Synthesis and characterization of some newer 1,3,4-oxadiazoles

Hitesh P. Shah
Sir P.P. Institute of Science, Bhavnagar University, Bhavnagar, (INDIA)
E-mail: hiteshshah@ymail.com
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ABSTRACT
Substituted 1,3,4-oxadiazoles are of considerable pharmaceutical interest. 4-chlorobenzylidine-1,3,4-oxadiazoles are associated with diverse biological activities by the virtue of -N = C-O- grouping. In the view of wide range of biological properties associated with 1,3,4-oxadiazole, we have synthesized substituted derivatives of 1,3,4-oxadiazole. © 2012 Trade Science Inc. - INDIA

INTRODUCTION
This work aims at the development of a newer isoniazid-based oxadiazole ring system. 1,3,4-Oxadiazole derivatives show a broad spectrum of biological activities, which include analgesic and anti-inflammatory, antimicrobial, anticonvulsant, antifungal, anticancer, antimycobacterial[1,2], etc. The research envisages a meaningful exploration of this lead molecule for novel analgesic, anti-inflammatory activities with minimum toxicity and high potency[5]. The lead compound was structurally modified by incorporating various substitutions at the second and fifth position of the heterocyclic ring system. From a review of the literature it is clear that 2,5 disubstituted 1,3,4-oxadiazole derivatives of oxadiazole possess remarkable analgesic, anti-inflammatory activity[5,6].

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

REACTONSHEME
the values were found within ± 0.4 % of the theoretical values. IR (KBr) spectra were recorded on a Perkin-Elmer 157 infrared spectrometer (max in cm–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.

**TABLE 1**

<table>
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<tr>
<th>Sr.No.</th>
<th>R</th>
<th>Molecular Formula</th>
<th>M.V.</th>
<th>Yield %</th>
<th>M.P.°C</th>
<th>% of N</th>
<th>% of S</th>
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<td></td>
<td></td>
<td>(3)</td>
<td>(4)</td>
<td>(5)</td>
<td>(6)</td>
<td>(7)</td>
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<td>(2)</td>
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<td>-3-CH₃-C₆H₄</td>
<td>C₂₃H₁₉O₂N₃SCl</td>
<td>462.5</td>
<td>43</td>
<td>150</td>
<td>12.04</td>
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<td>46</td>
<td>138</td>
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<td>50</td>
<td>162</td>
<td>11.66</td>
<td>11.70</td>
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<td>(4)</td>
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<td>C₂₃H₁₉O₃N₃SCl</td>
<td>478.5</td>
<td>53</td>
<td>198</td>
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<td>-2-4-(CH₃)₂-C₆H₃</td>
<td>C₂₅H₂₁O₂N₃SCl₂</td>
<td>477.5</td>
<td>42</td>
<td>161</td>
<td>11.71</td>
<td>11.72</td>
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<tr>
<td>(8)</td>
<td>-2-NO₂-4-Cl- C₆H₃</td>
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<td>-2-4(NO₂)-C₆H₃</td>
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<td>514</td>
<td>47</td>
<td>178</td>
<td>11.85</td>
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**Preparation of p-amino benzoyl hydrazine**

Benzocaine (33.0 g, 0.2 mole) was dissolved in ethanol (70ml, 95%) with stirring. Hydrazine hydrate (80ml, 99%) was added dropwise and contents were refluxed on waterbath for four hours. Excess of solvent was distilled off and the reaction mixture was cooled to 4-5° C. The separated product was filtered, washed with chilled ethanol and dried in oven at 105° C. Recrystallised from ethanol. Yield, 23.5 g; 78% m.p. 209-10° C; Found: N, 27.78% C₂₃H₁₉O₂N₃S; Required: N, 27.81%

**Preparation of 5-(4-amino phenyl)-1,3,4-oxadiazol-2-thione**

p-Amino benzoyl hydrazine (15.1 g, 0.1 mole) was dissolved in solution of potassium hydroxide (5.6 g; 0.1 mole) in 100 ml water with constant stirring. Methanol (100 ml) was added dropwise and a clear solution was obtained. CS₂ (6ml, 0.1 mole) was added dropwise with constant stirring. The resulting solution was refluxed for six hours and then concentrated. Residual solution was poured in water and filtered. The filtrate was acidified with dilute HCl. The product thus obtained was filtered washed with water and dried. Recrystallised from ethanol. Yield, 16.51 g; 86 % m.p. 259-10° C; Found: N, 21.80% ; S 16.60% C₁₅H₁₀ON₃S; Required: N, 21.87% S 16.66%

**Preparation of 5-[4-(4-chloro benzylidin)-amino]–phenyl 1,3,4-oxadiazole -2-thione**

5-(4-Amino phenyl)-1,3,4-oxadiazole –2 – thione (19.2 g; 0.1 mole) was dissolved in spirit. p-chloro benzaldehyde (14.05g ; 0.1 mole) was added dropwise with constant stirring. Resultant solution was refluxed on a waterbath for three hours. Excess of solvent was distilled off. The contents were allowed to cool at room temperature. The separated product was filtered, washed with water and dried. Recrystallized from ethanol. Yield, 25.25 g; 81 % m.p. 156° C; Found: N, 13.26% ; S 10.09% C₁₅H₁₀ON₃SCl; Required: N, 13.31% S 10.14%

**Preparation of 2-[(N (3–Methyl phenyl) carboxamido-methyl thio)]-5- [4- (4- chloro benzylidin) amino] - phenyl 1,3,4-oxadiazole.**

5-[4-(4-chloro benzylidin)–amino)–phenyl 1,3,4-oxadiazol-2-thione (3.15 g, 0.01 mole) was dissolved in solution of potassium hydroxide (5 g) in water (20 ml). α-Chloro 4-chloro acetonilide (0.014 mole) was added with constant stirring at 80°C. Stirring was con-
continued and the reaction mixture maintained at 80° C for two hours.

The contents were left overnight. The crystals were filtered, washed with water and dried. Recrystallised from ethanol. Yield, 43 % m.p. 150° C; Found: N, 12.04 %; S 6.89 % C_{24}H_{19}O_{2}N_{4}SCl; Required: N, 12.10 % S 6.91 %

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

**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.

**REFERENCES**


