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Antifungal potential and synthesis of C-(2-hydroxyphenyl)-N-phenyl nitrone and its N-phenyl derivatives

Neelesh Kumar Pandey[1], Ravi Prakash[1], R B Singh[2]
[1] Department of Chemistry, B.S.A. College, Mathura, Uattar Pardesh, India
[2] Scienctist, Department of Zoology, School of Life Sciences, Dr. Bhimrao Ambedkar University, Khandari Campus, Agra, Uattar Pardesh, India

Abstract

C-(2-Hydroxyphenyl)-N-phenylnitrone and its N-phenyl derivatives (la-Va) were synthesized by condensing salicylaldehyde with phenylhydroxylamines (la-Va). Sodium borohydride reduction of nitrones (la-Va) yielded Schiff bases (lb-Vb). The products were characterized on the basis of elemental analysis and spectral studies and screened *in vitro* for the antifungal potential against *Alternaria alternata*, *Fusarium oxysporum*, *Myrothecium roridum* and *Ustilago tritici* by spore germination inhibition method. The test nitrones showed better antifungal potential against *M. roridum* and *A. alternata* whereas Schiff bases were found to possess better fungitoxicity against *A. tritici*

Keywords: Salicylaldehyde, phenylhydroxylamines, nitrones, schiff bases, antifungal potential

Introduction

Both Schiff bases and nitrones possess chemical and biological activity [1, 2] due to presence of carbon and nitrogen double bond in their molecules. In addition to carbon-nitrogen double bond, the nitrones contain an oxygen atom attached to nitrogen by co-ordinate bond. The Schiff bases have been extensively studied for their biological activity [3, 6], whereas very little work has been reported regarding the biological activity of nitrones [7, 8]. In continuation of our work on nitrones [9], this manuscript describes the synthesis of nitrones from salicylaldehyde, their characterization, reduction and antifungal potential.

Meterials and Methods

Synthesis of Nitrones: Salicylaldehyde (0.1 mol) was dissolved in chloroform (150 ml) in a conical flask (500 ml). Phenylhydroxylamine (0.1 mol), prepared by the reduction of nitrobenzene with zinc dust and ammonium chloride was added to the above solution with stirring. The reaction mixture was allowed to stand overnight at room temperature. Excess of the solvent was then removed and the contents were cooled. The solid which separated out was filtered and recrystallized from methanol to get C-(2-hydroxyphenyl)-N-phenyl nitrone (la).

Condensation of salicylaldehyde with substituted phenylhydroxylamines (II-V) by following the above procedure resulted in the formation of nitrones (IIa-Va), respectively.

Reduction of Nitrones: Sodium borohydride (2g) was added in small installments to a solution of C-(2-hydroxyphenyl)-N-phenylnitrone (0.01 mol) in methanol (50 ml) with stirring. The reaction mixture was allowed to stand at room temperature for 6 hours. It was then diluted with water and extracted with chloroform. Removal of the solvent gave the crude Schiff base, which was recrystallized from ethanol to get pure 2-hydroxybenzalaniline (lb). The nitrones (IIa-Va) were reduced by following the above procedure.

***In vitro* Screening for Antifungal Potential:** The stock solutions of compounds (Ia-Va) and (Ib-Vb) were prepared by dissolving each chemical (20 mg) in absolute alcohol (0.5 ml) and the volume was made to 10 ml with sterilized distilled water. The stock solutions (2000 ppm) thus prepared on active engrediant and the basis were kept in refrigerator till further use and subsequently diluted to obtain the requisite concentrations by adding sterilized distilled water as and when required.

Actively growing 10-day old cultures of the test fungi were taken from PDA slants and sterilized distilled water was added to form a suspension of the spores. After soaking the tube thoroughly, the suspension was filtered through three layers of sterilized cheese cloth under aseptic condition to remove mycelial and agar bits. Standardized spore suspension (1×10^6 spore/ml) was made with the help of haemocytometer.

Small droplets (0.02 ml) of the spore suspension in equal quantity with the solution of the test compound were mixed in the cavities of cavity slides. These slides were kept in petriplates lined with moist filter paper and incubated for 20 hours at 25±1°C. The germination of the spores was recorded and percent spore germination inhibition was determined from which ED_{50} values were calculated.

Results and Discussion

The crude solids compound was obtained by the condensation of salicylaldehyde with phenylhydroxylamine and substituted phenylhydroxylamines (I-V) were recrystallized from methanol and characterized as: C-(2-hydroxyphenyl)-N-phenylnitrone (la),

C-(2-hydroxyphenyl)-N-(2-chlorophenyl) nitrone (Ila), C-(2-hydroxyphenyl)- N-(4-chlorophenyl) nitrone (Illa), C-(2-hydroxyphenyl)- N-(2-tolyl) nitrone (IVa) and C-(2-hydroxyphenyl)-N-(4-tolyl) nitrone (Va) respectively on the basis of elemental analysis and spectral studies.as shown in Figure-1

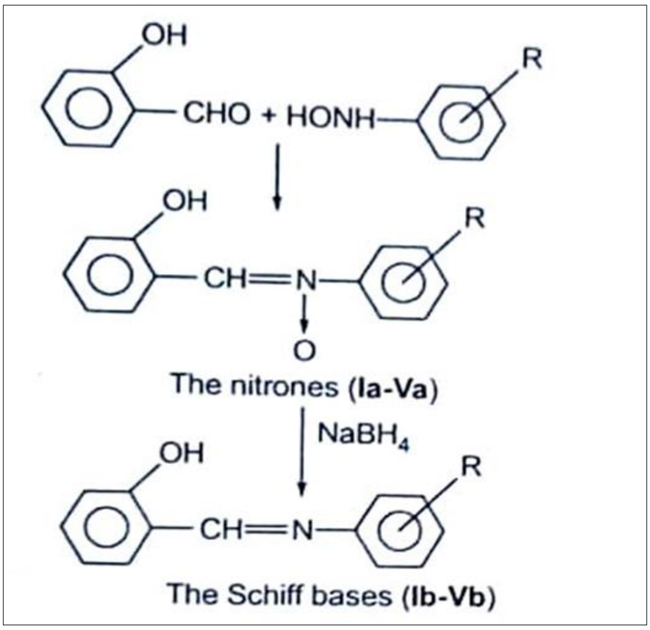

Fig 1: Structures of nitrones and their reduced products

The infra red spectra of the compounds contained bands at-1600, 1260 and 3400 cm^{-1} indicating the presence of carbon-nitrogen double bond, (N→O) linkage and hydroxyl group respectively. In PMR spectra of the nitronies in $CDCl_3$. all the protons resonated at the expected field. Multiplet signals of integration corresponding to nine protons in compound (la) and eight protons in other compounds (Ila-Va) observed between 7.2-8.1 δ accounted for aromatic protons [7]. A one proton singlet at about 8.5 8 exhibited to presence of azomethenic proton.

A one proton singlet at 9.4 δ was due to phenolic proton. A three-proton singlet observed at 2.4 δ in the PMR spectra of IVa and Va indicated the protons of methyl group in these products.

Sodiurn borohydride reduction of nitrones (la-Va) at room temperature yielded the corresponding Schiff bases (Ib-Vb). The Schiff bases were characterized on the basis of m.p., mixed melting point, elemental analysis and comparing IR and PMR spectra (Ib-Vb) with those of authentic samples [10]. The nitrones and their reduced products alongwith their characteristics are recorded in Table-1 and Table-2 respectively.

Table 1: Characteristics of nitrones of 2- Hydroxybenzaldehyde

Compound	R	M.p.*^{0}C	Yield (%)	Molecular Formula**
Ia	H	109	62	$C_{13}H_{11}NO_2$
IIa	2-CI	84	82	$C_{13}H_{10}NO_2CI$
IIIa	4-CI	78	46	$C_{13}H_{10}NO_2CI$
IVa	2-CH_3	120	81	$C_{14}H_{13}NO_2$
Va	4-CH_3	99	52	$C_{14}H_{13}NO_2$

* The melting points are uncorrected

* The compounds gave satisfactory elemental analysis

Table 2: Characteristics of reduced products (Schiff bases)

Compound	R	M.p.*^{0}C	Yield (%)	Molecular Formula**
Ib	H	77	88	$C_{13}H_{11}NO$
IIb	2-CI	59	85	$C_{13}H_{10}NOCI$
IIIb	4-CI	129	82	$C_{13}H_{10}NOCI$
IVb	2-CH_3	95	81	$C_{14}H_{13}NO$
Vb	4-CH_3	97	77	$C_{14}H_{13}NO$

* The melting points are uncorrected

* The compounds gave satisfactory elemental analysis

Antifungal Potential: The nitrones (la-Va) and their reduced products *viz* (lb-Vb) were screened *in vitro* for their antifungal potential against *Alternaria alternata*, *Fusarium oxysporum*, *Myrothecium roridum* and *Ustilago tritici* by spore germination inhibition method [11]. The antifungal potential has been expressed in terms of ED_{50} values are given in Table-3

Table-3: Antifungal activity of nitrones and their reduced products (Schiff bases)

T	**ED_{50} values (ppm) against**							
	Alternaria alternata		***Fusarium oxysporum***		***Myrothecium roridum***		***Ustilago tritici***	
	a	**b**	**a**	**b**	**a**	**b**	**a**	**b**
I	*	*	*	*	635	*	625	*
II	690	*	*	*	200	*	*	654
III	780	*	*	*	400	*	656	382
IV	*	*	*	*	700	*	220	200
V	720	*	*	*	625	*	792	320

*more than 1000 ppm

a = nitrones

b = Schiff bases

None of the Schiff bases possessed ED_{50} value less than 1000 ppm against *A. alternata* and *M. roridum*. Three of test nitrones showed moderate activity against A. alternata. All test nitrones had ED_{50} value less than 1000 ppm against *M. roridum* and the best among them was C-(2-hydroxypheny1)-N-(2-chlorophenyl) nitrone (Ila) with ED_{50} value of 200 ppm. All the test compounds except Ila and Ib possessed ED_{50} value of less than 1000 ppm against *U. tritici*, among these C-(2-hydroxyphenyl)-N-(2-tolyl) nitrone (IVa) and Schiff base derived from it (IVb) were found to possess promising activity against the test fungus with ED_{50} value of 220 and 200 ppm respectively. Moreover N-substituted Schiff bases (IIb-Vb) were found to be more potent than respective nitrone (Ila-Va) against *U. tritici*. All the test compounds, showed ED_{50} values more than 1000 against *F. oxysporum* species.

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