

Full Paper

Synthesis of New 4(3H)-Quinazolinone Derivatives Using 5(4H)-Oxazolones

Hooshang Hamidian, Ahmad Momeni Tikdari * and Hojatollah Khabazzadeh

Department of Chemistry, Shahid Bahonar University of Kerman, Kerman 76175-133, Iran

* Author to whom correspondence should be addressed; E-mail: amomeni@mail.uk.ac.ir

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Abstract: New derivatives of 5(4H)-quinazolinone containing 2-imidazolin-5-one rings have been prepared from 5(4H)-oxazolone derivatives.

Keywords: 4(3H)-Quinazolinone, 5(4H)-oxazolone, synthetic method.

Introduction

Quinazolinone derivatives are important compounds in chemistry and pharmacology. They have drawn much attention due to their broad range of pharmacological properties [1], which include anticancer [2], anti-inflammatory [3], anticonvulsant [4] and antidiuretic [5] activities. Consequently, considerable efforts have been made to explore new simple and direct approaches towards the construction of 5(4H)-quinazolinone skeletons such as via amidation of 2-aminobenzonitrile, followed by oxidative ring closure [6] and Pd-catalyzed heterocyclization of nitroarenes [7].

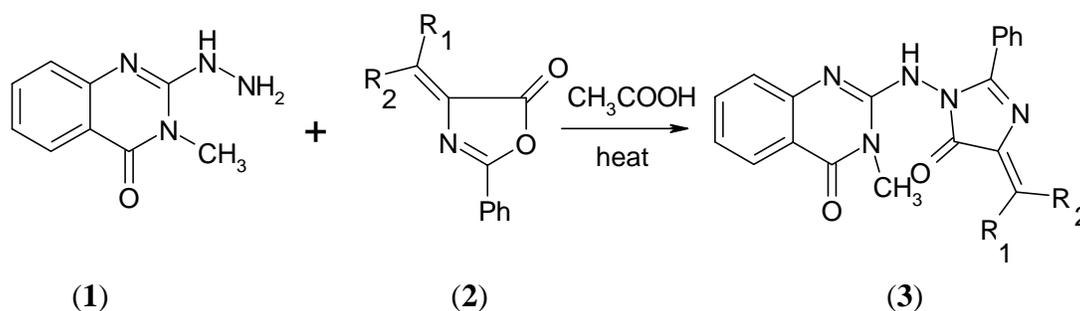
Results and Discussion

In this study we have prepared new 4(3H)-quinazolinone derivatives from 5(4H)-oxazolones. The initial step in the synthetic method involved the synthesis of 2-mercapto-3-methyl-3,4-dihydro-4-quinazolinone [8] by refluxing anthranilic acid and methyl isothiocyanate. In the second step, 2-mercapto-

3-methyl-3,4-dihydro-4-quinazolinone was refluxed with hydrazine hydrate to give 2-hydrazino-3-methyl-4(3H)-quinazolinone (**1**) [9].

2-Phenyl-5(4H)-oxazolone derivatives (**2a-d**) were prepared separately from hippuric acid, acetic anhydride, sodium acetate and an appropriate aldehyde or ketone [10]. In the last step 2-hydrazino-3-methyl-4(3H)-quinazolinone was reacted with the 2-phenyl-5(4H)-oxazolone derivatives (**2a-d**) in the presence of acetic acid (Scheme 1).

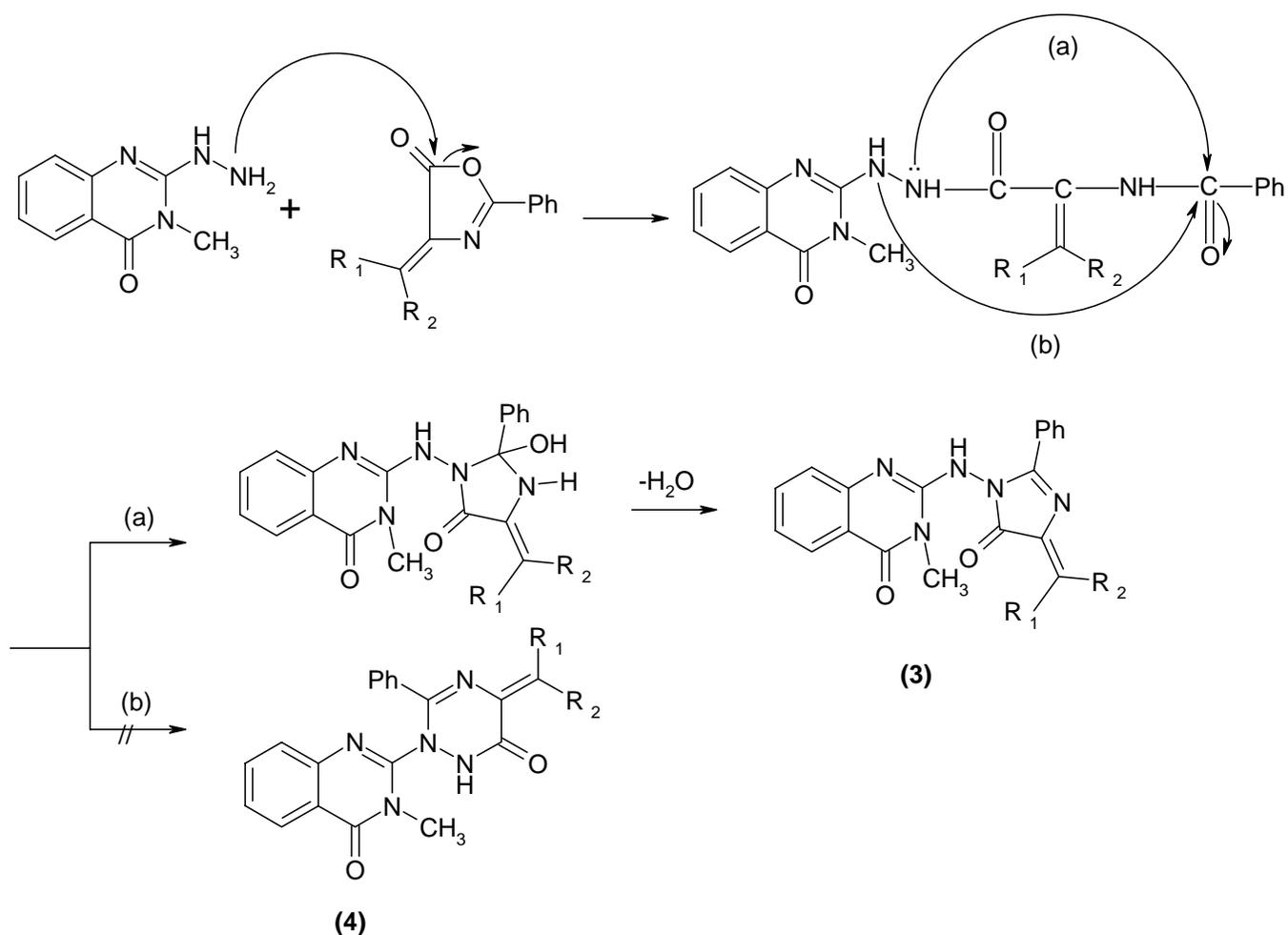
Scheme 1.



Compound	R ₁	R ₂
2a	C ₆ H ₅	H
2b	4-ClC ₆ H ₄	H
2c	4-CH ₃ OC ₆ H ₄	H
2d	Cyclohexyl	

In this reaction, 2-hydrazino-3-methyl-4(3H)-quinazolinone acts as a nucleophile. Compound (**1**) attacks the carbonyl group of the oxazolone ring and the ring is cleaved, then the 2-imidazolidin-5-one ring is formed. It was expected to obtain compound (**4**) but instead compound (**3**) were formed. This reaction cannot be carried out with aldehydes or ketones containing electron-withdrawing substituents such as 4-fluorobenzaldehyde and 2,2,2-trifluoro-1-phenylethanone or basic substituents such as N,N-dimethylbenzaldehyde. Basic groups react with acetic acid and convert it to an electron-withdrawing group. Electron-withdrawing substituents prevent the formation of the 2-hydroxy-imidazolidinyl ring (**3**) (Scheme 2).

Scheme 2.



Conclusions

We have presented a facile route for the synthesis of new 4(3H)-quinazolinone derivatives using 5(4H)-oxazolones.

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Experimental

General

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Mass spectra were obtained on a Shimadzu GC MS-QP 5050 operating at 70 eV. IR spectra were recorded with a Mattson 1000 FT-IR spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Bruker DRX-500 Avance spectrometer using tetramethylsilane (TMS) as an internal standard. Elemental analysis for C, H and N were determined by the National Iranian Oil Company Laboratory (Tehran) using a Heracus CHN-O-Rapid analyzer.

Preparation of 2-mercapto-3-methyl-3,4-dihydro-4-quinazolinone [8].

Anthranilic acid (**1**) (1.37 g, 0.01 mol), methyl isothiocyanate (0.73 g, 0.01 mol) and acetic acid (6 mL) were heated in a sealed tube at 150°C for 90 min. The solid that crystallized gave the pure thiol (1.10 g, yield 58%) as yellow prisms, mp 260-261°C, upon recrystallization from 96% ethanol and then from acetic acid.

Preparation of 2-hydrazino-3-methyl-3,4-dihydro-4-quinazolinone (**3**) [9].

A mixture of 2-mercapto-3-methyl-3,4-dihydro-4-quinazolinone (1.92 g, 0.01 mol) and hydrazine hydrate (2.5 mL, 0.05 mol) in *n*-butanol (40 mL) was stirred under reflux for 18 hr until the evolution of hydrogen sulfide ceased. The reaction mixture was allowed to cool and the resulting solid was filtered off. After dissolution of the product in 3M hydrochloric acid, it was reprecipitated by the addition of aqueous ammonia solution to pH=8, then filtered, washed with water and recrystallized from 96% ethanol to give 1.42 g (65%) of the title compound as white crystals, mp 209-210°C.

Preparation of 5(4H)-oxazolone derivatives (**2a-d**) [10]

A mixture of anhydrous sodium acetate (9.0 g, 0.1 mol), hippuric acid (18.0 g, 0.1 mol), acetic anhydride (35 mL) and the appropriate aldehyde or ketone was heated with intermittent shaking until the mixture had gone from a pink semi-solid to a deep orange liquid (ten to fifteen minutes). The mixture was then cooled to room temperature and the crystalline product which separated was removed by filtration. The crude product was recrystallized from ethanol to give the corresponding 5(4H)-oxazolone derivatives as fine white or yellow needles.

General procedure for the preparation of compounds (**3a-d**).

To a suspension of 2-hydrazino-3-methyl-3,4-dihydro-4-quinazolinone (1.9 g, 0.01 mol) in dioxane (50 mL) was added acetic acid (0.1 mL) and the appropriate 5(4H)-oxazolone (**2a-d**) (0.01 mol). The

mixture was refluxed for an appropriate time (see below) and then the mixture was poured into cold water (100 mL). The precipitate was filtered and recrystallized from ethyl acetate to give the corresponding 3(4H)-quinazolinone derivatives **3a-d** as yellow crystals.

3-Methyl-2-({5-oxo-2-phenyl-4-[1-phenylmethylidene]-4,5-dihydro-1H-imidazol-1-yl}amino)-4(3H)-quinazolinone (3a). Reflux time: 48 hr; yield 71%; m.p. 335-337°C (decomp.); IR (KBr) ν_{\max} : 3408 (N-H), 1714 (C=O), 1682 (C=O), 1617 (C=N), 1602 (C=N) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 3.37 (s, 3H, CH₃), 7.19-8.40 (m, 15H, vinyl, ArH), 10.97 (s, 1H, NH); $^{13}\text{C-NMR}$ (DMSO- d_6) δ ppm: 29.1, 116.1, 123.5, 127.2, 128.5, 129.4, 129.6, 130.9, 132.7, 133.0, 135.7, 147.2, 150.4, 151.4, 152.3, 153.0; MS m/z (%): 421 (M⁺, 19), 249 (24), 105 (100), 91 (54), 77 (62); Anal. Calcd. For C₂₅H₁₉N₅O₂: C, 71.26; H, 4.51; N, 16.63. Found: C, 71.42; H, 4.44; N, 16.73.

2-({4-[1-(4-Chlorophenyl)methylidene]-5-oxo-2-phenyl-4,5-dihydro-1H-imidazol-1-yl}amino)-3-methyl-4(3H)-quinazolinone (3b). Reflux time: 72 hr; yield 43%; m.p. 352-354°C (decomp.); IR (KBr) ν_{\max} : 3394 (N-H), 1714 (C=O), 1692 (C=O), 1626 (C=N), 1602 (C=N) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 3.40(s, 3H, CH₃), 7.02-8.33 (m, 14H, Vinyl, ArH), 10.98 (s, 1H, NH); $^{13}\text{C-NMR}$ (DMSO- d_6) δ ppm: 29.3, 119.3, 123.5, 127.9, 128.1, 129.3, 129.7, 130.9, 131.5, 133.6, 134.8, 35.7, 147.2, 151.4, 151.9, 153.1, 154.7; MS m/z (%): 457 (M+2, 5), 455 (M⁺, 14), 277 (36), 249 (22), 105 (100), 91 (88), 77 (62); Anal. Calcd. For C₂₅H₁₈N₅O₂Cl: C, 65.86; H, 3.95; N, 15.37. Found: C, 66.02; H, 4.10; N, 15.33.

2-({4-[1-(4-Methoxyphenyl)methylidene]-5-oxo-2-phenyl-4,5-dihydro-1H-imidazol-1-yl}amino)-3-methyl-4(3H)-quinazolinone (3c). Reflux time: 24 hr; yield 84%; m.p. 356-358°C (decomp.); IR (KBr) ν_{\max} : 3390 (N-H), 1700 (C=O), 1692 (C=O), 1632 (C=N), 1606 (C=N) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 3.39 (s, 3H, CH₃), 3.85 (s, 3H, OCH₃), 7.12-8.38 (m, 14H, vinyl, ArH), 10.91 (s, 1H, NH); $^{13}\text{C-NMR}$ (DMSO- d_6) δ ppm: 28.9, 55.9, 115.6, 121.2, 123.3, 126.3, 128.2, 128.7, 129.5, 130.5, 131.2, 133.1, 134.4, 134.7, 147.2, 151.6, 153.3, 154.7, 160.6; MS m/z (%): 451 (M⁺, 10), 277 (43), 105 (85), 91 (100), 77 (29); Anal. Calcd. For C₂₆H₂₁N₅O₃: C, 69.18; H, 4.66; N, 15.52. Found: C, 69.09; H, 4.51; N, 15.43.

2-[(4-Cyclohexyliden-5-oxo-2-phenyl-4,5-dihydro-1H-imidazol-1-yl)amino]-3-methyl-4(3H)-quinazolinone (3d). Reflux time: 36 hr; yield 74%; m.p. 340-343°C (decomp.); IR (KBr) ν_{\max} : 3400 (N-H), 2950 (C-H), 1714 (C=O), 1686 (C=O), 1636 (C=N), 1594 (C=N) cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 3.42 (s, 3H, CH₃), 1.43-2.22 (m, 10H, cyclohexyl), 7.17-8.40 (m, 9H, ArH), 10.76 (s, 1H, NH); $^{13}\text{C-NMR}$ (DMSO- d_6) δ ppm: 26.8, 27.4, 30.4, 31.1, 119.6, 121.2, 123.3, 126.2, 128.0, 128.9, 131.2, 132.2, 134.0, 135.4, 146.3, 150.6, 152.7, 153.1; MS m/z (%): 413 (M+, 16), 277 (18), 105 (100), 91 (95), 77 (69); Anal. Calcd. For C₂₄H₂₃N₅O₂: C, 69.73; H, 5.57; N, 16.95. Found: C, 69.79; H, 5.41; N, 16.86.

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Sample availability: available from the authors.