ether, and drying it on filter paper. The addition of amalgamated foils was repeated until the weight of all pieces of aluminum foil employed totaled 1 g. After completion of the above addition, the reaction mixture was stirred at room temperature for 7–10 h. The resulting precipitate was filtered off. It was washed repeatedly with tetrahydrofuran. The combined washings and the filtrate were dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to afford a residue, which was subjected to column chromatography on silica gel with 50% ether–50% hexane as eluent. The isolated yields of **6a**, **6b**, **7e**, **7f**, and **7g** were 60, 64, 54, 62, and 58% based on the corresponding starting compounds **4a**, **4b**, **5e**, **5f**, and **5g**.

Acknowledgment. Financial support from the Ministry of Education (Japan) in the form of post doctoral fellowship to S.M.A. is gratefully acknowledged.

Registry No. **1a**, 80675-53-2; **1b**, 65946-52-3; **1c**, 84393-10-2; **1d**, 63547-55-7; **1e**, 31469-16-6; **1f**, 118646-01-8; **1g**, 31469-17-7; **2a**, 37999-08-9; **2b**, 105019-17-8; **2c**, 65364-88-7; **2d**, 105019-18-9; **2e**, 37999-09-0; **2f**, 41771-06-6; **2g**, 105019-20-3; **4a**, 119770-04-6; **4b**, 119770-05-7; **4c**, 119770-06-8; **4d**, 119770-07-9; **5e**, 119770-08-0; **5f**, 119770-09-1; **5g**, 119770-10-4; **6a**, 7452-79-1; **6b**, 2983-38-2; **7e**, 1192-14-9; **7f**, 75750-10-6; **7g**, 35358-42-0; $(CH_2{=}CH)_2SO_2$, 77-77-0; $TiCl_4$, 7550-45-0.

Electroorganic Chemistry. 116. Electrochemical Transformation of Aldoximes to Nitriles Using Halogen Ions as Mediators: Intermediary Formation of Nitrile Oxides

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In our continuing studies on electroorganic synthesis using mediators,[1] we have found that aldoximes **1** are converted to nitriles **2** by using halogen ions as mediators (eq 1). This transformation is interesting from both synthetic and mechanistic viewpoints since it is achievable under much milder reaction conditions than those used in hitherto-known methods,[2] and also, passing electricity is necessary for the formation of **2** from **1** although it is formally a simple dehydration process which is unrelated to oxidation and reduction. Both synthetic results and mechanistic discussion are described in this report.

$$\underset{\mathbf{1}}{\text{R-CH=N-OH}} \xrightarrow[\text{supporting electrolyte}]{\text{electricity}} \underset{\mathbf{2}}{\text{R-CN}} \qquad (1)$$
MeOH

Electrochemical Transformation of Aldoximes 1 to Nitriles 2. Passing electricity through a solution of aldoximes **1** in methanol containing sodium chloride under conditions of constant current at room temperature using an undivided cell gave nitriles **2** in the yields shown in Table I after electricity of 2.5–8.0 F/mol was passed.

The yield of nitrile was found to be strongly dependent on the type of supporting electrolytes, as summarized in Table II. Sodium chloride gave the best result among the supporting electrolytes examined (run 2 in Table II), and the yields decreased in the order of $Cl^- > Br^- > I^- > ClO_4^- > TsO^-$ (runs 2–6 in Table II). Also, it was found that only a catalytic amount of sodium chloride was enough to transform **1** to **2** effectively as shown by a typical example in which 0.1 equiv of sodium chloride was used (run 1 in Table II).

Table I. Electrochemical Transformation of Aldoximes 1 to Nitriles 2

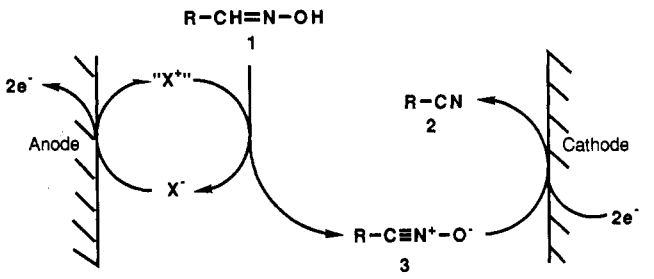
run	aldoximes 1; R	electricity, F/mol	isolated yields of nitriles 2, %
1	**1a**; $CH_3(CH_2)_5$	3.5	**2a**, 83
2	**1b**; $CH_3(CH_2)_8$	3.5	**2b**, 82
3	**1c**; cyclohexyl	3.5	**2c**, 71
4	**1d**; Ph(Me)CH	2.5	**2d**, 74
5	**1e**; $Ph(CH_2)_2$	3.8	**2e**, 73
6	**1f**; Ph	4.5	**2f**, 61
7	**1g**; *p*-ClPh	4.0	**2g**, 40
8	**1h**; *p*-MePh	3.0	**2h**, 54
9	**1i**; *p*-MeOPh	8.0	**2i**, 54
10	**1j**; 2,4,6-Me_3Ph	5.0	**2j**, 91

Table II. The Effect of Supporting Electrolytes

run	supporting electrolyte (SE)	molar ratio of SE to **1a**	yield (%) of **2a**[a]
1	NaCl	0.1	71
2	NaCl	0.5	83
3	NaBr	0.5	66
4	NaI	0.5	42
5	Et_4NOTs	0.5	16
6	$LiClO_4$	0.5	26

[a] Electricity, 5 F/mol, was passed at room temperature.

Scheme I



Reaction Mechanism. The transformation of **1** to **2** is formally a dehydration. An acid-catalyzed dehydration of **1** is one of the plausible mechanisms for the electrochemical formation of **2** from **1** since it has been suggested that some sort of acid is generated by passing electricity through a solution of a salt of a strong acid.[3] A small amount of **2** was indeed formed under such reaction conditions (runs 5 and 6 in Table II), but the high yields obtained under the reaction conditions using halogen ions cannot be explained by acid-catalyzed dehydration alone.

It is well-known that halogen anion (X^-) is oxidized to cationic active species ("X^+")[4] by electrochemical oxidation.[5] In this study, a mechanism involving "X^+" as an oxidizing agent[6] is proposed, as shown in Scheme I, where aldoximes **1** are oxidized to nitrile oxides **3**[8] followed by

(1) Shono, T. *Tetrahedron* **1984**, *40*, 811. Shono, T.; Matsumura, Y.; Katoh, S.; Inoue, K.; Matsumoto, Y. *Tetrahedron Lett.* **1986**, *27*, 6083. Shono, T.; Matsumura, Y.; Katoh, S.; Ohshita, J. *Chem. Lett.* **1988**, 1065.

(2) For example: Mai, K.; Patil, G. *Synthesis* **1986**, 1037. Arrieta, A.; Aizpurua, J. M.; Palomo, C. *Tetrahedron Lett.* **1984**, *25*, 3365. Attanasi, O.; Palma, P.; Serra-Zanetti, F. *Synthesis* **1983**, 741. Olah, G. A.; Narang, S. C.; Garcia-Luna, A. *Synthesis* **1980**, 659.

(3) Uneyama, K. *Yuki Gosei Kagaku Kyokaishi* **1985**, *43*, 557 and references cited therein.

(4) "X^+" denotes the cationic active halogen species generated by anodic oxidation of X^-.

(5) Kolthoff, I. M.; Coetzee, J. F. *J. Am. Chem. Soc.* **1957**, *79*, 1852.

(6) The reactivity of "X^+" is generally highly influenced by the reaction conditions. It is much higher than that of the corresponding X_2 in some cases as exemplified by the direct aromatic iodination,[7] while in other cases, it is similar to that of the corresponding X_2. In the transformation of **1** to **3**, the reactivity of "X^+" may belong to the latter.[8,9]

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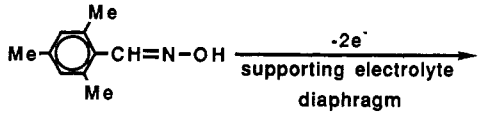
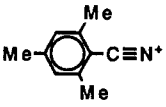
the cathodic reduction of **3** to **2**.

In order to establish the intermediacy of **3**, the electrochemical oxidation of **1** was carried out by using a divided cell since the reaction could not be terminated at the intermediate stage in an undivided cell. The result obtained for 2,4,6-trimethylbenzaldehyde oxime (**1j**) is shown in eq 2. As expected, **3j** was formed only in the cases where sodium halides were used as supporting electrolytes but not in the case using Et_4NOTs.

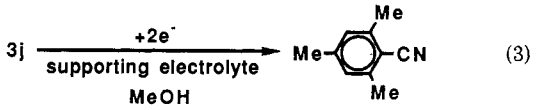


1j



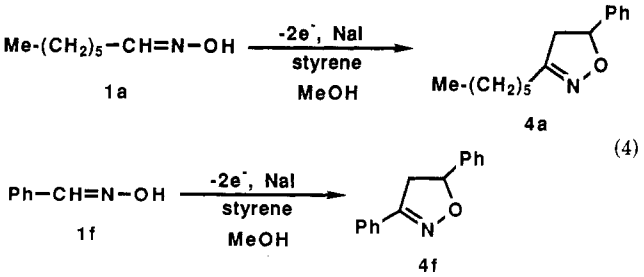
3j (2)

Furthermore, it was found that nitrile **2j** was formed by the electrochemical reduction of **3j** carried out under the same reaction conditions as those used in the transformation of **1** to **2** (eq 3). The fact that **2j** was formed in good yields in this reduction regardless of the type of supporting electrolyte (Et_4NOTs or NaX) suggests that **3j** was reduced to **2j** by the mechanism of direct electrochemical reduction.



2j (3)

Although 2,4,6-trimethylbenzonitrile oxide (**3j**) is a relatively stable nitrile oxide,[9] **3a–i** were not sufficiently stable to be isolated under the reaction conditions. The formation of nitrile oxides **3a** and **3f** was confirmed by their trapping with styrene. Namely, the electrochemical reaction of **1a** and **1f** carried out in the presence of styrene yielded the corresponding isoxazolines **4a** and **4f** (eq 4). Since the cycloaddition of nitrile oxides with some alkenes is known to yield 1,3-dipolar adducts,[11] these results strongly support the proposed mechanism (Scheme I). The effect of the type of halide anion on the yield of the formation of **2** may be explained in terms of the oxidizing ability of cationic halogen species.



1a 4a

1f 4f (4)

The catalytic nature of the halogen ions is also shown in Scheme I where X^- is regenerated at the step of the oxidation of **1** to **3** by "X^+", and X^- is reoxidized to "X^+" at the anode.

The mechanism of this reaction is unique since the oxidation of the starting material and the reduction of the key intermediate are achieved consecutively in one homogeneous reaction system.

Experimental Section

^1H NMR spectra were measured on a Varian Associates EM-360 or EM-390 spectrometer, with chemical shifts given in parts per million (δ) downfield from tetramethylsilane as an internal standard. IR spectra were recorded on a Hitachi 260-10 spectrometer. Elemental analyses were determined by the Center for Instrumental Analysis of Kyoto University. Melting points were uncorrected. Liquid chromatographic analysis was carried out by using a Shimadzu LC-6A instrument equipped with a RID-6A refractive index detector and a SPD-6AV UV–vis spectrometric detector monitored at 254 nm on a normal phase column Shimpack CLC-SIL 0.15 m × 6.0 mm i.d. (eluent: 0.2% *i*-PrOH/hexane, 0.5 mL/min). GLC analysis was carried out by using a Shimadzu GC-6AN on a PEG column (1 m × 3 mm i.d., at 180 °C, carrier gas 40 mL/min He). Electrolyses were carried out with a dc power supply, Takasago Seisakusho, Ltd., GP 050-2.

Materials. Unless stated otherwise, all reagents and chemicals were obtained commercially and used without further purification. **Aldoximes 1a–i** were known compounds and prepared from the corresponding commercially available aldehydes in a way similar to the synthesis of 2,4,6-trimethylbenzaldehyde oxime (**1j**).[12] **2,4,6-Trimethylbenzonitrile oxide (3j)** was prepared by the procedure described in the literature.[10] All of the yielded nitriles **2** were confirmed with GLC and LC by comparison with commercially available nitriles and **2j**.[13]

Electrochemical Transformation of Aldoximes 1 to Nitriles 2. Into an undivided cell equipped with two platinum electrodes (2 cm × 1 cm) and a magnetic stirring bar was placed a solution of methanol (5 mL) containing **1** (0.5 mmol) and sodium chloride (0.25 mmol). Electrolysis was carried out under the condition of constant current (0.05 A/cm^2) at room temperature. After the electricity of 2.5–8.0 F/mol was passed, the usual workup gave **2** in the yields shown in Table I. Electrochemical reactions with use of other supporting electrolytes were carried out in a similar manner. Small amounts of the corresponding esters and acetals were yielded as byproducts in each case.

Anodic Oxidation of 2,4,6-Trimethylbenzaldehyde Oxime (1j). Into the anodic chamber of a divided cell equipped with two platinum electrodes (2 cm × 1 cm) and a magnetic stirring bar was placed a solution of methanol (10 mL) containing **1j** (0.5 mmol) and sodium halides (0.25 mmol) or Et_4NOTs (0.25 mmol), and a solution of methanol (10 mL) containing sodium halides (0.25 mmol) or Et_4NOTs (0.25 mmol) was placed into the cathodic chamber. Electrolysis was carried out under the condition of constant current (0.025 A/cm^2) at room temperature. After the electricity of 4 F/mol was passed, the usual workup gave 2,4,6-trimethylbenzonitrile oxide (**3j**) in the LC yields of 23% for NaCl, 32% for NaBr, 27% for NaI, and 0% for Et_4NOTs.[14]

The yields were improved to 67% for NaCl and 66% for NaBr by carrying out the electrochemical reaction as follows: the cell was composed of two beakers which were connected by an agar bridge.[15] A methanolic solution (5 mL) containing **1j** (0.25 mmol) and NaX (0.25 mmol) was placed into the anodic chamber equipped with a platinum electrode (1 cm × 2 cm), and a methanolic solution (5 mL) containing NaX (0.25 mmol) was placed into the cathodic chamber equipped with a platinum electrode (1 cm × 2 cm). The electrochemical reaction and the workup were carried out in a manner similar to that described above except for the amount of electricity passed (5 F/mol).

Cathodic reduction of 2,4,6-trimethylbenzonitrile oxide (3j) was carried out in a manner similar to the electrochemical transformation of aldoximes **1** to nitriles **2**. After the electricity of 5 F/mol was passed, the usual workup gave 2,4,6-trimethyl-

(7) Miller, L. L.; Watkins, B. F. *J. Am. Chem. Soc.* **1976**, *98*, 1515.
(8) Oximes have been converted to nitrile oxides by bromine[9] or NBS.[10]
(9) Grundmann, C.; Dean, J. M. *J. Org. Chem.* **1965**, *30*, 2809.
(10) Grundmann, C.; Richter, R. *J. Org. Chem.* **1968**, *33*, 476.
(11) Grundmann, C. *Synthesis* **1970**, 344 and references cited therein.
(12) Hantzsch, A.; Lucas, A. *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 747.
(13) Grundmann, C.; Frommeld, H. *J. Org. Chem.* **1965**, *30*, 2077.
(14) The low yields were due to the diffusion of the anolyte solution into the cathodic chamber through the diaphragm during the electrochemical reaction since the presence of **2j** (the reduction product of **3j**) was observed in the cathodic chamber.
(15) The mechanism of this cell will be reported elsewhere.

benzonitrile (**2j**) in the GLC yields of 88% for NaCl, ca. 100% for NaBr, 88% for NaI, and 73% for Et_4NOTs.

Electrochemical Formation of Isoxazolines 4a and 4f. Into an undivided cell equipped with two platinum electrodes (2 cm × 2 cm) and a magnetic stirring bar was placed a solution of methanol (30 mL) containing aldoxime **1a** or **1f** (6 mmol), styrene (60 mmol), and sodium iodide (3 mmol). Electrochemical reaction was carried out under the condition of constant current (0.025 A/cm^2) at room temperature. After the electricity of 5–6 F/mol was passed, the usual workup gave isoxazolines **4a** and **4f**[16] in the yields of 56% and 34%, respectively.

3-Hexyl-5-phenyl-2-isoxazoline (4a): ^{1}H NMR (CCl_4) δ 0.85 (br t, 3 H, J = 5 Hz), 1.05–1.60 (m, 8 H), 2.23 (br t, 2 H, J = 7 Hz), 2.63 (dd, 1 H, J = 16 and 8 Hz), 3.20 (dd, 1 H, J = 16 and 10 Hz), 5.27 (dd, 1 H, J = 10 and 8 Hz), 7.11 (s, 5 H); IR (neat) 3065, 3040, 2960, 2930, 1625, 1609, 1500, 1460, 875, 760, 700 cm^{-1}. Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.73; H, 9.33; N, 6.29.

3,5-Diphenyl-2-isoxazoline (4f): ^{1}H NMR ($CDCl_3$) δ 3.18 (dd, 1 H, J = 16 and 9 Hz), 3.69 (dd, 1 H, J = 16 and 11 Hz), 5.58 (dd, 1 H, J = 11 and 9 Hz), 7.11–7.67 (m, 5 H), 7.25 (s, 5 H); IR (KBr) 3075, 3050, 2800, 1603, 1576, 1503, 1459, 1371, 1360, 935, 905, 870, 759, 701, 695 cm^{-1}; mp (from CCl_4) 71–73 °C (lit.[16] 76 °C). Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.66; H, 5.79; N, 6.12.

Acknowledgment. One of us (Y.M.) thanks the Ministry of Education, Science and Culture, Japan, for a Grant-in-Aid for Scientific Research on Priority Area 1 (62607001 and 63607001).

Registry No. **1a**, 629-31-2; **1b**, 13372-74-2; **1c**, 4715-11-1; **1d**, 59647-78-8; **1e**, 1197-50-8; **1f**, 100-52-7; **1g**, 104-88-1; **1h**, 104-87-0; **1i**, 123-11-5; **1j**, 487-68-3; **2a**, 629-08-3; **2b**, 1975-78-6; **2c**, 766-05-2; **2d**, 1823-91-2; **2e**, 645-59-0; **2f**, 100-47-0; **2g**, 623-03-0; **2h**, 104-85-8; **2i**, 874-90-8; **2j**, 2571-52-0; **3j**, 2904-57-6; **4a**, 119656-89-2; **4f**, 4894-23-9; NaCl, 7647-14-5; NaBr, 7647-15-6; NaI, 7681-82-5; Et_4NOTs, 733-44-8; $LiClO_4$, 7791-03-9; methanol, 67-56-1.

(16) Perold, G. W.; Steyn, A. P.; Reiche, F. V. K. *J. Am. Chem. Soc.* **1957**, *79*, 462.

An Enantioselective Synthesis of D-(−)-2-Amino-5-phosphonopentanoic Acid

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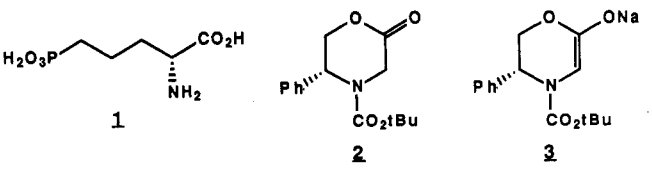
Received December 8, 1988

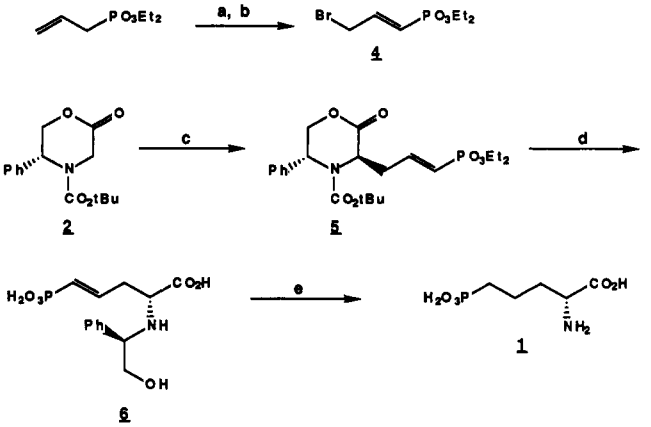
As a part of our program aimed at the synthesis of novel antagonists selective for the *N*-methyl-D-aspartic acid (NMDA) excitatory amino acid receptor subtype,[1] we had need for quantities of the NMDA selective antagonist D-(−)-2-amino-5-phosphonopentanoic acid (**1**, D-(−)-AP5, Chart I).[2] Watkins reported the synthesis and pharmacological characterization of a series of ω-phosphono-α-amino acids and showed that the compound known as AP5 was the most potent of the series as an antagonist of NMDA-mediated neurotransmission.[2] Watkins also demonstrated that the antagonist activity of AP5 resided in the D-(−) isomer.[2] We recently reported an efficient large-scale synthesis of D,L-AP5[3] and would like to report here our results aimed at the first enantioselective synthesis of D-(−)-AP5.

(1) For a recent review of NMDA receptor function, see: *Trends Neurosci.* **1987**, *10*, 263–302.
(2) Evans, R. H.; Francis, A. A.; Jones, A. W.; Smith, D. A. S.; Watkins, J. C. *Br. J. Pharmacol.* **1982**, *75*, 65.
(3) Ornstein, P. L. *Org. Prep. Proc.* **1988**, *20*, 371.

Chart I



Scheme I[a]



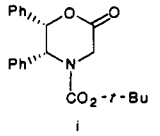
[a] (a) Br_2, CH_2Cl, 0 °C; (b) DBU, ether, 0 °C to room temperature; (c) i. $NaN(SiMe_3)_2$, THF, DME, −78 °C; ii. 4, THF, DME, −78 °C; (d) i. Me_3SiBr, CH_2Cl_2, room temperature; ii. 6 N HCl, room temperature; (e) H_2, 5% Pd/C, 55 °C, 60 psi.

The preparation of D- and L-AP5 by Watkins was achieved by resolution of the racemic mixture via the L-lysine salt.[2] This procedure was plagued by the inability to completely resolve the two enantiomers. We felt that the use of a chiral glycine synthon[4] would provide a more efficient means for preparation of the desired D-amino acid.

Dellaria[5] has recently reported on the preparation and use of the oxazinone **2** (Chart I) as a chiral glycine enolate synthon for the synthesis of amino acids via alkylation of the corresponding sodium enolate **3** (Chart I). We felt this method would be quite suitable to the preparation of D-(−)-AP5. The phenyl group of **2** is constrained to exist in a pseudoaxial conformation due to $A_{1,3}$ strain from the *tert*-butoxycarbonyl (BOC) protecting group on the nitrogen, therefore blocking the α-face of **3** and ensuring that alkylation occurs predominantly from the β-face of **3**. If we start with oxazinone **2** derived from D-phenylglycinol (as shown above) we will obtain the desired D isomer of AP5. Because alkylations with this enolate typically require more reactive alkylating agents, our synthesis of **1** necessitated the preparation of a suitably active reagent, e.g. the phosphono allylic bromide **4** (see Scheme I).

The synthesis of **1** was straightforward (see Scheme I). Treatment of diethyl allylphosphonate with bromine afforded the corresponding dibromide. This dibromide was not isolated but simply treated with DBU to provide the

(4) (a) Schollkopf, U.; Tiller, T.; Bardenhagen, J. *Tetrahedron* **1988**, *44*, 5293 and references cited therein. (b) Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 2501 and references cited therein.
(5) Dellaria, J. F.; Santarsiero, B. D. *Tetrahedron Lett.* **1988**, *29*, 6079. During the course of this work we also became aware of a structurally similar glycine enolate synthon i, that has also been used in alkylations. Williams, R. M.; Im, M.-N. *Tetrahedron Lett.* **1988**, *29*, 6075.



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