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Synthesis and characterization of novel heterocycles based on tetrazine and hydrazonoyl halides

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ABSTRACT

The present work describes the preparation and characterization of new pyridazine, thiohydrazonate, *bis*-pyrazole, *bis*-triazole and polypyrazoles based on tetrazine and hydrazonoyl halides. The structures of the newly synthesized were elucidated on the basis of their spectral data FT-IR, NMR, Mass and elemental analysis.

1. Introduction

1,2,4,5-Tetrazine is a strongly colored (red) molecule which is planar [1]. S-Tetrazines have been studied for several decades because their spectroscopic and photo dissociation properties lend themselves to modeling. Tetrazines are highly reactive for aromatic compounds, forming cycloaddition compounds. 1,2,4,5-Tetrazines with a large variety of substituents in the 3- and 6-positions of the heterocyclic are easily accessible, and due to their potential role in inverse-type Diels-Alder reactions, members of this heterocyclic class have found widespread use in many fields of organic chemistry [2]. The pyridazine nucleus is of considerable interest because of its synthetic applications [3-5], and important pharmacological activities [6,7], most of them related to the cardiovascular system [8,9].

The interest in the chemistry of hydrazonoyl halides is a consequence of the fact that they undergo a wide variety of reactions which provide routes to many of heterocyclic compounds [10-13].

The 1,3-dipolar cycloaddition, also known as the Huisgen cycloaddition [14], is a classic reaction in organic chemistry consisting of the reaction of a dipolarophile with a 1,3-dipolar compound that allows the production of various five membered heterocycles. Most of dipolarophiles are alkenes, alkynes and molecules possessing related heteroatom functional groups. A survey of literature revealed that pyrazoles belong among the most representative five-membered heterocyclic systems [15].

We report herein a convenient and efficient synthesis of new heterocycles based on tetrazine and hydrazonoyl halides.

2. Experimental

2.1. Instrumentation and chemicals

All the chemicals were purchased from Aldrich and Fluka, and used without further purification. Melting points were measured on an electrothermal Gallenkamp melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 with tetramethylsilane (TMS) as an internal standard using 300 MHz Varian Gemini spectrometer. The IR spectra were measured on a Fourier Transform and Pye Unicam Infrared spectrophotometers using potassium bromide wafer. Mass spectra were recorded on a GC/MS-QP 1000 EX spectrometer at an ionizing potential of 70 eV. Elemental microanalyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt.

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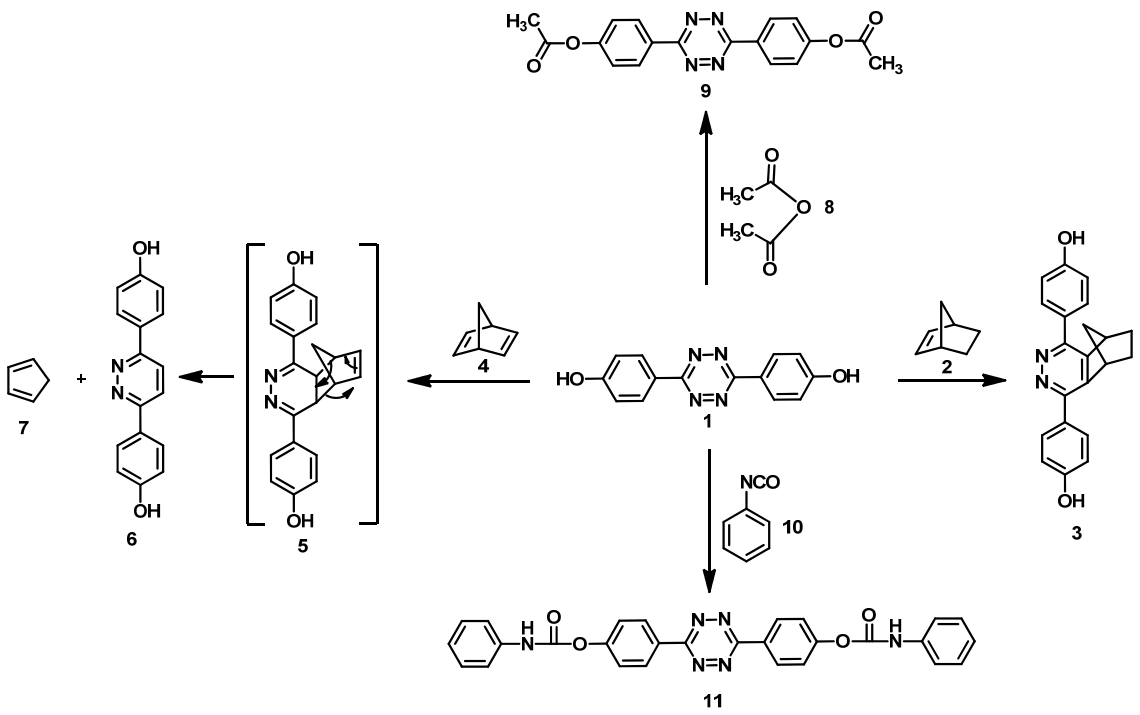


Scheme 1

The identification of compounds from different experiments were secured by mixed melting point's and super imposable IR spectra.

The starting reagents **1** [16], **12** [17], **15** [18], **16** [19], **20** [20], **21** [21], and **25** [22] were prepared as previously described.

2.2. Synthesis

2.2.1. Synthesis of 4,4'-((5R,8S)-5,6,7,8-tetrahydro-5,8-methanophthalazine-1,4-diyl)diphenol (3) and 4,4'-(pyridazine-3,6-diyl)diphenol (6)

To a dry 100 mL round-bottom flask were charged 3,6-*bis*-phenolyl-1,2,4,5-tetrazine (**1**) (2.66 g, 10 mmol) and bicycle [2.2.1]hept-2-ene (**2**) or bicyclo[2.2.1]hept-2,5-diene (**4**) (10 mmol) in DMF at room temperature. The solution were stirred, the progress of reaction was monitored by disappear of red color and TLC, when the reactions were stopped and DMF was removed. The final separation of the products dried and recrystallized from DMF-MeOH (5:15, *v*:*v*) to give the final products (Scheme 1).

4,4'-((5R,8S)-5,6,7,8-Tetrahydro-5,8-methanophthalazine-1,4-diyl)diphenol (**3**): Color: Pale Yellow. Yield: 92%. M.p.: > 350 °C. FT-IR (KBr, ν, cm^{-1}): 3219 (OH) (br, phenol), 1612 (C=N) (pyridazine), 1601 (C=C) (unsaturated). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.42-1.83 (q, 4H, CH_2), 2.21 (d, 2H, CH_2), 3.68 (p, 2H, CH), 7.12 (d, 4H, *J* = 9 Hz, Ar-H), 7.71 (d, 4H, *J* = 9 Hz, Ar-H), 10.53 (s, 2H, OH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 24.4, 43.3, 50.1, 116.2, 122.1, 131.4, 152.1, 152.2, 160.9. MS (EI, *m/z* (%)): 330 (M^+, 79). Anal. calcd. for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.29; H, 5.50; N, 8.46 %.

4,4'-(Pyridazine-3,6-diyl)diphenol (**6**): Color: Green. Yield: 96%. M.p.: > 300 °C. FT-IR (KBr, ν, cm^{-1}): 3138 (OH) (br, phenol), 1608 (C=N) (pyridazine), 1593 (C=C) (unsaturated). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.68 (d, 4H, *J* = 9 Hz, Ar-H), 7.95-8.18 (m, 6H, Ar-H), 10.02 (s, 2H, OH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 116.1, 124.0, 126.3, 128.4, 156.3, 159.9. MS (EI, *m/z* (%)): 264 (M^+, 61). Anal. calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.69; H, 4.62; N, 10.58 %.

2.2.2. Synthesis of (1,2,4,5-tetrazine-3,6-diyl)bis(4,1-phenylene) diacetate (9)

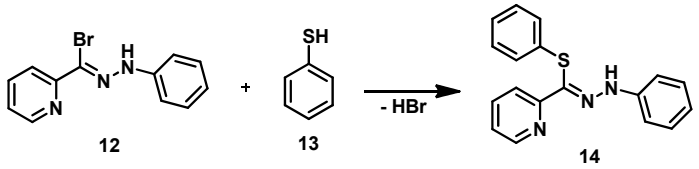
In 50 mL of acetic anhydradide **8** (20.4 g, 0.2 mol), 3,6-*bis*-phenolyl-1,2,4,5-tetrazine (2.66 g, 0.01 mol) **1** is refluxed for 5 h at 140 °C. The mixture was cooled; the solid filtered and washed will with methanol, recrystallized from DMF to give final product **9** (Scheme 1).

(1,2,4,5-Tetrazine-3,6-diyl)bis(4,1-phenylene) diacetate (**9**): Color: Violet. Yield: 94%. M.p.: > 300 °C. FT-IR (KBr, ν, cm^{-1}): 1752 (C=O) (ester), 1598 (C=C) (unsaturated), 1368 (CH_3). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.31 (s, 6H, CH_3), 7.01-8.39 (m, 8H, Ar-H). MS (EI, *m/z* (%)): 350 (M^+, 89). Anal. calcd. for $C_{18}H_{14}N_4O_4$: C, 61.71; H, 4.03; N, 15.99; Found: C, 61.69; H, 3.98; N, 15.92 %.

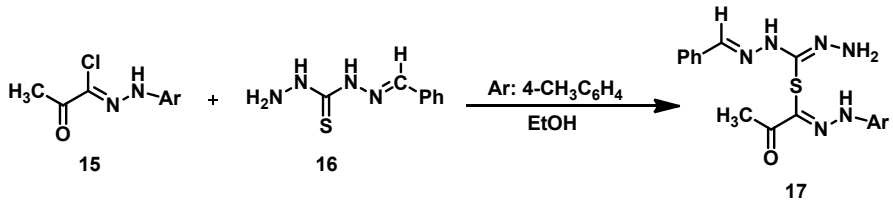
2.2.3. Synthesis of (1,2,4,5-tetrazine-3,6-diyl)bis(4,1-phenylene) bis(phenylcarbamate) (11)

A mixture of 3,6-*bis*-phenolyl-1,2,4,5-tetrazine (2.66 g, 0.01 mol) **1** and phenylisocyanate (2.38 g, 0.02 mol) **10** in 100 mL of dry DMF. The flask was then submerged into a 50 °C oil bath and magnetic stirring and the reaction was held at 50 °C for approximately 24 h when the reaction was stopped and the DMF was removed by rotary evaporation. The resulting precipitate was recrystallized from DMF-EtOH (5:15, *v*:*v*) to give final product **11**. ^{13}C NMR spectra for **11** could not be recorded. This was due to the poor solubility of the isolated products in the NMR solvents trialled (Scheme 1).

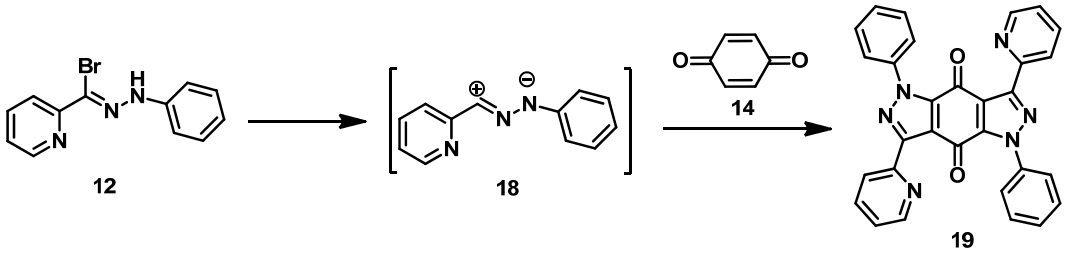
(1,2,4,5-Tetrazine-3,6-diyl)bis(4,1-phenylene)bis(phenyl carbamate) (**11**): Color: Purple. Yield: 92%. M.p.: > 300 °C. FT-IR (KBr, ν, cm^{-1}): 3110 (NH) (carbamate), 1715 (C=O) (carbamate), 1595 (C=C) (unsaturated), 1164 (C-O) (carbamate).



Scheme 2



Scheme 3



Scheme 4

^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.41-8.40 (m, 18H, Ar-H), 10.41 (s, 2H, NH). MS (EI, *m/z* (%)): 504 (M^+, 62). Anal. calcd. for $C_{28}H_{20}N_6O_4$: C, 66.66; H, 4.00; N, 16.66. Found: C, 66.41; H, 3.98; N, 16.71 %.

2.2.4. Synthesis of (Z)-Phenyl N'-phenylpyridine-2-carbo hydrazonothioate (14)

A mixture of 1-{bromo(pyridine-2-yl)methylene}-2-phenylhydrazine (2.75 g, 10 mmol) **12** and the appropriate of thiophenol (1.10 g, 10 mmol) **11** in pyridine or EtONa (20 mL) was stirred at room temperature for 15 h. The reaction mixture was then poured onto ice-cold hydrochloric acid with stirring. The solid that precipitated was collected. The resulting solids filtered, washed with water and recrystallized from MeOH (Scheme 2).

(Z)-Phenyl N'-phenylpyridine-2-carbohydrazonothioate (**14**): Color: Yellow brown. Yield: 62%. M.p.: 75 ^{o}C. FT-IR (KBr, ν, cm^{-1}): 3189 (NH), 1618 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.16-8.08 (m, 14H, Ar-H, pyrdinyl), 10.48 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 112.9, 116.6, 122.1, 124.3, 127.76, 128.45, 129.9, 132.1, 136.9, 133.7, 143.8, 149.5, 151.1, 154.5. MS (EI, *m/z* (%)): 305 (M^+, 60). Anal. calcd. for $C_{18}H_{15}N_3S$: C, 70.79; H, 4.95; N, 13.76. Found: C, 70.63; H, 4.94; N, 13.81%.

2.2.5. Synthesis of (1Z,2E)-2-benzylidenehydrazinecarbo hydrazonic (Z)-2-oxo-N'-(p-tolyl)propanehydrazonic thioanhydride (17)

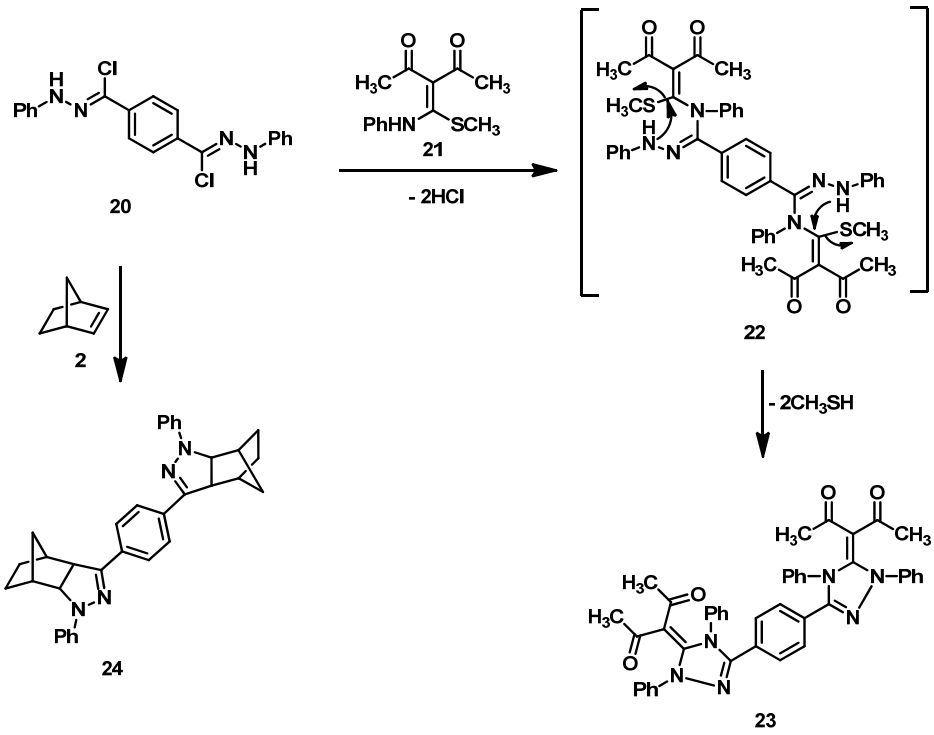
1-(2-p-Tolylhydrazono)-1-chloropropan-2-one (0.21 g, 10 mmol) **15** and phenylmethylene carbonothioic dihydrazide **16** in ethanol (40 mL) was refluxed for 30 minutes. The reaction mixture was cooled and solid formed was collected and recrystallized from DMF-EtOH (5:15, *v:v*) (Scheme 3).

(1Z,2E)-2-benzylidenehydrazinecarbohydrazonic (Z)-2-oxo-N'-(p-tolyl)propanehydrazonic thioanhydride (**17**): Color: Yellow. Yield: 95%. M.p.: 215 ^{o}C. FT-IR (KBr, ν, cm^{-1}): 3098 (=NH), 1595 (C=N), 1316 (CH_3). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.20 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 5.85 (s, 2H, NH_2), 7.08-7.81 (m, 10H, Ar-H and =CH), 10.06 (s, 1H, NH), 10.67 (s, 1H, NH). MS (EI, *m/z* (%)): 368 (M^+, 11). Anal. calcd. for $C_{18}H_{20}N_6OS$: C, 58.68; H, 5.47; N, 22.81. Found: C, 58.61; H, 5.42; N, 22.79 %.

2.2.6. Synthesis of 1,5-diphenyl-3,7-di(pyridin-2-yl)pyrazolo [3,4-f]indazole-4,8(1H,5H)-dione (19)

To an oven-dried round bottom flask was added 1,4-quinone (0.54 g, 5 mmol) **14** and 1-{bromo(pyridine-2-yl)methylene}-2-phenylhydrazine (2.75 g, 10 mmol) **12** and 20 mL dry chloroform and 4 mL DMF in the presence of excess triethylamine (1.52 g, 15 mmol). The round bottom flask was attached to a reflux condenser. The reaction mixture solution was heated to reflux for 12 h. The cold reaction mixture was then poured onto ice-cold hydrochloric acid with stirring. The solid that precipitated was collected, washed with water to give final product **19**, and dried to open air. The structure was elucidated on the basis of spectral data. Deep green solid recrystallized from MeOH (Scheme 4).

1,5-diphenyl-3,7-di(pyridin-2-yl)pyrazolo[3,4-f]indazole-4,8(1H,5H)-dione (**19**): Color: Deep green. Yield: 85%. M.p.: 205 ^{o}C. FT-IR (KBr, ν, cm^{-1}): 3101 (Ar-H), 1650 (C=O), 1604 (C=N), 1550 (pyridiny), 1488 (C=C), 1157 (N-N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.89-8.74 (m, 18H, Ar-H and pyrdinyl). MS (EI, *m/z* (%)): 494 (M^+, 28). Anal. calcd. for $C_{30}H_{18}N_6O_2$: C, 72.87; H, 3.67; N, 16.99. Found: C, 72.93; H, 3.59; N, 16.84%.



Scheme 5

2.2.7. Synthesis of 3,3'-(3,3'-(1,4-phenylene)bis(1,4-diphenyl-1H-1,2,4-triazole-3(4H)-yl-5(4H)-ylidene))bis(pentane-2,4-dione) (23)

To a mixture ketene N,S-acetal (2.49 g, 10 mmol) **21** and *bis*-hydrazonoyl dichlorides (1.92 g, 5 mmol) **20** in ethanol (30 mL) and DMF (10 mL) was added triethylamine (5 mmol) and the mixture was refluxed till methanethiol ceased to evolve 4-6 h. The precipitate that was formed was filtered off and crystallized from DMF:EtOH mixture (5:15, *v*:*v*) to give 3,3'-*bis*(1,2,4-triazole) derivative **23** (Scheme 5).

3,3'-(3,3'-(1,4-Phenylene)bis(1,4-diphenyl-1H-1,2,4-triazole-3(4H)-yl-5(4H)-ylidene))bis(pentane-2,4-dione) (**23**): Color: Brown. Yield: 40%. M.p.: 200 °C. FT-IR (KBr, ν, cm^{-1}): 1715 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.06 (s, 12H, $4CH_3$), 6.82-8.11 (m, 24H, ArH). MS (EI, *m/z* (%)): 712 (M^+, 56). Anal. calcd. for $C_{44}H_{36}N_6O_4$: C, 74.14; H, 5.09; N, 11.79. Found: C, 74.11; H, 5.14; N, 11.83 %.

2.2.8. Reaction of 1-((3aR,7aS)-1-phenyl-3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoindazol-3-yl)-4-((3aS,4S,7R,7aR)-1-phenyl-3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoindazol-3-yl)benzene (24)

A mixture of 4-[*N*,*N*'-diphenyl(*bis*-hydrazonoyl dichlorides)]benzene (1.92 g, 5 mmol) **20** and bicycle [2.2.1]hept-2-ene (0.94 g, 10 mmol) **2** in DMF (20 mL) was boiled under reflux for 5 h. The cold reaction mixture was then poured onto ice-cold hydrochloric acid with stirring. The solid that precipitated was collected. The resulting solids filtered, washed with water and recrystallized from EtOH (Scheme 45).

1-((3aR,7aS)-1-phenyl-3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoindazol-3-yl)-4-((3aS,4S,7R,7aR)-1-phenyl-3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoindazol-3-yl)benzene (**24**): Color: Green yellow. Yield: 71%. M.p.: 320 °C. FT-IR (KBr, ν, cm^{-1}): 1620 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.48 (q, 8H, CH_2), 2.23 (d, 4H, CH_2), 3.04 (p, 2H, CH), 3.38 (s, 2H, CH), 4.22 (s, 2H, CH), 5.34 (s, 2H, CH), 6.65-8.19 (m, 14H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 24.1, 27.6, 32.9, 54.1, 68.2, 113.1, 119.7, 121.2, 122.1, 126.3, 130.2, 144.1, 149.2. MS (EI, *m/z* (%)): 498 (M^+, 16). Anal. calcd. for $C_{34}H_{34}N_4$: C, 81.89; H, 6.87; N, 11.24. Found: C, 81.83; H, 6.90; N, 11.27 %.

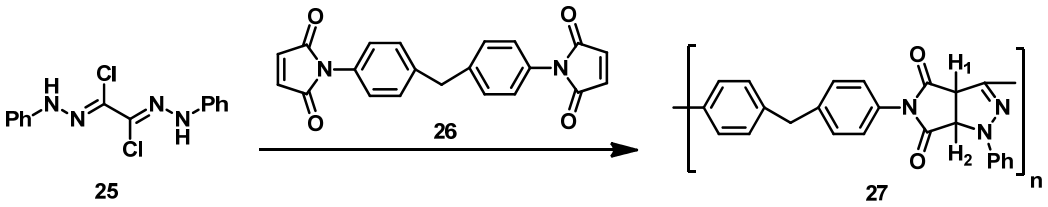
2.2.9. Synthesis of polypyrazole based on bismalimide (27)

A suspension of *bis*-hydrazonoyl dichlorides (1.53 g, 5 mmol) **25** and *bis*-maleimide (1.92 g, (5 mmol) **26** in 20 mL of DMF was heated at 105-110 °C until a slightly yellow solution was formed. The obtained solution was flashed with N_2 during 40 min, cooled to 75 °C, and stirred for 43 h. Cooling to the ambient temperature interrupted the reaction, and the solution was dropped into 100 mL of water. The obtained polymer adduct **27** was filtered off, and after reprecipitation from DMF into ethanol, the polymer was dried in a vacuum at ambient temperature (Scheme 6).

Bis-Malimide (**27**): Color: Yellow brown. Yield: 65%. FT-IR (KBr, ν, cm^{-1}): 1705 (C=O), 1555 (C=C). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.95 (s, 2H, CH_2), 4.24 (d, 1H, CH), 5.19 (s, 1H, CH), 6.14-7.79 (m, 13H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 41.9, 44.1, 53.8, 114.4, 116.1, 121.3, 126.9, 127.7, 129.8, 131.9, 133.6, 135.1, 137.2, 140.9, 142.3, 142.9, 169.9, 170.1.

3. Results and discussion

Electron-deficient heterocyclic tetrazine have proven to be useful reagents that often participate in well-defined inverse electron demand Diels-Alder reactions with electron-rich dienophiles, providing rapid access to a range of highly substituted heterocyclic systems [23]. We have extended these principles to prepare new pyridiazines by reacting of 3,6-*bis*-phenolyl-1,2,4,5-tetrazine **1** with bicycle[2.2.1]hept-2-ene **2** or bicycle[2.2.1]hept-2,5-diene **4** in DMF at room temperature. We use symmetric alkene to help us to give one isolated product.



Scheme 6

The progress of reaction was monitored by disappearance of red color of tetrazine and TLC to give one compound that appeared to be pyridazine as supported by ^{13}C NMR spectroscopy which showed pyridazine in oxidized. Treatment of 3,6-*bis*-phenolyl-1,2,4,5-tetrazine **1** with acetic anhydride **8** under heating to give 3,6-*bis*-phenylacetate-1,2,4,5-tetrazine **9** in good yield. Also, reaction of 3,6-bisphenolyl-1,2,4,5-tetrazine **1** with phenyl isocyanate **10** to give 3,6-*bis*-(phenyl phenylcarbamate)-1,2,4,5-tetrazine **11** as shown in Scheme 1. Structures of **3**, **6**, **9** and **11** were confirmed by elemental analysis and spectra data.

Previously reported arylhydrazonates had great attention and were prepared by reaction of phenols with hydrazonoyl [24]. Thiohydrazonate prepared by treating hydrazonoyl halides **12** or **15** with thiophenol **13** or phenylmethylene carbonothioic dihydrazide **16** to give the final product **14, 17** as shown in Scheme 2 and 3.

It is well known that 1,3-dipolar cycloaddtion reactions with 1,4-quinones provide a convenient one step synthesis of condensed heterocyclic quinones [25]. Nitrilimine **18** generated in situ, by the action of triethylamine on the corresponding hydrazonoyl halides **12**, was allowed to react with 1,4-quinone **14** via cycloaddation to afford the final product **19** as shown in Scheme 4. The chemical shifts of pyrazoline protons are analogue to those observed for some closely related pyrazoline derivatives [26] should be appear at 4.64-4.70 ppm but when examined auto oxidation happened.

The required 2-cyano-3-methylthio-3-phenylaminoacrylo nitrile **21** was prepared by the reaction of malononitrile with phenyl isothiocyanate in DMF in the presence of potassium hydroxide and the resulting thiolate was methylated with methyl iodide to give 2-cyano-3-methylthio-3-phenylamino acrylonitrile **21** [21]. Recently, the synthesis of *bis*-triazoles [27] from reactions of hydrazonoyl halides with ketene-N,S-acetal was reported. These principles were extended to the reaction of *bis*-hydrazonoyl dichlorides **20** with two mole equivalents of **21** in refluxing DMF:EtOH (5:15, *v*:*v*) in the presence of triethylamine proceeded smoothly to give a product that was identified as 3,3'-*bis*-(1,2,4-triazole) derivative **23**.

Treatment of *bis*-hydrazonoyl dichlorides **20** with bicycle [2.2.1]hept-2-ene **2** in DMF/TEA under heating to give final product **24** in good yield.

The structures of the products **23** and **24** were elucidated on the basis of its microanalysis and spectra data as shown in Scheme 5 (see Experimental).

The synthetic utility of nitrilimine cycloaddition reactions in the most cases deals with construction of low molecular weight five-membered heterocyclic ring systems [21]. The presented paper deals with the synthesis and investigations of new polymers which were prepared via 1,3-dipolar polycycloaddition of *bis*-hydrazonoyl dichlorides **26** and *bis*-maleimide **27**, two maleic protons (H1 and H2) can be assigned as multiplet at 4.24 and 5.19 ppm. The ^{13}C NMR spectrum showed sharp peaks for the pyrazolidine function at 77.3 and two signals for maelic carbone 74.5 and 42.8 ppm. The molecular weight of the polymer could not be recorded. This was due to poor solubility of isolated product in THF. Thermal properties of polymer was investigated by DSC measurements (TG) for polymer was found at 71 °C and (Tm) was found at 260 °C.

4. Conclusion

In summary, the synthesis of novel tetrazine, pyridazines, thiohydrazonate, *bis*-pyrazole, *bis*-triazole and polypyrazoline-bismaleimide derivatives based on tetrazine and hydrazonoyl halides are reported.

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