Synthesis, Characterization And Microbial Screening of Oxime And Hydrazone Derivatives of 2,5-Dichloro 3,4-Diformyl (N-substituted Phenyl) Pyroles

A.P. Rajput\textsuperscript{1}, A.R. Kankhare\textsuperscript{2}

\textsuperscript{1} Art’s Science and Commerce College, Bodwad, Dist Jalgaon.
\textsuperscript{2} P. G. Research Centre, Department Of Chemistry

ISSN: 2231-5381  \hspace{1cm} http://www.ijettjournal.org  \hspace{1cm} Page 560

Abstract — Oxime compounds frequently exhibit satisfactory fungicidal & insecticidal activities and many of them have the characteristics of low toxicity and residue. Since 1963, scientists have discovered that Tranid could be used as an agricultural pesticide. Hydrazone derivatives have been demonstrated to possess various pharmacological activities such as antimicrobial, Antitumoral, anticonvulsant, antimicrobial, and antimalarial.

Key Words : Vilsmeier-Haack, succinimides, oximes, hydrazones

Introduction

The design and synthesis of oxime derivatives have been very popular for researchers due to their biological and pharmacological activities. Carboxyamine oxime esters and oxime-phosphates were applied to agriculture as a class of insecticides, including Aldicard, Methomyl, Thiofanox, Alanyacarb, Poxime, Poxime-methyl, Chloropoxime, and U47319. Many synthetic methods of oximes and oxime derivatives have been reported. Most of the compounds bearing chlorine and alkyl groups have good biological activities. Hydrazones possessing an azomethine (\(-\text{NH-N=CH}\)) proton constitute an important class of compounds for new drug development. Hydrazones moieties are also the most important pharmacophoric cores of several anti-inflammatory and antiplatelet activities.

The succinimides were synthesized from succinic acid & substituted aryl amines. The succinimides on diformylation using Vilsmeier-Haack reaction formed 2,5-dichloro-3,4-diformyl (N-substituted phenyl) pyroles. These dichlorodiformyl pyroles having formyl groups & chlorine at ortho position to each other may show promising precursors of other novel pyrrole derivatives, keeping this view in mind we have carried out functional group interconversion of these compounds into oxime and hydrazone derivatives of 2,5-dichloro 3,4-diformyl (N-substituted phenyl) pyroles with the hope to get some biologically active compounds.

Materials & methods:

All melting points were determined in open capillary & are uncorrected. I.R. spectra were recorded on perkin-Elmer spectrum. \(H^1\)NMR were recorded on Bruker DRX 500 mHz. NMR spectrometer with DMSO-d\(_6\) as a solvent using TMS as internal reference. (chemical shift in \(\delta\) ppm).

General procedure for preparation of oxime derivatives of 2,5-dichloro -3,4-diformyl (N-substituted phenyl) pyroles.

To a solution of III (1 mmole) in methanol was added with stirring hydroxyl amine hydrochloride (2.4 mmole) and sodium acetate (2.4 mmole) and stirred at room temperature for another 40-60 minutes. The reaction mixture was then poured on to crushed ice whereupon white precipitate was formed. The product was filtered off, dried and purified by recrystallisation from aq. ethanol to form oxime derivatives of 2,5-dichloro -3,4-diformyl (N-substituted phenyl) pyroles.

\textbf{(IVa)}  (E)-(2,5-dichloro-1-phenyl-1H-pyrrole-3,4-diyl) bis (N-hydroxy methanimine).

Mol. formula : \(C_{12}H_{20}O_2N_3Cl_2\)

Physical nature : yellowish

Yield (%) : 85 %  M.P : 40-42\(^\circ\)C

Wt : 298

IR (KBr) cm\(^{-1}\) : 3400 (OH), 1654 (> C=N ).

\(H^1\)NMR (300MHz, DMSO-d\(_6\), \(\delta\) ppm) : 7.54-7 (m, 4H, Ar), 8.07 (s, 2H, 2CH=N), 8.98 (s, 2H, 2OH).

\(C^{13}\)NMR : 148 (> C=N), 119 (C-Cl), 121-129 (ArC-H).


\textbf{(IVb)} (E)-(2,5-dichloro-1-(4-chloro phenyl)-1H-pyrrole-3,4-diyl) bis(N-hydroxy methanimine).

Mol. formula : \(C_{12}H_{20}O_2N_3Cl_3\)

Physical nature : yellowish

Yield (%) : 80 %  M.P : 115-117\(^\circ\)C

Wt : 332.5

IR (KBr) cm\(^{-1}\) : 3309 (OH), 1658 (> C=N ).

\(H^1\)NMR (300MHz, DMSO-d\(_6\), \(\delta\) ppm) : 6.70-7.05 (m, 4H, Ar), 8.20 (s, 2H, 2CH=N), 8.90 (s, 2H, 2OH).
C\textsuperscript{13}NMR : 145 (\textsuperscript{13}C=N), 120 (\text{-Cl}), 120-130 (Ar C-H).


(IVc) (E)-[2,5-dichloro-1-(3-chloro phenyl)-1H-pyrrole-3,4-diy] bis(N-hydroxy methanimine).
Mol. formula : C\textsubscript{12}H\textsubscript{2}O\textsubscript{2}N\textsubscript{2}Cl\textsubscript{3} Physical nature : Brownish
Yield (%) : 75 % M.P : 130-134 \degree\text{C} Mol. Wt : 322.5
IR (KB)cm\textsuperscript{-1} : 3333 (-OH), 1614 (>C=N). H\textsuperscript{1}NMR (300MHz, DMSO-d\textsubscript{6}, \textit{\delta} ppm) : 7.44-7.20 (m, 4H, Ar-H), 8.30 (s, 2H, 2CH=N), 10.25 (s, 2H, 2OH). C\textsuperscript{13}NMR : 145 (>C=N), 120 (C-Cl), 120-130 (Ar C-H).


(IVd) (E)-[2,5-dichloro-1-(3-methoxy phenyl)-1H-pyrrole-3,4-diy] bis(N-hydroxy methanimine).
Mol. Formula : C\textsubscript{12}H\textsubscript{11}O\textsubscript{2}N\textsubscript{2}Cl\textsubscript{2} Physical nature : whitish
Yield (%) : 70 % M.P : 135-137\degree\text{C} Mol. Wt : 328
IR (KB)cm\textsuperscript{-1} : 3410 (-OH), 1651 (-C=N). H\textsuperscript{1}NMR (300MHz, DMSO-d\textsubscript{6}, \textit{\delta} ppm) : 7.58-7 (m, 4H, Ar-H), 8.19 (s, 2H, 2CH=N), 10.19 (s, 2H, 2OH). C\textsuperscript{13}NMR : 144 (>C=N), 128 (-Cl), 130-135 (Ar C-H).


(IVe) (E)-[2,5-dichloro-1-(4-methyl phenyl)-1H-pyrrole-3,4-diy] bis(N-hydroxy methanimine).
Mol. Formula : C\textsubscript{12}H\textsubscript{12}O\textsubscript{2}N\textsubscript{2}Cl\textsubscript{2} Physical nature : Grayish
Yield (%) : 72 % M.P : 110-112\degree\text{C} Mol. Wt : 312
IR (KB)cm\textsuperscript{-1} : 3430 (OH), 1640 (>C=N). H\textsuperscript{1}NMR (300MHz, DMSO-d\textsubscript{6}, \textit{\delta} ppm) : 7.55-7 (m, 4H, Ar-H), 8.23 (s, 2H, 2CH=N), 10.22 (s, 2H, 2OH). C\textsuperscript{13}NMR : 149 (>C=N), 122 (C-Cl), 123-133 (Ar C-H).


(IVf) (E)-[2,5-dichloro-1-(naphthalene-1-yl)-1H-pyrrole-3,4-diy] bis(N-hydroxy methanimine).
Mol. formula : C\textsubscript{22}H\textsubscript{15}O\textsubscript{2}N\textsubscript{2}Cl\textsubscript{2} Physical nature : Grayish
Yield (%) : 72 % M.P : 150-154\degree\text{C} Mol. Wt : 424
H\textsuperscript{1}NMR (300MHz,DMSO-d\textsubscript{6}, \textit{\delta} ppm) : 7.64-7 (m, 4H, Ar-H), 8.13 (s, 2H, 2CH=N), 10.14 (s, 2H, 2OH). C\textsuperscript{13}NMR : 155 (>C=N), 129 (C-Cl), 140-145 (Ar C-H).


General procedure for preparation of Hydrazone derivatives of 2,5-dichloro-3,4-difomyl (N-substituted phenyl) pyroles.

To a solution of III (1 mmole) in ethanol (5 ml) was added with stirring hydrazine hydrate (4 mmole, 99-100%) and the mixture was refluxed for 30-40 minutes. On cooling at room temperature, the reaction mixture was poured on to crushed ice whereupon yellow crystalline mass of the product which precipitated out was filtered off, washed with cold ethanol and water, dried and purified by recrystallisation from aq. Ethanol to give pure compounds Va-e.

(Va) 2,5-dichloro-3,4- bis [(E)hydrazinylidenemethyl]-1-(phenyl)-1H-pyrole.
Mol. formula : C\textsubscript{12}H\textsubscript{11}N\textsubscript{2}Cl\textsubscript{2} Physical nature : Yellowish
Yield (%) : 70 % M.P : 180-182 \degree\text{C} Mol. Wt : 296
IR (KB)cm\textsuperscript{-1} : 3335 (NH), 1600 (>C=N). H\textsuperscript{1}NMR (300MHz, DMSO-d\textsubscript{6}, \textit{\delta} ppm) : 7.54-7 (m, 4H, Ar-H), 8.30 (s, 2H, 2CH=N), 9.92 (s, 4H, 2NH\textsubscript{2}). C\textsuperscript{13}NMR : 143 (>C=N), 119 (-Cl), 121-129 (Ar C-H).


(Vb) 2,5-dichloro-3,4-bis(E)-hydrazinylidenemethyl]-1-(4-chlorophenyl)-1H-pyrole.
Mol. formula : C\textsubscript{12}H\textsubscript{10}N\textsubscript{2}Cl\textsubscript{3} Physical nature : whitish
Yield (%) : 70 % M.P : 145-147\degree\text{C} Mol. Wt : 330.5
IR (KB)cm\textsuperscript{-1} : 3330 (NH), 1610 (>C=N). H\textsuperscript{1}NMR (300MHz, DMSO-d\textsubscript{6}, \textit{\delta} ppm) : 7.74-7 (m, 4H, Ar-H), 8.40 (s, 2H, 2CH=N), 9.90 (s, 4H, 2NH\textsubscript{2}). C\textsuperscript{13}NMR : 148 (>C=N), 120 (C-Cl), 125-130 (Ar C-H).


(Vc) 2,5-dichloro-3,4-bis(E)-hydrazinylidenemethyl]-1-(3-chlorophenyl)-1H-pyrole.
Mol. formula : C\textsubscript{12}H\textsubscript{10}N\textsubscript{2}Cl\textsubscript{3} Physical nature : whitish
Yield (%) : 75 % M.P : 140-142\degree\text{C} Mol. Wt : 330.5
IR (KB)cm\textsuperscript{-1} : 3320 (NH), 1620 (>C=N). H\textsuperscript{1}NMR (300MHz, DMSO-d\textsubscript{6}, \textit{\delta} ppm) : 7.80-7 (m, 4H, Ar-H), 8.30 (s, 2H, 2CH=N), 9.88 (s, 4H, 2NH\textsubscript{2}). C\textsuperscript{13}NMR : 143 (>C=N), 119 (C-Cl), 121-129 (Ar C-H).

(Vd) 2,5-dichloro-3,4-bis(E)-hydrazinylidenemethyl]-1-(3-methoxyphenyl)-1H-pyrrole.

Mol. formula: C_{13}H_{13}ON_{6}Cl_{2}. Physical nature: whitish
Yield (%): 78 % M.P: 115-118°C Mol. Wt: 326
IR (KBr)cm⁻¹: 3330 (NH), 1610 (>C=N).
H¹NMR (300MHz, DMSO-d₆, δ ppm): 7.78-7 (m, 4H, Ar-H), 8.40 (s, 2H, 2CH=N), 9.90 (s, 4H, 2NH₂).
C¹³NMR: 140 (>C=N), 121 (C-Cl), 125-135 (Ar C-H).


Table 1 Shows physical data of compounds

<table>
<thead>
<tr>
<th>comp</th>
<th>R</th>
<th>M.F.</th>
<th>M.P(°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVa</td>
<td>-H</td>
<td>C_{12}H_{12}O_{2}N_{6}Cl_{2}</td>
<td>40-42</td>
<td>85</td>
</tr>
<tr>
<td>IVb</td>
<td>4-Cl</td>
<td>C_{12}H_{12}O_{2}N_{6}Cl_{3}</td>
<td>115-117</td>
<td>80</td>
</tr>
<tr>
<td>IVc</td>
<td>3-Cl</td>
<td>C_{12}H_{12}O_{2}N_{6}Cl_{3}</td>
<td>130-134</td>
<td>75</td>
</tr>
<tr>
<td>IVd</td>
<td>3-OCH₃</td>
<td>C_{13}H_{13}O_{2}N_{6}Cl_{2}</td>
<td>135-137</td>
<td>70</td>
</tr>
<tr>
<td>IVe</td>
<td>4-CH₃</td>
<td>C_{13}H_{13}O_{2}N_{6}Cl_{2}</td>
<td>110-112</td>
<td>72</td>
</tr>
<tr>
<td>IVf</td>
<td>Ar-CH</td>
<td>C_{13}H_{13}O_{2}N_{6}Cl_{2}</td>
<td>150-154</td>
<td>72</td>
</tr>
<tr>
<td>Va</td>
<td>-H</td>
<td>C_{12}H_{12}N_{6}Cl_{2}</td>
<td>180-182</td>
<td>70</td>
</tr>
<tr>
<td>Vb</td>
<td>4-Cl</td>
<td>C_{12}H_{10}N_{6}Cl_{3}</td>
<td>145-147</td>
<td>70</td>
</tr>
<tr>
<td>Vc</td>
<td>3-Cl</td>
<td>C_{12}H_{10}N_{6}Cl_{3}</td>
<td>140-142</td>
<td>75</td>
</tr>
<tr>
<td>Vd</td>
<td>3-OCH₃</td>
<td>C_{13}H_{13}O_{2}N_{6}Cl_{2}</td>
<td>115-118</td>
<td>78</td>
</tr>
<tr>
<td>Ve</td>
<td>4-CH₃</td>
<td>C_{13}H_{13}N_{6}Cl_{2}</td>
<td>170-172</td>
<td>80</td>
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</table>

Table 1 Shows physical data of compounds

<table>
<thead>
<tr>
<th>Culture name</th>
<th>Culture code</th>
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<tbody>
<tr>
<td>EC</td>
<td>Escherichia coli</td>
</tr>
<tr>
<td>PA</td>
<td>Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>SA</td>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>BS</td>
<td>Bacillus subtilis</td>
</tr>
<tr>
<td>AN</td>
<td>Aspergillus niger</td>
</tr>
</tbody>
</table>

Media used
For bacteria: Nutrient agar (Hi-media)
For yeast: MGYP
Inoculum size: 1 x 10 bacteria per ml.

 Yeast: 1 x 10 cells per ml.
 Concentration of compound:
(Prepared in ethanol) 100 μ gm 1 disc

method used
“___” means no zone of inhibition.

(Biological Testing of compounds)
Heterocyclic oxime and hydrazine compounds were evaluated for antibacterial against Escherichia coli (Ec), pseudoma S. aeruginosa (PA), staphylococcus aureus (SA), Bacillus subtilis (BS), and antifungal against candida albicans (CA), Asperginus niger (AN).

The result were obtained in the form of clearing zone and were recorded after the period of incubation (37°C for 24 hrs). The zone of inhibition was measured in mm and data is presented in table 2

<table>
<thead>
<tr>
<th>Sr</th>
<th>compound</th>
<th>EC</th>
<th>PA</th>
<th>SA</th>
<th>BS</th>
<th>CA</th>
<th>AN</th>
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<tbody>
<tr>
<td>1</td>
<td>IVa</td>
<td>23.9</td>
<td>22.2</td>
<td>24.0</td>
<td>21.23</td>
<td>-</td>
<td>-</td>
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<tr>
<td>2</td>
<td>IVb</td>
<td>13.4</td>
<td>12.5</td>
<td>17.9</td>
<td>15.56</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>IVc</td>
<td>10.4</td>
<td>9.48</td>
<td>10.7</td>
<td>10.12</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>IVd</td>
<td>14.6</td>
<td>11.2</td>
<td>11.3</td>
<td>11.22</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>IVe</td>
<td>10.1</td>
<td>11.1</td>
<td>8.94</td>
<td>11.24</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>IVf</td>
<td>8.81</td>
<td>9.16</td>
<td>9.50</td>
<td>10.11</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Va</td>
<td>10.2</td>
<td>9.13</td>
<td>9.24</td>
<td>9.68</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Vb</td>
<td>10.1</td>
<td>11.1</td>
<td>8.76</td>
<td>10.47</td>
<td>-</td>
<td>-</td>
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<tr>
<td>9</td>
<td>Vc</td>
<td>12.2</td>
<td>11.1</td>
<td>9.06</td>
<td>13.30</td>
<td>-</td>
<td>-</td>
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<tr>
<td>10</td>
<td>Vd</td>
<td>10.1</td>
<td>11.0</td>
<td>11.0</td>
<td>10.12</td>
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<td>-</td>
</tr>
<tr>
<td>11</td>
<td>Ve</td>
<td>12.1</td>
<td>10.1</td>
<td>10.2</td>
<td>13.60</td>
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<td>12</td>
<td>Chloramphenicol</td>
<td>28.6</td>
<td>24.4</td>
<td>27.6</td>
<td>26.30</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>13</td>
<td>Ciprofloxacin</td>
<td>21.1</td>
<td>22.2</td>
<td>23.3</td>
<td>21.23</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
Conclusion:

In the above research work we conclude that, the synthesized oxime and hydrazone compounds possess good yield. Compound IVa is found to be more antibacterial against EC, PA, SA and BS as compared to standard drug. Compound IVb is moderate in antibacterial activity against all the strains used for testing. All the compounds are characterized by IR, C\textsuperscript{13}NMR, H\textsuperscript{1}NMR, Mass etc. analytical methods.

Acknowledgment:

This work was supported by the Principal, JET’s Z.B. Patil College, Dhule. Spectroscopic data were obtained from University of Pune. Antimicrobial activity data were obtained from R.C.Patel College, Shirpur

Graph-2: Comparative antimicrobial activities for compounds (Va-e)