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ELECTROCHEMISTRY OF AMINOAZINES AND NITRONES: ELECTROCHEMICAL REDUCTIONS OF 2-AMINO-1,4-PYRAZINE WITH NITRONES TO FORM AMIDE COMPOUNDS AND ELECTROCHEMICAL OXIDATIONS OF ANILINES WITH NITRONES TO FORM IMINE COMPOUNDS AND BENZALDEHYDES

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Abstract - Electrochemical reductions of 2-amino-1,4-pyrazine in the presence of nitrone derivatives afforded two types of amide compounds, one of which was derived from both the pyrazine and the nitrones and the other from only the nitrones. The analogous reactions but using 2-aminopyridine or aniline instead of the pyrazine resulted in the recovery of the starting materials. On the other hand, electrochemical oxidations of the aminoazine derivatives in the presence of nitrones did not afford any isolatable products. However, the reaction using aniline derivatives formed imine compounds accompanied by benzaldehyde derivatives.

Electrochemistries of amine derivatives have attracted much attention of chemists from theoretical and synthetic view points.[1] However, researches on electrochemistries of amines conjugated with any heterocyclic moieties seem to be rare. As a series of our researches on the electrochemistries of heterocyclic compounds, such as azepines[2] or azulanones,[3] we intended to study electrochemical behaviors of amines conjugated with heterocyclic moieties, *i.e.*, aminoazine derivatives. The authors have also researched on cycloaddition reactions of nitrone derivatives with sterically hindered cyclic compounds.[4] These facts prompted us to study the reactions of aminoazines with nitrones under the electrochemical reaction conditions. Here the results are discussed.

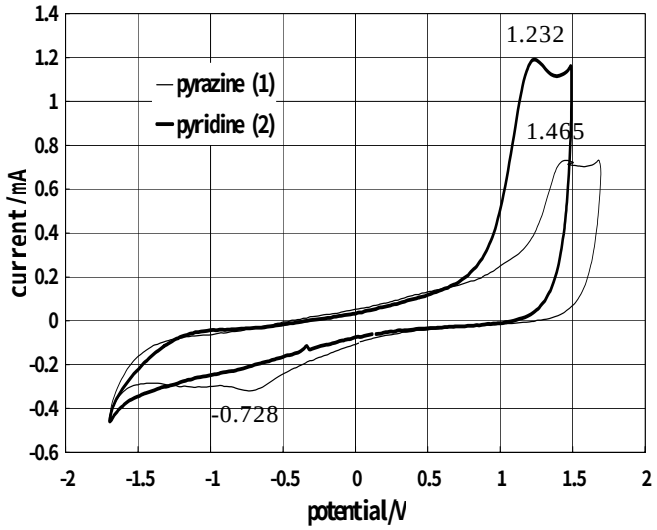


Figure 1. Cyclic Voltammograms of **1** and **2**.

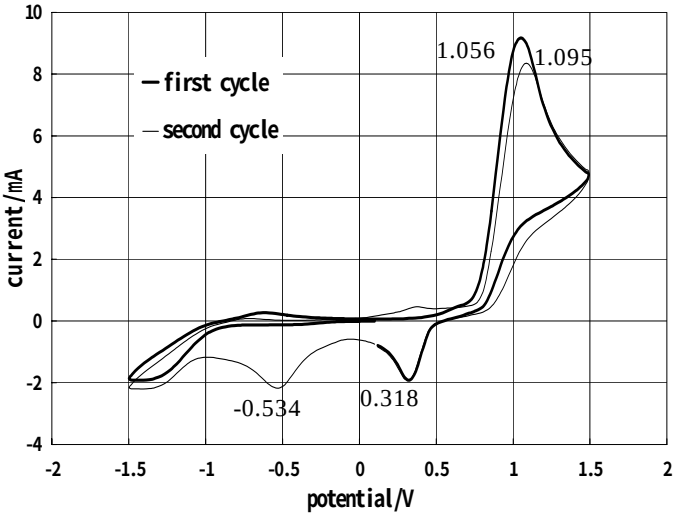
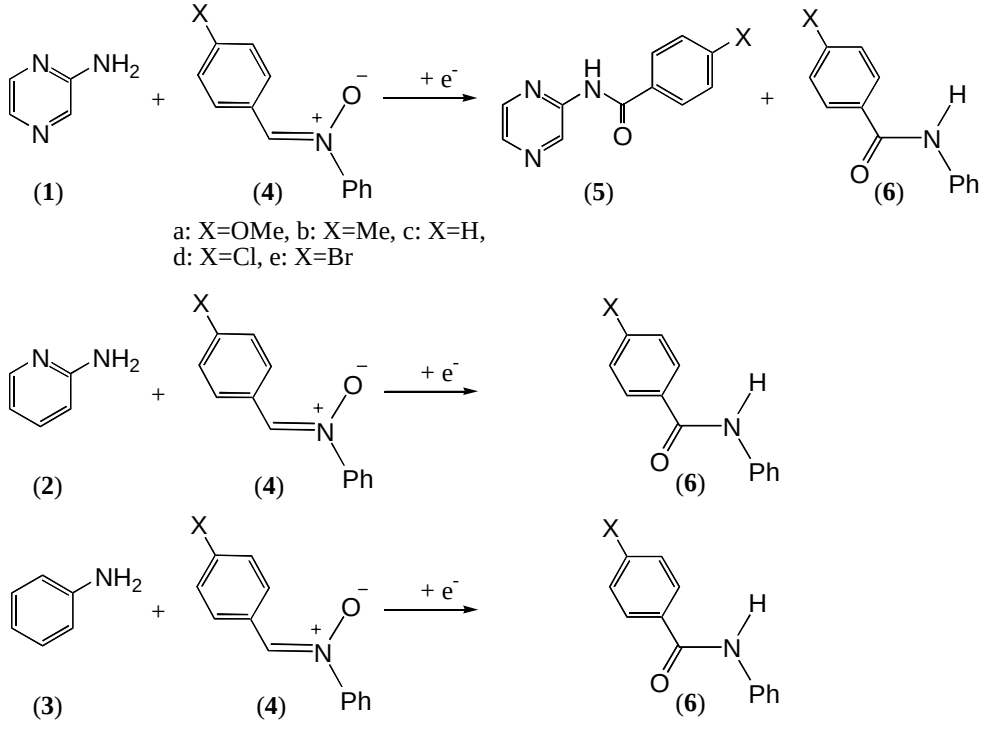


Figure **2**. Cyclic Voltammogram of **3**.[5]

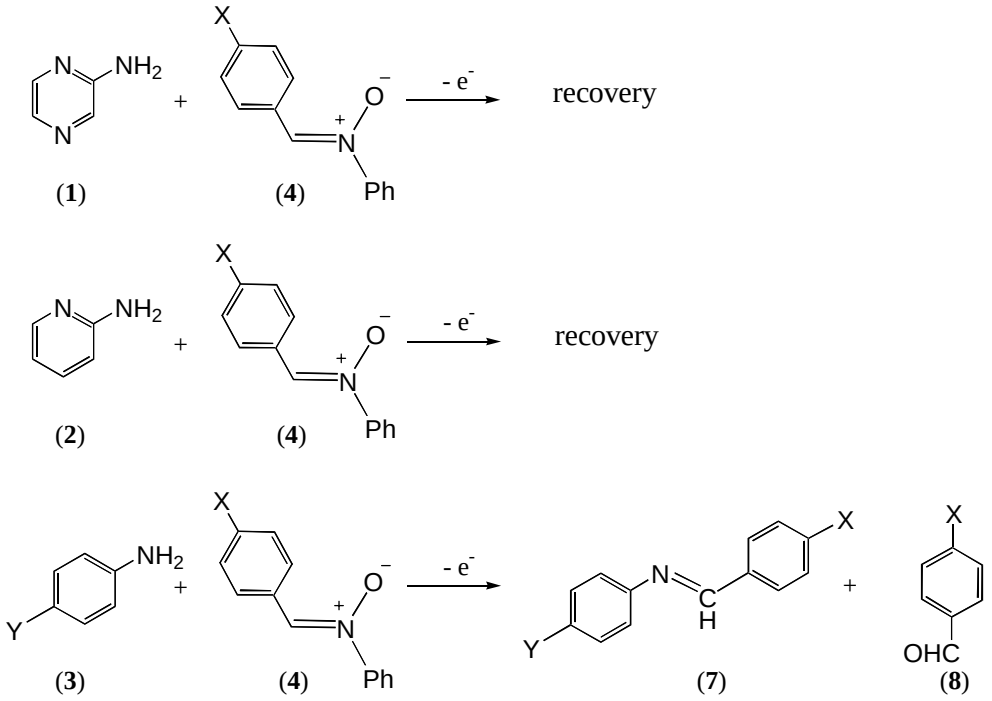
Cyclic voltammetries of 2-amino-1,4-pyrazine (**1**), 2-aminopyridine (**2**), and aniline (**3**) were measured as shown in the Figures 1 and 2. The oxidation potentials of **1**, **2**, and **3** were 1.465, 1.232, and 1.056 (second cycle: 1.095) V vs. Ag/AgCl (0.1 M KCl aq.) respectively, and the reduction potential of **1** was –0.728 V vs. Ag/AgCl (0.1 M KCl aq.). 2-Aminopyridine (**2**) showed no clear reduction potential. Aniline (**3**) seemed to polymerize at 1.056 V,[6] consequently, the reduction peaks are considered to be resulted from polyaniline. These potentials suggested that compound (**1**) is reduced most easily and **3** is oxidized most easily among the amines used in this work.



Scheme 1.

An anhydrous acetonitrile solution of **1** and an equimolar amount of *p*-methoxy-diphenylnitrone (**4a**) was electrochemically reduced in the presence of tetrabutylammonium perchlorate (TBAP) as a supporting electrolyte with a platinum gauze as a cathode and a platinum wire as an anode with a constant current (–30 mA) at 0 ℃ under a nitrogen stream.[7] After the evaporation of the solvent, the reaction mixture was chromatographed on silica gel to give 13 % yield of an amide compound (**5a**) derived from both **1** and **4a,** as well as 22 % yield of another type of an amide compound (**6a**) derived from the nitrone (**4a**). The analogous reactions using various types of nitrone derivatives (**4b**, **c**, **d**, **e**) afforded the corresponding amide compounds **5b** (11 %), **5c** (20 %), **5d** (19 %), **5e** (23 %), **6b** (12 %), **6c** (4 %), **6d** (34 %), and **6e** (6 %), respectively.[8, 9]

Similar electrochemical oxidation reactions using **2** or **3** instead of **1** afforded the amide compounds (**6**) derived from the nitrones but did not form the amide compounds of the type of **5**. The yields of **6** were 8 % (**6b**) and 10 % (**6e**) in the reactions of **2**, and 25 % (**6a**) and 2 % (**6e**) in the reactions of **3**.



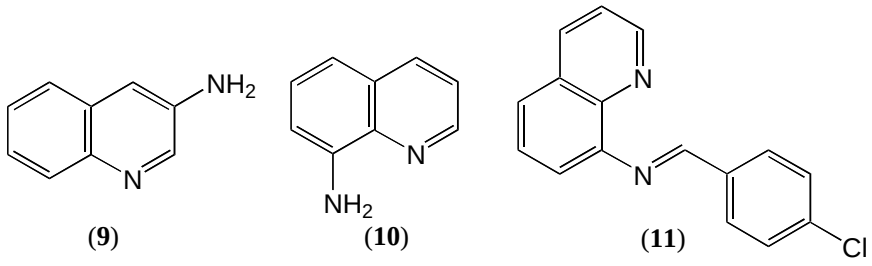
Scheme 2.

On the other hand, the electrochemical oxidation reactions of **1**, **2**, and **3** demonstrated the opposite order of the reactivity in these compounds, comparing to that in the electrochemical reduction reactions.

An anhydrous acetonitrile solution of **1** and two mole equivalents of **4a** was electrochemically oxidized in the presence of TBAP with a platinum gauze as an anode and a platinum wire as a cathode at +1.50 V vs. Ag/AgCl (0.1 M KCl aq.) at 0 ℃ under a nitrogen stream. The same workup of the reaction mixture as above afforded no isolable product and the starting material was recovered. Similar electrooxidation reaction using **2** instead of **1** resulted in the similar result as the case of **1**.

On the other hand, aniline derivatives (**3**) afforded imine derivatives (**7**) and benzaldehyde derivatives (**8**) as reaction products. Thus, an electrochemical oxidation of an anhydrous acetonitrile solution of *p*-methoxyaniline (**3a**) and a nitrone derivative (**4a**) at +0.83 V vs. Ag/AgCl (0.1 M KCl aq.) at 0 ℃ gave an imine derivative (**7aa**) in 24 % yield together with 46 % yield of a benzaldehyde derivative (**8aa**). The same reaction using aniline (**3b**) and **4a** afforded **7ba** and **8ba** in 30 and 54 % yields, respectively. A reaction with *p*-chloroaniline (**3c**) and **4a** or a reaction with **3a** and **4e** gave **7ca**, **8ca**, **7ae**, and **8ae** in 19, 78, 17, and 58 % yields, respectively.[10]

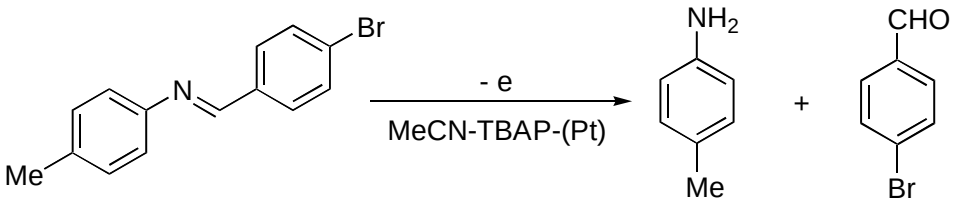
The difference in the reactivity between the aniline moiety and the pyridine moiety was also demonstrated by the following experiments. The electrochemical oxidation of 3-aminoquinoline (**9**) with *p*-chloronitrone (**4d**) afforded no isolatable compound, but the analogous reaction using 8-aminoquinoline (**10**) formed the corresponding imine derivative (**11**), though the yield was poor (6 %).



(**9**) (**10**) (**11**)

Figure 3.

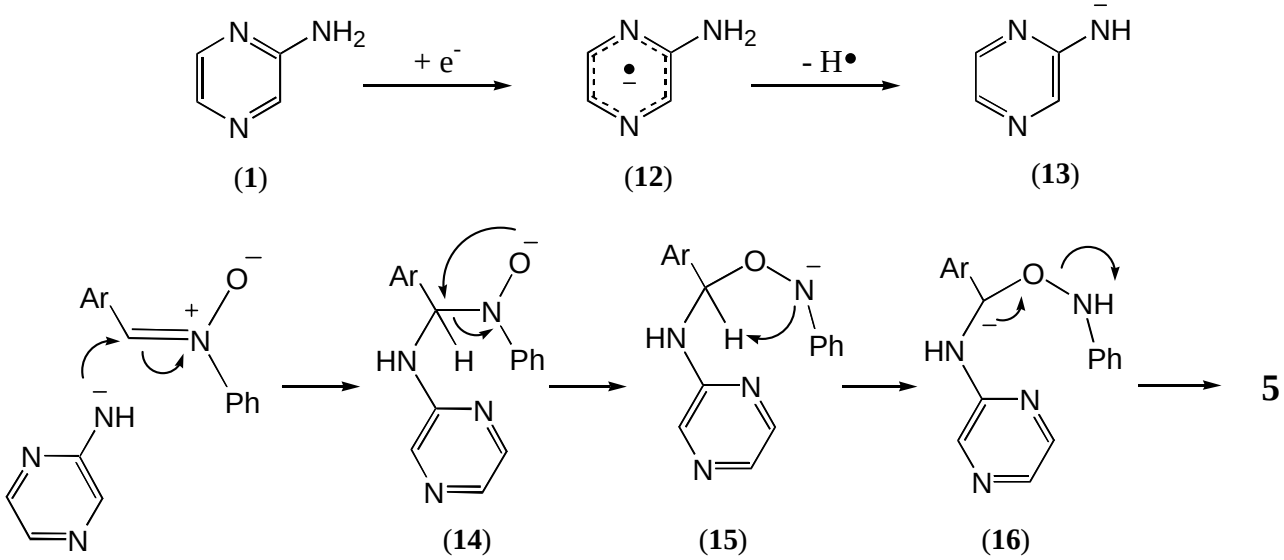
The fact that the electrooxidaion of the imine derivatives (**7**) under the reaction conditions of **3** with **4** formed the benzaldehyde derivatives (**8**) showed that **8** were secondary products derived from **7** under the reaction conditions.



(**7de**) (**3d**) (**8e**)

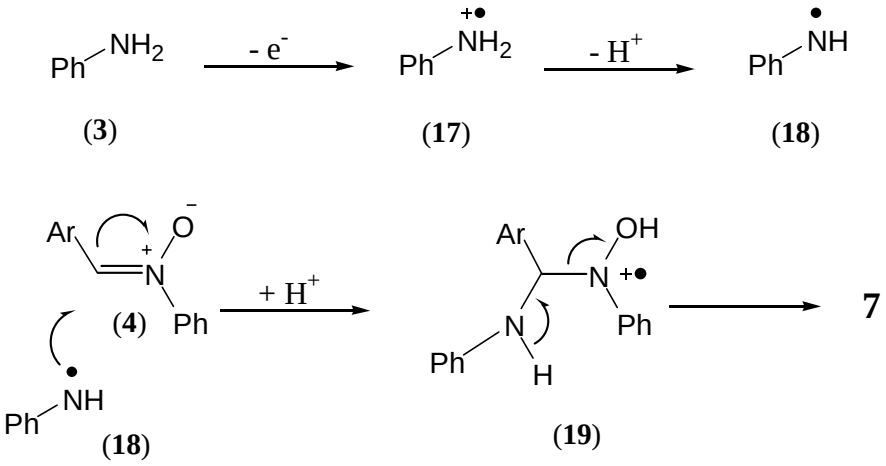
Scheme 3.

The formation of the amide compound (**5**) is considered to proceed through anion intermediates (**13-16**) as follows. An electrochemical one electron reduction of **1** forms an anion radical intermediate (**12**), which then generates **13** leaving a hydrogen radical. A nucleophilic attack of **13** on the imine-carbon atom of **4** affords **14**. An attack of the oxygen anion to the carbon atom to cleave the C-N bond forms **15**. A proton migration in **15** generates **16**, which then affords the final product (**5**) through the cleavage of the N-O bond.[11]



Scheme 4.

The formation mechanism of the imine derivative (**7**) is considered to be as follows. An electrochemical one electron oxidation of **3** forms a cation radical of aniline (**17**), which then generates a radical intermediate (**18**), leaving a proton. An attack of the radical (**18**) at the imine carbon atom of the nitrone (**4**) forms a cation radical intermediate (**19**), which then affords the final product (**7**) through an elimination of a hydroxyamine derivative.[12, 13]



Scheme 5.

ACKNOWREDGEMENT

The authors are indebted to Prof. T. Ohtsuka of Hokkaido University for his kind suggestions concerning the electrochemistry of aniline.

EXPERIMENTAL

Electrolysis was performed in a two compartment glass cell. The working electrode was a platinum gauze of a size of 5 cm depth and 12 cm width. The counter electrode was a platinum wire and the reference electrode was a silver wire. The controlled potential and current power were supplied from a Yanaco Potentio/Garvanostatic Electrolyser VE-9 apparatus. Acetonitrile was distilled from calcium hydride. Wakogel C200 was used for column chromatography. NMR and MS spectra were measured with Varian GEMINI 2000/300 and Hitachi 220A spectrometers, respectively. IR spectra were measured with a JASCO ET/IR-5300 spectrophotometer.

Typical measurements and reactions are below.

*Measurement of Cyclic Voltammetry of **1**.*

Cyclic voltammograms were measured with a Hokutodenko HZ-3000 potentiostat. Cyclic voltammogram of **1** was measured with 1.0×10^{-3} M solution in anhydrous acetonitrile with 0.1 M TBAP as a supporting electrolyte at a scan rate of 0.2 V/s on a wire platinum electrode.

*Electrochemical Reduction of **1** and **4a**.*

A solution of **1** (95 mg, 1.0 mmol), **4a** (229 mg, 1.0 mmol), and TBAP (7.0 g, 20 mmol) in acetonitrile (200 *mL*) was electrolyzed under a nitrogen stream at 0 ^{o}C at –30 mA. After removing the solvent by distillation, the resulting residue was chromatographed on silica gel to give **5a** (29 mg, 13 %, hexane-ethyl acetate (4:6)) and **6a** (51 mg, 22 %, hexane-ethyl acetate (7:3)).

*Electrochemical Reduction of **2** and **4b**.*

A solution of **2** (95 mg, 1.0 mmol), **4b** (212 mg, 1.0 mmol), and TBAP (7.0 g, 20 mmol) in acetonitrile (200 *mL*) was electrolyzed under the same reaction conditions as above to give **6b** (15 mg, 8 %, hexane-ethyl acetate (7:3)).

*Electrochemical Reduction of **3** and **4b**.*

A solution of **3** (100 mg, 1.1 mmol), **4b** (212 mg, 1.0 mmol), and TBAP (7.0 g, 20 mmol) in acetonitrile (200 *mL*) was electrolyzed under the same reaction conditions as above to give **6b** (60 mg, 25 %, hexane-ethyl acetate (7:3)).

*Electrochemical Oxidation of **1** and **4a**.* A solution of **1** (96 mg, 1.0 mmol), **4a** (228 mg, 1.0 mmol), and TBAP (7.0 g, 20 mmol) in acetonitrile (200 mL) was electrolyzed under a nitrogen stream at 0 °C at +1.50 V vs. Ag/AgCl (0.1 M aq. KCl) After removing the solvent, the resulting residue was chromatographed on silica gel to give the recovery of **4a** (206 mg, 90 %, hexane-ethyl acetate (4:6)).

*Electrochemical Oxidation of **2** and **4a**.*

A solution of **2** (94 mg, 1.0 mmol), **4a** (228 mg, 1.0 mmol), and TBAP (7.0 g, 20 mmol) in acetonitrile (200 *mL*) was electrolyzed at +1.50 V vs. Ag/AgCl (0.1 M aq. KCl) under the same reaction conditions as above. The same treatments as above gave the recovery of **4a** (204 mg, 89 %, hexane-ethyl acetate (4:6)).

*Electrochemical Oxidation of **3b** and **4a**.*

A solution of **3b** (186 mg, 2.0 mmol), **4a** (454 mg, 2.0 mmol), and TBAP (7.0 g, 20 mmol) in acetonitrile (200 *mL*) was electrolyzed at +0.83 V vs. Ag/AgCl (0.1 M aq. KCl) under the same reaction conditions as above to give **7ba** (86 mg, 30 %, hexane-ethyl acetate (8:2)) and **8ba** (101 mg, 54 %, hexane-ethyl acetate (7:3)).

*Electrochemical Oxidation of **9** and **4d**.*

A solution of **9** (145 mg, 1.0 mmol), **4d** (232 mg, 1.0 mmol), and TBAP (7.0 g, 20 mmol) in acetonitrile (200 *mL*) was electrolyzed at +0.83 V vs. Ag/AgCl (0.1 M aq. KCl) under the same reaction conditions as above. The same treatments as above gave the recovery of **4d** (209 mg, 90 %, hexane-ethyl acetate (4:6)).

*Electrochemical Oxidation of **10** and **4b**.*

A solution of **10** (288 mg, 2.0 mmol), **4b** (423 mg, 2.0 mmol), and TBAP (7.0 g, 20 mmol) in acetonitrile (200 *mL*) was electrolyzed at +0.83 V vs. Ag/AgCl (0.1 M aq. KCl) under the same reaction conditions as above to give **11b** (6 mg, 6 %, hexane-ethyl acetate (8:2)) and **8b** (33 mg, 72.9 %, hexane-ethyl acetate (7:3)).

*Electrochemical Oxidation of **7de**.*

A solution of **7de** (569 mg, 2.1 mmol), and TBAP (7.0 g, 20 mmol) in acetonitrile (200 *mL*) was electrolyzed at +0.83 V vs. Ag/AgCl (0.1 M aq. KCl) under the same reaction conditions as above to give **3d** (78 mg, 52 %, hexane-ethyl acetate (7:3)) and **8e** (214 mg, 83 %, hexane-ethyl acetate (8:2)).

*Electrochemical Oxidation of **4b***

A solution of **4b** (423 mg, 2.0 mmol), and TBAP (7.0 g, 20 mmol) in acetonitrile (200 *mL*) was electrolyzed at +0.83 V vs. Ag/AgCl (0.1 M aq. KCl) under the same reaction conditions as above. The same treatments as above gave the recovery of **4b** (414 mg, 98 %, hexane-ethyl acetate (5:5)).

REFERENCES AND NOTES

1. Y. Matsuda, A. Shono, C. Iwakura, Y. Ohshiro, T. Agawa, and H. Tamura, *Bull. Chem. Soc. Jpn.*, 1971, **44,** 2960; S. Wawzonek and T. W. McIntyre, *J. Electrochem. Soc.*, 1972, **119**, 1350; T. Fuchigami, Y. Fujita, and T. Nonaka, *J. Electroanal. Chem.,* 1990, **284**, 115; D. Larumbe, I. Gallardo, and C. P. Andrieux, *ibid.,* 1991, **304**, 241.
2. S. Kondo, H. Suzuki, T. Hattori, T. Ido, and K. Saito, *Heterocycles,* 1998, **48**, 1151.
3. T. Ido, S. Kondo, and K. Saito, *Heterocycles*, 1999, **50**, 63; K. Saito, T. Ido, Y. Awadu, T. Kanie, and S. Kondo, *ibid.*, 2000, **53**, 519.
4. K. Saito, A. Yoshino, H. Watanabe, and K. Takahashi, *Heterocycles*, 1990, **34**, 497.
5. The cyclic voltammogram of **3** showed no reproducibility.
6. S. Yonezawa, K. Kanamura, and Z. Takehara, *J. Electrochem. Soc.,* 1993, **140**, 629.
7. The attempted electrochemical reductions of **1** and **4** under controlled potential conditions (**4a**: –1.65 V vs. Ag/AgCl (0.1 M aq.KCl), **4b**: –1.60 V vs. Ag/AgCl (0.1 M aq. KCl)) failed to afford any isolatable products.
8. The structures of **5** were determined with their spectral properties, especially ^{1}HNMR spectral properties, and confirmed by the coincidence of these properties with these of the authentic samples.

   Sambaiah, T. Reddy, and K. Kondal, *Indian J. Chem., Sect. B*, 1992, 444-5.

   5a: ^{1}HNMR ($CDCl_3$) δ ppm: 1.82 (s, 3H), 7.33 (d, 2H, J=8.0 Hz), 7.94 (d, 2H, J=8.0 Hz), 8.24 (dd, 1H, J=2.7 Hz, J=1.5 Hz), 8.37 (d, 1H, J=2.7 Hz), 9.10 (br s, 1H), 9.73 (s, 1H, J=1.5 Hz).

   5b: MS m/z (rel intensity): 213.0 (49, M^+), 118.9 (100), 90.9 (55). IR (KBr): 3241, 3240, 1676, 1531, 1261 cm^{-1}. ^{1}HNMR ($CDCl_3$) δ ppm: 2.44 (s, 3H), 7.32 (d, 2H, J=8.0 Hz), 7.84 (d, 2H, J=8.0 Hz), 8.24 (dd, H, J=2.7 and 1.5 Hz), 8.37 (d, H, J=2.7 Hz), 8.65 (bs, 1H), 9.73 (d, 1H, J=1.5 Hz). ^{13}CNMR ($CDCl_3$) δ ppm: 21.6, 127.4, 129.6, 130.5, 137.3, 140.2, 142.1, 143.5, 148.4, 165.4.

   5c: ^{1}HNMR ($CDCl_3$) δ ppm: 7.52 (t, 3H, J=8.0 Hz), 7.96 (d, 2H, J=8.0 Hz), 8.28 (dd, 1H, J=2.5 and 1.4 Hz), 8.38 (d, 1H, J=2.5 Hz), 8.82 (br s, 1H), 9.72 (s, 1H, J=1.4 Hz).

   5d: MS m/z (rel intensity): 233.0 (44, M^+), 138.9 (100), 110.6 (45). ^{1}HNMR ($CDCl_3$) δ ppm: 7.13 (d, 2H, J=8.8 Hz), 7.90 (d, 2H, J=8.8 Hz), 8.29 (dd, 1H, J=2.5 Hz, J=1.6 Hz), 8.41 (d, 1H, J=2.5 Hz), 8.54 (bs, 1H), 9.71 (s, 1H, J=1.6 Hz).

   5e: ^{1}HNMR ($CDCl_3$) δ ppm: 7.66 (d, 2H, J=8.6 Hz), 7.83 (d, 2H, J=8.6 Hz), 8.24 (dd, 1H, J=2.6 and 1.5 Hz), 8.39 (d, 1H, J=2.6 Hz), 8.65 (br s, 1H), 9.68 (s, 1H, J=1.5 Hz).
9. The structures of **6** are determined with their spectral properties, especially ^{1}HNMR

spectral properties, and confirmed by the coincidence of these properties with these of the authentic samples.

SDBS Web; http://www.asit.go.jp/RIODB/SDBS/(2001.04.25).

6a: ^{1}HNMR ($CDCl_3$) δ ppm: 3.87 (s, 3H), 7.03 (dd, 2H, J=8.0 and 2.0 Hz), 7.09 (t, 1H, J=7.7 Hz), 7.33 (t, 2H, J=7.7 Hz), 7.84 (d, 2H, J=7.7 Hz), 7.98 (dd, 2H, J=8.0 and 2.0 Hz), 9.42 (br s, 1H).

6b: ^{1}HNMR (Acetone-d_6) δ ppm: 2.46 (s, 3H), 7.10 (t, 1H, J=7.2 Hz), 7.24 (dd, 2H, J=8.0 and 2.0 Hz), 7.33 (t, 2H, J=7.2 Hz), 7.86 (d, 2H, J=7.2 Hz), 8.03 (dd, 2H, J=8.0 and 2.0 Hz), 9.46 (br s, 1H).

6c: ^{1}HNMR ($CDCl_3$) δ ppm: 7.12 (t, 1H, J=8.0 Hz), 7.37 (t, 2H, J=8.0 Hz), 7.54 (dd, 2H, J=6.8 and 2.0 Hz), 7.58 (t, 1H, J=6.8 Hz), 7.87 (d, 2H, J=8.0 Hz), 8.00 (dd, 2H, J=6.8 and 2.0 Hz), 9.52 (br s, 1H).

6d: ^{1}HNMR (Acetone-d_6) δ ppm: 7.13 (t, 1H, J=7.7 Hz), 7.36 (t, 2H, J=7.7 Hz), 7.56 (dd, 2H, J=6.6 and 1.9 Hz), 7.84 (d, 2H, J=7.7 Hz), 8.02 (dd, 2H, J=6.6 and 1.9 Hz), 9.62 (br s, 1H).

6e: MS m/z (rel intensity): 276.8 (70, M^+), 274.7 (71), 184.9 (99), 182.9 (100). ^{1}HNMR (Acetone-d_6) δ ppm: 7.13 (t, 1H, J=7.7 Hz), 7.36 (t, 2H, J=7.7 Hz), 7.72 (dd, 2H, J=6.6 and 2.0 Hz), 7.84 (d, 2H, J=7.7 Hz), 8.65 (dd, 2H, J=6.6 and 2.0 Hz), 9.68 (br s, 1H). IR (KBr): 3341, 1659, 1532, 1258 cm^{-1}.

10.The structures of **7** were determined with their spectral properties, especially ^{1}HNMR spectral properties, and confirmed by the authentic samples synthesized by other method.

M. Nakamura, K. Komatsu, Y. Gondo, K. Ohta, and Y. Ueda, *Chem. Pharm. Bull.*, 1967, 5851.

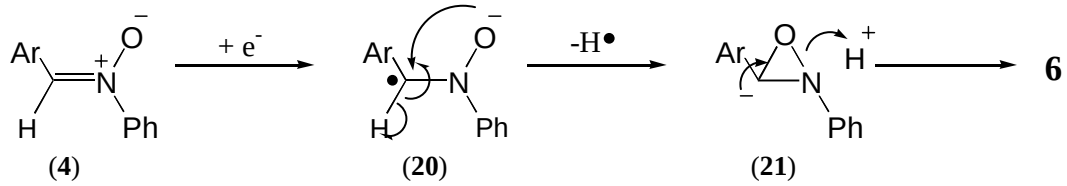
7aa: ^{1}HNMR ($CDCl_3$) δ ppm : 3.83 (s, 3H), 3.87 (s, 3H), 6.95 (dd, 4H), 7.21 (d, 2H), 7.86 (d, 2H), 8.42 (s, 1H). ^{13}NMR ($CDCl_3$) δ ppm: 55.4, 55.5, 114.1, 114.3, 122.1, 129.5, 130.2, 145.3, 157.9, 157.9, 162.0.

7ba: ^{1}HNMR ($CDCl_3$) δ ppm : 2.36 (s, 3H), 3.86 (s, 3H), 6.97 (d, 2H), 7.12 (d, 2H), 7.18 (d, 2H), 7.84 (d, 2H), 8.39 (s, 1H). ^{13}CNMR ($CDCl_3$) δ ppm: 21.0, 55.4, 114.1, 120.8, 129.4, 129.7, 130.4, 135.3, 149.7, 159.0, 162.1.

7ca: ^{1}HNMR ($CDCl_3$) δ ppm : 3.87 (s, 3H), 6.98 (d, 2H), 7.19-7.21 (m, 3H), 7.37-7.39 (m, 2H), 7.85 (d, 2H), 8.38 (s, 1H). ^{13}CNMR ($CDCl_3$) δ ppm: 55.4, 114.2, 120.9, 125.6, 129.1, 129.3, 130.5, 152.3, 159.7, 162.2.

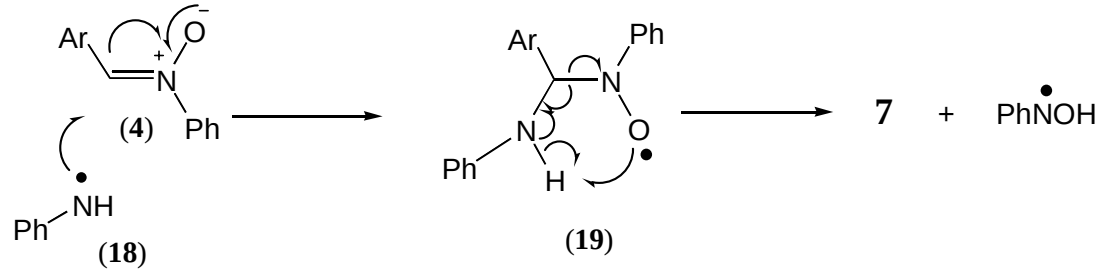
7ae: ^{1}HNMR ($CDCl_3$) δ ppm : 3.82 (s, 3H), 6.92 (d, 2H), 7.22 (d, 2H), 7.60 (d, 2H), 7.78 (d, 2H), 8.44 (s, 1H).

11.The formation of **6** is considered to proceed as follows. An electrochemical reduction of **4** forms a radical intermediate (**20**), which cyclizes to generate an anion intermediate (**21**) through an elimination of hydrogen radical. The subsequent ring opening reaction in **21** can afford the final product (**6**).



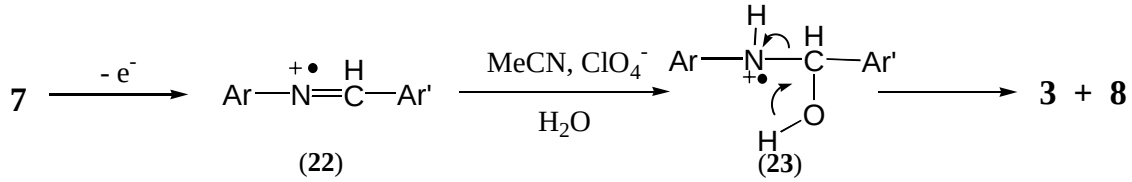
(**4**) (**20**) (**21**)

12.A referee suggested the following mechanism.



(**18**) (**19**)

13.The benzaldehyde derivative (**8**) is considered to be formed as follows. An electrochemical oxidation of **7** forms a cation radical (**22**). In the presence of a trace amount of water, **22** affords a cation radical (**23**), which then affords **8** and aniline derivative (**3**).



(**22**) (**23**)

M. Masui and H. Ohmori, *J. Chem. Soc., Perkin Trans. II*, 1973, 1112.