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 synthezied by condensation of N,N-dimethyl amino benzaldehyde with primary aromatic amine[N-(hydrazinyl methyl)benzamide]. These Sciff'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 confired 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 a 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 with drawal from alcohol[4].

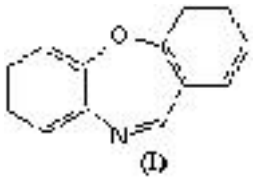
1,3-Oxazepine is an antidepressant with a mild sedative component to it is action. The mechanism of it is clinical action in man is not well understood. In animals, amoxapine reduced the uptake of noradrenaline and serotonine and blocked the response of dopamine receptors to dopamine[5].

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 important class of concerted reactions. A pericyclic reactions are characterized as a change in bonding relationship which takes place as a continuous concerted reorganization of electrons. The word "concerted" specifics 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.



(I)

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: SHIMADZU 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 DMSOd^6, measurements were made at chemistry department, AL-AL_Bayt university, Jordan.

Esterification[10]

To a mixture of glycinic 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)˚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

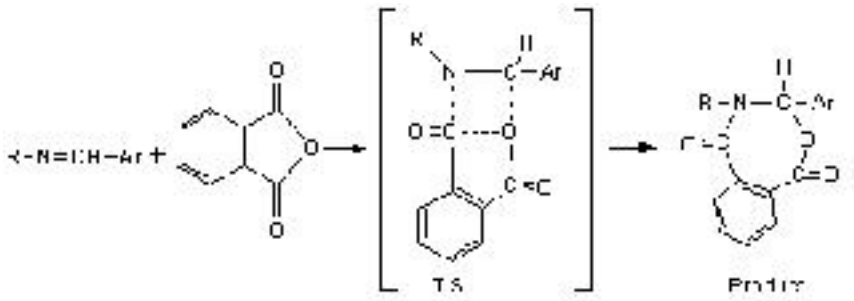
A mixture of (0.03 mol.) of imine compound (Schiffs bases)(S_3, S_4)and (0.03 mol.) of selected anhydride dissolved in (25 mL) dry benzene was refluxed in water bath for (4-5)hrs.The product was recrystallized from dry 1,4-Dioxane . Table (2) shows the physical properties of these compounds.

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 glycinic acid was converted to ester (S_1) by using dimethyl sulphate and sodium carbonate in dry acetone then the ester was hydrazonlysis with hydrazine hydrate to hydrazide derivative (S_2).The condensation reaction of equimolar quantity of primary amine (S_2) with the appropriate aromatic aldehydes was major method to prepare of Schiff's bases (S_3, S_4) 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 ($-NH_2$) 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, imploying 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].



R=Ph-CO-NH-CH_2-CO-NH- Ar=[4-N$(CH_3)_2$Ph],[4-CH_3Ph]

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

The compounds [S_5,S_6,S_7,S_8] 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 ^{1}H-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 indicater to formation of oxazepine compound, other data are listed in table (4).

^{1}H-NMR sprctrum of compound (S_5), showed the following characteristics chemical shifts (DMSO as asolvent) [19]: δ 2.6 s (–N–dimethyl) ; δ 4.09 d (–CH_2–) ; δ 7.3 s (–N–CH–) ; δ7.6-7.8 m, (aromatic) ; δ7.8s (–CO–NH–N–) ; δ 8.4 - 8.5t (–CO–N<u>H</u>–CH_2–)group.

^{1}H-NMR sprctrum of compound (S_8),figure 3, showed the following characteristics chemical shifts (DMSO as asolvent)[19]: δ 2.19 s (–CH_3) ; δ 4.09 d (–CH_2–) ; δ 6.9 d of d (CH=CH) ; δ 7.3 s (–N–CH–) ; δ7.5-7.9 m (aromatic) ; δ8.1 s (–CO–N<u>H</u>–N–) ; δ 8.6 - 8.8 t (–CO–N<u>H</u>–CH_2–).

All these reactions show the difference between classical organic reaction and pericyclic reaction.

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Table (1): The physical properties of Schiff's bases.

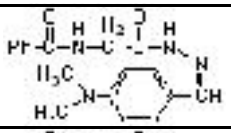
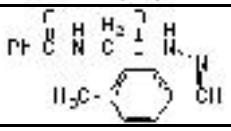
Comp. No.	Structural formula	colour	Molecular formula	Molecular weight	M.P. ˚C	Yield %
S_3		Red	$C_{18}H_{20}O_2N_4$	324	174-175	82
S_4		Yellow	$C_{17}H_{17}O_2N_3$	295	135-136	78

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

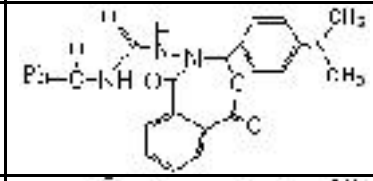
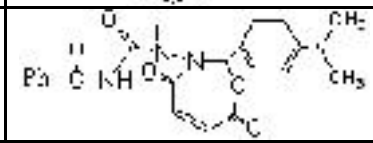
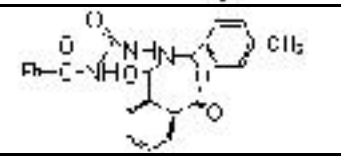
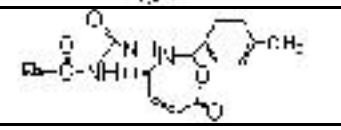
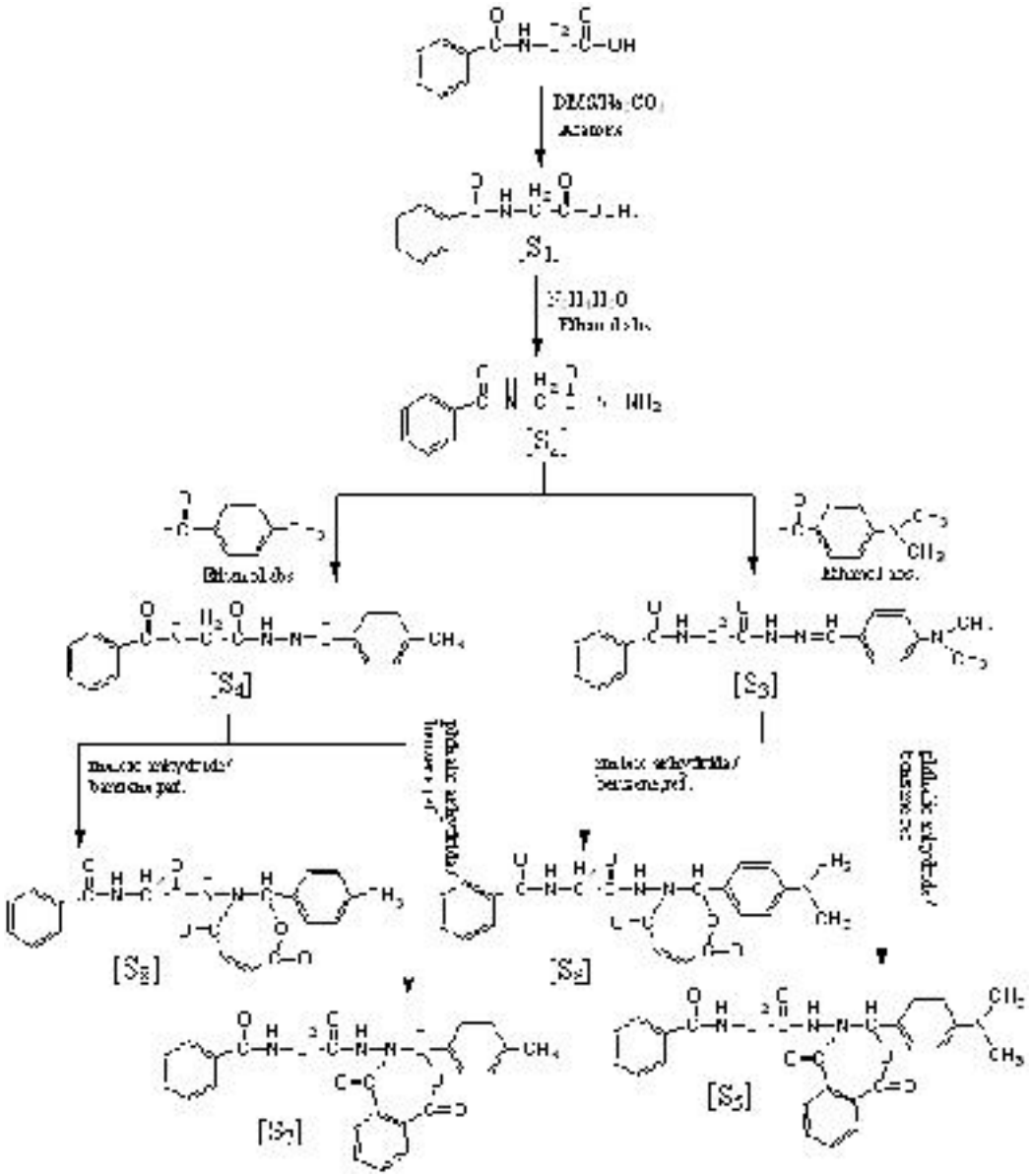
Comp. No.	Structural formula	colour	Molecular formula	Molecular weight	M.P. ˚C	Yield %
S_5		Orange	$C_{25}H_{22}O_5N_4$	472	148-149	75
S_6		Yellow	$C_{21}H_{20}O_5N_4$	422	Syrup	81
S_7		Yellow	$C_{24}H_{19}O_5N_3$	443	156-157	78
S_8		Yellow	$C_{20}H_{17}O_5N_3$	393	syrup	85

Table (3): The nomenclatures of compounds (S_2-S_8)

Comp. No.	nomenclatures
S_2	N-(hydrazinyl methyl)benzamide
S_3	N-((2-(4-(dimethylamino)benzylidene)hydrazinyl)methyl)benzamide
S_4	N-((2-(4-methyl benzylidene)hydrazinyl)methyl)benzamide
S_5	N-((3-(4-(dimethylamino)phenyl)-1,5-dioxobenzo[e][1,3]oxazepin-4-(1H,3H,5H)-ylamino)methyl)benzamide
S_6	(Z)-N-((2-(4-(dimethylamino)phenyl)-4,7-dioxo-1,3-oxazepin-3(2H,4H,7H)-ylamino)methyl)benzamide
S_7	N-((1,5-dioxo-3-p-tolybenzo[e][1,3]oxazepin-4(1H,3H,5H)-ylamino)methyl)benzamide
S_8	(Z)- N-((4,7--dioxo-2-p-tolyl-1,3-oxazepin-3(2H,4H,7H)-ylamino)methyl)benzamide

Table (4): FT.IR data of 1,3-oxazepine derivatives.

Comp. No.	C=O Lactam cm^{-1}	C=O Lacton cm^{-1}	C-O Lacton cm^{-1}	C-N str. cm^{-1}	C=C str. cm^{-1}
S_5	1715	1678	1276	1176	1639-1531
S_6	1724	1724	1232	1172	1643-1539
S_7	1710	1700	1278	1170	1643-1546
S_8	1732	1720	1230	1138	1643-1543



Schem(1)

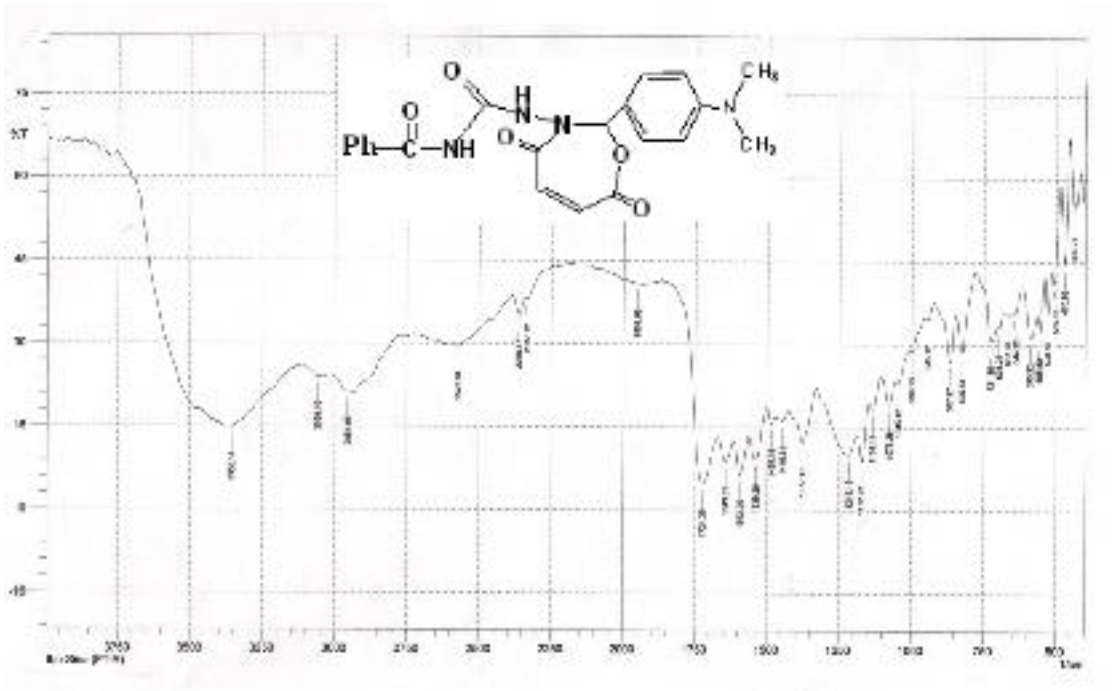


Fig.(1):FT.IR of compound (S_6)

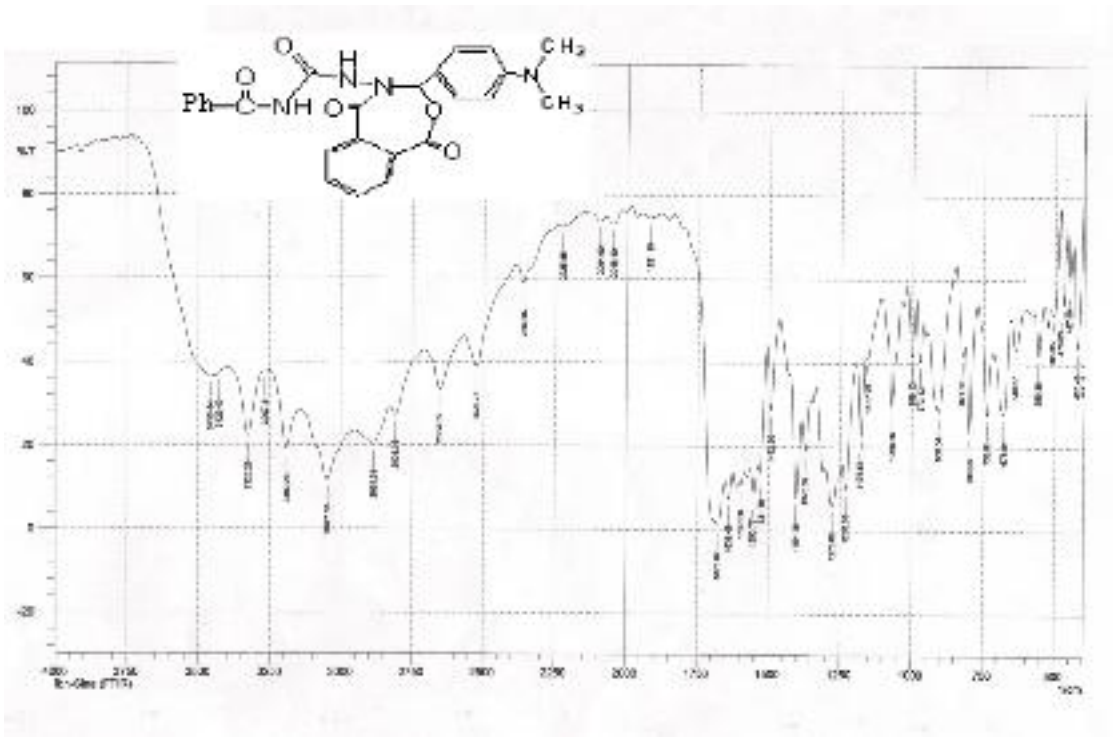


Fig.(2):FT.IR of compound (S_5)

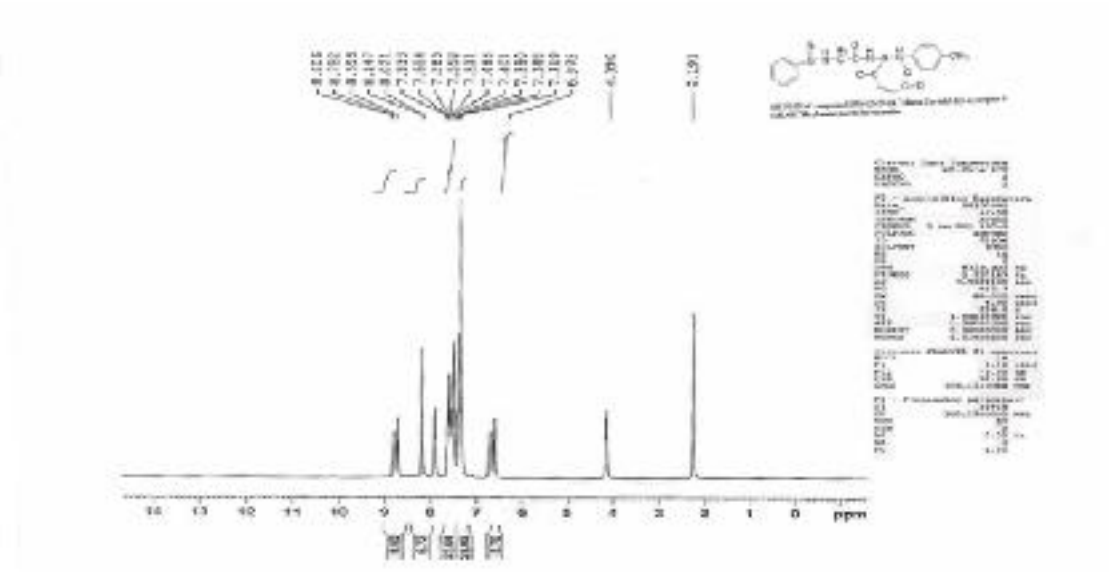


Fig (3) : ^{1}H-NMR of compound (S_8)

تحضـــير وتشـــخيص بعض مشـــتقات 3,1-اوكســـــازبين الجـديدة

استلم البحث في : 17 حزيران 2010
قبل البحث في: 8 شباط 2011

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الخلاصة

في هذه الدراسة حضرت قواعد شف من تكاثف ن-ثنائي مثيل امينو بنزالديهايد ،و4-مثيل بنزالديهايد مع امين حلقي اولي [ن-(مثيل هايدرازينيل) بنزامايد] .فوعلت قواعد شف المحضرة مع انهدريد الماليك و انهدريد الفثاليك لاعطاء مركبات 3,1-أوكسازبين [S_5,S_6,S_7,S_8] بنسبة منتوج جيدة. شخصت المركبات المحضرة بوساطة درجة الانصهار ، وصفائح الكروموتوكرافية الرقيقة ، وطيف الاشعة تحت الحمراء FT.IR ،وطيف الرنين النووي المغناطيسي ^{1}H-NMR.

الكلمات المفتاحية: 3,1-أوكسازبين