Compounds related to thiosemicarbazide Oxadiazoles and thiadiazoles synthesis and spectroscopic studies

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Abstract:

Several substituted cinnamoyl thiosemicarbazide and substituted alpha-phenyl cinnamoyl thiosemicarbazide are cyclized by the action of sodium hypobromide to give 2-amino (-5-sub. styryl)-1, 3, 4-oxadiazole. Some of the prepared thiosemicarbazide derivatives were converted to the corresponding. 2-amino-5-sub. styryl-1, 3, 4-thiadiazole by boiling with polyphosphoric acid. Styryl and p-methoxy styryl-1, 3, 4-oxadiazole -2- thiol have been prepared by the reaction of corresponding hydrazide with carbon disulfide in the presence of ethanolic potassium hydroxide. These compounds were characterized by IR. 'H-NMR and elemental analysis.

Introduction:

The heterocyclic compounds; triazole , oxadiazole and thiadiazole were prepared from substituted thiosemicarbazide by cyclisation reaction using different reagents. These compounds were considered as important compounds because of their biological activities. These classes of compounds have shown antibacterial [10]. antifungil [ll], and antitubercular properties [12,9].

Antibacterial activity of cinnamoyl thiosemicarbazides and corresponding triazole-2-thiol were studied [8].

cinchoninoyl and substituted cinchoninoyl thiosemicarbazides are known to possess antimicrobial activity [5]. Several bis (5-substituted -l, 3, 4-oxadiazole) sulfides and sulphones have been prepared and tested against two species of fungi [6] The another importance of these compounds their use as a good ligand for coordination with metals. A large group of coordination compounds were prepared from triazoles [3], oxadiazole [1], thiadiazoles [2] and transition metal ions .In this paper substituted cinnamoyl and alpha-phenyl cinnamoyl thiosemicarbazide were synthesised and cyclised to the corresponding, oxadiazole and thiadiazoles and characterized by IR, H-NMR and elemental analysis techniques.

Experimental:

All the chemicals and solvents used were of Alderich and Fluka products and were used with out further purification. Cinnamic and alpha-phenyl cinnamic acid derivatives were prepared in our laboratory by known methods [16] cinnamoyl and alpha-phenyl cinnamoyl thiosemicarbazides were prepared according to the method of Hoggarth [7], from acid chloride (0.01 mole) and thiosemicarbazide (0.01 mole) in the presence of pyridine as a base.

IR spectra were recorded on a Perkin-Elmer 375 B spectrophotometer as KBr discs. 'H-NMR spectra were determined on a Varian HA 80 MHz pulse nmr spectrometer using DMSO-d6 as solvent and TMS as internal standared. Melting points were determined on a Gallenkamp hot stage without any correction. (college of science , university of Baghdad).

Elemental analysis were performed at analytical laboratories of petroleum Exploration company, Baghdad.

Preparation of 2-Amino-5-substituted styryl-l,3,4-oxadiazole:

To a solution containing (0.01mole) of substituted cinnamoyl thiosemicarbazide in small amount 20ml dry pyridine, there was added 10ml sodium hypobromide(x) dropwise. The mixture was stirred and cooled in ice bath for 1-2 hrs. A precipitate was obtained immediately or by adding the solution to ice containing hydrochloric acid. The solid was filtered off, washed with water and dried. The resulting compounds were recrystallized form ethanol.

(x) Note:

Sodium hypobromide solution was prepared by adding bromine to 4N sodium hydroxide solution. The mixture was stirred and cooled in ice bath . The resulting solution was used directly in the subsequent synthesis.

Preparation of cinnamic acid hydrazide:

Cinnamic acid hydrazide was prepared according to literature [4,9] with few modification.

To a solution of 0.1 mole of cinnamic acid in 40 ml of dioxane. 0.1 mole of ethylchlorocarbonate was added, causing the temperature to rise to 0-5 c. The solution was stirred for 2-3 hrs, and then 0.1 mole of hydrazine hydrate was poured slowly. A white precipitate was appeared on the first addition of hydrazine. The product was filtered and recrystallized frome ethanol. Their analytical data agreed with those recorded in literature.

Preparation of 5-substituted styryl-l,3,4-oxadiazole-2-thiol:

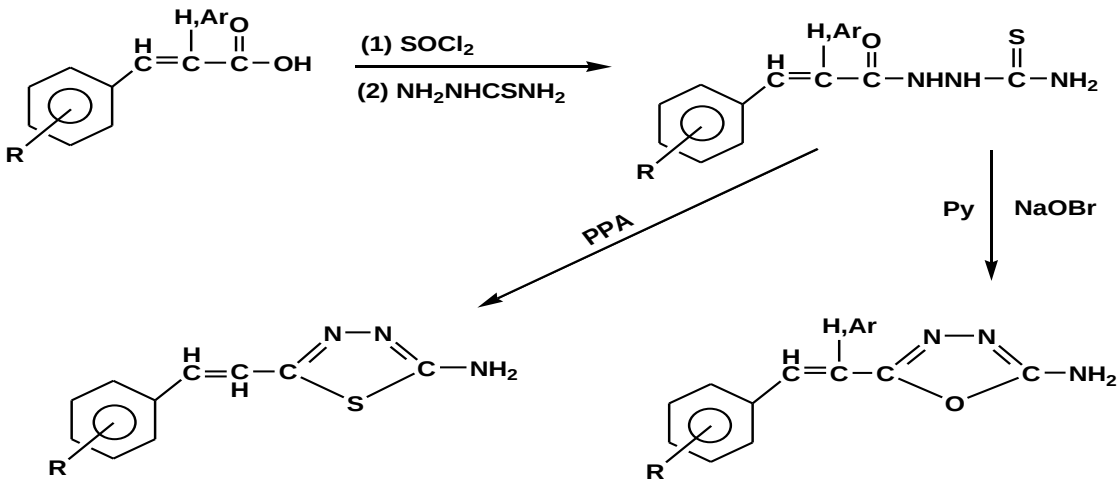
To a solution containing 60 ml of ethanol and 0.03 mole of potassium hydroxide, 0.03 mole of substituted cinnamoyl hydrazide was added. Ten ml of carbon disulfide were added and the mixture was held at reflux for 2-3 hours. After concentration of the solution to a small volume, A precipitate was obtained by adding the resultant solution to ice containing hydrochloric acid. The solid was filtered off, washed with water and recrystallized from ethanol [7].

Preparation of 2-Amino-5-substitutied styryl-l,3,4-thiadiazole:

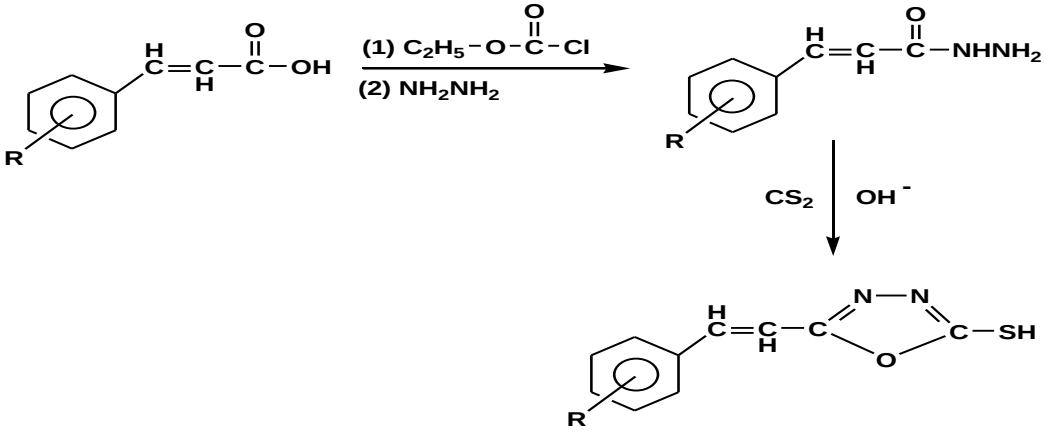
To a solution of polyphosphoric (PPA) acid 30 ml, 0.04 mole of substituted cinnamoyl thiosemicarbazide was added. The mixture was stirred and heated to (100-120 ° C) for 1-1.30 hour after which time the mixture was poured to about 200 ml of ice containing ammonia solution. The resultant solid was filtered off and was hed with cold water and recrystallized from ethanol.

Results and Discussion:

The synthesis of these compounds was carried out according to the step outlined in scheme 1 and 2.



Scheme 1



Scheme 2

R = H , P-OCH_3

The thiosemicarbazides of substituted cinnamic acid were prepared according to the method of Hoggarth [7], from the reaction of substituted cinnamoyl chloride with thiosemicarbazide in dry pyridine. Their analytical data where in agood agreement with those recorded in literature [8].

The cyclizaticn of thiosemicarbazide to corresponding 5-substituted styryl - 1, 3, 4- oxadiazole -2- amino was achieved by the action of sodium hypobromide in pyridine as a base and solvent, while the action of polyphosphoric acid to thiosemicarbazide derivatives was cyclization to corresponding 5-substituted styryl -1, 3, 4- thiadiazole -2-amino . The physical properties of these compounds are given in Tables 1 and 2.

Cinnamoyl acid hydrazide was synthesized according to method of mixed anhydridet [4], which requires the preparation of cinnamic acid ethyl chlorocarbonate anhydride and then reaction with hydrazine hydrate. The cyclization of cinnamoyl acid hydrazide to corresponding 5-substituted styryl 1, 3, 4 oxadiazole -2- thiol was achieved by refluxing the hydrazide with carbon disulfide in the presence of ethanolic sodium hydroxide.

Physical properties of these compounds are given in Table 3.

Table(1): physical properties of 5-substitutcd styryl-1,3,4-oxadiazole-2-amino

Comp. No	R	Ar	Molecular formula	M. P C°	Yield%	Crystallization solvent
1	P-chioro	H	$C_{10}H_8N_3OCl$	236-239	55	ethanol
2	P-methoxy	H	$C_{11}H_{11}N_3O_2$	254-256	65	=
3	P-methy1	H	$C_{11}H_{11}N_3O$	234-236	60	methanol
4	P-Nitro	H	$C_{10}H_8N_4O_3$	285-287	70	ethanol
5	2.3-dimethoxy	H	$C_{12}H_{13}N_3O_3$	265-266	66	ethanol
6	Hydrocinnamoy1		$C_{10}H_{11}N_3O$	194-195	77	ethanol
7	P-methoxy	C_6H_5	$C_{17}H_{15}N_3O_2$	191-193	60	ethanol
8	m-Nitro	C_6H_5	$C_{16}H_{12}N_4O_3$	173-175	70	methanol
9	P-methy1	C_6H_5 C_6H_5	$C_{17}H_{15}N_3O$	180-182	65	methanol
10	2.6dich1oro	C_6H_5	$C_{16}H_{11}N_3OCl_2$	227-229	67	ethanol
11	2.3-dimethoxy		$C_{18}H_{17}N_3O_3$	260-262	70	ethanol

Table 2: physical properties of 5-substitutcd styry1-1,3,4 thadiazole-2-amino

Comp. No	R	Molecular formula	M. P C	Yield%	Crystallization solvent
12	P-Chloro	$C_{10}H_8N_3SCl$	198-201	55	ethanol
13	2.6dichloro	$C_{10}H_7N_3SCl_2$	205-208	50	ethanol

Table 3: physical properties of 5-substitutcd styry1-1,3,4- oxadiazole-2-thiol.

Comp. No	R	Molecular formula	M. P C	Yield%	Crystallization solvent
14	H	$C_{10}H_8N_2OS$	138-140	65	ethanol
15	P-methoxy	$C_{11}H_{10}N_2O_2S$	190-192	70	methanol

Infrared Spectra:

The structure of the prepared compounds have been Identified from their ir, nmr and elemental analysis. The Characteristic ir absorption of thiosemicarbazides derivatives show the presence of four bands(band 1,2,3 and 4) which discussed in the previous work [8]. The main features of the ir spectra of 5-substituted-l,3,4-oxadiazole-2-amino are the presence of N-H stretching at (3310- 3390) cm^{-1} and N-H bending at (1530-1575) cm^{-1} . Symmetrical and asymmetrical C-O-C group stretching vibration at (1250-1290) and (1160-1185) cm^{-1} respectively [15] . The olefinic C=C and C=N appear as a strong band at (1600-1695) and (1660-1695) cm^{-1} respectively. The stretching vibration of C=C aromatic ring appear in the region near 1600 and 1500 cm^{-1} [13] .The ir spectral data for these compounds are given in Table 4 .

The infrared absorption of 5-substituted –l , 3, 4 - thiadiazole 2-amino were recorded in Table 5. In all cases υ (NH) was obtained as a tow medium bands in (3340-3350) and 3320 cm-l region,υ (C=C)olefinic and υ (C=N) in the (1640-1660) cm^{-1} region, υ (C=C) aromatic in the ~1600 and ~ 1500 cm^{-1} region, , υ = C-H trans stretching vibration in ~ 3110 cm-l region, and =C-H trans bending in 980 cm-l region. The strong band at 1680 cm^{-1} due to C=O group in the corresponding IR of thiosemicarbazide derivatives was disappeared on thiadiazole spectra.

Infrared spectra of cinnamoy1 hydrazide show bands at 3125, 1545, 1670, (1610, 1495), 3025 , 990 cm^{-1} region assignable to υ(NH), b.(N-H), υ(C=O and C=C Olfinic), υ (C=C) aromatic, υ =C-H trans stretching and =C-H bending respectively [9]. In the 5-sub. stryry1-1, 3, 4-oxadiazole-2-thiol, the band position due to (C=C)remains almost unaltered where as υ (C=N and C=C Olefinic) are observed in 1680$cm^{-1}$and υ(C=C) aromatic appeared at~1630 and 1495cm^{-1}. In addition υ as (C-O-C) at ~1280 and υ s C-O-C at ~1175cm^{-1}, υ (=C-H) trans stretching vibration at 2850 cm^{-1} and(=C-H) trans banding at 985 cm^{-1} region were observed.

These results indicate that the cyclization reaction occur between acid hydrazide and carbon disulfide in basic medium. The infrared spectral data of oxadiazole-2-thiol derivatives were recorded in Table 6.

Table(4) : Infraed spectra of 5-sub-stry 1-1, 3, 4-oxadiazole-2-amino.

Comp No.	str.N-H ben.N-H	C=C olef. C=N	C=C Ar	C-O-C	C-N	=C-H trans str.	=C-H trans ben.
1	3355w 1540m	1680 s 1680 s	1620s 1495s	1285s 1170s	860 m	3076m	980s
2	3310w 1535m	1660 s 1670 s	1600s 1500s	1260s 1175s	850 m	3095m	985s
٣	3333w 1530m	1640 s 1660 s	1575s 1485s	1265m 1170s	850 m	3070m	980s
٤	3345w -	1600 s 1685s	1620s 1520s	1280m 1185m	870 m	3040m	990s
٥	3350m 1540m	1620 s 1670 s	1600s 1505s	1260m 1170s	860 m	3050m	985s
٦	3390w 1550m	1615 s 1660 s	1590s 1510s	1295m 1160m	840 m	-	-
٧	3390w 1565m	1675 s 1675 s	1610s 1515s	1255s 1175s	860 m 860 m	3075m -	995m
٨	3330w 1575m	1685 s 1685 s	1600s 1520s	1255s 1180s	830 m	3030w	1000m
٩	3340w 1560m	1650 s 1670 s	1610s 1500s	1260s 1170s	850 m	3040w	990m
١٠	3390w 1560m	1695 s 1695 s	1620s 1500s	1280s 1185s	890 m	3075m	1000s
١١	3370m 1550m	1670 s 1680 s	1600s 1515s	1270s 1170s	880 m	3045m	980m

Table 5: Infrared spectra of 5-sub. styry 1-1, 3, 4- thiadiazole-2-amino.

Comp No.	C=C olefinic	C=N	C=C Ar	=C-H trans str.	=C-H trans bend	N-H
12	1650 s	1650 s	1600s 1490 s	3155 w	985 m	3350m 3320m
13	1640 s	1660 s	1610 s 1500 s	3110 m	980 m	3340m 3320m

Table 6: Infrared absorption of 5-sub. styryl -1, 3, 4- oxadiazole-2-thiol.

Comp No.	C=C olefinic	C=N C-N	C=C Ar	C-O-C	=C-H trans str.	=C-H trans bend
14	1680 s	1680 s 875 s	1630 s 1495 s	1280 s 1175m	3000 w	985 m
15	1660 s	1670 s 870 s	1610 s 1500 s	1270 s 1165 s	3020 w	990 m

s = strong m = medium w = weak

NMR spectra:

The nmr spectral data of the substituted cinnamoyl thiosemicarbazide are comprehensively described in the previous work [8]. The two characteristic bands, which is due to substituted amide (-CONH)and substituted thioamide(-CSNH) were disappeared in the nmr spectra of 5-substituted styryl- 1, 3, 4-oxadiazole-2-amino.

Olefinic proton appears as double-doublet, the first doublet appears at (6.80-6.40 ppm) and the second doublet in (6.72- 6.40 ppm)[13] .The coupling constant (14.10-16.5 Hz) indicates the trans configuration of these protons [14],while in the 5-alpha - phenyl styryl-l, 3, 4-oxadiazole-2-amino, the Olefinic proton appears asa single band at ~ 7-60 ppm, and a miltiplet band of alpha-pheny1 group is at. ~ 7-20 ppm.

These compounds have the main band in high field region at (3.25-3.35 ppm) due to amino group (NH_2) .The chemical shift of the aromatic protons are much effected with substitutions on the aromatic ring. Proton of (AB) system usually appears as double- doublets in all Para substituted styryl derivatives.

The chemical shift of the two protons are influenced by the resonance of inductive effects of substituent groups like nitro or methoxy. These groups cause a separation of the ($H_3$and H_5) absorption doublet from the (H_2 and H_6) absorption doublet due to their resonance and inductive effects on these protons [14]. Table 7 gives the nmr data for 5-sub- styryl-l, 3, 4-oxadiazole-2-amino .

Table (7): NMR spectral data of 5-substituted styryl -1, 3, 4 - oxadiazol-2-amino

Comp No.	NH_2	Pheny1	Olefinic group H-C=C-H	Alpha Pheny1	Jab(Hz)	NOTES
1	3.24s	7.60 m	6.89d 6.54d	-	16.50	-
2	3.24s	7.54 d 7.01 d	6.89d 6.73d	-	14.15	P.OCH_3=3.77s
3	3.24s	7.19 d 6.83 d	6.72d -	-	11.79	P. CH_3=1.94s
4	3.30s	7.90 d 8.19 d	7.66d 6.72d	-	16.50	-
5	3.33s	7.60 m -	6.80d 6.40d	-	16.40	o,m-di OCH_3= 3.70d
6	3.30s	6.78 s 7.25 s	-	-	-	CH_2CH_2- = 2.94
7	3.24s	6.95 d 6.72 d	7.66s -	7.19m	-	P-OCH_3=3.65s
8	3.24s	7.95 s 7.42 m	7.78s -	7.25m	-	-
9	3.30s	7.10 d 6.80 d	7.6 s	7.10m	-	P. CH_3= 1.90s
10	3.30s	7.31 s	7.54s	7.13m	-	-
11	3.25s	7.65 m	7.40s	7.20m		O.m. diOCH_3=3.60d

abbreviation s: singlet, d : doublet, m: multiplet, dd: double doublet

The compounds of 2-amino -(5-sub. styryl)-1, 3, 4-thiadiazole have the main band in high field region at 3.70 PPm due to the amino group. The olefinic proton appeared at 6.60 and 6.80 PPm as a double doublet, and

the coupling constant (16.5 H2) indicate the trans configuration. In addition the phenyl protons appeared at 7-15 PPm as a multiplet band.

cinnamoyl hydrazides have mainly two characteristic nmr bands The first band is attributed to the (NH) protons in amide (-CONH) group at 9.20 PPm, and the second band is due to amino group protons (-NH2) which appeard at higher field at about (3.30-3.40 PPm) [15] .

The variation of chemical shift of these two groups is due to hydrogen bonding formation in these compounds . The compounds of 5-sub. styryl -1,3,4- oxadiazol-2-thiol give singlet band at(13.44- 13.60 PPm)due to NH protons [9]. The broadness or sharpness of this band suggests a proton exchange with the adjacent thion group. It is presumed the presence of two tautomeric forms for these oxadiazoles. The olefinic protons show a downfield absorption at 6.48 and near 7, 3 PPm as a double doublet band, (J=16.50 HZ). The phenyl protons appear as multiplet bands in the region about 7.50 PPm.

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مركبات ذات علاقة بالثايوسيمكاربزيدات

اوكسادايزول وثايادايزول تحضير ودراسة طيفية

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الملخص:

تم في هذا البحث إجراء عملية الفلق الحلقي لمشتقات الثايوسيمكاربزيدات لحامض لسناميك والفا- فنيل السناميك باستخدام هايبوبروميد الصوديوم لإنتاج ٢-أمينو (-٥- معوض ستايريل) -١ و٣ و٤- اوكسادايزول- وقسم من مشتقات الثايوسيمكاربزيدات ثم تحويلها إلى ٢- اميتو (٥- معوض ستابريل) ١ و٣ و٤- ثايادايزول وذلك بتسخينها مع متعدد حامض الفسفوريك. وكذلك تم تحضير مركبات ستايريل – ١و ٣ و٤- اوكسادايزول -٢- ثايول من تفاعل مشتق الهيدرازيد المقابل مع ثنائي كبريتيد الكاربون بوسط كحولي لهيروكسيد البوتاسيوم. هذه المركبات تم تشخيصها باستخدام أطياف الأشعة تحت الحمراء وطيف الرنين النووي المغناطيسي والتحليل الدقيق للعناصر.