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QILU UNIVERSITY OF TECHNOLOGY

本科毕业论文（设计）

Synthesis of star-shape tetramine via thiol-ene click chemistry

通过巯基－烯点击反应合成星形四胺

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Contents

Abstract

A large amount of energy to provide high temperature and high pressure are usually needed in the chemical reaction and separation process of traditional synthesis methods, which results in serious energy waste. However，click chemistry reactions, which have some unique advantages such as high efficiency, high reaction speed and mild condition, are expected to address these challenges. In this paper, a new type star-shape tetramine was synthesized by Thiol-ene click reaction of pentaerythritol tetraacryalte (PET4A) and cysteamine. The obtained star-shape tetramine could be used as an intermediate of dendrimers. In this reaction, PET4A was synthesized by the esterification of pentaerythritol and acrylic acid. IR and ^{1}H NMR were used to characterize the structure of the obtained products.

Key words：Cysteamine; Pentaerythritol tetraacrylate; Thiol-ene click chemistry

摘　要

传统化学合成方法由于在化学反应和分离过程中使用大量的能量来提供高温高压环境导致严重的能源浪费。 具有快速、高效、反应条件温和的点击反应能有效解决这些问题。本文首先通过季戊四醇与丙烯酸的酯化反应制备的季戊四醇四丙烯酸酯，然后通过季戊四醇四丙烯酸酯与半胱胺的巯基-烯点击化学反应成功合成一种新型四臂胺类化合物，该化合物可作为树形大分子的合成反应中间体。所得产物的结构通过红外光谱和核磁共振氢谱进行表征。

关键词： 半胱胺　季戊四醇四丙烯酸酯　巯基-烯点击反应

Chapter 1 Introduction

The target product which could be used in the synthesis of polyurethane dendrimers is pentaerythritol tetraacrylate (PET4A) in the core, and the functional terminal group is the amino group. With the amino group, the target product has the possibility to react with epoxy group, alkyl halides and other functional groups. [1-2] The same four terminal groups can form symmetric molecules or dendrimers which may have specific properties.

1.1 The widely used dendrimers

Dendrimer is a kind of novel material which is widely applied in the field of chemistry, bioiatrology and environmental protection because of the controllability of the size and molecular mass during synthesis. The unique structure of dendrimer, neither as slender as linear polymers, nor as wide as net shaped polymers, remarkably improves the chemical and physical properties of the dendrimer. For example, the viscosity of the dendrimers solution is lower than that of the traditional linear polymers. [3] In addition, dendrimer can be used as a catalyst to improve industrial production efficiency because of the large surface area and good solubility of dendrimers. [4]

Generally, a dendrimer is composed of three parts: the central core, the inner repeating element and the outer end group. The central core molecules must have more than two effective functional groups in order to undergo the subsequent reaction to grow into dendrimers. The novel star-shape tetramine provides the possibility for the synthesis of new polyurethane dendrimers and other polymer materials, which need amine as functional group in the reaction.

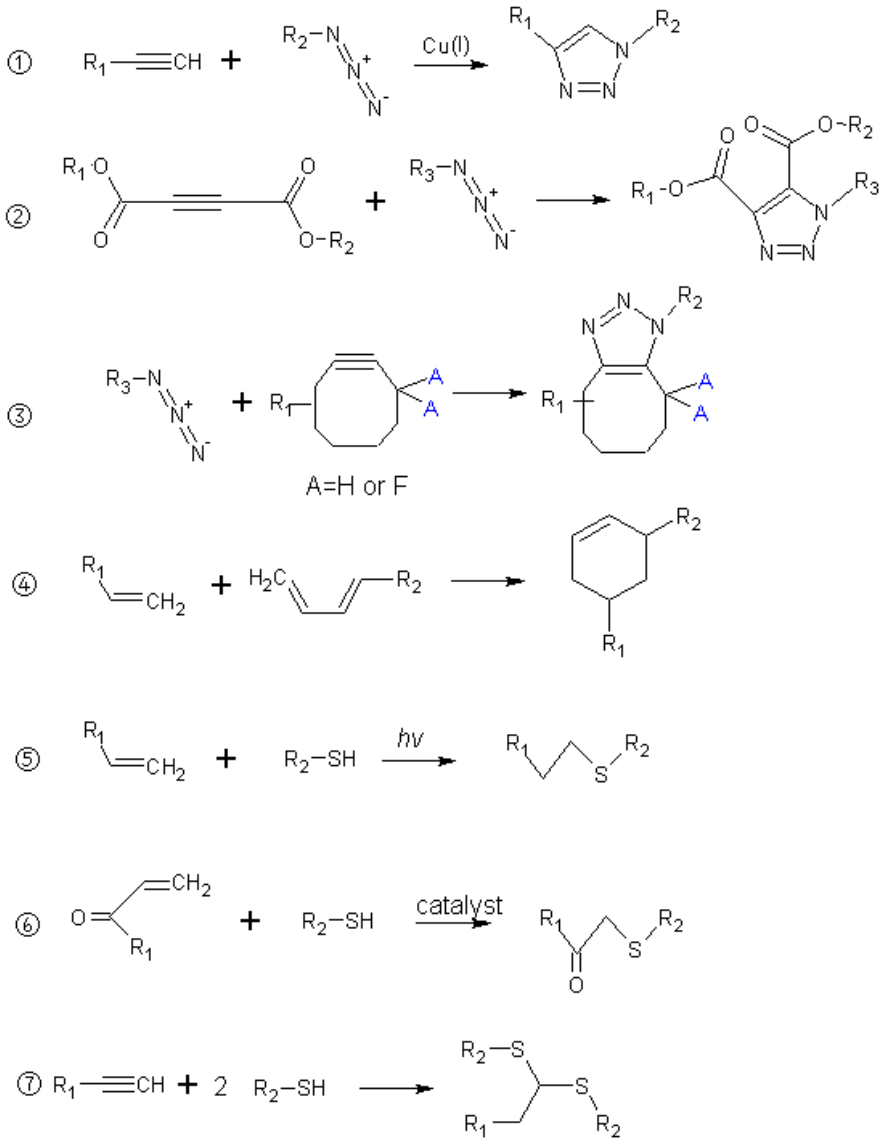
1.2 Click chemistry

In 2001, the concept of click chemistry was put forward by Nobel Prize winner Sharpless. The concept is characterized by small cell reactions, with particular

emphasis on the formation of heteroatom links with high selectivity under mild reaction conditions, with fast reaction, high yield, and controllable characteristics. [3]

Simple reaction condition which is ideally insensitive to water and oxygen is a typical characteristic for click reaction. In addition, easily available reactants, no solvent or benign solvent (such as water) or easily removed solvent and simple separation of product are required properties. If necessary, nonchromatographic methods, such as distillation and crystallization, can be used for the purification of the product, and the product must be stable under physiological conditions. [5]

There are several reaction types, such as cycloadditions, Diels-Alder reaction, nucleophilic substitution and Thiol-ene click reaction and so on. (**Scheme** 1) The concept of click chemistry has great contribution to the field of chemical synthesis, such as molecular engineering, drug synthesis, proteomics, biotechnology [6], polymer nanoparticles and drug carrier [7], materials science [8,9] and other fields show broad prospects.



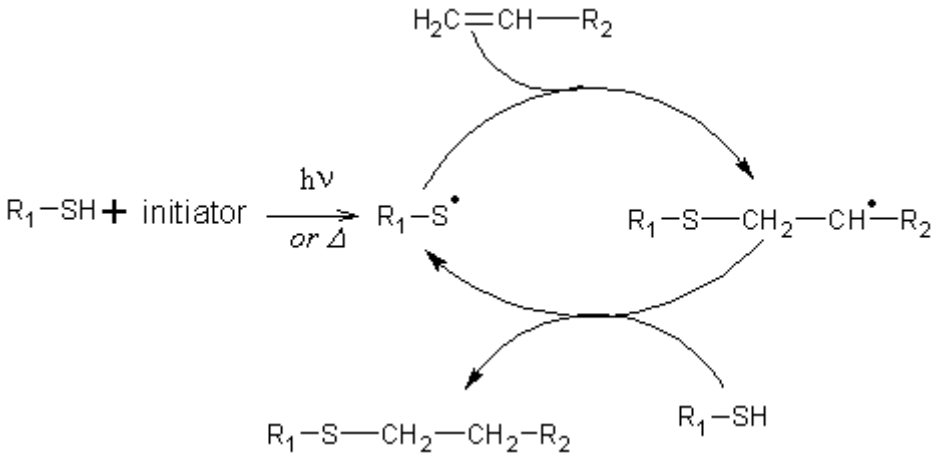
Scheme 1 Common click chemistry reaction types [3,10,11]

1.3 Thiol-ene click chemistry

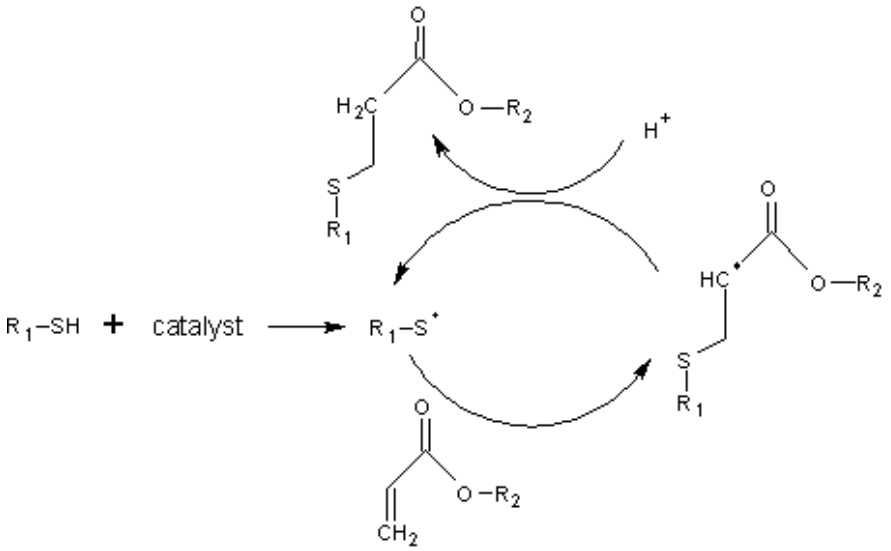
1.3.1 Mechanism of thiol-ene reactions

The essence of thiol-ene click chemistry is the Michael addition reaction of thiol with C=C bond in the presence of catalysts or initiator. According to the reaction mechanism, the thiol-ene click reaction could be divided into free radical thiol-ene click reaction and catalysts mediated thiol-ene click reaction. Free radical thiol-ene click reaction usually occurs under UV irradiation, which can be used for basic chemical synthesis and for synthesis of polymeric materials. Catalysts mediated thiol-ene click reactions usually occur in thiol and electron-deficient C=C bond, in addition, thiol and bromine, thiol and isothiocyanate group could also be subjected to thiol - Michael addition in the presence of catalysts. The main catalysts used are alkali, primary amines, secondary amines, tertiary amines, and nucleophilic alkyl phosphine

compounds. [12]



Scheme 2 Reaction mechanism of free radical thiol-ene click reaction [13]



Scheme 3 Reaction mechanism of catalysts mediated thiol-ene click reaction [13]

1.3.2 Applications of thiol-ene reactions

Chemical modification

The application fields of the materials depend on a variety of factors such as surface chemistry, stability, chemical and physical properties and so on. Surface modification of materials could not only provide functional groups on the surface of the substrate, but also enhance the adhesion, hydrophilicity, hydrophobicity, biocompatibility, surface hardness and roughness of the material. Thiol-ene click chemistry has great potential for surface modification because of its mild reaction conditions, strong stereoselectivity and atomic economy.

In order to make the surface of the stainless steel biocompatible, the surface of the stainless steel is modified and functionalized with a biocompatible carbohydrate

via thiol-ene click reaction, which is a new method of inactivation of biomedical implants. Buriak used carbohydrate having functional properties of biomolecules such as N-acetyl -D-glucose and D-galactose to functionalize stainless steel surface. The density of sugar content was controlled to ensure the surface with sufficient affinity. [9]

Andrea investigated a novel approach forming the surface-bound polymer membranes by amine catalyzed thiol-ene reaction. The surface was modified with thiol terminated monolayers (SAM), and acrylate monomers were used for surface treatment in the presence of an amine catalyst. The conjugated addition reaction occurred on the surface to connect the acrylate molecules to the surface. The fraction of the surface grafted acrylate was controlled by the reaction time. The surface density gradient of acrylate was formed, and the ranged of surface acrylate fraction was from 0 to 0.6. On the same surface, an orthogonal gradient consisting of the same acrylic functional group or multiple functional groups are obtained.The thickness of the film is increased in a controlled manner by the polymerization of the dithiol−diacrylate mixture on a surface modified with thiol group. And the thickness of the film was controlled at 0.1 to 6 nm by changing the stoichiometric ratio of the thiol−acrylate and the degree of the reaction. [12]

Preparation of hyperbranched polymers

A series of advantages of the thiol-ene click reaction have broad prospects in the field of hyperbranched polymer preparation. The preparation process of hyperbranched polymers by the monomer A_xB_y ($y \geqslant 2$), where A and B are functional groups with reaction activity, react with each other to make chain growth.

Balasubramanian introduced the preparation of hyperbranched resorcinol microcapsules in organic solvents via thiol-ene click chemistry. Bifunctional calixarene analogues containing thiol and C=C double bonds were initiated polymerization in organic solvents, such as chloroform, dichloromethane, ethyl acetate and tetrahydrofuran, to form nanocapsules under UV irradiation. The results of DLS and SEM show that different solvents play an important role in the formation of hyperbranched nanocapsules. [14]

Rim successfully synthesized a three-arm star oligomer with 1,3,5-triacryloylhexahydro-1,3,5-triazine as the nucleus. The first step of the reaction process was the formation of hydroxy compound, which obtained by the addition of

2-mercaptoethanol and the nucleobase double bond via thiol-ene click chemistry.

The second step was to esterify the terminal hydroxyl group with acryloyl chloride to convert it into a double bond. The results show that 2-mercaptoethanol and acryloyl chloride are alternately functionalized. [15]

Preparation of polymer gel

Polymer gels are hydrophilic polymers with a three-dimensional cross-linked network formed by chemical bonds, hydrogen bonds, Van Edward forces, or physical entanglement. And polymer gels are insoluble in water while could absorb large amount of water or physiological fluid and maintain gel solid state at same time. [16] Its potential applications in memory, switch, sensor, drug-controlled release, artificial muscle and active enzyme embedding have become a popular topic in functional polymer research field. Thiol-ene click reaction is less affected by water, so it is widely used in the preparation of polymeric hydrogel.

The polyethylene glycol gel was prepared via thiol-ene click reaction by Hult, and the effects of solvent type, reaction time, length of polyethylene glycol chain and thiol crosslinking agent on mechanical properties of the gel were systematically investigated. [17] The feasibility of using it as marine antifouling coating has also been researched. [18]

Application in Nanoimprint Lithography

Nanoimprint lithography, based on the principle of mechanical imprinting, has the advantages of avoiding the use of expensive light sources and projecting optical systems, without the physical limitations of the shortest exposure wavelength of optical lithography and the simplicity of the process. At present, nano imprint technology has a certain application in the light detector, blood glucose monitoring, and organic electronic devices, LED package and so on. Nanoimprint lithography is mainly achieved by hot embossing and UV lithography. The most common UV lithography systems are: (methyl) acrylic acid system, epoxy resin system, vinyl ether system and so on. In recent years, the reaction of thiol double bond has been characterized by its high efficiency, fast reaction and mild reaction conditions. Therefore, the introduction of nanoimprint technology has attracted wide interest of researchers.

Hawker and his research group of University of California in 2006 in Santa

Barbara, first reported on the thiol double bond was prepared by the reaction of UV nanoimprint lithography based on glue. This method mainly used pentaerythritol tetrakis(2-mercaptoacetate) compounds as crosslinking agent and nano imprint glue formed by reaction of different polyfunctional monomer with double bond, this work showed that thiol-ene reaction can be effectively applied to nano imprint materials.[19] In subsequent studies, the group has reported the formation of nano imprint adhesive as a soft template using poly (methyl propyl) siloxane as crosslinker. The acrylate photoresist as soft templates compared with the traditional, based on double bond reaction of thiol groups. The photoresist has adjustable mechanical properties, easy surface modification, can further function and so on. [20,21]

Applications of biomedical materials

Thiol-ene click chemistry offers an excellent opportunity for the design and synthesis of biomedical materials of various uses. With the advantages of mild chemical reaction, good selectivity and high reaction efficiency, multifunctional biodegradable medical polymer materials can be prepared. Here, they mainly introduce the study of hydrogel controlled release system, because thiol click reaction is not sensitive to water, so thiol click reaction is unique in the preparation of hydrogel biological materials.

Storha and her group used pentaerythritol tetrakis(3-mercapto-propionate) (PEMP) and PET4A to synthesize Thiol- and acrylate-functionalized nanoparticles, which could be drug deliver, via thiol-ene click chemistry. The drugs could be released during the hydrolytic degradation of those nanoparticles, which could be a novel way to deliver drugs. PET4A and PEMP would be mixed into *n,n*-dimethylformamide (DMF) solution and reacted for 24 hours. The nanoparticles (sols) would be formed after added 2ml deionized water, which were purified for 24 hours using dialysis through cellulose-based membranes. [7]

Hou Dandan mainly describes its research in hydrogel controlled release systems, because thiol click reactions are insensitive to water, so thiol click reactions are unique in the preparation of hydrogel based biomaterials. They prepared a class of injectable hydrogels using three - arm polyethylene glycol acrylate and two thio - alcohol as raw materials. The gel can be formed in situ, has a mild reaction process, a good biological compatibility, and is capable of being injected and degraded, and can be applied to a variety of injection systems. [22]

Hubbell using mercapto-acrylate Michael addition reaction of polyethylene glycol and peptides, divinyl sulfone and dextran, protein and polyethylene glycol, hyaluronic acid and polyethylene glycol linked to prepare a variety of different functional biohydrogel materials. They also studied the rheological properties of these hydrogels, swelling mechanism and its application in tissue engineering. [5]

Chapter 2 Experimental

2.1 Materials

Pentaerythritol, acrylic acid, cysteamine, *p*-toluene sulfonic acid and hexamine were purchased from Aladdin and used as received. Toluene, hydroquinone, ethanol, acetone and other reagents were obtained from Sinopharm Chemical Reagent Co. Ltd and used without further purification. PET4A (as referece compound) was purchased from Aldrich.

2.2 Synthesis of PET4A

A certain amount (Table 2.1) of pentaerythritol, acrylic acid and toluene were

added into a three-necked flask equiped with stirrer bar, thermometer, water separator and reflux condenser. After stirring and degassing by nitrogen purge for 30 min, polymerization inhibitor hydroquinone (1.5%) and catalyst *p*-toluene sulfonic acid (2%) were added in the reactor. Then the mixture was heated by oil bath and the temperature was kept at about 120°C for 8~10 hours. The reaction can be finished when no more water was produced. The amount of water produced from the reaction was recorded and used to calculate the esterification ratio.

The obtained reaction mixture was filtered to remove the impurities and the insoluble polymerization inhibitor. The filtrate was transferred into a separatory funnel and washed with 5% NaOH solution, saturated NaCl solution and distilled water (three times), successively. The upper layer (oil layer) was separated and dried with anhydrate $CaCl_2$. The final product was obtained as a yellow viscous liquid after evaperation of remained toluene by rotary evaporators.

Table 2.1 The recipes and esterification of the synthesis of PET4A

Sample No.	t/h	Toluene/ ml	T/^{O}C	Acid-alcohol ratio	V_{water}/ ml	Esterification rate/%
1	8	13.7	100	3.6	2.2	57.9
2	8	18.3	110	4.0	2.4	63.2
3	8	23.5	120	4.4	2.4	63.2
4	10	19.6	100	4.4	2.9	76.3

2.3 Synthesis of star-shape tetramine

A certain amount of PET4A (Table 2.2) was firstly dissolved in acetone (solution A), and the cysteamine and the polymerizayion inhibitor hydroquinone were dissolved in ethanol (solution B). Solution A and B were transferred into a reactor. Then, amount of catalyst *n*-hexamine was added into the reactor. The mixture was stirred and kept constant at 30 °C in a water batch for 3 hours. The obtained white perticipate was filtered and washed with ethanol for 3 times, and recrystallized in the mixed solvent of ethanol and actone.

Table 2.2 The recipes of the synthesis of star-shape tetramine

Reagents	Amount
PET4A	1.7617 g
Cysteamine	1.543 g
Ethanol	2ml
Acetone	1ml

n-hexamine	0.002ml
Hydroquinone	0.069g

2.4 Charaterization

2.4.1 IR spectroscopy

The purified samples were diluted by actone and dropped onto a KBr disc. The FTIR spectra were measured in transmission mode with an FTIR Nicolet 380 spectrometer from Thermo Scientific.

2.4.2 ^{1}H NMR

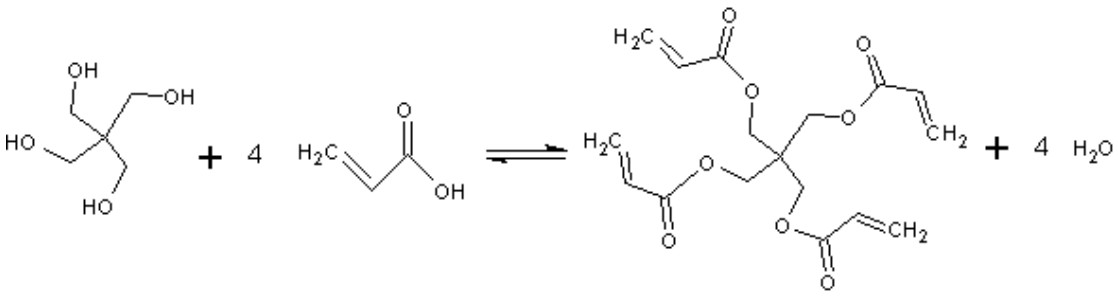
^{1}H NMR spectra were recorded on 1.0 w/v % sample solutions in $CDCl_3$ using a Bruker AVANCE Ⅱ400 spectrometer operating at 400 MHz.

Chapter 3 Results and Discussion

3.1 Synthesis of PET4A

PET4A is an ester compound with four arms and C=C double bond as terminal group, which is suitable to synthesize multi arms compounds or polymers. As we know, the Fischer esterification is equilibrium (usually with an unfavorable equilibrium constant), where, in general, ingenious techniques are necessary to achieve good yields of esters. For instance, a large excess of reagent, the alcohol or the acid, can be used. Removing one of the products, water, by adding a dehydrating agent can drive the reaction forward. Nonetheless, the purity of commercial available PET4A (obtained from Aldrich) is only about 60%, and the price is still pretty high.

According to the esterification reaction equation of pentaerythritol and acrylic acid(Scheme 3.1), at least 4 mol of acrylic acid should be reacted with 1 mol of pentaerythritol in order to get 1 mol of PET4A. To increase the yield of the PET4A, we can use a large excess acrylic acid and/or increase the reactant concentration of reactans. Meanwhile, water as one of the products should be timely removed from the reaction system.

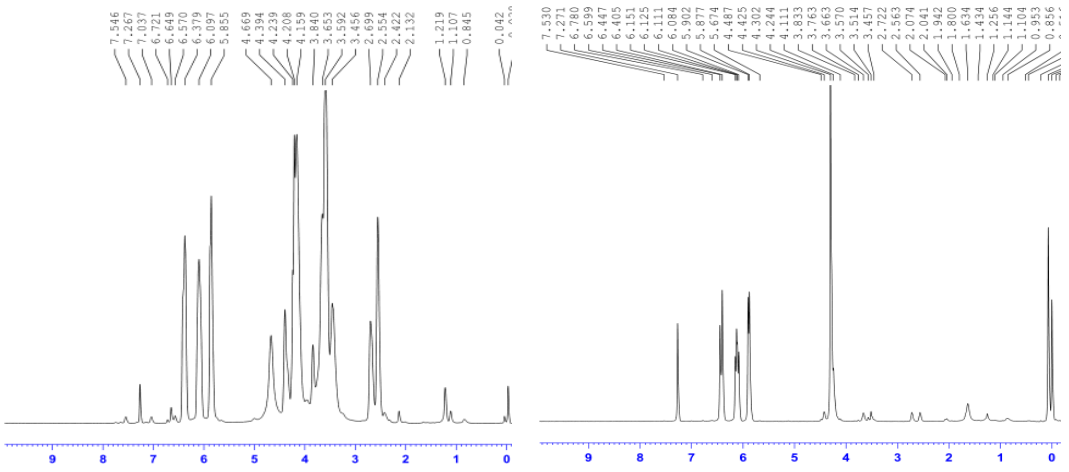


Scheme 3.1 reaction equation of the synthesis of PET4A

Catalytic amount of *p*-toluene sulfonic acid (better than condensed sulfuric acid) was used to accelerate the reaction. On the other hand, both acrylic acid and PET4A are active compounds containing C=C bonds. Therefore, in order to avoid the possible polymerization of acrylic acid or PET4A at esterification temperature, a small amount of polymerization inhibitor hydroquinone was also introduced to the reaction system. The pentaerythritol is a solid at room temperature. In order to increase the chance of collision between pentaerythritol and acrylic acid and to promote the reaction, a certain amount of toluene (Table 2.1) was used as solvent and dehydrating agent.

The crude product is the mixture of pentaerythritol tetraacrylate, pentaerythritol triacrylate, pentaerythritol biacrylate and even pentaerythritol monoacrylate. It's hard to separate PET4A from the mixture by common technqiues, such as distillation, recrystallization or liquid-liquid extraction. However, we also can use the amount of water to caculate the degree of the esterification. Table 2.1 shows that the esterification rate can reach to 76.3% after 10 hours of reaction at 100°C with 19.6mL of toluene and keeping the ratio of acrylic acid and pentaerythritol at 4.4.

The structure of the obtained PET4A and commercial PET4A were charaterized by ^{1}H NMR in $CDCl_3$ (Figure 3.1).



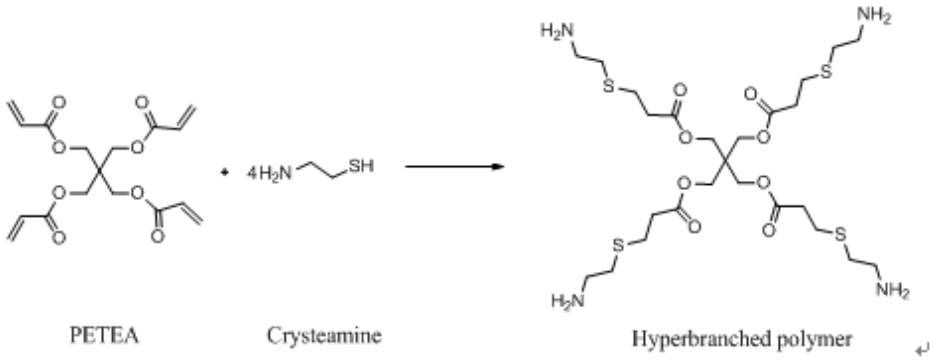
(a) (b)

Figure 3.1 the ^{1}H NMR spectra of the obtained PET4A (a) and commercial PET4A (b)

The protons of –C***H***=C***H₂*** as the end group of PET4A give rise to signals at δ 5.9, 6.1 and 6.4. The ^{1}H NMR spectrum of commercial PET4A also shows that the peaks at δ 5.9, 6.1 and 6.4 are divided into doublet, doulet-doublet and doulet by the spin-spin coupling between adjacent protons, respectively. The peaks at δ 4.3 (Figure 3.1 b) can be assigned to the protons of –O-C***H***$_2$-C. However, we should also notice that peaks at δ 2.6, 3.6, 4.4 and 4.9 in spectrum (a) cannot be assigned to any protons of PET4A. Compared with the ^{1}H NMR spectrum of pentaerythritol triacrylate, [23] these peaks can be assgined to the small amount byproduct-pentaerythritol triacrylate.

3.2 Synthesis of star-shape tetramine

The star-shape tetramine was synthesized from PET4A and cysteamine by thiol-ene click chemistry. Generally, the thiol-ene click chemical reactions are mild, efficient and fast. On the other hand, high temperature can drive the equlibrium of thiol-ene addition to the left. Therefore, the reaction device is very simple. According to the reaction formula (**Scheme** 3.2), 4 mol of cysteamine should be reacted with 1 mol of PET4A in order to obtain 1 mol of the final product. To improve the yield of the product, the molar ratio should be appropriately increased. Since the purity of commercial PET4A was less than 80%, the reaction molar ratio is determined to be 4: 1 (Table 2.2). A small amount of *n*-hexamine was used as catalyst in the reaction to accelerate the reaction and a small amount of inhibitor is added to avoid the polymerization of PET4A. The most commonly used catalysts in thiol-ene reaction are various amines, in which the catalytic activity of primary amines is better than secondary amines and tertiary amines. In this work, *n*-hexylamine was selected as the catalyst. Cysteamine and PET4A are solid at room temperature and could not be miscible with each other. Cysteamine is soluble in water and ethanol, while PET4A is completely insoluble in both solvents. In order to guarantee the addition reaction, the reactants have to be close enough for effective collision in one single system. Cysteamine and PET4A were dissolved in ethanol and acetone, respectively. The two solutions were mixed to start the reaction.

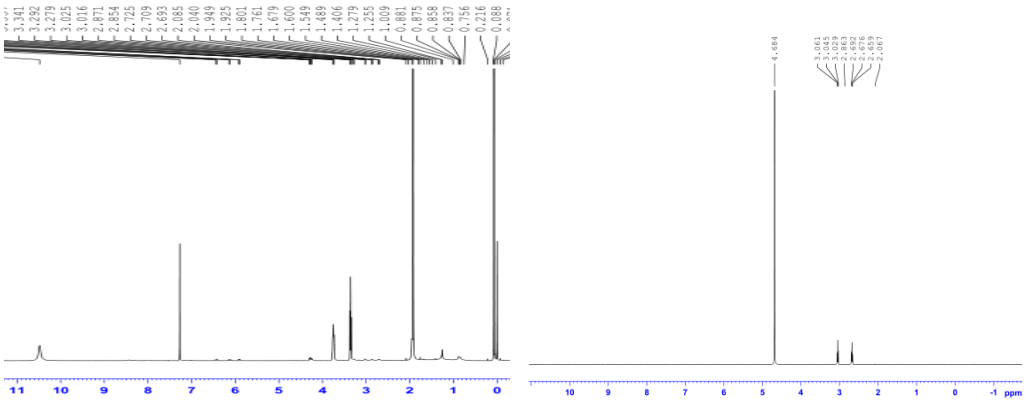


Scheme 3.2 Reaction formula of synthesize of traget product

Firstly, the mixture was opaque, and it became transparent with the addition of *n*-hexamine. After 2.5 hours of reaction, white precipitate was produced and the solution became cloudy gradually. The precipitate at the bottom of the reactor could be re-dissovled under heating and crystallized when the temperature decreased to room temperature. Meanwhile, the upper layer became transparent.

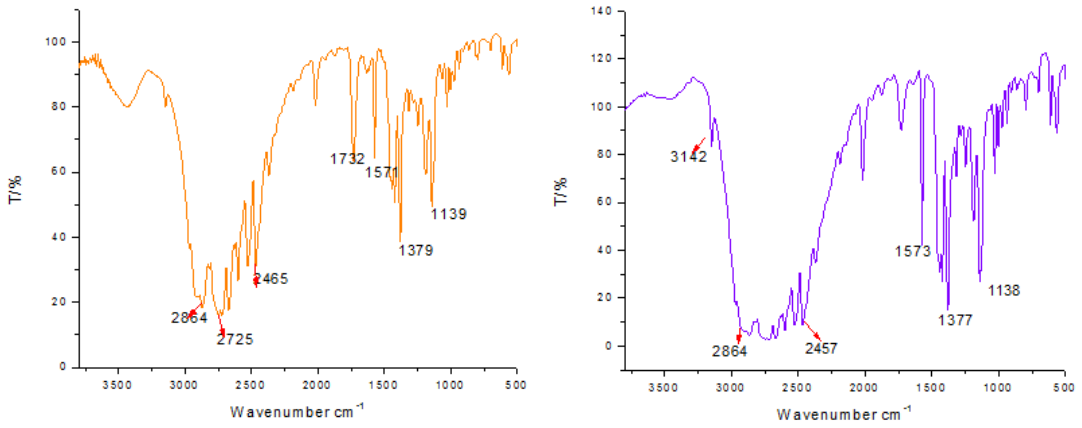
In order to determine whether the crystall was the final product, not only the crystall but also the upper layer liquid was characterized by IR and ^{1}H NMR (Figure 3.2). The uppper layer liquid was concentrated by rotary evaporator and crystall appeared as well.

From the Figure 3.2, we were able to see the characteristic peaks of–CH=CH2 (δ 5.9, 6.1 and 6.4), which indicated that there were PET4As in the product that did not participate in the reaction. In addition, the characteristic peaks of cysteamine at δ 2.7 ppm (-S-CH2-) and 3.5 ppm (-CH2-N) (Figure 3.3) also disappeared which indicated that all the cysteamine was consumed in the reaction.



(a) (b)

Figure 3.2. ^{1}H NMR spectra of the final product (precipitate) (a) and cysteamine (b)



(a) (b)

Figure 3.3 IR spectra of crystal (a) and precipitate (b)

From Figure 3.3, we could know the information of functional groups. There is the stretching vibration peak of -OH at 3511 cm^{-1}. That might the pentaerythritol tetraacrylates was not the pure substance. It was the mixture of pentaerythritol acrylates. Or the reason is that we washed the product with ethanol. From 1732 cm^{-1} to 1139 cm^{-1} is ester absorption peak. Absorption peak of amino is from 2864 cm^{-1} to 2465 $cm^{-1.}$ The IR spectrum analysis showed that the product is the target product.

As we can see from **Figure 3.3**, most places of the absorption peaks are the same. However, the stretching vibration peak of –OH group disappeared. The crystal formed by the heated cloudy reaction system. So we infer that they might be of the same substance.

Chapter 4 Conclusions

Thiol-ene click chemistry is widely used due to its high efficiency, fast and mild reaction conditions. The properties of metal free catalysts are suitable for the development of Organic Chemistry which has a broader prospect.

My target product is star-shape tetramine, which can be used in the synthesis of polyurethanes dendrimer. Due to thiol-ene click chemistry, during the reaction, no metal catalyst was used, and the reaction temperature was about 30 degrees celsius. Although we can infer the structure of the final product by IR spectra, we need to find a more direct way to prove its structure.

The possibility of synthesizing pentaerythritol tetraacrylate with acrylic acid and pentaerythritol under *p*-toluene sulfonic acid was proved by experiments. However, we still face great challenges in product separation.

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