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CHLORAMINE-T MEDIATED SYNTHESIS OF NOVEL 1,3,4-OXADIAZOLE DERIVATIVES

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ABSTRACT
A novel series of Schiff bases**(S1-9)** were prepared by reacting 4-nitrobenzhydrazide and substituted aromatic aldehydes in alcohol medium. The Schiff Bases undergoes selective cyclization with Chloramine-T to yield the title compounds 1,3,4-oxadiazole derivatives **(OX1-9).** The new compounds were characterized on the basis of IR, ^{1}H-NMR, Mass spectral data.

KEYWORDS: Schiff base, 1,3,4-oxadiazoles, Chloramine-T, anti-inflammatory activity

INTRODUCTION
Heterocyclic compounds are those cyclic compounds that contain at least one hetero atom. Nitrogen, oxygen, sulfur are the commonly seen hetero atoms. Since carbon atom is replaced by non-carbon atoms they are called hetero atoms. Many natural products like vitamins, hormones, antibiotics etc have heterocyclic subunit which increases their significance in life. Thus heterocyclic chemistry became an ever expanding field where discovery of new compounds and its innovative applications occurs.
Heterocyclic compounds gained considerable importance in the field of medicinal chemistry because of its varied activities it posses and its wide distribution. The heterocyclic nucleus, 1,3,4-oxadiazole has got wide attention in search of new therapeutic molecule. A five membered ring with one oxygen and two nitrogen is the 1,3,4-oxadiazoles.
Nowadays the study of heterocyclic compounds is of great importance due to its wide distribution. They gained considerable importance in the field of medicinal chemistry because of its varied activities it posses. Literature surveys suggested 1,3,4-oxadiazoles as a lead molecule for the development of bioactive molecules with different pharmacological activities. The various derivatives of oxadiazoles possess properties like anti-tumour[I], anti-oxidant[II], STAT3 inhibitor[III], anti-tubercular[IV], anti-bacterial[V], antifungal[VI], anti-inflammatory[VII], ulcerogenic[VIII], anti-convulsant[IX], glycogen-phosphorylase inhibitor[X], anti-malarial[XI] etc. These include the drug synthesis, preparation of dyes, synthesis of polymers, use in photography as tone improvers[XII].
Many derivatives of 1,3,4-oxadiazole have significant role in the medicinal chemistry. There are several examples for compounds containing 1,3,4-oxadiazole units currently in clinical

medicine such as Raltegravir (HIV-integrase inhibitor drug) used to treat HIV infection. Furamizole is a nitrofuran derivative with strong antibacterial activity. Nesapidil is class IV antiarrythmic drug. Zibotentan is an anticancer agent. Tiodazosin is an anti-hypertensive drug and Fenadiazole is a hypnotic drug.

In continuation of earlier work on synthesis of 1,3,4-oxadiazoles[XIII-XV] and based on the above observations, it was thought of worthwhile, to synthesize a novel series of 1,3,4-oxadiazoles by using Chloramine-T as an oxidative agent.

MATERIALS AND METHODS

Melting points were determined by Equiptronics digital melting point apparatus (Model EQ-730, India). FT-IR spectra were recorded with the help of KBr discs on Alpha bruker FT-IR Infrared Spectrophotometer (Germany) (cm^{-1}). Bruker Avance-II NMR spectrometer (USA) was employed to record ^{1}H-NMR spectra operating at 400 MHz with DMSO/$CDCl_3$ as a solvent. TMS was served as an internal standard. The recording of the mass spectra was carried out by Perkin -Elmer GC-MS**.**

Synthesis of Schiff bases (S1-9)

In a round bottom flask, 4-nitrobenzhydrazide **(1)** (0.01M) ethanol (25ml), few drops of glacial acetic acid and further aromatic aldehydes (0.01M) were added. The reaction contents were refluxed for 10-12 hrs. The reaction mixture is then cooled to room temperature and poured into crushed ice with stirring. The precipitated compound was filtered, washed, dried and recrystallized from ethanol. The physical data of the compounds **(S1-9)** is given in Tbale-1

N'-[(E)-(4-fluorophenyl)methylidene]-4-nitrobenzohydrazide: **S9: IR(KBr,cm^{-1}):** 3176(CONH), 3005(CH), 1646(C=O), 1597(C=N), 1559(C=C), 715(C-F); **^{1}H-NMR($CDCl_3$):** δ 12.16(CONH), δ 8.47-7.22(m, Ar-H+=CH); MASS: 287.24(M+2).

Table-1 : Physical data of Schiff bases (S1-9)

Comp	Ar-CHO	Molecular Formula	Molecular Weight	Melting Point (^{O}C)	Yield (%)
S1	4-OH	$C_{14}H_{11}N_3O_4$	285.25	188-90	81.45
S2	4-OCH_3	$C_{15}H_{13}N_3O_4$	299.28	176-78	84.3
S3	3,4-$(OCH_3)_2$	$C_{16}H_{15}N_3O_5$	329.30	145-47	77.42
S4	4-Cl	$C_{14}H_{10}ClN_3O_3$	303.70	136-38	79.71
S5	4-Br	$C_{14}H_{10}BrN_3O_3$	348.15	100-02	87.02
S6	H	$C_{14}H_{11}N_3O_3$	269.25	121-23	91.33
S7	3-OCH_3- 4-OH	$C_{15}H_{13}N_3O_5$	315.28	169-71	85.19
S8	2-Cl	$C_{14}H_9Cl_2N_3O_3$	338.14	115-17	78.44
S9	2-F	$C_{14}H_{10}FN_3O_3$	287.24	129-31	82.12

Synthesis of 1,3,4-oxadiazole derivatives (OX1-9)

In a round bottom flask ethanol (25ml), Schiff bases **(S1-9)** (0.01M) and Chloramine-T (0.01M) was added and kept for refluxing for 8-10 hrs. The solid sodium chloride which is separated is filtered and the tick solution obtained is then added to crushed ice after removing excess of solvent by evaporation. The precipitated product is filtered, washed, dried and recrystallized from ethanol[XIV]. The physical data of the title compounds **(OX1-9)** is given in Tbale-2.

Table-2: Physical data of 1,3,4-oxadiazole derivatives (OX1-9)

Comp	Ar-CHO	Molecular Formula	Molecular Weight	Melting Point (^{O}C)	Yield (%)
OX-1	4-OH	$C_{14}H_9N_3O_4$	283.23	119-21	62.46
OX-2	4-OCH_3	$C_{15}H_{11}N_3O_4$	297.26	106-08	63.11
OX-3	3,4-$(OCH_3)_2$	$C_{16}H_{13}N_3O_5$	327.29	96-98	65.73
OX-4	4-Cl	$C_{14}H_8ClN_3O_3$	301.68	136-38	72.41
OX-5	4-Br	$C_{14}H_8BrN_3O_3$	346.13	188-90	69.24
OX-6	H	$C_{14}H_9N_3O_3$	267.23	175-77	63.04
OX-7	3-OCH_3 -4-OH	$C_{15}H_{11}N_3O_5$	313.26	164-66	70.77
OX-8	2-Cl	$C_{14}H_7Cl_2N_3O_3$	336.12	141-43	69.18
OX-9	2-F	$C_{14}H_8FN_3O_3$	285.23	155-57	66.61

2-4-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]phenol: (OX1): IR(KBr,cm^{-1}): 3320(OH), 3028(C-H), 1595(C=N), 1545(C=C), 1074(COC) .

2-(4-methoxyphenyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole: (OX2): IR(KBr,cm^{-1}): 2984(CH), 1597(C=N), 1515(C=C), 1065(COC) ; **^{1}H-NMR($CDCl_3$):** δ 8.41-7.05(m, Ar-H, 8H), 3.82(s,OCH_3, 3H); MASS: 297.16 (M+)

2-(3,4-dimethoxyphenyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole: (OX3): IR(KBr,cm^{-1}): 2968(CH), 1600(C=N), 1515(C=C), 1018(COC) ; **^{1}H-NMR($CDCl_3$):** δ 8.20-6.80(m, Ar-H,8H), 3.40(s, 2XOCH_3,6H)

2-(4-chlorophenyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole: (OX4):IR(KBr,cm^{-1}): 2988(CH), 1597(C=N), 1520(C=C), 1011(COC), 703(C-Cl) ; **^{1}H-NMR($CDCl_3$):** δ 8.47-7.54(m, Ar-H, 8H); MASS: 301.06 (M+)

2-(4-bromophenyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole : (OX5): IR(KBr,cm^{-1}): 2946(CH), 1598(C=N), 1521(C=C), 1069(COC), 704(C-Br) ; **^{1}H-NMR($CDCl_3$):** δ 8.48-7.27(m, Ar-H, 8H). MASS: 341.11 (M+)

2-(4-nitrophenyl)-5-phenyl-1,3,4-oxadiazole: (OX6): IR(KBr,cm^{-1}): 2988(CH), 1601(C=N), 1522(C=C), 1058(COC) ; **^{1}H-NMR(CDCl$_3$):** δ 8.48-7.40(m, Ar-H, 9H). MASS: 267.13 (M+)

2-methoxy-4-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]phenol: (OX7): IR(KBr,cm^{-1}): IR(cm^{-1}) 3279(OH), 2947(CH), 1592(C=N), 1517(C=C), 1059(COC) ; **^{1}H-NMR(CDCl$_3$):** δ 11.60(s, OH, 1H), 8.41-6.40(m, Ar-H,7H), 3.60(s, OCH$_3$, 3H)

2-(2,4-dichlorophenyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole : ((OX8): : IR(KBr,cm^{-1}): 3067(CH), 1594(C=N), 1554(C=C), 1098(COC), 716(C-Cl) ; **^{1}H-NMR(CDCl$_3$):** δ 8.80-6.50(m,Ar-H,7H)

2-(4-fluorophenyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole : (OX9): IR(KBr,cm^{-1}):) 2948(CH), 1598(C=N), 1517(C=C), 1050(COC), 748(C-F) ; **^{1}H-NMR(CDCl$_3$):** δ 8.40-6.80(m, Ar-H, 8H)

RESULTS AND DISSCUSSION

The main aim of the study is to synthesis 1,3,4-oxadiazole derivatives from Schiff bases. The key intermediate Schiff bases were synthesized by reacting aromatic aldehydes and 4-nitro carbohydrazide in alcohol medium. The Schiff bases in the alcohol medium, in presence of Chloramine-T undergoes selective cyclization to yield the title compounds. The methodology was described in Scheme-1. All the synthesised compounds are obtained in good yields. The purity of the compounds was confirmed through melting points and TLC using silica gel G plates as stationary phase and Ethyl acetate: methanol (2:8) as the solvent system. They were further purified by recrystallization using appropriate solvents. The synthesised compounds were characterised by physicochemical and spectroscopic methods like IR, ^{1}H- NMR, Mass,

The IR spectra of the compound **2b** depicted the absorption bands at 2984 for aromatic (C-H), 1597 for (C=N), 1515 for (C=c) respectively. In the ^{1}H-NMR spectra of the compound, **2b** revealed the singlet signal for methoxy protons at δ 3.82 region. The aromatic protons were observed as multiplets in the region δ 7.05-8.41. The mass spectrum of compound **2b** showed a molecular ion peak at M/z = 297.16 (M+), which is in agreement with the molecular formula.

CONCLUSION

In this present work, a novel series of 1,3,4-oxadiazole derivatives and the structures of all the newly synthesised compounds were confirmed by IR, ^{1}H-NMR and Mass spectra. The method used for the synthesis resulted in products with good quality and yield. So Chloramine-T can be effectively used in the synthesis of 1,3,4-oxadizoles with good yields.

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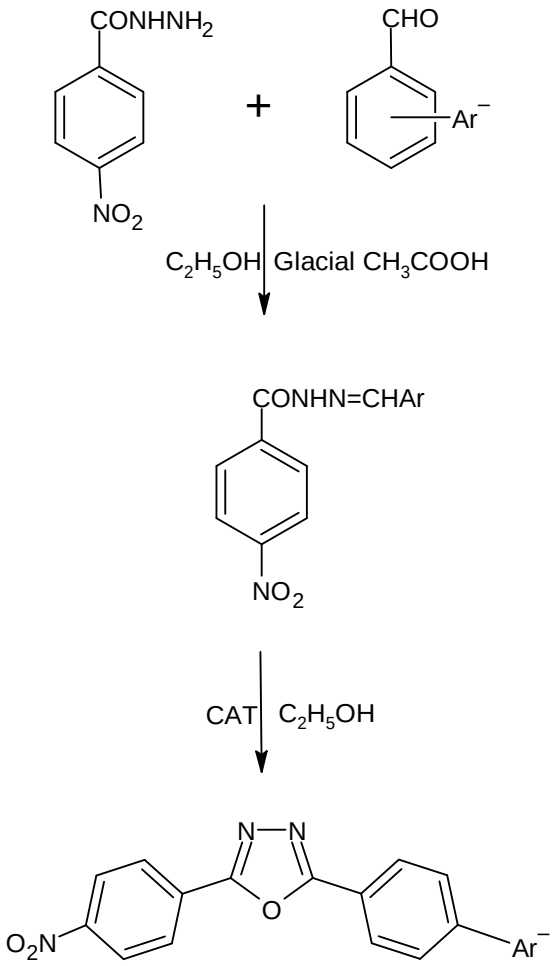
Scheme-01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CHO
Ar−
NO2
C2H5OH Glacial CH3COOH
CONHN=CHAr
NO2
CAT C2H5OH
N—N
O
O2N
Ar−