



Trade Science Inc.

Organic CHEMISTRY

*An Indian Journal***Short Communication**

OCAIJ, 5(2), 2009 [248-250]

Synthesis and biological evaluation of some new 5-oxo-imidazolines

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Received: 27th March, 2009 ; Accepted: 1st April, 2009

ABSTRACT

The target compounds 1-aryl-2-phenyl-4-[5'-(m,p-dichlorophenyl)-2'-furylidene]-5-oxo-imidazolines (**3a-o**) have been synthesized by the condensation of 4-oxo-2-phenyl-5-[5'-(m,p-dichlorophenyl)-2'-furylidene]-oxazole (**2**) with different arylamines in dry pyridine. All the products have been evaluated for their antimicrobial activity towards different strains of bacteria and fungi and antitubercular activity towards *Mycobacterium tuberculosis H37 Rv*.

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INTRODUCTION

5-oxo-imidazolines have been found to be associated with wide range of pharmacological activities^[1-3]. The large number of activities of furan containing heterocycle has been also reported^[4-5]. With an aim to develop better therapeutic agents, it was thought worthwhile to synthesize a new series of 5-oxo-imidazoline derivatives bearing furan nucleus.

The target compound (**3a-o**) have been synthesised by the condensation of 4-oxo-2-phenyl-5-[5'-(m,p-dichlorophenyl)-2'-furylidene]-oxazole (**2**) with different arylamines. The (**2**) was obtained by the reaction of 5-(m,p-dichlorophenyl)-2-furaldehyde (**1**) with benzoyl glycine, acetic anhydride and sodium acetate.

The constitution of all the synthesized products have been characterised using elemental analyses, IR and ¹H NMR spectroscopy. All the products have been screened *in vitro* for their antimicrobial activity towards different strains of bacteria and fungi and antitubercular activity towards *Mycobacterium tuberculosis H37 Rv*.

Antimicrobial activity

The antimicrobial activity was assayed by using the cup-plate agar diffusion method^[6] by measuring the inhibition zones in mm. All the compounds were screened

in vitro for their antimicrobial activity towards variety of bacterial strains such as *B.mega*, *S.aureus*, *E.coli*, *P.vulgaris* and fungi such as *Aspergillus niger* at a concentration of 40µg. Known antibiotics such as Ampicillin, Amoxicillin, Norfloxacin and Penicillin showed zones of inhibition at 17-22 mm, 18-24mm, 19-23 mm and 22-25 mm respectively towards bacterial strains and Greseofulvin showed zones of inhibition of 26 mm towards fungi *A. niger*. The antitubercular activity was tested at TAACF, the Southern Research Institute, USA towards *Mycobacterium tuberculosis H37 Rv* at a concentration of 12.5µg/ml in BACTEC 12B medium using the BACTEC 460 radiometric system. The antitubercular activity data have been compared with standard drug Rifampin which showed 90% inhibition, at 0.25µg/ml concentration.

EXPERIMENTAL

All the melting points were determined in an open capillary tubes and are uncorrected. IR spectra (KBr) were recorded on Shimadzu FT-IR-8400-spectrophotometer. ¹H NMR spectra were recorded on BRUKER spectrometer (300 MHz) using TMS as an internal standard. Purity of the compounds was checked by TLC

TABLE 1 : Physical data constants of compounds (3a-o)

| Sr. no. | R | Molecular formula | M.P. °C | Rf* Value | Yield % | % of Nitrogen | |
|---------|---|--|---------|-----------|---------|---------------|-------|
| | | | | | | Calcd. | Found |
| (3a) | C ₆ H ₅ - | C ₂₆ H ₁₆ Cl ₂ N ₂ O ₂ | 136 | 0.55 | 68 | 6.10 | 6.42 |
| (3b) | 4-COOC ₂ H ₅ -C ₆ H ₄ - | C ₂₉ H ₂₀ Cl ₂ N ₂ O ₄ | 174 | 0.65 | 66 | 5.27 | 5.55 |
| (3c) | 3-Cl-C ₆ H ₄ - | C ₂₆ H ₁₅ Cl ₃ N ₂ O ₂ | 200 | 0.68 | 70 | 5.67 | 5.48 |
| (3d) | 4-Cl-C ₆ H ₄ - | C ₂₆ H ₁₅ Cl ₃ N ₂ O ₂ | 143 | 0.79 | 62 | 5.67 | 5.55 |
| (3e) | 3-Cl,4-F-C ₆ H ₃ - | C ₂₆ H ₁₄ Cl ₃ FN ₂ O ₂ | 148 | 0.78 | 76 | 5.47 | 5.62 |
| (3f) | 2,6(Cl) ₂ -C ₆ H ₃ - | C ₂₆ H ₁₄ Cl ₄ N ₂ O ₂ | 212 | 0.50 | 66 | 5.30 | 5.05 |
| (3g) | 2,4(CH ₃) ₂ -C ₆ H ₃ - | C ₂₈ H ₂₀ Cl ₂ N ₂ O ₂ | 156 | 0.52 | 63 | 5.75 | 5.92 |
| (3h) | 4-F-C ₆ H ₄ - | C ₂₆ H ₁₅ Cl ₂ N ₂ O ₂ | 280 | 0.81 | 70 | 5.87 | 5.68 |
| (3i) | 2-OCH ₃ -C ₆ H ₄ - | C ₂₇ H ₁₈ Cl ₂ N ₂ O ₃ | 265 | 0.65 | 72 | 5.72 | 5.90 |
| (3j) | 4-OCH ₃ -C ₆ H ₄ - | C ₂₇ H ₁₈ Cl ₂ N ₂ O ₃ | 241 | 0.68 | 69 | 5.72 | 5.40 |
| (3k) | 2-CH ₃ -C ₆ H ₄ - | C ₂₇ H ₁₈ Cl ₂ N ₂ O ₂ | 208 | 0.55 | 66 | 5.92 | 5.82 |
| (3l) | 3-CH ₃ -C ₆ H ₄ - | C ₂₇ H ₁₈ Cl ₂ N ₂ O ₂ | 198 | 0.58 | 58 | 5.92 | 6.22 |
| (3m) | 4-CH ₃ -C ₆ H ₄ - | C ₂₇ H ₁₈ Cl ₂ N ₂ O ₂ | 201 | 0.72 | 66 | 5.92 | 6.15 |
| (3n) | 3-NO ₂ -C ₆ H ₄ - | C ₂₆ H ₁₅ Cl ₂ N ₃ O ₄ | 166 | 0.50 | 62 | 8.33 | 8.08 |
| (3o) | 4-NO ₂ -C ₆ H ₄ - | C ₂₆ H ₁₅ Cl ₂ N ₃ O ₄ | 184 | 0.71 | 64 | 8.33 | 8.52 |

using silica gel G. All the compounds gave satisfactory elemental analysis.

Synthesis of 5-(m,p-dichlorophenyl)-2-furaldehyde (1)

A mixture of 3,4-dichloroaniline (16.2g, 0.01M), dil. HCl (15%, 60 ml) and water (90 ml) was heated to get a clear solution. The solution was cooled to 0°C and diazotized with NaNO₂ solution (30%, 24 ml). The diazonium salt solution was filtered and to the filtrate, water (50 ml) and freshly distilled furfural (11.1 ml, 0.1 M) and aqueous cupric chloride (2.5 g in 10 ml of water) were added with stirring. The stirring was continued for 4 hrs. and the resulting mixture was kept overnight. The separated solid was collected by filtration and washed with cold ethanol, crystallised from a mixture of ethanol-DMF. Yield 80%, m.p. 270°C.

Synthesis of 4-oxo-2-phenyl-5-[5'-(m,p-dichlorophenyl)-2'-furylidene]-oxazole (2)

A mixture of 5-(m,p-dichlorophenyl)-2-furaldehyde (6.02g, 0.025M), benzoyl glycin (4.47g, 0.025 M), acetic anhydride (7.6 gm, 0.075 M) and sodium acetate (2.0 g) was heated on water bath for 4 hrs. Resulting mixture was poured into water, filtered and crystallised from methanol. Yield 70%, m.p. 210°C.

Synthesis of 1-(p-carbethoxyphenyl)-2-phenyl-4-[5'-(m,p-dichlorophenyl)-2'-furylidene]-5-oxo-imidazolines (3b)

A mixture of 4-oxo-2-phenyl-5-[5'-(m,p-dichlorophenyl)-2'-furylidene]-oxazole (3.84 g, 0.01

M) and benzocain (1.65 g, 0.01 M) in dry pyridine was refluxed for 6 hrs in oil bath. Resulting mixture was poured into crushed ice and neutralised with HCl, filtered and the product was crystallised from DMF. Yield 66%, m.p. 174°C (C₂₉H₂₀Cl₂N₂O₄ calcd. : C, 65.55 ; H, 3.79 ; N, 5.27% ; found : C, 65.32 ; H, 3.60 ; N, 5.00 %). IR (KBr) cm⁻¹ : 2962, 2846 (C-H str. asym and sym respectively) ; 1722 (C=O str.) ; 1596 (C=N str.) ; 1517 (C=C str.) ; 759 (C-Cl str.) ¹H NMR (CDCl₃) δ ppm : 1.39 (t, 3H, -CH₃) ; 4.35 (q, 2H, -CH₂) ; 6.54-8.02 (m, 14H, Ar-H) ; 8.56 (s, 1H, =CH).

Similarly other 5-oxo-imidazolines were prepared. The physical constants are recorded in (TABLE 1).

RESULTS AND DISCUSSION

By visualizing the antimicrobial data, it could be observed that compounds (3b) and (3j) were highly active towards *B. megaterium*. The compounds (3b), (3d) and (3e) were significantly active towards *S. aureus*. In case of *E. coli*, compounds (3a), (3l) and (3n) have displayed maximum activity. The compounds (3a), (3c), (3e) and (3m) showed comparable activity towards *P. vulgaris*. The compounds (3g) and (3j) were highly active towards fungi *A. niger*. Compound (3a) showed 60% inhibition towards *Mycobacterium tuberculosis* H37 Rv (TABLE 2).

Looking at the structure activity relationship, it can be concluded that remarkable inhibition was observed in compounds bearing R= phenyl, 4-carbethoxyphenyl, 4-methoxyphenyl substituents.

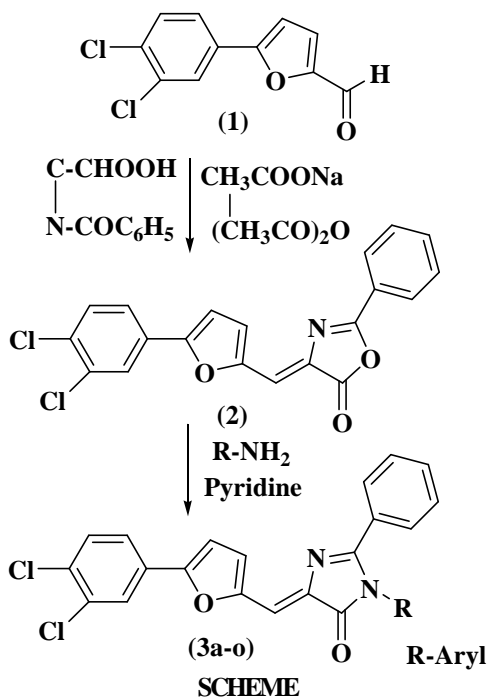
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TABLE 2 : Biological activities of the compounds (3a-o)

| Sr. no. | R | Antimicrobial activity zone of inhibition (mm) | | | Antifungal activity zone of inhibition (mm) | | Antitubercular activity mycobacterium tuberculosis H ₃₇ Rv % inhibition |
|---------|---|--|-----------------|-------------------|---|----------------|--|
| | | <i>B.mega</i> | <i>S.aureus</i> | <i>P.vulgaris</i> | <i>E.coli</i> | <i>A.niger</i> | |
| (3a) | C ₆ H ₅ - | 18 | 15 | 18 | 17 | 13 | 60 |
| (3b) | 4-COOC ₂ H ₅ -C ₆ H ₄ - | 20 | 17 | 16 | 15 | 18 | - |
| (3c) | 3-Cl-C ₆ H ₄ - | 16 | 14 | 14 | 18 | 14 | 46 |
| (3d) | 4-Cl-C ₆ H ₄ - | 17 | 18 | 13 | 13 | 13 | 37 |
| (3e) | 3-Cl,4-F-C ₆ H ₃ - | 16 | 13 | 14 | 19 | 17 | - |
| (3f) | 2,6(Cl) ₂ -C ₆ H ₃ - | 14 | 12 | 12 | 15 | 17 | - |
| (3g) | 2,4(CH ₃) ₂ -C ₆ H ₃ - | 16 | 13 | 13 | 12 | 20 | - |
| (3h) | 4-F-C ₆ H ₄ - | 15 | 15 | 12 | 13 | 17 | - |
| (3i) | 2-OCH ₃ -C ₆ H ₄ - | 17 | 14 | 13 | 13 | 18 | 49 |
| (3j) | 4-OCH ₃ -C ₆ H ₄ - | 19 | 16 | 14 | 15 | 19 | 49 |
| (3k) | 2-CH ₃ -C ₆ H ₄ - | 18 | 17 | 15 | 14 | 15 | - |
| (3l) | 3-CH ₃ -C ₆ H ₄ - | 18 | 12 | 17 | 15 | 14 | - |
| (3m) | 4-CH ₃ -C ₆ H ₄ - | 14 | 15 | 14 | 17 | 13 | - |
| (3n) | 3-NO ₂ -C ₆ H ₄ - | 13 | 14 | 17 | 14 | 15 | 52 |
| (3o) | 4-NO ₂ -C ₆ H ₄ - | 12 | 14 | 13 | 12 | 16 | - |

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ACKNOWLEDGMENTS

The authors are thankful to Dr. A. R. Parikh, Rtd. Professor and Head, Department of Chemistry for providing facilities and to TAACF, Southern Research Institute, USA for antitubercular activity. The authors also wish to thank Dr. P. H. Parsania, Professor and Head, Department of Chemistry for providing necessary support and FIST-DST and UGC-SAP for financial support to the department.