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Synthesis and Computational studies of synthesized 3-(4'-Bromophenyl)-5-(aryl substituted) Isoxazole derivatives

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Abstract:

The reaction of p-Bromo acetophenone with aromatic aldehydes in the presence of NaOH at low temperature gave 1-(aryl substituted)-3-(4'-Bromo phenyl) Prop-1-ene-3-ones, which was then converted into 3-(4'-Bromo phenyl)-5-(aryl substituted) isoxazoles by the action of anhydrous sodium acetate in hot glacial acetic acid and hydroxylamine hydrochloride.

Key words: Heterocyclic compounds, Isoxazole, Aromatic aldehydes.

1. Introduction:

Isoxazoles are an important series of compounds which possess interesting pharmacological properties[1]. Isoxazoles are unique in their chemical behavior not only among heterocyclic compounds in general but also among related azoles. This is because isoxazole possesses the typical properties of the aromatic system, which are in fact rather pronounced in these derivatives, together with high liability of the ring under certain conditions, particularly at the Nitrogen-Oxygen bond. Substituted Isoxazoles shows a broad spectrum of biological activity and therefore widely used in medicines and chemical means for the protection of plants[2]. Isoxazoles have been reported to be active fungicides[3] and insecticides [4-7.] A number of methods have been described previously for the halogenation of Isoxazoles[8-10]. Brominated Isoxazole are useful synthetic intermediates capable of undergoing transition metal catalyzed cross coupling reactions [11].

In the present work 3-(4'-Bromophenyl)-5-(aryl substituted) isoxazoles containing various substituents at position 5 of the Isoxazole ring were synthesized and it was also proposed to undertake a systematic investigation on synthesis of substituted isoxazoles their characterization i.e. IR, ^{1}HNMR, and the computational analysis of these derivatives with respect to their physico chemical properties. Their dependence on the structure features associated with the substituents and their probable effect in the biological activities have also been attempted.

2. Experimental:

Melting points was determined in open capillaries on a Campbell apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 297 spectrophoto meter and ^{1}H NMR spectra on Bruker 80 MHz instrument.

2.1 Method of preparation:

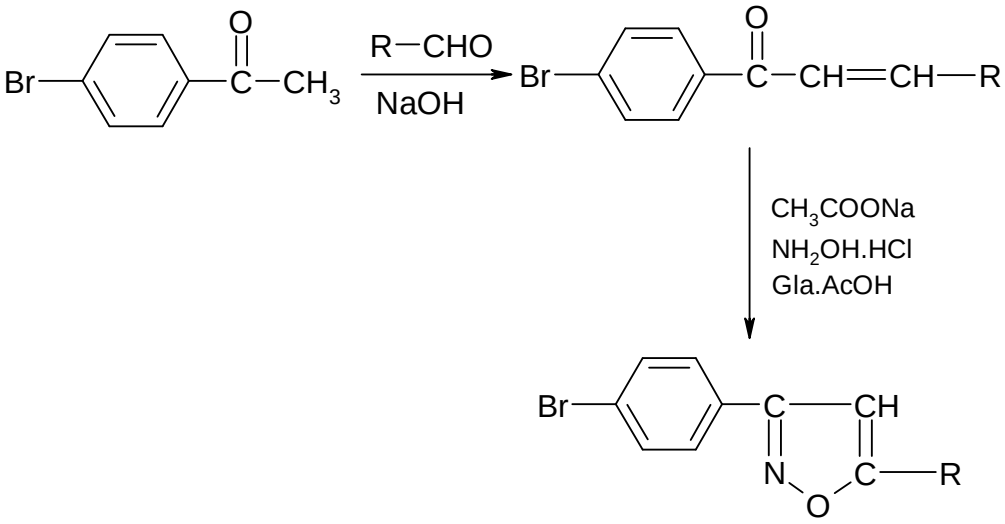
Step-I- Preparation of 1-(aryl substituted)-3-(4' –Bromophenyl) prop-1-one-3-ones.

To a solution of p–Bromo acetophenone (1 mol.) in ethanol (25 ml), aromatic aldehyde (1 mol.) was added and stirred well. Later NaOH (30%, 20 ml) was added keeping the temperature below 10^{o}C. The mixture was stirred well and kept at room temperature for 12 hours. Then it was rendered acidic with dil. HCl and poured over crushed ice. The solid thus obtained was washed with water and recrystallized from absolute alcohol.

Step-II- Preparation of 3-(4′- Bromophenyl)-5-(aryl substituted) Isoxazoles

Anhydrous sodium acetate (0.01 mol.) dissolved in a minimum amount of hot glacial acetic acid was added to a solution of $NH_2OH.HCl$ (0.01 mol) in ethanol (10 ml). This solution was added to a solution of 1-(aryl substituted) -3-(4'-Bromophenyl) prop-1-ene–3–one (0.01 mol) in ethanol (15 ml). The mixture was refluxed on sand bath for three hours, concentrated and poured over crushed ice and neutralized with NaOH. The precipitate formed was washed with water and recrystallized from absolute alcohol. The yields, melting points, elemental analysis and spectral data are given in tables. The purity of the compounds was checked by TLC.

2.2 Reaction sequence:



R=Phenyl;

4-Cl phenyl;

4-OH Phenyl; 4-OH, 3-OCH_3 Phenyl; 4-OCH_3 Phenyl.

The formation of Isoxazoles involves the 1, 2 addition of $NH_2OH.HCl$ to carbonyl group giving an adduct. The adduct then looses a water molecule to give monoxide which on cyclization and rearrangement give Isoxazol.

The Computational Studies of the synthesized compounds for evaluating physico-chemical properties have been done on PC model software.

Filter paper disc diffusion plate method was used for the determination of antibacterial and antifungal activity.

3. Results and Discussion:

The observed melting point values (Table 1) are in agreement with the theoretically expected values for the derivatives. The increased melting point states the increased stability of the synthesized compounds. The –OCH_3 substituted compounds are the compounds with –I effect i.e. their substitution to Isoxazole moiety lead to release in electron repulsion leading to greater stability as compared to the corresponding –OH and –Cl derivatives where the associated phenyl ring is expected to increase electron density around C-C bond in Isoxazole and 5- substituted phenyl moiety.

The IR frequencies obtained (Table 2) for the synthesized compounds show key IR bands at 1416-1487 cm^{-1} (C=N S/F), 1570-1590 cm^{-1} (C=C str.), 1250-1282 cm^{-1} (N-O str), 512-553 cm^{-1} (Ar-Br), in Isoxazole ring and 662 -694 cm^{-1} (C=C bend) in aromatic ring. The IR spectral frequencies obtained for different types of stretching and bending frequencies exhibits almost similar

sequence with respect to the phenyl substitution at fifth position in Isoxazole ring. Further verification of this may be obtained from the NMR shift values (Table 3) for the substituted ring, disubstituted benzene ring and H of C-H in Isoxazole ring. The obtained values vary almost regularly following the sequence of electron release and strain estimated due to phenyl substitution at fifth position. The computer simulated data obtained from PC model (Table 4) also justify the steric/ spatial arrangements extended by the substituents. The reliability of the values obtained from PC model have been examined by correlating there values with the theoretical values quoted by Hansch (Table 5) for various substituents at various positions for the present set of synthesized compounds. An almost linear dependence in the theoretical sum of electrical polarizability values to that of the dipole moment values obtained from the PC simulation supports the said correlation in the present study.

Tables 6a & 6b show the results obtained for the biological activity. The antibacterial and antifungal activity studies made on four bacteria and four fungi indicates a significant biological activity for the synthesized compounds with respect to a common fungal (Griseofulvin) and bacterial (Streptomycin) control taken for the present study. This indicates that the synthesized sample possess good bactericidal and fungicidal activity.

Table 1: Melting point values of Isoxazole derivatives:

Compound Code	Substituent	Melting Point (^oC)
Isox-01	H	145 ^oC
Isox-02	4-Cl	150 ^oC
Isox-03	4-OH	148 ^oC
Isox-04	4-OH, 3-OCH_3	165 ^oC
Isox-05	4- OCH_3	168 ^oC

Table 2: Key IR bands of Isoxazole derivatives:

Compound code	Substituent	C=N	C=C (str) In isoxazole ring	N-O str	Ar-Br	C=C (bend) in aromatic ring
Isox-01	4-H	1448.0	1589.9	1273.8	534.9	693.7
Isox-02	4-Cl	1487.8	1588.6	1282.1	531.3	682.1
Isox-03	4-OH	1483.4	1585.9	1270.5	553.2	684.5
Isox-04	4-OH, 3-OCH_3	1416.5	1578.7	1273.7	512.5	662.9
Isox-05	4-OCH_3	1459.8	1591.4	1253.8	534.7	663.5

Table 3: ^{1}H NMR data of Isoxazole derivatives (Chemical shift values in δ ppm)

Compound Code	Substituent	Br-Subs ring	Benzene Subs ring	C-H of Isoxazole ring		
Isox-01	4-H	6.384	6.512	4.426		
Isox-02	4-Cl	6.425	6.661	4.396		
Isox-03	4-OH	6.253	6.658	4.316	O-H 9.218	
Isox-04	4-OH,3-OCH_3	6.168	5.681	4.166	O-H 9.007	OCH3 2.561
Isox-05	4-OCH_3	6.237	6.65	4.253	OCH3 2.985	

Table 4: Computer simulated PC Model values for the synthesized Isoxazole derivatives

Compound code	Substituent	B.L C=C	B.L C-C	B.A (455a)	Dihed. Ang
Isox-01	4-H	1.327	1.483	105.63	3.04
Isox-02	4-Cl	1.327	1.483	105.64	3.04
Isox-03	4-OH	1.329	1.484	101.63	-1.838
Isox-04	4-OH,3-OCH_3	1.33	1.486	99.14	-22.105
Isox-05	4-OCH_3	1.329	1.484	101.61	-1.831
Compound code	Substituents	Mol. Vol.	VDW	Dip. Mom	MMX Energy
Isox-01	4-H	300.15	15.32	3.79	188.9
Isox-02	4-Cl	334.59	14.42	2.908	179.4
Isox-03	4-OH	316.14	14.24	2.414	186.5
Isox-04	4-OH,3-OCH_3	346.17	16.11	4.53	196.8
Isox-05	4-OCH_3	330.17	16.62	2.66	193.2

Table 5: Electrical polarizability as obtained by Hansch table for various Isoxazole derivatives and their dipole moment values

Compound No.	Isox-01	Isox-02	Isox-03	Isox-04	Isox-05
Electrical polarizability	4.15	4.38	3.78	3.90	3.88
Dipole Moment	3.79	2.90	2.41	4.53	2.66

Table 6(a): Antibacterial activity of Isoxazole derivatives

Compound code	*E. coli*		*Klebsiella pneumoniae*		*Pseudomonas alcaligens*		*Salmonella* sp.	
	2%	4%	2%	4%	2%	4%	2%	4%
Isox-01	+	++	+	+	++	++	+	++
Isox-02	++	++	+	++	+	++	++	++
Isox-03	++	+++	++	++	++	+++	++	++
Isox-04	++	++	+	+	+	++	+	++
Isox-05	+++	+++	++	+++	+++	+++	++	++
Standard drug	+++	++++	+++	++++	++++	++++	++	++

5-10 mm: +, 11-15 mm: ++, 16-20 mm +++, 21-25 mm: ++++
Standard drug for bacteria- Streptomycin

Table 6(b): Antifungal activity of Isoxazole derivatives

Compound code	*Penicillium citrinum*		*Aspergillus flavus*		*Chrysosporium* sp.		*Candida albicans*	
	2%	4%	2%	4%	2%	4%	2%	4%
Isox-01	+++	+++	++	+++	+++	+++	+++	+++
Isox-02	+	++	+	++	++	++	++	+++
Isox-03	++	+++	++	+++	+++	+++	+++	+++
Isox-04	+	++	+	++	++	++	++	+++
Isox-05	+++	+++	+++	+++	+++	++++	+++	++++
Standard drug	+++	+++	++	+++	+++	+++	+++	++++

5-10 mm: +, 11-15 mm: ++, 16-20 mm +++, 21-25 mm: ++++
Standard drug for fungi: Griseofulvin

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