Arab Gulf Journal of Scientific Research, 25 (1/2): 1- 5 (2007)

Research Paper Ref. No 2412

Synthesis, Characterization, and Antibacterial Activity of Some 5-aryl-1, 3-Diphenyl-4, 5-dihydro-1H-Pyrazoles

تحضير وتشخيص بعض مشتقات البيرازولين ودراسة المضادات البكتيرية لهذه المركبات

Nawal Hassan Al Bahtiti

نوال حسن البحطيطى

Chemistry Department, Faculty of Science, Applied Sciences Private University, Amman 11931, Jordan

ABSTRACT: The condensation of acetophenone (I) with arylaldehyde (II) was investigated, and the resulting chalcones 2-Arylidene 1-Acetophenone (III) were reacted with phenyl hydrazine and acetic acid to produce substituted 5-aryl-1, 3-diphenyl-4, 5-dihydro-1H-pyrazoles (IV). The structures of all products were studied by ^{1}H-NMR, IR, thermal and elemental analysis. Thermo gravimetric (TG) and differential thermal analysis (DTA) was applied to investigate the thermal behavior and structure of the synthesized compounds. 2-Pyrazolines (IV) exhibited moderate activity against *Streptococcus faecalis ATCC 19433, Klebsiella pneumoniae ATCC 13883, Proteus vulgaris ATCC 25922, Shigella sonnei ATCC 25931, and Peseudom oaeruginosa ATCC 27853.*
Keywords: *acetophenone, chalcones, arylaldehyde, pyrazoles, Pyrazoline, TG, DTA, thermal analysis, antibacterial activity*

المستخلص: تم تحري تكثيف الاسيتوفينون (I) مع الالدهيدات الأروماتية (II)، والشالكونات الناتجة Arylidene Acetophenone (III) دمجت/تفاعلت؟ مع phenyl hydrazine وحامض الخليك لإنتاج مُستبدل 1-aryl-5 و-3-diphenyl-4 و (IV) 5-dihydro-1H-pyrazoles. وتم دراسة جميع هذه المنتجات بواسطة طيف الرنين المغناطيسى(^{1}H-NMR) وطيف الأشعة تحت الحمراء (IR)، والتحليل الحراري والعنصري، كما تم تحرّى السلوك الحراري والتركيب المركب لهذه المنتجات بواسطة التحليل thermo-gravimetric (TG) والتحليل الحراري التفاضلي differential thermal analysis (DTA). ولقد تبين بأن مركب (IV) Pyrazolines 2 له نشاط بيولوجى معتدل ضد *Streptococcus faecalis ATCC 19433*، *Shigella sonnei ATCC 25931*، *Proteus vulgaris ATCC 25922*، *Klebsiella pneumoniae ATCC 13883* و*Peseudom oaeruginosa ATCC 27853*.

كلمات مدخلية: *مركب الاسيتوفينون، الشالكونات، الالدهيدات الاروماتية، البيرازولين، thermo-gravimetric (TG)، تحليل حراري تفاضلي، تحليل حرارى، نشاط مضاد للبكتريا.*

INTRODUCTION

Hydrazine and related compounds have been described as useful building blocks for the assembly of various heterocyclic rings (Albert and Josef, 2005a; Shenoy and Bhat, 2001; Rurack and Bricks, 2000; Wiley, 1967). Pyrazoles are prominent nitrogen heterocyclic compounds, and therefore, various procedures have been designed for their synthesis (Joaquin and Koen, 1998; Ahmet and Metin, 1998). Among the various pyrazoline isomers, 2-pyrazolines (4, 5-dihydro-1 H pyrazole) appear to be the most frequently investigated compounds. As a result, a large number of 2-pyrazolines have been described in the chemical literature, using different synthetic methods for their preparation. An especially popular procedure is based on

the reaction of chalcones with hydrazines (Albert and Josef, 2005a; Shenoy and Bhat, 2001; Rurack and Bricks, 2000; Wiley, 1967). 2-Pyrazolines have fluorescence, non linear-optical mesogenic properties (Albert and Josef, 2005b). The 2-pyrazolines compounds have been reported to exhibit bactericidal, fungicidal, and analgesic properties (Albert and Josef, 2005b; Ahmet and Metin, 1998). For all these facts we synthesized some chalcones III (a-d) and 2-pyrazolines compounds IV (a-d) and investigated the chemical characteristics and biological effect of such compounds.

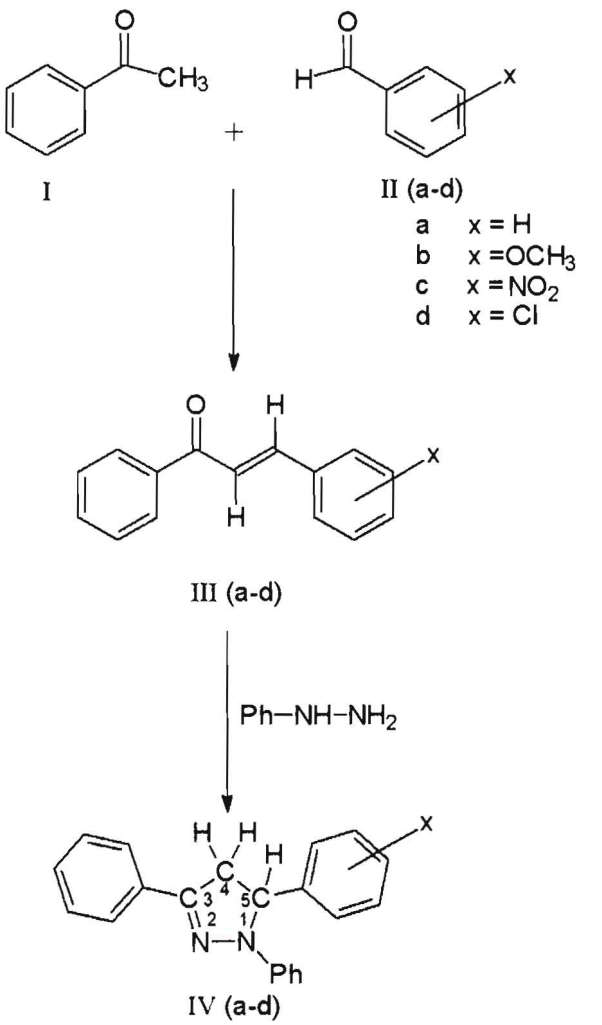
MATERIALS AND METHODS

Chalcones are best prepared as described above (Albert and Josef, 2005b) by the Claisen-Schmidt reaction with minor modifications. The chalcones were re-crystallized from ethanol. The synthetic route to the compounds is shown in Figure 1. The 2-pyrazolines compounds (IV) were prepared by reaction of chalcones III with phenyl hydrazine following the procedures indicated in the literature (Polanc, 1999). Ethanol was chosen as the solvent at a temperature range of 30-40 °C to ensure the dissolution of the reactants and the precipitation of the cyclized products.

Elemental analysis, IR, ^{1}H-NMR, and thermal analysis have characterized all compounds. IR was run on Nicollet impact 400, and UV Spectra were recorded on Supertonic 1201 Melton-Ray at the laboratories of Applied Science Private University. ^{1}H-NMR was run on DBX 3000 at the laboratories of Jordan University.

The compounds were tested for their antimicrobial in vitro by the agar dilution technique (Sretton and Manson, 1989), with 80 mg of all compounds were dissolved in 1 mL of DMSO for their antibacterial test; solutions were sterilized by membrane filtration. Aliquots of compounds were diluted 10 times, and 0.5 mL was taken from the first tube contained the compound and was transferred to diluted tube, and so on until tube no.9. The content of the 10 tubes were added to universal tubes that contain melted tryptic Soya agar, shaked well and poured into 10 Petri dishes. Petri dishes were stored at 4 °C and left to solidify.

The microorganisms used in this study were *Streptococcus faecalis ATCC 19433, Klebsiella pneumoniae ATCC 13883, Proteus vulgaris ATCC 25922, Shigella sonnei ATCC 25931, and Peseudom aeroginosa ATCC 27853.* The microorganisms were incubated to grow in *typtic Soya broth, a*nd incubated at 37 °C for 18 hours. The concentrations of microorganisms were diluted to 10^{-4} times and the number of bacterial cells standardized by Haemocytometer to give concentrations of 2000, 1500, 1000, 500, 62.5 and 31.3 µg/mL. The MIC values were recorded after 24 hours incubation at 37 °C.



Key of Compounds	
Compound	Ar
IVa	C_6H_5
Ivb	p-OCH3-C_6H_4
IVc	p-NO2--C_6H_4
IVd	p-Cl-C_6H_4

Fig. 1. Synthetic routes of 5-ary-1, 3-diphenyl-4, 5-dihydro-1 H-pyrazoles.

RESULTS AND DISCUSSION

The reaction of chalcones with phenyl hydrazine follows a general mechanism that was studied previously. In ^{1}H-NMR spectra of 2-pyrazolines, the three hydrogen atoms attached to the C-4 and C-5 carbons atoms of the heterocyclic rings gave an ABX spin system. Measured chemical shift and coupling constant values investigate the 2-pyrazoline structures (Badawy and Mansour, 1998).

Thermal analysis of chalcones and pyrazoline compounds showed that compounds decomposed between 100 and 360 °C (Figures 2, 3, and 4). Pyrazolines lost N2 (should it be N_2) as gas and left cyclopropane. Volatility and molar mass control the evolution of N2 group. All compounds melted to give an isotropic liquid.

In order to compare the electronic and structural effects, data were presented in Tables 1, 2, 3 and 5. Minimum inhibitory concentration (MIC) of pyrazolines IV compounds is summarized in Table 4. All compounds showed activity against *Klebsiella pneumoniae* ATCC 13883, and, *Shigella sonnei, ATCC 25931*. The NO_2 group in compound IVc enhances activity against *Klebsiella pneumoniae*. A similar observation was made by *S*tretton and Manson (1989) for Bronopol. A study performed in Bangkok on Hexetidine also showed the same effect on bacteria (Sheie, 1989).

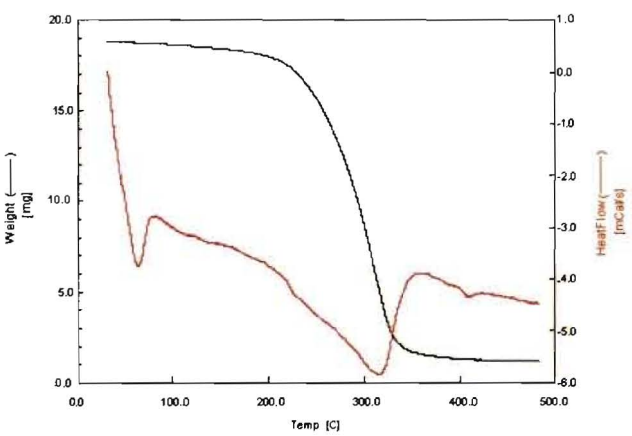


Fig. 2. Thermal analysis of 2-benzylidene-1-acetophenone (IIIa).

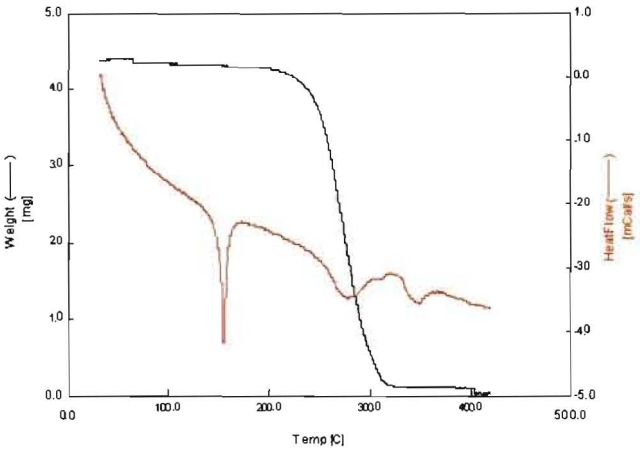


Fig. 3. Thermal Analysis of 1, 3-diphenyl-5-p-methoxy phenyl-2-pyrazoline (IVb).

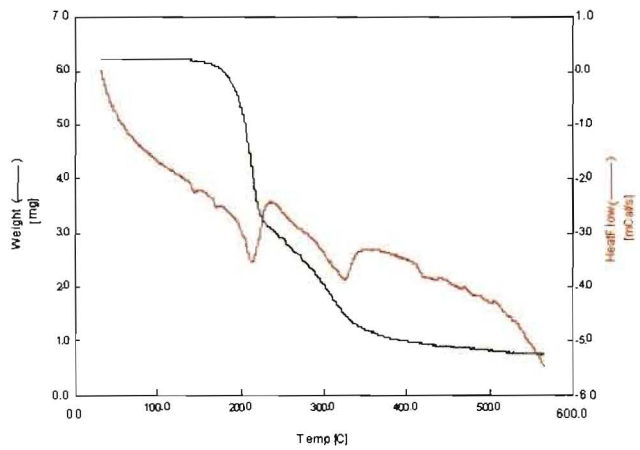


Fig. 4. Thermal Analysis of 1, 3-diphenyl-5-p-nitrophenyl-2-pyrazoline (IVc).

Table 1. Physical Properties of Compounds III and IV.

Compound	Formulae	Melting Point (°C)	Yield (%)
IIIa	C15H12O	55-57	90
IIIb	C16H15O2	68	92
IIIc	C15H12NO3	92	94
IIId	C15H12ClO	74	92
IVa	C21H18N2	195	78
IVb	C22H20N2O	186	78
IVc	C21H17N3O2	102	89
IVd	C21H17N2Cl	180	74

Table 2. Elemental analyses data of III and IV.

Compound	M. wt. g/ mol	Found (calculated), %		
		C	H	N
IIIa	208	86.5(86.4)	5.8(5.8)	
IIIb	239	80.3(80.2)	6.3(6.4)	
IIIc	242	74.4(74.4)	5.0 (5.1)	
IIId	243	73.9(73.8)	4.9(4.8)	
IVa	298	84.6(84.6)	6.0(6.0)	9.4(9.3)
IVb	328	80.5(80.5)	6.1(6.1)	8.54(9.3)
IVc	343	73.5(73.5)	5.0(5.0)	12.2(12.2)
IVd	332	75.8(75.8)	5.1(5.1)	8.4(8.4)

Table 3. IR data of III and IV.

Compounds	Significant Frequencies (cm $^{-1}$)	Inferences
IIIa-d	1690-1700	C=O stretch
	1640-1660	C=C stretch
	3100-3080	C-H aromatic stretch
IVa-d	1515-1550	C=N stretch
	1380-1388	C-N stretch

Table 5. ^{1}H NMR spectral data of compounds III and IV (solvent $CDCl_3$).

Compounds	δ	Integration	Type of peak	Inferences
IIIa	6.9	1 H	d	Ha
	7.3-7.9	11 H	m	Hb and Ar-H
IIIb	2.6	3 H	s	OCH_3
	6.3	1 H	d	Ha
	6.9-7.9	11 H	m	Hb and Ar-H
IIIc	6.3	1 H	s	Ha
	6.9-7.9	11 H	m	Hb and Ar-H
IIId	6.3	1 H	s	Ha
	6.6-7.9	11 H	m	Hb and Ar-H
IVa	3.2	1 H	dd j=7.6	4-H (*trans*)
	3.96	1 H	dd j=12.1	4-H (*cis*)
	5.2	1 H	dd j=7.6	5-H
	6.4-8.0	15 H	m	Ar-H
IVb	2.7	3 H	s	OCH_3
	3.22	1 H	dd j=7.6	4-H (*trans*)
	3.96	1 H	dd j=12.1	4-H (*cis*)
	5.2	1 H	dd j=7.6	5-H
	6.4-7.9	14 H	m	Ar-H
IVc	3.3	1 H	dd j= 7.6	4-H (*trans*)
	3.96	1 H	dd j=12.1	4-H (*cis*)
	5.2	1 H	dd j=7.6	5-H
	6.4-7.9	14 H	m	Ar-H
IVd	3.3 3.8	1 H	dd j=7.6	4-H (*trans*)
		1 H	dd j=12.1	4-H (*cis*)
	5.1	1 H	dd j= 7.6	5 H
	6.6-7.9	14 H	m	Ar-H

Table 4. Minimum inhibitory concentration (MIC), μg/ml of 5-aryl-1, 3-diphenyl-4, 5-dihydro-1 H pyrazoles (IV) compounds.

Microorganisms	IVa	IVb	IVc	IVd
Streptococcus.*faecalis* ATCC 19433	1000	250	31.3	250
Klebsiella.*pneumoniae* ATCC13883	125	65	125	65
Proteus.*vulgaris* ATCC 25922	250	500	2000	500
Shigella.*sonnei* ATCC 25931	65	500	125	125
Peseudom aeroginose ATCC 27853	500	65	1000	250

CONCLUSION

We could show that 1,3,5-triaryl-2-pyrazolines compounds, with their rigid but only partly unsaturated central 2-pyrazoline ring, exhibit a special ability to strongly interact with UV and visible radiation. Furthermore the 5-Aryl substitutes of 2-pyrazoline enhance thermal stability of pyrazolines to 360 °C, and may lose nitrogen gas. Variation of substituted Aryl group does not affect the spectral pattern or thermal stability. On the other hand, such pyrazolines possesses better microbial activity than less substituent pyrazolines that previously synthesized (Bahtiti, 2005). It is expected that the activity may increase by chelating with legands, which require further investigation.

ACKNOWLEDGEMENT

The author wish to thank Dr. Mahmoud Alawaii and Dr. Zahra, Jordan University, Dr. Bassam Al-Iswed, for providing elemental analysis data from Hashemite university and Mr. Ahmed Al-Najar for his assistance in doing IR, UV spectra, and Thermal analyses at ASU (Private) laboratories.

REFERENCES

Ahmet, S, and **Metin, B** (1998) Some novel reactions of 4-benzoyl-5-phenyl-2,3-furandion. *J. of Qafqaz University* **1**(2):121.

Albert, L, and **Josef, J** (2005a) Synthesis of hydroxylated 3,5-diaryl-2- pyrazolines by the reaction of hydroxychalcones with hydrazines. *Org. Ark. Journal* **5**(11):1524-1560.

Albert, L, and **Josef, J** (2005b) Synthesis and structure of 5-acylhydrazine-3,3,5-trimenthylisoxazolidines. *Journal of Arkat University* **110** (1):15- 24.

Badawy, M , and **Mansour, A** (1998) Reactions of 3-hydrazino-5,6-diphenyl-1,2,4-triazine with 4-arylidine-2-phenyl-5 (4H)-oxazolones. *J. Heterocyclic chem.* **25**:1813-1815.

Bahtiti, N (2005) Antimicrobial activity of some heterocyclic derivatives of chalcones. *Journal of Jordan Appl. Sci.* **7**(2):51-57

Joaquin, B, and **Koen, C** (1998) Mesogenic properties of selected 2-pyrazoline derivatives. *J. Mater. Chem.* **8**(8):1725-1730.

Polanc, S (1999) Recent application of hydrazines and related compounds for the synthesis of heterocycles. *Heterocyclic. Syst.* **33**(3):91-97.

Rurack, K, and **Bricks, L** (2000) Substituted 1,5-diphenyl-3- benzothiazol-2-yl-Δ^2-pyrazoline *J. Phys. Chem. A,* **104**(26):6171-6188.

Sheie, A (1989) modes of action of currently known chemical ant plaque agent. *J. dent. Res.* **68**:1609-1616

Shenoy, G, and **Bhat, AR** (2001) Synthesis and antimicrobial activity of 1,3,5 trisubstitued 2-pyrazolines. *Indian J. Heterocyclic Chem.* **10** (3):197-200.

Sretton, R, and **Manson, T** (1989) Some aspects of the mode of action of the antibacterial compound. *J. Appl. Bact.* **36**:61-67.

Wiley, K (1967) The *Chemistry of Heterocyclic, vol. 22: Pyrazoles.* Interscience Publishers, New York.

Ref. (2412)
Rec. 12/ 12/ 2006
In-Revised Form 10/ 04/ 2007