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Synthesis of Novel Fungicidal Organomercurials Using Microwaves

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Summary. Mercury derivatives of substituted 1,3,4-thiadiazoles and 1,2,4-triazine have been synthesized under microwave irradiation in open vessels using a domestic microwave oven as well as in a conventional way. The reaction time could be cut down from hours to minutes employing microwaves, accompanied by marginally improved yields. The compounds show promising fungicidal activity.

Keywords. Microwaves; Organomercurials; Fungicidal activity.

Mikrowellenunterstützte Synthese neuer fungizider Organoquecksilberverbindungen

Zusammenfassung. Quecksilberderivate substituierter 1,3,4-Thiadiazole und 1,2,4-Triazine werden sowohl unter der Einwirkung von Mikrowellen (offene Gefäße, Haushaltsmikrowellenherd) als auch auf konventionelle Weise hergestellt. Die Anwendung von Mikrowellen verkürzt die Reaktionszeit von Stunden auf Minuten, die Ausbeuten steigen geringfügig. Die Verbindungen zeigen vielversprechende fungizide Aktivität.

Introduction

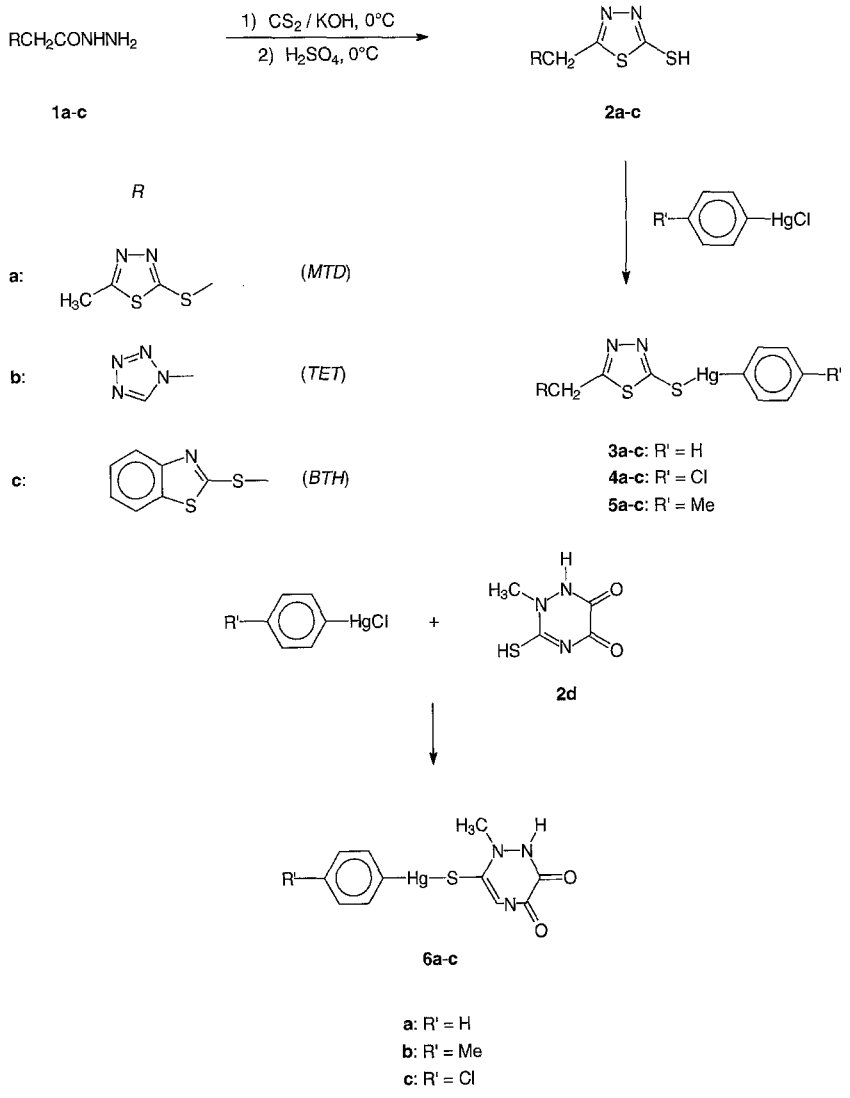
Organomercurials exhibit a wide range of biological activities [1–3]. Recently, the use of microwave irradiation in connection with the synthesis of heterocycles [4–6] has become a field of interest in our laboratory [7].

Keeping in view their biological importance [8] and in continuation of our earlier work on organomercurials [9–10] we report herein the synthesis of 2-(aryl-mercurythio)-5-(5-methyl-1, 3, 4-thiadiazol-2-yl-sulfanyl/tetrazol-1-yl/benzothiazol-2-yl-sulfanyl)-methyl-1,3,4-thiadiazole and 3-(aryl-mercurythio)-2-(methyl-5,6-dioxo-1*H*,1,2,4-triazine).

Results and Discussion

Upon reaction with CS_2 and KOH, hydrazides **1a–c** afforded dithiocarbazate salts which were cyclized in the presence of H_2SO_4 to give 5-substituted methyl-1,3,4-thiadiazole-2-thiol. Their IR spectra show the absence of bands at 3200–3400 and 1650–1680 cm^{-1} due to $NHNH_2$ and $CONH_2$ groups, respectively. A weak band at 2500–2540 cm^{-1} appears due to SH stretching. ^1H NMR and mass spectra also confirmed the formation of thiadiazoles **2a–c**.

Organomercurials have been synthesized by reaction of 2-mercaptothiadiazoles/3-mercapto-1,2,4-triazine with (phenyl/4-chloro-phenyl/4-methyl-phenyl)-mercuric chloride [9].



Elemental analyses of all compounds show a 1:1 stoichiometric ratio of the arylmercury and the thiadiazole or triazine moieties. In the ^{1}H NMR spectrum of the organomercurials, the signal for the SH proton is missing, and signals for aryl groups were present when compared with the ^{1}H NMR spectra of the parent thiadiazoles.

Experimental

Melting points were taken on an electrothermal melting point apparatus and are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded on a 1710 Perkin Elmer FTIR Spectrophotometer using KBr discs; ^{1}H NMR spectra were recorded on an FT NMR Hitachi R-600 using Me_4Si as internal standard (δ in ppm). Elemental analyses were performed on a Heracus CHN-Rapid Analyser.

*General procedure for the synthesis of 5-substituted methyl-1,3,4-thiadiazole-2-thioles (**2a–c**)*

KOH (0.01 mol) was dissolved in ethanol. Hydrazide (**1a–c**, 0.01 mol) was added, and the reaction mixture was cooled to 0–5°C. Then, CS_2 (0.012 mol) was added dropwise. After addition the reaction mixture was stirred for 30 min. The solid obtained was filtered, washed with chilled acetone, dried, and used without further purification for the subsequent reaction.

The above solid was added slowly to conc. H_2SO_4 with stirring at 0°C. After addition, the mixture was stirred for further 30 min. The reaction mixture was added to ice cold water, and the solid obtained was filtered and washed with an excess of water till the filtrate became neutral to litmus. Then it was dried and recrystallized from acetone.

2a: Yield: 63%; m.p.: 175–176°C; IR: 2650 (S-H), 1610 (C=N); ^{1}H NMR ($CDCl_3$ + *TFA*): 2.70 (s, 3H, CH_3), 4.5 (s, 2H, SCH_2) 11.7 (s, 1H, SH); MS: *m/z* = 262 (M^+).

2b: Yield: 67%; m.p.: 192–194°C; IR: 2600 (SH), 1640 (C=N); ^{1}H NMR ($CDCl_3$ + *TFA*): 6.1 (s, 2H, CH_2), 9.51 (s, 1H, H-5 of tetrazole ring), 11.5 (s, 1H, SH); MS: *m/z* = 200.

2c: Yield: 65%; m.p.: 198–200°C; IR: 2650 (SH), 1610 (C=N); ^{1}H NMR ($CDCl_3$ + *TFA*): 2.70 (s, 3H, CH_3), 4.5 (s, 2H, SCH_2), 11.4 (s, 1H, SH).

2d: Purchased from Cheils food company, South Korea.

*General procedure for the synthesis of 2-(aryl-mercurythio)-5-(5-methyl-1,3,4-thiadiazol-2yl-sulfanyl/tetrazol-1-yl/benzothiazol-2-yl-sulfanyl)-methyl-1,3,4-thiadiazole (**3a–c–5a–c**) and 3-(aryl-mercurythio)-2-(methyl-5,6-dioxo-1H-1,2,4-triazine) (**6a–c**)*

Method A:

The mercapto-substituted compound (0.01 mol) was dissolved in *DMSO* (10 ml). To this solution, anhydrous K_2CO_3 (4 g) and aryl mercuric chloride (0.01 mol) were added. The reaction mixture was heated for 4–5 h. The reaction mixture was cooled, filtered to remove the inorganic salt, and poured over crushed ice. The obtained solid was filtered, dried, and recrystallized from a mixture of *DMSO*/ EtOH.

Table 1. Physical data of compounds **3a–c – 6a–c**

	R	*R′*	m.p. (°C)	Method reaction time		Yield (%)		Molecular formula[a]
				A (h)	*B* (min)	*A*	*B*	
3a	*MTD*	H	162–164	6.0	1.5	68	79	$C_{12}H_{10}N_4S_4Hg$
3b	*TET*	H	126–128	7.5	2.0	71	80	$C_{10}H_8N_6S_2Hg$
3c	*BTH*	H	138–140	6.5	2.0	68	76	$C_{16}H_{11}N_3S_4Hg$
4a	*MTD*	Cl	152–154	6.0	1.5	73	87	$C_{12}H_9N_4S_4HgCl$
4b	*TET*	Cl	130–134	6.0	1.5	72	84	$C_{10}H_7N_6S_2HgCl$
4c	*BTH*	Cl	143–145	5.5	1.0	70	88	$C_{16}H_{10}N_3S_4HgCl$
5a	*MTD*	Me	146–148	7.5	2.5	65	76	$C_{13}H_{12}N_4S_4Hg$
5b	*TET*	Me	124–126	7.0	2.0	62	73	$C_{11}H_{10}N_6S_2Hg$
5c	*BTH*	Me	136–138	8.0	3.0	64	78	$C_{17}H_{13}N_3S_4Hg$
6a		H	102–104	7.0	2.5	59	70	$C_{10}H_9N_3SO_2Hg$
6b		Me	98–99	9.0	4.0	56	68	$C_{11}H_{11}N_3SO_2Hg$
6c		Cl	107–109	7.5	3.0	62	73	$C_{10}H_8N_3SO_2HgCl$

[a] All compounds gave satisfactory elemental analyses (C, H, N, Hg)

Method B:

To a solution of the mercapto compound (0.01 mol) in *DMF*, anhydrous K_2CO_3 (3 g) and aryl mercuric chloride (0.01 mol) were added in a 100 ml beaker. The beaker was irradiated inside a microwave oven for a period of 2–3 min at 2450 MHz. The reaction mixture was cooled and filtered

Table 2. Spectroscopic data of compounds **3a–c–6a–c**

	R	*R'*	IR (ν_1 cm^{-1})	^1H NMR (*DMSO*-d_6 + $CDCl_3$; δ_1 ppm)
3a	MTD	H	1610 (C=N)	2.9 (s, 3H, CH_3), 4.8 (s, 2H, SCH_2), 7.1–7.5 (m, 5H, Ar-H)
3b	TET	H	1640 (C=N)	6.0 (s, 2H, CH_2), 7.0–7.55 (m, 5H, Ar-H), 8.8 (s, 1H, H-5 of tetrazole ring)
3c	BTH	H	1620 (C=N)	4.9 (s, 2H, SCH_2), 7.0–7.5 (m, 9H, Ar-H)
4a	MTD	Cl	1640 (C=N)	2.9 (s, 3H, CH_3), 4.85 (s, 2H, SCH_2), 7.3–7.7 (m, 4H, Ar-H)
4b	TET	Cl	1665 (C=N)	6.1 (s, 2H, CH_2), 7.2–7.6 (m, 4H, Ar-H), 8.9 (s, 1H, H-5 of tetrazole ring)
4c	BTH	Cl	1630 (C=N)	4.95 (s, 2H, SCH_2), 7.1–7.6 (m, 8H, Ar-H)
5a	MTD	Me	1600 (C=N)	2.3 (s, 3H, 4'-CH_3), 2.85 (s, 3H, CH_3), 4.8 (s, 2HSCH_2), 7.0–7.4 (m, 4H, Ar-H)
5b	TET	Me	1610 (C=N)	2.4 (s, 3H, 4'-CH_3), 6.0 (s, 2H, CH_2), 7.1–7.4 (m, 4H, Ar-H), 8.8 (s, 1H, H-5 of terazole ring)
5c	BTH	Me	1600 (C=N)	2.5 (s, 3H, 4'-CH_3), 4.95 (s, 2H, SCH_2), 7.1–7.4 (m, 8H, Ar-H)
6a		H	1660 (C=O), 1610 (C=N)	3.55 (s, 3H, NCH_3), 7.2–7.4 (m, 5H, Ar-H), 8.45 (br s, 1H, CONH)
6b		Me	1640 (C=O), 1590 (C=N)	2.3 (s, 3H, 4'- CH_3), 3.5 (s, 3HNCH_3), 7.0–7.4 (m, 4H, Ar-H), 8.4 (br s, 1H, CONH)
6c		Cl	1680 (C=O) 1630 (C=N)	3.6 (s, 3H, NCH_3), 7.3–7.7 (m, 4H, Ar-H), 8.5 (br s, 1H, CONH)

Table 3. Antifungal activities of organomercurials

	Inhibition of aspergillus niger		Inhibition of aspergillus flavous	
	25 μg/ml	50 μg/ml	25 μg/ml	50 μg/ml
3a	+++++	+++++	+++++	+++++
3b	+++++	+++++	++++	++++
3c	++++	++++	+++	+++
4a	+++++	+++++	++++	++++
4b	+++	+++	+++	+++
4c	++++	++++	+++++	+++++
5c	++++	++++	+++	+++
5b	+++	+++	+++	+++
5c	+++++	+++++	+++++	+++++
6a	+++	+++	++	++
6b	+++++	+++++	++++	++++
6c	+++	+++	+++	+++
Salicylic acid	++++	++++	+++	+++

+: 3–9 mm; ++: 10–12 mm; +++: 13–16 mm; ++++: 17–21 mm; +++++: > 21 mm

to remove the inorganic salt. The clear filtrate was poured over crushed ice. The obtained solid was filtered, dried, and recrystallized from a *DMF*/EtOH mixture.

Antifungal activity

All synthesised compounds were screened for their antifungal activity against *a. niger* and *a. flavous* by the paper disc diffusion method [11]. The zone of inhibition was measured in millimeters. The antifungal activities of the test compounds were compared to standard salicylic acid (13–18 mm, [12]). *DMF* was used as solvent.

The results of the antifungal screening are given in Table **3**. All organomercurials display significant antifungal activity against *a. niger* and *a. flavous*, compounds **3a**, **3b**, **4a**, **4c**, **5c**, and **6b** being most active ones.

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