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SYNTHESIS OF QUINOXALINE 1,4-DIOXIDES FROM 5,6-DIETHYLBENZOFUROXAN ON SILICA GEL

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Abstract-5,6-Diethylbenzofuroxan (**1**) and 5-ethylbenzofuroxan (**2**) were synthesized in good yield *via* oxidation of *o*-nitroanilines by sodium hypochlorite. 4-Ethylbenzofuroxan (**3**) was prepared by the photochemical decomposition of 2-ethyl-6-nitrophenyl azide (**3N**). ^{1}H-NMR spectrum showed that the compound (**3**) rapidly rearranges between the two unsymmetrical bicyclic structures at 296.8 K. The 4-ethyl group may possibly function as a barrier against molecular rearrangement. Quinoxalines yields depended on the enol content in *β*-keto esters or 1,3-diketones. A comparison of the reactivity of **1** with benzoylacetone was made with that of other benzofuroxans. The reaction of **1** condensed with the carbonyl compound better than other benzofuroxans.

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

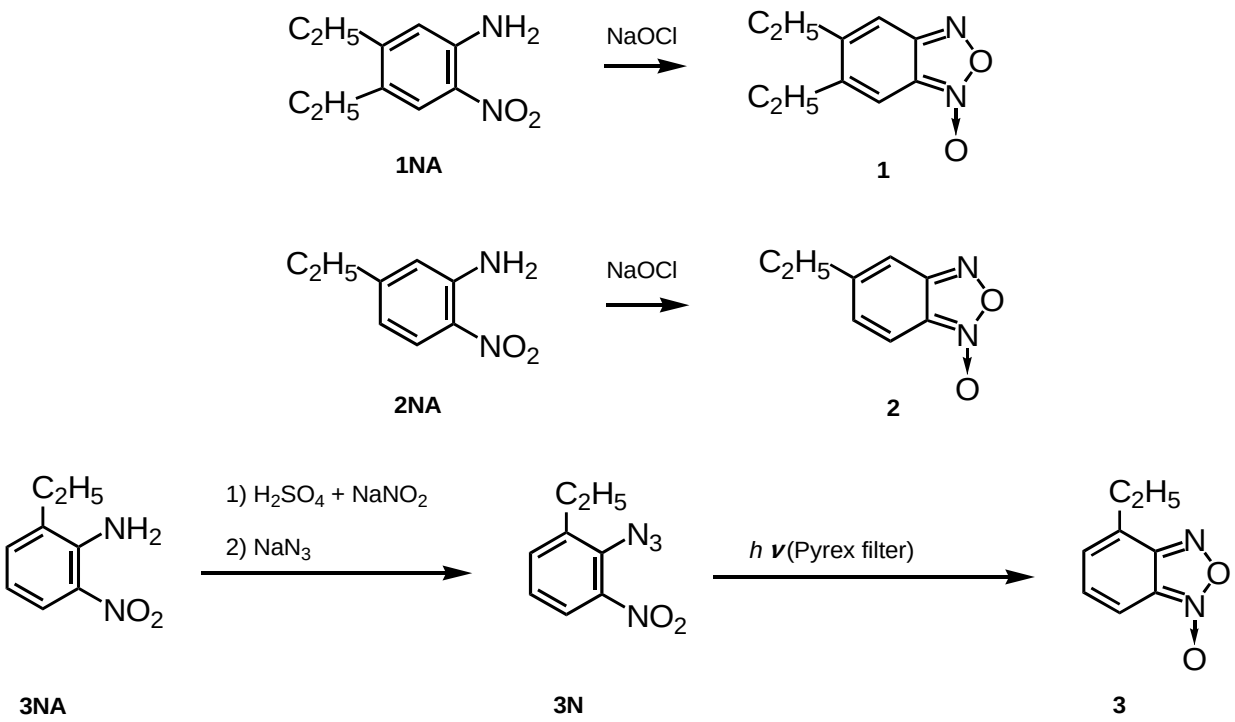
provide the corresponding phenazine 5,10-dioxide derivatives[8] and the antibacterial activity of phenazine 5,10-dioxide derivatives has been reported.[9] The toxicity of benzofurazans in *Escherichia coli* has been reported to be caused by an increase in intracellular flux of superoxide on aerobic incubation.[10] The 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]

This paper presents the synthesis of novel substituted quinoxaline dioxides from novel benzofuroxan derivatives with the enolic form of *β*-keto esters or 1,3-diketones catalyzed by silica gel.

RESULTS AND DISCUSSION

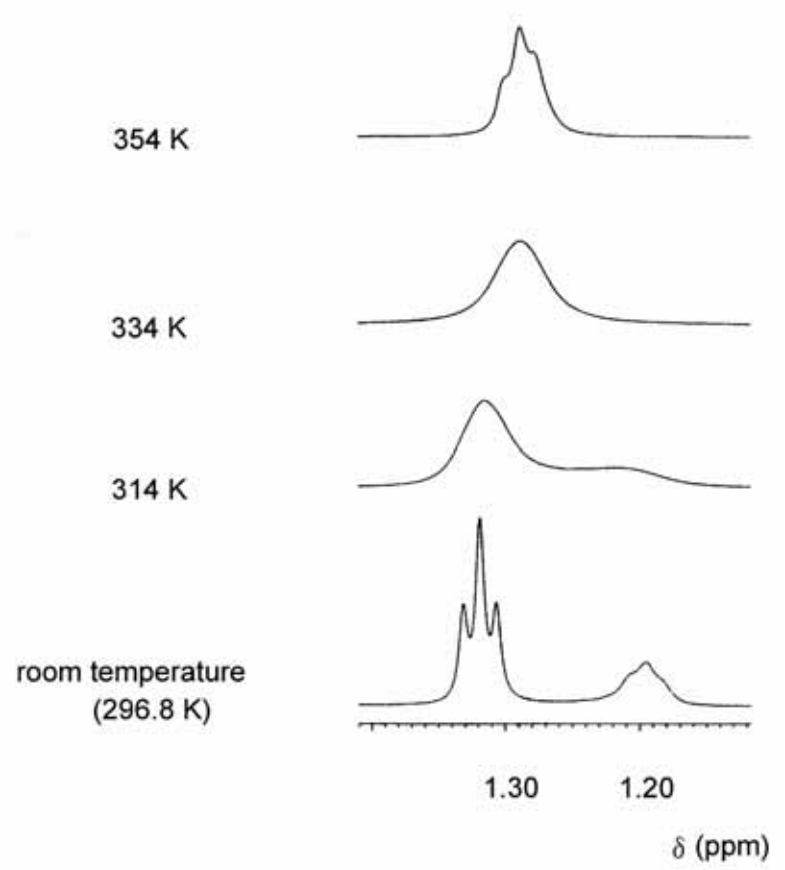
In this study, 5,6-diethylbenzofuroxan (**1**) and 5-ethylbenzofuroxan (**2**) were synthesized in good yield from oxidation of *o*-nitroanilines. 3,4-Diethyl-6-nitroaniline[13] (**1NA**) or 3-ethyl-6-nitroaniline[14] (**2NA**) was oxidized by sodium hypochlorite to give corresponding benzofuroxans. 4-Ethylbenzofuroxan (**3**) was synthesized from 2-ethyl-6-nitroaniline (**3NA**). 2-Ethyl-6-nitroaniline (**3NA**) sulfate was diazotized by sodium nitrite, and the diazo compound was converted to 2-ethyl-6-nitrophenyl azide (**3N**) by sodium azide followed by the photochemical decomposition of the azide in methanol (Scheme 1).

Scheme 1



The compound (**3**) has an interesting ^{1}H-NMR spectrum which showed two kinds of singlets from δ 1.1 to 1.4 ppm at 296.8 K. 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 354 K (Figure 1). After cooling, the ^{1}H-NMR spectrum returned to the former spectrum at 296.8 K spectrum.

Figure 1

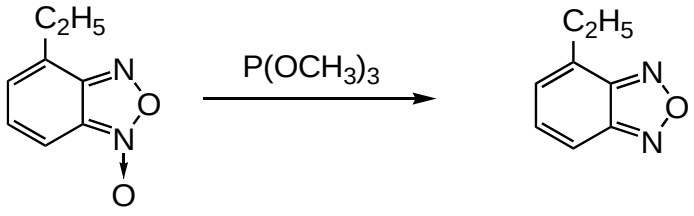


In general, benzofuroxan derivatives rapidly rearrange between the two unsymmetrical bicyclic structures *via* a transitional ring opened dinitroso form.[1a-d] We believe that the compound (**3**) must undergo the similar molecular rearrangement as other benzofuroxans. Then, two different kinds of ^{1}H-NMR spectra of the compound (**3**) were obtained at room temperature. The 296.8 K spectrum indicated the two equivalent unsymmetrical forms, and that at 354 K indicated the rapidly equilibrating mixture of the two equivalent unsymmetrical forms.

Next, for comparison with the chemical shift of ethyl protons of 2-ethylbenzofurazan (**3Z**), which has no *N*-oxide group and tautomerism, the compound (**3Z**) was prepared by reduction of the compound (**3**) with

trimethyl phosphite in excellent yield (Scheme 2). ^{1}H-NMR spectrum of the compound (**3Z**) did not show two kinds of signals as in compound (**3**)**,** but only one signal at room temperature (δ 1.35 (t, 3H, *J* = 7.6 Hz), 3.00(q, 2H, *J* = 7.6 Hz)).

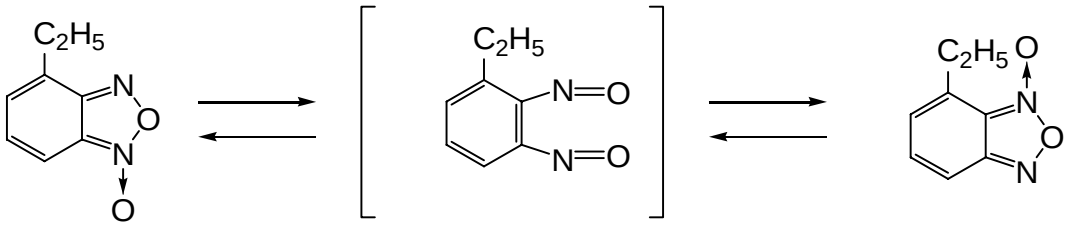
Scheme 2



3 **3Z**

It may be inferred that the effect of benzofuroxan tautomerism shows the two kinds of signals in the ^{1}H-NMR spectrum of compound (**3**) at room temperature. By comparing chemical shift of methyl proton of compound (**3**) with that of compound (**3Z**), we could assign a larger signal from the tautomer (**3a**) and a smaller signal from the tautomer (**3b**). The tautomer ratio in DMSO-d_6 at 296.8 K was determined from methyl proton integration of the ethyl group (Figure 2).

Figure 2



75%
(in DMSO-d_6)
at 296.8 K

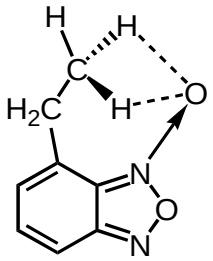
3a

25%
(in DMSO-d_6)
at 296.8 K

3b

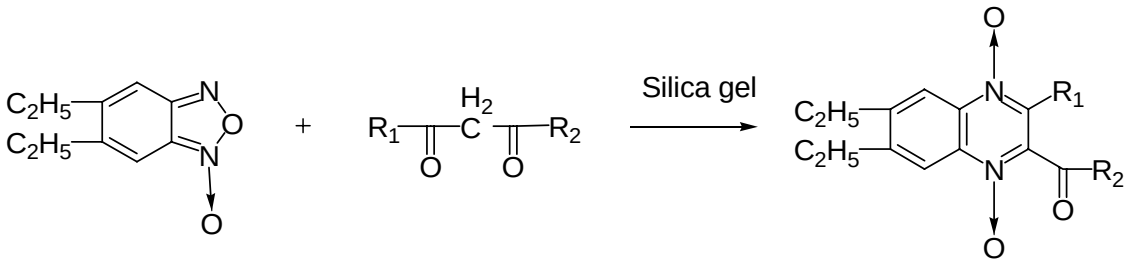
The above extra phenomenon exhibited by the compound (**3**) can be explained in terms of a weak hydrogen bonding between the oxygen atom of the *N*-oxide group and the ethyl group (Figure 3).

Figure 3



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.[15] The oxygen atom of the *N*-oxide group of the compound (**3**) is attracted by the methyl hydrogen atom of the 4-ethyl group. The ethyl 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. As a result of this effect of the 4-ethyl group, it is understandable that slow molecular rearrangement occurs and that there is more tautomer (**3a**) present than tautomer (**3b**) at room temperature.

Table 1



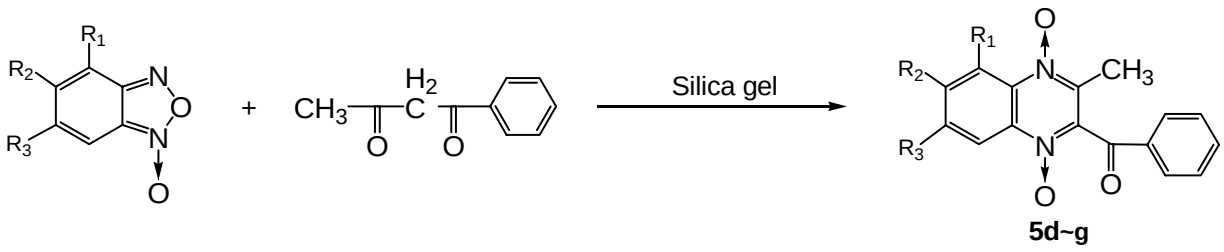
1 **4a~d** **5a~d**

Compound No.	R_1	R_2	Enol Content of **4**(%) (in Ethanol)	Yield (%) **5a~d**
4a	OCH_3	OCH_3	0	0
4b	CH_3	OCH_3	12.6 [8]	25
4c	CH_3	CH_3	84 [8]	43
4d	CH_3		94 [8]	74

Reaction of various β-keto esters and 1,3-diketones (**4a-d**) with compound (**1**) was examined (see Table 1). The method for synthesizing quinoxaline 1,4-dioxides derivatives was as follows: A solution of benzofuroxans and β-keto esters or 1,3-diketones in CH_2Cl_2 was evaporated in the presence of silica gel. Both benzofuroxans and β-keto esters or 1,3-diketones were adsorbed on the silica gel followed by standing at 110 ^oC. The reaction mixture was chromatographed to give the corresponding isomeric quinoxaline 1,4-dioxides derivatives.

Compound (**4a**) failed to react with compound (**1**) and unreacted **1** was almost completely recovered. The enol form of carbonyl compounds was previously shown to be necessary for the formation of quinoxalines, whose yields depended on the enol content in 1,3-diketones.[2] Silica gel may serve to enhance the stability of the enol form of carbonyl compounds and the dehydration capacity of catalysts may significantly determine the possibility of synthesis.

Table 2



5d~g

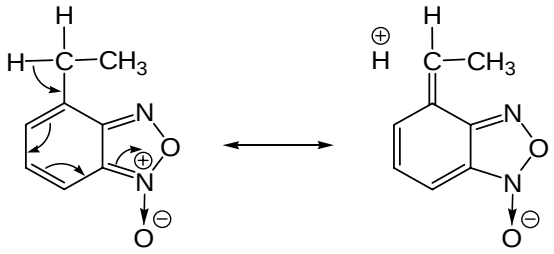
Substrate	Product No. and R		Yield (%)
1	**5d**	$R_1 = H$ $R_2 = R_3 = C_2H_5$	74
2	**5e**	$R_1 = R_3 = H$ $R_2 = C_2H_5$	52[a]
	5f	$R_1 = R_2 = H$ $R_3 = C_2H_5$	
3	**5g**	$R_1 = C_2H_5$ $R_2 = R_3 = H$	0

[a] Combined yield of compounds (**5e**) + (**5f**)

A comparison of the reactivity of compound (**3**) with benzoylacetone was made with that of other benzofuroxans. Table 2 shows the reaction of compound (**1**) to proceed in good yield. In contrast, compound (**2**) condensed with the carbonyl compound less than compound (**1**), and compound (**3**) did not react at all. Compound (**3**) was recovered almost unchanged in the reaction with benzoylacetone.

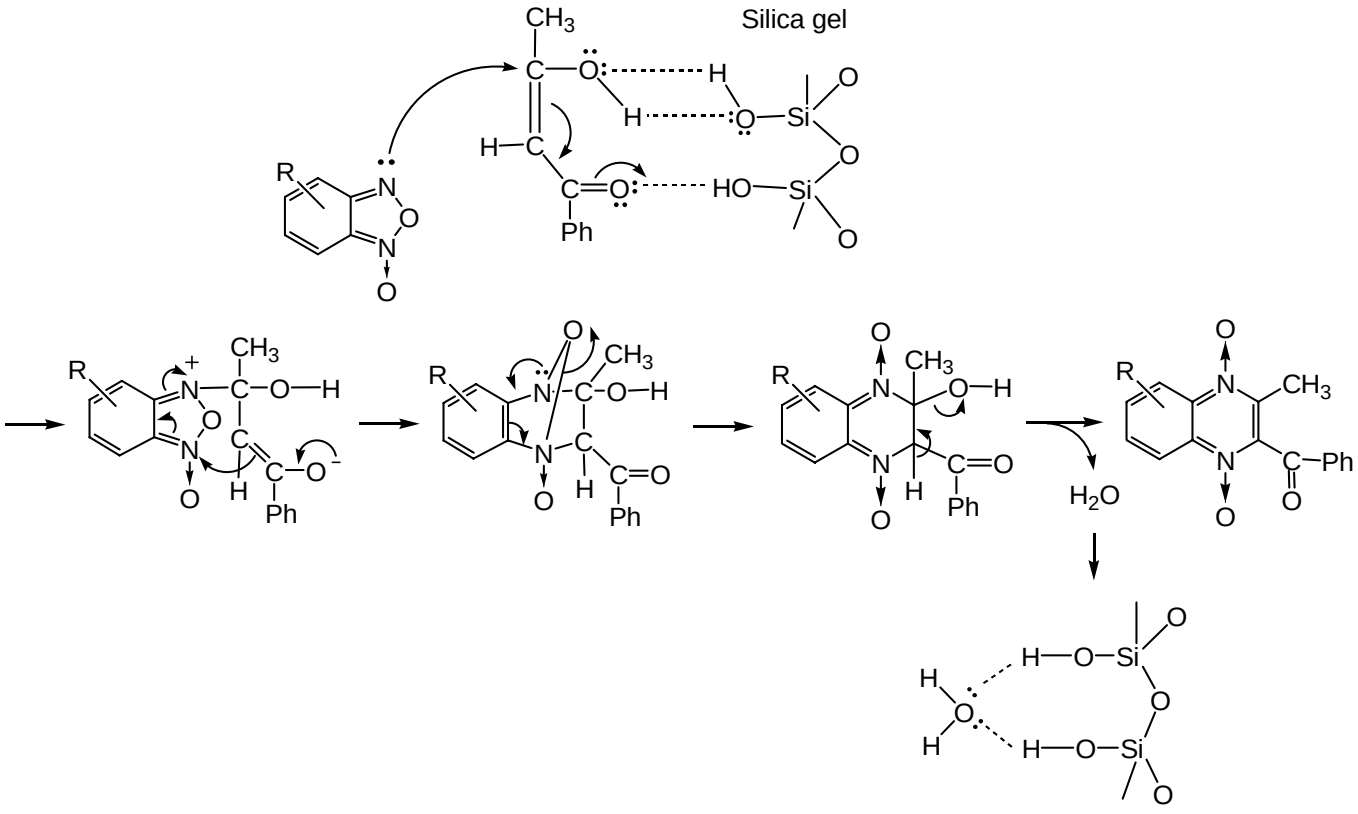
In these reactions, hyperconjugation of the 4-ethyl group with the *N*-oxide group may possibly lessen the electron affinity of 1-nitrogen atoms (Figure 4).

Figure 4



Additionally, in the compound (**3**) reaction (Table 2), it seems that steric hindrance between the 4-ethyl group and the *N*-oxide group contributes to the weakening of the stability of the transition state in the condensation reaction.

Figure 5



Therefore, the effect reflects inactivation of the nucleophilic attack toward benzoylacetone in the first step of quinoxaline synthesis. The reaction mechanism may thus be considered to be as shown in Figure 5.

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-LA 600 FT NMR System with TMS as the internal standard. The MS spectra were recorded on a JEOL JMS-GCmate spectrometer 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.

5,6-Diethybenzofuroxan (**1**).

A mixture of 3,4-diethyl-6-nitroaniline(**1NA**)(90 mg, 0.46 mmol) , KOH(2 g, 36 mmol) and H_2O (2 mL) in MeOH (10 mL) was cooled until the temperature of the solution becomes 0 ^oC. The 4% NaOCl solution (6 mL, 3.36 mmol) was added slowly with stirring. After 15 min with stirring at rt, the mixture was washed with CH_2Cl_2 50 mL (two times) to remove 5,6-diethylbenzofuroxan. Recrystallization from MeOH-H_2O (10:1(v/v)) afforded light yellow needles. 78 mg (88 %). mp 95-97 ^oC; IR (KBr) cm^{-1}: ν 1623, 1591, 1478, 1376; ^{1}H-NMR (DMSO-d_6): δ 1.23(br t, 6H, J = 7.2 Hz), 2.69(br q, 4H, J = 7.2 Hz), 7.39(br s, 2H); HRMS (EI) m/z: 192.0898. Calcd for $C_{10}H_{12}N_2O_2$: M, 192.0899. Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.40; H, 6.27; N, 14.44.

5-Ethybenzofuroxan (**2**).

A mixture of 3-ethyl-6-nitroaniline(**1NA**)(90 mg, 0.54 mmol) , KOH(2 g, 36 mmol) and H_2O (2 mL) in MeOH (10 mL) was cooled until the temperature of the solution becomes 0 ^oC. The 4% NaOCl solution (6 mL, 3.36 mmol) was added slowly with stirring. After 15 min with stirring at rt, the mixture was washed with CH_2Cl_2 50 mL (two times) to remove 5-ethylbenzofuroxan. Recrystallization from MeOH-H_2O (10:1(v/v)) afforded light yellow needles. 72 mg (81 %). mp 39-41 ^oC; IR (KBr) cm^{-1}: ν 1617, 1585, 1483, 1380; ^{1}H-NMR ($CDCl_3$): δ 1.21 (t, 3H, J = 7.5 Hz), 2.69(q, 2H, J = 7.5 Hz), 7.11(br s-like, 1H), 7.30 (br s-like, 1H), 7.48 (br s-like, 1H); HRMS (EI) m/z: 164.0586. Calcd for $C_8H_8N_2O_2$: M,164.0586. Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.36; H, 4.99; N, 16.84.

2-Ethyl-6-nitrophenylazide (**3N**).

A solution of 2-ethyl-6-nitroaniline (**3NA**) (166 mg, 1 mmol) in 20 % hydrochloric acid (6 mL) was cooled until the temperature of the solution became 0-5 °C and then the resulting mixture was treated with sodium nitrite (69 mg, 1 mmol) in H_2O (1 mL). To the resulting solution of the diazonium ion was added sodium azide (65 mg, 1 mmol) in H_2O (1 mL) and the solution was maintained at 0-5 °C. Stirring was then continued for 0.5 h at rt. The reaction mixture was then diluted with H_2O. The precipitate was collected, washed with H_2O and dried overnight. It was purified by column chromatography (Wakogel C-200, Wako Pure Chemical Industries) to give 2-ethyl-6-nitrophenylazide (**3N**), (*n*-hexane/CH_2Cl_2 (3:2)) yellow oil, 165 mg (86 %). 56-57 °C (decomp); IR (KBr) cm^{-1}: ν 2124, 1530, 1445, 1348; ^{1}H-NMR ($CDCl_3$): δ 1.26 (t, 3H, *J* = 7.4 Hz), 2.80(q, 2H, *J* = 7.4 Hz), 7.25(t, 1H, *J* = 8.0 Hz), 7.47(dd, 1H, *J* = 1.5, 8.0 Hz), 7.81(dd, 1H, *J* = 1.5, 8.0 Hz); HRMS (EI) *m*/*z*: 192.0648. Calcd for $C_8H_8N_4O_2$: M, 192.0647.

4-Ethylbenzofuroxan (**3**).

Compound (**3N**) (192 mg, 1 mmol) was dissolved in CH_3CN (10 mL) and placed in a merry-go-round type apparatus. The solution was irradiated using a 400W high pressure mercury lamp with a Pyrex filter at rt. After irradiation for 2 h, the solution was evaporated. It was purified by preparative TLC (Merck, Silica gel plate 60 F_{254} Art. 1.05717) to give 4-ethylbenzofuroxan (**3**) (*n*-hexane/ CH_2Cl_2 (1:1)), 77 mg (46 %). Recrystallization from *n*-hexane afforded light yellow needles. mp 61-62 °C; IR (KBr) cm^{-1}: ν 1615, 1576, 1482, 1381; ^{1}H-NMR (DMSO-*d*$_6$): at 296.8 K, δ 1.19(t, 0.75H, *J* = 7.3 Hz), 1.31(t, 2.25H, *J* = 7.3 Hz), 2.90(q, 2H, *J* = 7.3 Hz), 7.1-7.6 (m, 3H); HRMS (EI) *m*/*z*:164.0591. Calcd for $C_8H_8N_2O_2$: M, 164.0586. Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.47; H, 4.98; N, 17.08.

4-Ethylbenzofurazan (**3Z**).

A solution of compound (**3**) (164 mg, 1 mmol) and trimethyl phosphite (2 mL, 17 mmol) was refluxed for 0.5 h. It was purified by preparative TLC (Merck, Silica gel plate 60 F_{254} Art. 1.05717) to give 4-ethylbenzofurazan (**3Z**) (*n*-hexane/ CH_2Cl_2 (1:1)) as white needles. Yield 111 mg (75%). mp 30-31 °C; IR (KBr): ν 1619, 1531, 1400, 1354 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.35 (t, 3H, *J* = 7.6 Hz), 3.00(q, 2H, *J* = 7.6 Hz), 7.36(d, 1H, *J* = 6.6 Hz) , 7.54(dd, 1H, *J* = 8.9, 6.6 Hz) , 7.85(d, 1H, *J* = 8.9 Hz); HRMS (EI) *m*/*z*: Found:148.0634. Calcd for $C_8H_8N_2O$ (M):148.0637; Anal. Calcd for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.64; H, 5.53; N, 18.73.

Synthesis of Quinoxaline derivatives.

To a solution of benzofuroxans (0.1 mmol) and *β*-keto esters or 1,3-diketones (0.1 mmol) in CH_2Cl_2 (10 mL) was added silica gel (Wakogel C-200, 2 g) and the mixture was evaporated in an evaporator at 30 °C. The silica gel containing adsorbed benzofuroxans and *β*-ketoesters or 1,3-diketones was allowed to stand for 2 h at 110 °C. It was purified by preparative tlc (Merck silica gel plate 60 F_{254} Art. 5717) to give quinoxaline derivatives (CH_2Cl_2/ MeOH (98:2)).

2-Carbomethoxy-3-methyl-6,7-diethylquinoxaline 1,4-dioxide (**5b**).

Compound (**5b**): Yield 7 mg (25 %). Recrystallization from MeOH afforded yellow powder. mp 148-150 ^oC; IR (KBr): ν 1743 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.27(t, 3H, *J* = 7.4 Hz), 1.28(t, 3H, *J* = 7.4 Hz), 2.41(s, 3H), 2.87(q, 2H, *J* = 7.0 Hz), 2.88(q, 2H, *J* = 7.0 Hz), 4.01(s, 3H), 8.16(s, 1H) , 8.24(s, 1H); HRMS (EI) *m*/*z*: Found:290.1270. Calcd for $C_{15}H_{18}N_2O_4$ (M):290.1266; Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found: C, 61.93; H, 6.22; N, 9.40.

2-Acetyl-3-methyl-6,7-diethylquinoxaline 1,4-dioxide (**5c**).

Compound (**5c**): Yield 15 mg (52 %). Recrystallization from MeOH afforded yellow powder. mp 190-192 ^oC; IR (KBr): ν 1718 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.28(t, 3H, *J* = 6.4 Hz), 1.29(t, 3H, *J* = 6.4 Hz), 2.35(s, 3H), 2.64(s, 3H), 2.89(q, 2H, *J* = 7.0 Hz), 2.90(q, 2H, *J* = 7.0 Hz), 8.21(s, 1H) , 8.27(s, 1H); HRMS (EI) *m*/*z*: Found:274.1320. Calcd for $C_{15}H_{18}N_2O_3$ (M):274.1317; Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.79; H, 6.61; N, 10.14.

2-Benzoyl-3-methyl-6,7-diethylquinoxaline 1,4-dioxide (**5d**).

Compound (**5d**): Yield 25 mg (74 %). Recrystallization from MeOH afforded yellow powder. mp 198-200 ^oC; IR (KBr): ν 1721 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.28 (t, 3H, *J* = 7.5 Hz), 1.31 (t, 3H, *J* = 7.5 Hz), 2.29(s, 3H), 2.89(q, 2H, *J* = 7.5 Hz), 2.92(q, 2H, *J* = 7.5 Hz) ,7.57(t-like, 2H, *J* = 7.7Hz), 7.76(t-like, 1H, *J* = 7.7 Hz), 8.03(d, 2H, *J* = 7.2 Hz), 8.15(s, 1H), 8.32(s, 1H); HRMS (EI) *m*/*z*: Found:336.1473. Calcd for $C_{20}H_{20}N_2O_3$ (M):336.1473; Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.70; H, 6.27; N, 8.26.

2-Benzoyl-3-methyl-6-ethylquinoxaline 1,4-dioxide,

3-Benzoyl-2-methyl-6-ethylquinoxaline 1,4-dioxide (**5e**, **5f**).

We could not separate **5e** and **5f**. Compound (**5e**, **5f**): Yield 16 mg (52 %). Recrystallization from MeOH afforded yellow powder. A mixture of **5e** and **5f** had mp 115-117 ^oC; IR (KBr): ν 1718cm^{-1}; ^{1}H-NMR

($CDCl_3$): Major compound : Minor compound = 3 : 1 (The ratio was determined from methyl proton integration.), Major compound δ 1.36(t, 3H, J = 7.6 Hz), 2.50(s, 3H), 2.92(q, 2H, J = 7.6 Hz), 7.53(t-like, 2H, J = 7.6 Hz), 7.68(t-like, 1H, J =7.6 Hz), 7.77(dd, 1H, J = 2.0, 8.9 Hz), 7.90(d, 2H, J = 8.2 Hz), 8.36(d, 1H, J = 2.0 Hz), 8.59(d, 1H, J = 8.9 Hz). Minor isomer δ 1.39(t, 3H, J= 7.6 Hz), 2.46(s, 3H), 2.95(q, 2H, J = 7.6 Hz), 7.53(t-like, 2H, J = 7.6 Hz) 7.68(t-like, 1H, J = 7.6 Hz), 7.76(dd, 1H, J = 2.0, 8.9 Hz), 7.89(d, 2H, J = 8.2 Hz), 8.43(d, 1H, J = 2.0 Hz), 8.57(d, 1H, J = 8.9 Hz). HRMS (EI) m/z: Found: 308.1157. Calcd for $C_{18}H_{16}N_2O_3$ (M):308.1161; Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 69.91; H, 5.42; N, 8.91.

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