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Xanthate-mediated synthesis of functional bis(γ-thiolactones)

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ABSTRACT

A new methodology for the synthesis of bis(γ-thiolactones) including two different routes was developed. Both strategies are based on xanthate-mediated synthesis involving free radical addition to an unsaturated compound followed by thermolysis and thiolactonization steps. The first approach is based on the addition of a xanthate to different dienes whereas the second one uses the addition of a bis(xanthate) to various functional alkenes. These two different pathways led to a series of bis(γ-thiolactones) bearing phosphonated, hydroxy, bromide or boronate groups. This shows great promise for broader access to functional bis(γ-thiolactones) which can be envisioned as high potential building blocks for step-growth polymerization.

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1. Introduction

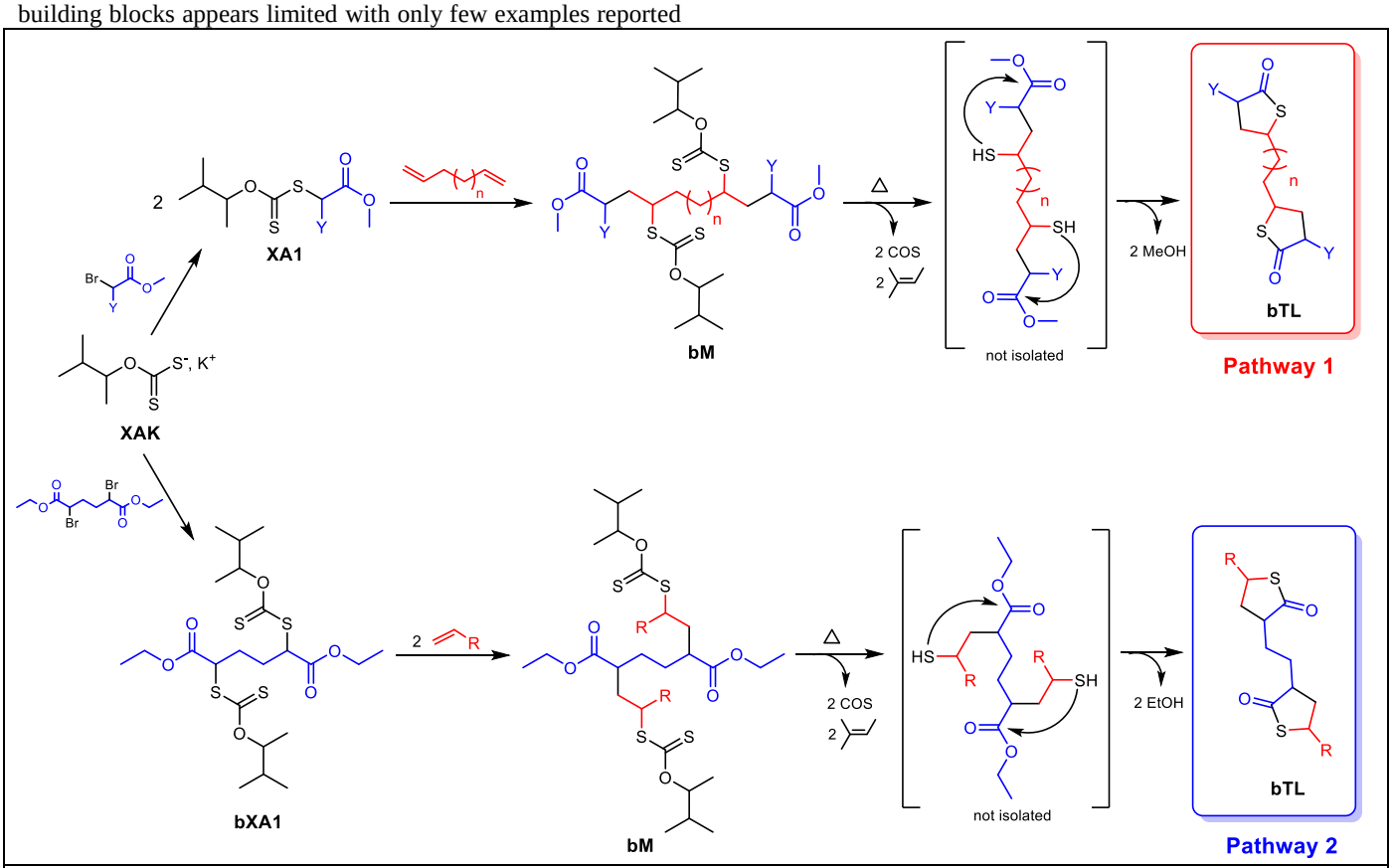
The use of five-membered γ-thiolactones in polymer science has been an increasing topic of interest since 2011, with the introduction of the amine-thiol-ene conjugation.[1,2] This reaction based on the ring-opening of a thiolactone by a primary amine reveals a thiol that can be scavenged by a thiol acceptor. It has been used for the synthesis of original macromolecules via step-growth polymerization,[1,3-11] reversible-deactivation radical polymerization[12-15] or ring-opening polymerization.[16]

Step-growth polymerizations of AB-type monomers containing a γ-thiolactone moiety have been reported for the synthesis of polyamides,[5] poly(amide-urethane)s,[3,4,6] poly(thioether-amide)s,[7,8,17] poly(thioether-urethane)s[1,9,10] or poly(amide-imide)s[18,19]. In the same way, bis(γ-thiolactones) have been polymerized with diamines to access thiol-functionalized polyamides.[5] The resulting pendant thiols were used to introduce functionalities such as PEG chains via Michael addition to obtain water-soluble polyamides. Poly(thioether-ester)s were also obtained using a bis(γ-thiolactone) opened by a primary amine to form a bis-thiol, which then reacted with a diacrylate by step-growth polymerization.[17]

Although bis(γ-thiolactones) represent an efficient route for the synthesis of functional polyamides by amine-thiol-ene reaction, the functionalities are mainly introduced through a further reaction involving the pendant thiols and not directly by the thiolactone units. In addition, the accessibility of these building blocks appears limited with only few examples reported in the literature. Möller et *al.* described an asymmetric bis(thiolactone) with the two thiolactones linked by an amide function, synthesized from the reaction of an acyl chloride γ-thiolactone and homocysteine γ-thiolactone.[5] Hong et *al.* reported a symmetrical bis(γ-thiolactone), synthesized by the connection of two homocysteine-γ-thiolactones to adipoyl chloride as a linker.[17] Finally, Zard et *al.* synthesized bis(γ-thiolactones) through the addition of a xanthate-functionalized γ-thiolactone to a diene, followed by a reductive removal of xanthate groups.[20]

These examples are based on the use of the commercially available homocysteine-γ-thiolactone bearing substituents differing in nature and length. All the reported synthetic pathways focus on connecting two thiolactone units with no functional groups on the thiolactones. A systematic access to functional bis(thiolactones) would allow the direct introduction of functionalities into the polymer during polymerizations, therefore extending the potential usefulness of bis(thiolactones) as monomers in step-growth polymerization.

In this report, we present two different synthetic procedures for the synthesis of substituted and functional bis(γ-thiolactones) using a versatile xanthate-mediated approach.



Scheme 1. General scheme for the synthesis of functional bis(γ-thiolactones) using two different xanthate-based pathways

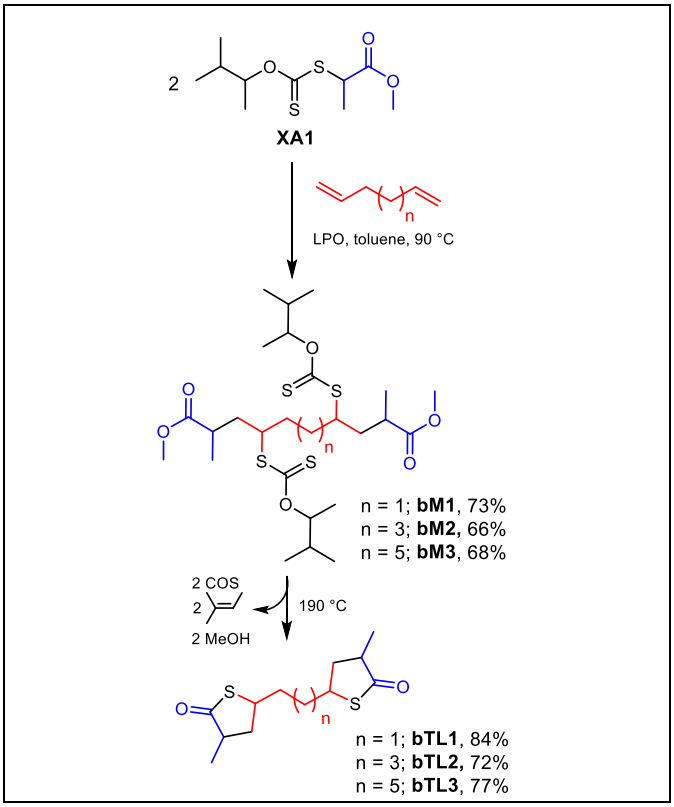
2. Results and discussion

In recent works, we reported the xanthate-mediated synthesis of functional γ-thiolactones.[11,21] This synthetic procedure involves the radical addition of an *O*-alkyl xanthate to a functional alkene followed by thermolysis of the xanthate group (Chugaev elimination) to form a thiol, which subsequently cyclizes with an ester group present on the starting xanthate to obtain the γ-thiolactone.

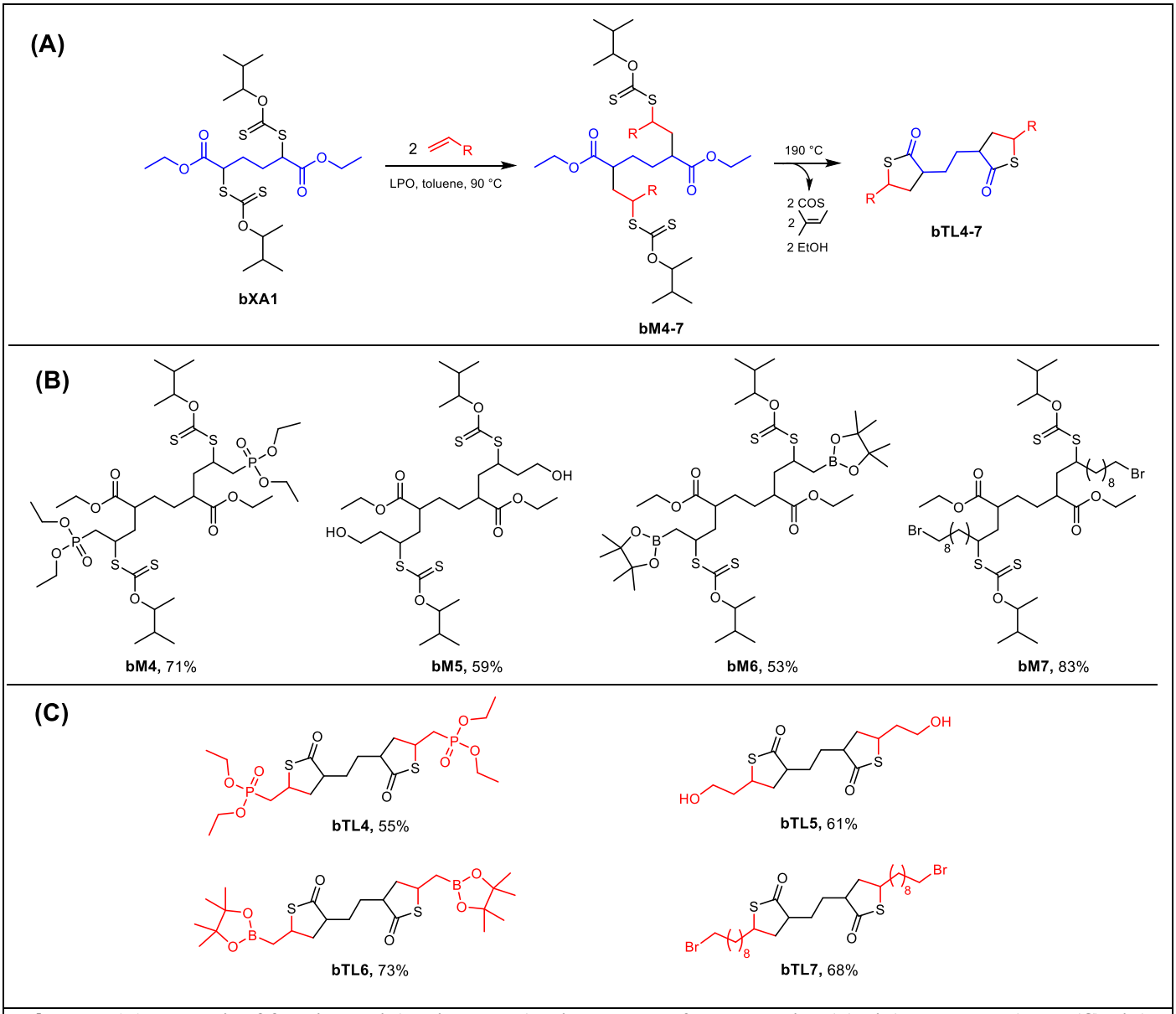
This xanthate approach was adapted and used in this work for the synthesis of a series of bis(γ-thiolactones) with the possibility to modulate the length of the linker between the two rings or even introduce functional groups directly attached to the cycles. Two different synthetic pathways are reported enabling access to substituted and functional bis(γ-thiolactones) (Scheme 1). The

first one (pathway 1, Scheme 2) corresponds to the radical addition of two equivalents of an *O*-(3-methylbutan-2-yl) xanthate to a diene to form a bis(monoadduct), followed by thermolysis and thiolactonization to form a bis(γ-thiolactone). Pathway 2 (Scheme 3) involves an *O*-(3-methylbutan-2-yl) bis(xanthate) and its radical addition to two equivalents of a functional alkene, to first form a bis(monoadduct). The functional bis(γ-thiolactone) is then obtained after thermolysis of the bis(monoadduct) and subsequent ring-closure of the resulting bis(thiol).

Pathway 1 was first investigated with radical addition of two equivalents of xanthate XA1 to 1,5-hexadiene, in the presence of lauroyl peroxide (LPO) as radical initiator in toluene at 90 °C. After 16h of reaction, the expected bis(monoadduct) bM1 was isolated by column chromatography with a yield of 73% (Scheme 2). The thermolysis of bM1 was performed at 190 °C without any solvent and after 30h led to the formation of the bis(γ-thiolactone) bTL1 with a good yield of 86% (Scheme 2). This synthetic procedure allowed access to bis(γ-thiolactones) with both rings linked together by their γ position, and the introduction of a methyl substituent in α position. In order to increase the spacer length between the two thiolactones, we selected 1,7-octadiene and 1,9-decadiene.



Scheme 2. Synthesis of bis(γ-thiolactones) through pathway 1



Scheme 3. (A) Synthesis of functional bis(γ-thiolactones) using pathway 2 and resulting (B) bis(monoadducts) and (C) bis(γ-thiolactones)

The radical addition of XA1 to these two dienes gave the expected bis(monoadducts) bM2 and bM3 with similar yields of 66% and 68% respectively. The thermolysis of bM2 and bM3 at 190 °C for 24h led to the formation of bTL2 and bTL3 with respective yields of 72% and 77% (Scheme 2).

The synthetic pathway 1 allows access to methyl-substituted bis(γ-thiolactones) in good yield, using commercial dienes. Although this method can modulate the spacer length between both thiolactones and bring a methyl substituent in the α position, it lacks versatility for the proper introduction of functional groups, thereby limiting the potential of bis(γ-thiolactones) for the synthesis of functional step-growth polymers. Therefore, we developed a second strategy aiming at obtaining bis(γ-thiolactones) bearing functional groups of interest.

This second methodology (pathway 2, Scheme 3) is based on the same radical approach involving the use of a bis(xanthate) and two equivalents of an alkene bearing a functional group. For this purpose, a new bis(xanthate) bXA1 was synthesized by reacting two equivalents of the xanthate salt XAK with diethyl *meso*-2,5-dibromoadipate in acetone, with a good yield of 82%. In order to demonstrate the concept of pathway 2, we first selected diethyl allylphosphonate (DEAP) as functional alkene. The reactivity of DEAP during the radical addition step and its positive influence on thiolactonization was demonstrated during the synthesis of phosphonated γ-thiolactones in our past work.[11] The addition of bXA1 to two equivalents of DEAP was performed in toluene, in the presence of LPO at 90 °C for 16h. The expected bis(monoadduct) bM4 (Scheme 3) was obtained in 71% yield after column chromatography. The thermolysis of bM4 at 190 °C for 1h led to the formation of the phosphonated bis(γ-thiolactone) bTL4 with a yield of 55% (Scheme 3).

To extend the range of functional bis(γ-thiolactones), hydroxy, boronic ester and bromo groups were introduced through the use of 3-buten-1-ol, allyl pinacol boronate and 11-bromo-1-undecene respectively. The radical addition of bXA1 to 3-buten-1-ol, allyl pinacol boronate and 11-bromo-1-undecene gave the expected bis(monoadducts) bM5, bM6 and bM7 with yields of 59%, 53% and 83%, respectively (Scheme 3). The thermolysis of these bis(monoadducts) at 190 °C led to the formation of the functional bis(γ-thiolactones) bTL5, bTL6 and bTL7, respectively. However, in contrast to the formation of bTL4, a longer reaction time of 16h was required. After purification by column chromatography, bis(γ-thiolactones) were

obtained with yields of 61%, 73% and 68%, for bTL5, bTL6 and bTL7 respectively (Scheme 3).

The synthetic pathway 2 allowed access to functional bis(γ-thiolactones) using commercial alkenes. Both thiolactone rings were linked by their α position with a linker introduced by the starting bis(xanthate), and functional groups are located on the γ position of the thiolactones. The large range of commercially available alkenes offer many possibilities in terms of functions that could be incorporated on the bis(γ-thiolactone). The chemical nature as well as the length of the linker between the cycles can be tuned by the choice of the initial bis(xanthate).

3. Conclusion

In summary, we reported the synthesis of functional bis(γ-thiolactones) through two different synthetic routes based on xanthate chemistry. In both cases, the radical addition of a xanthate group to an unsaturated compound, followed by a Chugaev elimination of the xanthate group and subsequent ring-closure were involved. The first pathway is based on the addition of a xanthate to a diene and allowed access to bis(γ-thiolactones) linked by the γ position of the rings. Depending on the diene, three bis(γ-thiolactones) with different spacer lengths were synthesized in good yield. The second synthetic strategy involves the radical addition of a bis(xanthate) to a functional alkene, leading to bis(γ-thiolactones) linked by the α position and bearing functional groups in γ positions. Four different bis(γ-thiolactones) with diethylphosphonate, hydroxy, boronic ester and bromide groups were synthesized using this methodology. The many possibilities offered by this xanthate-mediated route to functional bis(γ-thiolactones) open new horizons for new functional building blocks to produce step-growth polymers with tunable properties. This will be the subject of our future studies.

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Supplementary Material

General methods, instrumentations, experimental procedures and ^{1}H and ^{13}C NMR spectra for all new compounds.

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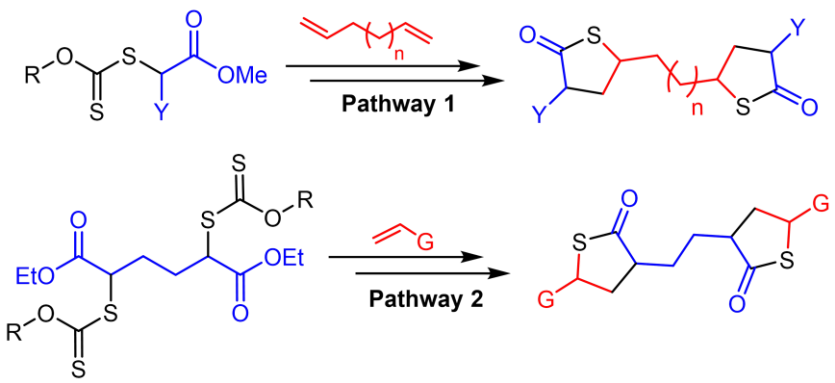
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