Faculty of Science

Novel One-Pot Synthesis of Hydrazone Derivatives Via Zirconocyclopentene Intermediates

تحضير مبتكر لمشتقات الهيدرازون بخطوة واحدة عبر مركبات زركونيوم-البنتين الحلقي كوسيط

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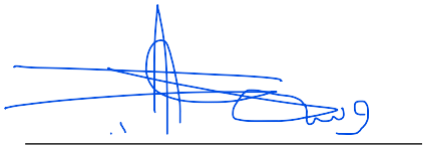

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Acknowledgment

(الْحَمْدُ لِلّهِ الَّذِي هَدَانَا لِهَذَا وَمَا كُنَّا لِنَهْتَدِيَ لَوْلا أَنْ هَدَانَا اللّهُ) الأعراف (43)

All the praise for God, the Almighty, who guides me toward knowledge and patience.

Deep gratitude and appreciation to my lovely family, my father, my mother, my sister Noor, and my brothers Osama and Anas, for their endless support and trust.

I’d like to express my sincerest appreciation to my advisor, Dr. Ghassan Albarghouti, for his patience, time, gaudiness, and great knowledge, which influenced me and always kept me motivated.

Abstract

Hydrazone derivatives represent a class of fundamental organic molecules of valuable building blocks for synthesizing natural and pharmaceutical products. The reactive azomethine group (–N=CH–) plays a crucial role in their bioactivity. Many studies demonstrate hydrazone bioactivities including antimicrobial, anticonvulsant, antidepressant, anti-inflammatory, analgesic, antiplatelet, antimalarial, anticancer, antifungal, antitubercular, antiviral, and cardioprotective activities. Herin hydrazone was synthesized using bis-cyclopentadienyl zirconium dichloride complex as Cp_2ZrCl_2/EtMgCl reagent for a cross-coupling reaction between alkynes and methyl diazoacetate. The reaction conditions were found to be optimum upon conducting the reaction in the absence of light with the addition of precursors at low temperatures of -78 ºC, six hours were required for reaction completion. The crude products were monitored with TLC and separated with column chromatography. Then, the isolated compounds were analyzed with GC-MS, ^{1}H-NMR, and ^{13}C-NMR. Thirteen different hydrazones were furnished upon this methodology using both simple alkynes and boronated alkynes. The percentage yields of the hydrazone compounds that were synthesized from boronated alkynes were higher than those synthesized from terminal alkynes and the best-isolated yield was 60% for the hydrazone that was synthesized from boronated 5-chloro-1-pentyne.

الملخص

تمثل مركبات الهيدرازون فئة من المركبات العضوية الأساسية التي تشكل لبنات بناء مهمة لتكوين العديد من المركبات الدوائية. حيث أن مجموعة الآزوميثاين المكونة من النيتروجين والكربون لها دور حاسم في فعاليتها الحيوية. تؤكد العديد من الدراسات على الفعالية الحيوية لمركبات الهيدرازون مما يعني دخولها في تركيب مضادات الميكروبات، مضادات الاكتئاب، مضادات الالتهاب، مسكنات الألم، مضادات الملاريا، علاج السرطان، مضادات الفطريات، مضادات السل، مضادات الفيروسات، وأدوية القلب. في هذا البحث، لقد تم توليف مركبات الهيدرازون باستخدام $Cp_2ZrCl_2/EtMgCl$ من أجل إجراء تفاعل يربط بين الألكاينات مع الميثيل ديازواسيتات. تم تحسين ظروف التفاعل بعد دراسة تأثير كل من الوقت، درجة الحرارة، الضوء، وكميات المواد المستخدمة في التفاعل على نسبة الناتج الفعلي و مدى نقاوته، حيث أنه و بناءً على النتائج فإنه يلزم إجراء التفاعل بغياب الضوء و يفضل إضافة المواد المتفاعلة على درجات حرارة منخفضة بحوالي -75 ºس. المدة الزمنية اللازمة لإجراء هذا التفاعل بأفضل مردود كانت ستة ساعات . تم فحص المركبات بواسطة الفصل الكروماتوغرافي على TLC قبل وبعد أن تم فصلها باستخدام عمود الفصل الكروماتوجرافي. تم تحليل جزء من المركبات النقية التي تم فصلها باستخدام تقنيات الفصل الكروماتوغرافي والرنين المغناطيسي GC-MS ، ^{1}H-NMR، و ^{13}C-NMR. تم تحضير ثلاثة عشر مركب هيدرازون مختلفاً بناءً على هذه المنهجية باستخدام كل من الألكاينات البسيطة والألكاينات التي تم تعديل تركيبها عن طريق ارتباط الألكاين مع بورونات الايستر بدلاً من وجود ذرة الهيدروجين الحمضية، حيث تم الحصول على أعلى ناتج بمقدار 60% من الهيدرازون المحضر من الألكاين 5-كلورو-1-بنتاين بعدما تم تعديل تركيبه بمتفرع بورونات الإيستر.

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Chapter 1. Background and General View:

1.1 Introduction to Hydrazones

1.1.1 Hydrazone Structure:

Hydrazones, well-known organic compounds derived from the Schiff-base family, are very attractive and valuable scaffolds for various applications with great versatility, particularly in the medicinal and pharmaceutical chemistry fields.[1,2] Imines are compounds containing (R_1R_2–C=N–R_3), in which R_1, R_2, and R_3 could be alkyl, aryl, or hydrogen atom. Schiff bases are sub-classes of imines containing the azomethine group (R_1R_2–C=N– R_3) in which R_3 could be an alkyl or aryl group, but not a hydrogen atom.[3] When R_3 in a Schiff base is an amine group it called hydrazone. Hydrazone groups popularity increased in the recent decade due to their direct synthesis processes and functional diversity, in addition, they are favored over other imines for their stability toward hydrolysis.[4]

The structural flexibility and application versatility of hydrazone moiety in the organic compounds and metal complexes are found to be directly correlated with its chemical structure which affects its chemical and physical properties. Taking a look at hydrazone's structure (R_1R_2C=N–NR_3R_4) that shown in (Figure 1), both nitrogen atoms are considered nucleophilic atoms but the amino-type nitrogen is more electrophilic than the adjacent imine nitrogen.[5–8] The presence of the reactive azomethine group (–N=CH–) has considerable importance in coordination and organometallic chemistry as well as in its bioactivity.[9–11] The

active hydrogen, in particular, is used widely as a center for coupling in chemical reactions, which allows hydrazones to act as intermediates for the synthesis of other important compounds, notwithstanding that hydrazones on their own are effective and valuable organic compounds with distinct bioactivity. An outstanding feature of hydrazones is their ability for further substitution using the free pair of electrons on the nitrogen atom in the imine bond via reaction with other functional groups, those electron pairs are conjugated with the imine bond (C=N).[12]

The imine bond in hydrazones is a main distinguishable feature that affects hydrazones activity. This bond is known for its ability to exhibit (E/Z) isomerism and photochromism. Usually, these configurations are produced simultaneously when hydrazones are synthesized. Several methods were employed to separate these isomers from each other including chromatographic techniques.[13] Hydrazone's isomerism is prominent and allows hydrazone compounds to work as molecular switches and photo-switch linkers.

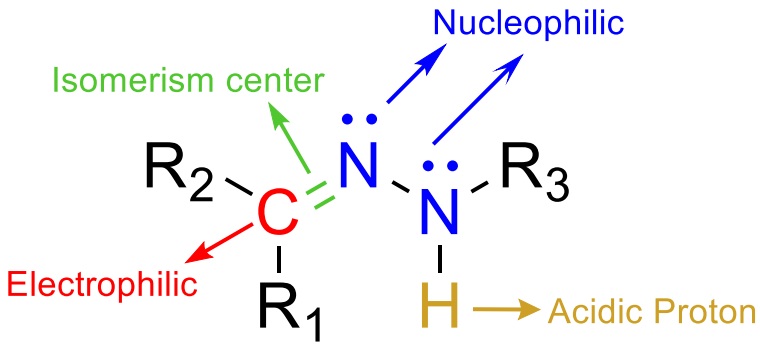


Figure 1. Demonstration of the functional diversity in the structure of hydrazone moiety.

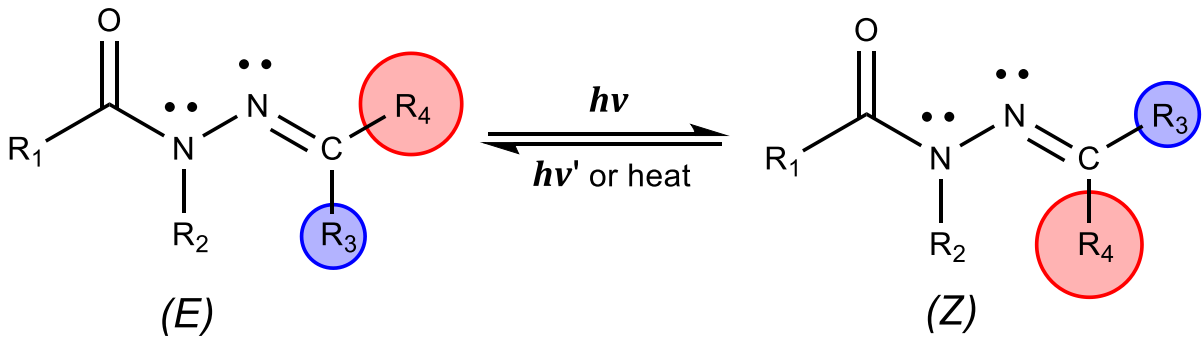
1.1.2 Hydrazones Applications:

As a result of these distinct structural properties of hydrazones' moieties in their structural molecules, several fields employed these compounds for a variety of specific functions in organic synthesis, drugs, fluorescent sensors, molecular switches, dyes, organometallic coordination, and supramolecular chemistry, also in security protection applications.[14]

1.1.2.1 Hydrazones as Molecular Switches:

Molecular switches are compounds that change their structure upon exposure to stimuli,[15] hydrazones undergo configurational switching and could be turned from one configuration to the other when exposed to light, UV irradiation, chemicals, or other changes in the surrounding environment like pH, resulting in changes in their molecular motion and properties as a consequence.[16]

Photo-switching of hydrazones is light-induced isomerism switching, in which the UV light provides sufficient energy to affect the rotation of the imine bond. The Z configuration is less favored in many cases which could be attributed to steric hindrance effects. However, it could be stabilized and favored over the E configuration through the intramolecular hydrogen bonding in some substituted hydrazones containing H-bond acceptors.[17] (Scheme 1) elucidates how hydrazones behave as molecular switches.



Scheme 1. Hydrazone behavior as a molecular switch when affected by light with different wavelengths (hv and hv`) or heat.

1.1.2.2 Hydrazones in Organometallics and Organic Synthesis:

Hydrazone ligands are attractive parts in metal complexes since they act as polydentate chelating agents and are used for selective metal extracting and spectroscopic transition metal characterization in analytical chemistry. On the other hand, they act as reactants in many chemical reactions such as hydrazone iodination; which represents the conversion of hydrazone into vinyl iodide via its oxidation with iodine using a non-nucleophilic base.[18]

Shapiro reaction Bamford-Stevens reaction transform hydrazone into alkene under basic conditions, Shapiro reaction utilizes moderate bases and gives the kinetic “less substituted” product, while Bamford-Stevens reaction utilizes strong bases and gives the thermodynamic “more substituted” product.[19] Moreover, hydrazones are used as intermediates in Wolff-Kishner reduction reactions to convert a carbonyl into a methylene group,[20] as well as in the synthesis of many heterocyclic compounds.[6] Hydrazones are also used extensively in the material

science field to synthesize hydrogels and fluorophores, in addition to the sensors field.[21]

1.1.2.3 Hydrazones Biological Activity:

Hydrazones are well-known compounds in pharmaceutical and medicinal chemistry due to their broad spectrum of biological activity, including antitumoral,[22,23] antiviral,[24,25] anti-inflammatory,[26,27] antifungal,[28,29] antimicrobial,[30,31] antiplatelet,[32,33] anticonvulsant,[34,35] analgesic,[36,37] antitubercular,[38,39] and anti-HIV activities. Furthermore, their derivatives are used in drugs for mental disorders treatment and leprosy.[6,11,40]

Hydrazones were utilized to manipulate the drug release to achieve selectivity by embedding the drug within their structure exploiting the influence of the surrounding conditions, such as the pH level. For example, hydrazones are found to be stable in the neutral pH level of the blood, whereas they are cleaved in the acidic conditions of the tumor cells surrounding and in cells' endosomes releasing their constituents of drugs in such sites. These properties allow hydrazones linkage within several drugs for many targets. The pH sensitivity of hydrazones is a crucial characteristic that enables their utilization for cancer treatment with controlled release of the active material of the medication.[12]

As mentioned before, hydrazones are capable of acting as chelating agents to form metal complexes, this approach is advantageous as they aid in the excretion

of the excess accumulated metals in the human body through the formation of stable complexes via binding to these metals. Studies indicated hydrazones chelation efficiency for cobalt and iron to avoid body metal poisoning with excess (Co) and the risk of (Fe) in the case of iron overload disorders.[41,42]

1.1.2.4 The Anticancer Activities of Hydrazones:

Cancer, the uncontrollable growth and proliferation of abnormal cells, is still a challenging chronic disease that ranks among the top three death-causing diseases worldwide.[43] The chemical compound structure including its electronic character and the type of functional groups that exist within the molecules are crucial in determining their activity as anticancer species and their influence on the mechanism of reaction with such malignant cells.

In the last decades, it has been demonstrated that one of the primary causes of cancer growth, progression, and metastasis in human cells is the disturbance of redox balance. It has been established that an increase in free radicals, predominantly the reactive oxygen species (ROS), is one of the main causes of this imbalance in redox homeostasis. The free radicals could emerge from either intrinsic sources, such as inflammatory cells, mitochondria, or complexes of cell enzymes, or extrinsic sources, such as radiations, pro-oxidant toxins, and chemicals from smoking, alcohol, or drugs.

Numerous studies proposed various anticancer mechanisms, one of the basic mechanisms based on electron transfer (ET), reactive oxygen species (ROS), and oxidative stress (OS). The ROS levels rise in the presence of cancer cells, however, its level is balanced through increased antioxidant capacity, since antioxidants act as scavengers for ROS.[44,45]

It is important to study the structure-activity relationship (SAR) since the compound structure and its electronic character have a direct effect on its activity against tumoral cell inhibition. Thus, functional groups have been studied widely to detect the effect of these groups in the development of malignant cells, for example, halides, amino, nitro, and carbonyl groups are electron-withdrawing groups have shown better activity than electron-donating groups, such as methyl and methoxy groups. However, we could not generalize this comparison for all the compounds, since many factors could affect the activity of these groups such as steric hindrance. Furthermore, the position of these groups could affect their activity, for example, the substituents at the *para* position were found to have good cancer cell growth and migration inhibition.[43]

Hydrazones exhibit their anticancer activities via various mechanisms including apoptosis induction, microtubule polymerization prevention, cyclin-dependent kinases inhibition, and blocking of histone deacetylases and phosphatidylinositol 3-kinases.[46] Over the past five years, researchers have synthesized several types of substituted hydrazones and tested them for anticancer activity on a variety of

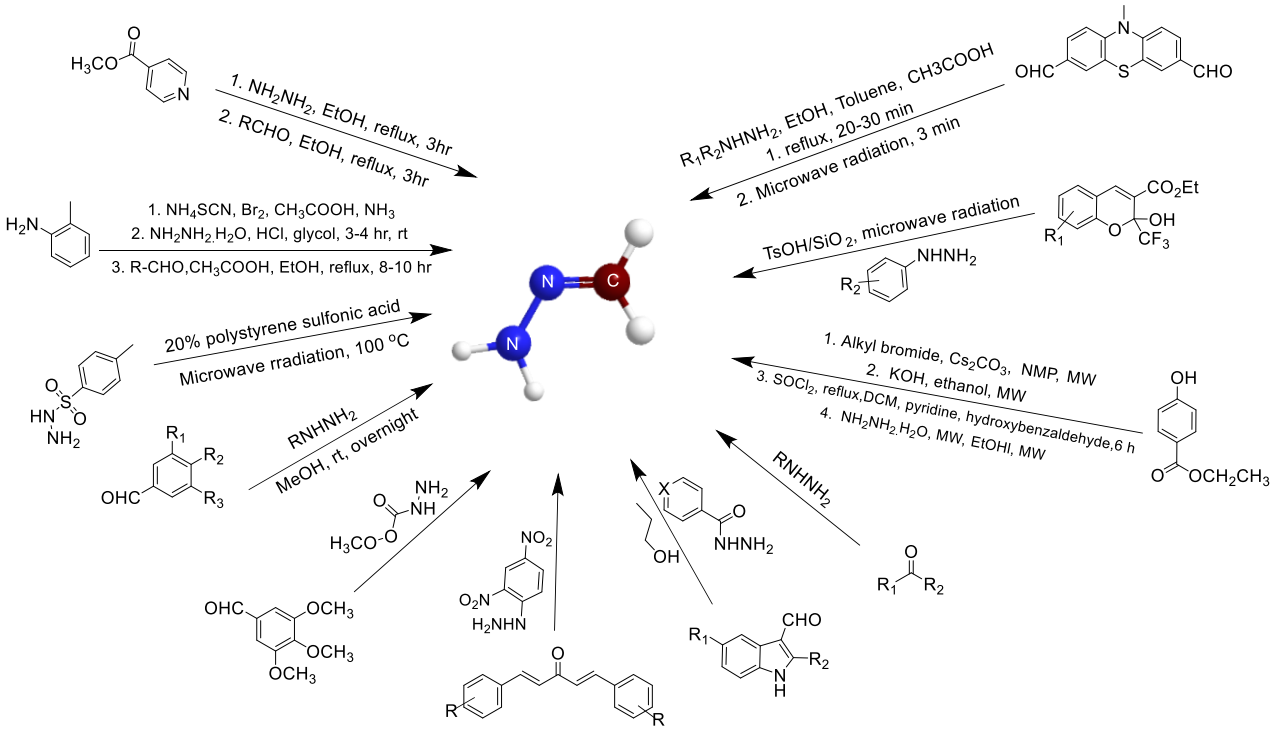
cell lines, including those from breast cancer, leukemia, lung cancer, colon carcinoma, gastric cancer, esophageal cancer, and pancreatic cancer. Different substituents on the hydrazone moiety mean variation of its activity and selectivity of interaction.[47]

1.1.3 Overview of The Synthetic Routes of Hydrazones:

Many studies demonstrated several methods for the synthesis of hydrazones. The most common method for the preparation of hydrazones utilizes hydrazide or hydrazine to react with a carbonyl compound, particularly aldehyde or ketone, with reflux in the presence of a compatible organic solvent, such as methanol, ethanol, butanol, tetrahydrofuran, and glacial acetic acid.[11,48,49] The traditional method requires heating for a long time and requires large amounts of organic solvents.

Coupling reactions such as the Japp-Klingemann reaction utilize aryldiazonium salts to react with β-keto esters or β-keto acids containing active hydrogen to synthesize hydrazones.[50] Green chemistry considerations started to be taken into account to avoid the large use of toxic solvents and by-products to achieve eco-friendly chemical reactions' methodologies. Regarding hydrazone syntheses, some of the recognized synthetic reactions are summarized below in (Scheme 2).[11] Other methods include the reactions of different amino acids with aldehydes.[51,52] Also, hydrazide-hydrazones compounds were synthesized by the reaction of Mannich bases with hydrazides incorporating piperidine, morpholine,

and piperazine units.[53] Limited studies introduced amino acids for Schiff bases synthesis,[8] such substrates contribute to enhancing the product bioactivities.



Scheme 2. Some of the discovered synthetic routes of hydrazone compounds.

1.2 Overview of Zirconocene:

1.2.1 Metallocenes:

Organometallic compounds are widely employed in organic synthesis fields to realize stoichiometric and catalytic reactions to obtain products with versatile physical, chemical, and biological characteristics.[54] Metallocenes are a well-known and remarkable category of organometallic compounds, a common name for metal sandwich compounds; which are bis(cyclopentadienyl) complexes. The general structure of metallocenes is composed of a central metal atom such as iron (Fe), hafnium (Hf), titanium (Ti), zirconium (Zr), and other metals, linked

with aromatic ligands, typically two cyclopentadienyl groups ($C_5H_5^-$) abbreviated as (Cp), the general formula is $[(\eta^5\text{-}C_5H_5)_2M]$.[55] Ferrocene $Fe(C_5H_5)_2$ is among the earliest known and employed metallocenes.

Currently, Group (IV) metallocenes become more attractive, such as titanocene (Cp_2Ti^{II}) and zirconocene (Cp_2Zr^{II}) species which are generally unstable 14-electron components and have a lone pair and two vacant valance orbitals, they usually are linked with two other ligands such as hydrogen or chloride. The possible interaction between such occupied and unoccupied orbitals greatly contributes to the reactivity of metallocenes with a variety of unsaturated compounds forming a d^0 pseudo-tetrahedral complex.[56,57] Metallocenes were utilized in a wide range of applications, for example, they were used as lubricants and gasoline antiknock additives, in addition to their use as catalysts for olefin polymerization in plastic industries. These compounds are also investigated as potential anticancer agents. Furthermore, they are employed extensively as intermediates in organic synthesis.[58,59]

1.2.2 Zirconium Element and Zirconium Compounds

Zirconium is a transition metal of group (IV) elements with the atomic number 40 and an atomic mass of 99.224 amu, its electronic configuration is [Kr] $4d^2\ 5s^2$. In 1925 zirconium was purified as a pure metal by van Arkel and de Boer after being isolated originally by Berzelius as an impure metal in 1824.[60] This metal is shiny metal with a silver to gray color as shown in (Figure 2). The

prominence of zirconium is observable through its compounds, which have several interesting applications. Zircon, zirconia, zirconate, and zirconocenes are all zirconium-based compounds. Zircon is the common ore of zirconium with the chemical formula ($ZrSiO_4$). Zirconia is zirconium dioxide (ZrO_2) which is used in a wide range of applications such as the dentistry field and ceramics.[61,62] Zirconate is obtained from zirconia fusion with other metal oxides. Bis-cyclopentadienyl zirconium dichloride is commonly called zirconocene dichloride with the formula (Cp_2ZrCl_2).

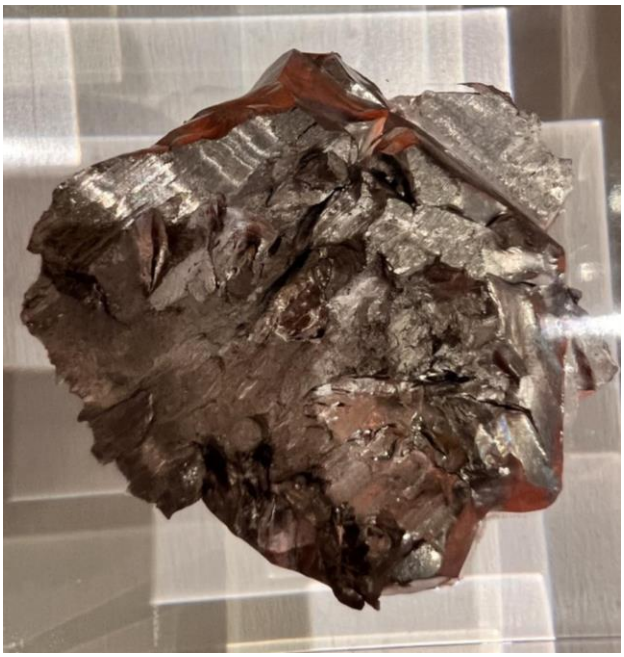


Figure 2. Image of zirconium metal.

1.2.3 Zirconocene Dichloride Complex:

The complex Cp_2ZrCl_2 is a bent metallocene as shown in (Figure 3), it attracted substantial attention for its reactivity. It is a non-hazardous air and moisture stable d^0 zirconocene and has thus been engaged widely in the catalytic

area.[63] This organometallic complex was synthesized through the reaction between zirconium(IV) chloride complex and cyclopentadienide sodium in a similar manner to the synthesis reaction of Cp_2ZrBr_2 introduced by Birmingham and Wilkinson.[64,65]

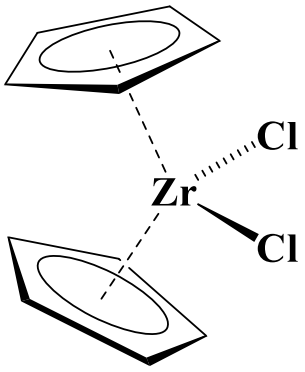


Figure 3. Zirconocene dichloride structure.

Cp_2ZrCl_2 has been investigated in the reactions of carbonyl group transformations,[66] intramolecular and cross-coupling catalyzed reactions, and a variety of organic synthesis reactions.[63] Cp_2ZrCl_2 reagent was utilized in a regioselective synthesis reaction of functionalized cyclopentenone derivatives.[67] Moreover, zirconocene coupling of alkenes and alkynes has been used extensively as a source for a novel, versatile pathway to functionalize organic compounds,[68] including different macromolecules with distinct characteristics and beneficial applications, especially in medicinal chemistry.

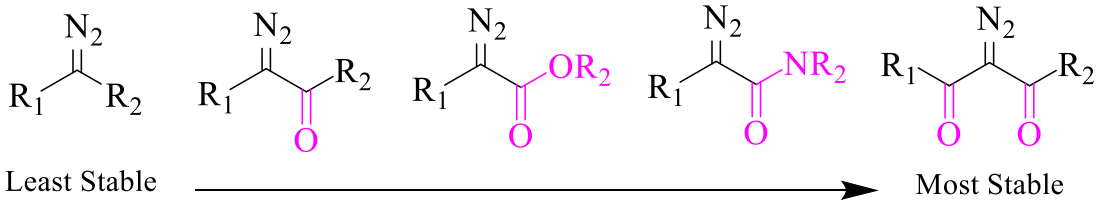
Many researchers used zirconocene to prepare different advantageous reagents such as Negishi, Rosenthal, and Schwartz's reagents. Negishi reagent synthesized via reaction between Cp_2ZrCl_2 with alkyl lithium or alkyl Grignard

to form intermediate species that represent a source of zirconocene (Cp_2Zr^{II}) which could undergo a variety of reactions, particularly in cyclization reactions of several unsaturated hydrocarbons.[69,70] Other reactions involved the reduction of Cp_2ZrCl_2 with magnesium in the presence of bis(trimethylsilyl)acetylene in THF to synthesize "Rosenthal's reagent".[71] "Schwartz's reagent" $Cp_2Zr(H)Cl$, has a substantial role in hydrozirconation of olefins to provide alkyl-zirconocenes, which in turns used for the preparation of alkyl halides upon reaction with electrophiles. "Schwartz's reagent" was also obtained from the reduction of Cp_2ZrCl_2 with lithium tri-tert-butoxyaluminum hydride $LiAlH(O\text{-}t\text{-}Bu)_3$, sodium bis(2-methoxyethoxy)aluminum hydride (RED-Al), or lithium aluminum hydride ($LiAlH_4$) by treatment with methylene chloride.[72]

1.3 Diazo Compounds and Diazoesters:

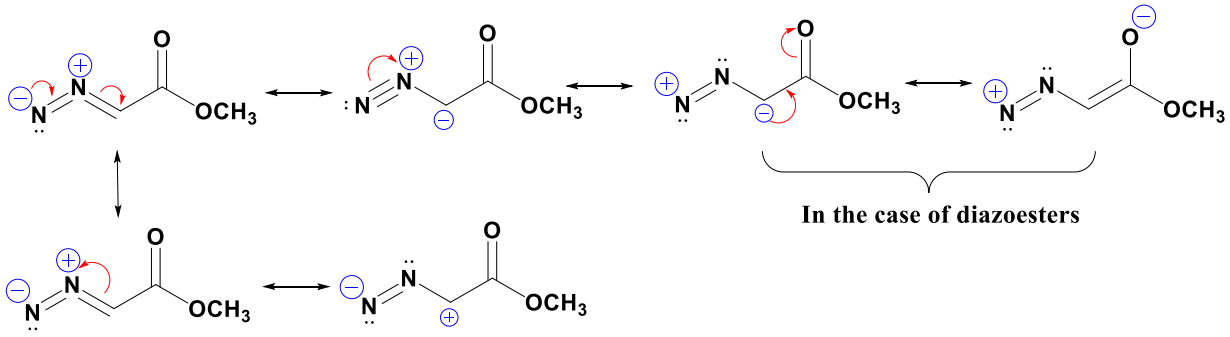
Diazo compounds, containing a couple of terminal nitrogen atoms, are significant building blocks in organic synthesis, medicinal chemistry, material science, and other fields. Diazoesters are safer for use than other diazo compounds such as diazomethane which is considered very explosive due to decomposition, especially in acidic conditions, and has hazardous effects on human health. The presence of electron-withdrawing groups increases the stability of diazo substrates while electron-donating groups reduce their stability and thus become more reactive and can lose N_2 easily as a well-known good leaving group (Scheme 3).[73] The ester moiety induces the stability of the

compound by resonance where the negative charge delocalizes through the diazoester structure. On the other hand, the high boiling point of diazoesters reduces their health hazards. However, such compounds must be handled carefully and at low temperatures.[74]



Scheme 3. Stability trends of diazo components.

Diazo compounds have a unique reactivity, they are known precursors for metal carbenes generation.[75] Furthermore, they undergo 1,3-dipolar cycloaddition due to their ylid nature;[74] ylid structure describes a compound containing adjacent atoms that are negatively and positively charged.[76] The utility of diazo esters has been studied widely as nucleophiles, but limited studies discussed their capability to react as electrophiles.[77,78] The electrophilic capability could be understood through electron delocalization in the resonance structures of the compound (Scheme 4).[76]



Scheme 4. Resonance structures of diazo compounds.

The Aim of This Study:

1. Synthesis of several aliphatic, aromatic, and halogenated hydrazones via a novel methodology in a flexible one-pot reaction using substituted zirconocene intermediate utilizing commercially available starting materials with the incorporation of organozirconium (Bis(cyclopentadienyl) zirconium dichloride as a negishi reagent for cross coupling reaction between alkynes and methyl diazoacetate. (Figure 4) summarizes the performed reaction in general.
2. Preparation of some of the utilized reagents including solvents drying, pinacol drying, boronate ester preparation, preparation of HCL in ether, alkyl diazoacetate preparation.
3. Utilization of diazo compounds to react in an unusual manner as an electrophile not nucleophile.
4. Functionalization of terminal alkynes with pinacol boronate ester to control its reactivity and enhance the percentage yield.

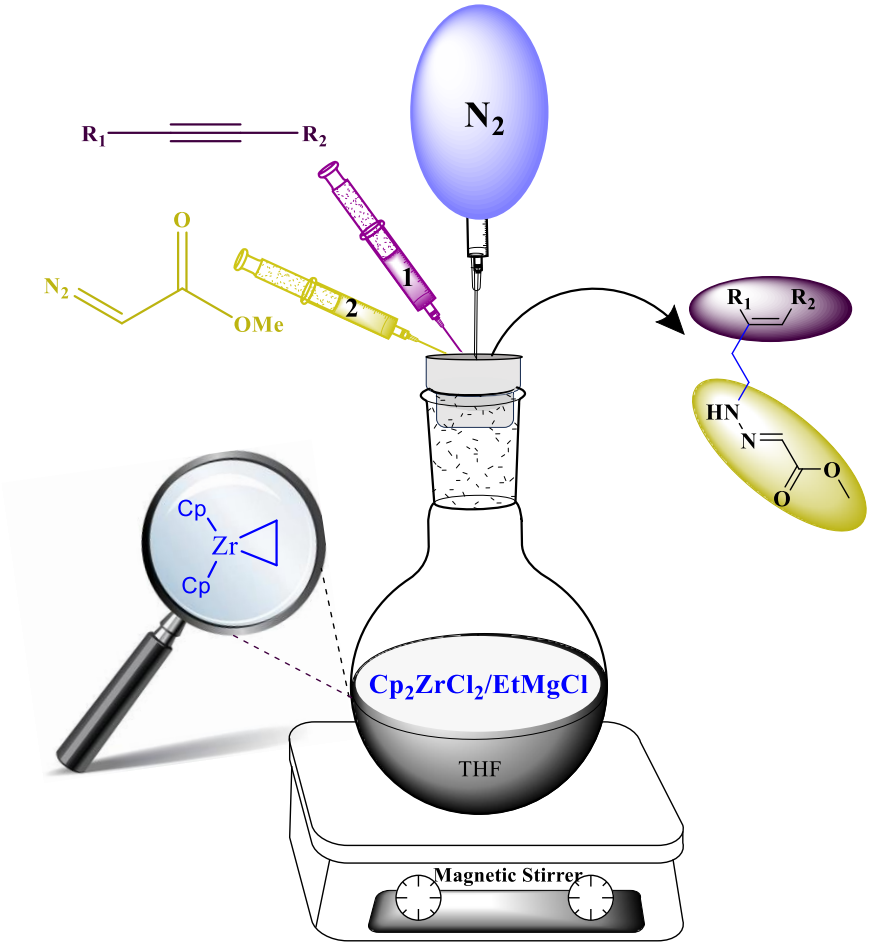


Figure 4. Schematic diagram of the performed one-pot synthesis reaction.

5. Recognizing the optimum conditions for the reaction to obtain the highest yield of hydrazones upon determining the effect of reaction time, temperature, amounts of precursors, and light on the product.
6. Characterization of the furnished compounds by ^{1}H NMR, ^{13}C NMR, and GC-MS.

Chapter 2. Experimental Part

In this chapter, the methodology of the hydrazone synthesis reaction in addition to the preparation methods of some of the precursors needed are presented and discussed in detail. All the reagents were purchased from Sigma Aldrich, Merck and other commercial suppliers.

Two routes were employed in the synthesis reaction, one utilizes simple alkynes as the starting material and the other utilizes alkynes after being functionalized as alkyne boronates. Variations of the reaction conditions were tested to adjust the optimum reaction conditions. Thin layer chromatography (TLC) on silica gel 60 F_{254} was employed to monitor the reaction progress and the purity of the product. The components were visualized on TLC plates with UV irradiation at 254 nm in addition to exposure to iodine vapor. Separation of the crude product components was accomplished with column chromatography using silica gel 60 and some of the isolated pure product was then identified using nuclear magnetic resonance spectroscopy (^{1}H NMR and ^{13}C NMR) in An-Najah National University, in addition to analysis with gas chromatography-mass spectrometry (GC-MS) in Birzeit university testing laboratory center to confirm their structure.

2.1 Tetrahydrofuran (THF) drying:

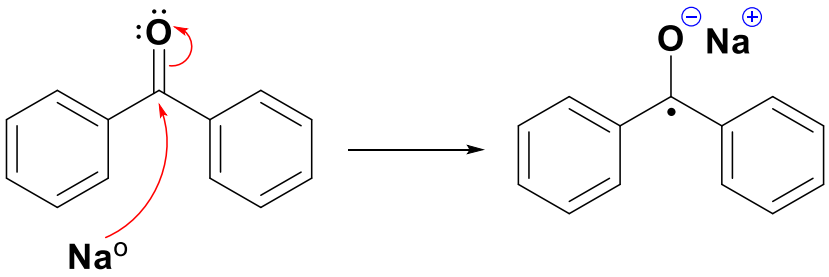
Dried conditions are very important in the hypothesized reaction. Zirconocene intermediate is sensitive to moisture and oxygen, thus all the utilized chemicals, solvents, as well as glassware apparatuses should be quite dried from

moisture and O_2. The organic solvent THF is a moderately polar aprotic water-miscible solvent, and its water content could easily be affected by air moisture and thus should be dried. According to literature procedures,[81] THF was dried in order to be free from moisture and O_2 by refluxing a mixture of THF, benzophenone, and sodium metal segments (Na^0) to be distilled under nitrogen with heat using a heating mantle, the setup is shown in (Figure 5).

Figure 5. THF drying setup.

Sodium metal acts as a dehydrating agent, in addition, it reduces one electron at the carbonyl group of the benzophenone to form a deep blue sodium-benzophenone ketyl radical anion (Scheme 5) that scavenges O_2 molecules besides water and peroxides, such intensive deep blue color indicates the

completeness of the dryness.[82] (Figure 6) shows the gradual color change from colorless to blue still. The dried colorless THF solvent is then collected under a nitrogen atmosphere after distillation and used in all the conducted reactions that require THF.



Scheme 5. Sodium reduction of benzophenone to form the ketyl species.

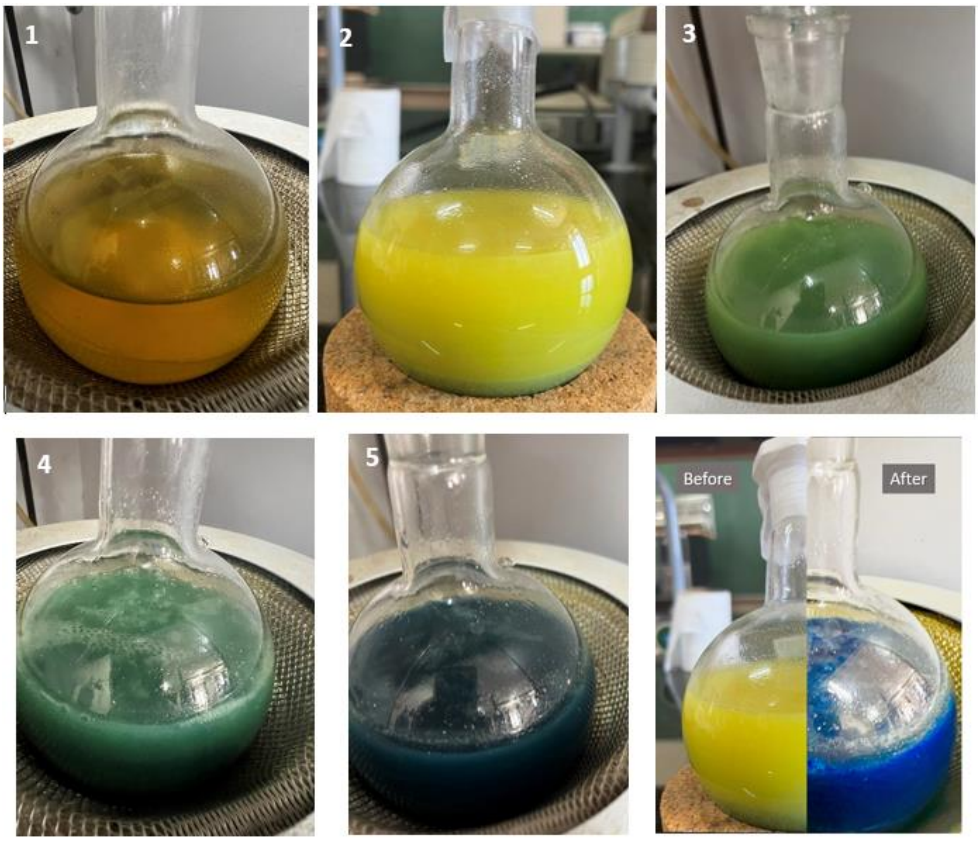


Figure 6. The gradual color changing through THF drying process.

2.2 Preparation of anhydrous hydrogen chloride in diethyl ether (HCl/Et_2O):

A reaction between sodium chloride (NaCl) and concentrated sulfuric acid (H_2SO_4) was carried out under dried conditions in a closed system (Scheme 6) and the evolved hydrogen chloride gas was bubbled in a specific volume of diethyl ether placed in an ice bath, ether should be previously dried over molecular sieves and sodium segments. Excess gas pressure was released continuously through paraffine oil (Figure 7). The concentration of the HCl in ether was determined from the mass difference of ether before and after the reaction completion. This solution was prepared to be used in the synthesis of alkyne boronate.

$$NaCl + H_2SO_4 \longrightarrow HCl + Na_2SO_4$$

Scheme 6. The chemical reaction equation for the preparation of HCl gas.

Figure 7. HCl/Et_2O preparation setup.

2.3 Preparation of boronate:

The compound 2-isopropyloxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, briefly called boronate or pinacol ester, was prepared from tiisopropylborate and pinacol in a similar manner to the literature procedures.[83] Pinacol, 2,3-dimethylbutane-2,3-diol, is a hygroscopic material and must be previously dried with Na_2SO_4 drying agent after being dissolved in dichloromethane (DCM) and then transferred through a long needle under the effect of pressure building up from nitrogen gas to a completely dried round bottom flask (Figure 8) to be distilled then under nitrogen with the rotary evaporator.

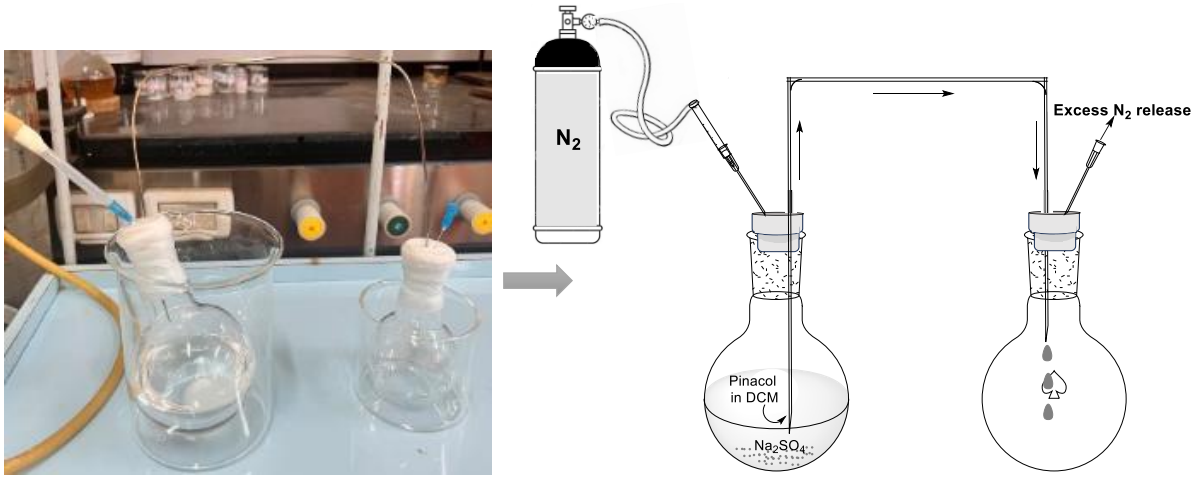
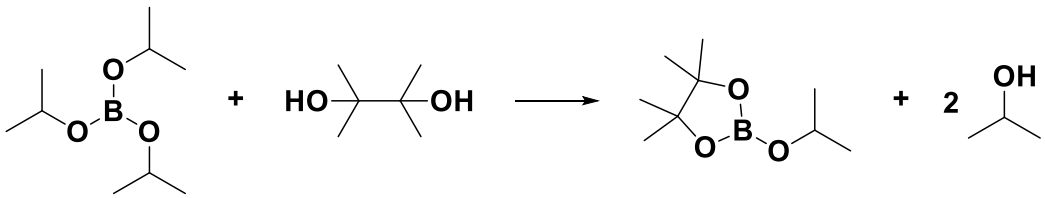


Figure 8. Pinacol transfer under dried conditions with nitrogen pressure building up.

Equivalent amounts of dried pinacol and triisopropylborate were mixed which allowed the borylation reaction to occur, boronate was then separated using vacuum distillation with heat (Scheme 7). Isopropyl alcohol was separated and collected at first as its boiling point was about 82 °C, then at higher temperatures

and reduced pressure pure boronate was distilled off and collected (Figure 9) to be used in the next step for alkyne functionalization.

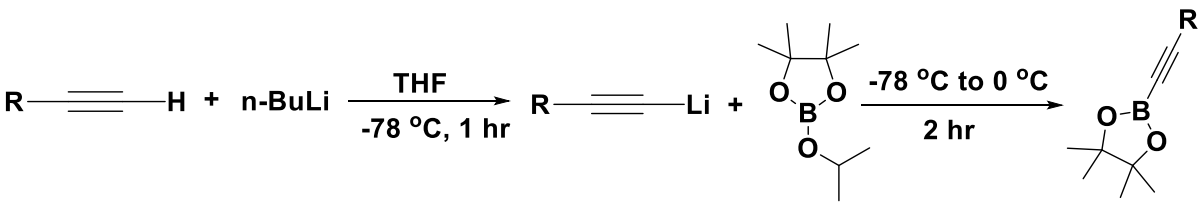


Scheme 7. Preparation reaction of boronate.

Figure 9. Distillation of boronate setup.

2.4 Functionalization of alkyne with borate ester:

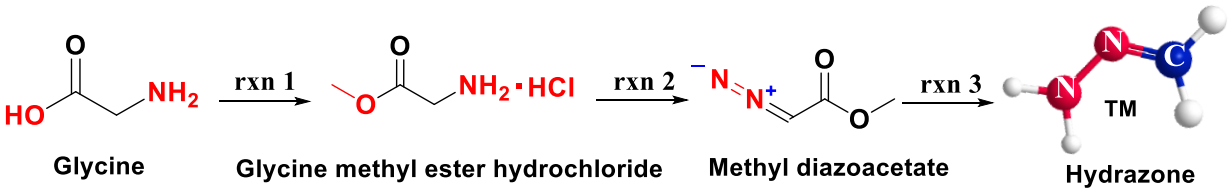
A new substituent for the alkyne was accomplished via functionalization with pinacol borane to give alkynylpinacolatoborane (Scheme 8) according to published procedures,[84] in which the terminal alkyne cyclohexyl acetylene (15.3 mmol, 1 equiv.) was dissolved in 30 ml THF in a pre-dried 150 ml round bottom flask flushed with nitrogen and stirred with butyllithium (15.3 mmol, 1 equiv.) which was added dropwise at -78 ºC to be stirred for 1 hour to form alkynyllithium. The borate ester (13.617 mmol, 0.89 equiv.) was then added dropwise to the reaction flask and stirred for 2 hours. According to literature stirring the reaction overnight is also possible and gives the same product. For the reaction workup, the mixture was quenched with 1M of HCl/Et_2O (15.3 mmol, 1 equiv.) at a temperature below 0 ºC to react with the released lithium ions and form lithium chloride (LiCl) salt that would later precipitate, Et_2O could also be used as a solvent instead of THF, since the solubility of the lithium salt in Et_2O is less than THF which facilitates its separation by suction filtration under nitrogen followed by vacuum distillation under nitrogen with rotary evaporator.



Scheme 8. Synthesis of alkyne boronate,

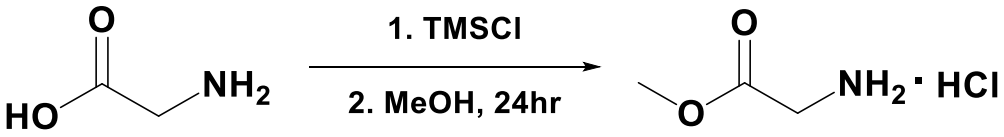
2.5 Preparation of Glycine Methyl Ester:

Although Glycine methyl ester hydrochloride is a commercially available compound, it was prepared in the lab from a simple amino acid to be used in the next step for the preparation of methyl diazoacetate, which will be the electrophile in the principal synthesis reaction of hydrazones (Scheme 9).



Scheme 9. Summary of the sequential steps to prepare the electrophile for hydrazone synthesis reaction.

Following a literature procedure,[79] glycine methyl ester hydrochloride was prepared by reacting (1 equiv.) of glycine amino acid with (2 equiv.) of trimethylsilyl chloride (TMSCl) in methanol and stirred at room temperature for 24 hours (Scheme 10). The product was confirmed by determining its melting point and analysis by IR spectroscopy.

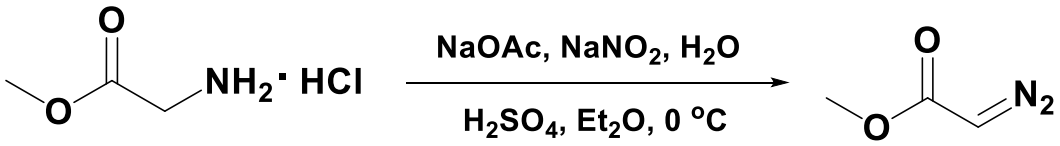


Scheme 10. Preparation of glycine methyl ester hydrochloride.

2.6 Preparation of methyl diazoacetate:

Following the literature procedure in a similar manner to the preparation of ethyl diazoacetate,[80] the preparation reaction of methyl diazoacetate (Scheme 11) started with dissolving the previously prepared glycine methyl ester hydrochloride (40.6 mmol, 1 equiv.) of, glycine methyl ester hydrochloride and sodium acetate (1.5 mmol, 0.036 equiv.) in water, the solution was stirred in an ice bath and then sodium nitrite (46.7 mmol, 1.15 equiv.) cold solution was added to the mixture to react followed by the addition of cold diethyl ether and 10% sulfuric acid (H_2SO_4). The solution was allowed to stir for reaction completion, the next step was the rapid cold extraction with neutralization of the organic layer with 10% sodium carbonate (Na_2CO_3), and the procedures were repeated to collect all the product.

The organic layer was then dried with sodium sulfate (Na_2SO_4). Finally, the solvents were removed using rotary evaporator under cold conditions using an ice bath. Methyl diazoacetate was prepared in this work even it is commercially available, since this material is very sensitive to temperature and must be stored under dried conditions at low temperatures, it decomposes directly at high temperatures, and even at room temperature. The prepared compound was analyzed with IR spectroscopy. Methyl diazoacetate is prepared to act as an electrophile in the principal reaction.



Scheme 11. The preparation reaction of methyl diazoacetate.

2.7 General procedure for the synthesis of hydrazones with the proposed methodology

According to the hypothesized methodology, zirconocene dichloride (1 mmol, 1.1 equiv.) was dissolved in 7 mL of dry THF in a pre-dried 100 mL round-bottom flask flushed with nitrogen and covered completely with aluminum foil, then grignard reagent 2M EtMgCl (2 mmol, 2 equiv.) was added to the solution dropwise at -78 ºC using dry ice in acetone (Figure 10). After being stirred for an hour the alkyne (0.91 mmol, 1 equiv.) was added and stirred at -78º C for an hour, then warmed to 0º C gradually and stirred for an additional hour. Finally, methyl diazoacetate (1 mmol, 1.2 equiv.) was added dropwise at -78º C for half an hour then warmed gradually to room temperature and allowed to stir for 3 hours. A nitrogen gas balloon was attached to the reaction flask during the process to maintain the inert atmosphere and allow gases to be safely released from the reaction flask. All the reagents were added using syringes and needles through the flask rubber septum stopper to avoid exposure to the atmospheric conditions.

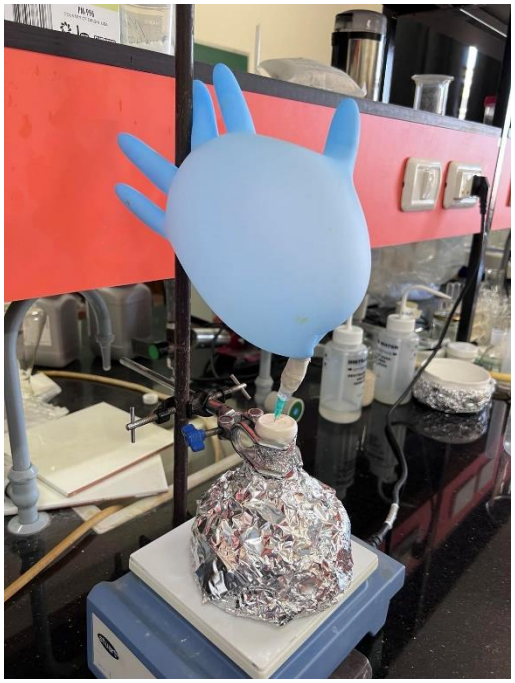


Figure 10. The setup for the synthesis reaction of hydrazones.

The reaction mixture was worked up by quenching with hydrochloric acid solution 10% HCl, then extracted with diethyl ether. The extracted organic layer was dried over sodium sulfate Na_2SO_4 drying agent (Figure 11). The product was concentrated through evaporation on the rotary evaporator to remove excess organic solvents. The targeted hydrazone compound was separated from the prepared crude product with column chromatography (SiO_2, 1-5% Et_2O/hexane).

Treatment of the zirconocene reagent in this methodology was developed analogously to the preparation of the Negishi reagent.[70] However, the manipulation of methyl diazoacetate to work as an electrophile for hydrazone synthesis was unprecedented. The reaction conditions including reaction time, temperature, light, and amounts of the utilized chemicals were optimized to obtain the highest product yield.

Hydrazones with vinylboronate substituent were synthesized via the same previously discussed procedures utilizing the prepared alkynylboronate as the starting material instead of simple alkynes with increasing the stirring time of boronated alkynes to three hours instead of two hours to confirm the formation of the five membered ring zirconocene intermediate. The separated components were monitored with TLC, using silica gel TLC plates with (1% Et_2O/hexane). A part of the prepared compounds was characterized by ^{1}H NMR, ^{13}C NMR, and GC-MS.

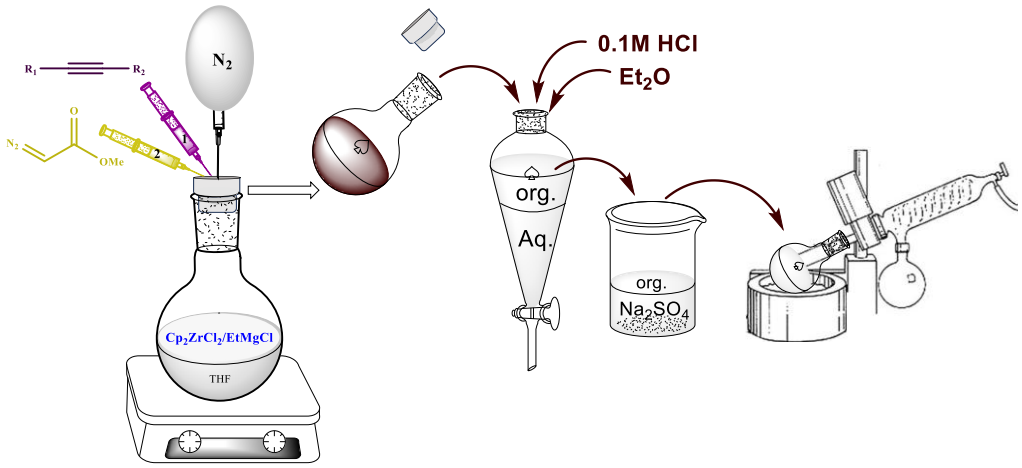
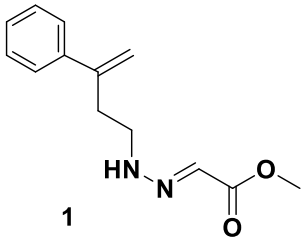


Figure 11. Schematic diagram of hydrazone synthesis methodology.

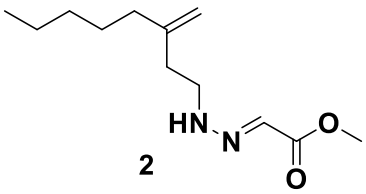
Synthesis of Methyl (E)-2-(2-(3-phenylbut-3-en-1-yl)hydrazineylidene) acetate (1)



1

The above procedures were applied using zirconocene dichloride (0.292 g,1 mmol), 2M EtMgCl (1 ml, 2 mmol), phenylacetylene (0.1 ml, 0.91 mmol), methyl diazoacetate (0.075 ml, 1.09 mmol) in dry THF. Column chromatography (SiO_2, 2% Et_2O/hexane) was employed for the purification of the crude product (R_f = 0.5) to afford the title compound (83 mg, 40%, yellow solid). **GC-MS** (EI, m/z): 232 (M^+).

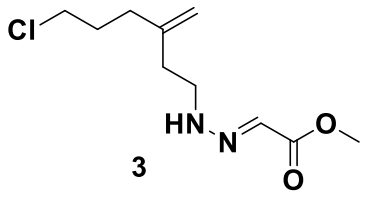
Synthesis of methyl (E)-2-(2-(3-methyleneoctyl)hydrazineylidene)acetate (2)



2

The above procedures were applied using zirconocene dichloride (0.244 g, 0.836 mmol), 2M EtMgCl (0.76 ml, 2 mmol), 1-heptyne (0.1 ml, 0.76 mmol), methyl diazoacetate (0.063 ml, 0.91 mmol) in dry THF. Column chromatography (SiO_2, 2% Et_2O/hexane) was employed for the purification of the crude product (R_f = 0.5) to afford the title compound (white solid). **GC-MS** (EI, m/z): 226 (M^+).

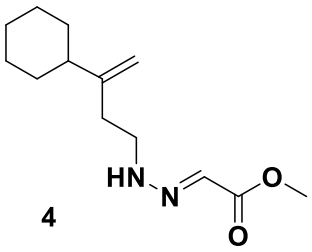
Synthesis of methyl (E)-2-(2-(6-chloro-3-methylenehexyl)hydrazineylidene) acetate (3)



3

The above procedures were applied using zirconocene dichloride (0.293 g, 1.1 mmol), 2M EtMgCl (1 ml, 2 mmol), 5-chloro-1-pentyne (0.1 ml, 0.91 mmol), methyl diazoacetate (0.075 ml, 1.1 mmol) in dry THF. Column chromatography (SiO_2, 2% Et_2O/hexane) was employed for the purification of the crude product (R_f = 0.5) to afford the title compound (15%, pale yellow solid).

Synthesis of methyl (E)-2-(2-(3-cyclohexylbut-3-en-1-yl)hydrazineylidene) acetate (4)

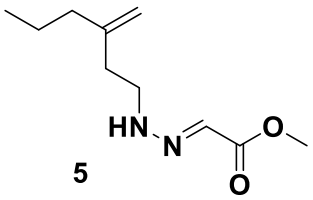


4

The above procedures were applied using zirconocene dichloride (0.246 g, 0.84 mmol), 2M EtMgCl (0.765 ml, 1.53 mmol), cyclohexyl acetylene (0.1 ml, 0.765 mmol), methyl diazoacetate (0.064 ml, 0.918 mmol) in dry THF. Column

chromatography (SiO_2, 2% Et_2O/hexane) was employed for the purification of the crude product (R_f = 0.5) to afford the title compound (13%, white solid).

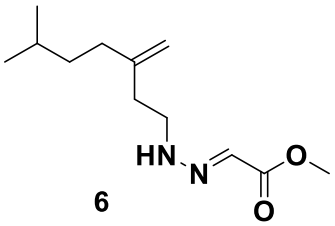
Synthesis of methyl (E)-2-(2-(3-methylenehexyl)hydrazineylidene)acetate (5)



5

The above procedures were applied using zirconocene dichloride (0.326 g, 1.115 mmol), 2M EtMgCl (1.01 ml, 2 mmol), 1-pentyne (0.1 ml, 1.01 mmol), methyl diazoacetate (0.084 ml, 1.217 mmol) in dry THF. Column chromatography (SiO_2, 2% Et_2O/hexane) was employed for the purification of the crude product (R_f = 0.5) to afford the title compound (26%, white solid).

Synthesis of methyl (E)-2-(2-(6-methyl-3-methyleneheptyl)hydrazineylidene) acetate (6)

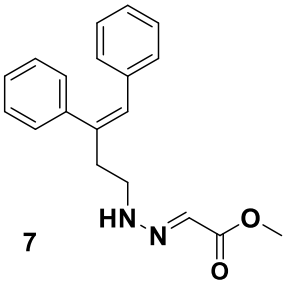


6

The above procedures were applied using zirconocene dichloride (0.244 g, 0.837 mmol), 2M EtMgCl (0.076 ml, 1.522 mmol), 5-methyl-1-hexyne (0.1 ml, 0.761 mmol), methyl diazoacetate (0.063 ml, 0.913 mmol) in dry THF. Column

chromatography (SiO_2, 2% Et_2O/hexane) was employed for the purification of the crude product (R_f = 0.5) to afford the title compound (22%, white solid).

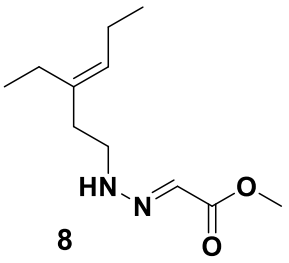
Synthesis of methyl (E)-2-(2-((Z)-3,4-diphenylbut-3-en-1-yl) hydrazineylidene)acetate (7)



7

The above procedures were applied using zirconocene dichloride (0.179 g, 0.61 mmol), 2M EtMgCl (0.056 ml, 1.11 mmol), diphenylacetylene (0.1 ml, 0.555 mmol), methyl diazoacetate (0.046 ml, 0.666 mmol) in dry THF. Column chromatography (SiO_2, 2% Et_2O/hexane) was employed for the purification of the crude product (R_f = 0.5) to afford the title compound (26%, white solid).

Synthesis of methyl (E)-2-(2-((E)-3-ethylhex-3-en-1-yl)hydrazineylidene) acetate (8)

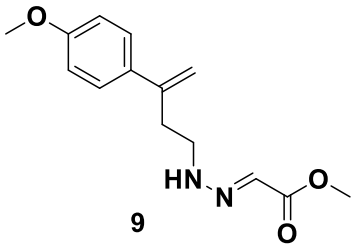


8

The above procedures were applied using zirconocene dichloride (1.92 g, 6.6 mmol), 2M EtMgCl (6.6 ml, 13.2 mmol), 3-hexyne (0.5 ml, 4.4 mmol), methyl diazoacetate (0.366 ml, 5.28 mmol) in dry THF. Column chromatography (SiO_2, 35% EtOAc/hexane) was employed for the purification of the crude product (R_f

= 0.4) to afford the title compound (41 mg, 45%, yellow oil). **GC-MS** (EI, m/z): 212 (M^+). **^{1}H NMR** (81 MHz, $CDCl_3$) δ 6.70, 6.49, 5.26, 5.17, 5.08, 3.32, 3.24, 3.18, 3.10, 2.40, 2.31, 2.23, 2.09, 2.04, 2.01, 1.95, 1.92, 1.86, 1.82, 1.36, 1.23, 1.18, 1.14, 1.11, 1.02, 0.93, 0.84. **^{13}C NMR** (20 MHz, $CDCl_3$) δ 50.59, 43.08, 32.70, 21.47, 19.91, 13.46, 12.14.

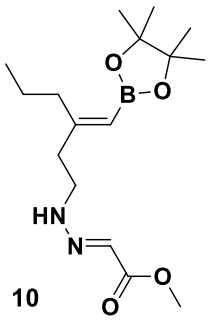
Synthesis of Methyl (E)-2-(2-(3-(4-methoxyphenyl)but-3-en-1-yl)hydrazineylidene)acetate (9)



9

The above procedures were applied using zirconocene dichloride (0.62 g, 2.12 mmol), 2M EtMgCl (1.93 ml, 3.85 mmol), 4-ethynylanisole (0.5 ml, 1.927 mmol), methyl diazoacetate (0.16 ml, 2.3 mmol) in dry THF. Column chromatography (SiO_2, 40% EtOAc/hexane) was employed for the purification of the crude product (R_f = 0.4) to afford the title compound (yellow to brown solid). **GC-MS** (EI, m/z): 262 (M^+). **^{1}H NMR** (81 MHz,) δ 7.19, 7.16, 6.83, 6.72, 6.48, 6.29, 6.00, 5.92, 3.74, 3.27, 2.51.

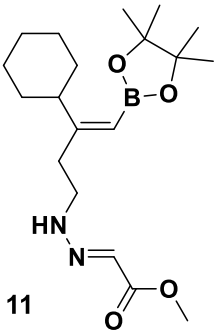
Synthesis of Methyl (E)-2-(2-((E)-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) methylene)hexyl)hydrazineylidene)acetate (10)



10

The above procedures were applied using zirconocene dichloride (1.044 g, 3.57 mmol), 2M EtMgCl (3.24 ml, 6.49 mmol), 4,4,5,5-tetramethyl-2-(pent-1-yn-1-yl)-1,3,2-dioxaborolane (0.5 ml, 3.247 mmol), methyl diazoacetate (0.27 ml, 3.896 mmol) in dry THF. Column chromatography (SiO_2, 40% EtOAc/hexane) was employed for the purification of the crude product (R_f = 0.4) to afford the title compound (white solid). **GC-MS** (EI, m/z): 324 (M^+).

Synthesis of methyl (E)-2-(2-((Z)-3-cyclohexyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan -2-yl)but-3-en-1-yl)hydrazineylidene)acetate (11)

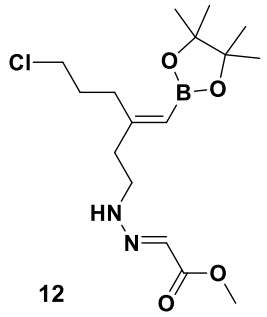


11

The above procedures were applied using zirconocene dichloride (0.34 g, 1.059 mmol), 2M EtMgCl (1.059 ml, 2.118 mmol), 2-(cyclohexylethynyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.22 ml, 1.05 mmol), methyl diazoacetate (0.09 ml, 1.27 mmol) in dry THF. Column chromatography (SiO_2, 40% EtOAc/hexane)

was employed for the purification of the crude product (R_f = 0.4) to afford the title compound (51%, white solid). **GC-MS** (EI, m/z): 364 (M^+). **^{1}H NMR** (81 MHz, $CDCl_3$) δ 7.26, 6.72, 6.50, 5.04, 3.79, 3.39, 3.31, 3.23, 3.17, 2.48, 2.39, 2.31, 2.03, 1.71, 1.25, 1.02, 0.94.

Synthesis of methyl (E)-2-(2-((E)-6-chloro-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)hexyl)hydrazineylidene)acetate (12)



12

The above procedures were applied using zirconocene dichloride (0.733 g, 2.5 mmol), 2M EtMgCl (1.68 ml, 4.56 mmol), 2-(5-chloropent-1-yn-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.5 ml, 2.28 mmol), methyl diazoacetate (0.189 ml, 2.736 mmol) in dry THF. Column chromatography (SiO_2, 40% EtOAc/hexane) was employed for the purification of the crude product (R_f = 0.4) to afford the title compound (48 mg, 60%, yellow to brown solid). **GC-MS** (EI, m/z): 358 (M^+). **^{1}H NMR** (81 MHz, $CDCl_3$) δ 7.66, 7.26, 6.73, 6.48, 5.21, 3.79, 3.51, 2.44, 1.86, 1.36, 1.25.

Chapter 3. Results and Discussion

3.1 Precursor characterization:

The prepared precursors were analyzed in different ways to confirm their structures. The melting point of glycine methyl ester hydrochloride was 176 - 178°C, in the range of the determined melting point of the same product in the literature.[85] (Figure 12) represents the IR spectrum of glycine and glycine methyl ester hydrochloride. From their spectra, the broad peak between 2500- 3200 cm^{-1} in glycine refers to the O-H group in the carboxylic acid part overlapping with the sp^3 C-H stretching peak, which developed in glycine methyl ester to a less broadened peak at 2881 cm^{-1} representing the sp^3 hybridized C-H group which is more clear in the ester with the methyl group than the carboxylic acid. Furthermore, the strong peak in the ester at 1742 cm^{-1} resulted from C=O absorption, such a peak also exists in glycine but vibrates with lower frequency due to resonance and this bond is stronger in the ester than in glycine.

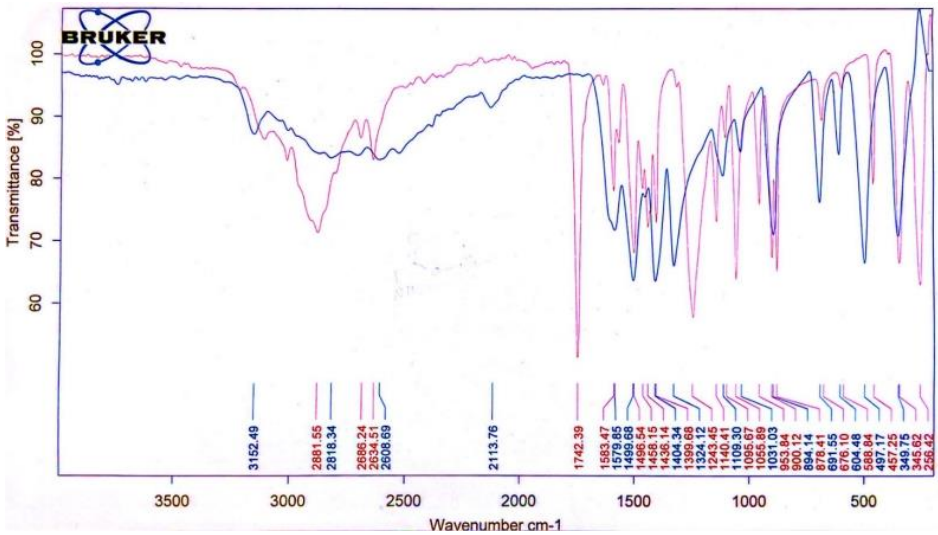


Figure 12. IR spectrum of (—) glycine and (—) glycine methyl ester.

Boronated alkynes are sensitive to oxygen and moisture, and thus are not easily to be characterized unless analysis is performed after sampling directly. Two of the alkyne boronates GC-MS spectra are represented below. (Figure 13) represent the chromatogram and mass spectra of the 1-pentyne after being functionalized with pinacol boronate ester with molecular weight of 194 amu, and (Figure 14) corresponds to boronated 4-ethynyl anisole with molecular weight 258 amu.

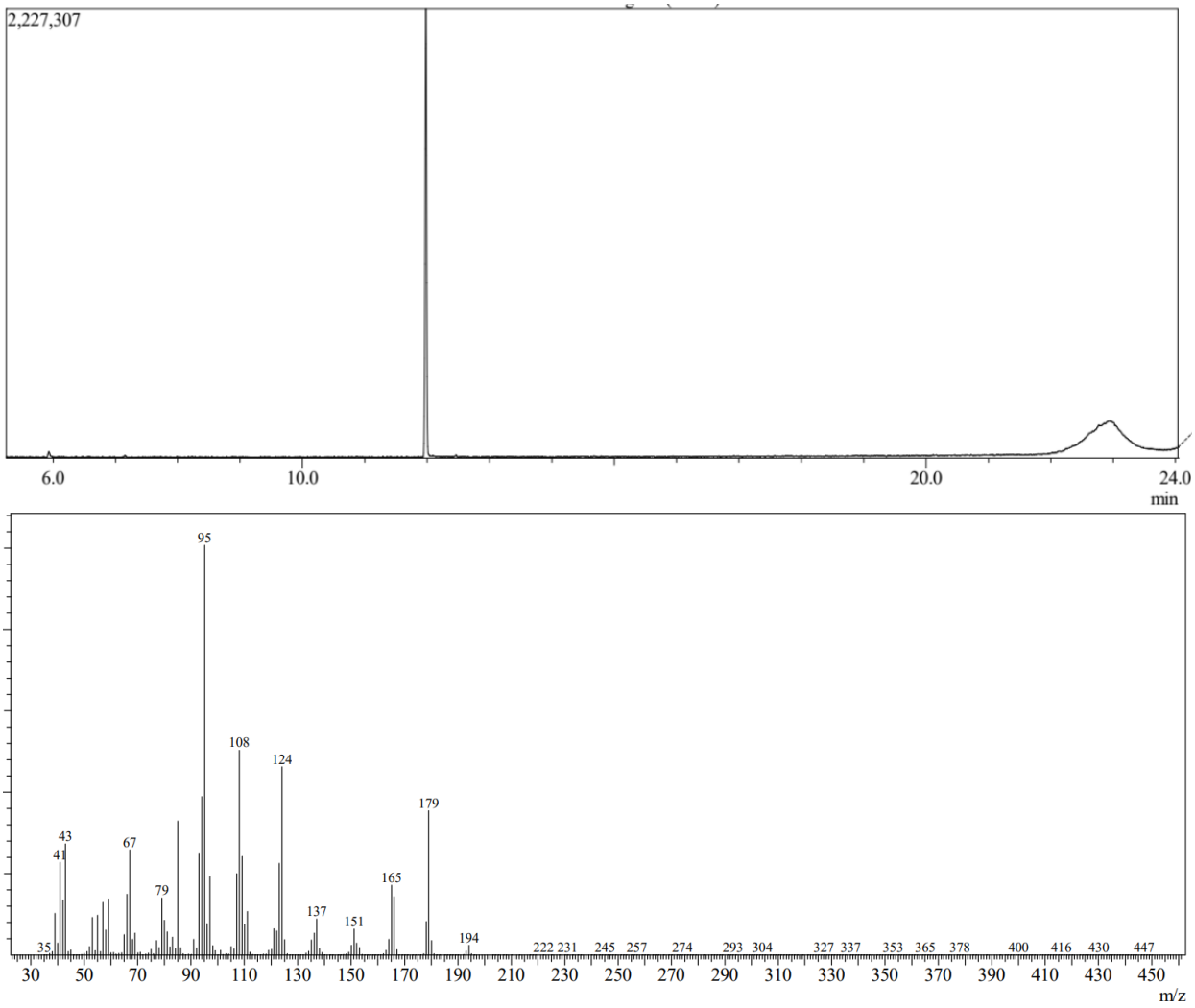


Figure 13. a. Total ion chromatogram of boronated 1-pentyne. **b.** mass spectrum of the compound with a retention time of 11.9 min.

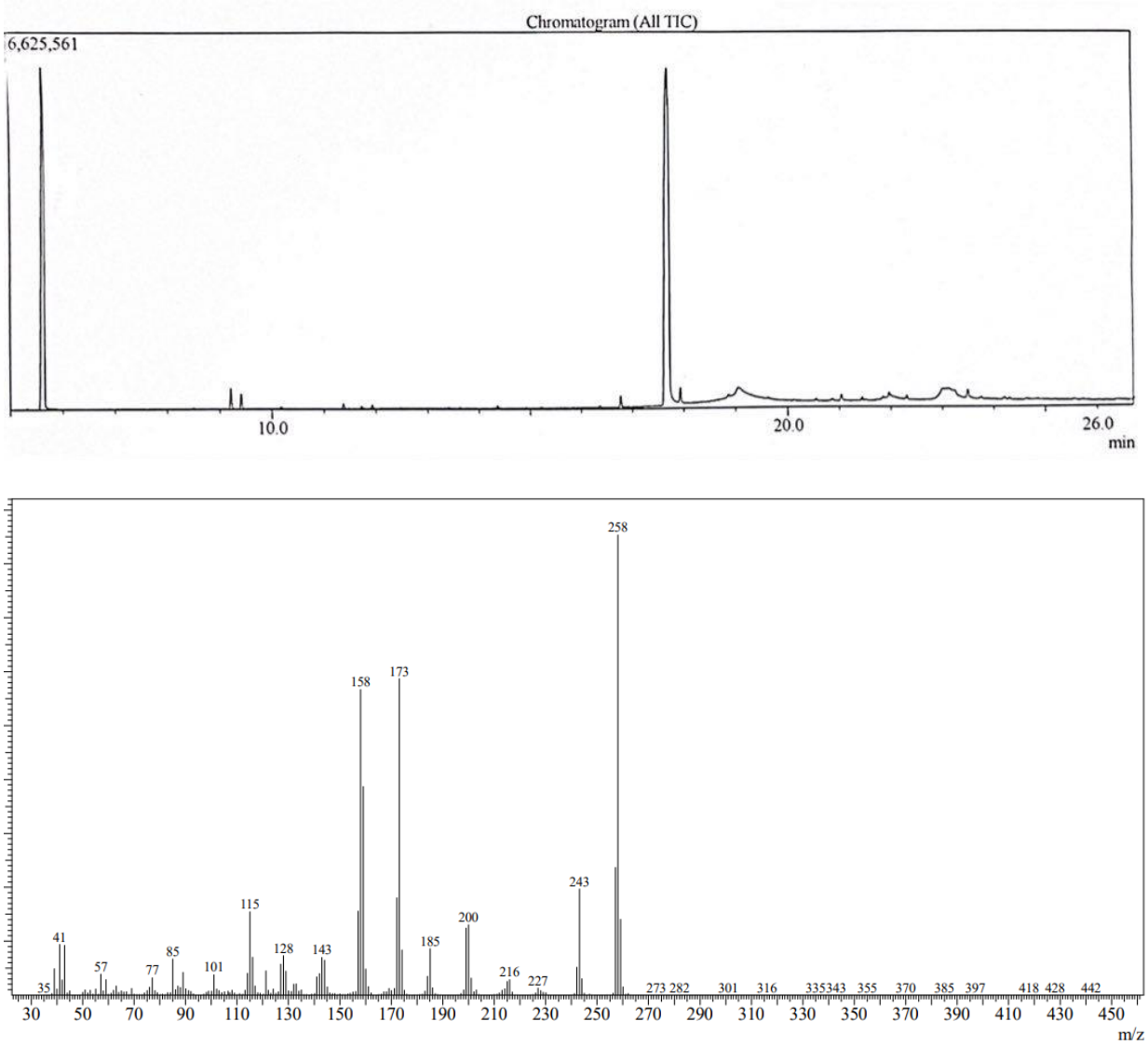


Figure 14. a. Total ion chromatogram of boronated 4-ethynyl anisole. **b.** mass spectrum of the compound with a retention time of 17.7 min.

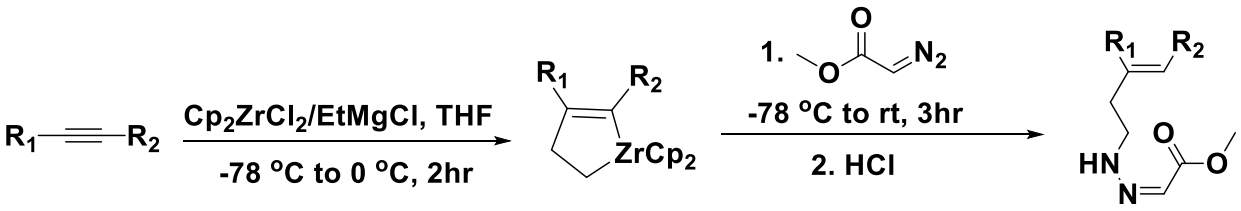
3.2 Reaction conditions optimization:

Focusing on the main objective of this research for the sake of the synthesis of substituted hydrazones according to the proposed novel methodology, using zirconacyclopentene intermediate via a one-pot synthesis reaction, the alkyne phenylacetylene was chosen as a model to test our hypothesis using 0.1 ml scale of the alkyne to recognize the optimum reaction conditions upon changing several parameters including time, amount, temperature, and light (Table 1).

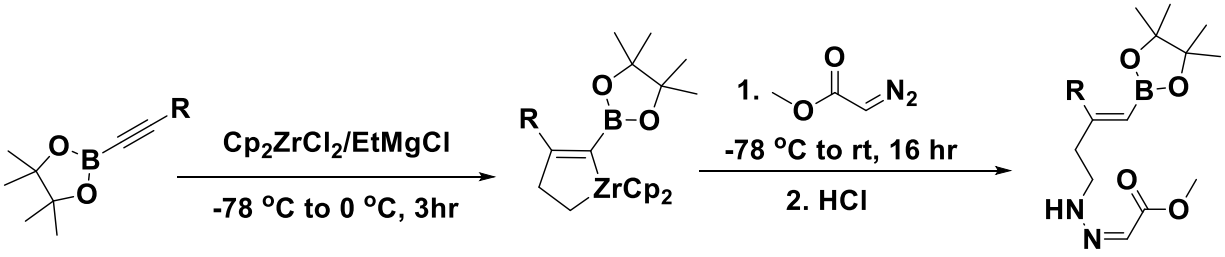
Later on, 1-heptyne, 5-chloro-1-pentyne, cyclohexyl acetylene, 1-pentyne, 5-methyl-1-hexyne, diphenyl acetylene, 3-hexyne, and 4-ethynyl anisole were utilized as simple alkynes for hydrazone synthesis.

When we talk about time adjustment then as mentioned in section 2.7 there are three periods of time that we can adjust. The first was the reaction time of zirconocene dichloride with Grignard reagent to generate zirconocene species before the alkyne addition step, and this period was adjusted to one hour for all the performed trials, the second period was the time after adding the alkyne to form the intermediate before diazo addition step, during the first hour of this interval the temperature was maintained always at -78 ^{o}C.

The third period was the time after diazo addition where the reaction left for completion before its workup (Scheme12) and (Scheme 13). All the reaction trials represented on (Table 1) utilized (0.1 ml, 1 equiv.) of the alkyne phenylacetylene.



Scheme 12. The scope of this work of synthesis of hydrazones from simple alkynes.



Scheme 13. The scope of this work of the synthesis of hydrazone from boronated alkyne.

Table 1. Optimization of hydrazone synthesis reaction conditions.

Entry	Reaction time (hr)	Temperature of diazoacetate addition (°C)	Diazoacetate equivalents	Exposure to light	Yield (%)[a]
1	Overnight	0	1.2	Yes	0
2	Overnight [b]	0	1.2	No	23.7
3	8[b]	0	1.2	No	22
4	7[c]	0	1.2	No	36.9
5	5.5[c]	0	2.2	No	7
6	6[c]	-78 followed by 1hr reflux	1.2	No	17
7	4.5[d]	0	1.2	No	36.6
8	5.5[d]	-78 [e]	1.2	No	21.5
9	6[d]	-78 [f]	1.2	No	39.30

[a] The isolated yield after purification with silica chromatography. [b] Stirring for 4 hr between alkyne and diazo. [c] Stirring for 3 hr between alkyne and diazo. [d] Stirring for 2 hr between alkyne and diazo. [e] Direct warming from -78 °C to room temperature. [f] Gradual warming from -78 °C to 0 °C to room temperature.

Zirconocene intermediate is sensitive to light and once the reaction was conducted in the presence of light without covering the reaction flask no hydrazone was obtained, so the rest of the reactions were performed with a flask covered completely with aluminum foil.

The utilized zirconium reagent was chosen to be Cp_2ZrCl_2 since it is more stable and inexpensive and favored when compared to the commercially available Schwartz's reagent Cp_2ZrHCl which is more sensitive to light, air, and moisture and thus has a short shelf life.[86] Zirconocene (Cp_2Zr^{II}) species once generated is sensitive to moisture and oxygen, thus the reaction atmosphere must be dried as much as possible and a nitrogen atmosphere is required.

Protic solvents are destructive as well, hence dried aprotic solvents were used either for precursors' preparation reactions or in the synthesis reaction itself. Moisture, oxygen, or polar solvents such as alcohols and acetone cause irreversible decomposition of zirconocene because of the formation of the strong (Zr-O) bond.[87]

Reaction time is important as well, this parameter was tested upon changing the time given for the formation of zirconocene intermediate before methyl diazoacetate addition to allow the reagents to react and form the intermediate, the results showed that the yield diminishes when a longer time is given for the intermediate formation, this could be ascribed to the intermediate breaking down

since intermediates are known to be sensitive and unstable, thus two or three hours were quiet enough for this stage as indicated in (entries **4** and **7)**.

The results also show that the time needed for the reaction completion after methyl diazoacetate addition is between 2 to 3 hours as in (entry **9)**. The subsequent performed reactions showed that 6 hours were enough for the formation of the product, furthermore, this product was quite stable even if the reaction was left for stirring overnight which made the time of proceeding the workup step more flexible. The temperature also clearly affects the results since it is a substantial parameter in the reaction mechanism as will be explained later on.

Based on the results obtained in (Table 1), the reaction methodology with the optimum reaction conditions includes stirring zirconocene with dry THF and Grignard reagent at -78 ºC using dry ice in acetone for 1hr, followed by the addition of (1 equiv.) alkyne and stirring for 1 hour at -78 ºC and an additional 1 hour at 0 ºC, then the addition of (1.2 equiv.) methyl diazoacetate with stirring for 30 min at -78 ºC then gradual warming with ice to 0 ºC to room temperature before the reaction workup step.

All the previous steps must be conducted in the absence of light with completely dried conditions in the presence of nitrogen balloon attached to the reaction flask. Fifteen different hydrazones using fifteen different alkynes as starting materials

were synthesized regarding these conditions and are demonstrated in (Table 2) and (Table 3).

From the structure of hydrazone as an organic compound it has a nonpolar structure bearing some polar functional groups, so 1-5% Et_2O/hexane was chosen as the TLC mobile phase to have a retention factor of about 0.5 on the TLC plate. As mentioned before we used column chromatography to isolate pure components using silica as the stationary phase and 1-5% Et_2O/hexane as the eluent. Two closed spots frequently appeared in this region with (R.F ~ 0.5) and were not easily isolated in pure fractions.

Many times, the two components were mixed in the isolated fractions. Those components were expected to be isomers since hydrazone can be formed in the *E* or *Z* conformations. The GC-MS results confirmed that both components are hydrazones with the same molecular weight, and thus interpreted with stereochemistry (Figure 15).

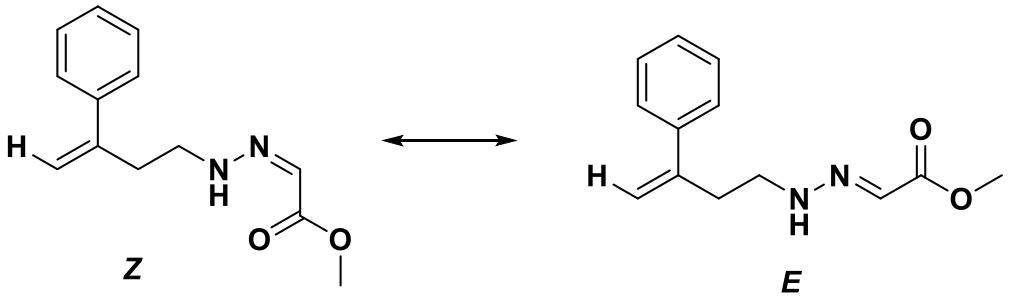
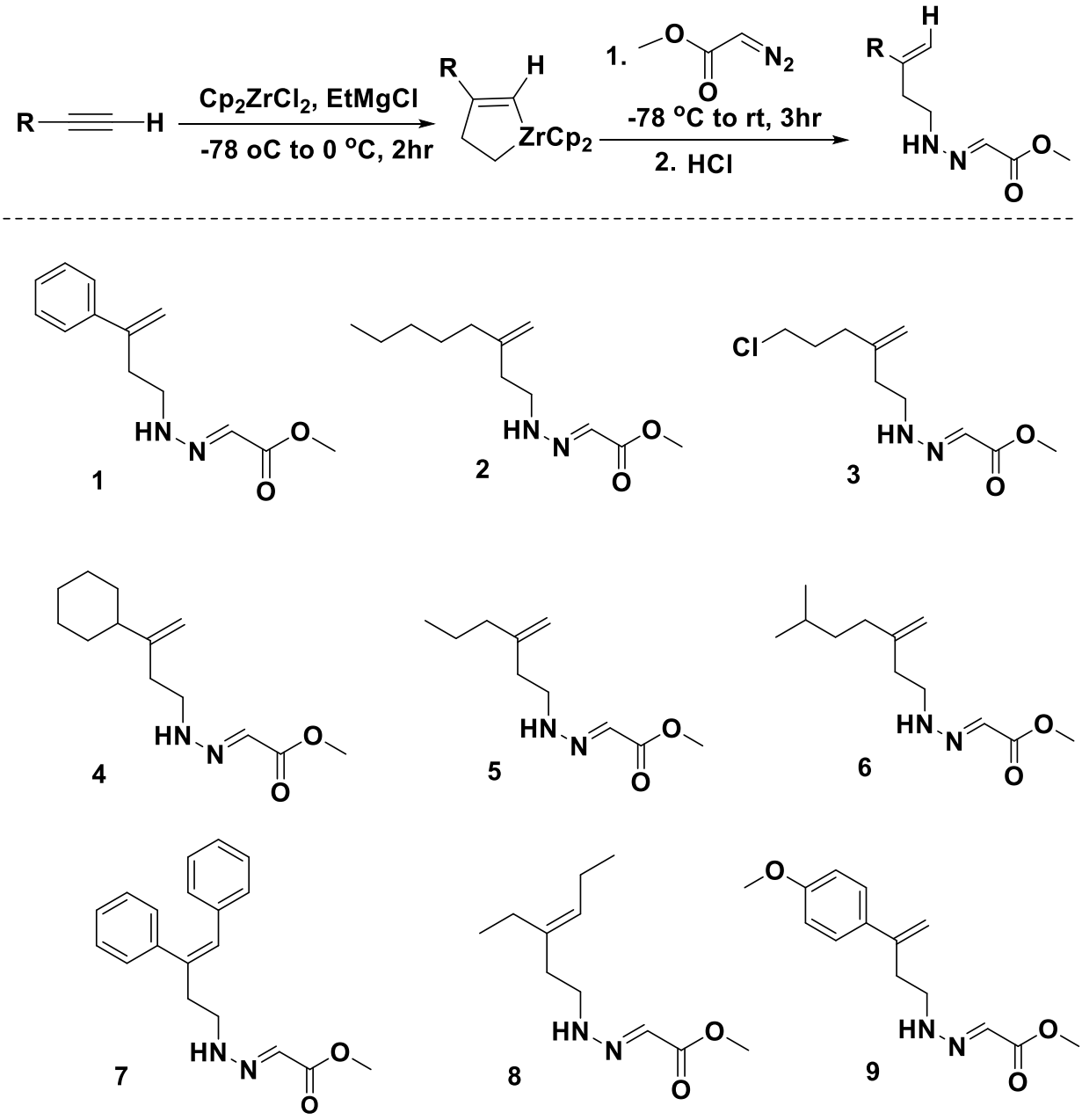


Figure 15. The isomers of methyl 2-(2-(3-phenylbut-3-en-1-yl)hydrazono)acetate.

Table 2. Substituted hydrazones synthesis.



In general, the percentage yield was not satisfying as it is supposed to be, TLC and GC-MS results indicate the formation of byproducts other than the desired hydrazone. According to the preliminary results on TLC using 1% Et_2O/hexane, the crude product from any reaction would separate every time at least into 4-5 spots. If we look to the prepared hydrazones on (Table 2) we will find that all of

them were prepared from terminal alkynes except **8** and **9** are synthesized from internal alkynes, and when the percentage yield of the hydrazone prepared from diphenyl acetylene and 3-hexyne the yield was increased to ~ 51% for 3-hexyne-based hydrazone, but does not differ that much for diphenyl acetylene.

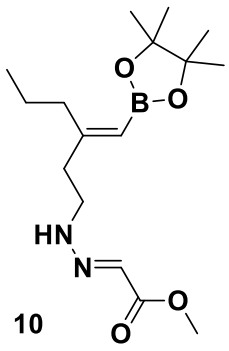
The insufficient yield of the terminal alkynes-based hydrazones could be ascribed to the formation of more byproducts as a result of the high reactivity of the terminal alkynes with highly acidic hydrogen. The low yield of the hydrazone synthesized from diphenylacetylene could be attributed to steric hindrance due to the presence of two phenyl rings attached to the triple bond, in addition to electron delocalization of the electrons of the alkyne bond over the phenyl groups which stabilizes the alkyne and reduce its reactivity.

As a consequence, developing the methodology upon working on the same terminal alkynes but after being functionalized was proposed to be the efficient way. On the other hand, we can explain the decreased yield with loss of some of it within the disposed aqueous layer since quenching with HCl could cause protonation of the nitrogen of hydrazone, although it is not highly probable to occur but still possible with long contact time, thus neutralization with 10% NaOH until basification of the organic layer was proceeded to avoid nitrogen protonation.

Pinacol boronate ester was chosen for the functionalization in a regioselective manner, it was used frequently in the literature for alkynes' functionalization. On the other hand, the presence of boronate ester as a substituent of the hydrazone structure accesses further substitution of the synthesized compounds which means a wider range of applications and ability to control its bioactivity.

Four different alkynes were functionalized with pinacol boronate ester and then utilized for hydrazone synthesis. Hydrazones from boronated 1-pentyne, cyclohexyl acetylene, 5-chloro-1-pentyne, and 4-ethynyl anisole are listed in (Table 3). The pure compound was separated on column chromatography using (40% Ethyl acetate/Hexane) as the mobile phase.

Table 3. The synthesized hydrazones from the boronated alkynes.



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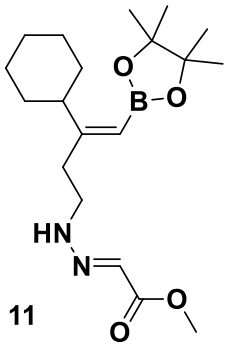

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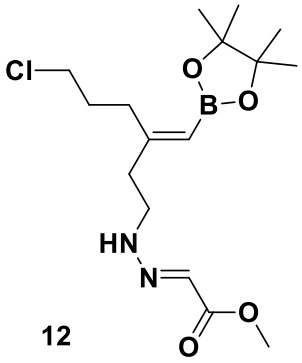

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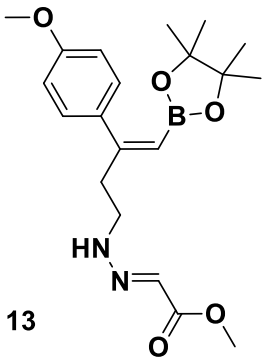
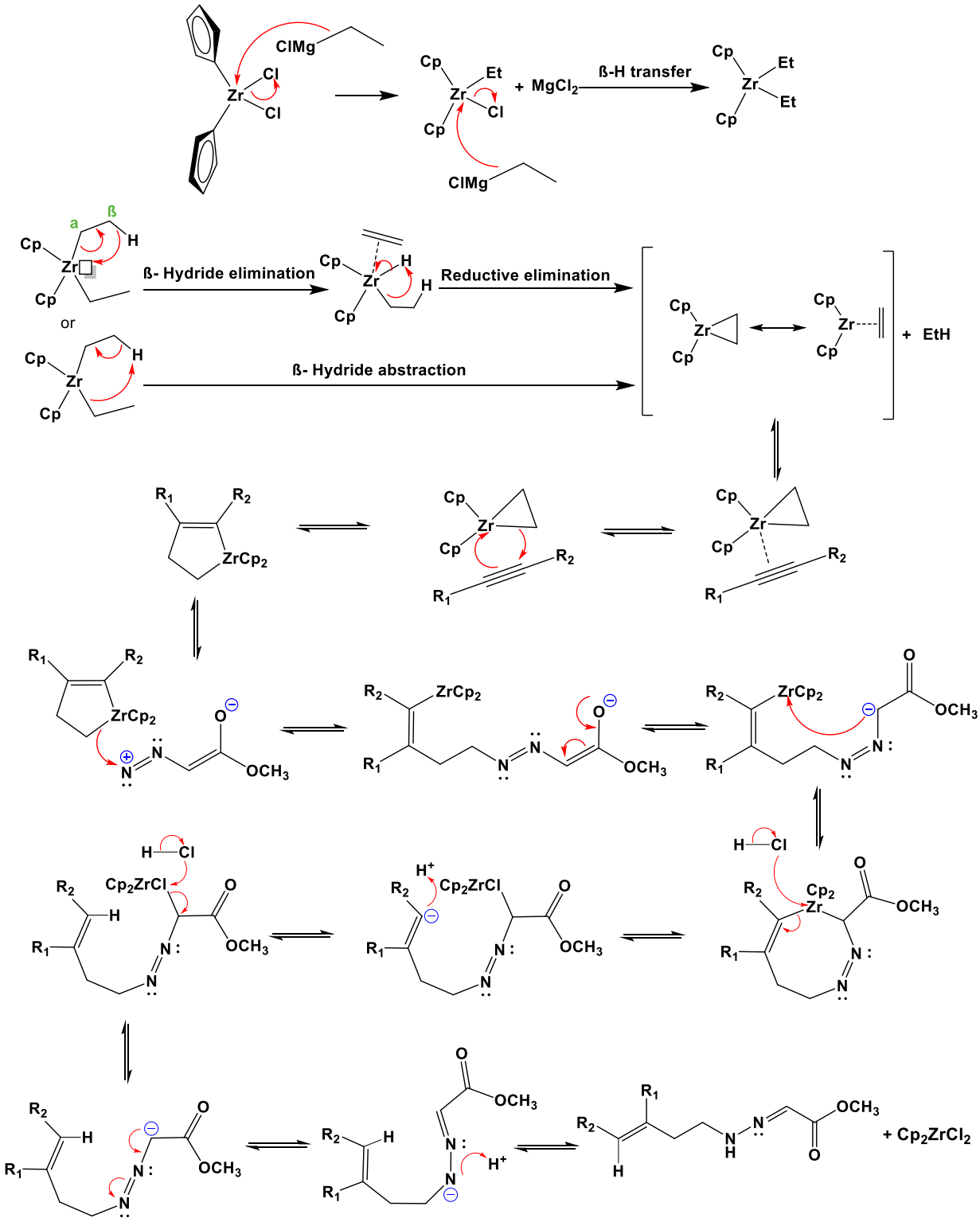


13

3.3 The proposed reaction mechanism:

The proposed reaction mechanism demonstrated in (Scheme 14) is a stoichiometric mechanism. Starting from the reaction of stoichiometric quantities of zirconocene dichloride with Grignard (EtMgCl) in the solvent THF with stirring for one hour at -78ºC.

Organomagnesium and organolithium reagents are strong bases, thus utilizing the Grignard reagent (EtMgCl) is crucial for the initialization of organozirconium (Cp_2ZrEt_2) to generate zirconocene (Cp_2Zr) species in situ upon the formation of ethylene zirconocene complex, a π complex with ethylene which is responsible for the regioselective cross coupling reaction. However, such reagents need much care to be handled under dry conditions since they react with moisture easily forming the corresponding alkane.



Scheme 14. The proposed reaction mechanism

A Key transaction in a wealth of transition metals catalyzed reactions is an intramolecular process that causes β hydride transfer. In fact, this transformation

is a bane for a variety of organometallic reactions, however, it is the crucial step in this mechanism. In this process, σ complex is converted into a π complex which happens in the case of a metal with a vacant site, and thus usually favored by 16 electron metals as in zirconium complexes, attached to an alkyl group with hydrogen bonded to the carbon at the β position (β hydrogen) of the metal alkyl group.[88]

The β hydrogen should be able to align with the metal in a *syn* (in the same position) coplanar (in the same plane) arrangement with zero dihedral angle. The bond between the metal and the alkyl group is a nucleophilic bond polarized toward the carbon atom. Indeed, there are two tolerable mechanistic pathways for this very fast transfer process, those are β hydride elimination and β hydride abstraction.

β hydride elimination process, the reverse pathway of hydrometallation or migratory insertion reactions,[76] is well-known and involves the transfer of β hydride to the vacant site of the metal center after being eliminated from the alkyl group followed by a simultaneous reductive elimination step, in which two adjacent ligands, here are the hydrogen and the second ethyl group, form a stronger Et-H bond and leave the complex as ethane resulting in the formation of an alkene complex which is a metal hydride olefin complex which also exists as zirconocenecyclopropane intermediate since alkenes are Lewis bases and form a π complex upon using the pair of electrons in the π bond.

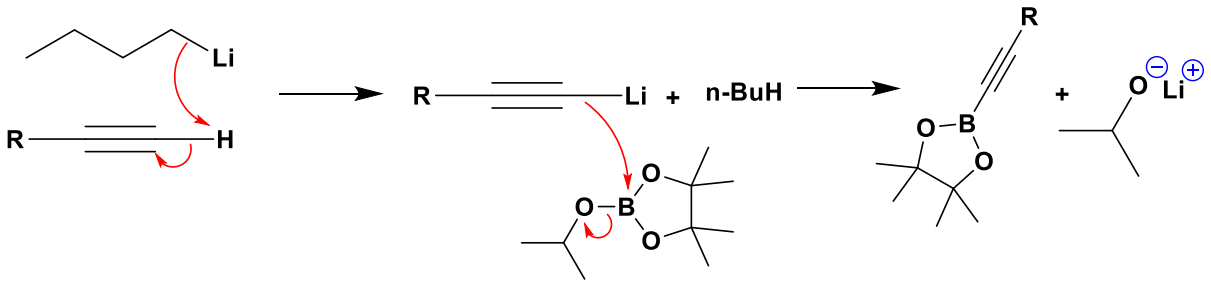
β hydride abstraction is less common but occurs most frequently in the case of d^0 metal dialkyl complexes, diethyl zirconocene in this work. Upon this pathway, one ethyl group uses the electrons bonding it with zirconium to abstract β hydrogen of the adjacent ethyl group, and then leaves the complex as the more stable ethane compound without forming the intermediate of metal-hydride that formed in the previously discussed hydride elimination.[89] Simultaneously, the electrons of the abstracted hydrogen at the β carbon form a new bond with zirconium resulting in zirconocenecyclopropane which could also exist as Zr(II) ethylene π complex, this implies that whether elimination or abstraction process occurs, the same products will come up.[76,88–90]

The generated π complex still has 16 valence electrons thus considered coordinatively unsaturated, and when the alkyne boronate is added to the zirconocenecyclopropane complex an addition reaction occurs in which the alkyne π bond electrons bind to the metal center to form an intermediate with 18 valence electrons. This intermediate undergoes a subsequent cyclization step via the intramolecular insertion reaction to form a 16-electron cyclopentene complex as an intermediate before diazo addition. Such coupling reactions are reversible in general and the reaction conditions contribute to the formation of the thermodynamic product.[91]

Terminal alkynes, having sp hybridized C–H bond with 50% s-character, are acidic with pK_a of about 25, thus able to be easily deprotonated by the strong base

n-BuLi.[76] Alkynyllithium (n-BuLi), as a strong base with (pKa ≈ 50),[92] was reacted with borate ester to form alkyne boronate as shown in (Scheme 15). In this way, the utilization of terminal alkyne in the presence of reactive acidic hydrogen was avoided and the structures of the synthesized hydrazones from boronated alkynes facilitate further functionalization of the product with new substituents easily.

Indeed, the presence of boronate ester as a substituent of the hydrazone structure could affect the potential to generate different isomers as a result of the effect of steric hindrance caused by the boronate moiety.



Scheme 15. The mechanism of the preparation reaction of boronated alkynes.

As mentioned before, diazo compounds have been rarely used to react as electrophiles and limited studies demonstrated their reactions as electrophiles with organometallics which is ascribed to the high reactivity of the generated intermediates.[93] From a kinetic point of view, methyl diazoacetate will react as a nucleophile, therefore, the low temperature of -78 °C is crucial to be maintained when methyl diazoacetate is added to allow the kinetic product to form and mitigate the potential of diazoacetate to interact as a nucleophile.

The Zr-C bond is still nucleophilic and polarized to the more electronegative carbon atom, and once the diazo compound is added, the nucleophilic carbon attack the electrophilic nitrogen of diazoacetate with breaking the Zr-O bond. A simultaneous cyclization step takes place since the diazo moiety has 1,3 dipolar character and the nucleophilic carbon adjacent to the two nitrogen atoms will directly attack the electropositive zirconium metal to form an eight-membered ring intermediate.

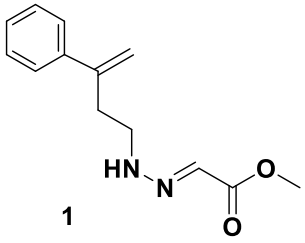
Although it is known that intermediates with five and six-membered rings are more stable than the unfamiliar eight-membered rings, this case is possible for zirconium compounds according to the literature, in which strained three and four-membered rings and unusual ten and eleven-membered metallocycles were confirmed to generate as intermediates in several zirconocene-based syntheses reaction.[94–97] The last step of the reaction mechanism is reductive elimination when the reaction is quenched with HCl to form the hydrazone while zirconcene is eliminated as Cp_2ZrCl_2 again, however, this complex mostly will not be stable in the aqueous and acidic conditions.

3.4 Hydrazone characterization results:

After separation of the crude product on column chromatography with the preliminary results of TLC the pure fractions with the retention factor ~ 0.4-0.5 were analyzed directly with GC-MS.

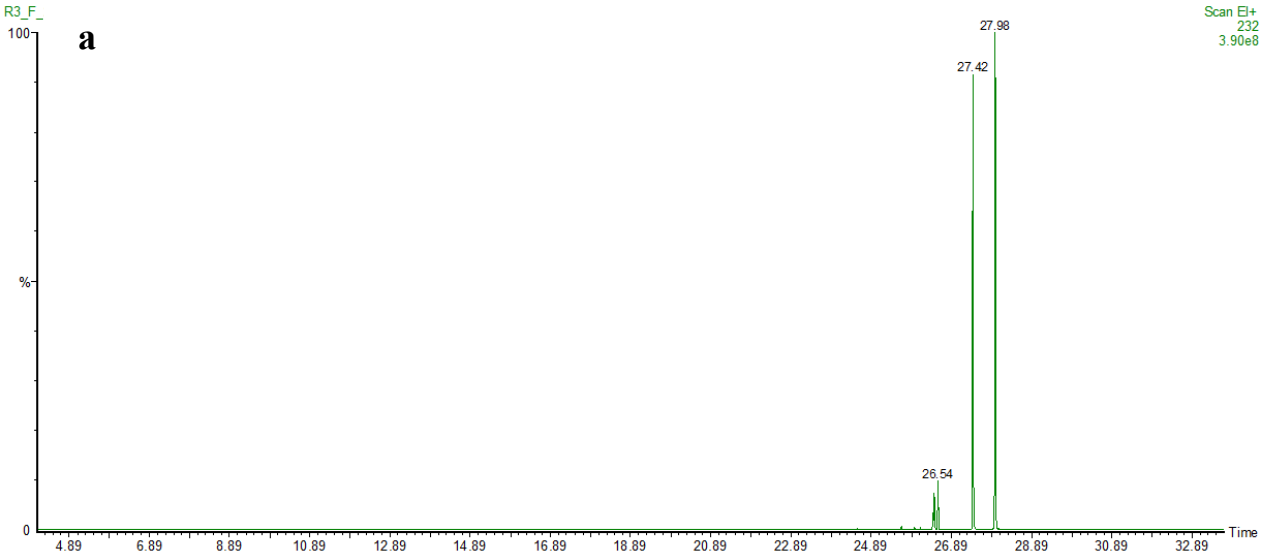
3.4.1 Analysis with GC-MS:

Methyl (E)-2-(2-(3-phenylbut-3-en-1-yl)hydrazineylidene)acetate (1):



1

This compound has a molecular weight of 232 amu, according to its chromatogram (Figure 16.a), there is two closed peaks at retention times 27.42 and 27.98 respectively and with nearly the same mass and the fragmentation pattern, this can be explained with stereochemistry as discussed previously, in which one of them represent the *Z* isomer and the other is *E* isomer, and such isomers would not easily separate on silica with column chromatography.



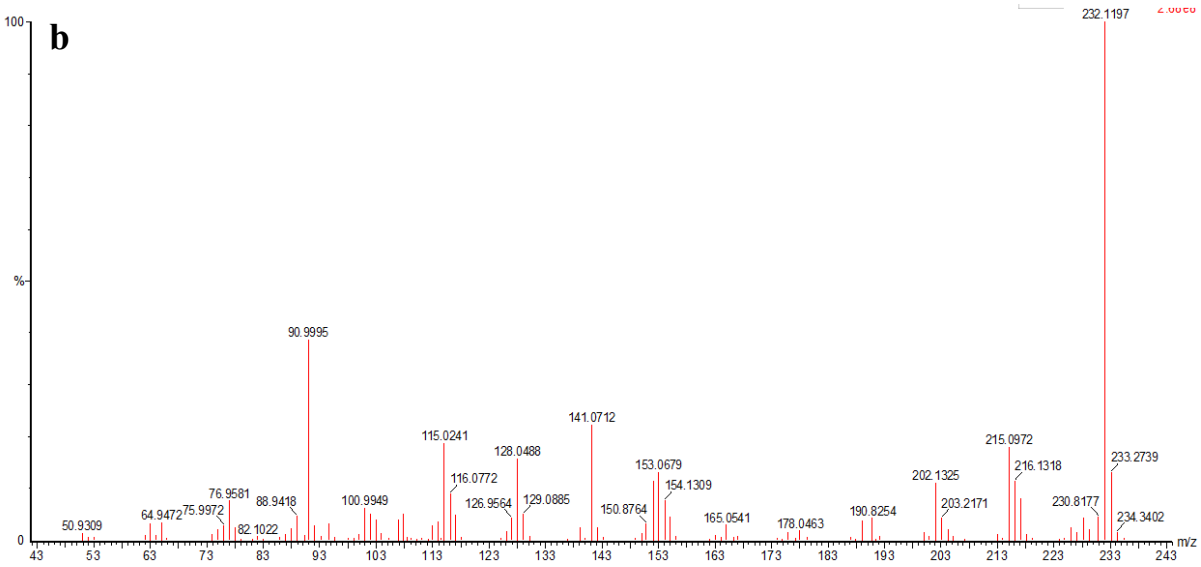
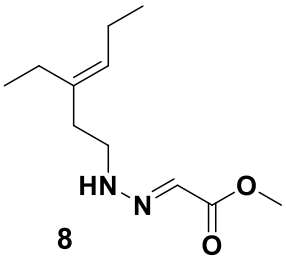


Figure 16. a. Total ion chromatogram of the fraction containing the hydrazone **(1)**. **b.** mass spectrum of the peak with a retention time of 27.98 min.

Methyl (E)-2-(2-((E)-3-ethylhex-3-en-1-yl)hydrazineylidene)acetate (8):



8

The results obtained from GC-MS analysis of the pure fraction of the synthesized hydrazone from 3-hexyne are shown in (Figure 17) where representative total ion chromatogram of the analyzed fraction is provided in (Figure 17.a) and the mass spectrum of the major peak with retention time of 11.8 min is represented in (Figure 17.b) and confirm the existence of the product with the molecular ion mass of 212 amu. The fragmentation pattern also matches with the product structure.

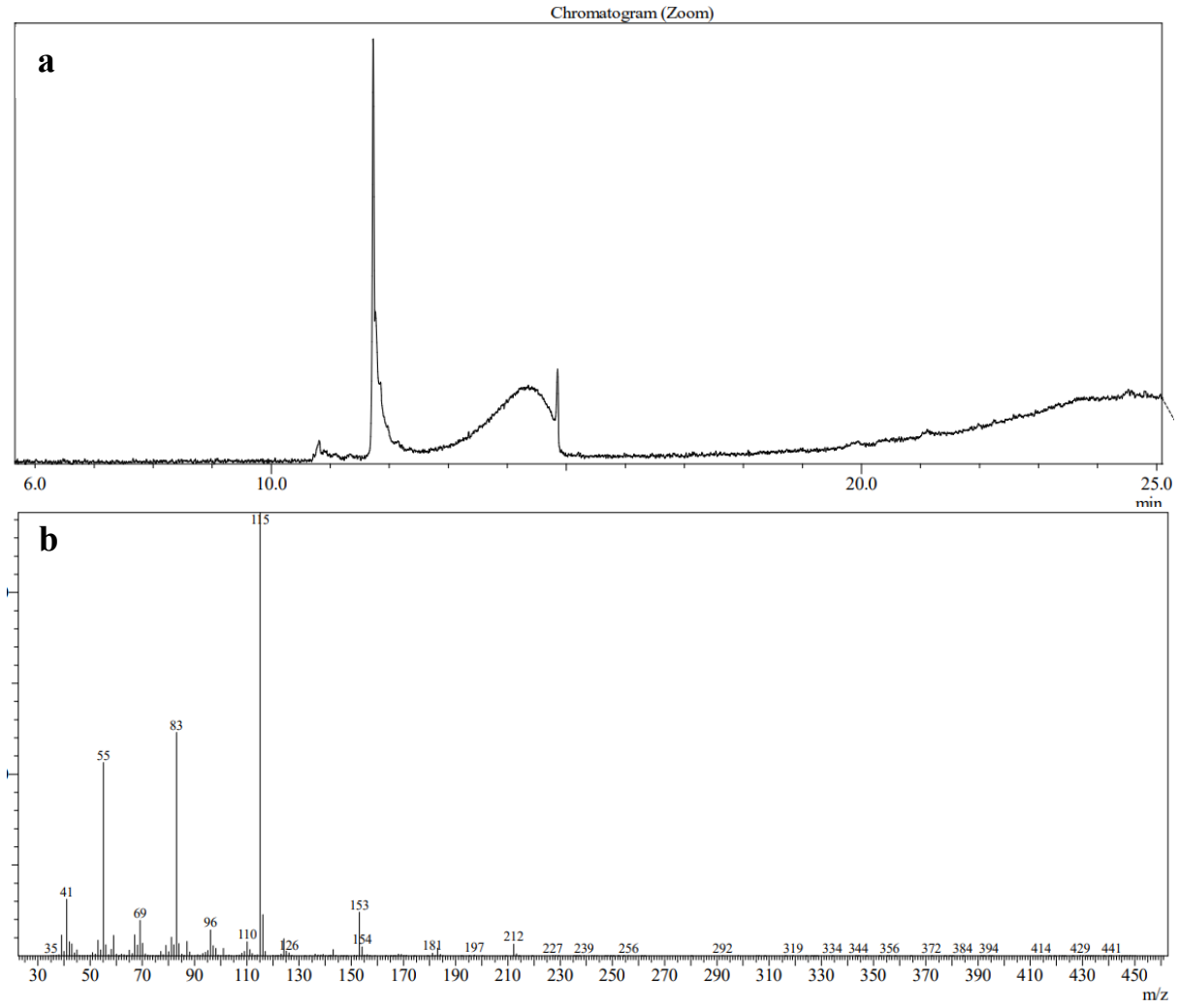
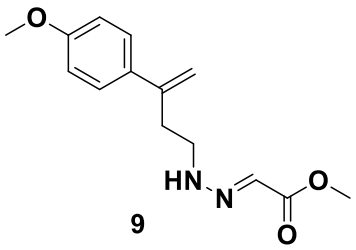


Figure 17. a. Total ion chromatogram of the fraction containing the hydrazone **(8)**. **b.** mass spectrum of the major peak with a retention time of 11.8 min.

Methyl (E)-2-(2-(3-(4-methoxyphenyl)but-3-en-1-yl)hydrazineylidene)acetate (9)



9

The molecular mass of the hydrazone **(9)** is 262 amu, this compound is confirmed with the mass spectrum in (Figure 18.b) at retention time of 19.7 min. The peak with retention time of 11.7 min in the chromatogram (Figure 18.a) refers to

butylated hydroxy toluene (BHT) which exist in most of the demonstrated GC chromatograms at the same retention time. BHT is a well-known antioxidant additive in a variety of the organic solvents.

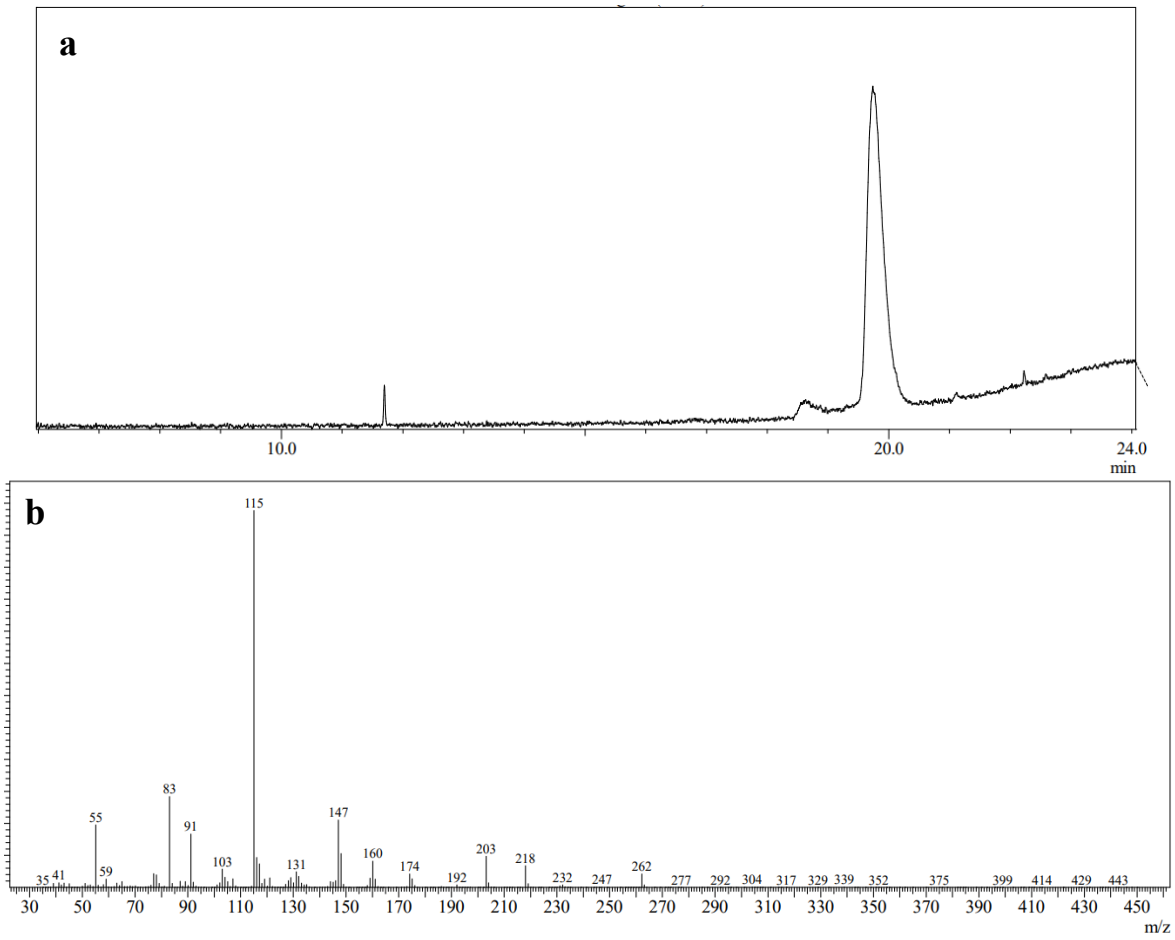
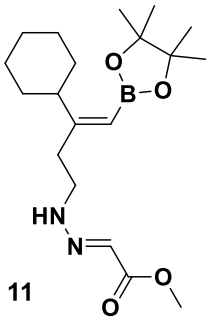


Figure 18. a. Total ion chromatogram of the fraction containing the hydrazone **(9)**. **b.** mass spectrum of the major peak with a retention time of 19.7 min.

methyl (E)-2-(2-((Z)-3-cyclohexyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)hydrazineylidene)acetate (11):



11

The molecular weight of the hydrazone **(11)** is 364 amu and matches its mass spectrum (Figure 19.b) and according to its chromatogram (Figure 19.a) this fraction was not totally pure.

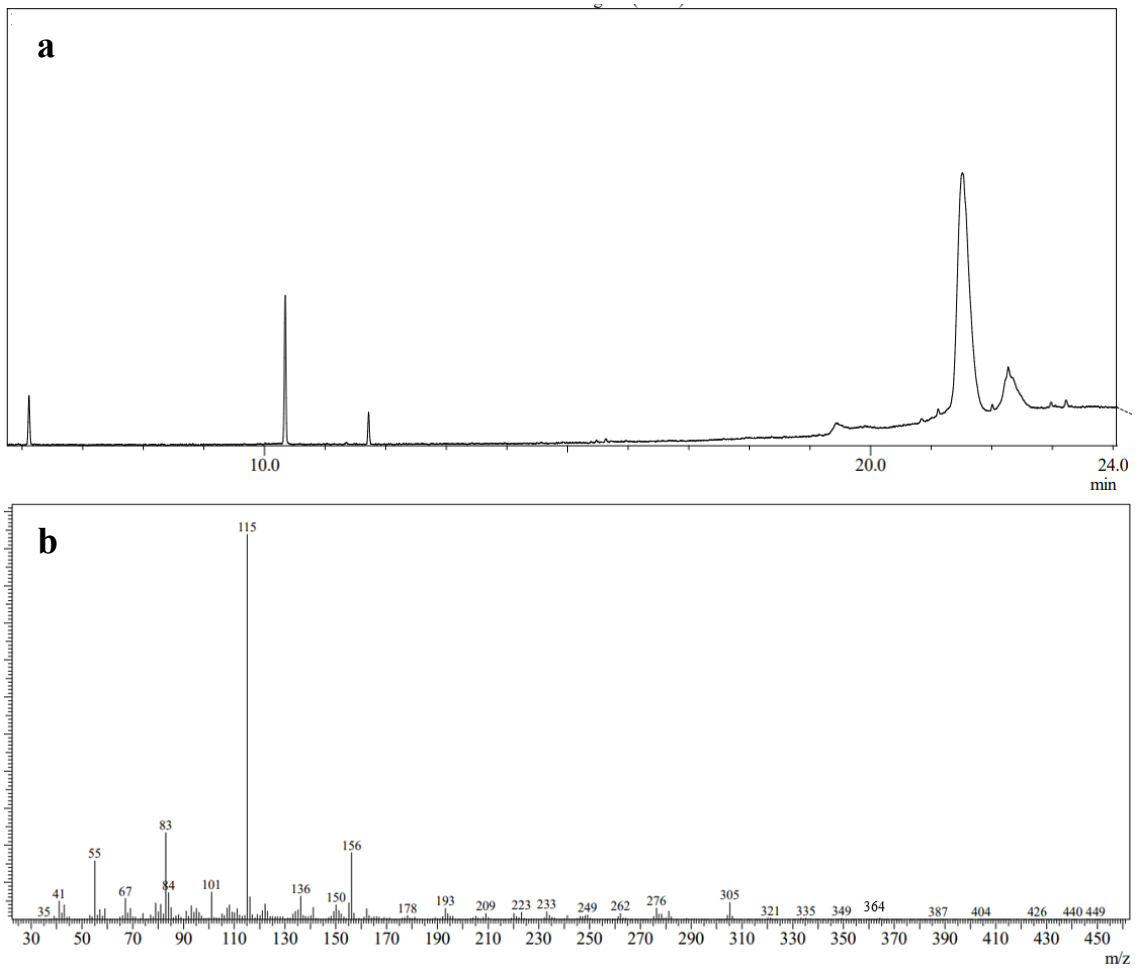


Figure 19. a. Total ion chromatogram of the fraction containing the hydrazone **(11)**. **b.** mass spectrum of the major peak with a retention time of 21.5 min.

3.4.2 Characterization with NMR:

NMR as a sophisticated analysis technique is reliable to emphasize the compound structure through providing structural information about carbon and hydrogen in different functional groups within a compound. ^{13}C-NMR and ^{1}H-NMR (80 MHz in $CDCl_3$) was conducted for some fractions.

Methyl (E)-2-(2-((E)-3-ethylhex-3-en-1-yl)hydrazineylidene)acetate (8):

^{1}H-NMR spectrum for the same compound represented in (Figure 20). The peak which appeared in all ^{1}H-NMR spectra at 7.26 ppm is the residual of $CDCl_3$ peak. Another peak appeared in several spectra at ~ 3.2 ppm is attributed to the solvent diethyl ether, the other triplet peak of the methyl groups of diethyl ether may merged with the product methyl groups. The fraction containing the pure compound **8** was analyzed with ^{13}C-NMR and ^{1}H-NMR and the ^{13}C-NMR spectrum is demonstrated in (Figure 21) followed by spectrum chemical shifts analysis in (Table 4).

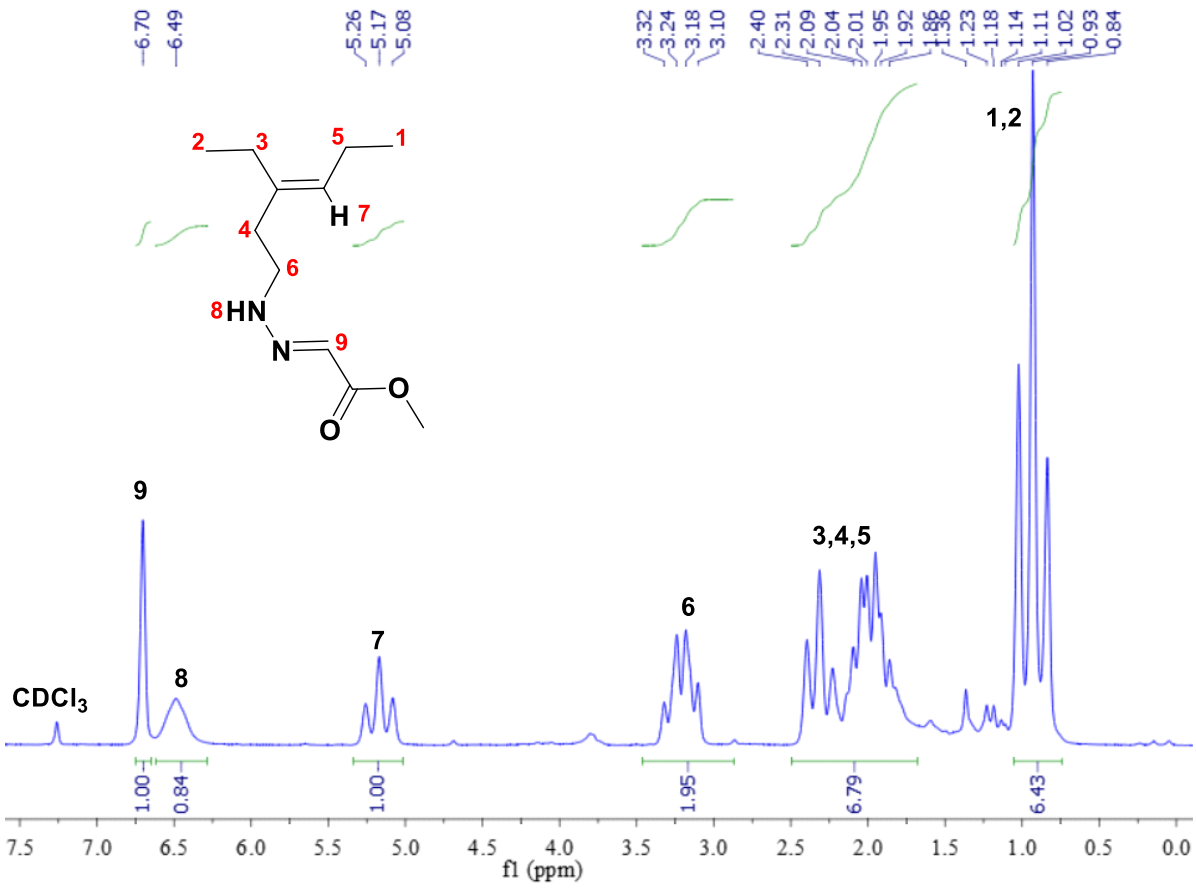


Figure 20. ^{1}H-NMR spectrum of the hydrazone (**8**).

Table 4. Chemical shifts analysis of ^{13}C-NMR signals of the synthesized hydrazone (8)

Signal	Chemical shift (ppm)	Functional group
1	13.16	sp^3 carbon ($-CH_3$)
2	14.47	sp^3 carbon ($-CH_3$)
3	20.83	sp^3 allylic carbon ($-CH_2-$)
4	22.39	sp^3 allylic carbon ($-CH_2-$)
5	33.63	sp^3 allylic carbon ($-CH_2-$)
6	44.01	sp^3 carbon ($-CH_2-NH$)
7	51.63	sp^3 ester carbon ($O-CH_3$)
8	120.46	sp^2 vinylic carbon ($=CH-$)
9	129.64	sp^2 hydrazone carbon ($N=CH-CO$)

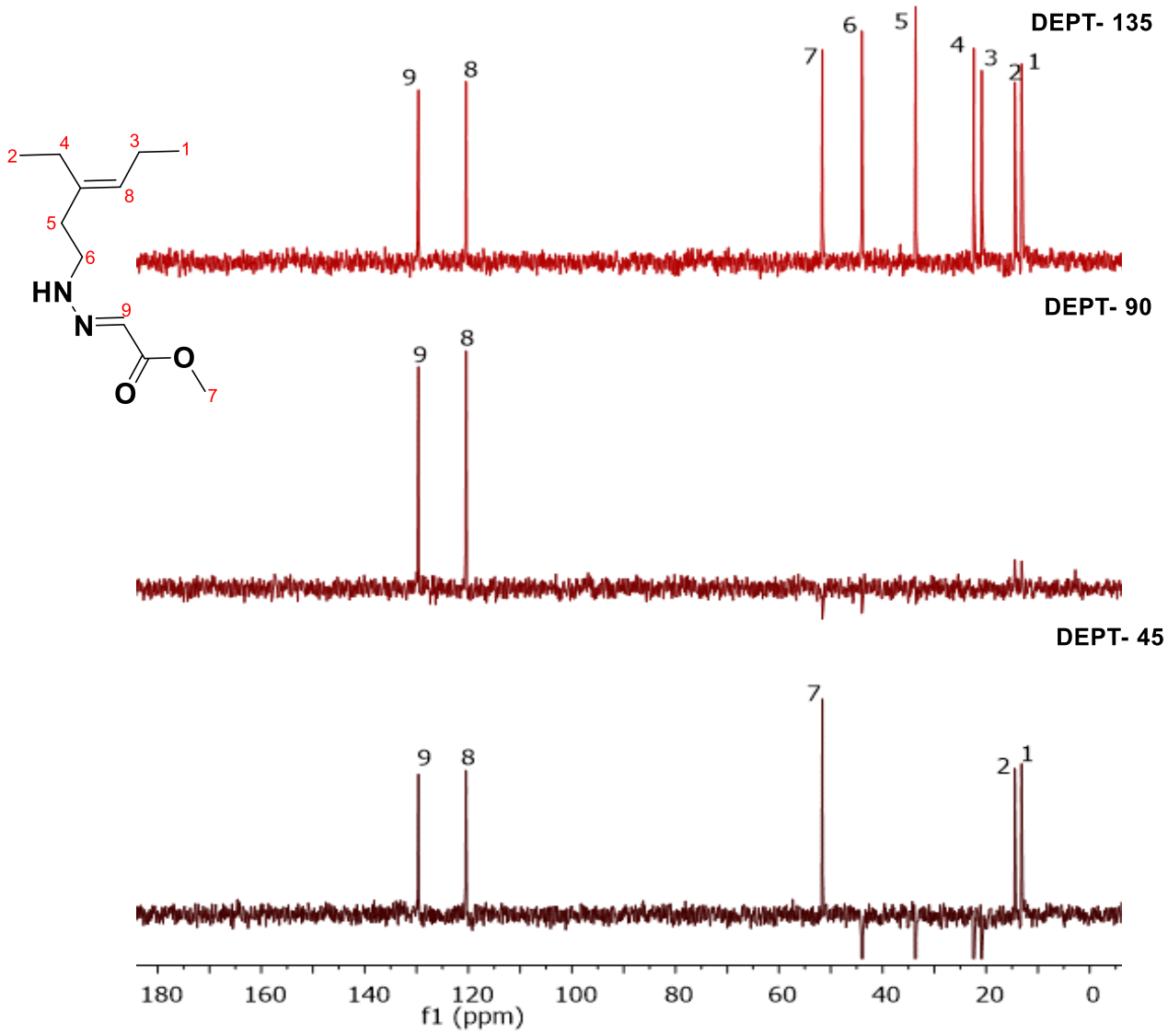


Figure 21. ^{13}C-NMR spectrum of the hydrazone (**8**).

Methyl (E)-2-(2-(3-(4-methoxyphenyl)but-3-en-1-yl)hydrazineylidene)acetate (9)

^{1}H-NMR spectrum for the compound **(9)** represented in (Figure 22). The signal at ~ 2.5 ppm is not a real quartet this could be attributed to impurities or the effect of the vinylic hydrogens. The signal at 1.5 ppm could appear due to the presence of traces of hexane solvent.

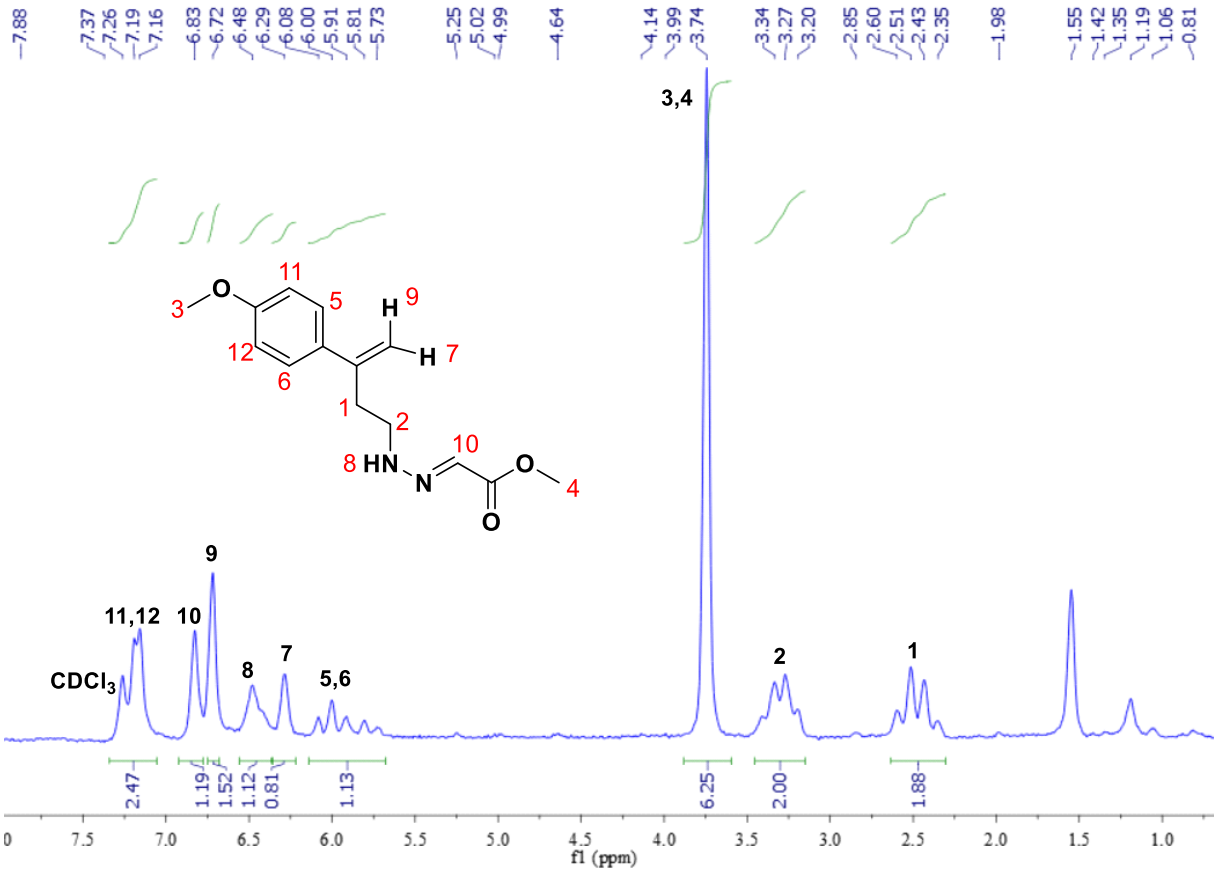


Figure 22. ^{1}H-NMR spectrum of the hydrazone **(9)**.

methyl (E)-2-(2-((E)-6-chloro-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)hexyl)hydrazineylidene)acetate (12):

According to ^{1}H-NMR spectrum of this compound (Figure 23) there is no clear singlet peak between 1-2.5 ppm to describe the hydrogens of the four methyl groups in the boronate ester moiety, so we could ascribe that to the hydrolysis of the boronate ester into boronic acid and the peaks of the two (OH) group could be either overlapped with the multiplet peak at 3.5 ppm, or exist at 4.8 ppm as a tiny broad peak.

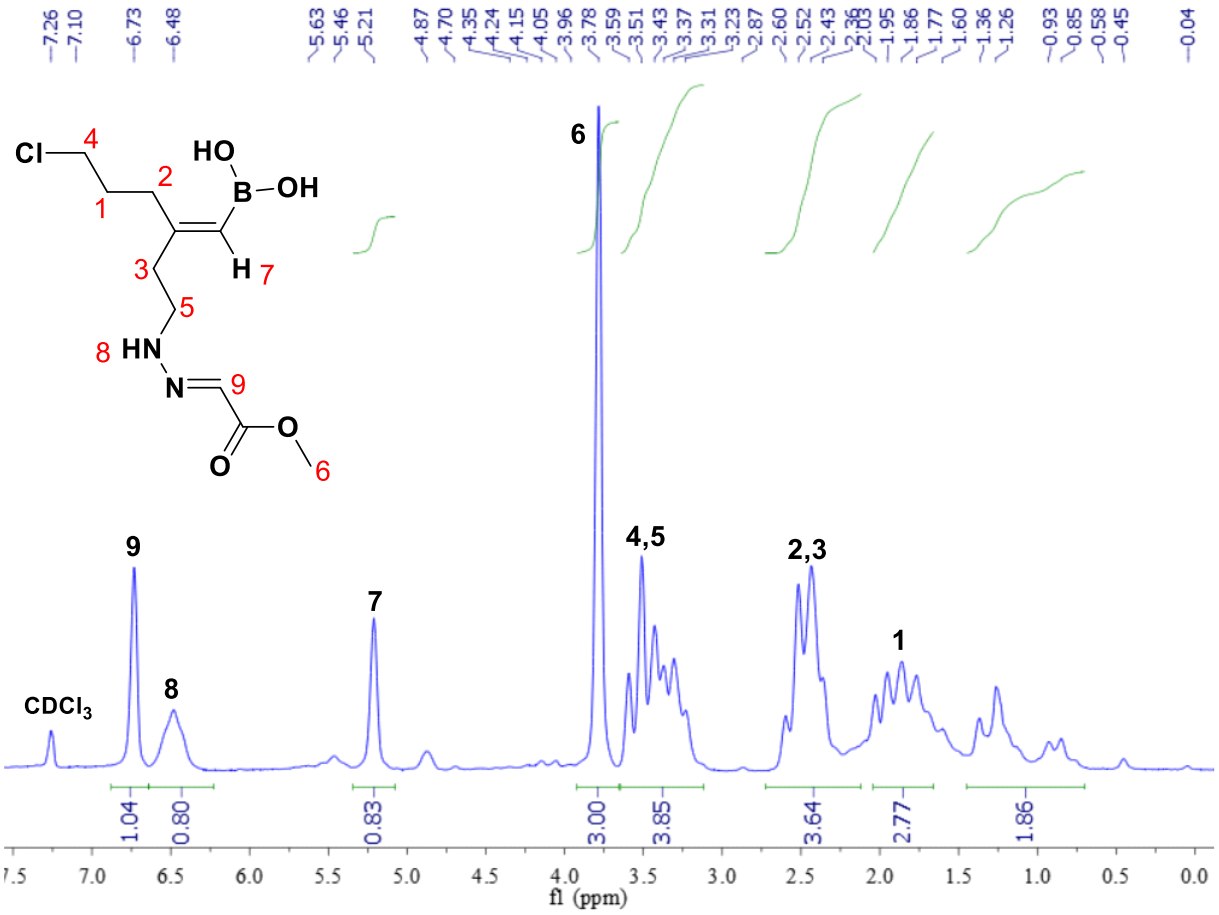


Figure 23. ^{1}H-NMR spectrum of the hydrazone (**12**) after hydrolysis.

Methyl (E)-2-(2-((Z)-3-cyclohexyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)hydrazineylidene)acetate (11):

According to ^{1}H-NMR spectrum of this compound (Figure 24) the hydrogens of the cyclohexyl group usually overlap as a distorted multiplets. The signals are compatible with the structure of the hydrazone which confirms its identiy.

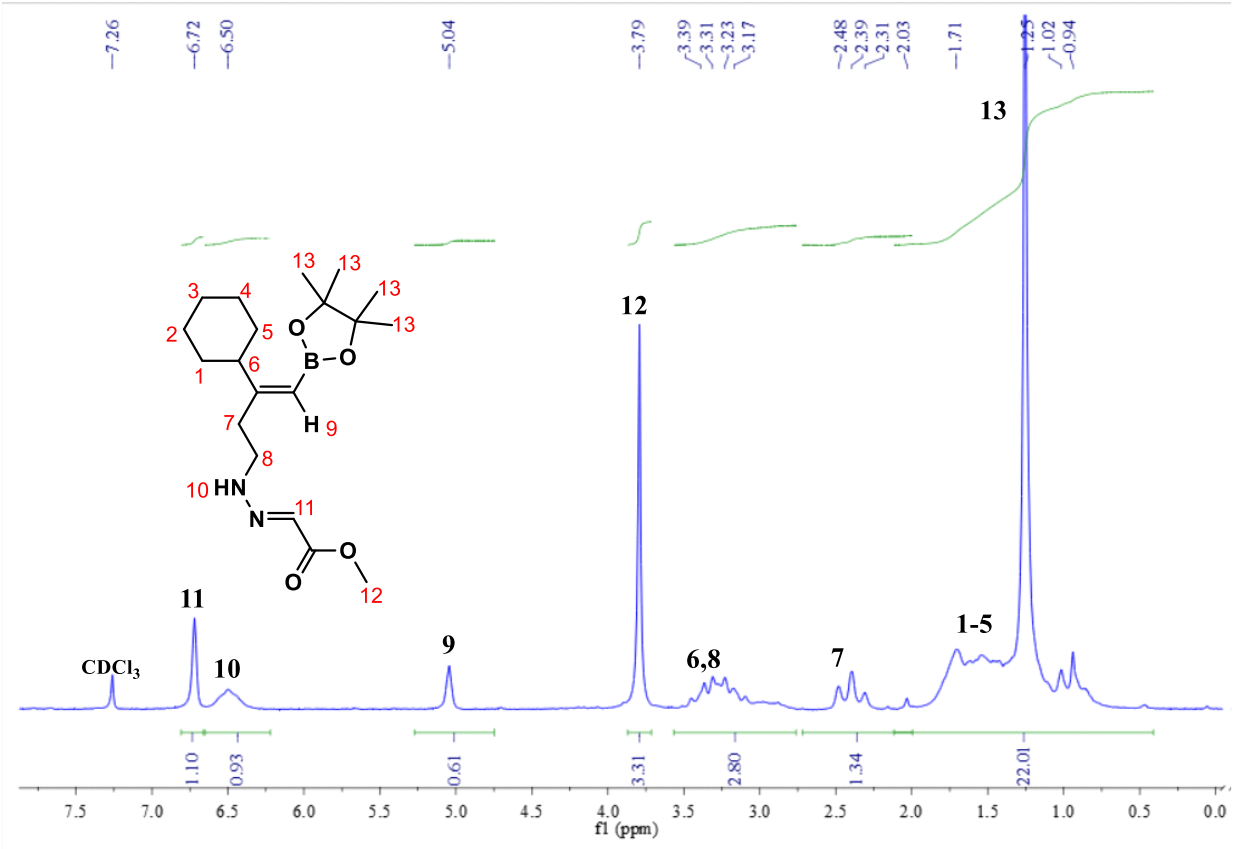


Figure 24. ^{1}H-NMR spectrum of the hydrazone **(11)** after hydrolysis.

3.5 Expected reaction byproducts:

In this methodology all the reagents and reactions must be dealt with in the absence of oxygen and moisture, but complete and perfect isolation mostly will not be achieved, thus from the highly probable byproducts to form is the hydrolyzed form of the five membered ring intermediate in which the alkyne will be converted to alkene and will not be suitable for cross coupling reaction with methyl diazoacetate. (Figure 25) demonstrate some of the possible byproducts. GC-MS of some of the separated fractions from column chromatography supports this supposition. Furthermore, in the case of boronated hydrazones, it is known

that the boronate ester moiety is a center for further substitution, which means it could be easily hydrolyzed to form the corresponding boronic acid with loss of 2,3-dimethylbutane, this will affect hydrazone's solubility and polarity as well.

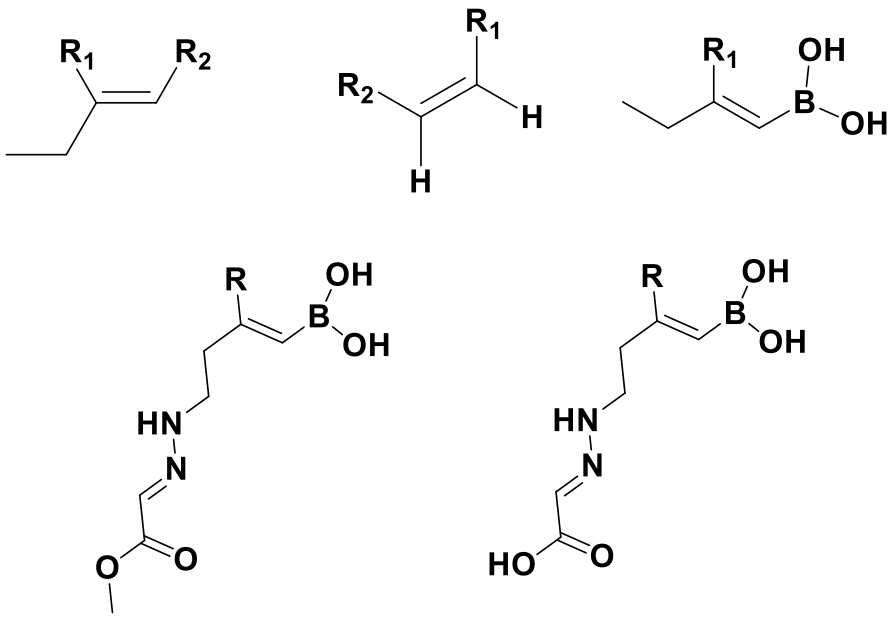


Figure 25. Some of the possible byproducts from the synthesis reaction.

Chapter 4. Conclusion and Future Studies

In this work thirteen different hydrazone compounds were synthesized with the proposed methodology, using Cp_2ZrCl_2/EtMgCl reagent which was reacted with the highly reactive simple alkynes and more stable boronated alkynes to form the key intermediate that converted into hydrazone after cross coupling reaction with diazo acetate in a regioselective manner. The reaction conditions directly affect the yield of the product, for example, all the addition steps of the precursors to the reaction flask have to be conducted at low temperatures of about -78 ^{o}C to control the yield of the thermodynamic product. The isolated hydrazones showed high stability with time and analyzed with GC-MS and NMR techniques.

Hydrazone synthesis with this methodology has been accomplished, and further optimization of the product yield and purity could be achieved. For example, a using catalyst may be effective, in addition, utilizing more stable diazo compounds other than methyl diazo acetate would avoid its decomposition or hydrolysis and affect the yield as a consequence. On the other hand, the synthesized hydrazones substituted with either boronate ester or boronic acid moieties could be easily substituted with alkyl halides for example to enhance its application or its bioactivity. The biological activity of all the isolated hydrazones has to be tested. X-ray crystallography is significant to confirm the previously discussed results of products spectra.

The investigated methodology in this work is flexible and valuable, it is capable of being modified in several ways to synthesize novel and substantial organic compounds since zirconocene intermediates are clearly efficient in the field of cross-coupling reactions.

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