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Quinazoline-4-thiones: formation and reaction with hydrazine hydrate

Milda M. Burbulienė*,

Rita Mažeikaitė,

Lina Rekovič,

Povilas Vainilavičius

Department of Organic Chemistry,
Faculty of Chemistry,
Vilnius University,
Naugarduko St. 24,
LT-03225 Vilnius, Lithuania

2-(Methylthio)quinazoline-4(3*H*)-thione was synthesized by the reaction of the corresponding 4-oxo quinazoline with Lawesson's reagent (LR). 2-(Methylthio-4-thioxoquinazolin-3-yl)acetate was obtained in a similar way, while (4-oxoquinazolin-3-yl) ketones reacted with LR to give a mixture of thionation products – (4-thioxoquinazolin-3-yl)ketones and [1,3]thiazolo[2,3-*b*]quinazoline-5-thiones. Alkylation of 2-(methylthio)quinazoline-4(3*H*)-thione with chloroacetone, ω-bromoacetophenone or ethyl bromoactate gave the corresponding 4-S-substituted derivatives, which in the reaction with hydrazine hydrate afforded 2-methylthio-4-hydrazinoquinazoline. Methyl (2-methylthio-4-thioxoquinazolin-3(4*H*)-yl)acetate with hydrazine hydrate under appropriate conditions underwent the heterocyclization reaction to form the 6-methylthio-2*H*-[1,2,4]triazino[4,3-*c*]quinazoline system.

Key words: thionation, quinazoline-4-thione, 4-hydrazinoquinazoline, heterocyclization, [1,2,4]triazino[4,3-*c*]quinazoline

INTRODUCTION

The quinazoline skeleton is an important pharmacophore found in naturally occurring and synthetic biologically active compounds [1, 2]. Quinazolinone derivatives are associated with a broad spectrum of different biological activities and abundant research information exists regarding this question [3, 4]. Conversion of oxo derivatives to the thioxo isosteres influences the biological properties [5–8]. Transformation of carbonyl-containing compounds into thiocarbonyl is an important task to synthetic organic chemists. Replacement of oxygen by sulfur in organic compounds can be performed with the assistance of thionation agents. Two reagents, Berzelius reagent (phosphorus decasulfide, P_4S_{10}) and Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide), are commonly used for such replacements [9–13]. Success of the thionation reaction depends on functional groups in the molecule. LR effectively converts the oxo group to thioxo in the presence of various functional groups. Nishio et al. [13] reported the reactivity order of LR toward functional groups. Lactams are among the most reactive groups, they could easily be thionated in the presence of various functional groups without affecting them [10, 12, 13].

Continuing our earlier work on the synthesis of functionalized quinazolines [14] it was of interest to examine the thionation reaction of some quinazolinones. Our strategy was based on employing earlier [14] synthesized quinazolin-4-ones bearing an additional oxo group at the $N_{(3)}$ position of the ring.

EXPERIMENTAL

Melting points were determined in open capillaries with a digital melting point IA9100 series apparatus (ThermoFisher Scientific) and are uncorrected. All reactions and purity of the synthesized compounds were monitored by TLC on Silica Gel 60 F_{254} aluminium plates (Merck). Visualization was accomplished by UV light. Column chromatography was performed using Silica gel 60 (0.040–0.063 mm) (Merck). The IR spectra were recorded on an FTIR spectrophotometer Spectrum BX II (Perkin-Elmer) in KBr discs. ^{1}H and ^{13}C NMR spectra were recorded on a Varian INOVA spectrometer (300 and 75 MHz, respectively) using residual solvent peaks as an internal standard. Elemental analyses were performed at the Microanalysis Laboratory of the Department.

Compounds **1, 5, 11, 12** were prepared according to the reported procedures [14].

2-(Methylthio)quinazoline-4(3*H*)-thione (2). A mixture of quinazolinone **1** (1 g, 5.2 mmol) and Lawesson's reagent (LR) (1.26 g, 3.12 mmol) in toluene (20 ml) was heated at reflux for 2 h. The hot reaction mixture was filtered off. The precipitate

* Corresponding author. E-mail: milda.burbuliene@chf.vu.lt

was recrystallized from 2-propanol to give yellow crystals of **2**. Yield 0.6 g (56%), m. p. 234–236 °C (m. p. 230–232 °C [15]). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.61 (s, 3H, SCH_3), 7.48 (t, *J* = 8.0 Hz, 1H, C6-H), 7.58 (d, *J* = 8.0 Hz, 1H, C8-H), 7.82 (t, *J* = 8.0 Hz, 1H, C7-H), 8.48 (d, *J* = 8.0 Hz, 1H, C5-H), 14.12 (s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 13.2, 126.8, 127.1, 127.3, 129.9, 136.0, 146.9, 156.1, 187.5.

General procedure for the synthesis of compounds 3a–c. To a mixture of 2-(methylthio)quinazoline-4-thione (2) (0.90 g, 4.32 mmol) and sodium methoxide (0.1 g, 4.35 mmol of sodium dissolved in 10 ml of methanol) the corresponding halo acyl derivative (4.35 mmol) was added dropwise. The reaction mixture was heated at reflux with stirring for a certain period of time. The inorganic salt was filtered off, the excess of the solvent was removed in vacuum and the residue was recrystallized from a mixture of 2-propanol/ether (1:2) to give **3a–c**.

Ethyl (2-methylthioquinazolin-4-ylthio)acetate (3a). Ethyl bromoacetate (0.73 g, 0.48 ml) was used, reaction time was 4 hours. Yield 0.85 g (67%), m. p. 83–84 °C; IR, ν = 1742 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$), δ, ppm: 1.33 (t, *J* = 7.2 Hz, 3H, CH_3), 2.66 (s, 3H, SCH_3), 4.13 (s, 2H, SCH_2), 4.29 (q, *J* = 7.2 Hz, 2H, OCH_2); 7.43–7.47 (m, 1H, C6-H), 7.78–7.79 (m, 2H, C7-H, C8-H), 7.98 (d, *J* = 8.2 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$), δ, ppm: 14.1, 14.2, 32.1, 62.0, 120.9, 123.9, 125.8, 127.3, 134.2, 148.9, 166.7, 168.6, 169.0. Anal. calcd. for $C_{13}H_{14}N_2O_2S_2$: C, 53.04; H, 4.79; N, 9.52. Found: C, 53.42; H, 4.77; N, 9.28.

1-(2-Methylthioquinazolin-4-ylthio)acetone (3b). 1-Chloroacetone (0.4 g, 0.37 ml) was used, reaction time was 6 hours. Yield 0.74 g (65%), m. p. 88–89 °C; IR, ν = 1720 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$), δ, ppm: 2.46 (s, 3H, CH_3), 2.68 (s, 3H, SCH_3), 4.16 (s, 2H, SCH_2), 7.47–7.49 (m, 1H, C6-H), 7.82–7.86 (m, 2H, C7-H, C8-H), 8.0–8.03 (m, 6H, C5-H); ^{13}C NMR ($CDCl_3$), δ, ppm: 14.4, 29.6, 40.0, 121.3, 124.3, 126.1, 127.6, 134.5, 149.3, 166.9, 169.1, 202.4. Anal. calcd. for $C_{12}H_{12}N_2OS_2$: C, 54.52; H, 4.58; N,10.60. Found: C, 54.46; H, 4.26; N, 10.87.

2-(2-Methylthioquinazolin-4-ylthio)-1-phenyletanone (3c). 2-Bromo-1-phenylethanone (0.866 g) was used, reaction time was 2 hours. Yield 1.06 g (75%), m. p. 128–130 °C; IR, ν = 1698 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$), δ, ppm: 2.54 (s, 3H, SCH_3), 4.87 (s, 2H, SCH_2), 7.46–7.60 (m, 3H, C6-H, Ph-H), 7.65–7.70 (m, 1H, Ph-H), 7.80–7.82 (m, 2H, C7-H, C8-H), 8.06–8.10 (m, 1H, C5-H), 8.14–8.17 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$), δ, ppm: 14.4, 37.4, 121.3, 124.4, 126.1, 127.6, 128.9, 134.0, 134.5, 136.1, 149.3, 166.9, 169.2, 193.7. Anal. calcd. for $C_{17}H_{14}N_2OS_2$: C, 62.55; H, 4.32; N, 8.58. Found: C, 62.48; H, 4.56; N, 8.24.

*Reaction of **3a–c** with hydrazine hydrate.* **4-Hydrazino-2-methylthioquinazoline (4).** A mixture of 0.2 ml of 64% hydrazine hydrate and each of compound 3 (1.5 mmol) in CH_3OH (5 ml) was stirred at room temperature (10 min. for comp. **3b**, 3 h for comp. **3a**) or 20 min. at 40 °C (for comp. **3c**). The solid was filtered off, washed with methanol and dried to give 4-hydrazino-2-methylthioquinazoline (**4**). Yield 95–68%, m. p. 216–218 °C; IR, ν = 3301, 3239, 3182, 3110 cm^{-1} (NH, NH_2); ^{1}H NMR (DMSO-D_6), δ, ppm: 2.50 (s, 3H, SCH_3), 4.76 (s broad, 2H, NH_2), 7.35 (t, *J* = 7.6 Hz, 1H, C6-H), 7.52 (d, *J* = 8.0 Hz, 1H, C8-H), 7.67 (t, *J* = 7.6 Hz, 1H, C7-H), 8.10 (d, *J* = 8.0 Hz, 1H, C5-H), 9.69 (s broad, 1H, NH); ^{13}C NMR (DMSO-D_6), δ, ppm: 13.9, 112.4, 122.9, 124.7, 126.4, 133.2, 149.7, 159.2, 167.4. Anal. calcd. for $C_9H_{10}N_4S$: C, 52.41; H, 4.89; N, 27.16. Found: C, 52.48; H, 4.69; N, 27.34.

Methyl (2-methylthio-4-thioxoquinazolin-3(4*H*)-yl)acetate (6). A mixture of ester 5 (1.32 g, 5 mmol) and Lawesson's reagent (1.46 g, 3.6 mmol) in dry toluene (40 ml) was heated at reflux for 12 h. The hot reaction mixture was filtered off. The filtrate was concentrated to ½ of volume. The solid formed was filtered and recrystallized from 2-propanol to give yellow crystals of 6. Yield 0.66 g (47%), m. p. 164–165 °C; IR, ν = 1744 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$), δ, ppm: 2.74 (s, 3H, SCH_3), 3.83 (s, 3H, OCH_3), 5.62 (s broad, 2H, NCH_2), 7.44 (t, *J* = 8.2 Hz, 1H, C6-H), 7.64 (d, *J* = 8.2 Hz, 1H, C8-H), 7.73–7.76 (m, 1H, C7-H), 8.73 (d, *J* = 8.2 Hz, 1H, C5-H). ^{13}C NMR ($CDCl_3$), δ, ppm: 16.1, 52.1, 53.1, 127.1, 127.3, 127.4, 131.7, 135.1, 142.8, 156.3, 166.8, 189.5. Anal. calcd. for $C_{12}H_{12}N_2O_2S_2$: C, 51.41; H, 4.31; N, 9.99. Found: C, 51.32; H, 4.33; N, 10.11.

Ethyl (2-methylthio-4-thioxoquinazolin-3(4*H*)-yl)acetate was prepared analogously from ethyl (2-methylthio-4-oxo-3(*4H*)-quinazolinyl)acetate. Yield 61%, m. p. 130–131 °C (2-propanol); IR, ν = 1739 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ, ppm: 1.34 (t, *J* = 7.2 Hz, 3H, CH_3), 2.74 (s, 3H, SCH_3), 4.31 (q, *J* = 7.2 Hz, 2H, OCH_2), 5.62 (s broad, 2H, NCH_2), 7.43 (t, *J* = 8.2 Hz, 1H, C6-H), 7.64 (d, *J* = 8.2 Hz, 1H, C8-H), 7.74–7.76 (m, 1H, C7-H), 8.72 (d, *J* = 8.2 Hz, 1H, C5-H)); ^{13}C NMR ($CDCl_3$), δ, ppm: 14.4, 16.2, 52.3, 62.3, 126.1, 127.1, 127.3, 131.7, 135.1, 142.8, 156.4, 166.3, 189.5. Anal. calcd. for $C_{13}H_{14}N_2O_2S_2$: C, 53.04; H, 4.79; N, 9.52. Found: C, 53.29; H, 4.91; N, 9.76.

Methyl (2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl) acetate (7). Hydrogen peroxide (7 ml, 29%) was added dropwise to a stirred solution of methyl ester **5** (0.4 g, 1.5 mmol) in acetic acid (10 ml) at 40–45 °C. The reaction mixture was stirred at this temperature for 6 h and distilled in vacuum to dryness. The solid was washed with H_2O, filtered off and recrystallized from ethyl acetate to give colorless crystals of **7**. Yield 0.19 g (54%), m. p. 212–213 °C; IR, ν = 1754, 1717, 1661 (CO), 3064 cm^{-1} (NH); ^{1}H NMR (DMSO-D_6), δ, ppm: 3.70 (s, 3H, CH_3), 4.69 (s, 2H, NCH_2), 7.23–7.26, 7.27–7.30 (2 m, 2 × 1H, C6-H, C8-H), 7.73 (t, *J* = 8.2 Hz, 1H, C7-H), 7.96 (d, *J* = 8.2 Hz, 1H, C5-H), 11.67 (s, 1H, NH); ^{13}C NMR (DMSO-D_6), δ, ppm: 42.0, 53.0, 114.0, 116.1, 123.6, 128.2, 136.2, 140.1, 150.5, 162.3, 169.3. Anal. calcd. for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.54; H, 4.30; N, 10.11.

Methyl (2-oxo-4-thioxo-1,2-dihydroquinazolin-3(4*H*)-yl) acetate (8)

I. A mixture of ester **7** (1.17 g, 5 mmol) and P_2S_5 (0.56 g, 2.5 mmol) in dry toluene (30 ml) was heated at reflux for 12 h and filtered off. The precipitate was recrystallized from ethanol to give yellowish crystals of **8**. Yield 0.61 g (49%), m. p. 220–222 °C; IR, ν = 1751, 1667 (CO), 3266 cm^{-1} (NH); ^{1}H NMR ($CDCl_3$), δ, ppm: 3.80 (s, 3H, OCH_3), 5.47 (s, 2H, NCH_2), 7.10–7.16 (m, 2H, C6-H, C8-H), 7.62–7.69 (m, 1H, C7-H), 8.54 (d, *J* = 8.2 Hz, 1H, C5-H), 10.54 (s, 1H, NH); ^{13}C NMR ($CDCl_3$), δ, ppm: 47.6, 53.0, 114.7, 115.7, 116.6, 128.1, 130.1, 136.7, 139.8, 168.5, 175.8. Anal. calcd. for $C_{11}H_{10}N_2O_3S$: C, 52.79; H, 4.03; N, 11.19. Found: C, 52.39; H, 4.31; N, 10.91.

II. A mixture of ester **5** (1 g, 3.8 mmol) and P_2S_5 (0.4 g, 1.8 mmol) in toluene (30 ml) was heated at reflux for 12 h. The solid was filtered off and recrystallized from ethanol to give 0.1 g (11%) of compound **8**, m. p. 220–222 °C. The reaction filtrate (toluene) was washed with 5% $NaHCO_3$ solution, water and dried over Na_2SO_4. The solvent was rotary evaporated. The residue was recrystallized from 2-propanol to give 0.31 g (33%) of 4-thioxo ester **6**, m. p. 164–165 °C.

6-Methylthio-2*H*-[1,2,4]triazino[4,3-*c*]quinazolin-3(4*H*)-one (9). To a solution of ester **6** (0.28 g, 1 mmol) in acetonitrile (5 ml) 85% hydrazine hydrate (0.25 ml) was added. The reaction mixture was stirred at reflux for 1 h and cooled to room temperature. The precipitate was filtered off, washed with ethanol and recrystallized from 2-ethoxyethanol to give **9** as a white powder. Yield 0.167 g (68%); m. p. > 250 °C; IR: 1672 (CO), 3188 cm^{-1} (NH); ^{1}H NMR (DMSO-D_6), δ, ppm: 2.57 (s, 3H, SCH_3), 4.46 (s, 2H, NCH_2), 7.25 (m, 2H, C8-H,C10-H), 7.50 (m, 1H, C9-H), 7.83 (d, *J* = 7.8 Hz, 1H, C11-H), 10.92 (s, 1H, NH); ^{13}C NMR: 14.8, 46.4, 118.6, 123.8, 126.0, 126.6, 132.5, 135.9, 143.4, 156.3, 159.1. Anal. calcd. for $C_{11}H_{10}N_4OS$: C, 53.64; H, 4.09; N, 22.75. Found: C, 53.53; H, 4.27; N, 23.02.

2*H*-[1,2,4]triazino[4,3-*c*]quinazolin-3,6(4*H*,7*H*)-dione (10). To a solution of ester **6** (0.28 g, 1 mmol) in dimethylformamide (5 ml) 85% hydrazine hydrate (0.25 ml) was added. The reaction mixture was stirred at reflux for 3 h, cooled to room temperature and poured onto ice. The precipitate was filtered off, washed with water and ethanol to give **10** as grayish powder. Yield 0.09 g (45%); m. p. >250 °C; IR: 1 677 (CO), 3207 cm^{-1} (NH); ^{1}H NMR (DMSO-D_6), δ, ppm: 4.50 (s, 2H, NCH_2), 7.47–7.50 (m, 1H, C5-H), 7.68–7.74 (m, 1H, C8-H), 7.99 (m, 2H, C9-H, C11-H), 9.36 (s, 1H, C6-H), 11.13 (s, 1H, NH); ^{13}C NMR (DMSO-D_6), δ, ppm: 45.6, 116.6, 125.9, 127.8, 130.5, 132.9, 134.0, 136.9, 146.8, 159.3. Anal. calcd. for $C_{10}H_8N_4O_2$: C, 59.99; H, 4.03; N, 27.99. Found: C, 55.78; H, 3.89; N, 28.43.

*Reaction of **11** with Lawesson's reagent.* **1-[2-Methylthio-4-thioxoquinazolin-3(4*H*)-yl]acetone (13). 2-Methyl-5*H*-[1,3]thiazolo[2,3-*b*]quinazoline-5-thione (14).** LR (0.49 g, 1.2 mmol) was added to a solution of compound **11** (0.5 g, 2.01 mmol) in o-xylene (20 ml). The reaction mixture was heated at reflux for 12 h and filtered. The solution was rotary evaporated. The oily residue was treated with hot 2-propanol, the solid formed was purified by column chromatography ($CHCl_3$:EtOAc = 10:1). Yield of **13** 0.055 g (10%), m. p. 164 °C; IR, ν = 1724 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$), δ, ppm: 2.38 (s, 3H, CH_3), 2.72 (s, 3H, SCH_3), 5.67 (s broad, 2H, NCH_2), 7.42–7.47 (t, *J* = 8.5 Hz, 1H, C7-H), 7.61–7.64 (d, *J* = 8.5 Hz, 1H, C8-H), 7.74–7.79 (t, *J* = 8.5 Hz, 1H, C6-H), 8.70–8.72 (d, *J* = 8.5 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$), δ, ppm: 16.3, 27.6, 60.6, 124.1, 125.9, 126.1, 130.0, 131.7, 143.3, 156.3, 189.7, 201.1. Anal. calcd. for $C_{12}H_{12}N_2OS_2$: C, 54.52; H, 4.58; N, 10.60. Found: C, 54.45; H, 4.67; N, 10.77.

Yield of **14** 0.065 g (14%), m. p. 156–157 °C; ^{1}H NMR ($CDCl_3$), δ, ppm: 2.54 (s, 3H, CH_3), 7.42–7.85 (3 m, 3 × 1H, C8,9,7-H), 8.56 (m, 1H, C(3)-H), 8.85–8.87 (d, *J* = 8.5 Hz, 1H, C6-H). ^{13}C NMR ($CDCl_3$), δ, ppm: 13.1, 126.3, 126.9, 127.6, 129.6, 131.2, 136.2, 143.1, 163.3, 179.3. Anal. calcd. for $C_{11}H_8N_2S_2$: C, 56.87; H, 3.47; N, 12.06. Found: C, 56.62; H, 3.33; N, 11.90.

*Reaction of **12** with Lawesson's reagent.* **2-[2-Methylthio-4-thioxoquinazolin-3(4*H*)-yl]-1-phenylethanone (15). 2-Phenyl-5*H*-[1,3]thiazolo[2,3-*b*]quinazoline-5-thione (16).** LR (0.49 g, 1.2 mmol) was added to a solution of compound **12** (0.5 g, 1.61 mmol) in o-xylene (20 ml). The reaction mixture was heated at reflux for 12 h and filtered. The solution was rotary evaporated. The oily residue was refluxed with 2-propanol for 5 min, the solid was filtered and purified by column chromatography ($CHCl_3$:EtOAc = 10:1). Yield of **15** 0.047 g (9%), m. p. 229–230 °C; IR, ν = 1720 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$), δ, ppm: 2.72 (s, 3H, SCH_3), 6.38 (s broad, 2H, NCH_2), 7.46–8.13 (m, 8H, Ph+C6,7,8-H), 8.73(d, *J* = 8.5 Hz, 1H, C5-H); ^{13}C NMR ($CDCl_3$), δ, ppm: 16.4, 56.6, 124.4, 125.9, 126.4, 128.0, 126.3, 128.3, 128.5, 131.2, 132.1, 133.0, 135.0, 145.7, 154.1, 187.1, 190.7. Anal. calcd. for $C_{17}H_{14}N_2OS_2$: C, 62.55; H, 4.32; N, 8.58. Found: C, 62.07; H, 4.77; N, 8.91.

Yield of **16** 0.12 g (25%), m. p. 212–213 °C; ^{1}H NMR ($CDCl_3$), δ, ppm: 7.51–7.87 (m, 8H, Ar-H-quinaz.+Ph-H), 8.88 (d, *J* = 8.5 Hz, 1H, C6-H). ^{13}C NMR ($CDCl_3$), δ, ppm: 121.2, 126.1, 126.7, 127.3, 129.7, 129.8, 130.3, 130.4, 131.0, 135.2, 143.2, 155,2, 181.7. Anal. calcd. for $C_{16}H_{10}N_2S_2$: C, 65.28; H, 3.42; N, 9.52. Found: C, 65.68; H, 3.65; N, 9.23.

3-(2-Hydrazonopropyl)-2-(methylthio)quinazolin-4(3*H*)-one (17). A mixture of **12** (0.3 g, 1.2 mmol) and hydrazine hydrate (0.24 g, 4.8 mmol) in methanol (2 ml) was heated at 55–60 °C temperature for 4 hours. Solid was filtered and recrystallized from 2-propanol to give white crystals of 17. Yield 0.14 g (44%), m. p. 153–155 °C; IR: ν = 3300, 3227 (NH_2), 1676 cm^{-1} (CO). ^{1}H NMR ($CDCl_3$), δ, ppm: 1.82 (s, 3H, CH_3), 2.67 (s, 3H, SCH_3), 4.93 (s, 2H, NCH_2), 5.10 (s, 2H, NH_2), 7.38–7.43 (m, 1H, C6-H), 7.59–7.75 (m, 2H, C7,8-H), 8.24–8.27 (m, 1H, C5-H)). ^{13}C NMR ($CDCl_3$), δ, ppm: 12.2, 15.4, 49.0, 119.4, 125.9, 126.4, 127.4, 134.6, 143.8, 147.9, 157.9, 162.2. Anal. calcd. for $C_{12}H_{14}N_4OS$: C, 54.94; H, 5.38; N, 21.36. Found: C, 55.50; H, 5.30; N, 21.56.

RESULTS AND DISCUSSION

Thionation of 2-methylthio-4-quinazolinone (**1**) was accomplished using LR (Scheme 1). While heating at reflux of the reaction mixture in dry toluene for 2 h, 4-thioxo derivative **2** was isolated in 56% yield. Then, alkylation of the ambident anion of 2-methylthio-4-thioxoquinazoline (**2**) with halo-acylmethyl derivatives afforded S-substituted derivatives **3a–c** in moderate to good yields. Reactions were carried out in a methanol/sodium methoxide solution.

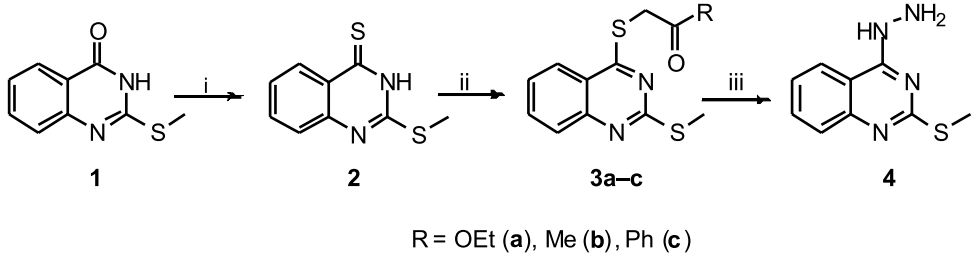
4-Thioxo ester **6** was synthesized by the thionation procedure similar to that described for compound **2**. Prolonged heating at reflux (12 h) of a mixture of 4-oxo ester **5** and LR in toluene yielded 47% of thioxo ester **6** (Scheme 2).

When **5** was allowed to react with P_4S_{10} in dry toluene at reflux (12 h), together with the desired ester **6** the reaction mixture yielded 11% of thioxo derivative **8**. Likely traces of moisture in a commercial phosphorus sulfide initiated ester **8** formation in the acidic reaction mixture.

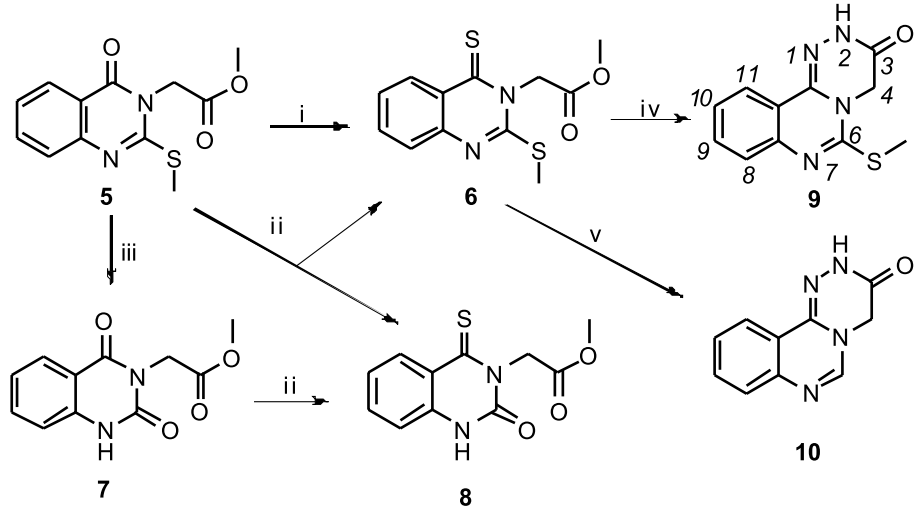
Use of LR to convert an oxo group to thioxo sometimes gives unexpected results [9, 10]. When conversion of ester **5** lactamic C=O to thiolactam C=S has been performed successfully in toluene at reflux, thionation of ketones **11**, **12** yielded a mixture of thiolactams **13**, **15** and the corresponding thiazoles **14**, **16** (Scheme 3). Reactions were performed in xylene at reflux. Apparently due to high reactivity of the ketone function towards LR, under experimental conditions thionation occurred not only at lactam C=O but also at the side chain oxo group. Because of possible thioxo-thiol tautomerism of the resulting intermediate and the electrophilicity of the C(2) position of the quinazoline ring, the following elimination of methanethiol gave rise to thiazoles **14**, **16** formation. The resulting mixtures were chromatographed and the corresponding thiolactams **13**, **15** and thiazoles **14**, **16** were isolated.

Structures of the synthesized compounds were characterized by means of spectroscopic data and elemental analysis. Structure of ester **8** was confirmed by an alternative thionation reaction of **7** to produce **8**.

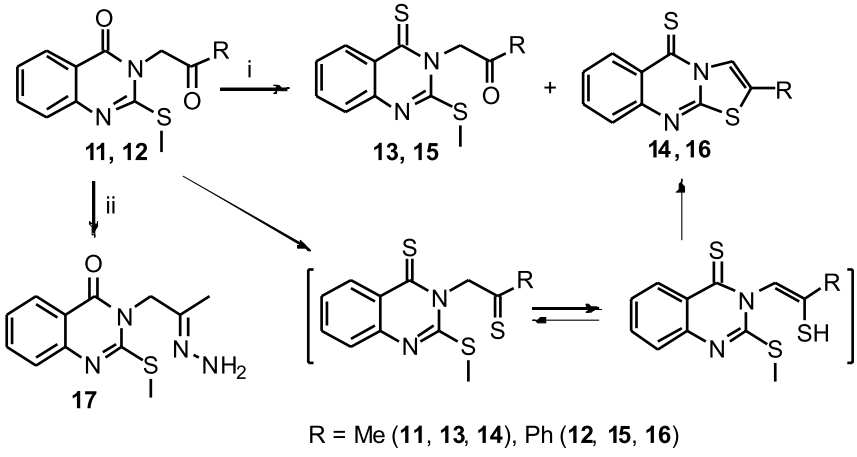
S-Acylmethyl derivatives **3a–c** have some nucleophile sensitive positions. The carbonyl function in these molecules could react with hydrazine hydrate to give the corresponding hydrazine derivatives. On the other hand, quinazoline 2-alkylthio substituents are prone to the nucleophilic substitution reaction [14, 16]. Our interest was to examine susceptibility of these compounds towards attack of a strong nucleophile, namely, hydrazine hydrate. The reactions of **3a–c** with



Scheme 1. Reagents and conditions: i – LR, xylene, reflux, 4 h; ii – $RCOCH_2$-Hal, MeONa, MeOH, reflux, 1–2 h; iii – $N_2H_4 \cdot H_2O$, MeOH, rt, 3 h



Scheme 2. Reagents and conditions: i – LR, toluene, reflux, 12 h; ii – P_4S_{10}, toluene, reflux, 12 h; iii – H_2O_2, acetic acid, rt, 3 h; iv – $N_2H_4 \cdot H_2O$, CH_3CN, reflux, 1 h; v – $N_2H_4 \cdot H_2O$, DMF, reflux, 3 h



Scheme 3. Reagents and conditions: i – LR, xylene, reflux, 12–16 h; ii – $N_2H_4 \cdot H_2O$, CH_3OH, rt, 3 h

hydrazine hydrate (Scheme 1) were performed in a methanol solution. The formation of 4-hydrazinoquinazoline **4** from **3a** and hydrazine hydrate at room temperature occurred within 3 hours, whereas **3b** at the same conditions reacted immediately. Reaction of **3c** with hydrazine was found to be somewhat slower compared to those described above. No reaction was observed at room temperature. Heating of the reaction mixture at 40 °C for 20 min gave a quantitative yield of **4**. Experiments with **3a–c** showed the C(4) electrophilic site of the quinazolines **3a–c** ring to be most sensitive to nucleophile attack. At given conditions hydrazine hydrate prefers to attack at the C(4) electrophilic site instead of the carbonyl group function either C(2) position.

Next, we investigated the reactivity of 4-thioxo ester **6** with hydrazine hydrate. Our earlier studies showed that reaction of 4-oxo analogue **5** with hydrazine hydrate gave the corresponding hydrazide, which under appropriate conditions underwent cyclization to form imidazo[2,1-*b*]quinazolin-4-one [14a]. Investigations of quinazoline fused heterocycles are underway, however, 1,2,4-triazinoquinazolines are studied insignificantly. Some time ago patents appeared by D. L. Trepanier and S. Sunder disclosing 1,2,4-triazino[4,3-*c*]quinazolines as pharmacologically active compounds on CNS [17]. Recently analogous structures were expected to show antimicrobial properties [18]. Several synthetic methodologies have been reported since that time. 1,2,4-Triazino[4,3-*c*]quinazolines can be prepared either from 1,2,4-triazine or quinazoline precursors. Starting with quinazoline, the most common pathway to triazinoquinazolines is cyclocondensation of 4-hydrazinoquinazoline derivatives with carbonyl compounds [18, 19]. The second one includes the reaction of (4-thioxoquinazolin-3-yl)acetic acid ester with hydrazine hydrate [20, 21].

In view of this, a number of experiments of thiolactam-N-acetic ester **6** with hydrazine hydrate in various solvents (methanol, acetonitrile and dimethylformamide) at different temperatures were carried out (Scheme 2). No result was observed at room temperature in methanol, whereas slow heterocyclization occurred at higher temperature. In methanol at reflux the reaction mixture yielded 30% of triazine **9**, besides 46% of unreacted starting ester **6** was recovered. The similar outcome was observed in acetonitrile at room temperature. The best yield of triazine **9** was achieved by refluxing of ester **6** with hydrazine hydrate in acetonitrile. When **6** was allowed to react with hydrazine hydrate in dimethylformamide at reflux, the complex reaction mixture was obtained, from which only [1,2,4]triazino[4,3-*c*]quinazoline **10** was isolated. The structure of triazines **9** and **10** was established on analytical and spectral data. In the ^{13}C NMR spectra of products **9** and **10** the chemical shift value characteristic for thione $C_{(4)} = S$ at ca 187 ppm disappeared. Comparing the ^{1}H NMR spectroscopic data of compound **10** with those of **9** clearly indicates the methylthio group degradation. One proton signal at ca 10.9 ppm was assigned to the C(2)-H proton of triazine **10**.

Ketone **11** reacted with hydrazine hydrate (Scheme 3) at room temperature to give hydrazine derivative **17** while ketone **12** at the same conditions did not react.

CONCLUSIONS

In summary, reaction of (2-methylthio)quinazolin-4-one or esters of 2-(methylthio-4-oxoquinazolin-3-yl)acetate with Lawesson's reagent (LR) gave the corresponding 4-thioxo quinazoline derivatives, while under similar conditions together with thionation of an oxo group at C4, the cyclization reaction of (2-methylthio-4-oxoquinazolin-3-yl) ketones occurred to form [1,3]thiazolo[2,3-*b*]quinazoline-5-thiones. Alkylation of 2-(methylthio)quinazoline-4(3*H*)-thione gave the corresponding 4-S-substituted derivatives, which in the reaction with hydrazine hydrate afforded 2-methylthio-4-hydrazinoquinazoline. Methyl (2-methylthio-4-thioxoquinazolin-3(4*H*)-yl)acetate with hydrazine hydrate under appropriate conditions underwent the heterocyclization reaction to form the 6-methylthio-2*H*-[1,2,4]triazino[4,3-*c*]quinazoline system.

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Milda M. Burbulienė, Rita Mažeikaitė, Lina Rekovič, Povilas Vainilavičius

4-CHINAZOLINTIONAI: SUSIDARYMAS IR REAKCIJA SU HIDRAZINHIDRATU

S a n t r a u k a

2-Metiltio-4-chinazolintionas ir (2-metiltio-4-tiokso-3-chinazolinil) acetatas buvo susintetinti veikiant atitinkamus 4-okso darinius Lawesono reagentu (LR). Panašiomis sąlygomis iš (2-metiltio-4-okso-3-chinazolinil) ketonų ir LR susidarė 4-tiokso dariniai ir ciklizacijos produktai – [1,3]tiazolo[2,3-*b*]chinazolin-5-tionai. Alkilinant 2-metiltio-4-chinazolintioną chloracetonu, ω-bromacetofenonu ar bromacto rūgšties etilesteriu, susidarė $S_{(4)}$-acilmetildariniai, kuriuos veikiant hidrazinhidratu kambario temperatūroje išskirtas 4-hidrazino-2-metiltiochinazolinas. (2-Metiltio-4-tioksochinazolinil) acetatas, reaguodamas su hidrazinhidratu acetonitrilo ar dimetilformamido virimo temperatūroje, ciklizuojasi ir sudaro 6-metiltio-2*H*-[1,2,4]triazino[4,3-*c*] chinazolino heterociklinę sistemą. Susintetintų junginių struktūra patvirtinama ^{1}H, ^{13}C BMR ir IR spektroskopijos bei elementinės analizės duomenimis.