

Synthesis of Some New Pyrazolines

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الخلاصة

يتضمن البحث تحضير سلسلة من الجالكونات (NO₂ , Me , OMe , Cl) وتكثيفها مع هايدرازيدات الحوامض الكربوكسيلية الاروماتية والاليفاتية (المحضرة ايضا) في وسط قاعدي لتنتج البايرازولينات الجديدة . تم اثبات الصيغ التركيبية باستخدام الطرق الفيزيائية و الطيفية .

ABSTRACT

The present work includes the preparation of a series of substituted chalcones (NO₂ , Me , OMe , Cl) and condensation of these chalcone with a series of prepared aromatic and aliphatic acid hydrazides in a basic medium to afford the new pyrazolines . Physical and spectral methods were used to confirm the structures .

INTRODUCTION

Various methods have been worked out for the synthesis of pyrazolines ^(1,2) . In this paper hydrazides were used instead of hydrazine and substituted hydrazines to afford the new 1-substituted 2-pyrazolines , by condensation with chalcones ⁽³⁾ , such as 1-substituted-3,5-diaryl-2-pyrazolines which are substituted in their aromatic rings by (Cl , Me , OMe , NO₂) .

Some chalcones were prepared by condensing acetophenone or substituted acetophenone with benzaldehyde or substituted benzaldehyde in ethanolic NaOH solution ⁽⁴⁾ . On the other hand salicylic , benzoic and octanoic hydrazides had been prepared by refluxing the methyl ester of the corresponding acid with hydrazine hydrate ⁽⁵⁾ .

A considerable attention has been concentrated on 2-pyrazolines , due to their interesting activity of variously substituted pyrazolines as biological agents . These compounds reflect a pharmaceutical importance which lies in the fact that they can be effectively afforded as : antibacterial , antifungal , antiviral , antiparasitic , antitubercular and insecticidal agents ^(6,7) .

EXPERIMENTAL

1. Melting Points were determined by Electrothermal 1A 9000 Digital- Series 1998 apparatus, (Uncorrected).
2. Shimadzu Japan, Fourier-Transform Infrared (FTIR-8400s) Spectrophotometer.
3. Ultra-Violet spectra were obtained using Shimadzu U.V-Visible Spectrophotometer U.V-160.
4. The theoretical calculations based on the data obtained from the minimized geometry were computed using Semi-empirical AM₁ module in CS Chem Office molecular modeling package.

1. Preparation of chalcones (General procedure)⁽⁴⁾.

In a (100ml) round-bottomed flask provided with a mechanical stirrer and immersed in an ice-bath, a mixture of (2.2 gm, 0.055 mole) of sodium hydroxide pellets, (20 ml) of water and (9.5 ml, 0.2 mole) of ethanol was stirred. A (0.043) mole of freshly distilled 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 (20-25) °C with a vigorous stirring for (2-3) hrs, until the mixture became thick (i.e: the stirring was no longer effective). The obtained mixture was 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 washed with (20 ml) ice-cold ethanol. The crude chalcone, after drying in air, was recrystallized from ethanol, the product should be handled with care since it cause skin irritation. The names, some physical properties and spectral data were illustrated in table (1).



Table-1: Names, some physical properties and spectral data of Chalcones

Cpd. No.	X	Y	M.p., °C Found/Lit ⁽⁹⁾	Colour	Yield (%)	Name of chalcone	U.V(CHCl ₃) λ _{max} (nm)	IR(KBr) cm ⁻¹	
								C = O	C = C
1	H	H	56-58 53-55	Yellow	82	1,3-Diphenyl-2-propen-1-one	328	1665	1619
2	H	4-CH ₃	74-76 77.5	Yellow	78	1-(p-Tolyl)-3-phenyl-2-propen-1-one	325	1665	1606
3	4-Cl	H	110-112 112-115	Yellow	67	1-phenyl-3-(p-chlorophenyl)-2-propen-1-one	314	1656	1620
4	3,4-DiCl	H	110-112 114-115	Yellow	77	1-phenyl-3-(3,4-dichlorophenyl)-2-propen-1-one	325	1627	1606
5	2-Cl	4-Cl	78-80	Orange	88	1-(p-chlorophenyl)-3-(2-chlorophenyl)-2-propen-1-one	332	1649	1601
6	4-OCH ₃	H	74-76 (76-78) ⁽¹⁰⁾	Yellow	46	1-phenyl-3-(p-methoxyphenyl)-2-propen-1-one	345	1638	1592
7	3-NO ₂	H	122-124 123-125	Violet	64	1-phenyl-3-(m-nitrophenyl)-2-propen-1-one	336	1665	1606
8	2-Cl	4-CH ₃	48-50	Yellow	80	1-(p-Tolyl)-3-(m-chlorophenyl)-2-propen-1-one	323	1656	1619

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2. Preparation of Acid Hydrazides (General procedure) ⁽⁵⁾.

A (90%) hydrazine hydrate (5 ml, 0.15 mole) was added to a solution of the desired methyl ester (0.1) mole in (150) ml ethanol. In a (250) ml round-bottomed flask fitted with a refluxing condenser, the reaction mixture was refluxed for (6) hrs then concentrated under vacuum, cooled and finally diluted with water. The resultant precipitate was then filtered, washed with ice-cold water, dried and crystallized from aqueous ethanol to give the corresponding products (9,10,11). Table (2) illustrates the names, some physical properties and spectral data of the afforded acid hydrazides.

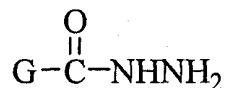


Table-2: Names, some physical properties and spectral data of Acid Hydrazides

Cpd. No.	G	M.p, °C Found/Lit ⁽¹¹⁾	Colour	Yield (%)	Name of Hydrazide	U.V(MeOH) λ _{max} (nm)	IR(KBr) cm^{-1}	
							C = O	N-H
9	2-(OH)C ₆ H ₄ -	130-132	White	80	Salicylic hydrazide	233	1683	3566
10	C ₇ H ₁₅ -	80-82	White	78	Octanoic hydrazide	211	1630	3315
11	C ₆ H ₅ -	115-116 113-14	White	90	Benzoic hydrazide	236, 257	1653	3299

3. Preparation of Δ^2 -Pyrazolines (General procedure) ⁽⁸⁾.

In a (100) ml round-bottomed flask, a mixture of (25) ml ethanol, (6) ml of 50 % sodium hydroxide ethanolic solution and (0.005) mole of the desired acid hydrazide was stirred by a magnetic stirrer for (10) minutes to afford a homogeneous mixture, then (0.005) mole of the desired chalcone was added to the stirred mixture at (25-40) °C for (60-120) minutes until there was no more colour change. The solvent (ethanol) was removed by vacuum, the produced coloured product was recrystallized from ethanol. Table (3) illustrates some physical properties and spectral data of the final products 1-Substituted-3,5-diaryl-2-pyrazolines (12-31).

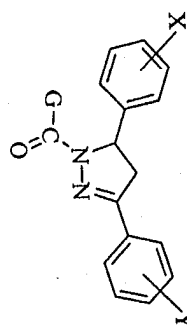


Table-3: Some physical properties and spectral data of 1-Substituted-2-pyrazolines (12-31)

Cpd. No.	X	Y	G	M.p., °C	Colour	Yield (%)	U.V(CHCl ₃) λ _{max} (nm)	IR(KBr) ν(cm ⁻¹)		
								C = O	C = N	ν _{N-H}
12	H	H	2-(OH)C ₆ H ₄ -	162d	Deep Yellow	80	212	1660	1540
13	H	4-CH ₃	2-(OH)C ₆ H ₄ -	182d	Yellow	53	226, 298	1670	1575	2360.41
14	4-Cl	H	2-(OH)C ₆ H ₄ -	285d	Yellow	88	228	1683	1541	2360.37
15	3,4-DiCl	H	2-(OH)C ₆ H ₄ -	112-114	White	67	241	1675	1577	2360.82
16	2-Cl	4-Cl	2-(OH)C ₆ H ₄ -	82-84	Deep Brown	77	227, 286	1670	1560
17	4-OCH ₃	H	2-(OH)C ₆ H ₄ -	104-106	Deep Brown	58	216	1640	1508	2360.72
18	3-NO ₂	H	2-(OH)C ₆ H ₄ -	213-215	Brown	66	210	1645	1540	2360.59
19	H	H	C ₇ H ₁₅ -	255d	Orange	25	225, 236	1670	1545
20	H	4-CH ₃	C ₇ H ₁₅ -	297d	Yellow	46	209	1683	1576	2360.46
21	4-Cl	H	C ₇ H ₁₅ -	300d	White	78	221	1683	1541	2360.42
22	2-Cl	4-Cl	C ₇ H ₁₅ -	245d	White	60	214	1670	1616	2360.59

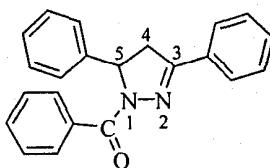
Table-3 Continued

23	4-OCH ₃	H	C ₇ H ₁₅ -	85-87	Yellow	59	227, 259	1667	1576	2360.51
24	3-NO ₂	H	C ₇ H ₁₅ -	198-200	Brown	50	215	1630	1560	2360.32
25	H	H	C ₆ H ₅ -	196-198	Orange	64	225	1635	1576	2360.32
26	H	4-CH ₃	C ₆ H ₅ -	300d	Distine Yellow	30	225, 258	1647	1576	2360.58
27	4-Cl	H	C ₆ H ₅ -	290d	Orange	36	225	1683	1576	2360.49
28	2-Cl	4-Cl	C ₆ H ₅ -	260d	Yellow	40	226	1645	1540
29	4-OCH ₃	H	C ₆ H ₅ -	208-209	Deep Red	50	217, 233	1652	1580	2360.46
30	3-NO ₂	H	C ₆ H ₅ -	97-99	Yellow	60	226	1650	1560
31	2-Cl	4-CH ₃	C ₆ H ₅ -	195d	White	70	286	1647	1576

RESULTS AND DISCUSSION

In order to get new compounds of chemical and biological importance, it is decided herein to investigate the condensation reaction of chalcones (1-8) with acid hydrazides (9-11), the reaction afforded the corresponding Δ^2 -Pyrazolines (12-31). The structures of the prepared chalcones and hydrazides were confirmed in the light of spectroscopic evidences. The physical properties and the spectral data were in quite good agreement with the published values⁽¹²⁾ (table 1,2,3). Accordingly, the reaction mechanism was studied depending on the identification of the product and the calculated heat of formation and steric energy of the intermediates or the transition states and the products.

The product (25) is selected as a representative model in discussing the spectral data.



(25)

1-Benzoyl-3,5-diphenyl- Δ^2 -pyrazoline

The IR spectrum⁽¹²⁾ (table-3) manifests a strong absorption band at 1635 cm^{-1} corresponds to the stretching vibration of carbonyl group and a band at 1576 cm^{-1} attributed to the stretching vibration of carbon - nitrogen double bond, while absorption at $(2360.82-2360.32)\text{ cm}^{-1}$ related to

The UV spectrum⁽¹³⁾ (table-3) exhibits a maximum absorption at wavelength of 225 nm which is matched with the published values⁽¹⁴⁾.

The suggested mechanism of the condensation of acid hydrazides (9-11) with chalcones (1-8) may proceed via the attack of the anion (Z) at the α,β -unsaturated bond of the chalcone (scheme-1) through either Michael addition (1,4-addition) or Claisen addition (1,2-addition). The reaction of benzoic hydrazide (9) with chalcone number (1) is selected as a representative model in discussing the mechanism of the reaction (the data of heat of formation H.F and steric energy S.E are listed in table-4).

i : Michael route

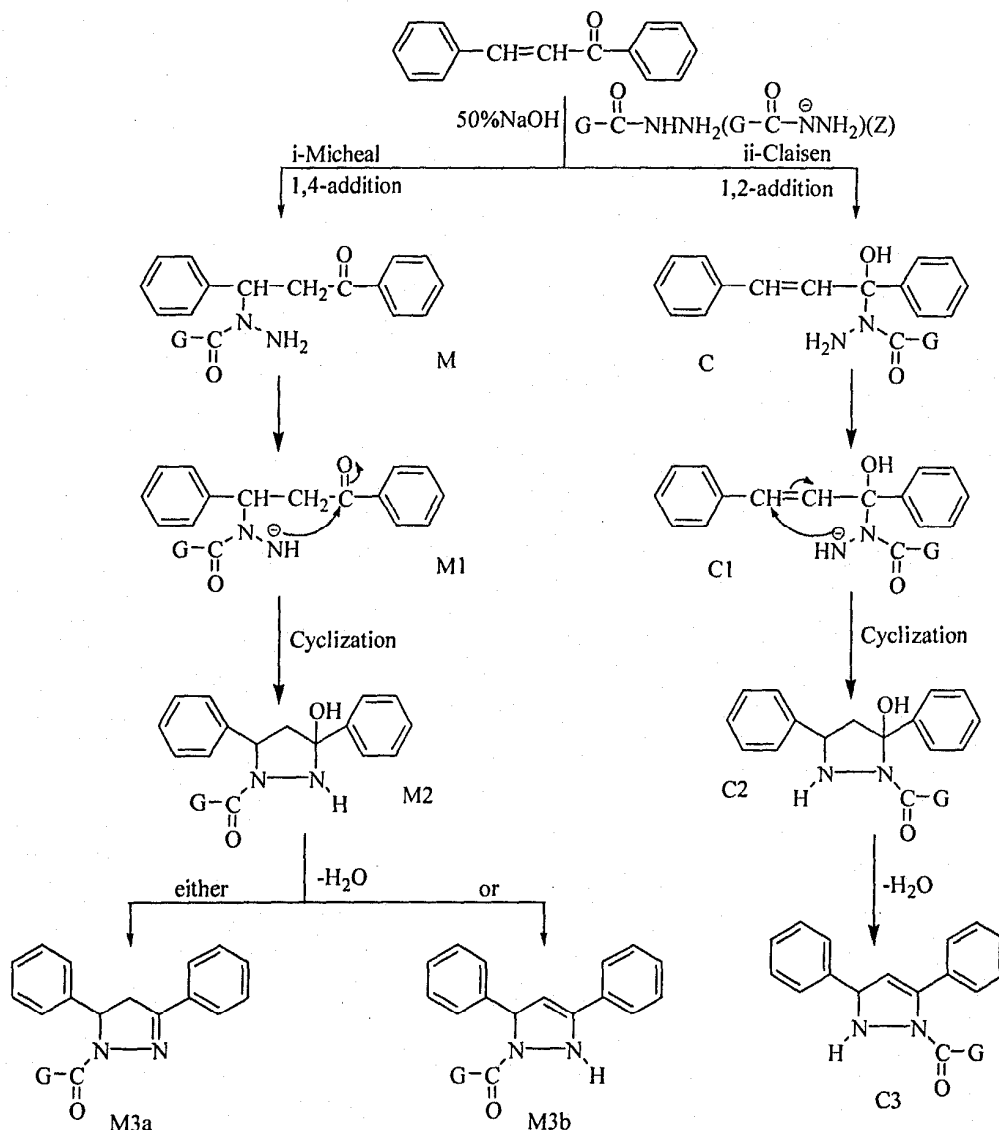
The anion (Z) may attack the β -carbon of the chalcone to give M (H.F=42.22661 Kcal / mole) which may lose an acidic proton from the terminal -NH₂ to produce M1 (H.F=49.06873 Kcal / mole) which in turn may cyclize via intramolecular Claisen addition at the carbonyl carbon to produce the cyclic hydroxy intermediate M2 (H.F=46.42538 Kcal / mole). M2 may lose a water molecule to afford either M3a (H.F=104.51666 Kcal / mole) which is considered as Δ^2 -Pyrazoline or M3b (H.F=116.90793 Kcal / mole) which is Δ^3 -Pyrazoline.

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ii : Claisen route

The anion (Z) may attack the carbonyl carbon to give C (H.F=61.98867 Kcal / mole) which may lose an acidic proton from the terminal -NH₂ to afford C1 (H.F=16.23559 Kcal / mole) which in turn may cyclize via intramolecular Michael addition at the β-carbon of the chalcone to yield the cyclic hydroxy intermediate C2 (H.F=47.91108 Kcal / mole) . C2 may lose a molecule of water to afford C3 (H.F=120.81519 Kcal / mole) .

The suggested mechanism is supported by the values of H.F of both intermediates M and C and final products M3a , M3b and C and that supports the formation of Δ²-Pyrazolines via (M → M1 → M2 → M3a) rather than (M → M1 → M2 → M3b) or (C → C1 → C2 → C3) and both M3b & C are Δ³-Pyrazolines .



Scheme-1 Reaction of Chalcone with Acid Hydrazone

Table-4: The values of heat of formation H.F and steric energy S.E of reactant, intermediates, and products of scheme-1

Cpd. No.	G	H.F Kcal / mole	S.E Kcal / mole
Chalcone	-----	33.48420	3.273
M	C ₆ H ₅ -	42.22661	9.222
M1	C ₆ H ₅ -	49.06873	-----
M2	C ₆ H ₅ -	46.42538	13.723
M3a	C ₆ H ₅ -	104.51666	15.825
M3b	C ₆ H ₅ -	116.90793	19.214
C	C ₆ H ₅ -	61.98867	9.568
C1	C ₆ H ₅ -	16.23559	-----
C2	C ₆ H ₅ -	47.91108	16.937
C3	C ₆ H ₅ -	120.81519	10.474

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