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A Comparative Study of the Behavior of Cyanothioformamide and Oxazolidine (Thiones or Iminothiones) Towards Some Binucleophiles

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ABSTRACT: *Reactions of cyanothioformamides (***I***) with o-phenylenediamines, o-aminophenol, and anthranilic acids furnished benzimidazole (***II,III***), benzoxazole (***VII***), and quinazoline (***IX***) derivatives, respectively. Oxazolidine (thiones or iminothiones) (***IV***) were reacted with the same binucleophiles to produce quinoxaline (***V***), benzimidazole (***VI***), and quinazoline (***XI***) derivatives.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:291–298, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10031

INTRODUCTION

Cyanothioformamides (**I**) [1,2] have been used widely for syntheses of heterocyclic compounds, such as imidazoles [3], oxazoles [4], and thiazoles [5,6]. Our program on ring-closure reactions [7], activated nitriles [8], and the chemistry of cyanothioformamides [9–12] led us to react **I** with chalcones, maleimides, and acetylenedicarboxylic acid to give the corresponding pyrroles [13].

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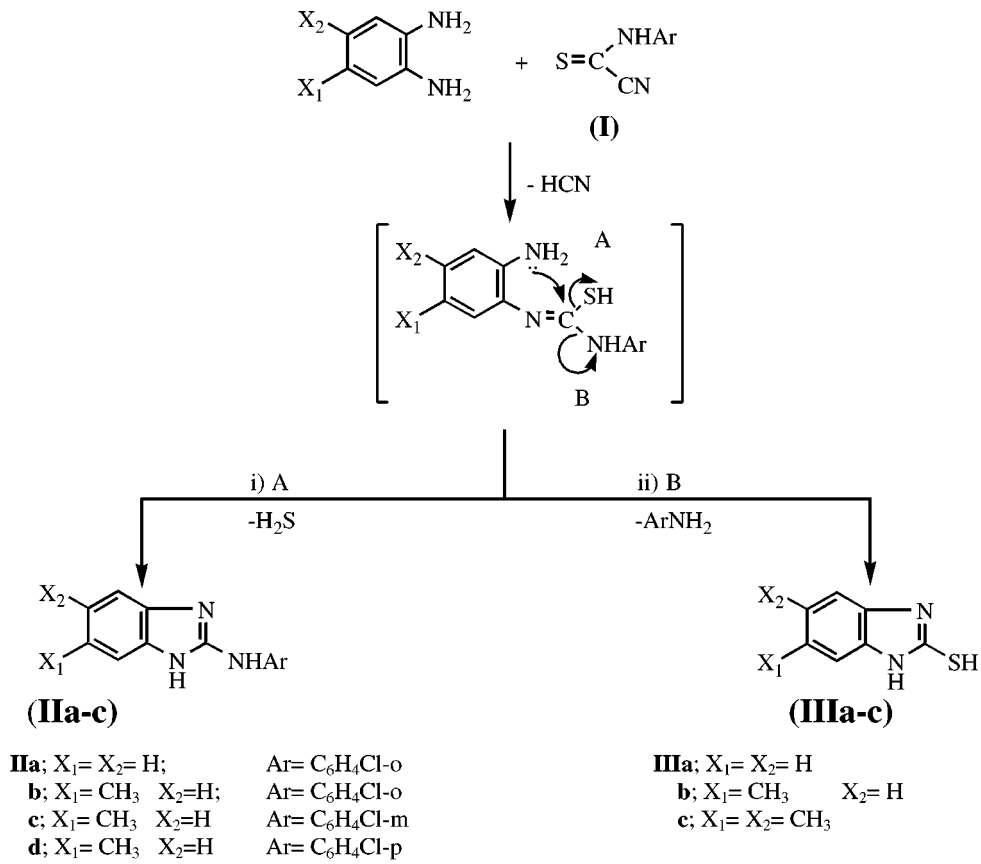
Recently, we published a comparative study of the reactions of (imidazolidine and oxazolidine) iminothiones with some nucleophilic reagents [14], and we found that the imidazolidine ring was stable towards these nucleophiles but that the oxazolidine ring was opened with the elimination of an aldehyde molecule.

RESULTS AND DISCUSSION

In the present investigation, we reacted compound **I** with some binucleophilic reagents such as *o*-phenylenediamines, *o*-aminophenol, and anthranilic acids to produce benzimidazole, benzoxazole, and quinazoline derivatives, respectively.

Also, we reacted oxazolidine iminothiones with the binucleophiles (mentioned above) to determine their behavior towards these reagents and to compare the results with those of cyanothioformamides with the same reagents.

Thus, reactions of **I** with *o*-phenylenediamine derivatives in DMF/TEA solution furnished compounds that contained no sulphur. IR, MS, and elemental analyses of the products indicated that they were 2-arylaminobenzimidazoles (**IIa–d**) (Scheme 1). However, repetition of those reactions



SCHEME 1

in EtOH/TEA gave organo-sulphur compounds that were found to be 2-mercaptobenzimidazoles (**IIIa–c**) (Scheme 1). Compound **IIIa** was found to be identical with that previously reported in the literature [15]. It can be said that compounds **II** and **III** could be produced either in EtOH/TEA or DMF/TEA but in DMF compound **II** was the major product while in EtOH compound **III** was the major one.

Reaction of oxazolidinethione (**IV**; X=O) with *o*-phenylenediamine in EtOH under reflux was reported previously by us [14] to produce quinoxaline derivatives (**Va,b**). However, we have now found that this reaction with **IV** (X=NH) in EtOH/TEA under reflux resulted in the formation of the benzimidazole derivative (**VI**). Plausible mechanisms for the formation of **V** and **VI** are depicted in Scheme 2.

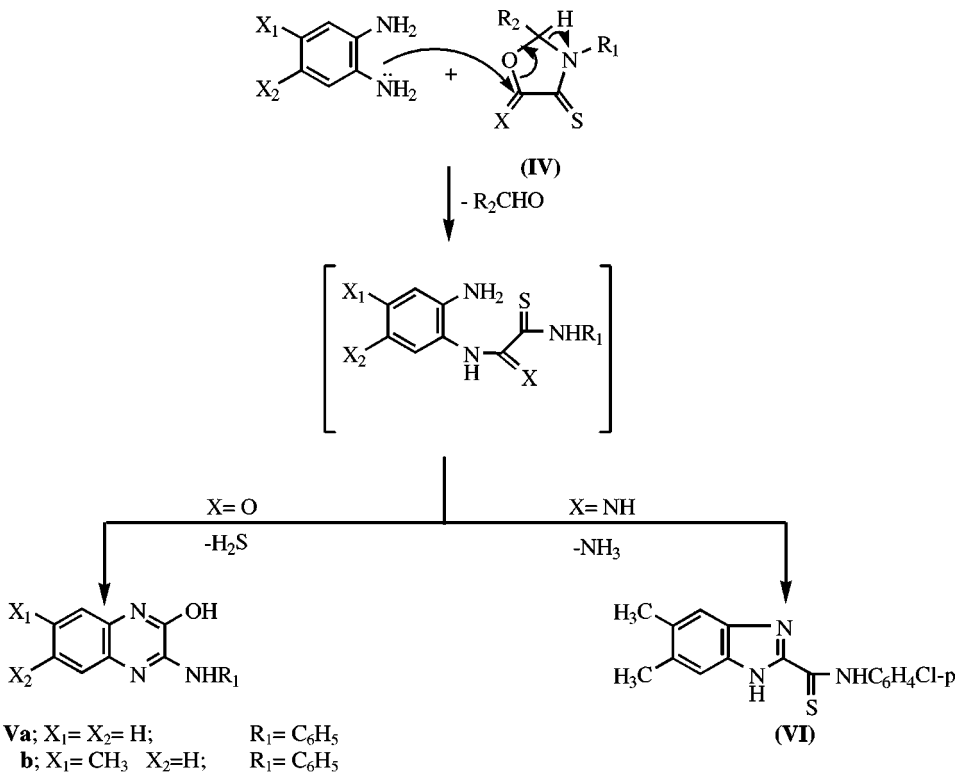
Similarly, reactions of **I** with *o*-aminophenol in DMF/TEA were found to produce 2-arylaminobenzoxazoles (**VIIa,b**; Scheme 3), through elimination of HCN and H_2S respectively. Compound **VIIa** was found to be identical with that reported in the literature [16].

On the other hand, refluxing of oxazolidine-4-thione (**IV**; X=O) with *o*-aminophenol in EtOH was previously reported by us [14] to produce the intermediate **VIII** (Scheme 3), by elimination of an aldehyde molecule only.

In a similar fashion, cyanothioformamides (**I**) were reacted with anthranilic acids in EtOH/TEA with elimination of HCN and H_2O so as to afford products with elemental and spectral data compatible with structure **IX**, 3-substituted quinazolinon-2-thiones (Scheme 4). The various compounds (**IXa–f**) were identical with those prepared previously according to the literature procedures: **IXa,b** [17]; **IXc** [18]; **IXd,e** [19], and **IXf** [18].

With *o*-chlorophenylcyanothioformamide, we have previously reported [20] its reactions with anthranilic acid and its derivatives to produce poly heterocyclic compounds **X**, as benzothiazolo[2,3-*b*]quinazolines by elimination of HCN, H_2O, and HCl (Scheme 4).

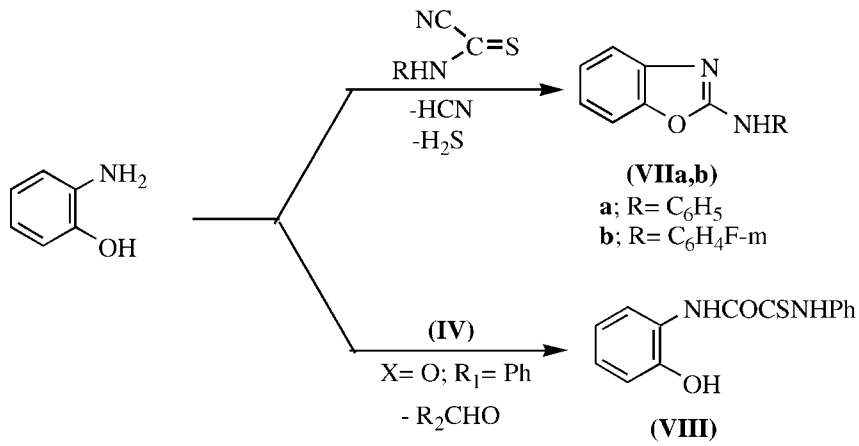
The oxazolidine iminothione **IV** (X=NH) has been found to undergo reaction with anthranilic acid and its chloro or bromo derivatives to furnish quinazolinone-2-thiocarbanilide derivatives (**XIa–i**; Scheme 4). The mechanism of formation of **XI** presumably proceeds by nucleophilic attack of the *o*-amino group of the anthranilic acid on the imino group of **IV** (X=NH) to afford a ring opening



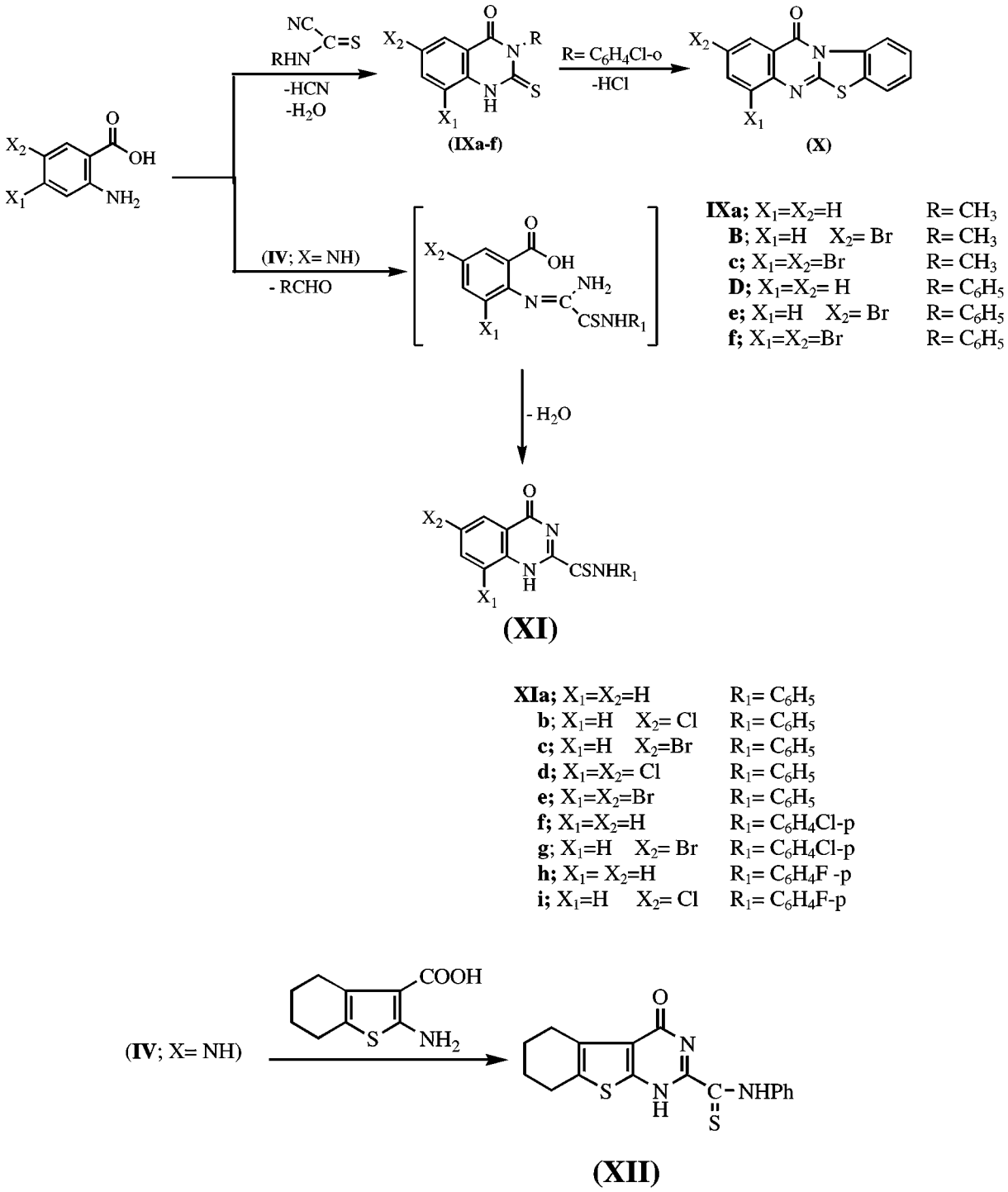
SCHEME 2

intermediate through elimination of an aldehyde molecule. A subsequent ring-closure reaction accompanied by elimination of water, completes the formation of the quinazolinone **XI**. The structures of these products were determined by IR, ^{1}H NMR, MS, and elemental analyses. The mass spectrum of **XIa,h** (fragmentation pattern depicted in Schemes 5 and 6) indicated that M − 1 was the base peak of both products. These findings encouraged us to use a heterocyclic *o*-aminocarboxylic acid, 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid, to react with oxazolidine iminothione (**IV**; X=NH). This reaction afforded 2-thiocarbanilide-5,6,7,8-tetrahydro[*b*]thieno[2,3-*d*]pyrimidine-4(3*H*)-one (**XII**; Scheme 3) (M^+, 95%, M + 1, 100%; Scheme 7).

From the above findings, it can be said that, the reactions of cyanothioformamides with binucleophiles, such as *o*-phenylenediamine, *o*-aminophenol, and anthranilic acids, pass through essentially the same mechanism, which involves two



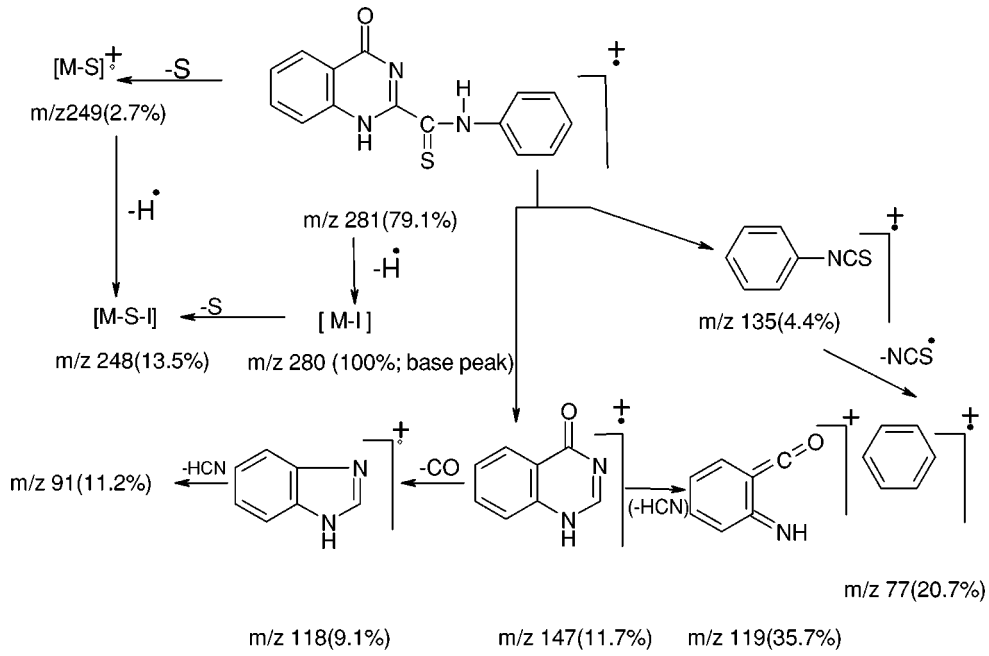
SCHEME 3



SCHEME 4

steps. At first, a nucleophilic attack by the amino group of the binucleophile occurs at the thione group of the cyanothioformamides with elimination of HCN. The second step involves cyclization via liberation of H_2S (as in *o*-phenylenediamine or *o*-aminophenol) or separation of H_2O (as in anthranilic acids) to produce the required benzimidazoles (**II**), benzoxazoles (**VII**), or quinazolinones (**IX**), respectively.

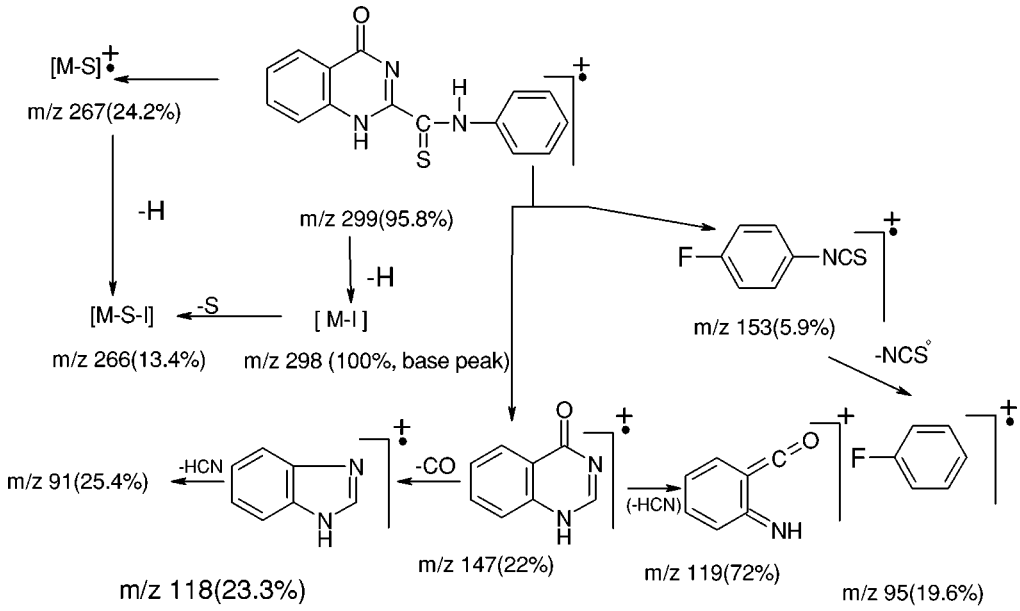
Similarly, oxazolidine thione (**IV**; X=O) or iminothione (**IV**; X=NH) reacts with the same binucleophiles by a similar mechanism which also



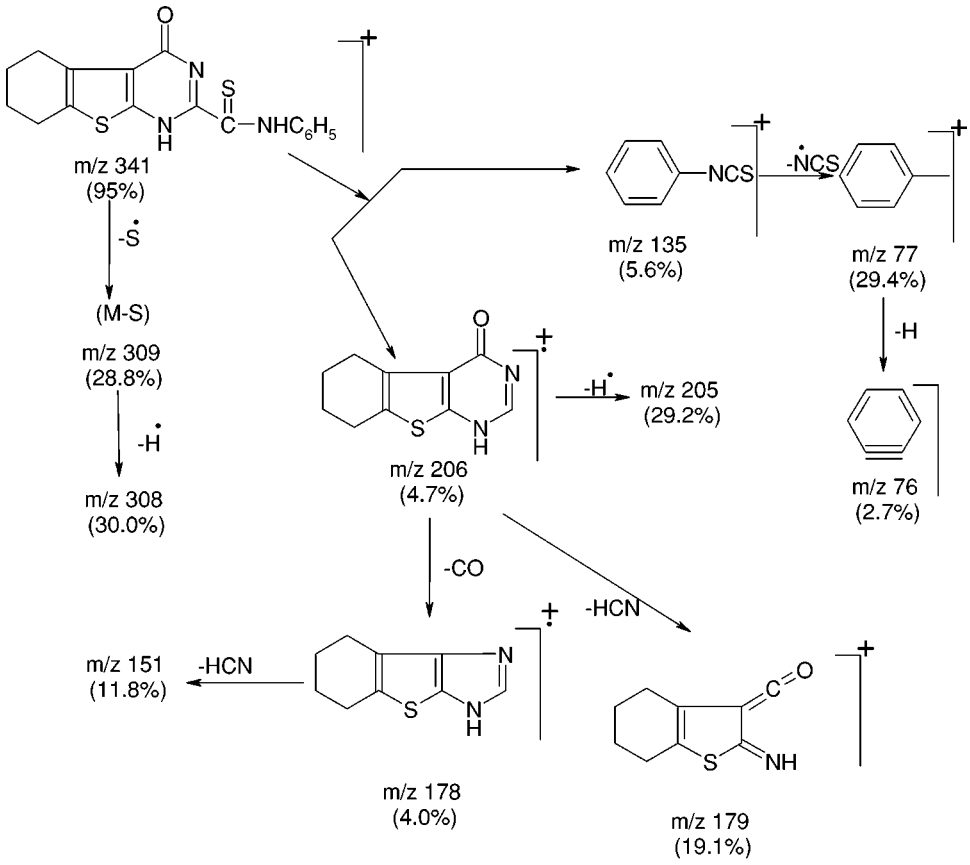
SCHEME 5 Fragmentation pattern of compound (**XIa**).

involves two steps. The first is a nucleophilic attack by the amino group of the binucleophile on the imino or the carbonyl group of **IV**, releasing an aldehyde molecule to give an open intermediate (**VIII**) as in case of *o*-aminophenol. The second step involves cyclization of this intermediate by elimination of H_2S or NH_3 (as in case of *o*-phenylenediamine) to yield quinoxaline (**V**) or benzimidazole (**VI**) derivatives, respectively. With anthranilic acids, cyclodehydration was affected by loss of H_2O to give the quinazoline derivatives (**XI**).

The behavior of oxazole in these reactions is in complete agreement with the previous findings obtained by Ketcham [4], who reported that these



SCHEME 6 Fragmentation pattern of compound (**XIb**).



SCHEME 7 Fragmentation pattern of compound (**XIII**).

oxazole can easily lose a molecule of aldehyde in reactions with appropriate nucleophiles.

EXPERIMENTAL

Melting points are uncorrected. Elemental analyses were carried out in the microanalytical unit at Cairo University. IR spectra (KBr) were measured on a Shimatzu 440 spectrometer, ^{1}H NMR spectra on a JEOL FX 90 Q (90 MHz) spectrometer, and mass spectra on a Shimadzu GC-MS QO 1000 EX spectrometer using a direct-inlet system.

*2-Arylaminobenzimidazoles (**IIa–d**)*

A mixture of **I** (0.01 mol) with *o*-phenylenediamine (0.01 mol) in DMF (10 ml) and TEA (0.5 ml) was heated under reflux for 3 h. The obtained product was recrystallized from the proper solvent to give **IIa–d** (Table 1). IR spectrum of **IIb** exhibited ν_{NH} at 3160, $\nu_{CH\ arom}$ at 3030, and $\nu_{CH\ aliph}$ at 2895 cm^{-1}. Mass spectrum of **IIc** showed at *m/z* 257 (M^+, 8.6%), 254 (22.3%), 169 (100%), 128 (37.2%), 111 (63%), 84 (91.5%), and 56 (55.6%).

*2-Mercaptobenzimidazole (**IIIa–c**)*

A mixture of cyanothioformamide (**I**; 0.01 mol), *o*-phenylenediamine or its derivatives (0.01 mol), and triethylamine (0.5 ml) in absolute ethanol (30 ml) was refluxed for 3 h. The solid that resulted was recrystallized from the proper solvent to give **IIIa–c** (Table 1). IR spectrum of **IIIb** exhibited ν_{NH} at 3200 cm^{-1}. Also, mass spectrum of **IIIc** showed a molecular ion peak at *m/z* 178 corresponding to the base peak. Compound **IIIa** was found to be identical with that obtained according to the literature [15].

*Reaction of (**IV**; X=NH) with 4,5-dimethyl-1,2-phenylenediamine*

A mixture of **IV** (X=NH; 0.01 mol) and 4,5-dimethyl-1,2-phenylenediamine (0.01 mol) in ethanol (25 ml) and triethylamine (0.5 ml) was heated under reflux for 18 h. The obtained product was recrystallized from ethanol to give **VI** (Table 1).

IR measurements of **VI** exhibited ν_{NH} (3150), $\nu_{CH\ arom}$ (3035), $\nu_{CH\ aliph}$ (2950), and $\nu_{N-C=S}$ (1510, 1250 cm^{-1}; amide **II** and **I**).

TABLE 1 Characterization Data for the Synthesized Compounds

Compound No.	Solvent for Crystallization	Mp (°C)	Yield (%)	Mol. Formula (M.Wt)	Elemental Analyses Required/Found (%)		
					C	H	N
IIa	Benzene	260	65	$C_{13}H_{10}ClN_3$ (246.69)	64.08 64.10	4.14 4.10	17.24 17.20
IIb	Ethanol	250	71	$C_{14}H_{12}ClN_3$ (257.73)	65.25 65.20	4.69 4.60	16.30 16.30
IIc	Benzene	120	64	$C_{14}H_{12}ClN_3$ (257.73)	65.25 65.20	4.69 4.60	16.30 16.30
IId	Ethanol	270	70	$C_{14}H_{12}ClN_3$ (257.73)	65.25 65.20	4.69 4.60	16.30 16.30
IIIa	Ethanol	>300	70	$C_7H_6N_2S$ (150)	55.97 55.80	4.02 4.00	18.65 18.40
IIIb	Ethanol	>300	72	$C_8H_8N_2S$ (164)	58.50 58.60	4.91 4.80	17.06 17.30
IIIc	Ethanol	287	73	$C_9H_{10}N_2S$ (178)	60.64 60.50	5.66 5.40	15.71 15.90
VI	Ethanol	181	60	$C_{16}H_{14}ClN_3S$ (315.83)	60.85 60.80	4.47 4.40	13.30 13.29
VIIa	Benzene	173	75	$C_{13}H_{10}N_2O$ (210)	74.27 74.10	4.79 4.60	13.32 13.10
VIIb	Ethanol	130	70	$C_{13}H_9FN_2O$ (228)	59.29 59.20	3.79 3.70	9.88 9.80
IXa	Ethanol	264 (267)	60	$C_9H_8N_2OS$ (192)			
IXb	Ethanol	270 (273)	64	$C_9H_7BrN_2OS$ (271)			
IXc	Ethanol	227 (229)	67	$C_9H_6Br_2N_2OS$ (350)			
IXd	Ethanol	305 (307)	61	$C_{14}H_{10}N_2OS$ (254)			
IXe	Ethanol	322 (325)	63	$C_{14}H_9BrN_2OS$ (333)			
IXf	Ethanol	300 (298)	62	$C_{14}H_8Br_2N_2OS$ (412)			
XIa	Dioxane	158	67	$C_{15}H_{11}N_3OS$ (281)	64.03 64.00	3.94 3.70	14.93 14.60
XIb	Dioxane	200	62	$C_{15}H_{10}ClN_3OS$ (315)	57.05 57.30	3.19 3.10	13.30 13.20
XIc	Dioxane	190	63	$C_{15}H_{10}BrN_3OS$ (360)	50.01 50.20	2.79 2.80	11.66 11.50
XId	Dioxane	265	64	$C_{15}H_9Cl_2N_3OS$ (350)	51.44 51.30	2.59 2.40	11.99 11.60
XIe	Dioxane	175	60	$C_{15}H_9Br_2N_3OS$ (439)	41.02 41.20	2.07 2.00	9.57 9.40
XIf	Ethanol	185	66	$C_{15}H_{10}ClN_3OS$ (315.5)	57.05 57.10	3.19 3.30	13.30 13.40
XIg	Dioxane	90	58	$C_{15}H_9BrClN_3OS$ (394.5)	45.65 45.20	2.29 2.10	10.64 10.30
XIh	Benzene	188	65	$C_{15}H_{10}FN_3OS$ (299)	60.19 60.20	3.37 3.30	14.03 14.10
XIi	Ethanol	150	55	$C_{15}H_9FN_3OS$ (378)	47.63 47.40	2.39 2.10	11.11 11.20
XII	Ethanol	195	65	$C_{17}H_{15}N_3OS_2$ (341)	59.79 59.80	4.42 4.40	12.38 12.50

Mass spectrum of **VI** showed a molecular ion peak at *m/z* 315 (19.3%), 314 (100%), 282 (56%), 256 (2%), 172 (66%), 146 (25%), and 118 (20%).

*2-Arylaminobenzoxazoles (***VIIa,b***)*

A mixture of cyanothioformamide (**I**; 0.01 mol), the *o*-aminophenol (0.01 mol), and triethylamine (0.5 ml) in DMF (10 ml) was refluxed for 3 h. The solid that obtained was recrystallized from the proper solvent to give **VIIa,b** (Table 1).

The IR spectrum of **VIIa** exhibited ν_{NH} at 3250 cm^{-1}. Also, the mass spectrum of **VIIa** exhibited a molecular ion peak at *m/z* 210 (92.5%), with a base peak at *m/z* 151. Compound **VIIa** was found to be identical with that obtained according to the literature [15].

The mass spectrum of **VIIb** exhibited a molecular ion peak at 228 (100%; which is the base peak).

*Preparation of Quinazolines (***IXa–f***)*

A mixture of each substituted cyanothioformamide (0.01 mol), anthranilic acid derivative (0.01 mol), and triethylamine (0.5 ml) in absolute ethanol (20 ml) was refluxed for 2 h. After evaporation of the solvent, the obtained solid was recrystallized from a proper solvent to give **IXa–f** (Table 1).

The IR spectrum of **IXb** showed ν_{NH} at 3170 cm^{-1} and $\nu_{C=O}$ at 1699 cm^{-1}. The mass spectrum of **IXa** showed a molecular ion peak at *m/z* 192 (9.3%).

These products (**IXa–f**) were found to be identical with those prepared according to the literature methods : **IXa,b** [17], **IXc** [18], **IXd,e** [19], and **IXf** [18].

*Preparation of Quinazolines (***XIa–i***)*

A mixture of **IV** (X=NH, 0.01 mol), the anthranilic acid derivative (0.01 mol), and triethylamine (0.5 ml) in absolute ethanol (30 ml) was refluxed for 12 h. The solid that was obtained was recrystallized from ethanol to give **XIa–i** (Table 1).

IR Spectrum of Compound **XI**

Compound No.	ν_{NH}	$\nu_{C=O}$	$\nu_{C=S}$
XIa	3225	1676	1472–1261
XIb	3225	1686	1462–1236
XIc	3225	1697	1491–1245
XId	3240	1678	1475–1260
XIe	3255	1680	1483–1229
XIf	3245	1693	1468–1229

The ^{1}H NMR spectrum of compound **XIa** ($CDCl_3$): 6.6–8.8 (9H, m, Ar-H), 11.4 (1H, s, NH; cancelled with D_2O), 12.2 (1H, s, CSNH; cancelled with D_2O). Also, ^{1}H NMR of compound **XIf** ($CDCl_3$): 7–8.8 (8H, m, Ar-H), 11.41 (1H, s, NH; cancelled with D_2O), 12.23 (1H, s, CSNH; cancelled with D_2O).

The mass spectrum of **XIa** exhibited a molar ion peak at *m/z* 281 (79%), together with a base peak at *m/z* 280 [($M^+ - 1$), 100%; Scheme 5]. Also, mass spectrum of compound **XIh** exhibited a molecular ion peak at *m/z* 299 (95.8%), together with a base peak at *m/z* 298 [($M^+ - 1$), 100%; Scheme 6].

*2-Thiocarbanilide-5,6,7,8-tetrahydrobenzo[b] thieno[2,3-d]pyrimidin-4(3H)one (***XII***)*

A mixture of **IV** (X=NH; 0.01 mol), 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (0.01 mol), and triethylamine (0.5 ml) in absolute ethanol (20 ml) was refluxed for 10 h. The solid that was obtained was recrystallized from the proper solvent to give **XII** (Table 1).

The IR spectrum of **XII** exhibited the following bonds: ν_{NH} at 3250 cm^{-1}, $\nu_{CH\ aliph}$ at 2900 cm^{-1}, $\nu_{C=O}$ at 1690 cm^{-1}, and $\nu_{C=S}$ at 1500 and 1290 cm^{-1}.

The ^{1}H NMR of compound **XII** ($CDCl_3$) exhibited the following signals: 1.8 and 2.4 (8H, cyclohexene), 7.9–8.5 (5H, m, Ar-H), 11.4 (1H, s, NH; cancelled with D_2O), 11.8 (1H, s, CSNH; cancelled with D_2O). Mass spectrum of **XII** assigned a molecular ion peak at *m/z* 341 (95%) (Scheme 7).

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