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Synthesis of Schiff bases of 2-thio-5-aryl-1,3,4-oxadiazole derivatives of possible biological activity

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Abstract:

In this study, new derivatives of Schiff bases of 2-thio-5-aryl-1,3,4-oxadiazole have been synthesized. The structures of these derivatives were characterized from their melting points, infrared spectroscopy and elemental analysis.
The Schiff bases derivatives were tested for inhibition of E-coli and were all found to be active.

Introduction:

1,3,4- oxadiazole derivatives are widely used in organic chemistry as intermediate compounds for the synthesis of various heterocyclic compounds. Despite the fact that some 1, 3, 4-oxadiazole derivatives have been found to possess remarkable biological activities [1-5]. 2,5-Disubstituted-1,3,4-oxadizoles have been found to exhibit diverse biological activities such as antibacterial [6], anti – HIV[6], antifungal [7], virucidal [8] and insecticidal [9]. Nagalakshmi[10] has synthesized different derivatives of 2,5-disubstitued–1,3,4-oxadiazoles with antimicrobial and antiflammatory activity [Figure 1].

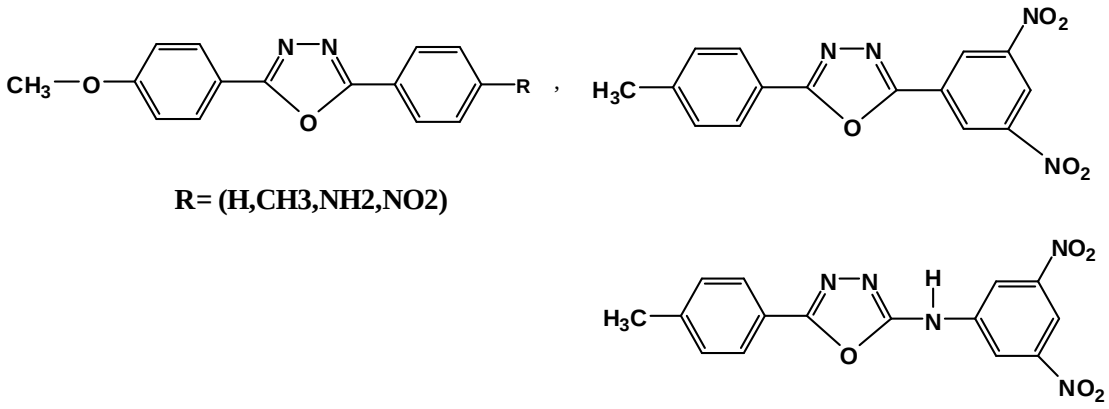


Figure 1

Eman [11] has synthesized different derivatives of 1,3,4-oxadiazole of possible biological activity
[Figure 2]

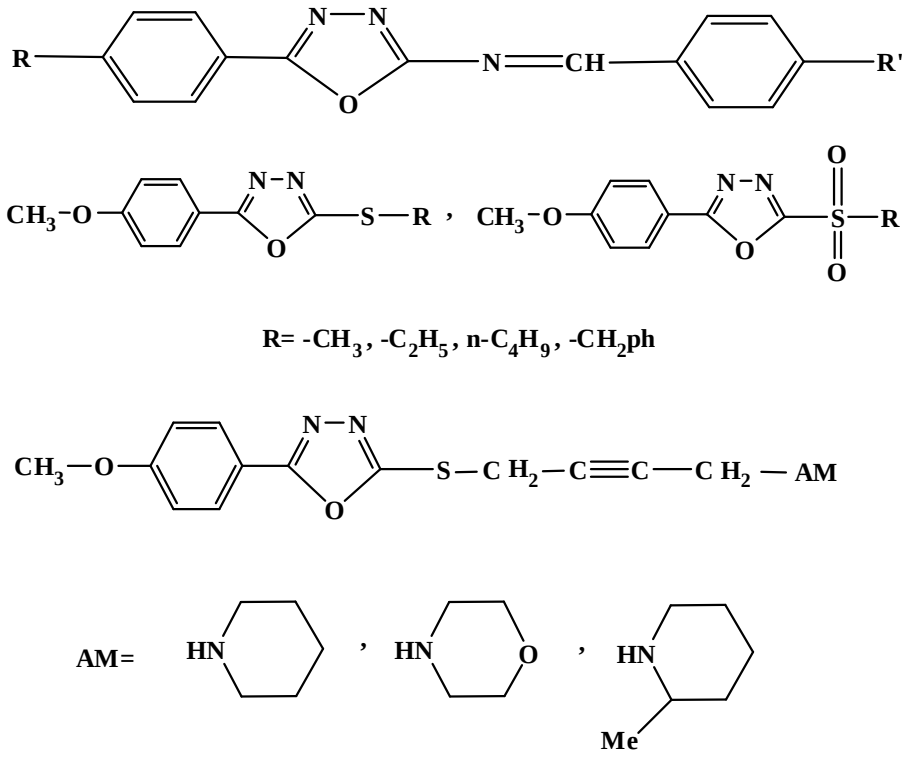
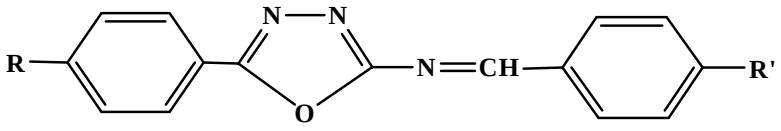


Figure 2

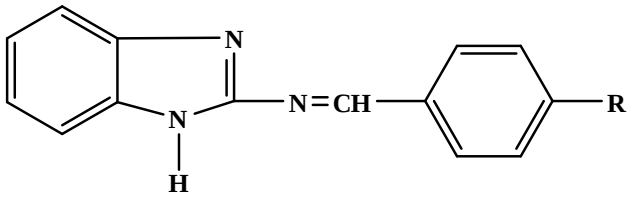
Biocidal activities of Schiff bases have also been well established. These have been attributed to the toxophoric C=N linkage in them [12]. Mishra etal [13] have been synthesized Schiff bases of 2-amino-5-aryl-1,3,4-oxadiazoles with different aromatic aldehydes [Figure 3]

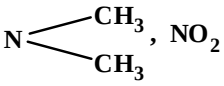


a: R= OCH_3 , R' = OCH_3
b: R = OCH_3 , R' = NO_2
c: R = NO_2 , R' = OCH_3
d:R = NO_2 , R = NO_2
e:R = Cl , R' = OCH_3
f:R = CH_3 , R = OH

[Figure 3]

Ibtisam etal [14] have prepared some Schiff bases compounds from 2-aminobenzimidazole with different substituted benzaldehydes in para position [Figure 4]. These derivatives were tested for inhibition of E-coli and staphylococcus and were all found to be active.



R = H,Cl,Br,F,OMe,  **, NO_2**

In this work we decided to synthesize new derivatives of Schiff bases of 2,5-disubstituted-1,3,4,-oxadiazole for their possible biological activity.

Experimental:

Materials:

All chemical used were supplied from Merk chemicals Fluka AG, BDH chemicals, Riedel De Haen AG,Acros Organics, Janssen Chemical and Hopkin and Wiliams. Infrared

spectra were recorded using Shimadzu-408 (KBr disc), elemental analyzer were carried out by using Carlo Erba/Mod 1106 and melting points were recorded using Electrothermal melting point apparatus. The biomaterials were obtained from Biomerieux Ltd.

Synthesis of 5-(4-Methoxyphenyl) – 1,3,4- oxadiazole – 2-thiol. (1)

Compound 1 was used as starting material, this derivative was prepared from the reaction of p-anisichydrazide with carbon disulphide according to the reference [11].

Synthesis of 5-(p-Methoxyphenyl) – 1,3,4-oxadiazole – 2 – thioacetic acid. (2)

Compound 1 (5 g, 24.03 mmol) and sodium hydroxide (0.96 g, 24.03 mmol) were dissolved in ethanol (30 ml) and refluxed for (1hr). A solution of chloroacetic acid (2.27 g,24.03 mmol) in (10 ml) ethanol was added, and the mixture was further refluxed for (24 hrs). The mixture was cooled to room temperature, then the white precipitate was formed filtered and recrystallized from ethanol [15].

Synthesis of 5-(p-Methoxyphenyl) – 1,3,4-oxadiazole – 2 – methyl thioacetate. (3)

Compound 2 (3 g, 11.27 mmol) was dissolved in acetone (75 ml) and anhydrous sodium carbonate (1.19 g, 11.27 mmol) was added. The mixture was refluxed for (1 hr). Dimethyl sulphate (3 ml) was added to the reaction mixture and the mixture was further refluxed for (24 hrs). The acetone was removed under reduced pressure and the residue diluted with water and extracted with ethyl acetate (2×30 ml).Combined organic layer dried over magnesium sulphate and the solvent

removed to give 3 as solid. This derivative was recrystallized from water and ethanol [16].

Synthesis of 5-(p-Methoxyphenyl) – 1,3,4-oxadiazole – 2 – thioacetic hydrazide. (4)

Compound 3 (5 g, 17.85 mmol) and hydrazine hydrate (20 ml) were dissolved in ethanol (30 ml). The mixture was refluxed for (24 hrs). the precipitate which separated on cooling was filtered and recrystallized from ethanol [17].

Synthesis of 5-[p-Methoxyphenyl]-2-[/2-(p-substituted benzylidine)] thioacetic hydrazide – 1,3,4-oxadiazole. (5-9)

General procedure:

A hot ethanolic solution of compound 4 (5 g, 17.85 mmol) was mixed with a solution of the selected aldehyde (17.85 mmol) in (25 ml) ethanol. The resulting mixture was then refluxed for (2 hrs). the product was filtered and recrystallized from ethanol[14].

Preliminary biological activity test :

Antimicrobial susceptibility test measure the ability of an antimicrobial agent to inhibit or kill bacterial growth in vitro. This ability may estimate by either the dilution method or diffusion method .In this study the broth dilution method was followed [18].
The minimum concentration of agent ,which inhibits growth ,is considered (M I C) [19].

Results and Discussion:

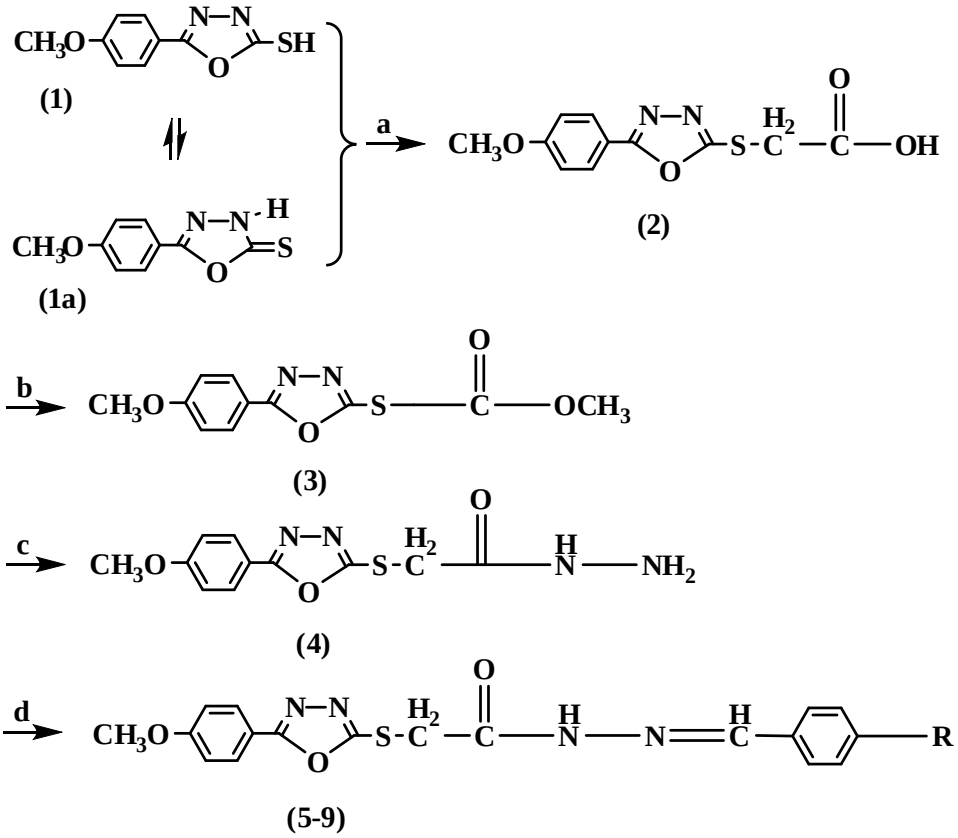
Compound 1 has been chosen as a starting material for synthesis of new derivative of 2-thio-5-aryl-1,3,4-oxadiazole. The strategy used for the synthesis of 2,3 and 4 was started with

derivative 1 in a series of reaction [Scheme 1]. The Schiff bases compounds (5-9) were synthesized from the reaction of derivative 4 with different substituted benzaldehydes in para position. Compound 2 was synthesized by the reaction of compound 1 with chloroacetic acid in basic medium. This reaction included nucleophillc attach by $\mathbf{S_N2}$ reaction [Scheme 2]. The IR spectrum of 2 showed the disappearance of stretching bands at 3220 cm^{-1} and 1085 cm^{-1} for (NH) and thion groups respectively with appearance of stretching bands at 2800 cm^{-1} and 1665 cm^{-1} for (OH) and (CO) groups respectively. Tables (1) and (2) showed the characteristic IR absorption bands and physical properties for all new derivatives. Treatment of compound 2 with dimethylsulphate in acetone under reflux gave 3. The IR spectrum of 3 showed the disapperance of stretching band of (OH) group with apperance of (CO) group at 1715 cm^{-1} which is displacement to high frequency. The hydrazide derivative 4 was prepared by using the Gatterman method [17]. The IR spectrum of 4 showed the displacement of (CO) group to low frequency at 1680 cm-1 with apperance of stretching band at 3350 cm^{-1} for (NH2) group. The Schiff bases compounds (5-9) were synthesized from the reaction of compound 4 with different substituted benzaldehydes in para position. The IR absorption bands of these derivatives showed the disappearance of stretching bands due to NH2 of hydrazide and (CO) group of different substituted benzaldehydes with appearance of stretching band in the range (1620 – 1650) cm^{-1} attribute to the imine (C=N) group. Compounds (5-9) were exhibited a biological activity against E-coli bacteria.

In table (3) is tabled results obtained on using the following compounds as anti microbial agents. The compounds (5-9) were found to be effective. The minimum inhibitory concentration was determined for each antibacterial agent and was found to be as follows :

compound 5 (0.3 gm \ ml), compound 6 (0.6 gm\ ml), compound 7 (0.4 gm\ ml), compound 8 (0.09 gm\ ml) and compound 9 (0.1 gm\ ml). This means that compound 8 is most potent among the tested agents.

[Scheme 1]



a: $ClCH_2COOH$, NaOH, C_2H_5OH

b: Na_2CO_3, $(CH_3)_2SO_4$, Acetone

c: NH_2-NH_2, C_2H_5OH

d: R—C$_6$H$_4$—CHO + C_2H_5OH

Where R =	H	OMe	Me	$N(CH_3)_2$	NO_2
Compound No	5	6	7	8	9

[Scheme 2]

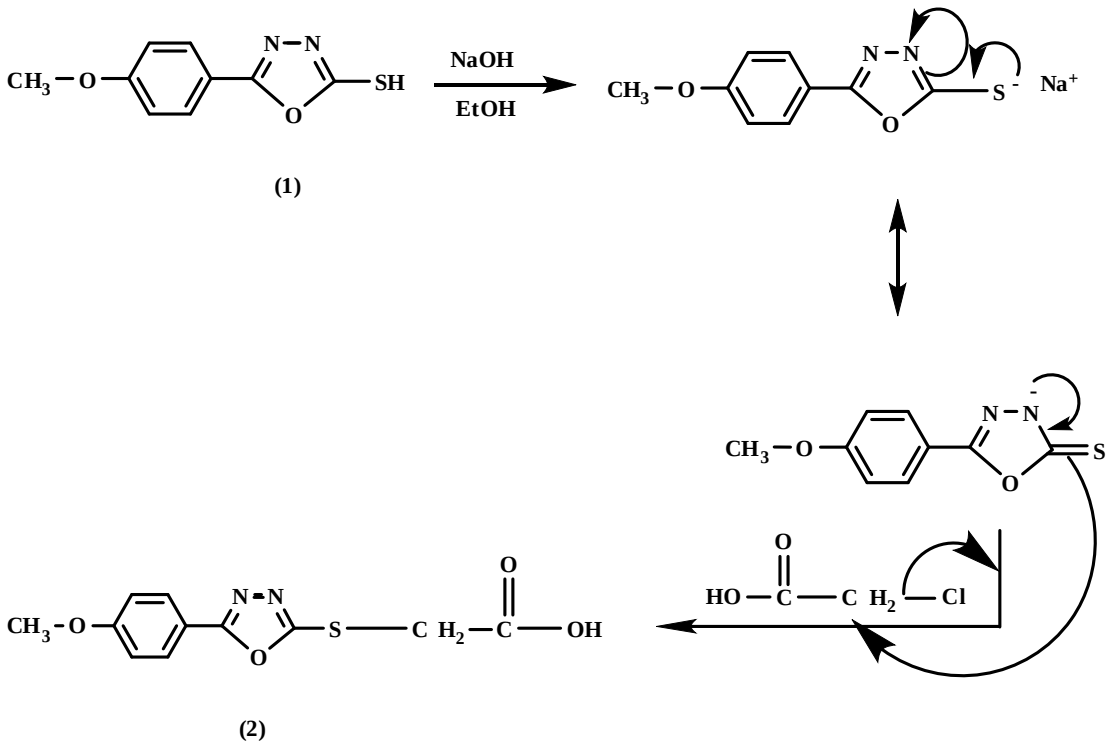


Table (1): Characteristic IR absorption bands of the new derivatives

Compound No.	Infrared data (υmax cm-1) (KBr disc)
2	(OH) 2800; (CO) 1685; (C=C) 1595 aromatic; (C=N) 1610; (C=C) bending 835.
3	(CO) 1715; (C=C) aromatic 1590; (C=N) 1610; (C=C) bending 810
4	(NH2) 3350; (CO) 1670; (C=C) aromatic 1595; (C=N) 1615; (C=C) bending 820
5	(NH) 3270-3300; (CO) 1680; (C=C) 1610 aromatic; (C=N) 1620; (C=C) bending 820
6	(NH) 3260-3300; (CO) 1685; (C=C) aromatic 1600; (C=N) 1640; (C=C) bending 835
7	(NH) 3280-3310; (CO) 1680; (C=C) 1590; (C=N) 1650; (C=C) bending 815
8	(NH) 3260-3300; (CO) 1685; (C=C) 1600; (C=N) 1645; (C=C) bending 820
9	(NH) 3260-3290; (CO) 1675; (C=C) 1595; (C=N) 1625; (C=C) bending 835

Table (2): physical properties for derivatives

Compound No.	Formula	Melting Point C°	Elemental analysis calculated (found)			Yield %
			C %	H %	N %	
2	$C_{11}H_{10}N_2O_4S$	206	49.62 (49.36)	3.75 (3.45)	10.52 (10.27)	80
3	$C_{12}H_{12}N_2O_4S$	101	63.15 (63.00)	5.26 (4.98)	12.28 (12.12)	75
4	$C_{11}H_{12}N_4O_3S$	199	47.14 (47.36)	4.28 (3.99)	20 (19.82)	82
5	$C_{18}H_{16}N_4O_3S$	135	58.69 (58.33)	4.34 (4.44)	15.21 (15.04)	60
6	$C_{19}H_{18}N_4O_4S$	186	57.28 (57.51)	4.52 (4.38)	14.07 (13.88)	70
7	$C_{19}H_{18}N_4O_3S$	200	59.68 (59.75)	4.71 (4.56)	14.65 (14.33)	85
8	$C_{20}H_{21}N_5O_3S$	89	58.39 (58.11)	5.10 (5.29)	17.03 (16.89)	50
9	$C_{18}H_{15}N_5O_5S$	240	52.30 (52.43)	3.63 (3.59)	16.94 (16.77)	65

Table (3): Effect of Antimicrobial Agents on Escherichia Coli.

No. of Compound	Effect of Schiff Bases Derivatives on the Growth of E-coli Bacteria											
	1	0.9	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1	0.09	Concentration gm/ml
5	-	-	-	-	-	-	-	+				
6	-	-	-	-	-	-	-	-	+			
7	-	-	-	-	-	-	+					
8	-	-	-	-	-	-	-	-	-	-	+	
9	-	-	-	-	-	-	-	-	-	+		
Blank	+											

(-) No growth
(+) Growth

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تحضير مشتقات جديدة من قواعد شف لـ 2- ثايو- 5 – اريل – 1،3،4 – اوكساديازول ذات فعّالية بايولوجية محتملة.

م.م.ايمان محمد حسين ،م.م. ضفاف فلاح حسن ،م.م. وسن سعدي حسين

قسم الكيمياء – كلية التربية – ابن الهيثم – جامعة بغداد

الخلاصة

تم في هذا البحث تحضير مشتقات جديدة من قواعد شف لـ 2- ثايو- 5 – اريل – 1،3،4 – اوكساديازول. حيث تم اختيار المشتق رقم 1 كمادة ابتدائية لتحضير قواعد شف بعد مروره بسلسلة من التفاعلات وصولا الى المشتق 4. تم مفاعلة المشتق 1 مع حامض كلوريد الخليك في وسط قاعدي لتحضير المشتق 2. عومل المشتق 2 مع كبريتات ثنائي المثيل حيث اعطى المشتق 3. ان تفاعل المشتق 3 مع الهيدرازين بوجود الكحول كمذيب اعطى مشتق الهيدرازيد 4. تم مفاعلة المشتق 4 مع عدة انواع من الالديهيدات المختارة ليتم الحصول على مشتقات جديدة قواعد شف من (5-9). تمت دراسة الفعّالية البايولوجية للمشتقات من 5-9 ضد بكتريا القولون وقد وجد بأن لها فعّالية بايولوجية واكثرها فاعلية كان المشتق 8.

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