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Integrated Electrochemical–Chemical Oxidation Mediated by Alkoxysulfonium Ions

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Supporting Information

ABSTRACT: Generation of carbocations by the "cation pool" method followed by reaction with dimethyl sulfoxide (DMSO) gave the corresponding alkoxysulfonium ions. Alkoxysulfonium ions could also be generated by in situ DMSO trapping of electrochemically generated carbocations. The resulting alkoxysulfonium ions were transformed into carbonyl compounds by treatment with triethylamine. The present integrated electrochemical–chemical oxidation can be applied to the oxidation of diarylmethanes to diaryl ketones, toluenes to benzaldehydes, and aryl-substituted alkenes to 1,2-diketones. Moreover, the oxidation of unsaturated compounds bearing a nucleophilic group in an appropriate position gives cyclized carbonyl compounds.

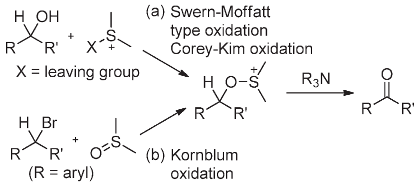
Organic synthesis has been developed mainly on the basis of step-by-step synthesis. However, combining multiple steps without isolating intermediates is strongly needed to enhance the power and efficiency of organic synthesis.[1,2] To this end, chemists have been interested in the integration of chemical reactions to develop synthetic transformations that would be otherwise impossible, such as the generation of unstable highly reactive species that are swiftly utilized for a further reaction before they decompose.[3]

In addition to chemical reactions using chemical reagents and/or catalysts, electrochemical reactions[4,5] using electron transfer on the surface of the electrode serve as a powerful means of generating highly reactive species. Electrochemistry allows for the selective introduction and removal of electrons under mild conditions, whereas this process usually requires harsh conditions when the chemical method is employed.

Among a variety of reactions used in organic synthesis, selective oxidation of organic compounds still remains as a major challenge.[6] We envisaged that integration of electrochemical oxidation and chemical oxidation would be a nice approach to this challenge, and we report here an example of such integration that is mediated by an unstable reactive intermediate.

We chose to use alkoxysulfonium ions as key intermediates because treatment of an alkoxysulfonium ion with a base such as triethylamine eventually gives the corresponding carbonyl compound; this serves as one of the mildest methods for oxidation of organic compounds [dimethyl sulfoxide (DMSO) oxidation] (Scheme 1).[7,8] Although alkoxysulfonium ions can be generated by several chemical methods, the oxidation state of the precursors ($RR'CHX$; X = heteroatom) and the resulting alkoxysulfonium ions ($RR'CH-OS^+Me_2$) are the same, and the overall reaction to give $RR'C{=}O$ is a two-electron oxidation. If substrates of lower oxidation state, for example $RR'CH_2$, could be used to generate alkoxysulfonium ions, the overall reaction would be a four-electron oxidation, and the method would serve as a highly useful way of oxidizing organic compounds.

Scheme 1. Chemical Oxidation Mediated by Alkoxysulfonium Ions



It is well-known that electrochemical oxidation serves as a powerful method for generating carbocations and onium ions under mild conditions.[4] In fact, various types of electrochemical oxidation reactions proceed by a mechanism involving carbocations, though carbocations are usually trapped spontaneously by nucleophiles that are present in the reaction medium. However, we have developed an effective method for generating and accumulating carbocations or onium ions by low-temperature electrochemical oxidation. The method, which is called the "cation pool" method, has been successfully applied to *N*-acyliminium ions,[9] alkoxycarbenium ions,[10] and diarylcarbenium ions.[11] On the basis of these backgrounds, we envisaged that carbocations generated by the cation pool method could be used for a subsequent reaction with DMSO to generate alkoxysulfonium ions, which would then react with an amine base to give the corresponding carbonyl compounds (Scheme 2). In fact, Mayr and co-workers observed in their mechanistic studies that diarylcarbenium ions generated by chemical S_N1 reaction reacted with DMSO and that subsequent treatment with triethylamine gave the diaryl ketones.[12] It should be noted that unlike the chemical methods, the oxidation state of the precursor in the electrochemical method is lower than that of the resulting alkoxysulfonium ion. Therefore, we initiated our studies of the integration of the electrochemical method and the chemical method mediated by alkoxysulfonium ions.

To test the feasibility of the present concept, we first examined the reaction of an electrochemically generated diarylcarbenium ion with DMSO. Thus, diarylcarbenium ion **2** was generated and

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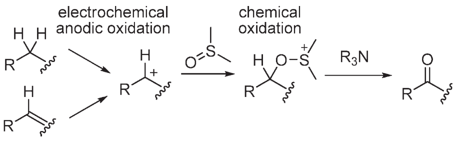
Scheme 2. Integrated Electrochemical−Chemical Oxidation Mediated by Alkoxysulfonium Ions



accumulated by the electrochemical oxidation of diarylmethane **1** in CD_2Cl_2 using Bu_4NBF_4 as a supporting electrolyte at −78 °C according to the "cation pool" method (Figure 1, method A).[11] The addition of DMSO to **2** gave alkoxysulfonium ion **3**, which was well-characterized by NMR analysis at −78 °C. Treatment of the solution of **3** with triethylamine gave the corresponding diaryl ketone **4** in 91% yield. This proof-of-principle experiment revealed that the electrochemical reaction and the chemical reaction could be integrated effectively through the intermediacy of a carbocation and an alkoxysulfonium ion. The method was also applicable to diarylmethane **5** to produce the corresponding diaryl ketone **6** (Table 1).

In-situ trapping of carbocations by DMSO is also effective when the substrate oxidation potential is lower than that of DMSO (1.76 V vs SCE). For example, the electrochemical oxidation of 4-methoxytoluene (**7**) (1.38 V vs SCE) in 1:2 DMSO-d_6/CD_2Cl_2 (Figure 1, method B) gave alkoxysulfonium ion **8**, which was characterized by NMR analysis. In this case, the electrolysis could be carried out at 24 °C because the alkoxysulfoniuim ion is more stable than the corresponding carbocation. Treatment of **8** with triethylamine gave aldehyde **9** in 86% yield. It is noteworthy that the cation pool method cannot be used in this case because 4-methoxybenzyl cation is not stable enough to accumulate in the solution even at −78 °C. It is also noteworthy that the success of the in situ method is attributed to the fact that **7** is more easily oxidized than DMSO. In contrast, the oxidation potential of diarylmethane **1** (1.96 V vs SCE) is higher than that of DMSO, and therefore, the electrochemical oxidation of **1** should be carried out in the absence of DMSO. However, a wide range of organic compounds can serve as substrates for the in situ method. For example, xanthene (**10**) was oxidized effectively by method B to give 9-xanthenone (**11**) (Table 1).

The present method could be extended to the oxidation of aryl-substituted alkenes. For example, 4,4′-dichloro-*trans*-stilbene (**12**) was electrochemically oxidized in the presence of DMSO-d_6 at 0 °C (Figure 2). The NMR study indicated the formation of dialkoxysulfonium ion **13** in the solution. Treatment of **13** with triethylamine gave the corresponding 1,2-diketone **14** in 83% yield. In contrast, chemical oxidation of *trans*-stilbene using $RuCl_3$/$NaIO_4$ gives the corresponding 1,2-diketone (benzil) in only 5% yield and the carbon−carbon bond cleavage product (benzoic acid) as the major product.[13] In addition, the electrochemical method also often suffers from overoxidation. For example, anodic oxidation of alkenes[14] and of 1,2-diols[15] and their derivatives often leads to carbon−carbon bond cleavage. The present method solves this otherwise formidable problem by integration with an extremely mild chemical method such as DMSO oxidation. Therefore, the present method serves as a powerful and highly selective method for the conversion of alkenes to 1,2-dicarbonyl compounds (Table 1).

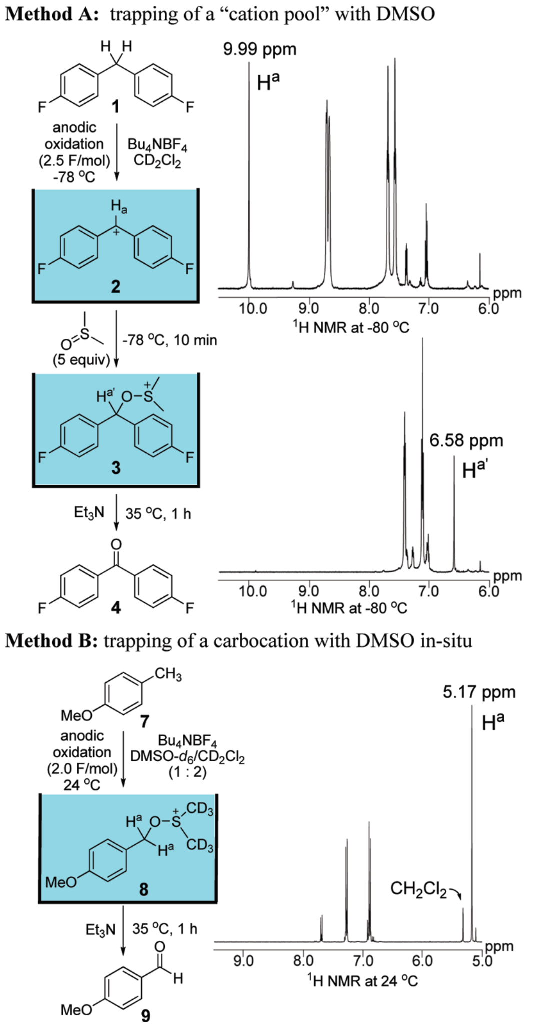


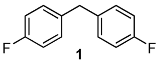
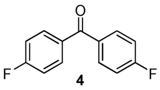
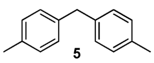
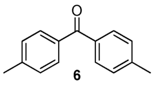
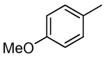
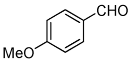
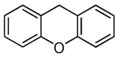
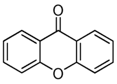
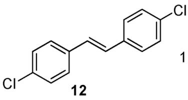
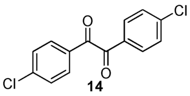
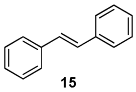
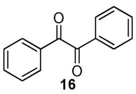
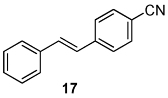
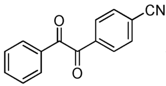
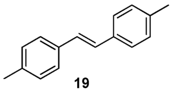
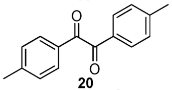
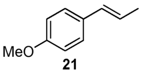
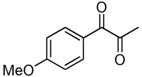
Figure 1. Typical examples of the integrated electrochemical−chemicaloxidation and ^{1}H NMR spectra of the cationic intermediates **2**, **3**, and **8**.

To demonstrate the utility and versatility of the present method, oxidation reactions of alkenes bearing a nucleophilic group in an appropriate position that can participate in the electrochemical oxidation were examined.[16,17] The electrochemical oxidation of **23** took place in the presence of DMSO-d_6 at 0 °C (Figure 3). The formation of cyclized alkoxysulfonium ion **24** was confirmed by NMR analysis. Treatment of **24** with triethylamine gave the corresponding cyclized carbonyl compound **25**.

The alkene substrate scope was also investigated (Table 2). Alkenes bearing a nucleophilic moiety such as a tosylamide (**23** and **26**), a hydroxyl group (**28**), or an aromatic ring (**30**) gave the corresponsing cyclized ketones in moderate to high yields. Moreover, the electrolysis of 1,6-dienes **32**, **34**, **36**, and **38** gave the corresponding cyclized products **33**, **35**, **37**, and **39**, respectively.

In order to gain deeper insight into the mechanism, we measured the oxidation potentials of the substrates (Table 2) and compared them with those of olefinic compounds without nucleophilic functional groups. The oxidation potentials of **23**, **26**, **28**, and **30** were less positive than that of β-methylstyrene (1.42 V vs SCE), indicating that the radical cation generated by one-electron oxidation undergoes rapid cyclization. Also, the oxidation potential of **32** (1.16 V vs SCE) was less postive than that of **40** (1.54 V vs SCE), suggesting that the radical cation rapidly reacts with the other carbon−carbon double bond,[18] as shown in Figure 4.

Table 1. Integrated Electrochemical−Chemical Oxidation of Organic Compounds[a]

substrate	oxidation potential (V)[b]	method	electricity (F/mol)	product	yield (%)[c]
 **1**	1.96	A	2.5	 **4**	91
 **5**	1.75	A	2.5	 **6**	62
 **7**	1.38	B	2.5	 **9**	86[d]
 **10**	1.36	B	4.0	 **11**	84
 **12**	1.36	B	2.1	 **14**	83
 **15**	1.31	B	2.1	 **16**	70 (71)[e]
 **17**	1.44	B	2.1	 **18**	50 (74)[f]
 **19**	1.20	B	2.1	 **20**	71
 **21**	1.09	B	2.5	 **22**	55

[a] The reactions were carried out on a 0.25 mmol scale. [b] Determined by rotating disk electrode (RDE) voltammetry in 0.1 M $LiClO_4/CH_3CN$ using SCE as a reference electrode. [c] Isolated yields are given, unless otherwise stated. [d] GC yield. [e] The reaction was carried out on a 1.3 mmol scale. [f] NMR yield.

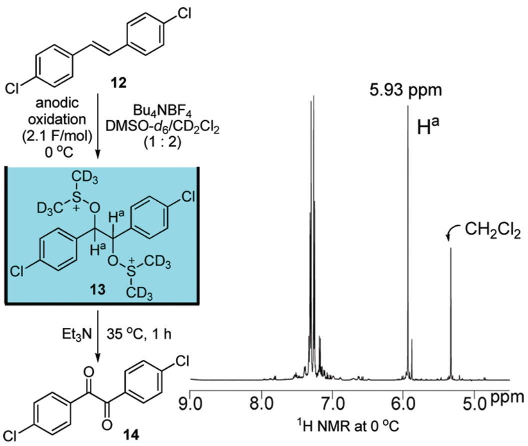


Figure 2. Integrated electrochemical−chemical oxidation of 4,4′-dichloro-*trans*-stilbene and the ^{1}H NMR spectrum of the cationic intermediate **13**.

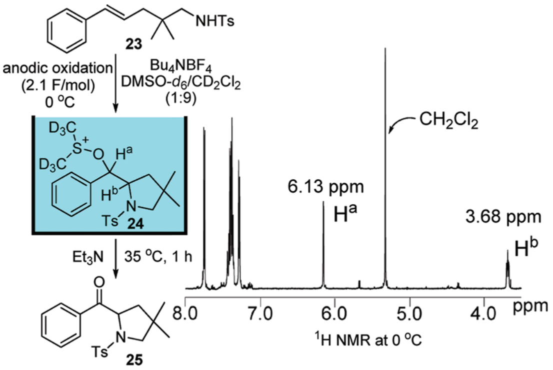


Figure 3. Integrated electrochemical−chemical oxidation of alkene **23** and the ^{1}H NMR spectrum of the cyclized cationic intermediate **24**.

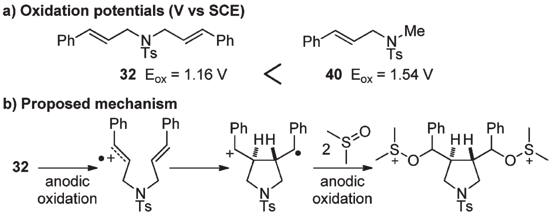
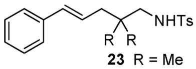
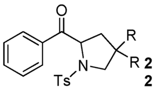
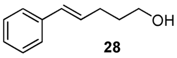
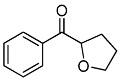
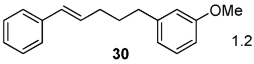
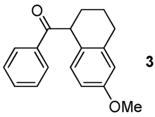
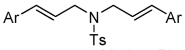
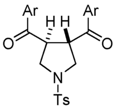
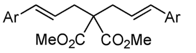
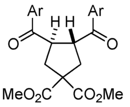


Figure 4. Comparison of oxidation potentials and a proposed mechanism involving the rapid cation radical cyclization.

Table 2. Integrated Electrochemical−Chemical Oxidation Involving Cyclization[a]

substrate	oxidation potential (V)[b]	electricity (F/mol)	product	yield (%)[c]
 **23** R = Me **26** R = H	1.34 1.31	2.1 2.5	 **25** **27**	86[d] 85
 **28**	1.20	3.0	 **29**	52[d]
 **30**	1.21	2.1	 **31**	73
 **32** Ar = Ph **34** Ar = 4-ClC_6H_4	1.16 1.23	2.2 2.1	 **33** **35**	72[e] 90[e]
 **36** Ar = Ph **38** Ar = 4-ClC_6H_4	1.17 1.24	2.1 2.1	 **37** **39**	78 76

[a] The reactions were carried out on a 0.25 or 0.13 mmol scale. [b] Determined by RDE voltammetry in 0.1 M $LiClO_4/CH_3CN$ using SCE as a reference electrode. [c] Isolated yields. [d] 1:2 $DMSO/CH_2Cl_2$ was used. [e] $Bu_4NB(C_6F_5)_4$ was used as a supporting electrolyte.

The electrochemical method is often cited as being environmentally favorable because it enables straightforward transformations under mild conditions without the use of hazardous strong chemical reagents.[19] The present method based on integration of the electrochemical method with an extremely mild, environmentally benign chemical method opens a new aspect of the chemistry of oxidation reactions. Further work to explore the full range of the scope of the present approach and its application to the synthesis of molecules with interesting biological activities and functions is in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental procedures, spectroscopic data for new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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