Regioselective Synthesis of $N_{(3)}$- and O-acylmethyl Derivatives of 2-Methylthio-4(3*H*)-quinazolinone

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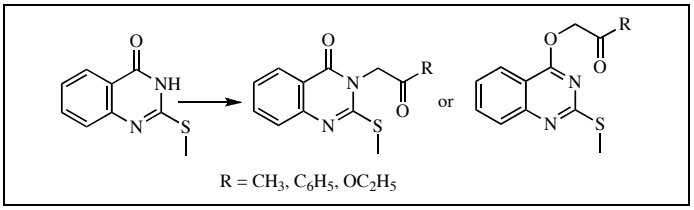

Reaction of 2-methylthio-4(3*H*)-quinazolinone with chloroacetone, ω-bromoacetophenone or ethyl bromoacetate in different solvents (methanol, acetonitrile, dimethylformamide and toluene) using sodium methoxide or potassium carbonate as a base were studied. Regioselective $N_{(3)}$-alkylation took place in toluene using potassium carbonate, whereas in dimethylformamide O-acylmethyl derivatives were obtained. However chloroacetone reacted with 2-methylthio-4(3*H*)-quinazolinone under various conditions to give a mixture of $N_{(3)}$/O-isomers.

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INTRODUCTION

4(3*H*)-Quinazolinones are of considerable interest due their wide range of useful biological activities. 4(3*H*)-Quinazolinone is a constituent of alkaloids [1-3]. The quinazolinone skeleton is considered to be a privileged structure and has been utilized as a druglike scafold in medicinal chemistry [4]. $N_{(3)}$-Substituted 4(3*H*)-quinazolinones show antimalarial [5-9], anti-inflammatory and antitumor [10] activities. A derivative of ($N_{(1)}$-quinazolinyl)acetic acid *Zanerestat* is a remedy of diabetic complications [11]. Substituted $N_{(3)}$-propyl 4(3*H*)-quinazolinone *Proquinazid* is a representative of a new class of antifungal agents, which show high activity on powdery mildew of cereal, grapes and other crops [12]. Some O-substituted derivatives of 4(3*H*)-quinazoline exhibit antifungal or insecticidal activity [13]. In consideration of diverse biological properties of N/O-substituted 4(3*H*)-quinazolinones it is important to develop convenient and efficient methods for synthesis of this type of compounds.

N-Substituted 4(3*H*)-quinazolinones usually are obtained during the quinazolinone ring formation procedure. Anthranilic acid or derivatives, carboxylic acids and amines are used for cyclocondensation reactions to form various 2,3-disubstituted 4(3*H*)-quinazolinones. [14-23]. Another way to N/O-substituted quinazolines is alkylation of ambident 4(3*H*)-quinazolinone anion [10,11,24-28]. However, dual reactivity of ambident anions frequently leads to the formation of mixtures of isomers. The direction of alkylation is dependent on the alkylating agent, substrate, reaction solvent and other reaction conditions [29]. Naturally, the ratio of N/O-substitution in the dual reactivity of 4(3*H*)-quinazolinone anion is determined by the influence of each of these factors. The effect of 2-substituent of the quinazoline ring, on the ratio of N-/O-alkyl products formation was studied by different authors [10,24,26].

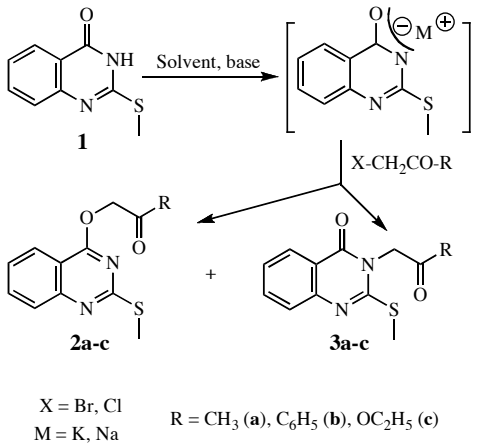
RESULTS AND DISCUSSION

Previously we have found that alkylation of 2-methylthio-4(3*H*)-quinazolinone with methyl bromoacetate in a methanol - sodium methoxide solution resulted in $N_{(3)}$-substituted ester formation [28].

As a continuation of our ongoing studies, herein we report the results of the reaction of 2-methylthio-4(3*H*)-quinazolinone **1** with chloroacetone, ω-bromoacetophenone and ethyl bromoacetate, that involves regioselective alkylation of the ambident anion. Convenient methods for the synthesis of O-acylmethyl substituted quinazolines (**2b**,**c**) and $N_{(3)}$-acylmethyl derivatives of 4(3*H*)-quinazolinone (**3a**-**c**) are presented (Scheme 1). Compounds **3b** and **3c** are known from the literature though they were prepared in a different way. Compound **3b** was obtained by Sinha [17] from 3-(2-oxo-2-phenylethyl)-2-thioxo-2,3-dihydro-4(1*H*)-quinazolinone alkylation with iodomethane [17]. The synthetic route to ester **3c** also utilized cyclocondensation reaction of anthranilic acid ester with the appropriate amine [19].

Reactions of ambident 4(3*H*)-quinazolinone anion **1** with halo acylmethyl derivatives were carried out in different solvents - methanol, acetonitrile, dimethylformamide and toluene. As a base in these reactions sodium methoxide or potassium carbonate was used.

Scheme 1



Reactions in dimethylformamide were carried out at room temperature. At higher temperatures formation of the mixtures of N/O-derivatives was observed. Reactions in other solvents were performed at reflux. The optimal reaction time for compounds **2a,b**, and **3a-c** is 14-18 hours.

The current results showed that regioselectivity to form $N_{(3)}$- or O-derivatives mainly depends on the solvent and the nature of the electrophile used. Reaction conditions and the ratio of isomers are depicted in Table 1.

Table 1

Reaction conditions and the ratio of isomers

Entry	R	Solvent	Base	Time (h)	Temp. (°C)	*Ratio of 2/3
1	CH_3	CH_3OH	$NaOCH_3$	14	reflux	-
2	CH_3	CH_3CN	$NaOCH_3$	18	reflux	1/6
3	CH_3	CH_3CN	K_2CO_3	18	reflux	1/1
4	CH_3	$C_6H_5CH_3$	K_2CO_3	18	reflux	0/1
5	CH_3	DMF	K_2CO_3	18	room t.	1/4
6	C_6H_5	$C_6H_5CH_3$	K_2CO_3	14	reflux	0/1
7	C_6H_5	DMF	K_2CO_3	16	room t.	1/0
8	OC_2H_5	$C_6H_5CH_3$	K_2CO_3	16	reflux	0/1
9	OC_2H_5	DMF	K_2CO_3	2	room t.	1/0

* Ratio of compounds 2/3 was estimated by the data of ^{1}H nmr.

The ratio of isomers was estimated from the data of ^{1}H nmr of the crude product. Surprisingly, chloroacetone did not react with **1** in sodium methoxide-methanol solution, while in acetonitrile a mixture of $N_{(3)}$/O-isomer was formed with the predominance of $N_{(3)}$-substituted derivative **3a** in ratio 6:1 (entry 2). In acetonitrile in the presence of potassium carbonate as a base, the content both of **2a** and **3a** in the mixture is equal (entry 3). Using dimethylformamide as a solvent, the direction and time of the reaction was determined by the electrophile. Reaction of **1** with ω-bromoacetophenone or ethyl bromacetate gave O-acylmethyl derivatives **2b**,**c** (entries 7, 9). It should be noted that formation of **2c** was complete within 2 hours, while reaction with ω-bromoacetophenone proceeded for 24 hours. Unexpectedly, chloroacetone reacted with **1** in dimethylformamide to give a mixture of **2a**/**3a** with marked predominance of $N_{(3)}$-acetylmethyl derivative **3a** (entry 5). Unfortunately we did not succeed to find out conditions for the regioselective synthesis of O-acetylmethyl derivative **2a**. The compound **2a** was isolated from the mixture of isomers by column chromatography.

It is evident that in an aprotic nonpolar solvent (toluene) in the presence of potassium carbonate regioselective $N_{(3)}$-substitution proceeded independently of the electrophile used (entries 4, 6, 8). The yields of compounds **3a**-**c** are about 70%.

The structure of compounds was identified by ir, ^{1}H and ^{13}C nmr data. In the ir spectra of **3a**-**c** strong absorption bands of the substituent acyl group are observed in the region of 1698-1728 cm^{-1} along with the quinazolinone C_4=O group absorption at 1673-1684 cm^{-1}, which is characteristic of 2-alkylthio-$N_{(3)}$-substituted 4(3*H*)-quinazolinones [30]. The ir spectra of O-acylmethyl derivatives **2a**-**c** showed strong peaks at 1698-1750 cm^{-1}, indicating acyl group absorption.

The nmr spectra are not informative enough to indicate whether N- or O-derivative was formed, however comparison of the data shows that CH_2 peaks in O-substituted derivatives 2 are shifted downfield compared to the corresponding peaks of $N_{(3)}$-substituted 3. For example, the OCH_2 peak of **2a** is at 5.13 and 70.7 ppm in the ^{1}H and ^{13}C nmr, respectively, whereas NCH_2 peak of **3a** is at 5.00 and 52.9 ppm, respectively. It was observed that solubility in organic solvents (methanol, 2-propanol, chloroform, hexane, benzene) is high and similar for both $N_{(3)}$- and O-isomers and consequently they could not be separated by crystallization. Melting points of **3a-c** are higher than those of **2a-c** by 20 to 40°C.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The ir spectra were recorded on a Spectrum BX FT-IR (Perkin-Elmer, Sweden) as potassium bromide pellets. Nuclear magnetic resonance (nmr) spectra were recorded on a Unity Varian INOVA spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C using $CDCl_3$ as a solvent. Chemical shifts (δ) are reported in ppm relative to TMS. The reactions and purity of compounds was controlled by tlc on Alugram Sil G/UV_{254} plates. Elemental analyses were performed at the Microanalytical Laboratory of the Department. All solvents were dried and distilled before use.

2-Methylthio-4(3*H*)-quinazolinone (**1**) was prepared as reported in [28].

1-(2-Methylthio-4-quinazolinyloxy)acetone (2a). A mixture of quinazolinone **1** (0.83 g, 4.3 mmol), potassium carbonate 0.42 g, 3 mmol) and acetonitrile (20 ml) was stirred for 10 min. at reflux and then a solution of chloroacetone (0.463 g, 0.42 ml, 5

mmol) in acetonitrile (2 ml) was slowly added dropwise. The reaction mixture was refluxed for 18 hours and filtered of. The solvent was evaporated and the crude material was purified by column chromatography using silica gel Kieselgel 60 (0.063-0.2 mm) with eluent chloroform-ethyl acetate (25:1); R_f = 0.78 (**2a**), R_f = 0.58 (**3a**). Compound **2a**, yield 0.19 g (18%), mp 99-100 °C: ir 1744 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.30 (s, 3H, CH_3), 2.63 (s, 3H, SCH_3), 5.13 (s, 2H, OCH_2), 7.44-7.50 (m, 1H, quinazoline), 7.79-7.80 (m, 2H, quinazoline), 8.14-8.17 (m, 1H, quinazoline) ppm; ^{13}C nmr: δ 14.4, 26.7, 70.7, 113.9, 123.9, 125.9, 126.6, 134.5, 152.3, 165.0, 167.2, 202.7 ppm. *Anal*. Calcd for $C_{12}H_{12}N_2O_2S$ (248.30): C, 58.05; H, 4.87; N, 11.28. Found: C, 58.24; H, 5.01; N, 11.23.

2-(2-Methylthio-4-quinazolinyloxy)-1-phenylethanone (2b). A mixture of quinazolinone **1** (0.83 g, 4.3 mmol), potassium carbonate 0.42 g, 3 mmol) and dimethylformamide (15 ml) was stirred for 10 min. at room temperature and then ω-bromoacetophenone (0.995 g, 5 mmol) was added portion wise over an hour. The reaction mixture was stirred at room temperature for 16 hours and filtered of. Water was added to the filtrate. The precipitate formed was collected by filtration and recrystallized from 2-propanol to give **2b** as a white solid, 0.91 g (68%), mp 133-135 C°: ir 1698 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.54 (s, 3H, SCH_3), 5.86 (s, 2H, OCH_2), 7.50-7.59 (m, 3H, Ar-H), 7.65-7.68 (m, 1H, Ar-H), 7.80-7.82 (m, 2H, Ar-H), 8.03-8.06 (m, 2H, Ar-H), 8.24-8.26 (m, 1H, Ar-H) ppm; ^{13}C nmr: δ 14.4, 68.4, 114.1, 124.2, 125.9, 126.5, 128.1, 129.2, 134.2, 134.4, 134.8, 152.4, 165.2, 167.2, 192.8 ppm. *Anal*. Calcd for $C_{17}H_{14}N_2O_2S$ (310.37): C, 65.79; H, 4.55; N, 9.03. Found: C, 66.04; H, 4.63; N, 8.89.

Ethyl (2-Methylthio-4-quinazolinyloxy))acetate (2c). Compound **2c** was prepared analogously **2b** using ethyl bromo acetate (5 mmol, 0.835 g, 0.57 ml). The reaction mixture was stirred at room temperature for 2 hours and isolated as above to give **2c** as a white solid, 0.96 g (80%), mp 75-76 °C: ir 1750 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.33 (t, J = 7.2 Hz, 3H, CH_3), 2.64 (s, 3H, SCH_3), 4.30 (q, J = 7.2 Hz, 2H, CH_2), 5.12 (s, 2H, OCH_2), 7.46-7.48 (m, 1H, quinazoline), 7.80-7.82 (m, 2H, quinazoline), 8.16-8.19 (m, 1H, quinazoline) ppm; ^{13}C nmr: δ 14.4, 14.5, 61.7, 63.5, 113.9, 124.1, 125.9, 126.5, 134.4, 152.4, 165.1, 167.1, 168.2 ppm. *Anal*. Calcd for $C_{13}H_{14}N_2O_2S$ (278.33): C, 56.10; H, 5.07; N, 10.06. Found: C, 56.07; H, 4.95; N, 10.34.

2-Methylthio-3-(2-oxopropyl)-4(3*H*)-quinazolinone (3a). A mixture of quinazolinone **1** (0.83 g, 4.3 mmol), potassium carbonate 0.42 g, 3 mmol) and toluene (20 ml) was stirred for 5 min. at reflux and then a solution of chloroacetone (0.463 g, 0.42 ml, 5 mmol) in toluene (2 ml) was slowly added dropwise. The reaction mixture was refluxed for 18 hours. The solid was collected by filtration and recrystallized from 2-propanol to give **3a**, yield 0.79 g (74%), mp 132-133 °C: ir 1685, 1728 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.33 (s, 3H, CH_3), 2.69 (s, 3H, SCH_3), 5.00 (s, 2H, NCH_2), 7.39-7.45, 7.60-7.64, 7.71-7.75, 8.21-8.24 (4m, 4x1H, quinazoline) ppm; ^{13}C nmr: δ 15.4, 27.5, 52.9, 119.2, 126.1, 126.6, 127.4, 134.9, 147.9, 156.5, 161.7, 200.2 ppm. *Anal*. Calcd for $C_{12}H_{12}N_2O_2S$ (248.30): C, 58.23; H, 4.83; N, 11.29. Found: C, 58.05; H, 4.87; N, 11.28.

2-Methylthio-3-(2-oxo-2-phenylethyl)-4(3*H*)-quinazolinone (3b). A mixture of quinazolinone **1** (0.83 g, 4.3 mmol), potassium carbonate 0.42 g, 3 mmol) and toluene (20 ml) was stirred for 5 min. at reflux and then ω-bromoacetophenone (0.995 g, 5 mmol) was added portion wise. The reaction mixture was stirred at reflux for 14 hours and filtered. Toluene was evaporated under reduced pressure. The remainder was crystallized from ethanol to give 0.93 g (70%) of **3b** as a white solid, mp 176-178 C°: ir 1673, 1698 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.69 (s, 3H, SCH_3), 5.68 (s, 2H, NCH_2), 7.40-7.46 (m, 1H, Ar-H), 7.55-7.78 (m, 5H, Ar-H), 8.07-8.11 (m, 2H, Ar-H), 8.24-8.27 (m, 1H, Ar-H) ppm; ^{13}C nmr: δ 15.4, 50.0, 119.3, 126.1, 126.6, 127.4, 128.4, 129.2, 134.3, 134.8, 135.0, 147.9, 162.0, 191.3 ppm. *Anal*. Calcd for $C_{17}H_{14}N_2O_2S$ (310.37): C, 65.79; H, 4.55; N, 9.03. Found: C, 65.60; H, 4.75; N, 8.77.

Ethyl (2-Methylthio-4-oxo-3-quinazolinyl)acetate (3c). A mixture of quinazolinone **1** (0.83 g, 4.3 mmol), potassium carbonate 0.42 g, 3 mmol) and toluene (20 ml) was stirred for 5 min. at reflux and then a solution of ethyl bromoacetate (0.835 g, 0.55 ml, 5 mmol) in toluene (2 ml) was slowly added dropwise. The reaction mixture was refluxed for 16 hours and filtered. The solvent was removed in vacuum. The remainder was stirred with 1% sodium hydroxide solution (*ca* 20 ml) at room temperature for 0.5 hour, then the pH was adjusted to 7 by dropwise addition of acetic acid. The precipitate was collected by filtration and crystallized from ethanol to give colorless crystals of **3c**, yield 0.86 g (72%), mp 108-109 °C (ref. [19] mp 107-109 °C): (ir 1685, 1728 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.33 (t, J = 7.2 Hz, 3H, CH_3), 2.71 (s, 3H, SCH_3), 4.29 (q, J = 7.2 Hz, 2H, CH_2), 4.95 (s, 2H, OCH_2), 7.42-7.45, 7.60-7.63, 7.72-7.75, 8.23-8.26 (4m, 4x1H, quinazoline) ppm; ^{13}C nmr: δ 14.4, 15.5, 45.1, 62.3, 119.2, 126.1, 126.5, 134.9, 147.8, 153.5, 161.8, 167.3 ppm. *Anal*. Calcd for $C_{13}H_{14}N_2O_2S$ (278.33): C, 56.10; H, 5.07; N, 10.06. Found: C, 56.14; H, 4.99; N, 10.14.

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