Preparation of 2 – thio ether – 1, 3, 4- oxadiazole derivatives used as antibacterial and antifungus agents

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Abstract

Isonicotinic acid, *o*-hydroxy benzoic acid, *p*-chlorobenzoic acid, *p*-nitro benzoicacid and *o*-acetyl benzoic acid, have been esterificated with absolute ethanol using Fisher method to prepare compounds [1-5]. These compounds were converted to acid hydrazides [6-10] by the reaction with hydrazine hydrate. The acid hydrazides were allowed to react with carbon disulfide (CS_2) in the presence of potassium hydroxide and ethanol to produce 2-substituted 1, 3, 4- oxadiazole -5-thiol [11-15]. Thio ether derivatives as two groups (16-20) and (21-25) respectively have been prepared by the reaction between compounds [11-15] and alkyl or aryl halide, (*p*-bromo benzyl bromide and 2,4- dinitrochlorobenzene) respectively. The prepared compounds were identified by FT.I.R , melting point and H^1-NMR was used to support the structure of the compounds 2-(4-chlorophenyl)-5-(2,4-dinitrophenylthio)-1,3,4-oxadiazole and 2-(2,4-dinitrophenylthio)-5-(4-nitrophenyl)-1,3,4-oxadiazole which can be used as anti bacterial and anti fungus agents.

تحضير بعض مشتقات مركبات ٢ – ثايوايثر – ١,٣,٤– اوكساديازول والتي تستخدم كمضادات بكتيرية وفطرية

أياد سليمان حمد عبد محمد ظاهر

المستخلص

تم استرة حامض الايزونيكوتنك , وحامض اورثوهيدروكسي البنزويك وحامض باراً كلورو البنزويك وحامض بارانيترو البنزويك وحامض أورثواستايل البنزويك بطريقة فيشر مع كحول الايثانول المطلق , لتحضير الاسترات (١-٥) . وتم تحويل هذه الاسترات الى هيدرازيدات الحوامض الكاربوكسيلية المقابلة (٦-١٠) بالتفاعل مع الهيدرازين المائي . وتم تحويل هذه الهيدرازيدات الى مشتقات ٢-معوض- ١,٣,٤- اوكسادايازول-٥- ثايول (١١-١٥) من خلال التفاعل مع ثنائي كبريتيد الكاربون في وسط قاعدي . اما مركبات الثايوايثر لمشتقات ١,٣,٤- اوكسادايازول فقد تم تحضيرها كمجموعتين هما :- المجموعة الأولى من (١٦-٢٠) والمجموعة الثانية من (٢١-٢٥) فقد تم الحصول عليها من تفاعل معوضات ٢-معوض-١,٣,٤- اوكسادايازول -٥- ثايول مع بروميد بازابرومو البازايل وكذلك ٢,٤- ثنائي نايترو كلوروبنزين على التوالي . شخصت المركبات المحضرة باستخدام طيف الأشعة تحت الحمراء وكذلك قياس درجة الانصهار وطيف الرنين النووي المغناطيسي لتشخيص المركبين ٢(٢، ٤ – كلوروفنيل)- ٥ – (٢، ٤- داي نايترو فنيل ثايو) - ١,٣,٤- اوكسادايازول و ٢-(٤ – داي نايترو فنيل ثايو)- ٥ – (٤- داي نايترو فنيل) - ١,٣,٤- اوكسادايازول والتي يمكن استخدامها كمضادات للبكتيريا ومضادات للفطريات بعد أن تم اختبارها على أنواع منها .

Introduction

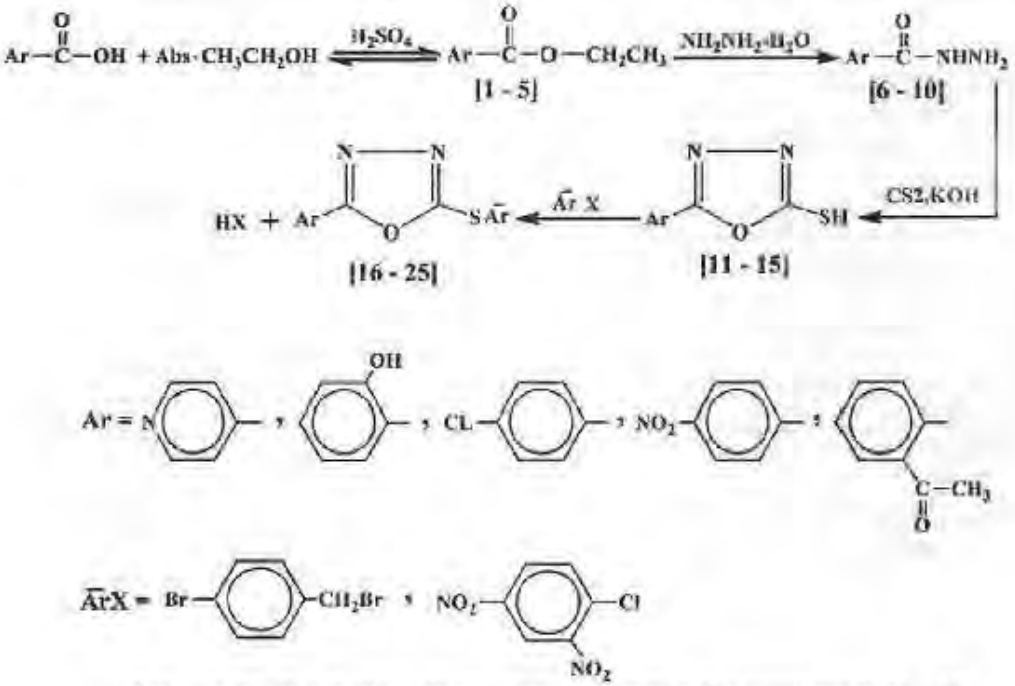
1,3,-4 oxadiazoles are known to have abroad spectrum of biological activities [1-3]. Acyl hadrazides have been ingeneral used as the starting materials for preparation of 1,3,-4 oxadiazole ring [4-5]. A new route was reported to prepare 5- furan -2 yl [1,3,-4] oxadiazoles -2- thiol and thiol-thione tautomeric equilibrium was described [5]. A series of 1,3,-4 oxadiazole moieties were prepared and their luminescence properties were studied [7]. 5, 5'-dibenzyl thio-bis-[1,3,-4 oxadiazoles-2yl] butane, was prepared by the reaction between 5,5'-dimercapto [bis-1,3,-4 oxadiazoles-2yl] butane with two moles of benzyl Bromide [8]. Starting from pyrazole -4-carboxylic acid hydrazide avariety of new -1,3,-4 oxadiazole have been prepared [9]. Some of thioether derivatives for 1, 3,-4 oxadiazole were converted to amino acid esters derivatives for 1, 3,-4 oxadiazole ring [10] Anew derivatives of 1,3,-4 oxadiazole have been prepared and tested a gainst some kinds of bacteria and fungus and Enzymes [11-12]

Experimental

1- Preparation of esters [1-5] and hydrazids [6-10]. These compounds have been prepared according to the procedure mentioned in the literature [13] and the physical data are listed in tables (1) and (2).

2- Preparation of the compounds 2-substituted 1,3,-4 oxadiazole -5-thiol [11-15] . These compounds have been prepared from the reaction of acids hydrazide [6-10] and carbon disulfide (CS_2) in the presence of (KOH) and ethanol according to the procedure mentioned in the literature [11]. Physical data is listed in table (3).

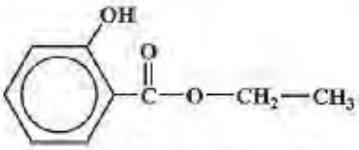
3- preparation of 2- substituted 1,3,-4 oxadiazoles -5- thioether: (0.01) mole of 2-substituted 1,3,-4 oxadiazole -5-thiol was mixed with (0.01) mole of alkyl or aryl halide in the presence of (0.01) mole (KOH) and 50 ml of ethanol , the mixture was refluxed for 2hrs, upon cooling , a white precipitates obtained, filtered and recrystallized from 80% ethanol [14]. Physical data is stated in tables (4) and (5).



Scheme (1): Synthetic path way for preparation the compounds [1 – 25]

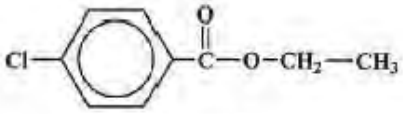
Preparation compounds [1 – 25]

1



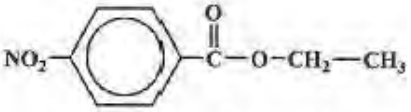
ethyl 2-hydroxybenzoate

2



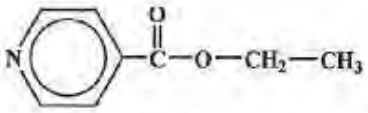
ethyl 4-chlorobenzoate

3



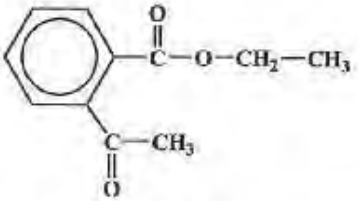
ethyl 4-nitrobenzoate

4



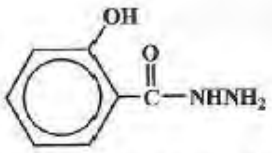
ethyl isonicotinate

5



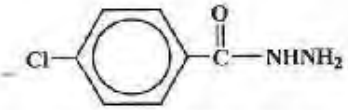
2-acetyl ethyl benzoate

6



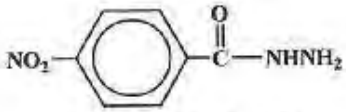
2-hydroxybenzohydrazide

7



4-chlorobenzohydrazide

8



4-nitrobenzohydrazide

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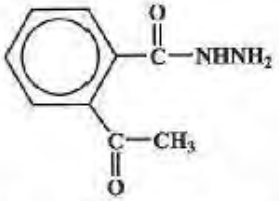
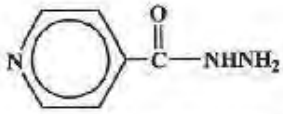


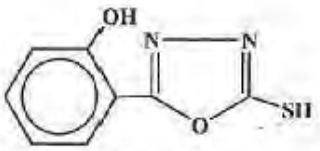
2-acetylbenzohydrazide

10



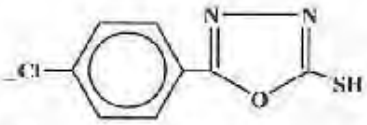
isonicotinohydrazide

11



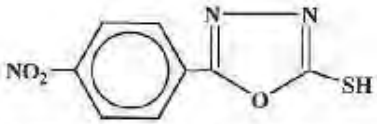
2-(5-mercapto-1,3,4-oxadiazol-2-yl)phenol

12



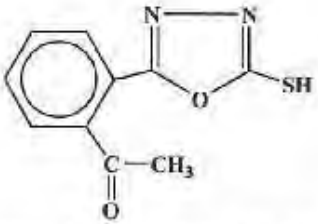
5-(4-chlorophenyl)-1,3,4-oxadiazole-2-thiol

13



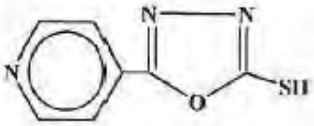
5-(4-nitrophenyl)-1,3,4-oxadiazole-2-thiol

14



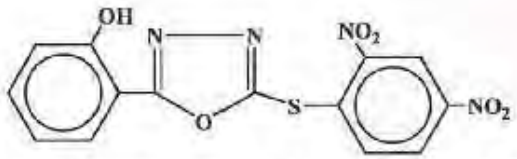
1- (5-mercapto-1,3,4-oxadiazol-2-yl) acetophenone

15



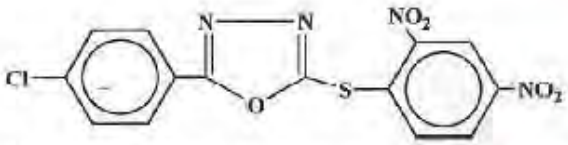
5-(pyridin-4-yl)-1,3,4-oxadiazole-2-thiol

16



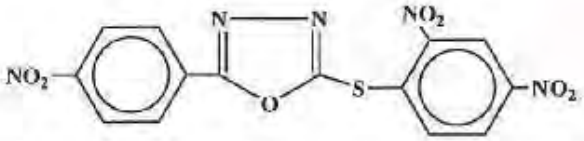
2-(5-(2,4-dinitrophenylthio)-1,3,4-oxadiazol-2-yl)phenol

17



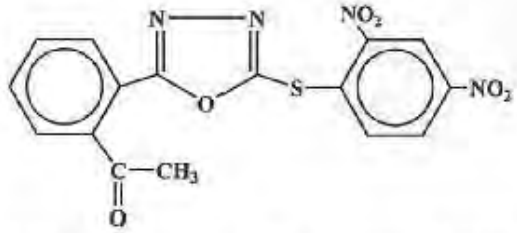
2-(4-chlorophenyl)-5-(2,4-dinitrophenylthio)-1,3,4-oxadiazole

18



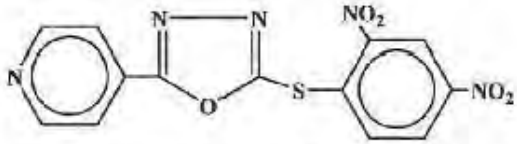
2-(2,4-dinitrophenylthio)-5-(4-nitrophenyl)-1,3,4-oxadiazole

19



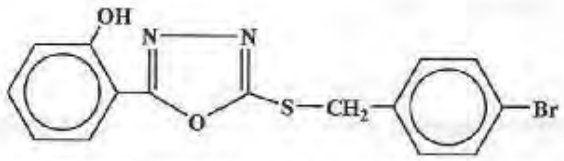
1-(2-(5-(2,4-dinitrophenylthio)-1,3,4-oxadiazol-2-yl)phenyl)ethanone

20



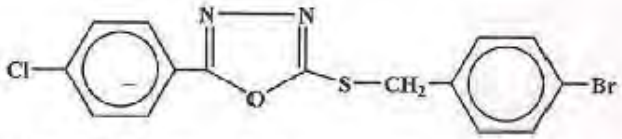
2-(2,4-dinitrophenylthio)-5-(pyridin-4-yl)-1,3,4-oxadiazole

21



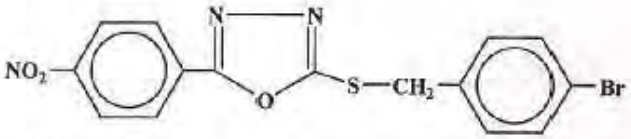
2-(5-(4-bromobenzylthio)-1,3,4-oxadiazol-2-yl)phenol

22



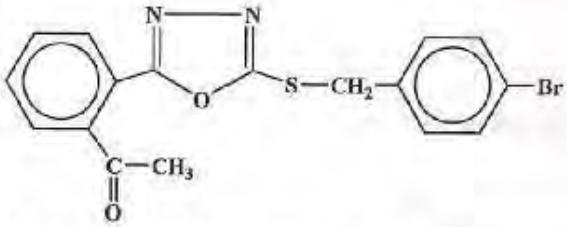
2-(4-bromobenzylthio)-5-(4-chlorophenyl)-1,3,4-oxadiazole

23



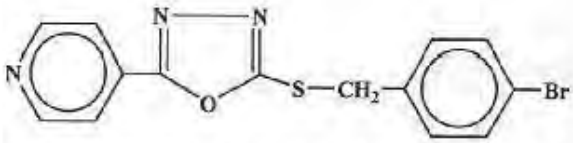
2-(4-bromobenzylthio)-5-(4-nitrophenyl)-1,3,4-oxadiazole

24



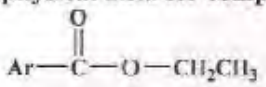
1-(2-(5-(4-bromobenzylthio)-1,3,4-oxadiazol-2-yl)phenyl)ethanone

25



2-(4-bromobenzylthio)-5-(pyridin-4-yl)-1,3,4-oxadiazole

Table (1) :- physical data for compounds [1-5]



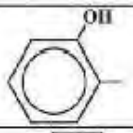
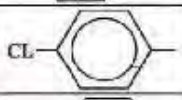
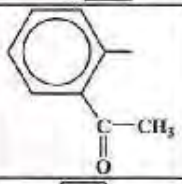
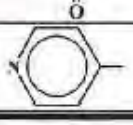
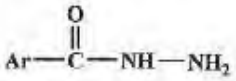
Comp. no.	Ar.	mp °C	colour	Yield %
1		B.p=234-236	Orange Liquid	20
2		B.p=237-239	Yellow Liquid	70
3		54-56	White Powder	80
4		B.p=210-212	Colourless Liquid	65
5		B.p=96-98	Colourless Liquid	48

Table (2) :- physical data for compounds [6-10]



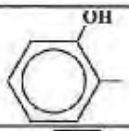
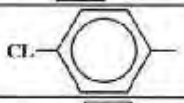
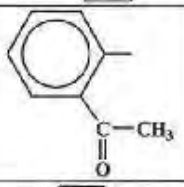
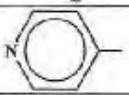
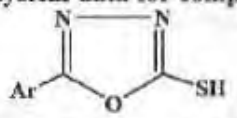
Comp. no.	Ar.	mp °C	colour	Yield %
6		147-149	White Powder	85
7		143-145	White Powder	75
8		217-219	Yellow Powder	80
9		B.p=110-112	Yellow Liquid	60
10		171-173	White Liquid	65

Table (3) :- physical data for compounds [11-15]



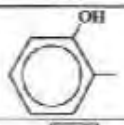
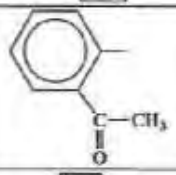
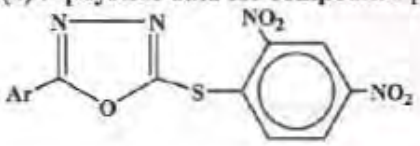
Comp. no.	Ar.	mp °C	colour	Yield %
11		198-200	White Powder	90
12		160-162	White Powder	70
13		210-212	White Powder	80
14		164-166	White Powder	90
15		270-273	Yellow Powder	85

Table (4) :- physical data for compounds [16-20]



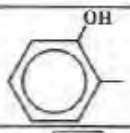
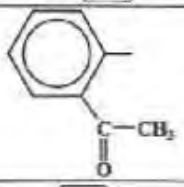
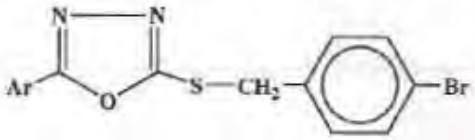
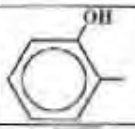
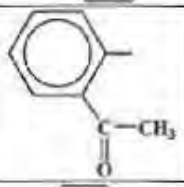
Comp. no.	Ar.	mp °C	colour	Yield %
16		173-175	Orange Powder	65
17		132-134	White Powder	70
18		206-208	White Powder	63
19		181-183	Orange Powder	60
20		102-104	White Powder	68

Table (5) :- physical data for compounds [21-25]



Comp. no.	Ar.	mp °C	colour	Yield %
21		100-102	White Powder	60
22		128-130	White Powder	66
23		201-203	Yellow Powder	65
24		84-86	White Powder	62
25		174-147	Yellow Powder	69

Experimental general

Melting point was determined on gallencamp melting point apparatus and was uncorrected. The I.R. spectra of the compounds were recorded on a shmadzu FT.I.R-470 spectra photometer KBr disc. H^1-N.M.R spectra were recorded at 300 MHZ Bruker 2003 Jordan in DMSO-d_6.

Result and discussion

The synthesis started from the aromatic carboxylic acid and absolute ethanol which esterification by **Fisher** method on produce compounds [1-5]. These compounds were readily converted to hydrazide derivatives [6-12] by the reaction with hydrazine hydrate. By heating under reflux with CS_2 in ethanolic solution of KOH, the hydrazide derivatives were cyclized to 5-substituted 1,3,-4 oxadiazole compounds [11-15] . Thiol groups in compounds [11-15] were converted to thioether groups by the reaction between compounds [11-15] with Aryl halide in precense of ethanolic solution of KOH to produce compounds [16-20] and (21-25). Scheme (1) states the synthesis of compounds [1-25]. FT.IR spectral data showed a peak at 3250-3400 cm^{-1} for $-NHNH_2$ group in compounds [6-10]. The observed peaks for compounds [11-15] and [16-20] evolve to the range 1610-1618 cm^{-1} as (-C=N), 688-695 cm^{-1} as(C-S), 1210 cm^{-1} (C=S), 3010cm^{-1} (C-H ar) and 3100cm^{-1} (CH aliphatic). H^1-N.M.R spectra support the structures of thioether derivative compounds, 5-(p-chloro-phenyl)-2-O and P-dinitrophenylthio-1,3,-4 oxadiazoles The signals at (7.3-

7.5) ppm due to the aromatic system of benzene ring protons [15] .

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