The Reactions of Benzofuroxan with Carbonyl Compounds on the Surface of Solid Catalysts

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The cyclocondensations of benzofuroxan **1a** with carbonyl compounds were smoothly and efficiently carried out by the adsorption of the components on the surface of silica gel or a molecular sieve to form a 2,3-disubstituted quinoxaline 1,4-dioxide. When the reactions using a molecular sieve 3A (powder) were carried out at 90°, the actual reaction times were reduced to 0.5-2 hours. Although Duerckheimer has reported the isolation of only the 7-substituted quinoxaline 1,4-dioxide when 5-methoxybenzofuroxan **1e** was allowed to react with ethyl acetoacetate **2j**, it produced only the 6-methoxy isomer as the reaction product by our method. 5-Carboxybenzofuroxan **1f** did not react with the carbonyl compound.

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It is well known that benzofuroxan (BFO) **1a** reacts with enolate anions of 1,3-diketones or β-ketoesters in basic medium to give quinoxaline 1,4-dioxides [1]. Substituent effects in the BFO reactions have been reported by several research groups. They involve the formation of a mixture of 6- and 7-substituted quinoxaline 1,4-dioxide isomers when 5(6)-substituted BFO's are condensed with various ketones [2]. We found that silica gel and a molecular sieve are a versatile synthetic tool for these reactions [3].

In the method using silica gel, the efficacy of the reactions varies considerably with the type of silica gel used. Suitable gels are Wakogel C-200 (Wako Pure Chemical Industries) and Silica gel 60 (Merck). The surface of the silica gel of the less suitable types was somewhat more acidic than that of the others [Silica gel 40, 100 (Merck)], as summarized in Table 1.

Table 1

Comparison of Various Silica Gel in the Reaction of BFO **1a** and Benzoylacetone **2a**

Silica Gel [a]	Poresize (Å)	*p*H [b]	Particle Size (μ)	Yield of **3** (%)
A	40	3.6	63-200	6
B	60	5.8	63-200	57
C	80	5.4	74-149	88
D	100	4.2	60-200	19

[a] A, B, D: Silica gel 40, 60, 100 (Merck); C: Wakogel C-200 (Wako Pure Chemical Industries). [b] The *p*H of surface of silica gel was obtained by a colorimetric method with the acid-base indicator solutions (bromophenol blue, bromocresol green and methylred) prepared by "JIS K 8006-1961".

Although the reaction times were 1-2 weeks at room temperature in the method using silica gel, the reactions using a molecular sieve for 1-3 days provide good yields. The efficacy of the reactions varied considerably with the type of molecular sieve used. The most suitable type is 3A (powder), and the less suitable types were 5A (powder) and 13X (powder) [Union Showa], as summarized in Table 2.

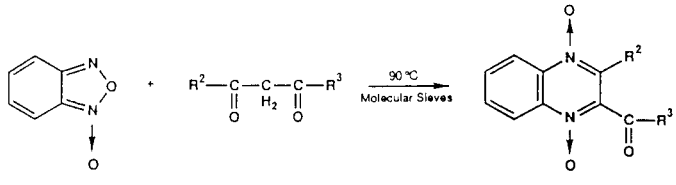
Table 2

Comparison of Various Molecular Sieve in the Reaction of BFO **1a** and Ethyl 4-Nitrobenzoylacetate **2b**

Molecular Sieve	Yield of **3** (%)
3A (powder)	83
4A (powder)	79
5A (powder)	37
13X (powder)	68

When the reactions using a molecular sieve 3A (powder) were carried out at 90°, the actual reaction times were reduced to 0.5-2 hours (see Table 3).

Scheme I



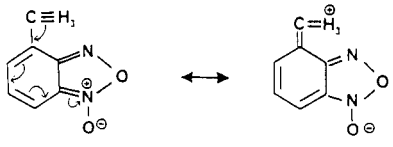
1a 2 3

The reactions of substituted BFO's with benzoylacetone **2a** varied considerably with the position of substituent. The reaction of 5,6-dimethyl-BFO **1c** provided a good yield of the corresponding quinoxaline 1,4-dioxide derivative. In contrast, 4-methyl-BFO **1b** condensed with the carbonyl compound only slightly, and 4,7-dimethyl-BFO **1d** did not react at all. In the **1b** 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 (position 1). In the **1d** 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 (see Table 4).

Table 3
The Reactions of BFO **1a** and Compound **2** on Molecular Sieve 3A at 90°

Compound No.	R^2	R^3	Reaction Time (h)	Yield of **3** (%) [a]	
2a	CH_3	C_6H_5	2	80	**3a**
2b	$C_6H_4NO_2$ (4)	OC_2H_5	0.75	78	**3b**
2c	C_6H_5	NHC_6H_5	0.75	80	**3c**
2d	CH_3	$NHC_6H_4OCH_3$ (2)	0.5	94	**3d**
2e	CH_3	$NHC_6H_4OCH_3$ (4)	0.5	84	**3e**
2f	CH_3	NHC_6H_4Cl (4)	0.5	81	**3f**
2g	CH_3	$NHC_6H_4CH_3$ (2)	0.5	82	**3g**
2h	C_6H_5	C_6H_5	0.5	83	**3h**
2i	CH_2COOCH_3	OCH_3	1	78	**3i**

[a] The products were characterised by comparison of their melting points, ir and ^1H nmr spectra with those of authentic samples prepared according to ref [3].



1b 1b'

Table 4
The Reactions of Methyl-BFO and Compound **2a** on Molecular Sieve 3A at 90° for 2 hours

Compound	R^1	Yield of **3** (%)	
1c	5,6-diCH_3	88	**3n**
1b	4-CH_3	18	**3o**
1d	4,7-diCH_3	0	

Although Duerckheimer reported the isolation of only the 7-substituted quinoxaline 1,4-dioxide when 5-methoxy-BFO **1e** was allowed to react with ethyl acetoacetate **2j** in basic medium, we found that compound **1e** produced only the 6-methoxy isomer of the quinoxaline derivative in the reaction on the surface of a molecular sieve. This result can be understood in terms of the tendency of compound **1e** to exist almost completely as the 5-substituted isomer in solution at 21°, as made clear by Boulton and his co-workers [4] (see Table 5).

In the reaction of 5-carboxy-BFO **1f** with dimethyl 1,3-acetonedicarboxylate **2i**, 94% of compound **1f** was recovered unchanged from the reaction mixture after compound **1f** was allowed to react for 2 hours.

In order to make clear the mechanism of these reactions, by comparing the yields of quinoxaline derivatives with the enol content of the carbonyl compounds, it was determined that the enol forms of the carbonyl compounds were involved in the process of formation of the quinoxaline derivatives (see Table 6). The reaction mechanism can therefore be assumed to proceed as follows.

Table 6
The Effect of the Enol Content of Carbonyl Compounds on the Condensations with BFO **1a**

Compound	R^2	R^3	Enol Content (%) of **2** (in Ethanol) [6]	Yield of **3** (%)	
2k	OCH_3	OCH_3	0	0	
2l	CH_3	OCH_3	13	16	**3l**
2m	CH_3	CH_3	84	58	**3m**
2h	C_6H_5	C_6H_5	90	66	**3h**
2a	CH_3	C_6H_5	94	88	**3a**

Scheme II

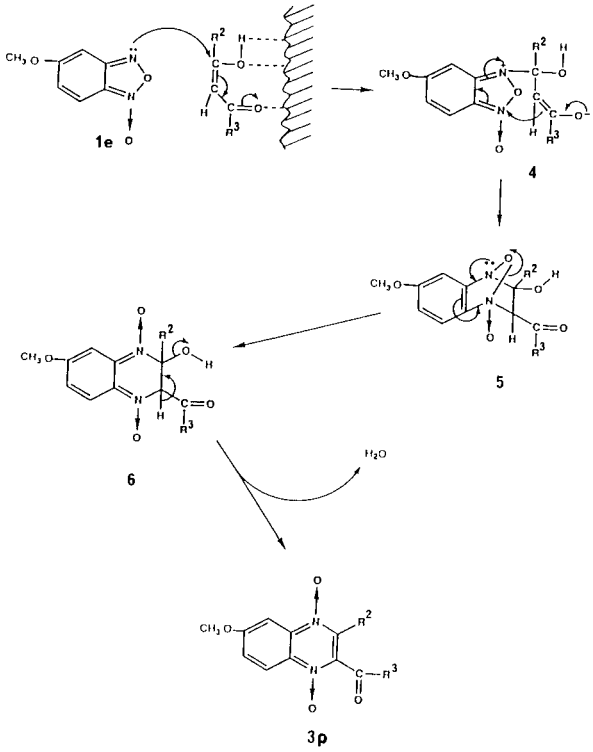


Table 5
Reaction Products **3p** from 5-Methoxy-BFO **1e** in Two Different Methods

Method	Product (Isomer of **3p**)	Yield (%)	Mp (°C)	NMR H-5	H-6	H-7	H-8	J (Hz)
Reaction in Alkaline Medium [4]	7-OCH_3	16	162-163	7.9 (*o*)	7.3 (*o* + *m*)	--	7.6 (*m*)	*o*: 9 ±0.5 *m*: 2.5±0.5
Adsorption on Molecular Sieve	6-OCH_3	26	156-157	7.72 (*m*)	--	7.59 (*o*+*m*)	8.38 (*o*)	*o*: 10 *m*: 3

EXPERIMENTAL

Melting points are uncorrected. The nmr spectra were recorded at 90 MHz with TMS as the internal standard. The ir spectra were run on a Jasco IR-810 spectrometer. The mass spectra were recorded on a Hitachi M-2000 spectrometer with an electron beam energy of 70 eV. Microanalyses were performed at the microanalytical laboratory of the Center for Instrumental Analysis in College of Science and Technology, Nihon University.

General Procedure.

3-Methyl-2-[2-methoxyphenyl]aminocarbonylquinoxaline 1,4-Dioxide **3d**.

To a solution of **1a** (2.00 g, 0.015 mole) and *o*-acetoacetanisidide (**2d**, 3.05 g, 0.015 mole) in methanol (50 ml) was added molecular sieve [3A (powder), 20 g] and the mixture is evaporated in an evaporator at 20°. The molecular sieve containing the adsorbed reagents was allowed to stand for 0.5 hour without drying, at 90°. It was then added to a silica gel column and product **3d** was eluted with dichloromethane/methanol (98/2), yield 4.78 g (94%). Recrystallization from methanol afforded yellow needles, mp 201-203°.

2-Benzoyl-3-methyl-6,7-dimethylquinoxaline 1,4-Dioxide **3n**.

This compound had mp 239-241°; ^{1}H nmr (deuteriochloroform): δ 2.48 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 7.50-7.94 (m, 5H, arom), 8.30 (s, 1H, H-5), 8.43 (s, 1H, H-8); ir (potassium bromide): ν 1678 cm^{-1} (C=O); hrms: (m/z) 308.1160. Calcd. for $C_{18}H_{16}N_2O_3$: M, 308.1160.

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.11; H, 5.23; N, 9.09. Found: C, 69.95; H, 5.19; N, 9.02.

2-Benzoyl-3-methyl-5-methylquinoxaline 1,4-Dioxide **3o**.

This compound had mp 198-200°; ^{1}H nmr (deuteriochloroform): δ 2.41 (s, 3H, CH_3), 3.17 (s, 3H, CH_3), 7.41-7.96 (m, 6H, arom), 8.43-8.65 (m, 2H, arom); ir (potassium bromide): ν 1679 cm^{-1} (C=O); hrms: (m/z) 294.0977. Calcd. for $C_{17}H_{14}N_2O_3$: M, 294.1003.

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.37; H, 4.80; N, 9.52. Found: C, 69.15; H, 4.72; N, 9.38.

2-Carboethoxy-3-methyl-6-methoxyquinoxaline 1,4-Dioxide **3p**.

This compound had mp 156~157°; ^{1}H nmr (DMSO-d_6): δ 1.36 (t, 3H, CH_2CH_3), 2.41 (s, 3H, CH_3), 3.98 (s, 3H, OCH_3), 4.50 (q, 2H, CH_2CH_3), 7.59 (q, 1H, H-7, $J_{5,7}$ = 3 Hz, $J_{7,8}$ = 10 Hz), 7.72 (d, 1H, H-5, $J_{5,7}$ = 3 Hz), 8.38 (d, 1H, H-8, $J_{7,8}$ = 10 Hz); ir (potassium bromide): ν 1732 cm^{-1} ($COOC_2H_5$); hrms: (m/z) 278.0910. Calcd. for $C_{13}H_{14}N_2O_5$: M, 278.0902.

Anal. Calcd. for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.232; H, 4.989; N, 10.004.

REFERENCES AND NOTES

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[1a] C. H. Issidorides and M. J. Haddadin, *J. Org. Chem.*, **31**, 4067 (1966); [b] R. V. Kasubick and R. L. Robertson, Pfizer Inc., German Patent (DBP) 2,215,320 (1972); *Chem. Abstr.*, **78**, 4280 (1973); [c] J. P. Dirlam, Pfizer Inc., German Patent (DBP) 2,624,923 (1977); *Chem. Abstr.*, **86**, 189740 (1977); [d] K. Ley, *Synthesis*, 415 (1975).

[2a] N. A. Mufarrij, M. J. Haddadin and C. H. Issidorides, *J. Chem. Soc., Perkin Trans. 1*, 965 (1972); [b] M. J. Haddadin, G. Agopian and C. H. Issidorides, *J. Org. Chem.*, **36**, 514 (1971).

[3] Portions of this work have been communicated: [a] M. Hasegawa and T. Takabatake, *Synthesis*, 938 (1985); [b] T. Takabatake and M. Hasegawa, *J. Heterocyclic Chem.*, **24**, 529 (1987).

[4] W. Duerckheimer, *Liebigs Ann. Chem.*, **756**, 145 (1972).

[5] A. J. Boulton, A. R. Katritzky, M. J. Sewell and B. Wallis, *J. Chem. Soc. (B)*, 914 (1967).

[6] K. H. Meyer, *Ber.*, **45**, 2848 (1912).