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Novel heterocyclization process novel design of spiroazoles

Mohammed Abd Elazim[1], Mohammed G. Assy[1], Maha A. Elmesalmy[1*], Yasser Selim[2]

[1]Chemistry Department, Faculty of Science, Zagazig University, ET-44519, Zagazig, Egypt;
[2]Faculty of Specific Education, Zagazig University, ET-44519, Zagazig, Egypt.
[*]Corresponding author, E-mail: dr.maha198907@gmail.com

Abstract: When malono hydrazide 1 was allowed to react with benzaldehyde; the reaction yielded spiro compound 2. The reaction may start via formation of condensed product 2; followed by the addition of activated methylene to activated C=N. Also, condensation of the target 1 with cyclopentanone produced the non-isolable Schiff product 4 that underwent intramolecular cycloaddition reaction to form the spiro product 5. The addition of nucleophilic NH_2 group of target 1 to heteroallene in basic medium resulted in triazole heterocyclization. The reaction may proceed via the formation of non-isolable thiosemicarbazide derivative 6; followed by intramolecular cyclization to furnish triazole derivative 7.

Pyrazole derivative 8 underwent Michael addition with heteroallene providing fused triazole derivative 10 which may be formed through the non-isolable thiourea derivative. The target 8 underwent cycloaddition reaction with carbon disulphide to produce fused thiadiazole 12. Compound 8 underwent double nitrozation when treated with NaNO2/acetic acid yielding nitroso derivative 13.

KEYWORDS: Hydrazide, spiropyrazole, pyrazolo triazole, pyrazole thiadiazole, nitrosopyrazole.

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I. INTRODUCTION

For pyrazoles, a number of pharmacological and biological actions have been reported including sodium channel blocker [1], antiglaucoma [2], antitubercular [3], antiviral [4], anti-inflammatory [5], antioxidant [6], anticancer [7:14], Spiroazoles offer a wide range of bioactivities, which has prompted researchers to come up with effective ways to make them and their analogues. Spiroazoles have incredible pharmacological effects, including antihyperglycemic [15:16], antimycobacterial [17], and antifungal [18] activities. They play a crucial function in the development of blood arteries by relaxing the smooth muscle cells within their walls, particularly large and smaller arterioles and large veins. As a result, they also have vasodilation activity [19]. Additionally, natural spiroazoles have been utilized to treat headache, vertigo, and epilepsy as antipyretic, antihypertensive, and anticonvulsant drugs [20].

II. MATERIALS AND METHODS

All melting points are uncorrected and were measured using an electro-thermal La 9100 apparatus. Infrared (IR) spectra (KBr), cm^{-1} were measured on a Nexus 670 FTIR Nicolet, Fourier transform spectrometer. The nuclear magnetic resonances (NMR) including ^{1}H- and ^{13}C-NMR spectroscopy were determined with a JEOL-JNM-LA 400, 100 MHz spectrometer using DMSO-d_6 as solvent. The chemical shift δ are expressed on the (ppm) scale using tetramethylsilane as the standard reference. Elemental analysis determined on a PerkinElmer 240 (microanalysis), Microanalysis center, Cairo University, Cairo, Egypt. (E. Merck).

4,9-Diphenyl-2,3,7,8-tetraazaspiro[4.4]nonane-1,6-dione (3): A mixture of malonohydrazide (0.01 mol), dissolved in 10 mL of di-methylformamide and benzaldhyde (0.02 mol) was refluxed for 5 hrs, then the reaction mixture was cooled down, and poured into ice water, the formed solid was separated and recrystallized from hot ethanol. Yield 3.12 g (68%), white powder, m.p. 255 ^{o}C. IR spectrum, ν, cm^{-1}: OH (3343), NH (3215), C=O

(1687), C=S (1655). ^{1}H-NMR, δ, ppm: 11.61 (s, H, OH, D_2O exchangeable), 11.52 (s, H, NH, D_2O exchangeable), 7.3-8.24 (m, 10H, Ar-H's), 2.51 (s, 2H, 2CH-Ph, D_2O exchangeable). ^{13}C-NMR spectrum, DMSO-d_6, δ, ppm: C=O (169.35), sp^2 carbon at 163.34, CH-Ph (127.21). Analytical for $C_{17}H_{16}N_4O_2$ (308.34); Found, %: C 66.2; H 5.26; N 18.15. Calculated, %: C 66.22; H 5.23; N 18.17.

4,9-Dicyclopentyl-2,3,7,8-tetraazaspiro[4,4]nonane-1,6-dione (5): A mixture of malonohydrazide (0.01 mol), dissolved in 10 mL of dimethylformamide and cyclopentanone (0.02 mol) was stirred for half an hour, then refluxed for 2 hrs, then the reaction mixture was cooled, and poured into ice water, the formed solid was separated and recrystallized from hot ethanol. Yield 2.45 g (75%), black powder, m.p. 120 ºC. IR spectrum, *ν*, cm^{-1}: NH (3367), C=O (1670). ^{1}H-NMR, δ, ppm: 1.67-3.0 (m, 20H, 2cyclopentyl + 2CHN), 9.8-10.1 (s, H, NH). Analytical for $C_{15}H_{24}N_4O_2$ (292.38); Found, %: C 66.65; H 8.4; N 19.12. Calculated, %: C 61.62; H 8.27; N 19.16.

(3,3'-Methylenebis(5-thioxo-1*H*-1,2,4-triazole-4,3(5*H*)-diyl))bis(phen-ylmethanone) (7): A solution of malonohydrazide (0.01 mol), benzoyl isothiocyanate (0.02 mol) and triethylamine (3 drops) was refluxed for 3 hrs, then the reaction was cooled down, poured into ice, and the solid obtained was filtered, dried and recrystallized from hot ethanol. Yield 2.3 g (65%), Beige powder, m.p. 250 ºC. IR spectrum, *ν*, cm^{-1}: 3205 (NH), 1670 (C=O), 1288 (C=S). ^{1}H-NMR, δ, ppm: 3.16 (s, H, CH), 7.43-7.93 (m, 15H, Ar-H), 10.51 (s, 4H, 4NH), 12.1 (s, 1H, OH). Analytical for $C_{19}H_{14}N_6O_2S_2$ (422.48); Found, %: C, 54.10; H, 3.32; N, 19.90. Calculated, %: C, 54.02; H, 3.34; N, 19.89.

5,5'-Dimethyl-3,3'-diphenyl-1,1'-dithioxo-5,5'-di-*p*-tolyl-1*H*,1'*H*-6,6'-spirobi[pyrazolo[1,2-*a*][1,2,4]triazole]-7,7'(5*H*,5'*H*)-dione (10): A soltion of 4,9-dimethyl-4,9-di-*p*-tolyl-2,3,7,8-tetraaza-spiro[4.4]nonane-1,6-dione (0.005 mol), dissolve in DMF (10 mL), benzoyl isothiocyanate (0.01 mol), triethylamine (3 drops) was refluxed for 3 hr, then the reaction was cooled down, poured into ice water, and the solid filtered off, dried and recrystallized from hot ethanol. Yield 1.9 g (71%), Dark beige powder, m.p. 130 ºC. IR spectrum, *ν*, cm^{-1}: 3309 (NH), 1681 (C=O), 1292 (C=S). ^{1}H-NMR, δ, ppm: 2.36 (s, 6H, 2CH_3, D_2O exchangeable), 2.51 (s, 6H, 2CH_3, D_2O exchangeable), 7.26-7.94 (m, 8H, Ar-H's). ^{13}C-NMR spectrum, DMSO-d_6, δ, ppm: C=O (182.49), C=C (168.28), sp^2 carbon at 125.23-139.93, sp^3 carbon at 11.89-27.03. Analytical for $C_{37}H_{30}N_6O_2S_2$ (654.81); Found, %: C 67.8; H 4.5; N 12.85. Calculated, %: C 67.87; H 4.62; N 12.83.

5,5'-Dimethyl-1,1',3,3'-tetrathioxo-5,5'-di-*p*-tolyltetrahydro-6,6'-spiro-bi[pyrazolo[1,2-c][1,3,4]thiadi-azole]-7,7'(1*H*,1'*H*)-dione (12): A mixture of 4,9-dimethyl-4,9-di-*p*-tolyl-2,3,7,8-tetraazaspiro[4.4]nonane-1,6-dione (0.005 mol), carbon disulphide (0.01 mol) and potassium hydroxide (0.01 mol) in DMF (10 mL) was refluxed for 4 hrs. The resulting solid was filtered off and re-crystallized from hot ethanol and dimethylformamide. Yield 1.23 g (75%), yellow powder, m.p. 130 ºC. IR spectrum, v, cm^{-1}: 1654 (C=O), 1292 (C=S). ^{1}H-NMR, δ, ppm: 2.26 (s, 6H, 2CH_3), 2.36 (s, 6H, 2CH_3), 7.26-7.82 (m, 8H, Ar-H's). Analytical for $C_{25}H_{20}N_4O_2S_6$ (600.82); Found, %: C 49.95; H 3.33; N 9.35. Calculated, %: C 49.97; H 3.36; N 9.32.

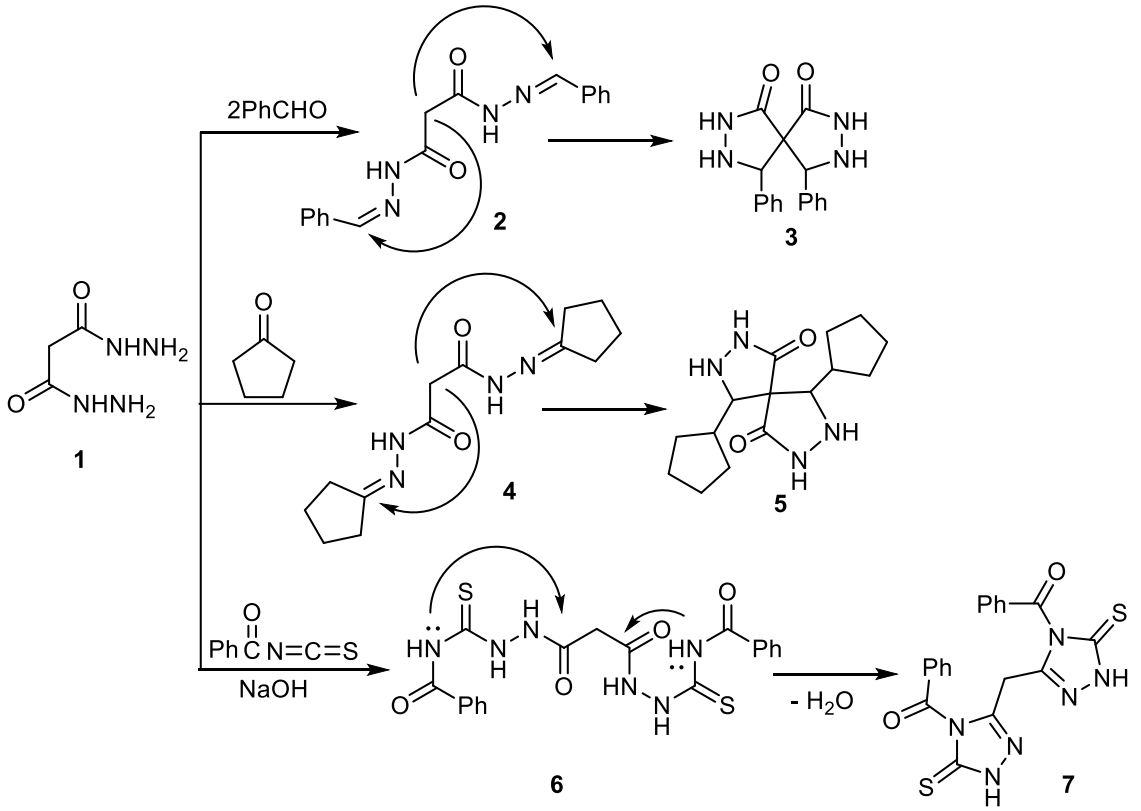
4,9-Dimethyl-2,3,7,8-tetranitroso-4,9-di-*p*-tolyl-2,3,7,8-tetraazaspiro-[4,4]nonane-1,6-dione (13): A mixture of 4,9-dimethyl-4,9-di-*p*-tolyl-2,3,7,8-tetraazaspiro[4.4]nonane-1,6-dione (0.005 mol), dissolve in DMF (10 mL) and 5 ml of acetic acid and sodium nitrite (0.01 mol) put into small amount of water and stirring continued for 1 hr to give the precipitate of product **13** which is filtered off and recrystallized from hot ethanol and dimethylformamide. Yield 1.9 g (69%,), yellow powder, m.p. 130 ºC. IR spectrum, *ν*, cm^{-1}: 3147 (NH), 1666 (C=O). ^{1}H-NMR, δ, ppm: 2.26 (s, 6H, 2CH_3), 2.36 (s, 6H, 2CH_3), 7.26-7.82 (m, 8H, Ar-H's). ^{13}C-NMR spectrum, DMSO-d_6, δ, ppm: N=O (157.91), N=O (139.88), sp^2 carbon at 135.73, sp^3 carbon at 15.06-21.36. Analytical for $C_{21}H_{20}N_8O_6$ (480.44); Found, %: C 52.6; H 4.3; N 23.35. Calculated, %: C 52.5; H 4.2; N 23.32.

III. RESULTS AND DISCUSSION

As a part of a project directed to the utilization of hydrazide (**1**) to get novel azines and azoles. The present article report the novel hetero-cyclization process of malonohydrazide, thus upon subjected malono-hydrazide **1** to react with benzaldehyde resulted spiro derivative **2**. The reaction may be started via condensation product **2** followed by the addition of activated methylene to polarized C=N bond (**Scheme 1**). IR spectra of **3** resulted in peaks at 3443, 3215, 1687 and 1655 for OH, NH, C=O and C=C, respectively. Down field exchangeable signals for (NH) were detected at 11.52 and 11.61 and methylene proton signal was observed at 2.51. Carbonyl carbon was resulted at 164.65 and 169.35 and sp^3 carbon was observed at 127.21.

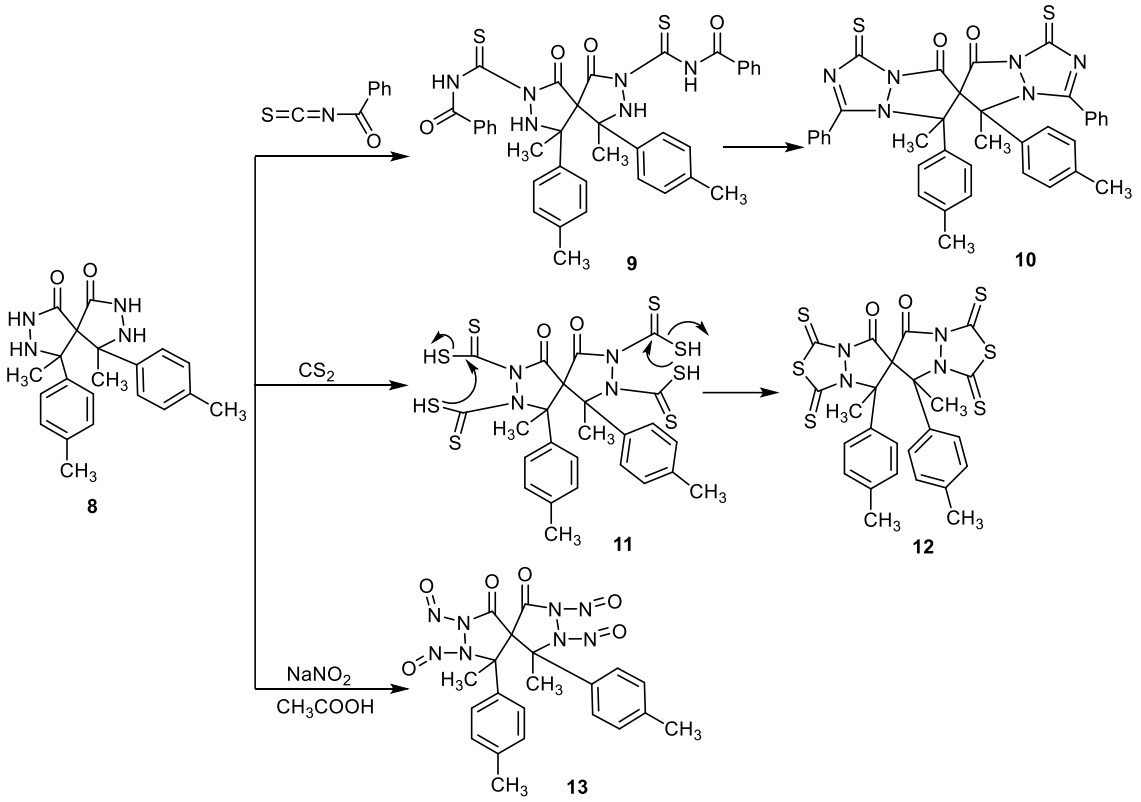
When the target **1** was allowed to react with cyclopentanone leads to non isolable Schiff product **4**, that undergo intramolecular Micheal reaction to furnish the spiro product **5** (**Scheme 1**). The stretching frequencies for NH and C=O were showed at 3367 and 1670 respectively. The (NH) broad signal was observed at 10.00, the

cyclopentanone protons was detected in up field region. The addition of nucleophilic NH_2 group of compound **1** to benzoyl isothiocynate in basic medium resulted in triazole cyclization. The reaction may be started with the formation of thiosemicarbazide derivative **6** followed by intramolecular cyclization affording triazole derivative **7** (**Scheme 1**). The NH, CO and C=S stretching frequencies were observed at 3422, 1653 and 1298 respectively. The OH and NH exchangeable broad signals were showed at 12.10 and 10.51.



Scheme 1: Formation of spiropyrazole derivative

Pyrazole derivative **8** undergo aza Michael with heteroallene providing pyrazolotriazole **10** may be through the non-isolable thiourea derivative (**Scheme 2**). IR of **10** leads to frequencies at 3300, 1681 and 1292 cm^{-1}. ^{1}H-NMR appears CH_3 signal at 2.36 while multiplet of Ar H's was detected in region 7.29-7.94. The C=O and C=C carbons were resonated at 182.49 and 168.28 respectively. The target **8** undergo addition reaction with S=C=S in basic medium followed by heterocyclization via evaluation of H_2S to furnish pyrazothiadiazole derivative **12** (**Scheme 2**). The IR spectra of **12** contained C=O and C=S at 1654 and 1292 respectively. ^{1}H-NMR leads to Ar H's multiplet at 7.26-7.82. Compound **8** undergo douple nitrozation when nitrosated using $NaNO_2$/acetic acid yielding nitroso derivative **13**. Aryl H's multiplet were detected in region 7.26 - 7.82, while CH_3 signal was observed at 2.51. ^{13}C-NMR of compound **13** leads to nitroso group signal at 157.91 and sp^3 carbon at 15.06 and 21.36.



Scheme 2: Design of substituted pyrazoles

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