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1, 2, 3-TRIAZOLE DERIVATIVES AS POSSIBLE ANTI-INFLAMMATORY AGENTS

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ABSTRACT

The syntheses of a series of novel Some 4, 5-Dihydro-1H-1, 2, 3-Triazoles derived from 2-azido-N-phenyl acetamide are described. A total of four new compounds were synthesized and characterized by spectral and elemental analyses. Some compounds were screened for their anti-inflammatory activity. All compounds carring aryl substituents at position five and the 1, 2, 3- triazole moiety at position one or two showed reasonable anti-inflammatory activity.

Keywords: 1, 2, 3-triazole, aroyl formic acid, hydrazine hydrate, anti-inflammatory activity.

INTRODUCTION

The chemistry of heterocyclic compounds continues to be an active field in the organic chemistry. Triazole- derivatives have occupied a unique position in heterocyclic chemistry due to their antimicrobial activities.[1, 2] 1, 2, 3- Triazoles exhibit a wide range of therapeutical properties.[3] The syntheses of 1,2,3-triazoles has also attracted wide spread attention due to the diverse agricultural, industrial and biological activities, including antibacterial, analgesic, antitumoral, anticonvulsant and tranquilizing activities shown by these compounds. In view of these observations and in continuation of our earlier work[4-14] on the syntheses of some 1,2,3- and 1,2,4- triazole derivatives, we now report the synthesis of more novel 4,5-Dihydro-1H-1, 2, 3-Triazoles derived from 2-azido-N-phenyl acetamide.

EXPERIMENTAL

Melting and boiling points were determined on a Gallen Kamp apparatus in open capillaries and are uncorrected. IR spectra (KBr in cm^{-1}) were recorded on a Jasco FT-IR 5300 spectrophotometer and proton magnetic resonance (PMR) spectra (DMSO-d6) on a Varian EM-390 spectrometer using TMS as an internal standard (chemical shift in δ ppm). Mass spectra were recorded on a Jeol JMS-D 300Mass spectrometer operating at 70eV.The purity of the compounds was confirmed by TLC using silica gel G and purified by column chromatography. For TLC, Merck silica gel 60G plate was used. For column chromatography, Merck silica gel 60 (0.063-0.200mm) was used. The necessary chemicals were obtained from Merck and Fluka. All compounds showed satisfactory elemental analyses.

General procedure for the preparation of Δ^2-1H-1, 2, 3-triazolines-4, 5-dihydro-1H-1, 2, 3-triazoles (3a-d) A solution of 0.5g of triazoline in methanol (10 mL) was added a solution of potassium hydroxide (2N, 10 mL) and the mixture was refluxed with stirring for 30 minutes. The reaction mixture was diluted with ice cold water and cooled to produce pure product **3a-d** (yield 40-65%).

3a: (yield 40%) m.p. 165 ^{0}C. Anal.Calc. for $C_{11}H_9N_4O_3Cl$: C, 60.10; H, 7.10; N, 23.00 %; Found C, 60.80; H, 7.30; N, 23.30% ; IR (KBr) : 1657 (C=O), 1492(CH_2) and 1595(CONHR) ; PMR: δ 4.5 (2H, s,

CH_2), 7.40 ppm (4H, m, ArH) and 8.30ppm (1H, s, NH) ; MS: m/z 324 (M^+) other peaks observed at 294, 285, 252 and176.

3b: (yield 40%) m.p. 180 ^{0}C. Anal.Calc. for $C_{11}H_9N_4O_3Br$: C, 60.22; H, 7.20; N, 23.10 %; Found C, 60.12; H, 7.16; N, 23.12% ; IR (KBr) : 1668 (C=O), 1498(CH_2) and 1595(CONHR) ; PMR: δ 7.60 (4H, m, ArH) and 8.20ppm (1H, s, NH) ; MS: m/z 246 (M^+) other peaks observed at 175 and 155.

3c: (yield 65%) m.p. 175^{0}C. Anal.Calc. for $C_{11}H_{10}N_4O_3$: C, 60.08; H, 7.32; N, 23.05 %; Found C, 60.21; H, 7.15; N, 23.17% ; IR (KBr) : 1670(C=O), 1446(CH_2) and 1600(CONHR) ; PMR: δ 4.20(2H, s, CH_2), 7.60 (5H, m, ArH) and 8.20ppm (1H, s, NH) ; MS: m/z 244 (M^+) other peaks observed at 213 and176.

3d: (yield 60%) m.p. 170 ^{0}C. Anal.Calc. for $C_{11}H_9N_5O_5$: C, 60.19; H, 7.18; N, 23.28 %; Found C, 60.41; H, 7.11; N, 23.19% ; IR (KBr) : 1674 (C=O), 1445(CH_2) and 1602(CONHR) ; PMR: δ 4.3 (2H, s, CH_2), 7.60 ppm (4H, m, ArH) and 8.30ppm (1H, s, NH) ; MS: m/z 292 (M^+) other peaks observed at 218 and 198.

Anti-inflammatory activity:

Anti-inflammatory activities of four compounds were measured using formal in induced rat find paw edema technique[15]. Male albino rats were injected with 0.1 mL of a 1% carageenan solution in saline in to sub planter region of the left find paw. The paw was marked with ink at the level of the lateral molecules and immersed in mercury up to this mark the paw volume was measured before and 1, 2, 3, 4 and 5 hour after the injection of carageenan by mercury displacement method plethysmographically. The edema volume was determined and expressed as percentage swellings, compared with initial find paw volume of each rat. Ibuprofen was used as reference standard. The screening results revealed that showed significant anti-inflammatory activity which was comparable with Ibuprofen[16]. **(**See **Table 1)**

Table-1: Evaluation of anti-inflammatory activity of the compounds

Compd.	Substituent	Percentage inhibition at the end of		
		1hr	3hr	5hr
3a	Cl	48.82	53.83	56.13
3b	Br	50.82	54.62	59.51
3c	H	63.28	67.12	66.32
3d	NO_2	63.43	68.07	66.35
Ibuprofen (Standard)		64.06	68.10	72.62

RESULTS AND DISCUSSION

The reaction between 2-azido-N-phenyl acetamide and cinnamic acid inpresence of ethanol to afforded 1, 2, 3-triazoline derivatives. Thr reaction of 1,2,3-triazoline derivatives with methanol and a solution of sodium hydroxide, afforded Δ^2-1H-1,2, 3-triazolines(4,5-dihydro-1H-1, 2, 3-triazoles), filtered, dried and recrystallized from chloroform. (See **Scheme 1).**

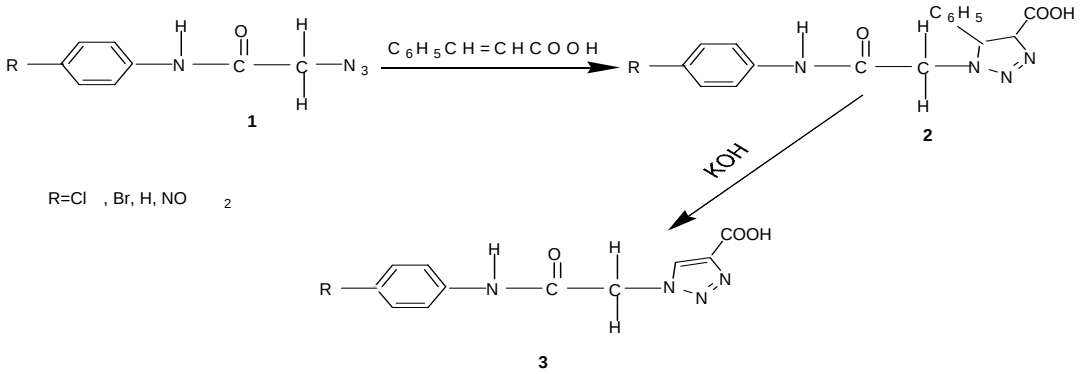
The IR spectrum of the compound **3a** showed characteristic absorption bands at 1657, 1492, and 1595 cm^{-1} for C=O, CH_2, and CONHR groups respectively. The PMR spectrum of **3a** exhibits a multiplet (4H) at δ 7.40 for aromatic protons, a singlet (2H) at δ 4.50 for CH_2 protons, a singlet (1H) at δ 8.30 for NH protons. Mass spectra showed the expected molecular ion peaks at m/z 324, 294, 285, 252 and 176(M^+) in agreement with their molecular formulae.

The IR spectrum of the compound **3b** showed characteristic absorption bands at 1668, and 1498 cm^{-1} for C=O and CH_2 groups respectively. The PMR spectrum of **3b** exhibits a multiplet (4H) at δ 7.60 for aromatic protons, a singlet (2H) at δ 4.20 for CH_2 protons, a singlet (1H) at δ 8.20 for NH protons. Mass spectra showed the expected molecular ion peaks at m/z 246, 175 and 155 (M^+) in agreement with their molecular formulae.

The IR spectrum of the compound **3c** showed characteristic absorption bands at 1670, 1446 and 1600 cm^{-1} for C=O, CH_2, and CONHR groups respectively. The PMR spectrum of **3c** exhibits a multiplet (5H) at δ 7.60 for aromatic protons, a singlet (2H) at δ 4.20 for CH_2 protons, a singlet (1H) at δ 8.20 for NH

protons. Mass spectra showed the expected molecular ion peaks at m/z 244, 213 and 176 (M^+) in agreement with their molecular formulae.

The IR spectrum of the compound **3d** showed characteristic absorption bands at 1674, 1445 and 1602 cm^{-1} for C=O, CH_2 and CONHR groups respectively. The PMR spectrum of **3d** exhibits a multiplet (4H) at δ 7.60 for aromatic protons, a singlet (2H) at δ 4.30 for CH_2 protons, a singlet (1H) at δ 8.30 for NH protons. Mass spectra showed the expected molecular ion peaks at m/z 292, 218 and 198 (M^+) in agreement with their molecular formulae. All compounds containing 1, 2, 3- triazole moiety showed significant anti-inflammatory activity. The structures of all the compounds are confirmed by IR, PMR & MS spectral data (experimental part).



1 2 3

Compound	R			
3	a	Cl	b	Br
	c	H	d	NO_2

Scheme 1

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