JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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One-Pot Multistep Reactions Based on Thiolactones: Extending the Realm of Thiol−Ene Chemistry in Polymer Synthesis

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Supporting Information

ABSTRACT: The *in situ* generation of thiols by nucleophilic ring-opening of a thiolactone with amines, followed by a UV-initiated radical thiol−ene reaction in a one-pot fashion, has been evaluated as an accelerated and versatile protocol for the synthesis of several types of polymeric architectures. After elaboration of a model amine−thiol−ene conjugation reaction, a number of routes based on readily available thiolactone-containing structures have been developed to successfully assemble functional, linear polymers and networks via a mild and facile radical photopolymerization process.

Recently, many organic reactions, generally labeled as 'click' chemistry and originally developed and applied in the synthesis of low-molecular-weight compounds, infiltrated the toolbox of synthetic macro- and supramolecular research groups.[1] One of the major virtues of the 'click' concept has been, since its introduction in polymer science,[2] the paradigm shift toward a modular construction approach of complex innovative polymeric architectures.[3] In addition to this awareness, the challenge was taken up to combine these robust, efficient, and orthogonal conjugation chemistries, resulting in the development of several elegant one-pot, multistep strategies, enabling the implementation of accelerated synthetic protocols.[4] An important class of one-pot, multistep reactions is characterized by the fact that all chemicals initially are mixed and consecutive reactions depend on each other. For example, a potentially explosive azide can be generated *in situ*, starting from the corresponding bromide via nucleophilic substitution or amine via diazotransfer, and can subsequently be converted to a triazole via the copper-catalyzed azide−alkyne cycloaddition (CuAAC) in the same pot.[5] So far, virtually all of these one-pot reaction sequences encompass the heavily exploited Huisgen CuAAC as the key step. The main disadvantage of this popular 'click' reaction, ruling out many potential applications, is the presence of complexed copper in the reaction products. Currently, metal-free methodologies which fulfill the set of 'click' requirements[6] are eagerly developed and evaluated.[7] The radical or nucleophilic addition of a thiol to a double bond (thiol−ene chemistry[8−10]) has recently been recognized as a valuable metal-free alternative for the CuAAC due to some inherent 'click' characteristics.

As Malkoch et al.[4] expressed the need to increase the range of available 'click' reactions that can be achieved without the need of metal catalysts and to develop libraries of compatible reactions, our ongoing interest is to develop an efficient one-pot process based on metal-free radical thiol−ene chemistry in order to modify or assemble polymeric materials. In addition to the fact that the commercial availability of thiols as starting materials is rather limited, thiols usually have an unpleasant smell and might have a poor shelf life due to oxidation reactions. Therefore it can be advantageous to generate thiols *in situ* and convert them in a one-pot process. In a very recent report on a metal-free two-step approach,[11] a dithiobenzoate at the ω chain end of a polymer obtained via RAFT (reversible addition−fragmentation chain transfer) was converted to the corresponding thiol via aminolysis and this thiol acted as a nucleophile in a subsequent thio-bromo 'click' reaction. Others previously reported the one-pot process that combines aminolysis of the trithiocarbonate end groups as latent thiols and nucleophilic Michael addition of the resulting thiols.[12]

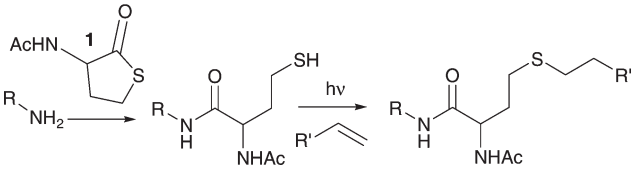
Our investigation was inspired by a decades-old method for the introduction of sulfhydryl groups in natural proteins.[13] This thiolation of proteins consists of the nucleophilic ring-opening of the readily available *N*-acetylhomocysteine thiolactone **1** by the ε-NH_2 groups of lysine residues. We anticipated the ability to adapt this methodology and combine it with the radical thiol−ene process in a one-pot fashion as a mild approach for the synthesis of polymeric architectures starting from stable amine containing compounds. Although the presented concept (Scheme 1) might not be broadly applicable due to the reactive nature of amines and radical species (orthogonality issues), this amine−thiol−ene conjugation as a simple, efficient, and modular linking process is considered to be a relevant extension of the currently quite popular thiol−ene chemistry, especially in polymer science.

In the first stage of this study, the one-pot two-step sequence was performed on low-molecular-weight model compounds in order to investigate the reaction kinetics and to analyze the composition of the obtained reaction mixture. Benzylamine **2** was treated with thiolactone **1** in the presence of 4-dimethylaminopyridine (DMAP) as a nucleophilic catalyst. In the initial reaction mixture, an excess of norbornene (ene-compound) **3** was added to allow for the subsequent radical thiol−ene reaction. The reaction mixture was irradiated by an external UV-light source, and 2,2-dimethoxy-2-phenyl acetophenone (DMPA) was selected as an efficient photoinitiator for thiol−ene conjugation.[14] Because of the extremely high reactivity of the norbornene double bond toward thiyl radicals,[9] the first step of the reaction sequence was considered to be rate-determining. In an online ^{1}H NMR experiment, the consumption of **2** was monitored by the decrease of the signal of the corresponding benzylic protons. This study pointed

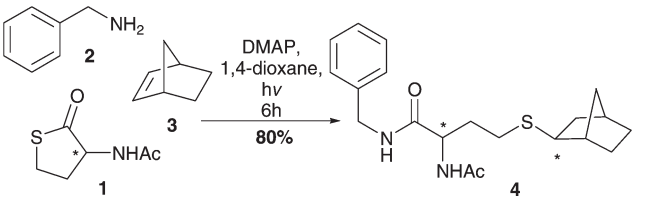
Received: November 1, 2010

   dx.doi.org/10.1021/ja1098098 | *J. Am. Chem. Soc.* XXXX, XXX, 000–000

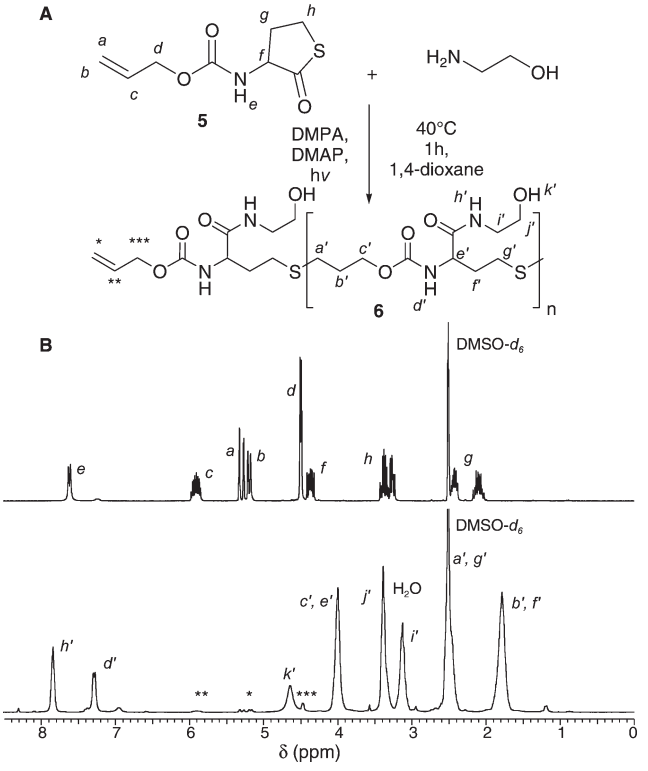
Scheme 1. General Concept of the Investigated Metal-Free One-Pot Reaction: Nucleophilic Opening of a Thiolactone (Aminolysis), Followed by a Radical *Thiol−Ene* Conjugation



Scheme 2. Model Amine−Thiol−Ene Conjugation: One-Pot Reaction between Benzylamine, *N*-Acetylhomocysteine Thiolactone, and Norbornene under UV-Irradiation without the Use of a Photoinitiator



Scheme 3. (A) Stepwise Photopolymerization of the Alloc-TL Monomer 5 in a One-Pot Process Yielding a Linear Polymer 6 with a Polythioether/Polyurethane Backbone and Pendant Hydroxyl Groups; (B) ^{1}H NMR Assignment (300 MHz) of the Alloc-TL Monomer 5 (top) and the Polymer 6 (bottom)



out that **2** was fully consumed after being in the presence of a 2-fold excess of **1** and 10 mol % of DMAP for 6 h (Figure S1). Furthermore, thorough analysis of the reaction mixture obtained after the two-step reaction by LC-MS revealed, in addition to the presence of the desired compound **4**, the formation of side products, originating from the reaction between **2** and radical fragments of DMPA (Figure S2). However, using optimal conditions (no photoinitiator) and after a straightforward chromatographic purification, the model reaction yielded the conjugation compound **4** with an isolated yield of 80% (Scheme 2).

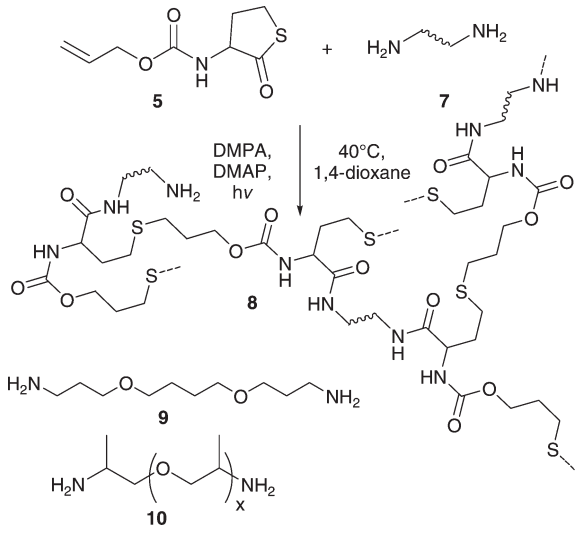
The structure of **4**, which is a mixture of diastereoisomers, was confirmed by NMR and MS analysis. An important conclusion drawn from this model study is that the use of a photoinitiator should be avoided or at least limited because of the interference between the amine and radical fragments of the photoinitiator. Radical thiol−ene conjugation can be performed in the absence of a photoinitiator through irradiation with UV-light or sunlight.[15] No further efforts were undertaken to modify the radical initiation process as earlier reports showed that thermal initiators are generally less efficient than photoinitiators for radical thiol−ene conjugation[14] and that H-abstraction type photoinitiators such as benzophenone and thioxanthone react with amines with the formation of the corresponding imines.[16]

Encouraged by the successful model study, we investigated the synthesis of a monomer containing both a double bond and a thiolactone unit. Similarly, Perrier et al.[17] recently reported on thiol−yne chemistry for the synthesis of hyperbranched structures using AB_2 type (macro)monomers, molecules bearing a thiol at one end of the molecule and an alkyne at the other. In our case, as a thiolactone moiety can be considered as a precursor of a thiol functionality, the combination with a double bond results in an AB′ type monomer. The valorization of the reactivity of this monomer, *N*-(allyloxy)carbonylhomocysteine thiolactone (Alloc-TL) **5**, upon aminolysis and subsequent UV-curing, would enable us to develop convenient and accelerated protocols for the synthesis of novel polymeric architectures. A scalable and high-yielding synthesis of the proposed ene−thiolactone monomer consisted of the treatment of homocysteine thiolactone with allyl chloroformate, introducing the corresponding (allyloxy)carbonyl or alloc group, a popular amino-protecting group.

Radical (photo)polymerization reactions between a thiol and an alkene occur in a stepwise fashion. Typically, a gradual increase of the molecular weight with increasing conversion is observed. In order to obtain high-molecular-weight poly addition compounds, the ratio between the involved functional groups should equal 1. The aminolysis of the thiolactone in the Alloc-TL monomer **5** to generate the thiol should therefore efficiently reach full conversion. When using benzylamine in the one-pot polyaddition reaction, polymer material could be identified by size-exclusion chromatography (SEC), but even after prolonged UV-curing, only low-molecular-weight material (M_n < 5 kDa) was formed, compromising the purification via precipitation and further analysis. On the other hand, in the presence of a 2-fold excess of the nucleophile ethanolamine and a small amount of DMPA (5 mol %), the polyaddition occurred and, after 1 h of UV-curing, a white precipitate was obtained (Scheme 3A). The purified polymer **6** was soluble in MeOH, DMSO, DMF, and DMA and was analyzed by SEC and 1D and 2D NMR. The SEC chromatogram displayed a unimodal distribution with a polydispersity index (PDI) of 1.6, and the M_n, determined via SEC, was 22 kDa. The quantification of M_n of the same polymer via end group analysis (double bond

dx.doi.org/10.1021/ja1098098 |*J. Am. Chem. Soc.* XXXX, XXX, 000–000

Scheme 4. Schematic Depiction of the Network Formation (One-Pot Reaction between the Alloc-TL Monomer 5 and a Diamine Cross-Linker 7 Results in a Polythioether Polyurethane Network 8) and Structure of 4,9-Dioxadodecanediamine 9 and Jeffamine D Series 10



protons) in the ^{1}H NMR spectrum (Scheme 3B) revealed a molecular weight of 7.8 kDa.

This mild and efficient one-pot polyaddition process yielded a polymer **6** with a polythioether/polyurethane backbone and pendant hydroxyl groups. We deliberately selected the ambident nucleophile ethanolamine for the aminolysis: under neutral conditions, hydroxyl functions are unable to open the thiolactone ring[18] and alcohols do not interfere with radical thiol−ene reactions.[10] Standard synthetic methods for the synthesis of hydroxyl functionalized polyurethanes would certainly require a protection/deprotection strategy. Generalization of this reaction concept emphasizes the fact that, as long as the additional functional group of the multifunctional amine does not interfere with either reactions in the one-pot multistep process (aminolysis and radical thiol−ene), linear polymers can be obtained with direct introduction of side chain functional groups, prone to post-polymerization modification.[19]

To further extend the scope of this methodology in material science, polymer networks **8** based on the AB′ type monomer **5** were targeted. Anticipation of network formation was based upon treatment of **5** with a diamine **7** under similar conditions as described above (Scheme 4). Polymer film formation was expected upon UV-irradiation of a homogeneous reaction mixture between two glass plates, separated by a thin silicone spacer.

The choice of the diamine cross-linker **7** regarding structure and molecular weight proved to be critical. 1,6-Hexanediamine was insoluble in the reaction mixture. The use of the more polar 4,9-dioxadodecanediamine **9** as a cross-linker yielded a clear, nontacky network film with good mechanical properties after UV-curing for 3 h. The use of the Jeffamine D series **10** (D-400, D-2000, and D-4000) as macromolecular cross-linkers was also attempted, but poor film formation was observed, probably because the amine group is located on a secondary carbon atom, thus sterically hampering cross-linking.

In conclusion, we have demonstrated that a thiolactone entity can serve as a precursor for thiols in a one-pot amine−thiol−ene reaction: the thiolactone ring opens upon aminolysis and the *in situ* generated thiol reacts with a double bond, already present in the same pot. A model study was elaborated to master the reaction conditions. In order to valorize this reaction concept as an accelerated protocol in polymer synthesis, an AB′ type monomer, consisting of a double bond and a thiolactone moiety, was synthesized and used to successfully assemble functional, linear polymers and networks via a mild and facile radical photopolymerization process. Future investigations will focus on the development and valorization of the analogous amine−thiol−yne reaction. Moreover, we are strongly convinced that this methodology will be useful for the modification of double/triple bond containing polymer materials.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures; synthesis of model compounds; monomers and polymers; kinetic studies; and NMR, LC-MS and IR data are included in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

The authors are grateful for the financial support from the Belgian Program on Interuniversity Attraction Poles initiated by the Belgian State, Prime Minister's office (Program P6/27).

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