Synthesis and Characterization of Some New 1,3-Oxazepine Derivatives

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Abstract

In this study, Schiff's bases \([S_3, S_4]\) were synthesized by condensation of N,N-dimethyl amino benzaldehyde with primary aromatic amine[N-(hydrazinyl methyl) benzamide]. These Schiff's bases were found to react with maleic anhydride and phthalic anhydride to give 1,3-Oxazepine\([S_5, S_6, S_7, S_8]\) in good yields. The structures confirmed by m.p, T.L.C., FT.IR and \(^1\)H-NMR (of some of them).

Key word 1,3-Oxazepine

Introduction

Discovery of the activity of 1,3-Oxazepine on the Central Nervous System (CNS)[1], encouraged further searching for new ways to build up this 7-membered heterocyclic ring system[2,3]. Diazepine is an analogue to oxazepine and thiazepile but the difference is nitrogen, oxygen, nitrogen atom. Diazepam (valium) is a substituted benzodiazepine introduced in 1964 which was used for the control of anxiety and tension states, the relief of muscle spasm and for the management of acute agitation during withdrawal from alcohol[4].

1,3-Oxazepine is an antidepressant with a mild sedative component to it is action. The mechanism of it is clinical action in man is not well understood. In animals, amoxapine reduced the uptake of noradrenaline and serotonine and blocked the response of dopamine receptors to dopamine[5].

Synthesis of oxazepine derivatives may occur in various ways; e.g., with the participation of C-6 or C-4 atom of the pyridazinone ring to form differently fused pyridazino ring systems[6], or oxazepine prepared from the reaction of Schiff's bases with maleic and phthalic anhydride to give 1,3-oxazepine-4,7-dione in dry benzene, according to pericyclic reactions[7].

The pericyclic reactions are an important class of concerted reactions. A pericyclic reaction is characterized as a change in bonding relationship which takes place as a continuous concerted reorganization of electrons. The word "concerted" specifies that there is a single transition state and thus no intermediate in the process. To maintain continuous smooth electron flow, pericyclic reactions occur through cyclic transition states. Frequently, the cyclic transition states must correspond to an arrangement of the participating orbitals that can maintain a bonding interaction between the reaction components throughout the course of the reaction. Indeed as we shall see later these requirements make pericyclic reactions highly predictable, in terms of such features as relative reactivity, stereo-specificity and regioselectivity[8].

Oxazepine derivatives such as compound (I) is used in chemical weapons as tear gas. Tear gas is the common name for substances which in low concentrations, cause pain to the eyes, flow of tears and difficulty in keeping the eyes open. It is used mainly in military,
exercises and riot control[9]. The aim of the work is synthesis new oxazepine derivatives which are expected to have a biological activity like those that have already been reported.

![Diagram](image)

**Experimental**

**Instruments**
1-Melting points were determined with: stuart melting point apparatus and were uncorrected.
2-Thin layer chromatography (T.L.C) $R_f<1$, was performed on alumina plates.
3-Infrared spectra were recorded with: SHIM ADZU from Ibn-Sina(FT.IR),8400,in KBr disc.
4-$^1$H-NMRwas recorded on fourier transform varian spectrometer , operating at 300 MHz with tetramethylsilane as internal standared in DMSO$_d^6$, measurements were made at chemistry department, AL-AL_Bayt university, Jordan.

**Esterification[10]**

To a mixture of glycic acid (14.3g,0.08mol) and anhydrous sodium carbonate (8.5g,0.08mol) in dry acetone (20mL), dimethyl sulphate (10g,0.08mol) was added, then refluxed for 4hr. The reaction was followed by(T.L.C). After cooling the reaction mixture it extracted with ethylacetate (3x) then dried to give syrup product of ester(methyl 2-benzamidoacetate). $S_1=$(Yield 82%,M.P.=syrup),[x = number of extracted].

**Synthesis of hydrazide[11]**

Hydrazine mono hydrate 85% (2g,0.04 mol) was added to methyl ester($S_1$) (7.7g,0.04 mol) in (10 mL) absolute ethanol with stirring ,then refluxed until the precipitate formed (1.5hrs.). After cooling ,the precipitate was filtered. And recrystallized from ethanol ,N-(hydrazinyl methyl)benzamide $S_2=$( yield 71% ,M.P.(150-152)$^\circ$c).

**Synthesis of Schiff's bases [12]**

**General procedure**

A mixture of hydrazide compound($S_2$)(1.9g,0.01 mol.), appropriate aromatic aldehyde (0.01 mol.) and abs. ethanol 98%(25 mL) in the presence of glacial acetic acid (3 drops ) was refluxed in water bath for (4-5)hrs. Table (1) shows the physical properties.

**Synthesis of 1,3-Oxazepine [13]**

**General procedure**

A mixture of (0.03 mol.) of imine compound (Schiff’s bases)($S_1,S_4$)and (0.03 mol.) of selected anhydride dissolved in (25 mL) dry benzene was refluxed in water bath for (4-5)hrs.The product was recrystallized from dry 1,4-Dioxane . Table (2) shows the physical properties of these compounds.
Results and Discussion

The reaction of Schiff's bases with anhydrides is pericyclic reaction rather than classical organic reactions. The classical organic reactions involve several steps or rearrangement, with side reactions and relatively low yield, the pericyclic reactions is one step-process, takes place through a single transition state with relatively high yield and frequently no side reaction.

The synthesis of compounds was outlined in schem (1) when the glycine acid was converted to ester (S₁) by using dimethyl sulphate and sodium carbonate in dry acetone then the ester was hydrazonolysis with hydrazine hydrate to hydrazide derivative (S₂). The condensation reaction of equimolar quantity of primary amine (S₂) with the appropriate aromatic aldehydes was major method to prepare of Schiff’s bases (S₃,S₄) the nomenclatures of these compounds are shown in table (3). The synthesized compounds were identified by their M.P and FT.IR. The FT.IR spectra show the disappearance of two absorption band due to (–NH₂) str. of hydrazide derivative with appearance band at (1676-1685)cm⁻¹ due to azomethene group (C=N)[14,15]. Moreover, all compounds exhibit significant stretching band near the region (1213,1230,1296) cm⁻¹, this indicated the presence of (–N–N=) group[16].

Schiff's bases are known to react with acid halides and anhydride to give the corresponding addition products [17]. Therefore, it is expected that would react with maleic anhydride or phthalic anhydride and was classified as a 5+2→7, implying a 5-atoms component plus 2-atoms component leading to 7-membered cyclic ring, but the mechanism (will be outlined below scheme (2)) involves addition of one σ bond (C–O) to one π-bond(C=N) to give 4-membered cyclic transition state which opens into maleic anhydride or phthalic anhydride (5-membered cyclic ring) to give (7-membered cyclic ring)[18].

\[
\begin{align*}
R=\text{Ph-CO-NH-CH}_2\text{-CO-NH-} & \quad \text{Ar=[4-N(CH}_3\text{)Ph],[4-CH}_3\text{Ph]
\end{align*}
\]

Schem (2) The suggested mechanism for the formation of the oxazepine derivatives.

The compounds [S₅,S₆,S₇,S₈] were obtained by the reaction of equimolar amount of imines with select anhydrides in dry benzene, the synthesized compounds were identified by their M.P,FT.IR and ¹H-NMR. analysis, the nomenclatures of these compounds are shown in table(3). The FT.IR spectra, figure 1 and 2, showed disappearance band at (1676,1685)cm⁻¹ due to (C=N) of Schiff's bases, while appearance important band due to stretching vibration of (C=O) lactone and (C=O)lactam that is indicative to formation of oxazepine compound, other data are listed in table (4).

¹H-NMR spectrum of compound (S₃), showed the following characteristics chemical shifts (DMSO as solvent) [19]: δ 2.6 s (–N–dimethyl); δ 4.09 d (–CH₂–); δ 7.3 s (–N–CH–); δ 7.6-7.8 m, (aromatic); δ 7.8s (–CO–NH–N–); δ 8.4 - 8.5t (–CO–NH–CH₂–) group.

¹H-NMR spectrum of compound (S₅), figure 3, showed the following characteristics chemical shifts (DMSO as solvent)[19]: δ 2.19 s (–CH₃); δ 4.09 d (–CH₂–); δ 6.9 d of d (CH=CH); δ 7.3 s (–N–CH–); δ 7.5-7.9 m (aromatic); δ 8.1 s (–CO–NH–N–); δ 8.6 - 8.8 t (–CO–NH–CH₂–).
All these reactions show the difference between classical organic reaction and pericyclic reaction.

Reference

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9- Tear Gases, Internet,(2002),AFOA Briefing Book on Chemical Weapons.
17- V.Ram, (1988), Chemotherapeutical agents, VII. Synthesis and pesticidal activities of sulphides and sulphones derived from bis[4-aryl-1,2,4-triazoline-5-thione-3-yl] alkane and 5-phenyl-1,3,4-oxadiazole-2-thione, J.Heterocyclic chem., 25: 253-256.
Table (1): The physical properties of Schiff's bases.

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Structural formula</th>
<th>colour</th>
<th>Molecular formula</th>
<th>Molecular weight</th>
<th>M.P. °C</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>S3</td>
<td></td>
<td>Red</td>
<td>C_{18}H_{20}O_{2}N_{4}</td>
<td>324</td>
<td>174-175</td>
<td>82</td>
</tr>
<tr>
<td>S4</td>
<td></td>
<td>Yellow</td>
<td>C_{17}H_{17}O_{3}N_{3}</td>
<td>295</td>
<td>135-136</td>
<td>78</td>
</tr>
</tbody>
</table>

Table (2): The physical properties of 1,3-Oxazepine.

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Structural formula</th>
<th>colour</th>
<th>Molecular formula</th>
<th>Molecular weight</th>
<th>M.P. °C</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>S5</td>
<td></td>
<td>Orange</td>
<td>C_{25}H_{22}O_{5}N_{4}</td>
<td>472</td>
<td>148-149</td>
<td>75</td>
</tr>
<tr>
<td>S6</td>
<td></td>
<td>Yellow</td>
<td>C_{21}H_{20}O_{3}N_{4}</td>
<td>422</td>
<td>Syrup</td>
<td>81</td>
</tr>
<tr>
<td>S7</td>
<td></td>
<td>Yellow</td>
<td>C_{24}H_{19}O_{3}N_{3}</td>
<td>443</td>
<td>156-157</td>
<td>78</td>
</tr>
<tr>
<td>S8</td>
<td></td>
<td>Yellow</td>
<td>C_{20}H_{17}O_{3}N_{3}</td>
<td>393</td>
<td>Syrup</td>
<td>85</td>
</tr>
</tbody>
</table>

Table (3): The nomenclatures of compounds (S\textsubscript{2}-S\textsubscript{8})

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>nomenclatures</th>
</tr>
</thead>
<tbody>
<tr>
<td>S2</td>
<td>N-(hydrazinyl methyl)benzamide</td>
</tr>
<tr>
<td>S3</td>
<td>N-((2-(4-(dimethylamino)benzylidene)hydrazinyl)methyl)benzamide</td>
</tr>
<tr>
<td>S4</td>
<td>N-((2-(4-methyl benzylidene)hydrazinyl)methyl)benzamide</td>
</tr>
<tr>
<td>S5</td>
<td>N-((3-(4-(dimethylamino)phenyl)-1,5-dioxobenzo[e][1,3]oxazepin-4-(1H,3H,5H)-ylamino)methyl)benzamide</td>
</tr>
<tr>
<td>S6</td>
<td>(Z)-N-((2-(4-(dimethylamino)phenyl)-4,7-dioxo-1,3-oxazepin-3(2H,4H,7H)-ylamino)methyl)benzamide</td>
</tr>
<tr>
<td>S7</td>
<td>N-((1,5-dioxo-3-p-tolybenzo[e][1,3]oxazepin-4(1H,3H,5H)-ylamino)methyl)benzamide</td>
</tr>
<tr>
<td>S8</td>
<td>(Z)- N-((4,7--dioxo-2-p-tolyl-1,3-oxazepin-3(2H,4H,7H)-ylamino)methyl)benzamide</td>
</tr>
</tbody>
</table>
Table (4): FTIR data of 1,3-oxazepine derivatives.

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>C=O Lactam cm(^{-1})</th>
<th>C=O Lacton cm(^{-1})</th>
<th>C-O Lacton cm(^{-1})</th>
<th>C-N str. cm(^{-1})</th>
<th>C=C str. cm(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>S(_5)</td>
<td>1715</td>
<td>1678</td>
<td>1276</td>
<td>1176</td>
<td>1639-1531</td>
</tr>
<tr>
<td>S(_6)</td>
<td>1724</td>
<td>1724</td>
<td>1232</td>
<td>1172</td>
<td>1643-1539</td>
</tr>
<tr>
<td>S(_7)</td>
<td>1710</td>
<td>1700</td>
<td>1278</td>
<td>1170</td>
<td>1643-1546</td>
</tr>
<tr>
<td>S(_8)</td>
<td>1732</td>
<td>1720</td>
<td>1230</td>
<td>1138</td>
<td>1643-1543</td>
</tr>
</tbody>
</table>

Schem(1)
Fig. (1): FT-IR of compound (S₆)

Fig. (2): FT-IR of compound (S₅)
Fig (3) : $^1$H-NMR of compound (S$_8$)
تحضير وتشخيص بعض مشتقات 3,1-أوكسازين الجديدة

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قبل البحث في: 8 شباط 2011

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الخلاصة
في هذه الدراسة حضرت قواعد شف من تكافل ن-ثنائي مثيل أميدو بنزالدبيهيد و 4-مثيل بنزالدبيهيد مع أمين حلقى أولي [N-(مثيل هيدروازينيل) بنزاميد] فعّلت قواعد شف المحضة مع انهدريد الملكيك و انهدريد الفثاليك لإعطاء مركبات 3,1-أوكسازين ـ [S5,S6,S7,S8] بنسبة منتوج جيدة. شُخصت المركبات المحضة بوساطة درجة الانصهار، وصفائح الكرموتوكرافيكية الرقيقة، وطيف الإشعة تحت الحمراء FTIR، وطيف الرنين النووي المغناطيسي 1H-NMR.

الكلمات المفتاحية: 3,1-أوكسازين