Reactions of Benzofuroxan with 1,3-Diketones or β-Ketoesters on Silica Gel or Alumina

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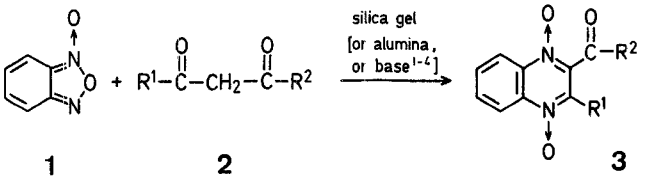
The cyclocondensation of benzofuroxan with 1,3-diketones, 3-oxoalkanoic esters, butanedioic esters, or 3-oxoalkanamides in the presence of silica gel (adsorption of the components on silica gel) represents a convenient method for the synthesis of 2,3-disubstituted quinoxaline-1,4-bis-oxides.

Quinoxaline di-*N*-oxide derivatives (**3**) are conventionally synthesized from benzofuroxan (**1**) and enolate anions of 1,3-diketones or β-ketoesters in a basic medium[1-4]. We report here that silica gel also provides a versatile synthetic tool for these reactions.



1 2 3

A solution of compound **1** and carbonyl compound **2** in methanol is evaporated in the presence of silica gel; both reagents are adsorbed on the silica gel which is then allowed to stand for 1–2 weeks without drying at room temperature. The mixture is chromatographed on silica gel to give the corresponding quinoxaline di-*N*-oxide derivative **3**.

The efficacy of the reactions varies considerably with the type of silica gel used. Convenient gels are Wakogel C-200 (Wako Pure Chemical Industries) and Silica gel 60 (Merck). The surface of silica gel of the less convenient types is somewhat more acidic than that of the others [Silica gel 40, 100 (Merck)]. It is assumed that there is a correlation between the content in enol form of the carbonyl compound **2** and the yield of product **3**.

Attempts to use alumina (basic, neutral, and acidic) in place of silica gel led to less satisfactory results. Neutral alumina was found to be the most effective alumina; thus, the reaction of compound **1** with benzoylacetone (**2f**) for 8 days afforded product **3f** in 49% yield (with silica gel: 88%). In all cases, the products obtained using alumina were contaminated with side products.

Table 1. Quinoxaline 1,4-Bis-oxides (**3**) prepared

3	R^1	R^2	Enol Content [%] of **2** (in Ethanol)[5]	Yield of **3**[a] [%]	m.p. [°C]	Molecular Formula[b] or m.p. [°C] reported	M.S. (high resolution), M^+ *m/e* calc.	*m/e* found
a	OCH_3	OCH_3	0	0[c]				
b	CH_3	OCH_3	12.6	16[d]	169°	168–172.5°[1]		
c	C_6H_5	OC_2H_5	27	63	122–124°	$C_{17}H_{14}N_2O_4$ (310.3)	310.0953	310.0957
d	CH_3	CH_3	84	58[d]	156–158°	153–154°[2]		
e	C_6H_5	C_6H_5	90–100	66[d]	232–234°	234°[2]		
f	CH_3	C_6H_5	94	88[d]	228–229°	229–231°[3]		
g	C_6H_5	—NH—C_6H_5		90	227–229°	$C_{21}H_{15}N_3O_3$ (357.35)	357.1111	357.1092
h	—C_6H_4—NO_2 (4)	OC_2H_5		81	160–162°	$C_{17}H_{13}N_3O_6$ (355.3)	355.0802	355.0783
i	—CH_2—$COOCH_3$	OCH_3		48	155–157°	$C_{13}H_{12}N_2O_6$ (292.3)	292.0694	292.0693

[a] Yield of isolated product. Reaction time for **3a–f**: 1 week, for **3g, h, i**: 2 weeks.

[b] The microanalyses were in satisfactory agreement with the calculated values: C ± 0.26, H ± 0.37, N ± 0.31.

[c] The starting materials were recovered almost quantitatively.

[d] The products were characterized by comparison of their m.p.s and I.R. and ^{1}H-N.M.R. spectra with those of authentic samples prepared according to Ref.[1,2,3].

Table 2. Spectral Data of the New Compounds **3**

Compound	I.R. (KBr) ν[cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ[ppm]
3c	1738 ($COOC_2H_5$)	1.08 (t, 3H, $COOCH_2$—CH_3); 4.26 (q, 2H, $COOCH_2$—CH_3); 7.57 (d, 5H_{arom}); 7.91 (m, 2H, 6-H, 7-H); 8.67 (m, 2H, 5-H, 8-H)
3g	1680, 1550 (CO—NH)	8.09 (q, 2H, 6-H, 7-H); 8.25 (q, 2H, 5-H, 8-H); 7.02–7.41 (m, 5H_{arom}); 7.48–7.83 (m, 5H_{arom}); 10.59 (s, 1H, CO—NH)
3h	1738 ($COOC_2H_5$); 1518, 1346 (NO_2)	7.99 (q, 2H, 6-H, 7-H); 8.68 (q, 2H, 5-H, 8-H); 1.18 (t, 3H, $COOCH_2$—CH_3); 4.45 (q, 2H, $COOCH_2$—CH_3); 7.88, 8.43 (2d, 2H each, J = 9 Hz each, 4H_{arom})
3i	1730, 1740 ($COOCH_3$)	7.93 (q, 2H, 6-H, 7-H); 8.63 (q, 2H, 5-H, 8-H); 3.79 (s, 3H, $COOCH_3$); 4.03 (s, 2H, CH_2—$COOCH_3$); 4.13 (s, 3H, CH_2—$COOCH_3$)

3-Phenyl-2-phenylaminocarbonylquinoxaline 1,4-Bis-oxide (3g); Typical Procedure:

To a solution of benzofuroxan (**1**; 2.00 g, 15 mmol) and benzoylacetanilide (**2g**; 3.59 g, 15 mmol) in methanol (60 ml) is added silica gel (Wako gel C-200; 20 g) and the mixture is evaporated in an evaporator at XX°C. The gel containing the adsorbed reagents is allowed to stand for 2 weeks without drying, at room temperature. It is then added to a silica gel column and product **3g** is eluted with dichloromethane/methanol (98/2); yield: 4.723 g (90%); m.p. 227–229°C.

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