Synthesis of Some Heterocyclic Compounds Containing Tetrahydroisoquinoline Moiety

Mohammad Ahmad Al-Iraqi* **Ahmad Waleed Najem**

Department of Chemistry, College of Science, University of Mosul.

maaliraqi_54@yahoo.com dr.alhilaly89@gmail.com

الملخص

تضمن البحث تحضير بعض المركبات الحلقية غير المتجانسة خماسية الحلقة باستخدام الـ 4,3,2,1- رباعي هيدروآيزوكوينولين مادةً أولية. تضمنت الخطوة الأولى تفاعل 4,3,2,1- رباعي هيدروآيزوكوينولين مع كلوروخلات الأثيل لتحضير (4,3,2,1) -α- رباعي هيدروآيزوكوينولين-2- يل) خلات الأثيل (1), الذي حول إلى مركب الهيدرازيد (2). أستخدم الهيدرازيد لتحضير عدد من المركبات الحلقية غير المتجانسة مثل الأوكسادايازولات (7-10، 23) والثايادايزولات (11-14) من خلال تحضير عدد من المركبات الوسطية مثل مركبات الثنائي أسيل هيدرازين (3-6) والهيدرازونات (15-18) وكذلك الأوكسادايازولينات (19-22) و (24-27). شخصت المركبات المحضرة استناداً إلى بعض البيانات الفيزياوية وطيف الأشعة تحت الحمراء.

ABSTRACT

This research involves synthesis of some five membered heterocyclic compounds using 1,2,3,4-tetrahydroisoquinoline as a synthone. The initial step in this research involves the reaction of 1,2,3,4-tetrahydroisoquinoline with ethyl chloroacetate to form ethyl α-(1,2,3,4-tetrahydroisoquinolin-2-yl) acetate (1), which was converted to the hydrazide (2). This hydrazide was used to prepare some heterocyclic compounds, such as substituted oxadiazoles (7-10, 23) and thiadiazoles (11-14) via preparation of intermediate compounds such as diacylhydrazines (3-6), hydrazones (15-18) and substituted oxadiazoline compounds (19-22) and (24-27). The synthesized compounds were identified on the basis of some physical and IR spectral data.

Key words: Tetrahydroisoquinoline, oxadiazole, thiadiazole, hydrazide, diacylhydrazine, heterocyclic compounds.

INTRODUCTION

Substituted tetrahydroisoquinolines are found abundantly in nature, especially in plants, soil and microorganisms.[1] Many of tetrahydroisoquinoline compounds have an important biological activity as anti-inflammatory, anti-microbial, anti-leukemic, anti-tumor,[2-4] anti-platelet aggregation.[5] On the other hand, the oxadiazole moiety has been shown to impart anti-inflammatory properties in compounds designed as orally-active non-ulcerogenic agents,[6] muscle relaxant and anti-meiotic activity.[7]

* ***Presented at the second conference on Chemistry, University of Mosul, college of Education, 17-18 Novamber-2013.***

The thiadiazole compounds are considered as important biologically active compounds and it has a wide spectrum of biological effects and can be used as anti-microbial,[8] antifungal[9] and anti-HIV agents. The synthesis of oxadiazoles and thiadiazoles incorporated with tetrahydroisoquinoline moiety is of very importance and may lead to many biological applications. The acid hydrazide system has been the subject of considerable research interest mainly due to its usefulness in synthetic organic chemistry and also because of the pharmacological properties associated with some of its derivatives.

Prompted by these observations and search of new biologically active compounds, herein, the synthesis of novel series of heterocyclic compounds containing tetrahydroisoquinoline moiety is reported.

EXPERIMENTAL

Melting points were determined with an Electro-thermal IA 9300 Digital-Series apparatus and are uncorrected. Infrared spectra were recorded on a Bruker FT-IR Spectrophotometer Tensor 27, using KBr and NaCl disks.

Preparation of ethyl α-(1,2,3,4-tetrahydroisoquinolin-2-yl)acetate (1):[10]

To an ice cooled solution of 1,2,3,4-tetrahydroisoquinoline (0.02 mol, 2.4 mL) in ethanol (10 mL), ethyl chloroacetate (0.02mol, 2.21 mL) was gradually added with stirring. The color of the solution becomes reddish-orange. The stirring was continued for 24 h. The mixture was treated with sodium carbonate solution then extracted with chloroform (3 * 10 mL). The organic layer was dried with anhydrous magnesium sulfate then evaporated to give 1.7 mL, 71% of oily ester.

Preparation of α-(1,2,3,4-tetrahydroisoquinolin-2-yl)acetic acid hydrazide (2):[11]

To a solution of the ester (1) (0.035 mol, 6.8 g) in an absolute ethanol (50 mL), hydrazine hydrate 85% (0.175 mol, 5.4 mL) was added with stirring. The mixture was refluxed for 24 h. The volatile components were evaporated and the gummy material was washed with small amount of cold ethanol then recrystallized from hexane to give white needle like crystals (m.p. 98-100 ^{o}C, 78% yield).

Preparation of N,N'-diacyl hydrazine compounds (3-6):[12]

To a solution of the hydrazide (2) (0.01 mol, 2.05 g) in benzene (30 mL), an acid chloride (0.01 mol) was added slowly with stirring. The mixture was refluxed for 4 h, then cooled. The solid product was filtered off, washed with cold ethanol then dried. The physical properties were listed in table (1).

Preparation of the oxadiazoles (7-10):[13]

A mixture of diacylhydrazine compounds (3-6) (0.002 mol) and phosphorous oxychloride (10 mL) was refluxed for 4 h. The mixture was poured on crushed ice (20 g). The mixture was treated with sodium bicarbonate solution (10%) and the precipitate was filtered off then recrystallized from ethanol. The physical properties were listed in Table (1).

Preparation of the thiadiazoles (11-14):[14]

A mixture of the diacyl hydrazine compounds (3-6) (0.012 mol) in DMF (10 mL) and diphosphorous pentasulfide (0.013 mol, 2.9 g) was refluxed for 12 h, then immediately filtered. The filtrate was evaporated to dryness. The solid product was washed with dry diethyl ether the dried. The physical properties were listed in Table (1).

Preparation of the hydrazones (15-18):[15]

To a solution of the hydrazide (2) (0.01 mol, 2.05 g) in absolute ethanol (30 mL), an appropriate aldehyde (0.01 mol) and (3 drops) of acetic acid were added. The mixture was refluxed for 24 h, then condensed to third its volume and the residue poured on a crushed ice (20 g). The precipitate was filtered off, washed thoroughly with water then recrystallized from ethanol. The physical properties were listed in Table (1).

Preparation of oxadiazolines (19-22):[16]

A mixture of the hydrazones (15-18) (0.005 mol) and acetic anhydride (15 mL) was refluxed for 12 h. The mixture was evaporated to dryness, and the residue washed thoroughly with water then dried to give powdered products. The physical properties were listed in Table (1).

Preparation of 5-[(1,2,3,4-tetrahydroquinolin-2-yl)methyl]-1,3,4-oxadiazol-2-thiol (23):[11]

To a mixture of the hydrazide (2) (0.01 mol, 2.05 g) and a solution of potassium hydroxide (0.02 mol, 1.12 g) in absolute ethanol (10 mL), carbon disulfide (0.04 mol, 3 mL) was added drop wise with stirring. The mixture was refluxed for 24 h, then the volatile components were evaporated. A crushed ice was added to the residue and the mixture was neutralized with diluted hydrochloric acid and left for an hour. The precipitate was filtered off and washed thoroughly with water then recrystallized from ethanol to give yellow powder (m.p. 82-84, 85 % yield).

Reaction of the oxadiazole (23) with aldehydes:[16]

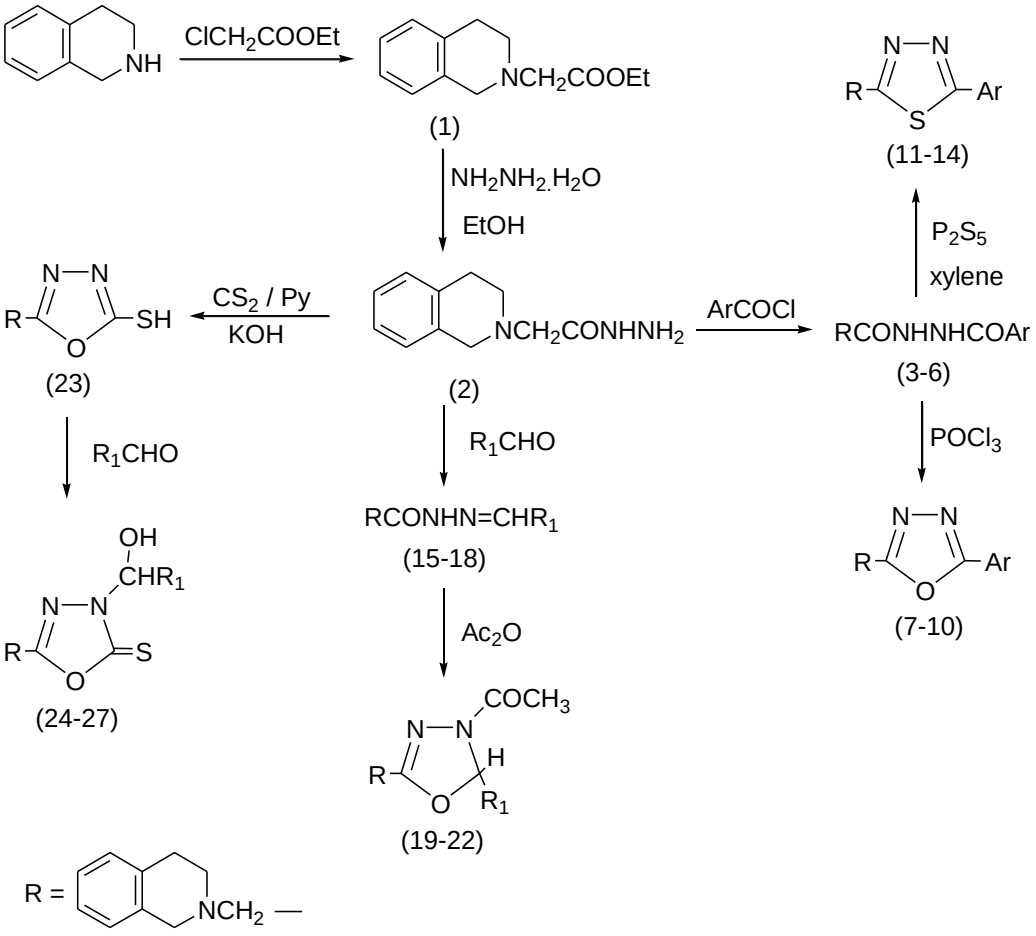
To a solution of oxadiazole (23) (0.001 mol, 0.233 g) in dimethyl sulfoxide (6 mL) and absolute ethanol (5 mL), an aldehyde (0.001 mol) was added. The mixture was refluxed for 3 h, then poured on a crushed ice. The resulted precipitate was filtered off and recrystallized from (3:7) DMSO:ethanol. The physical properties of compounds (24-27) were listed in Table (1).

Table 1: Some physical properties of the synthesized compounds (3-27):

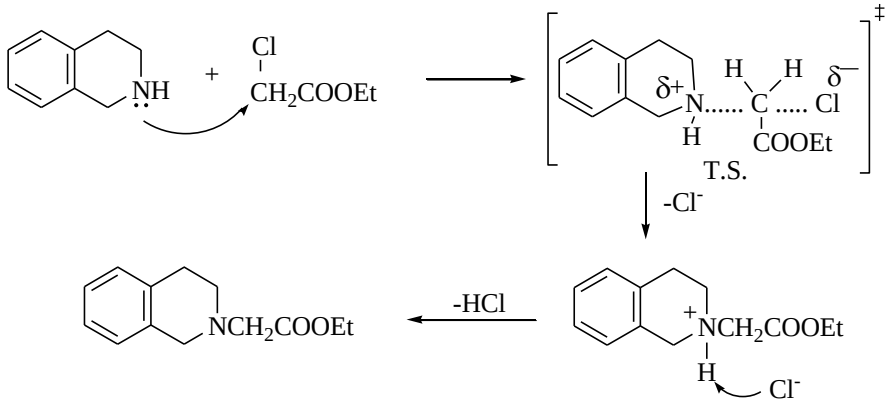
Compd. No.	m.p. ^{o}C	Yield %	Color
3	152-154	79	Faint yellow
4	185-187	80	Greenish white
5	140-142	85	Yellowish white
6	210-212	75	White
7	129-130	75	Yellowish white
8	141-143	77	Yellow
9	120-122	83	Faint yellow
10	192-194	71	White
11	180-181	58	Faint pink
12	210-212	63	Faint brown
13	190-192	60	Brown
14	224-225	67	Faint yellow
15	180-182	85	Green
16	166-168	82	Yellow
17	132-134	80	Greenish yellow
18	145-147	77	Orange
19	130-132	75	Brown
20	125-127	78	Brown
21	90-92	85	Brown
22	111-113	83	Faint brown
23	82-84	85	Yellow
24	156-158	71	Yellow
25	142-144	75	Deep yellow
26	120-122	82	Greenish yellow
27	129-131	77	pink

Results and Discussion

The synthetic routes of this research were summarized in Scheme 1.



The introduction of heterocyclic rings to the tetrahydroisoquinoline nucleus was started *via* the reaction of 1,2,3,4-tetrahydroisoquinoline with ethyl chloroacetate, which afforded ethyl α-(1,2,3,4-tetrahydroisoquinolin-2-yl) acetate (1). The reaction was proceeded *via* S_N2 mechanism.



This compound was identified on the basis of some spectroscopic data.[17] The IR spectrum showed the following characteristic absorption bands (KBr disc): at 1740 Cm^{-1} related to the ester C=O bond stretching, in addition to two bans at 1103 and 1269 Cm^{-1} corresponding to the symmetric and asymmetric C-O-C bond stretching. The UV spectrum of compound (1) showed two absorption bands at 334 and 294 nm due to the $n \rightarrow \pi^*$ electronic transitions.

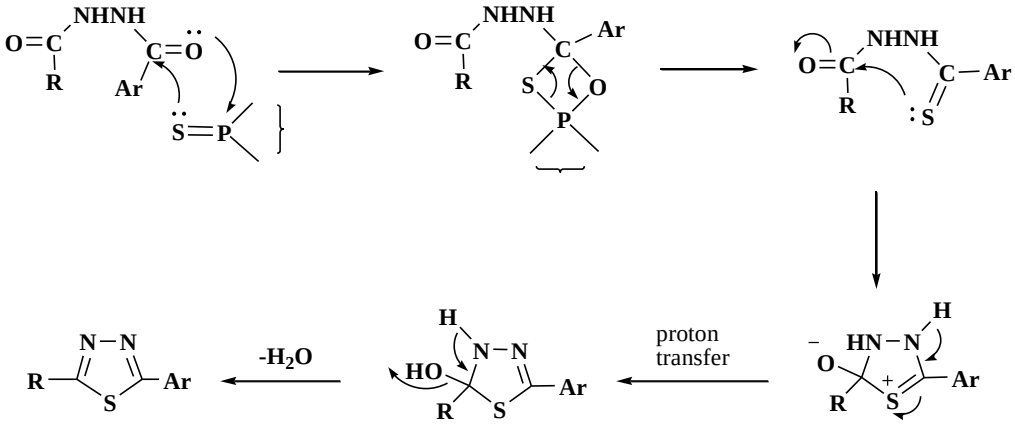
The refluxing of the ethanolic solution of the ester (1) in presence of hydrazine hydrate afforded the hydrazide (2) in a good yield. This product was formed *via* the tetrahedral nucleophilic addition mechanism. The IR spectrum of this compound showed an absorption band at 1655 Cm^{-1} related to the C=O bond stretching of the hydrazide moiety, in addition to a broad band at 3323 Cm^{-1} for the N-H bond stretching.

The hydrazide (2) was considered as a potential intermediate to synthesize the subsequent heterocyclic compounds. This hydrazide was, firstly, converted to the diacyl hydrazine compounds (3-6) *via* its reaction with appropriate carboxylic acid chlorides. These diacyl hydrazine compounds (3-6) were cyclized to the oxadiazoles (7-10) under the influence of $POCl_3$. The IR spectra of compounds (3-6), (Table 2), showed absorption bands at 1714-1653 and 1674-1649 Cm^{-1} for the aliphatic and aromatic C=O bond stretching respectively, in addition to, absorption bands at (3220-3186) Cm^{-1} for the N-H bond stretching. Whereas, the IR spectra of compounds (7-10) showed absorption bands at (1635-1624) Cm^{-1} for the C=N bond stretching and at (1089-1041) and (1281-1236) Cm^{-1} for the symmetric and asymmetric C-O-C bond stretching.

Table 2: Some IR spectral data of compounds (3-6) and (7-10):

Compd. No.	Ar-	IR (KBr disc, ν cm^{-1})				
		N-H	R-C=O Ar-C=O	C=N	C-O-C Sym, asym	NO_2 sym/asym
3	3-ClC_6H_4	3186	1711/1664	-	-	-
4	3-$NO_2C_6H_4$	3194	1714/1674	-	-	1352/1537
5	Ph-	3188	1664/1655	-	-	-
6	4-$NO_2C_6H_4$	3220	1653/1649	-	-	1340/1550
7	3-ClC_6H_4	-	-	1635	1058/1281	-
8	3-$NO_2C_6H_4$	-	-	1636	1089/1265	1395/1561
9	Ph-	-	-	1627	1070/1238	-
10	4-$NO_2C_6H_4$	-	-	1624	1041/1236	1339/1541

On the other hand, the cyclization of compounds (3-6) was, also, achieved by refluxing of these compounds with diphosphorous pentasulfide in xylene as a solvent to produce the thiadiazole compounds (11-14). The cyclization was proceeded according to the following mechanism.[18]

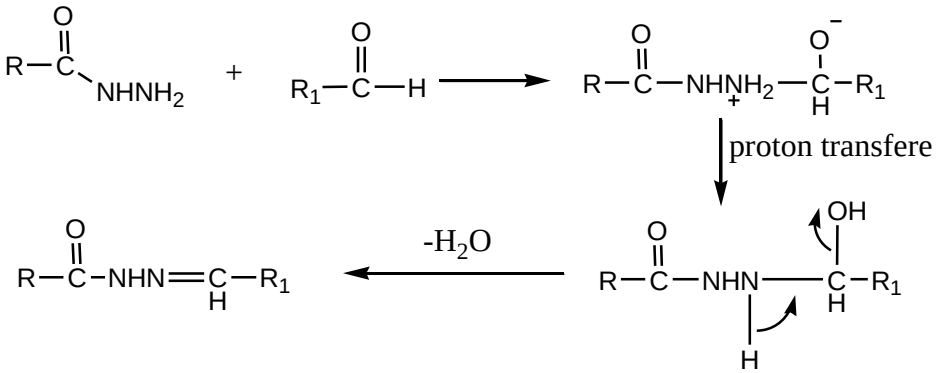


These compounds have been investigated using IR spectroscopy (Table 3). Beside the absorption bands at (1625-1590) Cm^{-1} for the C=N bond stretching, there have been identified absorption bands at (677-584) Cm^{-1} for the C-S bond stretching.

Table 3: Some IR spectral data of compounds (11-14):

Compd. No.	Ar-	IR (KBr disc, ν cm^{-1})		
		C=N	C-S-C	NO_2 sym/asym
11	3-ClC_6H_4	1618	619	-
12	3-$NO_2C_6H_4$	1590	677	1375/1551
13	Ph-	1605	584	-
14	4-$NO_2C_6H_4$	1625	617	1353/1545

Moreover, the hydrazide (2) was used to synthesize the hydrazone compounds (15-18), by its condensation with aldehydic compounds in presence of catalytic amount of acetic acid under reflux. The reaction was proceeded through the nucleophilic addition of the hydrazide to the aldehydic carbonyl carbon atom to form a hydrazinol intermediate which loss water molecule to form the hydrazone compounds.

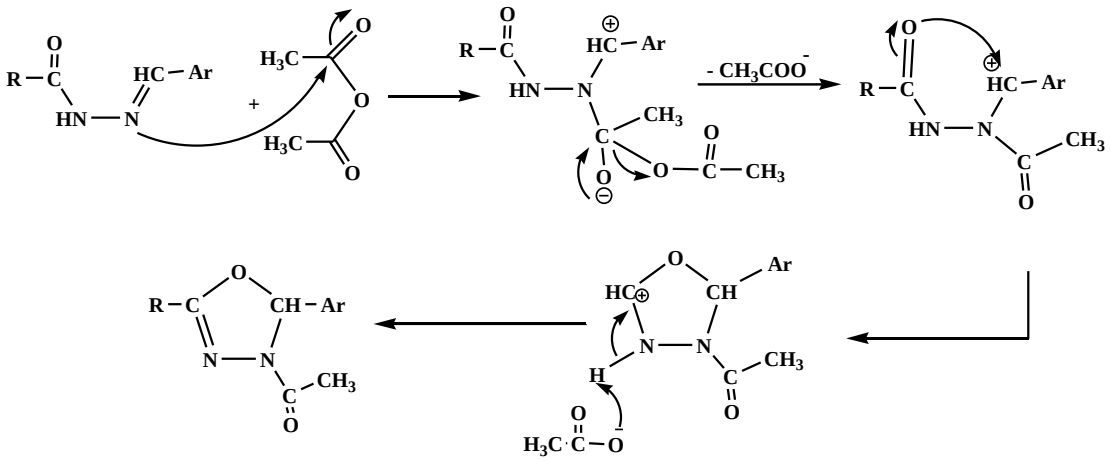


The IR spectra of compounds (15-18), (Table 4), showed absorption bands at (1689-1655) Cm^{-1} for the hydrazide C=O bond stretching and at (1636-1604) Cm^{-1} for the imino C=N bond stretching.

Table 4: Some IR spectral data of compounds (15-18):

Compd. No.	R_1	IR (KBr disc, ν cm^{-1})			
		C=O	C=N	C=C	other
15	2-NH_2 C_6H_4	1689	1624	1554	(N-H)/3404
16	2-HOC_6H_4	1655	1604	1541	(O-H)/3236
17	CH_3CH=CH	1684	1618	-	-
18	C_6H_4CH=CH	1676	1636	1554	-

Moreover, treatment of the hydrazon compounds (15-18) with acetic anhydride under reflux yielded the corresponding substituted 3-acetyl oxadiazoline compounds (19-22) via the following mechanism.[18]



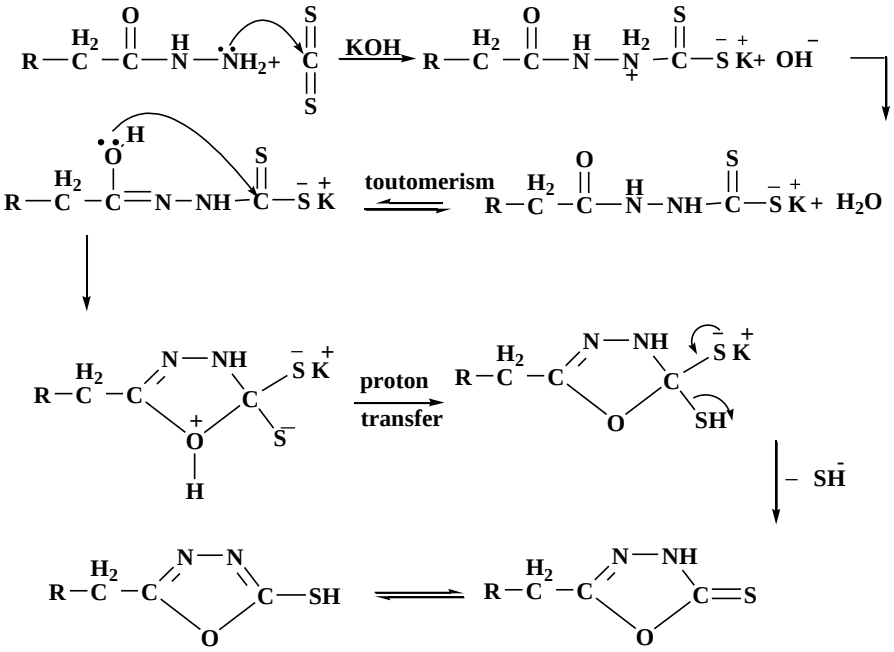
The IR spectra (Table 5) of compounds (19-22) revealed the presence of the band of C=O bond stretching of the acetyl group at (1697-1668) Cm^{-1} and absorption bands at (1610-1590) Cm^{-1} related to the C=N bond stretching, and two absorption bands at (1098-1075) and (1249-1219) Cm^{-1} for the symmetric and asymmetric C-O-C bond stretching.

Table 5: Some IR spectral data of compounds (19-22):

Compd. No.	R_1	IR (KBr disc, ν cm^{-1})			
		C=O	C=N	C-O-C Sym, sym	others
19	2-$NH_2C_6H_4$	1722	1641	1018-1230	(N-H)/3234
20	2-HOC_6H_4	1716	1634	1089-1249	(O-H)/3420
21	CH_3CH=CH	1684	1650	1069-1219	-
22	C_6H_4CH=CH	1676	1625	1075-1225	-

When the hydrazide (2) treated with carbon disulfide in pyridine in presence of alcoholic potassium hydroxide solution, it afforded 2-(1,2,3,4-tetrahydroisoquinolin-2-yl)methyl-1,3,4-oxadiazol-5-thione (23) which upon further reaction with different aliphatic and aromatic aldehydes gave the corresponding 3-(α-hydroxy alkyl)oxadiazolin-5-thiones (24-27). The

mechanism of formation of oxadiazolin-2-thione (23) from the reaction of the hydrazide (2) with CS_2 was illustrated below. The free amino group was, initially, reacts with CS_2 to generate the dithiocarbamate anion which undergoes cyclization to form the target products.[18]



The IR spectrum of compound (23) display the appearance of endocyclic C=N bond stretching at 1618 Cm^{-1}, and absorption bands at 3402 Cm^{-1} for the N-H bond stretching and two characteristic bands at 1020 and 1248 Cm^{-1} for the symmetric and asymmetric C-O-C bond stretching, in addition to the thione C=S bond stretching at 1248 Cm^{-1}.

Finally, the oxadiazoline-2-thione compound (23) reacts with aldehydes through nucleophilic addition mechanism to form the aminol compounds (24-27). The IR spectra (Table 6) of these compounds showed absorption bands at: (1217-1179) Cm^{-1} related to C=S bond stretching, two bands at (1101-1055) and (1290-1236) Cm^{-1} corresponding to the symmetric and asymmetric C-O-C bond stretching, (1610-1585) Cm^{-1} for the C=N bond stretching in addition to absorption bands at (3371-3310) Cm^{-1} for the O-H bond stretching.

Table 6: Some IR spectral data of compounds (24-27):

Compd. No.	R_1	IR (KBr disc, ν cm^{-1})			
		C=S	C=N	C-O-C Sym, sym	O-H
24	2-$NH_2C_6H_4$	1217	1606	1055/1290	3330
25	2-HOC_6H_4	1192	1610	1101/1282	3371
26	CH_3CH=CH	1174	1601	1072/1290	3310
27	C_6H_4CH=CH	1194	1585	1099-1236	3360

References

1. K.W. Bentley, *Nat. Prod. Rep.* **22**, 249-268, (2005).
2. J.D. Scott, R.M. Williams, *Chem. Rev.* **102**(5), 1669-1730, (2002).
3. K. Iwasa, M. Moriyasu, T. Yamori, T. Turuo, D.U. Lee, W. Wiegrebe. *J. Nat. Prod.* **64**(7), 896-898, (2001).
4. B.C. Revanasiddappa, E.V.S. Subrahmanyam, D. Satyanarayana, J. Thomas. *Int. J. Chem. Tech. Res.* **1**(4), 1100-1104, (2009).
5. S. Cheng, X. Zhang, W. Wang, M. Zhao, M. Zheng, H.W. Chang, J. Wu, S. Peng, *Eur. J. Med. Chem.* **44**, 4904-4919, (2009).
6. G. Roman, C. Agache, I. Manciulea, E. Comaniţă, L. Dumitrescu. *Revue Roumaine de Chimie*, **52**(12), 1103-1110, (2007).
7. J. Solovjova, V. Martynaitis, W. Holzer, S. Mangelinckx, N.D. Kimpe, A. Šačkus. *Arkivoc* **(vi)**, 48-62, (2009).
8. M.R. Shabban, T.S. Saleh, A.M. Farag. *Heterocycl.* **78**(1), 151, (2009).
9. P. Sah, N. Saraswat, M. Seth. *E- J. Chemistry***, 8**(1), 427, (2011).
10. A.I. Vogel, "A text book of practical organic chemistry including qualitative organic analysis" 3rd Ed., Longmans, Woolwish Polytechnic, London (1965).
11. M. Amir and K. Shikha, *Eur. J. Med. Chem.* **39**, 535-545, (2004).
12. A.R. Fraghaly and H. El-Kashef. Arkivoc. (xi) 76-90, (2006).
13. A. H. Elmasry, H.H. Fahmy and S.H. Ali Abdelwahed. Molecules, **5**, 1429-1438, (2000).
14. Z.M. Omer, M.Sc. Thesis, Mosul University, College of Science, Mosul, Iraq, (2012).
15. A.K. Sen-Gupta and K. Hajela, *J. Indian Chem. Soc.* **58**, 690, (1981).
16. M.A.E. Shaban , A.Z. Naser and S.M. El-badry. *J. Islamic Acad. Sci.*, **4**(3), 148, (1991).
17. Parikh, V.M. "Absorption spectroscopy of organic molecules" (1975).
18. M.A. Al-Gasso, M.Sc. Thesis, Mosul University, College of Science, Mosul, Iraq, (2010).
19. B.B. Al-dewachi, Ph.D. Thesis, Mosul University, College of Science, Mosul, Iraq, (2013).