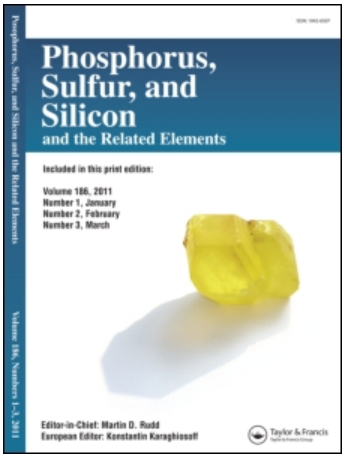

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Reactions of Hydrazonoyl Halides 47[1]: Synthesis of Some New 2,3-dihydro-1,3,4-thiadiazoles, Triazolo[4, 3-*a*]pyrimidines, and Pyrazolo[3, 4-*d*]pyridazines with Expected Biological Activity

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Reactions of Hydrazonoyl Halides 47[1]: Synthesis of Some New 2,3-dihydro-1,3,4-thiadiazoles, Triazolo[4,3-*a*]pyrimidines, and Pyrazolo[3,4-*d*]pyridazines with Expected Biological Activity

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*2,3-dihydro-1,3,4-thiadiazoles, triazolino[4,3-*a*]pyrimidines, and pyrazolo[3,4-*d*]pyridazines were synthesized in good yields from reactions of hydrazonoyl halides with alkyl carbodithioates, pyrimidine-2-thione, and substituted prop-2-ene-1-one, respectively. All structures of the newly synthesized compounds were elucidated by elemental analysis, spectral data, and an alternative synthesis method. Some of the new compounds were tested towards bacteria and fungi.*

Keywords 2,3-Dihydro-1,3,4-thiadiazolines; cycloaddition; pyrazolo[3,4-*d*]pyridazines; triazolino[4,3-*a*]pyrimidines

INTRODUCTION

1,3,4-thiadiazoles have activities on many biological systems such as antitumor,[2] and hypoglycemic properties,[3] antihistamine[4] and anticholinergic.[5] Also, triazolopyrimidines have been reported to exhibit in vivo leisshmanicidal activity against the mistigate stage of *Leishmaniadonovani*[6,7] and cardiovascular activity.[8,9] Also, thiadiazoles are cardiotonics and coronary vasadilatores, and they have antihypertensive properties.[10] As an extension of our study[11–18] and as

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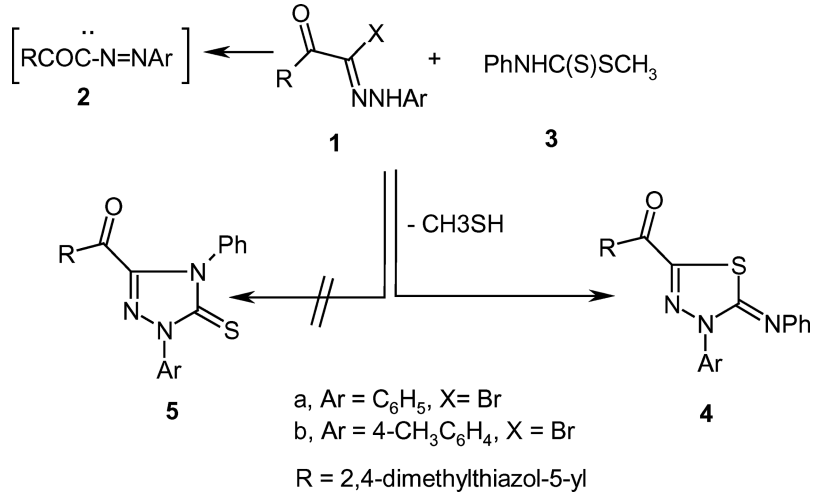
a part of our program aiming at the synthesis of different heterocyclic derivatives, we report here the utility of *C*-(2,4-dimethyl)thiazol-5-yl-*N*-arylhydrazonoyl bromides **1a** and **1b** in the synthesis of some 2,3-dihydro-1,3,4-thiadiazoles, triazolino[4,3-*a*]pyrimidines, and pyrazolo[3,4-*d*]pyridazines.

RESULTS AND DISCUSSION

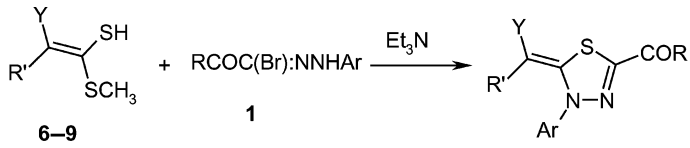
Treatment of *C*-(2,4-dimethyl)thiazol-5-yl-*N*-phenylhydrazononoyl bromide (**1a**) with methyl phenyldithiocarbamate (**3**)[19] in ethanolic triethylamine at r.t. gave one isolable product, evidenced by tlc, whose structure seemed to be either **4** or **5** (Scheme 1). Its IR spectrum revealed bands at 3060, 2923 (CH), 1634 (CO conjugated), 1593 (C=C) and no absorption band near 2100–2300 cm^{-1} due the absence of C=S. ^1H NMR showed signals at $\delta = 2.76$ (s, 3H), 2.79 (s, 3H) and 7.08–7.92 (m, 10H). On the basis of elemental and spectral data, the product was formulated as: 2-(azaphenylmethylene)-3-phenyl-(1,3,4-thiadiazolin-5-yl)-2,4-dimethylthiazol-5-yl ketone (**4a**).



SCHEME 1

Two possible pathways can account for the formation of **4**: (1) 1,3-the addition of the thiol isomer **3** to the hydrazonoyl bromide **1a** (or carbene **2a**, which was prepared in situ from **1a** and triethylamine) to afford **4** via the elimination of methyl mercaptan, and (2) alternatively, the 1,3-cycloaddition of the carbene **2a** to the C=S. Similarly, **1b** reacted with **2** to afford **3b** in a good yield (Scheme 1).

Similarly, the appropriate **1a,b** reacted with the appropriate methyl carbodithiates **6–9** in ethanolic triethylamine to give 2,3-dihydro-1,3,4-thiadiazole derivatives **10–13(a,b)**, respectively (Scheme 2).



6–9 **10–13**

R = 2,4-dimethylthiazol-5-yl
a, Ar = C_6H_5
b, Ar = 4-$CH_3C_6H_4$

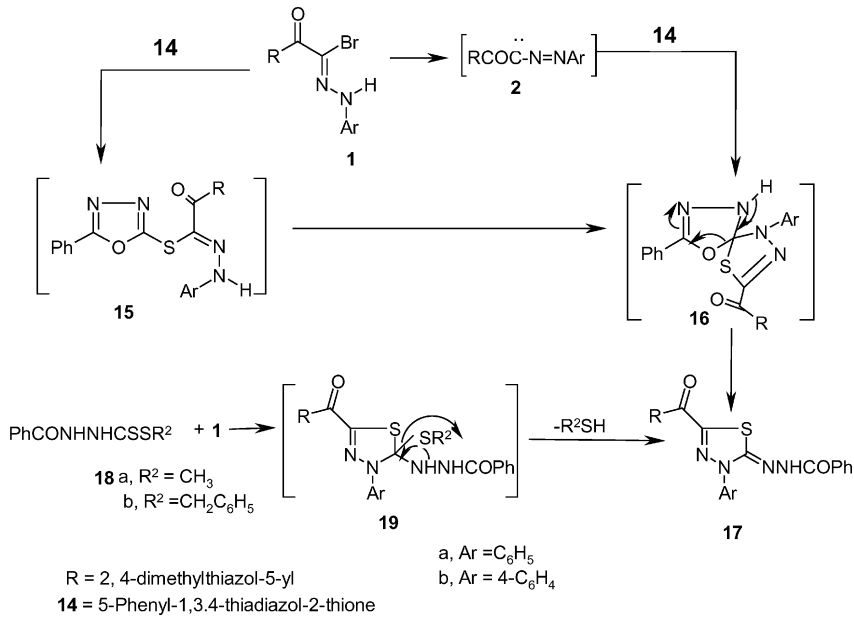
6,10, R' = 2-benzthiazolyl, Y = CN
7,11, R' = 2-(1-methyl)benzimidazolyl, Y = CN
8,12, Y-R' = 4-(3-methylpyrazolin-5-one)ylidenyl
9,13, Y-R' = 4-(3-methyl-1-phenylpyrazolin-5-one)ylidenyl

SCHEME 2

The treatment of the appropriate hydrazonoyl bromide **1a** and **1b** with 2-mercapto-5-phenyl-1,3,4-oxadiazole (**14**) and triethylamine in boiling chloroform under reflux gave *N*-(aza{5-[(2,4-dimethylthiazol-5-yl)carbonyl]-3-substituted 1,3,4-thiadiazolin-2-ylidene}-methylbenzamide **17a** and **17b**, respectively. Structure **17** was elucidated on the base of elemental analyses, spectral data, and an alternative synthesis method. Thus, the treatment of each **1a** and **1b** with the appropriate methyl benzoylhydrazinecarbodithioate **18a** (or ethyl benzoylhydrazinecarbodithioate (**18b**)) in ethanolic triethylamine afforded a product identical in all respects (m.p., mixed m.p., and spectra) with **17a** and **17b**, respectively.

In the light of the foregoing results, the mechanism outlined in Scheme 3 seems to be the most plausible pathway for the formation of **17** from the reaction **1** with 5-phenyl-1,3,4-oxadiazole-2-thione (**14**). The reaction involves an initial formation of the thiohydrazonate ester **15**, which undergoes intramolecular cyclization as soon as it is formed to yield the spirothiadiazole intermediate **16** or via the cycloaddition of carbene **2** to the C=S double bond of **14**. The formation of **15** and **16** are similar to the reaction of hydrazonoyl chloride with 5-phenyl-1,3,4-thiadiazloe-2(3H)-thione[20] and 1-phenyl-1,4-dihydrotetrazle-5-thione.[21] Alternatively, the formation of **17** can be explained via the elimination of alkyl mercaptan from the cycloadduct **19**.

Next, the treatment of 6-oxo-4-phenyl-2-thioxo-1,3-dihydropyrimidine-5-carbonitrile (**20**)[22] with **1a** in boiling chloroform containing triethylamine, a single product was isolated. The products were characterized as 3-[(2,5-dimethyl(1,3-thiazol-4-yl))carbonyl]-4-oxo-1,6-diphenyl-3a-hydro-1,2,4-triazolino[4,3-*a*]pyrimidine-5-carbonitrile (**26a**)

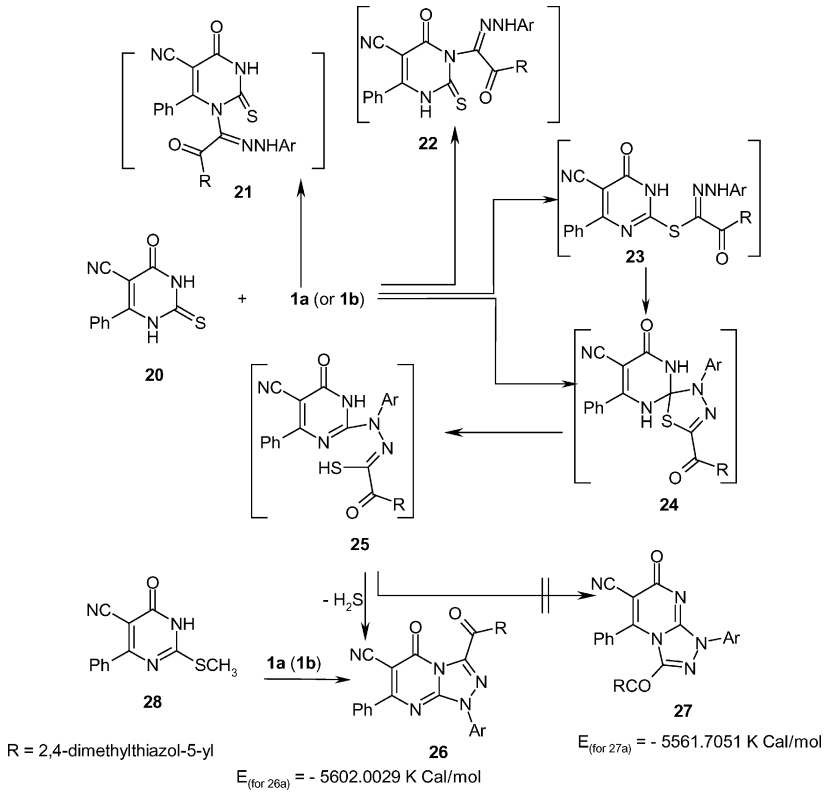


SCHEME 3

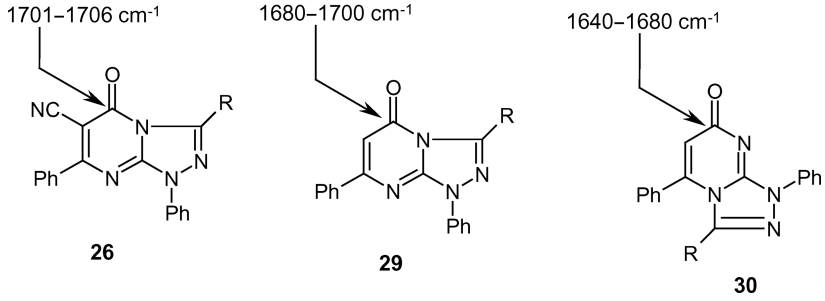
(Scheme 4) on the basis of elemental analysis, spectral data, and an alternative synthesis route. Thus, **1a** reacted with **28**[22] in ethanolic triethylamine and to give a product identical in all respects (m.p., mixed m.p., and spectra) with **26a**.

The reaction pathway accounting for the formation of **26** from **1** and **20** is outlined in Scheme 4. It is proposed that the reaction involves an initial 1,3-addition to give intermediates **21–23** or cycloaddition to afford intermediate **24**, which undergo a *Smiles* rearrangement to the thiohydrazide **25**. The latter then cyclizes with the concurrent elimination of hydrogen sulfide to give the final product, which has a structure of either **26** or isomer **27**.

The actual structure of the products was found to resemble **26** by their IR spectra and M.O. calculation. For example, the carbonyl stretching frequencies of **26** (1701–1705 cm^{-1}) were found to be near the structure **29** (1680–1705 cm^{-1}) and not **30** (1640–1660 cm^{-1}) (Scheme 5).[23,24] According to the M.O. calculation, using the Hyper Chem. AM1 semiemperical method, the total energy of structure **26** (E = −5602.0029 K Cal) is higher than isomer **27** (E = −5561.7051 K Cal). These data proved structure that **26** is the most stable isomer (Scheme 4).



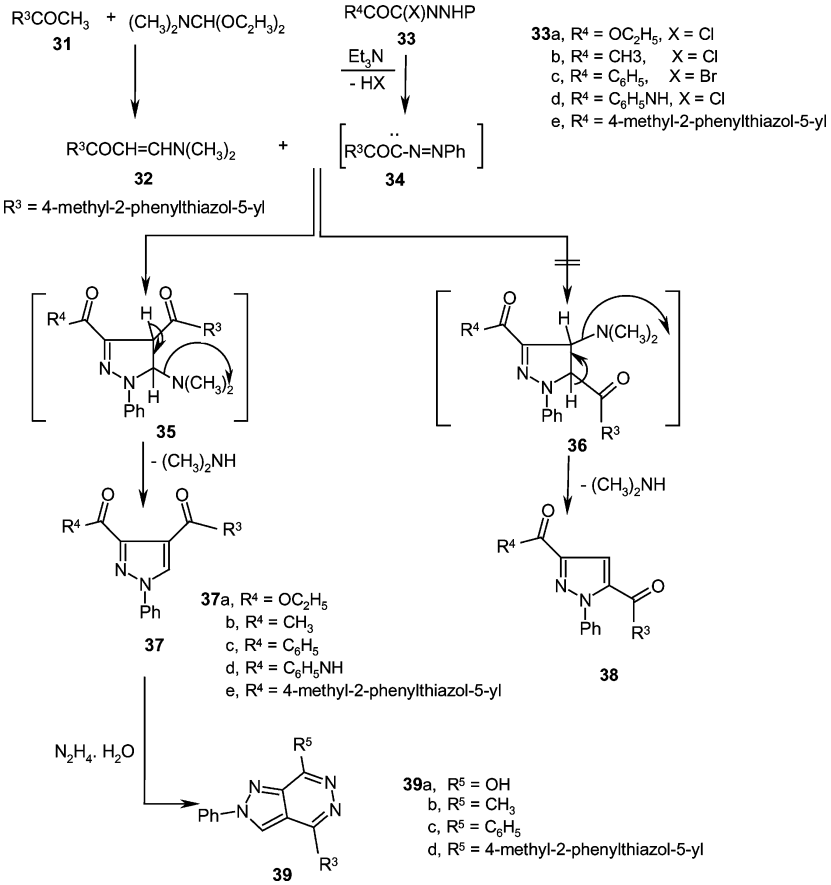
SCHEME 4



SCHEME 5

Finally, the treatment of the 5-acetyl-4-methyl-2-phenylthiazole **31** with dimethylformamide-dimethylacetal in boiling dry xylene under reflux gave 3-(dimethylamino)-1-(4-methyl-2-phenyl(1,3-thiazol-5-yl))prop-2-ene-1-one (**32**) in good yield. Structure **32** was confirmed

on the basis of elemental analysis, spectral data, and chemical transformation. Thus, the ^{1}H NMR spectrum of **32** showed signals at 2.79 (s, 3H), 2.92 (s, 3H), 3.11 (s, 3H), 5.43–5.64 (d, 1H), 6.95–7.18 (d, 1H) and 7.41–8.01 (m, 5H). Thus, the treatment of *C*-ethoxycarbonyl-*N*-phenylhydrazonoyl chloride **33a** with **32** in refluxing toluene containing triethylamine yielded one isolable product, evidenced by TLC, which formulated either ethyl 3-[(4-methyl-2-phenyl(1,3-thiazol-5-yl))carbonyl]-1-phenylpyrazole-4-carboxylate (**37a**) or ethyl 3-[(4-methyl-2-phenyl(1,3-thiazol-5-yl))carbonyl]-1-phenylpyrazole-5-carboxylate (**38a**) (Scheme 6).



SCHEME 6

Some of the newly synthesized compounds were tested toward Bacillus Ccereus (-ve bacteria) and Fusarium Oxysporum (fungal-plant pathogens) in $CHCl_3$ using the filter paper and hole plate method 26.

The formation of **37** can be explained via the reaction of nitrilum imide **34**, which formed in situ from hydrazonoyl halides and triethylamine, with **32** to afford the cyclo adduct intermediate **35** or **36** and then eliminate diethylamine to give pyazole as final product **37** or pyrazole **38**. Similarly, the appropriate hydrazonoyl halides **33b–e** reacted with the appropriate **32** to afford corresponding pyrazoles **37b–e**.

Pyrazolo[3,4-*d*]pyridazines **39a–d** were obtained in a good yield from boiling the appropriate pyrazoles **37a–e** with hydrazine hydrate in boiling ethanol (Scheme 6). Structure **39** was elucidated on the basis of elemental analysis, spectral data, and the alternative synthesis route. The ^{1}H NMR spectrum of **39b** showed signals at $\delta = 2.86$ (s, 3H), 3.01 (s, 3H), 7.13–8.00 (m, 10 H), and 8.66 (s, 1H, pyrazole C-5). Compound **37d** reacted with hydrazine hydrate in boiling ethanol to give an identical product in all respects (m.p., mixed m.p., and spectra) with **39a**.

Antimicrobial Activity

The tested microorganisms were gram −ve bacteria (*Bacillus cereus*). In addition, some fungal-plant pathogens (*Fusarium Oxysporum*) were tested. The sensitivity of the selected microorganisms to some synthesized compounds was determined in vitro culture in $CHCl_3$.The tests were carried out using the filter paper and hole plate method.[25]

Studies on the biological activity of compounds **39b** show that these compounds have negative biological activity against the tested bacteria, whereas **13a**, **13b**, and **15a** have moderate to weak biological activity against the tested bacteria. Compounds **14b, 15b**, and **35d** have strong activity against the tested bacteria (Table I). Finally, compound **37d** has strong antifungl activity, whereas compound **39c** has weak antifungal activity.

EXPERIMENTAL

All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$ solutions on a Varian Gemini 300 MHz spectrometer, and chemical shifts are expressed in δ units using TMS as an internal reference. Elemental analyses and antimicrobial were carried out at the Microanalytical Center of the Cairo University, Giza, Egypt.

TABLE I Response of Various Microorganisms to Some Synthesized Compounds In Vitro (Culture)

Compound no.	Antibacterial activity (% inhibition)	Antifungal activity (% inhibition)
13a	24.5	0.0
13b	22.2	0.0
14b	100.0	0.0
15a	20.0	0.0
15b	90.0	0.0
37d	68.0	60.0
39b	0.0	8.8
39c	34.0	30.0

Synthesis of (2,4-Dimethyl-1,3-thiazol-5-yl)[(5E)-4-phenyl-5-(phenylimino)-4,5-dihydro-1,3,4-thiadiazol-2-yl]methanone (4a) and (2,4-Dimethyl-1,3-thiazol-5-yl)[(5E)-4-(4-methylphenyl)-5-(phenylimino)-4,5-dihydro-1,3,4-thiadiazol-2-yl]methanone (4b)

An equimolar amount of the appropriate hydrazonoyl bromides[26] **1a** or **1b**, methyl phenyldithiocarbamate **3**, and triethylamine (5 mmol each) in ethanol (10 mL) were stirred for 2 h at r.t. The resulting solids were collected by filtration and crystallized from ethanol to give red crystals **4a** and **4b**, respectively (Tables II and III).

Synthesis of 2,3-Dihydro-1,3,4-thiadiazoline Derivatives 10–13(a,b)

An equimolar amount of the appropriate hydrazonoyl bromides **1a** or **1b**, the appropriate of methyl carbodithiates **6–9**[13,15,27,28] and triethylamine (5 mmol each) in ethanol (10 mL) were stirred for 2 h at r.t. The resulting solids were collected by filtration and crystallized from dioxan to give (**10–13)a,b** respectively (Tables II and III).

Synthesis of *N*-(Aza{5-[(2,4-dimethylthiazol-5-yl))carbonyl]-3-substituted 1,3,4-thiadiazolin-2-ylidene}methylbenzamide 17a and 17b

Method A

An equimolar amount of the appropriate hydrazonoyl bromides **1a** or **1b**, the appropriate alkyl benzoylhydrazinecarbodithiate, and triethylamine (5 mmol each) in ethanol (10 mL) were stirred for 2 h

TABLE II Characterization Data of the Newly Synthesized Compounds

Compound no.	M.P., °C solvent	Color yield %	Mol. formula mol. wt	% Analyses calcd./found			
				C	H	N	S
4a	195–197	Red	$C_{20}H_{16}N_4OS_2$	61.20	4.11	14.27	16.34
	EtOH	78	392.49	61.13	4.01	14.33	16.29
4b	175–177	Red	$C_{21}H_{18}N_4OS_2$	62.04	4.46	13.78	15.77
	EtOH	75	406.52	61.95	4.52	13.90	15.72
10a	>300	Brown	$C_{23}H_{15}N_5OS_3$	58.33	3.19	14.79	20.31
	Dioxan	83	473.59	58.29	3.15	14.76	20.36
10b	293–295	Yellow	$C_{24}H_{17}N_5OS_3$	59.11	3.51	14.36	19.73
	Dioxan	80	487.62	59.07	3.54	14.32	19.77
11a	>300	Brown	$C_{24}H_{18}N_6OS_2$	61.26	3.86	17.86	13.63
	Dioxan	74	470.57	61.30	3.84	17.92	13.58
11b	273–276	Yellow	$C_{25}H_{20}N_6OS_2$	61.96	4.16	17.34	13.23
	Dioxan	79	484.59	62.00	4.19	17.30	13.22
12a	>300	Red	$C_{18}H_{15}N_5O_2S_2$	54.39	3.80	17.62	16.13
	Dioxan	88	397.47	54.40	3.77	17.66	16.17
12b	>300	Red	$C_{19}H_{17}N_5O_2S_2$	55.46	4.16	17.02	15.58
	Dioxan	85	411.50	55.42	4.18	16.98	15.61
13a	265–267	Brown	$C_{24}H_{19}N_5O_2S_2$	60.87	4.04	14.79	13.54
	Dioxan	79	473.57	60.92	3.99	14.76	13.58
13b	295–297	Red	$C_{25}H_{21}N_5O_2S_2$	61.58	4.34	14.36	13.15
	Dioxan	77	487.59	61.61	4.30	14.33	13.21
17a	280–283	Red	$C_{21}H_{17}N_5O_2S_2$	57.91	3.93	16.08	14.72
	Dioxan	78	435.52	57.96	4.00	16.02	14.79
17b	252–254	Red	$C_{22}H_{19}N_5O_2S_2$	58.78	4.26	15.58	14.26
	Dioxan	75	449.55	58.74	4.29	15.53	14.33
26a	195–197	Brown	$C_{24}H_{16}N_6O_2S$	63.71	3.56	18.57	7.09
	EtOH	78	452.48	63.66	3.52	18.60	7.05
26b	180–183	Brown	$C_{25}H_{18}N_6O_2S$	64.36	3.89	18.01	6.87
	EtOH	74	466.51	64.40	3.94	17.08	6.85
32	122–124	Yellow	$C_{15}H_{16}N_2OS$	66.15	5.92	10.28	11.77
	EtOH	84	272.36	66.00	5.88	10.32	11.71
37a	159–161	Yellow	$C_{23}H_{19}N_3O_3S$	66.17	4.59	10.06	7.68
	EtOH	80	417.48	66.20	4.57	10.10	7.65
37b	140–142	Yellow	$C_{22}H_{17}N_3O_2S$	68.20	4.42	10.84	8.28
	EtOH	78	387.45	68.23	4.46	10.81	8.30
37c	178–180	Yellow	$C_{27}H_{19}N_3O_2S$	72.14	4.26	9.35	7.13
	EtOH	83	449.52	72.18	4.22	9.36	7.15
37d	245–247	Pale red	$C_{27}H_{20}N_4O_2S$	69.81	4.34	12.06	6.90
	EtOH	74	464.53	69.80	4.36	12.01	6.88
37e	150–152	Red	$C_{31}H_{22}N_4O_2S_2$	68.11	4.06	10.25	11.73
	EtOH	75	546.66	68.15	3.99	10.21	11.78
39a	276–278	Yellow	$C_{21}H_{15}N_5OS$	65.44	3.92	18.17	8.32
	EtOH	81	385.44	65.47	3.90	18.18	8.30
39b	213–215	Yellow	$C_{22}H_{17}N_5S$	68.91	4.47	18.26	8.36
	EtOH	85	383.47	68.88	4.45	18.30	8.38
39c	222–224	Yellow	$C_{27}H_{19}N_5S$	72.79	4.30	15.72	7.20
	EtOH	80	445.53	72.81	4.27	15.76	7.17
39d	212-215	Yellow	$C_{31}H_{22}N_6S_2$	68.61	4.09	15.49	11.82
	EtOH	77	542.67	68.45	3.89	15.70	11.58

TABLE III Spectra of Some Newly Synthesized Compounds

Compound no.	Spectral data
4a	IR: 3060, 2923 (CH), 1634 (CO conjugated) and 1593 (C═C). ^{1}H NMR: 2.76 (s, 3H), 2.79 (s, 3H) and 7.08–7.92 (m, 10H).
4b	IR: 3030, 2917 (CH), 1621 (CO conjugated) and 1583 (C═C). ^{1}H NMR: 2.17 (s, 3H), 2.47 (s, 3H), 2.79 (s, 3H) and 7.08–7.92 (m, 9H).
10a	IR: 3006, 2912 (CH), 2192 (CN) and 1651(CO conjugated). ^{1}H NMR: 2.69 (s, 3H), 2.84 (s, 3H) and 7.25–7.99 (m, 9H).
10b	IR: 3057, 2921 (CH), 2193 (CN) and 1655 (CO conjugated). ^{1}H NMR: 2.39 (s, 3H), 2.47 (s, 3H), 2.71 (s, 3H) and 7.32–7.96 (m, 8H).
11a	IR: 3037, 2924 (CH), 2193 (CN) and 1647 (CO conjugated). ^{1}H NMR: 2.49 (s, 3H), 2.82 (s, 3H), 3.78 (s, 3H) and 7.26–7.74 (m, 9H).
11b	IR: 3001, 2909 (CH), 2183 (CN) and 1622 (CO conjugated). ^{1}H NMR: 2.35 (s, 3H), 2.47 (s, 3H), 2.75 (s, 3H), 3.72 (s, 3H) and 7.26–7.41 (m, 8H).
12a	IR: 3320 (NH), 3020, 2949 (CH), 1705, 1659 (CO's) and 1594 (C═C). ^{1}H NMR: 1.11 (s, 3H), 2.53 (s, 3H), 2.75 (s, 3H), 7.42–7.74 (m, 5H) and 11.4 (s, 1H).
12b	IR: 3317 (NH), 3021, 2940 (CH), 1710, 1658 (CO's) and 1590 (C═C). ^{1}H NMR: 1.09 (s, 3H), 2.35 (s, 3H), 2.50 (s, 3H), 2.74 (s, 3H), 7.46–7.69 (m, 4H) and 11.6 (s, 1H).
13a	IR: 3061, 2920 (CH), 1705, 1653 (CO's) and 1604 (C═C). ^{1}H NMR: 1.24 (s, 3H), 2.46 (s, 3H), 2.72 (s, 3H) and 7.11–8.01 (m, 10H).
13b	IR: 3064, 2924 (CH), 1705, 1657 (CO) and 1609 (C═C). ^{1}H NMR: 1.23 (s, 3H), 2.35 (s, 3H), 2.46 (s, 3H), 2.80 (s, 3H) and 7.11–8.00 (m, 9H).
17a	IR: 3314 (NH), 3010, 2929 (CH), 1659 (CO) and 1593 (C═C). ^{1}H NMR: 2.43 (s, 3H), 2.75 (s, 3H), 7.22–7.94 (m, 10H) and 11.6 (s, 1H).
17b	IR: 3304 (NH), 2979, 2923 (CH), 1655 (CO) and 1597 (C═C). ^{1}H NMR: 2.32 (s, 3H), 2.46 (s, 3H), 2.74 (s, 3H), 7.29–7.91 (m, 9H) and 11.4 (s, 1H).
26a	IR: 3080, 2920 (CH), 2217, (CN), 1705 (CO), 1654 (CO conjugated) and 1594 (C═C). ^{1}H NMR: 2.47 (s, 3H), 2.74 (s, 3H) and 7.24–8.05 (m, 10H).
26b	IR: 3070, 2925 (CH), 2220, (CN), 1701 (CO), 1657 (CO conjugated) and 1589 (C═C). ^{1}H NMR: 2.35 (s, 3H), 2.49 (s, 3H), 2.78 (s, 3H) and 7.24–8.05 (m, 9H).
32	IR: 2904 (CH) and 1655 (CO conjugated). ^{1}H NMR: 2.79 (s, 3H), 2.92 (s, 3H), 3.11 (s, 3H), 5.43–5.64 (d, 1H), 6.95–7.18 (d, 1H) and 7.41–8.01 (m, 5H).
37a	IR: 3059, 2980 (CH), 1708 (CO), 1649 (CO conjugated) and 1598 (C═C). ^{1}H NMR: 1.18 (t, 3H, OCH_2CH_3), 2.75 (s, 3H), 4.25 (q, 2H, OCH_2CH_3), 7.38–7.95 (m, 10H, ArH's) and 8.26 (s, 1H, pyrazole C-5).
37b	IR: 3035, 2981 (CH), 1645 (CO conjugated) and 1597 (C═C). ^{1}H NMR: 2.47 (s, 3H), 2.55 (s, 3H), 7.25–7.95 (m, 10H, ArH's) and 8.20 (s, 1H, pyrazole C-5).

(Continued on next page)

TABLE III Spectra of Some Newly Synthesized Compounds *(Continued)*

Compound no.	Spectral data
37c	IR: 3059, 2923 (CH), 1643 (CO conjugated) and 1597 (C═C). ^{1}H NMR: 2.49 (s, 3H), 7.25–8.19 (m, 15H, ArH's) and 8.36 (s, 1H, pyrazole C-5).
37d	IR: 3432 (NH), 3061, 2983 (CH), 1673 (CO) and 1592 (C═C). ^{1}H NMR: 2.46 (s, 3H), 7.13–7.87 (m, 15H, ArH's), 8.36 (s, 1H, pyrazole C-5) and 10.79 (s, 1H).
37e	IR: 3052, 2970 (CH), 1661 (CO) and 1581 (C═C). ^{1}H NMR: 2.43 (s, 3H), 2.45 (s, 3H), 7.22–7.96 (m, 15H, ArH's) and 8.27 (s, 1H, pyrazole C-5).
39a	IR: 3448 (NH), 3080, 2997 (CH), 1679 (CO) and 1587 (C═C). ^{1}H NMR: 2.69 (s, 3H), 7.26–8.02 (m, 10H, ArH's), 8.50 (s, 1H, pyrazole C-5) and 10.19 (s, 1H).
39b	IR: 3045, 2991 (CH) and 1587 (C═C). ^{1}H NMR: 2.86 (s, 3H), 3.01 (s, 3H), 7.13–8.00 (m, 10 H, ArH's), 8.66 (s, 1H, pyrazole C-5.
39c	IR: 3052, 2956 (CH) and 1591 (C═C). ^{1}H NMR: 2.94 (s, 3H), 7.25–8.78 (m, 15 H, ArH's), 8.85 (s, 1H, pyrazole C-5.
39d	IR: 3052, 2956 (CH) and 1591 (C═C). ^{1}H NMR: 2.35 (s, 3H), 2.47 (s, 3H), 7.32–7.48 (m, 15H), 7.78 (s, 1H, pyrazole C-5.

at r.t. The resulting solids were collected and crystallized from dioxan to give red crystal **17a** and **17b**, respectively (Tables II and III).

Method B

A mixture of the appropriate hydrazonoyl bromides **1a** or **1b** (5 mmol) and 2-mercapto-5-phenyl-1,3,4-oxadiazole **14** (0.84 g, 5 mmol) in chloroform (20 mL) containing triethylamine (0.5 g (0.75 mL), 5 mmol) were refluxed for 10 h; chloroform was evaporated under reduced pressure and the residue solids were collected and crystallized to give products identical in all respects (m.p., mixed m.p., and spectra) with corresponding products obtained by Method A.

Synthesis of 3-[(2,5-Dimethyl(1,3-thiazol-4-yl))carbonyl]-4-oxo-1,6-diphenyl-3a-hydro-1,2,4-triazolino[4,3-a]pyrimidine-5-carbonitrile (26a) and (26b)

Method A

A mixture of the appropriate hydrazonoyl bromides **1a** or **1b** (5 mmol) and 6-oxo-4-phenyl-2-thioxo-1,3-dihydropyrimidine-5-carbonitrile (**22**)

(1.145 g, 5 mmol) in chloroform (20 mL) containing triethylamine (0.5 g (0.75 mL), 5 mmol) was refluxed for 10 h; chloroform was evaporated under reduced pressure and the residue solid was collected and crystallized to give **26a** and **26b** (Tables II and III).

Method B

An equimolar amount of the appropriate hydrazonoyl bromides **1a** or **1b**, 2-(methylthio)-6-oxo-4-phenyl-,6-dihydropyrimidine-5-carbonitrile (**28**), and sodium ethoxide (5 mmol each) in ethanol (20 mL) was refluxed for 3 h. The reaction mixture was cooled and the resulting solid was collected and crystalized to give products identical in all respected (m.p., mixed m.p., and spectra) with the appropriate **26a** or **26b**.

Synthesis of 3-(Dimethylamino)-1-(4-methyl-2-phenyl(1,3-thiazol-5-yl))prop-2-ene-1-one (32)

A mixture of 5-acetyl-4-methyl-2-phenylthiazole (**31)** (2.17 g, 10 mmol) and dimethylformamide-dimethylacetal (1.47 g, 10 mmol) were refluxed in dry xylene (10 mL) for 4 h. The hot solution was evaporated to its half volume and then cooled. The resulting solid was collected and crystallized to give **32** (Tables I and II).

Synthesis of 1-Phenyl-4-(4-methyl-2-phenyl)thiazol-5-yl-3-substituted Pyrazoles 37a–e

An equimolar amount of each of the appropriate **32** and appropriate hydrazonoyl halides **33a–e** (0.005 mole) were refluxed in dry toluene containing triethylamine for 3 h. The hot solution was filtered off and the filtrate was evaporated and triturated with petroleum ether (40–60°C). The resulting solid was collected and crystallized from ethanol to give **37a–e**, respectively (Tables I and II).

Synthesis of Pyrazolo[3,4-*d*]pyridazines 39a–d

An appropriate of 1-phenyl-4-phenylcarbonyl-3-substituted pyrazoles **37a–e** (0.5 g) and hydrazine hydrate (1 mL) in ethanol (15 mL) were refluxed for 1 h. The resulting solid was collected and crystallized to give the corresponding pyrazolo[3,4-*d*]pyridazines **39a–d** (Tables I and II).

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