PREPARATION, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF SOME NEW (2-ISOXAZOLINE) AND (2-PYRAZOLINE) DERIVATIVES FROM AROMATIC HETROCYCLIC CHALCONES[+]

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Abstract

In this paper new series of (2-Isoxazoline) VI_{a-c} and (2- Pyrazoline) V_{a-c} were prepared by condensation of aromatic Hetrocyclic Chalcones III_{a-c} with hydroxylamine hydrochloride and phenyl hydrazine using glacial acetic acid .The synthesized compounds III_{a-c}, VI_{a-c}, V_{a-c} were characterized by using FT/IR spectra, C.H.N. analysis. The validity of the expected chemical compounds to the prepared compounds in this search was obvious from FT/IR spectra and C.H.N. results. It also deals with study of the biological activity of the prepared compounds (VI_{a-c}), (V_{a-c}) which showed biological activity against (Escherichia coli and Staphylococcus aureus) in comparison to the aromatic Hetrocyclic Chalcones IIIa-c. The verification between (2-Isoxazoline) and (2- Pyrazoline) is in their abilities to inhibit the growth of gram positive and gram negative bacteria.

المستخلص

حضرت سلسلة من مركبات VI_{a-c} (2-Isoxazoline) و V_{a-c} (2- Pyrazoline) الحلقية غير المتجانسة من تكاثف الجالكونات الحلقية غير المتجانسة III_{a-c} مع الهيدروكسيل امين هيدروكلورايد والفينيل هيدرازين باستخدام حامض الخليك الثلجي على التوالي. تم تشخيص المركبات المحضرة III_{a-c} و VI_{a-c} و V_{a-c} باستخدام تحليل العناصر الدقيق(C.H.N) وطيف الأشعة تحت الحمراء وقد أثبتت هذه التحاليل صحة التراكيب المتوقعة للمركبات المحضرة . كما تمت دراسة الفعالية البايولوجية للمركبات المحضرة VI_{a-c} و V_{a-c} وقد تميزت بفعالية بايولوجية ضد نوعي البكتريا (Escherichia coli and Staphylococcus aureus) مقارنة مع المركبات الجالكونية الحلقية غير المتجانسة المحضرة III_{a-c} . وقد تباينت مركبات (2-Isoxazoline) و(2- Pyrazoline) في مدى تثبيط نمو الجراثيم الموجبة والسالبة لملون كرام.

Introduction

There are several methods for the synthesis of (2-Isoxazoline) and (2- Pyrazoline) derivatives. One approach is 1,3-dipolar cyclo addition reaction of nitrile oxide [1-2]and nitrile imine [3] with olefins according to the following equation: -

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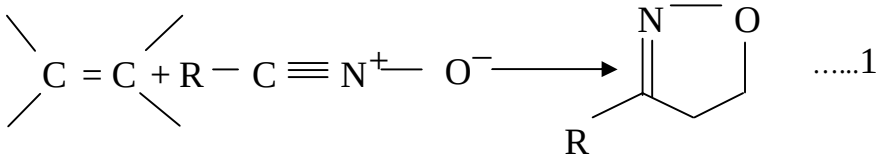

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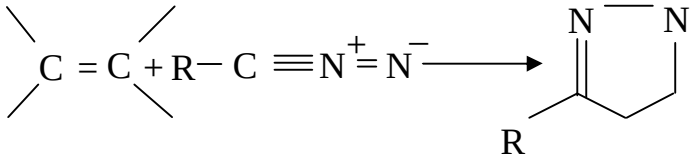

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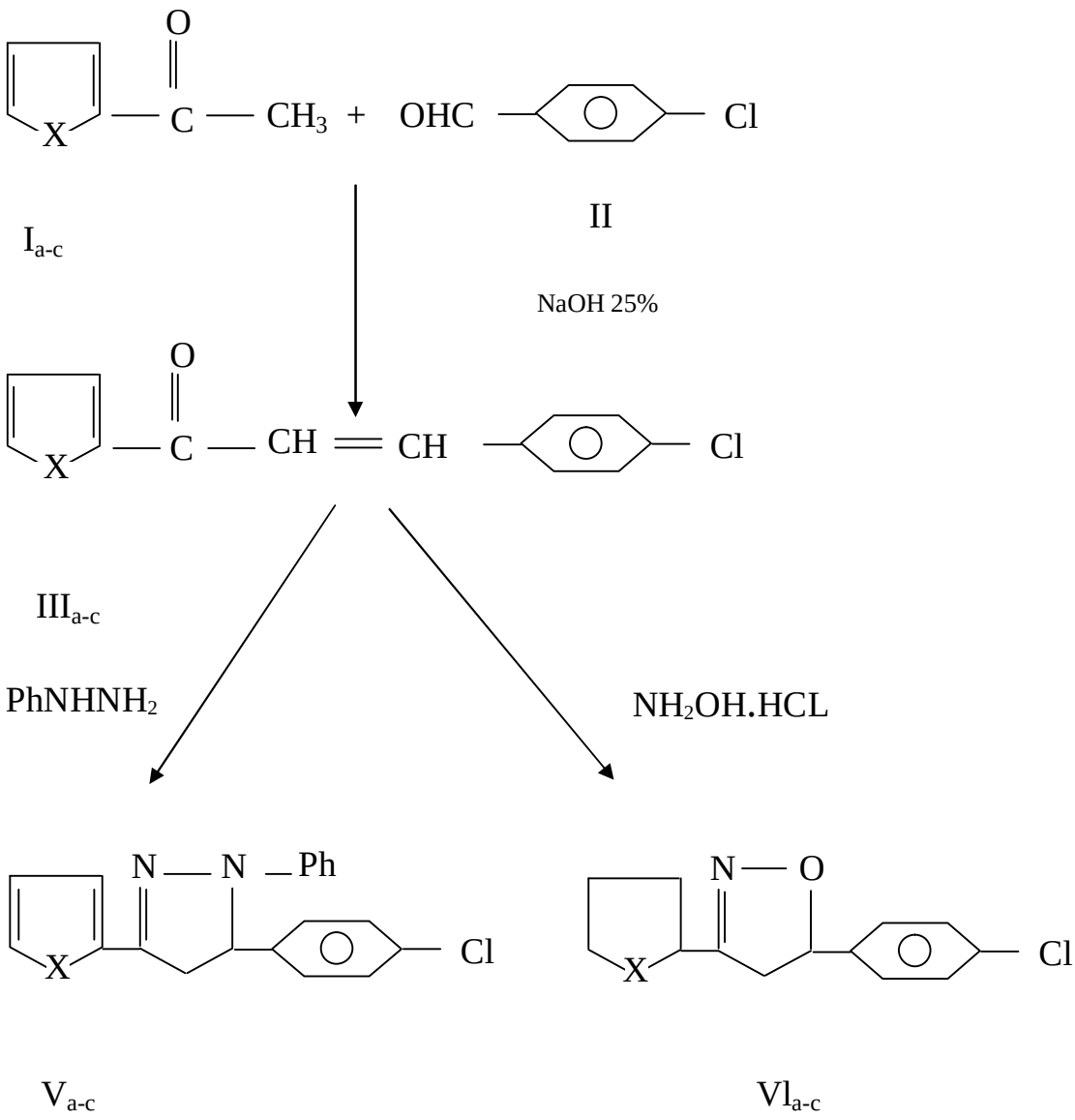
In recent years one of the methods used for the synthesis of (2-Isoxazoline) and (2- Pyrazoline) compounds includes condensation of Chalcones with hydroxylamine hydrochloride and phenyl hydrazine [4] alternatively according to scheme (1).

Isoxazoline and Pyrazoline derivatives have been reported to possess biological activities [1-2]. Some pyrazoline derivatives were used as bacteriostatic, fungicidal and anti cancer agents [5]

In addition, Isoxazoline compounds have been shown to have anti tuberculosis and anti- biotic activities [6-8].Our plan is to incorporate these active isoxazoline groups [1-3] with the structure of aromatic Hetrocyclic (five membered ring) containing [7] (S, N, O), with the aim of increasing their biological activity.

Scheme (1)



Xa=S; Xb=O; Xc=N

Experimental

Melting points were determined on Gallen Kamp Thermal point apparatus and are uncorrected. Reactions were monitored by using TLC plate silica gel (Merk) with 1:9 MeOH- Benzene and detection by exposure to iodine vapor.

Column chromatography was performed on silica gel (Merk, 230-400 mesh). IR spectra were recorded on a FT/IR Shimadzo 2000 instrument. The prepared

compounds were analyzed for C.H.N. by using (Calo Erba strumentazion Elemental / Analysis Lab.E.A.G.E.R 100) instrument.

Preparation of 3-(4'-chloro phenyl)-1-(α -Thiophene) propene-1-one III_a

2-Acetyl thiophene I_a (0.01mole) was dissolved in ethyl alcohol (25 ml) and (0.01 mole) of p-chloro benzaldhyde II was added, followed by the addition of solution of sodium hydroxide (25%).The mixture was prepared in ice bath and stirred for three hrs, then allowed to stand at $0c^0$ for 24hrs..The mixture was diluted with water (25 ml) and acidified with dilute solution (10%) acetic acid. The formed precipitate was filtered off. Purification was performed by using column chromatography followed by crystallization from methanol.

Preparation of 3-(4'-chloro phenyl)-1-(α -Furan) propene-1-one III_b

2-Acetyl furan I_b (0.01mole) was dissolved in ethyl alcohol (25 ml) and (0.01 mole) of p-chloro benzaldhyde II was added, followed by the addition of solution of sodium hydroxide (25%).The mixture was prepared in ice bath and stirred for three hrs, then allowed to stand at $0c^0$ for 24hrs..The mixture was diluted with water (25 ml) and acidified with dilute solution (10%) acetic acid. The formed precipitate was filtered off. Purification was performed by using column chromatography followed by crystallization from methanol.

Preparation of 3-(4'-chloro phenyl)-1-(α -Pyrrol) propene-1-one III_c

2-Acetyl pyrrol I_c (0.01mole) was dissolved in ethyl alcohol (25 ml) and (0.01 mole)of p-chloro benzaldhydeII was added, followed by the addition of solution of sodium hydroxide (25%).The mixture was prepared in ice bath and stirred for three hrs, then allowed to stand at $0c^0$ for 24hrs..The mixture was diluted with water (25 ml) and acidified with dilute solution (10%) acetic acid. The formed precipitate was filtered off. Purification was performed by using column chromatography followed by crystallization from methanol.

General Procedure for the Preparation of (2- Isoxazoline) [4] $VI_{(a-c)}$

Chalcones III_{a-c} (0.01 mole) were dissolved in ethanol (10ml) and a mixture of hydroxyl amine hydrochloride (0.8 gm) in ethanol (8 ml) and water (2 ml) was added, followed by few drops of potassium hydroxide (50%).The mixture was refluxed for 9hrs. The formed solid was filtered off and crystallized from ethanol.

General Procedure for the Preparation of (2- Pyrazoline) [4] $V_{(a-c)}$

Chalcones III_{a-c} (0.01 mole) were dissolved in glacial acetic acid (10 ml) and refluxed with phenyl hydrazine (1.1 ml) for 8 hrs. The reaction mixture was cooled and poured on to water. The precipitate thus formed was filtered off and crystallized from ethyl alcohol.

The prepared compounds III_{a-c}, VI_{a-c}, $V_{a-w}$are characterized by determination of their melting point Table (1). The C.H.N. analysis Table (2) and infrared spectra data in Table (3)

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Table (1)

No.	Compound	Yield %	m.p c^{o}
III_a	3-(4'-chloro phenyl)-1-(α-Thiophene) propene-1-one	85	130-132
III_b	3-(4'-chloro phenyl)-1-(α-furan) propene-1-one	92	140-142
III_c	3-(4'-chloro phenyl)-1-(α-pyrrol) propene-1-one	92	106-108
VI_a	2-(5-(4'-chloro phenyl)-2-isoxazoline-3-yl)thiophene	84	153-155
VI_b	2-(5-(4'-chloro phenyl)-2-isoxazoline-3-yl)furan	91	146-148
VI_c	2-(5-(4'-chloro phenyl)-2-isoxazoline-3-yl)pyrrol	62	76-78
V_a	2-(5-(4'-chloro phenyl)-2-pyrazoline-3-yl)thiophene	90	170-172
V_b	2-(5-(4'-chloro phenyl)-2- pyrazoline -3-yl)furan	72	159-161
V_c	2-(5-(4'-chloro phenyl)-2- pyrazoline -3-yl)pyrrol	68	113-115

Table (2)

No.	Molcular formula	Calculated			Found		
		C	H	N	C	H	**N**
III_a	$C_{13}H_9OSCl$	62.7766	3.6217	0	62.05699	3.5460	0
III_b	$C_{13}H_9O_2Cl$	67.0967	3.8709	0	67.0439	3.8191	0
III_c	$C_{13}H_{16}NOCl$	67.3866	4.3196	6.0475	67.2865	4.2562	6.0389
VI_a	$C_{13}H_{10}NOSCl$	59.2030	3.7950	5.313	59.2065	3.5592	5.5592
VI_b	$C_{13}H_{10}N O_2Cl$	63.0303	4.0404	5.6565	63.0065	4.0562	5.5689
VI_c	$C_{13}H_{11}N_2OCl$	63.2860	4.4624	11.3590	63.2765	4.4262	11.1102
V_a	$C_{19}H_{15}N_2SCl$	67.3559	4.4313	8.2717	67.2995	4.3912	8.1802
V_b	$C_{19}H_{15}N_2OCl$	70.6976	4.6511	8.6821	69.9965	4.6262	8.6192
V_c	$C_{19}H_{16}N_3Cl$	70.9175	4.9766	13.0637	70.8765	4.776	13.1102

Table (3) IR data of the prepared compounds

No.	Arom. (C-H) st	(N-H) st	(C=O) st	Alph. (C=C)	(C=N) st	(C-O) st	(C-N) st	(N- O) st	(C-S) st	(C-Cl) st
III_a	3010	–	1686	1620	–	1050	–	–	1100	510
III_b	3040	–	1668	1625	–	1070	–	–	–	515
III_c	3025	3490	1665	1623	–	1065	–	–	–	513
VI_a	3060	–	–	–	1635	1055	1020	1250	1110	500
VI_b	3065	–	–	–	1638	1030	1100	1270	–	506
VI_c	3078	–	–	–	1638	1080	1090	1325	–	510
V_a	2290	–	–	–	1585	1070	1110	1325	1150	530
V_b	3100	–	–	–	1590	1050	1080	1290	–	535
V_c	3010	–	–	–	1590	1030	1070	1280	–	520

Results and Discussion

As shown in scheme (2), the condensation of some 2-acetyl aromatic hetrocyclic compounds I_{a-c} with the p-Chloro benzalahyde II results in the corresponding Chalcones III_{a-c} . The condensation of Chalcones III_{a-c} with phenyl hydrazine in glacial acetic acide leads to the formation of (2-Pyrazoline) derivatives V_{a-c}. on the other hend condensation of Chalcones III_{a-c} with hydroxyl amine hydrochloride geves the (2-Isoxazoline) derivatives VI_{a-c}. The synthesized compounds characterized by using FT/IR and C.H.N. analysis which proved their structures.

The verification between (2-Isoxazoline) and (2-Pyrazoline) is in their abilities to inhibit the growth of gram positive and negative bacteria in comparison to aromatic heterocyclic Chalcones III_{a-c} . The results in table (4) show that (2-Isoxazoline) derivatives and (2-Pyrazoline) derivatives have higher biological activity than hetrocyclic Chalcones due to the presence of Isoxazoline and Pyrazoline groups attached to aromatic hetrocyclic rings.

Table (4)

No.	Escherichia Coli (mg\l)				Staphylococcus aureus (mg\l)			
	50	100	150	200	50	100	150	200
III_a	–	–	–	0.3	–	–	–	0.5
III_b	–	–	–	0.1	–	–	0.3	0.5
III_c	–	–	o.1	0.2	–	–	–	0.4
VI_a	–	0.2	0.5	1.0	0.8	1.0	1.1	1.2
VI_b	–	–	0.3	0.5	0.3	0.3	0.7	1.5
VI_c	–	–	0.2	0.5	–	–	0.4	0.7
V_a	–	0.1	0.3	0.6	–	0.6	0.9	1.0
V_b	–	0.1	0.2	0.4	–	0.6	0.7	1.2
V_c	–	–	0.1	0.3	–	–	0.3	0.5

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