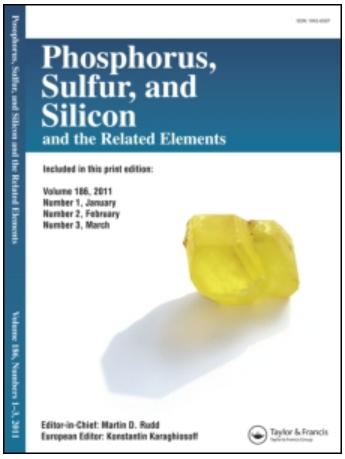

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A Convenient Synthesis of 1-Amino-4-methyl-4*H*-3-thia-4,5*a*,10-triazacyclopenta[*a*]fluoren-5-ones and Some New 2,3-Dihydro-1,3,4-thiadiazoles

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*1-amino-4-methyl-4H-3-thia-4,5a,10-triazacyclopenta-[*a*]fluoren-5-one and 6-methyl-6H-,9H-thia-4b,6,9,11,12-pentaazaindeno[1,2-*a*]-fluorene-5,8-dione derivatives were prepared from 2-methyl-1-oxo-3-thioxo-2,4,9*b*-trihydropyrimidino[1,6-*a*] benzimidazole-4-carbonitrile. Also, 2,3-dihydro-1,3,4-thidazoles were synthesized via a reaction of hydrazonoyl chlorides with 3-(methylamino)-2-substituted 3-thioxopropanenitrile. Structures of newly synthesized compounds were elucidated on the basis of elemental analyses, spectral data, and alternative methods synthesis whenever possible.*

Keywords Halo ketones; isothiocyanate; nitrilimine; pyrimido[1,6-*a*]benzimidazole

INTRODUCTION

Isothiocyanates remain very important starting materials for the construction of heterocycles.[1] Several benzimidazoles are known[2] to possess antimicrobial, anti-inflammatory, and anticancer activities. Also, 1,3,4-thiadiazole and its derivatives have become a very useful compound in medicine, agriculture, and in many fields of technology.[3] As

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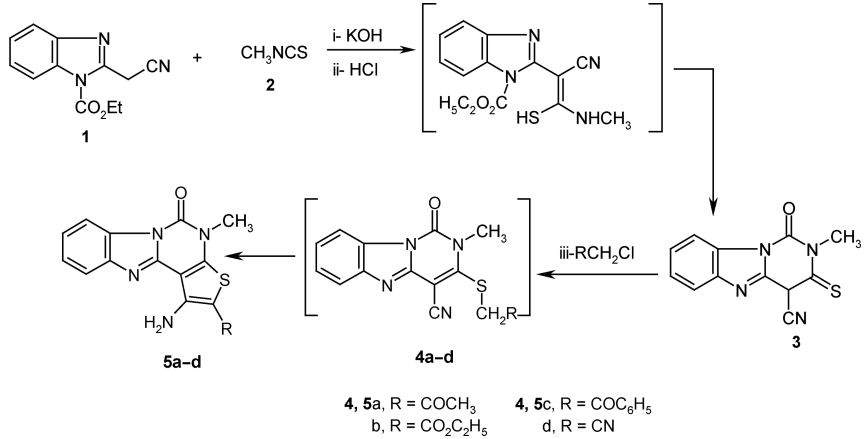
an extension of our study,[4–9] we report herein the synthesis of 1-amino-4-methyl-4H-3-thia-4,5a,10-triazacyclopenta[*a*]fluoren-5-one and 2,3-dihydro-1,3,4-thiadiazole derivatives.

RESULTS AND DISCUSSION

The treatment of 2-(1-ethoxycarbonoyl)benzimidazolylacetonitrile (**1**)[10] with methyl isothiocyanate (**2**) in the presence of potassium hydroxide followed by acidification gave one isolable product according to TLC, which is formulated as 2-methyl-1-oxo-3-thioxo-1,2,3,4-tetrahydrobenzoimidazo[1,2-*c*]pyrimidine-4-carbonitrile (**3**) (Scheme 1) based upon elemental analysis, spectral data, and chemical transformations.

Thus, the ^{1}H NMR spectrum of the product showed signals at $\delta =$ 3.72 (s, 3H), 3.81 (s, 1H), 7.41–7.45 (m, 3H), and 8.20–8.24 (d, 1H). The ^{13}C NMR showed signals at $\delta = 34$ (N—CH_3), 44 (CH_2), 115, 115, 116 (CN), 123, 123, 131, 139, 141, 150, and 196 (CO). Its IR spectrum revealed bands at 3076, 2987 (CH), 2217 (CN), 1706 (CO), and 1634 (C=N)



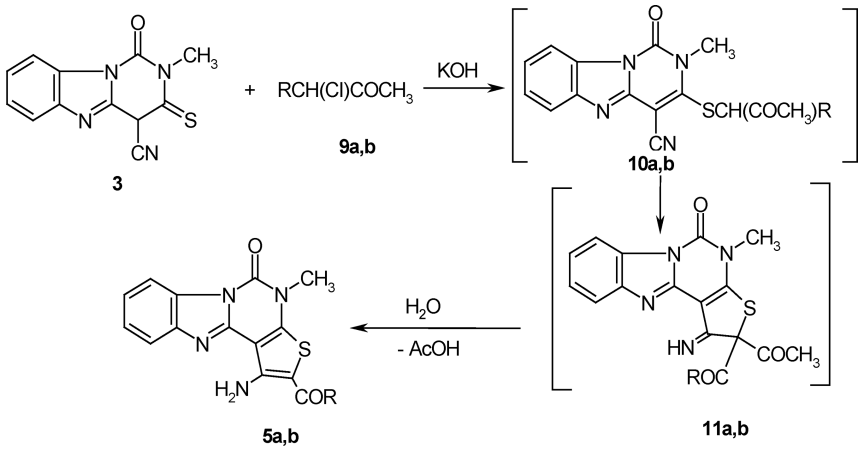
SCHEME 1

The treatment of **3** with chloroacetone in *N*,*N*-dimethylformamide in the presence of potassium hydroxide afforded 2-acetyl-1-amino-4-methyl-4H-3-thia-4,5a,10-triazacyclopenta[*a*]fluoren-5-one (**5a**) (Scheme 1). Structure **5a** was elucidated by elemental analysis and spectral data. Thus, the ^{1}H NMR spectrum showed signals at $\delta = 2.23$ (s, 3H), 3.45 (s, br., 2H), 7.38–7.49 (m, 2H), 7.73–7.77 (d, 1H), and 8.22–8.26 (1H). The ^{13}C NMR spectrum showed signals at $\delta = 28$ (N-$\underline{CH_3}$), 33 ($\underline{CH_3}$CO),

115, 115, 123, 123, 129, 129 131, 136, 139, 141, 143, 159, and 191 (CO). Its IR spectrum revealed bands at 3444, 3322 (NH_2), 1710, 1635 (CO's), and 1621 (C=C). No absorption band between 2000–2300 was observed due to the absence of the CN group.[11] The reaction seemed to proceed through dehydrochlorination to give intermediate **4a**, which underwent cyclization via the addition of $-SCH_2$-hydrogens to a nitrile function to give the final product **5a**.

Similarly, compound **3** was reacted with each of phenacylbromide, ethyl chloroacetate, or chloroacetonitrile to give 1-amino-4-methyl-2-substituted 4H-3-thia-4,5a,10-triazacyclopenta[a]fluoren-5-one **5b–d**, respectively (Scheme 1).

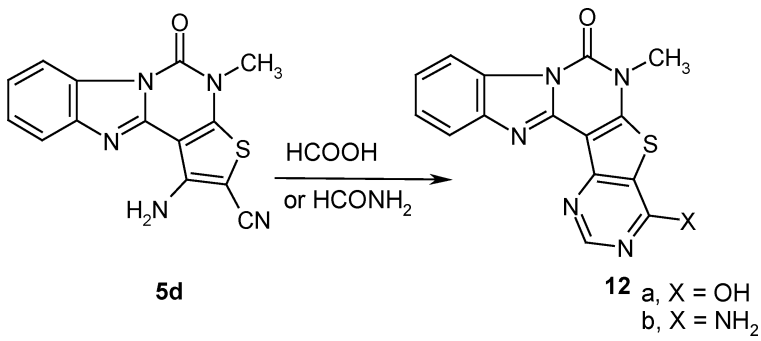
Also, compound **3** was reacted with either 3-chloropentan-2,4-dione or ethyl 2-chloro-3-oxobutanoate in *N*,*N*-dimethylformamide containing potassium hydroxide to afford products identical (m.p., mixed m.p., and spectra) with **5a** and **5b**, respectively (Scheme 2).



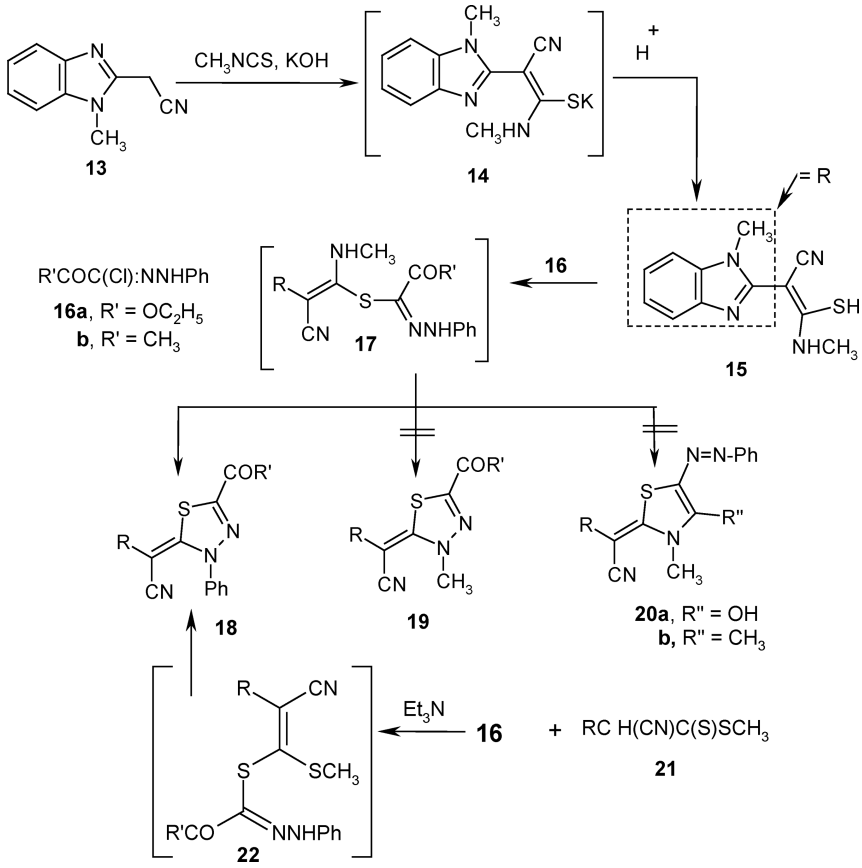
SCHEME 2

Compound **5d** was reacted with each of formic acid and formamide under reflux to afford the corresponding 6-methyl-6H-7-thia-4b,6,9,11,12-pentaazaindeno[1,2-*a*]fluorine-5,8-dione (**12a**) and 8-amino-6-methyl-6H-7-thia-4b,6,9,11,12-pentaazaindeno[1,2-a]fluoren-5-one (**12b**), respectively (Scheme 3).

The treatment of methyl isothiocyanate (**2**) with 2-(cyanomethyl)-1-methylbenzimidazole (**13**)[12] in *N*, *N*-dimethylformamide containing potassium hydroxide afforded the non-isolable intermediate **14**, which converted to thioamide **15** by the acidification with hydrochloric acid (Scheme 4). The structure of **15** was confirmed by elemental analysis, spectral data, and chemical transformation. Its ^{1}H NMR spectrum



SCHEME 3



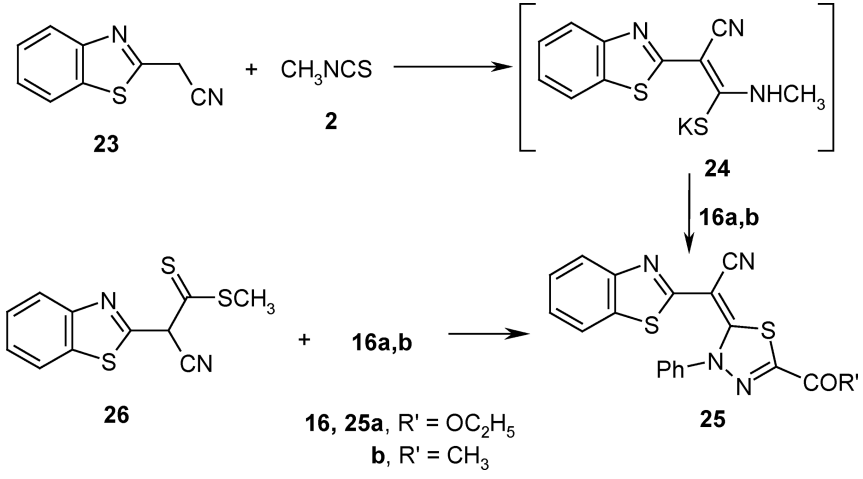
SCHEME 4

showed signals at $\delta = 2.18$ (s, 3H), 3.20 (s, 3H), 6.80 (s, br., 1H), 7.18–7.34 (m, 4H), and 14.08 (s, br., 1H).

Thus, the treatment of **15** with the appropriate hydrazonoyl halides[13,14] **16a**,**b** afforded 2,3-dihydro-1,3,4-thiadiazoles **18a**[15] and **18b**,[16] respectively (Scheme 4). Structure **18** was confirmed on the basis of elemental analysis, spectral data, and altrnative synthesis. The ^{1}H NMR spectrum of **18a** showed signals at $\delta = 1.4$ (t, J = 7 Hz, 3H), 3.0 (s, 3H), 4.4 (q, J = 7 Hz, 2H), and 7.12–8.0 (m, 9H). Its IR spectrum revealed bands at 2220 (CN) and 1713 (CO).

In the light of the foregoing results, the mechanism outlined in Scheme 4 seems to be the most plausible pathway for the formation of **18** from the reaction of **15** with **16**. The reaction involves an initial formation of thiohydrazonate **17**, which undergoes intermolecular cyclization as soon as it is formed to yield **18** via the elimination of methylamine, and structures **19** and **20** were ruled out. Also, the treatment of methyl carbodithioate **21** with **16a** afforded a product identical in all respects (m.p., mixed m.p., and spectra) with **18a**.

Similarly, the treatment of 2-cyanomethylbenzothiazole (**23**) with methyl isothiocyanate (**2**) in N,N-dimethylformamide containing potassium hydroxide gave the non-isolable intermediate **24**, which reacted with each hydrazonoyl chloride **16a** and **16b** to give the corresponding 2,3-dihydro-1,3,4-thiadiazoles **25a** and **25b**, respectively (Scheme 5). Also, compound **26** was reacted with the appropriate hydrazonoyl chlorides **16a,b** in ethanolic triethylamine afforded products identical in all respects (m.p., mixed m.p., and spectra) with **25a**,**b**, respectively.



SCHEME 5

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. ^{13}C NMR and ^{1}H NMR spectra were recorded in $(CD_3)_2SO$ solutions on a Varian Gemini 300 MHz spectrometer, and chemical shifts are expressed in δ units using TMS as an internal reference. Elemental analyses were carried out at the Microanalytical Center of the Cairo University, Egypt.

The Synthesis of 2-Methyl-1-oxo-3-thioxo-2,4,9b-trihydropyrimidino[1,6-a]benzimidazole-4-crbonitrile (3)

A mixture of 2-(1-ethoxycarbonoyl)benzimidazolylacetonitrile (**1**), methylisothiocyanate, and potassium hydroxide (5 mmol each) in *N*,*N*-dimethylformamide (15 mL) was stirred for 6 h. The reaction mixture was diluted with water (10 mL) and acidified with hydrochloric acid; then the resulting solid was collected and recrystallized from *N*,*N*-dimethylformamide to give **3** (Tables I and II).

The Synthesis of 1-Amino-4-methyl-2-substituted 4H-3-thia-4,5a,10-triazacyclopenta[*a*]fluoren-5-one Derivatives 5a–c. General Procedure

Equimolar amounts of 2-(1-ethoxycarbonoyl)benzimidazolylacetonitrile (**1**), methylisothiocyanate, and potassium hydroxide (5 mmol each) in *N*,*N*-dimethylformamide (15 mL) were stirred for 6 h. The appropriate chloroacetone (or 3-chloro-2,4-pentanedione), ethyl chloroacetate (or ethyl 2-chloro-3-oxobutanoate), or chloroacetonitrile (5 mmol) was added while stirring, and the reaction mixture was stirred for 2 h. The resulting solid was collected by filtration and recrystallized from *N*,*N*-dimethylformamide to give **5a–c** (Tables I and II).

The Synthesis of 6-Methyl-6H-7-thia-4b,6,9,11,12-pentaazaindeno[1,2-a]fluorine-5,8-dione (12a) and 8-amino-6-methyl-6H-7-thia-4b,6,9,11,12-pentaazaindeno[1,2-a]fluoren-5-one (12b)

Equimolar amounts of **5c** (0.5 g) was boiling in formic acid (10 mL, 99%) or formamide (2 mL) in *N*,*N*-dimethylformamide (10 mL) for 7 h. The reaction mixture was poured onto ice-cold water (40 mL); the resulting solid was collected and recrystallized from *N*,*N*-dimethylformamide to give **12a** and **12b**, respectively (Tables I and II).

TABLE I Characterization Data of the Newly Synthesized Compounds

Compound no.	M.P. °C (Solvent)	Color yield (%)	Mol. Formula (Mol. Wt.)	Elemental analysis [Calcd./Found (%)]			
				C	H	N	S
3	308–310	Colorless	$C_{12}H_8N_4SO$	56.24	3.15	21.86	12.51
	DMF	55	256.29	56.42	3.01	21.68	12.70
5a	272–273	Colorless	$C_{15}H_{12}N_4SO_2$	57.68	3.87	17.94	10.27
	DMF	50	312.35	57.80	3.65	18.10	10.40
5b	241–243	Colorless	$C_{16}H_{14}N_4SO_3$	56.13	4.12	16.36	9.37
	DMF	57	342.38	56.00	4.20	16.40	9.45
5c	243	Yellow	$C_{20}H_{14}N_4SO_2$	64.16	3.77	14.97	8.56
	DMF	60	374.42	64.20	3.90	15.12	8.65
5d	334–336	Pale Brown	$C_{14}H_9N_5SO$	65.94	3.07	23.71	10.86
	AcOH	62	295.32	66.10	2.90	23.90	10.60
12a	>300	Colorless	$C_{15}H_9N_5SO_2$	55.72	2.81	21.66	9.92
	DMF	57	323.34	55.60	2.90	21.80	10.20
12b	>300	Brown	$C_{15}H_{10}N_6SO$	55.89	3.13	26.07	9.95
	DMF	52	322.35	55.90	3.10	26.20	10.20
15	238–240	Brown	$C_{12}H_{12}N_4S$	58.99	4.95	22.93	13.12
	EtOH	55	244.32	58.80	4.70	22.80	13.10
18a	237–238	Yellow	$C_{21}H_{17}N_5SO_2$	62.52	4.25	17.36	7.95
	EtOH	60	403.47	62.50	4.10	17.20	7.90
18b	274–276	Orange	$C_{20}H_{15}N_5SO$	64.33	4.05	18.75	8.59
	DMF	57	373.44	64.10	4.15	18.80	8.95
21	248–250	Yellow	$C_{12}H_{11}N_3S_2$	55.15	4.24	16.08	24.54
	DMF	82	261.37	55.30	4.10	15.80	24.30
25a	240–242	Yellow	$C_{20}H_{14}N_4S_2O_2$	59.10	3.47	13.78	15.78
	EtOH	52	406.49	59.20	3.80	13.80	15.80
25b	248–250	Yellow	$C_{19}H_{12}N_4SO$	60.62	3.21	14.89	17.03
	EtOH	59	373.44	60.50	3.10	14.90	17.20

The Synthesis of 3-(Methylamino)-2-(1-methylbenzoimidazole-3-thioxopropanenitrile (15)

Equimolar amounts of 2-(1-methylbenzimidazol-2-yl)ethanenitrile, methyl isothiocyanate, and potassium hydroxide (5 mmol) in *N*, *N*-dimethylformamide (15 mL) were stirred for 3 h at r.t. and then acidified with hydrochloric acid (1N). The resulting solid was collected and recrystallized from ethanol to give **15**.

The Synthesis of 2-(1-Methylbenzoimidazol-2-l)-3-methylthio-3-thioxopropanenitrile (21)

Equimolar amounts of 2-(1-methylbenzimidazol-2-yl)ethanenitrile, carbon disulfide, and potassium hydroxide (5 mmol) in *N*, *N*-dimethylformamide (15 mL) were stirred for 3 h at r.t. Methyl iodide

TABLE II Spectra of Some Selected Synthesized Compounds

Compound no.	^{1}H NMR and IR Spectra
3	^{13}C NMR: δ = 34, 44, 115, 115, 116, 123, 123, 131, 139, 141, 150, 196. ^{1}H NMR: δ = 3.72 (s, 1H), 3.82 (s, 1H), 7.41–7.45 (m, 3H), and 8.20–8.24 (d, 1H). IR: 3076 (CH, aromatic), 2987 (CH, aliphatic), 2217 (CN), 1706 (CO), and 1634 (C=N).
5a	^{13}C NMR: δ = 28, 33, 115, 115, 123, 123, 129, 129 131, 136, 139, 141, 143, 159, 191. ^{1}H NMR: δ = 2.23 (s, 3H), 3.45 (s, br., 2H), 7.38–7.49 (m, 2H), 7.73–7.77 (d, 1H), and 8.22–8.26 (1H). IR: 3444, 3322 (NH_2) and 1710, 1635 (CO's).
5b	^{13}C NMR: δ = 14, 61, 34, 109, 115, 115, 123, 123, 129, 130, 131, 138, 141, 142, 159, 161. ^{1}H NMR: δ = 1.37 (t, 3H), 3.64 (s, 3H), 4.30 (q, 2H), 6.82 (s, br., 1H), 7.41–7.50 (m, 1H), 7.73–7.78 (d, 2H) and 8.33–8.38 (d, 1H). IR: 3449, 3339 (NH_2), 3061 (CH), 2971 (CH), 1706, 1666 (CO's), and 1633 (C=N).
5c	3.64 (s, 3H), 6.82 (s, 2H) and 7.27–8.31 (m, 9H). IR: IR: 3444, 3322 (NH_2), 2174 (CN), and 1710, 1635 (CO's)
5d	^{1}H NMR: δ = 3.54 (s, 3H), 7.19 (s, br., 2H), 7.42–7.54 (m, 2H), 7.77–7.80 (d, 1H), and 8.26–8.30 (d, 1H). IR: 3444, 2360 (NH_2), 2172 (CN) and 1707, 1635 (CO's).
12a	^{1}H NMR: δ = 3.70 (s, 3H), 7.47–8.37 (m, 5H) and 12.82 (s, br., 1H). IR: 3450 (OH), 17407, 1662 (CO's), and 1625 (C=N).
12b	^{1}H NMR: δ = 3.70 (s, 3H), 3.06 (s, 1H), 6.94 (s, br., 2H), 7.34–8.37 (m, 2H), 7.70–7.74 (d, 1H), and 8.21–8.25 (d, 1H). IR: 3434, 3305 (NH_2), 1732 (CO) and 1625 (C=N).
15	^{1}H NMR: δ = 2.18 (s, 3H), 3.20 (s, 3H), 6.80 (s, br., 1H), 7.18–7.34 (m, 4H) and 14.08 (s, br., 1H). IR: 3307 (NH), 2179 (CN), and 1625 (C=N).
18a	^{1}H NMR: δ = 1.4 (t, J = 7 Hz, 3H), 3.0 (s, 3H), 4.4 (t, J = 7 Hz, 2H), and 7.0–8.0 (m, 9H). IR: 2200 (CN) and 1710 (CO).
18b	^{1}H NMR: δ = 2.6 (s, 3H), 3.0 (s, 3H), and 7.0–8.0 (m, 9H). IR: 2200 (CN) and 1680 (CO).
21	^{1}H NMR: δ = 2.25 (s, 3H), 2.47 (s, 1H), 3.36 (s, 3H), 7.38–7.49 (m, 2H), 7.73–7.77 (d, 1H), 8.22–8.26 (1H). IR: 3327 (NH) and 2216 (CN).
25a	^{1}H NMR: δ = 1.4 (t, J = 7 Hz, 3H), 4.4 (t, J = 7 Hz, 2H) and 7.2-8.1 (m, 9H). IR: 2195 (CN) and 1720 (CO).
25b	^{1}H NMR: δ = 2.5 (s, 3H) and 7.2–8.1 (m, 9H). IR: 2188 (CN) and 1701 (CO).

(0.71 g, 0.32 mL) was added with stirring; the resulting solid was collected and recrystallized from *N*, *N*-dimethylformamide to give **21** as yellow crystals (Tables I and II).

The Synthesis of 2,3-Dihydro-1,3,4-thiadiazole Derivatives 18a,b and 25a,b

Method A

A mixture of the appropriate **15**, the appropriate hydrazonoyl chlorides **16a**,**b**(5 mmol each), and triethylamine (0.75 mL, 0.005 mol) in ethanol (20 mL) was stirred for 30 min. The resulting product was collected and recrystallized from the proper solvent to give 2,3-dihydro-1,3,4-thiadiazoles **18a**,**b** and **24a**,**b**, respectively (Tables I and II).

Method B

An equimolar amount of the appropriate hydrazonoyl chlorides **16a**,**b**, methylcarbodithioate **21** (or **26**[17]), and triethylamine (5 mmol, each) in ethanol (15 mL) was stirred at r.t. for 1 h. The resulting solid was collected and recrystallized from ethanol to give compounds **18a**, **18b**, **25a**, and **25b**, respectively.

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