Synthesis of Some3-Chloro-2,3-dimethyl-1-phenylpyrazolidin-5-one (Chlorophenazone)Derivatives

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Abstract

(E)-3-Chloro-4-arylidene-2,3-dimethyl-1-phenylpyrazolidin-5-one 1(a-c) which were used as synthon for synthesis of all target compounds were prepared from the reaction of 3-chloro-2,3-dimethyl-1-phenylpyrazolidin-5-one(Chlorophenazone)with aromatic aldehydes by 1,4-Michael addition .

4-Aryl-3-chloro-2,3-dimethyl-1-phenyl-2,3-dihydro-1H-pyrazolo[3,4-d]pyrimidine-6(5H)- one2(a-c) and -6(5H)-thiones 2(d-f)were prepared in low yields(40-50%) by the reaction of 1 (a-c) with urea or thiourea respectively in refluxing ethanol. The refluxing of 1(a-c)with hydrazine hydrate in presence of pyridine afford 3-chloro-4-aryl-2,3-dimethyl-1-phenyl-1,2,3,5-tetrahydropyrazolo[3,4-c]pyrazole 3(a-c).

Also, 2-benzyl-4-spiro-5-chloro-1,5- dimethyl-2-phenylpyrazolidin-3-one (4) was obtained via epoxidation of 1(a) by hydrogen peroxide in presence of anhydrous sodium carbonate, the reaction of this spiro compound with hydrazine hydrate gave 3-chloro-2,3-dimethyl-1,4-diphenyl-1,2,3,3a -tetrahydropyrazolo[3,4-c]pyrazole (5). Finally, the authentic samples of pyrazole (5) was prepared by the oxidation of 3(a) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) .

The structures of these compounds were confirmed by their physical properties in addition to the IR and UV Spectra.

Keywords: Chloro Phenazone , pyrazole, pyrimidine

تحضير بعض مشتقات 3- كلورو- 3,2- ثنائى مثيل -1- فنيل بايروزولدين -5- اون (كلوريد الفينازون)

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الخلاصة

حضرت مركبات (E)3 -4 كلوريد -4-اريليدين -3,2-ثنائي مثيل-1-فنيل بايروزولدين-5- اون1(c-a) والتي استخدمت كمواد أولية لتشييد كل المركبات المطلوبة من تفاعل 3- كلورو - 3,2- ثنائى مثيل -1-فنيل بايروزولدين -5- اون(كلوريد الفينازون) مع الالديهايدات العطرية بوساطة4,1- إضافة مايكل . كماحضرت المركبات 3- كلوريد -3،2- ثنائي مثيل – 1- فنيل -4- اريل 5 – رباعي هيدرو بايرازول [d4-3] بيريميدين -6- اون 2(c -a) و 6- ثايون 2(f -d) بنسبة منتج ضئيلة (40- 50%) بوساطة تفاعل (1) مع اليوريا والثايوريا على التوالى بالتصعيد بالايثانول. ان تصعيد 1(c-a) مع الهيدرازين المائى بوجود البيريدين أعطى 3- كلوريد -3،2- ثنائى مثيل – 1- فنيل -4- اريل - 4، 5 – رباعي هيدرو بايرازولو [d4-3] بايرازول 3(c-a). كذلك تم الحصول على 2- بنزيل – 4- سبايرو – 5 – كلورو1، 5_ثنائى مثيل -2-فنيل بايروزولدين-3- اون (4) عن طريق اكسدة 1(a) بوساطة بيروكسيد الهدروجين وبوجود كربونات الصوديوم اللامائية . وبتفاعل مركب السبايرو هذا مع الهيدرازين المائي أعطى 3- كلوريد -3،2- ثنائى مثيل – 4،1- ثنائى فنيل – 3،3،2،1 - 4، 5 – رباعى هيدرو بايرازول (5) .

وأخيرا . حضر النموذج التاكيدى للبايرازول 5 بأكسدة 3(a) بوساطة 3،2- ثنائي كلورو – 5- ثنائي سيانو 4،1- بنزوكوينون (DDQ) .

تم إثبات التراكيب الكيميائية للمركبات بوساطة خواصها الفيزيائية إضافة إلى أطيافها في منطقة الأشعة تحت الحمراء وفوق البنفسجية .

الكلمات الدالة: Chloro Phenazone ,pyrimidine pyrazole

Introduction

In the last decade an increasing attention has been focused on pyrazoline derivatives with its own moiety or fused with five or six membered azoheteocyclic rings (pyrazole or pyrimidine) [1-2]. One of the most important of 1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one(phenazone) moiety was a classic NSAID[3]. A variety of methods have been reported for the preparation of this class of compounds after the pioneering work of Fischer and Knoevenagel in the 19th century, the refluxing of α,β-unsaturated aldehydes or ketones with phenylhydrazine in acetic acid became one of the most popular methods for the preparation of 2-pyrazolines. [4].The reaction of chalcones and phenylhydrazine hydrochloride in the presence of sodium hydroxide was carried out in the absolute ethanol at 70°C, but there was a disadvantage due to long reaction time (8 hours) [5]. In 2005, the synthesis of 3,5-diaryl-2-pyrazolines by refluxing of chlorochalcones with phenylhydrazine in acetic acid for (3hours) was reported [6-7]. Finally, chloroimidazole derivatives were important precursors for the preparation of calcium channel modulators and angiotensine receptor antagonists[8]. For this reason, efficient synthesis of these valuable and versatile intermediates was of interested as part of continuous program directed toward the studies with polyfunctionally substituted heterocyclic's[9-10], it was became of interest to investigate some important reactions of 3-chloro-2,3-dimethyl-1-phenylpyrazolidin-3-one(**Chlorophenazone**) and to synthesis a new class of compounds of general formula 1-5 that combined elements of both chlorophenazone and heterocyclices and might showed enhanced biological properties.

Experimental

All melting points were determined on a Gallen Kamp and Electro thermal 1A9300 Digital-Series (1998) apparatus and were uncorrected. The IR – spectra (νmax cm^{-1} KBr disc) were recorded on Perkin – Elmer 590B Spectrophotometer. V-On Shimadzu UV-160 spectrophotometer use EtOH as solvent.

(E)-3-Chloro-4-arylidene-2,3-dimethyl-1-phenylpyrazolidin-5-one 1(a-c)1(a-c) : [10]

A mixture of benzaldehyde (1.06gm, 0.01 mol) and (0.25gm, 0.01 mole) of 5-chloro-1, 5-dimethyl-2-phenylpyrazolidin-3-one (Chlorophenazone) in (25 ml) ethanol and a solution of (3.3 gm)potassium hydroxide in (10 ml) absolute ethanol was added dropwise to the mixture with stirring at room temperature . The stirring was continuous overnight. The solution neutralized with dilute HCl and precipitated product was filtered, washed with water and crystallized with aqueous ethanol to yield compound1(a)[the procedure was repeated for compounds (1b- c)]. Physical and spectral data were listed in Table (1).

Table (1): Physical and spectral data of compounds 1(a-c)

Comp. No.ii*	Ar	M.P. ^{O}C	Yield %	IR, KBr ,Cm $^{-1}$			Uv λmax (nm) MeOH
				C=O	C=C	$C\equiv C$	
a	C_6H_5-	196-98	60	1657	1595	1531	284
b	4-MeO-C_6H_4-	168-70	66	1648	1620	1509	276
c	2-Cl-C_6H_4-	252-53	61	1667	1617	1509	270

*All these compounds were white to pale orange in color.

4-Aryl-3-chloro-2,3-dimethyl-1-phenyl-2,3-dihydro-1H-pyrazolo [3,4-d]pyrimidine-6(5H)- one 2(a-c) and -6(5H)-thiones 2(d-f): [11]

A mixture of (E)-5-chloro-4-benzylidene-1,5-dimethyl-2-phenylpyrazolidin-3-one 1(a) (0.25gm,0.0008mol) ,urea (0.048gm, 0.00008mole) or thiourea(0.06gm, 0.0008mole) in 25 ml ethanol and 3ml of 50% base(KOH or NaOH) was refluxed at 75 ^{O}C for 6 hours, cooled, concentrated under vacuum. The precipitated product was washed with diluted HCl to neutral , then washed with water, filtered, dried and crystallized from ethanol to afford compound 2(a)[the procedure was repeated for compounds (2b- f)]. Physical and spectral data were listed in Table (2).

Table (2): Physical and spectral data of compounds 2(a-f)

Comp. No.iii	Ar (X)	M.P. ^{O}C	Yield %	IR, KBr ,Cm -1		Uv λmax (nm) MeOH
				N-H	C=O	
A	C_6H_5- (O)	186-88	56	3526	1666	280
B	4-MeO-C_6H_4- (O)	180(dec.)	66	3427	1664	260
C	2-Cl-C_6H_4- (O)	252-254	50	3442	1681	250
D	C_6H_5- (S)	203-05	53	3445	1666	256
E	4-MeO-C_6H_4- (S)	265-67	48	3360	1668	240
F	2-Cl-C_6H_4- (S)	258-60	66	3440	1652	258

3-Chloro-4-aryl-2,3-dimethyl-1-phenyl-1,2,3,5-tetrahydropyrazolo[3,4-c]pyrazole 3(a-c): [11]

To a mixture of (E)-5-chloro-4-benzylidene-1,5-dimethyl-2-phenylpyrazolidin-3-one ii(a) (0.06gm,0.002mole) in 15ml ethanol and 80%hydrazine hydrate (3.75gm, 0.6 mole) was added pyridine (2 -3ml) . The mixture was refluxed for 6 hours, cooled, concentrated under vacuum, then poured into water and acidified with acetic acid The residue was filtered off ,washed with water and crystallized from methanol to afford compound 3(a)[the procedure was repeated for compounds (3b-c)]. Physical and spectral data were listed in Table (3).

Table (3): Physical and spectral data of compounds 3(a-c)

Comp. No.iv	Ar	M.P. °C	Yield %	IR, KBr ,Cm -1			Uv λmax (nm) MeOH
				NH-	C=N	C=C	
a	C_6H_5-	202-04	48	3526	1644	1592	286
b	4-MeO-C_6H_4-	143-45	41	3332	1668	1577	266
c	2-Cl-C_6H_4-	257(dec.)	54	3419	1577	1591	254

Formation of an authentic sample of 3-chloro-2,3-dimethyl-1,4-diphenyl-1,2,3,3a -tetrahydropyrazolo[3,4-c]pyrazole 5:

Method A; Via oxidation of compound 1a by H_2O_2

1-Synthesis of 2-benzyl-4-Spiro-5-chloro-1,5- dimethyl-2-phenylpyrazolidin-3-one (4): [12-13]

To a mixture of (1 g) sodium carbonate dissolved in (1 ml) water and 30% (1 ml)hydrogen peroxide, a hot solution of (1gm, 0.003mole) of (E)-5-chloro-4-phenylidene-1,5-dimethyl-2-phenylpyrazolidin-3-one 1(a) in (10 ml) ethanol was added .The mixture was allowed to stand for 24hours at room temperature. The solid was removed by filtration, washed with water to neutral, dried and crystallized from aqueous ethanol to give compound (4). Yield: 52 %, m.p. 196-98ºC, IR (KBr), (cm^{-1}):1667 C=O , 1289 epoxid ring ; Uv λmax (nm) MeOH, 258.

2-Reaction of compound (4)with hydrazine hydrate : [10]

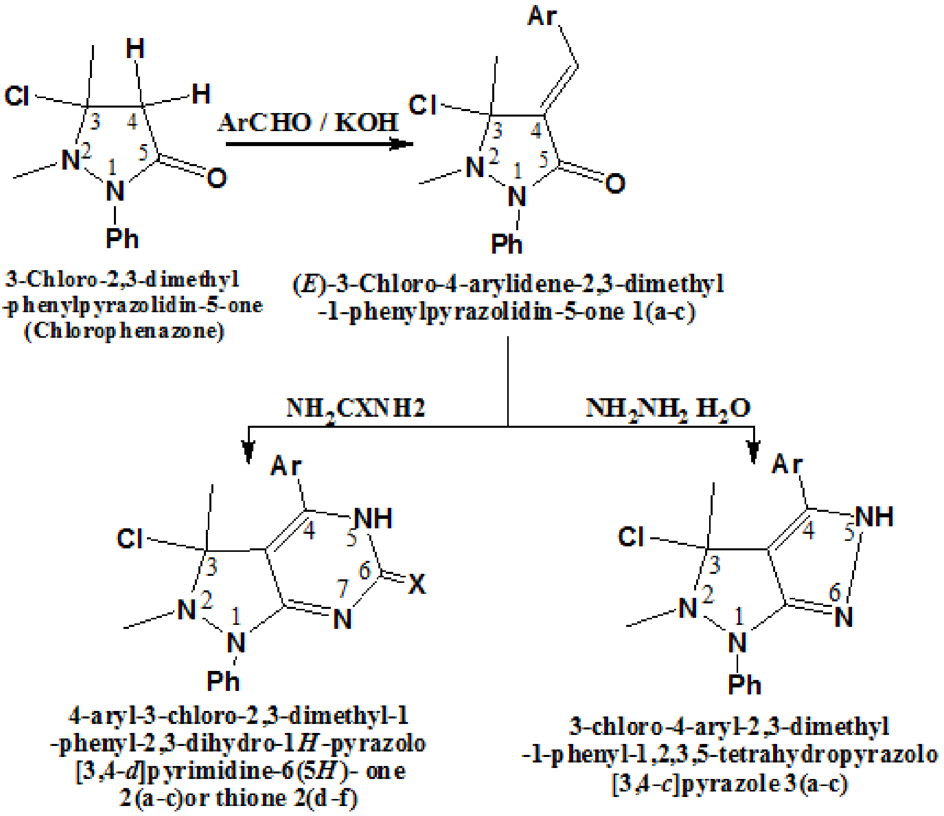
To a mixture of (0.38gm,0.012 mole) of compound(4) dissolved in (2ml) acetic acid and (10 ml) chloroform, hydrazine hydrate (0.68 gm, 0.6 mole) was added After 4 hours reflux, the solution was cooled and washed with diluted hydrochloric acid and diluted sodium carbonate solution respectively. The organic layer was dried and concentrated under vacuum to give an oil product which crystallized from benzene to give compound (5). Yield: 64 %, m.p. 196-98ºC, IR (KBr), (cm^{-1}):1667 C=O , 1594C=C ; UV λmax (nm) MeOH, 284.

Method B; Via oxidation of compound 3a by D.D.Q. : [13-14]

To a solution of 0.014 mole of 3(a) in 50 ml benzene was added (1g) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone(D.D.Q.),then the reaction mixture was refluxed for 8 hours and concentrated under vacuum. The crude product was chromatographed over 60g of Al_2O_3 .The column was eluted with benzene until the yellow color in benzene disappears. The benzene was removed under pressure and the solid product was crystallized from acetic acid to give compound (5). This compound has the same melting points, mixed melting point and spectral data with that produced via method A.

Results and discussion

A convenient synthesis of target compounds were accomplished by the route outlined in Scheme (1).



3-Chloro-2,3-dimethyl -1-phenylpyrazolidin-5-one (Chlorophenazone)

(*E*)-3-Chloro-4-arylidene-2,3-dimethyl -1-phenylpyrazolidin-5-one 1(a-c)

4-aryl-3-chloro-2,3-dimethyl-1 -phenyl-2,3-dihydro-1*H*-pyrazolo [3,4-*d*]pyrimidine-6(5*H*)- one 2(a-c)or thione 2(d-f)

3-chloro-4-aryl-2,3-dimethyl -1-phenyl-1,2,3,5-tetrahydropyrazolo [3,4-*c*]pyrazole 3(a-c)

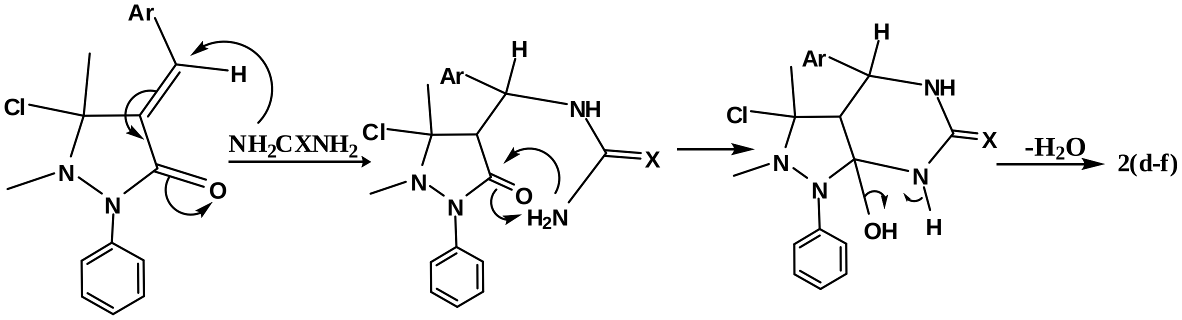
Scheme (1)
For Ar and X see Tables 1-4

(E)-3-Chloro-4-arylidene-2,3-dimethyl-1-phenylpyrazolidin-5-one 1(a-c)

The utility of Claisen–Schmidt condensation were demonstrated in the synthesis of these compounds by the reaction of 5-Chloro-1,5-dimethyl-2-phenyl pyrazolidin-3-one with the corresponding aromatic aldehydes in presence of KOH[10]. An examination of the reaction mixture by T.L.C. showed the presence of only one compound(E isomer) and no traces of a second isomer (Z isomer) was detected[E entgegen the two groups of higher priority (the aryl and exocyclic carbonyl) were on opposite side of the double bond] .The results were confirmed by IR and UV spectra of these products which showed the presence of conjugated carbonyl group at (1648-1667 cm^{-1})with the exocyclic double bond(1595-1620 cm^{-1}) ,Table (1).The decrease in the frequency was due to the decrease of the force constant result from conjugation, as well as to the effect of two nitrogen atoms which lowers this frequency[15].The UV absorption was (270-284nm) , Table(1) showing the relationship of these structures to that of related trans-chalcones which in general have strong UV absorption band[saied,2000].

4-aryl-3-chloro-2,3-dimethyl-1-phenyl-2,3-dihydro-1H-pyrazolo [3,4-d]pyrimidine-6(5H)- one 2(a-c) and -6(5H)-thiones 2(d-f):

These pyrimidines were formed by 1,4-Michael addition of nucleophiles urea or thiourea on β-carbon of arylidines 1(a-d) in refluxing ethanol as homogenous medium which gave low yields(40-50%)[13].The driving force for ring formation was the water elimination[4, 6]. The mechanism was showed in Scheme (2).



Scheme (2)

The IR spectra of compounds were reflected abroad band in the region(3422-3427 cm $^{-1}$)for NH vib., and strong band in the region (1676 cm $^{-1}$) and(1741 cm $^{-1}$) for C=O and C=S vibrations. The UV absorptions λ max(MeOH) were in the range(240-280nm) resemble to the published for similar compounds[10].

3-chloro-4-aryl-2,3-dimethyl-1-phenyl-1,2,3,5-tetrahydropyrazolo[3,4-c]pyrazole 3(a-c):

In refluxing ethanol, compounds 1(a-d) were reacted with hydrazine hydrate (in presence of pyridine) to give pyrazoline derivatives 3(a-d). These compounds were formed by the same mechanism of Michael addition.

This pyrazoline ring in these compounds were assigned from their UV and IR spectra, which came in agreement with this moiety[10].

The UV absorption were in the range (352-286nm), while the IR (KBr) spectrum showed the disappearing of carbonyl band and another bands at (1644-1670 cm $^{-1}$) of C=N str, and (3332-3526 cm $^{-1}$) for NH str. were appeared, Table (2).

3-Chloro-2,3-dimethyl-1-phenyl-4-aryl-1,2,3,3a-tetrahydropyrazolo[3,4-c]pyrazole (5)

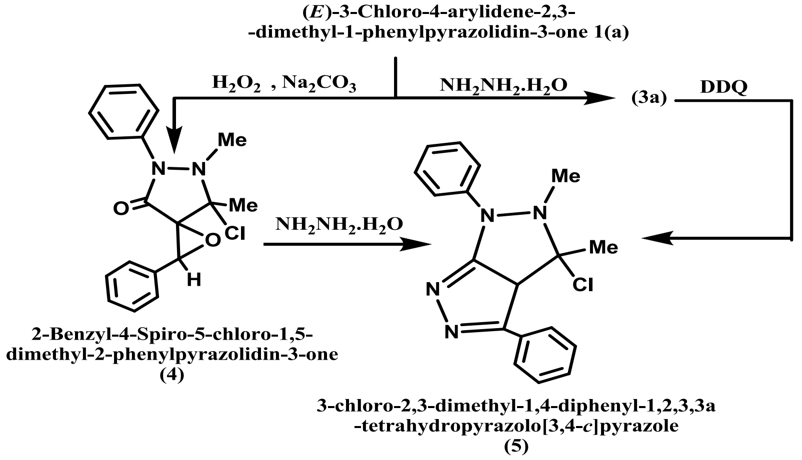
Method A; Oxidation by H_2O_2:

As the structural skeleton of these compounds were established spectroscopically , chemical behavior of these compounds could also be used for assigning the structure. Compound 1(a) was selected for this study via its direct epoxidation with H_2O_2 in presence of anhydrous sodium carbonate by 1,4-Michael addition afforded compound 2-benzyl-4-Spiro-5-chloro-1,5- dimethyl-2-phenylpyrazolidin-3-one (4), which on reaction with hydrazine hydrate gave compound (5) [9].

Method B; Oxidation by DDQ:

By the same manner the direct oxidation by DDQ gave compound (5), the structure of this compound was confirmed by the appearing of the C=N characteristic bands at (3332-3526 cm $^{-1}$) in its IR absorption spectrum and this was in agreement with the literatures[9].

The formation of the same product from two different compounds indicated the correct assignment for these compounds. Scheme(3)



(*E*)-3-Chloro-4-arylidene-2,3-
-dimethyl-1-phenylpyrazolidin-3-one 1(a)

2-Benzyl-4-Spiro-5-chloro-1,5-
dimethyl-2-phenylpyrazolidin-3-one
(4)

3-chloro-2,3-dimethyl-1,4-diphenyl-1,2,3,3a
-tetrahydropyrazolo[3,4-*c*]pyrazole
(5)

Scheme(3)
Synthesis of Authentic sample of compound viii

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