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MICROWAVE INDUCED NOVEL SYNTHETIC ROUTE TO ORGANOMERCURIALS

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Abstract—Organomercurials of 2-mercapto-5-methyl-1,3,4-thiadiazole and 2-mercapto-5-[4′-methyl quinolinyl-2-oxy methyl]-1,3,4-oxadiazole with aryl mercuric chloride have been synthesized under microwave irradiation in open vessels in a domestic microwave oven within a few minutes. This reaction rate was *ca* 100 times faster than the reaction rate in the conventional way. These organomercurials have a 1 : 1 stoichiometric ratio of aryl mercury and thiadiazole or oxadiazole moiety. Copyright © 1996 Elsevier Science Ltd

Organomercurials exhibit a wide range of biological activities.[1–4] Heterocyclic compounds containing mercury[5,6] are very potent fungicides, bactericides and pesticides.

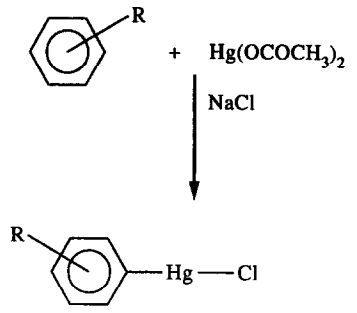
In recent times there has been much interest in the use of microwave irradiation in synthesis[7] due to substantial reduction in time. Most of the reactions carried out in an unaltered domestic microwave oven are either in sealed vessels[8] or in the solid phase.[9] Reaction can also be performed in open vessels.[10]

The substantial reduction in reaction time under microwave irradiation and the biological importance of organomercurials prompted us to synthesize the mercury derivatives from 2-mercapto-5-methyl-1,3,4-thiadiazole,[11] a side chain of the antibiotic cefazolin sodium and 2-mercapto-5-[4′-methyl quinolinyl-2-oxy methyl]-1,3-4-oxadiazole with aryl mercuric chloride.

EXPERIMENTAL

General procedure for the synthesis of aryl mercuric chloride **1 (a–e)**

Mercuric acetate (0.01 mol) was added to a mixture of DMF (10 cm^3) and substituted benzene (0.1 mol) in a 100 cm^3 beaker. The beaker was irradiated[8] inside a microwave oven for a period of 1.0–1.5 min at 2450 MHz. The contents were concentrated *in vacuo*. to remove most of the unreacted substituted benzene. To this alcohol (15 cm^3) was added. A boiling aqueous solution of NaCl (0.01 mol) was added slowly with stirring when a white precipitate separated out. Then boiling water (15 cm^3) was added. The solid obtained was filtered,



1 (a–e)

R = a H
b 4-CH_3
c 4-Cl
d 4-Br
e 4-OCH_3

Scheme 1.

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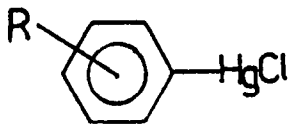
Table 1. Aryl mercuric chloride



Compound no.	R	Reaction time		m.p. (°C)		% Yield	
		Lit. h	M.W.I. min	Found	Lit.	Lit.	M.W.I.
1a	H	3.0	1.0	266–268	268	80	90
2a	4-CH_3	4.0	1.0	237	238–239	75	80
3a	4-Cl	4.5	1.5	208–210	210	70	80
4a	4-Br	5.0	1.5	248–249	250	60	75
5a	4-OCH_3	5.0	1.5	247–248	250	55	65

washed with water, dried and recrystallized from acetone. Their melting points were comparable to the reported m.p.s[12–15] (Table 1).

Synthesis of 2-hydroxy-4-methyl quinoline (**2**)

This was prepared according to a literature method.[16]

Synthesis of ethyl-[4-methyl quinolinyl-2-oxy] acetate (**3**)

To a solution of **2** (0.03 mol) in dry acetone, anhydrous K_2CO_3 (10 g) and ethylbromoacetate (0.03 mol) was added. The reaction mixture was refluxed with stirring for 12–13 h. The inorganic salt was filtered and washed with hot acetone. The combined acetone extract was evaporated under reduced pressure to give the product **3**. It was filtered, dried and recrystallized from alcohol, m.p. = 108–110°C; yield = 85%; IR (KBr) cm^{-1}: 1730 (—COO—), 1280 (—C—O—C); ^1H NMR* (acetone-d_6) δ (ppm): 1.30 (t, 3H, —$CH_2\underline{CH_3}$), 2.40 (s, 3H, 4′-CH_3), 4.20 (q, 2H, —$O\underline{CH_2}CH_3$), 5.45 (s, 2H, OCH_2CO), 7.2–7.6 (m, 5H, Ar-H). Found: C, 68.5; H, 6.1; N, 5.7. Calc. for $C_{14}H_{15}NO_3$: C, 68.6; H, 6.1; N, 5.7%.

Synthesis of 4-methyl quinolinyl-2-oxy acetic acid hydrazide (**4**)

A solution of **3** (0.006 mol) and hydrazine hydrate (99%, 0.006 mol) in absolute ethanol was refluxed for 4 h. The reaction mixture was concentrated under reduced pressure. The solid obtained was filtered, dried and recrystallized from alcohol; m.p. = 155°C; yield = 50%; IR (KBr) cm^{-1}: 3300 (—NH_2), 1640 (—CONH); ^1H NMR (DMSO-d_6) δ (ppm): 2.40 (s, 3H, 4′-CH_3), 4.10 (br, 2H, exchanged with D_2O, NH_2), 5.40 (s, 2H,—OCH_2CO—), 7.2–7.6 (m, 5H, Ar-H). Found: C, 62.3; H, 5.6; N, 18.1 Calc. for $C_{12}H_{13}N_3O_2$: C, 62.3; H, 5.6; N, 18.1%.

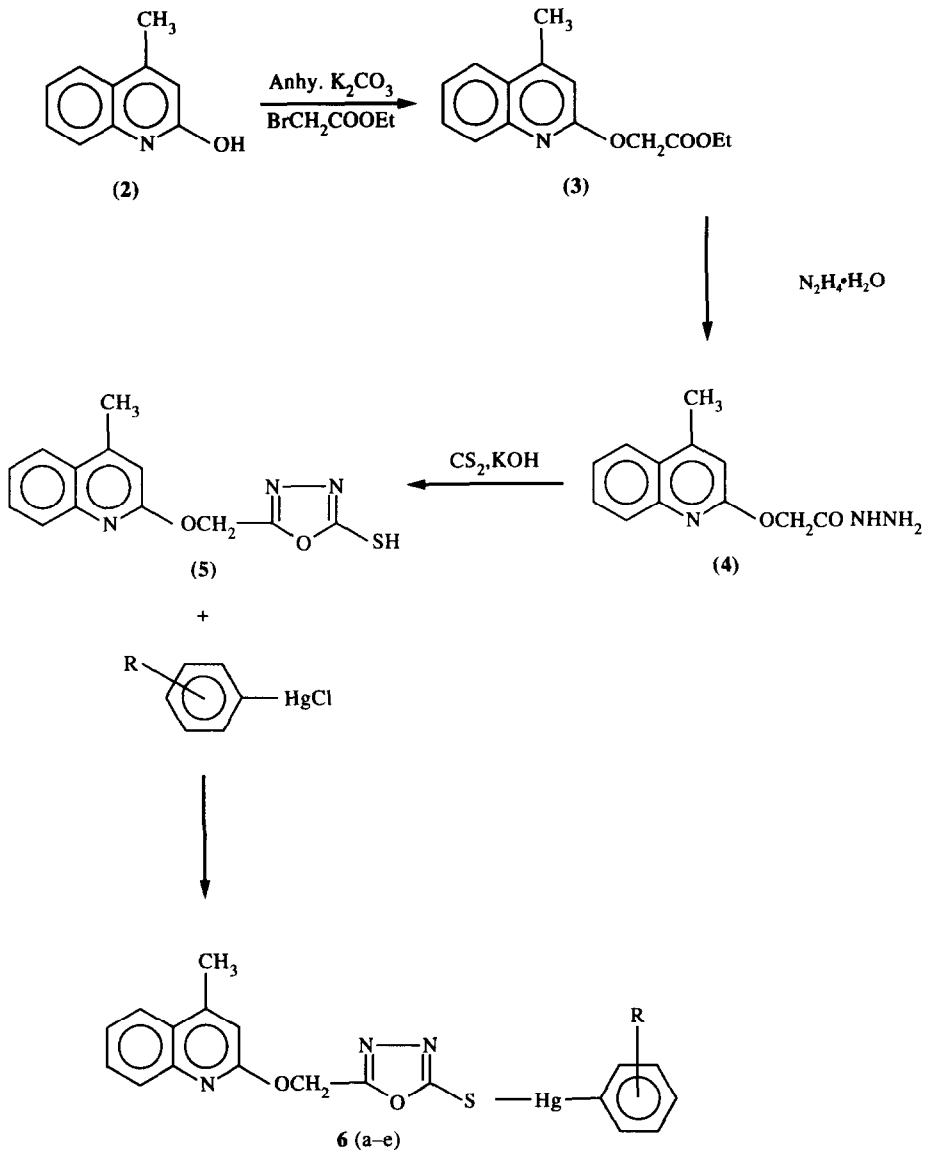
Synthesis of 3-mercapto-5-[4′-methyl quinolinyl-2-oxymethyl]-1,3,4-oxadiazole (**5**)

KOH (0.01 mol) was dissolved in alcohol. To this **4** (0.01 mol) and CS_2 (0.012 mol) was added slowly with stirring and the reaction mixture was refluxed for 12–14 h under anhydrous conditions. Excess solvent was distilled off. The residual mass was poured over crushed ice and neutralized with HCl to bring the pH down to 5. The solid obtained was filtered and washed with water. It was purified by redissolving in alkali and then reprecipitating with acid; m.p. = 275–277°C; yield = 70%; IR (KBr) cm^{-1}, 1530 (—C=N); ^1H NMR (DMSO-d_6) δ (ppm): 2.40 (s, 3H, 4′-CH_3), 5.45 (s, 2H, —OCH_2—), 7.2–7.6 (m, 5H, Ar-H) 13.2 (s, 1H, 2-SH). Found: C, 57.1; H, 4.0; N, 15.3. Calc. for $C_{13}H_{11}N_3O_2S$: C, 57.1; H, 4.0; N, 15.4%.

General procedure for the synthesis of 2-(aryl mercuri thio)-5-[4′-methyl quinolinyl-2-oxy methyl]-1,3,4-oxadiazole (**6a–e**)

Method A. To a solution of **5** (0.01 mol) in DMSO (10 cm^3), anhydrous K_2CO_3 (3 g) and aryl

* s for singlet, d for doublet, t for triplet, q for quartet, m for multiplet and Ar for aromatic.



Scheme 2.

mercuric chloride (0.01 mol) was added. The reaction mixture was heated with stirring at 100–110°C for 4–5 h. The reaction mixture was cooled and then filtered and the product dried and recrystallized from a mixture of DMSO and ethanol.

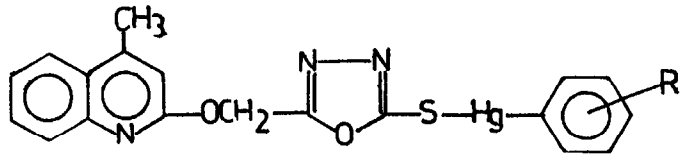
Method B. To a solution of **5** (0.01 mol) in DMF, anhydrous K_2CO_3 (3 g) and aryl mercuric chloride (0.01 mol) was added in a 100 cm^3 beaker. The beaker was irradiated inside a microwave oven for a period of 2.0–3.0 min at 2450 MHz. The reaction mixture was cooled and filtered to remove inorganic salt. The clear filtrate was poured over crushed ice. The solid obtained was filtered, dried and recrystallized from a DMF–ethanol mixture. Physical and spectral data are given in Table 2.

General procedure for the synthesis of 2-(*aryl mercuri thio*)-5-*methyl*-1,3,4-*thiadiazole* (**8a–e**)

Method A. To a solution of 2-mercapto-5-methyl-1,3,4,-thiadiazole, (0.01 mol) in acetone (10 cm^3) anhydrous K_2CO_3 (3 g) and aryl mercuric chloride (0.01 mol) was added. The reaction mixture was refluxed with stirring for 6–8 h. The reaction mixture was cooled and filtered to remove inorganic salt. Excess solvent from the clear filtrate was evaporated under reduced pressure. The solid obtained was filtered, dried and recrystallized from acetone–petroleum ether.

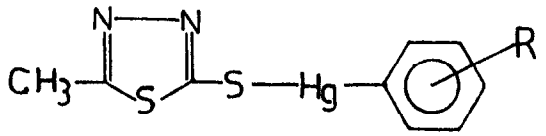
Method B. To a solution of **7** (0.01 mol) in dioxan (10 cm^3), anhydrous K_2CO_3 (3 g) and aryl

Table 2. Physical and spectral data of organomercurials

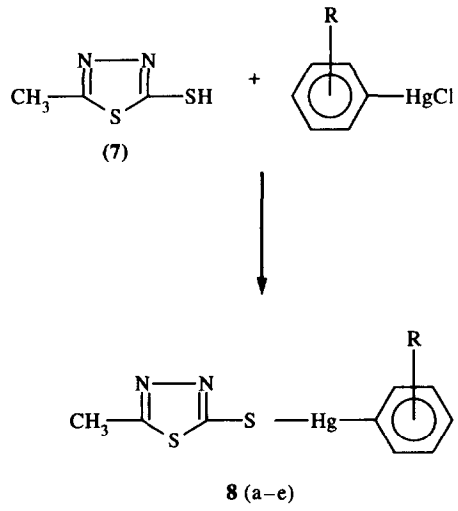


Compound no	R	m.p. (°C)	Found (Calc.)				Reaction time		% Yield		^{1}H NMR (acetone-d_6 + DMSO-d_6) δ(ppm)
			C	H	N	Hg	Method A (h)	Method B (min)	Method A	Method B	
6a	H	212–213	41.5 (41.5)	2.7 (2.7)	7.7 (7.7)	36.5 (36.4)	4.5	2.5	72	80	2.40 (s,3H,4′-CH_3), 5.55 (s,2H,—OCH_2—) 7.1–7.6 (m,10H,Ar-H)
6b	4-CH_3	245–247	42.6 (42.6)	3.0 (3.0)	7.5 (7.5)	35.6 (35.3)	5.0	3.0	64	78	2.30 (s,3H,4-CH_3), 2.40 (s,3H,4′-CH_3), 5.60 (s,2H,—OCH_2—), 7.0–7.6 (m,9H,Ar-H)
6c	4-Cl	253–255	39.1 (39.1)	2.4 (2.4)	7.2 (7.2)	34.3 (34.3)	4.0	2.0	78	92	2.40 (s,3H,4′-CH_3), 5.60 (s,2H,—OCH_2—), 7.4–8.0 (m,9H,Ar-H)
6d	4-Br	273–276	36.3 (36.3)	2.2 (2.2)	6.7 (6.7)	31.9 (31.8)	4.5	2.5	75	82	2.40 (s,3H,4′-CH_3), 5.50 (s,2H,—OCH_2),7.4–8.0 (m-9H,Ar-H)
6e	4-OCH_3	237–239	41.4 (41.4)	2.9 (2.9)	7.3 (7.2)	34.6 (34.5)	4.0	2.0	80	88	2.55 (s,3H,4′-CH_3), 3.70 (s,3H,—OCH_3), 5.60 (s,2H,—OCH_2—), 7.5–8.1 (m,9H,Ar-H)

Table 3. Physical and spectral data of organomercurials



Compound no	R	m.p. (°C)	Found (Calc.) C	H	N	Hg	Reaction time Method A (h)	Method B (min)	% Yield Method A	Method B	^{1}H NMR (acetone-d_6 + DMSO-d_6) δ(ppm)
8a	H	260–262	26.5 (26.5)	2.0 (2.0)	6.8 (6.8)	49.0 (49.0)	7.0	2.0	66	77	2.55 (s,3H,5-CH_3), 7.0–7.4 (m,5H,Ar-H)
8b	4-CH_3	243–244	28.4 (28.4)	2.4 (2.4)	6.7 (6.6)	47.4 (47.4)	8.0	2.0	60	70	2.30 (s,3H,4′-CH_3), 2.55(s,3H,5-CH_3), 7.0–7.4 (m,4H,Ar-H)
8c	4-Cl	215–217	24.4 (24.4)	1.6 (1.6)	6.4 (6.3)	45.2 (45.2)	6.0	1.0	70	85	2.55 (s,3H,5-CH_3), 7.3–7.7 (m,4H,Ar-H)
8d	4-Br	227–230	22.2 (22.2)	1.5 (1.4)	5.8 (5.7)	41.0 (41.1)	6.5	1.5	73	86	2.55 (s,3H,5-CH_3), 7.4–7.8 (m-4H,Ar-H)
8e	4-OCH_3	255–258	27.4 (27.4)	2.3 (2.3)	6.4 (6.4)	45.7 (45.7)	6.0	1.0	84	93	2.55 (s,3H,5-CH_3), 3.80 (s,3H,4′-OCH_3), 7.4–7.8 (m,4H,Ar-H)



Scheme 3.

mercuric chloride (0.01 mol) was added in a 100 cm^3 beaker. The beaker was irradiated inside a microwave oven for a period of 1–2 min at 2450 MHz. The reaction mixture was cooled and filtered to remove inorganic salt. Excess solvent from clear filtrate was evaporated under reduced pressure. The solid obtained was filtered, dried and recrystallized from acetone petroleum ether. Physical and spectral data is given in Table 3.

Repeated synthesis and elemental analysis gave reproducible results.

RESULTS AND DISCUSSION

All the organomercurials are white in colour and stable under atmospheric conditions. The reaction time in preparing aryl mercuric chloride under microwave irradiation is reduced *ca* 200 times with improved yield (Table 1).

Characterization of compounds **3–5**

In compound **3** synthesized by treating **2** with ethyl bromoacetate in the presence of anhydrous K_2CO_3 the IR absorption band at 1730 cm^{-1} confirms the presence of the carboxylate function. Hydrazinolysis of **3** with hydrazine hydrate afforded the corresponding hydrazide **4**, confirmed by IR absorption at 3300 and 1640 cm^{-1} of amine and amide functions. The cyclocondensation of **4** with CS_2 in the presence of KOH yielded mercapto oxadiazole (**5**), confirmed by the disappearance of bands at 3300 and 1640 cm^{-1} and the appearance of a band at 1530 cm^{-1} due to the formation of (—C=N). ^1H NMR and elemental analysis also confirmed the formation of these compounds.

Characterization of organo mercurials **6a–e** *and* **8a–e**

The elemental analysis of all the organomercurials indicated a 1 : 1 stoichiometric ratio of aryl mercury and oxadiazole or thiadiazole moiety. In the ^1H NMR spectrum the signal for SH proton was missing and the signal(s) for aryl group were present (see Tables 2 and 3).

The results shown in Tables 2 and 3 demonstrate the versatility of the process as considerable reaction rate enhancement has been observed by bringing down the reaction time from hours to minutes with improved yields.

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