Synthesis of New Schiff’s Bases Derived from 4-Phthalimidyl Acetophenone

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Abstract
Eight new Schiff’s bases were prepared in three steps. The first step includes synthesis of phthalamic acid from the reaction between phthalic anhydride with p-amino acetophenone which in turn fused in the second step to form the corresponding phthalimide. The third step involved condensation of the prepared phthalimide with different primary aromatic amines to form new Schiff’s bases. These compounds were characterized by FT-IR, $^1$H-NMR and $^{13}$C-NMR spectroscopy. Most of the synthesized compounds have been screened for their antimicrobial activities by using agar cup plate method against two types of bacteria. The results showed that the new Schiff’s bases exhibit good to moderate antibacterial activity.

Keywords: Schiff’s bases, amic acid, imide, biological activity.

Introduction
The chemistry of the carbon –nitrogen double bond plays a vital role in progresses of chemistry Science[1]. Schiff's bases can be synthesized from an aromatic amines and carbonyl compounds by nucleophilic addition forming a hemiaminal followed by dehydration to generate imine. They are well known intermediates for the preparation of azeindines, thiazolidinones, oxadiazelines and many other derivatives [2,3]. They have been used as analgestic, anthelmintic, antitubercular, plant growth regulator, antiviral and antitumor [4,5]. In this work a series of new Schiff’s bases derived from 4-phthalimidyl acetophenone were prepared, characterized and their antimicrobial activity were studied.

Experimental
Melting points were determined in Gallen Kamp melting point apparatus and were uncorrected. FTIR spectra were recorded on SHIMADZU FTIR - 8400 Fourier Transform Infrared spectrophotometer as KBr disc. $^1$HNMR and C$^{13}$NMR spectra were recorded on Bruker spectrospin ultra shield magnets 300 MHz instrument using tetramethyl silane (TMS) as an internal standard and DMSO-d$_6$ as a solvent in Ahl-Albate University in Jordan.

1. Preparation Of Phthalamic Acid (1) [6]
(0.01 mol) 1.4g of phthalic anhydride was dissolved in (10 mL) of acetone in a suitable round bottomed flask fitted with dropping funnel. The dropping funnel was supplied with (0.01 mol) 1.37 g of p-amino acetophenone dissolved in (10 mL) of acetone then this solution was added to the mixture dropwise with stirring for 1 hr at room temperature. The formed precipitate was filtered off then recrystallized from ethanol.

2. Preparation of Phthalimide (2) [7]
(0.01 mol) of amic acid (1) was placed in a wide dry pyrex tube which was immersed in an oil bath and provided with a thermometer. The oil bath was heated until fusion of amic acid then thermometer was maintained at ten –degrees above the melting point of amic acid for 45 min. The resulted fused material was cooled. The formed solid was recrystallized from hexane.

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

Preparation of Schiff’s Bases (3-10) [2]
A mixture of phthalimide (2) (0.0006 mol) and substituted aniline (0.0006 mol) was dissolved in absolute ethanol (10 mL) and few drops of glacial acetic acid were added. The mixture was refluxed for 4hrs on water bath then was poured into crushed ice with stirring. The separated solid was filtered, then recrystallized from suitable solvent.

Table (2) lists physical properties and FT-IR spectral data of Schiff’s bases (3-10).
4. Biological Activity [8]

Most of the synthesized compounds were tested for their biological activity by the agar cup plate method. The organism used were *Staphylococcus aureus* as gram positive bacteria and *Pseudomonas aeruginosa* as gram negative bacteria and dimethyl sulphoxide was used as sample solution. Using sterilized cork borer cups were scooped out of agar medium contained in a Petri dish which was previously inoculated with the microorganisms. The test compound solution (0.1 mL) was added in the cups and the Petri dishes were subsequently incubated at 37 °C for 48 hrs. Zones of inhibition produced by each compound was measured in mm and the results are listed in Table (5).

**Results and Discussion**

New eight Schiff's bases were synthesized from the reaction of phthalimide (2) with substituted anilines as shown in Scheme (1). These Schiff's bases posses good biological activities.

![Scheme (1).](image-url)
The first step includes synthesis of phthalamic acid from the reaction between phthalic anhydride and p-amino acetophenone. The second step includes synthesis of phthalimides via fusion of phthalamic acid, then the prepared imide was introduced in reaction with substituted anilines to form Schiff's bases. The % Yield of the prepared Schiff's bases were in the range (30-93) % suggesting the presence of electron with drawing constituents in aromatic ring caused increasing of yield percent of the prepared compounds.

These compounds were identified by FT-IR, $^1H$-NMR and $^{13}$C-NMR spectroscopy.

FT-IR spectrum of compound (1) showed clear absorption bands at (3326) Cm$^{-1}$, (3047) Cm$^{-1}$, (1704) Cm$^{-1}$, (1674) Cm$^{-1}$, (1589) Cm$^{-1}$ and (1326) Cm$^{-1}$ due to $\nu$(N-H),$\nu$(C-H) aromatic, $\nu$(C=O) ketone and $\nu$(C=O) amide, $\nu$(C=C) aromatic and $\nu$(C=N) respectively.

FT-IR spectrum of compound (2) showed clear absorption bands at (3055) Cm$^{-1}$, (1712) Cm$^{-1}$, (1596-1681) Cm$^{-1}$ and (1380) Cm$^{-1}$ due to $\nu$(C-H) aromatic, $\nu$(C=O) ketone and imide, $\nu$(C=C) aromatic and $\nu$(C-N) respectively. FT-IR spectra of Schiff's bases (3-10) showed clear absorption bands at (3047-3093) Cm$^{-1}$, (1704-1712) Cm$^{-1}$, (1504-1625) Cm$^{-1}$, (1596-1643) Cm$^{-1}$ and (1350-1388) Cm$^{-1}$ due to $\nu$(C-H) aromatic, $\nu$(C=O) ketone and imide, $\nu$(C=C) aromatic, $\nu$(C=N) and $\nu$(C-N) respectively.

FT-IR spectra of compounds (3), (6) and (7) showed clear absorption bands at (1087) Cm$^{-1}$, (1041) Cm$^{-1}$ and (1087) Cm$^{-1}$ due to $\nu$(C-Cl) [9,10].

Finally, FT-IR spectra of compounds (3), (6) and (9) showed clear absorption bands at (1388-1450) Cm$^{-1}$, (1350-1488) Cm$^{-1}$ and (1388-1481) Cm$^{-1}$ due to $\nu$(NO$_2$).

$^1H$-NMR spectra of compound (1) showed singlet signal at 2.3 ppm due to CH$_3$ group, multiplet signals at (6.5-8.1)ppm due to aromatic protons and NH group and singlet signal at 10.6 ppm due to OH carboxylic. While $^1H$-NMR spectra of compound (2) showed singlet signal at 2.5 ppm due to CH$_3$ group and multiplet signals at (7.6-8.1) ppm due to aromatic protons.

$^1H$-NMR spectra of compounds (3), (4) and (6) showed singlet signal at 2.5 ppm due to CH$_3$ group and multiplet signals at (6.2-8.1) ppm due to aromatic protons. Finally, $^1H$-NMR spectra of compound (9) showed singlet signal at 2.5 ppm due to CH$_3$ group, singlet signal at (3.8) ppm due to OCH$_3$ group and multiplet signals at (6.3-8.1) ppm due to aromatic protons [9,10].

$^{13}$C-NMR spectra of compound (1) showed signal at 27 ppm due to CH$_3$, signals at (112-136) ppm due to aromatic carbons, signal at (167) ppm due to C=O imide and signals at (195-197) ppm due to C=O ketone.

$^{13}$C-NMR spectra of compound (2) showed signal at 27 ppm due to CH$_3$, signals at (124-136) ppm due to aromatic carbons, signal at (136) ppm due to C=N, signal at (167) ppm due to C=O imide and signal at (197) ppm due to C=O ketone.

While $^{13}$C-NMR spectra of compounds (3), (4) and (6) showed signal at (27) ppm due to CH$_3$ group, signals at (107-136) ppm due to aromatic carbons, signals at (145-150) ppm due to C=N and signal at (167) ppm due to C=O imide.

Finally, $^{13}$C-NMR spectra of compound (9) showed signal at (27) ppm due to CH$_3$ group, signal at (56) ppm due to OCH$_3$, signals at (106-135) ppm due to aromatic carbons, signal at (146) ppm due to C=N and signal at (167) ppm due to C=O imide.

**Biological activity [11,12]**

The prepared phthalimide (2) and the prepared Schiff's bases (3-9) showed different biological activities against two types of bacteria gram positive and gram negative bacteria including *staphylococcus aureus and Pseudomonas aerugenosa*. The test results showed that all Schiff's bases are inactive except *staphylococcus aureus* compound (3) which showed very high activity against this bacteria.

While the Schiff's bases (3,4,6,8,9) showed moderate activity against *Pseudomonas* except compound (5) which was highly active and compounds (2,10) which are slightly active against this bacteria.

All these result are shown in Table (5).
Table (1)
Physical properties and FT-IR spectral data of compounds (1) and (2).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Compound structure</th>
<th>M.P. 0 °C</th>
<th>Yield %</th>
<th>Color</th>
<th>Major FTIR Absorptions Cm⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>v O-H</td>
</tr>
<tr>
<td>1</td>
<td><img src="image1" alt="Compound structure" /></td>
<td>218-219</td>
<td>76</td>
<td>Yellow</td>
<td>3240</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Compound structure" /></td>
<td>238-240</td>
<td>75</td>
<td>Yellow</td>
<td></td>
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</tbody>
</table>

Table (2)
Physical properties and FT-IR spectral data of Schiff's bases (3-10).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Compound Structure</th>
<th>M.P. 0 °C</th>
<th>Yield %</th>
<th>Color</th>
<th>Major FTIR Absorptions Cm⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>v C=O</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Compound structure" /></td>
<td>146-148</td>
<td>66</td>
<td>Orange</td>
<td>1712</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>v C-NO2</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Compound structure" /></td>
<td>112-114</td>
<td>71</td>
<td>Yellow</td>
<td>1712</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Compound structure" /></td>
<td>220-222</td>
<td>50</td>
<td>Off White</td>
<td>1712</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Compound structure" /></td>
<td>170-172</td>
<td>70</td>
<td>Gray</td>
<td>1712</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="Compound structure" /></td>
<td>68-70</td>
<td>93</td>
<td>Off White</td>
<td>1712</td>
</tr>
<tr>
<td>8</td>
<td><img src="image8" alt="Compound structure" /></td>
<td>165-166</td>
<td>30</td>
<td>Off White</td>
<td>1712</td>
</tr>
<tr>
<td>9</td>
<td><img src="image9" alt="Compound structure" /></td>
<td>138-140</td>
<td>75</td>
<td>Yellow</td>
<td>1712</td>
</tr>
<tr>
<td>10</td>
<td><img src="image10" alt="Compound structure" /></td>
<td>218-220</td>
<td>66</td>
<td>Gray</td>
<td>1712</td>
</tr>
</tbody>
</table>
Table (3)

$^1$H-NMR spectral data for some of the prepared compounds.

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Compound structure</th>
<th>$^1$H-NMR spectral data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![Structure 1]</td>
<td>$\delta = 6.5-8.1$ ppm, $\delta = 2.3$ ppmCH$_3$ Aromatic protons and N-H, 10.6 ppm OH carboxylic</td>
</tr>
<tr>
<td>2</td>
<td>![Structure 2]</td>
<td>$\delta = 7.1-8.1$ ppm, $\delta = 2.5$ ppmCH$_3$ Aromatic protons.</td>
</tr>
<tr>
<td>3</td>
<td>![Structure 3]</td>
<td>$\delta = 7-8.1$ ppm, $\delta = 2.5$ ppmCH$_3$ Aromatic protons.</td>
</tr>
<tr>
<td>4</td>
<td>![Structure 4]</td>
<td>$\delta = 7.2-8.1$ ppm, $\delta = 2.5$ ppmCH$_3$ Aromatic protons.</td>
</tr>
<tr>
<td>6</td>
<td>![Structure 6]</td>
<td>$\delta = 6.2-8.1$ ppm, $\delta = 2.5$ ppmCH$_3$ Aromatic protons.</td>
</tr>
<tr>
<td>9</td>
<td>![Structure 9]</td>
<td>$\delta = 6.3-8.1$ ppm, $\delta = 2.5$ ppmCH$_3$ Aromatic protons, $\delta = 3.8$ ppm OCH$_3$</td>
</tr>
</tbody>
</table>
Table (4)
$^{13}$C-NMR spectral for some of the prepared compounds.

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Compound structure</th>
<th>$^{13}$C-NMR spectral data</th>
</tr>
</thead>
</table>
| 1          | ![Structure](image) | δ=(112-136)ppm, δ=27 ppm CH$_3$
Aromatic carbons,
δ=167-169 ppm C=O Imide
δ=195-197 ppm C=O Ketone |
| 2          | ![Structure](image) | δ=(124-136)ppm, δ=27 ppm CH$_3$
Aromatic carbons,
δ=167 ppm C=O Imide
δ=197 ppm C=O Ketone |
| 3          | ![Structure](image) | δ=7 ppm CH$_3$, δ=(118-136)ppm
Aromatic carbons,
δ=145 ppm C=N,
δ=167ppm C=O imide |
| 4          | ![Structure](image) | δ=27 ppm CH$_3$, δ=(107-130) ppm
Aromatic carbons,
δ=149,150 ppm C=N,
δ=167ppm C=O imide |
| 6          | ![Structure](image) | δ=27 ppm CH$_3$, δ=(112-136) ppm
Aromatic carbons,
δ=149 ppm C=N,
δ=167ppm C=O imide |
| 9          | ![Structure](image) | δ=27 ppm CH$_3$
δ=56 ppm OCH$_3$,
δ=(106-135)ppm aromatic
carbons 146 ppm C=N
δ=167 ppm C=O imide |
Table (5)
Antimicrobial activity of the prepared compounds.

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Gram positive bacteria</th>
<th>Gram negative bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S.aureus</td>
<td>aerugenos Pseudomonas</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
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<tr>
<td>7</td>
<td>-</td>
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<tr>
<td>8</td>
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<td>++</td>
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<tr>
<td>9</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Key to symbols : Inhibition zone < 6= - Inactive
Slightly active 10= +
Moderately active 11-13=++
Highly active 15=++++
Very high activity20=++++

References

الخلاصة

تم تحضير ثمانية من فوائد شفيف جديدة مشتقة من 4-

فثال أميد أستيفون ين بثلاث خطوات:

تضمنت الخطوة الأولى تحضير حامض الفثال أميك من تفاعل إثيد الفثاليك مع بارا أمين أستيفون والذي

بدوره مسر في الخطوة الثانية للحصول على الفثال الأميد المقابل.

أما الخطوة الثالثة فقد تضمنت تكافئ الفثال الأميد المحضر مع أميدات اروماتية أولية مختلفة للحصول على

فوائد شفيف جديدة تم تشخيص المركبات المحضرة

و13C-NMR و 1H-NMR و FT-IR بمترايعية.

وقد وُردت الفعالية البيولوجية لهذه المركبات باتباع طريقة الحفر تجاه نوعين من البكتيريا وقد أظهرت المركبات فعالية واضحة نحو أحد نوعي البكتيريا في الدراسة.