Synthesis of New Some Imidazole Derivatives Containing β-Lactam Ring

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Abstract

In this work 5-methylene-yl - (2-methy –oxazole-4-one) (1H) imidazole (1) were synthesized from the reaction of L-Histidine with acetic anhydride and which converted to the of 5-methylene-yl-(2-methyl 3-amino imidazole-4-one)-1H-imidazole (2) by reaction with hydrazine hydrate. Schiff bases (3-6) were synthesized from the reaction of compound (2) with different aromatic aldehyde. Reaction of compounds (3-6) with chloroacetyl chloride gives azetidinone derivatives (7-10). These compounds were characterized by FT-IR and some of them with 1H-NMR and 13C-NMR spectroscopy.

Key words: L-Histidine, Schiff base, Imidazole.

Introduction:

Imidazole is an organic aromatic compound with formula C₃H₄N₂. Many drugs contain an imidazole ring such as antifungal drugs and nitroimidazole [1]. Nitrogen bridge head-fused heterocyclics which contain an imidazole ring are common structural motifs in pharmacologically important molecules, with activities spanning a diverse range of target [2]. The imidazole nucleus appears in a number of naturally occurring product like the amino acid histidine and purines which comprise many of the most important bases in nucleic acid [3]. The most important four-member system is undoubtedly the azetidin-2-one, also called β-lactam. β- lactam containing compounds have a wide spectrum antibiotic which found in natural and synthetic compounds, such as penicillin, cephalosporin, carbaphenems, and monobactams [4,5]. The chemistry of carbon – nitrogen double bond plays a vital role in the progresses of chemistry science [6]. Schiff bases can be synthesized by several methods but the most common method is the original reaction of an aromatic amines and carbonyl compounds by nucleophilic reaction with dehydration to generate imine [7,8]. They have been used as
analgesic, pain growth regulator [9, 10], antitumor, and other biological activities [11, 12]. In this work, we reported synthesis of some new imidazole derivatives containing β-lactam ring starting from amino acid histidine.

Materials and Methods
Melting point was determined in open capillary tubes on Gallenkamp melting point apparatus and was uncorrected. FT-IR spectra were recorded on SHIMADZU FT-IR -8400 Fourier Transform Infrared spectrophotometer as KBR disk. 1HNMR and 13CNMR spectra were recorded on Bruker 300MHz, instrument using TMS as internal reference and DMSO-d6 as a solvent in Jordon.

Synthesis of 5-methylene-yl - (2-methyloxazole-4-one) (1H) imidazole (1) [3]
A mixture of amino acid (L-Histidine) (1g, 0.0064 mole) and (2 ml, 0.0021 mole) acetic anhydride was refluxed for 3 hrs. Excess of acetic anhydride was neutralized with sodium bicarbonate then with water and dried over CaCO3 then evaporated. An oily Brown color was obtained. (Yield 61%).

Synthesis of 5-methylene-yl-(2-methyl 3-aminoimidazole-4-one)-1H-imidazole (2) [3]
To a solution of compound [1] (2g, 0.01 mole) in absolute ethanol (15 ml), hydrazine (15 ml, 99%) was added. The mixture was refluxed for 7 hrs. The solvent was removed and slurry product was collected from methanol. (Yield 69%).

Table (1) lists physical properties and FT-IR spectral data of compounds (1) and (2).

Synthesis of Schiff bases (3-6) [13]
A mixture of hydrazine derivatives (0.01 mole) and substituted aldehyde (0.01 mole) was dissolved in 15 ml absolute ethanol and few drops of glacial acetic acid were added. The mixture was refluxed for 3 hrs. The separated solid was filtered, and then recrystallized from suitable solvent ethanol: water (7:3).

Table (2) lists physical properties and FT-IR spectral data of Schiff bases (3-6).

Synthesis of azetidinone(7-10) [3]
A mixture of Schiff bases (0.00055 mole) and tri ethylamines (0.0011 mole) were dissolved in 1, 4-dioxane (10 ml) cooled and stirred. To this well-stirred cooled solution chloroacetyl chloride (0.0022 mole) was added drop wise for period 15 min at zero temperature. The reaction mixture was stirred for addition 3-6 hrs. And left at room temperature for 48 hrs.

Table (3) lists physical properties and FT-IR spectral data of compounds (7-10).

Results and Discussion
To obtain our target, the β-lactam cycle containing two imidazole ring, the amino acid L-histidine was chosen as starting material. The multistep synthetic route to these compounds are given in scheme (1).
Scheme (1): Synthetic route for synthesis imidazole derivatives

The first step includes synthesis of compound (1) from the cyclization reaction between L-histidine and acetic anhydride. The mechanism of this reaction was started with nucleophilic attack of amino group on carbonyl carbon according the following mechanism, as shown in scheme (2):

Scheme (2): Mechanism for synthesis of compound (1)
The second step includes synthesis of compound (2) the nucleophilic attack of hydrazine hydrate with compound (1), then compound (2) was introduced in reaction with substituted aromatic aldehyde in the third step to form Schiff's bases (3-6). The mechanism of Schiff base was started by nucleophilic attack on carbonyl by the lone-pair electron of amine gives a dipolar tetrahedral intermediate. Then a proton transferred from nitrogen to oxygen yielding a carbinolamine, which after protonation and dehydration gives an iminium ion. Losing hydride ion from nitrogen leading to form an imine as shown in scheme (3):

**Scheme (3): Mechanism for synthesis Schiff base**

The fourth step includes synthesis of compounds (7-10) from the reaction of compounds (3-6) with chloroacetyl chloride through addition cyclization reaction, yielding β-lactam ring according to the short mechanism in scheme (4).

**Scheme (4): Mechanism for β-lactam formation**

The percentage yield of the prepared Schiff's bases were in the range of {21-54} percent it was noticeable presence of electron with drawing substituent in aromatic ring caused increasing of yield percent of the prepared compounds. The percentage yield of the prepared compounds (7-10) was in the range of {23-96} percent. These compounds were identified by FT-IR and some of them with $^1$H-NMRand $^{13}$C-NMR spectroscopy.

FT-IR spectra of compound (1) and (2) shows clear absorption bands at (3441-3400) cm$^{-1}$, (1720-1690) cm$^{-1}$, (1647-1620) cm$^{-1}$ and (1373-1385) cm$^{-1}$ due to $\nu$(N-H), $\nu$, $\nu$(C=O) , $\nu$(C=C) aromatic and $\nu$(C-N) respectively. While FT-IR spectra of Schiff's bases (3-6) shows clear absorption bands at (1633-1728) cm$^{-1}$, (1342-1344) cm$^{-1}$ and (1568-1614) cm$^{-1}$ due to $\nu$(C=O), $\nu$(C-N) and $\nu$(C=N) respectively.
Figure (2) shows FT-IR spectrum of compound (5). Compounds (4) Figure (1) and (6) shows in addition to the above absorptions a stretching band at (1317 - 1402) cm⁻¹ and at (3126) cm⁻¹ due to ν (NO₂) and δ (OH) respectively.

FT-IR spectra of compounds (7-10) showed clear absorption bands at (3427-3481) cm⁻¹, (1636-1647) cm⁻¹, (1336-1398) cm⁻¹, (1608-1581) cm⁻¹ and (628-817) cm⁻¹ due to ν (N-H), ν (C=O), ν (C=N), ν (C-N) and ν (C-Cl) respectively[14,15].

Table (3) shows physical properties and FT-IR spectral data of compounds (3-6).

¹H-NMR spectra of compound (3) showed singlet signals at (1.2) ppm and (6.5) ppm due to (⁻³CH₃) and (⁻⁴CH⁻) group respectively, triplet signals at (3-3.5) ppm due to (⁻²CH⁻), doublet signals at (2-2.2) ppm due to (⁻¹CH₂⁻), multiplet signals at (7-8.81) ppm due to aromatic protons, singlet signal at (4) ppm due to OH and singlet signal at (11.2) ppm due to aromatic amine (tautomerism).

¹H-NMR spectra of compound (8) showed singlet signals at (9.9) and (1) ppm due to (⁻³CH₃) and (⁻⁵CH⁻) group respectively, triplet signals at (2.7-2.8) ppm due to (⁻²CH⁻), doublet signals at (3.2) ppm due to (⁻¹CH₂⁻), singlet signal at 4ppm due to (⁻¹CH=Cl) and multiplet signals at (7-8.5) ppm due to aromatic protons and NH group.

¹H-NMR spectra of compound (9) showed singlet signals at (1.1) (1.2) and (1.3) ppm due to (⁻³CH₃), (⁻⁶,⁻⁷CH₃ and (⁻⁵CH⁻) group respectively, triplet signals at (2-3) ppm due to (⁻²CH⁻), doublet signals at (3-3.2) ppm due to (⁻¹CH₂⁻), singlet signal at (4) ppm due to (⁻¹CH=Cl) and multiplet signals at (7-8.6) ppm due to aromatic protons and NH group. Finally, ¹H-NMR spectra of compound (10) Figure (3) shows singlet signals at 0.9 and 1.6 ppm due to (⁻³CH₃ and (⁻⁵CH⁻) group respectively, triplet signals at (2.2-3) ppm due to (⁻²CH⁻), doublet signals at (3.1-3.9) ppm due to (⁻¹CH₂⁻), singlet signal at (4) ppm due to (⁻¹CH=Cl), multiplet signals at (6.5-8.5) ppm due to aromatic protons and NH group and singlet signal at (10.1) ppm due to aromatic (O-H)[14,15].

Table (4) shows ¹H-NMR spectral data for some of the prepared compounds.

¹³C-NMR spectra of compound (3) Figure (4) shows signal at (20.1) ppm due to (⁻³CH₃), signal at (45.3) ppm due to (⁻²CH⁻), signal at (26.4) ppm due to (⁻¹CH₂⁻), signal at (52) ppm due to C=N oxazoline (116.2) ppm due to (⁻¹CH⁻), to signals at (126-145) ppm due to aromatic carbons, signal at (161.3) ppm due to C=N imine and signal at (171.8) ppm due to C=O imide.

¹³C-NMR spectra of compound (8) showed signal at (8) ppm due to (⁻³CH₃), signal at (26) ppm due to (⁻²CH⁻), signal at (40) ppm due to C-Cl, signal at (51) ppm due to (⁻¹CH₂⁻), signals at (51) ppm due to (⁻¹CH⁻), signals at (120-140) ppm due to aromatic carbons and signals at (169) ppm due to C=O imide.

¹³C-NMR spectra of compound (9) showed signal at (8) ppm due to (⁻³CH₃), (⁻⁶,⁻⁷CH₃ and (⁻⁵CH⁻), signal at (25) ppm due to (⁻²CH⁻), signal at (40) ppm due to C=Cl, signal at (51) ppm due to (⁻¹CH₂⁻), signals at (40.3) ppm due to (⁻⁵CH⁻), signals at (128-134) ppm due to aromatic carbons and signals at (169) ppm due to C=O imide.

Finally, ¹³C-NMR spectra of compound (10) showed signal at (8) ppm due to (⁻³CH₃), signal at (38) ppm due to (⁻²CH⁻), signal at (40) ppm due to C-Cl, signal at (45) ppm due to (⁻¹CH₂⁻), signals at (41) ppm due to (⁻¹CH⁻), signals at (117-131) ppm due to aromatic carbons and signals at (170) ppm due to C=O imide[14,15].

Table (5) shows ¹³C-NMR spectral data for some of the prepared compounds.
Table (1): Physical properties and FTIR spectral data of compounds (1) and (2)

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Compd. structure</th>
<th>M.P °C</th>
<th>Yield %</th>
<th>color</th>
<th>Major FTIR absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C=O</td>
</tr>
<tr>
<td>1</td>
<td><img src="image1" alt="Compound 1" /></td>
<td>syrup</td>
<td>61</td>
<td>Brown</td>
<td>1720</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Compound 2" /></td>
<td>syrup</td>
<td>69</td>
<td>Off white</td>
<td>1690</td>
</tr>
</tbody>
</table>

Table (2): Physical properties and FTIR spectral data of compounds (3-6)

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Compd. structure</th>
<th>M.P °C</th>
<th>Yield %</th>
<th>Color</th>
<th>Major FTIR absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C=O</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Compound 3" /></td>
<td>198-200</td>
<td>21</td>
<td>White</td>
<td>1633</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Compound 4" /></td>
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<td>Yellow</td>
<td>1633</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Compound 5" /></td>
<td>210-212</td>
<td>21</td>
<td>Deep Yellow</td>
<td>1728</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Compound 6" /></td>
<td>248-250</td>
<td>22</td>
<td>Gray</td>
<td>1631</td>
</tr>
</tbody>
</table>

Fig. (1): FTIR spectrum of compound (4)
Table (3): Physical properties and FTIR spectral data of compounds (7-10)

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Compd. structure</th>
<th>M.P °C</th>
<th>Yield %</th>
<th>color</th>
<th>Major FTIR absorption C=O C-N C=O N-H C-Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td><img src="image" alt="Structure" /></td>
<td>168-170</td>
<td>40</td>
<td>White</td>
<td>1639 1336 1581 3427 696</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Structure" /></td>
<td>180-182</td>
<td>23</td>
<td>Yellow</td>
<td>1636 1398 1608 3438 628</td>
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<tr>
<td>9</td>
<td><img src="image" alt="Structure" /></td>
<td>192-194</td>
<td>96</td>
<td>Red</td>
<td>1647 1371 1527 3429 817</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="Structure" /></td>
<td>160=162</td>
<td>60</td>
<td>White</td>
<td>1639 1336 1579 3481 696</td>
</tr>
</tbody>
</table>

Table (4): $^1$HNMR spectral data of compounds (3 and 8-10)

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Compound structure</th>
<th>$^1$HNMR spectral data</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td><img src="image" alt="Structure" /></td>
<td>$\delta=1.2$ ppm $^2$CH$_3$, $\delta=6.5$ ppm $^4$CH$_2$, $\delta=(3.3.15)$ ppm $^3$CH , $\delta=(2.2.2)$ ppm $^5$CH$_2$ and $\delta=(7.8.81)$ ppm aromatic protons, 4ppm OH and 11.2 ppm aromatic amine.</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Structure" /></td>
<td>$\delta=0.9$ 1 ppm $^2$CH$_3$, $\delta=1$ ppm $^4$CH$_2$, $\delta=(2.7-2.8)$ ppm $^3$CH , $\delta=(3.2)$ ppm $^5$CH$_2$, $\delta=4$ppm $^6$CH-Cl and $\delta=(7.8.5)$ ppm aromatic protons and NH group.</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Structure" /></td>
<td>$\delta=1.1$, 1.2 and 1.3 ppm $^2$CH$_3$, $^5$CH$_3$ and $^4$CH- , $\delta=(2-3)$ ppm $^3$CH , $\delta=(3-3.2)$ ppm $^5$CH$_2$, $\delta=4$ppm $^6$CH-Cl and $\delta=(7.8.6)$ ppm aromatic protons and NH group</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="Structure" /></td>
<td>$\delta=0.9$ and 1.6 ppm $^2$CH$_3$ and $^4$CH$_2$ group respectively, $\delta=(2.2-3)$ ppm $^3$CH , $\delta=(3.1-3.9)$ ppm $^5$CH$_2$, $\delta=4$ppm $^6$CH-Cl, $\delta=(6.5-8.5)$ ppm aromatic protons and NH group and $\delta=10.1$ ppm aromatic OH</td>
</tr>
</tbody>
</table>
Fig. (3): $^1$HNMR spectrum of compound (10)

Table (5): $^{13}$C-NMR spectral data of compounds (3 and 8-10)

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Compound structure</th>
<th>$^{13}$C-NMR spectral data</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td><img src="image" alt="Structure 3" /></td>
<td>δ= 20.1 ppm $^2$CH$_3$, δ= 45.3 ppm $^3$CH$_2$, δ= 26.4 ppm $^4$CH$_3$, 52 ppm C=N oxazoline, 116.2 ppm $^5$CH$_2$, δ= 126-145 ppm aromatic carbons, 161.3 ppm C=N imine and δ= 171.8 ppm C=O imide.</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Structure 8" /></td>
<td>δ= 8 ppm $^1$CH$_3$, δ= 26 ppm $^2$CH$_2$, δ= 40 ppm C-Cl, δ= 45 ppm $^3$CH$_2$, δ= 51 ppm $^4$CH$_2$, δ= 120-140 ppm aromatic carbons and δ= 169 ppm C=O imide.</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Structure 9" /></td>
<td>δ= 8 ppm $^1$CH$_3$, $^3$CH$_3$ and $^4$CH$_2$, δ= 25 ppm $^2$CH$_2$, δ= 40 ppm C-Cl, 51 ppm due to $^3$CH$_2$, δ= 40.3 ppm $^5$CH$_2$, δ= 128-134 ppm aromatic carbons and δ= 169 ppm C=O imide.</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="Structure 10" /></td>
<td>δ= 8 ppm $^1$CH$_3$, δ= 38 ppm $^2$CH$_2$, δ= 40 ppm C-Cl, δ= 45 ppm $^3$CH$_2$, δ= 41 ppm $^4$CH$_3$, δ= 117-131 ppm aromatic carbons and δ= 170 ppm due to C=O imide.</td>
</tr>
</tbody>
</table>
Fig. (4): $^{13}$C-NMR spectrum of compound (3).

References


تحضير بعض مشتقات الأميدازول الجديدة التي تحتوي حلقة β-لاكتام

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الخلاصة

في هذا البحث تم تحضير 3- ميثيلين-2-(2-مثيل اوكسازول -3-ون)-1-ايميدازول (1) من تفاعل ل-هستدين مع حامض الخليك الالاماني والذي تم تحويله الى 5- ميثيلين-1-(2-ميثيل-3-أمينو اميدازول-3-ون)-1-ايميدازول (2) عن طريق التفاعل مع هيدرات الهيدرازين. تم تحضير قواعد شيف (3-6) من تفاعل المركب (2) مع مالديهيدات أروماتية مختلفة. تم الحصول على مركبات ازيتيدين نوع مختلف (7-10) من تفاعل قواعد شيف المحضرة (3-6) مع كلوريد الكلرواسيتيل. شُخصت المركبات المحضرة بواسطة FT-IR وبعضها بـ $^{13}$C-NMR وبعضها بالمطياف H-NMR

الكلمات المفتاحية: ل- هستدين ، قواعد شيف ، ايميدازول