Synthesis and antibacterial activity of some new 1,3,4-oxadiazoles and 1,3,4-thiadiazoles

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Abstract:

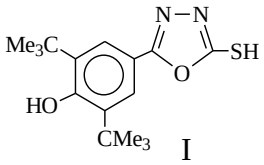
In this work the synthesis of some mono, disubstituted-1,3,4-oxadiazoles and 2-substituted-1,3,4-thiadiazoles are presented. Starting from some ethyl esters (1-4), the ester was treated with hydrazine hydrate in ethanol to give the corresponding hydrazides (5-8). The hydrazides then treated with formic acid to give 1-formyl-2-acyl hydrazine (9-12), the synthesized 1-formyl derivatives were converted to 2-substituted-1,3,4-oxadiazoles and 2-substituted-1,3,4-thiadiazoles (16-18) by their reaction with phosphorous oxychloride and phosphorous pentasulphide respectively. The reaction of acid hydrazide (6) with the esters (1,2) in presence of phosphoric acid gave 2,5-disubtituted-1,3,4-oxadiazoles (19,20). The structure of the synthesized compounds were established by the physical and spectral methods.

The synthesized compounds (13-20) were tested against six types of bacteria (*Staph. aureus, Bacillus subtilis, Proteus mirabilis, E. coli, K. pneumonia, Pseudomonas aemgioson*).

Keywords: 1,3,4-oxadiazole, 1,3,4-thiadiazole, biological evaluation.

Introduction:

The synthesis of substituted 1,3,4-oxadiazoles was studied by many research workers due to their high thermal stability[(1)], various biological activities as anti-inflammatory agent as compounds I and II and some other applications[(2,3)].



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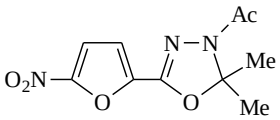
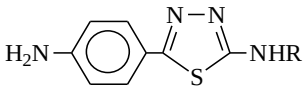


II

Some substituted 1,3,4-oxadiazoles were used in industry as pigments[(4)]. Mercapto-1,3,4-oxadiazoles were synthesized from acid hydrazides by their reaction with carbon disulfide in alcoholic potassium hydroxide solution[(5)] or in pyridine[(6)], ethyl 4-phenyl thiosemicarbazide-1-carboxylate, was converted to 2-ethoxy-1,3,4-oxadiazole-5-thiol by its treatment with concentrated hydrochloric acid[(7)].

Substituted 1,3,4-thiadiazoles were synthesized by many routes, thiosemicarbazide was treated with carboxylic acid in presence of sulfuric acid[(8)] or phosphorous oxychloride[(9)] to give substituted 1,3,4-thiadiazole, substituted thiosemicarbazide was treated with sulfuric acid to give 2,5-disubstituted-1,3,4-thiadiazole as compound III[(10)]. Other compounds were synthesized by the same method[(11,12)].



III

Phosphoric acid was used for cyclization of substituted thiosemicarbazide to 1,3,4-thiadiazole derivatives[(13,14)]. In this paper the synthesis and biological evaluation of some substituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles was studied.

Experimental:

Most of the chemicals were purchased from Flucka and BDH Chemical Ltd. The melting points were measured on an Electrothermal 9300 Engineering LTD and were uncorrected. IR spectra were recorded on Infrared Spectrophotometer Model Tensor 27, Bruker Co., Germany, using KBr discs. UV spectra were recorded on Shimadzu Double-Beam Spectrophotometer UV-210 A using ethanol as a solvent.

Synthesis of ethyl N-substituted glycine (1,2,4):

A mixture of aliphatic amine (0.15 mole), ethyl chloroacetate (0.15 mole) (0.3 mole for synthesis of compound 4) and sodium bicarbonate (12.5 g) in absolute ethanol was refluxed for (3) hours, most of the solvent was evaporated and the residue was poured on cold water (100 ml) the esters were isolated by extraction with methylene chloride. The solution was dried and evaporated to give a solid product, which was recrystallized from ethanol, Tables (1,2).

Table (1): Physical data of compounds (1-20)

Comp. No.	Molecular formula	Yield %	m.p. °C
1	$C_{10}H_{19}NO_2$	65	239-242
2	$C_{10}H_{21}NO_2$	61	144-146
3	$C_{14}H_{18}O_6$	40	92-94
4	$C_{14}H_{20}N_2O_4$	80	90-92
5	$C_8H_{17}N_3O$	90	78-80
6	$C_8H_{19}N_3O$	88	Oily
7	$C_{10}H_{12}N_4O_4$	91	244-246
8	$C_{10}H_{16}N_6O_2$	55	232-234
9	$C_9H_{17}N_3O_2$	79	154-156
10	$C_9H_{21}N_3O_2$	87	150-152
11	$C_{12}H_{14}N_4O_6$	52	228-230
12	$C_{12}H_{16}N_6O_4$	85	196-198
13	$C_9H_{15}N_3O$	80	116-118
14	$C_{12}H_{10}N_4O_4$	62	114-116
15	$C_{12}H_{12}N_6O_2$	74	118-120
16	$C_9H_{15}N_3S$	32	240-242
17	$C_9H_{17}N_3S$	40	204-206
18	$C_{12}H_{10}N_4O_2S_2$	38	170-173
19	$C_{16}H_{30}N_{40}$	66	Oily
20	$C_{16}H_{32}N_4O$	55	202-204

Table (2): Spectral data of compounds (1-20)

Comp. No.	IR νcm^{-1}				UV (nm) λ_{max} EtOH
	N-H	C=O	C-O-C	Others	
1	3310	1745	-	-	258
2	3220	1775			251
3	3210	1735	1045	1590 (C=C)	-
4	3005	1760	-	1572 (C⋯C)	-
5	3340	1670	-	-	269
6	3365	1680	-	-	-
7	3300	1685	-	1560 (C⋯C)	-
8	3200	1685	-	1555 (C⋯C)	-
9	3320	1675, 1725	-	-	-
10	3260	1650, 1720	-	-	254
11	3270	1685, 1720	-	-	-
12	3300	1685, 1715	-	-	-
13	3060		1040	1610 (C=N)	-
14	-	-	1100	1660 (C=N)	271
15	3220	-	1040	1616 (C=N)	272
16	3160	-	-	1650 (C=N) 1048 (C-S-C)	264
17	3270	-	-	1655 (C=N) 1031 (C-S-C)	241
18	-	-	-	1640 (C=N) 1070 (C-S-C)	246
19	3419	-	1070	1636 (C=N)	-
20	3200	-	1050	1650 (C=N)	-

Synthesis of 1,4-di(ethoxy carbonyl methoxy) benzene (3):

A mixture of hydroquinone (15.5 g, 0.055 mole), anhydrous potassium carbonate (15.18 g, 0.11 mole) and ethyl bromoacetate (18.37 g, 0.11 mole) in dry acetone was refluxed for (18) hours. The solvent was evaporated under reduced pressure, then cold water was added. The solid product then filtered, washed with water and dried, recrystallized from ethanol to give crystals, Table (1,2).

Synthesis of carboxylic acid hydrazides (5-8):

The esters (1 or 2) (0.04 mole) was refluxed with hydrazine hydrate (0.2 mole, 10 ml) in ethanol (70 ml) for (3) hours, the solvent was evaporated under reduced pressure to give acid hydrazide (5 and 6), [for esters (3 and 4), (20 ml, 0.04 mole) hydrazine hydrate was used], Tables (1,2).

Synthesis of 1-formyl-2-acyl hydrazine (9-12):

A mixture of hydazide (5, 6, 7 or 8) (0.025 mole) and formic acid 98% (10 ml) was refluxed for 30 minutes. The solvent was evaporated and the solid then filtered, washed with water, dried and recrystallized from methanol, Tables (1,2).

Synthesis of 2-substituted-1,3,4-oxadiazoles (13-15):

One of 1-formyl hydrazides (9-11) was mixed with phosphorous oxychloride (10 ml), then refluxed for (1) hour. The mixture was poured on crushed ice followed by the addition of 20% sodium bicarbonate solution to obtain weakly basic solution. The precipitate was filtered, washed with water several times, dried and recrystallized from ethanol-water, Tables (1,2).

Synthesis of 2-substituted-1,3,4-thiadiazole (16-18):

To a solution of 1-formyl hydrazide (9 or 10) (0.0025 mole) [for synthesis of compound (18), (0.00125 mole) of 1-formyl hydrazide (11)] in xylene (100 ml), phosphorous pentasulphide (1.1 g, 0.005 mole) was added. The mixture was refluxed for (1) hour. The mixture was filtered and the solvent was evaporated under reduced pressure, the solid product was recrystallized from methanol, Tables (1,2).

Synthesis of 2,5-disubstituted-1,3,4-oxadiazoles (19,20):

Phosphoric acid 85% (10 ml) was added to a mixture of hydrazide (6) (0.0015 mole) and ester (1 or 2) (0.0015 mole). The mixture was heated at (120 °C) for (1) hour, after cooling the solution was neutralized with ammonium hydroxide, the precipitate of compound (20) was filtered off, washed with water and recrystallized from ethanol, while compound (19) was isolated by extraction with ether, the ether layer dried and evaporated to give compound (19), Tables (1,2).

The biological activity test:

In the present work the following bacteria were used *Staph. aureus, Bacillus subtilis, Proteus mirabilis, E. coli, K. pneumonia, Pseudomonas aemgioson*.

The procedure of Bauer[15] was used in sensitivity test as six colonies of the above mentioned bacteria which were transferred to the nutrient broth. The medium was incubated at 37 °C for 15-16 hours, and diluted with normal saline and then (0.1 ml) of this medium was transferred to the nutrient agar and distributed on the surface of the Petri-dishes, then left for about 30 minutes at 37 °C in the incubation.

To determine the inhibitory effect, filter paper discs were saturated with different concentration of solution for tested compounds (13-20) in DMSO and were distributed on the surface of the agar medium and then incubated for (15-16) hours. The antibiotic chloramphenicol and ciprofloxacin were used as a control.

Results and Discussion:

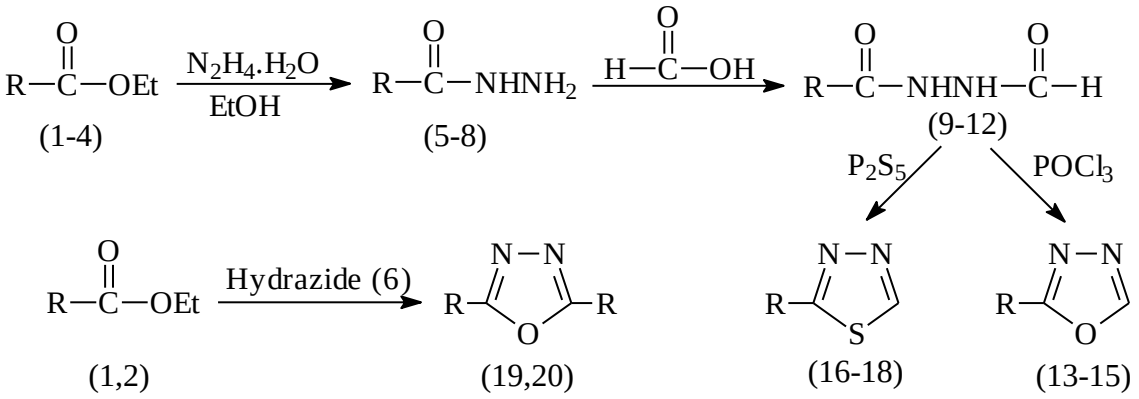
The synthesis of mono and disubstituted 1,3,4-oxadiazoles and monosubstituted 1,3,4-thiadiazoles is reported (Scheme 1). The ethyl esters [ethyl N-substituted glycine and 1,4-di(ethoxy carbonyl methoxy) benzene] (1-4) were treated with hydrazine hydrate in ethanol to give acid hydrazides (5-8). The hydrazides show absorption peaks at νcm^{-1} 3365-3200 (N-H), 1685-1670 (C=O) the compounds 7 and 8 show additional absorption peaks at νcm^{-1} 1560-1555 (C⋯C).

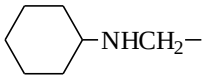
The hydrazides then treated with formic acid to give 1-formyl-2-acyl hydrazine (9-12) which were transferred to monosubstituted 1,3,4-oxadiazoles (13-15) and monosubstituted 1,3,4-thiadiazoles (16-18) by their reaction with phosphorous oxychloride and phosphorous pentasulphide respectively.

1-Formyl-2-acyl hydrazine (9-12) show absorption peaks at νcm^{-1} 3320-3260 (N-H) and 1685-1650 and 1725-1715 (2C=O) and compounds (13-15) show absorption νcm^{-1} at 3220-3060 (N-H), 1660-1610 (C=N) and 1100-1040 (C-O-C) while 1,3,4-thiadiazoles (16,17) show absorption νcm^{-1} at 3270, 3160 (N-H) and 1655, 1650 (C=N). While compound (18) showed absorption peak at νcm^{-1} 1636 (C=N) The ester 1 and 2 were treated with hydrazide (6) to give disubstituted 1,3,4-oxadiazoles (19,20). The later compounds show absorption at νcm^{-1} 3419, 3200 (N-H), 1650, 1636 (C=N) and 1070-1050 (C-

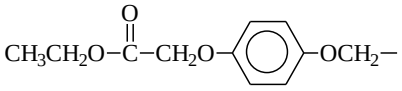
O-C). The UV spectral data were at near region and they are due to n-π* transitions.

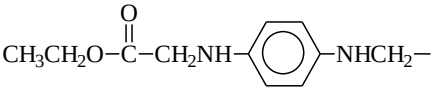
The IR and UV spectral data of the synthesized compounds were measured as well as the physical properties, Tables (1,2).

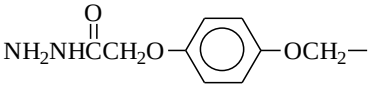


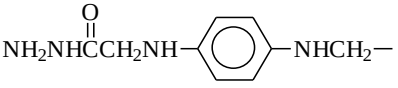
(1,5,9,13,16,19) R = 

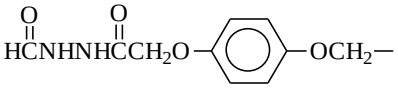
(2,6,10,17,20) R = $CH_3(CH_2)_5NHCH_2$-

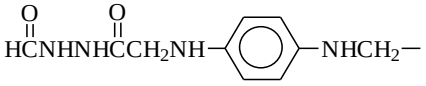
(3) R = 

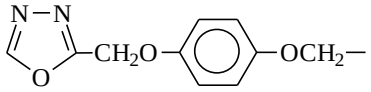
(4) R = 

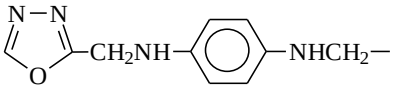
(7) R = 

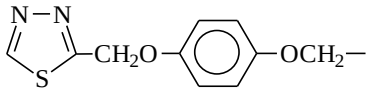
(8) R = 

(11) R = 

(12) R = 

(14) R = 

(15) R = 

(18) R = 

Scheme (1)

Biological activity

Antibacterial activity of compounds (13-20) was evaluated by agar plate diffusion technique against *Staph. aureus, Bacillus subtilis, Proteus mirabilis, E. coli, K. pneumonia, Pseudomonas aemgioson*.

The result indicate that the tested compounds have no activity against Proteus mirabilis, while compounds (13-20) show a certain activity against Staph. aureus. The effect on Bacillus subtilis, E. coli, K. pneumonia and Pseudomonas aemgioson was varied depend upon the tested compounds structures and the sample concentrations, Table (3).

Table (3): The antibacterial activity of compounds (13-20) as inhibitor zone (mm)

Comp. No.		*Proteus mirabilis*				*Staph. aureus*				*Bacillus subtilis*				*E. coli*				*K. pneumonia*				*Pseudo. aemiogioson*			
		10	1	0.1	0.01	10	1	0.1	0.01	10	1	0.1	0.01	10	1	0.1	0.01	10	1	0.1	0.01	10	1	0.1	0.01
13		-	-	-	-	16	13	10	9	15	10	10	7	18	15	12	10	18	13	12	9	15	13	11	9
14		-	-	-	-	17	12	9	-	-	-	-	-	9	-	-	-	13	9	7	-	15	10	9	-
15		-	-	-	-	20	15	14	11	11	8	-	-	-	-	-	-	-	-	-	-	-	-	-	-
16		-	-	-	-	15	13	9	7	15	14	10	-	-	-	-	-	-	-	-	-	19	15	11	9
17		-	-	-	-	18	12	9	-	-	-	-	-	10	-	-	-	-	-	-	-	-	-	-	-
18		-	-	-	-	15	13	-	-	-	-	-	-	12	-	-	-	-	-	-	-	-	-	-	-
19		-	-	-	-	13	9	4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
20		-	-	-	-	14	10	-	-	16	13	9	7	18	15	10	7	-	-	-	-	-	-	-	-
Ciprophloxacin 5 μg/ml	Control	-				-				-				17				15				9			
Chloramphenicol 30 μg/ml	Control	11				17				13				15				8				8			

* concentration 10, 1, 0.1 and 0.01 mg/disc

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تحضير ودراسة الفعالية التثبيطية ضد البكتريا لعدد من معوضات ٤،٣،١-اوكسادايازول و ٤،٣،١-ثاياديازول

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الملخص:

تم في هذا البحث تحضير عدد من مركبات ٤،٣،١-اوكسادايازول احادية وثنائية التعويض و ٤،٣،١-ثاياديازول احادي التعويض من عدد من الاسترات (١-٤). تم تحويل الاسترات الى هيدرازيدات الاحماض الكاربوكسيلية (٥-٨) من خلال مفاعلتها مع الهيدرازين المائي في الايثانول. كما تم مفاعلة الهيدرازيدات مع حامض الفورميك ليعطي مشتقات ١-فورميل-٢-اسيل هيدرازين (٩-١٢). حولت مشتقات ١-فورميل الى ٢-معوضات-٤،٣،١-اوكسادايازول و ٢-معوضات-٤،٣،١-ثاياديازول من خلال تفاعلها مع اوكسي كلوريد الفسفور وخماسي كبريتيد الفسفور على التوالي. اعطى تفاعل بعض الاسترات (٢،١) مع هيدرازيد الحامض (٦) بوجود حامض الفوسفوريك ٤،٣،١-اوكسادايازول-٥،٢-ثنائي التعويض (٢٠،١٩). شخصت المركبات المحضرة بالطرق الطيفية والفيزياوية.

اختبرت فعالية المركبات(١٣-٢٠) تجاه البكتريا *Staph. aureus* ، *Bacillus subtilis*، *Proteus mirabilis* ، *E. coli*، *K. pneumonia* ، *Pseudomonas aemgioson*.