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Novel Synthesis and Heterocyclization of Thiosemicarbazide and Cyclic Heterodienes derivative

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ABSTRACT

Addition of hydrazine to one equivalent of benzoylisothiocyanate furnished thiosemicarbazide 2 . The hydrazine derivative 2 was condensed with benzaldhyde to produce thiosemicarbazon derivative 3. Upon treatment, the Schiff base 3 with bromine/ acetic acid afforded thiadiazole derivative 4. Cyclocondensation of thiosemicarbazide 2 and cyclohexanone yielded benzopyrazole derivative 8. Benzopyrazole derivative 8 undergo Michael addition to polarized double bond of maleicunhydride producing poly heterocyclic compound via the formation of non-isolable adduct 9. Sodium hydroxide was reacted with two equivalents of benzylisothiocyanate 2 to form thiosemicarbazide of type 12 that cyclized to the thiadiazole derivative 13 . Upon keeping thiadiazole derivative 13 and polarized ene of benzylidenemalononitrile undergo [4+2] cycloaddition producing diazine 17a. Also, benzyldiene ethyl cyanoacetate reacted with heterocyclicdiene 13 to furnish diazine of type 17b . Upon treatment of compound 13 with I2 in acetic acid resulted in oxidation affording the oxidized product 18. Oxidation of compound 13 using H2O2 in acetic acid resulted in ring opening followed by oxidation producing semicarbazide 19. Thiadiazole derivative 13 undergo bromination in acetic acid to provide S,S-dibromo and N-bromo derivative 20, 21

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Introduction

Isothiocyanates are one of the most important synthetic intermediates for the preparation of heterocyclic compound containing nitrogen and sulfer **(Sun *et al.*, 2013)**. Isothiocyanates form a group of heterocumulenes containing -N=C=S that is of immense importance in organic synthesis. The presence of carbonyl group in aryl isothiocyanates give more reactivity to aryl isothiocyanate **(santos *et al.*, 2011**

). The azoles have received considerable attention in recent years of their versatility in the synthesis of many other heterocyclic compounds biological activities including antimicrobial, anti-inflammatory, analgesic,anti-convulsive, and many uses **(Ghorab, *et al*., 2001, Palaska, *et al*., 2002, Labanauskas, *et al*.,** this field affords a comprehensive handbook about their uses and applications **(Foroumadi, A., *et al*., 2001, Lee, C., *et al*., 2001, shaw *et al*., 2010)**. Azines (2,3-diazabutadiens) are important because of their biological, chemical and physical properties **(Holla *et al*., 2006)**. Azines react as these "ene" component in [3+2] additions and useful compounds.

Experimental:

Melting points were uncorrected and measured using an Electro thermal IA 9100 apparatus with open capillary tube, all experiments were carried out using drying solvents. Products were -JNM-

LA spectrometer using DMSO as a solvent. All chemical shifts were expressed on the δ (ppm) scale using TMS as an internal standard reference. The coupling constant (J*)* values are given in Hz. Analytical data were obtained from the

because

(Holla, B., *et al*., 2006). Azoles are known for their broad spectrum of **2001, Zhongyi, *et al*.,2001)**. They are also used in the protection of plants and in industry. The rapid development in

they becoming increasingly important in the synthesis of C–C bond formations **(Ghorab, *et al*., 2001)**. For example, the pyridazine ring system is a 1, 2- diazine or *o*-diazabenzene. It is a planar molcule for having a maximum of two kekule structures **(Tawfiq 2015)**. Pyridazines and their derivatives received attention with the recent discovery of medicinally recrystallized. The IR spectrum (KBr disc) was recorded on a Pye Unicam Sp-3-300 or a Shimadzu FTIR 8101 PC infrared spectrophotometer. The H^1 NMR (400 MHz), D_2O (400MHz) and ^{13}C NMR (100 MHz) spectrum were measured on a JEOL

Microanalysis Center at faculty of pharmacy, Cairo University.

***N*-(hydrazinecarbonothioyl) acetamide Compound (2):**

To a solution of benzoylisothiocyanate (0, 2 mol) in (30 mL) dioxane and hydrazine

hydrate (0.2 mol) (12 mL) was added dropwise with stirring, precipitate of water was filtered. Crystallized from ethanol to give white crystals of compound **2**. MP: 170 °C, yield: 80%. IR: 3410.15 cm^{-1} (NH_2), 3209.55 cm^{-1} (NH), 1674.21 cm^{-1} (C=O), 1635.64 cm^{-1} (C=C), 1168.86 cm^{-1} (C=S). H^1NMR: δ 10.31 (s, 1H, NH), 8.14−8.12 (d, 2H, NH_2), 7.67−7.53 (m, 5H, ArH`s).

benzylidenehydrazine-carbonothioyl) acetamide Compound (3):

A mixture of compound **2**(0.01 mol) **and** benzaldhyde (0, 01 mol) in (20 mL) ethanol was heated under reflux for two hours, solid formed collected by filtration and dried. Crystallized from ethanol to give buff crystals of compound **3**, mp 165 °C, yield: 50%. IR: 3421.72 cm^{-1} (NH), 1670.35 cm^{-1} (C=O), 1631.78 cm^{-1} (C=N), 1253.73 cm^{-1} (C=S). H^1NMR: δ 13.17 (s, 1H, NH), 12.75 (s, 1H, NH), 10.51 (s, 1H, CH), 7.98− 7.55 (m, 10H, ArH`s).

***N*-(5-phenyl-1,3,4-thiadiazol-2-yl) benzamide Compound (4):**

A mixture of compound **3** (0.01 mol) dissolved in (20 mL) acetic acid and (0.01 mol) of bromine was added during stirring left the mixture for 6 hours at room temperature, then solid was collected by filtration and dried. Crystallized from ethanol to give white crystals of compound **4**. MP > 300 °C, yield: 60%. IR: 3128.54 cm^{-1} (NH), 1689.64 cm^{-1} (C=O), 1658.78 cm^{-1} (C=N), 164721 cm^{-1} (C=C). ^{1}H NMR: δ 12.74 (s, 1H, NH), 7.69− 7.56 (m, 5H, ArH`s). C^{13}NMR: 165.5 ppm, 156.4 ppm, 133.3 ppm, 132.1 ppm, 129.1 ppm, 128.7 ppm and 49 ppm.

***N*-(1H-indazol-3-yl)benzamide compound 8:**

A mixture of (0.01 mol) compound **2** and (0.01 mol) cyclohexanone in (20 mL) ethanol was heated under reflux for 3 hours, solid formed and collected by filtration, crystallized from ethanol to give buff crystals of compound **8**. MP: 275 °C, yield: 65 %. IR: 3201 cm^{-1} (NH), 1670.35 cm^{-1} (C=O), H^1NMR: δ 10.51 (s, 1H, NH, D_2O exchangeable), 7.61− 7.51 (m, 10H, ArH`s). ^{13}C NMR: 181.09, 168.33, 166.50, 165.58, 165.18, 133.71,

133.59, 133.37, 132.94, 132.65, 132.44, 132.41, 132.29, 132.06, 131.19, 130.53, 129.90, 129.20, 128.10, 127.90, 127.41, 126.11.

(*E*)-9-(benzoylimino)-3-oxo-1,2,3,9-tetrahydropyrazolo[1,2-a]indazole-1-carboxylic acid compound 10:

A mixture of (0.01 mol) compound **8**, (0.01 mol) maleicunhydride and three drops of TEA in (20 mL) ethanol was heated under reflux for 4

-2,5-diyl) dibenzamide compound 13:

A mixture of (0.01 mol) compound **2** and (0.01 mol) sodium hydroxide (0.4 gm) in (20 mL) ethanol was heated under reflux for 2 hours, solid yellow crystals of compound **13**. MP: 292 °C -294 °c, yield: 70%. IR: 3201.83 cm^{-1} (NH), 1670.35 cm^{-1} (C=O), 1288 cm^{-1} (C-S). ^{1}H NMR: δ 10.51 (s, 1H, NH, D_2O exchangeable), 8.15 − 7.47 (m, 10H, ArH`s). ^{13}C NMR: 168.3 ppm, 167.8 ppm, 166.4 ppm, 165.6 ppm, 132.9 ppm, 132.6 ppm.

(*Z*)-*N*-(6-benzamido-4,4-dicyano-5-(3-nitrophenyl)pyridazin-3(4*H*)-ylidene)benzamide compound 17a:

yellow crystals of compound **17a**. MP: 228 °C -230 °C, yield: 60%. IR: 3321.42 cm^{-1} (NH), 2200 cm^{-1} (CN), 1627 cm^{-1} (C=O), 1585.49 cm^{-1} (C=N). H^{1}NMR: δ 10.50 (s, 1H, NH, D_2O exchangeable), 8.14− 7.50 (m, 14H, ArH`s). ^{13}C NMR: 129.16, 129.13, 129.02, 128.85, 128.75, 128.40,

hours, solid formed and collected by filtration, crystallized from ethanol to give brown crystals of compound **10.** MP: 190 °C, yield: 50 %. IR: 3421 cm^{-1} (OH), 1670, 1639 cm^{-1} (C=O), ^{1}H NMR: δ 13.16 (s, 1H, OH), 7.69− 7.52 (m, 10H, ArH`s).

***N,N'*-(1,3,4-thiadiazole**

formed by concentration and dilution followed by acidification by hydrochloric acid and collected by filtration, crystallized from ethanol to give

A mixture of compound **14** (0.01 mol) and compound **13** (0.01 mol, 1.7g) in (20 mL) ethanol and few drops of triethylamine (TEA) and heated under reflux for 4 hour. Solid formed upon dilution and addition of acetic acid, solid collected by filtration and dried. Crystallized from ethanol to give

165.8 ppm, 161.6 ppm, 161.2 ppm, 134.5 ppm, 130.7 ppm, 129.1 ppm, 129 ppm, 128.7 ppm, 127.9 ppm, 115.9 ppm, 115.5 ppm, 83.9 ppm, 83.5 ppm, 63.9 ppm.

(*Z*)-ethyl 6-benzamido-3-(benzoylimino)-4-cyano-5-(3-

nitrophenyl)-3,4-dihydropyridazine-4-carboxylate compound 17b:

A mixture of compound **14** (0.01 mol) and of compound **13 (**0.01 mol) in (20 mL) ethanol and few drops of triethylamine (TEA) was heated under reflux for 4 hours, solid formed after dilution and addition of acetic acid. Solid collected by filtration and dried, recrystallized from ethanol and DMF to give brown crystals of compound **17a**. MP: 100 °C, yield: 45%. IR: 3448.72 cm^{-1} (NH), 1743.65 cm^{-1} (CN), 1674.21 cm^{-1} (C=O), 1620.21 cm^{-1} (N=N). ^{1}H NMR: δ 9 (s, 1H, NH), 8.40− 7.65 (m, 14H, ArH`s), 4.12− 3.85 (t, 3H, CH3), 3.84− 3.44 (q, 2H, CH2).

(*Z*)-ethyl 6-benzamido-3-(benzoylimino)-4-cyano-5-phenyl-3,4-dihydropyridazine-4-carboxylate compound 17c:

A mixture of compound **14** (0.01 mol) and compound **13 (**0.01 mol) in (20 mL) ethanol and few drops of triethylamine (TEA) was heated under reflux for 4 hours. Solid formed after dilution and addition of acetic acid, solid collected by filtration and dried. Crystallized from ethanol and dimethylformamide to give rose crystals of compound **17b**. MP: 180 °C, yield: 48%. IR: 3140.11 cm^{-1} (NH), 2218 cm^{-1} (CN), 1728 cm^{-1} (N=N), 1670.35 cm^{-1} (C=O). ^{1}H NMR: δ 10.52 (s, 1H, NH, D_2O exchangeable), 8.16− 7.40 (m, 15H, ArH`s), 4.33−4.11 (t, 3H, CH3), 3.35− 2.9 (q, 2H, CH_2). C^{13} NMR: 166.4ppm, 162.2 ppm, 155.5 ppm, 133.8 ppm, 133.5 ppm, 133 ppm, 132.3 ppm, 131.2 ppm, 129.8 ppm, 129.7 ppm, 129.2 ppm, 129.1 ppm, 129.1 ppm, 128.9 ppm, 128.8 ppm, 128.7 ppm, 127.9 ppm, 127.4 ppm, 116 ppm, 103.1 ppm, 97.2 ppm and 62.8 ppm.

(*Z*)-*N*-(6-benzamido-4,4-dicyano-5-phenylpyridazin-3(4*H*)-ylidene)benzamide compound 17d:

A mixture of of compound **14** (0.01 mol) and compound **13 (**0.01 mol, 1.7g) in (20 mL) ethanol and few drops of triethylamine (TEA) was heated under reflux for 4 hour. Solid formed upon dilution and addition of acetic acid, solid collected by filtration and dried. Crystallized from ethanol to give yellow crystals of compound **17b**. MP: 228 °C - 230 °C, yield: 60%. IR: 3321.42 cm^{-1} (NH), 2200 cm^{-1} (CN), 1585.49 cm^{-1} (C=O), ^{1}H NMR: δ 10.50 (s, 1H, NH, D_2O exchangeable), 8.14− 7.50 (m, 15H, ArH`s). ^{13}C NMR: 165.8 ppm, 161.6 ppm, 161.2 ppm, 134.5 ppm, 130.7 ppm, 129.1 ppm, 129 ppm, 128.7 ppm, 127.9 ppm, 115.9 ppm, 115.5 ppm, 83.9 ppm, 83.5 ppm, 63.9 ppm.

***N,N'*-(1,1-dioxido-1,3,4-thiadiazole-2,5-diyl)dibenzamide compound 18:**

A mixture of (0.01 mol) of compound **13** dissolved in (20 mL) ethanol, then add (0.01 mol) of iodine left the mixture at

room temperature for 6 hours. Solid collected by filtration and dried, recrystallized from ethanol and DMF to give red crystals of compound **18**. MP. > 300 °C, yield: 70%. IR: 3155.54 cm^{-1} (NH), 1670 cm^{-1} (C=O). H^1NMR: δ 12.75 (s, 1H, NH, D_2O exchangeable), 8.14− 7.55(m, 10H, ArH`s). C^{13}NMR:165.4 ppm, 156.4 ppm, 133.3 ppm, 132.1 ppm, 129.1 ppm and 128.7 ppm.

N1,N2*-dibenzoylhydrazine-1,2-dicarboxamide compound 19*:

A mixture of (0.01 mol) of compound **13** dissolved in (20 mL) acetic acid and (0.01 mol) of hydrogen peroxide left the mixture at room temperature for 6 hours, solid collected by filtration ignored, put water on filtrate. Another solid formed and collected by filtration and dried, recrystallized from ethanol and DMF to give yellow crystals of compound **19**. MP. > 188 °C, yield: 40%. IR: 3271 cm^{-1} (NH), 1654.92 cm^{-1} (C=O). H^1NMR: δ 11.78 (s, 1H, NH, D_2O exchangeable), 11.13 (s, 1H, NH, D_2O exchangeable), 8.00− 7.52(m, 10H, ArH`s).

S,S'*-(1,1-dibromo-1,3,4-thiadiazole-2,5-diyl)dibenzamide compound 20*:

A mixture of (0.01 mol) of compound **13** dissolved in (20 mL) acetic acid and (0.01 mol) of Bromine left the mixture at room temperature for 6 hours, solid collected by filtration, recrystallized from ethanol and DMF to give white crystals of compound **20.** MP. > 300 °C, yield: 50 %. IR: 3421 cm^{-1} (NH), 1670 cm^{-1} (C=O). H^1NMR: δ 12.75 (s, 1H, NH), 8.14−7.56 (m, 10H, ArH`s).

***N,N'*-(1,3,4-thiadiazole-2,5-diyl) bis(N-bromobenzamide) compound 21 :**

The filtrate of compound 20 poured on water and another solid formed collected by filteration and dried, recrystallized from ethanol to give white crystals of compound 21. MP: 210 °C -212 °C, yield: 50 %. IR: 1716 cm^{-1} (C=O). H^1NMR: δ 8.14− 7.55 (m, 10 H, ArH`s).

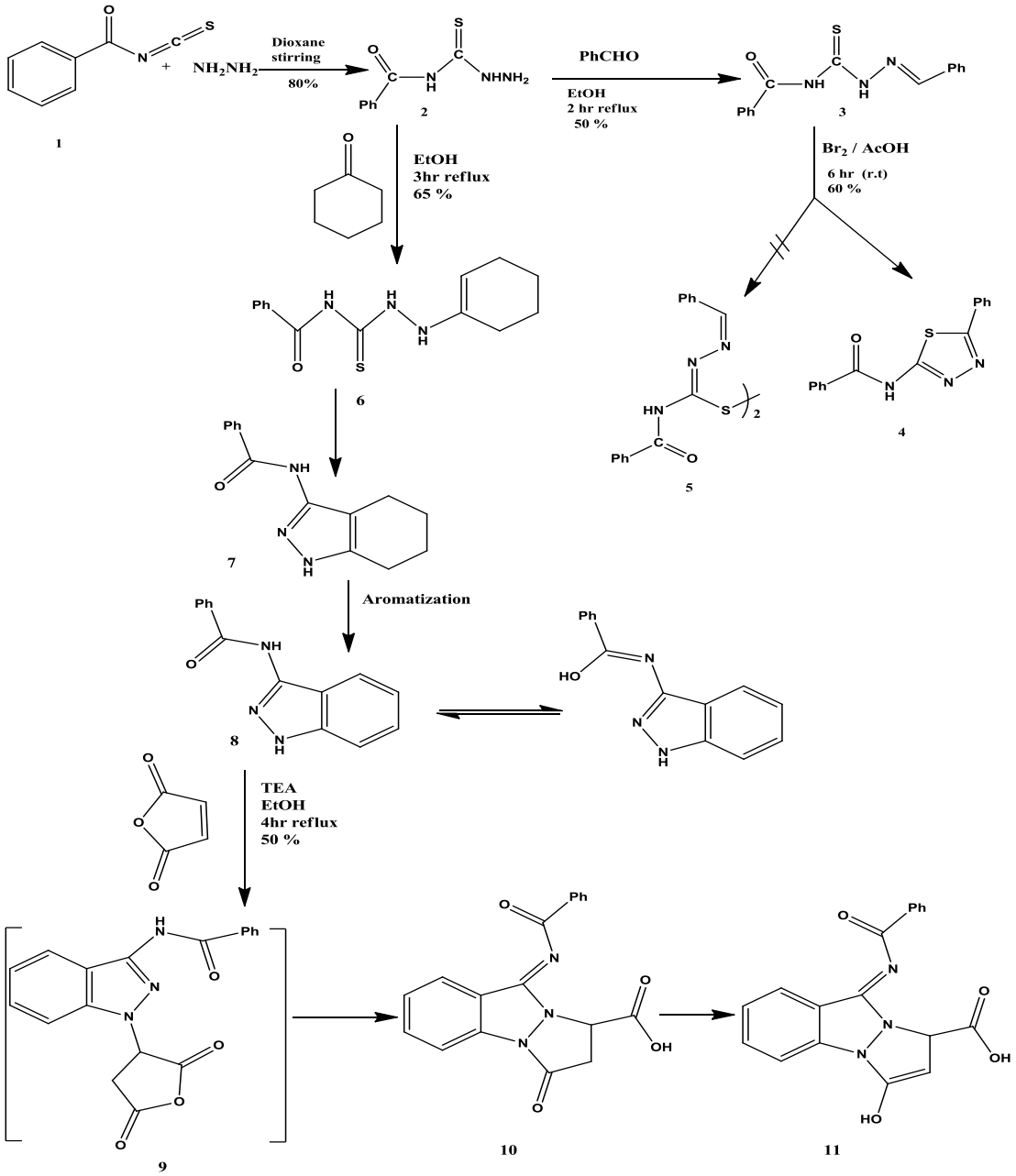
Results and Discussion:

Addition of hydrazine to one equivalent of benzoylisothiocyanate furnished thiosemicarbazide **2 (scheme 1) (Hemdan, *et al.*, 2008).** Compound **2** was characterized by H^1NMR and IR spectra. The ^{1}H NMR had peaks corresponding to NH_2 and NH protons at low field in addition to aromatic multiplet in region 7.67−7.53 ppm. IR spectrum of compound **2** revealed absorption bands at 3410 cm^{-1}, 1674 cm^{-1} and 1168 cm^{-1} for NH_2, C=O and C=S respectively.

The hydrazine derivative **2** was condensed with benzaldehyde to produce thiosemicarbazone derivative **3 (scheme 1) (Benmohammed *et al.*, 2014)**. ^{1}H NMR spectrum of compound **3** revealed peaks corresponding to NH at low field (exchangeable with D_2O) and multiplet in

region 7.98 − 7.55 due to ArH`s. IR spectrum of **3** revealed absorption bands at 3421 cm^{-1}, 1670 cm^{-1} and 1253 cm^{-1} for NH, C=O and C=S respectively.

Upon treatment, the Schiff base **3** with bromine/ acetic acid resulted in oxidative cyclization affording thiadiazole derivative **4** and none of disulphide **5** was obtained **(scheme 1).** ^{1}H NMR of **4** exhibited down field signal at 12.74 ppm for NH proton. Compound **4** also showed absorption frequencies at 3128 cm^{-1} and 1689 cm^{-1} due to NH and C=O groups respectively. . ^{13}C NMR showed signal at 165.5 ppm for C=O carbon in addition to C=N carbon at 156.4 ppm. Cyclocondensation of thiosemicarbazide **2** and cyclohexanone yielded benzopyrazole derivative **8**, the reaction proceeds via the formation of thiosemicarbazone derivative **7** followed by attack of enamic carbon of cyclohexyl group to the thioxo group with the evolution of H_2S and subsequent aromatization **(scheme 1)**. Compound 8 showed carbonyl absorption at 1670 cm^{-1} for carbonyl group. Also resonate at δ 10.51 for NH proton. Carbon signal was observed at δ 181.09 ppm for carbonyl carbon. Benzopyrazole derivative **8** undergo Michael addition to polarized double bond of maleic anhydride producing poly heterocyclic compound via the formation of non-isolable adduct **9**. Compound **10** revealed absorption peak at 1670 cm^{-1}, 1639 cm^{-1} for carbonyl group. ^{1}H NMR contain two down field signals at 13.16 ppm and 11.77 ppm for OH proton.

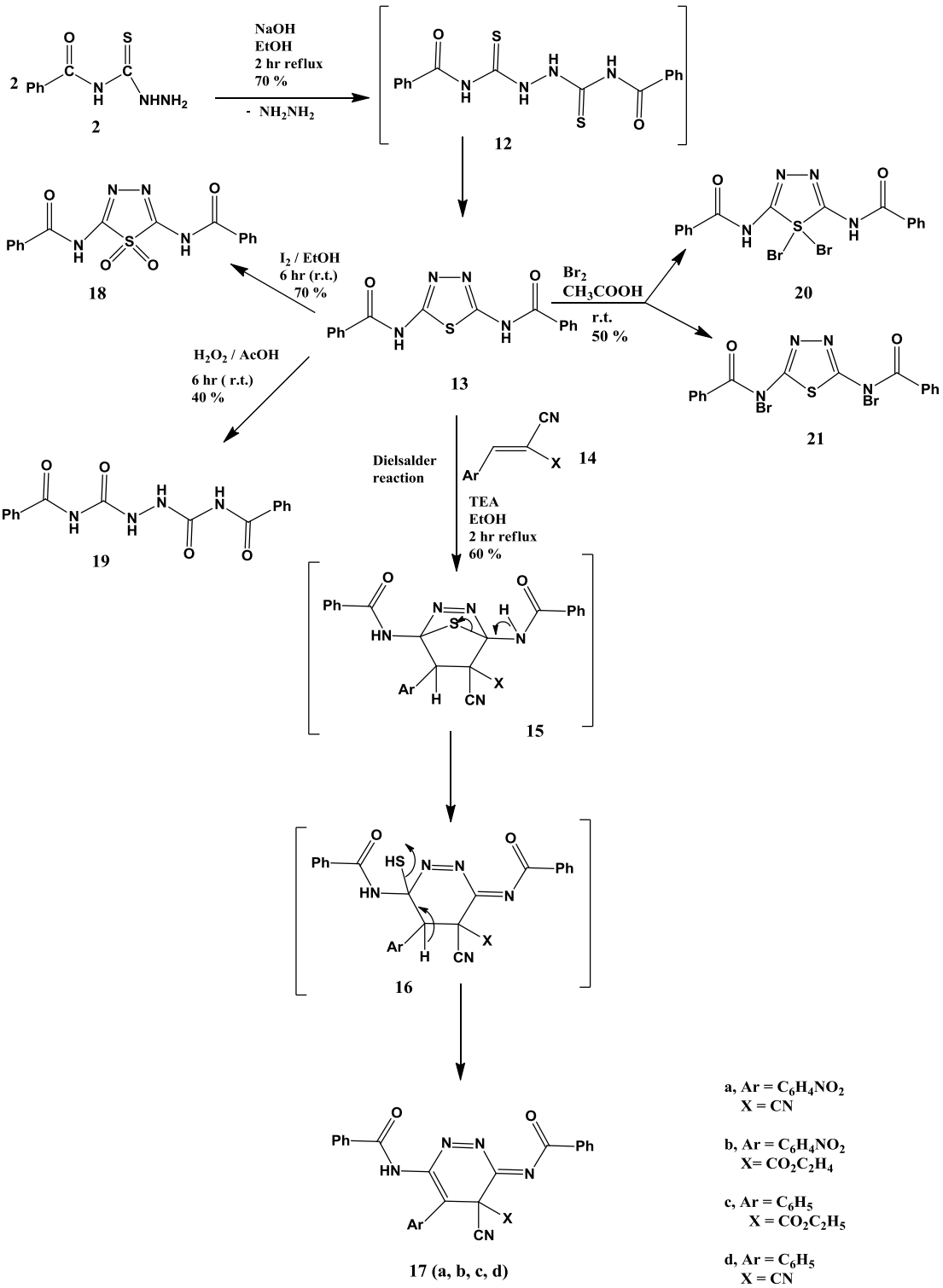


Scheme 1

Cyclization of hydrazine by one mol of PhCONCS

Sodium hydroxide was reacted with two equivalents of benzyl isothiocyanate **2** to form thiosemicarbazide of type **12** that cyclized directly during the work up to the thiadiazole derivative **13 (scheme 2)**. ^{1}H NMR spectrum of **13** exhibited a deshielded (D_2O exchangeable) signal at δ 10.51 ppm for NH proton. IR spectrum of **13** contained absorption peaks at 3201 cm^{-1} and 1670 cm^{-1} for NH and C=O groups respectively. ^{13}C NMR revealed signal at 168 and 167 for C=O and C=N carbon respectively. Compound **13** seemed to be act as a good diene. Thus, upon keeping

thiadiazole derivative **13** and polarized ene of benzyldienemalononitrile undergo [4+2] cycloaddition producing Diels Alder adduct **15**, compound **15** form alicyclic compound **16**, that loss H_2S gas forming the final diazine **17a (scheme 2)**. ^{1}H NMR spectrum of **10a** exhibited a down field signal at 10.50 ppm (D_2O exchangeable) for NH proton. IR showed absorption peaks at 3321 cm^{-1}, 2200 cm^{-1} and 1627 cm^{-1} for NH, CN and C=O respectively. Also, ethyl benzylidenecyanoacetate reacted with heterocyclicdiene **7** to furnish diazine of type **17b (scheme 2)**. ^{1}H NMR of **17b** exhibited a low field signal for NH (D_2O exchangeable). IR spectrum of **17b** revealed absorption band at 3410 cm^{-1}, 2218 cm^{-1} and 1728 cm^{-1} for NH, CN and C=O groups, respectively. ^{13}C NMR contained 166.42 ppm, 155.50 ppm, 133.80 ppm for C=O groups. Upon treatment of compound **13** with I_2 in acetic acid resulted in oxidation affording the oxidized product **18 (scheme 2)**. ^{1}H NMR of compound **11** resulted in a down field signal (D_2O exchangeable) at 12.75 ppm for NH proton. Oxidation of compound **13** using H_2O_2 in acetic acid resulted in ring opening followed by oxidation producing semicarbazide **19**. Compound **19** resonated at low field (D_2O exchangeable) signal for NH. IR spectrum of **19** revealed absorption bands at 3271 cm^{-1} and 1654 cm^{-1} for NH and C=O groups. Thiadiazole derivative **13** undergo bromination in acetic acid to provide *S*,*S*-dibromo and *N*-bromo derivative **20**, **21.** Compound **20** showed peak at 1670 cm^{-1} for carbonyl group, and provided down field signal at δ 12.75 ppm for NH proton, while compound **21** lack proton signal in ^{1}H NMR



Scheme 2

Reference

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