Synthesis and Characterization of New Oxazepines Compounds Derived From D- Galactose

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Abstract

New Schiff bases derived from D-galactose were synthesized by condensation of aldehyde (1,2:3,4-Di-*O*-isopropylidene-6-carboxaldehyde-α-D-galactopyranose) with different aromatic amines such as (4-bromo, 3-hydroxy, 4-iodo, 4-methoxy) aniline in dry benzene using glacial acetic acid as a catalyst. These compounds were converted to oxazepine derivatives by addition
reaction with maleic anhydride in dry benzene as a solvent. The structures of the synthesized compounds have been characterized by elemental analysis, FTIR spectra, some of them by using ^{1}HNMR spectra and measurement of its physical properties.

Key words: Schiff bases, 1,3-oxazepine, D-galactose.

Introduction

Compounds containing an azomethine group (-CH=N-), known as Schiff bases are formed by the condensation of a primary amine with a carbonyl compound. Schiff bases of aliphatic aldehydes are relatively unstable and are readily polymerizable while those of aromatic aldehydes, having an effective conjugation system, are more stable. Schiff bases have number of applications viz., preparative use, identification, detection and determination of aldehydes or ketones, purification of carbonyl or amino compounds, or protection of these groups during complex or sensitive reactions. They also form basic units in certain dyes[1]. Schiff bases are reported to exhibit antibacterial[2-5], antifungal [6] and antitumor activity[7]. In addition, the compounds and their metal complexes exhibit interesting photophysical properties[8].

1,3-oxazepine-diones is a seven-membered ring containing nitrogen, oxygen and two carbonyl group. Many researchers have investigated the molecular properties of the 1, 4-, 4, 1-, and 1, 5-benzoxazepines they constitute an important class of heterocyclic compounds which have many biological uses[9-18]. A considerable number of methods towards the

formation of oxazepine ring have been reported in recent years[19,20]. However, convenient and efficient way to form the oxazepine rings is still preferred owing to its importance as pharmaceutical drugs and active substances in biological systems.

Experimental

Melting points were determined by electrothermal Stuart melting point apparatus and are uncorrected. FTIR spectra (in KBr) were recorded on 8400s Shimadzu FT infrared spectrophotometer. ^{1}HNMR spectra were recorded on Ultra Shield (300 MHz) spectrometer with tetramethylsilane as internal standard. Elemental analysis of carbon, hydrogen and nitrogen were determined on a Euro Vector EA 3000A elemental analyzer. Thin layer chromatography (TLC) was performed on aluminum plates coated with layer of silica gel, supplied by Merck. The spots were detected by iodine vapor. All chemicals were obtained from Fluka or BDH.

Synthesis of 1,2:3,4-Di-*O*-isopropylidene-α-D-galagtopyranose (I)[21].

The method reported by Whistler and Wolfrom is adopted to prepare 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (I). Anhydrous zinc chloride (21.6, 0.15mole) was rapidly weighed into a 500ml (Elenmeyer) flask. Dry acetone (225ml, 3.0mole) was added; the flask was stoppered, and the suspension was stirred magnetically until the zinc chloride has dissolved. Concentrated sulfuric acid (0.72ml) was then added dropwise from a pipette. Finely powdered anhydrous D-galactose (18g, 0.1mole) was added; the flask was stoppered, and the suspension was stirred magnetically for 24 h. A suspension of (36g) of sodium carbonate in 63ml of water was added in portions, and the mixture was stirred (at first, cautiously, and then vigorously). The suspension was filtered under suction, and the precipitate was washed several times with acetone. The solution was evaporated until the acetone has been removed; the desired acetal was separated as an oily upper layer.

The mixture was extracted with ether (3×50ml) and the combined ether extracts was dried over anhydrous sodium sulfate and evaporated to yield yellow syrup (78.8%) of the di-acetone galactose (I).

Synthesis of 1,2;3,4-Di-*O*-isoprpylidene-6-carboxaldehyde-α-D-galactopyranose(II)[22].

Compound (I) (13g, 0.05mole) was stirred for 72 h in DMSO (100ml) and Ac_2O (20ml) at room temperature. By that time, TLC (benzene:methanol, 9.5:0.5) indicated complete reaction of the starting material.

The solution was poured into (250g) of ice-water and some of the upper layer was decanted. The oil layer was extracted with chloroform (2×50 ml),

washed with water, saturated aqueous sodium hydrogen carbonate (2×100ml) and water (2×100ml) and then dried over anhydrous magnesium sulfate. Chloroform was evaporated to produce (II) (69.8%) as pale yellow syrup.

Synthesis of Schiff bases (III-VI)

A mixture of primary aromatic amines (0.002 mole) , aldehyde (II) (0.5 g ,0.002 mole) , dry benzene (15 ml) and 3 drops of glacial acetic acid were refluxed for 20 hrs. The solvent was evaporated and the residue crystallized from chloroform: petroleum ether (60-80 ˚C) (1:4) (v:v). The physical properties of synthesized compounds are listed in Table (1).

Synthesis of 1,3-oxazepines (VII-X)

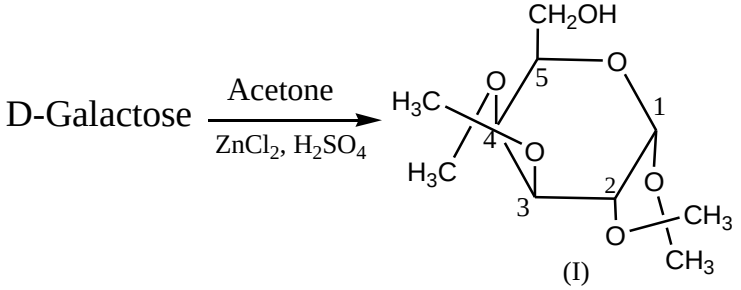
A mixture of equimolar amounts (0.001 mole) of Schiff bases (III-VI) and maleic anhydride (0.001 mole) in dry benzene was refluxed for 20 hrs . The solvent was removed and the resulting colored solid recrystalized from ethanol to obtained 1,3-oxazepines (VII-X). The physical properties of synthesized compounds are listed in Table (1).

Results and discussion

Synthesis and characterization of oxazepines

The oxazepines derivative (VII-X) were obtained from D-galactose which is initially converted to the diacetone galactose (I) by its reaction with dry acetone in presence of zinc chloride as Lewis acid calalyst. This method was adopted because it gives (I) in a good yield (78.8 %) and in good purity .

The FTIR spectrum of the diacetone (I) showed a broad stretching vibration band located at 3510 cm^{-1} to hydroxyl group (OH). A strong (C-H) stretching vibration band located at 2989 cm^{-1} for the four diisopropylidene methyl groups, and stretching vibration band located between 1039 to 1257 cm^{-1} a signed for the acetal groups (C-O-C).

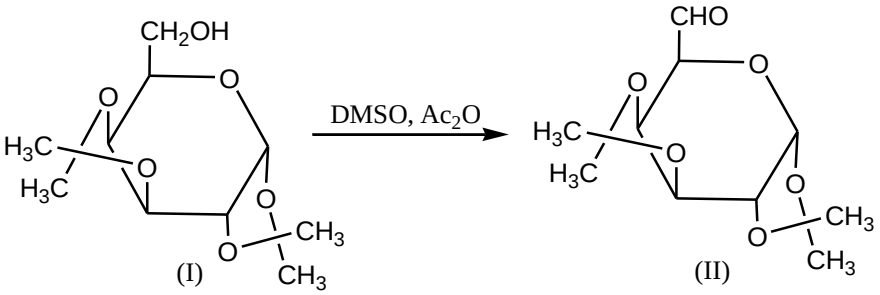


(I)

The diacetone galactose (I) was then oxdated to aldehyde derivative (II) using DMSO and Acetic anhydride. This method is similar to that described by Godman and Horton[22]. The FTIR spectrum of the aldehyde (II) showed stretching vibration band located at 1743 cm^{-1} to carbonyl group (C=O). A strong band at (2987) cm^{-1} for (C-H) acetal and stretching

vibration bands located at (2841 and 2781) cm^{-1} a signed for the (C-H) aldehydic.

The ^{1}HNMR for compound (II) showed the following signals: singlet at δ(9.7) ppm for aldehydic proton , double at δ(5.66-5.32) ppm and quartet at δ(4.56-4.86) ppm for (1H, C_1-H, and C_5-H) respectively, triplet at [δ(4.25-4.33), δ(3.83-3.99) and δ(3.65-3.81)] ppm for (1H, C_2-H,C_4-H and C_3-H) respectively, singlet at δ(1.46-2.16) ppm for (12 H, $4CH_3$) acetal groups.

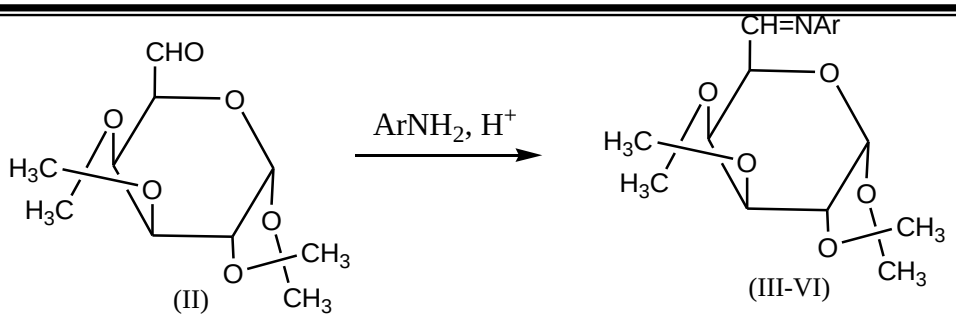


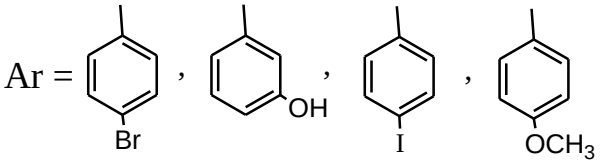
Schiff bases (III-VI) were prepared from reaction of aldehyde (II) with different amines in presence of dry benzene as a solvent and glacial acetic acid as a catalyst. This method is similar to that describe by Mukhlis and Al-Rawi[23].

The FTIR spectra of the Schiff bases (III-VI) showed stretching vibration band located at (1614-1681) cm^{-1} due to (C=N). Elemental analysis Table (1) were matched the theoretical data. Table (2) showed the FTIR spectra bands for Schiff bases.

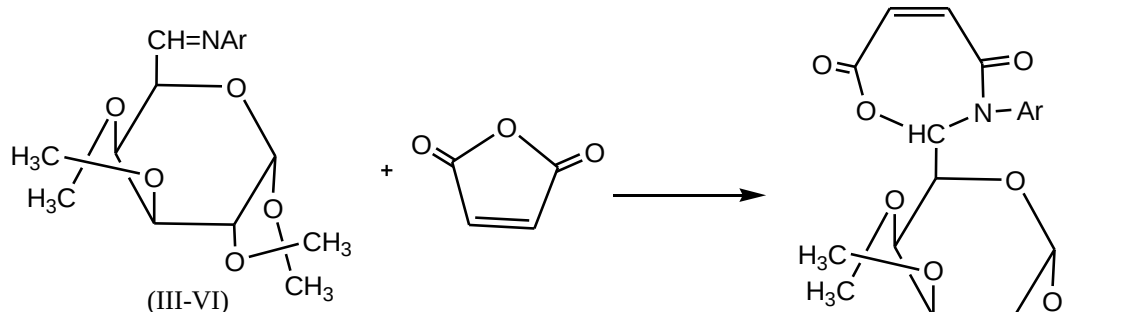
The ^{1}HNMR spectrum ($CDCl_3$) for compound (V) showed the following signals: singlet at δ(9.3) ppm for (1H,CH=N), doublet doublet at δ(7.36-8.92) ppm for (4H, aromatic) , doublet at δ(6.93) ppm for (1H,C_1-H), triplet at δ(6.5-6.86, 4.01-4.07 and 4.16-4.82) ppm for (1H, C_5-H, C_2-H , C_3-H and C_4-H), singlet at δ(0.63- 2.32) ppm for (12H, $4CH_3$ acetal).

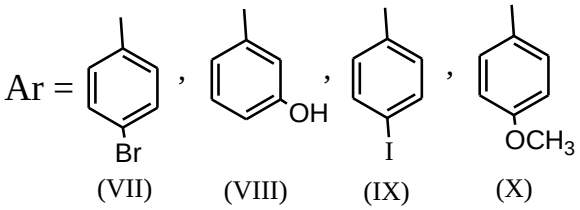
The ^{1}HNMR ($CDCl_3$) spectrum of compound (VI) showed the following signals: singlet at δ(8.33-8.48) ppm for (1H,CH=N) ,doublet doublet at δ(6.75-7.60) ppm for (4H, aromatic), doublet at δ(5.21-5.87) ppm for (1H, C_1-H) , triplet at [δ(4.09-4.29), δ(4.51-4.60) and δ(4.72-4.86)] ppm due to (1H, C_5-H, C_3-H and C_4-H, C_2-H) , singlet at δ(3.74-4.09) ppm for (3H, OCH_3) ,singlet at δ(1.39- 2.97) ppm for (12H, $4CH_3$ acetal).





The 1,3-oxazepin derivatives (VII-X) were prepared from addition reaction of Schiff bases (III-VI) with maleic anhydride in presence of dry benzene as solvent.



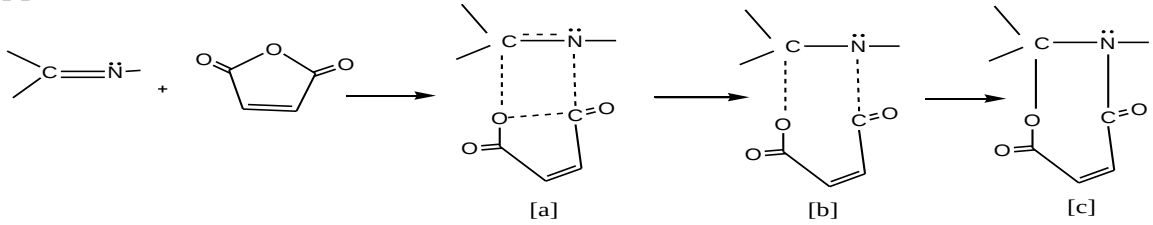


The mechanism for this reaction may be outlined in scheme (1). The mechanism involves the addition of σ-carbonyl to π-band (N=C) to give 4-membered cyclic and 5-membred cyclic ring of anhydride in the same transition state $[T.S]_a$ ring 1,3-oxazepine [C].

The FTIR spectra showed stretching vibration bands located at (1701-1712) cm^{-1} for lactone and (1616-1668) cm^{-1} for lactam. Table (2) showed the FTIR spectra bands for oxazepin derivatives. Elemental analysis Table (1) were matched the theoretical data.

The ^{1}HNMR ($CDCl_3$) spectrum of compound (XI) showed the following signals: doublet doublet at δ(7.40-7.70) ppm for (4H, aromatic) , doublet at δ(6.69-6.79) ppm for (2H, HC=), doublet at δ(4.85-4.49) ppm for (1H, HC-N), doublet at δ(4.56-4.62) ppm for (1H,C_1-H) , triplet at [δ(4.35-4.46), δ(4.06-4.28) and δ(2.1-2.3)] ppm due to (1H, C_5-H, C_2-H and C_3-H, C_4-H), singlet at δ(1.20- 1.60) ppm for (12H,4CH_3 acetal).

The ^{1}HNMR spectrum ($CDCl_3$) for compound (X) showed the following signals: doublet doublet at δ(7.39-8.75) ppm for (4H, aromatic), doublet at δ(6.09-6.97) ppm for (2H, HC=), doublet at δ(5.69-5.73) ppm for (1H, HC-N), doublet at δ(5.27-5.51) ppm for (1H, C_1-H) , triplet at [δ(4.91-5.13), δ(3.21-3.56) and δ(2.86-3.05)] ppm due to (1H, C_5-H, C_2-H and C_3-H, C_4-H), singlet at δ(4.67) ppm for (3H, OCH_3) ,singlet at δ(1.84- 2.41) ppm for (12H, 4CH_3 acetal).



Scheme (1)

Table (1) : physical properties of synthesized compounds (III-X)

Comp. No.	Nomenclature	Molecular Formula	Molecular Weight g/mole	M.P ˚C 0r dec.	Colour	Yield %	Elemental analysis Calculate / Found		
							C %	H %	N %
III	6-deoxy-[4-bromophenyl-imino]-1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose	$C_{18}H_{22}O_5NBr$	412	90-92	Light brown	63	52.4 53.03	5.339 5.74	3.398 3.81
IV	6-deoxy-[3-hydroxyphenyl-imino]-1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose	$C_{18}H_{23}O_6N$	349	250 dec.	Brown	75	61.84 62.04	6.59 6.80	4.01 4.40
V	6-deoxy-[4-iodophenyl-imino]-1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose	$C_{18}H_{22}O_5NI$	459	105-107	Light brown	68	47.058 48.05	4.79 4.97	3.05 3.11
VI	6-deoxy-[4-methoxyphenyl-imino]-1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose	$C_{19}H_{25}O_6N$	363	63-65	Brown	65	62.80 63.02	6.88 6.13	3.85 4.01
VII	6-deoxy-[4-bromophenyl]-4,7-dione-2,3-dihydro-1,3-oxazepin-3(2H)-yl]-1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose	$C_{22}H_{24}O_8NBr$	510	80-82	Deep brown	73	51.76 51.24	4.70 4.63	2.74 2.77
VIII	6-deoxy-[3-hydroxyphenyl]-4,7-dione-2,3-dihydro-1,3-oxazepin-3(2H)-yl]-1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose	$C_{22}H_{25}O_9N$	447	230 dec.	Brown	66	59.06 59.36	5.59 5.27	3.13 3.76
IX	6-deoxy-[4-iodophenyl]-4,7-dione-2,3-dihydro-1,3-oxazepin-3(2H)-yl]-1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose	$C_{22}H_{24}O_8NI$	557	78-80	Deep brown	80	47.39 47.56	4.308 4.005	2.51 2.32
X	6-deoxy-[4-methoxyphenyl]-4,7-dione-2,3-dihydro-1,3-oxazepin-3(2H)-yl]-1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose	$C_{23}H_{27}O_9N$	461	56-58	Deep brown	70	59.86 59.61	5.85 5.97	3.036 3.00

Table (2): The FTIR spectra data of prepared compounds (III-X)

Comp. no.	OH	C-H ar.	C-H ace.	C-H ali.	C=O lactone	C=O lactam	C=N	C=C ali.	C=C ar.	C-O-C est.
III	-	3099	2985	2933	-	-	1681	-	1593	-
IV	3385	3090	2968	2929	-	-	1614	-	1504	-
V	-	3099	2981	2924	-	-	1680	-	1587	-
VI	-	3064	2989	2935	-	-	1672	-	1608	-
VII	-	3062	2989	2933	1712	1668	-	1627	1593	1072-1257
VIII	3369	3096	2976	2935	1701	1616	-	1583	1492	1001-1215
IX		3078	2980	2916	1708	1625	-	1585	1527	1004-1249
X		3064	2991	2937	1712	1656	-	1608	1585	1031-1247

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تحضير وتشخيص مركبات الاوكسازبين الجديدة المشتقة من D- كالكتوز

رسمية محمود رميز

قسم الكيمياء/ كلية التربية للعلوم الصرفة- ابن الهيثم / جامعة بغداد

الخلاصة

يتضمن هذا البحث تحضير قواعد شف جديدة مشتقة من D- كالكتوز من تكاثف الالديهايد (2,1: 4,3 - ثنائي-O- 6-كاربوكسي الديهايد -α-D- -كالكتوبايرنوز) مع امينات مختلفة مثل (4-برومو, 3-هيدروكسي, 4- ايودو, 4- ميثوكسي) انيلين في البنزين الجاف وباستخدام حامض الخليك الثلجي كعامل مساعد. بعدها حولت هذه المركبات الى مشتقات الاوكسازبين بوساطة تفاعل الاضافة مع انهيدريد الماليك في البنزين الجاف كمذيب. شخصت تراكيب المركبات بوساطة تحليل العناصر, اطياف الاشعة تحت الحمراء, وبعضها باستخدام اطياف الرنين النووي المغناطيسي وقياس الخصائص الفزيائية.