SYNTHESIS OF NEW 4-[4-(4-METHOXYPHENYL)-5-(2-PHENYL-QUINAZOLIN-4-YL)-1,3-THIAZOL-2-YL]MORPHOLINE AND N^4-[5-(4-METHOXYPHENYL)-1,3-OXATHIOL-2-YLIDEN]-(2-PHENYLQUINAZOLIN--4-YL)-AMINE

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Abstract
The reaction of N^3,N^3-(3-oxapentan-1,5-diyl)-N^1-(2-phenyl-3,4-dihydroquinazolin-4-yliden)thiourea with 4-methoxyphenacyl bromide afforded either the kinetically controlled reversible reaction product N^4-[5-(4-methoxyphenyl)-1,3-oxathiol-2-yliden]-(2-phenylquinazolin-4-yl)-arnine or the thermodynamically controlled reaction product 4-[4-(4-methoxyphenyl)-5-(2-phenylquinazolin-4-yl) -4,5-dihydro-1,3-thiazol-2-yl]morpholine *via* domino-reaction by two different reaction pathways.
Keywords: quinazolines, 1,3-oxathioles, 1,3-thiazoles, domino-reaction, cyclization, retro-cyclization

Introduction

The nucleophilic *S/N* competition reactions with electrophiles on a thioamide structural fragment were considered as essential element for the preparation of a number of heterocyclic compounds.

Our research laboratory continued the studies of *S/N* thioamide nucleophilic competition reactions with electrophiles (1-3). The compound N^3,N^3-(3-oxapentan-1,5-diyl)-N^1-(2-phenyl-3,4-dihydroquinazolin-4-ylidene)thiourea **1** is an excellent precursor for this type of studies.

Discussion

The thiourea **1** was prepared by the domino-reaction of *N*-(2-cyanophenyl)benzimidoyl isothicyanate with morpholine (1). We now found that the reaction of 4-methoxyphenacyl bromide **2** with **1** in the presence of triethylamine afforded **4** at room temperature after ca 30 min. On the other hand, the prolongation of reaction time or a temperature elevation gave **6** *via* multi-step domino-reaction (Scheme 1).

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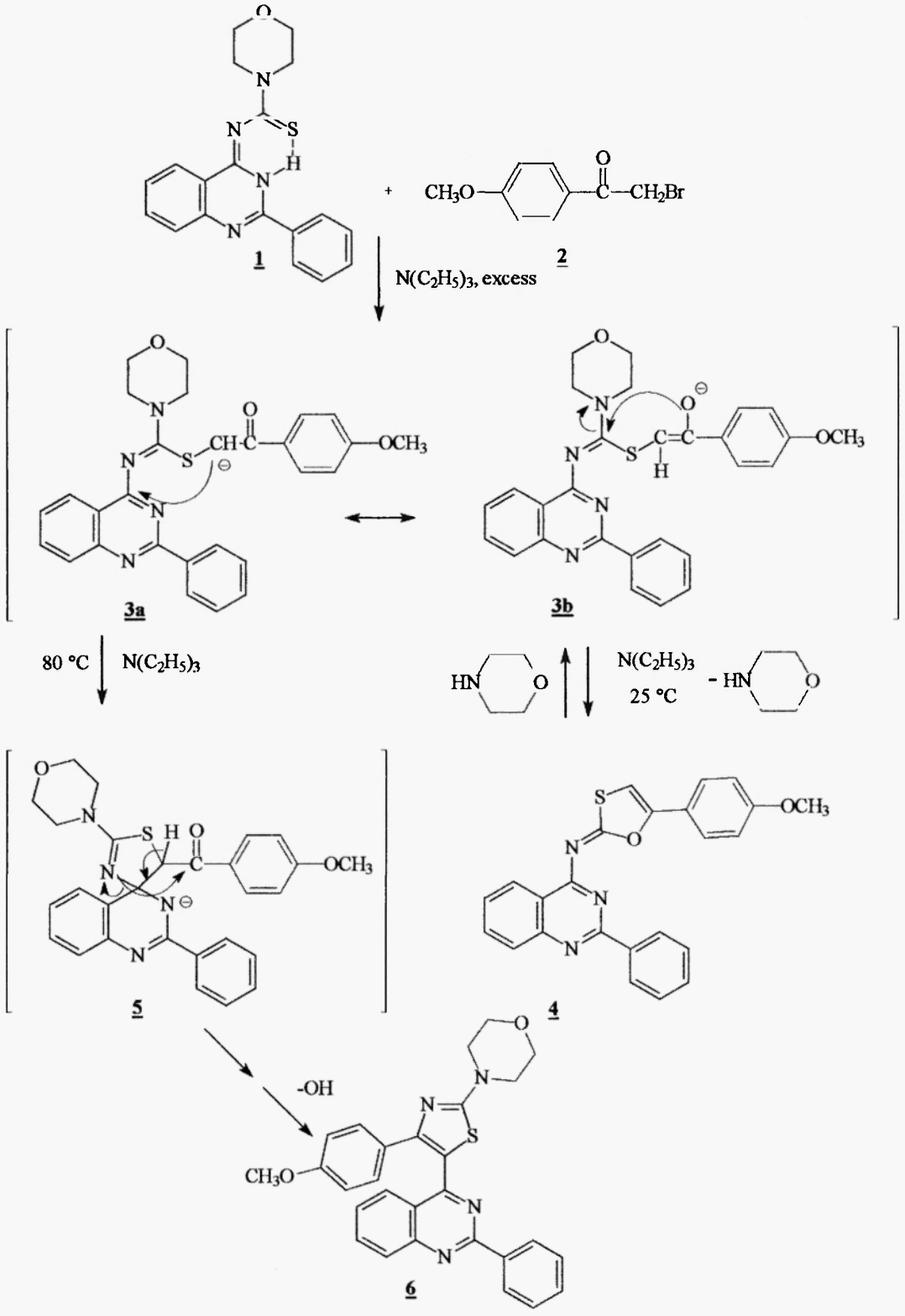

Scheme 1. Domino-reaction of **1** with 4-methoxyphenacyl bromide **2**

The first step of the process is a regioselective *S*-phenacylation of **1** by **2** and the intermediary isothiourea is formed. This is in the presence of base in equilibrium with an enolate ambident anion, which can be described by two mesomeric forms **3a** and **3b**. The ambident nucleophile **3** reacts further by two different pathways. A kinetically controlled reversible pathway runs *via* the oxygen hard attack of enolate anion **3b** at the imino carbon and the consequent elimination of the morpholine to finally give **4**. On the other hand, the extension of reaction time evoked the morpholine to reverse attack on the oxathiole derivative **4** to reform the enolate **3**.

A thermodynamically controlled way proceeds by the carbanion form **3a** intramolecular soft attack at the electrophilic C4 carbon atom of the quinazoline ring accompanied with a series of ring transformations to finally afford the thiazoles **6** (Scheme 1).

Identity of structures **4** and **6** was confirmed by IR, ^{1}H, ^{13}C NMR and in the case of **6** by X-ray structural analysis, too (Figure 1).

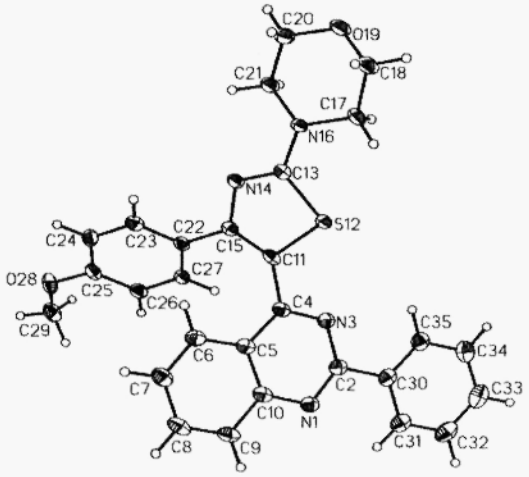

Figure 1: The ORTEP diagram of X-ray structure analysis of 4-[4-(4-methoxyphenyl)-5-(2-phenyl-quinazolin-4-yl)-1,3-thiazol-2-yl]morpholine **6**.

Conclusion

The reaction of thiourea **1** with 4-methoxyphenacyl bromide **2** afforded either the kinetically controlled reversible reaction product **4** or the thermodynamically controlled reaction product **6** *via* two competition reactions of intermediary enolate **3**.

Experimental

For general methods, techniques, and equipments see (**4**).

*N^4-[5-(4-Methoxyphenyl)-1,3-oxathiol-2-yliden]-(2-phenylquinazolin-4-yl)-amine **4***

To a solution of **1** (1.0 g, 2.8 mmol) (1) in DMF (30 mL) was added triethylamine (0.5 mL, 3.5 mmol) and 4-methoxyphenacyl bromide **2** (0.65 g, 2.8 mmol). The reaction mixture was stirred at room temperature for 30 minutes. The solvent was then evaporated under reduced pressure and a residue was crystallized from ethyl alcohol. Yield 0.78 g (66 % pure product) mp 200-201°C; ^{1}H NMR δ / ppm: 3.72 (s, 3H, OCH_3), 6.73 (1H, s, CH-oxathiole), 6.91-8.71 (m, 13H, Ar); ^{13}C NMR δ / ppm 55.69 (OCH_3), 99.08 (CH), 120.72 (C_q), 125.34 (CH), 125.43 (CH), 126.72 (C_q), 127.88 (CH), 128.21 (CH), 128.72 (CH), 129.13 (CH), 130.03(CH), 133.86 (CH), 133.89 (CH), 138.89 (C_q), 148.59 (C_q), 152.18 (C_q), 160.18 (C_q), 161.86 (C_q).

*4-[4-(4-Methoxyphenyl)-5-(2-phenylquinazolin-4-yl)-4,5-dihydro-1,3-thiazol-2-yl]-morpholine **6***

To a solution of **1** (1.0 g, 2.8 mmol) (1) in DMF (30 mL) was added triethylamine (0.5 mL, 3.5 mmol) and **2** (0.65 g, 2.8 mmol). The mixture was heated at 80 °C for 4 hours. The solvent was then evaporated and an oily residue was cooled till solidification and crystallized from ethyl alcohol. Yield 0.63 g (46 % pure product): mp 216-217°C; ^{1}H NMR δ / ppm: 3.67 (t, 3H, $2NCH_2$, J = 5.29 Hz), 3.72 (s, 3H, OCH_3), 3.89 (t, 4H, $2OCH_2$, J = 5.28 Hz), 6.59-8.62 (m, 13H, Ar); ^{13}C NMR δ / ppm 48.46 (NCH_2), 55.40 (OCH_3), 66.41 (OCH_2), 113.92 (CH), 120.99 (C_q), 126.61 (CH), 127.68 (CH), 128.23 (C_q), 128.71 (CH), 128.96 (CH), 130.47 (CH), 130.70 (CH), 133.70 (CH), 138.19 (C_q), 152.21 (C_q), 152.79 (C_q), 159.82 (C_q), 160.36 (C_q), 161.99 (C_q), 171.28 (C_q), 173.11 (C_q). Crystallographic data for **6** are presented at (5).

Acknowledgments

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References

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(4) W. Fathalla, J. Marek, and P. Pazdera, Heterocyclic Commun., in press.
(5) Crystallographic data for **6**: $C_{28}H_{24}N_4O_2S$, M = 480.57, triclinic crystal system, S.G. P-1, a = 10.2343(8) Å, b = 10.8493(6) Å, c = 11.6946(8) Å, α = 91.205(5)°, β= 113.783(7)°, γ = 100.065(6)°, V = 1163.90(14) $Å^3$, Z = 2, D_{calc} = 1.371 $Mg.m^{-3}$. Number of collected / independent reflections was 6647 / 3974; R_{int} = 0.0521. The final R indices [$I>2\sigma(I)$]: R1 = 0.0454, wR2 = 0.1105, the largest diff. peak and hole were 0.281 and –0.459 e. $Å^{-3}$. Coordination have been deposited at the CCDC, deposition number CCDC 169181.

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