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Indirect Cation Pool Method. Rapid Generation of Alkoxycarbenium Ion Pools from Thioacetals

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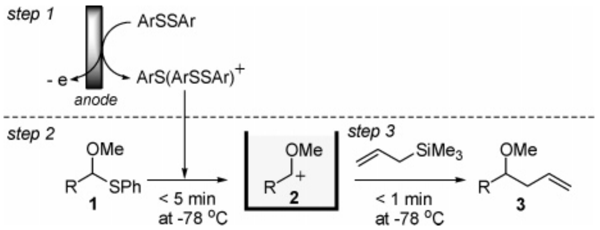
We have recently developd the "cation pool" method,[1] in which highly reactive organic cations[2] are generated and accumulated in the absence of nucleophiles. In the cation pool method, cations are generated by the low temperature electrochemical oxidation of a substrate. Because electrochemical reactions take place only on the surface of the electrode, the accumulation of a cation usually takes several hours. Therefore, the applicability of the method strongly depends on the stability of the cation that is accumulated.[3] To solve the problem, we have been investigating a sequential one-pot indirect method,[4] in which an active reagent is generated and accumulated electrochemically (step 1) and is subsequently allowed to react with a precursor to generate a cation pool (step 2). The cation pool thus generated is allowed to react with a nucleophile (step 3). Herein we report the realization of the indirect cation pool method, which serves as a powerful tool not only for mechanistic studies on highly reactive cations but also for rapid parallel synthesis.

We chose to study the generation of alkoxycarbenium ion **2**, which is unstable and decomposes quickly above −50 °C,[5] from thioacetal **1** (Scheme 1)[6] because this type of reaction serves as a useful method for glycosylation.[7]

Scheme 1



We envisioned that ArS^{+} [8] would be quite effective for the generation of **2** from **1** because ArS^{+} should be highly thiophilic. Extensive studies on the electrochemical oxidation of ArSSAr have been carried out.[9] ArS^{+} has been assumed to be generated as an intermediate in CH_2Cl_2, although some doubts have been advanced of their existence in this form in the solution phase. Since the nature of the reactive species generated from ArSSAr has not been firmly established, we first carried out spectroscopic studies. ^{1}H NMR (−80 °C) spectrum of the solution obtained by the anodic oxidation of ArSSAr (Ar = p-FC_6H_4) in $Bu_4NBF_4/CH_2Cl_2-CD_2Cl_2$ at −78 °C (0.67 F/mol)[10] showed a spectrum similar to that of $ArS(ArSSAr)^{+}$ generated by the reaction of ArSSAr and $SbCl_5$.[11] CSI-MS (cold-spray ionization mass spectroscopy)[12] (spray temperature = 0 °C) provides strong evidence for the formation of $ArS(ArSSAr)^{+}$ (m/z = 381, Figure 1). Therefore, we concluded that $ArS(ArSSAr)^{+}$ is the reactive species. The electrochemical method is very simple and is superior to the chemical method that needs the use of toxic $SbCl_5$.

Next, the reaction of electrogenerated $ArS(ArSSAr)^{+}$ with thioacetal **1** (R = C_8H_{17}) was examined. After the conversion of **1** to **2** (step 2), a process that requires only 5 min at −78 °C, allyltrimethylsilane (10 equiv) was added. The allylated product **3** was obtained in 98% yield,[13] suggesting that alkoxycarbenium ion **2** was generated efficiently. High reactivity of $ArS(ArSSAr)^{+}$ and homogeneity of the reaction system seem to be responsible for fast generation of **2**. The reaction of **2** with the allylsilane (step 3) was extremely fast, as well. It was complete within 1 min at −78 °C.[14] Other ArSSAr (Ar = p-ClC_6H_4, 96%; C_6H_5, 79%; p-$CH_3C_6H_4$, 79%; p-$MeOC_6H_4$, 69%) were also effective, although the yield of **3** depends on the nature of the substituent on the aryl group.

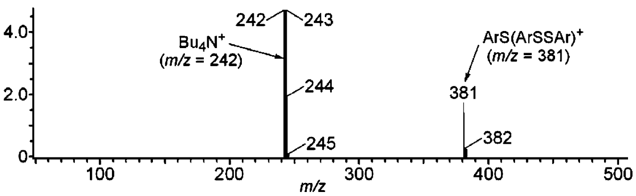
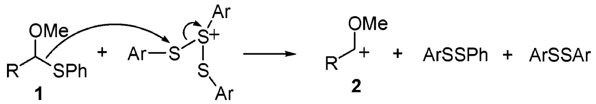


Figure 1. CSI-MS of electrogenerated $ArS(ArSSAr)^{+}$ (Ar = p-FC_6H_4).

The detailed mechanism for the reaction of **1** with $ArS(ArSSAr)^{+}$ (step 2) has not been clarified as yet, but **2** seems to be generated according to Scheme 2. The possibility of a single electron-transfer mechanism cannot be ruled out.

Scheme 2



The formation of **2** was confirmed by NMR spectroscopy. A solution obtained by the reaction of **1** with the electrogenerated $ArS(ArSSAr)^{+}$ (Ar = p-FC_6H_4) exhibited signals at 9.53 and 4.92 ppm due to the methine proton and methyl protons, respectively (^{1}H NMR), and a signal at 230.6 ppm due to the methine carbon (^{13}C NMR). These chemical shifts are quite similar to those obtained by the direct electrochemical oxidation of $C_8H_{17}CH(OMe)SiMe_3$ (9.55, 4.95, and 231.0 ppm).[5a] Such similarity in chemical shifts indicated that the sulfur-containing byproducts, such as ArSSPh and ArSSAr, which were present in the solution, did not change the nature of alkoxycarbenium ion **2** appreciably.

As described above, alkoxycarbenium ion **2** generated by the present indirect method has reactivity similar to that generated by the direct anodic oxidation of $C_8H_{17}CH(OMe)SiMe_3$[5a] (step 3 was complete within 1 min at −78 °C). Thus, we next compared the thermal stability of **2** as follows. The cation pool generated at −78 °C was allowed to warm to a second temperature. After being kept there for 30 min, the pool was then allowed to react with allyltrimethylsilane. The yield of **3** is plotted against the temperature in Figure 2. The cation pool of **2** generated by the indirect method exhibited thermal stability similar to that obtained by the direct method.

To test the applicability of the present indirect method, the generation of alkoxycarbenium ions from several thioacetals and

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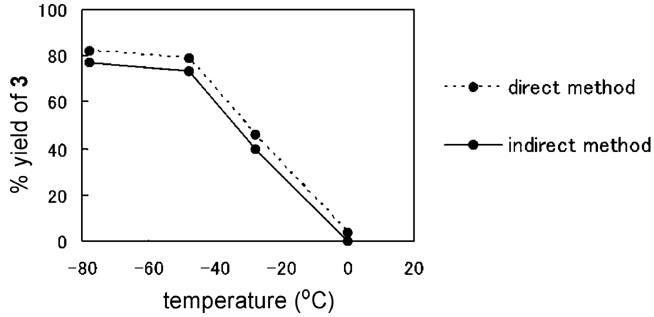
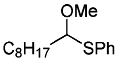
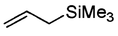
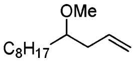
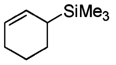
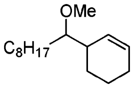
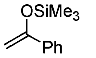
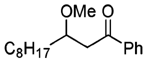
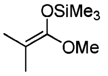
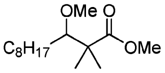
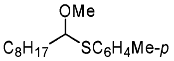
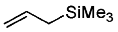
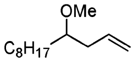
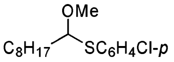
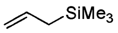
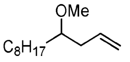
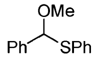
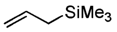
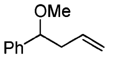
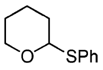
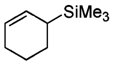
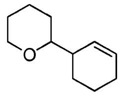
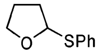
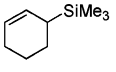
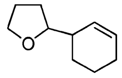


Figure 2. Thermal stability of alkoxycarbenium ion **2** generated by the direct method[5a] and the present indirect method.

Table 1. Indirect Generation of Cation Pools and Their Reactions with Carbon Nucleophiles[a]

substrate	carbon nucleophile	product	% yield
			89 (98)[b]
			91 (5:4)[d]
			79
			67
			72
			82
			91[c]
			85 (7:1)[d]
			86 (9:1)[d]

[a] ArSSAr (Ar = p-FC_6H_4, 0.40 mmol) was oxidized electrochemically in 0.3 M Bu_4NBF_4/CH_2Cl_2 at −78 °C using 0.67 F/mol of electricity. The solution thus obtained was allowed to react with 0.20 mmol of thioacetal at −78 °C for 5 min. Then a nucleophile (0.50 mmol, 2.5 equiv) was added, and the resulting solution was stirred at −78 °C for 15 min and the reaction was quenched with Et_3N. [b] Allyltrimethylsilane (10 equiv) was used. [c] Reaction of thioacetal with $ArS(ArSSAr)^+$: −78 °C, 10 min. Reaction with allylsilane: −78 °C, 1 h. [d] Diastereomeric ratio.

their reactions with several carbon nucleophiles (2.5 equiv) were examined (Table 1).[15] Allylsilanes, enol silyl ethers, and ketene silyl acetals were effective as carbon nucleophiles. The p-MeC_6H_4S and p-ClC_6H_4S groups were also effective as leaving groups. Alkyl- and aryl-substituted thioacetals, including cyclic substrates, were found to be effective.

In conclusion, we have developed a sequential one-pot indirect method for the generation of alkoxycarbenium ion pools. The reagent electrochemically generated from ArSSAr is well characterized spectroscopically, and its reaction with a thioacetal to generate cation pools is very fast. The results obtained here add a new dimension of the cation pool method, which serves as a powerful tool for carbocation chemistry. Applications of the present method to the generation and accumulation of highly unstable cations are in progress.

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Supporting Information Available: Experimental procedures, spectroscopic data of compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Reactions of thioacetals with allylsilanes have been achieved by the action of a Lewis acid, such as $SnCl_4$ and $BF_3{-}OEt_2$. (a) Braga, L.; Dornelles, L.; Silveira, C.; Wessjohann, A. *Synthesis* **1999**, 562. (b) Sato, T.; Okura, S.; Otera, J.; Nozaki, H. *Tetrahedron Lett.* **1987**, *28*, 6299. (c) Nishiyama, H.; Narimatsu, S.; Sakuta, K.; Itoh, K. *J. Chem. Soc., Chem. Commun.* **1982**, 459. However, when **1** (R = C_8H_{17}) was treated with $SnCl_4$ or $BF_3{-}OEt_2$ in the absence of an allylsilane, **2** was not observed by ^1H NMR, indicating that the equilibrium lay so far to **1**, and the concentration of **2** was extremely small with such acids.

(14) The reaction of **2** with 2 equiv of allyltrimethylsilane at −78 °C for 1 min followed by the treatment with 1-(trimethylsilyloxy)cyclohexene (2 equiv) at −78 °C for 10 min gave **3** in 81% yield. Only a trace amount of the product derived from 1-(trimethylsiloxy)cyclohexene was obtained, indicating that the reaction of **2** with allyltrimethylsilane was complete within 1 min at −78 °C.

(15) The anodic oxidation of ArSSAr (Ar = p-FC_6H_4) (0.40 mmol) in 0.3 M Bu_4NBF_4/CH_2Cl_2 was carried out in an H-type divided cell equipped with a carbon felt anode and a platinum plate cathode under the constant current condition at −78 °C. To the anodic chamber containing electrogenerated $ArS(ArSSAr)^+$ was added **1** (0.20 mmol), and the mixture was stirred for 5 min at −78 °C. Allyltrimethylsilane (0.50 mmol) was added, and the resulting solution was stirred at −78 °C for 15 min to obtain **3**.

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