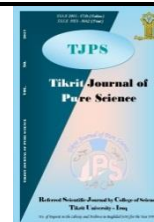




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Synthesis and Study of some Heterocyclic Compounds from Schiff Base of Pinacolone

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ABSTRACT

In this work, the synthesis of some heterocyclic compound of four, five and seven membered rings were done. On oxidation of the pinacolone alcohol using concentrated sulphuric acid pinacolone were obtained and used as a precursor for the synthesis of three new Schiff's base through the reaction with para substituted anilines compounds. These imines were allowed to react with chloroacetyl chloride in dry dioxane to give the azetidine -2- one compounds. Also some thiazolidinone compounds were synthesized from the reaction of the corresponding imines with thioglycolic acid in the presence of zinc chloride in dry benzene and 1, 3-oxazepine-4,7-diones, were obtained from the reaction of imines with maleic and phthalic anhydrides in dry benzene. The synthesized compounds were characterized by IR spectroscopy and physical parameters.

Introduction

Schiff bases are condensation products of primary amines with carbonyl compounds. They were first reported by Schiff [1] in 1864. The common structural feature of these compounds is azomethine group with a general formula $RHC=NR'$, where R and R' are alkyl, aryl, cyclo alkyl or heterocyclic groups which may be variously substituted. These compounds are also known as imines or azomethine. Several studies[2-5] showed that the presence of a lone pair of electrons in a sp^2 hybridized orbital of nitrogen atom of the azomethine group is of considerable chemical and biological importance. Schiff bases have been reported in their biological properties, such as, antibacterial, antifungal activities[6-8]. Schiff bases are active against a wide range of organisms for example; *Candida Albicans*, *Escherichia Coli*, *Staphylococcus aureus*, *Bacillus polymyxa*, *Trychophyton gypseum*, *Mycobacteria*, *Erysiphe graminis* and *plasmopora*. They serve as models for biologically important species. Schiff base derivatives have attracted great deal of interest in synthetic chemistry. These compounds have interesting biological activities such as anti-inflammatory, analgesic, anticonvulsant, antituberculous, antitumor, anti-HIV and antimicrobial activity[9,10]. Many of these derivatives are heterocyclic compounds containing

heteroatom as nitrogen or oxygen. The aim of this paper is to prepare some derivatives of Schiff bases as azetidinone, oxazepine-dione and 4-thiazolidinone. azetidinone are four membered ring compounds (β - lactams) having many methods for their synthesis [11]. They have a wide and very important in medicinal chemistry as a part of the structures of many antibiotics as penicillins and cephalosporins [12]. A large number of 3-chloro monocyclic β - lactams having substitution in position 1 and 4 possess powerful antimicrobial, anticonvulsant and antitubercular activity[13-15]. Oxazepine compounds that contain heteroatoms as oxygen or nitrogen are seven membered heterocycles. These compounds were recently prepared and studied their antimicrobial activity against different types of bacteria[16], 4-thiazolidine derivatives are an important group of heterocyclic compounds possessing a variety of biological effects[17], including antitumor[18,19], anti-inflammatory[20], antimicrobial[21].

Experimental

All chemicals were purchased from Fluka Company and used as such, since all are purists.

IR spectra were recorded in Infrared spectrophotometer model Tensor 27 Bruker Com. Germany (as KBR discs). Melting points were

measured using Electrothermal Melting point Apparatus.

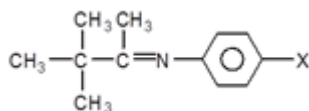
(not corrected).

¹H NMR spectra were recorded on BRUKER-300 MHz operating with TMS as an internal stander in CDCl₃ as a solvent.

Preparation of the Schiff bases (1-3):

A series of Schiff bases was prepared according to the following procedure. The ethanolic solutions of one of three substituted anilines (*p*-NO₂, *p*-Br or *p*-Cl) (0.01 mole in 40 ml absolute ethanol) and (0.01mole, 1.02g in 20 ml absolute ethanol) of pinacolone were mixed and refluxed for about 6 hrs. The reaction mixture was evaporated to a small volume and left to cool. The resulting Schiff base precipitated on cooling and then was filtered off, washed with ethanol and recrystallized from ethanol. The yield of Schiff bases was 75%.

Table (1): physical properties and yield of Schiff bases (1-3):

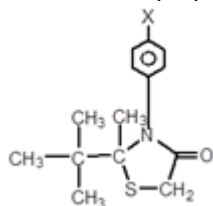


Comp. NO	X	m.p c°	Yield %	Color
1	<i>p</i> -NO ₂	141-143	75	Yellow
2	<i>p</i> -Br	58-60	74	Violet
3	<i>p</i> -Cl	64-66	72	Yellow

Preparation of 3-(substituted phenyl)-2-methyl-2-tert-butyl-4-thiazolidinone (4-6):

A mixture of different substituted Schiff base (0.009 mol) in absolute ethanol (30ml) was added to mercapto acetic acid (0.009mol). The reaction mixture was refluxed for (4hrs). A solid product was obtained after cooling, recrystallized in ethanol.

Table (2): The physical properties and yield of 4-thiazolidinone (4-6):

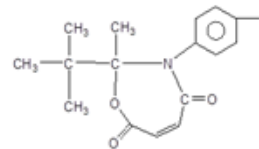


Comp. NO	X	m.p. c°	Yield %	Color
4	<i>p</i> -NO ₂	148-149	95	Yellow
5	<i>p</i> -Cl	63-64	80	White
6	<i>p</i> -Br	200-202	90	White

Preparation of 1-(substituted phenyl) -2-methyl-2-tert-butyl-1,3-oxazepine-4, 7-dione (7-12):

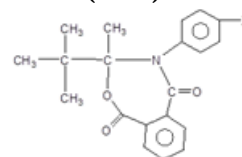
A mixture of different substituted Schiff base (0.01 mol) in (30 ml) of absolute ethanol and (0.01 mol) of anhydride (maleic or phthalic anhydride) was refluxed for (4hrs). The solvent was evaporated under reduced pressure, the precipitate washed with cold methanol and recrystallized from ethanol.

Table (3): The physical properties of oxazepines (7-9):



Comp. NO	X	m.p. c°	Yield %	Color
7	<i>p</i> -NO ₂	133-135	92	Yellow
8	<i>p</i> -Cl	197-200	51	Brown
9	<i>p</i> -Br	223-225	36	Green

Table (4): The physical properties of benzoxazepines (10-12):

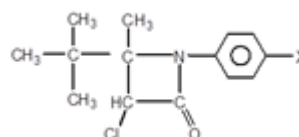


Comp. NO	X	m.p. c°	Yield %	Color
10	<i>p</i> -NO ₂	128-130	95	Yellow
11	<i>p</i> -Cl	129-131	54	Brown
12	<i>p</i> -Br	152-155	52	White

Preparation of 1-(substituted phenyl)-4-methyl-4-tert-butyl-3-chloro-2-azetadinone (13-15):

A mixture of different substituted Schiff base (1-3) (0.001 mol) and triethyl amine (0.002 mol) dissolved in (20 ml) of dry dioxane, (0.2241g, 0.002 mol) of chloroacetylchloride was added with stirring and cooling, for (24hrs). Then the mixture was stayed at room temperature for another (18hrs) to complete the reaction, the mixture was poured in to ice and the solid product were recrystallized from ethanol.

Table (5): The physical properties of azetadinones (13-15)



Comp.	X	m.p c°	yield%	Color
13	<i>p</i> -NO ₂	119-120	93	White
14	<i>p</i> -Cl	162-163	75	White
15	<i>p</i> -Br	173-174	83	White

Results and Discussion

A series of new Schiff base were synthesized by using a synthetic approach (schem 1) in which alcoholic solution of substituted aniline added dropwise to the alcoholic solution of pinacolone and refluxed for 6hrs. The required starting material (pinacolone) (I) was prepared in good yields by oxidation of pinacole alcohol using concentrated sulphuric acid.

IR spectrum of pinacolone showed an intense band at 1705 cm⁻¹ attributed to the appearance of C=O group stretching vibration, further evidence for the formation of target compound were obtained from the

reaction with 2,4-dinitrophenylhydrazine which gave a yellow precipitate of hydrazine.

The IR (KBr cm^{-1}) spectral data table (6) indicates the presses of

$\nu(\text{C}=\text{N})$ at $(1612-1631)\text{cm}^{-1}$, $\nu(\text{Ar}-\text{H})$ at $(3107-3195)\text{cm}^{-1}$, $\nu(\text{Ar}-\text{C}=\text{C})$ at $(1400, 1510, 1618)\text{cm}^{-1}$ with the disappearance of the carbonyl group band at 1705cm^{-1} .

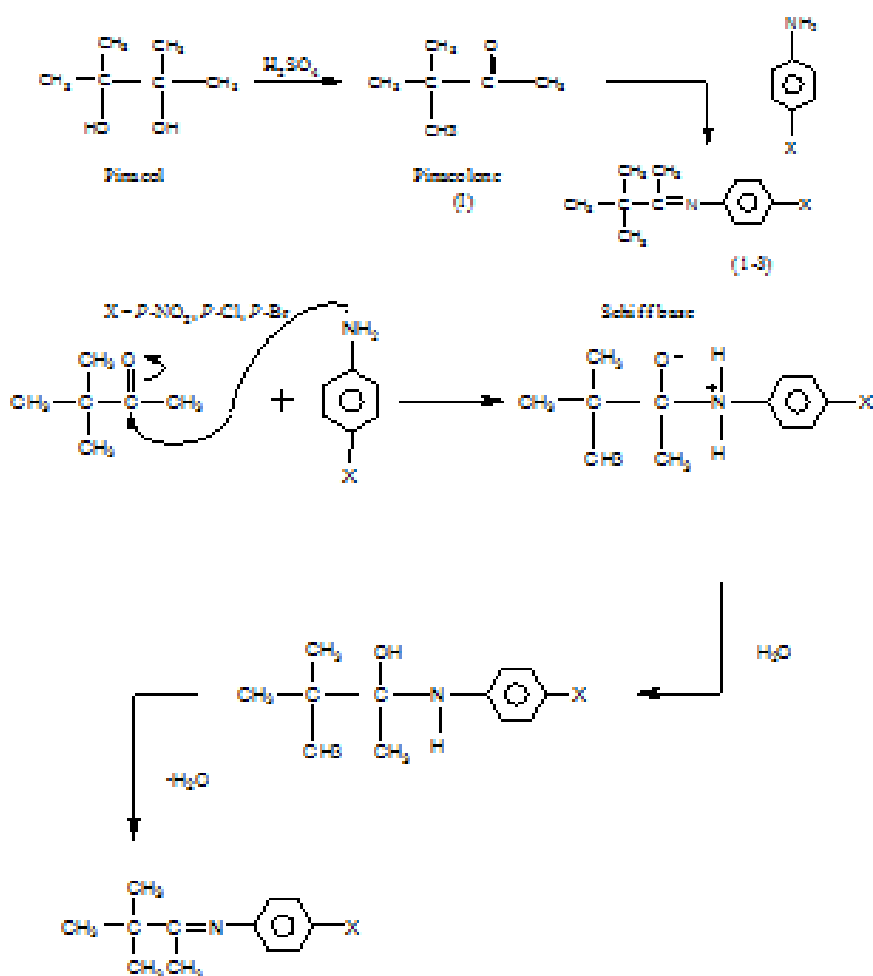
Table (6): spectral data of the Schiff base (1-3).

Comp. NO	X	C=NAr	C-H stretch Ar	C-H stretch allph	C=C Ar	Others
1	<i>p</i> -NO ₂	1631	3188	2980	1402,1510, 1631	NO ₂ sy (1306) Asy (1540)
2	<i>p</i> -Cl	1618	3195	2985	1402,1493, 1600	Cl (698)
3	<i>p</i> -Br	1612	3107	2990	1400,1493, 1618	Br (818)

NMR spectra of compound (1) indicates the presence of the following signals : ^1H NMR (300 MHz) ; ($\delta = 1.21$ ppm) singlet, equivalent to nine protons of the isobutyl protons, ($\delta = 1.87$ ppm) singlet, equivalent to three protons of the methyl group at the double bond;

and the AB quartet at ($\delta = 7.26 - 7.75$ ppm) of the para substituted aromatic protons.

Pinacolone was prepared from the oxidation of pinacol alcohol using diluted sulphuric acid scheme (1) describe the reaction rough.



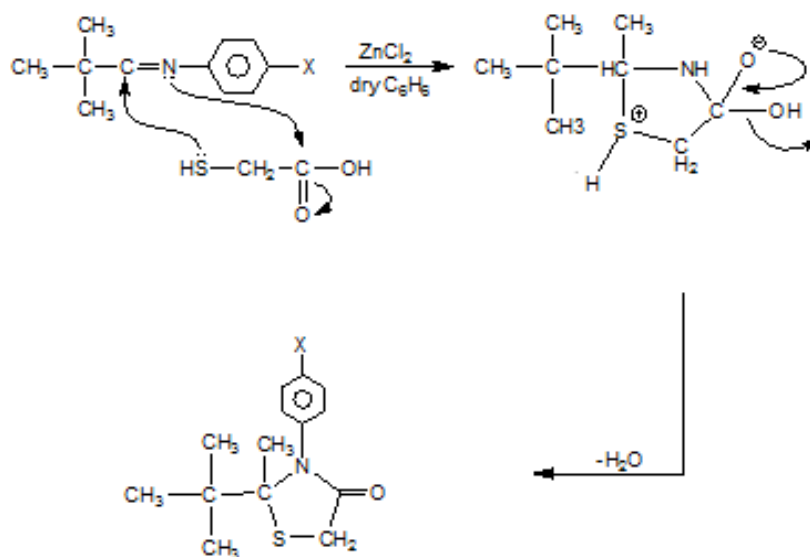
Scheme (1): Preparation of Schiff base (1-3)

Compounds (1-3) were allowed to react with mercapto acetic acid as in scheme (2) resulting in to the formation of 4-thiazolidinone compounds (4-6). The structures of these compounds were confirmed according to the IR spectral data which indicate the presence of carbonyl group for β -lactam with the range of $(1648-1666)\text{cm}^{-1}$, the C-N band at $(1522-1547)\text{cm}^{-1}$, the C-S band at $(1109-1117)\text{cm}^{-1}$ for sym and $(1182-1188)\text{cm}^{-1}$ for asym. The Ar-H stretching

$(3049-3084)\text{cm}^{-1}$ while C-H stretching of alkyl group at $(2924-2939)\text{cm}^{-1}$ and the C=C bands of an aromatic system are at $(1469-1493)\text{cm}^{-1}$ and $(1597-1618)\text{cm}^{-1}$. Compound (5) gives the following signals in ^1H NMR (300 MHz):

($\delta = 1.22$ ppm) equivalent to nine protons of isobutyl, ($\delta = 2.10$ ppm) singlet equivalent to three protons of methyl group ($\delta = 3.65$ ppm) singlet, two protons of

the $-\text{CH}_2-$ group and AB quartet at ($\delta = 7.31$ - 7.82 ppm of the aromatic protons.



Scheme (2): Mechanism of the synthesis of 3-(substituted phenyl)-2-methyl-2-tert-butyl-4-thiazolidinones (4-6).

1, 3-oxazepine compounds were obtained from the reaction of Schiff base (1-3) with either maleic anhydride for compounds (7-9) or phthalic anhydride for compounds (10-12) as in scheme (3).

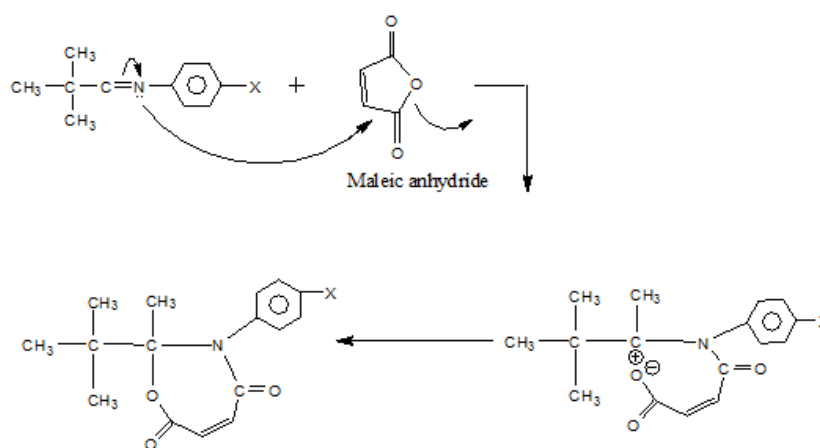
The structures of these compounds were investigated according to the IR spectral data which indicate the presence of the carbonyl group for both lactam and lactone within the range (1630 - 1643) cm^{-1} , (1703 - 1712) cm^{-1} respectively, also the other bands of

aromatic and aliphatic are appeared exactly as expected.

Compound (9) gives the following signals in 300 MHz NMR spectra:

(1.20^δ , singlet, 9H), (2.71^δ , singlet, 3H), (6.22 - 6.41^δ , doublet, 2H) of the ethylene protons; and AB quartet at (7.41 - 7.73^δ , 4H) of the aromatic protons.

The mechanism of the formation of the above compounds can be proposed as follows in scheme (3).



Scheme (3): Mechanism of the formation of 1-(substituted phenyl)-2-methyl-2-tert-butyl-1,3-oxazepine-4,7-dione (7-9) and 1-(substituted phenyl)-2-methyl-2-tert-butyl-5,6-(benz)-1,3-oxazepine-4,7-dione (10-12).

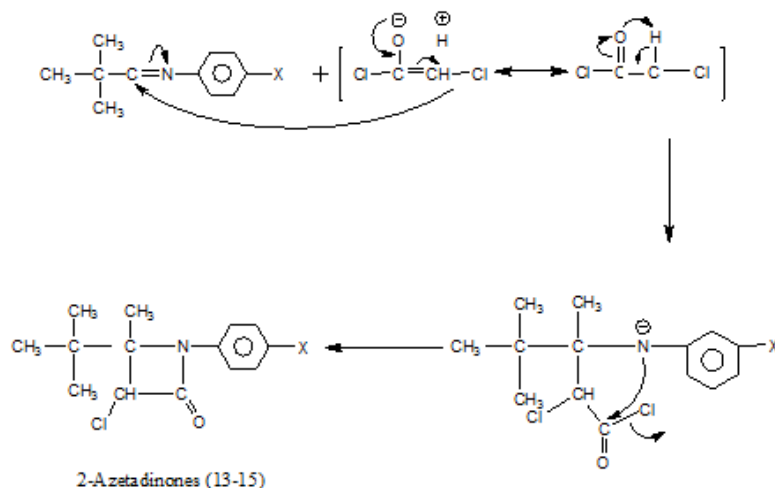
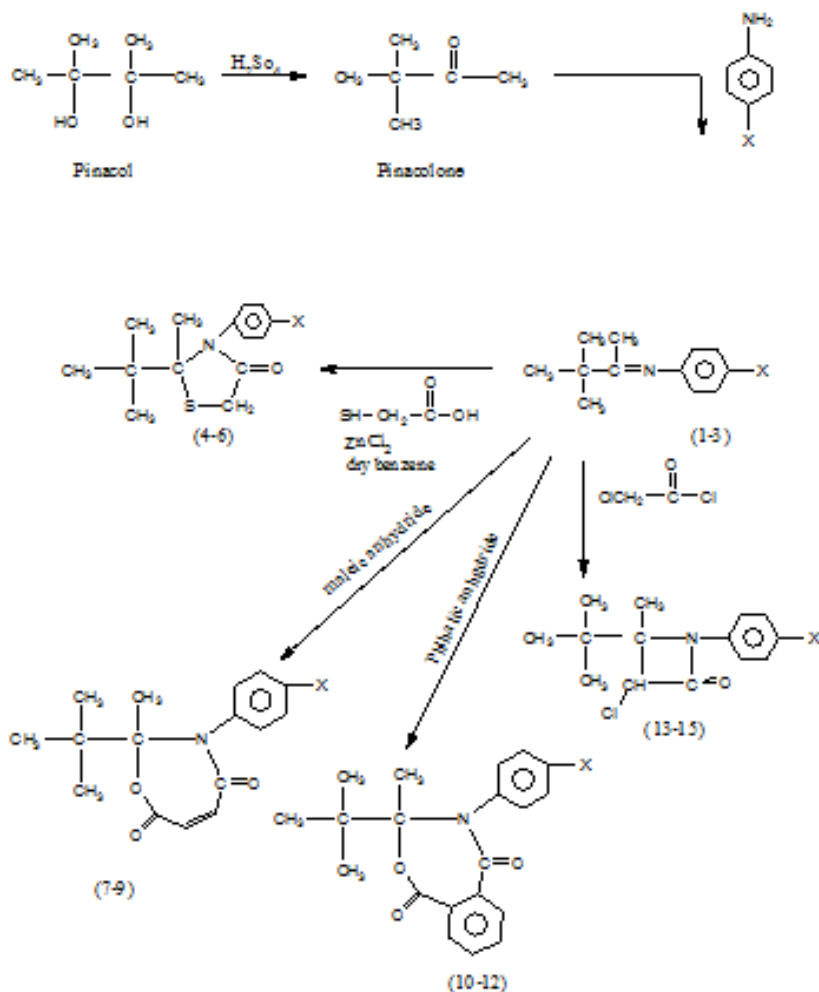
These Schiff base (1-3) was allowed to react with chloroacetyl chloride as mentioned in the experimental section of this work. The resulting azetidine-2-one compounds (13-15) were characterized according to the IR spectral data table

(6), which indicate the presence of the carbonyl group of the β -lactam ring absorbed within the range ν (1672 - 1687) cm^{-1} , ν (C-N) (1248 - 1257) cm^{-1} the N-H stretching absorption at (3280 - 3300) cm^{-1} , the other spectral data could be shown in table (7).

Table (7): spectral data of the azetidine -2- one compounds (13-15).

Comp. NO.	X	C-H Ar	C-H alph	C=O	C-N	C=C Ar.	C-Cl
13	<i>p</i> -NO ₂	3084	2951	1672	1248	1614	777
14	<i>p</i> -Cl	3107	2941	1687	1257	1630	752
15	<i>p</i> -Br	3078	2999	1672	1248	1608	773

The mechanism of the formation of azetidine compounds can be illustrated as:

**Scheme (4): Mechanism formation of 1-(substituted phenyl) -4-methyl-4-tert-butyl-3-chloro-2-azetidinone.****Scheme (5): The total synthesis pathways of all compounds**

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تحضير ودراسة بعض المركبات الحلقية غير المتجانسة من قواعد شيف للبيناكولون

ناطق غانم احمد ، هديل سمير عزيز ، غفران ذنون صديق

قسم الكيمياء ، كلية التربية للعلوم الصرفة ، جامعة الموصل ، الموصل ، العراق

الملخص

في هذا العمل تم تحضير عدد من المركبات الحلقية غير المتجانسة الرباعية والخماسية والسباعية الحلقة. عند اكسدة كحول البيناكولون باستعمال حامض الكبريتيك المركز تم الحصول على البيناكولون الذي استعمل كمادة اولية لتحضير ثلاث قواعد شيف جديدة من خلال تفاعله مع الانيلين المعوض، عند مفاعلة هذه الاليمينات مع كلورو اسيتيل كلوريد في الداويكسان الجاف اعطت مركبات الازدتين -2- اون كذلك بعض مركبات الثايوزولودين تم تحضيرها من تفاعل الاليمينات المذكورة مع حامض الثايوكلايكوليك بوجود كلوريد الخارصين في البنزين الجاف وتم الحصول على 1،3- اوكسازينين -4،7- ثنائي اون من تفاعل الاليمينات مع انهيديريد الماليك والفتاليك في البنزين الجاف. تم تشخيص المركبات المحضرة بوساطة طيف الاشعة تحت الحمراء (IR) وطيف الرنين النووي المغناطيسي (^1H NMR) والخواص الفيزيائية.