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Synthesis of novel 1,3,4-oxadiazole derivatives and their biological properties

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ABSTRACT

A novel series of 1,3,4-oxadiazoles have been synthesized from substituted aromatic acid with the aim to get better anti-inflammatory and analgesic agents with minimum or without side effects (ulcerogenicity). Structures of the synthesized compounds were supported by means of IR, ¹H NMR and mass spectroscopy. Title compounds were evaluated for their antibacterial activities. All compounds were found to have significant antibacterial activities. © 2012 Trade Science Inc. - INDIA

KEYWORDS

1,3,4-oxadiazoles;
Aroylpropionic acid;
Anti-inflammatory;
Analgesic activity;
Antibacterial activity.

INTRODUCTION

Heterocyclic compounds containing the five-membered oxadiazole nucleus possess a diversity of useful biological effects. 1,3,4-Oxadiazole and 3-arylopropionic acid moieties are important because of their versatile biological actions. In particular, compounds bearing the 1,3,4-oxadiazole nucleus are known to have unique antioedema and anti-inflammatory activities^[1-3]. Differently substituted oxadiazole moieties have also been found to have other interesting activities such as analgesic^[2,3], antimicrobial^[4], antitubercular^[5], anticonvulsant^[6] and anti-hepatitis B viral activities^[7]. Non-steroidal anti-inflammatory drugs NSAIDs form a class of therapeutic agents that are most widely used because of their anti-inflammatory, analgesic and antipyretic effects. The prevalent side effects of NSAIDs are the occurrence of gastrointestinal side effects like gastric upset, irritation and ulceration^[8]. 3-(4-Bromobenzoyl)propionic acid is an example of the well known aroylpropionic acid class of non steroidal anti-inflammatory agents. Aroylpropionic

acids are effective anti-inflammatory agents and some of them are commercially available; however, they are associated with gastrointestinal side effects^[9,10]. Studies suggest that direct tissue contact of these agents plays an important role in the production of side effects^[11] and the reported literature confirms that gastrointestinal side effects of aroylpropionic acids are due to the presence of a free carboxylic group in the parent drug^[10-12]. Thus, developing new agents with minimum or without side effects is an extensive research area at present.

EXPERIMENTAL

Chemicals were procured from E. Merck (India) and S. D. Fine Chemicals (India). Melting points were taken in open capillary tubes and are uncorrected. Microanalysis of the compounds was done on a Perkin-Elmer model 240 analyzer (Perkin-Elmer, USA) and the values were found within ± 0.4 % of the theoretical values. IR (KBr) spectra were recorded on a Perkin-Elmer 157 infrared spectrometer (ν_{\max} in cm⁻¹

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1) (Perkin-Elmer, USA) and ¹H NMR spectra were recorded on a Varian E-360 MHz (Perkin-Elmer, USA) or Bruker spectrometer DPX-300MHz (Bruker, Germany) with tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a Jeol JMS-D 300 instrument (Jeol, Japan) fitted with a JMS 2000 data system at 70 eV. Spectral data are consistent with the assigned structures. The progress of the reactions was monitored on silica gel G plates using iodine vapour as visualizing agent. All solvents were distilled prior to use.

Preparation of methyl phenyl acetate

Phenyl acetic acid (40.8 g; 0.3 mole) was dissolved in methanol (200 ml) and con. Sulphuric acid (3 ml, 98%) was added drop wise. The reaction mixture was refluxed on water bath for four hours. The reaction mixture was allowed to cool and poured in ice-cooled water. The mass was transferred to separatory funnel, thoroughly shaken and allowed to settle. Organic layer was collected, washed several times with water, dried and transferred to distillation flask. Ester was collected at 192° C. Yield : 38.6 g ; 86% C₉H₁₀O₂ b.p. 192° C.

Preparation of phenyl acetyl hydrazine

Methyl phenyl acetate (30.0 g, 0.2 mole) was mixed with ethanol (50 ml, 95%) and hydrazine hydrate (30 ml, 8%) was added. The reaction mixture was refluxed on waterbath for three hours. Excess of ethanol was distilled off. Residue was cooled to 4-5° C. The separated crystals were filtered and washed 2-3 times with ether. The product was recrystallised from ethanol. Yield, 27.6 ; 92% ; m.p.114°C (Rep. 116°C) Found N, 16.61% C₈H₁₀ON₂ : Req. N, 16.89%

Preparation of 5-benzyl-1,3,4-oxadiazole-2-thione

Phenyl acetyl hydrazine (75.0 g: 0.5 mole) was dissolved in potassium hydroxide (56.0 g: 1.0 mole) in 100 ml water and 100 ml methanol with constant stirring. To this clear solution, carbon disulphide (60.0 ml, 1.0 mole) was added drop wise with constant stirring. The resulting solution was heated under reflux for six hours. Reflux condenser was removed and solution was filtered to remove any unreacted material or impurities. The filtrate was acidified with dilute hydrochloric acid. The compound thus obtained was filtered, washed with water and dried in oven at 105° C. Recrystallised from alcohol. Yield, 58.56g 61% m.p.210° C; Found: N, 14.50%; S, 16.6% C₉H₈ON₂S; Required: N, 14.58%; S, 16.66%

Preparation of 2-(N-phenyl carboxamido methyl thio) -5-benzyl-1,3,4-oxadiazole

5-Benzyl-1,3,4-oxadiazole -2-thione (1.92g; 0.01 mole) was dissolved in solution of potassium hydroxide (10g) in water (20 ml). To this, α-chloro acetanilide (2.37 g; 0.014 mole) was added with constant stirring at 80 C. The reaction mixture was kept at 80 C for two hours with stirring and after that left overnight. The crystalline mass that separated out was filtered, washed with cold water and dried. Recrystallised from ethanol. Yield, 1.91 g; 59% m.p.125°C; Found: N, 12.89%; S, 9.80% C₁₇H₁₅O₂N₃S; Required: N, 12.92%; S, 9.84%

Spectral data: The IR Spectra of 2-(N-phenyl carboxamido methyl thio) -5- benzyl- 1,3,4 -oxadiazole, showed following characteristic bands at: 3290 cm⁻¹ (-NH str. , acetamido group), 1720 cm⁻¹ (> C= O str., acyclic), 1650 cm⁻¹ (-CO-NH linkage), 1600 cm⁻¹ (> C=N -Stri., cyclic), 1520 cm⁻¹ (C-O-C str., cyclic), 1430 cm⁻¹ (-CH₂, benzylic), 1420 cm⁻¹

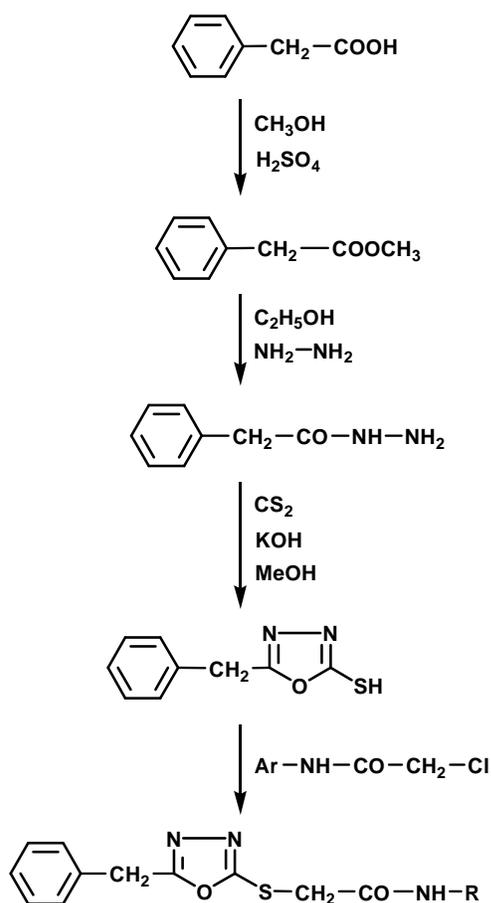
TABLE 1 : Physical properties of 2-(N- substituted carbamido methyl thio)-5- benzyl 1,3,4- oxadiazoles

No.	R	M.F.	M.W.	Yield	M.P.°C	% of N		% of S	
						Found	Reqd.	Found	Reqd.
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
1.	-C ₆ H ₅	C ₁₇ H ₁₅ O ₂ N ₃ S	325	59	121	12.89	12.92	9.80	9.84
2.	-2-NO ₂ -C ₆ H ₄	C ₁₇ H ₁₄ O ₄ N ₄ S	370	61	75	15.11	15.13	8.61	8.69
3.	-3-NO ₂ -C ₆ H ₄	C ₁₇ H ₁₄ O ₄ N ₄ S	370	58	118	15.15	15.13	8.65	8.64
4.	-4-NO ₂ -C ₆ H ₄	C ₁₇ H ₁₄ O ₄ N ₄ S	370	51	140	15.10	15.13	8.62	8.64
5.	-2-CH ₃ -C ₆ H ₄	C ₁₈ H ₁₇ O ₂ N ₃ S	339	65	105	12.40	12.38	9.45	9.43
6.	-3-CH ₃ -C ₆ H ₄	C ₁₈ H ₁₇ O ₂ N ₃ S	339	69	85	12.35	12.38	9.40	9.43
7.	-4-CH ₃ -C ₆ H ₄	C ₁₈ H ₁₇ O ₂ N ₃ S	339	55	91	12.40	12.38	9.41	9.43

TABLE 2 : Antibacterial and antitubercular activity of some 2-(N-substituted carbamido methyl thio)-5- benzyl 1,3,4-oxadiazoles

Sr. No	Ar.	Antibacterial activity Zone of inhibition in mm			Antitubercular activity.	
		E.coli	S.aureus	Salmonella typhi Para A	Conc. 5	In g/ml 10
(1)	(2)	(3)	(4)	(5)	(6)	(7)
1.	-C ₆ H ₅	20	18	19	-	+
2.	-2-NO ₂ -C ₆ H ₄	18	17	23	-	+
3	-3-NO ₂ -C ₆ H ₄	18	17	17	+	+
4	-4-NO ₂ -C ₆ H ₄	18	22	17	+	+
5	-3-CH ₃ -C ₆ H ₄	20	16	16	-	-
6	-3-CH ₃ -C ₆ H ₄	20	15	18	-	-
7	-4-CH ₃ -C ₆ H ₄	20	20	17	-	+

REACTIONS SCHEME



(S-CH₂ str., methylene str., strong band), 1280 cm⁻¹ (=N-N=C<str., cyclic str.) 690 and 740 cm⁻¹ (C-H bending for mono substituted benzene ring). PMR spectrum of the compound showed signals as follows. 9.6 δ (broad signal due to -NH proton), 6.8 - 7.2 δ (multiplet, aromatic protons), 2.8 (S-CH₂-sin-

glet), 2.3δ (-CH₂ singlet).

Similarly different substituted 1,3,4-oxadiazoles have been prepared by using substituted α-chloro acetanilide

CONCLUSIONS

A new class of oxadiazoles was synthesized by cyclization of the terminal carboxylic group of an aroyl propionic acid with the objective to develop better anti-inflammatory and analgesic molecules with or without ulcerogenic activity. The results of biological tests make novel oxadiazoles interesting lead molecules for further synthetic and biological evaluation. It can be concluded that this class of compounds certainly hold great promise for discovering safer anti-inflammatory agents.

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