The synthesis of new N^3-aryl-N^1-(2-phenylquinazolin-4-yl)thioureas

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Abstract

Domino-reactions between N^2-(2-cyanophenyl)-N^1-thioxomethylidenebenzene-1-carboximidamide and aryl amines leading to the N^3-aryl-N^1-(2-phenylquinazolin-4-yl)thioureas are described. FTIR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy and X-ray structural analysis made identity of the synthesized compounds.

Keywords: Thioureas, domino-reactions, aryl amines, spectral analysis

Introduction

Our recent work provides a convenient method for the preparation of several quinazoline derivatives bearing a thiourea functional group at position C4[1,2]. This functional group have a respectable evaluation in the eye of heterocyclic chemists since it could be used as a building block of a number of heterocycles such as pyrimidines, pyrazoles, oxathioles, thiazoles, etc.

The demand for novel active compounds led to the synthesis of analogues compounds containing the quinazoline ring system.

Results and Discussion

We have prepared the N^3-R-N^1-(2-phenylquinazolin-4-yl)thioureas and N^3,N^3-di-R-N^1-(2-phenyl-3,4-dihydroquinazolin-4-yliden)thioureas by the domino-reaction of amines to N^2-(2-cyanophenyl)-N^1-thioxo-methylidenebenzene-1-carboximidamide **1**.

This carboximidamide was easily prepared from N^1-(2-cyanophenyl)benzamide, which was further transformed to N^1-(2-cyanophenyl)benzene-1-carboximidoyl chloride and finally to N^2-(2-cyanophenyl)-N^1-thioxo-methylidenebenzene-1-carboximidamide by the reaction with PCl_5 and KSCN, respectively. The reaction of N^2-(2-cyanophenyl)-N^1-thioxo-methylidenebenzene-1-carboximidamide **1** with anilines gave the intermediary thiourea derivative **2** that underwent a spontaneous intramolecular cycloaddition reaction at the cyano group to afford the quinazolinyl

thiourea **3** like the intermediates and finally Dimroth rearrangement product to give the N^3-aryl-N^1-(2-phenylquinazolin-4yl)thioureas **4**[2].

The reaction was extended to involve further aryl substituents as shown in Table 1. The structures of the synthesized compounds were confirmed by the comparison between the ^{1}H and ^{13}C NMR spectra of the prepared compounds with the spectrum of the aniline derivative **4a**. The X-ray structural analysis and the computational results of **4a** indicate among others hydrogen bond interaction between arylamino N-H…N3 of quinazoline ring with a bond distance about 1.86 Å and 1.94 Å, respectively.

However, this hydrogen bond interaction was identified once again from the ^{1}H NMR spectra of compounds **4,** measurement into $CDCl_3$ or DMSO, giving a chemical shifts ranging from 13.99–14.26 ppm. The ^{1}H NMR spectra also show chemical shift ranging from 8.91–8.96 ppm for the quinazolinyl-4-amine N-H group of **4.**

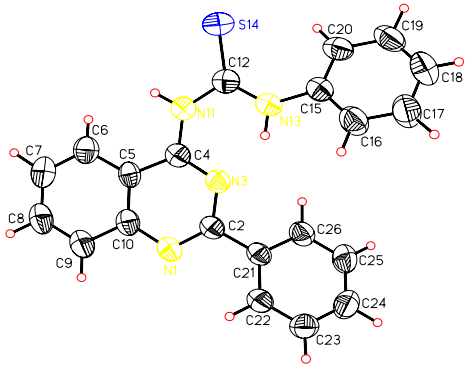
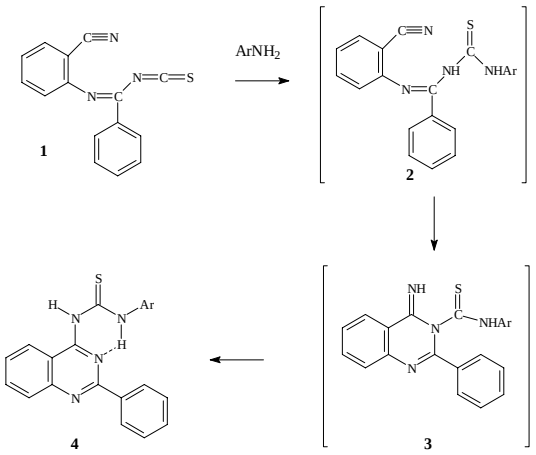


Figure 1. The ORTEP diagram of **4a**.



Scheme 1. The reaction pathway for the **4** compounds formation.

^{13}C NMR spectra gave good agreement with the proposed structures **4**. It gave a chemical shift at 178.62–180.85 corresponding to C=S group. The measured ^{13}C and ^{1}H NMR spectra were correlated with those obtained by simulation. The IR spectra was our last tool for the confirmation of the arylamino N-H…N3 of quinazoline ring hydrogen bond giving an absorption band at 3205–3374 cm^{-1} referring to νNH band. Additional spectral data used for compounds **4** are represented at Tables 2 and 3.

Table 1. The aryl substituent representations of **4**

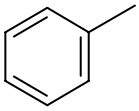
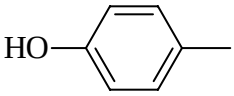
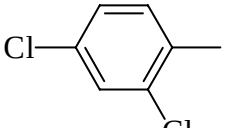
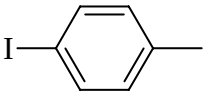
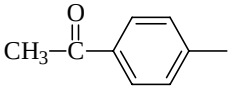
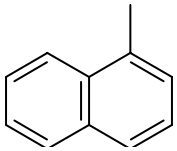
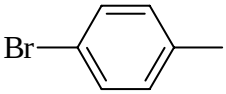
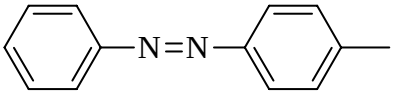
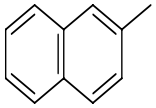
4	**Ar**	**4**	**Ar**	**4**	**Ar**
a		**d**		**g**	
b		**e**		**h**	
c		**f**		**i**	

Table 2. Characteristic data of prepared compounds **4**

Compd.	Formula	M.p., °C	Calculated / found				
	(M.wt.)	Yield, %	% C	% H	% N	% S	others
4a	$C_{21}H_{16}N_4S$	165-166	70.76	4.52	15.72	8.99	
	(356.44)	43%	70.58	4.52	15.64	8.83	
4b	$C_{21}H_{15}IN_4S$	186-187	52.29	3.13	11.62	6.65	26.31 % I
	(482.34)	46%	52.12	2.98	11.45	6.59	26.28 % I
4c	$C_{21}H_{15}BrN_4S$	175-176	57.94	3.47	12.87	7.36	18.35 % Br
	(435.34)	49%	57.78	3.41	12.67	7.25	18.24 % Br
4d	$C_{21}H_{16}N_4OS$	220-221	67.72	4.33	15.04	8.61	
	(372.44)	53%	67.57	4.24	14.86	8.59	
4e	$C_{23}H_{18}N_4OS$	169-170	69.33	4.55	14.06	8.05	
	(398.48)	48%	69.29	4.43	14.01	7.88	
4f	$C_{27}H_{22}N_6S$	200-201	70.41	4.38	18.25	6.96	
	(460.55)	39%	70.38	4.37	18.11	6.76	
4g	$C_{21}H_{14}Cl_2N_4S$	182-183	59.30	3.32	13.17	7.54	16.67 % Cl
	(435.33)	73%	59.28	3.26	13.08	7.35	16.55 % Cl
4h	$C_{25}H_{18}N_4S$	168-169	73.87	4.46	13.78	7.89	
	(406.50)	45%	73.83	4.46	13.77	7.84	
4i	$C_{25}H_{18}N_4S$	179-180	73.87	4.46	13.78	7.89	
	(406.50)	66%	73.74	4.38	13.61	7.80	

Table 3. Spectral[a] data of prepared compounds **4**

	^{1}HNMR (δ, ppm)				^{13}CNMR			I.R		
	CHAr	N(11)	N(13)	others	C=S	C(2)	others	NH	C=N	others
4a	8.35-7.29	8.93	14.26		178.62	158.57		3436	1617	
	(14H)	(1H)	(1H)					3418		
4b	8.30-7.53	8.94	14.36		178.59	155.95		3350	1618	
	(13H)	(1H)	(1H)					3215		
4c	8.33-7.56	8.95	14.39		179.43	159.64		3328	1621	
	(13H)	(1H)	(1H)					3246		
4d	8.39-7.43	8.91	14.43		178.74	157.32		3387	1617	1138 C-O
	(13H)	(1H)	(1H)					3250		
4e	8.31-7.56	8.96	14.62	2.65	178.32	158.74	27.8	3335	1621	1672 C=O
	(13H)	(1H)	(1H)	(3H)	169.72	C=O		3205		
4f	8.36-7.47	8.96	14.57		178.32	158.53		3424	1619	
	(18H)	(1H)	(1H)					3285		
4g	8.36-7.37	9.09	13.99		180.85	156.98		3348	1621	
	(12H)	(1H)	(1H)					3270		
4h	8.28-7.29	9.16	14.27		180.79	156.24		3429	1619	
	(19H)	(1H)	(1H)					3250		
4i	8.72-7.63				179.30	156.98		3429	1618	
	(19H)							3374		

[a] All the NMR samples were measured in $CDCl_3$ except for compound **4i** was measured in CF_3COOD

Experimental Section

General Procedures. Melting points of all the compounds were measured on a Boetius Rapido PHMK 79/2106 (Wägetechnik) instrument. TLC was carried out on Silufol UV 254 plates (Kavalier, Votice). TLC detected by Fluotes universal (Quarzlampen, Hanau) and iodine vapors. Purity of compounds **4a-i** was proved by the elemental analysis on an (Erba) instrument 1102. Eluent used was the mixture of acetone/benzene 20: 80. FTIR spectra were taken on a spectrometer Genesis (Unicam) in potassium bromide pellets. ^{1}H, ^{13}C NMR spectra were measured on a Bruker Avance DRX-500 spectrometer at 25 °C and $CDCl_3$ for compounds **4a-h** or CF_3COOD for compound **4i** were used. Tetramethylsilane was applied as an internal standard. The measured NMR spectra were correlated with those obtained by simulation (Advanced Chemistry Development, Inc., Toronto, Canada).

N^1-(2-Cyanophenyl)benzamide, *N*^{1}-(2-cyanophenyl)benzene-1-carboximidoyl chloride and *N*^{2}-(2-cyanophenyl)-*N*^{1}-thioxo-methylidenebenzene-1-carboximidamide were prepared as reported[1,2].

***N*^{3}-Aryl-*N*^{1}-(2-phenylquinazolin-4yl)thioureas 4. General method.** To the solution of *N*^{2}-(2-cyanophenyl)-*N*^{1}-thioxo-methylidenebenzene-1-carboximidamide in acetone, the corresponding equimolar amount of aniline was added portion wise while stirring at room temperature over a period of 1h. The reaction mixture was then stirred for 24h. The precipitated quinazoline **4** was filtered off and crystallized from ethyl alcohol. Spectral data are given Tables 2 and 3.

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