



SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL SCREENING OF SOME 3, 4, 5-SUBSTITUTED 1, 2, 4-TRIAZOLE

J. W. DHORE* and G. D. THORAT

Department of Chemistry, Sant Gadge Baba Amravati University, AMRAVATI (M.S.) INDIA

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ABSTRACT

Condensation of substituted 1,3,4-oxadiazoles and isoniazide gives N-((3,5-substituted)-4H-1,2,4-triazole-4yl)isonicotinamide(D_{1,4}). The IR, ¹H NMR, and nitrogen analysis characterized all these compounds. The newly synthesized compounds were screened for antibacterial and antifungal activity.

Key words: Triazoles, Isonicotinamide, Antimicrobial activity.

INTRODUCTION

The chemistry of heterocyclic compounds is an interesting area in medicinal chemistry as it offers challenging task in the development of novel synthetic strategies¹. Nitrogen heterocycles A five member ring containing three nitrogen is known as triazole such as 1.2.3 triazole, or 1.2.4 triazole. 1,2,4-triazoles, are among the various heterocycles that have received the most attention during the last two decades as potential antimicrobial agents². The pharmacologically important heterocycles with nitrogen bridge derived from 1,2,4-triazole played the way toward active research in triazole chemistry³. 1,2,4-triazole and their derivatives are found to be associated with various biological activities such as anticonvulsant^{4,5}, antifungal⁶⁻⁸, anticancer⁹⁻¹², antiinflammatory¹³⁻¹⁵, antibacterial properties¹⁶⁻¹⁹. Compounds including a 1,2,4 triazole nucleus & 4-N- substituted derivatives are known to possess various biological activities²⁰.

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^{21,22}.

Isoniazide also known as isonicotinoyl hydrazine (INH) is an organic compound. In 1951 it was found to be effective against tuberculosis. Isoniazide also has an antidepressant effect & it was one of the first anti-depressant discovered. Isonicotinamide derivative also exhibit excellent anticonvulsant activity & no neurotoxicity in comparison to reference drug phenytoin²³.

In view of the versatile importance of the triazoles and isonicotinamide considered worthwhile to prepare and study some 3,4,5-substituted 1,2,4-triazoles.

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. ¹H NMR spectrum of ligand was recorded in a mixed solvent (CDCl₃ + DMSO) on a Bruker AC-300 F spectrometer using TMS as an internal standard.

The following 3,4,5-substituted 1,2,4- triazole compounds has been synthesized.

1. N-(3-(phenyl)-5-(4-nitrophenyl)- 4H-1,2,4-triazole-4 yl)-isonicotinamide. (4a)
2. N- (3-(2 chlorophenyl)-5-(4-nitrophenyl)-4H-1,2,4-triazole-4-yl)-isonicotinamide.(4b)
3. N-[3-(4-methoxyphenyl) -5-phenyl- 4H- 1, 2, 4-tirazole-4yl]isonicotinamide.(4c)

Preparation of compound (1A-B)

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 scheme is as shown in Fig. 1.

A mixture of (1a/1b) and hydrazine hydrate (0.02 mol) was refluxed in ethanol (25 mL) 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 recrystallized from ethanol. The scheme is as shown in Fig. 2.

Preparation of compound (2A-B)

Preparation of compounds (3a-c) (2,5-substituted , 1,3,4-oxadiazoles)

A mixture of appropriate benzohydrazide (2a/2b) (0.01mole) and a benzoic acid (0.01mole) in POCl₃ (5 mL) was refluxed for 5-6 hr. 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. The scheme is as shown in Fig. 3.

Preparation of 3,4,5-substituted 1,2,4- triazoles (4a-c)

A mixture of substituted 1,3,4-oxadiazole (0.01 mole) and isoniazid (0.01 mole) in dry pyridine (10 mL) was refluxed for 6-8 hr. 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 Fig. 4.

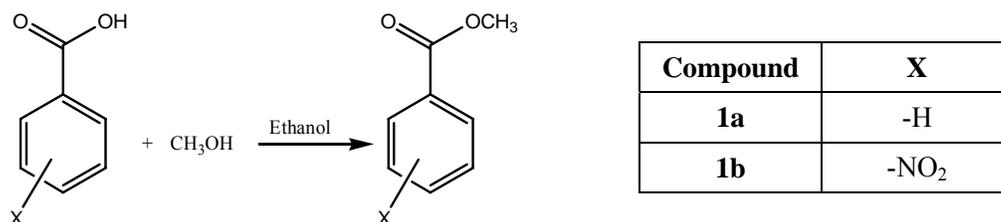


Fig. 1: Preparation of compound 1a-b

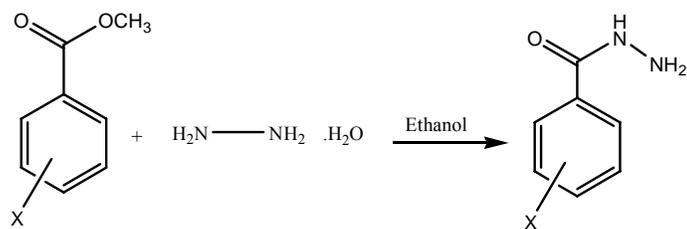


Fig. 2: Preparation of compound 2a-c

Compound	X
2a	-H
2b	-NO ₂

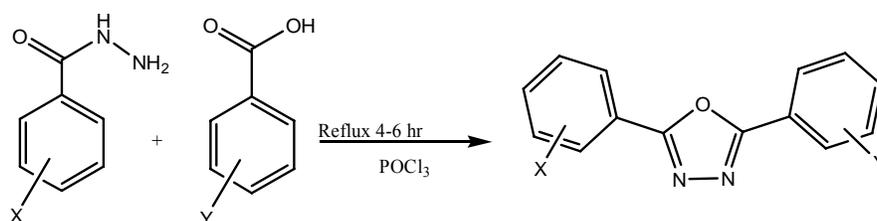


Fig. 3: Preparation of compound 3a-c

Compound	X	y
3a	4-NO ₂	H
3b	4-NO ₂	2-Cl
3c	H	4-OMe

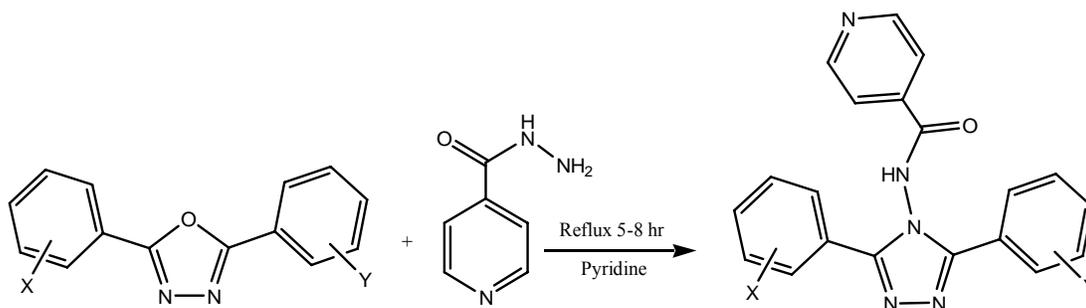


Fig. 4: Preparation of compound 4a-c

Compound	X	y
4a	4-NO ₂	H
4b	4-NO ₂	2-Cl
4c	H	4-OMe

RESULTS AND DISCUSSION

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 isoniazide in dry pyridine. The compounds were confirmed on the basis of IR, NMR and nitrogen analysis. The analytical data of (4a-c) compounds are given in Table 1.

Table 1: Analytical data of 3, 4, 5-substituted 1, 2, 4-triazoles (4a-c)

Compound	Molecular Formula	Mol. Wt. (g)	M. P. ($^{\circ}$ C)	Yield%	% of Nitrogen	
					Cal.	Found
4a	C ₂₀ N ₆ O ₃ H ₁₃	586	176	68	21.76	19.00
4b	C ₂₀ N ₆ O ₃ H ₁₃ Cl	414	187	56	20.76	17.04
4c	C ₂₁ N ₅ O ₂ H ₁₄	358	162	69	19.55	18.20

Spectral data

IR spectral data of synthesized triazoles (cm⁻¹)

S. No.	Compound	C = N	N-H	C = O	C = C Ar
1	4a	1587	3120	1720	1514
2	4b	1608	3100	1720	1520
3	4c	1600	3120	1720	1522

¹H NMR Spectra

The ¹H-NMR spectra of the triazolyl compounds have signals in the range 7.22-7.32 δ (S, 1H, NH), 7.1-7.8 δ (m, Ar H) and 8.2-8.8 (m, 4H, pyridyl H).

Biological activity: Antibacterial activity was evaluated by the paper disk plate method.

Table 2: Biological activity of triazoles

Compound	Antimicrobial		Antifungal	
	<i>E. coli</i>	<i>S. aureus</i>	<i>A. niger</i>	<i>C. albicans</i>
4a	22	21	13	12
4b	25	24	14	16
4c	25	12	12	13

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