*Available online www.jocpr.com*

**Journal of Chemical and Pharmaceutical Research, 2015, 7(4):253-256**

**Research Article**

**ISSN : 0975-7384**
**CODEN(USA) : JCPRC5**

# Benzothiazine containing thiosemicarbazides are important synthetic intermediates for synthesis of triazole and oxadiazole derivatives

**Bhikan J. Khairnar and Bhata R. Chaudhari***

*Department of Chemistry, JET's Z.B. Patil College, Dhule, India*

---

**ABSTRACT**

*A series of novel 3-methyl-7-substituted-4H-1,4-benzothiazine-2-carbohydrazide (**3a-e**) and corresponding thiosemicarbazide (**4a-q**) have been synthesized from 2-amino-5-substituted-thiophenol (**1a-e**) through the synthesis of 2-carboethoxy-3-methyl-7-substituted-1,4-benzothiazine (**2a-e**). The 1,4-benzothiazine thiosemicarbazides i.e. 2-[(3-methyl-7-substituted-4H-1,4-benzothiazin-2-yl) carbonyl]-N-arylhydrazine carbothiamide (**4a-q**) when cyclised with 2N sodium hydroxide via intramolecular dehydrative cyclisation gave benzothiazonyl-1,2,4-triazoles; and the thiosemicarbazide when cyclized with iodine via intramolecular cyclisation gave benzothiazonyl 1,2,4-oxadiazoles in high yields.*

**Key words:** 1,4-Benzothiazine, Thiosemicarbazide, Intramolecular cyclisation, 1,2,4-Triazole, 1,2,4-Oxadiazole.

---

## INTRODUCTION

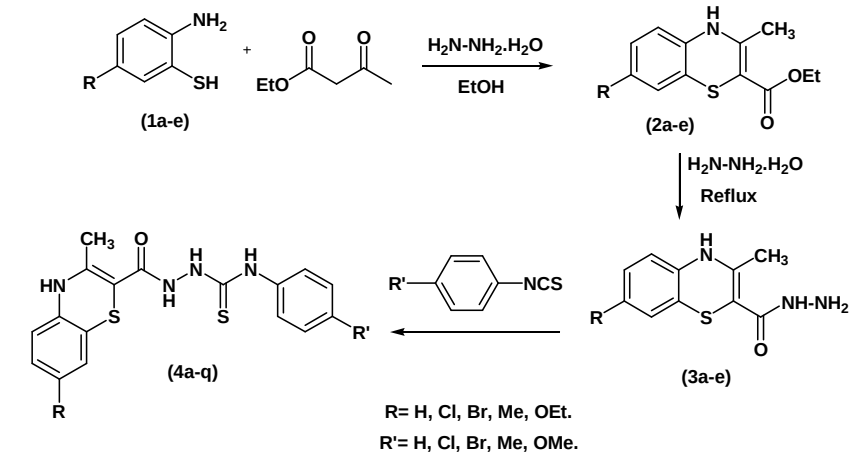
The chemistry of nitrogen containing heterocycles has been an interesting field of study for a long time. Benzothiazine possess the wide range of biological and pharmacological activities due to presence of fold along the nitrogen and sulphur axis, which is considered to be responsible as one of the structural features to impart their activities. The synthesis of novel 1,4-benzothiazine derivatives and investigation of their chemical and biological behaviour have gained more importance in recent decades for medicinal and agricultural reasons. In some cases 1,4-benzothiazine are also known for their utility as dyes[1], photographic developers [2], ultraviolet light absorbers and antioxidants [3]. The multifarious applications of 1,4-benzothiazine have directed organic chemists to synthesize new 1,4-benzothiazine bearing heteryl pharmacophores.

The literature survey revealed that some thiosemicarbazides had been used as plant growth regulators. Moreover, aroylthiosemicarbazide is also valuable synthetic intermediate for the synthesis of some thiadiazole derivatives [4]. Naturally occurring heterocyclic compounds containing azole core are one of the most active class of compounds possessing a wide range of biological activities. The synthesis of novel oxadiazole derivatives and investigation of their chemical and biological behaviour have gained more importance in recent decades for medicinal and agricultural reasons. Different classes of oxadiazole compounds possess an extensive spectrum of pharmacological activities, particularly in compounds bearing 1,3,4-oxadiazole nucleus which are known to exhibit unique anti-edema and anti-inflammatory activity [5]. Substituted oxadiazole moiety has been found to have important activities such as analgesic [6], antimicrobial [7,8], antitumor [9], antimalarial [10] and antihepatities [11].

The triazole derivative has been found as anti-thyroid agents, useful for the treatment of gastric ulcer, tuberculastatic activity, tranquillizer & sedative. The heterocyclic systems encompassing 1,2,4-triazole are explored to the maximum extent owing to their wide spectrum of pharmacological activities, such as antitumor, anti-inflammatory, antiviral & CNS-stimulant properties and also have herbicidal, insecticidal, bactericidal &fungicidal activities. [12,13]

These observations prompted us to synthesize some new compounds wherein biologically active moieties are present. In addition, in order to improve the biological ability of compounds, much attention has been paid to the development of the functional group in the ring. In view of this, we are working on the synthesis of new 1,4-benzothiazine containing azole derivatives, because it is common observation that combination of two or more biologically active heterocyclic rings in some compounds results in enhancement of biological profiles of such compounds by many folds. It is significant that the combined effect of all the entities will result in increased biological activity. In view of these and in continuation of our earlier work on the synthesis of 1,4-benzothiazine containing thiosemicarbazide and its intramolecular cyclized azole derivatives [7,12,14], we report some new compounds containing oxadiazole and triazole rings.

**Reaction Scheme 1:-**




## EXPERIMENTAL SECTION

All chemicals and reagents were purchased from commercial suppliers. The purity of compounds andthe progress of the reaction were checked by TLC. Melting points were determined in open capillaries in a liquid paraffin bath and are uncorrected. Infrared spectra were recorded in the region of 4000cm$^{-1}$ to 400cm$^{-1}$ on FT-IR-Alpha Bruker IR spectrometer in KBr pellets. The $^1$HNMR spectra in DMSO-$d_6$ using TMS as internal standard.

***Step I: Preparation of 2-carboethoxy-3-methyl-7-substituted-1,4-benzothiazine (2a-e)***

A mixture of 2-amino-5-substituted-thiophenol (**1a-e**) (0.1mol) and hydrazine hydrate (0.01mol) was heated at 100°C for 2-3 min before introducing the ethyl acetoacetate (0.1mol) and warming the reaction mixture to 100°C for further 10 min. After cooling to room temperature, 4-5 mL of ethyl alcohol was added. The solid was separated by filtration and recrystallized from ethyl alcohol. The other compounds (**2a-e**) were prepared in same fashion and their physical constants are given in Table 1.

***Step II: Preparation of 3-methyl-7-substituted-4H-1,4-benzothiazine-2-carbohydrazide (3a-e)***

To the (**2a-e**)(0.1mol) in ethanol (20mL), hydrazine hydrate (0.1mol, 99%) was added, followed by the addition of a catalytic amount of conc. $H_2SO_4$ (2-3drops). The mixture was refluxed for 2h. Excess solvent was removed and on cooling a solid was formed. The obtained solid was recrystallized by ethanol. The compounds (**3a-e**) were prepared in the same method and their physical constants are given in Table 1.

**Table 1. Characterization data of synthesized compounds (2a-e) and (3a-e)**

| Compound No. | -R | Compound 2 | | Compound 3 | |
|---|---|---|---|---|---|
| | | Yield(%) | M.P. (°C) | Yield(%) | M.P. (°C) |
| a | H | 92 | 145 | 60 | 92 |
| b | Cl | 88 | 166 | 65 | 190 |
| c | Br | 84 | 160 | 65 | 198 |
| d | $CH_3$ | 90 | 174 | 70 | 217 |
| e | $OC_2H_5$ | 86 | 196 | 56 | 240 |

***Step III: Preparation of 2-[3-methyl-7-substituted-4H-1,4-benzothiazine-2-yl]-N-(aryl) hydrazine carbothiamide (4a-q).***

The acid hydrazide (**3a-e**) (0.1mol) was treated with 4-substitued phenyl isothiocyanate (0.2 mol) in the presence of ethyl alcohol. The reaction mixture was refluxed for 2 h, cooled, solid obtained was filtered, wash with aq. ethanol

and recrystallized from ethyl alcohol. The compounds (**4a-q**) were prepared in the same fashion and their physical constants are given in Table 2.

**Reaction Scheme 2 :-**

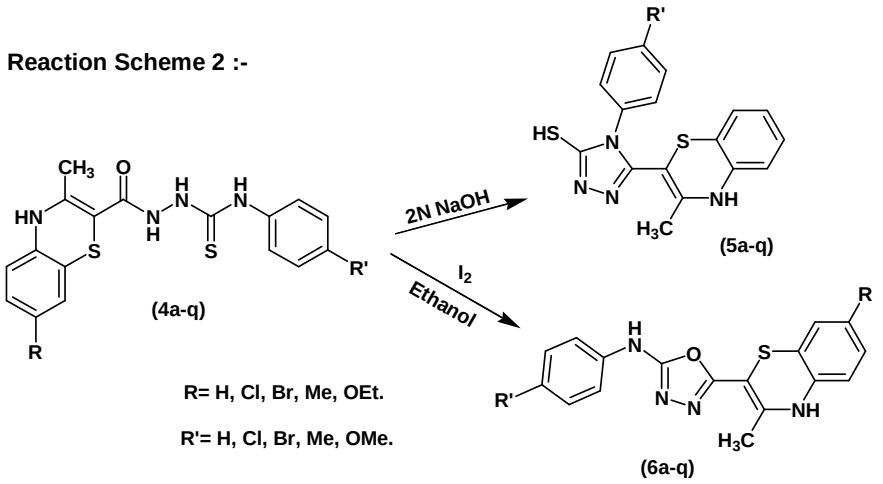



**Table 2: Characterization data for the synthesized compounds (4.a-q, 5a-q and 6a-q)**

| Sr. No | Substituents -R | -R' | Compound 4 Comp. code | Yield (%) | M.P. (°C) | Compound 5 Comp. code | Yield (%) | M.P. (°C) | Compound 6 Comp. code | Yield (%) | M.P. (°C) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | H | H | **4a** | 56 | 138 | **5a** | 62 | 207 | **6a** | 64 | 107 |
| 2 | H | Cl | **4b** | 66 | 216 | **5b** | 66 | 90 | **6b** | 68 | 234 |
| 3 | H | Br | **4c** | 62 | 232 | **5c** | 64 | 175 | **6c** | 62 | 224 |
| 4 | H | $CH_3$ | **4d** | 67 | 170 | **5d** | 60 | 140 | **6d** | 66 | 190 |
| 5 | H | $OCH_3$ | **4e** | 54 | 210 | **5e** | 58 | 112 | **6e** | 60 | 168 |
| 6 | Cl | H | **4f** | 58 | 173 | **5f** | 62 | 140 | **6f** | 66 | 215 |
| 7 | Cl | Cl | **4g** | 64 | 225 | **5g** | 66 | 91 | **6g** | 62 | 174 |
| 8 | Cl | Br | **4h** | 68 | 177 | **5h** | 62 | 255 | **6h** | 68 | 255 |
| 9 | Cl | $CH_3$ | **4i** | 63 | 221 | **5i** | 64 | 152 | **6i** | 58 | 235 |
| 10 | Cl | $OCH_3$ | **4j** | 58 | 232 | **5j** | 56 | 167 | **6j** | 56 | 248 |
| 11 | $CH_3$ | H | **4k** | 56 | 198 | **5k** | 62 | 94 | **6k** | 68 | 249 |
| 12 | $CH_3$ | Cl | **4l** | 61 | 187 | **5l** | 68 | 198 | **6l** | 64 | 222 |
| 13 | $CH_3$ | Br | **4m** | 64 | 176 | **5m** | 64 | 87 | **6m** | 62 | 242 |
| 14 | $CH_3$ | $CH_3$ | **4n** | 65 | 153 | **5n** | 60 | 82 | **6n** | 60 | 170 |
| 15 | $CH_3$ | $OCH_3$ | **4o** | 62 | 194 | **5o** | 58 | 103 | **6o** | 62 | 228 |
| 16 | Br | Cl | **4p** | 56 | 102 | **5p** | 60 | 94 | **6p** | 60 | 82 |
| 17 | $OC_2H_5$ | Cl | **4q** | 54 | 272 | **5q** | 54 | 134 | **6q** | 58 | 104 |

**Step IV: Preparation of azole derivatives:-**

***Preparation of 5-(3-methyl-7-substituted-4H-1,4-benzothiazine-2-yl)-4-aryl-4H-1,2,4-triazole-3-thiols (5a-q)***

The thiosemicarbazide (4a-q) (0.1 mol) was refluxed in 2N NaOH solution (10 mL) for 3 hours, after completion of reaction monitored by TLC, poured the reaction mixture into chilled water. Then on acidification with glacial acetic acid gave the crude product (5a-q) which was filtered, washed with water and the residue was recrystallized with ethanol or purified by column chromatography (mobile phase: hexane: ethylacetate- 4:5) to give the final pure product. The compounds (5a-q) were prepared in the same method and their physical constants are shown in Table 2.

***Preparation of 5-(3-methyl-7-substitued-4H-1,4-benzothiazin-2-yl)-N-aryl-1,3,4-oxadiazol-2-amine (6a-q)***

A mixture of thiosemicarbazide (4a-q) (0.1 mol) and iodine (0.01 mol) was refluxed in ethanol (25 mL) till the colour of iodine persisted. After completion of reaction monitored by TLC, poured the reaction mixture into chilled water and filtered it. The filtered solid was purified by column chromatography (mobile phase: hexane: ethyl acetate – 4:5) to give the final pure product (**6a-q**). The compounds (**6a-q**) were prepared in the same fashion and their physical constants are given in Table 2.

## RESULTS AND DISCUSSION

In conclusion, we have developed a mild and convenient method for the synthesis of entitled compounds. The present study reports an efficient method for the synthesis of 1,2,4-triazole by using 2N NaOH in water from

thiosemicarbazide derivatives and the second iodine catalysed intramolecular cyclisation method gives the 1,2,4-oxadiazoles derivatives in good yields.

**Acknowledgment**
The authors are thankful to the Management, Principal & Head (Dept. of Chemistry), JET's Z. B. Patil College, Dhule for providing the lab facilities and constant encouragement. One of the author Dr. B. R. Chaudhari is thankful to the University Grant Commission, Western Zone Poona (M.S.) for providing the financial support through minor research project. Sanction File no.47-258/12(WRO) dated 25.02.2013.

## REFERENCES

[1] R Tanaka; K Teramura; S Yokoyama. *Jpn Pat.*,**1966**, 5833. *Chem Abstr.*, **1966**, 65, 9062.
[2] WH Strain; JB Dickey. *US Pat*., 2381935; *Chem Abstr.*, **1946**, 40, 1889.
[3] CR Rasmussen. *US Pat.*, 37877400; *Chem Abstr.*, **1974**, 80, 95987.
[4] Y Hu; CY Li; XM Wang; YH Yang; HL Zhu.*Chem. Rev.*, **2014**, 114(10), 5572-5610.
[5] A Husain; P Ahuja. *Acta Poloniae Pharm.*, **2008**, 65, 527.
[6] B Narayana; KK Vijatraj; BV Ashalatha; NS Kumari. *Arch Pharm.*, **2005**, 338(8), 373-377.
[7] BJ Khairnar; RS Salunke; PB Patil; SA Patil; RJ Kapade; PS Girase; BR Chaudhari. *E-J. Chem.***2012**, 9(1), 318-322.
[8] SL Gaonkar; KM Rai. *Eur J Med Chem.*, **2006**, 41(7), 841-846.
[9] NMM Bezerra; SP De-oliveria; RM Srivastava; JR Da Silva. *Farmaco.*,**2005**,60, 955-960.
[10] M Zareef; R Iqbal; J Rodrigues; CT Supuran. *J Enzyme Inhib Med Chem.*,**2007**, 22(3),301-308.
[11] TM Tan; Y Chen; KH Kong; J Bai; Y Li; SG Lim; TH Ang; Y Lam. *Antiviral Res.*,**2006**, 71, 7.
[12] BJ Khairnar; PS Girase; BR Chaudhari. *Orient. J. Chem*., **2013**, 29(1), 285-289.
[13] SK Narwade; VB Halnor; ND Dalvi; CH Gill; BK Karale. *Indian J. Chem*, **2006**, 45(B): 2776-2780.
[14] BJ Khairnar; PS Girase; BR Chaudhari. *J Chem. Pharm. Res.*,**2015,** 7(2):561-564.