (s), 3030 (s), 2923 (s), 1635 (m), 1537 (m), 1490 (s), 1291 (m), 848 (s), 695 (m) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{24}H_{18}NO$ ($M + H^+$) 336.1383, found 336.1393.

4-Cyano-*N*-phenethylbenzamide (3q): R_f = 0.18 (ethyl acetate/hexane = 1:4); white solid; yield 94% (91 mg, 68%); mp 115−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8 Hz, 2H), 7.70 (d, *J* = 8 Hz, 2H), 7.35 – 7.32 (m, 2H), 7.28 – 7.22 (m, 3H), 6.21 (br s, 1H), 3.76 – 3.71 (m, 2H), 2.95 (t, *J* = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 138.6, 132.5, 128.9, 128.9, 127.6, 126.9, 118.1, 115.1, 41.4, 35.6; IR (KBr) $\tilde{\nu}$ 3306 (w), 3085 (s), 2923 (s), 2852 (s), 2228 (s), 1633 (m), 1543 (m), 1497 (s), 1313 (s), 857 (s), 753 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{15}N_2O$ ($M + H^+$) 251.1178, found 251.1192.

4-Bromo-*N*-phenethylbenzamide (3r): R_f = 0.35 (ethyl acetate/hexane = 1:4); white solid; yield 87% (71 mg, 62%); mp 113−116 °C (lit.[61] 143−144 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 4H), 7.35 – 7.32 (m, 2H), 7.27 – 7.22 (m, 3H), 6.08 (br s, 1H), 3.71 (dd, *J* = 12, 8 Hz, 2H), 2.93 (t, *J* = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 138.8, 133.5, 131.9, 131.8, 128.9, 128.5, 126.8, 126.2, 41.3, 35.7; IR (KBr) $\tilde{\nu}$ 3419 (w), 2923 (s), 2848 (s), 1639 (m), 1542 (s), 1482 (s), 1317 (s), 1068 (s), 1009 (s), 755 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{15}BrNO$ ($M + H^+$) 304.0331, found 304.0348.

4-Nitro-*N*-phenethylbenzamide (3s): R_f = 0.20 (ethyl acetate/hexane = 1:4); white solid; yield 93% (95 mg, 76%); mp 152−156 °C (lit.[62] 151 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8

Hz, 2H), 7.83 (d, *J* = 8 Hz, 2H), 7.34 – 7.22 (m, 5H), 6.31 (br s, 1H), 3.74 (dd, *J* = 12, 6 Hz, 2H), 2.96 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 149.6, 140.3, 138.6, 128.9, 128.8, 128.1, 126.9, 123.9, 41.5, 35.5; IR (KBr) $\tilde{\nu}$ 3328 (m), 3063 (s), 2923 (s), 1643 (m), 1597 (m), 1541 (m), 1517 (m), 1452 (s), 1352 (s), 1193 (s), 867 (s), 753 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{15}N_2O_3$ ($M + H^+$) 271.1077, found 271.1077.

4-Methyl-*N*-phenethylbenzamide (3t): R_f = 0.25 (ethyl acetate/hexane = 1:4); white solid; yield 79% (99 mg, 71%); mp 82−84 °C (lit.[63] 76−77 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8 Hz, 2H), 7.33 (d, *J* = 8 Hz, 2H), 7.27 – 7.21 (m, 5H), 6.15 (br s, 1H), 3.72 (dd, *J* = 12, 8 Hz, 2H), 2.94 (t, *J* = 6.8 Hz, 2H), 2.39 (s, 3H). ^{13}CNMR (100 MHz, $CDCl_3$) δ 167.5, 141.9, 139.1, 131.9, 129.3, 128.9, 128.8, 126.9, 126.7, 41.2, 35.8, 21.5; IR (KBr) $\tilde{\nu}$ 3313 (m), 3026 (s), 2937 (s), 1637 (m), 1534 (m), 1307 (m), 1199 (s), 836 (s), 749 (s), 697 (m) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{17}NNaO$ ($M + Na^+$) 262.1202, found 262.1211.

3-Nitro-*N*-phenethylbenzamide(3u): R_f = 0.20 (ethyl acetate/hexane = 1:4); white solid; yield 90% (97 mg, 78%); mp 118−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.35 (d, *J* = 8 Hz, 1H), 8.08 (d, *J* = 8 Hz, 1H), 7.63 (t, *J* = 8 Hz, 1H), 7.32 (dt, *J* = 17, 7.8 Hz, 5H), 6.28 (br s, 1H), 3.77 (dd, *J* = 12, 6 Hz, 2H), 2.98 (t, *J* = 6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 148.3, 138.6, 136.4, 133.1, 130.0, 128.9, 128.9, 126.9, 126.1, 121.8, 41.5, 35.6; IR (KBr) $\tilde{\nu}$ 3305 (m), 3085 (s), 3032 (s), 2923 (s), 1644 (m), 1530 (m), 1350 (m), 1322 (m), 906 (s), 814 (s), 719 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{15}N_2O_3$ ($M + H^+$) 271.1077, found 271.1088.

***N*-(3,5-bis(trifluoromethyl)benzyl)-4-cyanobenzamide (3v):** R_f = 0.32 (ethyl acetate/hexane = 1:4); white solid; yield 85% (143 mg, 72%); mp 166−170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8 Hz, 2H), 7.82 – 7.81 (m, 3H), 7.77 (d, *J* = 8 Hz, 2H), 6.70 (br s, 1H), 4.775 (d, *J* = 4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 140.5, 137.6, 132.8, 132.4 (q, J_{CF} = 79.5 Hz), 128.1

(d, J_{CF} = 3 Hz), 127.9, 123.3 (q, J_{CF} = 543 Hz), 122.0 (q, J_{CF} = 7 Hz), 117.9, 115.8, 43.5; IR (KBr) $\tilde{\nu}$ 3407 (w), 3249 (m), 3050 (s), 2920 (s), 2851 (s), 2234 (s), 1642 (m), 1543 (m), 1307 (s), 1278 (m), 1160 (s), 1116 (m), 985 (s), 703 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{11}F_6N_2O$ ($M + H^+$) 373.0770, found 373.0770.

***N*-(3,5-bis(trifluoromethyl)benzyl)-4-chlorobenzamide (3w):** R_f = 0.40 (ethyl acetate/hexane = 1:4); white solid; yield 83% (124 mg, 65%); mp 137−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 3H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 6.58 (s, 1H), 4.76 (d, *J* = 6.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 140.9, 138.5, 132.3 (q, J_{CF} = 66 Hz), 132.1, 129.2, 128.6, 128.0 (d, J_{CF} = 3 Hz), 123.3 (q, J_{CF} = 542 Hz), 121.8 (q, J_{CF} = 8 Hz), 43.4; IR (KBr) $\tilde{\nu}$ 3286 (w), 3076 (m), 2927 (s), 1640 (s), 1538 (m), 1487 (m), 1278 (s), 1173 (s), 1132 (s), 845 (m), 705 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{11}ClF_6NO$ ($M + H^+$) 382.0428, found 382.0451.

***N*-(3,5-bis(trifluoromethyl)benzyl)-4-nitrobenzamide (3x):** R_f = 0.27 (ethyl acetate/hexane = 1:4); white solid; yield 89% (133 mg, 73%); mp 165−167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8 Hz, 2H), 7.98 (d, *J* = 8 Hz, 2H), 7.82 (s, 3H), 6.72 (br s, 1H), 4.795 (d, *J* = 4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 150.1, 140.4, 139.2, 132.4 (q, J_{CF} = 66 Hz), 128.4, 128.2 (d, J_{CF} = 3 Hz), 123.2 (q, J_{CF} = 542 Hz), 124.2, 122.0 (q, J_{CF} = 8 Hz), 43.6; IR (KBr) $\tilde{\nu}$ 3298 (m), 3056 (s), 2989 (s), 2929 (s), 2851 (s), 1644 (m), 1600 (m), 1519 (m), 1352 (m), 1282 (m), 1124 (m), 985 (s), 896 (s), 870 (s), 738 (m) cm−1; HRMS (ESI-TOF) calcd for $C_{16}H_{11}F_6N_2O_3$ ($M + H^+$) 393.0668, found 393.0673.

***N*-(3,5-bis(trifluoromethyl)benzyl)-4-methylbenzamide (3y):** R_f = 0.40 (ethyl acetate/hexane = 1:4); white solid; yield 82% (147 mg, 70%); mp 107−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.54 (m, 5H), 7.23 (s, 2H), 6.91 (s, 1H), 4.72 (s, 2H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 142.7, 141.4, 132.1 (q, J_{CF} = 67 Hz), 130.9, 129.5, 127.9, 127.1, 123.3 (q, J_{CF} = 542 Hz),

121.5 (q, J_{CF} = 7 Hz), 43.2, 21.5; IR (KBr) $\tilde{\nu}$ 3303 (w), 3047 (s), 2934 (s), 1634 (m), 1538 (m), 1505 (m), 1380 (m), 1355 (m), 1278 (m), 1173 (m), 1133 (m), 889 (m), 837 (m), 705 (m), 682 (m) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{14}F_6NO$ ($M + H^+$) 362.0974, found 362.0986.

***N*-(3,5-bis(trifluoromethyl)benzyl)-3-nitrobenzamide (3z):** R_f = 0.27 (ethyl acetate/hexane = 1:4); white solid; yield 88% (138 mg, 76%); mp 152−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.40 (d, *J* = 8 Hz, 1H), 8.21 (d, *J* = 8 Hz, 1H), 7.83 (s, 3H), 7.69 (t, *J* = 8 Hz, 1H), 6.82 (br s, 1H), 4.805 (d, *J* = 4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 148.4, 140.5, 135.3, 133.5, 132.4 (q, J_{CF} = 66.5 Hz), 130.3, 128.2 (d, J_{CF} = 3 Hz), 126.7, 123.3 (q, J_{CF} = 536 Hz), 122.0 (q, J_{CF} = 10 Hz), 43.7; IR (KBr) $\tilde{\nu}$ 3315 (w), 3087 (m), 2924 (m), 2853 (s), 1645 (m), 1531 (s), 1351 (s), 1278 (s), 1174 (m), 1133 (m), 898 (s), 705 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{11}F_6N_2O_3$ ($M + H^+$) 393.0668, found 393.0680.

***N*-(4-fluorobenzyl)-3-nitrobenzamide (3aa):** R_f = 0.20 (ethyl acetate/hexane = 1:4); white solid; yield 84% (93 mg, 73%); mp 119−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.36 (d, *J* = 7.3 Hz, 1H), 8.18 (d, *J* = 7.1 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.34 (s, 2H), 7.05 (t, *J* = 7.5 Hz, 2H), 6.57 (brs, 1H), 4.64 (d, *J* = 4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 162.5 (d, $^1J_{CF}$ = 245 Hz), 148.3, 135.9, 133.5 (d, $^4J_{CF}$ = 3 Hz), 133.4, 130.0, 129.9 (d, $^3J_{CF}$ = 8 Hz), 126.4, 121.9, 115.9 (d, $^2J_{CF}$ = 21 Hz), 43.8; IR (KBr) $\tilde{\nu}$ 3290 (w), 3087 (s), 1640 (m), 1557 (m), 1525 (s), 1509 (s), 1350 (s), 1320 (m), 1216 (m), 1157 (s), 1095 (s), 820 (m), 673 (s) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{12}FN_2O_3$ ($M + H^+$) 275.0826, found 275.0829.

4.6 NOTES AND REFERENCES

1. Akhavan, J., Introduction of explosives. In *The Chemistry of Explosives, 2nd Edition*, Akhavan, J., Ed. The Royal Society of Chemistry2004; pp 1.
2. Yoshizawa, M.; Kusukawa, T.; Fujita, M.; Yamaguchi, K., *J. Am. Chem. Soc.* **2000,** *122*, 6311.
3. Warmuth, R., *Angew. Chem. Int. Ed.* **1997,** *36*, 1347.
4. Cram, D. J.; Tanner, M. E.; Thomas, R., *Angew. Chem. Int. Ed. Engl.* **1991,** *30*, 1024.
5. Warmuth, R.; Marvel, M. A., *Angew. Chem. Int. Ed.* **2000,** *39*, 1117.
6. Mal, P.; Breiner, B.; Rissanen, K.; Nitschke, J. R., *Science* **2009,** *324*, 1697.
7. Yoshizawa, M.; Takeyama, Y.; Okano, T.; Fujita, M., *J. Am. Chem. Soc.* **2003,** *125*, 3243.
8. Iwasawa, T.; Hooley, R. J.; Rebek, J., *Science* **2007,** *317*, 493.
9. Tornieporth-Oetting, I.; Klapötke, T., *Angew. Chem. Int. Ed. Engl.* **1990,** *29*, 677.
10. Nicolaou, K. C.; Baran, P. S.; Kranich, R.; Zhong, Y.-L.; Sugita, K.; Zou, N., *Angew. Chem., Int. Ed.* **2001,** *40*, 202.
11. Hassel, O., *Science* **1970,** *170*, 497.
12. Wang, G.-W., *Chem. Soc. Rev.* **2013,** *42*, 7668.
13. Balaz, P.; Achimovicova, M.; Balaz, M.; Billik, P.; Cherkezova-Zheleva, Z.; Criado, J. M.; Delogu, F.; Dutkova, E.; Gaffet, E.; Gotor, F. J.; Kumar, R.; Mitov, I.; Rojac, T.; Senna, M.; Streletskii, A.; Wieczorek-Ciurowa, K., *Chemical Society Reviews* **2013,** *42*, 7571.
14. Friščić, T.; Halasz, I.; Beldon, P. J.; Belenguer, A. M.; Adams, F.; Kimber, S. A. J.; Honkimäki, V.; Dinnebier, R. E., *Nature Chem.* **2013,** *5*, 66.
15. Ley, S.; O'Brien, M.; Denton, R., *Synthesis* **2011**, 1157.

16. Do, J.-L.; Mottillo, C.; Tan, D.; Štrukil, V.; Friščić, T., *Journal of the American Chemical Society* **2015,** *137*, 2476.

17. James, S. L.; Adams, C. J.; Bolm, C.; Braga, D.; Collier, P.; Friscic, T.; Grepioni, F.; Harris, K. D. M.; Hyett, G.; Jones, W.; Krebs, A.; Mack, J.; Maini, L.; Orpen, A. G.; Parkin, I. P.; Shearouse, W. C.; Steed, J. W.; Waddell, D. C., *Chem. Soc. Rev.* **2012,** *41*, 413.

18. Giri, C.; Sahoo, P. K.; Puttreddy, R.; Rissanen, K.; Mal, P., *Chem. Eur. J.* **2015,** *21*, 6390.

19. Hernandez, J. G.; Butler, I. S.; Friscic, T., *Chem. Sci.* **2014,** *5*, 3576.

20. Stolle, A.; Szuppa, T.; Leonhardt, S. E. S.; Ondruschka, B., *Chem. Soc. Rev.* **2011,** *40*, 2317.

21. Takacs, L., *Chem. Soc. Rev.* **2013**.

22. Yusubov, M. S.; Wirth, T., *Org. Lett.* **2005,** *7*, 519.

23. Achar, T. K.; Maiti, S.; Mal, P., *RSC Adv.* **2014,** *4*, 12834.

24. Studer, A.; Curran, D. P., *Nature Chem.* **2014,** *6*, 765.

25. Girard, S. A.; Knauber, T.; Li, C.-J., *Angew. Chem., Int. Ed.* **2014,** *53*, 74.

26. Louillat, M.-L.; Patureau, F. W., *Chem. Soc. Rev.* **2014,** *43*, 901.

27. Noisier, A. F. M.; Brimble, M. A., *Chem. Rev.* **2014,** *114*, 8775.

28. Guin, S.; Rout, S. K.; Banerjee, A.; Nandi, S.; Patel, B. K., *Org. Lett.* **2012,** *14*, 5294.

29. Fu, Z.; Lee, J.; Kang, B.; Hong, S. H., *Org. Lett.* **2012,** *14*, 6028.

30. Su, W.; Yu, J.; Li, Z.; Jiang, Z., *J. Org. Chem.* **2011,** *76*, 9144.

31. Nobuta, T.; Tada, N.; Fujiya, A.; Kariya, A.; Miura, T.; Itoh, A., *Organic Letters* **2013,** *15*, 574.

32. Vanjari, R.; Guntreddi, T.; Singh, K. N., *Org. Lett.* **2013,** *15*, 4908.

33. Gao, J.; Wang, G.-W., *The Journal of Organic Chemistry* **2008,** *73*, 2955.

34. Collet, F.; Lescot, C.; Dauban, P., *Chem. Soc. Rev.* **2011,** *40*, 1926.

35. McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J., *Nature* **2014,** *510*, 129.

36. Sharma, A.; Hartwig, J. F., *Nature* **2015,** *517*, 600.

37. Schranck, J.; Tlili, A.; Beller, M., *Angew. Chem. Int. Ed. Engl.* **2014,** *53*, 9426.

38. He, J.; Li, S.; Deng, Y.; Fu, H.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J.-Q., *Science* **2014,** *343*, 1216.

39. Studer, A.; Curran, D. P., *Angew. Chem. Int. Ed.* **2011,** *50*, 5018.

40. Antonchick, A. P.; Samanta, R.; Kulikov, K.; Lategahn, J., *Angew. Chem. Int. Ed.* **2011,** *50*, 8605.

41. Zhdankin, V. V., *ARKIVOC* **2009**, 1.

42. Maiti, S.; Mal, P., *Adv. Synth. Catal.* **2015,** *357*, 1416.

43. Valeur, E.; Bradley, M., *Chem. Soc. Rev.* **2009,** *38*, 606.

44. Pattabiraman, V. R.; Bode, J. W., *Nature* **2011,** *480*, 471.

45. Achar, T. K.; Mal, P., *J. Org. Chem.* **2015,** *80*, 666.

46. Zhdankin, V. V.; Stang, P. J., *Chem. Rev.* **2008,** *108*, 5299.

47. Dauban, P.; Dodd, R. H., *Synlett* **2003**, 1571.

48. Geraskin, I. M.; Pavlova, O.; Neu, H. M.; Yusubov, M. S.; Nemykin, V. N.; Zhdankin, V. V., *Adv. Synth. Catal.* **2009,** *351*, 733.

49. Yusubov, M. S.; Yusubova, R. Y.; Nemykin, V. N.; Maskaev, A. V.; Geraskina, M. R.; Kirschning, A.; Zhdankin, V. V., *Eur. J. Org. Chem.* **2012**, 5935.

50. Prasad, V.; Kale, R. R.; Mishra, B. B.; Kumar, D.; Tiwari, V. K., *Organic Letters* **2012,** *14*, 2936.

51. Allen, C. L.; Williams, J. M. J., *Chem. Soc. Rev.* **2011,** *40*, 3405.

52. Sun, H.; Pan, Y.; Zhao, Y.; Jackson, W. A.; Nuckles, L. M.; Malkina, I. L.; Arteaga, V. E.; Mitloehner, F. M., *J. Environ. Qual.* **2008,** *37*, 608.

53. Hall, H. K., *J. Am. Chem. Soc.* **1957,** *79*, 5441.

54. Koposov, A. Y.; Netzel, B. C.; Yusubov, M. S.; Nemykin, V. N.; Nazarenko, A. Y.; Zhdankin, V. V., *Eur. J. Org. Chem.* **2007,** *2007*, 4475.

55. Petricci, E.; Mugnaini, C.; Radi, M.; Corelli, F.; Botta, M., *J. Org. Chem.* **2004,** *69*, 7880.

56. Mahdavi, H.; Amani, J., *Tetrahedron Lett.* **2008,** *49*, 2204.

57. Ockey, D. A.; Dotson, J. L.; Struble, M. E.; Stults, J. T.; Bourell, J. H.; Clark, K. R.; Gadek, T. R., *Bio. Med. Chem.* **2004,** *12*, 37.

58. Fairfull-Smith, K. E.; Jenkins, I. D.; Loughlin, W. A., *Org. Biomol. Chem.* **2004,** *2*, 1979.

59. Agwada, V. C., *J. Chem. Eng. Data* **1982,** *27*, 479.

60. Suzuki, T.; Khan, M. N. A.; Sawada, H.; Imai, E.; Itoh, Y.; Yamatsuta, K.; Tokuda, N.; Takeuchi, J.; Seko, T.; Nakagawa, H.; Miyata, N., *J. Med. Chem.* **2012,** *55*, 5760.

61. Boehner, C. M.; Marsden, D. M.; Sore, H. F.; Norton, D.; Spring, D. R., *Tetrahedron Lett.* **2010,** *51*, 5930.

62. Hu, Z.; Wang, Y.; Shi, D.; Tan, H.; Li, X.; Wang, L.; Zhu, W.; Cao, Y., *Dyes and Pigments* **2010,** *86*, 166.

63. Xing, D.; Xu, X.; Yang, L., *Synthesis* **2009,** *2009*, 3399.

^{1}H and ^{13}C NMR Spectra

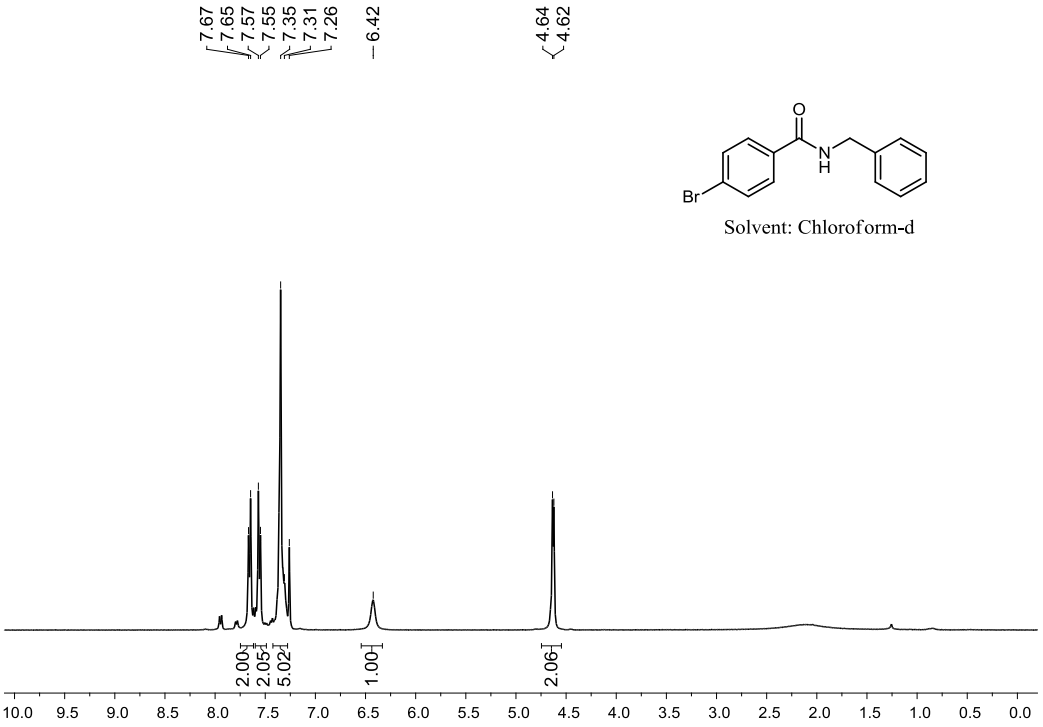


Figure 4.7 ^{1}H NMR spectrum of *N*-Benzyl-4-bromobenzamide (**3a**).

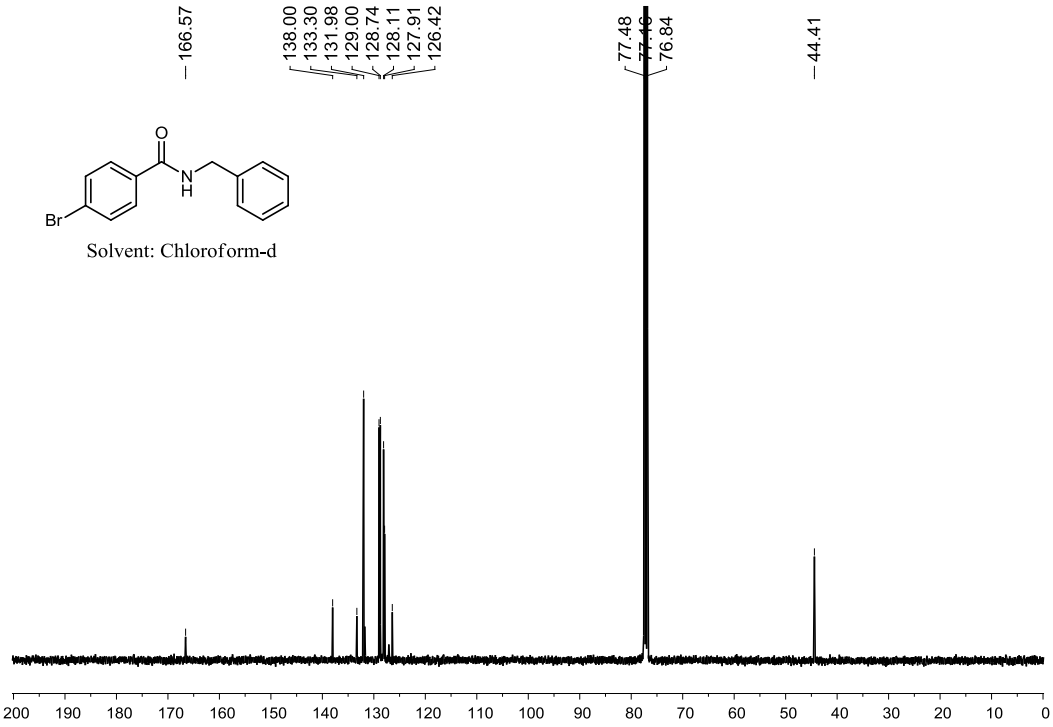


Figure 4.8 ^{13}C NMR spectrum of *N*-Benzyl-4-bromobenzamide (**3a**)

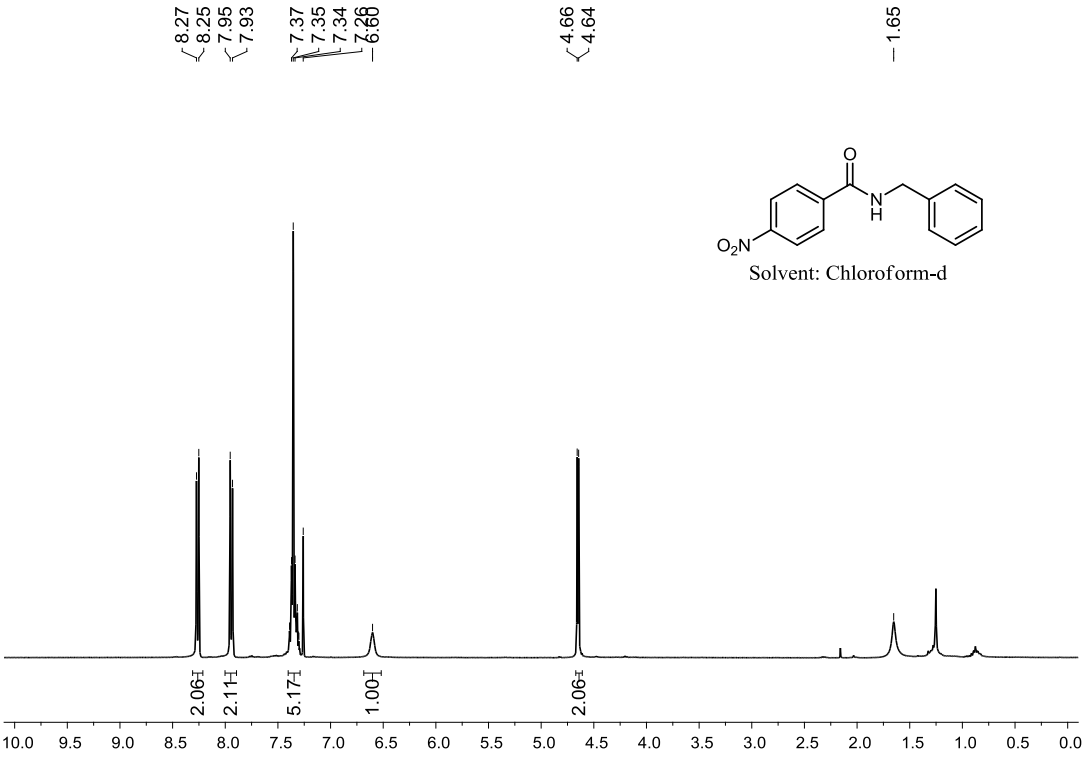


Figure 4.9 ^{1}H NMR spectrum of *N*-Benzyl-4-nitrobenzamide (**3b**)

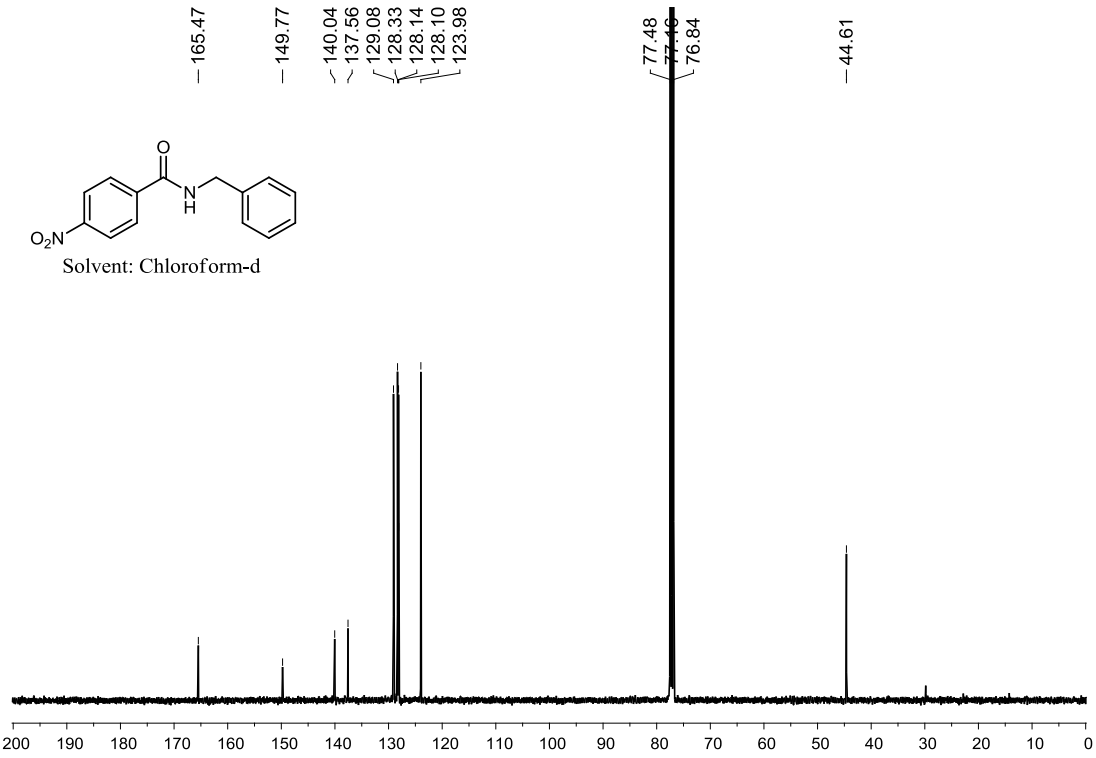


Figure 4.10 ^{13}C NMR spectrum of *N*-Benzyl-4-nitrobenzamide (**3b**)

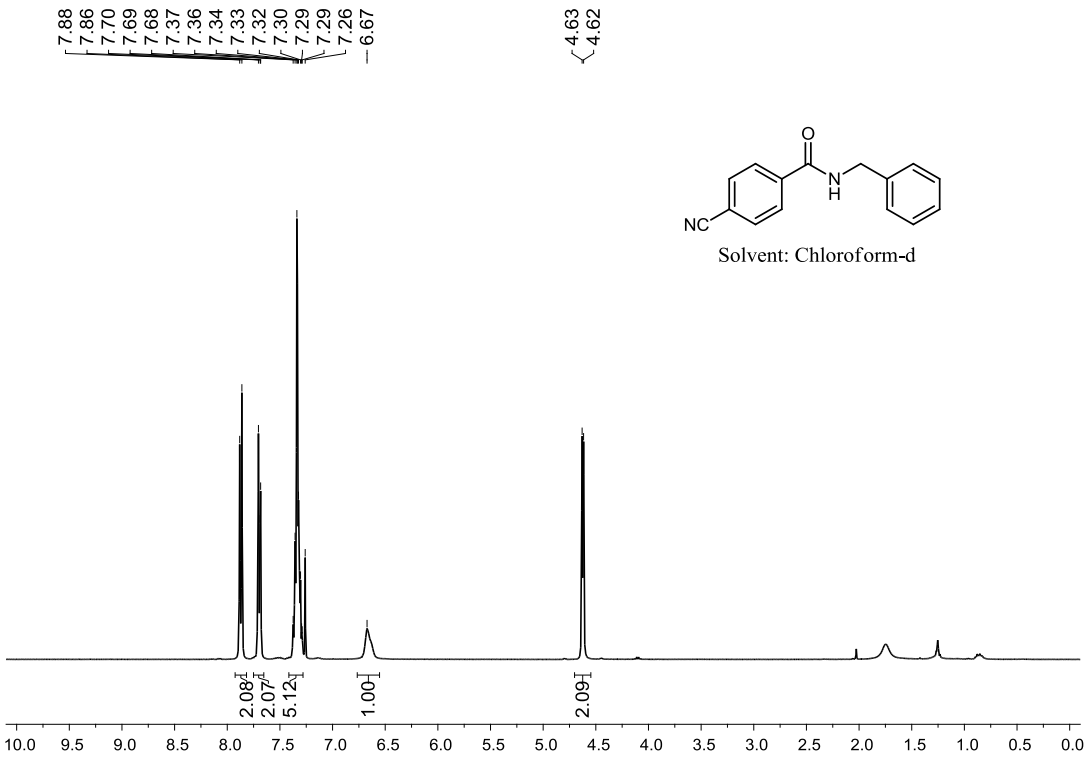


Figure 4.11 ^{1}H NMR spectrum of *N*-Benzyl-4-cyanobenzamide (**3c**)

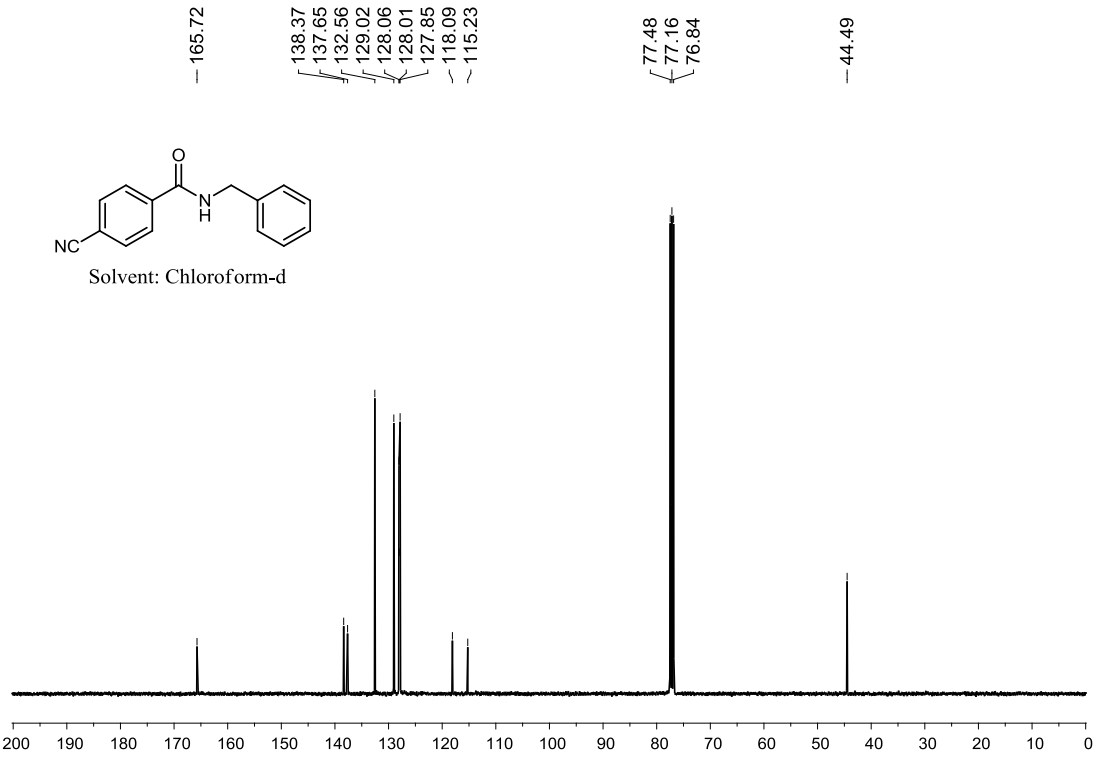


Figure 4.12 ^{13}C NMR spectrum of *N*-Benzyl-4-cyanobenzamide (**3c**)

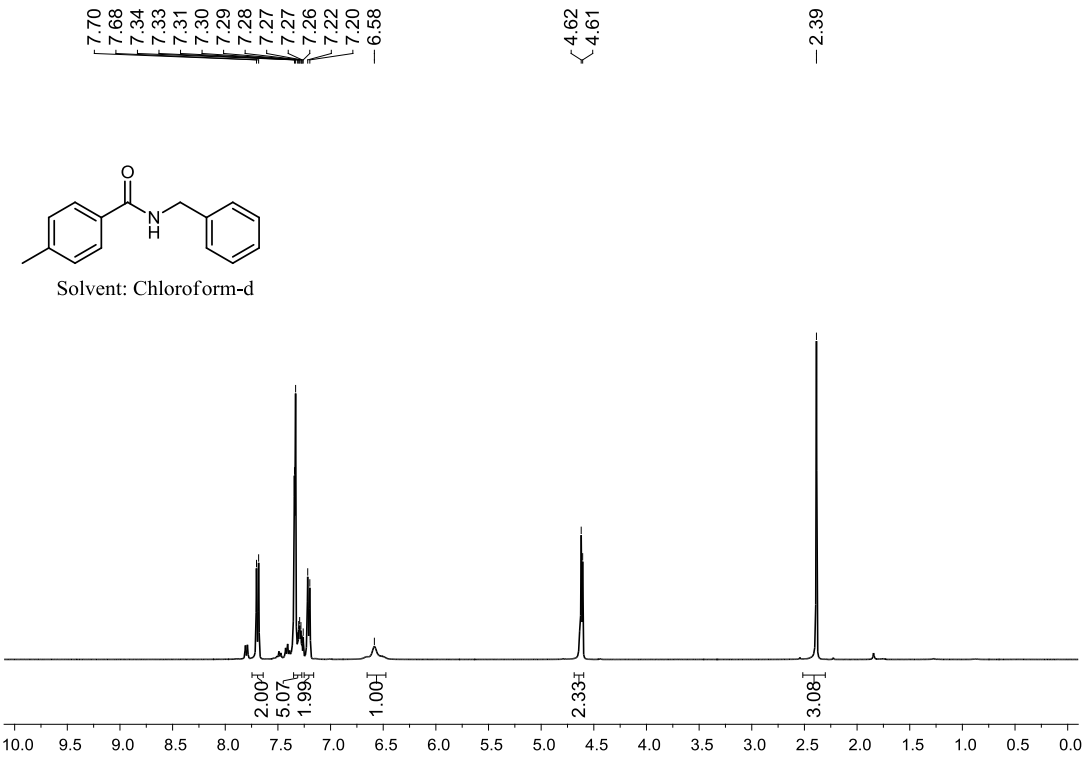


Figure 4.13 ^{1}H NMR spectrum of *N*-Benzyl-4-methylbenzamide (**3d**)

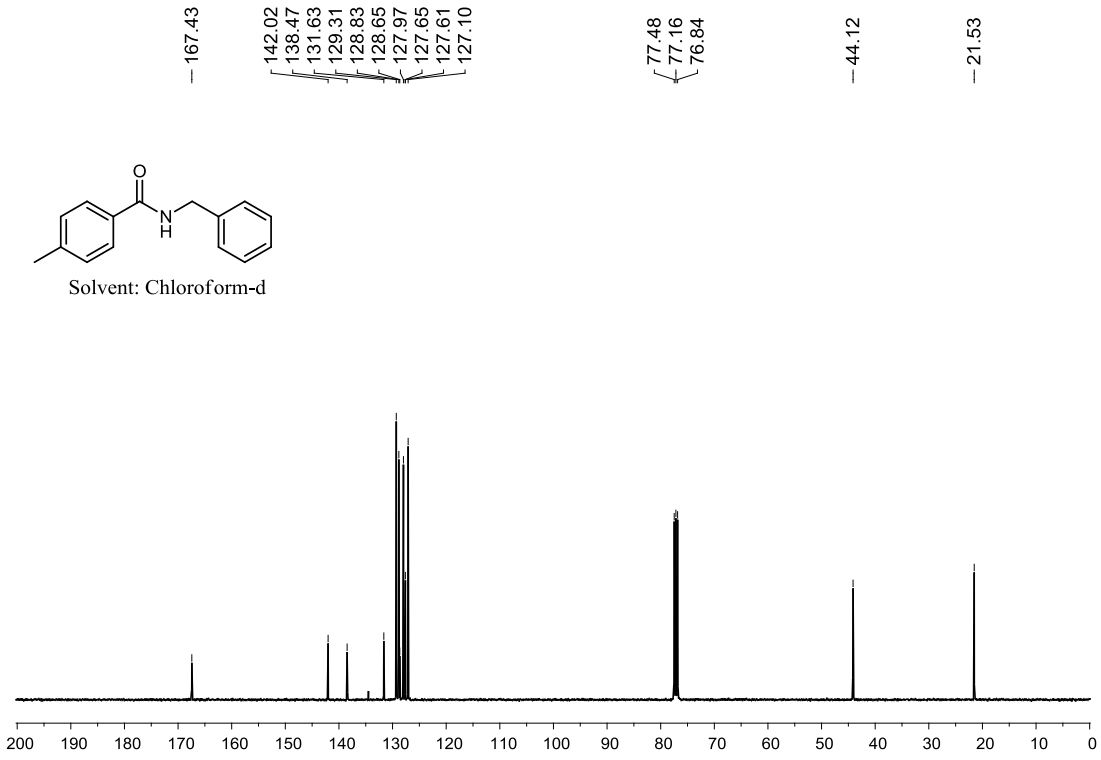


Figure 4.14 ^{13}C NMR spectrum of *N*-Benzyl-4-methylbenzamide (**3d**)

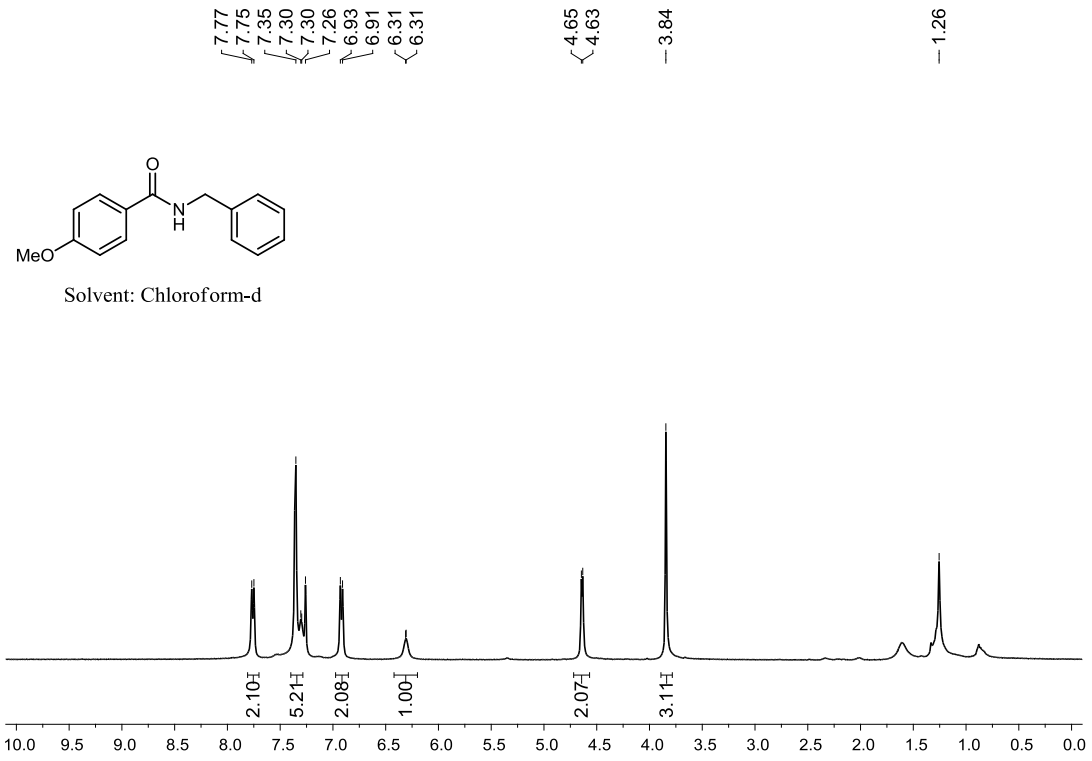


Figure 4.15 ^{1}H NMR spectrum of *N*-Benzyl-4-methoxybenzamide (**3e**)

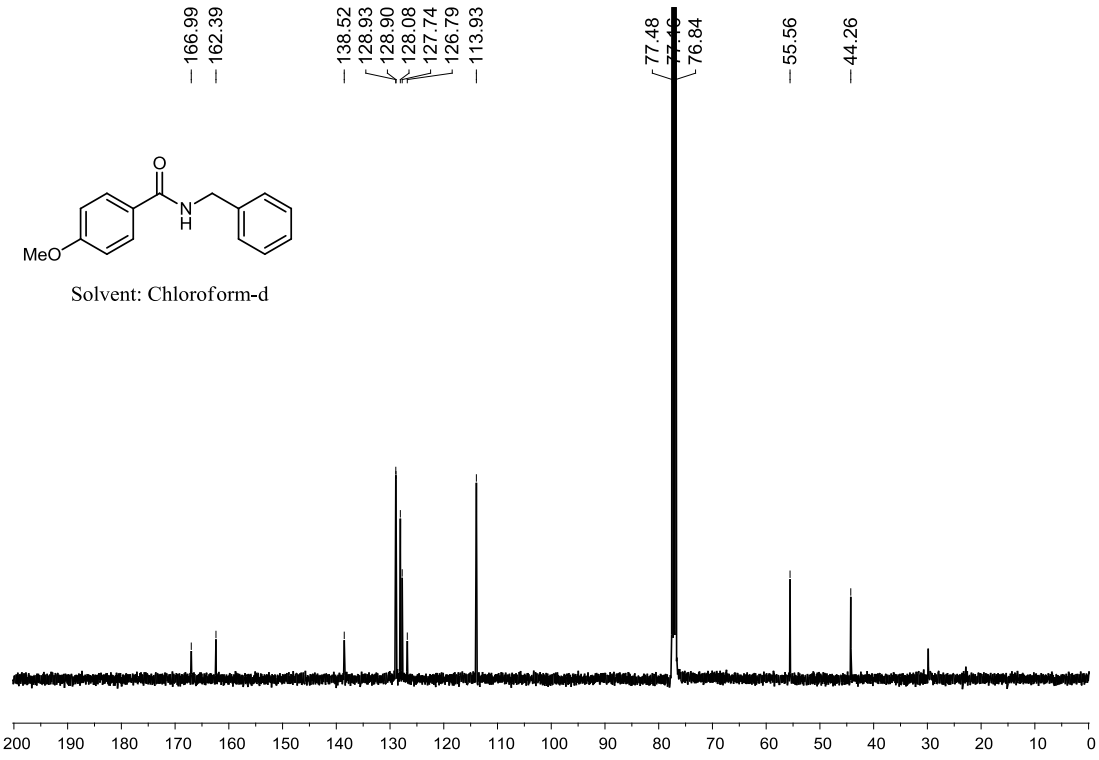


Figure 4.16 ^{13}C NMR spectrum of *N*-Benzyl-4-methoxybenzamide (**3e**)

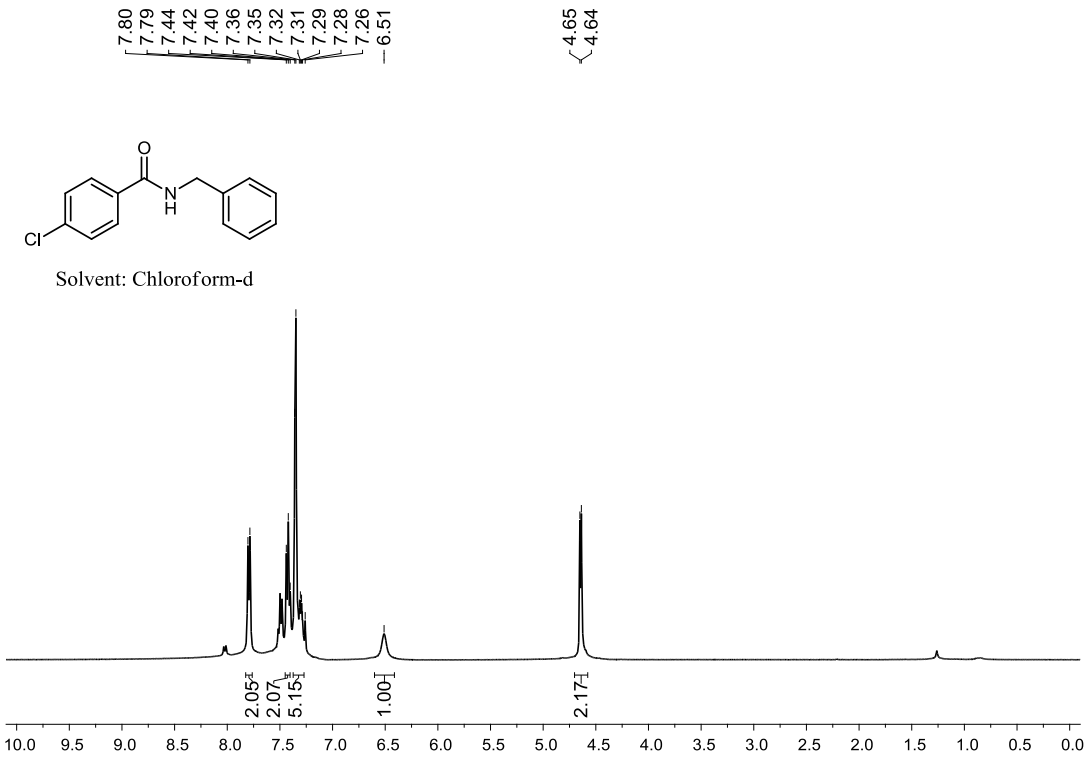


Figure 4.17 ^{1}H NMR spectrum of *N*-benzyl-4-chlorobenzamide (**3f**)

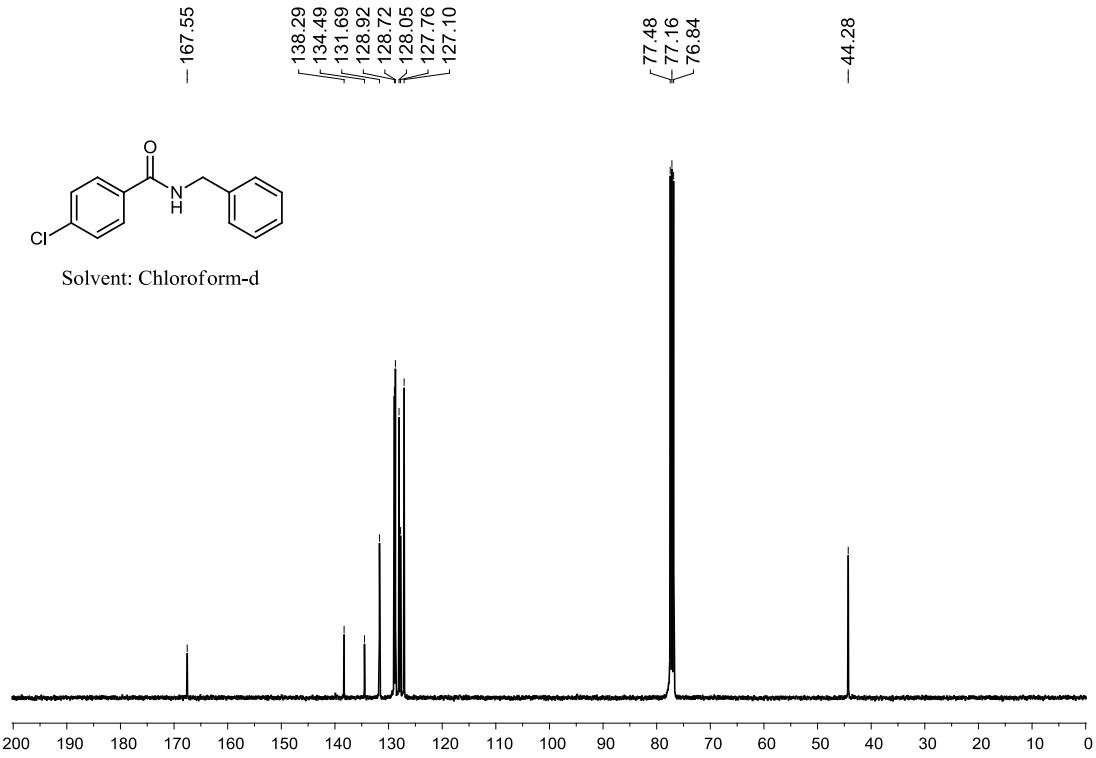


Figure 4.18 ^{13}C NMR spectrum of *N*-benzyl-4-chlorobenzamide (**3f**)

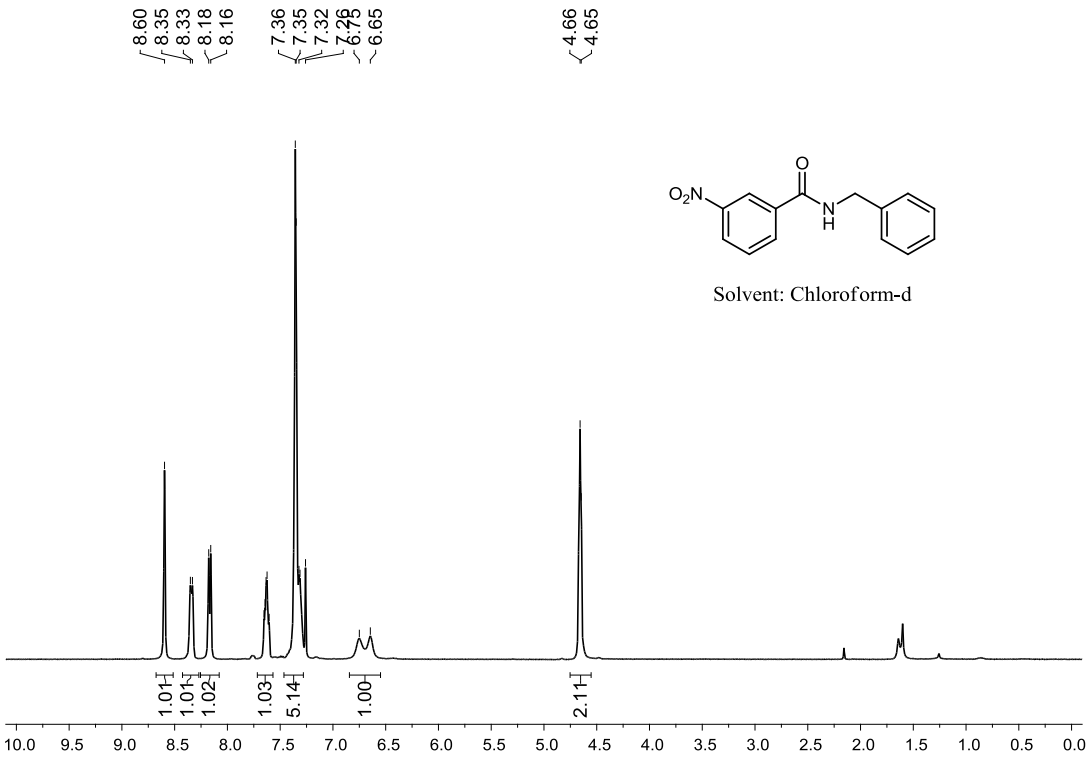


Figure 4.19 ^{1}H NMR spectrum of *N*-benzyl-3-nitrobenzamide (**3g**)

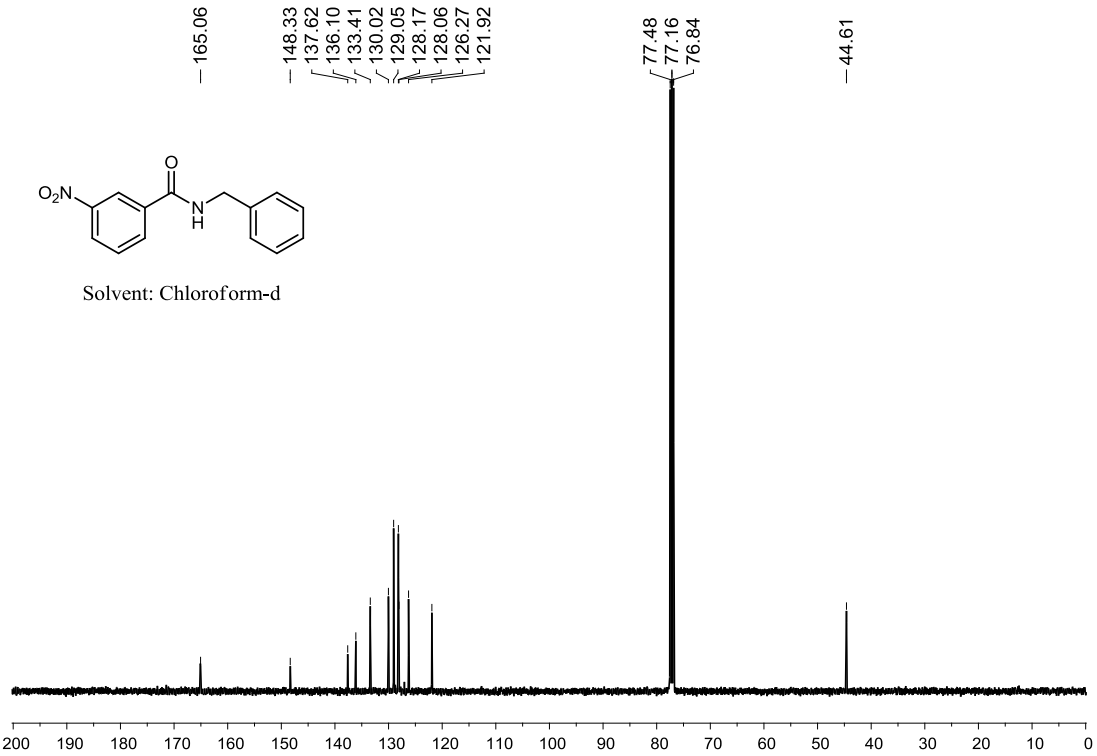


Figure 4.20 ^{13}C NMR spectrum of *N*-benzyl-3-nitrobenzamide (**3g**)

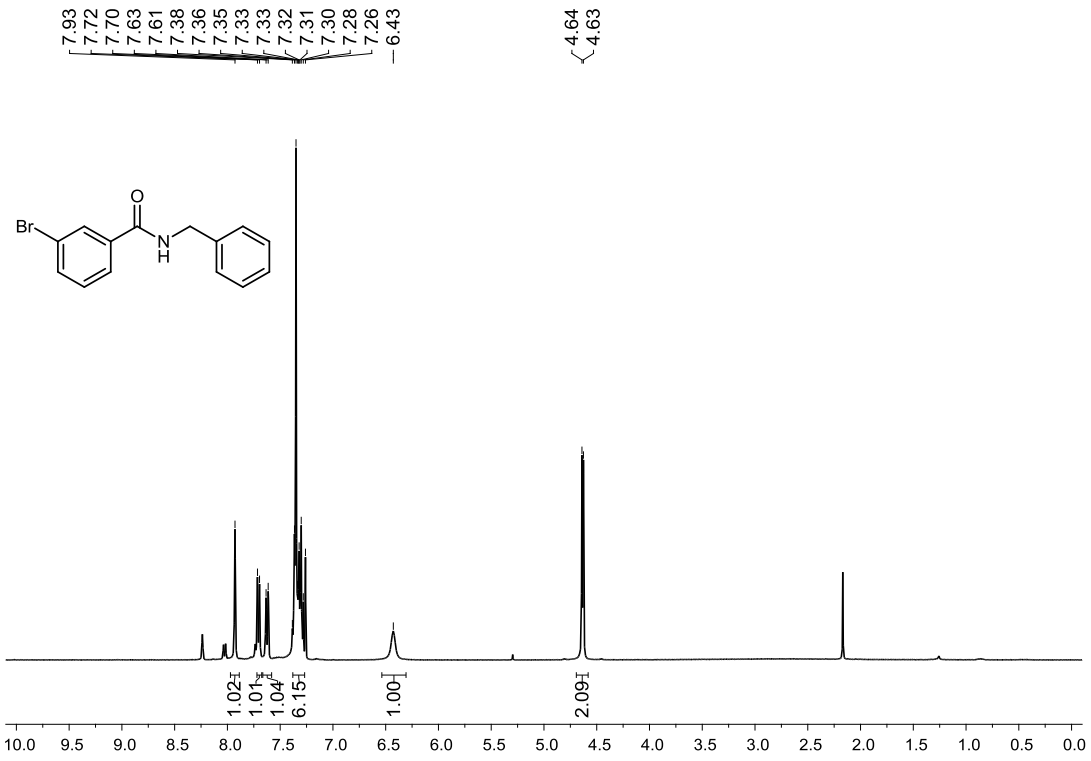


Figure 4.21 ^{1}H NMR spectrum of *N*-Benzyl-3-bromobenzamide (**3h**)

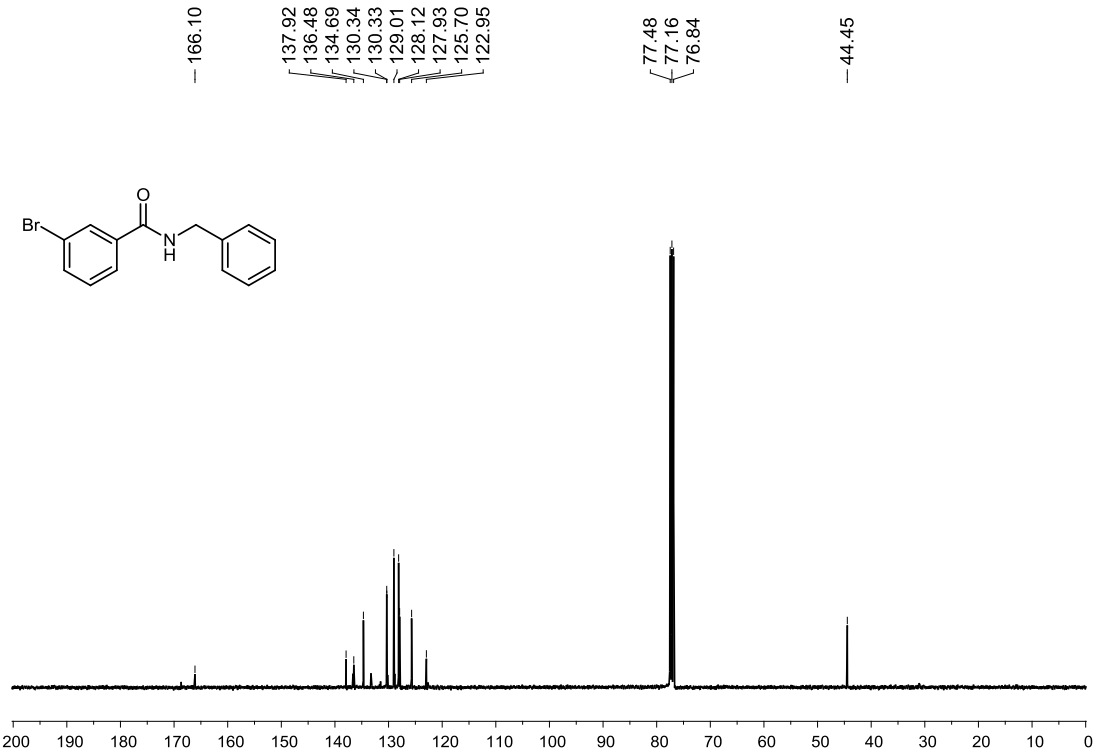


Figure 4.22 ^{13}C NMR spectrum of *N*-Benzyl-3-bromobenzamide (**3h**)

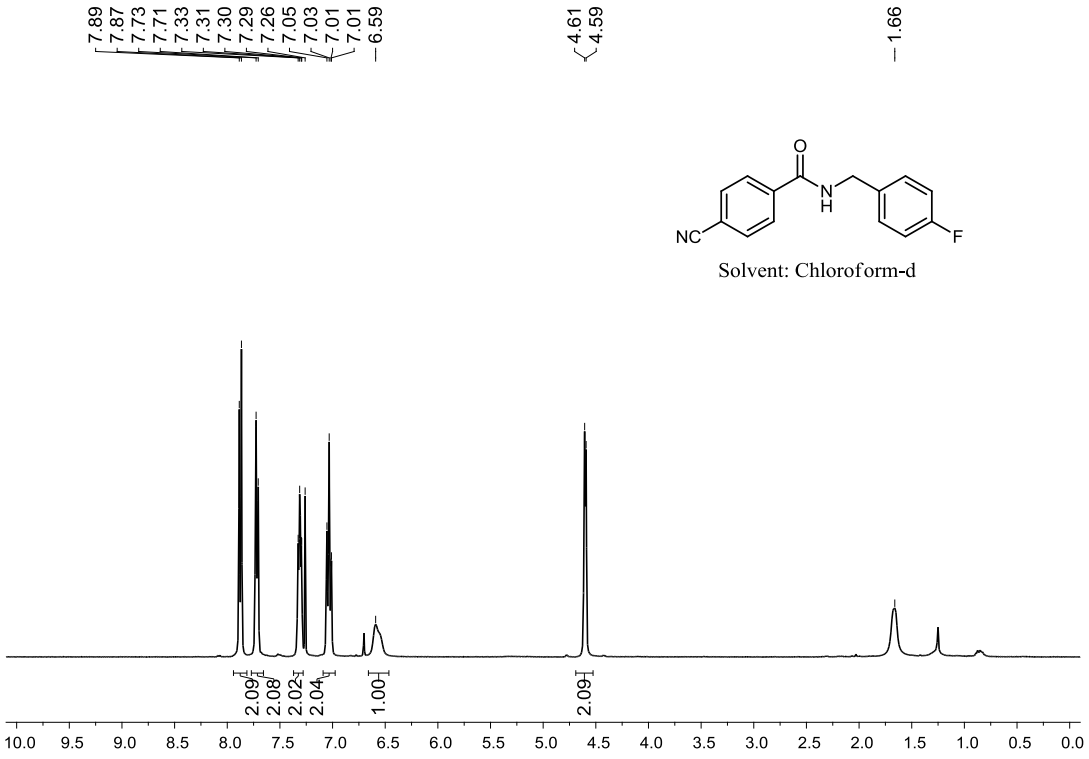


Figure 4.23 ^{1}H NMR spectrum of 4-Cyano-N-(4-fluorobenzyl)benzamide (**3i**)

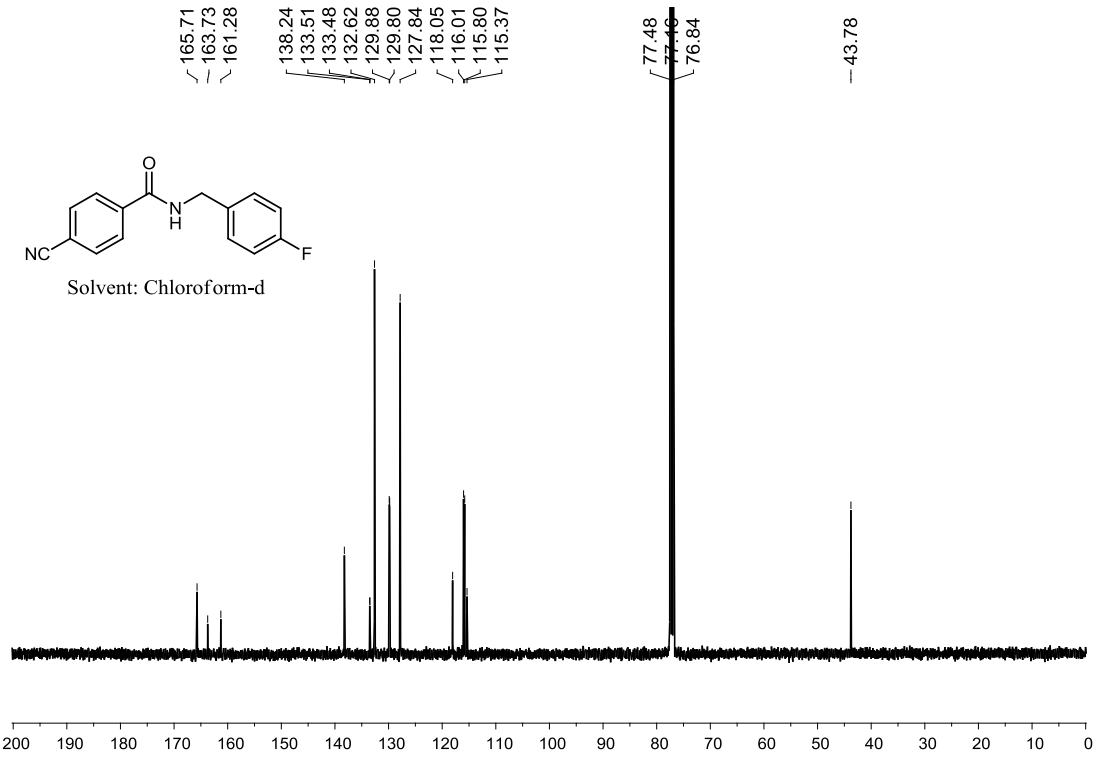


Figure 4.24 ^{13}C NMR spectrum of 4-Cyano-N-(4-fluorobenzyl)benzamide (**3i**)

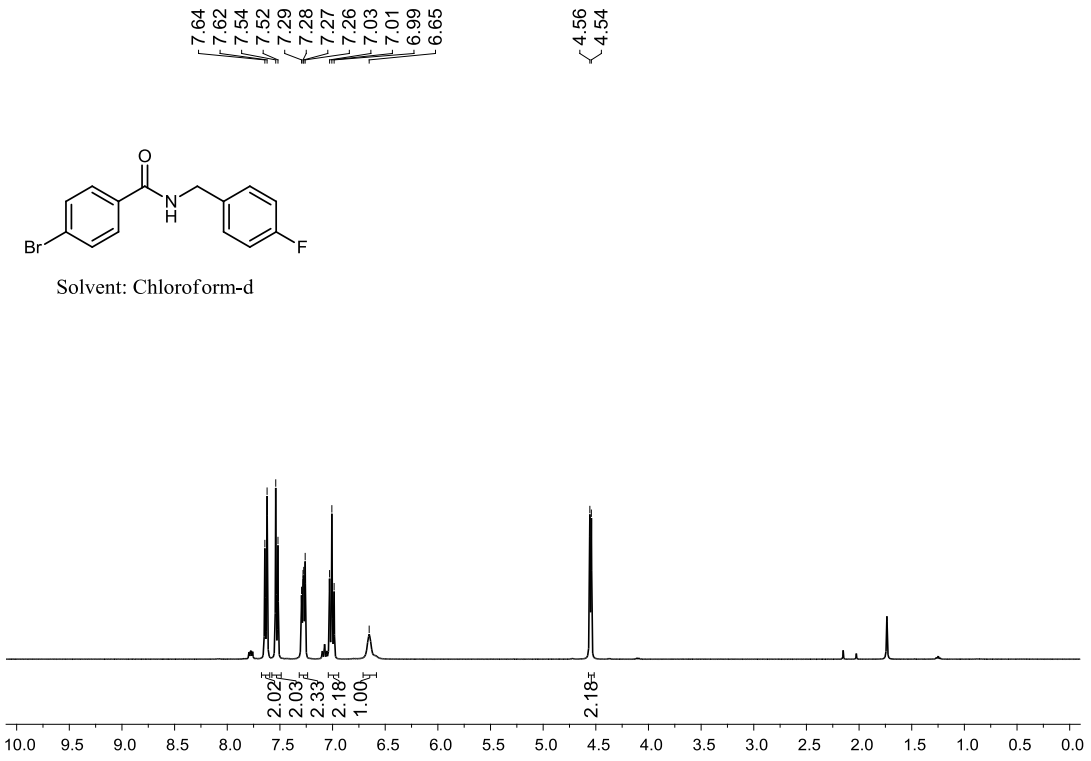


Figure 4.25 ^{1}H NMR spectrum of 4-Bromo-*N*-(4-fluorobenzyl)benzamide (**3j**)

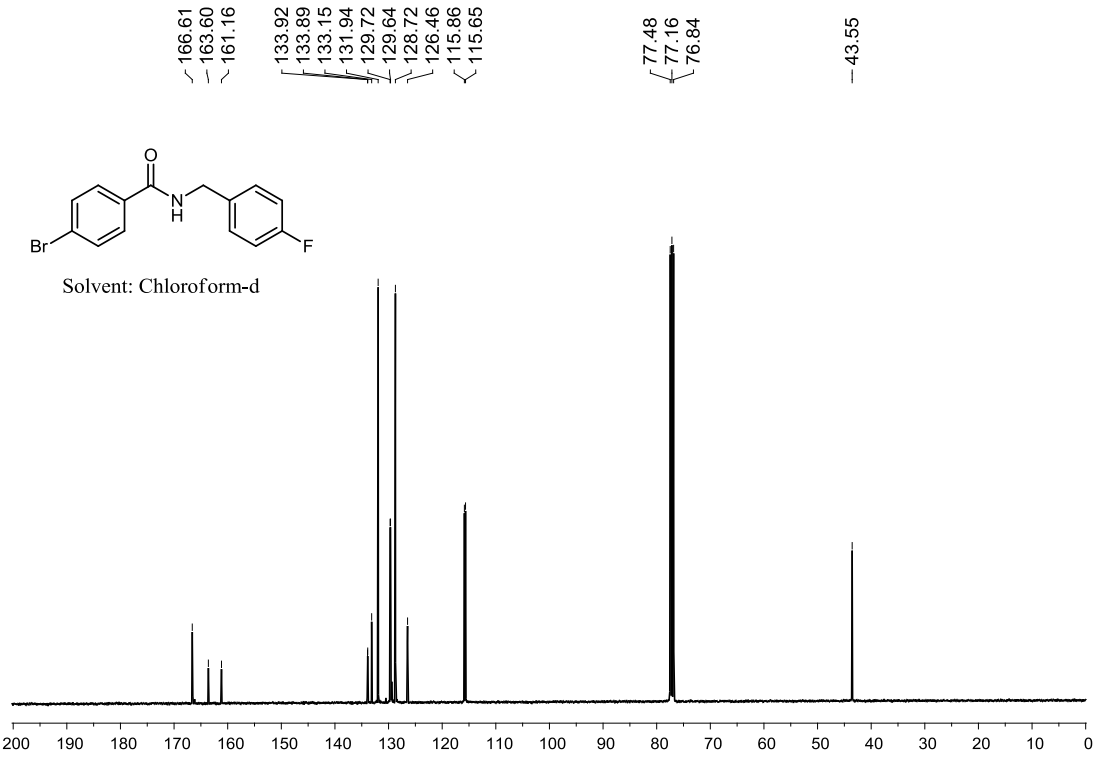


Figure 4.26 ^{13}C NMR spectrum of 4-Bromo-*N*-(4-fluorobenzyl)benzamide (**3j**)

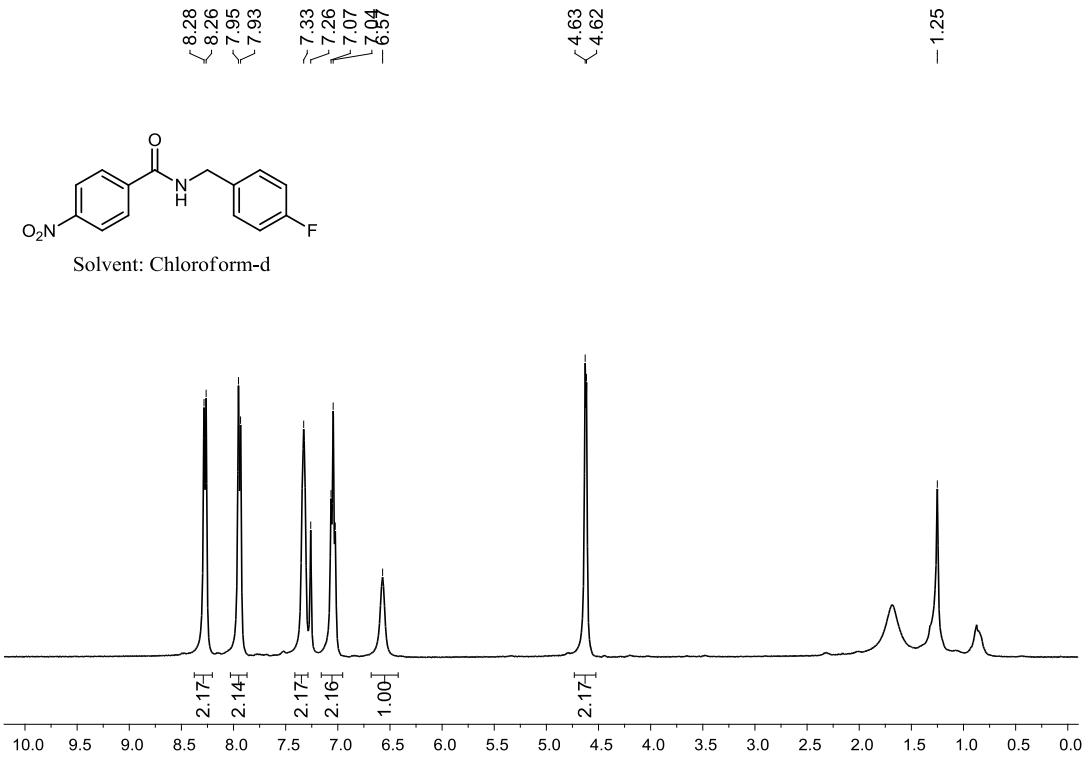


Figure 4.27 ^{1}H NMR spectrum of *N*-(4-fluorobenzyl)-4-nitrobenzamide (**3k**)

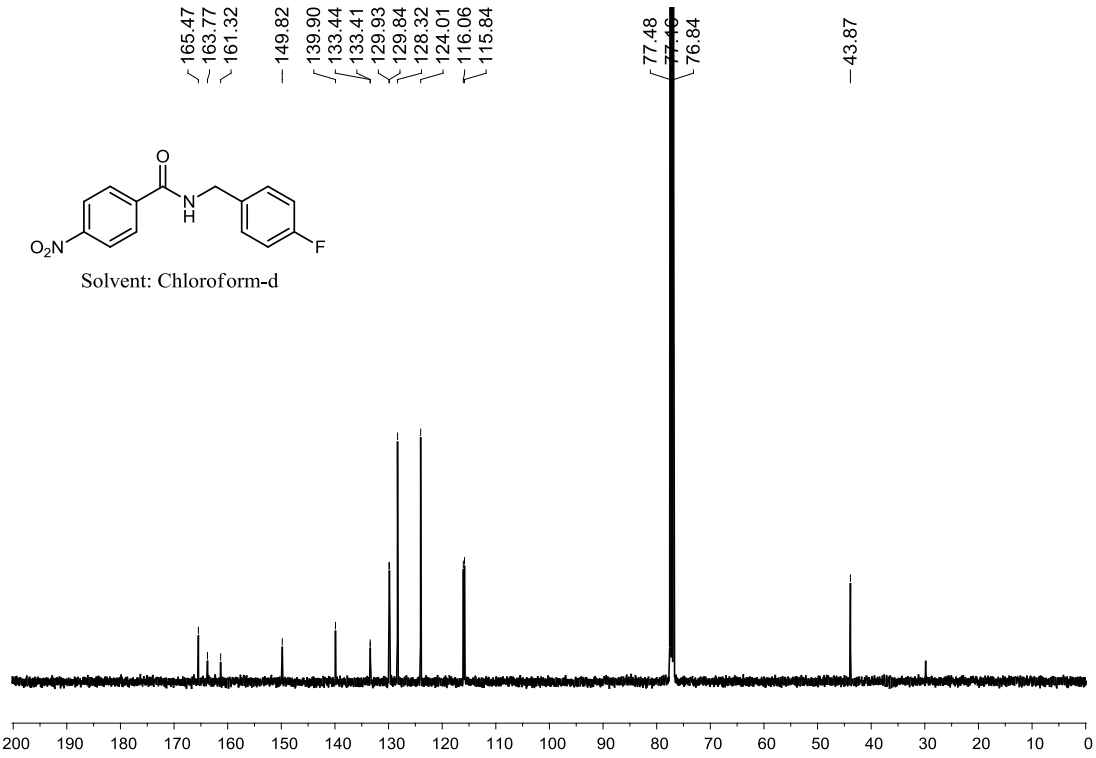


Figure 4.28 ^{13}C NMR spectrum of *N*-(4-fluorobenzyl)-4-nitrobenzamide (**3k**)

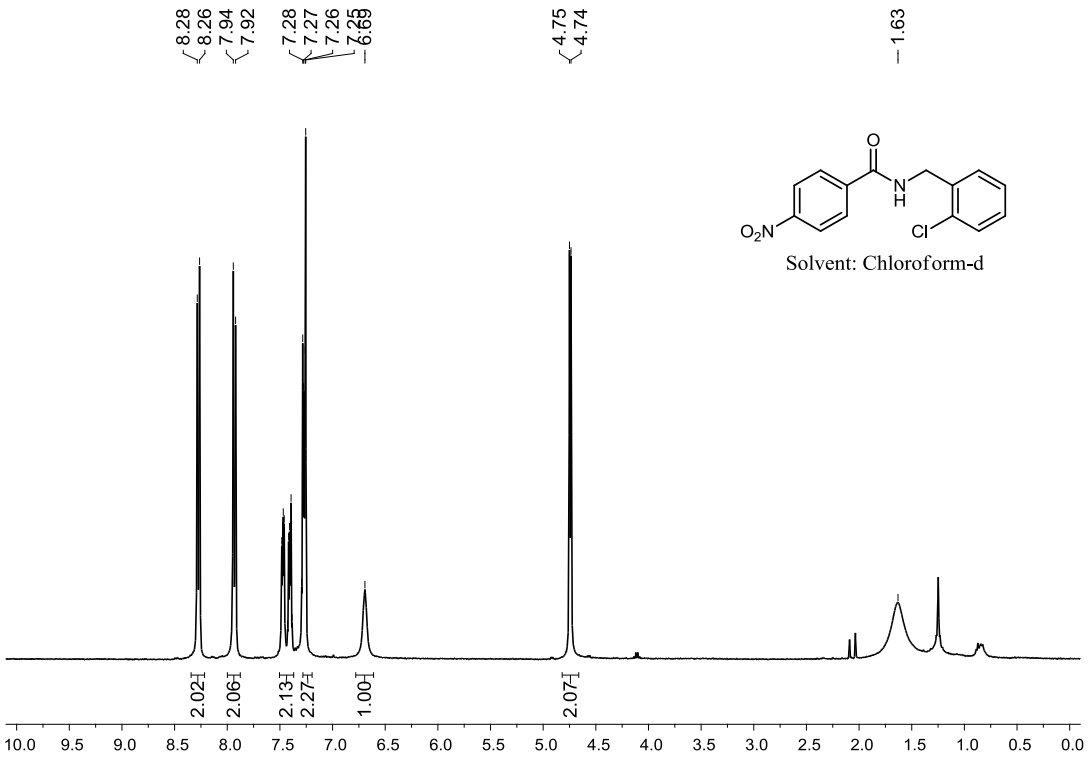


Figure 4.29 ^{1}H NMR spectrum of *N*-(2-chlorobenzyl)-4-nitrobenzamide (**3l**)

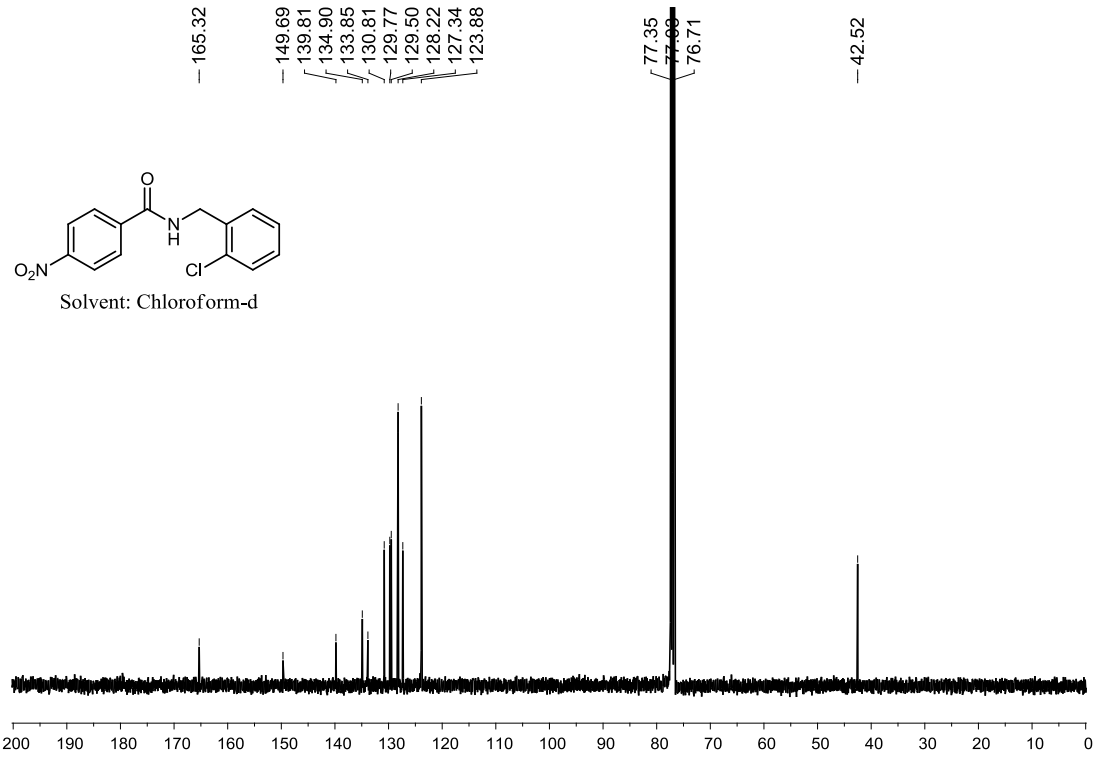


Figure 4.30 ^{13}C NMR spectrum of *N*-(2-chlorobenzyl)-4-nitrobenzamide (**3l**)

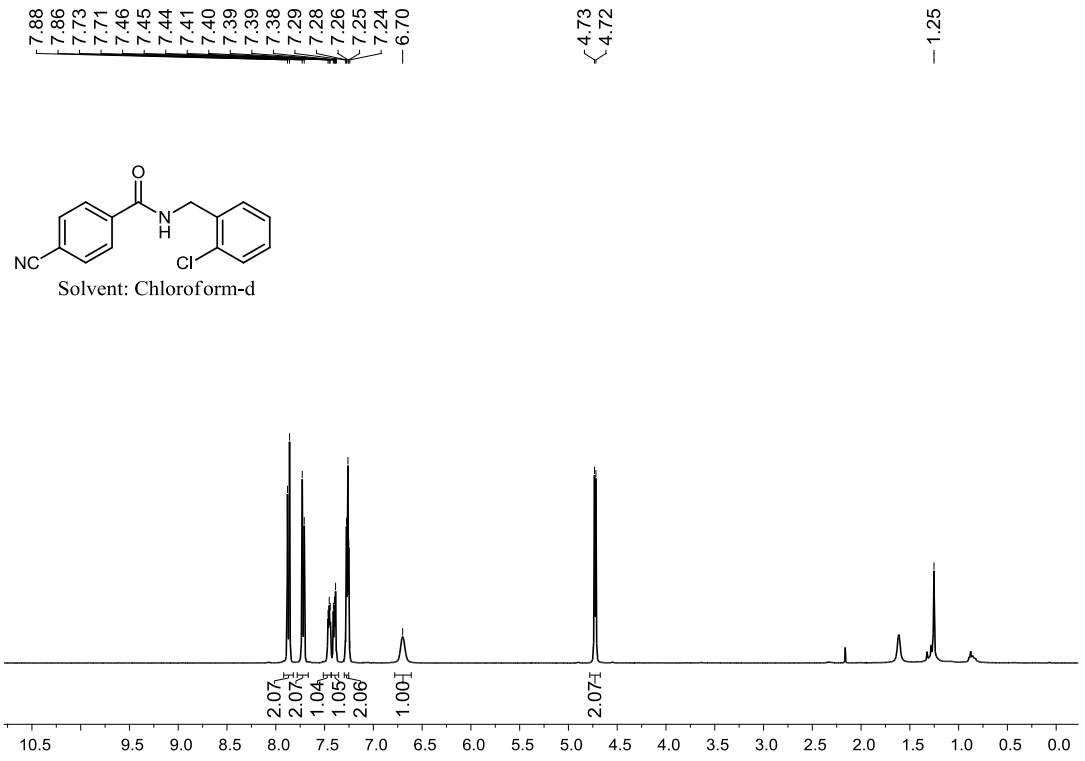


Figure 4.31 ^{1}H NMR spectrum of *N*-(2-chlorobenzyl)-4-cyanobenzamide (**3m**)

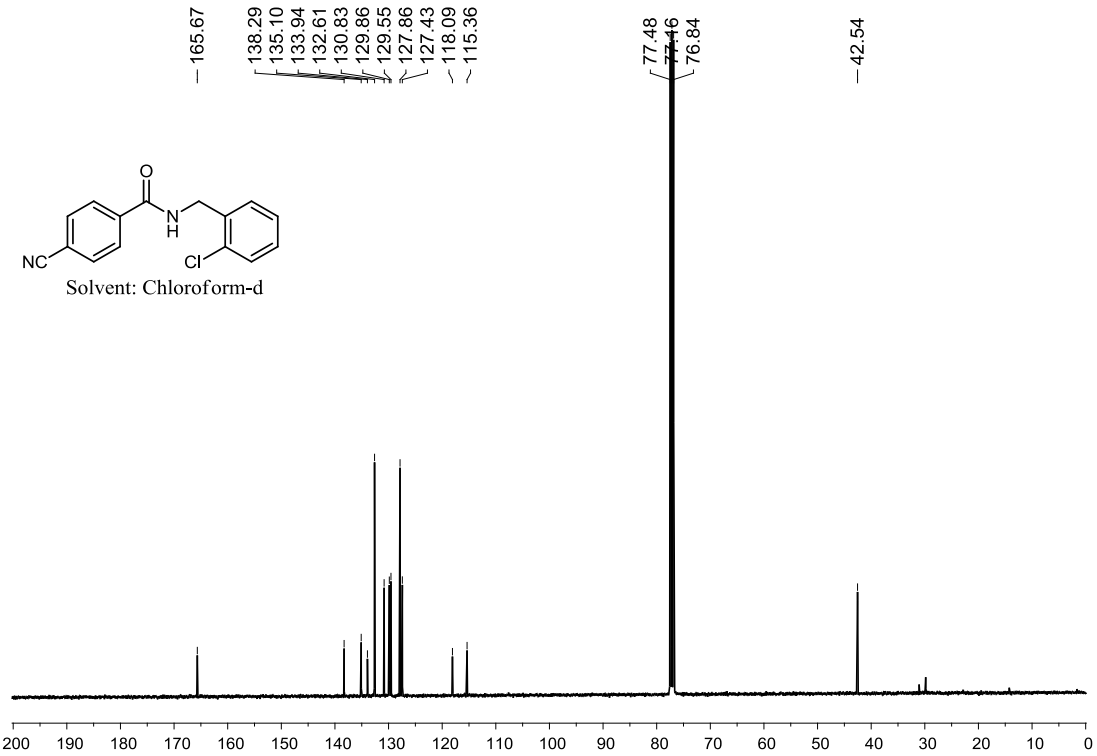


Figure 4.32 ^{13}C NMR spectrum of *N*-(2-chlorobenzyl)-4-cyanobenzamide (**3m**)

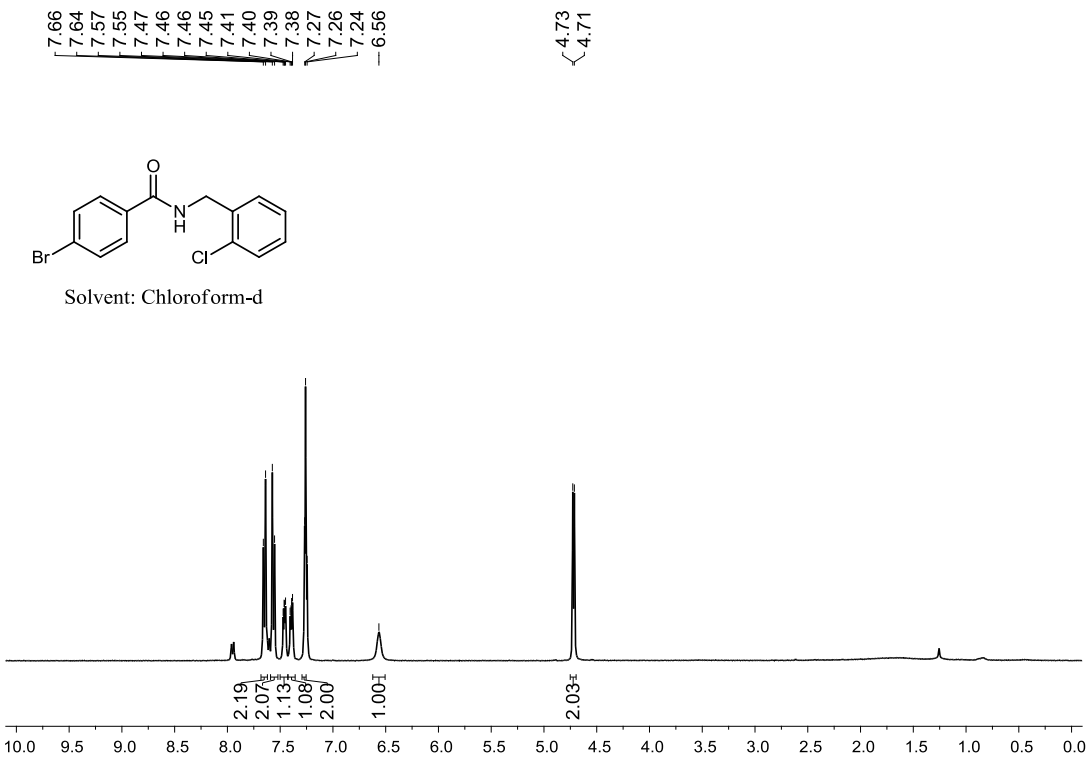


Figure 4.33 ^{1}H NMR spectrum of 4-Bromo-*N*-(2-chlorobenzyl)benzamide (**3n**)

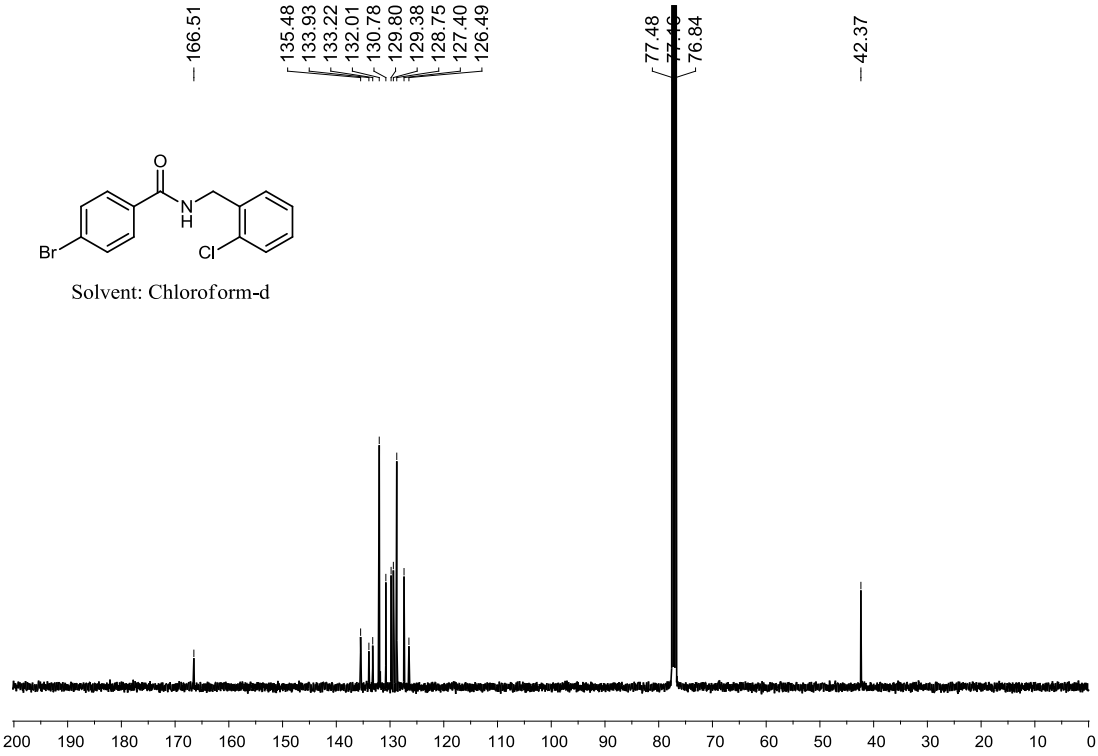


Figure 4.34 ^{13}C NMR spectrum of 4-Bromo-*N*-(2-chlorobenzyl)benzamide (**3n**)

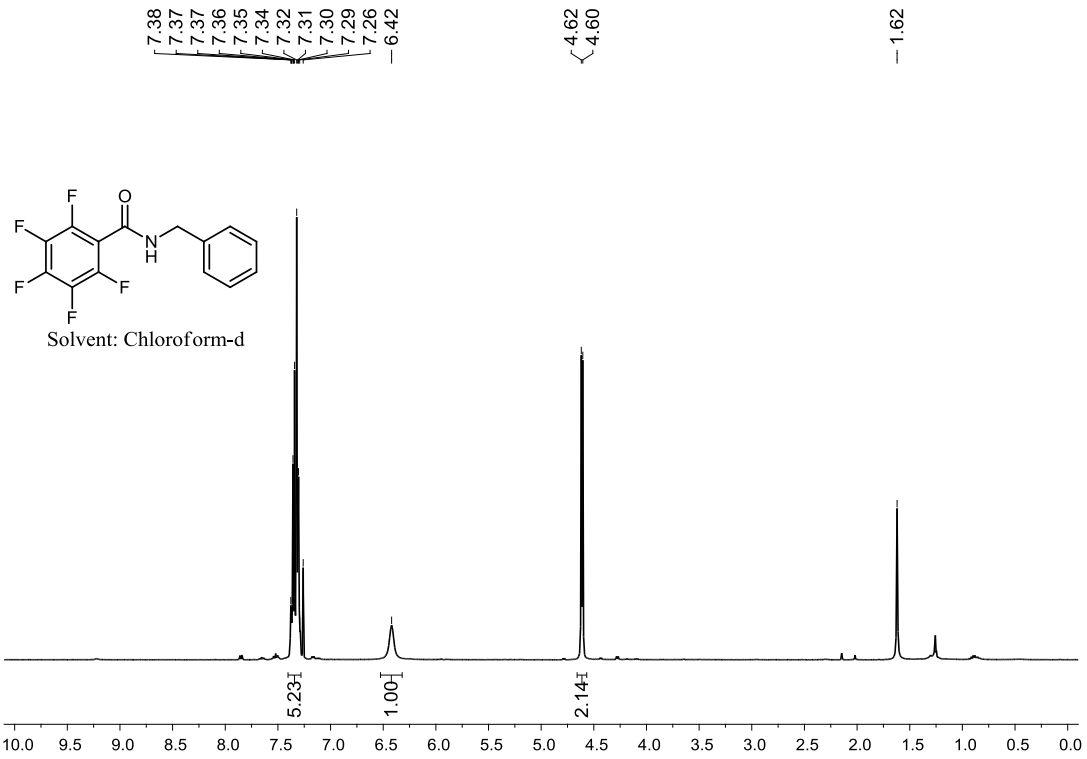


Figure 4.35 ^{1}H NMR spectrum of *N*-Benzyl-2,3,4,5,6-pentafluorobenzamide (**3o**)

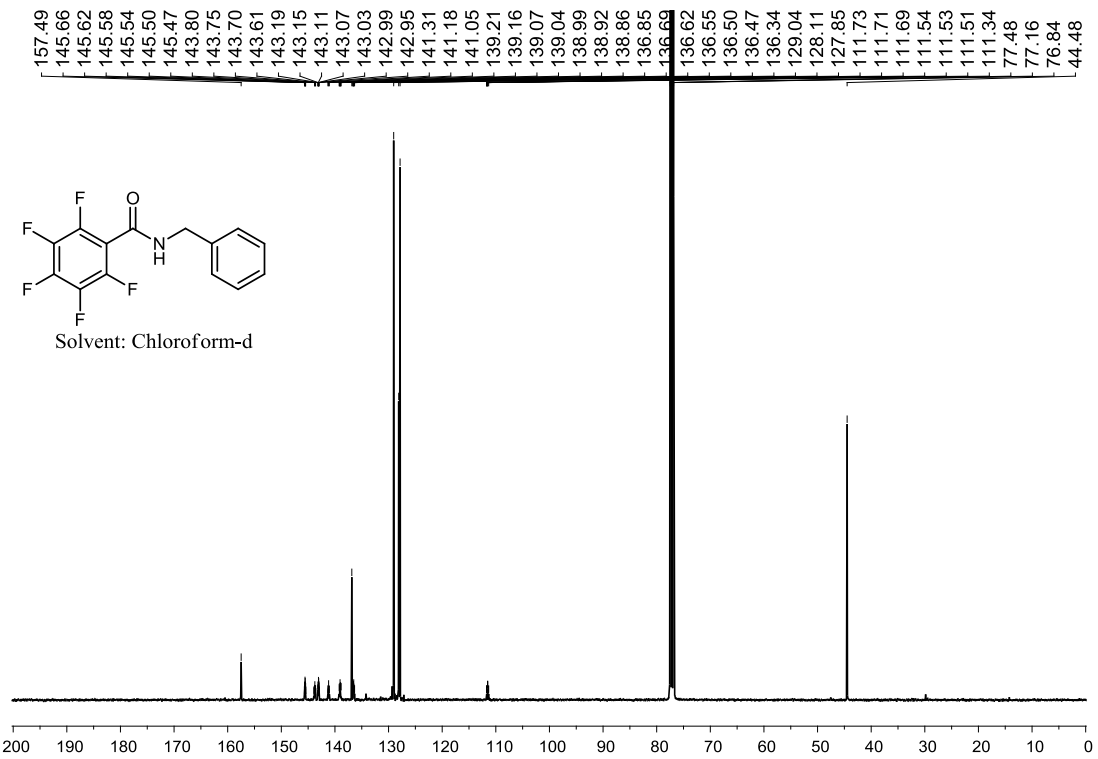


Figure 4.36 ^{13}C NMR spectrum of *N*-Benzyl-2,3,4,5,6-pentafluorobenzamide (**3o**)

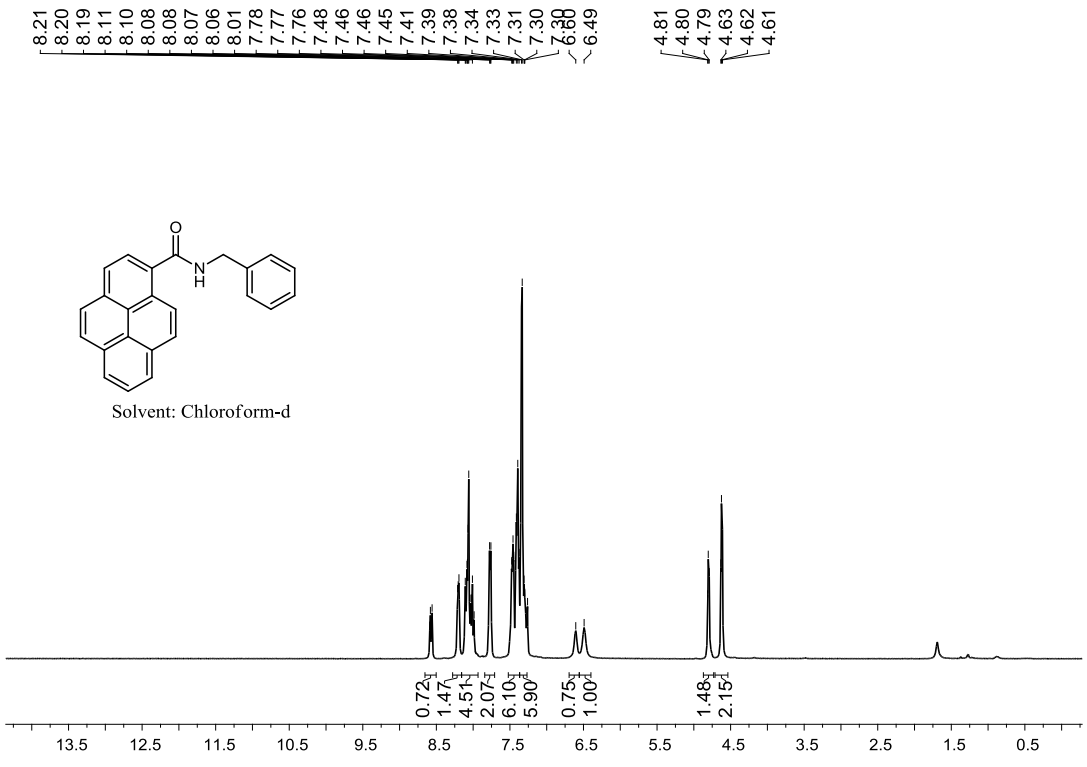


Figure 4.37 ^{1}H NMR spectrum of *N*-benzylpyrene-1-carboxamide (**3p**)

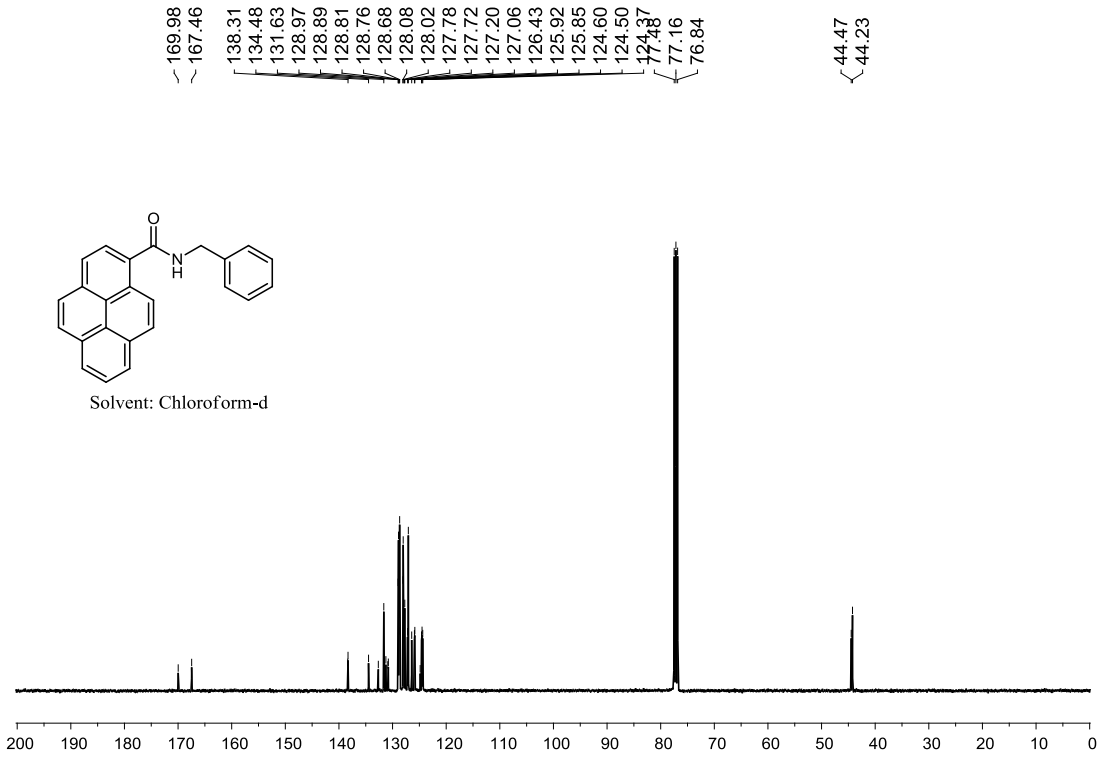


Figure 4.38 ^{13}C NMR spectrum of *N*-benzylpyrene-1-carboxamide (**3p**)

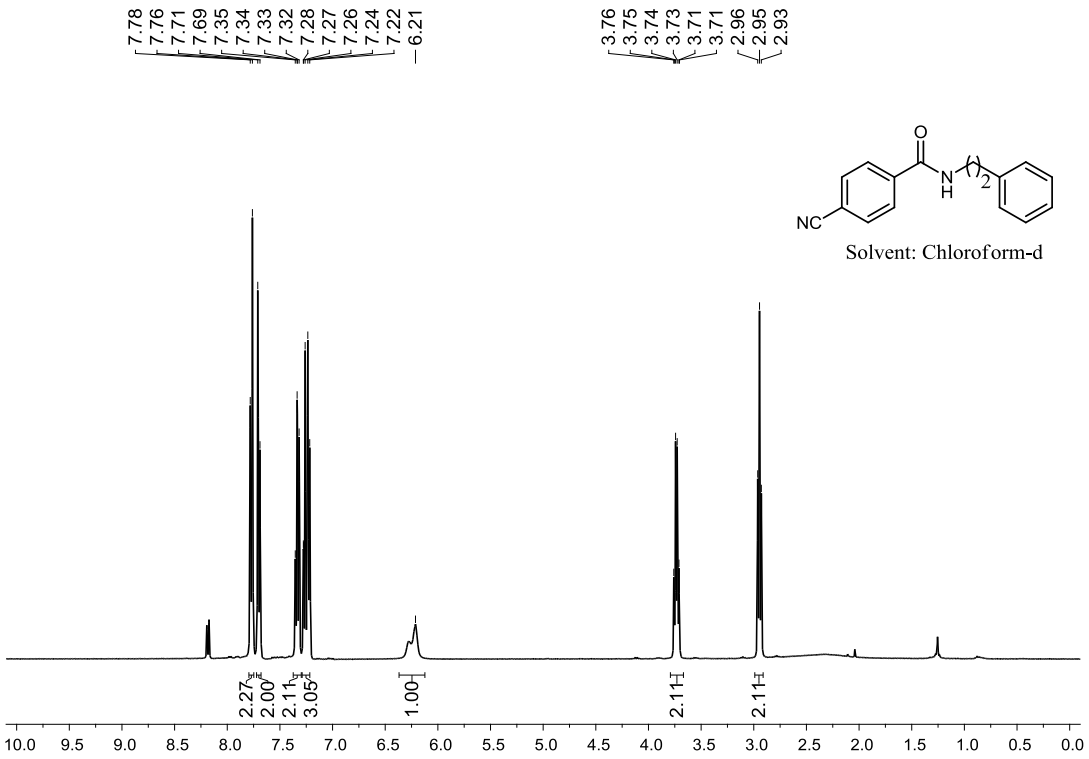


Figure 4.39 ^{1}H NMR spectrum of 4-Cyano-*N*-phenethylbenzamide (**3q**)

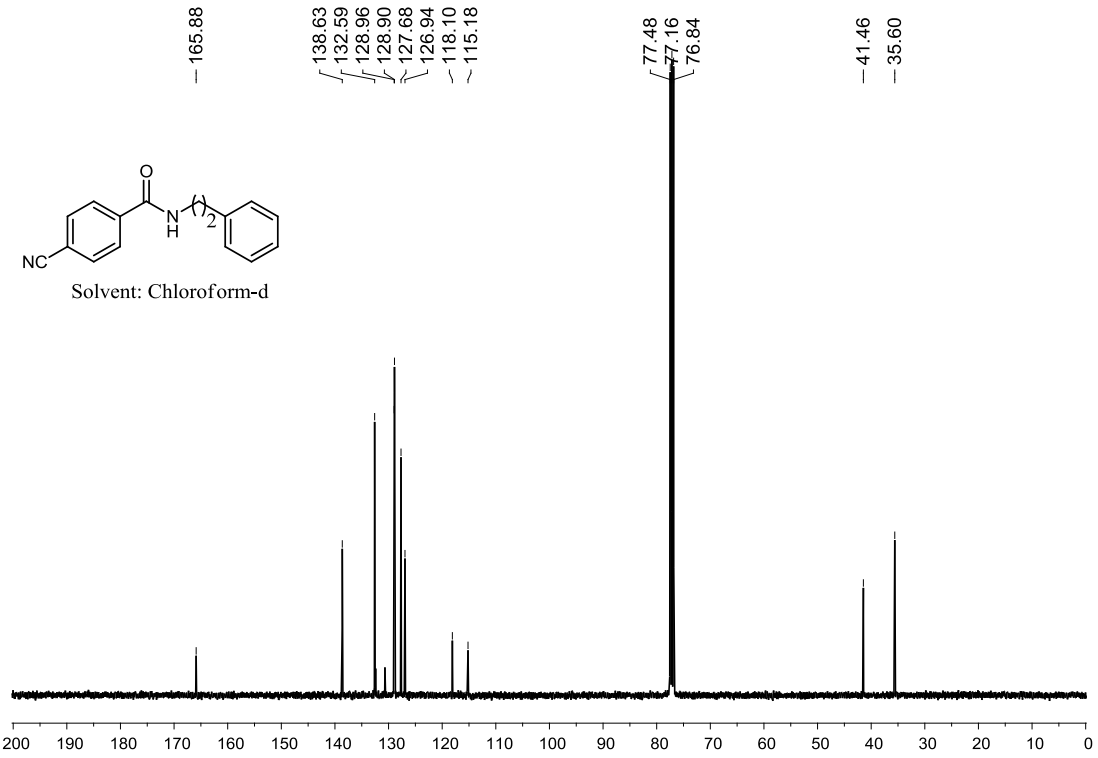


Figure 4.40 ^{13}C NMR spectrum of 4-Cyano-*N*-phenethylbenzamide (**3q**)

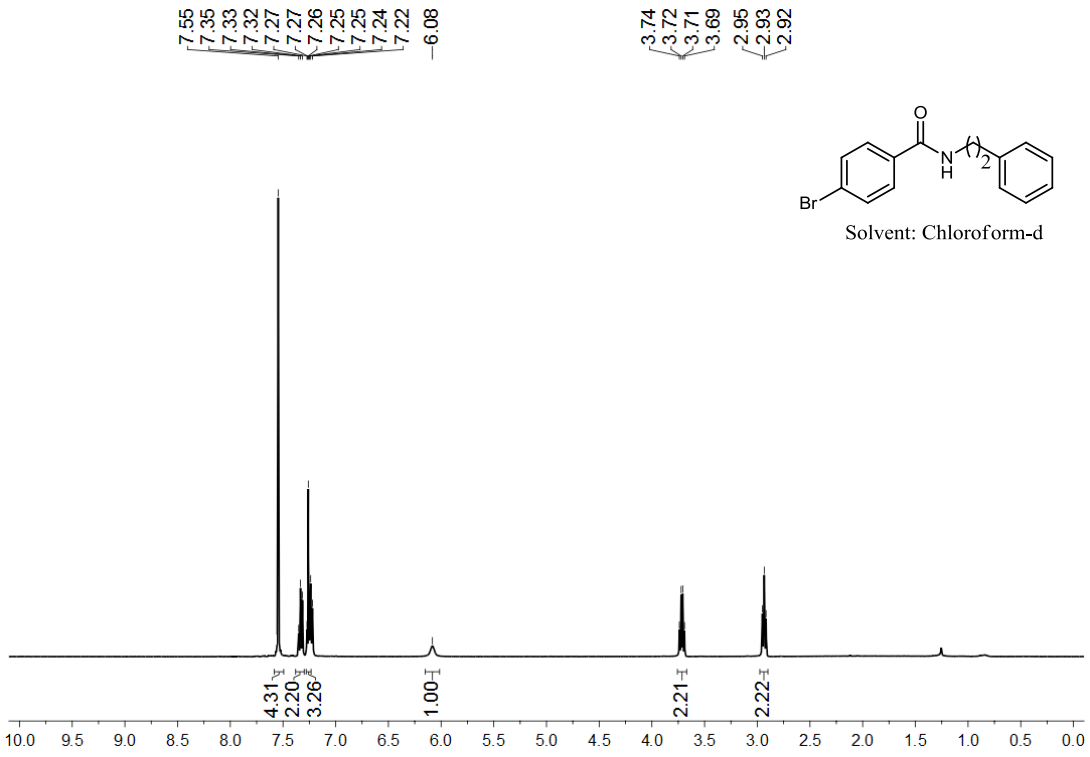


Figure 4.41 ^{1}H NMR spectrum of 4-Bromo-*N*-phenethylbenzamide (**3r**)

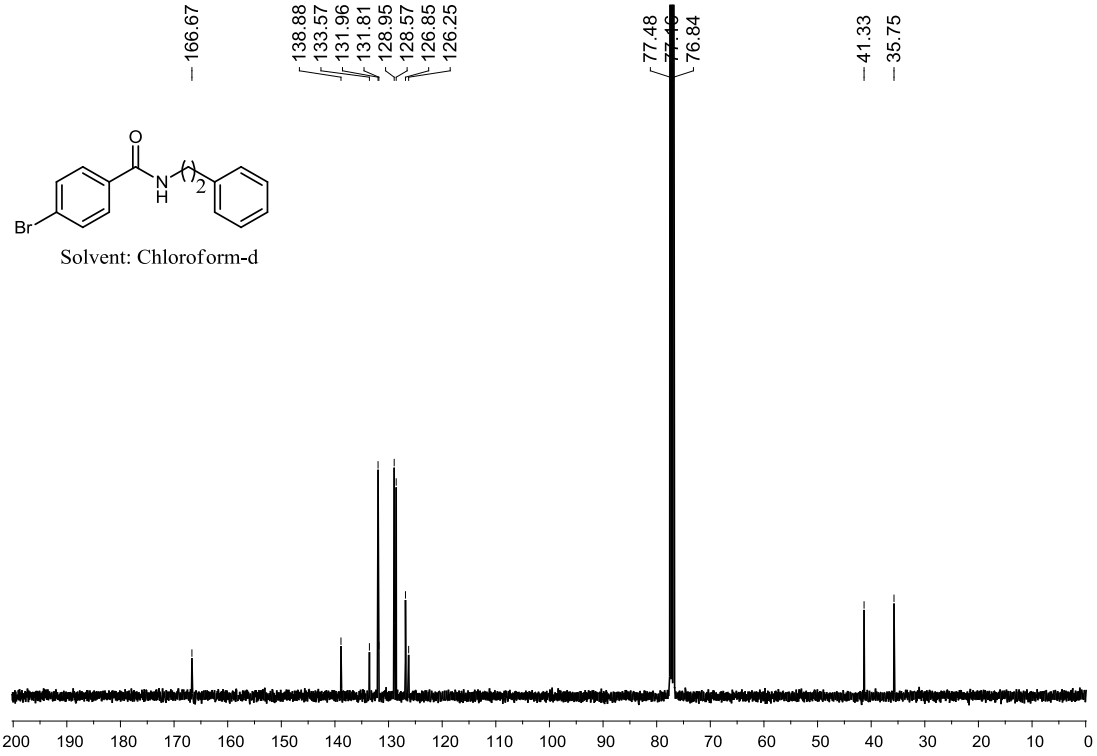


Figure 4.42 ^{13}C NMR spectrum of 4-Bromo-*N*-phenethylbenzamide (**3r**)

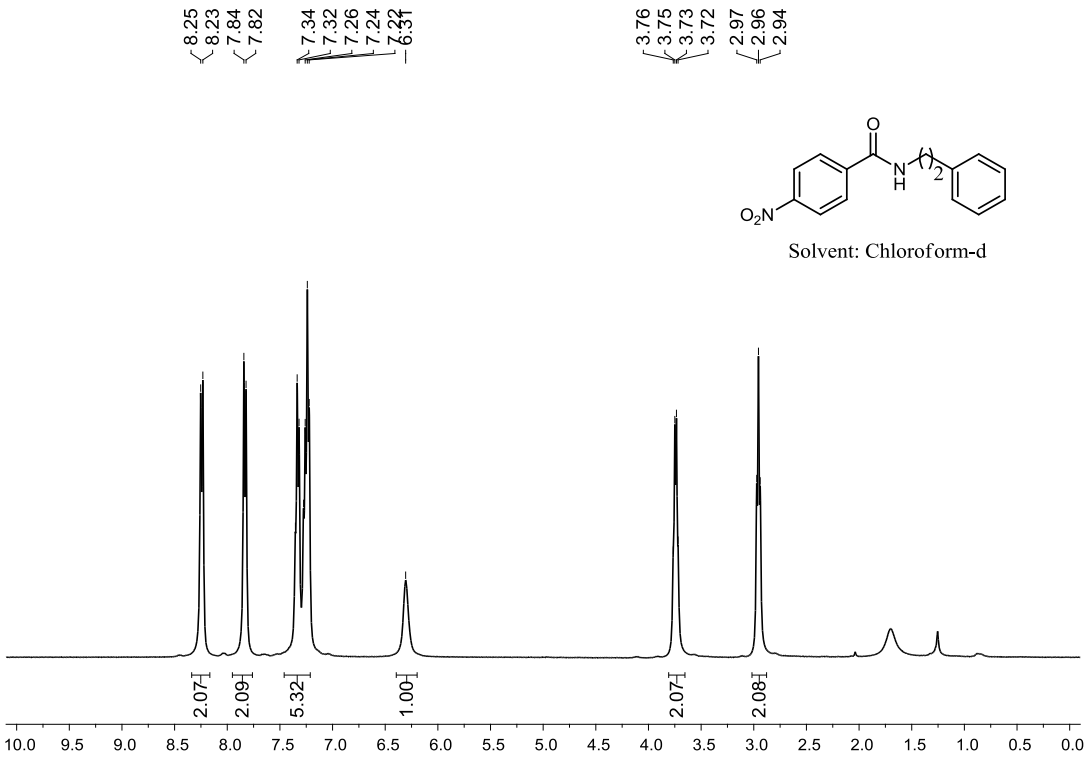


Figure 4.43 ^{1}H NMR spectrum of 4-Nitro-*N*-phenethylbenzamide (**3s**)

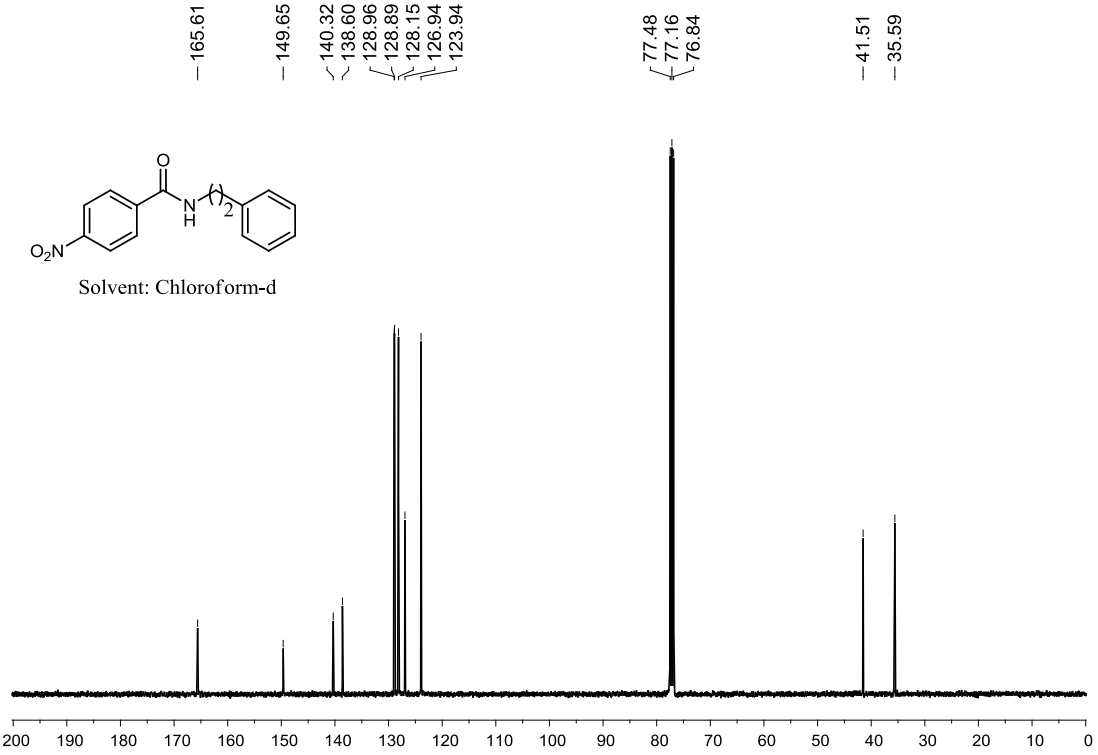


Figure 4.44 ^{13}C NMR spectrum of 4-Nitro-*N*-phenethylbenzamide (**3s**)

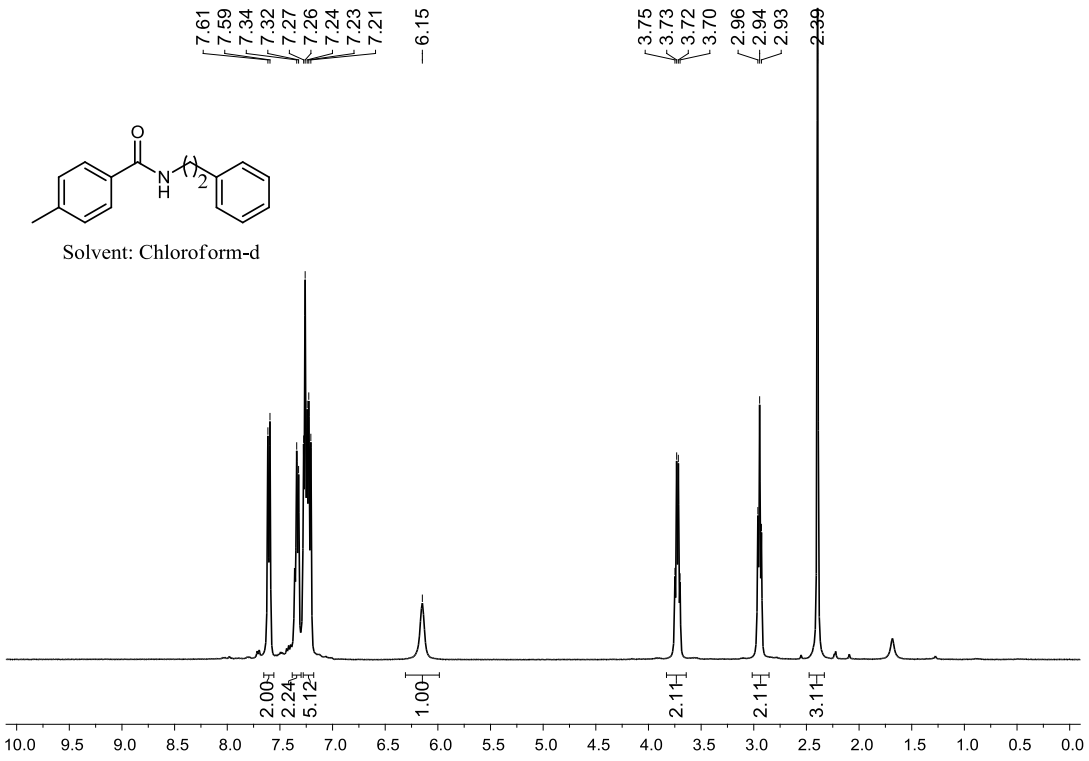


Figure 4.45 ^{1}H NMR spectrum of 4-Methyl-N-phenethylbenzamide (**3t**)

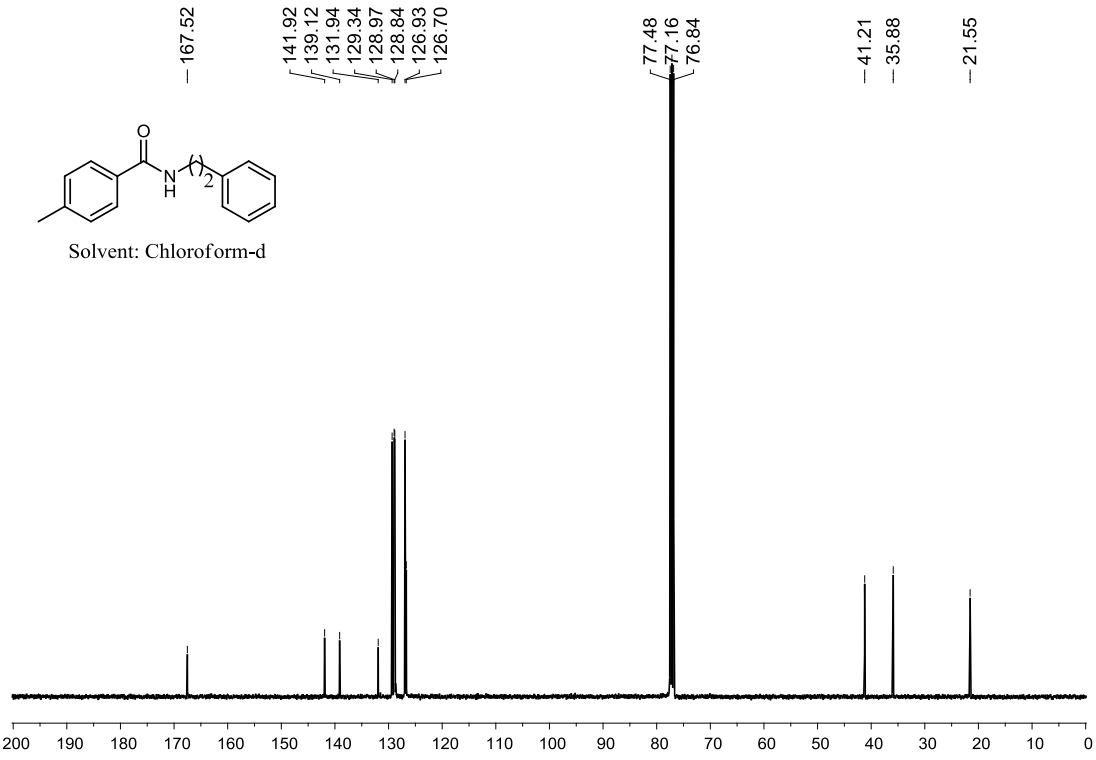


Figure 4.46 ^{13}C NMR spectrum of 4-Methyl-N-phenethylbenzamide (**3t**)

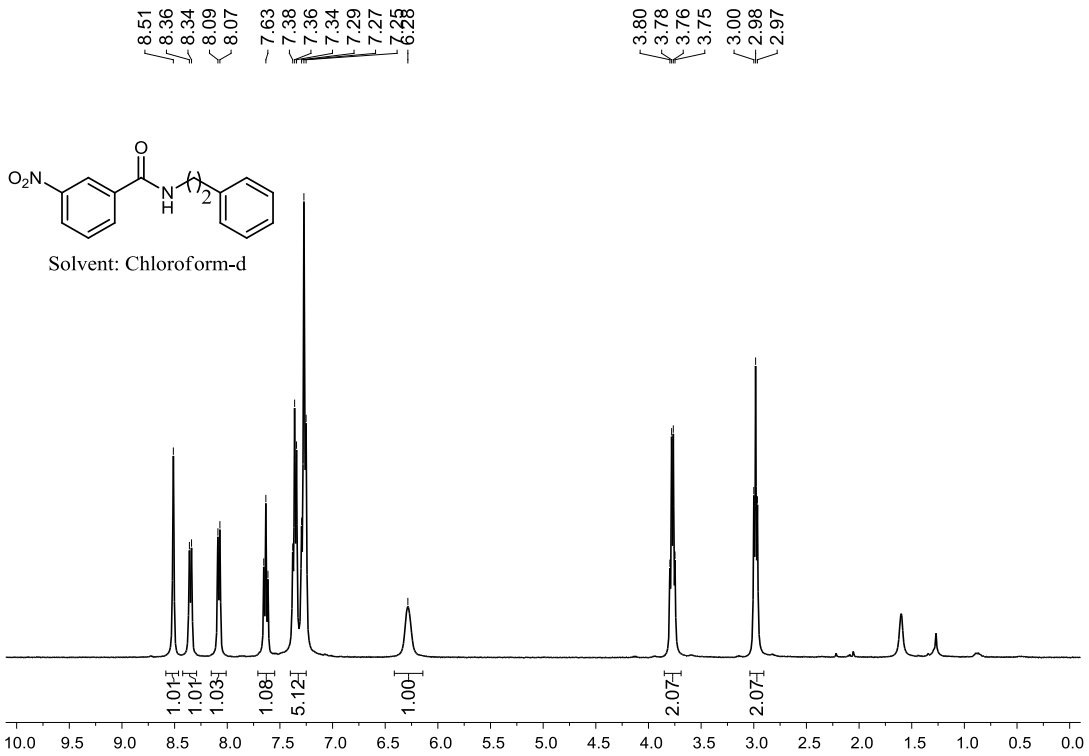


Figure 4.47 ^{1}H NMR spectrum of 3-Nitro-*N*-phenethylbenzamide (**3u**)

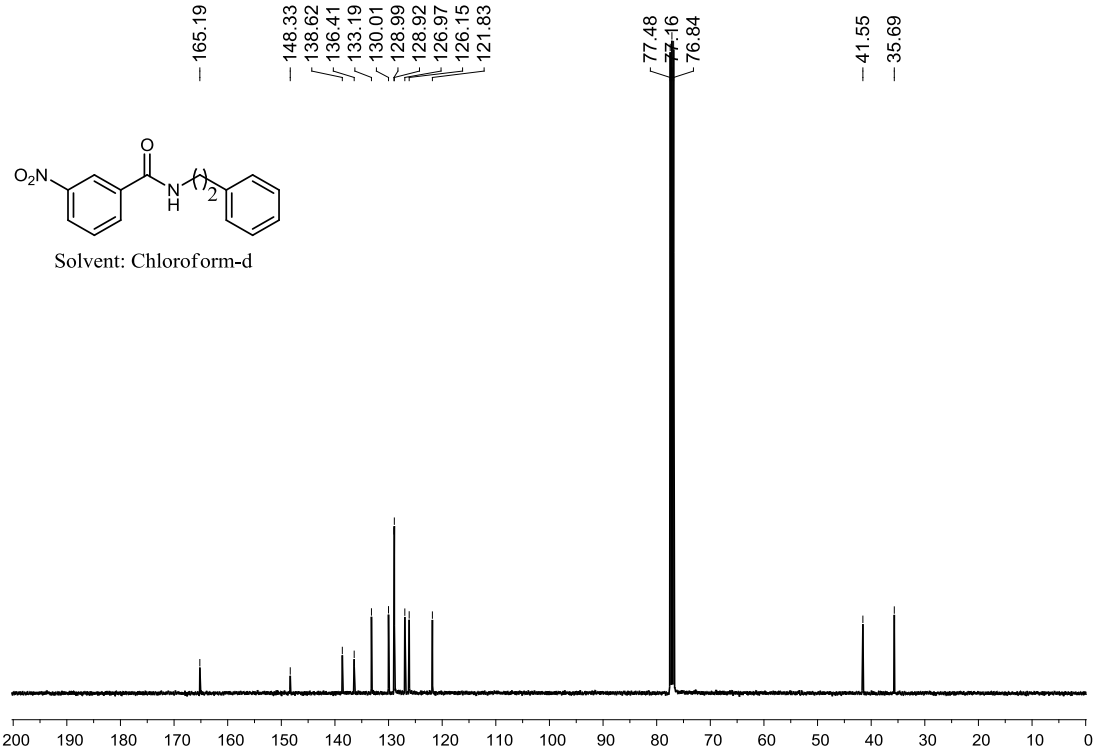


Figure 4.48 ^{13}C NMR spectrum of 3-Nitro-*N*-phenethylbenzamide (**3u**)

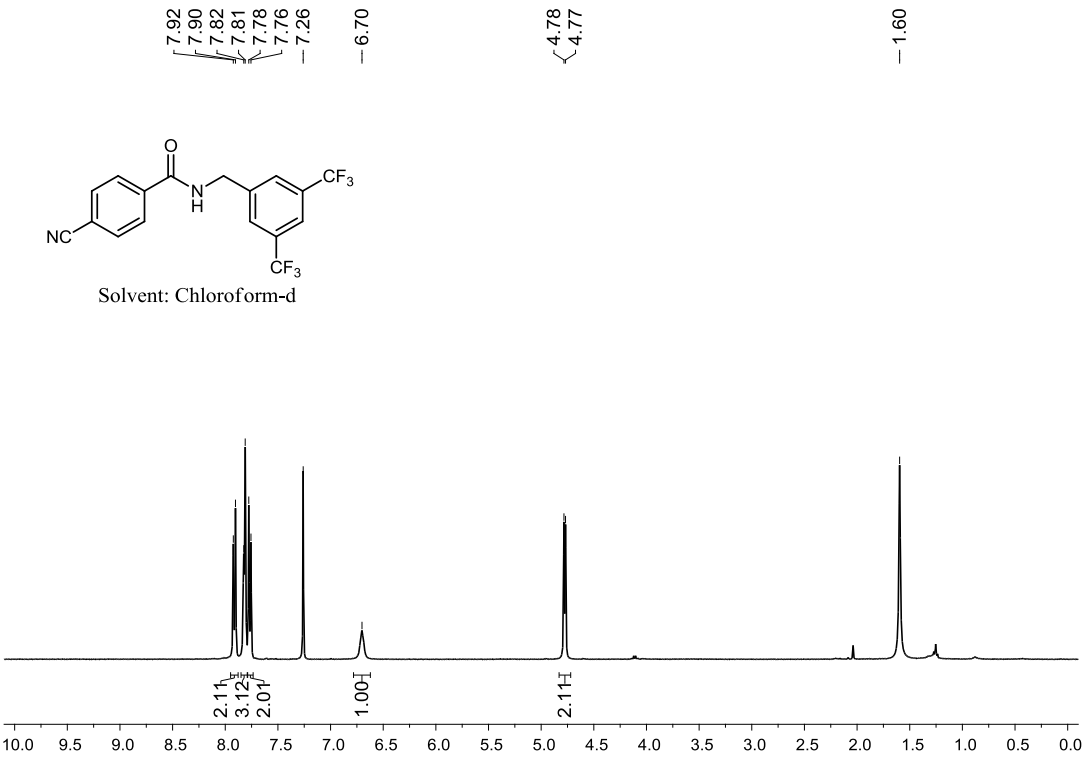


Figure 4.49 ^{1}H NMR spectrum of *N*-(3,5-bis(trifluoromethyl)benzyl)-4-cyanobenzamide (**3v**)

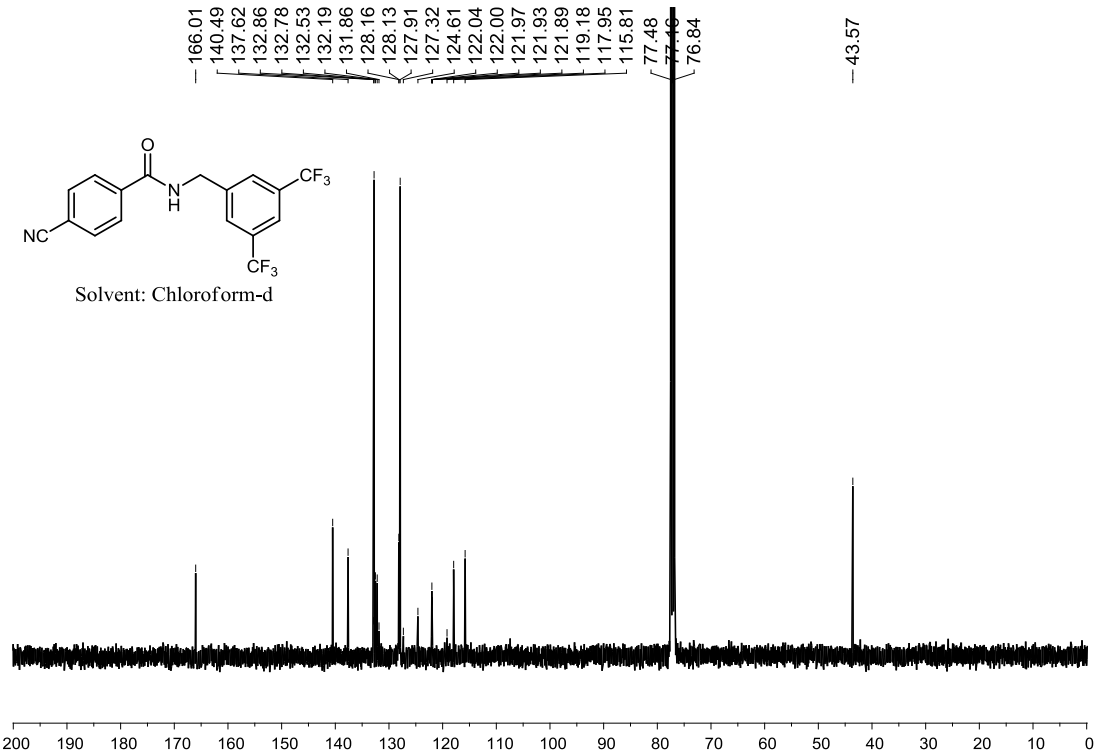


Figure 4.50 ^{13}C NMR spectrum of *N*-(3,5-bis(trifluoromethyl)benzyl)-4-cyanobenzamide (**3v**)

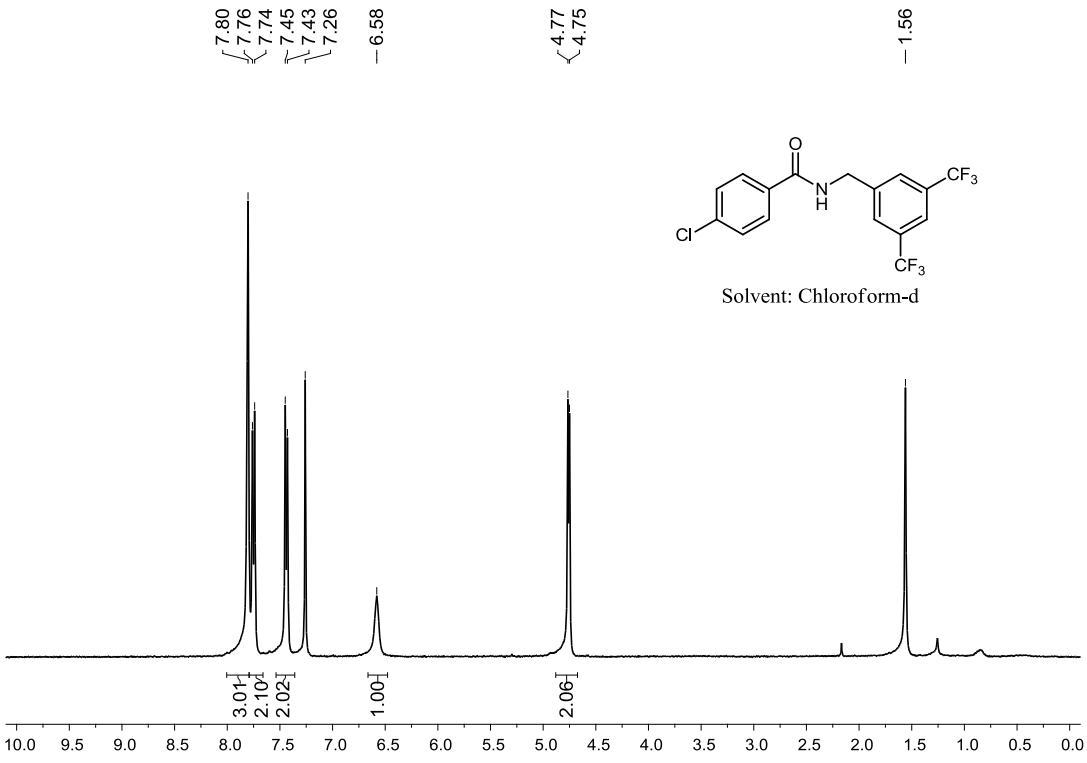


Figure 4.51 ^{1}H NMR spectrum of *N*-(3,5-bis(trifluoromethyl)benzyl)-4-chlorobenzamide (**3w**)

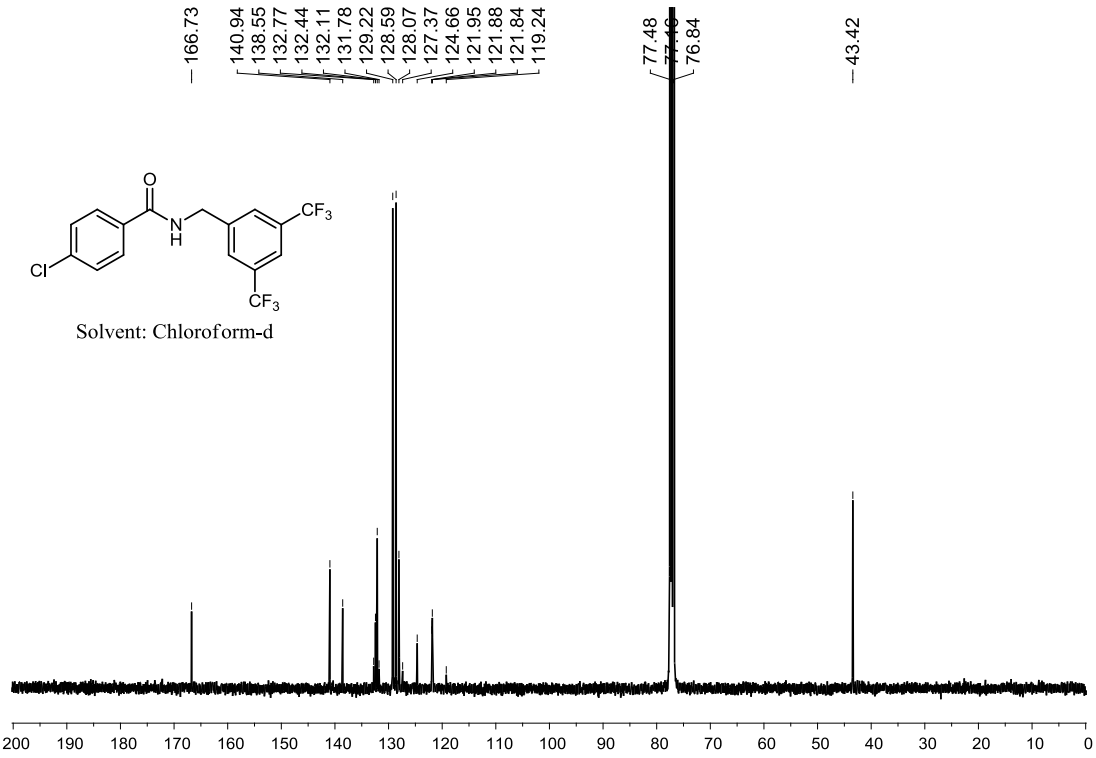


Figure 4.52 ^{13}C NMR spectrum of *N*-(3,5-bis(trifluoromethyl)benzyl)-4-chlorobenzamide (**3w**)

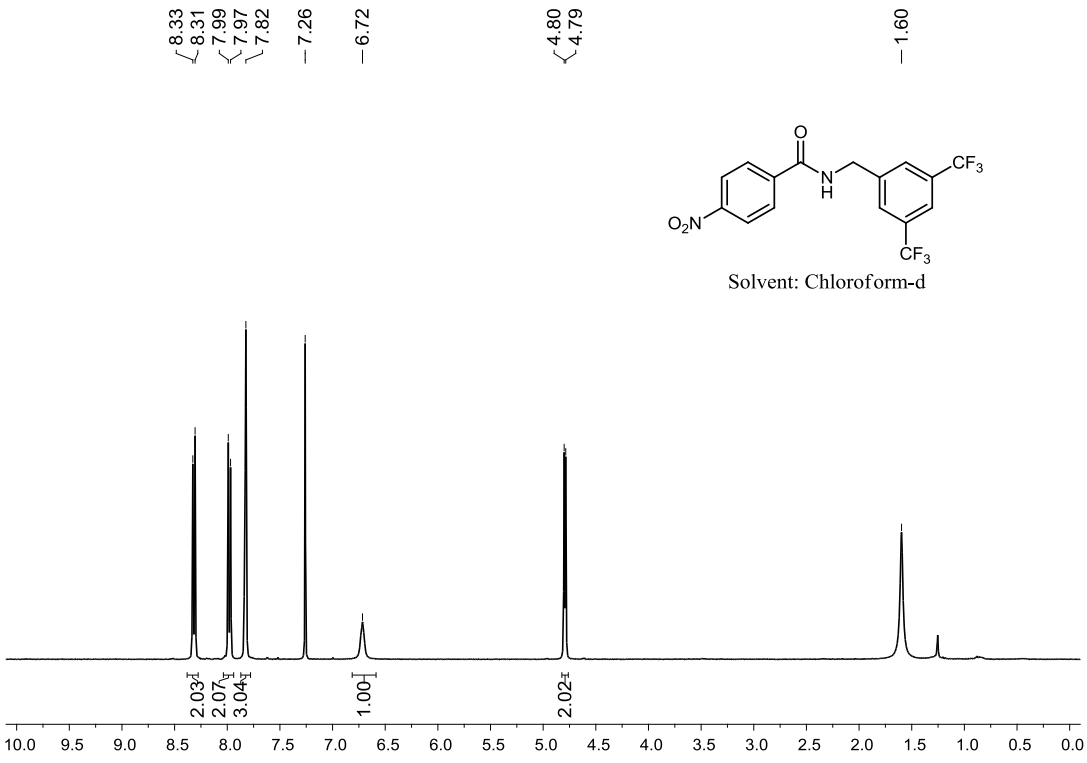


Figure 4.53 ^{1}H NMR spectrum of *N*-(3,5-bis(trifluoromethyl)benzyl)-4-nitrobenzamide (**3x**)

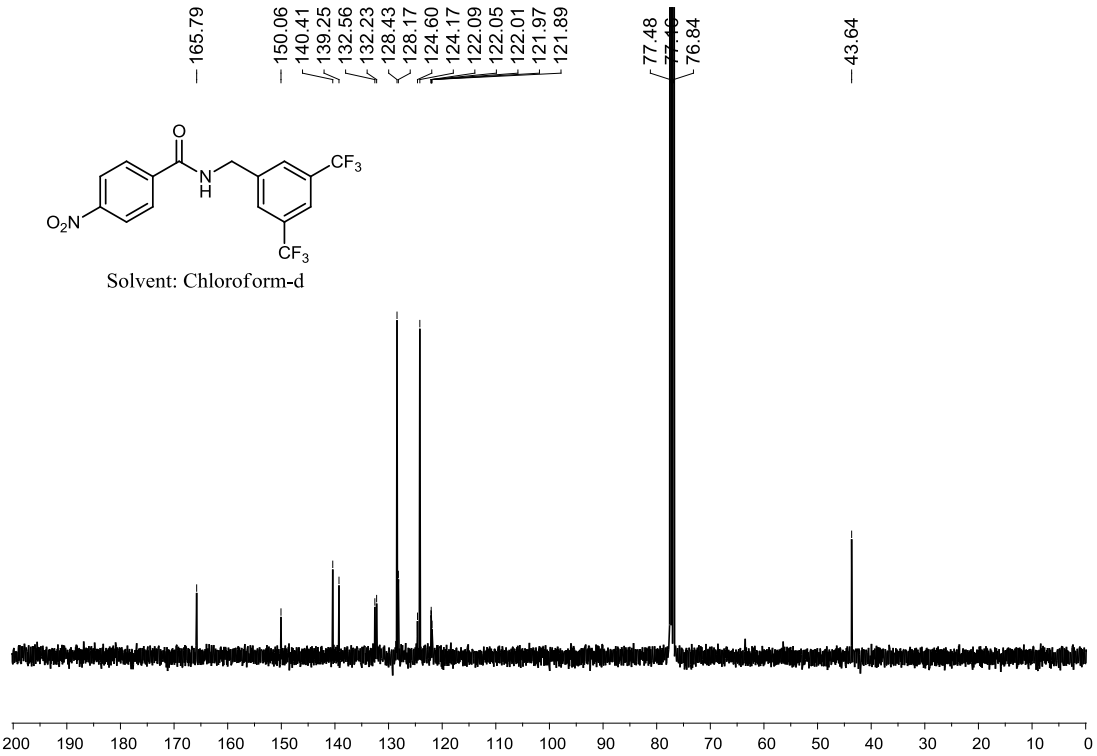


Figure 4.54 ^{13}C NMR spectrum of *N*-(3,5-bis(trifluoromethyl)benzyl)-4-nitrobenzamide (**3x**)

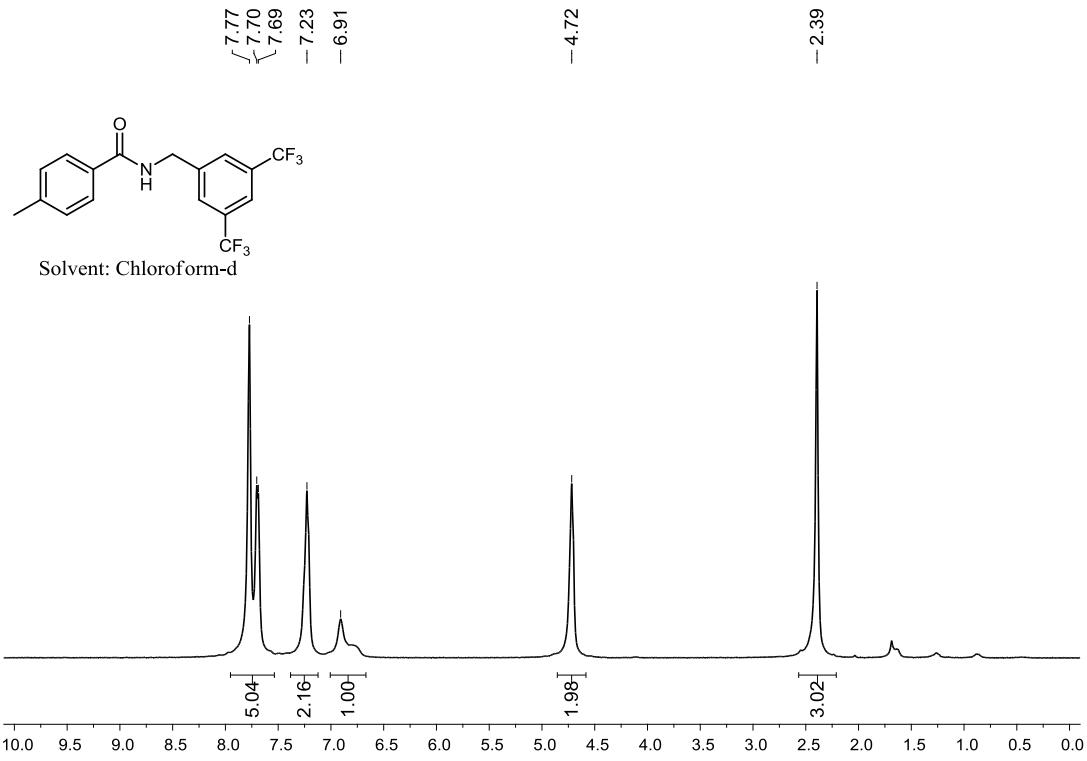


Figure 4.55 ^{1}H NMR spectrum of *N*-(3,5-bis(trifluoromethyl)benzyl)-4-methylbenzamide (**3y**)

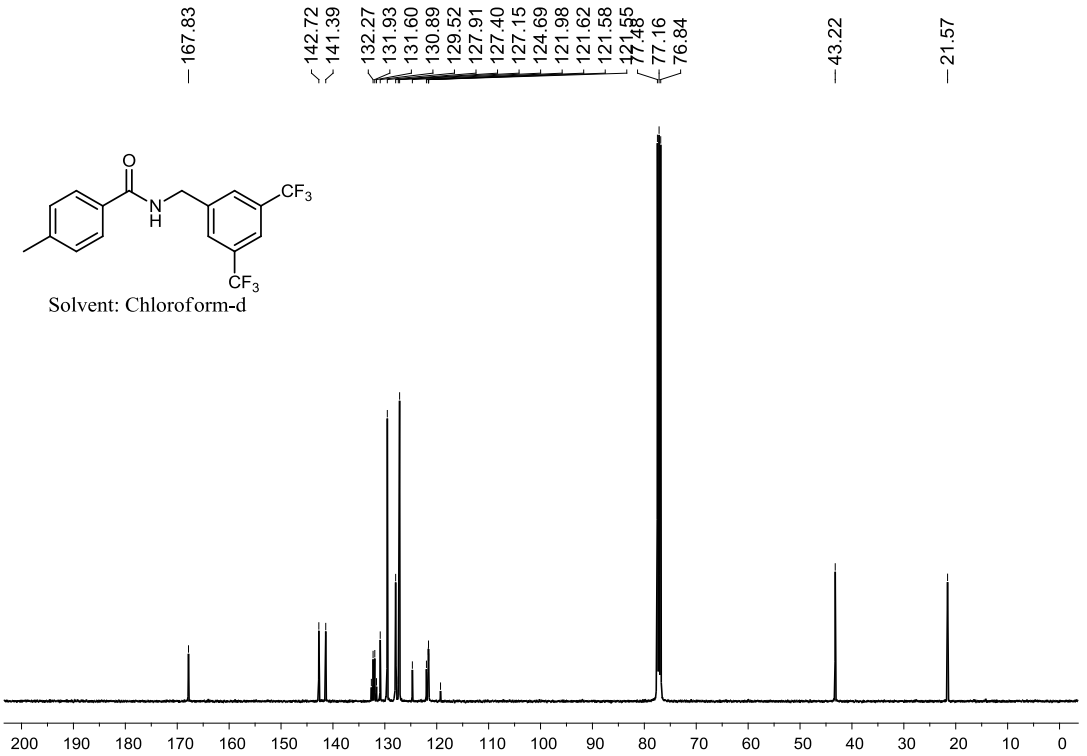


Figure 4.56 ^{13}C NMR spectrum of *N*-(3,5-bis(trifluoromethyl)benzyl)-4-methylbenzamide (**3y**)

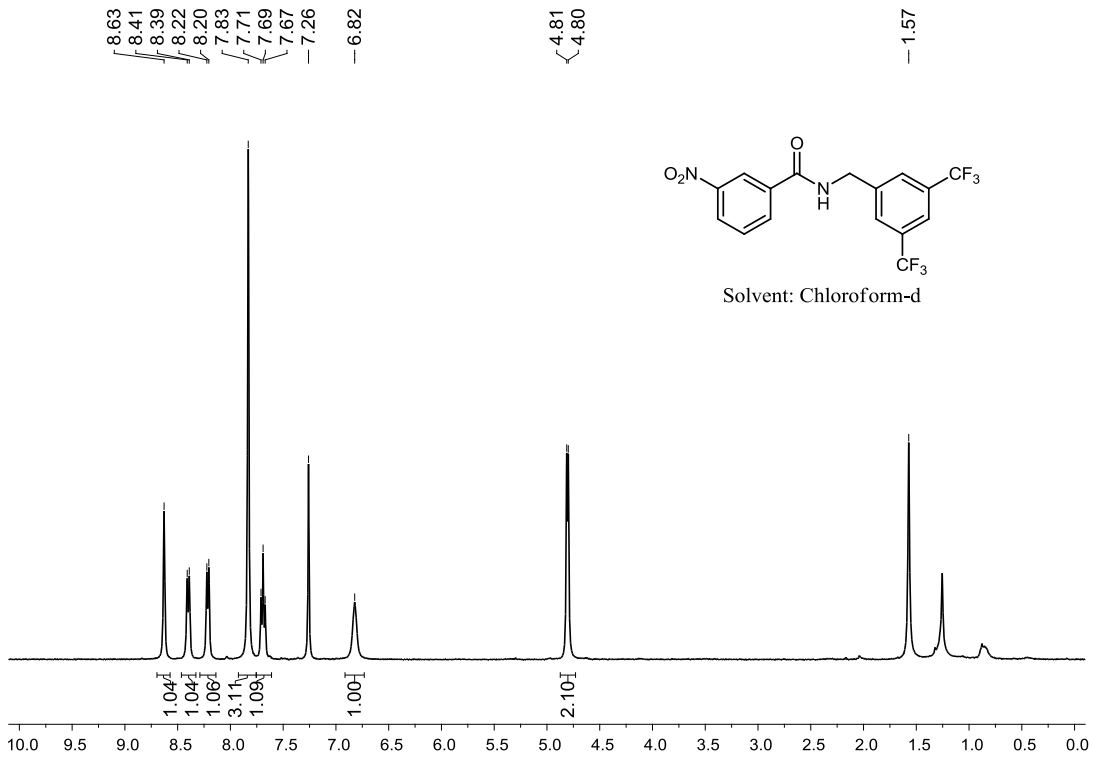


Figure 4.57 ^{1}H NMR spectrum of *N*-(3,5-bis(trifluoromethyl)benzyl)-3-nitrobenzamide (**3z**)

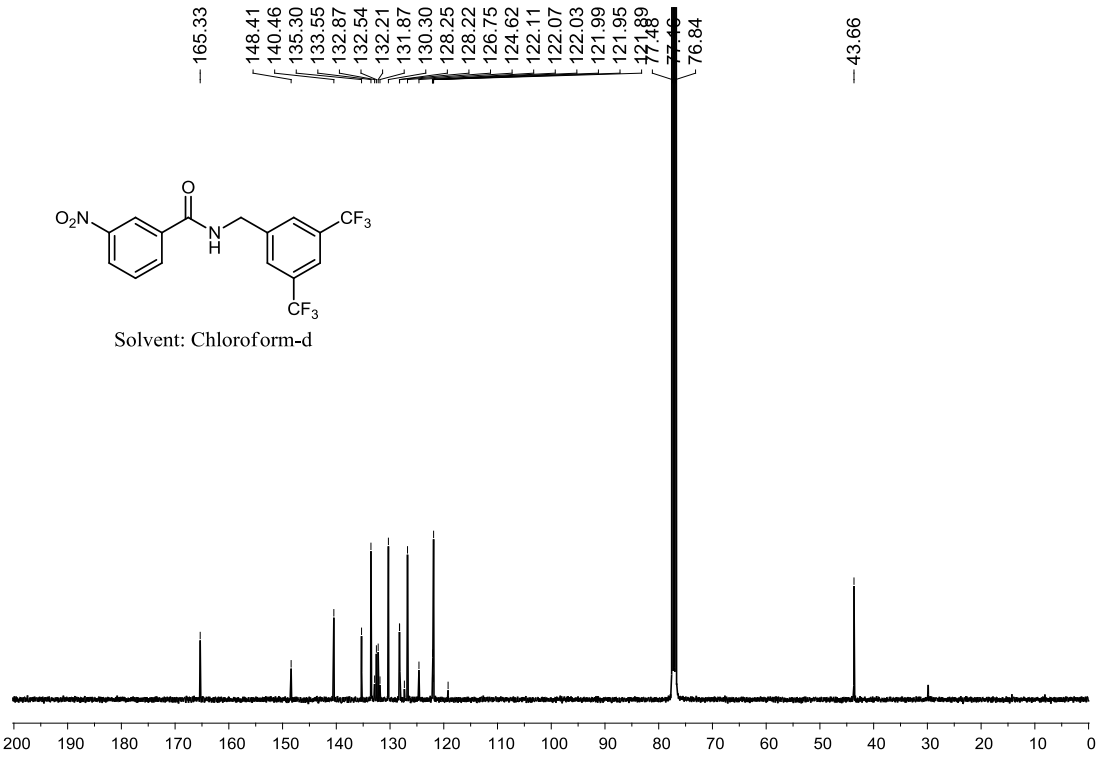


Figure 4.58 ^{13}C NMR spectrum of *N*-(3,5-bis(trifluoromethyl)benzyl)-3-nitrobenzamide (**3z**)

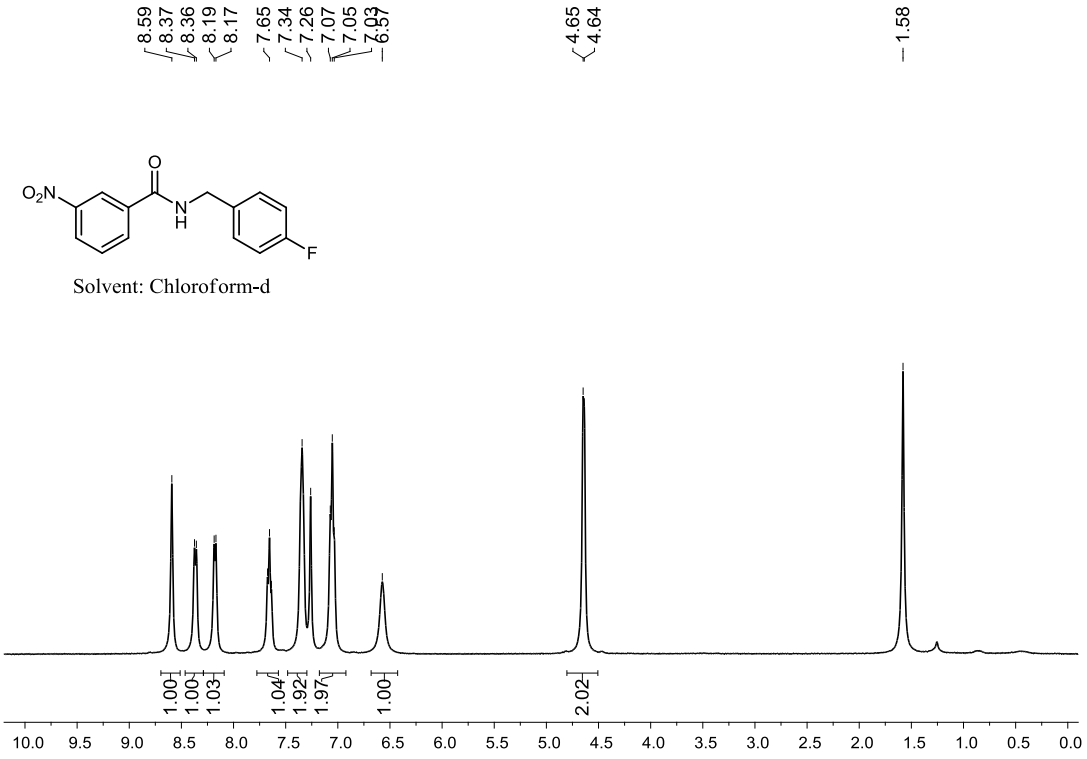


Figure 4.59 ^{1}H NMR spectrum of *N*-(4-fluorobenzyl)-3-nitrobenzamide (**3aa**)

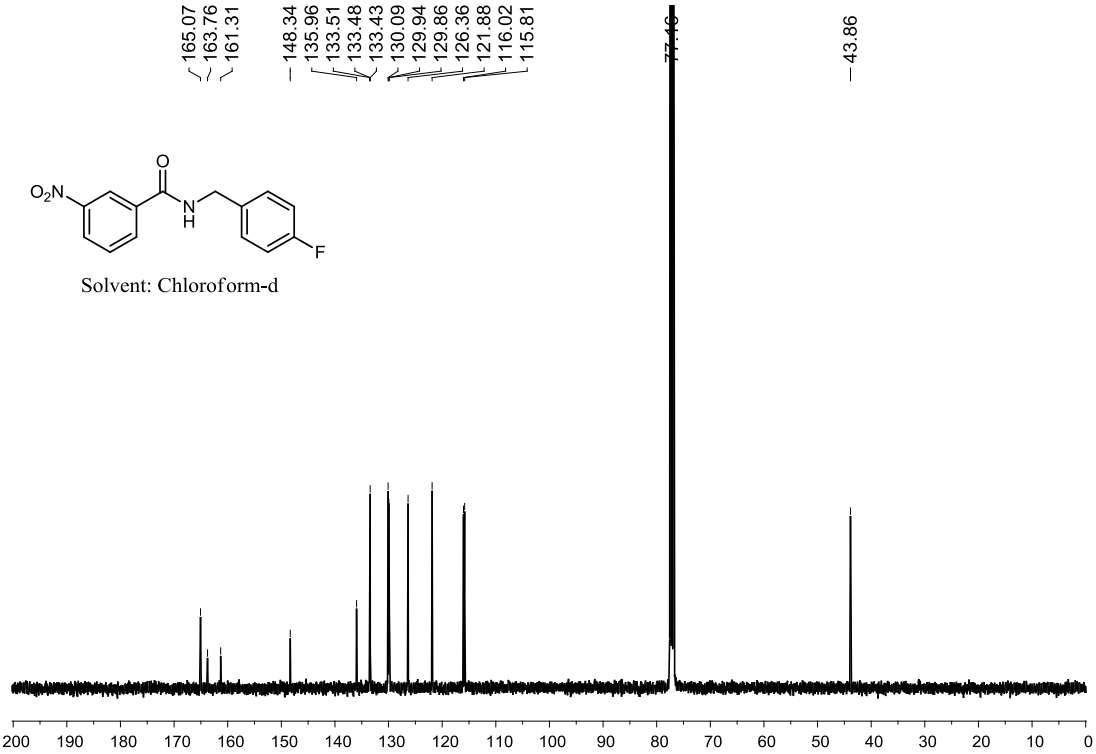
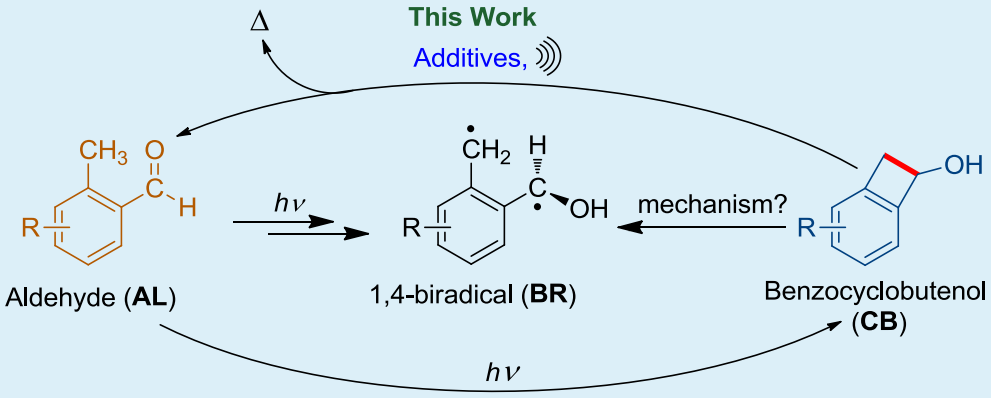


Figure 4.60 ^{13}C NMR spectrum of *N*-(4-fluorobenzyl)-3-nitrobenzamide (**3aa**)

CHAPTER 5

Input Controlled Mechano-Responsive C–C Bond Scission on Benzocyclobutenols

5.1 ABSTRACT



Mechanochemical scission of C–C bond, as occurs in polymers, is terra incognita for small molecules. Unprecedentedly, here we report robust on-set and quenching of mechano-sensitivity of benzocyclobutenols due to substitutions by cyano and bromo, respectively. First principle calculations suggest substantial reduction in dissociation barrier of the non-aromatic C–C bond possibly due to intermolecular hydrogen bonding interaction between the hydroxyl-H and cyano-N involving multiple adjacent molecules. The consequent large dilation of O–H bond reduces the non-aromatic C–C bond dissociation energy below 3 kcal/mol. The polymeric assembly suggested by –CN substituted benzocyclobutenols supports their observed lack of crystallinity and facilitates absorption of energy from low frequencies mechanochemical excitations. The observed mechano-activity can be altered by solvent polarity, additives, or electronic control. These results and the proposed mechanism thus suggest the possibility to turn small molecules into mechanophores by tuning them intra- or intermolecularly.

5.2 INTRODUCTION

Mechanical force induced scission of thermodynamically stable and kinetically inert C–C single bonds[1] in polymeric assemblies are well documented in literature[2-7]. However, the possibility of a similar mechanism in small molecules has remained largely unexplored[8]. Herein, we discuss robust and switchable mechano-response of substituted benzocyclobutenols (**CB**s)[9], demonstrated through exergonic scission of the C–C single bond of the cyclobutene ring in cyano substituted **CB**s upon sonication at ultrasonic frequencies. In addition to intramolecular substituents, mechano-responsivity could also be influenced by external factors like solvent polarity, ionic substrates as additives, and reagents facilitating hydrogen bonds. We focus primarily on how intramolecular substitutions influence mechano-response and the generality of the mechanism in order to prescribe a systematic pathway *en route to* programmable functional molecules for mechanochemically activated smart materials[10].

5.3 RESULTS AND DISCUSSIONS

Synthetically important CBs[11], obtained photochemically from *o*-tolualdehydes[12] can thermally isomerize to *o*-quinodimethanes[13] *via* electrocyclic (4πe) ring opening[14]. Such opening of ring can also be initiated through PET (Photoinduced Electron Transfer)[15], catalyzed by base[16] or promoted by exposure to X-ray radiation[17]. However, under optimized conditions benzocyclobutenes display high thermal stability up to 700 °C[18], calling for a suitable methodology to activate the cycloreversion process at ambient temperature in non-hazardous environment. Pertinently, in this work we find that mechanical force (ultrasound)[19,20] may possibly be used to achieve the same in small molecules with appropriate functionalization. Indeed, under ultra-sonication (US, 27 kHz), we find the C_{sp3}–C_{sp3} bond of certain CBs to cleave at 30 ^{0}C. However, in the straightforward pathway proposed in Figure 5.1a, the formation of intermediate 1,4-biradical (BR) may contradict the Woodward Hoffmann

rule of conservation of orbital symmetry of 4πe systems[21]. Alternately, first-principle calculations suggest an energetically more favorable pathway depicted in Figure 5.8 where the cleavage of the C–C single bond is preceded by stretching of the hydroxyl OH due to intermolecular interactions involving possibly more than two molecules.

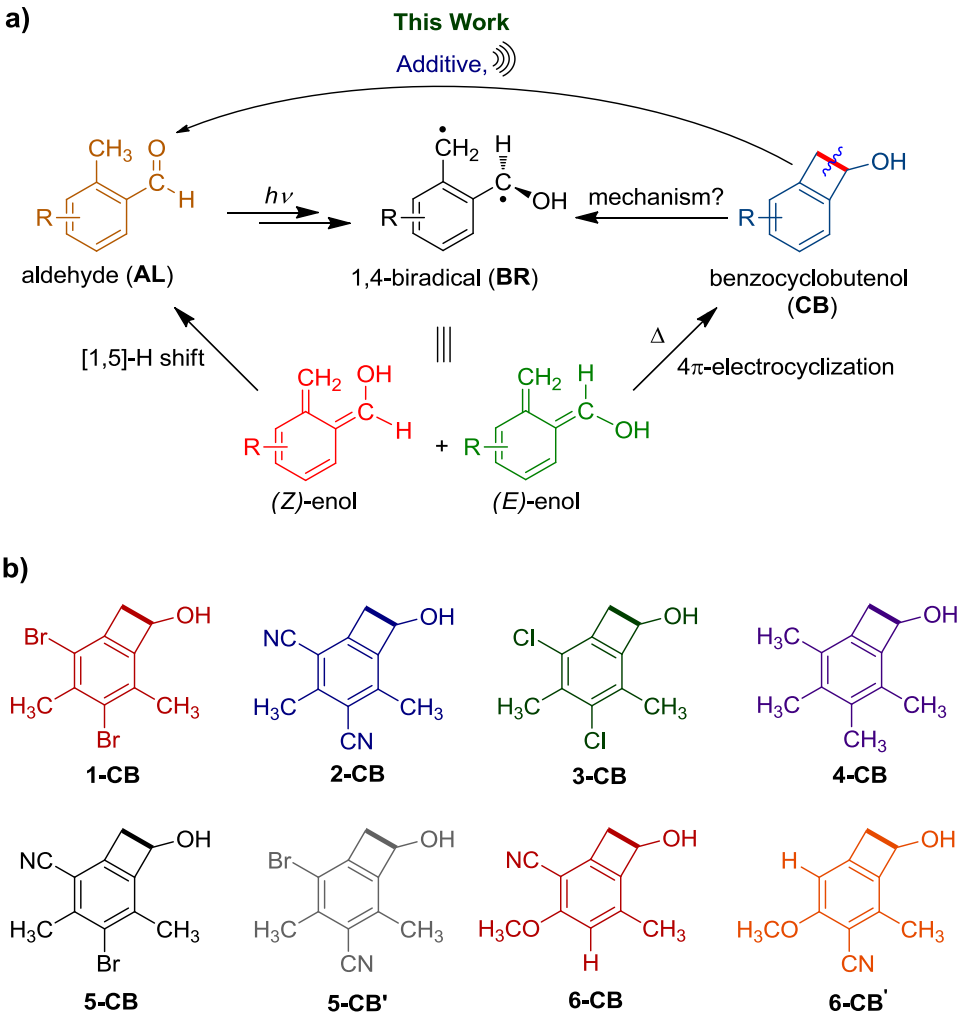


Figure 5.1| (a) Photo-initiated transformation (left to right) of *o*-alkyl aromatic aldehydes (**AL)** to the corresponding **CB**s *via* 1,4-biradical (**BR**) and followed by (*E*)-enol[12]. In turning around (**CB** to **AL** conversion as conventionally expected)[22]: Mechanically scission of C_{sp3}-C_{sp3} bond of **CB** yielded **BR** followed by intermediate (*Z*)-enol[22] before generation of **AL**. The C_{sp3}-C_{sp3} bond of **CB**'s is shown as thick line. (**b**) The **CB**s used for present study; regio-isomers of **5-CB** (**5-CB'**) and **6-CB** (**6-CB'**) were used as mixture.

Aldehydes, pentamethyl-benzaldehyde (**4-AL**) was commercially available and used as received. However, aldehydes **1-AL**, **2-AL**, **5-AL** and **6-AL** (Figure 5.2) were synthesized by following known procedure available in literature[12]. Aldehyde 3,5-dichloro-2,4,6-trimethyl-

benzaldehyde (**3-AL**) was synthesized by di-chlorination of 2,4,6-trimethyl-benzaldehyde using *N*-chloro succinimide. Solid state photolysis of the **AL**s led to **CB**s (Figure 5.3)[12]. A straightforward hypothesis for the synthesis of **CB**s are proposed in Figure 5.1a, although first principle calculations suggests alternate pathway. Single isomers were used for **CB**s like **1-CB** to **4-CB**, and regio-isomers of **5-CB** (**5-CB'**) and **6-CB** (**6-CB'**) were used as mixture.

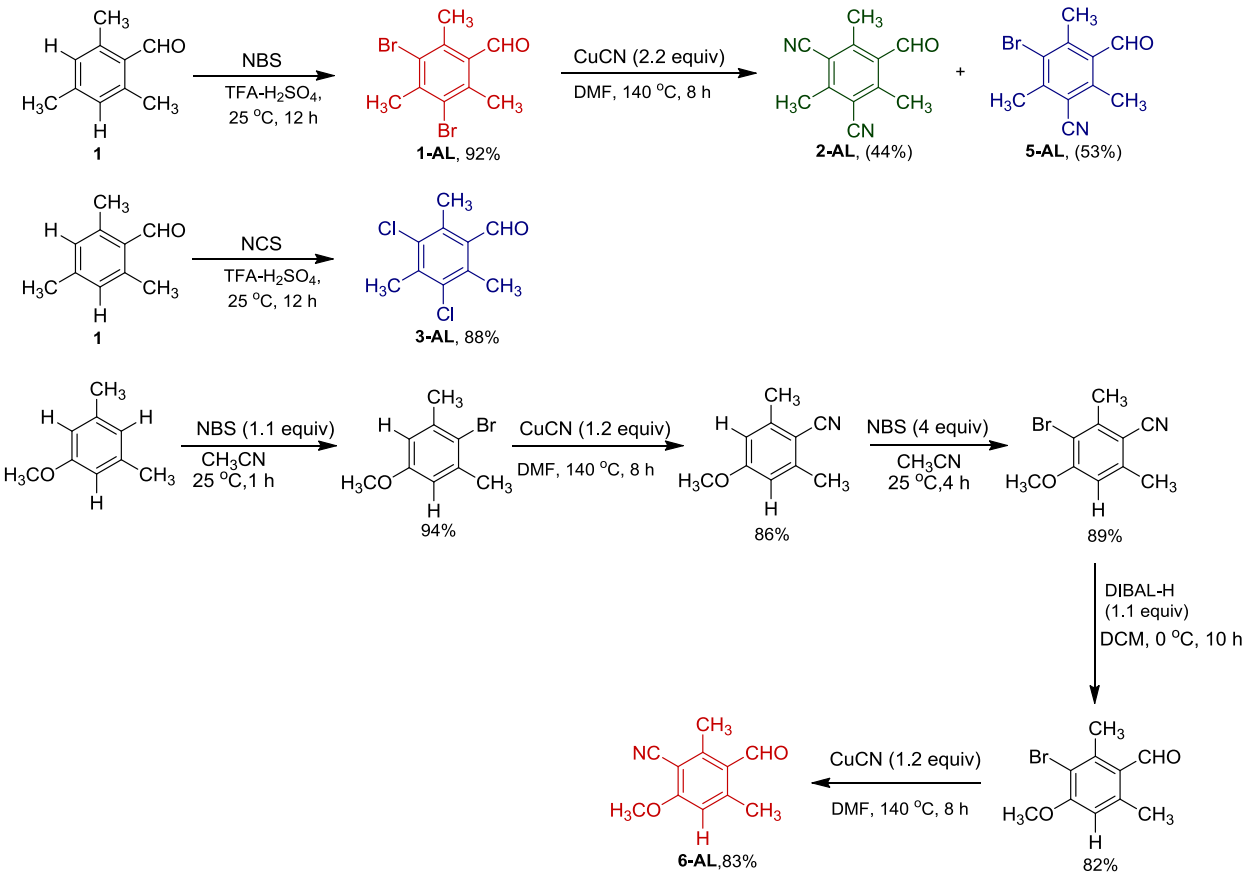


Figure 5.2| Synthesis of aldehydes (**ALs**)

The results of mechanochemical conversion of **CB**s (**1-CB** and **2-CB**) to **AL**s shown in Figure 5.4a unambiguously imply a higher degree of mechanochemical activation of **2-CB** than that of **1-CB**. Results also reflect the effect of solvents from dimethyl sulfoxide (DMSO or DMSO-d_6) to chloroform ($CHCl_3$ or $CDCl_3$) and additives like DDQ and $AgBF_4$. DMSO is a well-

known hydrogen bond (H-bond) acceptor likely to form O-H···O hydrogen bond with the OH at C_7 of **CB**s (Figure 5.4b). Charge transfer interaction was also observed for **CB**-DDQ using IR and UV-Visible studies (Figure 5.6). Furthermore, solvent dependent ^{1}H NMR shift of OH proton ($\Delta\delta \sim +3.0$ ppm in C_6D_6 to DMSO-d_6) also confirm H-bonding (Figure 5.5). Notably, O-H···O hydrogen bonding with the OH at C_7 of **CB**s (Figure 5.4b) leads to weakening of the C_7-C_8 bond on account of the partial negative charge developed in the process on Hydroxyl-O. Thus the marked enhancement in mechano-response of the **CB**s observed by changing the solvents from $CDCl_3$ (non H-bond participant) to DMSO-d_6 gives us an early hint that inter-molecular H-bonding might hold the key to the underlying mechanism.

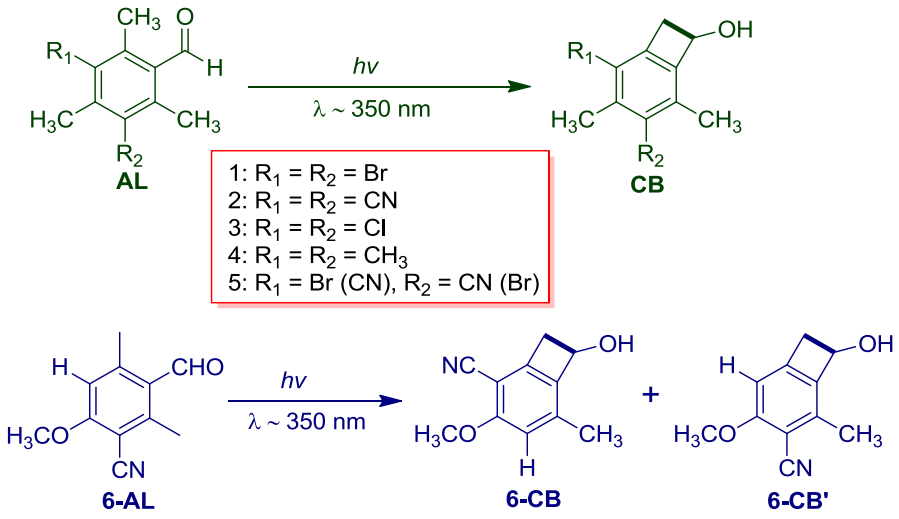


Figure 5.3| Photochemical synthesis of benzocyclobutenols (**CBs**)

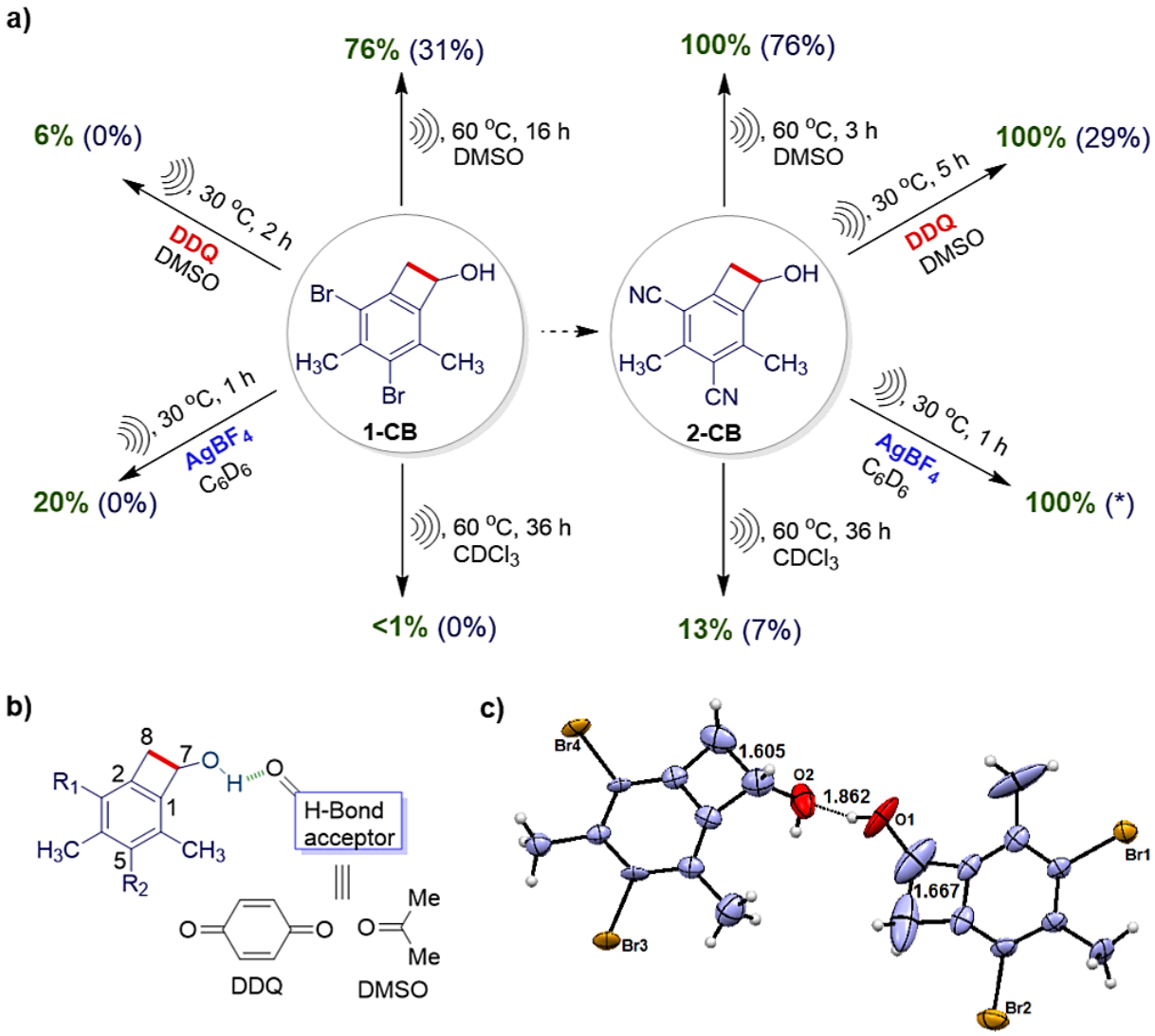


Figure 5.4| (a) Mechanochemical effect for the conversion of **CB**s to **AL**s. Solvents effect and effect of additives are shown for **1-CB** and **2-CB**. In bracket, the conversion in absence of ultrasound are shown; *inconclusive. (b) Hydrogen bonding of DMSO with **CB**s are also shown. c) X-ray crystal structure of **1-CB**; intermolecular O-H···O hydrogen bonding among two **1-CB**s are shown.

To rationalize the role of $AgBF_4$ we note that coordination of Ag^+ ion with the hydroxyl-O of **CB**s (Figure 5.7) *via* ion-dipole interaction[23] may also possibly lead to weakening of the C_7-C_8 bonds. However, since both the **CB**s have same number of Hydroxyl group, they should allow the inter-**CB** or solvent assisted O-H···O hydrogen bonding, as well as the ion-dipole interactions, on similar footing. In fact, X-ray crystal structure of **1-CB** (Figure 5.4c) shows

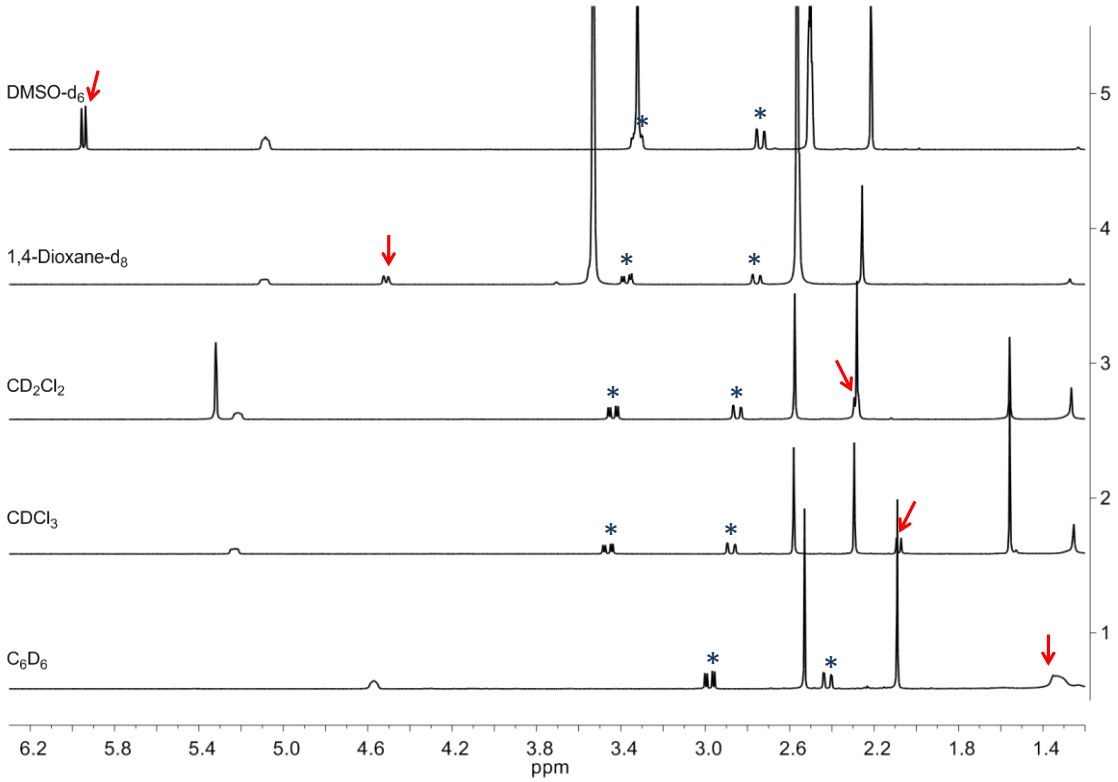


Figure 5.5| ^{1}H NMR spectra for solvent dependent shift of –OH (→) and –CH_2 (*) peaks of **1-CB**.

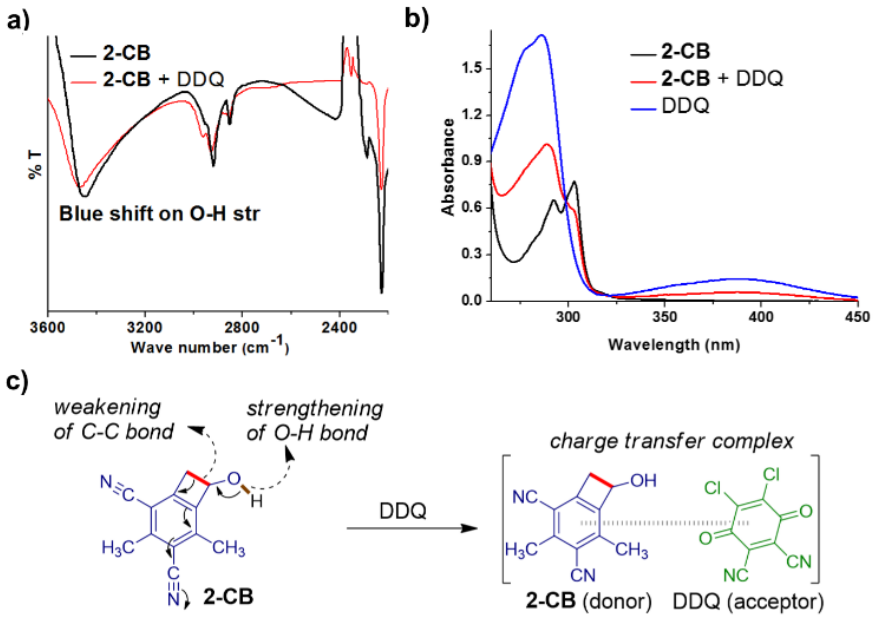


Figure 5.6| a) IR and b) UV-vis spectra of **2-CB** and in presence of DDQ.

intermolecular O-H···O hydrogen bonding and dilation of the C_7-C_8 of the H-bond donor to 1.67 Å compared to 1.61 Å for H-bond acceptor. However, the lack of mechano-response of **1-CB** suggests that the marginal dilation of the O–H bond due to the O-H···O interaction is expectedly not sufficient to facilitate dissociation of the C_7-C_8 bond.

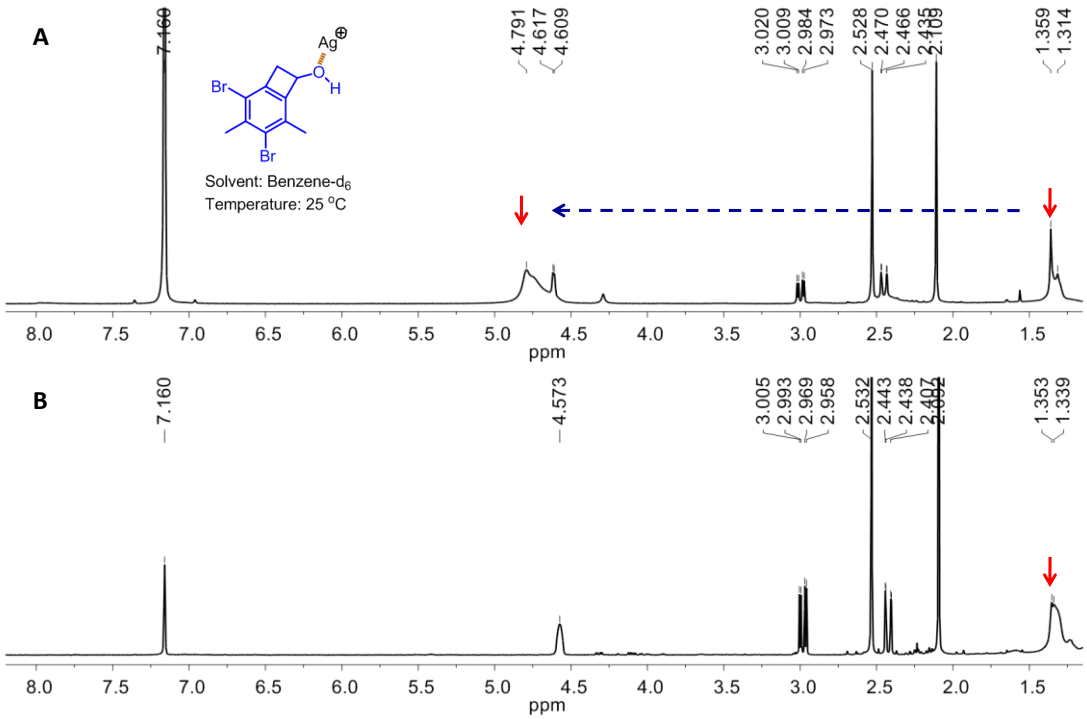


Figure 5.7| Change in ^{1}H NMR chemical shift of –OH peak (**1-CB**) in presence of $AgBF_4$ in C_6D_6 (equilibration time 1 h). (**A**) ^{1}H NMR Spectrum of **1-CB** after addition of $AgBF_4$. (**B**) before addition of $AgBF_4$ in C_6D_6 at 25 ^{0}C.

That the observed mechano-responsivity of the **CB**s are indeed in addition to the thermal effects, is clearly established from the studies shown in Figure 5.4a, where the results obtained without ultrasound while having other conditions identical to those with ultrasound, are shown within bracket. Even after 96 h, at 60 °C, negligible amount of conversion from **1-CB** to **1-AL** was observed (< 1%), thus ruling out the possibility of C_7-C_8 bond scission due to only thermal effect.

The mechanochemical response of the **CB**s are shown in Table 5.1. The cyano substituted **CB**s (**2-CB**, **5-CB** and **6-CB**) systematically show better mechano-responsivity than non-cyano substituted derivatives (**1-CB**, **3-CB** and **4-CB**).

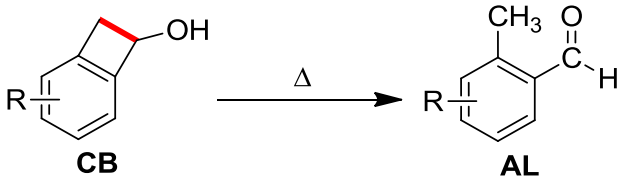
Table 5.1 Mechanochemical response of **CBs** to **ALs**.

Entry	CB's	Solvent[a] additive, time (h), conv. (%)				
		C_6D_6	$CDCl_3$	CD_2Cl_2	DMSO-d_6	DMF-d_7
1	**1-CB**	Nil, 15 h, 0	Nil, 36 h, 0	Nil, 18 h, 0	Nil, 36 h, 5	Nil, 12 h, 0
		$AgBF_4$, 1 h, 20	DDQ, 9 h, 27	DDQ, 20 h, 19	DDQ, 2 h, 6	DDQ, 24 h, 0
2	**2-CB**	$AgBF_4$, 1 h, 100	Nil, 36 h, 13	Nil, 17 h, 21	Nil, 3 h, 100	Nil, 12 h, 100
					$AgBF_4$, 0.5 h, 100	
3	**3-CB**	Nil, 26 h, 0	Nil, 26 h, 0	Nil, 20 h, 0	Nil, 26 h, 61	Nil, 24 h, 23
		DDQ, 4 h, 0	DDQ, 4 h, 7	DDQ, 20 h, 20	DDQ, 20 h, 11	DDQ, 24 h, 2
4	**4-CB**	Nil, 24 h, 0	Nil, 24 h, 0	Nil, 24 h, 0	Nil, 24 h, 0	Nil, 24 h, 0
5	**5-CB**	Nil, 24 h, 3	Nil, 10 h, 13	Nil, 17 h, 4	Nil, 3 h, 100	Nil, 12 h, 56
6	**6-CB**	Nil, 14 h, 0	Nil, 14 h, 0	Nil, 14 h, 0	Nil, 14 h, 43	Nil, 24 h, 70
		DDQ, 20 h, 8	DDQ, 20 h, 8	DDQ, 20 h, 5	DDQ, 20 h, 0	DDQ, 24 h, 29

[a]All the reactions were performed at 30 °C (± 5 °C) and under inert atmosphere

That the observed mechano-responsivity of the **CB**s are not due to thermal effects, is clearly established from the studies shown in Table 5.2. Even after 96 h, at 60 °C, negligible amount of conversion from **1-CB** to **1-AL** was observed (< 1%). Similar observations were made for other **CB**s as well. Interestingly, no significant variation of chemical shift in Variable Temperature - ^{13}C NMR spectra (25 to 40 °C) was observed. These observations rule out the possibility of C_7-C_8 bond scission due to thermal effect.

Table 5.2 Thermoresponce of **CBs** to **ALs**.



Entry	CB	Condition (Δ)	Conv. (%)
1	1-CB: $R_1 = R_2 = Br$	60 ^{0}C, $CDCl_3$, 96 h	< 1
2	5-CB: $R_1 = Br$, $R_2 = CN$	60 ^{0}C, $CDCl_3$, 96 h	15
3	2-CB: $R_1 = R_2 = CN$	60 ^{0}C, $CDCl_3$, 96 h	42
4	3-CB: $R_1 = R_2 = Cl$	60 ^{0}C, $CDCl_3$, 96 h	1
5	4-CB: $R_1 = R_2 = -CH_3$	60 ^{0}C, $CDCl_3$, 96 h	<1
6	6-CB:	60 ^{0}C, $CDCl_3$, 96 h	15

To investigate the reason behind the observed contrasting outcome of sonication of the two substituted CBs, we resort to exploring possible pathways and their energetics from first principles using density functional theory (DFT).[30] We use a planewave based implementation[31] of DFT and approximate the many-electron exchange-correlation interaction by a gradient corrected PBE[32] functional which is well known to be appropriate for isolated systems. Total energies and forces are converged respectively up to plane-wave cut off over 1000 eV and below 0.0001 Ryd/Bohr. Formation energy of the conventionally expected intermediates – the BRs proposed in Figure 5.1a, are found to be higher by about 14 kcal/mol and 10 kcal/mol for 1-CB and 2-CB, respectively. Such BRs preventing the conversion from CBs to ALs through BRs, in agreement with the comparable energetics of the BRs offers no clue to the contrasting mechano-response of the CBs, rather, also appears to suggest that there

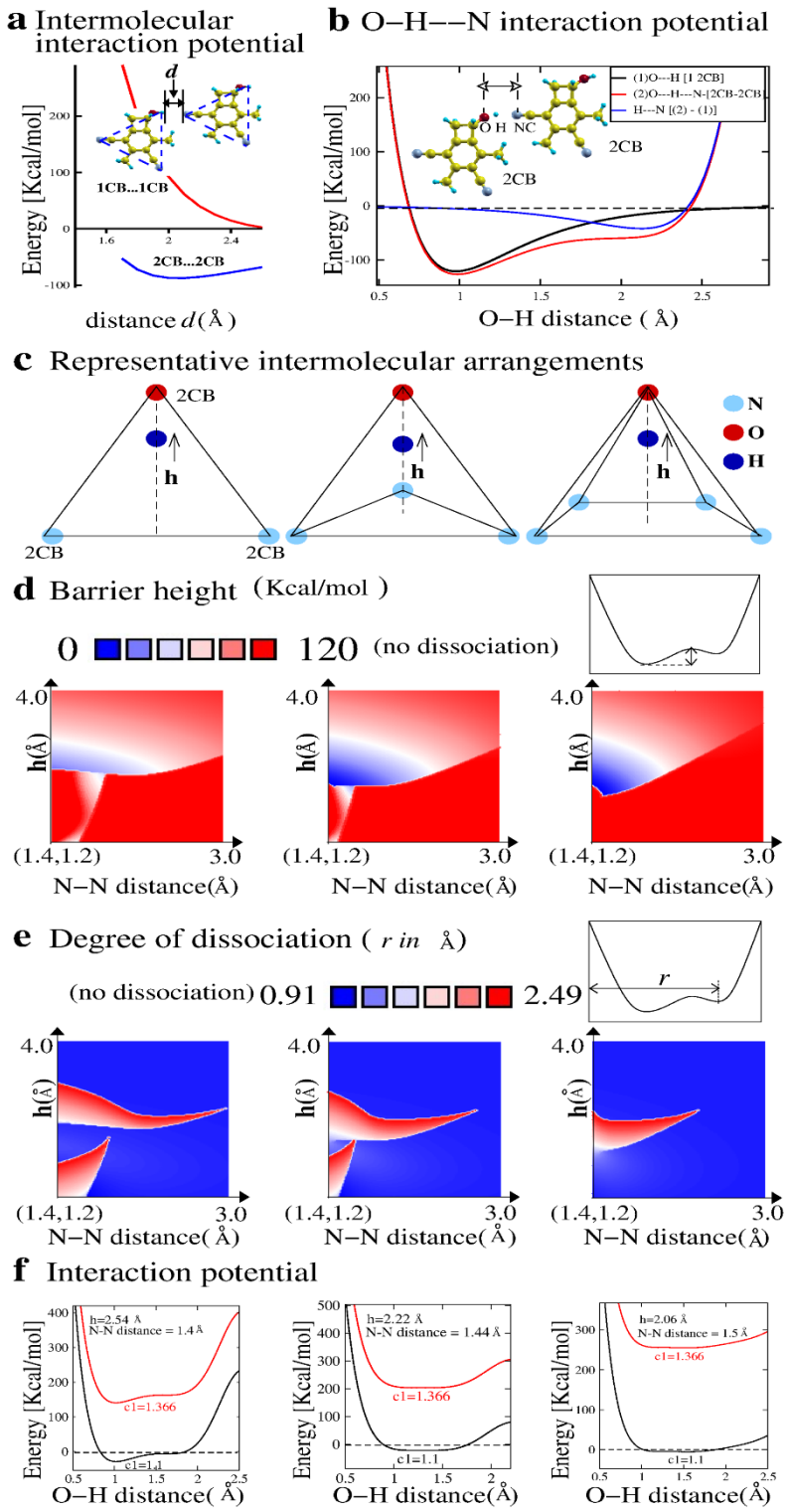


Figure 5.8| (a) Intermolecular interaction potentials between **CB**s along O-H···Br-C and O-H···N-C alignment. **(**b) Interaction potential of a hydroxyl-H as a function of O-H distance in a **2-CB** in presence of another **2-CB**. (c) Three possible geometries of interaction between hydroxyl-H of a **2-CB** and cyano-N of adjacent two, three and four **2-CB**s. (d) 2D plot of activation barrier for dilation of -O-H bond as function of intermolecular N-N distance (*d*) and height (*h*) of O from basal line or plane as shown in Fig 3c. (e) Dilated O–H bond length as functions of N-N distance and *h*. (f) Net interaction potential of the hydroxyl-H as a function of O-H distance corresponding to the minimum activation barrier, plotted for one value of the leading term in the Morse potential for (**2-CB**)N···N(**2-CB**) steric repulsion.

could be large activation barriers in conversion of CBs to inconsistency of formation BRs with the Woodward-Hoffman rule of electrocyclic ring opening for 4πe system. Among the other possibilities, inter-molecular O-H···O interaction cannot be the reason for cleavage of the C_7-C_8 bond, since it should then be possible with both CBs, as already discussed. However, in addition to the O-H···O interaction, the **2-CB**s should allow intermolecular O-H···N interactions as well, as evident from the negative interaction potential between two **2-CB**s along O-H···N-C plotted in Figure 5.8a. Accordingly, we next explore in details the effects of this enhanced scope of intermolecular interactions among the **2-CB**s over that among the **1-CB**s, and argue it to be possibly responsible for the strikingly different physiochemical properties of the two CBs, reflected by the lack of mechano-response of **1-CB** and crystallization of **2-CB**.

The potential energy of an H-atom between the hydroxyl-O and a cyano-N of two adjacent **2-CB** molecules 3Å apart, plotted in Figure 5.8b in red, reveals an activation barrier of about 63.56 kcal/mol, beyond which, the potential varies slowly over a distance of about 0.5 Å. Although the implied activation energy for dilation of the O-H bond is far too large for mechanical excitations to be effective, the extended plateau of the interaction potential indicates the possibility of larger dilation of the O-H bond, if the dissociation barrier could be reduced, so that the consequent increase in charge withdrawn on hydroxyl-O could reduce the dissociation barrier of the C_7-C_8 bond substantially. Noting that the depth of the -OH and -N···H interaction potentials (in black and blue in Figure 5.8b) are of same order in magnitude, we explore the possibility of reduction of the O-H dissociation barrier in the eventuality of multiple O-H···N interactions amounting to multi-centered O-H···*n*N H-bonding.[33-35] Such proximity of more than one cyano-N in the vicinity of a hydroxyl-H may not be implausible given the imbalance in the number of H-bond donor (the hydroxyl-H) and acceptor (two cyano-N and the hydroxyl-O) per **2-CB** molecule. In fact, we show latter with CH_3OH and CH_3CN that

assemblies leading to O-H···*n*N, with even $n = 3$, can even be barrier less. We consider few representative configurations depicted in Figure 5.8c involving more than two **2-CB**s to test our hypothesis. Given the computational enormity of the unit-cell with the chosen configurations, we estimate the net interaction potential in these scenarios by adding the Morse potential fits to the first principles estimates of – (1) the OH interaction in **2-CB**, (2) interaction of an H atom with a cyano-N of **2-CB**, and (3) the (**2-CB**)N···N(**2-CB**) steric repulsion. The net interaction is estimated as function of the vertical distance (*h*) of the hydroxyl-O of a **2-CB** from the line or plane of the cyano-N atoms, one each from two or more **2-CB** molecules, and the distance (*d*) between the nearest neighboring cyano-N atoms. The activation barrier for displacement of hydroxyl-H away from the hydroxyl-O towards the center of mass of the cyano-N atoms, and the degree of such displacement (the second minimum from O in the net interaction potential of H), plotted in Figure 5.8d and 5.8e respectively, clearly indicates the possibility of large dilation of the OH bond with more than two cyano-N, particularly with three of them approaching the hydroxyl-H symmetrically. Red and blue regions respectively in Figure 5.8d and 5.8e marks values of *h* and *d* for which the OH bond can be stretched beyond 1.5 Å with potential barrier in the order of 1 kcal/mol or less, conducive for the low energy mechanical excitations to be effective. In Figure 5.8f we plot the interaction potential corresponding to the lowest activation barrier for O–H bond dilation for minimum steric repulsion between appropriately oriented adjacent **2-CB** molecules indicating the possibility of O–H bond dilation at room temperature. Reduced steric repulsion due to smaller H-bonding reagents like DMSO is thus expected to facilitate the O–H bond dilation process at ambient conditions, in agreement with observations.

In Figure 5.9, we present the energy profile indicating the intake or release of energy per molecule for steps envisaged for mechanically activated conversion of **2-CB** to **2-AL**. With 60% dilation of O–H bond the amount of charge retained by the hydroxyl-O in **2-CB** is about

0.4e. For dilation to increase further towards dissociation of the O–H bond, the average uptake of energy required per molecule is of the order of 10 kcal/mol, which is less than the energy released upon exergonic conversion of the intermediates B to C (Figure 5.9d,e). We consider a **2-CB** with 0.4e excess charge with the O–H bond completely dissociated, and estimate the activation barrier for scission of the C_7-C_8 bond using the nudged elastic band (NEB)[31] approach. With 0.4e charge on the dissociated hydroxyl-O, NEB calculations suggest a dissociation barrier of about 3 kcal/mol for the C_7-C_8 bond, which decreases further with increase in charge withdrawn on O above 0.4*e*. Since 0.4e charge on the hydroxyl-O occurs with 60% dilation of the O-H bond, with completely dissociates O–H bond we naturally expect the charge on O to increase further leading thus to further reduction in the C_7-C_8 dissociation barrier. Energetics of the next step (Figure 5.9f) suggests chemisorption of the dissociated H-atom on the under-coordinated carbon atom of the intermediate D to form **2-AL**. Notably, the net uptake of energy to overcome the barriers in the primary rate-limiting steps, which is the dilation of the O–H bond leading to dissociation, appears to be less than the net release of energy by about 20 kcal/mol or more, which in turn is close to the net uptake itself, thus promising the possibility of cascading chain reaction. In fact, according to Figure 5.9, even with one cyano-N interacting with the hydroxyl-H the net uptake of energy required to overcome all the activation barriers is close to the net release of energy in steps Figure 5.9d, Figure 5.9e and Figure 5.9f. Thus the, multi-centered H-bonding proposed to facilitate dissociation of the O–H bond through low energy mechanical excitations, is in principle required only to initiate the reaction, which can be there-after be energetically self-sustaining.

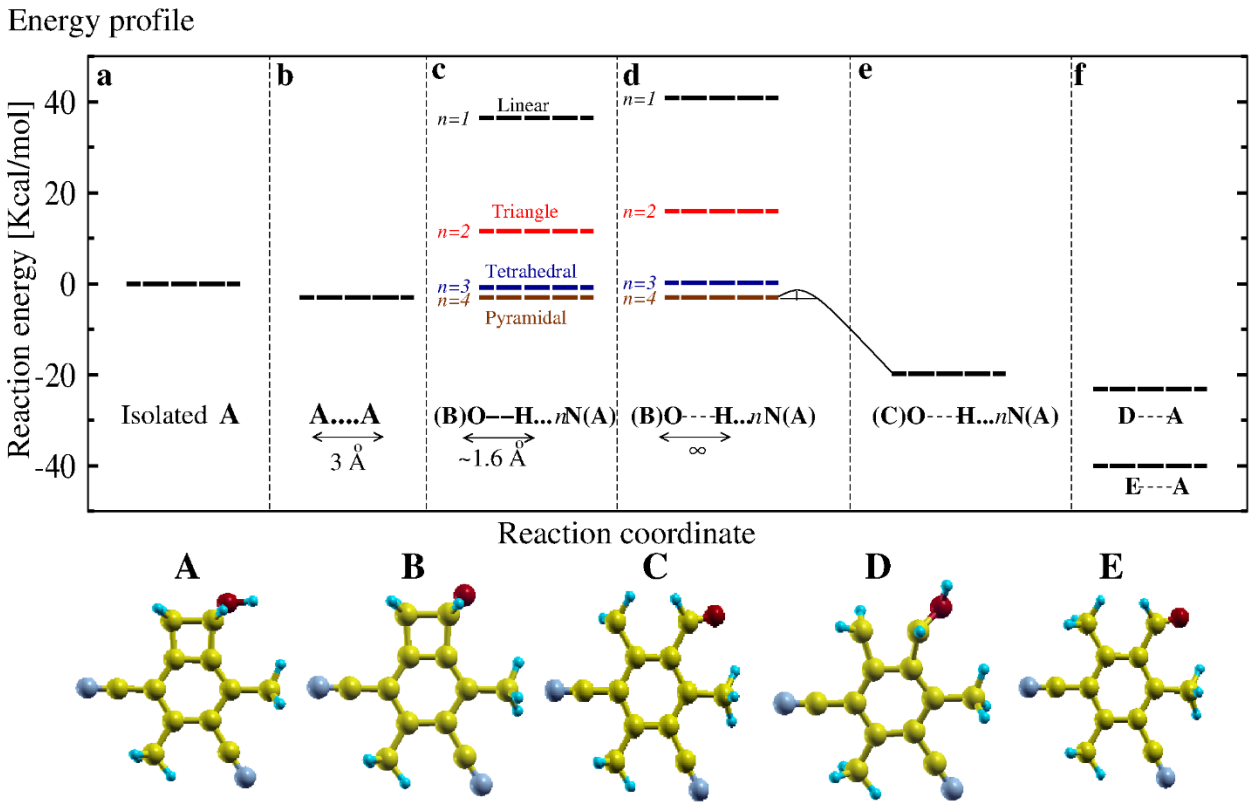


Figure 5.9| (a) Energy profile per molecule with reference to an isolated **2-CB** describing. (b) Release of energy upon cohesion of two **2-CB**s. (c) Barrier for dilation of O–H bond and (d) Its subsequent dissociation, followed by (e) The activation barrier and release of energy upon dissociation of the non-aromatic C–C bond, and (f) Subsequent formation of **2-AL**.

To rationalize the model potential based proposal made above for dilation of the O-H bond from first principles we choose smaller representative molecules CH_3OH and CH_3CN as H-bond donor and acceptor respectively and calculate the interaction potential in the same configurations for the hydroxyl-O and cyano-N atoms as depicted in Figure 5.8c. As evident in Figure 5.10a-c, we find the lowest activation barrier for O–H bond dilation to be possible with three cyano-N acceptors interacting with the hydroxyl-H in tetrahedral configuration with values of *d* and *h* in the range of 1.5Å to 2Å, which is consistent with predictions from model potential. Interestingly in Figure 5.10b the distance (*r*) of the second minima from O is larger than *h*, implying complete dissociation of the O–H bond since the H atom would pass through

the N-N-N triangle to the other side and find a local potential minimum at about 0.6Å away from the NNN plane as shown in Figure 5.10e. Thus the steps **c** t**o** **d** in Figure 5.9 might actually be barrier less. To substantiate the possibility of assembly of three CH_3CN molecules to constitute the N-N-N triangle, we show in Figure 5.10d that indeed the three molecules, driven by the O-H···(3)N multi-centered H-bonding interaction, can overcome their mutual steric repulsion and simultaneously approach a CH_3OH molecule without any barrier up to proximity of about 3.5Å of each other, after which the dilation of the O-H bond would facilitate further proximity of the cyano-N atoms. However Figure 5.10e also suggests that once the O-H bond is completely dissociated, the H atom then can possibly be held hostage by the three cyano-N atoms, which is consistent with the finite barrier of about 20 kcal/mol for the H to be free (profile shown in black in Figure 5.10d), thus facilitating cleavage of the C_7-C_8 bond. In Figure 5.10f we plot the difference between the total charge density and the sum of the charrge densities of the isolated CH_3OH and CH_3CN molecules. The quantum mechanical nature of the interaction between the hydroxyl-H and the cyano-N atoms are evident from the +ve (red) iso-surfaces between them pointing towards the H atom. The red and blue iso-surfaces on the O-H bond reveals electron withdrawal towards the hydroxyl-O.

In support of the observed lack of crystal structure of **2-CB**s, we note that with three H-bond acceptor (one hydroxyl-O and two cyano-N) and one H-bond donor (hydroxyl-H), supplemented by the possibility of multi-centered H-bonding with one H-bond donor engaging more than one H-bond acceptor, the **2-CB** molecules are likely to be entropically driven to self-assemble into extended fractal-like polymeric[36] assemblies, for example the rheologically important Cayley tree polymers.[37-39] Advantageously, the large number of intermolecular H-bonding interactions responsible for each extended assembly of **2-CB**s would allow a wide range of low frequency vibrational modes through which mechanical energy can be absorbed

through resonance. The **1-CB**s on the other hand, with one each of strong H-bond donor (hydroxyl-H) and acceptor (hydroxyl-O), are able to passivate both of them into stable H-bonding configurations, which, along with to Vander Waals interactions, would lead to their easy crystallization, as observed.

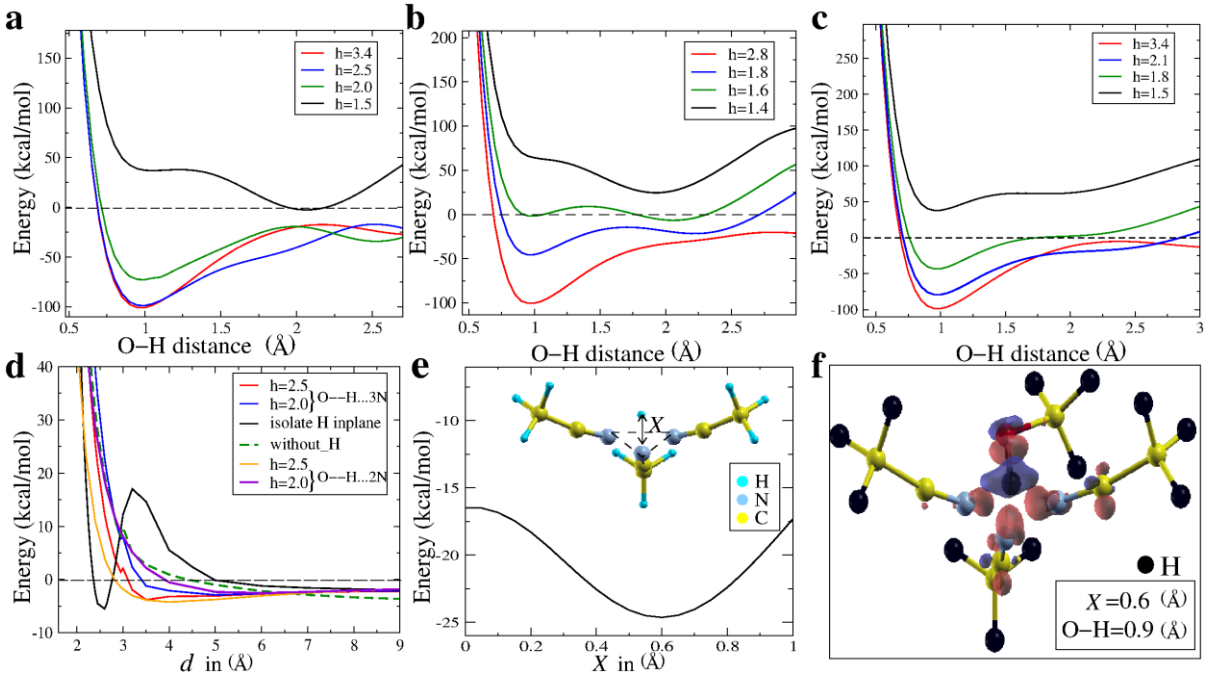


Figure 5.10| Interaction potential of a hydroxyl-H as a function of O-H distance for different *h* and *d* = 2.0 Å of the three configurations: (a) O–H···2N, b) O–H···3N, c) O–H···4N (as shown in Figure 5.8c). (d) Interaction potential between an isolated H or CH_3OH and two to three CH_3CN with the cyano-N atoms oriented towards the isolated or hydroxyl-H as shown in Figure 5.8c, as function of *d* for different H position. (e) Interaction potential of single H atom and three CH_3CN molecules with *d*=2.0 Å and (f) 3D Iso-surface of charge density difference (Total - 3 Isolated CH_3CN – Isolated CH_3OH).

5.4 CONCLUSION

In summary, through demonstration of ultrasonically induced scission of the C_{sp3}-C_{sp3} bond in appropriately substituted **CB**s, mechanical excitation has been shown to be a probable source of energy to control reactivity of small molecules, if they are functionalized to support intermolecular interactions up to an appropriate level, such that, they can collectively compete with covalent interactions and substantially reduce dissociation barrier selectively of certain bonds, and can also entropically lead to polymeric self-assembly of molecules enabling absorption of mechanical energy through a wide range of low energy vibrational modes. Calculated energetics suggests release of energy of about 10-20 kcal/mol upon the mechanically initiated exergonic bond scission leading to conversion from **CB** to aldehyde (**AL**). Given that the **CB**s were photochemically synthesized from **AL**s, the mechano-responsive **CBs** thus promise a new class of molecules for absorption and storage of light energy,[40] and their subsequent controllable release at ambient conditions, through a energetically self-sustaining pathway.[41] The derived mechanistic understanding will facilitate designing new chemical reactions by promoting mechano-response through intra- or intermolecular control.[42] In wider perspective, our results can also add a new dimension towards understanding the effect of clinical ultrasound on strained proteins.[43]

5.5 EXPERIMENTAL SECTION

Methods. NMR spectra were measured on a Bruker AV 400 (400 MHz) at room temperature mainly in deuterated solvents. UV-Visible and IR spectra were recorded on PerkinElmer (Lambda 750) and PerkinElmer FT-IR Spectrometer, respectively. X-ray data collection was performed on Bruker SMART APEX CCD-based X-ray diffractometer system equipped with a Mo-target X-ray tube (λ = 0.71073 Å) operated at 50kV and 40mA at 100 K. Data reduction

and absorption correction were done by program SAINT and SADABS respectively. Solid-State photolysis were carried out in Luzchem reactor (λ_{max} = 350 nm). The sonochemical irradiation[44, 45] was performed in Sineo UWave-1000 and 27 kHz frequency was used for the irradiation.

Preparation of 3,5-Dibromomesitaldehyde (1-AL). To a solution of **1** (1.0 g, 6.7 mmol) in trifluoroacetic acid (TFA, 3 mL) was added 6 mL conc. H_2SO_4 (98%). To this reaction mixture, *N*-bromosuccinimide (NBS, 3.0 g, 16.9 mmol) was added and stirred at room temperature for 12 h. After that, the contents were poured into crushed ice and the solution was made alkaline with 10% NaOH. The organic matter was extracted with chloroform. The combined extracts were washed with water, dried over anhydrous Na_2SO_4, filtered and solvent removed in vacuo. The residue was washed with absolute ethanol and dried under high vacuo to get 1.75 g (85%) of 3,5-dibromomesitaldehyde **1-AL** as a colorless crystalline solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.45 (s, 1H), 2.72 (s, 3H), 2.55 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.9, 142.3, 137.5, 134.9, 127.5, 26.7, 20.2.

Preparation of 3,5-dicyanomesitaldehyde (2-AL) and 3-cyano-5-bromomesitaldehyde (5-AL). To a solution of CuCN (0.7 g, 7.8 mmol) in 5 mL of DMF was added 3,5-dibromomesitaldehyde **1-AL** (1.0 g, 3.3 mmol) and the resultant mixture was heated at reflux (140-150 °C) for 8 h, then cooled to room temperature. After that a solution of $FeCl_3$ (24.0 g in 32 mL of 2.4 N HCl) was added. The mixture was heated at 70-80 °C for 25 min and cooled. The organic matter was extracted with chloroform, washed with water, dried over anhydrous Na_2SO_4 and the solvent removed in vacuo. The residue was subjected to column chromatography (4% EtOAc/Hexane) to obtain 0.285 g (44%) of 3,5-dicyanomesitaldehyde **2-**

AL and 0.437 g (53%) of 3-Cyano-5-bromomesitaldehyde **5-AL** as a colorless crystalline material.

2-AL: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.53 (s, 1H), 2.84 (s, 6H), 2.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.6, 149.9, 147.9, 132.5, 115.4, 115.0, 20.9, 18.8.

5-AL: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H), 2.72 (s, 2H), 2.70 (s, 1H), 2.69 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 146.3, 144.4, 142.1, 133.8, 128.1, 116.4, 114.9, 24.2, 20.7, 18.3.

Preparation of 3,5-dichloromesitaldehyde (3-AL). To a solution of **1** (0.5 mL, 3.4 mmol) in trifluoroacetic acid (TFA, 2 mL) was added 5 mL conc. H_2SO_4 (98%). To this reaction mixture, *N*-chlorosuccinimide (NCS, 1.8 g, 13.5 mmol) was added and stirred at room temperature for 24 h. After that, the contents were poured into crushed ice and the solution was made alkaline with 10% NaOH. The organic matter was extracted with chloroform. The combined extracts were washed with water, dried over anhydrous Na_2SO_4, filtered and solvent removed in vacuo. The residue was washed with ethanol and dried under high vacuo to get 0.648 g (88%) of 3,5-dichloromesitaldehyde **3-AL** as a colorless crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.52 (s, 1H), 2.57 (s, 3H), 2.55 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 139.3, 135.6, 134.7, 134.2, 19.9, 16.8.

2,3,4,5,6-Pentamethylbenzaldehyde (4-AL). Commercially available, CAS No. 17432-38-1

Preparation of 3-formyl-6-methoxy-2,4-dimethylbenzonitrile (6-AL).

General Procedure for bromination of 3,5-dimethylanisole derivatives using NBS. To a solution of 3,5-dimethylanisole (2.0 mmol) in 4.0 mL of CH_3CN was added NBS (2.2 mmol)

and the reaction mixture was stirred at room temperature for 2 h (48 h for 4-methoxy-2,6-dimethylbenzonitrile with 4.0 equiv of NBS). After completion of the reaction as monitored by TLC, the solvent was removed in vacuo and water was added to the resulting residue. The organic matter was extracted with ethyl acetate, washed with water, dried over anhyd Na_2SO_4 and the solvent removed in vacuo. The organic material was subjected to silica-gel column chromatography (EtOAc/pet. ether) to isolate the pure product.

Reduction of cyano derivative. A 10 mL solution of 3-bromo-4-methoxy-2,6 dimethylbenzonitrile (1.5 g, 6.25 mmol) in dichloromethane was taken in a 25 mL 2-necked round bottom flask under a nitrogen gas atmosphere and cooled to 0 °C in an ice bath. After 10 min, 5.36 mL (7.5 mmol, 1.4 M in toluene) of DIBALH in toluene was slowly introduced into the reaction flask. The reaction mixture was gradually allowed to attain room temperature. After stirring for 10 h, it was quenched with dil HCl and the contents heated at reflux for 30 min. Subsequently, the reaction mixture was extracted with dichloromethane, dried over anhyd Na_2SO_4, filtered and solvent removed in vacuo. The crude product was subjected to silica-gel column chromatography (10% EtOAc/pet. ether) to obtain 1.25 g (82%) of 3-bromo-2,6-dimethyl-*p*-anisaldehyde as a colorless crystalline solid.

Cyanation of 3-bromo-2,6-dimethyl-*p*-anisaldehyde by following the same procedure for synthesis of **2-AL**, 3-formyl-6-methoxy-2,4-dimethylbenzonitrile **6-AL** was synthesized as a colorless crystalline solid in 83% yield. ^{1}H NMR (400 MHz, CDCl3) δ 10.52 (s, 1H), 6.78 (s, 1H), 3.95 (s, 3H), 2.76 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 190.7, 165.1, 149.7, 146.55, 121.8, 117.0, 110.9, 108.2, 56.3, 22.2, 19.3.

Solid-State Photolysis of the Aldehydes (AL).[12] A generalized procedure as follows: *ca*. 50 mg of the well-grounded crystals of an aldehyde were dispersed in a quartz tube and closed with a rubber-septum followed by purged with flow of N_2 for 15 min. The solid sample was irradiated in a Luzchem reactor (λ ~ 350 nm) for 24 h. Finally, the irradiated mixture (**CB**s) was purified through silica-gel column chromatography and characterized.

1-CB: IR (KBr) cm^{-1} 3331, 2922; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.23 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.4 Hz), 3.46 (dd, 1H, J_1 = 14.6 Hz, J_2 = 4.8 Hz), 2.87 (dd, 1H, J_1 = 14.8 Hz, J_2 = 1.6 Hz), 2.58 (s, 3H), 2.29 (s, 3H), 2.08 (d, 1H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.92, 141.46, 138.45, 133.45, 127.29, 116.80, 68.95, 42.18, 24.33, 18.40.

2-CB: IR (KBr) cm^{-1} 3458, 2921, 2228; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.35 (s, 1H), 3.73 (dd, 1H, J_1 = 16 Hz, J_2 = 4.4 Hz), 3.20 (d, 1H, J = 1.6 Hz), 2.77 (d, 1H, J = 1.2 Hz), 2.73 (s, 3H), 2.52 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.55, 147.95, 145.38, 142.57, 115.86, 114.68, 114.40, 107.59, 69.71, 42.35, 20.51, 16.49.

3-CB: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (s, 1H), 3.53 (dd, J = 14.5, 4.4 Hz, 1H), 2.94 (dd, J = 14.5, 1.3 Hz, 1H), 2.45 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 137.6, 135.5, 134.9, 130.8, 127.1, 69.4, 40.9, 18.1, 15.3.

4-CB: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (d, J = 3.8 Hz, 1H), 3.49 (dd, J = 13.9, 4.4 Hz, 1H), 2.86 (d, J = 13.9 Hz, 1H), 2.21 (s, 3H), 2.19 (s, 3H), 2.17 (s, 2H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 138.1, 136.6, 134.6, 129.4, 129.1, 69.9, 40.8, 16.2, 15.8, 15.1, 14.8.

5-CB (5-CB'): 1:1 isomeric mixture; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (s, 1H), 5.25 (s, 1H), 3.63 (dd, *J* = 15.2, 4.4 Hz, 1H), 3.54 (dd, *J* = 15.3, 4.5 Hz, 1H), 3.05 (dd, *J* = 15.2, 1.7 Hz, 1H), 2.98 (dd, *J* = 15.3, 1.6 Hz, 1H), 2.61 (s, 3H), 2.59 (s, 3H), 2.41 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 145.3, 144.9, 144.5, 143.2, 143.0, 139.9, 136.6, 127.3, 117.0, 116.9, 115.8, 114.2, 107.2, 70.0, 68.4, 42.6, 41.5, 23.3, 21.7, 18.9, 15.6.

6-CB (6-CB'): 1:3 isomeric mixture; NMR data for major isomers, ^{1}H NMR (400 MHz, CDCl3) δ 6.58 (s, 1H), 5.25 (d, *J* = 2.6 Hz, 1H), 3.88 (s, 3H), 3.61 (dd, *J* = 15.2, 4.4 Hz, 1H), 3.03 (dd, *J* = 15.2, 0.9 Hz, 1H), 2.33 (s, 3H), 1.63 (d, *J* = 17.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl3) δ 162.7, 147.1, 141.0, 138.9, 111.5, 104.4, 94.6, 69.5, 56.3, 41.3, 17.6.

Procedure for Sonochemical conversion of CBs to ALs. In a typical experiment, *ca*. 5 mg of the **CB**s (2 equiv. of additive, wherever it was necessary) were dissolved in the appropriate solvent in a j-young NMR tube. Then the tube was closed and was purged with a stream of nitrogen gas for 10 min. After that the tube was subjected to ultrasound irradiation. The reaction was monitored and the yield of the aldehyde was calculated by ^{1}H NMR analysis.

Computational Details. To calculate energetics of the possible intermediate states we use a plane-wave implementation (QUANTUM ESPRESSO)[48] of density functional theory (DFT)[49, 50] along with a gradient corrected PBE[51] functional for exchange-correlation used in ultra-soft[52] pseudopotentials. Relaxed (energy minimized) structures have been obtained within the BFGS[53] scheme for energy minimization, wherein a structure is updated using the Hellmann-Feynman forces calculated from the ground state electronic structure converged up to plane-wave cutoff over 1000 eV. Forces have been converged below 10^{-4} Rydberg/Bohr.

Nudged Elastic Band (NEB) method. To calculate energy barrier and reaction pathway we have used Nudged Elastic Band (NEB) method as implemented in PWneb[48] package of QUANTUM ESPRESSO. For this calculation we use 12 intermediate images between **2-CB** and **2-AL**, both without their hydroxyl-H, in simulation box size 16×16×16 $Å^3$ and total charge -0.4e with plane-wave cutoff over 1000 eV(~100 Ry). The amount of charge on the molecule is estimated by adding Lowdin charges of atoms obtained through projection of wave-functions on atomic orbitals. In the NEB calculations we have used the Broyden algorithm and allowed positions of only the relevant atoms to be updated.

5.6 NOTES AND REFERENCES

1. Chen, Y.; Spiering, A. J. H.; Karthikeyan, S.; Peters, G. W. M.; Meijer, E. W.; Sijbesma, R. P., *Nature Chem.* **2012,** *4*, 559.
2. Wang, J.; Kouznetsova, T. B.; Niu, Z.; Ong, M. T.; Klukovich, H. M.; Rheingold, A. L.; Martinez, T. J.; Craig, S. L., *Nature Chem.* **2015,** *7*, 323.
3. May, P. A.; Moore, J. S., *Chem. Soc. Rev.* **2013**.
4. Beyer, M. K.; Clausen-Schaumann, H., *Chem. Rev.* **2005,** *105*, 2921.
5. Ribas-Arino, J.; Marx, D., *Chem. Rev.* **2012,** *112*, 5412.
6. Black, A. L.; Lenhardt, J. M.; Craig, S. L., *J. Mater. Chem.* **2011,** *21*, 1655.
7. Li, J.; Nagamani, C.; Moore, J. S., *Acc. Chem. Res.* **2015**, 10.1021/acs.accounts.5b00184.
8. Carnall, J. M. A.; Waudby, C. A.; Belenguer, A. M.; Stuart, M. C. A.; Peyralans, J. J.-P.; Otto, S., *Science* **2010,** *327*, 1502.
9. Mehta, G.; Kotha, S., *Tetrahedron* **2001,** *57*, 625.
10. Andreasson, J.; Pischel, U., *Chem. Soc. Rev.* **2010,** *39*, 174.
11. Sadana, A. K.; Saini, R. K.; Billups, W. E., *Chem. Rev.* **2003,** *103*, 1539.
12. Moorthy, J. N.; Mal, P.; Natarajan, R.; Venugopalan, P., *J. Org. Chem.* **2001,** *66*, 7013.
13. Segura, J. L.; Martín, N., *Chem. Rev.* **1999,** *99*, 3199.
14. Hoffmann, R.; Woodward, R. B., *Acc. Chem. Res.* **1968,** *1*, 17.
15. Takahashi, Y.; Miyamoto, K.; Sakai, K.; Ikeda, H.; Miyashi, T.; Ito, Y.; Tabohashi, K., *Tetrahedron Lett.* **1996,** *37*, 5547.
16. Fitzgerald, J. J.; Pagano, A. R.; Sakoda, V. M.; Olofson, R. A., *J. Org. Chem.* **1994,** *59*, 4117.

17. Marcinek, A.; Michalak, J.; Rogowski, J.; Tang, W.; Bally, T.; Gebicki, J., *J. Chem. Soc., Perkin Trans. 2* **1992**, 1353.

18. Eaton, B. E.; Laganis, E. D.; Boekelheide, V., *Proc. Natl. Acad. Sci. U. S. A.* **1981,** *78*, 6564.

19. Cravotto, G.; Gaudino, E. C.; Cintas, P., *Chem. Soc. Rev.* **2013,** *42*, 7521.

20. Baig, R. B. N.; Varma, R. S., *Chem. Soc. Rev.* **2012,** *41*, 1559.

21. Hickenboth, C. R.; Moore, J. S.; White, S. R.; Sottos, N. R.; Baudry, J.; Wilson, S. R., *Nature* **2007,** *446*, 423.

22. Netto-Ferreira, J. C.; Scaiano, J. C., *J. Am. Chem. Soc.* **1991,** *113*, 5800.

23. Ikeda, A.; Tsudera, T.; Shinkai, S., *J. Org. Chem.* **1997,** *62*, 3568.

24. Stolle, A.; Szuppa, T.; Leonhardt, S. E. S.; Ondruschka, B., *Chem. Soc. Rev.* **2011,** *40*, 2317.

25. Wang, G.-W., *Chem. Soc. Rev.* **2013,** *42*, 7668.

26. Sahoo, P. K.; Giri, C.; Haldar, T. S.; Puttreddy, R.; Rissanen, K.; Mal, P., *Eur. J. Org. Chem.* **2016**, DOI: 10.1002/ejoc.201600005.

27. Sahoo, P. K.; Bose, A.; Mal, P., *Eur. J. Org. Chem.* **2015**, 6994.

28. Maiti, S.; Mal, P., *Adv. Synth. Catal.* **2015,** *357*, 1416.

29. Giri, C.; Sahoo, P. K.; Puttreddy, R.; Rissanen, K.; Mal, P., *Chem. Eur. J.* **2015,** *21*, 6390.

30. Kohn, W.; Sham, L. J., *Phys. Rev.* **1965,** *140*, A1133.

31. Paolo, G.; Stefano, B.; Nicola, B.; Matteo, C.; Roberto, C.; Carlo, C.; Davide, C.; Guido, L. C.; Matteo, C.; Ismaila, D.; Andrea Dal, C.; Stefano de, G.; Stefano, F.; Guido, F.; Ralph, G.; Uwe, G.; Christos, G.; Anton, K.; Michele, L.; Layla, M.-S.; Nicola, M.; Francesco, M.; Riccardo, M.; Stefano, P.; Alfredo, P.; Lorenzo, P.; Carlo,

S.; Sandro, S.; Gabriele, S.; Ari, P. S.; Alexander, S.; Paolo, U.; Renata, M. W., *J. Phys.: Condens. Matter* **2009,** *21*, 395502.

32. Perdew, J. P.; Burke, K.; Ernzerhof, M., *Phys. Rev. Lett.* **1996,** *77*, 3865.
33. Blight, B. A.; Hunter, C. A.; Leigh, D. A.; McNab, H.; Thomson, P. I. T., *Nature Chem.* **2011,** *3*, 244.
34. Torshin, I. Y.; Harrison, R. W.; Weber, I. T., *Protein Eng.* **2003,** *16*, 201.
35. Adhikary, R.; Zimmermann, J.; Liu, J.; Forrest, R. P.; Janicki, T. D.; Dawson, P. E.; Corcelli, S. A.; Romesberg, F. E., *J. Am. Chem. Soc.* **2014,** *136*, 13474.
36. Justino, L. L. G.; Ramos, M. L. s.; Knaapila, M.; Marques, A. T.; Kudla, C. J.; Scherf, U.; Almásy, L. s.; Schweins, R.; Burrows, H. D.; Monkman, A. P., *Macromolecules* **2010,** *44*, 334.
37. Watanabe, H.; Matsumiya, Y.; van Ruymbeke, E.; Vlassopoulos, D.; Hadjichristidis, N., *Macromolecules* **2008,** *41*, 6110.
38. van Ruymbeke, E.; Orfanou, K.; Kapnistos, M.; Iatrou, H.; Pitsikalis, M.; Hadjichristidis, N.; Lohse, D. J.; Vlassopoulos, D., *Macromolecules* **2007,** *40*, 5941.
39. van Ruymbeke, E.; Muliawan, E. B.; Hatzikiriakos, S. G.; Watanabe, T.; Hirao, A.; Vlassopoulos, D., *J. Rheol.* **2010,** *54*, 643.
40. Durgun, E.; Grossman, J. C., *J. Phys. Chem. Lett.* **2013,** *4*, 854.
41. Takacs, L., *Faraday Discuss.* **2014,** *170*, 251.
42. James, S. L.; Adams, C. J.; Bolm, C.; Braga, D.; Collier, P.; Friscic, T.; Grepioni, F.; Harris, K. D. M.; Hyett, G.; Jones, W.; Krebs, A.; Mack, J.; Maini, L.; Orpen, A. G.; Parkin, I. P.; Shearouse, W. C.; Steed, J. W.; Waddell, D. C., *Chem. Soc. Rev.* **2012,** *41*, 413.
43. Kaiser, C. M.; Tinoco, I., *Chem. Rev.* **2014,** *114*, 3266.
44. Xie, Y.; Zheng, X.; Jiang, X.; Lu, J.; Zhu, L., *Inorg. Chem.* **2002,** *41*, 387.

45. Babicz, I.; Leite, S. G. F.; de Souza, R. O. M. A.; Antunes, O. A. C., *Ultrason. Sonochem.* **2010,** *17*, 4.

46. Duan, J.; Zhang, L. H.; Dolbier Jr, W. R., *Synlett* **1999,** *1999*, 1245.

47. Ellis, G. P.; Romney-Alexander, T. M., *Chem. Rev.* **1987,** *87*, 779.

48. Giannozzi, P.; Baroni, S.; Bonini, N.; Calandra, M.; Car, R.; Cavazzoni, C.; Ceresoli, D.; Chiarotti, G. L.; Cococcioni, M.; Dabo, I.; Dal Corso, A.; de Gironcoli, S.; Fabris, S.; Fratesi, G.; Gebauer, R.; Gerstmann, U.; Gougoussis, C.; Kokalj, A.; Lazzeri, M.; Martin-Samos, L.; Marzari, N.; Mauri, F.; Mazzarello, R.; Paolini, S.; Pasquarello, A.; Paulatto, L.; Sbraccia, C.; Scandolo, S.; Sclauzero, G.; Seitsonen, A. P.; Smogunov, A.; Umari, P.; Wentzcovitch, R. M., *J. Phys.: Condens. Matter.* **2009,** *21*, 395502.

49. Kohn, W.; Sham, L. J., *Physical Review* **1965,** *140*, A1133.

50. Hohenberg, P.; Kohn, W., *Physical Review* **1964,** *136*, B864.

51. Perdew, J. P.; Burke, K.; Ernzerhof, M., *Phys. Rev. Lett.* **1996,** *77*, 3865.

52. Vanderbilt, D., *Phys. Rev. B* **1990,** *41*, 7892.

53. Fletcher, R. Practical Methods of Optimization ; Wiley: New York; 1987

^{1}H and ^{13}C NMR Spectra

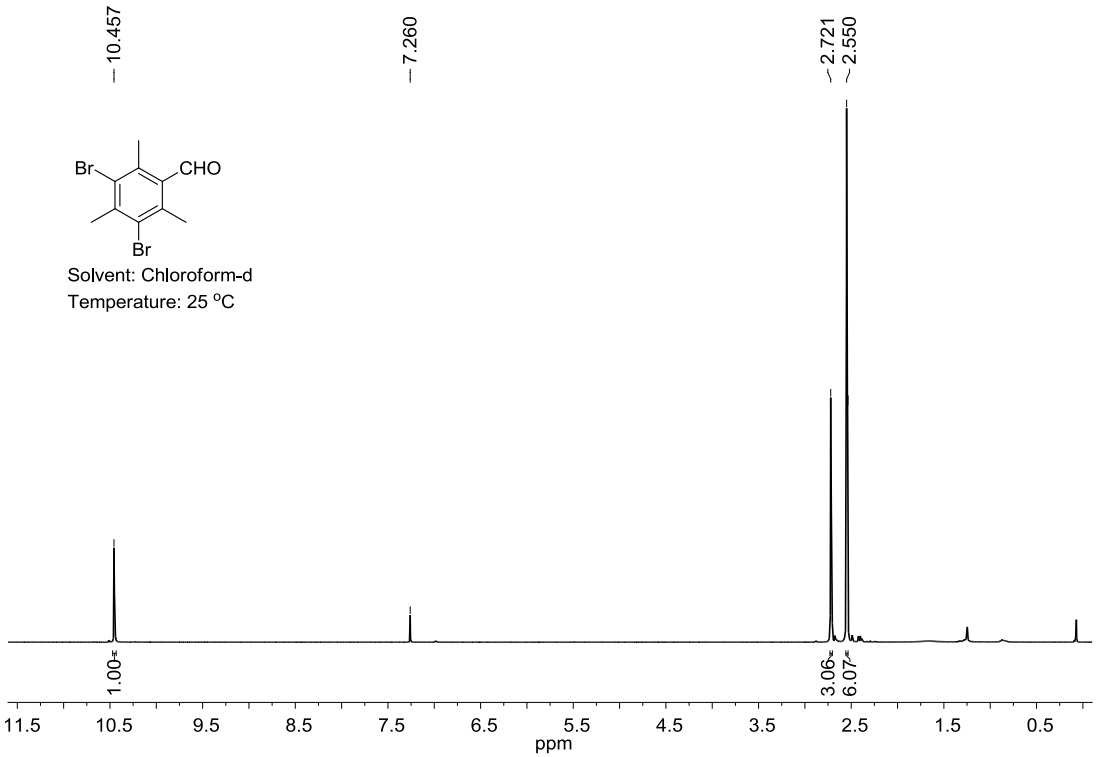


Figure 5.11. ^{1}H NMR spectra of **1-AL** at 25 °C in $CDCl_3$.

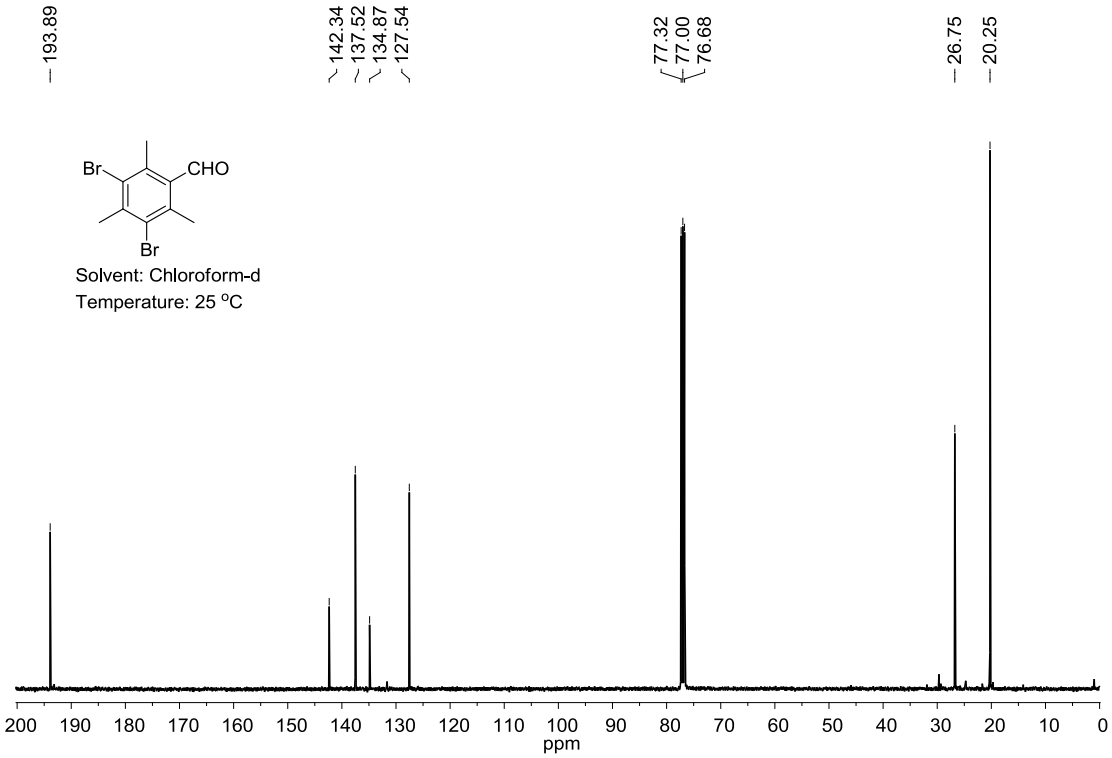


Figure 5.12. ^{13}C NMR spectra of **1-AL** at 25 °C in $CDCl_3$.

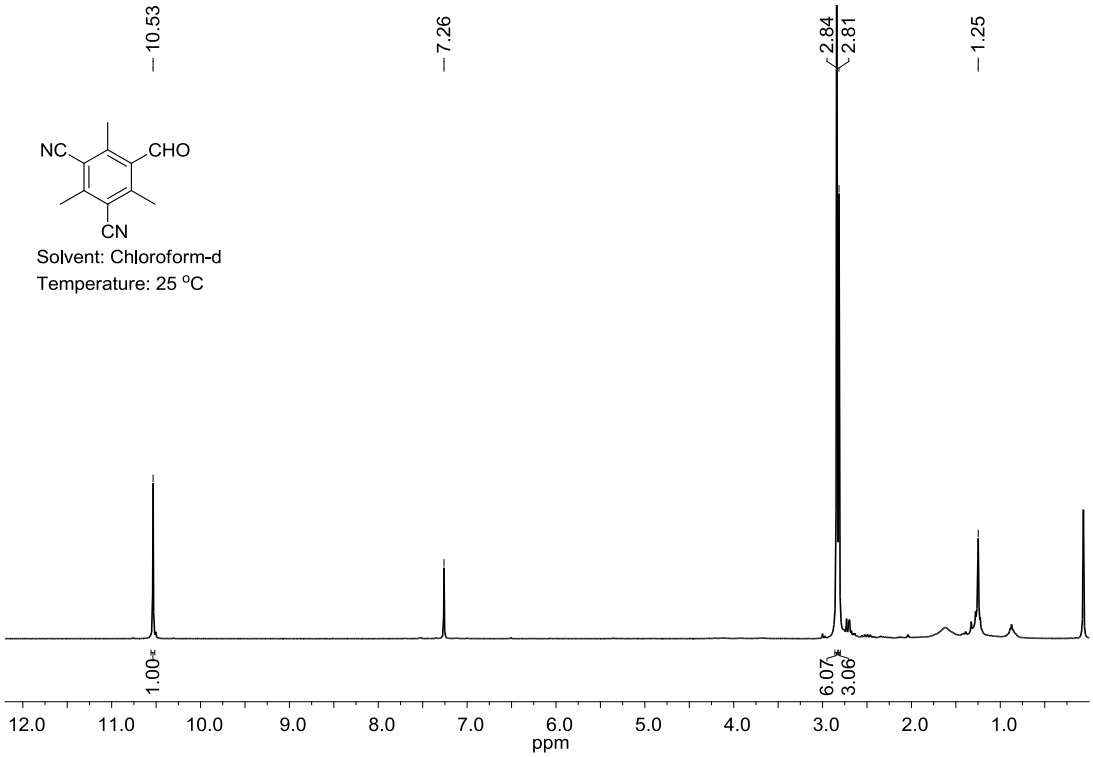


Figure 5.13. ^{1}H NMR spectra of **2-AL** at 25 ^{0}C in $CDCl_3$.

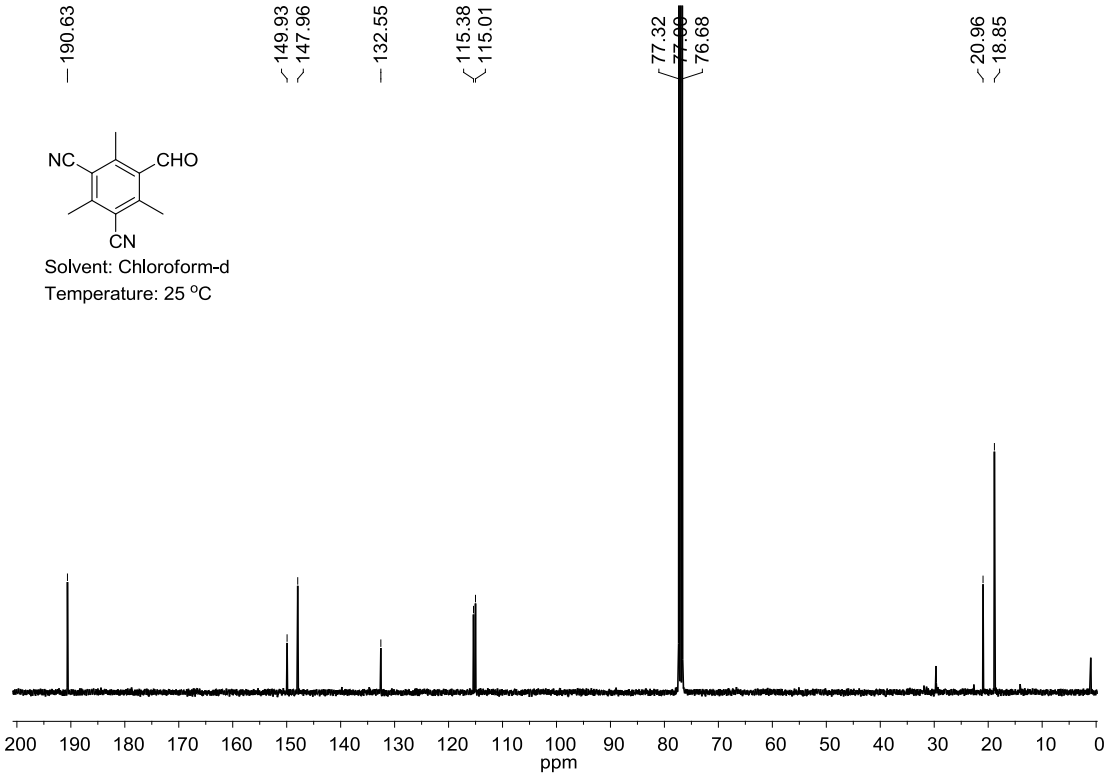


Figure 5.14. ^{13}C NMR spectra of **2-AL** at 25 °C in $CDCl_3$.

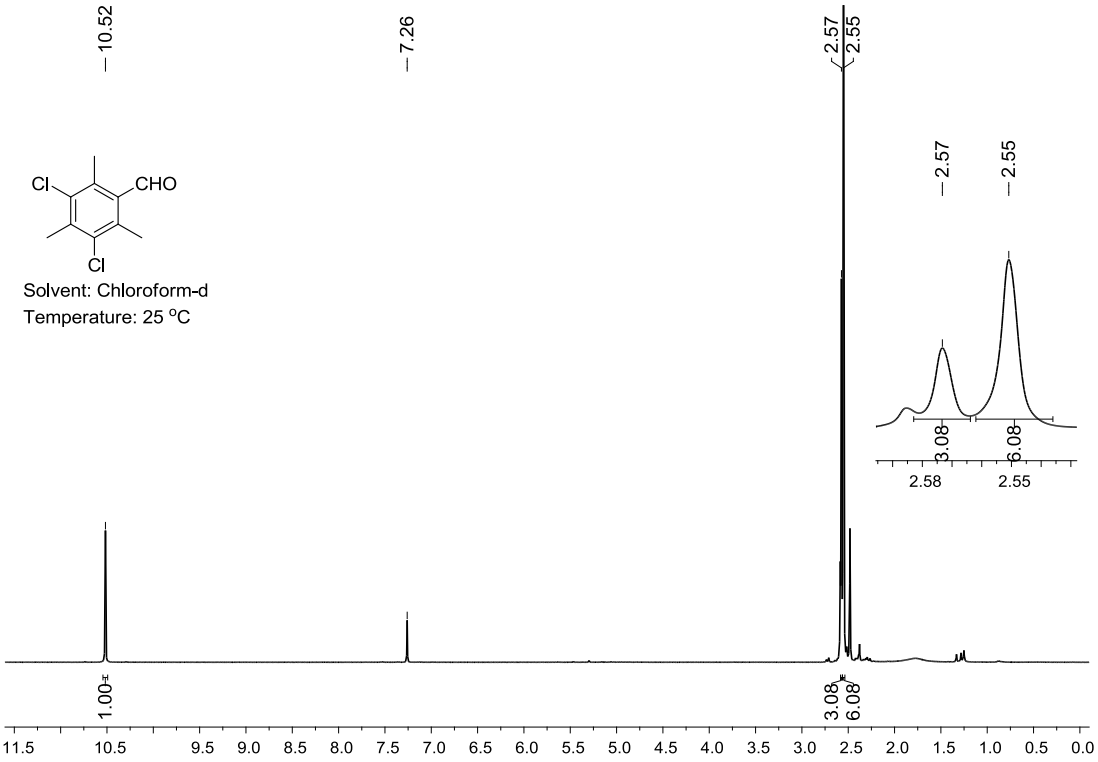


Figure 5.15. ^{1}H NMR spectra of **3-AL** at 25 °C in $CDCl_3$.

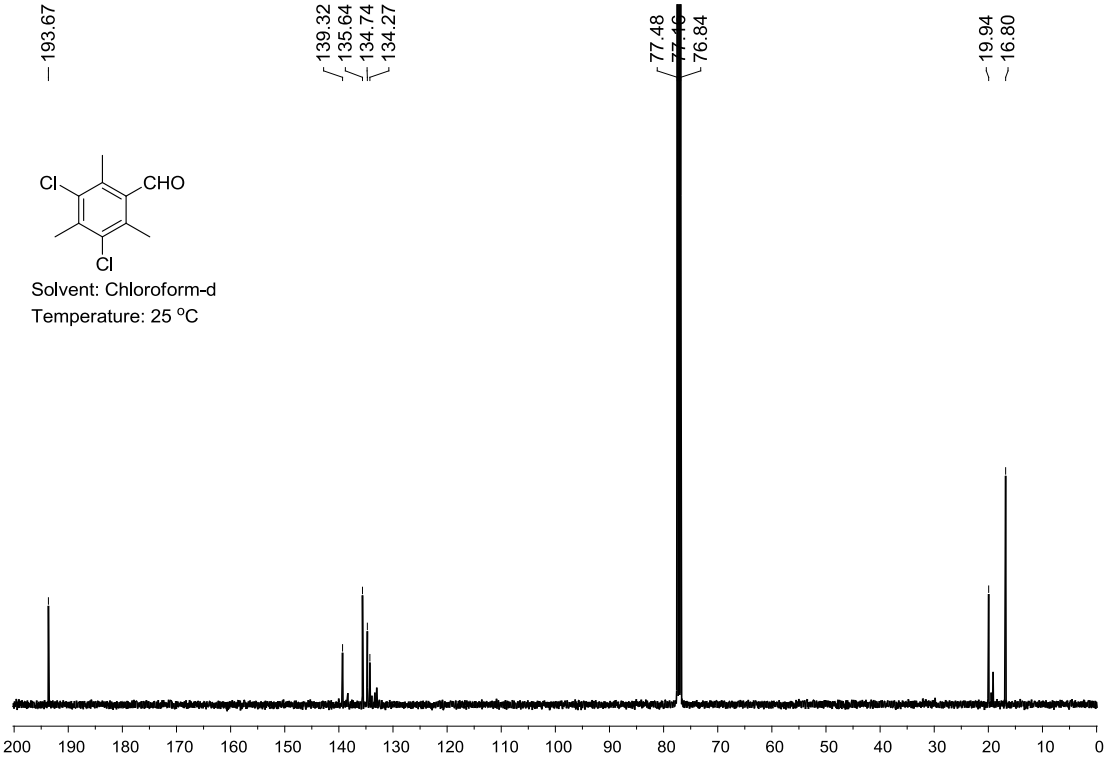


Figure 5.16. ^{13}C NMR spectra of **3-AL** at 25 °C in $CDCl_3$.

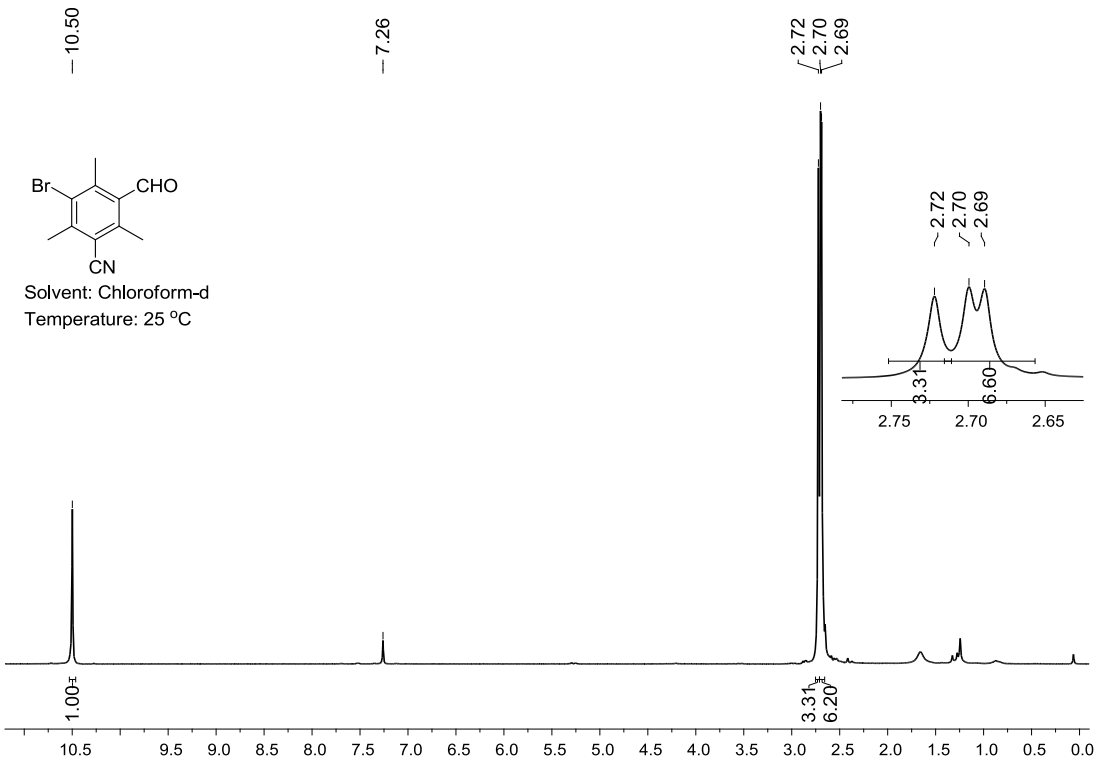


Figure 5.17. ^{1}H NMR spectra of **5-AL** at 25 °C in $CDCl_3$.

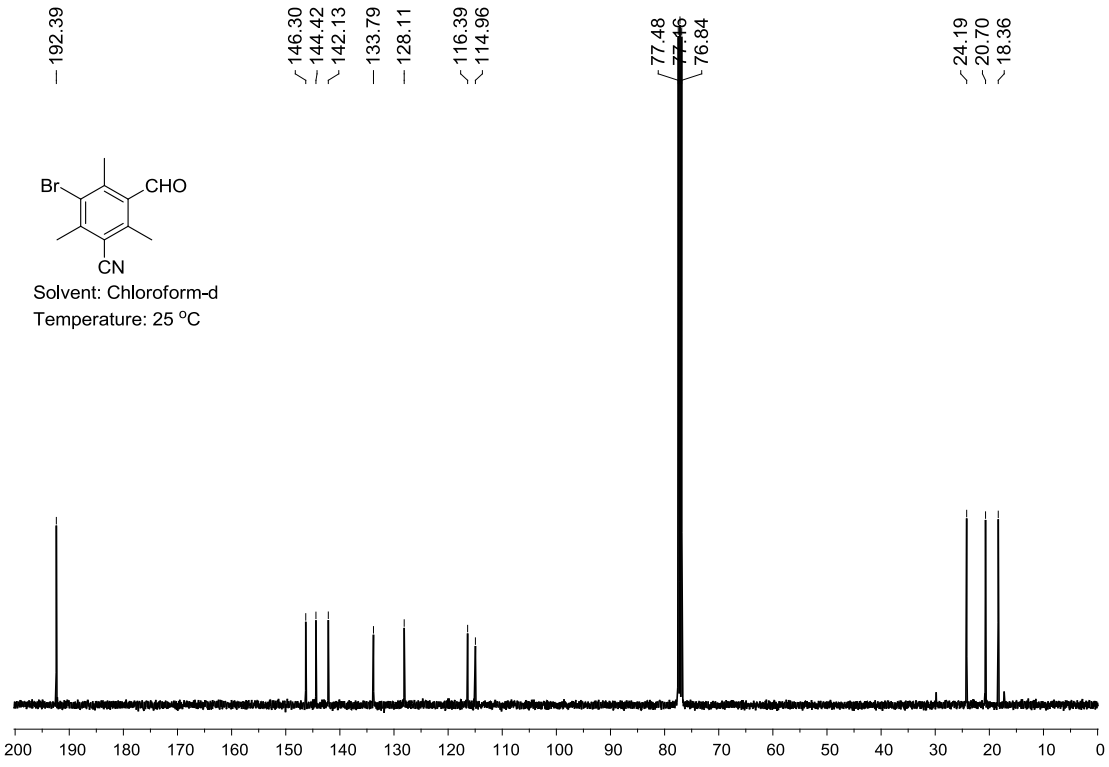


Figure 5.18. ^{13}C NMR spectra of **5-AL** at 25 °C in $CDCl_3$.

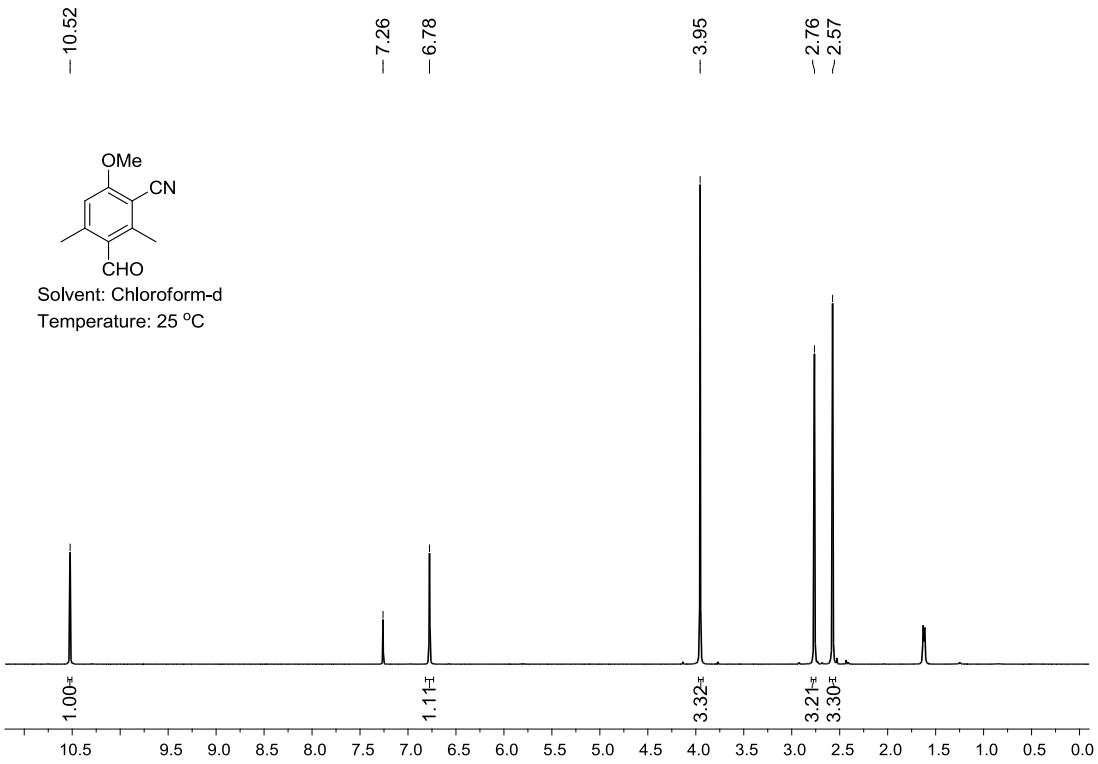


Figure 5.19. ^{1}H NMR spectra of **6-AL** at 25 °C in $CDCl_3$.

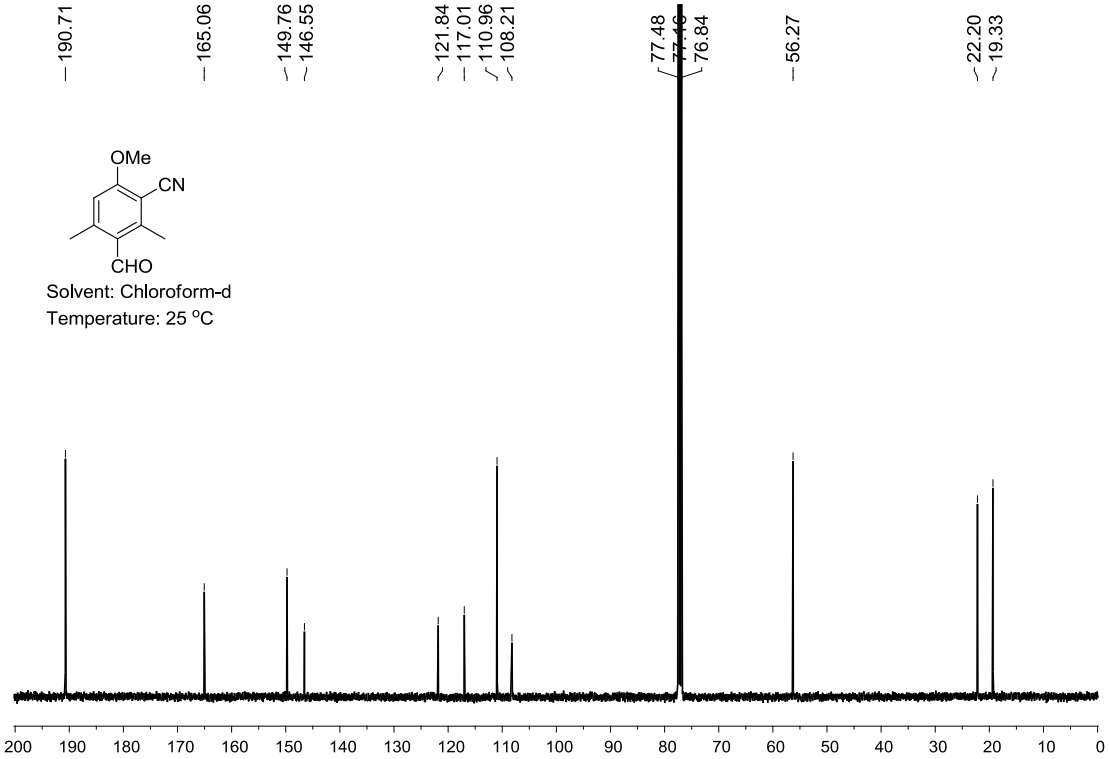


Figure 5.20. ^{1}H NMR spectra of **6-AL** at 25 °C in $CDCl_3$.

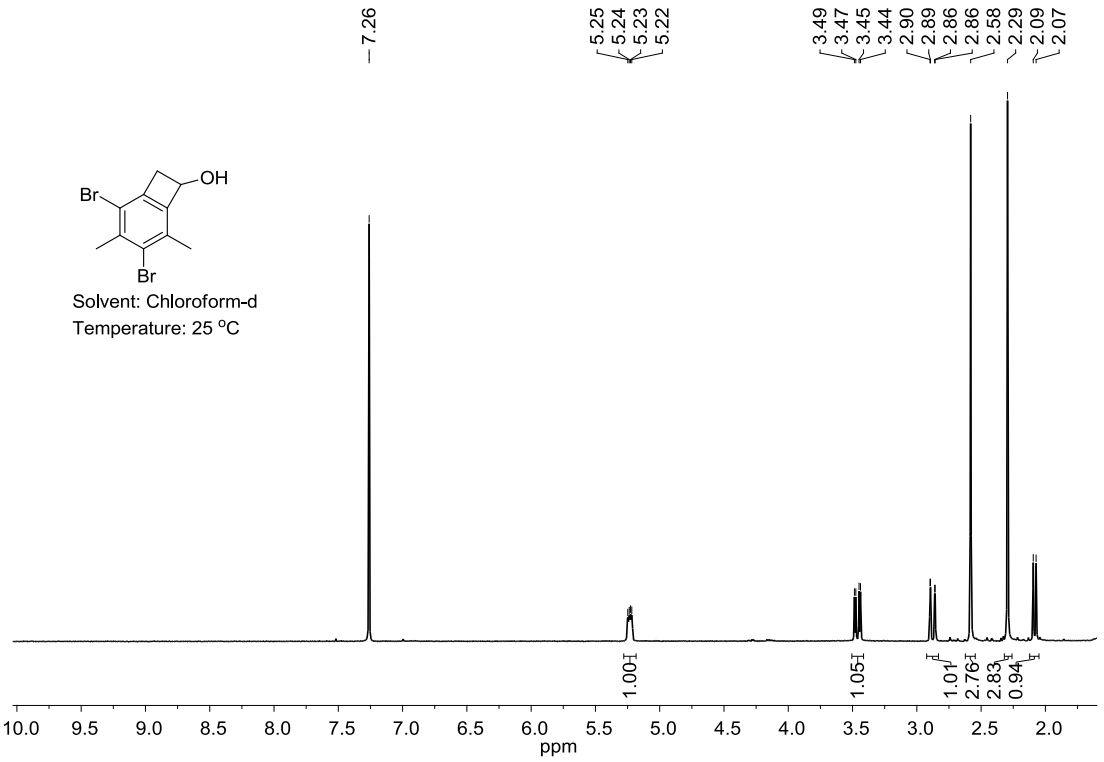


Figure 5.21. ^{1}H NMR spectra of **1-CB** at 25 °C in $CDCl_3$.

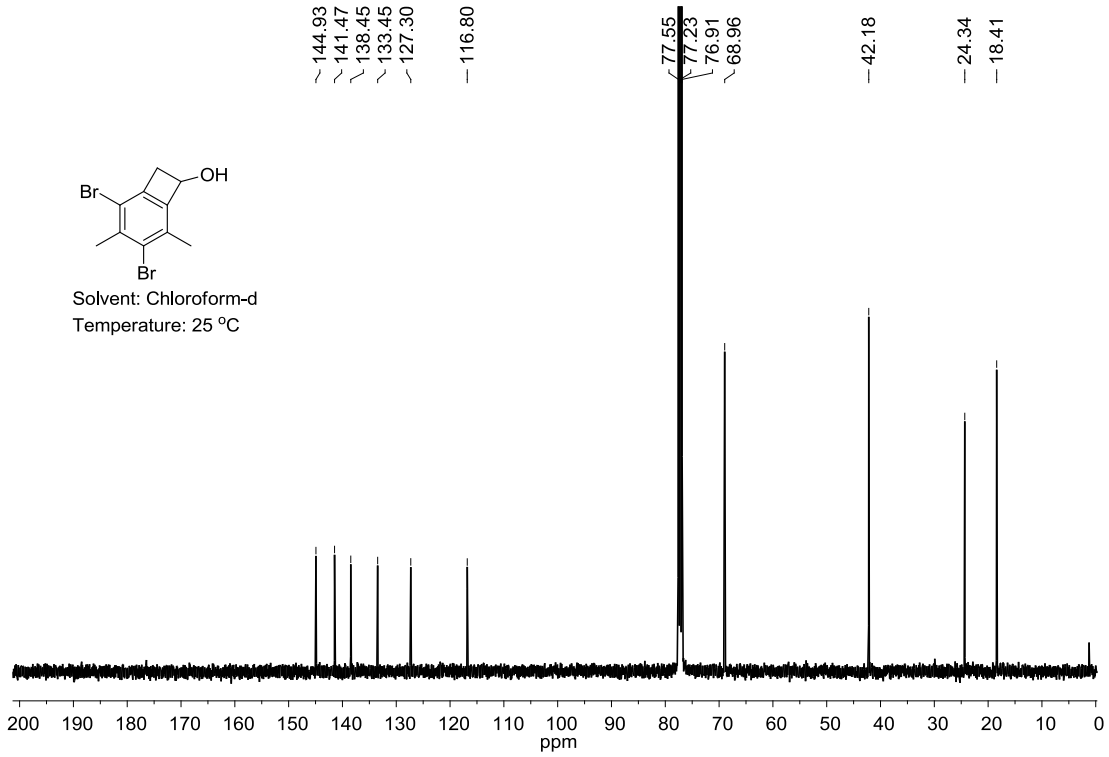


Figure 5.22. ^{13}C NMR spectra of **1-CB** at 25 °C in $CDCl_3$.

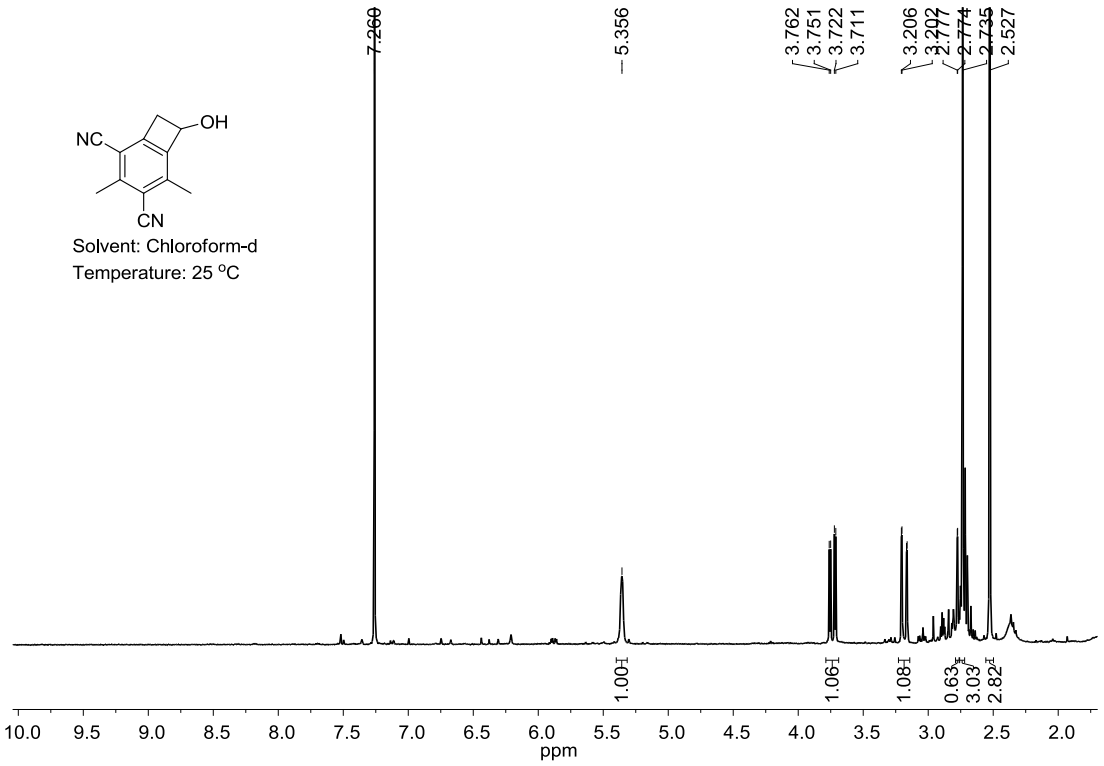


Figure 5.23. ^{1}H NMR spectra of **2-CB** at 25 °C in $CDCl_3$.

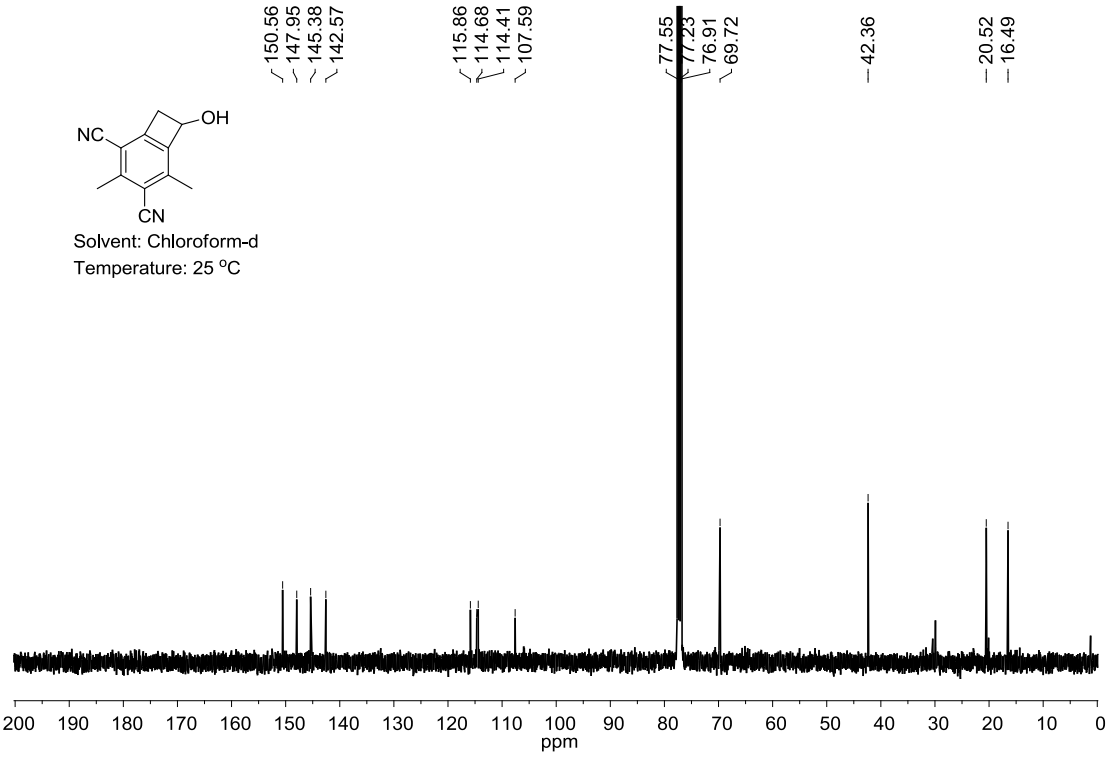


Figure 5.24. ^{13}C NMR spectra of **2-CB** at 25 °C in $CDCl_3$.

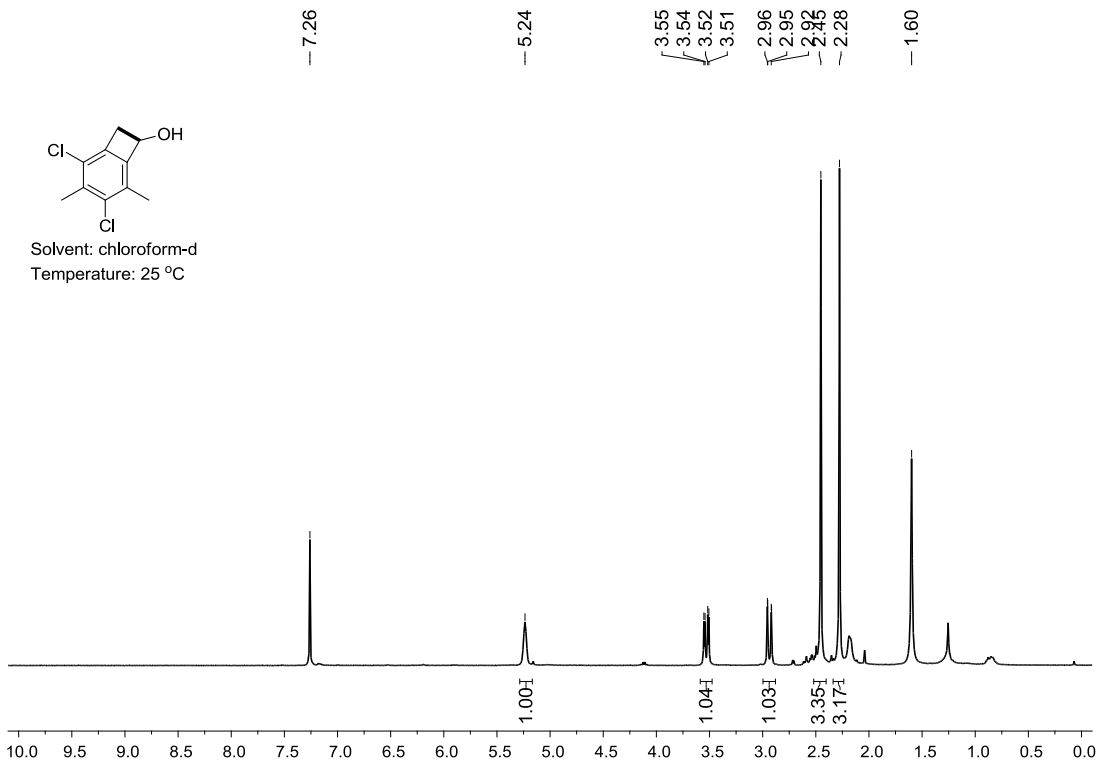


Figure 5.25. ^{1}H NMR spectra of **3-CB** at 25 °C in $CDCl_3$.

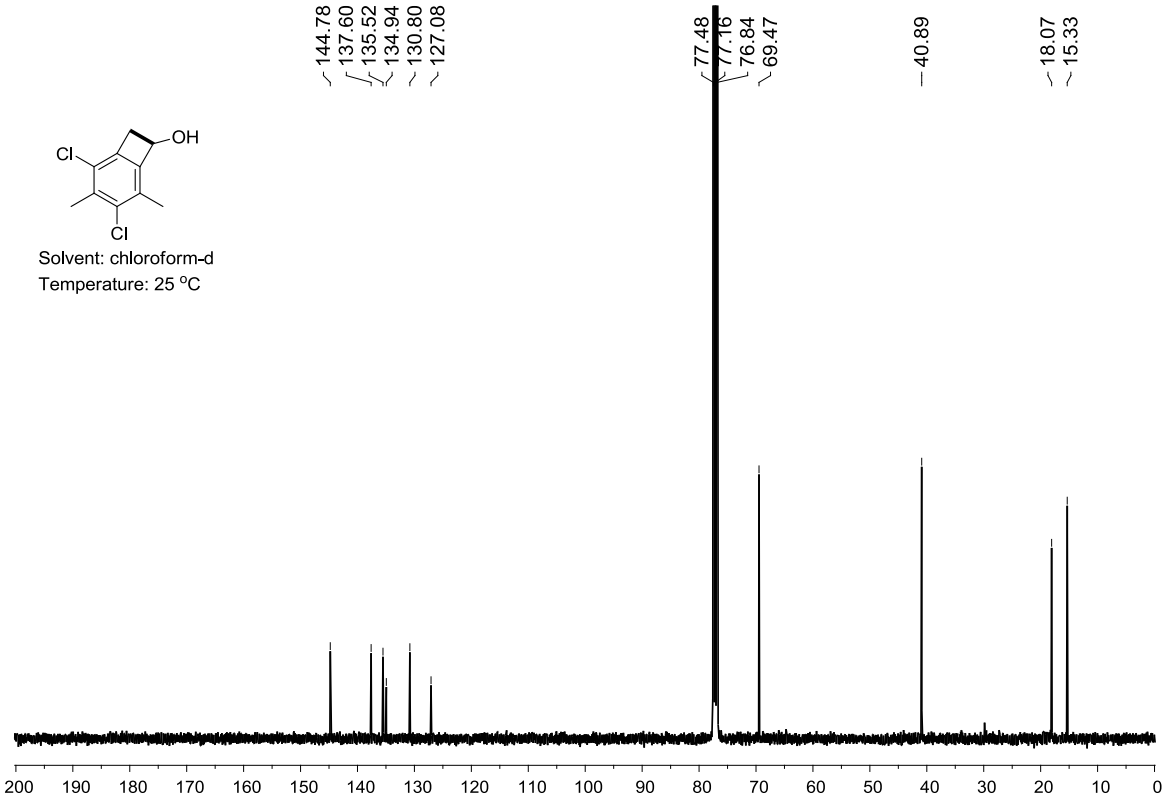


Figure 5.26. ^{13}C NMR spectra of **3-CB** at 25 °C in $CDCl_3$.

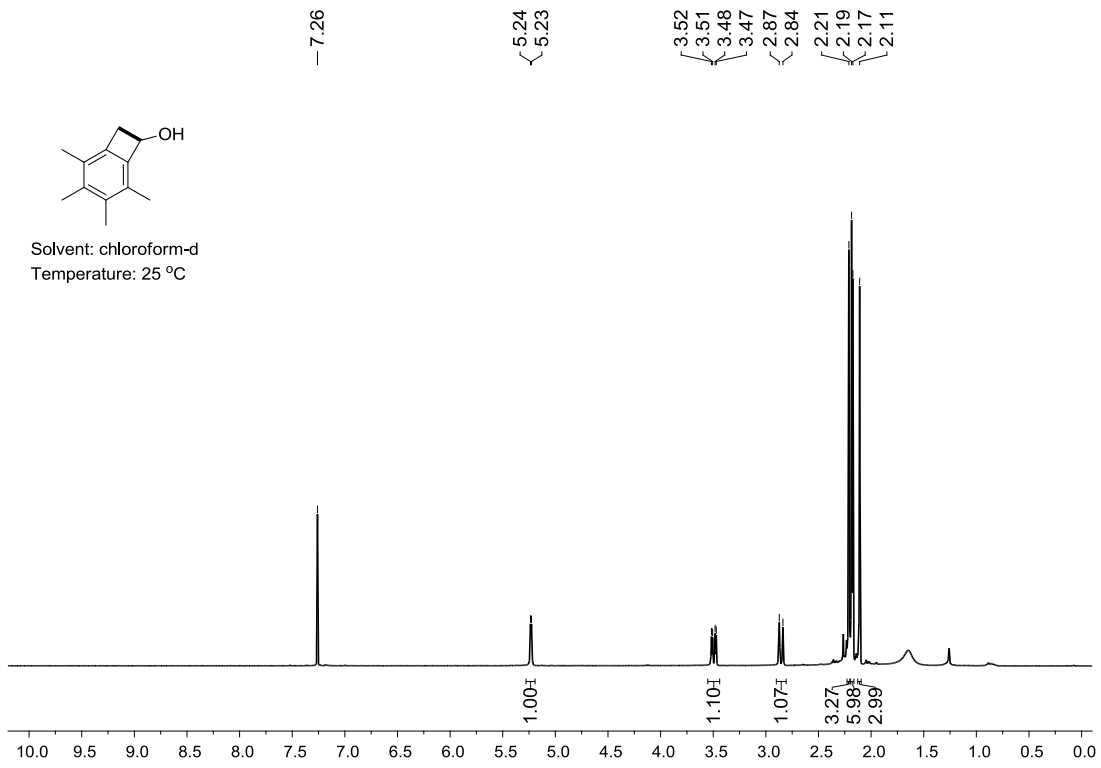


Figure 5.27. ^{1}H NMR spectra of **4-CB** at 25 °C in $CDCl_3$.

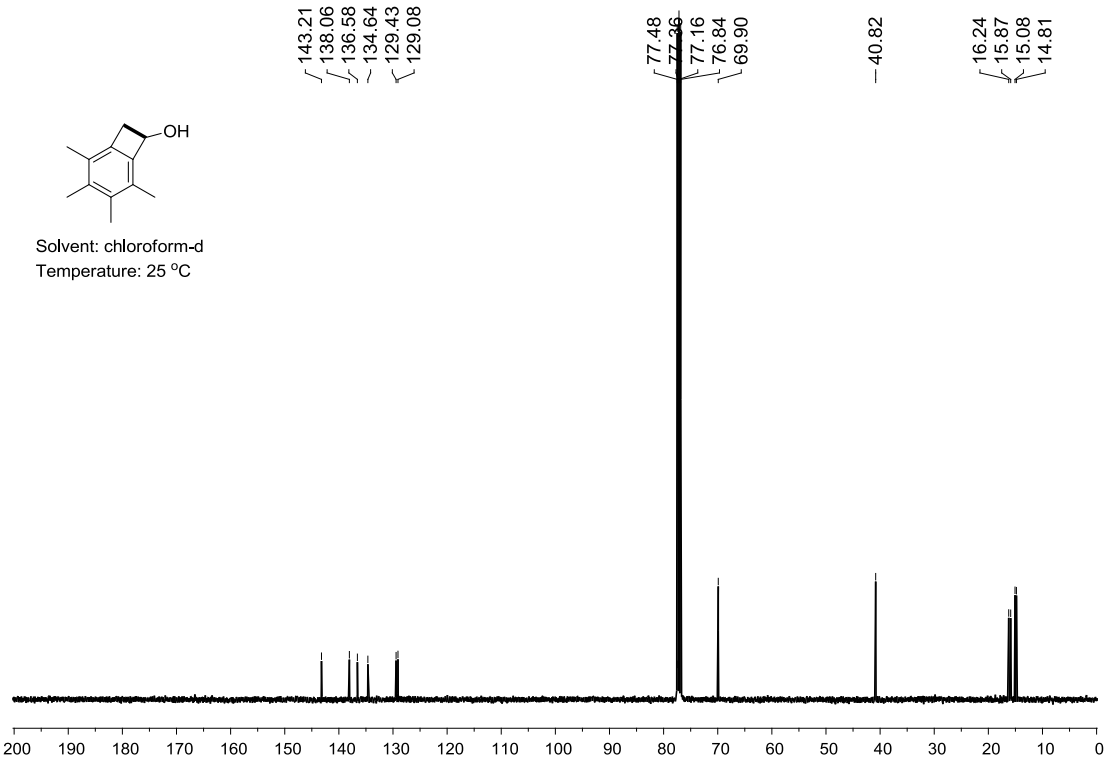


Figure 5.28. ^{13}C NMR spectra of **4-CB** at 25 °C in $CDCl_3$.

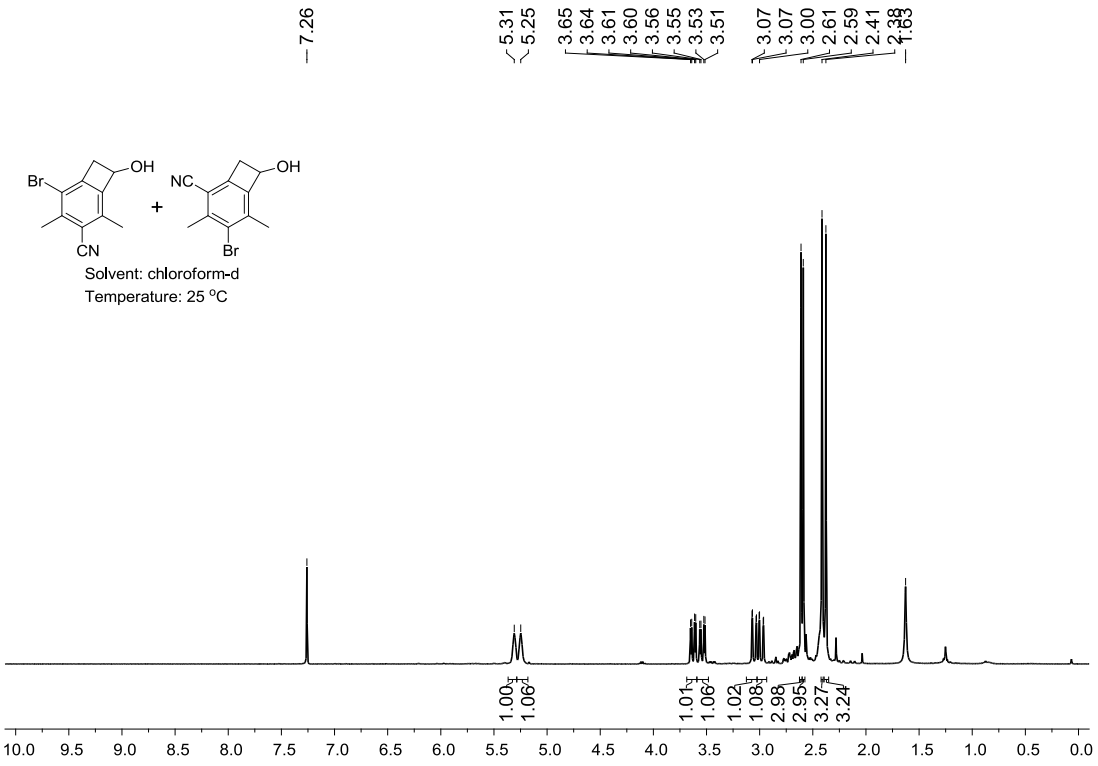


Figure 5.29. ^{1}H NMR spectra of **5-CB** at 25 °C in $CDCl_3$.

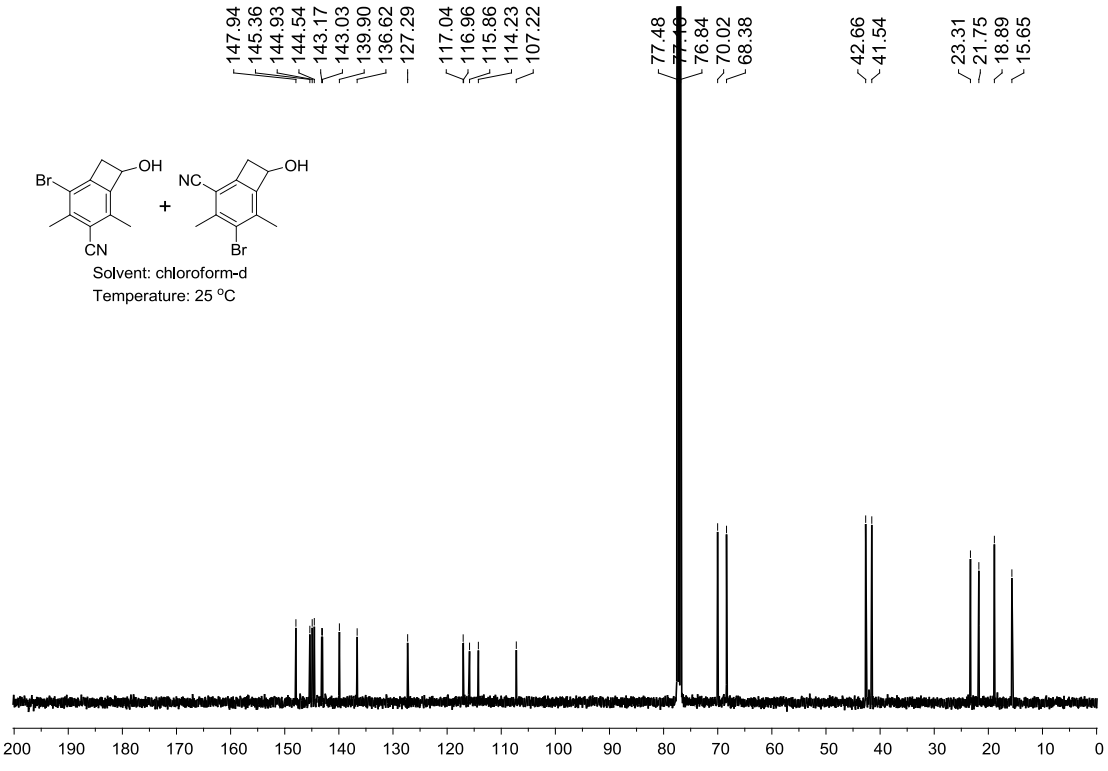


Figure 5.30. ^{13}C NMR spectra of **5-CB** at 25 °C in $CDCl_3$.

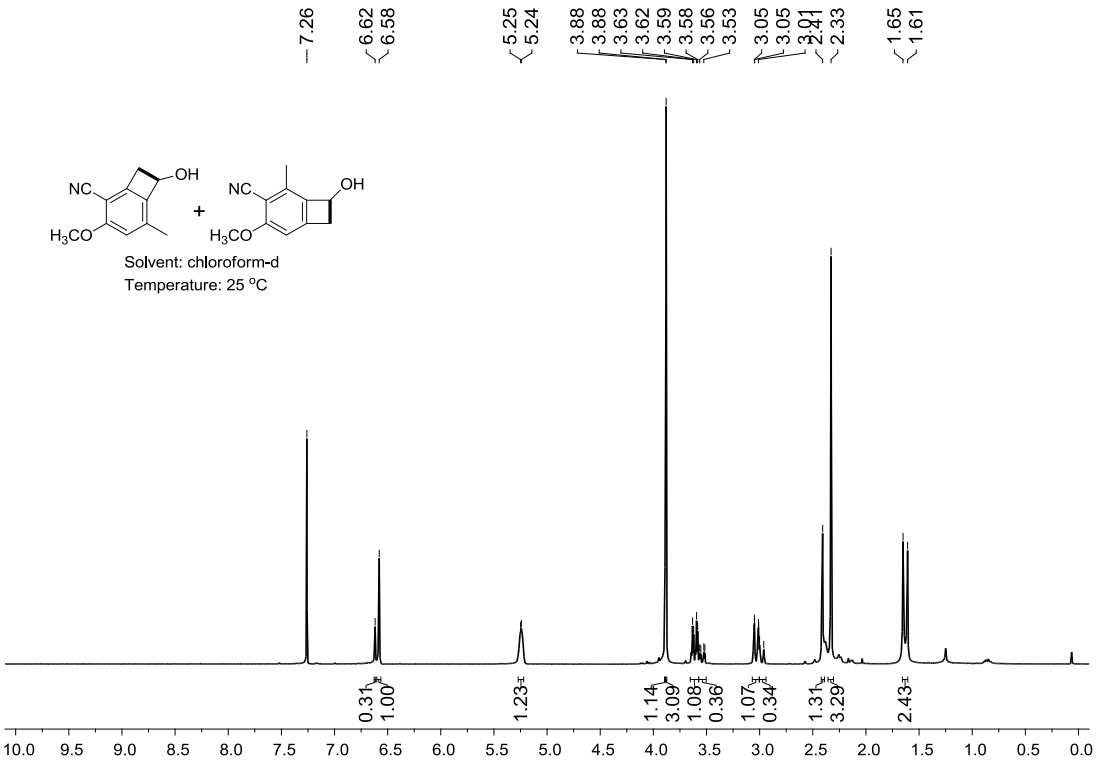


Figure 5.31. ^{1}H NMR spectra of **6-CB** at 25 °C in $CDCl_3$.

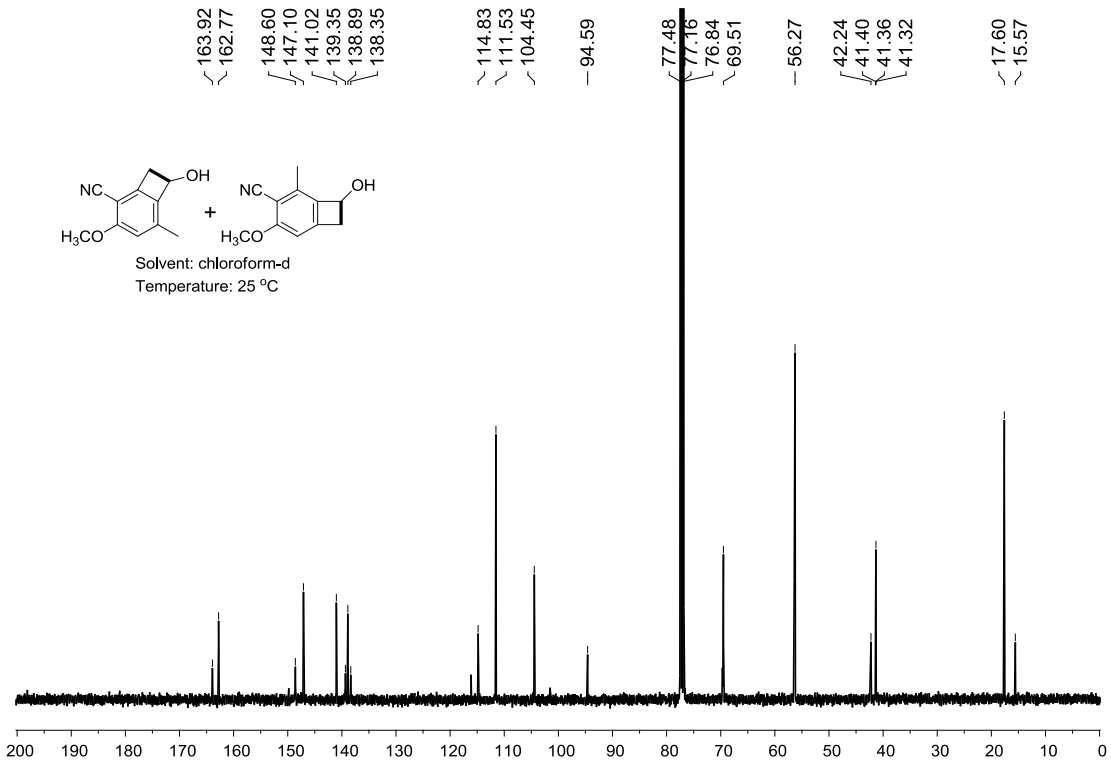
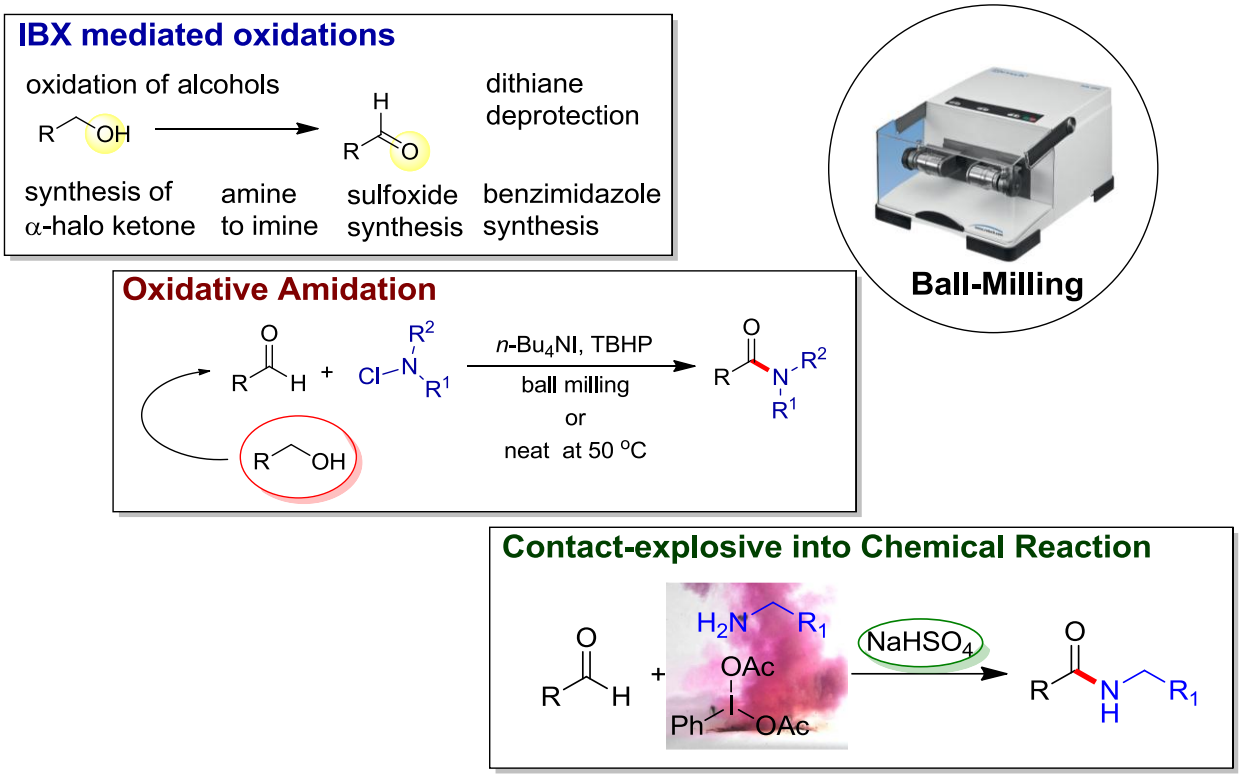
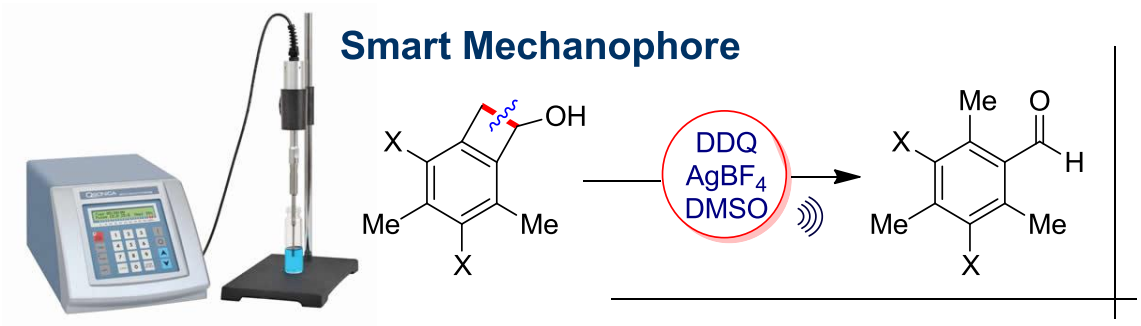


Figure 5.32. ^{13}C NMR spectra of **6-CB** at 25 °C in $CDCl_3$.

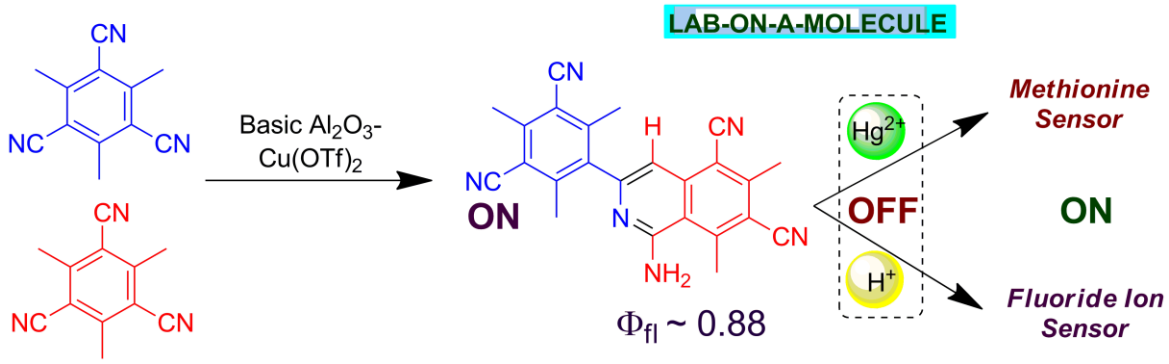
SUMMARY


IBX mediated oxidations
oxidation of alcohols
dithiane deprotection
synthesis of α-halo ketone
amine to imine
sulfoxide synthesis
benzimidazole synthesis
Ball-Milling
Oxidative Amidation
n-Bu4NI, TBHP
ball milling
or
neat at 50 °C
Contact-explosive into Chemical Reaction
NaHSO4


Smart Mechanophore
DDQ
AgBF4
DMSO

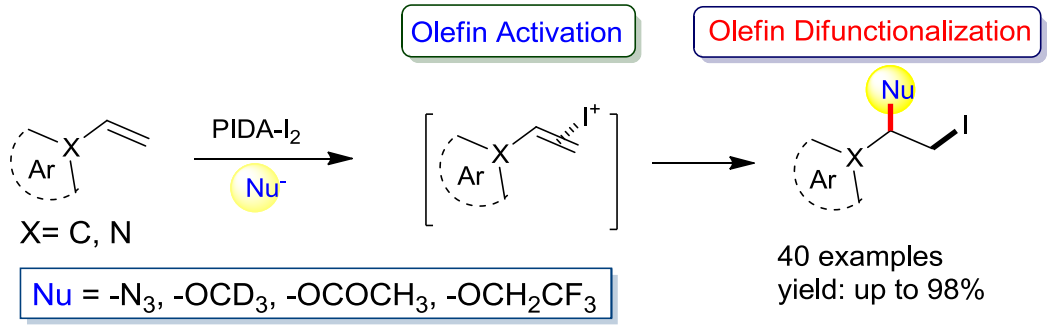
Works are NOT Part of the Thesis

Isoquinoline as a molecular logic gate



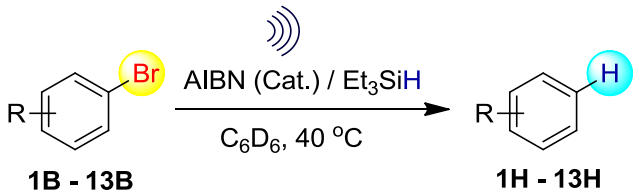
Achar, T. K.; Prakash, V.; Biswal, H. S.; Mal, P., *Tetrahedron Lett.* **2013**, *54*, 1067.

PIDA-I_2 mediated vicinal difunctionalization



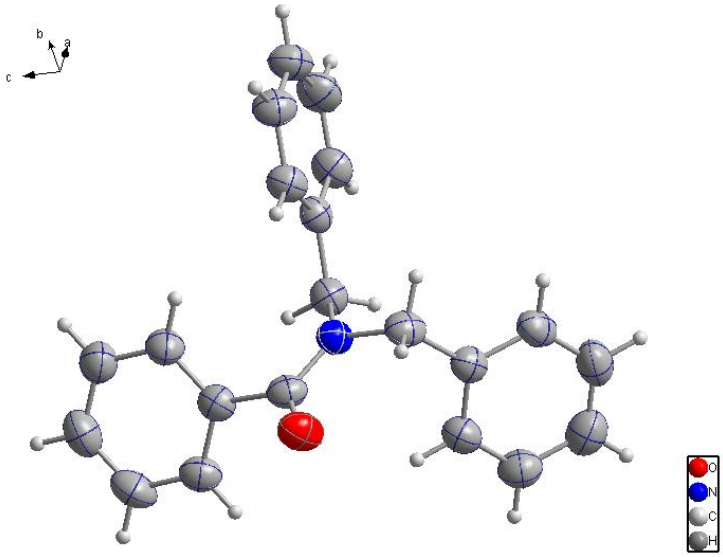
Achar, T. K.; Maiti, S.; Mal, P., *Org. Biomol. Chem.* **2016**. *DOI: 10.1039/c6ob00532b*

Sonochemical Reductive Debromination



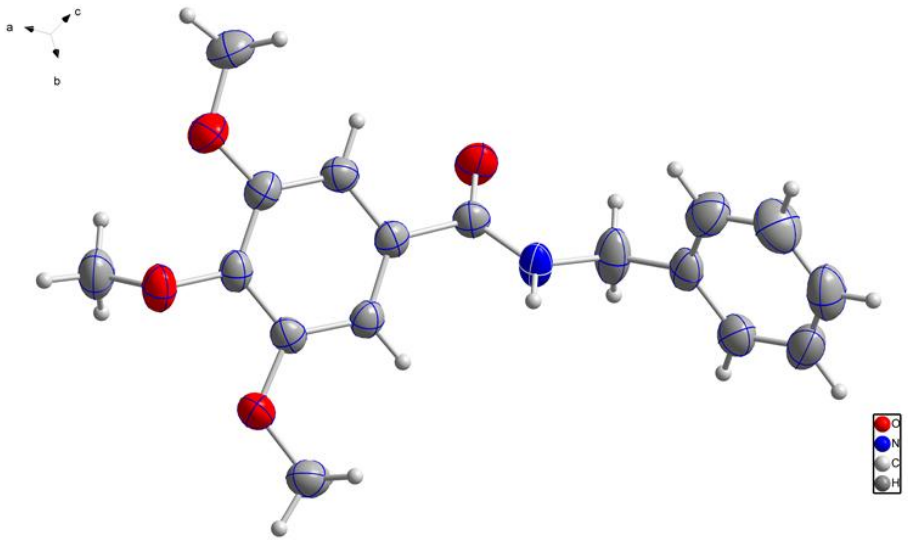
Achar, T. K.; Kumar, N.; Mal, P., *Under Preparation*

- Crystallographic Data for **3c** (Chapter 3, figure 3.3); CCDC 1013915



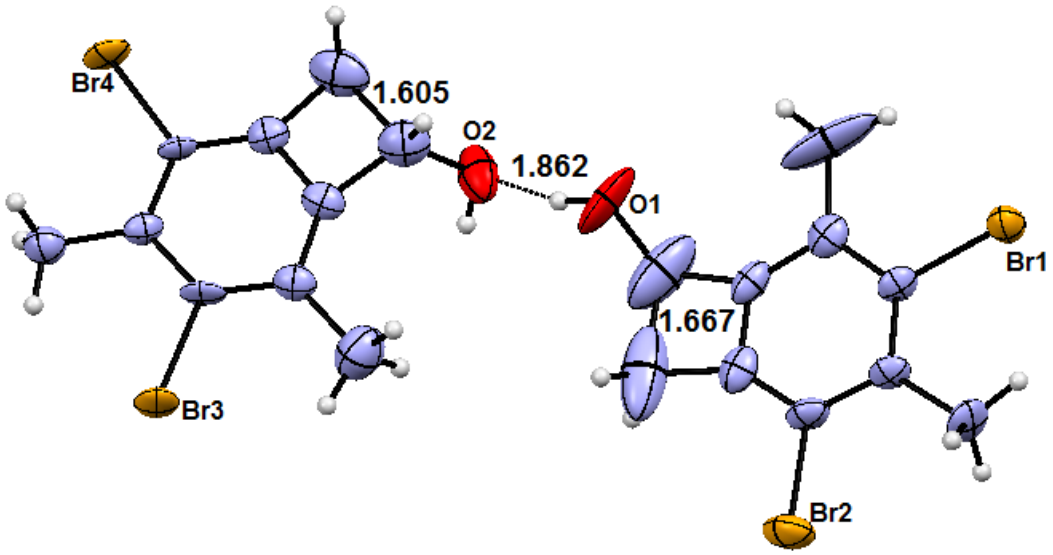
Empirical formula	C21 H19 N O	
Formula weight	301.37	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 5.7438(3) Å	α = 90°.
	b = 18.2969(10) Å	β = 90.528(4)°.
	c = 15.3844(8) Å	γ = 90°.
Volume	1616.74(15) $Å^3$	
Z	4	
Density (calculated)	1.238 Mg/m^3	
Crystal size	0.16 x 0.14 x 0.12 mm^3	
Final R indices [I > 2sigma(I)]	R1 = 0.0438, wR2 = 0.0969	
R indices (all data)	R1 = 0.0779, wR2 = 0.1122	

- Crystallographic Data for **3l** (Chapter 3, figure 3.3); CCDC 1016504



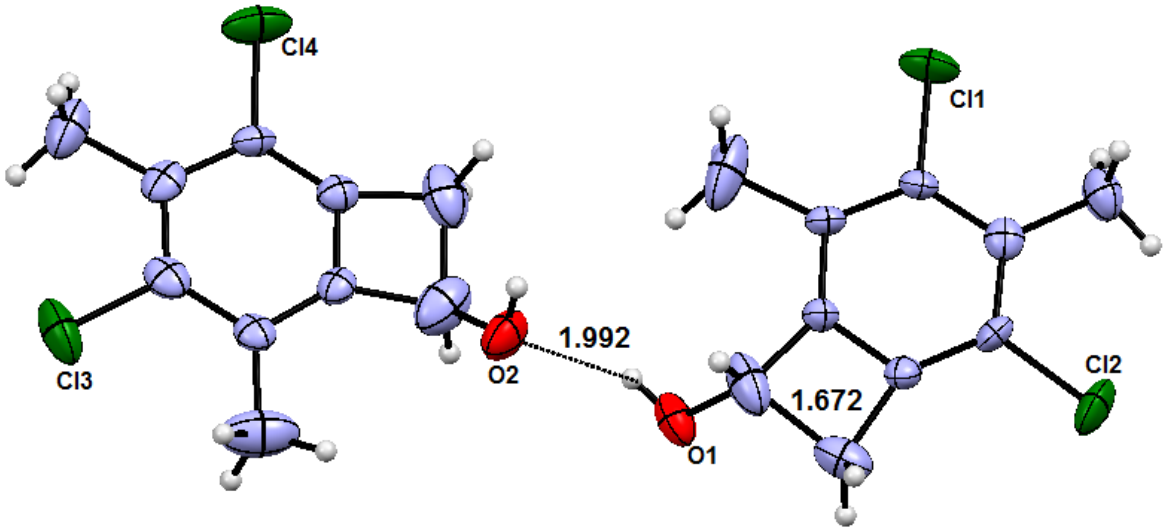
Empirical formula	C17 H19 N O4	
Formula weight	301.33	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 22.9995(8) Å	α = 90°.
	b = 5.0912(2) Å	β = 95.103(3)°.
	c = 12.9419(5) Å	γ = 90°.
Volume	1509.43(10) $Å^3$	
Z	4	
Density (calculated)	1.326 Mg/m^3	
Crystal size	0.12 x 0.11 x 0.09 mm^3	
Final R indices [I > 2sigma(I)]	R1 = 0.0399, wR2 = 0.0970	
R indices (all data)	R1 = 0.0576, wR2 = 0.1090	

- Crystallographic Data for **1-CB** (Chapter 5, figure 5.3); CCDC 1016504



Empirical formula	C10 H10 Br2 O	
Formula weight	306 g/mol	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 8.0928(3) Å	α = 90°.
	b = 31.2023(9)Å	β = 116.276(2)°.
	c = 9.0462(3)Å	γ = 90°.
Volume	2048.26(12) $Å^3$	
Z	8	
Density Diffrn	1.985 g/cm^3	
Crystal size	0.2 × 0.2 × 0.1 mm^3	
Final R indices [I > 2sigma(I)]	R1 = 0.0552, wR2 = 0.1341	
R indices (all data)	R1 = 0.0895, wR2 = 0.1535	

- Crystallographic Data for **3-CB** (Chapter 5, figure 5.3); CCDC 1414986



Empirical formula	C10 H10 Cl2 O	
Formula weight	217.08 g/mol	
Crystal system	Monoclinic	
Space group	P12 (1) /c1	
Unit cell dimensions	a = 14.259(3) Å	α = 90°.
	b = 15.594(4) Å	β = 98.118(15)°.
	c = 9.089(2) Å	γ = 90°.
Volume	2000.7(8) $Å^3$	
Z	8	
Density Diffrn	1.441g/cm^3	
Crystal size	0.22 × 0.16 × 0.14 mm^3	
Final R indices [I > 2sigma(I)]	R1 = 0.1062, wR2 = 0.2576	
R indices (all data)	R1 = 0.1891, wR2 = 0.2973	