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Synthesis and Characterization of 2H-3(o-nitrophenyl)-3,4-dihydro-Chloro-1,3-benzoxazine studies of Antimicrobial and Antifungal activity

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Abstract

4H-3,1-Benzoxazinone derivatives bear saturated aliphatic substituent's at key position e.g. CH_3, CH_2COCH_3, CH_2CN, $C_3H_7(n)$ and CH_2CH_2COOH, have electronically unsaturated character which make their synthesis difficult because their are not satisfactorily stable rings (so called dynamic benzoxazinones) New organic substituent's with special properties in steric and electronic manner helped to solve this problem. Synthesis and behavior of 2-carboxyvinyl-4H-3,1-Benzoxazinone towards nucleophiles have been reported with the aim of studying the effect of conjugated double bond and the stability of oxazinone ring via the interaction of 3,5-dibromoanthanilic acid viz. maleic anhydride in boiling n-butanol. One of the most important features in 4H-3, 1-Benzoxazinone chemistry is their use as key starting materials for synthesizing new heterocyclic systems with potential biological activity. The present work is in conjugation with our ongoing programe on the utilizing of readily obtainable starting materials for the synthesis of heterocyclic systems.

Keywords: Azoles, Oxazoles, Isoxazolines, Isothiazolines, Heterocyclic.

Introduction

Literature survey of 1, 3-oxazines There are many stable benzoxazine ring containing polystyrene macro monomers[1], that have been synthesized and characterized by Baris Kishan and other co-workers. The chemistry of benzoxazine synthesis[2], offers a wide range of molecular design flexibility by using appropriate starting materials[3].

The 1, 3-oxazines ring containing heterocyclic compounds play major contribution to the medicinal chemistry. 1, 3-oxazines ring is present in various drugs, dyes, anaesthetics, antioxidants and agrochemicals. The two tautomeric forms are in equilibrium with each other. It therefore follows that in 1, 3-oxazines there can be only two carbon alkyl derivative 3-(or-5) and 4, if, however, the amino hydrogen is replaced by an alkyl (or) aryl group, the position for various substituents can be well defined. Diversely substituted 1, 3-oxazines and their derivatives embedded with variety of functional groups are important biological agents and a significant amount of research activity has been directed towards this class. In particular, they are used as antitumor, antibacterial, antifungal antiviral, antiparasitic, anti-tubercular and insecticidal agents. Some of these compounds have also anti-inflammatory, anti-diabetic, anaesthetic, analgesic, and potent selective activity such as Nitric oxide synthase (NOS) inhibitor and cannobinoid CB1 receptor antagonists activity. A classical synthesis of these compounds involves the base catalyzed aldol condensation reaction of aromatic ketones and aldehydes to give α, β unsaturated ketones (chalcones), which undergo a subsequent cyclization reaction with hydrazines affording 2-pyrazolines in this method, hydrazones are formed as intermediates, which can be subsequently cyclizing to 2-pyrazolines in the presence of a suitable cyclizing reagent like acetic acid. In recent years, a significant portion of research in heterocyclic chemistry has been devoted to 2-pyrazolines containing different aryl group as substituents, as evident from the literature[4-7]. The preceding section of the review is focusing on the recent development on 1, 3-oxazines along with their biological properties[8]. Synthesis and characterization of 1, 3-oxazines derivatives has been a developing field within the realm of heterocyclic chemistry for the past several year because of their ready accessibility and broad spectrum of biological activity[9]. 1, 3-oxazines derivative have been found to be antitumor[10] and immunosuppressive[11] agents. Survey of literature in recent past reveals that some 1, 3-oxazines derivatives possess cerebro-protective[12] effect and CNS-depressent[13] activity.

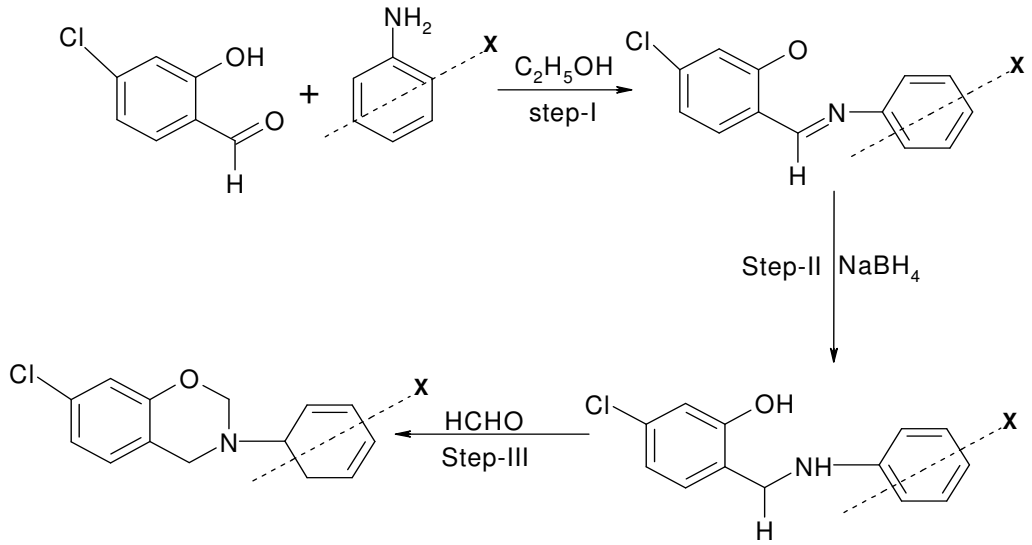
Methodology

Preparation of 2-(arylimino)-5—Chloromethyl phenols: 5-chlorosalicylaldehyde(I) 2 gm and appropriate aromatic amine 2 gm were refluxed in ethanol (20 ml) for 30 min crystalline residue deposited on cooling was further purified by crystallization from chloroform-petroleum ether (2:8 v/v) to furnish (II) the amines taken were aniline (Clbenz.17), p-chloro-aniline, (Clbenz.18), o-nitroaniline, (Clbenz.19), m-nitro aniline (Clbenz. 20), p-nitro aniline and (Clbenz.21), p-bromo-aniline.

Preparation of 2-(Arylamino-5-Chloromethyl phenols: Sodium borohydride (0.5 gm) was added to solution of 2-(arylimino)-5-Chloromethyl phenol (2 gm) in methanol (10 ml)

and the mixture stirred for 30 min at room temperature.The residue obtained on pouring the solution in to cold water was further crystallized from ethanol to afford (III).

Preparation of 2H-3-Aryl-3, 4-Dihydro-1,3-Chlorobenzoxazine: 2-(aryl amino)-5-Chloromethyl phenol 2 gm and formalin (35% 10 ml) were refluxed in ethanol (10 ml) for 6 h. The residue obtained after pouring the reaction mixture into cold water was crystallized from ethanol to give the yields and melting points of the 1, 3-oxazines are given in Table-1.The molecular formulae of these compounds were calculated from their elemental analysis given the table. The structure of 1,3-oxazines were confirmed by their IR spectra. NMR spectra of compounds have been scanned with Perkin-Elmer spectrophotometer using KBr pellets.



Scheme-1
Preparation of comp-3Sub-o, m, p, Cl derivatives of Chloro benzoxazine

Result and Discussion

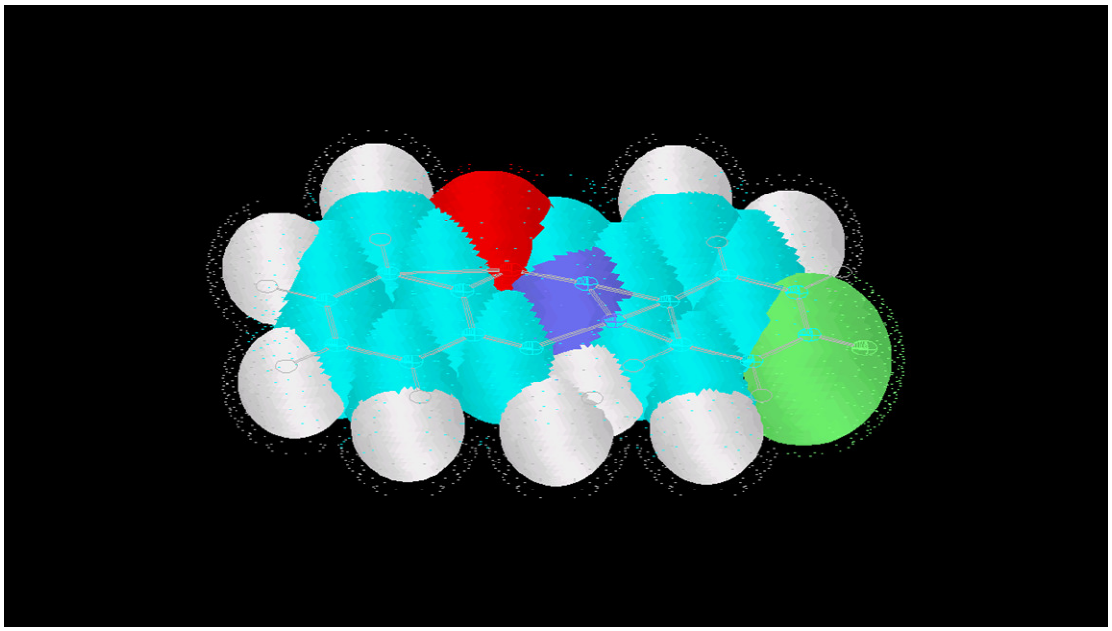


Figure-1
Experimental figure

Table-1
Physical data of compound Clbenzx

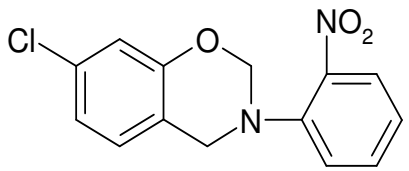
Name	**2H-3(o-nitrophenyl)-3,4-dihydro-Chloro-1,3-benzoxazine**					
Mol. Wt.	276.5					
M.P.°C	129					
Yield (%)	85					
Mol.For.	$C_{14}H_{11}NO_3Cl$					
Elemental Analysis	C %		H %		N %	
	Found	Calcu.	Found	Calcu.	Found	Calcu.
	60.72	60.75	3.95	3.97	5.05	5.06

Table-2
Characterization of compound Clbenzx. IR data

Group type	**Vibration mode**	**Frequency (cm^{-1})**
Oxazine ring	-CH (str.) in–OCH_2	2916.53
	-CH (str.) in –NCH_2	2843.15
	-C-N (str.) in –NCH_2	1269.50
	C-O(str.) in –OCH_2	0062.80
	-CH (bend.) in–OCH_2	1510.20
	-CH (bend.) in –NCH_2	1441.47
Aromatic ring	-CH (str.)	3042.57,3014.19
	C=C (str.)	1605.77
	-CH (bend.)	1021.47
Ar-NO_2	C-N(str.) in Ar-NO_2	1531.49
	N-O (str.) in-NO_2	1352.48
Ar-Cl	C-Cl(str.) in Ar-Cl	769.12

Table-3
Characterization of compound Clbenzx. ^{1}HNMR data

Signal No.	Chemical shift (in δ ppm)	Multiplicity	Relative no. of protons	Inference
1.	7.00-7.73	Multiplet	7	Ar-H
2.	4.66	Singlet	2	-OCH_2 of Benzoxazine ring
3.	3.56	Singlet	2	-NCH_2 of Benzoxazine ring

Table-4
Characterization and Chemical Shift of ^{13}C NMR data

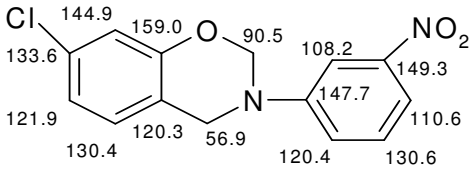
Compound code Clbenzx.19, NO_2 –ph	Inference	Relative no. of carbon (δ ppm)
Stru. 	(O-C-N)	(C),90.5,
	(C-NO_2)	(C), 149.3
	(N-C)	(C), 56.9
	((C-Cl-Benzene ring)	(C),133.6
	Ar-NO_2	(C) 110.8, 130.6, 120.4, 150.0, 108.2
	Benzene Ring	(C), 159.6, 114.9, 133.6,121.0,130.4, 120.3

Table-5
IR Characterization data for compatible substituent derivative

1.3-Benzoxazine				Methoxy benzoxazine			Chloro- benzoxazine		
Comp. Code	**Subs.**	C=C (str.)	N-C (str.)	**Comp. Code**	C =C (str.)	N-C (str.)	**Comp. Code**	C=C (str.)	N-C (str.)
Benzx.3	4-Cl	1607.7	1274.5	Mebenzx.11	1612.6	1268.5	Clbenzx.17	1610.6	1279.5
Benzx.4	2-NO_2	1606.5	1280.6	Mebenzx.12	1599.7	1256.7	Clbenzx.18	1605.6	1269.6
Benzx.5	3-NO_2	1602.7	1286.5	Mebenzx.13	1601.6	1262.6	Clbenzx.19	1608.7	1271.5
Benzx.6	4-NO_2	1599.7	1283.5	Mebenzx.14	1610.7	1248.5	Clbenzx.20	1604.7	1277.5
Benzx.8	4-Br	1598.7	1277.6	Mebenzx.16	1610.7	1261.6	Clbenzx.21	1597.5	1278.6

Table-6
IR characterization data for specific bonds in substituted chlorobenzoxazine derivatives

Compound Code	Substi-tuent	Benzoxazine ring				Disubstituted Ring	
		C=N	C-O	C-H(str) inNCH_2	C-H(bend) in$N\text{-}CH_2$	C=C	Ar-Cl
benzx.-1	4-Cl	1279.5	1056.8	2846.1	1472.4	1610.7	767.4
benzx.-2	2-NO_2	1269.6	1062.8	2843.1	1441.4	1605.6	769.9
benzx.-3	3-NO_2	1271.5	1056.7	2840.2	1452.4	1608.7	770.9
benzx-.4	4 –NO_2	1277.5	1058.6	2838.12	1456.4	1604.7	774.8
benzx.-5	4 - Br	1278.6	1062.8	2842.2	1473.5	1597.7	621.4

Table-7
Variation in the ^{1}H-NMR spectra for substituted Chlorobenzoxazine derivatives

Compound code	Substituent	Cl-Subs ring	-OCH_2 of benzoxazine ring	-NCH_2 of benzoxazine ring
Clbenzx.-1	4 -Cl	7.19-7.77	4.60	3.59
Clbenzx.-2	2-NO_2	7.00-7.73	4.66	3.56
Clbenzx.-3	3-NO_2	7.02-7.72	4.62	3.52
Clbenzx-.4	4-NO_2	7.39-7.64	4.63	3.67
Clbenzx.-5	4 – Br	7.16-7.71	4.68	3.63

This may be the expected trend on account of the PC Model data obtained for these compounds.

Table-8
Computer simulated PC Model data for marked bonds and their subsequent angles

Compound code	Substi-tuent	B.L.C-N	B.A. N-C	Dihed. Ang	Mol. Volu	VDW	Dip. Mom	MMX Energy
Clbenzx.-	4 -Cl	1.463	120.82	165.82	280	9.245	1.899	27.338
Clbenzx.-1	2-NO_2	1.459	112.26	156.94	276.5	11.76	5.033	44.908
Clbenzx.-2	3-NO_2	1.457	111.60	160.96	276.5	11.74	3.938	29.41
Clbenzx-.3	4-NO_2	1.464	120.81	166.19	275	10.13	2.516	22.208
Clbenzx.-4	4 – Br	1.463	120.82	165.82	356.7	9.363	1.954	27.582

B.L.–Bond Length, B.A.- Bond angle, D.A.-Dihedral angle.

The deviations may be due to the steric hindrance in these cases. On similar lines, the NMR shift values showed the following trend. 4-Br, 2-NO_2 ,3-NO ,4-NO_2 ,4-Cl

The overall, correlation between the experimental characterization and PC model data justify the results obtained in spectral characterization and also certify the potential of the PC model simulation. The reliability of the PC model simulated data was further justified by correlating PC model values with the electrical polarizability values as described by Hansch for different substituents at different positions (ortho, Meta, para) for the present series of synthesized compounds. Table-9 records the electrical polarizability for the set substituents of along with their dipole moment values.

Table-9
Records the electrical polarizability for the set substituents of along with their dipole moment values

Z-Matrix Parameters for Compounds of as obtained from PC Model Precisegnorm=0.01								
Clbenzx								
1	C	0	0	0	0	0	0	0 0 0
2	C	1.400826	1	0	0	0	0	1 0 0
3	C	1.399225	1	120.00864	1	0	0	2 1 0
4	C	1.400656	1	119.98795	1	0	1	3 2 1
5	C	1.39919	1	120.02103	1	0	1	4 3 2
6	C	1.400849	1	119.98498	1	0	1	5 4 3
7	C	1.103121	1	120.01207	1	-180	1	5 4 3
8	O	1.103109	1	119.99246	1	-180	1	6 5 4
9	N	1.256618	1	117.43067	1	-180	1	7 5 4
10	C	1.31541	1	123.1931	1	0	1	8 6 5
11	C	2.958653	1	178.23785	1	180	1	9 7 5
12	C	1.400829	1	179.19814	1	0	1	11 9 7
13	C	1.399224	1	59.189938	1	0	1	11 9 7
14	C	1.40065	1	119.98841	1	180	1	13 11 9
15	C	1.399194	1	120.02096	1	0	1	14 13 11
16	C	1.400848	1	119.98478	1	0	1	15 14 13
17	N	1.1	1	120.05267	1	-180	1	16 15 14
18	H	1.100001	1	120.05957	1	-180	1	1 2 3
19	CL	1.100002	1	119.93871	1	180	1	2 3 1
20	H	1.1	1	119.95538	1	-180	1	3 2 1
21	H	1.1	1	120.04145	1	180	1	4 3 2
22	H	1.110107	1	105.00813	1	-55.221523	1	7 5 4
23	H	1.110108	1	105.00808	1	55.221699	1	7 5 4
24	H	1.110107	1	111.36369	1	121.58316	1	10 8 6
25	H	1.110107	1	111.36356	1	-121.58288	1	10 8 6
26	H	2.238753	1	127.83814	1	-154.47368	1	12 11 9
27	H	1.1	1	119.95526	1	0	1	13 11 9
28	H	1.1	1	120.0411	1	-180	1	14 13 11
29	H	1.1	1	119.94897	1	180	1	15 14 13
30	O	2.168798	1	154.86253	1	-173.2612	1	17 16 15
31	O	3.298058	1	133.82022	1	19.70731	1	17 16 15

Conclusion

One of the most important features in 4H-3, 1-Benzoxazinone chemistry is their use as key starting materials for synthesizing new heterocyclic systems with potential biological activity. The present work is in conjugation with our ongoing programe on the utilizing of readily obtainable starting materials for the synthesis of heterocyclic systems.

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