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Synthesis of Functionalized Aliphatic Polyesters by the "Click" Copper-Catalyzed Alkyne-Azide Cycloaddition

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Abstract

The functionalization of aliphatic polyesters by the copper-mediated azide-alkyne Huisgen's cycloaddition is very efficient under mild conditions, which prevents degradation from occurring. The implementation of this reaction requires the synthesis of aliphatic polyesters bearing pendant alkynes and azides, which can be carried out either by polycondensation or by ring-opening polymerization.

Keywords : Ring-opening polymerization ; aliphatic polyester ; copper-mediated azide-alkyne cycloaddition ; click chemistry

1. Introduction

Aliphatic polyesters combine the rarely met properties of biodegradability and biocompatibility, which accounts for their wide use as biomaterials and as environmentally friendly thermoplastics. Nevertheless, the lack of functional groups along the chains is a severe limitation to develop new applications. It is thus highly desirable to implement efficient processes to graft functional groups onto aliphatic polyesters in order to tailor properties such as hydrophilicity, crystallinity, biodegradation rate or bioadherence. Moreover, the presence of functional groups along the chains paves the way to their use for any coupling reaction enabling to graft drugs, targeting molecules or probes in view of biomedical applications.

Aliphatic polyesters can be synthesized either by step-growth polymerization or by chain-growth polymerization. At the one hand, step-growth polymerization relies mainly on the polycondensation of diols and diacids or on the direct polycondensation of hydroxyacids. Nevertheless, it is very difficult to synthesize aliphatic polyesters with high molecular weights by this approach. At the other hand, chain-growth polymerization is based on the ring-opening polymerization of lactones and lactides. Many initiators/catalysts have been found to be selective enough to prevent transesterification reactions from occurring, which allows synthesizing aliphatic polyesters with predetermined and high molecular weights. The more widely used initiators are metal alkoxides (Al, Sn, Y, Ti, Ca,...) and tin octoate.

In order to graft functional groups onto aliphatic polyesters, two main routes were investigated. The first approach relies on the synthesis and the polymerization of a lactone or a dilactone substituted by a functional group. Nevertheless, this strategy suffers from several drawbacks. Firstly, several functions such as alcohol, carboxylic acid or epoxide are not tolerated by metal alkoxides. The use of protection/deprotection reactions is then unavoidable, which complicate the synthetic strategy. Secondly, the synthesis of each novel aliphatic polyesters requires the synthesis of new monomer. Thirdly, the presence of the functional substituent might modify the polymerizability of the monomer, which is a further complication.

A straightforward approach relies on the direct grafting of functional groups onto aliphatic polyesters. Vert et al.[1, 2] reported on the metallation of poly(oxepan-2-one) (PCL for poly(ε-caprolactone) by lithium diisopropylamide (LDA) into a poly(enolate), which was finally reacted with a series of electrophiles, such as carbon dioxide and benzaldehyde (Scheme 1). The use of protection/deprotection reactions is not necessary anymore because the functionalization takes place after the polymerization step. Interestingly enough, no toxic reagents are used, which is a prerequisite for the developments of applications in the biomedical field. Nevertheless, enolates are nucleophilic species prone to react with esters. Chain degradation is thus unavoidable and can only be minimized under optimized conditions. Furthermore, the functionalization efficiency is not very high because no more than 30% of the repeating units can be functionalized.

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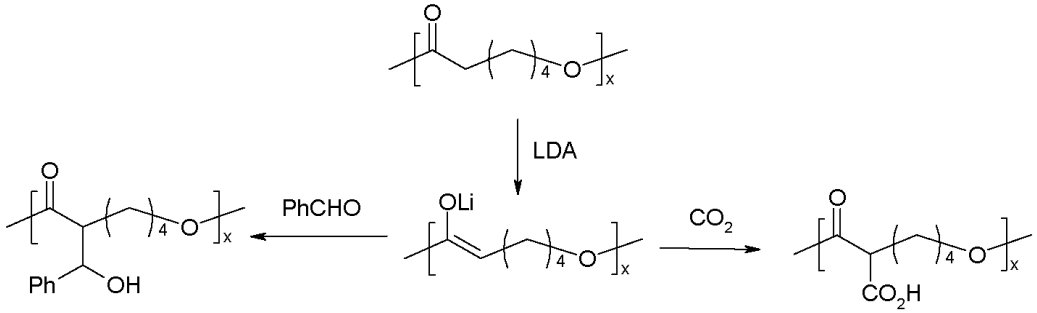
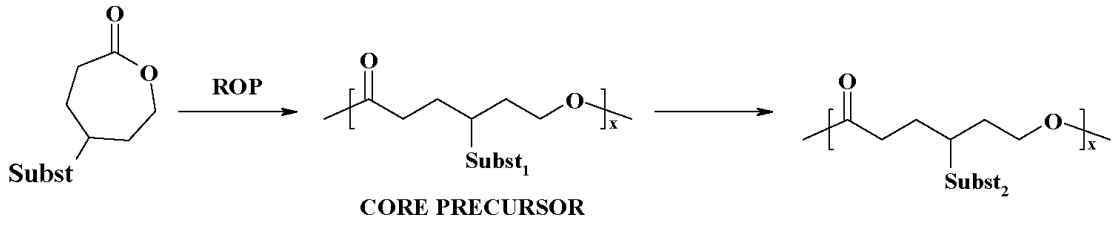
Scheme 1. *Chemical functionalization of PCL by an anionic route.*



In order to overcome these problems, it appears that a two-step process might be a valuable alternative (Scheme 2).[3] Thus, oxepan-2-one (εCL for ε-caprolactone) substituted by a properly selected functional group might be polymerized. The derivatization of the first substituent into a variety of other functional groups might be carried out by any reaction known in the state of the art. A wide range of aliphatic polyesters could accordingly be made available from a single precursor.

Scheme 2. *Direct chemical functionalization of PCL.*



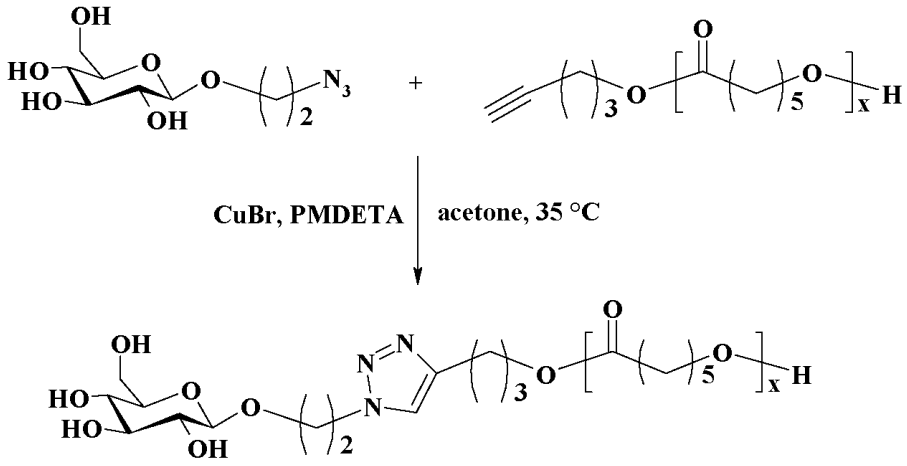
Several reactions such as Michael addition, ring-opening of epoxides, reaction of ketones and oxyamines, atom transfer radical addition, were used to implement the strategy shown in Scheme 2. Nevertheless, if some success was met, it remains highly desirable to find more efficient reactions, which tolerate many functional groups and can be carried out under mild conditions to prevent degradation from occurring.

Recently, Meldal et al.[4] and Sharpless et al.[5] reported the beneficial effect of copper(I) catalysts on the azide-alkyne Huisgen's cycloaddition. Interestingly, this reaction fulfill the requirements of a click reaction.[6] This reaction is highly efficient and regioselective, can be carried out under mild conditions and tolerates many functional groups, which avoids the use of protection/deprotection reactions. Nowadays, the copper azide-alkyne cycloaddition (CuAAC) is so popular that this reaction is many times considered as the only click reaction. The CuAAC reaction is often used in macromolecular engineering, as witnessed by several reviews recently published.[7-15] All these recent advances prompted us to investigate the efficiency of this reaction to functionalize aliphatic polyesters.

2. Functionalization of the Chain-End

The more simple and direct approach allowing functionalizing aliphatic polyesters by the CuAAC reaction is based on the derivatization of chain-ends. For instance, Li et al. reacted azide-containing sugars with α-alkynyl-PCL synthesized by ring-opening polymerization (Scheme 3).[16] Remarkably, no protection of the hydroxyl groups is required. Moreover, the CuAAC reaction is quantitative and no significant degradation of the aliphatic polyester was reported.

Scheme 3. *Coupling of an azide-containing sugar with α-alkynyl-PCL.*[16]



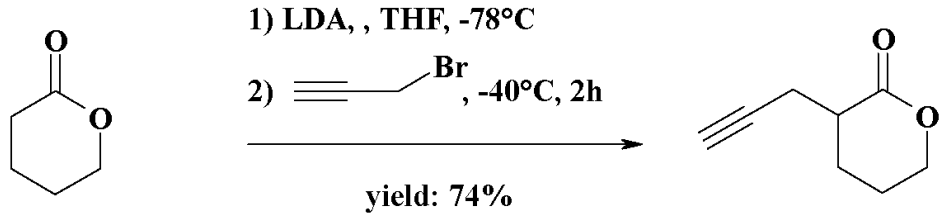
3. Random Functionalization

In order to increase the number of functional groups along the polyester chains, it was decided to extend the strategy shown in Scheme 2 to the CuAAC reaction, which requires the synthesis of aliphatic polyesters containing pendant alkynes or azides.

3.1. Synthesis of Aliphatic Polyesters by Ring-Opening Polymerization

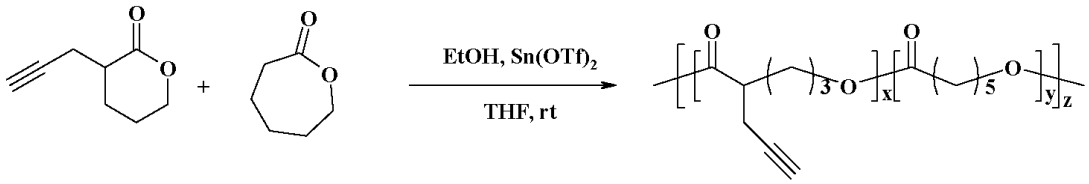
In order to prepare aliphatic polyesters by ring-opening polymerization, Emrick et al. synthesized 3-(prop-2-yn-1-yl)tetrahydro-2*N*-pyran-2-one (αAδVL for α-alkyne-δ-valerolactone) by a two step-procedure. Tetrahydro-2*N*-pyran-2-one (δVL for δ-valerolactone) was firstly reacted with LDA to obtain the corresponding enolate, which was finally reacted with 3-bromoprop-1-yne to obtain the targeted αAδVL with a yield of 74% (Scheme 4).[17] Nevertheless, the yields depend on the size of the ring. Indeed, when the reaction is carried out onto εCL rather than δVL, the yield is low (<50%), even under optimized conditions, due to the occurrence of the undesired lactone oligomerization initiated by the enolate.[18]

Scheme 4. *Synthesis of α-alkynyl δ-valerolactone according to Emrick et al.*[17]



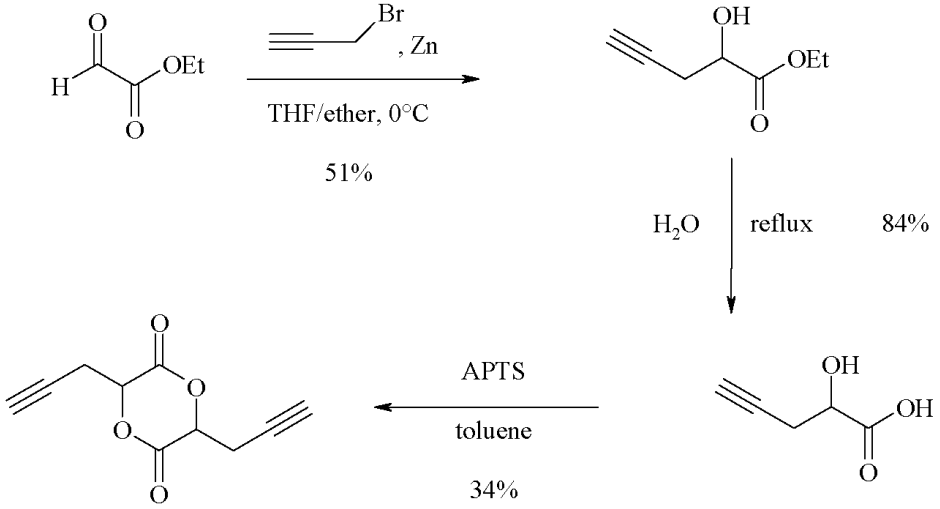
The ring-opening hompolymerization of the αAδVL was successfully mediated by $Sn(OTf)_2$ in the presence of ethanol as reported by Emrick et al.[17] The molecular weight increased steadily with conversion and was predetermined by the monomer-to-alcohol molar ratio. The initiation was fast compared to propagation and a very low polydispersity index around 1.1 was obtained provided that the polymerization was stopped before reaching complete conversion. When the polymerization was allowed to proceed to full conversion, the polyesters displayed a higher polydispersity index (around 1.3-1.4) due to the occurrence of transesterification reactions, which competes with propagation at low monomer concentration. Last but not least, the number of pendant functional groups can be chosen at will by copolymerizing αAδVL and εCL.

Scheme 5. *Copolymerization of αAδVL and εCL according to Emrick et al.*[17]

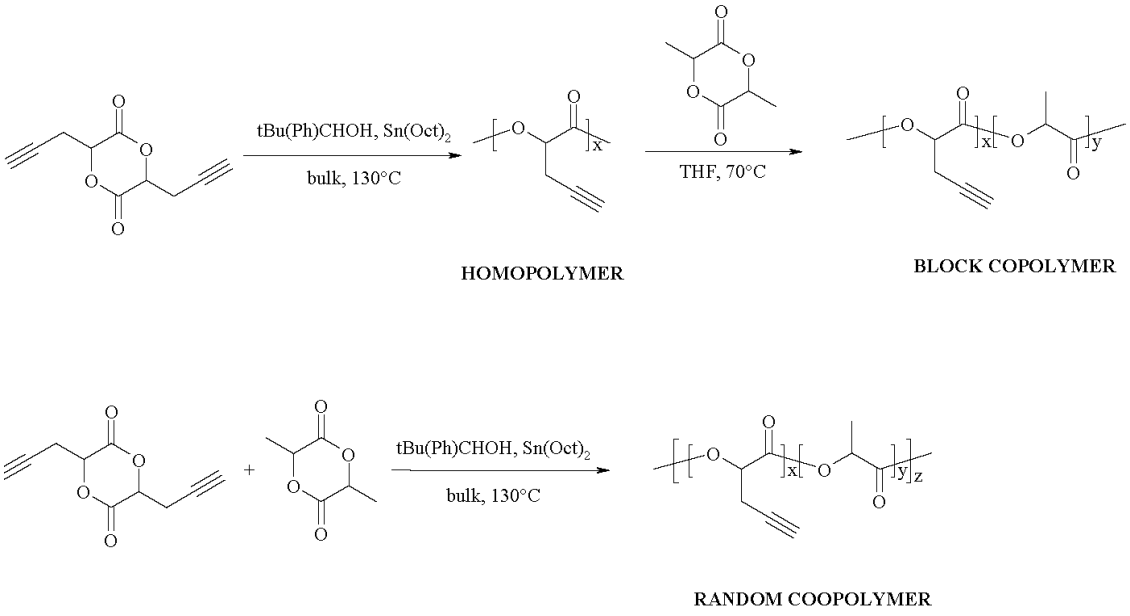


Very recently, Baker et al. reported on the synthesis of 3,6-di(prop-2-yn-1-yl)-1,4-dioxane-2,5-dione from ethyl oxoacetate by a three-step procedure shown in Scheme 6.[19] It is worth noting that the yield is quite low (15%), This monomer was homopolymerized in bulk at 130°C by using tin octoate as a catalyst and 4-tert-butylbenzylalcohol as an initiator (Scheme 7). The synthesis of statistical and block copolyesters with lactide was also reported (Scheme 7).

Scheme 6. *Synthesis of 3,6-di(prop-2-yn-1-yl)-1,4-dioxane-2,5-dione according to Baker et al.*[19]

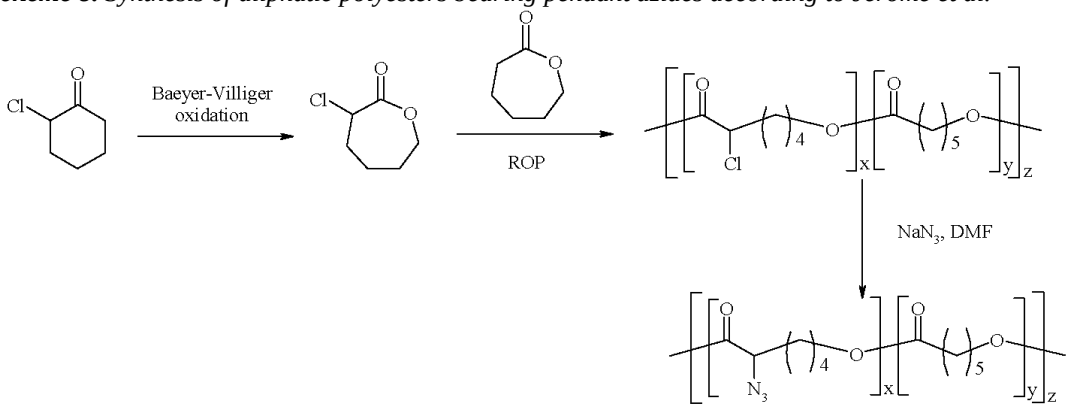


Scheme 7. *Homopolymerization of 3,6-di(prop-2-yn-1-yl)-1,4-dioxane-2,5-dione according to Baker et al.*[19]



Riva et al. reported on the synthesis of an azide-containing PCL by a strategy based on ring-opening polymerization.[20, 21] For this purpose, 3-chlorooxepan-2-one (αClεCL for α-chloro-ε-caprolactone) was synthesized by the Baeyer-Villiger oxidation of 2-chlorocyclohexanone and copolymerized with εCL (Scheme 8).[22] Unfortunately, aluminum isopropoxide was not efficient for the control of the polymerization for reasons which are still unclear. Nevertheless, tin(IV) alkoxides turned out to be more efficient to control the molecular weight, even though the polydispersity index was high (1.2-1.5) due to slow initiation. The statistical polymerization of a mixture of αClεCL and εCL was also reported.[22] Later on, Lee and Huang showed that the ring-opening polymerization of αClεCL can be initiated by alcohols in the presence of tin octoate.[23] The α-chloro substituents were then reacted with sodium azide with formation of the expected poly(εCL-co-αN_3εCL) copolymer (Scheme 8).

Scheme 8. *Synthesis of aliphatic polyesters bearing pendant azides according to Jérôme et al.[20-22]*

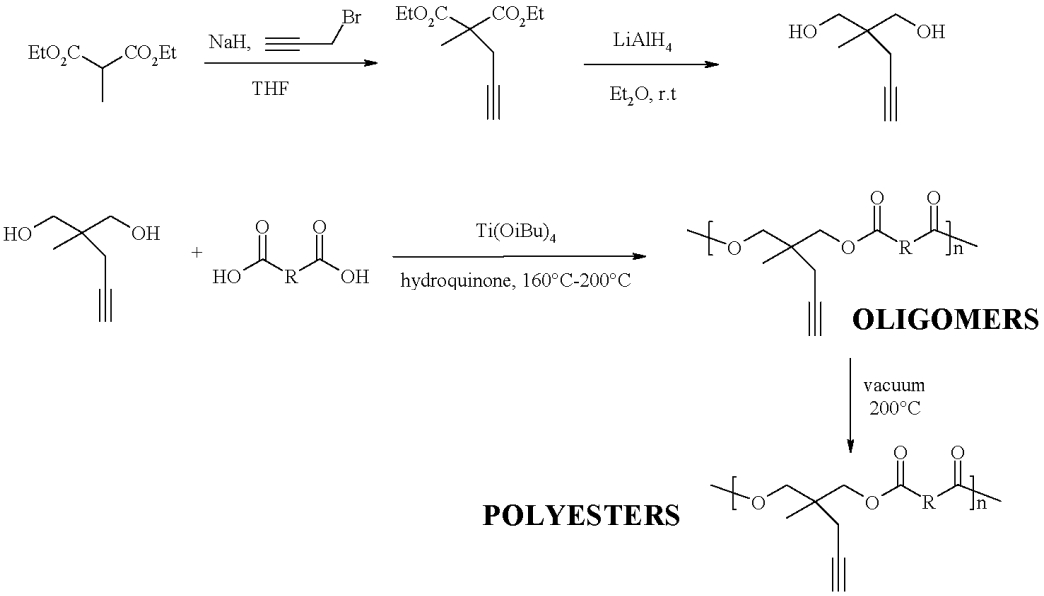


An alternative strategy relies on the ring-opening polymerization of 5-bromooxepan-2-one (γBrεCL for γ-bromo-ε-caprolactone) followed by the conversion of pendant bromides into azides by reaction with sodium azide. Unlike αClεCL, aluminum isopropoxide turned out to be a very efficient initiator of the ring-opening polymerization of γBrεCL and polyesters with predetermined molecular weight and low polydispersity indexes were synthesized.[24] The main drawback relies on the more difficult synthesis of γBrεCL, which requires three steps as shown in another chapter in this book dedicated to the functionalization of aliphatic polyesters.

3.2. Synthesis of Aliphatic Polyesters by Step-Growth Polymerization

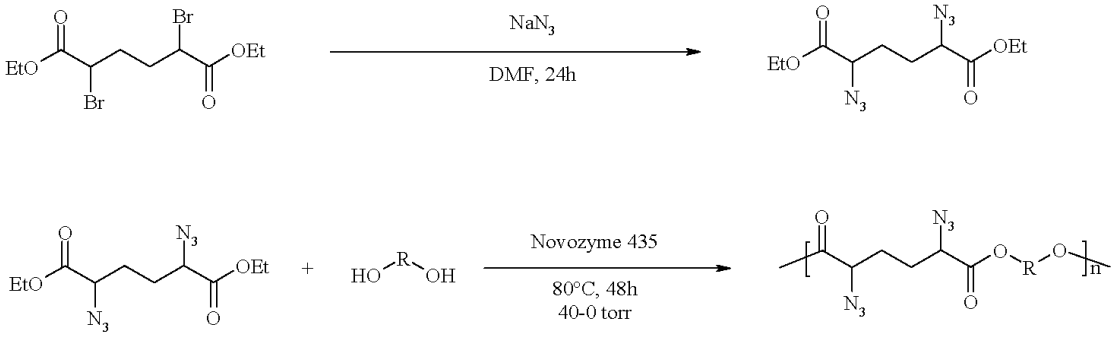
Aliphatic polyesters containing pendant azides and alkynes were alternatively made available by step-growth polymerization. Du Prez et al. reported very recently the synthesis of aliphatic polyesters bearing pendant alkynes by step-growth polycondensation of 2-methyl-2-(prop-2-yn-1-yl)propane-1,3-diol (Scheme 9).[25] The step-growth polycondensation was carried out by a two-step process. Firstly, oligomers were obtained in the presence of tin tetrabutoxide. In order to prevent undesired radical reaction of the alkyne, hydroquinone was added in the medium. Finally, higher molecular weights were obtained by removing water at high temperature (200°C) and under reduced pressure.

Scheme 9. *Synthesis of aliphatic polyesters attached with pendant alkynes according to Du Prez et al.*[25]



Sheares et al. reported the polycondensation of diols and diethyl 2,5-diazidoadipate, easily synthesized by reaction of diethyl 2,5-dibromohexanedioate with sodium azide (Scheme 10).[26] Due to the known trend of azides to explode, especially at high temperature, it is mandatory to avoid using the conditions used by Du Prez et al.,[25] because the temperature (200°C) is too high to handle azides safely. In the work of Brown and Sheares, [26] the polycondensation was catalyzed at 80°C by Novozyme 435 (Scheme 10).

Scheme 10. *Synthesis of aliphatic polyesters bearing pendant azides according to Brown and Sheares.*[26]



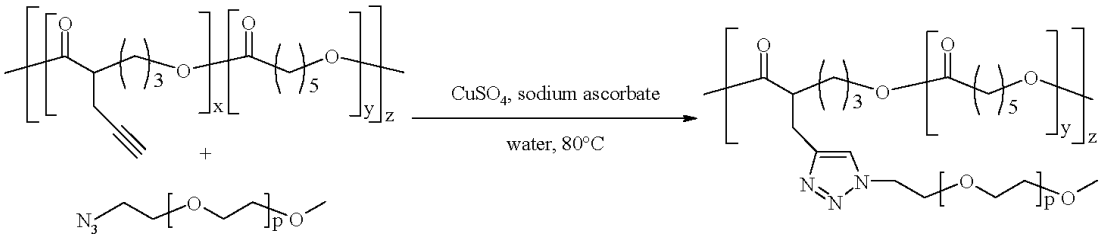
The main advantage of the approach based on step-growth polymerization is the very easy synthesis of the monomers. Interestingly, a wide range of azide-functionalized aliphatic polyesters might be synthesized just by changing the structure of one of the partners of the polycondenation (diacid or diol). As far as the strategy based on ring-opening polymerization is concerned, only a very limited number of lactones substituted by alkynes and halogenides are reported, which limits severely the number of aliphatic polyesters, which can be made available. At the other hand, the control of the polymerization in terms of molecular weight and molecular weight distribution is by far better by ring-opening polymerization compared to step-growth polymerization. Ring-opening polymerization must also be preferred to prepare aliphatic polyesters of high molecular weight.

3.3. Functionalization of Aliphatic Polyesters by Cuaac

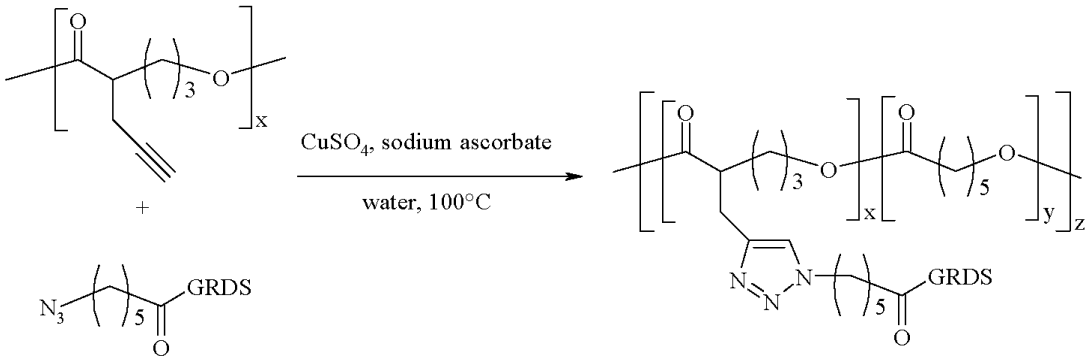
Emrick et al. were the very first ones to report the functionalization of aliphatic polyesters by the CuAAC

reaction.[17] Indeed, α,ω-PEG monomethyl ether azide was grafted onto a copolyester of αAδVL and εCL (Scheme 11), whose synthesis was shown in Scheme 5. The reaction was carried out in water at 80°C by in the presence of copper(II) sulfate and sodium ascorbate. The role of sodium ascorbate is to reduce copper(II) into Cu(I), which is the active catalyst for the CuAAc reaction. Nevertheless, the polyester is not water-soluble, and was solubilized in a minimum amount of acetone before being added to the polymerization mixture. This solvent evaporates during the grafting. Interestingly, the coupling took place very quantitatively after one night of stirring. The use of water instead of organic solvents is very advantageous in view of future developments of biomedical applications. The strategy was successfully extended to the grafting of an azide-terminated GRGDS peptide onto the poly(αAδVL) homopolyester (Scheme 12).[17] Interestingly, the authors claim that no degradation by hydrolysis was detected. The copolyester based on PCL used by Emrick et al. is not very sensitive to hydrolysis. Nevertheless, Riva et al. observed that many other polyesters are more sensitive and degrade in water at 80°C in the presence of a copper salt.[20] It was thus necessary to implement milder conditions in order to functionalize a wider range of aliphatic polyesters without degradation. Riva et al. proposed to carry out the functionalization of aliphatic polyesters by CuAAC in an organic solvent (DMF or THF) rather than in water.[20] They showed that prop-2-yn-1-yl benzoate was grafted onto poly(εCL-*co*-αN_3εCL) in the presence of 10 mol% of copper iodide and 10 mol% of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or triethylamine, in THF and in DMF, at 35°C (Scheme 13). The reaction reached completion within 2 h and no degradation was observed by SEC.

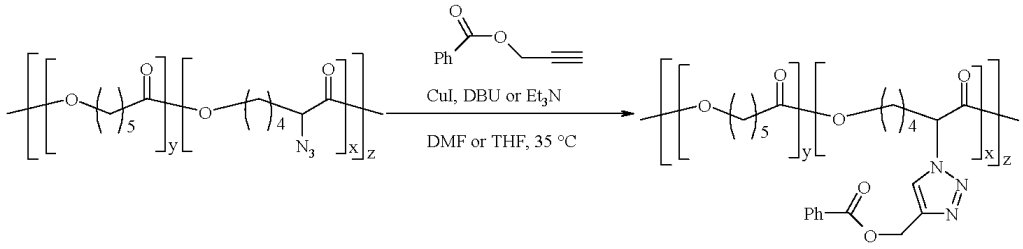
Scheme 11. *Graftging of PEO onto alkyne-containing PCLs by the CuAAC reaction according to Emrick et al.[17]*



Scheme 12. *Graftging of a peptide onto alkyne-containing PCLs by the CuAAC reaction according to Emrick et al.[17]*



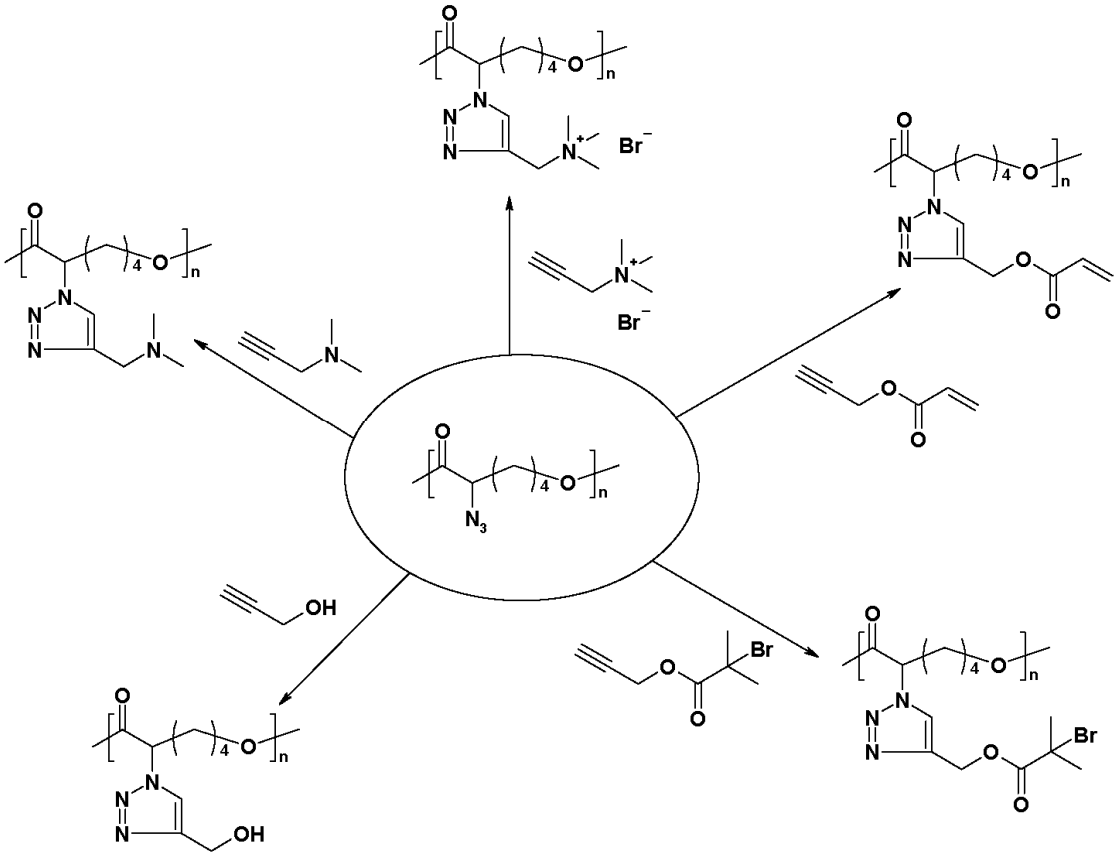
Scheme 13. *Derivatization of azide-containing PCLs by the CuAAC reaction according to Riva et al.[20]*



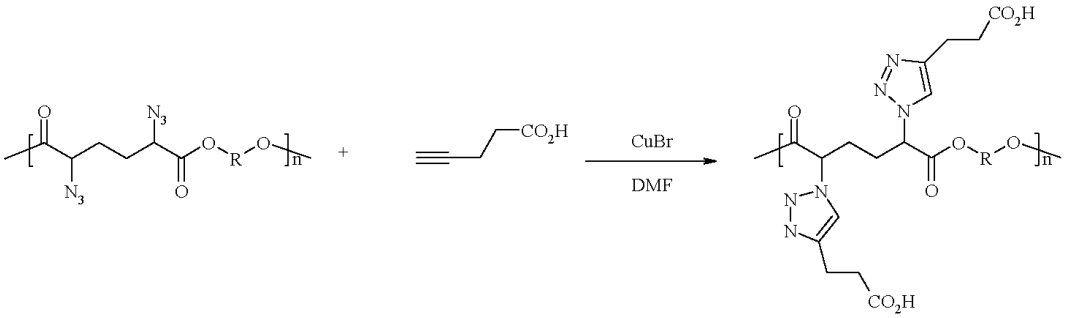
One main advantage of the CuAAC reaction remains its high tolerance to many functional groups without any need of cumbersome protection/deprotection reaction. Riva et al. grafted various functional groups onto PCL, e.g. hydroxyl, bromide, acrylic unsaturation, amine and ammonium salt (Scheme 14).[21, 27] A slight degradation by transesterification reactions was only observed when but-3-yn-1-ol was used to graft hydroxyl groups. In all the other instances, lack of degradation was the rule. The strategy was then extended to the grafting of alkyne-terminated PEO onto azide-containing copolyesters[21, 27-29] It is worth noting that, although CuAAC is very efficient, the grafting efficiency was lower than the unity, most probably for steric reasons, especially when high grafting density was targeted. The same trend was reported for similar reactions[30, 31] Finally, the coupling of α,ω-dialkynyl-PEG with azide-containing PCL was successfully implemented to synthesize amphiphilic conetworks.[32] Interestingly, CuAAC was used to obtain functional networks by a two-step procedure based on the functionalization of azide-containing polyesters followed the final cross-linking step.

The strategy based on the CuAAC reaction is thus an effective tool for tailoring extensively the properties and reactivity of PCL. For instance, the grafting of hydroxyl groups increases importantly the hydrophilicity of PCL. Ammonium-containing PCL is hydrosoluble, which is also the case of amine-containing PCL as far as the pH is low enough for the amino groups to be protonated. More recently, Brown and Sheares extended this approach to the grafting of pent-4-ynoic acid onto the azide-functionalized aliphatic polyester prepared by polycondensation as shown in Scheme 15.[26] Besides, the CuAAC reaction is also a very efficient tool to couple biologically active molecules in view of biomédical application. For example, Parish and Emrick grafted azide-substituted camptothecin, an anticancer drug, onto poly(αAδVL-*co*-εCL).[33] In another example, azide-functionalized sugars, such as glucose and mannose, were grafted onto an alkyne-containing polycarbonate, that was prepared by ring-opening copolymerization of lactide and 5-methyl-5-propargyloxycarbonyl-1,3-dioxan-2-one (Scheme 16).[34] The binding affinity of the grafted sugars for lectins makes the copolymer prone to target living cells, which is a key issue in controlled drug delivery.

Scheme 14. *Grafting of various functional groups onto azide-functionalized aliphatic polyesters according to Riva et al.[21]*

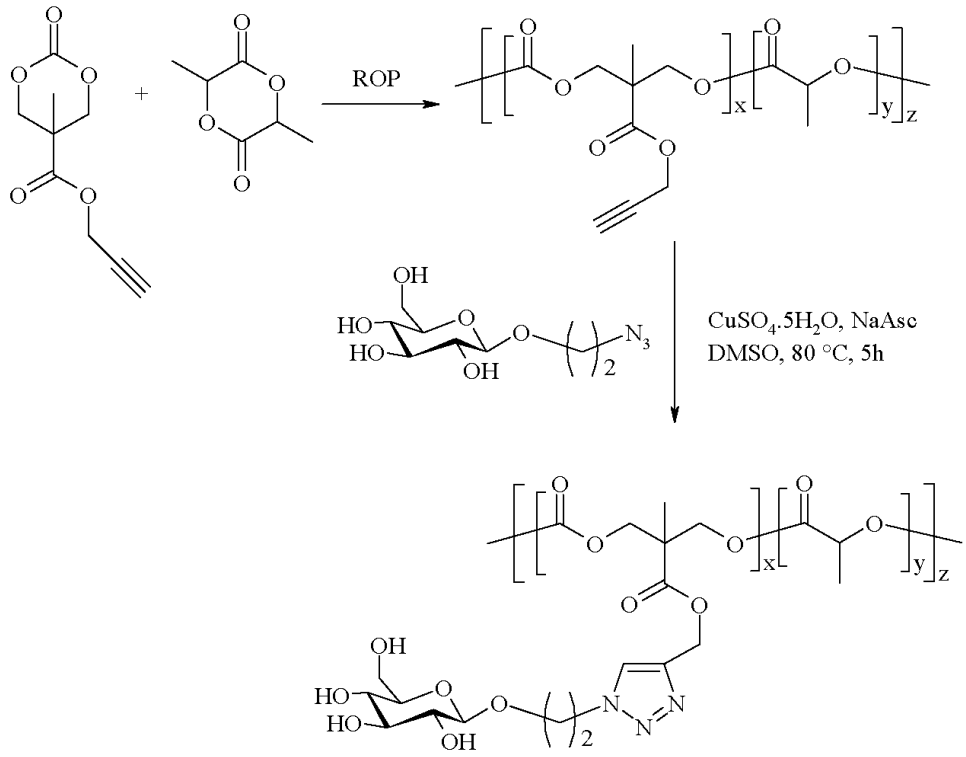


Scheme 15. *Grafting of carboxylic acids onto azide-functionalized aliphatic polyesters according to Brown and Sheares.*[26]

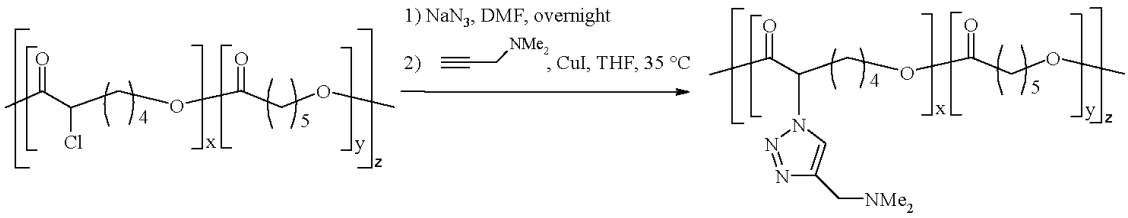


It must be pointed out that when a polymer with a high content of azides is handled, the risk of explosion may not be disregarded. The storage of this polymer at low temperature (-20°C) is a basic precaution. Whenever possible, a "one-pot" procedure should be worked out, such that the azide-containing polymer is not isolated but directly reacted with the derivatization agent. For instance, a poly(αClεCL-*co*-εCL) copolyester containing 50 mol% of pendant chlorides was reacted with 60 mol% of sodium azide in DMF overnight. A solution of 65 mol% of *N*,*N*-dimethylprop-2-yn-1-amine and 6 mol% of copper iodide in THF was added to the reactor, and the click reaction went to completion within 2 h at 35°C (Scheme 17).[21] In this example, the amino substituent of the terminal alkyne acted as a base, which explains that DBU or triethylamine was not added to the reaction medium. As a rule, the "one-pot" procedure turned out to be as efficient as the common "two-pot" technique.

Scheme 16. *Grafting of glucose onto a terminal alkyne containing PLA.*[34]



Scheme 17. *"One-pot" process in which the intermediate azide derivative is not isolated.*[21]

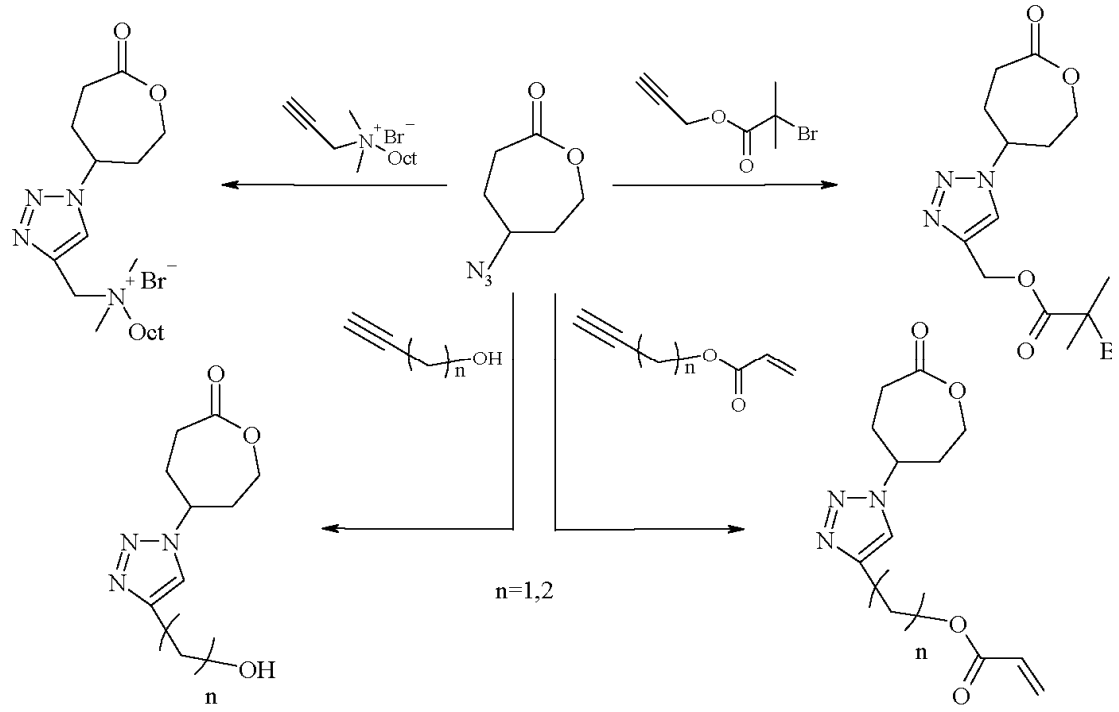


The successful implementation of the CuAAC reaction to functionalize azide- and alkyne-containing PCL paves the way to the extension of the process of aliphatic polyesters more sensitive to degradation than PCL. Riva et al. succeeded to graft PEO end-capped by an alkyne and prop-2-yn-1-yl benzoate onto an azide-copolyester obtained by ring-opening copolymerization of lactide and αClεCL followed by conversion of pendant chlorides into azides by reaction with sodium azide. The grafting by the CuAAC reaction turned out to be more difficult due to highest sensibility of the copolyester. It was necessary to protect the hydroxyl end-groups by reaction with acetyl chloride. Besides, when the first trials of CuAAC were attempted, DBU turned out to be too basic and was replaced by triethylamine. Under these conditions, the grafting by CuAAC turned out to be very efficient and no degradation was observed. Later on, Baker et al. reported the functionalization by the CuAAC reaction of alkyne-containing poly(lactide) synthesized as shown in Schemes 6 and 7.[19]

4. Synthesis of Functional Lactones

Riva et al. implemented a reverse strategy by achieving the functionalization by the CuAAC reaction prior to polymerization. Indeed, a wide range of functionalized lactones were synthesized by coupling duly substituted terminal alkynes onto $\gamma N_3\varepsilon CL$ (Scheme 18).[35] One main advantage relies on the easy purification of these lactones by simple crystallization. Nevertheless, their use as monomer for ring-opening polymerization has not yet been reported. It must be noted that although the grafting of terminal alkynes onto $\alpha N_3\varepsilon CL$ was successful, the lactone was unstable and rearranged into a non cyclic compound. The position of the substituent on the lactone ring has thus a decisive impact on the ring stability.

Scheme 18. *New functional εCLs synthesized by Riva et al.*[35]



5. Conclusions

The CuAAC reaction turned out to be a very efficient reaction to functionalize aliphatic polyesters under mild conditions for which no degradation was observed. The best conditions rely on the use of an organic solvent such as DMF or THF at low temperature (20-40°C). The CuAAC reaction can even be carried out in water provided that the aliphatic polyester is not too sensitive to hydrolytic degradation.[17] The CuAAC reaction is very efficient to synthesize polyesters with various architectures, as recently reviewed.[36] This reaction has thus a great potential for the synthesis of novel degradable and biocompatible aliphatic polyesters with tailored properties. Nevertheless, the contamination of the polyester by catalytic residues is a severe limitation, especially if biomedical applications are targeted. In the future, it will be highly desirable to find efficient processes to eliminate the use of the metal or to find new metal-free reactions as efficient as the CuAAC reaction.

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