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Methyl α-[(4-oxoquinazolin-2-yl)thio]acetate as Precursor to New Heterocyclic Compounds

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Abstract: Methyl α-[(4-oxoquinazolin-2-yl)thio]acetate (3) is one of the important heterocyclic compounds. It is used as a precursor to synthesize new derivatives of quinazolin-4-one moiety. The compound (4) was synthesized *via* a series of steps from anthranilic acid. Firstly, the anthranilic acid was converted to its methyl ester (1) by esterification with methanol under acidic condition. The ester (1) was reacted with chloroacetyl chloride to produce methyl α-chloroacetamido benzoate (2). The chloro compound (2) was converted to the to the target precursor (3) by boiling of the chloro compound (2) with ammonium thiocyanate for 12 h. The compound (3) was used as synthon to synthesize new series of five membered ring heterocyclic derivatives, *via* its conversion to the corresponding acid hydrazide (4). The acid hydrazide (4) was reacted with carbon disulfide under boiling condition to produce 1,3,4-oxadiazole-5-thione derivative (5). The oxadiazole compound (5) was reacted with alkyl halides to afforded the corresponding alkylthio compounds (6-11), and with aromatic aldehydes to afforded the carbinol derivatives (12-18). The synthesized compounds were identified *via* the physical and spectral data.

Keyword: 2-Mercaptoquinazolin-4-one, Methyl 2-chloroacetaminobenzoate, Methyl anthranilate, 1,3,4 Oxadiazol, Alkylthio derivatives, Acetohydrazide compounds

Introduction

Quinazolin-4(3)-one is one of most important nucleus in heterocyclic chemistry owing to its participation in building block enormous number of biologically active compounds, by incorporation of the quinazolin-4(3)-one nucleus with deffirent heterocyclic moieties, such as triazole, thiadiazole and oxadiazole moieties. These compounds have been entice the medicinal chemists to find and design novel structures having pharmacological activity (Vijai Anand etal., 2009)[1]. Quinazolin-4(3H)-one derivatives showed diversity of biological activity such as analgesic, anti-inflammatory (Bhalla et al ;1993),[2] anti-hypertensive (Kotto et al; 1985),[3] anti-histaminic, anti-cancer (Brana et al; 1994),[4] (Boyle et al; 1993),[5] (Parasharya and Parkh, 1994),[6] anti-tumor (Al-Omary et al; 2012),[7] sedative, hypnotic and anti-microbial activity (Khalil; 1989)[8] (Vogel's; 1994),[9] anti-leishmanial activity (Agarwal et al; 2009)[10] and as anti-oxidant (Decker; 2008).[11] So, the previous views encouraged us to synthesize novel compounds containing quinazolin-4(3H)-one nucleus incorporated with oxadiazole moiety starting from methyl α-[(4-oxoquinazolin-2-yl)thio]acetate.

Experimental

Melting points were recorded on a Stuart melting point SMP30 apparatus and were uncorrected. IR spectra were recorded as neat using Bruker system 2000 FT.IR spectrophotometer. 1H NMR spectra were measured on a Bruker DPX(400) super conducting NMR Spectrometer (400 MHz) using DMSO-d6 as a solvent and TMS as an internal standard.

Synthesis of methyl anthranilate (1) (Bhasker et al.1996)[12]

A solution of anthranilic acid (0.1mol, 14.7 g) in absolute methanol (250 ml) was cooled to 0-5 ^{o}C, then a concentrated sulfuric acid (20 ml) was added dropwise with stirring. After the addition was completed, the mixture was refluxed for 72 h. The volatile components were evaporated under reduced pressure. A cold water (100 ml) was added to the residue. The mixture was basified by dropwise addition of (5 %) sodium bicarbonate solution, then the resulted mixture extracted with (20 * 30 ml) dichloromethane. The organic layers were collected, dried over magnesium sulfate, then evaporated. The crude product was recrystallized from methanol to give red crystals in 85% yield: melting point 22-23 ^{o}C. IR spectrum (neat, ν Cm^{-1}): 3369 (N-H), 1704 (C=O), 1604 (C=C), 1442 (CH3), 1245 (C-O). 1H NMR (DMSO-d6) (δ, ppm): 3.39 (s, 3H, CH3), 6.66 (s, 2H, NH2), 6.53 (t, 1H, H5), 6.79 (d, 1H, H3), 7.25 (t, 1H, H4), 7.71 (d, 1H, H6).

Methyl N-(α-chloroacetyl)anthranilate (2) (Behbehani and Ibrahim, 2013)[13]

To a solution of methyl anthranilate (0.01mol, 1.52 g) in chloroform (50 ml), chloroacetyl chloride (0.012 mol, 1.36 g) and potassium carbonate (0.015 mol, 2.1 g) were added. The reaction mixture was refluxed for 12 h. the volatile material was evaporated under reduced pressure. The residue was washed thoroughly with water then with 5% sodium bicarbonate solution and finally with water. The resulted product was dried then recrystallized from ethanol to give white crystals, in 98% yield, m.p. 90-91 oC, IR (neat, ν, cm -1): 3194 (N-H), 1682, 1676 (2C=O), 1441 (CH3),1226 (C-O). 1H NMR (DMSO-d6): δ, ppm: 3.89 (s, 3H, CH_3), 4.45 (s, 2H, CH_2), 7.27 (t, 1H, H5) , 7.66 (t, 1H, H4), 7.99 (d, 1H, H3), 8.40 (d, 1H, H6), 11.33 (s,1H, NH).

Synthesis of methyl α-[(4'-oxoquinazolin-2'-yl)thio]acetate (3):

To a solution of methyl 2-(α-chloroacetamino)benzoate (2) (0.01 mol, 2.27 g) in methanol (30 ml), ammonium thiocyanate (0.015 mol, 1.15 g) was added with stirring. The mixture was refluxed for 12h then cooled to room temperature. The resulted precipitate was filtered off, washed with water, dried then recrystallized from methanol to give pale yellow crystals in 98 % yield, m.p. 191-192 ^{o}C. IR (neat, ν,cm^{-1}): 3170 (N-H), 1734, 1682 (2C=O), 1375 (CH_3), 681 (C-S). 1H NMR (DMSO-d6): δ, ppm: 3.69 (s, 3H, CH_3), 4.11 (s, 2H, CH_2), 7.4 (t, 1H, H6) , 7.75 (t, 1H, H7), 7.98 (d, 1H, H5), 8.23 (d, 1H, H8), 11.14 (s,1H, NH).

Synthesis of α-[4'-oxoquinazolin-2'-yl)thio]acetohydrazide (4):

A solution of methyl α-(4'-oxoquinazolin-2'-yl)thio]acetate (3) (0.01 mol, 2.64 g), hydrazine hydrate (99.5 %) (0.015 mol, 0.75 g) in absolute ethanol (30 ml) was refluxed with stirring for 12 h. The solid product was separated by filtration, washed with cold water, dried, then recrystallized from ethanol to give green crystals in 90 % yield, m.p. 248 ^{o}C. IR (neat, ν, cm-1): 3289, 3128 (NH_2, N-H), 1662 (2 C=O), 682 (C-S). ^{1}H NMR (DMSO-d6): δ, ppm: 4.41 (s, 2H, CH_2), 5.43 (s, 2H, NH_2) (D_2O exchangeable), 5.88 (s, 1H, NNH), 7.14 (t, 1H, H6), 7.31 (d,1H, H5), 7.70 (d, 1H, H8), 7.48 (t, 1H, H7), 8.23 (s, 1H, H3).

Synthesis of 5-[(4'-oxoquinazolin-2'-yl)thiomethyl]-1,3,4-oxadiazol-2-thiole (5) (Behbehani and Ibrahim, 2013)[13]

To a solution of potassium hydroxide (0.01 mol, 0.65 g) in absolute ethanol (100 ml), the acetohydrazide (4) (0.005, 1.25 g) was added with stirring, followed by carbon disulfide (0.02 mol, 1.52 g). The mixture was refluxed for about 24h or until the release of H_2S was ceased (using lead acetate paper). The volatile materials were evaporated and the residue was added to a crushed ice. The mixture was acidified with diluted hydrochloric acid and the precipitate was filtered off, washed thoroughly with water, dried and recrystallized from ethanol to give yellow crystals in 85 % yield, m.p. 213-215 ^{o}C. IR (neat, ν, cm^{-1}): 3148, 3183 (N-H),1685(C=O); 1234 (C=S). ^{1}H NMR (DMSO-6d): δ, ppm: 4.56 (s, 1H, CH_2), 7.34 (t, 1H, H6), 7.38 (d,1H, H5), 7.79 (t, 1H, H7), 8.45 (d, 1H, H8), 10.2 (d, 1H, SH).

Synthesis of of 5-[(4'-oxoquinazolin-2'-yl)thiomethyl]-1,3,4-oxadiazol-2-alkylthiole (6-11)

A solution of 5-[(4'-oxoquinazolin-2'-yl)thiomethyl]-1,3,4-oxadiazol-2-thiole (5) (0.01mol, 0.3 g) and (0.01 mol) of alkyl halide (methyl iodide or other alkyl bromide) in (25 ml) methanol was refluxed for 10 h, then cooled and poured on ice water (50 ml). The precipitate was filtered off, washed with water, dried then recrystallized from ethanol . The physical and the IR spectral data of compounds (6-11) were listed in Table 1.

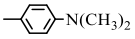
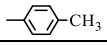
Table 1. The physical and IR spectral data of compounds (6-11)

Compd. No.	R	Yield %	m.p. °C	color	IR (neat, ν, Cm^{-1})		
					C=O	C=N	N-H
6	CH_3-	98	235-237	green	1689	1632	3080
7	$CH_3CH_2CH_2CH_2$-	85	179-180	White	1680	1639	3090
8	CH_2=CH-CH_2-	98	195-197	Green	1685	1636	3108
9	ph-$COCH_2$-	98	167-169	Orange	1683	1635	3082
10	phCH_2-	98	269-270	White	1688	1635	3107
11	2-Br-phCH_2-	95	230-231	Yellow	1681	1633	3108

Synthesis of 5-[(4'-oxoquinazolin-2'-yl)thiomethyl]-2-(subistituted carbinol)-1,3,4-oxadiazol-2-thione (12-18):[12]

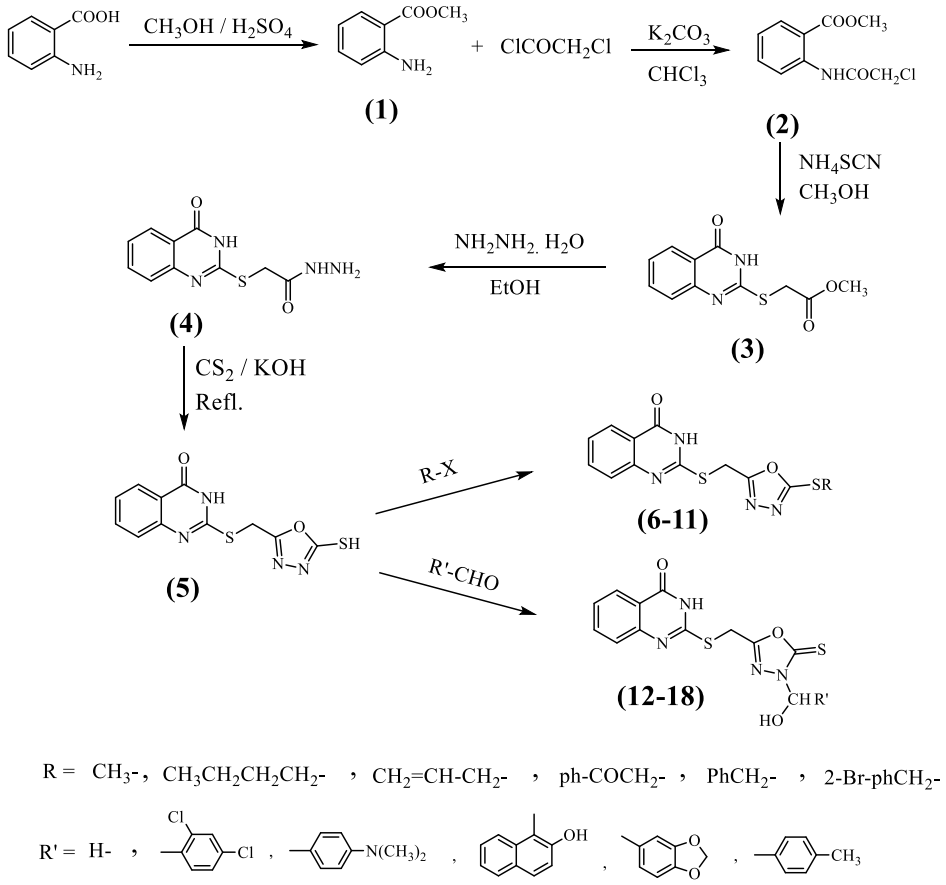
To an ice cooled solution of 5-[(4'-oxoquinazolin-2'-yl)thiomethyl]-1,3,4-oxadiazol-2-thiole (5) (0.02 mol, 0.3 g) in (50 ml) of ethanol, an aldehyde (0.02 mol) was added with stirring. The stirring was continued for further 10 h. The resulted precipitate was filtered off, washed with cold ethanol then recrystallized from ethanol. The physical and the IR spectral data of compounds (12-18) were listed in Table 2.

Table 2. The physical and chemical properties of compounds (12-18).

Compd. No.	R'-	Yield %	m.p. ℃	color	IR (neat) , ν (Cm^{-1})			
					C=N	C=O	C=S	O-H
12	H-	90	345-346	light yellow	1604	1672	1205	3393
13		90	296-297	white	1606	1674	1207	3389
14		90	268-269	brown	1602	1668	1210	3399
15		90	235-237	yellow	1611	1675	1212	3390
16		90	256-257	brown	1610	1670	1202	3377
17		90	295-296	white	1608	1678	1208	3392
18		90	287-288	white	1606	1665	1209	3378

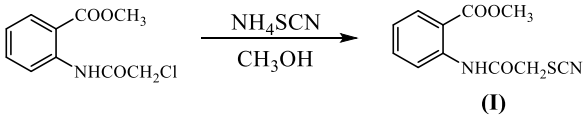
Result and Discussion

The synthetic route of the quinazolin-4(3H)-one derivatives (3-18) was illustrated in Scheme 1. The primal precursor for these heterocyclic compounds is α-[(4'-oxoquinazolin-2-yl)thio]acetohydrazide (4). This compound was synthesized from anthranilic acid via four steps. The anthranilic acid was converted to its methyl ester through



Scheme 1

the conventional acid catalyzed esterification method. The ester (1) was reacted with chloroacetyl chloride in the presence of potassium carbonate as a base to afford methyl 2-(α-chloroacetamino)benzoate (2). The ^{1}H NMR spectrum of compound (2) showed the following chemical shifts (δ, ppm): 3.89 (s, 3H, CH_3), 4.45 (s, 2H, CH_2), 7.27 (t, 1H, H5) , 7.66 (t, 1H, H4), 7.99 (d, 1H, H3), 8.40 (d, 1H, H6), 11.33 (s,1H, NH) [Crews et al, 1998].[14] The reaction of compound (2) with ammonium thiocyanate in absolute ethanol under reflux for 12 h afforded methyl α-[(4-oxoquinazolin-2-yl)thio]acetate (3) via the formation and cyclization of un-isolated methyl 2-(α-thiocyanato acetamino)benzoate (I) as an intermediate compound.



The IR spectrum of the quinazolinone compound (3) showed IR absorption bands at 3170 $Cm^{-1}$for the N-H bond stretching of the quinazolinone nucleus, and two absorption bands at 1734, 1682 Cm^{-1} for the C=O bond stretching of the ester and the amide respectively. The proton NMR spectrum of compound (3) showed the following chemical shifts (δ, ppm): 3.69 (s, 3H, CH_3), 4.11 (s, 2H, CH_2), 7.4 (t,1H, H6), 7.75 (t, 1H, H7), 7.98 (d, 1H, H5), 8.23 (d, 1H, H8), 11.14 (s, 1H, NH). The ester (3) was converted to the corresponding hydrazide compound (4) by its refluxing with hydrazine hydrate in absolute ethanol. The absence of the C=O bond stretching of the ester at 1704 Cm^{-1} indicates the full conversion of the ester (3) to the hydrazide (4). The ^{1}H NMR spectrum of the hydrazide (4) (DMSO-d6) showed the following chemical shifts: δ, ppm: 4.41 (s, 2H, CH_2), 5.43 (s, 2H, NH_2), 5.88 (s, 1H, NNH), 7.14 (t, 1H, H6), 7.31 (d,1H, H5), 7.70 (d, 1H, H8), 7.48 (t, 1H, H7), 8.23 (s, 1H, H3). The hydrazide (4) was used as precursor to synthesize the posterior heterocyclic compounds (5-18). Firstly, the hydrazide (4) was reacted with carbon disulfide in presence of ethanolic potassium hydroxide solution to give 5-[(4'-oxoquinazolin-2'-yl)thiomethyl]-1,3,4-oxadiazol-2-thiole (5). This compound was present in a tautomeric thiol-thione equilibrium as indicated from the IR and ^{1}H NMR spectra. It present as thione in the solid state, while present as thiol in the solution. The IR spectrum of the oxadiazole compound (5) showed absorption bands at 3148, 3183 Cm^{-1} for the (N-H) bond stretching of quinazolinone and

oxadiazole moieties respectively, at 1685 for the (C=O) bond stretching and at 1234 for the (C=S) bond stretching. The ^{1}H NMR (DMSO-6d) spectrum of compound (5) showed the following chemical shifts: δ, ppm: 4.56 (s, 1H, CH_2), 7.34 (t, 1H, H6), 7.38 (d, 1H, H5), 7.48 (t, 1H, H7), 7.82 (d, 1H, H8), 8.21 (s, 1H, H3), 10.2 (d, 1H, SH). Furthermore, two series of derivatives were prepared from the 1,3,4-oxadiazol-5-thiole compound (5). The first one involves the reaction of compound (5) with different alkyl halides to synthesize the alkyl thio derivatives (6-11). This reaction takes place *via* S_N2 mechanism. These compounds showed an absorption bands in the IR spectra at 1680-1689 Cm^{-1} for C=O bond stretching, in addition to absorption band at 1704 Cm^{-1} for the ketonic C=O bond stretching related to compound (9), and at 1632-1639 Cm^{-1} for C=N bond stretching. The ^{1}H NMR (DMSO-6d) spectrum of compound (6) showed the following chemical shifts: δ, ppm: 2.63 (s, 3H, CH_3), 3.90 (s, 2H, CH_2), 7.47 (d, 1H, H5), 7.73 (t, 1H, H6), 7.85 (t, 1H, H7), 7.93 (d, 1H, H8), 8.29 (s, 1H, H3). The ^{1}H NMR (DMSO-6d) spectrum of compound (8) showed the following chemical shifts: δ, ppm: 1.24 (d, 2H, allylic CH_2), 3.90 (s, 2H, CH_2), 4.09 (d, 1H, =CH), 6.1 (d, 2H, =CH_2), 7.37 (t, 1H, H6), 7.48 (t, 1H, H7), 7.47 (d, 1H, H5), 7.83 (d, 1H, H8), 8.19 (s, 1H, H3). The ^{1}H NMR (DMSO-6d) spectrum of compound (10) showed the following chemical shifts: δ, ppm: 3.18 (s, 2H, benzylic CH_2), 3.86 (s, 2H, CH_2), 7.39 (t, 1H, H6), 7.46 (t, 1H, H7), 7.48 (d, 1H, H5), 7.71(d, 1H, H8), 7.81-8.21 (m, 5H, ph-H), 8.26 (d, 1H, H3). The second series involves the reaction of compound (5) with different aldehydes to synthesize the carbinol derivatives (12-18). These compounds showed an absorption bands in their IR spectra at 1665-1678 Cm^{-1} for C=O bond stretching, at 1602-1611 Cm^{-1} for C=N bond stretching, at 1202-1212 Cm^{-1} related to C=S bond stretching and at 3377-3399 Cm^{-1} for the O-H bond stretching. The ^{1}H NMR (DMSO-6d) spectrum of compound (12) showed the following chemical shifts: δ, ppm: 2.09 (s, 2H, SCH_2), 3.18 (s, 2H, NCH_2), 7.39 (t, 1H, H6), 7. 62 (t, 1H, H5), 7.85(t, 1H, H7), 8.00 (s, 1H, H3), 8.21 (d, 1H, H8), 13.48 (s, 1H, OH). The ^{1}H NMR (DMSO-6d) spectrum of compound (13) showed the following chemical shifts: δ, ppm: 2.09 (s, 2H, SCH_2), 3.17 (s, 1H, NCH), 7.24-7.35 (m, 3H, Ar-H), 7. 78 (t, 1H, H6), 7.97 (t, 1H, H7), 8.20 (d, 1H, H5), 8.50 (d, 1H, H8), 9.60 (s, 1H, H3), 13.48 (s, 1H, OH). The ^{1}H NMR (DMSO-6d) spectrum of compound (17) showed the following chemical shifts: δ, ppm: 2.09 (s, 2H, SCH_2), 3.18 (s, 1H, NCH), 6.17 (s, 2H, OCH_2O), 7.20-7.41 (m, 3H, Ar-H), 7. 76 (t, 1H, H6), 7.84 (t, 1H, H7), 7.96 (d, 1H, H5), 8.82 (d, 1H, H8), 9.81 (s, 1H, H3), 13.83 (s, 1H, OH).

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