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Facile Synthesis of Mono and Bisfurazanopiperazines

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Abstract

A simple and convenient synthesis of monofurazanopiperazine (4,5,6,7-tetrahydro[1,2,5]oxadiazolo[3,4-*b*]pyrazine) and bisfurazanopiperazine (4H,8H-bis[1,2,5]oxadiazolo[3,4-*b*;3′,4′-*e*]pyrazine) was achieved in excellent yields. Diaminofurazan was synthesized by the cyclocondensation of diaminoglyoxime under solvent-free condition and further used in the synthesis of both the compounds.

Keywords: *Heterocycles, Small rings, Diaminofurazan, Diaminoglyoxime, Energetic materials*

1. Introduction

Furazan is a five-membered heterocyclic compound with one oxygen and two nitrogen atoms. This heterocyclic ring has been established as a useful moiety for the design of potential high-energy molecules [1]. The derivatives of furazan are important owing to their relatively insensitive nature and favorable oxygen balance along with other attractive properties of energetic materials [2,3]. Furazan ring fused to a six-membered ring containing two heteroatoms in positions 1 and 4 such as furazano[3,4-*b*]pyrazine (**1**), furazano[3,4-*b*]oxazine (**2**), 1,4-dioxino[2,3-*c*]furazan (**3**), and 1,4-dithiino[2,3-*c*]furazan (**4**) (Figure 1) have been used in different applications including high-energy molecules. Furazan-based high-energy molecules are an interesting class of compounds owing to their low susceptibility and high compactness arising from the planarity of the ring, positive heat of formation, and high percentage of nitrogen content [4]. The close proximity of the three heteroatoms in the furazan ring provides the necessary electron-withdrawing character. Because of strong bond localization in this moiety, there is no possibility of annular-group tautomerization [5–8].

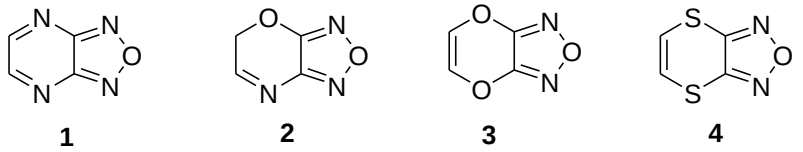
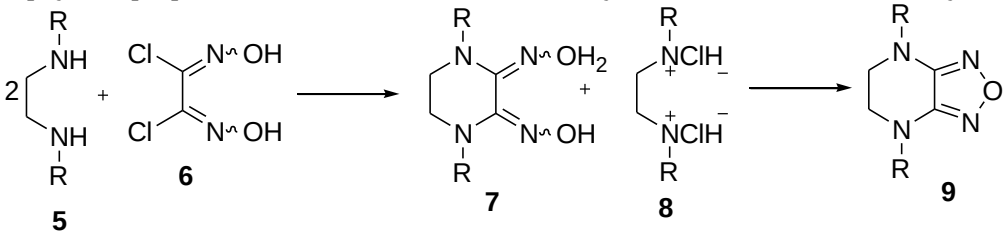


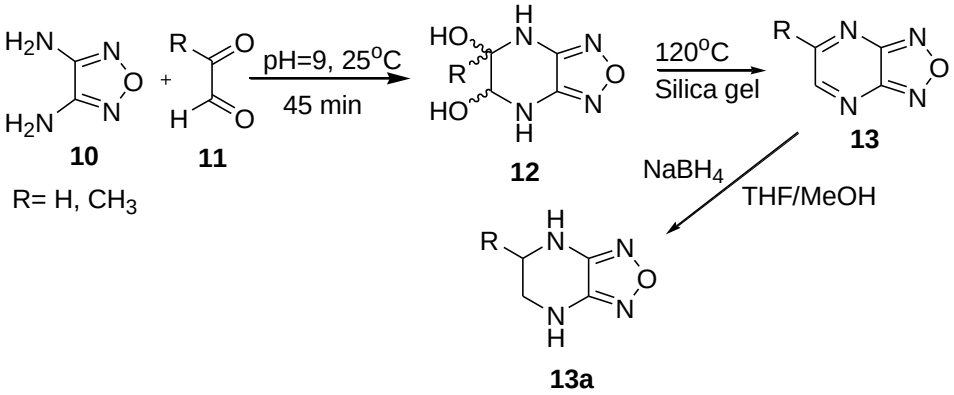
Figure 1. Furazan derivatives

Systematic studies on high-energy molecules based on furazanopiperazines have led to the development of diverse components for explosives and propellants. These studies have provided a deep insight into the chemistry and reactivities of furazanopiperazines and their polyfunctional derivatives [9]. However, it is challenging to synthesize these molecules in good yields and at low cost.4,5,6,7-Tetrahydro-[1,2,5]oxadiazolo[3,4-*b*]pyrazine (**9**) has been synthesized from *N*,*N*′-disubstituted 2,3-piperazinedione dioximes (**7**) following the base-promoted dehydration route (Scheme 1). The dioximes were synthesized by reacting the suitable *N*,*N*′-disubstituted ethylenediamine (**5**) with dichloroglyoxime (**6**). The main drawback was the isolation of products from the diamine dihydrochloride by-products because of similar physical properties of the unsubstituted and methyl derivative such as solubility [2].



Scheme 1. Synthesis of 4,5,6,7-tetrahydro-[1,2,5]oxadiazolo[3,4-*b*]pyrazine

Another synthetic route involves 3,4-diaminofurazan or 3,4-diamino[1,2,5]oxadiazole (**10**) and glyoxal, affording a diol (5,6-dihydroxy-4,5,6,7-tetrahydro[1,2,5]oxadiazolo[3,4-*b*]pyrazine (**12**) that on heating at 120 °C afforded [1,2,5]oxadiazolo[3,4-*b*]pyrazine (**13**). The reduction of **13** with sodium borohydride in THF furnished the desired monofurazanopiperazine (**13a**) in 92% yield (Scheme 2) [10]. Different analogs of furazanopiperazines have been synthesized by reacting diamine (**5)** with preformed glyoxal adducts in the presence of weakly basic amines or NH_4Cl in the presence of acids [11–13]. Very few synthetic routes are available for the synthesis of 4H,8H-bis[1,2,5]oxadiazolo[3,4-*b*;3′,4′-*e*]pyrazine (**19**) [14–16]. They have been synthesized from 3,4-diaminofurazan [15] and dihalofurazanopyrazines [16].



Scheme 2. Synthesis of monofurazanopiperazine from 3,4-diaminofurazan

2. Materials and methods

The solvents and reagents were purchased from reputed companies and used as received without further purification. The melting points were determined using a Thomas Hoover Unimelt capillary melting apparatus and uncorrected. The IR spectra were recorded using a Thermo Scientific, Nicolet 380 series FTIR spectrophotometer, and the ν_{max} values were expressed in cm^{-1}. The ^1H NMR spectra were recorded using a Bruker spectrophotometer (400 MHz) using TMS as the internal standard, and the chemical shifts are expressed in ppm. The abbreviations s and bs stand for singlet and broad singlet, respectively. The elemental analyses were carried out using a PerkinElmer 2400 CHNS/O elemental analyzer. The thin-layer chromatography (TLC) was performed on aluminum-coated silica plates purchased from Merck.

Diaminoglyoxime (15): Diaminoglyoxime (**15**) was prepared following the literature procedure [17]. Yield: 15.89 g (62%); yellow crystals; m.p. 203 °C (lit. [16] m.p. 203–205 °C); IR (KBr): NOH 3467, NH 3366, 2925, C=N 1653, N–O 938 cm^{-1}; ^1H NMR: (DMSO-d_6, 400 MHz) δ 5.15 (s, 4H NH_2), 9.75 (s, 2H, OH). Anal Calcd for $C_2H_6N_4O_2$: C, 20.34; H, 5.12; N, 47.44. Found: C, 20.33; H, 5.14; N, 47.43.

3,4-Diaminofurazan (10): In a 100 mL round-bottom flask equipped with a mechanical stirrer and thermometer, diaminoglyoxime (**15**, 1.5 g, 12 mmol) was added and heated at 170 °C (bath temperature) for 2 h. The reaction mixture was cooled to room temperature and extracted with ethyl acetate (3×50 mL). The ethyl acetate layer was concentrated under reduced pressure to afford diaminofurazan (**7**) as pale yellow crystals. Yield: 1.09 g (73%); m.p. 175 °C (lit. [17] m.p. 178–180 °C); IR (KBr): NH 3423, 3319, C=N 1636 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 5.79 (s, 4H, NH_2). Anal Calcd for $C_2H_4N_4O$: C, 24.00; H, 4.03; N, 55.98. Found: C, 24.03; H, 4.04; N, 55.97.

4,5,6,7-Tetrahydro-[1,2,5]oxadiazolo[3,4-*b*]pyrazine (9): To a solution of 3,4-diaminofurazan (**10**) (0.1 g, 1 mmol) in acetonitrile (3 mL), dibromoethane (0.188 g, 1 mmol) was added. K_2CO_3 (0.2 g) was added, and the reaction mixture was refluxed for 4 h till all the reactant was consumed (monitored by TLC, dichloromethane/methanol 4:1 v/v). After the completion of the reaction, the solvent was evaporated under vacuum, affording the crude product. The product was recrystallized from diethyl ether. Yield: 0.17 g (93%); yellow crystals; m.p. 150 °C. (lit. [10] m.p. 153–155 °C); IR (KBr): NH 3419, C=N 1667 cm^{-1}. ^1H NMR (acetone-d_6, 300 MHz) δ 2.95 (s, 4H), 5.30 (s, 2H). Anal Calcd for $C_4H_6N_4O$: C, 38.09; H, 4.80; N, 44.42. Found: C, 38.11; H, 4.82; N, 44.45.

4H,7H-[1,2,5]Oxadiazolo[3,4-*b*]pyrazine-5,6-dione (17): To a cooled solution of **10** (0.05 g, 0.5 mmol) in THF (5 mL), DBU (1 mL) was added. The mixture was stirred at 4–5 °C for 15 min. To this mixture, oxalyl chloride **16** (0.063 g, 0.5 mmol) was added using a dropping funnel at such a rate that the temperature did not increase beyond 4–5

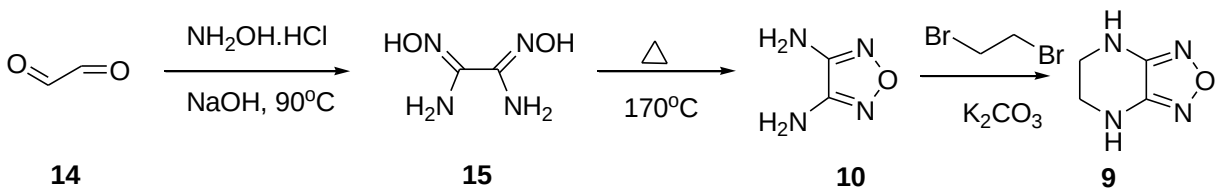
°C. After all the oxalyl chloride was added, the solution was stirred at room temperature for 6 h. The reaction was monitored by TLC (dichloromethane/methanol 4:1 v/v). After the completion of the reaction, water was added, and the reaction mixture was extracted with chloroform (3×50 mL). The organic layer was evaporated under reduced pressure, affording the crude product as a pure red solid. Yield: 0.04 g (80%); m.p. 275–278 °C, IR (KBr): CO 1740, C=N 1612, N–O 801 cm^{-1}; ^{13}C NMR (DMSO-d_6, 400 MHz): δ 144 (quaternary C) and 154 (CO). Anal Calcd for $C_4H_2N_4O_3$: C, 31.18; H, 1.31; N, 36.36. Found: C, 31.20; H, 1.34; N, 36.38.

4H,7H-[1,2,5]oxadiazolo[3,4-*b*]pyrazine-5,6-dione dioxime (18): NaOH (0.256 g, 6.4 mmol) was dissolved in cold ethanol (7 mL). To this mixture, hydroxylamine hydrochloride (0.451 g, 6.4 mmol) was added in portions over a period of 10 min. The reaction mixture was stirred for 10 min at 4–5 °C. The solution was filtered. To the filtrate, **17** (0.5 g, 3.24 mmol) was added in one portion. The precipitated crude product was filtered. The filtrate was evaporated under vacuum to obtain the product (**18**) in a crude form. This was recrystallized from ethanol. Yield: 0.45 g (90%); m.p. 315 °C, (lit. [16] m.p. 320 °C); white solid. IR (KBr): NOH 3432, N–O 848 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 10.59 (4H, s, NH, OH). Anal Calcd for $C_4H_4N_6O_3$: C, 26.09; H, 2.19; N, 45.65. Found: C, 26.11; H, 2.17, N, 45.75.

4H,8H-Bis[1,2,5]oxadiazolo[3,4-*b*;3′,4′-*e*]pyrazine (19): In a 100 mL round-bottom flask equipped with a mechanical stirrer and a thermometer, 4H,7H-[1,2,5]oxadiazolo[3,4-*b*]pyrazine-5,6-dione dioxime (**18**) (0.5 g, 2.7 mmol) was added, and the reaction mixture was heated at 170 °C (bath temperature) for 2 h. The reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 × 50 mL). The ethyl acetate layer was concentrated under reduced pressure to afford **19**. Yield: 0.41 g (83%); m.p. 290–292 °C, (lit [16] mp 294 °C); IR (KBr): NH 3250, C=N 1654 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 11.68 (s, 2H, NH); ^{13}C NMR: δ 142 (quaternary C). Anal Calcd for $C_4H_2N_6O_2$: C, 28.92; H, 1.21; N, 50.60. Found: C, 28.97; H, 1.19, N, 50.66.

3. Results and Discussions

The mono and bisfurazanopiperazines were synthesized as shown in Schemes 3 and 4. We modified the previous routes for synthesizing 4,5,6,7-tetrahydro-[1,2,5]oxadiazolo[3,4-*b*]pyrazine (**9**) and 4H,8H-bis[1,2,5]oxadiazolo[3,4-*b*;3′,4′-*e*]pyrazine (**19**) from an easily available and inexpensive starting material, glyoxal (**14**). The treatment of glyoxal with hydroxylamine hydrochloride in the presence of NaOH afforded diaminoglyoxime (**15**) [17]. Diaminoglyoxime was heated in solvent-free conditions, producing the condensed product. This was then coupled with dibromoethane to give **9** (Scheme 3). The reaction of glyoxal (**14**) with hydroxylamine hydrochloride is an example of nucleophilic substitution at the carbonyl group with the loss of oxygen atom. Hydroxylamine itself is very unstable and prone to aerial oxidation; hence, it is stored as the salt of hydrochloric acid. A base, often NaOH, is used to obtain the free hydroxylamine *in vitro*; hence, NaOH was used to obtain the free hydroxylamine. In this study, 4 moles of hydroxylamine hydrochloride were used for 1 mol of glyoxal to obtain the desired diaminoglyoxime (**15**) in 62% yield.



14 **15** **10** **9**

Scheme 3. Synthesis of 4,5,6,7-tetrahydro-[1,2,5]oxadiazolo[3,4-*b*]pyrazine from glyoxal

The cyclocondensation of diaminoglyoxime (**15**) with 3,4-diaminofurazan (**10**) is the typical step in the synthesis. The previous methods for the synthesis of 3,4-diaminofurazan involved the use of steel reactors [17], heating diaminoglyoxime in a high boiling solvent such as ethylene glycol [18], and the use of solid supported alkali or micelles [19]. These conventional methods suffer from harsh reaction conditions such as a long reaction time, high temperature, high pressure, and the use of special reaction vessels such as steel reactors [17,18]. Therefore, mild conditions with less reaction time and good yields are needed. We mainly focused on the cyclocondensation of **15** to **10** under different reaction conditions. Compound **15** was heated and later refluxed in high boiling solvents such as toluene, DMF, DMSO, and diphenyl ether, but could not obtain product **10** in a good yield. A better result was obtained by heating **15** under solvent-free condition at 170 °C. The prepared diaminofurazan was further used in the synthesis of both monofurazanopiperazine and bisfurazanopiperazine. The optimization of reaction condition is shown in figure 2.

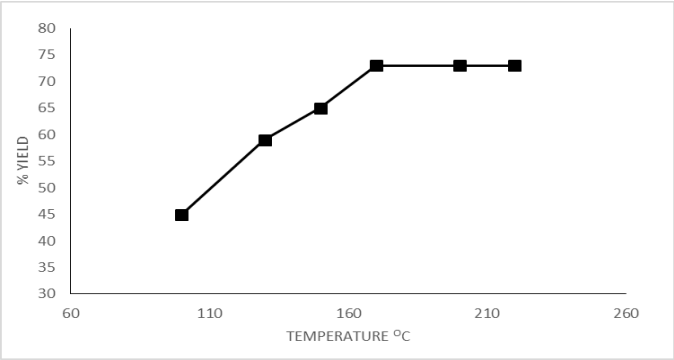
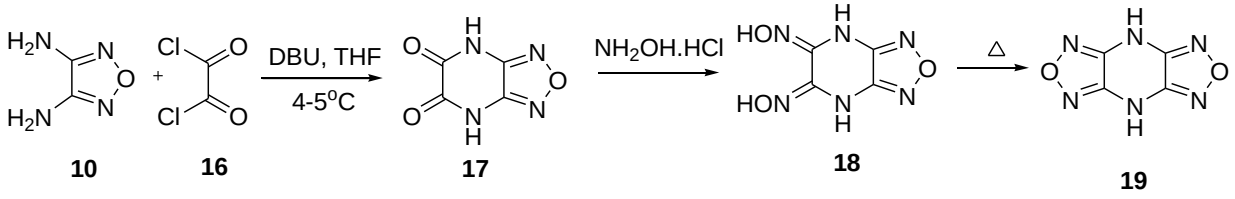


Figure 2. Yield of 3,4-diaminofurazan as a function of temperature.

The reaction of diaminofurazan (**10**) with dibromoethane under basic condition afforded 4,5,6,7-tetrahydro-[1,2,5]oxadiazolo[3,4-*b*]pyrazine (**9**) in 93% yield. The formation of the product was confirmed from the melting point and spectroscopic data such as IR, ^{1}HNMR, and elemental analysis. In the ^{1}HNMR spectrum, a singlet at 2.94 ppm can be attributed to the CH_2 protons attached to the NH protons in the molecule, and the singlet at 5.30 ppm can be assigned to the NH protons. This was further confirmed by D_2O exchange.



10 **16** **17** **18** **19**

Scheme 4. Synthesis of 4H,8H-bis[1,2,5]oxadiazolo[3,4-*b*;3′,4′-*e*]pyrazine from diaminofurazan

For the synthesis of 4H,8H-bis[1,2,5]oxadiazolo[3,4-*b*;3′,4′-*e*]pyrazine (**19**), diaminofurazan was reacted with oxalyl chloride (**16**) to afford diketo derivative (**17**) using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), which is a commercially available, inexpensive homogeneous catalyst. It is a sterically hindered amidine nonnucleophilic base and particularly useful where side reactions due to the inherent nucleophilicity of basic nitrogen are a problem [20–25]. The diketo derivative (**17**) was then reacted with hydroxyl amine hydrochloride to afford dioxime derivative (**18**), which was then cyclocondensed by heating under solvent-free conditions to produce bisfurazanopiperazine (**19**) in 83% yield. The formation of the product was confirmed from the melting point and spectroscopic data such as IR, ^{1}H, ^{13}C NMR, and elemental analysis. In the ^{1}H NMR spectrum, the peak at 11.68 ppm indicates the presence of NH protons, and the peak at 142 ppm in the ^{13}C NMR spectrum indicates the presence of four quaternary carbons.

4. Conclusion

Monofurazanopiperazine (4,5,6,7-tetrahydro-[1,2,5]oxadiazolo[3,4-*b*]pyrazine) and bisfurazanopiperazine (4H,8H-bis[1,2,5]oxadiazolo[3,4-*b*;3′,4′-*e*]pyrazine) were synthesized by a simple and convenient method with excellent yields. The diaminofurazan was synthesized by the cyclocondensation of diaminoglyoxime under solvent-free condition and shown to be a useful precursor for the synthesis of energetic compounds.

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