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Tetrahedron Letters 46 (2005) 8975–8979

Tetrahedron Letters

Water-soluble *N*-oxyl compounds-mediated electrooxidation of alcohols in water: a prominent access to a totally closed system

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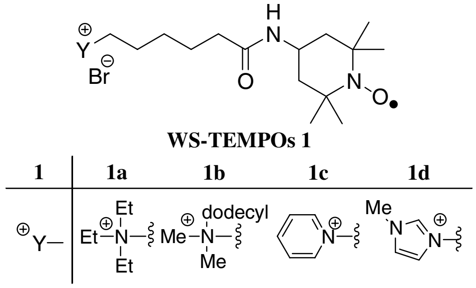
Received 27 September 2005; revised 20 October 2005; accepted 24 October 2005

Abstract—Electrooxidation of alcohols in water involving water-soluble *N*-oxyl compounds (**WS-TEMPOs**) proceeded smoothly to afford the corresponding ketones and aldehydes in good yields. Notably, most of **WS-TEMPOs** in water remained intact after the electrolysis. The aqueous solution containing **WS-TEMPOs** was recovered easily and repeatedly used for the electrooxidation of alcohols, offering a totally closed system.

Water is an ideal solvent for organic synthesis since water is a safe, cheap, and environmentally friendly solvent; thus, organic reactions in water have received significant attention of organic chemists.[1] Electroorganic reaction is one of the most promising tools for environmentally benign protocol because only passage of required electricity can promote the reaction without consumption of any oxidants or reductants. Therefore, electroorganic reaction in water must be one of the most challenging subjects in green organic synthesis.[2] Along this line, we have developed the electrooxidation of alcohols in a disperse system with an *N*-oxyl-immobilized silica gel[3] or polymer particles[4,5] as the disperse phase and aqueous saturated $NaHCO_3$ containing 20 wt % NaBr as the disperse media.[5] Both the disperse phase and the disperse media could be recovered by simple operations and used for the subsequent electrolysis, thereby offering a totally closed system for the electrooxidation of alcohols. In our continuing studies on electrooxidation of alcohols **2** in water, we found that the electrooxidation of alcohols could be achieved in water containing water-soluble *N*-oxyl compounds[6] (**WS-TEMPOs**, Scheme 1) **1a–d** in which **WS-TEMPOs** would work as an emulsifier as well as a mediator (electron transfer catalyst). Extractive work-up afforded the corresponding ketones and aldehydes **3** in good to moderate yields. It is worthy to note that most of the **WS-TEMPOs** dissolved in water remained intact after extractive workup process. The recovered aqueous solution containing **WS-TEMPOs** could be used repeatedly for the electrooxidation of alcohols, thereby offering a novel totally closed electrolysis system as illustrated in Figure 1. Herein, we report the electrooxidation of alcohols **2** in water containing **WS-TEMPOs**.



Scheme 1. Water-soluble *N*-oxyl compounds (**WS-TEMPOs**).

Water-soluble *N*-oxyl compounds (**WS-TEMPOs**) **1a–d** were prepared in the manner as illustrated in Scheme 2. 6-Bromohexanoic acid (**4**) was treated with 4-amino-2,2,6,6-tetramethylpiperidine-*N*-oxyl (4-amino-TEMPO) in CH_2Cl_2 in the presence of DCC and a catalytic amount of DMAP at room temperature for 18 h to afford 4-(6-bromohexanoylamino)-2,2,6,6-tetramethylpiperidine-*N*-oxyl **(5)** in 93% yield. Treatment of **5** with triethylamine in refluxing ethanol for 24 h afforded **WS-TEMPO 1a** in 98% yield. **WS-TEMPO 1a** was

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Keywords: Electrooxidation; Alcohols; Water-soluble mediators; *N*-Oxyl compounds; Aqueous solution.

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doi:10.1016/j.tetlet.2005.10.114

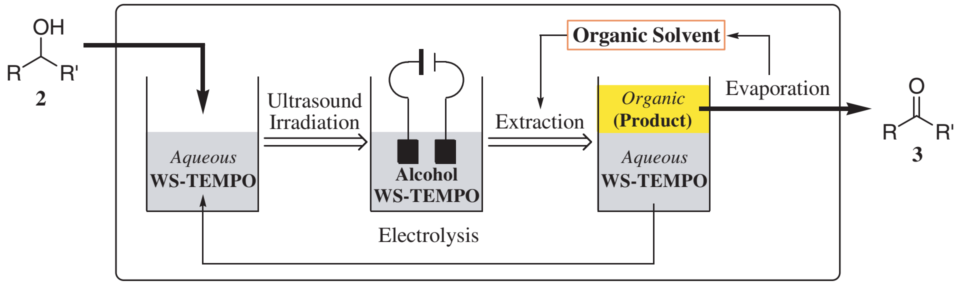
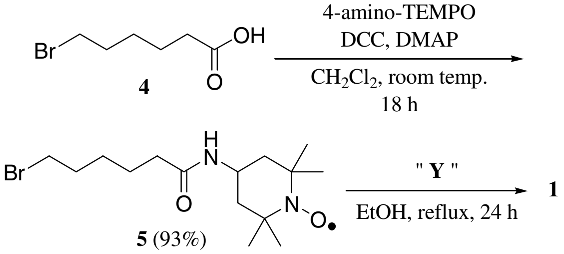


Figure 1. A totally closed system for the electrooxidation of alcohols in water.



Scheme 2.

soluble (>1.0 g/mL) in water, methanol, ethanol, 2-propanol, acetone, CH_2Cl_2, THF, acetonitrile, and DMF, but hardly soluble (<4 mg/mL) in hexane, EtOAc, Et_2O, benzene, and toluene. In a similar manner, the reaction of **5** with *N*,*N*-dimethyldodecylamine, pyridine, and *N*-methylimidazole afforded the corresponding **WS-TEMPOs 1b–d** in quantitative yields, respectively. **WS-TEMPOs 1b–d** are also soluble in water (>1.0 g/mL).

The high solubility of **WS-TEMPOs 1** in water prompted us to investigate electrooxidation of alcohols **2** in water containing **1**. A typical electrolysis procedure is as follows: in a test tube was placed a mixture of 1-(4-methylphenyl)ethanol (**2a**, 0.70 mmol) and a catalytic amount of **WS-TEMPO 1a** (10 mol %) in an aqueous saturated $NaHCO_3$ solution containing sodium bromide (20 wt %) (Fig. 2A). The mixture was irradiated by ultrasound for a few minutes to afford an emulsion (Fig. 2B). Into the mixture were immersed two platinum electrodes (1×1 cm^2) and a regulated dc power (30 mA) was supplied under vigorous stirring at 0 °C. After passage of 2.5 F/mol of electricity, the aqueous solution was extracted with EtOAc (5×5 mL) (Fig. 2C), the combined extracts were dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed by short-path column (SiO_2) to afford

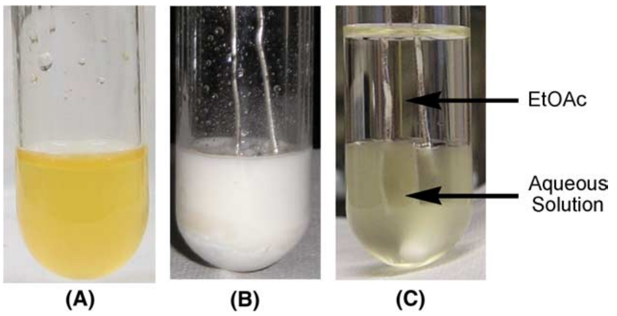
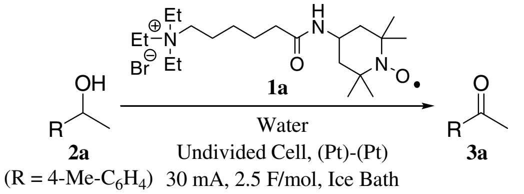


Figure 2. A solution of (A) **WS-TEMPO 1a** in ion-free water, (B) a mixture of **WS-TEMPO 1a**, 1-(4-methylphenyl)ethanol **2a** in ion-free water after ultrasonic irradiation, and (C) extraction of the aqueous solution with EtOAc.

Table 1. Electrooxidation of alcohol **2a** in **WS-TEMPO 1a**/Water[a]



Entry	**1a** (mol%)	Additives	Yield **3a** (%)[b]	Recov. **2a** (%)[b]
1	10	20 wt % NaBr, Satd $NaHCO_3$	74	23
2	10	20 wt % NaBr	74	20
3	10	Satd $NaHCO_3$	18	71
4	10	—	92	7
5	—	20 wt % NaBr	26	76
6	—	aq Satd $NaHCO_3$	3	91
7	—	4-$PhCO_2$-TEMPO (10 mol %), Hexadecyl-$Me_3N^+Br^-$ (10 mol %)	29	40

[a] Electrooxidation of **2a** (0.70 mmol) using **WS-TEMPO 1a** (10 mol %) in aqueous solution was carried out at a constant current (30 mA/cm^2, 2.5 F/mol) in an undivided cell under cooling with ice bath.

[b] Isolated yield.

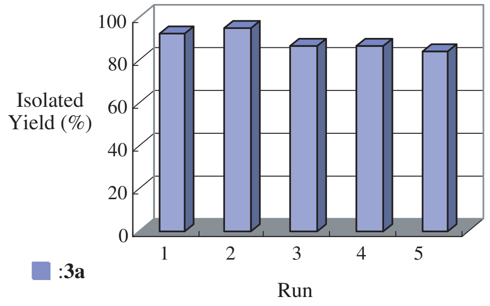
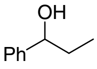
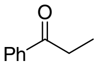
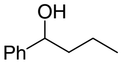
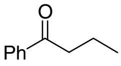
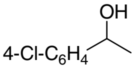
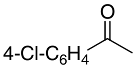
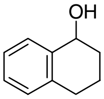
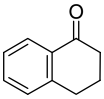
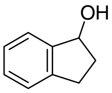
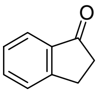
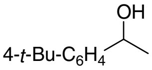
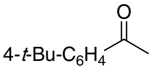
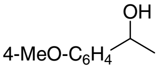
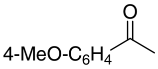
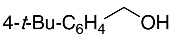
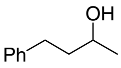
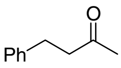
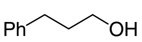
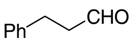
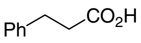


Figure 3. Recycle use of the solution containing **WS-TEMPO 1a**.

4-methylacetophenone (**3a**) in 74% yield together with recovered **2a** in 23% (Table 1, entry 1). No appreciable amount of **1a** was recovered from the extracts, suggesting that most of **1a** remained intact in the aqueous phase after the extractive workup.

No significant change of the yield of **3a** was observed when the electrolysis was carried out in the absence of $NaHCO_3$ (entry 2). On the other hand, the oxidation did not efficiently proceed in the presence of $NaHCO_3$ alone (entry 3). In the previous paper, we have developed the electrooxidation of alcohols in an organic/aqueous two phase system, for example, CH_2Cl_2/aq satd $NaHCO_3$ containing 20 wt % NaBr, in which two redox couples (*N*-oxyl/*N*-oxoammonium and Br^-/Br^+) work as mediators, and both bromide ion and $NaHCO_3$ are indispensable for the efficient electrooxidation of alcohols in two phase system.[7] In sharp contrast, the

Table 2. Electrooxidation of alcohols **2** using **WS-TEMPO 1a**[a]

Entry	Alcohol		Product (yield)[b]	
1		**2b**		**3b** (81%)
2		**2c**		**3c** (78%)
3[c]		**2d**		**3d** (81%)
4[d]		**2e**		**3e** (80%)
5[d]		**2f**		**3f** (85%)
6[d]		**2g**		**3g** (79%)
7		**2h**		**3h** (49%)[e]
8		**2i**	4-*t*-Bu-C_6H_4-CHO	**3i** (80%)
9		**2j**		**3j** (3%)
10[f]				**3j** (90%)
11		**2k**	 	**3k** (trace) **6** (—)
12[g]				**3k** (28%)[h] **6** (19%)[h]
13[g]				**3k** (—)[i] **6** (78%)[i]

[a] Electrooxidation of **2** (0.70 mmol) using WS-TEMPO **1a** (10 mol %) in aqueous solution was carried out under a constant current (30 mA, 2.5 F/mol) in an undivided cell under cooling with ice bath.

[b] Isolated yield.

[c] 3.0 F/mol of electricity was passed.

[d] 3.5 F/mol of electricity was passed.

[e] 4-Bromoanisole (4%), 1-(3-bromo-4-methoxyphenyl)ethanol (8%), and 3-bromo-4-methoxyacetophenone (6%) were obtained.

[f] In the absence of 20 wt % NaBr.

[g] In the presence of 30 wt % NaBr.

[h] 3-Phenylpropyl 3-phenylpropanoate (6%) and 1,1-bis(3-phenylpropoxy)-3-phenylpropane (10%) were also obtained.

[i] 5.0 F/mol of electricity was passed.

electrooxidation of **2a** in the present emulsion system proceeded most efficiently in the absence of both $NaHCO_3$ and NaBr, affording **3a** in excellent yield (entry 4). The presence of **WS-TEMPO 1a** is indispensable for the efficient oxidation of alcohol **2a**; thus the yield of **3a** decreased to 26% and 3%, respectively, when the electrolysis was carried out without **1a** (entries 5 and 6). These results indicate that **1a** would play significant roles in the electrooxidation, presumably as both emulsifier and mediator. Notably, the electrooxidation of **2a** was not efficiently achieved with a combination of 10 mol % of 4-benzyloxy-2,2,6,6-tetramethylpiperidine-*N*-oxyl (mediator) and 10 mol % of hexadecyltrimethylammonium bromide (emulsifier), affording only 29% yield of **3a** (entry 7). In a similar manner, the electrooxidation of **2a** in water containing other **WS-TEMPOs 1b–d** was examined. The yield of **3a** decreased in the order: 92% (**1a**) > 72% (**1c**) > 71% (**1d**) > 54% (**1b**).

As mentioned above, most of the **WS-TEMPO 1a** remained intact in the aqueous solution after the extractive workup process. This fact enabled us to investigate the recycled use of the aqueous solution (Fig. 3). After the first run, electrooxidation of **2a** using the recovered aqueous solution of **1a** (second run) was carried out in a similar manner to that described above to afford the corresponding ketone **5a** in 95% yield. The same process was repeated for totally five times. The yield of **3a** varied in the range 84–95%, demonstrating that the aqueous solution of **WS-TEMPO 1a** could be used repeatedly.

The scope of the electrooxidation of alcohols in water containing the recyclable mediator **1a** was investigated and the results are shown in Table 2. The electrooxidation of benzylic *sec*-alcohols **2b** and **2c** give the corresponding ketones **3b** and **3c** in good yields, respectively (entries 1 and 2). The oxidation of alcohols **2d**, **2e**, **2f**, and **2g** was also performed successfully when a slightly excess amount of electricity was passed (entries 3–6). However, the present electrolysis system could not successfully be applied to the oxidation of 1-(4-methoxyphenyl)ethanol **2h** since the electron-donating substituent facilitated the bromination on the aromatic ring, affording significant amounts of brominated products, for example, 4-bromoanisole, 1-(3-bromo-4-methoxyphenyl)ethanol, and 3-bromo-4-methoxyacetophenone (entry 7). Electrooxidation of benzylic *prim*-alcohol **2i** proceeded smoothly to give the corresponding aldehyde **3i** in 80% yield and no appreciable amount of over-oxidation product was isolated (entry 8). In contrast, the electrooxidation of aliphatic *sec*-alcohol **2j** did not efficiently proceed under similar conditions to those described above, affording only 3% of the ketone **3j** (entry 9). The yield of ketone **3j** was improved significantly when the electrolysis was carried out in 20 wt % NaBr solution (entry 10). On the other hand, electrooxidation of aliphatic *prim*-alcohol **2k** afforded only a trace amount of the corresponding aldehyde **3k**, and most of the alcohol **2k** was recovered (entry 11). Upon a similar electrolysis in the presence of 30 wt % NaBr, the oxidation took place but gave a mixture of aldehyde **3k**, carboxylic acid **6**, acetal, and ester, together with the recovered alcohol **2k**, respectively (entry 12). When an excess amount of electricity (5.0 F/mol) was passed, **6** was obtained as an only isolated product (entry 13).

In conclusion, water-soluble *N*-oxyl compounds (**WS-TEMPOs**) **1a–d** were prepared and used for the mediator of the electrooxidation of alcohols in water. Electrooxidation of benzylic *sec*-alcohols **2a–g** in water containing **1a** proceeded smoothly to afford the corresponding ketones **3a–g** in good yields. Electrooxidation of aliphatic alcohols was similarly performed in the presence of 20–30 wt % NaBr, affording the corresponding ketone or carboxylic acid. After the extractive workup, most of **1a** remained intact in the aqueous solution and the recovered aqueous solution of **1a** could be used repeatedly for the electrooxidation of alcohols.

Acknowledgements

We thank the SC-NMR Laboratory of Okayama University for ^{1}H and ^{13}C NMR analysis.

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