ISTANBUL TECHNICAL UNIVERSITY ★ GRADUATE SCHOOL OF SCIENCE ENGINEERING AND TECHNOLOGY

SYNTHESIS OF FULLY FUNCTIONALIZED FURAN MAIN CHAIN POLYESTER THROUGH MULTI COMPONENT REACTIONS

M.Sc. THESIS

Alp HIZAL

Department of Chemisty

Chemistry Programme

DECEMBER 2017

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Alp HIZAL
(509101089)

Department of Chemistry

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Thesis Advisor: Assoc. Prof. Dr. Hakan DURMAZ

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TAM FONKSİYONEL FURAN ANA ZİNCİRLİ POLYESTERLERİN ÇOK BİLEŞENLİ REAKSİYON YOLU İLE SENTEZİ

YÜKSEK LİSANS TEZİ

Alp HIZAL
(509101089)

Kimya Anabilim Dalı

Kimya Programı

Tez Danışmanı: Doç. Dr. Hakan DURMAZ

ARALIK 2017

Alp HIZAL, a **M.Sc.** student of İTU **Graduate School of Science Engineering and Technology** student ID **509101089**, successfully defended the thesis/dissertation entitled "**SYNTHESIS OF FULLY FUNCTIONALIZED FURAN MAIN CHAIN POLYESTER THROUGH MULTI COMPONENT REACTIONS**", which he prepared after fulfilling the requirements specified in the associated legislations, before the jury whose signatures are below.

Thesis Advisor : **Assoc. Prof. Dr. Hakan DURMAZ**
Istanbul Technical University

Jury Members : **Prof. Dr. Ümit TUNCA**
Istanbul Technical University

Assoc. Prof. Dr. Mehmet Atilla TAŞDELEN
Yalova University

Date of Submission : 13 November 2017
Date of Defense : 14 December 2017

To my sons Sarp & Kaan,

FOREWORD

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This master study has been carried out at the Istanbul Technical University

November 2017 Alp HIZAL

TABLE OF CONTENTS

Page

FOREWORD ..... **ix**
TABLE OF CONTENTS ..... **xi**
ABBREVIATIONS ..... **xiii**
SYMBOLS ..... **xv**
LIST OF TABLES ..... **xvii**
LIST OF FIGURES ..... **xix**
SUMMARY ..... **xxi**
ÖZET ..... **xxiii**
1. INTRODUCTION **1**
2. THEORETICAL PART **3**
2.1 Multi Component Reactions 3
2.2 Passerini Reaction 4
2.3 Ugi Reaction 5
2.4 The Chemistry of Isocyanides 6
2.4.1 Synthesis of 2-aminofuran compounds 6
2.4.2 Synthesis of 2-aminopyrrole compounds 8
2.5 Step-Growth Polymerization 10
2.6 Polyesters 11
3. EXPERIMENTAL PART **13**
3.1 Materials 13
3.2 Instruments 13
3.3 Synthetic Procedures 13
3.3.1 Synthesis of polyester containing alkyne repeating unit (A1) 13
3.3.2 General procedure for the preparation of fully-substituted furan main chain polyester 14
4. RESULTS AND DISCUSSION **15**
5. CONCLUSION **21**
REFERENCES **23**
CURRICULUM VITAE **27**

ABBREVIATIONS

^{13}C NMR	: Carbon nuclear magnetic resonance spectroscopy
^{1}H NMR	: Hydrogen nuclear magnetic resonance spectroscopy
3CR	: Three-component reaction
ADCA	: Acetylenedicarboxylic acid
CuAAC	: Copper-catalyzed azide–alkyne cycloaddition
DMAD	: Dimethyl acetylenedicarboxylate
FPT	: Freeze-pump-thaw
GPC	: Gel permeation chromatography
KF	: Kabachnik-Fields reaction
MCR	: Multi component reaction
mL	: Milliliter
mmol	: Millimole
P-3CR	: Passerini three-component reaction
PS	: Polystyrene
PTSA	: p-Toluenesulfonic acid monohydrate
THF	: Tetrahydrofuran
UV	: Ultraviolet

SYMBOLS

$M_{n,GPC}$	: Number-average molecular weight
$M_{w,GPC}$	: Weight-average molecular weight
M_w/M_n	: Polydispersity

LIST OF TABLES

Page

Table 2.1 : The basic MCR types. **3**
Table 2.2 : Reaction of various aldehydes with DMAD and cyclohexyl isocyanide.. **8**
Table 2.3 : MCRs of tosylimines with DMAD and cyclohexyl isocyanide..... **9**
Table 2.4 : MCRs of tosylimines with DMAD and tert-butyl isocyanide. **10**
Table 4.1 : Experimental conditions and the utilized equivalents during the MCRs. **17**
Table 4.2 : GPC Characterization of MCR products. **19**

LIST OF FIGURES

Page

Figure 2.1 : Suggested mechanism for the P-3CR. **5**
Figure 2.2 : Suggested mechanism for the Ugi reaction. **6**
Figure 2.3 : MCR for the synthesis of 2-aminofuran compounds. **6**
Figure 2.4 : Possible structures of the zwitterionic intermediate. **7**
Figure 2.5 : Reaction mechanism for the formation of 2-aminofurans. **7**
Figure 2.6 : MCR for the synthesis of 2-aminopyrrole compounds. **8**
Figure 2.7 : Reaction mechanism for the formation of 2-aminopyrroles. **9**
Figure 2.8 : Esterification of hydroxy acid. **11**
Figure 2.9 : Esterification of diol and diacid. **11**
Figure 2.10 : Esterification of diol and diacid chloride. **11**
Figure 4.1 : Schematic representation of polyesterification reaction between ADCA and 1,4-butanediol in benzene at 100 ^{o}C overnight. **15**
Figure 4.2 : ^{1}H (up) and ^{13}C NMR (down) spectra of A1 in $CDCl_3$ (500 and 125 MHz, respectively). **16**
Figure 4.3 : Schematic representation of MCRs between A1, cyclohexyl isocyanide and 1,4-butanediol in 1,4-dioxane overnight. **16**
Figure 4.4 : ^{1}H NMR spectrum of fully substituted furan main chain polymer in $CDCl_3$ (500 MHz). **18**
Figure 4.5 : ^{13}C NMR spectrum of fully substituted furan main chain polymer in $CDCl_3$ (125 MHz). **18**
Figure 4.6 : Overlay GPC traces of fully substituted furan main chain polymers A1 (red), Run 5 (green), Run 9 (blue) and Run 12 (grey) in THF at 30 ^{o}C. **20**

SYNTHESIS OF FULLY FUNCTIONALIZED FURAN MAIN CHAIN POLYESTER THROUGH MULTI COMPONENT REACTIONS

SUMMARY

Chemical reactions that possess properties such as high efficiency, atom-economy, modularity and ease of execution/purification are very much looked after in polymer chemistry and many other research areas like life and material sciences, organic chemistry and chemical biology.

A reaction category with such attributes is the “click reaction”, first described by K. B. Sharpless and colleagues in 2001. In parallel to the progress based on “click” reactions in organic chemistry area, many notable applications to polymer chemistry such as copper-catalyzed azide–alkyne cycloaddition (CuAAC), thiol– ene/yne free-radical addition and the (hetero) Diels–Alder reaction were introduced.

Multicomponent reactions (MCRs) is another example of such sought after chemical reactions, as they offer an elegant way of producing highly selective products in which majority of the atoms of the starting materials (more than two) are present. Interestingly, MCRs made their debut in the area of polymer chemistry only recently although their unique properties are acknowledged since more than 150 years from today. For instance, Passerini, Ugi and Kabachnik-Fields are notable examples of MCRs that are widely utilized in the area of polymer chemistry.

Another popular application in the organic chemistry research area is the synthesis of heterocyclic compounds such as furans and pyrroles via MCRs.

We have developed the idea of bringing together the applications of MCRs in organic chemistry to synthesize heterocyclic compounds and their use in polymer chemistry. In the context of current MCR literature, we have identified that utilizing MCRs to prepare polymers with fully functionalized heterocyclic main and/or side chains as an exciting and so far unexplored application of MCRs. Therefore, the objective in this thesis is to employ MCRs for the first time in the preparation of fully functional furan main chain polyesters.

Initially, the polyester having an electron deficient alkyne function on the main chain was prepared and later reacted with cyclohexyl isocyanide and benzaldehyde in various MCR conditions. The impact of temperature, duration, aldehyde equivalents with respect to isocyanide and the alkyne components on the MCR were studied.

The furan main chain polyester was characterized by GPC and its structure was confirmed by both ^{1}H and ^{13}C NMR spectra. MCR efficiencies were calculated by the use of ^{1}H NMR spectra.

TAM FONKSİYONEL FURAN ANA ZİNCİRLİ POLYESTERLERİN ÇOK BİLEŞENLİ REAKSİYON YOLU İLE SENTEZİ

ÖZET

Polimer kimyası, malzeme bilimleri, organik kimya ve biyoloji gibi araştırma alanlarında gerçekleştirilecek kimyasal reaksiyonların yüksek verimlilik ve atom ekonomisine sahip olması istenir. Ayrıca reaksiyonların gerçekleştirilmesi ve saflaştırma aşamalarındaki kolaylık da, amaca uygun reaksiyonların seçilmesi anlamında en az sıralanan diğer reaksiyon özellikleri kadar önem taşımaktadır.

"Click" reaksiyonları ilk olarak 2001 yılında K. B. Sharpless ve çalışma arkadaşları tarafından tanımlanmış olup, yukarıda bahsedilen özellikleri taşıyan bir reaksiyon türüdür. Organik kimya alanında bir çok uygulaması olan "click" reaksiyonları, polimer kimyası alanında da kullanılmaktadır. Bunlara örnek olarak şu reaksiyonlardan bahsedilebilir; bakır katalizli azid-alkin siklokatılması, tiyol-en/in serbest radikal katılması ve (hetero) Diels-Alder reaksiyonu.

"Click" reaksiyonları ayrıca, yer seçicilik ve stereo seçicilik özelliklerinin yüksek olması, ılımlı tepkime koşullarında yüksek verilmlilik göstermesi, ana ürünün elde edilmesindeki kolaylık, çözücüden bağımsız olması ve birçok fonksiyonel grupla çalışabilmesi gibi özelliklere sahiptir.

Yüksek derecede konjuge edilmiş polimerlere ve biyomoleküllere olan ihtiyaç, nanoteknoloji ve biyoteknoloji alanındaki yeni araştırmalar çerçevesinde giderek artmıştır. Polimer veya küçük moleküllerin farklı polimer blokları ile konjuge edilmesi için; halka açılma polimerizasyonu, yaşayan polimerizasyonlar, kontrollü radikal polimerizasyonlar ve halka açılma metatez polimerizasyonu gibi yöntemler kullanılmaktadır. Bahsedilen teknikler, yapısı iyi tanımlanmış polimerler elde edilmesine imkan sağlasa da, karmaşık yapıya ve topolojiye sahip makromoleküllerin elde edilmesinde bu teknikler yetersiz kalmaktadır. "click" kimyası bu tür moleküllerin elde edilmesine imkan sağlamaktadır.

Modüler sentez yaklaşımı temel alınarak sentetik polimerlerin “click” kimyası ile elde edilmesi, „Barner-Kowollik“ ve „Inglis“ tarafından, yeni polimer ve malzeme tasarımlarının gerçekleştirilebilmesi için “çığır açıcı” olarak değerlendirilmiştir.

Sharpless’tan sonra, “click” reaksiyonları tanımı diğer araştırmacılar tarafından genişletilmiştir. Etkin ve kolay bir saflaştırma, kısa reaksiyon süreleri, modüler yapıların eşdeğer mol oranında kullanılabilmesi ve ılımlı reaksiyon koşulları, bu genişletilmiş tanımı oluşturmaktadır.

Çok bileşenli reaksiyonlar olarak adlandırılan reaksiyonlar da uygulamadaki kolaylık, hedef molekülün yüksek seçicilik ile sentezlenmesine olanak sağlanması ve çıkış moleküllerinde bulunan atomların büyük çoğunluğunun hedef moleküle aktarılabilmesi açılarından oldukça dikkat çekici reaksiyonlardır. Çok bileşenli reaksiyonların bu özellikleri neredeyse 150 yıldır bilinmesine rağmen, bu reaksiyonların polimer kimyası alanına uyarlanması ancak son yıllarda gerçekleşmiştir. Passerini, Ugi ve Kabachnik-Fields isim reaksiyonları, çok bileşenli reaksiyonların polimer kimyası alanındaki tanınmış uygulamalarına örnektir.

Furan ve pirol gibi heterosiklik bileşiklerin çok bileşenli reaksiyonlar yolu ile sentezlenmesi, organik kimya alanında sıkça kullanılan bir yöntem haline gelmiştir.

Bu çalışma, çok bileşenli reaksiyonların organik kimya alanında heterosiklik bileşiklerin sentezindeki ve polimer kimyası alanındaki uygulamalarının bir araya getirilmesi fikrinden yola çıkarak hazırlanmıştır. Çok bileşenli reaksiyonlar alanında yapılan literatür araması sonucu, heterosiklik ana ve/veya yan zincire sahip polimerlerin çok bileşenli reaksiyonlar ile sentezlenmesi konusunda önceden herhangi bir çalışma yapılmadığı ortaya çıkmıştır. Bu sonuçtan yola çıkarak, tam fonksiyonel furan ana zincirli polyesterlerin çok bileşenli reaksiyonlar yolu ile sentezi, tez çalışmasının konusu olarak belirlenmiştir.

Öncelikle ana zincirde alkin fonksiyonu taşıyan polyester sentezlenmiş ve bu polimerin siklohekzil izosiyanür ve benzaldehit ile değişik koşullardaki çok bileşenli reaksiyonları gerçekleştirilmiştir. Sıcaklık, süre, aldehit’in izosiyanür ve alkin bileşenlerine oranı gibi değişkenlerin çok bileşenli reaksiyon üzerindeki etkileri araştırılmıştır.

Furan ana zincirli polyesterlerin karakterizasyonu GPC ile yapılmıştır. Polyester ana zincirinde furan oluşumu ise ^{1}H ve ^{13}C NMR kullanılarak doğrulanmıştır. Çok bileşenli reaksiyon verimleri ise ^{1}H NMR ile hesaplanmıştır.

1. INTRODUCTION

Although firstly described by K. B. Sharpless and coworkers in 2001, click reactions have actually attracted broader attention since their application in polymer chemistry.[1–6] Due to their 'click' properties, such as easy operation and purification and being highly efficient, atom-economic, and modular etc., click reactions have been welcomed in many research areas outside organic chemistry, such as materials science, life science, chemical biology and polymer chemistry.[7–13] The introduction of click reactions, such as copper-catalyzed azide–alkyne cycloaddition (CuAAC), thiol–ene/yne free-radical addition, the (hetero) Diels–Alder reaction etc., has led to a rapid research storm in polymer chemistry.[2, 14–19]

Besides the successful introduction of two component click reactions into polymer chemistry, more and more other charming organic reactions have been reassessed from the angle of polymer synthesis and have been introduced into polymer chemistry. Among them, multicomponent reactions (MCRs) show unique values. MCRs are reactions that combine more than two reactants in a sequential manner to give highly selective products that retain the majority of the atoms of the starting materials. Although known for over 150 years in organic chemistry, only recently, these reactions have been well adopted to polymer chemistry. Series of MCRs such as the tri-component Passerini reaction, Ugi reaction, the Biginelli reaction, the Kabachnik-Fields (KF) reaction, thiolactone-based reactions etc. have been reconsidered from the perspective of polymer chemistry and utilized to prepare polymers with desired applications [20-24]. Without a doubt, among those reactions, the Passerini and Ugi reactions have found tremendous applications in polymer literature since the desired end-functionalized polymers as well as monomers can be readily attained employing these reactions.

It is well known that MCRs have also been extensively used for the preparation of different heterocyclic compounds such as furan pyrrole etc. However, unlike the above-mentioned MCRs, there is no report in literature to prepare polymers with heterocyclic main chains or side chains formed by MCRs. In this thesis, the aim is to

employ MCRs for the first time to prepare fully functionalized furan main chain polymers. To this end, polyester of electron deficient alkyne in the main chain was prepared and reacted with cyclohexyl isocyanide and benzaldehyde. Various experimental conditions such as reaction temperatures, time, aldehyde equivalents with respect to the isocyanide and to the alkyne were tested.

2. THEORETICAL PART

2.1 Multi Component Reactions

Multicomponent reactions (MCRs) are reactions in which a minimum of three starting materials react in a convergent fashion to form a product. A major portion of the atoms from the components of the MCRs is carried on to the formed product.

Although some reactions cannot be categorized, the basic types of MCRs can be outlined as the following (Table 2.1)

Table 2.1 : The basic MCR types.

MCR Type	General Reaction Scheme
I	$A + B \rightleftharpoons C \rightleftharpoons \cdots O \rightleftharpoons P$
II	$A + B \rightleftharpoons C \rightleftharpoons D \ldots O \rightleftharpoons P$
III	$A \rightarrow B + C \rightarrow D \rightarrow \cdots O \rightarrow P$

The starting reagents, intermediates and products of the type I MCRs exist in an equilibrium, which suggests possible yields between 0 and 100 % depending on the state of balance. In case the reaction is not complete, further impurities could be generated by side reactions. Isolation of the product from the mixture of starting materials and intermediates may be cumbersome.

A type II MCR comprises of an equilibria followed by an irreversible partial reaction. The total equilibrium is shifted to the product side by the last irreversible reaction, creating an advantage for preparative applications.

Sequences of irreversible biochemical reactions from the living world can be categorized as type III MCRs. These irreversible partial reactions rarely occur in

preparative chemistry due to the lack of an enzyme, which accelerates the reaction and increases selectivity.

Compared to the sequential (or multi-step) synthesis of complex molecules, MCRs offer many advantages. In case of MCRs, several bonds are formed in one sequence, which results in a high bond forming efficiency [25]

In contrast to the sequential synthesis, target molecules in MCRs are formed in only one operation (also in one-pot) eliminating the need to isolate intermediates, add further reagents or changing reaction conditions. These attributes of MCRs enable high throughput synthesis of complex molecules in a time and cost efficient way. Drug discovery process is one of the many areas in applied chemistry where MCRs offer advantages over the traditional sequential approach [26]

Another interesting aspect of the MCRs is the fact that a very large number of products can be synthesized by the minimal effort of a one-pot reaction. The number of potential products in a MCR is equal to NX, where X represents the number of different component classes and N is the number of starting materials for each of the classes used in the specific reaction. In case of the Ugi 4 component reaction (Ugi-4CR), an unusually high number of products (10^{12}) are potentially accessible from 4.000 starting materials, when 103 starting materials for each class (X=4; RCOOH, R'NH2, R"CHO, R"'NC) are used [27] The access to such massive amount of chemical structures via high efficiency of MCRs attracts a lot of attention and enables a great number of patent applications to be made.

2.2 Passerini Reaction

The first MCR involving isocyanides was reported by Passerini in 1921. [28] The Passerini three-component reaction (P-3CR) is a one-step reaction between carboxylic acids, oxo compounds and C-isocyanides and yields stable α-acyloxycarbox-amides. Acceleration of the Passerini reaction in aprotic solvents suggest a non-ionic reaction mechanism. [29] High concentrations of starting components in an inert solvent at or below room temperatures are preferred conditions for the Passerini reaction.

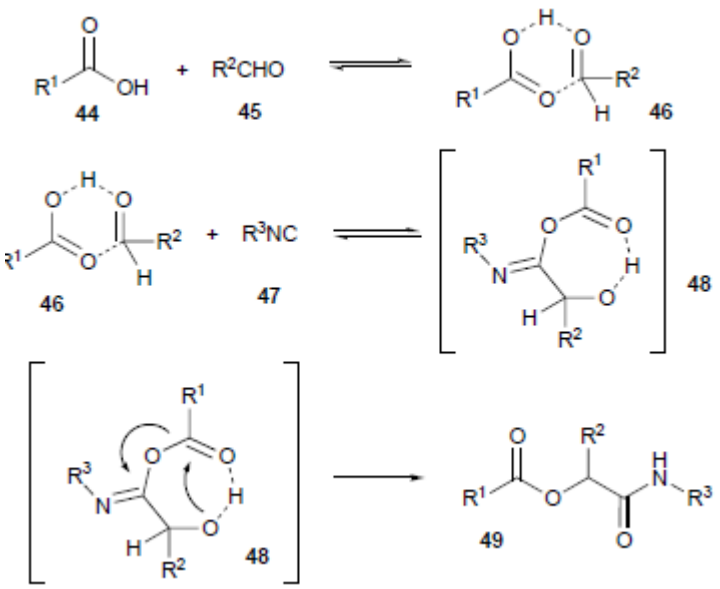


Figure 2.1 : Suggested mechanism for the P-3CR.

At the first stage of the suggested mechanism (Figure 2.1), the carboxylic acid and the carbonyl compound form a hydrogen-bonded adduct. This is followed by an α-addition of the electrophilic carbonyl carbon and the nucleophilic oxygen atom of the carboxylic acid to the isocyanide carbon. At this stage a cyclic transition state in which all three parent components are present is formed. This α-adduct cannot be isolated and it rearranges via an intramolecular transacylation to form a stable α-acyloxycarbox-amide.

2.3 Ugi Reaction

As one of the most famous MCRs, the Ugi reaction has been verified as a highly efficient and atom-economic organic reaction for the total synthesis of natural products. The Ugi reaction is named after Ivar Karl Ugi, who first reported this reaction in 1959. [30,31] The Ugi reaction is a four-component reaction involving a ketone or aldehyde, an amine, a carboxylic acid and an isocyanide to form a bis-amide while only losing one water as the byproduct. First, an imine is formed from the aldehyde and amine components. The imine is then protonated by the carboxylic acid. Later, the isocyanide reacts in an α-addition with the activated (protonated) imine and carboxylate to form the corresponding imidate. Subsequent Mumm rearrangement yields the final Ugi product (Figure 2.2). [32] Recently, Ugi reactions have been introduced into polymer chemistry, and are a proven good tool for macromolecular architecture design. [33]

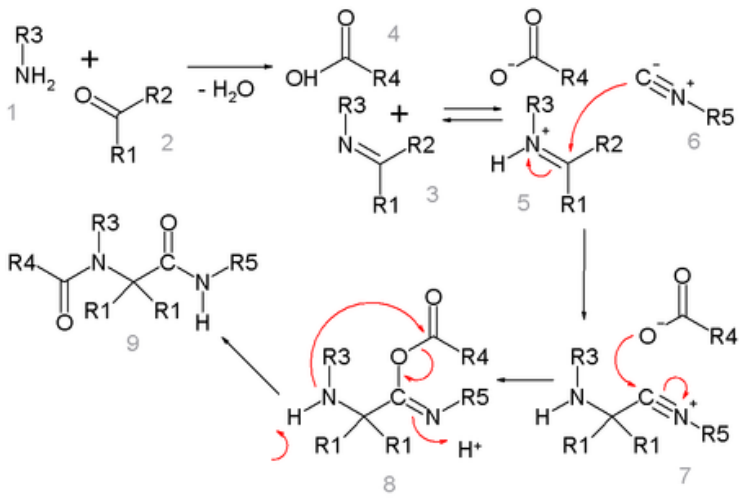


Figure 2.2 : Suggested mechanism for the Ugi reaction.

2.4 The Chemistry of Isocyanides

There is no doubt isocyanides are indispensable constituents of MCRs. In addition to the abovementioned role in Passerini and Ugi reactions, isocyanides have used in many cycloaddition reactions and proved themselves to be irreplaceable building blocks in modern multi component chemistry because they are able to react with both nucleophiles and electrophiles at the same carbon. [34,35] Variety of heterocyclic compounds have been successfully synthesized through the isocyanide-based MCRs. Among those reactions, the synthesis of furan and pyrrole derivatives have gained much interest due to their widespread applicability to organic chemistry as well as polymer and material science.

2.4.1 Synthesis of 2-aminofuran compounds

It has been reported that the MCR between cyclohexyl isocyanide, dimethyl acetylenedicarboxylate (DMAD) and 3-nitrobenzaldehzde affords the respective 2-aminofuran compound in 69 % yield. [36]

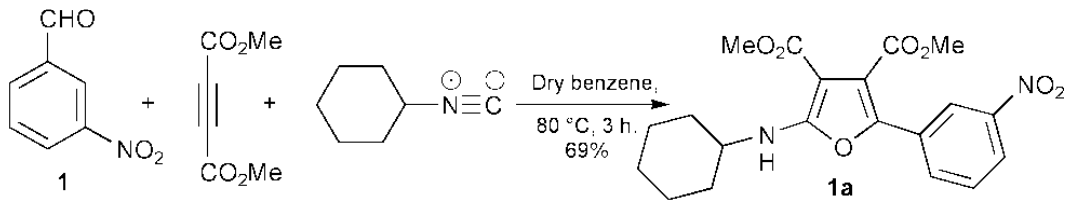


Figure 2.3 : MCR for the synthesis of 2-aminofuran compounds.

The aldehyde plays an important role in this reaction by trapping the highly reactive zwitterionic intermediate formed by the addition of cyclohexyl isocyanide to the DMAD, ultimately increasing the yield of the 2-aminofuran product. The chemistry between nucleophilic carbenes (such as isocyanides) and DMAD leading to such zwitterions (which can show carbanion, carbene or cyclopropenone character) shown in Figure 2.4 has been a topic of investigation. [37-39] There has been unsuccessful attempts to trap this intermediate with olefinic dipolarophiles. [40]

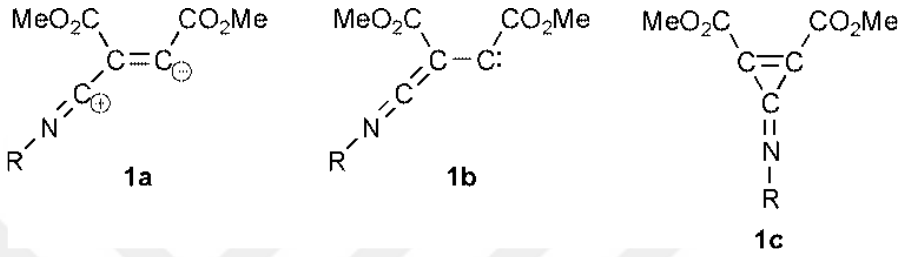


Figure 2.4 : Possible structures of the zwitterionic intermediate.

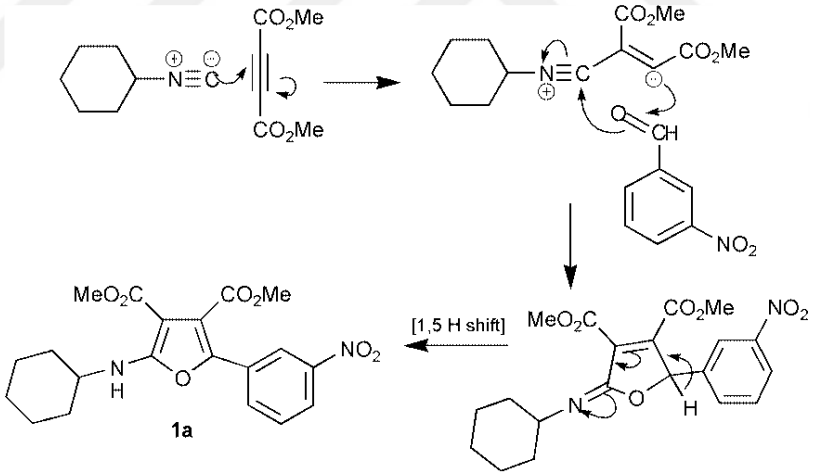
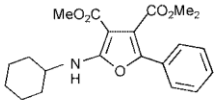
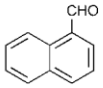
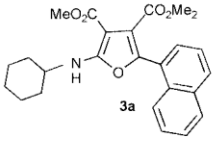
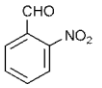
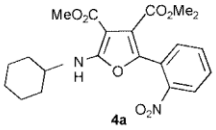
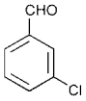
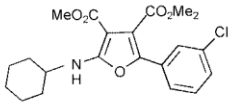
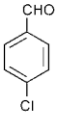
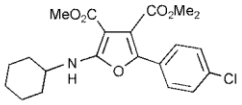
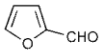
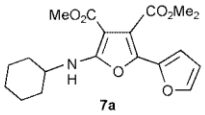


Figure 2.5 : Reaction mechanism for the formation of 2-aminofurans.

Yields up to 69 % are reported depending on the type of aldehyde used in the reaction with DMAD and cyclohexyl isocyanide by Vijay et al. (Table 2.2)

Table 2.2 : Reaction of various aldehydes with DMAD and cyclohexyl isocyanide.

Entry	Aldehyde	*t*/h	Product	Yield(%)[a]
2		8	 **2a**	61
3		8	 **3a**	54
4		3	 **4a**	68
5		2	 **5a**	61
6		2.5	 **6a**	67
7		3	 **7a**	68

[a]Isolated yield.

2.4.2 Synthesis of 2-aminopyrrole compounds

Vijay et al. have demonstrated that the 3CR between N-tosylimines, DMAD and isocyanides (cyclohexyl isocyanide and tert-Butyl isocyanide) leads to 2-aminopyrroles in high yields ranging from 72 to 96 %. [41]

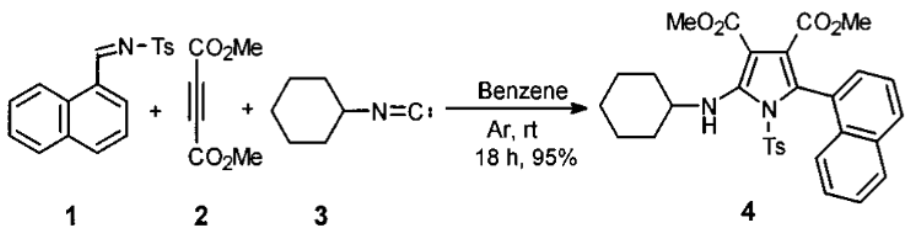


Figure 2.6 : MCR for the synthesis of 2-aminopyrrole compounds.

The following reaction mechanism involving the formation of the typical zwitterionic intermediate between DMAD and the isocyanide is proposed.

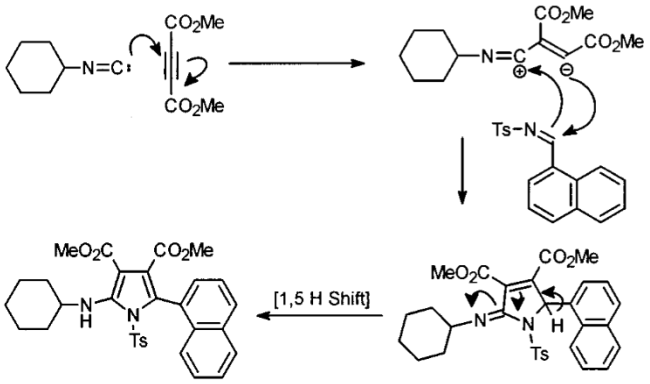
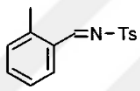
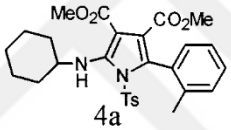
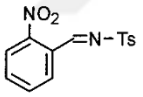
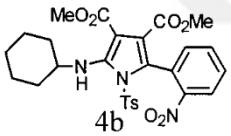
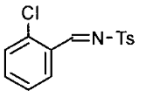
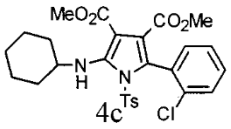
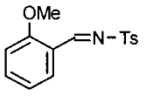
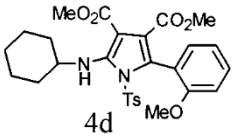
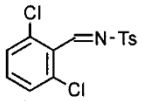
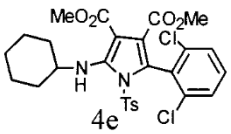
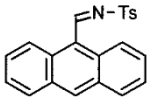
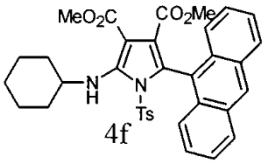


Figure 2.7 : Reaction mechanism for the formation of 2-aminopyrroles.

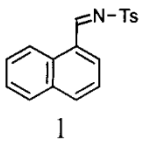
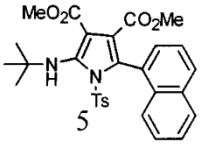
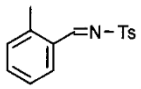
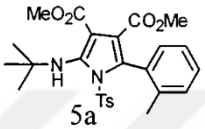
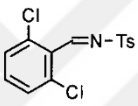
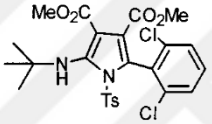
It is reported that various types of stable 2-aminopyrroles products listed in Table 2.3 were isolated with good yields using tosylimines of ortho substituted aldehydes.

Table 2.3 : MCRs of tosylimines with DMAD and cyclohexyl isocyanide.

Entry	Tosylimines	Conditions	Product	Yield(%)[a]
1	 1a	Benzene Ar, rt, 22 h	 4a	92%
2	 1b	Benzene Ar, rt, 20 h	 4b	87%
3	 1c	Benzene Ar, rt,16 h	 4c	82%
4	 1d	Benzene Ar, rt, 15 h	 4d	79%
5	 1e	Benzene Ar, rt, 21 h	 4e	94%
6	 1f	Benzene Ar, Reflux 2 h	 4f	93%

In the same study, the cyclohexyl isocyanide is replaced by tert-Butyl isocyanide and a similar reactivity with DMAD and N-tosylimines is observed. Yields of respective reactions are listed in Table 2.4.

Table 2.4 : MCRs of tosylimines with DMAD and tert-butyl isocyanide.

Entry	Tosylimines	Conditions	Product	Yield(%)[a]
1	 1	Benzene Ar, rt, 19 h	 5	72%
2	 1a	Benzene Ar, rt, 14 h	 5a	96%
3	 1e	Benzene Ar, rt,15 h	 5e	93%

It is worth mentioning that the authors reported that the attempt on the 3CR between dibenzoyl acetylene, methyl propiolate and tetracyanoethylene as a substitute for DMAD was not successful and no product could be isolated.

2.5 Step-Growth Polymerization

In a step-growth polymerization, the molecular weight of the polymer chain builds up slowly and there is only one reaction mechanism for the formation of polymer. The distinct initiation, propagation, and termination steps of chain-growth polymerization are meaningless in step-growth polymerization. A difunctional monomer or equal molar amounts of two different difunctional monomers are necessary at least to form a linear high molecular weight polymer. The polymerization reaction proceeds by individual reactions of the functional groups on the monomers. Thus, two monomers react to form a dimer. The dimer may now react with another dimer to produce a tetramer, or the dimer may react with more monomer to form a trimer. This process continues, each reaction of the functional groups proceeding essentially at the same

reaction rate until over a relatively long period of time a high molecular weight polymer is obtained [42-44].

There are three critical requirements for the step-growth polymerization to yield a high molecular weight linear polymer. First, a perfect stoichiometric balance of the two difunctional monomers must be introduced, or alternately a self-balancing reaction is necessary. Second, a high degree monomer purity is necessary. Third, the reaction responsible for the polymerization must be a very high yield reaction with the absence of side reactions. Among those polymers could be achieved by step-growth polymerization, polyesters are privileged.

2.6 Polyesters

Polyesters are one of the most versatile synthetic copolymers. Polyesters are produced in high volume that exceeds 30 billion pounds a year worldwide [45-48]. They are widely used commercially as fibers, plastics, composites and for coatings applications too. Polyesters are heterochain macromolecules that possess carboxylate ester groups as an integral component of their polymer backbones.

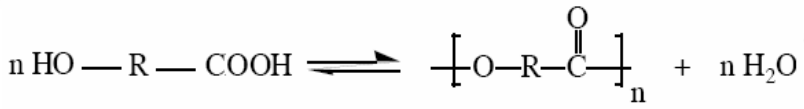


Figure 2.8 : Esterification of hydroxy acid.

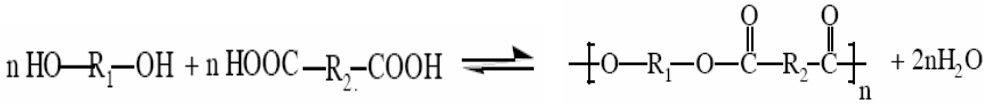


Figure 2.9 : Esterification of diol and diacid.

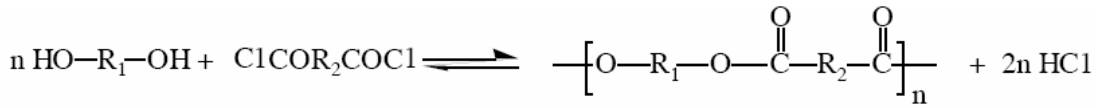


Figure 2.10 : Esterification of diol and diacid chloride.

3. EXPERIMENTAL PART

3.1 Materials

Acetylenedicarboxylic acid (ADCA) (95%, Aldrich), 1,4-Butanediol (99%, Alfa Aesar), *p*-Toluenesulfonic acid monohydrate (PTSA) (98%, Alfa Aesar), Methanol (99.8%, Aldrich), diethyl ether (99.7%, Aldrich) and anhydrous Benzene (99,8%, Aldrich) were used as supplied for the synthesis of alkyne repeating unit polymer. Cyclohexyl isocyanide (98%, Aldrich), Benzaldehyde (>99%, Aldrich) and 1,4-Dioxane (99,8%, Aldrich) were used as received. Tetrahydrofuran (THF, 99.8%, J.T. Baker) was dried and distilled using benzophenone-sodium.

3.2 Instruments

^{1}H (500 MHz) and ^{13}C (125 MHz) spectra were recorded using an Agilent VNMRS 500 instrument in $CDCl_3$. The conventional 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 columns were 2000–4,000,000, 50–100,000, 500–30,000, and 500–20,000 g/mol, respectively. THF was used as eluent at a flow rate of 0.3 mL/min at 30 ^{o}C and toluene was used as an internal standard. The molecular weights of the polymers were calculated based on linear polystyrene (PS) standards (Polymer Laboratories).

3.3 Synthetic Procedures

3.3.1 Synthesis of polyester containing alkyne repeating unit (A1)

In a round bottom flask, ADCA (2.00 g, 17.5 mmol, 1 equivalent) was dissolved in 40 mL of benzene and stirred under nitrogen. 1,4-Butanediol (1.58 g, 17.5 mmol, 1 equivalent) followed by PTSA (0.33 g, 1.75 mmol, 0.1 equivalent) were added to the

solution. The mixture was gradually heated, with a Dean-Stark apparatus attached, in an oil bath set to 100 °C and stirred overnight. After the reaction, solvent was removed under reduced pressure; THF was added to the residue and finally precipitated in methanol. The obtained polymer (A1) was dried overnight in a vacuum oven at 40 °C (Yield 2.56 g, 87 %). ($M_{n,GPC}$ = 4550 g/mol, $M_{w,GPC}$ = 7500 g/mol, M_w/M_n = 1.43, relative to PS standards)

3.3.2 General procedure for the preparation of fully-substituted furan main chain polyester

A1 (0.1 g, 0.6 mmol, 1 equivalent) was dissolved in 3 mL of Dioxane and transferred to a 10 mL schlenk tube and stirred for 5 minutes. Predetermined amount of cyclohexyl isocyanide and benzaldehyde were added to the solution. The reaction mixture was degassed through two freeze-pump-thaw (FPT) cycles and stirred overnight at given temperatures. The reaction mixture was precipitated in 40 mL Methanol. It is possible that a milky solution will be formed when the reaction mixture is poured into methanol. In such cases, the methanol was evaporated to dryness and the remaining material was dissolved in THF and later precipitated in diethyl ether.

4. RESULTS AND DISCUSSION

Multicomponent reactions (MCRs) are extremely popular owing to their facile execution, high atom-efficiency and the high diversity of products. MCRs can be used to access various heterocycles and highly functionalized scaffolds, and thus have been invaluable tools in total synthesis, drug discovery and bioconjugation [25]. Given the polymer science, MCRs have recently become important owing to mild and metal-free experimental conditions. Taking these advantages, several groups have utilized MCRs to synthesize polymers with various topologies as well as post-polymerization functionalization of the obtained polymers for a variety of applications [20-24]. However, to prepare polymers of heterocyclic main or side chains utilizing the MCRs have remained challenge. We envisioned that if we prepare polymer possessing electron deficient triple bond in the main chain, we could subsequently obtain fully substituted furan main chain polymer on the backbone using MCRs. The idea here is based on the three-component reaction between a polymer involving reactive alkyne repeating unit with isocyanide and aldehyde. The details on the reaction mechanism is given in the theoretical part (2.4 and 2.4.1). To achieve this, we first prepared a polyester, **A1**, involving electron deficient triple bond in the main chain by reacting commercially available ADCA and 1,4-butandediol in the presence of catalytic amount of PTSA in benzene at 100 ^{o}C to yield the polyester as outlined in Figure 4.1.

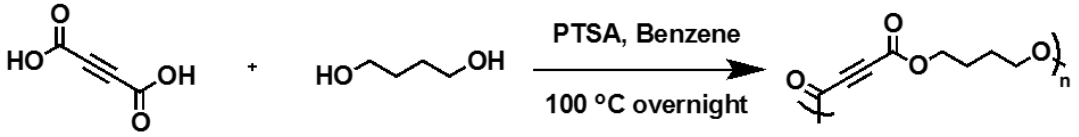


Figure 4.1 : Schematic representation of polyesterification reaction between ADCA and 1,4-butanediol in benzene at 100 ^{o}C overnight.

The obtained polymer was characterized by ^{1}H and ^{13}CNMR, respectively. From ^{1}H NMR spectrum it is clear that the methylene signals between the ester groups are appeared at 4.3 (C=OOC***H***$_2$CH$_2$CH$_2$C***H***$_2$OC=O) and 1.82

(C=OOCH$_2$C***H***$_2$C***H***$_2$CH$_2$OC=O) ppm, respectively. The ^{13}C NMR spectrum is more informative for elucidating the structure of the polyester while displaying signals at around 151.6 and 74.5 ppm assignable to the C=O and C≡C groups, respectively.

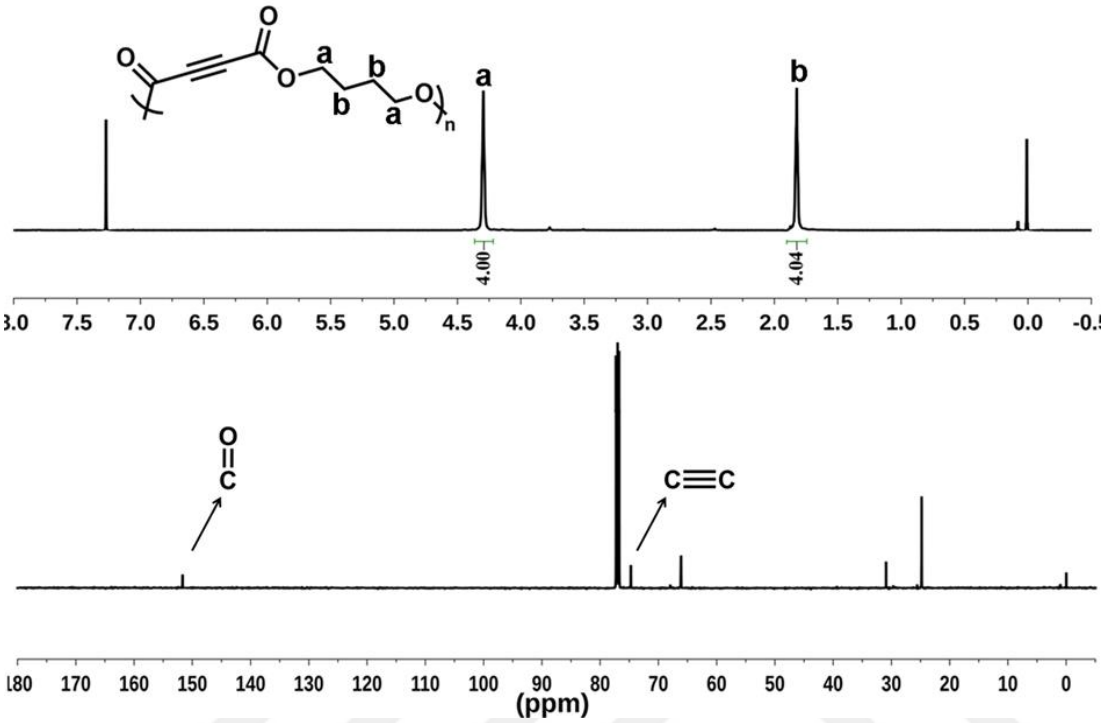


Figure 4.2 : ^{1}H (up) and ^{13}C NMR (down) spectra of **A1** in $CDCl_3$ (500 and 125 MHz, respectively).

After the preparation of polyester, the fully substituted furan main chain polymers were synthesized through the MCRs. Cyclohexyl isocyanide was selected as the nucleophilic reagent whereas the benzaldehyde was utilized as the trapping agent of highly reactive zwitterionic intermediate formed by the addition of cyclohexyl isocyanide to the reactive alkyne.

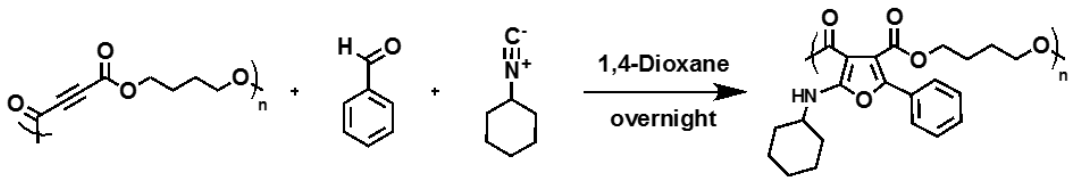


Figure 4.3 : Schematic representation of MCRs between A1, cyclohexyl isocyanide and 1,4-butanediol in 1,4-dioxane overnight.

To reveal the scope of the reaction conditions, different equivalents of benzaldehyde with respect to cyclohexyl isocyanide as well as to alkyne repeating unit were examined. The details on the experimental conditions are given in Table 4.1.

Table 4.1 : Experimental conditions and the utilized equivalents during the MCRs.

	Equivalent					
RUN	Polymer (A1)	Cyclohexyl isocyanide	Benzaldehyde	Temperature (°C)	Time (h)	*eff.*[a] (%)
1	1	1.2	1.2	25	-	*gel*
2	1	1.2	1.8	25	-	*gel*
3	1	1.2	2.4	25	-	*gel*
4	1	1.2	3	25	8	22
5	1	1.2	3	25	16	34
6	1	1.2	3	25	24	36
7	1	1.2	6	25	16	52
8	1	1.2	3	40	-	*gel*
9	1	1.2	6	40	16	59
10	1	1.2	6	80	8	59
11	1	1.2	6	80	16	69
12	1	1.2	9	80	16	75

[a]MCR efficiency calculated based on ^{1}H NMR integral ratios.

It is clear from Table 4.1 that when equal amounts of cyclohexyl isocyanide and benzaldehyde or slightly excess of benzaldehyde with respect to cyclohexyl isocyanide were used, gelation occurred during the reaction (Run 1-3). However, when the amount of benzaldehyde was increased soluble polymers were obtained (Run 4-7, Run 9-12). Moreover, the increase of benzaldehyde amount in the reaction medium has led to a prominent increase in MCR efficiency. Besides, temperature and time are also crucial to increase the MCR efficiency. It is also evident that increasing the temperature resulted in the increase of MCR efficiency (Run 4-12). Yet, when the duration of the reactions was increased, the MCR efficiencies increased as well (Run 4-6, Run 10-11). However, there are no clear differences between the MCR efficiencies of the obtained polymers at 16 h (Run 5) and 24 h (Run 6), thus the optimum reaction duration was set to 16 h for the rest of the experiments.

The MCR efficiencies were found by ^{1}H NMR analysis. As an example, the polymer of highest MCR efficiency (Run 12) was examined in detail. As can be seen in Figure 4.4, the characteristic signal of aromatic protons appeared between 7.7-7.2 ppm. In addition, the methine proton belonged to cyclohexyl group was detected at 3.6 ppm and NH signal next to furan was detected at 6.6 ppm.

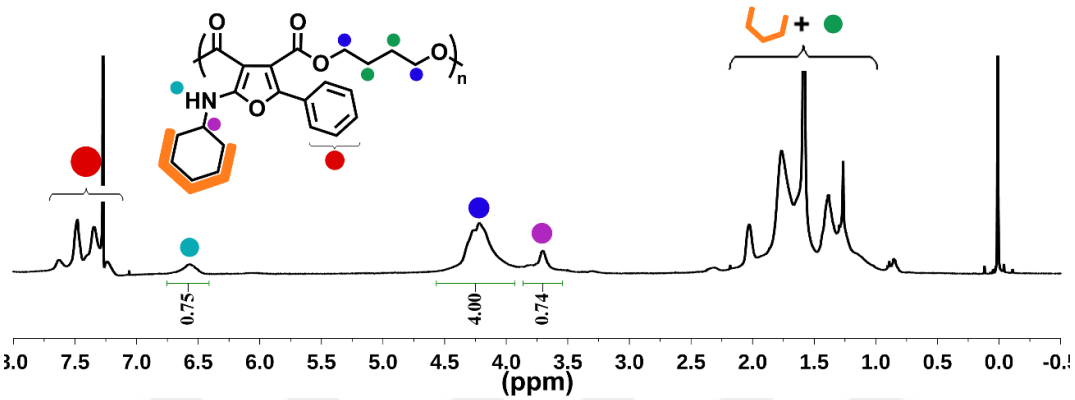


Figure 4.4 : ^{1}H NMR spectrum of fully substituted furan main chain polymer in $CDCl_3$ (500 MHz).

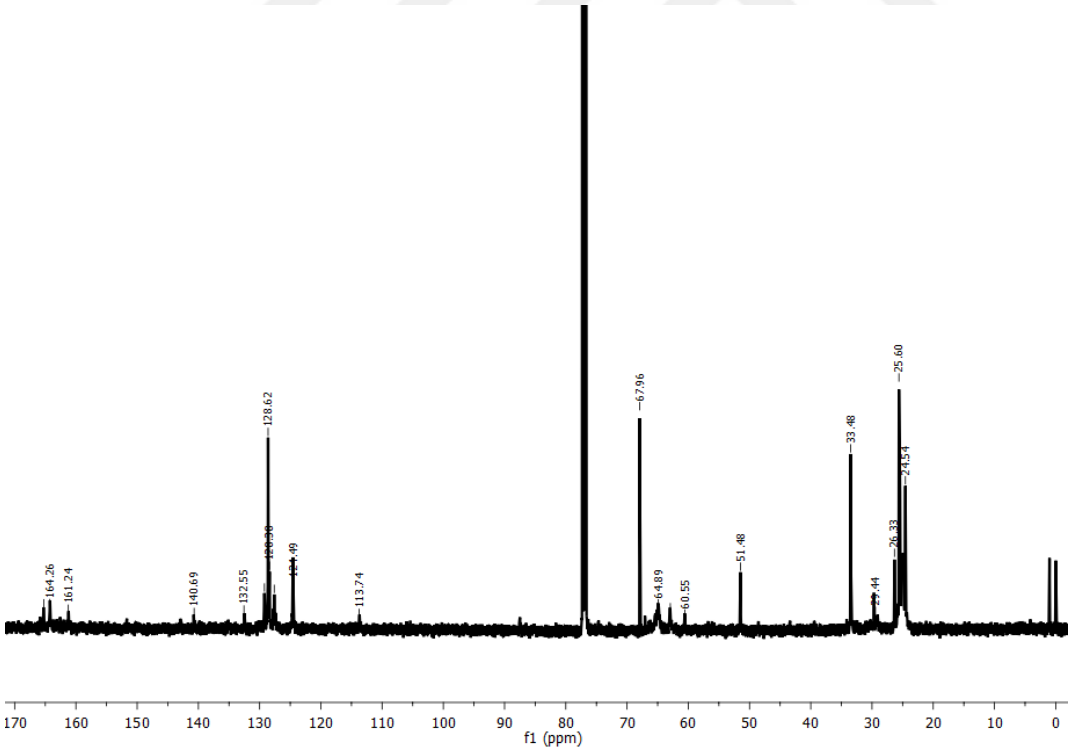


Figure 4.5 : ^{13}C NMR spectrum of fully substituted furan main chain polymer in $CDCl_3$ (125 MHz).

Both ^{1}H and ^{13}C NMR spectra confirm that the expected fully substituted furan main chain polymer was smoothly obtained.

The soluble polymers were characterized by GPC and the obtained results are collected in Table 4.2.

Table 4.2 : GPC Characterization of MCR products.

Polymer	$M_{n,GPC}$[b] (g/mol)	$M_{w,GPC}$[b] (g/mol)	M_w/M_n[b]
A1	4550	7220	1.58
Run 4	7700	42400	5.50
Run 5	10350	40000	3.86
Run 6	12100	72000	5.95
Run 7	12560	45410	3.61
Run 9	11500	53350	4.64
Run 10	12700	89700	7.06
Run 11	13850	73250	5.28
Run 12	13250	33650	2.54

[a]GPC calibrated on the basis of linear PS standards in THF at 30 °C.

It is obvious from the table that all polymers obtained after MCRs showed a very broad polydispersity index along with many shoulders as compared to the precursor polymer. The reason behind this fact might be attributed to the inter- or intra-molecular attack of zwitterionic intermediate to other alkyne groups before trapping by the aldehyde. Therefore, the expected cyclization which had to occur in the final step was prevented. Notably, the polymer obtained by using highest benzaldehyde amount exhibited low dispersity index in addition to the highest MCR efficiency. All these results clearly indicate the crucial role of aldehyde during the MCRs.

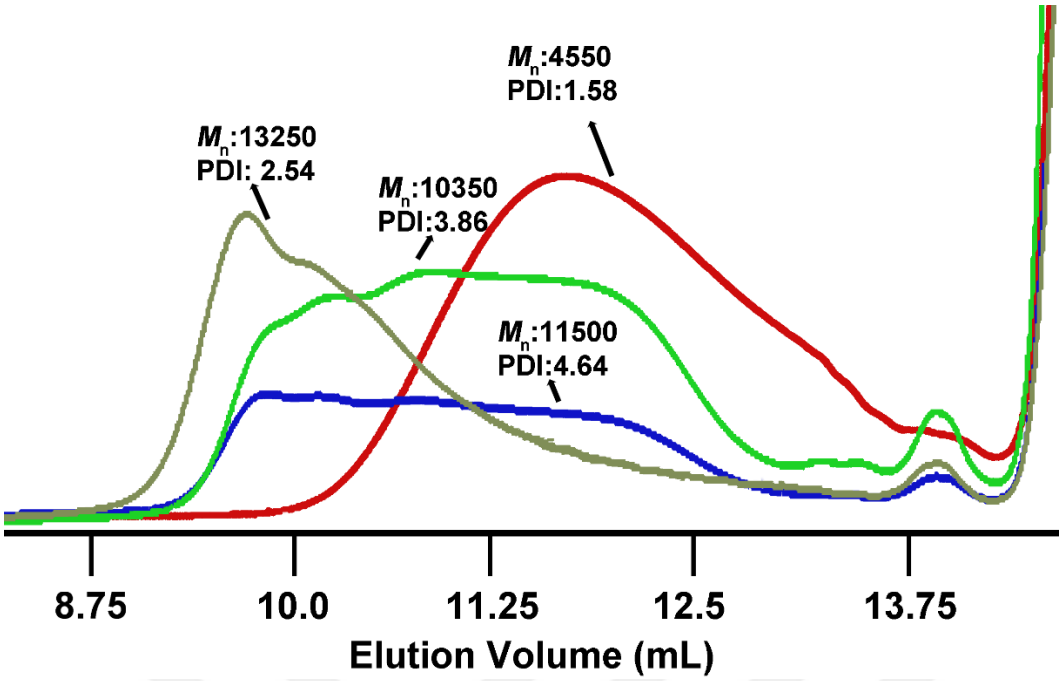


Figure 4.6 : Overlay GPC traces of fully substituted furan main chain polymers A1 (red), Run 5 (green), Run 9 (blue) and Run 12 (grey) in THF at 30 ^{o}C.

5. CONCLUSION

In this thesis, we synthesized a polyester possessing reactive triple bond in the main chain. Afterwards, the obtained polymer was reacted with cyclohexyl isocyanide and benzaldehyde through the MCRs to form fully substituted furan main chain polymers. It was found that when an equal amount of cyclohexyl isocyanide and benzaldehyde or slightly excess of benzaldehyde with respect to cyclohexyl isocyanide were used, gelation occurred during the reaction. Soluble polymers were obtained when the benzaldehyde amount was increased with respect to cyclohexyl isocyanide as well as to alkyne repeating unit. The highest MCR efficiency (75 %) was obtained when the benzaldehyde amount was used much excess (9 equivalent). The time and temperature were also important parameters to increase the MCR efficiencies. According to the obtained results, the optimum duration was found to be 16 h and the optimum temperature was 80 ^{o}C. On the other hand, the GPC traces of all polymers obtained after MCRs showed a very broad polydispersity index along with many shoulders as compared to the precursor polymer. The reason behind this fact might be attributed to the inter- or intra-molecular attack of zwitterionic intermediate to other alkyne groups before trapping by aldehyde. Notably, the polymer obtained by using highest benzaldehyde amount exhibited low dispersity index in addition to the highest MCR efficiency. All these results clearly indicate the crucial role of aldehyde during the MCRs. We believe that these preliminary results are promising in terms of synthesizing polymers possessing a heterocyclic structure on the backbone via MCR.

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CURRICULUM VITAE

Name Surname **: Alp HIZAL**

Place and Date of Birth **: Şişli, 25.09.1987**

E-Mail **: alphizal@gmail.com**

EDUCATION

- **B.Sc.** **: 2009**, Istanbul Technical University, Faculty of Science and Letters, Chemistry

PROFESSIONAL EXPERIENCE AND REWARDS:

- 2009 – 2010 Cognis Corporation USA, Mauldin SC, USA
- 2010 – 2011 Cognis Kimya A.Ş., Istanbul, Turkey
- 2011 – 2013 BASF Türk Kimya San. ve Tic. Ltd. Şti., Istanbul, Turkey
- 2013 – BASF SE, Ludwigshafen am Rhein, Germany

OTHER PUBLICATIONS, PRESENTATIONS AND PATENTS:

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