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SYNTHESIS OF QUINOXALINE 1,4-DIOXIDES FROM BENZOFUROXAN PROCEEDS NOT IN, BUT ON ZEOLITE

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Abstract - Quinoxaline synthesis using Na-zeolite A as a catalyst to proceeds in a better yield than that using zeolite X. The pore diameter of zeolite X is large enough to allow the benzofuroxan derivatives access to cages, therefore part of benzofuroxan is adsorbed in the internal surface of zeolite X. Whereas the windows to the cages of Na-zeolite A are too small to allow the benzofuroxan derivatives access to the cages, therefore all the benzofuroxan is adsorbed on the external surface of zeolite. The reactions of benzofuroxans with benzoylacetone was catalyzed by zeolite proceed not in, but on zeolite.

INTRODUCTION

Benzofuroxan (benzofurazan *N*-oxide) has been shown to have numerous pharmacological and industrial applications.[1a-d] As a part of benzofurazan chemistry, reactions of various benzofuroxans with active methylene compounds catalyzed by silica gel[2] or molecular sieves[3-4] yield the corresponding quinoxaline 1,4-dioxides, and the antibacterial activity of

quinoxaline 1,4-dioxides has been reported.[5] Pyrido[2,3-*b*]pyrazine 1,4-dioxides have been obtained from a reaction of pyrido[2,3-*c*]furoxan with active methylene compounds catalyzed by treatment with silica gel, alumina, or molecular sieves[6] and the antibacterial activity of pyrido[2,3-*b*]pyrazine 1,4-dioxides has been reported.[7] Reactions of benzofuroxan with various phenolic compounds catalyzed by silica gel, alumina, or molecular sieves provide the corresponding phenazine 5,10-dioxide derivatives[8] and the antibacterial activity of phenazine 5,10-dioxide derivatives has been reported.[9] The toxicity of benzofurazans in *Escherichia coli* has been reported to be caused by an increase in intracellular flux of superoxide on aerobic incubation.[10] Superoxide production was confirmed using the cytochrome *c* reduction method and ESR spectra.[11] 4,7-Dimethylbenzofurazan was transformed by $^1O_2$ into 4,7-dimethylbenzofurazan 4,7-endoperoxide, in excellent yields.[12] In this study, we present that a reaction of benzofuroxans with benzoylacetone catalyzed by synthetic zeolite (molecular sieves) occurs on, not in, zeolite.

Zeolites are crystalline inorganic microporous solids with the general formulation $M_x[(AlO_2)_x(SiO_2)_y] \cdot nH_2O$ which find wide application as dehydration agents, catalysts, and ion exchangers. SiO_4^{4-} and AlO_4^{5-} tetrahedra form the primary building blocks of zeolite. These tetrahedra are linked by all their corners to form channels and cages or cavities with discrete sizes. The total framework charge of an aluminum containing zeolite is negative and hence must be balanced by an exchangeable alkali or alkaline-earth metal cation. Na-zeolite A (molecular sieves 4A) and zeolite X (molecular sieves 13X) have the following typical unit cell composition.

Na-zeolite A	$Na_{12}[(AlO_2)_{12}(SiO_2)_{12}] \cdot 27H_2O$
zeolite X	$Na_{86}[(AlO_2)_{86}(SiO_2)_{106}] \cdot 264H_2O$

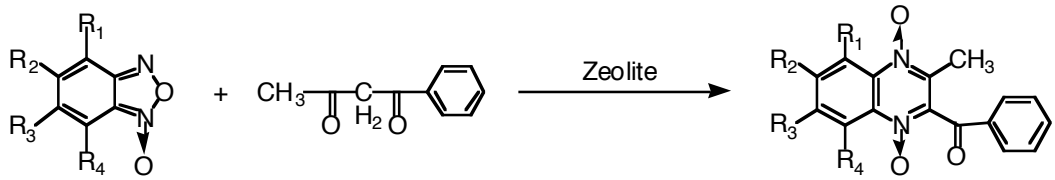
The water can also be displaced without destroying the framework and can be replaced by other molecules whose dimensions are smaller than the pore size of the cavities. The structure of zeolite X consists of an interconnecting three-dimensional network of relatively large spherical cavities, termed a supercage (diameter of approximately 1.3 nm). Each supercage is connected tetrahedrally to four other supercages through a pore

approximately 0.74 nm. [13] Molecular models suggest that Na-zeolite A possesses a pore opening approximately 0.41 nm to its 1.1 nm internal α–cage. [13]

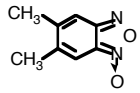
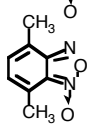
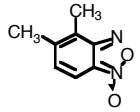
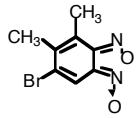
RESULTS AND DISCUSSION

The method for synthesizing quinoxaline 1,4-dioxides derivatives was as follows: A solution of benzofuroxans and benzoylacetone in CH_2Cl_2 was evaporated in the presence of Na-zeolite A or zeolite X. Both reagents were adsorbed on the zeolites followed by standing at 90 °C. The benzofuroxans seemed to be adsorbed by the zeolite X as well as Na-zeolite A. The reaction mixture was chromatographed to give the corresponding isomeric quinoxaline 1,4-dioxides derivatives (Table 1).

Table 1



1~6 **7~11**

Compound No.		Product No. and R	Zeolite X Yield (%)	Na-Zeolite A Yield (%)	Reaction time (h)
1		**7** $R_1 = R_2 = R_3 = R_4 = H$	58	79	2
2		**8** $R_1 = R_4 = H$; $R_2 = R_3 = CH_3$	68	88	2
3		**9** $R_2 = R_3 = R_4 = H$; $R_1 = CH_3$	9	18	2
4		$R_1 = R_4 = CH_3$; $R_2 = R_3 = H$	0	0	24
5		**10** $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$ **11** $R_1 = R_2 = H$, $R_3 = R_4 = CH_3$	0.1[a] 10 [a]	2 [a] 26 [a]	2 24
6		$R_1 = R_2 = CH_3$; $R_3 = Br$, $R_4 = H$	0	0	24

[a] : the sum of the yields of both compounds (**10**) and (**11**)

In comparison with 2 kinds of catalysts, Table 1 shows the results of the reactions using Na-zeolite A as a catalyst to give a better yield than those using zeolite X.

Extraction results of benzofuroxan derivatives were shown in Table 2. After benzofuroxans were adsorbed by the zeolite X or Na-zeolite A, the adsorbed benzofuroxans were washed with CH_2Cl_2 to remove extra benzofuroxans from the external surface of zeolite. Then, the zeolite was collected by filtration. After dissolving the entire zeolite framework in H_2SO_4, the benzofuroxans, which were adsorbed in the internal surface of zeolite, were able to be extracted with CH_2Cl_2. In comparison with the amount of extracted benzofuroxan before dissolving the zeolite in acid, benzofuroxans were obtained in perfect recovery in the case of Na-zeolite A. So pore diameter of Na-zeolite A is approximately 0.41 nm, the windows to the cages of Na-zeolite A are too small to allow the benzofuroxan derivatives access to the cages, therefore all benzofuroxan were adsorbed on the external surface in the case of Na-zeolite A.

Table 2

Compounds	Zeolite X		Na-Zeolite A	
	On zeolite (%)	In zeolite (%)	On zeolite (%)	In zeolite (%)
1	76	23	100	0
2	72	27	100	0
3	65	32	100	0
4	68	30	100	0
5	70	28	100	0
6	89	10	100	0

In the case of zeolite X, before dissolving the zeolite in acid, all benzofuroxans were recovered insufficiently. The pore diameter of zeolite X is approximately 0.74 nm and large enough to allow the benzofuroxan derivatives access to the cages, therefore part of the benzofuroxan was adsorbed in the internal surface of zeolite X. So, the benzofuroxans were not able to be completely recovered without dissolving the zeolite in acid.

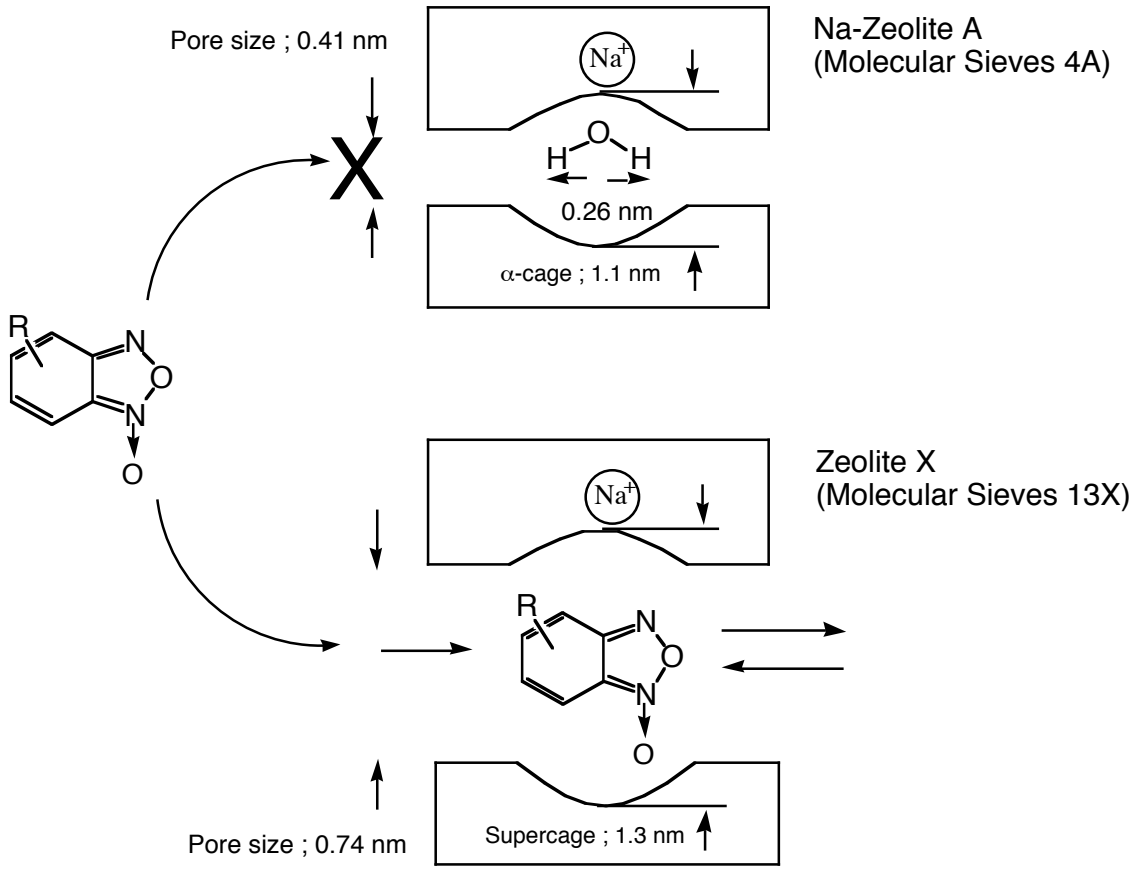


Figure 1

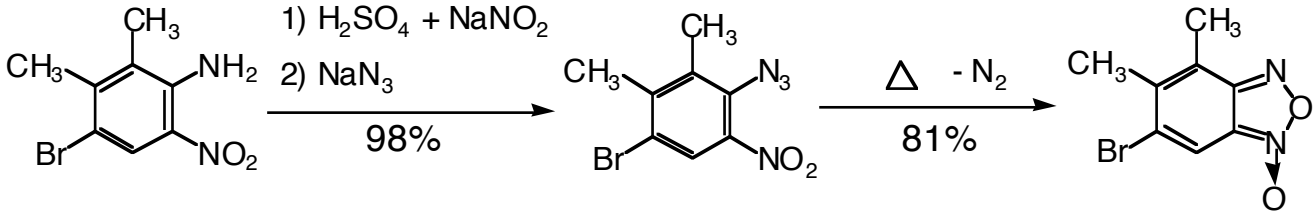
When benzofuroxans were adsorbed on zeolite X followed by extraction with CH_2Cl_2, the amount recovered depends largely on the soaking time during the CH_2Cl_2 extraction. Longer soaking time yields a higher recovery. However, when benzofuroxans were adsorbed on Na-zeolite A, all benzofuroxans were recovered after CH_2Cl_2 extraction and the percent recovery was independent of soaking time. Since no adsorption inside the

zeolite is possible with Na-zeolite A, the difference is presumably due to adsorption inside the zeolite supercage structure.

The results of the reactions using Na-zeolite A to give better yields of quinoxalines than those using zeolite X, is due to the difference in pore size. The benzofuroxan adsorbed in the internal surface of zeolite X cannot react with benzoylacetone. Synthesis of quinoxalines seems to proceed on zeolites, not in zeolites.

In this study, compound (**6**) was synthesized in good yield from 4-bromo-2,3-dimethyl-6-nitroaniline (**6NA**). 4-Bromo-2,3-dimethyl-6-nitroaniline sulfate was diazotized by sodium nitrite. The diazo compound was converted to 4-bromo-2,3-dimethyl-6-nitrophenylazide (**6N**) by sodium azide. The thermal decomposition of the azide in diethylene glycol gave **6** (Scheme 1).

Scheme 1



6NA **6N** **6**

The compound (**6**) has an interesting ^{1}H-NMR spectrum which showed two kinds of singlets from δ 7.8 to 8.2 ppm at room temperature. The spectrum showed different chemical shifts that looked like they were derived from two compounds. The two kinds of signals changed to one kind of signal at 60 °C (Figure 2). After cooling, the ^{1}H-NMR spectrum returned to the former spectrum at room temperature spectrum. In general, benzofuroxan derivatives rapidly rearrange between the two unsymmetrical bicyclic structures *via* a transitional ring opened dinitroso form.[1a-d] We believe that the compound (**6**) must undergo the similar molecular rearrangement as other benzofuroxans (Figure 3).

Then, two different kinds of ^{1}H-NMR spectra of the compound (**6**) were obtained at room temperature. The room temperature spectrum indicates the two equivalent unsymmetrical forms, and that at 60 ºC indicates the rapidly equilibrating mixture of the two equivalent unsymmetrical forms.

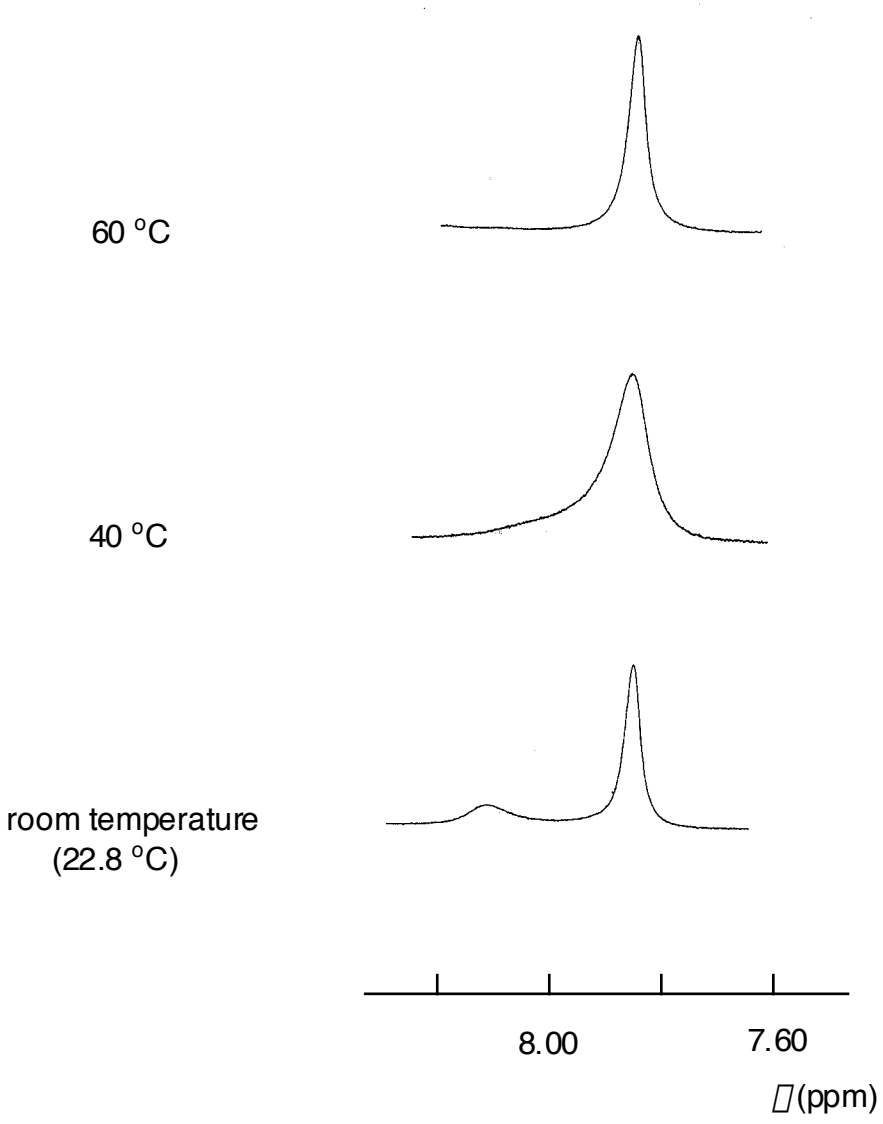
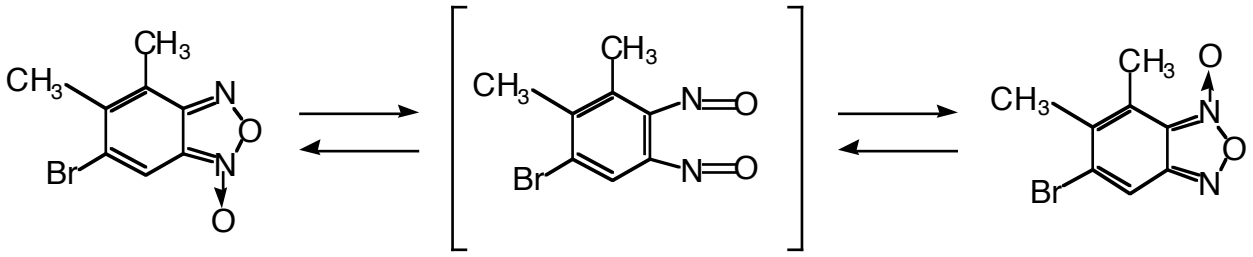


Figure 2

In general, the oxygen atom of the N-oxide group in benzofuroxans causes a high-field shift of all the aromatic protons, especially at the 7-position.[1b,d] Thus in the ^{1}H -NMR spectrum at room temperature, the compound (**6**) showed two kinds of signals, a larger signal from the tautomer (**6a**) and a smaller signal from the tautomer (**6b**). The above

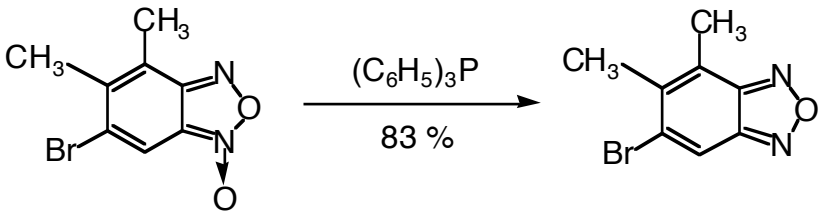
tautomer ratio in DMSO-d6 at room temperature was determined from the aromatic proton integration (Figure 3).



85 % (in DMSO-d_6) **6a** 15 % (in DMSO-d_6) **6b**

Figure 3

Next, for comparison with the chemical shift of aromatic protons of 6-bromo-4,5-dimethylbenzofurazan (**6Z**), which has no *N*-oxide group and tautomerism, the compound (**6Z**) was prepared by reduction of the compound (**6**) with triphenylphosphine in excellent yield (Scheme 2). ^{1}H-NMR spectrum of the compound (**6Z**) did not show two kinds of signals as in compound (**6**) but only one singlet at room temperature.



6 **6Z**

Scheme 2

It may be inferred that the effect of benzofuroxan tautomerism shows the two kinds of singnals in the ^{1}H-NMR spectrum of compound (**6**) at room temperature.

The above extra phenomenon exhibited by the compound (**6**) can be explained in terms of a weak hydrogen bonding between the oxygen atom of the *N*-oxide group and the active

methyl group. Ikekawa and Sato also reported the presence of a weak hydrogen bonding between the oxygen atom of the *N*-oxide group and the hydrogen atom of the 2-methyl group as in the case of 2-methylpyridine 1-oxide.[14] The oxygen atom of the *N*-oxide group of the compound (**6**) is attracted by the hydrogen atom of the methyl group. The methyl group may then possibly function as a barrier against molecular rearrangement and so molecular rearrangement is so slow that different chemical shifts exist at room temperature. The electron-withdrawing 6-position bromine may produce the effect as shown in Figure 4. It is possible that the electron movement make tautomer (**6b**) into an opened dinitroso form. The transformation to the ring opened dinitroso form from the tautomer (**6b**) may be made easier than from tautomer (**6a**) by influence of bromine. As a result of these effects of the methyl group and 6-position bromine, it is understandable that slow molecular rearrangement occurs and that more tautomer (**6a**) is present than tautomer (**6b**) at room temperature.

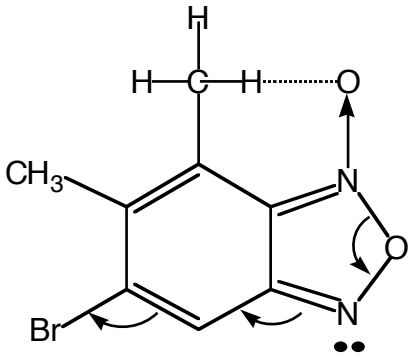


Figure 4

The enol form of carbonyl compounds was previously shown to be necessary for the formation of quinoxalines or pyridopyrazines, whose yields depend on the enol content in 1,3-diketones.[2, 6] Molecular sieves or other catalysts may serve to enhance the stability of the enol form of carbonyl compounds and the dehydration capacity of catalysts may determine significantly the possibility of synthesis.

Compound (**6**) was not able to react with benzoylacetone (Table 1). The 6-position bromine may produce the effect as shown in Figure 4. It is possible that the effect of electron-withdrawing bromine decreases the charge density of the non-bonding electron pair on the nitrogen atom of the furazan ring. Therefore, the effect reflects inactivation of the nucleophilic attack toward benzoylacetone in the first step of quinoxaline synthesis (Figure 5).

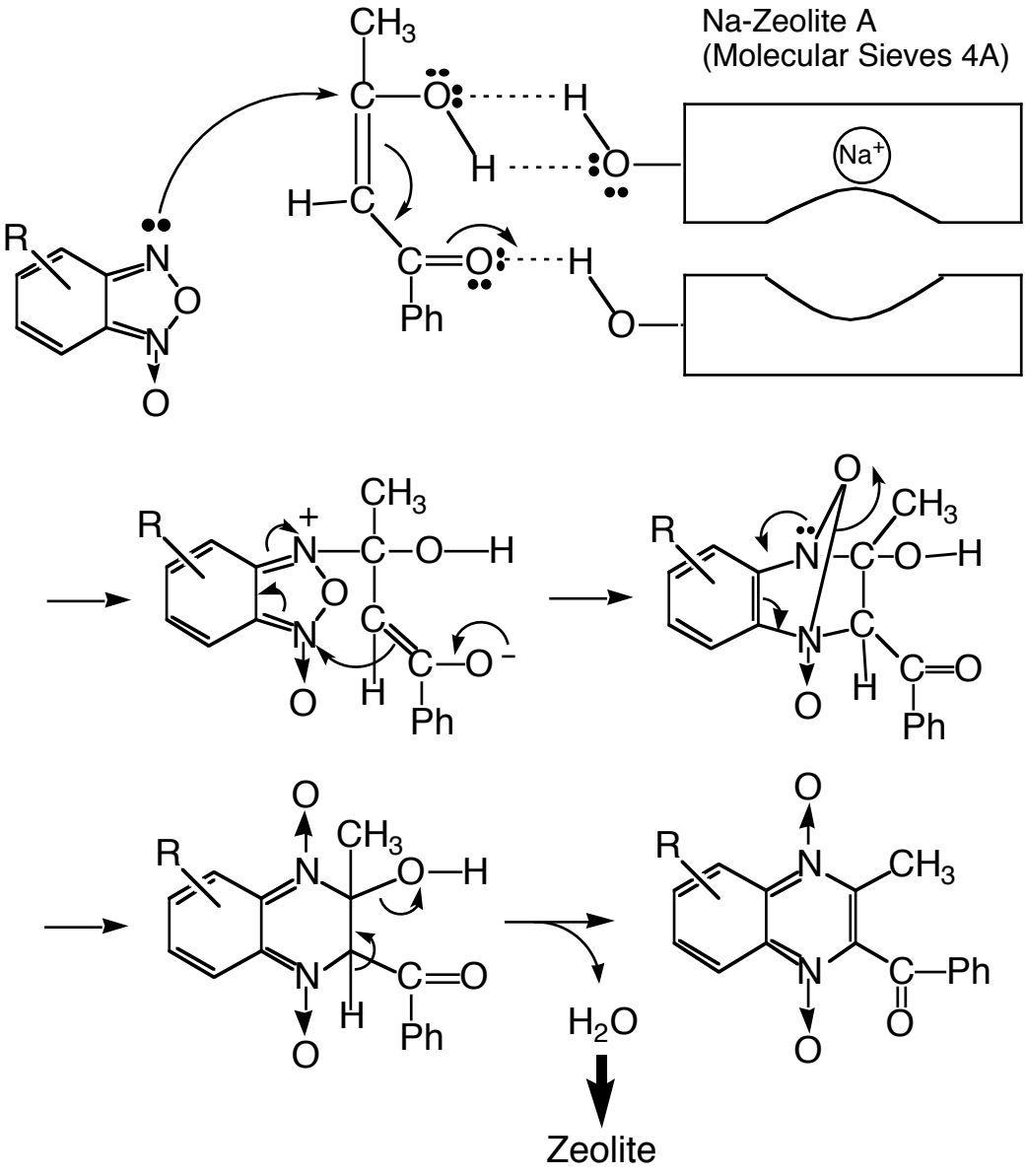


Figure 5

The reaction of compound (**2**) provided a good yield of the corresponding quinoxaline 1,4-dioxide derivative. In contrast, compound (**3**) condensed with the carbonyl compound only slightly, and compound (**4**) did not react at all. In the compound (**3**) reaction, it might be supposed that hyperconjugation of the 4-methyl group with the *N*-oxide group would weaken the electron affinity of the nitrogen atom (Figure 6). Additionally, in the compound (**4**) reaction, it seems that steric hindrance between the 7-methyl group and the *N*-oxide group contributes to the weakening of the stability of the transition state in the condensation reaction.

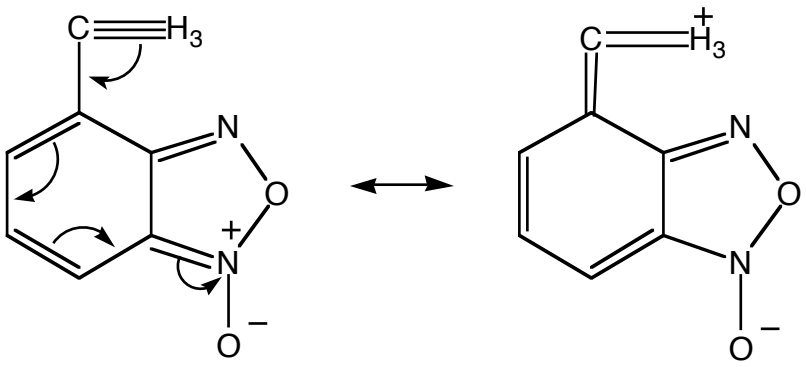


Figure 6

EXPERIMENTAL

Melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. The IR spectra were recorded on a JASCO ir-810 spectrophotometer. The ^{1}H-NMR spectra were recorded on a JNM-GSX 400 FT NMR System with TMS as the internal standard. The MS spectra were recorded on a Hitachi M-2000 and JEOL JMS-GCmate spectrometers with an electron beam energy of 70 eV. Microanalysis was performed at the microanalytical laboratory of the Center for Instrumental Analysis in the College of Science & Technology, Nihon University.

4-Bromo-2, 3-dimethyl-6-nitrophenylazide (**6N**).

A solution of 4-bromo-2,3-dimethyl-6-nitroaniline (**6NA**) (2.45 g, 0.01 mol) in glacial acetic acid (300 mL) and concd sulfuric acid (8 mL) was cooled until the temperature of

the solution becomes 0-5 ºC and water (80 mL) was added to the solution and then the resulting mixture was treated with sodium nitrite (0.865 g, 0.025 mol) in water (1.5 mL). To the resulting solution of the diazonium ion was added sodium azide (1.5 g, 23 mmol) in water (1.5 mL) and the solution was maintained at 0-5 ºC. Stirring was then continued for 0.5 h at rt. The reaction mixture was then diluted with water. The precipitate was collected, washed with water and dried overnight. It was purified by column chromatography (Wakogel C-200, Wako Pure Chemical Industries) to give 4-bromo-2,3-dimethyl-6-nitrophenylazide (**6N**), (*n*-hexane/CH_2Cl_2 (95:5)) 2.67 g (98%). Compound (**6N**) mp 70-72 ºC; IR (KBr) cm^{-1}: ν 2140, 1566, 1517, 1344; ^{1}H-NMR ($CDCl_3$): δ 2.42 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 8.09 (s, 1H, H-7); HRMS (EI) m/z: 269.9751. Calcd for $C_8H_7N_4O_2Br$: M, 269.9747. Anal. Calcd for $C_8H_7N_4O_2Br$: C, 35.45; H, 2.60; N, 20.67. Found: C, 35.50; H, 2.67; N, 20.56.

6-Bromo-4,5-dimethylbenzofuroxan (6).

Compound (**6N**) (1.355 g, 5 mmol) was dissolved in diethylene glycol (20 mL) and the solution was heated at 150 ºC for 3 h and then this reaction mixture was poured onto crushed ice. The crude product was collected, washed with water, and dried over night. It was purified by column chromatography (silica gel) to give 6-bromo-4,5-dimethylbenzofuroxan (**6**), (*n*-hexane/ CH_2Cl_2 (9:1)) 0.985 g (81%). Recrystallization from *n*-hexane afforded light yellow needles. Compound (**6**) mp 104-106 ºC; IR (KBr) cm^{-1}: ν1610, 1565, 1531, 1470, 1374; ^{1}H- NMR (DMSO-d_6): at 23.8 ºC, δ 2.36 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 7.87 (s, 0.85H, H-7a) , 8.12 (br s, 0.15H, H-7b), at 40 ºC, δ 2.37 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 7.87 (bs, 1H, H-7) , at 60 ºC, δ 2.38 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 7.88 (s, 1H, H-7); HRMS (EI) m/z: 241.9690. Calcd for $C_8H_7N_2O_2Br$: M, 241.9687. Anal. Calcd for $C_8H_7N_2O_2Br$: C, 39.53; H, 2.90; N, 11.53. Found: C, 39.49; H, 2.92; N, 11.39.

6-Bromo-4,5-dimethylbenzofurazan (6Z)

A solution of compound (**6**) (121.6 mg, 0.5 mmol) and triphenylphosphine (144.3 mg, 0.55mmol) in xylene (5 mL) was refluxed for 6 h. The mixture was purified by column chromatography (silica gel) to give 6-bromo-4,5-dimethylbenzofurazan (**6Z**) (*n*-hexane/

CH_2Cl_2 (95:5)) and furthermore purified by preparative TLC (Merck, Silica gel plate 60 F_{254} Art. 1.05717) with *n*-hexane/CH_2Cl_2 (9:1). Yield 94.2 mg (83%). Compound (**6Z**) mp 53-55 ºC; IR (KBr): ν 1605, 1534, 1456, 1290 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.48(s, 3H, CH_3), 2.69(s, 3H, CH_3), 8.02(s, 1H, H-7); HRMS (EI) m/z: Found: 225.9748. Calcd for $C_8H_7N_2OBr$ (M): 225.9741; Anal. Calcd for $C_8H_7N_2OBr$: C,42.32; H, 3.11; N, 12.34. Found: C, 42.43; H, 3.23; N, 12.20.

Synthesis of Quinoxaline derivatives

To a solution of benzofuroxans (1 mmol) and benzoylacetone (1.1 mmol) in CH_2Cl_2 (10 mL) was added zeolites (molecular sieves 4A powder, 13X powder, Union Showa, 2 g) and the mixture was evaporated in an evaporator at 30 °C. The zeolites containing adsorbed reagents were allowed to stand for 2 h at 90 °C. It was purified by column chromatography (silica gel) to give quinoxaline derivatives (CH_2Cl_2/methanol (98:2)). They were furthermore purified by preparative tlc (Merck silica gel plate 60 F_{254} Art. 5717) with CH_2Cl_2/methanol (97:3).

Extraction of benzofuroxan derivatives from zeolites

To a solution of benzofuroxans (0.5 mmol) in CH_2Cl_2 (10 mL) was added zeolites (molecular sieves 4A powder, 13X powder, Union Showa, 2 g). After 0.5 h later (soaking time), the mixture was evaporated in an evaporator at 25 °C. Immediately, the zeolites, which contained benzofuroxans, were washed with CH_2Cl_2 50 mL (three times) to remove extra benzofuroxans from the external surface of the zeolites. Then, the zeolites were collected by filtration. To the zeolites powder was added 200 mL of H_2O/H_2SO_4 (4:1). Stirring was then continued for 0.5 h at rt. After dissolution of the entire zeolite framework, the benzofuroxans were extracted, which were adsorbed in the internal surface of zeolite, with CH_2Cl_2 50 mL (three times).

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* To whom correspondence should be addressed.

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