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Formation of 1-methyl[1,2,4]triazolo[4,3-*a*] quinazolin-5(4*H*)-ones by reaction of 2-hydrazinoquinazolin-4(3*H*)-ones with acetylacetone

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Abstract: Reaction of 2-hydrazinoquinazolin-4(3*H*)-ones with acetylacetone results in the formation of 1-methyl[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones instead of 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)quinazolin-4(3*H*)-ones. Under similar conditions, the 7-hydrazinocarbonyl group in quinazolin-4(3*H*)-one moiety is transformed into a pyrazole derivative, which can be replaced by amine with the amide formation.

Keywords: acetylacetone; amide formation; 2-hydrazinoquinazolin-4(3*H*)-one; pyrazole; [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one.

Introduction

The reaction of hydrazines with β-dicarbonyl compounds is the common approach to the synthesis of pyrazoles [1, 2]. However, in the case of heterocyclic hydrazines, such as 2-hydrazino-3-methylquinoxaline, the formation of a triazole has been reported [3, 4]. 1,4-Dimethyl-1,2,4-triazolo[4,3-*a*]quinoxaline has been identified as the side product of the reaction of 2-hydrazino-3-methylquinoxaline with 1-phenyl-1,3-butanedione [4].

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Results and discussion

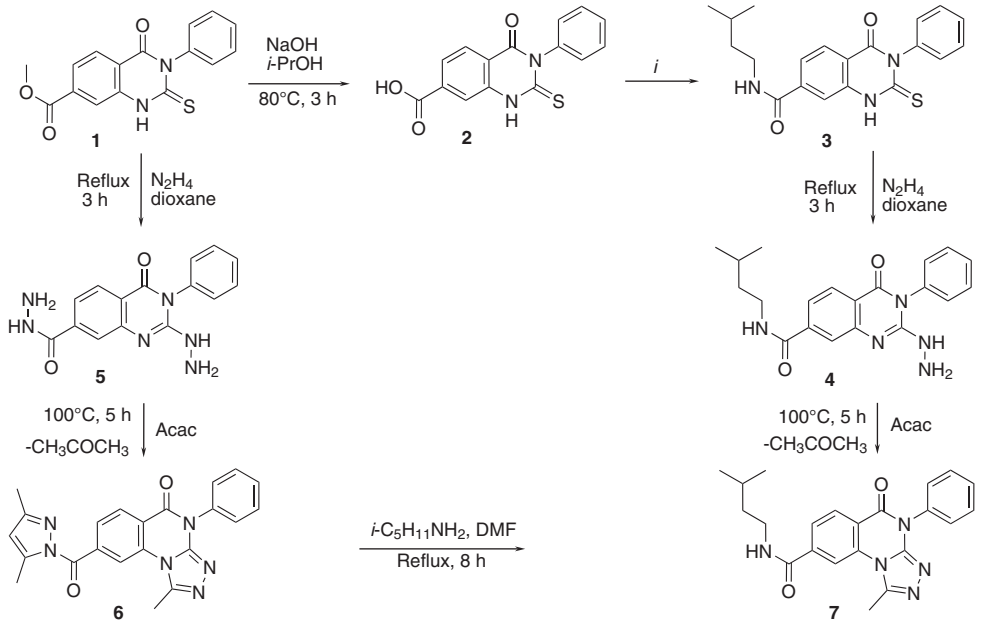
Our attempt to obtain pyrazole derivatives by treatment of 2-hydrazinoquinazolin-4(3*H*)-ones **4**, **5** with acetylacetone led to the formation of [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones **6**, **7** as main products. Under similar conditions, the 7-hydrazinocarbonyl group in 2-hydrazino-7-hydrazinocarbonyl-4-oxo-3-phenyl-3,4-dihydroquinazoline (**5**) was converted into a pyrazole derivative **6** (Scheme 1). In a full agreement with this result, the treatment of **6** with 2-methylbutylamine gave the expected amide **7**.

The purity and structures of synthesized compounds were confirmed by LC/MS and ^{1}H NMR spectroscopy data. The singlet for 1-CH_3 group at 2.36 ppm is characteristic for [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones **6**, **7**. Other singlets at 2.12 and 2.55 ppm are attributed to the respective 3-CH_3 and 5-CH_3 groups of the pyrazole. The singlet at 6.26 ppm in the ^{1}H NMR spectrum of **6** belongs to 4-H of the pyrazole. The signal of the NHCO proton of amides **3**, **4**, **7** appears as triplet at 8.55 ppm.

The formation of [1,2,4]triazolo[4,3-a]quinazolin-5(4*H*)-ones by reaction of 2-hydrazinoquinazolin-4(3*H*)-ones with acetylacetone is consistent with the suggestion that heterocyclic hydrazines may react with β-diketones via intermediate dihydro[1,2,4]triazole, such as **8** followed by cleavage of the ketone residue, as shown in Scheme 2 [4].

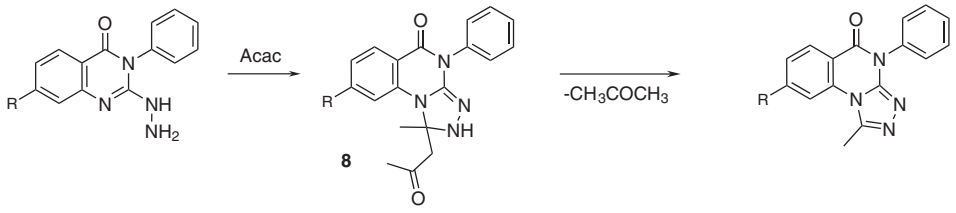
Conclusion

Reaction of 2-hydrazinoquinazolin-4(3*H*)-ones with acetylacetone results in the formation of triazole derivatives instead of pyrazole.



i CDI, dioxane, reflux 1 h; *i*-$C_5H_{11}NH_2$, dioxane, reflux 2 h

Scheme 1



Scheme 2

Experimental

^{1}H NMR-spectra were recorded in DMSO-d_6 on Varian WXR-400 (400 MHz) spectrometer. ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker DRX-300 spectrometer (100 MHz). Elemental analysis was performed on a Euro EA-3000 apparatus. Melting points were measured with a Buchi B-520 melting point apparatus and were not corrected. LC/MS spectra were recorded with a PE SCIEX API 150EX liquid chromatograph equipped with a UV detector (λ_{max} 215 and 254 nm) and using a Luna-C_{18} column, Phenomenex (100×4 mm). Elution started with water and ended with acetonitrile/water (95:5, v/v) using a linear gradient at a flow rate of 0.15 mL/min and an analysis cycle time of 25 min. Starting 2-hydrazinoquinazolin-4-ones **4**, **5** were obtained from commercially available methyl 4-oxo-3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylate (**1**) according to a published method [5].

4-Oxo-3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylic acid (2) To an agitated suspension of methyl 4-oxo-3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylate (**1**, 3.12 g, 10 mmol) in 30 mL of isopropanol, 20% aqueous solution of NaOH (5 mL) was added. The solution was heated under reflux for 3 h then diluted with 50 mL of water and neutralized with 3 mL of 10% aqueous HCl. The precipitate was filtered and crystallized from a mixture of DMF (5 mL) and isopropanol (20 mL): yield 2.56 g (86%); a creamy solid; mp>300°C (dec.); ^{1}H NMR: δ 7.08 (t, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.80 (dd, *J* = 7.8 Hz, *J* = 2.0 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 2H), 7.95 (d, *J* = 2.0 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 13.10 (s, 1H, NH), 13.50 (br s, 1H, OH); ^{13}C NMR: δ 118.8, 123.8, 125.1, 126.8, 128.3, 129.2, 130.4, 139.00, 139.3, 146.2, 153.6, 167.1, 170.0. Anal. Calcd for $C_{15}H_{10}N_2O_3S$: C, 60.39; H, 3.38; N, 9.39. Found: C, 60.47; H, 3.36; N, 9.34.

***N*-(3-Methylbutyl)-4-oxo-3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxamide (3)** The mixture of 4-oxo-3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylic acid (**2**, 1.79 g, 6 mmol) and 1-(1*H*-imidazol-1-ylcarbonyl)-1*H*-imidazole (CDI, 1.05 g, 6.5 mmol) in 30 mL of anhydrous dioxane was heated under reflux with stirring for 1 h. Then 2-methylbutylamine (0.52 g, 6 mmol) was added. The mixture was heated under reflux for 2 h. After cooling, the mixture was diluted with water (50 mL) and allowed to stand overnight to form a precipitate, which was filtered, washed with water, and crystallized from a mixture of dimethylformamide (10 mL) and isopropanol (20 mL): yield 1.92 g (87%); a white solid; mp 290–292°C; ^{1}H NMR: δ 0.88 (d, *J* = 7.0 Hz, 6H), 1.40 (q, *J* = 7.0 Hz, 2H), 1.52–1.72 (m, 1H), 3.25 (q, *J* = 7.0 Hz, 2H), 7.08 (t, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 2H),

7.80 (dd, *J* = 7.8 Hz, *J* = 2.0 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 2H), 7.95 (d, *J* = 2.0 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 8.55 (t, *J* = 7.0 Hz, 1H, CONH), 13.10 (s, 1H, NH); ^{13}C NMR: δ 22.7, 25.1, 38.4, 41.2, 118.7, 123.9, 125.0, 126.3, 128.3, 129.2, 130.3, 139.0, 139.6, 146.3, 153.6, 166.8, 169.9. Anal. Calcd for $C_{20}H_{21}N_3O_2S$: C, 65.37; H, 5.76; N, 11.44. Found: C, 65.43; H, 5.74; N, 11.48.

2-Hydrazino-*N*-(3-methylbutyl)-4-oxo-3-phenyl-3,4-dihydroquinazoline-7-carboxamide (4) A mixture of dioxane (10 mL), hydrazine hydrate (3 mL), and *N*-(3-methylbutyl)-4-oxo-3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxamide (**3**, 1.84 g, 5 mmol) was heated under reflux with stirring for 3 h. The lower dioxane layer was separated and diluted with water (20 mL). The precipitate was filtered, washed with isopropanol (10 mL), and crystallized from mixture of DMF (10 mL) and isopropanol (20 mL): yield 1.29 g (68%); a white solid; mp>300°C (dec.); ^{1}H NMR: δ 0.88 (d, *J* = 7.0 Hz, 6H), 1.40 (q, *J* = 7.0 Hz, 2H), 1.52–1.72 (m, 1H), 3.25 (q, *J* = 7.0 Hz, 2H), 5.70 (s, 2H, $NHNH_2$-2), 7.06 (t, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.57 (dd, *J* = 7.8 Hz, *J* = 2.0 Hz, 1H), 7.75 (d, *J* = 2.0 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 2H), 7.98 (d, *J* = 7.8 Hz, 1H), 8.55 (t, *J* = 7.0 Hz, 1H, CONH), 9.33 (s, 1H, $NHNH_2$-2); ^{13}C NMR: δ 22.7, 25.0, 38.4, 41.2, 118.8, 123.9, 125.6, 126.8, 128.4, 129.1, 130.0, 139.1, 139.7, 146.1, 154.1, 159.2, 166.8. Anal. Calcd for $C_{20}H_{23}N_5O_2$: 65.73; H, 6.34; N, 19.16. Found: C, 65.79; H, 6.31; N, 19.21.

2-Hydrazino-4-oxo-3-phenyl-3,4-dihydroquinazoline-7-carbohydrazide (5) A mixture of dioxane (10 mL), hydrazine hydrate (4 mL), and methyl 4-oxo-3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylate (**1**, 1.56 g, 5 mmol) was heated and stirred under reflux for 3 h. The lower dioxane layer was separated and diluted with water (20 mL). The resultant precipitate was filtered, washed with isopropanol (10 mL), and crystallized from a mixture of DMF (10 mL) and isopropanol (20 mL): yield 1.21 g (78%); a white solid; mp>300°C (dec.); ^{1}H NMR: δ 4.55 (br. s, 2H, $CONHNH_2$), 5.70 (s, 2H, $NHNH_2$-2), 7.08 (t, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.57 (dd, *J* = 7.8 Hz, *J* = 2.0 Hz, 1H), 7.75 (d, *J* = 2.0 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 2H), 8.00 (d, *J* = 7.8 Hz, 1H), 9.40 (s, 1H, $NHNH_2$-2), 10.02 (s, 1H, $CONHNH_2$); ^{13}C NMR: δ 118.6, 123.4, 125.7, 126.9, 128.3, 129.1, 130.4, 139.1, 140.0, 144.2, 155.5, 161.7, 166.0. Anal. Calcd for $C_{15}H_{14}N_6O_2$: C, 58.06; H, 4.55; N, 27.08. Found: C, 57.97; H, 4.58; N, 27.13.

8-[(3,5-Dimethyl-1*H*-pyrazol-1-yl)carbonyl]-1-methyl-4-phenyl[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one (6) The suspension of 2-hydrazino-4-oxo-3-phenyl-3,4-dihydroquinazoline-7-carbohydrazide **5** (1.55 g, 5 mmol) in acetylacetone (20 mL) was heated at 100ºC with stirring for 5 h. After cooling, the mixture was diluted with isopropanol (50 mL). The resultant precipitate was filtered, washed with isopropanol (10 mL), and crystallized from a mixture of DMF (10 mL) and isopropanol (20 mL): yield 1.47 g (74%); a creamy solid; mp 296–298°C; ^{1}H NMR: δ 2.12 (s, 3H), 2.36 (s, 3H, CH_3-1), 2.55 (s, 3H), 6.26 (s, 1H), 7.52–7.76 (m, 6H), 8.00 (d, *J* = 2.0 Hz, 1H), 8.31 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR: δ 12.6, 13.3, 14.1, 113.6, 118.8, 123.5, 125.8, 126.9, 128.3, 129.2, 130.8, 135.3, 139.0, 139.9, 141.8, 144.3, 152.3, 155.3, 161.5, 166.1; LC/MS: *m*/*z* 399.3 [M+H$^+$] (64%). Anal. Calcd for $C_{22}H_{18}N_6O_2$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.39; H, 4.52; N, 21.16.

1-Methyl-*N*-(3-methylbutyl)-5-oxo-4-phenyl-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinazoline-8-carboxamide (7): Protocol A The suspension of 2-hydrazino-*N*-(3-methylbutyl)-4-oxo-3-phenyl-3,4-dihydroquinazoline-7-carboxamide **4** (1.83 g, 5 mmol) in acetylacetone (20 mL) was heated at 100ºC with stirring for 5 h. After cooling, the mixture was diluted with isopropanol (50 mL). The resultant precipitate was filtered, washed with isopropanol (10 mL), and crystallized from a mixture of DMF (10 mL) and isopropanol (20 mL): yield 1.29 g (68%), a white solid; mp>300°C; ^{1}H NMR: δ 0.88 (d, *J* = 7.0 Hz, 6H), 1.40 (q, *J* = 7.0 Hz, 2H), 1.52–1.72 (m, 1H), 2.36 (s, 3H, CH_3-1), 3.25 (q, *J* = 7.0 Hz, 2H), 7.42–7.56 (m, 5H), 7.74 (dd, *J* = 7.8 Hz, *J* = 2.0 Hz, 1H), 8.00 (d, *J* = 2.0 Hz, 1H), 8.26 (d, *J* = 7.8 Hz, 1H), 8.55 (t, *J* = 7.0 Hz, 1H, CONH); ^{13}C NMR: δ 13.4, 22.7, 25.1, 38.36, 4.2, 118.6, 123.4, 125.8, 126.9, 128.3, 129.1, 130.7, 135.4, 139.0, 139.9, 144.2, 155.5, 161.6, 166.9; LC/MS: *m*/*z* 390.4 [M+H$^+$] (62%). Anal. Calcd for $C_{22}H_{23}N_5O_2$: C, 67.85; H, 5.95; N, 17.98. Found: C, 67.78; H, 5.99; N, 18.03.

Protocol B A solution of 8-[(3,5-dimethyl-1*H*-pyrazol-1-yl)carbonyl]-1-methyl-4-phenyl[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one (**6**, 0.80 g, 2 mmol) and 2-methylbutylamine (0.26 g, 3 mmol) in anhydrous DMF (10 mL) was heated under reflux for 8 h. After cooling, the mixture was diluted with water (30 mL) and the resultant precipitate was filtered, washed with isopropanol (10 mL), and crystallized from a mixture of DMF (5 mL) and isopropanol (10 mL): yield 0.64 g (84%); a white solid; mp>300°C (dec.). This sample was identical to the sample obtained by protocol A both by ^{1}H NMR spectrum and LC/MS data.

References

[1] Elguero, J. Pyrazoles. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F., Eds. Pergamon Press: Oxford, 1996; Vol. 3, pp. 1–75.

[2] Alvarez-Builla, J.; Vaquero, J. J.; Barluenga, J. Modern Heterocyclic Chemistry; Wiley-VCH: Weinheim, 2011; Vol. 1, p. 659.

[3] Shiho, D.; Tagami, S. Studies on compounds related to pyrazine. II. The reaction of 3-substituted-2-hydrazinoquinoxalines with carbonyl compounds. *J. Am. Chem. Soc.* **1960**, *82*, 4044–4054.

[4] Aggarwal, R.; Sumran, G.; Kumar, R.; Singh, Sh. P. Reaction of 2-hydrazino-3-methylquinoxaline with aryl-1,3-diketones: a structural reinvestigation. *ARKIVOC* **2007**, *15*, 292–302.

[5] Danilchenko, S. Yu.; Drushlyak, O. G.; Kovalenko, S. M. Synthesis of substituted 2-hydrazinoquinazolin-4-ones as intermediates for heterocyclic compounds synthesis. *J. Org. Pharm. Chem.* **2014**, *12*, 66–73 [*Zhurn. Org. Pharm. Chim.* **2014**, *12*(3), 66–73].