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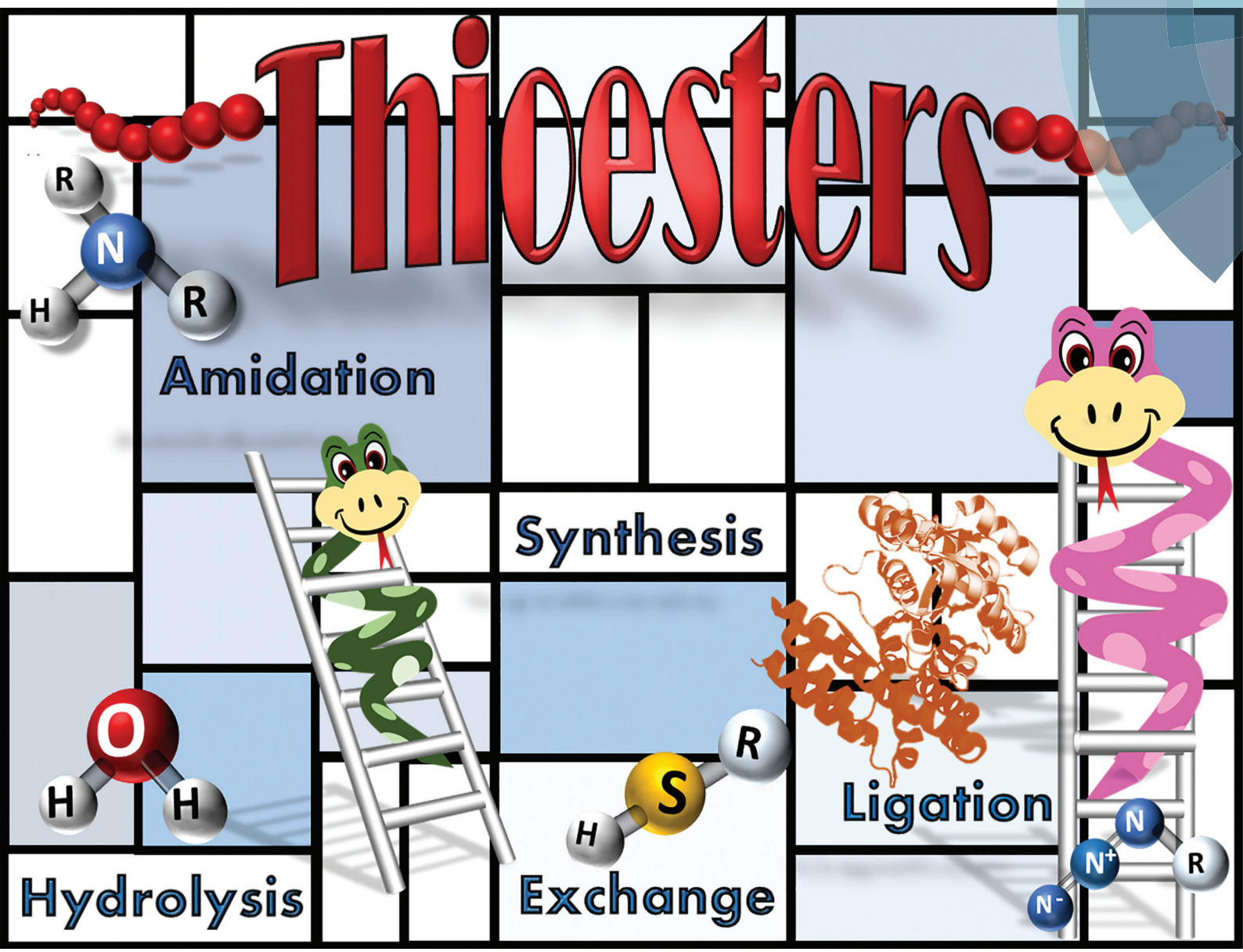

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C. Remzi Becer *et al.*
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Thioester functional polymers

Suzan Aksakal, Resat Aksakal and C. Remzi Becer *

Inspired by the uniqueness and ubiquity of thioesters in nature, much attention has been paid to thioester functionalized materials, yielding applications ranging from responsive polymers to bioconjugates and (bio)degradable polymers. This review focuses on various applications of thioesters in polymer science, covering the synthesis and polymerisation of thioester containing monomers, thioester generation *via* polymerization processes or the presence of thioesters in chain ends, such as initiators or chain transfer agents. Examples of post-polymerization modifications with various compounds (*e.g.* thiols, azides, amines and cysteine containing peptides) to enable modification *via* pathways such as ligation, amidation or exchange reactions are also presented.

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1. Introduction

Sulfur-containing polymers represent an attractive tool for the next generation of functional materials. These materials have already attracted significant interest and led to multifaceted applications, including the construction of thiolated polymers with high mucoadhesive ability,[1] optical materials with higher refractive indices,[2] robust self-assembled monolayers[3–5] (SAMs) including gold nanoparticles[6] (AuNP) for imaging and bioconjugates of polymers and thiol-containing biomolecules.[7] However, the use of free thiols in polymerization reactions requires protected thiols due to their low stability and high reactivity compared to esters,[8–10] which can be called their hydroxy counterparts.[11] Nevertheless, there are many straightforward ways to introduce thiols in a protected state into a polymer[12,13] and numerous studies on various designs, consisting of a source of thiols in acrylic, vinyl or heterocyclic systems (*e.g.* thiazole,[14] thiophene[15,16] or thiolactones[17–19]) have been reported to date. The latter one is still of great interest as thiolactones have been demonstrated to be a versatile and unique structural motif in the construction of sequence defined oligomeric and polymeric materials.[17–19]

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2. Thioesters: structural features, synthesis and reactions

The thioester bond is a common functional group in biology as it displays a wealth of attractive properties and exists as a

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fundamental key component or intermediate in biological systems. In contrast to thioesters, esters are stabilized by a resonance structure where the lone pair of the singly bonded oxygen atom is delocalized into the carbonyl structure This is manifested in a partial double bond character and somewhat hindered rotation around the C–O single bond.[20] For thioesters a similar resonance structure can be drawn; however this structure does not greatly contribute to the stability of thioesters since the orbital overlap of the 3p orbital of the sulfur atom and the 2p orbital of the oxygen atom is poor. As a consequence of this, thioesters are a lot more electrophilic and therefore susceptible to nucleophilic attacks.[21] This makes them excellent acyl transfer reagents. As mentioned, nature exploits this property as can be seen with acetyl-CoA, which serves as an acetylating reagent in the metabolism of cellular components (*e.g.* peptides, fatty acids, sterols, terpenes, lipids and porphyrins).[22] In the presence of a suitable nucleophile, an ester is formed, whilst a thiolate anion in the form of $CoAS^-$ is released.[23] The aforementioned factors make the more reactive carbonyl in thioesters more favourable against oxoesters for the linkage in CoA.

There are numerous known methodologies for the synthesis of thioesters. Esterification reactions of an acyl compound (*e.g.* carboxylic acid,[24–26] acid anhydride[27,28] or acid chloride[29–32]) with a thiol or disulfide conducted in the presence of a base is a convenient and a standard protocol for the synthesis of these organosulfur compounds. Aldehydes have also been widely explored for the synthesis of thioesters.[28,33–38] An alternative methodology is the acylation of thiols using various catalysts (*e.g.* triflates, CsF, NBS, zeolites, rongalite, Lewis acids, zinc, and ionic liquids).[39] An inexpensive and efficient method for the synthesis of thioesters by acid-catalyzed *S*-acetylation of a wide range of aromatic and aliphatic thiols with isopropenyl acetate has also been reported recently.[40] Additionally, one-step conversion of the thioester group into other functional groups is very attractive in organic synthesis. A particular significant conversion is the transformation of thioesters into amides. Reactions of thioesters with primary and secondary amines, azides[41–43] or cysteine-containing structures[44,45] result in an amide functionality in the molecule, whereas a reaction with a thiol in a thiol–thioester exchange reaction[46,47] forms a new thioester bond. Numerous studies have elaborated their reactivity in contrast to oxoester analogues and have proven a 100-fold faster reaction rate with amines.[21] The mechanism and progress of this amidation process with mono- and bifunctional amines on a dithioester have been described in 1990,[48] catalysed with arylthiols,[49] and outlined in more detail by Castro for thioesters and thiocarbonates.[50] Thioesters can undergo both acid and base-catalyzed hydrolysis.[22] Treatment with triethylsilane and a catalytic amount of Pd/C can lead to the respective aldehyde,[51,52] whereas treatment with an organozinc compound furnishes ketones.[51] Very recently, the transformation of thioesters to their thioethers has been reported on arylthioesters *via* Pd- and Ni-catalyzed decarbonylative conversion, under base and thiol free conditions.[53] In an attempt to develop new rigid-rod polymers, the thia-Michael reaction was employed between molecular rods, bearing terminal thiols and bismaleimides.[54] Interestingly, cyclic oligomers were mainly obtained contrary to the expected linear polymers, which was attributed to the folded conformation of the building blocks.

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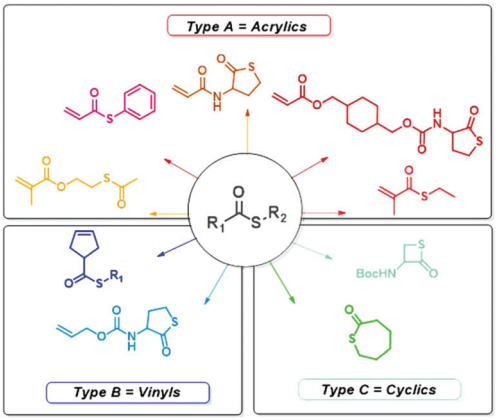
3. Preparation of thioester containing structures

In the past few years, manifold thioesters have become widely available and have drawn widespread attention in polymer science. For example, the aminolysis of dithiocarbonates, dithiocarbamates and thioesters has been evaluated in atom transfer radical polymerization (ATRP) and reversible addition fragmentation chain transfer (RAFT) polymerization. Interestingly, the dithiocarbamate group could not be cleaved under mild conditions and led to side-reactions during the radical polymerization of styrene and (meth)acrylates. Thiocarbonyl and thioesters did not induce any side-reactions and could be cleaved under mild conditions. Moreover, up to eight times higher reactivity towards amines of a dialkyl xanthate in comparison with an alkyl thioacetate was reported.[11]

Additionally, a 100-fold higher reactivity towards thiolate nucleophiles and at least a 2000-fold higher reactivity towards carbanion nucleophiles have been observed in experiments and computational studies, attributed mainly to the lower electron delocalization in thioesters compared to oxoesters.[21]

One approach to incorporate a thioester functionality into a polymer describes the direct utilization of thioester containing



Scheme 1 Categorization of thioester containing monomers.

monomers in the polymerization process and several successful protocols have been reported to date (Scheme 1).

Among these in particular are three main classes, each of which corresponds to the nature of the monomeric unit, namely acrylics, vinyls, and cyclic monomers. Type A can be classified as acrylics – for instance thio(meth)acrylates, thioester containing (meth)acrylates and (meth)acrylamides. Type B monomers include olefins, such as thioester functionalized cyclopentene and *N*-(allyloxy) carbonyl-homocysteine thiolactone. Cyclic monomers, which are polymerized by diverse ring-opening polymerization techniques (*e.g.* thiolactones), fall into Type C.

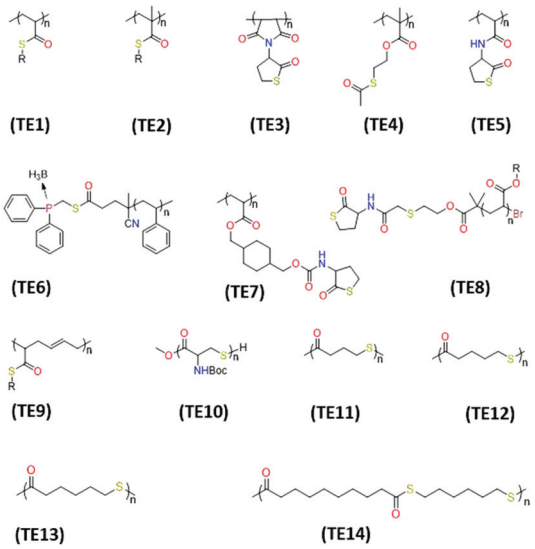
Polymers that contain thioester functionalities are prepared *via* different routes as listed in Table 1.

The polymerization techniques, concerning monomers with pendant thioester groups, range from free radical polymerization (FRP) to various reversible deactivation radical polymerization (RDRP) techniques, such as copper-mediated RDRP (Cu-RDRP) and RAFT. Furthermore, thioesters can not only be incorporated in the form of a thioester containing monomer, but also formed through a polymerization process such as β-thioesters *via* reactions of thiols with either an acrylate in a thiol–ene process or in an acid condensation reaction. Thioesters can also be found in the polymer chain end, integrated as thioester functionalized initiators or Chain Transfer Agents (CTAs). Moreover, cyclic thioesters (*e.g.* thiolactones with different numbers of carbon atoms in the heterocycle) exhibit thioesters distributed along the polymer chain.

3.1 Access to thioester containing polymers: thioesters in the monomer side chain

Based on the reports in the literature, the introduction of a thioester group into a polymerizable unit from Type A can be further divided into three groups, depending on the nature of the thioester. The organosulfur compound can be incorporated as a thioacrylic derivative in the form of thio(meth)acrylates, (meth)acrylates or (meth)acrylamides. One very distinct factor is the local occurrence of the thioester, as it can be either somewhere in the sidechain as in a (meth)acrylate or

Table 1 Thioester containing monomers, initiators, and CTAs used in various polymerization techniques



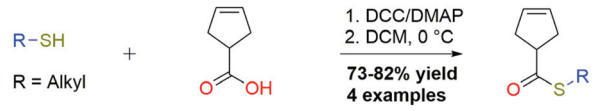
Tech.	Type	Name	Code	Ref.
FRP	Mon	Thioacrylates (TA)	**TE1**	55
		Thiomethacrylates (TMA)	**TE2**	56–58
		Maleimide thiolactone (MITla)	**TE3**	59
RAFT	Mon	Thioacrylates (TA)	**TE1**	60
		2-(Acetylthio)ethyl methacrylate	**TE4**	61
		N-Thiolactone acrylamide (TLAm)	**TE5**	62 and 63
		Maleimide thiolactone (MITla)	**TE3**	59
	CTA	Thioester trithiocarbonate	**TE6**	43
Cu-RDRP	Mon	Thiolactone acrylate (TLA)	**TE7**	64
	Ini	Thioester ATRP initiator	**TE8**	65
ROMP	Mon	Cp-Thioesters	**TE9**	66
ROP	Mon	β-Thiolactone	**TE10**	67
		γ-Thiolactone	**TE11**	68
		δ-Thiolactone	**TE12**	68
		ε-Thiolactone	**TE13**	68–70
eROP	Mon	ε-Thiolactone	**TE13**	69
		Cyclic dithioester	**TE14**	70

Mon: Monomer; Ini: Initiator; CTA: Chain transfer agent.

(meth)acrylamide based structure or it can be directly connected to the polymerizable unit as a thio(meth)acrylate. The latter is still at a lower level of esteem than other acrylics, but reports in the past have shown promising features. For this class of monomers, sporadic entries to the literature concerning the (meth)acrylic thioester counterpart to (meth)acrylates have appeared in 1956. In these initial reports, Marvel *et al.* showed the synthesis of a range of alkyl thioacrylates by the reaction of α,β-dibromopropionyl chloride with alkylthiols.[55]

In 1977, Hadjichristidis *et al.* reported the preparation of thiomethacrylates by treating methacryloyl chloride with respective thiols in aqueous sodium hydroxide solution with successive distillation.[56,57]

More recently, Becer *et al.* described a modified synthesis for thioacrylates to overcome the Michael addition of used thiols with a double bond of the (meth)acryloylchloride. For this purpose, a four-step protocol *via* thioesterification of alkyl- and arylthiols with either bromoacetic acid or bromoacetyl



Scheme 2 Synthesis of thioester functionalized cyclopentene monomer. Adapted from ref. 66.

bromide followed by the subsequent addition of triphenylphosphine to yield the phosphonium salt was used. Deprotonation with potassium carbonate gave the corresponding phosphonium ylide.

Reacting the ylide with paraformaldehyde gave the respective thioacrylates *via* the Wittig reaction.[60]

Another elegant and more recent example presents a cyclic monomer with a thioester as a pendant group, such as cyclopent-3-enecarbothioate (Scheme 2). In a one-step synthesis, monomers were obtained by simple thioesterification of 3-cyclopentene-1-carboxylic acid with four alkythiols of different lengths. Differential scanning calorimetry (DSC) analysis highlighted higher glass transition temperatures (T_g) and melting temperatures (T_m) for thioester containing polymers than those for the structurally identical counterparts with ester pendants.[66]

Thermogravimetric analysis (TGA) elucidated slightly lower thermal stability than that of their counterparts without sulfur.[66,71]

In addition to thiols as starting materials, thiolactones (TLs) have also been proven to be ideal precursors for thioester containing monomers.

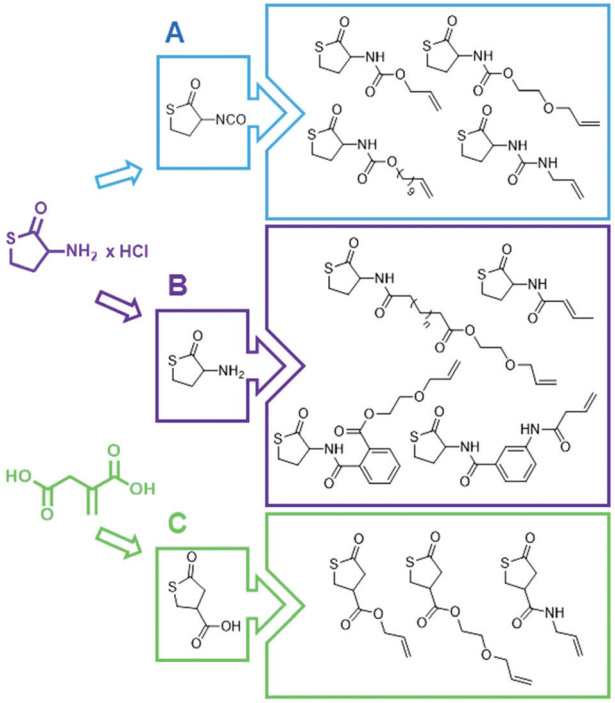
Among these, in particular, vinylic thiolactones are the most established building blocks. A large set of thiolactone based structures, either derived from itaconic acid or homocysteine thiolactone, have been reported in multi-gram amounts (Scheme 3).[72]

Reactions of thiolactone isocyanate with different alcohols yielded thiolactone carbamides. The same thiolactone can be functionalized with allylamine and result in a thiolactone urea (Route A in Scheme 3).

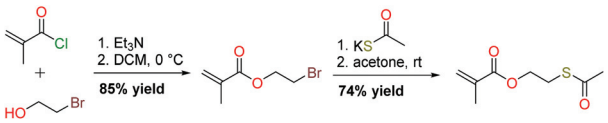
Homocysteine thiolactone reacted with either acids or cyclic anhydrides with different alcohols yielding thiolactone amides. Bisthiolactones derived from difunctional acid chlorides were obtained (Route B in Scheme 3) and the esterification of thioparaconic acid with alcohols led to a set of thiolactone esters. Additionally, a thiolactone amide could be synthesised from the same starting material, but *via* a thioparaconic acid chloride and allylamine (Route C in Scheme 3).

On the other hand, a prominent example of a thioester bearing methacrylate is 2-(acetylthio)ethyl methacrylate (AcSEMA), resulting from a two-step synthesis.[61,73] For this, methacryloyl chloride was reacted with 2-bromoethanol under basic conditions. The resulting 2-bromoethyl methacrylate was further reacted with potassium thioacetate to yield the thioester containing methacrylate (Scheme 4).[61]

Möller and coworkers reported the synthesis of thiol functionalized poly(meth)acrylates, starting from modified MA or



Scheme 3 Overview of the chemical synthesis of thiolactone derived vinyl monomers in ref. 72.



Scheme 4 Synthesis of the AcSEMA monomer. Adapted from ref. 61.

MMA monomers by enzymatic transacylation with a lipase (Novozyme 435, a lipase from *C. antarctica*) with various alcohols at ambient temperatures. After the removal of the enzyme from the reaction mixture, polymerization was carried out in bulk; utilizing AIBN as an initiator in FRP gave polymers with weights up to 40 kDa.[74]

The incorporation of the thioester group into a specific position on a polymer chain proves to be easy and useful when further functionalisation is desired. In general, not only the thioester, but any functional group, if present, is typically found along the backbone, the chain end or in the monomeric repeating unit. By incorporating the thioester function into the monomer, it is possible to tailor the polymer by varying the targeted DP or by introducing comonomers to obtain random or block copolymers. Hence, this methodology allows further functionalisation of thioesters at specific points along the polymer, which could lead to changes in physical, thermal and structural properties.

In the 1980s, Hadjichristidis *et al.* reported the synthesis of a new class of an acrylic monomer, namely thiomethacrylate, in which the methacrylic ester oxygen was replaced with a sulfur atom. A series of phenylic polymethacrylates and poly-

thiomethacrylates were prepared at different chain lengths *via* free radical polymerisation, using azobisisobutyronitrile (AIBN) at 50 °C with relatively good control (PDI < 1.4). The chain flexibility of the polymers prepared was investigated from their thermal properties. Generally, the substituents in poly(phenyl thiomethacrylate) were found to be more flexible (higher flexibility factor σ) when compared to poly(phenyl methacrylate), which was attributed to the increased length of the less polar bond between sulfur and carbon, caused by the substitution of the oxygen atom by a sulfur atom.[56,57]

Inspired by this, Becer *et al*. recently reported the synthesis and controlled radical polymerization of a range of thioacrylates *via* RAFT polymerization to obtain excellent control over the polymerisation (PDI: 1.11–1.19) with quantitative conversions (Scheme 5).[60]

For example, ethyl thioacrylate (ETA) was found to polymerize at a similar rate compared to its oxoester acrylic counterpart ethyl acrylate (EA), whereas polydispersities remained low and the observed molecular weight was close to the theoretical value. It was shown that this new monomer class can be polymerised *via* more modern controlled radical polymerisation techniques, allowing better control over the architecture. Finally, both the water contact angle and the T_g for P(ETA) were observed to be significantly higher than those for P(EA), which provides evidence that thioacrylates give access to new materials with different properties, which could help improve our understanding of the material–property relationship.[60]

Similarly, Song *et al*. have reported the polymerisation of a range of thioester functionalised cyclopentenes *via* ring opening metathesis polymerisation (ROMP) with high conversions, while retaining control over dispersity.[66] A comparison of the thermal properties between the oxoester containing polymers and the reported thioester containing polymers revealed a similar trend as above, in which the latter displayed a higher T_g.

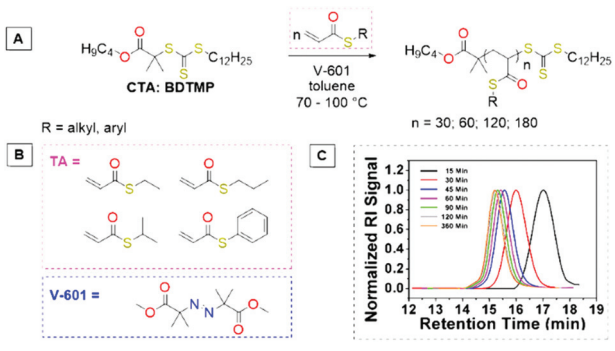
Another method of incorporating a thioester into the polymer in the form of a thioacetate monomer was shown by Boyer *et al*. In this case, 2-(acetylthio)ethyl methacrylate (AcSEMA) was copolymerised with oligo(ethylene glycol) methyl ether methacrylate (OEGMA) *via* RAFT at different molar ratios and thoroughly characterised.[61] The obtained polymers were hydrolysed to yield a free thiol, allowing the formation of gold nanoclusters. Interestingly, random copolymer stabilised gold nanoclusters displayed a higher emission intensity in comparison with block copolymer stabilised gold nanoclusters.

Du Prez *et al*. generated a large library of thiolactone containing monomers, which found application in a wide range of polymerization techniques. For example, a radical amine–thiol–ene polymerization has been performed in a one pot reaction *via* nucleophilic ring opening of a thiolactone with an amine (aminolysis), followed by a radical thiol–ene conjugation. Typically, a free thiol group was generated *in situ* after aminolysis, which reacted with a double bond already present in the same reactor. Using this protocol, a thiolactone bearing a double bond (*i.e. N*-(allyloxy)carbonylhomocysteine thiolactone) and various amines were employed to obtain linear polymers and networks by a radical photopolymerization process.[17] Radical thiol–ene polymerization was performed on *N*-(allyloxy)carbonylhomocysteine thiolactone and 10-undecenoyl thiolactonamide after aminolysis.[17] The same group used a similar strategy to polymerise a thiolactone containing acrylate *via* Cu-RDRP LRP to form the backbone of a graft copolymer. Furthermore, propylamine and poly(ethylene glycol) acrylate were added to react with the thiolactone ring, forming brush structures.[64]

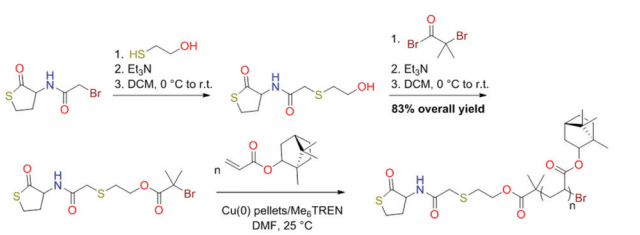
3.2 Access to thioester containing polymers: thioester in the chain end

Instead of having a number of thioesters incorporated, initiators for CRP can be functionalized to provide a thioester functionality at the chain end of a polymer. A TL-based initiator used in Cu(0) mediated polymerization of isobornyl acrylate was evaluated as an efficient ATRP initiator, while the presence of the thioester end group of the polymer was confirmed by ^{1}H NMR (Scheme 6).[65]

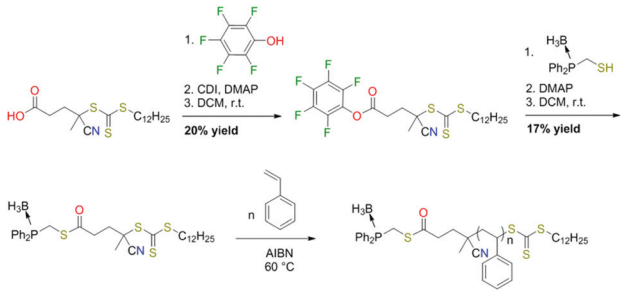
In a similar manner, the synthesis of functionalised cyclic polymers *via* RAFT utilizing a thiolactone based CTA was shown. After the aminolysis on the thioester functionality, the free thiol was rearranged with the ω-chain end under high dilution, which afforded the targeted cyclic polymers.[75]



Scheme 5 (A) Conditions for homopolymerization of thioacrylates *via* RAFT, (B) structure of monomers used in this work, (C) GPC traces of poly(isopropyl thioacrylate) with DP = 60 in toluene at 70 °C and [I] = 0.1 mol%. Adapted from ref. 60.



Scheme 6 One-pot, two-step synthesis of a thiolactone containing initiator and Cu(0)-mediated polymerization of isobornyl acrylate *via* a thiolactone-initiator. Adapted from ref. 65.



Scheme 7 Two step preparation of thioester containing CTA and polymerization of styrene. Adapted from ref. 43.

In another approach, a CTA was tethered to the polymer end group and was used for the homopolymerization of styrene with further modification. Voit *et al.* reported a protocol for the esterification of a carboxylic-acid containing CTA with pentafluorophenyl and the subsequent reaction with thiolphosphine. The obtained CTA was utilized for the synthesis of polystyrene *via* RAFT (Scheme 7).[43]

3.3 Access to thioester containing polymers *via* the polymerization process

As stated above, polythioesters can be described as polymers containing thioester moieties along the backbone. The synthesis of a polythioester was first reported by Kotch as early as 1951, where a range of dibasic acid chlorides were reacted with aliphatic dithiols, such as the reaction between adipoyl chloride and hexane-1,6-dithiol.[76] The obtained polythioesters were found to be low in molecular weight and displayed evidence of some crystallinity in their X-ray patterns, with their melting points being higher compared to their oxygen analogues. Similarly, polycondensations of methyl mercaptoacetate at different lengths were also described.[77] Later, the enzyme catalysed polycondensation of hexane-1,6-dithiol with a range of diesters was demonstrated using a lipase (Novozyme 435), yielding low molecular weight polythioesters with 75–90% yields (M_n: 3700–6000 g mol^{-1}, PDI: 1.7–2.0).[78]

Higher molecular weights could also be obtained when aromatic groups were included in the backbone. For example, Kowalewska *et al.* showed the synthesis of an aromatic polythioester by interfacial polycondensation of 1,4-di(mercaptomethy1)-tetramethylbenzene phthaloyl, isophthaloyl and terephthaloyl chloride, in which the aqueous to organic solvent ratio as well as the type of organic phase and the molar ratio of reagents were investigated, in order to determine the optimal reaction conditions to allow high conversion.[79]

Another route to polythioesters is ring-opening-polymerization (ROP).[80] Further experiments confirmed the same trend for higher melting points compared to the corresponding polyesters. Polymers were prepared by anionic ROP of ε-thiocaprolactone for the first time, initiated with potassium *tert*-butoxide.[81] An extended study by the same group investigated the effect of the number of carbon atoms in the thiolactone ring and the reactivity of the thiolactones towards polymerization dependent on the ring size. Polymerization occurred for four-, six- and seven-membered thiolactones, whereas the five-membered thiolactone could not be polymerized. While this trend could also be observed for lactones,[68] γ-thiolactones have been shown to copolymerize in the presence of trimethylene carbonate. Although NMR and MALDI ToF MS analysis proved its incorporation, the percentage of thiolactone found was limited to only 9 mol%.[82]

ε-Thiocaprolactone has also been used as an initiator for the anionic polymerization of ε-caprolactame, and a higher polymerization rate with initiation by the sulfur compound compared to the oxygen analogue was observed.[83]

Moreover, different metal alkoxides (Sn, Cd, Mn, *etc.*) as catalysts and thiol or alcohol initiators have been used for the polymerization of cyclic thioesters.[84,85] Lipase has also been employed for an alternative "greener" enzyme-catalyzed ROP (eROP) and generated high molecular weight polymers.[69,70] Polythioesters with higher molecular weights (M_n > 50 000 g mol^{-1}, PDI 2.3) could be prepared by enzymatic ring opening polymerization of cyclic polythioesters at 120 °C for 2 days.[86]

Using various dithiols and diacrylates, Junkers *et al.* showed the design and synthesis of biodegradable poly (β-thioesters) *via* step-growth polymerization.[87] The obtained polymers were found to be semi-crystalline materials with low T_g values due to the incorporation of thiols. Similarly, when more than difunctional thiols and acrylates were used, poly (β-thioesters) containing networks with broad molecular weight distributions were synthesised *via* thiol–ene Michael addition.[88]

In the same manner, Michael addition was employed to obtain well-defined amphiphilic triblock copolymers of poly (β-thioesters), containing an azo linkage in the middle of the chain. TEM images of these polymers showed their formation into micelles, which could be thermally degraded upon heating to 95 °C.[89] Long *et al.*, on the other hand, made use of the thia-Michael addition chemoselectivity towards an acrylate over a methacrylate to synthesise segmented poly(β-thioesters) in a one-pot approach.[90] Bis–thiol compounds were initially reacted with diacrylates to obtain thiol terminated soft segment oligomers, which were further reacted with oxamide containing dimethacrylates as the hard segments. Nishikubo *et al.* developed the synthesis of polythioethers by the acyl transfer polymerization of thiiranes with thioesters.[91] A similar approach was used when cyclic dithioesters were employed, in order to increase the ring size to yield cyclic(thioester-*alt*-thioether).[92]

3.4 Access to thioester-bearing structures *via* a post-modification approach

The second route evolves thiols, which form thioesters during polymerization. These include mainly β-thioester from thiol–ene reactions, ring opening with a thiol or exchange reactions. One way to introduce thioesters into a polymer is by using thioacetic acid. For example, various dithiols and glycidyl propargyl ether were used in an attempt to obtain polymers *via* thiol–yne chemistry.[93] In further post-polymerization

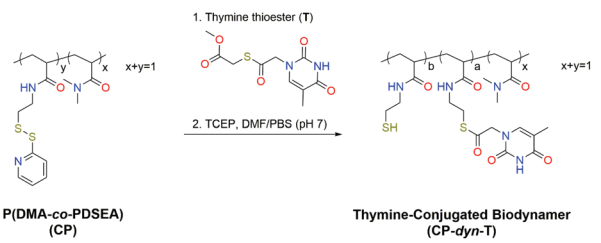
functionalization, the epoxide in the side chain was ring-opened using thioacetic acid in the presence of triethyl amine to form thioesters in the side chain. Similarly, a highly efficient synthesis pathway to polysiloxanes containing thiols as end or side groups was demonstrated, when vinyl end-functionalised polydimethylsiloxane or polymethyl-vinylsiloxanes were reacted with thioacetic acid.[94] This allowed the formation of thioesters along the side chain or at the chain ends, which were reduced to the corresponding thiols. Although relatively stable to aminolysis, it is well known that thioesters can readily undergo transesterification with thiol groups to form new thioesters. An elegant example of thioester incorporation *via* an exchange reaction was demonstrated by Liu *et al.* (Scheme 8).[95]

To construct dynamic nucleobase containing copolymers, dimethylacrylamide was copolymerised with pyridyldisulfide ethylacrylamide *via* RAFT. Thymine thioester reacted with the *in situ* generated pendant thiol group *via* a thiol thioester exchange reaction. This newly formed reversible thioester linkage was also shown to be glutathione responsive.

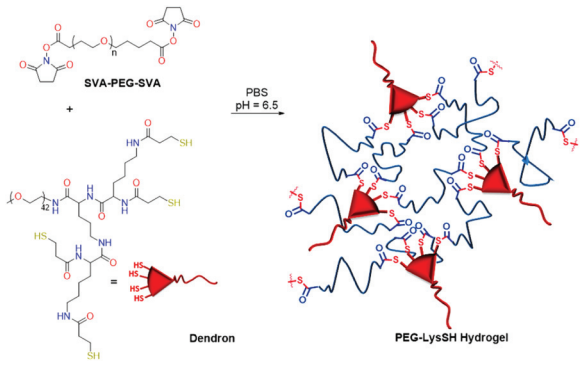
Reactions where new bonds are formed are the most used tools in synthesis and much progress has been made in the field of thioester containing reaction partners, yielding valuable products such as amides. For example, a thioester can lead to an *S*-acyl intermediate in the presence of cysteine, which can then spontaneously form amide bonds over an *S*- to *N*-acyl migration. This has been reported by Messersmith *et al.*, when initially a four arm poly(ethylene glycol) tetra amine was transformed into a tetra thioester.[96]

The native chemical ligation method was employed to covalently cross-link these macromonomers with a four-arm cysteine macromonomer into a hydrogel. It was also shown that no concurrent reactions to form hydrogels (*i.e.* disulfide bond, thioester exchange) took place during the NCL. Grinstaff *et al.* similarly obtained hydrogels when a poly(ethylene glycol) based peptide dendron possessing four terminal thiols was crosslinked over thioesters with poly(ethylene glycol disuccinimidyl valerate) (SVA-PEG-SVA) (Scheme 9).[97]

Unlike other examples, their dissolution by breaking of the thioester bond was shown for the first time. Among others, L-cysteine methyl ester was used to fully promote the dissolution of the hydrogel *via* a thiol–thioester exchange reaction within 12 minutes.

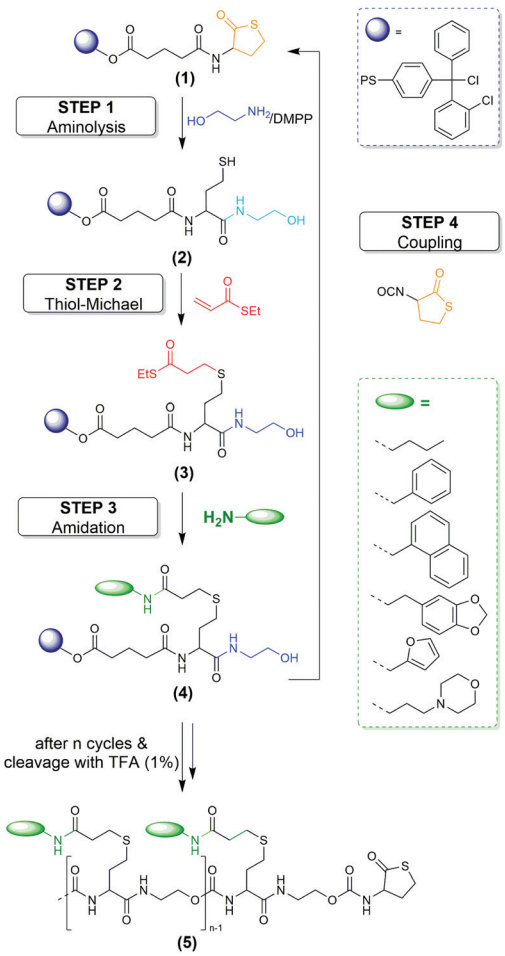


Scheme 8 Outline for the synthesis of thymine-conjugated biodynamer CP-dyn-T by RAFT polymerization *via* a thiol–thioester exchange reaction. Adapted from ref. 95.



Scheme 9 A crosslinked PEG-LysSH hydrogel formed by the reaction of a dendron and SVA-PEG-SVA by thiol–thioester exchange. Adapted from ref. 97.

In a collaborative work between Becer *et al.* and Du Prez *et al.*, a new synthetic protocol for the synthesis of sequence-defined oligomers was developed (Scheme 10). Using an iterative protocol based on thiolactone chemistry, a backbone was

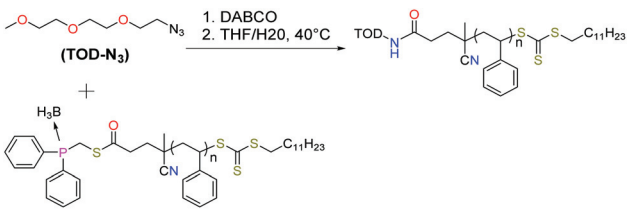


Scheme 10 Solid phase protocol with incorporated thioacrylates *via* thia-Michael reaction and subsequent amidation with various primary amines. Adapted from ref. 98.

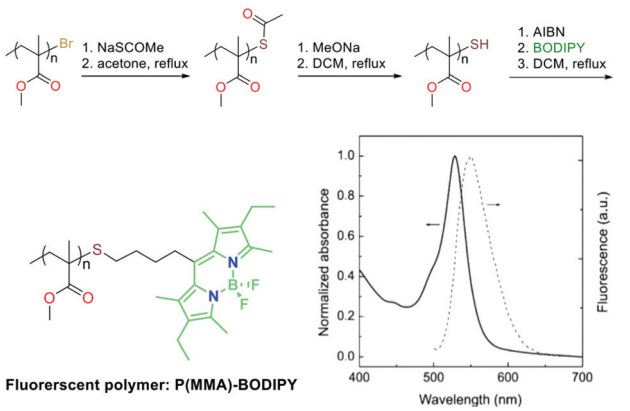
obtained. Test reactions between the free thiol and acrylamides to form a side chain were proven to be unsuccessful. By incorporating thioacrylates into the side chain over a thiol–ene chemistry however, it was possible to introduce different amines over an amidation reaction. This overcame the inefficiency of the reactions between the thiol and acrylamides, yielding sequences of high purity.[98]

As mentioned previously in Table 1, Voit *et al.* demonstrated the synthesis of poly(styrene) using a phosphine containing thioester based CTA, which was incorporated to allow further functionalisation with an azide *via* Staudinger ligation (Scheme 11). Hence, using 3,6,9-trioxodecyl azide, the end group modification was carried out on the thioester, yielding an amide bond on the chain end in an almost quantitative manner.[43]

Furthermore, París *et al.* prepared thioester containing polymers *via* modification on the polymer end of a typical bromine functionalized ATRP initiator.[99] In a one-step protocol, various polymethacrylates were synthesised and the bromine end group was transformed into the corresponding thioester by a substitution reaction with potassium thioacetate. By subsequent hydrolysis, a thiol terminated polymer was generated and could be further modified *via* a thiol–ene reaction with a fluorescent alkene (a synthetic alkene tethered to a 4,4-difluoro4-bora-3a,4a-diaza-*s*-indacene (BODIPY) fragment). By this, quantification of the quantitative thiol–ene process could be performed from UV-Vis measurements (Scheme 12).



Scheme 11 Staudinger ligation of thioester containing CTA with TOD-N_3. Adapted from ref. 43.



Scheme 12 Route for the formation of BODIPY end-functionalized P(MMA) *via* thio-ester end-functionalization and subsequent hydrolysis to a thiol end-functionalized polymer. "Click" reaction with BODIPY to yield a fluorescent polymer, whose absorption spectrum is displayed on the bottom right (solid lines) along with fluorescence (dashed lines) (ref. 99).

4. Conclusion and outlook

This review provides a brief overview of the literature on polymers containing thioesters to give the reader an initial understanding of interesting reports on their synthesis and their possible further functionalisation routes. Thioester groups are easily included into polymers, which can be from a thioester containing monomer or that can be generated during the polymerisation process. Moreover, reports reveal that the position of the thioester can be specific and easily incorporated into any region and position on the polymer, giving the materials tailored thermal or structural properties.

While there are reports on thioesters containing initiators for ATRP or chain transfer agents for RAFT that allow the positioning thereof mainly in the chain end, their inclusion in the side chain is best achieved *via* RAFT polymerization. On the other hand, ring opening-, polycondensation or thia-Michael polymerization techniques allow the incorporation of (α-, β-) thioesters along the backbone. In addition, thioesters allow reactions, which would otherwise lead to side reactions, when carried out for example in the presence of free thiols, which are rather reactive in radical and nucleophilic reactions (*e.g.* early termination of ATRP due to the thiobromo "click" reaction). The free thiol can then be generated *via* post-polymerization modification. The introduction of thioesters to change the flexibility of the backbone or the sidechain in contrast to its ester or amide analogues allows modification of the thermal properties, while retaining similarities in the core structure (*i.e.* control of T_g in poly(ethyl acrylate) *vs.* poly(ethyl thioacrylate)). Exchange reactions, amidation on the thioester and ligation reactions are main functionalisation pathways of thioesters and are well established in incorporating further functionalities. Many reports also contain the synthesis of complex structures, whereas the thioester bond can be transformed into different linkages. In contrast, current limitations and focus are mainly on finding novel uses that can be transformed into direct applications. Although thioesters on polymers are well understood, future research on the implementation of thioester chemistry in living systems to polymers could improve the understanding of polymer interactions with organisms (as biomacromolecule mimics, in polymer–peptide conjugates or drug delivery *etc.*), which could allow new strategies and chemistries to be developed.

Conflicts of interest

The authors declare no conflict of interest.

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References

1 C. E. Kast and A. Bernkop-Schnürch, *Biomaterials*, 2001, **22**, 2345–2352.
2 M. Tatsuhito, F. Yasuaki, Y. Masahiro, Y. Tetsuya and T. Tsuguo, *J. Appl. Polym. Sci.*, 2000, **76**, 45–49.
3 Y. Xue, X. Li, H. Li and W. Zhang, *Nat. Commun.*, 2014, **5**, 4348.
4 H. Häkkinen, *Nat. Chem.*, 2012, **4**, 443.
5 J. C. Love, L. A. Estroff, J. K. Kriebel, R. G. Nuzzo and G. M. Whitesides, *Chem. Rev.*, 2005, **105**, 1103–1170.
6 E. Boisselier and D. Astruc, *Chem. Soc. Rev.*, 2009, **38**, 1759–1782.
7 M. H. Stenzel, *ACS Macro Lett.*, 2013, **2**, 14–18.
8 I.-H. Lee, E. H. Discekici, S. L. Shankel, A. Anastasaki, J. Read de Alaniz, C. J. Hawker and D. J. Lunn, *Polym. Chem.*, 2017, **8**, 7188–7194.
9 G. Delaittre and L. Barner, *Polym. Chem.*, 2018, **9**, 2679–2684.
10 S. Agar, E. Baysak, G. Hizal, U. Tunca and H. Durmaz, *J. Polym. Sci., Part A: Polym. Chem.*, 2018, **56**, 1181–1198.
11 M. Le Neindre and R. Nicolay, *Polym. Chem.*, 2014, **5**, 4601–4611.
12 S. H. Yu, F. Ercole, N. A. Veldhuis, M. R. Whittaker, T. P. Davis and J. F. Quinn, *Polym. Chem.*, 2017, **8**, 6362–6367.
13 S. Iimura, K. Manabe and S. Kobayashi, *Org. Lett.*, 2003, **5**, 101–103.
14 K. Nakabayashi, A. Matsumura, Y. Abiko and H. Mori, *Macromolecules*, 2016, **49**(5), 1616–1629.
15 Y. Qiao, X. Yin and C. Tang, *Sci. China: Chem.*, 2015, **58**, 1641–1650.
16 C. Zhao, Y. Zhang, S. Pan, L. Rothberg and M.-K. Ng, *Macromolecules*, 2007, **40**, 1816–1823.
17 P. Espeel, F. Goethals and F. E. Du Prez, *J. Am. Chem. Soc.*, 2011, **133**, 1678–1681.
18 P. Espeel, L. L. G. Carrette, K. Bury, S. Capenberghs, J. C. Martins and F. E. Du Prez, *Angew. Chem., Int. Ed.*, 2013, **52**, 13261–13264.
19 S. Martens, J. Van den Begin, A. Madder, F. E. Du Prez and P. Espeel, *J. Am. Chem. Soc.*, 2016, **138**, 14182–14185.
20 J. F. Marlier, E. J. Fogle, R. L. Redman, A. D. Stillman, M. A. Denison and L. I. Robins, *J. Org. Chem.*, 2015, **80**, 1905–1908.
21 W. Yang and D. G. Drueckhammer, *J. Am. Chem. Soc.*, 2001, **123**, 11004–11009.
22 P. Bracher, P. Snyder, B. Bohall and G. Whitesides, *Origins Life Evol. Biospheres*, 2011, **41**, 399–412.
23 I. V. Koval, *Russ. J. Org. Chem.*, 2005, **41**, 631–648.
24 B. Neises and W. Steglich, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 522–524.
25 N. Iranpoor, H. Firouzabadi, D. Khalili and S. Motevalli, *J. Org. Chem.*, 2008, **73**, 4882–4887.
26 Y.-L. Chou, Y. Jhong, S. P. Swain and D.-R. Hou, *J. Org. Chem.*, 2017, **82**, 10201–10208.
27 A. Temperini, D. Annesi, L. Testaferri and M. Tiecco, *A simple acylation of thiols with anhydrides*, 2010.
28 A. T. Khan, L. H. Choudhury and S. Ghosh, *Eur. J. Org. Chem.*, 2005, 2782–2787.
29 M. Lakouraj, B. Movassagh and Z. Fadaei, *Convenient Synthesis of Thiol Esters from Acyl Chlorides and Disulfides Using Zn/AlCl 3*, 2002.
30 B. C. Ranu, S. S. Dey and A. Hajra, *Green Chem.*, 2003, **5**, 44–46.
31 B. Basu, S. Paul and A. K. Nanda, *Green Chem.*, 2010, **12**, 767–771.
32 P. Singh and R. K. Peddinti, *Harnessing the catalytic behaviour of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP): An expeditious synthesis of thioesters*, 2017.
33 K. A. Ogawa and A. J. Boydston, *Org. Lett.*, 2014, **16**, 1928–1931.
34 J. M. Yost, G. Zhou and D. M. Coltart, *Org. Lett.*, 2006, **8**, 1503–1506.
35 C. Junyong, S. U. Ryung, C. Supill and C. Y. Keun, *ChemCatChem*, 2016, **8**, 318–321.
36 C. He, X. Qian and P. Sun, *Org. Biomol. Chem.*, 2014, **12**, 6072–6075.
37 Y.-T. Huang, S.-Y. Lu, C.-L. Yi and C.-F. Lee, *J. Org. Chem.*, 2014, **79**, 4561–4568.
38 C.-L. Yi, Y.-T. Huang and C.-F. Lee, *Green Chem.*, 2013, **15**, 2476–2484.
39 M. Kazemi and L. Shiri, *Thioesters synthesis: Recent adventures in the esterification of thiols*, 2015.
40 K. Kuciński and G. Hreczycho, *Org. Process Res. Dev.*, 2018, **22**, 489–493.
41 H. Staudinger and J. Meyer, *Helv. Chim. Acta*, 1919, **2**, 635–646.
42 B. L. Nilsson, L. L. Kiessling and R. T. Raines, *Org. Lett.*, 2000, **2**, 1939–1941.
43 R. Pötzsch, S. Fleischmann, C. Tock, H. Komber and B. I. Voit, *Macromolecules*, 2011, **44**, 3260–3269.
44 E. C. B. Johnson and S. B. H. Kent, *J. Am. Chem. Soc.*, 2006, **128**, 6640–6646.
45 W. Chen, G. Qing-Xiang and F. Yao, *Chem. – Asian J.*, 2011, **6**, 1241–1251.
46 M. G. Woll and S. H. Gellman, *J. Am. Chem. Soc.*, 2004, **126**, 11172–11174.
47 X.-H. Sun, H.-Z. Yu, S.-Q. Pei and Z.-M. Dang, *Chin. Chem. Lett.*, 2015, **26**, 1259–1264.
48 M. Deletre and G. Levesque, *Macromolecules*, 1990, **23**, 4733–4741.
49 N. Stuhr-Hansen, N. Bork and K. Stromgaard, *Org. Biomol. Chem.*, 2014, **12**, 5745–5751.
50 E. Castro, *ChemInform Abstract: Kinetics and Mechanism of the Aminolysis of Thioesters and Thiocarbonates in Solution*, 2009.

51 H. Tokuyama, S. Yokoshima, T. Yamashita, L. Shao-Cheng, L. Leping and T. Fukuyama, *J. Braz. Chem. Soc.*, 1998, **9**, 381–387.
52 T. Fukuyama, S. C. Lin and L. Li, *J. Am. Chem. Soc.*, 1990, **112**, 7050–7051.
53 N. Ichiishi, C. A. Malapit, Ł. Woźniak and M. S. Sanford, *Org. Lett.*, 2018, **20**, 44–47.
54 P. Wessig, T. Schulze, A. Pfennig, S. M. Weidner, S. Prentzel and H. Schlaad, *Polym. Chem.*, 2017, **8**, 6879–6885.
55 C. S. Marvel, S. L. Jacobs, W. K. Taft and B. G. Labbe, *J. Polym. Sci.*, 1956, **19**, 59–72.
56 D. Kokkiaris, B. Touloupis and N. Hadjichristidis, *Polymer*, 1981, **22**, 63–66.
57 N. Hadjichristidis, *Macromolecules*, 1981, **14**, 128–130.
58 G. Sumrell, J. Briskin, G. E. Ham and C. H. Schramm, *J. Am. Chem. Soc.*, 1959, **81**, 4308–4310.
59 T. Rudolph, P. Espeel, F. E. Du Prez and F. H. Schacher, *Polym. Chem.*, 2015, **6**, 4240–4251.
60 Suzan Aksakal and C. Remzi Becer, *Polym. Chem.*, 2016, **7**, 7011–7018.
61 N. N. M. Adnan, S. Ahmad, R. P. Kuchel and C. Boyer, *Materials Chemistry Frontiers*, 2017, **1**, 80–90.
62 S. Reinicke, P. Espeel, M. M. Stamenovic and F. E. Du Prez, *Polym. Chem.*, 2014, **5**, 5461–5470.
63 S. Montolio, O. Zagorodko, R. Porcar, M. Isabel Burguete, S. V. Luis, H. Tenhu and E. Garcia-Verdugo, *Polym. Chem.*, 2017, **8**, 4789–4797.
64 F. Driessen, R. Herckens, P. Espeel and F. E. Du Prez, *Polym. Chem.*, 2016, **7**, 1632–1641.
65 F. Driessen, F. E. Du Prez and P. Espeel, *ACS Macro Lett.*, 2015, **4**, 616–619.
66 S. Song, Z. Zhang, X. Liu, Z. Fu, J. Xu and Z. Fan, *J. Polym. Sci., Part A: Polym. Chem.*, 2017, **55**, 4027–4036.
67 M. Suzuki, K. Makimura and S.-I. Matsuoka, *Biomacromolecules*, 2016, **17**, 1135–1141.
68 C. G. Overberger and J. K. Weise, *J. Am. Chem. Soc.*, 1968, **90**, 3533–3537.
69 S. W. Duchiron, E. Pollet, S. Givry and L. Avérous, *Eur. Polym. J.*, 2017, **87**, 147–158.
70 M. Kato, K. Toshima and S. Matsumura, *Biomacromolecules*, 2007, **8**, 3590–3596.
71 S. Song, Z. Fu, J. Xu and Z. Fan, *Polym. Chem.*, 2017, **8**, 5924–5933.
72 D. Frank, P. Espeel, S. Claessens, E. Mes and F. E. Du Prez, *Tetrahedron*, 2016, **72**, 6616–6625.
73 M. Liras, I. Quijada-Garrido, M. Palacios-Cuesta, S. Munoz-Durieux and O. Garcia, *Polym. Chem.*, 2014, **5**, 433–442.
74 E. Hrsic, H. Keul and M. Möller, *Eur. Polym. J.*, 2012, **48**, 761–768.
75 M. M. Stamenovic, P. Espeel, E. Baba, T. Yamamoto, Y. Tezuka and F. E. Du Prez, *Polym. Chem.*, 2013, **4**, 184–193.
76 C. S. Marvel and A. Kotch, *J. Am. Chem. Soc.*, 1951, **73**, 1100–1102.
77 H. R. Kricheldorf and K. Bösinger, *Die Makromolekulare Chemie*, 1973, **173**, 67–80.
78 M. Kato, K. Toshima and S. Matsumura, *Macromol. Rapid. Comm.*, 2006, **27**, 605–610.
79 W. Podkoscielny and W. Kowalewska, *J. Polym. Sci., Part A: Polym. Chem.*, 1984, **22**, 1025–1033.
80 T. J. Bannin and M. K. Kiesewetter, *Macromolecules*, 2015, **48**, 5481–5486.
81 C. G. Overberger and J. Weise, *J. Polym. Sci., Part B: Polym. Lett.*, 1964, **2**, 329–331.
82 M. Langlais, O. Coutelier, S. Moins, J. De Winter, O. Coulembier and M. Destarac, *Polym. Chem.*, 2018, **9**, 2769–2774.
83 M. Matzner, J. E. McGrath, S. W. Chow, J. V. Koleske and L. M. Robeson, *J. Appl. Polym. Sci.*, 1973, **17**, 983–986.
84 C. G. Seefried and J. V. Kodeske, *Polym. Eng. Sci.*, 1976, **16**, 526–528.
85 P. E. Fritze, Union Carbide; USA: Thiolactone Polymerization and Catalysts, *US Patent*, 3755268, 1972.
86 M. Kato, K. Toshima and S. Matsumura, *Biomacromolecules*, 2005, **6**, 2275–2280.
87 N. Zaquen, B. Wenn, K. Ranieri, J. Vandenbergh and T. Junkers, *J. Polym. Sci., Part A: Polym. Chem.*, 2014, **52**, 178–187.
88 J. Vandenbergh, M. Peeters, T. Kretschmer, P. Wagner and T. Junkers, *Cross-linked degradable poly(β-thioester) networks via amine-catalyzed thiol-ene click polymerization*, 2014.
89 H. Sun, D. J. Dobbins, Y. Dai, C. P. Kabb, S. Wu, J. A. Alfurhood, C. Rinaldi and B. S. Sumerlin, *ACS Macro Lett.*, 2016, **5**, 688–693.
90 N. G. Moon, R. J. Mondschein and T. E. Long, *Polym. Chem.*, 2017, **8**, 2598–2608.
91 A. Kameyama, M. Kiyota and T. Nishikubo, *Tetrahedron Lett.*, 1994, **35**, 4571–4574.
92 H. Kudo, S. Makino, A. Kameyama and T. Nishikubo, *Macromolecules*, 2005, **38**, 5964–5969.
93 Y. Zheng, S. Cai, L. Peng, Y. Jin, H. Xu, Z. Weng, Z. Gao, B. Zhao and C. Gao, *Polym. Chem.*, 2016, **7**, 6202–6210.
94 E. Perju, S. J. Dünki and D. M. Opris, *J. Polym. Sci., Part A: Polym. Chem.*, 2016, **54**, 2940–2948.
95 L. Liu, L. Wu, J. Tan, L. Wang, Q. Liu, P. Liu and L. Liu, *Polym. Chem.*, 2015, **6**, 3934–3941.
96 B.-H. Hu, J. Su and P. B. Messersmith, *Biomacromolecules*, 2009, **10**, 2194–2200.
97 C. Ghobril, K. Charoen, E. K. Rodriguez, A. Nazarian and M. W. Grinstaff, *Angew. Chem., Int. Ed.*, 2013, **52**, 14070–14074.
98 J. O. Holloway, S. Aksakal, F. E. Du Prez and C. R. Becer, *Macromol. Rapid Commun.*, 2017, **38**, 1700500.
99 M. Liras, O. García, I. Quijada-Garrido and R. París, *Macromolecules*, 2011, **44**, 1335–1339.

