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Research Article

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Synthesis and Antimicrobial Activity of Imidazo [2,1-b] Thiazoles

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ABSTRACT

A series of imidazo[2,1-b]thiazole were synthesized by reacting 4, 5-diphenylimidazole-2-thione with ketones in presence of iodine or bromine in a single step. The products were generated in good yields and characterized by standard analytical techniques such as IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry. The synthesized products were also screened for their antimicrobial activities.

Keywords: Imidazo[2,1-b] thiazoles; IR; 1H-NMR; Biological activity

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INTRODUCTION

Thiazole is a heterocyclic compound with the empirical formula C_3H_3NS. It has a 5-membered ring structure. Thiazole rings are planar and aromatic. It is a clear to pale yellow flammable liquid with pyridine like odor [1]. It's boiling point is about 116 to 118°C or 241 to 244°F. Thiazole is used for manufacturing biocides, fungicides, pharmaceuticals, and dyes [2]. Several methods [3-6] are available for the synthesis of thiazole compounds. The only method which directly yields 2-unsubstituted thiazole derivatives is the condensation of α-haloketone or aldehyde with thioformamide. This method has been employed for the synthesis of a number of thiazole derivatives. Although this appears to be the best method but there are many drawbacks such that the yield in the preparation of thioformamide on a large scale is unsatisfactory also it is not very stable particularly under acidic conditions and the yields are not uniformly good. The other method that is used for the synthesis of thiazole compounds is the condensation of thiourea with α-haloketone or aldehyde. The method has many advantages viz., thiourea is very cheap, condensation could be carried out in distinctly acidic condition and also the yield is very good. But many researchers recorded their inability to repeat many of the previous findings and also after many trials these authors not get more than 20% yield [7]. In light of following demerits we have tried to synthesis thiazole derivatives by a new rout. The observation that ketones and halogens can replace ∝-haloketones in the synthesis of 2-aminothiazoles [8], 5,6-dihydroimidazo [2,1-b] thiazoles [9] and 4,5,6,7-tetrahydrothiazolo [3,2-a] pyrimidines [10] has been utilized in the present investigations for the synthesis of imidazo[2,1-b]thiazole (II). The iodine and bromine methods adopted here have distinct advantage in dispensing with the difficulty available ∝-heloketones by using ketones and halogens.

EXPERIMENTAL SECTION

Chemicals and Equipments

All the chemicals used for synthesis were of analytical reagent grade. Melting points (m.p.) were taken in open capillaries in paraffin-oil-bath or an electronic apparatus are corrected. The Infrared (IR) spectra were scanned on KBr pellets or nujol mulls on perkin-Elmer 842 IR spectrophotometer and Perkin Elmer 1430 grating spectrophotometer. The proton Magnetic resonance ('H-NMR) spectra were recorded on Solution in $CDCl_3$ and

$CDCl_3$-DMSO.d6 on a Multinuclear Brucker 300 AC. FT-NMR. Purity of the compounds was checked by TLC. TLC plates were coated with silica gel suspended in Chloroform-methanol mixture (1:1) and iodine vapours were used as the visualizing agent.

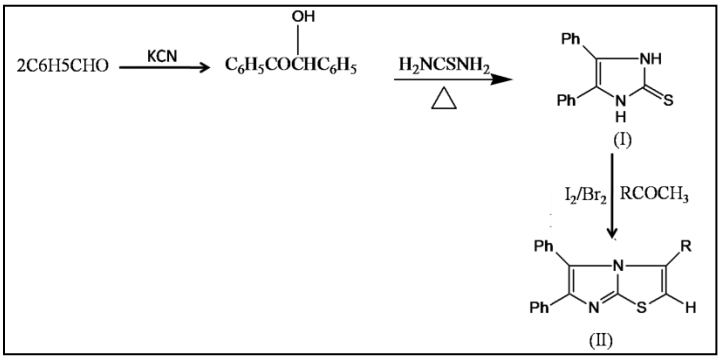
Synthesis of 4, 5-Dipheylimidezole –2-thione (I)

4, 5-Diphenylimidezole-2-thione (I) was prepared by following the method reported by Bhatt et al. [11] According to the method, benzoin is heated with thiourea in oil bath at 180-200 °C for half an hour which give compound I with 65% yield. The compound was crystallized from N-N-Di-methyl-formamide giving colourless crystals having m.p. above 300°C.

Synthesis of Imidazo[2,1-*b*]thiazole (II a-e)

The compound can be synthesized by two different methods a mixture containing 4,5-diphenylimidazole-2-thione(I; 2.52 g, 0.01 mol), p- substituted acetophenone { *p*-MeC_6H_4 (for compound IIa), *p*-$O_2NC_6H_4$ (for compound IIb), *p*-BrC_6H_4 (for IIc), *p*-ClC_6H_4 (for IId) or *p*-$COCH_3$ (for IIe)} (1.2 g, 0.01 mol), iodine (2.55 g, 0.01 mol) and anhydrous benzene (30 ml) was heated under reflux for 20 hours on a water bath and again for 10 hours without condenser. The reaction mixture was kept in contact with ether for 48 hours with occasional shaking to remove uncharged ketone. The residual iodine was removed by treating the reaction mixture with sodium thiosulphate solution. The resulting solid was dissolved in boiling water and purified by charcoal treatment. The filtrate was cooled to give hydroiodide salt which on dissolving in aqueous ethanol and basification with potassium carbonate solution yielded free base imidazo[2,1-b]thiazoles (II a-e).

A mixture of 4, 5-diphenylimidazole-2-thione (I) (2.52 g, 0.01 mol) and p- substituted acetophenone {*p*-MeC_6H_4 (for compound IIa), *p*-$O_2NC_6H_4$ (for compound IIb), *p*-BrC_6H_4 (for IIc), *p*-ClC_6H_4 (for IId) or *p*-$COCH_3$ (for IIe)} (1.2 g, 0.01 mol) in anhydrous ethanol (30 ml) was taken in a round bottom flask. After that bromine (1.6 g, 0.01 mol) was added drop wise with constant shaking and cooling under running water. The reaction mixture was then heated slowly on a water bath for 20 hours under reflux and for another 10 hours after removing the condenser. The crude product thus obtained was kept in contact with ether for 24 hours with occasional shaking. The resulting reaction mixture was than treated with very dilute thio-sulphate solution to remove traces of bromine. The solid thus obtained was dissolved in aqueous ethanol on boiling and purified by charcoal treatment. The filtrate on cooling gave hydro bromide salt which on treatment with potassium carbonate solution yielded free base imidazo[2,1-b]thiazoles (II a-e). Scheme 1 represents process for the synthesis of compound.



Scheme 1: Synthesis of imidazo[2,1-b]thiazoles (II a-e)

Where "R" = *p*-MeC_6H_4 (for compound IIa), *p*-$O_2NC_6H_4$ (for compound IIb), *p*-BrC_6H_4 (for IIc), *p*-ClC_6H_4 (for IId) or *p*-$COCH_3$ (for IIe).

Biological Activity

The synthesized products i.e., imidazo[2,1-b]thiazole (II a-e) have been tested for their antibacterial and antifungal activities *in vitro*. *Salmonella typhi* was used for testing antibacterial activities and *Candida albicans* was used for anti-fungal activities. For this dehydrated media were used [12]. Nutrient broth was used for *Salmonella typhi* and Potato dextrose broth was used for *Candida albicans* [13,14]. The inactive culture were revived by adding in their growth favourable media [15] and incubated. Serial dilutions were made to bring the organism count in countable range. 'Pour Plate Method' was used [16] for growing organism. Positive control (for checking suitability of media) and Negative control (for checking sterility of media) and two plates/solution were prepared [16] using different w/v

percentages of synthesized products (II a-e). After incubation data was collected for *Salmonella typhi* and *Candida albicans*.

Preparation of Inoculums

Inactive strains of organism were revived by transferring, mixing and keeping for 3 to 4 hrs in autoclave. The column was finalized by further shaking and incubating [14,17] it as per Table 1.

Table 1: Conditions for preparing inoculums

Sr.No.	Organism	Media	Total Volume	Incubating Temp.	Incubation Period
				(°C)	(hrs.)
1	*Salmonella typhi*	Bismuth Sulphite Agar	100 ml	35°C	24 hrs.
2	*Candida albicans*	Sabouraud Dextrose Agar	100 ml	25°C	24 hrs.

After incubation period, each suspension of organism was diluted serially to reduce the number of organism to 50 cfu/0.1 ml with sterile saline solution. The inoculums size was achieved at 10^{-6} dilution for *Salmonella typhi*; 10^{-5} dilution for *Candida albicans*. For antimicrobial study of the synthesized products (II a-e), the compound was dissolved in methanol and water (50:50) to prepare 2% and 5% w/v solutions. Two plates/ standard solution were prepared using each organism along with positive and negative control as per Table 2.

Table 2: Preparation of plates/ standard solution

Plate No.	Ingredient
1	Sterile Media negative control of experiment
2	Sterile Media + 0.1 ml of culture for positive control of experiment.
3a,b	Sterile Media + 0.1 ml of culture + 1 ml of 2% solution of compound
4a,b	Sterile Media + 0.1 ml of culture + 1 ml of 5% solution of compound

Colonies were counted on all plate at successive interval of 24 hrs to see biological activities of the synthesized compound II (a-e).

RESULTS AND DISSCUSION

The structure of products (II a-e) was confirmed by melting point (m.p.) and IR spectroscopy. The absence of a band around 1660-1700 cm^{-1} in the IR spectrum of the product indicates the absence of a carbonyl group that proves that cyclization had indeed taken place. The structure of the cyclized product was proved by mixed melting point, showing no depression with the authentic sample obtained by usual ∝-haloketonemethod (Tables 3 and 4).

Table 3: Physical data of imidazo [2, 1-b] thiazoles (II a-e) synthesized by iodine method

Comp.	R	Yield	m.p.	IR data due to	
		(%)	(°C)	(N-H) Stretch	(C=N) Stretch
a	p-MeC_6H_4	51	158	2840 cm^{-1}	1630 cm^{-1}
b	p-$O_2NC_6H_4$	49	220	2850 cm^{-1}	1620 cm^{-1}
c	p-BrC_6H_4	45	168	2880 cm^{-1}	1660 cm^{-1}
d	p-ClC_6H_4	46	156	2870 cm^{-1}	1650 cm^{-1}
e	*p*-$COCH_3$	51	158	3226 cm^{-1}	1690 cm^{-1}

Table 4: Physical data of imidazo [2,1-b] thiazoles (IIa-e) synthesized by Bromine method

Comp.	R	Yield	m.p.	IR data due to	
		(%)	(°C)	(N-H) Stretch	(C=N) Stretch
a	p-MeC_6H_4	68	158	3420 cm^{-1}	1680 cm^{-1}
b	p-$O_2NC_6H_4$	65	220	3410 cm^{-1}	1720 cm^{-1}
c	p-BrC_6H_4	68	168	3460 cm^{-1}	1710 cm^{-1}
d	p-ClC_6H_4	66	156	3440 cm^{-1}	1690 cm^{-1}
e	*p*-$COCH_3$	56	158	3420 cm^{-1}	1690 cm^{-1}

Biological Activities

It was observed that the growth of all pathogens was affected by higher concentration of synthesized compounds. The standard solution containing 2% w/v of any of the synthesized 2-substituted thiazole slightly reduced the growth while solution with 5% w/v of compound brought the count of micro-organism to all most nil. The solution with 6% w/v of 2-substituted thiazole (II a-e) showed almost same antimicrobial effects as of 5% w/v solution. So, the compound imidazo [2,1-b] thiazoles (IIa, IIb, IIc, IId and IIe) were biologically active.

Colonies were counted on all plate at successive interval of 24 hrs and results obtained were as per Tables 5 and 6.

Table 5: Colonies count for *Salmonella typhi*

(Black Colonies)				
(Cfu)				
Plate No.	24 hrs.	48 hrs.	72 hrs.	96 hrs.
1	-	-	-	-
2	20	35	42	42
3a	22	40	41	39
3b	20	38	40	40
4a	2	4	3	4
4b	1	2	2	1

Table 6: Colonies count for *Candida albicans*

(Creamy – White Colonies)				
(Cfu)				
Plate No.	24 hrs.	48 hrs.	72 hrs.	96 hrs.
1	-	-	-	-
2	20	35	36	34
3a	20	30	33	32
3b	19	31	32	34
4a	2	3	2	2
4b	1	2	1	1

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