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N-NITROSATION OF SECONDARY AMINES EFFECTED BY ELECTROCHEMICAL OXIDATION OF NITRITE ION IN WEAKLY BASIC MEDIA

Masaichiro Masui,* Norihiko Yamawaki, and Hidenobu Ohmori
Faculty of Pharmaceutical Sciences, Osaka University, 1-6
Yamadaoka, Suita, Osaka 565, Japan

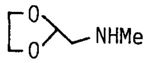
Constant current electrolysis of sodium nitrite in aqueous acetonitrile containing secondary amines at ambient temperature resulted in the formation of the corresponding N-nitrosamines in good yields.

KEYWORDS —— N-nitrosation; secondary amine; sodium nitrite; electrochemical oxidation; constant current electrolysis

N-Nitrosamines (1), known as potential carcinogenic substances, are usually prepared using the reaction of secondary amines with sodium nitrite under acidic conditions.1) Recently, however, the preparation of 1 in non-acidic media has received considerable attention,2) probably because 1 with acid-labile functional groups in the molecules are also needed in cancer research. It has been reported that dinitrogen tetroxide (N_2O_4) is a powerful nitrosating agent for secondary amines in neutral or basic aqueous media and in organic solvents,3) though nitration of the amines takes place concurrently under certain conditions. Meanwhile, electrochemical oxidation of nitrite ion in acetonitrile has been suggested to afford N_2O_4 together with other active nitrogen species.4) It is therefore possible to achieve an electrochemical preparation of 1 in neutral or weakly basic media without using the poisonous gas as the nitrosating agent. We report here the results of electrolysis of nitrite ion in the presence of secondary amines to give 1 in good yields.

A typical procedure is as follows. Sodium nitrite (1.2 g) and a solution of a secondary amine (1 mmol) in H_2O-MeCN (5:95 v/v) (40 ml) containing 0.15 M $NaClO_4$ were placed5) in an undivided electrolysis cell6) equipped with a graphite plate anode and a Pt foil cathode inserted through a silicon stopper. The system was subjected to constant current electrolysis (10 mA; current density ca. 2.6 mA/cm^2) at ambient temperature until 2.5 F per mole of the amine had been passed (ca. 7 h).7) The electrolyzed solution was adjusted to 50.0 ml by adding MeCN. Part of the solution (2.0 ml) was diluted 2.5 times with EtOH then subjected to GLC analysis to determine the yield of 1 (Shimadzu capillary column HiCap-CBP-M25-025; internal standard, naphthalene). The results are summarized in Table I, where nitration of the amines is shown to be negligible. Since the products 1 are carcinogenic, we did not dare to prepare them in large amounts. However, electrolysis on a larger scale is feasible. For example, a solution containing 2,2,6,6-tetramethylpiperidine (2 g, ca. 14 mmol) and $NaNO_2$ (3 g) in H_2O-MeCN (5:95) (100 ml, 0.15 M $NaClO_4$) was electrolyzed similarly (30 mA, ca. 2.6 mA/cm^2). Water (100 ml) was added to the electrolyzed solution, and the resulting mixture was extracted with CH_2Cl_2 (50 ml x 3). The extract, after being washed with saturated aq. NaCl solution, was dried over $MgSO_4$. The CH_2Cl_2 was removed under reduced pressure, and the residue was subjected to vacuum distillation to give the corresponding nitrosamine (1.7 g, 71%), which is believed to be noncarcinogenic.

Table I. Electrochemical Preparation of 1

Run	Amine	Yield(%) of 1[a]
1	Dibutylamine	90
2	Piperidine	92
3[b]	Piperazine	70[c]
4[d]	Morpholine	93
5		∿100
6	2,2,6,6-Tetramethyl-piperidine	96
7	(-)-Ephedrine	87[e]

a) Determined by GLC.
b) H_2O/MeCN = 2.5/97.5, 5 F/mole of the amine.
c) N,N'-Dinitrosated product.
d) H_2O/MeCN = 1/9. e) Isolated yield.

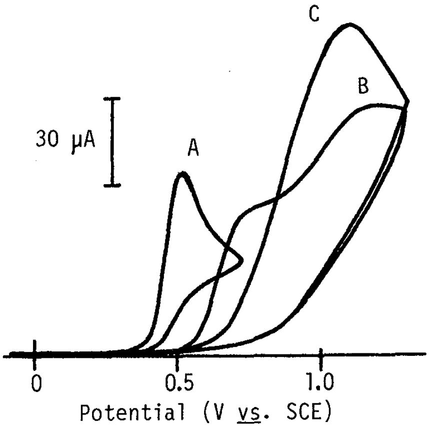


Fig. 1. Cyclic Voltammograms of $NaNO_2$

$NaNO_2$, 6.5 mM in H_2O-MeCN (5/95)(A), in H_2O-MeCN (1/1)(B), and in H_2O (C). At a glassy carbon electrode (area, 0.071 cm^2) at 25°C: voltage sweep rate, 50 mV/s; each solvent containes 0.15 M $NaClO_4$ as supporting electrolyte.

The yield of 1 depended on the current density and the amount of water in the solvent system: current densities of 2—5 mA/cm^2 and water contents of 2—10% were found to give favorable results. In nominally anhydrous MeCN, the yield was low and the nitration (10—20%) was unavoidable. The yield of 1 also decreased on electrolysis at higher current density or in the presence of larger amounts of water (>10%). The voltammetric behavior of $NaNO_2$ (Fig. 1) is indicative of these results. Since the oxidation of secondary amines begins at 1—1.2 V vs. SCE, higher water content in the medium would cause simultaneous oxidation of nitrite ion and the amine because of the closer oxidation potentials of both species.8) Higher current densities will exhibit the same effect because of the limited solubility of $NaNO_2$ in MeCN containing less than 10% water.

Although further studies will be required to elucidate the optimum process for the formation of 1, Chart 1 can be tentatively proposed for the reaction in the light of the suggested mechanisms for the electrochemical oxidation of nitrite ion4) and for the reaction of N_2O_4 with secondary amines.3) According to this mechanism (Chart 1), the electrolysis as a whole produces one equivalent of hydroxide ion along with the conversion of one equivalent of amine to 1, and hence the reaction medium is kept basic throughout the run.

It is interesting to note that electrochemical oxidation of a mixture containing nitrite ion and aromatic hydrocarbons or olefins usually results in nitration.[9] Anodic nitrosation of β-naphthol has been reported,[10] but was accompanied by considerable nitration. Thus, the exclusive nitrosation in the present study constitutes a new departure in the electrochemical oxidation of nitrite ion. In addition, this method for 1 is versatile and has advantages over other methods in neutral or basic media, because it uses no special or toxic reagents and can be accomplished by a simple procedure under mild conditions.

At the anode: $2NaNO_2 - 2e \longrightarrow 2Na^+ + 2NO_2^{\bullet}$; $2NO_2^{\bullet} \rightleftarrows O_2N\text{-}NO_2$

In solution (and/or at the anode):

$$O_2N\text{-}NO_2 \rightleftarrows ON\text{-}O\text{-}NO_2$$

$$ON\text{-}O\text{-}NO_2 + RR'NH \longrightarrow RR'N\text{-}NO\ (1) + NO_3^- + H^+$$

At the cathode: $H^+ + e \longrightarrow 1/2H_2$; $H_2O + e \longrightarrow 1/2H_2 + OH^-$

Chart 1

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5) The sodium nitrite does not necessarily dissolve in the medium completely.
6) A sample tube (volume, 50 ml) was used for the electrolysis cell.
7) At this stage, the amine was found to have essentially disappeared in the reaction mixture.
8) In aqueous solution, the electrochemical oxidation of nitrite ion has been sugggested to give nitronium ion (NO_2^+)(ref. 10).
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