

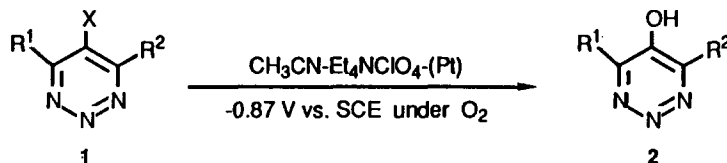
REACTION OF 5-HALO-1,2,3-TRIAZINES WITH SUPEROXIDE; SYNTHESIS OF 5-HYDROXY-1,2,3-TRIAZINES

Takashi Itoh, Kazuhiro Nagata, Mamiko Okada, and Akio Ohsawa*

*School of Pharmaceutical Sciences, Showa University, Shinagawa-ku
Tokyo 142, Japan*

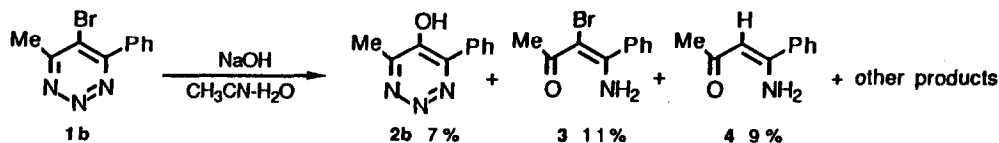
Summary: 5-Halo-1,2,3-triazines were allowed to react with electrolytically produced superoxide to give 5-hydroxy-1,2,3-triazines. Reaction with hydroxide anion gave ring opening products, therefore this substitution was specific for superoxide.

Among six membered heteroaromatic compounds, monocyclic 1,2,3-triazines¹⁾ are highly π -deficient because of three nitrogen atoms in the ring. Their aromaticity was suggested by ¹H-NMR²⁾ and X-ray crystallographic analysis,³⁾ but the ring system is moderately unstable⁴⁾ and the nucleophilic reaction occurred at 4-position to cause the ring opening along with evolution of nitrogen.⁵⁾ Hence, the general method for the substitution of π -deficient six membered heteroaromatics⁶⁾ (nucleophilic attack followed by oxidation) is not available for the substitution of 1,2,3-triazine. In order to prepare 1,2,3-triazines which have functional groups at their 5-positions, we synthesized 5-halo-1,2,3-triazines 1⁷⁾ and attempted the nucleophilic reactions to them. In this paper we report the synthesis of 5-hydroxy-1,2,3-triazines 2 by a nucleophilic reaction which is feasible only with electrogenerated superoxide. Hydroxytriazines such as 2 are of general interest from the viewpoint of aromaticity and tautomerism.⁸⁾



scheme 1

Introduction of the leaving group at 5-position could not change the reaction site of 1 with hydroxide anion. For example, treatment of 1b with sodium hydroxide in CH₃CN-H₂O for 5hr gave the many products, part of which were arising from the attack of 4-position and succeeding ring opening(3 and 4), and 5-hydroxytriazine 2b was obtained only in a poor yield (scheme 2).



scheme 2

However when 1 were electrolyzed in an atmosphere of oxygen, the reaction proceeded at the reduction potential of O₂ and gave 2 (scheme 1 and Table). In the typical experiment, 1a was dissolved in 0.1M 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 potential was set and maintained at -0.87 V vs. SCE until the starting material was entirely consumed (30 min for 1a). The solvent was evaporated and the residue was dissolved in ether to remove insoluble supporting electrolyte. After that the solution was evaporated to leave the residue which was chromatographed on silica gel to give 2a. The reaction proceeded at the potential of one electron reduction of oxygen, which suggests the participation of superoxide anion. However, the reaction with potassium superoxide resulted in low yields of 2, because the trace amount of hydroxide anion⁹⁾ in reaction medium caused the ring opening of 1 much faster than the substitution with KO₂.

Although superoxide has redox, anionic, and radical nature,¹⁰⁾ and is biologically one of the most important radical species,¹¹⁾ the reactivity in itself is relatively low for synthetic use.¹²⁾ There are few reports that presented the aromatic nucleophilic substitution with superoxide,^{13,14)} and their substrates were limited to the ones that reacted also with hydroxide anion to afford the same results. Frimer et al. proposed that one electron transfer from superoxide followed by addition of molecular oxygen proceeded rather than direct nucleophilic attack in the case of halonitrobenzenes as substrates.¹⁴⁾ The similar mechanism might be conceivable in our cases because 1 is highly π -deficient as same as halonitrobenzenes. The reaction mechanism is now under investigation.

Table Reaction of 5-halo-1,2,3-triazines with electrolytically produced superoxide

substrate	R ¹	R ²	X	E _{1/2} (V)	yield of 2 (%)
1a	Me	Me	Br	-1.48	95
1b	Me	Et	Br	-1.52	97
1c	Et	Et	Br	-1.46	66
1d	Me	Ph	Br	-1.27	74
1e	Ph	Ph	Cl	-1.26	25 ¹⁵⁾

ACKNOWLEDGEMENT This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan.

References and Notes

- 1) A. Ohsawa, H. Arai, H. Ohnishi, T. Itoh, T. Kaihoh, M. Okada, and H. Igeta, *J. Org. Chem.*, **50**, 5520 (1985).
- 2) A. Ohsawa, H. Arai, H. Ohnishi, and H. Igeta, *J. Chem. Soc., Chem. Commun.*, **1981**, 1174.
- 3) K. Yamaguchi, A. Ohsawa, H. Arai, H. Ohnishi, H. Igeta, and Y. Iitaka, *Chem. Pharm. Bull.*, **31**, 3762 (1983).
- 4) 1,2,3-Triazines were fragmented to acetylenes, nitriles, and nitrogen under FVP (flash vacuum pyrolysis) conditions or by photolysis.
- 5) Sodium borohydride reduction of 1 is the sole reaction that the 5-position was attacked. A. Ohsawa, H. Arai, H. Ohnishi, T. Kaihoh, T. Itoh, K. Yamaguchi, H. Igeta, and Y. Iitaka, *Yakugaku Zasshi*, **105**, 1122 (1985).
- 6) O.N. Chupakhin, V.N. Charushin, and H.C. van der Plas, *Tetrahedron*, **44**, 1 (1988).
- 7) A. Ohsawa, T. Kaihoh, T. Itoh, M. Okada, C. Kawabata, K. Yamaguchi, and H. Igeta, *Chem. Pharm. Bull.*, **36**, 3838 (1988).
- 8) P. Beak, *Acc. Chem. Res.*, **10**, 186 (1977).
- 9) KO₂ reacts with H₂O very quickly to cause the formation of KOH.
- 10) D.T. Sawyer and J.S. Valentine, *Acc. Chem. Res.*, **14**, 393 (1981).
- 11) I. Fridovich, *Acc. Chem. Res.*, **15**, 200 (1982).
- 12) H. Yamamoto, T. Mashino, T. Nagano, and M. Hirobe, *Tetrahedron Lett.*, **1989**, 4133 and references cited therein.
- 13) P.F. Levonovich, H.P. Tannenbaum, and R.C. Dougherty, *J. Chem. Soc. Chem. Commun.*, **1975**, 597.
- 14) A. Frimer and I. Rosenthal, *Tetrahedron Lett.* **1976**, 2809.
- 15) 5-Bromo-4,6-diphenyltriazine could not be synthesized by reported method⁷⁾ probably because of the steric hindrance, and the reactivity of 1e was considered to be low by the influences of both chloro and phenyl groups.