Electroinitiated Reactions

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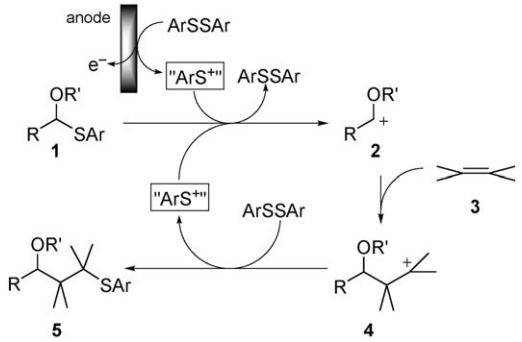
An Electroinitiated Cation Chain Reaction: Intramolecular Carbon–Carbon Bond Formation between Thioacetal and Olefin Groups**

*Kouichi Matsumoto, Shunsuke Fujie, Koji Ueoka, Seiji Suga, and Jun-ichi Yoshida**

In memory of Yoshihiro Matsumura

In organic synthesis, radical chain reactions are widely utilized for the synthesis of complex organic molecules.[1] In contrast, cationic chain reactions[2] are not so widely used, although carbocationic reactions[3] and cationic chain-growth polymerization[4] are applied extensively in organic and polymer synthesis, respectively. Herein we report an example of a cationic chain reaction which is initiated by an electrochemically generated cationic species.

This work stems from our earlier observation[5] that the low-temperature electrochemical oxidation of ArSSAr[6] leads to the formation of $ArS(ArSSAr)^+$,[7] an equivalent of ArS^+[8] that reacts with thioacetal **1**[9] to give the corresponding alkoxycarbenium ion **2**[10] and ArSSAr (Scheme 1). We envisaged that the reaction of the thus-obtained alkoxycarbenium ion with an olefin **3** leads to the formation of a second cation **4**,[11] which might react with ArSSAr to give a sulfenylated product **5** to regenerate "ArS^+". The "ArS^+" species would act as an activator of another molecule of **1**. Therefore, the overall reaction should take place with a catalytic amount of "ArS^+".



Scheme 1. Concept of a "ArS^+"-mediated chain reaction of thioacetal and olefin.

[*] K. Matsumoto, S. Fujie, K. Ueoka, Dr. S. Suga, Prof. J. Yoshida
Department of Synthetic and Biological Chemistry
Graduate School of Engineering
Kyoto University
Kyotodaigakukatsura, Nishikyo-ku, Kyoto, 615-8510 (Japan)
Fax: (+81) 75-383-2727
E-mail: yoshida@sbchem.kyoto-u.ac.jp

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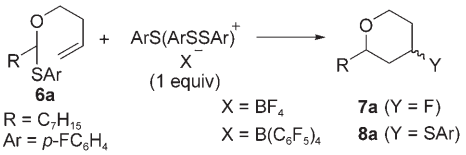
For the mechanism, there are several points to be considered.[12] The conversion of **1** into **2** takes place quantitatively, as we reported previously.[5] However, the reaction of **2** and **3** might be unfavorable because **4** does not have a neighboring cation-stabilizing group such as an oxygen atom, and this step might be a bottleneck for the overall reaction.[13] The last step to form a stable product **5** from unstable cation **4**, however, could be energetically favorable, making the overall reaction successful. Another important point to be considered is that the second step could be made entropically favorable by intramolecularization of the reaction.

On the basis of the above considerations, we started to work on the cation chain reactions initiated by electrochemically generated "ArS^+". We decided to focus our research on the intramolecular version of the reaction. Thus, thioacetal **6a** (Scheme 2, $R = C_7H_{15}$, $Ar = p\text{-}FC_6H_4$) bearing a carbon–carbon double bond was allowed to react with $ArS(ArSSAr)^+BF_4^-$ (1 equiv), which was prepared by anodic oxidation of ArSSAr using Bu_4NBF_4 as a supporting electrolyte in CH_2Cl_2 at −78 °C (0.67 F mol^{-1} based on ArSSAr).[14] As shown in Scheme 2, the reaction at −78 °C led to the formation of cyclized compound **7a**[15] (81% yield) as a mixture of two diastereomers (*cis*/*trans* 6.8:1). Fluoride, instead of ArS, is introduced onto the olefinic carbon atom, indicating that BF_4^- or a fluoride ion derived from BF_4^- serves as a nucleophile.

To avoid the fluoride attack, $Bu_4NB(C_6F_5)_4$ was used as a supporting electrolyte for the initial electrolysis. The formation of $ArS(ArSSAr)^+B(C_6F_5)_4^-$ was confirmed by ^1H NMR spectroscopy and cold-spray ionization (CSI) mass spectrometry.[16] The reaction with **6a** at −78 °C led to effective formation of **8a** (72% yield). In this case ArSSAr attacks the cyclized cation as a nucleophile. It is interesting to note that only the *cis* isomer was obtained (see below).

If the concept shown in Scheme 1 is feasible, the reaction should take place with a catalytic amount of $ArS(ArSSAr)^+$. Thus, the reaction using 20 mol% of $ArS(ArSSAr)^+$ was examined, but the yield of **8a** was low (33%). However, the presence of an excess amount of ArSSAr gave rise to effective



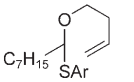
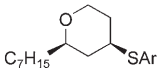
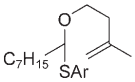
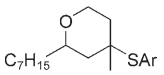
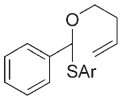
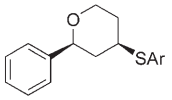
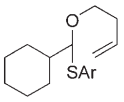
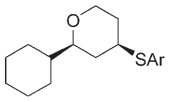
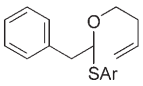
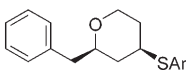
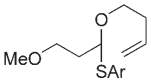
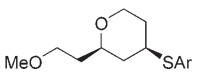
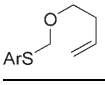
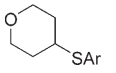
Scheme 2. Intramolecular reaction of thioacetal and olefin.

formation of **8a** in 82% yield. In this case, ArSSAr (1.00 mmol) was electrolyzed with 0.04 F mol^{-1} of electricity (initiation method A; see Table 1), and the thus-obtained solution containing ArS(ArSSAr)$^+$ (0.04 mmol) and ArSSAr (0.94 mmol) was allowed to react with **6a** (0.2 mmol). Further decrease of the amount of ArS(ArSSAr)$^+$ (0.02 mmol) resulted in a decrease of the yield (47%), but the yield could be increased by increasing the reaction temperature (69% at −20 °C, 75% at 0 °C).

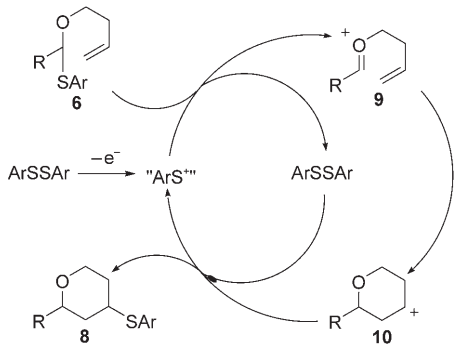
This reaction is generally applicable to various unsaturated thioacetals (**6a**–**g**), and six-membered ring formation takes place effectively as shown in Table 1. The tetrahydropyran rings obtained in this reaction serve as common structural units in a variety of biologically active molecules.[17] It is also noteworthy that the ArS group can be used for further transformations.

This intramolecular carbon–carbon bond-formation reaction seems to proceed by a cation chain mechanism (Scheme 3). The initial electrolysis generates "ArS$^+$", which reacts with **6** to give alkoxycarbenium ion **9** and ArSSAr. The cyclization[18,19] gives **10**, which reacts with ArSSAr to give product **8**. In the last step "ArS$^+$" is regenerated to initiate the next sequence. A high stereoselectivity was observed (exclusive formation of the *cis* isomers, except in **8b**), which

Table 1: Intramolecular carbon–carbon bond formation catalyzed by "ArS$^+$".

Thioacetal		Initiation method[a]	Product		Yield [%][b]
	**6a**	A		**8a**	82[c]
		B			63[c]
	**6b**	A		**8b**	84[d,e]
		B			73[d,f]
	**6c**	A		**8c**	65
		B			60
	**6d**	A		**8d**	88
		B			70
	**6e**	A		**8e**	75
		B			68
	**6f**	A		**8f**	62
		B			51
	**6g**	A		**8g**	63
		B			52

[a] Initiation method A: ArSSAr (Ar = *p*-FC$_6$H$_4$; 1.00 mmol) was electrolyzed in 0.1 M Bu$_4$NB(C$_6$F$_5$)$_4$/CH$_2$Cl$_2$ (8 mL) at −78 °C by using 0.04 F mol^{-1} of electricity. The solution thus obtained was allowed to react with thioacetal **6** (0.20 mmol) at −78 °C for 20 min. Then the reaction was quenched with Et$_3$N (1.0 mL). Initiation method B: A solution containing thioacetal **6** (0.20 mmol) and ArSSAr (Ar = *p*-FC$_6$H$_4$; 1.00 mmol) in 0.1 M Bu$_4$NB(C$_6$F$_5$)$_4$/CH$_2$Cl$_2$ (8 mL) was electrolyzed (0.20 F mol^{-1} based on **6**) under constant-current conditions at −78 °C. [b] Yield of isolated product. [c] Yield determined by GC methods. [d] 3 equiv of ArSSAr was used. [e] d.r. = 9.9:1 *cis*/*trans*. [f] d.r. = 9.7:1 *cis*/*trans*.



Scheme 3. Mechanism of the electroinitiated cation chain reaction.

indicates that the carbon–carbon bond formation and the subsequent reaction of thus-generated **10** with ArSSAr take place in a somewhat concerted manner. The fact that the use of an excess amount of ArSSAr accelerates the reaction is consistent with this mechanism. At a higher concentration of ArSSAr this step becomes more favorable, and hence, the overall reaction is accelerated.

It is noteworthy that the direct (in-cell) electrolysis of a mixture of **6** and ArSSAr was also effective in initiating the reaction (Table 1, initiation method B). Thus, a catalytic amount of electricity (0.20 F mol^{-1} based on **6a**) was passed through a solution of **6a** (0.2 mmol) and ArSSAr (1.0 mmol) in 0.1 M Bu$_4$NB(C$_6$F$_5$)$_4$/CH$_2$Cl$_2$ under constant-current conditions. After the electrolysis the reaction mixture was stirred for 20 min to obtain **8a** in 63% yield. This initiation method is generally applicable to other substrates, as shown in Table 1.

In conclusion, we have developed a chain reaction initiated by the electrochemically generated "ArS$^+$" cation, which involves intramolecular carbon–carbon bond formation. In-cell electrolysis was also effective for the initiation. This electroinitiated cation chain reaction adds a new dimension to organic cation chemistry[3] and organic electrochemistry.[20] Applications of this concept to other cation chain reactions are in progress in our laboratory.

Experimental Section

Electrochemical generation and accumulation of ArS(ArSSAr)$^+$-B(C$_6$F$_5$)$_4^-$ (Ar = *p*-FC$_6$H$_4$): The anodic oxidation was carried out in an H-type divided cell (4G glass filter) equipped with a carbon felt anode and a platinum plate cathode (40 × 20 mm^2). In the anodic chamber was placed a solution of ArSSAr (Ar = *p*-FC$_6$H$_4$; 103 mg, 0.405 mmol) in 0.1 M Bu$_4$NB(C$_6$F$_5$)$_4$/CH$_2$Cl$_2$ (8.0 mL). In the cathodic chamber were placed 0.1 M Bu$_4$NB(C$_6$F$_5$)$_4$/CH$_2$Cl$_2$ (8.0 mL) and trifluoromethanesulfonic acid (44.2 mg, 0.295 mmol). The constant-current electrolysis (8 mA) was carried out at −78 °C with magnetic stirring until 0.67 F mol^{-1} of electricity was consumed. The anodic solution thus obtained was analyzed by CSI-MS (spray temperature 0 °C): HRMS (CSI) calcd for C$_{18}$H$_{12}$F$_3$S$_3^+$ (ArS(ArSSAr)$^+$ (Ar = *p*-FC$_6$H$_4$), [*M*$^+$]): 381.0047; found: 381.0084. The NMR measurement was carried out at −80 °C. Chemical shifts are reported using the methylene signal of CH$_2$Cl$_2$ at $\delta = 5.32$ ppm (^{1}H NMR) as a standard. The large signal coming from CH$_2$Cl$_2$ was reduced by the usual pulse techniques: ^{1}H NMR (600 MHz, 10:1 CH$_2$Cl$_2$/CD$_2$Cl$_2$): $\delta = 7.22$–7.30 (t, J = 8.6 Hz, 6H), 7.35–7.60 ppm (br s, 6H). The ^{1}H NMR spectrum was very similar to that of ArS(ArSSAr)$^+$BF$_4^-$ reported previously.[5]

Typical procedure for initiation method A: The anodic oxidation was carried out in an H-type divided cell as described above. In the anodic chamber was placed a solution of ArSSAr (Ar = *p*-FC_6H_4; 254 mg, 1.00 mmol) in 0.1 M $Bu_4NB(C_6F_5)_4/CH_2Cl_2$ (8.0 mL). In the cathodic chamber were placed 0.1 M $Bu_4NB(C_6F_5)_4/CH_2Cl_2$ (8.0 mL) and trifluoromethanesulfonic acid (6.8 mg, 0.0453 mmol). The constant-current electrolysis (8 mA) was carried out at −78 °C with magnetic stirring until 0.04 F mol^{-1} of electricity was consumed. To the anodic chamber containing electrogenerated $ArS(ArSSAr)^+$-$B(C_6F_5)_4^-$ was added 3-butenyl 1-(4-fluorophenylthio)octyl ether (**6a**; 60.5 mg, 0.195 mmol) and the mixture was stirred for 20 min at −78 °C. The reaction was quenched with Et_3N (1 mL). The solvent was removed under reduced pressure and the residue was quickly filtered through a short column (height 2 cm, diameter 3 cm) of silica gel to remove $Bu_4NB(C_6F_5)_4$. The silica gel was washed with ether (150 mL). The GC analysis of the combined filtrate indicated that **8a** was formed in 82% yield (GC retention time 17.5 min, CBP-1 column; diameter 0.22 mm, thickness 0.25 μm, length 25 m; initial oven temperature 100 °C; rate of temperature increase 10 °C min^{-1}). **8a**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 6.8$ Hz, 3H), 1.18–1.62 (m, 14H), 1.76–1.90 (m, 2H), 3.08 (dddd, $J = 12.0$, 12.0, 4.0, 4.0 Hz, 1H), 3.16–3.25 (m, 1H), 3.37 (ddd, $J = 12.0$, 12.0, 2.0 Hz, 1H), 3.99 (ddd, $J = 12.0$, 6.4, 1.6 Hz, 1H), 6.96–7.03 (m, 2H), 7.38–7.44 ppm (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 14.1$, 22.6, 25.4, 29.2, 29.6, 31.8, 33.3, 36.2, 38.8, 44.7, 67.6, 77.6, 116.0 (d, $J = 21.5$ Hz), 128.3, 135.8 (d, $J = 8.6$ Hz), 162.6 ppm (d, $J = 245.6$ Hz); LRMS (EI): *m/z*: 310 [M^+], 183 [$M^+ - SC_6H_4F$]; HRMS (EI) calcd for $C_{18}H_{27}FOS$ [M^+]: 310.1767; found 310.1767.

Typical procedure for initiation method B: The anodic oxidation was carried out in an H-type divided cell as described above. In the anodic chamber was placed a solution of 3-butenyl 1-(4-fluorophenylthio)octyl ether (**6a**; 62.0 mg, 0.200 mmol) and ArSSAr (Ar = *p*-FC_6H_4; 254.1 mg, 1.00 mmol) in 0.1 M $Bu_4NB(C_6F_5)_4/CH_2Cl_2$ (8.0 mL). In the cathodic chamber were placed 0.1 M $Bu_4NB(C_6F_5)_4/CH_2Cl_2$ (8.0 mL) and trifluoromethanesulfonic acid (10.2 mg, 0.0680 mmol). The constant-current electrolysis (8 mA) was carried out at −78 °C with magnetic stirring until 0.20 F mol^{-1} of electricity (based on **6a**) was consumed. The mixture was stirred for 20 min at −78 °C, and then the reaction was quenched with Et_3N (1 mL). The solvent was removed under reduced pressure and the residue was quickly filtered through a short column (height 2 cm, diameter 3 cm) of silica gel to remove $Bu_4NB(C_6F_5)_4$. The silica gel was washed with ether (150 mL). The GC analysis of the combined filtrate indicated that **8a** was formed in 63% yield.

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