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Oxo-Thiolation of Cationically Polymerizable Alkenes Using Flow Microreactors

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Abstract: The present study describes the cationic oxo-thiolation of polymerizable alkenes using highly reactive cationic species generated by anodic oxidation. These highly reactive cations were able to activate alkenes before their polymerization. Fast mixing of flow microreactors effectively controlled chemoselectivity, enabling higher reaction temperatures.

Alkene difunctionalization is a class of reactions that involves the forming of bonds with nucleophiles and/or electrophiles at two adjacent sp² carbons of alkenes.^[1] Because it results in the rapid construction of complex structures, alkene vicinal functionalization plays a crucial role in modern organic synthesis. The ability of cationic three-membered ring intermediates to react in a stereo- and regioselective manner results in the rapid and selective transformation of these intermediates. These reactions, however, have a potential limitation; as cationic alkene difunctionalization is not applicable to polymerizable alkenes such as styrenes. Because of their cationic properties, intermediates may react with unreacted alkenes as nucleophiles, yielding polymers. Because the generation of cationic species is often reversible, gradually generated cations activate alkenes sequentially, enabling abundant surrounding alkenes to react and form polymers, despite the number of nucleophiles being sufficient. Thus, cationic difunctionalization of polymerizable alkenes is generally challenging.

One possible solution may be the irreversible generation and accumulation of cationic species in the absence of alkenes. The high reactivity of cationic species results in the rapid conversion of alkenes to three-membered intermediates prior to the start of polymerization. Cationic species may be generated irreversibly by

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electrochemical reactions^{[2][3]}, and we have described the electrochemical generation and accumulation of organic cations (cation pool method).^{[4][5]} In this system, low-temperature anodic oxidation irreversibly generates cationic species, which can react with nucleophiles following the end of electrolysis. As an extension, we have developed heteroatom cation pools that undergo alkene difunctionalization with high efficiency.^[6] Using this method, diaryl disulfide, for example, is electrochemically oxidized in the presence of dimethyl sulfoxide (DMSO) to generate the O-arylsulfenyl alkoxysulfonium ion (ArS-OS+Me₂). The latter reacts with alkenes, yielding the corresponding threemembered ring cationic intermediates (thiiranium ions). DMSO attacks the cyclic intermediates, opening the ring and generating α -substituted alkoxysulfonium ions, an intermediate of DMSO oxidation reactions, such as Swern oxidation and Kornblum oxidation).^[7] Treatment of these intermediates with an amine base resulted in their oxidization to the corresponding carbonyl compounds (Figure 1a). Although this integrated^[8] difunctionalization reaction is applicable to a range of alkenes, it is especially applicable to the polymerization of polymerizable alkenes such as styrenes. Because this arylsulfenium cation is stabilized by DMSO, its reactivity is milder than that of bare cation, thus preventing the wholesale conversion of styrenes to thiiranium ions. Gradually generated thiiranium ions may accumulate at the growing ends of polymers (Figure 1b). A similar problem may occur during the general cationic oxo-thiolatioin of styrenes, suggesting that these transformations are generally performed using radical mechanisms.^[9]

To address this challenge, we hypothesized that highly reactive cationic species may enable the rapid conversion of polymerizable alkenes to thiiranium ions, which can react with DMSO to yield α -thiocarbonyl products before polymerization. We have described the anodic generation of arylsulfonium ions coordinated by diaryl disulfide (ArS(ArSSAr)⁺) and the reactions of these ions.^[10] In particular, sulfonium cation can react with carbon–carbon unsaturated compounds to generate three-membered ring intermediates, which react with nucleophiles in a manner resulting in alkene difunctionalization.^[11] This reactive cation pool may prevent polymerization. The present study reports the cationic difunctionalization of polymerizable alkenes using electrochemically generated sulfur cations (Figure 1c).

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(c) Reaction of Styrenes with Arylbis(arylthio)sulfonium Cation Pool (This Work)



Figure 1. (a) Alkene difunctionalization with DMSO-stabilized cation pool.

The first step consisted of oxo-thiolation of 4-methoxystyrene, a good monomer for cationic polymerization (Scheme 1). Using a DMSO-stabilized monovalent sulfur cation, the corresponding product was, as expected, obtained at low yield (Method 1). Therefore, we used arylsulfonium ions (ArS(ArSSAr)+, Ar = 4-F- C_6H_4), which were generated from anodic oxidation of diaryl disulfide (ArSSAr), using Bu₄NBF₄ as a supporting electrolyte, at -78 °C. Stepwise addition to the solution of 4-methoxystyrene of the cation pool, DMSO (1.3 equiv.), and trimethylamine at 5 minute intervals generated the desired product, but at lower yields (Method 2). This disappointing result suggested that 4methoxystyrene polymerizes within minutes, or possibly seconds. After determining the reaction time scale, we arranged the reaction conditions. Specifically; DMSO was added to 4methoxystyrene solution, followed by the addition of the cation pool, trapping the thiiranium ion with DMSO prior to polymerization of the intermediate (Method 3). This trial provided a good result, with the desired α -thiocarbonyl product being obtained at a yield of 74%. To our knowledge, this is the first successful example of cationic oxo-thiolation of styrenes.^[12]





Scheme 1. Initial trials of 4-methoxystyrene oxo-thiolation with 3 different methods. "Ar" means 4-fluorophenyl group.

After finding that the concept was feasible, we started to optimize the reaction conditions (Table 1). We attempted to shorten the time required for the reaction by increasing the reaction temperature when adding cation to the solution containing alkene and DMSO. We found, however, that increasing the reaction temperature reduced the reaction yields (entries 1-5). In contrast, yields were increased when Bu₄NB(C₆F₅)₄ was used instead of Bu₄NBF₄ as a supporting electrolyte for anodic oxidation (entry 6), presumably because the softer counter anion made the sulfur cation more reactive. We assumed that this condition was optimal, and we started investigating the scope of the alkenes that could be used in these reactions. Unsubstituted styrene (entry 7), electron-deficient substituted styrene (4-bromostyrene, entry 8), and 1,3-diene (1,3cyclohexadiene, entry 9) were converted to their corresponding a-thiocarbonyl compounds at high yields, whereas their reactions with DMSO-stabilized sulfenium ion (method 1) resulted in low vields. Non-polymerizable alkenes were also found to be good reactants for transformation using the same reaction conditions (entries 10-13). Because the intermediates were positively charged, dienes were selectively mono-reacted (entries 9 and 13). Although the yield of the reaction with vinvlether was low (entry 14), this yield was slightly increased by using 3 equiv. of DMSO, The very high reactivity of vinylethers may have interfered with this transformation even at -78 °C.

Table 1. Reactions of anodically generated surfonium ions with alkenes^[a]

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[a] Reactions were carried out 1.3 eq. of cations generated from anodic oxidation using Bu₄NB(C₆F₅)₄ as a supporting electrolyte. Ar = 4-F-C₆H₄. [b] Isolated yield. [c] Yields were determined by ¹H NMR. [d] Bu₄NBF₄ was used as a supporting electrolyte. [e] 3 equiv. of DMSO was used.

Although styrene underwent cationic difunctionalization, this transformation required extremely low temperatures (-78 °C), ruining the utility of this concept. To overcome this limitation, we again examined the effects of the reaction temperature (entries 1-5), observing that higher temperatures yielded greater amounts of polymers, as indicated by GPC analyses (Figure 2a). This tendency correlated with the lower product yields at higher temperatures (Figure 2b), suggesting that higher temperatures result in poorer chemoselectivity and unselective reactions (polymerization). Polymerization of 4-methoxystyrene took place, was observed, even at -78 °C, with non-negligible amounts of polymers generated (Fig. 3). This finding suggested that sufficiently rapid mixing of ArS(ArSSAr)⁺ with styrenes (and DMSO) allowed the oxo-thiolation to proceed effectively, even at higher temperatures.





Figure 2. (a) GPC trace of crude products on the reaction of $ArS(ArSSAr)^+$ with 4-methoxystyrene. (b) bar: Area of polymer peak on GPC (elution time from 6 min to 8.5 min), line: product yields on the reaction temperature.

A flow microreactor system may allow transformation at higher temperatures. Flow microreactors have been shown to enable highly chemoselective reactions by fast mixing and precise control of residence (reaction) times.[13-15] To evaluate this hypothesis, cation flow syntheses were performed (Table 2).^[16] Anodically generated arylsulfonium ion solution was mixed with a solution of polymerizable alkenes and DMSO in a micromixer 1 (M1, $\phi = 500 \ \mu$ m). After 17 seconds of residence, the mixed solution was allowed to flow into M2 (ϕ = 500 µm), where it reacted with Et₃N solution. The solution was subsequently allowed to flow into a round-bottomed-flask, and the contents of the flask were stirred at room temperature for 1 hour to complete the deprotonation reaction.^[17] The α -thiocarbonyl product of 4methoxystyrene was obtained at 95% yield at a reaction temperature of -50 °C, whereas the batch reaction at the same temperature resulted in a 32% yield. These findings indicate that the flow microreactor plays a vital role in the reaction. Fast mixing prevented localization of the chemicals, allowing alkenes to react with the arylsulfonium cation pool prior to polymerization. Using the same flow microreactor system, 4-bromostyrene was converted to the corresponding product at a higher temperature (0 °C). Surprisingly, this system was effective with vinylether, in that the reaction of cyclohexyl vinyl ether produced a good yield of the corresponding ester product, whereas the batch reaction yielded only 17% of the product. These results indicate that rapid mixing by the flow microreactor enabled highly efficient reactions that require low temperatures in a batch reactor.

Table 2. Flow Syntheses of α -thiocarbonyl compounds^[a].

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[a] Anodic generation of ArS(ArSSAr)⁺ (Ar = 4-F-C₆H₄) at -78 °C using Bu₄NBF₄ as a supporting electrolyte. In a flow reactor, the reaction required 1.3 eq of ArS(ArSSAr)⁺, 1.3 eq of DMSO, and 5 eq of Et₃N. [b] Obtained yields. [c] Yield when 3 equiv. of DMSO was used.

Finally, to assess the synthetic utility of these transformations, we investigated the cationic cyclization reactions of the 1,6-diene type of alkenes. At optimized conditions, nitrogen-bridged 1,6-diene was converted to the corresponding piperidine product as a single diastereomer at high yield (Figure 2). Carbon-bridged dienes (dimethyl malonates) were also converted to cyclized products at high yields. This stereoselectivity was likely derived from the chair-like transition state, which is similar to that of polyene cyclization in nature.^[18]



Figure 3. Cyclization reaction using anodically generated thionium ions..

In conclusion, this study demonstrated the cationic difunctionalization of polymerizable alkenes using anodically generated highly reactive cationic species. These findings confirmed that the use of highly reactive cationic species can prevent polymerization, resulting in the cationic oxo-thiolation of styrenes. Moreover, fast mixing using a flow microreactor system can result in the selective activation of polymerizable alkenes prior

to their polymerization. The method described in the present study is applicable to non-polymerizable alkenes and can be used to constructing complex cyclized frameworks. This improvement may result in novel reaction control methods and may also open a new aspect of cationic chemistry.

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Keywords: anodic oxidation • cationic species • flow microreactor • polymerizable alkenes • electrochemistry

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Highly reactive arylsulfonium ions generated by anodic oxidation provide oxothiolation of polymerizable alkenes such as styrenes prior to their polymerization. Fast mixing based on flow mixcoreactor systems enables this transformation at a higher temperature. Dr. Yosuke Ashikari, Dr. Kodai Saito, Prof. Dr. Toshiki Nokami, Prof. Dr. Junichi Yoshida,* and Prof. Dr. Aiichiro Nagaki*

Oxo-Thiolation of Cationically Polymerizable Alkenes Using Flow Microreactors

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