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Synthesis and Characterization of some N-(3,5 subtituted) -4n- 1,2,4 - triazole-4yl) isonicotinamide

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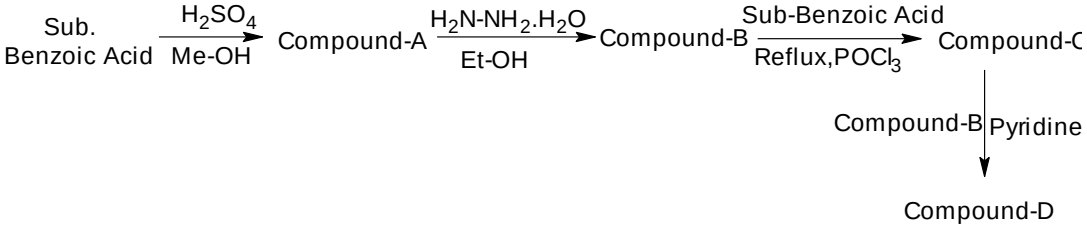
ABSTRACT

The required 1,3,4- oxadiazoles prepared by refluxing a mixture of substituted benzohydrazide and substituted benzoic acid in phosphorus oxychloride for 4-6 hours.Then these oxadiazoles were refluxed with ionized in dry pyridine. Condensation of substituted 1,3,4-oxadiazoles and isoniazide gives N-(3,5 subtituted) -4n- 1,2,4 triazole-4yl) isonicotinamide (D_{1-4}) the IR, 1H-NMR,MS and nitrogen analysis Characterized all these compounds.

GRAPHICAL ABSTRACT :-



Keywords **- Antimicrobial activity, Isonicotinamide , 1,3,4- oxadiazoles , substituted benzohydrazide ,Triazoles.**

1. INTRODUCTION

Triazoles are heterocyclic compounds featuring five member ring of two carbon atoms and three nitrogen atoms as part of the aromatic five-member ring. Triazole refers either one of a pair of isomeric chemical compounds with molecular formula C2H3N3. In recent year heterocyclic compounds analogues and derivatives have attracted strong interest due to their useful biological and pharmacological properties.

Heterocyclic compounds have acquired immerse industrial importance due to versatility in their use particularly they are widely used in pharmaceutical industries for manufacture of a large variety of common drugs such as antipyretics analysics. Antimalerials, Anti-inflammatory anaesthetics. etc due to varried applications their structure physicochemical, Physiological and related, Studies have been undertaken in recent year. Several of the important compound contain heterocyclic rings eg. Vitamin-B complex alkaloids, antibiotics, cholorophyll, morphine , heroin and cocaine. Oxadiazole and triazloes continue to attract great interest due to their wide spectrum of biological activity (**1**). A generalized and efficient method for the synthesis of 1,3,4-oxadiazoleshave been reported by (**2**). Alkyl 1,3,4-oxadiazoles was synthesized by cyclization of aryl hydrazide with aromatic or aliphatic acids in the presence of phosphorus oxychloride. Nitrogen, oxygen, sulphur containing heterocycles like 1,3, 4-oxadiazoles and 1,2,4-triazoles are a class of heterocycles they are ofsignificant interest in medicine and pesticide chemistry.A five member ring containing three nitrogen and two carbon is known as triazole such as 1.2.3 triazole or 1.2.4. triazole. 1.2.4. triazole showed mild central Neruous system and respiratory system stimulants. They also inhibited formulation of granulomata and were useful in preating rheumatoid arthritis 1.2.4.trizole derivative are found to b e associated with various biological activities such as anticonulsant(3-5) antifungle (6-9) anticancer (10). anti-inflammatory(11-13) and anti-bacterial activities(14-17). 1, 2, 3-oxadiazoles can also be used as HIV integrase inhibitors [**18**] or as prostaglandin receptor antagonists [**19**].One of the most important methods of obtaining 1,2,4-triazole system is based on recyclization reaction of 1,3,4-oxadiazoles under the action of amines and hydrazines[20,21].1,2,4-triazole displayed by far the greatest activity among all nucleofiles tested . 1,2,4-triazole anion serves as an effective acyle transfer catalyst in both aminolysis and transesterification reactions[22]. 4,5-dihydro-1H, 1,2,4-triazole-5-one derivatives synthesized by O. Gursoy Kol et al demonstrate a marked capacity for

iron binding[23].In view of the versatile importance of the triazoles and isonicotinamide considered worthwhile to prepare and study some triazolyl isonicotinamides.

2. EXPERIMENTAL

All the chemicals were of A.R. grade and used without further purification. The melting points of all synthesized compounds were recorded and purity is checked by TLC Elemental analysis (C-H-N) was carried out with a Carlo Erba 1108 analyzer in micro analytical laboratory, ,CDRI, Lucknow. IR spectra were recorded on a Perkin-Elmer-RX1 spectrophotometer using KBr pellets ^{1}H NMR Spectrum of ligand was recorded in a mixed solvent ($CDCl_3$ + DMSO) On a Bruker Ac-300 F spectrometer using TMS as an internal standard.

The following triazoyl isonicotinamide compounds has been synthesis.

1) N-{3-(4-methoxyphenyl) 5-phenyl-4H-1.2,4- triazole -4yl} isonicotinamide
2) N-{3-(3-nitrophenyl) 5-Phenyl-4H-1,2,4-triazole-4yl} isonicatinamide
3) N- { 3 (Phenyl) -5-(4-nitrophen 4H -1,2,4- triazole -4yl) } isonicotinamide.
4) N-{ 3-(2 Chlorophenyl) 5-(4-nitrophenyl)-4H-1,2,4-triazole-4yl) isonicotinamide

2.1. Synthetic Methods

2.1.1. Preparation of compound (A-1) (Methyl benzoate):-

A solution of an appropriate benzoic acid (0.01 mol) in Absolute methanol (0.1 mol) was refluxed in the presence of sulphuric acid (2-3 ml) for 3 hours. After completion of reaction. The reaction mixture was poured into ice-cold water. The oily layer that deposited was extracted with diethyl ether and on evaporation of solvent yields pure liquid mass.The sceme is as shown in fig.1. M.P. 128^0 c yield. 61%.

2.1.2. Preparation of compound (A-2) (methyl-paranitro benzoate) ;-

A solution of an appropriate p-nitro benzoic acid (0.01 mol) in Absolute methanol (0.1 mol) was refluxed in the presence of sulphuric acid reaction. The reaction mixture was poured into ice-cold water. The oily layer that deposited was extracted with diethyl ether and on evaporation of solvent yields pure liquid mass. The scheme is as shown in fig.1 M.P. 94 yeild
72 %.

2.1.3. Preparation of compound (B-1) (Benzohydrazide):-

A mixture of (A-1) and hydrazine hydrate(0.02 mol) was refluxed in ethanol (25ml) for 4-6 hours . After the completion of reaction it was cooled and poured on to crushed ice; the solid thus obtained was filtered off. Washed with water and recrystalized from ethanol (B-1) the scheme is as shown in fig2. M.p.112.5^{0}c yield 61 %.

2.1.4. Preparation of compound (B-2) (p-nitro-Benzolydrazide):-

In methanol,nitro-benzoic acid (0.01 mole) was dissolved & added 2-3 drops of concentrated sulphuric acid, refluxed for 4-5 hours to form ester (A-2). For this scheme is as shown in fig1. Then added hydrazine hydrate (0.01 mole) and refluxed for 4 hours. Removed methanol to obtain residue and recrystallized by m ixture of cold water and alcohol.the scheme is as shown in fig2. M.p. 94-98 ^{0}C yield-72%.

2.1.5. Preparation of compound (C-1) :

Preparation of 2-(4 methoxyphenyl) 5-(phenyl) 1,3,4-oxadiazole)

A mixture of benzolydrazide(B-1) (0.01 mole) and a p-methoxy benzoic acid (0.01 mole) in $POCl_3$ (5ml) was refluxed for 5-6 hours the reaction mixture was cooled to room temp. and then the contents were poured on to crushed ice and neutradised with bicarbonate solution the resulting solid was dried and crystallized from ethanol (C-1) the scheme is as shown in fig3 M.P. 162 ^{0}C yield 69%

2.1.6. Preparation of compound (C-2):

Preparation of 2-(4 nitro phenyl) 5-(phenyl) 1,3,4- oxadiazole):-

A mixture of benzohydrazide (B-1) (0.01 mole) and a p-nitro benzoic acid (0.01 mole) in $POCl_3$ (5 ml) was refluxed for 5-6 hours the reaction mixture was cooled to room temperature and and then the contents were poured on to crushed ice and neutralized with bicarbonate solution.the resulting solid was dried and crystallized from ethanol the scheme is as shown in fig3. M.p. 162 ^{0}Cyield 69 % .

2.1.7. Preparation of Compound (C-3):

Preparation of 2-(4-nitrophenyl)5-phenyl 1,3,4, Oxadiazole):-

A mixture of p-nitro benzohydrazide (B-2) (0.01 mole) and a benzoic acid (0.01 mole) in $POCl_3$ (5ml) was refluxed for 5-6 hour the reaction mixture was cooled to room temperature and then the contents were poured on to crushed ice and neutralized with bicarbonate solution . the resulting solid was dried and crystallized from ethanol (C-3) the scheme is as shown in fig.3. m.p. 189 yield 66 % .

2.1.8. Preparation of compound (C-4):

Preparation of 2-(2 Chlorophenyl) 5-(4-nitrophenyl) 1.3.4 Oxadiazole):-

A mixture of p-nitro benzohydrazide (B-2)(0.01) and a 2-chlorobenzoic acid (0.01 mole) in $POCl_3$ (5 ml) was refluxed for 5-6 hours. The reaction mixture was cooled to room temp. and then the contents were poured on to crushed ice and neutralized with bicarbonate solution . The resulting solid was dried and crystallized from ethanol (C-4) the scheme is as shown in fig3 m.p. 162 ^{0}C yield 69 % .

2.1.9. Preparation of Triazoyl Isonicotinamide (D_1 D_2 D_3 D_4)

Mixture of substituted 1.3.4 Oxadiazole (0.01 mole) and Isoniazide (0.01 mole) in dry pyridine (10 ml) was refluxed for 6-8 hours. The reaction mixture was cooled to room temperature and then the contents were poured on to crushed ice and neutralized with dilute HCl solution. The resulting solid was dried and crystallized from glacial acetic acid the scheme is as shown in fig4.

Scheme-I

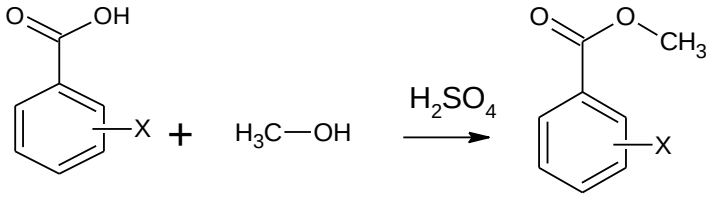


Fig.1 Preparation of compound A
Compound A-1, X = -H, Compound A-2,X = $-NO_2$

Scheme-II

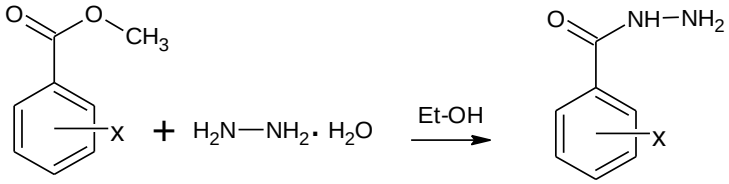


Fig.2 Preparation of compound B
Compound B-1, X = -H, Compound B-2, X = $-NO_2$

Scheme-III

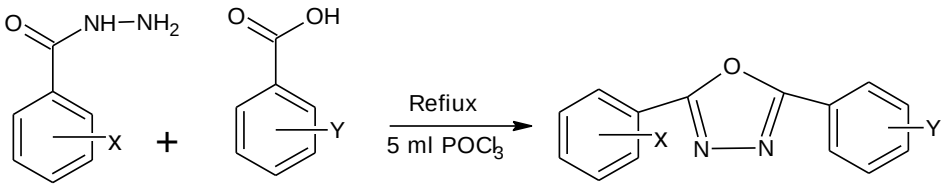


Fig.3 Preparation of compound C
Compound C-1, X = -H, Y = $-OCH_3$, Compound C-2, X = -H, Y = $-NO_2$
Compound C-3, X = $-NO_2$, Y = -H , Compound C-4, X = $-NO_2$, Y = -Cl

Scheme-IV

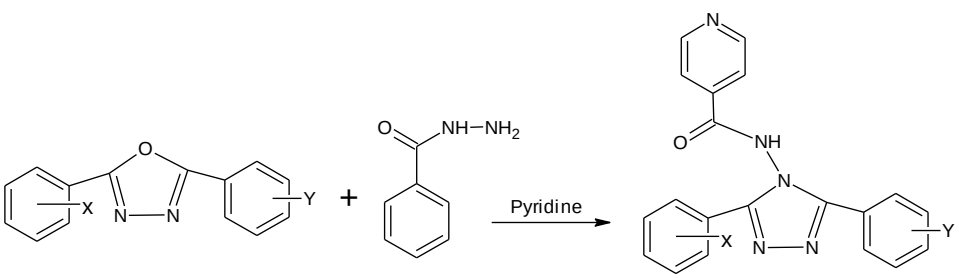


Fig.4 Preparation of compound D
Compound D-1, X = -H, Y = $-OCH_3$, Compound D-2, X = -H, Y = $-NO_2$
Compound D-3, X = $-NO_2$, Y = -H , Compound D-4, X = $-NO_2$, Y = -Cl

4. RESULT AND DISCUSSION

The required 1.3.4 oxdiazoles prepared by refluxing a mixture of substituted benzohydrazide and substituted benzoic acid in phosphorus oxychloride for 4-6 hours.Then these oxadiazoles were refluxed with ionized in dry pyridine. The compounds were confirmed on the basis of IR, NMR and nitrogen analysis. The analytical data of D_1 D_2 D_3 D_4 compounds are given below

4.1. Spectral data of synthesized compounds

4.1.1)N-{3-(4-methoxyphenyl) 5-phenyl-4H-1.2,4-triazole -4yl} isonicotinamide (D1):-
m.p. 162 ^{0}C,Yield-69% , IR (V max , cm^{-1}) = 1580(C=N), 3120(N-H), 1620(C=O), 1500(C=C)
^{1}H – NMR($CDCl_3$ + DMSO) (δ ppm) = δ 7.25 (S1H NH), δ 7.03 (m,9H, Ar), δ 8.8- 8.6 (m, 4H, pyridyl H), δ 8.9- (S 1H – OCH_3). MS *m/z* =368 (M^+).Mol.Form. $C_{21}N_5O_2$ H_{14} % Nitrogen = Cal. 19.55% Found-18.20%

4.1.2)N-{3-(3-nitrophenyl) 5-Phenyl-4H-1,2,4-triazole-4yl} isonicatinamide (D2):-
m.p. 187 ^{0}C,Yield- 56% , IR (V max , cm^{-1}) =1580(C=N), 3180 (N-H), 1640 (C=O), 1500(C=C)
^{1}H – NMR($CDCl_3$ + DMSO) (δ ppm) = ð 7.2 (S1, H, NH), ð 7.6 (m.9H, Ar), ð 8.4 -8.6 (m, 4H, pyridyl H) , MS *m/z* =372 (M^+).Mol.Form. C_{20} N_5O_3 H_{14} % Nitrogen = Cal. 21.76% Found-18.40 %

4.1.3)N- { 3 (Phenyl) -5-(4-nitrophen 4H -1,2,4-triazole -4yl) } isonicotinamide. (D3):-
m.p. 176 ^{0}C,Yield- 68% , IR (V max , cm^{-1}) =1587 (C=N), 3180 (N-H), 1608 (C=O), 1522 (C=C), ^{1}H – NMR($CDCl_3$ + DMSO) (δ ppm) = ð 7.2 (S,1H, NH), ð 8.12 (m,8H, Ar) ð 8.8 – 8.6 (m, 4H pyridyl H), MS *m/z* =385 (M^+). Mol.Form. C_{20} N_5O_3 H_{14} % Nitrogen = Cal. 21.76% Found-19.00 %
4.1.4)N-{ 3-(2 Chlorophenyl) 5-(4-nitrophenyl)-4H-1,2,4-triazole-4yl) isonicotinamide (D4):-
m.p. 187 ^{0}C,Yield- 56% , IR (V max , cm^{-1}) =1600 (C=N), 3180 (N-H), 1718 (C=O), 1522 (C=C), ^{1}H – NMR($CDCl_3$ + DMSO) (δ ppm) = ð 7.32 (S,1H,NH) ð 7.1 (m,8H,Ar), MS *m/z* =406 (M^+). Mol.Form. C_{20} N_5O_3 $H_{13}Cl$ % Nitrogen = Cal. 20.76 % Found-17.04 %

5. CONCLUSION

The prepared Trizol isonicotinamide are conformed by IR, NMR and nitrogen analysis. The all prepared Trizol isonicotinamide are Antimicrobiologically active against E. coli and S. aures.

6. ACKNOWLEDGEMENT

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