Synthesis of 2-substituted-quinoxaline-1,4-dioxides

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Six new 2-substituted-quinoxaline-1,4-dioxides(3) have been prepared by reacting benzofuroxan (BFO)(1) with alkenes(2). The reaction is proposed as a free radical mechanism.

Benzofuroxan (BFO)(1) and its derivatives have been shown to have numerous pharmaceutical applications. Recent results have shown that benzofuroxan derivatives have potential antitrypanosomal activity and antiarrrhythmic activity. The reactivity of benzofuroxan towards various substrates in the Beirut reaction has been observed in the presence of ammonia or an amine. Beirut reaction has also been observed using silica gel or molecular sieves as solid catalysts instead of a basic medium.

We have first reported a variety of arenealdoxime dehydrodimers reacting with styrene in refluxing chloroform to afford linear adducts, bisnitrones and nitrone-oximinates and, also proposed its free radical mechanism based on ESR study. To continue our interest in benzofuroxan chemistry and their various biological activities, we decided to explore the reaction of BFO with alkenes in neutral condition and its possible mechanism.

Some benzopyrazine-fused furoxans were reported to react with alkynes and alkenes. They have been found to be more reactive than simple benzofuroxans, evidently because of the electron-withdrawing fused pyrazine ring, which activates the neighboring furoxan ring towards nucleophiles. Although reacting BFO with alkylene in boiling chloroform for 14 hr the mixture remained unchanged, we found that BFO could react with alkenes in neutral boiling chloroform, giving ring addition products which is analogous to Beirut reaction. The reaction could be promoted by adding oxidatives \([\text{HCrO}_4]_2(\text{py})_4\text{Co}\), which was confirmed by control reaction. A free radical mechanism could be proposed by reacting with 1,1-diphenylethylene in chloroform at 45°C and having observed signals of the radicals by ESR technique. Herein we wish to report the reaction of BFO with styrene and its analogs(2) and the synthesis of 2-substituted-quinoxaline-1,4-dioxides(3).

Structural assignment was made on the basis of spectral data (IR, HNMR, MS) and elemental analyses. The infrared spectra of the products indicated the lack of the strong absorption band at \(v=1600\ \text{cm}^{-1}\) (characteristic for furoxan ring) and the presence of a strong absorption bond at 1325-1350 cm\(^{-1}\) (characteristic for N-oxide), implying the addition of styrene to the BFO’s furoxan ring. The HNMR spectra showed the presence of substituted quinoxaline ring system and resemble well with the proposed structures. The mass spectra showed that the parent ions of the products appear at 70 eV, with correct molecular ions and two consecutive losses of 16 units (typical and highly diagnostic for aromatic di-N-oxides).

Experimental Section

General Procedure for the preparation of 2-substituted-quinoxaline-1,4-dioxides 3a-f. To a solution of BFO (0.952 g, 7 mmoles) in dry chloroform (25 mL) was added the appropriate alkene (2 mmoles) in dry chloroform (25 mL) and the mixture was boiled and refluxed for 30-72 hr. The reaction was monitored by TLC. The mixture was cooled to room temperature. The precipitates were collected to give crude 3, which was recrystallized by ethanol.

2-Phenyl-quinoxaline-1,4-dioxides 3a. This compound was obtained as yellow plates in 42.5% yield, mp 205°C. Anal. Found: C, 70.58; H, 4.29; N,
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11.73. Calcd for C₁₄H₁₀N₂O₂: C, 70.56; H, 4.28; N, 11.77%; IR: 3040, 1600, 1490, 1360, 1240, 860, 790, 730 cm⁻¹; ¹H NMR (DMSO-d₆): δ 8.74-8.75 (1H, m, C6-H), 8.05-8.06 (1H, m, C5-H), 8.86 (1H, s, C7-H); MS: m/z(%): 269 (M⁺, 100); 253 (M⁺-16, 45.5), 127 (29), 83 (51.4). 2-(4'-Pyridyl)-quinoxaline-1,4-dioxide 3b. This compound was obtained as yellow crystals in 35% yield, mp 224-26°C. Anal. Found: C, 65.62; H, 3.87; N, 17.60. Calcd for C₁₃H₉N₂O₂: C, 65.24; H, 3.79; N, 17.58%; IR: 3061, 1596, 1498, 1371, 1324, 1249, 878, 819, 741 cm⁻¹; ¹H NMR (DMSO-d₆): δ 8.79-8.90 (4H, m, C6,7,2',3',4',5'-H), 8.48-8.50 (1H, m, C5-H), 8.56-8.58 (1H, m, C3-H) ppm; MS: m/z(%): 238 (M⁺, 100), 22 (M⁺-16, 76.6), 206 (M⁺-32, 30.2), 193 (35.6), 129 (7.0), 102 (29), 77 (23.9).

2-(4'-Methoxyphenyl)-quinoxaline-1,4-dioxide 3c. This compound was obtained as yellow crystals in 58.2% yield, mp 214-16°C. Anal. Found: C, 67.37; H, 4.60; N, 10.60. Calcd for C₁₃H₁₂N₂O₃: C, 67.14; H, 4.51; N, 10.45%; IR: 3021, 1067, 1495, 1371, 1333, 1262, 844, 786, 735 cm⁻¹; ¹H NMR (DMSO-d₆): δ 3.87 (3H, s, OCH₃), 7.08 (2H, d, 1=8.7, C3',5'-H), 7.93-7.97 (2H, m, C6,7-H), 8.05 (2H, d, 1=8.7, C2',6'-H), 8.46-8.48 (1H, m, C5-H), 8.55-8.57 (1H, m, C3-H), 8.83 (1H, s, C7-H) ppm; MS: m/z(%): 283 (M⁺, 41.8), 267 (M⁺-16, 100), 251 (M⁺-32, 28.5), 129 (9.4), 102 (23.5).

2-(4'-Chlorophenyl)-quinoxaline-1,4-dioxide 3d. This compound was obtained as yellow plates in 52.3% yield, mp 240-42°C. Anal. Found: C, 61.85; H, 3.59; N, 10.40. Calcd for C₁₄H₁₀ClN₂O₂: C, 61.64; H, 3.33; N, 10.28%; IR: 3440, 1600, 1580, 1360, 1335, 1240, 865, 810, 760 cm⁻¹; ¹H NMR (DMSO-d₆): δ 8.75 (2H, d, J=8.5, C6-H), 7.95-7.98 (2H, m, C₈,7-H), 8.05 (2H, d, J=8.5, C6-H), 8.47-8.49 (1H, m, C5-H), 8.55-8.57 (1H, m, C3-H), 8.86 (1H, s, C7-H); MS: m/z(%): 272 (M⁺, 100), 256 (M⁺-16, 82.3), 240 (M⁺-32, 23.8), 193 (29.3), 129 (8), 111 (24), 102 (28).

2-(4'-Nitrophenyl)-quinoxaline-1,4-dioxide 3e. This compound was obtained as yellow prisms in 30% yield, mp 280-82°C. Anal. Found: C, 59.03; H, 3.09; N, 14.64. Calcd for C₁₄H₁₀N₂O₄: C, 59.34; H, 3.20; N, 14.84%; IR: 3040, 1590, 1360, 1340, 1240, 855, 760 cm⁻¹; ¹H NMR (DMSO-d₆): δ 8.80-8.04 (2H, m, C₆-H), 8.26 (2H, d, J=8.5, C₂',₈'-H), 8.39 (2H, d, J=8.5, C₅',₇'-H), 8.50-8.52 (1H, m, C₅-H), 8.75-8.58 (1H, m, C₃-H), 8.99 (1H, s, C₇-H); MS: m/z(%): 283 (M⁺, 41.8), 267 (M⁺-16, 100), 251 (M⁺-32, 28.5), 129 (9.4), 102 (23.5).

2-(2'-Thiazolyl)-quinoxaline-1,4-dioxide 3f. This compound was obtained as yellow prisms in 61.8% yield, mp 222-24°C. Anal. Found: C, 58.80; H, 3.18; N, 11.25. Calcd for C₁₂H₁₀ClN₂O₂: C, 59.01; H, 3.30; N, 11.47%; IR: 3050, 1600, 1516, 1495, 1380, 1360, 1280, 760 cm⁻¹; ¹H NMR (DMSO-d₆): δ 7.30-7.50 (2H, m, C₃',₄'-H), 7.93-8.67 (5H, m, C₃',₅',₆',₇',₈'-H), 9.67 (1H, s, C₃-H) ppm; MS: m/z(%): 244 (M⁺, 100), 228 (M⁺-16, 76.5), 212 (M⁺-32, 10.1), 129 (20.3), 102 (20.9), 108 (18.0), 83 (6.2).

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References