Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2014, 6(11):460-464

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis and characterization of some novel thiosemicarbazone derivatives containing the tetrazole moiety

Ajit Popat Ingale

Department of Chemistry, Dada Patil Mahavidyalaya, Karjat, Ahmednagar, India

---

ABSTRACT

Thiosemicarbazones belong to a class of compounds that occupy a wide range of biological activities and have been studied for their activity against tuberculosis, virus and most important against various cancerous cells. The tetrazole moiety is a versatile lead molecule in pharmaceutical development and has a wide range of biological activities. The diverse properties of tetrazoles and Thiosemicarbazones have prompted us to synthesize them in order to study their anti-inflammatory activity which has not been reported yet. In the present work some novel thiosemicarbazones derivatives containing the tetrazole moiety are synthesized and their structures have been confirmed by FT-IR, NMR and Mass spectra and elemental analysis.

Keywords: Thiosemicarbazone, tuberculosis, tetrazole, anti-inflammatory.

INTRODUCTION

Cancer is the uncontrolled growth and spread of cells. It can affect any part of the body. The growth of often invade surrounding tissue and metastasize to distant sites. Cancer can be caused 90-95% by factors such as tobacco, obesity, infections, radiation and 5-10% due to heredity[1].Thus, invention of newer anti-cancer agents has now become a key aim worldwide[2].

Thiosemicarbazone belong to a class of compounds that occupy a wide range of biological activity and have been studied for their activity against tuberculosis[3],virus and most important against various cancerous cells. SAR studies showed that a large number Thiosemicarbazone of an N-heterocyclic compounds have low π-electron density at the side chain part and the ring N- atom should be reasonably a good electron pair donor to transition metals to form co-ordination compounds[4]. Thiosemicarbazone in their neutral or deprotonated form, behave as an *N N S* thiodentate chelate towards metals ion essential for life. Important finding was that as *N N S* ligand system was a common features of all compounds with carcinogenic potency[5]. Also there is a strong correlation between tumor growth rate and the enzyme Ribonucleoside Diphosphate Reductase[6](RDR).So, it has been suggested that an inhibitor to RDR would be a good agent for the treatment of cancer and metal complexes formed by thiosemicarbazones are this type of compounds. The synthesis of transition metal complexes with thiosemicarbazones ligand has been receiving considerable attention due to the pharmacological properties of both ligand and complexes[7]. The deprotonated thiosemicarbazones ligands usually coordinate to platinum, copper, ruthenium, and osmium through oxygen, nitrogen and sulphar donor atoms in their (N,S) bidentate form or(N N S) tridentate form, to form metallic complexes of different molecular geometry and all these complexes are active against different cancer cells in their different geometries. Some synthetic analogues of thiosemicarbazone already

exist in market like Triapine, Merboran, etc**.** Triapine[8] is a potent ribonucleotide reductase inhibitor and used in cancer treatment.

The tetrazole system is a five-membered heterocyclic ring structure composed of four nitrogen atoms and used in the synthesis of pharmaceuticals. The tetrazole moiety is a versatile lead molecule in pharmaceutical development and has a wide range of biological activities[9]. The diverse properties of tetrazoles and Thiosemicarbazone have prompted us to synthesize them in order to study their anti-inflammatory activity[10] which has not been reported yet. The compound containing tetrazole nucleus find unique place in medicinal chemistry and pharmaceutical chemistry and play significant role, as they are associated with immense biological activity. Tetrazole are an increasingly popular functionality with wide ranging application[11]. They have found use in co-ordination chemistry and in various materials sciences applications including photography, speciality explosive, information recording systems and agricultural composition[12]. In addition extensive work has been carried out in field of medicinal chemistry[13]. Similarly Thiosemicarbazone play an essential role in agricultural, pharmaceutical and industrial chemistry and they are used in catalyst, in various biological systems, polymers and dyes, besides some uses antifertility and enzymatic agents[14].

Literature survey reveals that till no tetrazole containing Thiosemicarbazone has been evaluated for anti-inflammatory activity. From the study of the literature survey the extensive application of Thiosemicarbazone and tetrazole in recent development of medicinal chemistry, I have to synthesized the Thiosemicarbazone derivatives containing the tetrazole moiety and their structures is confirmed by spectral analysis data.

EXPERIMENTAL SECTION

All compound were dried using appropriate drying agents, employing standard laboratory technique. All moisture sensitive reaction were carried out using the calcium chloride guard tube. Solvents used for column chromatography were distilled using simple distillation. Column chromatography was performed using hexane or mixture of hexane and ethyl acetate.100-200 mesh silica gel was used for column chromatography. Analytical TLC was performed on homemade plates using silica gel containing 15% calcium sulphate as binder and were exposed to iodine vapours for visualization. Melting points were determined by using open capillary and are uncorrected. All the ^{1}H-NMR spectra were recorded using Gemini 20 MHz instrument in $CDCl_3$ solvents unless chemical shifts were reported relative to tetra methyl silane(TMS) as an internal standard.

General procedure for the synthesis of substituted 5-phenyl tetrazole:
A mixture of benzonitrile (3.3 g, 0.10 mol), sodium azide (0.65 g, 0.10 mol) dimethylformamide (10 mL) and ammonium chloride (5.3 g, 0.10 mol) was heated in an oil bath for 7 h at 125 °C. The solvent was removed under reduced pressure. The residue was dissolved in 100 mL of water and carefully acidified with concentrated hydrochloric acid to pH 2. The solution was cooled to 5°C in ice bath. It is recrystallized from aqueous methanol. The pure product was obtained in (2.5 g) 75.75% yield.

In same manner, other p-chloro, p-nitro, p-bromo, p-menthyl, p-carboxylic substituted 5-phenyl tetrazole were synthesized and characterized.

General procedure for the synthesis of substituted-5-phenyl-1-acetyl-tetrazole:
A solution of 5-phenyl tetrazole (12.8g, 0.08 moles), acetic anhydride (0.08 mole) and 2-3 drops of concentrated sulphuric acid was heated for 15-20 min. on a water bath, then cooled and poured into ice cold water. The product separated was filtered and dried. It was further purified by crystallization from ethanol. The pure product was obtained in (8.5 g) 66.40% yield.

In same manner, other p-chloro, p-nitro, p-bromo, p-menthyl, p-carboxylic substituted 5-phenyl tetrazole were synthesized and characterized.

General procedure for synthesis of thiosemicarbazone derivatives:
a) Synthesis of 1-(1-(5-phenyl-1-1H-tetrazol-1-yl)ethylidene)thiosemicarbazone (C_1)
A typical procedure is described here for the synthesis of 1-(1-(5-phenyl-1-1H-tetrazol-1-yl)ethylidene)thiosemicarbazone (C_1)

The thiosemicarbazide(0.1mol) and 10 drops of glacial acetic acid were added to a warm solution of 5-phenyl-1-acetyl tetrazole (0.1 mol) in methanol (6 ml).The reaction mixture was heated at reflux temperature for 2 hours .The product was obtained upon cooling, and then dried. Product was re-crystallized by 95% ethanol. The reaction progress was checked by TLC taking ethyl acetate and toluene (4:1)as mobile phase. The product was white colour solid with 65 % yield and melting point at 205^0C.

IR (KBr):3250 (N-H), 1189 (C=S), 1514 (C=N), 1590-1620 (C=C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.45 (m, 5H), 6.72 (s, 1H), 2.3 (s,2H), 1.3 (s,3H).

Mass (ESI): m/z M^+ 261.08 (found) 261.31 (Actual), [M+2] 263.08. Anal.calcd.for $C_{10}H_{11}N_7S$ (M.W.261.31): C, 45.96; H, 4.24; N, 37.52; S, 12.27. Found: C, 45.64; H, 4.22; N, 37.49; S, 12.25%.

In the same manner, other thiosemicarbazone derivatives were synthesized and characterized.

b) **Synthesis of 1-(1-(5-(4-chlorophenyl)-1H-tetrazol-1-yl)ethylidene)thiosemicarbazone (C_2)**
White colored solid; 89% yield; m.p.178-180^0C; IR (KBr):3453 (N-H), 1213 (C=S), 1532 (C=N), 1620-1645 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (dd, 2H), 7.32 (dd, 1H), 6.72 (s, 1H), 2.3 (s, 2H), 1.3 (s, 3H). Mass (ESI): m/z M^+ 295.04 (found) 265.75 (Actual), [M+2] 297.04. Anal.calcd.for $C_{10}H_{10}ClN_7S$ (M.W.295.75): C, 40.61; H, 3.41; Cl, 11.99; N, 33.15; S, 10.84. Found: C, 40.58; H, 3.39; Cl, 11.95; N, 33.12; S, 10.82%.

c) **Synthesis of 1-(1-(5-(4-nitrophenyl)-1H-tetrazol-1-yl)ethylidene)thiosemicarbazone (C_3)**
Yellowish colored solid; 83% yield; m.p.232^0C; IR (KBr):3380 (N-H), 1240 (C=S), 1555 (C=N), 1625-1645 (C=C) 1390-1540(N=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (dd, 2H), 7.63 (dd, 1H), 6.67 (s, 1H), 2.4 (s, 2H), 1.3 (s,3H). Mass (ESI): m/z M^+ 306.3 (found) 306.06 (Actual), [M+2] 308.06. Anal.calcd.for $C_{10}H_{10}N_8O_2S$ (M.W.306.3): C, 39.21; H, 3.29; O, 10.45; N, 36.58; S, 10.47. Found: C, 39.19; H, 3.26; O, 10.43; N, 36.55; S, 10.45%.

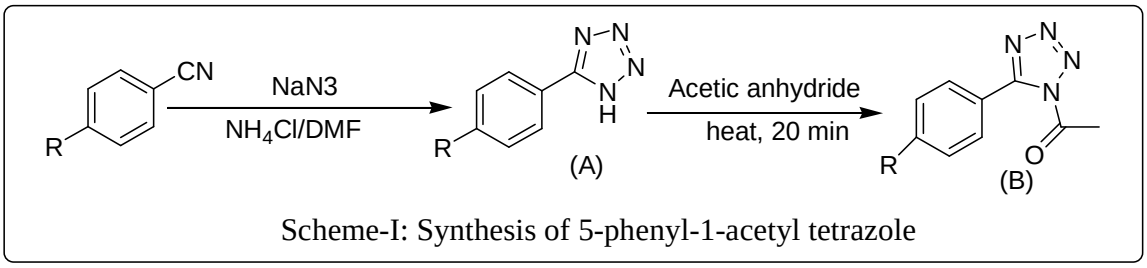
d) **Synthesis of 1-(1-5-p-tolyl)-1H-tetrazol-1-yl)ethylidene)thiosemicarbazone (C_4)**
White colored solid; 55% yield; m.p.155^0C; IR (KBr):3315 (N-H), 1140 (C=S), 1455 (C=N), 1595-1625 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (dd, 2H), 7.12 (dd, 1H), 6.23 (s, 1H), 2.2 (s, 2H), 2.3 (s, 3H), 1.1 (s,3H). Mass (ESI): m/z M^+ 275.10 (found) 275.33 (Actual), [M+2] 277.09. Anal.calcd.for $C_{11}H_{13}N_7S$ (M.W.275.10): C, 47.98; H, 4.76; N, 35.61; S, 11.65 . Found: C, 47.95; H, 4.74; N, 35.59; S, 11.63%.

e) **Synthesis of 1-(1-(5-(4-bromophenyl)-1H-tetrazol-1-yl)ethylidene)thiosemicarbazone (C_5)**
White colored solid; 75% yield; m.p.190^0C; IR (KBr):3370 (N-H), 1240 (C=S), 1515 (C=N), 1605-1625 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (dd, 2H), 7.32 (dd, 1H), 6.33 (s, 1H), 2.2 (s, 2H), 1.1 (s, 3H). Mass (ESI): m/z M^+ 338.99 (found) 340.2 (Actual), [M+2] 340.99. Anal.calcd.for $C_{10}H_{10}BrN_7S$ (M.W.340.2): C, 35.30; H, 2.96; Br, 23.49; N, 28.82; S, 9.43. Found: C, 35.28; H, 2.95; Br, 23.45; N, 28.80; S, 9.41%.

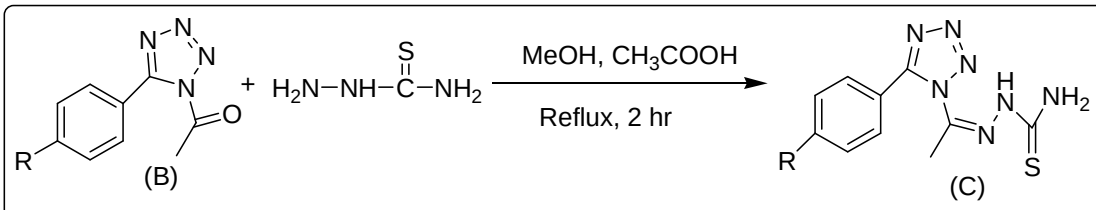
d) **Synthesis of 4-(1-(1-thiosemicarbazidoethyl)-1H-tetrazol-5-yl)benzoic acid (C_6)**
White colored solid; 70% yield; m.p.145^0C; IR (KBr):3350 (N-H), 1230 (C=S), 1435 (C=N), 1625-1635 (C=C), 3450 (O-H), 1728 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.23 (s, 1H), 8.16 (dd, 2H), 7.83 (dd, 1H), 6.38 (s, 1H), 2.4 (s, 2H), 2.2 (s, 3H), 1.2 (s,3H). Mass (ESI): m/z M^+ 305.07 (found) 305.32 (Actual), [M+2] 307.07. Anal.calcd.for $C_{11}H_{11}O_2N_7S$ (M.W.305.07): C, 43.27; H, 3.63; O, 10.48; N, 32.11; S, 10.50. Found: C, 43.25; H, 3.61; O, 10.45; N, 32.07; S, 10.46%.

RESULTS AND DISCUSSION

The titled compounds were synthesized according to scheme I and II. The structure of all synthesized compounds were confirmed by spectral data. The compound A was prepared by the reaction of substituted benzonitrile with sodium azide in presence of ammonium chloride. The substituted 5-phenyltetrazole A was converted into substituted 5-phenyl -1-acetyl tetrazole B by reaction with acetic anhydride using catalytic amount of sulphuric acid. The synthesis of Thiosemicarbazone derivatives containing the tetrazole moiety is outlined in scheme-II. The condensation of monosubstituted thiosemicarbazide with 5-phenyl-1-acetyl tetrazole B in presence of glacial acetic acid in methanol by warm condition to give target compound C .



Scheme-I: Synthesis of 5-phenyl-1-acetyl tetrazole

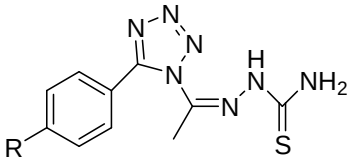


Where, C_1 = R = -H
C_2 = R = -Cl
C_3 = R = $-NO_2$
C_4 = R = $-CH_3$
C_5 = R = -Br
C_6 = R = -COOH

Scheme-II: Synthetic pathways for preparation of thiosemicarbazone derivatives

A series of compounds were synthesized by simple condensation reaction between thiosemicarbazide and different substituted compound B_1-B_6 to form the target structures C_1-C_6. The melting point and yields of these synthesized compound are shown in Table I.

Table I : Yields and M.P.for synthesized compounds C_1 to C_6



Sr.No.	Compound	R	M.P (^{0}C)	Reaction Time	Yields (%)
1	C_1	-H	205^{0}C	2.0 hours	65
2	C_2	-Cl	178^{0}C	1.5 hours	89
3	C_3	$-NO_2$	232^{0}C	1.5 hours	83
4	C_4	$-CH_3$	155^{0}C	2.0 hours	55
5	C_5	-Br	190^{0}C	2.5 hours	75
6	C_6	-COOH	145^{0}C	3.0 hours	70

CONCLUSION

In summary, I have successfully synthesized and chacterised a novel thiosemicarbazone derivatives containing the tetrazole moiety. The biological activity of these Thiosemicarbazone derivatives have been evaluated in future.

Acknowledgements
The authors are thankful to the Board of college and university development, Savitribai Phule Pune University, Pune for financial supports and also to Director, National Chemical Laboratory, Pune for recording spectral data.

REFERENCES

[1] Anand P & Kunnumakkara A B, *Pharma Res*, 25, **2008,** 2097.
[2] World Health Organization. Cancer: Data and Country Profiles.
[3] Sepkowitz K A, *New Engl J Med*, 344, **2001**, 1764.
[4] Weiss R A, *Science Journal*, 260, **1993**, 1273.
[5] Kallings L O, *J Intern Med*, 263, **2008**, 218.
[6] Easmon J, Heinisch G, Holzer W & Rosenworth B, *J Med Chem*, 35, **1992,** 5228.
[7] Hitesh Dahyabhai Patel, Saavani Malove Divatia, Erik de Clercq, *Indian J of Chem, Sec-B*, 52, **2013,** 535-545.
[8] Mylonas S & Mamalis A, *J Heterocycl Chem*, 42, **2005**, 1273.
[9] Dilovic I, Ruccic M, Vrdoljak V, Kraljevic S & Cindric M, *J Bioorg Med Chem*, 16, **2008,** 5189.
[10] Rajasekaran A. and Thampi P, *Eur. J. Med. Chem, 40*, **2005,** 1359.
[11] Adamec J, Waisser K, Kunes J, & Kaustova, *J Arch Pharma, 338*, **2005**, 385.
[12] Mohite P B, Bhaskar V H, *Journal of Optoelectronics and Biomedical Materials, 2*, **2010,** 249.
[13] Sangapure S, Bodke Y & Raga B, *Indian J Heterocyclic Chem, 11*, **2011,** 31.
[14] Ashish K T, Anil M, *Indian J. Chem, 45B, **2006 ,*** 489.