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Synthesis and spectral characterization of some heterocyclic nitrogen compounds

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ABSTRACT

Quinazolines and pyrimidines are most important class of compounds and have received much attention from both synthetic and medicinal chemists, because of the diverse range of their pharmacological properties. Owing to their versatile chemotherapeutic importance, a number of quinazolin-2,4-dione derivatives were synthesized using appropriate synthetic routes and characterized by IR, ^{1}H NMR, MS, and elemental analysis.

1. Introduction

It is well known that the quinazolines and pyrimidines derivatives are compounds with high biological activities. As an important class of electron-rich *N*-containing heterocycles, pyrimidines are widely present in biologically active compounds and have also versatile synthetic applications. Many derivatives of pyrimidines showed antifungal [1], antibacterial [2], anti-inflammatory [3] anticonvulsant [4-6]. Pyrimidines [7] encourage the authors to gather these moieties hoping to produce valuable new compounds of expected antibacterial and antifungal activity. We report here the synthesis of novel quinazolin-2,4-dione derivatives starting from (2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl)-acetic acid hydrazide (**3**). All the synthesized compounds have been supported by their spectral data.

2. Experimental

2.1. Instrumentation

Melting points were uncorrected and determined on an electric melting point apparatus (Kofler). The IR spectra (KBr) were recorded on a Shimadzu 408 spectrometer. The ^{1}H NMR spectra were recorded using 300 MHz Varian EM 390 spectrometer; chemical shifts are reported in ppm with TMS as an internal standard and are given in δ units. Electron impact mass spectra were obtained at 70 eV with Shimadzu GC-MS (QP-2010 plus). Elemental analyses were carried out at the Microanalysis Unit at Cairo University. The purity of the compounds was detected by TLC.

2.2. Synthesis

2.2.1. (2,4-Dioxo-1,4-dihydro-2H-quinazolin-3-yl)-acetic acid ethyl ester (2)

A mixture of *N*-phenylsulphonyloxyphthalimide (**1**) (5 g, 0.016 mol) and glycine ethyl ester hydrochloride (2.99 g, 0.02 mol) in pyridine (20 mL) was refluxed for 9 hours. After cooling; the reaction mixture was acidified with cold dilute hydrochloric acid (1:1), and the solid formed was filtered off and dried. The target product was crystallized from benzene to give compound **2** as a gray crystal (Scheme 1). Yield: 3.7 g, 90%. M.p.: 206-208 ^{o}C. FT-IR (KBr, ν, cm^{-1}): 3380 (NH), 1719, 1671 (C=O' s). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.1 (t, 3H, CH_3), 4.1 (q, 2H, CH_2), 4.6 (s, 2H, N-CH_2), 7.2-7.9 (m, 4H, arom.), 11.6 (s, 1H, NH). MS (*m/z*, %): 248 (31.1 %) (M^+). Anal. calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.25; H, 4.89; N, 11.35%.

2.2.2. (2,4-Dioxo-1,4-dihydro-2H-quinazolin-3-yl)-acetic acid hydrazide (3)

To a solution of compound **2** (2.5 g, 0.01 mol) in absolute ethanol (30 mL), 5 mL of hydrazine hydrate was added; the reaction mixture was refluxed for 8 hours. The reaction mixture was allowed to cool and the separated product was filtered and dried. Crystallization of the crude product with ethanol and acetic acid, afforded compound **3** as a white crystal (Scheme 1). Yield 1.6 g, 62 %. M.p.: >300. FT-IR (KBr, ν, cm^{-1}): 3296 (NH), 3196 (NH_2), 1714, 1665 (C=O' s). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 4.5 (s, 2H, CH_2), 4.2 (s, 2H, NH_2), 7.1-7.9 (m, 4H, arom.), 9.2 (s, 1H, NH), 11.5 (s, 1H, NH).

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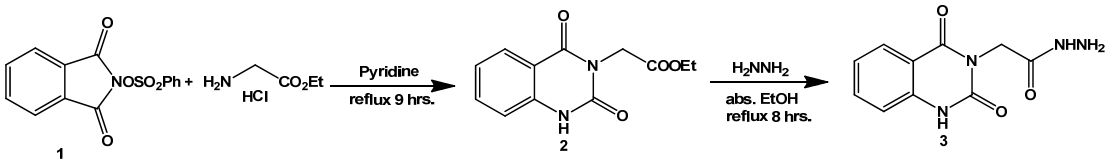
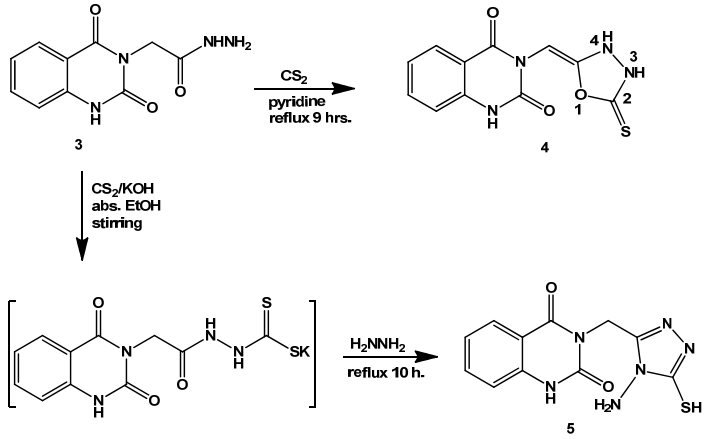


Scheme 1



Scheme 2

MS (*m/z*, %): 234 (20.1 %) (M^+). Anal. calcd. for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30; N, 23.92. Found: C, 51.49; H, 4.31; N, 23.98%.

2.2.3. 3-(5-Thioxo-[1,3,4]oxadiazolidin-2-ylidenemethyl)-1H-quinazoline-2,4-dione (4)

To a solution of compound **3** (0.5 g, 0.002 mol) in pyridine (20 mL), 1 mL of carbon disulphide was added; the reaction mixture was refluxed for 10 hours or until the hydrogen sulfide has been evolved. After cooling; the reaction mixture was acidified with cold dilute hydrochloric acid (1:1), and the solid formed was filtered off and dried. The product was crystallized from acetic acid to give compound **4**, as a yellowish white crystal (Scheme 2). Yield 0.3 g, 60 %. M.p.: 274 °C. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 4.6 (s, 1H, Olifinic CH), 5.1 (s, 1H, NH(4)), 7.2-7.9 (m, 4H, arom.), 10.2 (s, 1H, NHCS), 11.5 (s, 1H, NH). Anal. calcd. for $C_{11}H_8N_4O_3S$: C,47.82; H,2.92; N, 20.28; S, 11.61. Found: C, 48.02; H, 2.94; N, 20.35; S, 11.59%.

2.2.4. 3-(4-Amino-5-mercapto-4H-[1,2,4]triazol-3-ylmethyl)-1H-quinazoline-2,4-dione (5)

To a solution of (2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl)-acetic acid hydrazide (**3**) (1 g, 0.004 mol) in absolute ethanol (30 mL), potassium hydroxide (0.45 g, 0.008 mol) and carbon disulfide (3 mL) were added, respectively. The mixture was stirred for 8 hours in ice bath. The yellow formed salt was filtered off and dried. Then the solid was dissolved in distilled water (50 mL) and hydrazine hydrate (0.1 mol) was added to this solution with reflux for 10 hours, after that the mixture was neutralized with diluted acetic acid to form white precipitate which collected by filtration. The resulting product was recrystallized from ethanol to give compound **5** as a white crystal (Scheme 2). Yield 0.8 g, 66%. M.p.: 282 °C. FT-IR (KBr, ν, cm^{-1}): 3304 (NH), 3203, 3169 (NH_2), 1715, 1660 (C=O' s). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 5.1 (s, 2H, NH_2), 5.7 (s, 2H, CH_2), 7.2-7.9 (m, 4H, arom.), 11.6 (s, 1H, NH), 13.5 (s, 1H, SH). Anal. calcd. for $C_{11}H_{10}N_6O_2S$: C, 45.51; H, 3.47; N, 28.95; S, 11.04. Found: C, 45.80; H, 3.49; N, 29.02; S, 11.24%.

2.2.5. General procedures for synthesis of arylidines (6a-d)

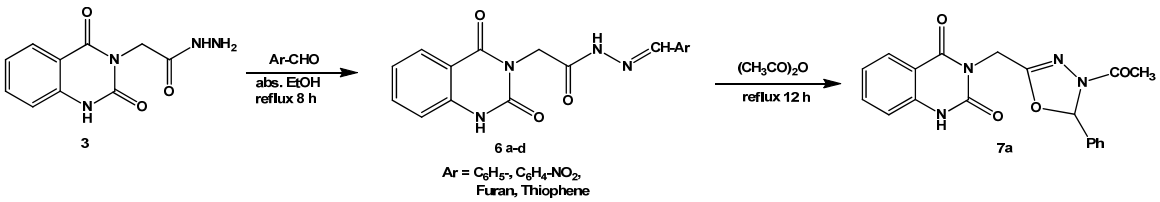
(2,4-Dioxo-1,4-dihydro-2*H*-quinazolin-3-yl)-acetic acid hydrazide **3** (0.45 g, 0.002 mol) was heated under reflux for 10-12 hours with the appropriate aromatic aldehydes namely benzaldehyde, *p*-nitrobenzaldehyde, 2-furaldehyde and thiophenecarbaldehyde (0.003 mol) in absolute ethanol (20 mL) and in presence of piperidine as a catalyst. After cooling; the reaction mixture was filtered off and crystallized from appropriate solvent to give the arylidine derivatives **6a-d**, respectively (Scheme 3).

(2,4-Dioxo-1,4-dihydro-2H-quinazolin-3-yl)-acetic acid benzylidene hydrazide (**6a**): White crystal. Yield: 0.3 g, 55%. M.p.: > 300 °C. FT-IR (KBr, ν, cm^{-1}): 3258 (NH), 3102 (CH aliphatic), 1722, 1693 (C=O' s). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 5.0 (s, 2H, CH_2), 7.2-8.2 (m, 9H, arom.), 8.01 (s, 1H, CH), 11.54 (s, 1H, NH), 11.65 (s, 1H, NH). MS (*m/z*, %): 322 (2.4 %). Anal. calcd. for $C_{17}H_{14}N_4O_3$: C, 63.35; H, 4.38; N, 17.39. Found: C, 63.53; H, 4.41; N, 17.45%.

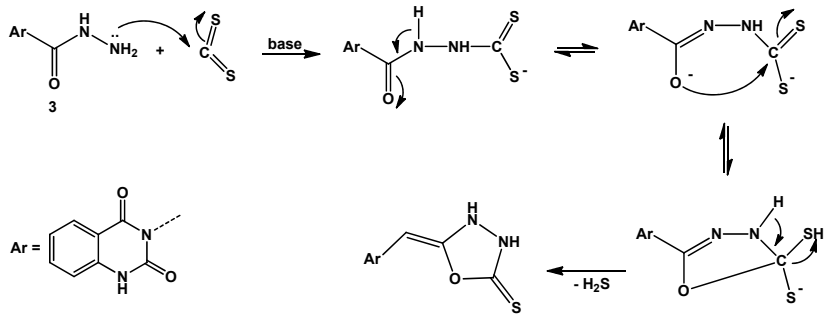
(2,4-Dioxo-1,4-dihydro-2H-quinazolin-3-yl)-acetic acid (4-nitrobenzylidene)-hydrazide (**6b**): White crystal .Yield 0.34 g, 56%. M.p.: > 300 °C. FT-IR (KBr, ν, cm^{-1}): 3206 (NH), 3183 (CH aliphatic), 1715, 1694 (C=O' s). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 5.0 (s, 2H, CH_2), 7.2-8.3 (m, 8H, arom.), 8.0 (s, 1H, CH), 11.6 (s, 1H, NH), 12.0 (s, 1H, NH). MS (*m/z*, %): 367 (3.0 %). Anal. calcd. for $C_{17}H_{13}N_5O_5$: C,55.58; H,3.56; N,19.04. Found: C, 55.60; H, 3.58; N, 19.02%.

(2,4-Dioxo-1,4-dihydro-2H-quinazolin-3-yl)-acetic acid (furan-2-ylmethylene)-hydrazide (**6c**): Yellow crystal. Yield: 0.4 g, 72%. M.p.: > 300 °C. FT-IR (KBr, ν, cm^{-1}): 3383 (NH), 3009 (CH aliphatic), 1739, 1638 (C=O' s). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 4.9 (s, 2H, CH_2), 6.6 (dd, 1H, H_X), 6.8 (dd, 1H, H_M), 7.7 (dd, 1H, H_A), 7.2-7.9 (m, 4H, arom.), 8.09 (s, 1H, CH=N), 11.59 (s, 1H, NH), 11.67 (s, 1H, NH). Anal. calcd. for $C_{15}H_{12}N_4O_4$: C, 57.68; H, 3.85; N, 17.93. Found: C, 57.60; H, 3.86; N, 17.91%.

(2,4-Dioxo-1,4-dihydro-2H-quinazolin-3-yl)-acetic acid (thiophen-2-ylmethylene)-hydrazide (**6d**): Yellow crystal. Yield: 0.39 g, 75%. M.p.: > 300 °C. FT-IR (KBr, ν, cm^{-1}): 3201 (NH), 2924, 2852 (CH aliphatics), 1740, 1659 (C=O' s).



Scheme 3



Scheme 4

^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 4.9 (s, 2H, CH_2), 7.1 (dd, 1H, H_X), 7.5 (dd, 1H, H_M), 7.8 (dd, 1H, H_A), 7.2-7.9 (m, 4H, arom.), 8.4 (s, 1H, CH=N.), 11.5 (s, 1H, NH), 11.7 (s, 1H, NH). Anal. calcd. for $C_{15}H_{12}N_4O_3S$: C, 54.86; H, 3.67; N, 17.05, S, 9.76. Found: C, 54.98; H, 3.80; N, 17.11, S, 9.74%.

2.2.6. 3-(4-Acetyl-5-phenyl-4,5-dihydro-[1,3,4]oxadiazol-2-ylmethyl)-1H-quinazoline-2,4-dione (7a)

A solution of compound **6a** (0.4 g, 0.0012 mol.) with acetic anhydride (20 mL) was heated under reflux for 12 hours. After cooling; the reaction mixture was poured into crushed ice to give white precipitate which collected by filtration then crystallized from ethanol to give compound **7a** as a white crystal (Scheme 3). Yield: 0.42 g, 70%. M.p.: > 300 ^{o}C. FT-IR (KBr, ν, cm^{-1}): 3198 (NH), 1740, 1637 (C=O' s). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.1 (s, 3H, CH_3), 4.8 (s, 2H, CH_2), 7.0 (s, 1H, CH), 7.1-7.9 (m, 9H, arom.), 11.5 (s, 1H, NH). Anal. calcd. for $C_{19}H_{16}N_4O_4$: C, 62.62; H, 4.40; N, 15.37. Found: C, 62.64; H, 4.42; N, 15.42%.

3. Results and discussion

In this study, our target was to synthesize novel quinazolindiones derivatives which based on the reaction between glycine ethyl ester hydrochloride and *N*-phenylsulphonyloxyphtahlimide *via* Lossen rearrangement [8-9] giving quinazoline-2,4-dione derivatives. In the course of the present work, we found, reacting of *N*-phenylsulphonyl oxyphthalimide (**1**) with glycine ethyl ester hydrochloride in pyridine under reflux for 9 hours afford (2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl)-acetic acid ethyl ester (**2**), which then converted to starting material (2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl)-acetic acid hydrazide (**3**) in a good yield through its reaction with hydrazine hydrate in absolute ethanol. The synthetic procedures to obtain the target compounds are depicted in Scheme 1.

Scheme 2 outlines the synthetic pathway used to obtain 3-(5-thioxo-[1,3,4]oxadiazolidin-2-ylidenemethyl)-1*H*-quinazoline-2,4-dione (**4**) which prepared by treatment of compound **3** with with carbon disulphide in pyridine under reflux for 9 hrs. as given mechanism in Scheme 4. Also, we can obtain 3-(4-amino-5-mercapto-4*H*-[1,2,4]triazol-3-ylmethyl)-1*H*-quinazoline-2,4-dione (**5**) by reaction of hydrazide (**3**) with carbon disulphide and ethanolic potassium hydroxide followed by treatment the resulted intermediate with hydrazine hydrate in distilled water.

Scheme 3 outlines our strategies for the synthesis of arylidines (**6a-d**) which produced by reaction of hydrazide (**3**) with some aromatic aldehydes like benzaldehyde, *p*-nitrobenzaldehyde, furan aldehyde and thiophenealdehyde, respectively, in ethanol. Also, we can use compound **6a** to synthesis oxadiazole ring attached to quinazoline moiety by treatment of compound **6a** with acetic anhydride under reflux for 12 hrs. afford 3-(4-acetyl-5-phenyl-4,5-dihydro-[1,3,4]oxa diazol-2-ylmethyl)-1*H*-quinazoline-2,4-dione (**7a**).

4. Conclusion

In conclusion, an efficient synthesis of tetrachloro quinazolindione derivatives has been developed.

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