Synthesis of some new substituted (α،α-diphenyl-α-hydroxymethyl) -1,3,4-oxadiazoles as possible biological active compounds

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(Recevied on 6/3 /2011) **(Accepted for publication 27/9 /2011)**

Abstract

The reaction of benzilic acid hydrazide (1) with carbon disulfide in the presence of potassium hydroxide yielded 5-(α،α-diphenyl –α-hydroxymethyl)-1,3,4-oxadiazoline -2-thione (2) ,this product was subjected to the following reactions :Alkylation with methyl iodide and potassium hydroxide to give 5-(α،α-diphenyl –α-hydroxymethyl)-2-thiomethyl-1,3,4-oxadiazole (3).Reaction with substituted aldehyde was carried out to give 5- (α،α-diphenyl –α-hydroxymethyl)-3-(α-aryl-α-hydroxymethyl)-1,3,4-oxadiazoline -2-thione (4a-f). Finally reaction with different amines was performed to afford 5- (α،α-diphenyl –α-hydroxymethyl) -3-(substituted amino methyl)-1,3,4-oxadiazoline -2-thione(5a-f) by the Mannich reaction . The structures of all compounds were confirmed by physical and spectral methods.

الخلاصة

يتضمن البحث مفاعلة هيدرازيد حامض البنزيليك (1) مع ثنائي كبريتيد الكاربون بوجود هيدروكسيد البوتاسيوم للحصول على المركب 5-(α،α ثنائي فنيل-α- هيدروكسي مثيل)-4,3,1 –اوكساديازولين-2- ثايون (2) والذي تم استخدامه كمادة وسطية لتحضير مركبات مختلفة ،فقد تم مفاعلة المركب (2) مع يوديد المثيل بوجود هيدروكسيد البوتاسيوم حيث أعطى الناتج 5-(α،α ثنائي فنيل-α- هيدروكسي مثيل)-2-ثايومثيل-4,3,1 –اوكساديازول (3)وكذلك مفاعلته مع البنزالديهايد ومعوضاته للحصول على مركبات 5-(α،α ثنائي فنيل-α-هيدروكسي مثيل)-3 –(α-أريل-α-هيدروكسي مثيل)-4,3,1 –اوكساديازولين-2- ثايون(4a-f). كما تمت مفاعله المركب(2) مع الأمينات المختلفة بوجود الفورمالديهايد بواسطة تفاعل مانيخ لإعطاء 5-(α،α ثنائي فنيل-α- هيدروكسي مثيل)-2- معوضات-4,3,1 –اوكساديازول (5a – f).

تم إثبات الصيغ التركيبية للمركبات المحضرة من خلال استخدام الطرق الطيفية المختلفة والطرق الفيزيائية المتوفرة.

Introduction

Over the past years substituted oxadiazole derivatives have become as one of the most extensively studied classes of heterocyclic compounds ,receiving much attention from organic synthetic chemists because of their application in several areas such as medicine and agriculture as antimicrobial [1] ,antifungal [2] ,antiflammatory and analgesic agents [3]. Most of 1,3,4-oxadiazole compounds are best obtained by synthesis from acyclic precursors such reactions are mainly " one bond " or two bond " cyclizations. Studies by many authors showed that the main rout to the synthesis of 1,3,4-oxadizoles -5-thione is the cyclization of substituted acid hydrazides in presence of alkali ,mostly potassium hydroxide ,and carbon disulfide under reflux condition [4,5] .

It is well-known that substituted -1,3,4 –oxadiazole can be used as synthons for others biologically important compounds [6] .So, it was of interest to investigate aspects of its reaction with different reagents ,namely methyl iodide , potassium hydroxide ,aldehyde and amines in presence of formaldehyde, aiming to synthesize new series of suspected biological active nitrogenous compounds.

A literature survey has revealed that the major reaction of such nucleus are the nucleophilic substitution reaction ,this has been observed in the reaction of oxadiazoline -2-thione with substituted aldehydes as well as the reaction with different amines in presence of formaldehyde so-called Mannich reaction [8].

Experimental

Melting points were determined using electro thermal 9300melting point apparatus and are uncorrected .IR spectra were recorded on a Perkin-Elmer 590B spectrophotometer using KBr disk.^{1}H NMR spectra were obtained on 60 MHz Hitachi Perkin-Elmer spectrophotometer, with TMS as internal standard. No clear splitting is observed due to the low resolution of the instrument .UV spectra were recorded on Shimadzu UV-160 spectrophotometer using methanol as a solvent .Elemental analysis were performed on Carlo-Erba type 1106 CHN Analysis .Reaction progress and product mixture were monitor routinely by thin-layer chromatography (TLC) on silica gel precoated plates. The benzilic acid hydrazide (1) was prepared by the author [9] .

Preparation of 5- (α،α-diphenyl –α-hydroxymethyl)-1,3,4-oxadiazoline -2-thione (2) [10]:

To a solution containing (25 ml) ethanol ,(0.56 gm,0.01 mole) potassium hydroxide and (25ml) water, benzilic acid hydrazide (1)(2.4gm,0.01mole) was added with stirring . Slightly more than one equivalent of carbon disulfide was added and the mixture was refluxed for (20 hrs.) until all hydrogen sulfide was evolved (tested by lead acetate solution) .After concentration of the solution to a small volume, the residue was dissolved in water. The solution was added to ice-water, containing hydrochloric acid(5%,10ml) and the resulting precipitate was crystallized from aqueous ethanol to give the product (2.75gm,97%) m.p. (138-139˚C).

Preparation of 5- (α،α-diphenyl –α-hydroxymethyl)-2-thiomethyl -1,3,4-oxadiazole (3)[10]:

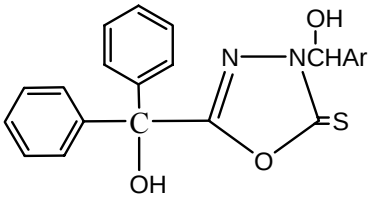
To oxadiazoline (2) (0.3gm,0.001mole) was dissolved in a solution of (1N,20ml) hydroxide and (5ml)ethanol. Methyl iodide (0.45gm,0.005mole) was added potassjm and the mixture stirred at room temperature for one hour. The

reaction mixture was acidified with (10% hydrochloric acid) and extracted with ether (3x10ml),the ether layer was washed with water ,dried with magnesium sulfate and filtered. Evaporated under vacuum afforded the product (3) as a white solid (1.5gm,72%) (m.p. 163 - 165˚ C).

Preparation of 5- (α،α-diphenyl –α-hydroxymethyl)-3-(α-aryl–α-hydroxymethyl)-1,3,4-oxadiazoline-2-thiones(4a - f)[11]:

The oxadiazoline (2) (0.3gm , 0.001mole) was dissolved in ethanol (30 ml) and cooled with ice-water at (0℃) . To this solution ,a suitable aldehyde (0.001 mole)was added and the mixture was stirred about three hours at (0℃) and kept overnight at room temperature ,the resulting solution was concentrated in vacuum ,cooled and diluted with water to give the solid product which was filtered, wash with ethanol and crystallized from aqueous ethanol to afford the corresponding products(4a- f) .Physical and spectral data are listed in tables (1 and 3).

Table 1: Physical data for compounds(4a –f):

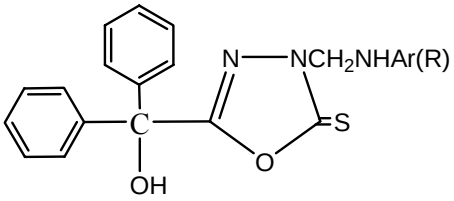


Compds. No.	Ar	m.p. ℃	Yield %	Molecular formula	Analysis% Found(calcd.) C% H% N%
4a	C_6H_5	197-98	65	$C_{22}H_{18}N_2O_3S$	67.63 4.52 7.03 (67.69 4.61 7.17)
4b	2-Cl-C_6H_4	205-06	64	$C_{22}H_{17}ClN_2O_3S$	61.93 3.89 6.43 (62.19 4.0 6.59)
4c	α-naphthyl	136-38	66	$C_{26}H_{20}N_2O_3S$	70.68 4.42 6.31 (70.90 4.54 6.36)
4d	β-naphthyl	102- 04	58	$C_{26}H_{20}N_2O_3S$	70.75 4.49 6.72 (70.9 4.54 6.36)
4e	3-pyridyl	110 -12	69	$C_{21}H_{17}N_3O_3S$	64.27 4.36 10.62 (64.45 4.34 10.74)
4f	3-Indolyl	119-21	74	$C_{24}H_{19}N_3O_3S$	67.1 4.23 9.76 (67.13 4.42 9.79)

Preparation of 5- (α،α-diphenyl –α-hydroxymethyl)-3-substituted amino methyl -1,3,4-oxadiazoline-2-thiones(5a - f) [12]:

A mixture of ethanolic solution of 5- (α،α-diphenyl –α-hydroxymethyl)-1,3,4-oxadiazoline -2-thione (2) (0.3gm,0.001mole) and formaldehyde (15ml,35%) was added slowly on ethanolic solution of appropriate amine (0.001mole) .The reaction mixture was stirred for three hours at room temperature and kept overnight in a refrigerate .The solid thus obtained was filtered ,washed with cold ethanol ,dried and crystallized form aqueous methanol to give compounds (5a – f).Physical and spectral data are listed in tables (2 and 4).

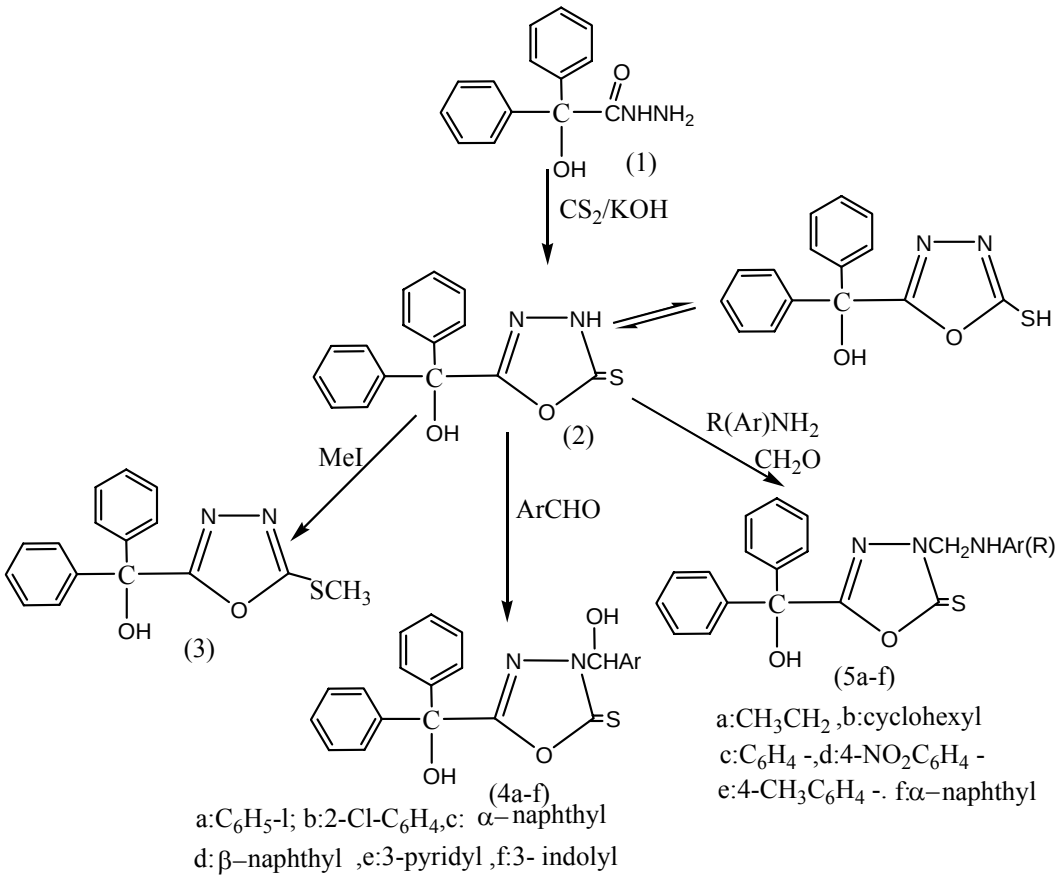
Table 2 : Physical data for compounds (5a –f):



Compds. No.	Ar (R)	m.p. ℃	Yield %	Molecular formula	Analysis% Found(calcd.) C% H% N%
5a	CH_3CH_2-	Oily	42	$C_{18}H_{19}N_3O_2S$	63.21 5.42 12.19 (63.34 5.57 12.31)
5b	cyclohexyl	191-93	61	$C_{22}H_{25}N_3O_2S$	66.87 6.27 10.54 (66.83 6.33 10.63)
5c	C_6H_5-	135-37	55	$C_{22}H_{19}N_3O_2S$	67.81 4.82 10.69 (67.86 4.88 10.79)
5d	4-$NO_2C_6H_4$-	194-96	60	$C_{22}H_{18}N_4O_4S$	60.61 3.95 12.84 (60.82 4.14 12.90)
5e	4-$CH_3C_6H_4$-	187-89	48	$C_{23}H_{21}N_3O_2S$	68.31 4.88 10.40 (68.41 5.21 10.42)
5f	α-naphthyl	143-45	45	$C_{26}H_{21}N_3O_2S$	71.11 4.69 9.62 (71.07 4.78 9.56)

Results and Discussions

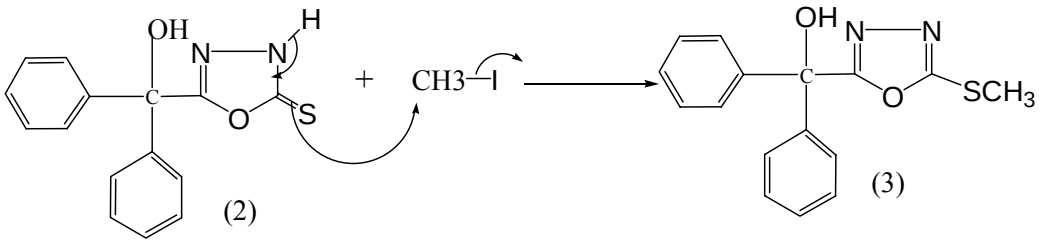
It was found that compounds containing oxadiazole ring systems have attracted many workers due to their biological activities [13,14,15] .In this account we wish to report suitable methods for the preparation of this nucleus from acid hydrazide (1) (Scheme 1).



Scheme 1

Reaction of the later compound with carbon disulfide in alkaline solution ,caused hydrogen sulfide to evolve and forming oxadiazole ring(2)[16]. The structure of compound (2) was identified by UV , IR and ^{1}H NMR spectral data .UV spectrum shows λmax (MeOH)at (216nm).The IR spectrum disclosed the presence of C=N at 1633 cm^{-1},C-O-C at 1282 cm^{-1} and C=S at 1156 cm^{-1} bands with no absorbance at around 2600 cm^{-1} of thiole form [17] . This is further supported by ^{1}H NMR spectrum which shows no absorbance at 11- 13 ppm for SH group i.e. the thione form was predominate [18].

The reaction of oxadiazoline (2) with methyl iodide and potassium hydroxide gave thiomethyl derivative (3) by nucleophilic attack of sulfur atom at the methyl iodide group followed by expelling hydrogen iodide molecule as follows:



The S-metylation was identified by physical and spectral analysis. The IR (KBr disk) spectra of this product showed characteristic absorption at 1615 cm^{-1} due to C=N group , 1228 cm^{-1} due to C-O-C group. ^1H NMR ($CDCl_3$)spectra showed a singlet at δ(2.55 ppm) due to CH_3 group, δ(6.2 ppm) for one proton assigned for OH. δ(7.1 - 7.4 ppm) as a multiplet for aromatic absorption .The UV spectra showed λmax (MeOH)at (243 nm).

It was found that ,basicity of nitrogen atom in oxadiazole moiety of compound (2) makes its reaction with different aromatic aldehydes possible to give the corresponding compounds (4 a – f).The spectral data UV,IR and ^1H NMR of these compounds (Table 3)showed that these compounds were in good agreement with the proposed structure .Furthermore, the CHN microanalysis of compounds (4 a- f) supported their molecular formula (Table 1).

Table 3 :Spectral data for compounds (4a – f):

Compd No.	IR(KBr)γ cm^{-1}			UV λmax(nm)	^1H-NMR δ(ppm) DMSO-d_6
	C=N	C=S	C-O-C		
4a	1660	1087	1275	279	6.3(bs,2H,2OH),6.9-7.5(m,15H,3Ph),8.1(d,1H,CH)
4b	1655	1024	1292	272	6.5(bs,2H,2OH),6.5-7.4(m,14H,2Ph+ArH),7.9(d,1H,CH)
4c	1612	1098	1195	283	6.2(bs,2H,2OH),6.8-7.4(m,17H,2Ph+ArH),8.2(d,1H,CH)
4d	1632	1080	1290	290	6.5(bs,2H,2OH),6.6-7.3(m,17H,2Ph+ArH),8.1(d,1H,CH)
4e	1618	1093	1180	301	6.25(bs,2H,2OH),6.8 (m,10H,2Ph):7.1-7.5(m,4H,ArH):,8.1(d,1H,CH)
4f	1602	1125	1207	312	6.6(bs,2H,2OH),6.5-7.2(m,16H,2Ph+ArH:),7.8(d,1H,CH)

The Mannich reaction of compound (2)with appropriate amine in the presence of formaldehyde (35 %) gave 5- (α،α-diphenyl –α-hydroxymethyl)-3-substituted amino methyl -1,3,4-oxadiazoline-2-thiones(5a - f). The structure of theses compounds were identified by UV,IR and ^1H-NMR spectral data which show similar patterns to those of amino methyl oxadiazole -2- thiones .The UV spectra the range of λmax (MeOH)at (302 - 385 nm). Further more the IR spectra of compounds (5a-e) showed characteristic absorptions at(1655-1585 cm^{-1}) due to C=N

group,(1195-1080 cm^{-1}) due to C=S group and (3330-3200 cm^{-1}) for NH , ^{1}H-NMR (DMSO-d_6)spectra showed the presence of Mannich bases characteristic chemical shifts ,it shows a doublet at δ(4.3-4.8 ppm) integrating for two protons assigned for N-CH_2-N and a broad at δ(5.0-5.6 ppm) integrating for one proton assigned for NH .This comes in agreement with the spectra of other substituted -1,3,4-oxadiazoline-2-thiones . Finally ,the CHN microanalysis of compounds (5a-f) supported their molecular formula (Table 2).

Table 4 :Spectral data for compounds (5a – f):

Compd No.	IR(KBr)γ cm^{-1}			UV λmax(nm)	^{1}H NMR δ(ppm) DMSO-d_6
	C=N	C=S	NH		
5a	1585	1174	3237	302	1.3(t,3H,CH_3):2.7(q,2H,CH_2): 4.3(d,2H,N-CH_2-N):5.6(bs,1H ,NH),6.2(s,1H,OH),7.1(s,10H,2Ph)
5b	1645	1165	3200	344	0.8-1.6(m,11H,Cyclohexyle):4.8(d,2H,N-CH_2-N):5.6(bs,1H,NH),6.4(s,1H,OH),7.3(s,10H,2Ph).
5c	1620	1135	3330	330	4.3(d,2H,N-CH_2-N):5.4(bs,1H ,NH),6.5(s,1H,OH),6.8-7.4(s,15H,3Ph)
5d	1608	1080	3310	344	4.4(d,2H,N-CH_2-N):5.1(s,1H ,NH),6.2(s,1H,OH),6.9-7.6(m,17H,2Ph+ArH)
5e	1602	1195	3320	385	2.6(s,3H,CH3):4.5(d,2H,N-CH_2N):5.2(bs,1H ,NH),6.6(bs,1H,OH),7.4(s,10H,2Ph):6.7-7.4(m,4H,ArH)
5f	1598	1168	3297	362	4.5(d,2H,N-CH_2-N):5.1(bs,1H ,NH),6.2(s,1H,OH),5.8-7.3(m,10H,2Ph+ArH)

Finally, the prepared compounds showed promising biological activity , the detail of which it beyond the scope of this research.

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