

The Reactions of 2-Methyl-1,2,3-triazinium Iodides and Related Compounds

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The 2-methyl-1,2,3-triazinium iodides **2** reacted with various nucleophiles to give the corresponding 2,5-dihydro-adducts. When **2** was treated with potassium superoxide, it was dimerized to 5,5'-bi(2-methyl-2,5-dihydrotriazinyl). The 2,5-dihydro-1,2,3-triazines also gave the dimers on reaction with superoxide. These reactions revealed the unique dual reactivities of superoxide with triazine derivatives.

Keywords 1,2,3-triazine; 2-methyl-1,2,3-triazinium iodide; 2,5-dihydro-2-methyl-1,2,3-triazine; redox property; superoxide; reduction; oxidation

The monocyclic 1,2,3-triazines **1**¹⁾ are among the six-membered π -deficient heteroaromatics. They readily react with nucleophilic reagents including Grignard reagents,²⁾ electron rich dienophiles,³⁾ alkoxide anion,⁴⁾ and so on. Their reactive sites are mainly the C-4 position, and the 1,4-dihydro-adducts undergo ready N₂ elimination to form the ring-opened products.⁵⁾ On the contrary, electrophilic reactions on the ring carbons of **1** have never been observed. Attack on the nitrogen atoms by alkyl halides⁶⁾ or *m*-chloroperbenzoic acid⁷⁾ occurs in the same way as with other heteroaromatics such as pyridines or pyridazines, although the reaction rates are slower (Chart 1). 2-Methyl-1,2,3-triazinium iodides **2**⁶⁾ were expected to be highly electron-deficient and to react with nucleophiles more easily than **1**. Moreover the reactivities of **2** are of interest in comparison with those of pyridinium or pyridazinium salts. In this paper we wish to report the nucle-

ophilic reactions of **2**, and the redox reactions of **2** and the 2,5-dihydro-1,2,3-triazines **3**, which were obtained by reduction of **2** with NaBH₄.

Reaction of **2 with Nucleophilic Reagents (Chart 2)** The treatment of **2** with diethyl malonate in the presence of sodium hydride in tetrahydrofuran afforded the diethyl 2,5-dihydro-2-methyl-1,2,3-triazine-5-malonates **4** in good yields. When **2** was allowed to react with Grignard reagents, the corresponding 5-substituted 2,5-dihydro derivatives **5** were obtained. The low isolated yield of **5a** (R = Me) was due to the high volatility of the compound. The reaction with hydroxide anion provided the 5(2*H*)-triazinones **6** in low yields; they were supposed to have been formed *via* oxidation of the 5-hydroxy-2,5-dihydro derivatives.

Reaction of **2 with Potassium Superoxide** Superoxide is known to be one of the most widely occurring active oxygen species,⁸⁾ and its reactivity has attracted much

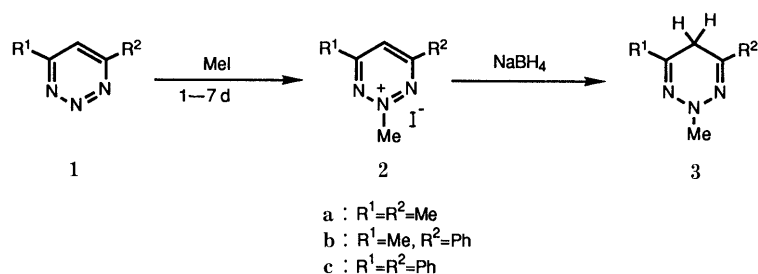


Chart 1

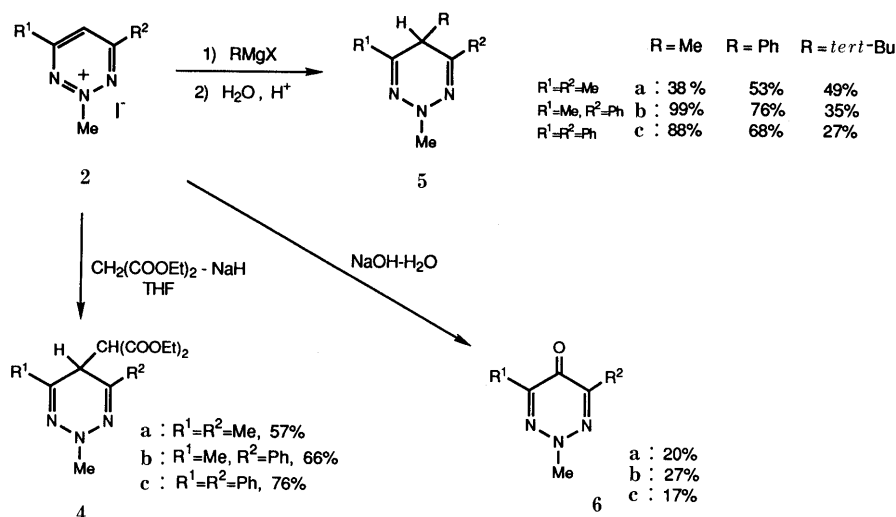


Chart 2

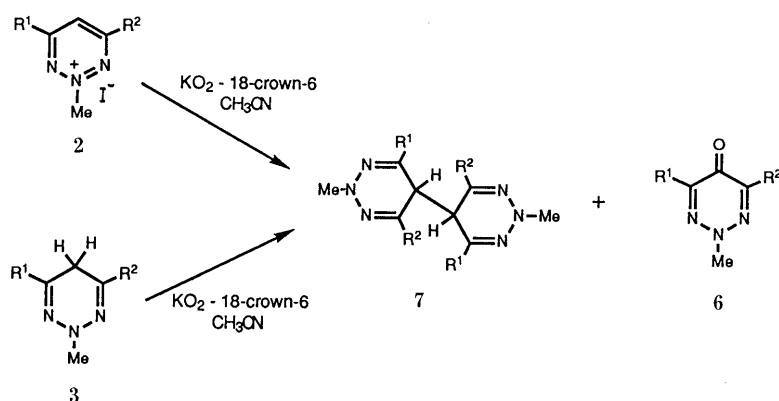


Chart 3

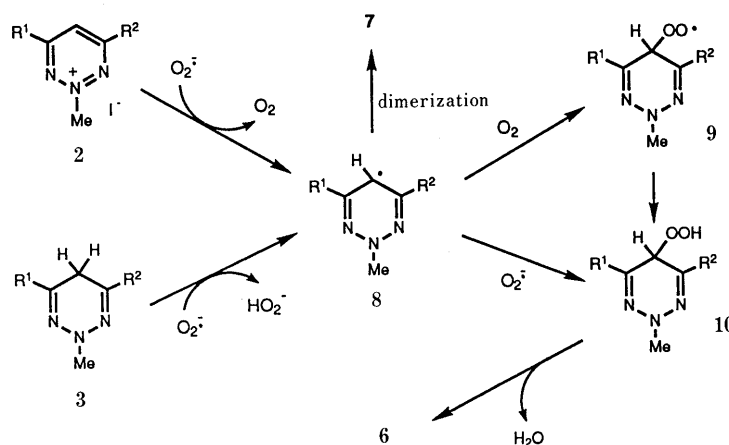


Chart 4

TABLE I. Reaction of 2-Methyl-1,2,3-triazinium Iodide 2 with Potassium Superoxide

| Substrate | Conditions | Yield of 7 (%) | Yield of 6 (%) |
|-----------|-----------------------------|----------------|----------------|
| 2a | | 52 | 12 |
| 2b | 10 min under Ar | 54 | 6 |
| 2c | | 57 | 13 |
| 2a | | 58 | 7 |
| 2b | 10 min under O ₂ | 61 | 11 |
| 2c | | 65 | 13 |

TABLE II. Reaction of 2-Methyl-2,5-dihydrotriazine 3 with Potassium Superoxide

| Substrate | Conditions | Yield of 7 (%) | Yield of 6 (%) |
|-----------|--------------------------|----------------|----------------|
| 3a | | 14 | 64 |
| 3b | 24 h under Ar | 73 | 10 |
| 3c | | 69 | 15 |
| 3a | | 4 | 73 |
| 3b | 2 h under O ₂ | 16 | 55 |
| 3c | | 3 | 85 |

attention from both biological⁹⁾ and chemical¹⁰⁾ viewpoints. Superoxide has a variety of chemical reactivities including one-electron reduction,¹¹⁾ nucleophilic substitution,¹²⁾ hydrogen abstraction,¹³⁾ and the action as a base.¹⁴⁾ It has the characteristic feature that it can act as both a reductant and an oxidant depending upon the nature of the substrates. Thus we study the reactivity of 2 and 3 with superoxide.¹⁵⁾ When 2 was allowed to react with 1.2 eq of potassium superoxide under an argon or oxygen atmosphere, one-electron reduction of 2 occurred readily to afford the 5,5'-bi(2-methyl-2,5-dihydrotriazinyl) 7 accompanied with small amounts of the 2-methyl-5(2H)-triazinone 6 (Chart 3 and Table I). The lack of influence of the atmosphere suggested that the one-electron reduction was so fast that the intermediate radical (Chart 4, 8) was formed at high concentration to afford 7.

Reaction of 3 with Potassium Superoxide Next, com-

pound 3 was allowed to react with KO₂ in CH₃CN under an argon or oxygen atmosphere. The consumption of 3 was much slower than that of 2, although compound 7 was obtained in almost the same yields as in the case of 2 as the substrate. The presence of oxygen accelerated the reaction to form 6 as the major product, which was different from the above case (Chart 3 and Table II). When the reaction was carried out with electrolytically generated superoxide under oxygen, it was revealed that compound 6 was formed through a radical chain reaction, at least in part. That is, the electroreduction of oxygen in the presence of 3 resulted in the formation of 6 before one equivalent of electric current had been consumed (0.5 F/mol for 3a). Thus the reaction mechanism might be summarized as shown in Chart 4.

Superoxide is supposed to act as a one-electron reductant for 2, and as a hydrogen abstractor for 3 to form a com-

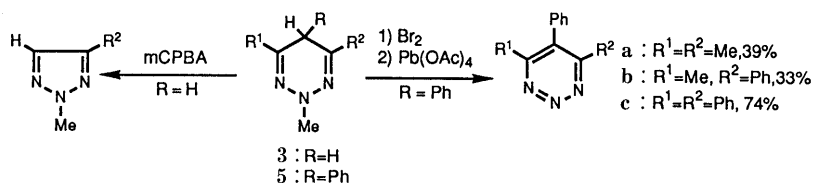


Chart 5

mon radical intermediate **8**. The reduction of **2** proceeded promptly to give **8** in high concentration, and therefore the dimerization to **7** occurred preferentially even under an oxygen atmosphere. On the other hand, the hydrogen abstraction from **3** is considered to be slow because of its electron deficiency, and hence the radical **8** was formed at low concentration to react with triplet oxygen under the oxygen atmosphere instead of the dimerization. The peroxy radical **9** thus formed abstracted hydrogen to give a peroxide **10**. When the hydrogen source was **3**, the radical **8** was regenerated to bring about the radical chain reaction. The other hydrogen source is supposed to be acetonitrile. In the case of **3a** as a substrate, compound **6a** was mainly obtained even in the absence of triplet oxygen, so there seemed to be another pathway to **10** other than the path *via* **9**, although the reason for the selection remained unclear. We supposed it to be the reaction of **8** with superoxide. The peroxide **10** thus formed was dehydrated to afford the 5-oxo derivative **6**. The above reaction is of interest from the viewpoint of the analogy with the reaction of dihydropyridine with superoxide. Sawyer and Nanni reported the reaction of *N*-benzyl-1,4-dihydropyridine (BNAH) with potassium superoxide.¹⁶⁾ It was shown that superoxide oxidized BNAH by a hydrogen abstraction process to give the *N*-benzyl-nicotinamide (BNA) radical, which is highly reactive, making the reaction complicated. Since **3** is more electron-deficient than BNAH,¹⁷⁾ the reaction with superoxide was slow, but the radical **8** is supposed to be more stable than BNA·, having a sufficient life time to afford the dimer **7**. On the contrary, **2** is reduced more readily than BNA⁺,¹⁸⁾ and therefore the radical **8** was formed at high concentration, causing the formation of **7** even in the presence of oxygen.

The reaction of heteroaromatic quaternary salts with superoxide was revealed to afford specific reaction indices for superoxide. The application of the reaction to benzo-thiazolium salts was reported,¹⁹⁾ and a further study of the reaction mechanism is in progress.

Oxidation of 3 or 5 with Other Oxidants In most cases, dihydrotriazines (**3** or **5**) were decomposed by the oxidation, so the reaction is generally not available for synthetic purposes. Compound **3** was reoxidized to **2** in quantitative yield with iodine.²⁰⁾ When **3** was treated with *m*-chloroperbenzoic acid, ring contraction occurred to form a 1,2,3-triazole (Chart 5).²¹⁾ The oxidation of **5** was of use only when the 5-phenyl derivative was oxidized with bromine and lead tetraacetate to give 5-phenyl-1,2,3-triazine (Chart 5). In the reaction, bromine oxidized **5** at first to the quaternary salt **2**, and lead tetraacetate reacted with the methyl group of the N-2 position, which might be eliminated as formaldehyde.

In this paper, we describe the nucleophilic reaction of **2**,

which is considered to be highly π -deficient, and the redox properties of **2** and **3** with superoxide. Further investigations on the reaction of electron-deficient heteroaromatics with superoxide seem to be of interest.

Experimental

All melting points were taken on a Yanaco micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded with a JASCO A-102 spectrometer. The mass spectra (MS) were measured with a JEOL JMS-D300 instrument. The nuclear magnetic resonance (NMR) spectra were taken on JEOL JNM-FX100 and GX400 spectrometers using tetramethylsilane as an internal standard. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet.

The Reactions of 2 with Diethyl Malonate A mixture of diethylmalonate (4 mmol) and NaH (60%, 4.78 mmol) in tetrahydrofuran (THF) (25 ml) was added to the solution of **2** (2 mmol) in THF (5 ml) under a nitrogen atmosphere at 0°C. The reaction was continued for 1 h, then H₂O (20 ml) and CH₂Cl₂ were added to the solution, and the organic layer was separated, dried over MgSO₄, and evaporated to dryness. The residue was chromatographed on silica gel (hexane–AcOEt) to give **4a**: yield 57%. Pale yellow granules from hexane–pentane, mp 34–36°C. ¹H-NMR (CDCl₃) δ : 1.26 (6H, t, *J* = 7 Hz), 2.08 (6H, s), 3.45 (1H, d, *J* = 11 Hz), 3.45 (3H, s), 3.88 (1H, d, *J* = 11 Hz), 4.18 (4H, q, *J* = 7 Hz). Exact MS *m/z* (M⁺) Calcd for C₁₃H₂₁N₃O₄: 283.153. Found: 283.153. **4b**: yield 66%. Pale yellow granules from hexane, mp 54–55.5°C. *Anal.* Calcd for C₁₈H₂₃N₃O₄: C, 62.59; H, 6.71; N, 12.17. Found: C, 62.82; H, 6.88; N, 12.11. ¹H-NMR (CDCl₃) δ : 0.93 (3H, t, *J* = 7 Hz), 1.26 (3H, t, *J* = 7 Hz), 2.21 (3H, s), 3.50 (1H, d, *J* = 10 Hz), 3.66 (3H, s), 3.75 (2H, q, *J* = 7 Hz), 4.20 (2H, q, *J* = 7 Hz), 4.64 (1H, d, *J* = 10 Hz), 7.26–7.34 (3H, m), 7.75–7.82 (2H, m). **4c**: yield 76%. Pale yellow granules from hexane, mp 38–40°C. *Anal.* Calcd for C₂₃H₂₅N₃O₄: C, 67.79; H, 6.18; N, 10.31. Found: C, 67.98; H, 6.23; N, 10.23. ¹H-NMR (CDCl₃) δ : 0.97 (6H, t, *J* = 7 Hz), 3.56 (1H, d, *J* = 10 Hz), 3.86 (4H, q, *J* = 7 Hz), 3.87 (3H, s), 5.44 (1H, d, *J* = 10 Hz), 7.24–7.46 (6H, m), 7.77–8.01 (4H, m).

The Reactions of 2 with Grignard Reagents The triazinium salt (**2**) (1 mmol) was added in portion to a solution of Grignard reagent (1.2 mmol) prepared by the general method in absolute ether (5 ml) at 0°C. The reaction temperature was kept at 0°C until the red color of the starting material disappeared (10–20 min). Then saturated aqueous NH₄Cl was added to quench excess reagent, and the organic layer was dried over MgSO₄, and evaporated to dryness. The residue was chromatographed on alumina to give the products mentioned below.

2,5-Dihydro-2,4,5,6-tetramethyl-1,2,3-triazine: Yield 38%. Colorless oil. ¹H-NMR (CDCl₃) δ : 1.03 (3H, d, *J* = 7 Hz), 2.02 (6H, s), 2.59 (1H, q, *J* = 7 Hz), 3.35 (3H, s). Exact MS *m/z* (M⁺) Calcd for C₇H₁₃N₃: 139.111. Found: 139.112. 2,5-Dihydro-2,4,5-trimethyl-6-phenyl-1,2,3-triazine: Yield 99%. Colorless oil. ¹H-NMR (CDCl₃) δ : 0.96 (3H, d, *J* = 7 Hz), 2.07 (3H, s), 3.48 (3H, s), 3.52 (1H, q, *J* = 7 Hz), 7.25–7.40 (3H, m), 7.63–7.76 (2H, m). Exact MS *m/z* (M⁺) Calcd for C₁₂H₁₅N₃: 201.126. Found: 201.126. 2,5-Dihydro-2,5-dimethyl-4,6-diphenyl-1,2,3-triazine: Yield 88%. Yellow needles from hexane, mp 88°C. *Anal.* Calcd for C₁₇H₁₇N₃: C, 77.53; H, 6.51; N, 15.96. Found: C, 77.41; H, 6.63; N, 15.97. ¹H-NMR (CDCl₃) δ : 1.08 (3H, d, *J* = 7 Hz), 3.68 (3H, s), 4.29 (1H, q, *J* = 7 Hz), 7.24–7.40 (6H, m), 7.67–7.86 (4H, m). 2,5-Dihydro-2,4,6-trimethyl-5-phenyl-1,2,3-triazine: Yield 53%. Colorless viscous oil. ¹H-NMR (CDCl₃) δ : 1.96 (6H, s), 3.34 (3H, s), 3.75 (1H, s), 7.05–7.28 (5H, m). ¹³C-NMR (CDCl₃) δ : 20.83, 44.05, 47.10, 127.41, 128.09, 128.89, 136.88, 141.26. Exact MS *m/z* (M⁺) Calcd for C₁₂H₁₅N₃: 201.126. Found: 201.125. 2,5-Dihydro-2,4-dimethyl-5,6-diphenyl-1,2,3-triazine: Yield 76%. Colorless viscous oil. ¹H-NMR (CDCl₃) δ : 2.10 (3H, s), 3.51 (3H, s), 4.52 (1H, s), 7.18 (5H, s), 7.20–7.31 (3H, m), 7.58–7.77

(2H, m). $^{13}\text{C-NMR}$ (CDCl_3) δ : 21.28, 40.63, 47.33, 125.77, 127.16, 127.45, 128.13, 128.48, 128.75, 135.30, 137.17, 137.47, 141.55. Exact MS m/z (M^+) Calcd for $\text{C}_{17}\text{H}_{17}\text{N}_3$: 263.142. Found: 263.142. 2,5-Dihydro-2-methyl-4,5,6-triphenyl-1,2,3-triazine: Yield 68%. Yellow needles from hexane, mp 152 °C. *Anal.* Calcd for $\text{C}_{22}\text{H}_{19}\text{N}_3$: C, 81.20; H, 5.89; N, 12.91. Found: C, 81.24; H, 5.77; N, 12.88. $^1\text{H-NMR}$ (CDCl_3) δ : 3.72 (3H, s), 5.51 (1H, s), 7.18 (5H, s), 7.30–7.48 (6H, m), 7.82–7.98 (4H, m). $^{13}\text{C-NMR}$ (CDCl_3) δ : 36.32, 47.52, 125.97, 127.04, 127.42, 128.31, 128.51, 128.72, 135.34, 137.39, 138.16. 5-*tert*-Butyl-2,5-dihydro-2,4,6-trimethyl-1,2,3-triazine: Yield 49%. Yellow oil. $^1\text{H-NMR}$ (CDCl_3) δ : 0.92 (9H, s), 2.05 (6H, s), 2.69 (1H, s), 3.27 (3H, s). $^{13}\text{C-NMR}$ (CDCl_3) δ : 23.07, 28.56, 38.81, 46.10, 49.51, 138.51. 5-*tert*-Butyl-2,5-dihydro-2,4-dimethyl-6-phenyl-1,2,3-triazine: Yield 35%. Yellow oil. $^1\text{H-NMR}$ (CDCl_3) δ : 0.86 (9H, s), 2.16 (3H, s), 3.45 (3H, s), 3.50 (1H, s), 7.22–7.38 (3H, m), 7.73–7.80 (2H, m). $^{13}\text{C-NMR}$ (CDCl_3) δ : 24.10, 29.46, 40.07, 45.14, 47.06, 125.10, 127.67, 128.09, 136.89, 138.06, 140.87. Exact MS m/z (M^+) Calcd for $\text{C}_{15}\text{H}_{23}\text{N}_3$: 243.173. Found: 243.168. 5-*tert*-Butyl-2,5-dihydro-2-methyl-4,6-diphenyl-1,2,3-triazine: Yield 27%. Yellow oil. $^1\text{H-NMR}$ (CDCl_3) δ : 0.82 (9H, s), 3.61 (3H, s), 4.33 (1H, s), 7.18–7.42 (3H, m), 7.70–7.88 (2H, m). $^{13}\text{C-NMR}$ (CDCl_3) δ : 29.29, 39.76, 40.23, 47.10, 125.38, 128.22, 128.45, 138.08, 138.47. Exact MS m/z (M^+) Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3$: 305.189. Found: 305.193.

Reaction of 2 with Potassium Hydroxide An aqueous solution (1 ml) of KOH (1 mmol) was added to a methanol (3 ml) solution of **2** (0.5 mmol) at room temperature, and the mixture was stirred for 2 h. Then the mixture was extracted with CH_2Cl_2 (10 ml \times 3). The organic layer was dried over MgSO_4 , and evaporated to leave the residue, which was chromatographed on alumina to afford **6** in 20, 27 and 17% yields (for **6a**, **6b** and **6c**, respectively). The spectral data for **6a** and **6b** were previously reported.³⁾ 2-Methyl-4,6-diphenyl-1,2,3-triazine-5(2*H*)-one (**6c**): Colorless plates from Et_2O ; mp 115 °C. *Anal.* Calcd for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}$: C, 72.98; H, 4.98; N, 15.94. Found: C, 73.23; H, 4.83; N, 15.69. $^1\text{H-NMR}$ (CDCl_3) δ : 4.29 (3H, s), 7.35–7.40 (6H, m), 8.16–8.24 (4H, m). $^{13}\text{C-NMR}$ (CDCl_3) δ : 50.80, 128.20, 128.50, 130.20, 132.40, 152.11, 161.60.

The Reaction of 2 or 3 with Potassium Superoxide Compound **2** or **3** (0.2 mmol) was dissolved in 10 ml of absolute CH_3CN , then KO_2 (0.24 mmol) and 0.03 mmol of 18-crown-6-ether were added under an argon or oxygen atmosphere at -10°C . The mixture was allowed to stand at room temperature until the starting material was consumed, then it was filtered to remove insoluble salt. The filtrate was evaporated to leave the residue, which was chromatographed on alumina ($\text{hexane}:\text{CH}_2\text{Cl}_2 = 1:1$) to give the products.^{2,2)} The spectral data for **7a**^{2,3)} were previously reported. 5,5'-Bi(2,5-dihydro-2,4-dimethyl-6-phenyl-1,2,3-triazinyl) (**7b**): Yellow needles from hexane-ether; mp 168 °C. *Anal.* Calcd for $\text{C}_{22}\text{H}_{24}\text{N}_6$: C, 70.94; H, 6.50; N, 22.57. Found: C, 70.90; H, 6.53; N, 22.51. $^1\text{H-NMR}$ (CDCl_3) δ : 1.72 (3H, s), 3.68 (3H, s), 4.00 (1H, s), 7.24–7.42 (3H, m), 7.60–7.75 (2H, m). 5,5'-Bi(2,5-dihydro-2-methyl-4,6-diphenyl-1,2,3-triazinyl) (**7c**): Yellow granules from benzene, mp 200 °C. *Anal.* Calcd for $\text{C}_{32}\text{H}_{28}\text{N}_6$: C, 77.39; H, 5.68; N, 16.93. Found: C, 77.54; H, 5.58; N, 16.85. $^1\text{H-NMR}$ (CDCl_3) δ : 3.90 (6H, s), 4.92 (2H, s), 7.04–7.20 (6H, s), 7.40–7.52 (4H, s). $^{13}\text{C-NMR}$ (CDCl_3) δ : 26.65, 47.67, 125.98, 128.10, 128.90, 134.63, 137.80.

Reaction of 3 with Electrolytically Generated Superoxide The electroreduction was carried out with a Nikko Keisoku potentiogalvanostat, NPGS-2501. The dihydrotriazine **3a** (1.0 mmol) was dissolved in 40 ml of 0.1 M tetraethylammonium perchlorate solution of CH_3CN and a stream of oxygen was bubbled into the solution through a gas dispersion tube which was inserted into the cathode chamber of an H cell containing platinum electrode. The potential was set and maintained at $-0.87\text{ V vs. saturated calomel electrode (SCE)}$ until the starting material was entirely consumed. The electric current was measured with a Nikko Keisoku digital column meter, NDCM-4. About a half equivalent of electric current was enough for the consumption of **3a**, then the solvent was evaporated off and the residue was extracted with ether (30 ml \times 3). The ether layer was dried over MgSO_4 , and evaporated to leave the residue, which was chromatographed on alumina to afford the product in 85% yield.

Oxidation of 5 (5-Phenyl Derivative) with Bromine and Lead Tetraacetate Bromine (0.5 mmol) in 2 ml of CH_2Cl_2 was added dropwise to a CH_2Cl_2 solution of **5** (0.5 mmol) at room temperature. After 2 h, 0.61

mmol of $\text{Pb}(\text{OAc})_4$ was added and stirring was continued for 1 h. Then aqueous Na_2CO_3 solution was added to neutralize the reaction mixture, and the whole was filtered to remove insoluble salts. The residual organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 . The organic solutions were combined, dried over MgSO_4 , and evaporated to dryness. The residue was chromatographed on alumina to give the 5-phenyltriazine. 4,5,6-Triphenyl-1,2,3-triazine has already been reported.²⁴⁾ 4,6-Dimethyl-5-phenyl-1,2,3-triazine: Colorless needles from hexane-ether, mp 127 °C. *Anal.* Calcd for $\text{C}_{11}\text{H}_{11}\text{N}_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.66; H, 5.98; N, 22.36. $^1\text{H-NMR}$ (CDCl_3) δ : 2.44 (6H, s), 7.08–7.23 (2H, s), 7.40–7.56 (3H, s). MS m/z : 157 ($\text{M}^+ - \text{N}_2$). 4-Methyl-5,6-diphenyl-1,2,3-triazine: Colorless needles from benzene-hexane, mp 131 °C. *Anal.* Calcd for $\text{C}_{16}\text{H}_{13}\text{N}_3$: C, 77.71; H, 5.30; N, 16.99. Found: C, 77.57; H, 5.26; N, 16.87. $^1\text{H-NMR}$ (CDCl_3) δ : 2.62 (3H, s), 7.09–7.50 (10H, m).

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- 22) The products **6** and **7** are easily separated under the conditions employed. For example, **6c** and **7c** showed *Rf* values of 0.23 and 0.54, respectively.
- 23) T. Itoh, K. Nagata, T. Kaihoh, M. Okada, C. Kawabata, H. Arai, H. Ohnishi, K. Yamaguchi, H. Igeta, A. Ohsawa, and Y. Iitaka, *Heterocycles*, **33**, 631 (1992).
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