ISTANBUL TECHNICAL UNIVERSITY ★ GRADUATE SCHOOL OF SCIENCE ENGINEERING AND TECHNOLOGY

MULTIARM STAR POLYMER WITH A CLICKABLE PHOTOLABILE GROUP AT PERIPHERY

M.Sc. THESIS

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Department of Chemistry

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JANUARY 2014

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İSTANBUL TEKNİK ÜNİVERSİTESİ ★ FEN BİLİMLERİ ENSTİTÜSÜ

DIŞTA FOTOAYRILABİLİR GRUP İÇEREN ÇOK KOLLU YILDIZ POLİMER

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To my family,

FOREWORD

This master study has been carried out at İstanbul Technical University, Chemistry Department of Science & Letter Faculty.

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I would like to dedicate the this thesis to my family Sümmani YILMAZ,Aliye YILMAZ, Güldane YILMAZ, Gül YILMAZ ,Volkan YILMAZ and Ebru YILMAZ for their encouragement, support and especially for their parental guidance and endless devotion throughout my education and my life.

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ABBREVIATIONS

^{1}H NMR	**:** Hydrogen Nuclear Magnetic Resonance Spectroscopy
ATRP	**:** Atom Transfer Radical Polymerization
ABCVA	**:** 4,4′-Azobis(4-cyanovaleric acid)
CH_2Cl_2	**:** Dichloromethane
$CDCl_3$	**:** Deuterated chloroform
EtOAc	**:** Ethyl acetate
DMF	**:** *N*,*N*-dimehthylformamide
DVB	**:** Divinyl benzene
EtOAc	**:** Ethyl acetate
GC	**:** Gas Chromatography
GPC	**:** Gel Permeation Chromatography
MWD	**:** Molecular Weight Distribution
NMP	**:** Nitroxide Mediated Polymerization
PDI	**:** Polydispersity Index
PMDETA	**:** *N, N, N',N'', N''*-Pentamethyldiethylenetriamine
PS	**:** Poly(styrene)
RAFT	**:** Reversible Addition Fragmentation Chain Transfer
St	**:** Styrene
TD-GPC :	**:**Triple Detector-Gel Permeation Chromatography
TEA	**:** Triethylamine
THF	**:** Tetrahydrofuran
UV	**:** Ultra Violet

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λ	: Wavelength
$R^{\cdot}$	: Radical
f	: Number of arm
nm	: Nanomether
g′	: Contraction factor
$[\eta]$	: Intrinsic viscosity
R_h	: Hydrodynamic radius
C	: Concentration
A	: Absorbance
ε	: Molar extinction coefficient
k_{act}	: Activation rate constant
k_{deact}	: Deactivation rate constant
R_p	: Rate of polymerization
d_n/d_c	: Refractive index increment
K	: Mark-Houwink-Sakurada constant
ppm	: Parts per million
^oC	: Celsius
M	: Molarity
T_g	: Glass-transition temperature
M_n	: The number average molecular weight
M_w	: The weight average molecular weight
M_w/M_n	: The molecular weight distribution

MULTIARM STAR POLYMER WITH A CLICKABLE PHOTOLABILE GROUP AT THE PERIPHERY

SUMMARY

Well-defined biodegradable and biocompatible polymers are becoming more and more important materials nowadays. These type of polymers are used for a variety of biomedical applications such as devices for controlled drug release that the drug stays stabile until it reaches the right place where it is used for and also controlling the amount of the drug. Other examples are anti-cancer drugs, implants and bioresorbable prostheses etc.

Star polymers are branched polymers consisting of several linear chains linked to a central core. Among all branched structures, star polymers have been certainly the most investigated architectures, attracting much experimental and theoretical interest. There are two general strategies used to produce star polymers: the arm-first and core-first techniques. In the arm-first strategy, a polymer with a proper end-group functionality is reacted with an appropriate multifunctional core to give a star polymer. In the second strategy (core-first), the polymer chain is simultaneously grown from a multifunctional initiator. In recent years, the use of controlled/living radical polymerization techniques in the synthesis of complex macromolecules (star and dendrimeric polymers) has quickly increased because of the variety of applicable monomers and greater tolerance to experimental conditions in comparison with living ionic polymerization routes. The most widely used methods for C/LRP include atom transfer radical polymerization (ATRP), nitroxide mediated radical polymerization (NMP), and reversible addition-fragmentation chain transfer polymerization (RAFT).

In 2001, Sharpless et al. described a new concept for conducting organic reactions, which was based upon the premise that organic synthesis should take advantage of the long history of development and progress during the 20th century and focus attention on highly selective, simple orthogonal reactions that do not yield side products and that give hetheroatom-linked molecular systems with high efficiency under a variety of mild conditions. Several efficient reactions, which are capable of producing a wide catalogue of functional synthetic molecules and organic materials have been grouped accordingly under the term click reactions. Characteristics of modular click reactions include a) high yields with by-products (if any) that are removable by nonchromatographic processes, b) regiospecificity and stereospecificity, c) insensitivity to oxygen or water, d) mild, solventless (or aqueous) reaction conditions, e) orthogonality with other common organic synthesis reactions, and f) amenability to a wide variety of readily available starting compounds. The most popular click reactions are the copper catalyzed azide–alkyne cycloaddition (CuAAC), Diels–Alder cycloaddition, thiol-ene, thiol-yne, and nitroxide radical coupling (NRC) reactions.

Amoung the click reactions, thiol-ene click raction is considered the most encouraging the green aspects. This metal-free reaction can be performed in the

absence of solvents in some cases, and can be photochemically controlled (even in the absence of a photoinitiator). Some stuedies have showed that the thiol-ene click reaction is more efficient when initiated by light than by thermally.

DIŞTA FOTOAYRILABİLİR GRUP İÇEREN ÇOK KOLLU YILDIZ POLİMER

ÖZET

Son yıllarda biyobozunur ve biyouyumlu polimerler, biyomedikal uygulamalarda ve malzeme bilimi alanlarında giderek artan önem kazanmışlardır. Biyobozunur polimerler, biyolojik moleküllerle fonksiyonlandırılarak ilaç salınım sistemlerinde ve doku mühendisliğinde kullanılmaktadır.

Üstün özellikler gösteren ileri polimer malzemelerin sentezi konusunda yoğun çaba harcanmaktadır. Mekanik ve fiziksel özellikleri birarada bulundurmalarından dolayı blok kopolimerler ve yıldız polimerler en çok rağbet edilen ileri malzemelerdir. Çok geniş uygulama alanlarına rağmen, blok kopolimerlerin ve yıldız polimerlerin iyi-tanımlı olarak sentezlenmesi halen bir meseledir.

Yıldız polimerler birkaç linear polimer zincirinin bir merkez çekirdeğe bağlı olduğu dallanmış yapılardır. Tüm dallanmış yapılar arasında, şüphesiz yıldız polimerler en çok araştırılan, deneysel ve teorik açıdan ilgi çeken yapılardır. Yıldız polimerlerin elde edilmesinde kullanılan iki genel yöntem vardır: kol öncelikli ve çekirdek öncelikli yöntemleri. Kol öncelikli yönteminde, uygun uç grup fonksiyonalitesine sahip polimer ona uygun çok fonksiyonlu bir çekirdekle yıldız polimer elde etmek için reaksiyona sokulur. İkinci yöntemde (çekirdek öncelikli) ise, polimer zinciri çok fonksiyonlu bir başlatıcıdan eşzamanlı bir şekilde büyümektedir.

Kontrollü kompozisyon ve yapılarda iyi tanımlanmış makromoleküllerin sentezi polimer biliminde yeni bir alan açan iyonik polimerizasyon yöntemlerinin gelişimine kadar kimyagerler için sorun olmuştu. Ancak, iyonik polimerizasyon araştırmalarının gelişimi zorlu işlem koşulları; yüksek saflık ve çeşitli fonksiyonel monomerlerle uyumsuzluk söz konusu olduğundan bazı ciddi engeller ile karşılaşmaktadır. Serbest radikal polimerizasyonu safsızlıklara daha toleranslıdır ve çok çeşitli vinil monomerlerinin polimerleştirilmesi yeteneğine sahiptir fakat en büyük dezavantajı iyonik polimerizasyondaki gibi polimer yapı ve fonksiyonalite kontrolünün aynı derecede mümkün olmamasıdır. Bu nedenle, kaydadeğer çabalar serbest radikal polimerizasyonunu kontrollü bir şekilde gerçekleştirmek için harcanmıştır. Neyse ki, serbest radikal polimerizasyonunundaki devrim herhangi bir zorlu deneysel koşul gereksinimleri olmayan, iyi tanımlanmış makromoleküllerin inşasına erişim kolaylığı sağlayan kontrollü/"yaşayan" radikal polimerizasyon (C/LRP) yöntemlerinin gelişimlerine yol açmıştır. Günümüzde, en etkili ve en sık kullanılan üç C/LRP yöntemi: kararlı serbest radikal polimerleşmesi (SFRP) veya en sık kullanılan ifadesi ile nitroksit ortamlı radikal polimerleşmesi (NMP), atom transfer radikal polimerleşmesi (ATRP), ve tersinir eklenme-ayrılma zincir transfer polimerleşmesidir. Sonuç olarak, bu yöntemlerin polimer sentezinde geniş bir yelpazede yaygın olarak kabulu ve yararlanılması iyi tanımlanmış makromoleküllerin kontrollü kompozisyon, yapı ve fonksiyonalitede yapılmasındaki sınırsız potansiyellerine dayanır.

Monomerden kolaylıkla polimer elde etmeyi mümkün kılan L/CRP türlerinden biri ATRP olmuştur. ATRP'nin temeli, radikal oluşumu ve polimerizasyonun oluşan radikal üzerinden yürümesidir. Radikal polimerizasyonu birkaç monomerden yüzlerce monomere kadar polimerleşmeyi gerçekleştirebildiği gibi, su ortamında emülsiyon ya da süspansiyon polimerizasyonunu da mümkün kılar. ATRP'de kullanılan geçiş metallerinin halojenli bileşikleri, redoks reaksiyonu ile indirgenip-yükseltgenerek, tersinir bir mekanizmayı meydana getirir. İşte bu tersinir mekanizma ile polimer zincirleri neredeyse aynı anda meydana gelerek, düşük polidispersiteli polimerlerin eldesini sağlar.

2001 yılında Sharpless ve çalışma arkadaşları organik reaksiyonları yürütmek için yeni bir kavram ortaya atmışlardır. Click kimyası 2001 yılında Sharpless tarafından tanımlanmıştır. Tek cümle ile click kimyasından bahsedecek olursak molekülleri birbirine kolayca bağlamak diyebiliriz.Bu yeni kavramın temelinde, organik sentezlerin, 20. yüzyıl boyunca olan bütün gelişmelerden yararlanması ve yüksek seçicilikte, basit ortogonal reaksiyonlara odaklanması yer almaktadır. Bu reaksiyonlar ılımlı reaksiyon koşullarında, yan ürünler olmaksızın, yüksek verimle hetheroatoma bağlı moleküler sistemler oluşturabilmelidir. Geniş yelpazede, fonksiyonel sentetik molekülleri ve organik maddeleri üretebilen birkaç etkili reaksiyon "Click" reaksiyonlar kavramı altında gruplandırılmıştır. Modüler click reaksiyonları şu özelliklere sahip olmalıdır:

- Yüksek verimli olması; eğer yan ürünler var ise, bu ürünlerin kromatografik olmayan yöntemlerle uzaklaştırılabilir olması.
- Regioseçici ve stereoseçici olması.
- Oksijen ve suya karşı hassas olmaması.
- Ilımlı, çözücüsüz (veya sulu) reaksiyon koşullarında gerçekleşebiliyor olması.
- Diğer bilinen organik sentez reaksiyonları ile uyumlu olabilmesi.
- Çok çeşitli ve kolay elde edilebilen çıkış bileşiklerine karşı yatkın olabilmesi.

En yaygın kullanılan click reaksiyonları, bakır katalizli azid-alkin siklokatılma (CuAAC) reaksiyonu, Diels-Alder siklokatılma reaksiyonu, tiyol-en ve tiyol-in reaksiyonları ve nitroksit radikal kenetlenme reaksiyonlarıdır.

Tiyol-in click reaksiyonları ile tiyol bileşikleri polimer zincirinde bulunan üçlü bağ ile yapıya radikalik olarak bağlanılmaktadır. Thiol-ene click reaksiyonları termal yolla yapılabileceği gibi ışıkla da yapılabilmektedir. Işıkla gerçekleştirilen bu reaksiyonlarda ortama foto başlatıcılar konulmaktadır ve de mekanizma radikalik olarak yürümektedir. Işık altında gerçekleştirilen thiol-ene reaksiyonu, termale göre daha etkili olduğu çeşitli yayınlarda belirtilmiştir. Reaksiyon ortamında bulunan nem ya da hava reaksiyon üzerine pek olumsuz etki yapmazken; havanın oksijeni radikal oluşumunu artırıp reaksiyon verimini artırmaktadır. Herhangi bir metal bulunmaması bu reaksiyonunun yeşil kimyayı desteklemesini ortaya koymaktadır. Tiyol-in reaksiyonlarının bazı dezavantajları vardır. Bunlar; disülfit oluşumu ve coupling (radikallerin baş başa katılması) gibi yan reaksiyonlardır.

o-Nitrobenzil grubu UV bölgede ışık absorplanmasıyla polimer yapısından ayrılabilmektedir. Bu olay fotoliz olarak adlandırılıp, grubun ayrılmasıyla karboksilik asit fonksiyonelitesi yapıya kazandırılmaktadır. Bu işlem için çalışılan dalga boyu 260 nm den 400 nm ye kadar olabilmektedir. Ancak en iyi ayrılmanın gerçekleştiği dalga boyu yaklaşık olarak 350 nm dir. Bu dalga boyundaki ışık aynı zamanda gün ışığında da bulunmaktadır. Elde edilen polimerin yapısına göre UV ışığıyla muamelenin süresi değişebilmektedir. *o*-Nitrobenzil grubunun uç grup olması yada polimer zincirlerini birbirine bağlayan yapı olması gibi durumlar sonucu bu süre 5-10 dakika gibi bir süreden uzun saatlere kadar kayabilmektedir. Kullanılan

ışığın gücü, lamba sayısı gibi etkenler de reaksiyon süresini etkileyen önemli parametrelerdir. Polimer yapısında bulunan grup ile ayrılan grup UV spektroskopisinde farklı dalga boylarında absorbans vermektedirler.

Bu çalışmada ilk olarak; click reaksiyonları için uygun olan alkin grubu ve polimere fotoparçalanabilirlik özelliği kazandıran *ortho*-nitro-benzyl alkol kullanılarak eterleşme reaksiyonu gerçekleştirildi.Elde edilen maddeye esterleşme reaksiyonu ile brom fonksiyonu katılarak ATRP reaksiyonu için başlatıcı üretildi.Daha sonra stiren monomeri kullanılarak alkyne-*o*-NB-PS-Br lineer polimeri elde edildi.Lineer polimere tiyolin click reaksiyonu ile sistein biyomolekülü takıldı (cysteine-o-NB-PS-Br) ve sonrasında UV ışığı ile fotoparçalama gerçekleştirildi.Böylece sistein nitro grubu ile beraber lineer polimer yapısından ayrıldı.Fotoliz reaksiyonu sonrasında linner polimerin uç grubunda karboksilik asit oluştu ve bu polimerin suda ki çözünürlüğünü arttırdı.

İkinci çalışmada, Alkyne-*o*-NB-PS-Br makrobaşlatıcısı kullanılarak kol öncelikli metot ile çok kollu yıldız polimer olan (Alkyne-*o*-NB-PS)$_n$-polyDVB sentezlendi. Sonra tiyolin click reaksiyonu ile *N*-asetil-L-sistein metil ester fonksiyonlu (Cysteine-*o*-NB-PS)$_n$-polyDVB çok kollu yıldız polimer elde edildi. Son olarak (Cysteine-*o*-NB-PS)$_n$-polyDVB multiarm star polimer parçalanıp sisteinin salınımı için fotoliz reaksiyonu gerçekleştirildi.Parçalanma sonucunda çok kollu yıldız polimerde çok sayıda karboksillik asit oluştugu için jelleşme meydana geldi .

Karakterizasyon işlemleri ^{1}H NMR , GPC, TD-GPC, UV ile gerçekleştirilmiştir.

1. INTRODUCTION

Emerging technologies, such as bio- and nanotechnologies, have increasingly demanded novel well-defined polymers, which raise the necessity to be able to conjugate polymers and/or biomolecules (or small molecules) with various polymer blocks in an easy mode [1]. One of the major aims of contemporary synthetic polymer chemistry is to achieve well-defined macromolecular architectures (linear and nonlinear topologies), such as precise control of composition, molecular weight, polydispersity, and endfunctionality to fulfill the requirements of emerging technologies [2-7].

Star polymers have a fascinating macromolecular architecture due to their unique properties that differentiate them from their linear counterparts, such as a smaller hydrodynamic volume and lower viscosity at a given molecular weight as a consequence of their compact structure and globular shape. To date, known synthetic strategies for the formation of star polymers can be generalized into three main categories: (1) “core-first”; (2) “arm-first”; and (3) “coupling onto”. The core-first technique involves the use of a multifunctional initiator. The arm-first technique involves the synthesis of preformed arms followed by reaction with a cross-linking agents usually by using a divinyl cross-linker. The third method is a slight variation of the arm-first technique, which involves the synthesis of preformed arms followed by reaction with a cross-linking agent.

The research to design novel macromolecular architectures with unusual properties has led to the synthesis of star polymers with well-defined end functional groups, controlled molecular weights, and narrow molecular weight distributions. Traditionally, control of polymerization processes has been achieved with “living” polymerization techniques such as ionic (anionic or cationic), group transfer and transition-metal-catalyzed processes [8-13]. However, these methods suffer from rigorous process conditions imposed by the high purity required and incompatibility with a variety of functional monomers. Therefore, much interest has recently been focused toward free radical chemistry to achieve control over polymerization process

due to their tremendous commercial significance [14]. Even though free radical initiated polymerizations are synthetically less rigorous and are compatible with a wide range of monomers, they, in general, lack the ability to accurately control molecular weight distribution and end functional groups. The main drawback of radical polymerizations is that they have not been able to offer the same degree of control over the polymer structure and functionality as do ionic polymerizations. In this connection, there is increasing interest in methods based on radical chemistry that allow for the preparation of polymers in controlled fashion. Eventually, the concept of controlled/‘‘living” radical polymerization (C/LRP) has been introduced in which the control and precision of living polymerization and the robustness of radical polymerization are put together in a single process [15-17]. Several methods have been developed over the years to attain control of radical polymerizations. Particularly, the three most well-known C/LRP techniques are nitroxide mediated radical polymerization (NMP) [18,19], atom transfer radical polymerization (ATRP) [20-24], and reversible addition-fragmentation chain transfer (RAFT) polymerization [25-27].

“Click chemistry” is a chemical term defined in 2001 by Sharpless and describes chemistry tailored to generate substances quickly and reliably by joining small units together. Click chemistry can be summarized with only one sentence: ‘’Molecules that are easy to make. ‘’ Sharpless also introduced some criteria in order to fullfill the requirements as reactions that: are modular, wide in scope, high yielding, create only inoffensive by-products, are stereospecific, simple to perform and that require benign

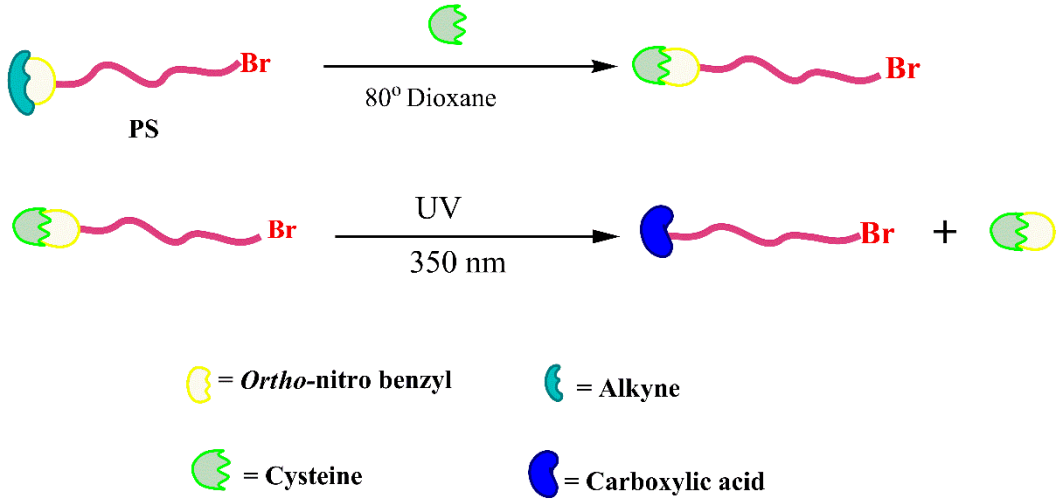


Figure 1.1: General synthetic scheme for linear polymers

or easily removed solvent. Nowadays there are several processes have been identified under this term in order to meet these criterias such as nucleophilic ring opening reactions; non-aldol carbonyl chemistry; thiol additions to carbon–carbon multiple bonds (thiol-ene and thiol-yne); and cycloaddition reactions. Among these selected reactions, copper(I)-catalyzed azide-alkyne (CuAAC) and Diels-Alder (DA) cycloaddition reactions and thiol-ene reactions have gained much interest among the chemists not only the synthetic ones but also the polymer chemists.

The thiol-yne click reaction has realized between a thiol and an alkeyne to form a thioether linkage. More specifically, the sulfur–carbon bond formation follows an anti-Markonikov process that can be promoted by UV light radiation or by radical initiators. Thiol-yne click reactions are discovered in chemistry at early times, but have been rather extensively studied over the last century.

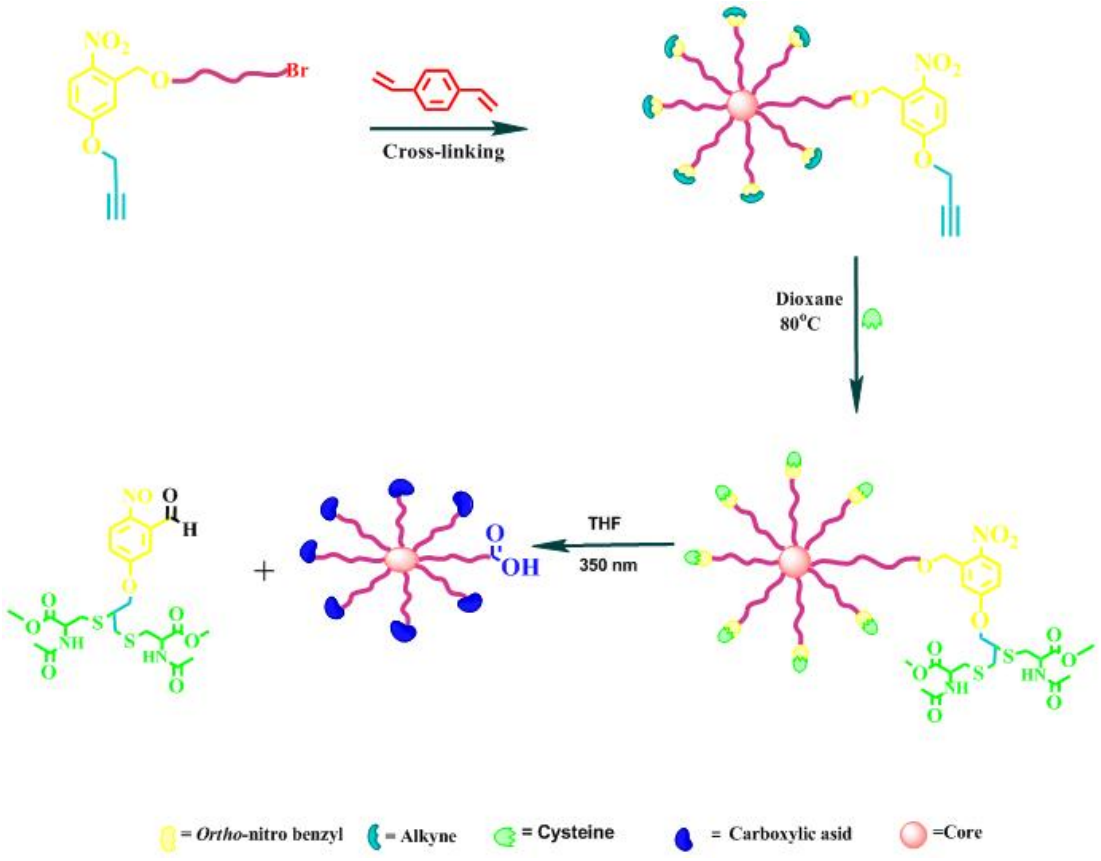


Figure 1.2: General synthetic scheme for multiarm star polymers

In this thesis, we prepared multiarm star and linear polymers by the combination of ATRP and cross-linking based on the arm-first method. For this purpose ω-bromide terminated PS was synthesized by using alkyne-*ortho*-nitrobenzyl as initiator. Well defined linear polymer was reacted with *N*-acetyl-L-cysteine methyl-ester via thiol-

yne click reaction. After dissection of Cysteine-*o*-NB-PS linear polymer with UV radiation, COOH-PS linear polymer and cysteine-*o*-nitrobenzaldehyde were obtained (Figure 1.1).

Star polymer was obtained by using the alkyne-*o*-NB-PS macroinitiator and DVB as a cross-linker. The resulted well defined multiarm star polymer was reacted with *N*-acetyl-L-cysteine methyl-ester via thiol-yne click reaction (Figure 2.1).

2. THEORETICAL PART

2.1. Controlled/ ‘‘Living” Polymerizations

A living polymerization is defined as a chain polymerization without chain transfer and chain termination as indicated by Szwarc. Well-defined polymers, can only be synthesized by living ionic polymerizations or controlled/ “living” radical polymerization (C/LRP) methods [28]. Until recently, ionic polymerizations (anionic or cationic) were the only living techniques that efficiently controlled the structure and architecture of vinyl polymers. These polymerization techniques ensure low polydispersity materials, controlled molecular weight and defined chain ends but they are not useful for the polymerization and copolymerization of a wide range of functionalized vinylic monomers [29]. Furthermore, these techniques require stringent reaction conditions and pure reagents. To overcome all these limitations polymer chemists developed new concepts. These new concepts are often called controlled radical polymerization, living radical polymerization, control/“living” radical polymerization [30, 31].

Living polymerization provides end-group control and enables the synthesis of block copolymers by sequential monomer addition. However, it does not necessarily provide polymers with molecular weight (MW) control and narrow molecular weight distribution (MWD). To obtain well defined polymers the initiator should be consumed at early stages of polymerization and that the exchange between species of various reactivities should be at least as fast as propagation [32-34].

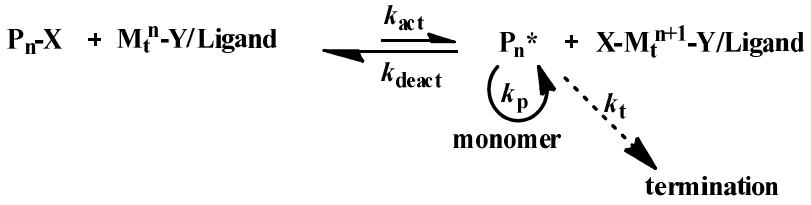
2.1.1. Controlled/ ‘‘living” radical polymerizations

Living free radical polymerizations have attained a tremendous following in polymer chemistry. A great deal of effort has been made to develop and understand different living free radical polymerization (LFRP) methods. Georges and co-workers first introduced true nitroxide mediated polymerization (NMP) in 1993, Matyjaszewski and Sawamoto developed metal catalzed (Cu, Ru) living radical polymerization also called atom transfer radical polymerization (ATRP) in 1995, and Moad, Rizzardo

and Thang reported reversible addition-fragmentation chain transfer polymerization (RAFT) in 1998 [35, 36, 37, 26].

2.1.1.1. Atom transfer radical polymerization (ATRP)

Atom transfer radical polymerization (ATRP) is a living radical polymerization process, which is consisting of the monomer, initiator, and catalyst composed of transition metal species with any suitable ligand. The ATRP system is consisting of the monomer, initiator, and catalyst composed of transition metal species with any suitable ligand. ATRP, which is the most versatile method of the controlled radical polymerization system, uses a wide variety of monomers, catalysts, solvents, and reaction temperature. ATRP is one of the most convenient methods to synthesize well-defined low molecular weight polymers [38].



(2.1)

Equation 2.1 represents the general mechanism of ATRP. The radicals the propagating species Pn*, are generated through a reversible redox process catalyzed by a transition metal complex. Radicals react reversibly with the oxidized metal halide complexes, $X–M_t^{n+1}$ / ligand, the deactivator, to reform the dormant species and the activator. These processes are fast, and the dynamic equilibrium that is established favors the dormant species. By this way, all chains can begin growth at the same time, and the concentration of the free radicals is quite low, resulting in reduced amount of irreversible radical-radical termination. Since the deactivation rate constant is substantially higher than that of the activation reaction $K_{eq} = K_{act} / Kd_{eact}$ ~10-7; each polymer chain is protected by spending most of the time in the dormant state, and thereby the permanent termination via radical coupling and disproportionation is substantially reduced. Polymer chains grow by the addition of the free radicals to monomers in a manner similar to a conventional radical polymerization, with the rate constant of propagation, k_p. Termination reactions (k_t) also occur in ATRP, mainly through radical coupling and disproportionation; however, in a well-controlled ATRP, only several percents of the chains become

dead via termination [39]. Polydispersities in ATRP decrease with conversion, with the rate constant of deactivation and also with the concentration of deactivator. The molecular conversion and the amount of initiator used, DP = $\Delta[M]/[I]_0$; polydispersities are low, $M_w / M_n < 1,3$ [40].

Monomers

A variety of monomers have been used for atom transfer radical polymerization. The most common monomers are methacrylates, acrylonitriles, styrenes, acrylates and (meth)acrylamides in bulk, solution using organics or water as solvents, and emulsion, supercritical carbon dioxide, producing polymers with well-controlled molecular weights and structures [41].

Initiators

In ATRP, alkyl halides are typically used as the initiator and the rate of the polymerization is first order with respect to the concentration of alkyl halides. To obtain well-defined polymers with narrow molecular weight distributions, the halide group X, must rapidly and selectively migrates between the growing chain and the transition-metal complex. Thus far, bromine and chlorine are the halogens that afford the best molecular weight control [42-45]. Iodine works well for acrylate polymerizations; however, in styrene polymerizations the hetherolytic elimination of hydrogen iodide is too fast at high temperatures [46].

The amount of the initiator in the ATRP dethermines the final molecular weight of the polymer at full monomer conversion. The main role of the initiator is to dethermine the number of growing polymer chains. If initiation is fast and transfer and termination negligible, then the number of growing chains is constant and equal to the initial initiator concentration. The theoretical molecular weight or degree of polymerization (DP) increases reciprocally with the initial concentration of initiator in a living polymerization.

The most frequently used initiator types used in the atom transfer radical polymerization systems are, 1-Bromo-1-phenyl ethane (Styrene), 1-Chloro-1-phenyl ethane (Styrene), Ethyl-2-bromo propionate (Methyl methacrylate) and Ethyl-2-bromo isobutyrate (Methyl methacrylate). Two paramethers are important for a

successful ATRP initiating system; first, initiation should be fast in comparison with propagation. Second, the probability of side reactions should be minimized [47].

Catalysts

Catalyst is another important component of ATRP. Catalyst dethermines the position of the atom transfer equilibrium and the dynamics of exchange between the dormant and active species. There are several prerequisites for an efficient transition metal catalyst. First, the catalyst should react with initiator fast and quantitatively to ensure that all the polymer chains start to add monomer at the same time. Second, the catalyst must have moderate redox potential to ensure an appropriate equilibrium between dormant and active species. In general, a low redox potential of the catalyst leads to formation of the high Cu(II) concentration (equilibrium is shifted toward transient radicals). Consequently, a fast and uncontrolled polymerization is observed. In contrast, high redox potential strongly suppresses Cu(II) formation (equilibrium is shifted toward dormant species) via a halogen atom abstraction process leading to very slow polymerization. Third, the catalyst should be less sterically hindered, because large steric congestion around the metal center of catalyst results in a reduction of the catalyst activity. Fourth, a good catalyst should not afford side reactions such as Hoffman elimination, β-H abstraction, and oxidation/reduction of radicals [48].

A variety of transition metal complexes with various ligands have been studied as ATRP catalysts. The majority of work on ATRP has been conducted using copper as the transition metal. Apart from copper-based complexes, iron, nickel, rhenium, ruthenium, rhodium, and palladium have been used to some extent [49, 50, 51-54]. Recent work from Sawamoto and co-workers shows that the Ru-based complexes can compete with the Cu-based systems on many fronts. A specific Fe-based catalyst has also been reported to polymerize vinyl acetate via an ATRP mechanism [55].

Ligands

The major roles of the ligand in ATRP is to solubilize the transition metal salt in the organic media and to adjust the redox potential and halogenophilicity of the metal center forming a complex with an appropriate reactivity and dynamics for the atom transfer. The ligand should complex strongly with the transition metal, should also

allow expansion of the coordination sphere, and should allow selective atom transfer without promoting other reactions.

The most common ligands for ATRP systems are substituted bipyridines, alkyl pyridylmethanimines and multidentate aliphatic tertiary amines such as N,N,N′,N″,N″ pentamethyldiethylenetriamine (PMDETA), and tris[2-(dimethylamino) ethyl]amine (Me_6-TREN) [56]. In addition to those commercial products, it has been demonstrated that hexamethyltriethylene tetramine (HMTETA) provides better solubility of the copper complexes in organic media and entirely homogeneous reaction conditions [57]. Since copper complexes of this new ligand are almost insoluble in water, ATRP technique can be employed in preparing poly(acrylate esters) in aqueous suspensions [58].

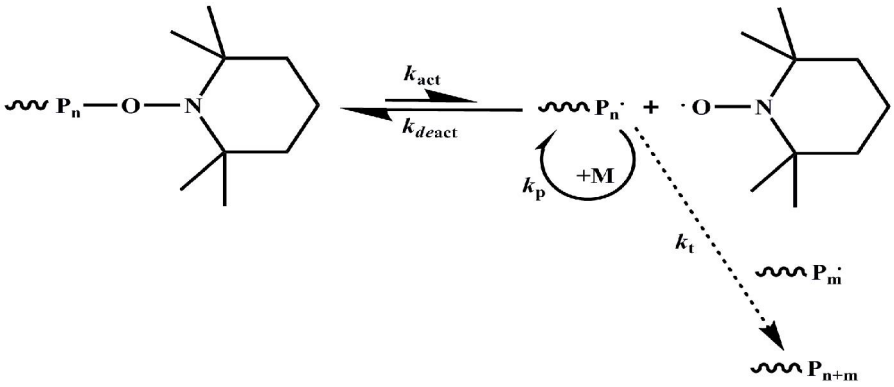
Solvents

ATRP can be carried out either in bulk, in solution or in a hetherogeneous system (e.g., emulsion, suspension). Various solvents such as benzene, toluene, anisole, diphenyl ether, ethyl acetate, acetone, dimethyl formamide (DMF), ethylene carbonate, alcohol, water, carbon dioxide and many others have been used for different monomers. A solvent is sometimes necessary especially when the obtained polymer is insoluble in its monomer [59].

2.1.1.2. Nitroxide-mediated radical polymerization (NMP)

Nitroxide–mediated radical polymerization (NMP) belongs to a much larger family of processes called stable free radical polymerizations. In this type of process, the propagating species (P_n°) reacts with a stable radical (X°) as seen in equation 2.2. The resulting dormant species (P_n-X) can then reversibly cleave to regenerate the free radicals once again. Once P_n° forms it can then react with a monomer, M, and propagate further. The most commonly used stable radicals have been nitroxides, especially 2,2,6,6-tetramethylpiperidinoxy (TEMPO). The 2,2',6,6'-tetramethylpiperidine-1-oxyl radical (TEMPO) was used as the nitroxide component in these initial studies. The alkoxyamine is formed in situ during the polymerization process [60]. Although NMP is one of the simplest methods of living free radical polymerization (LFRP), it has many disadvantages. Many monomers will not polymerize because of the stability of the dormant alkoxyamine that forms. Also, since the reaction is kinetically slow, high temperatures and bulk solutions are often

required. Also, the alkoxyamine end groups are difficult to transform and require radical chemistry [61].



(2.2)

The chain end functionalization of polymers synthesized by NMP is a significant problem because dormant chains containing alkoxyamines can regenerate terminal radicals which can depolymerize at high temperatures. A very interesting chain end functionalization process has also been discovered by Hawker et. al. which involves the controlled monoaddition of maleic anhydride or maleimide derivatives to the alkoxyamine chain end. The alkoxyamine can then be easily eliminated and other functional groups can be introduced [62].

2.1.1.3. Reversible-addition fragmentation chain transfer (RAFT)

The most recent report of a controlled/"living" free radical polymerization has been reported by Haddleton and co-workers as well as Thang et al. Reversible addition-fragmentation chain transfer (RAFT) is achieved by performing a free radical polymerization in the presence of dithio compounds, which act as efficient reversible addition-fragmentation chain transfer agents [63].

Reversible addition-fragmentation chain transfer (RAFT) incorporates compounds, usually dithio derivatives, within the living polymerization that react with the propagating center to form a dormant intermediate. The dithio compound can release the alkyl group attached to the opposite sulfur atom which can then propagate with the monomer. The greatest advantage to RAFT is the incredible range of polymerizable monomers. As long as the monomer can undergo radical polymerization, the process will most likey be compatible with RAFT. However, there are many major drawback that arise when using this process. The dithio end groups left on the polymer give rise to toxicity, color, and odor and their removal or

displacement requires radical chemistry. Also, the RAFT agents are expensive and not commercially available [64].

2.2. Star Polymers

Polymer properties are influenced by their structure and topology. Therefore, the synthesis of complex macromolecular architectures to control polymer properties is an ongoing field of study in polymer science. Branching in polymers is a useful structural variable that can be used advantageously to modify polymer physical properties and the processing characteristics as a result of changing the melt, solution, and solid-state properties of polymers [65]. It has been shown that branching results in a more compact structure in comparison to linear polymers of similar molecular weight, due to their high segment density, which affects the crystalline, mechanical, and viscoelastic properties of the polymer. A branched polymer structure was described as a nonlinear polymer comprised of molecules with more than one backbone chain radiating from branch points (junction points; atoms or small group from which more than two long chains emanate) [66]. Star polymers constitute the simplest form of branched macromolecules where all the chains as arm segments of one molecule are linked to a centre (Figure 2.1).

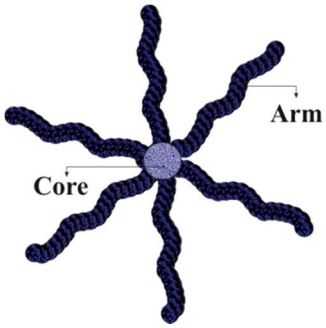


Figure 2.1: Illustration of a star polymer.

Based on the chemical compositions of the arm species, star polymers can be classified into two categories (Figure 2.2): homoarm (or regular) star polymer and miktoarm (or hetheroarm) star copolymer [67, 68]. Homoarm star polymers consist of a symmetric structure comprising radiating arms with similar molecular weight and identical chemical composition. In contrast, a miktoarm star molecule contains two or more arm species with different chemical compositions and/or molecular weights [69].

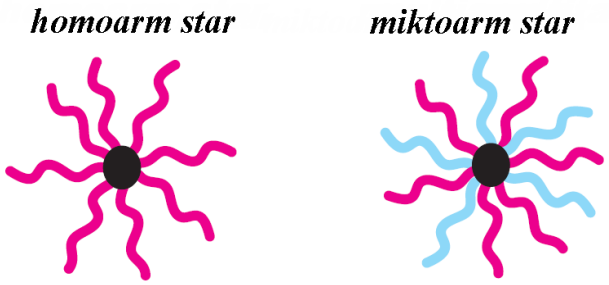


Figure 2.2: Illustration of star polymer categories.

2.2.1. Preparation of star polymers

The methodology of living polymerization is ideally suited for the preparation of star polymers since it is possible to vary and control important structural paramethers such as molecular weight, molecular weight distribution, copolymer composition and microstructure, tacticity, chain end functionality and the number of branches per molecule. Because termination and chain transfer reactions are absent and the chain-ends may be stable for sufficient time periods, these polymerizations have the following useful synthetic attributes for star polymer synthesis:

I. One polymer is formed for each initiator molecule, so that the number average molecular weight of polymers or block segments can be predicted from the reaction stoichiometry. Multifunctional initiators with functionality *n* can form stars with *n* arms.

II. If the rate of initiation is rapid or competitive with the rate of propagation, polymers with narrow molecular weight distributions are formed [70].

III. When all of the monomer has been consumed, the product is a polymer with reactive chain ends that can be participate in a variety of post polymerization reactions:

a. block copolymerization by addition of a second monomer, and/or

b. end-linking with multifunctional linking agents to form the corresponding star polymers with uniform arm lengths.

There are three general synthetic methods for the preparation of star-shaped polymers. These methods have been based on two approaches: arm-first and core-first.

I. End linking with multifunctional linking agent (coupling-onto),

II. Use of multifunctional initiators (core-first),

III. Use of difunctional monomers (arm-first).

2.2.1.1. End linking with multifunctional linking agent (Coupling-onto)

In the first method, referred to as the "arm-first" method, monofunctional living chains of known length and low polydispersity are used as precursor. Subsequently, the active sites located at chain end are reacted with a compound carrying a number of appropriate reactive functions, whereupon chemical links are formed. The number of arms corresponds to the functionality of the linking agent as shown in figure: 2.3. The precursor chains become the star branches, and the linking agent becomes the core.

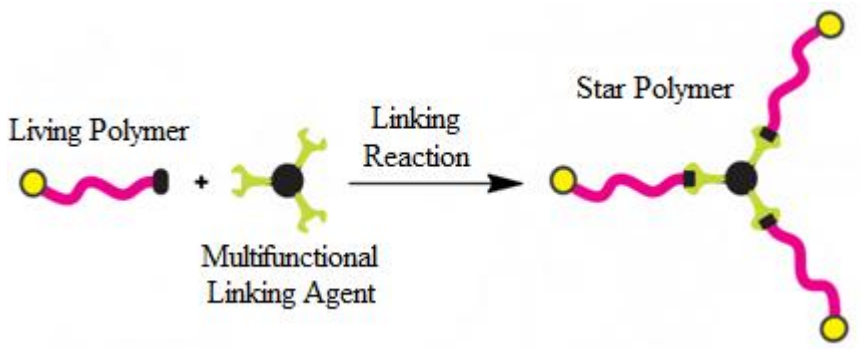


Figure 2.3: Illustration of the synthesis of star polymers by arm-first method.

The main advantage of this method is that the arms of the resulting star polymer are well-defined because the precursor arms can be characterized independently from the star. Because of the well-defined arms, the number of arms can be readily dethermined by measuring the molecular weight of the star. In principle, a variety of well defined, star polymers with different numbers of arms can be prepared using this methodology by varying the functionality of the linking agents. Disadvantages of the method can be considered the sometimes long time required for the linking reaction and the need to perform fractionation in order to obtain the pure star polymer, since in almost all cases a small excess of the living arm is used in order to ensure complete linking.

2.2.1.2. Use of multifunctional initiators (core-first method)

The "core-first" method involves the use of a multifunctional initiator (core). The number of arms per star polymer is dethermined by the number of initiating

functionalities on each initiator (Figure 2.4). There are several requirements that a multifunctional initiator has to fulfill in order to produce star polymers with uniform arms, low molecular weight distribution, and controllable molecular weights. All the initiation sites must be equally reactive and have the same rate of initiation. Furthermore, the initiation rate must be higher than the propagation rate [67].

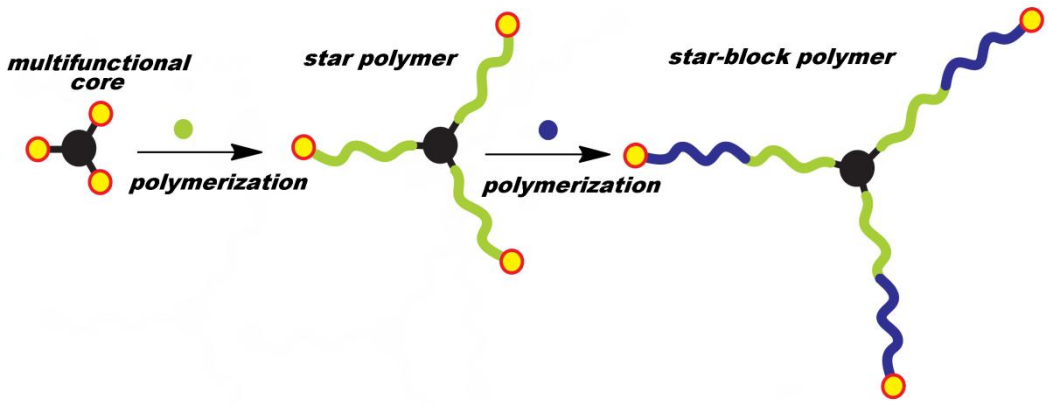


Figure 2.4: Illustration of the synthesis of star and star block copolymers by "core first" method.

2.2.1.3. Use of difunctional monomers (arm-first method)

In the "arm-first method", a star polymer is synthesized by crosslinking of linear arm precursors to form the core with cross-linking agents usually by using a divinyl cross-linker (Figure 2.5).

While the "core-first" and "coupling onto" methods based on multifunctional initiators or cores with an accurate number of functional groups can afford star polymers with the desired number of arms, the arm-first with divinyl compounds of linear polymers results in statistically distributed numbers of arms due to occurring cross-linking reactions. However, the "arm-first" method can produce star polymers with a large number of arms (10-100) and consists of relatively simple procedures. This method is more practical than the "core-first" and "coupling onto" methods which require the complicated synthesis of the multifunctional agents.

The star polymer synthesis based on the "arm-first" aproach was first developed in a living anionic polymerization. Zilliox et al. first employed anionic polymerization to prepare star polymers in high yield via the cross-linking of living PS with divinylbenzene (DVB) [71]. On the other hand, the "arm-first" aproach has been studied in living cationic polymerization. The successful preparation of star polymers

was first reported by Kanaoka et al. and involved the cationic polymerization of poly(isobutyl vinyl ether) with divinyl ether cross-linkers [72].

With the development of the C/LRP methods have superseded both living anionic and cationic polymerisation methods mainly due to the less stringent reaction conditions and wide range of monomers. So far, ATRP has been extensively used to prepare star polymers via the arm-first method. Matyjaszewski and coworkers first reported the synthesis of star polymers with a coss-linked core by ATRP. In this case, they established that cross-linker (DVB)/ macroinitiator molar ratios of between 5 and 15 were optimal for the formation of core cross-linked star polymers from PS [73] and P*t*BA macroinitiators[74]. Following the preliminary study of Matyjaszewski and coworkers several research groups have conducted detailed examinations into the preparation of core cross-linked star polymers via ATRP [75-78].

Regardless of the linear arm precursors, the preparation of core cross linked star polymers by "arm-first" technique can be categorized into two broad strategies: macroinitiator and macromonomer (Figure 2.5). In the macroinitiator strategy, the star macromolecules formed by crosslinking linear macroinitiator, where both the initiating sites and the arms of the star molecule originate from the macroinitiator. A major drawback to star synthesis using linear macroinitiator as the arm precursor is that the star polymer usually have a broad polydispersity due to the significant level of star-star coupling reactions. When a linear macromonomer is employed to copolymerize with divinyl cross-linker by using a low-molar-mass initiator, the number of arms (derived from macromonomer) per star molecule is independently controlled. Thus, a low molar ratio of initiator to macromonomer decreases the number of initiating sites in the star core, which effectively limits the extent of star-star coupling reactions and results in star polymers with low polydispersity.

In addition, the further chain extension of the preserved initiating sites from the core to initiate the polymerization of another monomer will induce formation of miktoarm star polymer by the ''in-out'' method (Figure 2.5).

There are several paramethers in an ATRP that should be controlled carefully in order to maximize the yield of stars and prevent star–star coupling reactions. The effects of type of cross-linker, cross-linker/macroinitiator molar ratio, macroinitiator DP, macroinitiator concentration, catalyst concentration, solvent nature, reaction

temperature, and reaction time on the structure and yield of core cross-linked star polymers prepared via ATRP were investigated in several reports.

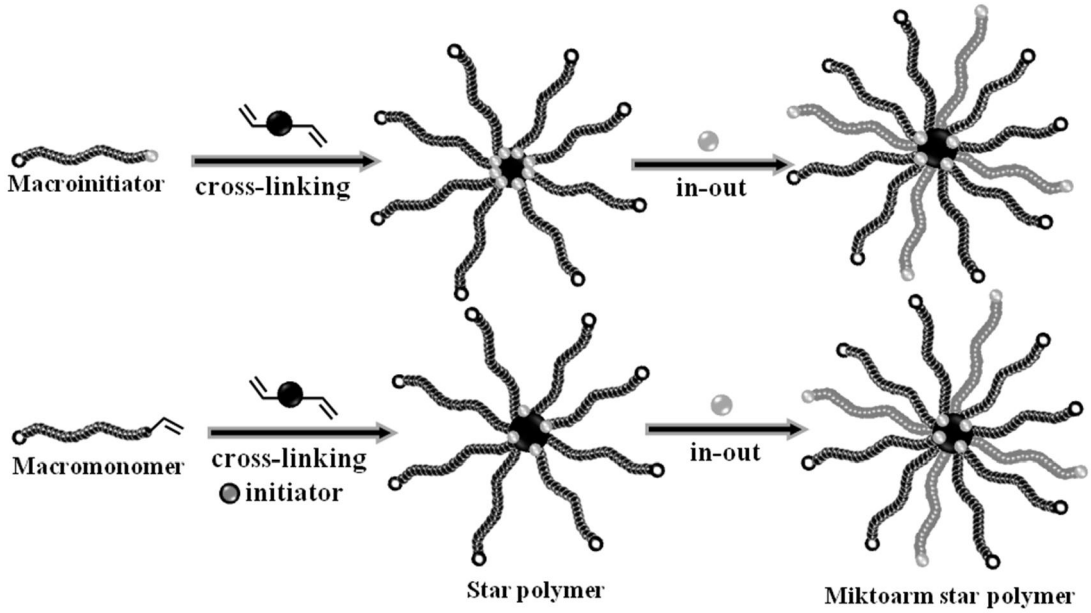


Figure 2.5: Schematic representation of the "arm-first" method for star polymer synthesis.

It is important to note that the "arm-first" process leads to preparation of multifunctional star polymers when functional initiators are used for the synthesis of the arms. Indeed, this method provides an efficient route to prepare multiarm star homo and block copolymers.

In that sence, a particularly well-suited example comes from Tunca and coworkers who have prepared multiarm star block copolymers based on the combination of ''arm first'' method with Diels-Alder click reaction to conjugate building blocks [79]. In this case, an α-anthracene and α-maleimide end functionalized polymers : Anth-PS, MI-PMMA and MI-P*t*BA were prepared by ATRP. Then, multiarm star polymer with anthracene functionality as reactive periphery group was synthesized by a cross-linking reaction of DVB using Anth-PS as a macroinitiator. Subsequently, the formation of multiarm star block copolymers were achieved via Diels–Alder click reaction between the reactive core and maleimide-end functionalized polymers (Figure 2.6).

This successful approach was further expand to prepare multiarm star triblock terpolymers using double click reactions sequentialy [80].

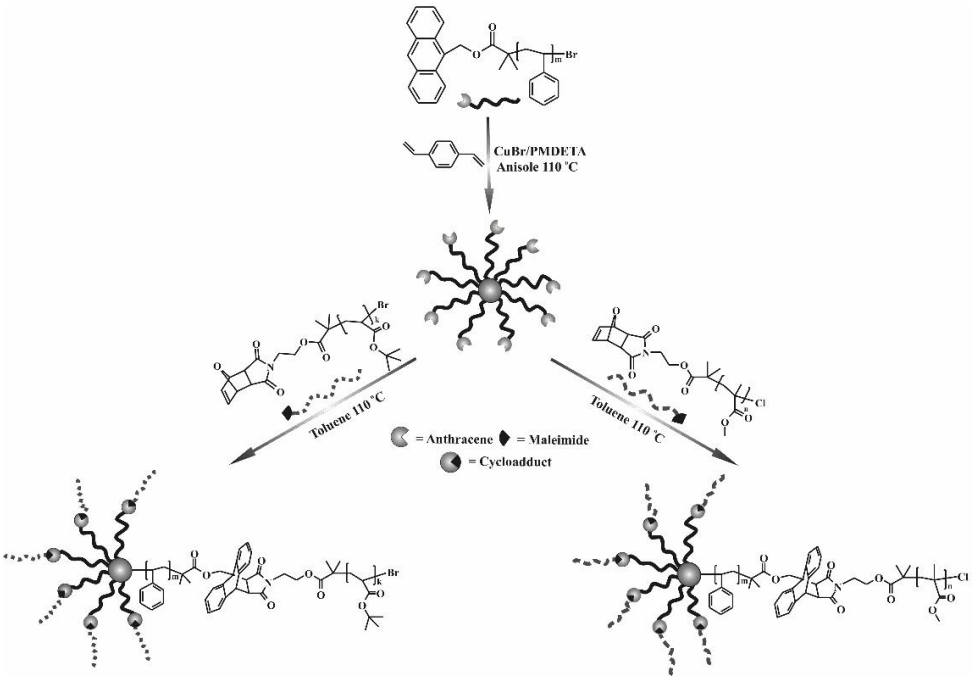


Figure 2.6: Scheme of Multiarm star synthesis and Diels-alder click reactions

In order to synthesize miktoarm star polymers with potentially any desired molar ratio and composition of the arms, Gao et al. reported a new strategy for the synthesis of miktoarm star copolymers using a simple and general ‘‘arm-first’’ method, i.e. one-pot ATRP cross-linking a mixture of different linear macroinitiators and/or macromonomers with a divinyl cross-linker [81]. When linear macromonomers were partially or completely used as arm precursors instead of macroinitiators, miktoarm star copolymers with a high star yield and a low polydispersity were successfully synthesized (Figure 2.7).

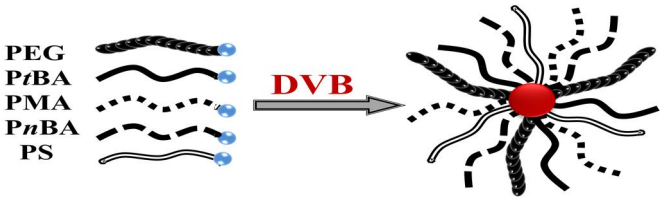


Figure 2.7: Scheme of miktoarm star polymers

Alternatively, NMP has been applied to the design of core cross-linked star polymers. Solomon and co-workers first prepared poly(4- *tert*-butylstyrene) via NMP followed by synthesizing the $(PS)_n$-polyDVB star polymers via ‘‘arm-first’’ aproach using DVB as cross-linker [82]. In order to increase the high star, different molar ratios of DVB to macroinitiators were examined to get optimum conditions in several reports [83-85]. The desire to prepare star polymers with high star yield and narrow

polydispersities has provided a progressive impetus to the development of new strategies for their creation. The NMP approach has since been refined by the introduction of improved alkoxyamine functionalised initiators, which have permitted the use of a wide range of monomer families and enabled the production of narrow polydispersity core cross-linked star polymers, in high yield, using a variety of alkoxyamine terminated macroinitiators and functional monomers [86, 87].

Compared to the broad applications of ATRP and NMP for the synthesis of functional star polymers using the "arm-first" method, only limited success has been obtained with RAFT polymerizations. Moad first proposed the possibility of using the "arm-first" method in RAFT polymerization for the synthesis of star polymers with a cross-linked core [88]. The first experimental proof of the synthesis of star polymers with a cross-linked core by RAFT was reported by Davis and coworkers although the synthesized $(PS)_n$-polyDVB star polymers were poorly controlled with low star yield and high polydispersity [89].

2.3. Click Chemistry

Contemporary synthetic polymer chemistry aims to enable the design and synthesis of macromolecules with not only precise molecular weight and narrow molecular weight distributions but also well-defined topology and chemical composition. Furthermore, emerging technologies, such as bio- and nanotechnologies, have increasingly demanded novel well-defined polymers, which raise the necessity to be able to conjugate polymers and/or biomolecules (or small molecules) with various polymer blocks in an easy mode. Living polymerization techniques such as anionic, cationic polymerizations, living/controlled radical polymerizations (L/CRPs), ring opening polymerization (ROP) and ring opening metathesis polymerization (ROMP) may provide polymers with the above mentioned well-defined properties to a certain extent. Moreover, challenges in employing these polymerization techniques alone manifest themselves when topologically as well as compositionally intricate macromolecular constructs are targeted. A combination of the living polymerization techniques with highly efficient click chemistry-based conjugation methodologies expands the vast toolbox of polymer chemists to obtain a wide range of well-defined polymer structures. [1,90].

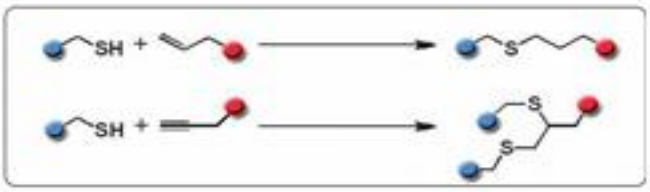
The click reaction defined by Sharpless and co-workers in 2001 should display high stereo- and regioselectivity, high yield under mild reaction conditions, simple recovery of the main product, a capability of working in a wide range of solvents, and tolerance of a wide range of functional groups [91]. The reaction must be modular, wide in scope, give very high yields, generate only inoffensive by-products that can be removed by non-chromatographic methods, and be stereospecific. The required process characteristics include simple reaction conditions, readily available starting materials and reagents, the use of no solvent or a solvent that is benign or easily removed, and simple product isolation [92]. The most popular click reactions are the thiol-ene, thiol-yne, copper catalyzed azide–alkyne cycloaddition (CuAAC), Diels–Alder cycloaddition,.

2.3.1. Thiol-yne and thiol-ene reaction

Thiol–yne and thiol-ene (TE) reactions (Equation 2.3) attracted attention due to the wide range of commercially available thiols and alkynes. Additionally, TE reactions can proceed via two routes,anti-Markovnikov radical addition or base catalyzed Michael addition (MA).Hawker and coworkers demonstrated the use of TE ‘‘click’’ reactions for the formation of monodisperse dendrimers. Schlaad and coworkers successfully utilized this chemistry for the functionalization of 1,2-polybutadiene side groups, as well as poly(2-oxazoline)s bearing pendant alkene moieties. Other thiol based ‘‘click’’ reactions have been developed and can be listed as thiol–maleimide addition, thiol-isocyanate addition, pyridyl–disulfide exchange, and thiol–parafluoro.Thiol terminated polymers can be easily obtained by reversible addition–fragmentation chain transfer (RAFT) polymerization of a wide range of monomers and a subsequent cleavage of the chain transfer agent. Alternatively, disulfide containing bifunctional ATRP initiators can be used for the preparation of thiol functionalized polymers. [93]

The thiol-ene click reaction has realized between a thiol and an alkene to form a thioether linkage. More specifically, the sulfur–carbon bond formation follows an anti-Markonikov process that can be promoted by UV light radiation or by radical initiators. Thiol-yne and thiol-ene click reactions are discovered in chemistry at early times, but have been rather extensively studied over the last century [94-96] Thiol-ene click reaxtions depicted in1926 by Braun and Murjahn [97]. During the time that

thiol-ene polymerizations utilize for the formation of networks [98, 99] or for the purpose of controlling molecular weight in radical polymerizations, thiol-ene reaction is more recently also referred to as a click reaction [100]. Among the ‘‘click’’ reactions, thiol-ene click is considered the most encouraging the green aspects of these reactions. Furthermore, this metal-free reaction can be performed in the absence of solvents in some cases, and can be photochemically controlled (even in the absence of a photoinitiator). Recent reports has showed that the thiol-ene click reaction is more efficient when initiated by light than by thermally [101]. The another advantage is that water- tolerant and oxygen makes it even more attractive.



(2.3)

Radicalic thiol-yne click proceeds by the same mechanism with chain transfer polymerization mechanism. Firstly, a thiyl radical is generated from a thiol-functionalized molecule by hydrogen abstraction from an initiator-derived radical, which subsequently reacts with carbon–carbon triple bond. This is like propagation step. And then, the radical abstracts a proton from another thiol to form the reaction product and recover a thiyl radical (Figure 2.8). But unfortunately, thiol-yne chemistry has significant side reactions [102], the whole process may not be considered a click reaction, as this is a direct paradox to the click concept. Known side reactions are disulfide formation and another one is head-to-head coupling of the carbon centered radicals..

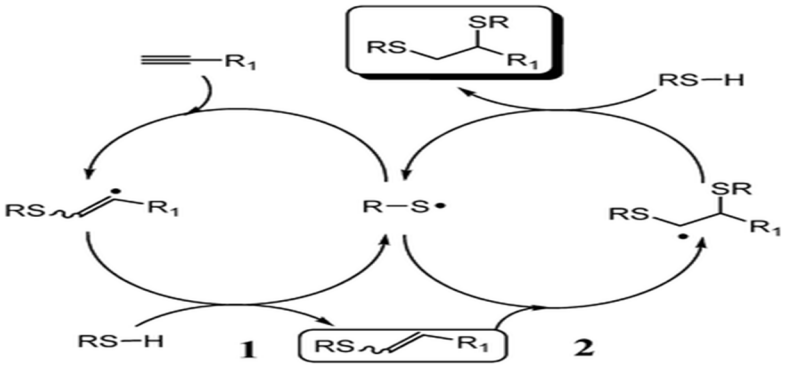
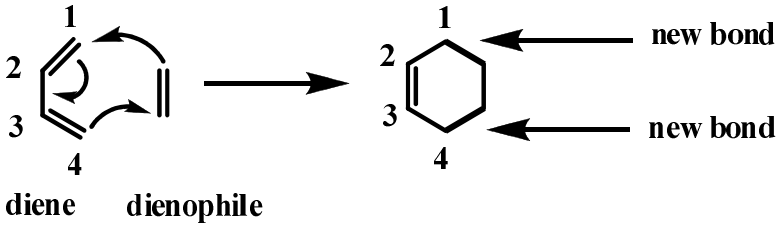


Figure 2.8: Presentation of Thiol-yne Reaction.

2.3.2. Diels-Alder reaction

The Diels-Alder (DA) reaction is a concerted [4π+2π] cycloaddition reaction of a conjugated diene and a dienophile. This reaction is one of the most powerful tools used in the synthesis of important organic molecules. The three double bonds in the two starting materials are converted into two new single bonds and one new double bond to afford cyclohexenes and related compounds (Equation 2.4). This reaction is named for Otto Diels and Kurt Alder, who received the 1950 Nobel prize for discovering this useful transformation [103-105].



(2.4)

Typically, the DA reaction works best when either the diene is substituted with electron donating groups (like -OR, -NR2, etc) or when the dienophile is substituted with electron-withdrawing groups (like -NO2, -CN, -COR, etc) [106].

2.3.3. Copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC)

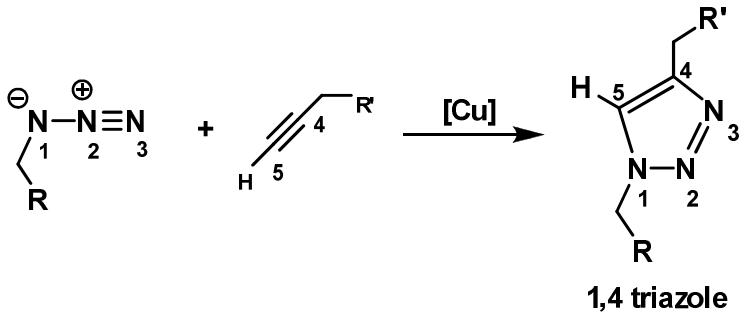
Huisgen's 1,3-dipolar cycloaddition of alkynes and azides yielding triazoles is, undoubtedly, the premier example of a click reaction [107]. Recently, 1,3-dipolar cycloadditions, such as reactions between azides and alkynes or nitriles, have been applied to macromolecular chemistry, offering molecules ranging from the block copolymers to the complexed macromolecular structures [108].

Sharpless and co-workers have identified a number of reactions that meet the criteria for click chemistry, arguably the most powerful of which discovered to date is the Cu(I)-catalyzed variant of the Huisgen 1,3-dipolar cycloaddition of azides and alkynes to afford 1,2,3-triazoles [109]. Because of Cu(I)-catalyzed variant of the Huisgen 1,3-dipolar cycloaddition of azides and alkynes reactions' quantitative yields, mild reaction condition, and tolerance of a wide range of functional groups, it is very suitable for the synthesis of polymers with various topologies and for polymer modification [110]. Because of these properties of Huisgen 1,3-dipolar

cycloaddition, reaction is very practical. Moreover, the formed 1,2,3-triazole is chemically very stable [111].

In recent years, triazole forming reactions have received much attention and new conditions were developed for the 1,3-dipolar cycloaddition reaction between alkynes and azides [112]. 1,2,3-triazole formation is a highly efficient reaction without any significant side products and is currently referred to as a click reaction [113].

Copper(I)-catalyzed reaction sequence which regiospecifically unites azides and terminal acetylenes to give only 1,4-disubstituted 1,2,3 triazoles (Equation 2.5).



(2.5)

In fact, the discovery of Cu(I) efficiently and regiospecifically unites terminal alkynes and azides, providing 1,4-disubstituted 1,2,3-triazoles under mild conditions, was of great importance. On the other hand, Fokin and Sharpless proved that only 1,5-disubstituted 1,2,3-triazole was obtained from terminal alkynes when the catalyst switched from Cu(I) to ruthenium(II) [111].

2.4. Photolysis of *o*-Nitrobenzyl Group

Photolabile groups have been used extensively in synthetic organic chemistry and have found numerous applications in academia and industry. While organic synthesis engaged the use of photolabile protecting groups as a tool for orthogonal deprotection, the development of photoacid generators, which act as H^+ sources upon irradiation, and acid-sensitive photoresists have enabled the production of photosensitive materials employed in the microelectronic1and coatings industries. Bochet has previously summarized the various photolabile groups that find intensive application in synthetic chemistry. o-Nitrobenzylic polymers have been used in various synthetic and biological applications especially for caged biomolecules.

Polymers featuring photolabile groups are the subject of intense research because they allow the alteration of polymer properties simply by irradiation. In particular, the (o-NB) is utilized frequently in polymer and materials science. This Perspective pays particular attention to the increasing utilization of this chemical group in polymer chemistry. It covers the use of (i) o-NB-based cross-linkers for photodegradable hydrogels, (ii) o-NB side chain functionalization in (block) copolymers, (iii) o-NB side chain functionalization for thin film patterning, (iv) o-NB for self-assembled monolayers, (v) photocleavable block copolymers, and (vi) photocleavable bioconjugates (Figure 2.9) [114].

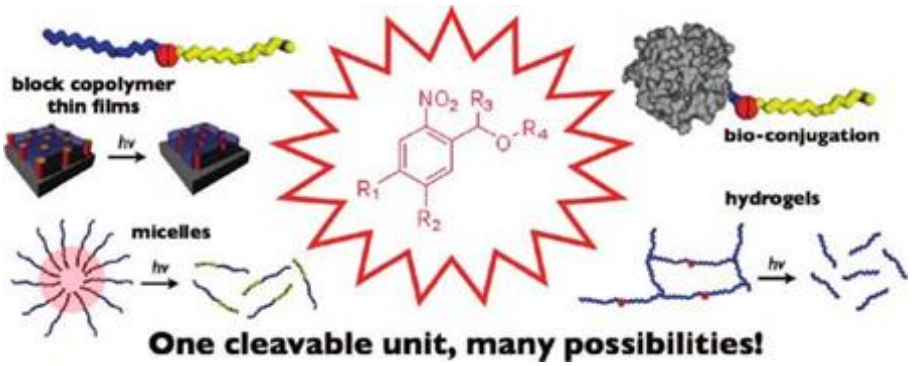


Figure 2.9: Application of o-nitrobenzyl group containing polymers [114]

o-Nitrobenzyl (*o*-NB) and 1-(2-nitrophenyl)ethyl derivatives which carry a leaving group at the benzylic position release the protected substrate if any UV irradiation happens. The reaction proceeds by flash photolysis at $\lambda_{max} \approx 350$ nm.

o-Nitrobenzyl group can be leaved under UV. Earlier reports on their photochemistry [115] including the one on the photoisomerization of o-nitrobenzaldehyde into the corresponding nitrosobenzoic acid [116] (Figure 2.10).

Photolabile protecting groups have been used in applications in chemistry extensively [120-122]. The removal of this category of protecting groups is “clean”: in contrast to most other protecting strategies because the release of the protected (“caged”) substrate requires no added reagent, just with light. This feature makes them particularly favorable if access to the reaction site is difficult or if chemical reagents are of restricted use. We observe these cases with living organisms. In these systems, addressing biological issues often requires delivery of biologically active part of the drug at a given time and to a given location. This may be achieved by

manipulating microsyringes. A noninvasive alternative involves adding to the biological medium caged compounds that reveal their biological activity only upon

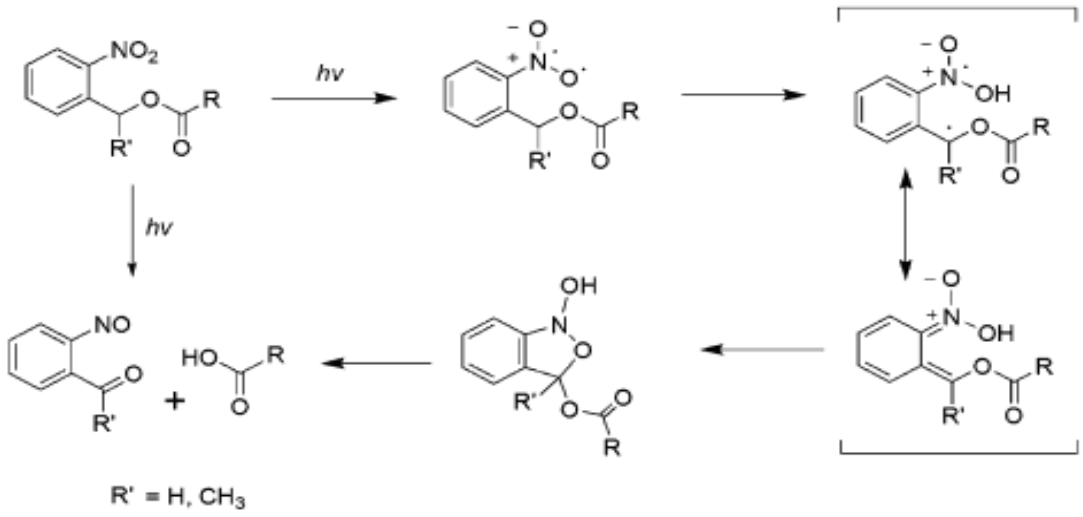


Figure 2.10: Photoisomerization mechanism of o-nitrobenzyl alcoholinto an o-nitrosobenzaldehyde, releasing a carboxylic acid [117,118,119]

illumination. A pulse of a focussed laser beam provides temporal and spatial control over the delivery of the material [123].

Scott L. Diamond and his group have employed photo-decomposition reactions various photo-active compounds and various irradiation protocols for biochemical or chemical research. The photoreactions carried out in the body tend to use photosource with comparable long wavelength (k > 300 nm) to minimize damage to tissue. Therefore, we have chosen o-nitrobenzyl group which can be activated by photoirradiation of 365 nm.

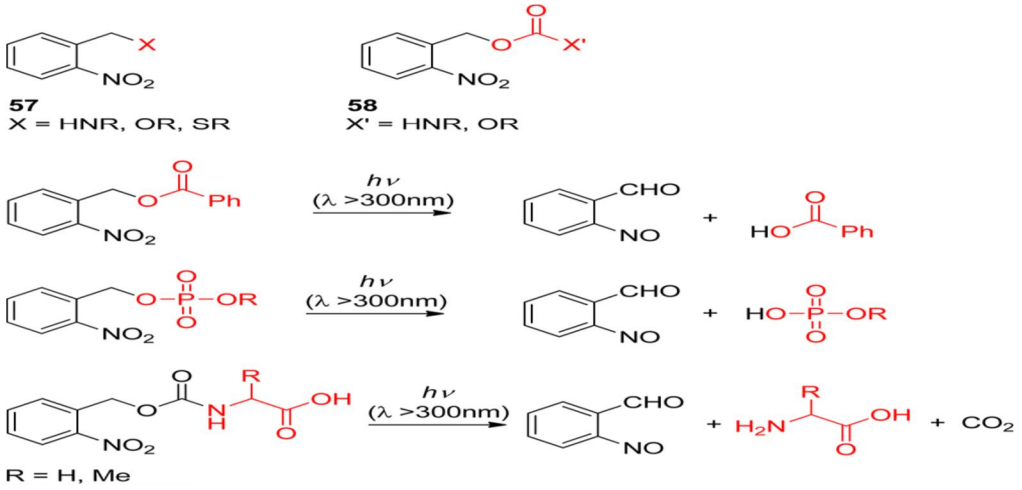


Figure 2.11: Photolysis of Some o-Nitrobenzyl Derivatives.

Also they have showed decomposition and wave length relation. As seen in the graph maximum decomposition is at 300 nm but when we use this polymer as a drug this wave length can damage tissues [124]. This study also shows that decomposition is percentage is very high at wavelength 300 nm. Photocleavage efficiency tends to improve when wavelengths near 300 nm are used, as the o-NB linker itself displays an absorption maximum at or near this wavelength. (Figure 2.12).

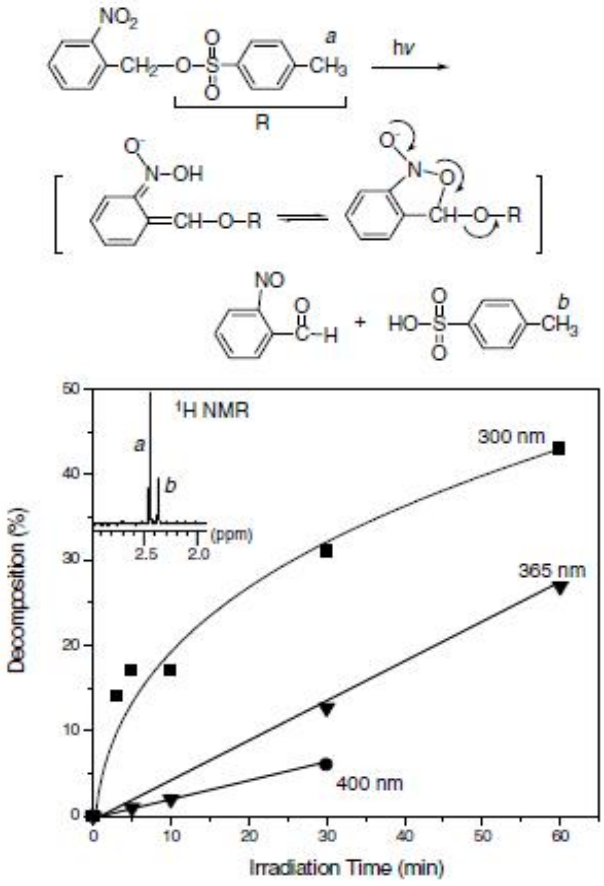


Figure 2.12: GPC traces (UV detector) of o-NB-(PS-b-PEO)

3. EXPERIMENTAL WORK

3.1. Materials

Styrene (St, 99%, Merck) was passed through basic alumina column to remove inhibitor and then distilled from CaH_2 in vacuum prior to use. *N*, *N*, *N*', *N*'', *N*''-pentamethyldiethylenetriamine (PMDETA, 99%, Aldrich) was distilled over NaOH prior to use. Propargyl bromide (80 wt. % in toluene, Aldrich), α-bromoisobutryl bromide (98%, Aldrich), 4-dimethylaminopyridine (DMAP, 99%, Acros), o-nitrobenzyl alcohol (97%, Aldrich), triethylamine (99.5%, Aldrich), divinylbenzene (DVB, 80%, Aldrich), CuBr (99.9%, Aldrich), potasium carbonate (K_2CO_3, 99%, Aldrich), *N*-acetyl-L-cysteine methyl-ester (90%, Aldrich), 4,4′-Azobis(4-cyanovaleric acid) (ABCVA, 98%, Aldrich) were used as received. Dichloromethane (CH_2Cl_2, Aldrich) was used after distillation over P_2O_5. Tetrahydrofuran (THF; 99.8%, J.T. Baker) was dried and distilled over benzophenone-Na. Anisole(99.7%, Aldrich), *N,N*-Dimethylformamide (DMF, 99.8%, Aldrich), Diethyl ether (99.7%, Aldrich), 1.4-dioxane (99.8%, Aldrich), toluene (99.8%, Aldrich), methanol (99.8%, Aldrich) were used without further purification. Ethyl acetate (EtOAc) and hexane were in technical grade and distilled prior to use.

3.2. Instrumentation

Nuclear magnetic resonance spectroscopy (NMR)

^1H NMR measurements were recorded in $CDCl_3$ with $Si(CH_3)_4$ as internal standard, using an Agilent VNMRS 500 MHz instrument.

UV-visible spectrophotomether (UV-vis)

UV spectra were recorded on a Shimadzu UV-1601 spectrophotomether in CH_2Cl_2.

Gel permeation chromatography (GPC)

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 diamether, 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 standards (Polymer Laboratories).

Triple detector gel permeation chromatography (TD-GPC)

The second GPC system with an Agilent model isocratic pump, four Waters Styragel columns (guard, HR 5E, HR 4, HR 3, and HR 2), a Viscotek TDA 302 triple detector (RI, dual laser light scattering (LS) (λ = 670 nm, 90° and 7°) and a differential pressure viscomether) (TD-GPC) was conducted to measure the absolute molecular weights in THF with a flow rate of 0.5 mL/min at 35 °C. All three detectors were calibrated with a PS standard having narrow molecular weight distribution (M_n = 115,000 g/mol, M_w/M_n = 1.02, [η] = 0.519 dL/g at 35 °C in THF, dn/dc = 0.185 mL/g) provided by Viscotek company. Typical sample concentrations for GPC-analysis were in the range of 2–8 mg/mL depending on molecular weight of analyzed polymers. Data analyses were performed with OmniSec 4.5 software from Viscotek Company.

Gas chromatography (GC)

DVB conversion was dethermined using the Agilent 6890N gas chromatograph, equipped with an FID detector using a wide-bore capillary column (HP5, 30 m x 0.32 mm x 0.25μm, J&W Scientific). Injector and detector were kept constant at 280 and 285 ºC, respectively. Initial column temperature is 40 ºC, finally reaching up to 120 ºC at a heating rate of 40 ºC/min.

3.3. Synthesis Methods

(2-nitro-5-(prop-2-yn-1-yloxy)phenyl)methanol (1), 1.1.1 2-nitro-5-(prop-2-yn-1-yloxy)benzyl2-bromo-2-methylpropanoate (2), Alkyne-*o*-NB-PS-Br (3), Cysteine-*o*-NB-PS-Br(4), HOOC-PS (5), (Alkyne-*o*-NB-PS)$_n$-polyDVB (6), (Cysteine-*o*-NB-PS)$_n$-polyDVB (7).

3.3.1. Synthesis of (2-nitro-5-(prop-2-yn-1-yloxy)phenyl)methanol

5-hydroxy-2-nitrobenzyl alcohol (1.0 g, 5,9 mmol) was added to a 100 mL of round bottom flask with 10 mL of DMF. K_2CO_3 (2.35 g, 17.7 mmol) was added and the mixture was stirred at 60 ºC for 30 minutes. Propargyl bromide (0.63 mL, 7.0 mmol in %80 toluene) was added dropwise within 15 minutes via syringe and the mixture was stirred 60 ºC for overnight. After solvent was removed under reduced pressure, and residue was dissolved in ethylacetate (EtOAc) and extracted with water. The aqueous layer was extracted with EtOAc, combined organic layers were dried over Na_2SO_4 and filtered. Removal of the solvent under reduced pressure gave yellow-brown solid. The residue dissolved ethylacetate (15 ml) and was crystallized from cool cyclohexane (90 ml) and obtained brown crystals. Therefore the crystals dissolved ethylacetate. A small amount of active carbon which absorbed brown color was added to the mixture. The mixture was stirred at higher than room temperature. Mixture was filtered to removed from active carbon.After solvent was removed under reduced pressure to give **1** as a yellow solid.

Yield=1.04 g (85%). ^{1}H NMR ($CDCl_3$, δ) 8.20 (d, H, Ar*H*), 7.33 (d, H, Ar*H*), 7.01 (m, H, Ar*H*) 5.02 (s, 2H, C≡CC*H*$_2$O), 4.82 (d, 2H, C*H*$_2$OH) 2.59 (t, 6H, C≡C*H*)

3.3.2. Synthesis of 2-nitro-5- (prop-2-yn-1-yloxy) benzyl 2-bromo-2-methylpropanoate

Previously obtained product **(1)** (0,65 g, 3.1 mmol) and DMAP (0,19 g, 1.55 mmol) were dissolved in 125 mL of THF, and Et_3N (1.50 mL, 7.75 mmol) was added. The reaction mixture was then cooled to 0 ºC. 2-bromo isobutyryl bromide (0.58 mL, 4.65 mmol) was added in 30 mL of THF dropwise within 30 minutes to this solution. The reaction mixture was stirred for 15 minutes at 0 ºC and then for overnight at room tempeature. The ammonium salt was filtered off and the solvent was evaporated under reduced pressure. The remaining residue was extracted with CH_2Cl_2, and saturated aqueous $NaHCO_3$. The aqueous phase again extracted with CH_2Cl_2, and combined organic phases dried over Na_2SO_4. Excess CH_2Cl_2 was evaporated under reduced pressure the remaining product was purified by column chromatography over silica gel eluting with hexane/ ethylacetate (4:1) to give yellow liquid product.

Yield: 1,0 g (95%). ^{1}H NMR ($CDCl_3$, δ) 8.23 (d, 1H, Ar*H*,), 7.30 (d, 1H, Ar*H*), 7.04 (m, 1H, Ar*H*), 5,69 (s, 2H, CH_2OC=OC), 4.82 (d, 2H, C≡CCH_2O), 2.59 (t, 1H, C≡C*H*), 2.03 (s, 6H, C(CH_3)$_2$-Br).

3.3.3. Synthesis of Alkyne-*o*-NB-PS

St (20 mL, 174 mmol), PMDETA (0.364 mL, 1.74 mmol), CuBr (0.25 g, 1.74 mmol), previously product **(2)** (0.6 g, 1.74 mmol) and anisole (12,12 mL, % St-40) were added to a 100 mL of Schlenk tube and the reaction mixture was degassed by three FPT cycles and left in vacuum and placed in a thermostated oil bath at 90 ºC for 6 hours [125]. After the specified time, the polymerization mixture was diluted with THF, passed through a column of neutral alumina to remove catalyst and precipitated into methanol. The polymer was dried in a vacuum oven at 40 °C

Yield: 6.0 g (33%) ^{1}H NMR 7.40-6.25 (Ar*H* of polystyrene), 8.16, 7.43, 7.5-6.5 (Ar*H* of *o*-nitrobenzyl), 4.73 (CH_2OC=OC), 2.52 (C≡C*H*), 2,2-0,6 (aliphatic protons of polystyrene).

3.3.4. Termal thiol-yne reaction of alkyne-*o*-NB-PS linear polymer

Alkyne-*o*-NB-PS (0.30 g, 67,0 μmol, $M_{w,TD\text{-}GPC}$= 5900 g/mol) polymer, *N*- acetyl-L-cysteine methyl ester (0.24 g, 1.33 mmol), ABCVA(0.04 mg, 0.27 mmol) were dissolved in dioxane (30 mL) in 50 mL of Schlenk tube. Reaction mixture was degassed by three FPT cycles, left in vacuum and stirred for overnight at 80 ºC .After, the reaction was stopped via exposure to air. The mixture extracted with CH_2Cl_2 three times and combined organic phases dried over Na_2SO_4. CH_2Cl_2 was evaporated under reduced pressure. The remain product precipitated into methanol and dried under vacuum at 40 ºC for 24 h**.**

Yield: 0.25 g (83%) ^{1}H NMR 8.09, 7.48 (Ar*H* of *ortho*-nitrobenzyl), 7.40-6.25 (Ar*H* of polystyrene), 4.91 (CH_2OC=OC), 3.78 (CH_3OC=O), 3.68 (CH_2CHS), 2.26 (CH_3C=ONH), 2.2-0.6 (aliphatic protons of polystyrene).

3.3.5. Photolysis of the *ortho*-nitrobenzyl group of polystyrene linear polymer

Cysteine-*o*-NB-PS linear polymer (0.18 g, $M_{n,GPC}$= 6670 g/mol) was added in a 250 mL of round bottom flask with THF (200 mL). The flash was placed in a photoreactor with 350 nm for 8 hours. After that, THF is evaporated and polymer is

precipitated in methanol. The polymer was dried for 24 h in a vacuum oven at 40 °C. Yield: 0.12 g (67%) ^{1}H NMR 7.40-6.25 (Ar*H* of polystyrene), 2.2-0.6 (aliphatic protons of polystyrene).

3.3.6. Preparation of (Alkyne-*o*-NB-PS)$_n$-polyDVB multiarm star polymer

Alkyne-*o*-NB-PS macroinitiator (2.00 g, 0.4 mmol, $M_{n,GPC}$= 5900 g/mol), DVB (0.95 mL, 6,0 mmol), PMDETA (0.093 mL, 0.4 mmol), CuBr (0.064 g, 0.4 mmol) and anisole (21 mL) were charged to a Schlenk tube equipped with a magnetic stirrer bar under argon atmosphere. The first sample was quickly taken from the reaction mixture for GC measurement, before the reaction mixture was degassed by using three FPT cycles. The reaction flask was back-filled with argon and immersed in oil bath at 110 °C. At time intervals, the samples were taken from the reaction mixture with argon purged-syringe under positive argon atmosphere and then diluted with THF, purified by passing through short neutral alumina column to remove the copper salt and filtered through poly(tetrafluoroethylene) (PTFE) filter (0.2 μm pore size) prior to GC and GPC analyses. After 26 h at 72 % conversion, the reaction was stopped via exposure to air. The polymerization mixture was diluted with THF, filtered through a column filled with neutral alumina to remove the copper complex and the star polymer was precipitated in methanol. The crude product was dissolved in THF, precipitated into methanol/diethyl ether (1/5; v/v) and dried under vacuum at 40 °C for 24 h.

Yield: 0,55 g ^{1}H NMR ($CDCl_3$, δ) 8.15, 7.48 (br, Ar*H* of ortho-nitrobenzyl), 7.5-6.25 (br, Ar*H* of PS), 4.74 (br, (CH_2O=O), 2.52 (br, C≡C*H*), 2.0-0.9 (br, aliphatic protons of PS)

3.3.7. Termal thiol-yne reaction of (Alkyne-*o*-NB-PS)$_n$-polyDVB multiarm star

(Alkyne-*o*-NB-PS)$_n$-polyDVB (0.20 g 1.15 μmol, $M_{w,TD-GPC}$= 173440 g/mol) multiarm star polymer, *N*-acetyl-L-cysteine methyl ester (0,1 g, 0,55 mmol) and ABCVA (3,1 mg, 11,1 μmol) as termal initiator were dissolved in dioxane (50 mL) in 100 mL of Schlenk tube. Reaction mixture was degassed by three FPT cycles, left in vacuum and stirred for overnight at 80 °C. After, the reaction was stopped via exposure to air. The mixture extracted with CH_2Cl_2 three times and combined organic phases dried over Na_2SO_4. CH_2Cl_2 was evaporated under reduced pressure.

The remain product precipitated into methanol and dried under vacuum at 40 ºC for 24 h.

Yield: 0.14 g ^{1}H NMR ($CDCl_3$, δ) 8.06, 748 (br, Ar*H* of *ortho*-nitrobenzyl), 7.40-6.25 (br, Ar*H* of PS), 4.92 (br, (CH_2O=O), 3,83(br, BrC*H*), 3.77((br, C*H*$_3$OC=O), 3.72 (br, C*H*$_2$CHS), 2.26 (br, C*H*$_3$C=ONH), 2.0-0.9 (br, aliphatic protons of PS)

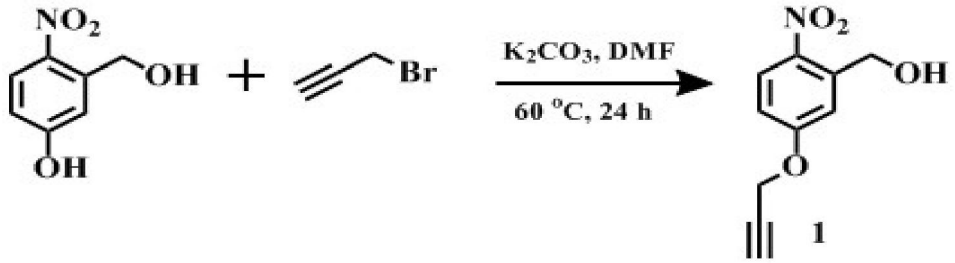
3.3.8. Photolysis of the *ortho*-nitrobenzyl group of multiarm star polymer

(Cysteine-*o*-NB-PS)$_n$-polyDVB multiarm star (0.1 g, $M_{n,GPC}$= 341980 g/mol), was added in a 250 mL of round bottom flask with 200 mL THF. The flash was placed in a photoreactor with 350 nm for 8 hours. After that, THF is evaporated and polymer is precipitated in methanol. The polymer was dried for 24 h in a vacuum oven at 40 ºC.

4. RESULTS AND DISCUSSION

4.1. Synthesis of Initiator

First of all, ortho-nitrobenzyl alcohol and propargyl bromide were reacted in DMF at 60 ^{o}C for overnight to give (2-nitro-5-(prop-2-yn-1-yloxy)phenyl)methanol (1) (Equation 4.1).



(4.1)

The 1H NMR spectrum of 1 showed aryl protons at 8.20, 7.33, 7.01 ppm, methyl protons next to methylene group at 5.02, methyl protons next to OH at 4.82 ppm and alkyne proton at 2.59 ppm (Figure 4.1).

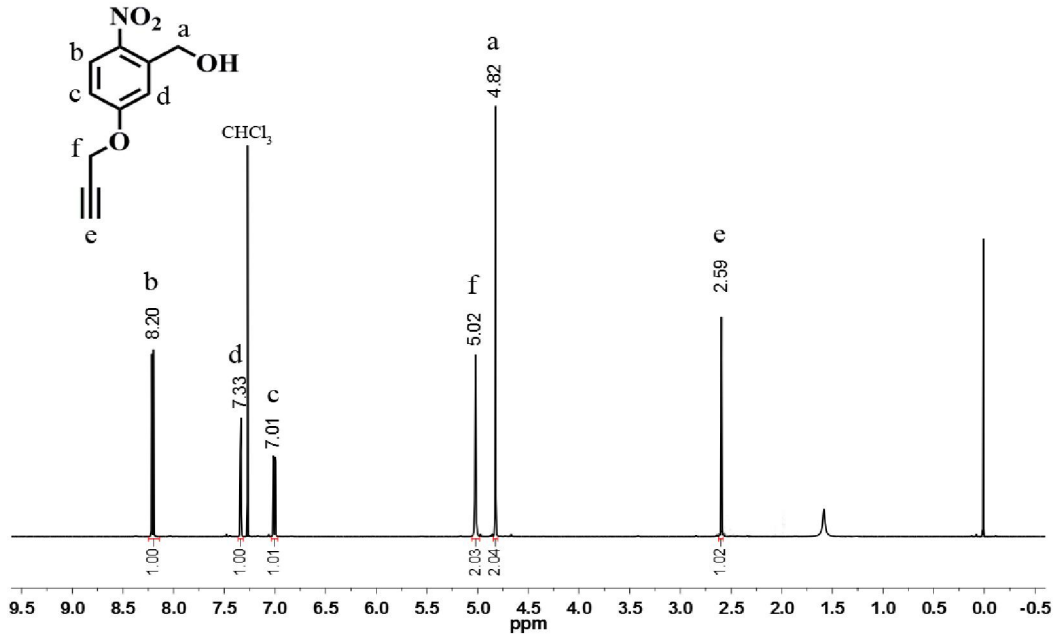
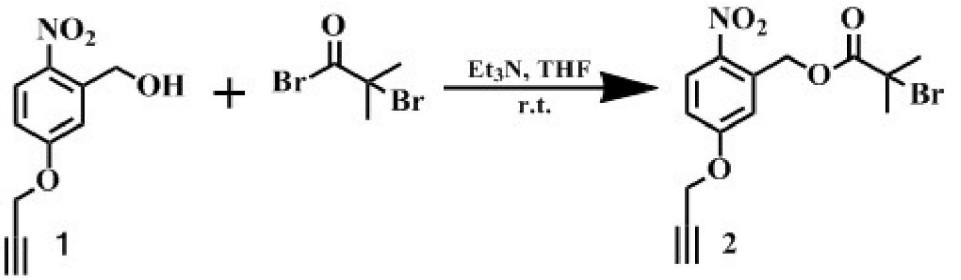


Figure 4.1: 1H NMR spectrum of (2-nitro-5-(prop-2-yn-1-yloxy)phenyl)methanol (1) in CDC13.

The synthesis of 2-nitro-5-(prop-2-yn-1-yloxy)benzyl 2-bromo-2-methylpropanoate **(2)** was obtained via an esterification reaction between **1** and 2-bromoisobutryl bromide in THF at room temperature (Equation 4.2). Thus, the initiators with proper functionalities for ATRP reaction were first prepared.



(4.2)

The ^{1}H NMR spectrum of **2** showed aryl protons at 8.23, 7.30 and 7.04 ppm, methyl protons next to ester unit at 5.69, methyl protons next to methylene group at 4.82 ppm, alkyne proton at 2.59 ppm, methyl protons next to Br at 2.03 ppm (Figure 4.2)

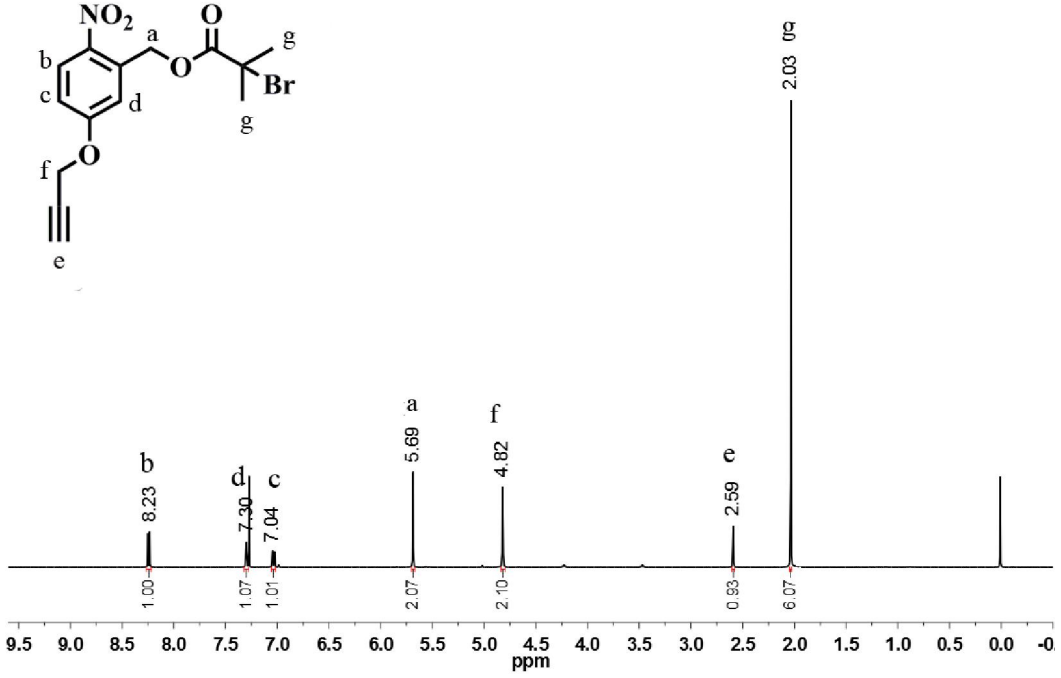
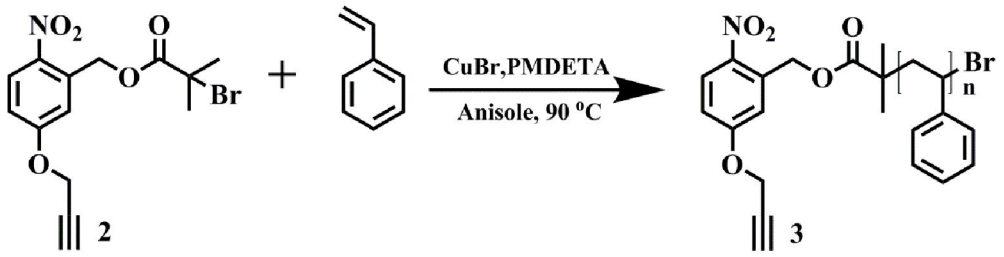


Figure 4.2: ^{1}H NMR spectrum of 2-nitro-5-(prop-2-yn-1-yloxy)benzyl 2-bromo-2-methylpropanoate (2) in $CDC1_3$.

4.2. Synthesis, Functionalization and Photolysis of Linear Polymers

4.2.1. Alkyne-*o*-NB-PS linear polymer

Then compound **3** was used as an initiator in ATRP of Styrene in the presence of CuBr/PMDETA as a catalyst system in anisole at 90 ºC for 6 h to obtain linear Alkyne-*o*-NB-PS (Equation 4.3)



(4.3)

From ^{1}HNMR spectrum of the polymer, the aryl protons of *o*-NB group were detected at 8.16, 7.43 ppm. The $M_{n,NMR}$= 5500 g/mol of Alkyne-*o*-NB-PS was dethermined from a ratio of integrated peaks at 7.40-6.25 ppm (Ar*H* protons of PS) to methyl protons next to ester unit at 4.73 ppm (Figure 4.3).

$M_{n,NMR}$= 49 X 104.15 + 356,17 (MW of **2**) = 5500 g/mol.

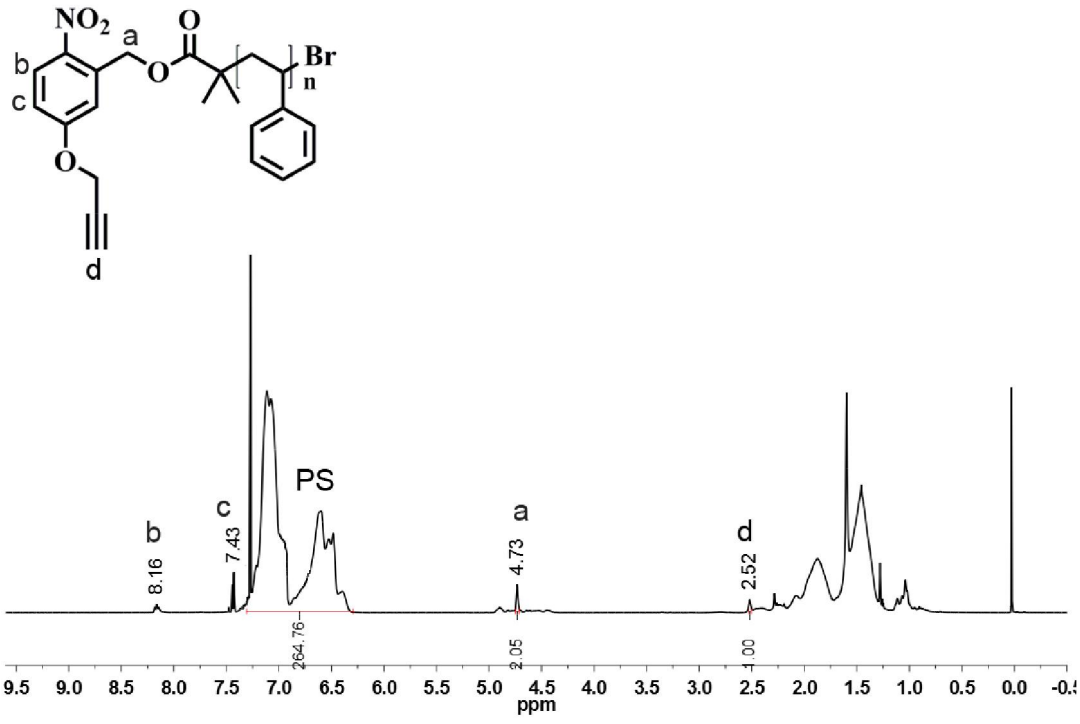
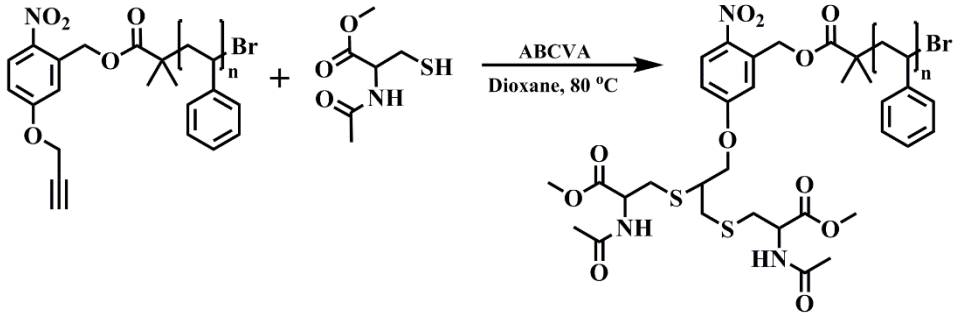


Figure 4.3: ^{1}H NMR spectrum of Alkyne-o-NB-PS in $CDCl_3$.

4.2.2. Thiol-yne reaction of Alkyne-*o*-NB-PS linear polymer

N-acetyl-L-cysteine methyl-ester functionalized Alkyne-*o*-NB-PS linear polymer was carried out by thermal thiol-yne click reaction between *N*-acetyl-L-cysteine methyl-ester and Alkyne-o-NB-PS in the presence of thermal initiator 4,4′-azobis(4-cyanovaleric acid) at 80 °C for overnight (Equation 4.4)



(4.4)

From ^{1}HNMR spectrum of the polymer, the aryl protons of *o*-NB group were detected at 8.09, 7.48 ppm. The appearance of new signals corresponding to the C*H*$_3$OC=O, NCHC*H*$_2$S and SCHC*H*$_2$ at 3.78, 2.27 and 3.68 ppm, respectively confirmed the structure of cysteine-*o*-NB-PS-Br.). Importantly, the peak at 3.9 ppm was assigned to the C*H*(Ph)Br, indicating that the end-group was intact.

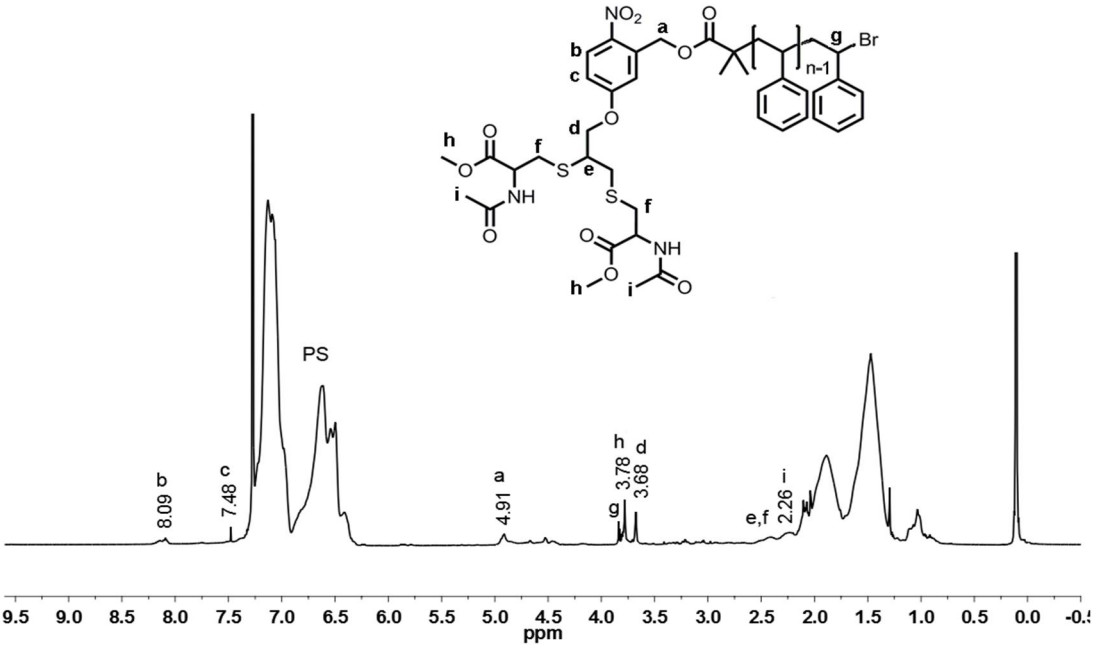
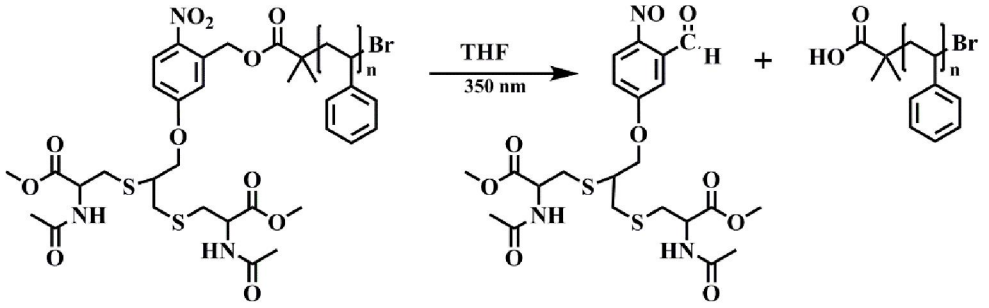


Figure 4.4: ^{1}H NMR spectrum of Cysteine-*o*-NB-PS in $CDCl_3$.

4.2.3. Photolysis of the *o*-Nitrobenzyl group of polystyrene linear polymer

Cysteine-o-NB-PS linear polymer in THF was irradiated by a photoreactor at 350 nm at room temperature for 8 h.(Equation 4.5)



(4.5)

In ^{1}H NMR of the polymer, aryl protons of polystyrene and aliphatic protons were observed at 7.40-6.25 and 2.2-0.9 ppm respectivly.Both o-nitrobenzyl's and cysteine's peak disappeared which this proves that there happened photo degredation.

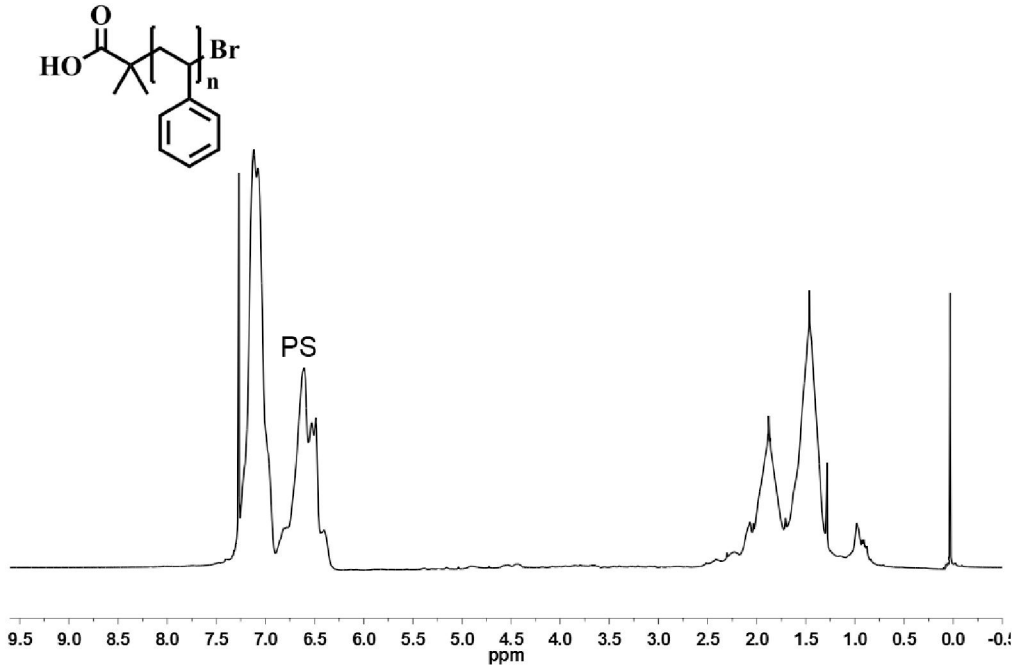


Figure 4.5: ^{1}H NMR spectrum of HOOC-PS in $CDCl_3$.

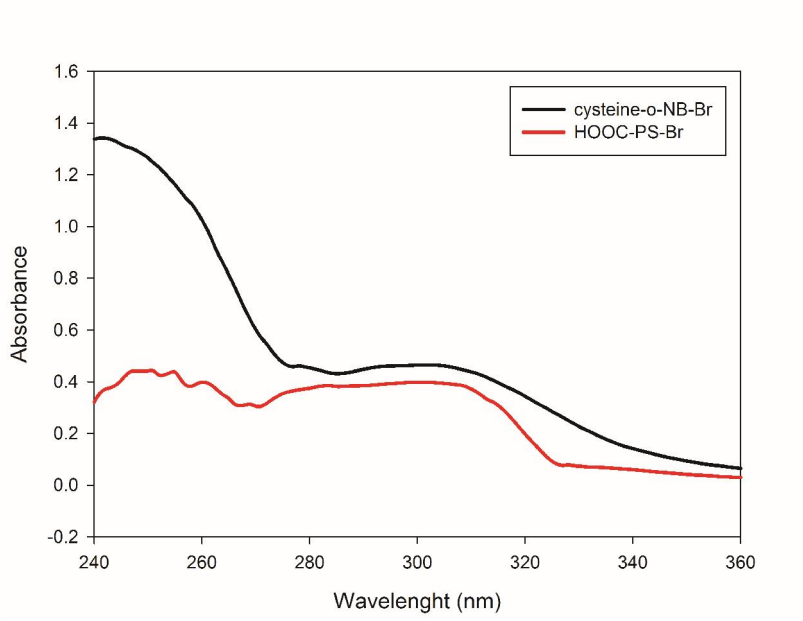


Figure 4.6: UV spectrum of cysteine-*o*-NB-PS and HOOC-PS in CH_2CI_2.

Table 4.1: The result of the linear polymers

Polymer	$M_{n,GPC}$	$M_{w,GPC}$	$M_{w,TD\text{-}GPC}$ (g/mol)	M_w/M_n TD-GPC	$M_{n,NMR}$ (g/mol)	$M_{n,theo}$ (g/mol)
Alkyne-*o*-NB-PS-Br[a]	4650	5400	5900	1.31	5500	3800[d]
Cysteine-*o*-NB-PS-Br[b]	4600	5250	6670	1.17	5700	4000[f]
HOOC-PS-Br[c]	4700	5380	6250	1.15	4000	3300[e]

[a] Synthesized by ATRP of Styrene in anisole using CuBr as a catalyst and 2-nitro-5-(prop-2-yn-1-yloxy)benzyl2-bromo-2-methylpropanoate as an initiator at 110 °C. $[M]_0:[I]_0 = 100$.
[b]Thiol-yne click reaction between alkyne-o-NB-PS and *N*-acetyl-L-cysteine methyl-ester in dioxane at 80° for overnight.
[c] Obtained by flash photolysis at $\lambda_{max} \approx 350$ nm) in THF for 8 h.
[d] $M_{n,theo} = ([M]_o/[I]_o)$ X conversion % X M_W of monomer + M_W of initiator.
[e] $M_{n,theo} = M_n$ of alkyne-*o*-NB-PS + M_W of *N*-acetyl-L-cysteine methyl-ester.
[f] $M_{n,theo} = M_n$ of cysteine-*o*-NB-PS - M_W of *N*-acetyl-L-cysteine methyl-ester *ortho*-nitrophenyl ether.

GPC analysis showed monomodal traces for the mentioned example. A clear shift was not shown for GPC traces of these polymers (Figure 4.7).

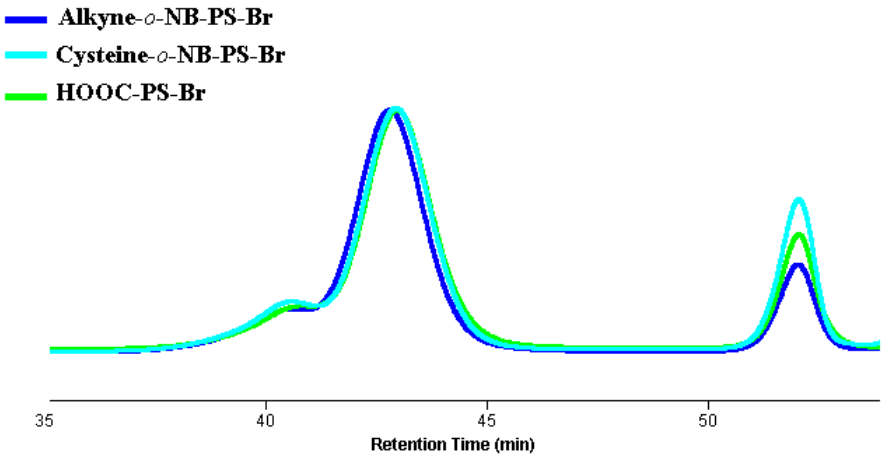
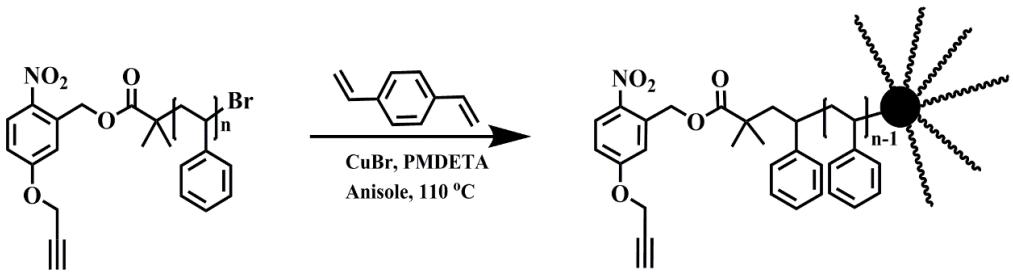


Figure 4.7: GPC traces of α-cysteine-o-NB-ω-bromide-terminated PS (cysteine-o-PS-Br), α-cysteine-o-NB-ω-bromide-terminated (cysteine-o-NB-PS-Br), α-carbocyclic acid-ω-bromide-terminated PS (HOOC -PS-Br).

4.3. Synthesis, Functionalization and Photolysis of Multiarm Star Polymer

4.3.1. Synthesis of (Alkyne-*o*-NB-PS)$_n$-polyDVB multiarm star polymer

In this study, after the preparation of the alkyne-PS-Br, star polymer was produced. For this purpose DVB, PMDETA, and CuBr was used and star polymer synthesized using the "arm first" methodology (Equation 4.6)



(4.6)

In this respect, alkyne PS (alkyne-*o*-NB-PS) was used as a macroinitiator DVB as cross-linker in ATRP condition at 110 ºC to give (alkyne-*o*-NB-PS)$_n$-polyDVB multiarm star homopolymer.

The DVB conversion was followed by GC analysis and as seen in GPC chromatogram of multi arm star polymer, the polymerization was stopped at 26 h via exposuring to air with 72% DVB conversion. And polymer was precipitated in methanol/diethyl ether mixture to remove unreacted polystrene. Figure 4.8 shows a series of conventional GPC curves of the reaction products at a given polymerization

time and the purified multiarm star polymer. It was observed that the peak corresponding to the star polymer was shifted to the higher molecular weight region of the chromatogram and the RI signal corresponding to the PS macroinitiator decreased with the extent of cross-linking reaction. These results clearly indicated that the formation of the multiarm star polymer was achieved. For the purification of multiarm star polymer, it was dissolved in THF and reprecipitated into methanol/diethyl ether mixture (1/5 v/v) to remove unreacted PS macroinitiator. The effectiveness of the purification procedure was confirmed by a complete disappearance of PS macroinitiator peak in an overlaid GPC chromatogram of purified sample in Figure 4.8.

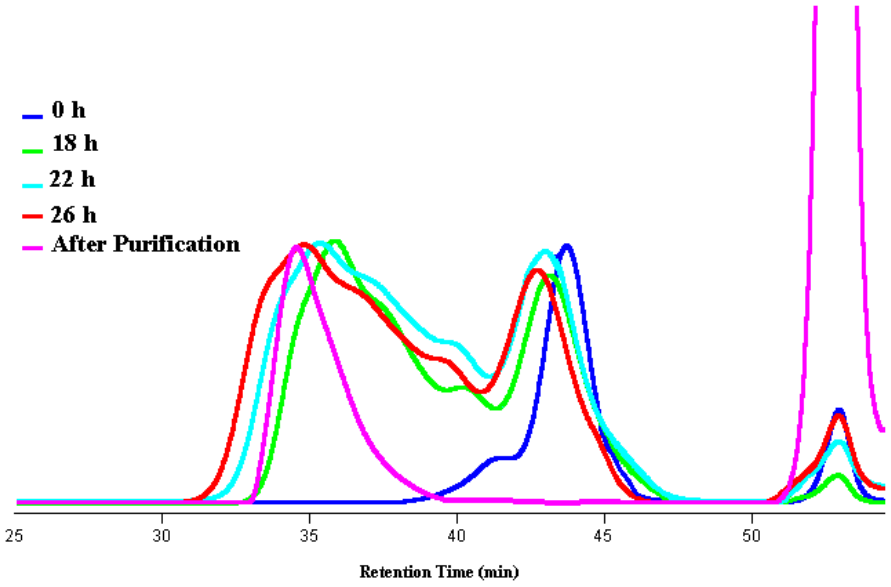


Figure 4.8: GPC traces during the synthesis of $(PCL)_n$-polyDVB multi-arm star polymer. Experimental conditions: [DVB]/15 = [Anth-PCL-Br] = [CuBr] = [PMDETA] in anisole at 110 °C. GPC conditions: RI detector, relative to linear PS standards.

A monomodal GPC trace and narrow molecular weight distribution for (alkyne-*o*-NB-PS)$_n$-polyDVB multiarm star polymer were detected.Additionally,the molecular weight values (M_n, M_w, and M_p) of (Alkyne-*o*-NB-PS)$_n$-polyDVB star polymer obtained using conventional GPC and TD-GPC instruments were given in Table 4.2. It should be noted that there is a discrepancy between the molecular weight values obtained by conventional GPC and TD-GPC. This is expected that because star polymers have more compact structure than linear polymer of equivalent molecular weight and composition resulting in smaller hydrodynamic volume. Thus, apparent molecular weight of star polymers is underestimated by conventional GPC.

Refractive index (RI), light scattering (LS) and differential viscomether detectors in TD-GPC instrument provides more advanced and accurate technique to measure the absolute molecular weight of star polymer, if refractive index increment (d*n*/dc) value of the analyzed polymer is known. Although, d*n*/dc value of linear PS is available, an attempt has been made to clarify the effect of cross-linked DVB core on d*n*/dc value of multi arm PS star polymer. Therefore, the d*n*/dc of (Alkyne-*o*-NB-PS)$_n$-polyDVB was measured by TD-GPC instrument and found to be 0.185 mL/g in THF at 35 ^oC, which is equal to that of linear PS. The weight average arm number (*f*) of multiarm (Alkyne-*o*-NB-PS)$_n$-polyDVB star polymer was calculated using the following equation based on the absolute molecular weights (M_w) of multiarm star polymer.

$$f = \frac{WF_{arm} \times M_{w,star}}{M_{w,arm}} = \frac{M_{w,star}}{M_{w,arm} + M_{DVB} \times conv_{DVB} \times [DVB]/[\text{Alkyne-}o\text{-NB-PS}]} \quad \textbf{(4.7)}$$

Where WF_{arm} is the weight fraction of PS arm in the star polymer, $M_{w,star}$ and $M_{w,arm}$ are the absolute molecular weights of the (Alkyne-*o*-NB-PS)$_n$-polyDVB star and the alkyne-*o*-NB-PS arm, respectively obtained from TD-GPC instrument introducing the predethermined d*n*/dc value of PS to OmniSEC software, M_{DVB} is the molecular weight of DVB, [DVB]/[alkyne-o-NB-PS] is a feed molar ratio of the DVB to α-alkyne-*o*-NB-PS before cross-linking polymerization. The conversion of DVB ($conv_{DVB}$) was dethermined by GC. Thus, the *f* of multiarm (Alkyne-*o*-NB-PS)$_n$-polyDVB star polymer was calculated to be 24 and listed in Table 4.2. It is generally accepted that the intrinsic viscosity comparison of star polymer and its linear counterpart provides the most convenient method to elucidate the structure of star polymers, where g*'* is the contraction factor as given in (4.8).

$$g' = [\eta]_{star} / [\eta]_{linear} \ (M = \text{constant}) \quad \textbf{(4.8)}$$

Where $[\eta]_{star}$ and $[\eta]_{linear}$ are the intrinsic viscosities of star polymer and the linear polymer with the same molecular weight and the composition, respectively [248]. It is also shown that in regular (equal arm length) star polymers, *g'* is related with the number of arms, *f* as follows:

$$\log g' = 0.36 - 0.8 \log f \qquad (\mathbf{4.9})$$

Mark-Houwink-Sakurada (MHS) parameters K and *a* for linear PS were dethermined to be 1.44×10^{-4} dL/g and 0.707, respectively in THF at 35 °C using a series of linear narrow PS standards by TD-GPC. Then, using these parameters $[\eta]_{linear}$ was calculated to be 0.729 dL/g for a specified molecular weight (M_w = 173440) of linear PS. Moreover, the $[\eta]_{star}$ of (Alkyne-o-NB-PS)$_n$-polyDVB star polymer was measured to be 0.141 dL/g by the viscomether detector in TD-GPC.

The number of arms, *f* was calculated to be 22 using equations. 4.5-6 and in close agreement with that obtained from equation 4.10. All data were given in Table 4.2. And here is the ^{1}H NMR spectrum of multi arm star polymer.The ^{1}H NMR spectrum of **(**alkyne-*o*-NB-PS)$_n$-polyDVB showed aryl protons of *ortho*-nitrobenzyl at 8.15, 7.48 ppm, aryl protons of polystyrene at 7.40-6.25, methyl protons next to ester unit at 4.74 ppm, (Figure 4.9).

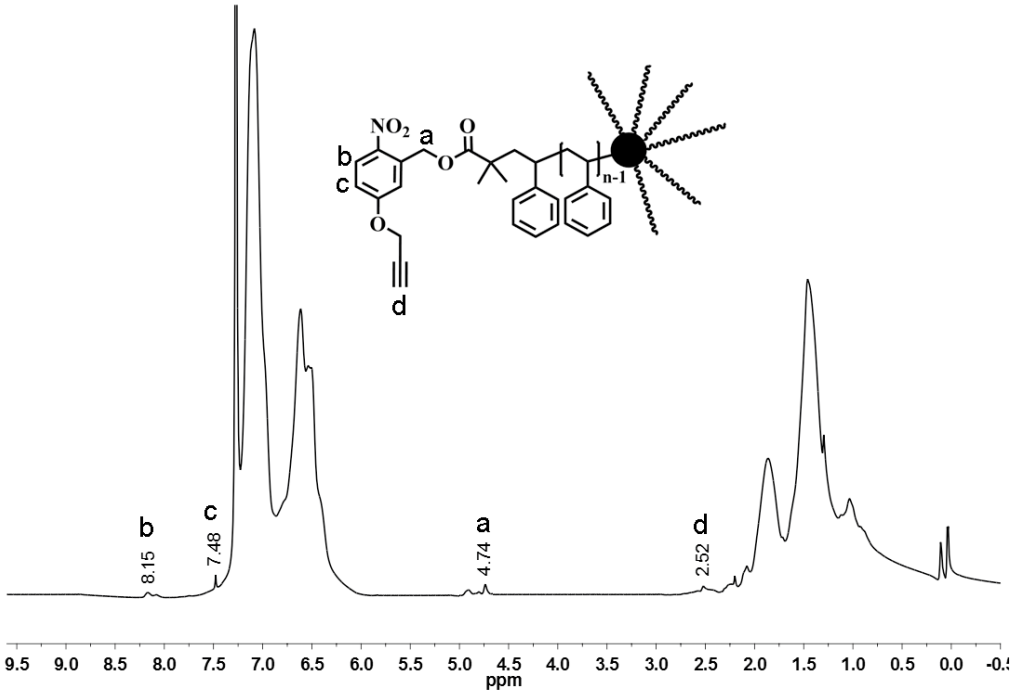
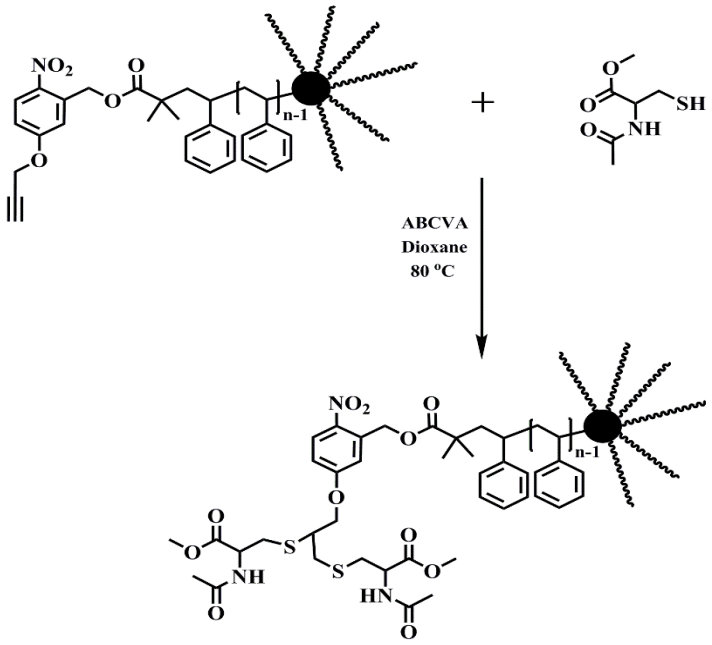


Figure 4.9: ^{1}H NMR spectrum of the multiarm star polymer in $CDCl_3$.

4.3.2. Termal thiol-yne reactions of (Alkyne-*o*-NB-PS)n-polyDVB multiarm star polymer

Using the thiol-yne click reaction, the (Alkyne-*o*-NB-PS)$_n$-polyDVB star polymer was further reacted with 10 equiv of *N*-acetyl-L-cysteine methyl ester together with ABCVA as termal initiator in dioxane at 80 ^oC for overnight (Equation 4.10).



(4.10)

From ^{1}HNMR spectrum of the polymer, the aryl protons of *ortho*-nitrobenzyl group were detected at 8.06, 7.48 ppm. The appearance of new signals corresponding to the C*H*$_3$OC=O, SCHC*H*$_2$ and NCHC*H*$_2$S at 3.77, 3.72 and 2.27 ppm, respectively confirmed the structure of (Cysteine-*o*-NB-PS)$_n$-polyDVB. (Figure 4.10)

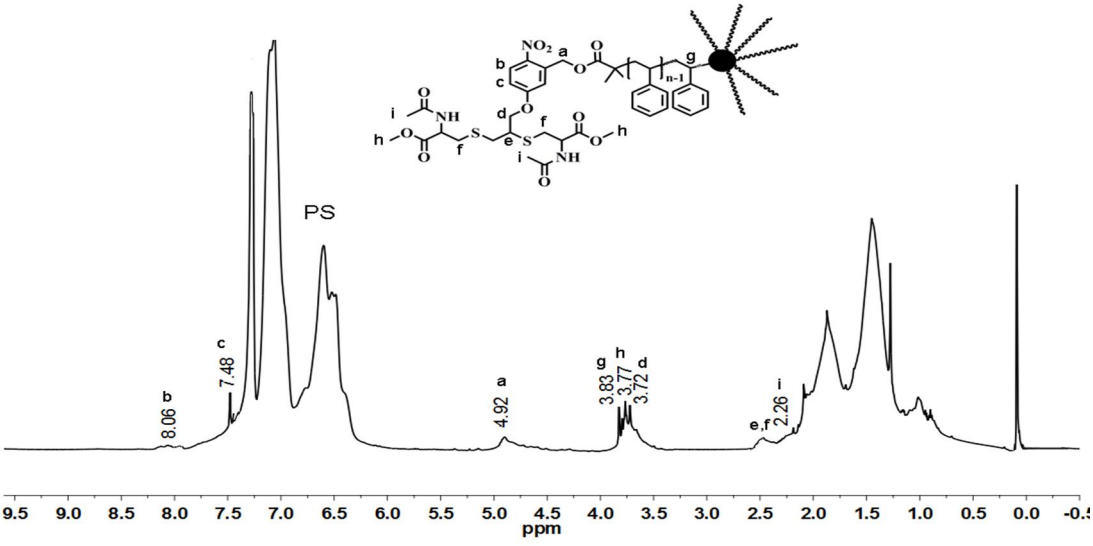


Figure 4.10: ^{1}H NMR spectrum of *N*-acetyl-L-cysteine methyl ester functionalized the multiarm star polymer in $CDCl_3$.

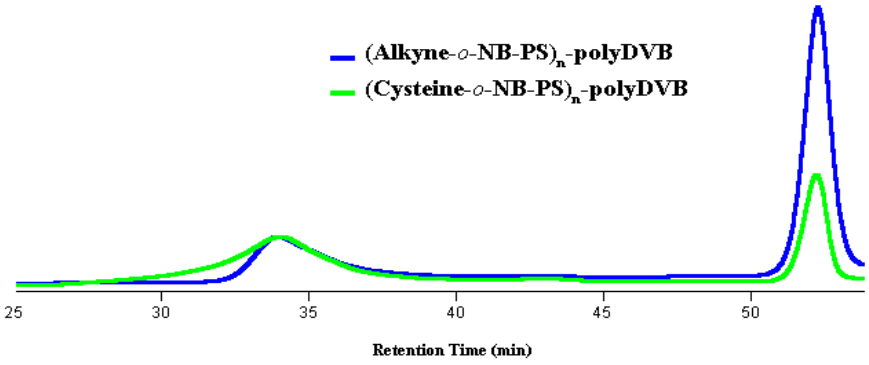
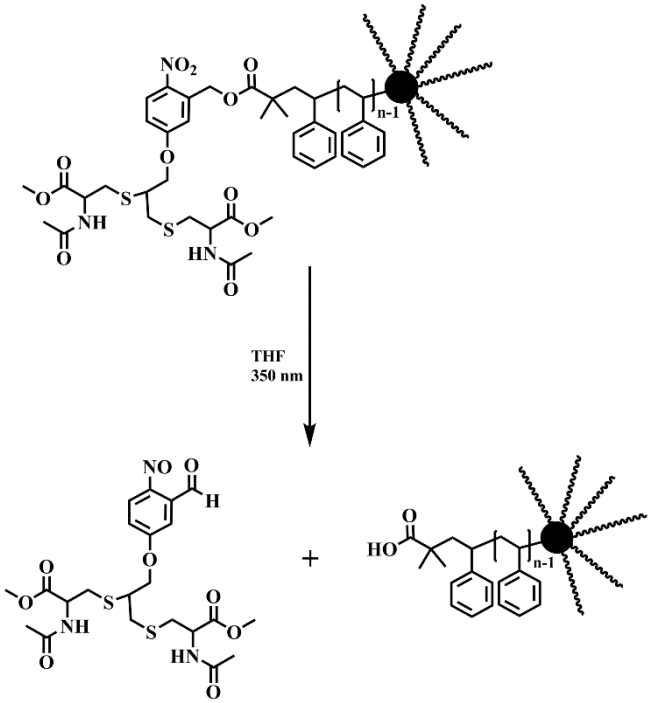


Figure 4.11: GPC traces of (Alkyne-o-NB-PS)$_n$-polyDVB and (Cysteine-o-NB-PS)$_n$-polyDVB.

GPC analysis showed monomodal traces for example. GPC traces between (alkyne-*o*-NB-PS)$_n$-polyDVB and (cysteine-*o*-NB-PS)n-polyDVB didn't show a clear shift (Figure 4.11).

4.3.3. Photolysis of the *o*-Nitrobenzyl Grups of (Cysteine-*o*-NB-PS)$_n$-polyDVB Multiarm Star Polymer

(Cysteine-*o*-NB-PS)$_n$-polyDVB star polymer in THF was irradiated by a photoreactor at 350 nm at room temperature for 8 h (Equation 4.11)



(4.11)

After this reaction, 24 carboxylic units occurred. Carboxylic units caused to intramolecular and intermolecular hydrogen bonds. Existance of these hydrogen bonds result in gelation.

Table 4.2: The result of multiarm alkyne end-functional star and multiarm cysteine end-functional star polymers.

	GPC			TD GPC								
Polymers	M_n (g/mol)	M_w (g/mol)	M_w/M_n	M_n (g/mol)	M_w (g/mol)	M_p (g/mol)	$[\eta]$ (dL/g)	R_h (nm)	dn/dc (mL/g)	g'	f [b]	f' [c]
(Alkyne-*o*-NB-PS)$_n$-polyDVB[a]	47000	62300	1.32	154800	173500	172500	0.14	7,18	0.185	0.193	24	22
(Cysteine-*o*-NB-PS)$_n$-polyDVB	71800	145710	2.02	306400	350000	27400	0.15	9.20	0.185	-	-	-

[a] [DVB]/15 = [Alkyne-*o*-NB-PS-Br] = [CuBr] = [PMDETA] in anisole at 110 °C.
[b] Number of arms in multi arm star polymer, calculated according to 4.7.
[c] Calculated according to Eqs. 4.8 and 4.9.

5. CONCLUSION

The aim of this M.Sc. dissertation was to synthesize well-defined linear and multiarm star polymers having photolabile groups with biomolecule end functionalities. After that, protected biomolecules were released from polymers by using just light without addition of any reagents.

In the first study, linear PS having photolabile properties was synthesized. For this purpose, first, we have prepared the *ortho*-nitrobenzyl ether end-functionalized alkyne (1), which can be used in click reactions to link new molecules, with etherication reaction. The product converted to tertiary α-bromoester (2) as initiator for ATRP. Alkyne-*o*-NB-PS-Br (3) was syntesized by ATRP. *N*-acetyl-L-cysteine methyl ester as biomolecule was added to the structure (3) via thiol-yne click reaction. As a result of this, cysteine-*o*-NB-PS-Br (4) was synthesized. Finally, the protected cysteines by polymer were released by flash photolysis at $\lambda_{max} \approx 350$ nm. As result of photolysis, PS functionalized carbocyclic acid and *N*-acetyl-L-cysteine methyl ester terminated ortho-nitrobenzil aldehyde was happened. Photocleavable reaction was proved by UV spectroscopy. Moreover, GPC, TD-GPC and ^{1}H NMR analysis confirmed these polymers.

In the second study, firstly (alkyne-*o*-NB-PS)$_n$-polyDVB multiarm polymer was synthesized. For this purpose, we prepared the α-alkyne-*ortho*-nitrobenzyl and ω-bromo functional PS macroinitiator from ATRP. Multiarm star polymer with bromide functionality was synthesized by a cross-linking reaction of divinyl benzene using alkyne-*o*-NB-PS macroinitiator. The formation of (cysteine-*o*-NB-PS)$_n$-polyDVB was achieved via thiol-yne click reaction. This multiarm star polymer was irradiated by 350 nm UV light. (HOOC-PS)$_n$-polyDVB multiarm star has many of carboxylic acid unit, so the gelation occured in this study.

In the future we will focus on the synthesis of multiarm star polymer with no gelation behavior. Moreover, in accordance with this purpose we will synthesize star and miktoarm star polymer that will have less photo-degradable arms.

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