

Synthesis of Pyrazino[2,3-*b*]quinoxaline 1,4-Dioxides

Maria S. Vrettou, John K. Gallos and Demetrios N. Nicolaides*

Laboratory of Organic Chemistry, University of Thessaloniki,
Thessaloniki, Greece

Received October 2, 1987

Pyrazino[2,3-*b*]quinoxaline 1,4-dioxides **3a-e** were prepared by reacting Furoxano[3,4-*b*]quinoxaline with alkynes and alkenes.

J. Heterocyclic Chem., **25**, 813 (1988).

Quinoxaline *N,N'*-dioxides are of current interest because of their powerful bacteriostatic properties and are conventionally synthesized through the reaction of benzofuroxans (BFO's) with enamines and enolates [1-3]. This process which is frequently referred as the Beirut reaction, has been observed using a number of substrates. Recently the use of silica gel, instead of a basic medium, has been reported to provide a versatile synthetic tool for these reactions [4]. Although nitro-substituted BFO's react with butadienes by addition to the benzene ring [5], BFO gives with dienamines and with 1-aza-1,3-butadienes the corresponding quinoxaline *N,N'*-dioxide enamines [6] and imines [7] respectively.

Of the heterocyclic-ring-fused furoxans the thienofuroxan and some pyrido- and pyrimidofuroxans are reported to condense with malonitrile or with ketones in the presence of dimethylamine giving thieno-, pyrido- and pyrimidopyrazine *N,N'*-dioxides respectively [8,9].

In connection with our previous work on the prepara-

tion of furoxano[3,4-*b*]quinoxalines [10] and their transformation to pyrazino[2,3-*b*]quinoxalines *via* reactions with phosphorus ylides [11] we wish to report now the synthesis of the pyrazino[2,3-*b*]quinoxaline 1,4-dioxides **3a-e** by condensation of furoxano[3,4-*b*]quinoxaline (**1**) [10] with alkynes **2a-c** and with alkenes **4a-c**, as it is depicted in the reaction Scheme.

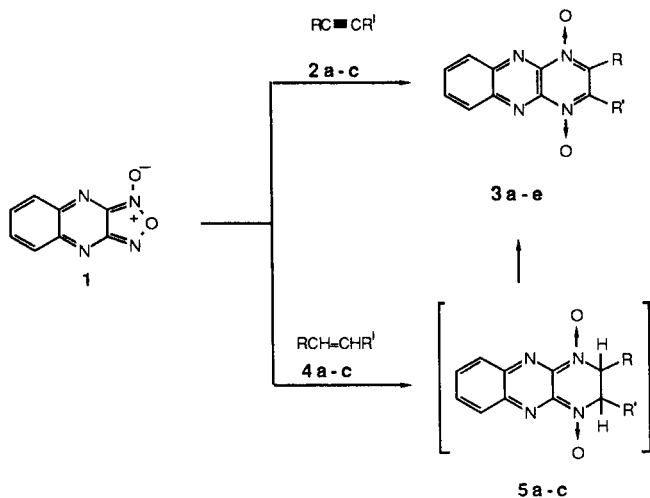
All reactions of furoxan **1** were carried out in boiling dry chloroform with an equimolar amount of the appropriate alkyne or alkene and the reaction products were separated by column chromatography. The reactions of **1** with alkynes **2a-c** afforded the di-*N*-oxides **3a-c**. The pyrazino[2,3-*b*]quinoxaline 1,4-dioxides **3a**, **3d**, **3e** were also isolated as the final products from the reactions of **1** with alkenes **4a-c**, obviously by the further oxidation of the initially formed dihydro-derivatives **5a-c** and by analogy to the reported oxidation of the intermediate dihydroquinoxaline *N,N'*-dioxides in other Beirut reactions [6,7].

The structures of the di-*N*-oxides prepared were confirmed by their elemental analysis and spectral data, given in Tables I and II. All the products showed a strong ir band at 1325-1350 cm^{-1} (*N*-oxide) [12,13]. The mass spectra showed correct molecular ions, with exception of compound **3b** and two consecutive losses of 16 units, typical and highly diagnostic for aromatic di-*N*-oxides [6]. The $^1\text{H-nmr}$ spectra resemble well with the proposed structures.

Some efforts for a Beirut reaction of furoxan **1** with preformed 2-amino-2-butene or with ethyl acetoacetate in the presence of morpholine failed, since in a control experiment it was found that compound **1** is unstable in the presence of morpholine. A similar behaviour is also reported in some reactions of BFO's with amines [14,15]. It is of interest to note that in an attempted reaction of BFO with alkyne **2a** in boiling chloroform for 14 hours the mixture remained unchanged, as it was indicated by tlc. Also furoxan **1** as well as its 6,7-dimethyl analog reacted with phosphorus ylides in a different way to that observed for BFO [11].

EXPERIMENTAL

Melting points were determined with a Kofler Hot-stage apparatus and



2a, R = R' = C₆H₅
b, R = C₆H₅, R' = H
c, R = R' = *p*-CH₃O-C₆H₄

3a, R = R' = C₆H₅
b, R = C₆H₅, R' = H
c, R = R' = *p*-CH₃O-C₆H₄
d, R = C₆H₅, R' = *p*-CH₃-C₆H₄
e, R = C₆H₅, R' = *p*-CH₃O-C₆H₄

4,5a, R = R' = C₆H₅
b, R = C₆H₅, R' = *p*-CH₃C₆H₄
c, R = C₆H₅, R' = *p*-CH₃O-C₆H₄

Table I

Preparation of Pyrazino[2,3-*b*]quinoxaline 1,4-Dioxides **3a-e**

Compound No.	Alkyne or Alkene used	Reaction Time (hours)	Yield (%)	Mp (°C)	Molecular formula	Analyses (%)					
						Calcd. C	Calcd. H	N	C	Found H	N
3a	2a	5	22	213-215	C ₂₂ H ₁₄ N ₄ O ₂ (366.36)	72.12	3.85	15.29	71.97	3.94	15.21
3a	4a	31	31	212-214							
3b	2b	4	41	159-161	C ₁₆ H ₁₀ N ₄ O ₂ (290.27)	66.20	3.47	19.30	65.85	3.63	19.01
3c	2c	3	47	193-195	C ₂₄ H ₁₈ N ₄ O ₄ (426.42)	67.60	4.25	13.14	67.90	4.18	13.15
3d	4b	80	19	182-184	C ₂₃ H ₁₆ N ₄ O ₂ (380.39)	72.62	4.24	14.73	72.40	4.52	14.68
3e	4c	43	20	124-126	C ₂₃ H ₁₆ N ₄ O ₃ (396.39)	69.69	4.07	14.14	69.42	4.33	14.38

Table II

Spectral Data of Compounds **3a-e**

Compound	IR (nujol) cm ⁻¹	¹ H-NMR (Deuteriochloroform) (δ ppm)	Mass Spectra (relative intensity)
3a	1615, 1580, 1500, 1450, 1440, 1380, 1330, 1320	7.42 (br s, 10H), 7.96-8.30 (m, 2H), 8.45-8.79 (m, 2H)	366 (M ⁺ , 1), 350 (M-16, 10), 334 (M-32, 100), 246 (14), 231 (24)
3b	1610, 1570, 1530, 1380, 1350	7.53-7.77 (m, 3H), 8.00-8.33 (m, 4H), 8.45-8.75 (m, 2H), 8.93 (s, 1H)	274 (M-16, 7), 272 (4), 258 (M-32, 100), 246 (9), 231 (7)
3c	1608, 1578, 1520, 1505, 1440, 1380, 1327, 1310, 1296, 1260	3.82 (s, 6H), 6.83 (d, J = 9 Hz, 4H), 7.35 (d, J = 9 Hz, 4H), 7.85-8.17 (m, 2H), 8.32-8.63 (m, 2H)	426 (M ⁺ , 2), 411 (3), 410 (M-16, 9), 395 (28), 394 (M-32, 100), 380 (6), 379 (17), 364 (5), 363 (14), 276 (34)
3d	1608, 1498, 1380, 1327, 1310	2.30 (s, 3H), 6.98-7.53 (m, 9H), 7.83-8.17 (m, 2H), 8.30-8.63 (m, 2H)	380 (M ⁺ , 1), 364 (M-16, 11), 349 (27), 348 (M-32, 100), 333 (12), 276 (27), 277 (42), 260 (8), 246 (14), 245 (16), 231 (16)
3e	1608, 1575, 1520, 1500, 1380, 1327, 1298, 1260	3.80 (s, 3H), 6.82 (d, J = 9 Hz, 2H), 7.15-7.50 (m, 7H), 7.90-8.23 (m, 2H), 8.35-8.68 (m, 2H)	3.96 (M ⁺ , 1), 394 (2), 380 (M-16, 7), 365 (30), 364 (M-32, 100), 350 (5), 349 (17), 334 (6), 333 (6), 246 (30), 239 (26), 231 (13)

are uncorrected. The IR spectra were obtained with a Perkin-Elmer 297 spectrophotometer as Nujol mulls. The ¹H-NMR spectra were recorded with deuteriochloroform as the solvent on a Varian A60-A spectrometer, with tetramethylsilane as the internal standard. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6L spectrometer. The ionization energy was maintained at 70 eV.

Preparation of Pyrazino[2,3-*b*]quinoxaline 1,4-Dioxides **3a-e**. General Procedure.

To a solution of furoxan **1** (0.188 g, 1 mmole) in dry chloroform (25 ml) was added the appropriate alkyne **2a-c** or alkene **4a-c** (1 mmole) and the mixture was boiled under reflux for 3-80 hours (see Table I). The reaction was monitored by tlc. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (25 g), using ethyl acetate as eluant. Products **3a-e** were obtained in the fractions of 700-1000 ml of solvent eluted and were recrystallized from methylene chloride-hexane.

Acknowledgements.

The authors wish to thank the Ministry of Research and Technology, Greece, for financial support.

REFERENCES AND NOTES

[1] K. Ley and F. Seng, *Synthesis*, 415 (1975).

[2] A. Gasco and A. J. Boulton, in "Advances in Heterocyclic Chemistry", Vol 29, A. R. Katritzky and A. J. Boulton, eds, Academic Press, New York, 1981, p 251.

[3] R. M. Paton, in "Comprehensive Heterocyclic Chemistry", Vol 6, A. R. Katritzky and C. W. Rees, eds, Pergamon Press, Oxford, 1984, p 393.

[4] M. Hasegawa and T. Takabatake, *Synthesis*, 938 (1985).

[5] G. Kresze and H. Bathelt, *Tetrahedron*, 29, 1043 (1973).

[6] H. N. Borah, P. Devi, J. S. Sandhu and J. N. Baruah, *Tetrahedron*, 40, 1617 (1984).

[7] P. Devi and J. S. Sandhu, *J. Heterocyclic Chem.*, 21, 1247 (1984).

[8] H. Von Döbenek, E. Weil, E. Brunner, H. Deubel and D. Wolkenstein, *Ann. Chem.*, 1424 (1978).

[9] D. Binder, German Offen. 2,703,369 (1977); *Chem. Abstr.*, 87, 152274 (1977).

[10] D. N. Nicolaides and J. K. Gallos, *Synthesis*, 638 (1981).

[11] N. G. Argyropoulos, J. K. Gallos and D. N. Nicolaides, *Tetrahedron*, 42, 3631 (1986).

[12] M. J. Haddadin, M. U. Taha, A. A. Jarrar and C. H. Issidorides, *Tetrahedron*, 32, 719 (1976).

[13] A. M. Vega, M. J. Gil and E. Fernandez-Alvarez, *J. Heterocyclic Chem.*, 21, 1271 (1984).

[14] M. Z. Nazer, C. H. Issidorides and M. J. Haddadin, *Tetrahedron*, 35, 681 (1979).

[15] D. W. S. Latham, O. Meth-Cohn and H. Suschitzky, *Tetrahedron Letters*, 5365 (1972).