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Reactions with Hydrazonoyl Halides XXVIII*: Synthesis of Some 2-Thiazolylimino-2,3-Dihydro-1,3,4-thiadiazoles

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ABSTRACT: *Hydrazonoyl halides have been caused to react with each of methyl 5-ethoxycarbonyl-4-methylthiazole-2-aminothiocarbamate, benzyl 5-ethoxycarbonyl-4-methylthiazole-2-aminothiocarbamate, and 5-ethoxycarbonyl-4-methylthiazol-2-ylphenylthiourea in the presence of triethylamine to give 2-imino-(5-ethoxycarbonyl-4-methyl)thiazolyl-2,3-dihydro-1,3,4-thiadiazoles in good yields. Structures of the new compounds were elucidated on the basis of elemental analyses, spectral data, and alternative methods of synthesis whenever possible.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:213–217, 2000

INTRODUCTION

A large number of thiazole derivatives have been found to exhibit pharmacological activity [1]. 1,3,4-thiadiazoles were used in the pharmaceutical area as antibacterial reagents similar to those of the well-known sulfanamide drugs [2]. In continuation of our interest in the chemistry of hydrazonoyl halides [3–6], we have investigated the reaction of the nitrilium imide **9** (which was generated in situ from hydrazonoyl chloride **3** with triethylamine) with alkyl 5-ethoxycarbonyl-4-methylthiazol-2-ylcarbodithioates **2.**

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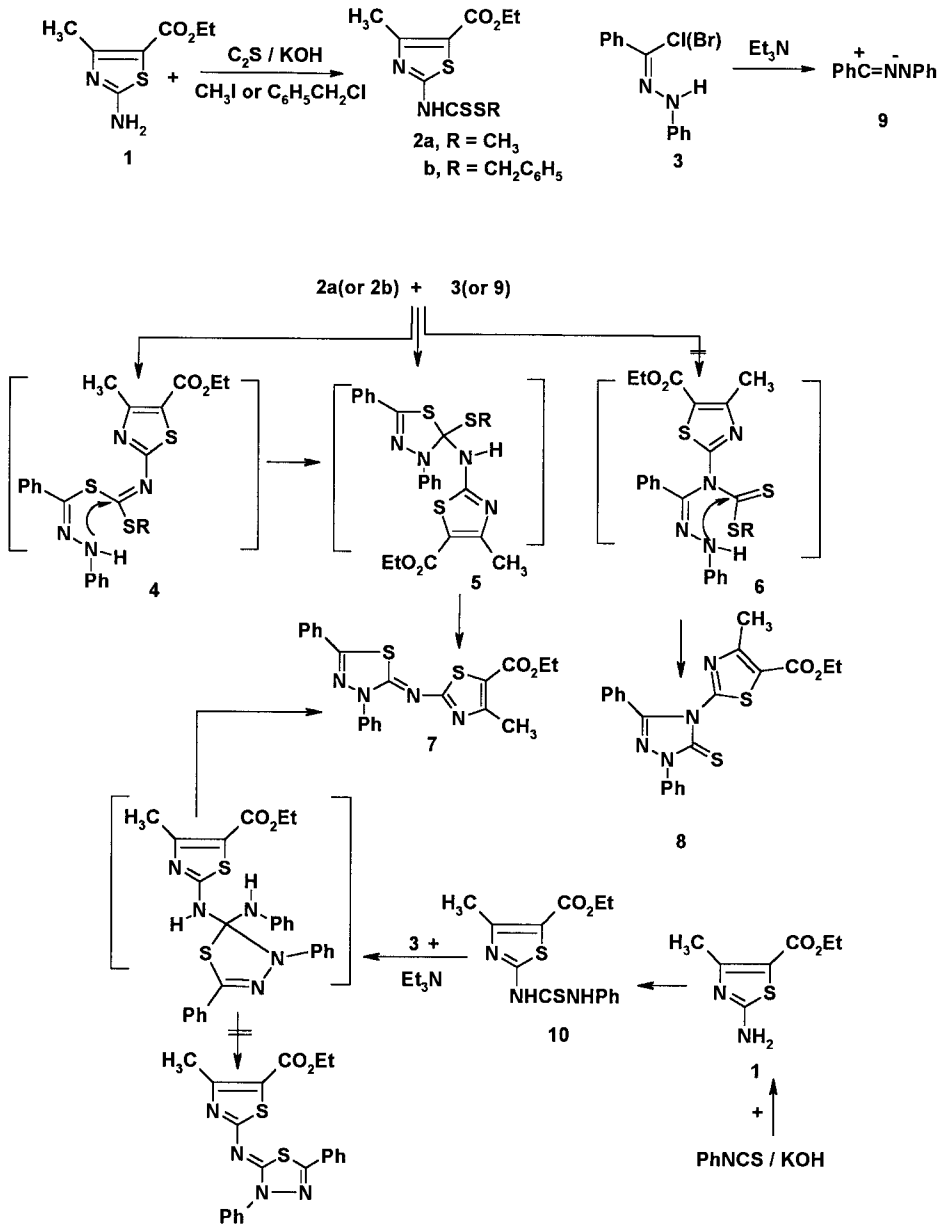
RESULTS AND DISCUSSION

The reaction of equimolar amounts of the 2-amino-5-ethoxycarbonyl-4-methylthiazole, carbon disulfide, and potassium hydroxide in *N,N*-dimethylformamide with methyl iodide and benzyl chloride, respectively, gave the corresponding alkyl thiocarbamates **2a,b** in excellent yields. The elemental and spectral data of each **2** are consistent with the assigned structures.

Compound **2** is considered to be a versatile reagent for the construction of heterocyclic systems. Thus, **2a** reacted with an equimolar amount of C-phenyl-*N*-phenylhydrazonoyl chloride (**3**) to produce a product that conceivably could be formulated as 3,5-diphenyl-2-(5′-ethoxycarbonyl-4′-methyl)-2′-thiazolylimino-2,3-dihydro-1,3,4-thiadiazole (**7**) or 1,3-diphenyl-4-(5′-ethoxycarbonyl-4′-methyl)thiazolyl-1,2,4-triazole-5-thione (**8**). The same product was also obtained when the hydrazonoyl chloride **3** was treated with benzyl thiocarbamate **2b** (cf. Scheme 1). The structure **8** was excluded from further consideration on the following basis: (1) an authentic sample of **7** was obtained by reaction of **3** with 5-ethoxycarbonyl-4-methylthiazol-2-ylphenylthiourea **10**; (2) the IR spectrum of the product revealed the absence of any bands at 1200 cm^{-1} attributable to a C = S group; and (3) the product **7** was recovered unchanged after boiling with mercuric oxide in acetic acid.

Two possible pathways can account for the formation of **7.** 1,3, Addition of the thiol tautomer of **2** to the nitrile imineq **3** can give the thiohydrazonate ester **4,** which undergoes nucleophilic cyclization to



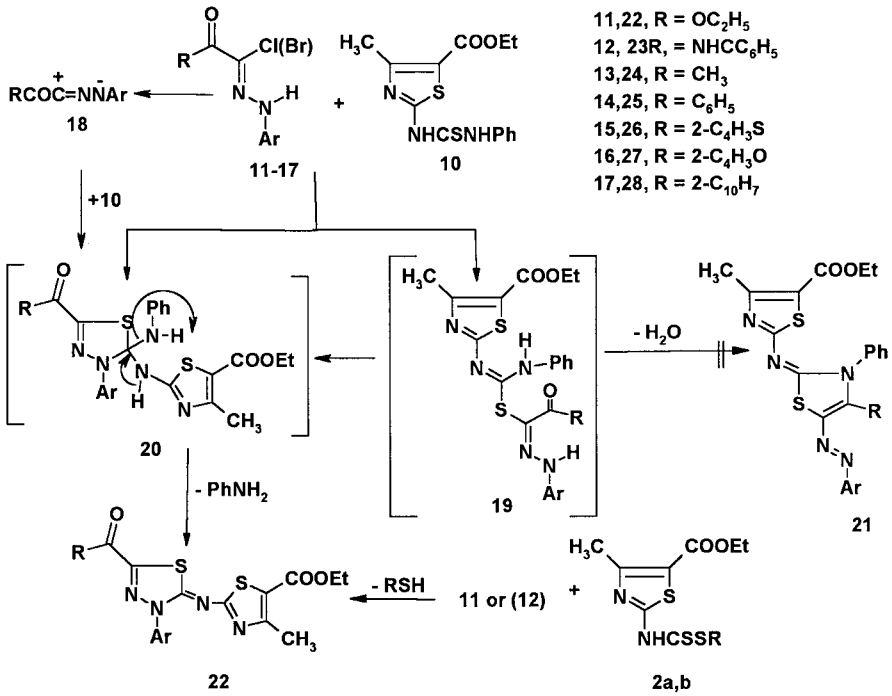
SCHEME 1

yield **5,** which then affords **7** by loss of RSH. Alternatively, 1,3-cycloaddition of the nitrilum imide **9** to the C=S tautomer of **2** can give **5** directly.

α-Keto hydrazonoyl halide **11a** readily reacted with the thiazolylthiourea **10** in ethanol containing triethylamine to afford 5-ethoxycarbonyl-2-(5′-ethoxycarbonyl-4′-methyl)thiazo-2′-ylimino-3-phenyl-2,3-dihydro-1,3,4-thiadiazole **22a** or the thiazole form **21** (cf. Scheme 2). However, the thiadiazole structure **22** was preferred over the thiazole form on the basis of spectroscopic data and the independent synthesis of **22.** Thus, the IR (cm^{-1}) spectrum of **22a** revealed the absorption band at 22, 1706 (CO). ^1H NMR spectra showed signals at δ = 1.35(t, 3H), 1.41(t, 3H), 2.65(s, 3H), 4.21(q, 2H), 4.42(q, 2H) and 7.32–7.89(m, 5H), and the mass spectrum revealed peaks at *m/e* = 418, 346, 274, 177, and 133.

Product **22a** could be obtained via an independent stepwise synthetic route involving the reaction of the appropriate thiocarbamate **2a,b** with an equimolar amount of hydrazonoyl chloride **11a** in the presence of triethylamine to give a single product found to be identical in all respects with **22a** (cf. Scheme 2).

Similarly, the appropriate hydrazonoyl halides **12–17** reacted with each of the thiocarbamates **2a** or



SCHEME 2

2b or with the thiazolylphenylthiourea **10** to give the corresponding 2,3-dihydrothiadiazoles **22–28,** respectively (cf. Tables 1 and 2).

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 200 MHz spectrometer, and chemical shifts were expressed in δ units using TMS as internal reference. MS spectra were recorded on a Shimadzu mass spectrometer, GC-MS QP1000 EX, operating at 70 eV. Elemental analyses were carried out at the Microanalytical Center of the University of Cairo, Giza, Egypt. Hydrazonoyl halides **3** and **11–17** [7–16] were prepared as previously reported.

Alkyl imino-5-Ethoxycarbonyl-4-methylthiazol-2-imino-thiocarbamate **2a,b**

A mixture of equimolar amounts of 2-amino-5-ethoxycarbonyl-4-methylthiazole [17], carbon disulfide, and potassium hydroxide (0.01 mol, each) in *N,N*-dimethylformamide (15 mL) was boiled under reflux at 80°C for 2 hours. The reaction mixture was cooled to 0°C, and then the appropriate alkyl halide (methyl iodide or benzyl chloride) (0.01 mol) was added dropwise with stirring. Stirring was continued for 1 hour at room temperature, and the resulting solid was collected and crystallized from ethanol to give **2a** and **2b,** respectively (cf. Tables 1 and 2).

5-Ethoxycarbonyl-4-methylthiazol-2-ylphenylthiourea (**10**)

A mixture of 2-amino-5-ethoxy-4-methylthiazole, phenyl isothiocyanate, and potassium hydroxide in *N,N*-dimethylformamide (20 mL) was stirred at room temperature for 6 hours. The reaction mixture was diluted with water (30 mL) then acidified with dilute acetic acid. The resulting solid was collected and crystallized from acetic acid to give **10** in 78% yield (cf. Tables 1 and 2).

Synthesis of 2-N-(5'-ethoxycabonyl-4'-methyl)-2'-thiazolyl-2,3-dihydro-1,3,4-thiadiazoles 7 and **22–28**

General Procedure. Triethylamine (0.75 mL, 5 mmol) was added to a solution of the appropriate **2a** or **2b,** (5 mmol) and the appropriate hydrazonoyl halide **3** or **11a,b–17a,b** (5 mmol) in ethanol (20 mL) with stirring at room temperature for 1 hour. The formed precipitate was collected, washed with ethanol, and crystallized from acetic acid or ethanol. Analytical and spectroscopic data of compounds **7** and **22a,b–28a,b** are listed in Tables 1 and 2.

TABLE 1 Characterization Data of the Newly Synthesized Compound

Compound	m.p.(°C)	Yield (%) Color	Mol. Formula, Mol. Wt.	% Analysis C	% Analysis H	Calcd./Found N	Calcd./Found S
2a	122–123	Colorless	$C_9H_{12}N_2O_2S_3$	39.11	4.38	10.14	34.80
			276	39.20	4.50	10.30	34.60
2b	150–152	Colorless	$C_{15}H_{16}N_2O_2S_3$	51.11	4.58	7.95	27.29
			352.50	51.00	4.80	8.10	27.10
7	258–260	Yellow	$C_{21}H_{18}N_4O_2S_2$	59.70	4.29	13.26	15.18
			422.53	59.90	4.10	13.40	15.30
10	188–90	beige	$C_{14}H_{15}N_3O_2S_2$	52.52	4.70	13.07	19.95
			321.40	52.50	4.80	12.80	20.10
22a	173–175	Yellow	$C_{18}H_{18}N_4O_4S_2$	51.66	4.34	13.39	15.32
			418.50	51.70	4.40	13.80	15.20
22b	185–187	Yellow	$C_{19}H_{20}N_4O_4S_2$	52.76	4.66	12.95	14.83
			432.52	52.60	4.40	13.10	15.00
23a	232–235	Yellow	$C_{22}H_{19}N_5O_3S_2$	56.76	4.11	15.04	13.77
			465.56	56.60	4.00	14.80	13.90
23b	233–235	Yellow	$C_{23}H_{21}N_5O_3S_2$	57.60	4.41	14.60	13.37
			479.50	57.40	4.20	14.80	13.50
24a	245–247	Yellow	$C_{17}H_{16}N_4O_3S_2$	52.56	4.15	14.42	16.51
			388.47	52.60	4.00	14.20	16.40
24b	198–200	Yellow	$C_{18}H_{18}N_4O_3S_2$	53.71	4.51	13.92	15.93
			402.50	53.50	4.40	13.70	16.10
25a	203–205	Yellow	$C_{22}H_{18}N_4O_3S_2$	58.65	4.03	12.44	14.23
			450.54	58.60	3.80	12.60	14.30
25b	220–222	Yellow	$C_{23}H_{20}N_4O_3S_2$	59.47	4.34	12.06	13.80
			464.57	59.60	4.20	12.20	13.60
26a	257–259	Orange	$C_{20}H_{16}N_4O_3S_3$	52.61	3.35	12.27	21.07
			456.57	52.70	3.50	12.10	21.20
27a	**272–274**	Yellow	$C_{20}H_{16}N_4O_4S_2$	54.53	3.66	12.72	14.56
			440.50	54.70	3.70	12.50	14.30
28a	235–237	Yellow	$C_{26}H_{20}N_4O_3S_2$	62.38	4.03	11.19	12.81
			500.60	62.20	4.10	11.10	12.60

Ar, a = C_6H_5
Ar, b = 4 − $CH_3C_6H_4$

TABLE 2 IR and ^{1}H NMR Spectral Data of Some Newly Synthesized Compounds

Compound	$\nu_{max}(cm^{-1})$	$\delta_H(ppm)$
2a	2584(SH) and 1701(CO)	1.34(t, 3H), 2.53(s, 3H), 2.87(s, 3H), 4.28(q, 2H) and 12.67(s, 1H).
2b	2580(SH) and 1706(CO)	1.37(t, 3H), 2.64(s, 3H), 4.32(q, 2H), 4.53(s, 2H) 7.28–7.34(m, 5H) and 12.23(s, 1H).
7	1707(CO)	1.33(t, 3H), 2.61(s, 3H), 4.43(q, 2H) and 7.23–7.87(m, 10H).
22a	1722, 1706	1.34(t, 3H), 1.42(t, 3H), 2.73(s, 3H), 4.28(q, 2H), 4.49(q, 2H) and 7.42–7.87(m, 5H).
22b	1616, 1710	1.34(t, 3H), 1.41(t, 3H), 2.47(s, 3H), 2.72(s, 3H), 4.28(q, 2H), 4.44(q, 2H), 7.26–7.33(d, 2H) and 7.68–7.72(d, 2H).
23a	3345(NH), 1714(CO) and 1685(CO).	1.33(t, 3H), 2.75(s, 3H), 4.23(q, 2H) and 7.21–7.89(m, 10H).
23b	3340(NH), 1710(CO) and 1680(CO).	1.33(t, 3H), 2.45(s, 3H), 2.75(s, 3H), 4.23(q, 2H) and 7.21–7.89(m, 10H).
24a	1693, 1674(COs).	1.275(t, 3H), 2.63(s, 3H), 2.66(s, 3H), 4.23(q, 2H) and 7.56–6.86(m, 5H).
24b	1692, 1675(COs).	1.275(t, 3H), 2.47(s, 3H), 2.63(s, 3H), 2.66(s, 3H), 4.23(q, 2H) and 7.56–6.86(m, 4H).
25a	1708, 1651(COs).	1.34(t, 3H), 2.74(s, 3H), 4.28(q, 2H) and 7.45–8.37(m, 10H)

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