SYNTHESIS, CHARACTERIZATION OF 1- PHENYL- 3(2) - HYDRAZINO -1, 3- SUBSTITUTED BENZOTHIOZOLYL THIOCARBAMIDE.

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Abstract:
Serial of 1- phenyl- 3(2)-hydrazino-1,3-substituted benzothiozolyl thiocarbamide has been synthesized by the interaction of phenyl isothiocynate with 2 -hydrazino-1,3-benzothiazoles in acetone medium The reaction mixture was kept at room temp for 24 hrs. then acetone is evaporated and product is recrystallised by petroleum ether (60-80%). The title compounds were characterized on the basis of elemental analysis and IR, ^{1}HNMR and Mass spectral analysis. Hydrazine hydrate comprises a novel mechanistic class of antitumor agent. 2-aminobenzothiazole has received much attention due to their unique structure and interesting biological properties that leads to their use as anticonvulsant antibacterial and muscle relaxant agent. Especially interesting are hydrazine hydrate derivative, which are known to possess remarkable amyloidal – imaging, antimicrobial vulcanization accelarators and starting material for various pharmaceutical industries.

Keywords: phenyl isothiocynate , 2 -hydrazino-1,3-benzothiazoles, substituted benzothiozolyl thiocarbamide

1. Introduction:

Benzothiazole, a multifaceted nucleus, has been under research for the last two decades. Being a heterocyclic compound, benzothiazole finds use in research as a starting material for the synthesis of larger, usually bioactive structures. Its aromaticity makes it relatively stable, although as a heterocycle, it has reactive sites which allow for functionalization.

Hydrazine hydrate comprises a novel mechanistic class of antitumor agent. 2-aminobenzothiazole has received much attention due to their unique structure and interesting biological properties. From the literature survey, it has been found that extensive work has been reported on 2-substituted benzothiazole derivatives in past and evaluated for different activities like antibacterial [1], anticancer [2], antiviral [3], antitumor [4], antifungal [5], anti-inflammatory [6], antioxidative and radioprotective [7], antidiabetic [8,9], anthelmintic [10], anti-leishmanial [11], anticonvulsant [12], neuroprotective [13], a topical carbonic anhydrase inhibitor and an antihypoxic. Taking this into view, and in continuation of our search for biologically potential benzothiazole derivatives, a certain new derivatives were synthesized taking benzothiazole as the basic moiety.

A number of 2-aminobenzothiazole were intensively studied in medicinal chemistry and reported cytotoxic on cancer cells [14]. 2-aminobenzothiazole, substituted benzothiazole have found application in several areas of chemistry. 2-aminobenzothiazole are broadly found in bioorganic and medicinal chemistry with application in drug discovery and development of treatment of diabetes [15], epilepsy [16,17], thrombin inhibitors [18]

Hence, in present work, different benzothiazoles react with hydrazine hydrate and this hydrazino benzothiazoles then focused to fuse with Phenyl isothiocyanate.

2. Experimental

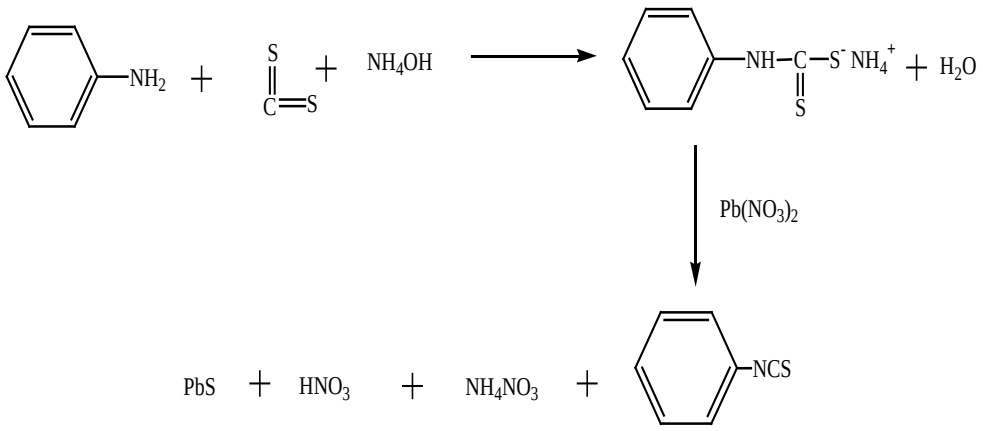
2.1 Material and Methods

All chemicals were research grade. Melting points determined are uncorrected. IR spectra were recorded in KBr on a FT-IR Perkin-Elmer RXI(4000-450cm^{-1}) spectrophotometer. ^{1}H NMR measurements were performed on a Bruker DRX-300 (300 MHz FT NMR) NMR spectrometer in $CDCl_3$ solution with TMS as internal reference. The Mass spectra were recorded on a THERMO Finnigan LCQ Advantage max ion trap Mass spectrometer. Thin layer chromatography (TLC) was performed on silica Gel G and spots were visualized by iodine vapour. The compounds describe in this paper were first time synthesized by the multistep reaction protocol.

2.1 Preparation of Phenyl isothiocynate

Equip a 500 ml three-necked flask with a powerful mechanical stirrer and separatory funnel leave the third neck open or loosely stopper. Introduce, while the flask is cooled in a freezing mixture ice and salt, 30ml of concentrated ammonia solution (d.0.88) and 15ml of pure carbon disulphide. Stir the mixture and run in 18ml of aniline from the separatory funnel during about 20 minute. Stir for the further 30 minutes and allow standing for another 30 minutes. A heavy precipitate of ammonium phenyl dithiocarbamate separate.

Transfer the salt to 2-litre RBF by four extraction with 100ml portion of water. Add to the resulting solution with constant stirring a solution of 65gm of Lead Nitrate in 150ml of distilled water Lead Sulphide precipitate. Steam distils the mixture into a receiver containing 10ml of 0.5m H_2SO_4 as long as organic material possess over. Separate the oil dry it over anhydrous Calcium Chloride or Magnesium sulphide and distilled under diminished pressure. Collect the Phenyl isothiocynate. (**Scheme 1**)



Phenylisothiocynate

(1)

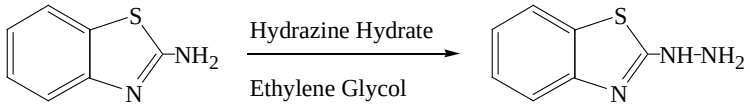
2.2 Preparation of 2- hydrazino-1, 3-benzothiozole

a) Preparation of benzothiozole

The required substituted benzothiazoles has been prepared by the oxidative cyclization of aryl thiocarbamide with the help of molecular bromine. To the chloroformic paste of phenyl thiocarbamide (5gm in 10ml) molecular bromine (20%) was added gradually with constant stirring until a slight excess of bromine was added as evident from an orange red colour. It was then allow standing for 5 to 6 hrs. to resultant acidic solid was treated with cold ethanol, the solid dissolved in ethanol. On basification with dilute ice cold NH_4OH 2-aminobenzothiozole was separated out as a white solid (3gm). M.P. 130^{o}C.

b) Preparation of 2- hydrazino-1,3-benzothiozole

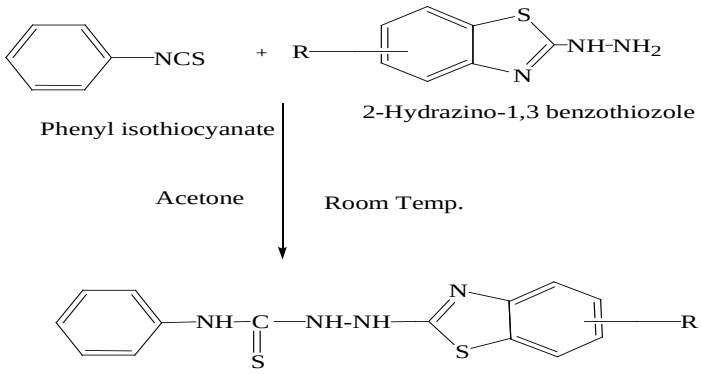
Concentrated HCl (1mL) was added drop wise to hydrazine hydrate (0.2 M, 1mL 80%) at 5-10^{o}C followed by ethylene glycol (20mL). To the above solution 2-aminobenzothiazole (0.01 M, 1.85g) was added in portions. It was then refluxed for 3 h, cooled and poured onto crushed ice. The separated solid was filtered, dried and recrystalized from ethanol. **2(a-g). (Scheme-2)**



2 amion-1,3 benzothiozole 2-Hydrazino-1,3 benzothiozole

(2)

2.3 Preparation of 1- phenyl- 3(2)-hydrazino-1,3- substituted benzothiozolyl thiocarbamide A acetone solution of Phenyl isothiocyanate (0.025M, 2.5g in 20mL) was mixed with acetone solution of 2-hydrazino-1,3-benzothiazole (0.025M, 0.37g in 10mL), and mixture after shaking for sometime was kept at room temperature for 24 hrs. Acetone was distilled off to obtained sticky residue. This residue was triturated several times with petroleum ether to afford a light coloured solid. **(1-7). (Scheme-3).**



1- phenyl- 3(2)-hydrazino-1,3- substituted benzothiozolyl thiocarbamide

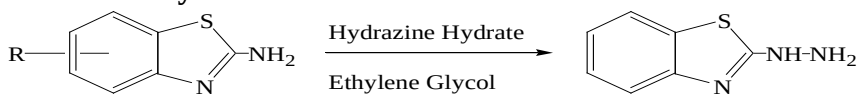
(3)

Where, R= (a) Phenyl, (b) o-Cl-Phenyl, (c) m-Cl-Phenyl, (d) p-Cl-Phenyl, (e) *o*-tolyl, (f) *m*-tolyl , (g) *p*-tolyl,

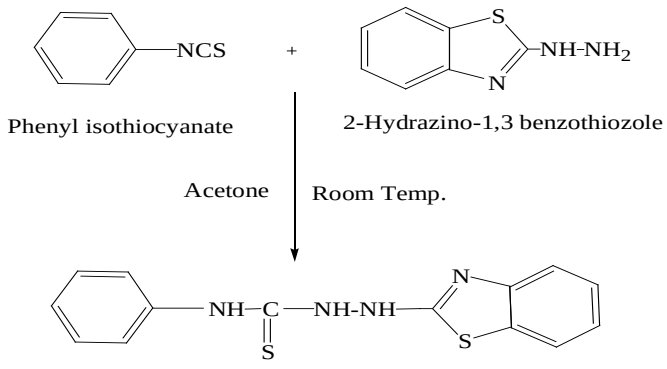
3. Results and discussion

Herein, we report the synthesis of various 1-phenyl- 3(2)-hydrazino-1,3- substituted benzothiozolyl thiocarbamide **(1-7)** by interaction of Phenyl isothiocyanate **(1)** and substituted 2-hydrazino-1,3-benzothiazole 2 **(1-7)** in acetone medium. All products were crystallized from ethanol before recording the physical data (Table-1). The purity of compounds was checked by TLC. The spectral analysis [19-21] IR, 1H NMR and Mass spectra of the product were observed. **(Scheme-2).**

Scheme for synthesis shown as follows:



2 amion-1,3 benzothiozole 2-Hydrazino-1,3 benzothiozole



1- phenyl- 3(2)-hydrazino-1,3- substituted benzothiozolyl thiocarbamide

Where, R= (a) Phenyl, (b) *o*-tolyl, (c) *m*-tolyl , (d) *p*-tolyl, (e) o-Cl-Phenyl, (f) m-Cl-Phenyl, (g) p-Cl-Phenyl

1: IR (KBr):υ 3363 (N-H), 3201 (Ar-H), 1523 (C=N), 1154 (C=S), 783.10 (C-S), H NMR (δ in ppm, $CDCl_3$): δ 6.92-6.41 (3H, s, N-H), δ 8.22-7.00(9H, m, aromatic protons), Mass (m/z): 300 (M^+), 223, 166,77,; Anal. Calcd for $C_{15}H_{12}N_4S_2$: C, 56.00; H, 4.00; N,18.66; S, 21.33; Found: C, 56.32; H, 4.05; N, 18.60.; S, 21.50.

On the basis of all above facts the product with m. p. 145^{o}C was assigned the structure 1-phenyl- 3(2)-hydrazino-1,3- Phenyl substituted benzothiozolyl thiocarbamide . When the reaction of phenyl isothiocyanate was extended to several other 2- hydrazino-1,3-benzothiozole corresponding 1- phenyl- 3(2)-hydrazino-1,3-substituted benzothiozolyl thiocarbamide has been synthesized.

2: IR (KBr):υ 3358 (N-H), 3062 (Ar-H), 1620 (C=N), 1127 (C=S), 785.10 (C-S), H NMR (δ in ppm, $CDCl_3$): δ 6.82-6.43 (3H, s, N-H), δ 8.20-7.00 (8H, m, aromatic protons), Mass (m/z): 334 (M^+), 300, 223, 166, 77; Anal. Calcd for $C_{14}H_{12}N_4S_2Cl$: C, 50.22; H, 3.28; N, 16.74; S, 19.13; Found: C, 50.28; H, 3,.20; N,16.70.; S, 19.00.

On the basis of all above facts the product with m. p. 135^{o}C was assigned the structure 1-phenyl- 3(2)-hydrazino-1,3- o-Cl-Phenyl substituted benzothiozolyl thiocarbamide.

5: IR (KBr):υ 3300 (N-H), 3017 (Ar-H), 1628 (C=N), 1120 (C=S), 780 (C-S), H NMR (δ in ppm, $CDCl_3$): δ 6.92-6.41 (3H, s, N-H), δ 8.22-7.00(9H, m, aromatic protons), δ 2.12-2.00 (3H, s, aliphatic Protons) Mass (m/z): 314 (M^+), 300, 166, 77; Anal. Calcd for $C_{15}H_{14}N_4S_2$: C, 57.32; H, 4.45; N, 17.83; S, 20.38; Found: C, 57.30; H, 4.50; N, 17.80; S, 20.32.

On the basis of all above facts the product with m. p. 115^{o}C was assigned the 1- phenyl- 3(2)-hydrazino-1,3- o-Tolyl substituted benzothiozolyl thiocarbamide.

Table -1: Physical data for characterization of compounds (1-7)

Compd	Yield %	R_f	M.P. ^{0}C	Analysis (%): Found (calcd)	
				N	S
1	69.00	0.50	145	18.60(18.66)	21.50(21.33)
2	65.00	0.48	135	16.70 (16.76)	19.00(19.13)
3	73.00	0.55	110	16.80 (16.76)	19.1519.13)
4	65.00	0.60	125	16.78 (16.76)	19.18(19.13)
5	72.00	0.53	115	17.80(17.83)	20.32(20.38)
6	80.00	0.58	107	17.85 (17.83)	20.40(20.38)
7	60.00	0.62	128	17.88 (17.83)	20.30(20.38)

C and H analysis was found satisfactory in all cases.

Conclusion

Derivatives were synthesized and characterized for their structure elucidation. As outline in synthesis process, important novel -1,3-substituted benzothiozolyl thiocarbamide has been synthesized. All the structure of the above compounds was in good agreement with Spectral and Analytical data. Various chemical and spectral data supported the structures.

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