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Electrochemical Oxidation of Secondary Alcohols Using Thioanisole as an Organic Mediator in the Presence of 2,2,2-Trifluoroethanol

Yoshihiro Matsumura* **and Masaki Yamada**

Faculty of Pharmaceutical Sciences, Nagasaki University,
1-14 Bunkyo-machi, Nagasaki 852, Japan

Naoki Kise and Michitake Fujiwara

Division of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University,
Yoshida, Sakyo, Kyoto 606-01, Japan

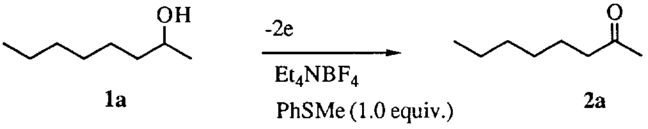
Abstract: Electrochemical oxidation of secondary alcohols gave the corresponding ketones in good yields when 2,2,2-trifluoroethanol was used as a solvent or a co-solvent of MeCN containing Et_4NBF_4 as a supporting electrolyte.

Electrochemical method is an ideal tool to oxidize organic compounds since these can be in principle oxidized without use of any oxidizing reagents which often bring about troublesome working up.[1] The hitherto known direct electrochemical oxidations of alcohols, however, seem still inconvenient because of ineffectiveness caused by high oxidation potentials of alcohols.[2] One of devices to avoid the ineffectiveness is to use a mediatory system in which a mediator is converted to its oxidized form at less positive potential than that required for direct oxidation of alcohols and the oxidized form of the mediator oxidizes alcohols. Although a variety of mediatory systems have been exploited,[3] there have been reported few organic mediators.[4] Organic mediators are very much interesting since a variety of their derivatives are easily available by the structural modification and as the result we can expect the selective oxidation while this depends on the mediators.

Most of electrochemical oxidation using mediators are carried out in a two-phases system, that is, a heterogeneous system consisting of water and organic solvents, but a homogeneous system is desirable for effective oxidation in the cases using organic mediators which have less solubility to water or are sensitive to water during oxidation. Although we have already reported that thioanisole can be used as an organic mediator for oxidation of secondary alcohols, it disliked water. So benzonitrile was used as an unreactive solvent but it was very inconvenient from a synthetic viewpoint.[4a] Recently, 2,2,2-trifluoroethanol (TFE) has been recognized by Schäfer's,[5] Becker's,[6] and our groups[7] as a suitable solvent for direct electrochemical oxidations of some organic compounds because of its easy handling and hardly oxidizable properties. So, we examined the possibility of TFE as a solvent for oxidation of alcohols using thioanisole as a mediator. This paper describes the results showing that the efficient electrochemical oxidation using a mediator is achieved by using TFE as a solvent or an additive.

Results and Discussion

In our continuing study on the usefulness of TFE in electrochemical reaction,[7] we found herein that secondary alcohols could be oxidized by electrochemical oxidation in the presence of thioanisole in TFE. A typical example represented by 2-octanol **1a** is shown in eq 1 which indicates the necessity of TFE in this oxidation reaction. Since the system using TFE as a solvent was very convenient at the stage of working up in contrast with benzonitrile system which was used in our previous work,[4a] we surveyed some factors affecting this oxidation reaction.



1a **2a** (1)

	3F/mol
in MeCN	10%
in TFE	51%

Effect of Solvent

Results obtained in the oxidation of **1a** carried out under a variety of solvents are shown in Table 1 in which the passed electricity was 3F/mol for comparison and the amount of thioanisole was 0.5~1.0 mol equiv. to **1a**. As shown in entry 1, the absence of TFE gave only 10% of 2-octanone **2a**. In this case, the surface of platinum cathode was gradually covered with undissolved unknown materials which increased the terminal voltage (from 3V to 10~15V). On the other hand, the use of TFE as a solvent improved the yield of **2a** (entries 2, 3) with little deposite of unknown materials on cathode surface and little increase of the terminal voltage (3~5V). One of the reasons why TFE increased the yield of **1a** might be due to a property as a protic solvent which keeps the electric conductivity of the solvent system constant during electrolysis. Water as a typical protic solvent could not be replaced with TFE for the formation of **2a** since the presence of water increased the yield of methyl phenyl sulfoxide. In fact, a small amount of methyl phenyl sulfoxide was formed in TFE possibly bacause of a small amount of water contaminated in TFE, and its amount was increased to 65% with a complete consumption of thioanisole by passing an electricity (3F/mol) through a solution of thioanisole (2.5mmol) in TFE (10mL) to which water (10.0mmol) was in advance added.[8] Methyl phenyl sulfoxide might be formed by the reaction of active species generated from thioanisole with water.

The difficulty of getting absolutely dried TFE and the high cost of TFE prompted our effort to decrease the amount of TFE as a solvent. So, we tried the oxidation of **1a** in TFE mixed with other solvents, and found that the oxidation of **1a** in MeCN containing a small amount of TFE (1.0~2.0 equiv. to **1a**) gave satisfactory results (entries 4, 5). Under these reaction conditions, the oxidation smoothly proceeded since deposite on the surface of electrodes was little, and the working up was very easy. On the other hand, MeCN mixed with MeOH (entry 6), MeCN mixed with *t*-BuOH (entry 7), MeOH mixed with TFE (entry 8) or CH_2Cl_2 mixed with TFE (entry 9) gave poor results. In these solvents, protic solvents such as methanol might be oxidized in preference to **1a**.

Table 1. Effect of Solvent on Electrochemical Oxidation of 2-Octanol **1a** in the presence of PhSMe[1-3)]

entry	TFE or ROH (mmol)	Co-solvent (10mL)	2-Octanol **1a** (mmol)	PhSMe (mmol)	Yield(%) of ketone **2a**	Recovery(%) of starting alcohol **1a**
1	TFE (0)	MeCN	5.0	2.5	10	72
2	TFE[4)]	–	5.0	2.5	42	58
3	TFE[4)]	–	5.0	5.0	51	49
4	TFE (10.0)	MeCN	5.0	2.5	76	17
5	TFE (10.0)	MeCN	10.0	2.5	86	9
6	MeOH (10.0)	MeCN	5.0	2.5	17	77
7	*t*-BuOH (10.0)	MeCN	5.0	2.5	6	82
8	TFE (10.0)	MeOH	5.0	2.5	3	93
9	TFE (10.0)	CH_2Cl_2	5.0	2.5	20	66

1) 3F/mol of electricity was passed. 2) Pyridine (5.0mmol) was used as a base.
3) Et_4NBF_4 (2.5mmol) was used as a supporting electrolyte.
4) TFE (10mL) only was used as a solvent.

Effect of Supporting Electrolyte

Effect of supporting electrolytes on the yields of **2a** was shown in Table 2. Tetrafluoroborate gave a better result than perchlorate (entries 1, 3). This result is explained in terms of the difference of their oxidation potentials.[9] On the other hand, tosylate was not a good electrolyte possibly because it might be oxidizable under the reaction conditions (entry 2). In fact, ethyl *p*-tosylate was electrochemically oxidized in TFE to give an acetal of ethyl *p*-formylbenzenesulfonate.[10]

Table 2. Effect of Supporting Electrolyte on Electrochemical Oxidation of 2-Octanol **1a**[1-4)]

entry	Supporting electrolyte (2.5mmol)	Yield(%) of ketone **2a**	Recovery(%) of starting alcohol **1a**
1	Et_4NBF_4	76	17
2	Et_4NOTs	25	61
3	$LiClO_4$	60	33

1) 3F/mol of electricity was passed. 2) Pyridine (5.0mmol) was used as a base.
3) The amount of 2-octanol was 5.0mmol.
4) A mixture of MeCN(10mL)/TFE(10.0mmol) was used as a solvent.

Effect of Base

As described in the section of Discussion, a base plays an important role in this oxidation. Thus, effect of bases on the oxidation of **1a** was studied (Table 3). In general, electrogenerated bases (EGB) have been known to be present under electrolytic conditions.[11] So, **2a** was formed in 68% yield even though any bases were not added (entry 1). A similar yield of **2a** was obtained in the presence of sodium carbonate which did not dissolve in the mixed solvent (TFE/MeCN) (entry 2). A little increase in the yield of **2a** was observed in the cases of pyridine and 2,6-lutidine (entries 3 and 4) but the addition of triethylamine resulted in a low yield (entry 5) possibly because of the low oxidation potential of triethylamine.[12]

Table 3. Effect of Base on Electrochemical Oxidation of 2-Octanol **1a**[1-4)]

entry	Base (mmol)	Yield(%) of ketone **2a**	Recovery(%) of starting alcohol **1a**
1	non	68	28
2	Na_2CO_3 (5.0)	67	26
3	pyridine (5.0)	76	17
4	2,6-lutidine (5.0)	72	25
5	Et_3N (5.0)	15	78

1) 3F/mol of electricity was passed. 2) The amount of 2-octanol was 5.0mmol.
3) Et_4NBF_4 (2.5mmol) was used as a supporting electrolyte.
4) A mixture of MeCN(10mL)/TFE(10.0mmol) was used as a solvent.

Effect of Mediator

It was clarified by scrutinizing the effect of mediator (Table 4) that the electrochemical oxidation of **1a** was largely dependent on thioanisole. Namely, the absence of thioanisole almost did not give **2a** (entry 1) but the electrochemical oxidation in the presence of thioanisole (0.5 equiv.) afforded **2a** in 76% yield at 3F/mol (entry 2). Effect of phenyl alkyl sulfides other than thioanisole and diphenyl sulfide on the yield of **2a** was also examined and the yield of **2** was found to be decreased in the order of Me >> Et > *i*-Pr > *t*-Bu ~ Ph (entries 2~6). These results suggest the importance of methyl group as alkyl group of alkyl phenyl sulfides. Also, methyl octyl sulfide did not give a good yield of **2a** (entry 7), suggesting that oxidation potential of sulfides was an important factor to determine the yield of **2a**. Halide ions were found to be ineffective (entries 8~10).

Electrochemical Oxidation of Some Alcohols

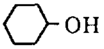
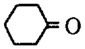
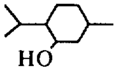
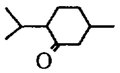
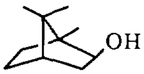
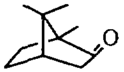
On the bases of the results described above, the best reaction conditions among examined so far were as follows: thioanisole as a mediator, pyridine or 2,6-lutidine as a base, TFE/MeCN as a solvent, and Et_4NBF_4 as a supporting electrolyte. Some secondary alcohols **1a-d** were electrochemically oxidized under the reaction conditions to afford the corresponding ketones **2a-d** (Table 5).

Table 4. Effect of Mediator on Electrochemical Oxidation of 2-Octanol **1a**$^{1\text{-}5)}$

entry	Mediator$^{6)}$	Ep (V vs Ag/Ag$^+$)	Yield(%) of ketone **2a**	Recovery(%) of starting alcohol **1a**
1	non	-	3	85
2	PhSMe	1.21	76	17
3	PhSEt	1.24	25	67
4	PhSPr^i	1.27	10	90
5	PhSBu^t	1.40	2	88
6	PhSPh	1.30, 1.58	0	91
7	n-C_8H_{17}SMe	1.60	14	72
8	Et_4NCl	0.98	10	64
9	Et_4NBr	052, 0.77	8	54
10	Et_4NI	0.10	0	98

1) 3F/mol of electricity was passed. 2) The amount of 2-octanol was 5.0mmol.
3) Et_4NBF_4 (2.5mmol) was used as a supporting electrolyte.
4) A mixture of MeCN(10mL)/TFE(10.0mmol) was used as a solvent.
5) Pyridine (5.0mmol) was used as a base. 6) The amount of mediator was 2.5mmol.

Table 5. Electrochemical Oxidation of Secondary Alcohols **1a-d** Using Thioanisole as a Mediator$^{1\text{-}4)}$

entry	Substrate **1a-d** (5.0mmol)	Mediator PhSMe (mmol)	Yield(%) of ketone **2a-d**		Recovery(%) of starting alcohol **1a-d**
1	**1a**	2.5	**2a**	76	17
2	**1a**	5.0	**2a**	95	4
3	 **1b**	2.5	 **2b**	67	27
4	**1b**	5.0	**2b**	79	19
5	 **1c**	2.5	 **2c**	72	28
6	**1c**	5.0	**2c**	80	18
7	 **1d**	2.5	 **2d**	55	36
8	**1d**	5.0	**2d**	85	13

1) 3F/mol of electricity was passed. 2) Et_4NBF_4 (2.5mmol) was used as a supporting electrolyte.
3) A mixture of MeCN(10mL)/TFE(10.0mmol) was used as a solvent.
4) Pyridine (5.0mmol) was used as a base.

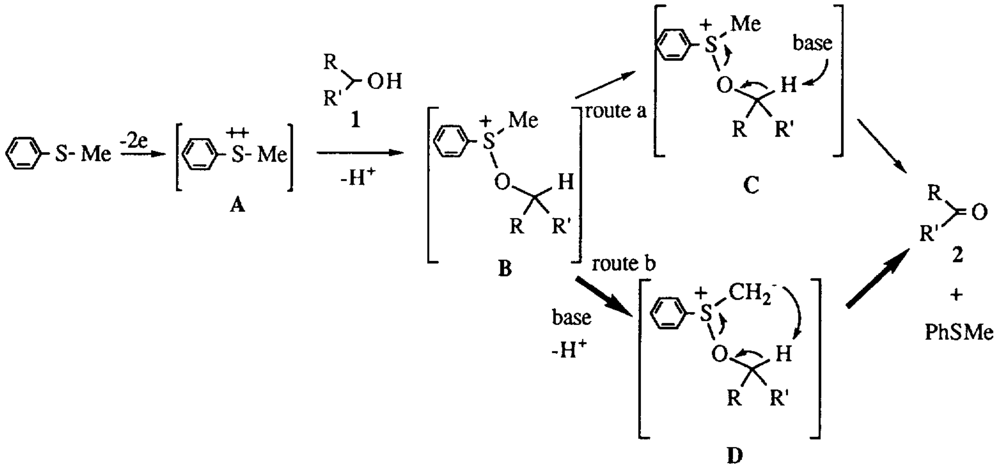
Reaction Mechanism

The plausible reaction mechanism is described in Scheme 1. The initiation step may involve two-electrons transfer from thioanisole to anode giving an active species **A** since cyclic voltammetry of thioanisole showed irreversible Ep at 1.21 V in MeCN which was not shifted by addition of TFE and/or **1** into a solution of thioanisole in MeCN.[13] The active intermediate **A** reacts with alcohols **1** to give the second intermediate **B** with removal of a proton which is trapped with an added base or EGB. In the case of TFE only as a solvent, **A** might react with alcohols but also with water contaminated in TFE to give methyl phenyl sulfoxide which did not work as a mediator, and thus much amount of thioanisole than the amount of water contaminated in TFE was required.

Two routes a and b are conceivable as paths from **B** to final product **2**: (route a) a base abstracts an α-hydrogen of alcoholic part of **B** like **C** and (route b) a base abstracts a hydrogen from methyl group of intermediate **B** followed by intramolecular abstraction of an α-hydrogen of alcoholic part like **D**. On the bases of the results that the yields of **2a** were dependent on R of alkyl phenyl sulfides in the order of Me >> Et > *i*-Pr > *t*-Bu ~ Ph, we postulate that **2** may be generated through route b.[14]

Although the role of TFE in this reaction mechanism is not clear yet, the transformation from **A** through **B** and **D** to **2** may be more accelerated in protic solvents (MeCN/TFE) than MeCN only.

The formation of aldehydes from primary alcohols under reaction conditions similar to the oxidation of **1** to **2** was not so efficient as those of **1**. The yields of aldehydes were low (3F/mol, 20~30%). The reactivity of **A** toward primary alcohols should be clarified but this subject is under investigation.



Scheme 1. Mechanism for electrochemical oxidation of alcohols **1** using PhSMe as a mediator

EXPERIMENTAL

General. GC was measured on a GC-12A of Shimadzu Seisakusho Inc., and CV on a 100B/W&CV50W of B.A.S. Inc.. ^{1}H NMR spectra were measured on a Varian Gemini 200 spectrometer with TMS as an internal standard. Mass spectra were obtained on a JEOL IMS-DX 300 instrument. Electrochemical reactions were carried out by using DC Power Supply (GP 050-2) of Takasago Seisakusho, Inc..

Materials. MeCN was distilled over P_2O_5. 2,2,2-Trifluoroethanol was distilled after standing on molecular Sieve 4A overnight. Methylene chloride and *t*-butanol were distilled after dried on $CaCl_2$. Methanol was distilled after dried by sodium methoxide. Pyridine (special grade) was used after distillation on KOH pellets. Anhydrous Et_4NCl, Et_4NBr, Et_4NI, Et_4NBF_4, Et_4NOTs and $LiClO_4$ were commercially available and used without further purification. All starting alcohols **1a-d** and the products ketones **2a-d** were commercially available.

Electrochemical oxidation of 1a-d: A typical electrochemical oxidation was carried out as follows: Into an undivided cell equipped with platinum anode and cathode (1 x 2cm^2) was added a solution of **1** (5.0~10.0mmol) in 2,2,2-trifluoroethanol (TFE;10mL) or MeCN(10mL)/TFE(10.0mmol) containing tetraethylammonium tetrafluoroborate (2.50mmol) as a supporting electrolyte. After 3F/mol of electricity was passed with a constant current (100 mA), a standard sample was added to the electrolyte, and the resulting solution was poured into water and the organic portion was extracted with ether (3 x 50mL). The yields of **1** and the products **2** were obtained by GC method. The identification of **2a-d** were achieved by ^{1}H NMR spectra of crude products and by comparison of their retention times on GC with those of authentic samples. The yields of **2a-d** and the recovery of **1a-d** were obtained by GC internal standard method.

CV measurement: Typical measurement was carried out as follows; a solution of PhSMe (0.1mmol) in MeCN(10mL) containing 0.1M Et_4NBF_4 was measured. Reference electrode was $Ag/Ag^+/MeCN/Bu_4NClO_4$, a working electrode was a glassy carbon, and a counter electrode was platinum. Scan rate was 100mV/s.

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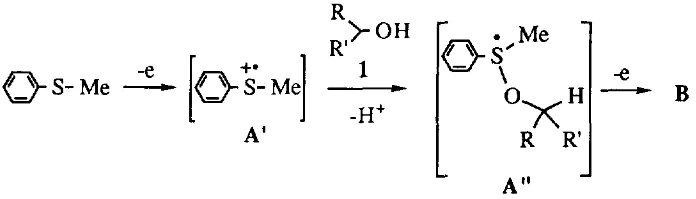

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