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Heterocyclization and Biological Evaluation of Malonic Hydrazide; Novel Synthesis of Some Azoles and Azines

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Abstract

Cyclocondensation of malonic hyrazide with two equimolar of dibenzal acetophenone **2** resulted in cyclohexane pyrazole **4** presumably via the non-isolable aza Michel product **3** followed by losing H_2O. Three equivalent amount of benzoyl isothiocynate and malonohydrazide undergo Michel addition providing polythiourea derivative **6**. The hydrazone type **7** cyclocondensed with two mole of CS_2 to furnish pyridazine derivative **9**. Nitrosation of target **7** resulted in hydrazone of type **11** that cyclized to oxadiazine **12**. Compound **7** undergo Michel addition to hetero-allene followed by cyclization yielding pyrimidine **15**.

Keywords Malonic hydrazide; azines; azoles; condensed system; polythiourea.

1. Introduction

One of the most important methods used in the field of drug development is the synthesis of heterocyclic compounds. One of the most significant heterocyclic moieties found is pyrimidine. It is a crucial component of DNA and RNA and is therefore widely transmitted in living things [1]. The antitumor [2], anti-inflammatory [3,4], analgesic, antiviral, anti-HIV [5,6], antineoplastic [7], antitubercular [8,9], and diuretic [10] properties of pyrimidine derivatives have all been documented. Oxadiazine derivatives have wide range of biological and pharmacological properties, such as their antibacterial, anticancer, antifungal, and antiulcer effects [11-14].

A five-membered aromatic ring made up of three carbon atoms and two nearby nitrogen atoms is present in pyrazole molecules. Despite the rarity of a pyrazole core in natural molecules, synthetic pyrazole derivatives are widely used in many different industries. Applications include medicines and agrochemicals [15]. Due to their biological and pharmacological activities as potential HIV-1 inhibitors [16], pesticides [17], fungicides [18], antihypertensive agents [19], and anticancer activity [20], several pyrazole derivatives have drawn a lot of attention. They are also significant and practical starting materials for the synthesis of other fused heterocyclic systems.

2 EXPERIMENTAL

All melting points are uncorrected and were measured using an electro-thermal La 9100 apparatus. IR spectra (KBr, cm^{-1}) were measured on a Nexus 670 FTIR Nicolet, Fourier transform spectrometer. The ^{1}H- and ^{13}C-NMR spectroscopy were determined with a JEOL-JNM-LA 400, 75 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).

1,3-bis((*E*)-7-benzylidene-3-phenyl-2,3,4,5,6,7-hexahydro-1*H*-indazol-1-yl)-propane-1,3-dione (4).

A mixture of malonohydrazide (1.3 g, 0.01 mol), dibenzalcyclohexanone (6.9 g, 0.02 mol)) and triethylamine (2 ml) was refluxed for 5h, then the reaction mixture was cooled down, and poured into ice water with acetic acid (2 ml), the formed solid was separated and recrystallized from hot ethanol. Yield 3.12 g (68%), yellowish brown powder, m.p. 100 °C. IR spectrum, *v*, cm^{-1}: 3367 (NH), 1666 (C=O). ^{1}H-NMR, δ, ppm: 1.37-1.38 (m, 4H, $2CH_2$), 2.64-2.67 (m, 8H, $4CH_2$), 3.21 (s, 2H, 2 CH-Ph), 7.02-7.66 (m, 22H,Ar-H), 8.47 (s,2H,2NH). Elemental analysis for $C_{43}H_{40}N_4O_2$ (644.32); Found %: C 80.3; H 6.28; N 8.66, Calculated %: C 80.1; H 6.25; N 8.69.

N,N'-(2,2'-(2-benzoylcarbamothioyl)malonyl)bis(hydrazinecarbonothioyl) dibenzamide (6).

A mixture of malonohydrazide (1.3 g; 0.01 mol), dissolved in small amount of di-methylformamide, benzoyl isothiocyanate (3.26 ml, 0.02 mol), was refluxed for 3 h, then the reaction was cooled down,

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poured into crushed ice, and the solid filtered off, dried and recrystallized from hot ethanol. Yield 2.3 g (65%), Beige powder, m.p. 250 °C. IR spectrum, *v*, 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). Elemental analysis for $C_{27}H_{23}N_7O_5S_3$ (621.09); Found %: C 52.11; H 3.9; N 22.54, Calculated %: C 52.16; H 3.73; N 22.51.

1,3-bis(3-phenyl-5-thioxo-5,6-dihydropyridazin-1(4*H*)-yl)propane-1,3-di-one(9)

A mixture of (N'1E)-N'1,N'3-bis(1-phenylethylidene)malonohydrazide (3.36 g, 0.01 mol), dissolve in DMF and carbon disulphide (1.2 mL, 0.02 mol) and potassium hydroxide (1.12 g, 0.02 mol) was refluxed for 4 h then it was cooled down. The resulting solid was filtered off and recrystallized from hot ethanol and dimethylformamide. Yield 2.45 gm (75%), yellow powder, mp 215 °C. IR spectrum, v, cm^{-1}: 1604 (C=O), 1566 (C=N), 1284 (C=S). ^{1}H-NMR, δ, ppm: 2.28 (s, 4H, $2CH_2$), 2.51(s, 4H, $2CH_2$), 3.34 (s, 2H, $COCH_2CO$), 7.46-7.94 (m, 10H, Ar-H). Elemental analysis for $C_{21}H_{20}N_4O_2S_4$ (448.10); Found %: C 51.65; H 4.15; N 11.44., Calculated %: C 51.64; H4.16; N 11.44.

1,3-bis(4-phenyl-2*H*-1,2,3-oxadiazin-2-yl)propane-1,3-dione (12).

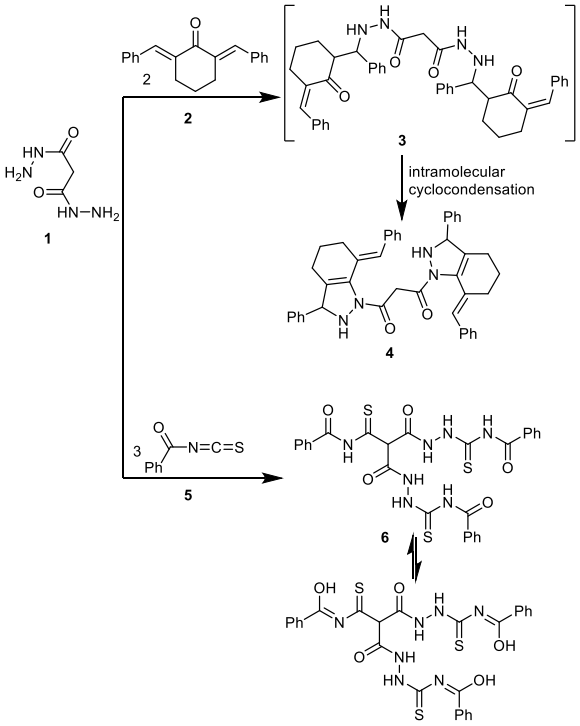
A mixture of (N'1E)-N'1,N'3-bis(1-phenylethylidene)malonohydrazide (3.36 g, 0.01 mol) dissolve in DMF and 5 ml of acetic acid and heated the mixture after that put it into ice, sodium nitrite (1.4 g, 0.02 mol) put into small amount of water and ice, then put into hydrazone, stirring continued for 1 h to give the precipitate of product 12 which is filtered off and recrystallized from hot ethanol and dimethylformamide. Yield 3.8 g (69%,), yellow powder, m.p. 220 °C. IR spectrum, *v*, cm^{-1}: 3190 (NH), 1685 (C=O), 1604 (C=N). ^{1}H-NMR, δ, ppm: 2.50(s, 2H, CH_2), 7.28-7.93 (m, 14, Ar-H's, 4 CH=). Elemental analysis for $C_{21}H_{16}N_4O_4$ (388.12); Found %: C 64.91; H 4.18; N 14.45, Calculated %: C 64.94; H 4.15; N 14.43.

2,2'-methylenebis(6-phenylpyrimidine-4(5*H*)-thione) (15).

A mixture of (N'1E)-N'1,N'3-bis(1-phenylethylidene)malonohydrazide (3.36 g, 0.01 mol) dissolve in DMF, benzoyl isothiocyanate (3.26 ml, 0.02 mol), was refluxed for 3 h, , then the reaction was cooled down, poured into crushed ice, and the solid filtered off, dried and recrystallized from hot ethanol. Yield 3.9 g (71%), Beige powder, m.p. 119 °C. IR spectrum, *v*, cm^{-1}: 1604 (C=N), 1284 (C=S). ^{1}H-NMR, δ, ppm: 2.28(s, 2H, CH_2), 2.51(s, 2H, CH_2), 7.46-7.93 (m, 10H, Ar-H). Elemental analysis for $C_{21}H_{16}N_4S_2$ (388.08); Found %: C 64.95; H 4.18; N 14.45, Calculated %: C 64.92; H 4.15; N 14.42.

3 RESULTS AND DISCUSSION

Malonohydrazide pears polynucleophilic and electrophilic centers for further functionalities and heterocyclization producing polyheterocyclic systems. Thus upon cyclocondensation of malonohydrazide (1) and dibenzylidenecyclohexanone (2); which was obtained from the reaction of cyclohexanone with two equivalent of benzaldehyde in presence of sodium hydroxide, resulted in pyrazole cyclization producing polyheterocyclic compound 4 via the formation of non-isolable aza Michael adduct 4 followed by intramolecular cyclo-dehydration via the attack of nucleophilic nitrogen to electrophilic carbonyl carbon (Scheme 1). The target 6 (keto-enol form) leads to stretching frequencies at 3205 and 1670 cm^{-1} for NH and CO respectively. The sharp signal was observed at 10.51 ppm for NH protons.



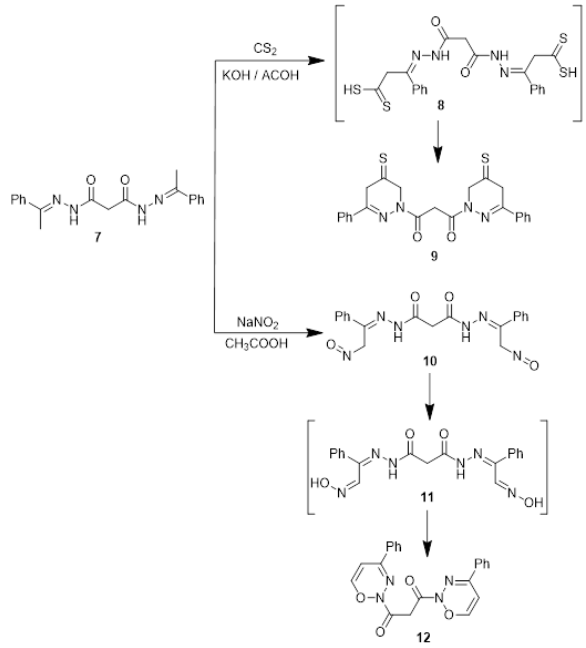
Scheme1: Synthesis of condensed pyrazole and thiourea derivative

The hydrazone of type **7** [21] added its enamenic carbon to electrophilic carbon of carbon di sulphide in presence of KOH producing thiadiazine **9** via formation of **8** that undergo oxidative cyclization (Scheme **2**). Compound **9** showed peaks at 1604, 1566 and 1284 cm^{-1} for CO, C=N and C=S respectively. The CH_2 signals were observed at 2.28, 2.51 ppm, and multiplet signal at 7.46-7.94 ppm for aromatic protons.

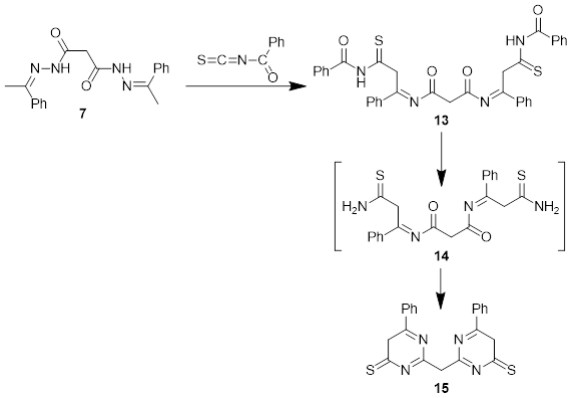
Nitrozation of hydrazone **7** resulted in oxadiazine presumably via nitroso derivative followed by 1,3 H shift and subsequent dehydrogenation affording oxadiazine derivative **12**. IR spectra produced carbonyl absorption at 1686 cm^{-1}. CH_2 signal was observed at 2.28 ppm.

Theoretical amount of malonic hydrazide was added to benzoyl isothiocynate to furnish pyrimidinethione derivative. The reaction may be started via formation

of 1,4 adduct **13** followed by hydrolysis and subsequent cyclohydration. The reaction product **15** was potentiated by the absence of C=O and the presence peak at 12.84 for C=S also ^{1}H-NMR showed the presence aromatic protons.



Scheme 2: Design of pyridazine and oxadiazine derivative



Scheme 3: Synthesis of pyrimidine derivative

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