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REACTIONS WITH β-(4-ARYL-3-THIOSEMICARBAZONO) BUTYRONITRILES

By

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ABSTRACT

β-(4-Aryl-3-thiosemicarbazono) butyronitriles 3a-e were prepared from 4-arly-3-thiosemicarbaizdes 1a-e and β-iminobutyronitrile 2. Compound 3b reacted with salicylaldehyde to yield coumarin derivative 7. Coumpound 7 underwent cyclization with choloroacetic acid 8 and with phenacyl bromide 11 to give thiazolylcoumarin derivatives 9 and 12, respectively.

3b Reacted with benzendiazonium chloride to give the pyrazole derivative 14.

3b Also reacted with phenyl isothiocyanate 15 to give the intermediate potassium sulphide salt 16. Reaction of 16 with α - haloketones such as phenacyl bromide 11, ethyl bromoacetate 19, chloroacetic acid 8, ethyl cyanobromoacetate 25 and chloroacetyl chloride 29, resulted in the formation of thiazole and thiophene derivatives 18, 20, 24, 27 and 31.

INTRODUCTION

Thiosemicarbazides are versatile reagents which have recently been used as synthetic intermediates for a large number of heterocyclic and fused heterocyclic compounds[1-3]. The reactivity of 4-aryl-3-thiosemicarbazides towards ketones, cyanomethylene reagents and dimeric adducts attracted the attention in recent years. The results showed the formation of thiazole, pyrazole, pyridine and 1, 3, 4 - thiadiazine derivatives[4, 5]. In continuation of this work, I report here a new series of reactions involving the use of the title reagents in the synthesis of coumarin,

thiazole, pyrazole, and thiophene derivatives of expected potential biological activity[6, 7].

DISCUSSION

The reaction of 4 - aryl - 3 - thiosemicarbazide derivatives 1a-e with β-iminobutyronitrile 2 in ethanol afforded products with molecular formulae $C_{11}H_{12}N_4S$, $C_{12}H_{14}N_4S$, $C_{12}H_{14}N_4OS$, $C_{12}H_{14}N_4OS$ and $C_{11}H_{11}ClN_4S$, respectively. Tow possible isomeric structures 3a-e and 4a-e were considered. The possibility of structures 4a-e was ruled out based on IR and ^1H - NMR spectra (cf. Table 2).

Further confirmation for the structure 3a-e was obtained through studying its reactivity towards some chemical reagents. Thus, compound 3b reacted with salicylaldehyde 5 to give the coumarin derivative 7. Structure of 7 was confirmed on the basis of analytical and spectral data (cf. Tables 1 and 2). Formation of 7 was assumed to take place through arylidene formation followed by addition of the OH group to the CN group and hydrolysis of the formed imino group to keto group. Formation of coumarin via such reaction route was reported[8 - 10].

The reaction of 7 with monochloroacetic acid 8 afforded the thiazole derivative 9. Structure of compound 9 was established on the basis of analytical and spectral data (cf. Tables 1 and 2). Further confirmation for the structure 9 was obtained through its synthesis via another reaction route. Thus, the reaction of 3b with monochloroacetic acid 8 in refluxing ethanol gave the thiazole derivative 10. Reaction of 10 with salicylaldehyde 5 gave the same product 9 (mixed m. p. and identical IR).

In a similar manner, reaction of 7 with phenacyl bromide 11 afforded the thiazole derivative 12. The structure of 12 was confirmed on the basis of analytical and spectral data (cf. Tables 1 & 2).

The reaction of 3b with benzenediazonium chloride gave the phenylhydrazone derivative 13 which underwent ready cyclization upon heating under reflux in ethanolic sodium hydroxide solution to give the aminopyrazole

derivative 14. Structure of compound 14 was based on analytical and spectral data (cf. Tables 1 and 2).

The reactivity of the cyano methylene group in 3b towards the reaction with phenyl isothiocyanate followed by cyclization with α - haloketones was studied. Such type of reactions received considerable attention as it afforded thiazole and thiophene derivatives of potential biological activities[11, 12]. The reaction of 3b with phenyl isothiocyanate 15 in dimethylformamide containing potassium hydroxide afforded the intermediate potassium sulphide salt 16. Treatment of 16 with phenacyl bromide 11 afforded the thiazole derivative 18. The structure of 18 was established on the basis of analytical and spectral data (cf. Tables 1 & 2).

The reaction of 16 with ethyl bromoacetate 19 afforded the thiophene derivative 20. Its structurewas based on analytical and spectral data (cf. Tables 1 and 2). Reaction of 20 with aniline 21 gave the anilide derivative 22.

In a similar way, the reaction of 16 with monochloroacetic acid 8 afforded the thiophene derivative 24. The reaction took place through the intermediate formation of 23 followed by decarboxylation.

The reaction of 16 with ethyl cyanobromoacetate 25 gave the thiazole 4 - one derivative 27. The reaction took place through the intermediate formation of 26 followed by ethanol elimination, hydrolysis of the cyano group and decarboxylation. Structure of 27 was based on analytical and spectral data which revealed keto - enol tautomeric forms (cf. Tables 1 and 2). The reaction of 27 with benzenediazonium chloride gave the phenylazo derivative 28. Its structure was based on analytical and spectral data (cf. Tables 1 and 2).

Moreover, the reaction of 16 with chloroacetyl chloride 29 afforded the thiazole - 5 - one derivative 31. The structure of 31 was confirmed on the basis of analytical and spectral data (cf. Tables 1 & 2).

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded (KBr) on a

Pye Unicam SP - 1000 spectrophotometer. The ^1H - NMR spectra were measured on a Varian EM 390 - 90 MHz in CD_3SOCD_3 as a solvent using TMS as internal standard and chemical shifts are expressed as δ ppm. Analytical data were obtained from the Microanalytical Unit at Cairo University.

β-(4-Aryl-3-thiosemicarbazono) butyronitriles 3a-e (General procedure) :

To a solution of 1a-e (0.01 mol) in absolute ethanol (50 ml), β-iminobutyronitrile 2 (0.01 mol) was added. The reaction mixture was heated undre reflux for 4 h (in case of 1a, 1c, 1d), but for 1 h (in case of 1b, 1e). The solid product; formed upon cooling; was collected by filtration.

3-[(4'-p-Tolyl-3'-thiosemicarbazono) acetyl] coumarin 7 :

Equimolar amounts of 3b (2.46 g; 0.01 mol) and salicylaldehyde 5 (1.22 g; 0.01 mol) in dimethylformamide (40 ml) containing piperidine (0.5 ml) were heated under reflux for 10 h. The solid product, formed upon evaporating the solvent under vacuo and triturating with ether, was collected by filtration and crystallized from ethanol.

3-(4-Hydroxy-2-p-tolyliminothiazol-3-yl) iminoacetyl] coumarin 9:

To a solution of 7 (3.51 g; 0.01 mol) in absolute ethanol (50 ml), monochloroacetic acid 8 was added. The reaction mixture was heated under reflux for 8 h, then left to cool. The solid product, formed upon dilution with water containing few drops of sodium hydroxide solution, was collected by filtration and crystallized from dioxan.

β-(4-Hydroxy-2-p-toyliminothiazole-3-yl) iminobutyronitrile 10 :

To a solution of 3b (2.46 g; 0.01 mol) in dimethylformamide (40ml), monochloroacetic acid 8 was added. The reaction mixture was heated under reflux for 3 h. The solid product, formed upon dilution with water containing few drops of sodium hydroxide solution, was collected by filtration and crystallized from dioxan.

Conversion of 10 into 9 :

To a solution of 10 (2.86 g; 0.01 mol) in dimethylformamide (20 ml) containing piperidine (0.5 ml), salicylaldehyde 5 (1.22 g; 0.01 mol) was added. The reaction mixutre was heated under reflux for 12 h then evaporated in vacuo. The remaining residue was triturated with ether and the formed solid product was collected by filtration to give the same product 9 (mixed m. p. and identical IR spectra).

3-[(4-Phenyl-2-p-tolyliminothiazol-3-yl) iminoacetyl] coumarin 12:

To a solution of 7 (3.51 g; 0.01 mol) in absolute ethanol (50 ml), phenacyl bromide (2.00 g; 0.01 ml) was added. The reaction mixture was heated under reflux for 10 h, then left to cool. The solid product, formed upon pouring onto ice cold water, was collected by filtration and crystallized from dioxan.

α-phenylhydrazono-β-(4-p-tolyl-3-thiosemicarbazono) butyronitrile 13:

To a cold solution (at 0-5°C) of 3b (2.46 g;0.01 mol) in absolute ethanol (50 ml) containing sodium hydroxide solution (0.5 g in 10 ml water), a solution of benzenediazonium chloride (0.01 mol) [prepared by adding sodium nitrite solution (0.7 g;0.01 mol) to a cold solution (0-5°C) of aniline (0.9 g; 0.01 mol) containing the appropriate quantity of hydrochloric acid] was addeed with continuous stirring for 4 h. The solid product, so formed, was collected by filtration and crystallized from ethanol.

5-Amino-3-methyl-4-phenylazo-1-(p-tolylaminothiocarbonyl) pyrazole 14:

A solution of 13 (3.5 g; 0.01 mol) in absolute ethanol (30 ml) containing sodium hydroxide (0.5 g) was heated under reflux for 3 h, then left to cool. The solid product, formed upon pouring into water containing few drops of hydrochloric acid (till pH=6), was collected by filtration and crystallized from dimethylformamide.

α-(3',4'-Diphenylthiazol-2-eno)-β-(4-p-tolyl-3-thiosemicarbazono) butyronitrile 18:

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) phenyl isothiocyanate 15 (1.35 g; 0.01 mol)was added. The reaction mixture was stirred at room temperature for 24 h, then phenacyl bromide 11 (2.00 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 dilution with ice/water containing hydrochloric acid (till pH=6); was collected by filtration and then crystallized from dioxan.

4-Amino-5-ethoxycarbonyl-2-phenylamino-3-[(4-p-tolyl-3-thiosem icarbazono) acetyltyl]thiophene 20 :

The same experimental procedure described for the synthesis of 18 was carried out except for the use of ethyl bromoacetate 19 instead of 11. The solid product; formed upon dilution with water containing hydrochloric acid (till pH=6) followed by extraction with chloroform and evaporation under vacuo; was triturated with ethanol then collected by filtration and crystallized from dioxan.

4-Amino-2-phenylamino-5-phenylformamido-3-[(4-p-tolyl-3-thios emicarbazono) acetyl] thiophene 22 :

To a dry solid of 20 (4.67 g; 0.01 mol), aniline 21 (0.93 g; 0.01 mol) was added. 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 and crystallized from dimethylformamide.

4-Amino-2-phenylamino-3-[(4-p-tolyl-3-thiosemicarbazono) acetyl]thiophene 24 :

The same experimental procedure described for the synthesis of 18 was carried out except for the use of monochloroacetic acid 8 instead of 11.

α-(4-Hydroxy-3-phenylthiazol-2-eno)-β-(4'-p-tolyl-3'-thiosemicarbazono) butyronitrile 27 :

The same experimental procedure described for the synthesis of18 was carried out except for the use of ethyl cyanobromoacetate 25 instead of 11.

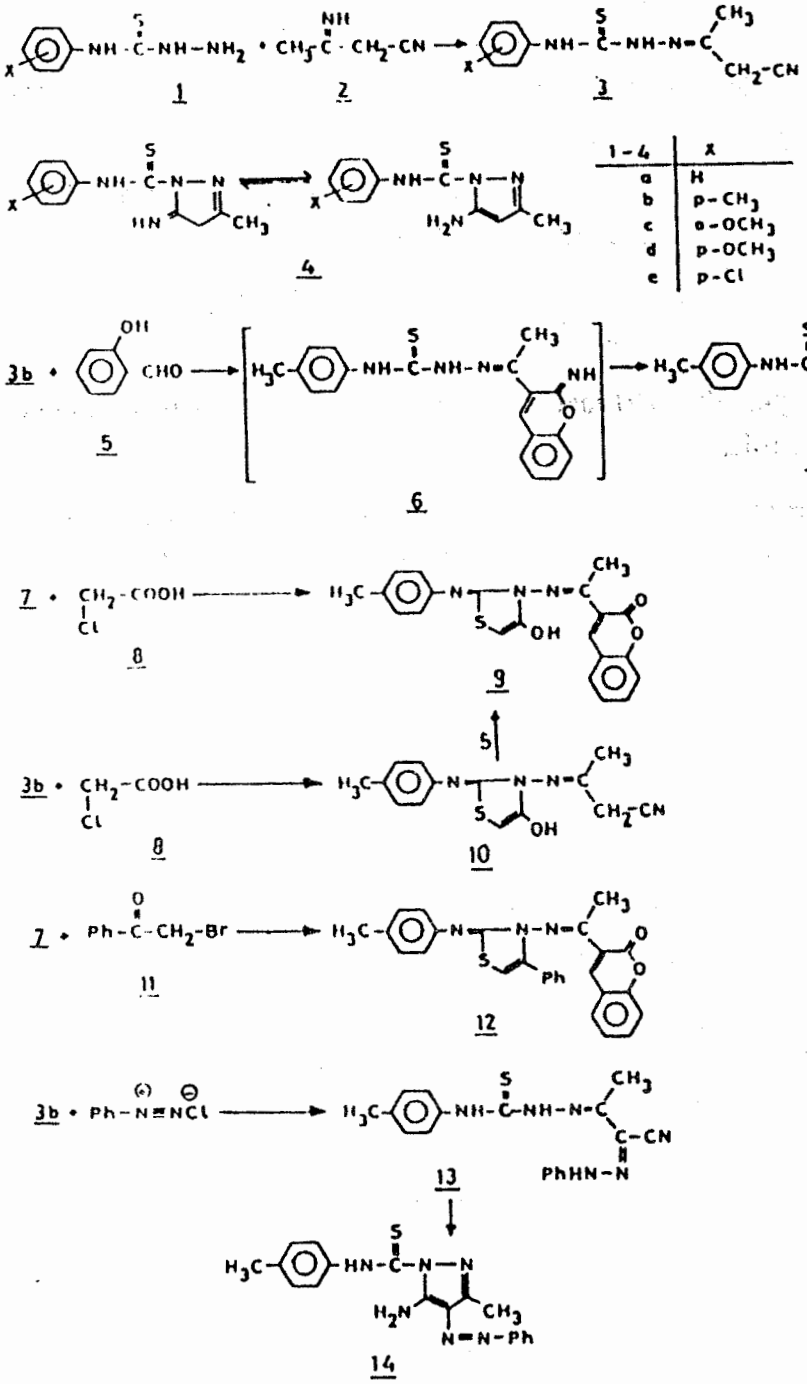
α-(4-Hydroxy-5-phenylazo-3-phenylthiazol-2-eno)-β-(4'-p-tolyl-3'-thiosemicarbazono) butyronitrile 28 :

The same experimental procedure described for the synthesis of 13 was carried out except for the use of 27 instead of 3b.

α-(5-Hydroxy-3-phenylthiazol-2-eno)-β-(4'-p-tolyl-3'-thiosemicarbazono) butyronitrile 31 :

The same experimental procedure described for the synthesis of 20 was carried out except for the use of chloroacetyl chloride 29 instead of 19.

Reactions with ß-(4-Aryl -3- Thiosemicarbazono) Butyronitriles.



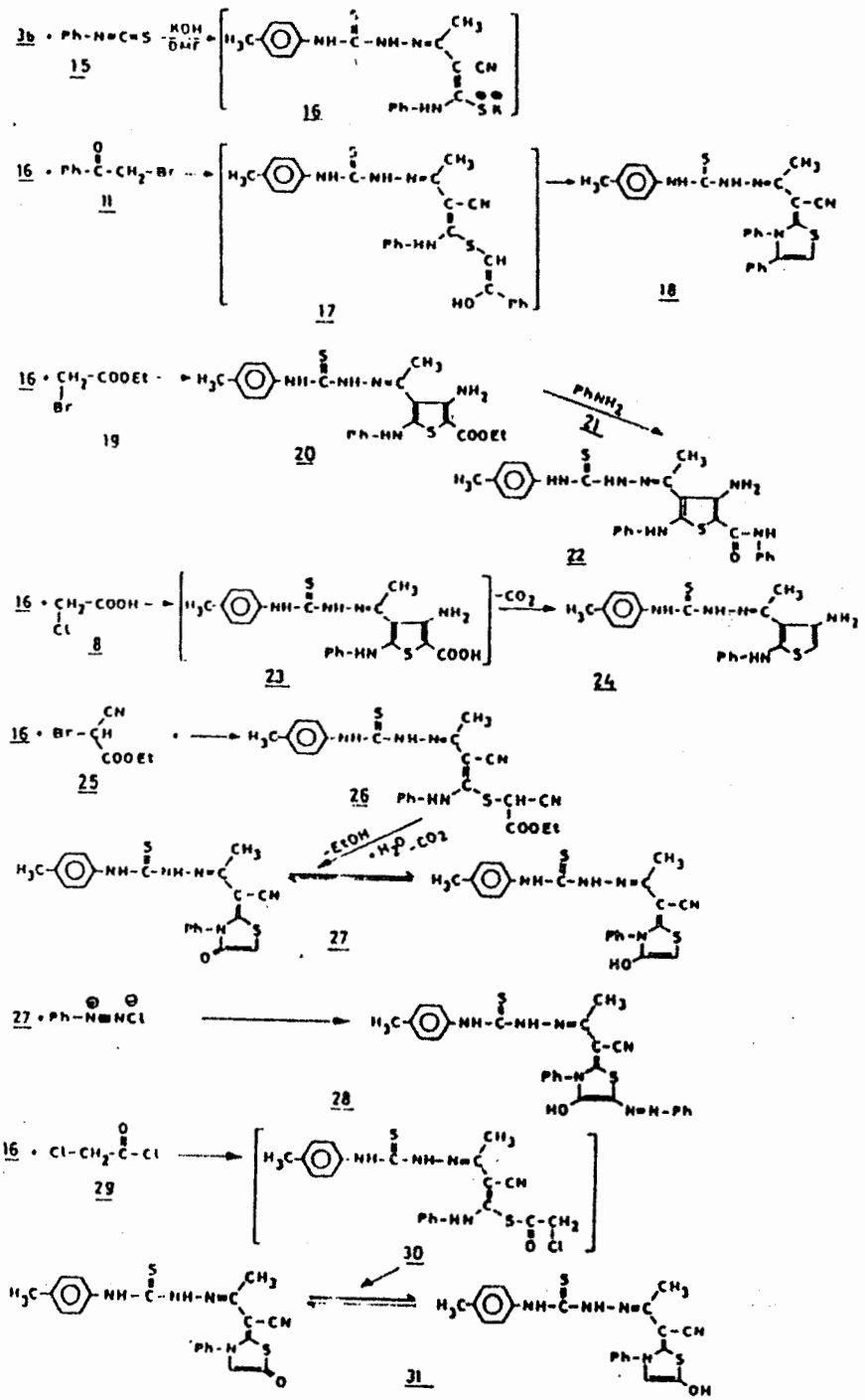


Table 1: Experimental data for the new synthesized compounds.

Compd.	Mol. form Mol. wt	M.P* °C	Yiled %	% Analysis (Caled/Found)			
				C	H	N	S
3a	$C_{11}H_{12}N_4S$ (232.30)	167a	80	56.87 56.5	5.21 5.4	24.12 24.3	13.80 14.1
3b	$C_{12}H_{14}N_4S$ (246.33)	185a	90	58.51 58.7	5.73 5.9	22.74 22.4	13.02 13.2
3c	$C_{12}H_{14}N_4OS$ (262.33)	130a	70	54.94 54.6	5.38 5.5	21.36 21.1	12.22 12.5
3d	$C_{12}H_{14}N_4OS$ (262.33)	205a	75	54.94 54.6	5.38 5.2	21.36 21.2	12.22 12.4
3e	$C_{11}H_{11}ClN_4S$ (266.75)	95a	80	49.53 49.6	4.16 4.6	21.00 21.4	12.02 11.7
7	$C_{19}H_{17}N_3O_2S$ (351.42)	168a	78	64.94 64.6	4.88 4.6	11.96 12.1	9.12 9.2
9	$C_{21}H_{17}N_3O_3S$ (391.45)	200b	75	64.44 64.6	4.38 4.5	10.73 10.6	8.19 8.4
10	$C_{14}H_{14}N_4OS$ (286.35)	220b	80	58.72 58.5	4.93 4.7	19.57 19.8	11.20 11.4
12	$C_{27}H_{21}N_3O_2S$ (451.54)	90b	79	71.82 71.9	4.69 4.8	9.31 9.5	7.1 7.3
13	$C_{18}H_{18}N_6S$ (350.44)	200a	90	61.70 61.9	5.18 5.3	23.98 23.7	9.15 9.4
14	$C_{18}H_{18}N_6S$ (350.44)	191c	80	61.70 61.9	5.18 5.3	23.98 23.7	9.15 9.3
18	$C_{27}H_{23}N_5S_2$ (481.64)	225b	88	67.33 67.1	4.81 4.5	14.54 14.7	13.31 13.5
20	$C_{23}H_{25}N_5O_2S_2$ (467.61)	155b	70	59.08 59.3	5.39 5.6	14.98 14.7	13.71 13.4
22	$C_{27}H_{26}N_6OS_2$ (514.67)	278c	77	63.01 63.3	5.09 5.2	16.33 16.6	12.46 12.6
24	$C_{20}H_{21}N_5S_2$ (395.55)	235b	88	60.73 60.4	5.35 5.5	17.71 17.4	16.21 16.4
27	$C_{21}H_{19}N_5OS_2$ (421.54)	190a	90	59.84 59.6	4.54 4.7	16.61 16.4	15.21 15.5
28	$C_{27}H_{23}N_7OS_2$ (525.66)	131-3a	82	61.69 61.3	4.41 4.2	18.65 18.4	12.20 12.4
31	$C_{21}H_{19}N_5OS_2$ (421.54)	155b	85	59.84 59.7	4.54 4.6	16.61 16.5	15.21 15.4

* Crystallized from a = ethanol, b = dioxane, c = DMF

Table 2: Spectral data of the new synthesized compounds.

Compd.	IR (cm^{-1})	^{1}H-NMR (ppm)
3a	3460-3380 (2NH); 3060 (CH aromatic); 2220 (CN); 1660 (C=N); 1200-1190 (C=S).	1.99 (s, CH_3); 4.79 (s, CH_2); 7.28-7.44 (m, C_6H_5); 8.32, 8.62 (2s, 2NH).
3b	3440-3390 (2NH); 3060 (CH aromatic); 2220 (CN); 1660 (C=N); 1200-1190 (C=S).	2.19, 2.23 (2s, $2CH_3$); 4.89 (s, CH_2); 7.32-7.45 (m, C_6H_4); 8.2, 8.34 (2s, 2NH).
3c	3460-3380 (2NH); 3060 (CH aromatic); 2220 (CN); 1660 (C=N); 1200-1190 (C=S).	2.22, 2.42 (2s, $2CH_3$); 4.89 (s, CH_2); 7.31-7.42 (m, C_6H_4); 8.23, 8.41 (2s, 2NH).
3d	3430-3390 (2NH); 3060 (CH aromatic); 2220 (CN); 1660 (C=N); 1220-1190 (C=S).	2.22, 2.42 (2s, $2CH_3$); 4.89 (s, CH_2); 7.31-7.42 (m, C_6H_4); 8.23, 8.41 (2s, 2NH).
3e	3420-3390 (2NH); 3060 (CH aromatic); 2220 (CN); 1670 (C=N); 1200-1190 (C=S).	2.89 (s, CH_3); 4.86 (s, $2CH_2$); 7.31-7.41 (m, C_6H_4), 8.21, 8.39 (2s, 2NH).
7	3420-3345 (2NH); 3060 (CH aromatic); 1690 (C=O); 1660 (C=N); 1630 (C=C); 1250 (C=S).	2.22, 2.25 (2s, $2CH_3$); 6.89 (s, coumarin H_4); 7.29-7.46 (m, $2C_6H_4$); 8.23, 8.53 (2s, 2NH).
9	3480-3345 (OH); 3045 (CH aromatic); 1695 (C=O); 1670 (C=N); 1630 (C=C).	1.98, 2.02 (2s, $2CH_3$); 6.69 (s, thiazole H-5); 6.99 (s, coumarin H_4); 7.34-7.49 (m, $2C_6H_4$); 10.11 (s, OH).
10	3540-3375 (OH); 3050 (CH aromatic); 2225 (CN); 1660 (C=N).	2.23, 2.28 (2s, $2CH_3$); 4.18 (s, CH_2); 6.75 (s, thiazole H_5); 7.31-7.42 (m, C_6H_4); 10.38 (s, OH).
12	3055 (CH aromatic); 1695 (C=O); 1660 (C=N); 1635 (C=C).	2.23, 2.25 (2s, $2CH_3$); 6.45 (thiazole H-5); 6.89 (s, coumarin H-4); 7.32-7.49 (m, C_6H_5, $2C_6H_4$).
13	3480-3320 (3NH); 3060 (CH aromatic); 2220 (CN); 1655 (C=N); 1250-1230 (C=S).	2.22, 2.28 (2s, $2CH_3$); 7.32-7.46 (m, C_6H_5, C_6H_4); 8.22, 8.34, 8.40 (3s, 3NH).
14	3460-3360 (NH_2, NH), 3050 (CH aromatic); 1660 (C=N); 1635 (C=C); 1200 (C=S).	2.21, 2.32 (2s, $2CH_3$); 4.8 (s, NH_2); 7.33-7.46 (m, C_6H_5, C_6H_4); 8.36 (s, NH).

Compd.	IR (cm^{-1})	^{1}H-NMR (ppm)
18	3450-3330 (2NH); 3050 (CH aromatic); 2220 (CN); 1660 (C=N); 1635 (C=C); 1250 (C=S).	2.19, 2.25 (2s, $2CH_3$); 6.88 (s, thiazole H_5); 7.32-7.59 (m, $2C_6H_5$, C_6H_4); 8.42, 8.76 (2s, 2NH).
20	3460-3330 (NH_2, 3NH); 3060 (CH aromatic); 1690 (C=O); 1655 (C=N); 1635 (C=C); 1220-1200 (C=S).	1.14 (t, J=8.02 Hz, CH_3); 2.22-2.26 (2s, $2CH_3$); 4.42 (q, J=8.02, CH_2); 5.2 (s, NH_2); 7.30-7.38 (m, C_6H_5; C_6H_4); 8.22, 8.34, 8.75 (3s, 3NH).
22	3460-3320 (NH_2, 4NH); 3060 (CH aromatic); 1680 (C=O); 1660 (C=N); 1635 (C=C); 1250 (C=S).	2.22, 2.26 (2s, $2CH_3$); 4.56 (s, NH_2); 7.31-7.46 (m, $2C_6H_5$, C_6H_4); 8.21, 8.76-8.82 (4s, 4NH).
24	3460-3320 (NH_2, 3NH); 3060 (CH aromatic); 1655 (C=N); 1635 (C=C); 1200 (C=S).	2.22, 2.31 (2s, $2CH_3$); 4.38 (s, NH_2); 6.36 (s, thiophene H_5); 7.30-7.43 (m, C_6H_5, C_6H_4); 7.31, 8.41, 8.62 (3s, 3NH).
27	3560-3370 (OH, 2NH); 3050 (CH aromatic); 2220 (CN); 1655 (C=N); 1635 (C=C); 1250 (C=S).	2.21, 2.23 (2s, $2CH_3$); 6.56 (s, thiazole H_5); 7.23-7.40 (m, C_6H_5, C_6H_4); 8.25, 8.32 (2s, 2NH); 10.21 (s, OH).
28	3540-3365 (OH, 2NH); 3060 (CH aromatic); 2225 (CN); 1650 (C=N); 1635 (C=C); 1250 (C=S).	2.20, 2.24 (2s, $2CH_3$); 7.28-7.43 (m, $2C_6H_5$, C_6H_4); 8.32, 8.36 (2s, 2NH); 10.25 (s, OH).
31	3560-3370 (OH, 2NH); 3050 (CH aromatic); 2220 (CN); 1655 (C=N); 1635 (C=C); 1250 (C=S).	2.21, 2.23 (2s, $2CH_3$); 6.56 (s, thiazole H_5); 7.23-7.40 (m, C_6H_5, C_6H_4); 8.25, 8.32 (2s, 2NH); 10.21 (s, OH).

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Reactions with β-(4-Aryl -3- Thiosemicarbazono) Butyronitriles.

تفاعلات لمركبات β - (4 - أريل - 3 - ثيوسيميكر بازونو) بيوتيرونيتريل

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ملخص البحث :

حضرت مركبات β - (4 - أريل - 3 - ثيوسيميكر بازونو) بيوتيرونيتريلات 3a - e من تفاعل 4 - أرايل - 3 - ثيوكاربازيدات 1a - e مع β - إيمينو بيوتيرونيتريل (2). يتفاعل 3b مع السلسيلالدهيد ليعطى مشتق الكومارين 7 يتحولق المركب 7 فى وجود كلورو حمض الخليك 8 وفى وجود بروميد الفيناسيل 11 ليتكون مشتقات ثيازوليل الكومارين 12 ,9 على الترتيب. يتفاعل مركب 3b مع كلوريد البنزين ديازونيوم ليعطى مشتق البيرازول 14. يتفاعل 3b أيضاً مع أيزوثيوسيانات الفينيل 15 ليعطى ملح كبريتات البوتاسيوم 16 كمركب وسيط. عند تفاعل 16 مع α - هالوكيتونات تتكون مشتقات للثيازول والثيوفين.