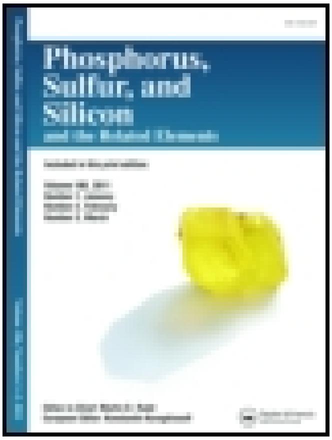

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Reaction of Hydrazonoyl Halides 51[1]: A Facile Synthesis of 5-Arylthiazoles and Triazolino[4,3- a]pyrimidines as Antimicrobial Agents

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Reaction of Hydrazonoyl Halides 51[1]: A Facile Synthesis of 5-Arylthiazoles and Triazolino[4,3-*a*]pyrimidines as Antimicrobial Agents

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*[5-Substituted 2-(3-phenyl-5-substituted 2-pyrazolinyl)(1,3-thiazol-4-yl)]phenyldiazenes, triazolo[3,4-*a*]pyrimidines, and 2,3-dihydro-1,3,4-thiadiazoles were synthesized with good yields from reactions of hydrazonoyl halides with 5-substituted-3-phenyl-4,5-dihydropyrazole-1-carboximidothionic acid, pyrimidine-2-thione, methyl carbodithioate, respectively. All structures of the newly synthesized compounds were elucidated by elemental analysis, spectral data, and alternative synthesis methods. Newly developed compounds are capable of inhibiting the growth of bacteria (gram positive and gram negative) greatly.*

Keywords 1,3,4-Thiadiazolines; aryazothiazoles; hydrazonoyl halides; triazolino[4,3-*a*]pyrimidines

INTRODUCTION

Variously substituted pyrazolines and their derivatives are important biological agents, and a significant amount of research activity has been directed towards this class. In particular, they are used as antitumor,[2] antibacterial, antifungal, antiviral, antiparasitic, antitubercular, and insecticidal agents.[3–11] Some of these compounds also have anti-inflammatory, antidiabetic, anaesthetic, and analgesic properties.[12–15] Moreover, pyrazololines have played a crucial part in the development of theory in heterocyclic chemistry.[16–20] In this article, we report the reactivity of α-keto hydrazonoyl halides towards

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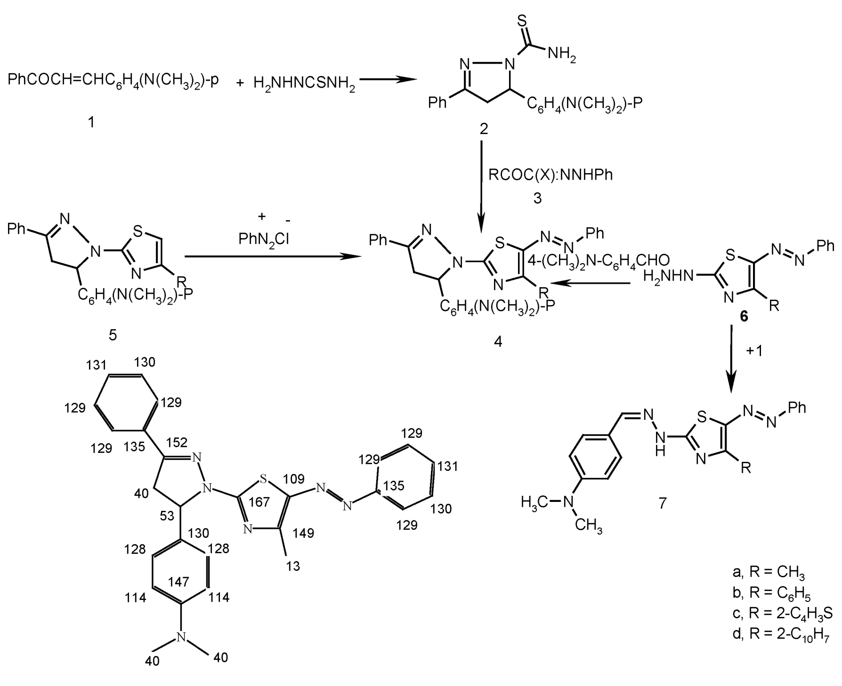
4,5-dihydropyrazole-1-carboximidothionic acid, methyl carbodithioate, and 1,3-dihydropyrimidine-2-thione derivatives.

RESULTS AND DISCUSSION

3-(4-Dimethylaminophenyl)-1-phenylpropenone (**1**) was reacted with thiosemicarbazide in ethanol containing catalytically amount of triethylamine gave 5-(4-dimethylaminophenyl)-3-phenyl-4,5-dihydropyrazol-1-carbothioic acid amide (**2**). Structure **2** was elucidated by elemental analysis, spectra, and chemical transformation. ^{1}H NMR spectra showed signal at $\delta = 2.81$ (s, 6H, $N(CH_3)_2$), 3.26 (dd, J = 15.0, 8.2 Hz, 1H, $CH_{2(pyraz)}$), 3.82 (dd, J = 15.0, 12.2 Hz, 1H, $CH_{(pyraz)}$), 5.36 (br., s, 2H, NH_2), 5.68 (dd, J = 12.2, 8.2 Hz, 1H, $CH_{2(pyraz)}$), 7.21–7.81 (m, 9H, ArH's). Thus, compound **2** was reacted with *C*-acetyl-*N*-phenylhydrazonoyl chloride (**3a**) in boiling ethanolic triethylamine gave dimethyl-4-[2-(5-methyl-4-phenylazothiazo-2-yl)-5-phenyl-3,4-dihydro-2H-pyrazol-3-yl]phenylamine (**4a**) (Scheme 1).



SCHEME 1

Structure **3** was elucidated by elemental analysis, spectra and alternative synthesis route. ^{1}H NMR spectrum of **4a** showed signals δ = 2.47, (s, 3H, CH_3), 2.81 (s, 6H, $N(CH_3)_2$), 3.26 (dd, J = 15.0, 8.2 Hz, 1H, $CH_{2(pyraz)}$), 3.82 (dd, J = 15.0, 12.2 Hz, 1H, $CH_{(pyraz)}$), 5.68 (dd, J = 12.2, 8.2 Hz, 1H, $CH_{2(pyraz)}$), 7.21–7.81 (m, 14H, ArH's). ^{13}C NMR showed signals agreement with its structure (Scheme 1). Also, treatment of **6a**[1] with **1** gave product identical in all respects (m.p., mixed m.p., and spectra) with **4a.** Also, **5a** was reacted with benzendiazonium chloride in ethanolic sodium acetate solution afforded **4a**. Meanwhile, the appropriate **6a–c** was reacted with 4-(N,N-dimethyl)aminobenzaldehyde gave the corresponding thisemicarbazone **7a–c**, respectively.

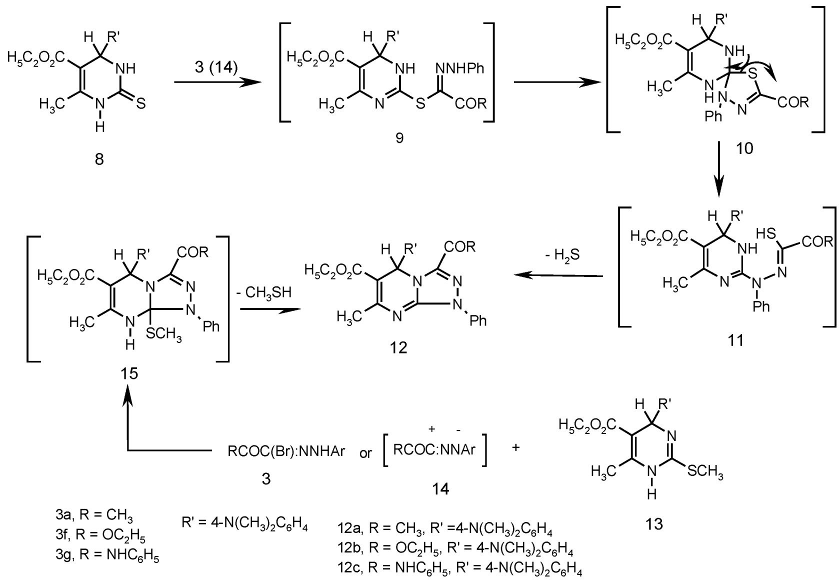
Treatment of ethyl 6-[4-(dimethylamino)phenyl]-4-methyl-2-thioxo-1,3,6-trihydropyrimidine-5-carboxylate (**8**) with the appropriate hydrazonoyl halides **3a–c** in boiling chloroform under reflux gave triazolino[4,3-*a*]pyrimidines **12a–c**, respectively.

Structure of **12** was elucidated on the basis of elemental analysis, spectral data and alternative synthesis route. Thus, treatment of **3a** with ethyl 4-[4-(dimethylamino)phenyl]-6-methyl-2-methythio-3,4-dihydropyrimidine-5-carboxylate (**13**) in boiling ethanolic sodium ethoxide solution under reflux afforded product identical in all respects (m.p., mixed m.p., and spectra) with **12a**.

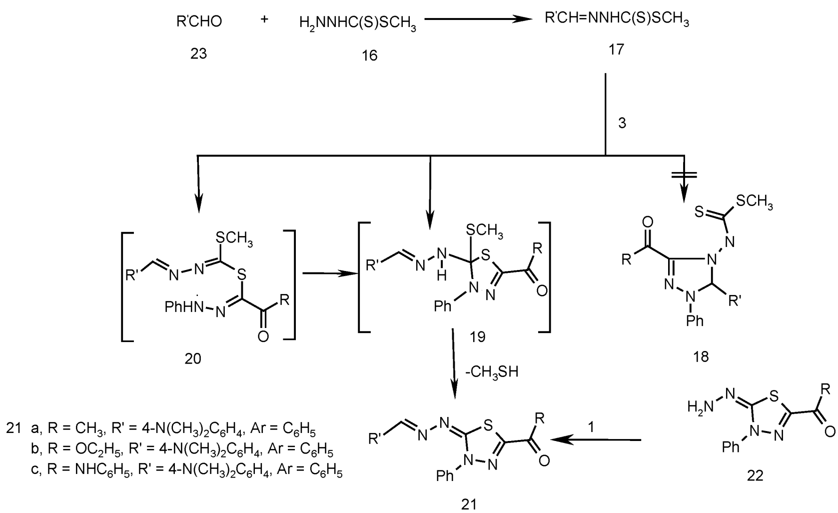
Two possible pathways can account for the formation **12** via 1,3-addition of the thiol tautomer of **8** to the nitrilium imide **14**, (which prepared insitu from hydrazonoyl halide and triethylamine), can give the thiohydrazonate ester **9**, which undergoes nucleophilic cyclization to yield spiro compounds **10** or 1,3-cycloaddition of nitrilium imide **14** to C=S double bond of **8** can give directly **10**. The latter intermediate **10** was converted to **11,** which cyclized immediately to yield **12** by loss hydrogen sulfide (Scheme 2).

On the other hand, treatment of *N*, *N*-dimethylbenzaldehyde with methyl hydrazinecarbodithioate[21] (**16**) in 2-propanol afforded (1-aza-2-[4-(dimethylamino)-phenyl]vinylamino)methylthiomethane-1-thione (**17**) (Scheme 3).

Structure **17** was elucidated by elemental analysis, spectral analysis, and chemical transformation. Compound **17** reacted with **3b** in ethanolic triethylamine at room temperature to give one isolate product formulated as: ethyl 2-1,2-diaza-3-[4-(dimethylamino)phenyl]prop-2-enylidene-3-phenyl-1,3,4-thiadiazoline-5-carboxylate (**21b**). Structure **21** was confirmed by elemental analysis and spectral data alternative synthesis route. Thus, 2,3-dihydro-1,3,4-thiadiazole **22**[22] was reacted with 4-N,N-dimethylbenzaldehyde (**23**) in ethanol afforded product identical in all respects (m.p., mixed m.p. and spectra) with **21b**.



SCHEME 2



SCHEME 3

Antimicrobial Activity

The tested microorganisms were gram +ve bacteria, gram −ve bacteria, and some Fungal-plant. Sensitivity of the selected microorganisms

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

Microorganisms/ Compound no.	*Bacillus subtilis* *(G^+)*	*Echerichia coli* *(G^-)*	*Staphylococcus albus* *(G^+)*	*Streptococcus faecalis* *(G^+)*	*Candida albicans* *(Fungus)*	*Aspergills flvus* *(Fungus)*
Ampicillin/ Tetracycline	33/30	39/34	34R / 27	37/31	20/37	0.0/0.0
4b	14	14	13	15	13	0.0
4c	14	14	14	14	13	0.0
4d	14	15	15	15	14	0.0
7a	15	14	15	14	15	0.0
7b	13	13	15	14	13	0.0
7c	13	13	14	15	13	0.0
7d	14	14	13	14	15	0.0
12a	15	15	15	14	16	12
12b	16	15	15	16	16	0.0
12c	15	15	14	15	13	0.0
17	14	15	15	14	14	0.0
21a	14	13	14	13	13	0.0
21b	15	14	14	14	14	0.0
21c	13	14	13	13	13	0.0

St. Reference standard; Chloramphenicol was used as a slandered antibacterial agent; Terbinafin was used as a slandered antifungal agent. Values show zone of inhibition in mm. Diameter of the inhibition zones were: high (11–15 mm), moderate (6–10 mm), slight (1–5 mm), and negative (0).

to some synthesized compounds were determined by in vitro culture that were dissolved in chloroform; the tests were carried out using the filter paper and hole plate method.[23,24] Studies on the biological activity of compounds in comparison with Ampicillin and tetracycline showed in Table 1. In general all tested compounds were capable of a high inhibiting the growth of gram positive and gram negative. Also, all compounds were a high inhibition towards *Candida albicans* and negative *Aspergills flvus* (except **12a** is high).

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 and ^{13}C 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 microorganism tests were carried out at the Microanalytical Center of the Cairo University. Hydrazonoyl halides were prepared as previously reported.[25–30]

5-(4-Dimethylaminophenyl)-3-phenyl-4,5-dihydropyrazol-1-carbothioic Acid Aide (2)

A mixture of 3-(4-dimethylaminophenyl)-1-phenylpropenone (**1**) (1.25 g, 5 mmol), thiosemicardazide (0.0.45 g, 5 mmol) in ethanol (20 mL) and triethylamine (2 drops) were boiled under reflux for 2 h. The resulting solid, which formed after cooling, was collected and crystallized from ethanol to give **2** (Tables II and III).

Dimethyl-4-[2-(5-substituted 4-phenylazothiazo-2-yl)-5-phenyl-3,4-dihydro-2H-pyrazol-3-yl]phenylamine (4a–d)

A mixture of the appropriate hydrazonoyl halides (**3a–d**) (5 mmol), 5-(4-dimethylaminophenyl)-3-phenyl-4,5-dihydropyrazol-1-carbothioic acid amide (**2**) (1.67 g, 5 mmol), triethylamone (0.75 mL, 5 mmol) in ethanol (20 mL) were boiled under reflux for 3 h. The resulting solid was collected and recrystallized from acetic acid to give **4a–d**, respectively (Tables II and III).

Synthesis of (4a): Alternative Methods

Method (A)

A mixture of (4-methyl-5-phenylazothiazol-2-yl)hydrazine (**6a**)[1] (1.97, 5 mmol) and 3-(4-dimethylaminophenyl)-1-phenylpropenone (**1**) (1.25 g, 5 mmol) in ethanol (20 mL) containing catalytically amount of piperdine (2 drops) was boiled under reflux for 2 h to give **4a**.

Method (B)

Benzenediazonium chloride (5 mmol), which prepared from aniline (0.45 mL, 5 mmol), hydrochloric acid (6 N, 6 mL), and sodium nitrite (0.35g, 5 mmol), was added dropwise with stirring to a cold solution of a mixture of dimethyl4-[1-(4-methyl)(1,3-thiazol-2-yl))-3-phenyl(2-pyrazolin-5-yl)]phenylamine (**5**) (1.81 g, 5 mmol) and sodium acetate trihydrate (1.3 g, 10 mmol) in ethanol (50 ml). The resulting solid was collected and recrystallized to give product identical with **4a**.

Synthesis of Dimethyl4-[1-(4-methyl)(1,3-thiazol-2-yl))-3-phenyl(2-pyrazolin-5-yl)]phenylamine (5)

A mixture of 5-(4-dimethylaminophenyl)-3-phenyl-4,5-dihydropyrazol-1-carbothioic acid amide (**2**) (1.67 g, 5 mmol) and chloroacetone (0.46 g, 5 mmol) in ethanol (20 mL) were heated under reflux for 2 h. The resulting solid was collected and recrystallized from ethanol to give **5** (Tables II and III).

TABLE II Characterization Data of the Newly Synthesized Compounds

Compd. no.	M.p., °C solvent	Yield % colour	Mol. formula mol. wt.	% Analyses C	H	calcd./found N	S
2	198–200	83	$C_{18}H_{20}N_4S$	66.64	6.21	17.27	9.88
	EtOH	Yellow	324.45	66.42	6.32	17.20	10.00
4a	165–66	80	$C_{27}H_{26}N_6S$	69.50	5.62	18.01	6.87
	DMF/EtOH	Deep red	466.61	69.60	5.42	17.92	6.70
4b	194–95	78	$C_{32}H_{28}N_6S$	72.70	5.34	15.90	6.06
	DMF/EtOH	Deep red	528.68	72.92	5.43	15.75	5.85
4c	188–90	68	$C_{30}H_{26}N_6S_2$	67.39	4.90	15.72	11.99
	DMF/EtOH	Deep red	534.71	67.52	4.80	15.60	12.12
4d	165–57	74	$C_{36}H_{30}N_6S$	74.71	5.22	14.52	5.54
	DMF/EtOH	Deep red	578.74	74.62	5.10	14.72	5.42
5	210–12	86	$C_{21}H_{22}N_4S$	69.58	6.12	15.46	8.85
	EtOH	Yellow	362.50	69.65	5.95	15.62	8.64
7a	190–91	88	$C_{19}H_{20}N_6S$	62.61	5.53	23.06	8.80
	Dioxan	Red	364.48	62.54	5.35	22.85	8.65
7b	194–95	75	$C_{24}H_{22}N_6S$	67.58	5.20	19.70	7.52
	Dioxan	Red	426.55	67.70	5.12	19.61	7.45
7c	149–51	78	$C_{22}H_{20}N_6S_2$	61.09	4.66	19.43	14.82
	Dioxan	Deep red	432.57	61.20	4.55	19.34	14.72
7d	195–61	83	$C_{28}H_{24}N_6S$	70.56	5.08	17.63	6.73
	Dioxan	Deep red	476.61	70.65	4.89	17.50	6.80
8	200–202	72	$C_{16}H_{21}N_3O_2S$	60.16	6.63	13.15	10.04
	EtOH	Yellow	319.43	60.30	6.53	13.23	10.12
12a	185–87	82	$C_{25}H_{27}N_5O_2$	67.40	6.11	15.72	—
	EtOH	Yellow	445.53	67.50	6.18	15.85	—
12b	165–66	78	$C_{26}H_{29}N_5O_4$	65.67	6.15	14.73	—
	EtOH	Yellow	475.55	65.70	5.84	14.90	—
12c	150–521	82	$C_{30}H_{30}N_6O_3$	68.95	5.79	16.08	—
	EtOH	Yellow	522.61	68.80	5.90	15.88	—
13	138–40	85	$C_{17}H_{23}N_3O_2S$	61.23	6.95	12.60	9.62
	EtOH	Yellow	333.46	61.12	6.80	12.48	9.71
17	190–91	82	$C_{11}H_{15}N_3S_2$	52.14	5.97	16.58	25.31
	EtOH	Yellow	253.39	52.00	5.85	15.72	25.22
21a	148–49	74	$C_{19}H_{19}N_5OS$	62.45	5.24	19.16	8.77
	EtOH	Dioxan	365.46	62.55	5.40	19.30	8.85
21b	200–202	77	$C_{20}H_{21}N_5O_2S$	60.74	5.53	17.71	8.11
	EtOH	Dioxan	395.49	60.68	5.35	17.90	8.20
21c	205–207	71	$C_{24}H_{22}N_6OS$	65.14	5.01	18.99	7.25
	EtOH	Dioxan	442.55	65.26	5.00	19.12	7.30

[4-(2-Aza-2-[4-substituted 5-phenyldiazenyl)(1,3-thiazol-2-yl)]aminovinyl)phenyl]-dimethylamine 7a–c

A mixture of 4-(N,N-dimethylamino)benzaldehyde (**23**) (0.74a, mmol), the appropriate **6a–c** (5 mmol) and acetic acid (2 drops) in ethanol (20

TABLE III Spectra of Some Newly Synthesized Compounds

Comp. no.	Spectral data
2	^{1}H NMR: 2.81 (s, 6H, $N(CH_3)_2$), 3.26 (dd, J = 15.0, 8.2 Hz, 1H, $CH_{2(pyraz)}$), 3.82 (dd, J = 15.0, 12.2 Hz, 1H, $CH_{(pyraz)}$), 5.36 (br., s, 2H, NH_2), 5.68 (dd, J = 12.2, 8.2 Hz, 1H, $CH_{2(pyraz)}$), 7.21–7.81 (m, 9H, ArH's).
4a	^{1}H NMR: 2.47, (s, 3H, CH_3), 2.81 (s, 6H, $N(CH_3)_2$), 3.26 (dd, J = 15.0, 8.2 Hz, 1H, $CH_{2(pyraz)}$), 3.82 (dd, J = 15.0, 12.2 Hz, 1H, $CH_{(pyraz)}$), 5.68 (dd, J = 12.2, 8.2 Hz, 1H, $CH_{2(pyraz)}$), 7.21–7.81 (m, 14H, ArH's).
4b	^{1}H NMR: 2.81 (s, 6H, $N(CH_3)_2$), 3.26 (dd, J = 15.0, 8.2 Hz, 1H, $CH_{2(pyraz)}$), 3.82 (dd, J = 15.0, 12.2 Hz, 1H, $CH_{(pyraz)}$), 5.68 (dd, J = 12.2, 8.2 Hz, 1H, $CH_{2(pyraz)}$), 7.21–7.81 (m, 19H, ArH's).
4c	^{1}H NMR: 2.81 (s, 6H, $N(CH_3)_2$), 3.26 (dd, J = 15.0, 8.2 Hz, 1H, $CH_{2(pyraz)}$), 3.82 (dd, J = 15.0, 12.2 Hz, 1H, $CH_{(pyraz)}$), 5.36 (br., s, 2H, NH_2), 5.68 (dd, J = 12.2, 8.2 Hz, 1H, $CH_{2(pyraz)}$), 7.21–7.81 (m, 17H, ArH's).
4d	^{1}H NMR: 2.81 (s, 6H, $N(CH_3)_2$), 3.26 (dd, J = 15.0, 8.2 Hz, 1H, $CH_{2(pyraz)}$), 3.82 (dd, J = 15.0, 12.2 Hz, 1H, $CH_{(pyraz)}$), 5.36 (br., s, 2H, NH_2), 5.68 (dd, J = 12.2, 8.2 Hz, 1H, $CH_{2(pyraz)}$), 7.21–7.81 (m, 21H, ArH's).
5	^{1}H NMR: 2.47, (s, 3H, CH_3), 2.81 (s, 6H, $N(CH_3)_2$), 3.26 (dd, J = 15.0, 8.2 Hz, 1H, $CH_{2(pyraz)}$), 3.82 (dd, J = 15.0, 12.2 Hz, 1H, $CH_{(pyraz)}$), 5.68 (dd, J = 12.2, 8.2 Hz, 1H, $CH_{2(pyraz)}$), 7.21–7.81 (m, 14H, ArH's).
7a	^{1}H NMR: 2.21(t, 3H, CH_3), 2.85 (s, 6H, $N(CH_3)_2$, 6.46-7.48 (m, 9H, ArH's), 8.21(s, 1H, CH=N), 9.24 (s, br., 1H, NH).
7b	2.85 (s, 6H, $N(CH_3)_2$, 6.46-7.48 (m, 14H, ArH's), 8.21(s, 1H, CH=N), 9.24 (s, br., 1H, NH).
7c	^{1}H NMR: 2.85 (s, 6H, $N(CH_3)_2$, 6.46-7.48 (m, 12H, ArH's), 8.21(s, 1H, CH=N), 9.24 (s, br., 1H, NH).
7d	^{1}H NMR: 2.85 (s, 6H, $N(CH_3)_2$, 6.46-7.89 (m, 19H, ArH's), 8.21(s, 1H, CH=N), 9.24 (s, br., 1H, NH).
8	^{1}H NMR: 1.30 (t, 3H, CH_2CH_3), 1.74 (s, 3H, CH_3), 2.85 (s, 6H, $N(CH_3)_2$, 4.12 (q, 2H, CH_2CH_3), 4.59 (s, 1H, pyrimidine C4), 6.46-6.88 (m, 4H, ArH's), 9.45 (s, br., 2H, 2NH).
12a	^{1}H NMR: 1.31 (t, 3H, CH_2CH_3), 1.71 (s, 3H, CH_3), 2.0 (s, 3H, CH_3), 2.85 (s, 6H, $N(CH_3)_2$, 4.19 (q, 2H, CH_2CH_3), 4.59 (s, 1H, pyrimidine C4), 6.46-7.04 (m, 9H, ArH's). IR: 3056, 2984 (CH), 1713, 1665 (CO's), 1620 (C=N) and 1600 (C=C).
12b	^{1}H NMR: 1.31 (t, 3H, CH_2CH_3), 1.29 (t, 3H, CH_2CH_3), 1.71 (s, 3H, CH_3), 2.85 (s, 6H, $N(CH_3)_2$, 4.19 (q, 2H, CH_2CH_3), 4.22 (q, 2H, CH_2CH_3), 4.59 (s, 1H, pyrimidine C4), 6.46-7.05 (m, 9H, ArH's). IR: 3060, 2975 (CH), 1713 (CO's), 1625 (C=N) and 1610 (C=C).
12c	^{1}H NMR: 1.31 (t, 3H, CH_2CH_3), 1.71 (s, 3H, CH_3), 2.85 (s, 6H, $N(CH_3)_2$, 4.19 (q, 2H, CH_2CH_3), 4.59 (s, 1H, pyrimidine C4), 6.46-6.88 (m, 4H, ArH's), 9.45 (s, br., 1H,1NH). IR: 3065, 2989 (CH), 1713, 1680 (CO's), 1620 (C=N) and 1605 (C=C).
13	^{1}H NMR: 1.31 (t, 3H, CH_2CH_3), 1.71 (s, 3H, CH_3), 2.0 (s, 3H, CH_3), 2.85 (s, 6H, $N(CH_3)_2$, 4.19 (q, 2H, CH_2CH_3), 4.59 (s, 1H, pyrimidine C4), 6.46-6.88 (m, 4H, ArH's), 9.45 (s, br., 1H, 2NH).
17	^{1}H NMR: 2.12 (s, 3H, CH_3), 2.85 (s, 6H, $N(CH_3)_2$, 6.61–7.42 (m, 9H, ArH's), 8.45 (s, 1H, CH=N), 9.23 (s, br., 1H. NH).
21a	^{1}H NMR: 1.31 (t, 3H, CH_2CH_3), 2.85 (s, 6H, $N(CH_3)_2$, 4.22 (q, 2H, CH_2CH_3),) 6.46–7.48 (m, 9H, ArH's), 8.45 (s, 1H, CH=N) IR: 1665 (CO), 1620 (C=N) and 1600 (C=C).
21b	^{1}H NMR: 2.20 (t, 3H, CH_3), 2.85 (s, 6H, $N(CH_3)_2$, 6.46–7.48 (m, 8H, ArH's), 8.45 (s, 1H, CH=N). IR: 1713 (CO), 1625 (C=N) and 1600 (C=C).
21c	^{1}H NMR: 2.85 (s, 6H, $N(CH_3)_2$, 6.46–7.65 (m, 14H, ArH's), 8.45 (s, 1H, CH=N), 9.35 (s, br., 1H, NH). IR: 1685 (CO), 1620 (C=N) and 1600 (C=C).

mL) was stirred for 1 h. The resulting solid was collected and recrystallized from dioxan to give **7a–c**, respectively in a good yield (Tables II and III).

Ethyl 6-[4-(Dimethylamino)phenyl]-4-methyl-2-thioxo-1,3,6-trihydropyrimidine-5-carboxylate (8)

A mixture of 4-dimethylaminobenzaldehyde (7.45 g, 50 mmol), ethyl 3-oxobutanoate (6.50 g, 50 mmol) and thiourea (3.8 g, 50 mmol) in ethanol (25 mL) contain hydrochloric acid (1 ml, 12 N) were boiled under reflux for 6 h. The resulting solid, which formed after cooling, was collected and recrystallized from ethanol to give **8** (Tables II and III).

Ethyl 4-[4-(Dimethylamino)phenyl]-6-methyl-1-phenyl-3-(1-acyl)-4,3a-dihydro-1,2,4-triazololino[4,3-a]pyrimidine-5-carboxylate 12a-c

Method A

A mixture of the appropriate hydrazonoyl halides **3a–c** (5 mmol) and **8** (1.59 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 crystallized from ethanol to give ethanol to give **12a–c** (Tables II and III).

Method A

A mixture of the appropriate hydrazonoyl halides **3a–c** (5 mmol),**13** (1.66 g, 5 mmol), and sodium ethoxide (0.34 g, 5 mmol) in ethanol (20 mL) was refluxed for 3 hrs. The reaction mixture was cooled and the resulting solid was collected and crystallized from dioxane gave products identical in all respects (m.p., mixed m.p., and spectra) with corresponding products obtained by Method A.

Ethyl 4-[4-(Dimethylamino)phenyl]-6-methyl-2-methythio-3,4-dihydropyrimidine-5-carboxylate (13)

A mixture of **8** (1.95 g, 5 mmol) and sodium methoxide (0.29 g, 5 mmol) in methanol (20 ML) were stirred for 3 hrs. Iodomethane (0.72 g, 5 mmol) was added while stirring; after 2 h the resulting solid was collected and recrystallized from ethanol to give **13** (Tables II and III).

(1-Aza-2-[4-(dimethylamino)phenyl]-vinylamino)methylthiomethane-1-thione (17)

A mixture of the 4-dimethylaminobenzaldehyde (1.49 g, 10 mmol) and methyl hydrazinecarbodithioates **16**[31] (1.22 g, 10 mmol) in 2-propanol (10 mL) were stirred for 2 h at room temperature. The resulting solid was collected and crystallized from ethanol to give yellow crystals**17** (Tables II and III).

5-Acyl-2-1,2-diaza-3-[4-(dimethylamino)phenyl]prop-2-enylidene-3-phenyl-1,3,4-thiadiazolines 21a–c

A mixture of the methyl carbodithioate **17** (1.26 g, 5 mmol), the appropriate hydrazonoyl halides **3a- c** (5 mmoles), and triethylamine (0.75 mL, 0.005 mol) in ethanol (20 mL) was stirred for 2 h at room temperature. The resulting solid was collected and recrystallized to give 2,3-dihydro-1,3,4-thiadiazoles **21a–c**, respectively (Tables II and III).

Alternative Method

A mixture of ethyl 2-hydrazino-3-phenyl-1,3,4-thiadiazoline-5-carboxylate (**22**) (1.32 g, 5 mmol) and 4-dimethylaminobenzaldehyde (0.74 g, 5 mmol) in 2-propanol (10 ml) were stirred for 2 h at room temperature. The resulting solids were collected and recrystallized from ethanol to give **21a** (Tables II and III).

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