Spring 2019

Anion Pool Directed Electroorganic Synthesis

D.M.M. Madushanka Mevan Dissanayake

ANION POOL DIRECTED ELECTROORGANIC SYNTHESIS

by

D.M.M. Madushanka Mevan Dissanayake

Bachelor of Science
University of Colombo, 2013

Submitted in Partial Fulfillment of the Requirements

For the Degree of Doctor of Philosophy in

Chemistry

College of Arts and Sciences

University of South Carolina

2019

Accepted by:

Aaron K. Vannucci, Major Professor

Ken Shimizu, Committee Member

Dimitry Peryshkov, Committee Member

John Regalbuto, Committee Member

Cheryl L. Addy, Vice Provost and Dean of the Graduate School

DEDICATION

This work is dedicated to my family who supported me unconditionally through both good and bad times. To my mother, whose constant encouragement was a bliss to succeed as a graduate student. To my father, for believing in me to be successful. To my brother, being constantly supportive.

ACKNOWLEDGEMENTS

At first my sincere appreciation goes to Prof. Aaron Vannucci for his guidance throughout my life in graduate school to accomplish the research presented in this dissertation. I'm ever grateful to him for providing me a strategic theme for my research which culminated through the development of "Anion pool". His mentoring has been of tremendous support to stay focused in the tough times with projects. A deep debt of gratitude is owed to my committee members Prof. Ken Shimizu, Prof. Dimitry Peryshkov, and Prof. John Regalbuto. Their insightful comments have always helped me to extend my research into new directions. I appreciate their invaluable advice offered whenever possible.

I must gratefully acknowledge Prof. Brian Benecewicz for allowing us to use the GC-MS instrument in him laboratory. I am particularly thankful to current and former members of Vannucci Research Group; Dr. Avishek Paul, Dr. Niveditha Das, Nicholas DeLucia, Pooja Ayare, Ryan Key, Victoria Bobo, Alex Melville, James Sitter, Mathew Warner, Maize Helton, and Jordan Reed. I am no less grateful to Dr. Perry Pellechia, Dr. Mike Walla, Mark D. Smith, and Helga Cohen for the support extended. I am indeed thankful to members of Wiskur group, Linda Shimizu group and John Regalbuto group for the support extended in numerous ways during research.

It is with great affection that I remember my high-school chemistry teacher Mrs. Chrishanthi de Silva and my undergraduate research mentor Prof. Dilip de Silva for theirinspiration to select chemistry as a career. I must also remember my mother, father, and my brother for their unconditional love and constant support through all chapters of my life. I cannot for a moment forget the support I received from Dr. Muditha Dias, Dr. Sahan Salpage, Dr. Randima Galhenage, Dr. Gaya Elpitiya, Dr. Shani Egodawatte, Dr. Aminda Samaranayake, Sachith Wickremasinghe, Shehani Wettasinghe, Gayathri Gange, Chathumal Jayaweera, Indika Pathirana, Thathsara Maddumapatabandi, and Niranji Ekanayake.

Finally, I extend my sincere appreciation to all professors and teachers who have inspired and guided me throughout the years. Further, a big thank you goes to everyone at University of South Carolina, who have extended their help in numerous ways including the staff of Department of Chemistry, International Student Services and Ms. Jackie and Honeycomb cafe crew for their warm greetings and refreshments all the time.

ABSTRACT

The “Anion pool” approach introduces a greener approach for derivatization of pharmaceutically important molecules by amalgamating both electrochemistry and organic synthesis. This is a base and metal free procedure carried out in organic solvents recommended for pharmaceutical preparations. The anion pool procedure generates reactive nitrogen nucleophiles *in situ* via electrochemical reduction of heteroaromatic substrates. The adoption of such a methodology prevents generation of waste from bases used for deprotonation. Hydrogen is the main by-product of generation of anion pool, which, if produced at a large enough scale could be used as a renewable fuel. These attributes comply with the principles of green chemistry, allowing synthetic chemists to carry out reactions in an atom-economic and environmentally friendly manner.

The anion pool method was first used to derivatize of benzimidazoles with alkyl, acyl and benzyl halides. We were able to achieve selective substitution at the 1*H* position in high yields with a variety of benzimidazoles and electrophiles bearing a variety of functional groups. The second study was aimed at selective acylation of indazoles at the *N1* position. Indazoles bear two nitrogen atoms on the pyrazole ring that tend to undergo non-selective reactions with electrophiles. By adopting the anion pool approach, we were able to achieve great selectivity to *N1*-position while also improving the yields, decreasing chemical additives, and utilizing safe solvents and less moisture sensitive acid anhydrides. This procedure can be carried out in an inexpensive set-up connected to a 9

V battery, indicating that this reaction could easily be adapted to being driven by the power of a basic solar cell. The adoptability of such a user-friendly set up makes it easier to incorporate green chemistry experiments to classroom teaching. This procedure is applicable for amidation reactions. Amide formation avoiding poor atom economy reagents has been identified as a priority for the ACS GCI Pharmaceutical roundtable. The anion pool method can be extended with a nucleophilic substitution to produce two pharmaceutically important compounds in a single cell with very good atom economy.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

1.1 Introduction

The ongoing social discussion on sustainable development has led towards a stronger emphasis on ecological footprint of a product or innovation.[1-2] Industries have moved towards renewable energy sources with the aim of reducing carbon dioxide emission and waste generation. In the same vein, introduction of novel approaches for organic synthesis, that serves to enhance the greenness of synthetic processes that generate commercial products is highly desirable. In the grand scheme, this supports building a sustainable world that enables an advancing economy. Adopting green chemistry practices support unique market positions for industrial brands that enables improved customer relations and retention of talent. Consequently, the "greenness" of a process elevates its recognition and permits a competitive advantage in facing "selection pressure" generated from ever evolving synthetic methods.[3]

Organic electrochemistry embodies a myriad of opportunities for synthetic chemists.[3-5] Electrosynthesis enables synthetic chemists to approach traditional synthesis methods in a sustainable manner. Electrons are inherently clean reagents that can be channeled into and out of a molecule by tuning the electrochemical potential of the system. This is a greener route to traditional oxidations and reductions which produce stoichiometric quantities of toxic waste. The additional benefit to an industrial chemist is the reduction of cost of waste remediation. The government of redox processes by tuning electrochemical potential of the system allows exploration of atom economic reaction pathways. Examples of such reactivities include polarity reversal in molecules,[6]electro-generation of bases and nucleophiles[7], and reactivities of electrochemical mediators.[8] As a result, more functional group tolerant and broadly applicable synthesis strategies can be

formulated. Conventionally, energy is channeled into organic reactions through thermal energy. However, the energy economy of thermal reactions suffers from associated dissipation processes. Electrochemical methods allow energy to be channeled in directly into reactions and thereby short-circuit energy transformations.[9] As a result, electricity generated from renewable sources such as wind, solar or hydro energy can sustainably be employed for chemical transformations.[10] The employment of mediators permits reduction or oxidation of substrates at further low potentials than they would otherwise undergo redox transformations.[11] Therefore, there is the potential to develop a competitive technology amenable to pertinent sustainability needs using available expertise and equipment in electrochemistry.

Electrosynthesis is an enabling tool to pharmaceutical industry to realize their efforts in adopting 12 principles of green chemistry in manufacturing processes.[12-14] Green chemistry is defined as "the design of chemical products and processes that reduce or eliminate the generation of hazardous substances".[1, 15] The waste from pharmaceutical productions originates from solvents, unreacted starting materials, redox reagents, bases and additives. By using flow methods for electrochemical reactions, solvent use can be minimized while improving reaction efficiency.[16] As reagents, electrons do not leave any waste and therefore, are inherently clean reagents that facilitate electrochemical redox reactions. Electrochemical oxidations and reductions potentially replace chemical oxidants, reductants and bases.[4] Thus, electrochemical methods potentially prevent waste generated by oxidants, reductants and bases. Elimination of waste generation improves atom economy through efficient utilization of starting material to form products. In

addition, the selectivity of electrochemical reactions minimize protection and deprotection steps in organic synthesis, which also improves atom economy.

Introduction of electro-synthetic methods further serves to enhance practicing green chemistry principles. The substitution of conventional redox reagents and reactive bases with electric current diminishes the hazards associated with conventional reagents. Recoverable and reusable ionic liquids are used as greener solvent replacements in electrochemical reactions.[17] These reactions can be carried out at room temperature and thereby it saves energy used for heating and cooling of reaction vessels. Electrochemical conversions can be done by using renewable feedstocks such as biomass by making use of electro-active functional groups and green chemistry principles encourage to use renewable feedstocks.[18] Real time analysis of reaction progress is possible by coupling synthetic process with techniques such as GC-MS. Clearly, electrosynthesis provides pharma an alternative route for green process designs evaluated by green chemistry metrices.

1.2 Definitions of Green chemistry parameters

Green chemistry metrics are used to benchmark the adoption of green chemistry principles for manufacturing processes.[19] As indicators of "greenness", they permit comparison of different manufacturing routes to the same pharmaceutical product.

Atom economy proposed by Trost in 1991, is a frequently used parameter to evaluate the "greenness" of a process.[20] The ratio of the molecular weight of products to molecular weight of raw materials and reagents converted into a percent provides the atom economy(Figure 1.1 a). This parameter considers the theoretical stoichiometry of starting materials and theoretical yield, assuming complete conversion of starting materials to

products. Therefore, atom economy can be applied at any scale, however, it disregards other additives and solvents.[21]

Process Mass Intensity (PMI) is another parameter proposed by EPA and ACS Green Chemistry Institute in 2006.[22] PMI is calculated by the ratio of the mass of material input including solvents and mass of pharmaceutically important products (Figure 1.1 b). Reports have indicated that PMI values for pharmaceutical products are in the range of 47-86.[23] Unlike atom economy, PMI considers the amount of conversion of starting material to products.

a) Atom Economy

$$AE = \frac{MW(products)}{\sum MW\ (raw\ materials) + \sum MW\ (reagents)} * 100\ \%$$

b) Process Mass Intensity

$$PMI = \frac{\sum m(Input\ materials\ and\ solvents)}{\sum m(products)}$$

Figure 1.1. Formulae for key green chemistry matrices[20, 22]

1.3 Principles of Organic Electrochemistry

1.3.1 Components of electrochemical setup

A typical electrochemical cell consists of two or more electrodes immersed in a solution of an ionic conductor called the electrolyte.[24-25] Transition metals, reticulate vitreous carbon, and boron doped diamond are available choices for electrodes. Transition metals are no longer popular choices because of cost and sustainability concerns.[3] Reticulate vitreous carbon is an inert and inexpensive material that offers high surface area to volume ratio. This is advantageous for high conversion of raw material to products.[25] Boron doped diamond is a semi-conductor electrode that has demonstrated the highest

over-potential for hydrogen evolution, by which it provides a broader potential window.[26] As a result, boron doped diamond electrodes are used in green chemistry applications such as waste water treatment[27], carbon dioxide reduction[28], and anodic cross coupling reactions.[29]

1.3.2 Choice of Solvent

The electron transfers from electrode to substrates occur through a layer of solvent in contact with the surface. The accessible potential window, dielectric constant, dipole moment, and solubility of electrolytes and substrates are important parameters to consider for solvent choice.[30] The potential window of solvent/ electrolyte combinations have been reviewed extensively.[24, 30-31] The solvent choice clearly impacts the nucleophilicity and stability of intermediates.[32-33] The solvents used for electrochemistry comprise two categories: protic solvents and aprotic solvents. Sulfuric acid, trifluoroacetic acid, water and methanol are examples of protic solvents. Protic solvents can be used as a proton source for the reactions, however, they can protonate anions generated and scavenge radical cations in oxidation reactions.[24, 34] The examples of aprotic solvents are acetonitrile, dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), propylene carbonate and tetrahydrofuran (THF).

In addition to chemical and physical parameters, it is necessary to consider environmental footprint of a solvent. Recent analysis reveals that more than 70% of pharmaceutical waste originates from solvent.[35] As a result, pharmaceutical companies such as GSK,[36] Astra Zenca,[37] Pfizer,[38] and ACS Green Chemistry Institute Pharmaceutical Roundtable[39] have developed solvent guides. Safety parameters and health hazards associated with solvents, their impact on air and water and waste produced have been taken

into consideration in developing these guides. Lot of solvent selection guides have listed dichloromethane and dimethylformamide as undesirable for pharmaceutical preparations.[38] Ionic liquids such as imidazolium tetrafluoroborate have been introduced as green solvents for electrosynthesis.[36-37] The amount of solvent used can be reduced by adopting flow methods and reducing the amount of solvent used improves process mass intensity of the process.[38]

1.3.3 Choice of Electrolyte

During electrolysis experiments, an electrolyte is dissolved in solvent to improve the conductivity. The choice of the electrolyte relies on its solubility, redox potential window and ease of separation.[40] Cathodic electrolyses require reductively stable cationic species in the electrolyte such as tetrabutylammonium ions. Such large cations have negligible chelation interactions with organic substrates. Lithium salts have been used in polar solvents. The anionic component of electrolyte requires to be stable to oxidation.[40] The commonly reported anions are $[PF_6]^-$, $[BF_4]^-$, and $[ClO_4]^-$. Iodide ions have demonstrated the initiation of radical reaction pathways at anode, and therefore not suitable as inert electrolytes.[41] The cations stabilize anionic intermediates and anions stabilize radical cations generated during electron transfer.[42-43]

Implementation of green chemistry principles require recovery and reuse of electrolytes. Ideally, an electrolyte that is more soluble in water can be easily removed from the reaction mixture after the reaction. Several ionic liquids have been developed in the past decade with the aim of improving reusability of electrolyte.[18, 44] Ionic liquids are salts in liquid state at low temperatures and are composed of ion pairs.[17] Cations such as tetrabutyl ammonium, pyrrolidinium, piperidinium and imidazolium ions and anions such

as $[PF_6]^-$ and $[BF_4]^-$ compose ionic liquids. These attributes enable ionic liquids to be used as both electrolytes and solvents. This directly impacts improving PMI values of synthesis. Oxidative and reductive reactions such as Shono oxidation[45] and CO_2 reduction[46] and polymerization reactions[47] have been reported in ionic liquids.

1.3.4 Different Types of Electrolyses

Two types of electrolytic methods are employed for preparative electrolysis of organic compounds: control potential (potentiostatic) and control current (galvanostatic) electrolysis.[24, 48] Control potential electrolysis is conducted at constant potential with reference to a reference electrode. Therefore, a reference electrode such as saturated mercury electrode or silver/silver chloride electrode should be employed. The substrate is consumed as the reaction progresses, and the progress of the reaction is indicated by the variation of current with respect to time. The total quantity of charge passed equates to the area under the current vs time curve. The completion of the reaction is indicated by a sharp drop of the current. The selectivity of the reaction is governed by the potential applied.

During constant current electrolysis, the current passed through solution is fixed and the potential difference between electrodes fluctuate to maintain constant current.[10] Initially, the substrate with the lowest oxidation potential undergoes oxidation at the anode. The potential at anode remains at the corresponding value until the substrate has depleted completely. Next, the anodic potential increases until it reaches the oxidation of the solvent in the absence of any other organic substrates. Efficiency of the process can be improved using low current densities. This process doesn't require a reference electrode. The charge passed can be controlled by altering the current.

Both these types of electrolyses can be carried out in single compartment and two compartment cells.[48-49] In a single compartment cell, both anode and cathode are contained in a single chamber. This method offers less resistance to movement of ions in the solution. However, it's not a viable option for "pool" methods that involve generation of a pool of reaction intermediates at one electrode. In a two-compartment cell; the anodic chamber is separated from the cathodic chamber by a frit. The frit lowers conductivity of the cell. Such a divided cell is ideal for both "cation" and "anion" pool methods; where the intermediates generated at one electrode should be protected from reaching the other electrode.[50-53]

1.3.5 Electron transfer at the electrode

Electron transfers from electrode to substrate (abbreviated as E) and vice versa are essential for electro-chemical processes. During reductions, when a negative potential is applied to the electrode, the energy of the Fermi level is raised and electrons flow into LUMO levels of substrate molecules generating radical anions (Figure 1.2 a).[12, 40] In an analogous way, the energy of Fermi level is lowered by applying a positive potential during oxidations. Consequently, an electron is transferred from the electroactive species to the electrode generating a radical cation. (Figure 1.2 b) Both radical anions and cations are unstable species that undergo subsequent chemical reactions (abbreviated as C). Electron transfers and chemical reactions can occur in a variety of kinetic sequences such as EC, ECE, CE, and EE.[12] Both bulk electrolysis and cyclic voltammetry are great techniques to generate short lived species and study their reactivity trends.

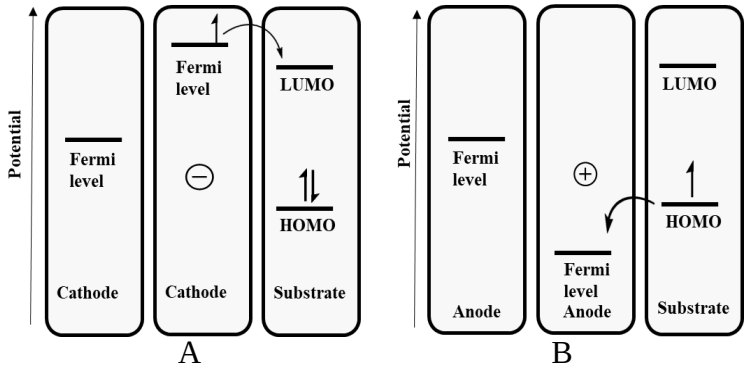


Figure 1.2. Heterogenous electron transfer a) from electrode to substrate during reduction b) from substrate to electrode during oxidation. Adapted from reference [40, 48]

1.4 History

Historically, redox chemistry investigations have been intricately linked with advances in electrochemistry. The invention of the first electric battery the "volta pile" enabled initial applications of electricity to chemical transformations.[49, 54-55] Michael Faraday formulated laws of electrolysis in 1834 and generated foundations of knowledge to develop practical uses of electricity.[55] His laws determined the relationship between the quantity of products formed and the amount of electricity passed. His descriptions of electrolysis popularized new terms such as electrode, electrolyte, and ions. The introduction of Cottrell equation by F.G. Cottrell in 1903 to relate electrode kinetics to mass-transfer laid the foundations for chronoamperometry was another milestone.[56]

These initial efforts progressed towards the invention of Kolbe electrolysis of carboxylic acids to produce symmetric dimers (Figure 1.3.a). Electrolysis of carboxylic acids was first studied by Faraday and followed by studies of Kolbe.[57] This oxidative decarboxylation method proceeds through radical intermediates. This process provided a

greener and operationally simple alternative to Wurtz reaction, which required stoichiometric quantities of highly reactive sodium metal.[58] However, Kolbe's method produces a lot of side products such as alkenes due to the instability of the intermediates formed. In addition to dimerization, the radical intermediates can undergo rearrangements. Therefore, the outcome is highly sensitive to nature of substrate, current density, substrate concentration and pH of the medium.[59] A pertinent example of synthetic utility of Kolbe reaction has been reported by Marco *et al*. to obtain long chain alkanes from short chain carboxylic acids.[60] (Figure 1.3.b) During this process, decarboxylation is followed by radical cyclization.

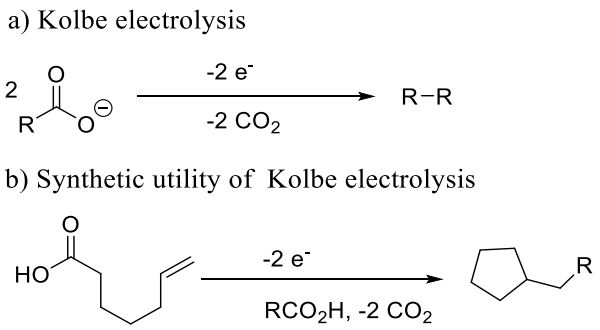


Figure 1.3. Kolbe reaction(a)[57] and Kolbe reaction directed radical cyclization(b)[60]

Simons Fluorination process, invented in 1949, was developed to be a commercialized process that obviates fluorination with fluorine, which is a hazardous substance (Figure 1.4).[61] During this process, organic compounds such as acid chlorides, esters, and some aliphatic heterocyclic compounds are electrolyzed in anhydrous HF to substitute all the hydrogens.[62] This process is used to produce fluorinated material such as perfluorinated carboxylic acids and amines. The hazards associated with initial process have been reduced by introducing KF·2HF as the electrolyte.

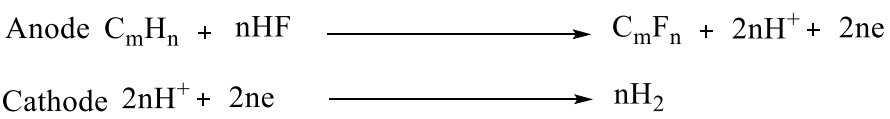


Figure 1.4. Electrochemical reactions of Simons fluorination[61-62]

The Monsanto adiponitrile process invented in 1960 was another major leap in introducing an electrochemical approach for commercial productions (Figure 1.5).[49] Adiponitrile (ADP) is a raw material of hexamethylenediamine (HMD) which is also a raw material for nylon 6,6 fibers. In this reaction, an electron deficient alkene is reduced to produce an anionic intermediate that dimerizes to form adiponitrile.[11] The electrochemical process avoids hydrogenation of the double bond and selectively dimerizes monomers to produce adiponitrile in water. In 2005, 0.481 million metric tons of adiponitrile were produced via Monsanto route.[63]

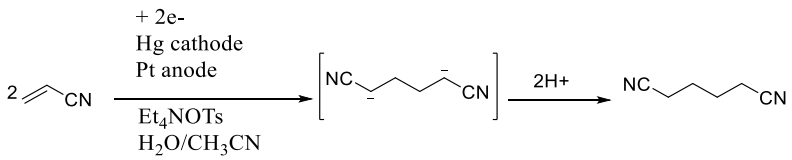


Figure 1.5. Electrochemical adiponitrile synthesis[31, 63]

The discovery of triarylamine mediator[64] (1960), chiral electrodes by Miller[65] (1975), and Shono oxidation[66] (1975) have demonstrated their impact through a variety of applications. Historical developments of electro-organic chemistry have been reviewed extensively.[49] The increasing demand for broadly applicable and greener synthetic methods has fueled the renaissance of electro-synthetic methods. Next, several recent developments of the renaissance that are important for contemporary organic synthesis will be discussed.

1.5 Pertinent Green Electro-Oxidative Synthetic Methods

Electrochemical methods have been used to generate unstable reactive intermediates under mild conditions in the absence of bases and oxidants. Such methods introduce a greener alternative to conventional methods that use stoichiometric quantities of bases and oxidants. Some pertinent examples that introduce greener approaches by introducing electrochemistry will be reviewed in following sections.

1.5.1 Cation pool method

Cation pool method introduced by Yoshida *et al*. provides a greener method for the generation of unstable cationic intermediates.[53, 67] Cation pool method has found applications into cross coupling,[68] alkane oxidation,[69] alkylation,[70] allylation,[53] and halogenation.[53, 59, 71] The cation pool method is a two-steps procedure that generates the cations via anodic oxidation at -72 $^{\circ}$C during the initial step. This is an irreversible step and low temperature electrolysis allows for stabilizing the carbocation generated via oxidation. The solvent, counter-ion and stability of the cation are vital for the success of this reaction. In the subsequent step, nucleophiles are added to the "cation pool". The reaction of cations with nucleophiles generates a carbon-carbon bond (Figure 1.6). This pool technique allows electrophiles and nucleophiles to be separated by space and time. Therefore, nucleophiles of lower oxidation potential than the starting material can be used for these reactions. The cations generated via low temperature electrolysis includes N-acyliminium,[67] alkoxycarbenium,[72-73] diarylcarbenium,[74] glycosyl,[75] silyl,[76] iodine,[71] alkoxysulfonium,[77] benzylaminosulfonium,[68] arene,[78] thioarenium cations,[79] and thionium cations.[52] A variety of nucleophiles including cyanides, allylsilanes, silyl enol ethers, ketene silyl acetals,

organomagnesium, and organozinc compounds have demonstrated good reactivity with "cation pools".[53, 70]

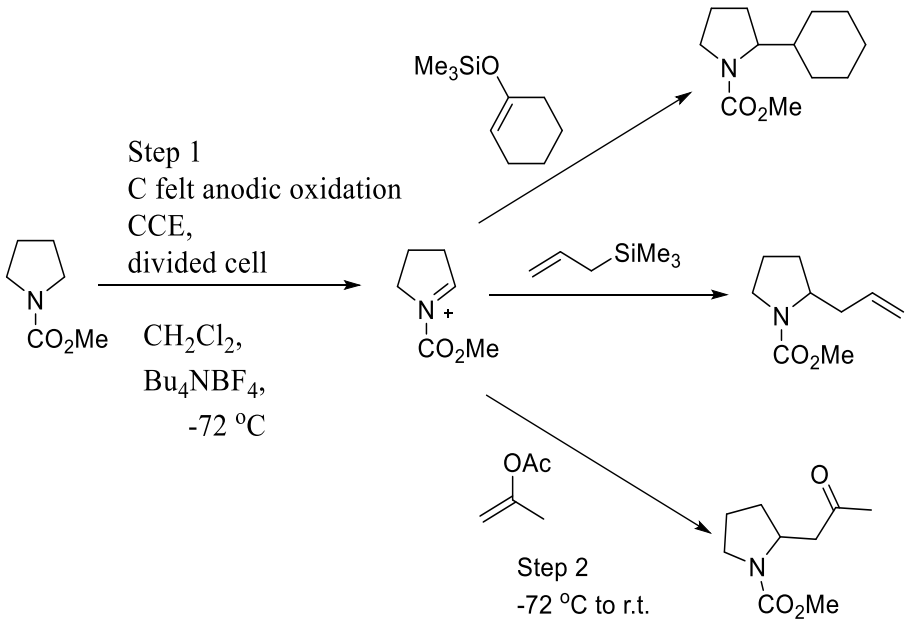


Figure 1.6. Cation pool approach for direct functionalization of carbamates[53, 59]

For substrates that are not easily oxidizable, a silyl group has been used as an electro-auxiliary to reduce the oxidation potential (Figure 1.7 a).[52] The reaction of N-acyliminium ions with aromatic compounds provides an alternative route to electrophilic aromatic substitution (Figure 1.7 b).[80] This reaction has been attempted in a flow microreactor system equipped with micromixers to achieve selectivity to monoalkylated product. The N-acylium cations generated through cation pool approach can be reduced to form radicals (Figure 1.7 c).[81] The radical intermediate undergoes an addition reaction with methyl acrylate. The dimerization of thus formed radicals has also been reported.[81]

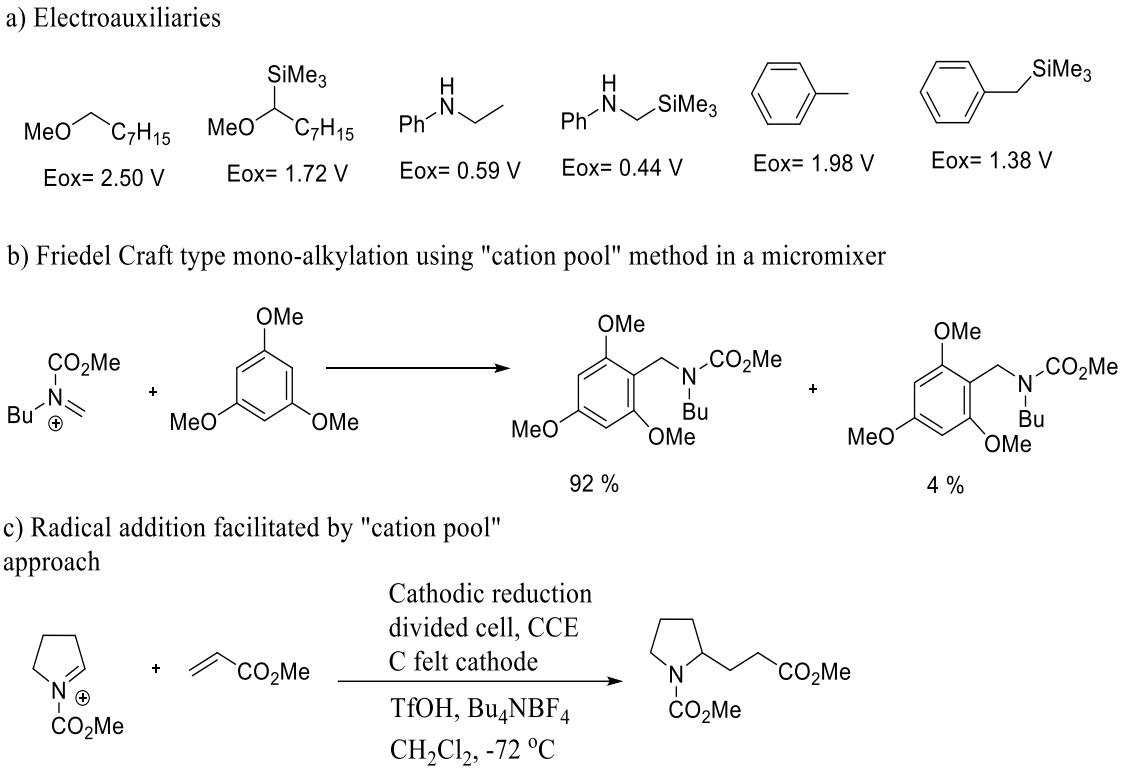


Figure 1.7. a) Influence of electroauxiliary on the oxidation potential[52] b) "Cation pool directed selective monoalkylation using micromixing[80] c) Radical mediated C-C bond formation[81]

1.5.2 C-H Amination

Yoshida and co-workers reported an amination procedure of aromatic compounds that involves direct conversion of C-H bonds to C-N bonds (Figure 1.8).[82-83] The oxidation of aromatic compounds in the presence of pyridine using carbon felt anodes results in N-arylpyridinium[82] cations. N-mesylimidazole[83] and pyrimidine[84] are two other heterocycles that can substitute for pyridine in the generation of oxidatively inactive cationic intermediates. N-aryl pyridinium ions are subsequently converted to NH_2 groups through the reaction with nucleophiles such as aliphatic amines. The use of a sacrificial base to stabilize the cations obviates the introduction of amines into reaction mixture under

oxidizing conditions. This procedure is carried out in acetonitrile under base, oxidant, and metal free conditions. Functional group tolerance has been demonstrated over iodo, methoxy, carbonyl, nitro, and ester functionalities.[82] The applicability of the procedure has been extended to the synthesis of N-alkylaniline derivatives with alcohol and amino functionalities in the alkyl chain.[85]

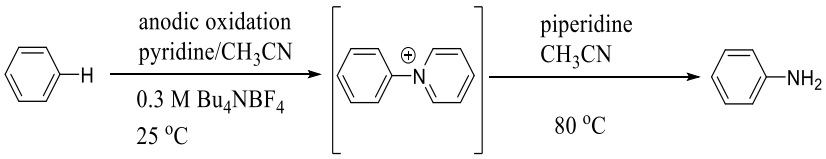


Figure 1.8. Electrochemical amination for primary amine synthesis[82]

Waldvogel and coworkers expanded the scope of Yoshida's strategy to a variety of alkylated arenes (Figure 1.9).[86] Boron doped diamond (BDD) electrodes were used for this study. Several reports indicate higher performance of sp^3- carbon based boron doped diamond electrodes over sp^2 - carbon based graphite electrodes at high anodic potentials. A broad range of alkyl arenes including *tert*-butyl and isopropyl benzene, mesitylene, and tetrahydronapthalene produced good yields. By adopting a similar strategy, the same group has demonstrated two-fold amination of naphthalene via dipyridinium derivative.[87]

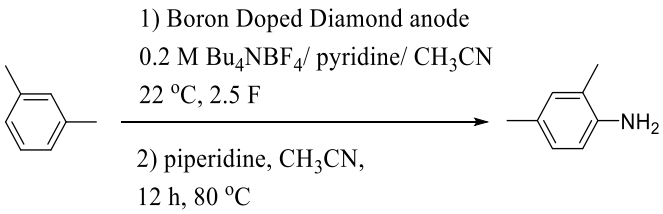


Figure 1.9. Electrochemical amination of alkylated amines using BDD electrodes[86]

1.5.3 Heterocycle Formation via Anodic coupling

Moeller's group has reported a C-N bond forming cyclization procedure for the synthesis of pyrrolidine and piperidine rings (Figure 1.10).[88] The yields of the reaction were influenced by the nature of substituents in the alkene, electrolyte, solvent and alkaline conditions. Higher yields are obtained with less polar olefins under alkaline conditions. The anodic coupling protocol is initiated by oxidation of the alkene to generate a radical cation, which is trapped by the nucleophilic moiety in the olefin, leading to cyclization followed by a second oxidation (Figure 1.10.a). Alcohols, amines, and sulfonamides were used as nucleophilic moieties. Use of a strong base such as LiOMe facilitates the generation of nucleophilic anion and improves yields. Oxygen and nitrogen heterocycles of ring sizes five-seven were synthesized. By using amides and anilides, synthesis of lactams has been reported following this procedure (Figure 1.10.b).[89] These reactions can be run in an operationally simple set up powered by a photovoltaic cell.[10]

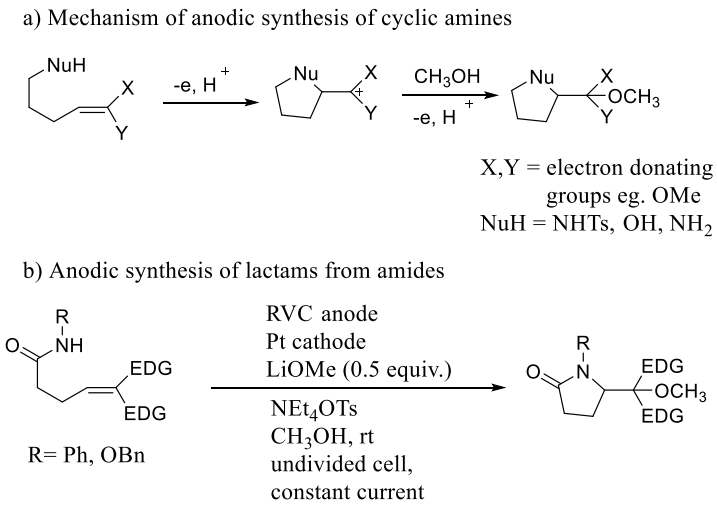


Figure 1.10. Anodic cyclizations a) mechanism of intramolecular anodic olefin coupling[88] b) Electrochemical cyclization of amides to form lactams[89]

1.5.4 Halogen Mediated Green Synthesis of Indolines

Little and co-workers reported a green procedure for the synthesis of 3-methoxy-1-phenylsulfonylindolines (Figure 1.11).[90] Constant current electrolysis of 2-vinylphenyl sulfonamide derivatives in methanol using n-Bu_4NI as a redox catalyst, leads to amino oxygenation of the alkene affording the cyclized product. Functional group tolerance has been demonstrated over electron donating and withdrawing moieties. Electrolysis is carried out in a single cell using graphite electrodes. The paired electrolysis generates methoxide nucleophiles via cathodic reduction of methanol. Therefore, no bases and oxidants are required for the synthesis procedure. Further, excess electrolyte wasn't required for scaled up reaction.[41]

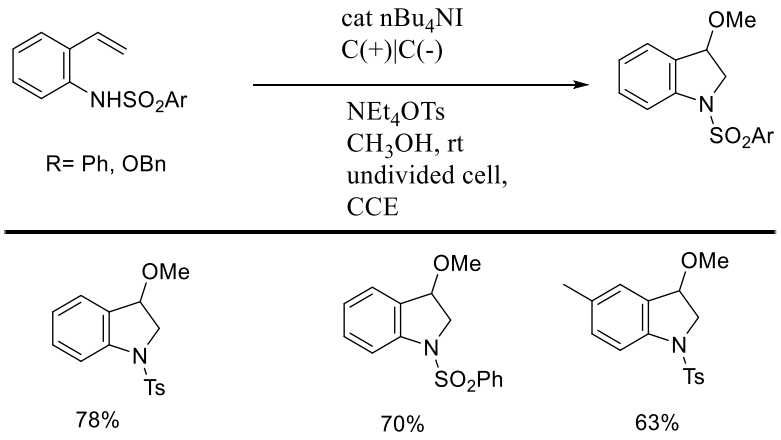


Figure 1.11. Electrochemical amino oxygenation for the synthesis of indolines[90]

1.6 Pertinent Green Electro-Reductive Synthetic Methods

1.6.1 Electrochemical Pinacol Coupling

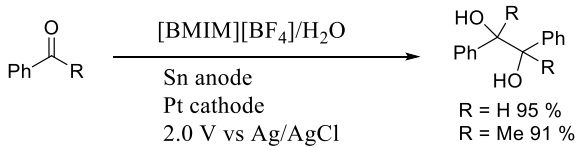


Figure 1.12. Electrochemical pinacol coupling of aromatic carbonyl compounds in ionic liquids[18]

Direct reduction of organic functional groups to generate functional groups such as aldehydes, ketones, alcohols and ethers has been known long.[49] Ketyl radicals generated from reduction of ketones can be dimerized through pinacol coupling to produce 1,2-diols.[91] Pinacol coupling is employed in synthetic strategies of taxol, cotylenol, and HIV-I protease. Manchanayakage *et. al.* reported a metal-free electrochemical procedure for pinacol coupling of aromatic aldehydes and ketones in ionic liquids (Figure 1.12).[18] The use of an ionic liquid obviates the necessity of excess electrolytes. The recyclability and reusability of the ionic liquid up to five times enhances the greenness of the procedure.

1.6.2 Cathodic Reduction of Esters

Chemoselectivity of ester reduction has always relied on the choice of reducing agent. Markó *et al.* has reported an electrochemical procedure for the reduction of toluate esters that demonstrates a relationship between reaction solvent and product composition.[32-33] Reduction of toluate esters produces a radical intermediate which decomposes to the corresponding alcohol in protic solvents and the alkane in aprotic solvents (Figure 1.13). It has been applied for the reduction of a variety of substrates. This

process is greener than the corresponding Barton-McCombie reaction that requires toxic reagents such as tin reagents.[92]

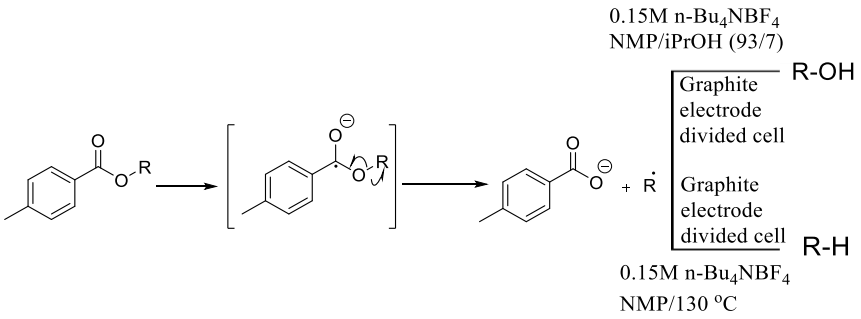


Figure 1.13. Decomposition of intermediates of ester reduction in different solvents[32-33]

1.6.3 Electrocatalytic Reductive Cross Coupling

Electrocatalytic methods have been developed for organic reactions that require stoichiometric reductants such as cross electrophile coupling (Figure 1.14).[93-94] Nickel pyridyl complexes have been reported as electrocatalysts of cross electrophile coupling. In electrocatalysis, the molecular catalyst receives electrons from the electrode initially via heterogenous electron transfer. The reduced species (Ni (0) complex) undergoes oxidative addition with aryl halides raising the oxidation state of the metal center. The high valent species thus produced reacts with a radical derived from the alkyl halide or ester. The Ni (III) species generated undergoes reductive elimination to produce the cross coupled species. The Ni(I) species formed after reductive elimination plays a key role in the origination of radicals from alkyl halides and N-hydroxypthalimide esters. Caron dioxide is formed on radical generation from N-hydroxypthalimides.[27, 93] Both reports have demonstrated broad scope of functional group tolerance.[93-94]

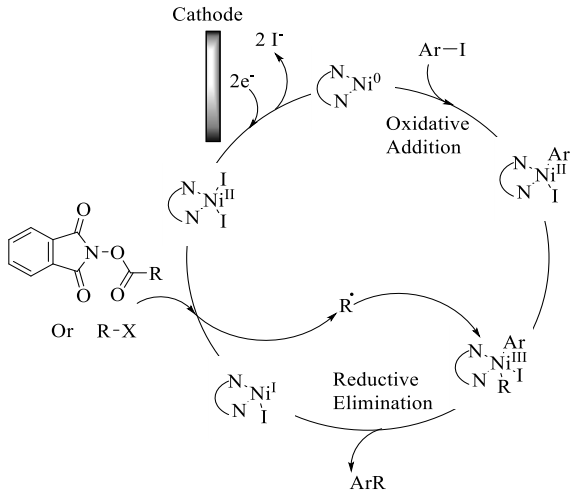


Figure 1.14. Catalytic cycle of electrochemical cross electrophile coupling/ reductive cross coupling.[93-94]

Adopting a redox mediated approach allows generation of catalytic intermediates in a selective and controlled manner.[8] The mediator allows the electron transfers to occur at fairly low potentials and avoid over oxidations and reductions of molecules. The electric current obviates consumption of stoichiometric quantities of reductants for reductive coupling. Decarboxylative cross coupling has successfully been attempted in an industrial electrochemical flow reactor using continuous flow method.[27]

1.6.4 Electrocatalytic Amination

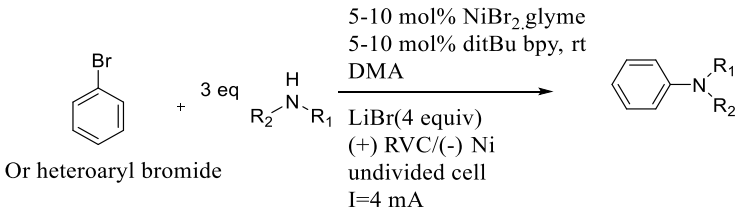


Figure 1.15. Nickel catalyzed electrochemical amination.[95]

Using conditions similar to reductive electrochemical cross coupling, Baran et al. have reported nickel catalyzed electrochemical amination (Figure 1.15).[95] Amine functionalities are prevalent entities in medicinal compounds.[96-97] Therefore, a scalable and broadly applicable procedure is highly desirable as an alternative to numerous amination procedures available.[97] This reaction is carried out at room temperature, under mild conditions in a base free environment. In this procedure, aryl halides and aliphatic amines are coupled in the presence of a nickel catalyst in an undivided cell using carbon anodes and nickel cathodes. Broad functional group tolerance has been demonstrated over acid and base sensitive functionalities and electron donating and withdrawing groups.

1.6.5 Electrochemical Smiles Rearrangement

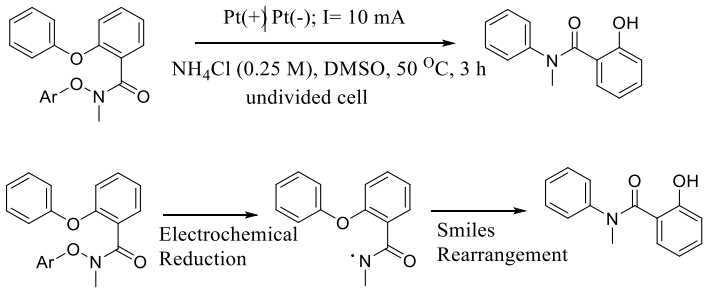


Figure 1.16. Electrochemical Smiles Rearrangement[98]

Electrochemical reductive Smiles rearrangement is a recent example of a conventional organic reaction approached from an electrochemical perspective (Figure 1.16).[98] The classical Smile rearrangement proceeds through an anionic intermediate to effect nucleophilic aromatic substitution.[99] The electrochemical procedure leads to generation of an amidyl radical at the cathode from the cleavage of N-O bond. No bases

and reductants are used. A variety of amides have been synthesized. The applicability of the reported strategy to synthesis of axially chiral aniline derivatives has been demonstrated. This is a new strategy that enables formation of C-N bonds under mild conditions using available precursors that is highly desirable for total synthesis procedures.

1.6.6 Electrogenerated Bases

The acidic protons in weakly acidic organic molecules can be reduced to hydrogen with co-production of anions, in aprotic solvents. Studies of cathodic generation of bases were pioneered by Manuel Baizer,[43] Lund,[100] Iversen,[100] and Shono.[101] The electrogenerated reduced species can be a radical anion, anion or a dianion. The anionic species can behave either as nucleophiles or bases depending on reaction conditions. The counter ion of the electrolyte helps in stabilizing the anionic species.[42-43] The reaction 1 in Figure 1.17 is an example of an electrogenerated base used to generate a nucleophile at a tertiary carbon.[42] Triphenyl methyl anion species is formed by electro-reduction of triphenyl methane. The anion acts as a non-nucleophilic base for regioselective deprotonation of 2-methyl cyclohexanone. The anionic carbon is next alkylated forming an unsymmetric cyclic ketone. In reaction 2 of Figure 1.17, the base generated from reduction of 2-pyrrolidinone is used to deprotonate trifluoromethane.[43] The trifluoromethyl anion reacts with various carbonyl compounds to produce (trifluromethyl) carbinols in the presence of hexamethyl disilazane (HMDS).

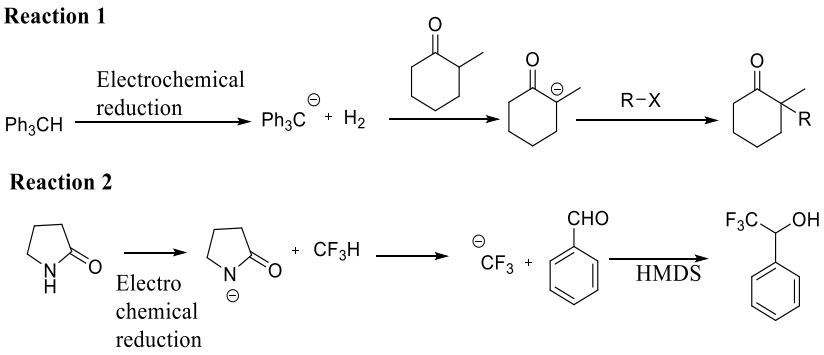


Figure 1.17. Carbanions as electrogenerated bases[42-43]

Inesi et al. have reported the generation of N- Heterocyclic Carbenes via electrochemical reduction in ionic liquids (Figure 1.18).[44] The formation of the carbene on electrolysis is evidenced by nucleophilic addition of carbene to benzaldehyde to afford the adduct in Figure 1.18 reaction 1.[102] Further, the NHCs have been used as bases to deprotonate benzoxazolones.[44] The recovery and reuse of ionic liquid up to five times has been demonstrated.

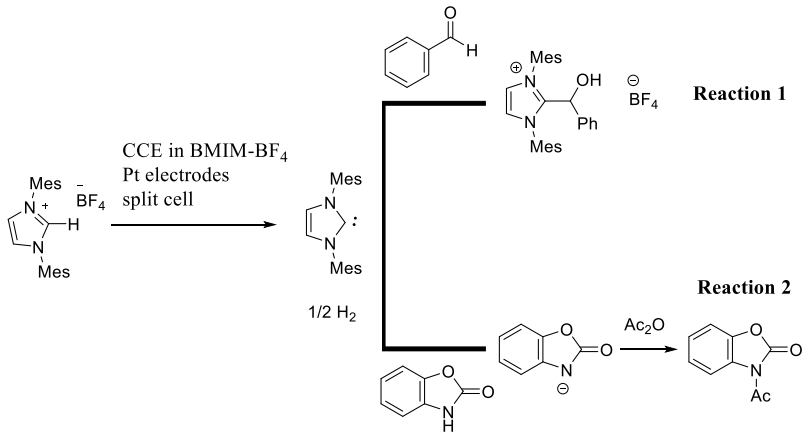


Figure 1.18. Reactions of electrogenerated N-Heterocyclic Carbenes.[44, 102]

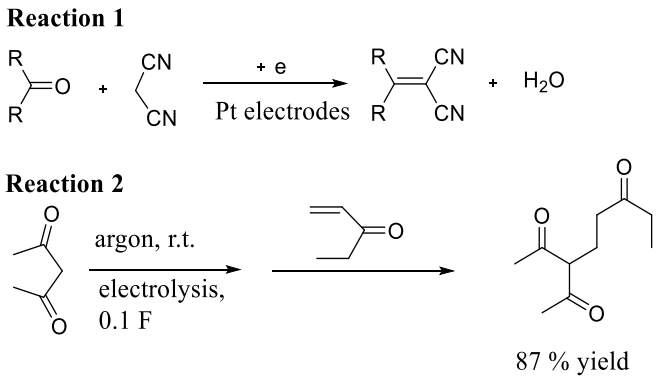


Figure 1.19. Electrochemical Knoevenagel condensation (reaction 1) and Michael addition (reaction 2).[103-104]

Electrochemical Michael addition and Knoevenagel condensation are two early reports of electrogenerated carbon nucleophiles.[103-104] In Knoevenagel condensation, a C-C bond is formed by base catalyzed condensation of a carbonyl compound with a methylene compound like diethyl malonate. Inesi et al. reported Knoevenagel condensation under solvent and supporting electrolyte free conditions at 40 °C (Reaction 1, Figure 1.19).[103] In this process, constant current electrolysis of the reactants is carried out using Pt electrodes in a single or divided cell. In electrochemical Michael addition, a β-dicarbonyl compound is electrolyzed with a Michael acceptor at room temperature in a divided cell using Pt electrodes (Reaction 2, Figure 1.19).[104] This report explores Michael addition with β-diketones, β-ketoesters, and malonate esters.

Alizadeh *et al.* have reported the use of electrogenerated carbene in the synthesis of phenylcarbonimidoyl dyes (Figure 1.20).[105] This is a paired electrosynthesis procedure carried out using a stainless-steel cathode and carbon anode. At the cathode malonitrile is reduced to the carbanion. At the anode, both Fast Violet B(FVB) and Fast Blue B(FBB)

are oxidized. The oxidized species reacts with the carbanion malonitrile to yield carbonimidoyl dicyanide derivatives. This is a catalyst free procedure, carried out at room temperature using a non-toxic solvent.

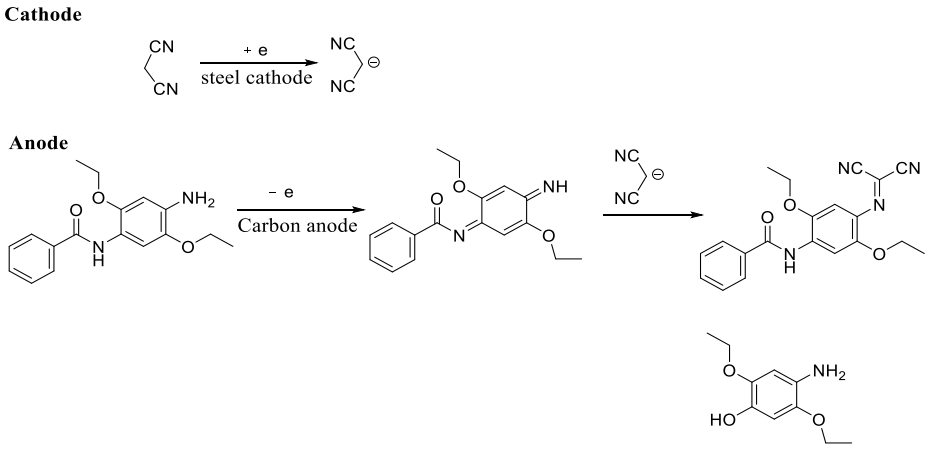


Figure 1.20. Electrochemical synthesis of phenyl carbonimidoyl dyes using electrogenerated carbon nucleophiles[105]

1.7 Anion pool method

"Anion pool" driven organic synthesis incorporates both electrochemistry and organic synthesis for greener derivatization of pharmaceutically important molecules. This is a base and metal free procedure carried out in organic solvents recommended for pharmaceutical preparations. The anion pool procedure generates reactive nitrogen nucleophiles *in situ* via electrochemical reduction of heteroaromatic substrates.[50-51] The adoption of such a methodology prevents generation of waste from bases used for deprotonation. Hydrogen is the main by-product of generation of anion pool, which, if produced at a large enough scale could be used as a renewable fuel. These attributes comply with the principles of green chemistry, allowing synthetic chemists to carry out reactions in an atom-economic and environmentally friendly manner.

The "anion pool" method was first used to derivatize of benzimidazoles with alkyl, acyl and benzyl halides. We were able to achieve selective substitution at the 1*H* position in high yields with a variety of benzimidazoles and electrophiles bearing a variety of functional groups.[50] The second study was aimed at selective acylation of indazoles at the *N1* position. Indazoles bear two nitrogen atoms on the pyrazole ring that tend to undergo non-selective reactions with electrophiles. By adopting the anion pool approach, we were able to achieve great selectivity to *N1*-position while also improving the yields, decreasing chemical additives, and utilizing safe solvents and less moisture sensitive acid anhydrides.[103] This procedure can be carried out in an inexpensive set-up connected to a 9 V battery, indicating that this reaction could easily be adapted to being driven by the power of a basic solar cell. The adoptability of such a user-friendly set up makes it easier to incorporate green chemistry experiments to class-room teaching. This procedure is applicable for amidation reactions. Amide formation avoiding poor atom economy reagents has been identified as a priority for the ACS GCI pharmaceutical roundtable. The anion pool method can be extended with a nucleophilic substitution to produce two pharmaceutically important compounds in a single cell with very good atom economy.

1.8 Future Perspectives

The last decade has seen a significant increase in electrosynthetic reports. They have uncovered new reactivity trends providing unique methods to synthesize a variety of organic compounds under mild and environmentally benign conditions. Some recent discoveries have been benchmarked with process greenness scores. The discovery of novel reactivity trends and benchmarking their greenness present a strategic approach to substitute pertinent synthetic processes in pharma with greener alternatives.

1.9 References

1. Feroci, M.; Orsini, M.; Palombi, L.; Inesi, A., Electrochemically induced Knoevenagel condensation in solvent- and supporting electrolyte-free conditions. *Green Chemistry* **2007,** *9* (4), 323-325.

2. Anastas, P. T.; Warner, J. C., *Green chemistry: Theory and practice*. TPB: 2012.

3. Li, C.-J.; Trost, B. M., Green chemistry for chemical synthesis. *Proceedings of the National Academy of Sciences* **2008,** *105* (36), 13197.

4. Horn, E. J.; Rosen, B. R.; Baran, P. S., Synthetic Organic Electrochemistry: An Enabling and Innately Sustainable Method. *ACS Central Science* **2016,** *2* (5), 302-308.

5. Frontana-Uribe, B. A.; Little, R. D.; Ibanez, J. G.; Palma, A.; Vasquez-Medrano, R., Organic electrosynthesis: a promising green methodology in organic chemistry. *Green Chemistry* **2010,** *12* (12), 2099-2119.

6. Little, R. D.; Moeller, K. D., Introduction: Electrochemistry: Technology, Synthesis, Energy, and Materials. *Chemical Reviews* **2018,** *118* (9), 4483-4484.

7. Sutterer, A.; Moeller, K. D., Reversing the Polarity of Enol Ethers: An Anodic Route to Tetrahydrofuran and Tetrahydropyran Rings. *Journal of the American Chemical Society* **2000,** *122* (23), 5636-5637.

8. Utley, J. H., Electrogenerated bases. In *Electrochemistry I*, Springer: 1987; pp 131-165.

9. Francke, R.; Little, R. D., Redox catalysis in organic electrosynthesis: basic principles and recent developments. *Chemical Society Reviews* **2014,** *43* (8), 2492-2521.

10. Sauermann, N.; Meyer, T. H.; Qiu, Y.; Ackermann, L., Electrocatalytic C–H Activation. *ACS Catalysis* **2018,** *8* (8), 7086-7103.

11. Nguyen, B. H.; Perkins, R. J.; Smith, J. A.; Moeller, K. D., Photovoltaic-driven organic electrosynthesis and efforts toward more sustainable oxidation reactions. *Beilstein Journal of Organic Chemistry* **2015,** *11*, 280-287.

12. Moeller, K. D., Using Physical Organic Chemistry To Shape the Course of Electrochemical Reactions. *Chemical Reviews* **2018,** *118* (9), 4817-4833.

13. Cardoso, D. S. P.; Šljukić, B.; Santos, D. M. F.; Sequeira, C. A. C., Organic Electrosynthesis: From Laboratorial Practice to Industrial Applications. *Organic Process Research & Development* **2017,** *21* (9), 1213-1226.

14. Cue, B. W.; Zhang, J., Green process chemistry in the pharmaceutical industry. *Green Chemistry Letters and Reviews* **2009,** *2* (4), 193-211.

15. Schäfer, H. J., Contributions of organic electrosynthesis to green chemistry. *Comptes Rendus Chimie* **2011,** *14* (7), 745-765.

16. Erythropel, H. C.; Zimmerman, J. B.; de Winter, T. M.; Petitjean, L.; Melnikov, F.; Lam, C. H.; Lounsbury, A. W.; Mellor, K. E.; Janković, N. Z.; Tu, Q.; Pincus, L. N.; Falinski, M. M.; Shi, W.; Coish, P.; Plata, D. L.; Anastas, P. T., The Green ChemisTREE: 20 years after taking root with the 12 principles. *Green Chemistry* **2018,** *20* (9), 1929-1961.

17. Pletcher, D.; Green, R. A.; Brown, R. C. D., Flow Electrolysis Cells for the Synthetic Organic Chemistry Laboratory. *Chemical Reviews* **2018,** *118* (9), 4573-4591.

18. Kathiresan, M.; Velayutham, D., Ionic liquids as an electrolyte for the electro synthesis of organic compounds. *Chemical Communications* **2015,** *51* (99), 17499-17516.

19. Kronenwetter, H.; Husek, J.; Etz, B.; Jones, A.; Manchanayakage, R., Electrochemical pinacol coupling of aromatic carbonyl compounds in a [BMIM][BF4]–H2O mixture. *Green Chemistry* **2014,** *16* (3), 1489-1495.

20. Veleva, V. R.; Cue, B. W.; Todorova, S., Benchmarking Green Chemistry Adoption by the Global Pharmaceutical Supply Chain. *ACS Sustainable Chemistry & Engineering* **2018,** *6* (1), 2-14.

21. Trost, B. M., The atom economy--a search for synthetic efficiency. *Science* **1991,** *254* (5037), 1471.

22. Sheldon, R. A., Metrics of Green Chemistry and Sustainability: Past, Present, and Future. *ACS Sustainable Chemistry & Engineering* **2018,** *6* (1), 32-48.

23. Jimenez-Gonzalez, C.; Ponder, C. S.; Broxterman, Q. B.; Manley, J. B., Using the Right Green Yardstick: Why Process Mass Intensity Is Used in the Pharmaceutical Industry To Drive More Sustainable Processes. *Organic Process Research & Development* **2011,** *15* (4), 912-917.

24. Roschangar, F.; Sheldon, R. A.; Senanayake, C. H., Overcoming barriers to green chemistry in the pharmaceutical industry – the Green Aspiration Level™ concept. *Green Chemistry* **2015,** *17* (2), 752-768.

25. Hammerich, O.; Speiser, B., *Organic electrochemistry: revised and expanded*. CRC Press: 2015.

26. Sperry, J. B.; Wright, D. L., The application of cathodic reductions and anodic oxidations in the synthesis of complex molecules. *Chemical Society Reviews* **2006,** *35* (7), 605-621.

27. Lips, S.; Waldvogel, S. R., Use of Boron-Doped Diamond Electrodes in Electro-Organic Synthesis. *ChemElectroChem* **2018,** *0* (0).

28. Li, H.; Breen, C. P.; Seo, H.; Jamison, T. F.; Fang, Y.-Q.; Bio, M. M., Ni-Catalyzed Electrochemical Decarboxylative C–C Couplings in Batch and Continuous Flow. *Organic Letters* **2018,** *20* (5), 1338-1341.

29. Nakata, K.; Ozaki, T.; Terashima, C.; Fujishima, A.; Einaga, Y., High-Yield Electrochemical Production of Formaldehyde from CO2 and Seawater. *Angewandte Chemie International Edition* **2014,** *53* (3), 871-874.

30. Kirste, A.; Schnakenburg, G.; Stecker, F.; Fischer, A.; Waldvogel, S. R., Anodic Phenol–Arene Cross-Coupling Reaction on Boron-Doped Diamond Electrodes. *Angewandte Chemie International Edition* **2010,** *49* (5), 971-975.

31. Schulz, L.; Waldvogel, S. R., Solvent Control in Electro-Organic Synthesis. *Synlett* **2019,** *30* (03), 275-286.

32. Luca, O. R.; Gustafson, J. L.; Maddox, S. M.; Fenwick, A. Q.; Smith, D. C., Catalysis by electrons and holes: formal potential scales and preparative organic electrochemistry. *Organic Chemistry Frontiers* **2015,** *2* (7), 823-848.

33. Lam, K.; Markó, I. E., Chemoselective Chemical and Electrochemical Deprotections of Aromatic Esters. *Organic Letters* **2009,** *11* (13), 2752-2755.

34. Lam, K.; Markó, I. E., Organic electrosynthesis using toluates as simple and versatile radical precursors. *Chemical Communications* **2009,** (1), 95-97.

35. Lagowski, J. J., *The Chemistry of Nonaqueous Solvents III*. Elsevier: 2012.

36. Raymond, M. J.; Slater, C. S.; Savelski, M. J., LCA approach to the analysis of solvent waste issues in the pharmaceutical industry. *Green Chemistry* **2010,** *12* (10), 1826-1834.

37. Alder, C. M.; Hayler, J. D.; Henderson, R. K.; Redman, A. M.; Shukla, L.; Shuster, L. E.; Sneddon, H. F., Updating and further expanding GSK's solvent sustainability guide. *Green Chemistry* **2016,** *18* (13), 3879-3890.

38. Diorazio, L. J.; Hose, D. R. J.; Adlington, N. K., Toward a More Holistic Framework for Solvent Selection. *Organic Process Research & Development* **2016,** *20* (4), 760-773.

39. Alfonsi, K.; Colberg, J.; Dunn, P. J.; Fevig, T.; Jennings, S.; Johnson, T. A.; Kleine, H. P.; Knight, C.; Nagy, M. A.; Perry, D. A.; Stefaniak, M., Green chemistry tools to influence a medicinal chemistry and research chemistry based organisation. *Green Chemistry* **2008,** *10* (1), 31-36.

40. Prat, D.; Hayler, J.; Wells, A., A survey of solvent selection guides. *Green Chemistry* **2014,** *16* (10), 4546-4551.

41. Elgrishi, N.; Rountree, K. J.; McCarthy, B. D.; Rountree, E. S.; Eisenhart, T. T.; Dempsey, J. L., A Practical Beginner's Guide to Cyclic Voltammetry. *Journal of Chemical Education* **2018,** *95* (2), 197-206.

42. Liu, K.; Song, C.; Lei, A., Recent advances in iodine mediated electrochemical oxidative cross-coupling. *Organic & Biomolecular Chemistry* **2018,** *16* (14), 2375-2387.

43. Fuchigami, T.; Suzuki, K.; Nonaka, T., Electrogenerated triphenylmethyl anion species—a highly useful base for selective organic synthesis. *Electrochimica Acta* **1990,** *35* (1), 239-244.

44. Shono, T.; Ishifune, M.; Okada, T.; Kashimura, S., Electroorganic chemistry. 130. A novel trifluoromethylation of aldehydes and ketones promoted by an electrogenerated base. *The Journal of Organic Chemistry* **1991,** *56* (1), 2-4.

45. Chiarotto, I.; Feroci, M.; Orsini, M.; Sotgiu, G.; Inesi, A., Electrogenerated N-heterocyclic carbenes: N-functionalization of benzoxazolones. *Tetrahedron* **2009,** *65* (18), 3704-3710.

46. Bornemann, S.; Handy, S. T., Synthetic Organic Electrochemistry in Ionic Liquids: The Viscosity Question. *Molecules* **2011,** *16* (7), 5963-5974.

47. Grills, D. C.; Matsubara, Y.; Kuwahara, Y.; Golisz, S. R.; Kurtz, D. A.; Mello, B. A., Electrocatalytic CO2 Reduction with a Homogeneous Catalyst in Ionic Liquid: High Catalytic Activity at Low Overpotential. *The Journal of Physical Chemistry Letters* **2014,** *5* (11), 2033-2038.

48. Zane, D.; Raffaele, A.; Curulli, A.; Appetecchi, G. B.; Passerini, S., Electrosynthesis of poly(o-phenylenediamine) in a room temperature ionic liquid. *Electrochemistry Communications* **2007,** *9* (8), 2037-2040.

49. Waldvogel, S. R.; Lips, S.; Selt, M.; Riehl, B.; Kampf, C. J., Electrochemical Arylation Reaction. *Chemical Reviews* **2018,** *118* (14), 6706-6765.

50. Yan, M.; Kawamata, Y.; Baran, P. S., Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance. *Chemical Reviews* **2017,** *117* (21), 13230-13319.

51. Dissanayake, D. M. M. M.; Vannucci, A. K., Transition-Metal-Free and Base-Free Electrosynthesis of 1H-Substituted Benzimidazoles. *ACS Sustainable Chemistry & Engineering* **2018,** *6* (1), 690-695.

52. Dissanayake, D. M. M. M.; Vannucci, A. K., Selective N1-Acylation of Indazoles with Acid Anhydrides Using an Electrochemical Approach. *Organic Letters* **2019,** *21* (2), 457-460.

53. Yoshida, J.-i.; Kataoka, K.; Horcajada, R.; Nagaki, A., Modern Strategies in Electroorganic Synthesis. *Chemical Reviews* **2008,** *108* (7), 2265-2299.

54. Yoshida, J.-i.; Shimizu, A.; Hayashi, R., Electrogenerated Cationic Reactive Intermediates: The Pool Method and Further Advances. *Chemical Reviews* **2018,** *118* (9), 4702-4730.

55. Ma, C.; Fang, P.; Mei, T.-S., Recent Advances in C–H Functionalization Using Electrochemical Transition Metal Catalysis. *ACS Catalysis* **2018,** *8* (8), 7179-7189.

56. Lund, H., A century of organic electrochemistry. *Journal of The Electrochemical Society* **2002,** *149* (4), S21-S33.

57. Cottrell, F., Application of the Cottrell equation to chronoamperometry. *Z Physik Chem* **1902,** *42*, 385.

58. Kolbe, H., Beobachtungen über die oxydirende Wirkung des Sauerstoffs, wenn derselbe mit Hülfe einer elektrischen Säule entwickelt wird. *Journal für Praktische Chemie* **1847,** *41* (1), 137-139.

59. Morton, A. A.; Davidson, J. B.; Newey, H. A., Condensations by Sodium. XXII. The General Theory of the Wurtz Reaction. The Initial Step. *Journal of the American Chemical Society* **1942,** *64* (10), 2240-2242.

60. Möhle, S.; Zirbes, M.; Rodrigo, E.; Gieshoff, T.; Wiebe, A.; Waldvogel, S. R., Modern Electrochemical Aspects for the Synthesis of Value-Added Organic Products. *Angewandte Chemie International Edition* **2018,** *57* (21), 6018-6041.

61. Lebreux, F.; Buzzo, F.; Markó, I. E., Synthesis of Five- and Six-Membered-Ring Compounds by Environmentally Friendly Radical Cyclizations Using Kolbe Electrolysis. *Synlett* **2008,** *2008* (18), 2815-2820.

62. Groult, H.; Leroux, F.; Tressaud, A., *Modern Synthesis Processes and Reactivity of Fluorinated Compounds: Progress in Fluorine Science*. Elsevier: 2016.

63. Sartori, P.; Ignat'ev, N., The actual state of our knowledge about mechanism of electrochemical fluorination in anhydrous hydrogen fluoride (Simons process). *Journal of Fluorine Chemistry* **1998,** *87* (2), 157-162.

64. Botte, G. G., Electrochemical manufacturing in the chemical industry. *The Electrochemical Society Interface* **2014,** *23* (3), 49-55.

65. Seo, E. T.; Nelson, R. F.; Fritsch, J. M.; Marcoux, L. S.; Leedy, D. W.; Adams, R. N., Anodic Oxidation Pathways of Aromatic Amines. Electrochemical and Electron Paramagnetic Resonance Studies. *Journal of the American Chemical Society* **1966,** *88* (15), 3498-3503.

66. Watkins, B. F.; Behling, J. R.; Kariv, E.; Miller, L. L., Chiral electrode. *Journal of the American Chemical Society* **1975,** *97* (12), 3549-3550.

67. Shono, T.; Hamaguchi, H.; Matsumura, Y., Electroorganic chemistry. XX. Anodic oxidation of carbamates. *Journal of the American Chemical Society* **1975,** *97* (15), 4264-4268.

68. Yoshida, J.-i.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K., Direct Oxidative Carbon−Carbon Bond Formation Using the "Cation Pool" Method. 1. Generation of Iminium Cation Pools and Their Reaction with Carbon Nucleophiles. *Journal of the American Chemical Society* **1999,** *121* (41), 9546-9549.

69. Hayashi, R.; Shimizu, A.; Yoshida, J.-i., The Stabilized Cation Pool Method: Metal- and Oxidant-Free Benzylic C–H/Aromatic C–H Cross-Coupling. *Journal of the American Chemical Society* **2016,** *138* (27), 8400-8403.

70. Ashikari, Y.; Nokami, T.; Yoshida, J.-i., Integrated Electrochemical–Chemical Oxidation Mediated by Alkoxysulfonium Ions. *Journal of the American Chemical Society* **2011,** *133* (31), 11840-11843.

71. Suga, S.; Okajima, M.; Yoshida, J.-i., Reaction of an electrogenerated 'iminium cation pool'with organometallic reagents. Direct oxidative α-alkylation and-arylation of amine derivatives. *Tetrahedron Letters* **2001,** *42* (11), 2173-2176.

72. Kataoka, K.; Hagiwara, Y.; Midorikawa, K.; Suga, S.; Yoshida, J.-i., Practical Electrochemical Iodination of Aromatic Compounds. *Organic Process Research & Development* **2008,** *12* (6), 1130-1136.

73. Yoshida, J.-i., Flash chemistry using electrochemical method and microsystems. *Chemical Communications* **2005,** (36), 4509-4516.

74. Suga, S.; Suzuki, S.; Yamamoto, A.; Yoshida, J.-i., Electrooxidative Generation and Accumulation of Alkoxycarbenium Ions and Their Reactions with Carbon Nucleophiles. *Journal of the American Chemical Society* **2000,** *122* (41), 10244-10245.

75. Nokami, T.; Watanabe, T.; Musya, N.; Morofuji, T.; Tahara, K.; Tobe, Y.; Yoshida, J.-i., Direct dendronization of polystyrenes using dendritic diarylcarbenium ion pools. *Chemical Communications* **2011,** *47* (19), 5575-5577.

76. Nokami, T.; Shibuya, A.; Tsuyama, H.; Suga, S.; Bowers, A. A.; Crich, D.; Yoshida, J.-i., Electrochemical Generation of Glycosyl Triflate Pools. *Journal of the American Chemical Society* **2007,** *129* (35), 10922-10928.

77. Nokami, T.; Soma, R.; Yamamoto, Y.; Kamei, T.; Itami, K.; Yoshida, J.-i., Generation of pyridyl coordinated organosilicon cation pool by oxidative Si-Si bond dissociation. *Beilstein Journal of Organic Chemistry* **2007,** *3*, 7.

78. Ashikari, Y.; Shimizu, A.; Nokami, T.; Yoshida, J.-i., Halogen and Chalcogen Cation Pools Stabilized by DMSO. Versatile Reagents for Alkene Difunctionalization. *Journal of the American Chemical Society* **2013,** *135* (43), 16070-16073.

79. Morofuji, T.; Shimizu, A.; Yoshida, J.-i., Metal- and Chemical-Oxidant-Free C□H/C□H Cross-Coupling of Aromatic Compounds: The Use of Radical-Cation Pools. *Angewandte Chemie* **2012,** *124* (29), 7371-7374.

80. Matsumoto, K.; Kozuki, Y.; Ashikari, Y.; Suga, S.; Kashimura, S.; Yoshida, J.-i., Electrophilic substitution reactions using an electrogenerated ArS(ArSSAr)+ cation pool as an ArS+ equivalent. *Tetrahedron Letters* **2012,** *53* (15), 1916-1919.

81. Kärkäs, M. D., Electrochemical strategies for C–H functionalization and C–N bond formation. *Chemical Society Reviews* **2018,** *47* (15), 5786-5865.

82. Suga, S.; Nagaki, A.; Yoshida, J.-i., Highly selective Friedel–Crafts monoalkylation using micromixing. *Chemical Communications* **2003,** (3), 354-355.

83. Suga, S.; Suzuki, S.; Yoshida, J.-i., Reduction of a "Cation Pool": A New Approach to Radical Mediated C−C Bond Formation. *Journal of the American Chemical Society* **2002,** *124* (1), 30-31.

84. Morofuji, T.; Shimizu, A.; Yoshida, J.-i., Electrochemical C–H Amination: Synthesis of Aromatic Primary Amines via N-Arylpyridinium Ions. *Journal of the American Chemical Society* **2013,** *135* (13), 5000-5003.

85. Morofuji, T.; Shimizu, A.; Yoshida, J.-i., Direct C–N Coupling of Imidazoles with Aromatic and Benzylic Compounds via Electrooxidative C–H Functionalization. *Journal of the American Chemical Society* **2014,** *136* (12), 4496-4499.

86. Morofuji, T.; Shimizu, A.; Yoshida, J.-i., Electrochemical Intramolecular C□H Amination: Synthesis of Benzoxazoles and Benzothiazoles. *Chemistry – A European Journal* **2015,** *21* (8), 3211-3214.

87. Morofuji, T.; Shimizu, A.; Yoshida, J.-i., Heterocyclization Approach for Electrooxidative Coupling of Functional Primary Alkylamines with Aromatics. *Journal of the American Chemical Society* **2015,** *137* (31), 9816-9819.

88. Herold, S.; Möhle, S.; Zirbes, M.; Richter, F.; Nefzger, H.; Waldvogel, S. R., Electrochemical Amination of Less-Activated Alkylated Arenes Using Boron-Doped Diamond Anodes. *European Journal of Organic Chemistry* **2016,** *2016* (7), 1274-1278.

89. Möhle, S.; Herold, S.; Richter, F.; Nefzger, H.; Waldvogel, S. R., Twofold Electrochemical Amination of Naphthalene and Related Arenes. *ChemElectroChem* **2017,** *4* (9), 2196-2210.

90. Xu, H.-C.; Moeller, K. D., Intramolecular Anodic Olefin Coupling Reactions and the Synthesis of Cyclic Amines. *Journal of the American Chemical Society* **2010,** *132* (8), 2839-2844.

91. Xu, H.-C.; Campbell, J. M.; Moeller, K. D., Cyclization Reactions of Anode-Generated Amidyl Radicals. *The Journal of Organic Chemistry* **2014,** *79* (1), 379-391.

92. Liang, S.; Zeng, C.-C.; Luo, X.-G.; Ren, F.-z.; Tian, H.-Y.; Sun, B.-G.; Little, R. D., Electrochemically catalyzed amino-oxygenation of styrenes: n-Bu4NI induced C–N followed by a C–O bond formation cascade for the synthesis of indolines. *Green Chemistry* **2016,** *18* (7), 2222-2230.

93. Eberson, L.; Schäfer, H., Organic electrochemistry. In *Organic Electrochemistry*, Springer: 1971; pp 1-182.

94. Barton, D. H. R.; McCombie, S. W., A new method for the deoxygenation of secondary alcohols. *Journal of the Chemical Society, Perkin Transactions 1* **1975,** (16), 1574-1585.

95. Koyanagi, T.; Herath, A.; Chong, A.; Ratnikov, M.; Valiere, A.; Chang, J.; Molteni, V.; Loren, J., One-Pot Electrochemical Nickel-Catalyzed Decarboxylative Sp2–Sp3 Cross-Coupling. *Organic Letters* **2019,** *21* (3), 816-820.

96. Perkins, R. J.; Pedro, D. J.; Hansen, E. C., Electrochemical Nickel Catalysis for Sp2-Sp3 Cross-Electrophile Coupling Reactions of Unactivated Alkyl Halides. *Organic Letters* **2017,** *19* (14), 3755-3758.

97. Li, C.; Kawamata, Y.; Nakamura, H.; Vantourout, J. C.; Liu, Z.; Hou, Q.; Bao, D.; Starr, J. T.; Chen, J.; Yan, M.; Baran, P. S., Electrochemically Enabled, Nickel-Catalyzed Amination. *Angewandte Chemie International Edition* **2017,** *56* (42), 13088-13093.

98. Sabatini, M. T.; Boulton, L. T.; Sneddon, H. F.; Sheppard, T. D., A green chemistry perspective on catalytic amide bond formation. *Nature Catalysis* **2019,** *2* (1), 10-17.

99. Louillat, M.-L.; Patureau, F. W., Oxidative C–H amination reactions. *Chemical Society Reviews* **2014,** *43* (3), 901-910.

100. Chang, X.; Zhang, Q.; Guo, C., Electrochemical Reductive Smiles Rearrangement for C–N Bond Formation. *Organic Letters* **2019,** *21* (1), 10-13.

101. Xia, S.; Wang, L.-Y.; Zuo, H.; Li, Z.-B., Smiles Rearrangement in Synthetic Chemistry. *Current Organic Synthesis* **2013,** *10* (6), 935-946.

102. Iversen, P. E.; Lund, H., Electrolytic generation of strong bases I. Wittig reaction. *Tetrahedron Letters* **1969,** *10* (40), 3523-3524.

103. Shono, T.; Mitani, M., Organic synthesis by electrolysis. I. Electrolytic formation of phosphonium ylides. *Journal of the American Chemical Society* **1968,** *90* (10), 2728-2729.

104. Sotgiu, G.; Chiarotto, I.; Feroci, M.; Orsini, M.; Rossi, L.; Inesi, A., An electrochemical alternative strategy to the synthesis of β-lactams: Part 3 [1]. Room-temperature ionic liquids vs molecular organic solvents. *Electrochimica Acta* **2008,** *53* (27), 7852-7858.

105. Palombi, L.; Feroci, M.; Orsini, M.; Inesi, A., An innovative strategy for electrochemically-promoted addition reactions. *Chemical Communications* **2004,** (16), 1846-1847.

106. Jamshidi, M.; Nematollahi, D.; Taheri, F.; Alizadeh, H., Paired Electrochemical Method for Synthesis of New Phenylcarbonimidoyl Dicyanide Dyes. *ACS Sustainable Chemistry & Engineering* **2019,** *7* (2), 1956-1962.

CHAPTER 2

TRANSITION METAL FREE AND BASE FREE ELECTROSYNTHESIS OF 1-H SUBSTITUTED BENZIMIDAZOLES

[*] Dissanayake, D. M. M. M.; Vannucci, A.K.; "Transition-Metal-Free and Base-Free Electrosynthesis of 1*H*-Substituted Benzimidazoles." *ACS Sustain. Chem.* 2018, 6, 690-695.

2.1 Abstract

A direct electrochemical synthesis of 1*H*-substituted benzimidazoles is described. Benzimidazole is a commonly used nitrogen heterocycle in U.S. FDA approved drugs, therefore a direct, and sustainable approach that limits chemical waste for the synthesis of substituted benzimidazoles is appealing. The electrosynthetic approach described within is able to synthesize a variety of 1*H*-substitubed benzimidazoles while concurrently producing H_2, without a transition metal catalyst or added bases. Furthermore, the procedure works efficiently with only simple carbon electrodes, thus avoiding commonly employed platinum and gold electrodes. This electrochemical procedure also exhibited good functional group tolerance. Desired products were achieved with up to 88% yield, illustrating the range and possible sustainability of this approach.

2.2 Introduction

Nitrogen heterocycles and their derivatives are significantly widespread as structural units of many medicinally important compounds as well as compounds of interest for material sciences.[1-2] A broad range of biological activities of benzimidazole are known.[3-6] According to a recent analysis benzimidazole is one of the top 25 of most frequent nitrogen heterocycles in U.S. FDA approved drugs.[7] Moreover, 46 % of U.S. FDA approved pharmaceuticals that contain benzimidazoles are substituted at the 1*H*-position.[7] The substituents may vary from alkyl, benzyl groups to cycloalkyl moieties appropriately substituted with different functionalities as shown in the select drug structures in Figure 2.1. The 1*H*-substituted benzimidazole derivatives are traditionally prepared through either reductive amination[8] or through deprotonation followed by nucleophilic substitution with carbon electrophiles.[9-10]

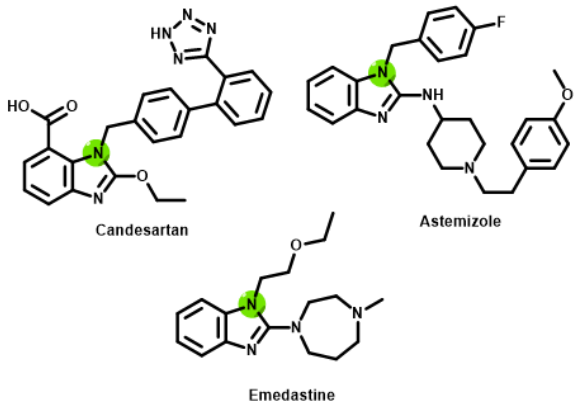


Figure 2. 1. Selected examples of U.S. FDA approved pharmaceuticals containing the benzimidazole moiety. The 1*H*-position has been highlighted.

For the deprotonation synthetic route, the weak acidity of the NH group can necessitate the use of strong bases and elevated reaction temperatures. These harsh conditions can lead to particularly challenging preparations of benzimidazole derivatives that contain base sensitive functionalities. Moreover, competing side reactions of carbon electrophiles, such as dehydrohalogenation, might also limit benzimidazole functionalization. The conventional procedures may also lead to over-alkylation of benzimidazole producing quaternary salts.[11] In addition, stoichiometric quantities of waste are generated from the used base in the reaction.

With respect to the reductive amination route, the generation of a benzimidazole nucleophile with a chemical reductant requires judicial choice of the reductant. The reductant ideally should avoid toxic waste generation or excessive side reactions. Mild chemical reductants may lead to inefficient or a lack of product formation. Conversely, strong chemical reductants often require rare transition metal catalysts for selective product

formation.[12-16] Therefore, the development of effective and sustainable synthetic procedure for the production of benzimidazole derivatives remains highly desirable.

Electrochemistry offers a chemical-reductant-free route to the generation of nucleophilic bases. Electrochemistry replaces possibly toxic chemical redox reagents with electrical current for the *in-situ* generation reactive species.[17-18] The topic of electrogenerated nucleophiles has been reviewed.[19-20] The *in-situ* generation of short-lived nucleophiles from nitrogen heteroaromatics has also been reported.[18, 21] The versatility of electro-organic chemistry is derived from its ability to apply precise electrical potentials to a reaction mixture, therefore, avoiding the problem of over reduction/oxidation that can be incurred during chemically driven redox reactions.[12] This is a helpful feature in developing a chemoselective synthesis with high functional group tolerance.

Electrochemistry has received considerable attention as a tool for incorporation of principles of green chemistry in redesigning conventional synthetic processes to minimize their negative environmental effects.[22-24] Greener synthetic routes are of importance in an era where the manufacture and disposal of synthetic chemicals have impacted the human health and environment considerably.[25] The adoption of this methodology helps in reduction of the cost of raw material as well as the cost of waste disposal.[22] From a process chemistry perspective, eliminating cooling down of reaction vessels is attractive for reducing energy consumption. These attributes comply with the principles of green chemistry, allowing synthetic chemists to carry out reactions in an atom-economic and environmentally friendly manner.[26]

Herein, we report the direct electrochemical functionalization of benzimidazoles. The synthetic process is both transition metal and base-free. The reactions are also carried

out at room temperature and do not require noble metal electrodes. Direct reduction of benzimidazole from reticulated vitreous carbon (RVC) electrodes generates a strong nucleophile capable of reacting with a variety of carbon electrophiles. This process is selective for C–N bond formation at the 1*H*-position of the benzimidazole substrates and over-reduced products were not observed.

2.3 Results and Discussion

Experiments were performed to optimize the yields of derivatized benzimidazole product and minimize the use of corrosive bases and rare metals. We were encouraged by an initial experiment showing that 51% yield could be obtained in a base- and metal-free electrochemical synthesis (Table 2.1, conditions A). This initial controlled potential electrolysis experiment was performed by mixing both benzimidazole and 1-iodohexane in a divided cell containing acetonitrile with 0.1 M tetrabutylammonium hexafluorophosphate electrolyte. Traditional methods for benzimidazole derivatization typically use DMF and DMAc solvents, which are not regarded as safe for pharmaceutical preparations. However, acetonitrile, which is used in this study, has been labeled as safe for pharmaceutical preparations.[27] A potential of -2.4 V vs. NHE was then applied to a RVC working electrode for 7 hours. This potential was chosen because cyclic voltammetry experiments indicated benzimidazole in acetonitrile leads to a cathodic current response above background current near -2.4 V vs. NHE (Figure A.1).

Controlled current electrolysis experiments were also attempted to illustrate the feasibility of using galvanostatic methods for these reactions. Galvanostatic methods are easier to scale up and commonly employed with industrial electrochemical processes.[28] In an undivided cell with a constant current of 5 mA, the reaction shown in Table 1 was

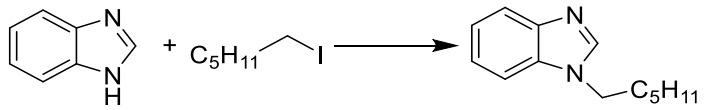
attempted. The yield of desired product for this experiment was only 27%. We hypothesized that the reduced benzimidazole substrates could subsequently be oxidized at the counter electrodes in an undivided cell, thus leading to lower product yields. To test this hypothesis, a controlled current electrolysis at 5 mA was performed in a divided cell. Product yields increased to 68% using the divided cell without optimizing current density. However, due to the IR drop across a fritted cell, the applied potential during this experiment averaged 6.7 V, thus the divided cell expectedly required a greater cell voltage than the undivided cell. Despite the trade-off between product yields and applied cell voltage, these experiments show that galvanostatic methods can be used to synthesize substituted benzimidazoles without transition metal catalysts or added bases. For this study we chose to examine the syntheses using potentiostatic methods to optimize the following two step process and avoid over-reduction of the products and reactants.

The electrosynthetic conditions for controlled potential electrolysis experiments were then altered in an attempt to optimize the yield of the desired product. To prevent direct reduction of the halocarbon substrate, the electrosynthetic procedure was altered. Initial reduction of benzimidazole was performed until the current response dropped to 90% of the initial value. This first-step of the synthesis generates a "pool" of anions, analogous to Yoshida's "cation pool" electrosynthesis procedures.[29] After the initial generation of benzimidazole anions, the electrophilic halocarbon substrate was added to the solution. Removing any applied potential upon halocarbon addition led to even lesser yields (Table 2.1, B). Performing a direct reduction of the benzimidazole at -2.4 V, followed by lowering the applied potential to -1.0 V after halocarbon addition once again led to lower than optimized yields (Table 2.1, C). Performing a direct reduction of the

benzimidazole at -2.4 V, followed by applying a potential of -2.0 V after halocarbon addition, however, increased the yield of desired product to 73% (Table 2.1, D). The hypothesis on why sequential electrode potentials are necessary for optimal yields rests on the stability of the generated benzimidazole anions. Similar to the "cation pool" work, the pool of anions does not appear to be stable in the absence of applied potential. Maintaining an applied potential of -2.4 V results in direct reduction of the added electrophile and prevents the desired reaction. Thus our optimization tests showed that an applied potential of -2.0 V is capable of keeping the anion pool stabilized and minimizing reduction of the halogenated substrates.

A constant applied potential of -2.0 V over the course of the entire 7-hour electrolysis, however, led to only 8% yield (Table 2.1, E). This lower yield is likely due to incomplete reduction of the benzimidazole substrate. Removing all applied potential led to 0% yield. Furthermore, replacing the carbon counter electrode with a Pt coil did not have an effect on the overall yield of the desired product, as can be seen in Table 2.1, G. This result shows that expensive, rare metal electrodes are not required to promote product formation. Adding a large excess of 1-iodohexane, in an attempt to increase the efficiency of the organic reaction, actually lead to a decrease in desired product. Furthermore, setting up the reaction without exclusion of water or air using conditions D once again lead to 70% product yield. The reaction, however, required four more hours of electrolysis to obtain comparable yields and nearly double the amount of charge was passed, likely due to O_2 reduction at the working electrode. Lastly, different solvents were examined. Using the solvents tetrahydrofuran, dimethylformamide, or dichloromethane instead of the chosen solvent acetonitrile all led to yields of less than 20%.

Table 2.1. Optimization of the electrochemical alkylation reaction



	Initial Potential	2nd Potential	Electrode	% Yield
A	-2.4 V	-2.4 V	Carbon	51
B	-2.4 V	0.0 V	Carbon	23
C	-2.4 V	-1.0 V	Carbon	32
D	-2.4 V	-2.0V	Carbon	73
E	-2.0 V	-2.0 V	Carbon	8
F	0.0 V	0.0 V	Carbon	0
G	-2.4 V	-2.0 V	Platinum	72

All reactions performed at room temperature under conditions mentioned in experimental section unless otherwise stated.

For reductive electrosynthesis to occur at the cathode, a chemical must be oxidized at the anode. In the absence of an added sacrificial chemical, the solvent or electrolyte may be oxidized at the anode. Reactions were also carried out to examine the ability to examine the extent of solvent/electrolyte consumption, otherwise stated as the ability to recycle the electrolyte and solvent for multiple reactions. Conditions D were used to carry out the reaction illustrated in Table 2.1. After the reaction was completed, acetonitrile was removed from the reaction mixture via vacuum distillation. The product was then extracted from the supporting electrolyte at 74% yield in a minimal amount of diethyl ether. Following product extraction, excess ether was used to crystallize the electrolyte. The

electrolyte was then filtered and dried and recovered with an 85% recovery yield. The recovered acetonitrile and electrolyte were then used to perform a second reaction. Following the exact procedure just discussed, the second experiment containing recycled electrolyte and solvent resulted in a 72% yield of the desired benzimidazole product. A second recovery of the starting materials led to a 78% recovery of the electrolyte. These results show that electrolyte appears to be consumed during the reaction, but that optimal product yields can still be obtained with recycled solvent and electrolyte.

To avoid electrolyte consumption, 10 μL of water was added to the reaction mixture to act as a sacrificial reductant. With added water, 70% yield for the desired product was still obtained, showing that these reactions are not moisture sensitive. More importantly, water oxidation can account for the anodic reactions, thus minimizing the electrolyte consumption. For traditional base catalyzed reactions, at least one mole of base must be consumed per reaction with or without added water. Thus, for the minimal consumption of water/electrolyte this approach can synthesize high value benzimidazole products.

Having established optimized conditions, the focus was laid on determining the versatility of this approach through expanding the substrate scope. Initial explorations focused on the reactivity between the 1*H*-position of benzimidazoles and various halocarbons. Table 2.2 summarizes the results for a variety of primary and secondary alkyl halides. Electrochemical coupling between benzimidazole and primary alkyl halides was generally efficient. Straight chain halocarbons containing both electron donating and withdrawing groups all resulted in good yields (Table 2.2, **1**-**3**). The presence of ester functionalities resulted in lower yields (**4** and **5**), however, this electrochemical approach was tolerant of alkene functional groups with yields up 73% (reactions **6**, **7**, and **11**). The

reaction between benzimidazole and an alkyl halide containing a heterocycle was also successful (reaction **8**).

Faradaic efficiencies for the reaction trended with the product yields. For example, the Faradaic yield of reaction 1 was 81%, while the Faradic yield for reaction 9 was 25%. This trend implies the reaction mechanism in Figure 2.2. Complete reduction of the benzimidazole substrates occurs with high Faradaic efficiencies, however, the subsequent organic reactions are not completely efficient and both product yield and Faradaic yield are effected by the limited organic reactivity.

Reactions involving secondary alkyl bromides were generally less efficient when compared to primary alkyl halides, as can be seen by the yields of reactions 9 and 10. The reaction between 3-bromocyclohexene and benzimidazole, however, resulted in a good 59% yield. Addition of a secondary benzylic carbon to benzimidazole, reaction 12, also resulted in a 58% yield. As shown in Figure 2.1, there are multiple examples of pharmaceutical products which involve benzylic functionalization of the 1*H*-position of benzimidazoles.

No observable products were obtained when using tertiary carbon electrophiles. The lack of reactivity with sterically hindered carbon electrophiles supports a general S_N2 nucleophilic substitution mechanism, as illustrated in Figure 2.2. The electrochemically generated benzimidazole nucleophile, in the second step, reacts with the carbon electrophile without prior dissociation of the halide atom. A related mechanism has been proposed for the N-functionalization of benzoxazolones.[18] In the first step, electrochemical reduction of benzimidazole generates an anionic benzimidazole product and one-half equivalence of molecular hydrogen. Evidence to support this step was achieved by

performing an electrolysis in a tightly sealed cell, followed by analysis of the headspace using gas chromatography. Post-reaction a peak was observed in the gas chromatograph at the retention time expected for H_2 when compared to standards. This peak was absent from the headspace gas before the reaction was performed. This result indicates that this procedure is able to concurrently produce both substituted benzimidazoles and H_2.

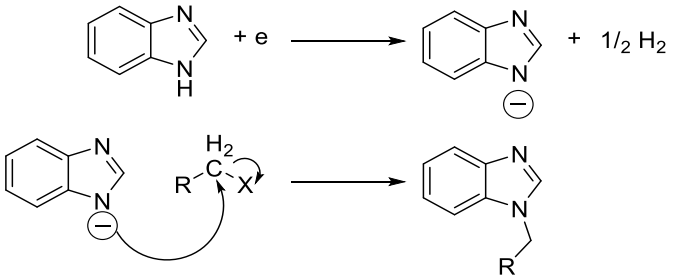
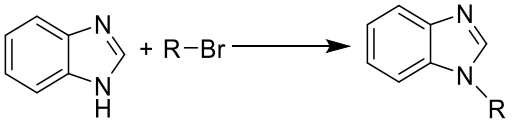
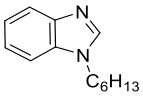
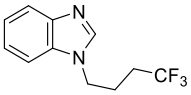
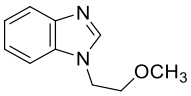
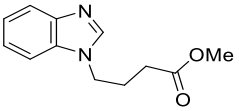
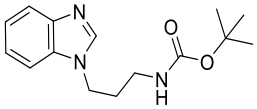
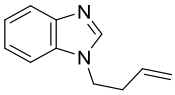
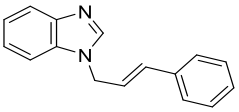
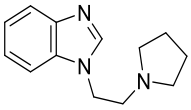
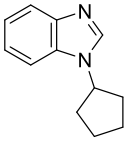
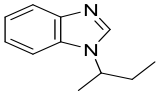
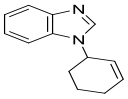
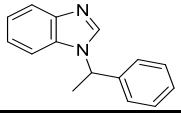


Figure 2.2. Possible mechanism for the functionalization of the 1*H*-position of electrochemically generated benzimidazole nucleophiles.

Further exploration on the reactivity of benzylic halides with benzimidazoles was undertaken due to their prevalence in medicinal compounds. Numerous protocols for the synthesis of benzyl benzimidazoles have been developed, which typically require the use of excess base and elevated temperatures.[30-33] Further, some reports indicate that debenzylation can lead to loss of products under similar conditions in the presence of a base.[34-35] Other catalytic procedures for the synthesis of benzyl benzimidazoles require transition metal catalysts.[11, 15, 36-37] A base-free and transition metal-free procedure, however, has yet to be reported.

Table 2.2. Electrochemical coupling of benzimidazole with alkyl bromides.



#	Product	% Yield
1		76
2		61
3		68
4		32
5		22
6		73
7		47
8		46
9		21
10		10
11		59
12		58

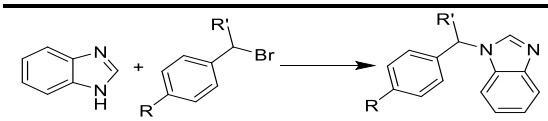
All reactions performed at room temperature under conditions mentioned in Section 2.6

Table 2.3 summarizes the yields obtained from our electrochemical approach to benzylic functionalization of the 1*H*-position of benzimidazoles. The results indicate that this procedure works well with benzylic halides under ambient conditions. Notably, this method is tolerant of easily reducible substituents such as nitro and cyano functionalities, Table 2.3, reactions **15** and **16**, and furnishes the desired products in comparable yields to literature reports.[15] Furthermore, the reaction is selective for benzylic halides over aryl halides as shown with the 66% yield for reaction **14**. No reaction was observed between aryl halides and benzimidazoles. This observed selectivity is an advantage of this electrochemical approach over transition metal based coupling between halocarbons and benzimidazoles. Reaction **17** resulted in an excellent yield, indicating this approach is most efficient with electron deficient benzylic substrates. This approach was also successful in coupling an acyl chloride with benzimidazole (reaction **18**). Both traditional and organocatalytic strategies for acylation of benzimidazole with carboxylic acids require stoichiometric quantities of activating reagents.[38-40] Therefore, this reported strategy introduces a sustainable and broadly applicable approach for such syntheses.

To further demonstrate the utility of this method, a variety of benzimidazoles were also probed. As can be seen from Table 2.4, benzimidazoles with mercapto and pyridyl substitutions are the 2-position were efficient substrates for reactions with alkyl halides (reactions 19-22). Benzimidazoles such as 2-mercapto benzimidazole and 2-(2-pyridyl) benzimidazole, are reported to exhibit biological activity.[41-42] Reaction 23 further illustrates the selectivity of this approach for reactivity of benzylic halides over aryl halides. Functionalization of the 1*H*-position of 5(6)-bromo-1*H*-benzimidazole was achieved with 72% yield. It is worth noting that the 6-bromo product is illustrated in Table

2.4, though the 5-bromo tautomer likely also is present. Tautomerism of benzimidazoles has been observed.[43] By retaining the bromide at the 6-position this electrochemical approach has synthesized a product which can undergo further, selective functionalization of the benzimidazole. This selectivity helps limit the number of chemical steps to form complex molecules, hence reducing waste and energy input.

Table 2.3. Reactions between benzimidazole and benzylic or acyl halides



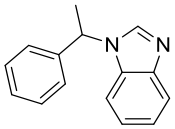
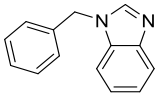
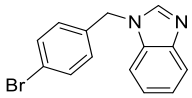
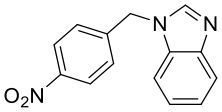
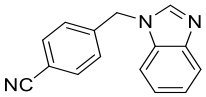
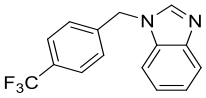
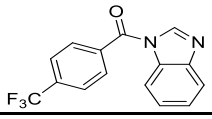
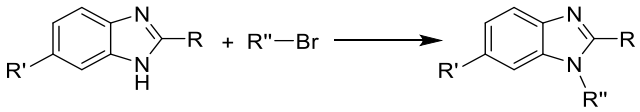
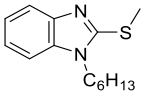
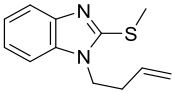
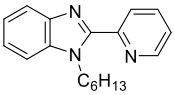
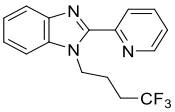
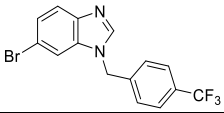
#	Product	% Yield
12		58
13		44
14		66
15		69
16		50
17		88
18		46

Table 2.4. Reactions between halocarbons and substituted benzimidazoles.



#	Product	% Yield
19		75
20		68
21		75
22		64
23		72

. To further demonstrate the utility of this method, a variety of benzimidazoles were also probed. As can be seen from Table 2.4, benzimidazoles with mercapto and pyridyl substitutions are the 2-position were efficient substrates for reactions with alkyl halides (reactions 19-22). Benzimidazoles such as 2-mercapto benzimidazole and 2-(2-pyridyl) benzimidazole, are reported to exhibit biological activity.[41-42] Reaction 23 further illustrates the selectivity of this approach for reactivity of benzylic halides over aryl halides. Functionalization of the 1*H*-position of 5(6)-bromo-1*H*-benzimidazole was achieved with 72% yield. It is worth noting that the 6-bromo product is illustrated in Table 2.4, though the 5-bromo tautomer likely also is present. Tautomerism of benzimidazoles

has been observed.[43] By retaining the bromide at the 6-position this electrochemical approach has synthesized a product which can undergo further, selective functionalization of the benzimidazole. This selectivity helps limit the number of chemical steps to form complex molecules, hence reducing waste and energy input.

2.4 Conclusion

In conclusion, an electrochemical procedure for the functionalization of the 1*H*-position of benzimidazoles has been developed. Using electrochemical methods for this synthesis also leads to the co-production of molecular hydrogen, which is a renewable fuel and widely useful in chemical industry. This procedure achieved efficient reactivity while not using transition metal catalysts or added bases. In addition, there is no loss in reactivity when only carbon electrodes are used in place of expensive platinum electrodes. This procedure is applicable for both various classes of electrophiles as well as unsubstituted and substituted benzimidazoles. Overall good functional group tolerance was also achieved. Lastly, the selectivity of the procedure for reactions with alkyl halides over aryl halides was exploited to produce unique compounds capable of facile, further functionalization.

2.5 Experimental

Materials

Anhydrous acetonitrile (MeCN) 99.8%, water ≤ 50 ppm) was used for all reactions. All solutions used for electrochemical measurements contained 0.1 M tetrabutylammonium hexafluorophosphate ($TBAPF_6$) further purified by recrystallization from ethanol and dried under vacuum at 80 ºC for 24 hours.

General procedure for electro-synthetic experiments.

Isolated product yields are reported for preparations setup inside a N_2-filled glove box to confirm inert atmosphere, though reactions set up on the bench top were able to obtain comparable product yields with decreased Faradaic efficiencies due to O_2 reduction. Preparative electrolytic studies were carried out in a divided cell that contained an anode in a secondary container separated from the cathodic area by a glass frit. High surface area RVC electrodes were used for both the working and counter electrodes. The reference electrode used was a saturated calomel electrode (SCE). All potentials are reported versus NHE (SCE +0.24 V vs. NHE). The solution was continuously stirred at 400 rpm during the experiment.

During the electrolysis experiments, a 0.1 M solution of $TBAPF_6$ in anhydrous acetonitrile solvent containing 0.5 mmol of benzimidazole was initially reduced at -2.4 V vs NHE. After the current has dropped by 90%, the electrophile was added. After addition of the electrophiles, the reaction potential was lowered to -2.0 V vs NHE. After electrolysis, the solvent was evaporated off and organic contents were extracted into ether and purified by preparative thin layer chromatography. Gas chromatography measurements were taken with an HP 5890 Series II gas chromatograph equipped with a Carboxen 1010 PLOT capillary column and a thermal conductivity detector using Ar as the carrier gas. The oven temperature was held constant at 70 ºC.

2.6 References

1. Park, Y.; Kim, Y.; Chang, S., Transition Metal-Catalyzed C–H Amination: Scope, Mechanism, and Applications. *Chem. Rev.* **2017,** *117*, 9247-9301.

2. Waldman, A. J.; Ng, T. L.; Wang, P.; Balskus, E. P., Heteroatom-Heteroatom Bond Formation in Natural Product Biosynthesis. *Chem. Rev.* **2017,** *117*, 5784-5863.

3. Gaba, M.; Singh, S.; Mohan, C., Benzimidazole: an emerging scaffold for analgesic and anti-inflammatory agents. *Eur. J. Med. Chem.* **2014,** *76*, 494-505.

4. Keri, R. S.; Hiremathad, A.; Budagumpi, S.; Nagaraja, B. M., Comprehensive Review in Current Developments of Benzimidazole-Based Medicinal Chemistry. *Chem. Biol. Drug Des.* **2015,** *86*, 19-65.

5. Sachs, G.; Shin, J. M.; Howden, C. W., Review article: the clinical pharmacology of proton pump inhibitors. *Aliment. Pharmacol. Ther.* **2006,** *23 Suppl 2*, 2-8.

6. Bansal, Y.; Silakari, O., The therapeutic journey of benzimidazoles: a review. *Bioorg. Med. Chem.* **2012,** *20*, 6208-36.

7. Vitaku, E.; Smith, D. T.; Njardarson, J. T., Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. *J. Med. Chem.* **2014,** *57*, 10257-74.

8. Abdel-Magid, A. F.; Mehrman, S. J., A review on the use of sodium triacetoxyborohydride in the reductive amination of ketones and aldehydes. *Org. Process Res. Dev.* **2006,** *10*, 971-1031.

9. Al-Azmi, A.; George, P.; El-Dusouqui, O. M., Alkylation of azoles: Synthesis of new heterocyclic-based AT1-non-peptide angiotensin (II) receptor antagonists. *J. Heterocyclic Chem.* **2007,** *44*, 515-520.

10. Begtrup, M.; Larsen, P., Alkylation, Acylation and Silylation of Azoles. *Acta Chem. Scand.* **1990,** *44*, 1050-1057.

11. Chen, Z.; Li, H.; Cao, G.; Xu, J.; Miao, M.; Ren, H., Copper-Catalyzed Double C–N Bond Formation for the Synthesis of Diverse Benzimidazoles from N-Alkyl-2-iodoaniline and Sodium Azide. *Synlett* **2017,** *28*, 504-508.

12. Robinson, B., The reduction of indoles and related compounds. *Chem. Rev.* **1969,** *69*, 785-97.

13. Liu, Q. X.; Zhao, X. J.; Wu, X. M.; Guo, J. H.; Wang, X. G., New mercury(II) and silver(I) complexes containing NHC metallacrown ethers with the pi-pi stacking interactions. *J. Organomet. Chem.* **2007,** *692*, 5671-5679.

14. Sevov, C. S.; Zhou, J. S.; Hartwig, J. F., Iridium-catalyzed, intermolecular hydroamination of unactivated alkenes with indoles. *J. Am. Chem. Soc.* **2014,** *136*, 3200-7.

15. Xia, Q.; Chen, W.; Qiu, H., Direct C-N coupling of imidazoles and benzylic compounds via iron-catalyzed oxidative activation of C-H bonds. *J. Org. Chem.* **2011,** *76*, 7577-82.

16. Xue, Q.; Xie, J.; Li, H.; Cheng, Y.; Zhu, C., Metal-free, highly efficient organocatalytic amination of benzylic C-H bonds. *Chem. Commun.* **2013,** *49*, 3700-2.

17. Francke, R.; Little, R. D., Redox catalysis in organic electrosynthesis: basic principles and recent developments. *Chem. Soc. Rev.* **2014,** *43*, 2492-521.

18. Chiarotto, I.; Feroci, M.; Orsini, M.; Sotgiu, G.; Inesi, A., Electrogenerated N-heterocyclic carbenes: N-functionalization of benzoxazolones. *Tetrahedron* **2009,** *65* (18), 3704-3710.

19. Utley, J. H. P., Electrogenerated Bases. *Top. Curr. Chem.* **1987,** *142*, 131-165.

20. Hammerich, O.; Speiser, B., *Organic Electrochemistry Revised and Expanded*. 5th ed.; CRC Press: Boca Raton, FL, 2015.

21. Utley, J. H. P.; Nielsen, M. F.; Wyatt, P. B., Electrogenerated Bases and Nucleophiles. In *Organic Electrochemistry*, 5th ed.; Hammerich, O.; Speiser, B., Eds. CRC Press: Boca Raton, 2015; pp 1625-1656.

22. Frontana-Uribe, B. A.; Little, R. D.; Ibanez, J. G.; Palma, A.; Vasquez-Medrano, R., Organic electrosynthesis: a promising green methodology in organic chemistry. *Green Chem.* **2010,** *12*, 2099-2119.

23. Schafer, H. J., Contributions of organic electrosynthesis to green chemistry. *Comptes Rendus Chimie* **2011,** *14*, 745-765.

24. Horn, E. J.; Rosen, B. R.; Baran, P. S., Synthetic Organic Electrochemistry: An Enabling and Innately Sustainable Method. *ACS Cent Sci* **2016,** *2*, 302-8.

25. Vaughn, B.; Winquist, A.; Steenland, K., Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. *Environ. Health Perspect.* **2013,** *121*, 1313.

26. Bryan, M. C.; Dillon, B.; Hamann, L. G.; Hughes, G. J.; Kopach, M. E.; Peterson, E. A.; Pourashraf, M.; Raheem, I.; Richardson, P.; Richter, D.; Sneddon, H. F., Sustainable practices in medicinal chemistry: current state and future directions. *J. Med. Chem.* **2013,** *56*, 6007-21.

27. Jessop, P. G., Searching for green solvents. *Green Chemistry* **2011,** *13* (6), 1391-1398.

28. *Encyclopedia of Applied Electrochemistry*. 1 ed.; Springer-Verlag: New York, New York, 2014.

29. Yoshida, J.-i.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K., Direct Oxidative Carbon−Carbon Bond Formation Using the "Cation Pool" Method. 1. Generation of Iminium Cation Pools and Their Reaction with Carbon Nucleophiles. *Journal of the American Chemical Society* **1999,** *121* (41), 9546-9549.

30. Lygin, A. V.; de Meijere, A., Synthesis of 1-Substituted Benzimidazoles from o-Bromophenyl Isocyanide and Amines. *Eur. J. Org. Chem.* **2009,** *2009*, 5138-5141.

31. Meng, X.; Li, X. L.; Chen, W. L.; Zhang, Y. Q.; Wang, W.; Chen, J. Y.; Song, J. L.; Feng, H. J.; Feng, B. H., Facile One-Pot Synthesis of N-Alkylated Benzimidazole and Benzotriazole from Carbonyl Compounds. *J. Heterocyclic Chem.* **2014,** *51*, 349-356.

32. Mochona, B.; Le, L.; Gangapuram, M.; Mateeva, N.; Ardley, T.; Redda, K. K., Synthesis of 2-(N-benzylpyrrolyl)-benzimidazoles using polyphosphoric acid prompted cyclocondensation. *J. Heterocyclic Chem.* **2010,** *47*, 1367-1371.

33. Zhao, Z. R.; Peng, Y. S.; Dalley, N. K.; Cannon, J. F.; Peterson, M. A., Bergman cycloaromatization of imidazole-fused enediynes: the remarkable effect of N-aryl substitution. *Tetrahedron Lett.* **2004,** *45* (18), 3621-3624.

34. Rombouts, F.; Franken, D.; Martinez-Lamenca, C.; Braeken, M.; Zavattaro, C.; Chen, J. S.; Trabanco, A. A., Microwave-assisted N-debenzylation of amides with triflic acid. *Tetrahedron Lett.* **2010,** *51*, 4815-4818.

35. Haddach, A. A.; Kelleman, A.; Deaton-Rewolinski, M. V., An efficient method for the N-debenzylation of aromatic heterocycles. *Tetrahedron Lett.* **2002,** *43*, 399-402.

36. Saidulu, G.; Kumar, R. A.; Reddy, K. R., Iron-catalyzed C-N bond formation via oxidative C-sp3-H bond functionalization adjacent to nitrogen in amides and anilines: Synthesis of N-alkyl and N-benzyl azoles. *Tetrahedron Lett.* **2015,** *56*, 4200-4203.

37. Zhu, K.; Hao, J.-H.; Zhang, C.-P.; Zhang, J.; Feng, Y.; Qin, H.-L., Diversified facile synthesis of benzimidazoles, quinazolin-4 (3 H)-ones and 1, 4-benzodiazepine-2, 5-diones via palladium-catalyzed transfer hydrogenation/condensation cascade of nitro arenes under microwave irradiation. *RSC Adv.* **2015,** *5*, 11132-11135.

38. Ding, W.; Song, Q. L., Cu-catalyzed aerobic oxidative amidation of aryl alkyl ketones with azoles to afford tertiary amides via selective C-C bond cleavage. *Org Chem Front* **2015,** *2*, 765-770.

39. Kim, M.; Han, K. J., Convenient Synthesis of N-Hydroxysuccinimide Esters from Carboxylic Acids Using Triphosgene. *Synth. Commun.* **2009,** *39*, 4467-4472.

40. Tan, B.; Toda, N.; Barbas, C. F., 3rd, Organocatalytic amidation and esterification of aldehydes with activating reagents by a cross-coupling strategy. *Angew. Chem. Int. Ed.* **2012,** *51*, 12538-41.

41. Rao, S. S.; Reddy, C. V. R.; Dubey, P. K., A Green Approach for the Synthesis of 1-Methyl-2-(alkylthio)-1H-benzimidazoles. *Asian J. Chem.* **2014,** *26*, 5995-5997.

42. Hasty, S. J.; Bandara, M. D.; Rath, N. P.; Demchenko, A. V., S-Benzimidazolyl (SBiz) Imidates as a Platform for Oligosaccharide Synthesis via Active-Latent, Armed-Disarmed, Selective, and Orthogonal Activations. *J. Org. Chem.* **2017,** *82*, 1904-1911.

43. Ozturk, S.; Akkurt, M.; Kucukbay, H.; Okuyucu, N.; Fun, H.-K., 3,3'-Diethyl-1,1'-butylenedi[5(6)-methylbenzimidazolium] diiodide dihydrate. *Acta Crystallographica Section E* **2003,** *59* (7), o1014-o1016.

CHAPTER 3

SELECTIVE N-1 ACYLATION OF INDAZOLES WITH ACID ANHYDRIDES USING AN ELECTROCHEMICAL APPROACH*

* Dissanayake, D. M. M. M.; Vannucci, A.K.; "Anion Pool Synthesis for Selective Electrosynthesis of 1*H*-Substituted Indazoles." *Org Lett.* **2019,** 21, 2, 457-460.

3.1 Abstract

An electrochemical synthesis method for the selective N1-acylation of indazoles has been developed. The "anion pool" approach electrochemically reduces indazole molecules generating indazole anions and H_2. Acid anhydrides are then introduced to the solution resulting in selective acylation of the N1-position of the indazoles. This procedure can also be applied to the acylation of benzimidazole, indole, and imidazole. The reaction can also be performed using a 9V battery without loss of reaction efficiency.

3.2 Introduction

Nitrogen-containing heterocycles are immensely important building blocks for medicinally important compounds.[1] More specifically, indazole derivatives are prevalent in pharmaceutical research with over 40 new patents being recently filed on biologically interesting indazole compounds.[2] Research has been carried out on the role of indazole as a kinase inhibitor,[3] and examples of indazole-based drugs and drug candidates are shown in Figure 3.1.[4-7] Such drug structures possess various substituents such as alkyl, benzyl and acyl moieties at the *N-1* position. The structurally diverse indazole scaffolds can be synthesized by selectively manipulating the substitution pattern. As a result, methods for the selective functionalization of indazoles are appealing for both industry and academia.

Selective functionalization of indazoles has been previously explored through deprotonation of indazoles with added base, followed by functionalization at the nitrogen positions. The two non-equivalent nitrogen atoms of indazole should portend the ability to form selective products. Early results, however, showed the use of strong bases, such as NaH, to deprotonate indazoles led to a mixture of *N-1* and *N-2* substituted products.[8-9] Selective alkyl functionalization at the *N-2* position has since been achieved using weak non-deprotonating bases to increase the nucleophilicity of the *N-2* position.[9-10] Up to 135:1

selectivity for alkylation of the *N-1* position was also achieved using Cs_2CO_3 base in DMF.[11] Indazoles alkylated at the *N-1* position have also been synthesized via ring forming reactions between 2-halobenzonitriles and N-alkylhydrazines.[12] Recently, hetero-cyclization synthesis has also achieved *N-2* substituted indazoles using a phosphacycle catalyst.[13]

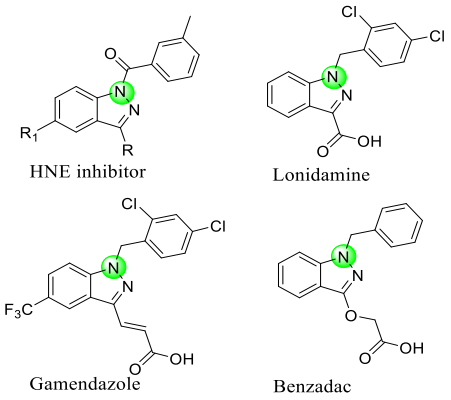


Figure 3.1. Selected examples of U.S. FDA approved pharmaceuticals and molecules under investigation containing the indazole moiety. The *N1*-position has been highlighted.

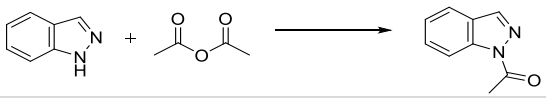
While impressive selectivities for the alkylation of indazoles has been achieved in the aforementioned studies, reports on selective acylation of indazoles are much rarer. Acylation of indoles via acyl group transfer has been extensively investigated.[14-19] However, to the best of our knowledge, just two reports of acyl group transfer to indazoles have been reported.[17, 19] In both reports, a single acylated indazole was reported with yields between 60 – 70% and without mention of reaction selectivity towards the *N-1* position. As can be seen in Figure 3.1, acylated indazoles are drug targets, therefore, the development of a general and efficient method for the selective acylation of indazoles is important.

To address the challenges of general applicability and operational simplicity while achieving reaction efficiency, we have utilized an electrochemical procedure for the chemoselective acylation of indazoles. This electrochemical procedure, called the "anion pool method" was recently developed by our group for the electrochemical synthesis of alkylated benzimidazoles.[20] The anion pool method builds on principles of the previously developed cation pool method,[21] and is base, catalyst, and precious-metal-electrode free . The procedure generally operates via reduction of substrates to form electrogenerated nucleophiles.[22] Electrochemistry allows for precise control of the applied reduction potentials, and the base-free environment makes this procedure applicable to substrates with base sensitive, electron withdrawing and electron donating functional groups. Furthermore, in this base-free environment, acid anhydrides can be used for acylation reactions without being consumed by side reactions. Lastly, the *in situ* generated nucleophiles can react directly with acid anhydrides without the assistance of an acyl transfer catalyst.

3.3 Results and Discussion

This reported procedure was carried out through the use of constant current electrolysis using a two-electrode setup (Figure B.2). Inexpensive reticulated vitreous carbon (RVC) electrodes were utilized to avoid the use of expensive, rare transition metals. The reaction conditions were optimized with the aim of developing an efficient method for the acylation of indazoles with high chemoselectivity for the *N-1* position. Table 3.1 summarizes the results of the optimization studies.

Table 3.1. Optimization of the electrochemical acylation reaction



conditions	initial current	second current	% yield *N-1* product	*N-2* product
A	8.0	8.0	81	-
B	4.0	4.0	62	-
C	16.0	16.0	77	-
D	8.0	0.5	82	-
E	8.0	0.0	53	-
F[a]	8.0	0.5	52	11
G[b]	8.0	8.0	45	22
H	0.0	0.0	18	5
I[c]	0.0	0.0	56	12

All reactions performed at room temperature, unless otherwise noted, with 0.1 M Bu_4NPF_6 electrolyte, 0.75 mmol of 1*H*-indazole, 1.4 eqs. of acetic anhydride in acetonitrile on cathode side, 0.05 M Fc on anode side. RVC anode and cathode. Current units in mA. [a]single cell set-up with iron anode. [b]1*H*-indazole and acetic anhydride initially mixed. [c]carried out at 55 °C.

For the initial experimental conditions (A in Table 3.1) a two-compartment electrochemical H-cell was used with a glass frit separating the anodic and cathodic sides of the cell. The solution in the cathodic chamber was initially composed of just *1H*-indazole substrate and 0.1 M tetrabutylammonium hexafluorophosphate (NBu_4PF_6) in acetonitrile. The anodic chamber contained 0.05 M ferrocene and 0.1 M NBu_4PF_6 in acetonitrile. The ferrocene was added as an electron donor for the system and to avoid excessive

consumption/degradation of the solvent or electrolyte. The stable ferrocenium cation generated during the electrolysis could be reduced back to ferrocene for recycled use, thus limiting chemical waste. With these initial solutions set up, 8 mA of current was applied between the two electrodes for a total of 3 hours. This controlled current electrolysis generates a "pool" of indazole anions. After the initial three hours, 1.4 equivalents of acetic anhydride were added while maintaining the applied 8 mA of current. The electrolysis was continued for three more hours with stirring, at which time the electrolysis was terminated and the reaction solution was purified to give the desired *N-1* acylated indazole product in 81% yield. GC-MS analysis of the reaction mixture and NMR analysis of the separated reaction components showed no evidence for the *N-2* product isomer.

With promising initial results in hand, the experimental conditions were varied to explore for further optimizations. Changing the applied current to 4 mA or 16 mA maintained the reaction selectivity, but decreased the overall yields (B and C, Table 3.1). Varying the current applied after the addition of the acetic anhydride was also explored. Lowering the current to 0.5 mA (D, Table 3.1) led to nearly identical yields when compared to reaction A, but is advantageous due to the lower applied current consuming less energy over the course of the reaction. Completely turning off the electrolysis after addition of anhydride (E, Table 3.1), however, led to a sharp decrease in product yield. It is hypothesized that the anion pool is only stable while external current is being applied,[20] thus cutting off the applied current leads to a loss of the indazole anions and a decreased product yield. The use of a single component electrochemical cell was explored (F, Table 3.1), but both selectivity and product yield for the reaction dropped. This result implies that having a positively charged anode near the anion pool is detrimental for this reaction.

Initially adding both the 1H-indazole and the acetic anhydride together before generating an anion pool (G, Table 3.1) also led to decreased yields and selectivity. This shows the importance of adopting a two steps procedure to obtain the N-1 acetylated product selectively. Directly stirring the acetic anhydride and the 1H-indazole together at room temperature without an applied current (H, Table 3.1) did result in some product, but with poor selectivity. Addition of base was heating the reaction up to 55 °C without applied current did result in 63% conversion of the 1H-indazole (I, Table 3.1), but once again the selectivity for the N-1 product was poor.

Having established conditions D in Table 3.1 as the optimized experimental conditions, the substrate scope with respect to acid anhydrides was explored. A range of commercially available anhydrides delivered N1-acylated products in consistently high yields as shown in Figure 3.2. In all cases, no evidence for the N2-acylated product was observed indicating this electrochemical synthesis procedure is completely selective for the desired N1-product. Acetic (1), isobutyric (3), and pentanoic anhydride (5) substrates were all successfully used for the acylation reactions. Anhydrides containing an aromatic group (2) and unsaturation (6) also led to high yields. Further functional group tolerance was also illustrated with diethyl dicarbonate (7) and 2-chloroacetic anhydride (4) substrates. The chloroacetic acylation reaction is of added interest as the chloro group adds another synthetic handle for potential further functionalization of product 4. In addition to these N-C bond forming reactions, tosyl anhydride was also utilized to form an N-S bond and product 8 in 73 % yield.

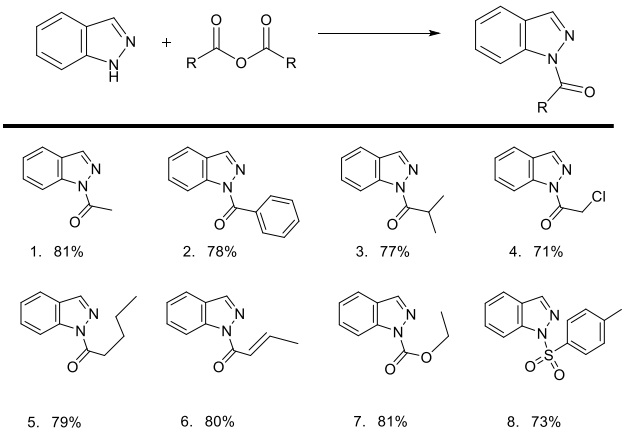


Figure 3.2. Selective *N1*-acylation of indazole with various anhydrides.

Continuing the investigation, a series of indazoles substituted with a variety of functional groups was explored and shown in Figure 3.3. These results shed light on adopting this method for N-benzoylation, which is a common practice for protection of an amine group in a multi-step synthesis.[23] This anion pool method was able to selectively acylate the *N1*-position of 5-iodo-indazole. Once again, the iodo-group on the ring of the indazole moiety offers an excellent synthetic handle for further functionalization of product **9**. Acylation of indazoles containing halogen functional groups was expanded to products **11**, **12**, and **13** which all contain a bromo-substitution at the 6-position of the indazole ring. Products **12** and **13** a containing aldehyde and ester functionalities were also obtained with good yields. Successful acylation reactions involving base-sensitive substrates illustrates an advantage of this base-free anion pool approach. In addition, the strong electron withdrawing nitro-functionality also performed well under the optimized reaction conditions (**10**). Furthermore, the benzoylated products in Figure 3.3 can be reduced to benzylated products through Wolff-Kishner reduction. This is an advantageous strategy in place of direct benzylation that produces a mixture of both isomers.[24]

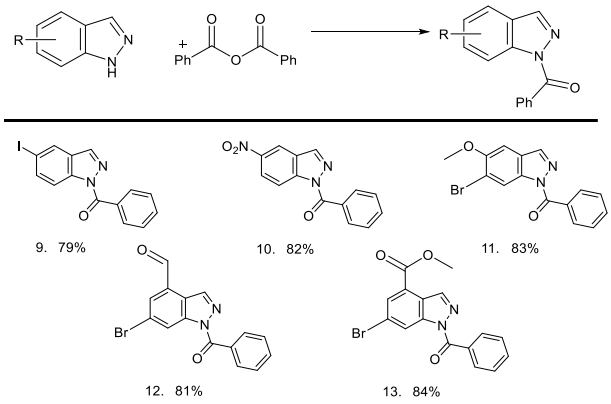


Figure 3.3. Selective *N1*-acylation of a variety of substituted indazole compounds.

Gratifyingly, this method could be effectively applied to various other azole compounds, as shown in Figure 3.4. The ubiquitous presence of azoles in bioactive compounds makes new greener and broadly applicable methods for making their derivatives in demand. Both benzimidazole (**14**) and 2-methylthiol-benzimidazole (**15**) were successfully acylated, thus providing a base free method for the functionalization of the benzimidazole NH group. Numerous base-assisted synthetic protocols for the protection of benzimidazoles have been reported.[25] Indole also reacted with both acetic (**17**) and benzoic (**18**) anhydrides with complete selectivity to *N1* position. Lastly, this anion pool method also exhibited good acylation reactivity with the imidazole substrate (**19**).

The results in Figures 3.2 – 3.4 show that this anion pool approach is applicable for the acylation of indazoles, and azole compounds in general. It is understood, however, that many synthetic labs are not equipped with potentiostats in order to perform highly controlled electrolysis reactions. To address this possible shortcoming of the anion pool approach, the reaction used to obtain product 2 in Figure 3.2 was setup up using a standard

9 V battery instead of a potentiostat (Figure B3). For this battery driven reaction, the same reaction procedure was followed, where the indazole substrate was stirred in the cell for 3 hours, before addition of the benzoic anhydride. The anhydride was stirred in the reaction mixture for another 3 hours before the battery was disconnected and the reaction solution was analyzed. The battery powered reaction led to a 72% isolated yield of the *N1*-acylated product without evidence for the *N2*-product. This result illustrates the operational simplicity of the anion pool approach.

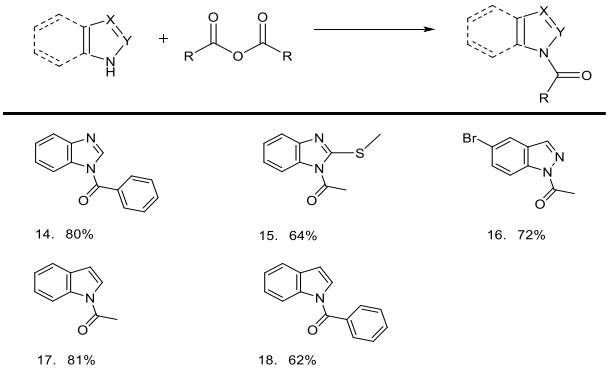


Figure 3.4. Electrochemical acylation of various azole compounds.

To gain insight into the highly selective nature of this reaction, acylation of 7-methyl indazole was investigated (Figure 3.5). The reaction proceeded with only 22% conversion of the starting 7-methyl indazole. In addition, GC-MS analysis of the post reaction solution indicated both *N1*- and *N2*-acylated products formed in a 1.4:1 mixture (Figure B25). Chromatographic separation of the two isomers proved difficult, but a ^{1}H NMR spectrum of the isomer mixture is shown in Figure B27). This result indicates that steric hindrance at the 7-position of the indazole moiety is detrimental to the reaction selectivity and efficiency. Furthermore, the effect of counter cation size was examined. In a previous report, the selectivity for the *N-1* product during the base-assisted alkylation of

indazoles was greatly increased when cesium carbonate base was used instead of potassium and sodium bases.[11] For this study, using $LiClO_4$ supporting electrolyte instead of NBu_4PF_6 led to a 2:1 ratio of the *N-1*:*N-2* product as evidenced by GC-MS analysis. Thus, larger counter cations in the supporting electrolyte increase the selectivity for the *N-1* product, which is consistent with previous reports.

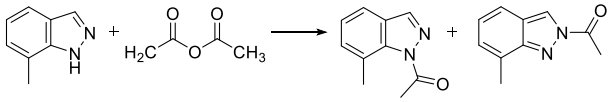


Figure 3.5. Acylation of 7-methyl-indazole. Reaction conditions are identical to conditions D from Table 1.

3.4 Conclusion

In conclusion, we have developed a general and operationally simple electrochemical procedure for the acylation of indazoles and azoles in general. This "anion pool" procedure is completely selective for the acylation of the *N1*-position of indazoles with the exception of 7-substituted indazole substrates. Since the procedure is base-free, acid anhydrides can be used as the acylation substrate. This avoids the use of acid chlorides and the stoichiometric production of HCl by-product.[26] The adoption of electrochemical approaches such as this can allow process chemists to incorporate green chemistry principles that increase atom-economy by generating stoichiometric by-products, such as ferrocenium, that can easily be recycled.

3.5 Experimental

Materials

Anhydrous acetonitrile (MeCN) 99.8%, water ≤ 50 ppm) was used for all reactions. All solutions used for electrochemical measurements contained 0.1 M

tetrabutylammonium hexafluorophosphate ($TBAPF_6$) further purified by recrystallization from ethanol and dried under vacuum at 80 ºC for 24 hours.

General procedure for electro-synthetic experiments.

The preparations of the setup were performed inside a N_2-filled glove box to confirm inert atmosphere. Preparative electrolytic studies were carried out in a split compartment H-cell. During the electrolysis experiments, a 0.1 M solution of tetrabutylammonium hexafluorophosphate ($TBAPF_6$) containing 0.65 mmol of indazole was initially reduced in the cathode chamber by passing a current of 8 mA for 3 hrs. Each compartment had 15 mL of anhydrous acetonitrile. The anode chamber contained 0.65 mmol of ferrocene. After 3 hrs, 1.6 eq of the anhydride is added and the current is decreased to 0.5 mA. During the reactions with chloroacetic anhydride and tosyl anhydride, the potentiostat was turned off to avoid the reduction of anhydrides. The reaction is allowed to proceed for 2 more hours. After electrolysis, the solvent was evaporated off and organic contents were purified by preparative thin layer chromatography using appropriate solvent systems; for indazoles pentane: ethyl acetate (1:3), benzimidazoles pentane: ethyl acetate (3:1) and indoles pentane: ethyl acetate (1:1). Gas chromatography measurements were taken with an HP 5890 Series II gas chromatograph equipped with a Carboxen 1010 PLOT capillary column and a thermal conductivity detector using Ar as the carrier gas. The oven temperature was held constant at 70 ºC.

3.6 References

1. Vitaku, E.; Smith, D. T.; Njardarson, J. T., Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014,** *57* (24), 10257-10274.

2. Denya, I.; Malan, S. F.; Joubert, J., Indazole derivatives and their therapeutic applications: a patent review (2013-2017). *Expert Opin. Ther. Pat.* **2018,** *28* (6), 441-453.

3. Binch, H.; Brenchley, G.; Golec, J. M.; Knegtel, R.; Mortimore, M.; Patel, S.; Rutherford, A., Indazole compounds useful as protein kinase inhibitors. U.S. Patent No. 7,041,687. Washington, DC: U.S. Patent and Trademark Office.: 2006.

4. Crocetti, L.; Schepetkin, I. A.; Cilibrizzi, A.; Graziano, A.; Vergelli, C.; Giomi, D.; Khlebnikov, A. I.; Quinn, M. T.; Giovannoni, M. P., Optimization of N-Benzoylindazole Derivatives as Inhibitors of Human Neutrophil Elastase. *J. Med. Chem.* **2013,** *56* (15), 6259-6272.

5. Georg, I. G.; Tash, J. S.; Chakrasali, R.; Jakkaraj, S. R.; Calvet, J. P., Lonidamine analogues and treatment of polycystic kidney disease. Google Patents: 2013.

6. Naas, M.; El Kazzouli, S.; Essassi, E. M.; Bousmina, M.; Guillaumet, G., Palladium-Catalyzed Oxidative Direct C3- and C7-Alkenylations of Indazoles: Application to the Synthesis of Gamendazole. *Org. Lett.* **2015,** *17* (17), 4320-4323.

7. Shen, H.; Gou, S.; Shen, J.; Zhu, Y.; Zhang, Y.; Chen, X., Synthesis and biological evaluations of novel bendazac lysine analogues as potent anticataract agents. *Bioorg. Med. Chem. Lett.* **2010,** *20* (7), 2115-2118.

8. Greene, T. W.; Wutz, P. G. M., *Protective Groups in Organic Synthesis*. Wiley: New York, 1991; Vol. 2nd ed. .

9. Luo, G.; Chen, L.; Dubowchik, G., Regioselective Protection at N-2 and Derivatization at C-3 of Indazoles. *J. Org. Chem.* **2006,** *71* (14), 5392-5395.

10. Cheung, M.; Boloor, A.; Stafford, J. A., Efficient and Regioselective Synthesis of 2-Alkyl-2H-indazoles. *J. Org. Chem.* **2003,** *68* (10), 4093-4095.

11. Hunt, K. W.; Moreno, D. A.; Suiter, N.; Clark, C. T.; Kim, G., Selective Synthesis of 1-Functionalized-alkyl-1H-indazoles. *Org. Lett.* **2009,** *11* (21), 5054-5057.

12. Liu, H.-J.; Hung, S.-F.; Chen, C.-L.; Lin, M.-H., A method for the regioselective synthesis of 1-alkyl-1H-indazoles. *Tetrahedron* **2013,** *69* (19), 3907-3912.

13. Nykaza, T. V.; Harrison, T. S.; Ghosh, A.; Putnik, R. A.; Radosevich, A. T., A Biphilic Phosphetane Catalyzes N–N Bond-Forming Cadogan Heterocyclization via PIII/PV═O Redox Cycling. *J. Am. Chem. Soc.* **2017,** *139* (20), 6839-6842.

14. Yang, X.; Birman, V. B., Acyl Transfer Catalysis with 1,2,4-Triazole Anion. *Org. Lett.* **2009,** *11* (7), 1499-1502.

15. Maki, B. E.; Scheidt, K. A., Single-Flask Synthesis of N-Acylated Indoles by Catalytic Dehydrogenative Coupling with Primary Alcohols. *Org. Lett.* **2009,** *11* (7), 1651-1654.

16. Umehara, A.; Ueda, H.; Tokuyama, H., Condensation of Carboxylic Acids with Non-Nucleophilic N-Heterocycles and Anilides Using Boc2O. *J. Org. Chem.* **2016,** *81* (22), 11444-11453.

17. Ta, L.; Sundén, H., Oxidative organocatalytic chemoselective N-acylation of heterocycles with aromatic and conjugated aldehydes. *Chem. Commun.* **2018,** *54* (5), 531-534.

18. Heller, S. T.; Schultz, E. E.; Sarpong, R., Chemoselective N-Acylation of Indoles and Oxazolidinones with Carbonylazoles. *Angew. Chem. Int. Ed.* **2012,** *51* (33), 8304-8308.

19. Zhao, J.; Li, P.; Xia, C.; Li, F., Direct N-acylation of azoles via a metal-free catalyzed oxidative cross-coupling strategy. *Chem. Commun.* **2014,** *50* (36), 4751-4754.

20. Dissanayake, D. M. M. M.; Vannucci, A. K., Transition-Metal-Free and Base-Free Electrosynthesis of 1H-Substituted Benzimidazoles. *ACS Sustainable Chemistry & Engineering* **2018,** *6* (1), 690-695.

21. Yoshida, J.-i.; Shimizu, A.; Hayashi, R., Electrogenerated Cationic Reactive Intermediates: The Pool Method and Further Advances. *Chemical Reviews* **2018,** *118* (9), 4702-4730.

22. Utley, J. H. P., Electrogenerated bases. In *Electrochemistry I*, Springer: 1987; pp 131-165.

23. Fan, W.; Yang, Y.; Lei, J.; Jiang, Q.; Zhou, W., Copper-Catalyzed N-Benzoylation of Amines via Aerobic C–C Bond Cleavage. *J. Org. Chem.* **2015,** *80* (17), 8782-8789.

24. Jaffari, G. A.; Nunn, A. J., Methylation of indazoles and related reactions. *J. Chem. Soc., Perkin Trans. 1* **1973,** (0), 2371-2374.

25. Gu, Z.-S.; Chen, W.-X.; Shao, L.-X., N-Heterocyclic Carbene-Palladium(II)-1-Methylimidazole Complex-Catalyzed Direct C–H Bond Arylation of (Benz)imidazoles with Aryl Chlorides. *J. Org. Chem.* **2014,** *79* (12), 5806-5811.

26. Okauchi, T.; Itonaga, M.; Minami, T.; Owa, T.; Kitoh, K.; Yoshino, H., A General Method for Acylation of Indoles at the 3-Position with Acyl Chlorides in the Presence of Dialkylaluminum Chloride. *Org. Lett.* **2000,** *2* (10), 1485-1487.

CHAPTER 4

ELECTROCHEMICAL ANION POOL SYNTHESIS OF AMIDES WITH CONCURRENT BENZYL ESTER SYNTHESIS

4.1 Abstract

"Anion pool" method is applied to improve the atom economy of amidation. Amides are prevalent moieties in a variety of bioactive compounds and commercialized synthetic products. The excessive utilization of amide bond forming methods has necessitated ACS Green Chemistry Institute Pharmaceutical Roundtable to identify atom economic amidation as a priority. By applying "anion pool" approach, the anionic nucleophile is generated from the amine through electrochemical reduction. The amine nucleophiles then react with acid anhydrides to generate amides, and the by-product from this reaction undergoes further chemical transformations to generate pharmaceutically relevant benzoic esters. These one-pot reactions are operationally simple, are performed at room temperature, and avoid rare transition metals and added bases. The amide synthesis is amenable to primary and secondary amines and a variety of anhydrides with yields up to 90 % obtained. Atom economy and process mass index (PMI) values calculated for this procedure indicate that this process can be considered greener compared to traditional amide synthesis routes used by industry. Furthermore, this electrochemical approach showed unique selectivity when substrates that contained two inequivalent amine moieties were examined.

4.2 Introduction

The amide linkage is a ubiquitous structural element in biological systems and in chemical products relevant to the pharmaceutical and medicinal industries. In fact, amide bond forming reactions have been estimated as the most frequently used chemical reaction in the pharmaceutical industry.[1] Due to the extensive use of this reaction, minimizing the waste and increasing the sustainability of amide bond forming reactions is a major research

goal. For the past decade, the American Chemical Society's (ACS) Green Chemistry Institute (GCI) Pharmaceutical Roundtable have made greener amide syntheses a top target.[2-3]

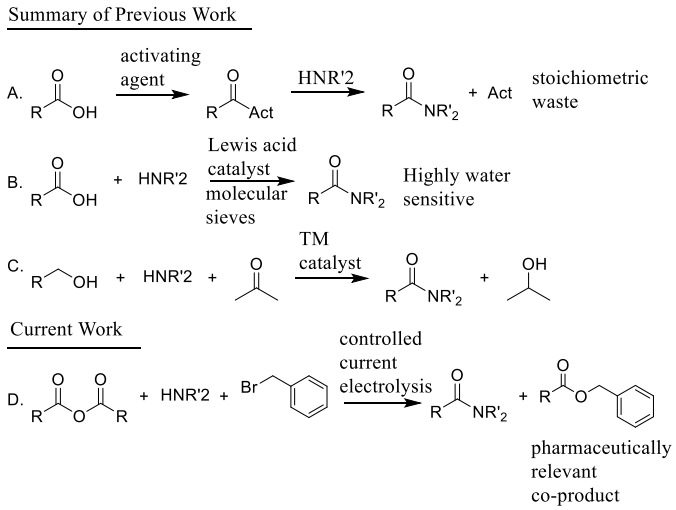


Figure 4.1. Comparison of various approaches to synthesize amides from amines.

Ideally, amides could be synthesized via a direct condensation of carboxylic acids and amines, where water would be the only reaction side product. The acid/base chemistry of these condensation reactions, however, tends to favor formation of carboxylate ammonium salts.[4] Thus activation of carboxylic acids prior to reactions with amines, as shown in Figure 4.1A, is typically required. This classical approach is efficient in amide bond formation and the most commonly used industrial route, but it generates at least a stoichiometric amount of waste, leading to poor atom-economy.[5] Common activating agents include thionyl chloride, oxalyl chloride and carbonyldiimidzaole which produce waste such as sulfur dioxide, carbon dioxide, and hydrochloric acid. In addition, the activating agents and additives needed can vary widely depending on the amine.[6]

Further limiting the green chemistry of these reactions is the required solvent. Many amidation reactions are carried out in solvents such as DMF, DMA, and DCM, which bear safety concerns and subjected to heavy regulation.[5] Therefore, an atom economic and an environmentally safe amidation procedure remains highly desirable.

Over the past decade, since the Pharmaceutical Roundtable made an initial call for greater atom-economy with amide reactions, widespread work has been performed on catalytic amide formation.[7-8] Enzyme catalyzed amide formations have exhibited high efficiency, but also incur high isolation costs and individual enzymes tend to lack wide substrate scope capabilities.[9] Catalytic aminocarbonylation routes have shown promise in improving the atom economy of amidation reactions compared to the classical approach.[10] These aminocarbonylation reactions, however, tend to require expensive palladium catalysts, high reaction temperatures, and toxic carbon monoxide.

Extensive work has been dedicated to the development of Lewis acid catalysts for the direct coupling of carboxylic acids and amines (Figure 4.1B).[4-5] Such methods employ catalysts based on inexpensive, earth abundant elements such as Ti, Zr, and boron based systems.[7] The Lewis acidity of these catalysts can activate the carboxylic acid substrate without the need for a sacrificial activating agent. Tuning Lewis acidity leads to large applicability and these catalysts tend to have high functional group tolerance.[11-13] Even though this approach produces very little waste, the common necessity of high reaction temperatures and azeotropic removal of water have limited the adaptation of this procedure by industry.[5] Furthermore, most of these catalyzed reactions have high process mass intensity (PMI) values of 200 – 500.[5] The water sensitivity typically requires the addition of molecular sieves to the reaction mixture, though performing these reactions in

micelles immersed in aqueous solution has been achieved.[14-15] Direct coupling of carboxylic acids and amines has also been achieved without the need for water removal through the use of an excess tetramethyl orthosilicate (TMOS) catalyst, though TMOS is highly toxic.[16]

Transition metal catalyzed amide formation starting from aldehydes or alcohols also offers a promising approach. Work in this field has burgeoned following the report of a ruthenium pincer complex capable of the direct coupling of an alcohol with an amine yielding H_2 as the only byproduct.[17] Many reports have followed this approach and shown great efficiency with primary amines.[18-22] These catalysts, however, tend to employ rare transition metals and show limited reactivity with secondary amines. The efficiency of this catalytic approach towards a variety of amine starting materials can be increased by using hydrogen transfer reagent as shown in Figure 4.1C.[18, 21] For example, a recent report builds on this transition metal catalyzed theme for amide formations starting from carboxylic acids and amines.[23] This report uses a Ru catalyst and an alkyne to activate the carboxylic acid for coupling to the amine substrate while generating a stoichiometric ketone by-product.

Research on forming amides from reactions between amines and substrates that can be considered 'activated carboxylic acids' has also been explored. Reactions between acyl chlorides and amines are efficient for amide formation, but produce stoichiometric amounts of corrosive hydrochloric acid.[24] Formylating reagents have been shown to promote N-C bond formation for the synthesis of N-formyl products that could be converted to amides.[25] It has also been shown that acid anhydrides are excellent reagents for the formation of tertiary amides.[26] For all of these examples the 'activated carboxylic

acid' substrate generated stoichiometric by-products that have no use to the pharmaceutical industry and were essentially treated as waste.

To address the issue of generating waste from amidation reactions starting from activated carboxylic acids we envisioned a synthetic route where the by-product of amide formation is utilized to produce a second product of pharmaceutical relevance. Thus one operationally simple procedure is used to synthesize two high value products, in turn limiting waste production. Here we report the development of a procedure for the electrochemical co-synthesis of amides and benzylic esters starting from amines and acid anhydrides, as shown in Figure 4.1D. The benzylic esters, which are widely used in medicines and fragrances, are formed in one-pot from the by-product of the amide synthesis. This procedure is operational at room temperature, water tolerant, base-free, and does not require rare transition metals. In addition, this reaction exhibits functional group tolerance with the acid anhydrides and produces good yields of amide products starting from both primary and secondary amides. Lastly, this electrochemical approach has allowed for unique regioselectivity without a need for protecting groups.

4.3 Results and discussion

To address the low atom economy challenges of amide synthesis starting from activated carboxylic acids and amines, an electrochemical synthesis method was employed. This electrochemical "anion pool method" was developed by our group and has been utilized for the synthesis of alkylated benzimidazoles and acylated indazoles.[27-28] This method uses inexpensive reticulated vitreous carbon (RVC) electrodes, acetonitrile solvent and is base, catalyst, and precious-metal free. For this study, the electrochemical synthesis of amides with the co-formation of benzoic esters is carried out via the reaction scheme

shown in Figure 4. 2. Reduction of an amine substrate at the carbon electrode generates a strong nucleophile and half an equivalent of hydrogen gas, as confirmed by GC analysis. Subsequent addition of an acid anhydride to the reaction solution leads to the formation of an amide product and one equivalent of carboxylate (Figure 4.2b). The base-free nature of this approach allows for the usage of acid anhydrides as an amidation substrate. Lastly, instead of treating the carboxylate as waste, addition of a benzylic halide leads to the formation of a benzoic ester product (Figure 4.2c). Benzoic esters are high value products that are widely used in the fragrance industry and certain benzoic esters have been used by the pharmaceutical industry to treat lice.[29] This co-production of useful products limits the chemical waste produced.

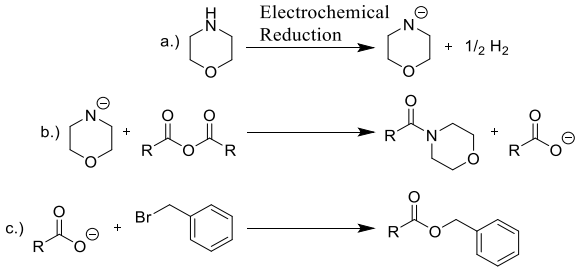


Figure 4.2. Reaction scheme for electrochemical anion pool synthesis of amides and benzylic esters.

Reaction parameters were explored with the goal of optimizing an efficient method for the synthesis of amides and benzylic esters. Table 4.1 summarizes the results of those optimization studies. The experimental conditions consisted of a controlled current electrolysis performed at room temperature in a two-compartment H-cell separated with a fine glass frit unless otherwise noted. The cathodic chamber contained 50 mM morpholine and 0.1 M tetrabutylammonium hexafluorophosphate (NBu_4PF_6) and the anodic chamber contained 0.05 M ferrocene and 0.1 M NBu_4PF_6 in anhydrous acetonitrile. The ferrocene

was added as a reversible electron donor for the system to avoid excessive consumption of the solvent or electrolyte. The stable ferrocenium cation generated during the electrolysis could be reduced back to ferrocene for recycled use, thus limiting chemical waste.

For the initial experiment (A, Table 4.1), 16 mA of current was applied between the two electrodes. Once 1 $Fmol^{-1}$ of charge was passed relative to the morpholine substrate, 1.2 equivalents of benzoic anhydride was added to the electrochemical cell. Excess anhydride was initially investigated because excess anhydride was required to optimize yields during the electrochemical acylation of indazole.[28] With a continuously applied current of 16 mA, the cell was stirred for an additional two hours before the current was turned off and benzyl bromide was added to the cell. Stirring of the reaction mixture for an additional two hours at room temperature was followed by GC/MS analysis of the product mixture. This procedure was repeated, but with 8 mA and 4 mA applied, as shown in B and C in Table 4.1 respectively. The results of these initial experiments led us to choose 8 mA of applied current between the two electrodes as the optimal electrolysis conditions. Additional conditions were then explored to either further optimize product yields or improve on the overall efficiency of the electrochemical reaction.

Variation of the applied current after the addition of the benzoic anhydride was explored. Turning off all applied current following the addition of anhydride (Table 4.1, D) led to a sharp decrease in ester product formation. GC/MS analysis of the reaction mixture identified unreacted benzyl bromide. Instead of ending the applied current, lowering the applied current to 0.5 mA after addition of the anhydride (E, Table 4.1) led to good yields of both the amide and the ester. The yields for reaction E in Table 4.1 are

comparable to reaction B, but are advantageous due to the lower applied current consuming less energy over the course of the reaction.

The ratio of reactants and the order of the addition of reactants were also explored. For F in Table 4.1, the amount of anhydride added to the mixture after the initial reduction of the amine was lowered to 1 equivalent. We were pleased to find that efficient product yields for both the amide and the benzyl ester were maintained with adding just a stoichiometric amount of the anhydride. Avoiding excess anhydride clearly increases the atom economy of this procedure. Experiment G in Table 1 added the anhydride and amine together at the beginning of the electrolysis. While efficient amide formation was observed, decreased yields in the ester product were once again observed. We hypothesize that possible reduction of the anhydride under these conditions would lead to degradation and subsequent decreased ester formation. This hypothesis is supported by identifying unreacted benzyl bromide in the product mixture. Next, a reaction was performed with 5.5 mM of water added. Remarkably, the yield of the amide product was not affected by added water (H, Table 4.1). This is an advantage over amide synthesis via condensation reactions, which are typically highly sensitive to the presence of water.[5] Unfortunately, the addition of water did impair the formation of the benzylic ester product as water led to the formation of benzoic acid from the *in situ* formed benzoate.

Lastly, the possible advantages of this electrochemical synthesis approach were examined. For conditions I in Table 4.1, the supporting electrolyte was changed from NBu_4PF_6 to $LiClO_4$. The change in supporting electrolyte once again had negligible effects on amide formation, but retarded benzyl ester formation. The smaller, more Lewis acidic lithium cation likely reduced the reactivity of the benzoate and as unreacted benzyl bromide

Table 4.1. Optimization of Electrochemical Anion Pool Amidation Reaction.

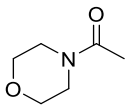
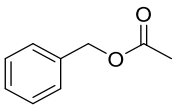
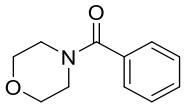
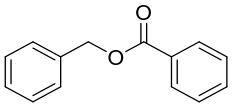
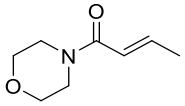
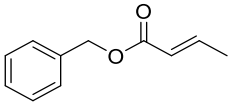
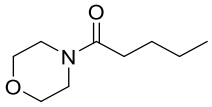
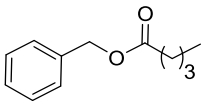
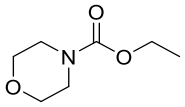
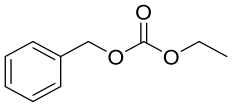
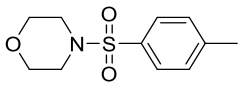
Conditions	Initial current	Second current	% Yield Amide product	% Yield Ester product
A	16.0	16.0	68	69
B	8.0	8.0	70	68
C	4.0	4.0	66	32
D	8.0	0.0	68	22
E	8.0	0.5	71	72
F[a]	8.0	0.5	69	70
G[b]	8.0	0.5	70	42
H[c]	8.0	0.5	70	15
I[d]	8.0	0.5	69	0
J[e]	8.0	0.5	52	0
K	0.0	0.0	0	0
L[f]	0.0	0.0	66	0

Reaction conditions unless otherwise noted: room temperature, 0.1 M Bu_4NPF_6 electrolyte, 0.75 mmol of morpholine, 1.2 eqs. of benzoic anhydride, 1.2 eq. benzylbromide in acetonitrile. 0.05 M Fc added to anodic chamber. RVC anode and cathode. Current units in mA. [a]1.0 eq. of benzoic anhydride. [b]morpholine and benzoic anhydride added to cell at same time. [c]5.5 mM of water added to the reaction. [d]0.1M $LiClO_4$ as supporting electrolyte. [e]reaction performed in a single-cell setup. [f]performed at 55 °C.

was observed in the product mixture. The use of a single component electrochemical cell was explored (J, Table 4.1), but the yield of both the amide and ester dropped considerably. This is likely due to the re-oxidation of the amine and oxidation of generated benzoate

anion. Performing these reactions in the absence of an applied current at room temperature led to no observed reactivity (K, Table 4.1). Heating the reaction mixture to 55 °C did lead to a 66 % yield of the desired amide product, but no observed ester was formed (L, Table 4.1).

Table 4.2. Isolated Yields of Amide and Ester Products Starting from Morpholine and Various Anhydrides.

 1a. 74%	 1b. 68%
 2a. 71%	 2b. 72%
 3a. 68%	 3b. 64%
 4a. 67%	 4b. 62%
 5a. 73%	 5b. 68%
 6a. 77%	N/A

With the optimized conditions in hand (F, Table 4.1), the applicability of this approach with respect to the identity of the acid anhydride was explored. Table 4.2 shows that a variety of anhydrides were compatible with this approach and resulted in good yields

for both amide and ester formation. Acetic (1), and pentanoic anhydride (4) substrates were successfully employed for these reactions. This procedure was also amenable to alkene functionality (3) without observed alkene reduction. Further functional group tolerance was also illustrated with diethyl dicarbonate (5). In addition to these N-C bond forming reactions, tosyl anhydride was also utilized to form an N-S bond and product 6 in 77 % yield, though ester formation is not possible with this anhydride.

The Faradaic efficiencies for all of the reported reactions track linearly with the isolated yields with Faradaic yields being roughly 5% lower than the isolated percent product yield. During the controlled current electrolysis of the amine substrate, the charge passed is equivalent to one electron per amine molecule (1 $Fmol^{-1}$). For the concentrations employed in these reactions, 72 Coulombs of charge are passed during the first step of the electrolysis. During the second step of the electrolysis, where the applied current is dropped to 0.5 mA after addition of the anhydride substrate, an additional 3.6 Coulombs are passed. Thus, for each reaction 75.6 C are used to generate product that requires a Faradaic minimum of 72 Coulombs of charge for quantitative yield.

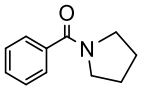
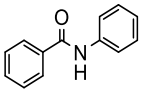
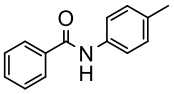
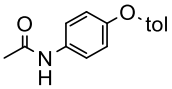
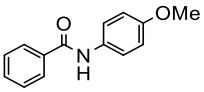
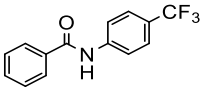
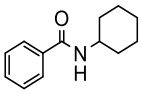
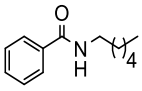
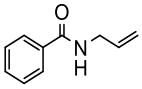
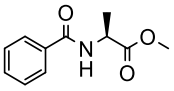
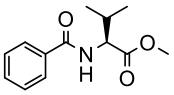
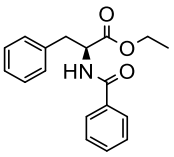
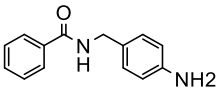
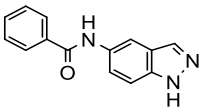
Having established amide formation starting from the secondary amine morpholine and various anhydrides, the substrate scope with respect to the identity of the amine substrate was examined. For the amine substrate scope, benzoic anhydride was chosen in order to form benzyl benzoate, which is a pharmaceutically relevant ester product. As can be seen from Table 4.3, this anion pool approach for the concurrent synthesis of amides and esters can be widely applied to a variety of amine substrates while also achieving good yields of the ester products. Pyrrolidine (7) was another successful secondary amine utilized for amide synthesis. Furthermore, aniline and a series of substituted aniline

compounds underwent successful amidation using this procedure (8 – 12). Primary amines lacking aromaticity were also converted to the corresponding amides as shown by cyclohexylamine (13) and 1-hexylamine (14). Another example of this procedure being compatible with unsaturation is shown with product 15. Amide formation analogous to peptide bond formation was also achieved with products 16 and 17. Amide bond formation was also achieved on an enantiopure sample of *L*-phenylalanine (18).

Of particular intrigue was the unique selectivity obtained during amide bond formation of substrates containing multiple reactive NH bonds. Starting from 4-aminobenzylamine, this anion pool approach resulted in exclusive amidation at the benzylamine position without a need to protect the aniline amino group (19). The benzyl amine moiety of 4-aminobenzylamine is the more reactive amino group and expected to have a lower reduction potential when compared to the aniline moiety. The precise control of this electrochemical approach allows for the sole reduction of the benzyl amine. Limiting the charge passed to 1 $Fmol^{-1}$ of starting material helps avoid over reduction of the aniline moiety. This is a clear advantage of this electrochemical approach over reactions performed via thermal control, which are not expected to be able to achieve such selectivity.

The selectivity of this electrochemical approach was extended to the amidation of 5-aminoindazole. Without using a protecting group for the 1*H*-position of the indazole, complete selectivity was obtained for amide bond formation at the 5-amino position (20). Eliminating the need for protecting groups also eliminates the need for extra chemical reactions and purifications. Minimizing synthesis steps and extra purifications is the most efficient way to increase the atom economy of reactions.

Table 4.3. Electrochemical anion pool amidation of various amines.

	Amide	Amide % yield	Ester % yield
7		77	72
8		74	74
9		79	72
10		69	69
11		74	73
12		62	71
13		78	71
14		77	71
15		76	70
16		74	64
17		71	61
18		74	62
19		71	70
20		77	71

The efficiency of this reaction scaled up to produce at least 1.0 gram of product was also examined. The reaction shown in Figure 4.3 was examined in 15 mL of acetonitrile containing 0.1 M NBu_4PF_6 electrolyte. At this higher concentration of starting material, 1.1 grams of product were isolated with the percent yield of the amide product actually increasing to 90 %. This increased percent yield of the scaled up reaction is likely due to greater ease of isolating a larger amount of product with column chromatography. Unfortunately, for the scaled up reaction, the yield of the corresponding ester product dropped to just 25 %. We hypothesized that the high concentration of the benzoate formed during the amidation reaction may form ion pairs as benzoate is known to form homoconjugated dimers.[30] Indeed, adding a catalytic amount of potassium carbonate base (80 mg) with the addition of the benzyl bromide substrate resulted in an 80 % yield of the ester product with no change in the yield of the amide product.

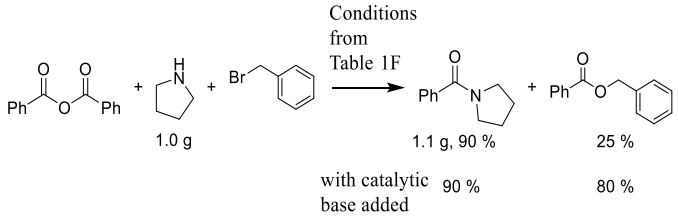


Figure 4.3. Results of scaled up reactions.

The results shown in Tables 4.2 and 4.3 show that this anion pool approach is capable of performing amidation reactions with concurrent ester synthesis with good efficiency, however, being able to perform this reaction without the need for an expensive potentiostat would improve the operational simplicity of this approach. To address this challenge, the reaction used to obtain product 7 in Table 4.3 was setup using a household

9-V battery instead of a potentiostat (Figure C2). The reaction sequence was as follows: a battery was connected to electrodes immersed in a solution containing only amine substrate and supporting electrolyte in the cathodic chamber of the cell and ferrocene and supporting electrolyte in the anodic chamber. This cell solution was stirred for 2 hours before addition of the benzoic anhydride substrate. The solution was stirred for an additional 2 hours, and then the battery was disconnected from the electrodes and the benzyl bromide substrate was added to the reaction mixture. After stirring for an additional 3 hours the products were isolated and purified. The yields were 76 % for the amide product and 72 % for the ester, showing that this reaction can be performed using just a standard household battery for the power source.

To gain insight into the potential green chemistry benefits of this approach, the atom economy and PMI value for the reaction shown in Figure 4.3 was calculated. It is understood that PMI values tend to be more applicable to larger scale reactions, but these calculations are just used as a general comparison of the green chemistry principles of this approach.[31-32] Typical PMI values for generally used pharmaceutical processes lie between 26 and 100.[32-33] The PMI value calculated for this anion pool approach was 30.1 taking into account the masses of the substrates, electrolyte and ferrocene added to the reaction. This PMI value being on the more favorable end of the PMI spectrum shows the possible green chemistry advantages for this electrochemical approach. Furthermore, the atom economy of the reaction shown in Figure 4.3 was calculated to be 82.7 %. This value also compares well to the atom economy of the conventionally used amide synthesis using thionyl chloride as an activating agent, which has an atom economy value of only 61.2 %.

4.4 Conclusion

Electrochemistry has received rejuvenated attention as a synthetic strategy and a tool for incorporation of principles of green chemistry.[34-36] This reported procedure uses the electrochemical anion pool approach to synthesize a variety of pharmaceutically relevant amides with the co-synthesis of benzyl esters. The room temperature and base-free approach allows for the use of acid anhydrides as starting substrates for the facile formation of amides from primary and secondary amines. The subsequently generated benzoate side product from the amide formation reaction can then be trapped with a benzylic substrate to generate high value benzyl ester products. The production of two useful products from this approach leads to favorable PMI and atom economy values when compared to pharmaceutical standards. Furthermore, the precise control of reaction conditions offered from electrochemical approaches allows for unique amide bond formation selectivity without the need for protecting group chemistry.

4.5 Experimental

The solvents and electrolytes were prepared as mentioned in Chapter 2. The setup of the electrochemical cell was performed inside a N_2-filled glove box to confirm inert atmosphere. Oxygen was kept out of the cell to avoid oxygen reduction at the cathode. The electrosyntheses were carried out in a split compartment H-cell as shown in Figure C1 in appendix 4. Each compartment contained a 0.1 M solution of tetrabutylammonium hexafluorophosphate (NBu_4PF_6) in 15 mL of anhydrous acetonitrile. During the electrolysis experiments, 0.75 mmol of amine were initially reduced in the cathode chamber by passing a current of 8 mA for 3.5 hrs which is equivalent to 1 $Fmol^{-1}$ of charge being passed. The anode chamber contained 0.75 mmol of ferrocene as a recyclable

electron donor. After 3.5 hrs, 0.9 mmol of the acid anhydride substrate was added to the cathodic chamber and the applied current was decreased to 0.5 mA. During the reaction with tosyl anhydride, the potentiostat was turned off after the addition of anhydride to avoid the reduction of the tosyl anhydride. After anhydride addition the reaction mixture was stirred for 2 more hours. At the end of the 2 hours, the electrolysis was discontinued and 0.9 mmol of benzyl bromide was added and stirring was continued for 4 more hours. After the reaction was complete, the solvent was evaporated off, and a preparative thin layer chromatographic separation was performed with hexane as the mobile phase. The band around 0.5 R_f is the ester product and this was isolated by scrapping off and sonicated with ether/DCM and filtered. The bottom layer of preparative TLC plate corresponded to the amide product and was scraped off, sonicated with DCM, and filtered.

4.6 References

1. Roughley, S. D.; Jordan, A. M., The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. *J. Med. Chem.* **2011,** *54* (10), 3451-3479.

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., Key green chemistry research areas—a perspective from pharmaceutical manufacturers. *Green Chemistry* **2007,** *9* (5), 411-420.

3. Bryan, M. C.; Dunn, P. J.; Entwistle, D.; Gallou, F.; Koenig, S. G.; Hayler, J. D.; Hickey, M. R.; Hughes, S.; Kopach, M. E.; Moine, G.; Richardson, P.; Roschangar, F.; Steven, A.; Weiberth, F. J., Key Green Chemistry research areas from a pharmaceutical manufacturers' perspective revisited. *Green Chemistry* **2018,** *20* (22), 5082-5103.

4. Wang, X., Challenges and outlook for catalytic direct amidation reactions. *Nature Catalysis* **2019,** *2* (2), 98-102.

5. Sabatini, M. T.; Boulton, L. T.; Sneddon, H. F.; Sheppard, T. D., A green chemistry perspective on catalytic amide bond formation. *Nature Catalysis* **2019,** *2* (1), 10-17.

6. Valeur, E.; Bradley, M., Amide bond formation: beyond the myth of coupling reagents. *Chem. Soc. Rev.* **2009,** *38* (2), 606-631.

7. Allen, C. L.; Williams, J. M. J., Metal-catalysed approaches to amide bond formation. *Chem. Soc. Rev.* **2011,** *40* (7), 3405-3415.

8. Lundberg, H.; Tinnis, F.; Selander, N.; Adolfsson, H., Catalytic amide formation from non-activated carboxylic acids and amines. *Chem. Soc. Rev.* **2014,** *43* (8), 2714-2742.

9. Wang, M.-X., Enantioselective Biotransformations of Nitriles in Organic Synthesis. *Top. Catal.* **2005,** *35* (1), 117-130.

10. Brennführer, A.; Neumann, H.; Beller, M., Palladium-Catalyzed Carbonylation Reactions of Aryl Halides and Related Compounds. *Angew. Chem. Int. Ed.* **2009,** *48* (23), 4114-4133.

11. Maki, T.; Ishihara, K.; Yamamoto, H., 4,5,6,7-Tetrachlorobenzo[d][1,3,2]dioxaborol- 2-ol as an Effective Catalyst for the Amide Condensation of Sterically Demanding Carboxylic Acids. *Org. Lett.* **2006,** *8* (7), 1431-1434.

12. Mylavarapu, R. K.; Gcm, K.; Kolla, N.; Veeramalla, R.; Koilkonda, P.; Bhattacharya, A.; Bandichhor, R., Boric Acid Catalyzed Amidation in the Synthesis of Active Pharmaceutical Ingredients. *Org. Process Res. Dev.* **2007,** *11* (6), 1065-1068.

13. Arnold, K.; Davies, B.; Hérault, D.; Whiting, A., Asymmetric Direct Amide Synthesis by Kinetic Amine Resolution: A Chiral Bifunctional Aminoboronic Acid Catalyzed Reaction between a Racemic Amine and an Achiral Carboxylic Acid. *Angew. Chem. Int. Ed.* **2008,** *47* (14), 2673-2676.

14. Gabriel, C. M.; Keener, M.; Gallou, F.; Lipshutz, B. H., Amide and Peptide Bond Formation in Water at Room Temperature. *Org. Lett.* **2015,** *17* (16), 3968-3971.

15. Lipshutz, B. H., When Does Organic Chemistry Follow Nature's Lead and "Make the Switch"? *J. Org. Chem.* **2017,** *82* (6), 2806-2816.

16. Braddock, D. C.; Lickiss, P. D.; Rowley, B. C.; Pugh, D.; Purnomo, T.; Santhakumar, G.; Fussell, S. J., Tetramethyl Orthosilicate (TMOS) as a Reagent for Direct Amidation of Carboxylic Acids. *Org. Lett.* **2018,** *20* (4), 950-953.

17. Gunanathan, C.; Ben-David, Y.; Milstein, D., Direct Synthesis of Amides from Alcohols and Amines with Liberation of H<sub>2</sub&gt. *Science* **2007,** *317* (5839), 790.

18. Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J., Ruthenium-Catalyzed Oxidation of Alcohols into Amides. *Org. Lett.* **2009,** *11* (12), 2667-2670.

19. Nordstrøm, L. U.; Vogt, H.; Madsen, R., Amide Synthesis from Alcohols and Amines by the Extrusion of Dihydrogen. *J. Am. Chem. Soc.* **2008,** *130* (52), 17672-17673.

20. Zhang, Y.; Chen, C.; Ghosh, S. C.; Li, Y.; Hong, S. H., Well-Defined N-Heterocyclic Carbene Based Ruthenium Catalysts for Direct Amide Synthesis from Alcohols and Amines. *Organometallics* **2010,** *29* (6), 1374-1378.

21. Zweifel, T.; Naubron, J.-V.; Grützmacher, H., Catalyzed Dehydrogenative Coupling of Primary Alcohols with Water, Methanol, or Amines. *Angew. Chem. Int. Ed.* **2009,** *48* (3), 559-563.

22. Nguyen, T. T.; Hull, K. L., Rhodium-Catalyzed Oxidative Amidation of Sterically Hindered Aldehydes and Alcohols. *ACS Catal.* **2016,** *6* (12), 8214-8218.

23. Krause, T.; Baader, S.; Erb, B.; Gooßen, L. J., Atom-economic catalytic amide synthesis from amines and carboxylic acids activated in situ with acetylenes. *Nat Commun* **2016,** *7*, 11732.

24. Zhang, L.; Wang, X.-j.; Wang, J.; Grinberg, N.; Krishnamurthy, D.; Senanayake, C. H., An improved method of amide synthesis using acyl chlorides. *Tetrahedron Lett.* **2009,** *50* (24), 2964-2966.

25. Chapman, R. S. L.; Lawrence, R.; Williams, J. M. J.; Bull, S. D., Formyloxyacetoxyphenylmethane as an N-Formylating Reagent for Amines, Amino Acids, and Peptides. *Org. Lett.* **2017,** *19* (18), 4908-4911.

26. Li, Y.; Ma, L.; Jia, F.; Li, Z., Amide Bond Formation through Iron-Catalyzed Oxidative Amidation of Tertiary Amines with Anhydrides. *J. Org. Chem.* **2013,** *78* (11), 5638-5646.

27. Dissanayake, D. M. M. M.; Vannucci, A. K., Transition-Metal-Free and Base-Free Electrosynthesis of 1H-Substituted Benzimidazoles. *ACS Sustainable Chemistry & Engineering* **2018,** *6* (1), 690-695.

28. Dissanayake, D. M. M. M.; Vannucci, A. K., Selective N1-Acylation of Indazoles with Acid Anhydrides Using an Electrochemical Approach. *Organic Letters* **2019,** *21* (2), 457-460.

29. Brühne, F.; Wright, E., *Ullmann's Encyclopedia of Industrial Chemistry: Benzyl Alcohol*. Wiley-VCH: Weiheim, 2000.

30. Izutsu, K., *Acid-Base Dissociation Constants in Dipolar Aprotic Solvents*. Blackwell Scientific: Oxford, U.K., 1990.

31. Jimenez-Gonzalez, C.; Ponder, C. S.; Broxterman, Q. B.; Manley, J. B., Using the Right Green Yardstick: Why Process Mass Intensity is Used in the Pharmaceutical Industry to Drive More Sustainable Processes. *Org. Process Res. Dev.* **2011,** *15*, 912-917.

32. Sheldon, R. A., Metric of Green Chemistry and Sustainability: Past, Present, and Future. *ACS Sustainable Chemistry & Engineering* **2018,** *6*, 32-48.

33. Roschangar, F.; Sheldon, R. A.; Senanayake, C. H., Overcoming barriers to green chemistry in the pharmaceutical industry – the Green Aspiration Level™ concept. *Green Chemistry* **2015,** *17* (2), 752-768.

34. Frontana-Uribe, B. A.; Little, R. D.; Ibanez, J. G.; Palma, A.; Vasquez-Medrano, R., Organic electrosynthesis: a promising green methodology in organic chemistry. *Green Chemistry* **2010,** *12* (12), 2099-2119.

35. Schafer, H. J., Contributions of organic electrosynthesis to green chemistry. *Comptes Rendus Chimie* **2011,** *14*, 745-765.

36. Horn, E. J.; Rosen, B. R.; Baran, P. S., Synthetic Organic Electrochemistry: An Enabling and Innately Sustainable Method. *ACS Cent Sci* **2016,** *2*, 302-8.

CHAPTER 5

CONCLUSIONS AND FUTURE WORK

The anion pool method is an electrochemical approach for the derivatization of pharmaceutically important compounds. It has proven to be a value synthetic tool that has accessed selective functionalitzation routes with high product yields. This method provides a base and metal free procedure that is carried out in solvents recommended for pharmaceutical preparations. Hydrogen is the main by-product of generation of anion pool, which, if produced at a large enough scale could be used as a renewable fuel. These attributes comply with the principles of green chemistry, allowing synthetic chemists to carry out reactions in an atom-economic and environmentally friendly manner. Being able to carry out these transformations using a 9 V battery makes it adoptable for laboratories not equipped with sophisticated electrochemical instrumentation. Expansion of anion pool applications to amidation serves to address a challenge identified by ACS Green Chemistry Institute Pharamaceutical roundtable.

Anion pool approach provides some new applications for the concept of electrogenerated bases/ nucleophiles. There're a lot of opportunities that exist in the realm of conventional organic chemistry to introduce an electrochemical approach. Nucleophilic aromatic substitution in Figure 5.1 represents a potential area.[235] Our preliminary investigations have indicated that electrogenerated benzimidazole nucleophile can substitute fluorine in fluoropyridine. The yields remain to be optimized and substrate scope to be broadened.

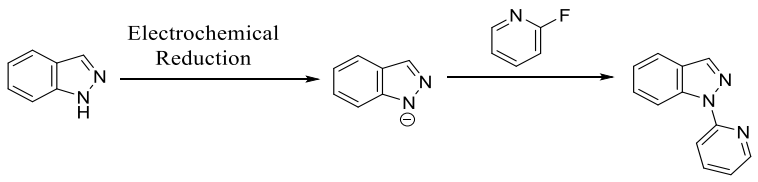


Figure 5.1 "Anion pool" driven nucleophilic aromatic substitution

Rearrangement reactions represent another important area to be addressed electrochemically. In Favorskii rearrangement in figure 5.2, the nucleophile is generated by using bases.[236] Introduction of an electrochemical approach widens the substrate scope of Favorskii rearrangement to substrates with base sensitive moieties such as aldehydes and esters.

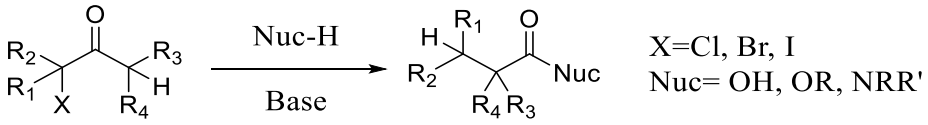


Figure 5.2 Favorskii rearrangement

The anion pool approach can be introduced into synthesis of medicinal compounds. The total synthesis of a medicinally important compound using sustainable methodologies such as photochemistry and electrochemistry remains to be reported.[62, 237-238] It provides the opportunity to explore the applicability of recently introduced techniques such as electrocatalytic reductive cross coupling,[62, 237] electrocatalytic amination,[238] and cation pool[103] approach in total synthesis. In order to reduce the solvent consumption in anion pool approach, a flow system can be introduced.[239] Carrying out anion pool reactions in ionic liquids represent another area for investigation.

References

1. Bunnett, J. F., Aromatic substitution by the SRN1 mechanism. *Accounts of Chemical Research* **1978,** *11* (11), 413-420.

2. Baumann, M.; Baxendale, I. R., Continuous photochemistry: the flow synthesis of ibuprofen via a photo-Favorskii rearrangement. *Reaction Chemistry & Engineering* **2016,** *1* (2), 147-150.

3. Durandetti, M.; Nédélec, J.-Y.; Périchon, J., Nickel-Catalyzed Direct Electrochemical Cross-Coupling between Aryl Halides and Activated Alkyl Halides. *The Journal of Organic Chemistry* **1996,** *61* (5), 1748-1755.

4. Li, H.; Breen, C. P.; Seo, H.; Jamison, T. F.; Fang, Y.-Q.; Bio, M. M., Ni-Catalyzed Electrochemical Decarboxylative C–C Couplings in Batch and Continuous Flow. *Organic Letters* **2018,** *20* (5), 1338-1341.

5. Li, C.; Kawamata, Y.; Nakamura, H.; Vantourout, J. C.; Liu, Z.; Hou, Q.; Bao, D.; Starr, J. T.; Chen, J.; Yan, M.; Baran, P. S., Electrochemically Enabled, Nickel-Catalyzed Amination. *Angewandte Chemie International Edition* **2017,** *56* (42), 13088-13093.

6. Hayashi, R.; Shimizu, A.; Yoshida, J.-i., The Stabilized Cation Pool Method: Metal- and Oxidant-Free Benzylic C–H/Aromatic C–H Cross-Coupling. *Journal of the American Chemical Society* **2016,** *138* (27), 8400-8403.

7. Endrődi, B.; Bencsik, G.; Darvas, F.; Jones, R.; Rajeshwar, K.; Janáky, C., Continuous-flow electroreduction of carbon dioxide. *Progress in Energy and Combustion Science* **2017,** *62*, 133-154.

APPENDIX A

EXPERIMENTAL DETAILS AND CHARACTERIZATION INFORMATION FOR

CHAPTER 1

A.1. General methods

The electrochemical experiments were conducted on a Pine wavedriver 20 biopotentiostat system. Preparative thin layer chromatography was performed on 0.5 mm Analtech® Silica gel (UV 254) plates using shortwave UV light for visualization. NMR spectra were recorded on Bruker Avance III 400 MHz NMR spectrometer and were calibrated using residual undeuterated solvent as an internal reference. (deuterated acetone: ^{1}H NMR 2.09 and ^{13}C NMR 29.92, 206.68).

A.2. Cyclic voltammetric studies of benzimidazoles

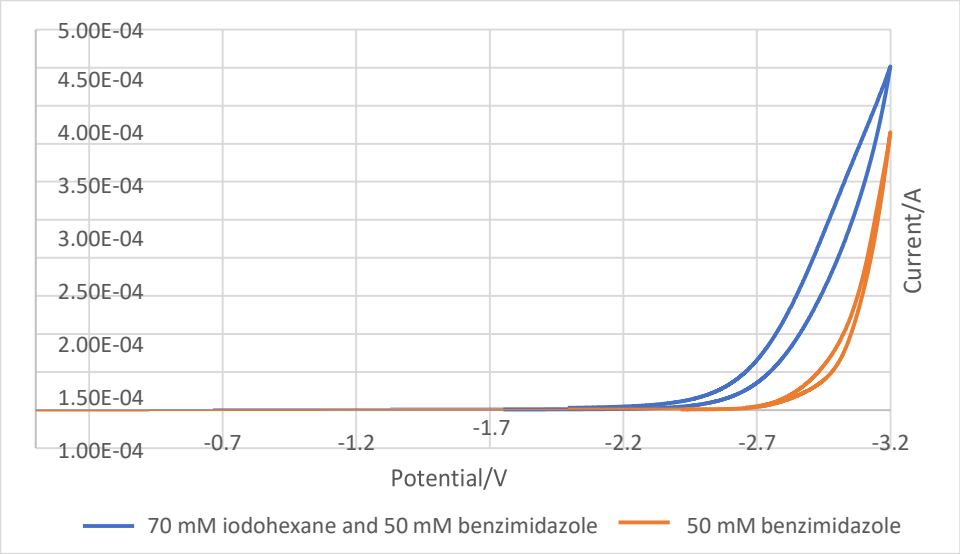


Figure A.1 Electrochemical data of benzimidazole obtained from experiments performed with a 0.1 M solution of tetrabutylammonium hexafluorophosphate (TBAPF6) in acetonitrile containing 0.5 m mol of benzimidazole. A glassy carbon electrode was employed as the working electrode, Pt as the counter electrode and saturated calomel electrode (SCE) as the reference electrode. The cyclic voltammograms were obtained at the scan rate of 100 m V/s.

A.3. Gas chromatographic detection of hydrogen

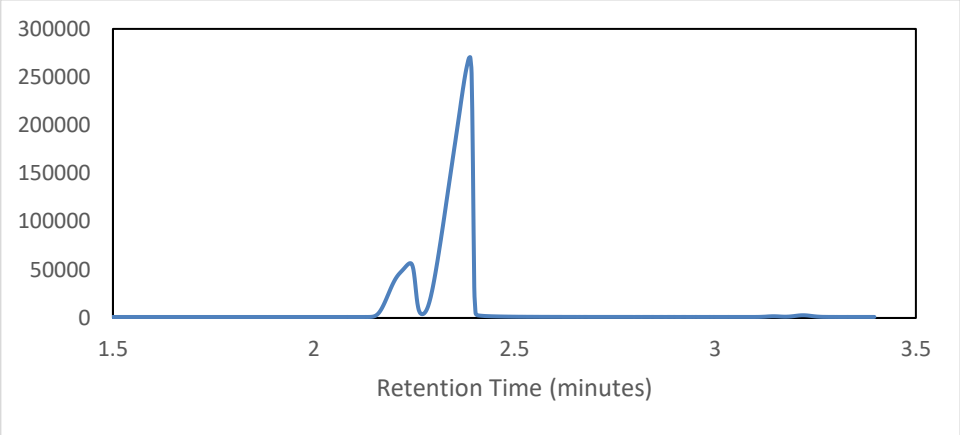


Figure A.2 Response for 100% H_2 on the HP 5890 Series II gas chromatograph equipped with a Carboxen 1010 PLOT capillary column using Ar as the carrier gas at a constant oven temperature of 70 ^oC.

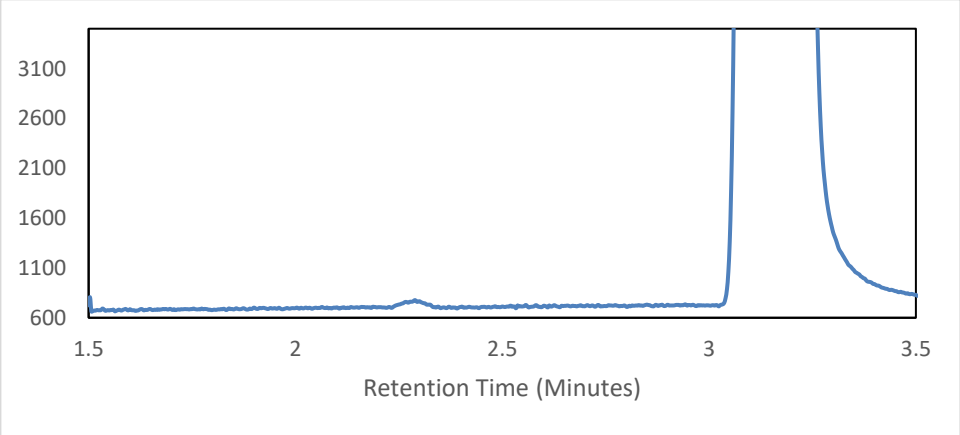


Figure A.3 Chromatograph of the headspace gas post reaction showing a peak at a retention time between 2.25 and 2.3 minutes indicating the presence of H_2 in the reaction head-space gas. The large peak above 3 minutes retention is N_2. GC conditions as described in Figure S2.

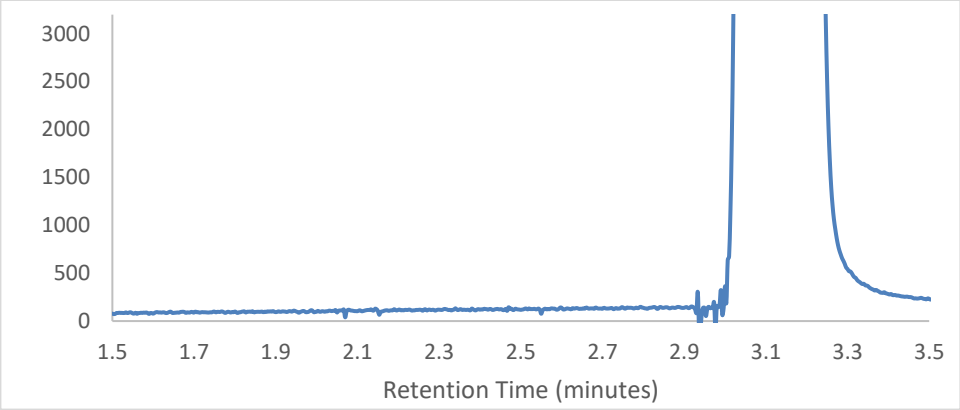
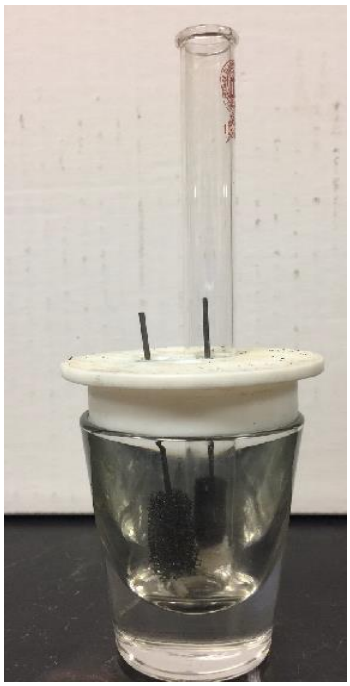


Figure A.4 Chromatograph of the reaction head space before the reaction was performed. No peak is observed between 2 and 2.5 minutes retention showing the absence of H_2.

A.4. Illustration of the electrochemical cell



A.5 . Spectra of synthesized compounds

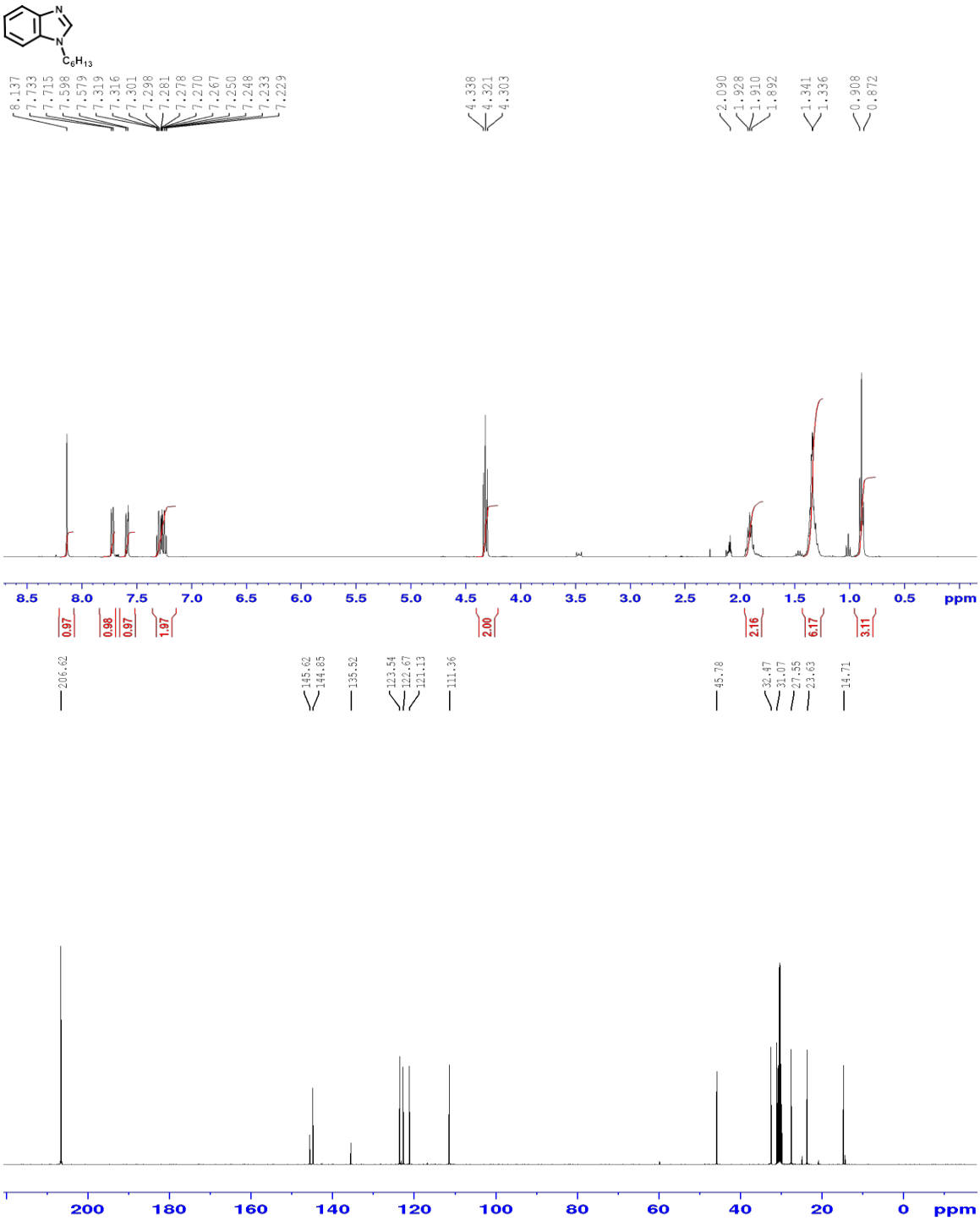


Figure A.5 ^{1}H & ^{13}C spectra of product 1 in chapter 2. The spectra matched reference[1]

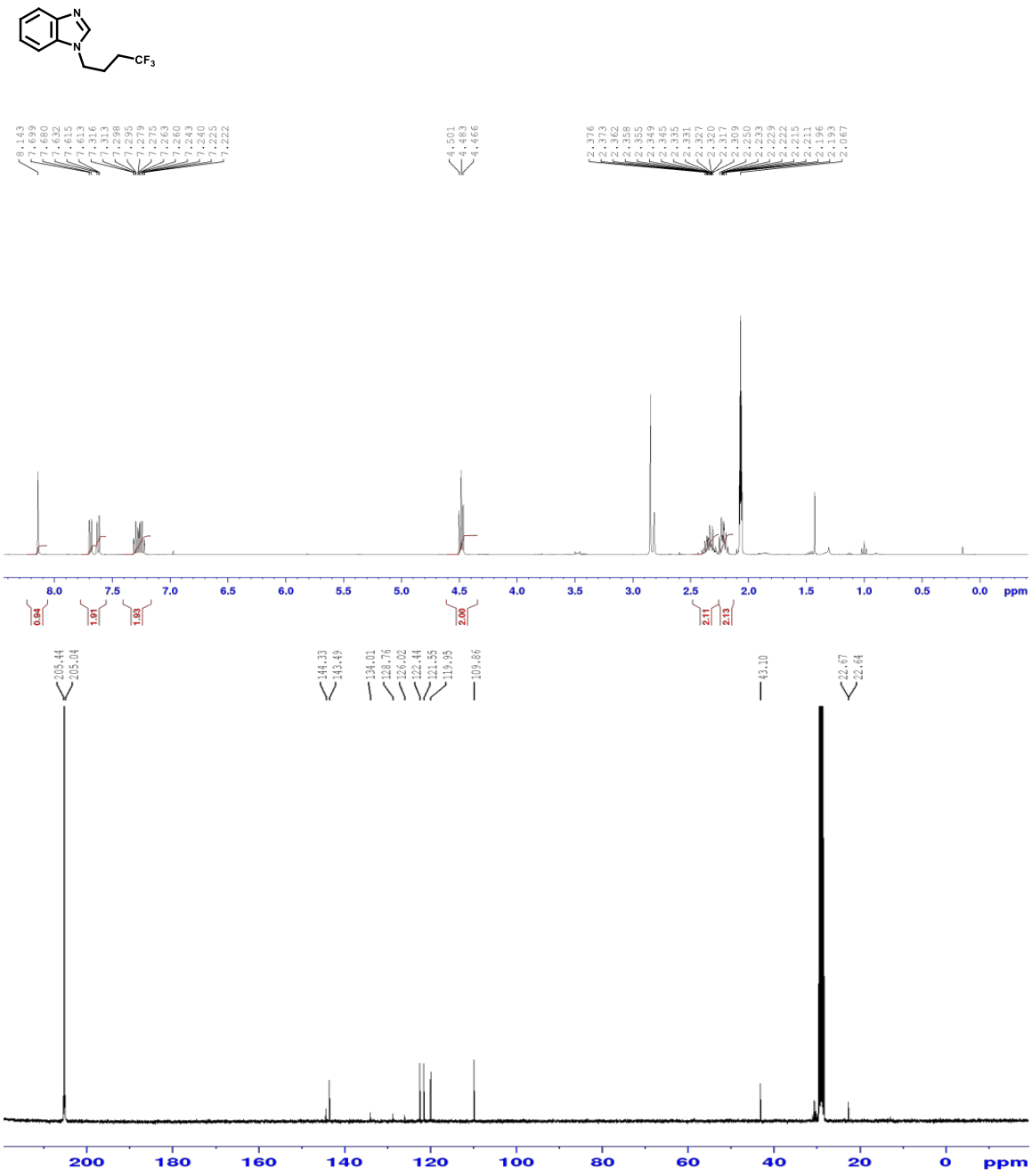


Figure A.6 ^{1}H & ^{13}C spectra of product 2 in chapter 2.

C, H, N analysis

Anal. Calcd for $C_{11}H_{11}F_3N_2$: C, 57.89; H, 4.86; N,12.28. Found: C, 57.65; H, 5.31; N, 10.90.

GC-MS (EI) m/z : 131(100%), 209(2%), 228(51%)

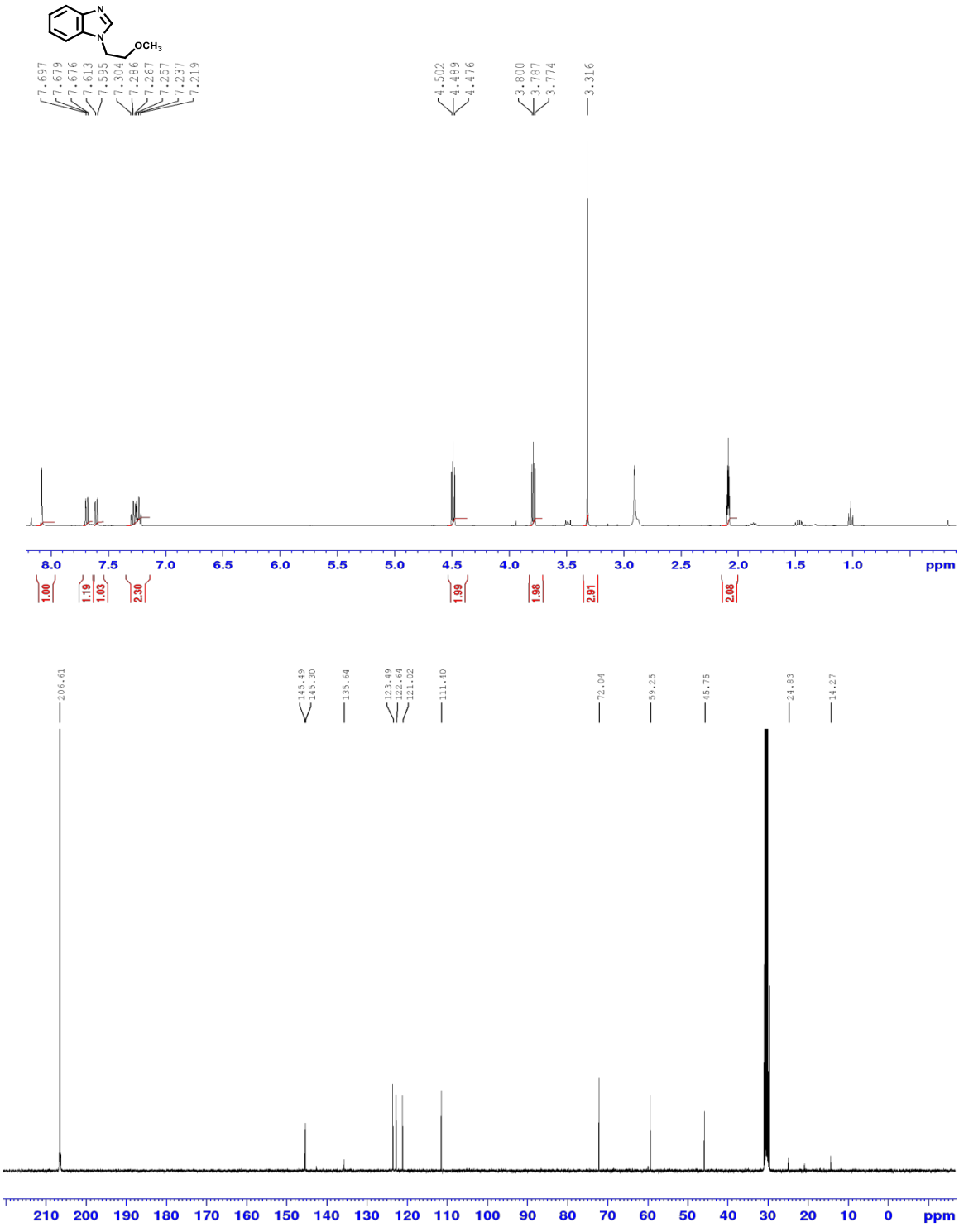


Figure A.7 ^{1}H & ^{13}C spectra of product 3. The spectra matched reference[3]

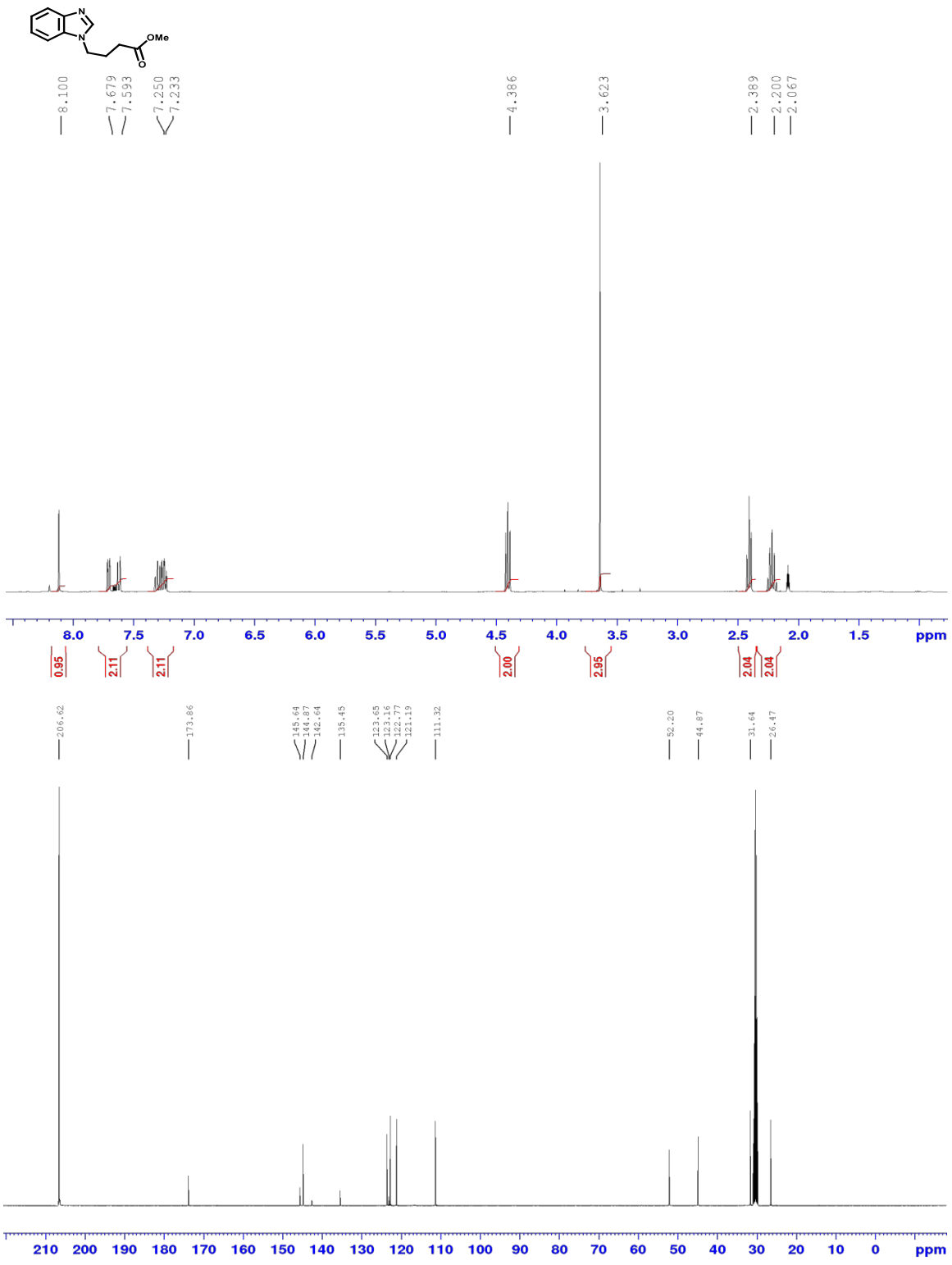


Figure A.8 ^{1}H & ^{13}C spectra of product 4. The spectra matched reference[3]

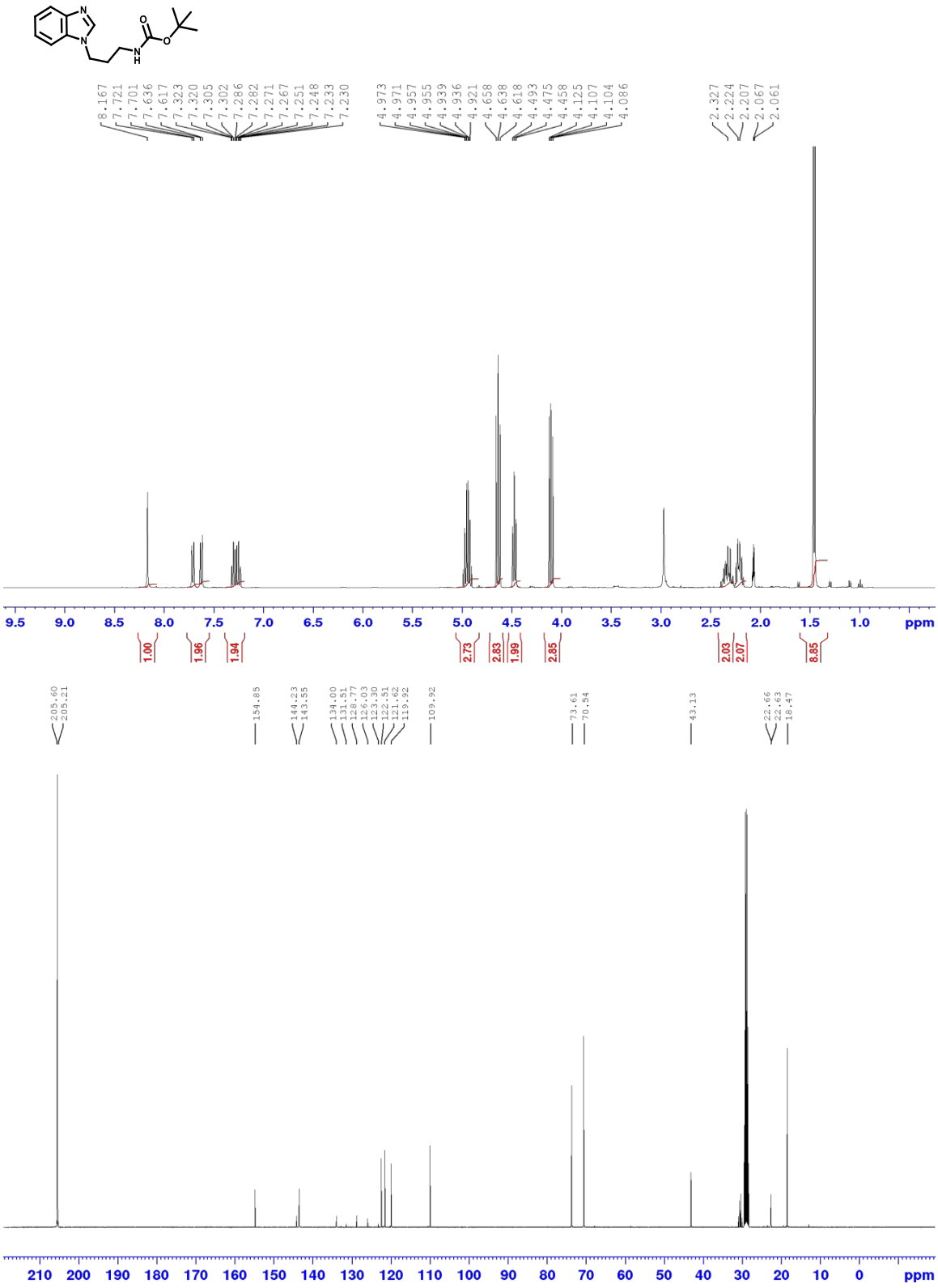


Figure A.9 ^{1}H & ^{13}C spectra of product 5. The spectra matched reference[4]

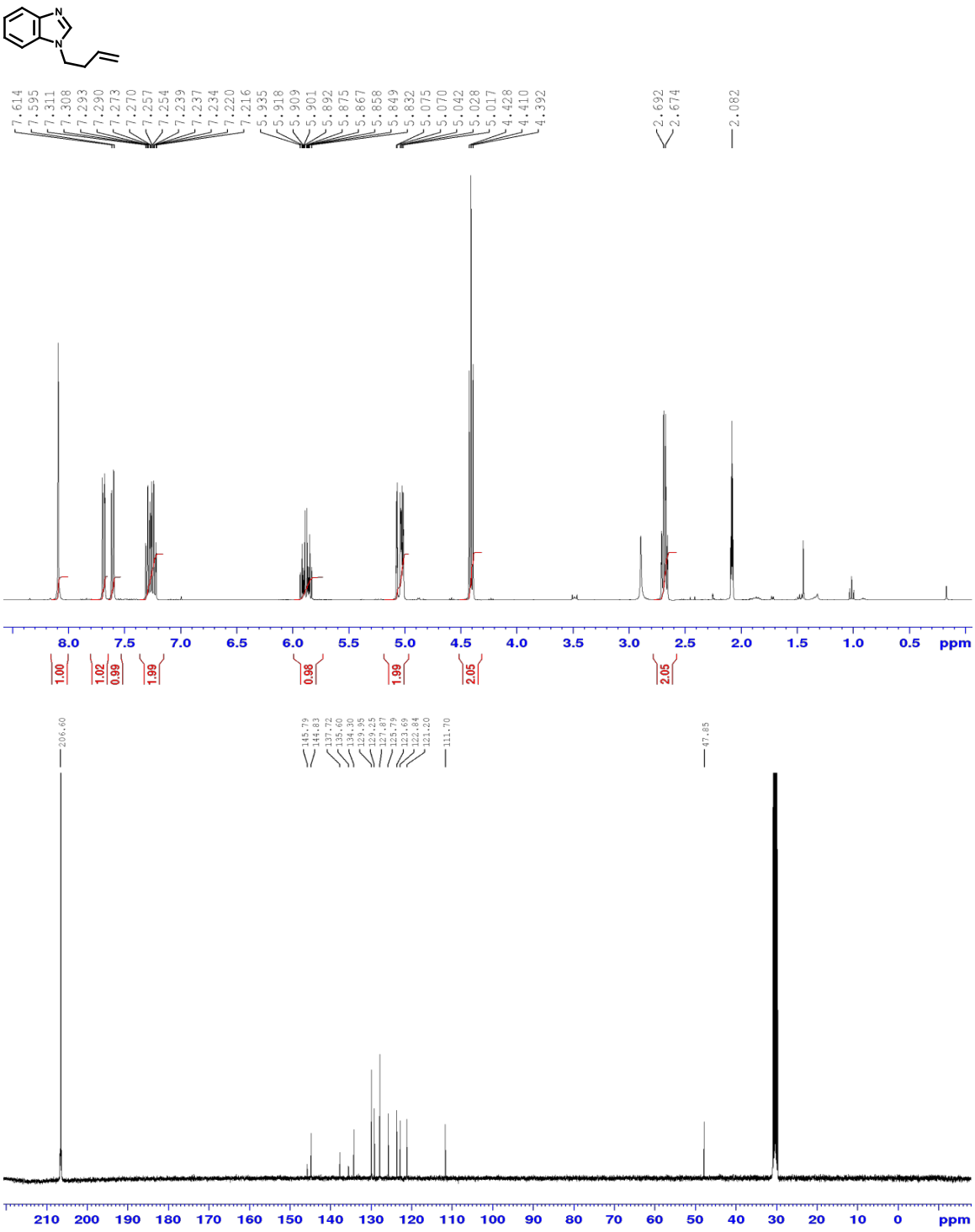


Figure A.10 ^{1}H & ^{13}C spectra of product 6. The spectra matched reference[5]

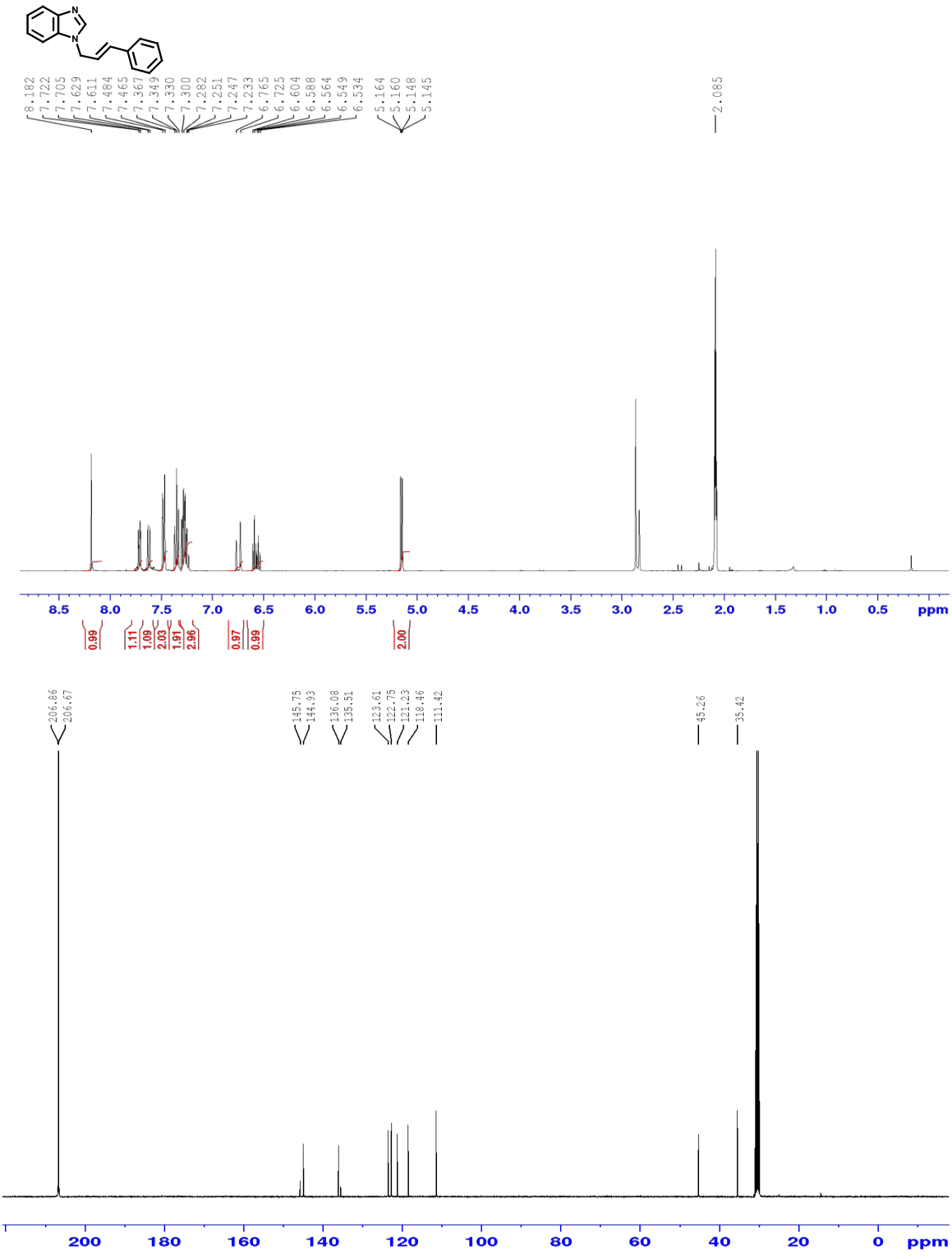


Figure A.11 ^{1}H & ^{13}C spectra of product 7. The spectra matched reference[6]

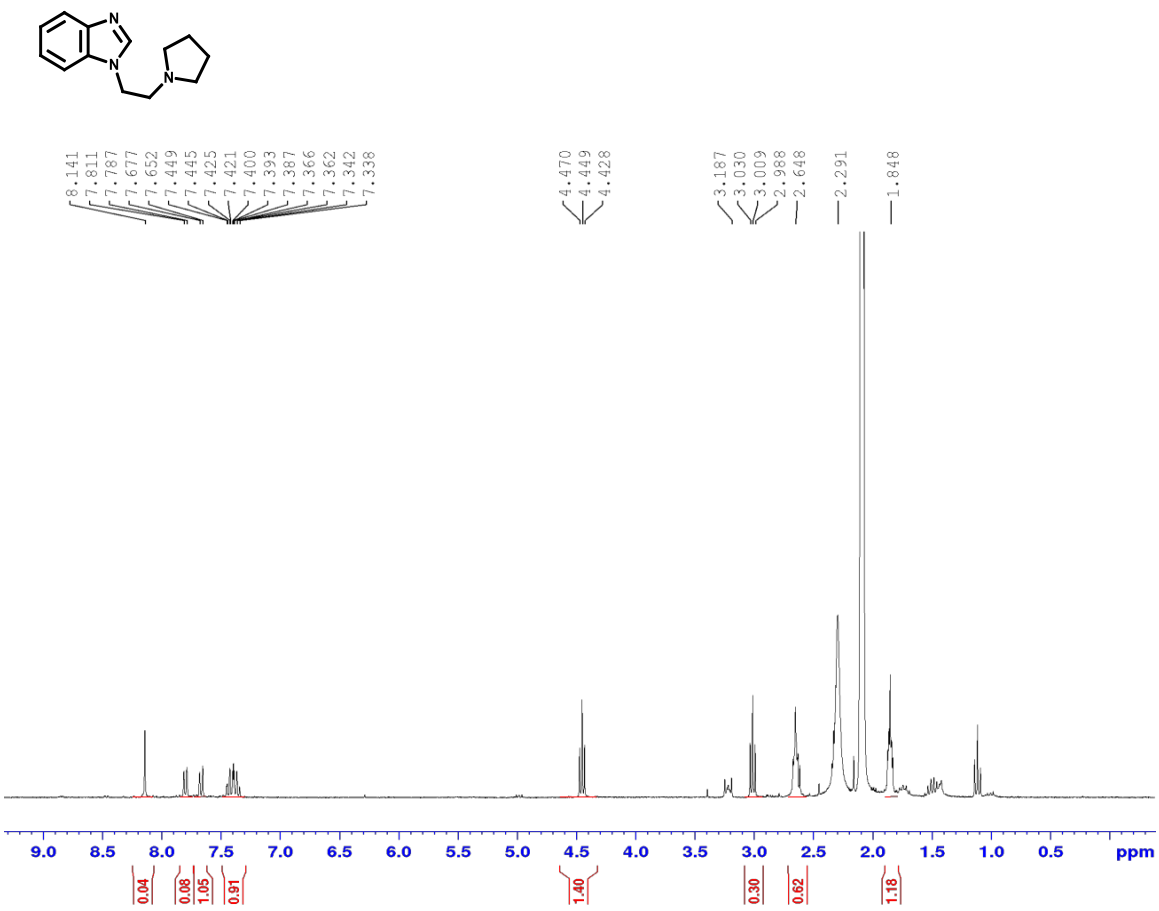


Figure A.12 ^{1}H spectrum of product 8. The spectrum matched reference[7]

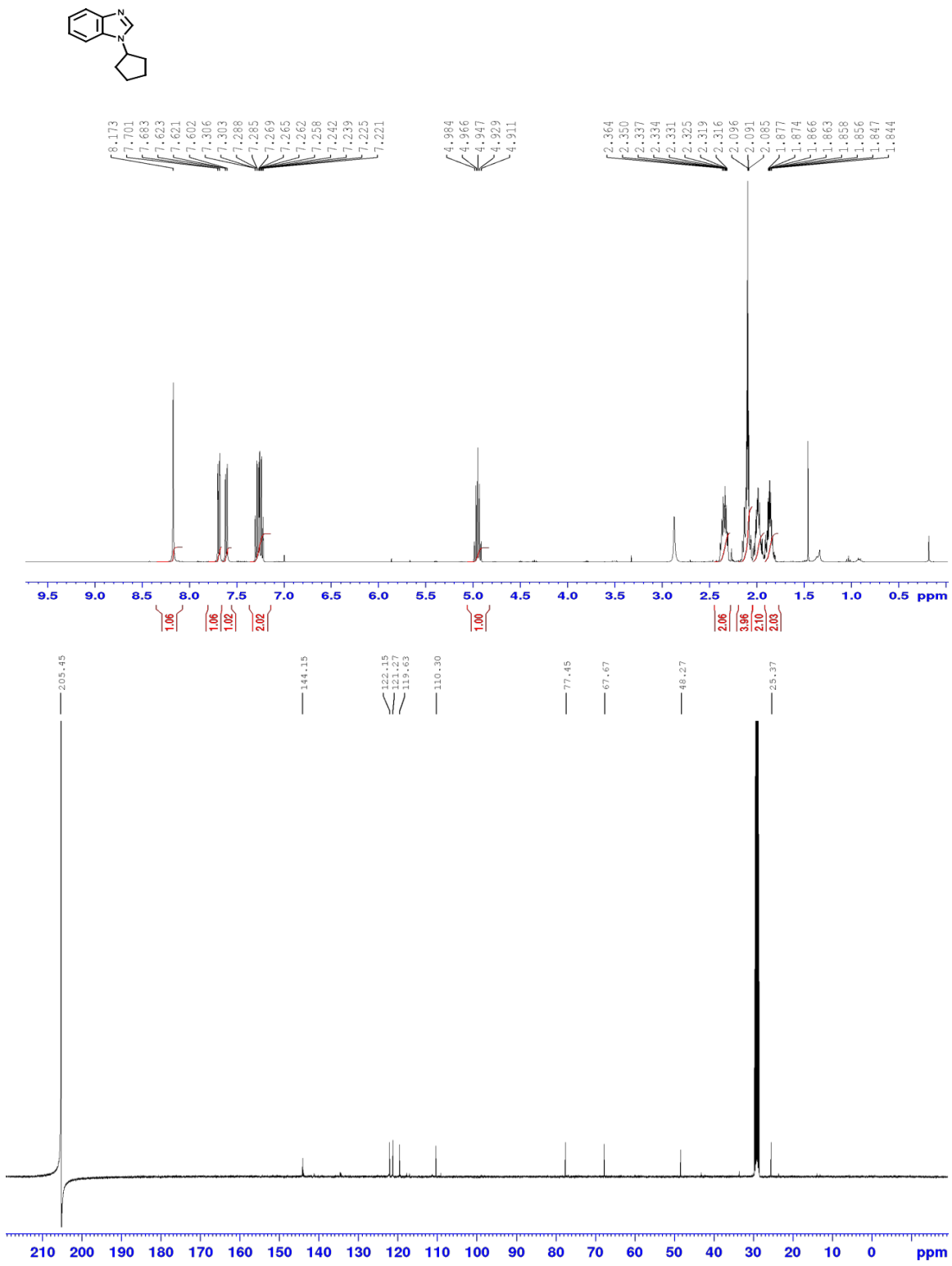


Figure A.13 ^{1}H & ^{13}C spectra of product 9. The spectra matched reference[8]

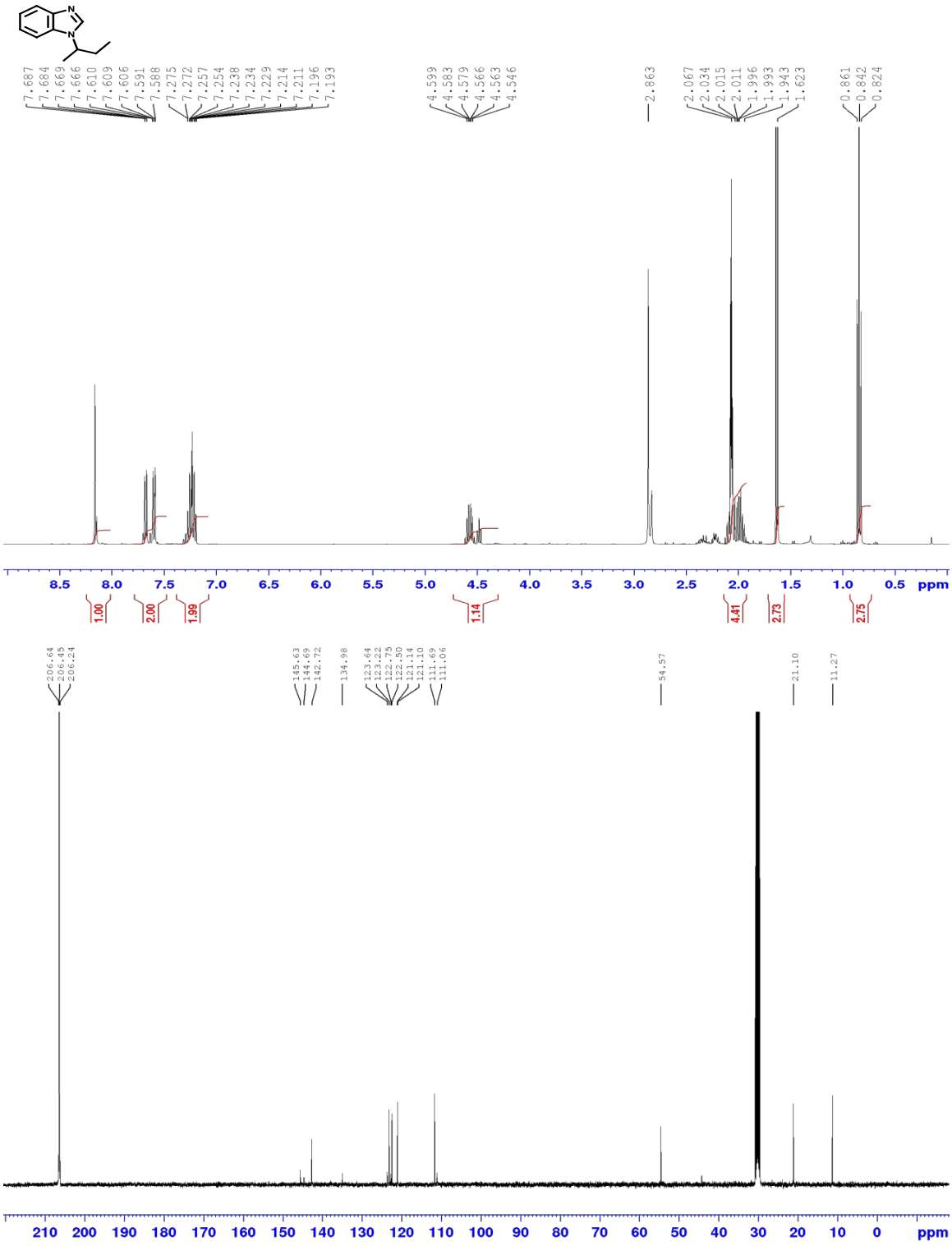


Figure A.14 ^{1}H & ^{13}C spectra of product 10. The spectra matched reference[9]

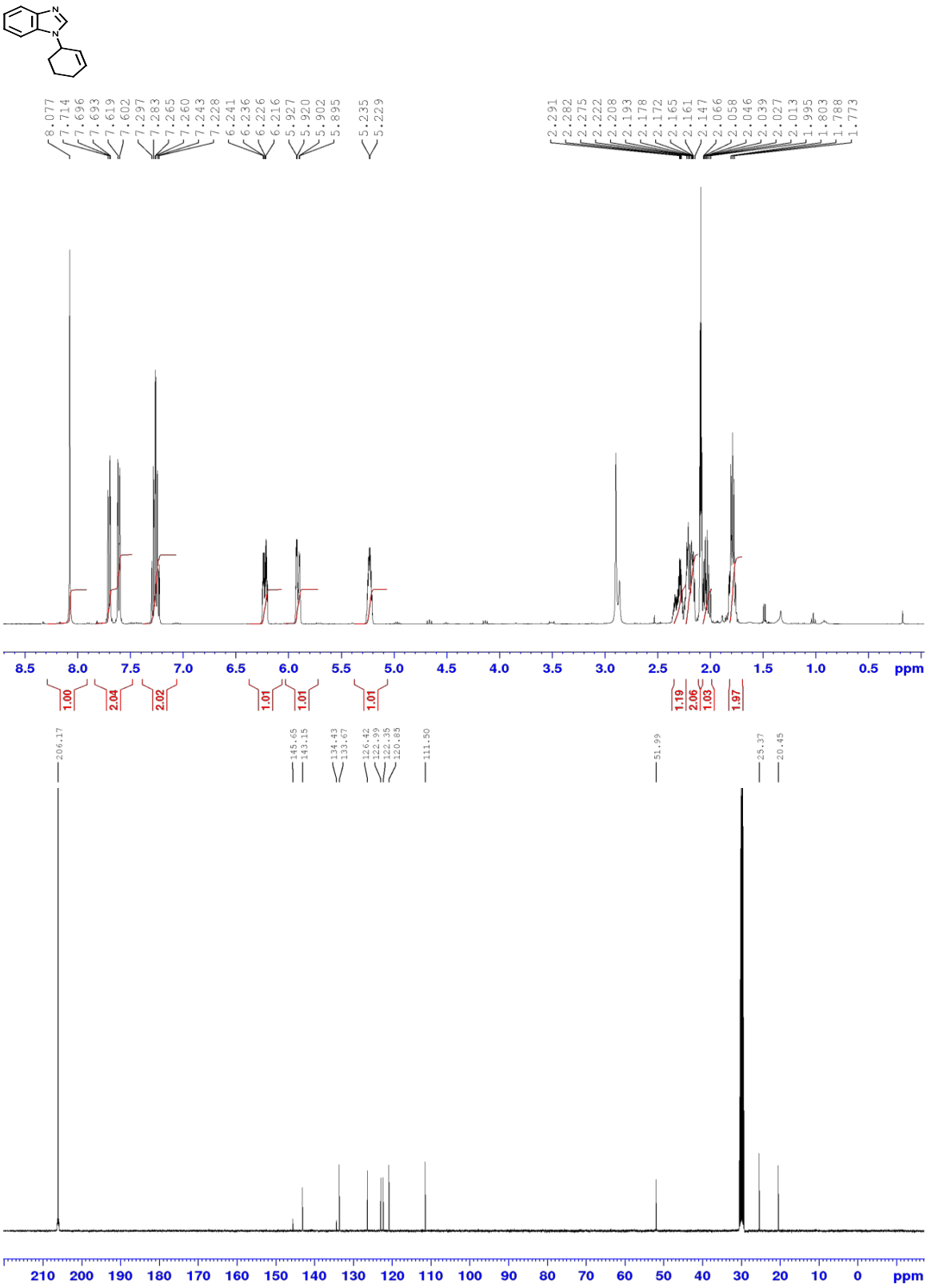


Figure A.15 ^{1}H & ^{13}C spectra of product 11. The spectra matched reference[10]

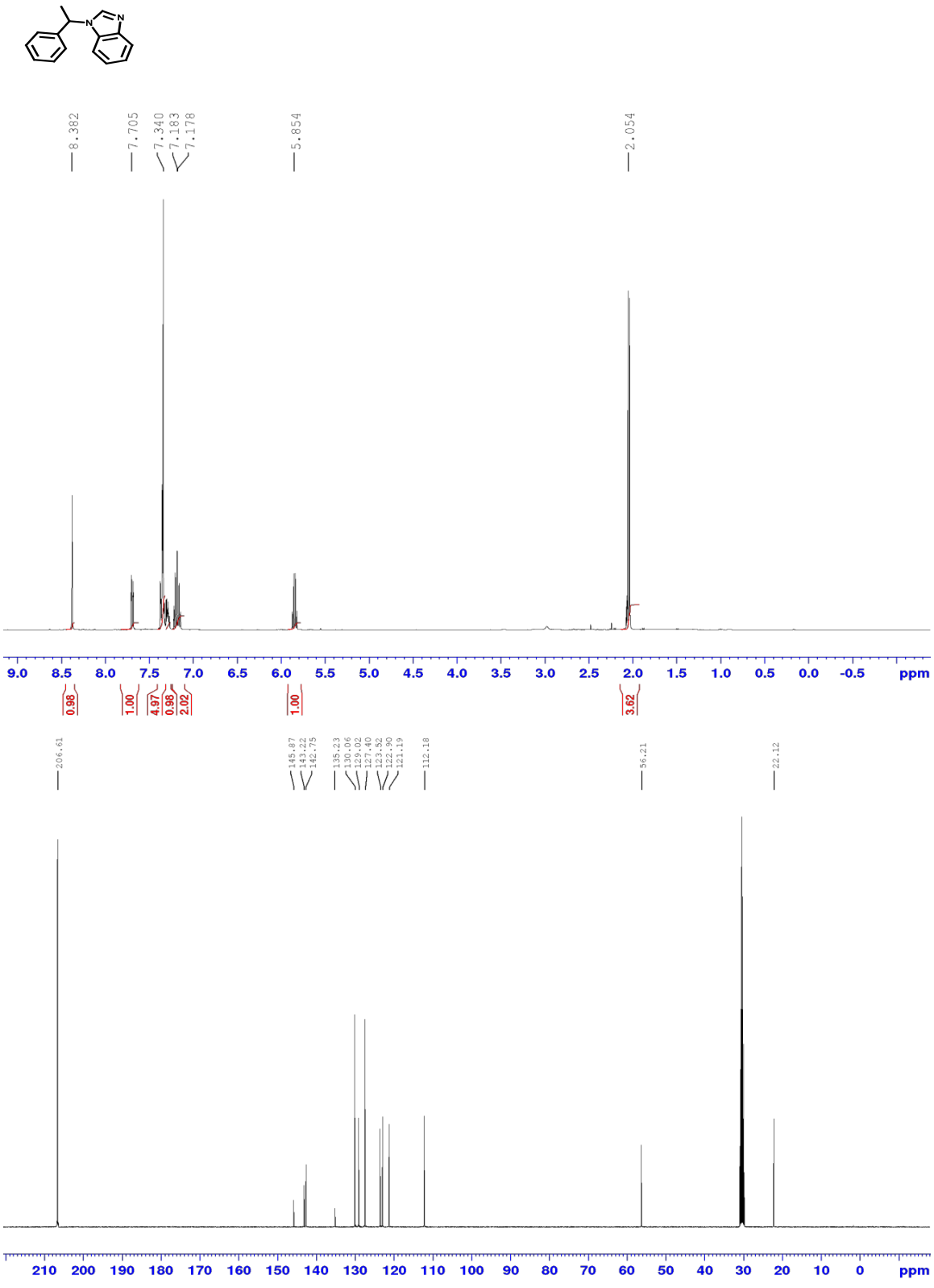


Figure A.16 ^{1}H & ^{13}C spectra of product 12. The spectra matched reference[11]

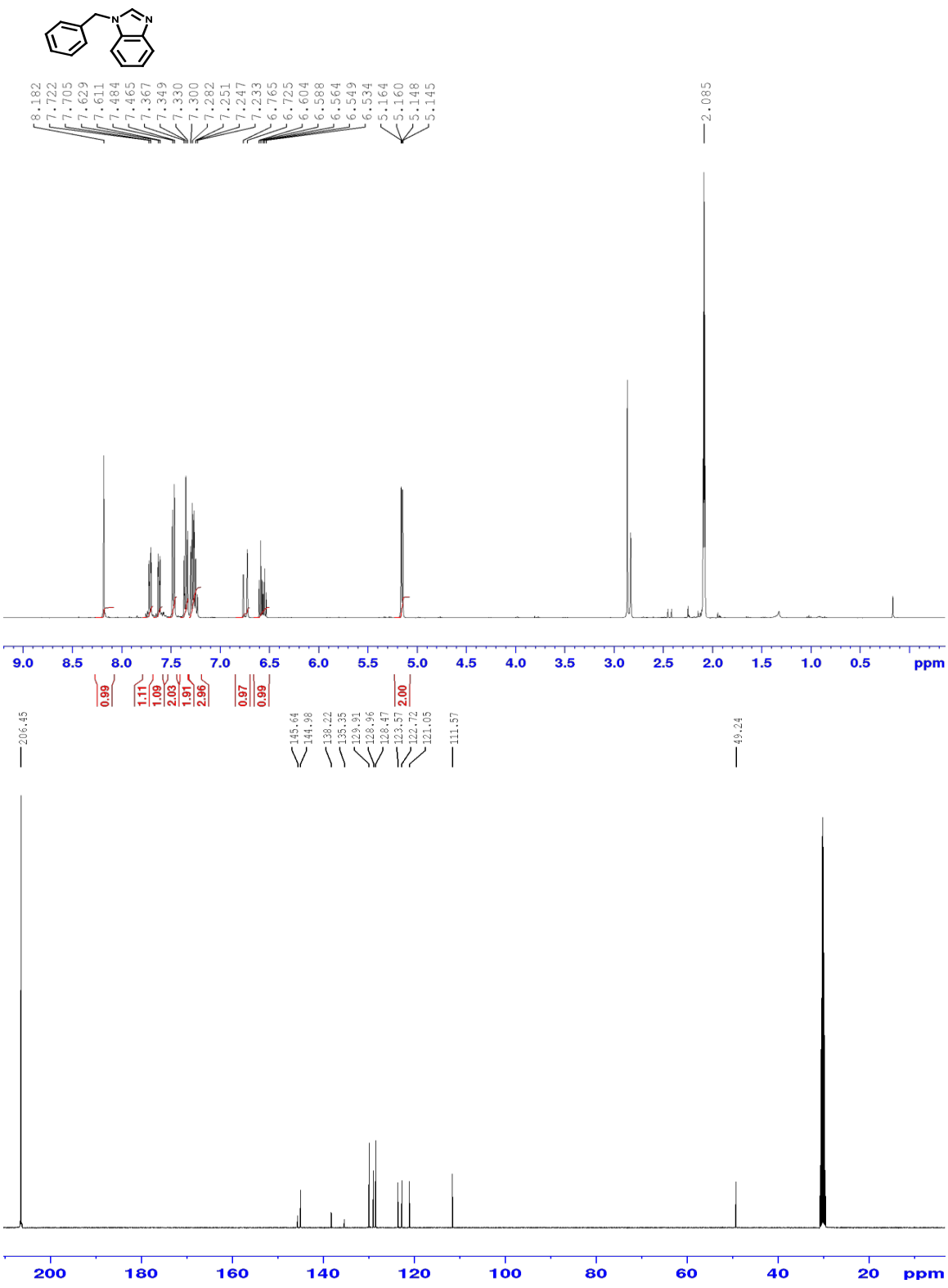


Figure A.17 ^{1}H & ^{13}C spectra of product 13. The spectra matched reference[9]

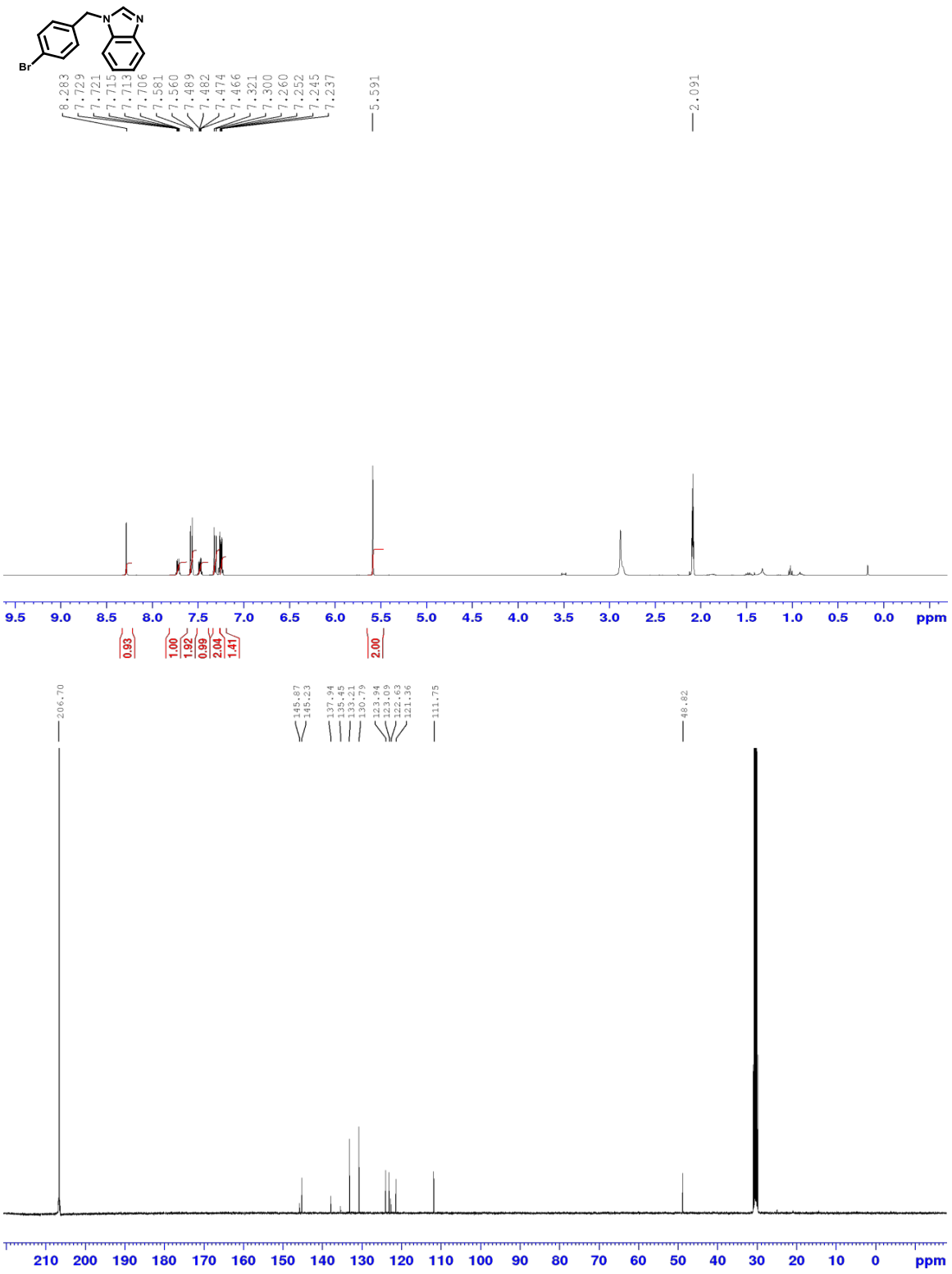


Figure A.18 ^{1}H & ^{13}C spectra of product 14. The spectra matched reference[12]

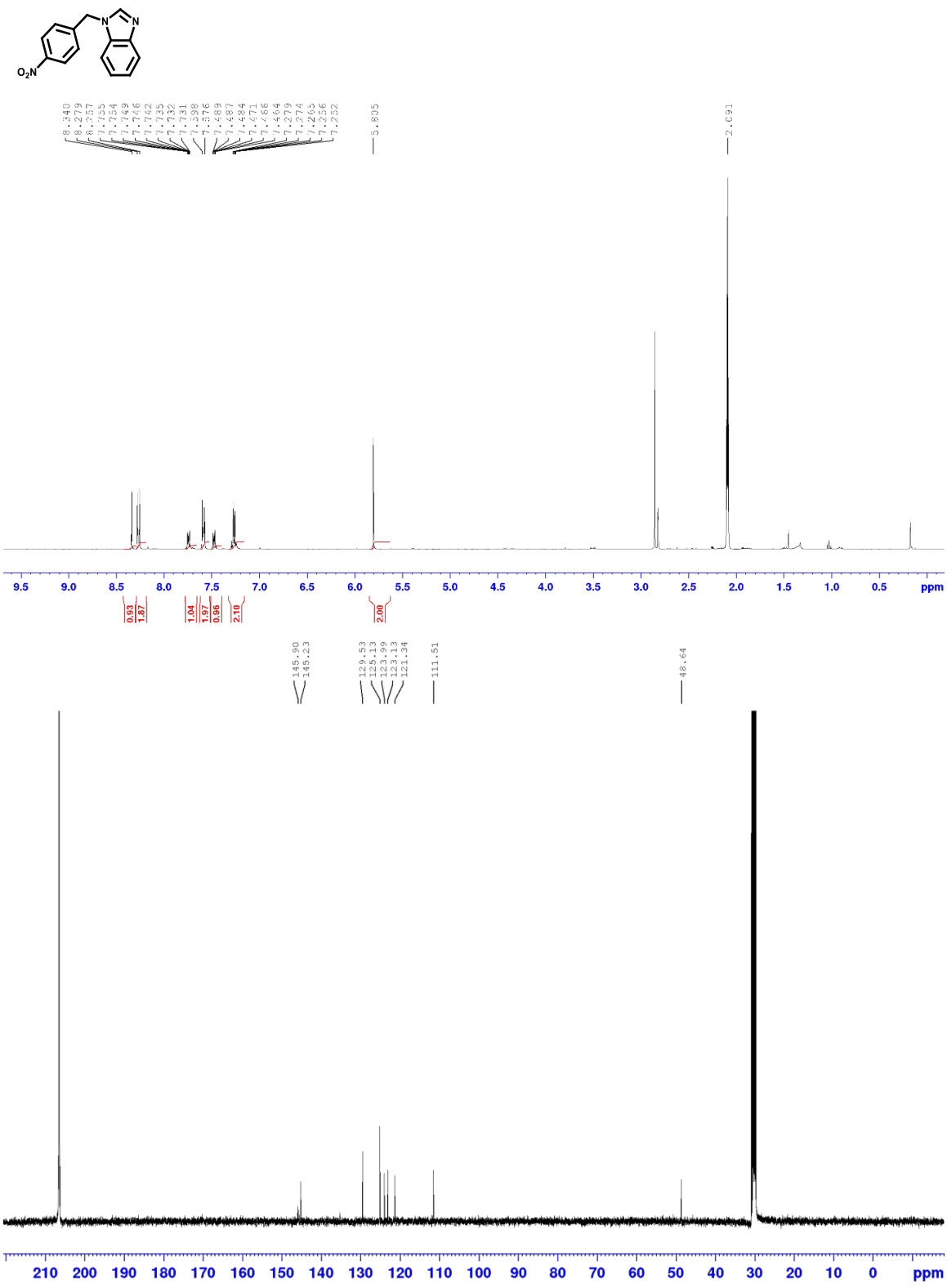


Figure A.19 ^{1}H & ^{13}C spectra of product 15. The spectra matched reference[13]

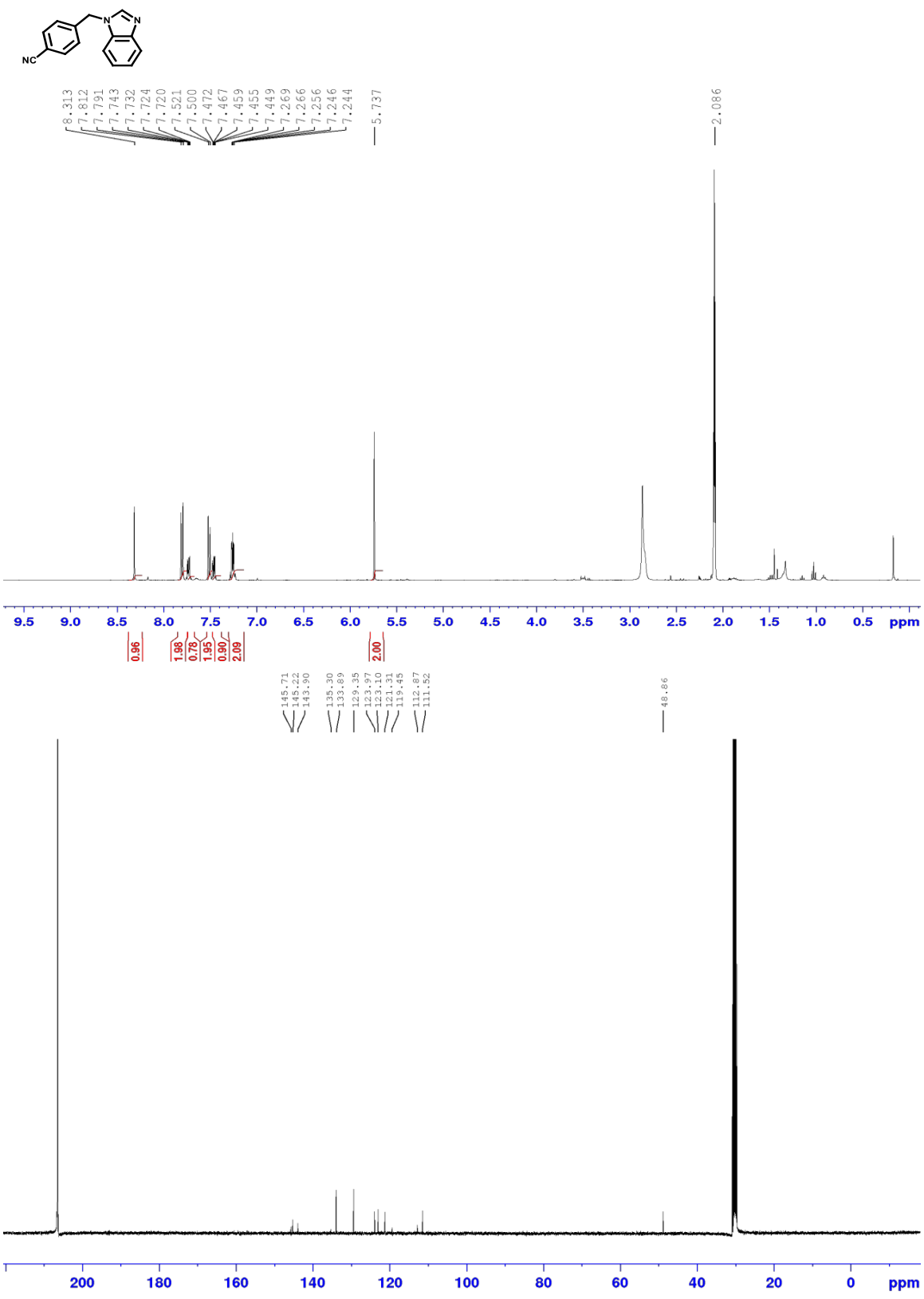


Figure A.20 ^{1}H & ^{13}C spectra of product 16. The spectra matched reference[13]

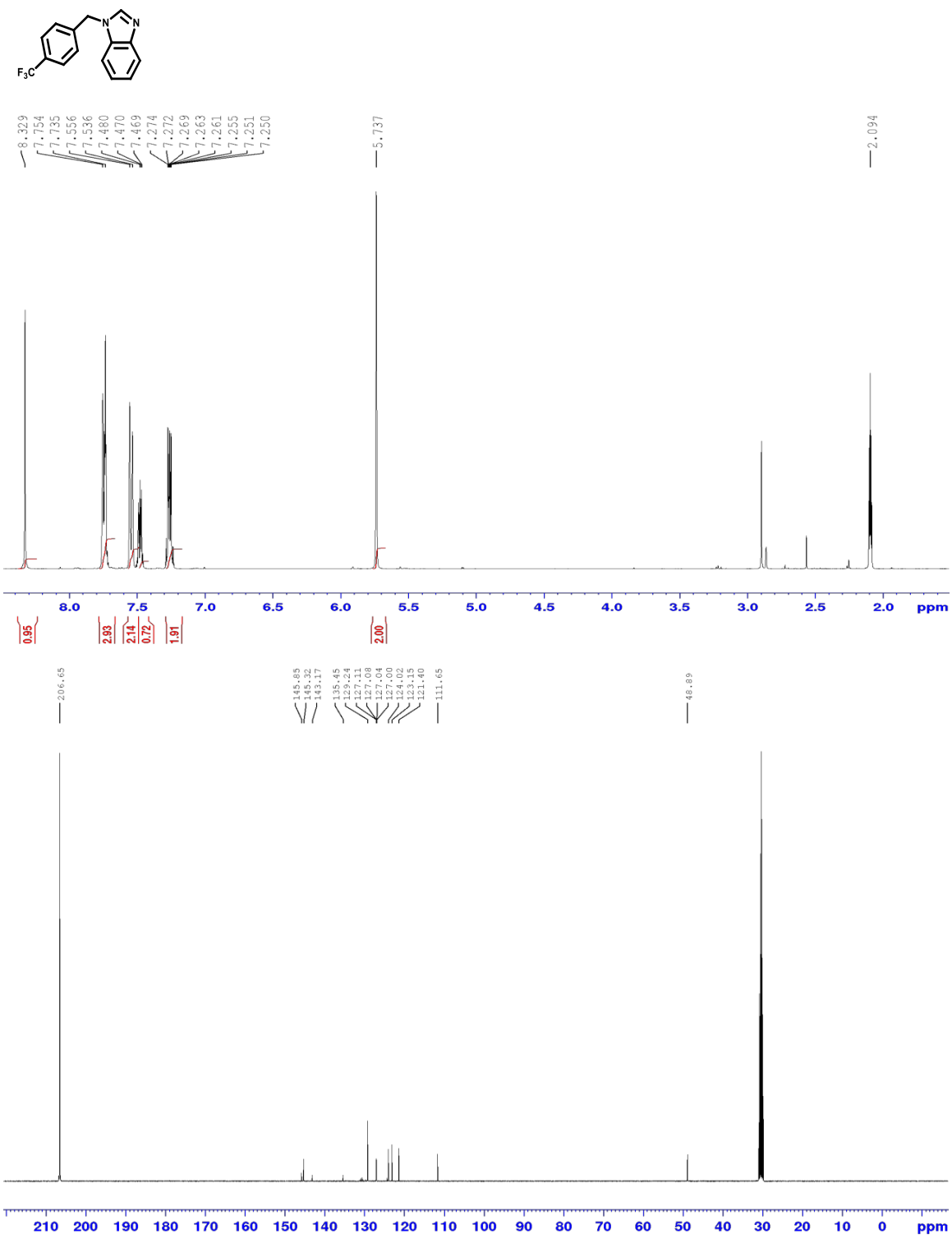


Figure A.21 ^{1}H & ^{13}C spectra of product 17. The spectra matched reference[14]

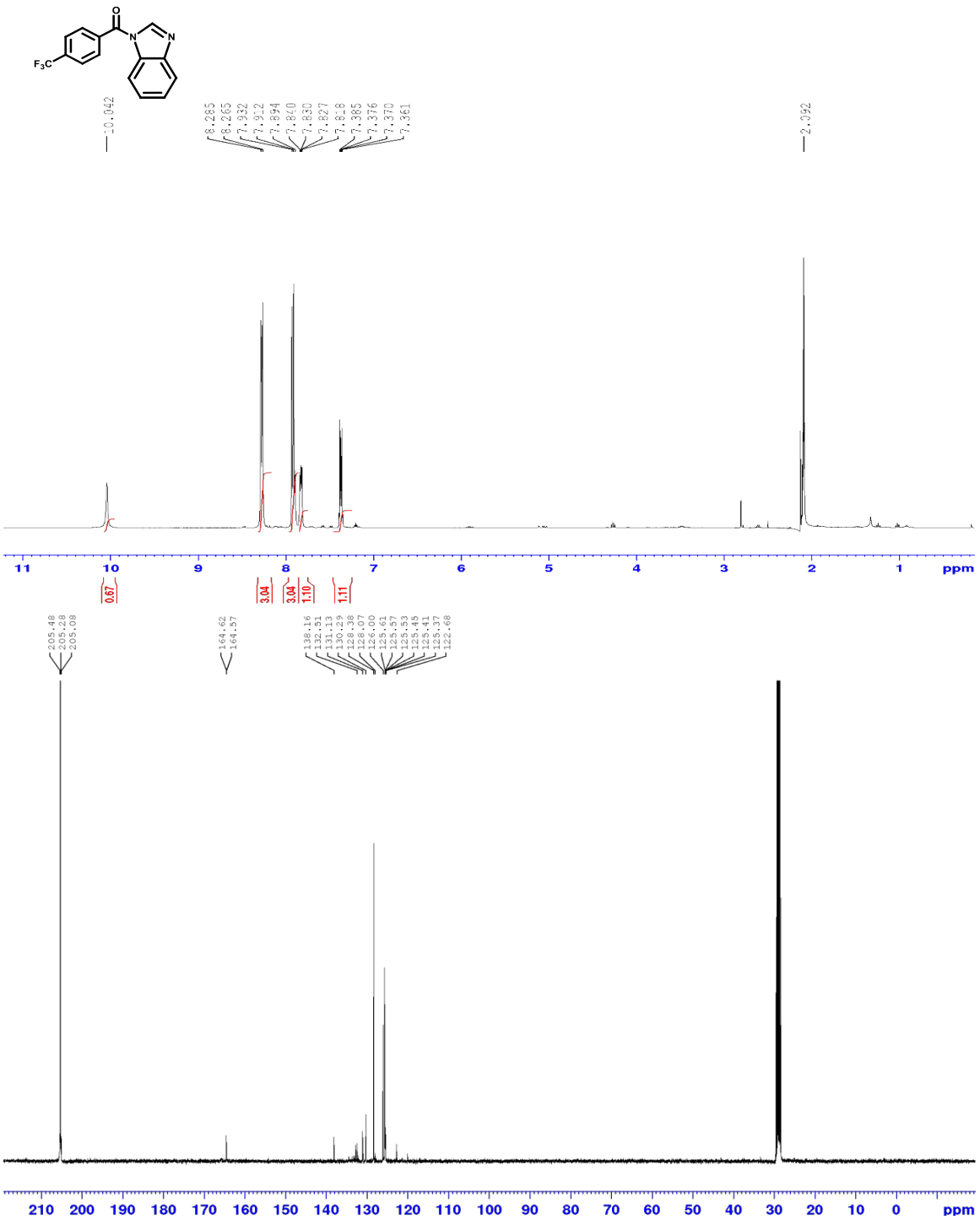


Figure A.22 ^{1}H & ^{13}C spectra of product 18. The spectra matched reference[15]

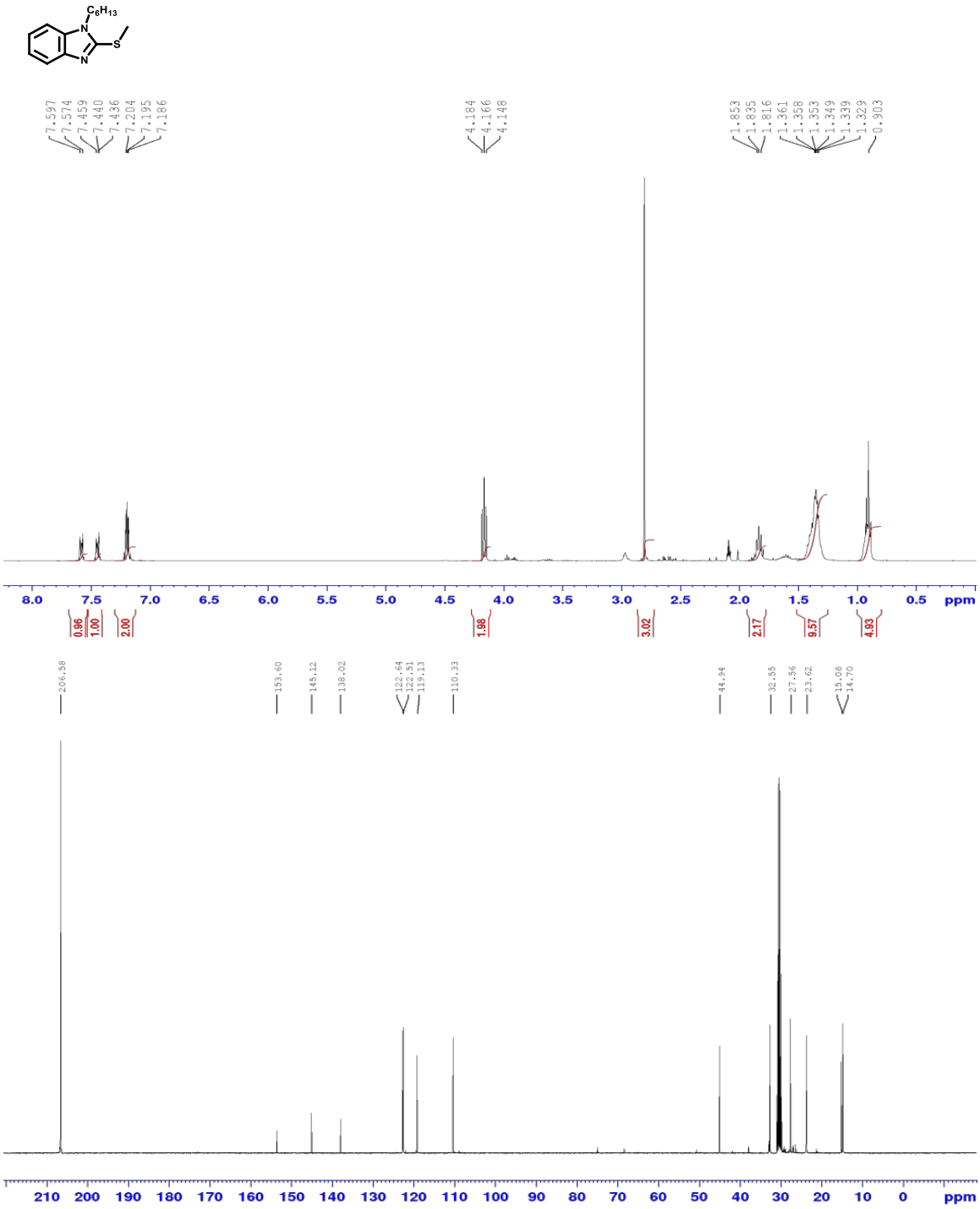


Figure A.23 ^{1}H & ^{13}C spectra of product 19

C, H, N analysis

Anal. Calcd for $C_{14}H_{20}N_2S$ C, 67.70; H,8.12; N,11.28. Found: C, 67.05; H,8.68; N,11.25. GC-MS (EI) m/z : 242(100%), 249(50%)

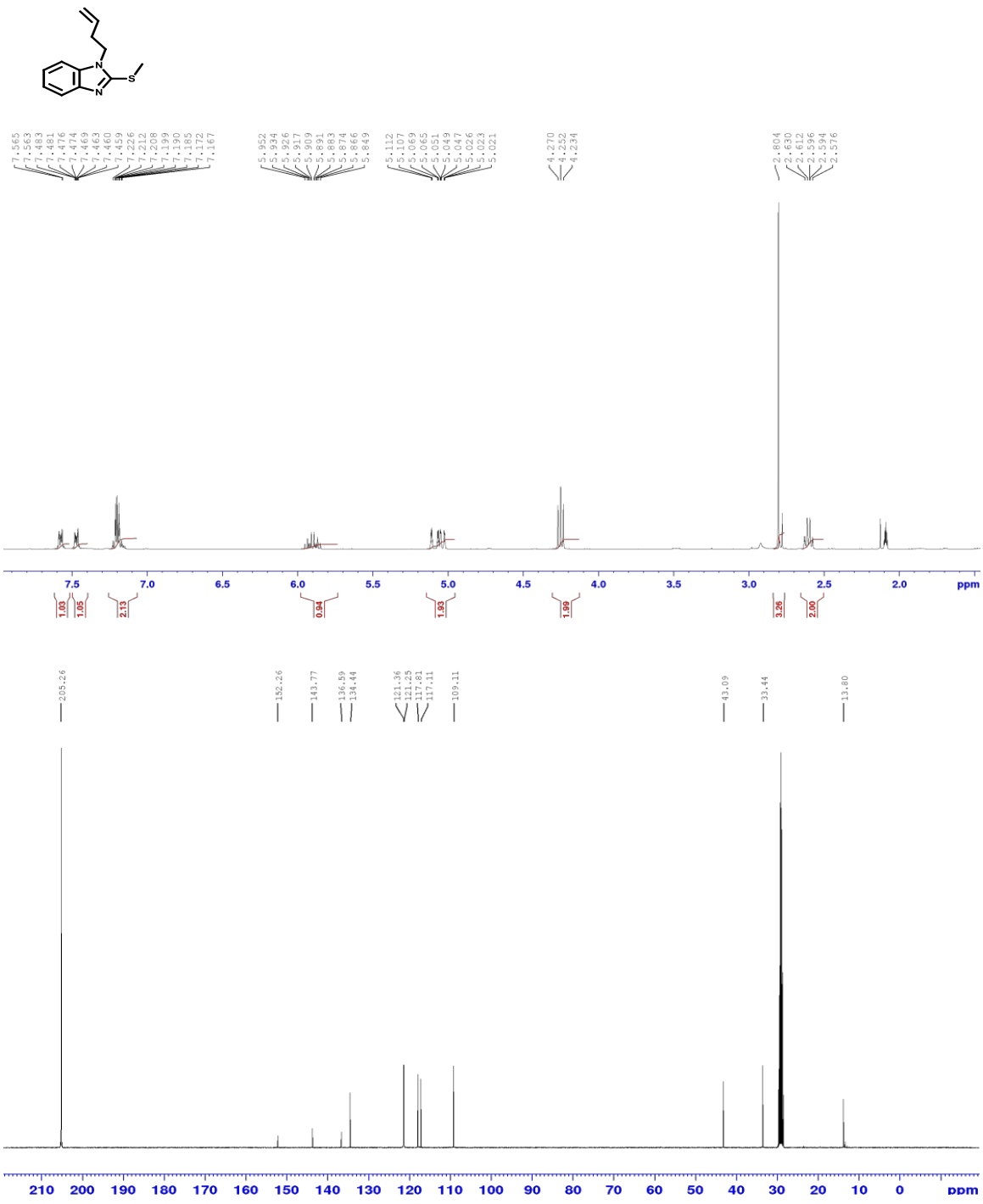


Figure A.24 ^{1}H & ^{13}C spectra of product 20.

C, H, N analysis

Anal. Calcd for $C_{12}H_{14}N_2S$ C,66.02; H,6.46; N,12.83. Found: C,65.71; H,6.38; N,12.50. GC-MS (EI) m/z : 165(10%), 219(100%)

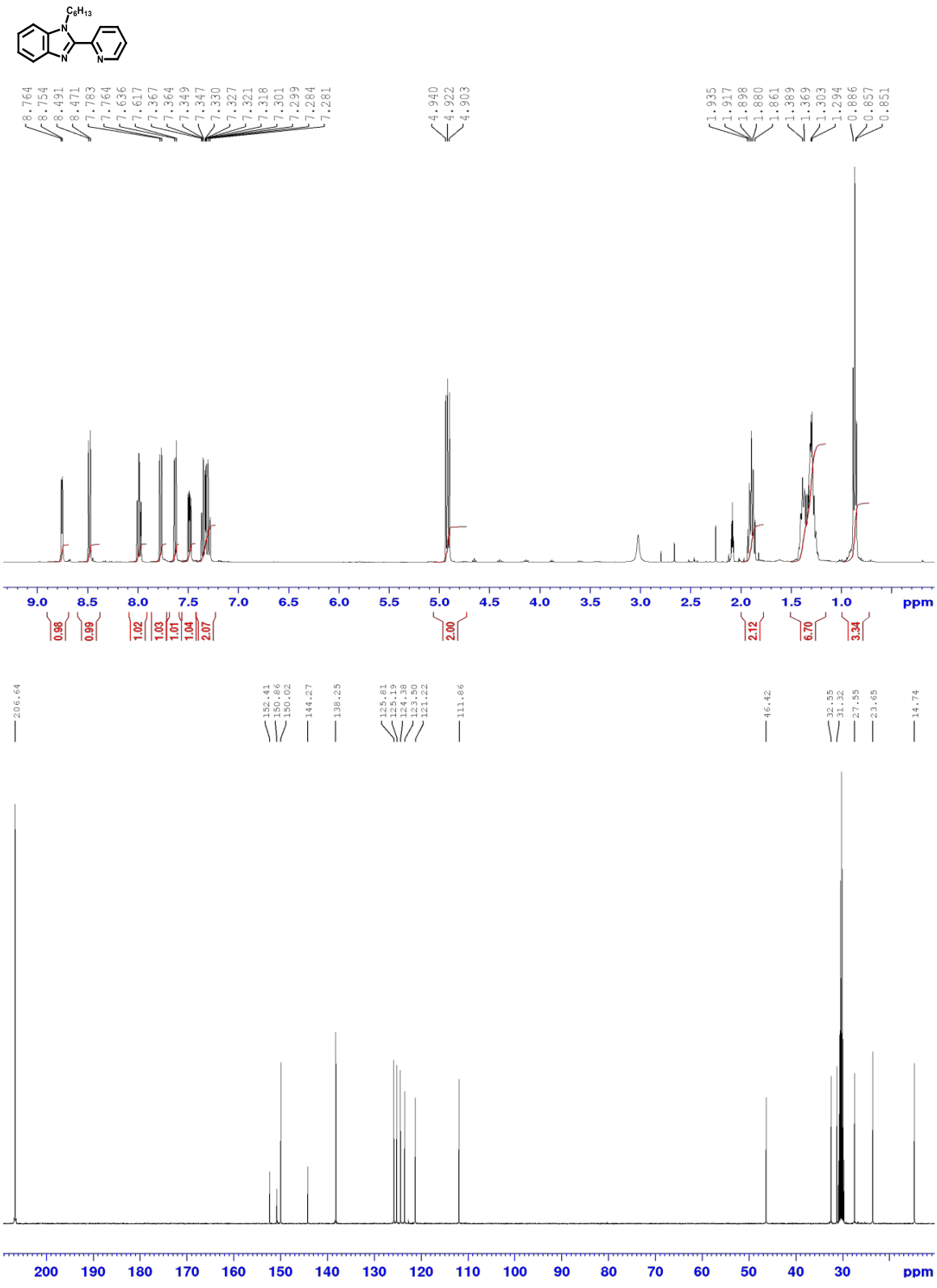


Figure A.25 ^{1}H & ^{13}C spectra of product 21. The spectra matched reference[16]

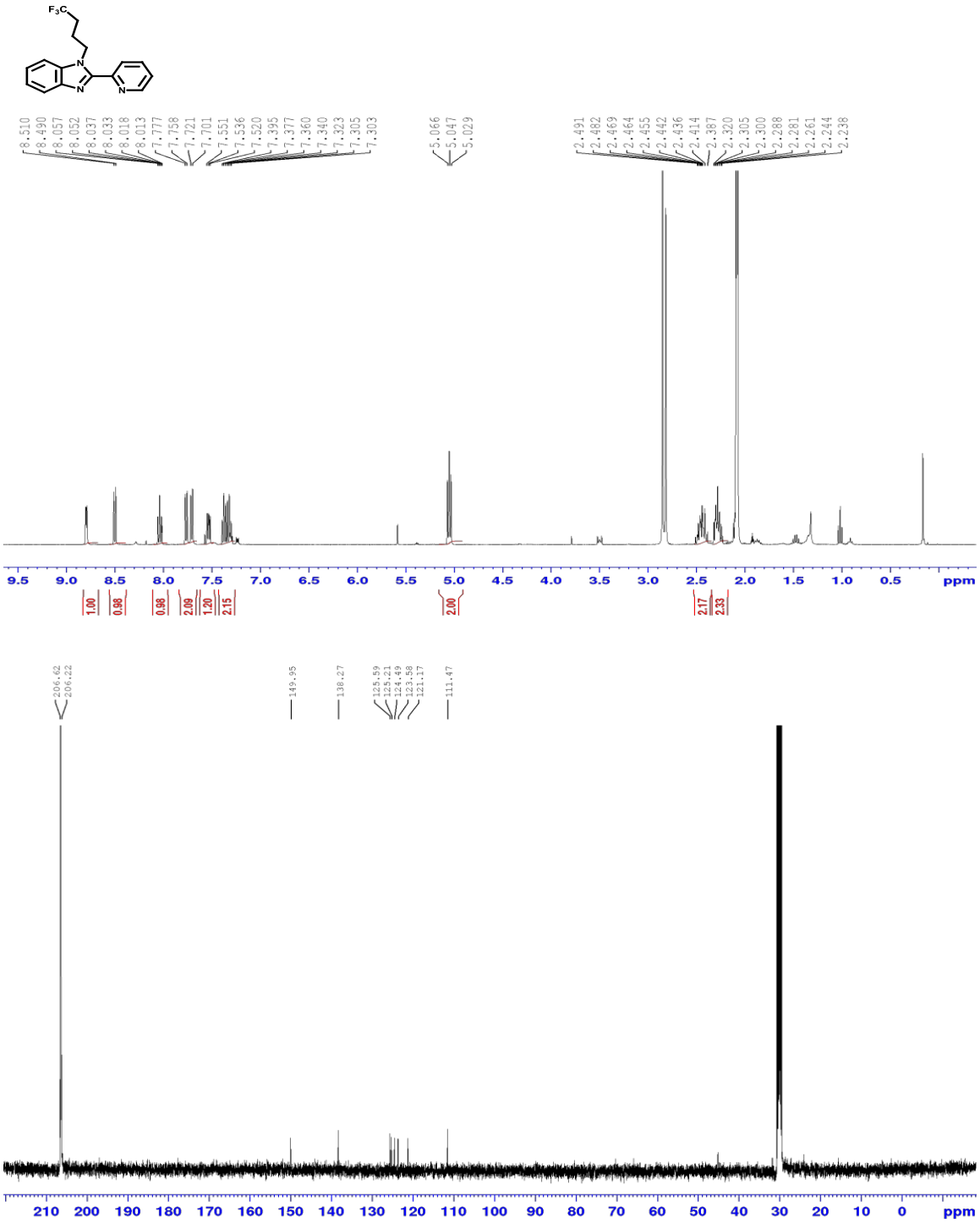


Figure A.26 ^{1}H & ^{13}C spectra of product 22.

C, H, N analysis

Anal. Calcd for $C_{14}H_{20}N_2S$ C, 62.95; H,4.62; N,13.76. Found: C, 62.44; H,4.08; N,11.97. GC-MS (EI) m/z : 242(10%), 306(100%)

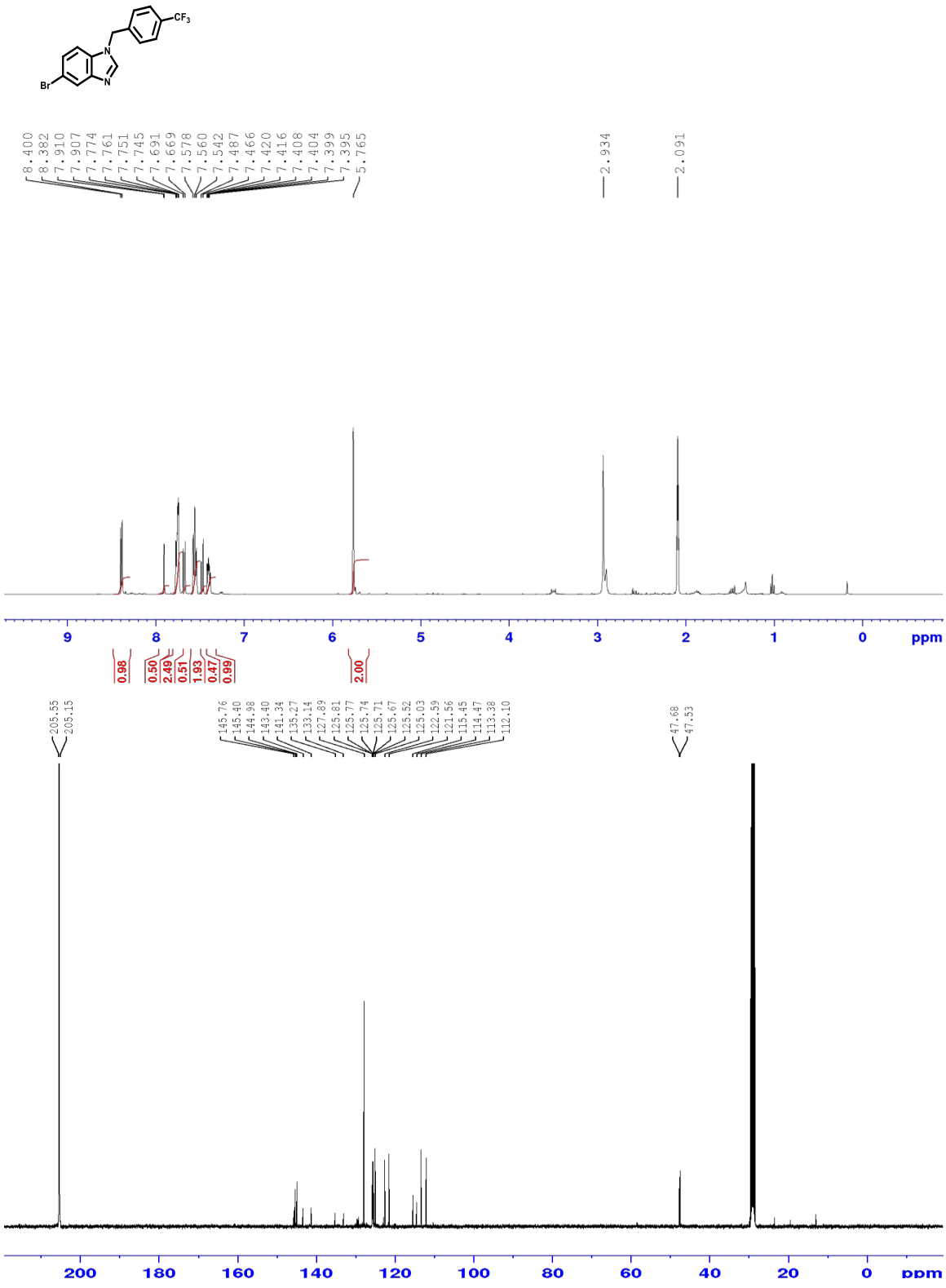


Figure A.27 ^{1}H & ^{13}C spectra of product 23. The spectra matched reference[17]

A.6. References

1. Wannalerse, B.; Tuntulani, T.; Tomapatanaget, B., Synthesis, optical and electrochemical properties of new receptors and sensors containing anthraquinone and benzimidazole units. *Tetrahedron Lett.* **2008,** *64*, 10619-10624.

2. Özdemir, İ.; Şahin, N.; Gök, Y.; Demir, S.; Çetinkaya, B., In situ generated 1-alkylbenzimidazole–palladium catalyst for the Suzuki coupling of aryl chlorides. *J. Mol. Catal. A: Chem.* **2005,** *234*, 181-185.

3. Coyle, R.; Fahey, K.; Aldabbagh, F., Barton esters for initiator-free radical cyclisation with heteroaromatic substitution. *Org. Biomol. Chem.* **2013,** *11*, 1672-1682.

4. Eissa, A. G.; Blaxland, J. A.; Williams, R. O.; Metwally, K. A.; El-Adl, S. M.; Lashine, E.-S. M.; Baillie, L. W.; Simons, C., Targeting methionyl tRNA synthetase: design,synthesis and antibacterial activity against Clostridium difficile of novel 3-biaryl-N-benzylpropan-1-amine derivatives. *J. Enzyme Inhib. Med. Chem.* **2016,** *31*, 1694-1697.

5. Tan, K. L.; Vasudevan, A.; Bergman, R. G.; Ellman, J. A.; Souers, A. J., Microwave- assisted C− H bond activation: a rapid entry into functionalized heterocycles. *Org. Lett.* **2003,** *5*, 2131-2134.

6. Küçükbay, H.; Şireci, N.; Yılmaz, Ü.; Akkurt, M.; Yalçın, Ş. P.; Nawaz Tahir, M.; Ott, H., Synthesis, characterization and microwave-assisted catalytic activity of novel benzimidazole salts bearing piperidine and morpholine moieties in Heck cross-coupling reactions. *Appl. Organomet. Chem.* **2011,** *25*, 255-261.

7. Özdemir, İ.; Şahin, N.; Çetinkaya, B., Transfer hydrogenation of ketones catalyzed by 1- alkylbenzimidazole ruthenium (II) complexes. *Monatshefte für*

Chemie/Chemical Monthly **2007,** *138* (3), 205-209.

8. Fatima, T.; Haque, R. A.; Iqbal, M. A.; Razali, M. R., A new approach for the synthesis of tetrabenzimidazolium salt as a precursor for the tetra-N-heterocyclic carbene dinuclear silver (I) complex. *J. Organomet. Chem.* **2017,** *831*, 50-54.

9. Dohi, K.; Kondo, J.; Yamada, H.; Arakawa, R.; Sakaguchi, S., Functionalized N-Heterocyclic Carbene Ligands for Dual Enantioselective Control in the Cu-Catalyzed Conjugate Addition of Dialkylzinc Compounds to Acyclic Enones. *Eur. J. Org. Chem.* **2012,** *2012*, 7143- 7152.

10. Meng, X.; Li, X.; Chen, W.; Zhang, Y.; Wang, W.; Chen, J.; Song, J.; Feng, H.; Feng, B., Facile One-Pot Synthesis of N-Alkylated Benzimidazole and Benzotriazole from Carbonyl Compounds. *J. Heterocycl. Chem.* **2014,** *51*, 349-356.

11. Xia, Q.; Chen, W.; Qiu, H., Direct C–N Coupling of Imidazoles and Benzylic Compounds via Iron-Catalyzed Oxidative Activation of C–H Bonds. *J. Org. Chem.* **2011,** *76*, 7577-7582.

12. Wan, Y.; Wallinder, C.; Plouffe, B.; Beaudry, H.; Mahalingam, A.; Wu, X.; Johansson, B.; Holm, M.; Botoros, M.; Karlén, A., Design, synthesis, and biological evaluation of the first selective nonpeptide AT2 receptor agonist. *J. Med. Chem.* **2004,** *47*, 5995-6008.

13. Apohan, E.; Yilmaz, U.; Yilmaz, O.; Serindag, A.; Küçükbay, H.; Yesilada, O.; Baran, Y., Synthesis, cytotoxic and antimicrobial activities of novel cobalt and zinc complexes of benzimidazole derivatives. *J. Organomet. Chem.* **2017,** *828*, 52-58.

14. Lygin, A. V.; de Meijere, A., Synthesis of 1-Substituted Benzimidazoles from o-Bromophenyl Isocyanide and Amines. *Eur. J. Org. Chem.* **2009,** *2009*, 5138-5141.

15. Renga, J. M.; McLaren, K. L.; Ricks, M. J., Process Optimization and Synthesis of 3-(4- Fluorophenyl)-4, 5-dihydro-N-[4-(tri-fluoromethyl) phenyl]-4-[5-(trifluoromethyl)-2-pyridyl]-1 H-pyrazole-1-carboxamide. *Org. Process Res. Dev.* **2003,** *7*, 267-271.

16. Xu, W.; Liu, S.; Sun, H.; Zhao, X.; Zhao, Q.; Sun, S.; Cheng, S.; Ma, T.; Zhou, L.; Huang, W., FRET-based probe for fluoride based on a phosphorescent iridium (III) complex containing triarylboron groups. *J. Mater. Chem.* **2011,** *21*, 7572-7581.

17. Zhu, J.; Zhang, Z.; Miao, C.; Liu, W.; Sun, W., Synthesis of benzimidazoles from o- phenylenediamines and DMF derivatives in the presence of PhSiH 3. *Tetrahedron Lett.* **2017,** *73*, 3458-3462.

APPENDIX B

EXPERIMENTAL DETAILS AND CHARACTERIZATION INFORMATION FOR CHAPTER 2

B.1. Cyclic voltammetric studies of indazole

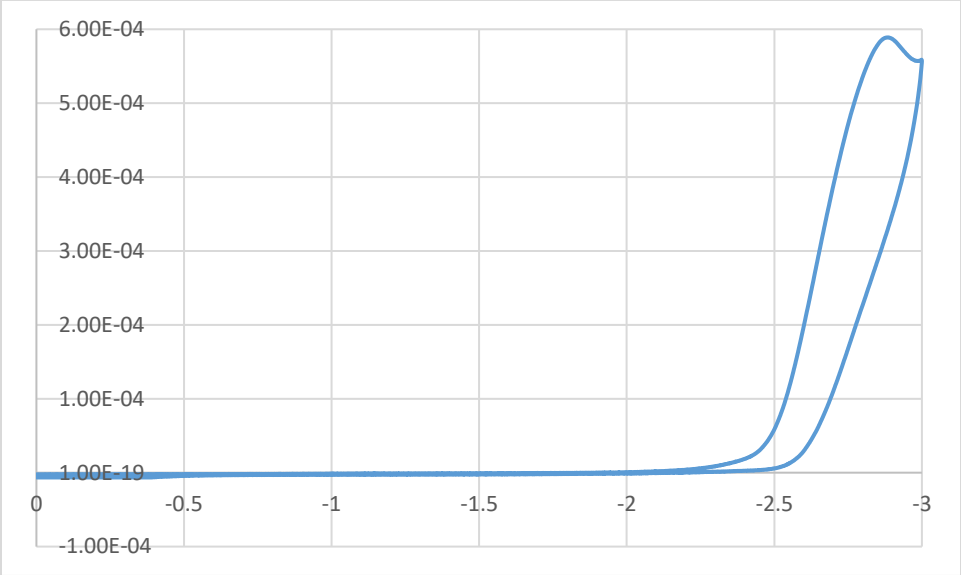


Figure B.1 Electrochemical data of indazole obtained from experiments performed with a 0.1 M solution of tetrabutylammonium hexafluorophosphate ($TBAPF_6$) containing 0.5 m mol of indazole in acetonitrile. A glassy carbon electrode was employed as the working electrode, Pt as the counter electrode and saturated calomel electrode (SHC) as the reference electrode. The cyclic voltammograms were obtained at the scan rate of 100 m V/s.

B.2. Illustration of the electrochemical cell

Figure B.2 Electrochemical acylation of indazole in an H-Cell performed with a 0.1 M solution of tetrabutylammonium hexafluorophosphate ($TBAPF_6$) containing 0.65 m mol of indazole in acetonitrile in the cathode side and 0.65 m mol of ferrocene on anode side. Reticulate Vitreous Carbon electrodes were employed as cathode and anode.

B.3. Illustration of the user-friendly setup

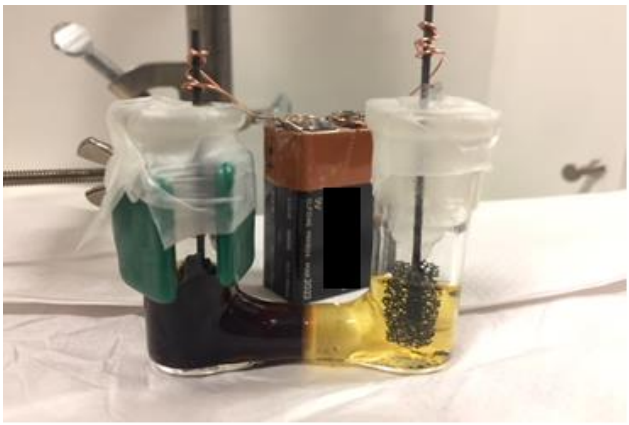


Figure B.3 Electrochemical acylation of indazole in an H-Cell performed with a 0.1 M solution of tetrabutylammonium hexafluorophosphate ($TBAPF_6$) containing 0.5 m mol of indazole in acetonitrile in the cathode side and 0.5 m mol of ferrocene on anode side. Acetic anhydride (0.5 m mol) was added after 2 hrs. Reticulate Vitreous Carbon electrodes were employed as cathode and anode. Constant Current Electrolysis is carried out by connecting the electrodes to a commercially available battery.

B.4. Detailed procedure for synthesis of product 1

During the preparations, 0.58 g (1.50 mmol) of the electrolyte tetrabutylammonium hexafluorophosphate (2 portions), 0.186 g (1.0 mmol) of ferrocene and 0.118 g (1.0 mmol) of indazole were weighed out. The preparations of the setup with reactants were performed inside a N_2-filled glove box to confirm inert atmosphere. Each compartment of the H-cell had 15 mL of anhydrous acetonitrile. The cathode chamber contained 0.118 g of indazole and 0.58 g of electrolyte dissolved in acetonitrile. The anode chamber contained 0.186 g of ferrocene and 0.58 g of electrolyte in acetonitrile. During the electrolysis experiments, the indazole substrate is initially reduced in the cathode chamber by passing a current of 8 mA for 3 hrs. After 3 hrs, the 94.4 µL (1.6 m mol) of acetic anhydride is added and the current is decreased to 0.5 mA. The reaction is allowed to proceed for 2 more hours. After electrolysis, the solvent was evaporated off and the organic contents were purified by preparative thin layer chromatography using the solvent system pentane: ethyl acetate (1:3). The product was the top band on the prep TLC plate. The band was removed from the plate and sonicated in diethyl ether, filtered and the ether was evaporated to give a white solid (0.13 g, 0.82 mmol, 82 % yield) that resulted in the NMR spectra show in Figure B4.

B.5. Spectra of synthesized compounds

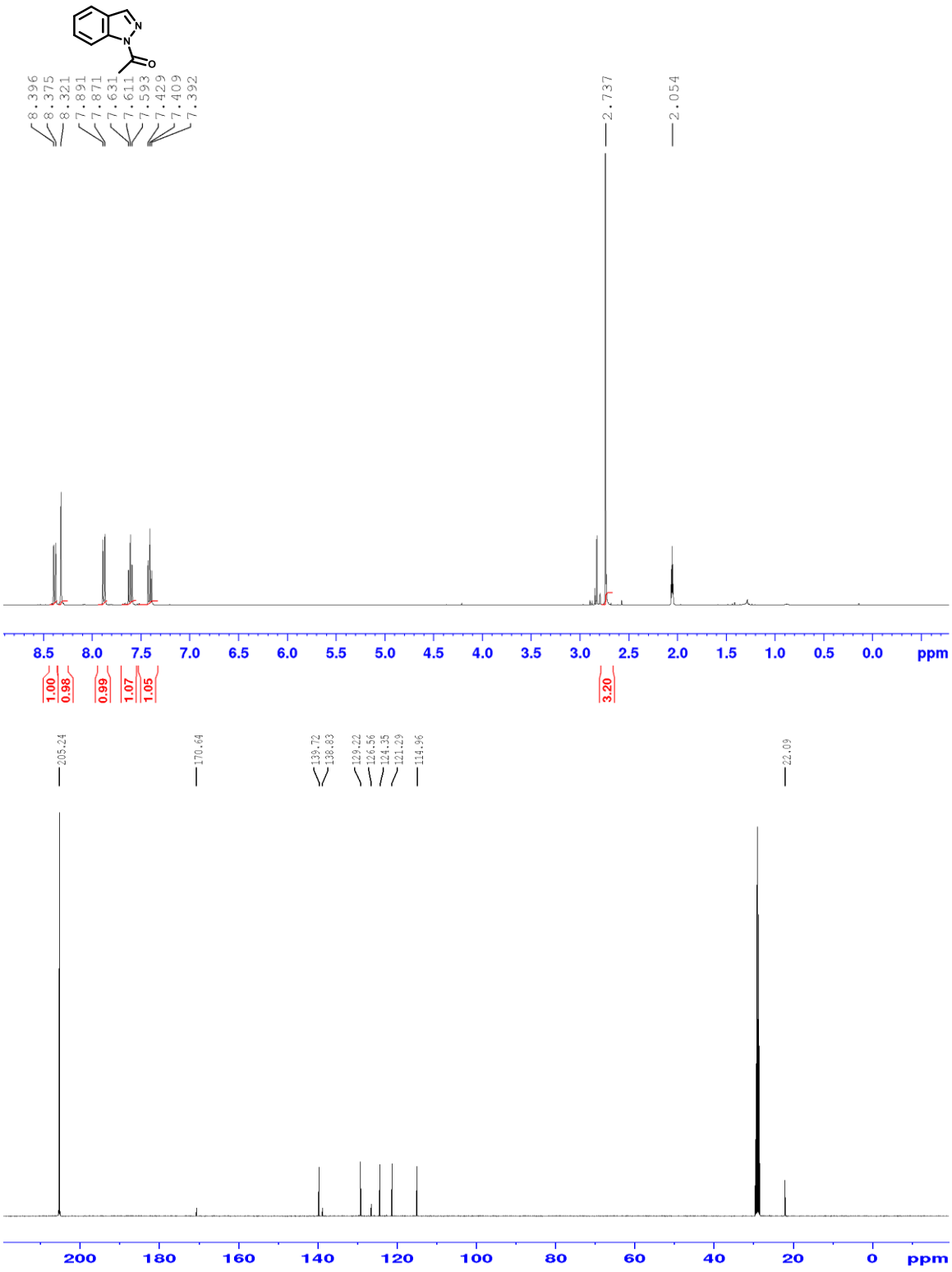


Figure B.4 ^{1}H & ^{13}C spectra of product 1. The spectra matched reference[23]

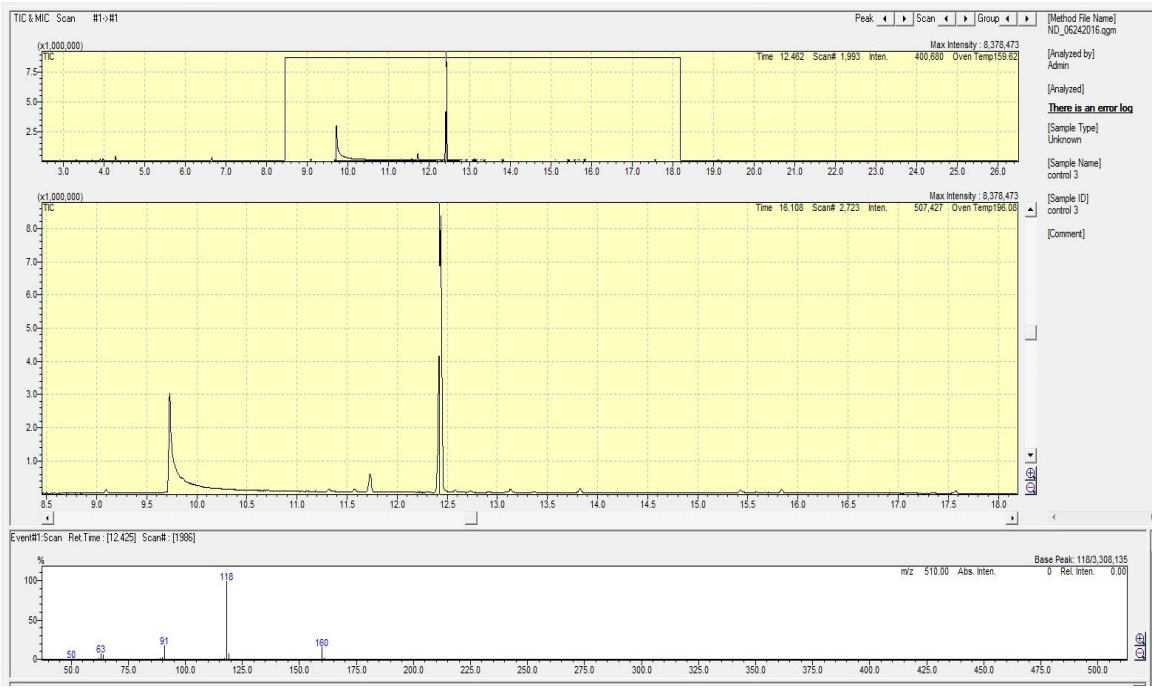


Figure B.5 GC MS trace of the post-reaction mixture

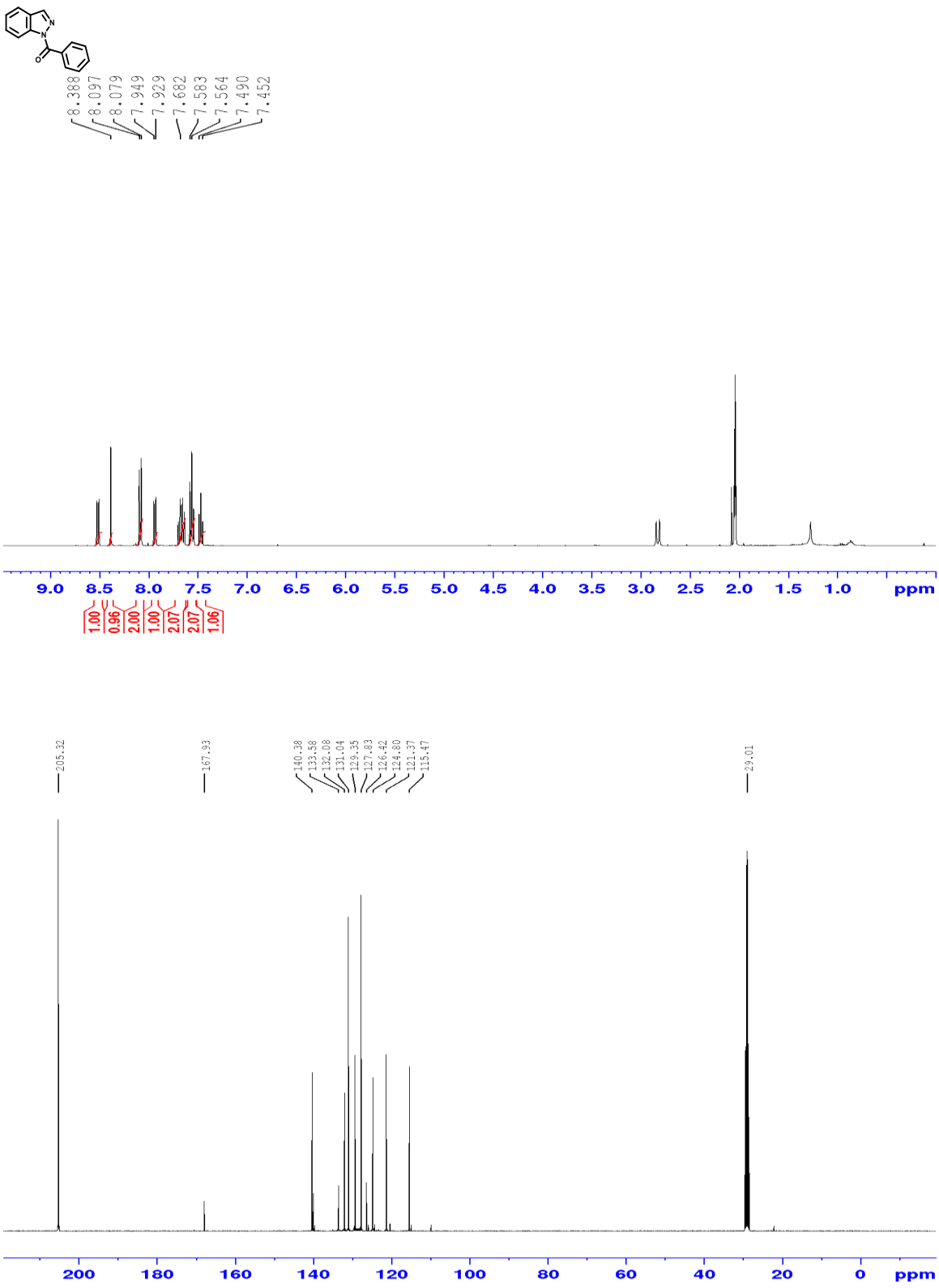


Figure B.6 ^{1}H & ^{13}C spectra of product 2. The spectra matched reference[16]

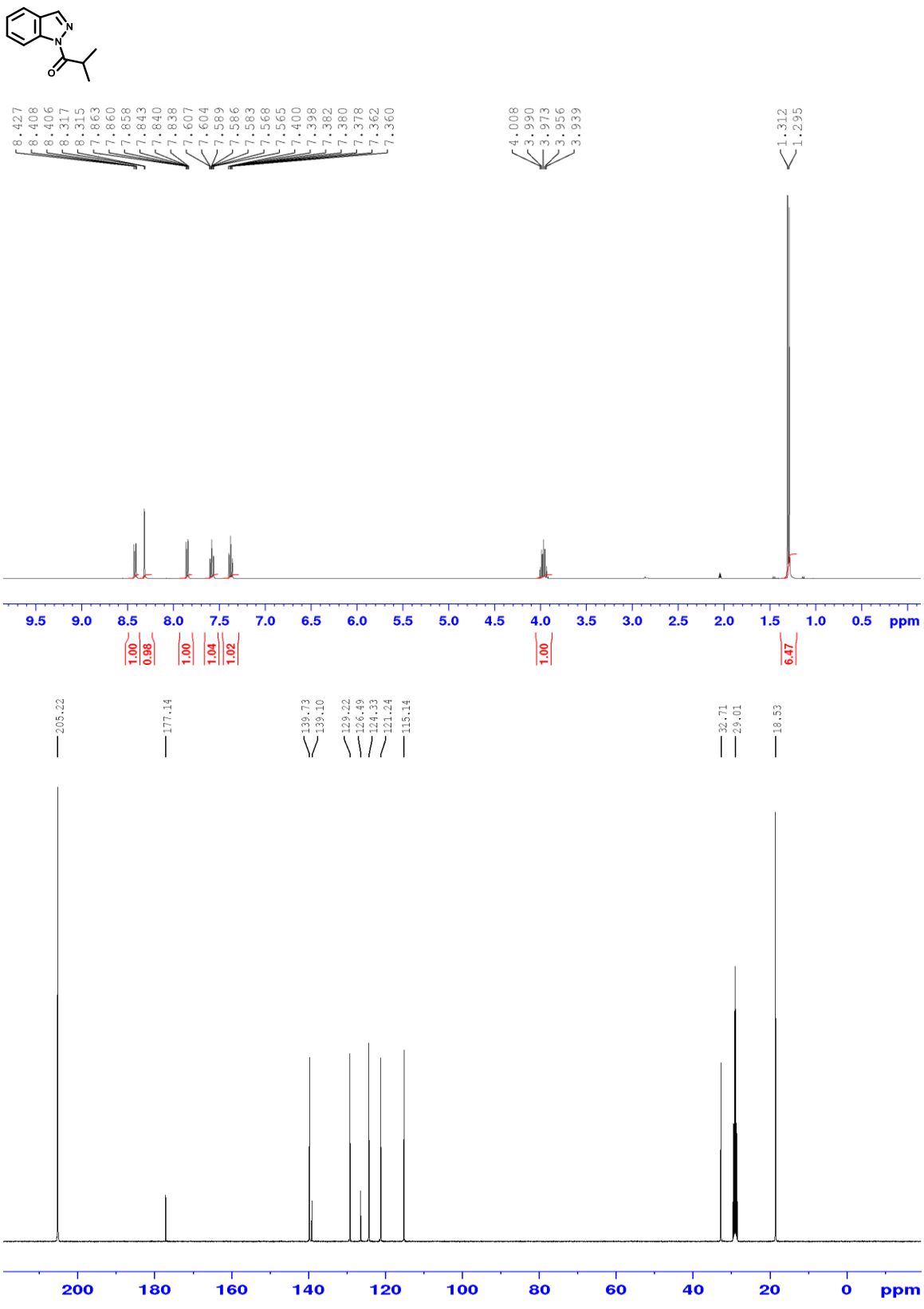


Figure B.7 ^{1}H & ^{13}C spectra of product 3. The spectra matched reference [23]

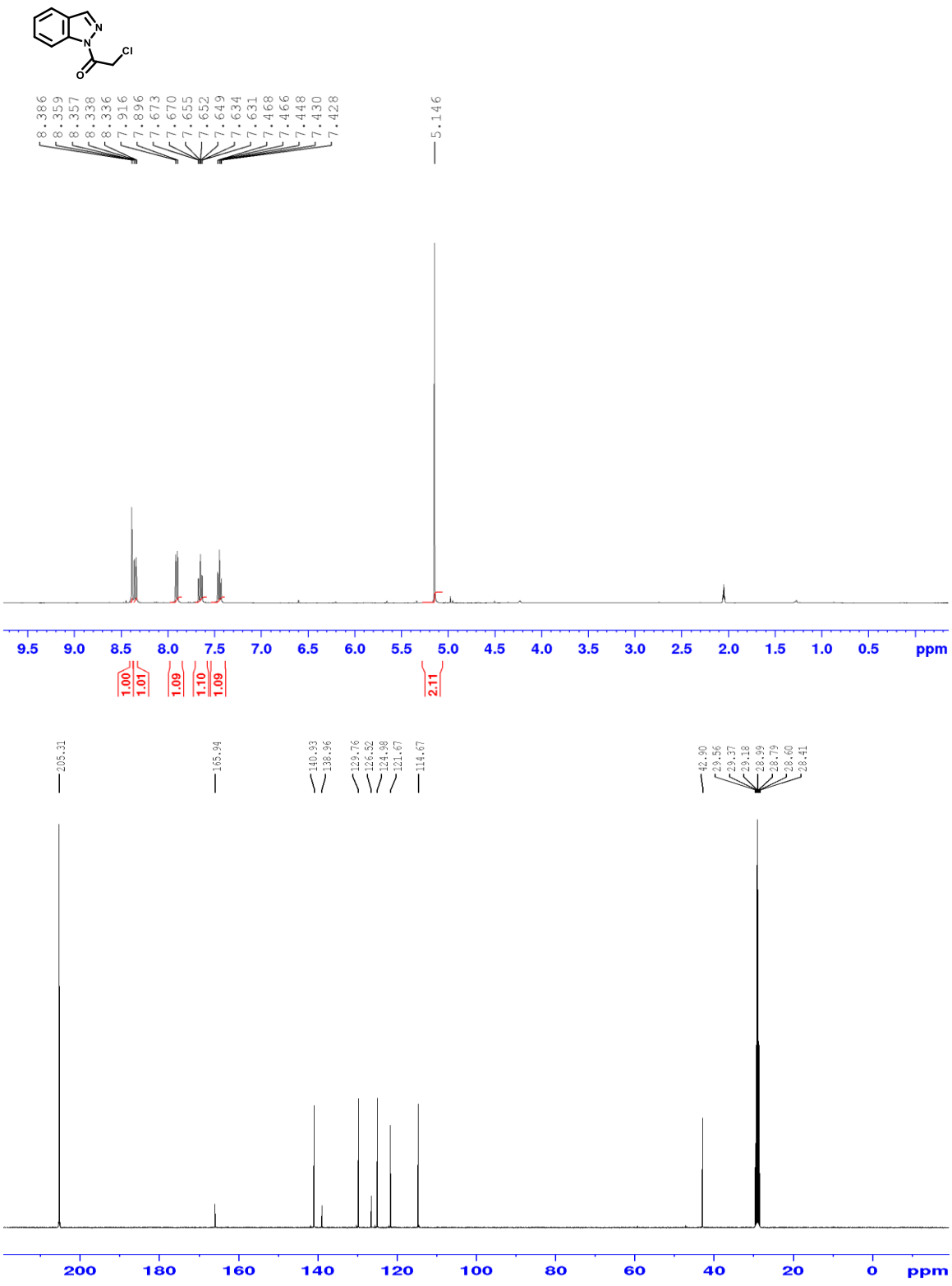


Figure B.8 ^{1}H & ^{13}C spectra of product 4. The spectra matched reference[13]

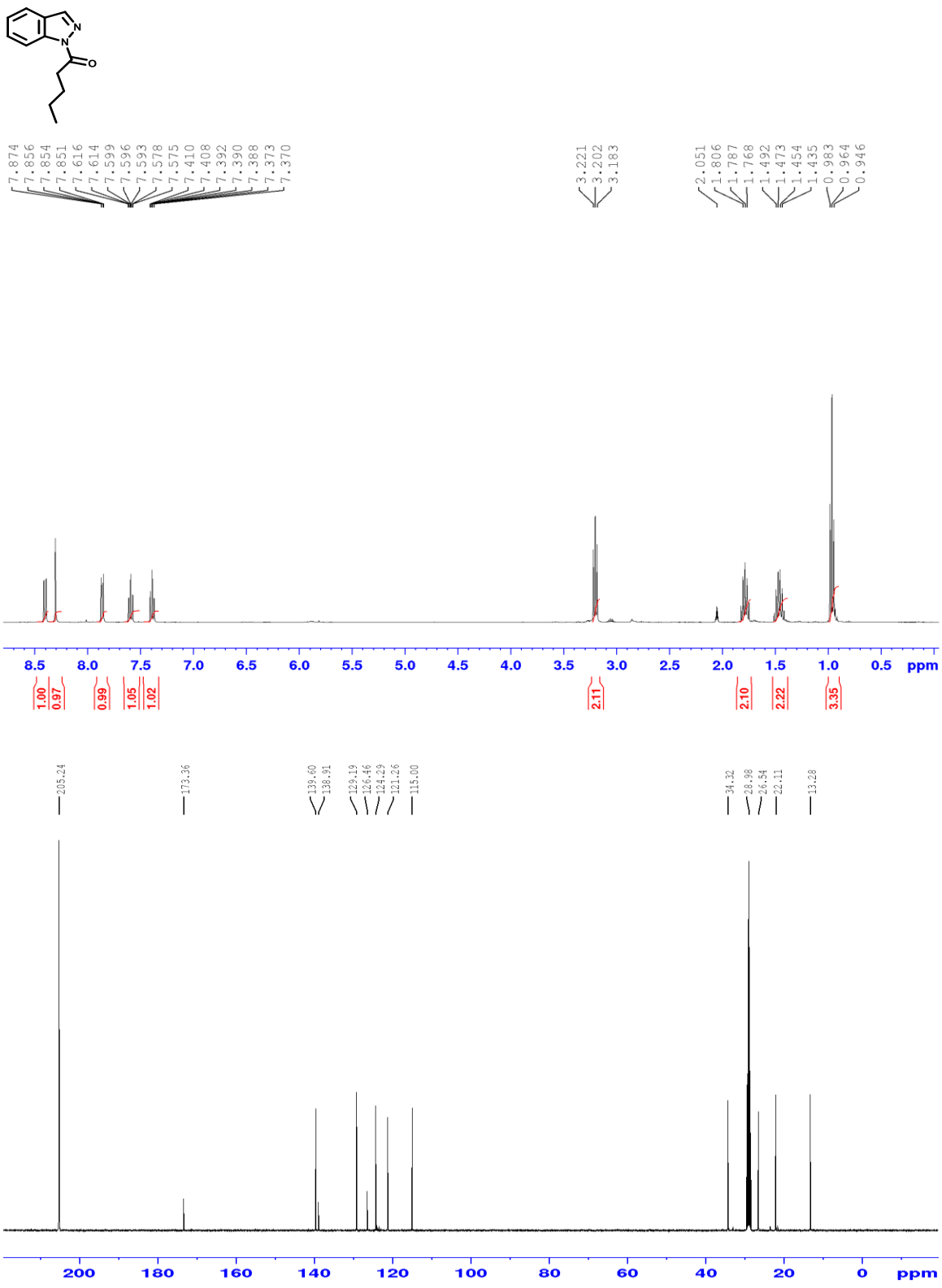


Figure B.9 ^{1}H & ^{13}C spectra of product 5. The spectra matched reference[2]

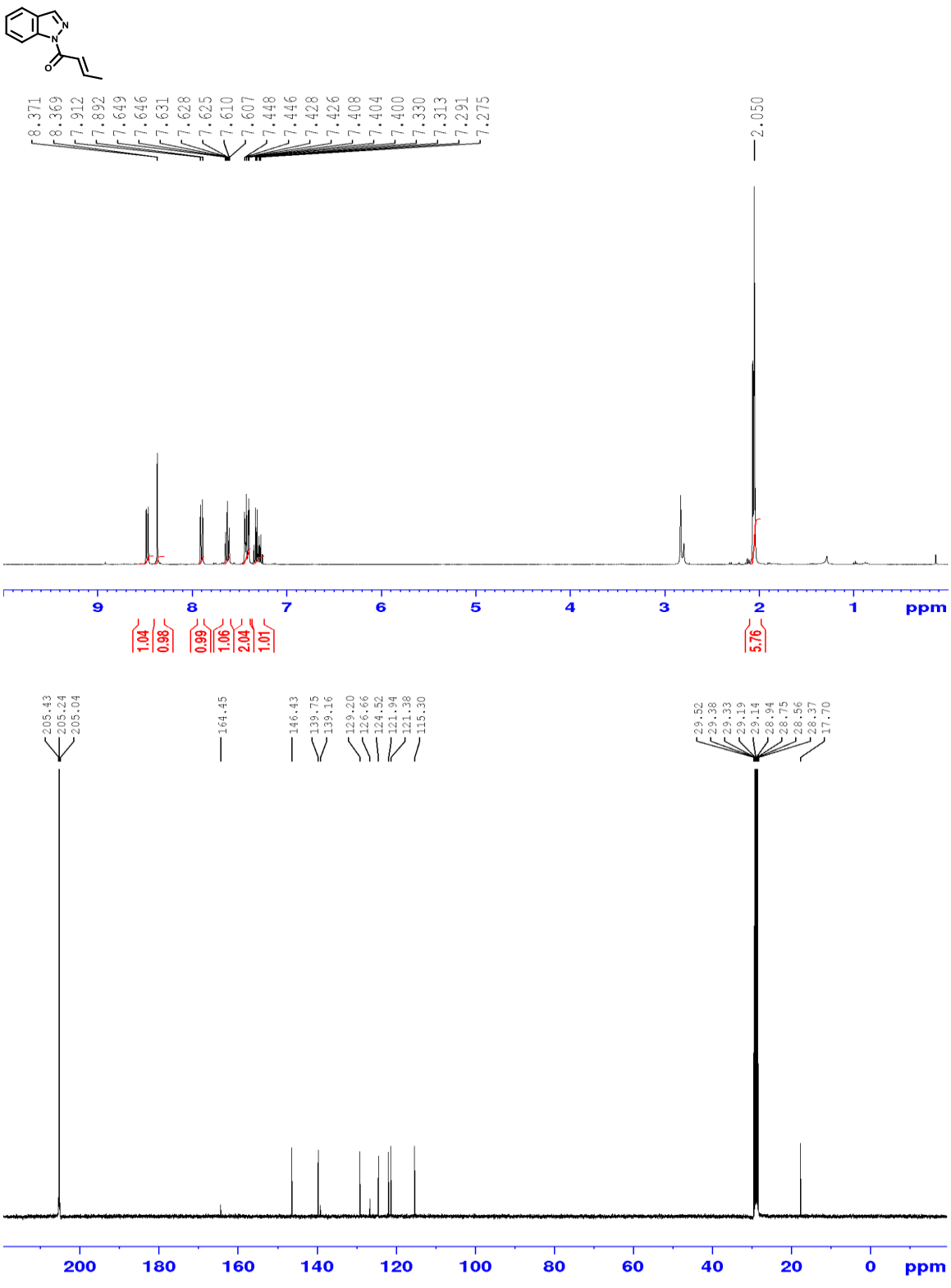


Figure B.10 ^{1}H & ^{13}C spectra of product 6. The spectra matched reference[3]

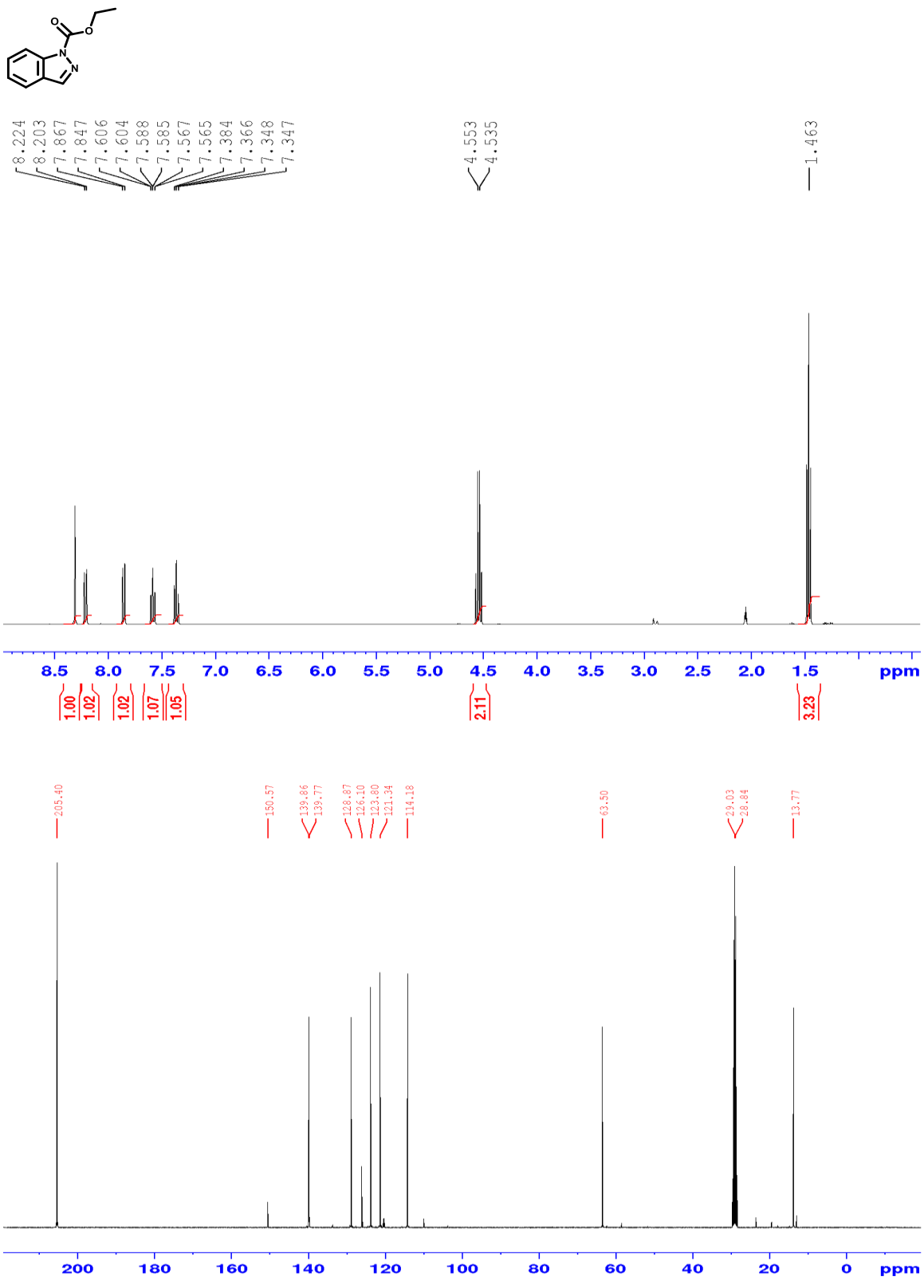


Figure B.11 ^{1}H & ^{13}C spectra of product 7. The spectra matched reference[11]

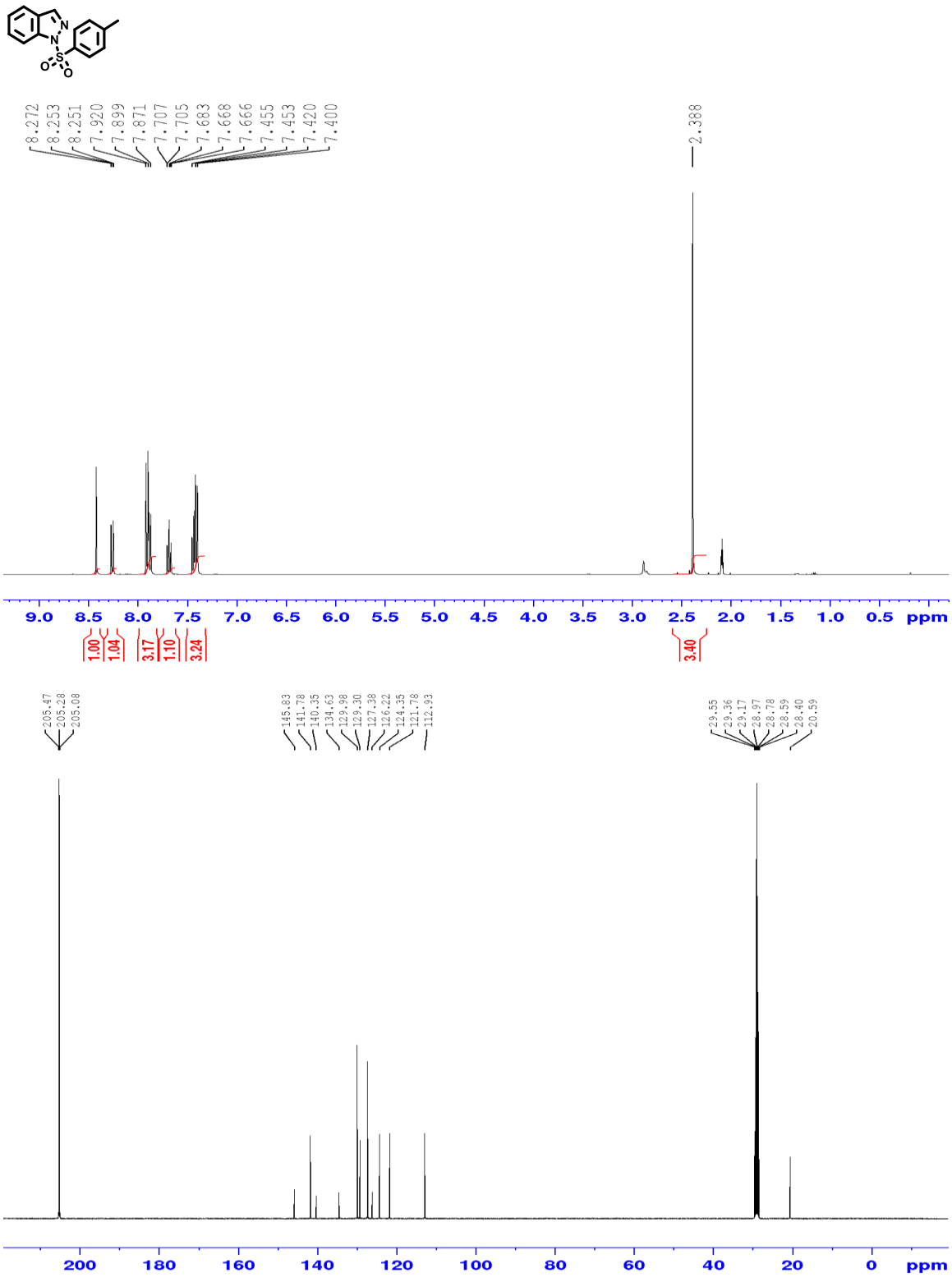


Figure B.12 ^{1}H & ^{13}C spectra of product 8. The spectra matched reference[6]

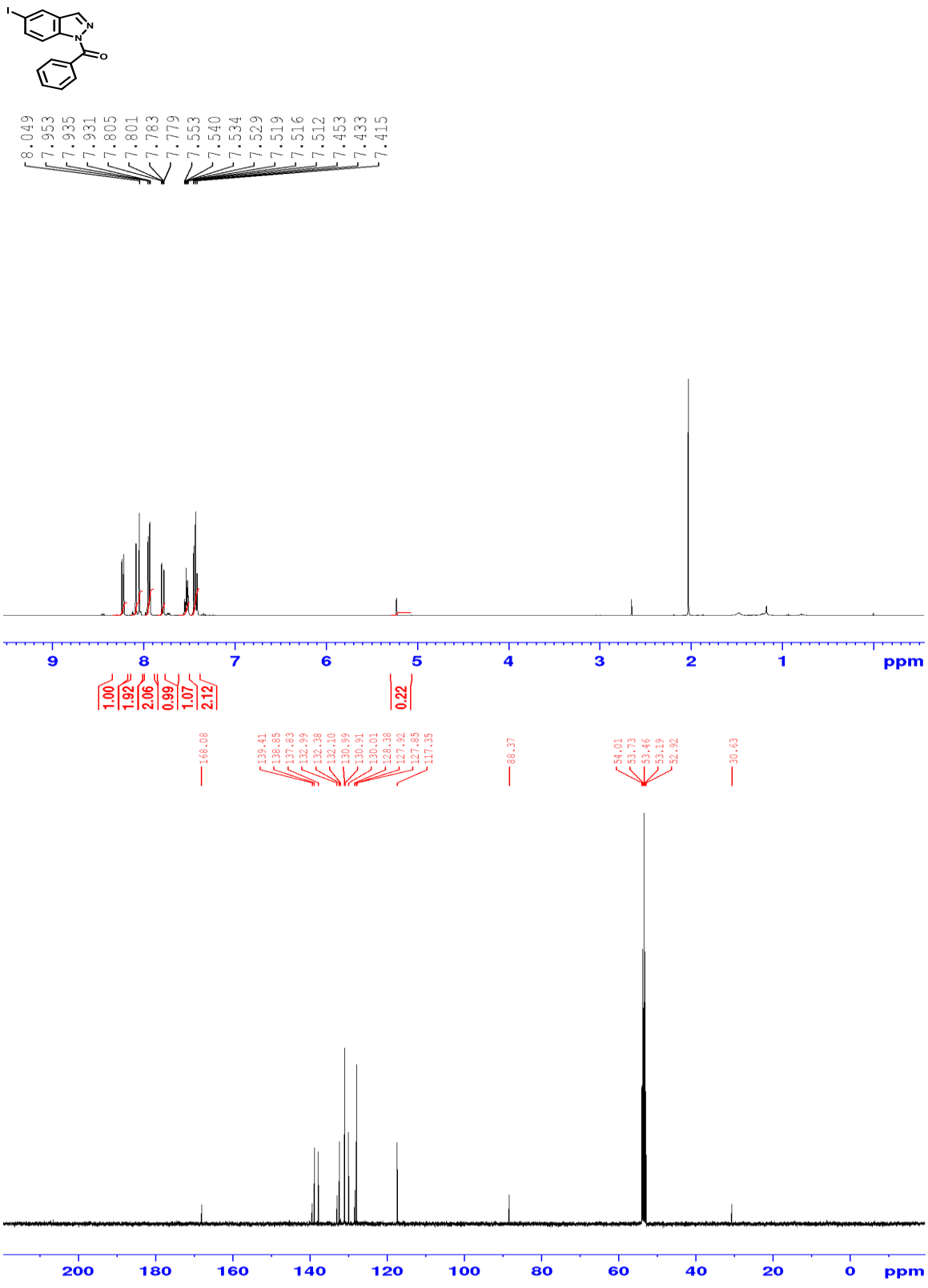
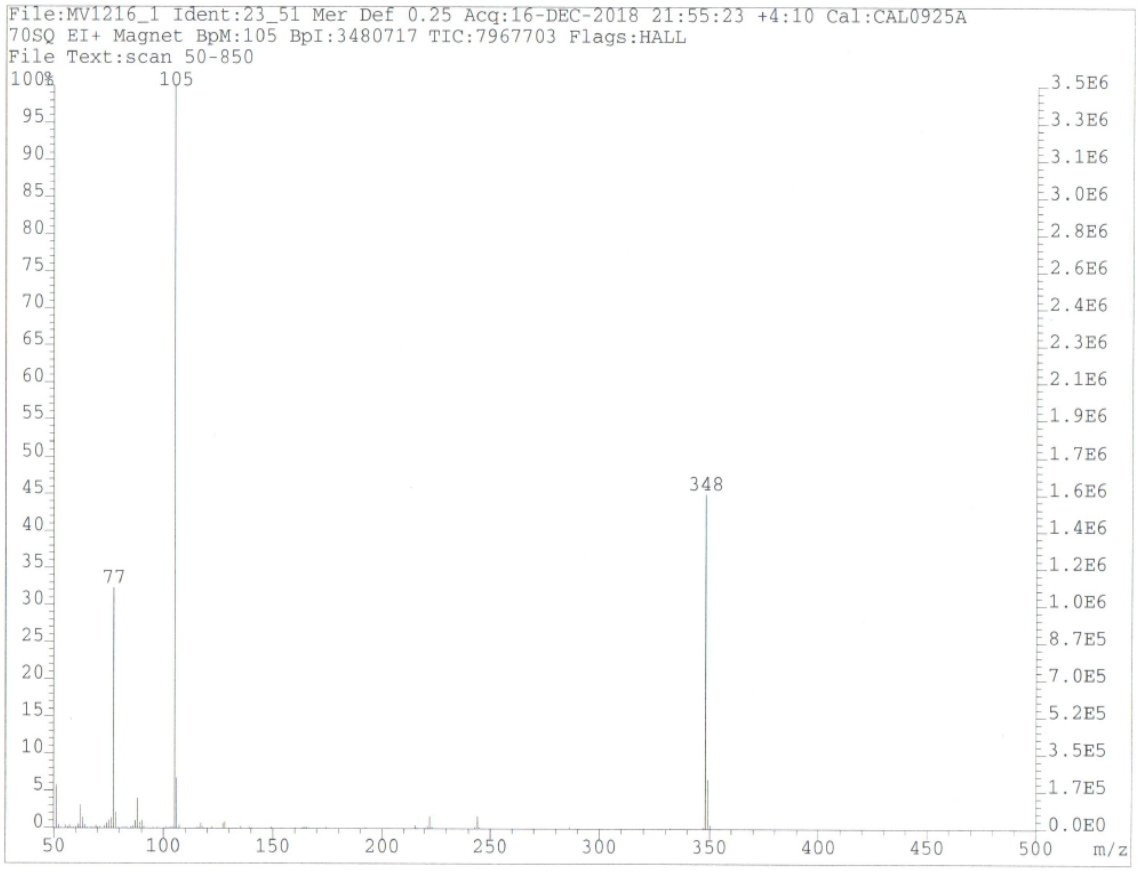


Figure B.13 ^{1}H & ^{13}C spectra of product 9 in deuterated DCM.



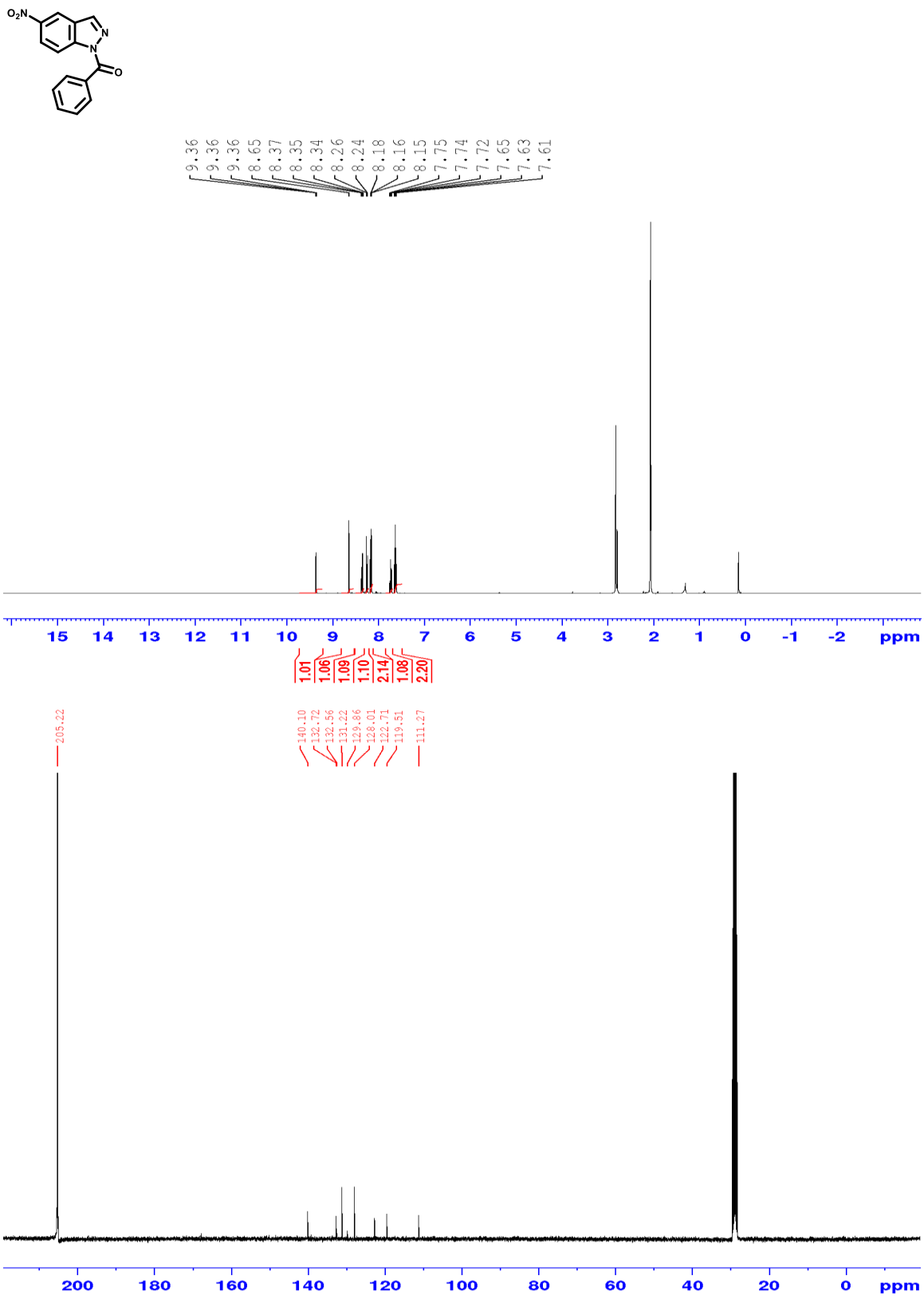


Figure B.14 ^{1}H & ^{13}C spectra of product 10. The spectra matched reference[5]

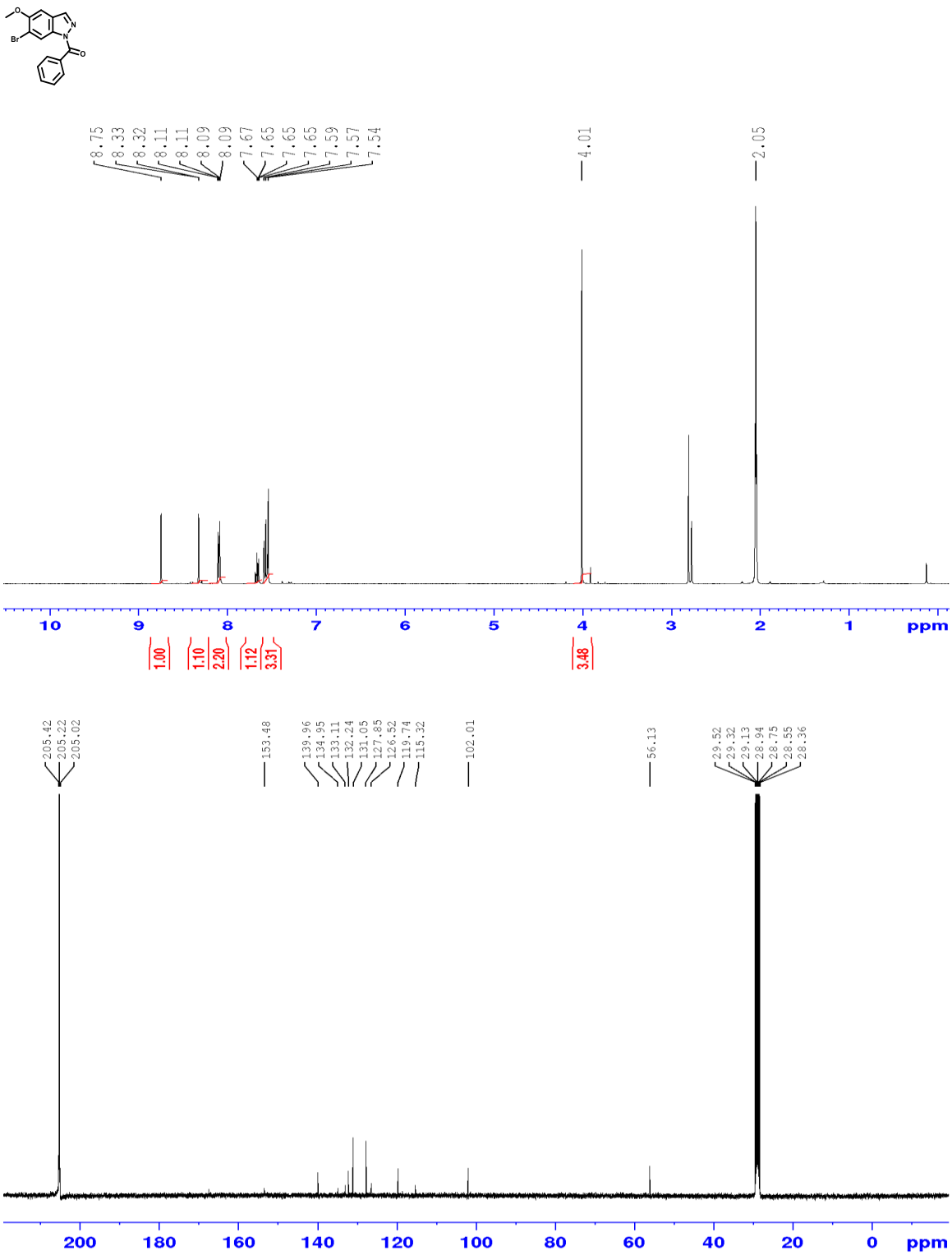
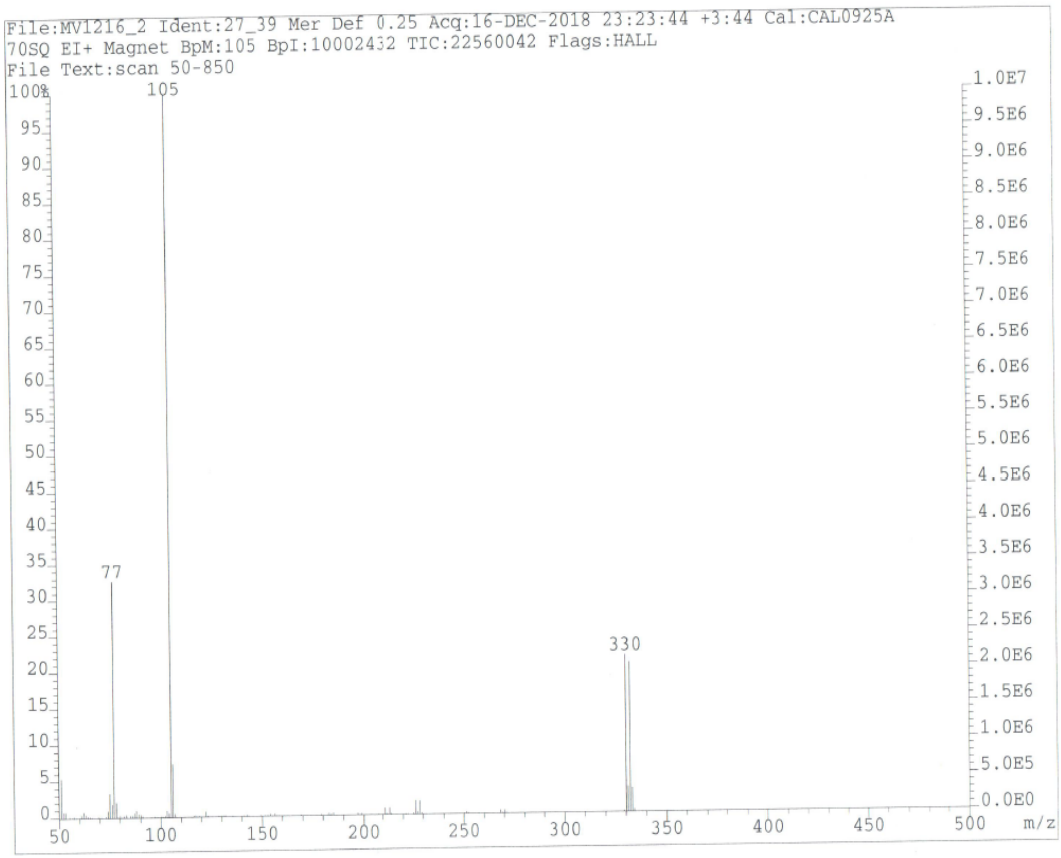


Figure B.15 ^{1}H & ^{13}C spectra of product 11.



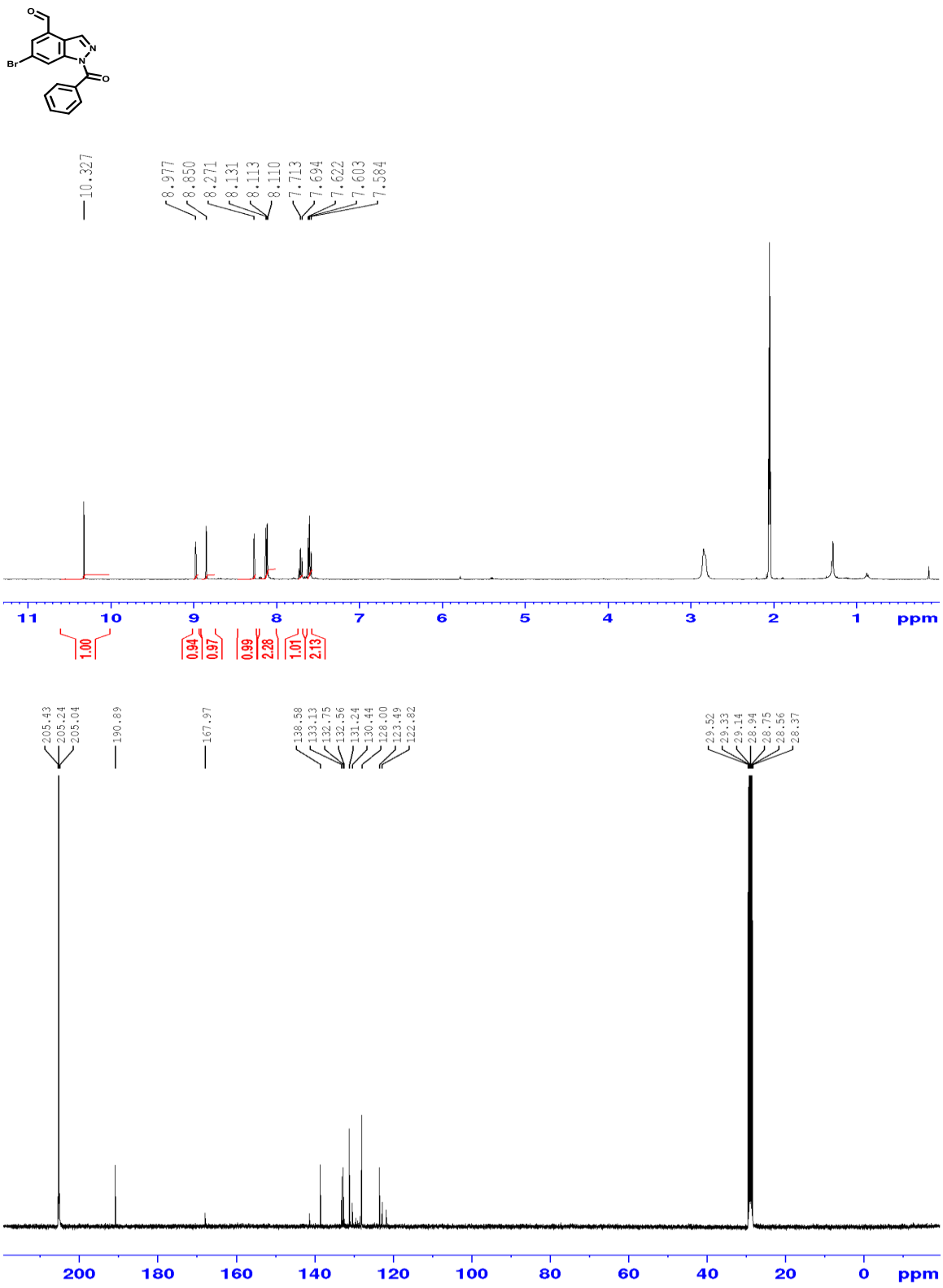
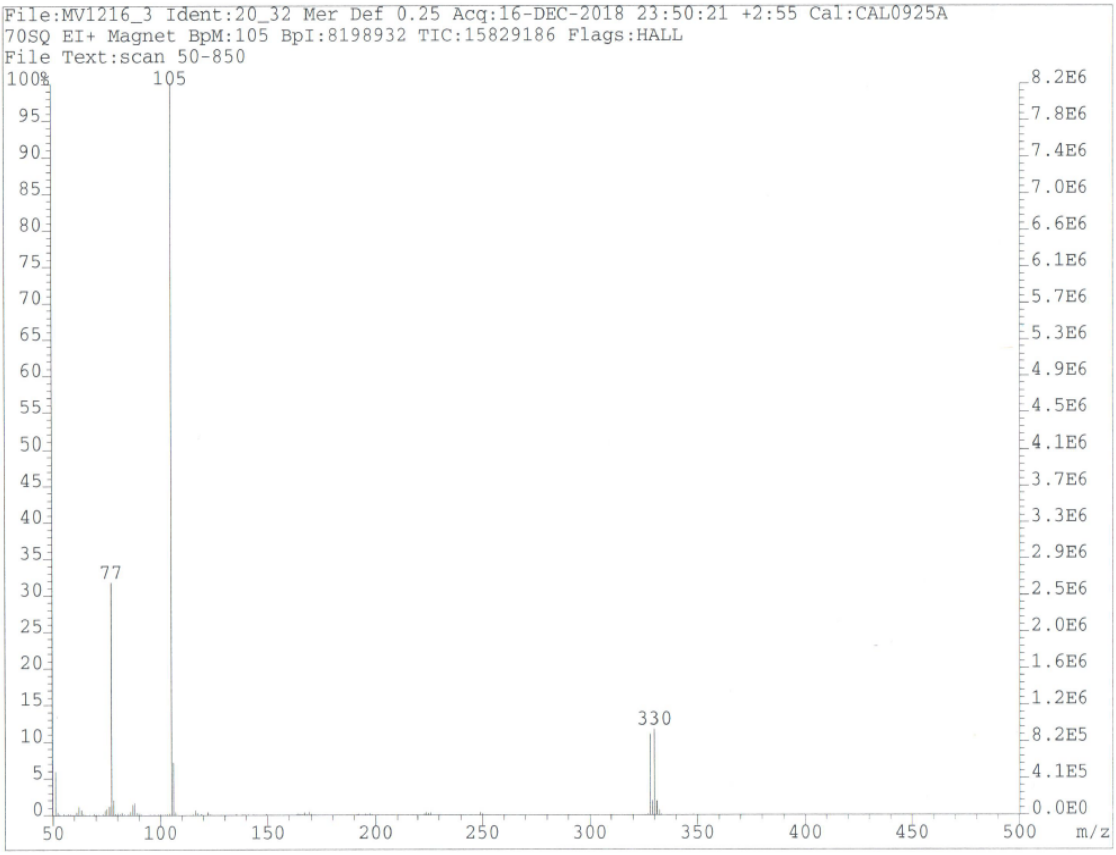


Figure B.16 ^{1}H & ^{13}C spectra of product 12.



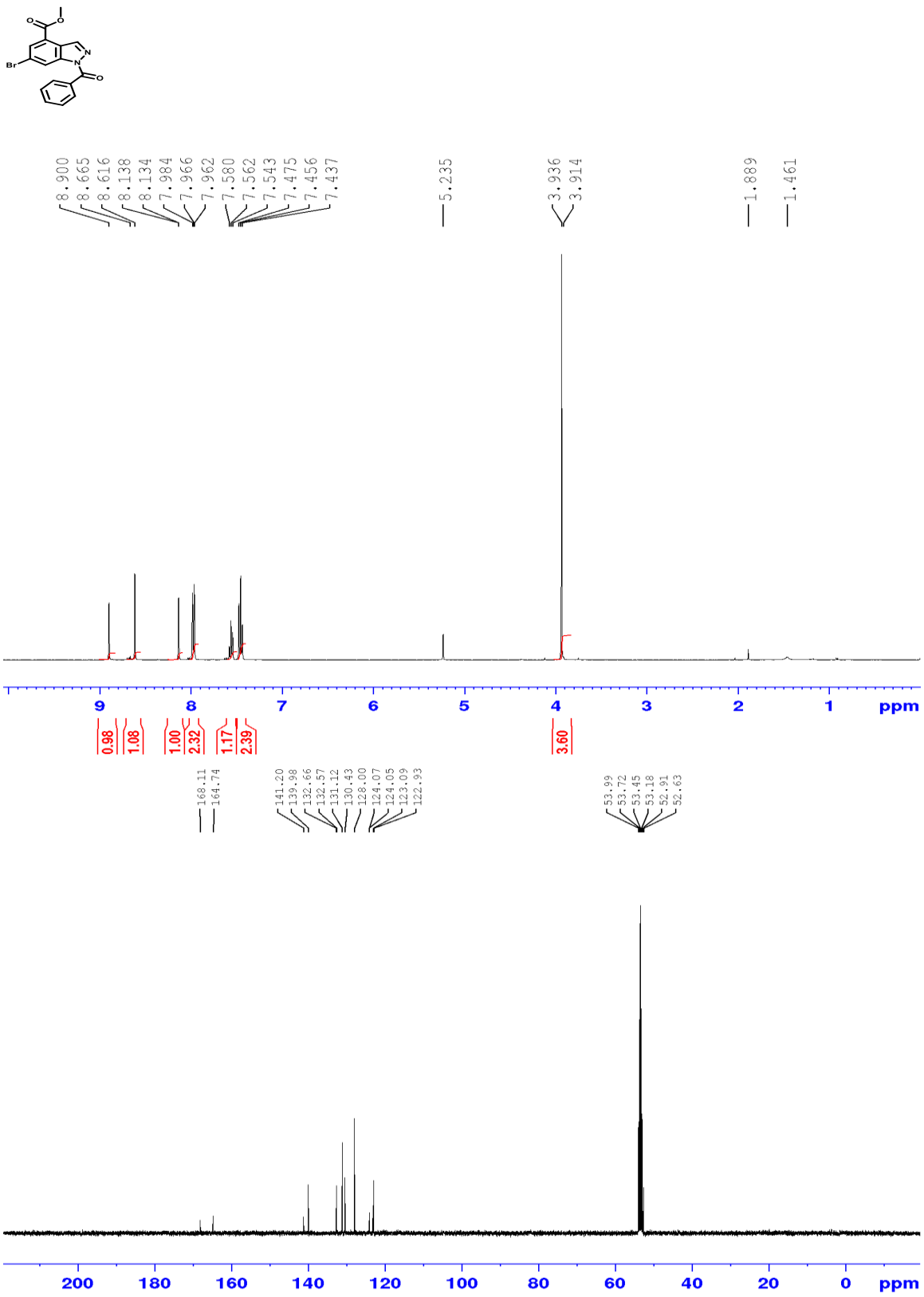


Figure B.17 ^{1}H & ^{13}C spectra of product 13. The spectra matched reference[34]

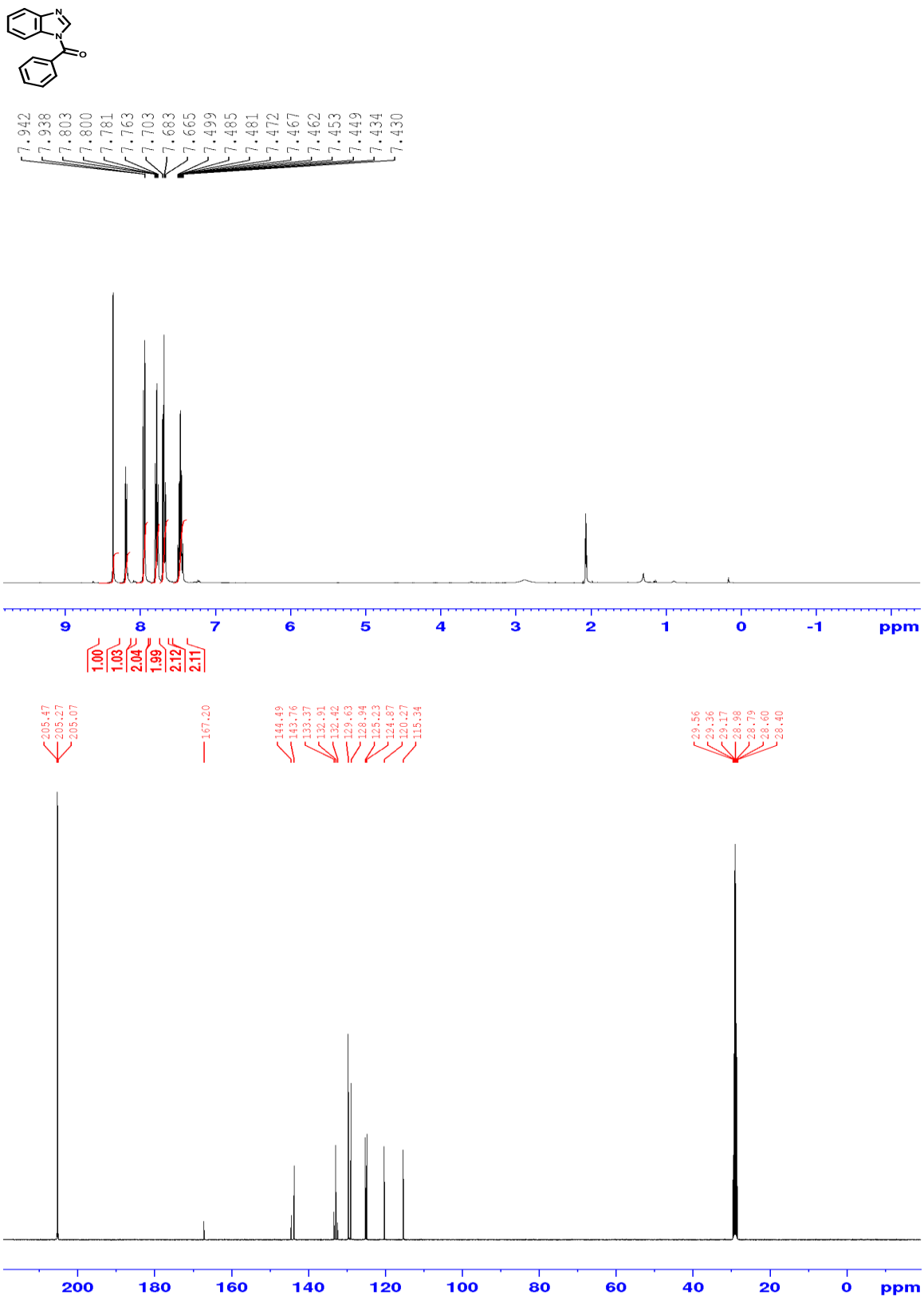


Figure B.18 ^{1}H & ^{13}C spectra of product 14. The spectra matched reference[18]

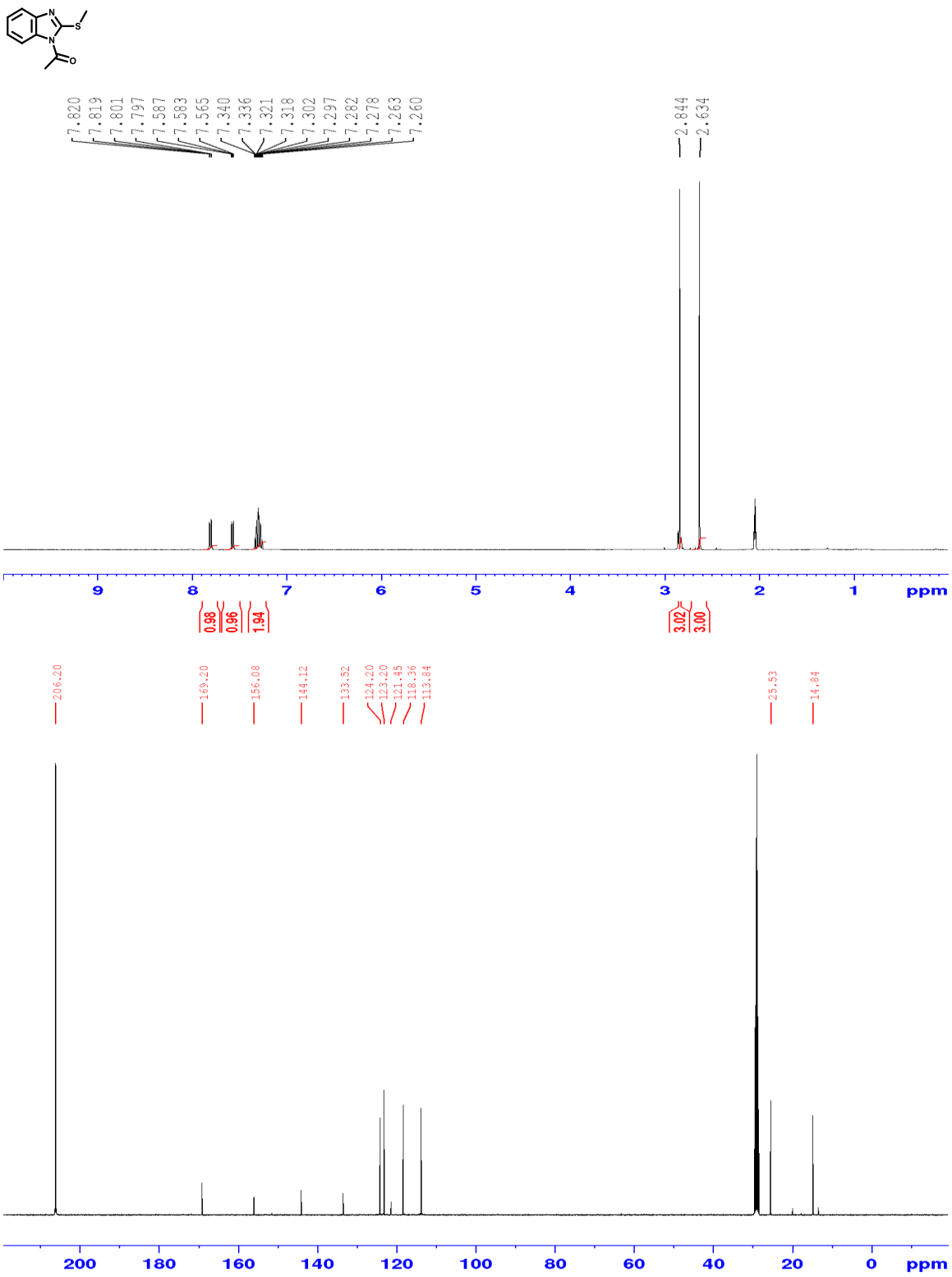


Figure B.19 ^{1}H & ^{13}C spectra of product 15. The spectra matched reference[8]

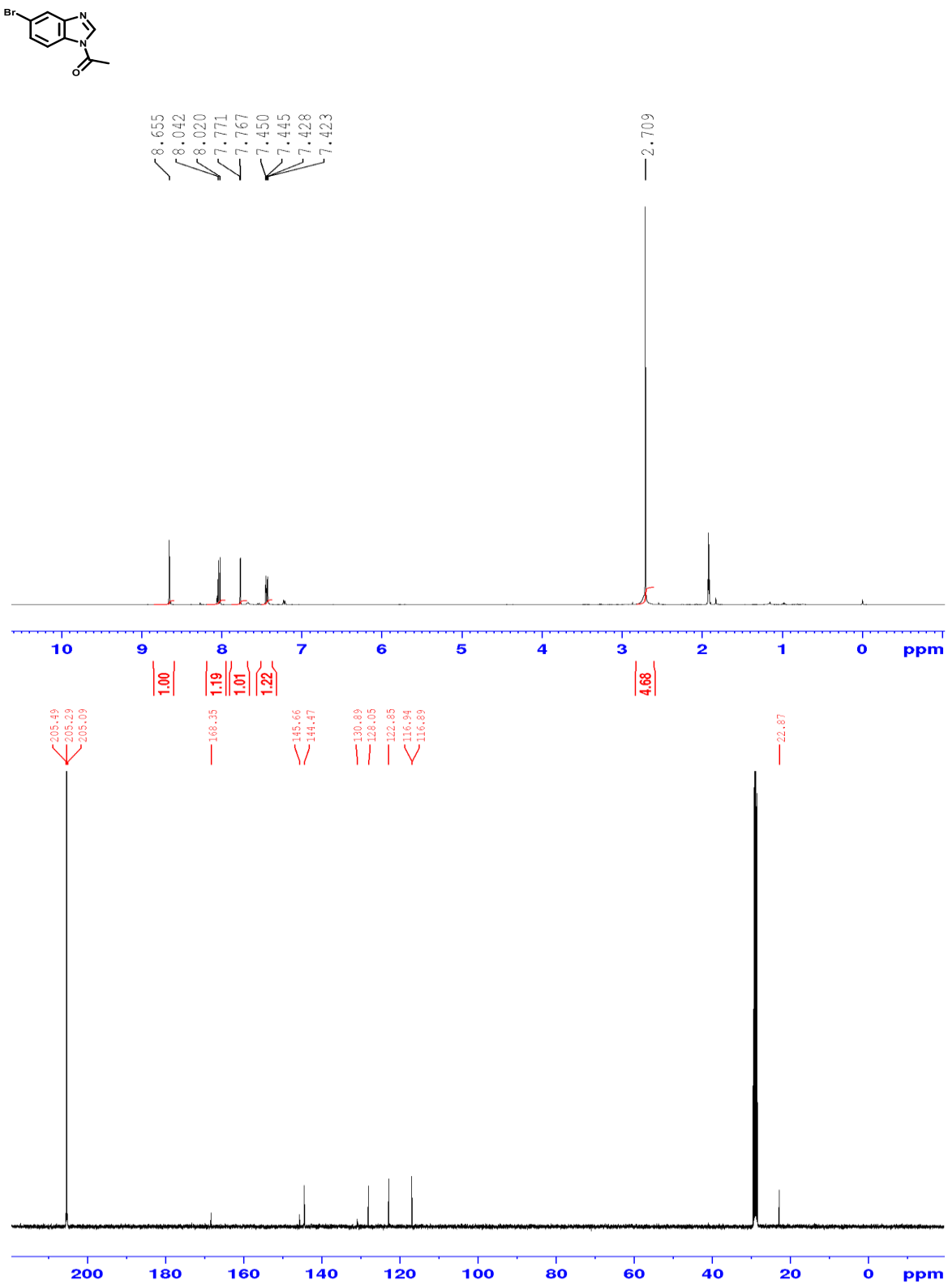


Figure B.20 ^{1}H & ^{13}C spectra of product 16(1). The spectra matched reference[4]

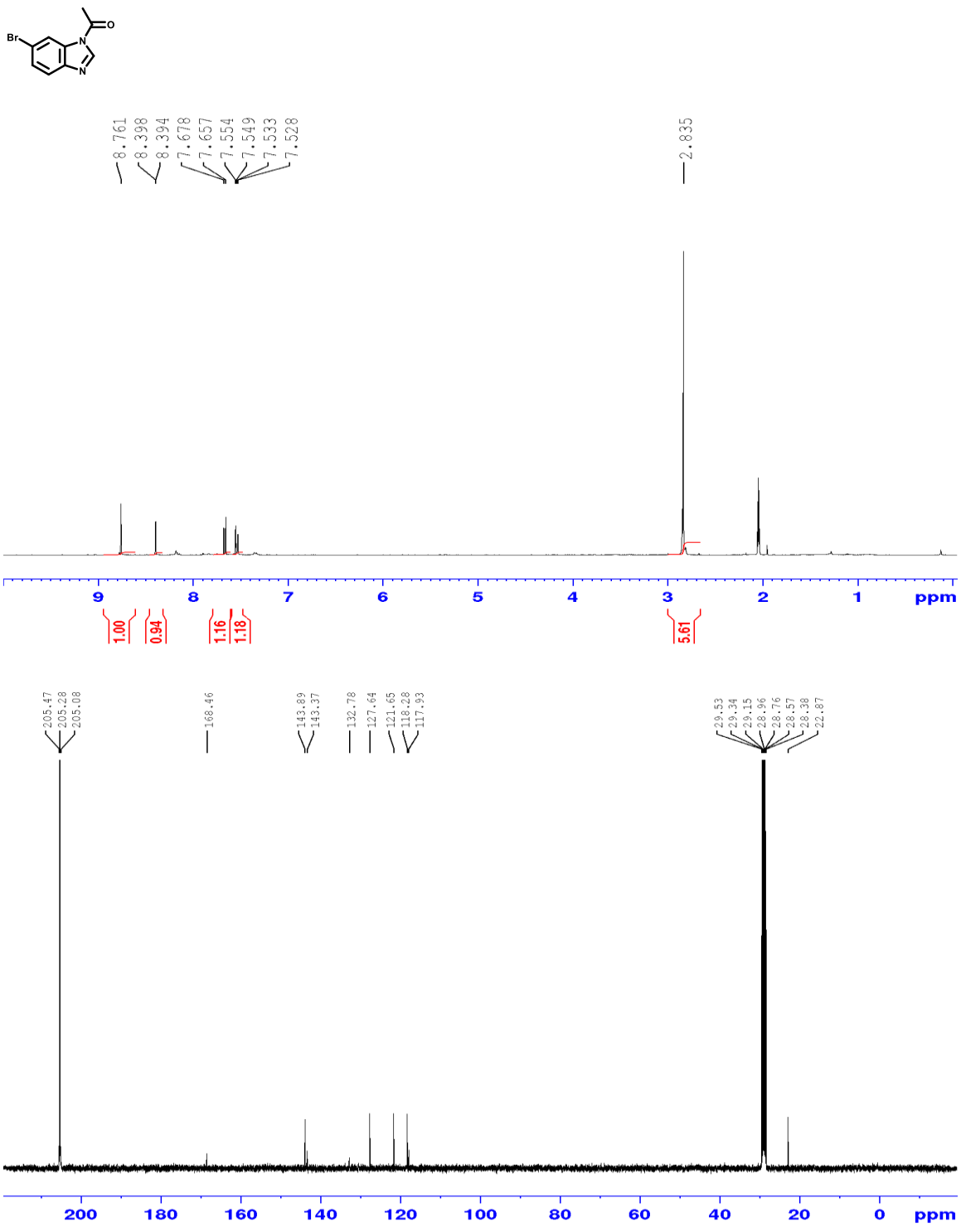


Figure B.21 ^{1}H & ^{13}C spectra of product 16(2). The spectra matched reference[4]

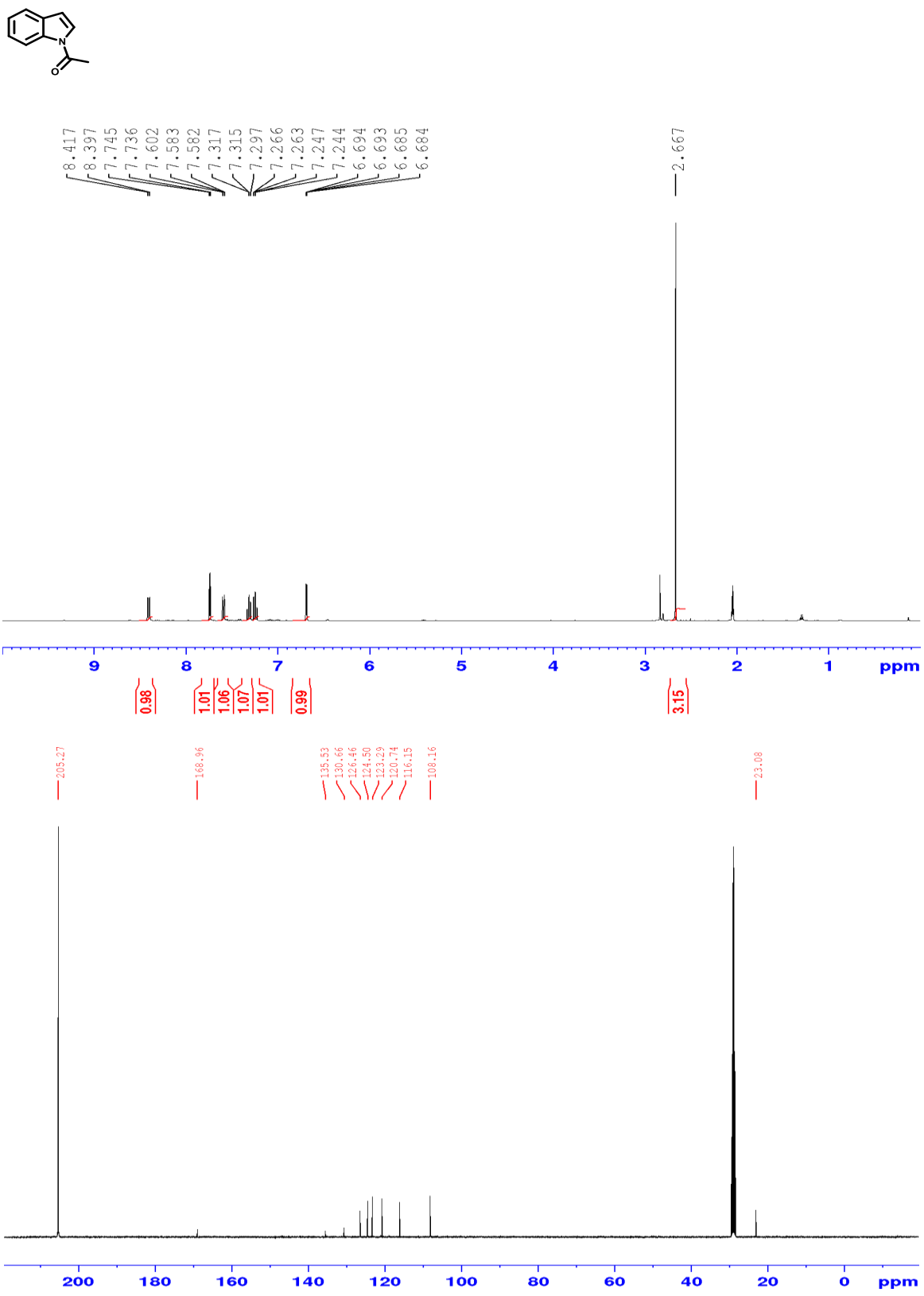


Figure B.22 ^{1}H & ^{13}C spectra of product 17. The spectra matched reference[15]

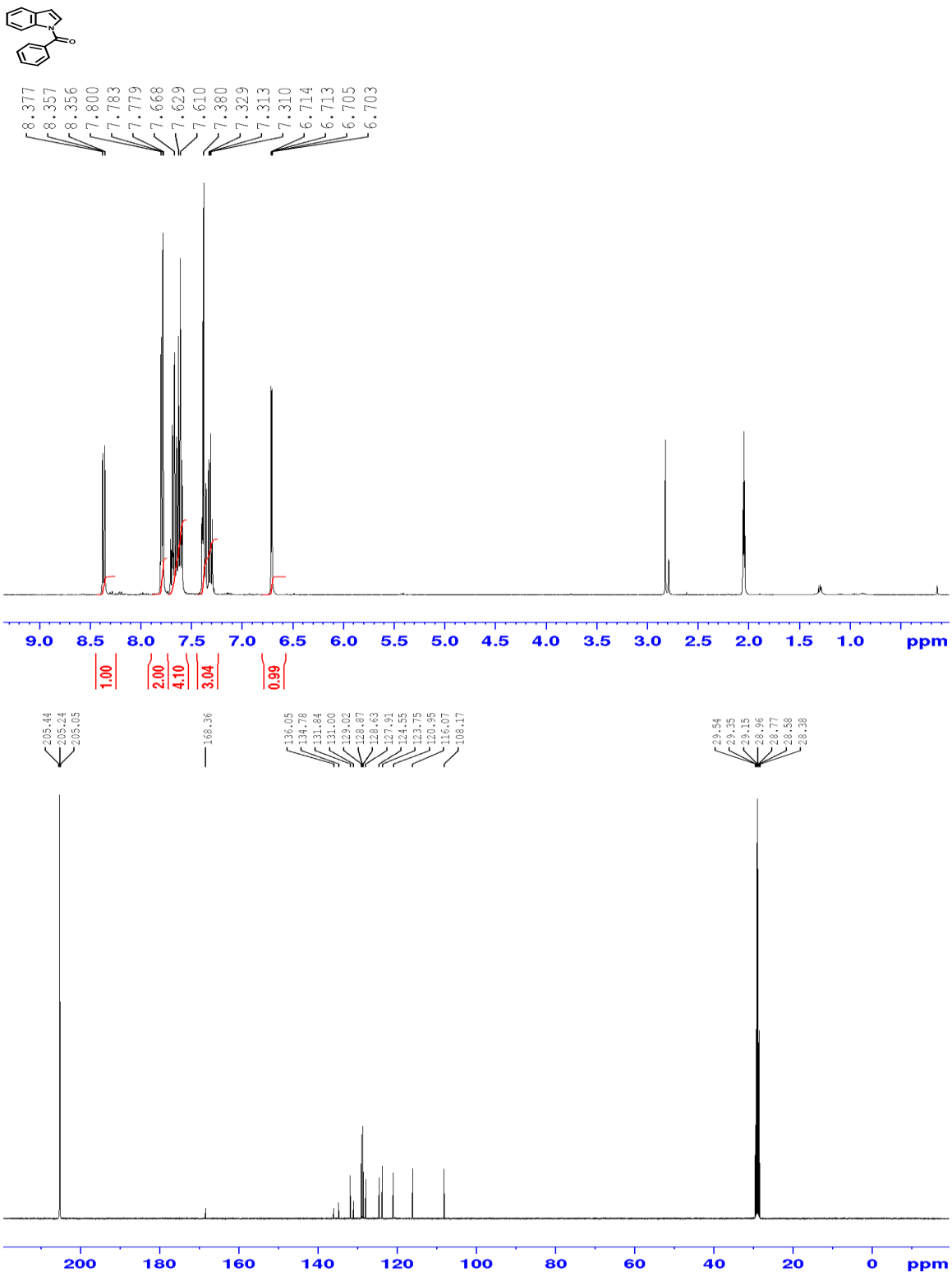
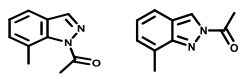


Figure B.23 ^{1}H & ^{13}C spectra of product 18. The spectra matched reference[14]



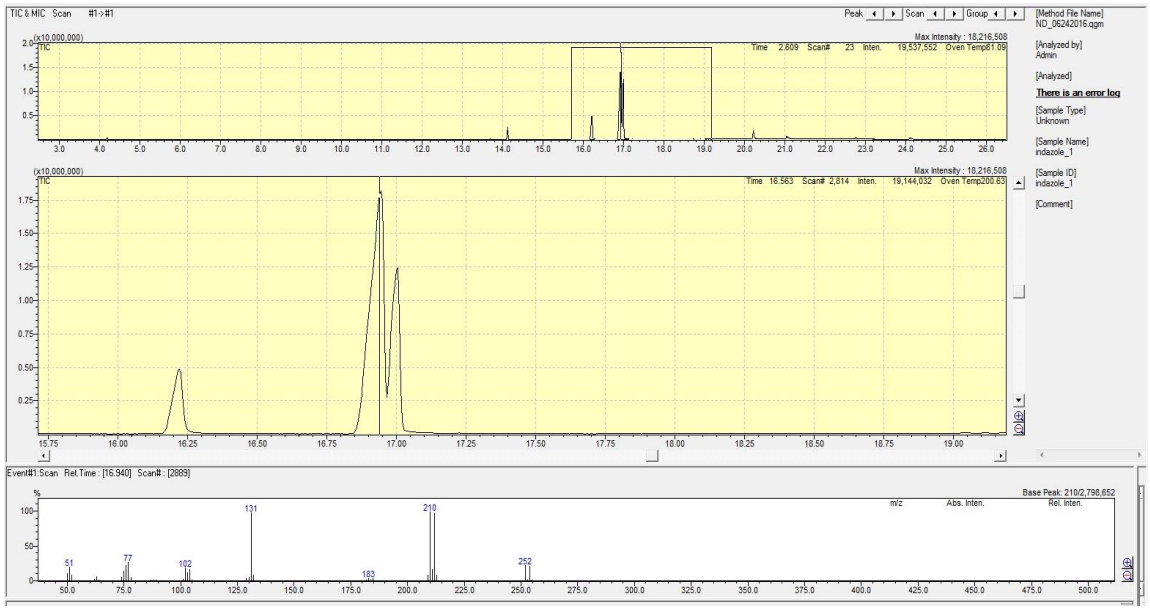


Figure B.24 GC-MS trace of products 19 and 20

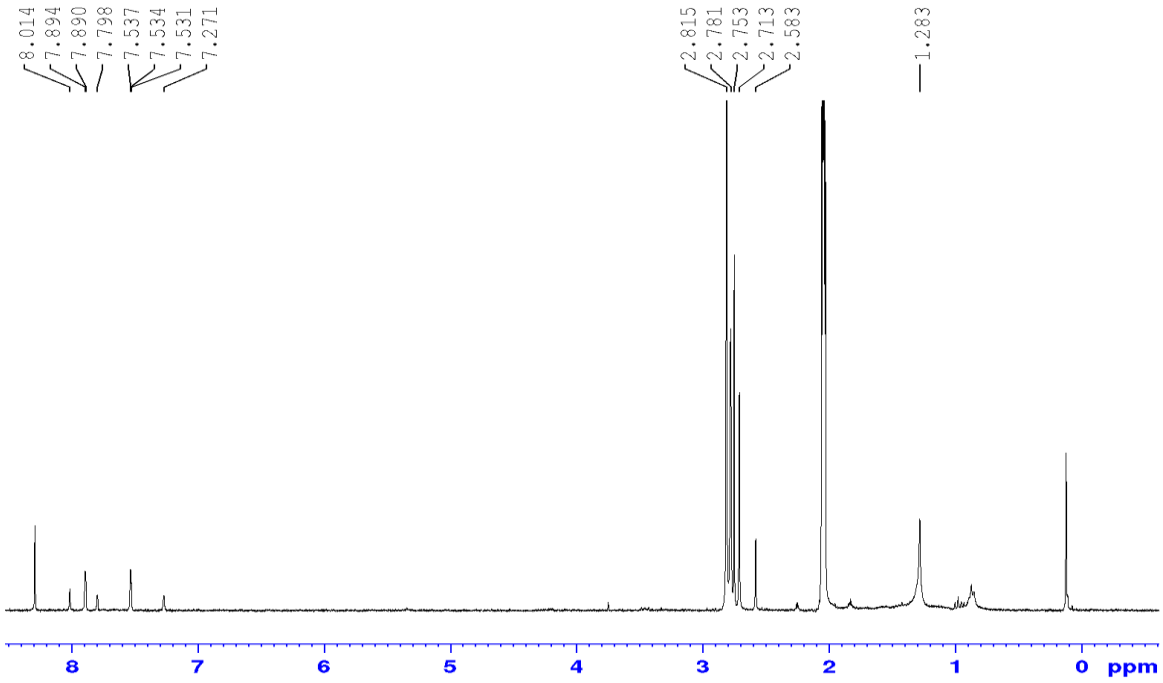


Figure B.25 ^{1}H NMR of products 19 and 20

B.6. References

1. Sato, R.; Hotta, Y.; Matsuura, K., Silver halide photographic material. Google Patents: 1983.

2. Sibi, M. P.; Chen, J.; Stanley, L., Enantioselective Diels-Alder reactions: Effect of the achiral template on reactivity and selectivity. *Synlett* **2007,** *2007* (02), 0298-0302.

3. Mohammed, F.; Bakeer, H.; El-Hashash, M., Studies on 2-Substituted-6, 8-dibromo-4 (H)-3, 1-benzoxazin-4-one. *Asian J. Chem.* **2009,** *21* (7), 5004.

4. Uff, B.; HO, Y. P.; Brown, D.; Fisher, I.; Popp, F.; KANT, J., Reissert Compound Formation with Fused Five-Membered Ring Heterocycles. *ChemInform* **1990,** *21* (14), no-no.

5. Tang, R.-J.; Milcent, T.; Crousse, B., Regioselective Halogenation of Arenes and Heterocycles in Hexafluoroisopropanol. *J. Org. Chem.* **2018,** *83* (2), 930-938.

6. Sarhan, A. E.-W. A.; El-Sherief, H. A.; Mahmoud, A. M., A convenient one-pot synthesis of 2-benzimidazolyl-thioacetophenones and thiazolo [3, 2-a] benzimidazoles. *Tetrahedron* **1996,** *52* (31), 10485-10496.

7. Ramesh, S.; Arunachalam, P. N.; Lalitha, A., Regioselective ethoxy-carbonylation of indoles and indazoles using DEAD and tetraethylammonium cyanide. *RSC Adv.* **2013,** *3* (23), 8666-8669.

8. Lucescu, L.; Bţcu, E.; Belei, D.; Shova, S.; Rigo, B.; Gautret, P.; Dubois, J.; Ghinet, A., Synthesis and biological evaluation of a new class of triazin–triazoles as potential inhibitors of human farnesyltransferase. *Res. Chem. Intermed.* **2016,** *42* (3), 1999-2021.

9. Xia, H.-D.; Zhang, Y.-D.; Wang, Y.-H.; Zhang, C., Water-Soluble Hypervalent Iodine(III) Having an I–N Bond. A Reagent for the Synthesis of Indoles. *Org. Lett* **2018,** *20* (13), 4052-4056.

10. Yu, Y.; Zhou, Y.; Song, Z.; Liang, G., An efficient t-BuOK promoted C3-chalcogenylation of indoles with dichalcogenides. *Org. Biomol. Chem.* **2018,** *16* (27), 4958-4962.

11. Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T., Analysis of the reactions used for the preparation of drug candidate molecules. *Org. Biomol. Chem.* **2006,** *4* (12), 2337-2347.

12. Tanii, S.; Arisawa, M.; Tougo, T.; Yamaguchi, M., Catalytic Method for the Synthesis of C–N-Linked Bi(heteroaryl)s Using Heteroaryl Ethers and N-Benzoyl Heteroarenes. *Org. Lett* **2018,** *20* (7), 1756-1759.

13. Kerr, W. J.; Lindsay, D. M.; Owens, P. K.; Reid, M.; Tuttle, T.; Campos, S., Site-Selective Deuteration of N-Heterocycles via Iridium-Catalyzed Hydrogen Isotope Exchange. *ACS Catal.* **2017,** *7* (10), 7182-7186.

14. Yang, X.; Li, F.; Konze, K. D.; Meslamani, J.; Ma, A.; Brown, P. J.; Zhou, M.-M.; Arrowsmith, C. H.; Kaniskan, H. Ü.; Vedadi, M.; Jin, J., Structure–Activity Relationship Studies for Enhancer of Zeste Homologue 2 (EZH2) and Enhancer of Zeste Homologue 1 (EZH1) Inhibitors. *J. Med. Chem.* **2016,** *59* (16), 7617-7633.

APPENDIX C

EXPERIMENTAL DETAILS AND CHARACTERIZATION INFORMATION FOR CHAPTER 3

C.1. Illustration of the electrochemical cell

Figure C.1 Electrochemical acylation of indazole in an H-Cell performed with a 0.1 M solution of tetrabutylammonium hexafluorophosphate ($TBAPF_6$) containing 0.75 m mol of amine in acetonitrile in the cathode side and 0.75 m mol of ferrocene on anode side. Reticulate Vitreous Carbon electrodes were employed as cathode and anode.

C.2. Illustration of the user-friendly setup

Figure C.2 Electrochemical acylation of indazole in an H-Cell performed with a 0.1 M solution of tetrabutylammonium hexafluorophosphate ($TBAPF_6$) containing 0.2 m mol of indazole in acetonitrile in the cathode side and 0.5 m mol of ferrocene on anode side. Benzoic anhydride (0.24 m mol) was added after 2 hrs. Reticulate Vitreous Carbon electrodes were employed as cathode and anode. Constant Current Electrolysis is carried out by connecting the electrodes to a commercially available battery.

C.3. Spectra of synthesized compounds

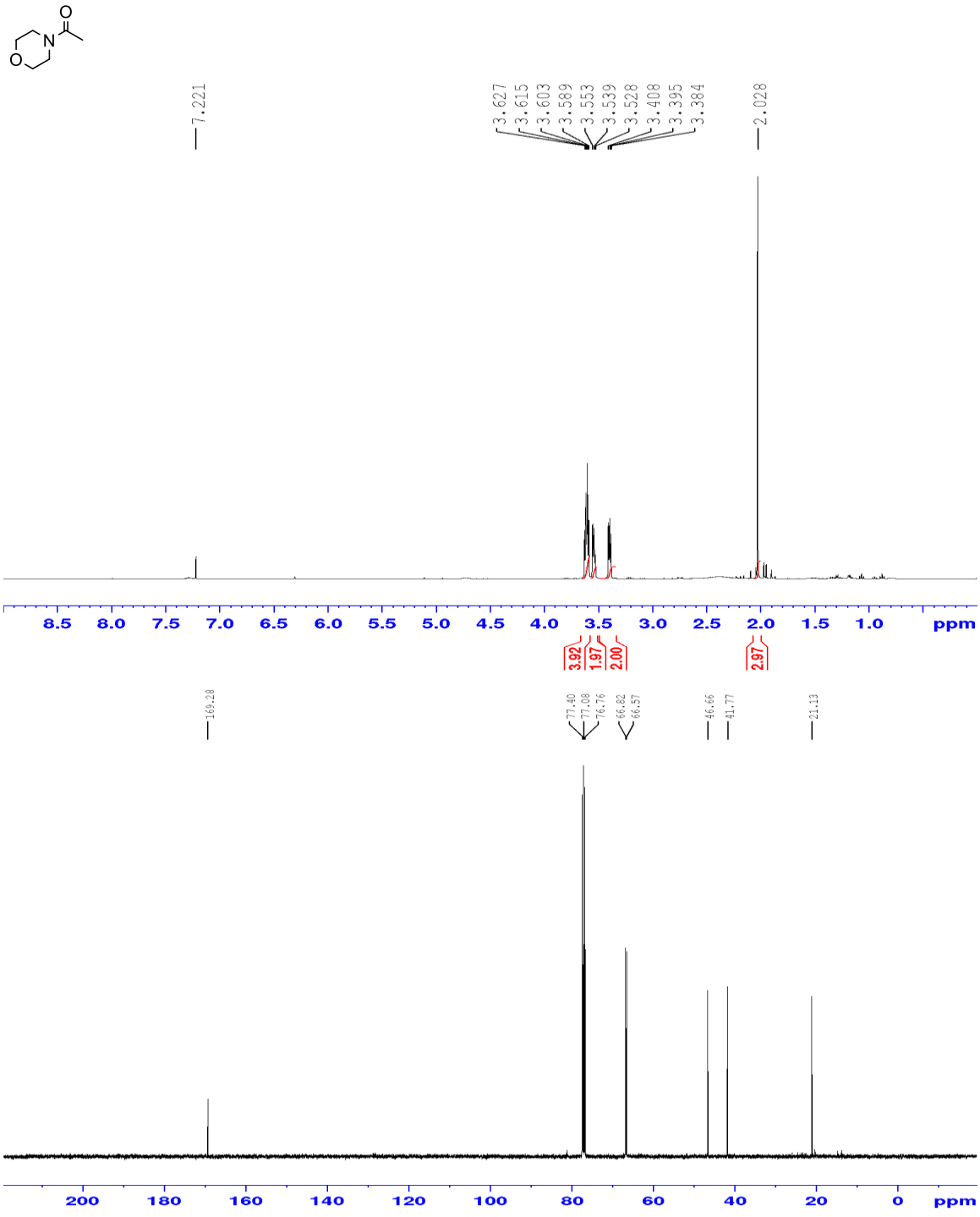


Figure C.3 ^{1}H & ^{13}C spectra of product 1a. The spectra matched reference[18]

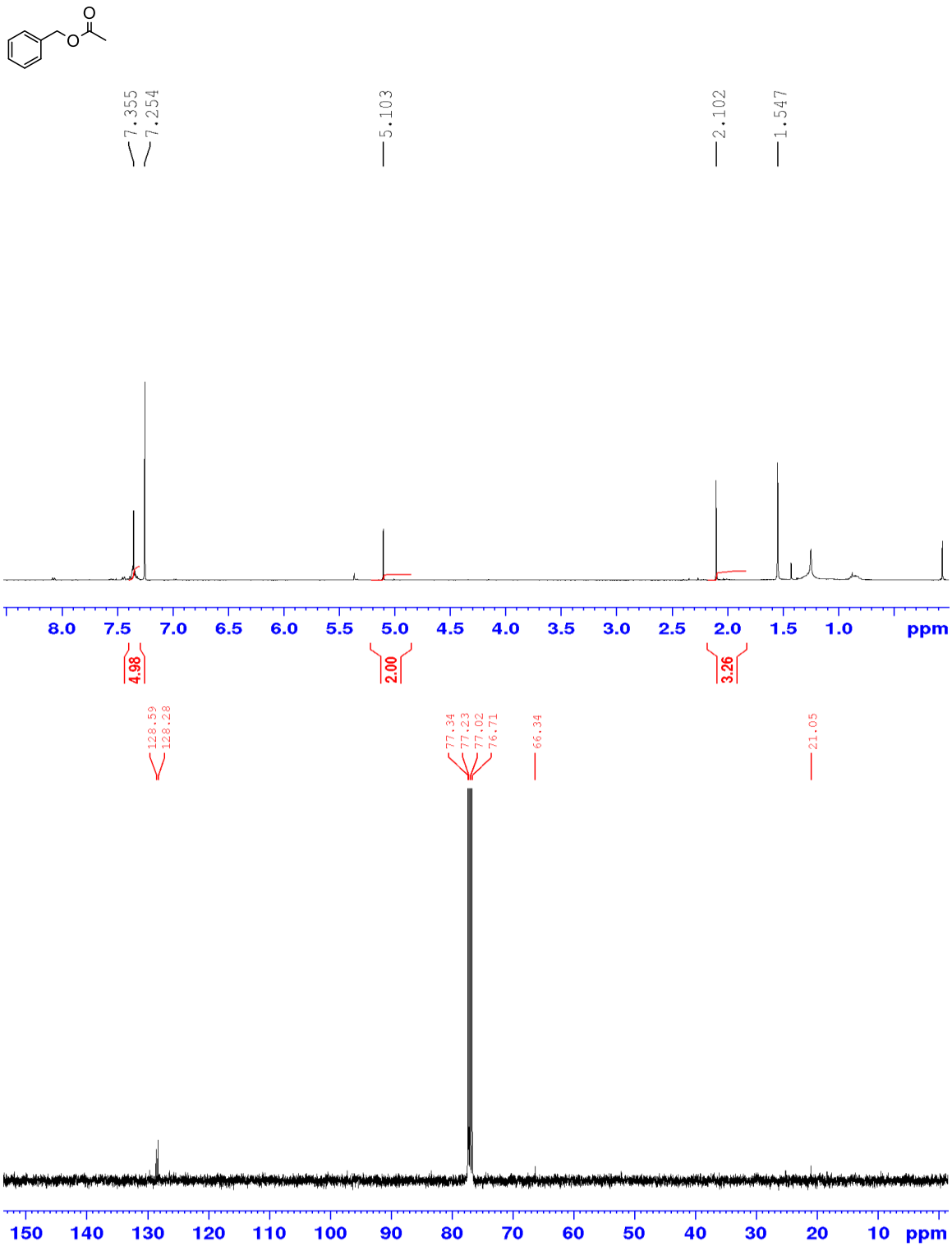


Figure C.4 ^{1}H & ^{13}C spectra of product 1b. The spectra matched reference[3]

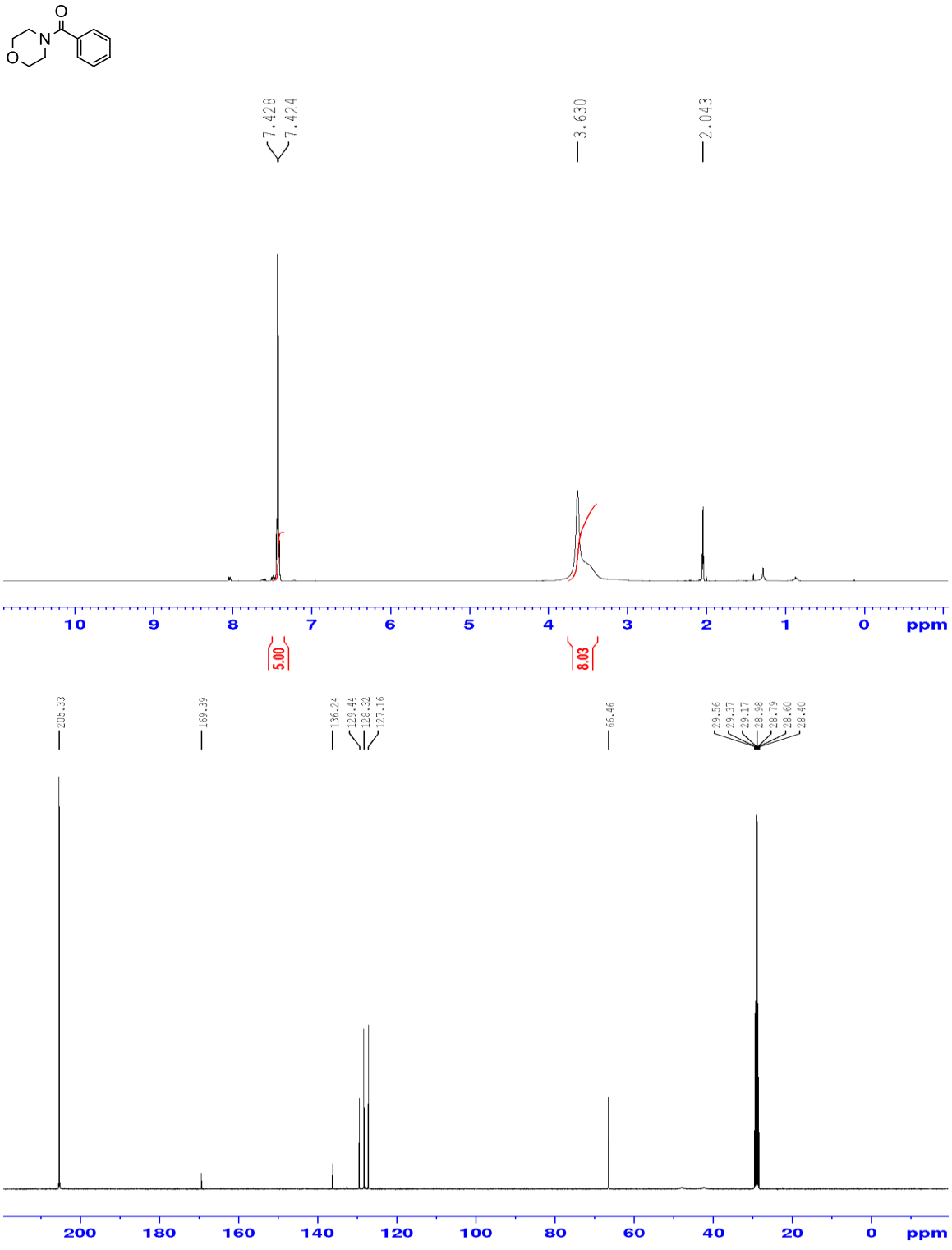


Figure C.5 ^{1}H & ^{13}C spectra of product 2a. The spectra matched reference[11]

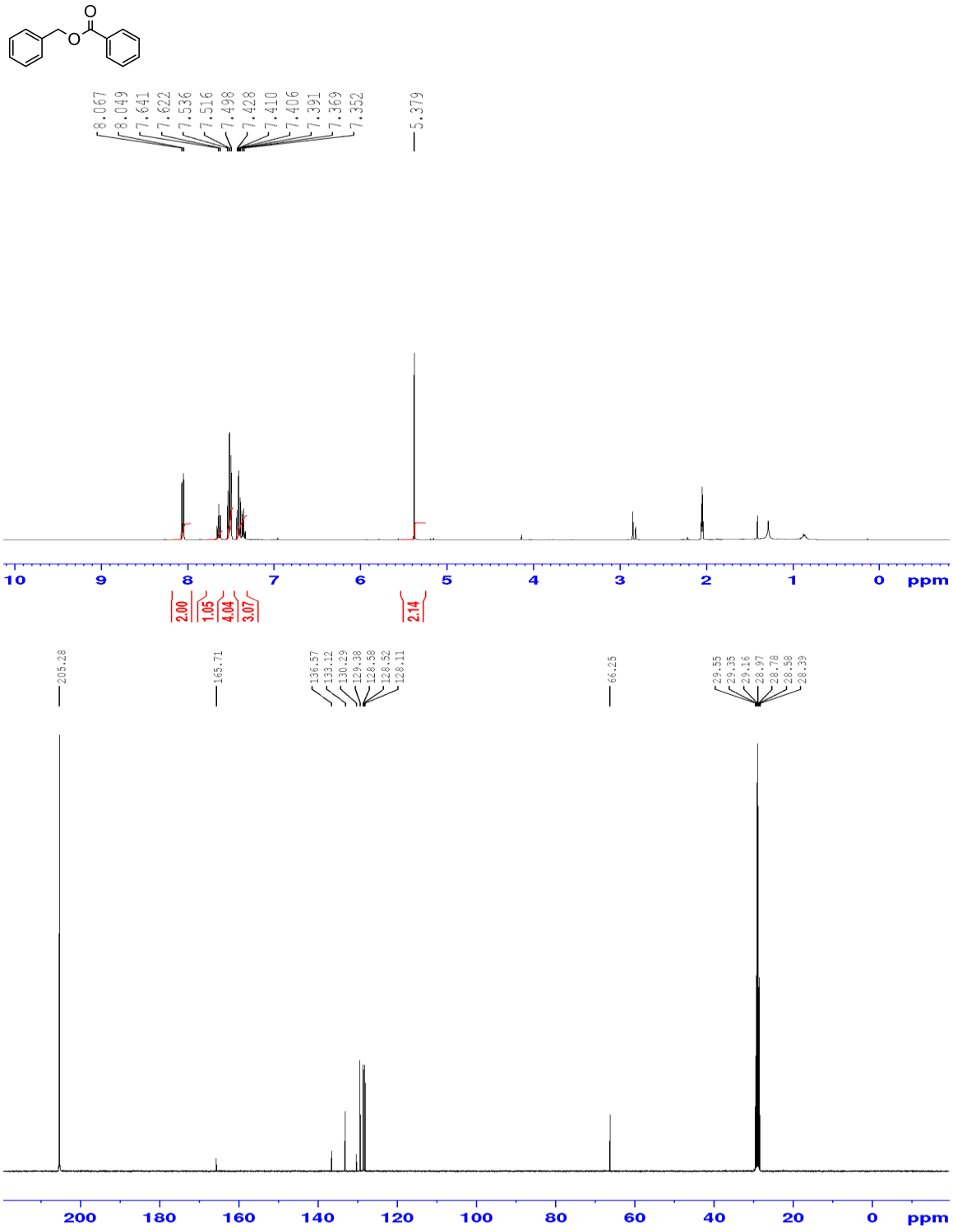


Figure C.6 ^{1}H & ^{13}C spectra of product 2b. The spectra matched reference[16]

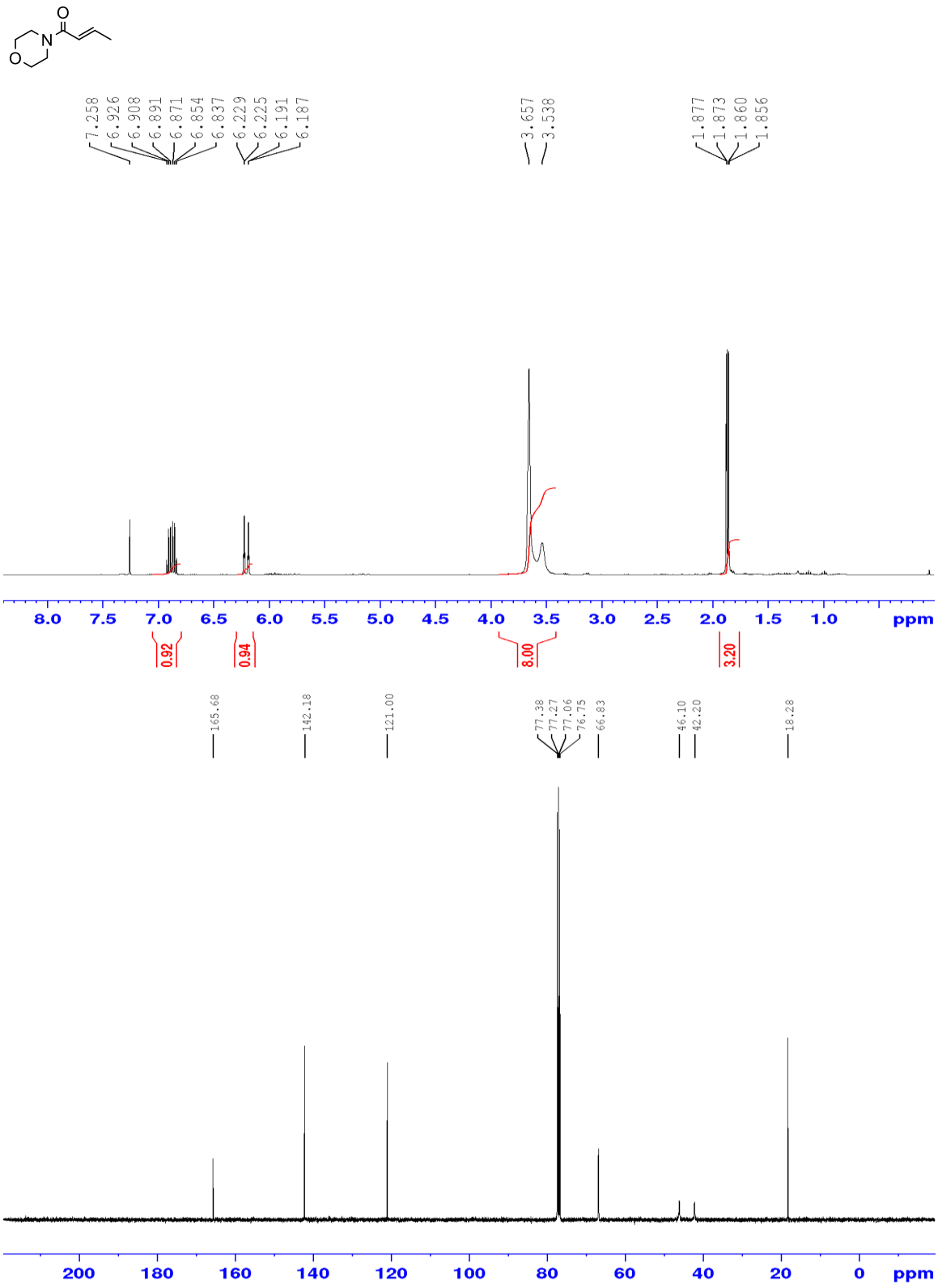


Figure C.7 [1] H & [13] C spectra of product 3a. The spectra matched reference[21]

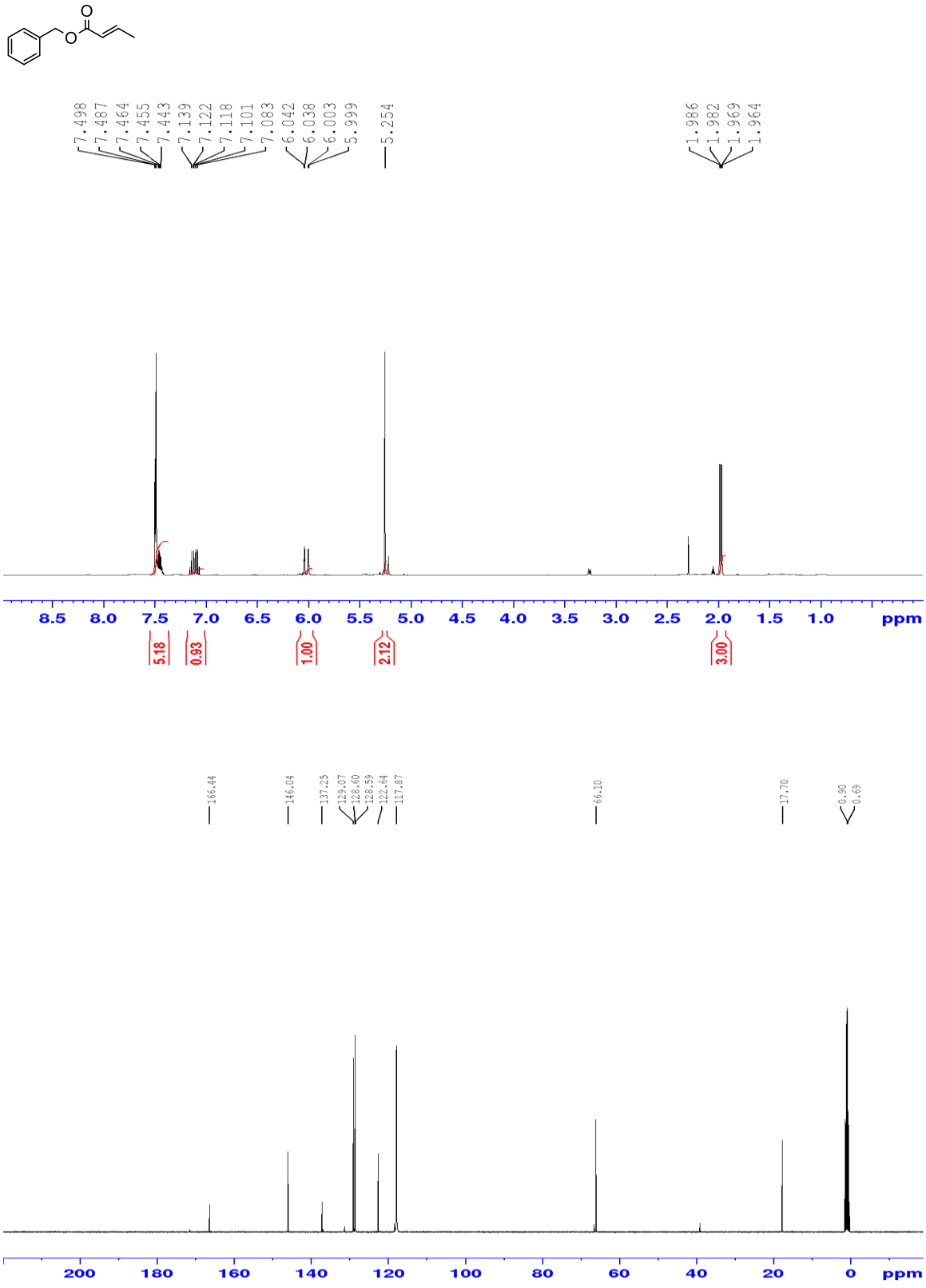


Figure C.8 ^{1}H & ^{13}C spectra of product 3b. The spectra matched reference[17]

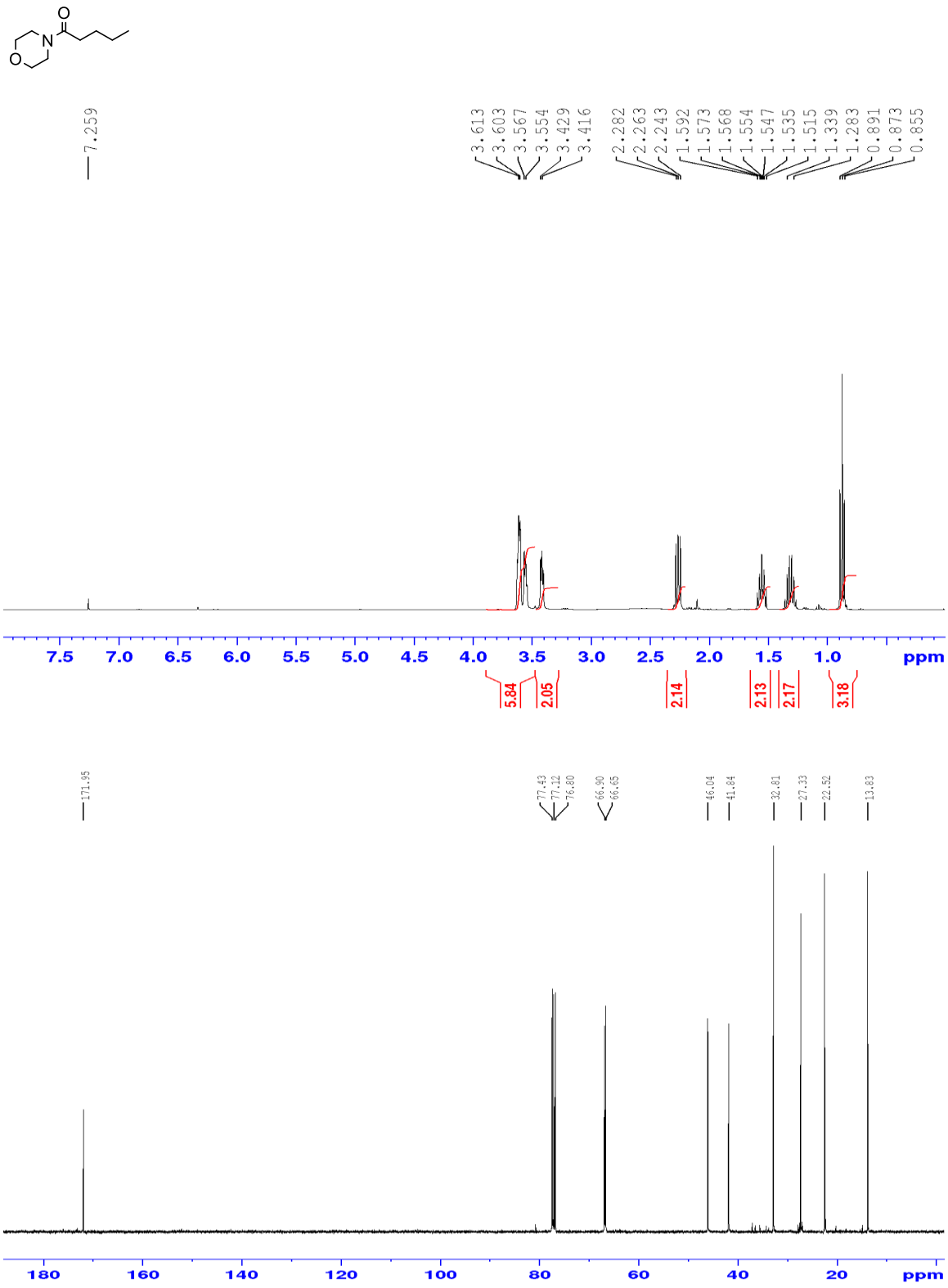


Figure C.9 ^{1}H & ^{13}C spectra of product 4a. The spectra matched reference[12]

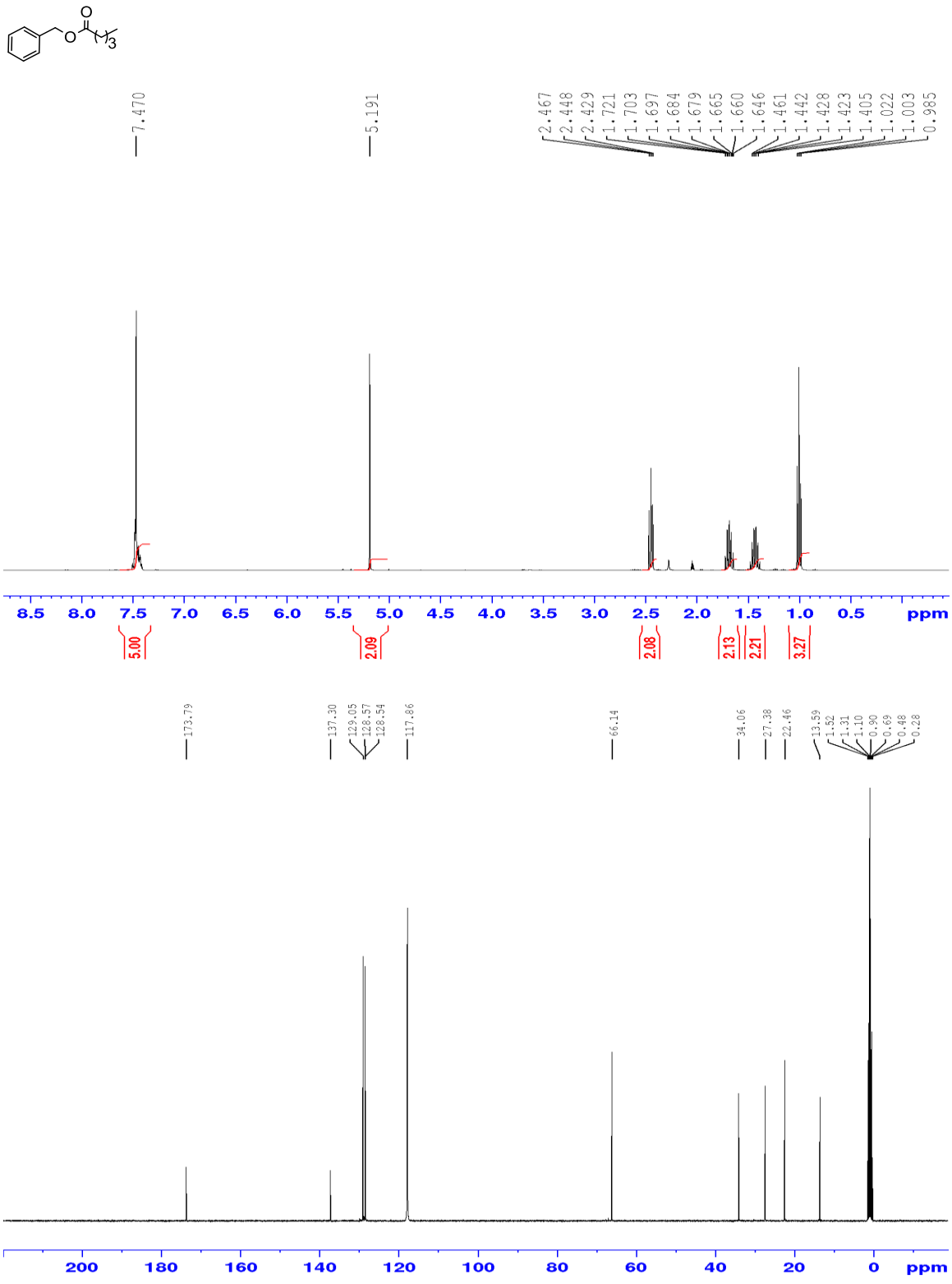


Figure C.10 [1] H & [13] C spectra of product 4b. The spectra matched reference[7]

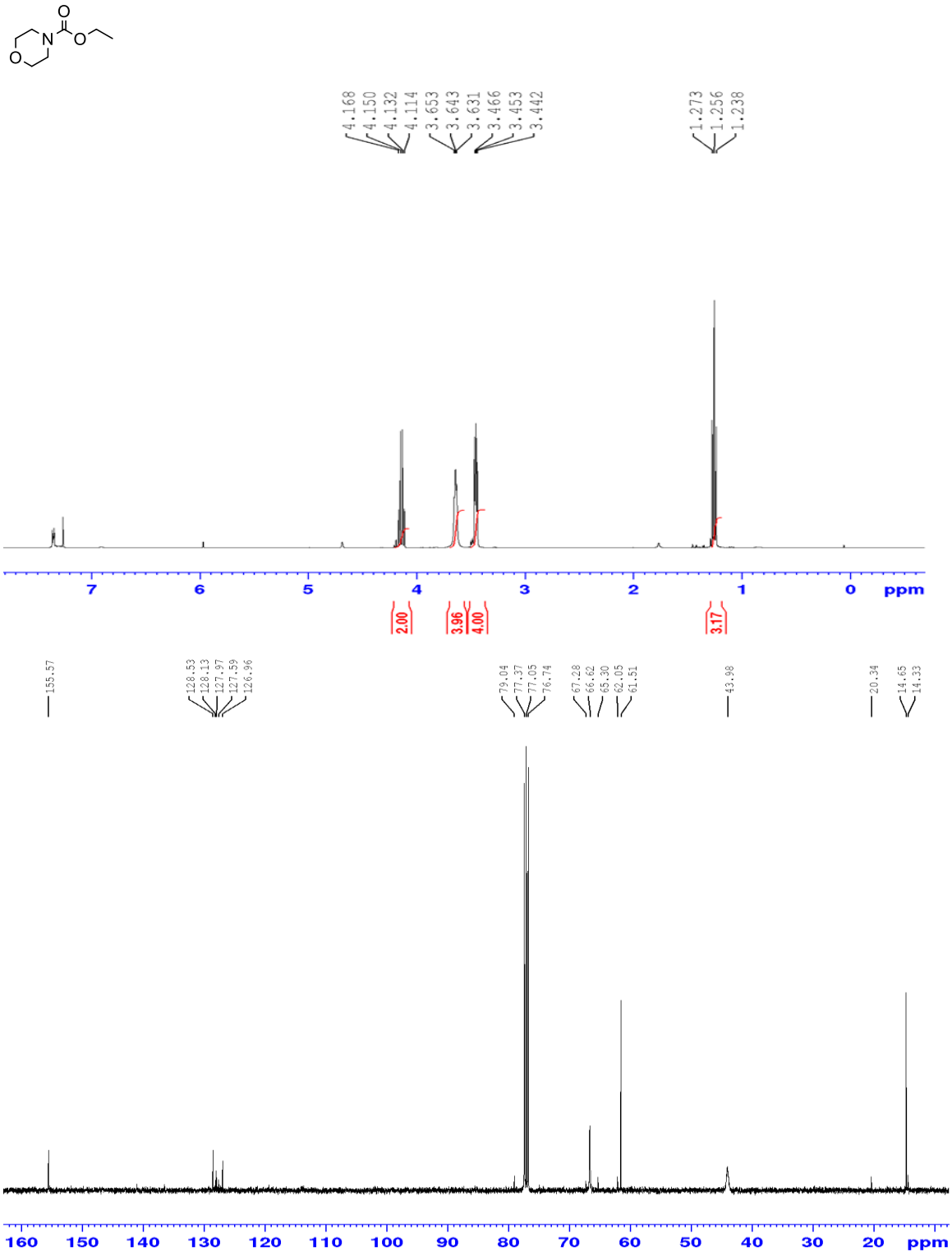


Figure C.11 [1] H & [13] C spectra of product 5a. The spectra matched reference[5]

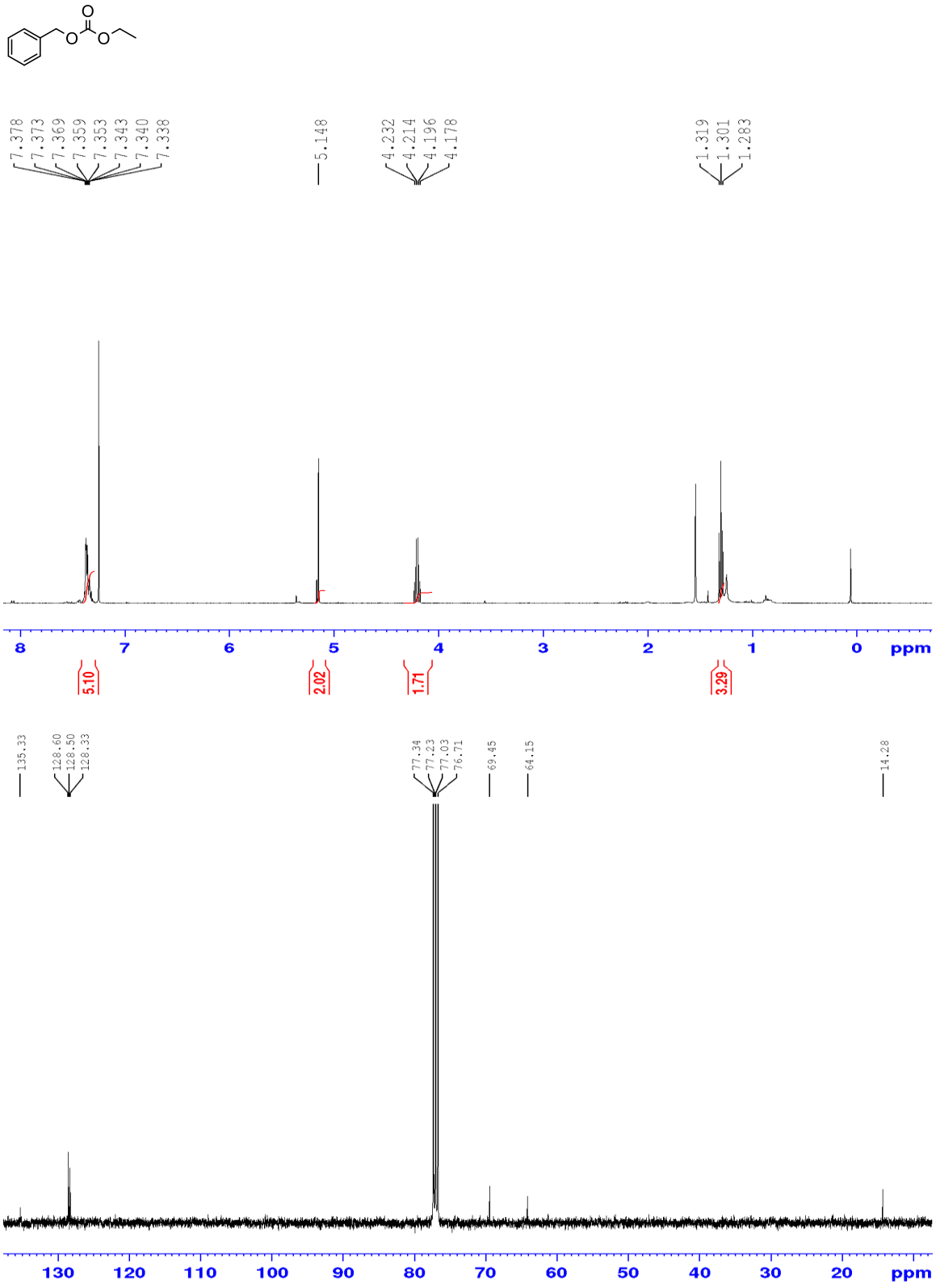


Figure C.12 [1] H & [13] C spectra of product 5b. The spectra matched reference[6]

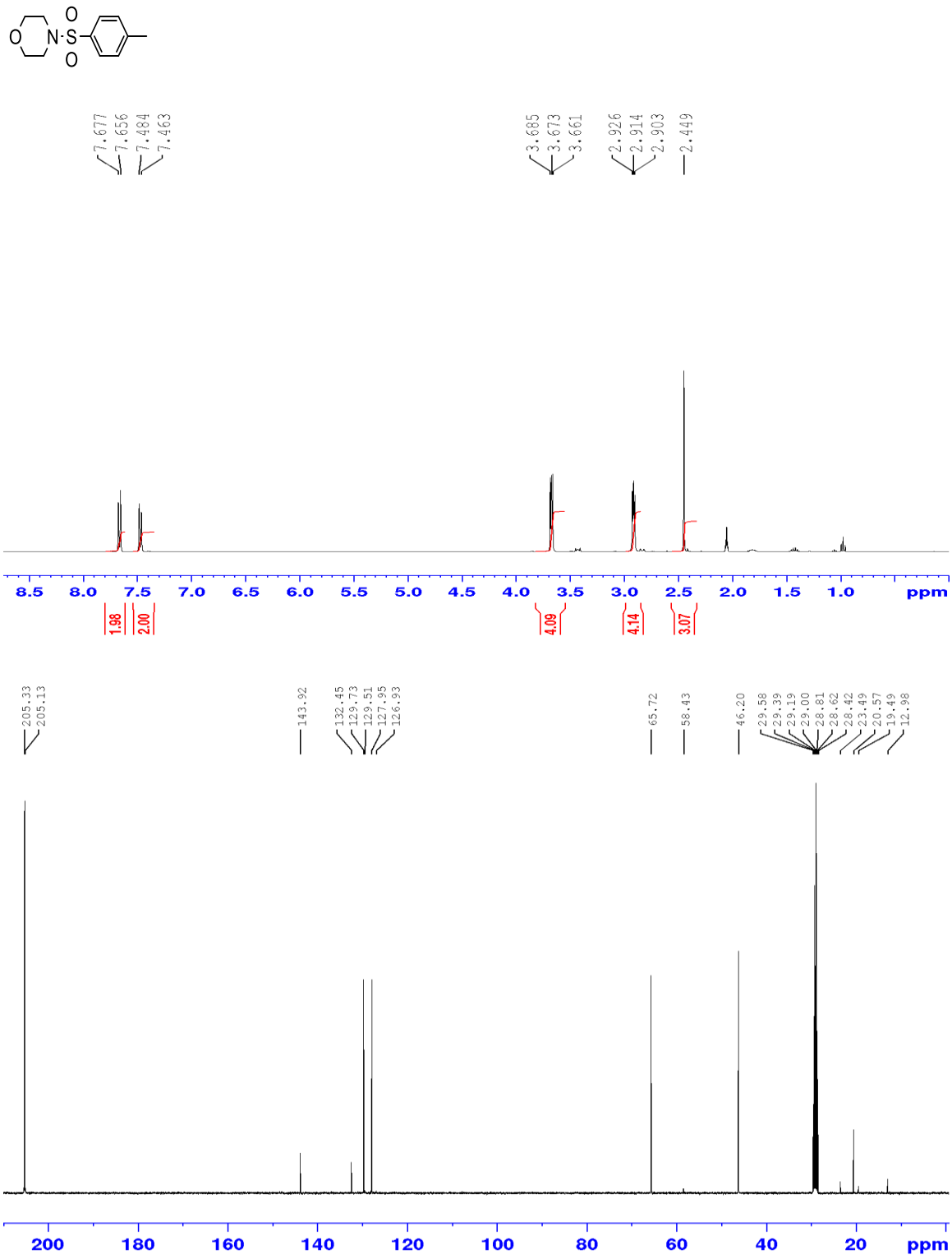


Figure C.13 [1] H & [13] C spectra of product 6a. The spectra matched reference[13]

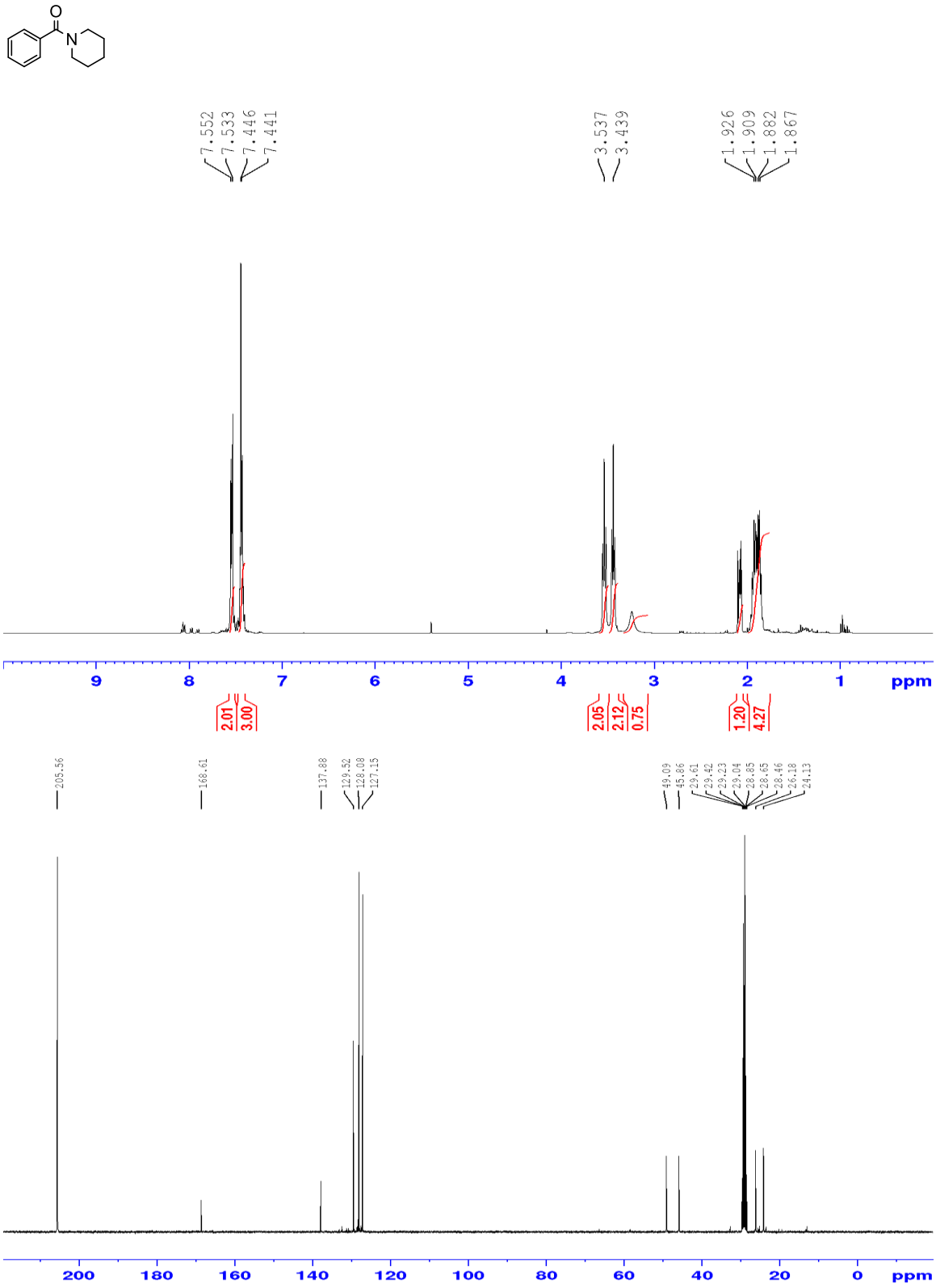


Figure C.14 [1] H & [13] C spectra of product 7. The spectra matched reference[11]

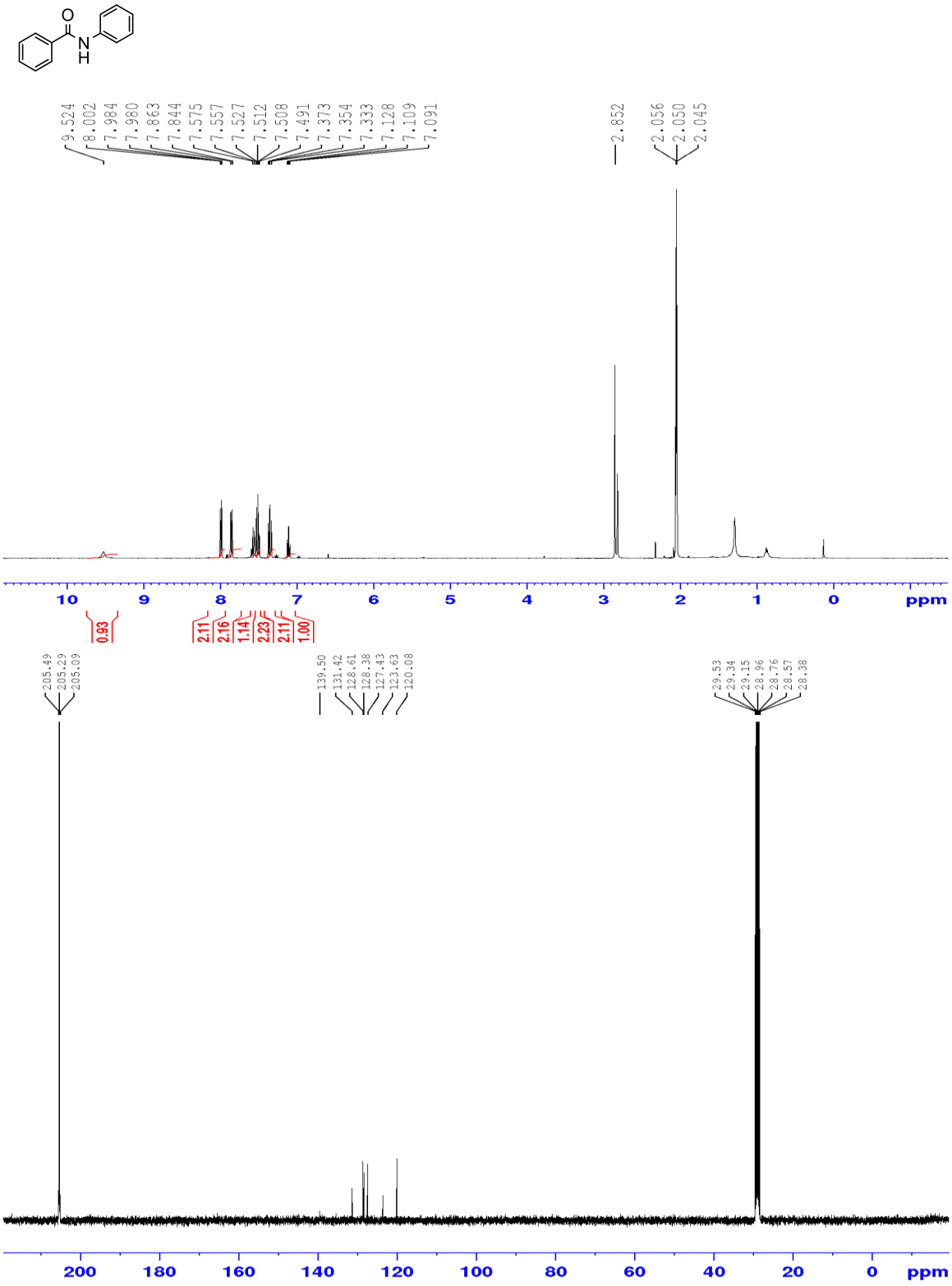


Figure C.15 ^{1}H & ^{13}C spectra of product 8. The spectra matched reference[15]

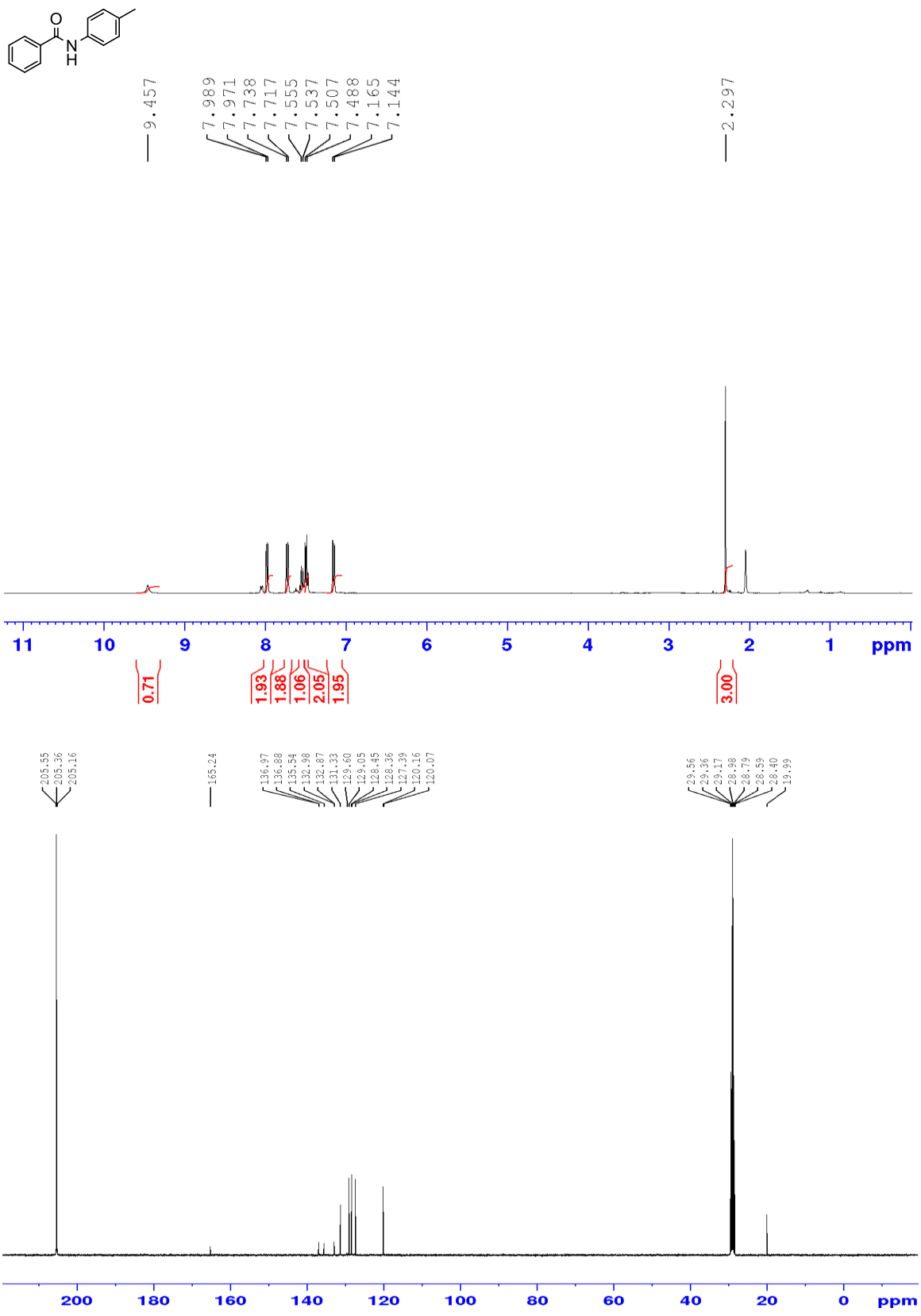


Figure C.16 [1] H & [13] C spectra of product 9. The spectra matched reference[8]

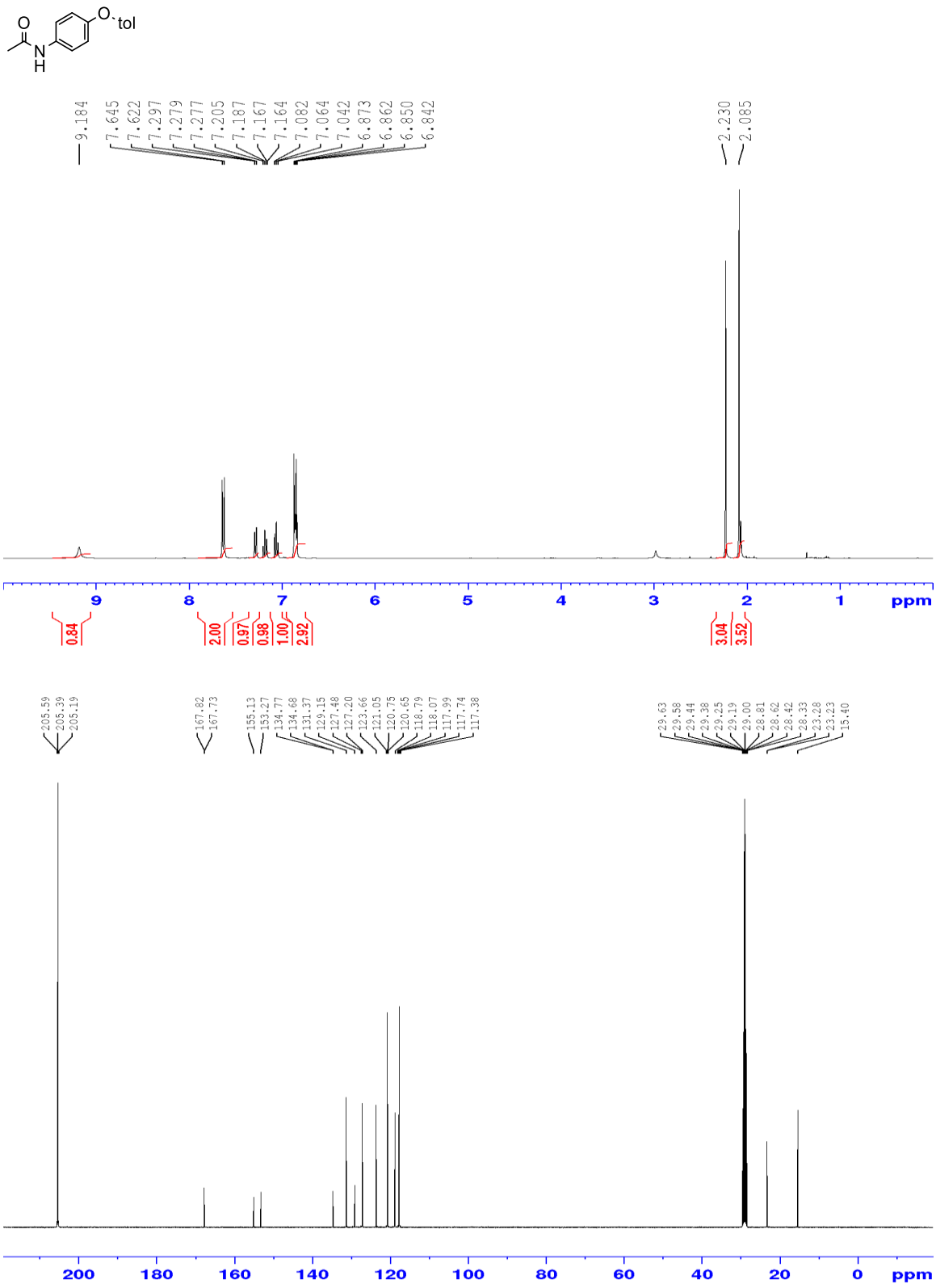


Figure C.17 [1] H & [13] C spectra of product 10. The spectra matched reference[2]

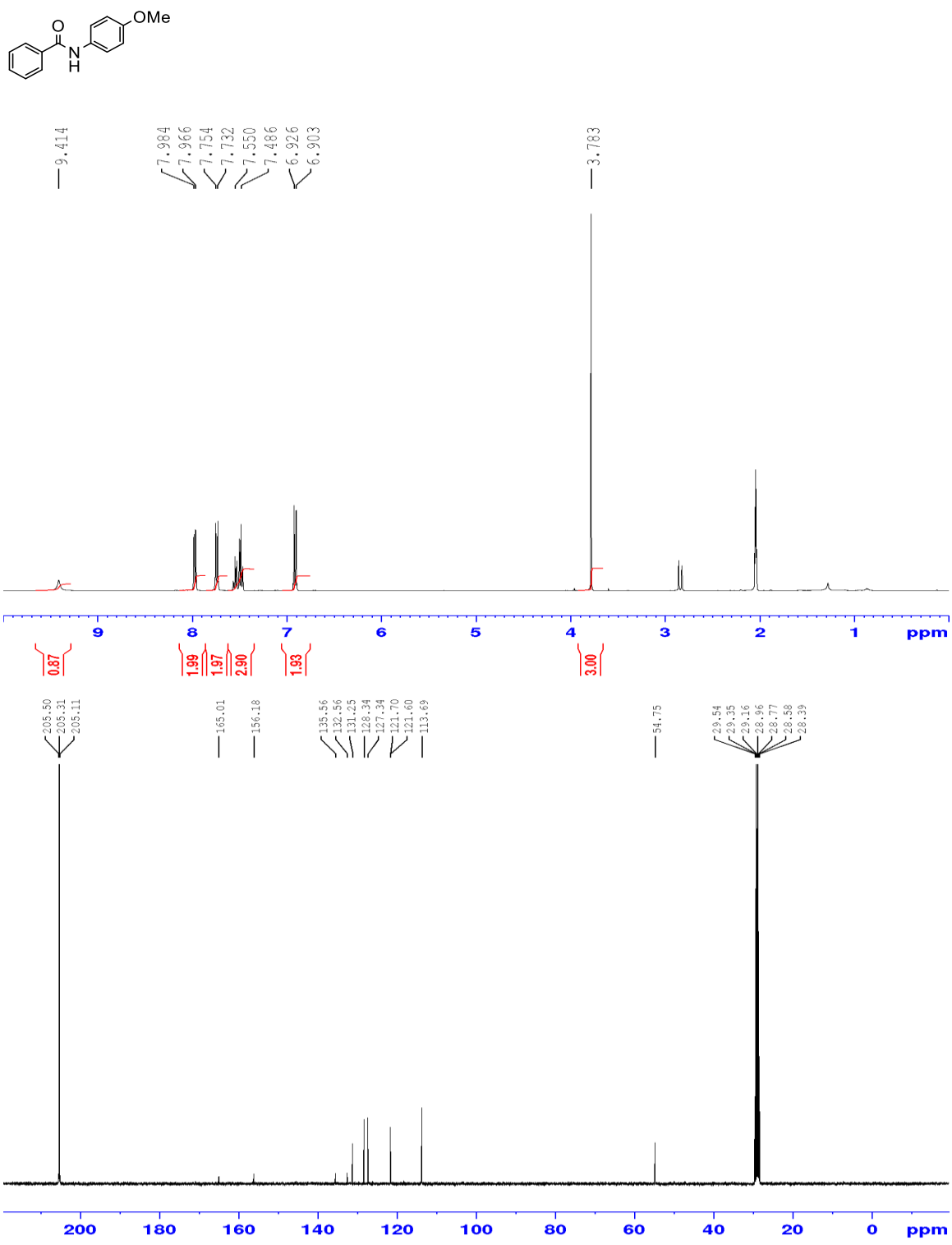


Figure C.18 [1] H & [13] C spectra of product 11. The spectra matched reference[8]

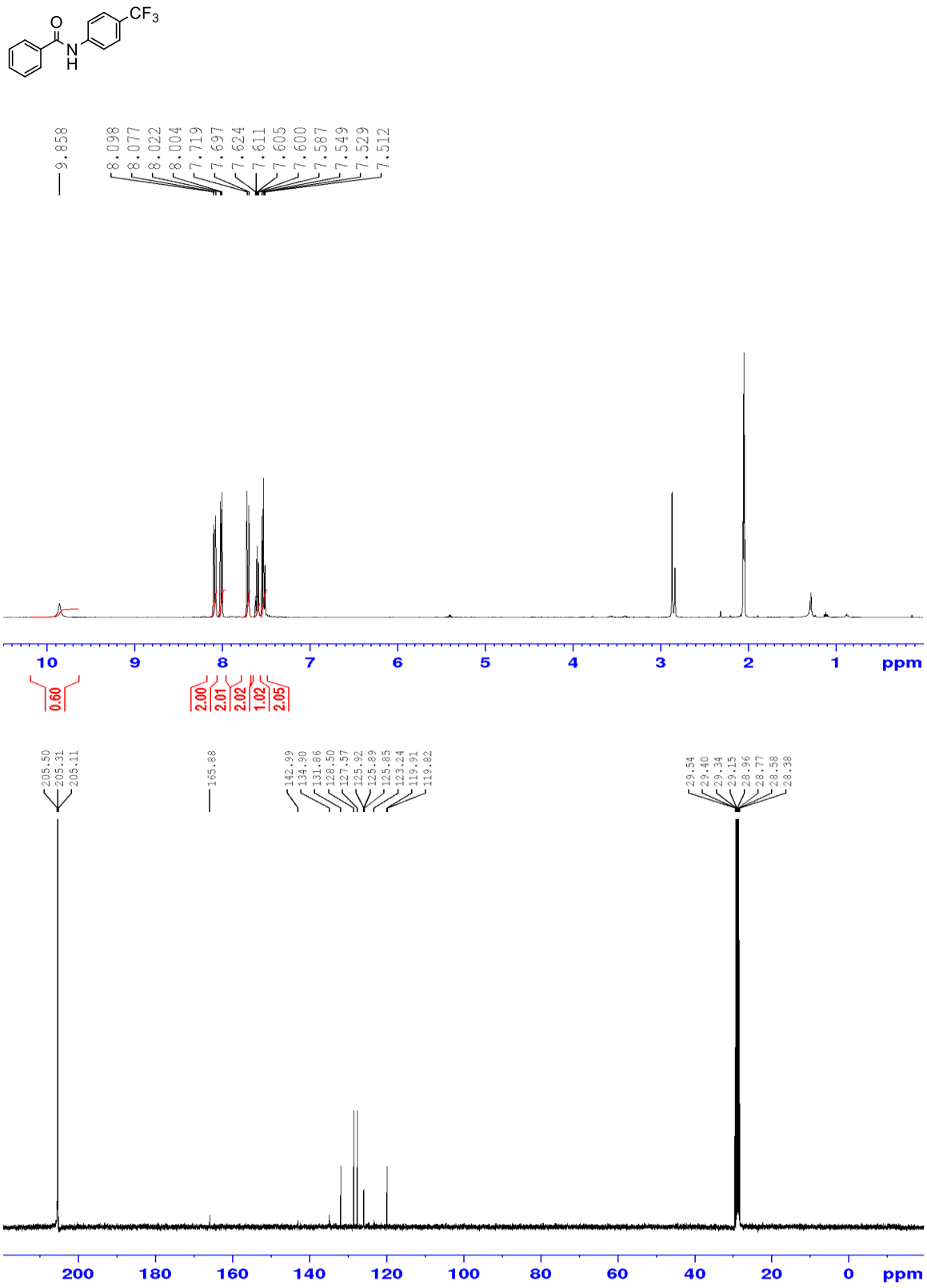


Figure C.19 ^{1}H & ^{13}C spectra of product 12. The spectra matched reference[16]

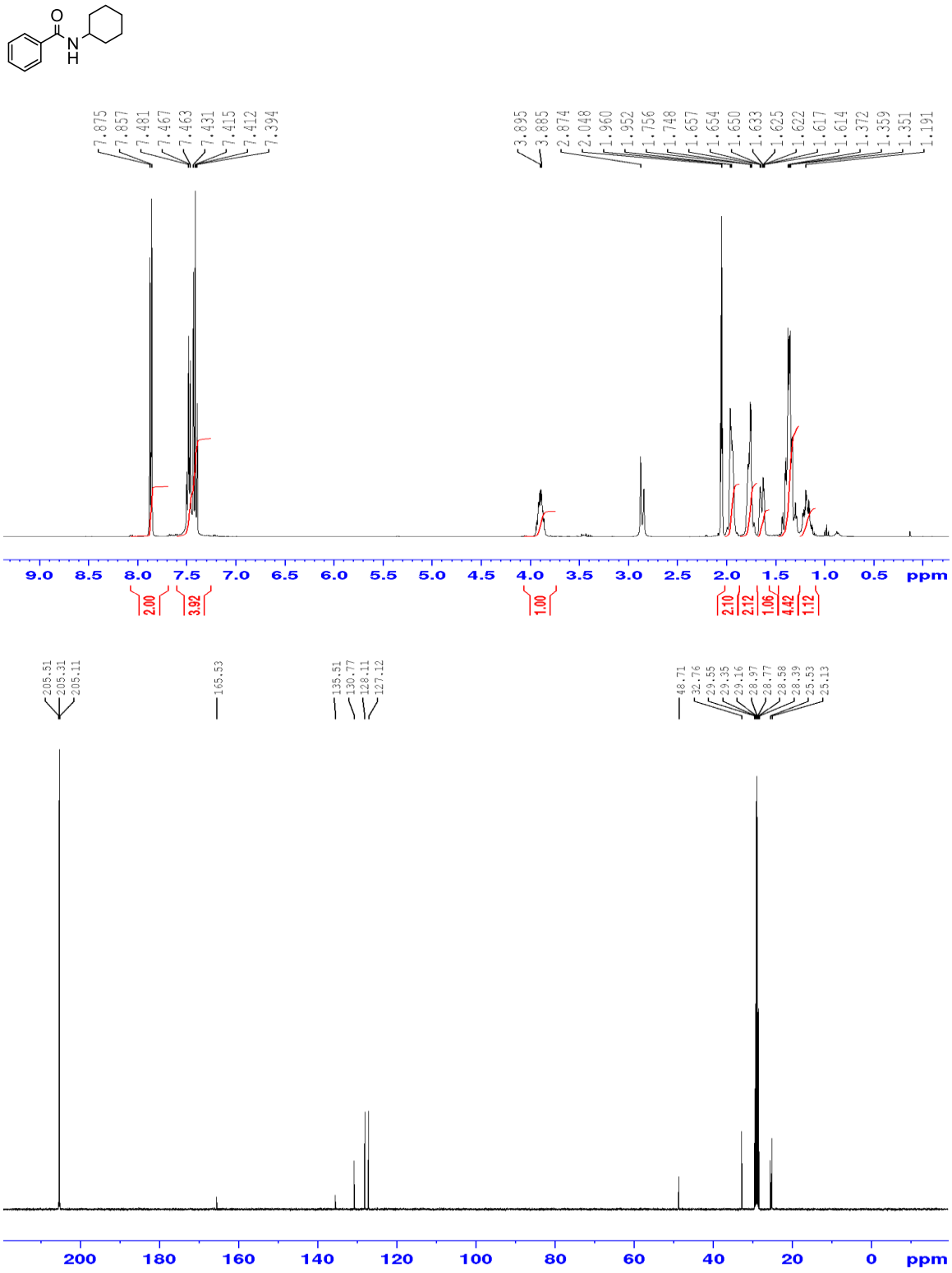


Figure C.20 [1] H & [13] C spectra of product 13. The spectra matched reference[4]

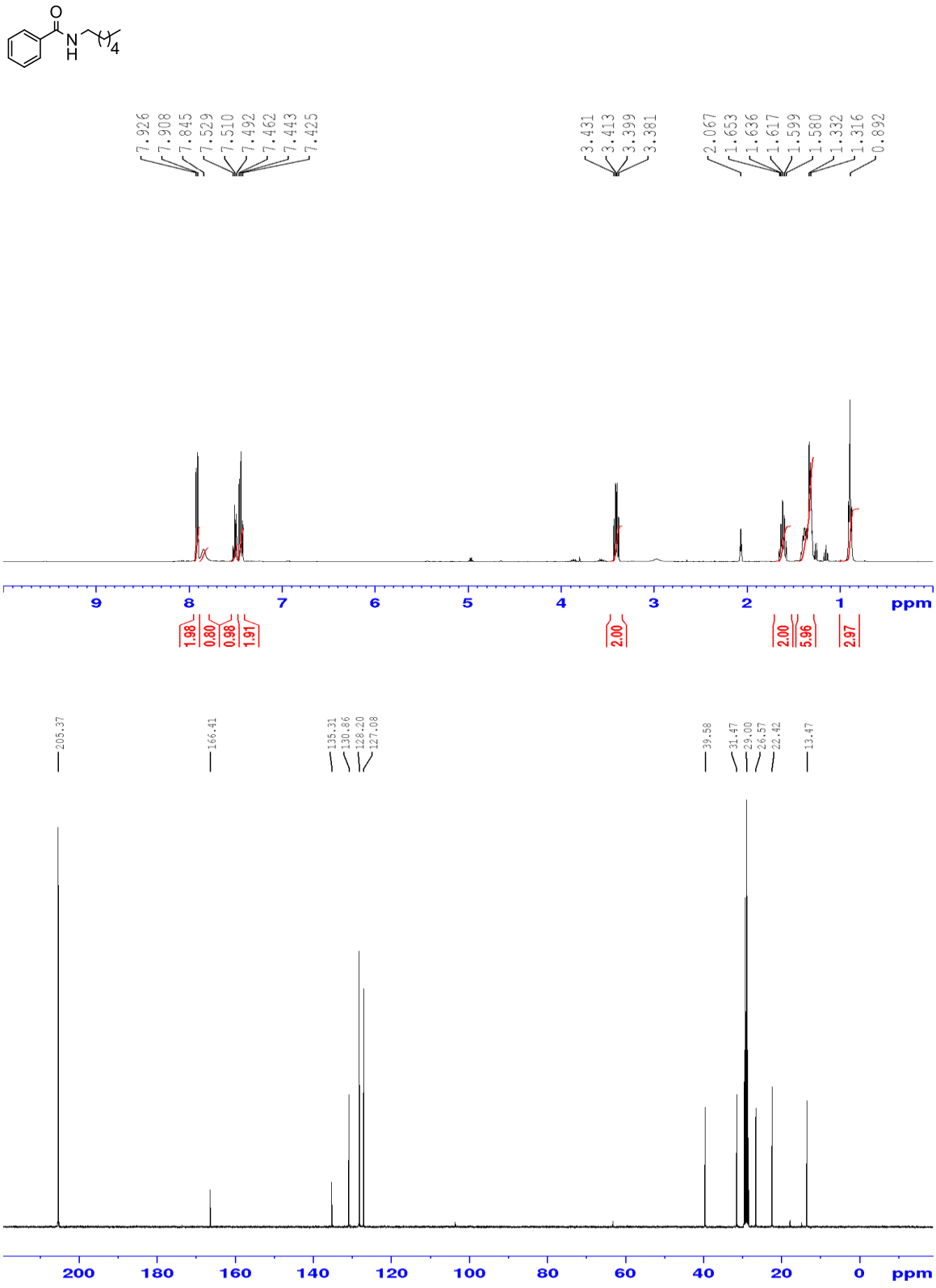


Figure C.21 ^{1}H & ^{13}C spectra of product 14. The spectra matched reference[10]

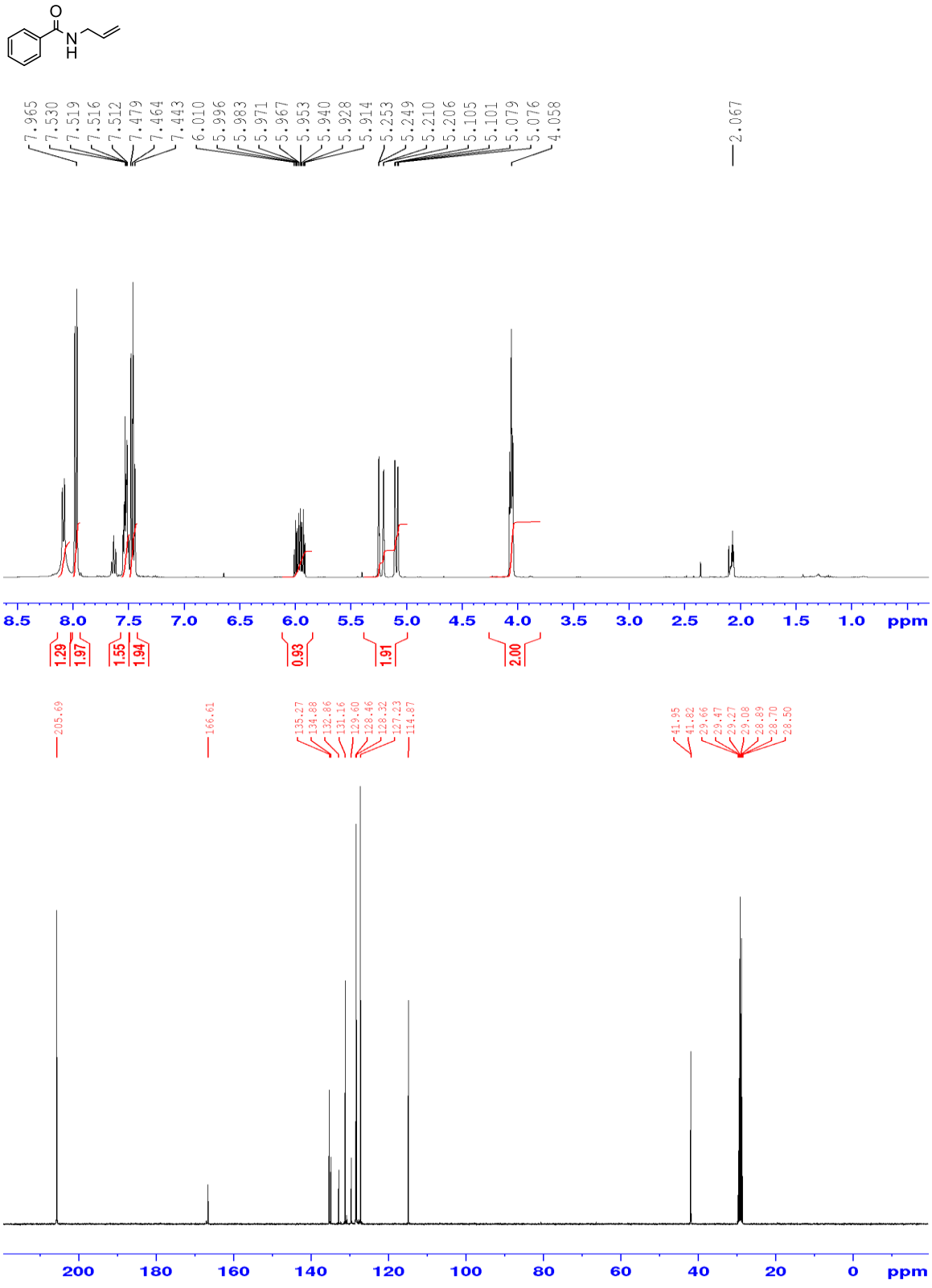


Figure C.22 ^{1}H & ^{13}C spectra of product 15. The spectra matched reference[20]

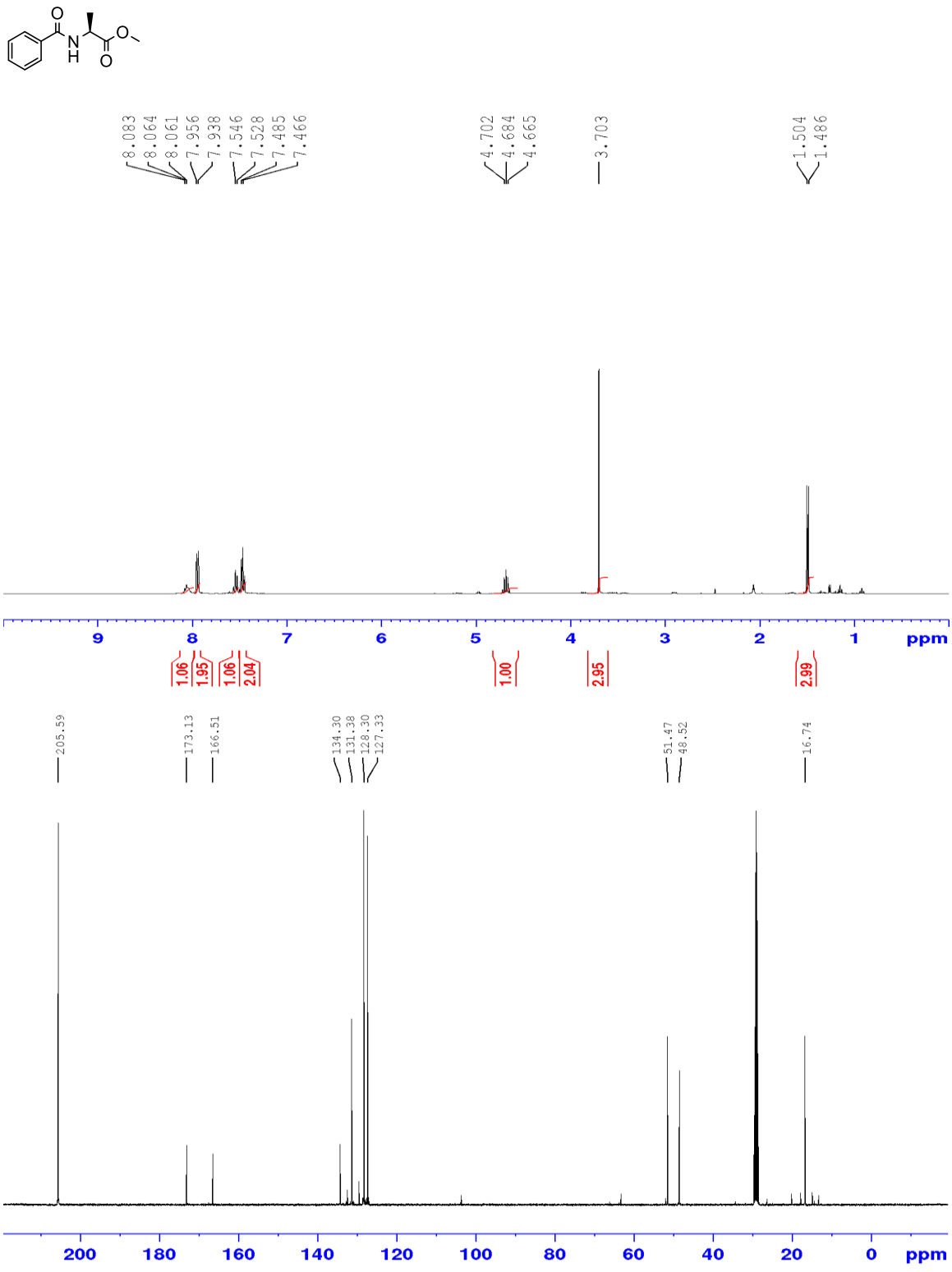


Figure C.23 ^{1}H & ^{13}C spectra of product 16. The spectra matched reference[19]

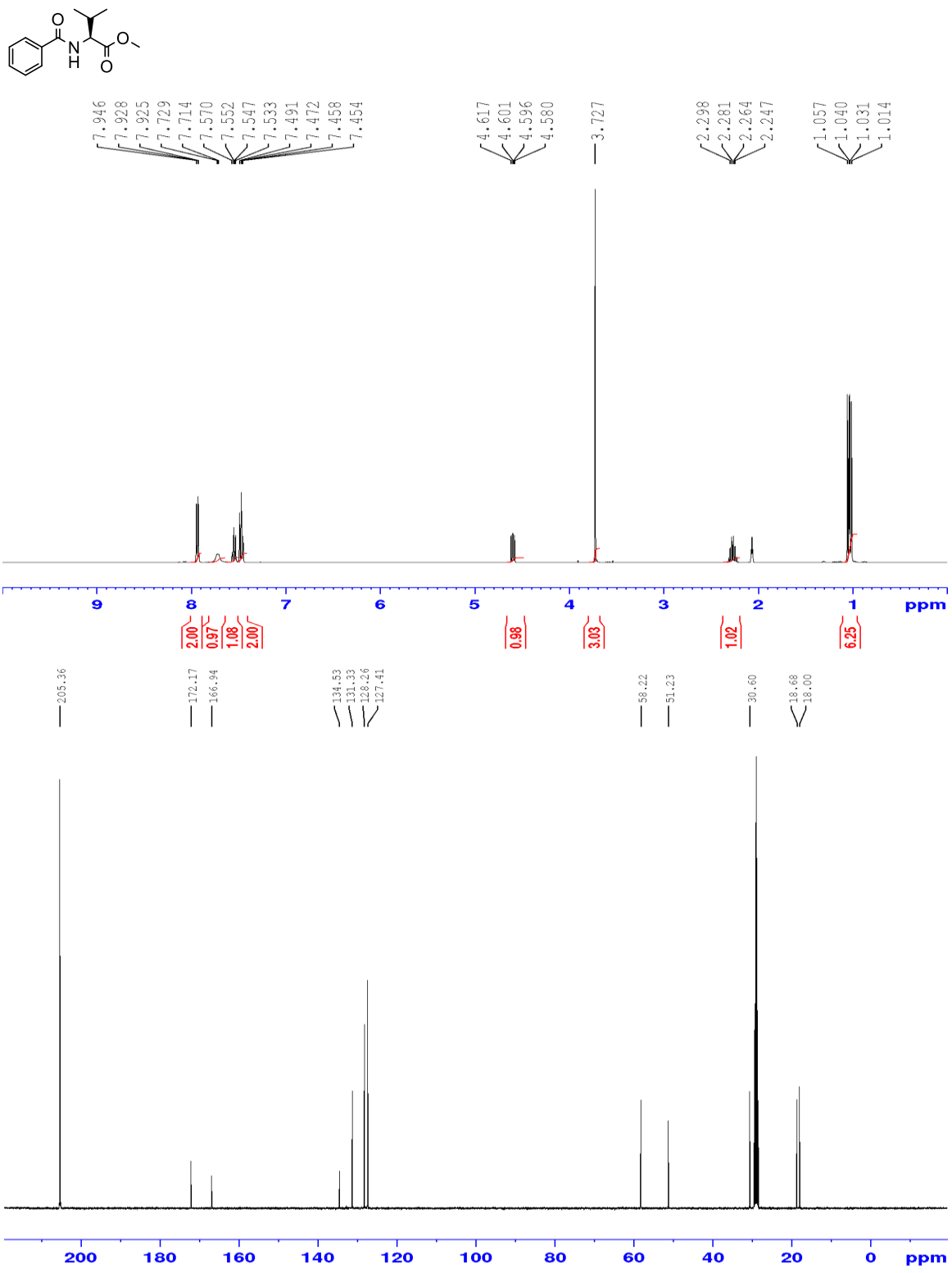


Figure C.24 [1] H & [13] C spectra of product 17. The spectra matched reference[9]

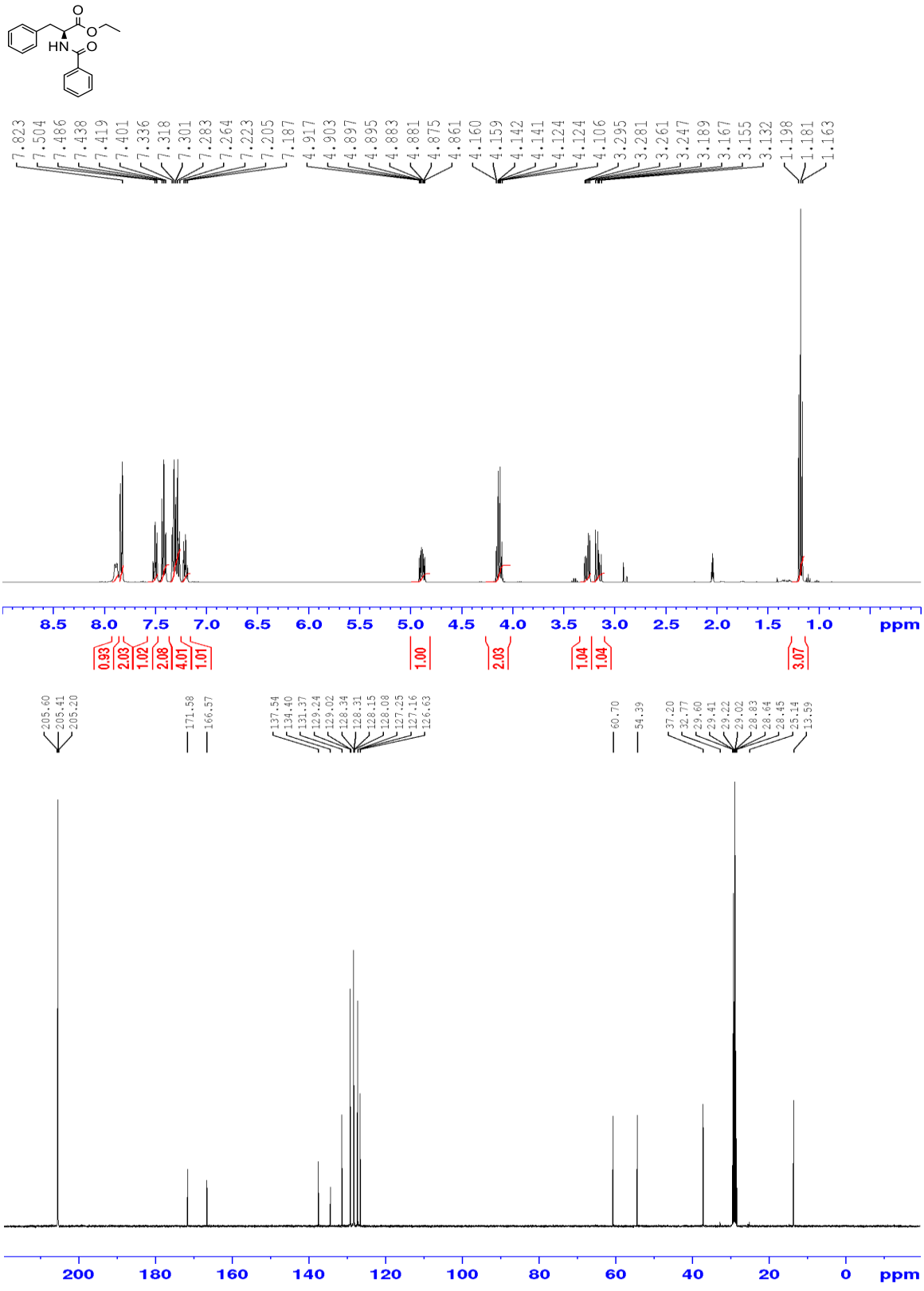


Figure C.25 [1] H & [13] C spectra of product 18. The spectra matched reference[14]

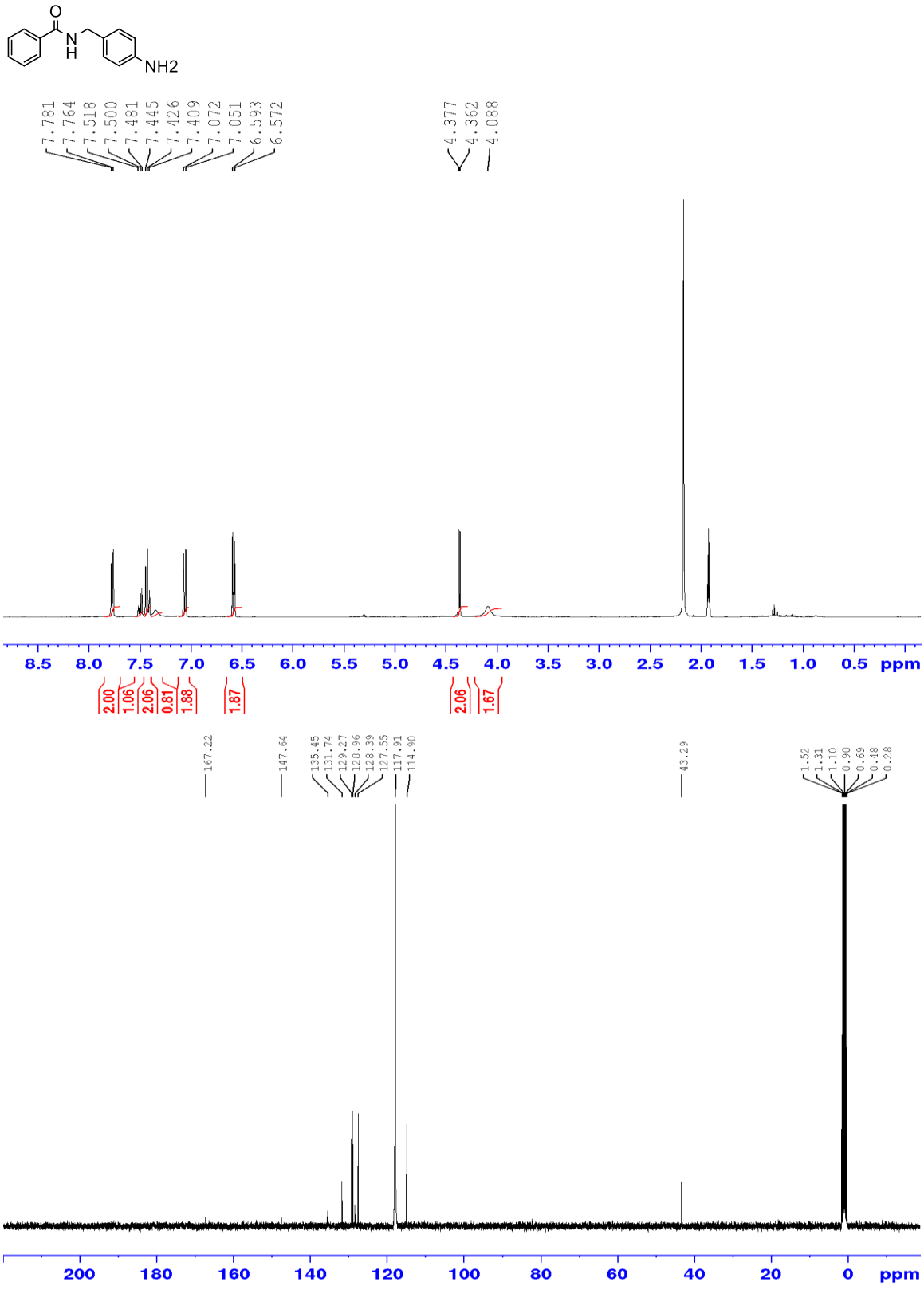


Figure C.26 [1] H & [13] C spectra of product 19. The spectra matched reference[14]

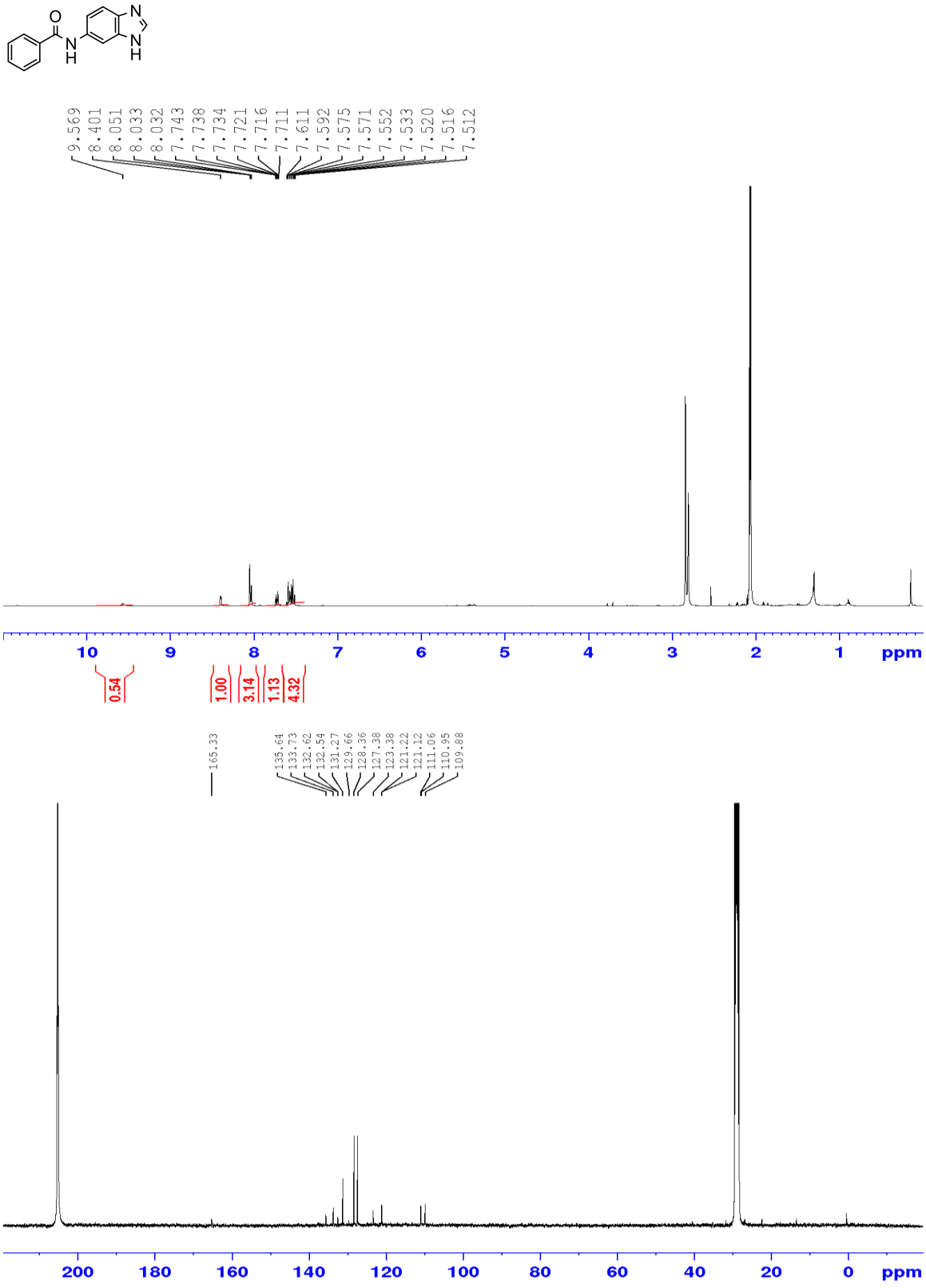


Figure C.27 ^{1}H & ^{13}C spectra of product 20. The spectra matched reference[1]

C.4. PMI calculation for pyrrolidine amidation

Mass of pyrrolidine = 0.018 g

Mass of benzoic anhydride = 0.056 g

Mass of benzyl bromide = 0.059 g

Mass of solvent = 5.5 g

Mass of electrolyte = 0.134 g

Mass of Ferrocene = 0.046 g

Mass of the amide = 0.096 g

Mass of the ester = 0.097 g

PMI = 5.813/0.193 = 30.12

C.5. References

1. Moustakim, M.; Christott, T.; Monteiro, O. P.; Bennett, J.; Giroud, C.; Ward, J.; Rogers, C. M.; Smith, P.; Panagakou, I.; Díaz-Sáez, L.; Felce, S. L.; Gamble, V.; Gileadi, C.; Halidi, N.; Heidenreich, D.; Chaikuad, A.; Knapp, S.; Huber, K. V. M.; Farnie, G.; Heer, J.; Manevski, N.; Poda, G.; Al-awar, R.; Dixon, D. J.; Brennan, P. E.; Fedorov, O., Discovery of an MLLT1/3 YEATS Domain Chemical Probe. *Angewandte Chemie International Edition* **2018,** *57* (50), 16302-16307.

2. Schareina, T.; Zapf, A.; Cotte, A.; Müller, N.; Beller, M., Bio-inspired copper catalysts for the formation of diaryl ethers. *Tetrahedron Letters* **2008,** *49* (11), 1851-1855.

3. Janza, B.; Studer, A., Stereoselective Cyclization Reactions of IBX-Generated Alkoxyamidyl Radicals. *The Journal of Organic Chemistry* **2005,** *70* (17), 6991-6994.

4. Hsieh, J.-C.; Cheng, C.-H., Nickel-catalyzed coupling of isocyanates with 1,3-iodoesters and halobenzenes: a novel method for the synthesis of imide and amide derivatives. *Chemical Communications* **2005,** (36), 4554-4556.

5. Dagade, S. P.; Dongare, M. K.; Kumar, P., Synthesis of Carbamates Using Yttria-Zirconia Based Lewis Acid Catalyst AU - Pandey, Rajesh K. *Synthetic Communications* **2003,** *33* (23), 4019-4027.

6. Zhang, L.; Niu, D.; Zhang, K.; Zhang, G.; Luo, Y.; Lu, J., Electrochemical activation of CO2 in ionic liquid (BMIMBF4): synthesis of organic carbonates under mild conditions. *Green Chemistry* **2008,** *10* (2), 202-206.

7. Ochiai, M.; Yoshimura, A.; Hoque, M. M.; Okubo, T.; Saito, M.; Miyamoto, K., Oxidation of Primary Aliphatic and Aromatic Aldehydes with Difluoro(aryl)-λ3-bromane. *Organic Letters* **2011,** *13* (20), 5568-5571.

8. Karthik, S.; Muthuvel, K.; Gandhi, T., Base-Promoted Amidation and Esterification of Imidazolium Salts via Acyl C–C bond Cleavage: Access to Aromatic Amides and Esters. *The Journal of Organic Chemistry* **2019,** *84* (2), 738-751.

9. Yamamoto, E.; Wakafuji, K.; Furutachi, Y.; Kobayashi, K.; Kamachi, T.; Tokunaga, M., Dynamic Kinetic Resolution of N-Protected Amino Acid Esters via Phase-Transfer Catalytic Base Hydrolysis. *ACS Catalysis* **2018,** *8* (7), 5708-5713.

10. Sureshbabu, P.; Azeez, S.; Chaudhary, P.; Kandasamy, J., tert-Butyl nitrite promoted transamidation of secondary amides under metal and catalyst free conditions. *Organic & Biomolecular Chemistry* **2019,** *17* (4), 845-850.

11. Ohshima, T.; Iwasaki, T.; Maegawa, Y.; Yoshiyama, A.; Mashima, K., Enzyme-Like Chemoselective Acylation of Alcohols in the Presence of Amines Catalyzed by a Tetranuclear Zinc Cluster. *Journal of the American Chemical Society* **2008,** *130* (10), 2944-2945.

12. Tona, V.; de la Torre, A.; Padmanaban, M.; Ruider, S.; González, L.; Maulide, N., Chemo- and Stereoselective Transition-Metal-Free Amination of Amides with Azides. *Journal of the American Chemical Society* **2016,** *138* (27), 8348-8351.

13. Jiang, Y.-y.; Wang, Q.-Q.; Liang, S.; Hu, L.-M.; Little, R. D.; Zeng, C.-C., Electrochemical Oxidative Amination of Sodium Sulfinates: Synthesis of Sulfonamides Mediated by NH4I as a Redox Catalyst. *The Journal of Organic Chemistry* **2016,** *81* (11), 4713-4719.

14. Mandai, H.; Hongo, K.; Fujiwara, T.; Fujii, K.; Mitsudo, K.; Suga, S., Dynamic Kinetic Resolution of Azlactones by a Chiral N,N-Dimethyl-4-aminopyridine Derivative Containing a 1,1′-Binaphthyl Unit: Importance of Amide Groups. *Organic Letters* **2018,** *20* (16), 4811-4814.

15. Sinha, S.; Sikari, R.; Sinha, V.; Jash, U.; Das, S.; Brandão, P.; Demeshko, S.; Meyer, F.; de Bruin, B.; Paul, N. D., Iron-Catalyzed/Mediated C–N Bond Formation: Competition between Substrate Amination and Ligand Amination. *Inorganic Chemistry* **2019,** *58* (3), 1935-1948.

16. Li, L.; Sheng, H.; Xu, F.; Shen, Q., Heterometal Clusters Ln2Na8(OCH2CH2NMe2)12(OH)2 as Homogeneous Catalysts for the Tishchenko Reaction. *Chinese Journal of Chemistry* **2009,** *27* (6), 1127-1131.

17. Peter, D.; Brückner, R., A New Approach to Models of the 4,5-Dihydroxycyclopentenone Core of the Kodaistatins A–D: Elucidation of the Diol Configuration in Kodaistatin A. *Chemistry – A European Journal* **2017,** *23* (50), 12104-12109.

18. Rao, C. B.; Rao, D. C.; Babu, D. C.; Venkateswarlu, Y., Retro-Claisen Condensation with FeIII as Catalyst under Solvent-Free Conditions. *European Journal of Organic Chemistry* **2010,** *2010* (15), 2855-2859.

19. Reddy, K. R.; Maheswari, C. U.; Venkateshwar, M.; Kantam, M. L., Oxidative Amidation of Aldehydes and Alcohols with Primary Amines Catalyzed by KI-TBHP. *European Journal of Organic Chemistry* **2008,** *2008* (21), 3619-3622.

20. Zhang, X.; Cao, B.; Yu, S.; Zhang, X., Rhodium-Catalyzed Asymmetric Hydroformylation of N-Allylamides: Highly Enantioselective Approach to β2-Amino Aldehydes. *Angewandte Chemie International Edition* **2010,** *49* (24), 4047-4050.

21. Ando, K.; Tsuji, E.; Ando, Y.; Kunitomo, J.-i.; Kobayashi, R.; Yokomizo, T.; Shimizu, T.; Yamashita, M.; Ohta, S.; Nabe, T.; Kohno, S.; Ohishi, Y., Synthesis of 2-, 4- and 5-(2-alkylcarbamoyl-1-methylvinyl)-7-alkyloxybenzo[b]furans and their leukotriene B4 receptor antagonistic activity. *Organic & Biomolecular Chemistry* **2005,** *3* (11), 2129-2139.

APPENDIX D

PERMISSION TO REPRINT

Permission to reprint chapter 2

Permission to reprint chapter 3

Copyright Clearance Center RightsLink®

Home | Create Account | Help

ACS Publications
Most Trusted. Most Cited. Most Read.

Title: Selective N1-Acylation of Indazoles with Acid Anhydrides Using an Electrochemical Approach

Author: D. M. M. Mevan Dissanayake, Aaron K. Vannucci

Publication: Organic Letters

Publisher: American Chemical Society

Date: Jan 1, 2019

Copyright © 2019, American Chemical Society

LOGIN

If you're a copyright.com user, you can login to RightsLink using your copyright.com credentials.

Already **a RightsLink user** or want to learn more?

PERMISSION/LICENSE IS GRANTED FOR YOUR ORDER AT NO CHARGE

This type of permission/license, instead of the standard Terms & Conditions, is sent to you because no fee is being charged for your order. Please note the following:

- Permission is granted for your request in both print and electronic formats, and translations.
- If figures and/or tables were requested, they may be adapted or used in part.
- Please print this page for your records and send a copy of it to your publisher/graduate school.
- Appropriate credit for the requested material should be given as follows: "Reprinted (adapted) with permission from (COMPLETE REFERENCE CITATION). Copyright (YEAR) American Chemical Society." Insert appropriate information in place of the capitalized words.
- One-time permission is granted only for the use specified in your request. No additional uses are granted (such as derivative works or other editions). For any other uses, please submit a new request.

BACK | CLOSE WINDOW