European Journal of Chemistry 2 (1) (2011) 51-57

European Journal of Chemistry
Journal homepage: www.eurjchem.com

Studies with aza-heterocyclic *N*-oxides: Synthesis of some new aromatic *N*-oxide derivatives

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ARTICLE INFORMATION

Received: 16 August 2010
Received in revised form: 04 October 2010
Accepted: 28 October 2010
Online: 31 March 2011

KEYWORDS

Heterocyclic *N*-oxides
Benzofuroxan
Rhodanine
o-Quinone dioximes
Thiocarbohydrazide
Curtius rearrangement

ABSTRACT

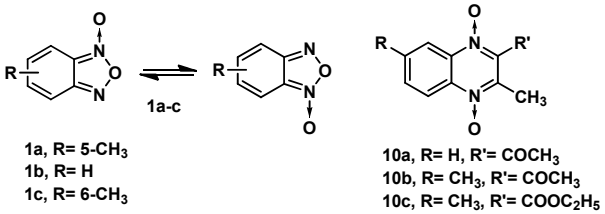
Benzofuroxan derivative (**1a**) reacts with the cyanoacetanilides (**2a-d**) to give the benzimidazole derivatives (**3a-d**). Benzofuroxan (**1b**) reacts with rhodanine derivatives (**4a**,**b**) in presence of sodium ethoxide to give the arylaminobenzoimidazole derivatives (**6a**,**b**); while the last reaction afforded the thiazolidinone derivatives (**8a**,**b**) and the *o*-benzoquinone dioxime derivatives (**9a**,**b**) when it was repeated in the presence of sodium acetate. Moreover, a series of quinoxalinyl 1,4-di-*N*-oxide derivatives were prepared starting from quinoxalin-1,4-di-*N*-oxide derivatives (**10a-c**). Plausible mechanisms to account for the formation of the products are discussed.

1. Introduction

Over the last three decades we have been involved in a program aiming to develop new simple procedures or novel precursors for the synthesis of heterocyclic compounds of biological interest from cheap laboratory available starting materials to be evaluated as biodegradable agrochemicals [1-8].

Benzofuroxans display several biochemical and pharmacological properties and specific studies were devoted to these aspects [9-11]. Several authors have reported about the biological importance of quinoxaline 1,4-dioxides (QdNO's) since 1940's. Classical and more recent methods of the synthesis of the quinoxaline 1,4-dioxides and some of their most important reactions were also reported [12,13].

Furthermore quinoxaline 1,4-di-*N*-oxide derivatives were reported to exhibit hypoxia-selective cytotoxins and anticancer activities [14,15] as well as mycobacterium tuberculostatic activities [16,17]. In view of these facts and in continuation of our earlier interest [18-20], we report here the results of our investigations on benzofuroxans 1-oxide (**1a-b**) and quinoxaline 1,4-di-*N*-oxide (**10a-c**) derivatives (Scheme 1).



Scheme 1

2. Experimental

All melting points are recorded on Gallenkamp electric melting point apparatus and are uncorrected. The IR spectra (υ, cm^{-1}; KBr) were recorded on Perkin Elmer Infrared Spectrophotometer Model 157, Grating. The ^1H NMR spectra were run on Varian Spectrometer at 200 MHz using TMS as an internal reference and DMSO-d_6 as solvent and chemical shifts are expressed in δ (ppm). The mass spectra (EI) were run at 70 eV with Kratos MS equipment and/or a Varian MAT 311 A Spectrometer. Elemental analyses were carried out at the micro analytical center of Cairo University, Giza, Egypt. Benzofuroxans (**1a**,**b**) were prepared according to a procedure reported previously [21].

2.1. Synthesis of 2-(arylcarbamoyl)-1-hydroxy-5-methyl-1H-benzo[d]imidazole-3-oxide (3a-d)

A mixture of benzofuroxan (**1a**) (0.45 g, 3 mmol) and cyanoacetanilide derivatives (**2a**) (0.523 g, 3 mmol), (**2b**) (0.523 g, 3 mmol), (**2c**) (0.571 g, 3 mmol) or (**2d**) (0.571 g, 3 mmol) was stirred in ethanol (30 mL) with piperidine (3 mL) overnight. The obtained precipitates were filtered off, dried and recrystallized from ethanol to afford the benzimidazole derivatives (**3a-d**).

3a, Dirty yellow solid, M.p.: 217 °C. Yield: 70%. IR (KBr, ν_{max}, cm^{-1}): 3430 (OH), 3250 (NH), 1660 (C=O), 1620 (C=N), 1236, 1317 (N→O). ^1H NMR (DMSO, δ ppm): 2.0 (s, 1H, OH), 2.12 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 7.06-7.50 (m, 7H, Ar-H), 9.15 (s, 1H, NH). MS (m/z, %): 296 (M^+-1, 26). Anal. Calcd. for $C_{16}H_{15}N_3O_3$ (297.31): C, 64.64; H, 5.09. Found: C 64.56; H, 5.12.

3b, Dirty yellow solid, M.p.: 206 °C. Yield: 75%. IR (KBr, ν_{max}, cm^{-1}): 3452 (OH), 3226 (NH), 1691 (C=O), 1618 (C=N),

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online)
DOI:10.5155/eurjchem.2.1.51-57.249

1231, 1323 (N→O). ^{1}H NMR (DMSO, δ ppm): 2.0 (s, 1H, OH), 2.34 (s, 6H, 2CH_3), 7.06-7.56 (m, 7H, Ar-H), 9.15 (s, 1H, NH). MS (m/z, %): 297 (M^+, 60). Anal. Calcd. for $C_{16}H_{15}N_3O_3$ (297.31): C, 64.64; H, 5.09; N, 14.13. Found: C 64.41; H, 4.97; N, 14.37.

3c, Yellowish red solid, M.p.: 196 °C. Yield: 60%. IR (KBr, ν_{max}, cm^{-1}): 3448 (OH), 3248 (NH), 1680 (C=O), 1632 (C=N), 1236, 1335 (N→O). ^{1}H NMR (DMSO, δ ppm): 2.0 (s, 1H, OH), 2.34 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 6.73-7.50 (m, 7H, Ar-H), 9.15 (s, 1H, NH). MS (m/z, %): 313 (M^+, 33). Anal. Calcd. for $C_{16}H_{15}N_3O_4$ (313.31): C, 61.34; H, 4.83; N, 13.41. Found: C 61.19; H, 4.86; N, 13.56.

3d, Reddish yellow solid, M.p.: 300 °C. Yield: 77%. IR (KBr, ν_{max}, cm^{-1}): 3437 (OH), 3236 (NH), 1687 (C=O), 1627 (C=N), 1234, 1314 (N→O). ^{1}H NMR (DMSO, δ ppm): 2.34 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 7.07-7.50 (m, 7H, Ar-H), 9.15 (br., s, 1H, NH). MS (m/z, %): 314 (M^++1, 43). Anal. Calcd. for $C_{16}H_{15}N_3O_4$ (313.31): C, 61.34; H, 4.83. Found: C 61.37; H, 4.88.

2.2. Synthesis of 1-hydroxy-1H-benzo[d]imidazole-3-oxides (6a, b)

A mixture of benzofuroxan (**1b**) (0.45 g, 3 mmol) and rhodanine derivatives (**4a**) (0.67 g, 3 mmol) or (**4b**) (0.718 g, 3 mmol) was heated under reflux for 6 hours in ethanol (30 mL) in the presence of sodium ethoxide (0.069 g, 3 mmol). The reaction mixture was left to stand at room temperature for 3 hours, then poured into crushed ice and acidified with dilute HCl, effervescence with evolution of CO_2 was observed. The formed precipitate was filtered, dried and crystallized from ethanol to give benzimidazole derivatives (**6a**,**b**).

6a, Reddish brown crystals, M.p.: 254 °C. Yield: 70%. IR (KBr, ν_{max}, cm^{-1}): 3250 (NH), 1248, 1343 (N→O). ^{1}H NMR (DMSO, δ ppm): 2.0 (s, 1H, OH), 2.2 (s, 3H, CH_3), 4.10 (s, 1H, NH), 6.85-8.56 (m, 8H, Ar-H). MS (m/z, %): 239 (M^+-16, 15). Anal. Calcd. for $C_{14}H_{13}N_3O_2$ (255.27): C, 65.87; H, 5.13. Found: C, 65.53; H, 5.32.

6b, Reddish brown crystals, M.p.: 160 °C. Yield: 60%. IR (KBr, ν_{max}, cm^{-1}): 3250 (NH), 1248, 1343 (N→O). ^{1}H NMR (DMSO, δ ppm): 2.0 (s, 1H, OH), 2.34 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 4.10 (s, 1H, NH), 6.18-7.50 (m, 8H, Ar-H). MS (m/z, %): 272 (M^++1, 16). Anal. Calcd. for $C_{14}H_{13}N_3O_3$ (271.27): C, 61.99; H, 4.83; N, 15.49. Found: C, 61.74; H, 5.11; N, 15.56.

2.3. Synthesis of 2,2'-dithiano-Δ5,5'-bi-4-thiazolidinones (8a,b)

A mixture of benzofuroxan (**1b**) (0.45 g, 3 mmol), rhodanine derivatives (**4a**) (0.67 g, 3 mmol) or (**4b**) (0.718 g, 3 mmol), and catalytic amount of anhydrous sodium acetate (0.5 g, 6 mmol) in acetic acid (20 mL) was heated on water bath at 90 °C for 2-3 hours. The reaction mixture was then filtered, dried then heated with hot ethanol filtered while hot to give 4-thiazolidinone dimers (**8a**,**b**).

8a, Dark yellow solid, M.p.: > 300 °C. Yield: 82%. IR (KBr, ν_{max}, cm^{-1}): 3232 (NH), 1248, 1343 (N→O). ^{1}H NMR (DMSO, δ ppm): 2.42 (s, 6H, 2CH_3), 6.89-7.59 (m, 8H, Ar-H). MS (m/z, %): 442 (M^+, 75). Anal. Calcd. for $C_{20}H_{14}N_2O_2S_4$ (442.60): C, 54.27; H, 3.19; N, 6.33; S, 28.98. Found: C, 54.40; H, 3.26; N, 6.25; S, 29.08.

8b, Reddish brown solid, M.p.: >300 °C. Yield: 90%. IR (KBr, ν_{max}, cm^{-1}): 3250 (NH), 1236, 1335 (N→O). ^{1}H NMR (DMSO, δ ppm): 3.80 (s, 6H, 2OCH_3), 6.91-7.50 (m, 8H, Ar-H). MS (m/z, %): 474 (M^+, 12). Anal. Calcd. for $C_{20}H_{14}N_2O_4S_4$ (474.60): C, 50.61; H, 2.97. Found: C, 50.58; H, 2.93.

2.4. Synthesis of 3-methyl-E-2-(1-(2-(hydrazinecarbono thioyl)-hydrazono)-ethyl)- quinoxalin-1,4-dioxide (12)

To a boiling solution of **10a** (0.655 g, 3 mmol) in methanol (15 mL) containing 2 drops of conc. HCl, was added a methanolic solution of thiocarbohydrazide (**11**) (0.318 g, 3 mmol in 10 mL methanol) with stirring. The reaction mixture was refluxed for 5 hours and then allowed to stand at room temperature overnight. The separated product was filtered off and recrystallized from methanol to give **12**. Yellow crystals, M.p.: 237 °C. Yield: 72%. IR (KBr, ν_{max}, cm^{-1}): 1250 (C=S), 1320 (N→O), 1620 (C=N), 3220 (NH), 3410 (NH_2). ^{1}H NMR (DMSO, δ ppm): 1.81 (s, 3H, CH_3), 2.01 (s, 2H, NH_2), 2.9 (s, 3H, CH_3), 8.2-8.6 (m, 4H, Ar-H), 8.68 (br. s., 2H, 2NH). MS (m/z, %): 308 (M^++2, 43). Anal. Calcd. for $C_{12}H_{14}N_6O_2S$ (306.34): C, 47.05; H, 4.61; N, 27.43; S, 10.47. Found: C, 46.91; H, 4.64; N, 27.50; S 10.55.

2.5. Reaction of 12 with formic acid: Formation of 3-methyl-E-2-(1-(2-(1,3,4-thiadiazol-2-yl)-hydrazono)-ethyl)-quinoxaline 1,4-dioxide (15)

A mixture of **12** (1 g, 3 mmol) and formic acid (15 mL) was heated under reflux for 4 hours. The reaction mixture was then allowed to stand overnight at room temperature. The excess formic acid was evaporated under *vacuo* and the residue was crystallized from ethanol to give **15**. Dark yellow crystals, M.p.: 80 °C. Yield: 60%. IR (KBr, ν_{max}, cm^{-1}): 3315 (NH), 1610 (C=N), 1330 (N→O). ^{1}H NMR (DMSO, δ ppm): 2.91 (s, 3H, CH_3), 2.95 (s, 3H, CH_3), 7.0 (s, 1H, NH), 7.5 (s, 1H, CH), 8.1-8.6 (m, 4H, Ar-H). MS (m/z, %): 316 (M^+, 71). Anal. Calcd. for $C_{13}H_{12}N_6O_2S$ (316.34): C, 49.36; H, 3.82. Found: C, 49.39; H, 3.87.

2.6. Synthesis of 2,6-dimethyl-3-(2-hydroxy-2-oxoindolin-3-yl)acetyl)- quinoxaline-1,4-dioxide (16)

To a mixture of isatin (0.397 g, 2.7 mmol) and 2,6-dimethyl-3-acetylquinoxaline-1,4-dioxide (**10b**) (0.627 g, 2.7 mmol) in absolute ethanol (15 mL), 5 drops of piperidine were added and the reaction mixture was allowed to stand overnight at room temperature. The separated crystals was filtered off and crystallized from ethanol to give **16**. Dark yellow powder, M.p.: >300 °C. Yield: 90%. IR (KBr, ν_{max}, cm^{-1}): 1335 (N→O), 1700 (cyclic imide), 3447 (OH). ^{1}H NMR (DMSO, δ ppm): 2.33 (s, 3H, CH_3), 2.91 (s, 3H, CH_3), 3.65 (s, 1H, OH), 4.13 (s, 2H, CH_2), 6.85-7.72 (m, 7H, Ar-H), 8.2 (s, 1H, NH). MS (m/z, %): 379 (M^+, 14). Anal. Calcd. for $C_{20}H_{17}N_3O_5$ (379.37): C, 63.32; H, 4.52; N, 11.08. Found: C, 63.25; H, 4.47; N, 11.00.

2.7. Synthesis of (E)-2,6-dimethyl-3-(2-oxoindolin-3-ylidene)acetyl)-quinoxalin-1,4-dioxide (17)

A mixture containing **16** (1.897 g, 5 mmol), (0.5 mL) conc. HCl, and glacial acetic acid (20 mL) was refluxed for 2 hours and then left to stand at room temperature overnight, fine needles were formed. The formed precipitate was filtered off and recrystallized from acetic acid to give **17**. Brownish yellow powder, M.p.: 265 °C. Yield: 65%. IR (KBr, ν_{max}, cm^{-1}): 1725 (α,β-unsaturated ketone), 1330 (N→O). ^{1}H NMR (DMSO, δ ppm): 2.34 (s, 3H, CH_3), 2.91 (s, 3H, CH_3), 6.97-8.74 (m, 7H, Ar-H), 7.32 (s, 1H, CH), 8.2 (s, 1H, NH). MS (m/z, %): 362 (M^++1, 35). Anal. Calcd. for $C_{20}H_{15}N_3O_4$ (361.35): C, 66.48; H, 4.18; N, 11.63. Found: C, 66.40; H, 4.13; N, 11.70.

2.8. Synthesis of 3-cinnamoyl-2,6-dimethyl-quinoxalin-1,4-dioxides (18)

A mixture of 2-methyl-3-acetyl-quinoxalin-1,4-dioxide (**10a**) (0.655 g, 3 mmol) and benzaldehyde (0.318 g, 3 mmol) in methanolic sodium hydroxide (10 mL, 5%) was stirred for 5-10 minutes at room temperature. The formed yellow to orange precipitate was filtered off, washed with water and crystallized from the appropriate solvent (acetic acid) to give the cinnamoyl derivative **18**. Yellow crystals, M.p.: 197 °C. Yield: 80%. IR (KBr, ν_{max}, cm^{-1}): 1725 (C=O), 1590 (C=C), 1242, 1325 (N→O). ^{1}H NMR (DMSO, δ ppm): 2.31 (s, 3H, CH_3), 2.9 (s, 3H, CH_3), 6.7 (d,

1H, CH), 7.7 (d, 1H, CH), 7.2-7.8 (m, 8H, Ar-H). MS (m/z, %): 321 (M^++1, 23). Anal. Calcd. for $C_{19}H_{16}N_2O_3$ (320.34): C, 71.24; H, 5.03. Found: C, 71.19; H, 5.00.

2.9. Synthesis of 2,6-dimethyl-3-(5-phenyl-4,5-dihydro-1H-pyrazole-3-yl)quinoxalin-1,4-dioxide (19)

To a solution of **18** (0.961 g, 3 mmol) in ethanol (15 mL), hydrazine hydrate (98%, 0.0751 g, 1.5 mmol) was added. The reaction mixture was refluxed for 3 hours and left to cool. The crystalline precipitate was filtered off, dried and crystallized from ethanol to give **19**. Yellowish crystals, M.p.: 184 °C. Yield: 70%. IR (KBr, ν_{max}, cm^{-1}): 3250 (NH), 1620 (C=N), 1320 (N→O). ^{1}H NMR (DMSO, δ ppm): 2.3 (s, 3H, CH_3), 2.9 (s, 3H, CH_3), 3.9 (dd, *J*=1.90 Hz, 1H, CH), [3.19 (dd, *J*=1.85 Hz, 1H), 3.44 (dd, *J*=1.85 Hz, 1H) CH_2], 7.06-7.72 (m, 8H, Ar-H), 8.3 (s, 1H, NH). MS (m/z, %): 333 (M^+-1, 63). Anal. Calcd. for $C_{19}H_{18}N_4O_2$ (334.37): C, 68.25; H, 5.43. Found: C, 68.00; H, 5.20.

2.10. The reaction of 18 with phenyl hydrazine: Synthesis of 2,6-dimethyl-3-(1,5-diphenyl-4,5-dihydro-1H-pyrazol-3-yl)-quinoxaline-1,4-dioxide (20)

Compound **18** (0.961 g, 3 mmol) was boiled with phenyl hydrazine (0.162 g, 1.5 mmol) in acetic acid (10 mL) for 3 hours. The reaction mixture was left to cool and poured into crushed ice. The formed precipitate was filtered, dried and crystallized from ethanol to give **20**. Lemon yellow crystals, M.p.: 105 °C. Yield: 67%. IR (KBr, ν_{max}, cm^{-1}): 1620 (C=N), 1320 (N→O). ^{1}H NMR (DMSO, δ ppm): 2.34 (s, 3H, CH_3), 2.91 (s, 3H, CH_3), 3.90 (dd, *J*=1.95 Hz, 1H, CH), 3.20 (dd, *J*=1.88 Hz, 1H), 3.40 (dd, *J*=1.88 Hz, 1H) CH_2, 7.2-7.5 (m, 13H, Ar-H). MS (m/z, %): 410 (M^+, 62). Anal. Calcd. for $C_{25}H_{22}N_4O_2$ (410.47): C, 73.15; H, 5.40; N, 13.65. Found: C, 73.00; H, 5.11; N, 13.58.

2.11. The reaction of 18 with hydroxylamine hydrochloride: Synthesis of 2,6-dimethyl-3-(5-phenyl-4,5-dihydroisoxazol-3-yl)-quinoxaline-1,4-dioxide (21)

A mixture of **18** (0.961 g, 3 mmol), hydroxylamine hydrochloride (0.104 g, 1.5 mmol), sodium hydroxide (0.1 g, 2.5 mmol) and ethanol (15 mL) was refluxed for 4 hours. After cooling, the separated material was filtered off and crystallized from ethanol to give **21**. Light yellow crystals, M.p.: 102 °C. Yield: 72%. IR (KBr, ν_{max}, cm^{-1}): 1626 (C=N), 1340 (N→O). ^{1}H NMR (DMSO, δ ppm): 2.34 (s, 3H, CH_3), 2.91 (s, 3H, CH_3), [3.13 (dd, *J*=2.03 Hz, 1H), 3.39 (dd, *J*=2.03 Hz, 1H) CH_2], 5.96 (dd, *J*=2.09 Hz, 1H, CH), 7.06-7.70 (m, 8H, Ar-H). MS (m/z, %): 335 (M^+, 18). Anal. Calcd. for $C_{19}H_{17}N_3O_3$ (335.36): C, 68.05; H, 5.11; N, 12.53. Found: C, 68.30; H, 5.36; N, 12.65.

2.12. Synthesis of 2,6-dimethyl-3-(2-pyridinyl-4,6-diphenyl)quinoxalin-1,4-dioxide (24)

To a solution of phenacyl pyridinium bromide (**22**) (0.834 g, 3 mmol) and ammonium acetate (2 g) in glacial acetic acid (10 mL) a solution of **18** (0.961 g, 3 mmol) in glacial acetic acid (10 mL) was added gradually with continuous stirring. The reaction mixture was refluxed for 2 h and then left to cool and poured into crushed ice. The formed precipitate was filtered off, dried and crystallized from methanol to afford **24**. Yellowish brown crystals, M.p.: 186 °C. Yield: 80%. IR (KBr, ν_{max}, cm^{-1}): 3000-3077 (CH streching), 1620 (C=N), 1330 (N→O). ^{1}H NMR (DMSO, δ ppm): 2.35 (s, 3H, CH_3), 2.93 (s, 3H, CH_3), 8.11 and 8.56 (2s, 2H, Py H`s), 7.06-8.30 (m, 13H, Ar-H). MS (m/z, %): 419 (M^+, 30). Anal. Calcd. for $C_{27}H_{21}N_3O_2$ (419.47): C, 77.31; H, 5.05. Found: C, 77.09; H, 4.89.

2.13. Synthesis of 3-(6-amino-5-cyano-4-phenylpyridine-2-yl)-2,6-dimethyl-quinoxalin-1,4-dioxide (25)

A mixture of **18** (0.961 g, 3 mmol), malononitrile (0.198 g, 3 mmol) and ammonium acetate (0.164 g, 2 mmol) was heated at 150 °C for 4 hours. The solid material was washed with water and recrystallized from benzene to give **25**. Coffee Brown crystals, M.p.: 100 °C. Yield: 70%. IR (KBr, ν_{max}, cm^{-1}): 3470 (NH_2), 2220 (CN), 1640 (C=N), 1320 (N→O). ^{1}H NMR (DMSO, δ ppm): 2.30 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 7.05-7.70 (m, 8H, Ar-H), 7.60 (s, 2H, NH_2), 8.2 (s, 1H, py-H). MS (m/z, %): 383 (M^+, 90). Anal. Calcd. for $C_{22}H_{17}N_5O_2$ (383.40): C, 68.92; H, 4.47; N, 18.27. Found: C, 69.03; H, 4.53; N, 18.45.

2.14. Synthesis of 2,6-dimethyl-3-(hydrazinecarbonyl)-quinoxalin-1,4-dioxide (26)

A mixture of 2,6-dimethyl-3-carboethoxyquinoxalin-1,4-dioxide (**10c**) (0.787 g, 3 mmol) and hydrazine hydrate (80%, 3 mL) in absolute ethanol (20 mL) was refluxed for 6 hours and left to stand overnight at room temperature. The separated crystals were filtered off, dried and crystallized from ethanol to give **26**. Yellow crystals, M.p.: 218 °C. Yield: 70%. IR (KBr, ν_{max}, cm^{-1}): 3380 (NH_2), 3350 (NH), 1650 (C=O), 1330 (N→O). ^{1}H NMR (DMSO, δ ppm): 2.00 (s, 2H, NH_2), 2.30 (s, 3H, CH_3), 2.91 (s, 3H, CH_3), 7.06 (s, 1H, Ar-H), 7.23 (d, 1H, Ar-H), 7.70 (d, 1H, Ar-H), 8.00 (s, 1H, NH). Anal. Calcd. for $C_{11}H_{12}N_4O_3$ (248.24): C, 53.22; H, 4.87; N, 22.57. Found: C, 53.07; H, 4.91; N, 22.64.

2.15. Synthesis of 2,6-dimethyl-3-(5-thioxo-1',3',4'-oxadiazolo-2'-yl)-quinoxalin-1,4-dioxide (27)

A mixture of **26** (1.201 g, 5 mmol) in ethanol (10 mL), potassium hydroxide (0.281 g, 5 mmol) in water (3 mL) and carbon disulfide (0.381 g, 5 mmol) was heated under reflux for 7 hours or until the evolution of H_2S ceased. The reaction mixture was left to cool, poured into crushed ice and acidified with conc. HCl. The precipitate was filtered off, washed with water, dried and crystallized from ethanol to give **27**. Brownish crystals, M.p.: 210 °C. Yield: 85%. IR (KBr, ν_{max}, cm^{-1}): 1595 (C=N), 1330 (N→O), 1300-1100 (C=S), 2600-2620 (SH). ^{1}H NMR (DMSO, δ ppm): 2.34 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 7.00 (s, 1H, NH), 7.06 (s, 1H, Ar-H), 7.23 (d, 1H, Ar-H), 7.70 (d, 1H, Ar-H). MS (m/z, %): 290 (M^+, 33). Anal. Calcd. for $C_{12}H_{10}N_4O_3S$ (290.30): C, 49.65; H, 3.47. Found: C, 49.77; H, 3.54.

2.16. Synthesis of 3,7-dimethyl-1,4-dioxyquinoxaline-2-carboxylic acid N`-(3,7-dimethyl-1,4-dioxyquinoaline-2-carbonyl)hydrazide derivative (29)

A mixture of **26** (0.721 g, 3 mmol), acetoacetanilide (0.532 g, 3 mmol) in glacial acetic acid (15 mL) was refluxed for 3 h. After cooling, the precipitate was filtered off, dried and recrystallized from acetic acid to give **29**. Dark yellow powder, M.p.: >300 °C. Yield: 60%. IR (KBr, ν_{max}, cm^{-1}): 3250, 3280 (NH/NH), 1700 (two C=O), 1327 (N→O). ^{1}H NMR (DMSO, δ ppm): 2.55 (s, 6H, $2CH_3$), 2.91 (s, 6H, $2CH_3$), 6.80-7.60 (m, 6H, Ar-H), 9.50 (br. s., 2H, NH/NH). MS (m/z, %): 432 (M^+-32, 20). Anal. Calcd. for $C_{22}H_{20}N_6O_6$ (464.43): C, 56.89; H, 4.34; N, 18.10. Found: C, 56.97; H, 4.42; N, 18.36.

2.17. Synthesis of 3-(3-carboxamido-2,6-dimethyl-1-phenylquinoxalin-1,4-dioxide)thiourea (30)

Phenylisothiocyanate (0.406 g, 3 mmol) was added to a solution of **26** (0.721 g, 3 mmol) in ethanol (20 mL) and the reaction mixture was heated for 4 hours on water bath then left to cool. The precipitated solid product was filtered off and

crystallized from ethanol to give **30**. Orange crystals, M.p.: 192 °C. Yield: 88%. IR (KBr, ν_{max}, cm^{-1}): 3250, 3300, 3350 (NH/NH), 1220 (C=S), 1350 (N→O). ^{1}H NMR (DMSO, δ ppm): 2.00 (s, 1H, NH), 2.34 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 4.20 (s, 1H, NH), 6.80-7.70 (m, 8H, Ar-H), 9.35 (s, 1H, NH), 9.55 (s, 2H, NH/NH). MS (m/z, %): 383 (M^+, 80). Anal. Calcd. for $C_{18}H_{17}N_5O_3S$ (383.42): C, 56.38; H, 4.47; N, 18.27. Found: C, 56.32; H, 4.41; N, 18.38.

2.18. Synthesis of 3-(2,6-dimethylquinoxalin-1,4-dioxide)-5-mercapto-4-phenyl-4H-1,2,4-triazole (31)

A solution of **30** (1.15 g, 3 mmol) in potassium hydroxide (10%, 20 mL) was refluxed for 8 hours. The reaction mixture was kept to stand overnight at room temperature, then poured into crushed ice and acidified with dilute acetic acid. The solid product was filtered off, washed with water, dried and crystallized from ethanol to give **31**. Orange powder, M.p.: 248 °C. Yield: 70%. IR (KBr, ν_{max}, cm^{-1}): 2600-2550 (SH), 1600 (C=N), 1337 (N→O), 1300-1100 (C=S). ^{1}H NMR (DMSO, δ ppm): 2.35 (s, 3H, CH_3), 2.91 (s, 3H, CH_3), 3.42 (s, 1H, SH), 7.05-7.55 (m, 8H, Ar-H). MS (m/z, %): 365 (M^+, 5), 366 (M^++1, 10). Anal. Calcd. for $C_{18}H_{15}N_5O_2S$ (365.41): C, 59.16; H, 4.14; N, 19.17; S, 8.78. Found: C, 59.32; H, 4.27; N, 19.10; S, 8.85.

2.19. Synthesis of 3-(2,6-dimethylquinoxalin-1,4-dioxide)-2-phenylimino-4-thiazolidinone (32)

To a solution of **30** (1.15 g, 3 mmol) in glacial acetic acid (20 mL) was added monochloroacetic acid (0.284 g, 3 mmol) and anhydrous sodium acetate (0.3 g). The reaction mixture was refluxed for 8 hours, then left to cool at room temperature and then poured into crushed ice. The separated solid was filtered off, washed thoroughly with water, dried and crystallized from ethanol to give **32**. Light yellow crystals, M.p.: 86 °C. Yield: 60%. IR (KBr, ν_{max}, cm^{-1}): 3250 (NH), 1680, 1600 (C=O), 1535 (C=N), 1335 (N→O). ^{1}H NMR (DMSO, δ ppm): 2.34 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 4.10 (s, 2H, CH_2), 7.06-7.70 (m, 8H, Ar-H). MS (m/z, %): 423 (M^+, 20). Anal. Calcd. for $C_{20}H_{17}N_5O_4S$ (423.45): C, 56.73; H, 4.05; N, 16.54; S, 7.57. Found: C, 56.68; H, 4.08; N, 16.45; S, 7.60.

2.20. Synthesis of 3-carbazido-2,6-dimethylquinoxalin-1,4-dioxide (33)

To a suspension of **26** (0.721 g, 3 mmol) in dioxane (10 mL) and acetic acid (10 mL), sodium nitrite (0.5 g) in water (1.3 mL) was added with stirring at 0-2 °C. Stirring was continued for further 30 minutes after complete addition of sodium nitrite solution. The separated material was filtered off, washed with water and crystallized from acetic acid to give **33**. Yellow crystals, M.p.: 78 °C. Yield: 55%. IR (KBr, ν_{max}, cm^{-1}): 2157 (strong N_3), 1691 (CO), 1341 (N→O). ^{1}H NMR (DMSO, δ ppm): 2.35 (s, 3H, CH_3), 2.93 (s, 3H, CH_3), 7.08 (s, 1H, Ar-H), 7.21 (d, *J*=7.5 Hz, 1H, Ar-H), 7.65 (d, *J*=7.5 Hz, 1H, Ar-H). MS (m/z, %): 259 (M^+, 35). Anal. Calcd. for $C_{11}H_9N_5O_3$ (259.22): C, 50.97; H, 3.50; N, 27.02. Found: C, 51.02; H, 3.56; N, 27.17.

2.21. Synthesis of 2,6-dimethyl-3-ethoxycarbonylamino quinoxalin-1,4-dioxide (34)

The azide **33** (0.778 g, 3 mmol) in absolute ethanol (30 mL) was refluxed for 5 hours and the reaction mixture was filtered while hot to remove any insoluble material. The filtrate was evaporated and the residue crystallized from ethanol to give **34**. Yellow crystals, M.p.: 200 °C. Yield: 72%. IR (KBr, ν_{max}, cm^{-1}): 3382 (NH), 1723 (CO, ester), 1339 (N→O). ^{1}H NMR (DMSO, δ ppm): 1.80 (t, *J*=13.7 Hz, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 3.50 (q, *J*=13.7 Hz, 2H, CH_2), 6.70-7.30 (m, 3H, Ar-H), 8.00 (s, 1H, NH). MS (m/z, %): 277 (M^+, 13). Anal. Calcd. for $C_{13}H_{15}N_3O_4$ (277.28): C, 56.31; H, 5.45; N, 15.15. Found: C, 56.43; H, 5.57; N, 15.27.

2.22. Synthesis of 2,6-dimethyl-3-isocyanatoquinoxalin-1,4-dioxide (35)

The azide **33** (0.778 g, 3 mmol) in dry toluene (20 mL) was refluxed for 3 hours. After cooling, the separated material was filtered off, dried and crystallized from benzene to give **35**. Reddish crystals, M.p.: 244 °C. Yield: 66%. IR (KBr, ν_{max}, cm^{-1}): 1700 (C=O), 1330 (N→O). ^{1}H NMR (DMSO, δ ppm): 2.38 (s, 3H, CH_3), 2.91 (s, 3H, CH_3), 7.30 (d, *J*=8.30 Hz, 1H, H7), 7.70 (d, *J*=8.30 Hz, 1H, H8), 7.06 (s, 1H, H5). MS (m/z, %): 230 (M^+-1, 70). Anal. Calcd. for $C_{11}H_9N_3O_3$ (231.21): C, 57.14; H, 3.92. Found: C, 57.01; H, 3.80.

2.23. Synthesis of 3-amino-2,6-dimethylquinoxalin-1,4-dioxide (36)

The carbazide **33** (0.778 g, 3 mmol) in acetic acid (5 mL) and dioxane (5 mL) was heated for 30 minutes and then left to cool. The reaction mixture was poured into water (30 mL) and then extracted with ether (three times), dried over anhydrous magnesium sulfate; the solvent was evaporated under *vacuo* to afford **36**. Greyish crystals, M.p.: 202 °C. Yield: 70%. IR (KBr, ν_{max}, cm^{-1}): 3480-3440 (NH_2), 1350 (N→O). ^{1}H NMR (DMSO, δ ppm): 2.34 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 6.90 (s, 2H, NH_2), 6.06-7.70 (m, 3H, Ar-H). MS (m/z, %): 189 (M^+-16, 50), 173 (100). Anal. Calcd. for $C_{10}H_{11}N_3O_2$ (205.21): C, 58.53; H, 5.40. Found: C, 58.62; H, 5.52.

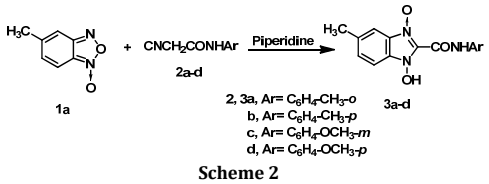
2.24. Diazotization and coupling of 40 with β–naphthol: Synthesis of 2,6-dimethyl-E-3((2-hydroxynaphthalen-1-yl)diazenyl)-quinoxalin-1,4-dioxide (37)

2,6-Dimethyl-3-aminoquinoxalin-1,4-dioxide (**36**) (0.616 g, 3 mmol) was dissolved in conc. hydrochloric acid (6 mL) and cooled to 0 °C in ice bath. Cold aqueous solution of sodium nitrite (0.3 g in 5 mL water) was added in small portions to the above amine hydrochloride solution. To the resulting sodium salt solution was added a cold solution of β–naphthol (0.433 g, 3 mmol) in sodium hydroxide (10%, 10 mL), the precipitated solid material was filtered off, washed with water and crystallized from ethanol to give **37**. Orange powder, M.p.: 238 °C. Yield: 80%. IR (KBr, ν_{max}, cm^{-1}): 3500 (OH), 1618 (C=N), 1495 (N=N), 1345 (N→O). ^{1}H NMR (DMSO, δ ppm): 2.30 (s, 3H, CH_3), 2.96 (s, 3H, CH_3), 5.40 (s, 1H, OH), 7.06-8.07 (m, 9H, Ar-H). MS (m/z, %): 360 (M^+, 27). Anal. Calcd. for $C_{20}H_{16}N_4O_3$ (360.37): C, 66.66; H, 4.48; N, 15.55. Found: C, 66.57; H, 4.53; N, 15.68.

3. Results and discussion

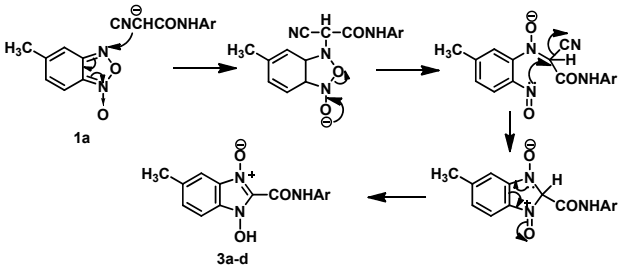
It is well established that Benzofuroxan derivatives exist at room temperature as a mixture of tautomers. The substituents in the benzene ring could occupy the 5- or 6-position and the proportion of both tautomers in the equilibrium depends on the electronic characteristics of the substituents [22].

The reaction of benzofuroxan (BFO) **1a** with the cyano-acetanilides **2a-d** in the presence of piperidine as catalyst at room temperature afforded the 2-(arylcarbamoyl)-1-hydroxy-5-methyl-1*H*-benzo[*d*]imidazol-3-oxide derivatives **3a-d,** respectively; (Scheme 2).



Scheme 2

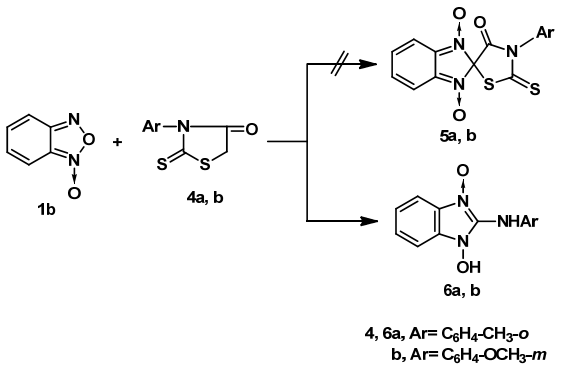
A probable mechanism, in line with other carbanion reactions of BFO's is outlined in (Scheme 3).



Scheme 3

The structures of **3a-d** were elucidated from their spectral and elemental analysis. Thus, the IR spectra of **3a-d** reveal the presence of OH and NH groups (3430 and 3250 cm^{-1}), respectively, amide carbonyl (1660 cm^{-1}), C=N (1620 cm^{-1}) and (N→O) functions (1236, 1317 cm^{-1}). The ^1H NMR spectrum of **3d** shows two singlets each integrated for 3H at δ 2.34 and 3.83 attributable to methyl and methoxy protons, respectively, and the aromatic protons appears at δ 7.07-7.50 (m, 7H, Ar-H), while the NH proton appears as a broad singlet at δ 9.15 ppm.

Moreover, rhodanines are important anticonvulsant [16], anti-inflammatory [17], antitubercular [18], and antibacterial agents [19]. So, compounds having a combination of benzofuroxan with rhodanine moieties are expected to posses marked biological properties. Unexpectedly when **1b** was reacted with rhodanines **4a**,**b** as active methylene compounds, in the presence of sodium ethoxide, 1-hydroxy-2-(arylamino)-1*H*-benzo[*d*]imidazole-3-oxide **6** was obtained instead of the thioxospirobenzoimidazole-thiazolidine-1,3-dioxide **5** (Scheme 4).

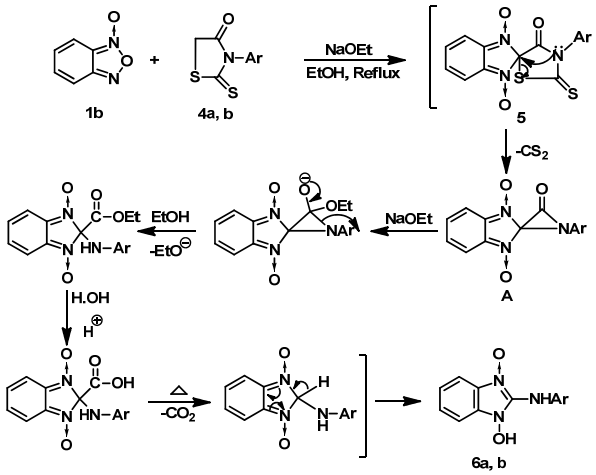


Scheme 4

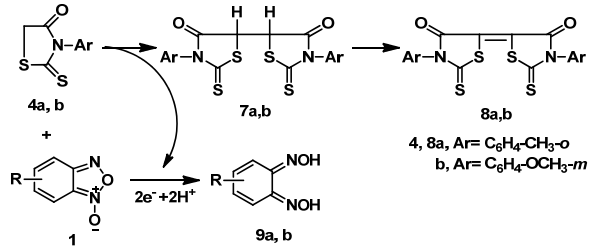
The IR, ^1H NMR and mass spectra of **6a**,**b** are in agreement with their proposed structures (Scheme 5).

If the above reaction afforded compound **5**, so, it would not have shown bands in both the IR and ^1H NMR spectrum for NH group.

On the other hand, we report here the reaction of BFO's with rhodanine in the presence of a weaker base, such as freshly fused sodium acetate and drops of acetic acid. This versatile synthesis has afforded novel compounds *hitherto* inaccessible by classical synthetic methods. Thus, surprisingly, the reaction of rhodanines **4a**,**b** with benzofuroxan **1a**,**b** and catalytic amount of freshly fused sodium acetate does not give the expected spiro benzimidazolyl-4-thiazolidinone **5**, but resulted in the formation of 2,2'-dithiano-$\Delta^{5,5'}$-bi-4-thiazo lidinones **7a**,**b** which are auto-oxidized to 2,2'-dithiano-$\Delta^{5,5'}$-bi-4-thiazolidinones **8a**,**b**, in which the benzofuroxan acts as oxidizing agent and in the same time it was reduced to *o*-quinone dioxime **9**. The oxidizing capacity [21] of benzofuroxan and its ability to oxidize rhodanine to the dimer derivatives **8a**,**b** via the formation of **7** based on initial one or two electron oxidation and the subsequent formation of *o*-quinone dioximes **9a**,**b** as side products are illustrated in (Scheme 6). The structures were assigned to the bi-thiazolidinones class on the basis of the chemical shift of the methyl groups and aromatic rings in the ^1H NMR spectra.



Scheme 5



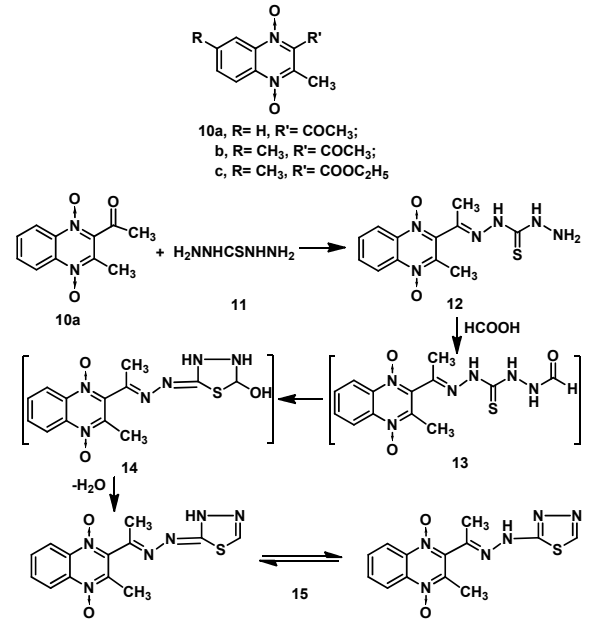
Scheme 6

In addition, thiocarbohydrazide has been reported to show tubercular activities [30], in vitro and high insecticidal activity towards the house-fly in comparison with DDT [31]. Thus, the quinoxaline *N*-dioxide **10a** reacts with the thiocarbohydrazide **11** to afford the condensation product **12** which reacts with excess formic acid to give 3-methyl-*E*-2-(1-(2-(1,3,4-thiadiazol-2-yl)hydrazono)ethyl)-quinoxaline-1,4-dioxide **15** presumably via the intermediates **13** and **14**. Here, formic acid was expected to reduce the C=N to the corresponding secondary amine, however, formylation of NH_2 group took place and the intermediate **14** was formed, which then loses a water molecule to give **15**. All attempts to isolate the intermediate **14** failed (Scheme 7).

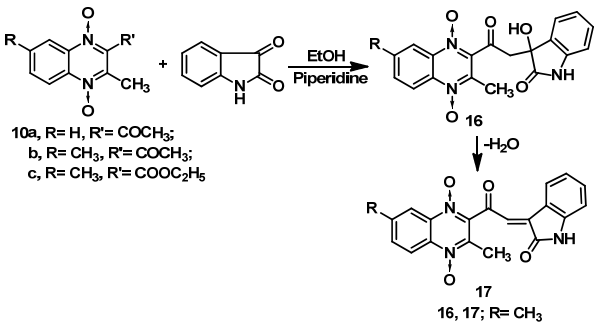
Structures **12** and **15** were established on the basis of analytical and spectral data (see experimental part).

On the other hand, it has been found that the reaction of isatin with quinoxaline derivatives **10b** [29], in the presence of piperidine, afforded 3-(2-hydroxy-2-oxoindolin-3-yl)acetyl)-2,6-dimethyl-quinoxalin-1,4-dioxide **16**, in quantitative yield (Scheme 8). The structure of **16** was established from micro analytical data as well as the IR spectrum which showed well defined bands in the region 3447 cm^{-1} (OH) and 1700 cm^{-1} (cyclic imide). Dehydration of **16** by dilute alcoholic hydrochloric acid or by hydrochloric acid in the presence of acetic acid gave (*E*)-2,6-dimethyl-3-(2-oxoindolin-3-ylidene)acetyl) quinoxaline-1,4-dioxide **17** in good yield. IR spectrum of **17**

showed a characteristic band at 1725-1703 cm^{-1} (α,β-unsaturated ketone).



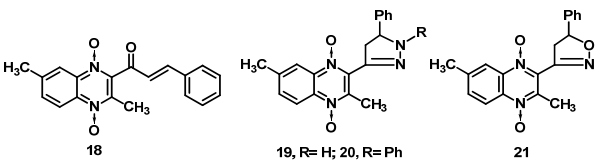
Scheme 7



Scheme 8

α,β-Unsaturated ketones provide a valuable intermediate for building up various heterocycles. Thus, condensation of hydrazine hydrate or phenyl hydrazine with 3-cinnamoyl-2,6-dimethylquinoxaline-1,4-dioxide **18** in boiling ethanol yielded the yellow pyrazoline derivative, 2,6-dimethyl-3-(5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)quinoxaline-1,4-dioxide **19** and its *N*-phenyl isomer **20**, respectively.

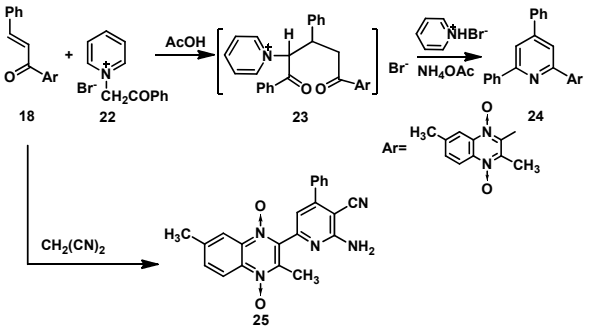
The formation of an isoxazoline ring could be effected by the reaction of **18** with hydroxylamine. Thus, when **18** was boiled with hydroxylamine hydrochloride in alcoholic sodium hydroxide solution, the corresponding isoxazoline; 3-(3-quinoxaliolyl-2,6-dimethyl-1,4-dioxide)-5-phenyl-4,5-dihydro-1H-isoxazoline **21** was obtained (Scheme 9).



Scheme 9

Krohnke [30] and Madhar [31] studied the reactivity of pyridinium ylides; however their synthetic applications remained unexplored. With a view to explore the synthetic potentiality of this reaction we report here the synthesis of 3-pyridyl-2,6-dimethylquinoxaline-1,4-dioxide **24** via the cyclization reaction of the α,β–unsaturated ketone **18** with *N*-phenacyl pyridinium bromide **22** in acetic acid in the presence of ammonium acetate as the cyclization agent.

The reaction presumably proceeds via the intermediary of ylide carbanion which is generated from pyridinium salt (Scheme 10). This undergoes Michael type addition to α,β–unsaturated carbonyl systems to yield 1,5-dicarbonyl pyridinium derivative **23** as intermediate which on reaction with ammonium acetate gave **24**.



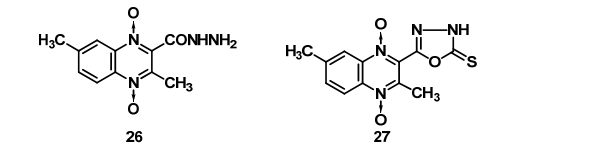
Scheme 10

The condensation of **18** with malononitrile in the presence of ammonium acetate gave 3-(6-amino-5-cyano-4-phenyl pyridine-2-yl)-2,6-dimethylquinoxaline-1,4-dioxide **25**. Structures **24** and **25** were supported by ^{1}H NMR and IR spectral data (see experimental part).

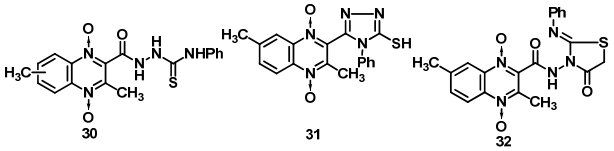
When 2,6-dimethyl-3-carbethoxyquinoxalin-1,4-dioxide **10c** was allowed to react with hydrazine hydrate (80%), 2,6-dimethyl-3-(hydrazinecarbonyl)-quinoxalin-1,4-dioxide **26** was obtained. Treatment of **26** with potassium hydroxide and carbon disulphide gave 2,6-dimethyl-3-(5-thioxo-4,5-dihydro-1',3',4'-oxadiazol-2'-yl)quinoxalin-1,4-dioxide **27**.

Unexpectedly, when the hydrazide **26** was heated with acetoacetanilide in the presence of acetic acid, the product was not the expected 3-pyrazole-1-carbonylquinoxaline derivative **28** but the 3,7-dimethyl-1,4-dioxyquinoxaline-2-carboxylic acid *N*`-(3,7-dimethyl-1,4-dioxyquinoaline-2-carbonyl)hydrazide derivative **29** was obtained (Scheme 11).

On refluxing the hydrazide **26** in dry ethanol with phenylisothiocyanate, the 1-phenyl-3-(2,6-dimethyl-3-carbox amido-quinoxalin-1,4-dioxide)thiourea **30** was separated out. Heating the thiourea derivative **30** under reflux with chloroacetic acid and sodium acetate in acetic acid produced 3-(2,6-dimethylquinoxalin-1,4-dioxide)-2-phenylimino-4-thia-zolidinone **32** in good yield (Scheme 12).



Scheme 11

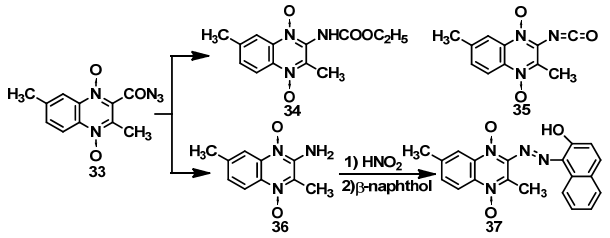


Scheme 12

The IR, ^{1}H NMR and mass spectra of **26-32** are in agreement with the proposed structures as shown in the experimental part.

2,6-Dimethyl-3-carbohydrazidoquinoxalin-1,4-dioxide **26** on treatment with HNO_2 gave 2,6-dimethyl-3-carbazidoquin oxalin-1,4-dioxide **33** which on refluxing with ethanol for 5 h produced 2,6-dimethyl-3-ethoxycarbonylamino quinoxalin-1,4-dioxide **34** in good yield. The IR spectra of compounds **33** and **34** were in agreement with assigned structures.

The decomposition of azides to isocyanate and nitrogen is known as the Curtius rearrangement. The reaction is a preparative method for isocyanate and compounds derivable from isocyanates, such as urethans, ureas, amides, and amines. When coupled with a hydrolytic step, the Curtius rearrangement becomes a particular procedure for replacing the azide group by an amino group. Thus azides undergo rearrangement in inert solvents like benzene, toluene and chloroform, forming isocyanates. In the presence of polar solvents like alcohol or water, the resulting isocyanate will react with these solvents to form urethans or ureas. Amines or their salts are obtained by hydrolysis of the isocyanate, urethans or ureas. However, heating of the carbazide **33** in toluene for 3 hours gives the isocyanate derivative **35**. On the other hand, hydrolysis of the carbazide **33** yielded the corresponding 3-amino-2,6-dimethylquinoxalin-1,4-dioxide derivative **36,** which is diazotized and coupled with β–naphthol in alkaline medium to afford the corresponding azo-β-naphthol derivative **37** (Scheme 13).



Scheme 13

4. Conclusion

We could prepare some novel benzimidazole and thiazolidinone derivatives from Benzofuroxan. Moreover, a series of quinoxalinyl 1,4-di-*N*-oxide derivatives could be derived from quinoxalin-1,4-di-*N*-oxides. Plausible mechanisms to account for the formation of the products are suggested. All the reactions are eco-friendly, no heavy metals or hazardous solvents (mostly ethanol and acetic acid) are involved.

Acknowledgement

F. M. Abdelrazek thanks the Alexander von Humboldt Foundation (Germany) for granting short research fellowships and Prof. Dr. Peter Metz, Institute of Organic Chemistry, TU-Dresden, for his kind hospitalities. This work was also supported in part by the Research fund of the Faculty of Science, Cairo University.

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