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Der Chemica Sinica, 2013, 4(4):12-16

Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

Novel one-pot synthesis and antimicrobial activity of 7-chloro-4-phenyl-3,4-dihydro-2*H*-1,3-benzoxazin-2-one derivatives

Sayaji S. Didwagh and Pravina B. Piste*

P. G. Department of Chemistry, Yashavantrao Chavan Institute of Science, Satara, Maharastra, India

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ABSTRACT

A novel one-pot synthesis of 7- chloro – 4 - phenyl - 3,4 - dihydro-2H- 1,3 - benzoxazin- 2- one derivatives ***[1a-1i]*** *by condensation of a variety of aromatic aldehydes with p-chlorophenol and urea in the presence of wet cyanuric chloride under solvent free condition. All synthesized compounds were characterized on the basis of IR,NMR spectroscopic data and Elemental Analysis. All the compounds have been screened for antimicrobial activity by the cup-plate method. The results reveal that some of the synthesized 1,3-benzoxazine derivatives were exhibited good to moderate antibacterial and antifungal activity.*

Keywords: Synthesis, 1,3-benzoxazin-2-one, cyanuric chloride, aldehyde, solvent free, antimicrobial activity.

INTRODUCTION

The synthesis of new analogs of bioactive heterocyclic compounds represents a major challenge in synthetic organic and medicinal chemistry [1].Due to their wide range of biological activities. Aromatic condensed oxazinone derivatives have received considerable attention due to the attractive pharmacological properties associated with their hetrocyclic scaffold [2].Nitrogen heterocycles are of special interest because they constitute an important class of natural and nonnatural products, many of which exhibit useful biological activities [3].Oxazine derivatives are an important class of heterocyclic compounds. They possess varied biological activites such as antimicrobial [4-9] and anticoagulant activites [10-11], anticancer [12],] and analgesic, anti-inflammatory [13] antimycobacterial [14], anti-tubercular [15-18], ant malarial [19], anti-HIV [20]. fungicidal [21], antibacterial [22-23],antidiabetic and hypolipidaemic [24], antiproliferative [25], Antiplatelet aggregation [26-27], Enzyme inhibitory [28-30] activites. The 1,3-oxazine nucleus features prominently in many biologically important natural products and other bioactive molecules [31]. Owing to the above facts and in continuation of our research work on novel biologically active hetrocycles and their increasing importance in pharamaceuatical and biological field. Therefore ,we synthesized new 7- chloro – 4 - phenyl - 3,4 - dihydro-2*H*- 1,3 - benzoxazin- 2- one derivatives using parachlorophenol with various aromatic aldehydes and urea in the presence of wet cyanuric chloride under solvent free condition and screened their antimicrobial activities.

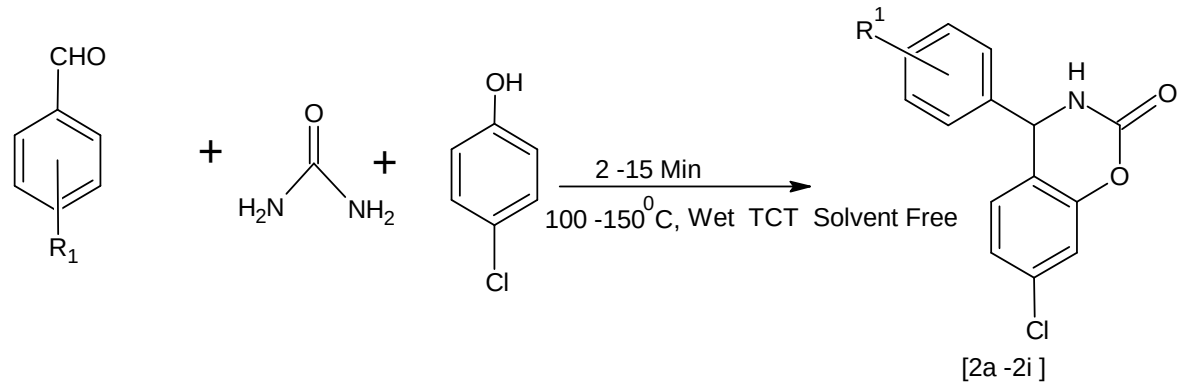
MATERIALS AND METHODS

The melting points were recorded on electro-thermal apparatus and are uncorrected. The purity of the compounds was checked by TLC on pre-coated SiO_2 gel (HF254, 200 mesh) aluminium plates (E Merk) using hexane and ethyl acatate visualized in iodine chamber. IR spectra were recorded in KBr on a perkin-Elmer model-983. 1HNMR

spectrum recorded on Varian Mercury 300MHz instrument using $CDCl_3$, DMSO-d_6 as solvent (chemical shift in δ ppm),using TMS as internal standard. Elemental analysis was performed on a Heracus CHN analyzer and was within the ±0.5% of the theoretical values.

General procedure for the preparation of 7-chloro-4-phenyl-3,4-dihydro-2*H*-1,3-benzoxazin-2-one derivatives [1a-1i]

A mixture of P-Chlorophenol (1 mmol),aromatic aldehyde (1 mmol), urea (1mmol), TCT (0.1 mmol, 0.0184 g) and water (1-2 drops) mixed well and was heated at 100 - 150°C for an appropriate time (Table 1).. After the completion of the reaction monitored by TLC, the reaction mixture diluted with water (4-5 mL) and stirred for 5-10 minutes. The solid product was filtered and the crude product was crystallized with ethanol to afford the pure product.



[2a -2i]

Spectroscopic data of synthesized compounds [1a-1i] :

7-chloro-4-phenyl-3,4-dihydro-2*H*-1,3-benzoxazin-2-one [1a]

M.F=$C_{14}H_{10}ClNO_2$; M.W=257.6; IR. (KBr, cm-1): 3345(N-H), 2930(C-H), 1695 (C=O), 1633, 1456((C=C), 1171(C-O), 775(C-Cl); ^{1}HNMR(300MHz, $CDCl_3$, DMSO-d_6, ppm) 8.65(1H, s, NH), 6.15(1H, s, CH), 7.09-7.67 (7H, m, Ar-H).

7-chloro-4-(4-methoxyphenyl)-3,4-dihydro-2*H*-1,3-benzoxazin-2-one[1b]

M.F=$C_{15}H_{12}ClNO_3$; M.W= 289.6; IR(KBr, cm-1): 3351 (N-H), 2927(C-H), 1692(C=O), 1635, 1451 (C=C), 1173(C-O), 775(C-Cl); ^{1}HNMR(300MHz, $CDCl_3$, DMSO-d_6, ppm: 8.73(1H, s, NH), 6.21(1H, s, CH, 7.12-7.79 (6H, m, Ar-H).

7-chloro-4-(4-chlorophenyl)-3,4-dihydro-2*H*-1,3-benzoxazin-2-one [1c]

M.F=$C_{14}H_9Cl_2NO_2$; M.W=294.1; IR(KBr, cm-1): 3353 (N-H), 2931(C-H), 1693(C=O), 1633, 1451 (C=C), 1173(C-O), 775(C-Cl); ^{1}HNMR(300MHz, $CDCl_3$, DMSO-d_6, ppm): 8.71(1H, s, NH), 6.19(1H, s, CH), 7.15-7.78 (6H, m, Ar-H).

7-chloro-4-(2-chlorophenyl)-3,4-dihydro-2*H*-1,3-benzoxazin-2-one [1d]

M.F=$C_{14}H_9Cl_2NO_2$; M.W=294.1; IR(KBr, cm-1): 3355 (N-H), 2933(C-H), 1696(C=O), 1637, 1453 (C=C), 1175(C-O), 775(C-Cl); ^{1}HNMR(300MHz, $CDCl_3$, DMSO-d_6, ppm): 8.71(1H, s, NH), 6.27(1H, s, CH), 7.12-7.77 (6H, m, Ar-H).

7-chloro-4-(4-hydroxyphenyl)-3,4-dihydro-2*H*-1,3-benzoxazin-2-one [1e]

M.F=$C_{14}H_{10}ClNO_3$; M.W=273.5; IR(KBr,cm-1): 3327 (N-H), 2930(C-H), 1695(C=O), 1633, 1457 (C=C), 1172(C-O), 775(C-Cl); ^{1}HNMR(300MHz, $CDCl_3$, DMSO-d_6, ppm): 8.69(1H, s, NH), 6.23(1H, s, CH), 7.13-7.75 (6H, m, Ar-H).

7-chloro-4-[4-(dimethylamino)phenyl]-3,4-dihydro-2*H*-1,3-benzoxazin-2-one [1f]

M.F=$C_{16}H_{15}ClN_2O_2$; M.W=302.7; IR(KBr, cm-1): 3335(N-H), 2937(C-H), 1685(C=O), 1639, 1451 (C=C), 1171(C-O), 775(C-Cl); ^{1}HNMR(300MHz, $CDCl_3$, DMSO-d_6, ppm): 8.67(1H, s, NH), 6.21(1H, s, CH), 7.11-7.73 (6H, m, Ar-H).

7-chloro-4-(4-nitrophenyl)-3,4-dihydro-2*H*-1,3-benzoxazin-2-one [1g]
M.F=$C_{14}H_9ClN_2O$; M.W=304.6; IR (KBr, cm-1): 3349 (N-H), 2934(C-H), 1689(C=O), 1635, 1449 (C=C), 1173(C-O), 775(C-Cl); ^{1}HNMR(300MHz, $CDCl_3$, DMSO-d_6, ppm): 8.69(1H, s, NH), 6.19(1H, s, CH), 7.15-7.79 (6H, m, Ar-H).

7-chloro-4-(3-nitrophenyl)-3,4-dihydro-2*H*-1,3-benzoxazin-2-one[1h]
M.F=$C_{14}H_9ClN_2O_4$; M.W=304.6; IR(KBr, cm-1): 3357 (N-H), 2937(C-H), 1698(C=O), 1635, 1459 (C=C), 1177(C-O), 776(C-Cl); ^{1}HNMR(300MHz, $CDCl_3$, DMSO-d_6, ppm): 8.71(1H, s, NH), 6.23(1H, s, CH), 7.19-7.81 (6H, m, Ar-H).

7-chloro-4-(4-methylphenyl)-3,4-dihydro-2*H*-1,3-benzoxazin-2-one[1i]
M.F=$C_{15}H_{12}ClNO_2$; M.W=271.7; IR (KBr, cm-1): 3345 (N-H), 2933 (C-H), 1687(C=O), 1633, 1451 (C=C), 1171(C-O), 775(C-Cl); ^{1}HNMR (300MHz, $CDCl_3$, DMSO-d_6, ppm): 8.67(1H, s, NH), 6.17(1H, s, CH), 7.11-7.76 (6H, m, Ar-H).

Table No. 1: Physical and Elemental analysis of Synthesized compounds(1a-1i):

Comp No	R1	Time (min)	M.P. ^{0}C	Yield %	Elemental analysis				
					%C	%H	%N	%O	%Cl
1a	C_6H_5	9	161	59	64.3	3.6	4.9	12.2	13.4
1b	4-$OCH_3C_6H_4$	2	175	71	62.1	3.9	4.3	16.3	12.1
1c	4- ClC_6H_4	8	165	67	56.9	3.0	4,7	10.3	24.1
1d	2-ClC_6H_4	11	159	69	57.1	3.0	4,6	10.5	24.1
1e	4- OHC_6H_4	3	178	75	60.6	3.4	5.0	17.1	12.8
1f	4.$N(CH_3)_2C_6H_4$	5	231	67	62.8	4.3	9.1	10.3	11.6
1g	4- $NO_2C_6H_4$	4	196	65	54.9	2.8	8.7	21.0	11.3
1h	3- $NO_2C_6H_4$	7	191	73	55.0	2.7	8.9	20.4	11.0
1i	4-$CH_3C_6H_4$	15	209	63	64.2	4.0	5.1	11.6	12.2

Antimcrobial activity:
The synthesised compounds **(1a-1i)** were screened for their in vitro antimicrobial activity by using cup plate method [32]. Antibacterial activity was screened against two gram positive bacteria *Staphylococcus aureus*, *Bacillus subtilis* and two gram negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa* by measuring the zone of inhibition on agar plates at concentrations 100 µg/mL. Antifungal activity was screened against *Candida albicans*, *Aspergillus niger* by measuring the zone of inhibition on agar plates at concentrations 100 µg/mL and reported in Table-3. Nutrient agar was employed as culture medium and DMSO was used as solvent control for antimicrobial activity. Streptomycin and griseofulvin were used as standard for antibacterial and antifungal activities respectively.

RESULTS AND DISSCUSSION

Benzoxazin-2-one derivatives were synthesised in moderate yields by reacting with p-chlorphenol with different aromatic aldehydes and urea in the presence of wet cyanuric chloride under solvent free condition. The structure of compounds are confirmed by IR, 1H NMR spectroscopy. To check the applicability of the synthesized compounds, they were screened for their antibacterial and antifungal activity by using cup-plate method. The antibacterial and antifungal activity of each compound was compared with standard drug Streptomycin and griseofulvin . Most of the compounds exhibited good to moderate antitbacterial and antifungal activity against the tested microorganisms. The antibacterial activity are shown in Table 2. The Compound bearing **1a** (R1 = H), **1b** (4-OCH_3), **1c** (4-Cl), **1d** (2-Cl),**1g**(4-NO_2) substitutents showed good activity against gram-positive *Staphylococcus aureus*, *Bacillus subtilis* and gram-negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa*. While other compounds **1e** (4-OH), **1f** (4-$N(CH_3)_2$, **1h** (2-NO_2) **1i** (4-CH_3) exhibited moderate to poor activity as compared to standard drug. The antifungal activity are shown in Table 2. The Compounds bearing **1a** (R1 = H), **1b** (R =4-OCH_3), **1c** (4-Cl), **1d** (2-Cl), **1e** (4 – OH), **1g** (4-NO_2), **1h**(2-NO_2) substitutents showed good activity against *Candida albican* , *Aspergillus niger*. while The remaining compounds **1f** (4-$N(CH_3)_2$, **1i** (4-CH_3) exhibited moderate to poor activity as compared to standard drug Streptomycin and griseofulvin. As we consider all results obtained from antibacterial and antifungal tests together we can say that entire compounds tested are active towards bacteria and fungi.

Table No. 2 : Antimicrobial activity of Synthesized Compounds

Comp. (100µg/ml)	Antibacterial				Antifungal	
	S. Aureus	*B. Subtilis*	*E. Coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
1a	13	15	17	12	15	12
1b	12	17	15	18	19	14
1c	17	19	20	15	20	17
1d	16	17	19	17	19	13
1e	04	09	06	03	14	15
1f	05	03	10	09	07	09
1g	13	20	17	15	17	17
1h	06	05	03	10	16	12
1i	04	09	06	07	08	05
Streptomycin	17	20	22	19	-	-
Griesofulvin	-	-	-	-	21	17

CONCLUSION

The synthetic procedure to get series of 7- chloro – 4 - phenyl - 3,4 - dihydro-2*H*- 1,3 - benzoxazin- 2- one derivatives **[1a -1i]** from P-Chlorophenol and substituted aromatic aldehyde and urea in the presence of wet cyanuric chloride under solvent free condition. Moderate yields, easy work up, short reaction times and avoiding the use of organic solvent. The newly synthesized compounds were confirmed by the spectral analysis and further evaluated for their antimicrobial activities against various types of bacteria and fungi. Some of the compounds of the series exhibited promising antibacterial and antifungal activity compared to standard drugs.

Acknowledgement
We are very thankful to the Head Department of Chemistry, Principal Y.C.I.S. Satara for providing laboratory Facilities and Shivaji University Kolhapur, National Chemical Laboratory Pune, for providing necessary instrumental facilities

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