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Microwave-mediated synthesis of some novel heterocycles containing thiazole, oxazole, thiazine, oxazine, thiadiazine and triazolo-thiadiazine moiety

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5,5-Dimethyl cyclohexane-1,3-dione **1** has been brominated to yield 2-bromo-5,5-dimethyl cyclohexane-1,3-dione **2** which on further reaction with substituted thiocarbamides, carbamides, 2-aminothiophenols, 2-aminophenol, thiocarbohydrazones, thiosemicarbazones and triazoles has furnished 2-substituted imino-5,5-dimethyl-2,3,5,6 -tetrahydro-4*H*-benzothiazol-7-one **3**, 2-substituted imino-5,5-dimethyl-2,3,5,6-tetrahydro-4*H*-benzoxazol-7-one **4**, 7-substituted-2,2-dimethyl-2,3-dihydro-1*H*,10*H* -phenothiazin-4-one **5**, 2,2-dimethyl-2,3-dihydro-1*H*,10*H*-phenoxazin-4-one **6**, Schiff base of 2-hydrazino-6,6-dimethyl-6,7-dihydro-4*H*,5*H*-benzo[1,3,4]thiadiazine-8-one **7**, Schiff base of 2-amino-6,6-dimethyl-6,7-dihydro-4*H*,5*H*-benzo[1,3,4] thiadiazin-8-one **8** and 3-substituted alkyl-7,7-dimethyl-7,8-dihydro-5*H*,6*H*-1,2,4-triazolo[3,4-b][1,3,4]benzothiadiazin-9-one **9** respectively. All the final compounds have been synthesized by microwave irradiation as well as by conventional method.

Keywords: 2-Bromo-5,5-dimethyl cyclohexane-1,3-dione, thiocarbamide, carbamide, 2-aminothiophenol, 2-aminophenol, thiocarbohydrazone, thiosemicarbazone, triazole

IPC Code: Int. Cl.[8] C07D

The compounds bearing thiazole and oxazole moiety have been found to possess antibacterial[1], antitubercular[2] and anti-inflammatory[3] activity. Similarly, heterocycles containing thiazine and oxazine moiety are well known for their diverse biological activity and play a key role as anti-psychotic[4], antiviral[5] and anti-microbial agents[6]. Thiadiazine nucleus is a versatile pharmacophore, which exhibits a wide variety of biological activity. Many of the compounds are anti-microbial[7], anti-irradiation[8] and antiparasitic agents[9]. Fused *s*-triazoles and their derivatives have been investigated for their potential pharmacological properties such as antifungal[10], antidepressant[11] and plant growth regulators[12]. In view of the biological potential of the above pharmacophores, synthesis of various derivatives has been undertaken.

In the recent years, Microwave-induced Organic Reaction Enhancement (MORE) chemistry[13] has received considerable attention due to several advantages. The salient features of the microwave approach are rapid reaction rates, cleaner reaction conditions and enhancement in chemical yields[14,15]. Another area of interest which has been under focus recently is to avoid the use of organic solvent, use of which leads to wastage, and is detrimental to the environment[16]. Thus, keeping in view the utility of MORE chemistry a series of five and six membered fused ring heterocyclic compounds have been synthesized by microwave irradiation as well as by conventional methods.

Results and Discussion

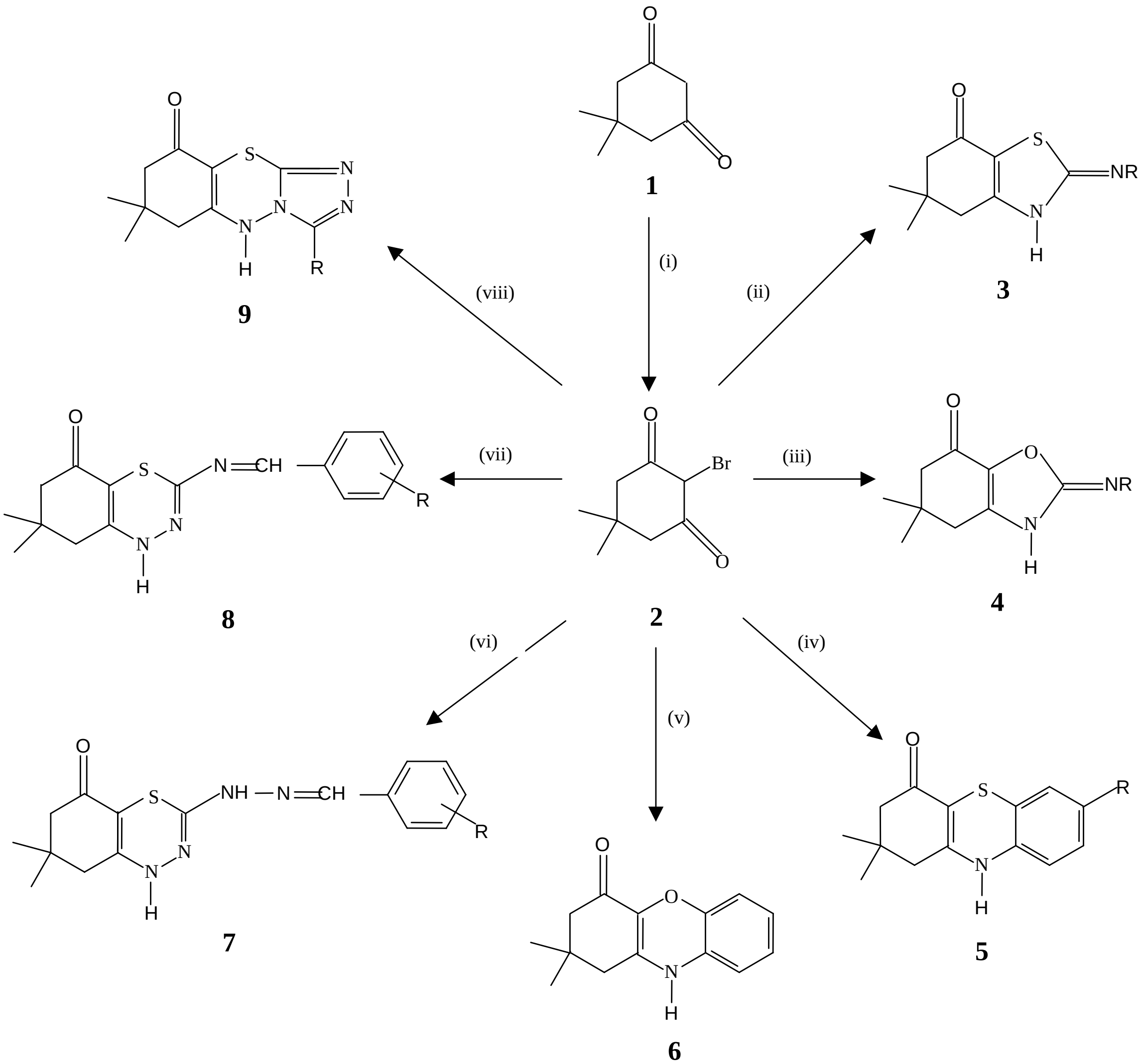
The synthesis of 2-bromo-5,5-dimethyl cyclohexane-1,3-dione **2** was achieved from 5,5-dimethyl cyclohexane-1,3-dione (ref. 17) **1** using reported procedure[18]. The title compounds 2-substituted imino-5,5-dimethyl-2,3,5,6 - tetrahydro - 4*H*-benzothiazol-7-one **3a-f,** 2-substituted imino-5,5-dimethyl-2,3,5,6-tetra-hydro-4*H*-benzoxazol-7-one **4a-f** and 7-substituted-2, 2-dimethyl-2, 3-dihydro-1*H*,10*H*-phenothiazin-4-one **5a-e** were synthesized by reacting bromo compound **2** with substituted thiocarbamides[19], carbamides[20] and 2-aminothiophenols[21,22] respectively, in presence of piperidine using ethanol as solvent. The bromo compound **2** on reaction with 2-aminophenol using DMSO as solvent in presence of sodium fluoride as catalyst provided 2,2-dimethyl-2,3-dihydro-1*H*,10*H*-phenoxazin-4-one **6a**. The condensation of thiocarbo-hydrazide[23] and thiosemicarbazide[24] with different aromatic aldehydes in ethanol containing catalytic amount of glacial acetic acid yielded the corresponding hydrazones[25] which were treated with 2-bromo-5,5-dimethylcyclohexane-

1,3-dione **2** to give Schiff base of 2-hydrazino-6,6-dimethyl-6, 7-dihydro-4*H*, 5*H*-benzo[1,3,4]thiadiazin-8-one **7a-f** and Schiff base of 2-amino-6,6-dimethyl-6,7-dihydro-4*H*,5*H*-benzo[1,3,4]thiadiazin-8-one **8a-f** respectively.The products **9a-c** containing triazolo-thiadiazine moiety were obtained by reaction of bromo compound **2** with different triazoles[26] (**Scheme I**).

As compared to classical thermal method the time required for completion of these reactions under microwave conditions is considerably less and the products are obtained with improved yields **(Table I)**. The formation of title compounds has been delineated by spectral analyses **(Table I)**.

Experimental Section

Melting points of all the compounds were determined in open ended capillary tubes on an electrothermal apparatus and are uncorrected. The homogeneity of the compounds was determined by thin layer chromatography on silica gel coated aluminium plates (Merck) as adsorbent and UV light as visualizing agent. IR spectra (KBr) were recorded on Perkin-Elmer spectrometer in the spectral range of



(i) Br_2/GAA/UV Light
(ii) Thiocarbamides/Piperidine/Ethanol
(iii) Carbamides/Piperidine/Ethanol
(iv) 2-Aminothiophenols/Piperidine/Ethanol
(v) 2-Aminophenol/Sodium fluoride/DMSO
(vi) Thiocarbohydrazones/Piperidine/Ethanol
(vii) Thiosemicarbazones/Piperidine/Ethanol
(viii) Triazoles/Piperidine/Ethanol

Scheme I

Table I—Physical and spectral characterization data of compounds

Compd	R	Mol. formula	m.p.	Yield, %		^{1}H NMR data (δ ppm)
			°C	MWI	CON	
3a	H	$C_9H_{12}N_2OS$	230	76	71	
3b	C_6H_5	$C_{15}H_{16}N_2OS$	218	78	69	
3c	4-Cl-C_6H_4	$C_{15}H_{15}N_2OSCl$	190	81	76	1.04 (s, 6H, 2 × CH_3), 1.25 (s, 2H, CH_2 at C_4), 2.38 (s, 2H, CH_2 at C_6), 7.2-7.5 (m, 4H, ArH), 8.63 (s, 1H, NH)
3d	4-OCH_3-C_6H_4	$C_{16}H_{18}N_2O_2S$	196	65	59	
3e	2-CH_3-C_6H_4	$C_{16}H_{18}N_2OS$	202	79	66	
3f	4-CH_3-C_6H_4	$C_{16}H_{18}N_2OS$	182	78	72	
4a	H	$C_9H_{12}N_2O_2$	170	63	60	
4b	C_6H_5	$C_{15}H_{16}N_2O_2$	166	69	67	
4c	4-Cl-C_6H_4	$C_{15}H_{15}N_2O_2Cl$	206	84	72	0.97 (s, 6H, 2 × CH_3), 1.22 (s, 2H, CH_2 at C_4), 2.18 (s, 1H, CH at C_6), 5.87 (s, 1H, OH at C_7), 7.2-7.6 (m, 4H, ArH), 8.63 (s, 1H, NH)
4d	4-OCH_3-C_6H_4	$C_{16}H_{18}N_2O_3$	120	76	71	
4e	2-CH_3-C_6H_4	$C_{16}H_{18}N_2O_2$	160	72	67	
4f	4-CH_3-C_6H_4	$C_{16}H_{18}N_2O_2$	154	86	84	
5a	H	$C_{14}H_{15}NOS$	264	89	83	1.10 (s, 6H, 2 × CH_3), 2.17 (s, 2H, CH_2 at C_1), 2.30 (s, 2H, CH_2 at C_3), 6.2-7.2 (m, 4H, ArH), 8.96 (s, 1H, NH)
5b	Br	$C_{14}H_{14}NOSBr$	240	94	91	
5c	Cl	$C_{14}H_{14}NOSCl$	215	90	88	0.97 (s, 6H, 2 × CH_3), 2.13 (s, 2H, CH_2 at C_1), 2.17 (s, 2H, CH_2 at C_3), 6.4-7.0 (m, 3H, ArH), 8.94 (s, 1H, NH)
5d	OCH_3	$C_{15}H_{17}NO_2S$	246	78	73	
5e	CH_3	$C_{15}H_{17}NOS$	194	62	60	
6a	H	$C_{14}H_{15}NO_2$	154	81	74	1.04 (s, 6H, 2 × CH_3), 2.21 (s, 2H, CH_2 at C_1), 2.70 (s, 2H, CH_2 at C_3), 7.0-7.5 (m, 4H, ArH), 9.61 (s, 1H, NH)
7a	H	$C_{16}H_{18}N_4OS$	162	75	66	
7b	4-Cl	$C_{16}H_{17}N_4OSCl$	120	62	60	
7c	2-OH	$C_{16}H_{18}N_4O_2S$	191	70	61	1.04 (s, 6H, 2 × CH_3), 2.48 (s, 2H, CH_2 at C_5), 2.76 (s, 2H, CH_2 at C_7), 6.8-7.5 (m, 4H, ArH), 8.54 (s, 1H, N=CH), 10.29 (s, 1H, NH-N), 10.40 (s, 1H, NH), 10.84 (s, 1H, OH)
7d	4-OH	$C_{16}H_{18}N_4O_2S$	198	72	60	
7e	4-OH-3-OCH_3	$C_{17}H_{20}N_4O_3S$	220	73	68	
7f	4-OCH_3	$C_{17}H_{20}N_4O_2S$	125	65	56	
8a	H	$C_{16}H_{17}N_3OS$	210	80	69	1.04 (s, 6H, 2 × CH_3), 1.15 (s, 2H, CH_2 at C_5), 2.43 (s, 1H, CH at C_9), 2.73 (s, 1H, CH at C_7), 4.2 (s, 1H, OH at C_8), 7.2-8.0 (m, 6H, ArH & N=CH)
8b	4-Cl	$C_{16}H_{16}N_3OSCl$	198	72	64	
8c	2-OH	$C_{16}H_{17}N_3O_2S$	202	77	61	
8d	4-OH	$C_{16}H_{17}N_3O_2S$	216	79	63	
8e	4-OH-3-OCH_3	$C_{17}H_{19}N_3O_3S$	235	75	69	
8f	4-OCH_3	$C_{17}H_{19}N_3O_2S$	228	79	61	
9a	H	$C_{10}H_{12}N_4OS$	261	77	74	
9b	CH_3	$C_{11}H_{14}N_4OS$	246	65	60	0.99 (s, 6H, 2 × CH_3), 2.31 (s, 2H, CH_2 at C_6), 2.33 (s, 3H, CH_3), 2.38 (s, 2H, CH_2 at C_8), 11.72 (s, 1H, NH)
9c	C_2H_5	$C_{12}H_{16}N_4OS$	240	78	67	

Method A/ MWI: Time reqd. 3 to 4 min.
Method B/ CON: Time reqd. 4 to 5 hr.
All the compounds gave satisfactory C, H and N analyses.

4000-400 cm^{-1}. ^{1}H NMR spectra were recorded on Bruker 500 MHz NMR spectrometer using CDCl$_3$/DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). Microwave irradiations were carried out in an unaltered domestic microwave oven (Samsung, Model No. M1630N, 2450 MHz, 900 W).

2-Bromo-5,5-dimethylcyclohexane-1,3-dione, 2

5,5-Dimethylcyclohexane-1,3-dione **1** (0.01 mole) was dissolved in minimum quantity of gl. acetic acid. A solution of bromine (0.01 mole) in gl. acetic acid was added dropwise with continuous stirring in presence of UV light. The reaction mixture was then quenched into ice-cold water and the product separated out was filtered, washed several times with cold water and purified by recrystallization from ethanol to give 2-bromo-5,5-dimethyl cyclo-hexane-1,3-dione **2**, yield 86%, m.p.174°C (Lit[18] m.p.176°C).

2-Substituted imino-5,5-dimethyl-2,3,5,6-tetrahydro-4*H*-benzothiazol-7-one, 3a-f

Method A (MWI)

2-Bromo-5,5-dimethylcyclohexane-1,3-dione **2** (0.001 mole) and substituted thiocarbamide (0.001 mole) were taken in ethanol (5 mL) in an Erlenmeyer flask.

Piperidine (0.002 mole) was added to it as a catalyst and the reaction mixture was irradiated for 3 min. Progress of the reaction was monitored by TLC. After completion of reaction, the contents were poured into crushed ice. The solid obtained was filtered off, washed with water and purified by recrystallization from ethanol to get thiazoles **3a-f**.

Method B (Conventional)

An equimolar mixture of compound **2** (0.01 mole) and substituted thiocarbamide (0.01 mole) in ethanol (20 mL) was refluxed in presence of piperidine (0.02 mole) for about 4-5 hr. On work-up as described above in method A (MWI) the thiazoles **3a-f** were obtained.

The characterization data of the compounds **3a-f** are given in **Table I**.

2-Substituted imino-5,5-dimethyl-2,3,5,6-tetrahydro-4*H*-benzoxazol-7-one, 4a-f

Method A (MWI)

A solution of bromo compound **2** (0.001 mole), substituted carbamide (0.001 mole) and piperidine (0.002 mole) in ethanol (5 mL) taken in an Erlenmeyer flask was exposed to microwave irradiation for 4 min. The reaction mixture was quenched into crushed ice. The product precipitated out was filtered, washed with water and purified by recrystallization from ethanol to give oxazoles **4a-f**.

Method B (Conventional)

The compound 2 (0.01 mole) was dissolved in ethanol (20 mL) containing piperidine (0.02 mole) as a catalyst. Appropriate carbamide (0.01 mole) was added to it and the reaction mixture was refluxed for about 4-5 hr. After completion of the reaction, the product was isolated as described above in method A (MWI).

The characterization data of the compounds **4a-f** are given in **Table I**.

7-Substituted-2,2-dimethyl-2,3-dihydro-1*H*,10*H*-phenothiazin-4-one, 5

Method A (MWI)

A solution of compound **2** (0.001 mole), substituted 2-aminothiophenol (0.001 mole) and piperidine (0.002 mole) in ethanol (5 mL) was taken in an Erlenmeyer flask and irradiated for 3 min. After completion of the reaction, the mixture was poured into ice-cold water. The yellow product **5** obtained was filtered off, washed with dilute HCl followed by water and purified by recrystallization from ethanol.

Method B (Conventional)

The bromo derivative **2** (0.01 mole) in ethanol (20 mL) was refluxed with substituted 2-aminothiophenol (0.01 mole) in presence of piperidine (0.02 mole) for about 4-5 hr. The reaction mixture was worked-up as described above.

The characterization data of the compounds **5a-e** are given in **Table I**.

2,2-Dimethyl-2,3-dihydro-1*H*,10*H*-phenoxazin-4-one, 6

Method A (MWI)

An equimolar mixture of compound **2** (0.001 mole) and 2-aminophenol (0.001 mole) was taken in DMSO (5 mL) containing sodium fluoride (0.002 mole) in an Erlenmeyer flask and irradiated in a microwave oven for 3 min. The contents were poured into crushed ice. The solid obtained was filtered, washed with dilute HCl, water and purified by recrystallization from ethanol to yield **6**.

Method B (Conventional)

The bromo compound **2** (0.01 mole) was added to a solution of 2-aminophenol (0.01 mole) and sodium fluoride (0.02 mole) in DMSO (20 mL). The reaction mixture was refluxed for about 4-5 hr. The product **6** was isolated as described above.

The characterization data of the compound **6a** is given in **Table I**.

Schiff base of 2-hydrazino-6,6-dimethyl-6,7-dihydro-4*H*,5*H*-benzo[1,3,4] thiadiazin-8-one, 7a-f

Method A (MWI)

To a solution of compound **2** (0.001 mole) and substituted thiocarbohydrazone (0.001 mole) in ethanol (5 mL) taken in an Erlenmeyer flask, piperidine (0.002 mole) was added as catalyst. The reaction mixture was subjected to microwave irradiation for 3 min. The reaction mixture was poured into ice-cold water and the resulting solid obtained was filtered off, washed several times with water, dried and purified by recrystallization from ethanol to give **7a-f**.

Method B (Conventional)

A mixture of bromo compound **2** (0.01 mole), substituted thiocarbohydrazone (0.01 mole) and piperidine (0.02 mole) in ethanol (20 mL) was refluxed for about 4-5 hr. The solid product **7a-f** was isolated in pure form by following the work-up as described above.

The characterization data of the compounds **7a-f** are given in **Table I**.

Schiff base of 2-amino-6,6-dimethyl-6,7-dihydro-4*H*,5*H*-benzo[1,3,4]thiadiazin-8-one, 8a-f

Method A (MWI)

The compound **2** (0.001 mole), substituted thiosemicarbazone (0.001 mole) and piperidine (0.002 mole) in ethanol (5 mL) were irradiated in an Erlenmeyer flask under microwave irradiation for 3 min. The contents were poured into crushed ice. The product precipitated out was filtered, washed with water, dried and purified by recrystallization from ethanol to yield Schiff base **8a-f**.

Method B (Conventional)

Appropriate thiosemicarbazone (0.01 mole) was added to a solution of the bromo compound **2** (0.01 mole) in ethanol (20 mL). A catalytic amount of piperidine (0.02 mole) was added to it and the mixture was refluxed for about 4-5 hr. The product **8** was obtained on work-up as described above in method A (MWI).

The characterization data of the compounds **8a-f** are given in **Table I**.

3-Substituted alkyl-7,7-dimethyl-7,8-dihydro-5*H*,6*H*-1,2,4-triazolo[3,4-b][1,3,4]benzothiadiazin-9-one, 9a-c

Method A (MWI)

An equimolar solution of compound **2** (0.001 mole) and substituted triazole (0.001 mole) in ethanol (5 mL) containing piperidine (0.002 mole) was taken in an Erlenmeyer flask and subjected to microwave irradiation for 3 min. The mixture was quenched into crushed ice. The triazolo-thiadiazine **9a-c** obtained was filtered, washed with water and purified by recrystallization from ethanol.

Method B (Conventional)

The bromo derivative **2** (0.01 mole) was dissolved in ethanol (20 mL) and substituted triazole (0.01 mole) was added to the clear solution followed by addition of piperidine (0.02 mole). The reaction mixture was refluxed for about 4-5 hr. Upon completion of the reaction (progress monitored by TLC), the product **9a-c** was isolated as described above.

The characterization data of the compounds **9a-c** are given in **Table I**.

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