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Synthesis of New 1-Substituted-4-(2-phenylquinazolin-4-yl and 4-ylidene) Thiosemicarbazide

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ABSTRACT:

Two new 1-substituted-4-(2-phenylquinazolin-4-yl and 4-ylidene) thiosemicarbazides **3** and **5** were formed by multistep domino reaction of imidoyl isothiocyanate derivative **1** with 1,1-di-R hydrazine in acetone solution. Applied hydrazine hydrate under the same reaction condition afforded 4-(2-phenylquinazolin-4(3*H*)-ylidene)-2-(prop-1-en-2-yl)-1-(propan-2-lidene) thiosemicarbazide (**7**) *via* six step three component domino reaction. Compounds **3, 5** and **7** were identified by CHNS elemental analysis, ^{1}H-NMR, ^{13}C-NMR spectral data and their correlation with ones from known structural motives.

Key words: quinazoline, thiosemicarbazide, domino reaction, hydrogen bond interaction

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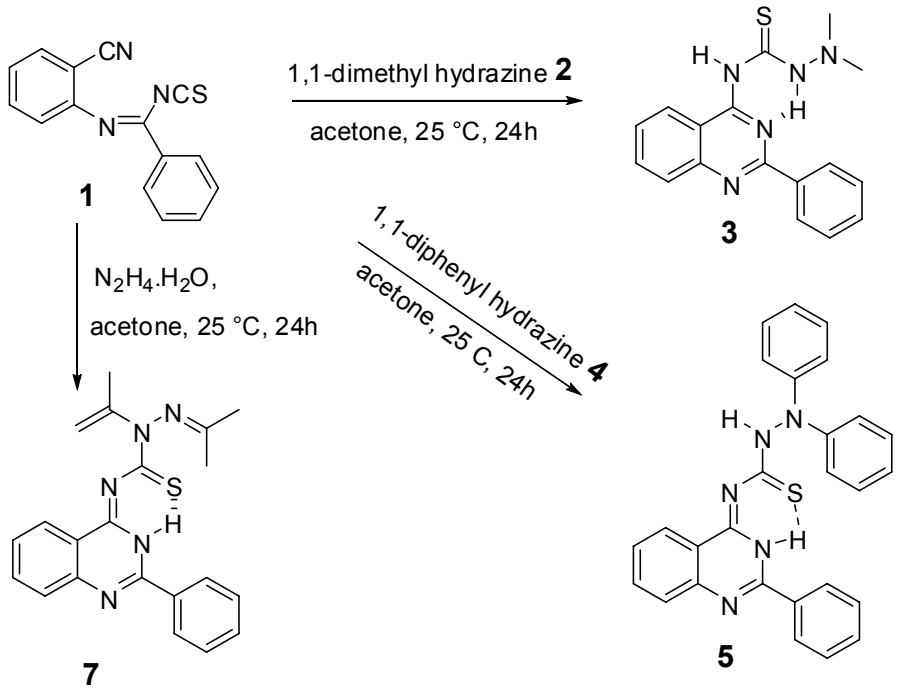
INTRODUCTION

Finding new methodologies for the synthesis of a family of biologically potent compounds by employing building blocks with multi-functional groups is a key issue for drug discovery. Thioureas and thiosemicarbazides appear to be ideal candidates for the development of such processes, since they are the core feature in 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 isothiocayantes [11].

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

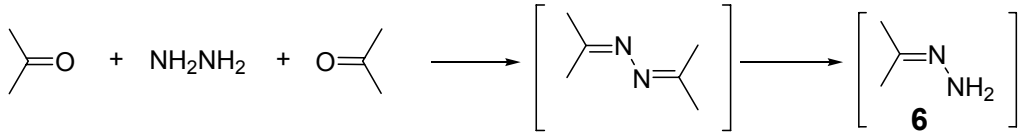
RESULTS AND DISCUSSION

Herein we report an efficient synthesis 1-substituted-4-(2-phenylquinazolin-4-yl and 4-ylidene) thiosemicarbazides by the simple reaction of *N*-(2-cyanophenyl)benzimidoyl isothiocyanate (**1**) with hydrazines. Thus the reaction of imidoyl isothiocyanate **1** with 1,1-dimethylhydrazine (**2**), 1,1-diphenylhydrazine (**4**) or hydrazine hydrate in acetone gave three different interesting solutions: 1,1-dimethyl-4-(2-phenylquinazolin-4-yl) thiosemicarbazide (**3**), 1,1-diphenyl-4-(2-phenylquinazolin-4(3H)-ylidene) thiosemicarbazide (**5**) or 4-(2-phenylquinazolin-4(3H)-ylidene)-2-(prop-1-en-2-yl)-1-(propan-2-lidene) thiosemicarbazide (**7**), respectively (Scheme 1).



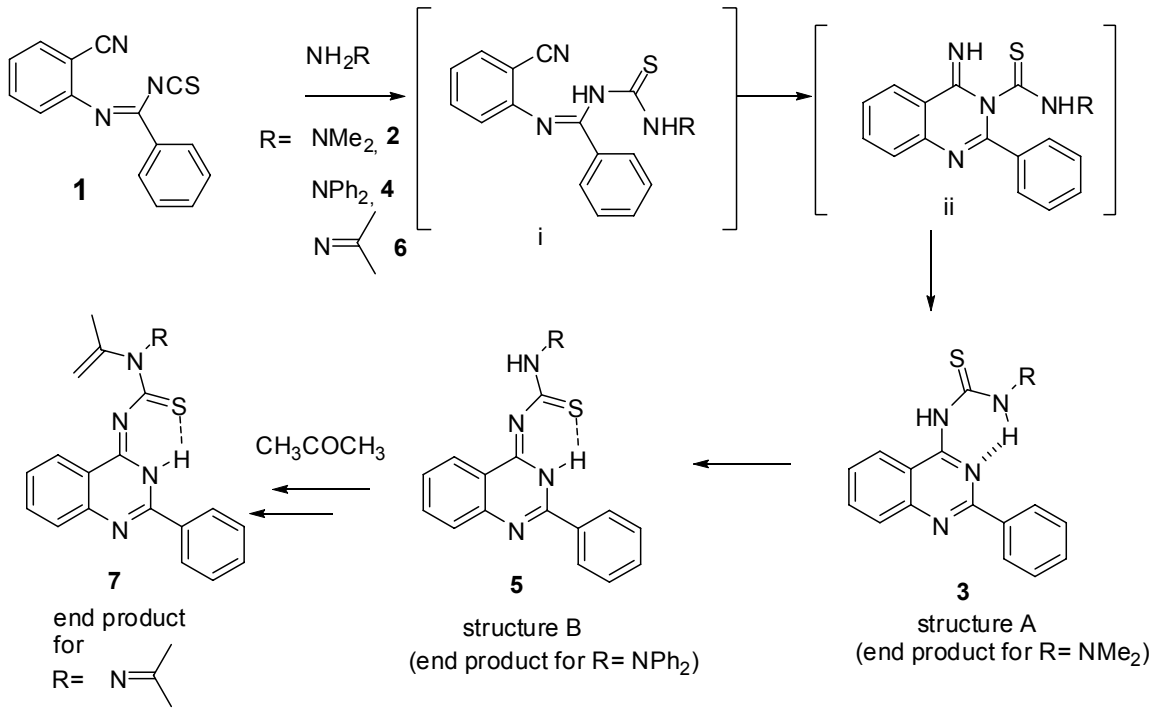
Scheme 1.

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



Scheme 2.

The reaction is assumed to proceed *via* three steps to six steps domino reactions as follows (Scheme 3).
The hydrazines with free NH_2 group (1,1-di-R-hydrazine **2** or **4** and the *in situ* generated hydrazone **6**) add to the isothiocyanate function of **1** to give the thiosemicarbazide intermediates **i**, that in the next step cyclize by the intramoleculor addition of NH to cyano group under 4-iminoquinazoline intermediates (ii) formation; Dimroth rearrangement furnishes the isolated product structure A **3** (R = NMe_2). A further tautomerisation of structure **A** to structure **B** was observed for **5** (R = NPh_2). Structure **B** (R = N=CMe_2) subsequently condense with an additional acetone molecule at the free active NH group to finally form the thiosemicarbazide **7**.
This method has the advantage of a domino reaction with an overall moderate yield at room temperature.



Scheme 3. Possible reaction pathway for the formation of thiosemicarbazides **3**, **5** and **7**.

The structure assignment of the thiosemicarbazides **3, 5** and **7** is based on CHNS elemental analysis, ^{1}H , ^{13}C NMR spectral data and on the correlation with full analyzed references *N*-(2-phenylquinazolin-4(3H)-ylidene)pyrrolidine-1-carbothioamide [12] and 1-benzyl-3-(2-phenylquinazolin-4-yl) thiourea [13], Figure 1.

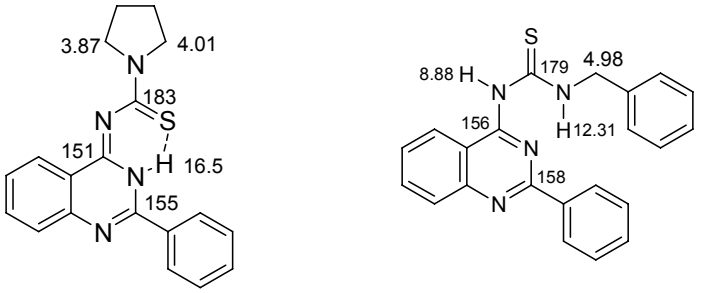


Figure 1. Selected ^{1}H and ^{13}C NMR spectral data of *N*-(2-phenylquinazolin-4(3*H*)-ylidene)pyrrolidine-1-carbothioamide [12] and 1-benzyl-3-(2-phenylquinazolin-4-yl)thiourea [13]

The ^{1}H NMR spectrum of **3** exhibits two by deuterium oxide exchangeable signals 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 (structure **A**) participate in the stabilization of this structure and the consequent formation of a single tautomer [13-15, 20]. The ^{13}C NMR spectrum of **3** reveals carbon signals at δ 178.20, 158.79, 155.75 and 47.14 ppm assigned to C=S, C2, C4 and CH_3, respectively.

On the other hand, both thiosemicarbazides **5** and **7** exhibited a single exchangeable signal at ~ δ 16.72 ppm corresponding to one NH group. This implies that the NH group participate in an intramolecular hydrogen bond interaction of the type N–H···S=C [12]; and the consequent formation of most stable product structure **B**. According to our previous results [13-15]; structure **A** might be expected when imidoyl isothiocyanate **1** reacts with 1,1-diphenylhydrazine (**4**). Structure **A** was hampered probably because N–H···N=C system in the expected structure **A** 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 structure of both phenyl groups, and better conjugation make the structure **5** more favourable. The ^{13}C NMR spectrum of **5** gave signal at δ 188 ppm assigned to C=S group participating in hydrogen bond interaction and extended conjugation as in structure **B**. Both the ^{1}H NMR and ^{13}C NMR data were in good agreement with results reported for the reference compound 1,1-diphenyl-3-(2-phenyl-3H-quinazolin-4-ylidene) thiourea [12] prepared by the reaction of diphenyl amine and imidoyl isothiocyanate. The ^{13}C NMR spectrum of thiosemicarbazide **7** gave signals at 181.91, 155.85, 149.34, 67.45, 55.52, 27.96 and 17.05 ppm assigned to C=S, C2, C4 $\underline{C}$=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.

Conclusions

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

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