Chemistry of Heterocyclic Compounds, Vol. 44, No. 11, 2008

SYNTHESIS OF NEW 1-SUBSTITUTED 4-(2-PHENYLQUINAZOLIN-4-YL)- AND 4-(2-PHENYLQUINAZOLIN-4-YLIDENE) THIOSEMICARBAZIDES

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Two new 1-substituted 4-(2-phenylquinazolin-4-yl)- and 4-(2-phenylquinazolin-4-ylidene) thiosemicarbazides were formed by a multistep domino reaction of imidoyl isothiocyanate derivative with 1,1-di-R-hydrazine in acetone solution. Application of hydrazine hydrate under the same reaction conditions afforded 4-(2-phenylquinazolin-4(3H)-ylidene)-2-(propen-2-yl)-1-(propan-2-ylidene) thiosemicarbazide via a six-step triple-component domino reaction.

Keywords: quinazoline, thiosemicarbazide, domino reaction, hydrogen bond interaction.

Finding a new methodologies for the synthesis of a family of biologically potent compounds by employing building blocks with multifunctional groups is a key target for drug development. Thioureas and thiosemicarbazides appear to be ideal candidates for the development of such processes since they are the core structural fragments in the families of compounds known to display biological activities, e.g. pyrazole [1], 1,2,4-triazoles [1–5], 1,3,4-oxadiazoles [3, 4], 1,3,4-thiadiazoles [1, 4, 5], 1,3-thiazoles [6], 1,2,4-triazepine [7], 1,3,4-thiadiazine [8], 1,3,4-thiadiazepine [9, 10], etc. The reported synthetic routes for thioureas and thiosemicarbazides were usually addition of amines and hydrazines to isothiocyanates [11].

Recently we described the domino syntheses of 3,3-disubstituted 1-(2-phenyl-3H-quinazolin-4-ylidene)-thioureas [12] and 3-N-substituted 1-N-(2-phenylquinazolin-4-yl)thioureas [13–15] by a simple reaction of the *in situ* generated N-(2-cyanophenyl)benzimidoyl isothiocyanate with secondary and primary amines, respectively.

Herein we report an efficient synthesis of 1-substituted 4-(2-phenyl- quinazolin-4-yl)- and 4-(2-phenyl-quinazolin-4-ylidene) thiosemicarbazides by a simple reaction of N-(2-cyanophenyl)benzimidoyl isothiocyanate (**1**) with hydrazines. Thus, the reactions of imidoyl isothiocyanate **1** with 1,1-dimethyl-hydrazine (**2**), 1,1-diphenylhydrazine (**3**), or hydrazine hydrate in acetone gave three different interesting products: 1,1-dimethyl-4-(2-phenylquinazolin-4-yl) thiosemicarbazide (**4**), 1,1-diphenyl-4-(2-phenylquinazolin-4(3H)-ylidene) thiosemicarbazide (**5**), or 4-(2-phenylquinazolin-4(3H)-ylidene)-2-(propen-2-yl)-1-(propan-2-ylidene) thiosemicarbazide (**6**), respectively (Scheme 1).

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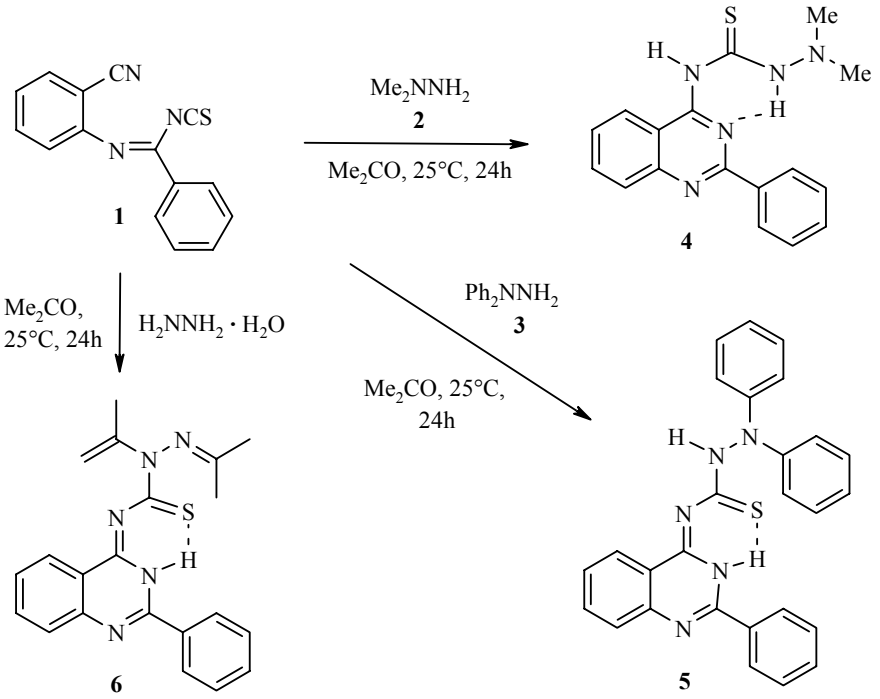
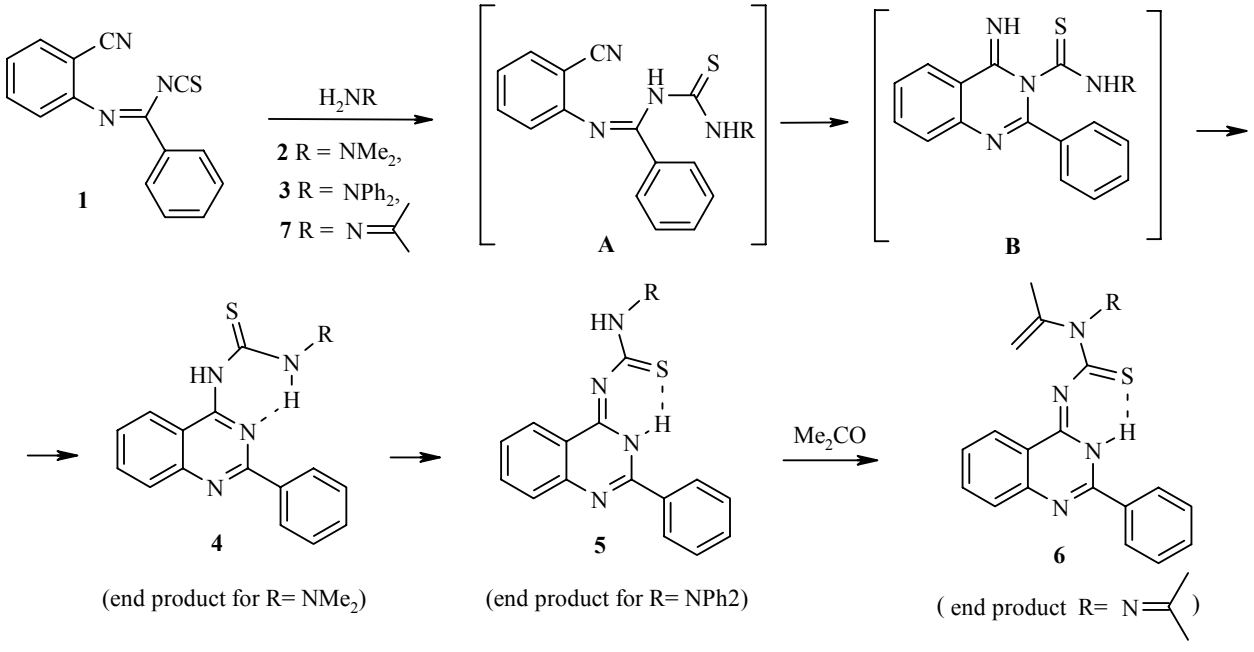
Scheme 1



The sophistic approach to the synthesis of all three thiosemicarbazides **4**, **5**, and **6** is shown in Scheme 2 [12–15]. The reaction between hydrazine and acetone to form dimethylketazine (N,N'-diisopropylidene-hydrazine) is well known [16, 17]. This azine reacts further with an additional molar equivalent of hydrazine hydrate or hydrolyzed under acidic conditions to give hydrazone intermediate **7** (Scheme 3) [18, 19]. Hydrazone **7** was proved to be a key intermediate for dimethylketazine formation [17, 18].

The reaction is assumed to proceed *via* three- to six-step domino reactions as follows (Scheme 2).

Scheme 2

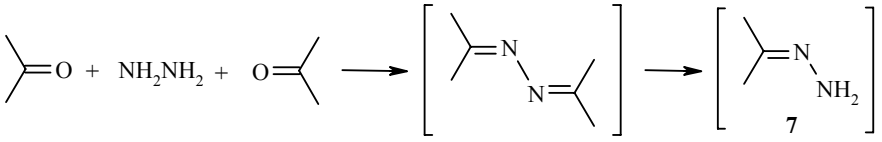


(end product for R= NMe_2) (end product for R= NPh2) (end product R= N=C(CH3)2)

The hydrazines with a free NH_2 group (1,1-di-R-hydrazine **2** or **3** and the *in situ* generated hydrazone **7**) add to the isothiocyanate function of compound **1** to give the thiosemicarbazide intermediates **A**, which in the next step cyclize by the intramolecular addition of NH to the cyano group to give 4-imino- quinazoline intermediates **B.** Dimroth rearrangement furnishes the isolated product **4** (R = NMe_2). A further tautomerization of compound **4** to compound **5** was observed for R = NPh_2. Compound **5** (R = $N{=}CMe_2$) subsequently condenses with an additional acetone molecule in the free active NH group to finally form thiosemicarbazide **6**.

This method has the advantage of a domino reaction with an overall moderate yield at room temperature.

Scheme 3



The structure assignment of thiosemicarbazides **4**–**6** is based on elemental analysis, ^1H, ^{13}C NMR spectral data, and on the correlation with fully analyzed references for N-(2-phenylquinazolin-4(3H)-ylidene)pyrrolidine-1-carbothioamide [12] and 1-benzyl-3-(2-phenylquinazolin-4-yl)thiourea [13] (Fig. 1).

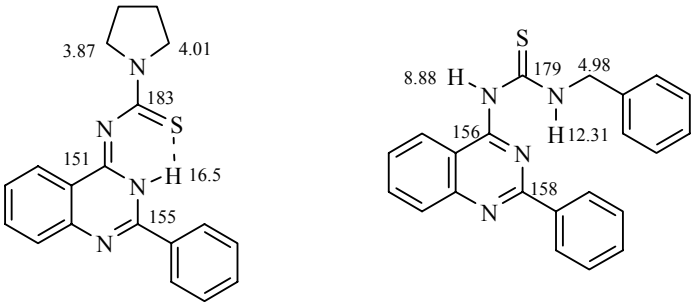


Fig. 1. Selected ^1H and ^{13}C NMR spectral data of N-(2-phenylquinazolin-4(3H)-ylidene)pyrrolidine-1-carbothioamide [12] and 1-benzyl-3-(2-phenylquinazolin-4-yl)thiourea [13].

The ^1H NMR spectrum of compound **4** exhibits two signals exchangeable by deuterium oxide at δ 12.98 and 8.77 ppm corresponding to 1-NH and 3-NH of the thiosemicarbazide moiety, respectively. We might conclude that an intramolecular hydrogen bond interaction of the type N–H···N=C participates in the stabilization of this structure and the consequent formation of a single tautomer [13-15, 20]. The ^{13}C NMR spectrum of compound **4** reveals carbon signals at δ 178.20, 158.79, 155.75, and 47.14 ppm assigned to C=S, C-2, C-4, and CH_3, respectively.

At the same time, both thiosemicarbazides **5** and **6** exhibit a single exchangeable signal at ~ δ 16.72 ppm corresponding to one NH group. This implies that the NH group participates in an intramolecular hydrogen bond interaction of the type N–H···S=C [12], and the consequent formation of the most stable product **5**. According to our previous results [13–15] the structure of compound **4** might be expected when imidoyl isothiocyanate **1** reacts with 1,1-diphenylhydrazine **3**. The structure of compound **4** was hampered probably because the N–H···N=C system in the expected compound **4** moves the two phenyl groups closer to the quinazoline ring making this compound more strained, as shown in Scheme 1. On the other hand, the long bond C=S and the exocyclic phenyl groups as well as better conjugation make the structure **5** more favorable. The ^{13}C NMR spectrum of compound **5** gave a signal at δ 188 ppm assigned to the C=S group participating in hydrogen

bond interaction and extended conjugation. Both the ^{1}H NMR and ^{13}C NMR data were in good agreement with the results reported for the reference compound 1,1-diphenyl-3-(2-phenyl-3H-quinazolin-4-ylidene)thiourea [12] prepared by the reaction of diphenylamine and imidoyl isothiocyanate. The ^{13}C NMR spectrum of thiosemicarbazide **6** gave signals at 181.91, 155.85, 149.34, 67.45, 55.52, 27.96, and 17.05 ppm assigned to C=S, C-2, C-4, $\underline{C}=CH_2$, $C=\underline{C}H_2$, $CH_2=C\underline{C}H_3$, and CH_3, respectively, which gave clear evidence for the participation of two acetone molecules in the reaction.

Thus, the reaction of N-(2-cyanophenyl)benzimidoyl isothiocyanate **1** with hydrazines **2, 3**, and **7** afforded thiosemicarbazides **4**, **5**, and **6,** respectively, in a three- to six-step domino reaction.

EXPERIMENTAL

The solvents were purified and dried in the usual way. The boiling range of the petroleum ether used was 40–60°C. Thin layer chromatography (TLC): silica gel 60 F_{254} plastic plates (E. Merck, layer thickness 0.2 mm) detected by UV-absorption. Melting points were measured on a Boetius Rapido PHMK 79/2106 (Wägetechnik) instrument. Elemental analyses were carried out with an Erba 1102 instrument. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively (DRX 300 Avance Bruker) in $CDCl_3$ solution with tetramethylsilane as an internal standard.

The starting compound **1** was prepared according to the method described in [12-15].

1-Substituted 4-(2-phenylquinazolin-4-yl) and 4-(2-phenylquinazolin-4-ylidene) thiosemicarbazides (General Method). To a solution of imidoyl isothiocyanate **1** (1.32 g, 5 mmol) [12-15] in acetone (10 ml) a hydrazine derivative (5-10 mmol) was added. The reaction mixture was stirred at room temperature (25°C) for 24 h. The solvent was evaporated under reduced pressure and the residue was crystallized from ethanol.

1,1-Dimethyl-4-(2-phenylquinazolin-4-yl) thiosemicarbazide (4). From compound **1** and 1,1-dimethyl-hydrazine (**2**) (0.4 ml). White crystals (0.89 g, 56%); mp 147-148°C. ^{1}H NMR spectrum, δ, ppm: 12.98 (1H, s, N–H···N=C); 8.77 (1H, s, NH); 8.45-8.32 (2H, m, ArH); 8.04-8.01 (1H, m, ArH); 7.9–7.89 (2H, m, ArH); 7.64-7.54 (4H, m, ArH); 2.91 (6H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 178.20 (C=S); 158.79 (C=N, C-2); 155.75 (C=N, C-4); 151.54 (C q); 137.64 (C q); 134.71 (CH Ar); 131.24 (CH Ar); 129.83 (CH Ar); 129.01 (CH Ar); 128.29 (CH Ar); 127.96 (CH Ar); 120.74 (CH Ar); 112.57 (C q); 47.41 (CH_3). Found, %: C 63.08; H 5.26; N 21.61; S 9.88. $C_{17}H_{17}N_5S$. Calculated, %: C 63.13; H 5.30; N 21.65; S 9.91.

1,1-Diphenyl-4-(2-phenylquinazolin-4(3H)-ylidene) thiosemicarbazide (5). From compound **1** and 1,1-diphenylhydrazine **4** (0.7 ml). White crystals (1.4 g, 64 %); mp 166-167°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.75 (1H, s, N–H···S=C); 8.32 (2H, d, *J* = 7.9, ArH); 7.82-7.32 (18H, m, ArH, NH). ^{13}C NMR spectrum, δ, ppm: 188.32 (N–H···S=$\underline{C}$); 155.85 (C=N, C-2); 149.34 (C=N, C-4); 148.54 (C q); 134.90 (CH Ar); 132.67 (C q); 132.08 (CH Ar); 129.35 (CH Ar); 129.22 (CH Ar); 128.15 (CH Ar); 127.61 (CH Ar); 127.53 (CH Ar); 126.11 (CH Ar); 121.43 (C q). Found: C 72.31; H 4.65; N 15.64; S 7.08. $C_{27}H_{21}N_5S$. Calculated, %: C 72.46; H 4.73; N 15.65; S 7.16.

4-(2-Phenylquinazolin-4(3H)-ylidene)-2-(propen-2-yl)-1-(propan-2-ylidene) thiosemicarbazide (6). From compound **1** and hydrazine hydrate (85%, 0.5 ml, 10 mmol). Yellow powder (0.63 g, 34 %), mp 162-163°C. ^{1}H NMR spectrum, δ, ppm: 16.72 (1H, s, N–H···S=C); 8.36-8.24 (3H, m, ArH); 7.78-7.64 (2H, m, ArH); 7.49-7.31 (4H, m, ArH); 2.89 (2H, s, CH_2); 2.13 (3H, s, CH_3); 1.80 (6H, s, $2CH_3$). ^{13}C NMR spectrum, δ, ppm: 181.91 (N–H···S=C); 155.56 (C=N, C-2); 149.98 (C=N, C-4); 149.40 (C q); 134.61 (CH Ar); 132.76 (C q); 131.97 (CH Ar); 129.32 (CH Ar); 128.60 (CH Ar); 127.67 (CH Ar); 127.30 (CH Ar); 125.41 (CH Ar); 121.73 (C q); 67.45 ($\underline{C}=CH_2$); 55.52 ($C=\underline{C}H_2$); 27.96 ($2CH_3$); 17.05 (CH_3). Found, %: C 66.95; H 5.51; N 18.43; S 8.48. $C_{21}H_{21}N_5S$. Calculated, %: C 67.17; H 5.64; N 18.65; S 8.54.

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