EFFICIENT SYNTHESIS OF SOME NOVEL SPIRO HETEROCYCLES CONTAINING THIAZOLE, OXAZOLE, THIADIAZOLE AND TRIAZOLO-THIADIAZOLE MOIETY UNDER MICROWAVE IRRADIATION

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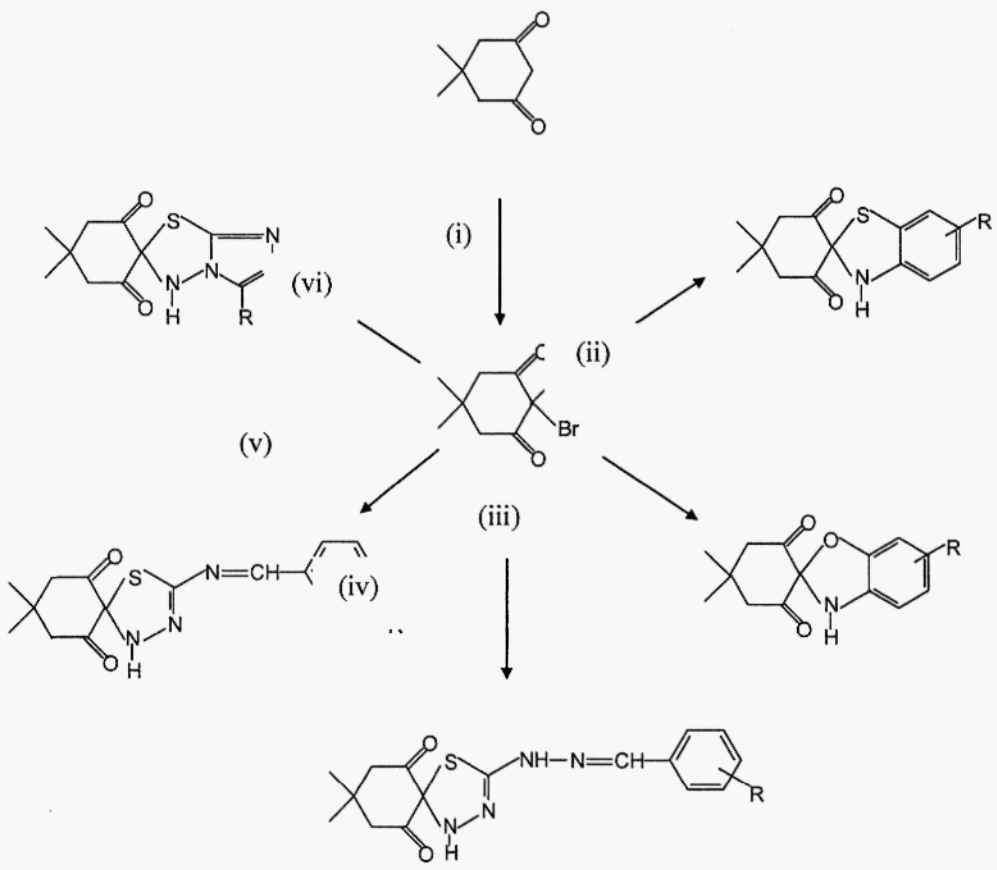
Abstract: 5,5-Dimethyl cyclohexane-1,3-dione 1 was treated with twice the molar quantity of bromine in glacial acetic acid to yield 2,2-dibromo-5,5-dimethyl cyclohexane-1,3-dione 2. The dibromo compound 2 was subjected to reaction with substituted 2-aminothiophenols, 2-aminophenol, thiocarbohydrazones, thiosemicarbazones and triazoles to furnish spiro-(2',6'-dioxo-4',4'-dimethyl cyclohexane)-6-substituted-1,3-benzothiazole 3, spiro-(2',6'-dioxo-4',4'-dimethyl cyclohexane)-6-substituted-1,3-benzoxazole 4, Schiff base of 1-thia-2-hydrazino-3,4-diaza-4*H*-6,10-dioxo-7,9-dihydro-8,8-dimethyl-spiro[4,5]dec-2-ene 5, Schiff base of 1-thia-2-amino-3,4-diaza-4*H*-6,10-dioxo-7,9-dihydro-8,8-dimethyl-spiro[4,5]dec-2-ene 6 and spiro-(2',6'-dioxo-4',4'-dimethyl cyclohexane)-1,3,4-thiadiazolo[2,3-d]-4-substituted-1,2,4-triazoles 7 respectively. All the final desired compounds have been synthesized by ensuing the microwave irradiation technique as well as classical thermal method. The structures of the newly synthesized compounds have been established by analytical and spectral methods.

Introduction

The quest for a more reliable and suitable drug is always fascinating and challenging. A number of drugs containing simple heterocyclic moiety or a combination of different heterocyclic moieties have been in use these days. The compounds containing thiazole ring system are known for their extensive therapeutic activities (1,2) in medicinal chemistry. Vitamin B, sulphathiazole, aminotriazole, promizole and thiobendazole, all contain thiazole moiety in one form or the other. Similarly, oxazole is also an important heterocyclic ring system and the targets containing oxazole moiety possess most remarkable and a wide range of biological activity (3). Thiadiazole nucleus, which incorporates a toxophoric N-C-S linkage, exhibits a large number of pharmacological activity (4). A number of 1,3,4-thiadiazoles possess anti-microbial properties comparable with sulphonamide drugs (5). Various 1,2,4-triazoles and N-bridged heterocycles derived from them such as 1,2,4-triazolo-thiadiazole have been found to possess promising pharmacological activities (6,7). The wide range of therapeutic value of above ring system prompted us to synthesize some novel spiro heterocyclic drug compounds.

The application of microwaves in organic synthesis has experienced exponential growth within the last decade. The usefulness of microwave energy for the preparation of a wide variety of organic compounds using a microwave system shows rate enhancement in reactions with better yields (8,9). In view of these observations, it was considered worthwhile to synthesize hitherto unknown title compounds (Scheme-1)



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

Scheme-1

Discussions

2,2-Dibromo-5,5-dimethyl cyclohexane-1,3-dione **2** was synthesized by treatment of 5,5-dimethyl cyclohexane-1,3-dione **1** (10) with twice the molar quantity of bromine in glacial acetic acid under UV light. The dibromo compound **2** was subjected to reaction with substituted 2-aminothiophenols (11,12) in presence of piperidine using ethanol as solvent to yield spiro-(2',6'-dioxo-4',4'-dimethyl cyclohexane)-6-substituted-1,3-benzothiazole **3a-e.** An equimolar proportion of the compound **2** and 2-aminophenol undergoes ring cyclisation in presence of sodium fluoride under microwave irradiation to form spiro-(2',6'-dioxo-4',4'-dimethyl cyclohexane)-6-substituted-1,3-benzoxazole **4a.** The hydrazones (13) obtained by the condensation of thiocarbohydrazide (14) and thiosemicarbazide (15) with different aromatic aldehydes were treated with dibromo derivative **2** to furnish Schiff base of 1-thia-2-hydrazino-

3,4-diaza-4*H*-6,10-dioxo-7,9-dihydro-8,8-dimethyl-spiro[4,5]dec-2-ene **5a-f** and Schiff base of 1-thia-2-amino-3,4-diaza-4*H*-6,10-dioxo-7,9-dihydro-8,8-dimethyl-spiro[4,5] dec-2-ene **6a-f** respectively. Spiro-(2',6'-dioxo-4',4'-dimethyl cyclohexane)-1,3,4-thiadiazolo[2,3-d]-4-substituted-1,2,4-triazoles **7a-c** were prepared by reaction of dibromo compound 2 with different triazoles (16) in presence of piperidine using ethanol as solvent.

The time required for completion of reaction and the yields in microwave technique were comparable with the traditional thermal method (**Table-1**). The spectral data and the elemental analysis were in keeping with the proposed structure assigned to the title compounds (**Table-1**).

Table-1: Characterization data of compounds

Sr No.	Compd	R	Molecular Formula	M.P.	Yield °C MWI	Yield % CON	Spectra IR (KBr cm^{-1})/ ^1H NMR (δ ppm)
1	3a	H	$C_{14}H_{13}NO_2S$	235	72	69	IR: 3275 (NH), 1620 (C=O) ^1H NMR: 1.08 (s, 6H, 2×CH_3), 2.17 (s, 4H, 2×CH_2), 6.2-7.2 (m, 4H, ArH), 9.04 (s, 1H, ring NH)
2	3b	4-Br	$C_{14}H_{14}NO_2SBr$	156	84	78	IR: 3290 (NH), 1640 (C=O)
3	3c	4-Cl	$C_{14}H_{14}NO_2SCl$	164	90	88	IR: 3280 (NH), 1640 (C=O)
4	3d	4-OCH_3	$C_{15}H_{17}NO_3S$	144	63	59	IR: 3280 (NH), 1650 (C=O)
5	3e	4-CH_3	$C_{15}H_{17}NO_2S$	217	67	61	IR: 3275 (NH), 1620 (C=O)
6	4a	H	$C_{14}H_{15}NO_3$	166	79	74	IR: 3348 (NH), 1660 (C=O) ^1H NMR: 1.58 (s, 6H, 2×CH_3), 2.17 (s, 4H, 2×CH_2), 7.3-8.0 (m, 4H, ArH), 8.16 (s, 1H, ring NH)
7	5a	H	$C_{16}H_{18}N_4O_2S$	154	77	68	IR: 3050 (NH), 1620 (C=O), 1540 (C=N)
8	5b	4-Cl	$C_{16}H_{17}N_4O_2SCl$	185	72	66	IR: 3100 (NH), 1612 (C=O), 1575 (C=N) ^1H NMR: 1.06 (s, 6H, 2×CH_3), 2.16 (s, 4H, 2×CH_2), 7.3-8.0 (m, 4H, ArH), 8.28 (s, 1H, N=CH), 9.58 (s, 1H, NH-N), 10.28 (s, 1H, ring NH)
9	5c	2-OH	$C_{16}H_{18}N_4O_3S$	130	74	67	IR: 3050 (NH), 1620 (C=O), 1540 (C=N)
10	5d	4-OH	$C_{16}H_{18}N_4O_3S$	148	72	60	IR: 3100 (NH), 1640 (C=O), 1520 (C=N)
11	5e	4-OH-3-OCH_3	$C_{17}H_{20}N_4O_4S$	132	69	68	IR: 3090 (NH), 1640 (C=O), 1520 (C=N)
12	5f	4-OCH_3	$C_{17}H_{20}N_4O_3S$	176	65	59	IR: 3100 (NH), 1612 (C=O), 1575 (C=N)
13	6a	H	$C_{16}H_{17}N_3O_2S$	162	83	77	IR: 3180 (NH), 1660 (C=O), 1580 (C=N)
14	6b	4-Cl	$C_{16}H_{16}N_3O_2SCl$	112	81	78	IR: 3140 (NH), 1650 (C=O), 1540 (C=N)
15	6c	2-OH	$C_{16}H_{17}N_3O_3S$	194	72	64	IR: 3100 (NH), 1620 (C=O), 1560 (C=N)
16	6d	4-OH	$C_{16}H_{17}N_3O_3S$	228	70	61	IR: 3290 (NH), 1607 (C=O), 1514 (C=N) ^1H NMR: 1.03 (s, 6H, 2×CH_3), 2.30 (s, 4H, 2×CH_2), 6.7-7.6 (m, 4H, ArH), 8.01 (s, 1H, N=CH), 9.94 (s, 1H, ring NH), 12.49 (s, 1H, OH)
17	6e	4-OH-3-OCH_3	$C_{17}H_{19}N_3O_4S$	179	75	69	IR: 3290 (NH), 1620 (C=O), 1514 (C=N)
18	6f	4-OCH_3	$C_{17}H_{19}N_3O_3S$	165	79	66	IR: 3190 (NH), 1650 (C=O), 1520 (C=N)
19	7a	H	$C_{10}H_{12}N_4O_2S$	248	77	74	IR: 3150 (NH), 1640 (C=O), 1510 (C=N)
20	7b	CH_3	$C_{11}H_{14}N_4O_2S$	230	86	81	IR: 3100 (NH), 1627 (C=O), 1590 (C=N) ^1H NMR: 0.98 (s, 6H, 2×CH_3), 2.34 (s, 4H, 2×CH_2), 2.39 (s, 3H, CH_3), 11.73 (s, 1H, ring NH)
21	7c	C_2H_5	$C_{12}H_{16}N_4O_2S$	175	78	67	IR: 3100 (NH), 1650 (C=O), 1550 (C=N)

Method A: Time reqd-1 to 3 mnts
Method B: Time reqd-2 to 5 hrs
Satisfactory C, H and N analysis were obtained for all the compounds.

Experimental

Melting points of all synthesized compounds were determined in open capillary tubes on an electrothermal apparatus and are uncorrected. The purity of the compounds was monitored by thin layer chromatography on silica gel coated aluminium plates (Merck) as adsorbent and uv light as visualizing agent. IR spectra (KBr in cm^{-1}) were recorded on Perkin-Elmer spectrophotometer in the range of 4000-400 cm^{-1}. ^1H NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer 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).

2,2-Dibromo-5,5-dimethyl cyclohexane-1,3-dione (2)
To a suspension of 5,5-dimethyl cyclohexane-1,3-dione **1** (0.01 mole) in minimum quantity of glacial acetic acid, a solution of bromine (0.02 mole) in glacial acetic acid was added drop wise with continuous stirring under uv light. The reaction mixture was then poured into ice-cold water and the product separated out was filtered, washed several times with cold water to remove any traces of acid and recrystallized from ethanol to obtain 2,2-dibromo-5,5-dimethyl cyclohexane-1,3-dione **2**, yield 84%, m.p.140°C.
Spiro-(2',6'-dioxo-4',4'-dimethyl cyclohexane)-6-substituted-1,3-benzothiazole (3)

Method A (MWI):
2,2-Dibromo-5,5-dimethyl cyclohexane-1,3-dione **2** (0.001 mole) and substituted 2-amino thiophenol (0.001 mole) were taken in ethanol (5 cm^3) in an Erlenmeyer flask. Piperidine (0.002 mole) was added to it as a catalyst and the reaction mixture was irradiated in a microwave oven for 3 mnts. The reaction was monitored by TLC and after completion of the reaction, the contents were poured onto crushed ice. The solid obtained was filtered off, washed with dilute HCl followed by water and crystallized from ethanol to get benzothiazoles **3**.

Method B (Conventional):
An equimolar mixture of compound **2** (0.01 mole) and substituted 2-amino thiophenol (0.01 mole) in ethanol (20 cm^3) was refluxed in presence of piperidine (0.02 mole) for about 4-5 hrs. After monitoring the reaction on TLC, the reaction mixture was worked-up in an analogous way as described above in method A (MWI).

The characterization data of the compounds **3a-e** are given in **Table-1**.
Spiro-(2',6'-dioxo-4',4'-dimethyl cyclohexane)-6-substituted-1,3-benzoxazole (4)

Method A (MWI):
The dibromo compound **2** (0.001 mole), 2-aminophenol (0.001 mole), sodium fluoride (0.002 mole) and DMSO (5 cm^3) in an Erlenmeyer flask were exposed to microwave irradiation for 3 mnts. Upon completion of the reaction (monitored by TLC), the reaction mixture was quenched onto crushed ice. The product precipitated out was filtered, washed with dilute HCl, water and recrystallized from ethanol to yield benzoxazole **4**.

Method B (Conventional):
A mixture of compound **2** (0.01 mole), 2-aminophenol (0.01 mole) and sodium fluoride (0.02 mole) in DMSO (5 cm^3) was refluxed for about 4-5 hrs. After monitoring the progress of reaction on TLC, the solid product was isolated in pure form by following the similar process as described above in method A (MWI).

The characterization data of the compound **4a** is given in **Table-1**.

Schiff base of 1-thia-2-hydrazino-3,4-diaza-4*H*-6,10-dioxo-7,9-dihydro-8,8-dimethyl-spiro[4,5]dec-2-ene (5)

Method A (MWI):
To a solution of dibromo compound **2** (0.001 mole) and substituted thiocarbohydrazone (0.001 mole) in ethanol (5 cm^3) taken in an Erlenmeyer flask, piperidine (0.002 mole) was added as catalyst. The reaction mixture was subjected to microwave irradiation for one minute and the progress of the reaction was monitored by TLC. Upon completion of the reaction the contents were dumped into ice-cold water. The resulting solid **5** obtained was filtered off, washed several times with water, dried and crystallized from ethanol.

Method B (Conventional):
The dibromo compound **2** (0.01 mole) was added to a solution of substituted thiocarbohydrazone (0.01 mole) in ethanol (20 cm^3) containing piperidine (0.02 mole) as catalyst. The reaction mixture was refluxed for about 2-3 hrs. The reaction was monitored by TLC and after completion, the mixture was worked-up by following the procedure described as above in method A (MWI).
The characterization data of the compounds **5a-f** are given in **Table-1**.

Schiff base of 1-thia-2-amino-3,4-diaza-4*H*-6,10-dioxo-7,9-dihydro-8,8-dimethyl-spiro[4,5]dec-2- ene (6)

Method A (MWI):
Appropriate thiosemicarbazone (0.001 mole) was added to a solution of compound **2** (0.001 mole) in ethanol (5 cm^3) in an Erlenmeyer flask. A catalytic amount of piperidine (0.002 mole) was added to it and the reaction mixture was irradiated under microwave irradiation for one minute. The progress of the reaction was monitored by TLC and upon completion, the mixture was poured onto crushed ice. The product precipitated out was filtered, washed with water and recrystallized from ethanol to furnish Schiff base **6**.

Method B (Conventional):
A mixture of dibromo derivative **2** (0.01 mole), substituted thiosemicarbazone (0.01 mole) and piperidine (0.02 mole) was dissolved in ethanol (20 cm^3) and refluxed for about 2-3 hrs. Upon completion of the reaction (monitored by TLC) the product **6** was worked-up in a similar way as described above in method A (MWI).

The characterization data of the compounds **6a-f** are given in **Table-1**.

Spiro-(2',6'-dioxo-4',4'-dimethyl cyclohexane)-1,3,4-thiadiazolo[2,3-d]-4-substituted-1,2,4-triazoles (7)

Method A (MWI):
An equimolar proportion of compound **2** (0.001 mole) and substituted triazole (0.001 mole) in ethanol (5 cm^3) containing piperidine (0.002 mole) were taken in an Erlenmeyer flask and subjected to microwave irradiation for 3 mnts. After monitoring the reaction on TLC, the mixture was quenched onto crushed ice. The product obtained was filtered, washed with water and crystallized from ethanol to yield triazolo-thiadiazole **7**.

Method B (Conventional):
Substituted triazole (0.01 mole) was added to a solution of dibromo compound **2** (0.01 mole) in ethanol (20 cm^3) followed by addition of piperidine (0.02 mole). The reaction mixture was refluxed for about 4-5 hrs and upon completion of the reaction, the product was isolated in a similar process as described above in method A (MWI).

The characterization data of the compounds **7a-c** are given in **Table-1**.

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