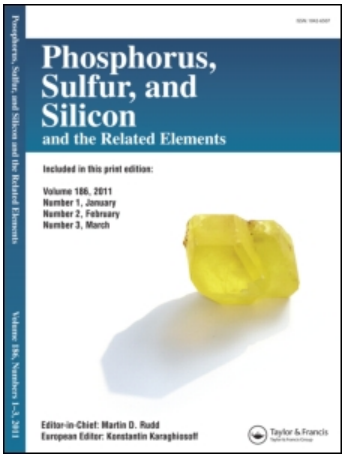

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

The Uses of 4-Aryl-3-Thiosemicarbazides in Heterocyclic Synthesis: Synthesis of Coumarin, Pyrazole, Thiazole and Thiophene Derivatives

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To cite this Article Mohareb, Rafat Milad , Ghabrial, Sami Selim and Wardakhan, Wagnat Wahba(1998) 'The Uses of 4-Aryl-3-Thiosemicarbazides in Heterocyclic Synthesis: Synthesis of Coumarin, Pyrazole, Thiazole and Thiophene Derivatives', Phosphorus, Sulfur, and Silicon and the Related Elements, 134: 1, 119 — 136
To link to this Article: DOI: 10.1080/10426509808545457
URL: http://dx.doi.org/10.1080/10426509808545457

Phosphorus, Sulfur and Silicon, 1998, Vol. 134/135, pp. 119-136
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THE USES OF 4-ARYL-3-THIOSEMICARBAZIDES IN HETEROCYCLIC SYNTHESIS: SYNTHESIS OF COUMARIN, PYRAZOLE, THIAZOLE AND THIOPHENE DERIVATIVES

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(Received 26 September, 1997; In final form 13 November, 1997)

The reaction of 4-phenyl-3-thiosemicarbazide derivatives **1a-e** with 3-aminoacetonitrile (**2**) gave the condensed products **3a-e**. The reactivity of the latter products toward variety of chemical reagents was studied. Moreover, the reaction of **3b** with phenylisothiocyanate; followed by cyclization with α-haloketones **6**, **7** and **16**, gave the thiazole and thiophene derivatives.

Keywords: Thiosemicarbazides; aminoacetonitrile; thiazole; thiophene

INTRODUCTION

Thiosemicarbazides are versatile reagents which have recently been used as synthetic intermediates for a large number of heterocyclic and fused heterocyclic compounds. [1–4] The reactivity of 4-aryl-3-thiosemicarbazides towards ketones, cyanomethylene reagents, and dimeric adducts attracted our attention in recent years. The results showed the formation of thiazole, pyrazole, pyridine and 1,3,4-thiadiazine derivatives.[5–7]

* Corresponding Author.

RESULTS AND DISCUSSION

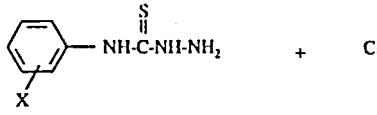
In continuation of our work, we have report here a new series of reactions involving the use of the title reagent in the synthesis of coumarin, thiazole, pyrazole and thiophene derivatives of potential biological activity.[8–11] The reaction of 4-aryl-3-thiosemicarbazide derivatives **1a-e** with β-iminobutyronitrile (**2**) in ethanol solution afforded products with molecular formulae $C_{11}H_{12}N_4S$, $C_{12}H_{14}N_4S$, $C_{12}H_{14}N_4S$), $C_{12}H_{14}N_4SO$ and $C_{11}H_{11}N_4SCl$, respectively. Two possible isomeric structures **3a-e** and **4a-e** were considered. The possibility of structures **4a-e** was ruled out based on IR spectra of the reaction products, which revealed in case of **3b** (as an example of the highest yield) the presence of two NH groups stretching at υ = 3460–3380 cm^{-1} and one CN group stretching at υ = 2220 cm^{-1}. Moreover, the ^1H NMR spectrum revealed the presence of two singlets at δ= 2.19, 2.23 for two CH_3 groups, a singlet at δ = 4.89 ppm for a CH_2 group, a multiplet at δ = 7.32–7.45 for a C_6H_4 group, and two singlets (D_2O exchangeable) at δ = 8.20, 8.34 for two NH groups. Such data are in agreement with structure **3b**.

Further confirmation for structure of **3b** was obtained through studying its reactivity. Compound **3b** reacted with benzaldehyde in ethanol solution containing a catalytic amount of piperidine to form the benzylidene derivative **5**. The reaction of **5** with monocholoroacetic acid (**6**) and with phenacyl bromide (**7**) afforded the thiazole derivatives **8a** and **8b**, respectively.

The reaction of **3b** with salicylaldehyde gave the coumarin derivative **9**. Structure of **9** was confirmed on the basis of analytical and spectral data. Thus, the IR spectrum of the reaction product revealed the presence of two NH groups stretchings υ = 3420–3345 cm^{-1}, one C=O group stretching at υ = 1690 cm^{-1}, and a C=S group stretching at υ = 1250 cm^{-1}. The ^1H NMR spectrum showed the presence of two singlets at δ = 2.22, 2.25 for two CH_3 groups, a singlet at δ = 6.89 for the coumarin H-4, a multiplet at δ = 7.29–7.46 for two C_6H_5 groups and two singlets (D_2O exchangeable) at δ = 8.23, 8.53 for two NH groups. Formation of **9** was assumed to take place through formation of an arylidene followed by a Micheal addition of the OH group to CN group and hydrolysis of the formed imino group to keto group.[12–14]

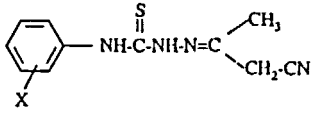
The reaction of **9** with monochloroacetic acid (**6**) or with phenacyl bromide (**7**) afforded the thiazole derivatives **10a** and **10b**, respectively. Structures of compounds **10a,b** were established on the basis of analytical and

spectral data (see experimental section). Further confirmation of structures **10a,b** was obtained through the synthesis of **10a** via another route. Thus, the reaction of **3b** with monochloroacetic acid (**6**) in refluxing ethanol solution give the thiazole derivative **11**. Reaction of **11** with salicylaldehyde gave the same product **10a** (identical IR and mixed mp).



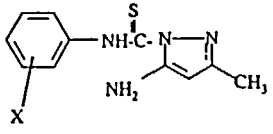
1a-e

1	X
a	H
b	p-CH_3
c	o-OCH_3
d	p-OCH_3
e	p-Cl

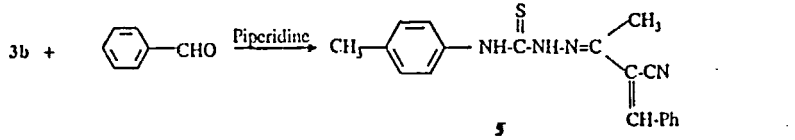


3a-e

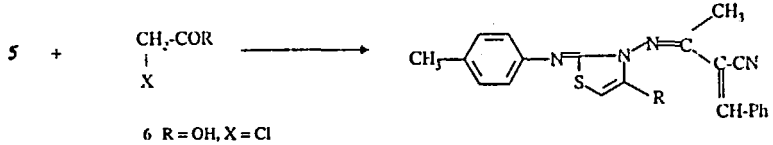
3	X
a	H
b	p-CH_3
c	o-OCH_3
d	p-OCH_3
e	p-Cl



4a-e



5



6 R = OH, X = Cl
7 R = Ph, X = Br

8a, R = OH
b, R = Ph

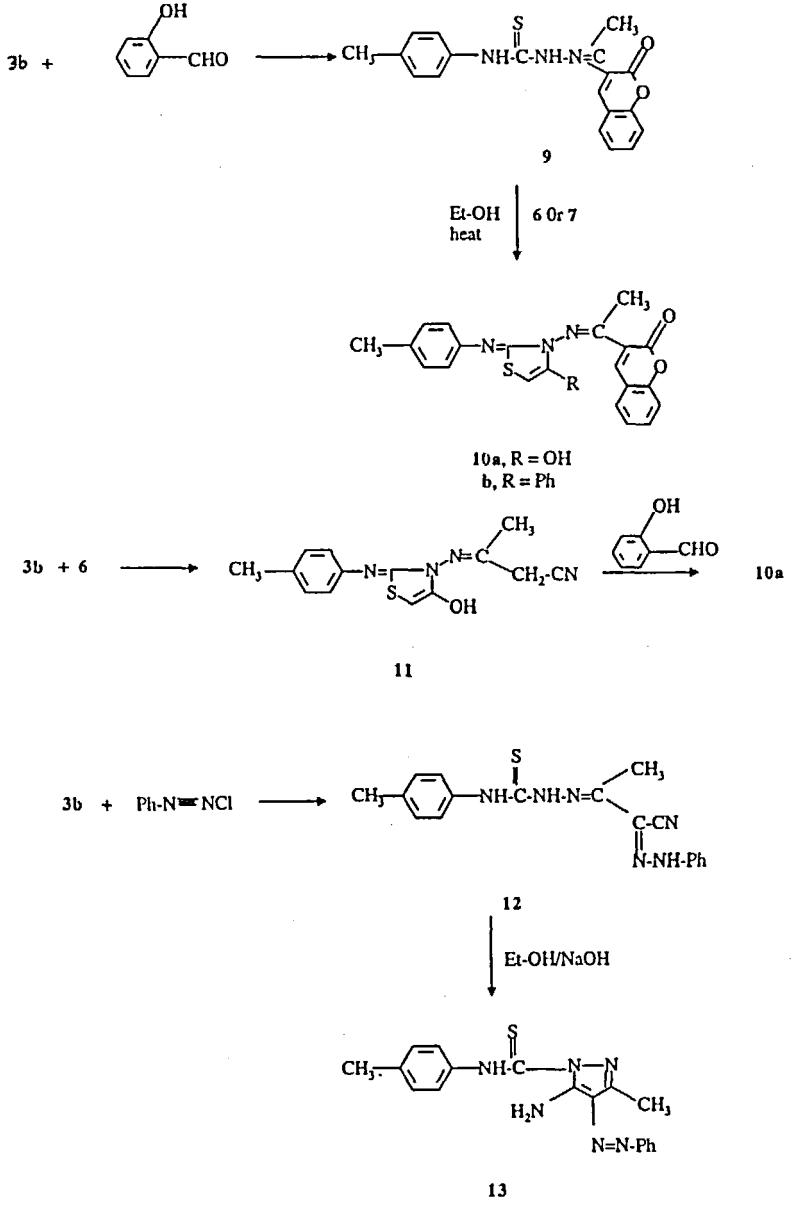
SCHEME 1

The reaction of **3b** with benzenediazonim chloride gave the phenylhydrazone derivative **12** which underwent ready cyclization upon heating under reflux in ethanolic sodium hydroxide solution to give the 5-aminopyrazole derivative **13**. The structure of compound **13** was established on the basis of analytical and spectral data (see Scheme 2).

The reactivity of the cyanomethylene group present in compound **3b** towards the reaction with phenylisothiocyanate followed by heterocyclization with α-haloketones was studied. Such reactions have received considerable attention in recent years by our research group and others and has led to thiazole and thiophene derivatives of potential biological activities.[15–18] However, the reaction of **3b** with phenylisothiocyanate in dimethylformamide containing potassium hydroxide afforded the intermediate potassium sulphide salt 14. Treatment of 14 with phenacyl bromide (7) afforded the thiazole derivative **15**. The structure of the latter product was established on the basis of analytical and spectral data. However, the ^{1}H NmR spectmm showed the presence of two singlets at $\delta = 2.19$, 2.25 for two CH_3 groups, a singlet at $\delta = 6.88$ for thiazole H-5, a multiplet at $\delta = 7.32$–7.59 for two C_6H_5 and C_6H_4 groups and two singlets (D_2O exchangeable) at $\delta = 8.42$, 8.76 for two NH groups.

The reaction of **14** with ethyl bromoacetate (**16**) afforded the thiophene derivative **17** whose structure was based on analytical and spectral data. However, the IR spectrum showed the presence of NH_2, NH stretchings at $\upsilon = 3460$–3330 cm^{-1} and one C=O stretching at $\upsilon = 1690$ cm^{-1}. Moreover, the ^{1}H NMR spectrum showed the presence of a triplet at 6 = 1.14 for the ester CH_3, two singlets at $\delta = 2.22$, 2.26 for two CH_3 groups, a quartet at $\delta = 4.42$ for the ester CH_2 group, a singlet at $\delta = 5.21$ (D_2O exchangeable) for NH_2 group, a multiplet at $\delta = 7.30$–7.38 for C_6H_5, C_6H_4 groups, and three singlets (D_2O exchangeable) at $\delta = 8.22$, 8.34, 8.75 for three NH groups. Reaction of **17** with aniline in an oil bath (140 °C) gave the anilide derivative **18**. In a similar way, the reaction of **14** with monochloroacetic acid (**6**) afforded the thiophene derivative **20**. The reaction probably took place through the intermediate formation of **19** followed by decarboxylation.

The reaction of **14** with ethyl bromocyanoacetate **21**[19] gave the thiazolone derivative **22**. The structure of **22** was based on analytical and spectral data. However, ^{1}H NMR spectrum which revealed the presence of two singlets at $\delta = 2.21$, 2.23 for two CH_3 group, a singlet at $\delta = 6.56$ for thiazole H-5, a multiplet at $\delta = 7.32$–7.40 for C_6H_5 and C_6H_4 groups, two sin-



SCHEME 2

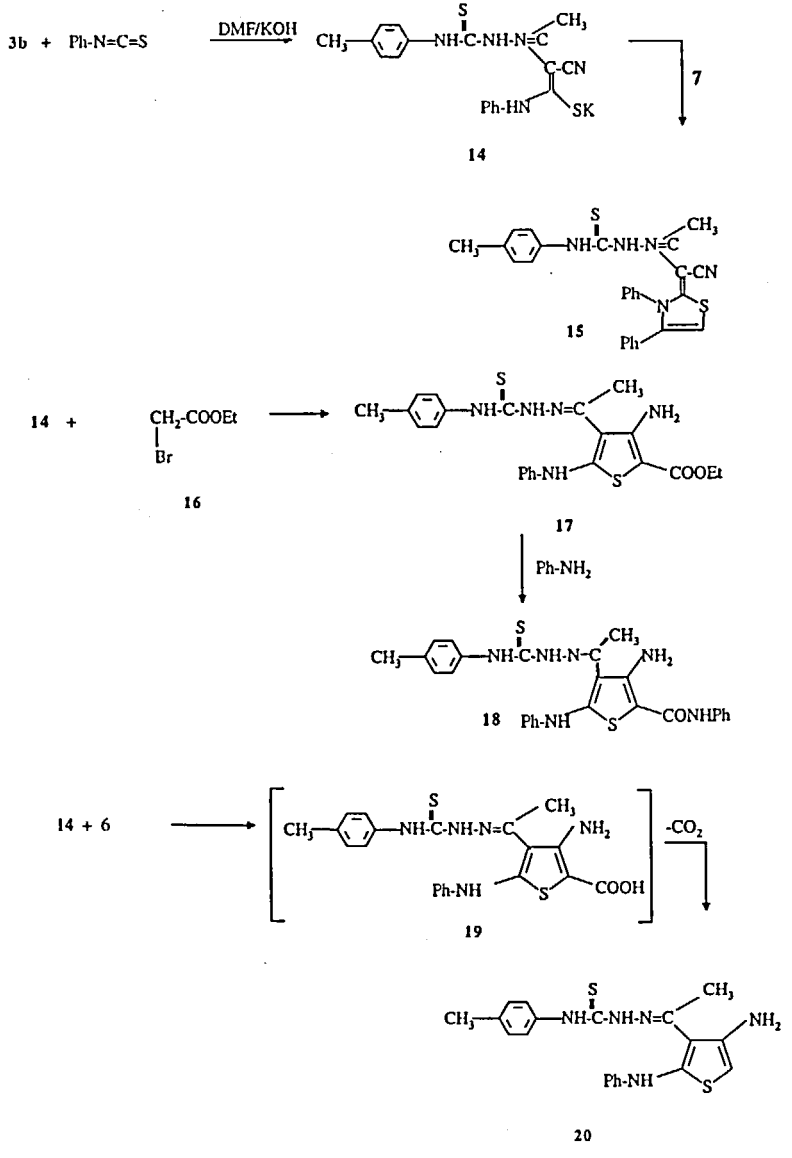
glets (D_2O exchangeable) at 6 = 8.25, 8.32 for two NH groups, and a singlet at δ = 10.21 for one OH group (see Scheme 3).

Moreover, the reaction of **14** with chloroacetyl chloride (23) afforded the thiazole-5-one derivative **24**. The structure of **24** was confirmed on the basis of analytical and spectral data.

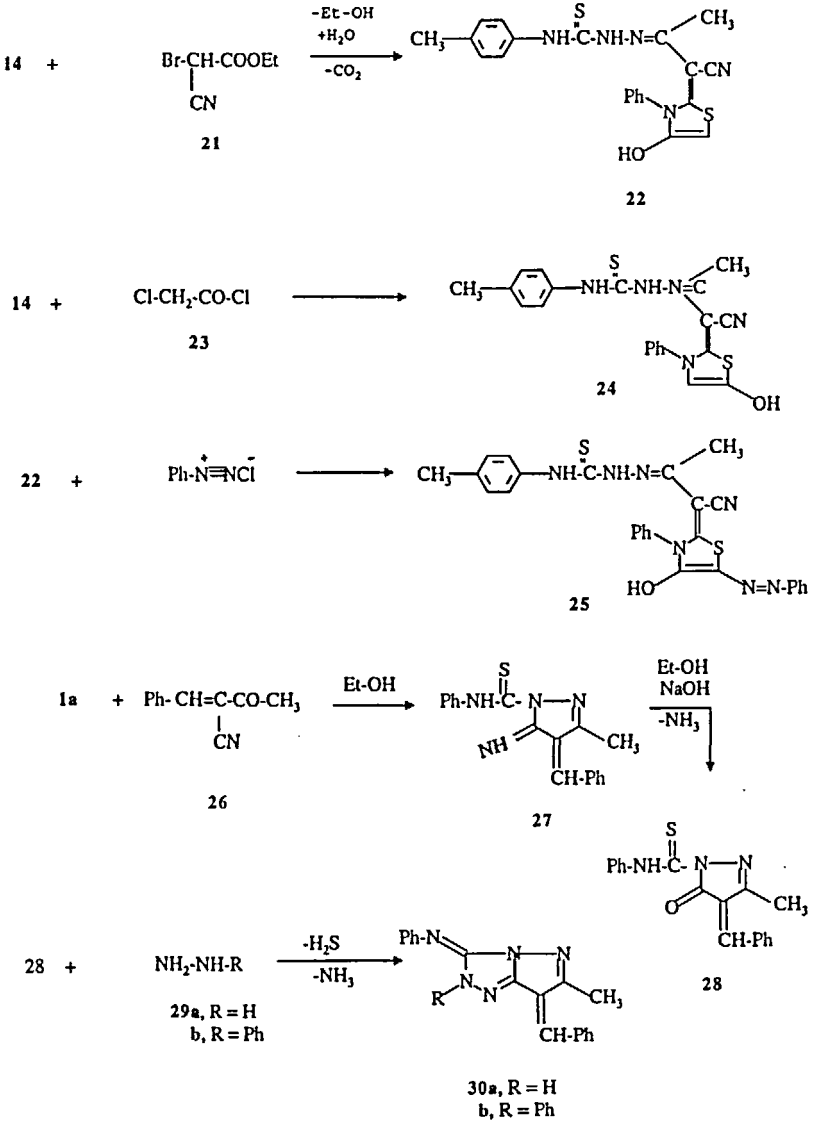
The reaction of **22** with benzenediazonium chloride gave the phenylazo derivative **25**. The structure of **25** was based on analytical and spectral data (see the experimental section).

We have also studied the reaction of **1a** with α-benzal-β-ketobutyronitrile (**26**)[20]. The reaction took place in boiling ethanol solution to give the pyrazole derivative **27**. The structure ofthe latter product was based on analytical and spectral data. Boiling of compound **27** in ethanol solution containing sodium hydroxide give the pyrazole-5-one derivative **28**. Formation of **28** took place via hydrolysis of the imino function present in **27** to afford a keto-function via loss of ammonia. The reactivity of **28** towards chemical reagents to afford pyrazole derivatives was studied. Thus, the reaction of **28** with hydrazine hydrate (**29a**) or with phenylhydrazine (**29b**) afforded the pyrazolo[3,2-c]-1,2,4-triazole derivative **30a,b.** Formation of **30a,b** occured through the loss of hydrogen sulphide and ammonia. The reaction of **28** with phenacyl bromide (**7**) gave the pyrazolo[2,3-c]thiazole derivative **31**. Its structure was based on analytical and spectral data (see the experimental section).

A new approach in our work involved studying the reactivity of **28** towards active methylene reagents. Thus, the reaction of **28** with each of malononitrile (**32a**) or ethyl cyanoacetate (**32b**) gave the same product namely the pyrazolo[2,3-*a*] pyrimidine derivative (**33**) (see Scheme 4). The reaction occured with the two reagents in two different mechanistic sequences, since in the reaction with malononitrile (**32a**), a Micheal addition occured via addition of the imino group into the cyano group followed by hydrolysis of the expected formed imino group into the carbonyl .The reaction of **28** with ethyl cyanoacetate (**32b**), loss of ethanol took place to give the same product **33** (identical IR and mixed mp).



SCHEME 3



SCHEME 4

EXPERIMENTAL SECTION

All melting points are not corrected. IR spectra were obtained (KBr) on a Pye Unicam SP-1000 spectrophotometer. ^1H NMR spectra were measured on Varian EM 390–90 Mhz in CD_3SOCD_3 as a solvent, using TMS as internal standard, and chemical shifts were expressed as δ values. Mass spectra were obtained on an AEI MS 30 specterometer, at 70 eV. Elemental analyses were obtained from the Microanalytical Data Unit at Cairo University,Giza, Egypt.

Butyronitrilo-3-(4-phenyl-3-thiosemicarbazone) (**3a**); Butyronitrilo-3-(4-*p*-methylphenyl-3-thiosemicarbazone) (**3b**); Butyronitrilo-3-(4-*o*-methoxy-3-thiosemicarbazone) (**3c**); Butyronitrilo-3-(4-*p*-methoxy-3-thiosemicarbazone)(**3d**) and Butyronitrilo-3-(4-*p*-chloro-3-thiosemicarbazone) (**3e**): *General procedure:* To a solution of **1a-e** (1.67 g, 0.01 mol) in absolute ethanol (50 ml) was added β-iminobutyronitrile **2** (0.82 g, 0.01 mol). The reaction mixture, in each case, was heated under reflux for **4** h. The solid product formed in each case, upon cooling was collected by filtration.

α-Butyronitrilo-β-(4-*p*-tolyl)-3-thiosemicarbazone (**5**) and 3-Acetyl-(4-*p*-tolyl-3-thiosemicarbazono)-coumarin (**9**): *General procedure:* To a solution of **3b** (2.46 g, 0.01 mol) in dimethylformamide (20 ml) containing piperidine (0.5 ml) , was added benzaldehyde (1.06 g, 0.01 mol) or salicyladehyde (1.22 g, 0.01 mol). The reaction mixture, in each case, was heated under reflux for 4h and then poured into ice/water containing few drops of hydrochloric acid. The formed solid product, in each case, was collected by filtration.

α-Benzal-β-imino-(2-*p*-tolylimino)-4-hydroxythiazolo-3-yl)butyronitrile (**8a**): To a solution of **5** (3.43 g, 0.01 mol) in dimethyformamide (50 ml) was added monochloroacetic acid (**6**) (0.94 g, 0.01 mol) . The reaction mixture was heated under reflux for 9h and then evaporated in vacuo. The remaining product was triturated with chloroform, and the formed solid product was collected by filtration.

α-Benzal-β-(2-*p*-tolylimino)-4-phenylthiazolo-3-yl)butyronitrile (**8b**): To a solution of **5** (3.43g, 0.01 mol) in dimethylformamide (50 ml) was added phenacyl bromide (**7**) (2.00g, 0.01 mol). The reaction mixture was heated under reflux for 10 h and then left to cool to room temperature. The solid product formed upon dilution with water containing few drops of sodium hydroxide, was collected by filtration.

TABLE I Physical and analytical data of the newly prepared compounds

Comp	*Colour (solvent)*	*mp (°C)*	*Yield (%)*	*Mol. Formula (m/e = M+)*	*Analysis % calcd/found*			
					C	*H*	*N*	*S*
3a	Buff (ethanol)	167	80	$C_{11}H_{12}N_4S$	56.87	5.21	24.12	13.8
				(232)	56.5	5.5	24.3	14.1
3b	Yellowish white (ethanol)	185	90	$C_{12}H_{14}N_4S$	58.51	5.73	22.74	13.01
					58.7	5.9	22.4	13.2
3c	Yellow (ethanol)	130	70	$C_{12}H_{14}NS$	54.94	5.39	21.36	12.22
					54.6	5.5	21.1	12.5
3d	Gray (ethanol)	205	75	$C_{12}H_{14}N_4SO$	54.94	5.38	21.36	12.22
					54.6	5.2	21.1	12.4
3e	Yellowish brown (ethanol)	95	80	$C_{11}H_{11}N_4SCl$	49.52	4.23	21.00	12.02
					46.6	4.5	21.4	11.7
5	White (dioxan)	235	72	$C_{19}H_{18}N_4S$	68.24	5.43	16.75	9.59
				(334)	68.4	5.7	16.4	9.3
8a	Buff (dioxan)	180	80	$C_{21}H_{18}N_4OS$	67.36	4.85	14.96	8.56
				(374)	67.7	4.5	14.6	8.8
8b	Yellow (dioxan)	210	75	$C_{27}H_{22}N_4S$	74.63	5.10	12.29	7.35
					74.4	5.3	12.5	7.6
9	Yellow (ethanol)	168	78	$C_{19}H_{17}N_3NSO_2$	64.94	4.88	11.96	9.12
					64.6	4.6	12.1	9.2

Comp	Colour (solvent)	mp (°C)	Yield (%)	Mol. Formula (m/e = M+)	Analysis % calcd/found			
					C	H	N	S
10a	Yellow (ethanol)	200	75	$C_{21}H_{17}N_3O_3S$	64.44	4.38	10.73	8.19
				(391)	64.6	4.5	10.6	8.4
10b	Brown (dioxan)	90	79	$C_{27}H_{21}N_3O_2S$	71.82	4.69	9.31	7.14
					71.9	4.8	9.5	7.3
	White (dioxan)	220	80	$C_{14}H_{14}N_4OS$	58.72	4.93	19.57	11.20
					58.5	4.7	19.8	11.4
12	Orange (ethanol)	200	90	$C_{18}H_{18}N_6S$	61.70	5.18	23.98	9.15
					61.9	5.3	23.7	9.4
13	Pale yellow (DMF)	191	80	$C_{18}H_{18}N_6S$	61.70	5.18	23.98	9.15
				(350)	61.9	5.3	12.7	9.3
15	Yellow (dioxan)	225	88		67.33	4.81	14.54	13.31
				$C_{27}H_{23}N_5S_2$	67.1	4.5	14.7	13.5
17	Buff (dioxan)	155	70	$C_{23}H_{25}N_5S_2O_2$	59.08	5.39	14.98	13.71
					59.3	5.6	14.7	13.4
18	Orange (DMF)	178	77	$C_{27}H_{26}N_6S_2O$	63.01	5.09	16.33	12.46
				(514)	63.3	5.2	16.6	12.6
20	Yellowish white (dioxan)	235	88	$C_{20}H_{21}N_5S_2$	60.73	5.35	17.71	16.21
					60.4	5.5	17.4	16.4
24	Buff (dioxan)	155	85	$C_{21}H_{19}N_5S_2O$	59.84	4.54	16.61	15.21
					59.6	4.7	16.4	15.4

Comp	*Colour (solvent)*	*mp (°C)*	*Yield (%)*	*Mol. Formula (m/e = M+)*	*Analysis % calcd/found*			
					C	*H*	*N*	*S*
25	Yellow	131–3	82	$C_{27}H_{23}N_7S_2O$	61.69	4.41	18.65	12.20
					61.3	4.2	18.4	12.4
27	Yellow (dioxan)	157	89	$C_{18}H_{16}N_3S$	70.56	5.26	13.71	10.46
					70.3	5.5	13.5	10.6
28	Yellow (dioxan)	159	92	$C_{18}H_{15}N_3SO$	67.21	4.70	13.07	9.98
				(321)	67.4	5.0	13.2	9.7
30a	Yellow (DMF)	180	69	$C_{18}H_{15}N_5$	71.77	5.02	23.24	
					71.4	5.2	23.1	
30b	Buff (dioxan)	140	66	$C_{24}H_{19}N_5$	76.37	5.07	18.55	
					76.5	5.3	18.6	
31	Yellowish brown (ethanol)	110	72	$C_{26}H_{19}N_3OS$	74.09	4.54	9.97	7.61
					74.3	4.6	9.7	7.4
33	Buff (DMF)	175	70	$C_{21}H_{15}N_5O$	71.38	4.28	19.82	
				(353)	71.5	4.5	19.6	

TABLE II IR and ^{1}H NMR data of the newly prepared compounds

Comp.	*IR cm^{-1}*	*^{1}H NMR (δ ppm)*
3a	3460–3385 (2 NH), 3000 (CH aromatic), 2980, 2875 (CH_3, CH_2), 2220 (CN), 1640 (C=C), 1200–1190 cm^{-1} (C=S).	1.99 (s, 3 H, CH_3), 4.79 (s, 2 H, CH_2), 7.28–7.44 (m, 5 H,C_6H_5), 8.32, 8.62 (2s, 2 H, 2 NH).
3b	3460–3850 (2 NH), 3060 (CH aromatic), 2980, 2875 (CH_3, CH_2), 2220 (CN), 1660 (C=N), 1645 (C=C), 1200–1190 cm^{-1} (C=S).	2.19, 2.23 (2s, 6 H, 2 CH_3), 4.89 (s, 2 H, CH_2), 7.32–7.45 (m, 4 H, C_6H_4), 8.20, 8.34 (2s, 2 H, 2 NH).
3c	3460–3380 (2 NH), 3060 (CH aromatic), 2980, 2875 (CH_3, CH_2), 2220 (CN), 1660 (C=N), 1640 (C=C), 1200–1190 cm^{-1} (C=S).	2.22, 2.42 (2s, 6 H, 2 CH_3), 4.89 (s, 2 H, CH_2), 7.31–7.42 (m, 4 H, C_6H_4), 8.23–8.41 (2s, 2 H, 2 NH).
3d	3460–3380 (2 NH), 3060 (CH aromatic), 2980, 2875 (CH_3, CH_2), 2220 (CN), 1660 (C=N), 1640 (C=C), 1200–1190 cm^{-1} (C=S).	2.22, 2.51 (2s, 6 H, 2 CH_3), 4.89 (s, 2 H, CH_2), 7.31–7.42 (m, 4 H, C_6H_4), 8.23–8.41 (2s, 2 H, 2 NH).
3e	3460–3380 (2 NH), 3060 (CH aromatic), 2980, 2875 (CH_3, CH_2), 2220 (CN), 1660 (C=N), 1640 (C=C), 1200–1190 cm^{-1} (C=S).	2.89 (2s, 3 H, CH_3), 4.89 (s, 2 H, CH_2), 7.31–7.42 (m, 4 H,C_6H_4), 8.23–8.41 (2s, 2 H, 2 NH).
5	3460–3370 (OH), 3066 (CH aromatic), 2965 (CH_3), 2220 (CN), 1660 (C=N), 1645 cm^{-1} (C=C).	2.12–2.33 (2s, 6 H, 2 CH_3), 6.12 (s, 1 H, thiazole H-5), 7.02 (s, 1 H, CH=C), 7.32–7.45 (m, 9 H, C_6H_5, C_6H_4), 10.24 (s, 1 H, OH).
8a	3065 (CH aromatic), 2965 (CH_3), 2220 (CN), 1660 (C=N), 1645 cm^{-1} (C=C).	2.12–2.33 (2s, 6 H, 2 CH_3), 6.59 (s, 1 H, thiazole H-5), 7.02 (s, 1 H, CH=C), 7.30 (m, 14 H, 2 C_6H_5, C_6H_4).
9	3420–3345 (2 NH), 3060 (CH aromatic), 2980 (CH_3), 1690 (C=O), 1660 (C=N), 1630 (C=C), 1250 cm^{-1} (C=S).	2.22, 2.25 (2s, 6 H, 2 CH_3), 6.89 (s, 1 H, coumarin H-4), 7.29–7.46 (m, 8 H, 2 C_6H_4), 8.23, 8.53 (2s, 2 H, 2 NH).
10a	3480–3345 (OH), 3045 (CH aromatic), 2980 (CH_3), 1695 (C=O), 1670 (C=N), 1630 cm^{-1} (C=C).	1.98, 2.02 (2s, 6 H, 2 CH_3), 6.69 (s, 1 H, thiazole H-5), 6.99 (s, 1 H, coumarin H-4), 7.34–7.49 (m, 8 H, 2 C_6H_4), 10.11 (s, 1 H, OH).
10b	3055 (CH aromatic), 2995 (CH_3), 1695 (C=O), 1660 (C=N), 1635 cm^{-1} (C=C)	2.23, 2.25 (2s, 6 H, 2 CH_3), 6.45 (s, 1 H, thiazole H-5), 6.89 (s, 1 H, coumarin H-4), 7.32–7.49 (m, 13 H, C_6H_5, 2 C_6H_4).
13	3460–3360 (NH_2, NH), 3050 (CH aromatic), 2980 (CH_3), 1660 (C=N), 1635 (C=C), 1200 cm^{-1} (C=S).	2.21, 2.32 (2s, 6 H,2 CH_3), 4.38 (s, 2 H, NH_2), 7.33–7.46 (m, 9 H, C_6H_5, C_6H_4), 8.36 (s, 1 H, NH).
15	3450–3330 (2 NH), 3050 (CH aromatic), 2980 (CH_3), 2220 (CN), 1660 (C=N), 1635 (C=C), 1250 cm^{-1} (C=S).	2.19, 2.25 (2s, 6 H,2 CH_3), 6.88 (s, 1 H, thiazole H-5), 7.32–7.59 (m, 14 H, C_6H_5, C_6H_4), 8.42, 8.76 (2s, 2 H, 2 NH).

Comp.	*IR cm^{-1}*	*^{1}H NMR (δ ppm)*
17	3460–3330 (NH_2, 3 NH), 3060 (CH aromatic), 2975 (CH_3), 2890 (CH_2), 1690 (C=O), 1655 (C=N), 1635 (C=C), 1220–1200 cm^{-1} (C=S).	1.14 (t, 3 H, J = 8.02 Hz, CH_3), 2.22, 2.26 (2s, 6 H,2 CH_3), 4.42 (q, 2 H, J = 8.02, 2 H, CH_2), 5.21 (s, 2 H, NH_2), 7.30–7.38 (m, 9 H, C_6H_5, C_6H_4), 2.22, 8.34, 8.75 (3s, 3 H,3 NH).
18	3460–3320 (NH_2, 4 NH), 3060 (CH aromatic), 2980 (CH_3), 1680 (C=O), 1660 (C=N), 1635 (C=C), 1250 cm^{-1}2 (C=S).	2.22, 2.26 (2s, 6 H,2 CH_3), 4.56 (s, 2 H, NH_2), 7.31–7.46 (m, 14 H, C_6H_5, C_6H_4), 8.21, 8.76–8.82 (m, 4 H, 4 NH).
19	3560–3370 (OH, 2 NH), 3050 (CH aromatic), 2985 (CH_3), 2220 (CN), 1675 (C=O), 1655 (C=N), 1635 (C=C), 1250 cm^{-1}(C=S).	2.22–2.31 (2s, 6 H, 2 CH_3), 4.32 (s, 2 H, NH_2), (s, 1 H, thiophene H-5), 7.30–7.43 (m, 9 H, C_6H_5, C_6H_4), 7.37, 8.41, 8.62 (3s, 3 H, 3 NH).
22	3560–3370 (OH, 2 NH), 3050 (CH aromatic), 2985 (CH_3), 2220 (CN), 1675 (C=O), 1655 (C=N), 1635 (C=C), 1250 cm^{-1}(C=S).	2.21, 2.23 (2s, 6 H, 2 CH_3), 6.56 (s, 1 H, thiazole H-5), 7.23–7.40 (m, 9 H, C_6H_5, C_6H_4), 8.25, 8.32 (2s, 2 H, 2 NH), 10.21 (s, 1 H, OH).
24	3560–3370 (OH, 2 NH), 3050 (CH aromatic), 2985 (CH_3), 2220 (CN), 1655 (C=N), 1635 (C=C),1250 cm^{-1} (C=S).	2.21, 2.23 (2s, 6 H, 2 CH_3), 6.56 (s, 1 H, thiazole H-4), 7.23–7.40 (m, 9 H, C_6H_5, C_6H_4), 8.25, 8.32 (2s, 2 H, 2 NH), 10.21 (s, 1 H, OH).
25	3540–3365 (OH, 2 NH), 3060 (CH aromatic), 2980 (CH_3), 2225 (CN), 1650 (C=N), 1635 (C=C), 1205 cm^{-1} (C=S).	2.20, 2.24 (2s, 6 H, 2 CH_3), 7.28-7.43 (m, 14 H, C_6H_5, C_6H_4), 8.32, 8.36 (2s, 2 H, 2 NH), 10.25 (s, 1 H, OH).
27	3430–3375 (2 NH), 3060 (CH aromatic), 2960 (CH_3), 1660 (C=N), 1635 (C=C), 1250 cm^{-1} (C=S).	2.02 (s, 3 H, CH_3), 5.98 (s, 1 H, CH), 7.33–7.46 (m, 10 H, 2 C_6H_5), 8.21, 8.34 (2s, 2 H, 2 NH).
28	3430–3375 (NH), 3060 (CH aromatic), 2960 (CH3), 1690 (C=O), 1660 (C=N), 1635 (C=C), 1250 cm^{-1} (C=S).	2.02 (s, 3 H, CH_3), 6.98 (s, 1H, CH), 7.33–7.46 (m, 10H, 2 C_6H_5), 8.21 (s, 1 H, NH).
30a	3060 3450–3400 (NH), 3060 (CH aromatic), 2970 (CH_3), 1680 (exocyclic C=N), 1655 (CN), 1640 cm-1 (C=C).	2.22 (s, 3 H, CH_3), 6.30 (s, 1 H, CH), 7.32–7.45 (m, 10H, 2 C_6H_5), 8.09 (s, 1 H, NH).
30b	3060 (CH aromatic), 2975 (CH_3), 1675 (exocyclic C=N), 1655 (C=N), 1635 cm^{-1} (C=C).	2.13 (s, 3 H, CH_3), 6.32 (s, 1 H, CH), 7.32–7.51 (m, 15 H, 3 C_6H_5).
31	3060 (CH aromatic, 2975 (CH_3), 1690 (C=O), 1670 (exocyclic C=N), 1660 (C=N), 1635 cm^{-1} (C=C).	2.02 (s, 3 H, CH_3),6.32 (s, 1 H, CH), 7.34–7.47 (m, 10 H, 2 C_6H_5), 8.23 (s, 1 H, NH).

3-Imino-(3′-acetylcoumarino)-4-hydroxy-2-(*p*-tolylimino)thiazole (**10a**); and 2-(*p*-Tolylimino)-3-imino-(3′-acetylcoumarino)-4-phenylthiazole (**10b**): *General procedure:* To a solution of **9** (3.51 g, 0.01 mol) in absolute ethanol (50 ml) was added monochloroacetic acid (**6**) (0.94 g, 0.01 mol) or phenacylbromide (**7**) (2.0 g, 0.01 mol). The reaction mixture was heated under reflux for 8 h and then left to cool. the solid product formed, in each case, upon dilution with water containing sodium hydroxide was collected by filtration.

β-Imino-(2-*p*-tolylimino-4-hydroxythaizolo-3-yl)butyronitrile (**11**) : To a solution of **3b** (2.46 g, 0.01 mol) in dimethylformamide(40 ml) was added monochloroacetic acid (**6**) (0.94 g, 0.01 mol). The reaction mixture was heated under reflux for 3 h. The solid product formed, upon dilution with water containing few drops of sodium hydroxide, was collected by filtration.

Conversion of **11** into **10a**: To a solution of **11** (2.86 g, 0.01 mol) in dimethylformamide (20 ml) containing piperidine (0.5 ml) was added salicylaldehyde (1.22 g, 0.01 mol). The reaction mixture was heated under reflux for 12 h and then evaporated in vacuo. The remaining product was triturated with diethyl ether and the formed solid product was collected by filtration to afford the same product **18** (identical mp, mixed mp and IR spectra).

α-Phenylhydrazono-β-(4-*p*-tolyl)-3-thiosemicarbazono)butyronitrile (**12**) and α-(4-hydroxy-5-phenylazo-3-phenylthiazolidin-2-eno)-β-(4′-*p*-tolyl-3′-thiosemi-carbazono)butyronitrile (**25**): *General procedure*: To a cold solution of **3b** (2.46 g, 0.01 mol) or **22** (4.22 g, 0.01 mol) in ethanol at 0 °C containing sodium hydroxide (10 ml, 10 %) was added a solution of benzenediazonium chloride (0.01 mol) [prepared by adding sodium nitrite solution (0.69 g, 0.01 mol) to a cold solution (0–5 °C) of aniline (0.93 g, 0.01 mol) containing the appropriate quantity of hydrochloric acid] with continuous stirring for 4 h. The solid product formed was collected by filtration.

5-Amino-3-methyl-4-phenylazo-1-(*p*-tolylaminothiocarbonyl)pyrazole (**13**): A solution of **12** (3.5 g, 0.01 mol) in absolute ethanol (30 ml) containing sodium hydroxide (0.5 g) was heated under reflux for 3 h and then left to cool. The solid product formed upon pouring into water containing few drops of hydrochloric acid (pH = 6) was collected by filtration.

3-Acetyl-(4'-(*p*,-tolyl)-3'-thiosemicarbazono)-4-amino-2-phenylamino-5-phenyl-formamidothiophene (**18**): To a dry solid **17** (4.67 g, 0.01 mol)

was added the appropriate quantity of aniline **30** (0.93 g, 0.01 mol). The reaction mixture was heated in an oil bath at 140 °C. The solid product formed upon cooling was triturated with ethanol then collected by filtration.

α-(3',4'-Diphenylthiazolidin-2-eno-β-(4-*p*-tolyl-3-thiosemicarbazono)-butyronitrile (**15**); 3-Acetyl-(4'-*p*-tolyl-3'-thiosemicarbazono)-4-amino-2-phenylaminothiophene (**20**); α-(4-Hydroxy-3-phenylthiazolidin-2-eno)-β-(4'-p-tolyl-3'-thiosemicarbazono)butyronitrile (**24**): *General procedure:* To a cold solution of **3b** (2.46 g, 0.01 mol) in dimethylformamide (20 ml) containing finely divided potassium hydroxide (0.57 g, 0.01 mol) was added phenylisothiocyanate (1.35 g, 0.01 mol) and the reaction mixture was stirred at room temperature for 24 h. Phenacyl bromide (**7**), monochloroacetic acid (**6**) (0.94 g, 0.01 mol), ethyl cyanobromoacetate (**21**) (1.94 g, 0.01 mol) or chloroacetyl chloride (**23**) (1.13 g, 0.01 mol) was added. The whole reaction mixture was stirred at room temperature for an additional 24 h. The solid product formed, upon addition of water containing hydrochloric acid (pH = 6) and stirring for 6h, was collected by filtration.

4-(Benzal-5-imino-3-methyl-1-phenylthiocyanatopyrazole (**27**): To a solution of **1a** (1.81 g, 0.01 mol) in absolute ethanol (40 ml) was added α-benzal-β-ketobutyronitrile **26** (1.71 g, 0.01 mol). The reaction mixture was heated under reflux for 4 h. The solid product formed from the cold solution was collected by filtration.

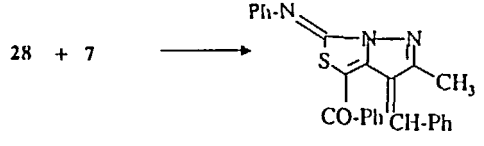
4-Benzal-3-methyl-1 -phenylisothiocyanatopyrazol-5-one (**28**): A solution of **27** (3.06 g, 0.01 mol) in absolute ethanol (30 ml) containing sodium hydroxide (0.5 g) was heated under reflux for 3 h and then left to cool. The solid product, so formed upon pouring into water containing few drops of hydrochloric acid (pH = 6), was collected by filtration.

6-Benzal-5-methyl-2[H]-3-phenyliminopyrazolo[3,2-*c*] 1,2,4-triazole (**30a**); 6-Benzal-5-methyl-2-phenyl-3-phenyliminopyrazolo[3,2-*c*] 1,2,4-triazole (**30b**): *General procedure:* To a solution of **28** (3.21 g, 0.01 mol) in dimethylformamide (50 ml) was added hydrazine hydrate (0.5 g, 0.01 mol) or phenylhydrazine (1.1 g, 0.01 mol). The reaction mixture, in each case, was heated under reflux for 10 h. the solid product formed upon cooling was collected by filtration.

6-Benzal-1-benzoyl-5-methyl-3-phenyliminopyrazolo[2,3-*c*]thiazole (**31**): To a solution of **28** (3.21 g, 0.01 mol) in absolute ethanol (50 ml) was added phenacyl bromide (**7**) (2.0 g, 0.01 mol). The reaction mixture was

heated under reflux for 12h and then left to cool. The solid product formed upon pouring into ice/water mixture containing few drops of sodium hydroxide was collected by filtration.

7-Benzal-3-cyano-6-methyl-2-oxo-4-phenylaminopyrazolo[2,3-*a*]pyrimidine (**33**): To a solution of **28** (3.21 g, 0.01 mol) in dimethylformamide (30 ml) containing piperidine (0.5 ml) was added malononitrile **32a** (0.66g, 0.01 mol) or ethyl cyanoacetate **32b** (1.13g, 0.01 mol) . The reaction mixture was heated under reflux for 8h. The solid product formed ,after adding on ice/water mixture, was collected by filtration.



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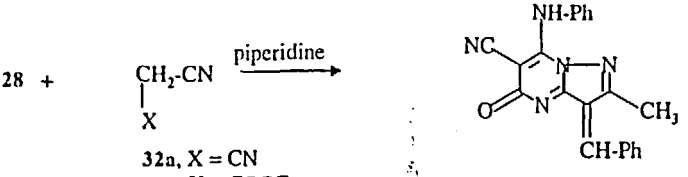

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