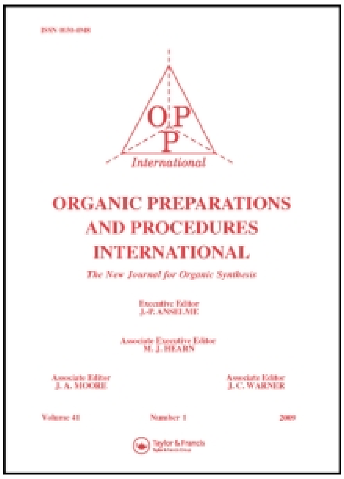

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MICROWAVE-ASSISTED REACTION OF HYDRAZONOYL HALIDES WITH CARBODITHIOIC ACID HYDRAZONES

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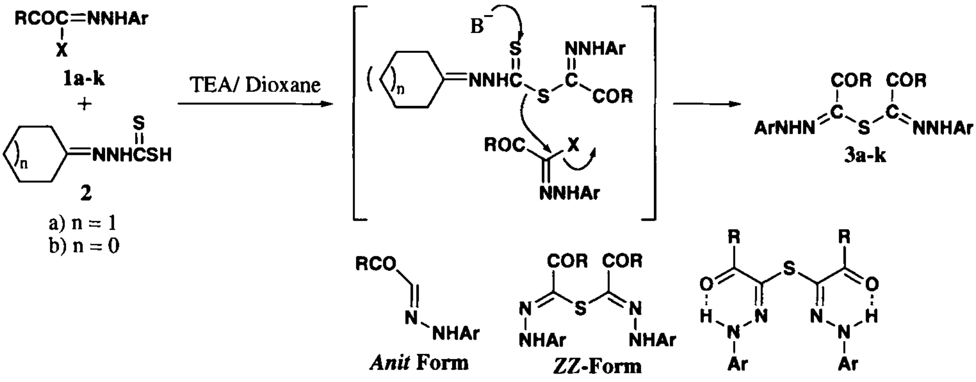
Hydrazonoyl halides are versatile reagents and their chemistry has received considerable attention.[1-3] In basic media, they generate nitrilimines that undergo a variety of 1,3-dipolar additions.[4-7] Hydrazonoyl halides are also active acylating agents and react with carbanionic species under mild conditions to yield alkylation products that readily cyclize into aromatic heterocycles.[8,9] Despite recent interest in microwave as energy source,[10-13] the utility of microwave in reactions of hydrazonoyl halides has received only limited study. In conjunction with our interest in adopting microwave heating in synthesis,[14-17] we now report the results of our study of the reactivity of hydrazonoyl halides **1a-k** toward hydrazone carbodithioic acids **2a,b** both under microwave irradiation and by conventional thermal heating. To our knowledge this reaction has not yet been investigated.

Heating hydrazonoyl halides **1a-k** with 2-cycloalkylidenehydrazine carbodithioic acids (**2a,b**) in dioxane in the presence of triethylamine for 1-2 minutes in a microwave oven, or 4-6 hours by conventional thermal heating, afforded products of condensation of the sulfur atom of **2** with two molecules of **1** to lead to **3a-k** as shown in *Table 1* (*Scheme 1*).



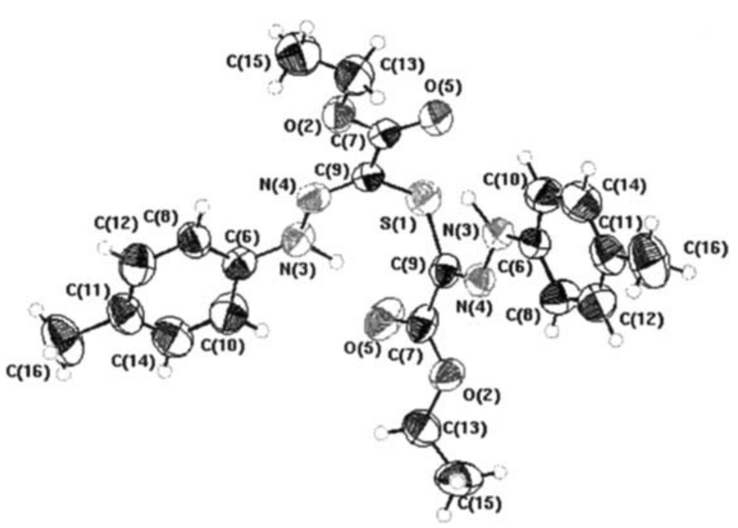
Scheme 1

Table 1. Formation of **3a-k** using Microwave and Conventional Heating Procedures

Cmpd	R	X	Ar	Microwave Irradiation Time (min)	Microwave Irradiation Yield (%)	Conventional Heating Time (h)	Conventional Heating Yield (%)
3a	EtO	Cl	C_6H_5	1.5	52	6	55
3b	EtO	Cl	4-MeC_6H_4	1.5	52	6	50
3c	EtO	Cl	4-ClC_6H_4	1.5	54	6	50
3d	CH_3	Cl	C_6H_5	1	50	6	60
3e	CH_3	Cl	4-MeC_6H_4	1	51	6	60
3f	CH_3	Cl	$4\text{-NO}_2C_6H_4$	1	52	6	62
3g	PhNH	Cl	C_6H_5	1	60	5	60
3h	PhNH	Cl	4-ClC_6H_4	1	62	5	62
3i	Ph	Br	C_6H_5	1	60	5	55
3j	Ph	Br	4-ClC_6H_4	1	63	6	55
3k	2-Thienyl	Br	4-ClC_6H_4	1.5	65	5	60

Compounds **3a-k** had been obtained earlier from reaction of **1** with cyanothioacetamide,[18] α-thiocarbamoylcinnamonitrile,[19] α,β-unsaturated thiolates,[20] benzoylthiosemicarbazide[21] and N-(5-substituted-1,2,4-triazol-3-yl)-N'-phenylthiourea with hydrazonoyl halides.[22]

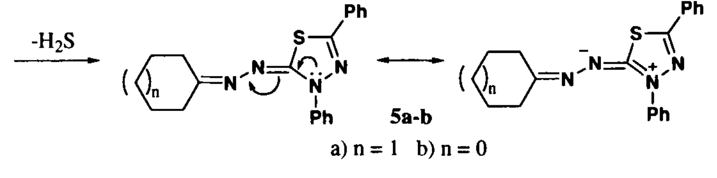
We believe that **3a-k** are formed *via* initial formation of the thiocarboxylic acid derivatives that are then attacked by a second molecule of **1** to yield final products **3a-k** (*cf. Scheme 1*). These products were believed earlier to exist in the *E,E*-hydrogen-bonded hydrazone form probably to account for appearance of low field NH at δ 11.3. However X-ray crystal structure determination (*Fig. 1*) shows that the reaction products, at least in solid state, prefer the *Z,Z* form. Recently Al-Awadi *et al.*[23] and Elnagdi *et al.*[24] have shown that arylhydrazonoketones also adopt an *anti* configuration in the solid state. Although structures **3** do not have a plane of symmetry as shown by IR that revealed two different bands for hydrazone NH at 3178, 3124, room temperature ^{1}H-NMR showed that all protons on both sides of the sulfur bridge resonate at the same field. This may be due to rapid free rotation around the sulfur bridge. As can be realized from X-ray both carbonyl C=O and NH bond lengths are in the expected range for non-hydrogen bonded functions. Thus, the low field NH is believed to result from efficient delocalization of nitrogen lone pair. This parallels similar recent assumptions made to account for appearance of hydrazone ^{1}H-NMR NH at low field in 2-arylhydrazonoketones.[24] The X-ray crystal structure determination of ethyl 2-[2-aza-1-(carbethoxy)-2-(4-methylphenylamino)vinylthio]-3-aza-3-(4-methylphenylamino) prop-2-enoate (**3b**) is shown in *Fig. 1*.



Crystal structure of **3b**

Fig. 1

In contrast to these compounds, C-phenylhydrazonoyl chloride **4** reacted with **2** under the same conditions to yield 2,3-dihydro-3,5-diphenyl-1,3,4-thiadiazole derivatives **5** (*Scheme 2*).

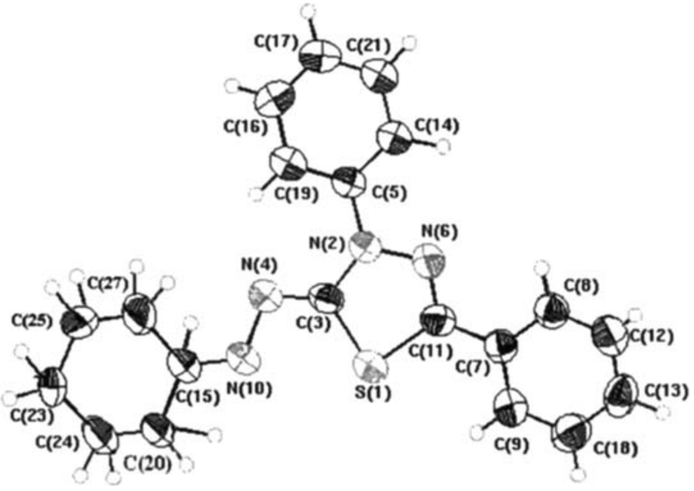


Scheme 2

Table 2. Formation of Compounds **5a-b** using Microwave and Conventional Heating Procedures

Cmpd	n	Microwave Irradiation		Conventional Heating	
		Time (min)	Yield (%)	Time (h)	Yield (%)
5a	1	1.5	80	6	85
5b	0	1.5	82	6	86

An X-Ray crystal structure determination confirmed that **5a** exists solely in a *transoid* form which is the most stable conformation at least in the solid state.



Crystal structure of **5a**

Fig. 2

The data clearly showed that the thiadiazole ring is planar and aromatic. Both ring-nitrogens showed bond angles for sp^2 hybridized nitrogen whereas the exocyclic nitrogen showed bond angle corresponding for an sp^3 nitrogen indicating that the nitrogen N-1 lone pair is extensively delocalized and the system has appreciable contribution of charge separated structure (*Fig. 2*, the ring numbered C(15), C(20) through C(27) is cyclohexylidene ring).

The dependence of the nature of the final product of reacting **2a,b** with hydrazonoyl halides may be accounted for in terms of different basicties of hydrazone NH in **1** and **4**. The latter is sufficiently nucleophilic and thus undergoes intramolecular cyclization affording (A) which then subsequently loses H_2S.

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EXPERIMENTAL SECTION

Melting points were recorded on Gallenkamp apparatus and are uncorrected. Infrared spectra (KBr) were determined on a Perkin-Elmer 2000 FT-IR system. ^1H NMR was obtained on a Bruker DPX 400 MHz spectrometer in $CDCl_3$ as solvent using TMS as internal standard. Mass spectra were measured on MS 30 and MS 9 (AEI) spectrometers, with EI 70 eV. Elemental analyses were determined by means of LECO CHNS-932 Elemental Analyzer. The microwave accelerated reactions were carried out by using induced microwave convection operating at 900 W generating 2450 MHz frequency. In order to compare microwave irradiation with conventional heating, the reactions were performed under similar experimental conditions (weight of reactants, solvents, bases). 1-Cycloalkyliden-1-hydrazinecarbodithioic acids **2a-b**[25], hydrazonoyl halides **1a-k** and **4**[26-31] were prepared by literature methods. Hydrazonoyl halides are toxic and cause skin irritation, so proper safety precautions should be taken and it is recommended to protect hands with rubber gloves.

Crystallographic Analysis and Crystal Data

The crystals were mounted on a glass fiber. All measurements were performed on an ENRAF NONIUS FR 590. The data were collected at a temperature of 25°C using the ω scanning technique to a maximum of a 2θ of 22.986°. The structure was solved by direct method using SIR 92 and refined by full-matrix least squares. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located geometrically and were refined isotropically.

$C_{22}H_{26}N_4O_4S$, M = 442.17, monoclinic, a = 20.9023 (9), b = 4.3643 (2), c = 25.3660 (14) A°, v = 2293.4 (2), α = γ = 90.00°, β = 97.649 (2), space group: H-M `C 2/c, D_x = 1.456 Mg m^{-3} reflection 914 measured, θ_{max} = 22.71°, ωR factor = 0.108. *Figure 1* illustrates the structure as determined.

$C_{20}H_{20}N_4S$, M = 343.432, monoclinic, a = 14.7495 (7), b = 5.4362 (3), c = 22.5212 (14) A°, v = 1805.5 (2), α = γ = 90.00°, β = 90.959 (2), space group: $P2_1/c$, Z = 4, D_x = 1.263 Mg m^{-3} reflection 3605 measured, θ_{max} = 23.00°, ωR factor = 0.131. *Figure 2* illustrates the structure as determined. Full data can be obtained on request from the CCDC.[32]

Table 3. Physical Constants and Elemental Analysis of Products **3a-k** and **5a-b**

Cmpd	mp (°C) Solvent^a	*lit.* mp (°C)	Color	Elemental Analysis (Found) C	H	N	S
3a	136-138$^{(a)}$	135[18]	Yellow	57.96 (57.99)	5.35 (5.44)	13.52 (13.51)	7.74 (7.57)
3b	169-170$^{(a)}$	170[18]	Yellow	59.72 (59.66)	5.92 (5.94)	12.66 (12.79)	7.25 (6.91)
3c	176-178$^{(a)}$	183[18]	Pale Yellow	49.70 (49.64)	4.17 (4.32)	11.59 (11.78)	6.63 (6.41)
3d	210-212$^{(a)}$	226[18]	Dark Yellow	61.00 (61.16)	5.12 (5.17)	15.81 (15.71)	9.05 (8.96)
3e	222-224$^{b)}$	215[18]	Dark Yellow	62.80 (62.51)	5.80 (5.81)	14.65 (14.48)	8.38 (8.27)
3f	246-248$^{(b)}$	----	Dark Yellow	48.65 (48.74)	3.63 (3.73)	18.91 (18.68)	7.22 (7.21)
3g	230-232$^{(b)}$	227[18]	Yellowish Green	66.12 (65.91)	4.76 (4.89)	16.52 (16.53)	6.30 (6.00)
3h	225-227$^{(b)}$	----	Pale Green	58.24 (58.15)	3.84 (3.91)	14.55 (14.68)	5.55 (5.31)
3i	215-217$^{b)}$	205[18]	Yellow	70.27 (70.25)	4.63 (4.69)	11.71 (11.87)	6.70 (6.55)
3j	253-255$^{b)}$	----	Yellow	61.43 (61.44)	3.68 (3.76)	10.23 (10.42)	5.86 (5.73)
3k	254-255$^{b)}$	----	Yellow	51.52 (51.59)	2.88 (3.04)	10.01 (10.13)	17.19 (17.14)
5a	141-143$^{(a)}$	----	Green	68.93 (68.74)	5.79 (5.81)	16.08 (15.97)	9.20 (9.11)
5b	153-155$^{(a)}$	----	Pale Green	68.23 (58.11)	5.42 (5.32)	16.75 (16.82)	9.59 (9.48)

Recrystallization solvent: a) EtOH; b) H_2O/ Dioxane mixture

Table 4. Spectral Data of the Products **3a-k** and **5a-b**

Cmpd	IR cm^{-1}	^{1}HNMR (δ) ppm	MS (*m/z*, %)
3a	3178, 3124 (2 NH), 1679 (2CO), 1603 (C=N)	1.41 (t, 6H, 2CH$_3$), 4.39 (q, 4H, 2CH$_2$), 7.02-7.41 (m, 10H, Ar-H), 11.3 (s, 2H, 2NH)	414 (M+, 15), 307 (100), 150 (46), 93 (95), 77 (98)
3b	3176, 3119 (2 NH), 1678 (2CO), 1600 (C=N)	1.41 (t, 6H, 2CH$_3$), 2.36 (s, 6H, 2Ar-CH$_3$), 4.40 (q, 4H, 2CH$_2$), 7.15 (d, 4H, Ar-H), 7.30 (d, 4H, Ar-H), 11.3 (s, 2H, 2NH)	442 (M+, 10), 321 (100), 106 (70), 91 (75)
3c	3167, 3110 (2NH), 1680 (2CO), 1598 (C=N)	1.41 (t, 6H, 2CH$_3$), 4.41 (q, 4H, 2CH$_2$), 7.28 (d, 4H, Ar-H), 7.32 (d, 4H, Ar-H), 11.34 (s, 2H, 2NH)	483 (MH+, 15), 341 (100), 126 (65), 111 (57)
3d	3151, 3107 (2NH), 1650 (2CO), 1598 (C=N)	2.56 (s, 6H, 2COCH$_3$), 7.11-7.48 (m, 10H, Ar-H), 11.57 (s, 2H, 2NH)	354 (M+, 10), 246 (100), 193 (35), 92 (55), 77 (40)
3e	3157, 3108 (2NH), 1648 (2CO), 1598 (C=N)	2.36 (s, 6H, 2Ar-CH$_3$), 2.55 (s, 6H, 2COCH$_3$), 7.19 (d, 4H, Ar-H), 7.28 (d, 4H, Ar-H), 11.55 (s, 2H, 2NH)	382 (M+, 10), 261 (100), 106 (70) 91 (75)
3f	3166, 3107 (2NH), 1660 (2CO), 1597 (C=N)	2.63 (s, 6H, 2COCH$_3$), 7.28 (d, 4H, Ar-H), 8.31 (d, 4H, Ar-H), 11.85 (s, 2H, 2NH)	444 (M+, 5), 291 (100), 238 (30), 137 (10), 90 (15)
3g	3448, 3383 (2NH), 3161, 3109 (2NH), 1660 (2CO), 1600 (C=N)	7.08-7.70 (m, 20H, Ar-H), 8.68 (s, 2H, 2NH), 11.82 (s, 2H, 2CONH)	508 (M+, 18), 402 (44), 328 (38), 180 (52), 93 (72), 77 (100)
3h	3383, 3199 (2NH), 3164, 3108 (2NH), 1662 (2CO), 1599 (C=N)	7.17-7.36 (m, 10H, Ar-H), 7.42 (d, 4H, Ar-H), 7.67 (d, 4H, Ar-H), 8.61 (s, 2H, 2NH), 11.88 (s, 2H, 2CONH)	577 (M+, 10), 421 (35), 395 (62), 180 (52), 138 (100), 119 (54), 77 (48)
3i	3151, 3105 (2NH), 1627 (2CO), 1601 (C=N)	7.10-7.99 (m, 20H, Ar-H), 12.21 (s, 2H, 2NH)	478 (M+, 10), 315 (10), 105 (75), 77 (100)
3j	3145, 3109 (2NH), 1622 (2CO), 1598 (C=N)	7.33-7.61 (m, 10H, Ar-H), 7.63 (d, 4H, Ar-H), 7.95 (d, 4H, Ar-H), 12.24 (s, 2H, 2NH)	546 (M+, 10), 405 (15), 105 (100), 77 (37)
3k	3156, 3109 (2NH), 1622 (2CO), 1603 (C=N)	7.19-7.54 (m, 6H, Ar-H), 7.75 (d, 4H, Ar-H), 8.20 (d, 4H, Ar-H), 12.20 (s, 2H, 2NH)	559 (M+, 8), 417 (32), 11 (100), 83 (10)
5a	1625 (C=N)	1.27-2.76 (m, 10H, Cyclohex-H), 7.27-8.21 (m, 10H, Ar-H)	348 (M+, 100), 239 (25), 194 (80), 91 (82), 77 (25)
5b	1622 (C=N)	1.27-2.88 (m, 8H, Cyclopent-H), 7.31-7.89 (m, 10H, Ar-H)	334 (M+, 100), 180 (72), 77 (22)

General Procedure for the Synthesis of *bis*-Hydrazonoyl Sulfides (3a-k) and 2,3-Dihydro-3,5-diphenyl-1,3,4-thiadiazole Derivatives (5a-b). Thermal Method.- To a solution of hydrazonecarbodithioic acid **2a** or **2b** and the appropriate hydrazonoyl halides **1a-k** (1 mmol of each) in dioxane (20 mL) was added triethylamine (0.14 mL, 1 mmol) at room temperature. The reaction mixture was refluxed in an oil bath at 120°C till all of the starting materials had disappeared (4-6 h, monitored by TLC). The solvent was evaporated and the residue was triturated with methanol. The solid formed was collected and recrystallized from the appropriate solvent as shown in *Table 3*.

Microwave Method.- To a solution of hydrazonecarbodithioic acid (**2a** or **2b**) and the appropriate hydrazonoyl halides (**1a-k**, 1 mmol of each) in dioxane (20 mL) was added triethylamine (0.14 mL, 1 mmol) at room temperature. The reaction mixture was transferred to closed vessel and irradiated in a microwave oven at 120°C for 1-1.5 min. at a power of 900 W. After cooling to room temperature, the solution was extracted with chloroform (3 x 10 mL). The organic extracts were dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The solid residue was recrystallized from the appropriate solvent (*Table 3*). The physical constants and the spectral data of compounds **3a-k** and **5a-b** are listed in Tables 3 and 4.

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32. Crystal data for **3b**, **5a** (ref. CCDC 296101) may be obtained on request from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EW, UK.

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