Synthesis of New Benzoxadiazole Compounds Derived from Ethyl-4- (7- Nitro-2.1,3,- Benzoxadiazole -4-Yl) Amino Benzoate

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Abstract

Refluxing of the 4-chloro –7-nitro- -2,1.3, - benzoxadiazole with ethyl (p-amino) benzoate in absolute ethanol at 78 C^o for 12 hrs to give ethyl-4 -(7- nitro-2.1,3,- benzoxadiazole) -4-yl) amino benzoate (1) with 60% yield.

Compound (1) was reacted with hydrazine hydrate in absolute ethanol for 5hrs to obtain the carboxylic acid hydrazide (2). The product (2) was treated with phenylisothiocyanat in absolute ethanol to synthesize 2-{4-[(7-nitro-2,1,3-benzoxadiazol-4-yl) amino] benzoyl}-*N*-phenylhydrazinecarbothioamide (3).

Cyclization of the compound (3) using base has afforded 5-{4-[(7-nitro-2,1,3-benzoxadiazol-4-l) amino] phenyl} - 4-phenyl-4*H*-1,2,4- triazole-3-thiol (4).

The synthesized triazoles (4) derivative have been reacted once (alkyl ,aryl halides) and with appropriate secondary amine in dry dioxane to give (alkyl, aryl) thio derivative (5-9) and N-{4-[5-(N,N- substituted)-4-phenyl-4H-1,2,4-triazol-3-yl]phenyl}-7-nitro-2,1,3-benzoxadiazol-4- amine derivatives (11-13).

The synthesized compounds have been characterized by their physical and chemical properties, spectral analysis (FT-IR, U.V) in addition to the micro analysis of the elements(C.H.N).

Introduction

Variety of compounds including oxadiazole ring have been found to possess a wide spectrum of pharmacological, medical and biological activity. Several investigators have shown that some oxadiazoles derivatives exhibit in vitro tuberculostatic activity [1], besides their anti-inflammatory and central nervous system action [2]. Further more, some oxadiazoles have been found to exhibit antimycobacterial as well as fungicidal activity.

They have also shown that such compounds have (N-C=S) and (C-O-C) moiety which are perhaps responsible for their fungicidal activity[3] .

Many benzoxadiazole derivatives have been found to be considrable interest because of their biological activity [4,5,6] Some of these derivatives are useful anthiypers tensive agent [7], analgesic and for their antitbercular activity [8,9] further more ,several derivative have found to posses Herbicides [10], antifungal and anti cancer activity [11-14] .

In the present work, many (4- substituted) -7-nitro-2.1,3,-benzoxadiazole were introduced.

Experimental

All chemical used were of reagent grade (supplied by either Merck or fluka) and used as supplied. The FTIR spectra in the range (4000-400) cm^{-1} were recorded on FTIR.84005 Shimadzu Spectrophotometer as KBr discs. The UV-visible spectra were measured in ethanol using (Hitachi U-2000) Ultra-violet Spectrophotometer in the range (200-800) nm. Gallencamp M.F.B600.010 F melting point apparatus was used to measure the melting points all the prepared compounds. Elemental microanalysis was carried out using CHNOS elemental analyzer model 5500 Carlo-Erba instruments.

*Synthesis of ethyl-4-[(7-nitro-2.1,3,-benzoxadiazole -4-yl) amino] benzoate (1).

A mixture of the 4-chloro-7-nitro -2,1,3-.-benzoxadiazole (0.01mole) and ethyl (p-amino) benzoate (0.01 mole) in ethanol absolute(100ml) was refluxed for (12hrs). The solvent was removed in vacuum and the crude product was collected. The product was purified from ethanol.The physical properties of compound [1] was listed in Table (1) and the (C.H.N) analysis list in Table (2).

***Synthesis of 4- [(7-nitro-2.1, 3,-benzoxadiazole-4-yl) amino] benzohydrazide (2).**

A mixture of the compound (1) (0.01mole) in ethanol (50ml) and hydrazine hydrate (80%) was refluxed for (5hrs) .The product seprated out, filtered and recrystallized from ethanol [2]. The physical properties of compound (2) was listed in Table (1).

*** Synthesis of 2-{4-[(7-nitro-2,1,3-benzoxadiazol-4-yl) amino] benzoyl} -N phenylhydrazine carbothioamide (3).**

A mixture of the compound (2) (0.01mole), and phenylisothiocyanate (0.01mole) in absolute ethanol (50ml) was refluxed for (4hrs). The contents were poured into crushed ice (100 gm.), filtered and the product was recrystallized from ethanol to give (3). The physical properties of compound (3) is listed in Table (1).

***Synthesis of [5-{4-[(7-nitro-2,1,3-benzoxadiazol-4-yl) amino]phenyl} -4-phenyl-4H-1,2,4-triazole-3-thiol (4).**

Compound [3] (0.005mole) was reflux in NaOH (4%) for 5 hrs., cooled, poured into excess of water, stirred and filtered, on acidification of the filtered, the product was washed with cold water dried and recrystallized from ethanol. The physical properties of compound [4] is listed in Table (1) and the (C.H.N) analysis listed in Table (2).

***Synthesis of N-{4-[5-(substituted thio)-4-phenyl -4H-1,2,4-triazol-3-yl]phenyl}-7-nitro-2,1,3- benzoxadiazol-4- amine (5-9).**

To compound (4) (0.01 mole) in absolute ethanol (20ml) was added potassium hydroxide (0.01 mole) and appropriate alkyl or aryl halide (0.012mole) ,the mixture was refluxed for (5hrs.), then cooled and acidified with dilute HCI (10 %) till to get crystalline products .filtration and recrystallization from ethanol gave the intended compounds (5-9). The physical properties of compounds (5-9) are listed in Table (1) and the (C.H.N) analysis for compound (9) is listed in Table (2).

***Synthesis of N-{4-[5-(N,N- substituted)-4-phenyl-4H-1,2,4-triazol-3- yl]phenyl}-7-nitro -2,1,3- benzoxadiazol-4- amine (10-13).**

To compound (4) (0.001 mole) in 10ml of dry dioxane was added appropriate secondary amine (0.001 mole in 10 ml of dry dioxane. the mixture was refluxed for 5hrs. After cooling, the precipitate was filtred and recrystallized from ethanol. The physical properties of compounds (10-13) are listed in Table (1).

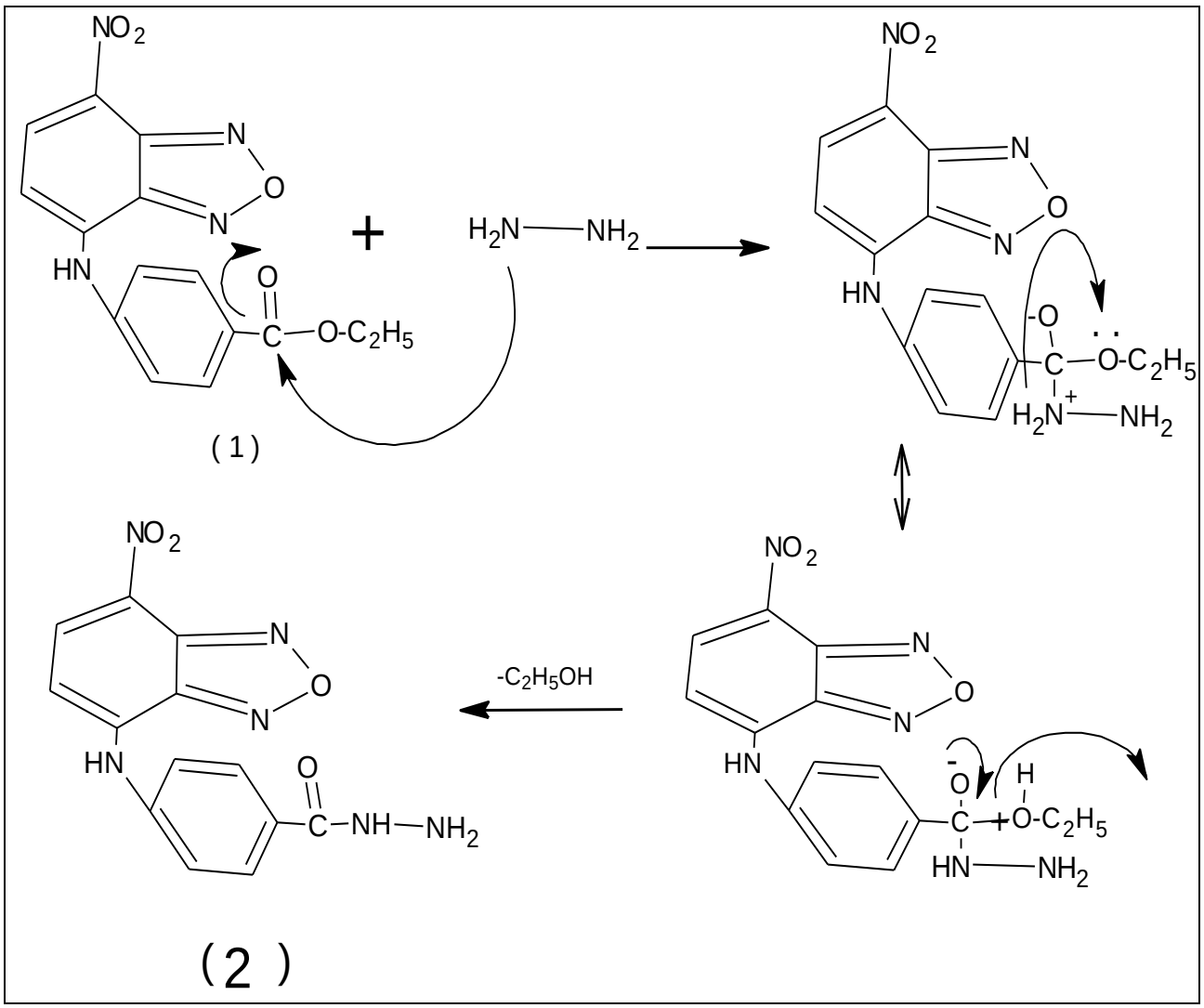
Results and Discussion

The intermediate ethyl-4- (7- nitro-2.1,3,-benzoxadiazole -4-yl) amino benzoate (1) was obtained in yield (60%) by refluxing of 4-chloro –7-nitro- -2,1.3, - benzoxadiazole with ethyl (p-amino) benzoate in ethanol for 12 hrs. the structure of the compound (1) has been established on the basis of their FT.IR and U.V spectral data. (Table (3)). The spectra of FTIR shows Fig.(1) the disappearance of C-CI group of an absorption bands at 731 cm^{-1}, and the appearance of an absorption band at 3210 cm^{1-} due to (NH) stretching vibration.

The U.V spectra of compound (1) in ethanol shows absorption band at (216, 261) nm due to (π-π*) transition and absorption band at (337nm) which is assigned to (n-π*) transition. Micro analysis of (C.H.N.) element of the compound (1) has been in agreement with the calculated value.

Treatment of compound (1) with hydrazine hydrate in boiIIing ethanol for (6 hrs.) gave hydrazide derivative [2]. the structure of the compound [2] has been established on the basis of their FT.IR and U.V spectral data. (Table(3)).The spectra of FTIR shows Fig.(2) disappearance of $\upsilon_{C=O}$ group of an absorption bands at 1733 cm^{-1},and the appearance of of new bands at(3200-3424)cm^{-1} ,and1660 which alternatively belonged to υ_{N-H} and $\upsilon_{C=O}$ amide respectively cm^{1-} , Micro analysis of(C.H.N.) element of the compound (2) has been in agreement with the calculated value.

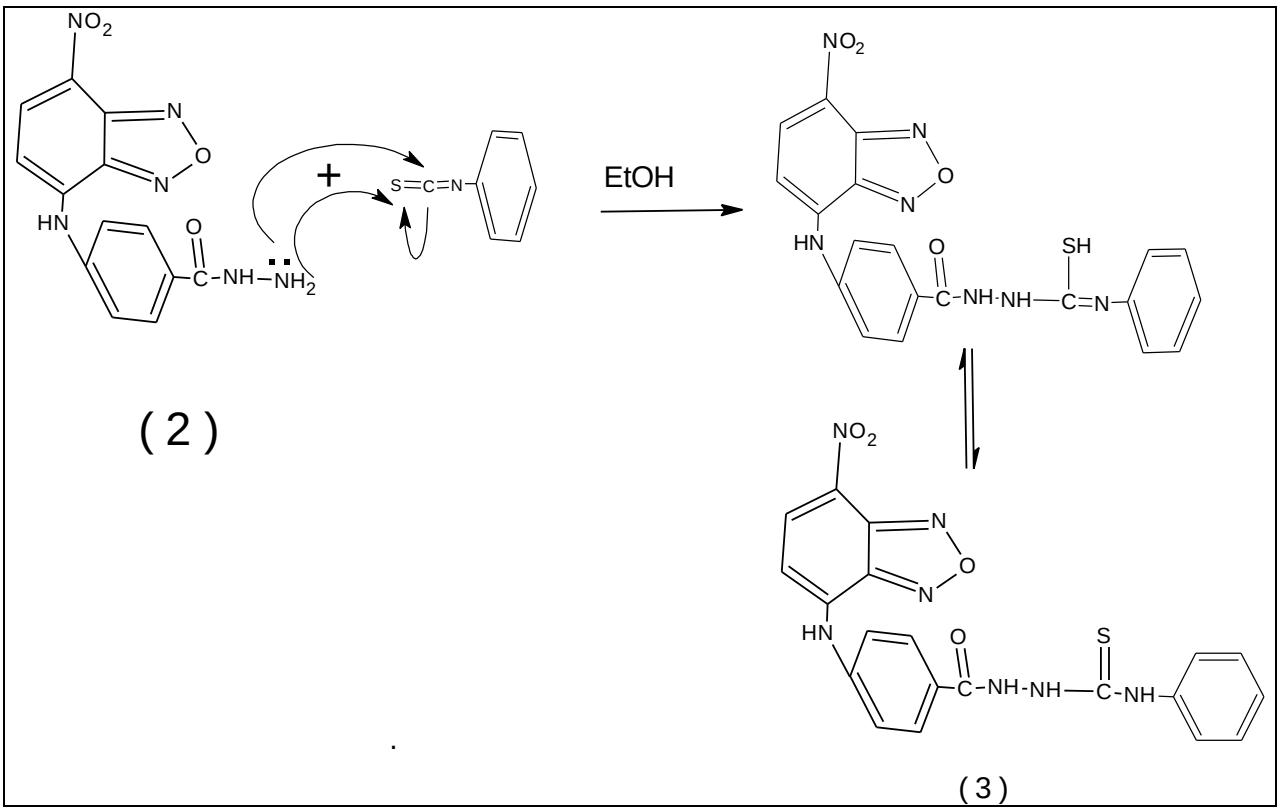
The U.V spectra of compound (2), in ethanol shows absorption band at (223, 268) nm due to (π-π*) transition and absorption band at (340 nm) which is assigned to (n-π*) transition. The reaction may be following the mechanism shown in Scheme (1) [15].



Scheme [1]

The acid hydrazide (2) have been used for the preparation of 2-{4-[(7-nitro-2,1, 3-benzoxadiazol-4-yl) amino] benzoyl}-N-phenylhydrazinecarbothioamide (3).which is after cyclized to the corresponding triazole (4) (see Scheme (3)).

The compound (3) has been synthesized via the condensation of their corresponding with phenylisothiocyanate in refluxing ethanol for 4 hrs. The mechanism of the reaction may be depicted as follows [16] :-

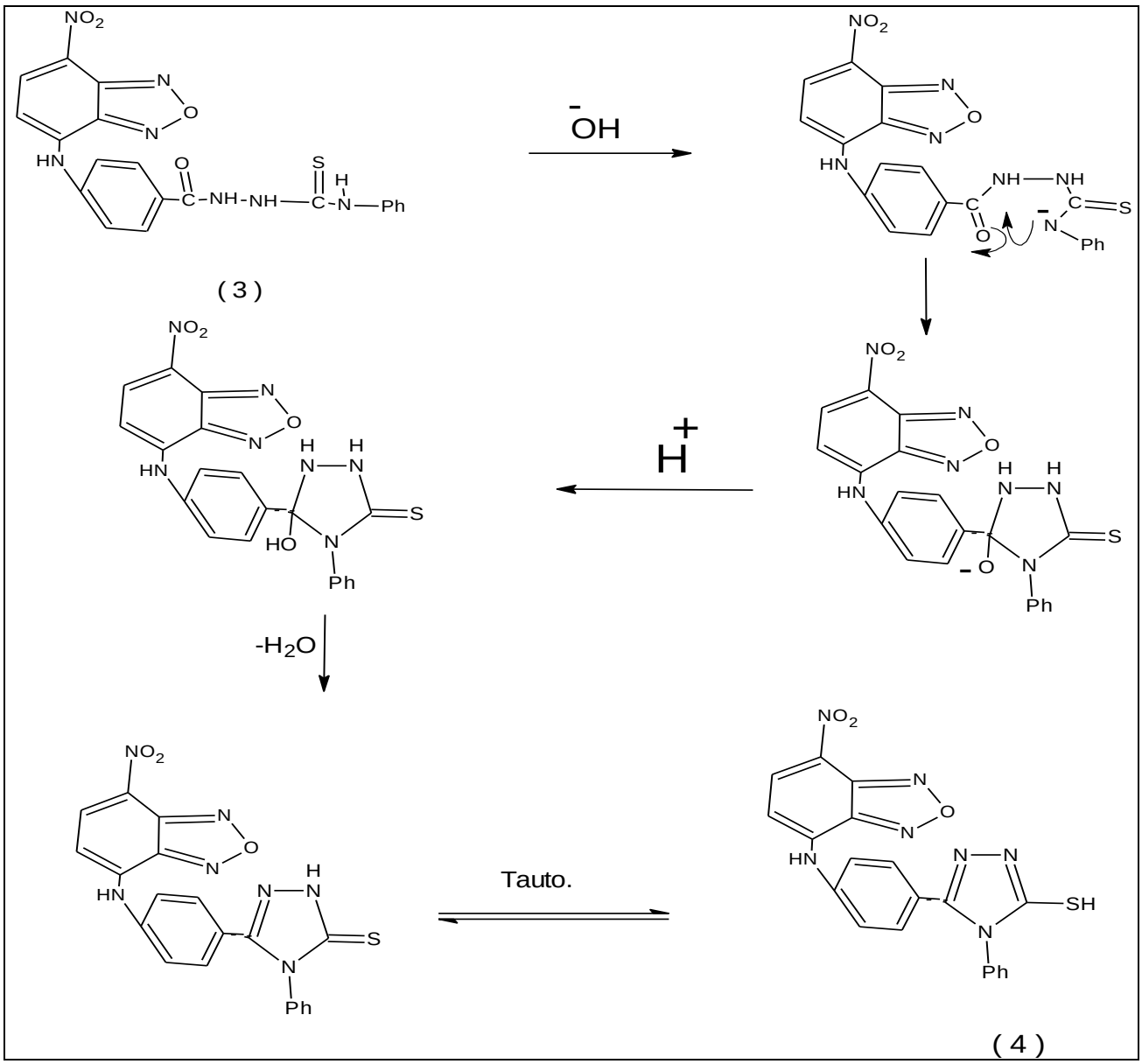


Scheme [2]

The structure of the compound (3) has been established on the basis of their FT.IR and U.V spectral data (Table (3)). The spectra of FTIR shows absorption bands at (3260cm^{-1}) which is assigned to the (N-H) stretching vibration, (1220cm^{-1}) and (2520cm^{-1}) are refered to the (C=S),(S-H) groups respectively. The structure of the compound [3] has been assigned by the U.V spectra Table (3).

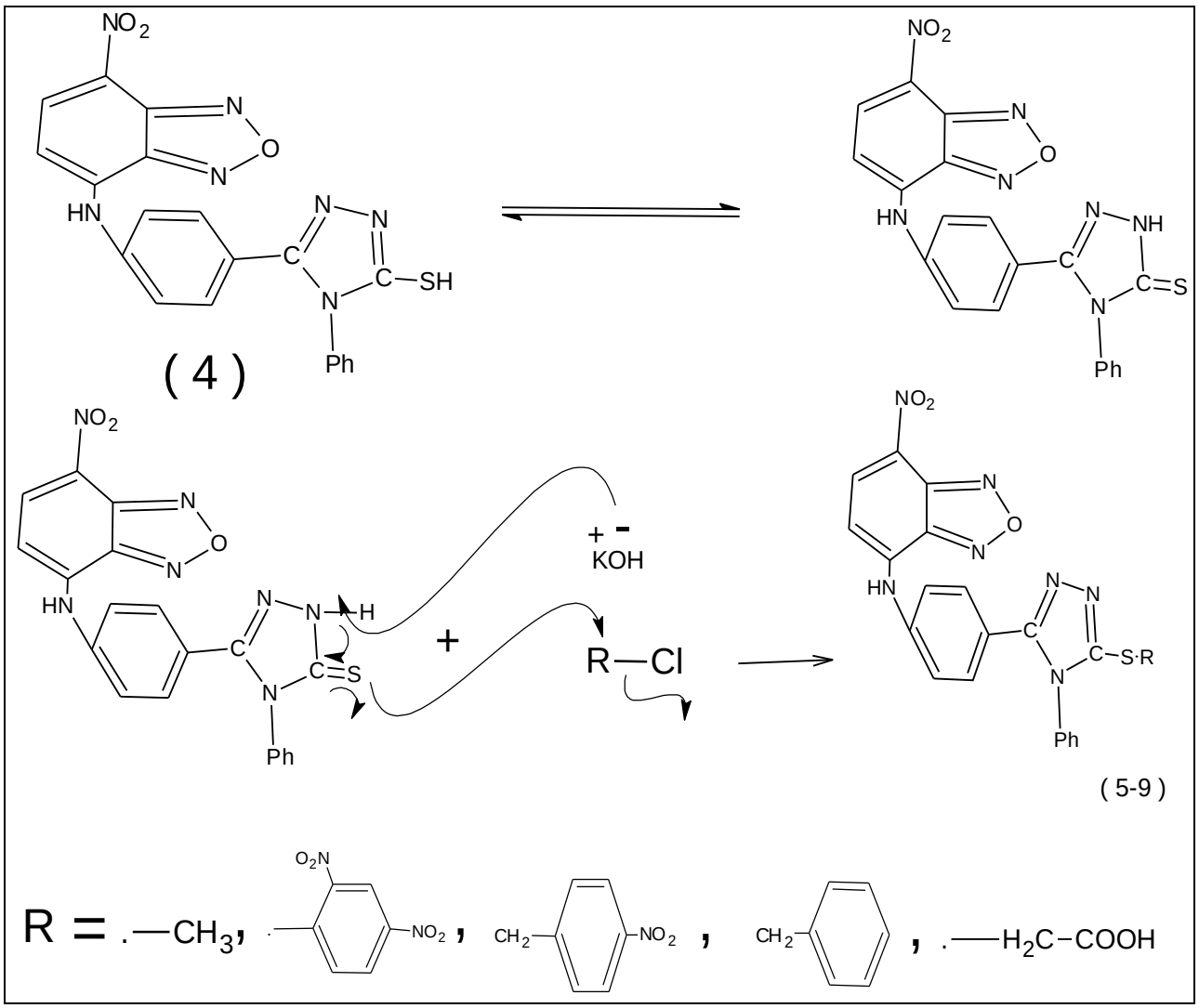
Treatment of the compound (3) with 5% aqueous sodium hydroxide under reflux afforded the traizole compound [4].

The FT-IR spectra of compound (4) discloses the presence bands at 2600, 1190 and 1575cm^{-1} being to υ_{S-H}, $\upsilon_{c=s}$, and υ_{NHph} groups respectively. Forthemore, a band at 1670 was disappearance that attributed to $\upsilon_{C=O}$. The structure of the compound [4] has been also assigned by the U.V spectra Table (3). The mechanism is shown in Scheme (3) below [17].



Scheme [3]

The synthesis of these derivatives (5-9) has been accomplished by condensation the triazole (4) with alkyl \ aryl halide in the presence of potassium hydroxide in ethanol. The mechanism of the reaction outlined as follow:-

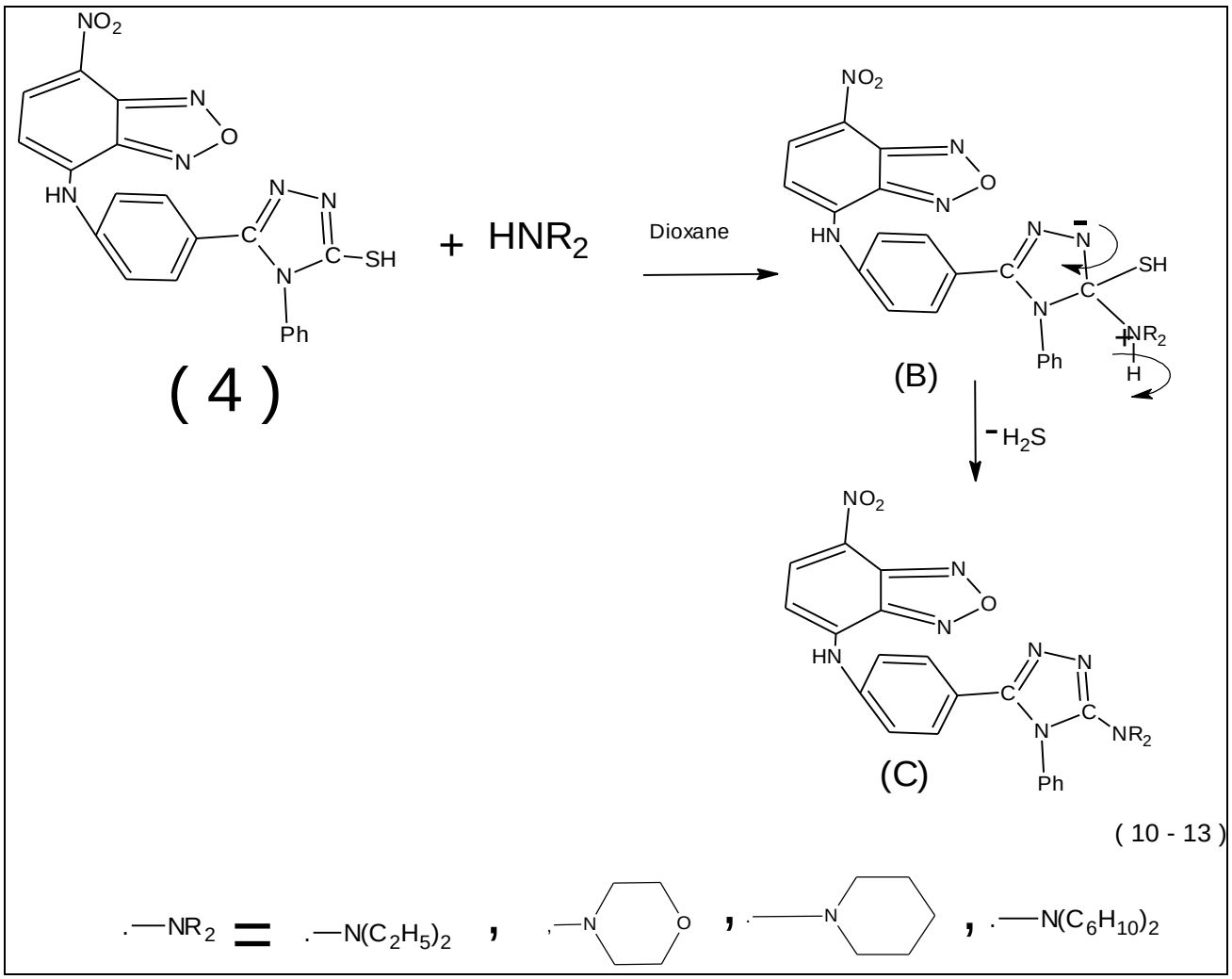


Scheme [4]

The reaction proceed by a nucleophilic attack of sulfur of atom on the carbon atom of alkyl \ aryl halide.

The structure of these compounds (5-9) have been confirmed of the basis of their U.V and FT-IR spectral (Table (3)) .The FT-IR of these compounds show the (SH) and (C=S) bands which appear at 2600 cm^{-1}, 1190 cm^{-1} which identifying the starting material is completely absent. The U.V absorption spectra of these compound are showed in Table (3). Fig.(3) shows the FT-IR of compound (8)

In this work, compound (4) has been used for the synthesis of new substituted 1,3,4 triazles (10-13). The synthesis of thess derivatives has been achieved via the reaction of the corresponding triazole (4) with appropriate secondary amine in refluxing dry dioxane as solvent for four hours, the suggested mechanism of nucleophilic substitution of the thiol group may be visualized as follows [18]:-



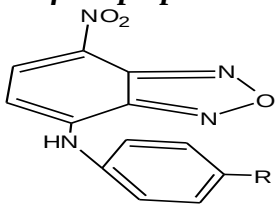
Scheme [5]

The reaction is initiated by nucleophilic addition of the amine group to from the intermediate (B) which eliminates the better leaving group (-SH) to give the corresponding triazole derivative (c).

The physical properties of compounds (10-13) are listed in Table (1), Micro analysis of (C.H.N.) element of the compound [9] has been in agreement with the calculated value.

The structure of compounds (10-13) have been characterized and identified on the basis of their UV, FT-IR spectral. IR spectra shows the disappearance of the band characterzing $\upsilon_{C=S}$, υ_{S-H} in the expected region (1190, 2600) cm^{-1}. Figure [4] shows the FT-IR of compound (13).

Table (1)
Physical properties of the prepared compounds (1-13).



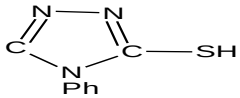
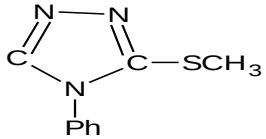
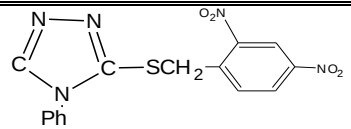
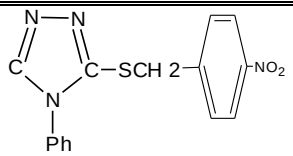
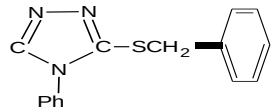
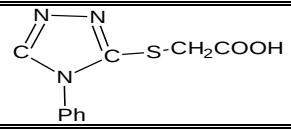
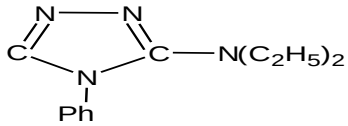
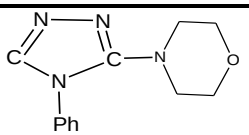
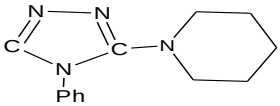
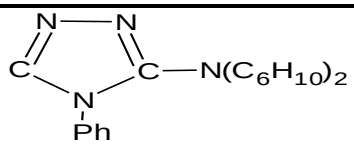
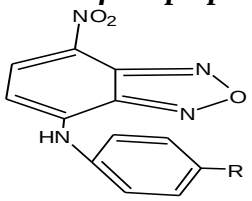
Com. NO.	*-R*	*Melting point C^o*	*Color*	*Yeild %*	*Re- Crystallization Solvent*	*M.Formala (M.Wt)*
1	$COOC_2H_5$	200-203	brown	60	EtOH	$C_{15}H_{12}N_4O_5$ (328)
2	$CONHNH_2$	190-192	yellow	70	EtOH	$C_{13}H_{10}N_6O_4$ (314)
3	CONHNHCSNHpH	222-219	yellow	60	EtOH	$C_{20}H_{15}N_7O_4S$ (449)
4		193-190	dark yellow	60	EtOH	$C_{20}H_{13}N_7O_3S$ (431)
5		227-226	yellow	63	EtOH	$C_{21}H_{15}N_7O_3S$ (445)
6		199-197	yellow	55	EtOH	$C_{26}H_{15}N_9O_7S$ (597)
7		203-205	yellow	70	EtOH	$C_{27}H_{18}N_8O_5S$ (566)
8		212-210	yellow	70	EtOH	$C_{27}H_{19}N_7O_3S$ (521)
9		192-190	yellow	70	EtOH	$C_{22}H_{15}N_7O_5S$ (489)
10		163-165	yellow	40	EtOH	$C_{24}H_{22}N_8O_3$ (470)
11		172-173	orange	35	EtOH	$C_{25}H_{17}N_8O_3$ (477)
12		295-293	brown	38	EtOH	$C_{25}H_{17}N_8O_3$ (477)
13		240-238	brown	40	EtOH	$C_{32}H_{32}N_8O_3$ (576)

Table (2)
C.H.N Analysis for some prepare compounds.

Comp No.	*M.Formala (M.Wt)*	*%*	*C*	*H%*		*N%*	
		Cal	Fou.	Ca	Fo.	Cal	Fo
1	$C_{15}H_{12}N_4O_5$ (328)	54.87	55.12	3.65	4.08	17.07	17.37
2	$C_{13}H_{10}N_6O_4$ (314)	49.68	50.22	3.18	3.99	26.75	26.98
4	$C_{20}H_{13}N_7O_3S$ (431)	.6855	55.98	3.01	3.88	22.73	22.99
9	$C_{22}H_{15}N_7O_5S$ (489)	53.98	54.18	3.06	3.88	20.04	20.30

Table (3)
IR and Visible spectral data of the prepared compounds(1-13).



Com No.	*λ_{max} Ethanol (95%)*10^{-4} (nm)*	*υ C-H arom. cm^{-1}*	*υ C =C cm^{-1}*	*υ C=N cm^{-1}*	*υ N-O cm^{-1}*	*υ C -NO2 cm^{-1}*	*υ Others cm^{-1}*
1	337,261,216	3097	1522	1630	1314	1550,1387	υ NH(3210)· υ C-N(1230)υ c=o(1733), υc-o(1360) C-H alph (2870,2996)
2	375,340,281.223	3100	1530	1625	1325	1550,1380	υ NH (3424-3200), υ c=o (1660)
3	338.,292,228	3095	1526	1632	1330	1550,1370	υ NH (3260), υ, C=O(1670) υ C=S (1220), υ SH (2520)
4	340,280,255,	3100	1532	1629	1315	1550,1380	υ NH (3210) , υ C-s(610), υ C=S(1190) υ SH (2600) ,υ N-N (1050), υ Nph(1575)
5	284,355, 246	3095	1529	1629	1325	1550,1370	υ NH (3210) υ S-CH3(1445)
6	384,364,285,241	3100	1527	1640	1334	1550,1380	υ N H (3210) , υ υc-s(760) υ C-NO2 (1340,155O)
7	336,306,282,244	3100	1529	1635	1330	1550,1370	υ NH (3210) , υ C-S(730)
8	305,250,3 32	3098	1530	1635	1330	1550,1380	υ NH (3220), υ c-s(755) , υ C-H alph(2850,2990)
9	306253,244,	3100	1529	1640	1330	1550,1370	υ NH (3220) , υ c-s(760) ,υ OH(3300) υ C=N interference with υCO
10	256218,284,	3098	1530	1620	1315	1550,1370	υ NH (3230), υ C- N (1120), υ C-H alph (2850,2990)
11	386,302.250,	3100	1529	1625	1330	1550,1380	υ NH (3250) , υ C- N (1220), υ C-o(1240)
12	340, ,282,240	3098	1532	1640	1325	1550,1370	υ NH (3270) , υ C- N (1220)
13	,293,258348	3100	1529	1625	1330	1550,1380	υ NH (3310), υ C- N (1200), υ C-H (2850 ,2900)

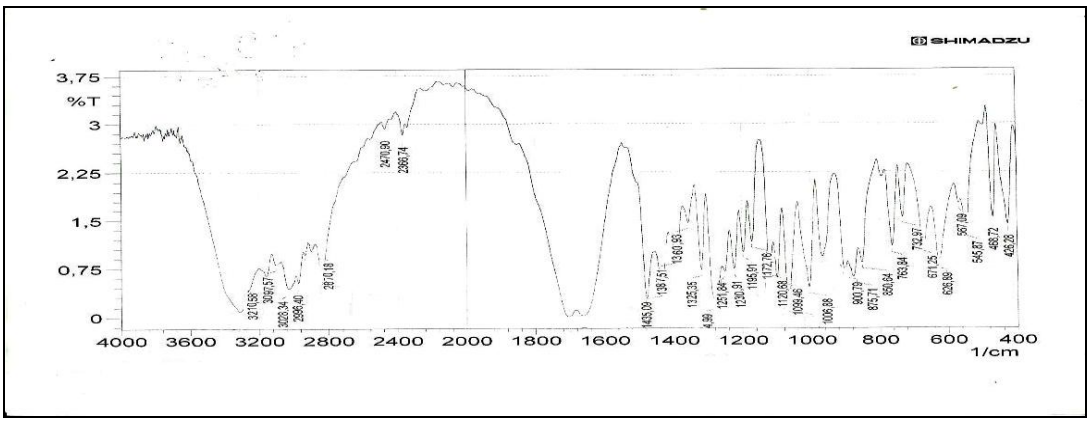


Fig.(1) The FT-IR spectrum of compound (1) in KBr disk.

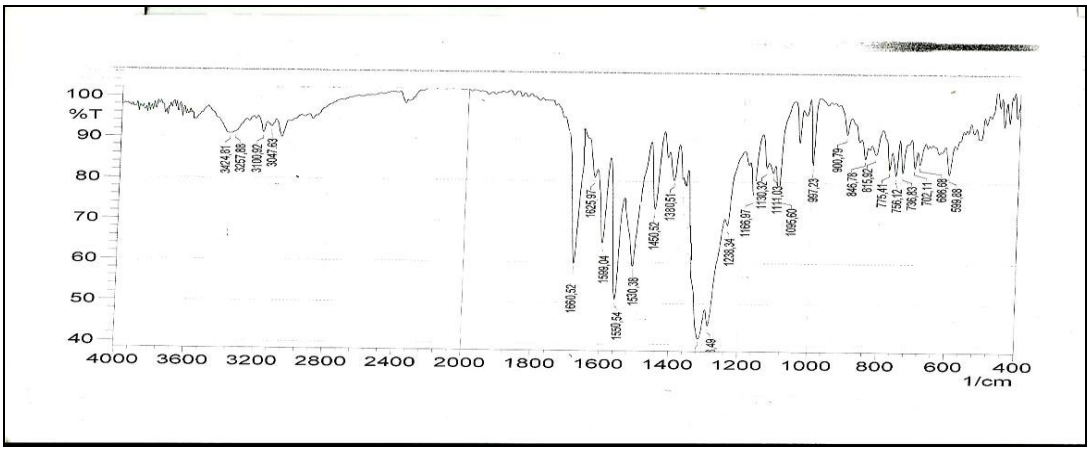


Fig.(2) The FT-IR spectrum of compound (2) in KBr disk.

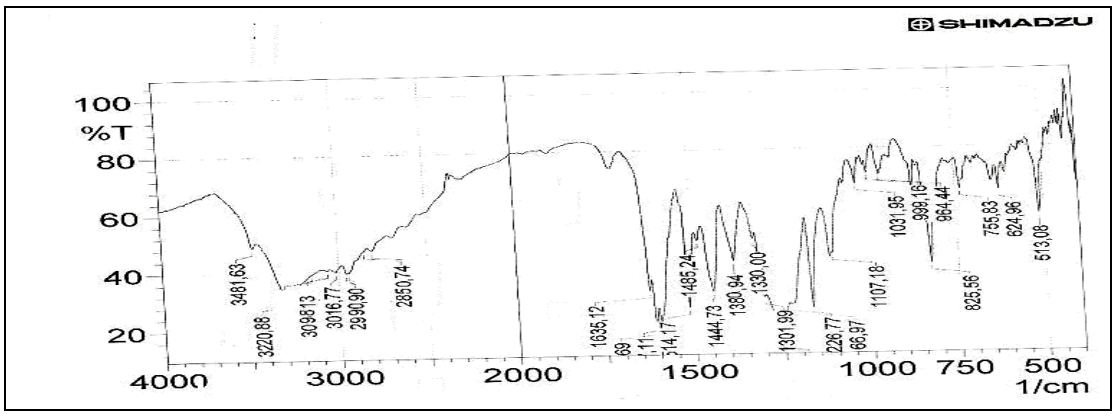


Fig.(3) The FT-IR spectrum of compound (8) in KBr disk.

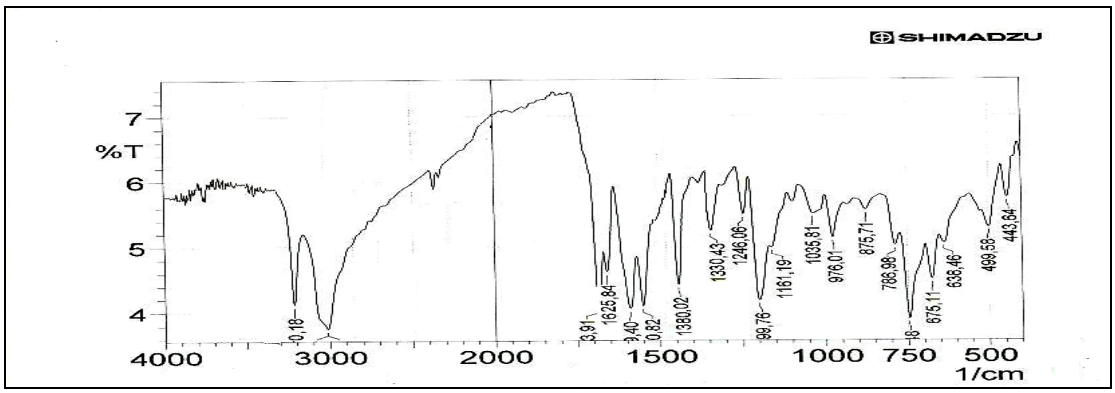


Fig.(4) The FT-IR spectrum of compound (13) in KBr disk.

References

[1] M. S. Yar, A.A. Siddiqui and M.A. Ali" Synthesis and Anti Tuberculostatic Activity of Novel 1,3,4,-Oxadiazole derivatives", J. Chinese, Chem,Soc, 54, 2007, 5-8.

[2] B,G.Mohamed, A. A.Abdel-Alim and M. A.Hussein "Synthesis of 1-acyl -2-alkylthio -1,2,4- triazolobenzimidazoles with antifungal, anti-inflammatory and analgesic effect " , Acta Pharm, 56, 2006, 31- 48.

[3] Y. Liu, J. Liu, "Stereo selective synthesis and fungicidal activities of (E)-A a (methoxyimino) - benzeneacetate derivatives containing 1,3,4- oxadiazole ring", Bio &Med Chem, 16 , 2006 ,8.

[4] M. S. Pinglea, S. P. Vartale, V.N. Bhosale and Sh. V. Kuberka, "A convenient synthesis of 3- cyano- 4-imino- methylthio - 4Hpyrimido[2,1-b] [1,3] benzo- oxazole and its reactions with selected nucleophiles", ARKIVOC (x), 2006, 190-198.

[5] N. C._Kun_, F. T. Tat, "Synthesis and Reactivity of Tetrahydroimidazo [1,5-b][1,2,4] oxadiazol-2(1H)- thiones, "Turk. J.chem, 28, 7, (2004).

[6] H. W. Peter, F. Asobo, R.A. Cherkasov, Z. T. Fomum, and D. Doepp, "Heterocycles of biological importance: Part 8.1 Formation of pyrimido [1,2-a] benzimidazoles and oxazolo [3,2-a] benzimidazoles by conjugate addition of 2- aminobenzimidazoles to 4-hydroxy-2-alkynenitriles " ARKIVOC, (i),2004 130-137.

[7] J.C, Jochims, In "Comprehensive Heterocyclic Chemistry, in Katritzky A.R.; Rees, C.W.Scriven, E.F.D., Eds.; Elsevier Oxford, Science: 1996,4, pp. 179-228.

[8] M. A. Shaban, A. Z. Naser, S . M. El-badry "synthesis and biological activites of some - 1,3,4-oxadiazoles and Bis (1,3,4- oxadiazoles)" J. of Islamic aAcademy of Sciences ,4,3, 1991,184-191.

[9] Najer H, Giudicelli R, Moral C, Menin M : Synthesis of some 5- aryl-2-dimethylamino- 1,3,4- oxadiazoles with anti -inflammatory action. Bull. Soc. Chem. France 1966, 153-159.

[10] Kennedy D.A, Summers L.A "Chemical constitution and activity of Herbicides. Part XIV. Reduction potential and herbicidal activity of 4,4-(1,3,4-thiadiazole- 2,5- diyl)- and 4,4-(1,3,4-oxadiazole- 2,5- diyl) bis (1-methylpyridinium) diiodides" J. Hetrocyc. Chem., 1981 ,409-410 ,

[11] Hemming, K. "Recent developments in the synthesis, chemistry and applications of the fullyunsaturated 1,2,4-oxadiazoles", J.Chem. Res. 2001, 209-216.

[12] Ricardo A.W., Neves Filho and Rajendra M. Srivastava A .Handy and Solventless" Direct Route to Primary 3-[3-Aryl)-1,2,4-oxadiazol- 5- yl] propionamides Using Microwave Irradiation "Molecules, 11,2006, 318-324

[13] Adel M. Awadallah," Reaction of aryl – and hetro aryl benzoyl and acetyl hydrazones with phenylisocyanat synthesis of substituted-2,3- dihydro -1,3,4-oxadiazole". The Islamic University Journal (Series of Natural Studies and Engineering) 14,1, 2006, 129-133 ISSN 1726-6807.

[14] Mohammed A. E., Shaban Adel Z. Nasr, Susan M. "Synthesis and biological activitives of some 1,3,4- oxadiazole and Bis (1,3,4- oxadiazole)", Journal of Islamic Academy of Sciences, 4 ,3,1991, 184-191

[15] N. Mohammed. "Synthesis and spectroscopic study for some new phenol bar bital derivatives and expected Biological activity "Ph.D, thesis, Al-Mustansiria univ., (2004).

[16] P. Sykes, "'A Guide Book to Mechanism in Organic Chemistry" 3rd .Ed., Longmans, London, (1970).

[17] J.Henichart, R,Houssin, and B.Lablanche, J.Heterocyclic. Chem.,14,615-619, (1977). From Mohamed R.' preparation of hetrocyclic compounds derive from Benzo [b] Thiophen' thesis, Al-Mustansiria univ., (2001).

[18] J.Sanstrum, Acta. Chem. Scand., 15 1961, 1300 from 'Wafaa F.; Synthesis and reaction study of hetro cyclic compounds derivative From 1,2,4-Triazine[5,6-b] indol -3-thione' thesis, Al- Mustansiria univ., (2002).

الخلاصة

صعد المركب 4- كلورو- 7-نايترو - 3,1,2 - بنزاوكسادايازول مع بارا امينو اثيل بنزوات عند درجة 78 م لمدة 12 ساعة يودي الى تكوين اثيل- 4-[(7-نايترو-2و1و3-بنزاوكسادايازول) يل) امينو]بنزوات (1) وبناتج % 60.

عند معاملة المركب (1) مع الهيدرازين المائي اعطي مشتق الهيدرازايد (2) الذي عومل مع فنيل ايزوثايوسيانات ادى الى تكوين مشتق الثايوسميكاربازايد (3) وعند معاملته مع قاعدة ااعطي مركب الترايازول(4) . فوعل المركب (4)مع هاليدات الالكيل والاريل تارة ومع الامينات الثانوية تارة اخرى فاعطي علي التوالي مشتقات الثايو (الكيل ، اريل) و مشتقات جديدة من الترايازول.

شخصت المركبات المحضرة باستخدام بعض الطرق الطيفية (FT.IR .UV) والتحليل الدقيق للعناصر لبعض منها.