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New 1,3,4- oxadiazoles as an antitubercular agents

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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.

KEYWORDS

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

INTRODUCTION

Heterocyclic compounds containing the five-membered oxadiazole nucleus possess a iversity of useful biological effects. 1,3,4-Oxadiazole and 3-aroylpropionic 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 (*n*max in cm–

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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 ws 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% $C_9H_{10}O_2$ 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% $C_8H_{10}ON_2$: 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 condensor 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% $C_9H_8ON_2S$; Required : N, 1458%; S, 16.66%

Preparation of 2-[N(4–ethoxyphenyl) 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 3-methoxy acetanilide (0.014 mole) was added with constant stirring at 80 C. The reaction mixture was kept at 80 C fro 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, 59% m.p.98° C; Found : N, 11.35% ; S, 8.70% $C_{19}H_{19}O_3N_3S$; Required : 11.38%; S, 8.67%

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

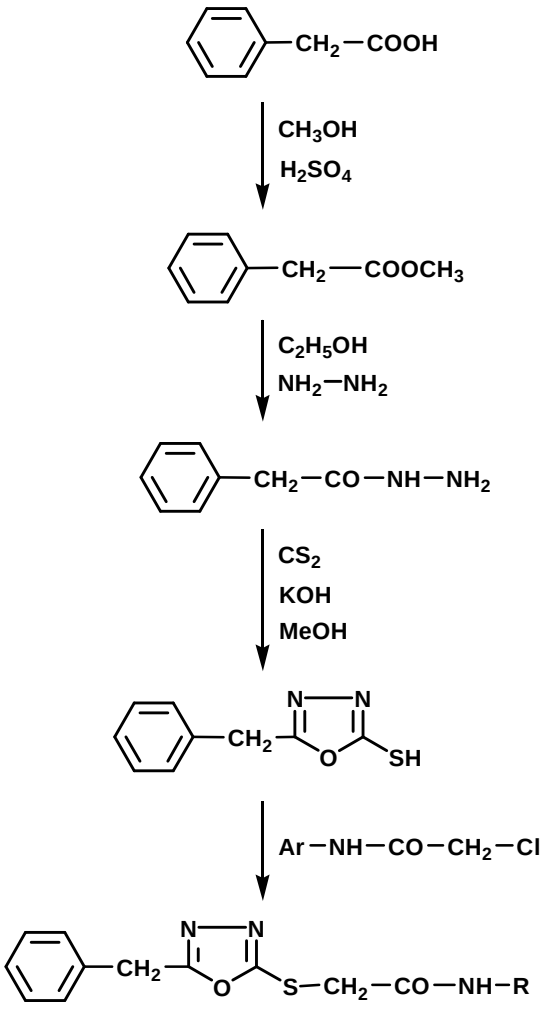
TABLE 1 : Physical properties of 2-(N-substituted carbxamido methyl thio)-5- benzyl 1,3,4-oxadiazoles

No.	R	M.F.	M.V.	Yield	M.P.°C	% of N		% of S	
						Found	Reqd.	Found	Reqd.
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
1	-4-OC_2H_5-C_6H_4	$C_{19}H_{19}O_3N_3S$	369	59	98	11.35	11.38	8.70	8.67
2	-2-4-Cl_2-C_6H_3	$C_{17}H_{13}O_2N_3SCl_2$	394	61	85	10.62	10.65	8.09	8.12
3	-2-4-$(CH_3)_2$-C_6H_3	$C_{19}H_{19}O_2N_3S$	353	54	125	11.85	11.89	9.01	9.06
4	-2-NO_2-4-Cl- C_6H_3	$C_{18}H_{13}O_4N_4SCl$	416.5	61	115	13.40	13.14	7.63	7.68
5	-2-Cl-4-NO_2- C_6H_3	$C_{18}H_{13}O_4N_4SCl$	416.5	55	119	13.47	13.44	7.65	7.68

TABLE 2 : Antilbacterial and antitubercular activity of some 2-(N-substituted carbxamido 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	-4- OC_2H_5- C_6H_4	17	18	17	-	+
2	-2-,4-$(Cl)_2$ - C_6H_3	17	15	20	-	-
3	-2-,4-$(CH_3)_2$ - C_6H_3	20	17	17	-	-
4	-2-NO_2 -4-Cl- C_6H_3	18	20	17	-	+
5	-2-Cl -4-NO_2- C_6H_3	15	17	20	-	-

REACTION SCHEME



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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