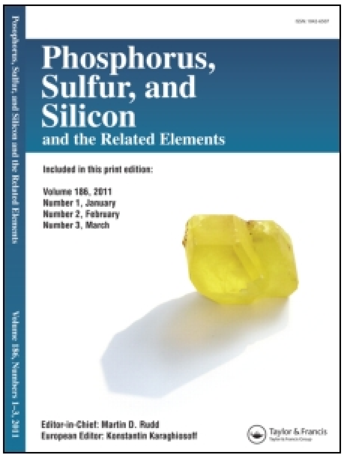

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REACTIONS WITH HYDRAZONOYL HALIDES XIV[1]. A CONVENIENT SYNTHESIS OF 2,3-DIHYDRO- 1,3,4-THIADIAZOLE DERIVATIVES

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REACTIONS WITH HYDRAZONOYL HALIDES XIV[1]

A Convenient Synthesis of 2,3-Dihydro- 1,3,4-Thiadiazole Derivatives

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Hydrazonoyl halides react with methyl arylmethylenehydrazinecarbodithioate in the presence of triethylamine to give 2,3-dihydro-1,3,4-thiadiazoles.

Keywords: Hydrazonoyl halides; Nitrilimine; 1,3-Dipolar cycloaddition; 2,3-Dihydro-1,3,4-thiadiazole; Hydrazinecarbodithioates; Aldehydes

INTRODUCTION

Hydrazonoyl halides are versatile reagents which have been extensively utilized in heterocyclic synthesis.[2–4] No publications have appeared in the literature dealing with their reactions with alkyl arylmethylenehydrazinecarbodithioates derivatives. In continuation of our interest in the chemistry of hydrazonoyl halides,[5–10] we report herein their utility in the convenient and efficient synthesis of thiadiazoline derivatives. It is reported that 1,3,4-thiadiazoles have applications in different areas[11] as antibacterial, antitumour, anti-inflammatory agents, pesticides, dyes, lubricants and analytical reagents.

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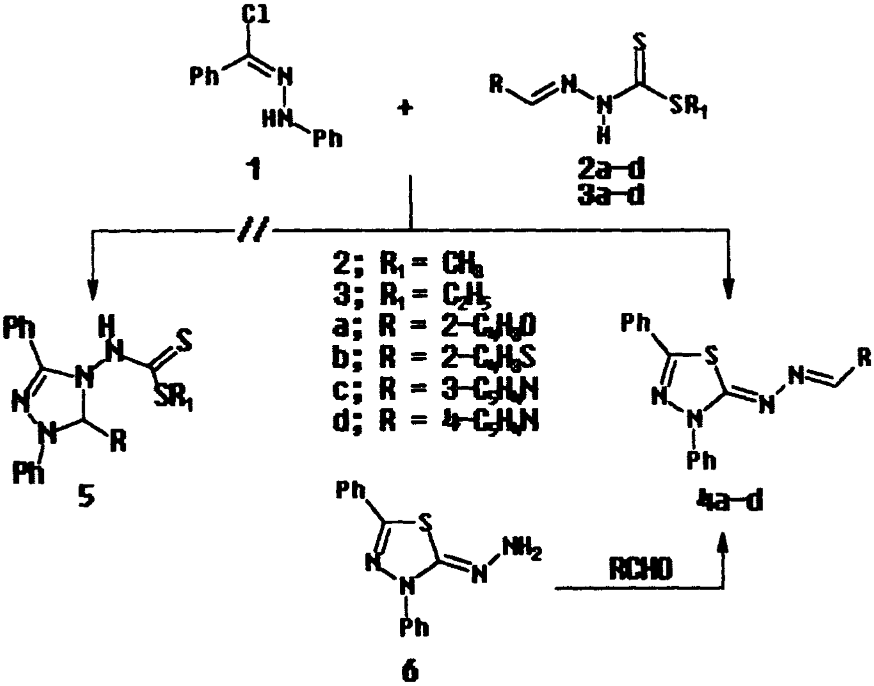
*Corresponding author.

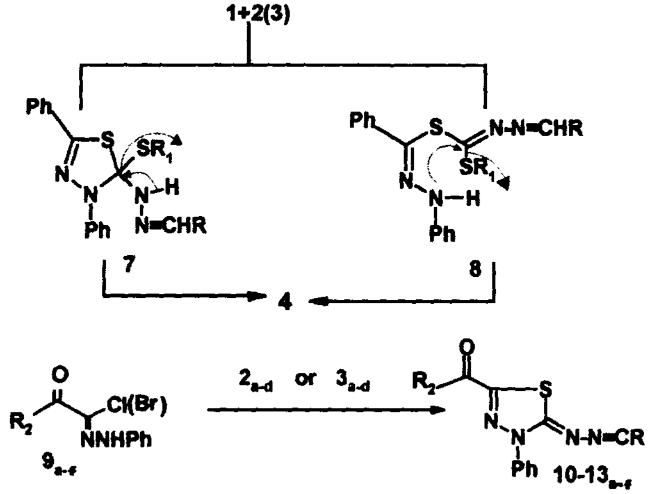


SCHEME 1

RESULTS AND DISCUSSION

The reaction of N-phenylbenzhydrazonoyl chloride (1) with methyl furylmethylenehydrazinecarbodithioate (2a), in ethanol in the presence of triethylamine, afforded a product which analyzed correctly for $C_{19}H_{14}N_4OS$, 4a. The structure of 4a was inferred from its spectral data. Thus, the IR spectrum of 4a showed no absorption bands around 3500–3100 cm^{-1} corresponding to the NH group. The ^1H-NMR spectrum of 4a revealed a multiplet at δ(ppm) 6.41–7.72(m, 13H, aromatic and furan protones) and 7.96(s, 1H, CH = N) corresponding to aromatic and furan protons and no signals appeared attributable to the methyl and NH protons. The structure of 4a was further confirmed by its alternative synthesis. Thus, treatment of **1** with ethyl furylmethylenehydrazinecarbodithioate 3a, at room temperature in ethanolic triethylamine solution, gave a product identical in all respects (m.p., mixed m.p., IR, ^1H-NMR and MS) with 4a (*cf.* Scheme 1).

Unequivocal support for the structure of 4a was achieved *via* the reaction of 2-hydrazino-3,5-diphenyl-1,3,4-thiadiazoline[12,13] (6) with furfural in ethanol to



10, R= 2-C_4H_3O a, R_2= EtO d, R_2= Ph
11, R= 2-C_4H_3S b, R_2= PhNH e, R_2= 2-C_4H_3O
12, R= 3-C6H4N c, R_2= CH_3 f, R_2= 2-C_4H_3S
13, R= 4-C_6H_4N

SCHEME 2

afford a product formulated as the thiadiazoline derivative **4a**. Evidence for the proposed structure was provided on the basis of elemental analysis and spectral data studies. Accordingly, structure **5** was excluded.

The formation of **4a** can be explained *via* elimination of methyl mercaptan (or ethyl mercaptan) from the corresponding cycloadduct **7**, which is assumed to be formed from the 1,3-dipolar cycloaddition of **1** to the C=S double bond in **2a** or **3a** (Scheme 2). Alternatively, the formation of **4a** can also be explained by the stepwise path involving substitution to give the acyclic hydrazone **8**. Cyclization of the latter is achieved by elimination of methyl mercaptan (or

11d: M^{+1} = 310(11.4%), M^+ = 309(43.6%), M^{+1} - $C_5H_4N_2S$ =267(42.6%) and M^+-$C_{15}H_{10}N_4S$ = 96(100%).

12b: M^{+2} = 402(4.2%), M^{+1} = 401(12.8%), M^+ = 400(46.4%), M^{+1}- $C_6H_5N_3$ = 282(25.5%) and M^+- $C_{15}H_{11}N_5OS$ = 91(100%).

SCHEME 3

TABLE I Characterization of the newly synthesized compounds

Compd.	*M.p.°C*	*Mol. Formula*	*Analyses % Found/Calcd.*			
No.	*Solvent*	*M.Wt.*	*%C*	*%H*	*%N*	*%S*
3b	140–2	$C_8H_{10}N_2S_3$	41.50	4.30	12.00	41.70
	EtOH	(230.37)	41.71	4.38	12.16	41.76
3c	162–4	$C_9H_{11}N_3S_2$	48.10	4.80	18.90	28.50
	EtOH	(225.34)	47.97	4.92	18.65	28.46
3d	156–8	$C_9H_{11}N_3S_2$	47.90	4.90	18.70	28.30
	EtOH	(225.34)	47.97	4.92	18.65	28.46
4a	135–6	$C_{19}H_{14}N_4OS$	65.60	3.90	16.00	9.10
	EtOH	(346.41)	65.88	4.07	16.17	9.26
4b	166–7	$C_{19}H_{14}N_4S_2$	62.80	4.00	15.20	17.50
	HOAc	(362.48)	62.96	3.89	15.46	17.69
4c	195–7	$C_{20}H_{15}N_5S$	67.00	4.10	19.70	9.10
	dil. HOAc	(357.44)	67.21	4.23	19.59	8.97
4d	194–5	$C_{20}H_{15}N_5S$	67.10	4.30	19.40	9.00
	dil. HOAc	(357.44)	67.21	4.23	19.59	8.97
10a	108–10	$C_{16}H_{14}N_4O_3S$	55.90	4.00	16.00	9.50
	EtOH	(342.38)	56.13	4.12	16.36	9.37
10b	168–70	$C_{20}H_{15}N_5O_2S$	61.80	4.00	17.70	8.40
	dil. HOAc	(389.44)	61.68	3.88	17.98	8.23
10c	177–9	$C_{15}H_{12}N_4O_2S$	57.50	3.80	17.60	10.10
	Dioxan	(312.35)	57.68	3.87	17.94	10.27
10d	149–50	$C_{20}H_{14}N_4O_2S$	63.90	3.70	15.20	8.40
	EtOH/Dioxan	(374.42)	64.16	3.77	14.96	8.56
10e	200–202	$C_{18}H_{12}N_4O_3S$	59.10	3.10	15.20	8.90
	HOAc	(364.39)	59.33	3.32	15.38	8.80
10f	165–6	$C_{18}H_{12}N_4O_2S_2$	57.00	3.00	14.90	17.00
	EtOH	(380.45)	56.83	3.18	14.73	16.86
11a	112–4	$C_{16}H_{14}N_4O_2S_2$	53.40	4.10	15.40	17.80
	EtOH	(358.44)	53.61	3.94	15.63	17.89
11b	155–7	$C_{20}H_{15}N_5OS_2$	59.00	3.70	17.40	15.90
	HOAc	(405.50)	59.24	3.73	17.27	15.81
11c	165–7	$C_{15}H_{12}N_4OS_2$	55.00	3.50	16.80	19.40
	EtOH/Dioxan	(328.42)	54.86	3.68	17.06	19.53
11d	160–2	$C_{20}H_{14}N_4OS_2$	61.20	3.40	14.10	16.20
	HOAc	(390.49)	61.52	3.61	14.35	16.42
11e	188–90	$C_{18}H_{12}N_4O_2S_2$	57.00	3.10	14.90	16.70
	HOAc	(380.45)	56.83	3.18	14.73	16.86
11f	169–70	$C_{18}H_{12}N_4OS_3$	54.20	2.90	13.90	24.00
	HOAc	(396.50)	54.52	3.05	14.13	24.26
12a	191–3	$C_{17}H_{15}N_5O_2S$	57.50	4.10	19.60	9.00
	EtOH	(353.41)	57.78	4.28	19.82	9.07
12b	196–8	$C_{21}H_{16}N_6OS$	63.10	3.90	20.80	7.90
	HOAc	(400.47)	62.98	4.03	20.99	8.01
12c	165–6	$C_{16}H_{13}N_5OS$	59.10	3.90	21.80	10.00
	EtOH	(323.38)	59.43	4.05	21.66	9.92
12d	140–2	$C_{21}H_{15}N_5OS$	65.20	3.80	18.00	8.50
	HOAc	(385.45)	65.44	3.92	18.17	8.32
12e	207–8	$C_{19}H_{13}N_5O_2S$	60.60	3.30	18.40	8.40
	HOAc	(375.41)	60.79	3.49	18.66	8.54
12f	177–9	$C_{19}H_{13}N_5OS_2$	58.00	3.30	18.00	16.40
	EtOH	(391.48)	58.29	3.35	17.89	16.38
13a	132–4	$C_{17}H_{15}N_5O_2S$	57.50	4.10	20.10	9.00
	EtOH	(353.41)	57.78	4.28	19.82	9.07
13b	217–9	$C_{21}H_{16}N_6OS$	63.10	3.90	20.80	7.90

TABLE I *continued*

Compd. No.	*M.p.°C Solvent*	*Mol. Formula M.Wt.*	*Analyses % Found/Calcd.* %C	%H	%N	%S
	Dioxan	(400.47)	62.98	4.03	20.99	8.01
13c	167–8	$C_{16}H_{13}N_5OS$	59.20	4.10	21.40	10.00
	EtOH/Dioxan	(323.38)	59.43	4.05	21.66	9.92
13d	168–70	$C_{21}H_{15}N_5OS$	65.30	4.00	17.90	8.20
	EtOH	(385.45)	65.44	3.92	18.14	8.32
13e	218–20	$C_{19}H_{13}N_5O_2S$	61.00	3.40	18.50	8.40
	HOAc	(375.41)	60.79	3.49	18.66	8.54
13f	169–71	$C_{19}H_{13}N_5OS_2$	58.00	3.20	18.00	16.50
	EtOH	(391.48)	58.29	3.35	17.89	16.38

ethyl mercaptan). All attempts to isolate either the cycloadduct **7** or the open-chain arylhydrazone **8** were unsuccessful.

Similarly, Compounds **2b–d** (or **3a–d**) reacted with hydrazonoyl halides **1** and **9a–g**, in ethanolic triethylamine solution, to give the corresponding thiadiazoline derivatives **4b–d** and **10–13a–g**, respectively. Scheme 3 shows the mass spectrometric fragmentation of compounds **11d** and **12b**:

EXPERIMENTAL

All melting points were uncorrected. IR spectra were recorded (KBr) on a Shimadzu FT-IR 8201 PC spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer and chemical shifts were expressed in δ (ppm) units using TMS as internal reference. Mass spectra were recorded on a GC-MS QP1000 EX Shimadzu, Japan. Elemental analyses were carried out at the Microanalytical Center of the University of Cairo, Giza, Egypt. Compounds **2a–d**,[14] **3a**,[15] **1**[16] and **9a–g**[17–22] were prepared as previously described.

Synthesis of 3b–d

General procedure

Ethyl hydrazinecarbodithioate (0.7 g, 5 mmol) and the appropriate aldehyde (2-thiophene aldehyde, 3-pyridine aldehyde and 4-pyridine aldehyde) (5 mmol) were dissolved in 2-propanol (20 ml). The solutions were heated under reflux for 3 hrs. After cooling, the solid was collected, washed with cold 2-propanol and crystallized from ethanol to give compounds **3b–d**, in almost quantitative yields. The analytical and spectral data for compounds **3b–d** are listed in Table I and II.

TABLE II Spectroscopic data for selected compounds from Table I.

Compd.	ν_{max}/cm^{-1}	δ_H/ppm
3b	3360(NH), 2964(CH_3), 2942(CH_2), 1612(C=N)	1.33(t, 3H, $-CH_2-\underline{CH_3}$); 2.41(q, 2H, S-$\mathit{CH_2}$-CH_3); 7.65–7.65(m, 3H, thiophene); 7.96(s, 1H, CH=N) and 11.14(s, 1H, NH).
3c	3460(NH), 2964(CH_3), 2924(CH_2), 1612(C=N)	1.31(t, 3H, $-CH_2-\underline{CH_3}$); 2.39(q, 2H, S-$\underline{CH_2}$-CH_3); 7.15–8.21(m, 4H, pyridine); 8.02(s, 1H, CH=N) and 11.15(s, 1H, NH).
3d	3465(NH), 2961(CH_3), 2920(CH_2), 1595(C=N)	1.30(t, 3H, $-CH_2-\underline{CH_3}$); 2.25(q, 2H, S-$\underline{CH_2}$-CH_3); 7.32–8.60(m, 4H, pyridine); 7.96(s, 1H, CH=N) and 11.10(s, 1H, NH).
4a	1624(C=N), 1610(C=C)	6.41–7.72(m, 13H, ArH's and furan H's) and 7.96(s, 1H, CH=N).
4b	1606(C=N), 1595(C=C)	7.21–7.81(m, 13H, ArH's and thiophene H's) and 7.91 (s, 1H, CH=N).
4c	1604(C=N), 1586(C=C)	7.31–8.51(m, aromatic, pyridine and CH=N protons).
4d	1606(C=N), 1595(C=C)	7.25–8.39(m, aromatic, pyridine and CH=N protons).
10a	3115(CH), 1713(CO), 1619(C=N).	1.25(t, 3H, $-CH_2-\underline{CH_3}$); 4.65(q, 2H, $-\underline{CH_2}-CH_3$); 6.52–7.52(m, 8H, ArH's and furan H's); 7.92(s, 1H, CH=N)
10b	3279(NH), 1662(CO), 1618(C=N).	6.41–8.11(m, ArH's, furan H's, NH and CH=N).
10c	1683(CO), 1614(C=N).	2.63(s, 3H, CH_3CO) and 6.38–7.56(m, 8H, ArH's and furan H's) and 7.88(s, 1H, CH=N).
10f	1660(CO), 1613(C=N).	6.35–7.46(m, 11H, ArH's, furan H's and thiophene H's) and 7.91(s, 1H, CH=N).
11a	1703(CO), 1601(C=N).	1.22(t, 3H, $-CH_2-\underline{CH_3}$); 4.46(q, 2H, $-\underline{CH_2}-CH_3$); 7.21–7.76(m, 8H, ArH's and thiophene H's) and 7.88(s, 1H, CH=N)
11c	1684(CO), 1610(C=N).	2.58(s, 3H, CH_3CO) and 7.26–7.90(m, 9H, ArH's, thiophene H's and CH=N).
11d	1638(conjugated CO), 1617(C=N), 1598(C=C)	7.15–8.04(m, ArH's, thiophene H's and CH=N).
12b	3327(NH), 1670(CO), 1606(C=N).	7.15–8.04(m, ArH's, pyridine H's and CH=N).
12c	1683(CO), 1613(C=N).	2.51(s, 3H, CH_3CO) and 7.21–9.10(m, 10H, ArH's,

TABLE II *continued*

Compd.	ν_{max}/cm^{-1}	δ_H/ppm
		pyridine H's and CH = N).
13a	1738(CO), 1613(C = N).	1.21(t, 3H, -CH_2- $\underline{CH_3}$); 4.21(q, 2H, - $\underline{CH_2}$-CH_3); 7.20–9.41(m, 10H, ArH's, pyridine H's and CH = N).
13c	1676(CO), 1611(C = N).	2.56(s, 3H, CH_3CO) and 7.26–9.14(m, 10H, ArH's pyridine H's and CH = N).
13e	1643(CO), 1614(C = N).	6.37–8.91(m, ArH's, furan H's, pyridine H's and CH = N).

Synthesis of 2,3-dihydro-1,3,4-thiadiazoles 4a–d and 10–13a–f

General procedure

To a solution of the appropriate **2**a–d or **3**a–d (5 mmol) and the appropriate hydrazonoyl halides **1** and **9**a–f (5 mmol) in ethanol (20 ml) was added triethylamine (0.7 ml, 5 mmol), at room temperature with stirring. Stirring was continued for 2 hrs. The formed precipitate was collected, washed with ethanol and crystallized from the appropriate solvent. The analytical and spectral data for compounds **4**a–d and **10–13**a–f are listed in Table I and II.

Synthesis of 4a–d

Alternative method

Equimolar amounts of each of 1,3-diphenyl-2-hydrazino-1,3,4-thiadiazoline (**6**) and the appropriate aldehyde (2-thiophene aldehyde, 3-pyridine aldehyde and 4-pyridine aldehyde) (5 mmol each) in 2-propanol (20 ml) were heated under reflux for 2 hrs. After cooling, the formed precipitate, in each case, was collected, washed with cold 2-propanol and crystallized from the appropriate solvents. The compounds prepared by this method were identical in all respects (m.p., mixed m.p., IR and ^1H NMR) with those obtained above.

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