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THE SUBSTITUTION OF 5-HALO-1,2,3-TRIAZINES WITH ELECTROLYTICALLY GENERATED SUPEROXIDE

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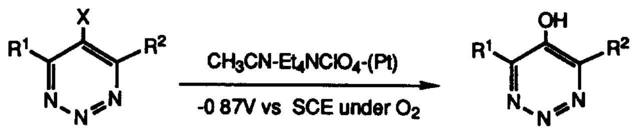
Summary Electrolytically generated superoxide reacted with 5-halo-1,2,3-triazines **1** to afford 5-hydroxy-1,2,3-triazines **2** Reaction of **1** with hydroxide anion or potassium superoxide resulted in complicated mixture of products, therefore the reaction was specific for electrogenerated superoxide The reaction mechanism was investigated with electrochemical methods, and it was revealed that one electron transfer from superoxide to **1** initialized the reaction

Monocyclic 4,6-disubstituted 1,2,3-triazines **3**[1] have such high π-deficiency that they are easily attacked with nucleophiles The reaction site was mainly C-4,[2] and succeeding ring opening occurred to form α,β-unsaturated β-aminoketone derivatives [3] Thus the direct introduction of substituents by the nucleophilic substitution[4] was unsuccessful for **3** Moreover, general method for the synthesis of **3** involved the oxidation of corresponding 1-aminopyrazoles,[5] therefore it was impossible to introduce previously the functional group which was labile under oxidative conditions In order to prepare 1,2,3-triazines having functional groups, we synthesized 5-halo-1,2,3-triazines **1**,[6] and investigated the reactivity of **1** As a result, **1** was allowed to react with electrolytically generated superoxide to give 5-hydroxy-1,2,3-triazine **2** [7] In this paper, we report the detailed results of the reaction and the reaction mechanism using electrochemical methods

Oxygen molecule is known to be reduced electrolytically (-0 87V vs saturated calomel electrode SCE) in aprotic solvent to form superoxide anion radical [8] When the reduction was carried out in the presence of **1** in CH_3CN, substitution reaction proceeded to form **2** (scheme 1 and Table 1)



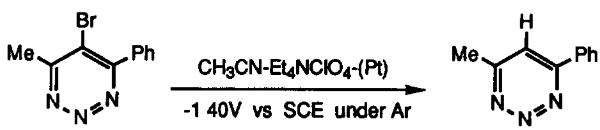
1 2

scheme 1

Table 1 Reaction of 5-Halo-1,2,3-triazines 1 with Electrolytically Generated Superoxide

substrate	R1	R2	X	$E_{1/2}$(V)	react time	yield of 2 (%)
1a	Me	Me	Br	-1 48	1 0 hr	95
1b	Me	Et	Br	-1 55	1 0 hr	97
1c	Et	Et	Br	-1 56	1 0 hr	66
1d	Me	Ph	Br	-1 27	1 0 hr	74
1e	Ph	Ph	Cl[9]	-1 26	4 0 hr	25

First reduction potentials of all substrates 1 were considerably less than the applied potential, thus only oxygen was supposed to be reduced electrolytically in these conditions No electric current was observed on the reduction at -0 87V in the absence of oxygen (under argon atmosphere), and the reduction at -1 4V under argon resulted in the formation of corresponding triazine (scheme 2) [10]



yield 70%[11]

1 d 3 d

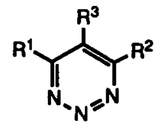
scheme 2

For the analysis of the reaction mechanism, the study using cyclic voltammetry was performed Table 2 shows the reduction potentials of 1 and corresponding 1,2,3-triazines 3 Halotriazine 1 had two irreversible reduction waves, and the value of the second one was almost as same as that of 3 The fact indicated that one electron reduction of 1 resulted in the formation of 3, which was performed by halide release followed by hydrogen abstraction

Fig 1 shows the cyclic voltammogram of 5-bromo-4,6-dimethyl-1,2,3-triazine 1a under argon atmosphere It was observed that one electron reduction occurred irreversibly, and the oxidation wave of bromide anion appeared on the reverse positive-going sweep [12] This phenomenon also suggested that one electron reduction of 1a caused the elimination of bromide anion, even in the absence of superoxide or oxygen

Table 2 Redox Potentials of Halotriazines 1 and Triazines 3 in CH_3CN/Et_4NClO_4

	R^1	R^2	R^3		E1/2(V)SCE	
1a	Me	Me	Br	-1 48		-1 93
3a	Me	Me	H		-1 95	
1b	Me	Et	Br	-1 55		-1 96
3b	Me	Et	H		-1 96	
1c	Et	Et	Br	-1 56		-2 01
3c	Et	Et	H		-2 03	
1d	Me	Ph	Br	-1 27		-1 80
3d	Me	Ph	H		-1 82	
1e	Ph	Ph	Cl	-1 26		-1 68
3e	Ph	Ph	H		-1 64	



1 or 3

Fig 2 affords the cyclic voltammograms of oxygen in the absence or in the presence of **1a** It was shown that the increasing concentration of **1a** caused the cathodic peak current of O_2 and the anodic peak current of Br^- to increase, and also caused the anodic peak current of superoxide to decrease Thus it was revealed that the electrogenerated superoxide reacted with **1a**, and bromide anion was released in the same way as the one electron reduction of **1a** Thus superoxide was suggested to act as one electron reductant

The above results indicated us the reaction mechanism as shown in scheme 2 At first, halotriazine **1** was reduced by superoxide to form anion radical **4** The release of halide anion from **4** was occurred spontaneously to afford a radical **5**, which was supposed to abstract hydrogen atom from the solvent to produce triazine **3** in the absence of oxygen The presence of oxygen caused the formation of a peroxy radical **6**, which led to hydroxytriazine **2** There are few reports that presented the aromatic substitution with superoxide [13,14] Frimer et al proposed that one electron transfer from superoxide followed by addition of molecular oxygen took place in the case of halonitrobenzenes as substrates [13] The reaction mechanism shown in scheme 2 is similar to the case, except that the nucleophilic addition of oxygen occurred after halide elimination [15]

A specific feature of our reaction system was that potassium superoxide was not available for the substitution Reactions with KO_2/18-crown-6[16] instead of electrogenerated superoxide resulted in the complicated mixture of products, part of which were derived from ring-opening reaction, and the

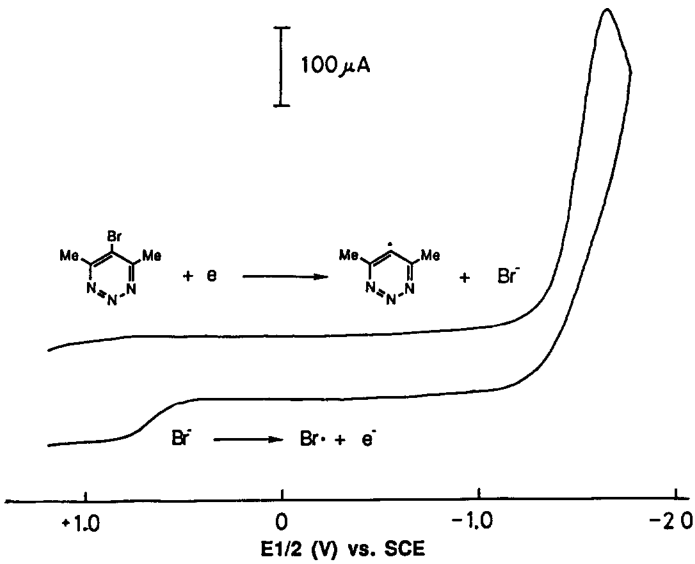


Fig. 1 Cyclic voltammogram for **1a** under argon atmosphere in acetonitrile (0 1M tetraethylammonium perchlorate) at mercury electrode

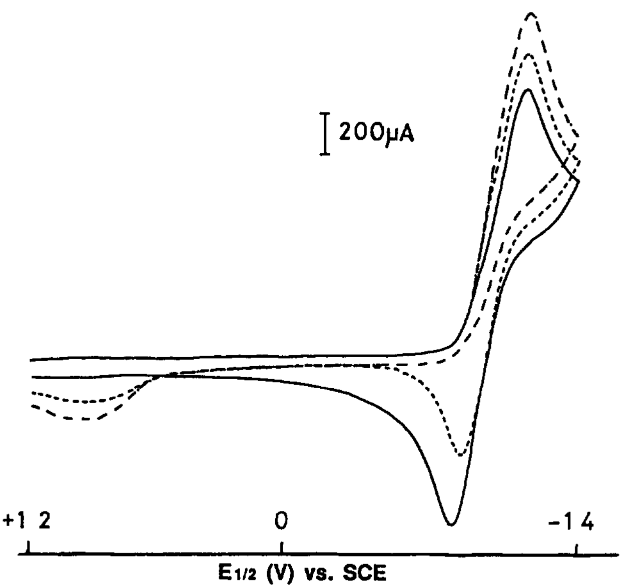
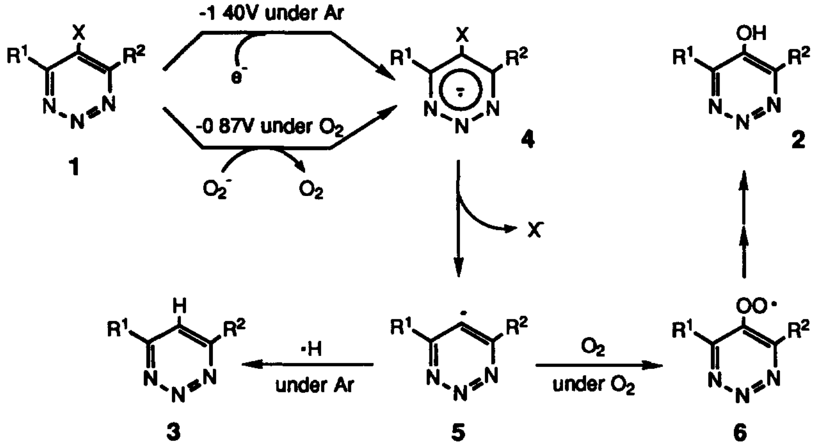


Fig. 2 Cyclic voltammogram for molecular oxygen in the absence and presence of **1a** in acetonitrile(0 1 M tetraethylammonium perchlorate) at mercury electrode

Concentration of 5-bromo-4,6-dimethyltriazine **1a**
(a) —— 0 mM (b) ---- 2 5 mM (c) - - - 7 5 mM

reaction rate was much slower The result was almost the same as in the case of KOH as a reagent, which means that KO_2 was not an effective reductant for 1 The slight solubility and low reduction ability[17] of potassium superoxide might cause the slow reaction rate, and the trace amount of hydroxide anion[18] in the reaction medium would attack C-4 position of triazine to bring about the ring opening [19]



scheme 3

In this paper we described the novel aromatic substitution with electrogenerated superoxide The method may be useful for the substitution of the compounds which are labile under basic condition. Hydroxytriazines thus obtained are of interest from the viewpoint of aromaticity and tautomerism[20] The physical properties of them are the subjects of continuing studies

EXPERIMENTAL

All melting points were taken on a Yanaco micro melting point apparatus and are uncorrected The mass spectra were measured with a JEOL JMS-D300 instrument The nuclear magnetic resonance spectra were taken on JEOL JNM-FX100 and GX400 spectrometers using tetramethylsilane as an internal standard

General Procedure for the Preparation of 5-Halo-1,2,3-triazines Compounds **1a**, **1d**, and **1e** were already reported[6b] The other substrates **1b** and **1c** were synthesized by the oxidation of corresponding 1-aminopyrazoles with *N*-bromosuccinimide (NBS) 1-Aminopyrazoles were obtained from the *N*-amination of corresponding pyrazoles with hydroxylamine *O*-sulfonic acid in EtOH at 65°C A methylene chloride solution of 1-aminopyrazole was treated with a solution of NBS (2 molar eq with respect to the aminopyrazole) at 0°C After 2hrs' reaction, the reaction mixture was filtrated to remove insoluble substance, and the filtrate was evaporated to leave the residue, which was chromatographed on alumina (hexane-CH_2Cl_2) to give 5-bromo-1,2,3-triazine

1-Amino-3-ethyl-5-methylpyrazole: Yellow oil. Mixture with 1-amino-5-ethyl-3-methylpyrazole. ^1H-NMR ($CDCl_3$) of the major one, δ: 1 20 (3H, t, J=7Hz), 2 24 (3H, s), 2.65 (2H, q, J=7Hz), 5 66 (1H, s) ^1H-NMR ($CDCl_3$) of the minor one, δ 1 24 (3H, t, J=7Hz), 2 18 (3H, s), 2 62 (2H, q, J=7Hz), 5 80 (1H, s) Exact MS *m/z* (M^+), Calcd for $C_6H_{11}N_3$: 125 095 Found 125 095

1-Amino-3,5-diethylpyrazole: Yellow oil. ^1H-NMR ($CDCl_3$) δ 1 18 (6H, t, J=7Hz), 2 52 (2H, q, J=7Hz), 2 62 (2H, q, J=7Hz), 4 71 (2H, bs), 5 66 (1H, s). ^{13}C-NMR ($CDCl_3$) δ 12 9, 13 6, 18 5, 21 5, 100 0, 144 9, 150 8 Exact MS *m/z* (M^+), Calcd for $C_7H_{13}N_3$ 139.111. Found 139 113

5-Bromo-4-ethyl-6-methyl-1,2,3-triazine (1b): Colorless oil ^1H-NMR ($CDCl_3$) δ 1 39 (3H, t, J=7Hz), 2 76 (3H, s), 3 08 (2H, q, J=7Hz) ^{13}C-NMR ($CDCl_3$) δ 11 6, 22.6, 28 9, 126 4, 160 1, 163 3 Exact MS *m/z* (M+), Calcd for $C_6H_8N_3Br$ 200 990. Found 200 992

5-Bromo-4,6-diethyl-1,2,3-triazine (1c): Colorless oil ^1H-NMR ($CDCl_3$) δ 1 40 (6H, t, J=7Hz), 3 09 (4H, q, J=7Hz) ^{13}C-NMR ($CDCl_3$) δ 11 5, 30 0, 125 9, 163 4. Exact MS *m/z* (M^+), Calcd for $C_7H_{10}N_3Br$ 214 999 Found 215 002

General Procedure for the Reaction of 5-Halotriazines with Electrolytically Produced Superoxide 5-Halotriazine (1mmol) was dissolved in 40 ml of 0 1 M tetraethylammonium perchlorate solution of acetonitrile and a stream of oxygen was bubbled into the solution through a gas dispersion tube which was inserted into the cathode chamber of a H cell containing platinum electrode. The electrolysis was carried out with Yanaco VE-9 potentio/galvanostatic electrolyzer and Nikko Keisoku potentiogalvanostat NPGS-2501 The potential was set and maintained at -0 87 V vs SCE until the starting material was entirely consumed In the case of **1e**, the substrate was detected even after 4hr, though the other substrates were reacted within 1hr After the electrolysis, the solvent was evaporated and the residue was dissolved in ether to remove insoluble supporting electrolyte The residual solution was evaporated, and the residue was chromatographed on silica gel to give 5-hydroxy-1,2,3-triazine **2**

5-Hydroxy-4,6-dimethyl-1,2,3-triazine (2a): Yield 95 % Colorless needles from hexane-AcOEt, mp 206°C Elemental analysis was unsuccessful because of **2a**'s high subliminableness ^1H-NMR ($CDCl_3$) δ 1 90 (1H, bs), 2 28 (6H, s) ^{13}C-NMR ($CDCl_3$) δ 15 6, 152 7, 165 6 Exact MS *m/z* (M^+), Calcd for $C_5H_7N_3O$ 125 059 Found 125 059

4-Ethyl-5-hydroxy-6-methyl-1,2,3-triazine (2b): Yield 97 % Colorless granules from CH_3OH, mp 181°C *Anal* Calcd for $C_6H_9N_3O$ C, 51 78, H, 6 52, N, 30 20 Found C, 52 09, H, 6 59, N, 30 00 ^1H-NMR ($CDCl_3$) δ 1 20 (3H, t, J=7Hz), 2 24 (1H, bs), 2 29 (3H, s), 2 76 (2H, q, J=7Hz) ^{13}C-NMR ($CDCl_3$) δ 10 1, 15 8, 22 4, 153 3, 156 6, 165 2

4,6-Diethyl-5-hydroxy-1,2,3-triazine (2c): Yield 66 %. Colorless granules from CH_3OH; mp 172°C *Anal* Calcd for $C_7H_{11}N_3O$, C, 54.88, H, 7.24, N, 27 43 Found C, 55 08, H, 7.35; N, 27 24 ^{1}H-NMR ($CDCl_3$) δ 1 19 (6H, t, J=7Hz), 2 18 (1H, bs), 2 79 (4H, q, J=7Hz). ^{13}C-NMR ($CDCl_3$) δ 10 17, 22.41, 156 9, 164 9

5-Hydroxy-4-methyl-6-phenyl-1,2,3-triazine (2d): Yield 74 % Colorless granules from CH_3OH, mp 182°C *Anal* Calcd for $C_{10}H_9N_3O$ C, 64.16, H, 4 85, N, 22 45 Found· C, 64 31, H, 4 84, N, 22 26 ^{1}H-NMR ($CDCl_3$) δ 2 17 (1H, bs), 2 41 (3H, s), 7 31-7 41 (3H,s), 8 12-8 25 (2H, s) ^{13}C-NMR ($CDCl_3$) δ 15 5, 127 7, 127 9, 129 5, 132 3, 147 7, 156 4, 164 1

5-Hydroxy-4,6-diphenyl-1,2,3-triazine (2e): Yield 25 % Colorless granules from CH_3OH, mp 197°C *Anal* Calcd for $C_{15}H_{11}N_3O$· C, 72 27, H, 4 45, N, 16 86 Found: C, 71 98, H, 4 25, N, 16 26 ^{1}H-NMR ($CDCl_3$) δ 1 28 (1H, bs), 7 32-7 40 (6H, m), 8 10-8 20 (4H, m) ^{13}C-NMR ($CDCl_3$) δ 127 8, 128 2, 129 7, 132 4, 151 8, 163 1 Exact MS *m/z* (M^+), Calcd for $C_{15}H_{11}N_3O$ 249 090 Found 249 091

Cyclic voltammogram The substrate (0 1 mmol) was dissolved in 10 ml of 0 1 M tetraethylammonium perchlorate solution of CH_3CN The redox potential and cyclic voltammogram were measured with a Yanaco P-1100 polarographic analyzer For the measurement of redox potential, **3b** and **3c** were newly synthesized according to the previously reported method [1a)]

4-Ethyl-6-methyl-1,2,3-triazine (3b): Colorless oil ^{1}H-NMR ($CDCl_3$) δ 1 38 (3H, t, J=7Hz), 2 67 (3H, s), 2 95 (2H, q, J=7Hz), 7 07 (1H, s) ^{13}C-NMR ($CDCl_3$) δ 12 4, 21 7, 28 6, 116 5, 159 4, 163 7 Exact MS *m/z* (M^+), Calcd for $C_6H_9N_3$ 123 080 Found 123 080

4,6-Diethyl-1,2,3-triazine (3c) Colorless oil ^{1}H-NMR ($CDCl_3$) δ 1 38 (6H, t, J=7Hz), 2 85 (4H, q, J=7Hz), 7 04 (1H, s) ^{13}C-NMR ($CDCl_3$) δ 12 4, 28 7, 115 3, 163 9 Exact MS *m/z* (M^+), Calcd for $C_7H_{11}N_3$ 137 095 Found 137 097

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9 5-Bromo-4,6-diphenyltriazine was not obtained by the oxidation of corresponding aminopyrazole with NBS. Bromine atom was supposed to be sterically too large to substitute between two phenyl groups. The reasons for low yield of **2e** is thought to be the steric hindrance of phenyl groups and the relatively low reactivity of chloro group toward substitution

10 When **1d** was electrolytically reduced at -1.60V, no products were obtained in spite of the complete consumption of **1d**. The electrogenerated base[21] is probably responsible for this result, because 1,2,3-triazine is unstable under basic condition

11 The reaction was carried out under the same conditions except that argon gas was bubbled instead of oxygen, and the potential was set at -1.40V. The yield was based on the conversion of **1d**. The conversion was low (30%) because of the decay of the electric current during the reaction

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15 When the cyclic voltammogram of 2,4-dinitrobromobenzene was measured under argon atmosphere,the release of bromide anion was not observed on the reverse positive-going sweep. Therefore, the nucleophilic attack of oxygen was occurred before the bromide elimination, which was different from our case

16 In the reaction, **1d** (1.0 mmol), KO_2 (3.0 mmol), and 18-crown-6 (1.0 mmol) were reacted in abs CH_3CN (5 ml) under O_2 atmosphere. It took 3 days for **1d** to be entirely consumed, and **2d** (10%),4-amino-3-bromo-4-phenyl-3-buten-2-one(<10%), 4-amino-4-phenyl-3-buten-2-one (<5%), and other unidentified minor products were obtained

17 In the reaction of some quaternary heterocycles,[22] KO_2 and electrogenerated superoxide exhibited quite different redox reactivities. The results will be shown in the following papers

18 KO_2 reacts readily with H_2O to give hydroxide anion

19 Nucleophilic attack to 1,2,3-triazines occurrs quite easily. For example, parent 1,2,3-triazine was decomposed by only dissolving in methanol

20 Preliminary results of the X-ray crystallography of **2e** showed the considerably short C5-O bond length (1.23Å), which indicated the keto form was predominant in the solid state. The detailed results will be reported elsewhere

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