

Selective Electrocatalytic Oxidation of *N*-Alkyl-*N*-methylanilines to *N*-Alkylformanilides Using Nitroxyl Radical

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Electrocatalytic oxidation of *N*-alkyl-*N*-methylanilines was studied using 4-benzoyloxy-2,2,6,6-tetramethylpiperidiny-*N*-oxyl as a nitroxyl radical. The reaction with *N*-alkyl-*N*-methylanilines led to direct formation of *N*-alkylformanilides in the presence of H₂O in reaction media in adequate conversion (>75.8%), high current efficiency (>89.2%) and high selectivity (>93.8%).

Key words mediator; nitroxyl radical; electrocatalytic oxidation; *N*-alkyl-*N*-methylaniline; *N*-alkylformanilide

Nitroxyl radicals such as 4-benzoyloxy-TEMPO (4-benzoyloxy-2,2,6,6-tetramethylpiperidiny-*N*-oxyl) (**1**) are usually stable organic radicals, and oxidized species (*i.e.*, oxoammonium ions) can be easily prepared electrochemically by one-electron oxidation (Chart 1).¹ Oxoammonium ions such as **2** are known to be specific and useful oxidants for several functional groups, and nitroxyl radicals have been used extensively as catalysts for the electrooxidation of alcohols,¹ thiols,² naphthols,³ and methylquinolines.⁴ Semmelhack and Schmid⁵ have developed the electrooxidation of amines to nitriles and carbonyl compounds with TEMPO as a nitroxyl radical catalyst, and MacCorquodale *et al.*⁶ have demonstrated that, based on ESR and cyclic voltammetry, poly(TEMPO-4-acrylic ester) acts as an efficient catalyst for electrochemical oxidation of amines. We have also achieved the electrocatalytic oxidation of amines to nitriles on a graphite felt (GF) electrode coated with a thin poly (acrylic acid) layer with immobilized 4-amino-TEMPO.⁷ However, most of this work prior has employed primary amine compounds as substrates. On the other hand, Hunter *et al.*^{8,9} reported stoichiometric oxidation of *N*-alkyl-*N*-methylanilines to *N*-alkylformanilides with 1-oxo-2,2,6,6-tetramethylpiperidinium chloride as oxidizing agent. From the viewpoint of electrosynthesis, we report in this paper a preparative electrocatalytic oxidation of *N*-alkyl-*N*-methylanilines to *N*-alkylformanilides using **1**.

Results and Discussion

Cyclic voltammetry was used to check the possibility of electron-transfer from oxidatively generated **2** to *N,N*-dimethylaniline. The cyclic voltammogram of **1** in the presence of *N,N*-dimethylaniline, H₂O and 2,6-lutidine in CH₃CN solution is shown in Fig. 1. 2,6-Lutidine is used as a weak base to avoid the inhibitory effect of a high acid concentration^{1,5} and to an abstract proton from substrate.^{10,11} The reversible wave at +0.68 V vs. Ag/AgCl, which corresponds to the 1/2 couple became irreversible; an increase in the catalytic peak

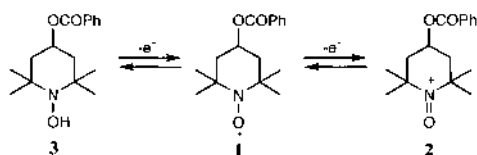


Chart 1. A Reversible Redox System Based on **1**

height corresponded to oxidation of **1**, although *N,N*-dimethylaniline is not electroactive below +0.8 V vs. Ag/AgCl at a glassy carbon electrode. This means that **1** is electrocatalytically active for the oxidation of *N,N*-dimethylaniline.

Based on the cyclic voltammometry results, the preparative electrolysis of *N,N*-dimethylaniline was performed at +0.8 V vs. Ag/AgCl. During the electrolysis, the substrates and products were occasionally analyzed by GC and HPLC. The consumption of *N,N*-dimethylaniline and formation of *N*-hydroxymethyl-*N*-methylaniline and *N*-methylformanilide are plotted against electrolysis time in Fig. 2. A variation in the rate of conversion was observed and *N*-methylformanilide only becomes important when a substantial quantity of *N*-hydroxymethyl-*N*-methylaniline is formed. It is clear that the electro-oxidation reaction of *N,N*-dimethylaniline to *N*-methylformanilide by **1** is sequential. One mmol of *N,N*-dimethylaniline is consumed almost completely in about 20 h to yield *N*-methylformanilide. The current efficiency in the electrolysis is 94.5% during the course of electrolysis, and a small amount of *N*-methylaniline was observed (95.9% selectivity). The turnover number based on **1** (given by ratio of mole of product \times 4/mole of **1**) was calculated to be 35.8 at 20 h of electrolysis.

The preparative results for oxidation for four *N*-alkyl-*N*-methylanilines are shown in Table 1. The alkyl groups chosen were ethyl, *n*-butyl, isopropyl, and benzyl. All *N*-alkyl-*N*-methylanilines were oxidized to the corresponding *N*-alkylformanilides in adequate current efficiency (89.2–96.1%)

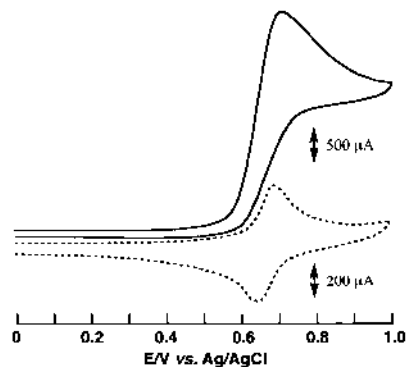


Fig. 1. Cyclic Voltammograms of 0.02 M **1** in the Presence (—) and Absence (-----) of 0.2 M *N,N*-Dimethylaniline, 0.8 M 2,6-Lutidine and 0.3 M H₂O in CH₃CN of 0.1 M NaClO₄ at Scan Rate of 50 mV · s⁻¹

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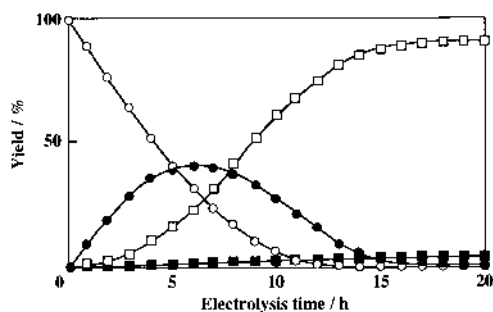



Fig. 2. Macroelectrolysis of 0.2 M *N,N*-Dimethylaniline by 0.02 M **1** in the Presence of 0.8 M 2,6-Lutidine and 0.3 M H₂O in CH₃CN of 0.1 M NaClO₄

○, *N,N*-dimethylaniline; ●, *N*-hydroxymethyl-*N*-methylaniline; □, *N*-methylformanilide; ■, *N*-methylaniline.

Table 1. Electrocatalytic Oxidation of *N*-Alkyl-*N*-methylanilines to *N*-Alkylformanilides Using **1**

R	Charge passed (C)	Current efficiency (%)	Conversion (%)	Selectivity (%)	Turnover number
Me	365.5	94.5	89.5 (3.8)	95.9	35.8
Et	326.0	92.7	78.3 (4.6)	94.5	31.3
<i>n</i> -Bu	347.7	93.9	84.6 (4.2)	95.3	33.8
iso-Pr	369.9	96.1	92.1 (2.3)	97.6	36.8
	328.0	89.2	75.8 (5.0)	93.8	30.3

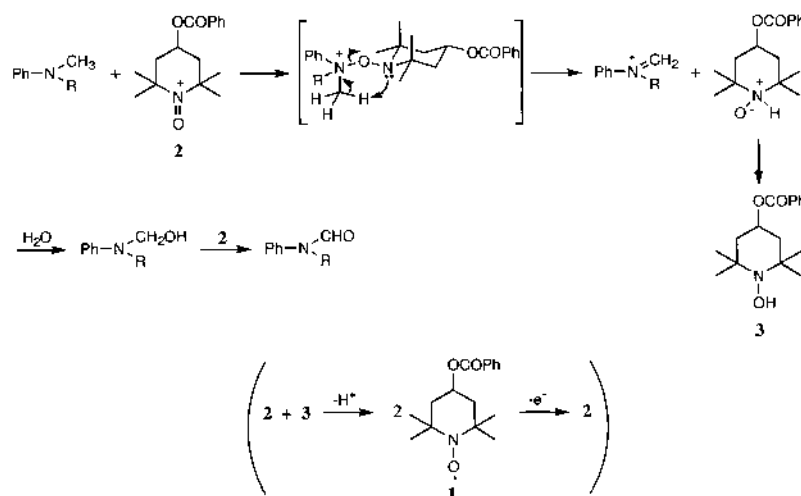


Chart 2. Proposed Mechanism of Oxidation of *N*-Alkyl-*N*-methylaniline to *N*-Alkylformanilide with **2**

and yield (75.8—92.1%). A slightly lower selectivity (93.8—97.6%) is ascribable to the formation of small amounts (2.3—5.0%) of *N*-alkylanilines. The turnover numbers are larger than 30.3. These product selectivities provide different results from those obtained by conventional organic chemistry, because electroorganic reactions are unusual and progress by electron-transfer on the electrode surface.

On the basis of the observed products, the reaction sequence shown in Chart 2 is postulated, which involves formation of an iminium ion intermediate (**4**). The oxoammonium ion (**2**) is expected to first react with the *N*-alkyl-*N*-methylaniline, that is, to eliminate a proton from the *N*-methyl group of aniline, then to change to the hydroxylamine (**3**). The iminium salt (**4**) is the expected unstable intermediate, which can be hydrolyzed to primary alcohol by H₂O in the reaction medium. This primary alcohol is readily oxidized to the formanilide by **1**. The reaction of **2** and **3** produces **1**, which is re-oxidized electrochemically to complete a catalytic cycle.¹⁾

In conclusion, the nitroxyl radical (**1**) catalyzed the oxidation reaction of *N*-alkyl-*N*-methylanilines to *N*-alkylformanilides in the presence of H₂O in reaction media. We are now exploring the electrocatalytic oxidation of many different types of tertiary amines.

Experimental

Cyclic Voltammetry A glassy carbon disk electrode (3 mm ϕ) and a platinum wire were employed as the working electrode and the counter electrode, respectively. The anode potentials were referred to Ag/AgCl (saturated AgCl and (CH₃)₃C₂H₅NCl in CH₃CN). Cyclic potential sweeps were generated by a Hokuto Denko Model HABF-501 potentiostat/galvanostat. Cyclic voltammograms were recorded on a Graphtec Model WX1200 X-Y recorder. All electrochemical measurements were carried out at room temperature (ca. 20 °C).

Macroelectrolysis Preparative potential-controlled electrolysis was performed in CH₃CN solution, using an 'H' type divided cell separated by a cationic exchange membrane (Nafion 117). The anolyte contained 1 mmol of substrate, 1.5 mmol of H₂O, 0.1 mmol of 4-benzoyloxy-TEMPO, 0.5 mmol of tetralin as gas chromatographic standard, 4 mmol of 2,6-lutidine and 0.5 mmol of NaClO₄ as a supporting electrolyte in a total volume of 5 ml. The catholyte was 5 ml of CH₃CN solution containing 0.5 mmol of NaClO₄. Controlled potential electrolysis was carried out at +0.8 V vs. Ag/AgCl. The GF electrode (Nippon Kynol Inc.), with a size of 5 \times 5 mm, was used as the working anode electrode. During electrolysis, the substrates and products were arbitrarily analyzed by GC (CP-Cyclodextrin-B-2,3,6-M-19, 0.25 mm ϕ \times 25 m/raising temperature 3 °C \cdot min⁻¹ from 80 to 150 °C, inj. temp. 200 °C, detection temperature 240 °C) and HPLC (Daicel CHIRALCEL OD column, 46 mm ϕ \times 250 mm/column temperature 40 °C, 2-propanol: *n*-hexane=2:33, flow rate; 0.7 ml \cdot min⁻¹, detection; UV absorption at 254 nm). The end of electrolysis was determined by a considerable decrease in current (less than 1 mA).

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References

- 1) Semmelhack M. F., Schmid C. R., Cortes D. A., Chou C. S., *J. Am. Chem. Soc.*, **105**, 4492—4493 (1983).
- 2) Kashiwagi Y., Ohsawa A., Osa T., Ma Z., Bobbitt J. M., *Chem. Lett.* **1991**, 581—584.
- 3) Kashiwagi Y., Ono H., Osa T., *Chem. Lett.* **1993**, 81—84.
- 4) Kashiwagi Y., Ono H., Osa T., *Chem. Lett.* **1993**, 257—260.
- 5) Semmelhack M. F., Schmid C. R., *J. Am. Chem. Soc.*, **105**, 6732—6734 (1983).
- 6) MacCorquodale F., Crayston J. A., Walton J. C., Worsfold D. J., *Tetrahedron Lett.*, **31**, 771—774 (1990).
- 7) Kashiwagi Y., Kurashima F., Kikuchi C., Anzai J., Osa T., Bobbitt J. M., *J. Chin. Chem. Soc.*, **45**, 135—138 (1998)
- 8) Hunter D. H., Barton D. H. R., Motherwell W. J., *Tetrahedron Lett.*, **25**, 603—606 (1984).
- 9) Hunter D. H., Racok J. S., Rey A. W., Ponce Y. Z., *J. Org. Chem.*, **53**, 1278—1281 (1988).
- 10) Kishioka S., Ohsaka T., Tokuda K., *Chem. Lett.*, **1998**, 343—344.
- 11) Kishioka S., Ohki S., Ohsaka T., Tokuda K., *J. Electroanal. Chem.*, **452**, 176—196 (1998).