Synthesis and spectral characterization of some heterocyclic nitrogen compounds

Mamdouh Adly Hassan a, Maghrabi Ali Seleem b, Ahmed Mohamed Mosallem Younes b, Mohamed Mobark Taha b and Abou-Bakr Haredi Abdel-Monsef b, *

a Pharmaceutical Chemistry Department, Faculty of Pharmacy, Sinius University, Arish, 45518, Egypt
b Chemistry Department, Faculty of Science, South Valley University, Qena, 83523, Egypt

*Corresponding author at: Chemistry Department, Faculty of Science, South Valley University, Qena, 83523, Egypt. Tel.: +20.96.5211281; fax: +20.96.5211279. E-mail address: bakooos2004@yahoo.com (A.H. Abdel-Monsef).

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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-2H-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 (Kofer). The IR spectra (KBr) were recorded on a Shimadzu 408 spectrometer. The 1H 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 °C. FT-IR (KBr, ν, cm⁻¹): 3380 (NH), 1719, 1671 (C=O's). 1H NMR (300 MHz, DMSO-d6, δ, ppm): 1.1 (t, 3H, CH3), 4.1 (q, 2H, CH2), 6.4 (s, 2H, N-CH2), 7.2-7.9 (m, 4H, arom.), 11.6 (s, 1H, NH). MS (m/z, %): 248 (31.1 %) (M⁺). Anal. calcd. for C13H14N2O3: 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 (NH₂), 1714, 1665 (C=O’s). 1H NMR (300 MHz, DMSO-d6, δ, ppm): 4.5 (s, 2H, CH2), 4.2 (s, 2H, NH₂), 7.1-7.9 (m, 4H, arom.), 9.2 (s, 1H, NH), 11.5 (s, 1H, NH).
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 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 acidified with cold dilute hydrochloric acid (1:1), and the solid has been evolved. After cooling, the reaction mixture was filtered off and centrifuged 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 benzilidene 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'). 1H NMR (300 MHz, DMSO-δ, δ, ppm): 4.6 (s, 1H, Olnf 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 C₁₇H₁₃N₅O₅: C, 55.58; H, 3.56; N, 19.04. Found: C, 55.60; H, 3.58; N, 19.02.

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

To a solution of compound 3 (0.5 g, 0.002 mol) in absolute ethanol (20 mL), potassium hydroxide (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'). 1H NMR (300 MHz, DMSO-δ, δ, ppm): 4.6 (s, 1H, Olnf 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 C₁₇H₁₃N₅O₅: C, 55.58; H, 3.56; N, 19.04. Found: C, 55.60; H, 3.58; N, 19.02.

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-2H-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'). 1H NMR (300 MHz, DMSO-δ, δ, ppm): 4.6 (s, 1H, Olnf 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 C₁₇H₁₃N₅O₅: C, 55.58; H, 3.56; N, 19.04. Found: C, 55.60; H, 3.58; N, 19.02.

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

MS (m/z, %): 234 (20.1 %) (M⁺). Anal. calcd. for C₉H₇N₅O₅: C, 51.28; H, 4.30; N, 23.92. Found: C, 51.49; H, 4.31; N, 23.98.
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 °C. FT-IR (KBr, v, cm⁻¹): 3198 (NH), 1740, 1637 (C=O’ s). 1H NMR (300 MHz, DMSO-d₆, δ, ppm): 2.1 (s, 3H, CH₃), 4.8 (s, 2H, CH₂), 7.0 (s, 1H, CH), 7.1-7.9 (m, 9H, arom.), 11.5 (s, 1H, NH). Anal. calc'd. for C₁₉H₁₈N₄O₄: 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 quinazolindione derivatives which based on the reaction between glycine ethyl ester hydrochloride and N-phenylsulphonyloxyphtalimide via Lossen rearrangement [8-9] giving quinazoline-2,4-dione derivatives. In the course of the present work, we found, reacting of N-phenylsulphonyloxyphtalimide (1) with glycine ethyl ester hydrochloride in pyridine under reflux for 9 hours afford (2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-acetic acid ethyl ester (2), which then converted to starting material (2,4-dioxo-1,4-dihydro-2H-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]oxadiazol-3-ylidemethyl)-1H-quinazolione-2,4-dione (4) which prepared by treatment of compound 3 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-4H-[1,2,4]triazol-3-ylmethyl)-1H-quinazolinedione-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 4 shows 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]oxadiazol-2-ylmethyl)-1H-quinazolinedione-2,4-dione (7a).

4. Conclusion

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

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References