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Synthesis and Biological Activity of Some Thiosemicarbazide

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ABSTRACT

In this paper, thiosemicarbazone derivatives have been prepared from substituted aromatic aldehyde and thiosemicarbazide in presence of sodium chloride. This method is an efficient, mild, inexpensive, non-toxic and environment benign catalyst. This protocol includes the reaction followed by using sodium chloride to accelerate the reaction in aqueous ethanol. The structure of synthesized compounds were determined by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopies as well as the compounds were also screened for antibacterial and antifungal activity against certain Gram-negative and Gram-positive bacteria and fungal pathogens.

KEYWORDS

Thiosemicarbazide, Sodium chloride, Antibacterial, Antifungal.

INTRODUCTION

Thiosemicarbazides are potent intermediate in the field of medicinal chemistry. They are used for the synthesis of pharmaceutical and bioactive materials. The imine bond (-N=CH-) in this compound are useful in organic synthesis. In this era for developing ecofriendly process, the chemists are trying to focus on to increase the possibilities of reaction by using the raw material which are easily available in nature and its use will not be responsible for disturbing to the nature. Water is the most desirable solvent in the green context and many successful examples of reactions in aqueous medium are known. Though water has been used in many successful reaction. In many instance aqueous-ethanol is also a good mixture for reaction to accelerate the rate of reaction [1].

The use of sodium chloride as a catalyst in organic synthesis is due to its nature as a excellent solubility in water, non-toxic, easily available, nonconventional and commonly available in nature. The literature survey also reveals that the sodium chloride is a useful catalyst in construction of carbon-carbon and carbon-hetero atom bonds [2,3].

Thiosemicarbazone derivative has special importance among the researchers due to its numerous biological and pharmaceuticals activities. Thiosemicarbazone belongs to a group of thiourea derivative [4].

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In the beginning of 20th century, thiosemicarbazone moiety has application in the synthesis of drug molecules. Thiosemicarbazide are potent intermediates for the synthesis of pharmaceutical and bioactive material and thus, they used extensively in the field of medicinal chemistry. The imine bond (-N=CH) in this compound are useful in organic synthesis [5]. The thiosemicarbazone have been evaluated as antiviral, antibacterial, antifungal, antimalerial, anticancer, leprosy. Thiosemicarbazone is also known as an iron chelating group, bonding the sulfur and azomethine nitrogen atom. The complexes of nitrogen and sulfur atoms with metal ion may be considered potential biological agents. thiosemicarbazone derivatives have demonstrated wide range of biological activities [6].

Thiosemicarbazones have been investigated for medicinal studies for a long while due to their wide range of biological activities. Presently the areas in which thiosemicarbazones are receiving more attention can be broadly classified according to their anticancer, antitumor, sodium channel blocker, antibacterial and antifungal activity [7-13]. So, in present study we have carried out the synthesis of thiosemicarbazone and their antibacterial and antifungal activity of different derivatives is reported.

EXPERIMENTAL

All chemicals used in the synthesis were purchased from Sigma-Aldrich and S. D. Fine chem. of laboratory grade and used without purification. Reactions were monitored by thin layer chromatography (TLC), visualized with ultraviolet cabinet. Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on FTIR jasco 4100 KBr pellets with absorptions in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on a BRUKER AVANCE DPX spectrometer using DMSO-d_6 as solvent and TMS as an internal standard and given in δ units.

General procedure for synthesis of thiosemicarbazone derivative: A mixture of thiosemicarbazide (**2**) (1 mmol), aromatic aldehyde (**1**) (1 mmol) and sodium chloride (10 mmol %) were taken in a round bottomed flask containing 5 mL (1:1) ethanol:water mixture and stirred for 20-30 min at 50-60 °C. The progress of reaction was monitored by thin layer chromatography (TLC).The obtained solid was filtered, washed with water and recrystallized from ethanol to give the product **3**. All the synthesized compounds were confirmed by their physical constants and characterized by IR, ^1H and ^{13}C NMR and mass spectroscopy.

Spectral data of selected compounds

2-(3-Nitrobenzylidene)thiosemicarbazone (3b): IR (KBr, ν_{max}, cm^{-1}): 3390 (NH), 3181(C-H),1600 (C=C), 1521 (C=N),1469 (C_6H_5), 1346 (NO_2); 1241 (C-N); ^1H NMR (DMSO-d_6, 400 MHz), δ (ppm): 7.55 (t, 1H, Ar-H), 7.39 (s, 1H, Ar-H), 7.42 (d, 1H, Ar-H), 7.53 (d, 1H, Ar-H), 7.560 (2H, $–NH_2$), 8.02 (s, 1H, CH), 11.99 (s, 1H,-NH-); ^{13}C NMR 100 (MHz, DMSO): δ 178.3 (C=S), 148.85 (Ar) 140.39 (CH=N) 136.65 (Ar), 134.01 (CH Ar), 130.60 (CH Ar), 124.40 (CH Ar), 121.83 (CH Ar) MS 225.0 (M+1).

2-(4-Hydroxybenzylidene)thiosemicarbazone (3c): IR (KBr, ν_{max}, cm^{-1}): 3358 (OH), 3182 (C-H), 1577 (C=C), 1552 (C=N), 1438 (C_6H_5), 1373 (C-O), 1226 (C-N); ^1H NMR (DMSO-d_6, 400 MHz), δ (ppm): 7.61 (d, 2H, Ar-H), 6.84 (d, 2H, Ar-H), 8.52 (2H, $–NH_2$), 7.90 (s, 1H, CH), 6.79 (s,1H, Ar-OH), 3.3 (s,1H,-NH-); ^{13}C NMR 100 (MHz, DMSO): δ 177.86 (C=S), 159.79 (C-OH) 143.20 (CH=N) 130.53 (Ar), 129.49 (CH Ar), 125.54.60 (CH Ar), 116.23 (CH Ar), 116.02 (CH Ar) MS 196.0 (M+1).

Antibacterial activity

Preparation of standard bacterial suspension: The cultures of *Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, Salmonella typhi* were cultivated in Mueller-Hinton agar (MHA). Dimethyl sulphoxide were used as a solvent and as control. Ofloxacin was used as a standard for comparison of the result. The diameter of zone of inhibition was measured in millimeter (mm).

Preparation of plates (media) for bacterial strains: Liquified sterile Mueller-Hinton agar (pH 7.3) is poured into plates (petri dishes) kept on a leveled surface. The depth of medium should be approximately 4 mm. After the medium has solidified, dry the plates for 0.5 h in incubator (35 ºC to 37 °C) to remove excess moisture from the surface. While pouring into plates, 5 % defibrinated sterile sheep blood should be aseptically added to MHA for testing organisms.

Disc diffusion method: Allow to pour pre-autoclaved liquid Mueller-Hinton agar medium into pre sterilized 90 mm petri plates under aseptic condition and was allowed to solidify at room temperature. Spread 0.1 mL of pure bacterial culture on MHA plates with the help of spreader in aseptic condition. For the preparation of discs Whatman filter paper were used to prepare disc. Paper discs are sterilized by auto calving each disc was impregnated with 10 µL of stock solution of respective synthetic compound. All the compounds were dissolved in dimethyl sulphoxide solvent then sterile disc of 10 mm were soaked in media and applied on plates. The petriplates were incubated at 37 °C for 24 h. Measure the zone of inhibition after 24 h [22-27].

Antifungal activity

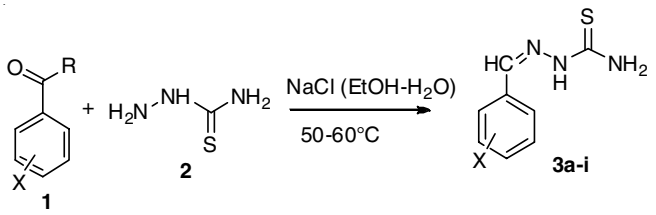
Preparation of standard bacterial suspension: The culture of fungal strains of *Candida albicans* and *Trychophyton rubrum* were cultivated on potato dextrose agar (PDA) being first incubated at 27 °C for about 3-4 days then stored at 4 °C. Fluconazole was used as a standard.

Preparation of media for bacterial strain: Potato dextrose agar (PDA) is used for the cultivation of fungi. Potato dextrose agar is composed of dehydrated potato infusion and dextrose that encourage luxuriant fungal growth. Added 39 g of commercial potato dextrose agar powder to 1 L of distilled water. Boil while mixing to dissolve. Autoclave for 15 min at 121 °C.

Disc diffusion method: Antifungal activity was performed by disc diffusion method. The medium used was potato dextrose agar (Mueller-Hinton agar). The medium was prepared and sterilized at 10 Psi in autoclave for 15 min. Then the compounds to be tested were added to the sterile medium in aseptic condition. A plate with DMSO was prepared as blank (negative control), similarly, a plate with fluconazole was prepared as standard reference plate (positive control) [14-17].

RESULTS AND DISCUSSION

In this work, a simple, efficient and rapid method for synthesis of thiosemicarbazone is reported. Various aromatic aldehydes (**1**) react with thiosemicarbazide (**2**) catalyzed by NaCl in aqueous ethanol at 50-60 °C (**Scheme-I**). The reaction was rapidly completed and gave desired products in good to excellent yields. The resulting thiosemicarbazone (**3a-i**), reaction conditions, yields and physical constants are shown in Table-1. The structures of the products were supported by the by IR, ^{1}H NMR, ^{13}C NMR and the previously reported melting points.



Scheme-I: Preparation of thiosemicarbazone

TABLE-1
PHYSICAL DATA OF THIOSEMICARBAZONE DERIVATIVE[a]

Entry	R-CHO	Yield[b] (%)	Time (min)	m.p. (°C)	Product[c]
1	C_6H_5	92	24	168-171	**3a**
2	3-$NO_2C_6H_4$	94	20	218-220	**3b**[c]
3	4-HO C_6H_4	93	25	190-193	**3c**[c]
4	4-Cl C_6H_4	96	21	195-198	**3d**
5	2-Cl C_6H_4	91	23	210-212	**3e**
6	4-OCH_3 C_6H_4	94	26	170-173	**3f**
7	4-NO_2 C_6H_4	92	27	200-204	**3g**
8	4-Fluoro C_6H_4	91	25	195-199	**3h**
9	2-furyl	92	28	150-152	**3i**

[a]Reaction condition: Aromatic benzaldehyde (1 mmol), thiosemicarbazide (1 mmol), catalyst NaCl (10 mol %) were stirred in 10 mL of solvent at 50-60 °C; [b]isolated yield, [c]Synthesized compounds were characterized by spectral analysis such as FTIR, ^{1}H NMR, mass.

In order to investigate, the effect of catalyst and temperature on condensation. The reaction between benzaldehyde (1 mmol) in aqueous ethanol and sodium chloride as a catalyst at 50-60 °C as model reaction. Initially we used 2 mol % of catalyst at 60 °C less yield observed (*i.e.* 50 %) of the product. Then increase the catalyst amount from 2 to 5 mol % with same reaction condition, the yield of product slightly higher about (70 %), the again increase the concentration of catalyst to 10 mol % the yield of the product increase about 94 % (Table-2, entry 3), further again increase the concentration of catalyst to 20 mol %, 30 mol % respectively quantity wise screening of sodium chloride by aqueous ethanol. It is observed that 10 mol % of NaCl is sufficient to give higher percentage of yield. It is essential that even though increases in concentration of NaCl did not affect the yield and time of reaction. Hence, it is concluded that the combination of 10 mol % NaCl and 10 mL of aqueous ethanol at 50-60 °C is an ideal condition for the synthesis of thiosemicarbazone (Table-2).

Antibacterial activity and antifungal activity: The compounds **3a-i** were screened for antibacterial and antifungal activity by using disc diffusion method by measuring zone of inhibition. It is found that the synthesized compounds exhibited good antibacterial activity (Table-3) but no antifungal activity.

TABLE-2
EFFECT OF AMOUNT OF CATALYST

Entry	Amount of catalyst (mol %)	Time (min)	Isolated yield (%)
1	02	45	50
2	05	35	70
3	10	24	92
4	20	24	92
5	30	24	90

TABLE-3
MEASUREMENT STUDY OF
ZONE DIAMETER (mm) IN BACTERIA

Entry	Test compounds	Gram-positive		Gram-negative	
		S. aureus	*S. pyogenes*	*E. coli*	*S. typhi*
1	**3a**	15	60	25	18
2	**3b**	–	15	–	–
3	**3c**	–	45	–	12
4	**3d**	–	25	–	–
5	**3e**	25	–	12	16
6	**3f**	–	–	15	18
7	**3g**	18	–	-	25
8	**3h**	18	–	20	24
9	**3i**	20	–	25	36
10	Ofloxacin	45	60	42	35
11	Control	–	–	–	–

Conclusion

We have developed an advance protocol for one pot synthesis of highly functionalized thiosemicarbazone derivatives using aldehydes, thiosemicarbazide in the presence of sodium chloride as an easily available reaction promoter. The use of NaCl in aqueous ethanol acts as a green reaction medium for carrying out this organic transformations. Present method is highly efficient, easy workup, environment benogn, high yield. The synthesized thiosemicarbazones is highly active against Gram-positive and Gram-negative bacteria.

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