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## Note

# Synthesis and characterization of fused and spiro heterocycles by ultrasonic methods

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Treatment of 1,4-diazacyclohexan-2,5-dione **1** with bromine in carbon tetrachloride has yielded 1,4-diaza-3-bromo-2,5-dioxocyclohexane **2** and 1,4-diaza-3,3-dibromocyclohexane-2,5-dione **7**. The reaction of **2** with carbamides/thiocarbamides has produced 6-oxo-oxazolo[4,5-*b*] piperazine **5** /2-substituted imino-6-oxo-thiazolo[4,5-*b*] piperazine **6**. Compound **7** on combination with carbamides/ thiocarbamides is transformed to 1-oxo-2-substituted imino-3,5,8-triaza-3*H*,5*H*,8*H*,7-dihydro-6,9-dioxo-spiro [3.5] nonane **9** and 1-thia-2-substituted imino-3,5,8-triaza-3*H*,5*H*,8*H*-7dihydro-6,9-dioxo-spiro [3.5] nonane **9**. The structures of the synthesized compounds have been confirmed by IR, $^1$H and $^{13}$C NMR spectral data analyses.

**Keywords**: Thiazole, oxazole

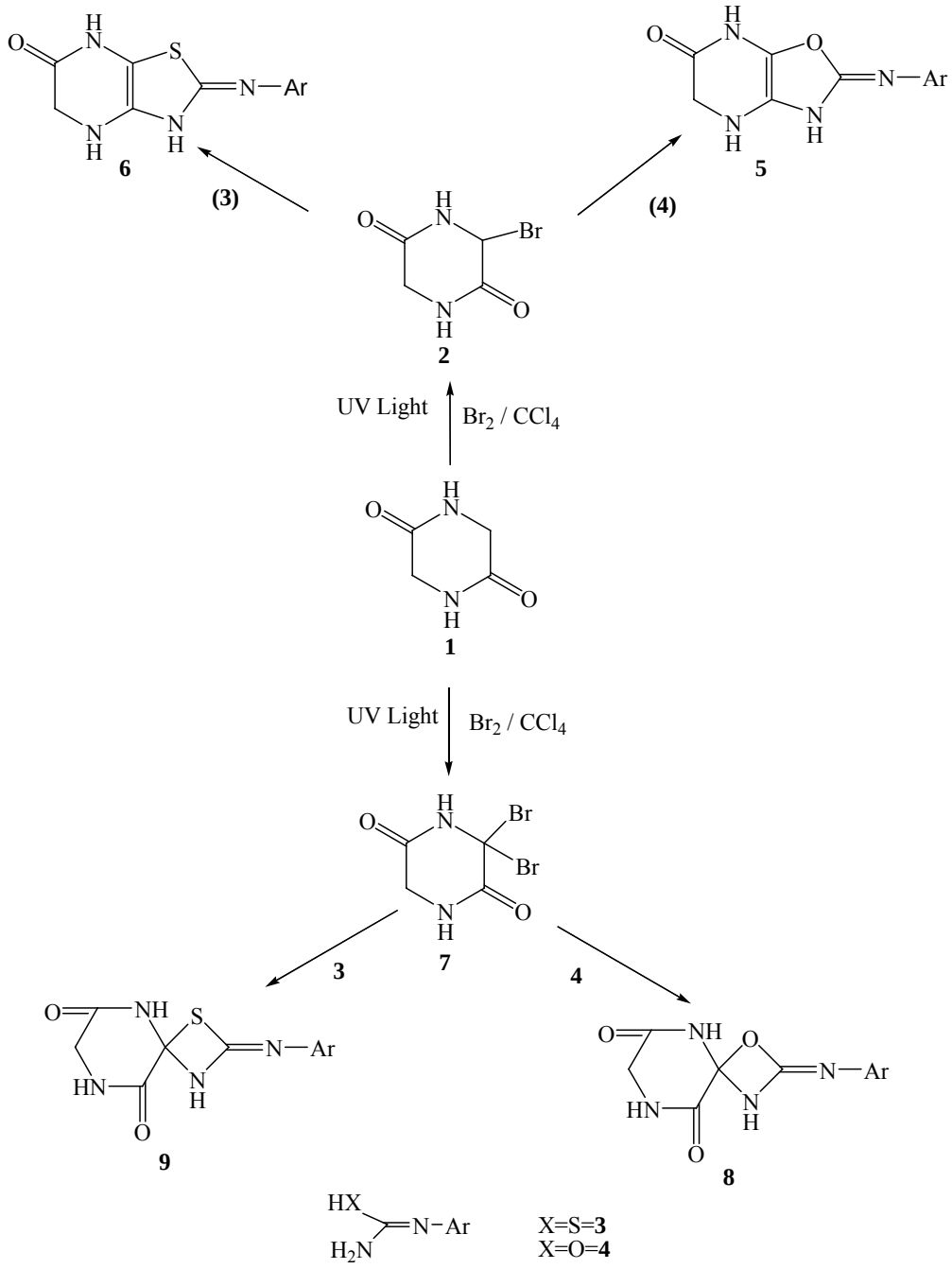
Spiro compounds have been found to exhibit narcotic, hypotensive, skeletal muscle relaxant as well as anti viral activities[1]. Wieser and Berndt reported the first examples of sterically stabilized oxazetidine from the thermal intramolecular cyclization[2]. Compounds such as N-phenyl-1,3-oxazetidin-2-one also shows drug activity and its usefulness as a drug[3]. Oxazetidine system has been suggested as a fused ring intermediate in flavins responsible for light producing intermediate in bacterial luciferase chemiluminiscence[4].

The compounds bearing thiazole and oxazole moiety have been found to possess antibacterial[5], antitubercular[6], anti-inflammatory activity[7] and HIV infection[8]. The uses of ultrasonication technique for carrying out various types of reaction are well documented in the literature[9-12]. Its application in chemistry has received attention only in recent past. Due to enhancement in yield and subsequent reduction in reaction time[13-19], there is considerable interest in rapid chemical synthesis under ultrasound technique. The wide range of therapeutic activities of above compounds and importance of ultrasound prompted us to synthesized spiro and fused compounds using bromo piperazine as it has less explored. The same compounds have been synthesized by conventional method[20] for comparative study. The structures of the newly synthesized compounds were confirmed by various spectroscopic techniques.

## Result and Discussion

The synthesis of 1,4-diaza-3-bromo-2,5-dioxo cyclohexane **2** was achieved by bromination of 1,4-diaza cyclohexane-2,5-dione **1**. The reaction of **2** with carbamides in the presence of pyridine as base gave 2-substituted imino-6-oxo-oxazolo[4,5-*b*]piperazine **5**. Formation of compound **5** was evidenced by the appearance of signal at δ 7.9 (-NH-) in $^1$H NMR spectra and in IR spectra band due to carbonyl observed at 1600 cm$^{-1}$. Similarly the reaction of **2** with thiocarbamides in the presence of pyridine as base gave 2-substituted imino-6-oxo-thiazolo [4,5-*b*]piperazine **6.** In $^1$H NMR spectra of compound **6**, the signal at δ 3.6 and 8.1 was observed due to $CH_2$ and –NH respectively where as IR spectra of compound **6** revealed band at 1616 cm$^{-1}$ (C=O) and 1593 cm$^{-1}$ (CN).

In $^{13}$C NMR spectra of compound **6**, the signals at δ 40.33 was observed due to $CH_2$, 156.56 (CN) and 166.16 (C=O) respectively. Similarly compound **1** was brominated with 2 mole of bromine in $CCl_4$ under UV irradiation to yield 1,4-diaza-3,3-dibromo cyclohexane 2,5-dione **7**. Further compound **7** was treated with carbamides in the presence of pyridine to form 1-oxa-2-substituted imino-3,5,8-triaza-*3H*, *5H*, *8H*-7-dihydro-6,9-dioxo-spiro[3.5] nonane **8**. The spectral data is in agreement with the proposed structures, the IR spectrum of **8** showed C=O band at 1670 cm$^{-1}$, -NH band at 3223 cm$^{-1}$ and CN band at 1596 cm$^{-1}$. In its NMR spectrum the chemical shifts due to $CH_2$ of ring was observed at δ 3.69 and –NH at 8.00 confirmed the formation of **8**. Similarly compound **7** was also treated with thiocarbamides in the presence of pyridine to form 1-thia-2-substituted imino-3,5,8-triaza-*3H*,*5H*,*8H*-7-dihydro-6,9-dioxo-spiro[3.5] nonane **9** (**Scheme I**). In $^1$H NMR spectra of the compound **9**, the signal at δ 3.70 was observed due to $CH_2$ and at 7.99 due to –NH and in IR spectra of compound **9**, the band at 3220 cm$^{-1}$ was observed due




**Scheme I**

to –NH, 1635 $cm^{-1}$ was due to C=O and CN band was obtained at 1576 $cm^{-1}$.

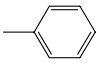
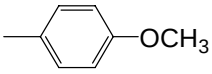
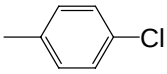
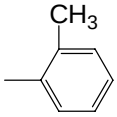
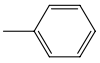
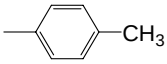
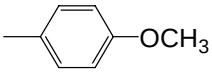
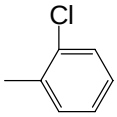
Physical characterization data are included in **Tables I** and **II**. The structures of the compounds have been confirmed by analysis IR, $^{1}H$ and $^{13}C$ NMR data.

## Experimental Section

Melting points of all synthesized compounds were determined in open capillary tubes on an electro-thermal apparatus and are uncorrected. The homogeneity 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, $cm^{-1}$) were recorded on Perkin-Elmer spectrophotometer in the range of 4000-400 $cm^{-1}$.

$^{1}H$ NMR spectra were scanned on Varian 500 MHz NMR spectrometer using $CDCl_3$/DMSO-$d_6$ as solvent and TMS as an internal standard (chemical

**Table I —** Characterization data of synthesized compound

| Compd | Ar | m.p (°C) | Yield (%) Conventional | Yield (%) Ultrasonication | Mol. formula | $^1$H and $^{13}$C NMR (DMSO-$d_6$) (δ, ppm) |
|---|---|---|---|---|---|---|
| **5a** | H | 245-47 | 65 | 72 | $C_5H_6N_4OS$ | $^1$H NMR: 3.2 (s,2H, $CH_2$), 5.5 (s, 1H, NH), 7.4 (s, 1H, NH), 7.90 (s,1H, NH), 8.3 (s, 1H, NH). |
| **5b** |  | 239-41 | 68 | 73 | $C_{11}H_{10}N_4OS$ | — |
| **5c** |  | 251-53 | 66 | 74 | $C_{12}H_{12}N_4O_2S$ | $^1$H NMR: 3.15 (s, 2H, $CH_2$), 3.78 (s, 3H, $OCH_3$), 6.9 – 7.4 (m, 4H, ArH), 8.1 (s, 1H, NH), 8.56 (s, 1H, NH), 9.72 (s, 1H, NH). |
| **5d** |  | 237-39 | 70 | 78 | $C_{11}H_9N_4OSCl$ | — |
| **5e** |  | 231-33 | 71 | 76 | $C_{12}H_{12}N_4OS$ | $^1$H NMR: 2.3 (s, 3H, $CH_3$), 3.24 (s, 2H, $CH_2$), 7.1 – 7.52 (m, 4H, ArH), 8.15 (s, 1H, NH), 8.63 (s, 1H, NH), 9.78 (s, 1H, NH). |
| **6a** | H | 210-12 | 72 | 78 | $C_5H_6N_4O_2$ | $^1$H NMR: 3.6 (s, 2H, $CH_2$), 5.4 (s, 1H, NH), 7.3 (s, 1H, NH), 8.17 (s, 1H, NH), 8.9 (s, 1H, NH). |
| **6b** |  | 224-26 | 65 | 72 | $C_{11}H_{10}N_4O_2$ | — |
| **6c** |  | 241-43 | 70 | 76 | $C_{12}H_{12}N_4O_2$ | — |
| **6d** |  | 204-06 | 68 | 78 | $C_{12}H_{12}N_4O_3$ | $^1$H NMR: 3.15 (s, 2H, $CH_2$), 3.72 (s, 3H, $OCH_3$), 6.8 – 7.2 (m, 4H, ArH), 8.01 (s, 1H, NH), 8.28 (s, 1H, NH), 9.58 (s, 1H, NH); $^{13}$C NMR: 40.33 ($CH_2$), 55.25 ($OCH_3$), 125 – 131 (Aromatic C atoms), 156.56 (C=N), 166.16 (C=O). |
| **6e** |  | 209-11 | 69 | 76 | $C_{11}H_9N_4O_2Cl$ | — |

shifts in δ, ppm) and mass spectra were recorded on a Jeol SX-102/PA-6000 (EI) spectrometer. CHN estimation were obtained on Carlo Erba 1108 (CHN) Elemental Analyser. Compounds **3** and **4** were synthesized by reported procedure[21,22].

**1,4-Diaza-3-bromo cyclohexane-2,5-dione, 2**

1,4-Diaza cyclohexane-2,5-dione **1** (0.01 mole) was dissolved in minimum quantity of carbon tetrachloride. A solution of bromine (0.01 mole) in carbon tetrachloride ($CCl_4$) was added dropwise with continuous stirring in presence of UV light. After complete addition of bromine, reaction mixture was stirred for 30 min and **2** was isolated as solid mass by distillation of $CCl_4$ which was purified by recrystallization from hot water. Yield 82%, m.p. 240°C

**1,4-Diaza-3,3-dibromo cyclohexane-2,5-dione, 7**

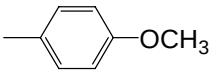
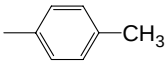
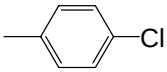
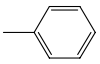
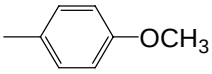
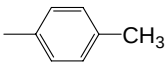
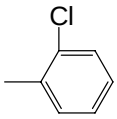
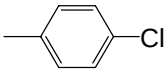
Compound **1** (0.01 mole) was dissolved in minimum quantity of carbon tetrachloride. A solution of bromine (0.02 mole) in carbon tetrachloride was added dropwise with continuous stirring in presence of UV light. **7** was isolated in similar manner to **2**. Yield 80%, m.p. 268°C.

**2-Substituted imino-6-oxo-oxazolo[4,5-*b*] piperazine, 5a-e**

**Method A (Ultrasound Method): General Procedure**

Compound **2** (0.192 g, 0.001 mole), substituted carbamide (0.001 mole), pyridine (0.002 mole), absolute ethanol (10 mL) were taken in round bottom flask (100 mL), and subjected to ultrasonication for

**Table II** — Characterization data of synthesized compound

| Compd | Ar | m.p (°C) | Yield (%) Conventional | Yield (%) Ultrasonication | Mol. formula | $^1$H NMR (DMSO-$d_6$) (δ, ppm) |
|---|---|---|---|---|---|---|
| **8a** | H | 189-91 | 72 | 78 | $C_5H_6N_4O_3$ | 3.69 (s, 2H, $CH_2$), 3.93 (s,1H, NH), 7.03 (s,1H,NH), 8.00 (s, 1H, NH), 8.7 (s, 1H, NH). |
| **8b** |  | 207-09 | 65 | 70 | $C_{12}H_{12}N_4O_4$ | — |
| **8c** |  | 220-22 | 63 | 73 | $C_{12}H_{12}N_4O_3$ | 2.2 (s, 3H, $CH_3$), 3.65 (s, 2H, $CH_2$), 7.0 – 7.4 (m, 4H, ArH), 8.1 (s, 1H, NH), 8.8 (s, 1H, NH), 9.3 (s, 1H, NH) |
| **8d** |  | 211-13 | 72 | 81 | $C_{11}H_9N_4O_2Cl$ | — |
| **8e** |  | 190-92 | 69 | 75 | $C_{11}H_{10}N_4O_3$ | — |
| **9a** | H | 247-49 | 45 | 51 | $C_5H_6N_4O_2S$ | 3.70 (s, 2H, $CH_2$), 3.97 (s,1H, NH), 7.05 (s,1H,NH), 7.99 (s, 1H, NH), 8.72 (s, 1H, NH). |
| **9b** |  | 209-11 | 52 | 60 | $C_{12}H_{12}N_4O_3S$ | — |
| **9c** |  | 217-19 | 55 | 62 | $C_{12}H_{12}N_4O_2S$ | 2.1 (s, 3H, $CH_3$), 3.68 (s, 2H, $CH_2$), 7.1 – 7.4 (m, 4H, ArH), 8.03 (s, 1H, NH), 8.75 (s, 1H, NH), 9.6 (s, 1H, NH) |
| **9d** |  | 187-89 | 65 | 78 | $C_{11}H_9N_4O_2SCl$ | — |
| **9e** |  | 177-79 | 67 | 75 | $C_{11}H_9N_4O_2SCl$ | — |

CHNS analysis was found satisfactory.

15 min. Progress of reaction was monitored by TLC. After completion of reaction, the contents were dumped in crushed ice and filtered to yield **5a-e**. The product was purified by recrystallization from ethanol. The physical characterization data is given in the **Table I**

**Method B (Conventional Method): General Procedure**

Compound **2** (0.192 g, 0.001 mole), substituted carbamide (0.001 mole) pyridine (0.002 mole), absolute ethanol (10 mL) were taken in round bottom flask (100 mL), refluxed for 3-4 hr. Progress of reaction was monitored by TLC. After completion of reaction, the product was dumped in crushed ice and separated by filtration. The product was purified by recrystallization from ethanol which was compared and found identical to **5**.

**2-Substituted imino-6-oxo-thiazolo[4,5-*b*] piperazine, 6a-e**

**Method A (Ultrasound Method): General Procedure**

Mixture of compound **2** (0.192 g, 0.001 mole), substituted thiocarbamide (0.001 mole), pyridine (0.002 mole) absolute ethanol (10 mL) in round bottom flask (100 mL), was subjected to ultrasonication for 15 min. Progress of reaction was monitored by TLC. After completion of reaction, the contents were dumped into crushed ice and filtered to obtained **6a-e**. The product was purified by recrystallization from ethanol. The physical characterization data is given in **Table I**

**Method B (Conventional Method): General Procedure**

Compound **2** (0.192 g, 0.001 mole), substituted thiocarbamide (0.001 mole)**,** and pyridine (0.002 mole), absolute ethanol (10 mL) were taken in round bottom flask (100 mL) and refluxed for 3-4 hr. Progress of reaction was monitored by TLC. After completion of reaction, the product was dumped into crushed ice and separated by filtration. The product was purified by recrystallization from ethanol which was compared and found identical to **6**.

**1-Oxa-2-substituted imino-3,5,8-triaza-*3H,5H,8H*-7-dihydro-6,9-dioxo-spiro [3.5] nonane, 8a-e**

**Method A (Ultrasound Method): General Procedure**

Compound **7** (0.272 g, 0.001 mole), substituted carbamide (0.001 mole), pyridine (0.002 mole) absolute ethanol (10 mL) were taken in round bottom flask (100 mL), was subjected to ultrasonication for 8 min. Progress of reaction was monitored by TLC. After completion of reaction, the contents were dumped into crushed ice and filtered to give **8a-e**. The product was purified by recrystallization from ethanol. The physical characterization data is given in the **Table II**

**Method B (Conventional Method): General procedure**

Compound **7** (0.272 g, 0.001 mole), substituted carbamide (0.001 mole), pyridine (0.002 mole) absolute ethanol (10 mL) and were taken in round bottom flask (100 mL), and refluxed for 3-4 hr. Progress of reaction was monitored by TLC. After completion of reaction, the contents were dumped into crushed ice and filtered. The product was recrystallized from ethanol. The physical data is given in the **Table II**

Compound **8** obtained by both the method was found to be identical.

**1-Thia-2-substituted imino-3,5,8-triaza-*3H,5H,8H*-7-dihydro-6,9-dioxo-spiro [3.5] nonane, 9a-e**

**Method A (Ultrasound Method): General Procedure**

Compound **7** (0.272 g, 0.001 mole), substituted thiocarbamide (0.001 mole), pyridine (0.002 mole), absolute ethanol (10 mL) and were taken in round bottom flask (100 mL), and subjected to ultrasonication for 8 min. Progress of reaction was monitored by TLC. After completion of reaction, the contents were dumped into crushed ice and filtered. The product was purified by recrystallization from ethanol and identified as **9**. The physical characterization data of **9a-e** is given in the **Table II**

**Method B (Conventional Method): General Procedure**

Compound **7** (0.272 g, 0.001 mole), substituted thiocarbamide (0.001 mole), pyridine (0.002 mole), absolute ethanol (10 mL) were taken in round bottom flask (100 mL), and refluxed for 3-4 hr. Progress of reaction was monitored by TLC. After completion of reaction, the contents were dumped into crushed ice and filtered. The product was purified by recrystallization from ethanol. The physical characterization data is given in the **Table II**. Compound **9** obtained by both the methods were found to be identical.

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**References**

1 Bell F W, Hoberg M & Zhou X-X, *J Med Chem*, 38, **1995,** 4959.

2 Wiser K & Berndt A, *Angew Chem Int Ed (Engl)*, 14, **1975**, 70.

3 Ozaki S, *JP* 6937025, **1969**.

4 Lowe J N & Ingrahem L L, *Biochem Biophys Res Commun*, 73, **1976**, 465.

5 Kalluraya B, Isloor B, Frank P V & Jagdeesha R L, *Indian J Het Chem*, 13, **2004**, 245.

6 Metzer J V, *Comprehensive Heterocyclic Chemistry,* edited by A R Katritzky & C W Rees (Pergamon Press, Oxford), 5, **1984**, 328.

7 Lambardino J, Wiseman E & Josephine C, *J Med Chem*, 16, **1973**, 493.

8 Bell F W, Hoberg M & Zhou X-X, *J Med Chem*, 38**, 1995,** 4959.

9 Osman A N & Kandeel M M, *Indian J Chem*, 35B, **1996**, 1073.

10 Kalluraya B, Isloor B, Frank P V & Jagdeesha R L, *Indian J Het Chem*, 13, **2004,** 245.

11 Metzer J V, *Comprehensive Heterocyclic Chemistry,* edited by A R Katritzky & C W Rees (Pergamon Press, Oxford), 5, **1984,** 328.

12 Lambardino J, Wiseman E & Josephine C, *J Med Chem*, 16, **1973,** 493.

13 Sanghvi Y S, Lorson S B, Robinse R K & Revenkar G R, *J Med Chem*, 32, **1989**, 945.
14 Abramoviton R A, *Org Prep & Proc Int*, 23, **1991,** 685.
15 Rahmouni M, Derdour A, Bazurean J P & Hamelin J, *Tetrahedron Lett*, 23, **1994**, 4563.
16 Caddick S, *Tetrahedron*, 51, **1995,** 10403.
17 Galema S A, *Chem Soc Rev*, 26, **1997**, 233.
18 Khadilkar B, *Indian J Chem*, 40B, **2001**, 433.
19 Abramoviton R A, *Org Prep & Proc Int*, 23, **1991,** 683.
20 Dabholkar V V & Mishra S K, *Heterocyclic Commun*, 12(3-4), **2006,** 241.
21 Joshua C P, *J Org Chem*, 28, **1963,** 1293.
22 Rabjohn N, *Org Synth*, Coll Vol IV (John Wiley and Sons Inc, New York), **1963,** 52.