ISTANBUL TECHNICAL UNIVERSITY ★ GRADUATE SCHOOL OF SCIENCE ENGINEERING AND TECHNOLOGY

EFFICIENT SYNTHESIS of KETONE END FUNCTIONALIZED PEG THROUGH OXYMERCURATION REACTION

M.Sc. THESIS

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OKSİMERKÜRASYON REAKSİYONUYLA ETKİLİ BİR ŞEKİLDE KETON UÇLU PEG SENTEZİ

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ARALIK 2015

To my mother,

FOREWORD

This master study has been carried out at Istanbul Technical University, Chemistry Department of Science & Letter Faculty.
I would like to express my gratitude to my thesis supervisor, Prof. Dr. Gürkan HIZAL and co-supervisor Prof. Dr. Ümit TUNCA for offering invaluable help in all possible ways, continuos encouragement and helpful critisms throughout this research.
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December 2015

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ABBREVIATIONS

^{1}H NMR	**:** Hydrogen Nuclear Magnetic Resonance Spectroscopy
^{12}C NMR	**:** Carbon Nuclear Magnetic Resonance Spectroscopy
GPC	**:** Gel Permeation Chromatography
UV	**:** Ultra Violet
IR	**:** Infrared
$CDCl_3$	**:** Deuterated chloroform
CH_2Cl_2	**:** Dichloromethane
THF	**:** Tetrahydrofuran
EtOAc	**:** Ethyl acetate
PEG	**:** Poly(ethylene glycol)
p-TSA	**:** para Toluene Sulphonic Acid
CuAAC	**:** Copper catalyzed azide-alkyne cycloaddition
PDI	**:** Polydispersity Index
λ	**:** Wavelength
nm	**:** Nanometer
°C	**:** Celsius
mmol	**:** Milimole
µmole	**:** Micromole
µL	**:** Microlitre

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EFFICIENT SYNTHESIS OF KETONE END FUNTIONALIZED PEG THROUGH OXYMERCURATION REACTION

SUMMARY

For the longest time, effective, easy and inexpensive formation of one terminal group to another reactive terminal group is a desirable case not only in organic chemistry but in polymer chemistry as well. For this instance, researches are made either to find a new technique for polymers or to adapt and modify organic chemistry reactions in order to apply then in polymer chemistry.

Ketones are desirable terminal groups in polymer chemistry since they can form imine forms when they react with terminal amine functionalized protein or peptides. But inevitably, alkyne functioned polymers are being used in such manner via CuAAC "Click" reactions to give biomolecule- polymer binding. Unfortunately, CuAAC reactions are limited to use to give such products due to the usage of Cu as the catalyst which has severe effects on human body functions.

Hydration of alkynes is an easy way to obtain ketone function. This reaction is done by a mercury (II salt as a catalyst and acidic media, known as oxymercuration reactions. In addition, using such inexpensive chemicals and in a short period of time (4 hours), alkyne function can successfully changes to ketone function, quantitavely. Further observations showed that it is also possible to get rid of mercury (II) salts easily during the work-up processes, which provides the pathway to use oxymercuration reactions in biological aspects.

In this work, we have chosen to use commercially available alkyne functionalized polyethylene glycol (PEG), which is also bio-compatible. Experimental works showed that when applied heat or worked in room temperature, it is possible to observe alkyne to ketone formation with high yields. Also, it was made clear that ketone functionalized PEG can successfully forms imines when reacted with an amine functionalized structure in our model reaction.

Firstly, PEG-OH was reacted with 4-pentionic acid, giving PEG-Alkyne which is bio-compatible. Then, optimum reaction conditions were tried to be found in order to form the ketone conversion. But unlike in the organic synthesis, sulfuric acid and hydrochloric acid is found to be ineffective in this reaction, because both hydrolyzed the polymer structure. Instead, para-toluene sulfonic acid was used since its low toxicity, inexpensiveness and effectiveness in this reaction. Different equivalents and temperatures were tried with the most compatible mercury salt and acid, found to be the optimum reaction condition was 0.25 equivalent of p-TSA, $HgSO_4$ in 50^oC and 0.50 equivalent of p-TSA, $HgSO_4$ in room temperature and observed quantitave formation. In light of these informations, optimum reaction time was observed as 4 hours from the kinetic studies.

In light of this information firstly, two different electronic structıred alkyne terminated PEG was synthesised and alkyne- ketone conversion optimum reaction conditions were studied.

OKSİMERKÜRASYON REAKSİYONUYLA ETKİLİ BİR ŞEKİLDE KETON UÇLU PEG SENTEZİ

ÖZET

Bir reaktif uç grubun başka bir reaktif uç gruba etkin, ucuz ve kolay şartlarda çevrilebilmesi sadece organik kimya alanında değil aynı zamanda polimer kimyasında da her zaman arzu edilen bir durum olmuştur. Bunun için yapılan çalışmalarda, ya polimerik yapılar için yeni yöntemler bulunmaya çalışılmış, ya da organik kimyada kullanılan reaksiyonlar polimerik yapılar için modifiye edilmeye çalışılmıştır.

Polimer kimyasında aldehit ve keton uç grubuna sahip polimerler biomoleküller ve polimerler arasında konjugasyon reaksiyonlarına imkan verdiklerinden oldukça rağbet görmektedirler. Şüphesiz, yalnızca alkin fonksiyonelitesine sahip polimerler de CuAAC "click" tepkimeleri ile yukarıda belirtilen polimer-biyo molekül birleşmelerinde aktif olarak kullanılmakatadır. Ancak, CuAAC reaksiyonunun gereksinimi olan bakırın insan vücudu için zararlı olması bu kimyasının polimer-biyo molekül birleşmelerinde kullanımını sınırlamaktadır.

Organik kimyada yaygın olarak kullanılan alkinlere su katılma reaksiyonları alkinlerden karbonil bileşikleri elde etmede oldukça faydalı reaksiyonlardır. Bu katılma reaksiyonları Civa(II) tuzları katalizörlüğünde ve ortamda asit varlığında gerçekleşen oksimerkürasyon reaksiyonlarıdır. Bu sayede alkin fonksiyonelitesine sahip bileşiklere keton fonksiyonelitesi kazandırılmış olur. Bu yöntem sayesinde son derece ılımlı reaksiyon koşullarında ve oldukça ucuz kimyasallar kullanılarak, dört saat gibi kısa bir zamanda kantitatif olarak alkinlerdn keton eldesi gerçekleşir. Saflaştırma basamaklarında, kullanılan civa(II) tuzundan kolayca kurtulunması da, canlı sağlığı açısından sorun teşkil etmediği için oksimerkürasyon reaksiyonu tercih edilebilir bir yöntemdir.

Bu çalışmada hedef polimer olarak artık ticari olarak da satılan alkin fonksiyonelitesine sahip biyouyumlu bir polimer olan poli(etilen glikol) (PEG) seçilmiştir. Deneysel olarak farklı koşullarla çalışılan bu çalışmada hem oda sıcaklığında hem de ısı uygulanarak elde edilen sonuçlar yüksek verimle alkin-keton geçisinin gerçekleştiğini göstermiştir. Ayrıca, elde edilen keton uç gruplu PEG ve serbest amin yapısına sahip bir model bileşik ile yapılan çalışmalar imin reaksiyonunun da son derece verimli bir şekilde gerçekleştirildiğini göstermiştir. Elde edilen veriler ışığında farklı elektronik etkilere sahip alkin uçlu polimerler de sentezlenerek, bu polimerlerde de alkin uc grubunun keton uç gruba çevrilmesi için uygun koşullar belirlenmiştir.

İlk olarak PEG-OH'ın, 4-pentinoik asitle esterleşme reaksiyonu yapılmış ve bunun sonucunda alkin uç fonksiyonuna sahip biyouyumlu bir polimer elde edilmiştir (Alkyne-PEG) Daha sonra bu alkin uç fonksiyonunun ketona çevrilmesi için en uygun reaksiyon koşulları belirlenmeye çalışılmıştır. Organik yapılarda sıkça kullanılmalarına karşın, polimerde hidrolize yol açmaları nedeniyle asit olarak H_2SO_4 ya da HCl kullanımı uygun görülmemiş , bunlar yerine toksik özellikleri, ucuz oluşu ve alkin keton çevrimini başarıyla yapmasından dolayı p-Toluensulfonik asit belirlenmiştir. Uygun asidin ve civa (II) tuzunun bulunmasıyla reaksiyonlar değişik oranlarda kimyasallar kullanılarak ve değişik sıcaklıklarda tekrarlandı.Sonuç olarak 0.25 ekivalent p-TSA ve HgSO4 kullanılarak ve 50 ^oC ile 0.5 ekivalent ve oda sıcaklığında alkinden keton dönüşümünün kantitatif olarak gerçekleştiği gözlemlendi. Bu bilgiler ışığında kinetik çalışmalar yapıldı ve tamamen alkin keton dönüşümü için 4 saatin her iki koşul için de yeterli bir süre olduğu gözlemlenmiş oldu. Elde edilen polimerlerin yapısı ^1H NMR, UV Spektrometresi ve FT-IR Spektromeresi kullanılarak aydınlatıldı.

Çalışmanın devamında elektronik etkilerin gözlemlenebilmesi amacıyla farklı elektronik etkilere sahip alkin uç fonksiyonlu polimerler sentezlendi ve bunların keton dönüşümleri incelendi.Bu amaçla propargyl bromide ve propargyl alkol kullanarak esterik ve eterik yapıda iki farklı Alkin- PEG sentezlendi. Polimerlerdeki alkin uçların ketona dönüşümü için yukarıda bahsedilen koşullar kullanıldı ve sonuç olarak proparjil bromürden elde edilen eterik yapı için dönüşüm 50^oC de 10 saatte olurken oda sıcaklığında 18 satte gerçekleşti. Proparjil alkolden elde edilmiş esterik

yapıdaki PEG için dönüşüm 50 ^{o}C de 8 saat olarak bulundu, ancak oda sıcaklığında kimyasal miktarı iki katna çıkarılmasına rağmen etkin bir dönüşüm gözlemlenemedi.

Bu çalışmaların sonunda organik kimyada yaygın olarak kullanılan alkinlere, bir civa tuzu varlığında asit katalizörlüğünde su katılması reaksiyonu olan oksimerkürasyon reaksiyonunun polimer kimyasında da uygun kimyasallar kullanılarak etkin bir dönüşüm sağlayabileceği kanıtlanmış oldu.

1. INTRODUCTION

Postpolymerization modification of functional polymers has proven to be a general route to materials that might otherwise be difficult or impossible to make by direct polymerization routes. General classes of postpolymerization modification reactions include main-chain modification, for example chlorination of natural rubber and polybutadiene to yield nonflammable materials; side-group modification, for example hydrolysis of poly(vinyl acetate) to poly(vinyl alcohol); and crosslinking reactions, for example vulcanization of rubber.1 The specific reactivity of alkyne functional groups, which can be added to polymer systems by postpolymerization sidegroup modification reactions, allows the preparation of a broad range of polymer-based materials. Addition of thiols, silanes,or aluminum hydrides to alkyne-functional polymers has been shown to lead to new polymers with alkenyl sulfide, alkenylsilane, or alkene moieties. Alkyne groups have been used in cycloaddition reactions to generate low dielectric constant materials for microprocessor and other semiconductor devices.

The application of highly efficient "click" reactions for postpolymerization modification of pendant or end-group alkynes by cyclization reactions with azides has enabled the preparation of a range of functional polymers. Alkyne-containing

polymers have also been employed as anchors for selective incorporation of metallic species through alkyne-specific reactions with inorganic species such as dicobalt octacarbonyl.

In polymer chemistry, click reactions are valued both for polymer growth and for modification of the polymer after the polymerisation process.Traditional approaches to designer polymers have involved controlled incorporation of functional moieties.Modification of the polymeric frame has obvious attractions, however, and the ability to control architecture and degree of functionalisation by click-type chemistry is very attractive.The limitations of the copper-promoted reaction, and the masked synthetic potential of the isoxazole ring, prompted us and others to explore

the potential of nitrile oxides as click cycloaddition partners for formation supramolecular constructs or polymers of predefined structure.

In polymer chemistry, ketone end functionalized polymers are favoured due to their ability to give specific imine reactions and being talked about human life click chemistry can not be suitable way to functionalizing of biocompatable polymers. For obtain biocompatle and ketone end-functionalized groups from alkynes, oxymercuration reactions which known as catalytic reactions of hydration of alkynes is a suitable pathway [1-8].

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2. THEORETICAL PART

2.1 Alkynes in Polymer Chemistry

In organic chemistry, an alkyne is an unsaturated hydrocarbon containing at least one carbon-carbon triple bond between two carbon atoms.The simplest acyclic alkynes with only one triple bond are shown with the general chemical formula C_nH_{2n-2}. Like other hydrocarbons, alkynes are generally hydrophobic but tend to be more reactive.

According to Ferdinand Bohlmann, the first naturally occurring acetylenic compound, dehydromatricaria ester, was isolated from an *Artemisia* species in 1826. In the nearly two centuries that have followed, well over a thousand naturally occurring acetylenes have been discovered and reported. Polyynes, a subset of this class of natural products, have been isolated from a wide variety of plant species, cultures of higher fungi, bacteria, marine sponges, and corals.Some acids like tariric acid contains an alkyne group. Diynes and triynes, species with the linkage RC≡C-C≡CR' and RC≡C-C≡C-C≡CR' respectively, occur in certain plants (*Ichthyothere*, *Chrysanthemum*, *Cicuta*, *Oenanthe* and other members of the Asteraceae and Apiaceae families). Some examples are cicutoxin, oenanthotoxin, falcarinol and carotatoxin. These compounds are highly bioactive, e.g. as nematocides.1-Phenylhepta-1,3,5-triyne is illustrative of a naturally occurring triyne.

Alkynes occur in some pharmaceuticals, including the contraceptive norethynodrel. A carbon–carbon triple bond is also present in marketed drugs such as the antiretroviral Efavirenz and the antifungal Terbinafine. Molecules called ene-diynes feature a ring containing an alkene ("ene") between two alkyne groups ("diyne"). These compounds, e.g. calicheamicin, are some of the most aggressive antitumor drugs known, so much so that the ene-diyne subunit is sometimes referred to as a "warhead." Ene-diynes undergo rearrangement via the Bergman cyclization, generating highly reactive radical intermediates that attack DNA within the tumor.

Alkynes are characteristically more unsaturated than alkenes. The reactions of alkynes closely parallel the reactions of alkenes. Addition reactions are typical. In these reactions, the C≡C triple bond is converted into a C=C double bond. The alkenes formed from these reactions can undergo a tautomerization (see the hydration reactions below) or react further to produce alkane derivatives

Thus they add two equivalents of bromine whereas an alkene adds only one equivalent in the reaction. Other reactions are listed below. In some reactions, alkynes are less reactive than alkenes. For example, in a molecule with an -ene and an -yne group, addition occurs preferentially at the -ene. Possible explanations involve the two π-bonds in the alkyne delocalising, which would reduce the energy of the π-system or the stability of the intermediates during the reaction. They show greater tendency to polymerize or oligomerize than alkenes do. The resulting polymers, called polyacetylenes (which do not contain alkyne units) are conjugated and can exhibit semiconducting properties [9-21].

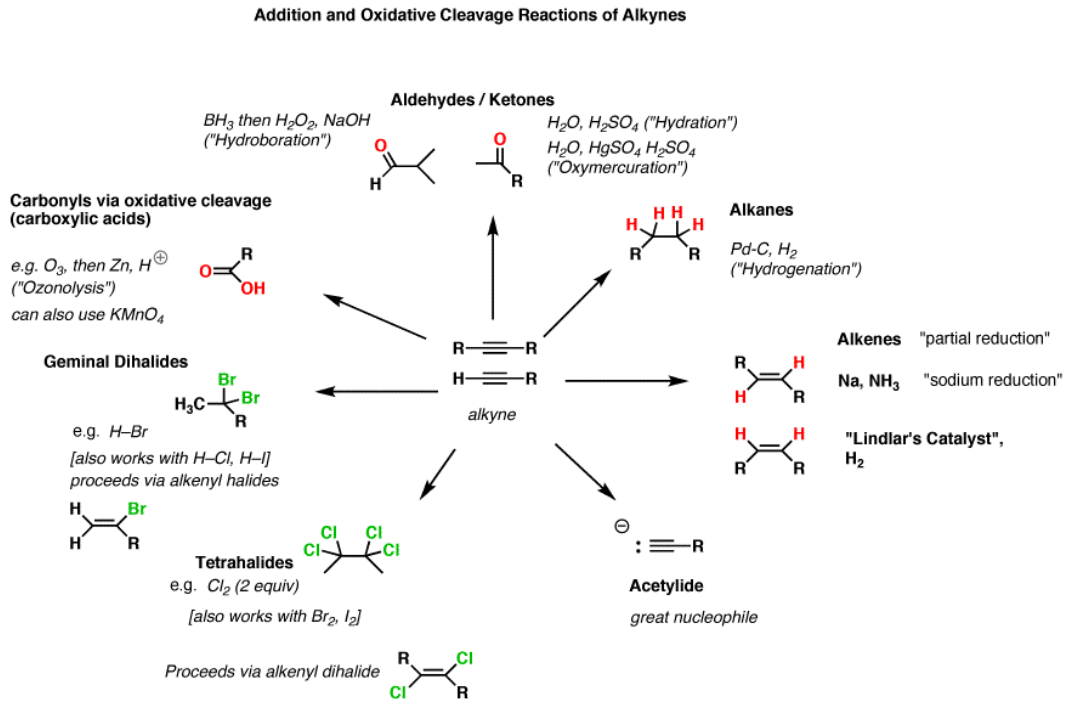
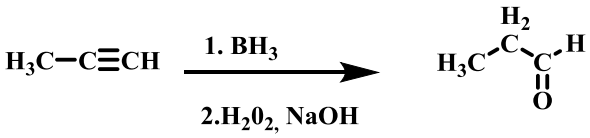


Figure 2.1: Addition and Oxidative Cleavage Reactions of Alkynes.

2.1.1 Hydroboration of alkynes

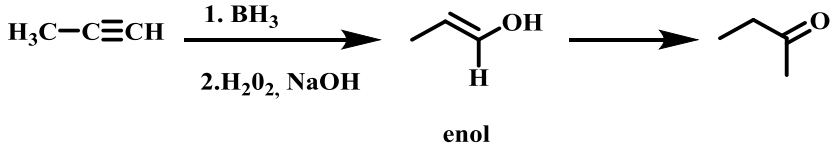
The hydroboration–oxidation reaction is a two-step organic reaction that converts an alkyne into a ketone. The hydrogen and hydroxyl group are added in a syn addition leading to cis stereochemistry. Hydroboration–oxidation is an anti-Markovnikov reaction, with the hydroxyl group attaching to the less-substituted carbon. The reaction was first reported by Herbert C. Brown in the late 1950s and it was recognized in his receiving the Nobel Prize in Chemistry in 1979. In order to prevent hydroboration across both the pi-bonds, a bulky borane like disiamyl (di-sec-iso-amyl) borane is used.

Diborane reacts readily with alkynes, but the formation of substituted alkene products leaves open the possibility of a second addition reaction. A clever technique for avoiding this event takes advantage of the fact that alkynes do not generally suffer from steric hindrance near the triple-bond (the configuration of this functional group is linear). Consequently, large or bulky electrophilic reagents add easily to the triple-bond, but the resulting alkene is necessarily more crowded or sterically hindered and resists further additions. The bulky hydroboration reagent needed for this strategy is prepared by reaction of diborane with 2-methyl-2-butene, a highly branched alkene. Because of the alkyl branching, only two alkenes add to a BH_3 moiety (steric hindrance again), leaving one B-H covalent bond available for reaction with an alkyne, as shown below. The resulting dialkyl borane is called disiamylborane, a contraction of di-secondary-isoamylborane (amyl is an old name for pentyl). The general form of the reaction is as follows (2.1):



(2.1)

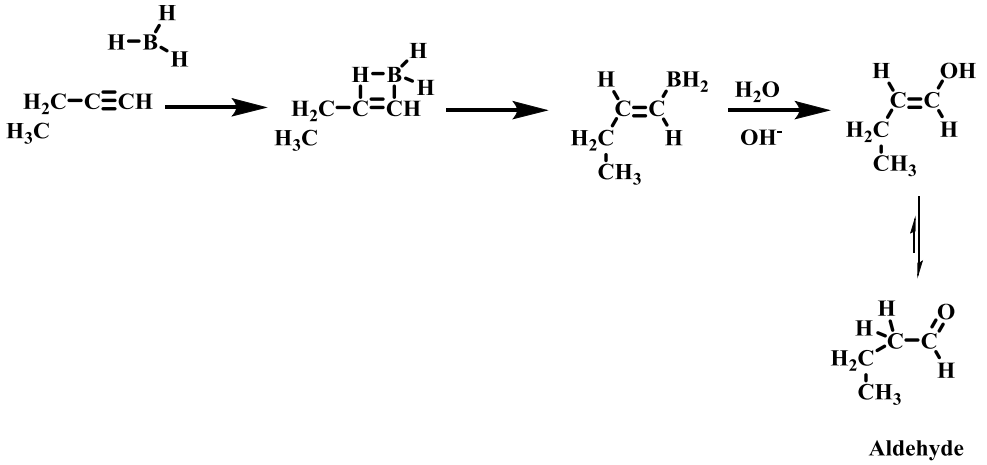
This reaction also proceeds through an enol which tautomerizes to the aldehyde. Note that the oxygen ends up on the least substituted carbon of the double bond(2.2).



enol

(2.2)

An important application of disiamylborane is its addition reaction to terminal alkynes. As with alkenes, the B-H reagent group adds in an apparently anti-Markovnikov manner, due to the fact that the boron is the electrophile, not the hydrogen. Further addition to the resulting boron-substituted alkene does not occur, and the usual oxidative removal of boron by alkaline hydrogen peroxide gives an enol which rapidly rearranges to the aldehyde tautomer. Thus, by the proper choice of reagents, terminal alkynes may be converted either to methyl ketones (mercuric ion catalyzed hydration) or aldehydes (hydroboration followed by oxidation) (2.3).



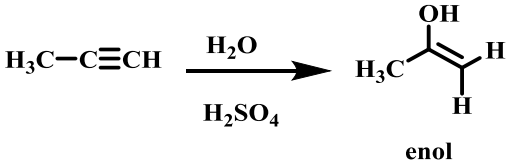
(2.3)

Hydroboration of internal alkynes is not a particularly useful procedure because a mixture of products will often be obtained, unless the triple-bond is symmetrically substituted. Mercuric ion catalyzed hydration gives similar results [22-28].

2.1.2 Hydration of alkynes and oxymercuration

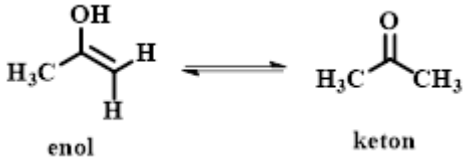
Resulting product in such reaction is a ketone, which is the tautomer of the highly substitued enol, in acidic media that obeys the Markovnikov rule of substitution, which is also the key part of the regioselectivity. Important points in oxymercuration reactions are can be stated as the protons are donated by the acid catalyst and water is the nucleophile of the reaction. Also, mercury salts play an important role in this reaction, because it highly improves the rate of the reaction as the catalyst as well.

Absence of mercury salts, hydration reactions occur so slowly but with same mechanism with oxymercuration.Reaction proceeds in two steps. First one is enol formation (2.4).



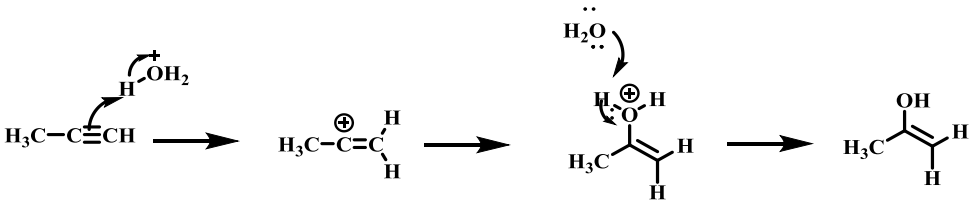
(2.4)

Second step is conversion of enol to ketone through tautomerism (2.5).



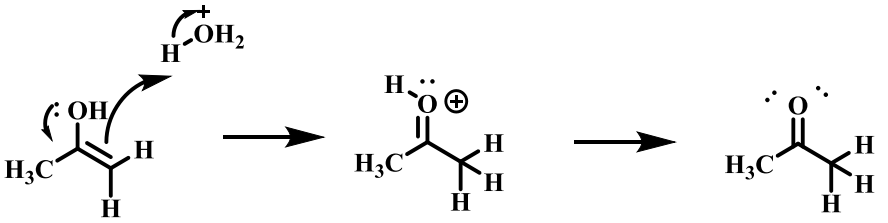
(2.5)

Step 1- Enol Formation



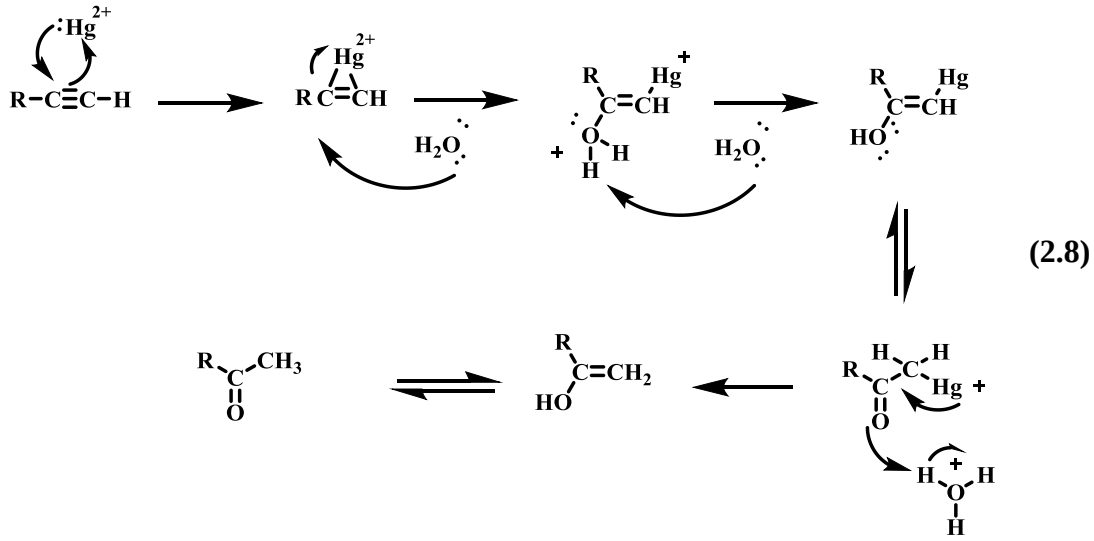
(2.6)

Step 2- Tautomerization



(2.7)

Oxymercuration reactions start with the protonation of the alkyne's π bonds, by the acid acting as a Lewis Acid, hence attack of the water as the nuclephile resulting with the formation of oxonium ion. This step continues with deprotonation of the structure and regaining the acid catalyst yet giving the unstable tautomer- enol and continues with reprotonation of the carbon, giving the oxonium ion by the aid of the oxygen's electrons and finishes with deprotonation- resulting in ketone form. It is also possible to observe this mechanism in 2.8 [29-45].



(2.8)

2.1.3 Hydrogenation of alkynes

Hydrogenation reactions in which hydrogen gas is passed over a metal powder and forming with a C-H sigma bond, breaking the olefinic C=C bond, and awarded with a Nobel Price, in 1912, to Paul Sabatier. This discovery was so phenomenol that it is still being used nowadays, in very wide scale.

Hydragenation can undergo with the palladium, rhodium, nickel and platinum catalyst and forming alkenes first, alkanes last yet with deactivation of the catalyst, it can give alkenes as a resulting product.

Since alkene is an intermediate product while reduction with metal catalyst, it is hard to isolate this product. In order to obtain alkene as the main product of the hydrogenation reaction, deactivated Pd catalyst known as Lindlar's catalyst is used fort his purpose. This catalyst is mainly prepared by the of Pd with quinoline and lead acetate, which poisons the metal and decrease its reactivity.

Reduction with Lindlar's catalyst is a regioselective reaction since alkyne approaches the surface of the metal hence substituing from one side resulting with "syn" product.

Another regioselective reaction is hydrogenation with sodium in ammonia catalyst system which results in giving "trans" product(2.9) [46-50].

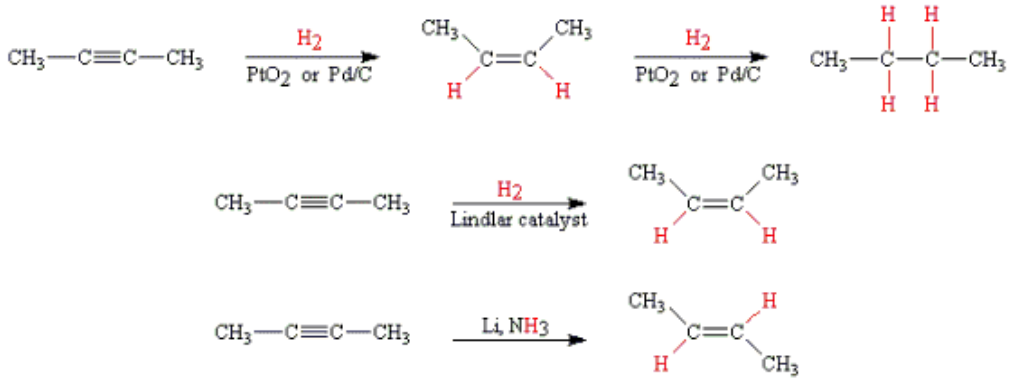
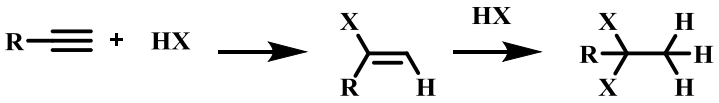


Figure 2.2: Hydrogenation of alkynes

2.1.4 Electrophilic addition of hydrogen halides and halides

It is expected to observe the same electrophilic halide addition, as in the alkenes, in alkyne chemistry. But it is found that, addition of such structures to alkynes are resulted with a more exothermic reaction also having the reaction dramatically slower than in the alkenes. Yet, all the regioselectivity rules are applied within these addition reactions. Also, when a halide addition is complete to an alkyne, it can still undergo to another addition since it still has olefinic C=C bond and fort his reason, even if the reaction is kept under control, there still will be two times substitued alkanes.

Addition of a hydrogen halide follows the Markovnikov rule which hydrogen bonds with the carbon that has more hydrogens and halide to bond with the less hydrogens. This indicates that protonation of the olefinic bond occurs in more hydrogenated carbon. Also excess hydrogen halide addition results in geminal dihaloalkene product (2.9).

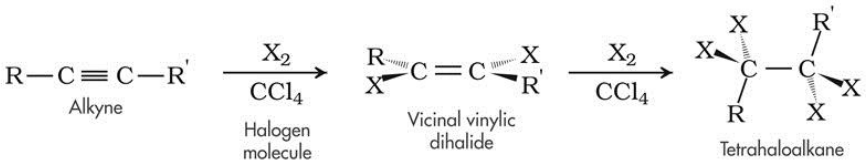


(2.9)

X: Cl, Br

Halogenation of an alkyne occurs in anti Marvoknikov rule, which results in giving anti product. Also mechanism of this reaction undergoes with the cyclic halonium ion. When halogen approaches the olefinic bond, it polarizes and triple bond attacks the polarized halogen atom and resultin in a cyclic halogen- carbon bond and giving

a carbocation. While this cyclization occuring, other halogen acts as the nuclephile and attacks this complex from the carbocation which results in giving an “anti” alkene. This reaction’s mechanism is shown in (2.10) [51-52].

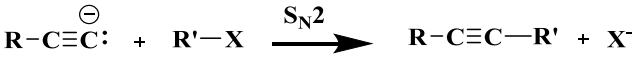


(2.10)

2.1.5 Nucleophilic reactions of alkynes

Terminal alkynes can be used in substitution reactions as a nucleophile. This means that terminal alkyne’s terminal hydrogen atom is acidic hence when treated with a base, it forms its conjugated base that is also known as acetylide anion. Stability of such ion comes from the dominance of s character of the olefinic bond which is also directly related to the hybridization type of the carbon, which is sp. Acetylide anions are generally prepared with $NaNH_2$ which is a relatively strong base(2.11).

(2.11)

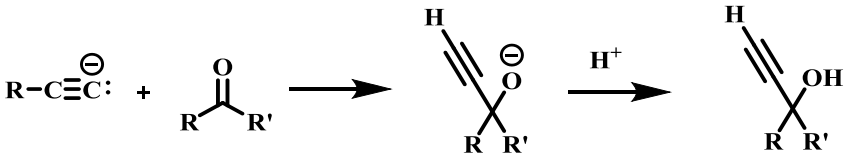


(2.12)

Since alkynes have strong basity and nucleophility, due to the reasons explained above, they can easiliy displace halides or good leaving groups in substitution reactions. Yet only primary alkyl halides can substitute easily and form alkylated alkyne. Other than that, secondary and tertiary alkyne halides are more likely to give elimination reactions.

Also, alkynes can be used in condensation reactions with carbonyl groups, especially aldehydes and ketones. Condensation between these to reactant results with a alkyne alcohol. But, having asymmetrical ketone results with a rasemic mixture of products,

unless asymmetrical catalayst is used. Resulting alkyne alcohol can be further modified, due to reactiveness of the alkyne, and can give substitued ketones and aldehydes[52].



(2.14)

2.2 Alkyne Reactions in Polymer Chemistry

2.2.1 Copper (I) catalyzed azide-alkyne cycloaddition (CuAAC)

The thermal reaction between organic azides and alkynes has been known for more than a century, the first 1,2,3-triazole being synthesized by A. Michael from phenyl azide and diethyl acetylenedicarboxylate in 1893. The reaction has been investigated in detail by Huisgen and coworkers in the middle of the 20th century in the course of their studies of the larger family of 1,3-dipolar cycloaddition reactions. The Huisgen 1,3-dipolar cycloaddition reaction of alkynes and organic azides has gained considerable the most attention of any click reaction since 2001, CuAAC was realized independently by Fokin and Sharpless, and Meldal in 2002 Theconventional Huisgen cycloaddition of azides and alkynes is not appropriate the criterion of a click reaction, because of the high temperature necessity (>110 °C) and the lack of regiospecificity which produce products with a racemic mixture of 1,4-triazole and 1,5-triazole products as seen in Figure 2.3. The copper catalyzed reaction allows to proceed much faster under much milder conditions and produces only one isomer which is 1,4-regiosomer triazole The great success of the Cu (I) catalyzed reaction is actually a virtually quantitative, very robust, insensitive, general, and orthogonal ligation reaction.

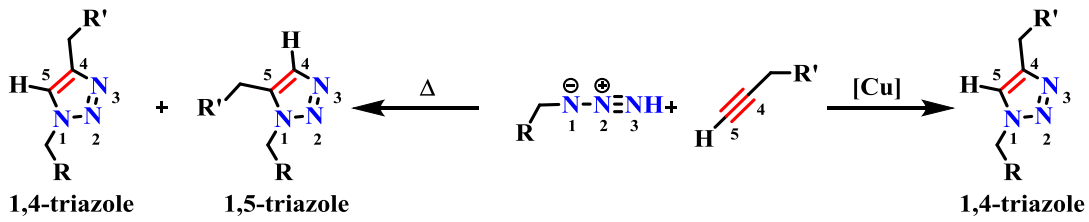


Figure 2.3 : Huisgen's 1,3-dipolar cycloaddition and CuAAC.

When the mechanism is catalyzed, Cu (I) can easily overcome the activation barrier as a result of this difference the CuAAC reaction rate is increased by a factor of 10^7 relative to the Huisgen 1,3-dipolar cycloaddition, so it considerably fast at and below room temperature. The reaction is not significantly affected by the steric and electronic properties of the functional groups attached to the azide and alkyne centers, and the CuAAC is fairly general with a broad range of alkynes and azides.

In fact, the discovery of Cu (I) as catalyst has a great importance which efficiently and regiospecifically combines terminal alkynes and azides under mild conditions. On the other hand, Fokin and Sharpless reported that only 1,5-disubstituted 1,2,3-triazole was obtained from terminal alkynes when the catalyst switched from Cu(I) to ruthenium(II)

Although CuAAC reaction was initially postulated in general for organic synthesis, this strategy has also an enormous potential in polymer chemistry. The importance of CuAAC in polymer chemistry is the synthesis of functionalized polymers and the construction of polymers with well-defined architectures. Since the first report of click chemistry in polymer science which is published by Hawker, Sharpless and coworkers, the construction of well-defined and complex macromolecular architectures via click chemistry has been used in many study and the number of publications in this field has increased dramatically within the years [52-62].

2.2.2 Thiol-yne reaction

In general, click reactions have many advantages such as giving high yield without side products, simplicity of execution, trivial or non-existent separation of required products and orthogonality with other reactions. In addition, thiol-ene and thiol-yne reactions are reported as they provide these advantages. Apart from those, nearly homogenous cross-linked polymers can be obtained in from such reactions.

Alkynes are easy to synthesis so they are more desirable structures hence being in high yields in CuAAC, it is thought that alkyne reactions should be extended more, which lead to other types of highly efficient reactions, such as “Thiol-yne” reaction. Thiol-yne reaction also extends the opportunties of thiol-ene but gathering more substances to use and different results at the end. Network film formation, polymer functionalization and even in hydrogels, thiol-yne reaction can be used. Thiol-yne reactions can undergo both with radicalic mediators or metallic catalysts.

Metal catalysts that are used in thiol-yne reactions can give different products as the metal changes. For example, $Pd(OAc)_2$ generally gives Markovnikov products but on the other hand, Ruthenium based catalyst give anti-Marvoknikov products. Also, sometimes an isomerization reaction occurs and can give vinylthioethers by the metals Pd,Pt and Ni.

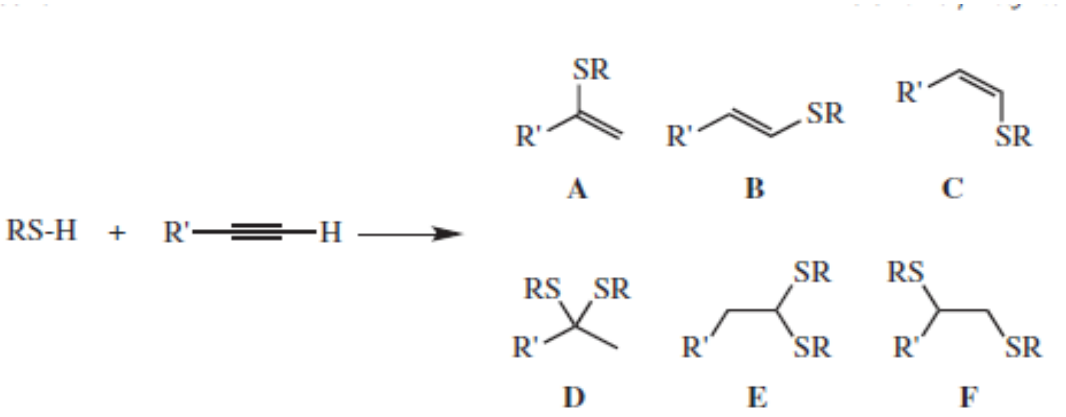


Figure 2.4 : Products of thiol-yne reactions

Radical thiol-yne reaction gives 1,2 addition product as shown in Figure 2.4 .This spesific reaction is done by using two or more equivalents of the thiol and generally as known as thiol-yne reaction. Thiol-yne and thiol-ene follows each other in this reaction mechanism. At first, thiyl radicals are generated photochemically or thermally. In presecence of an alkyne, resulting situation is addition of this radical to the alkyne's triple bond, giving a vinyl thioether radical. To continue with,between vinyl thioether radical and an additional thiol, chain transfer reaction occurs and gives the vinyl thiother intermediate product, due to the sensitivity of the vinyl thioether to the thiols. Resulting intermediate is highly reactive to the thiyl radicals hence reaction continues with the addition of the thiyl radical to the vinyl thioether's double bond. This will cause another radical to generate therefore continues with another chain transfer reaction in order to give the resultin 1,2-addition products. It can be noted that, as a result of hydrothiolation, a chiral carbon is genarated and this carries a biological importance (Figure 2.5) [63-64].

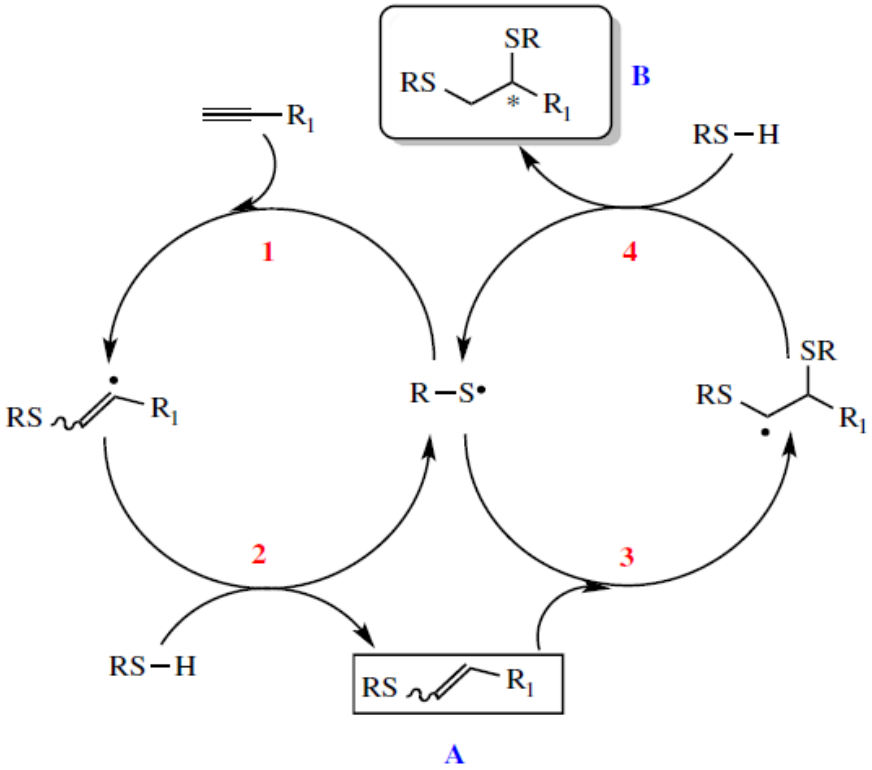


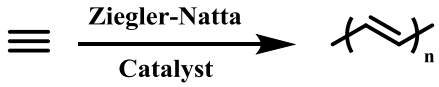
Figure 2.5: Generally accepted mechanism for the double hydrothiolation of a terminal alkyne bond under radical conditions.

2.2.3 Polyacetylene synthesis

Polyacetylene usually refers to an organic polymer with the repeating unit $(C_2H_2)n$. The name refers to its conceptual construction from polymerization of acetylene to give a chain with repeating olefin groups. This compound is conceptually important as the discovery of polyacetylene and its high conductivity upon doping helped to launch the field of organic conductive polymers. The high electrical conductivity discovered by Hideki Shirakawa, Alan Heeger, and Alan MacDiarmid for this polymer led to intense interest in the use of organic compounds in microelectronics (organic semiconductors). This discovery was recognized by the Nobel Prize in Chemistry in 2000. Early work in the field of polyacetylene research was aimed at using doped polymers as easily processable and lightweight "plastic metals." Despite the promise of this polymer in the field of conductive polymers, many of its properties such as instability to air and difficulty with processing have led to avoidance in commercial applications.

Compounds called polyacetylenes also occur in nature, although in this context the term refers to polyynes, compounds containing multiple acetylene groups ("poly" meaning many), rather than to chains of olefin groups

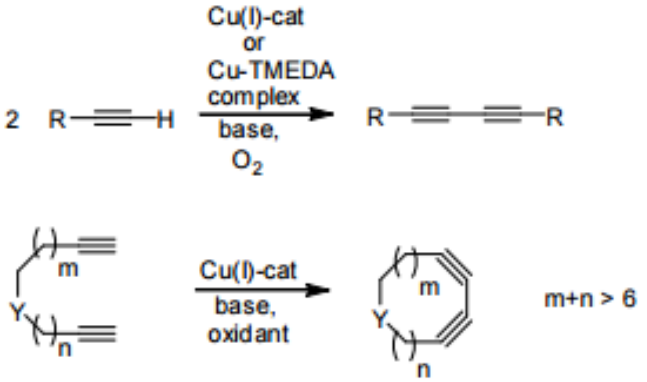
A variety of methods have been developed to synthesize polyacetylene, from pure acetylene as well as other monomers. One of the most common methods uses titanium and aluminum catalysts, known as Ziegler-Natta catalysts, with gaseous acetylene(2.15). This method allows control over the structure and properties of the final polymer by varying temperature and catalyst loading. Mechanistic studies suggest that this polymerization involves metal-insertion into the triple bond of the monomer [64-65].



(2.15)

2.2.4 Glaser coupling

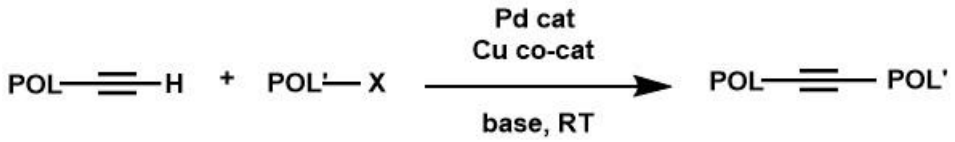
The Glaser coupling is a self coupling reaction of terminal alkynes to yield the symmetric or cyclic bisacetylenes using cuprous salts (CuCl and CuBr) and an additional oxidant i.e. oxygen (O_2). Hay coupling is an alternative to Glaser coupling and many advantages as compared to Glaser coupling. In Hay coupling copper-tetramethylethylenediamine (Cu/TMEDA) complex employed as a catalyst, which is soluble in a wide range of solvents(2.16) [66].



(2.16)

2.2.5. Sonogashira coupling

The Sonogashira reaction is a cross-coupling reaction of terminal alkynes with aryl or vinyl halides in presence of palladium catalyst, copper (I) salts (co-catalyst) and a base. As compared to other coupling reaction, it requires anhydrous and anaerobic conditions. Recent, developments of Sonogashira reaction avoids these limitations(2.17) [67].



(2.17)

3. EXPERIMENTAL PROCEDURE

3.1 Materials and Chemicals

Poly(ethylene glycol) monomethylether (Me-PEG-OH,M_n = 2000 , Fluka) were dried by azeotropic distillation with anhydrous toluene. Tetrahydrofuran (THF, 99.8%, J.T. Baker) was dried and distilled from benzophenone-Na. Dichloromethane (CH_2Cl_2, 99%, J. T. Baker) was dried and distilled over and P_2O_5. 2,4-Dinitrophenylhydrazine (97%, Aldrich, p-Toluenesulfonic acid monohydrate (98.5%, Aldrich), Trifluoroacetic acid (99%, Aldrich), *N,N'*-dicyclohexylcarbodiimide (DCC, 99%, Aldrich), 4-dimethylaminopyridine (DMAP, 99%, Aldrich), 4-pentynoic acid (98%, Aldrich), Mercury(II) Sulfate (Aldrich, 99.0%) were used as recieved. Diethyl ether (99.7%, Aldrich) and methanol (99.8 %, Aldrich) were used without further purification.

3.2 Instrumentation

^1H and ^{12}C NMR spectra were recorded in $CDCl_3$ with $Si(CH_3)_4$ as internal standard, using an Agilent VNMRS 500 (500 MHz) instrument. The conventional Gel Permeation Chromatography (GPC) measurements were carried out with an Agilent instrument (Model 1100) consisting of a pump, refractive index, and UV detectors. Four Waters Styragel columns (HR 5E, HR 4E, HR 3, HR 2), (4.6 mm internal diameter, 300 mm length, packed with 5 μm particles) were used in series. The effective molecular weight ranges were 2000-4.000.000, 50-100.000, 500-30.000, and 500–20.000, respectively. THF was used as eluent at a flow rate of 0.3 mL/min at 30°C. Toluene was used as an internal standard. The molecular weights of the polymers were calculated on the basis of linear PS and PMMA standards (Polymer Laboratories). UV measurements were recorded using VWR UV-1600 PC spectrophotometer in CH_2Cl_2. FT-IR spectra were recorded on an Agilent Technologies Cary 630 FTIR instrument over the range 4000- 5000 cm^{-1}.

3.3 Synthetic Procedures

Alkyne functionalized PEG**(1),** Ketone functionalized PEG**(2)** and Hydrazine functionalized PEG**(3)** were synthesized according to literature procedures.

3.3.1 Synthesis of alkyne end-functionalized PEG (Alkyne-PEG from 4-Pentynoic acid) (1)

Me-PEG (M_n = 2000) (2 g, 1 mmol) was dissolved in 25 mL of CH_2Cl_2 . 4-Pentynoic acid (0.294 g, 3.00 mmol) and DMAP (0.12 g, 1.0 mmol) was added successively. DCC (0.62 g, 3.0 mmol) was dissolved in 5 mL of CH_2Cl_2 was added to the solution in one portion. The reaction mixture was stirred overnight at room temperature. It was filtered, evaporated and the remaining product was dissolved in THF and precipitated into diethyl ether. This procedure was repeated two times. Finally, the polymer was dried for 24 h in a vacuum oven at 40 ^oC. Yield: 1.9 g (90%). ^1H NMR ($CDCl_3$, δ) 4.25 (t, 2H, PEG-OCH_2CH_2OC=O), 3.89 (t, 2H, PEG-OCH_2CH_2OC=O), 3.67-3.62 (m, 4H, -OCH_2CH_2, repeating unit of PEG), 3.54 (t, 2H, CH_3O-CH_2CH_2-O), 3.36 (s, 3H, PEG-OCH_3). 2.56-2.48 (m, 4H, CH≡CCH_2CH_2C=O), 1.97 (t, 1H, C*H*≡CCH_2CH_2C=O).

3.3.2 Synthesis of ketone end-functionalized PEG (Ketone-PEG) (2)

In a 25 mL of Schlenk tube, 1(0.4 g, 0.2 mmol) was dissolved in 5 mL THF. HgSO4 (0.015 g, 0.05 mmol), p-TSA (0.01 g, 0.05 mmol) and water (2 µL, 0.1mmol) were added to reaction mixture respectively. And the resulting solution was stirred for several hours at 50^oC. After cooling the mixture ambient temperature, solvent was removed under reduced pressure (max 40^oC), and residue was dissolved in 30 mL of CH_2Cl_2 and washed with 10 mL of water. The organic layer was separated, dried over Na_2SO_4, filtered and evaporated. The remaining product was dissolved in THF and precipitated into diethyl ether. Finally, the polymer was dried for 24 h in a vacuum oven at 40 ^oC. ^1H NMR ($CDCl_3$, δ) 4.25 (t, 2H, PEG-OCH_2CH_2OC=O), 3.89 (t, 2H, PEG-OCH_2CH_2OC=O), 3.67-3.62 (m, 4H, -OCH_2CH_2, repeating unit of PEG), 3.54 (t, 2H, CH_3O-CH_2CH_2-O), 3.36 (s, 3H, PEG-OCH_3). 2.76-2.62 (m, 4H, O=$CCH_3CH_2CH_2C$=O), 2.2 (t, 3H, O=$CCH_3CH_2CH_2C$=O).

3.3.3 Synthesis of hydrazine end-functionalized PEG (Hydrazine-PEG) (3)

2(0.125 g, 60 μmol) was dissolved in 4 mL THF and after that, 200 μL Trifluoro acetic acid (%5 volume of THF) and 2,4-Dinitrophenylhydrazine (0.12 g, 600 μmol) were added subsequently. The reaction mixture was stirred for overnight at room temperature. It was purified by column chromatography (silica gel) using THF to seperate unreacted 2,4-Dinitrophenylhydrazine and a MeOH/DCM mixture (2/8, v/v) eluent to collect the product. After evaporation of solvent, the remaining product was dissolved in THF and precipitated into diethyl ether. Finally, the product was dried for 24 h in a vacuum oven at 40 ^{o}C. ^{1}H NMR ($CDCl_3$, δ) 4.25 (t, 2H, PEG-OCH_2CH_2OC=O), 3.89 (t, 2H, PEG-OCH_2CH_2OC=O), 3.67-3.62 (m, 4H, -OCH_2CH_2, repeating unit of PEG), 2.12 (s, 3H, $CH_3CCH_2CH_2C$=O), 2,75 (m, 4H, $CH_3CCH_2CH_2C$=O), 11.08 (s, H, C=N$NHC_5H_3(NO_2)_2$)

3.3.4 Synthesis of alkyne end functionalized ether-PEG (from propargyl bromide) (4)

In a 250 mL two-necked round bottom flask were added to a solution of Me-PEG (M_n = 2000) (5 g, 2.5 mmol) in 150 mL THF and NaH (60% w/w in mineral oil) (0.3 g, 7.5 mmol) at room temperature. The mixture was stirred for 30 minutes under nitrogen.After that, propargyl bromide solution (80 % in toluene) (1.115 mL,10 mmol) was added slowly and finally the final rection mixture refluxed for 12 hours. After cooling the mixture to ambient temperature, it was filtered and solvent was removed under reduced pressure, and residue was dissolved in 150 mL of CH_2Cl_2 and washed with 3 × 100 mL of water. The organic layer was separated, dried over Na_2SO_4 and filtered. After evaporation of solvent, the remaining product was dissolved in THF and precipitated into diethyl ether. Finally, the product was dried for 24 h in a vacuum oven at 40 ^{o}C. Yield: 4.8 g (95%). ^{1}H NMR ($CDCl_3$, δ) 4.21 (t, 2H, PEG-$OCH_2CH_2OCH_2C$≡CH), 3.67- 3.62 (m, 4H, -OCH_2CH_2, repeating unit of PEG), 3.36 (s, 3H, PEG-OCH_3)., 2.44 (t, 1H, C*H*≡CCH_2CH_2C=O).

3.3.5 Synthesis of ketone end-functionalized ether-PEG (Ketone-PEG) (5)

In a 25 mL of Schlenk tube, **4** (0.4 g, 0.2 mmol) was dissolved in 5 mL THF. HgSO4 (0.015 g, 0.05 mmol), p-TSA (0.01 g, 0.05 mmol) and water (2 μL, 0.1mmol) were added to reaction mixture respectively. And the resulting solution was stirred for

several hours at 50°C. After cooling the mixture ambient temperature, solvent was removed under reduced pressure (max 40°C), and residue was dissolved in 30 mL of CH_2Cl_2 and washed with 10 mL of water. The organic layer was separated, dried over Na_2SO_4, filtered and evaporated. The remaining product was dissolved in THF and precipitated into diethyl ether. Finally, the polymer was dried for 24 h in a vacuum oven at 40 °C. ^{1}H NMR ($CDCl_3$, δ) 4.21 (t, 2H, PEG-$OCH_2CH_2OCH_2C{\equiv}CH$), 3.67- 3.62 (m, 4H, -$OCH_2CH_2$, repeating unit of PEG), 3.36 (s, 3H, PEG-OCH_3)., 2.44 (t, 1H, $CH{\equiv}CCH_2CH_2C{=}O$)., 2.2 (t, 3H, $O{=}CCH_3CH_2CH_2C{=}O$).

3.3.6 Synthesis of carboxylic acid end -functionalized-PEG (PEG-OH) (6)

In a 250 mL round bottom flask Me-PEG (M_n = 2000) (5 g, 2.5 mmol) was dissolved in 100 mL of CH_2Cl_2 . 4-Dimethylaminopyridine (0.46 gram, 3.75 mmol), Succinic anhydride (0.5 gram, 5 mmol) and Triethylamine (1.75 mL, 12.5 mmol) was added respectively and the reaction mixture was stirred for overnight at room temperature. Then poured into ice-cold water and extracted with CH_2Cl_2. The organic phase was washed with 1 M HCl, dried over Na_2SO_4 and concentrated. The product was precipitated in diethyl ether to give 6 as white crystal.

3.3.7 Synthesis of alkyne end-functionalized ester-PEG (PEG-ester from propargyl alcohol) (7)

6 (4.4 g, 2.1 mmol) was dissolved in DCM and propargyl alcohol (400 µL, 6.3 mmol), DMAP (0.27 g, 2.1 mmol) was added successively. DCC (1.36 g, 6.3 mmol) dissolved in 20 mL of CH_2Cl_2 was added to the reaction mixture and the solution was stirred at room temperature for overnight. It was filtrated and solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel) using EtOAC/ DCM (1/1, v/v) and a MeOH/DCM mixture (2/8, v/v) eluent to collect the product, respectively. After evaporation of solvent, the remaining product was dissolved in THF and precipitated into diethyl ether. Finally, the product was dried for 24 h in a vacuum oven at 40 °C. ^{1}H NMR ($CDCl_3$, δ) 4.25 (t, 2H, PEG-$OCH_2CH_2OC{=}O$), 3.89 (t, 2H, PEG-$OCH_2CH_2OC{=}O$), 3.67-3.62 (m, 4H, -OCH_2CH_2, repeating unit of PEG), 3.54 (t, 2H, CH_3O-CH_2CH_2-O), 3.36 (s, 3H, PEG-OCH_3). 2.68 (m, 4H, $CH{\equiv}CCH_2CH_2C{=}O$), 1.94 (t, 1H, $CH{\equiv}C{=}OCH_2OC{=}O$), 4.7 (s, 2H, $CH{\equiv}C{=}OCH_2OC{=}O$).

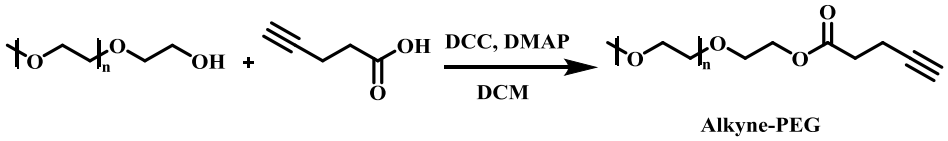
3.3.8 Synthesis of ketone end-functionalized ester-PEG (Ketone-PEG) (8)

In a 25 mL of Schlenk tube,**7** (0.4 g, 0.2 mmol) was dissolved in 5 mL THF. HgSO4 (0.015 g, 0.05 mmol), p-TSA (0.01 g, 0.05 mmol) and water (2 μL, 0.1mmol) were added to reaction mixture respectively. And the resulting solution was stirred for several hours at 50°C. After cooling the mixture ambient temperature, solvent was removed under reduced pressure (max 40°C), and residue was dissolved in 30 mL of CH_2Cl_2 and washed with 10 mL of water. The organic layer was separated, dried over Na_2SO_4, filtered and evaporated. The remaining product was dissolved in THF and precipitated into diethyl ether. Finally, the polymer was dried for 24 h in a vacuum oven at 40 °C. ^{1}H NMR ($CDCl_3$, δ) 4.25 (t, 2H, PEG-OCH_2CH_2OC=O), 3.89 (t, 2H, PEG-OCH_2CH_2OC=O), 3.67-3.62 (m, 4H, -OCH_2CH_2, repeating unit of PEG), 3.54 (t, 2H, CH_3O-CH_2CH_2-O), 3.36 (s, 3H, PEG-OCH_3). 2.68 (m, 4H, CH≡CCH_2CH_2C=O), 2.16 (s, 3H, CH_3C=OCH_2OC=O), 4.7 (s, 2H, CH≡C=OCH_2OC=O).

4. RESULTS AND DISCUSSION

4.1 Preparation of Alkyne-PEG(1) (from 4-Pentynioc acid)

Alkyne-PEG was obtained from a reaction of Me-PEG with 4-pentynoic acid at room temperature as depicted in reaction 4.1



(4.1)

^{1}H NMR spectrum revealed the structure of Alkyne-PEG (4.1), displaying characteristic peaks such as a triplet (C*H*≡C-) at 1.9 ppm and a multiplet (CH≡CCH_2CH_2C=O) at 2.5 ppm. $M_{n,NMR}$ of Alkyne-PEG was calculated from a ratio of peak areas of PEG repeating unit at 3.64 ppm and CH≡CCH_2CH_2C=O end group at 2.5 ppm.

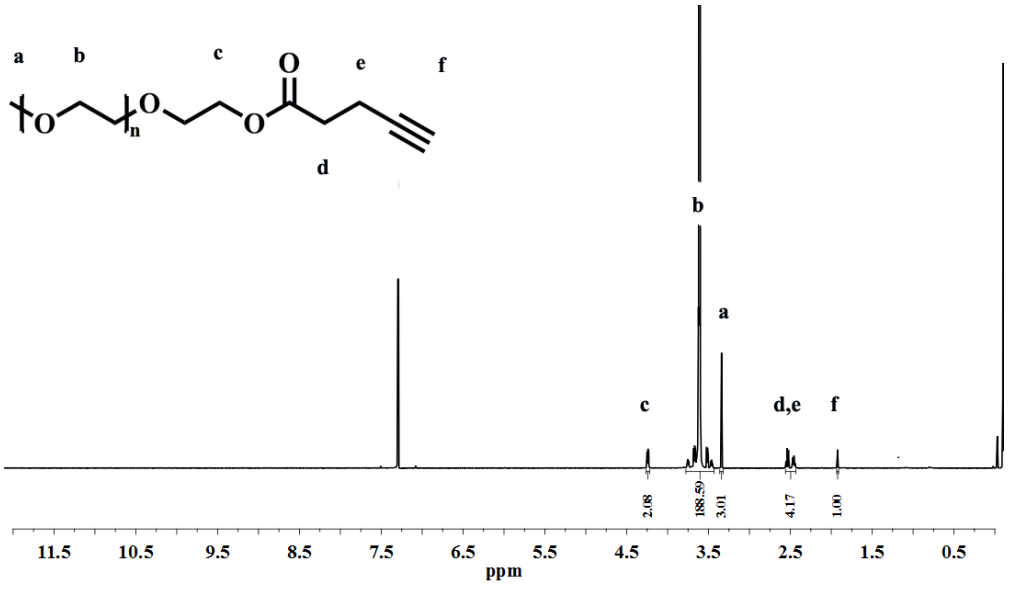
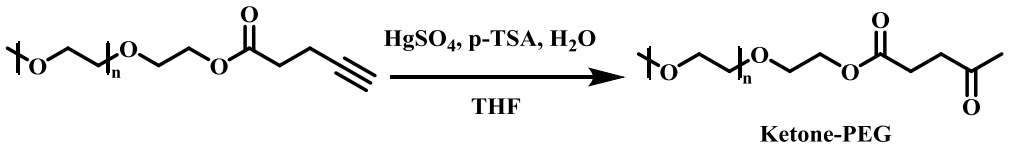


Figure 4.1: ^{1}H NMR spectrum of Alkyne- PEG (**1**) in $CDCl_3$.

4.2 Synthesis of Ketone-PEG via Oxymercuration Reaction

The alkyne functionality of **1** was converted to ketone via a reaction with water in the presence of $HgSO_4$/p-TSA catalyst system and THF as solvent in order to give **2** (reaction 4.2).



(4.2)

^{1}H NMR spectrum of **2** indicated the succesful conversion of alkyne to ketone. It was revealed that the alkyne protons at 1.9 ppm completely disappeared and new peak of methylene protones of carbonyl group was observed at 2.2 ppm. (Figure 4.2)

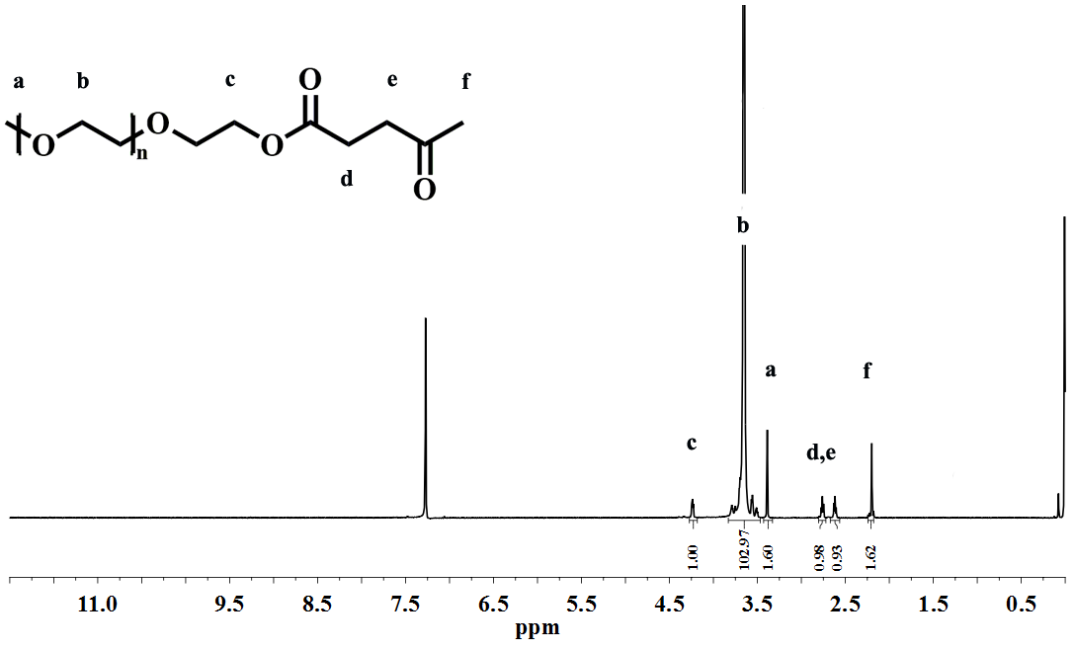


Figure 4.2: ^{1}H NMR spectrum of Ketone- PEG **(2)** in $CDCl_3$.

This reaction was repeated with different temperatures such as RT and 50^{o}C and different equivalents of HgSO4, p-TSA and water to observe the most efficient reaction system. Conversion of this alkyne to ketone conversion due to temperature and mol reaction shown below. (Table 4.1 and Table 4.2)

Table 4.1: Efficiency of alkyne to ketone conversion reaction at room temperature

Alkyne-PEG(1)	$HgSO_4$	p-TSA	Water	Time	Conversion
1 eq	0.1 eq	0.1 eq	0.2 eq	12 hours	-
1 eq	0.1 eq	0.1 eq	0.2 eq	24 hours	-
1 eq	0.25 eq	0.25 eq	0.5 eq	12 hours	-
1 eq	0.25eq	0.25eq	0.5 eq	24 hours	-
1 eq	0.5 eq	0.5 eq	1 eq	1 hour	-
1 eq	0.5 eq	0.5 eq	1 eq	2 hours	-
1 eq	0.5 eq	0.5 eq	1 eq	3 hours	92%
1 eq	0.5 eq	0.5 eq	1 eq	4 hours	100%

Table 4.2: Efficiency of alkyne to ketone conversion reaction at 50°C

Alkyne-PEG(1)	$HgSO_4$	p-TSA	Water	Time	Conversion
1 eq	0.1 eq	0.1 eq	0.2 eq	12 hours	-
1 eq	0.1 eq	0.1 eq	0.2 eq	24 hours	-
1 eq	0.25 eq	0.25 eq	0.5 eq	1 hour	-
1 eq	0.25eq	0.25eq	0.5 eq	2 hours	-
1 eq	0.25 eq	0.25 eq	0.5 eq	3 hours	95%
1 eq	0.25 eq	0.25 eq	0.5 eq	4 hours	100%

4.3 The Model Reaction Between Ketone-PEG and 2,4-Dinitrophenyl Hydrazine

Hydrazine end functionalized PEG (Hydrazine –PEG) was synthesized with a reaction of 2 in the presence of 2,4-Dinitrophenyl Hydrazine. When trifluoroacetic acid and THFwere used as the catalysts and the solvent respectively. **3** was obtained in a quantitative yield after purification with column chromatography and precipitation(4.3)

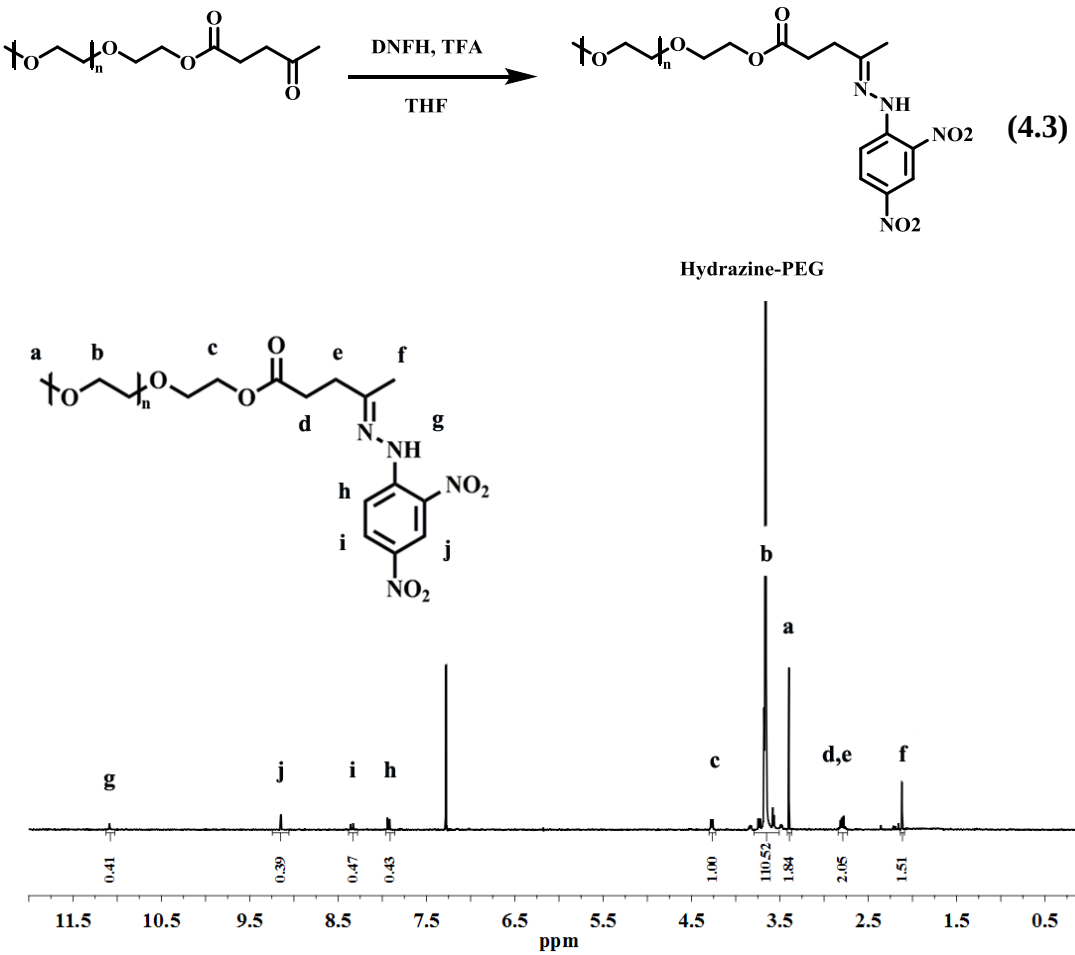


Figure 4.3: ^{1}H NMR spectrum of Hydrazine- PEG (**3**) in $CDCl_3$

Table 4.3: The GPC results of Alkyne-PEG**(1),** Ketone-PEG**(2)** and Hydrazine PEG**(3)** using RI detector in THF at 30 ^{o}C.

Polymer	$M_{n,GPC}$[a] (g/mol)	M_w/M_n[a]
1	2100	1.21
2	2300	1.1
3	2400	1.05

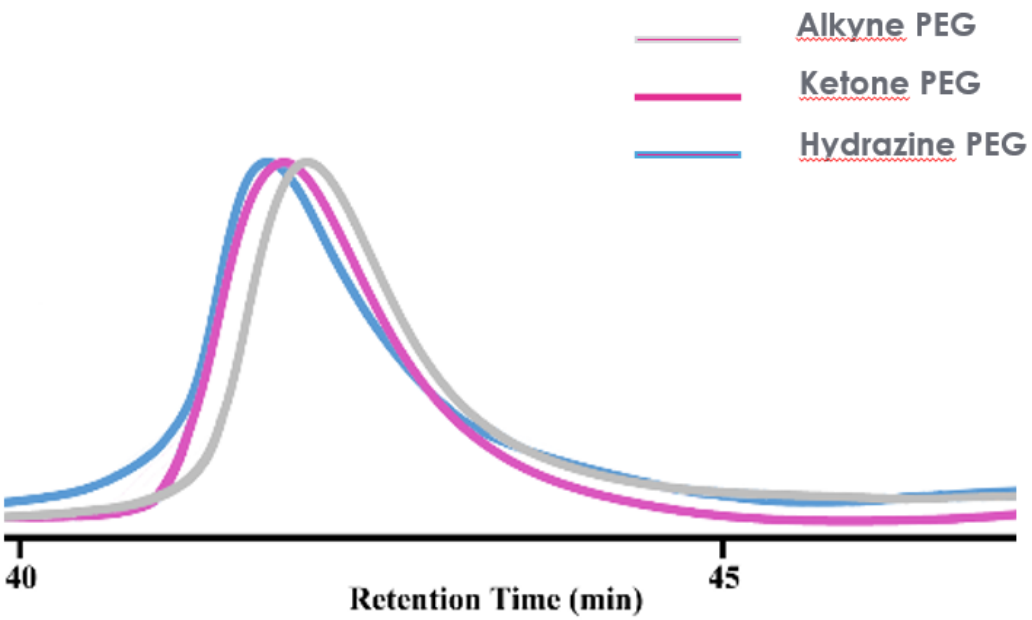


Figure 4.4: GPC traces of Alkyne-PEG(1), Ketone-PEG(2) and Hydrazine- PEG(3) using RI detector in THF at 30 ^{o}C.

GPC analysis showed a shift to higher molecular weight region after the conversion of alkyne to ketone and after the model reaction between ketone and 2,4-Dinitrophenylhydrazine as aspected.This reactions attributed to increase in hydrodynamic volume of final structures.

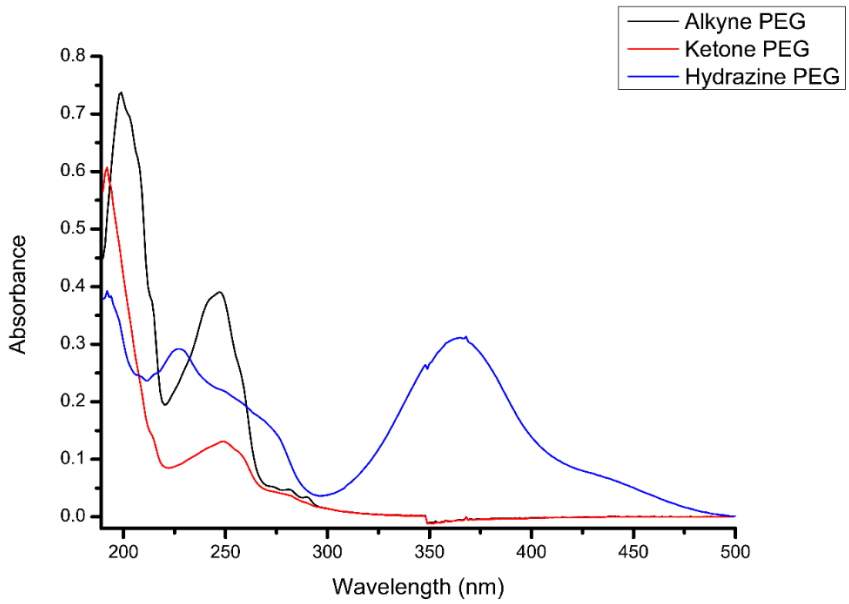


Figure 4.5: UV-Vis Spectra of Alkyne-PEG**(1)**, Ketone-PEG**(2)** and Hydrazine PEG**(3)**

It can be clearly seen from the UV- Vis Spectras of three different end functionalized PEG, reactions were processed succesfully. The obvious peak of hydrazine's at 375 nm shows that the model reaction between Ketone-PEG and 2,4-Dinitrophenylhydrazine was occured. And existence of ketone end functionalized polymer shows that the oxymercuration reaction is a good way to conversion of alkyne to ketone.

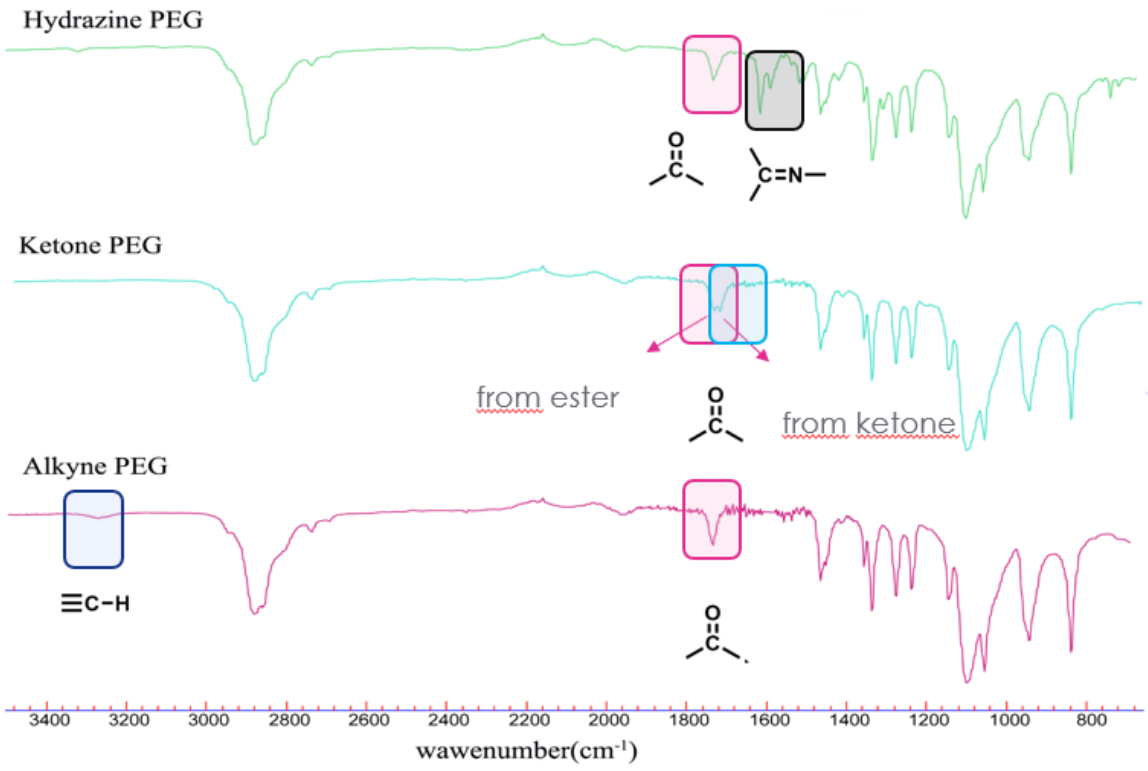
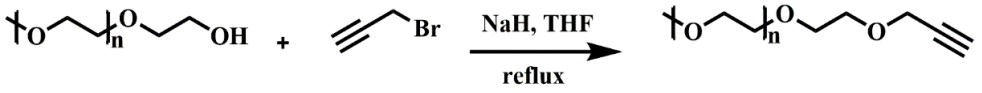


Figure 4.6: FT-IR Spectra of Alkyne-PEG, Ketone-PEG and Hydrazine-PEG

Alkyne to ketone formation can seen from the FT-IR spectra, too. Firstly, the absence of triple bond of alkyne at 3260 cm^{-1} in Ketone-PEG spectra demonstrate the conversion of alkyne to ketone conversion. Secondly, the carbon oxygen streching from carbonyl groups of ketone at 1720 cm^{-1} proves the ketone conversion. And lastly, Hydrazine PEG's spectrum shows that the model rection of ketone end PEG with 2,4- Dinitrophenyl Hydrazine has occurred succesfully due to the absense of carbonyl groups carbon- oxygen stretcing and the formation of carbon- nitrogen stretcing at 1600's cm^{-1} .

4.4 Preparation of Alkyne-PEG (4) (from propargyl bromide)

Alkyne-PEG**(4)** was obtained from a reaction of Me-PEG with NaH and propargyl bromide, respectively, as depicted in reaction 4.4



(4.4)

^{1}H NMR spectrum revealed the structure of Alkyne-PEG (Figure 4.7), displaying characteristic peaks such as a triplet (C*H*≡C-) at 2.45 ppm and a multiplet (CH≡CCH_2CH_2C=O) at 2.5 ppm. $M_{n,NMR}$ of Alkyne-PEG was calculated from a ratio of peak areas of PEG repeating unit at 3.67 ppm

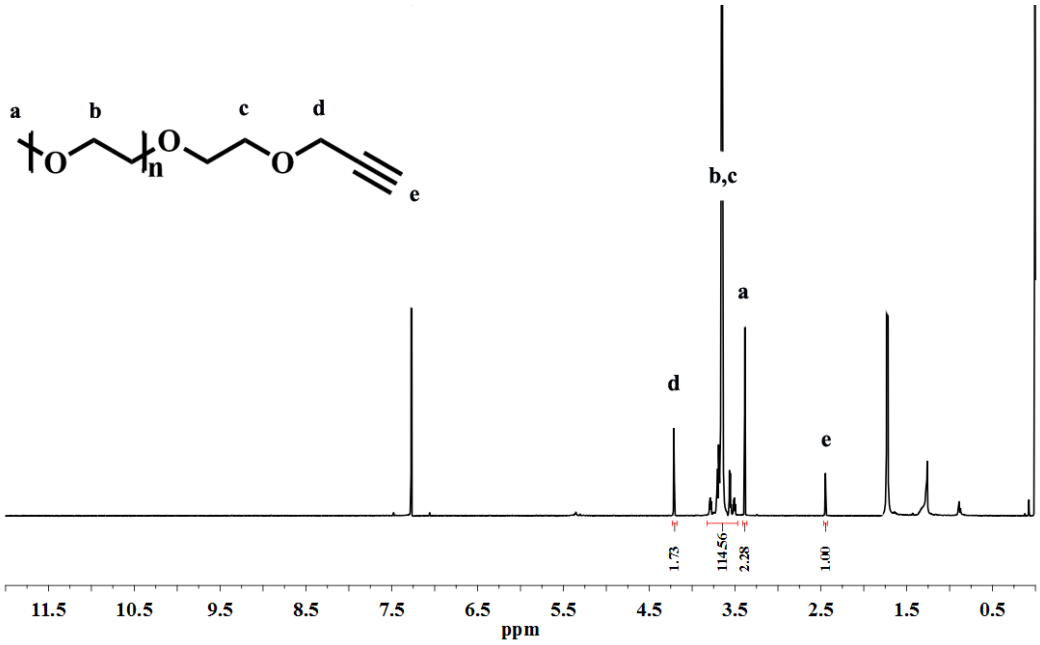
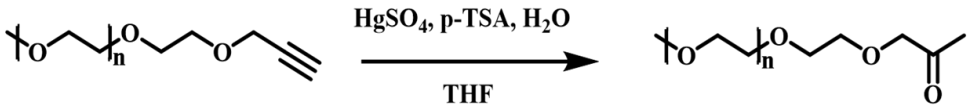


Figure 4.7: ^{1}H NMR spectrum of Alkyne- PEG (**4**) in $CDCl_3$.

4.5 Synthesis of Ketone-PEG (5) via Oxymercuration Reaction

The alkyne functionality of **4** was converted to ketone via a reaction with water in the presence of $HgSO_4$ and p-TSA as catalyst, THF as solvent in order to give **5** (reaction 4.5).



(4.5)

^{1}H NMR spectrum of **5** indicated the succesful conversion of alkyne to ketone. It was revealed that the alkyne protons at 2.45 ppm completely disappeared and new peak of methylene protones of carbonyl group was observed at 2.16 ppm. (Figure 4.8)

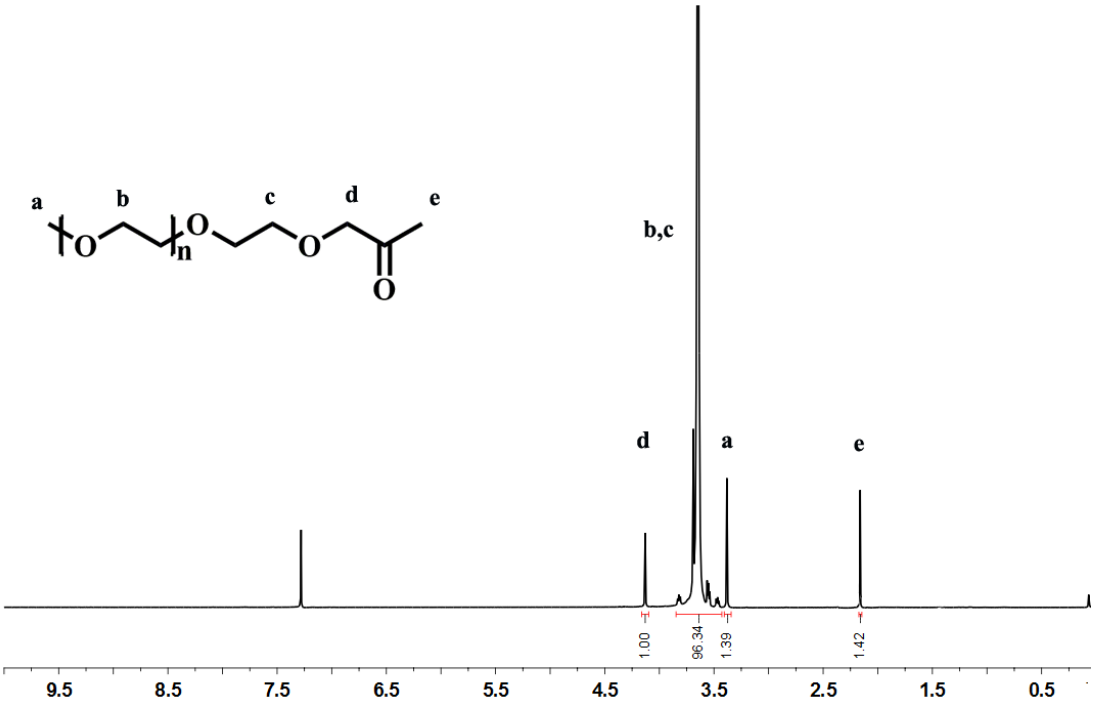


Figure 4.8: ^{1}H NMR spectrum of Ketone- PEG **(5)** in $CDCl_3$.

This reaction was repeated with different temperatures such as RT and 50°C and different equivalents of HgSO4, p-TSA and water to observe the most efficient reaction system. Results of this alkyne to ketone conversion due to temperature and mol shown below. (Table 4.3 and Table 4.4)

Table 4.4: Efficiency of alkyne to ketone conversion reaction at room temperature

Alkyne-PEG(1)	$HgSO_4$	p-TSA	Water	Time	Conversion
1 eq	0.5 eq	0.5 eq	1 eq	3 hours	-
1 eq	0.5 eq	0.5 eq	1 eq	6 hours	-
1 eq	0.5 eq	0.5 eq	1 eq	8 hours	< 5%
1 eq	0.5eq	0.5eq	1 eq	10 hours	89%
1 eq	0.5eq	0.5eq	1 eq	18 hours	100%

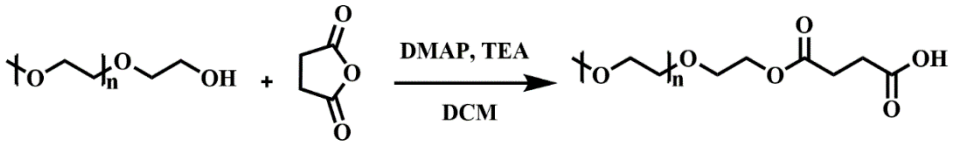
Table 4.5: Efficiency of alkyne to ketone conversion reaction at 50°C

Alkyne-PEG(1)	$HgSO_4$	p-TSA	Water	Time	Conversion
1 eq	0.25 eq	0.25 eq	0.5 eq	3 hours	-
1 eq	0.25 eq	0.25 eq	0.5 eq	6 hours	-
1 eq	0.25 eq	0.25 eq	0.5 eq	8 hours	< 10%
1 eq	0.25eq	0.25eq	0.5 eq	10 hours	100%

4.6 Preparation of Alkyne-PEG (7) (from propargyl alcohol)

For obtain Alkyne-PEG **(7)** the first step is the synthesis of carboxylic acid end-functionalized PEG **(6)** from Me- PEG with 4-Dimethylaminopyridine, Succinic anhydride and Triethylamine. After purification steps, **(6)** obtains as white solid.

Carboxylic acid end- functionalized PEG **(6)** reacted with propargyl alcohol with addition of DMAP and DCC to obtain Alkyne-PEG **(7)** as shown in reaction 4.6 and 4.7.



(4.6)

(4.7)

^{1}H NMR spectrum revealed the structure of Alkyne-PEG (Figure 4.9), displaying characteristic peaks such as a triplet (C*H*≡C-) at 2.45 ppm and a multiplet

(CH≡CCH_2CH_2C=O) at 2.5 ppm. $M_{n,NMR}$ of Alkyne-PEG was calculated from a ratio of peak areas of PEG repeating unit at 3.67 ppm

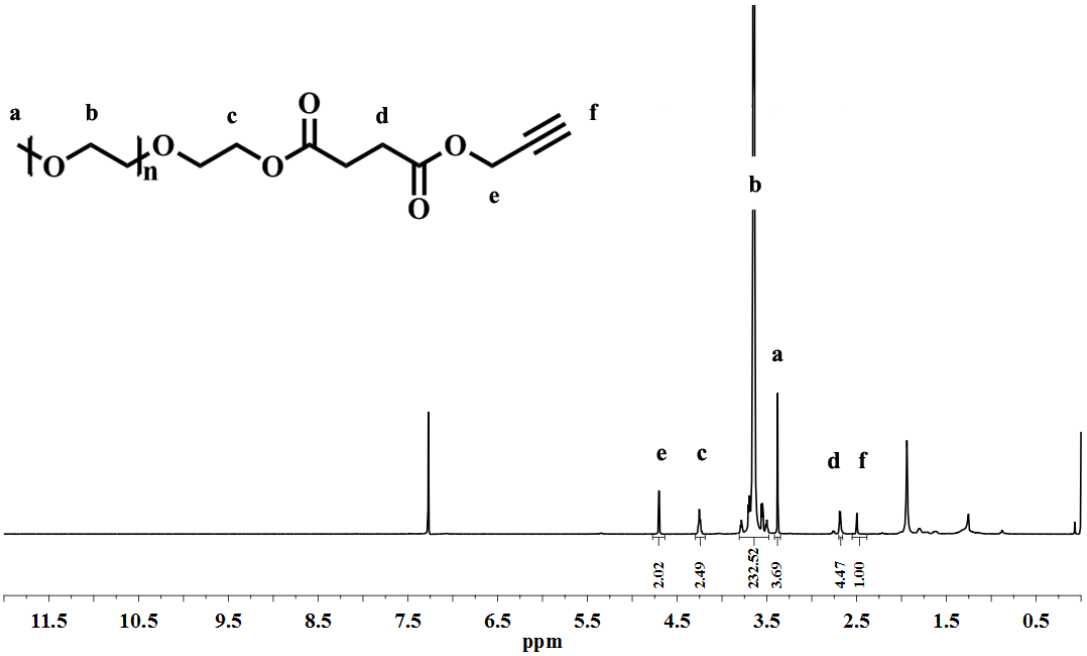
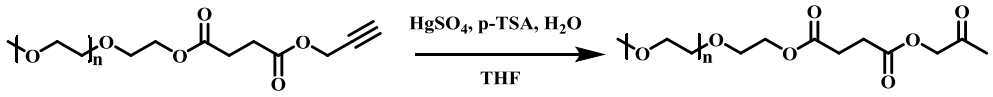


Figure 4.9: ^{1}H NMR spectrum of Alkyne- PEG **(7)** in $CDCl_3$.

4.7 Synthesis of Ketone-PEG (8) via Oxymercuration Reaction

The alkyne functionality of **7** was converted to ketone via a reaction with water in the presence of $HgSO_4$ and p-TSA as catalyst, THF as solvent in order to give **8** (reaction 4.8).



(4.8)

^{1}H NMR spectrum of **8** indicated the succesful conversion of alkyne to ketone. It was revealed that the alkyne protons at 1.9 ppm completely disappeared and new peak of methylene protones of carbonyl group was observed at 2.2 ppm. (Figure 4.10)

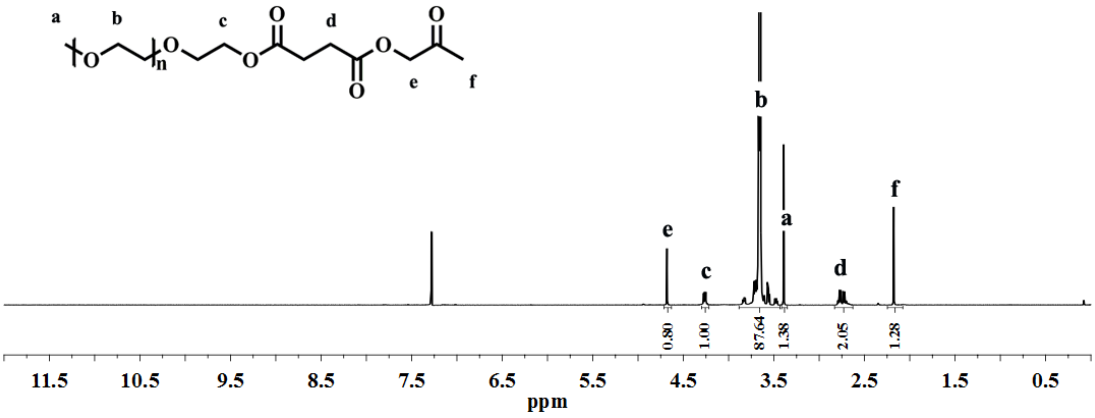


Figure 4.10: ^{1}H NMR spectrum of Ketone- PEG **(5)** in $CDCl_3$.

This reaction was repeated with different temperatures such as RT and 50°C and different equivalents of HgSO4, p-TSA and water to observe the most efficient reaction system. Results of this alkyne to ketone conversion due to temperature and mol shown below. (Table 4.5 and Table 4.6)

Table 4.6: Efficiency of alkyne to ketone conversion reaction at room temperature

Alkyne-PEG(1)	$HgSO_4$	p-TSA	Water	Time	Conversion
1 eq	0.5 eq	0.5 eq	1 eq	3 hours	-
1 eq	0.5 eq	0.5 eq	1 eq	6 hours	< 5%
1 eq	0.5 eq	0.5 eq	1 eq	8 hours	< 10%
1 eq	0.5 eq	0.5 eq	1 eq	12 hours	< 10%
1 eq	0.5 eq	0.5 eq	1 eq	24 hours	< 10%
1 eq	0.5 eq	0.5 eq	1 eq	48 hours	< 10%
1 eq	1 eq	1 eq	2eq	12 hours	< 10%
1 eq	1 eq	1 eq	2 eq	24 hours	< 10%
1 eq	1 eq	1 eq	2 eq	48 hours	< 10%

Table 4.7: Efficiency of alkyne to ketone conversion reaction at 50°C

Alkyne-PEG(1)	$HgSO_4$	p-TSA	Water	Time	Conversion
1 eq	0.25 eq	0.25 eq	0.5 eq	3 hours	-
1 eq	0.25 eq	0.25 eq	0.5 eq	4 hours	60%
1 eq	0.25 eq	0.25 eq	0.5 eq	6 hours	75%
1 eq	0.25eq	0.25eq	0.5 eq	8 hours	100%

5. CONCLUSIONS

In this study, a biocompable Alkyne end functionalized PEG was synthesis with an esterification reaction between PEG-OH and 4-pentynoic acid. Then, this alkyne functionalty in the terminal of polymer was converted to ketone with quantitative yield in easy,mild conditions with cheap chemicals via oxymercuration reaction. The obtained polymers were characterized by ^{1}H-NMR, UV, FT-IR and GPC. It can clealry be seen from the ^{1}H-NMR spectra that alkyne peaks have lost and new methylene protons from ketone group have appeared in 2.2 ppm. The GPC traces of all polymers showed mostly shift to high molecular weight region after functionalizations, as aspected. FT-IR spactra shows a little differences in carbonyl area, besause of the alkyne and after ketone functionality is end of the polymer chain.

And finally, UV spectra shows that imine reaction has processed successfully, and it shows that ketones could be syntesized from alkynes via oxymercuration reactions.

The quantitative conversions have taken both room temperature and at 50°C in 4 hours. This study lead us to know oxymercuration reactions is an efficient way polymer chemistry, as organic chemistry.

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