

Microwave accelerated synthesis of novel spiro heterocycles

Vijay V Dabholkar* & Sagar D Parab

Organic Research Laboratory, Department of Chemistry, K C College, Churchgate, Mumbai 400 020, India

E-mail: vijudabholkar@hotmail.com

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Interaction of 3,3-dibromo carbostyryl **1** with substituted triazoles **2**, amidinothiocarbamides **4**, amidinocarbamide **6**, guanidines **8** and thiocarbohydrazide **10** furnishes spiro(1'*H*-2',4'-dioxo-6',8'-disubstituted quinoline)-4*H*-1,3,4-thiadiazolo[2,3-*d*](3-substituted)-1,2,4-triazole **3**, 2-guanidino/substituted guanidino-spiro(1'*H*-2',4'-dioxo-6',8'-disubstituted quinoline)-1,3-thiazetidin-2-ene **5**, 2-guanidino-spiro(1'*H*-2',4'-dioxo-6',8'-disubstituted quinoline)-1,3-oxazetidin-2-ene **7**, 1*H*-2-amino/*N*-substituted amino-spiro(1'*H*-2',4'-dioxo-6',8'-disubstituted quinoline)-1,3-diazetidin-2-ene **9**, 8,9-(2',4'-disubstituted)-benzo-1-thia-2-hydrazino-3,4,7-triaza-4,7-dihydro-6,10-dioxo-spiro [4,5] dec-2-ene **11** respectively. The salient features of the microwave approach are rapid reaction rates, cleaner reaction condition and enhancement in chemical yields compared to classical method. The structures of synthesized compounds have been confirmed by IR, ¹H and ¹³C NMR.

Keywords: Dibromocarbostyryl, triazole, guanidine, thioguanidine, thiocarbohydrazide, quinoline

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The synthesis of spiro compounds has been a subject of great interest to research workers. Spiro compounds have compatible biological activity and exhibit diverse pharmacological and therapeutic properties^{1a}. Certain spiro compounds have been found to exhibit narcotic, hypotensive, skeletal muscle relaxant, analgesic and broad spectrum anti-bacterial as well as anti-viral activity^{1b}. Triazole nucleus are probably the most well-know heterocycle which are common and play an important role in a variety of biological activity such as inhibiting tumor proliferation, invasion and metastasis². Compounds carrying thiadiazole moiety exhibit herbicidal^{3,4} activity and are used as plant growth promoting agent⁵. The derivatives of thiazetidine have been utilized in surface treatment of water repellent textiles⁶. Many 1,3-oxoazetidine derivatives have been reported as useful drug⁷. *N*-phenyl-1,3-oxoazetidine-2-one has been suggested as the fused ring intermediate in flavins responsible for the light producing intermediate in bacterial luciferase chemiluminescence⁸. The application of microwave irradiation in organic synthesis has been the focus of considerable attention in recent years and is becoming an increasingly popular technology⁹⁻¹¹.

The pharmacophoric activity of above parent ring and ecofriendliness of microwave oven prompted the design and synthesis of novel spiro heterocycles. The same compounds have been also synthesized by classical thermal method for comparative studies. The structures of the newly synthesized compounds have been established by analytical and spectral data.

Results and Discussion

The synthetic routes of the newly synthesized compounds is shown in **Scheme I**. The reaction of 3,3-Dibromo carbostyryl **1** with substituted triazoles **2** proceeds in presence of piperidine and ethyl alcohol as a solvent to yield **3**. The title compounds **5** and **7** were synthesized by reaction of dibromo compound **1** with different amidinothiocarbamides **4** and amidinocarbamide **6** respectively in presence of DMSO as a solvent and fused sodium ethanoate as a catalyst. Compound **1**, which was cyclized with substituted guanidines **8** in presence of piperidine and DMSO as a solvent, afforded **9**. 3,3-Dibromo carbostyryl **1**, which when treated with thiocarbohydrazide **10** using DMSO as a solvent gave **11**. As compared to conventional method microwave leads to improved yields (**Table I**).

The starting materials were prepared by reported procedure¹²⁻¹⁷.

Experimental Section

Melting points of all synthesized compounds were determined in soft glass open capillaries in an electro thermal apparatus and are uncorrected. IR (KBr) spectra were recorded on a Perkin-Elmer spectro-

photometer. ¹H NMR spectra were recorded on a Bruker AMX 500 MHz spectrometer using TMS as internal standard (chemical shifts in δ ppm). The homogeneity of the compounds were checked on Aluminium backed silica gel coated TLC plates (Merck) as adsorbent and UV light was used for visualization. Samsung microwave oven (Model No. M1630N, 2450 MHz) was used for irradiation.

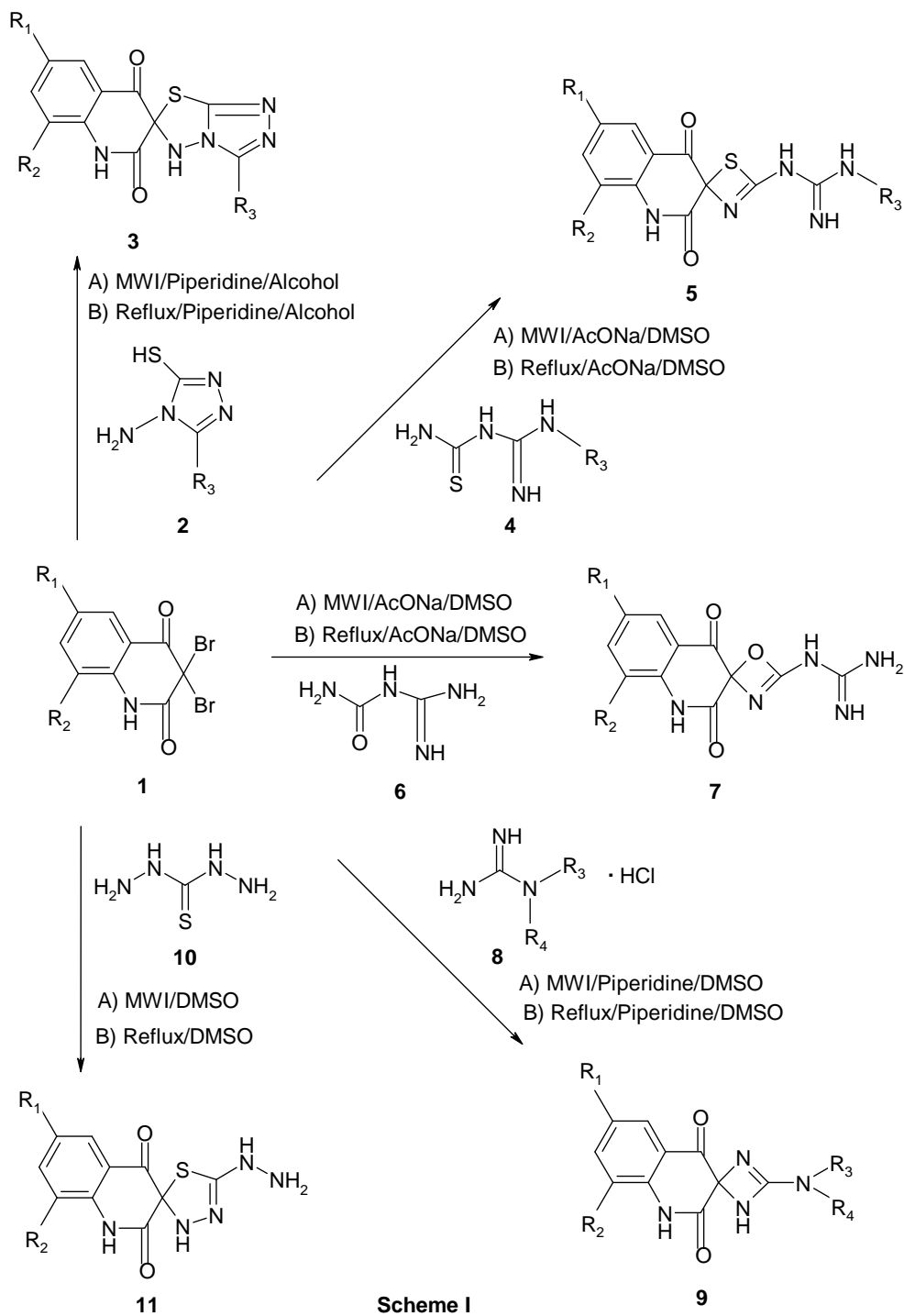


Table I—Analytical data of compounds **3a-b**, **5a-p**, **7a-g**, **9a-b**, **11a-g**

Compd	R ₁	R ₂	R ₃	R ₄	%Yield		m.p. °C	Spectral data ¹ H and ¹³ C NMR (DMSO- <i>d</i> ₆) δ, ppm
					MWI	Conv		
3a	H	H	CH ₃	-	64	48	224	¹ H NMR: 2.28(s, 3H, CH ₃), 7.2-7.9(m, 4H, Ar), 11.40 (s, ring NH), 11.54(s, ring NH). ¹³ C NMR: 30.62 (-CH ₃), 99.13 (tetrahedral C atom), 121.52-138.55 (aromatic carbons), 156.90 and (2×-C=N), 173.89 and 180.00 (2×-C=O).
		161.83						
3b	H	H	H	-	62	49	220	
3c	H	H	C ₂ H ₅	-	70	57	232	
3d	CH ₃	H	CH ₃	-	62	53	232	
3e	CH ₃	H	H	-	51	39	236	
3f	CH ₃	H	C ₂ H ₅	-	61	43	242	
3g	OCH ₃	H	CH ₃	-	62	52	230	
3h	OCH ₃	H	H	-	60	51	208	¹ H NMR: 3.84(s, 3H, -OCH ₃), 7.23-7.91(m, 4H, Ar, =CH), 11.45(s, ring NH), 11.63(s, ring NH).
3i	OCH ₃	H	C ₂ H ₅	-	63	58	262	
3j	Cl	H	CH ₃	-	68	51	196	
3k	Cl	H	H	-	65	52	210	
3l	Cl	H	C ₂ H ₅	-	69	58	232	¹ H NMR: 1.30(t, 3H, -CH ₃), 2.94(q, 2H, -CH ₂), 7.31-7.92(m, 3H, Ar), 9.97(s, ring NH), 10.69(s, ring NH).
5a	H	H	H	-	72	67	310	¹ H NMR: 2.28(s, 2H, NH ₂), 5.51(s, 1H, NH), 7.16-7.9 (m, 4H, Ar), 9.33(=NH), 10.16(s, ring NH). ¹³ C NMR: 106.20(tetrahedral C atom), 123.50-139.28, (aromatic carbons), 157.27 and 159.55 (2×-C=N), 177.85 and 180.44 (2×-C=O).
5b	H	H	C ₆ H ₅	-	68	60	245	
5c	H	H	<i>p</i> -CH ₃ - O-C ₆ H ₄	-	72	62	314	
5d	H	H	<i>p</i> -CH ₃ - C ₆ H ₄	-	73	66	300	
5e	CH ₃	H	H	-	74	63	258	
5f	CH ₃	H	C ₆ H ₅	-	66	59	280	¹ H NMR: 2.24(s, 3H, CH ₃), 5.25(s, 1H, NH), 7.20-7.95 (m, 8H, Ar), 9.52(=NH), 10.96(s, ring NH).
5g	CH ₃	H	<i>p</i> -CH ₃ - O-C ₆ H ₄	-	73	63	240	
5h	CH ₃	H	<i>p</i> -CH ₃ - C ₆ H ₄	-	79	68	268	
5i	OCH ₃	H	H	-	81	65	280	
5j	OCH ₃	H	C ₆ H ₅	-	71	63	318	
5k	OCH ₃	H	<i>p</i> -CH ₃ - O-C ₆ H ₄	-	70	61	290	
5l	OCH ₃	H	<i>p</i> -CH ₃ - C ₆ H ₄	-	77	70	310	
5m	Cl	H	H	-	79	68	280	
5n	Cl	H	C ₆ H ₅	-	68	57	240	
5o	Cl	H	<i>p</i> -CH ₃ - O-C ₆ H ₄	-	71	62	206	¹ H NMR: 3.84(s, 3H, OCH ₃), 5.40(s, 1H, NH), 7.10-7.9 (m, 7H, Ar), 9.65(=NH), 11.20(s, ring NH).
5p	Cl	H	<i>p</i> -CH ₃ - C ₆ H ₄	-	84	69	250	

Table I—Analytical data of compounds **3a-b**, **5a-p**, **7a-g**, **9a-b**, **11a-1g**—*Contd*

Compd	R ₁	R ₂	R ₃	R ₄	%Yield		m.p. °C	Spectral data ¹ H and ¹³ C NMR (DMSO- <i>d</i> ₆) δ, ppm
					MWI	Conv		
7a	H	H	-	-	64	58	270	¹ H NMR: 2.28(s, 2H, NH ₂), 5.55(s, 1H, NH), 7.25-8.0 (m, 4H, Ar), 9.49(=NH), 11.79(s, ring NH). ¹³ C NMR: 101.45(tetrahedral C atom), 124.50-138.89 (aromatic carbons), 155.95 and 158.58 (2×-C=N), 176.20 and 178.96 (2×-C=O).
7b	H	CH ₃	-	-	52	47	268	
7c	CH ₃	H	-	-	69	61	280	
7d	OCH ₃	H	-	-	64	59	252	
7e	H	Cl	-	-	61	54	225	
7f	Br	H	-	-	69	61	220	¹ H NMR: 2.28(s, 2H, NH ₂), 5.55(s, 1H, NH), 7.20-8.0 (m, 3H, Ar), 9.60(=NH), 11.67(s, ring NH).
7g	Cl	H	-	-	67	56	238	
9a	H	H	H	H	66	60	250	¹ H NMR: 3.78(-NH ₂), 7.26-7.98(m, 4H, Ar), 12.19(s, ring NH), 12.73(s, ring NH). ¹³ C NMR: 94.30(tetrahedral C atom), 121.50-136.24 (aromatic carbons), 158.36 (-C=N), 172.96 and 176.86 (2×-C=O).
9b	H	H	H	CH ₃	67	60	255	
9c	H	H	CH ₃	CH ₃	64	58	262	
9d	CH ₃	H	H	H	72	61	258	
9e	CH ₃	H	H	CH ₃	77	65	250	
9f	CH ₃	H	CH ₃	CH ₃	74	63	254	
9g	OCH ₃	H	H	H	66	57	245	
9h	OCH ₃	H	H	CH ₃	75	68	252	
9i	OCH ₃	H	CH ₃	CH ₃	73	61	260	
9j	Cl	H	H	H	67	61	235	¹ H NMR: 3.78(-NH ₂), 7.20-7.90(m, 3H, Ar), 12.10 (s, ring NH), 12.88(s, ring NH).
9k	Cl	H	H	CH ₃	69	56	239	
9l	Cl	H	CH ₃	CH ₃	65	51	245	
11a	H	H	-	-	66	53	210	¹ H NMR: 2.01(1H, exocyclic NH), 5.73(s, 2H, NH ₂), 7.20-7.91(m, 4H, Ar), 11.77(s, ring NH), 11.91 (s, ring NH). ¹³ C NMR: 103.68(tetrahedral C atom), 123.72-139.98 (aromatic carbons), 161.00 (-C=N), 177.93 and 179.03 (2×-C=O).
11b	H	CH ₃	-	-	62	54	270	
11c	CH ₃	H	-	-	67	59	318	
11d	OCH ₃	H	-	-	61	50	198	¹ H NMR: 2.19(1H, exocyclic NH), 3.78(s, 3H, OCH ₃), 5.70(s, 2H, NH ₂), 7.25-7.95(m, 3H, Ar), 11.65 (s, ring NH), 11.90(s, ring NH).
11e	H	Cl	-	-	60	52	200	
11f	Br	H	-	-	64	51	185	
11g	Cl	H	-	-	65	56	204	

C, H, N and S analysis was found satisfactory.

**Spiro (1'*H*-2', 4'-dioxo-6', 8'-disubstituted quino-
line)-4*H*-1, 3, 4-thiadiazolo[2,3-*d*]- (3-substituted)-
1,2,4-triazole, 3.**

Method A (MWI)

3,3 Dibromo carbostyryl **1** (1 mmole) and 4-amino-5-methyl-3-mercapto-1, 2, 4-triazole **2** (1 mmole) were taken in ethanol (5 mL) containing piperidine

(2 mmole) in Erlenmeyer flask and irradiated in microwave oven for 5 min. 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 water and purified by recrystallization from ethanol to get s-triazole **3**.

Method B (Conventional)

An equimolar mixture of compound **1** and compound **2** (1 mmole) and in ethanol (15 mL) was refluxed in presence of piperidine (2 mmole) for about 6 hr. After monitoring the progress of reaction on TLC, the reaction mixture was worked-up in an analogous way as described above in method A (MWI).

The spectral analysis data of compounds **3a-l** are given in **Table I**.

2-Guanidino/substituted guanidino-spiro(1'H-2',4'-dioxo-6',8'-disubstituted quinoline)-1,3-thiazetidin-2-ene, 5**Method A (MWI)**

Compound **1** (1 mmole), substituted amidinothiocarbamides **4** (1 mmole), fused sodium ethanoate (2 mmole) and DMSO (3 mL) were taken in an Erlenmeyer flask. The reaction mixture was subjected to microwave irradiation for 4 min. Upon completion of the reaction (monitored by TLC), the reaction mixture were dumped onto crushed ice. The solid mass obtained was filtered and washed several times with water. Purification by recrystallization from alcohol gave **5**.

Method B (Conventional)

A mixture of dibromo derivative **1** (1 mmole), substituted amidinothiocarbamide **4** (1 mmole), fused sodium ethanoate (2 mmole) and DMSO (8 mL) were refluxed for 5 hr. After completion of the reaction, the reaction mixture was worked-up as mentioned above.

The spectral analysis data of compounds **5a-p** are reported in **Table I**.

2-Guanidino-spiro(1'H-2',4'-dioxo-6',8'-disubstituted quinoline)-1,3-oxazetidin-2-ene, 7**Method A (MWI)**

Equimolar mixture of compound **1** (1 mmole), amidinocarbamide **6** (1 mmole) in DMSO (3 mL) and fused NaOAc (2 mmole) were taken in an Erlenmeyer flask and exposed to microwave irradiation for 4 min. The progress of reaction was monitored by TLC and the contents were poured onto crushed ice. The product **7** obtained was filtered off, washed several times with water, dried and purified by recrystallization from ethanol.

Method B (Conventional)

A dibromo compound **1** (1 mmole), amidinocarbamide **6** (1 mmole), fused NaOAc (2 mmole) and DMSO (8 mL) were refluxed for 5 hr. After monitoring the progress of reaction by TLC, the product was isolated in a similar manner as described above in method A to yield **7**.

Spectral characterization data of compounds **7a-g** are shown in **Table I**.

1H-2-amino/N-substituted amino-spiro(1'H-2',4'-dioxo-6',8'-disubstituted quinoline)-1,3-diazetid-2-ene, 9**Method A (MWI)**

Guanidine hydrochloride **8** (1 mmole) was added to the solution of 3, 3-dibromo carbostyryl (1 mmole) **1** in DMSO (3 mL) in an Erlenmeyer flask. A catalytic amount of piperidine (2 mmole) was added to it and the mass subjected to microwave irradiation for 3 min. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the reaction mixture was poured onto crushed ice, thus **9** was obtained. It was filtered, washed with water and purified by recrystallization from alcohol.

Method B (Conventional)

Equimolar mixture of compound **1** and **8** were refluxed for 6 hr in presence of piperidine (0.02 mmole) and DMSO (8 mL) solvent. Upon completion of the reaction (monitored by TLC), the reaction mixture was worked-up in the same fashion as mentioned above.

The spectral characterization data of compounds **9a-l** are shown in **Table I**.

8, 9-(2', 4'-disubstituted)-benzo-1-thia-2-hydrazino-3, 4, 7-triaza-4,7-dihydro-6, 10-dioxo-spiro[4, 5]dec-2-ene, 11**Method A (MWI)**

An equimolar solution of compound **1** (0.001 mole) and thiocarbonylhydrazide **10** (0.001 mole) in DMSO (3 mL) were taken in an Erlenmeyer flask and subjected to microwave irradiation for 1 min. After monitoring the progress of reaction on TLC, the mixture was quenched onto crushed ice. The desired compound **11** obtained was filtered, washed with water and purified by recrystallization from ethanol.

Method B (Conventional)

Compound **11** was also obtained by refluxing equal moles (0.001) of **1** and **10** in DMSO (8 mL) for 1 hr. After completion of the reaction, the product was isolated according to the procedure described in method A.

The spectral characterization data of compounds **11a-g** are given in **Table I**.

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