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# Anionic WS-TEMPO-mediatory electrooxidation of alcohols in water: halide-free oxidation directed towards a totally closed system

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**Abstract**—Electrooxidation of alcohols in water with water-soluble *N*-oxyl derivatives bearing a sulfonic acid group (anionic WS-TEMPOs) as a mediator proceeded to afford the corresponding ketones and aldehydes in moderate to good yields. The aqueous solution containing WS-TEMPOs could be readily recovered and reused for the electrooxidation of alcohols, thereby providing a totally closed system.

Water has received considerable attention as one of the most desirable reaction media, because it is cheap, safe, and environment-friendly.[1] From the environmental point of view, we developed an interest in the electrooxidative transformation system in water,[2] which provides a totally closed system. For instance, we have developed electrooxidation systems for alcohols in aqueous media dispersed with *N*-oxyl-immobilised silica gel[3] or polymer particles.[4] Both the dispersed phase and dispersion media could easily be recovered and reused. Recently, we developed an electrooxidation system in aqueous NaBr using a water-soluble *N*-oxyl derivative (cationic WS-TEMPO **1**) bearing an ammonium group as a cationic hydrophilic moiety.[5] In the system, the oxidised products could be easily isolated by an extractive workup. Because **1** that was dissolved in water remained in the aqueous phase after the extraction, the recovered aqueous phase could be reused for electrooxidation (Fig. 1). Though various primary and secondary alcohols could be oxidised by the cationic WS-TEMPO mediatory system, the addition of NaBr was indispensable for the reaction, probably because **1** could not be oxidised directly at the anode owing to the repulsion between the anode and the cationic TEMPO. Since the addition of NaBr occasionally causes undesired bromination of the substrates, an oxidation system without NaBr is preferable. We can reasonably expect that WS-TEMPO bearing a sulfonic acid group as an anionic hydrophilic

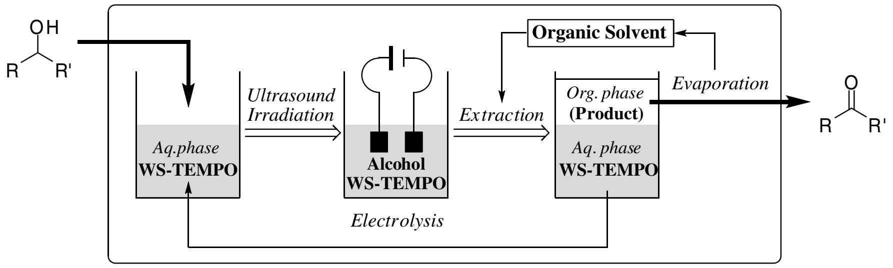

**Figure 1.** A totally closed system using WS-TEMPO for the electrooxidation of alcohols in water.

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*Keywords*: Electrooxidation; Alcohol; Water-soluble mediator; *N*-Oxyl; TEMPO; Water.

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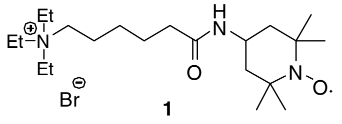
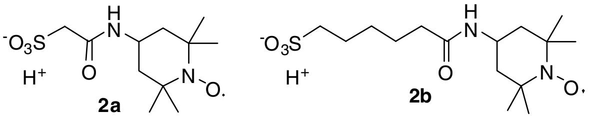
moiety (anionic WS-TEMPO) should be brought into direct contact with an anode, and the oxidation using anionic WS-TEMPO as a mediator should proceed smoothly without the addition of NaBr. In this study, we report an electrooxidation system for alcohols using anionic WS-TEMPO **2** as a mediator.[6,7] (see Schemes 1 and 2).

We first conducted the WS-TEMPO **2a**/**2b**-mediatory electrooxidation of benzylic alcohol **3a** in distilled water, and found that the reaction proceeded without NaBr as expected (Table 1). When 2.5 F/mol of electricity was passed through an aqueous solution of **3a**, the oxidation reaction proceeded to afford the corresponding ketone **4a** without the addition of NaBr (entries 1 and 2). With 4.5 F/mol of electricity, **3a** was entirely consumed and **4a** was obtained in 92% (using **2a**, entry 5) and 95% (using **2b**, entry 6) yields, respectively.

With regard to the abovementioned syntheses, the current efficiency of the electrooxidation method was unsatisfactory. To enhance the efficiency of the reaction, further optimisation of the anionic WS-TEMPO-mediatory electrooxidation system was carried out. During the course of this study, we found that the efficiency of the **2**-mediatory electrooxidation was highly influenced by the supporting electrolyte (Table 2). In particular, when **2b** was used as a mediator, the yield of **4a** drastically changed due to the addition of the electrolyte. Several types of electrolytes were employed for the electrooxidation of **3a**. $LiClO_4$ and $NaClO_4$ were not effective for the reaction. By the addition of $LiClO_4$ or $NaClO_4$, the yield of **4a** slightly increased to 68% and 63%, respectively (entries 4 and 6). Quaternary ammonium salts were found to be suitable for the oxidation. By using $Et_4NOTs$, **4a** was obtained in 83% yield (entry 8), and the optimum yield of **4a** (90%) was obtained when employing $Et_4NClO_4$ (entry 10).

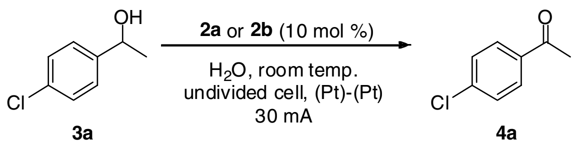


**Scheme 1.** Cationic WS-TEMPO **1**.



**Scheme 2.** Anionic WS-TEMPOs **2a** and **2b**.

**Table 1.** WS-TEMPO-mediatory electrooxidation of benzylic alcohol **3a**[a]

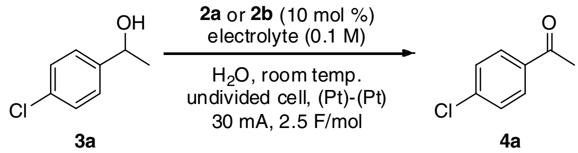


| Entry | Mediator | Electricity (F/mol) | Conv. (%) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | **2a** | 2.5 | 63 | 58 |
| 2 | **2b** | 2.5 | 63 | 57 |
| 3 | **2a** | 3.5 | 100 | 77 |
| 4 | **2b** | 3.5 | 100 | 86 |
| 5 | **2a** | 4.5 | 100 | 92 |
| 6 | **2b** | 4.5 | 100 | 95 |

[a] In the presence of **2** (10 mol %), **3** (1.0 mmol) was oxidised electrochemically in distilled water at room temperature (30 mA).

[b] Isolated yield.

**Table 2.** Electrooxidation of **3a** with a variety of electrolytes[a]



| Entry | Mediator | Electrolyte | Conv. (%) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | **2a** | — | 63 | 58 |
| 2 | **2b** | — | 63 | 57 |
| 3 | **2a** | $LiClO_4$ | 62 | 61 |
| 4 | **2b** | $LiClO_4$ | 72 | 68 |
| 5 | **2a** | $NaClO_4$ | 53 | 51 |
| 6 | **2b** | $NaClO_4$ | 64 | 63 |
| 7 | **2a** | $Et_4NOTs$ | 51 | 45 |
| 8 | **2b** | $Et_4NOTs$ | 87 | 83 |
| 9 | **2a** | $Et_4NClO_4$ | 69 | 58 |
| 10 | **2b** | $Et_4NClO_4$ | 94 | 90 |

[a] In the presence of **2**, benzylic alcohol **3a** (1.0 mmol) was oxidised electrochemically in aq 0.1 M supporting electrolyte solution at room temperature (30 mA, 2.5 F/mol).

[b] Isolated yield.

Recently, we found that the formation of a nanoemulsion complex of TEMPO and amphiphilic alcohols enhances the reactivity of the electrooxidation of alcohols in water.[8] We assumed that a similar phenomenon would occur in the anionic WS-TEMPO-mediatory electrooxidation of alcohols, that is, the anionic WS-TEMPO might form an anionic oil-in-water emulsion including benzylic alcohol, and the attractive force between the sulfonate ion and the positive charge of anode would facilitate direct electron transfer from the *N*-oxyl moiety to the anode (Fig. 2). The high reactivity of WS-TEMPO **2b** was probably caused by the high stability of the nanoemulsion formed by **2b**, which has a long hydrophobic alkyl chain.

Similar to **1**, **2a** and **2b** were found to remain intact in the aqueous solution after the extractive workup process, and the aqueous phase containing **2a** or **2b** could be reused. The recycle use of the aqueous phase containing **2b** is shown in Figure 3. After the first run, the electrooxidation of **3a** using the recovered aqueous solution of **2b** was carried out to afford **4a** in 95% yield. The same process was repeated for a total of five times. The yield of **3a** varied in the range of 80–95%; these results showed that the aqueous solution of **2b** could be reused.

Finally, the **2b**-mediatory electrooxidation of several alcohols was carried out in water (Table 3).[9] The

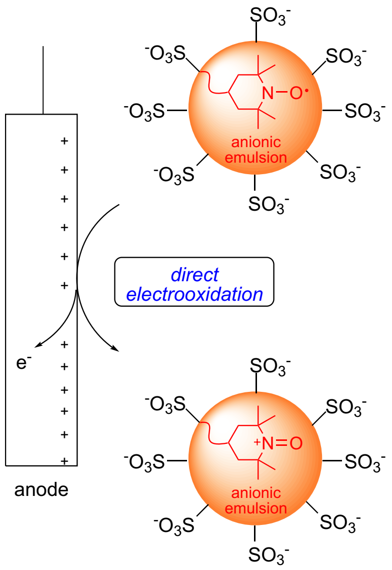


**Figure 2.** Plausible mechanism of oxidation of anionic WS-TEMPO at anode.

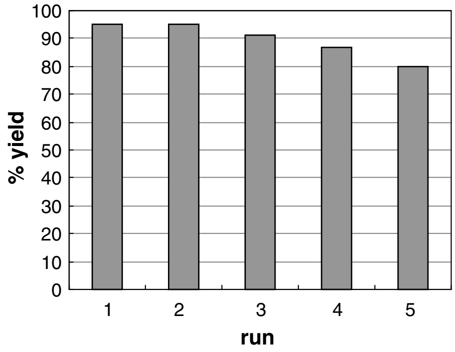
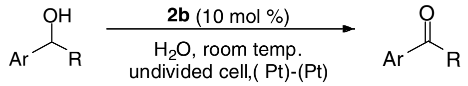


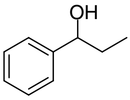
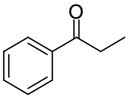
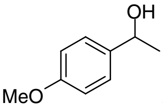
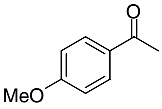
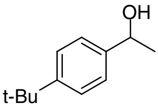
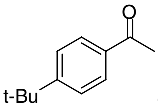
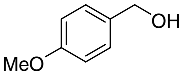
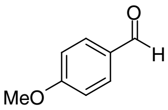
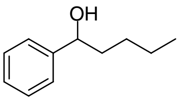
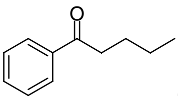
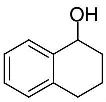
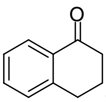
**Figure 3.** Recycle use of the $Et_4NClO_4$ solution containing **2b**.

electrooxidation of 1-phenyl-1-propanol (**3b**) in water gave **4b** in 81% yield (entry 1). In contrast to the reaction of **3a**, the reaction of benzylic alcohols, which do not have an electron-withdrawing group, proceeded smoothly in water, without the addition of an electrolyte. Several primary and secondary benzylic alcohols bearing electron-donating groups were electrooxidised under similar conditions, and the corresponding carbonyl compounds were obtained in good to high yields (entries 2–4). It is noteworthy that the oxidation of (4-methoxyphenyl)-1-ethanol, which was partially brominated by electrooxidation using NaBr, was not accompanied by side-reactions,

**Table 3.** **2b**-Mediatory electrooxidation of several alcohols[a]



**3** **4**

| Entry | Alcohol | Product | Yield[b] (%) |
|---|---|---|---|
| 1 |  **3b** |  **4b** | 81 |
| 2 |  **3c** |  **4c** | 91[c] |
| 3 |  **3d** |  **4d** | 88 |
| 4 |  **3e** |  **4e** | 87 |
| 5 |  **3f** |  **4f** | 63 |
| 6 |  **3g** |  **4g** | 22 |

[a] In the presence of **2b** (10 mol %), **3** (1.0 mmol) was oxidised electrochemically in $H_2O$ at room temperature (30 mA, 2.5 F/mol).

[b] Isolated yield.

[c] **2a** can also be utilized (92% yield).

and the desired ketone **4c** was obtained as the sole product (91% yield, entry 2). The electrooxidation of solid benzylic alcohol **3g** hardly proceeded, and the desired ketone **4g** was obtained only in 22% yield (entry 5); this was probably due to the difficulty in the formation of the emulsion complex of WS-TEMPO including the benzylic alcohol.

In summary, the **2a**- or **2b**-mediatory electrooxidation of benzylic alcohols was found to proceed smoothly without the addition of NaBr, and the corresponding carbonyl compounds were obtained selectively. The aqueous phase recovered after the oxidation reaction contained **2**, and could be reused for the next electrooxidation reaction. The further study of the anionic WS-TEMPO-mediatory electrooxidation is in progress in our laboratory.

## Acknowledgements

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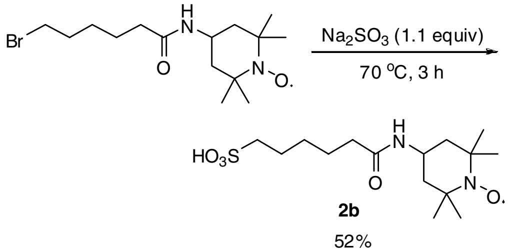
5. Kubota, J.; Shimizu, Y.; Mitsudo, K.; Tanaka, H. *Tetrahedron Lett.* **2005**, *46*, 8975.
6. WS-TEMPO **2a** was prepared according to the literature procedure, see: Akutsu, H.; Yamada, J.; Nakatsuji, S. *Chem. Lett.* **2003**, *32*, 1118.
7. WS-TEMPO **2b** was prepared as follows: To a solution of 4-(6-bromohexanoylamino)-2,2,6,6-tetramethylpiperidine-1-oxyl (1000 mg, 2.9 mmol) in EtOH (18 mL) was added dropwise a solution of $Na_2SO_3$ (378 mg, 3.0 mmol) in $H_2O$ (6 mL) and stirred at 70 °C for 3 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel ($CH_2Cl_2$/MeOH 5:1) to afford 6-(2,2,6,6-tetramethyl-piperidin-1-oxyl-4-ylamino)-6-oxohexane-1-sulfonic acid **2b** (529 mg, 52%). $^1$H NMR (200 MHz, $CD_3OD$) $\delta$ 1.17 (d, $J = 3.2$ Hz, 12H), 1.25–1.77 (m, 10H), 2.16 (t, $J = 7.7$ Hz, 2H), 2.80 (t, $J = 7.7$ Hz, 2H), 4.00–4.10 (m, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 20.3, 25.6, 26.6, 29.1, 32.5, 36.8, 41.9, 45.8, 52.3, 60.3, 175.1; IR (KBr) 3449, 2978, 1648, 1221, 1042 cm$^{-1}$. Anal. Calcd for $C_{15}H_{29}N_2O_5S$: C, 51.55; H, 8.36; N, 8.02. Found: C, 51.50; H, 7.86; N, 8.45.



**2b**

52%

8. Yoshida, T.; Kuroboshi, M.; Oshitani, J.; Goto, K.; Tanaka, H. *Synlett* **2007**, 2691.
9. The typical procedure of the electrooxidation is as follows: In a beaker-type undivided cell was placed a mixture of 1-(4-methoxyphenyl)ethanol **3c** (152 mg, 1.0 mmol) and **2b** (35 mg, 0.10 mmol) in $H_2O$ (8 mL). Two platinum electrodes were immersed in the mixture ($1.5 \times 1.0$ cm$^2$), and the entire apparatus was sonicated for 10 min. Subsequently, constant current electrolysis was carried out at room temperature with vigorous stirring until 2.5 F/mol of electricity was passed. After the electrolysis, the mixture was extracted with EtOAc ($4 \times 15$ mL). The combined organic phase was dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc 5:1) to afford 1-(4-methoxyphenyl)ethanone **4c** (137 mg, 91%).