# A Novel Synthetic Method for Fungicidal Organomercurials

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Fungicidal organomercurials of substituted 1,3,4-thiadiazole and 1,3,4-oxadiazole with arylmercurium chloride have been synthesized under microwave irradiation in dry media. Reactants adsorbed on a solid support afford the title compounds within 1—3 min in a high yield.

The environmentally-friendly goal of making organic compounds without using solvent has come several steps closer in recent years. The day may be coming when more drastic restrictions on "solvent pollution" will require the adoption of no solvent reaction conditions [1]. With the development of microwave ovens [2], reactions in dry media [3] became easier to do. Since the microwaves are only adsorbed by the reactants on the surface of common inorganic oxides [4] such as silica and alumina, numerous reagents supported on solid surfaces [5] can also be effectively utilized for conducting organic reactions under very safe and simple conditions. We are currently investigating the use of such methodology for a wide variety of organic reactions, the microwave-assisted solid state reactions may help to minimize the production of waste solvent and in general microwave-assisted reactions may lend themselves to automation [6]. The absence of solvent coupled with the high yields and short reaction times make this procedure very attractive for synthesis. To this purpose, the strategy of microwave-induced synthesis in dry media on solid inorganic supports seems to be most adapted.

Organomercurials [7], 1,3,4-thiadiazoles and 1,3,4-oxadiazoles [8] exhibit a wide range of biological activities. Heterocyclic compounds containing mercury [9] are very potent fungicides, bacteriocides, and pesticides. Keeping this in view and in continuation of our earlier work on the organomercurials using solution phase [10], we report herein on the synthesis of 2-(arylmercuriosulfanyl)-5-(phenyl/pyridin-4-yl)-1,3,4-thiadiazoles (*IIIa—IIIc, IVa—IVc*) and 2-(arylmercuriosulfanyl)-5-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanylmethyl]-1,3,4-oxadiazoles (*VIIa—VIIc*) on solid support (see Scheme 1) and screen them for their fungicidal activity.

## EXPERIMENTAL

Melting points were recorded on an electrothermal apparatus and are uncorrected. IR (KBr) spectra were obtained on a Perkin—Elmer FTIR-1710 spectrophotometer. $^1$H NMR spectra were recorded on a Perkin—Elmer R-32 (90 MHz) instrument using TMS as internal reference. Microwave irradiations were carried out in Padmini Essentia Oven, Model Brownie at 2450 MHz (using energy output 0.56 kW). Elemental analyses were performed on a Heraeus CHN-Rapid Analyzer. Silica gel-coated Al plates (Merck) were used for thin-layer chromatography. Yields were obtained after recrystallization. Aluminium oxide, basic, Brockmann I (Aldrich, $\approx$ 0.1 mm; specific surface area 155 $m^2\ g^{-1}$) was used as received. Characterization of the synthesized compounds is given in Table 1.

All the synthesized compounds were screened for their antifungal activity against fungi *A. niger* and *A. flavus* by paper disc diffusion method [11], the zone of inhibition was measured in millimeters. The antifungal activity of the tested compounds was compared with the standard salicylic acid [12] (13—18 mm). DMF was used as solvent.

5-Substituted 2-sulfanyl-1,3,4-oxadiazole (*VI*) was prepared according to the literature method [10]. Yield = 52 %, m.p. = 152—154 °C. IR spectrum, $\tilde{\nu}/cm^{-1}$: 2640 $\nu$(SH), 1610 $\nu$(C=N). $^1$H NMR spectrum (DMSO-$d_6$ + $CDCl_3$), $\delta$: 2.7 (s, 3H, $CH_3$), 4.5 (s, 2H, $SCH_2$), 11.8 (s, 1H, SH).

### 5-Substituted 2-Sulfanyl-1,3,4-thiadiazoles *IIa, IIb*

KOH (1 mmol) was dissolved in ethanol. Hydrazide *Ia, Ib* (1 mmol) was added and the mixture was cooled

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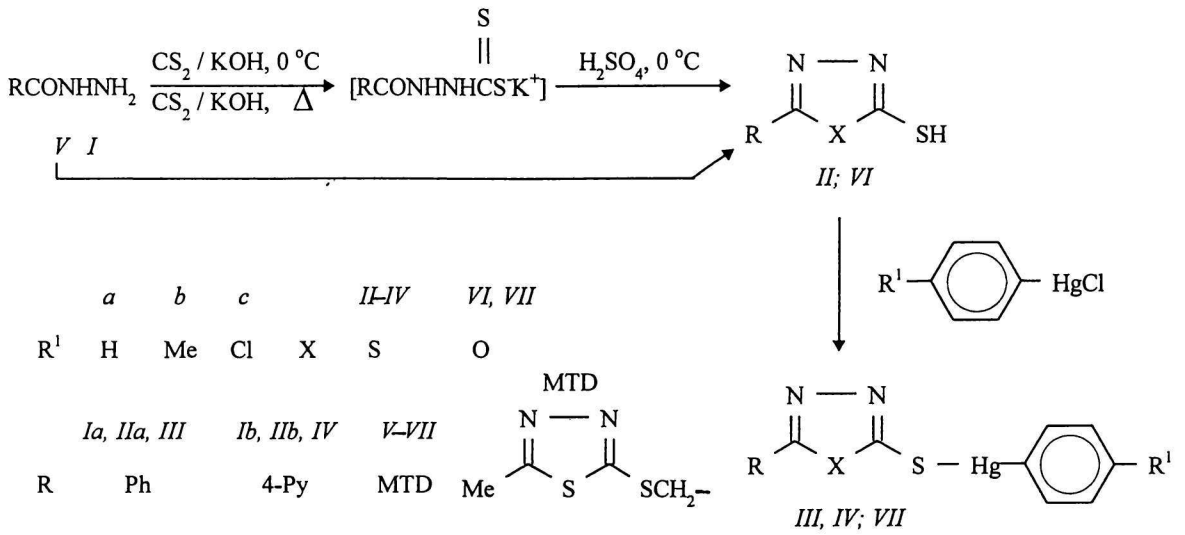


*Scheme 1*

to 0—5 °C. Then $CS_2$ (1.2 mmol) was added dropwise. After addition, the reaction mixture was stirred for 30 min. The obtained solid was filtered off and washed with chilled acetone, dried and used as such for further reaction. This solid was added slowly to concentrated $H_2SO_4$ with stirring at 0 °C. After addition, the mixture was stirred for another 30 min. The reaction mixture was added to ice cold water. The obtained solid was filtered off and washed with excess of water till the filtrate became neutral to litmus. It was dried and recrystallized from acetone.

*IIa*: Yield = 68 %, m.p. = 216—217 °C (Ref. [13] gives m.p. = 215—217 °C).

*IIb*: Yield = 55 %, m.p. = 218—219 °C. IR spectrum, $\tilde{\nu}$/cm$^{-1}$: 2650 $\nu$(SH), 1640 $\nu$(C=N). $^1$H NMR spectrum (DMSO-$d_6$ + $CDCl_3$), $\delta$: 7.7 (d, 2H, 3′,5′-CH, $J_{H—H}$ = 5.1 Hz), 8.75 (d, 2H, 2′,6′-CH, $J_{H—H}$ = 5.1 Hz), 13.0 (s, 1H, SH).

### 2-(Arylmercuriosulfanyl)-5-(phenyl/pyridin-4-yl)-1,3,4-thiadiazoles *IIIa—IIIc, IVa—IVc* and 2-(Arylmercuriosulfanyl)-5-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanylmethyl]-1,3,4-oxadiazoles *VIIa—VIIc*

Basic alumina (36 g) was added to the solution of sulfanyl-substituted compound (2 mmol) and arylmercurium chloride (2 mmol) dissolved in dichloromethane (5 cm$^3$) at room temperature. The reaction mixture was thoroughly mixed and adsorbed material was dried in air (beaker) and placed in an alumina bath inside the microwave oven [14] for a period of 1—3 min. Upon completion of the reaction as followed by TLC examination, the mixture was cooled to room temperature and then the product was extracted into dichloromethane (4 × 15 cm$^3$). Removal of the solvent under reduced pressure yielded the product which was purified by crystallization from the mixture methanol—dichloromethane.

## RESULTS AND DISCUSSION

Compounds *Ia, Ib* on reaction with $CS_2$ and KOH afforded dithiocarbazate salts which cyclized in the presence of concentrated $H_2SO_4$ to give sulfanylthiadiazoles *IIa, IIb* (Scheme 1). Their IR spectra show the absence of bands at $\tilde{\nu}$ = 3200—3400 cm$^{-1}$ and 1650—1680 cm$^{-1}$ due to $NHNH_2$ and CONH groups, respectively (Table 1). The cyclocondensation of hydrazide *V* with $CS_2$ in the presence of KOH on heating yielded sulfanyloxadiazole *VI* as evidenced by the disappearance of bands at $\tilde{\nu}$ = 3200—3350 cm$^{-1}$ and 1650—1680 cm$^{-1}$ due to $NHNH_2$ and CONH groups, respectively and the appearance of bands at $\tilde{\nu}$ = 2500—2540 cm$^{-1}$ and 1530—1570 cm$^{-1}$ due to the formation of SH and C=N groups, respectively. $^1$H NMR spectra also confirmed the formation of *IIa, İIb*, and *VI*.

2-Sulfanylthiadiazoles/2-sulfanyloxadiazoles and (phenyl/4-chlorophenyl/4-methylphenyl)mercurium chloride [10] have been adsorbed on alumina, mixed well and subjected to microwave irradiation to afford the organomercurials. For the same reaction longer time periods (≧ 10 h) are required using alternative heating modes (conventional oven or oil bath). The elemental analyses of all the compounds indicated a 1 : 1 stoichiometric ratio of arylmercurium to thiadiazole/oxadiazole moiety. In the $^1$H NMR spectrum of the organomercurials the signal for SH proton was missing and the signal for aryl group was present when compared with $^1$H NMR of parent thiadiazole and oxadiazole.

Results of antifungal screening showed that all the organomercurials displayed significant activity against *A. niger* and *A. flavus*. However, compounds *IIIc, IVb,*

**Table 1.** Characterization of the Synthesized Compounds

| Compound | Formula | $M_r$ | $w_i$(found)/% $w_i$(calc.)/% | | | | Reaction time/min (yield/%) | M.p. | IR $\tilde{\nu}(\nu(C{=}N))/cm^{-1}$ | $\delta$ ($^1$H NMR (DMSO-$d_6$ + $CDCl_3$)) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | Hg | | °C | | |
| *IIIa* | $C_{14}H_{10}N_2S_2Hg$ | 470.85 | 35.68<br>35.74 | 2.11<br>2.12 | 5.60<br>5.65 | 42.58<br>42.55 | 2.0 (92) | 155—157 | 1620 | 7.1—7.5 (m, 10H, $H_{arom}$) |
| *IIIb* | $C_{15}H_{12}N_2S_2Hg$ | 484.86 | 37.23<br>37.19 | 2.45<br>2.47 | 5.76<br>5.78 | 41.34<br>41.32 | 2.5 (89) | 117—119 | 1600 | 2.3 (s, 3H, 4-$CH_3$), 7.2—7.6 (m, 9H, $H_{arom}$) |
| *IIIc* | $C_{14}H_9N_2S_2ClHg$ | 505.30 | 33.27<br>33.30 | 1.76<br>1.78 | 5.51<br>5.55 | 39.62<br>39.64 | 1.5 (96) | 130—132 | 1630 | 7.3—7.7 (m, 9H, $H_{arom}$) |
| *IVa* | $C_{13}H_9N_3S_2Hg$ | 471.84 | 33.10<br>33.12 | 1.91<br>1.91 | 8.90<br>8.91 | 42.40<br>42.46 | 2.5 (91) | 178—180 | 1620 | 7.0—7.4 (m, 5H, $H_{arom}$), 7.7 (d, 2H, 3′,5′-CH, $J_{H—H}$ = 5.1 Hz), 8.75 (d, 2H, 2′,6′-CH, $J_{H—H}$= 5.1 Hz) |
| *IVb* | $C_{14}H_{11}N_3S_2Hg$ | 485.85 | 34.61<br>34.62 | 2.25<br>2.26 | 8.62<br>8.65 | 41.20<br>41.23 | 3.0 (88) | 120—122 | 1630 | 2.35 (s, 3H, 4-$CH_3$), 7.1—7.4 (m, 4H, $H_{arom}$), 7.75 (d, 2H, 3′,5′-CH, $J_{H—H}$ = 4.9 Hz), 8.8 (d, 2H, 2′,6′-CH, $J_{H—H}$ = 4.9 Hz) |
| *IVc* | $C_{13}H_8N_3S_2ClHg$ | 506.29 | 30.85<br>30.86 | 1.56<br>1.58 | 8.28<br>8.30 | 39.60<br>39.56 | 2.5 (94) | 85—87 | 1640 | 7.2—7.5 (m, 4H, $H_{arom}$), 7.9 (d, 2H, 3′,5′-CH, $J_{H—H}$ = 5.1 Hz), 8.95 (d, 2H, 2′,6′-CH, $J_{H—H}$ = 5.1 Hz) |
| *VIIa* | $C_{12}H_{10}N_4OS_3Hg$ | 524.50 | 27.54<br>27.58 | 1.90<br>1.91 | 10.70<br>10.72 | 38.30<br>38.31 | 1.5 (87) | 142—144 | 1580 | 2.5 (s, 3H, 5′-$CH_3$), 4.8 (s, 2H, $SCH_2$), 7.0—7.4 (m, 5H, $H_{arom}$) |
| *VIIb* | $C_{13}H_{12}N_4OS_3Hg$ | 538.51 | 28.96<br>29.10 | 2.20<br>2.23 | 10.45<br>10.44 | 37.31<br>37.34 | 2.0 (93) | 73—75 | 1590 | 2.2 (s, 3H, 4-$CH_3$), 2.55 (s, 3H, 5′-$CH_3$), 4.9 (s, 2H, $SCH_2$), 7.1—7.5 (m, 4H, $H_{arom}$) |
| *VIIc* | $C_{12}H_9N_4OS_3ClHg$ | 558.95 | 25.81<br>25.87 | 1.62<br>1.61 | 10.00<br>10.06 | 35.90<br>35.93 | 1.5 (95) | 185—187 | 1600 | 2.3 (s, 3H, 5′-$CH_3$), 4.85 (s, 2H, $SCH_2$), 7.2—7.6 (m, 4H, $H_{arom}$) |

**Table 2.** Antifungal Activity of Organomercurials

| Compound | Inhibition of *A. niger* | | Inhibition of *A. flavus* | |
|---|---|---|---|---|
| | 25 mg $cm^{-3}$ | 50 mg $cm^{-3}$ | 25 mg $cm^{-3}$ | 50 mg $cm^{-3}$ |
| *IIIa* | ++++ | ++++ | +++ | +++ |
| *IIIb* | +++ | +++ | ++++ | ++++ |
| *IIIc* | +++++ | +++++ | +++++ | +++++ |
| *IVa* | ++++ | ++++ | ++++ | ++++ |
| *IVb* | +++++ | +++++ | ++++ | ++++ |
| *IVc* | +++++ | +++++ | +++++ | +++++ |
| *VIIa* | ++++ | ++++ | ++ | ++ |
| *VIIb* | +++ | +++ | ++++ | ++++ |
| *VIIc* | +++++ | +++++ | ++++ | ++++ |
| Salicylic acid | ++++ | ++++ | +++ | +++ |

+ = 3—9 mm, ++ = 10—12 mm, +++ = 13—16 mm, ++++ = 17—21 mm, +++++ = > 21 mm.

*IVc*, and *VIIc* are the most active ones (Table 2).

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