Novel Synthesis and Heterocyclization of Thiosemicarbazide and Cyclic Heterodienes derivative

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ABSTRACT
Addition of hydrazine to one equivalent of benzyolisothiocyanate furnished thiosemicarbazide 2. The hydrazine derivative 2 was condensed with benzaldehyde 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, benzylidiene 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 sulfur (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 because of their versatility in the synthesis of many other heterocyclic compounds. Azoles are known for their broad spectrum of biological activities including antimicrobial, anti-inflammatory, analgesic, anti-convulsive, and many uses (Ghorab, et al., 2001, Palaska, et al., 2002, Labanauskas, et al., 2006). Azoles are used in the protection of plants and in industry. The rapid development in 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 recrystallized. The IR spectrum (KBr disc) was recorded on a Pye Unicam Sp-3-300 or a Shimadzu FTIR 8101 PC infrared spectrophotometer. The H1 NMR (400 MHz), D2O (400MHz) and 13C NMR (100 MHz) spectrum were measured on a JEOL-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 Microanalysis Center at faculty of pharmacy, Cairo University.

N-(hydrazinecarbonothioyl) acetamide Compound (2):

To a solution of benzoic isothiocyanate (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).

**Compound (2):**

A mixture of compound 2 (0.01 mol) and benzaldehyde (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). \(^1\)H NMR: \(\delta\) 13.17 (s, 1H, NH), 12.75 (s, 1H), 10.51 (s, 1H), 7.98–7.55 (m, 10H, ArH’s).

**Compound (3):**

A mixture of compound 2 (0.01 mol) and benzaldehyde (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). \(^1\)H NMR: \(\delta\) 13.17 (s, 1H, NH), 12.75 (s, 1H), 10.51 (s, 1H, CH), 7.98–7.55 (m, 10H, ArH’s).

**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, IR: 3128.54 cm\(^{-1}\) (NH), 1689.64 cm\(^{-1}\) (C=O), 1658.78 cm\(^{-1}\) (C=N), 1647 cm\(^{-1}\) (C=C). \(^1\)H NMR: \(\delta\) 12.74 (s, 1H, NH), 7.69–7.56 (m, 5H, ArH’s).

**Compound (5):**

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), 166.50, 165.58, 165.18, 133.71, 181.09, 168.33, 166.33, 133.71, 165.58, 165.18, 133.71, 181.09, 168.33, 166.33, 133.71, 165.58, 165.18, 133.71.

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133.59, 133.37, 132.94, 132.65, 132.44, 132.41, 132.29, 132.06, 131.19, 130.53, 129.90, 129.20, 129.16, 129.13, 129.02, 128.85, 128.75, 128.40, 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 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-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, D₂O 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-nitrophenyI)pyridazin-3(4H)-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). $^1$H NMR: δ 10.50 (s, 1H, NH, D₂O exchangeable), 8.14– 7.50 (m, 14H, 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.

(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). ¹H NMR: δ 8.40 (s, 1N) 7.65 (m, 14 Ar), 4.12– 3.85 (t, 3H, CH₃), 3.84– 3.44 (q, 2H, CH₂). C¹³ NMR: 166.4 ppm, 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(4H)-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), ¹H NMR: δ 10.50 (s, 1H, NH, D₂O exchangeable), 8.14– 7.50 (m, 15H, ArH’s). ¹³C 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)dibenzenamide 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 Abdelrahman et al
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). H¹NMR: δ 12.75 (s, 1H, NH, D₂O exchangeable), 8.14–7.55 (m, 10H, ArH’s). C¹³NMR: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. > 300 °C, yield: 70%. IR: 3155.54 cm⁻¹ (NH), 1670 cm⁻¹ (C=O). H¹NMR: δ 12.75 (s, 1H, NH, D₂O exchangeable), 8.14–7.55 (m, 10H, ArH’s).

N,N'-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). H¹NMR: δ 11.78 (s 1H, NH, D₂O exchangeable), 11.13 (s, 1H, NH, D₂O 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). H¹NMR: δ 12.75 (s, 1H, NH), 8.14–7.55 (m, 10H, ArH’s).

S,N'-bis(N-bromobenzamide) compound 21:

The filtrate of compound 20 poured on water and another solid formed collected by filtration and dried, recrystallized from ethanol to give white crystals of compound 21. MP: 210 ºC -212 ºC, yield: 50 %. IR: 1716 cm⁻¹ (C=O). H¹NMR: δ 8.14–7.55 (m, 10 H, ArH’s).

Results and Discussion:

Addition of hydrazine to one equivalent of benzyolisothiocyanate furnished thiosemicarbazide 2 (scheme 1) (Hemdan, et al., 2008). Compound 2 was characterized by H¹NMR and IR spectra. The H NMR had peaks corresponding to NH₂ 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 NH₂, 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). H¹NMR spectrum of compound 3 revealed peaks corresponding to NH at low field (exchangeable with D₂O) and multiplet in

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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. \(^1\)H NMR contained two down field signals at 13.16 ppm and 11.77 ppm for OH proton.

\(^{13}\)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 thiourea derivative 7 followed by attack of enamic carbon of cyclohexyl group to the thioxo group with the evolution of \(\text{H}_2\text{S}\) and subsequent aromatization (scheme 1). Compound 8 showed carbonyl absorption at 1670 cm\(^{-1}\) for carbonyl group. Also resonate at \(\delta\) 10.51 for NH proton. Carbon signal was observed at \(\delta\) 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. 

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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$_2$O exchangeable) signal at $\delta$ 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 act as a good diene. Thus, upon keeping...
thiadiazole derivative 13 and polarized ene of benzylidenemalononitrile undergo [4+2] cycloaddition producing Diels Alder adduct 15, compound 15 form alicyclic compound 16, that loss H2S gas forming the final diazine 17a (scheme 2). 1H NMR spectrum of 10a exhibited a down field signal at 10.50 ppm (D2O 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 heterocyclic diene 7 to furnish diazine of type 17b (scheme 2). 1H NMR of 17b exhibited a low field signal for NH (D2O 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. 13C NMR contained 166.42 ppm, 155.50 ppm, 133.80 ppm for C=O groups. Upon treatment of compound 13 with I₂ in acetic acid resulted in oxidation affording the oxidized product 18 (scheme 2). 1H NMR of compound 11 resulted in a down field signal (D2O exchangeable) at 12.75 ppm for NH proton. Oxidation of compound 13 using H2O2 in acetic acid resulted in ring opening followed by oxidation producing semicarbazide 19. Compound 19 resonated at low field (D2O 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 1H NMR.
Scheme 2

Abdelmadjid Benmohammed, Omar Khoumeri, Ayada Djafri, Thierry Terme and Patrice Vanelle, 2014, Synthesis of Novel Highly Functionalized 4-Thiazolidinone Derivatives from 4-

a, Ar = C₆H₅NO₂ X = CN
b, Ar = C₆H₅NO₂ X = CO₂C₂H₄

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