Synthesis and biological studies of mono, Bis 1,3,4-thiadiazole-2-amino derivatives

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Abstract:

In the present study, two methods (ordinary and acid chloride methods) were used to prepare new hydrazides and thiosemicarbazides derivatives from the mono and dicarboxylic acid:

1- Oxalic acid, 2-Malonic acid, 3-Succinic acid, 4-Adipic acid, 5-Pimelic acid, 6-Sebacic acid, 7-Palmitic acid, 8-Cinnamic acid, 9- 2,5-dihydroxy Benzoic acid and 10-Quinaldic acid.

These thiosemicarbazide derivatives were converted to 2-Amino- 1,3,4-thiadiazole by ring closer.

The direct reaction of carboxylic acid and thiosemicarbazide in concentrated H_2SO_4 was used for the first time in this conversion as well.

The prepared derivatives were identified by using melting point and infrared spectra studies.

The antibacteria strains has been investigated; an activity has been shown against Gram(+ve) bacteria (Staphylococcus aureus) and Gram (-ve) bacteria (Escherichia coli).

Introduction:

Various substituted 2-amino 1,3,4-Thiadiazole have recently received significant attention for their divers pharmacological properties [1-8].

On the bases of these observations and in continuation of our earlier work[9-10].

The synthesis and characterization of certain 1,3,4-Thiadizole –2-amino and Bis-1,3,4- thiadiazole –2-amino reported in this work for testing their antimicrobial activity.

Experimental:

Melting points were measured using Gallen kamp melting points apparatus or using Electro thermal Engineering LTD, and are uncorrected.

The IR spectra were obtained on a perkin-Elmer IR spectrophotometer, also and perkin-Elmer FT IR spectrophotometer on potassium bromide pellets.

The esters of mono and di carboxylic acid have been prepared following a reported procedure[1]. The structure of these compounds was confirmed by IR spectral data.

The acid hydrazides have been prepared flowing a reported procedure[4,12]. The structure of these compounds was confirmed by melting point and IR spectral data and some of these by elemental analysis (table 1).

Table(1): Physical properties of acid hydrazide derivatives H2NHNCO $(CH_2)_n$ $CONHNH_2$

Comp. No.	n	Moleucular formula	M. P C°	Yield %	Crystallization solvent
1	-	$C_2H_6N_4O_2$	146-148	55	Ethanol
2	1	$C_3H_8N_4O_2$	150-152	65	=
3	2	$C_4H_{10}N_4O_2$	186-188	75	=
4	4	$C_6H_{14}N_4O_2$	181-183	70	=
5*	14	$C_{16}H_{34}N_4O$	60-62	59	=

* CH_3 $(CH_2)_{14}$ $CONHNH_2$

Preparation of thiosemicarbazide derivatives:

Thiosemicarbazide derivatives were prepared by two methods:

1-Acid hydrazide method:

Ethanolic solution of an acid hydrazide (0.1mole) and ammonium thiocyanate (0.3mole,2-3g) was refluxed for 10 hr. and cooled. The solid separating out was filtered, washed with water and recrystallised to give compound (6-10).

2-Acid chloride methods [9]:

Thionyl chloride (0.03 mole) was added dropwise to the acid derivatives (0.03 mole), the mixture was heated and stirred on a water bath at 70 °C for 1 hr . The excess of thionyl chloride was distilled under vacuum. The resulting acid chlorides were used directly in the subsequent synthesis.

Equimolar quantities of the acid chloride and dried thiosemicarbazide were suspended in dry pyridine and cooled to 0 °C. The acid chloride/pyridine solution was added dropwise during ½ hr to thiosemicarbazide/pyridine solution. The mixture was stirred for 12 hrs. at room temperature. Excess pyridine was removed by vacuum distillation. Cold water was added to the residue and the precipitated thiosemicarbazide was filtered, washed with water and recrystallized.

The physical properties of the synthesized thiosemicarbazide are given in Table (2).

Table (2): Physical properties of thiosemicarbazide derivatives H_2 NCSHNHNCO $(CH_2)_n$ $CONHNHCSNH_2$

Comp. No.	n	Molecular formula	M. P °C	Yield %	Crystallization solvent
6	-	$C_4H_8N_6O_2S_2$	155-157	57	Methanol
7	1	$C_5H_{10}N_6O_2S_2$	176-178	59	=
8	2	$C_6H_{12}N_6O_2S_2$	190-192	65	=
9	4	$C_8H_{18}N_6O_2S_2$	٢٢٣-٢٢١	70	Ethanol
*10	14	$C_{17}H_{35}N_3OS$	80-82	60	=

* $CH_3-(CH_2)_{14}-\overset{O}{\overset{\|}{C}}-NHNH-\overset{S}{\overset{\|}{C}}-NH_2$

Preparation of 1,3,4-Thiadiazole derivatives:

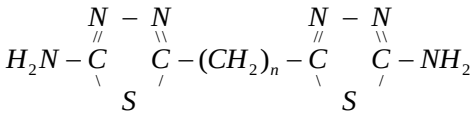
Thiadiazole derivatives were prepared by two methods:

1. Thiosemicarbazide methods: [13,14]

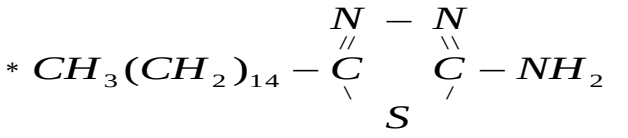
0.01 mole of the dried thiosemicarbazide derivatives was suspended in concentrated sulfuric acid or poly phosphoric acid. The mixture was stirred at room temperature, the precipitated thiadiazole derivatives was filtered, washed with water and reccrystallized from an appropriate solvent.

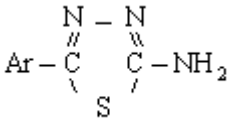
2. Direct methods: The carboxylic acid derivatives (0.1mole) and powder of thiosemicarbazide (0.02mole) in concentrated sulfuric acid was stirred over night. The mixture was poured over crushed ice. It was stirred, diluted with water and filtered. The obtained residue was washed with water and recrystallised.The prepared compounds are given in Table (3).

Table (3) Physical properties of α, ώ– Bis (1,3,4-thiadiazole –2- amino) alkane



Comp. No.	n	Molecular formula	M. P °C	Yield %	Crystallization solvent
11	-	$C_4H_4N_6S_2$	247-249	56	Ethanol
12	1	$C_5H_6N_6S_2$	250-252	70	Ethanol
13	2	$C_6H_8N_6S_2$	253-255	78	Ethanol
14	4	$C_8H_{12}N_6S_2$	245-247	73	=
15	5	$C_9H_{14}N_6S_2$	240-242	67	=
16	8	$C_{12}H_{20}N_6S_2$	221-223	69	=
*17	14	$C_{17}H_{33}N_6S_2$	68-70	93	Ethanol or Methanol





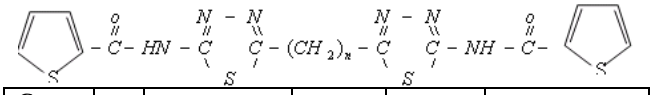
Comp. No.	Ar	Molecular formula	M. P °C	Yield %	Crystallization solvent
18	2,5-Dihydroxy Phenyl	$C_8H_7O_2N_3S$	248-250	69	Ethanol
19	Styryl	$C_{10}H_9N_3S$	178-180	79	Ethanol & Methanol
20	Quinaldenyl	$C_{11}H_8N_4S$	238-240	56	Ethanol

Reaction of thiadiazole derivatives with thiophenoyl chloride:

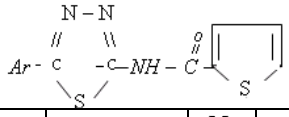
Thiadiazole derivatives (0.05 mole) was suspended in dry dioxane and pyridine (2ml). Thiophenoyl chloride (0.1 mole) was added drop wise during 1/2hr. the mixture was stirred for 12 hrs. at room temperature. Excess solvent was removed by vacuum distillation. Cold water was added to the residue and the precipitate was filtered, washed with water and recrystallized.

Physical properties of these derivatives are given in table (4).

Table (4) Physical properties of α, ώ-Bis – (1,3,4-thiadiazole –2-amino Thiophenoyl alkane



Comp. No.	n	Molecular formula	M. P °C	Yield %	Crystallization solvent
21	-	$C_{14}H_8N_6O_2S_4$	340-342	52	Dioxan
22	1	$C_{15}H_{10}N_6O_2S_4$	332-335	58	=
23	2	$C_{16}H_{12}N_6O_2S_4$	300-302	64	=
24	4	$C_{18}H_{16}N_6O_2S_4$	290-293	63	=
25	5	$C_{19}H_{18}N_6O_2S_4$	250-253	57	=
26	8	$C_{22}H_{24}N_6O_2S_4$	210-213	71	=
*27	14	$C_{22}H_{35}N_3OS_2$	199-202	56	=



Comp. No.	Ar	Molecular formula	M. P °C	Yield %	Crystallization solvent
28	2,5-Dihydroxy Phenyl	$C_{13}H_9N_3O_3S_2$	252-254	63	Ethanol
29	Styryl	$C_{15}H_{11}N_3OS_2$	310-312	73	Dioxan
30	Quinaldenyl	$C_{16}H_{10}N_4OS_2$	270-272	65	=

Method for antimicrobial testing of the prepared compounds:

A serial dilution as eight concentrations (6.4, 3.2, 1.6, 2, 0.8, 0.5, 0.4, 0.25 mg/ml) of the compounds under test was in sterilized test tubes.

Positive and negative controls were taken to act as controls of the clarity of the media. After incubation for turbidity due to bacterial growth were determined for the tube with the highest dilution of the compounds showing no visible turbidity and concentration of the compound for the minimum inhibitory concentration of the compound for the bacteria under test. The MIC values of select compounds against resistant bacteria are giveninTable(5,6).

Table (5) The results of minimum Inhibition concentration (MIC) of 2-amino –1,3,4- Thiadiazole derivatives mg / ml

Comp. No.	S. aureus	E. coli
11	0.5	1
12	1	1
13	1	1
14	1	2
15	0.25	0.5
16	1	2
17	2	2
18	0.25	2
19	1	2
20	2	2

Table (6) The results (MIC) of 2-amino thiophenoyl 1,3,4 Thiadiazole derivatives mg / ml.

Comp. No.	S. aureus	E. coli
21	1.6	1.6
22	0.4	0.4
23	3.2	3.2
24	1.6	0.8
25	0.8	0.8
26	0.8	0.8
27	0.8	0.8
28	1.6	3.2
29	0.8	0.8
30	3.2	3.2

Results and discussion:

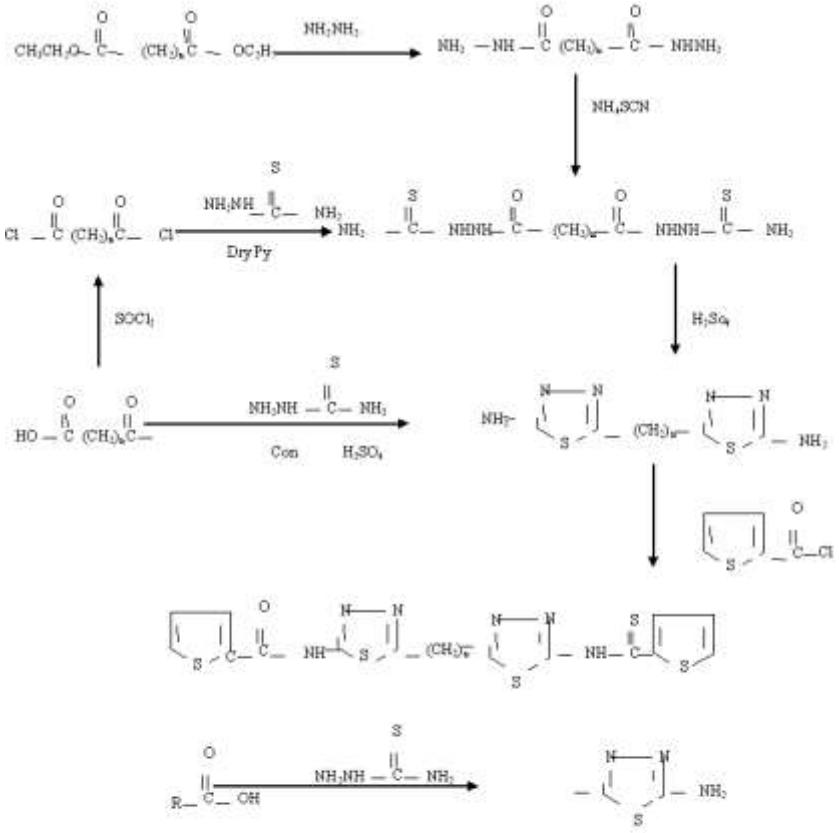
Substituted thiosemicarbazide were prepared by two methods, the first method by the reaction of acid hydrazide with ammonium thiocyanate in ethanol. The reaction mixtures were refluxed for 10 hours. The product were filtered off and crystallized from ethanol to give compound (6-10). The second method, by the reaction of acid chloride with thiosemicarbazide in dry pyridine at 0 ^{o}C according to the method of Hoggarth[13]. The reaction mixtures were allowed to stirring at room temperature,and after 12 hours the excess of pyridine was removed by vacuum distillation, then poured into cold water. The products were filtered off, washed with water and crystallized from ethanol or methanol. The acid chlorides were prepared from the corresponding acid by the reaction with thionyl chloride. Thiadiazole derivatives were prepared by two methods, the first method by treatment of corresponding thiosemicarbazide derivatives with concentrated sulfuric acid [14]. The reaction mixtures were allowed to stand at room temperature, and after (3-4) hours they were poured into water. The products were filtered off, washed with water and crystallized from ethanol or methanol.

The second method, by the direct reaction between the corresponding carboxylic acid and dry powder of thiosemicarbazide in concentrated sulfuric acid. The reaction mixture was allowed to stirring at room temperature, and after 12 hours, they are poured into crushed ice. The products were filtered off and crystallized from ethanol or methanol to give compound (11-20).

The prepared compounds of mono and Bis 1,3,4-thiodiazole –2-amino were reacted with thiophenoyl chloride in appropriate solvent (Dioxane or DMF), and pyridine (2 ml). The reaction mixture were allowed to stirring over night, and then poured into cold water. The precipitate was filtered, washed with water and crystallized from dioxane to give compounds (20-30).

The synthesis of these compounds were carried out according to the steps outlined in scheme 1.

The structure and physical properties of synthesized compounds (1-30) are given in Table 1,2,3 and 4.



n = 0,1,2,4,5,8

R = $CH_3(CH_2)_{14}$
= 2,5 – dihydroxy phenyl
= Cinnamyl
= 2-Quinaldyl

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The IR spectra of thiosemcarbazide derivatives showed four characteristic bands for the mixed -NH-CS vibration.

Band (2) at 1330-1350 cm^{-1} is due to C–N stretching vibration. Band (3) at 995 – 1100 cm^{-1} due to C = S stretching vibration and Band (4) at 900 - 930 cm^{-1} is a combination band of the last three modes of vibration [15].

The IR absorption spectra of mono and Bis-1,3,4–thiadiazole–2-amino derivatives showed the absence of carbonyl band and appear a broad band of NH_2 absorption at 3200-3380 cm^{-1}. A medium intensity band due to C = N stretching vibration is appeared at 1580-1650 cm^{1}. The νs and νas of CH_2 group appeared at the same region.

The IR spectra of mono and Bis-1,3,4-Thiadiazole 2-amino Thiophenoyl showed the absorption and the appearance of C = O absorption at 1675 – 1700 cm^{-1}, and stretching vibration of NH at 3380 – 3500 cm^{-1}, and the bending of NH appear in the region 1515-1587 $cm^{-1.}$

The major in infrared absorption of acid hydrazide, thiosemicarbazide, thiadiazole and their derivatives are given in Table (7,8, 9,10) respectively.

Antimicrobial testing of the prepared compounds

The antimicrobial activity of the prepared compounds towards two micro-organisms was determined by the serial dilution method [16]. The test organisms used were staphylococcus aurous and Escherichia coli. The results indicate that the compounds (11 - 20) of 1,3,4 – thiadiazole –2- amino derivatives were more reactive than 1,3,4 - Thiadiazole – 2 -amino thiophenoyl derivatives (21-30).

The measured MIC results are given in Table (5, 6).

Table (7): Infrared spectra data for acid hydrazide derivatives υ = Cm^{-1}

$$H_2NHN - \overset{O}{\overset{//}{C}} - (CH_2)_n - \overset{O}{\overset{//}{C}} - NHNH_2$$

Comp. No.	n	Amide I υ C=O	Amide II δ N - H	Amide III (C-N) and NH	υ N-H	υ asy. CH_2 υ sy. CH_2
1	-	1645	1545	1240	3300	=
2	1	1660	1540	1225	3290	2985 2970
3	2	1670	1550	1235	3275	2975 2965
4	4	1640	1535	1215	3260	2980 2960
*5	14	1635	1530	1230	3295	2970 2969

*

$$CH_3(CH_2)_{14} - \overset{O}{\overset{//}{C}} - NHNH_2$$

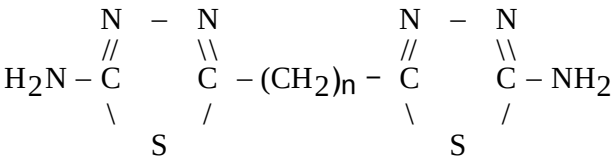
Table (8) Infrared spectra data for thiosemicarbazide derivatives υ = Cm^{-1}

$$H_2N - \overset{S}{\overset{//}{C}} - HNHN - \overset{O}{\overset{//}{C}} - (CH_2)_n - \overset{O}{\overset{//}{C}} - NHNH - \overset{S}{\overset{//}{C}} - NH_2$$

Comp. No.	n	Band I δ (N-H)	Band II υ (C-N)	Band III υ (C=S)	Band IV	υ N-H	υ C=O	υ asy. CH_2 υ sy. CH_2
6	-	1560	1340	995	910	3250	1680	2980 2970
7	1	1565	1330	1025	900	3300	1670	2990 2975
8	2	1590	1345	1030	920	3200	1675	2970 2960
9	4	1585	1350	1020	910	3220	1690	2975 2960
*10	14	1590	1345	1100	930	3200	1685	2980 2965

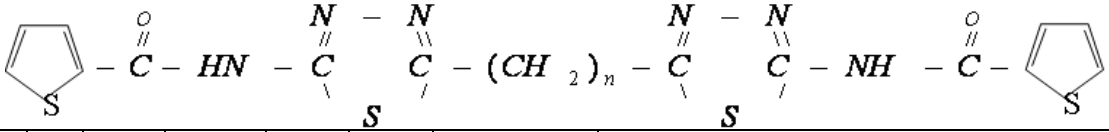
$$* \; CH_3(CH_2)_{14} - \overset{O}{\overset{//}{C}} - NHNH - \overset{S}{\overset{//}{C}} - NH_2$$

Table (9) Infrared spectra data for 1,3,4-thiadiazole –2-amino derivatives υ = Cm^{-1}



Comp. No.	n	υ NH_2	υ C=N	υ asy. CH_2 υ sy. CH_2	Notes
11	-	3200	1600	=	
12	1	3200	1600	2930 2930	
13	2	3250	1620	2910 2880	
14	4	3300	1610	2920 2870	
15	5	3325	1635	2940 2900	
16	8	3420	1650	2950 2950	
17	14	3350	1630	2900 2850	
18	-	3200	1580	=	υ (=C-H) Ar. 3000 υ (C=C) Ar. (1520 – 1600)
19	-	3380	1600	=	υ (=C-H) Ar. 3010 υ (C=C) Ar. (1510 – 1600) υ (H-C=C-H) Olefinic 980

Table (10) Infrared spectra data for 1,3,4-thiadiazole –2- amino thiophenoyl derivatives υ = Cm^{-1}



Comp. No.	n	υ N-H	δ N-H	υ C=N	υ C=O	υ asy. CH_2 υ sy. CH_2	Note
21	-	3495	1587	1635	1695	=	
22	1	3480	1562	1605	1680	2945 2895	
23	2	3395	1575	1639	1700	2935 2885	
24	4	3390	1555	1600	1685	2915 2890	
25	5	3490	1582	1625	1699	2940 2900	
26	8	3450	1567	1638	1690	2930 2898	
*27	14	3485	1550	1610	1698	2905 2889	
28	-	3380	1515	1640	1700	=	υ (=C-H) Ar. 3010 υ (C =C) Ar. (1500- 1610)
29	-	3400	1538	1605	1700	=	υ (=C-H) Ar. 3000 υ (C=C) Ar. (1560- υ (H – C = C – H) Olefinic 980
30	-	3415	1555	1640	1675	=	υ (=C-H) Ar. 3000 υ (C=C) Ar. (1555- 1599)

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تحضير ودراسة بايولوجية لمشتقات 4,3,1- ثايادايزول-2- امينو الأحادية والثنائية

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الملخص:

أما الطريقة الثانية فهي من التفاعل المباشر بين الحامض الكاربوكسيلي والثايوسيميكاربزايد بوسط من حامض الكبريتيك المركز.

وأخيراً تم تفاعل مشتقات2 _ أمينو 1, 3,4- ثايادايزول 2- أمينو مع كلوريد الثايوفينوايل للحصول على مشتقات الثايادايزول المعوضة بمجموعة الثايوفينوايل.

تضمنت الفعالية البايولوجية دراسة تأثير المركبات المذكورة على نوعين من البكتريا هما المكورات العنقودية الذهبية Staphylococcus aureus واشريشيا القولون Escherichia coli وقد تبين إن هذه المركبات هي ذات فعالية جيدة ضد هذين النوعين من البكتريا.تم تشخيص تراكيب المركبات المحضرة باستخدام أطياف الأشعة تحت الحمراء ودرجات الانصهار. و قسم منها استخدام التحاليل الدقيقة للعناصر.

يتضمن هذا البحث تحضير مشتقات الهيدرازيد والثايوسيميكاربزايد لبعض الحوامض الأحادية والثنائية الكاربوكسيل مثل حامض الاوكزالك، المالونك، السكسنيك، الادبيك، البيمالك، السيباسك، البالمتك، 2 , 5- ثنائي هيدروكسي بنزويك، السينامك والكوينالدك.

وقد تم تحضير مشتقات الثايوسيميكاربزايد بطريقتين، الأولى بتفاعل مشتقات الهيدرازايد مع ثايوسيانات الامونيوم. أما الطريقة الثانية فهي بتفاعل كلوريد الحامض مع مسحوق الثايوسيميكاربزايد بوسط من البيريدين. تم تحويل مشتقات الثايوسيميكاربزايد إلى مشتقات 2 _ أمينو 1 , 3 , 4- ثايادايزول المقابلة بطريقتين هما، طريقة الغلق الحلقي لمشتق الثايوسيميكاربزايد باستخدام حامض الكبريتيك المركز أو متعدد حامض الفسفوريك (PPA).