ISTANBUL TECHNICAL UNIVERSITY ★ GRADUATE SCHOOL

ONE-STEP MODIFICATION OF DIACID-FUNCTIONAL POLYTHIOETHERS VIA SIMULTANEOUS PASSERINI AND ESTERIFICATION REACTIONS

M.Sc. THESIS

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İSTANBUL TEKNİK ÜNİVERSİTESİ ★ LİSANSÜSTÜ EĞİTİM ENSTİTÜSÜ

DİKARBOKSİLİK ASİT FONKSİYONLU POLİTİYOETERLERİN EŞ ZAMANLI PASSERİNİ VE ESTERLEŞME REAKSİYONLARIYLA TEK ADIMLI MODİFİKASYONU

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Begüm Güngör, a M.Sc. student of ITU Graduate School student ID 509181304, successfully defended the thesis/dissertation entitled “ONE-STEP MODIFICATION OF DIACID-FUNCTIONAL POLYTHIOETHERS VIA SIMULTANEOUS PASSERINI AND ESTERIFICATION REACTIONS”, which she prepared after fulfilling the requirements specified in the associated legislations, before the jury whose signatures are below.

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Date of Submission : 21 January 2021
Date of Defense : 12 February 2021

To my family,

FOREWORD

Being a student at Istanbul Technical University was always a thing to proud of me. During my master's education, my commitment and love for this university got bigger and it is still increasing. While working at our laboratories I always feel that I do what I enjoy doing. Thanks to my friends and professors, I always feel like I'm home in the laboratory and the faculty. I am very happy that I never feel any negative force to do anything in my education life so far.

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ABBREVIATIONS

3-CR : 3-Component Reaction
C^o : Celsius
CHI: : Cyclohexyl isocyanide
^{13}C-NMR : Carbon Nuclear Magnetic Resonance Spectroscopy
DCM : Dichloromethane
DTBADC : Di-tert-butyl acetylene dicarboxylate
FT-IR : Fourier Transform Infrared Spectroscopy
GPC : Gel Permeation Chromatography
HDT : Hexanedithiol
^{1}H-NMR : Hydrogen Nuclear Magnetic Resonance Spectroscopy
IMCR : Isocyanide Based Multicomponent Reactions
kDa : kiloDalton
LS : Light Scattering
M : Molarity
MCR : Multicomponent Reactions
MHz : Megahertz
3-NBA : 3-nitrobenzaldehyde
NMR : Nuclear Magnetic Resonance Spectrometry
ppm : Parts per million
PS : Polystyrene
Rt : Room temperature
TBD : 1,5,7-triazabicyclo[4.4.0]dec-5-ene
TFA : Trifluoroacetic acid

SYMBOLS

cm^{-1} : Wavenumber

Đ : Dispersity

M_w : Mass average molar mass

δ : Chemical Shift

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POST-POLYMERIZATION MODIFICATION OF DICARBOXYLIC ACID FUNCTIONALIZED POLYTHIOETHER VIA 3 COMPONENT PASSERINI REACTIONS

SUMMARY

Over history, chemists all over the world try to seek a better, more eco-friendly, and more efficient method for their studies. Click chemistry is one of these friendly methods that chemistry has. Because of the various advantages of click chemistry, nowadays chemists try to highlight more information about it. Click chemistry can be described as a concept that involves results with high-efficiency, without or with harmless by-products that can be eliminated via non-chromatographic methods, and the possibility to realize the reaction as bulk or in a benign solvent [1, 2]. This method can also be used for polymerization. In this work, polythioethers will be synthesized with a method that can be considered as a click chemistry method.

According to Wender and Miller's ideal reaction definition; a reaction should undergo in one pot with a 100% yield without any by-products. Multicomponent reactions (MCRs) are very close to this definition. That's why these reactions made a hit in a very short time because they are favorable besides the traditional serial syntheses. Multicomponent reactions are the reactions where 3 or more components are reacted in one pot simultaneously, and almost every atom in these components are present in the final product. Besides, the yield and conversion rate is generally very high on these reactions. Thus these reactions are very favorable to use for the synthesis of complex structures. A subclass of the MCRs is isocyanide-based MCRs (IMCR) in which one of the components is an isocyanide. If the other two components are a carboxylic acid and an aldehyde or ketone; this reaction is called the Passerini reaction. Passerini reactions are one of the most documented reaction types of the MCRs because the isocyanides are very efficient to use as a component in reaction; they can react with both nucleophile and electrophile. Also, the Passerini reactions can be adapted to the polymer synthesis; it can be used for the synthesis of monomers; post-modification of polymers; and polycondensation process. The polythioethers that will be synthesized via the click method will be functionalized through Passerini reaction.

Polythioethers have become a very big interest in the polymer chemistry world. As there are not too many researches about their synthesis and functionalization, polythioethers are the chemical matters that easy to synthesize and functionalize. According to the previous works; polythioethers were synthesized using a dicarboxylate group and a dithiol. After the polymerization, hydrolysis of the polymer was done using trifluoroacetic acid. Finally, to functionalize the hydrolyzed polythioether with two carboxylic acid ending, the Passerini reaction was carried out with various aldehydes and isocyanides. All the characterizations were made by using C-NMR, H-NMR, FT-IR, GPC, and TGA.

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DİKARBOKSİLİK ASİT FONKSİYONLU POLİTİYOETERLERİN 3 BİLEŞENLİ PASSERINI TEPKİMESİ İLE POST-POLİMERİZASYON MODİFİKASYONU

ÖZET

Kimyagerler artık çalışma alanlarında kullanabilecekleri daha iyi, daha çevre dostu ve daha pratik yöntemler arama ve bulma peşindedirler. Aradıkları bu yöntemlerin çevre dostu, atom-ekonomik ve pratik olması istenir. Bu yöntemlerden biri de click kimyasıdır. Click kimyasının bir çok avantajı sebebiyle kimyagerler bu konsept üzerinde daha çok çalışıp kullanım alanını artırmayı amaçlamaktadırlar. Click kimyası genel olarak yüksek verimli, yan ürünsüz ya da kromatografik olmayan daha basit yöntemlerle ana ürünün kolayca saflaştırılacağı, tepkime ortamının solventsiz veya zararsız solventler olduğu, tepkime şartlarının hepsini içeren bir kimya konseptidir [1, 2]. Click kimyası denmesesinin sebebi, giren ürünlerin termodinamik lehine bir şekilde tepkimeye girmesidir. İlk olarak 2001 yılında Sharpless tarafından tanımlanan bu kavram pratikliği, hızlılığı ve etkinliği açısından hızla ilgi odağı olmuştur. Click kimyasının özelliklerini sıralayacak olursak, bunlar; geniş kapsamlı ve modüler olması, kolay tepkime şartları, kolay bulunan kimyasallar kullanılması, yüksek reaksiyon hızı, kararlı ürünler ve çok yüksek verimler, oluşan ürünün bünyesinde yan ürün olmaması ya da basit yan ürünler olması, kromatografik olmayan yöntemlerle hızlı saflaştırma, oksijen ve suya karşı hassas olmama, solvent kullanılmaması ya da zararsız organik solvent kullanımıdır. Click kimyası bir çok farklı alanda kullanılabilmektedir. Click kimyasına örnek olarak epoksilerin ve aziridinlerin nükleofilik halka açılma tepkimeleri, aldol tipi dışındaki karbonil tepkimeleri, karbon-karbon çoklu bağ oluşumları (epoksi oksidasyonu), siklokatılma tepkimeleri ve Michael katılma tepkimeleri verilebilir. Click kimyası aynı zamanda polimerleşme için de kullanılabilmektedir. Bu çalışmada sentezlenecek poltiyoeterler click kimyası yöntemiyle Michael katılmasıyla sentezlenecektir.

Michael katılma tepkimeleri tersinir bir prosedür olup nükleofillerin elektron çekici grupları olan doymamış yapılara katılması tepkimeleridir. Bu tepkimeler ilk olarak Arthur Michael tarafından 1887 yılında keşfedilmiştir. Genel bakış açısıyla; Michael katılmalarında tiyol, amin gibi bir nükleofil, α,β- doymamış aldehit, keton, vinil sülfon, vinil ester, imidazol veya maleimit gibi aktive olabilecek çift bağa sahip yapılarla tepkime verir. Bunun dışında oldukça kompleks yapıların ve makromoleküllerin de Michael katılma tepkimesiyle yüksek verimde elde edilebildiği görülmüştür. Michael katılmalarının bir çok çeşidi vardır; bunlar yapıya katılan farklı moleküllerin adına göre değişkenlik göstermektedir. Örneğin bunlardan bir kaçı; oksa-Michael, aza-michael ve tiyol-Michael tepkimeleridir. Bu çalışmada sentezlenen polimerler tiyol-Michael tepkimesi üzerinden yürümüştür. Tiyol-Michael

tepkimeleri ilk olarak 1960'lı yıllarda Allen ve ark. tarafından raporlanmıştır [3]. Tiyol grubuna sahip bu yapılarla gerçekleştirilen tepkimelerin çok yönlülüğü ve SH bağının yüksek aktivitesi nedeniyle çok çeşitli yapılar yüksek verimlerle elde edilebilmektedir. Bunun sebebi S atomunun kendiliğinden sahip olduğu elektron yoğunluğudur; sonuç olarak bu tip yapılar elverişli ortamlarda kolayca tepkime verebilmektedir. Tiyol-Michael tepkimeleri hem bazik hem nükleofilik ortamda gerçekleşebildiğinden kullanım alanları da oldukça geniş olmuştur. Baz katalizli tiyol-Michael katılma tepkimesi geleneksel olan tepkime olarak kabul edilmektedir. Ortamda trietilamin gibi bir baz olmalıdır. Nükleofil katalizli olanda ise baz yerine fosfin türevi bir yapı katalizör görevi görmektedir. Bu tepkimenin veriminde katalizörün nükleofillik özelliği önemli bir rol oynar. Bu çalışmada sentezlenecek politiyoeter baz katalizli tiyol-Michael katılmasıyla sentezlenmiştir; katalizör olarak bir organobaz olan 1,5,7-triazabisiklo[4.4.0]dek-5-en (TBD) kullanılmıştır.

Politiyoeterlerler hem akademik anlamda hem de endüstriyel olarak kullanılabilen malzemelerdir. Bu maddelerin ortaya çıkışı çok eski olmamakla birlikte bu konu hakkında çok sayıda yayın da bulunmamaktadır. Politiyoeter sentezinin en büyük avantajı; click kimyasına uygun olması ve tepkimelerin sonucunda yan ürün vermemesidir. Bunun yanı sıra tepkime yüksek verimlerle, yumuşak koşullarda ve hızla gerçekleştirilebilmektedir.

Wender ve Miller'ın ideal tepkime tanımına göre; bir tepkime herhangi bir yan ürün vermeksizin %100 verimle tek bir kapta gerçekleşmelidir. Çok bileşenli tepkimeler (ÇBT) bu tanıma en uygun kimya konseptlerinden biri olmuştur. ÇBT'ler geleneksel tepkimelerin (seri tepkimeler) yanı sıra çok daha kullanıma uygun olduklarından kısa sürede çok büyük bir ilgi alanına dönüşmüştür. Sahip olduğu avantajların en önemlisi ise 3 veya daha fazla bileşenin tek bir kapta aynı anda tepkimeye girip yan ürün vermeksizin yüksek verimle ürün verebiliyor olmasıdır. Ayrıca bu bileşenlerin içerdiği atomların hemen hemen hepsi final üründe de bulunmaktadır ve tepkimelerdeki dönüşüm ve verim yüzdesi çok yüksektir. Bu olağanüstü durum yeşil kimya yolları arayan kimyacılar için çok önemli bir bulgu olmuştur. Bu sebeple ÇBT'ler kompleks yapıların kolayca sentezlenmesi için de bir yol sunmaktadır. ÇBT'lerin bir alt başlığı olan izosiyanit esaslı ÇBT'ler bu tip tepkimelerin en sık kullanılanlarıdır. Eğer diğer iki bileşen karboksilik asit ve aldehit veya keton ise bu tepkimelere Passerini tepkimesi adı verilir. Passerini tepkimeleri ÇBT'ler içinde en çok belgelenen ve üzerinde çalışılan tepkime türü olmuştur. Bunun sebebi izosiyanitlerin tepkime bileşenlerinden biri olmasıdır. İzosiyanitlerin en büyük özelliği hem nükleofiller hem de elektrofillerle tepkime verebilmesidir. Bunun dışında, Passerini tepkiemelerine polimer çalışmalarında da yer verilmiştir. Örneğin, Passerini tepkimeleri monomer sentezi yapımında, polimerlerin modifikasyonu esnasında ve polikondenzasyon sürecinde kullanılabilmektedir. Sentezlenecek olan politiyoeterler, bir sonraki adımda Passerini tepkimeleri ile fonksiyonlandırılacaktır.

Daha önceki çalışmalardan yola çıkılarak bu çalışmada; click kimyasına uygun olan tiyol-Michael tepkimesiyle politiyoeter sentezi gerçekleştirilmiştir. Yüksek verimle ve 1 dakika gibi çok kısa bir sürede ter-bütil asetilen dikarboksilat ve 1,6-

hekzanditiyol kullanılarak bir organokatalizör olan TBD varlığında bu polimerleşme gerçekleştirilmiştir. Bu tepkimenin optimum koşulları (solvent, sıcaklık, süre, atmosfer gibi) bulunmuştur. Çift ester fonksiyonuna sahip bu yapı bir sonraki adımda trifloroasetik asit ile hidroliz tepkimesine sokularak bu çift ester grupları karboksilik asit grubuna dönüştürülmüştür. Bu tepkime de %97 gibi bir verimle gerçekleştirilmiştir. Son olarak fonksiyonlandırma yapılması adına, çift karboksilik asit gruplu bu polimer aldehit ve bir izosiyanit ile tepkimeye sokularak Passerini ürünü elde edilmesi amaçlanmıştır. Teorik olarak elde edilen ürünün iki karboksilik asit grubunun da Passerini ürünü vermesi beklenirken; solvent olarak tepkimede kullanılan alkolün yapıya katıldığı görülmüştür. İlk defa karşılaşılan bu durum bir takım ek deneyler yapılarak aydınlatılmış ve bir mekanizma önerilmiştir. Bu durumun çift karboksilik asit fonksiyonlu yapılara özgü olup olmadığınıı görmek adına da tek fonksiyonlu ter-bütil propiyolat ve 1,6-hekzanditiyol ile de polimer sentezlenmiş, aynı metotla hidroliz edilmiş ve elde edilen bir karboksilik asit fonksiyonlu polimer Passerini tepkimesine sokulmuştur. Görülmüştür ki bu tepkime sonucu oluşan polimerin fonksiyonel grubu %100 Passerini ürünü vermiştir. Buradan yola çıkılarak bu esterlerleşme-Passerini eş zamanlı tepkimelerinin iki karboksilik asit fonksiyonlu polimerlere özgü olduğu sonucuna varılmıştır. Tüm tepkime adımlarında oluşan ürünler ^{1}H-NMR, ^{13}C-NMR, FTIR GPC ve TGA cihazlarıyla karakterize edilmiş ve yorumlanmıştır. Sonuç olarak çift karboksilik asitli politiyoeter yapısında fonksiyonel grubun yalnızca %50'lik kısmının Passerini ürününün oluştuğu, diğer kalan %50'nin ise kullanılan farklı alkollere göre farklı oranda ester ürünü verdiği görülmüştür. Konu, farklı aldehitler ve farklı izosiyanitler kullanılarak çeşitlendirilmiş ve geçerliliği kanıtlanmıştır.

1. INTRODUCTION

The sustainability in polymer chemistry forces people to discover new methodologies that warrant zero side-reactions, one-pot synthesis as well as high yield and low cost. Nowadays, interest in the facile preparation and functionalization of polymers in highly practical and efficient means is growing rapidly [4-6]. The reactions classified under the click chemistry play a pivotal role in synthetic polymer chemistry since they provide endless possibilities for new approaches while not losing their popularity [1, 7-26]. Among them, Passerini 3-component reaction (Passerini-3CR) is one of the most intriguing and useful multi-component reactions (MCR) classified under the topic of click chemistry. In particular, the simultaneous reaction of a carboxylic acid, an isocyanide, and an aldehyde function in a single pot to obtain the desired products with high conversions make this chemistry one of the vital reactions of organic chemistry [27-29]. Passerini-3CR has been effectively exploited to produce organic compounds with diverse functionality for many years, Meier was the first to report the use of this reaction for renewable monomers and polymer synthesis [30]. Since then, Passerini-3CR has changed the basic routines in polymer science and found many applications from polymer synthesis to polymer modifications, and the formation of gels [31-41].

Michael addition reaction, a reaction between compounds containing reactive multiple bonds and a thiol-, nitrogen-, or an oxygen-containing nucleophile, has a significant place among the reactions classified under the click chemistry and found extensive applications in both organic and polymer chemistry since the reaction is carried out under mild conditions and providing high conversions [42-51]. Meanwhile, the presence of numerous electron-deficient multiple bonds containing compounds along with a huge library of above-mentioned nucleophiles makes this chemistry a reaction that can be conducted for any ready to use approach. Thus, this method provides great convenience in monomer synthesis, preparation of precursors, or post-polymerization modifications and thus allows the synthesis of many macrostructures from linear, hyperbranched, and dendritic polymers to gels [52-66].

In this regard, more recently Daglar et al. introduced a novel polymerization method to the polymer literature based on the Michael addition reaction. It was demonstrated that dialkyl acetylenedicarboxylate, a compound containing an electron-deficient triple bond, can react with a dithiol in the presence of an organocatalyst, 1,5,7-triazabicyclo [4.4.0] dec-5-ene (TBD), to produce linear polythioether [67]. The polymerization mechanism is simply based on the double thiol-Michael addition reactions of a dithiol to the C atoms of the triple bond between two carbonyl groups. Various forms of dialkyl acetylenedicarboxylate (e.g. dimethyl, diethyl, and di-*tert*-butyl) were used in polymerizations with 1,6-hexanedithiol (HDT) in $CHCl_3$ using TBD as a catalyst and it was found that all polymers were obtained rapidly with high molecular weights. Later, this strategy was extended to synthesize polymers with different topologies ranging from hyperbranched to linear fluorinated polythioethers [68-70]. Notably, two pendant ester functional groups in each repeating unit are perhaps the most special feature of this new polymer when the easy transformation of ester units is taken into account for further functionalization. Given this information, it was hypothesized that polythioether derived from di-*tert*-butyl acetylenedicarboxylate (DTBADC) (P_T) could undergo hydrolysis to yield dicarboxylic acid pendant polythioether (P_H), which could be further functionalized by Passerini-3CR reaction to produce novel polymer structures. As such, a polymerization reaction between HDT and DTBADC was carried out to give P_T, which was hydrolyzed in the second step to produce P_H. Afterward, employing Passerini-3CR, P_H was reacted with 3-nitrobenzaldehyde (3-NBA) and cyclohexyl isocyanide (CHI) in tetrahydrofuran (THF). However, a clear ^{1}H NMR spectrum could not be obtained to make a true judgment on product distribution, the same result was obtained when the reaction was repeated in a THF-dichloromethane (DCM) mixture. On the other hand, when methanol (CH_3OH) was added to the reaction medium as co-solvent, two different products were found in the resulting polymer by analyzing the ^{1}H NMR spectrum; one of them was the expected Passerini product and the other one was unexpected esterification product due to CH_3OH. This was a surprising result and this intriguing reaction and modification methodology should be investigated in detail.

In the current study, a one-pot and one-step Passerini & esterification reaction was studied based on P_H using various alcohols, 3-NBA, and CHI. The results indicate that both Passerini-3CR and esterification reactions occur simultaneously at a certain percentage regardless of the alcohol used, indicating a remarkable result in terms of synthetic polymer chemistry (Figure 1).

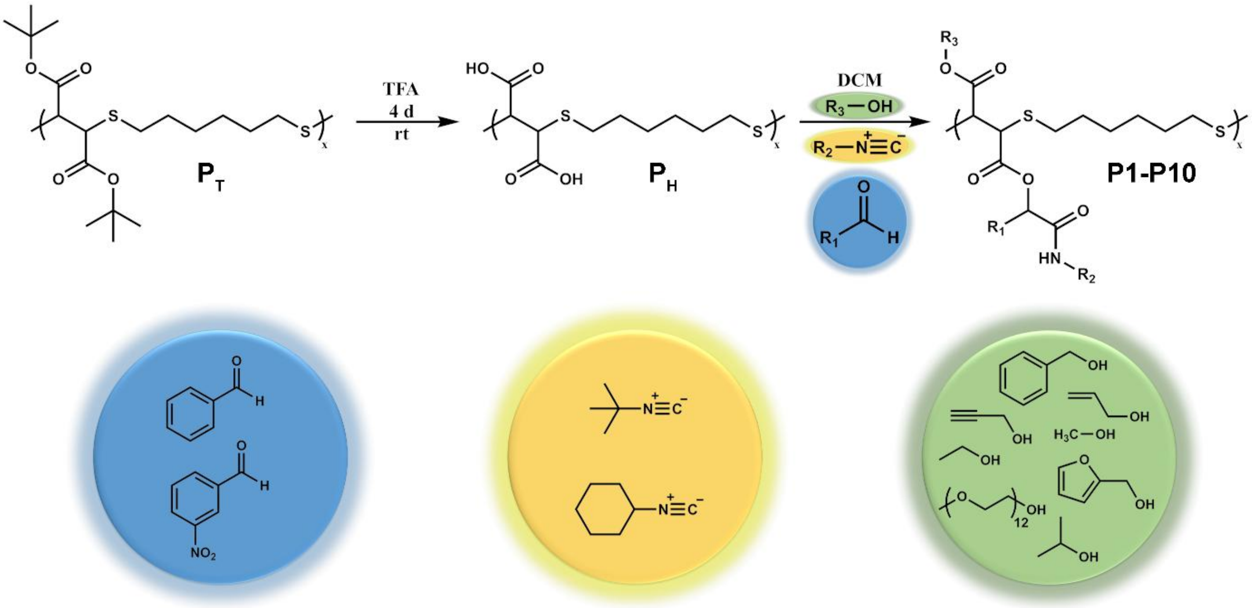

Figure 1 Schematic representation of all steps in one-step Passerini & esterification reaction**.**

2. THEORETICAL PART

2.1 Click Chemistry

'Click chemistry' is a concept introduced in 2001 by K. B. Sharpless to describe high-yielding, wide-ranging reactions that produce only by-products that can be extracted without chromatography, which are stereospecific, easy to conduct, and can be carried out in easily removable or benign solvents [1, 2]. The word "click" implies that as mechanical snap fasteners the molecules are as quickly joined together. Sharpless et al. described these reagents as "spring-loaded for a single trajectory". More precisely, the reactions must "click" each other very favorable thermodynamically, usually requiring an enthalpic driving force of at least 20 kcal/mol [1]. These reactions frequently proceed rapidly under mild conditions and appear to produce a single high-yield stereospecific product. To be useful from a practical point of view, a click reaction needs to satisfy many other criteria. A click reaction, for example, should be versatile, highly efficient, and suitable to small and large-scale manufacturing, and reagents should be easily obtainable. Sharpless and colleagues presented the general description of click chemistry as follows [1, 71] :

- Modular and wide in scope
- Smooth reaction conditions
- Easily available building blocks
- High reaction rates
- Stable reactions with excellent yields
- No or simple side products
- Quick purification via nonchromatographic methods
- stereospecific but not necessarily enantioselective
- insensitivity to oxygen and water

- no or just mild organic solvents

Preferably, accessible, non-toxic, stable chemicals with a weak or harmless odor should be used as starting materials. The reaction should be carried out in bulk, water, or in an environmentally sustainable solvent to reduce costs and, if required, purification or product separation should be performed by easy and efficient processes such as crystallization or distillation. Besides, under normal storage conditions, the final product(s) should be stable.

Several types of reactions that meet these requirements have been established, thermodynamically preferred reactions that directly lead to a single product, such as nucleophilic ring-opening reactions of epoxides and aziridines, non-aldol type carbonyl reactions, such as hydrazone and heterocycle formation, C-C multi-bond additions, such as epoxide oxidative formation, and Michael addition reaction and cycloaddition reaction.

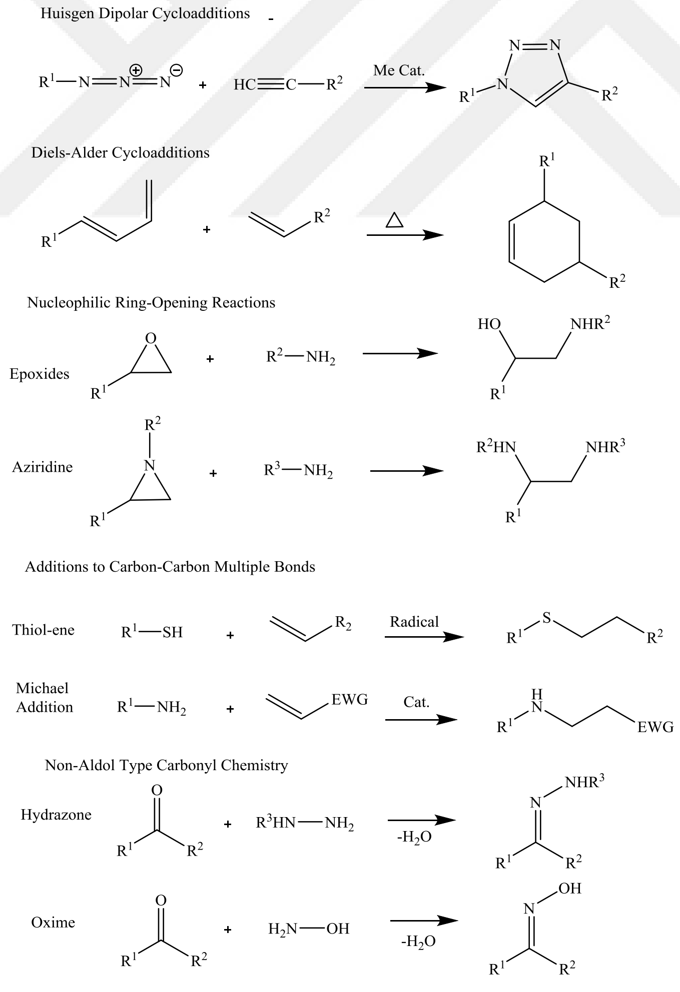

Figure 2.1 Types of Click Reactions Employed in Polymer Synthesis and Modifications.

2.2 Michael Addition

Michael addition reaction (or conjugated addition) is a versatile procedure for the addition of several nucleophiles to (conjugated) unsaturated compounds with electron-withdrawing substituents. Arthur Michael has first discovered this reaction in 1887 [72]. This reaction enables a broad variety of highly complex macromolecules to be synthesized under relatively mild conditions and also with quantitative yield in a very efficient manner. Essentially, in a Michael addition, a nucleophile such as a thiol, amine, or any stabilized carbanion gives reaction with any monomer with an activated double bond such as α, β-unsaturated aldehydes or ketones, vinyl esters, vinyl sulfones, imidazoles, and maleimides.

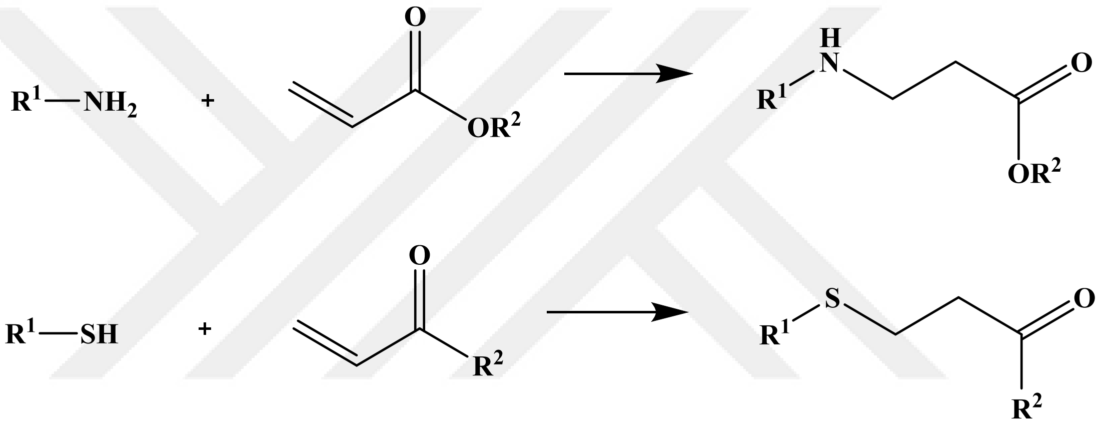

Figure 2.2 General Aspect to Michael Addition Reaction**.**

As mentioned in the review published in 2013, by Nair et al. there are many different types of Michael Addition; which are carbon-Michael reactions [73, 74], oxa-Michael reactions [75-77], aza-Michael reactions [42, 78-80], and the thiol-Michael reactions [81, 82].

2.2.1 Thiol-Michael addition reaction

The first thiol-Michael addition reaction is reported in the 1960s by Allen et al. [3] Because of the weak S-H bond’s versatility, the thiol-Michael addition can be started by lots of different precursor materials [43] and it can undergo efficiently under favorable conditions with accessible catalysts without using any solvent [43, 44, 52, 83]. Because of the natural electron density of the S atom; thiols can easily react under mild reaction conditions with the mildly catalyzed process with different substrates.

There are two different types of thiol-Michael addition reaction which are classified according to the used catalysts: base-catalyzed and nucleophile catalyzed thiol-Michael addition [43]. Both of them give no or minimum amount of side products and they both are rapid and end up with very high yield. They both are convenient for an ideal click reaction [43].

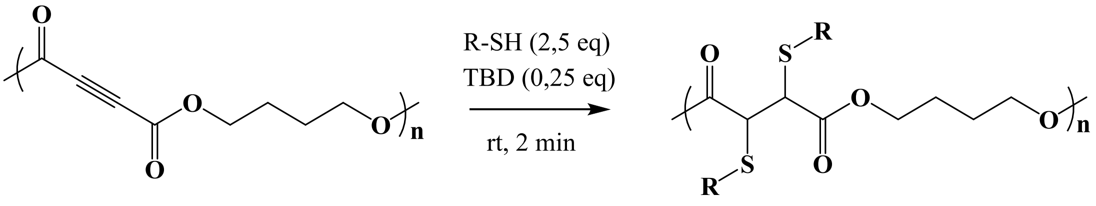

Figure 2. 3 Functionalization of a polyether via thiol-Michael addition reaction [46].

Base-Catalyzed Thiol-Michael Addition Reaction

This sort of reaction is considered the traditional method for the thiol-Michael addition reaction. In the mechanism; a common base such as triethylamine should be present in the reaction medium. A proton of the thiol leaves the structure to form a thiolate anion which is the conjugate acid of the base. The anion present across the electron-deficient β-carbon of the unsaturated structure should react to form an intermediate carbon-centered anion which is a strong base if the thiolate anion is a strong nucleophile. Then, the conjugate acid loses an electron, and the final product which is a thioether is formed [43].

Nucleophile-Catalyzed Thiol-Michael Addition

Nucleophile-catalyzed thiol-Michael addition is also efficient as the base-catalyzed one [84, 85]. In this type of reaction; instead of using a base as a catalyst if phosphine derivatives are used; the reaction would end faster with a higher yield [84-86]. In this reaction, the nucleophilicity of the catalyst plays an important role in the yield.

2.3 Polythioethers

Polythieothers can be used in industry and also in academia [67, 87]. The first synthesis of the polythioethers is not that old; its first synthetic method was found only ten decades ago [88, 89]. The most important feature of the polythioethers is that their synthesis methods are very convenient for click chemistry; the reactions can undergo very high yields without a big by-product [7, 90]. But still, rapid, simple synthesis of polythioethers with high molecular weight is a topic to work on [67].

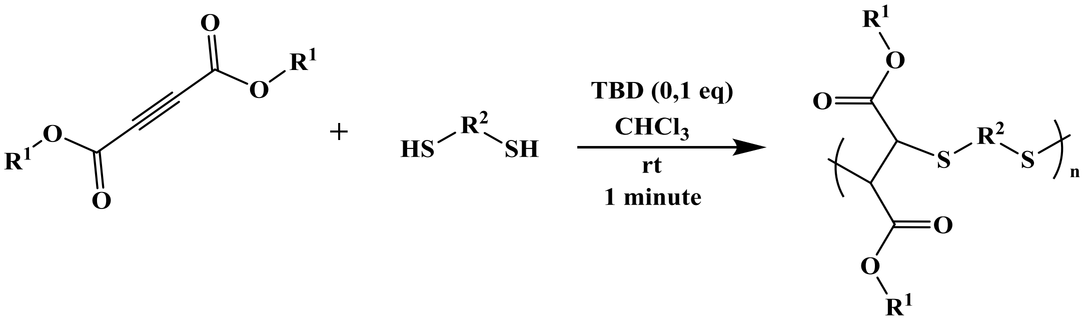

Figure 2.4 General Aspect of the synthesis of a polythioether using dialkyl acetylene dicarboxylates and dithiols [67].

2.4 Multicomponent Reactions

According to Wender and Miller's ideal synthesis definition; a reaction should be safe, simple, resource-effective, environmentally friendly and it should undergo using available starting materials in one pot with total conversion and 100% yield [91]. The ratio of waste chemicals to the final product of a fine chemical can reach up to 50/1; while this ratio can reach 100/1 in pharmaceutical production [92]. To prevent this global waste, chemists were always looking for a "greener" method to synthesize their products. Multicomponent reactions were the closest methods to the ideal synthesis definition; that's why these reactions are appreciated too much. Multicomponent reaction term (MCR) is a synthetic methodology in which three or more components are reacted simultaneously in one pot to synthesize only one product. In general, all or most of the atoms are present in that single new product [93]. These reactions are very favorable in polymer chemistry because unlike the traditional ones; the reactions can undergo in one pot and in one step without an inert or dry atmosphere that ends up as time and effort saving for chemists [92]. And also a very wide diversity of chemicals can be used at MCRs as components. There are more than 300 different scaffolds that have been synthesized and more will be found in time [94]. In MCRs, multiple bonds can be formed and broken simultaneously without changing the reaction media, the reaction conditions (temperature, pressure, or atmosphere), or adding any components. They are considered also as atom-economic, step-efficient, and eco-efficient. Besides these major advantages, the MCRs are preferred also in medicinal chemistry, material science, recognition chemistry, and catalyst design [92].

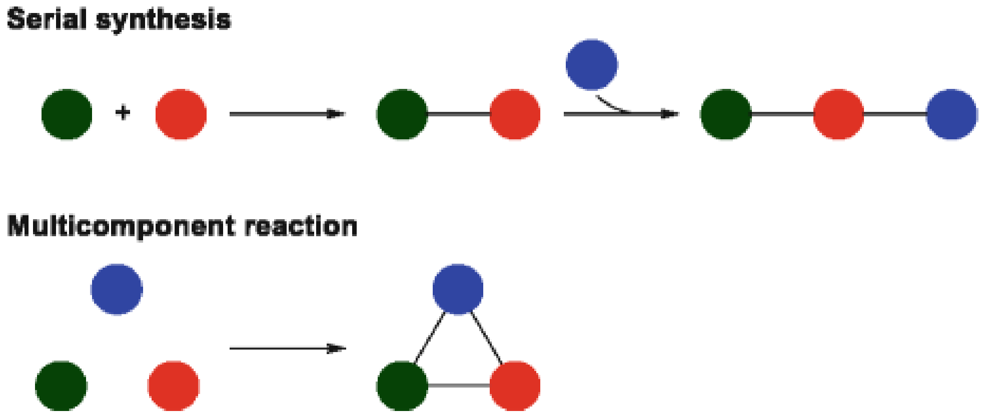

Figure 2. 5 Comparison of Traditional Reaction and MCR.

The first example of MCR is documented by Strecker in 1850. He named the synthesis after his name. The Strecker synthesis is a method for α-amino acid synthesis. In this reaction, three components which are an aldehyde, hydrogen cyanide, and ammonia are used [95].

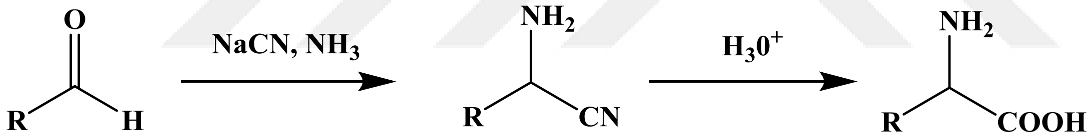

Figure 2.6 General Demonstration of Strecker Reaction.

There are different approaches to classify the MCRs. Considering the sort of using chemicals; there are dozen of different subclasses of MCRs (isocyanide based, sulfonyl azide based, etc.) The most documented one of the MCRs is the isocyanide based one. Isocyanides have lots of advantageous properties that favored the MCR. Isocyanide-based MCRs (IMCR) are more versatile and can be diversified easily than other sorts of MCRs. Isocyanides have a very reactive functional group; they can form lots of different bonds with both nucleophiles and electrophiles at the same time and they are chemoselective, regioselective, and stereoselective [27]. Most of IMCRs are associated with Passerini and Ugi reactions. Passerini reactions are 3-component isocyanide-based reactions; an oxo component, a nucleophile, and an isocyanide are used as components while Ugi reactions have 4 components (aldehydes, carboxylic acids, amines, and isonitriles). In the next chapter, Passerini reactions will be highlighted.

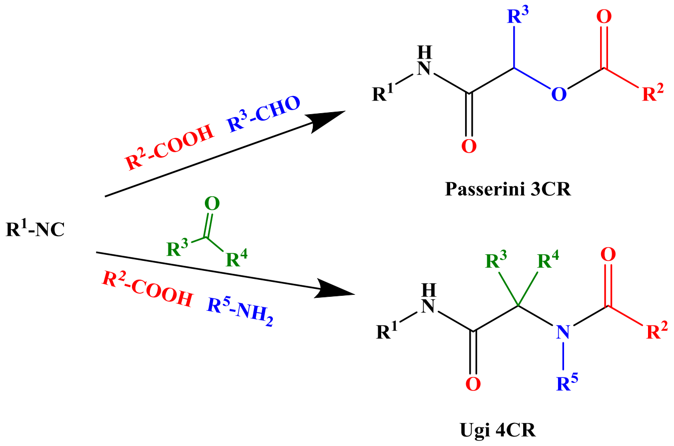

Figure 2.7 General Aspect of Passerini and Ugi Reactions [31].

2.4.1 Passerini reaction

The first 3-component reaction of carboxylic acid, aldehydes, and isocyanides has been reported in 1921 by M. Passerini et al. The mechanism of the reaction was supposed to have a zwitterionic medium [96]. Still, it's not clear but much researches are made to clarify the mechanism of the reaction. Several aspects try to lighten the mechanism. One of them which is most accepted proposes a hydrogen-bond intermediate formation [96]. In the mechanism, the aldehyde is activated first by the carboxylic acid and nitrilium intermediate is formed according to the addition of the isocyanide to the structure. To form the final α-acyloxy amide product; a Mummm type rearrangement undergoes at the end.

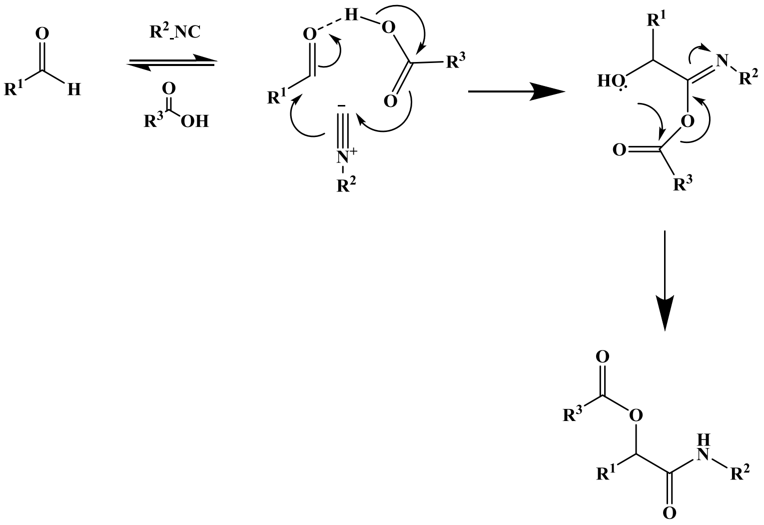

Figure 2.8 The proposed mechanism for the Passerini reaction [96].

Passerini reactions also became an interesting area for polymer chemistry. These reactions have been used both for synthesizing the monomers, for functionalization of polymers, and also for polycondensation [31]. The first example of monomer synthesis through the Passerini reaction is reported in 2011 by Meier et al. They used bio-renewable ricinoleic acid to synthesize monomers via Passerini reaction to use for acyclic metathesis polymerization and proved that Passerini reaction can be used for monomer synthesis [30]. Then, the same research group reported that the Passerini reaction is also convenient for the functionalization of polymers with carboxyl group endings. They saw that the functionalization reaction has the quantitative conversion of the carboxylic acid groups. Finally, they demonstrated that when they used dialdehydes, dicarboxylic acid, and isocyanides; polycondensation can undergo via Passerini reaction under step-growth conditions (40 ^{o}C, in solution) having high efficiency [30].

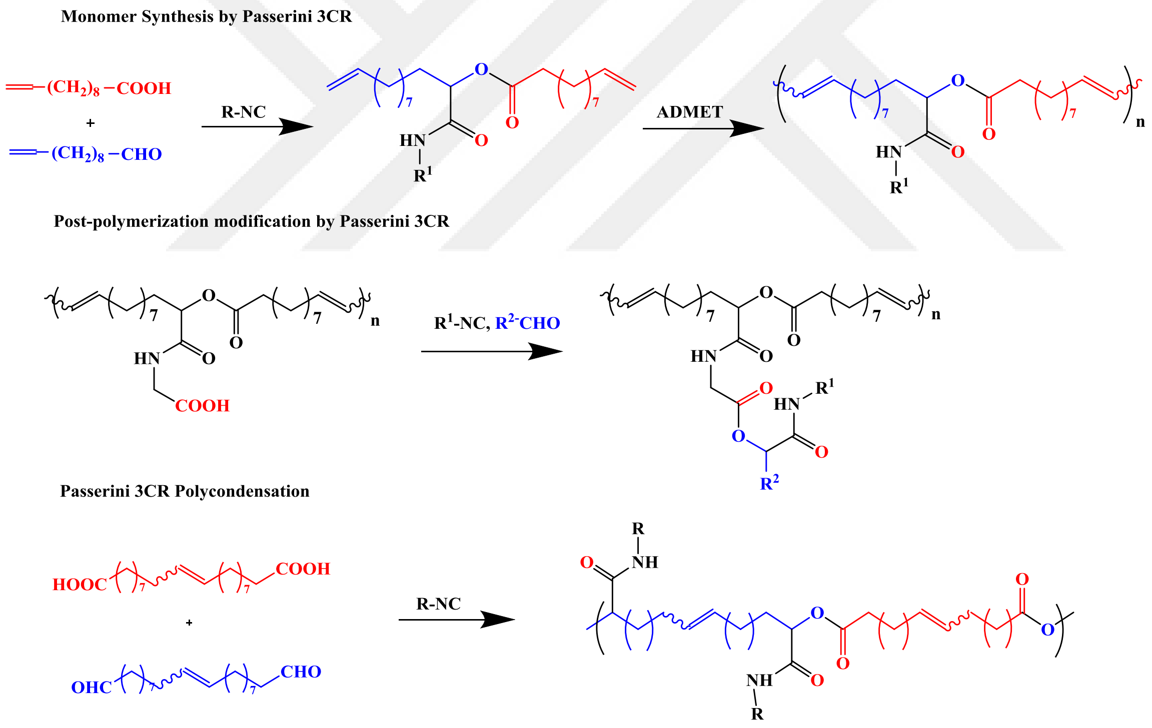

Figure 2.9 Different applications of Passerini reaction in polymer chemistry [31].

3. EXPERIMENTAL PART

3.1 Materials

Di-*tert*-butyl acetylenedicarboxylate (DTBADC, 98%, Aldrich), 1,6-hexanedithiol (HDT, 99.5%, Aldrich), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, 98%, Aldrich), chloroform ($CHCl_3$, 99%, Aldrich), trifluoroacetic acid (TFA, 99%, Aldrich), dichloromethane (DCM, 99%, Aldrich), tetrahydrofuran (THF, 99%, Aldrich), methanol (CH_3OH, 99%, Merck), ethanol (99.8%, Merck), allyl alcohol (98.5%, Merck), isopropyl alcohol (99%, Aldrich), benzyl alcohol (99%, Merck), furfuryl alcohol (98%, Merck), propargyl alcohol (99%, Aldrich), poly(ethylene glycol) monomethyl ether 550 (PEG_{550}, Aldrich), cyclohexyl isocyanide (CHI, 98%, Aldrich), *tert*-butyl isocyanide (98%, Aldrich), benzaldehyde (99%, Aldrich), 3-nitrobenzaldehyde (3-NBA, 98%, Aldrich), propionaldehyde (97% Aldrich).

3.2 Instrumentation

^{1}H (500 MHz) and ^{13}C (125 MHz) spectra were recorded using an Agilent VNMRS 500 instrument in $CDCl_3$. Fourier transform infrared (FT-IR) spectra were recorded on a Cary 630 FT-IR (Agilent Technologies) instrument over the range 4000−600 cm^{-1}. Gel permeation chromatography (GPC) measurements were carried out with an Agilent instrument (model 1100) with a pump, refractive index and UV detectors, and four Waters Styragel columns (HR 5E, HR 4E, HR 3, HR 2) (4.6 mm internal diameter, 300 mm length, packed with 5 μm particles). The effective molecular weight ranges of the columns were 2000−4000000, 50−100000, 500−30000, and 500−20000 g/mol, respectively. THF was used as eluent at a flow rate of 0.3 mL/min at 30 °C, and toluene was used as an internal standard. The weight-average molecular weights (M_w) and the dispersity ($Đ$) of the polymers were calculated based on linear polystyrene (PS) standards (Polymer Laboratories).

3.3 Polymer Synthesis

3.3.1 Synthesis of di-*tert*-butyl functional polythioether (P_T)

To a 10 mL of the round-bottom flask was added 3 mL of $CHCl_3$ at room temperature. DTBADC (679 mg, 3.00 mmol) and HDT (456 µL, 3.00 mmol) were then added to the flask, respectively. The catalyst, TBD (41.7 mg, 0.3 mmol) was added to the reaction mixture. Upon addition of TBD, an exothermic reaction occurred and the colorless solution instantly turned to pale yellow and the reaction medium became viscous. After 1 minute, the viscous solution was diluted with 3 mL of $CHCl_3$, precipitated into 50 mL of acidified CH_3OH, and the solvent was removed by decantation. The dissolution-precipitation procedure ($CHCl_3$-acidified CH_3OH) was repeated two times. The purified colorless sticky polymer was left to dry in a vacuum oven for 24 h. (Yield = 1.11 g, 99%) (M_w = 27.1 kDa, $Đ$ = 1.50). ^{1}H NMR ($CDCl_3$, δ) 3.35 (s, 2H, C=OC*H*C*H*C=O), 2.68 (m, 4H, CH_2S), 1.57 (m, 4H, main chain CH_2), 1.49-1.46 (d, 18H, $C(CH_3)_3$), 1.36 (m, 4H, main chain CH_2).

3.3.2 Hydrolysis of di-*tert*-butyl functional polythioether (P_H)

P_T (1 g, 2.66 mmol) was dissolved in 20 mL of DCM, TFA (1.02 mL, 13.33 mmol) was added to this solution and the reaction mixture was allowed to stir at room temperature for 4 days. Then, DCM was evaporated under reduced pressure and the resulting polymer was diluted with 4 mL of THF, precipitated into 80 mL of hexane and the solvent was decanted. The dissolution-precipitation process (THF-hexane) was repeated two times. The resulting colorless solid polymer was left to dry in a vacuum oven for 24 h. (Yield = 671 mg, 95%) (M_w = 17.8 kDa, $Đ$ = 1.57). ^{1}H NMR ($(CD_3)_2CO$, δ) 3.53 (m, 2H, O=CC*H*C*H*C=O), 2.79 (m, 4H, CH_2S), 1.62 (m, 4H, main chain CH_2), 1.52 (s, remaining $C(CH_3)_3$), 1.42 (m, 4H, main chain CH_2).

3.3.3 Modification of hydrolyzed polythioether P_H

Since the polythioether has two carboxylic acid functions on each repeating unit; aldehydes and isocyanides are used with excess amounts. As DCM which is the main solvent for Passerini doesn't dissolve the polymer; different alcohols are used for solubilization. The general procedure is the same for every functionalization reaction.

Synthesis of P1

P_H (50 mg, 0.19 mmol) was dissolved in 0.5 mL of methanol at room temperature. DCM (2 mL), 3-NBA (143 mg, 0.95 mmol), and CHI (118 µL, 0.95 mmol) were added respectively to this solution and the reaction mixture was left to stir at room temperature for 16 h. After the specified time, the mixture was precipitated into 5 mL of acidified CH_3OH and the solvent was decanted. This process (DCM-acidified CH_3OH) was repeated two times. The resulting white solid polymer was left to dry in a vacuum oven for 24 h. (Yield = 51 mg, 50%). ^1H NMR ($CDCl_3$, δ) 8.33-7.58 (m, 4H, ArH), 6.69 (br, 1H, NH), 6.30 (m, 1H, OCH(C=O)NH), 3.82 (m, 6H, O=CCHCHC=O, OCH_3, NHCH), 2.66 (br, 4H, SCH_2), 1.94-1.17 (m, remaining C(CH_3)$_3$, cyclohexyl and main chain CH_2).

Synthesis of P2

P_H (50 mg, 0.19 mmol) was dissolved in 0.5 ml of allyl alcohol at room temperature. DCM (2 mL), 3-NBA (143 mg, 0.95 mmol), and CHI (118 µL, 0.95 mmol) were added respectively to this solution and the reaction mixture was left to stir at room temperature for 16 h. After the specified time, the mixture was precipitated into 5 mL of acidified CH_3OH and the solvent was decanted. This process (DCM-acidified CH_3OH) was repeated two times. The resulting white solid polymer was left to dry in a vacuum oven for 24 h. (Yield = 73 mg, 70%). ^1H NMR ($CDCl_3$, δ) 8.33-7.58 (m, 4H, ArH), 6.68 (br, 1H, NH), 6.30 (m, 1H, OCH(C=O)NH), 5.93 (br, 1H, CH_2=CHCH$_2$O), 5.39-5.28 (m, 2H, CH_2=CHCH$_2$O), 4.70 (m, 2H, CH_2=CHCH_2O), 3.78 (m, 3H, O=CCHCHC=O, NHCH), 2.67 (br, 4H, SCH_2), 1.92-1.18 (m, remaining C(CH_3)$_3$, cyclohexyl and main chain CH_2).

Synthesis of P3

P_H (50 mg, 0.19 mmol) was dissolved in 0.5 mL benzyl alcohol at room temperature. DCM (2 mL), 3-NBA (143 mg, 0.95 mmol), and CHI (118 µL, 0.95 mmol) were added respectively to this solution and the reaction mixture was left to stir at room temperature for 16 h. After the specified time, the mixture was precipitated into 5 mL of acidified CH_3OH and the solvent was decanted. This process (DCM-acidified CH_3OH) was repeated two times. The resulting white solid polymer was left to dry in a vacuum oven for 24 h. (Yield = 69 mg, 62%). ^1H NMR ($CDCl_3$, δ) 8.32-7.29 (m, 9H, ArH), 6.64 (br, 1H, NH), 6.29-6.04 (m, 1H, OCH(C=O)NH), 5.24 (m, 2H, benzylic-C*H*$_2$) 3.78 (m, 3H, O=CC*H*C*H*C=O, NHC*H*), 2.59 (br, 4H, SC*H*$_2$), 1.91-1.18 m, remaining C(C*H*$_3$)$_3$, cyclohexyl and main chain C*H*$_2$).

Synthesis of P4

P$_H$ (50 mg, 0.19 mmol) was dissolved in 0.5 mL furfuryl alcohol at room temperature. DCM (2 mL), 3-NBA (143 mg, 0.95 mmol), and CHI (118 μL, 0.95 mmol) were added respectively to this solution and the reaction mixture was left to stir at room temperature for 16 h. After the specified time, the mixture was precipitated into 5 mL of acidified CH_3OH and the solvent was decanted. This process (DCM-acidified CH_3OH) was repeated two times. The resulting light brown sticky solid polymer was left to dry in a vacuum oven for 24 h. (Yield = 60,6 mg, 55%). ^{1}H NMR ($CDCl_3$, δ) 8.32-7.57 (m, 4H, Ar*H*), 7.44 (br, 1H, C*H* of furan), 6.68 (br, 1H, N*H*), 6.46-6.23 (m, 3H, OC*H*(C=O)NH, C*H* of furan), 5.18 (m, 2H, OC*H*$_2$C) 3.77 (m, 3H, O=CC*H*C*H*C=O, NHC*H*), 2.62 (br, 4H, SC*H*$_2$), 1.92-1.18 (m, remaining C(C*H*$_3$)$_3$, cyclohexyl and main chain C*H*$_2$).

Synthesis of P5

P$_H$ (50 mg, 0.19 mmol) was dissolved in 0.5 mL propargyl alcohol at room temperature. DCM (2 mL), 3-NBA (143 mg, 0.95 mmol), and CHI (118 μL, 0.95 mmol) were added respectively to this solution and the reaction mixture was left to stir at room temperature for 16 h. After the specified time, the mixture was precipitated into 5 mL of acidified CH_3OH and the solvent was decanted. This process (DCM-acidified CH_3OH) was repeated two times. The resulting light yellow solid polymer was left to dry in a vacuum oven for 24 h. (Yield = 63 mg, 60%). ^{1}H NMR ($CDCl_3$, δ) 8.33-7.58 (m, 4H, Ar*H*), 6.64 (br, 1H, N*H*), 6.30-6.16 (m, 1H, OC*H*(C=O)NH), 4.81 (m, 2H, OC*H*$_2$CC≡CH) 3.78-3.59 (m, 3H, O=CC*H*C*H*C=O, NHC*H*), 2.68-2.48 (br, 5H, SC*H*$_2$, OCH$_2$C≡C*H*), 1.92-1.18 (m, remaining C(C*H*$_3$)$_3$, cyclohexyl and main chain C*H*$_2$).

Synthesis of P6

P$_H$ (50 mg, 0.19 mmol) was dissolved in 0.5 mL ethanol at room temperature. DCM (2 mL), 3-NBA (143 mg, 0.95 mmol), and CHI (118 μL, 0.95 mmol) were added respectively to this solution and the reaction mixture was left to stir at room temperature for 16 h. After the specified time, the mixture was precipitated into 5 mL of acidified $\mathrm{CH_3OH}$ and the solvent was decanted. This process (DCM-acidified $\mathrm{CH_3OH}$) was repeated two times. The resulting white solid polymer was left to dry in a vacuum oven for 24 h. (Yield = 25.0 mg, 24%). ^{1}H NMR ($\mathrm{CDCl_3}$, δ) 8.34-7.58 (m, 4H, $\mathrm{Ar}H$), 6.73 (br, 1H, $\mathrm{N}H$), 6.19 (m, 1H, $\mathrm{OC}H\mathrm{(C{=}O)NH}$), 4.27-4.15 (br, 2H, $\mathrm{OC}H_2\mathrm{CH_3}$), 3.79-3.54 (m, 3H, $\mathrm{O{=}CC}H\mathrm{C}H\mathrm{C{=}O}$, $\mathrm{NHC}H$), 2.68 (br, 4H, $\mathrm{SC}H_2$), 1.92-1.20 (m, $\mathrm{OCH_2C}H_3$, remaining $\mathrm{C(C}H_3\mathrm{)_3}$, cyclohexyl and main chain $\mathrm{C}H_2$).

Synthesis of P7

$\mathrm{P_H}$ (50 mg, 0.19 mmol) was dissolved in 0.5 mL isopropyl alcohol at room temperature. DCM (2 mL), 3-NBA (143 mg, 0.95 mmol), and CHI (118 µL, 0.95 mmol) were added respectively to this solution and the reaction mixture was left to stir at room temperature for 16 h. After the specified time, the mixture was precipitated into 5 mL of acidified $\mathrm{CH_3OH}$ and the solvent was decanted. This process (DCM-acidified $\mathrm{CH_3OH}$) was repeated two times. The resulting white solid polymer was left to dry in a vacuum oven for 24 h. (Yield = 21 mg, 17%). ^{1}H NMR ($\mathrm{CDCl_3}$, δ) 8.34-7.58 (m, 4H, $\mathrm{Ar}H$), 6.75 (br, 1H, $\mathrm{N}H$), 6.30-6.10 (m, 1H, $\mathrm{OC}H\mathrm{(C{=}O)NH}$), 5.10 (m, 1H, $\mathrm{OC}H\mathrm{(CH_3)_2}$), 3.77 (m, 3H, $\mathrm{O{=}CC}H\mathrm{C}H\mathrm{C{=}O}$, $\mathrm{NHC}H$), 2.67 (br, 4H, $\mathrm{SC}H_2$), 1.92-1.20 (m, $\mathrm{OCH(C}H_3\mathrm{)_2}$, remaining $\mathrm{C(C}H_3\mathrm{)_3}$, cyclohexyl and main chain $\mathrm{C}H_2$).

Synthesis of P8

$\mathrm{P_H}$ (50 mg, 0.19 mmol) was dissolved in 0.5 mL poly(ethylene glycol) monomethyl ether-550 at room temperature. DCM (2 mL), 3-NBA (143 mg, 0.95 mmol), and CHI (118 µL, 0.95 mmol) were added respectively to this solution and the reaction mixture was left to stir at room temperature for 16 h. After the specified time, the mixture was precipitated into 5 mL of acidified $\mathrm{CH_3OH}$ and the solvent was decanted. This process (DCM-acidified $\mathrm{CH_3OH}$) was repeated two times. The resulting pale yellow solid polymer was left to dry in a vacuum oven for 24 h. (Yield = 94 mg, 65%). ^{1}H NMR ($\mathrm{CDCl_3}$, δ) 8.33-7.58 (m, 4H, $\mathrm{Ar}H$), 6.74 (br, 1H, $\mathrm{N}H$), 6.29-6.10 (m, 1H, $\mathrm{OC}H\mathrm{(C{=}O)NH}$), 4.35 (br, 2H, $\mathrm{OC}H_2\mathrm{CH_2(OCH_2CH_2)_{11}OCH_3}$), 3.79-3.49 (m, 49H, $\mathrm{O{=}CC}H\mathrm{C}H\mathrm{C{=}O}$, $\mathrm{NHC}H$, $\mathrm{OCH_2C}H_2\mathrm{(OC}H_2\mathrm{C}H_2\mathrm{)_{11}OCH_3}$), 3.39 (s, 3H, $\mathrm{OC}H_3$), 2.67 (br, 4H, $\mathrm{SC}H_2$), 1.90-1.18 (m, remaining $\mathrm{C(C}H_3\mathrm{)_3}$, cyclohexyl and main chain $\mathrm{C}H_2$).

Synthesis of P9

P_H (50 mg, 0.19 mmol) was dissolved in 0.5 mL allyl alcohol at room temperature. DCM (2 mL), benzaldehyde (96 µL, 0.95 mmol), and CHI (118 µL, 0.95 mmol) were added respectively to this solution and the reaction mixture was left to stir at room temperature for 16 h. After the specified time, the mixture was precipitated into 5 mL of acidified CH_3OH and the solvent was decanted. This process (DCM-acidified CH_3OH) was repeated two times. The resulting pale yellow solid polymer was left to dry in a vacuum oven for 24 h. (Yield = 21,6 mg, 23%). ^{1}H NMR ($CDCl_3$, δ) 7.42-7.35 (m, 5H, Ar*H*), 6.52 (br, 1H, N*H*), 6.19-6.07 (m, 1H, OC*H*(C=O)NH), 5.93-5.81 (br, 1H, $\mathrm{CH_2{=}C}\mathit{H}\mathrm{CH_2O}$), 5.41-5.19 (m, 2H, $\mathrm{C}\mathit{H}_2\mathrm{{=}CHCH_2O}$), 4.69-4.57 (m, 2H, $\mathrm{CH_2{=}CHC}\mathit{H}_2\mathrm{O}$), 3.81-3.49 (m, 3H, O=CC*H*C*H*C=O, NHC*H*), 2.67 (br, 4H, $\mathrm{SC}\mathit{H}_2$), 1.93-1.18 (m, remaining $\mathrm{C(C}\mathit{H}_3)_3$, cyclohexyl and main chain $\mathrm{C}\mathit{H}_2$).

Synthesis of P10

P_H (50 mg, 0.19 mmol) was dissolved in 0.5 mL allyl alcohol at room temperature. DCM (2 mL), 3-NBA (143 mg, 0.95 mmol), and *tert*-butyl isocyanide (107 µL, 0.95 mmol) were added respectively to this solution and the reaction mixture was left to stir at room temperature for 16 h. After the specified time, the mixture was precipitated into 5 mL of acidified CH_3OH and the solvent was decanted. This process (DCM-acidified CH_3OH) was repeated two times. The resulting colorless sticky polymer was left to dry in a vacuum oven for 24 h. (Yield = 40 mg, 40%). ^{1}H NMR ($CDCl_3$, δ) 8.32-7.58 (m, 4H, Ar*H*), 6.54 (br, 1H, N*H*), 6.21-6.08 (m, 1H, OC*H*(C=O)NH), 5.94-5.79 (br, 1H, $\mathrm{CH_2{=}C}\mathit{H}\mathrm{CH_2O}$), 5.41-5.17 (m, 2H, $\mathrm{C}\mathit{H}_2\mathrm{{=}CHCH_2O}$), 4.70 (m, 2H, $\mathrm{CH_2{=}CHC}\mathit{H}_2\mathrm{O}$), 3.77-3.55 (m, 3H, O=CC*H*C*H*C=O, NHC*H*), 2.67 (br, 4H, $\mathrm{SC}\mathit{H}_2$), 1.38 (br, remaining $\mathrm{C(C}\mathit{H}_3)_3$, main chain $\mathrm{C}\mathit{H}_2$ and $\mathrm{NHC(C}\mathit{H}_3)_3$).

Synthesis of P11

P_H (50 mg, 0.19 mmol) was dissolved in 0.5 mL allyl alcohol at room temperature. DCM (2 mL), propanal (69 µL, 0.95 mmol), and benzyl isocyanide (116 µL, 0.95 mmol) were added respectively to this solution and the reaction mixture was left to stir at room temperature for 16 h. After the specified time, the mixture was precipitated into 5 mL of acidified CH_3OH and the solvent was decanted. This process (DCM-acidified CH_3OH) was repeated two times. The resulting sticky light brown polymer was left to dry in a vacuum oven for 24 h. (Yield = 46 mg, 53%). ^{1}H NMR ($CDCl_3$, δ) 7.31 (br, 6H, Ar*H*, N*H*), 5.92 (br, 1H, CH_2=C*H*CH_2O), 5.40-5.26 (m, 3H, CH_2=CHCH_2O, OC*H*(C=O)NH), 4.68-4.46 (m, 4H, CH_2=CHCH_2O, benzyl-CH_2), 3.57 (br, 2H, O=CC*H*C*H*C=O), 2.65 (m, 4H, SCH_2), 1.55-1.00 (br, remaining C(CH_3)$_3$, main chain CH_2, CH_3CH_2CHO and C$H_3$$CH_2$CHO).

Synthesis of mono-*tert*-butyl Functional Polythioether (P_{MT})

To a 10 mL of the round-bottom flask was added 3 mL of $CHCl_3$ at room temperature. *Tert*-butyl propiolate (412 μL, 3.00 mmol) and HDT (459 μL, 3.00 mmol) were then added to the flask, respectively. The catalyst, TBD (41.7 mg, 0.3 mmol), was added to the reaction mixture. Upon addition of TBD, an exothermic reaction occurred and the colorless solution instantly turned to pale yellow. After 1 h, the solution was diluted with 3 mL of $CHCl_3$, precipitated into 50 mL of acidified CH_3OH, and finally, the solvent was removed by decantation. The dissolution-precipitation procedure ($CHCl_3$-acidified CH_3OH) was repeated two times. The purified colorless sticky polymer was finally dried in a vacuum oven for 24 h. (Yield = 733 mg, 88%) (M_w = 8.0 kDa, $Đ$ = 1.38). ^{1}H NMR ($CDCl_3$, δ) 4.15 (t, 1H, CH_2C*H*S), 2.68-2.59 (m, 6H, CH_2CHS and SCH_2), 1.60 (m, 4H, main chain CH_2), 1.47 (m, 9H, C(CH_3)$_3$), 1.41 (m, 4H, main chain CH_2).

Hydrolysis of mono-*tert*-butyl Functional Polythioether (P_{MH})

P_{MT} (663 mg, 2.40 mmol) was dissolved in 10 mL of DCM, TFA (459 μL, 6.00 mmol) was added to this solution and the reaction mixture was allowed to stir at room temperature for 2 days. Then, DCM was evaporated under reduced pressure and the resulting polymer was diluted with 2 mL of THF and precipitated into 40 mL of hexane, the solvent was decanted. The dissolution-precipitation process (THF-hexane) was repeated two times. The resulting polymer was left to dry in a vacuum oven for 24 h. (Yield = 444 mg, 84%) (M_w = 2.5 kDa, $Đ$ = 1.32). ^{1}H NMR ($(CD_3)_2CO$, δ) 4.27 (m, 1H, CH_2C*H*S), 2.93 (br, 6H, CH_2CHS and SCH_2), 1.66 (m, 8H, main chain CH_2).

Synthesis of P_{MP}

P_{MH} (150 mg, 0.68 mmol) was dissolved in 0.5 mL of allyl alcohol at room temperature. DCM (2 mL), 3-NBA (258 mg, 1.71 mmol), and CHI (212 μL, 1.71

mmol) were added respectively to this solution and the reaction mixture was left to stir at room temperature for 16 h. After the specified time, the mixture was precipitated into 15 mL of acidified CH_3OH and the remaining solvent was decanted. This process (DCM-acidified CH_3OH) was repeated two times. The resulting white solid polymer was left to dry in a vacuum oven for 24 h. (Yield = 265 mg, 81%) (M_w = 4.8 kDa, $Đ$ = 1.23). ^{1}H NMR ($CDCl_3$, δ) 8.31-7.56 (m, 4H, Ar*H*), 6.76 (br, 1H, N*H*), 6.19 (s, 1H, OC*H*(C=O)NH), 4.24 (t, 1H, $CH_2C\mathit{H}S$), 3.76 (m, 1H, NHC*H*), 3.01 (m, 2H, $C\mathit{H}_2CHS$) 2.70 (br, 4H, $SC\mathit{H}_2$), 1.92-1.17 (m, 18H, cyclohexyl and main chain $C\mathit{H}_2$).

4. RESULTS AND DISCUSSION

Recently Daglar et al. have introduced a straightforward and robust method based on a double thiol-Michael addition reaction between a dithiol and dialkyl acetylene dicarboxylate using TBD as a catalyst. Up to now, the outcome of the reaction is highly promising for the polymer community; various linear and nonlinear polythioethers have been prepared in 1 minute in high yields and moderate to high molecular weights. The polythioethers obtained by this method have also another feature that is diester functionality for each repeating unit, which can be further used for post-polymerization functionalization. It is assumed that rapid polythioether synthesis chemistry can be combined with Passerini-3CR with using polythioether carrying di-tert-butyl groups, which is a suitable candidate for this aim due to facile hydrolysis of tert-butyl groups to obtain the acid groups, one of the three functional groups required for a Passerini-3CR. To examine this, a polymerization reaction was performed between DTBADC (1.0 M) and HDT (1.0 M) in $CHCl_3$ using TBD (0.1 M) as a catalyst at room temperature for 1 minute [28]. The polythioether with di-tert-butyl ester functionality (P_T) displayed a molecular weight of M_w = 27.1 kDa and obtained in quantitative yield (>99 %). Subsequently, P_T was exposed to hydrolysis using TFA in DCM, but a series of experiments were required to determine the optimum reaction duration. In the first attempt, the polymer mixture was left to stir for one day in the presence of excess TFA (5 equiv. per repeating unit). After purification, the obtained polymer was analyzed by ^1H NMR spectroscopy by comparing the distinct signals of tert-butyl groups at δ 1.47 ppm with the main chain signals (Figure 4.1). It was found that the hydrolysis was achieved around 60% in one day, reached 90% in two days, and 95% in four days. However, complete hydrolysis was not achieved, which might be attributed to the low solubility of the resulting diacid structure in DCM. The formation of a precipitate around the reaction flask after the first day supports the idea of low solubility. On the other hand, increasing TFA amount (~10 equiv. per repeating unit) in the reaction medium caused a dramatic reduction in the polymer molecular weight (M_w = 6.1 kDa) in two days, which arguably indicates polymer main backbone degradation in the presence of such a strong acid. Therefore, dicarboxylic acid pendant polythioether (P_H) produced with 95% efficiency in four days using 5 equivalents of TFA was used in the post-functionalization studies. As expected, the molecular weight of P_H (M_w = 17.8 kDa) is reduced after hydrolysis. Notably, P_H displayed a different physical property than P_T. For instance, while CH_3OH does not dissolve P_T, it has become a suitable solvent for P_H, however, the polymer was partially miscible with water. As seen in Figure 4.1, the signal representing the *tert*-butyl groups' hydrogens as "a" became very small that it proved the high yield of the hydrolysis process.

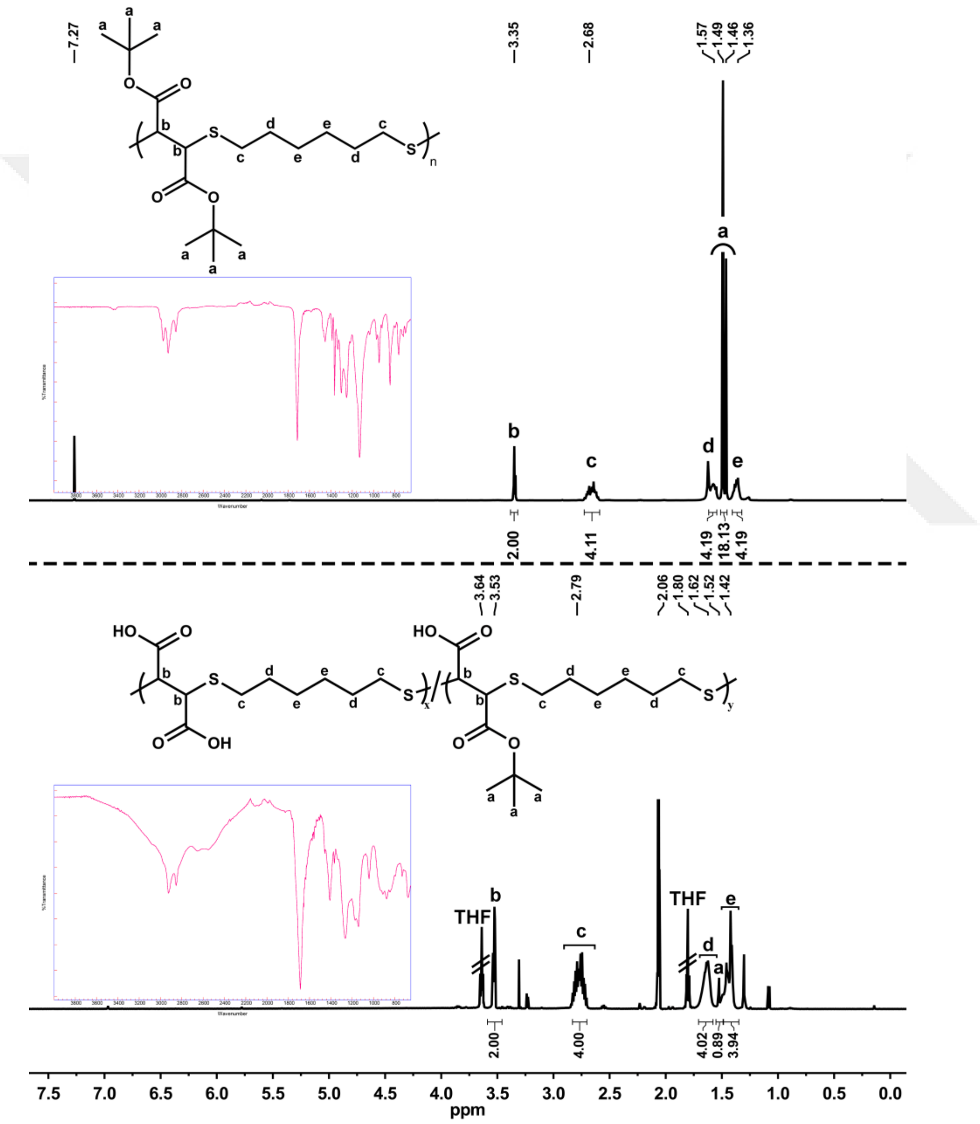

Figure 4.1 Overlaid ^{1}H NMR (in $CDCl_3$ (500 MHz)) and FT-IR (attached to NMR) spectra of P_T (up) and P_H (down).

It is worth mentioning here that dicarboxylic acid functionality in each repeating unit of a polymer makes it a highly attractive precursor for further modifications since desired groups can be installed twice to the polymer chain. In this regard, Passerini-

3CR has been employed for further functionalization of P_H owing to the mild conditions, and no additional additive is required for the process. Initially, an attempt was made to explore the appropriate solvent for the Passerini-3CR. As it is known, DCM is the most commonly used solvent in Passerini reactions applied to polymers [7, 31, 88-90, 92-95]. However, since P_H has very low solubility in DCM, THF was used primarily as a solvent for functionalization reactions. For this purpose, 5 equivalents (per diacid) of 3-NBA and CHI were reacted with P_H in THF for 16 h at room temperature. After purification, the resultant polymer was analyzed by ^1H NMR. Although the expected Passerini product was detected, very complicated, broad, and inseparable signals were observed in the spectrum, preventing to make a true judgment on the efficiency of the reaction. Using a mixed solvent system, THF: DCM (1/1, V/V), also did not lead to a proper ^1H NMR spectrum (Figure 4.2).

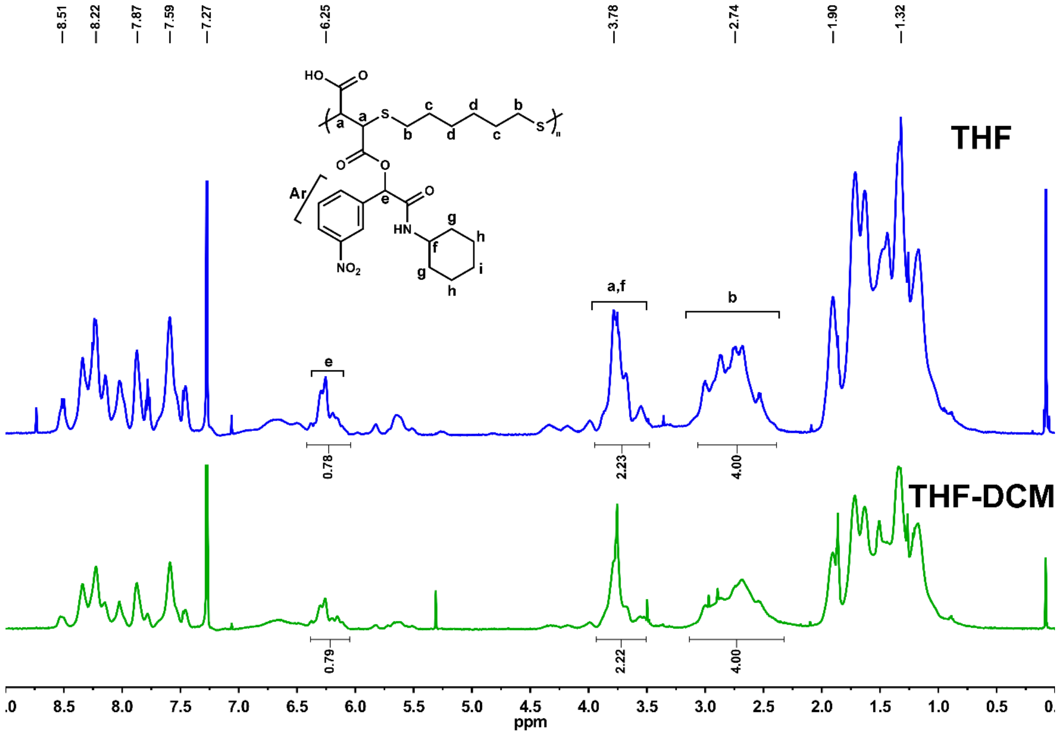

Figure 4.2 Overlaid ^1H NMR spectra of the Passerini reactions performed in THF and THF-DCM mixture in $CDCl_3$ (500 MHz).

In the next attempt, THF was replaced with CH_3OH (0.5 mL) since P_H was also soluble in CH_3OH, DCM (2 mL) is also added to the solution to prevent possible solubility issue while the formation of the Passerini product. Using the same compounds (3-NBA and CHI), the above-mentioned modification study was repeated in a CH_3OH: DCM (1/4, V/V) solvent mixture. Following the purification, ^1H NMR analysis of the product (P1) suggested a very smooth and clear spectrum, allowing for a proper integral ratio for the characteristic main chain protons with the Passerini product.

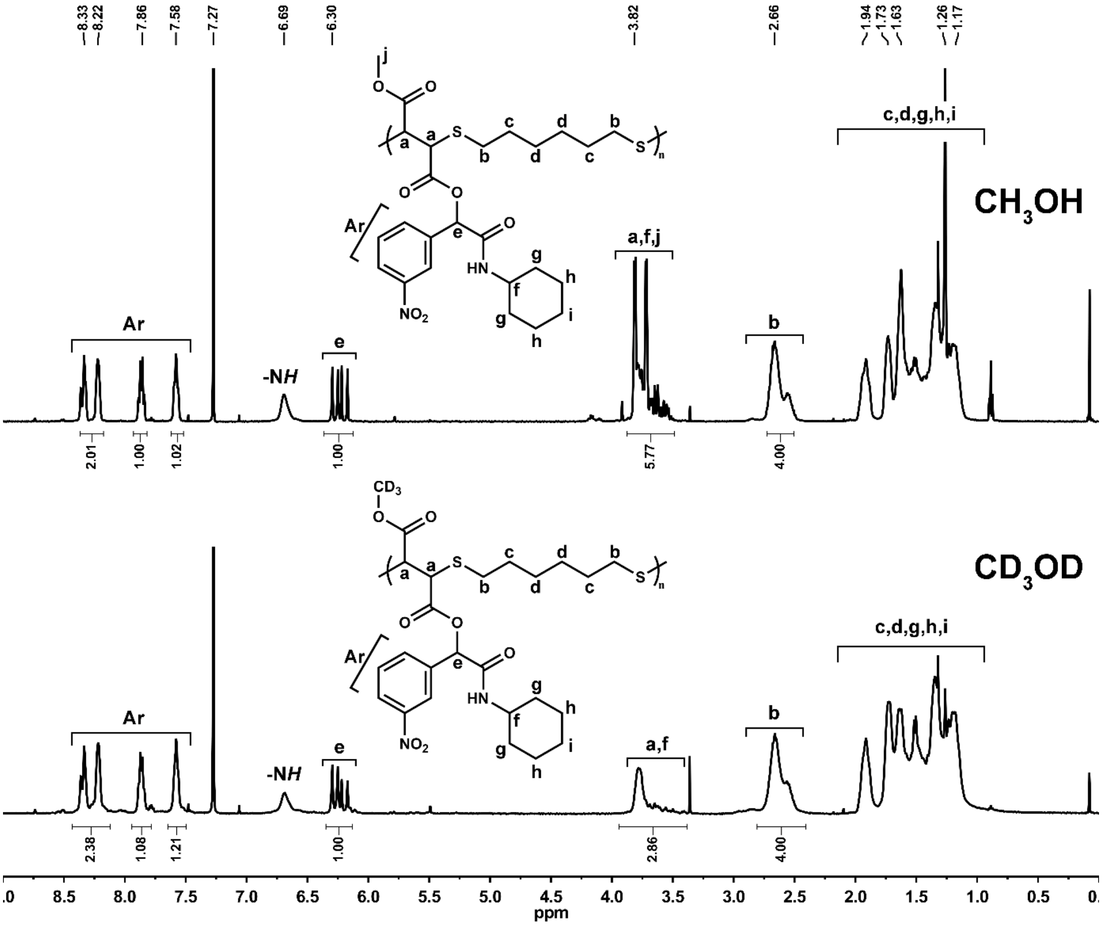

Figure 4.3 Overlaid ^1H NMR spectra of Passerini reactions in CH_3OH and CD_3OD in $CDCl_3$ (500 MHz).

Here, when 4 protons of main chain methylene protons (CH_2-S) at δ 2.66 ppm are compared to one of the aromatic protons between δ 7.5-8.4 ppm or methine proton at δ 6.30 ppm, a ratio of 4:1 was found. This result indicates that the modification was achieved with 50% efficiency, and thus the Passerini product was assumed to produce from only one carboxylic acid. However, an unexpected integral value was found at δ 3.82 ppm, which contains main chain methine protons (S-C*H*-C*H*-C=O) and a methine proton of cyclohexyl ring next to N. An integrated value of these protons was found to be 5.77, while it was expected to be 3.0 (Figure 4.3). This result is likely to indicate the formation of an unexpected product and CH_3OH may have somehow participated in the final structure via an esterification reaction. To be more conclusive on our idea, the above experiment is repeated in CD_3OD: DCM mixture. It is expected that if CH_3OH participated in the structure of the polymer, the integral value at 3.82 ppm should exhibit a significant reduction by replacing CH_3OH with CD_3OD. Indeed, the new integral ratio of the aforementioned protons was found to be 4:2.86 (expected 4:3), indicating that the extra protons at 3.82 ppm are due to the contribution of ester $C{=}OOC\mathit{H}_3$ protons. Here, it has been proven that a simultaneous Passerini & esterification occurred in the reaction in one-step, and this situation has never been encountered before in any Passerini-3CR at the macromolecular level.

This finding was stimulated to examine the one-step Passerini & esterification reaction in detail, by taking advantage of the CH_3OH co-reaction. A series of alcohols were tested during the reactions and the conditions used for the CH_3OH case were considered as the standard condition; alcohol: DCM (0.5 mL: 2 mL), same amounts of 3-NBA, and CHI (5 equiv. per diacid). Allyl alcohol was initially examined in detail for this purpose owing to its distinct protons in ^1H NMR. Employing standard conditions, the polymer (P2) obtained was analyzed by ^1H NMR. It was found that Passerini-3CR and esterification reactions occurred with 50% and 35% efficiencies (run 2, Table 1), respectively, by comparing $C\mathit{H}_2$-S (assigned as “b”) protons to the methine proton of Passerini product (assigned as “e”) and the methylene protons ($C\mathit{H}_2OC{=}O$) of allyl ester (assigned as “j) (Figure 4.6 a).

A significant decrease in the efficiency of the Passerini product from 50% to 35% was observed by reducing the equivalents of 3-NBA and CHI from 5 to 3 (per diacid), however, a dramatic increase up to 63% was found when their equivalents doubled. Additionally, no clear difference in the esterification efficiencies was observed in these products (run 3 and 4, Table 1). Doubling of allyl alcohol yielded the ester product with 41% efficiency, while no reduction was observed in the Passerini efficiency (run 5, Table 1). A unimodal GPC trace without tail or shoulder was observed for the polymer, indicating that there were no unwanted side reactions during the modification (Figure 4.4). Comparing the max. value of the GPC traces, it can be seen that the molecular weight of the P_T decreased while hydrolysis, then another decrease can be seen for the Passerini product P2. To elucidate more on P2, ^{13}C NMR and FT-IR spectroscopies were used, respectively. As seen in Figure 4.5 b, $\mathit{C}{=}O$ carbons in the structure were detected between 170-165 ppm, methine C (assigned as “6” in the spectrum) at 74.5 ppm, and ester $\mathit{C}H_2OC{=}O$ at around 67.0

ppm. FT-IR spectroscopy displayed two strong C=O stretching peaks assignable to the ester and amide at ~1750 cm^{-1} and ~1655 cm^{-1}, respectively, and a broad amide N-H stretching peak seen at ~3320 cm^{-1} (Figure 4.5 c).

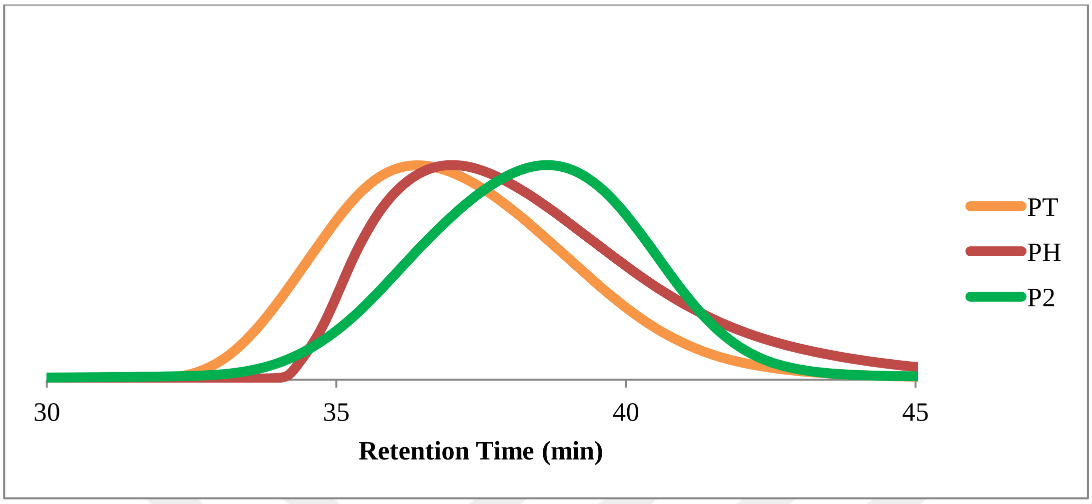

Figure 4.4 Overlaid GPC traces of P_T, $P_{H,}$ and P2 (in THF).

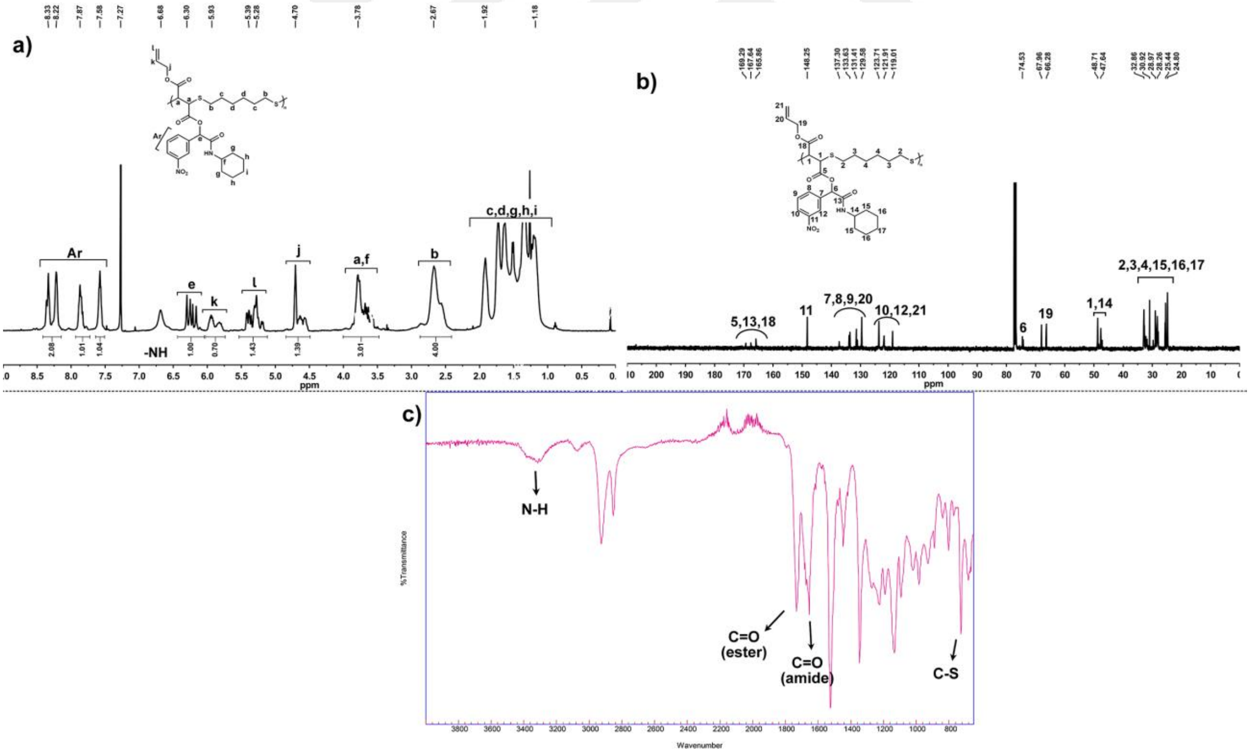

Figure 4.5 Overlaid ^{1}H NMR (a), ^{13}C NMR (b), FT-IR (c) spectra of P2.

Various alcohols with different chemical properties were then examined under standard conditions to diversify the ester structures and the results are collected in Table 1. The efficiencies of both Passerini and esterification reactions were delivered by following the same calculation method described for P2. Benzyl (P3), furfuryl (P4), propargyl (P5) alcohols, and ethanol (P6) produced the corresponding esters with 32-45%, efficiencies, while the Passerini products were obtained with 50% efficiencies in all cases. Notably, when secondary alcohol, isopropyl alcohol (P7), and PEG (P8), long-chain alcohol, were used in reactions, a dramatic reduction in the esterification efficiencies were observed, the P7 displayed 15% esterification efficiency, while a slight increase (18%) was observed for the P8, which might be attributed to their poor nucleophilicity. Figure 4.6 indicates that there are no such different values between M_w of the polymers. In Figure 4.7 the FT-IR spectra of the polymers can be seen. All the polymers were characterized by ^{1}H NMR, Figure 4.8 exhibits an overlay of representative examples. Methylene protons regarding the ester ($CH_2OC=O$) units are indicative for all polymers and were detected in all cases, in addition to the distinct signals of each alcohol used.

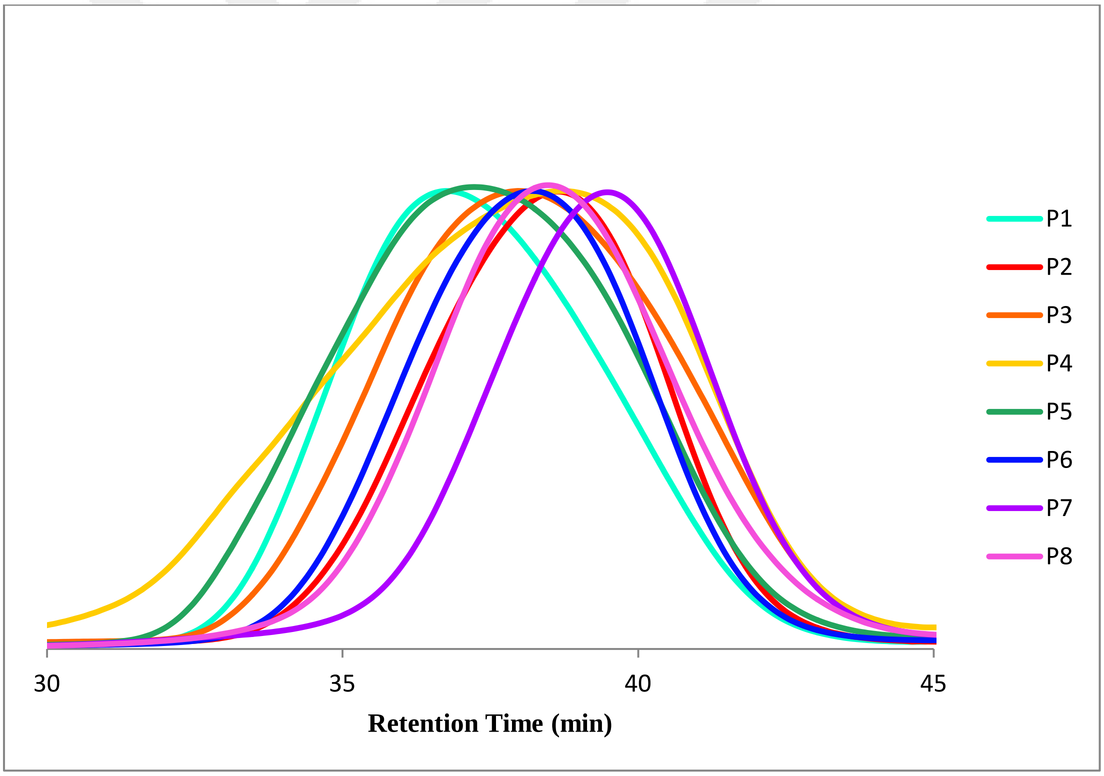

Figure 4.6 Overlaid GPC traces of P1-P8 (in THF).

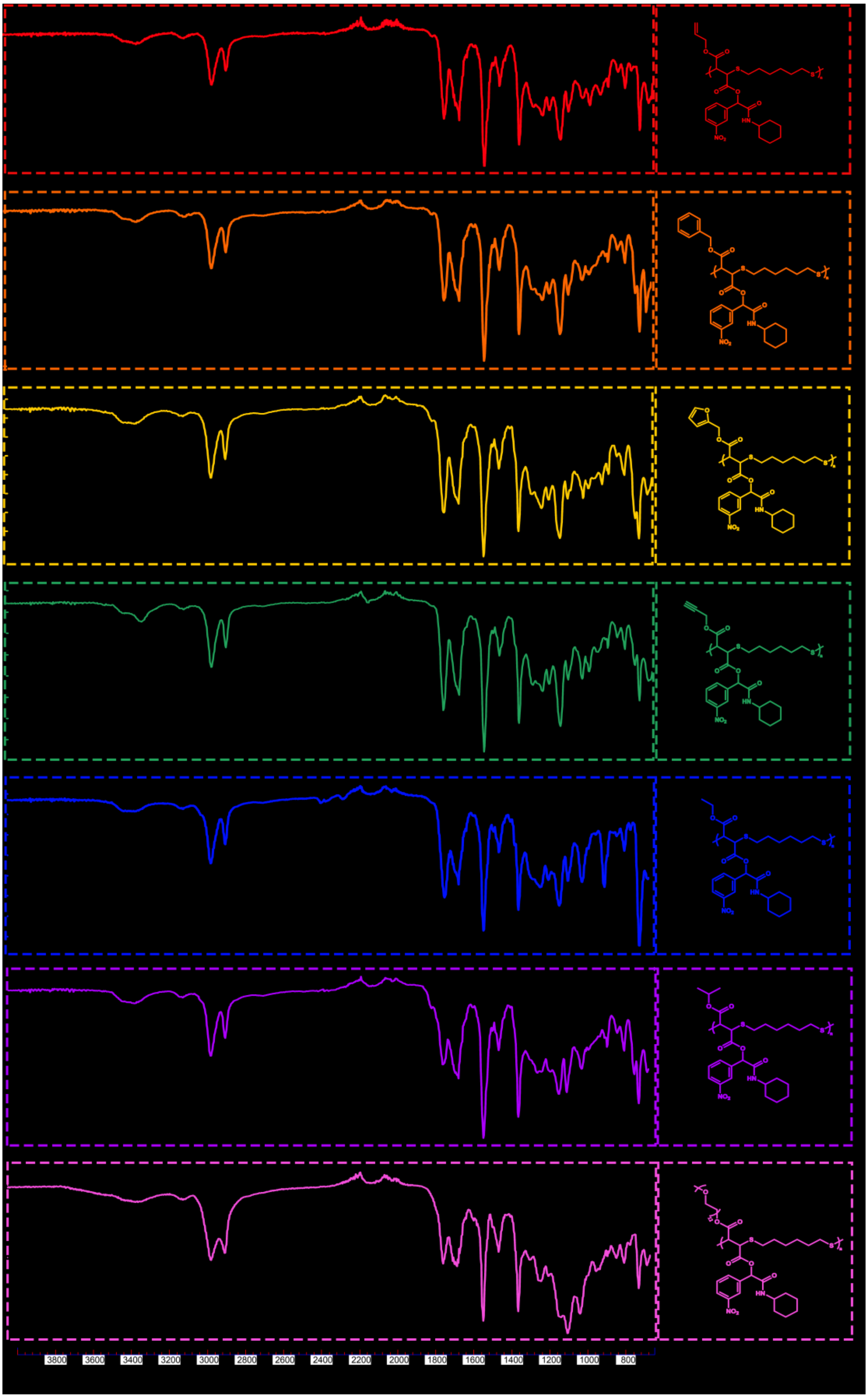

Figure 4.7 Overlaid FT-IR Spectra of P2-P9 (from top to bottom).

Table 1 Percentages of formations of the different products for P1-P14[a].

Run	Polymer	Aldehyde	Isocyanide	Alcohol	Passerini product (%)[e]	Esterification(%)[e]	Acid/*tert*-butyl (%)	$M_w/Đ$[f]
1	P1	3-NBA	CHI	Methanol	50	45	5	24.5/1.54
2	P2	3-NBA	CHI	Allyl alcohol	50	35	15	16.3/1.42
3[b]					35	35	30	18.8/1.40
4[c]					63	32	5	14.3/1.45
5[d]					50	41	9	13.9/1.36
6	P3	3-NBA	CHI	Benzyl alcohol	50	33	17	20.8/1.71
7	P4	3-NBA	CHI	Furfuryl alcohol	51	32	17	31.8/2.41
8	P5	3-NBA	CHI	Propargyl alcohol	50	35	15	26.7/1.71
9	P6	3-NBA	CHI	Ethanol	50	45	5	18.7/1.42
10	P7	3-NBA	CHI	Isopropyl alcohol	72	15	13	12.7/1.43
11	P8	3-NBA	CHI	PEG_{550}	60	18	22	16.3/1.50
12	P9	Benzaldehyde	CHI	Allyl alcohol	46	42	12	25.8/1.31
13	P10	3-NBA	*Tert*-butyl isocyanide	Allyl alcohol	50	38	12	25.0/1.32
14	P11	Propanal	Benzyl isocyanide	Allyl alcohol	48	31	21	28.7/1.47

[a] Reaction conditions: aldehyde/isocyanide (5 equiv. each per diacid), alcohol/DCM (0.5 mL/2 mL) at room temperature for 16 h. [b] 3 equiv. of aldehyde and isocyanide were used. [c] 10 equiv. of aldehyde and isocyanide were used. [d] 1 mL of allyl alcohol was used. [e] Calculated from ^1H NMR. [f] Determined by GPC calibrated based on linear PS standards in THF at 30˚C

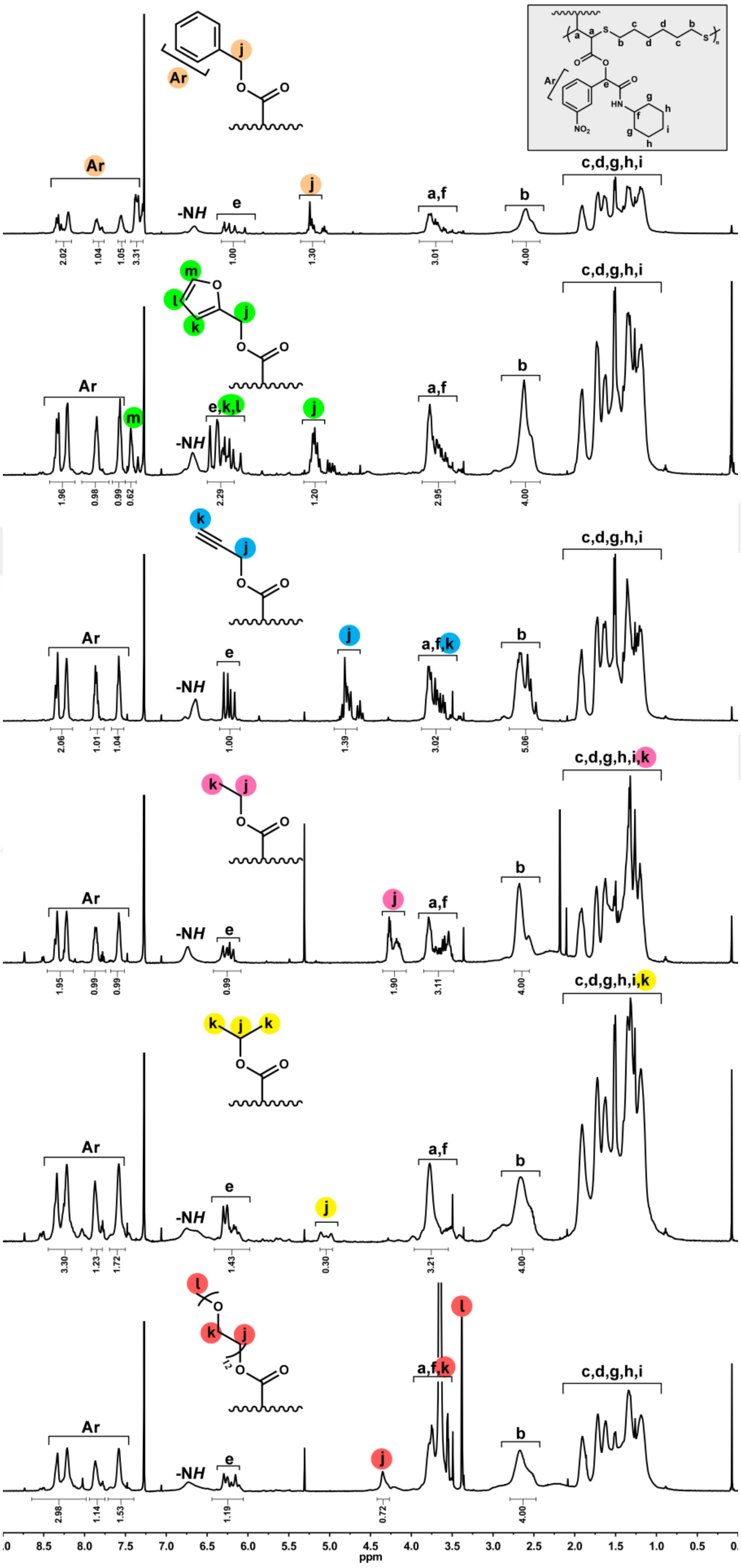

Figure 4.8 Overlaid ^{1}H NMR spectra of P3, P4, P5, P6, P7, and P8 (from top to down) in $CDCl_3$ (500 MHz).

Moreover, by using allyl alcohol, when benzaldehyde (P9) was replaced with 3-NBA or *tert*-butyl isocyanide (P10) with CHI, no different results were found than those obtained by using the above-mentioned functional alcohols. A similar result was also obtained when an aliphatic aldehyde and an aromatic isocyanide (P11) were reacted under the standard conditions using allyl alcohol, showing the robustness and versatility of this process. Meanwhile, the M_w of modified polymers were varying between 12.7-31.8 kDa, and unimodal GPC traces were observed for all cases (Figure 4.9).

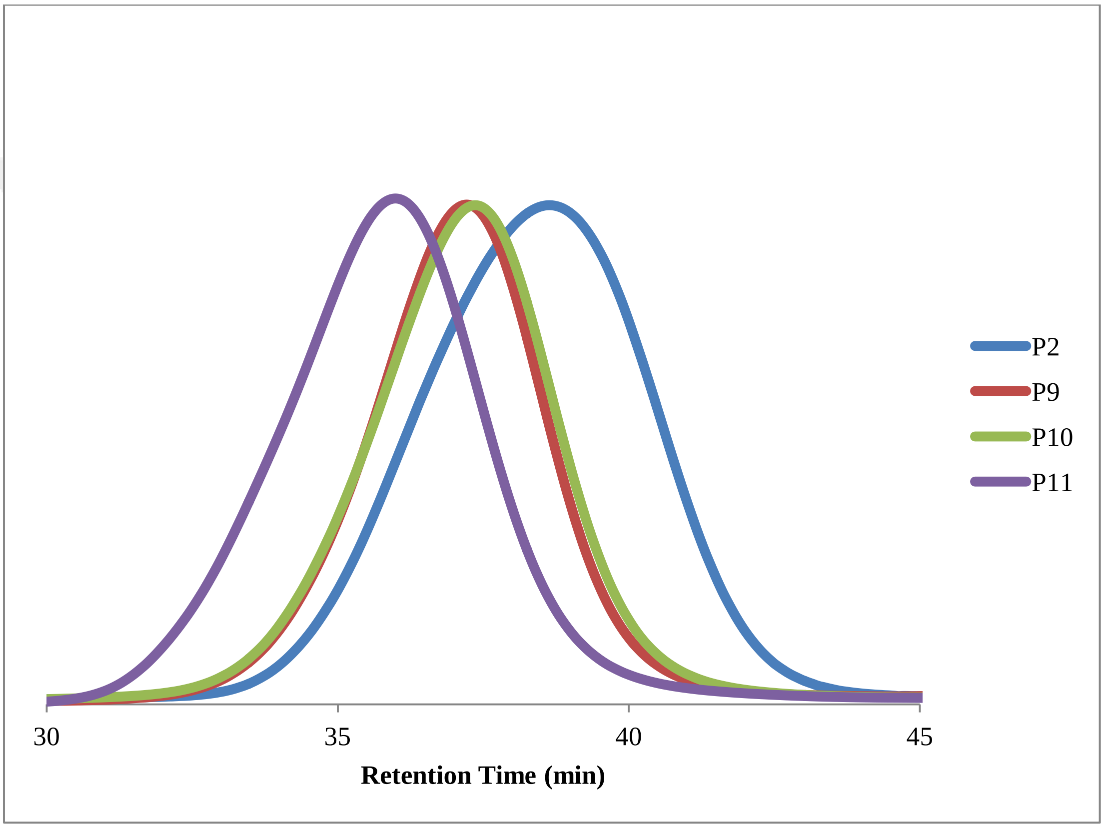

Figure 4.9 Overlaid GPC spectra of P2, P9, P10 and P11 (in THF).

Notably, except for P1 and P9, unreacted acid remained in the modified polymers, in addition to 5% (unhydrolyzed) *tert*-butyl groups (Table 1). In Figure 4.10, the difference between the signals of the polymers can be easily seen. Especially it can be clearly seen that the movement of the "e" signals of P11.

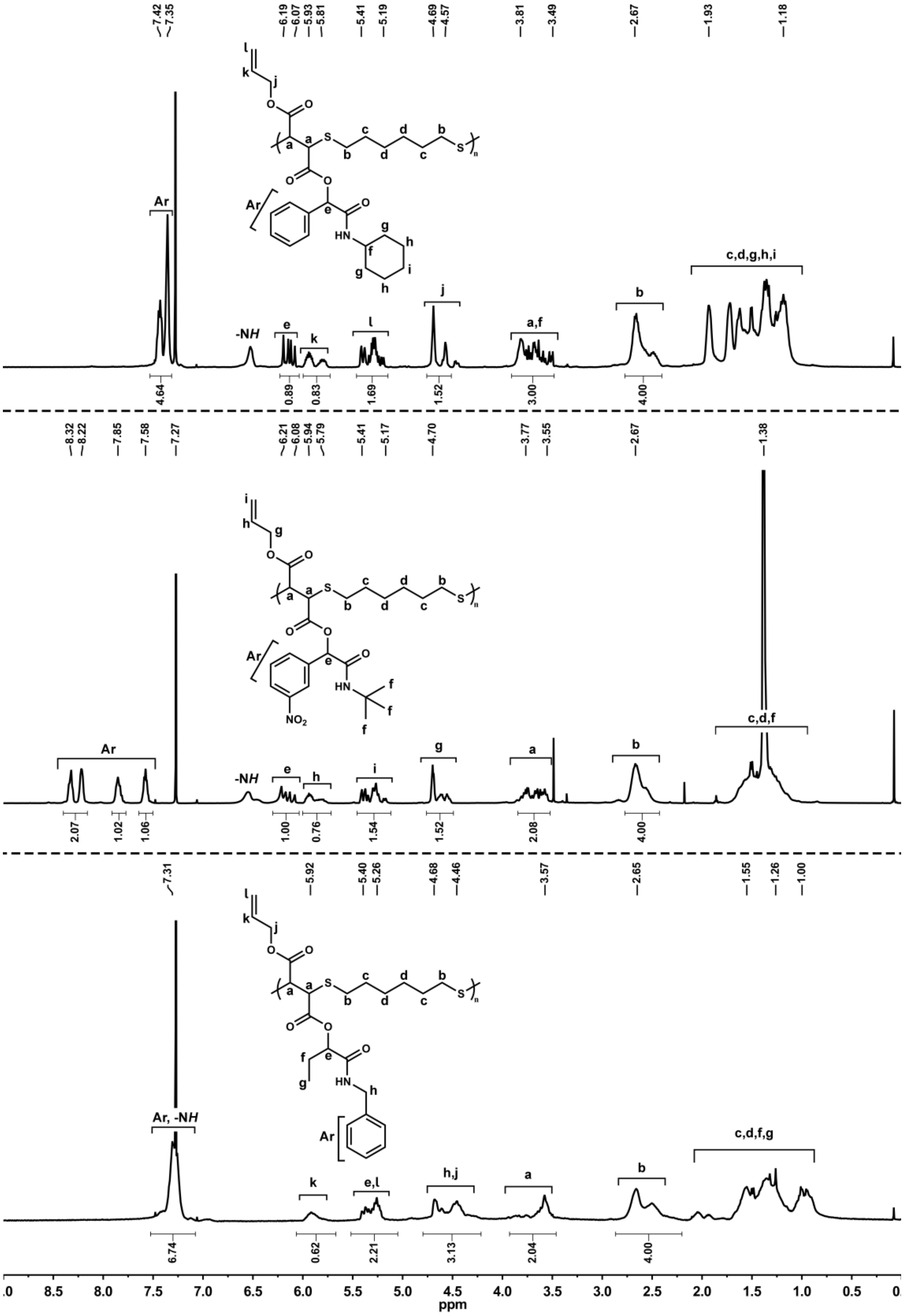

Figure 4.10 Overlaid ^{1}H NMR spectra of P9, P10, and P11 (from top to down) in $CDCl_3$ (500 MHz).

As the next intriguing question, it has been examined whether the one-step Passerini & esterification reaction described in this study is also applicable for a polythioether containing monocarboxylic acid (Figure 4.11). For this purpose, a polymerization reaction was conducted between tert-butyl propiolate and HDT using TBD as a catalyst at room temperature for 1 hour [67], resulting in the formation of polythioether with tert-butyl ester functionality (P_{MT}), followed by hydrolysis using TFA (2.5 equiv. per repeating unit) yielded polythioether with monocarboxylic acid (P_{MH}). Notably, in this case, complete hydrolysis was achieved, as confirmed by the ^{1}H NMR result, in two days. In the last step, P_{MH} was reacted with 3-NBA and CHI (2.5 equiv. per acid) in a mixture of allyl alcohol (0.5 mL) and DCM (2 mL) at room temperature for 16 hours. After purification, the obtained product (P_{MP}) was characterized by ^{1}H NMR.

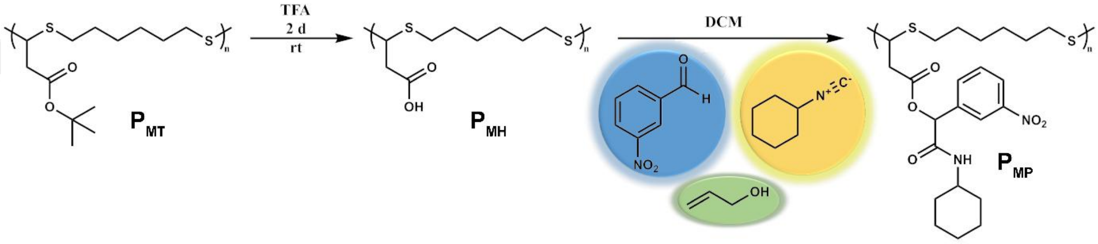

Figure 4.11 Schematic representation for the modification of monoacid containing polythioether (P_{MH}) via Passerini reaction.

As seen in Figure 4.13 (down), the Passerini product was obtained with quantitative efficiency by comparing the integral ratio of the above-mentioned protons, while yielding no ester formation. It is obvious from this result that a one step Passerini & esterification reaction is not applicable for a polythioether containing monocarboxylic acid, but rather for a polythioether containing dicarboxylic acid. Thus, it can be seen in Figure 4.12 that the molecular weight of the P_{MT} decreased after hydrolysis (P_{MH}) as expected.

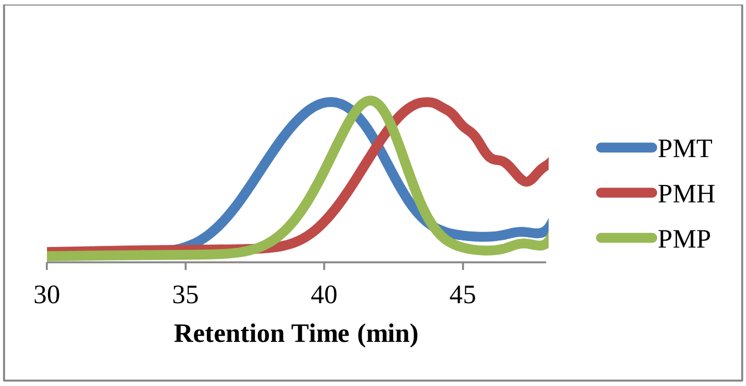

Figure 4.12 Overlaid GPC spectra of P_{MT}, P_{MH} and P_{MP} (in THF).

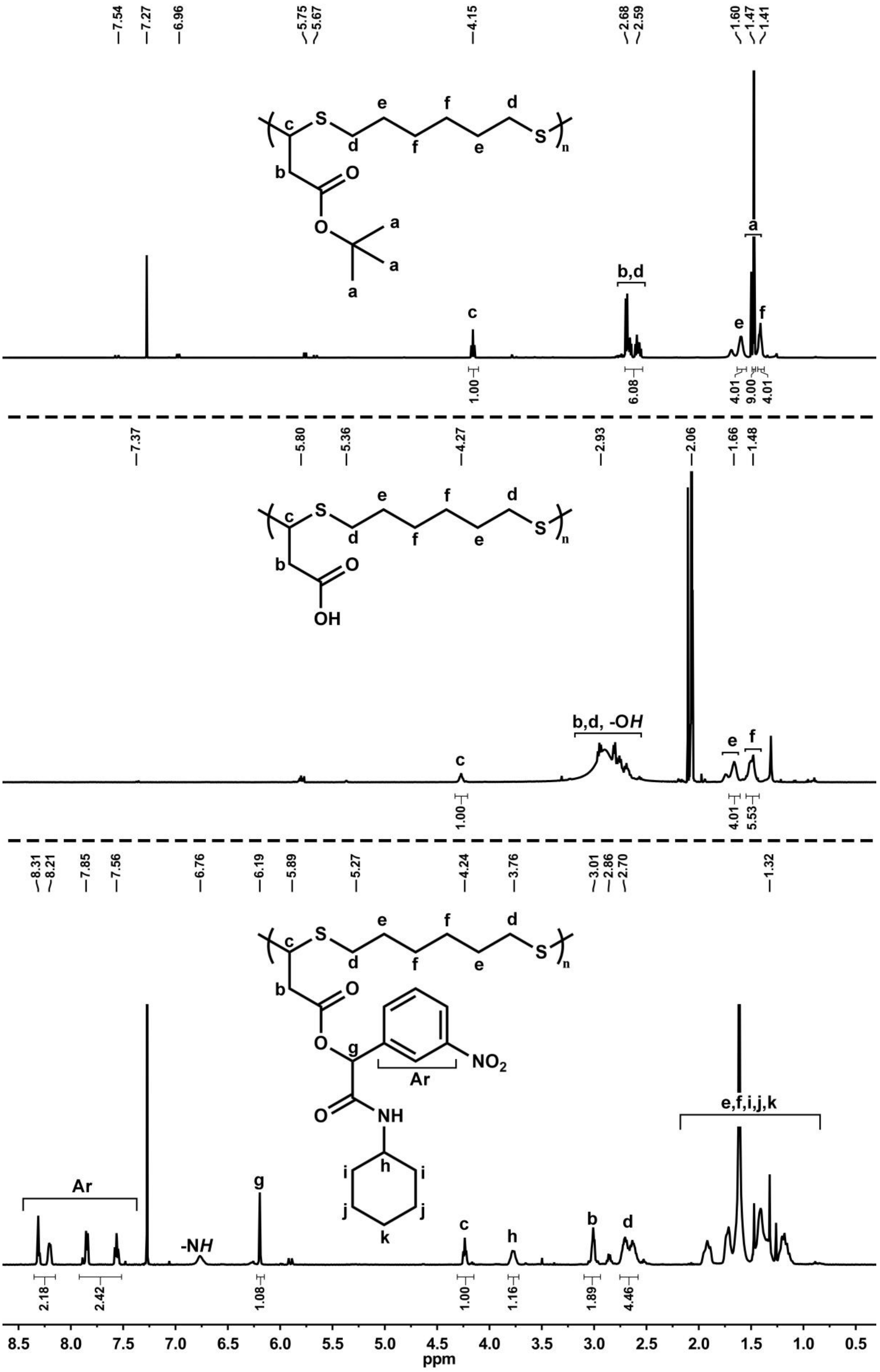

Figure 4.13 Overlaid ^{1}H NMR spectra of P_{MT} (up), P_{MH} (middle), and P_{MP} (down) in $CDCl_3$ (500 MHz).

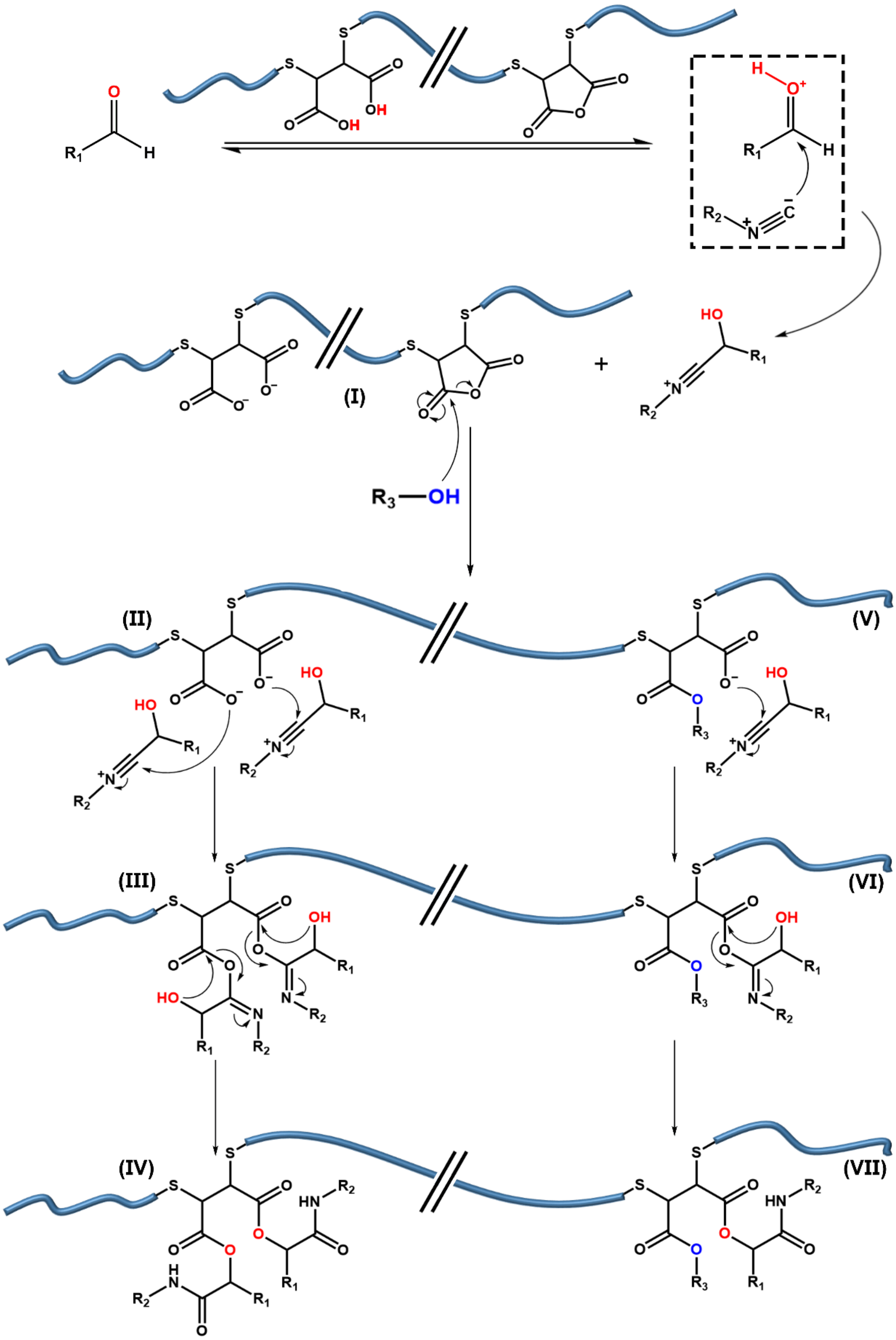

Figure 4.14 Proposed mechanism for product distribution during the modification of P_H via Passerini reaction.

Based on the above findings a general mechanism for the one-step Passerini & esterification reaction has been suggested. It is estimated that during the hydrolysis reaction some part of the pendant diacid units had turned to cyclic anhydride form. Hence, the formation of both Passerini and ester products are assumed to occur simultaneously in the reaction medium as depicted in Figure 4.14. Here, the protonation of aldehyde through the polymer-bound carboxylic acid followed by nucleophilic addition of the isocyanide to this aldehyde creates a nitrilium ion and a polymeric intermediate having both carboxylate and cyclic anhydride units (I). In the classical Passerini reaction; carboxylate attacks the nitrilium ion, followed by an intramolecular rearrangement, and finally, the amide tautomerization delivers the Passerini product (II-IV). In the meantime, the cyclic anhydride structure undergoes a nucleophilic ring-opening reaction with a solvent molecule, yielding the ester product and regenerates the carboxylate ion on the polymer (V). Following the same mechanisms described in steps II-IV, Passerini product could be reproduced on the polymer through the reaction between newly formed carboxylate ion and the excess of nitrilium ion present in the reaction medium (VI and VII) (Figure 4.14).

5. CONCLUSION

In conclusion, a novel and intriguing post-polymerization modification method was suggested for synthetic polymer chemistry. Polythioether, P_H, having pendant dicarboxylic acid groups was prepared in two steps and functionalized employing Passerini-3CR. An unexpected formation of methyl ester was discovered in the polymer chain, in addition to the Passerini product, through an esterification reaction when CH_3OH was used as co-solvent during the modification. The process called one-step Passerini & esterification reaction was subsequently extended to various alcohols to create an ester library. ^1H NMR analyses suggested that Passerini products were obtained with 50-72% efficiencies, while the ester products with 18-45%. Notably, except for secondary and long-chain alcohols, all examined functional alcohols provided very close esterification efficiencies, confirming the applicability of the proposed reaction. On the other hand, when a polythioether involving only monocarboxylic acid pendant groups, P_{MH}, was examined, solely the Passerini product was obtained, indicating that this process is applicable only for polythioether having dicarboxylic acid pendant groups. In summary, for the first time, a one-step Passerini & esterification reaction for the polymer community has been documented, which promises a high potential for future studies of functional modifications.

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