Synthesis of 1,3,4-Oxadiazole Derivatives from Ethyl-2-Piperidone-3-Carboxylate

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الملخص

في هذا البحث تم تحضير عدد من مشتقات ١،٣،٤-اوكسادايازول الجديدة وذلك باستخدام إستر اثيل-٢-باي‌بريدون-٣-كاربوكسيلات. إن تفاعل إستر الاثيل مع الهيدرازين المائي يعطي الهايدرازايد المقابل (I)، والذي عند مفاعلته مع عدد من الالديهايدات الاروماتية أدى إلى إعطاء عدد من مركبات الهيدرازون (II). وبعد ذلك حضرت مشتقات ١،٣،٤-اوكسادايازول بعملية الأكسدة الحلقية لمركبات الهيدرازون (II) باستخدام ثنائي أوكسيد الرصاص في حامض الخليك الثلجي.

تم إثبات الصيغ التركيبية للمركبات المحضرة باستخدام الطرائق الفيزياوية والطيفية.

ABSTRACT

In the present work, some new 1,3,4- Oxadiazole derivatives have been synthesized from Ethyl-2-Piperidone-3-Carboxylate. The reaction of the ethyl ester with hydrazine hydrate afforded the corresponding hydrazide (I). Treatment of the latter compound with different aromatic aldehydes yielded a new hydrazones (II). Preparation of 1,3,4-Oxadiazoles (III) have been achieved by oxidative cyclization of hydrazones (II) by the use of lead dioxide in glacial acetic acid.

The structural formula of the synthesized compounds were established by physical and spectral methods.

INTRODUCTION

Derivatives of 1,3,4-Oxadiazoles constitute an important family of heterocyclic compounds. Their synthesis could be achieved through oxidative cyclization of hydrazone compounds by the use of lead dioxide in glacial acetec acid [1].

1,3,4-oxadiazoles were found to have interesting biological activities such as antiinflammatory [2], antipyretic [3], antibacterial [4], antimicrobial [5], anticancer [6], Anti HIV-1 aids [7], antimtagenicity [8], antidepressant [9], anticonvulsant and muscle relaxant [10], neurotoxicity [11], ulcerogenic and lipid peroxidation [12][13], and analgesic [14].

On the other hand hydrazone compounds like Schiff bases could be synthesized easily by condensation reactions between aldehydes or ketones with primary amines [15]. Many of these compounds have a wide variety of applications in particular as biologecally active compounds, thus they have been employed in medical field as antitubercular [16], bactericidal and fungicidal [17], Hydrazones were also found to have significant importance in organic synthesis since they served as an intermediate compounds in the synthesis of heterocyclic compounds like 1,3,4-oxadiazoles [18].

This paper is concerned with the application of ethyl-2-piperidone-3-carboxylate as a precursor in the synthesis of hydrazones and their cyclization product 1,3,4-oxadiazoles which may possess a pharmaceutical activity.

EXPERIMENTAL

Melting points were determined using electrothermal 9300 melting point apparatus and are uncorrected. IR spectra were recorded by a Bruker, FT-IR spectrophotometer tensor 27, as KBr disc. UV spectra were recorded on shimadzu UV-Visible spectrophotometer UV-1650 PC using Methanol as a solvent.

Synthesis of 2-Piperidone-3-Carboxylic Acid Hydrazide (I): [19]

A mixture of ethyl-2-piperidone-3-carboxylate (0.025 mole, 4.28 gm) and hydrazine hydrate (80%) (0.1mole, 5 gm) in absolute ethanol (15 ml) was refluxed for (3 hrs). The solvent was evaporated to half of its volume. After cooling, the precipitate was filtered and recrystallized from ethanol to give the desired compound (I) as a white crystals of 82% yield and m.p. (151-153)°C. The spectral data for both infrared and ultraviolet spectroscopy showed the following characteristic absorption bands:

- $\upsilon_{C=O}$ 1646 as a broad band that belong to two amidic carbonyl groups
- υ_{N-H} 3307 as a broad band that belong to amidic group
- υ_{N-H} 3415 as a broad band that belong to hydrazonic group
- λ max (methanol) 216 nm.

Synthesis of Aldehyde-2-Piperidone-3-Carboxylic Acid Hydrazones (II): [20]

A solution of hydrazide (I) (0.01 mole, 1.57 gm) in absolute ethanol was added gradually to a solution of aldehyde (0.01 mole) in absolute ethanol (15ml). The mixture was refluxed for (2hrs) with stirring, then the solvent was evaporated to half of its volume and the mixture was cooled. The formed precipitate was filtered and recrystillized from ethanol to obtain the desired products (II). The physical and spectral data are listed in table (1).

Synthesis of 2-Aryl-5-(2-Piperidone-3-yl)-1,3,4-Oxadiazoles (III):[1]

A mixture of one of hydrazones (II) (0.01 mole) in glacial acetic acid (40 ml) was stirred till to be clear solution, lead dioxide (0.01 mole, 2.39 gm) was added and the mixture was stirried using magnetic bar at (25-30)°C for (1hr). The mixture was diluted with crushed ice (200 gm) and water (100 ml) and left for (24 hrs). The product was filtered and recrystallized from ethanol to obtain 1,3,4-oxadiazoles (III). The physical and spectral data are illustrated in table (2).

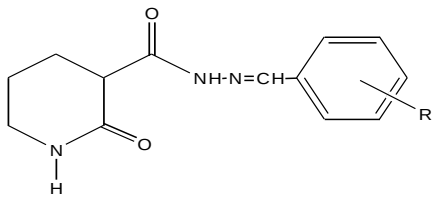


Table (1): Physical and spectral data for compounds (II1-12):

Compd. No.	Yield %	M.P. °C	Colour	IR (KBr), υ (cm^{-1})					UV(MeOH) λmax.(nm)
				C=O amidic	C=O hydraz.	C=N	N−H O−H	other	
II1	97	277-279	White	1681	1653	1610	3175 3228	—	304
II2	92	220-222	Brown	1671	1647	1633	3161 3325	—	306
II3	94	223-225	Brown	1675		1616	3181 3245	C−O−C 1138	320
II4	72	211-212	White	1666		1618	3191	C−O−C 1134	314
II5	89	259-261	Yellow	1672		1585	3215	NO_2 sym. 1401 asym.1515	320
II6	94	210-212	Pale brown	1670		1595	3192	NO_2 sym. 1407 asym.1522	286
II7	89	243-245	Yellow	1668		1605	3188	NO_2 sym. 1401 asym.1527	282
II8	85	220-222	White	1668		1599	3185	Cl 745	314
II9	85	199-200	White	1675	1651	1612	3181	—	300
II10	80	189-190	White	1682	1655	1606	3212	C−O−C 1171	294
II11	73	206-208	White	1691	1654	1614	3204	C−O−C 1055	314
II12	49	278 dec.	White	1671		1602	3189	—	344

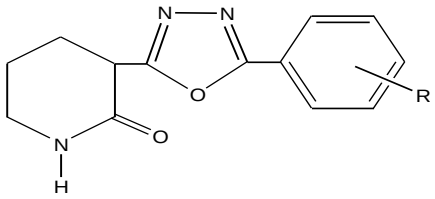
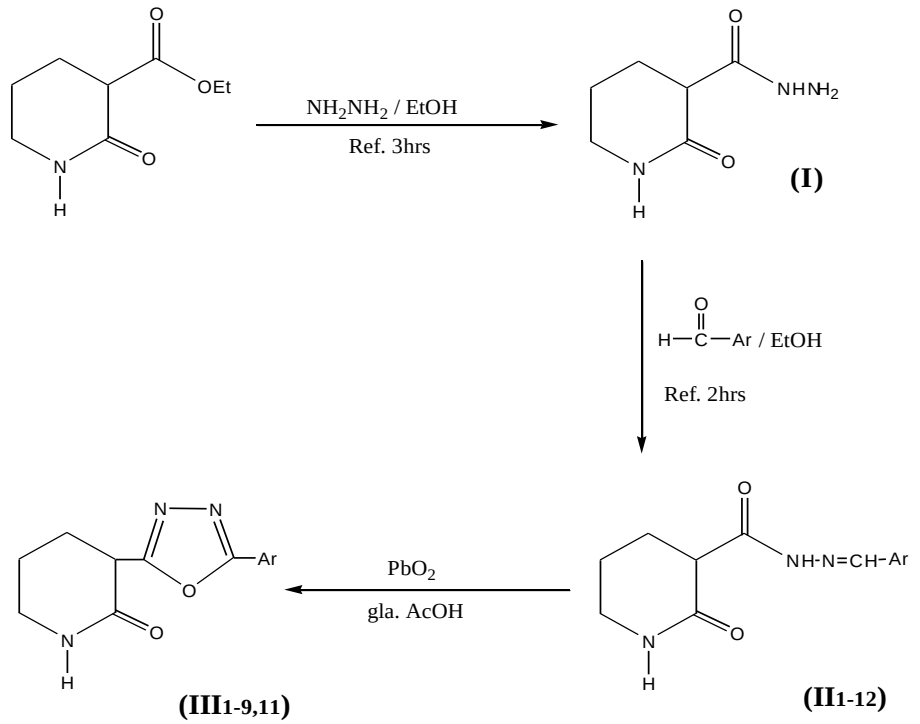


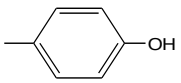
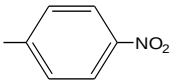
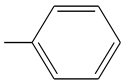
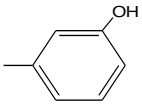
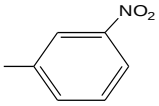
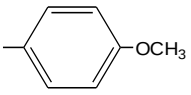
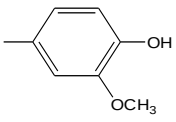
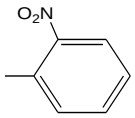
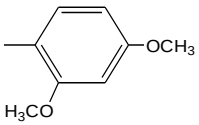
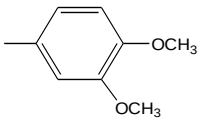
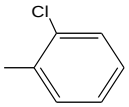
Table (2): Physical and Spectral data for compounds (III1-9,11):

Compd. No.	Yield %	M.P. ˚C	Colour	IR (KBr), υ (cm^{-1})				UV(MeOH) λmax.(nm)
				C=O amidic	C=N cyclic	N−H O−H	other	
III1	81	305 dec.	Brown	1647	1560	3449	—	290
III2	48	>300	Brown	1649	1562	3230 3384	—	284
III3	21	291 dec.	Yellowish white	1673	1587	3308	C−O−C 1147	284
III4	31	180-183	Brown	1656	1599	3340	C−O−C 1141	328
III5	70	247-249	Brown	1670	1599	3321	NO_2 sym. 1421 asym.1509	318
III6	43	144-146	Brown	1652	1527	3345	NO_2 sym. 1352 asym.1527	288
III7	83	213-215	Deep brown	1668	1589	3188	NO_2 sym. 1401 asym.1526	264
III8	74	215-218	White	1650	1596	3203	Cl 746	286
III9	—	gumy	—	—	—	—	—	—
III11	—	gumy	—	—	—	—	—	—

RESULTS AND DISCUSSION

Previous studies showed that 1,3,4-oxadiazole derivatives found to be pharmaceutically active compounds. Therefore, ethyl-2-piperidone-3-carboxylate (known as pharmaceutical intermediate) [21] was used as starting material in synthesis of new hydrazone compounds (II1-12) and 1,3,4-oxadiazoles (III1-9,11) which may show characteristic pharmaceutical activity. The route for the synthesis of these compounds was illustrated in Scheme (1).



Compd. No.	Ar	Compd. No.	Ar	Compd. No.	Ar
II1 , III1		II5 , III5		II9, III9	
II2 , III2		II6 , III6		II10	
II3 , III3		II7 , III7		II11, III11	
II4 , III4		II8 , III8		II12	

Scheme (1)

The synthesized compounds (II1-12 & III1-8) have been investigated according to their physical and spectral data (IR and UV) [22].

In IR spectra of hydrazone (II1-12), the two carbonyl groups (amidic and hydrazonic) were appeared as a two strong absorption bands at two

different regions and sometimes overlapped to be appeared as a strong absorption band at one region (1666-1675)cm^{-1}. Another new strong absorption band at (1585-1633)cm^{-1} is due to the appearance of $\upsilon_{C=N}$, while the broad bands at (3161-3325)cm^{-1} are due to υ_{N-H}(amidic) and υ_{O-H} (in compounds 1,2 & 3).

The UV spectra of hydrazones (II1-12) showed bathochromic shift (red shift) in λ max (286-344)nm as compared with that of hydrazide compound (I) (λ max 216 nm), this is due to the appearance of the conjugation effect which affect the electronic transition $(n \rightarrow \pi^*)$ in hydrazones (II1-12) as shown in table (1).

The IR spectra of 1,3,4-oxadiazoles (III1-8) showed two characteristic bands due to the stretching vibrations of (C=O amidic & C=N) which appeared at regions (1647-1673)cm^{-1} and (1527-1599) cm^{-1} respectively. Another broad band at (3188-3449)cm^{-1} is due to the stretching vibration of (N-H) bond and (O-H) bond (in compounds 1,2 & 3).

The UV spectra of 1,3,4-oxadiazoles (III1-8) generally showed hypsochromic shift (blue shift) in λ max (264-318)nm as compared with that of hydrazones (II1-12). The decreasing in λ max values was expected due to decreasing of conjugation effect on the electronic transition $(n \rightarrow \pi^*)$ which occurred in 1,3,4-oxadiazoles (III1-8) as shown in table (2).

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