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Synthesis of Several New Isoxazole, Imidazo[1,2-a]pyridine, Imidazo[1,2-a]pyrimidine, Benzoxadiazine and Benzothiazine Derivatives from Hydroximoyl Halides

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Abstract □ Furoylhydroximoyl chloride **3** reacted with 2-aminopyridine, 2-aminopyrimidine, *O*-aminophenol, *O*-phenylenediamine and aminothiophenol to afford imidazo[1,2-a]pyridine **6**, imidazo[1,2-a]pyrimidine **8**, benzoxadiazine **10**, nitrosobenzopyrazine **13a** and nitrosobenzothiazine **13b**, respectively. Isoxazoline **18** and pyrrolidino[3,4-d]isoxazolin-4,6-dione derivatives **19a** and **19b** obtained by the reaction of **3** with acrylonitrile and N-arylmaleimide. Hydroximoyl chloride **3** reacted with thiophenol and sodium benzenesulfinate to yield furylglyoxaloxime **16a** and **16b**, respectively. Hydroximoyl chloride **3** reacted also with some active methylene compound to give isoxazole derivatives **20-23**, respectively.

Keywords □ Hydroximoyl chlorides, imidazo[1,2-a]pyridines, imidazo[1,2-a]pyrimidines benzoxadiazines, benzothiazines, isoxazoles.

2-Oxazolines have been widely investigated for therapeutic uses, especially as tranquilizing agents and CNS regulants. They were also reported to have bacteriostatic, bactericidal and fungicidal activities[1]. In conjunction with our previous work[2-5], we reported here in the synthesis of several derivatives of isoxazole, imidazo[1,2-a]pyridine, imidazo[1,2-a] pyrimidine, pyrrolidino[3,4-d]isoxazolin-4,6-dione, benzo-1,2,4-oxadiazine and benzothiazine required for biological screening.

EXPERIMENTAL

Melting points were determined on a Galleen-Kamp melting piont apparatus and are uncorrected. IR spectra (KBr): on Pye Unicam sp-1000 spectrophotometer – ^{1}H-NMR spectra: Gemini 200 MHz – int. stand. $CDCl_3$: Chemical shifts in δ ppm. Elemental analyses were carried out in Microanalytical centre at Cairo University. 2-Bromoacetylfuran **1** was prepared as following lit[11,12].

1-(2'-furyl)ethane-1-one-2-dimethylsulfonium bromide, 2

A mixture of **1** (18.9g, 0.1 mol) and dimethylsulfide (6.2g, 0.1 mol) in ethanol (100 m*l*) was refluxed for 1h. The solvent was evaporated to one-half of its volume, ether (100 m*l*) was added, the solid so formed was collected and crystallized from ethanol to give **2** : 21.3g (85%) mp. 149℃ -$C_8H_{11}BrSO_2$ (251.13) calcd. C 38.3, H 4.41, Br 31.8, S 12.8, found C 38.4, H 4.40 Br 31.7, and S 12.6.

(2'-furoyl)hydroximoyl chloride, 3

To a solution of **2** (10g, 0.04 mol) and sodium nitrite (3.5g, 0.05 mol) in water (50 m*l*) and dioxan (50 m*l*). 100 m*l* of conc. HCl was added with stirring for a period of 1h at room temp. Stirring was continued for 2h to produce a page solid which was separated by filteration and crystallized from benzene to give **3**

5.2g (75%) mp. 185℃ -$C_6H_4ClNO_3$ (173.5) calcd. C 41.52, H 2.32, Cl 20.43, N 8.07, found C 41.6, H 2.40, Cl 20.2, N 7.9.

Synthesis of imidazopyridine 6 and imidazopyrimidine, 8

3 (0.85g, 0.005 mol) and 2-aminopyridine or 2-aminopyrimidine, (0.005 mol) in ethanol (25 m*l*), were stirred for 2h at room temperature. The green solid so formed was collected and crystallized from ethanol to give **6** and **8**, respectively.

2(2'-furyl)-3-nitrosoimidazo[1,2-a]pyridine, 6

0.9g (85%) mp. 195℃ -$C_{11}H_7N_3O_2$ (213.2) calcd. C 61.97, H 3.30, N 19.70, found C 61.9, H 3.40, N 19.8.

2(2'-furyl)-3-nitrosoimidazo[1,2-a]pyrimidine, 8

0.8g (75%) mp>360℃ -$C_{10}H_6N_4O_2$ (214.1). calcd. C 56.09, H 2.82, N 26.16, found C 55.8, H 2.90, N 26.1.

Synthesis of 2(2'-furoyl)-(4H)-1,3,4-benzoxadiazine, 10

3 (0.86g, 0.005 mol) and *O*-aminophenol (1.1g, 0.01 mol) in ethanol (20 m*l*) were stirred for 24h. at room temperature, the brown solid formed was collected, washed with water, recrystallized from ethanol to give **10**. 0.73g, (64%) mp. 133℃ -$C_{12}H_8N_2O_3$ (228.21) calcd. C 63.15, H 3.53, N 12.27, found C 63.2, H 33.70, N 12.4.

Synthesis of 2(2'-furyl)-3-nitroso-1,4-dihydrobenzopyrazine, 13a and 2(2'-furyl)-3-nitrosobenzo-1,4-thiazinee, 13b

3 (0.86g, 0.005 mol) and each of *O*-phenylenediamine (11.1g, 0.01 mol) in ethanol (25 m*l*) were stirred for 2h at room temperature. The yellow solid was collected and crystallized from ethanol to give **13a** and **13b**, respectively. **13a**, 1g (94%) mp. 228℃ -$C_{12}H_9N_3O_2$ (227.2) calcd. C 63.43, H 3.99, N 18.49, found C 63.4, H 4.00, N 18.3. **13b**, 1.1g (95%) mp. 232℃ -$C_{12}H_8N_2SO_2$ (244.2) calcd. C 59.02, H 3.30, N 11.47, S 13.12, found C 59.2, H 3.40, N 11.30, S 13.0.

Synthesis of 2 (2'-furyl)3-nitrosobenzopyrazine, 15

13a (1g) in acetic acid (15 m*l*) and hydrogen peroxide (30%, 5 m*l*) were stirred for 24h. at room temperature. The pale yellow precipitated was collected and crystallized from ethanol to give **15**: 0.51g (49 %), mp. 185℃ -$C_{12}H_7N_3O_2$ calcd. C 64.00, H 3.13, N 18.65, found C 64.9, H 3.10, N 18.5

Synthesis of 2-phenylsulfoxyfurylglyoxaloxime, 16a and 2-benzenesulfonylfurylglyoxaloxime, 16b

3 (0.86g, 0.005 mol) and sodium thiophenolate (0.005 mol) (prepared by dissolving thiophenol (0.5g, 0.005 mol) in ethanol containing sodium metal (0.11 g-atom) or sodium benzenesulfinate (0.82, 0.005 mol) in ethanol (20 m*l*) were stirred for 2h. The solid so formed was collected and crystallized from ethanol to give **16a** and **16b**, respectively. **16a** 1g (82%), mp. 114℃ -$C_{12}H_9NSO_3$ (247.2) calcd. C 58.30, H 3.66, N 5.66, S 12.96, found C 58.3, H 3.70, N 5.80, S 13.2-IR spectrum 1660 (CO), 2400-3200 (OH)-^{1}H-NMR spectrum (δ ppm) at 6.8-0 (m, 8H, ArH's and furan) and 10.8 (s, 1H, NOH). **16b**, 1.38g (95%), mp. 103℃ -$C_{12}H_9NSO_5$ (279.3) calcd. C 51.60, H 3.24, N 5.01, S 11.47, found C 51.50, H 3.40, N 5.10, S 11.60. IR spectrum: 1140, 1350 (SO_2), 1660 (CO), 2240-3100 (OH). ^{1}H-NMR spectrum (δ ppm) at 6.8-7.6 (m, 8H, ArH's and furan) and 10.6 (s, 1H, NOH).

Synthesis of 18 and 19a,b

A solution of **3** (0.086g, 0.005 mol) and acrylonitrile or the appropriate N-arylmaleimide (0.005 mol) in toluene (30 m*l*) was refluxed for 12h. The solvent was evaporated under vacuo and the residue was treated with pet. ether (60/80℃, 30 m*l*). The solid so formed was collected and crystallized from acetic acid to give **18** and **19a-b**, respectively.

5-Cyano-3(2'-furoyl)4,5-dihydro-5-isoxaole, 18

0.82g (87%), mp. 118℃ -$C_9H_6N_2O_3$ (190.2) calcd. C 56.83, H 3.17, N 14.72, found C 56.70, H 3.20, N 14.9.

3(2'-furoyl)-5-phenylpyrrolidino[3,4-d]isoxazolin-4,6-dione, 19a

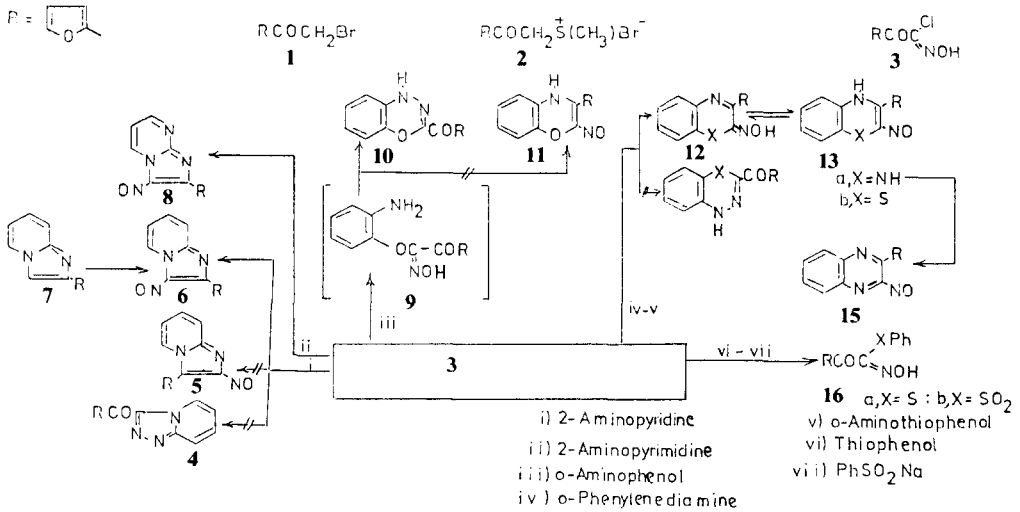
1.1g (76%) mp. 160-1℃ -$C_{16}H_{10}N_2O_5$ (310.3), calcd. C 61.93, H 3.24, N 9.02, found C 62.00, H 3.10, N 8.80.

3(2'-furoyl)-5-p-tolylpyrrolidino[3,4-d]isoxazolin-4,6-dione, 19b

1.1g (68%), mp. 177-8℃ -$C_{17}H_{12}N_2O_5$ (324.4), calcd. C 62.49, H 3.72, N 8.63, found C 62.80, H 3.80, N 8.80.

Synthesis of 20-23

3 (0.86g, 0.005 mol) in ethanol (10 m*l*) and the appropriate of acetylacetone, acetoacetanilide, β-



Scheme 1.

ketosulfone and or benzoylacetonitrile (0.005 mol) in ethanol (15 ml) containing 0.11g-atom sodium metal were stirred for 2h at room temperature. The precipitated was collected and crystallized from ethanol to give **20-23**, respectively.

4-acetyl-3-(2'-furoyl)-5-methylisoxazole, 20

0.7g (68%), mp. 73℃ -$C_{11}H_9NO_4$ (219.2) calcd. C 60.24, H 4.13, N 6.39, found C 60.10, H 4.10, N 6.3.

3-(2'-furoyl)-4-phenylcarbamoyl-5-methylisoxazole, 21

0.98 (64%), mp. 115℃ -$C_{16}H_{12}N_2O_4$ (296.3), calcd. C 64.85, H 4.08, N 9.45, found C 64.70, H 3.90, N 9.7-IR spectrum (cm^{-1}), 1660, 1680 (two CO) ^{1}H-NMR spectrum (δ ppm) 2.2 (s, 3H, CH_3 isoxazole C-5), 6.8-7.5 (m, 8H, ArH's and furan) and 8.0-8.2 (s, br., 1H, NH).

4-benzenesulfonyl-3-(2'-furoyl)-5-phenylisoxazole, 22a

1.2g (68%), mp. 151℃ -$C_{20}H_{13}NSO_5$ (379.4), calcd. C 63.32, H 3.45, N 3.69, S 8.44, found C 63.40, H 3.40, N 3.80, S 8.60.

4-benzenesulfonyl-3-(2'-furoyl)-5-furylisoxazole, 22b

1.1g (65%), mp. 167-8℃ -$C_{18}H_{11}NSO_6$ (363.3), calcd. C 58.54, H 3.00, N 3.79, S 8.66, found C 58.60, H 3.10, N 3.90, S 8.60.

4-benzenesulfonyl-3-(2'-furoyl)-5-thienylisoxazole, 22c

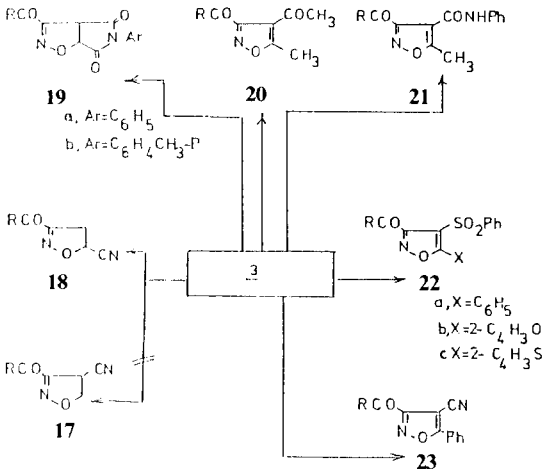
1.0 (60%), mp. 154-5℃ -$C_{18}H_{11}NS_2O_5$ (385.4), calcd. C 56.09, H 2.87, N 3.63, S 16.63, found C 56.00, H 3.70, H 3.80, S 16.50.

4-cyano-(2'-furoyl)-5-phenylisoxazole, 23

1g (76%) mp. 155℃ -$C_{15}H_8N_2O_3$ (264.2), calcd. C 68.18, H 3.05, N 10.60, found C 68.1, H 3.10, N 10.8.

RESULTS AND DISCUSSION

Hydroximoyl chloride **3** reacted with 2-aminopyridine in ethanol to give product $C_{11}H_7N_3O_2$ for which structures **4-6** seemed possible (cf. Scheme 1). Structure **4** was ruled out because no carbonyl band in the region 1650-1800 cm^{-1} in the IR spectrum of the reaction product. Structure **5** seems unlikely because 2-aminopyridine was reported to react with α-haloketones to give 2-substituted imidazo-[1,2-a]pyridines[6]. Furthermore, nitrosation of 2-(2'-furyl)imidazo[1,2-a]pyridine **7** yielded a product identical in all respect (mp., mixed mp. and spectra) with **6**. ^{1}H-NMR spectrum of **6** showed a one signal at δ 6.9-8.5 (m, ArH's and furan). Its IR spectrum absorption band at 1530 cm^{-1} due to nitroso group[7]. Based on the above results the 2-(2'-furyl)-3-nitrosoimidazo[1,2-a]pyridine structure **6** was ta-



Scheme 2.

ken to present the reaction product. Similarly, **3** reacted with 2-aminopyrimidine to give 2-(2′-furyl)-3-nitrosoimidazo[1,2-a]primidine **8**. **3** reacted with *O*-aminophenol in ethanol at room temperature to give a single product in 73% yield. On the basis of spectral data and elemental analyses, the product was assigned the structure of 2(2′-furoyl)-1,2,4-benzoxadiazine **10**. The reation take place through loss one molecule of hydrogen chloride give alicyclic **9** which easily cyclized by loss of one molecule of water to give **10** or **11**. The structure of **11** was ruled out because IR spectrum revealed band at 1650 cm $^{-1}$ due to the conjugated CO group and its ^{1}H-NMR (δ ppm) spectrum showed signals at 5.1 (s, 1H, NH) and 7.2-8.1 (m, 7H, ArH's and furan). **3** reacted also with *O*-phenylenediamine and *O*-aminothiophenol to afforded a single product in each case. On the basis of their spectral data and elemental analyses, the products were assigned as the structures of 2(2′-furyl)-3-nitrosobenzo-1,4-dihydropyrazine **13a** and 2(2′-furyl)-3-nitrosobenzo-1,4-dihydrothiazine **13b**, respectively the isomeric structure of **14** was rejected because the IR spectra revealed no band between 1650-1800 cm $^{-1}$ due to CO group. IR spectra of **13** showed a moderately strong band at 1540 cm $^{-1}$ due to the nitroso group[2,7], the presence of the nitroso group excludes the oxime structure **12**. **13a** was converted to **15** by hydrogen peroxide in acetic acid[5,8]. Also **3** reacted with sodium thiophenolate and sodium benzenesulfinate in ethanol to give the corresponding product **16a-b**, respectively. The structure of **16** was elucidated on the basis of elemental analyses and spectral data.

In order to examine the 1,3-dipolar cycloaddition reactivity, **3** was treated with acrylonitrile and with N-arylmaleimide in boiling toluene to give **18** and **19**, respectively (cf. Scheme 2). ^{1}H-NMR spectrum of **18** showed a signals at δ 3.8 (d, 2H, isoxazoline C-4), 5.4 (t, 1H, isoxazoline C-5) and 6.8-7.9 (m, 3H, furan). Its IR spectrum showed band at 1660 cm $^{-1}$ due to CO group and no absorption at 2220 cm $^{-1}$ for C≡N group, which supports the 5-cyano structure[4,9,10]. The N-arylmaleimide product was assigned as the structure of 3-(2′-furoyl)-5-arylpyrrolidino[3,4-d]isoxazolin-4,6-dione **19**. Its IR spectrum revealed absorption bands at 1660, 1710 and 1710-1780 cm $^{-1}$ due to CO and -CONRCO- groups, respectively. ^{1}H-NMR spectrum (δ ppm) of **19b** showed signals at 2.2 (s, 3H, Ar-CH_3-p), 4.7 (d, 1H, pyrrole C-4), 5.5 (d, 1H, pyrrole C-5) and 6.9-7.7 (m, 7H, ArH's and furan).

3 reacted with acetylacetone, acetoacetanilide, β-ketosulfones and benzoylacetonitrile in ethanolic sodium ethioxide solution to give isoxazoles **20-23**, respectively. The structures assigned for **20-23** were based on elemental analyses and spectral data. ^{1}H-NMR of 4-acetyl-3-(2′-furoyl)-5-methylisoxazole **20** showed signals at δ 2.3 (s, 3H, CH_3), 2.7 (s, 3H, CH_3CO) and 6.7-7.8 (m, 3H, furan). The IR spectrum of **20** revealed absorption bands at 1660 and 1680 cm $^{-1}$ due to (two CO) group.

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