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Synthesis of Some New 1, 3, 4-Oxadiazole Derivatives Containing Azo Group from 5-[4-(*p*-Methoxyphenyl)azophenyl]- 2-thiol- 1, 3, 4 – oxadiozole

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Abstract:

In this paper , the synthesis of 1,3,4-Oxadiazole derivatives containing azo group were achieved from 5-[4- (***P***-methoxyphenyl) azo phenyl]-2- thiol-1,3,4-Oxadiazole [4].Treatment of compound [4] with ethyl 1- chloroacetate in alcoholic potassium hydroxide resulted in the formation of 2-thioester derivative [5] which was then converted to acid hydaizide derivative [6] by the reaction with hydrazine hydrate in ethanol .The reaction of hydrazide with carbon disulfide in alcoholic potassium hydroxide afforded 2 - [5 - (4 -(***P*** - methoxyphenyl) azophenyl) -1,3,4 – oxadizol- 2 -yl methylthio] - 1,3,4 - oxadiazole -5- thiol [7] . the latter was treated with propargyl bromide in basic media to give (5- propynyl)thio derivative [8] which was then treated with formaldehyde and piperidine to give5-(4-piperidino)butynylthio derivative[9]. Compound [7] was also treated with n-butyl chloride in basic media to give 5 - thioalkyl derivative [10] which was then oxidized with potassium permanganate in acidic media to give 5-sulfonylalkyl derivative [11]. The structures of the sythesised compounds were confirmed by melting points ,FT-IR spectra as well as elemental microanalysis.

الخلاصة :

تم في هذا البحث تحضير مشتقات 4,3,1 – اوكسادايازول جديدة حاوية على مجموعة ازومن 5 - [4 -(بارا - ميثوكسي فنيل) ازو فنيل] - 2 – ثايول - 1 , 3 , 4 – اوكسادايازول [4]. ان معاملة المركب [4] مع 1 - كلورو اسيتات الاثيل في محلول كحولي لهيدروكسيد البوتاسيوم اعطت مشتق 2 - ثايو استر [5] والذي تم تحويله لاحقا الى مشتق الهيدرازايد [6] عن طريق التفاعل مع الهايدرازين المائي في الايثانول . ان مفاعلة مشتق الهيدرازايد مع ثنائي كبريتيد الكاربون في محلول هيدروكسيد البوتاسيوم الكحولي اعطت 2- [5 - (4 - (بارا ميثوكسي فنيل) ازو - 4,3, 1 - اوكسا دايازول - 2 - يل مثيل ثايو] -1 , 3 ,4 - اوكسا دايازول - 5 - ثايول [7] . تمت مفاعلة المركب [7] مع بروميد البروبارجيل في وسط قاعدي فتم الحصول على مشتق (5 - بروباينيل) ثايو [8] والذي تمت معاملته لاحقا مع الفورماليهايد والبايبريدين بوجود كلوريد النحاسوز فتم الحصول على مشتق 5 - (4 -بايبريدينو) بيوتاينيل ثايو [9] . كذلك تمت معاملة المشتق [7] مع كلوريد البيوتيل في وسط قاعدي فتم الحصول على مشتق 5 - ثايو الكيل [10] والذي تمت اكسدتة لاحقا بوساطة برمنكنات البوتاسيوم في وسط حامضي فتم الحصول على مشتق 5 - سلفونيل الكيل [11] . شخصت تراكيب المركبات المحضرة الجديدة بوساطة درجات الانصهار غير المصححه واطياف الاشعة تحت الحمراء والتحليل الدقيق للعناصر.

Introduction

1,3,4 - Oxadiazole derivatives may be achieved by the reaction of hydrazides with carbon disulfide and potassium hydroxide [1,2,3],phosgene [4]or phosphorous oxychloride[5,6].Many methods for preparing azo compounds were reported in the literature [7,8,9], such as coupling with diazonium salt which was considered the most common one.1,3,4-Oxadiazole derivatives have certain biological activities and medical applications,such as parasitic helminths[10,11],active against tuberculosis [12,13], antimicrobia l[14,15], anti inflammatory [16] ,anticonvulsant[17] and antimalarial [18].

The biological activity of azo compounds were widely known . some azo compounds are medically used as antibacterial , antiseptic ,antimelaria [19]and for treatment of Ulcerative colitis [20].

We reported here the synthesis of some new 1,3,4-oxadiazole derivatives containing azo group which might have some biological activities.

Experimental

All solvents used were redistilled. Thin layer chromatography were performed on asilica-gel SG - 40 (Merck). Spots were visualized with iodine vapour. The melting points were determined with Stuart Melting Point Apparatus. The FT-IR spectra were recorded on FT - IR - 8400S, Schimadzu-Spectrophotometer using KBr discs. Elemental analysis measured on EA-1108 Carlo-Erba elemental analyzer.

General Procedure for Preparation of Compounds.

1) 4 - (***p***-Hydroxy phenyl)azobenzoic acid [1] [(21)]

To amixture of 4-amino benzoic acid (2g ,0.0146 mole) and distilled water (10m**L**) contained in a small beaker , concentrated hydrochloric acid (4m**L**) was added with cooling and the mixture was cold at (0ºC) in an ice bath . a solution of sodium nitrite (1.3g ,0.0188 mole) in (10m**L**) of distilled water was added dropwise to the mixture with stirring , the temperature of the ice bath was controlled between (0-5ºC) . a solution of (1.372g ,0.0146 mole) of phenol in (15m**L**) of (10%) sodium hydroxide solution in (150m**L)** beaker was prepared and cold to (5ºC) by immersion in an ice bath. The phenol solution was stirred vigorously , then the cold diazonium salt solution was added very slowly to the phenol solution , a red colour developed and red crystals soon separate .when all the diazonium salt solution was added , the mixture was allowed to stand in an ice bath for 30 min. with occasional stirring. The solution was filtered , washed well with distilled water and recrystallized from ethanol and dried upon filter paper , yield 95% , m.p =264 - 266 ºC , reported 264-266ºC [(22)].

2) Methyl 4 - (***p***- methoxy phenyl)azobenzoate [2]

(2g ,0.0082 mole) of 4 - (***p*** - Hydroxyphenyl) azo benzoic acid was dissolved in (25m**L**) of dry acetone , then (0.876g ,0.0082 mole) of anhydrous sodium carbonate was added and the mixture was left with stirring at room temperature for 20 min.,then (1.041g ,0.0082 mole) of dimethyl sulphate was added and the mixture was refluxed with stirring at 50ºC for 24hr . The solvent was removed by evaporation and the prouduct was extracted from the mixture by addition of asaturated bicarbonate solution with distilled water (60m**L**) and ethyl acetate (4x25m**L**).The organic layer was dried with anhydrous magnisum sulphate and removed by evaporation , recrystallized from ethanol , Yield 88% , m.p= 147-149ºC,lit.m.p.=148-150ºC.[(23)]

3)4 - (***p***- methoxy phenyl)azobenzoic hydrazide [3]

A mixture of Methyl 4-(***p***- methoxy phenyl) azobenzoate [2](2g , 0.0074 mole) and hydrazine hydrate (0.370g ,0.0074 mole) in absolute ethanol (25m**L**) was refluexed at 70ºC for 6 hr . The hydrazide was precipitated on cooling , filtered off and recrystallized from ethanol , yield 80%,m.p =195-196ºC,lit.m.p.=194-196ºC.[(23)]

4) 5-[4-(***p***- methoxy phenyl)azo phenyl]- 2- thiol - 1,3,4,- oxadiazole[4]

To a solution of hydrazide derivative [3] (2g ,0.0074 mole) in absolute ethanol (25m**L**) at 0ºC , Potassium hydroxide (0. 415g ,0.0074 mole) and carbon disulfide (0.563 g ,0.0074 mole) were added respectively . The mixture was heated under reflux for 7hr . The solvent was removed by evaporation , the residue dissolved in (20m**L**) of cold distilled water and acidified with conc. hydrochloric acid (36%) .The precipitate was filtered and recrystallized from ethanol ,yield80%,m.p=230-232ºC,lit.m.p.=229-231ºC.[(23)]

5)5-[4-(***p***-methoxyphenyl)azo phenyl]- 2-thioethylacetate-1,3,4,- oxadiazole [5]

Ethyl chloro acetate (0.785g ,0.0064 mole) was added dropwise to astirred solution of compound [4] (2g ,0.0064 mole) and Potassium hydroxide (0.359 g ,0.0064 mole) in(25m**L)** absolute ethanol . The reaction mixture was refluxed at 60ºC for 8hr , after that the mixture was filtered and the filtrate poured on crushed ice . The resulting product was recrystallized from methanol , yield 80% , m.p =161 - 163 ºC .

6) 5-[4-(***p***- methoxy phenyl)azo phenyl]- 2- thio acetic hydrazid - 1,3,4,- oxadiazole [6]
A mixture of compound [5] (2g ,0.005 mole) and hydrazine hydrate(0.251 g ,0.005 mole) in absolute ethanol (25 m**L**) was refluxed at 70ºC for 6hr . The hydrazide was precipitated on cooling , filtered off and recrystallized from ethanol ,yield 75%, m.p=243-245ºC.

7)5-{5-[4-(4-Methoxyphenylazo)-phenyl]-[1,3,4]oxadiazol-2-ylsulfanylmethyl}-
[1,3,4]oxadiazole-2-thiol [7]
To a solution of hydrazide deravitive [6] (2g ,0.0052 mole) in absolute ethanol (25m**L)** at 0 ºC , Potassium hydroxide (0.291 g ,0.0052 mole) and carbon disulfide (0.396 g ,0.0052 mole) were added respectively . The mixture was heated under reflux for 8hr. The solvent was removed by evaporation, the residue dissolved in(20m**L**) of cold water and acidified with conc. hydrochloric acid (36%) . The precipitate was filtered and recrystallized from ethanol , yield 74%, m.p = 149 - 151ºC.

8)(4-Methoxyphenyl)-{4-[5-(5-prop-2-ynylsulfanyl-[1,3,4]oxadiazol-2-
ylmethylsulfanyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-diazene [8]
To a solution of compound [7] (1g ,0.0023mole) in (25 m**L**) of dry acetone ,(0.2488 g ,0.0023 mole) of anhydrous sodium carbonate was added . The mixture was refluxed with stirring at 50ºC for 2hr , then propargyl bromide (0.28g ,0.0023mole) , dissolved in (10m**L**) of dry acetone , was added dropwise to the mixture ,after end of addition the reaction mixture was held at reflux for 72hr . (T.L.C) showed that the reaction was completed . the solvent was evaporated and the product was extracted with ethyl acetate (3x25m**L**) and distilled water (30 m**L**) . the organic layer was dried with anhydrous magnesium sulphate , then the solvent was removed by evaporation , recrystallized from ethanol , yield 85% ,m.p = 136 -138 ºC .
9)(4-Methoxyphenyl)-(4-{5-[5-(4-piperidin-1-yl-but-2-ynylsulfanyl)-
[1,3,4]oxadiazol-2-ylmethylsulfany l]-[1,3,4]oxadiazol-2-yl}-phenyl)- diazene [9]
To a mixture of acetylenic derivative [8] (0.5 g ,0.001 mole) , para formaldehyde (0.032 g ,0.001 mole) and copperous chloride (0.2g) as catalyst in dry dioxane (25m**L**), piperidine (0.0916 g ,0.001mole) was added . The reaction mixture was refluxed with stirring at 80ºC for 2hr , then the mixture was cold and filtered for removal copperous chloride , then the filterate was poured to an ice - cold water and left at room temperature for 24 hr for completing the crystallization of precipitate . The precipitate was filtered, recrystallized from ethanol, yield 65%, m.p = 123-125ºC.
10)(4-Methoxyphenyl)-{4-[5-(5-Butylsulfanyl-[1,3,4]oxadiazol-2-
ylmethylsulfanyl)-[1,3,4]oxadiazol-2-y l]-phenyl}-diazene [10]
To a solution of compound [7] (1g ,0.0023mole) in dry dioxan (20m**L**) , potassium hydroxide (0.131 g ,0.0023mole), dissolved in avery small amount of distilled water , was added . The reaction mixture was refluxed for 20min , then (0.217 g ,0.0023 mole) of n-butyl chloride was added and the mixture was refluxed at 80ºC for 2hr. (T.L.C) showed that the reaction was completed . The solvent was removed by evaporation and the product was extructed with ethyl acetate(3x25m**L)** and distilled water (30m**L).** The organic layer was dried with anhydrous magnesium sulphate and removed by evaporation,recrystallized from methanol , yield 85% ,m.p = 116-118ºC.
11)(4-Methoxyphenyl)-(4-{5-[5-(butane-1-sulfonyl)-[1,3,4]oxadiazol- 2-
ylmethylsulfanyl]-[1,3,4]oxadiazol-2-yl}-phenyl)-diazene [11]
(0.5 g ,0.001mole) of compound [10] was dissolved in acetic acid (7m**L**) at 0 ºC , then (0.164 g ,0.001 mole) of potassium permanganate , dissolved in alittle amount of distilled water , was added dropwise . The mixture was left with stirring for 24hr at room temperature , then hydrogen peroxide (30%) was added dropwise until disappearance of colour of permangante . The product was extructed with ethyl acetate(2x25m**L**)anddistilled water (30m**L**) containing sodium bicarbonate for neutralizing acetic acid . The organic layer was dried with anhydrous magnesium sulphate and the solvent was evaporated , recrystallized from methanol, yield70%,m.p=167-169ºC.

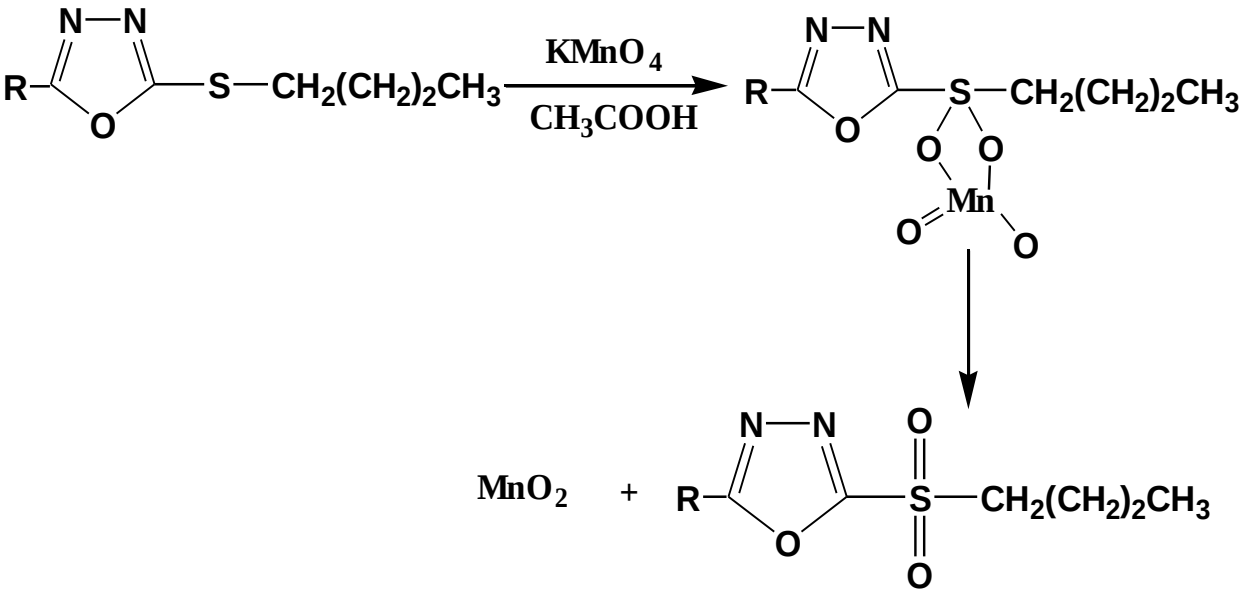
Table (1): Melting points , percent yields and C.H.N analysis of the prepared compound (1-11)

Comp. No.	M.P C°.	Yield%	M.F	M.WT g\mole	C.H.N analysis					
					Calculated%			Found%		
[1]	264-266	95	$C_{13}H_{10}N_2O_3$	242	C	H	N	C	H	N
					-	-	-	-	-	-
[2]	147-149	88	$C_{15}H_{14}N_2O_3$	270	-	-	-	-	-	-
[3]	195-196	80	$C_{14}H_{14}N_4O_2$	270	-	-	-	-	-	-
[4]	230-232	80	$C_{15}H_{12}N_4O_2S$	312	57.69	3.84	17.94	57.43	3.89	17.83
[5]	161-163	80	$C_{19}H_{18}N_4O_4S$	398	57.28	4.52	14.07	57.09	4.65	13.91
[6]	243-245	75	$C_{17}H_{16}N_6O_3S$	384	53.12	4.16	21.87	52.69	4.27	21.78
[7]	149-151	74	$C_{18}H_{14}N_6O_3S_2$	426	50.70	3.28	16.90	50.31	3.39	16. 82
[8]	136-138	85	$C_{21}H_{16}N_6O_3S_2$	464	54.31	3.44	18.10	54.43	3.51	18.02
[9]	123-125	65	$C_{27}H_{27}N_7O_3S_2$	561	57.75	4.81	17.46	57.36	4.93	17. 29
[10]	-118 116	85	$C_{22}H_{22}N_6O_3S_2$	482	54.77	4.56	17.42	54.47	4.65	17. 33
[11]	167-169	70	$C_{22}H_{22}N_6O_5S_2$	514	51.36	4.28	16.34	51.08	4. 38	16.26

Result and Discussion

In the present work , new 1,3,4 – oxadiazole derivatives containing azo group were synthesised from 5 - [4 - (***p*** - methoxy phenyl) azo phenyl] - 2 - thiol - 1,3,4 -oxadiazole [4] . 4 - (***p*** - hydroxy phenyl)azobenzoic acid [1] was prepared via a coupling reaction between phenol and diazonium salt of 4-aminobenzoic acid which was characterized with melting point 264 - 266 ºC as it was found in literature [22] . 4- (***p***-hydroxy phenyl)azo benzoic acid [1] was converted to the corresponding ester [2] by its reaction wth dimethyl sulphate , FT-IR spectra showed absorption at υ cm^{-1} 1720 (C=O, ester) , 1240 (C-O ,ester) and 1030 (O-CH_3 , ether) . The ester derivative was converted into hydrazide derivative [3] by the reaction with hydrazine hydrate .Compound [3] was characterized by FT-IR spectra which showed absorption at υ cm^{-1} 3310 (NH_2 , asym.) , 3190(NH_2,sym.) and 1650 (C=O , amide) . The hydrazide derivative [3] was converted to 1,3,4 - oxadiazole derivative [4] by the reaction with carbon disulfide in potassium hydroxide solution .The structure of 1,3,4-oxadiazole derivative was confirmed by C.H.N microanalysis and FT-IR spectra which showed disaappearance of υ (C=O) at 1650 cm^{-1} and appearance absorption bands at υcm^{-1} 1603 (C=N) , 1100 (C=S) and 3200 (N-H) . 2- thioester derivative [5] was obtained upon treatment of compound [4] with ethyl chloroacetate in alcoholic potassium hydroxide solution . FT - IR spectrum of compound [5] showed disappearance of (C=S) streching vibration at 1100 cm^{-1} and showed streching band at 1710 cm^{-1} for (C=O) group of ester . The ethoxy group of ester derivative [5] was displaced by the reaction with hydrazine hydrate in absolute ethanol and hydrazide derivative [6] was formed . Compound [6] was characterized with C.H.N microanalysis and FT- IR spectrum which was showed absorptions at υcm^{-1} 3330 (NH_2 ,asym.),3210(NH_2,

sym)and 1650 (C=O,amide) , FT -IR also showed disappearance of streching. Vibr. of (C=O ,ester) at 1710 cm^{-1} .The hydrazide derivative [6] was converted to 1,3,4- oxadiazole derivative [7] by the reaction with carbon disulfide in potassim hydroxide solution. FT-IR spectrum of compound [7] showed υ cm^{-1} 1635 (C=N) , 1135 (C=S) and 3270 (N-H) , FT - IR spectrum was also showed disappearance of υ (C=O , amide) at 1650 cm^{-1} and υ (NH_2 ,asym.) at 3300 cm^{-1} . Acetylenic derivative [8] was prepared from the reaction of 1,3,4 - oxadiazole derivative [7] with propargyl bromide in sodium carbonate solution . FT - IR spectrum of compound [8] showed disappearance of strech. vibr. absorption band of thionyl group (C=S) at 1135 cm^{-1} and appeared the strech.vibr.absorption bands of (=C-H) group at 3280 cm^{-1} and (C = C) at 2220 cm^{-1} . 2-(4-piperidino) butynyl thion derivative [9] have been synthesized by Mannich reaction through treatment of acetylenic derivative [8] with formaldehyde and piperidine in dry dioxan . Compound [9] was characterized by C.H.N microanalysis and FT - IR spectra which was showed diappearance of strech .vibr.band of (=C-H) group at 3280 cm^{-1} . Thiol group of compound [7] was also introduced in S_N2 reaction[23] with n-butyl chloride in dioxan and 2- thioalkyl derivative [10] was formed and identified by FT -IR which was showed disappearance of υ (C=S) at 1135cm^{-1} and υ (N-H) at 3270cm^{-1}.Reaction of compound [10] with aqueous permanganate solution in acetic acid at 0ºC introduced 2- sulfonylalkyl derivative as oxidation product . The latter reaction mechanism involved the formation of cyclic manganese ester in the first step , then the ester will be dissociated in the second step to give sulfone derivative :



Sulfone derivative [11] was characterized by C.H.N microanalysis and FT-IR spectrum which was showed absorbtions at υcm^{-1}1340 (O=S=O ,asym.) and 1125(O=S=O,sym)[24]

The synthesised compounds demonstrate C.H.N microanalysis ,melting points and FT -IR data as in tables (1-2) .