European Polymer Journal 180 (2022) 111576

Contents lists available at ScienceDirect

European Polymer Journal

journal homepage: www.elsevier.com/locate/europolj

Controlling tosylation versus chlorination during end group modification of PCL

Ivo A.O. Beeren [a], Pieter J. Dijkstra [a], Philippe Massonnet [b], Sandra Camarero-Espinosa [a,c,d], Matthew B. Baker [a,*], Lorenzo Moroni [a,*]

[a] Department of Complex Tissue Regeneration, MERLN Institute for Technology-Inspired Regenerative Medicine, Maastricht University, Universiteitssingel 40, 6211 LK Maastricht, The Netherlands
[b] Maastricht MultiModal Molecular Imaging (M4i) Institute, Maastricht University, Universiteitssingel 50, 6229 ER Maastricht, The Netherlands
[c] POLYMAT, University of the Basque Country UPV/EHU, Avenida Tolosa 72, Donostia / San Sebastián 20018, Gipuzkoa, Spain
[d] IKERBASQUE, Basque Foundation for Science, Bilbao, Spain

ARTICLE INFO

Keywords:
Tosylation
Chlorination
Poly(ε-caprolactone)
Solvent dependency

ABSTRACT

Synthetic biodegradable materials are commonly used to create constructs for medical devices and tissue engineered constructs. However, many of the homopolymers used in FDA approved devices such as poly (ε-caprolactone) (PCL), poly(lactic acid), or poly(carbonates) lack biogically relevant functional groups to steer biological responses in a controlled fashion. Commonly, an interconversion of the end groups is required to insert addressable moieties for the attachment of biologically active groups. In this study, the activation of the hydroxyl groups of a low molecular weight PCL-diol to the corresponding p-toluene sulfonate ester using p-toluenesulfonyl chloride was performed in both dichloromethane (DCM) and dimethylformamide (DMF). To our initial surprise, we only yielded the chlorinated product in DMF, while in DCM the tosylate ester was obtained. In a small series of reactions, we studied the solvent dependent switchability between tosylation and chlorination on PCL. We concluded that in polar aprotic solvents (DMF and dimethylsulfoxide), we rapidly and efficiently converted the hydroxyl into the chloride group, whereas in inert solvents (DCM and chloroform) we yielded the tosylated product. The data suggested that solvation effects of the polar aprotic solvents led to a S_n2 reaction of the tosyl group by the chloride. Furthermore, we utilized a polyethylene glycol (PEG) polymer to show translatability of the chlorination reaction to other (biomedical) polymers. This work highlights a new reaction pathway during the tosylation of a polymer end group, and presents a new useful strategy to insert clickable groups on synthetic polymers that are only soluble in polar aprotic solvents.

1. Introduction

The development of synthetic polymeric biomaterials has been fundamental to create a variety of devices and constructs for biomedical and pharmaceutical applications. Tailoring the molecular design of these polymers gives control over important parameters such as (bio) degradability, physical, and mechanical properties [1]. Subsequently, these polymers are processed into constructs that serve as a template for the native environment, often to induce repair or regeneration of damaged tissues [2]. Synthethic polymeric biomaterials generally lack specific biological interaction with the surrounding tissues and cannot efficiently direct cell adhesion, extracellular matrix production, or differentiation into desired lineages [3]. To insert biologically relevant moieties, post-modification methods are developed to introduce addressable functional groups in a controlled fashion.

There are a vast amount of synthetic biodegradable polymers available to create constructs for many tissues [4]. A very commonly used polymer in FDA-approved applications is PCL, which is relatively easily synthesized [5]. Moreover, PCL has rheological properties allowing a wide range of processing methods from electrospinning to additive

Abbreviations: PCL, poly(ε-caprolactone); DCM, dichloromethane; DMF, dimethylformamide; PEG, polyethylene glycol; PCLA, PCL-Azide; TEA, triethylamine; NaI, sodium iodide; p-TsCl, p-toluenesulfonyl chloride; DMSO, dimethylsulfoxide; NMR, nuclear magnetic resonance; HMBC, heteronuclear multiple bond correlation; Tof-SIMS, Time of Flight-Secondary ion mass spectrometry; RT, room temperature; TFA, trifluroacetic acid.

* Corresponding authors.
E-mail addresses: m.baker@maastrichtuniversity.nl (M.B. Baker), l.moroni@maastrichtuniversity.nl (L. Moroni).

https://doi.org/10.1016/j.eurpolymj.2022.111576
Received 26 August 2022; Accepted 7 September 2022
Available online 20 September 2022

manufacturing. The polymer is biocompatible and, depending on molecular weight and crystallinity, biodegrades within 2–4 years [6]. Some methods to introduce reactive groups on PCL as anchor point for biological motives include using a functional initiator during ring opening polymerization [7] and attaching terminal (protected) linkers [8]. Furthermore, the hydroxyl end group can be chemically converted into more reactive groups such as acrylates [9], carboxylic acids [10], or N-hydroxysuccinimide [11] groups to couple biological molecules. Alternatively, terminal azide groups can be used in either copper (I) catalyzed, or strain promoted alkyne azide click chemistry [12]. This type of chemistry is versatile, as the reaction is fast, highly specific, amenable to mild reaction conditions, and virtually any molecule with an alkyne group can be attached on the polymer. For example, Lancuski and co-workers have blended low molecular weight PCL-Azide (PCLA) with PCL_{80k} to tune the degree of surface functionalization of electrospun fibrous scaffolds with a complementary alkynated dye [13]. In addition, other studies have conjugated alkynated nanocellulose or polyhedral oligomeric silsequioxanes onto PCLA to design bio-nanocomposites [14]. Besides bio-functionalization, the mild click functionalization method is also used in branching and network formation [8,15].

Because the primary hydroxyl group of PCL is a poor leaving group in nucleophilic substitution reactions, conversion into a good leaving group is required. Commonly, activation of a hydroxyl group into a p-toluenesulfonate ester is applied and followed by reaction with a nucleophile [13]. In this study, we applied this methodology in various solvents to activate the hydroxyl end groups of PCL towards the introduction of azide groups. We observed a surprising switch between tosylation and chlorination depending on the solvent of the reaction, even on a PEG polymer. Irrespectively of the intermediate, the corresponding azide was obtained. After characterizing the conversion of the end-group of PCL step in a small set of solvent systems, we report a new potential pathway to modify polymers containing hydroxyl groups that are only soluble in polar aprotic solvents such as DMF.

2. Materials and methods

2.1. Materials

A PCL-diol with a molecular weight of 2 $kg.mol^{-1}$ (PCL_{2k}-diol), a poly(ethylene glycol) with a molecular weight of 3.3 $kg.mol^{-1}$ (PEG_{3k}), imidazole (>99%), triethylamine (TEA; >99%), sodium iodide (NaI), acetonitrile, trifluoroacetic acid (TFA), acetone, deuterated solvents and p-toluenesulfonyl chloride (p-TsCl; >99%) were purchased from Sigma-Aldrich and used as received. DMF, DCM, and chloroform ($CHCl_3$) were purchased anhydrous from Sigma-Aldrich and used as received. Dimethylsulfoxide (DMSO) was purchased from Sigma-Aldrich and dried over molecular sieves. Methanol (MeOH) was purchased from Normapur and diethyl ether from VWR. Sodium azide (NaN_3; >99%) was obtained from TCI chemicals.

2.2. Characterization

^1H nuclear magnetic resonance (NMR), ^{13}C NMR, and heteronuclear multiple bond correlation (HMBC) spectra were recorded using a Bruker 700 MHz instrument. All samples were dissolved in $CDCl_3$. Materials were spin-coated on glass slides for Time of Flight-Secondary ion mass spectrometry (ToF-SIMS) analysis, which was performed on a PHI nanoTOF II instrument (Physical Electronics, Chanhassen, USA). A 20 keV C_{60}^+ primary ion beam was used to chemically analyze the surface of the samples. The C_{60}^+ primary ion beam with a DC current of 1 nA was directed at the sample under an angle of 45° in relation to the normal and had a beam spot of 1 μm. Negative ion TOF-SIMS spectra were acquired over a field of view of 500 × 500 μm with a cycle time that allowed for a 0–1850 Da mass range. 50 frames were acquired for each spectrum, resulting in a total primary ion dose of 1.96×10^{12} ions/cm^2. No charge compensation was used. All negative mass spectra were internally calibrated using the same ions, namely CH^- at *m/z* 13.01, OH^- at *m/z* 17.00, CN^- at *m/z* 26.00 and CNO^- at *m/z* 42.00. All ToF-SIMS data was processed using the commercial PHI software (TOF-DR 3.0.0.13).

2.3. Synthesis

PCL_{2k}-di-OTs:

In a dry nitrogen atmosphere, PCL_{2k}-diol (1.5 g, $1.5x10^{-3}$ mol of hydroxyl end groups) was dissolved in anhydrous DCM at room temperature (RT) in an oven-dried flask. Imidazole (0.61 g, $9x10^{-3}$ mol, 6.0 equiv.) and pre-dissolved p-TsCl (1.72 g, $9x10^{-3}$ mol, 6.0 equiv.) in anhydrous DCM was dropwise added and the reaction mixture was stirred at RT overnight. The maximum concentration of polymer in DCM was always 0.15 g/mL. The polymer was precipitated in cold MeOH, centrifuged, and washed with cold MeOH two more times. The polymer was collected as a white powder and dried *in vacuo*. Yield: 50%. ^1H NMR PCL-OTs ($CDCl_3$, 700 MHz): δ (ppm) = 7.78 (d, aromatic C**H**, 2H, J = 8.23 Hz), δ = 7.35 (d, aromatic C**H**, 2H, J = 8.23 Hz), δ = 4.06 (t, C$\mathbf{H_2}$O, 27H, J = 6.71 Hz), δ = 4.02 (t, C$\mathbf{H_2}$OTs, 2H, J = 6.71 Hz), δ = 3.88 (s, C$\mathbf{H_2}$O, 2H), δ = 2.45 (s, C$\mathbf{H_3}$, 3H), δ = 2.31 (t, C$\mathbf{H_2}$CO, 27H, J = 7.55 Hz), δ = 1.65–1.64 (m, C$\mathbf{H_2}$, 54H), δ = 1.39 (m, C$\mathbf{H_2}$, 27H).

PCL_{2k}-di-Cl:

The same procedure as described above was also performed in DMF, except that we performed it both at RT and 70 °C. The polymer was collected as a white powder and dried *in vacuo*. Yield: 34%. ^1H NMR PCL-Cl ($CDCl_3$, 700 MHz): δ (ppm) = 4.06 (t, C$\mathbf{H_2}$O, 27H, J = 6.68 Hz), δ = 3.54 (t, C$\mathbf{H_2}$Cl, 2H, J = 6.68 Hz), δ = 3.88 (s, C$\mathbf{H_2}$O, 2H), δ = 2.31 (t, C$\mathbf{H_2}$CO, 27H, J = 7.66 Hz), δ = 1.65–1.64 (m, CH_2, 54H), δ = 1.39 (m, CH_2, 27H).

PCL_{2k}-di-OTs vs PCL_{2k}-di-Cl:

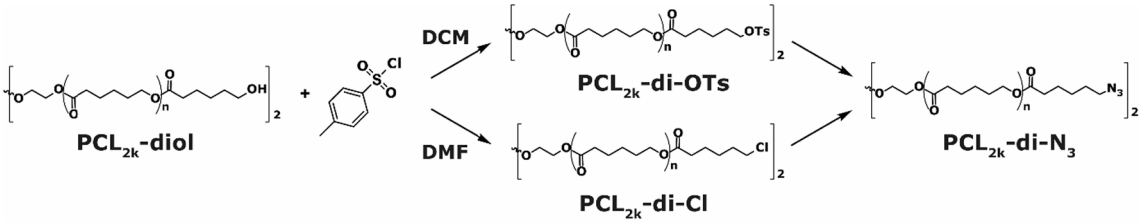
The same procedure as described was also performed at RT and with TEA as a base. Furthermore, the same procedure was performed at RT with imidazole as base in $CHCl_3$, DCM with a catalytic amount of DMF, and a 1:1 v/v mixture of DCM and DMF as solvent. In dimethylsulfoxide (DMSO), we performed the reaction according to the same procedure at 50 °C. The products were collected as a white solid and dried *in vacuo*. For a halogen test, 150 mg of polymer was dissolved in 1.5 ml of 15% w/v NaI in acetone solution and reacted for 10 min at RT and 5 min at 50 °C before assessing precipitate formation.

PCL-di-azide:

In a dry nitrogen atmosphere, PCL-di-Cl (0.23 g, ~$0.23x10^{-3}$ mol of chloride end group) was dissolved in 2 ml dry DMF at 70 °C. Then, NaN_3 (88 mg, $1.4x10^{-3}$ mol, 6.0 equiv.) was added and the solution was stirred overnight. The polymer was precipitated in cold MeOH, centrifuged, and washed with cold MeOH two more times. The product was collected as a white powder and dried *in vacuo*. Yield: 36%. ^1H NMR ($CDCl_3$, 700 MHz): δ (ppm) = 4.06 (t, C$\mathbf{H_2}$O, 32H, J = 6.68 Hz), δ = 3.88 (s, C$\mathbf{H_2}$O, 2H), δ = 3.28 (t, C$\mathbf{H_2}N_3$, 2H, J = 6.90 Hz), δ = 2.31 (t, C$\mathbf{H_2}$CO, 32H, J = 7.52 Hz), δ = 1.65–1.64 (m, C$\mathbf{H_2}$, 64H), δ = 1.39 (m, C$\mathbf{H_2}$, 32H).

CH_3O-$PEG_{3.3k}$-Cl:

In a dry nitrogen atmosphere, CH_3O-$PEG_{3.3k}$ (1.5 g, $0.90x10^{-3}$ mol of hydroxyl groups) was dissolved in anhydrous DMF at a concentration of 250 mg/mL. Imidazole (0.37 g, $5.4x10^{-3}$ mol, 6.0 equiv.) and subsequently pre-dissolved p-TsCl (1.02 g, $5.4x10^{-3}$ mol, 6.0 equiv.) in 2 ml of DMF were dropwise added. The reaction was left overnight at 70 °C. The reaction mixture was concentrated *in vacuo*, the polymer precipitated in diethyl ether, decanted, and dried *in vacuo*. The product was purified with reverse-phase silica chromatography using acetonitrile/water (25:75) + 0.1% TFA as solvent system. After elution of the first spot, the solvent was switched to acetonitrile/water (50:50) + 0.1% TFA. The product was collected as a white solid and dried *in vacuo*. Yield: 35%. ^1H NMR ($CDCl_3$, 700 MHz): δ (ppm) = 3.75 (t, C$\mathbf{H_2}$Cl, 2H, J = 5.89 Hz), δ = 3.64 (s, C$\mathbf{H_2}$O, 132H).



Scheme 1. Solvent dependent end-group conversion of a PCL_{2k}-diol into an activated intermediate, followed by conversion into the corresponding azide.

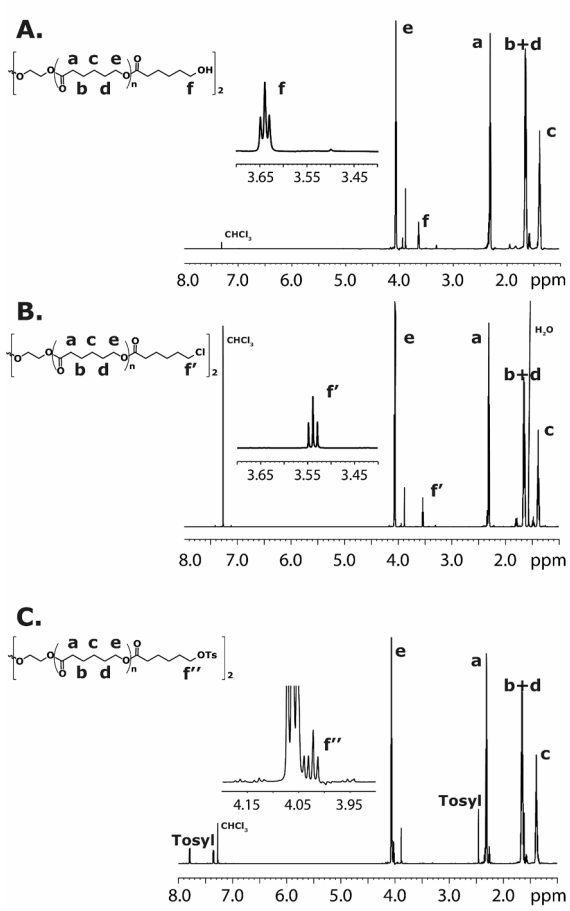


Fig. 1. ^{1}H NMR spectra of A) PCL_{2k}-diol, B) PCL_{2k}-di-Cl obtained after reaction with p-TsCl in DMF at 70 °C, and C) PCL_{2k}-di-OTs after reaction with p-TsCl in DCM at RT ($CDCl_3$).

3. Results and discussion

Activation of PCL hydroxyl chain end groups by conversion into the corresponding p-toluenesulfonate ester is a convenient way to introduce a reactive functional group. The p-toluenesulfonate groups can then be converted in other functional groups by a nucleophilic substitution reaction. The tosylation reaction on polymer hydroxyl end-groups is mostly performed at RT using inert solvents like DCM or tetrahydrofuran in the presence of a tertiary amine as a base with high conversion (Scheme 1, top) [13,14,16]. Alternatively, the tosylation reaction has also been performed in DMF albeit that in this study no information was reported on the characterization of the intermediate [17]. Moreover, aromatic bases such as pyridine have been applied in the tosylation reaction [18,19]. In this study, we aimed to synthesize PCL with terminal azide groups by tosylation of the hydroxyl end-groups and subsequent substitution reaction (Scheme 1). However, when we performed the tosylation reaction with imidazole as base in DMF, we observed full conversion into an initially unknown product after 18 h at 70 °C.

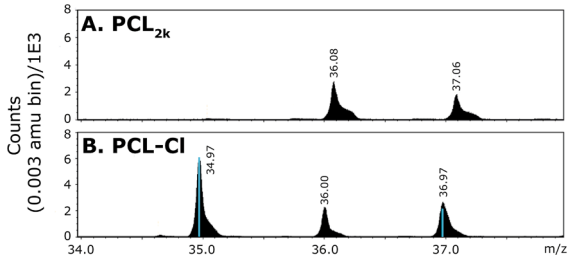


Fig. 2. TOF-SIMS analysis of a PCL_{2k}-di-Cl compared to PCL_{2k}-di-OH surface as control. (A) Close-up of the mass spectrum of PCL_{2k}. B) Close-up of the mass spectrum of PCL_{2k}-di-Cl, showing the presence of chlorine. The blue bars represent the theoretical signals for the abundances of the ^{35}Cl and ^{37}Cl isotopes.

Table 1
Solvent dependent conversion of PCL_{2k} hydroxyl end-groups upon reaction with p-TsCl[a].

Base	Solvent	Temperature (°C)	Product (NMR)	DoS (%)[b]
Imidazole	DMF	70	PCL-Cl	100
TEA	DMF	70	PCL-Cl	100[c]
Imidazole	DMF	RT	PCL-Cl	66[c]
Imidazole	DCM	RT	PCL-OTs	100
Imidazole	$CHCl_3$	RT	PCL-OTs	18[c]
Imidazole	Cat. DMF in DCM[d]	RT	PCL-OTs	16[c]
Imidazole	DCM:DMF[e]	RT	PCL-Cl	63[c]
Imidazole	DMSO	50	PCL-Cl	90[c]

[a] All reactions were carried out for 18 h.
[b] The degree of substitution was determined from ^{1}H NMR spectra.
[c] The spectra can be found in the SI (figure S5-10).
[d] A 1:1 M ratio of DMF relative to the hydroxyl groups was added.
[e] DMF and DCM were used in a 1:1 v/v ratio.

Although we observed a shift in the methylene protons belonging to the hydroxyl group (Fig. 1A) to 3.53 ppm in the isolated product (Fig. 1B), it did not match the expected downfield shift (4.03 ppm) when performing the tosylation in DCM at RT (Fig. 1C). Moreover, the tosyl peaks were absent and found in the MeOH filtrate, indicating washing away of small molecule tosylate groups (Figure S1). A reaction pathway yielding a chlorinated PCL was considered at this point. Turning to ^{13}C NMR, we observed a new signal at 45 ppm approaching the shift of an alpha carbon of a primary alkyl chloride (Figure S2). To further test the hypothesis of a chloride intermediate, we performed a halide test. The NaI in acetone solution turned cloudy, suggesting the presence of a halogen (Figure S3).

In order to observe more direct evidence of chlorination, we performed ToF-SIMS analysis on spin-coated surfaces to test for the presence of chloride ions. Indeed, these surfaces showed the typical 3:1 isotopic mass ratio of chloride atoms compared to a control PCL (Fig. 2 & Figure S4). Thus, we concluded that using DMF as a solvent during the tosylation yielded the PCL with chloride end-groups (Scheme 1,

bottom).

The conversion of a hydroxyl group into a chloride group using p-TsCl has been reported before, but occurred under specific reaction conditions [20,21]. For example, the substitution only occurred in presence of an adjacent benzyl group with electron withdrawing substituents, which increased the electron deficiency at the methylene carbon of the leaving group [20]. The adjacent conjugated system is absent in PCL and cannot explain a substitution of the tosylate with a weak nucleophile such as the chloride. A series of reactions was performed to gain more insight in the end-group conversion on a PCL_{2k}-diol (Table 1). In polyisobutylenes, also end-group chlorination was reported when attempting a tosylation in DCM with TEA as base and using a catalyst. In contrast to this study, the chlorinated product was only observed as minor product and formed slowly over the course of days [21]. Thus, we initially assessed the effect of the base type on the outcome. When we switched to TEA as base in DMF, we observed full conversion to the chlorinated PCL. Additionally, crude analysis displayed no shift in the methylene protons of the hydroxyl groups to 4.03 ppm, as shown in Fig. 1C, nor a downfield shift of the tosyl peaks (Figure S11). The ^{1}H NMR spectrum of the crude did show some presence of unreacted PCL-diol (~20%), but this was removed by the MeOH purification. Interestingly, in all reactions we did not find mixtures of tosylated and chlorinated products in the ^{1}H NMR spectra. In DMF at 70 °C, we even observed full conversion into the chloride after 30 min (Figure S12). Overall, these results suggested a fast and efficient chlorination mechanism with the reaction conditions of this study.

The TsCl might react with DMF according to a variant of the Vilsmeier reaction [22], potentially consuming most TsCl before tosylation. We dissolved p-TsCl in deuterated and left it overnight before recording the ^{1}H NMR spectrum. We did not observe total consumption of the p-TsCl nor found evidence for reaction of the DMF with p-TsCl, forming a Vilsmeier reagent (Figure S13). Due to hydrolysis, we did observe p-toluenesulfonic acid formation. Nevertheless, the DMF-TsCl complex might only exist as intermediate state, and thus fulfill a catalytic function [23]. Therefore, we added a small volume of DMF to DCM during the reaction (Table 1). Here, we only observed formation of the tosylate ester.

Subsequently, we investigated the effect of solvent polarity on the reaction (Table 1). When we used DMF, a one-to-one volume ratio of DMF to DCM or DMSO, the chlorinated product was yielded. In DMSO, we also observed formation of a side product (10%), but it was not the tosyl group as those peaks were absent (Figure S10). In inert solvents such as DCM and $CHCl_3$, the tosylated product was obtained. We attributed the differences in conversion rates in the different solvents to the reaction kinetics. The integral ratios of the end-group versus the backbone did not significantly change, which also indicates that no major side reactions were ongoing. Thus, this data suggested that the main driving force in this reaction is solvent dependent.

A reaction pathway where the hydroxyl groups were converted into their corresponding chlorides through an intermediate p-toluenesulfonate ester was now considered as viable mechanism. As known, polar aprotic solvents such as DMF accelerates nucleophilic substitution reactions by solvation of cations, such as our protonated imidazole, thereby increasing the nucleophilicity of the anion, which is the chloride ion. Since full conversion into the chloride is obtained after 30 min at 70 °C, a S_n2 mechanism seemed most viable. The absence of the solvation effect may therefore explain the slower conversion of the tosylate into the chloride on polyisobutylenes in DCM with TEA as base [21]. Taken together, we presented evidence that in polar aprotic solvents efficiently chlorination of the end group is achieved on PCL_{2k}-diols.

In order to see if this Cl/OTs selectivity was unique to PCL or more generally applicable, we assessed the solvent dependent outcome on a PEG polymer. Using DMF and high temperature reaction conditions, we confirmed the presence of a terminal chloride via ^{1}H NMR and ToF-SIMS (Figure S14). Interestingly, these results indicated that the solvent dependent conversion could be applied to other polymers with hydroxyl functional groups. Because some polymers are difficult to solubilize in non-polar solvents, polar aprotic solvents such as DMF must be used. The observations in this study suggest that attempted tosylation of polymers in DMF likely yields a chlorinated product.

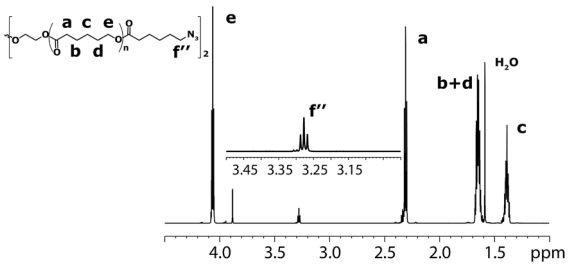


Fig. 3. ^{1}H NMR spectrum of the PCL_{2k}-di-azide obtained after reaction of the PCL_{2k}-di-Cl with sodium azide in DMF at 70 °C.

The end goal of these reaction pathways is often the functionalized polymer, in this case the azide. The conversion of PCL-OTs into the corresponding azide is already frequently reported in literature [13]. Finally, we also confirmed by ^{1}H NMR and HMBC spectroscopy that the PCL chloride end-groups could be fully converted into azide end-groups (Fig. 3 & Figure S15, respectively) using DMF as a solvent and at 70 °C. These results imply that irrespectively of the intermediate, an azidated product can be obtained that is applicable in click chemistry. Thus, one could still obtain the desired azidated product via a different intermediate pathway.

4. Conclusions

In this study, we show the solvent dependent conversion of hydroxyl end groups of PCL into either a tosylate ester or chloride. In material processing or polymer synthesis, often non polar solvents such as DCM or $CHCl_3$ are preferred due to their relatively high evaporation rates. However, some polymers intended for biological applications such as poly(ester-urethane)ureas are only soluble in polar aprotic solvents such as DMF. This study provides a methodology to activate the hydroxyl groups via chlorination and subsequent nucleophilic substitution, and highlights the ability of tosylation conditions to yield chlorinated products. This synthetic method unlocks potential strategies for end-group modification or preparation of polymer conjugates. For example, as shown in this study, azide groups can still be inserted onto the polymer suitable for performing click chemistry.

Data availability statement

The data that support the findings of this study are openly available in DataVerse at https://doi.org/10.34894/0D0JXE.

CRediT authorship contribution statement

Ivo A.O. Beeren: Methodology, Investigation, Validation, Formal analysis, Data curation, Visualization, Writing – original draft. **Pieter J. Dijkstra:** Validation, Formal analysis, Writing – original draft, Writing – review & editing, Supervision. **Philippe Massonnet:** Investigation, Formal analysis. **Sandra Camarero-Espinosa:** Conceptualization, Formal analysis, Supervision. **Matthew B. Baker:** Conceptualization, Methodology, Validation, Formal analysis, Writing – review & editing, Supervision. **Lorenzo Moroni:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank the CORE IMS lab, Division of Imaging Mass Spectrometry at The Maastricht Multimodal Molecular Imaging Institute (M4i), for the ToF-SIMS experiments. We are also grateful to the European Research Council starting grant "Cell Hybridge" for financial support under the Horizon2020 framework program (Grant #637308).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eurpolymj.2022.111576.

References

[1] D.A. Tirrell, R. Langer, Materials for Biology and Medicine, Nature 428 (2012) 25, https://doi.org/10.1038/nature02388.
[2] F.J. O'Brien, Biomaterials & scaffolds for tissue engineering, Mater. Today 14 (2011) 88–95, https://doi.org/10.1016/S1369-7021(11)70058-X.
[3] M.P. Lutolf, J.A. Hubbell, Synthetic biomaterials as instructive extracellular microenvironments for morphogenesis in tissue engineering, Nat. Biotechnol. 23 (2005) 47–55, https://doi.org/10.1038/nbt1055.
[4] L.S. Nair, C.T. Laurencin, Biodegradable polymers as biomaterials, Prog. Polym. Sci. 32 (2007) 762–798, https://doi.org/10.1016/j.progpolymsci.2007.05.017.
[5] M. Labet, W. Thielemans, Synthesis of polycaprolactone: A review, Chem. Soc. Rev. 38 (2009) 3484–3504, https://doi.org/10.1039/b820162p.
[6] M.A. Woodruff, D.W. Hutmacher, The return of a forgotten polymer - Polycaprolactone in the 21st century, Prog. Polym. Sci. 35 (2010) 1217–1256, https://doi.org/10.1016/j.progpolymsci.2010.04.002.
[7] T. Saito, Y. Aizawa, K. Tajima, T. Isono, T. Satoh, Organophosphate-catalyzed bulk ring-opening polymerization as an environmentally benign route leading to block copolyesters, end-functionalized polyesters, and polyester-based polyurethane, Polym. Chem. 6 (2015) 4374–4384, https://doi.org/10.1039/c5py00533g.
[8] M. Schappacher, A. Soum, S.M. Guillaume, Synthesis of polyester-polypeptide diblock and triblock copolymers using amino poly(ε-caprolactone) macroinitiators, Biomacromolecules 7 (2006) 1373–1379, https://doi.org/10.1021/bm060008m.
[9] T. Kuhnt, R. Marroquín García, S. Camarero-Espinosa, A. Dias, A.T. Ten Cate, C. A. Van Blitterswijk, L. Moroni, M.B. Baker, Poly(caprolactone-co-trimethylenecarbonate) urethane acrylate resins for digital light processing of bioresorbable tissue engineering implants, Biomater. Sci. 7 (2019) 4984–4989, https://doi.org/10.1039/c9bm01042d.
[10] Y. Pan, S. Neupane, J. Farmakes, B. Liu, W. Sun, Z. Yang, Spin-labeling of polymeric micelles and application in probing micelle swelling using EPR spectroscopy, J. Polym. Sci. Part B Polym. Phys. 55 (2017) 1770–1782, https://doi.org/10.1002/polb.24426.
[11] W. Zhang, T. Ji, S. Lyon, M. Mehta, Y. Zheng, X. Deng, A. Liu, A. Shagan, B. Mizrahi, D.S. Kohane, Functionalized Multiarmed Polycaprolactones as Biocompatible Tissue Adhesives, ACS Appl. Mater. Interfaces 12 (2020) 17314–17320, https://doi.org/10.1021/acsami.0c03478.
[12] Y. Zou, L. Zhang, L. Yang, F. Zhu, M. Ding, F. Lin, Z. Wang, Y. Li, "Click" chemistry in polymeric scaffolds: Bioactive materials for tissue engineering, J. Control. Release 273 (2018) 160–179, https://doi.org/10.1016/j.jconrel.2018.01.023.
[13] A. Lancuški, S. Fort, F. Bossard, Electrospun azido-PCL nanofibers for enhanced surface functionalization by click chemistry, ACS Appl. Mater. Interfaces 4 (2012) 6499–6504, https://doi.org/10.1021/am301458y.
[14] M.J. Fernández, M.D. Fernández, M. Cobos, Synthesis, characterization and properties of telechelic hybrid biodegradable polymers containing polyhedral oligomeric silsesquioxane (POSS), RSC Adv. 4 (2014) 21435–21449, https://doi.org/10.1039/c4ra02172j.
[15] R. Sedghi, A. Shaabani, N. Sayyari, Electrospun triazole-based chitosan nanofibers as a novel scaffolds for bone tissue repair and regeneration, Carbohydr. Polym. 230 (2020) 115707, https://doi.org/10.1016/j.carbpol.2019.115707.
[16] B.Z. Hailemeskel, W.-H. Hsu, K.D. Addisu, A.T. Andrgie, H.-Y. Chou, J.-Y. Lai, H.-C. Tsai, Diselenide linkage containing triblock copolymer nanoparticles based on Bi (methoxyl poly(ethylene glycol))-poly(ε-carprolactone): Selective intracellular drug delivery in cancer cells, Mater. Sci. Eng. C 103 (2019), 109803, https://doi.org/10.1016/j.msec.2019.109803.
[17] S. Camarero-Espinosa, I. Stefani, J. Cooper-White, Hierarchical "as-Electrospun" Self-Assembled Fibrous Scaffolds Deconvolute Impacts of Chemically Defined Extracellular Matrix- and Cell Adhesion-Type Interactions on Stem Cell Haptokinesis, ACS Macro Lett. 6 (2017) 1420–1425, https://doi.org/10.1021/acsmacrolett.7b00834.
[18] B.S. Min, Y.C. Park, J.C. Yoo, Triazole crosslinked polymer formed by the cycloaddition of azide end-capped polymer with dipolarophile acetylenic curative, Macromol. Res. 20 (2012) 429–432, https://doi.org/10.1007/s13233-012-0033-2.
[19] S. Matsumura, A.R. Hlil, C. Lepiller, J. Gaudet, D. Guay, Z. Shi, S. Holdcroft, A. S. Hay, Stability and Utility of Pyridyl Disulfide Functionality in RAFT and Conventional Radical Polymerizations, J. Polym. Sci. Part A Polym. Chem. 46 (2008) 7207–7224, https://doi.org/10.1002/pola.
[20] R. Ding, Y. He, X. Wang, J. Xu, Y. Chen, M. Feng, C. Qi, Treatment of alcohols with tosyl chloride does not always lead to the formation of tosylates, Molecules 16 (2011) 5665–5673, https://doi.org/10.3390/molecules16075665.
[21] B. Pásztói, T.M. Trötschler, Á. Szabó, G. Szarka, B. Kerscher, R. Mülhaupt, B. Iván, Synthesis of Tosyl- and Nosyl-Ended Polyisobutylenes with High Extent of Functionalities: The Effect of Reaction Conditions, Polym. 12 (11) (2020) 2504, https://doi.org/10.3390/polym12112504.
[22] H. Moghanian, M. Shabanian, H. Jafari, Microwave-assisted efficient synthesis of azlactone derivatives using TsCl/DMF under solvent-free conditions, Comptes Rendus Chim. 15 (2012) 346–349, https://doi.org/10.1016/j.crci.2011.11.011.
[23] J.D. Albright, E. Benz, A.E. Lanzilotti, L. Goldman, Reactions of sulphonyl chloride–NN-dimethylformamide complexes, Chem. Commun. (London). 0 (17) (1965) 413–414.