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Synthesis and Biological Activity Study of Some New Substituted Pyrrolidines

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ABSTRACT

Chalcones (1,3-diaryl-2-propen-1-ones) (1-13) were prepared using Claisen-Schmidt condensation, while Schiff bases (N-arylidene benzylamines) (14-20) were produced by the condensation of benzyl amine with substituted benzaldehydes. Schiff bases were added through 1,3-anionic cycloaddition to the double bond of chalcones under phase-transfer catalysis conditions to afford the corresponding heterocycles (pyrrolidines 21-30).

Spectral methods were used to support the structures of the new products, while the suggested mechanisms were investigated depending on the spectral identification as well as some theoretical parameters such as heat of formation (H.F) and steric energy (S.E). The biological activity of some reactants and some final products had been tested through its effects on two kinds of bacteria.

تحضير ودراسة الفعالية البايولوجية لبعض البايروليدينات المعوضة الجديدة

الملخص

حضرت الجالكونات (1،3-ثنائي اريل –2-بروبين-1-ون) (1-13) من خلال تكاثف كليزن-شميدت، بينما قواعد شيف (N-ارايليدين بنزايل أمين) (14-20) حضرت من تكاثف البنزايل أمين مع البنزالديهايدات المعوضة. لقد أضيفت قواعد شيف من خلال الإضافة الانيونية الحلقية نوع 1،3 إلى الاصرة المزدوجة في الجالكونات تحت ظروف التحفيز بانتقال الطور لتعطي الحلقات غير المتجانسة المقابلة (البايروليدينات 21-30) .استخدمت الطرق الطيفية لدعم تراكيب النواتج الجديدة، بينما تم التحقق من الميكانيكيات المقترحة اعتمادا على التشخيص الطيفي إضافة إلى بعض العوامل النظرية مثل حرارة التكوين (H.F) وطاقة الإعاقة (S.E). ان الفعالية البايولوجية لبعض المواد المتفاعلة وبعض النواتج النهائية قد اختبرت من خلال تأثيراتها على نوعين من البكتريا.

INTRODUCTION

Pyrrolidines are considered as an important medical compounds as well as naturally-occurring products, which possess biological activity (liotta, 2003).

Pyrrolidine dithiocarbamate (PDTC) is used as an anti-viral by inhibiting the gene which is responsible for influenza (Cox and Kawaoka, 1998), on the other hand oxopyrr - olidine substituted with different substituents e.g.: methylcarboxylate and hydroxymethyl are considered as an antimicroorganisms such as *Rod bacteria Enterococci* and *Anaerobes*.

Pyrrolidines substituted with hydroxyl group are important as: insecticidal, anti-viral and anti-aids compounds (Liotta, 2003). Polydroxy- pyrrolodines or polyhydroxpyrrolizidines both interesting compounds as potential glycosidase inhibitors (Andrea,1999). It is worth mentioning that there are many known natural and synthetic biologically active compounds, as well as chiral auxiliaries and ligands containing pyrrolidine moiety (Mercedes, 2003). 4-(Pyrrilidino) pyridine PPY is a potent nucleophilic catalyst for acyl transfer and related transformations, preliminary results pertaining to the use of PPYs as catalysts for kinetic resolutions KR of 1-phenylethanol are also described (Alan, 2000). Disubstituted pyrroles can serve as versatile precursors for the synthesis of polyhydroxylated pyrrolidines natural products with intriguing structures and potent biological activity, which centers around their ability to inhibit a variety of glycosidases (Timothy, 2003). It is found that the thermal or photochemical electrocyclic ring opening of aziridines led to azomethine ylides which play a prominent role in pyrrolidine synthesis, as 1,3-dipoles may be trapped in [3+2] cycloaddition reactions (Patrick, 2004).

EXPERIMENTAL

1. Melting points were determined by Electrothermal 1A 9000 Digital-Series Melting point 1998 Apparatus (uncorrected).
2. Ultraviolet spectra were obtained using Cintra 5 GBC Scientific U.V-Visible Spectro-photometer.
3. Infrared spectra were recorded on :
   a. Pye-Unicam Spectronic 2000,Infrared spectrophotometer.
   b.Thermo Nicolte, Fourier-transform infrared (FT-IR) Spectrophotometer.
4. Theoretical calculations

It was achieved by calculating the heat of formation (H.F) and steric energy (S.E) for prepared compounds using CS-Chem Office Version-6.0 in computer.

Preparation of Chalcones (1, 3- diaryl-2-propen-1-one)(1-13) (General procedure) (Vogel I., 1956):

In a 100ml round-bottomed flask provided with a mechanical stirrer and immersed in an ice-bath, a mixture of (2.2g, 0.055 mole) of sodium hydroxide pellets, (20 ml) of water and (12.5 ml, 0.2 mole) of ethanol was stirred. A (0.043 mole) of freshly distilled portion of the desired acetophenone was poured on the stirred mixture followed by (0.043 mole) of a freshly distilled benzaldehyde. The temperature of the mixture was kept at 20-25ºC with a vigorous stirring for (2-3) hours, until the mixture became thick, then kept in an ice chest or a refrigerator overnight. The product was filtered under vacuum and washed with water until the filtrates were neutral to litmus, then crude chalcone, after drying in air, was recrystillised from ethanol, see Table(1).

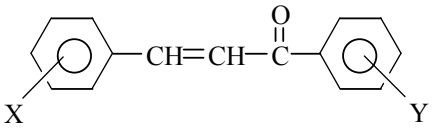


Table 1 : Some physical properties of prepared Chalcones (1-13).

Cpd. No.	X	Y	Reaction time (hr.)	Reaction temp.(°C)	Melting point Found /Lit*(°C)	Yield (%)
1	H	H	3	25	54-56 52-54	82
2	H	H	4	15	82-84	74
3	H	*p*-Cl	3	25	94-96 94-96	70
4	H	*P*-NO_2	3	20	133-135 132-134	65
5	H	*p*-Br	2	25	100-102 103-105	70
6	*o*-Cl	H	3	25	143-145	93
7	*o*-Cl	*P*-NO_2	3	20	161-163	60
8	*o*-Cl	*p*-Cl	2	20	79-81	60
9	*o*-Cl	*p*-Br	3	25	77-79	75
10	*o*-Cl	H	3	20	104-106	73
11	*m*-NO_2	*p*-Cl	3	20	144-146	85
12	*m*-NO_2	*p*-Br	3	25	156-154	80
13	*m*-NO_2	H	3	25	110-108 107-109 **	98

* (Toda,F.1998)
** (AL-Hamdany,2002)

The structures of prepared chalcones (1-13) were supported by spectral methods (IR,U.V), see Table (2).

Table 2 : Spectral data of chalcones (1-13).

Cpd. No.	IR (KBr) , ν (cm-1)		U.V
	C = O	C = C	λ max (nm)
1	1653	1610	341
2	1688	1609	338
3	1681	1631	315
4	1729	1629	303 , 306
5	1783	1600	324
6	1650	1612	307
7	1650	1607	314
8	1651	1604	331
9	1620	1600	292
10	1655	1605	301
11	1650	1605	314
12	1650	1605	360
13	1665	1620	243

Preparation of Schiff bases (N-arylidene benzylamines) (14-20) (Vogel II,1951):

In a 100ml beaker, (0.01 mole) of benzylamine was heated with (0.01 mole) of the desired benzaldehyde for (10 min.) at 100ºC after the addition of (10 ml) n-butanol. The reaction mixture was cooled and the precipitate was filtered which then recrystallised from ethanol (liquid products were purified by distillation), see Table (3).

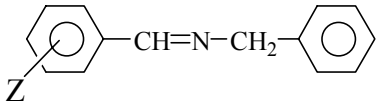


Table 3 : Some physical properties of prepared Schiff bases (14-20).

Cpd. No.	Z	Colour and shape	Melting or Boiling point Found /Lit*(ºC)	Yield (%)
14	H	Yellow liquid	144-146 143-144	81
15	*m*-NO_2	Yellow crystalline precipitate	59-60 59-61**	71
16	*o*-Cl	Colourless gel	115-117	97
17	2,4-DiMeO	Yellow liquid	210-212 212-215**	60
18	3,4-DiMeO	Indigo ppt.	55-57	48
19	*o*-NO_2	Dark yellow liquid	145-146	87
20	3,4-Di Cl	White ppt.	142-144	50

* (Aldrich,1990-1991)
** (AL-Hamdany, 2002)

The structures of the prepared Schiff bases (14-20) were supported by spectral methods (IR,U.V), see Table (4).

Table 4 : Spectral data of Schiff bases (14-20).

Cpd. No.	IR (KBr) , ν (cm-1)		U.V (CHCl3)
	C = N	N=O	λ max (nm)
14	1645	….	301
15	1665	1443	302
16	….	….	301
17	1665	….	302
18	1650	….	302
19	1675	1500	314
20	1655	….	334

Condensation of Chalcones, with Schiff bases (Synthesis of pyrrolidines 21-30) (AL-Hamdany, 2002):

General procedure:

A mixture of Schiff base (10 mmole) and chalcone (10 mmole) was magnetically stirred in the presence of benzyltriethylammonium chloride TEBA (0.12 gm, 0.5 mmole) and (3 ml) of 50% sodium hydroxide solution. The stirring was continued for (1 hr) at room temperature in dimethyl sulfoxide (DMSO) (10 ml) as a solvent. The mixture was allowed to stand overnight. Water (100 ml) was then added to the reaction mixture, the separated precipitate was washed with water until the filterate became clear and neutral. The solid product was then dried and recrystallised from methanol-ethyl acetate, see Table (5, 6).

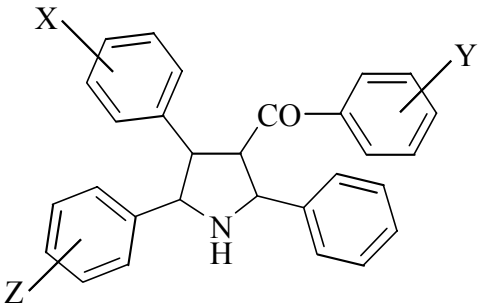


Table 5 : Some physical properties of synthesized pyrrolidines from the condensation of chalcones with Schiff bases (21-30).

Cpd. No.	X	Y	Z	Colour	Melting point (°C)	Yield (%)
21	H	H	H	Pale yellow	154-157	64
22	*m*-NO_2	H	3,4-DiMeO	Dark yellow	178-180	45
23	H	*p*-Cl	*m*-NO_2	Dark brown	133-137	55
24	H	*o*-Cl	*p*-Cl	Pale yellow	133-135	54
25	*o*-Cl	*p*-Br	3,4-Di Cl	Very pale yellow	173-177	71
26	H	*p*-Br	3,4-DiMeO	Pale yellow	95-99	84
27	H	*p*-NO_2	2,4-DiMeO	Yellow	142-146	41
28	*o*-Cl	H	*m*-NO_2	Pale yellow	113-115	76
29	*o*-Cl	*p*-Cl	H	Orange	89-91	64
30	*m*-NO_2	*p*-Cl	H	Dark yellow	297	54

RESULTS AND DISCUSSION

Pyrrolidines were the major products in the present work, which includes cyclic NH and had no C=C to be compared with chalcones.

The spectral data were used to support the structures of the synthesized pyrrolidines from chalcones and Schiff bases, see Table (6).

Table 6 : Spectral data of pyrrolidines(21-30).

Cpd. No.	IR (KBr) , ν (cm-1)					U.V (CHCl3)
	C = O	N - H	$\diagdown\overset{+}{}\diagup NH_2$	NO2	C---C	λ max (nm)
21	1662.8	3250	….	….	1595.5	340
22	1652.87	….	2360.61	1527.33	1558.70	368
23	1662	3250	….	….	1580.96	273
24	1648	3600	….	….	1577.6	287
25	1614.6	3500	….	….	1561.7	301
26	1638.7	3400	….	….	1566.5	309
27	1636.10	….	2360.69	1540.83	1558.61	367
28	1648.3	3470	….	….	1585.7	290
29	1652.96	….	2360.30	1540.49	1558.70	301
30	1635.76	….	2360.56	1540.55	1558.78	364

The IR spectra for compounds (21-30) showed strong absorption band in the range of (1662.8-1614.6 cm-1) related to the stretching vibration of carbonyl groups (Pstraugham and Wiker, 1976) and a broad absorption band in the range of (3600-3250 cm-1) related to the stretching vibration of NH (Crews and Rodrigues, 1998). The FT-IR spectra also manifests absorption bands in the range (2360.69-2360.30 cm-1) reflect the stretching vibration of $\diagdown\overset{+}{}\diagup NH_2$ which are due to the overtone bands of the cyclic secondary amine (Williams and Fleming, 1973). These spectra also showed absorption band at (1595.5-1558 cm-1) related to the stretching vibration of the aromatic ring (Williams and Fleming, 1973). The appearance of absorption bands at (1540.83-1527.33 cm-1) was assigned due to the nitro groups stretching vibrations (Williams and Fleming, 1973).

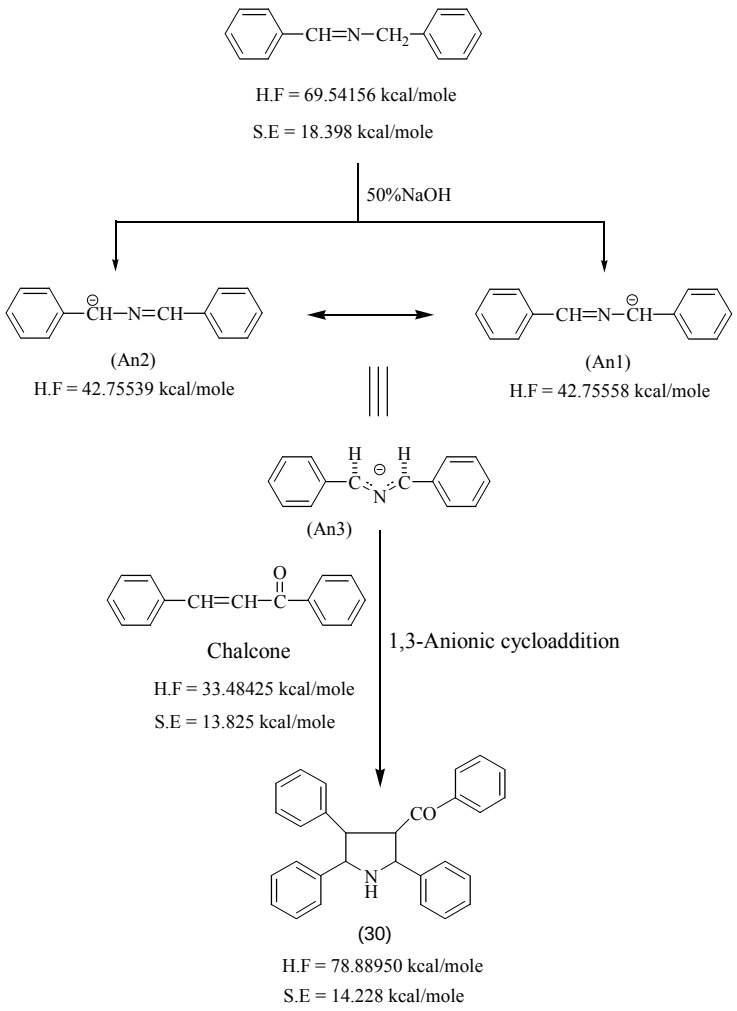
The U.V spectra showed wavelength at maximum absorption (λmax) (273-368 nm) which reflects a bathochromic shift (red shift) in comparison with the starting materials, chalcones (Table 2), probably due to the accumulation of unstauration and auxochromes, in addition, $n \longrightarrow \pi^*$ transitions of the carbonyl group in these compounds may interpret this shift.

The suggested mechanism for the formation of pyrrolidines (21-30) via cyclisation is the 1,3-anionic cycloaddition which may be explained as follows:

The first step is the formation of the anion An1 due to the abstraction of the proton from CH2 of the Schiff base by the strong base (Sodium hydroxide) which through the resonance transformed to the anion An2, the two anions An1 and An2 could be represented as An3 (Scheme 1).

The second step is the 1,3-anionic cycloaddition of An3 at the C=C of the chalcone to afford the five-membered ring pyrrolidine.

The afforded substituted pyrrolidines (21-30) are stable and the five-membered nucleous is planer as shown in Figure (1).



Scheme 1 :The 1,3-Anionic cycloaddition of Schiff base (14) to chalcone (1).

The three dimensional structure of pyrrolidine (21) is illustrated in figure-1

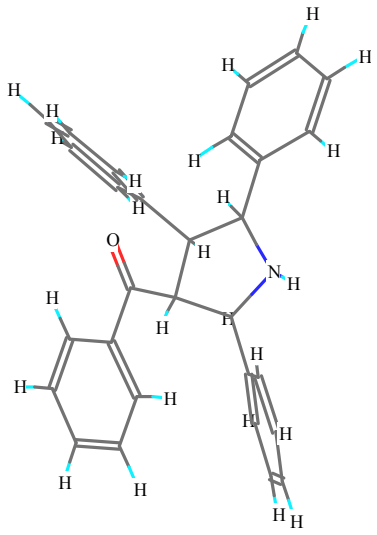


Figure 1 :The 3D-structure of pyrrolidine (21).

Preliminary biological study:

In the present work, preliminary biological study is carried out. The biological inhibitory effect (s) of certain products such as: Schiff bases, Chalcones and Pyrrolidines against two types of bacterial groups such as: Gram-negative, *E. coli* and Gram-positive *staphylococcus aureus* were investigated (Table 7).

The isolates were isolated and identified in Biology Dept. in the College of Science at Mosul University. The standard Kirby and Bauer method was used (Bauer and Kirby, 1966).

A loopful of each bacteria species were cultures in nutrient broth and incubated at (37ºC) for (14-16 hr), then evently distributed on the nutrient agar by using a sterile swab. The plates were incubated at (37 ºC) for (30 min). The filter paper (Whatmann No.1) discs were distributed on the agar and a certain equal amounts (1mg/1ml) or (1ml/1ml) of the compound per solvent (DMSO) was added. Prescott method was used to explain the sensitivity of the used abstract which depends on the inhibition belt (Prescott and Harley, 1996).

The control here were the standard antibiotics like: Tetracycline, Lincomycine and Nalidixic acid, the comparison depends on the diameter of the inhibition zone, so if the diameter of the inhibition zone of the tested compound is equal or larger then that of the standard antibiotic, it will be construct as a (Sensitive (S)), but if the diameter of the inhibition zone of the tested compound is less than that of the standard antibiotic, so the compound is (Resistant (R)). The results were interpreted according to the report of the (W.H.O).

The resistant (R) result represented the diameter of inhibition <(11)mm. However, the moderately sensitive (MS) result was regarded when the zone of inhibition was between (12-16) mm. The sensitive (S) result was over (16) mm (Table 7).

Table 7 : Inhibition effect of certain chalcones, Schiff bases and Pyrrolidines on growth of *Staphylococcus Aureus* and *Escherichia Coli* .

Compound NO.	**Test Organism**	
	E. coli	***Sta. Aureus***
2	S	S
14	S	S
15	MS	S
16	S	S
17	S	MS
23	R	MS
25	R	S
Control		
Tetracycline	S	S
Lincomycine	R	S
Nalidixic acid	S	R

S = sensitive, MS = moderate sensitive, R= resistant

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