Preparation and characterization of some new heterocyclic compounds with evaluating of its biological activity

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Abstract

A series of compounds of *p*-Nitro ethyl benzoate [2],*p*-Nitro benzoic hydrazide [3], 1-phenyl-4-(*p*-nitrophenyl) thiosemicarbazide [4], 3-mercapto-4-phenyl-5- (*p*-nitro phenyl)-1,2,4- Triazole[5], *3-hydrazino* -4-phenyl-5- (*p*-nitro phenyl)-1,2,4- Triazole [6], 3-(substituted benzylidene hydrazine)-4-phenyl-5- (*p*-nitro phenyl-2-yl)-1,2,4-triazole [7] and [8], 2-(substituted aryl)-3-(*p*-nitrophenyl)-2-yl)-2,3-dihydro-1,3-oxazpine-4,7-dione.[9] and [10], 2-(substituted aryl)-3-(*p*-nitrophenyl)-2-yl-2,3-benzo-1,3-oxazpine-4,7-dione [11] and [12], 2-(substituted aryl) –tetrazolo-1-yl)-[(3-hydrazino-4-phenyl)- 5-*p*-nitrophenyl)1,2,4-triazole] [9], 2-substituted aryl-3˜-[3-hydrazino—4-phenyl-5-(*p*-nitrophenyl)1,2,4-triazole]-2-yl-thiazolidin-4-one [15] and [16]. 2-(substituted aryl) –3\-[3-hydrazino—4-phenyl-5-(*p*-nitrophenyl)1,2,4-triazole]-2-yl-imidazolidin-4-one [17]and [18] were prepared and the chemical structures of these compounds were characterized by FT-IR , ^{1}H-NMR for some of them Uv/vis spectra , C.H.N analysis), melting points and the purity was checked. Biological activity of these compounds was evaluated.

تحضير وتشخيص بعض المركبات غير المتجانسة الجديدة وتقييم فعاليتها الحيوية.

وسام خليفة جاسم

قسم الكيمياء ,كلية التربية –ابن الهيثم ,جامعة بغداد –بغداد/ العراق.

الخلاصة

تضمن هذا البحث تحضير سلسلة جديدة من المركبات تشمل بارا نايترو اثيل بنزويت (2)/بارا نايترو بنزويك هيدرازايد (3)/ 1 فنيل-4-بارا نايترو فنيل ثايوسيميكاربازايد(4) /3-مركبتو-4-فنيل-5-بارا نايترو فنيل-1,2,4-ترايزول (5)/ 3-هيدرازينو-4-فنيل -5-بارا نايترو-1,2,4- ترايزول (6)/ 3- بنزليدين معوض هيدرازين-4-فنيل 5-بارا نايترو فنيل -2-يل-1,2,4-ترايزول (7) / و(8)/ 2- اريل معوض -3-بارا نايتروفنيل -2-يل2,3- ثنائي هيدرو-1,3-اوكسازبين-4,7-ثنائي اون (9) و(10) / 2-اريل معوض -3-بارانايتروفنيل -2-يل -2,3-بنزو -1,3-اوكسازبين-4,7-ثنائي اون (11)و(12) / 2-اريل معوض –تترازولو-1-يل-3-هيدرازينو-4-فنيل -5-بارانايتروفنيل -1,2,4-ترايزول)13)و(14) / 2-اريل معوض -3/- 3-هيدرازينو-4-فنيل -5-بارانايتروفنيل -1,2,4-ترايزول -2-يل ثايازوليدين-4-اون (15)و(16) / 2- اريل معوض -3/- 3- هيدرازينو-4-فنيل-5-بارانايتروفنيل-1,2,4-ترايزول-2-يل-اميدازوليدين (17) و (18) على التوالي . تم تشخيص المركبات المحضرة عن طريق اطياف الاشعة تحت الحمراء , فوق البنفسجية ,الرنين النووي المغناطيسي بالاضافة الى تحليل العناصر الدقيق ودرجات الانصهار وتحديد نقاوة المركبات كما تم تقييم الفعالية الحيوية لها.

Introduction

Triazoles and thiadiazoles and their derivatives countries an important class of organic compounds with divers agricultural, industrial and biological activities including anti-microbial, sedative, anti-convulsant-inflammatory[1-4].

The synthesis of these heterocylces has received considerable attention in recent years, The 2-ary1-5-(substituted methly1)-1,3,4- oxadiazoles have been reported to show antibacterial, antifungal analagic- anti-inflammatory, and hypoglycemic activity[4]. Their synthetic has also been demonstrated. The 2-azidomethly1-5 (4-chorophenly1-)-1,3,4- oxadizole, as 1,3- dipole, added efficiently nobornene found to be a good nitrone precursor[5-7].

1,3,4-Oxadiazole is the most thermally stable isomer which has attracted special attention, this is primarily due to the large number of uses in many diverse areas, including drugs, scintillation materials, dyes[8] and surface active agents [9]. Further, it was suggested that (-SH) group attached to a heterocyclic nucleus may include fungicidal activity [10].

Instruments

1- Melting points were measured using hot stage ***Gallen Kamp*** melting point apparatus and were uncorrected.

2- The F.T.IR spectra in the range (4000-400) cm^{-1} were recorded using KBr disk on a ***SHIMADZU*** F.T.IR 8300 spectrophotometer Japan.

3- Uv/vis spectra were recorded on Uv-Cary-100 spectrophoto-meters in (ISSC).

4-^{1}H-NMR spectra were recorded a BRUKER-400 MHz operating with tetra methyl silane as internal standard in $CDCl_3$ and DMSO-d_6 as a solvent, measurements were made at Chemistry Department, AL-Baath University-Syria.

5-Elemental Analysis (C.H.N) was carried out with : Euroea Elemental Analyzer Italia by Chemistry Department College of Science ,Babylon University.

6- Thin Layer Chromatography (TLC) was carried out using Fertigfollen precoated sheets type PolyGram silg, and the plates were developed with iodine vapor.

7- The biological activity was performed by biology department/ college of Science ,Tikrit University.

Methods

1-Synthesis of *p*-Nitro ethyl benzoate [2] *(11).*

The compound [2] was prepared as described previously [(11).] , compound [3] was prepared as in refernce [(12)] and compound [4] was prepared as in reference[(13)]

2-Synthesis of 3-mercapto-4-phenyl-5- (*p*-nitro phenyl)-1,2,4- Triazole[5]:

A stirring mixture of compound [4] (gm 0.01 mol) and (15 ml) of 2N sodium hydroxide solution was refluxed for 4 hours after cooling, the solution was acidified with hydrochloric acid and the precipitate was filtered, and re crystallized to give compound [5] , m.p (212-215) °C,yield (68%).

3- Synthesis of 3-hydrazino -4-phenyl-5-(*p*-nitro phenyl)-1,2,4- Triazole [6]:

Compound [5] (0.01mol) dissolved in ethanol,was added was added hydrazine hydrate (99%) (0.32 g, 0.317 ml, 0.01 mol) and the mixture was then refluxed for 6 hours, excess solvent was distilled off. The resulting solid then was separated out on cooling filtered and re crystallized from ethanol [(13)], m.p. (203-205 ^{o}C), yield (80%).

4-Synthesis of 3-(substituted benzylidene hydrazine)-4-phenyl-5- (*p*-nitro phenyl-2-yl)-1,2,4-triazole [7]and [8].

A mixture of compound [6] (0.01mol) and substituted benzaldehydes (0.01mol) was refluxed in absolute ethanol (15ml) containing few drops of glacial acetic acid for 3hrs. After cooling to room temperature the precipitate was filtered and dried. The products were re-crystallized from ethanol. Yield 80%.

Table (1): C.H.N.analysis for compounds (7,8)

Comp. No.	Molecular formula	C.H.N. analysis calc./found
7	$C_{21}H_{16}N_7O_4$	58.7/58.1 3.7/3.2 22.8/22.3
8	$C_{23}H_{21}N_7O_2$	64.6/64.4 4.9/4.6 22.9/22.7

5- Synthesis of 2-(substituted aryl)-3-(*p*-nitrophenyl)-2-yl-2,3-dihydro-1,3-oxazpine-4,7-dione.[9] and[10]:

A mixture of compound [7]or [8] (0.01 mole) of Schiff base and (0.01) mole of

maleic anhydride in (20 ml) of benzene was refluxed for (24) hours then the solvent evaporated and then the formed precipitate was re crystallized from appropriate solvents ,m.p (210,251) °C,yield (70%).

6- Synthesis of 2-(substituted aryl)-3-(*p*-nitrophenyl)-2-yl-2,3-benzo-1,3-oxazpine-4,7-dione.[11] and[12]:

A mixture of compound [7]or [8] (0.01 mol) of Schiff base and (0.01) mole of phthalic anhydride in (20 ml) of benzene was refluxed for (24) hours then the solvent evaporated and then the formed precipitate was re crystallized from appropriate solvents ,m.p (120 , 140) °C,yield (80%).

7-Synthesis of 2-(substituted aryl) –tetrazolo-1-yl-[(3-hydrazino-4-phenyl)- 5-*p*-nitrophenyl)1,2,4-triazole] [13] and [14]:

A mixture of (0.01mol) of Schiff bases [7],[8] tetrahydrofuran (THF) (15ml) and sodium azide (0.01mol) was heated on a water bath, the temperature of the water bath was controlled between (50-55)°C. The end of the reaction was checked by (TLC) which showed the disappearance of the starting material.

8-Synthsis of 2-substituted aryl-3˜-[3-hydrazino-4-phenyl-5-(*p*-nitrophenyl)1,2,4-triazole]-2-yl-thiazolidin-4-one [15] and [16]:

A (0.01) mole of 2- mercptoacetic acid was added dropwise to(0.01)mole of Schiff base in(20 ml)of dry benzene ,the mixture was refluxed for (24) hours then the solvent was evaporated and then the formed precipitate was re crystallized from ethylacetate and benzene, m.p (120,148) °C respectively ,yield (75%).

9-Synthesis of 2-(substituted aryl) –3\-[3-hydrazino—4-phenyl-5-(*p*-nitrophenyl)1,2,4-triazole]-2-yl-imidazolidin-4-one [17]and [18]:

A mixture of Schiff base (0.01mole) and glycine (0.01mole) in (20 ml) of THF was refluxed for (24) hours then it cold to room temperature and the formed precipitate was filtered and re crystallized from ethanol , m.p (219,156) °C,yield (75%).

Results and discussion

The FT-IR spectrum of the hydrazide showed disappearance of (C=O) stretching band which attributed to ester group at 1728 cm^{-1} with the appearance of bands at 1645 cm^{-1}due to carbonyl group of amide. Besides, the appearance of bands of $NHNH_2$ group at 3430 cm^{-1}. The triazole [5] was characterized using FT-IR spectrum which showed the disappearance of band of carbonyl at the region (1674-1650) cm^{-1}due to amide I and the appearance of bands in the region (1643-1612) cm^{-1} due to stretching vibration of (C=N) group, a band appeared in the region (2534.3)cm^{-1} due to ν(C=S)) stretching vibration. The analytical

and spectral data are in accordance with the structures assigned.

Treatment of 3-mercapto- 4-phenyl-5- (*p*-nitro phenyl)-1,2,4- Triazole with hydrazine hydrate in ethanol afford the hydrazine 3-hydrazino -4-phenyl-5- (*p*-nitro phenyl)-1,2,4- Triazole [6]. The structure of the hydrazine -phenyl-5- (*p*-nitro phenyl)-1,2,4- Triazole was confirmed from its melting point and F.T.IR spectrum.

The F.T.IR spectrum of compound [6] indicates the disappearance of the thiol bond at (2534.3 cm^{-1}) and appearance of doublet bands of NH_2 group asymmetric and symmetric at (3313.5, 3201.6 and ν NH stretching band at 3128.3 cm^{-1}). ^{1}H-NMR spectrum of compound [6], shows the following characteristic chemical shift, (DMSO-d_6) ppm.

(N-H) proton absorbed at(δ 4.4), NH_2 protons absorbed at(δ 3.4), four aromatic ring protons appear at the range (δ 7.3-7.8).

The title compounds [7] and [8] were synthesized from the reaction between compound [6] and appropriate aldehydes in absolute ethanol and glacial acetic acid[14-16].

These compounds [7,8] were characterized by their melting points and FT-IR spectra table (2) and C.H.N.S. analysis.

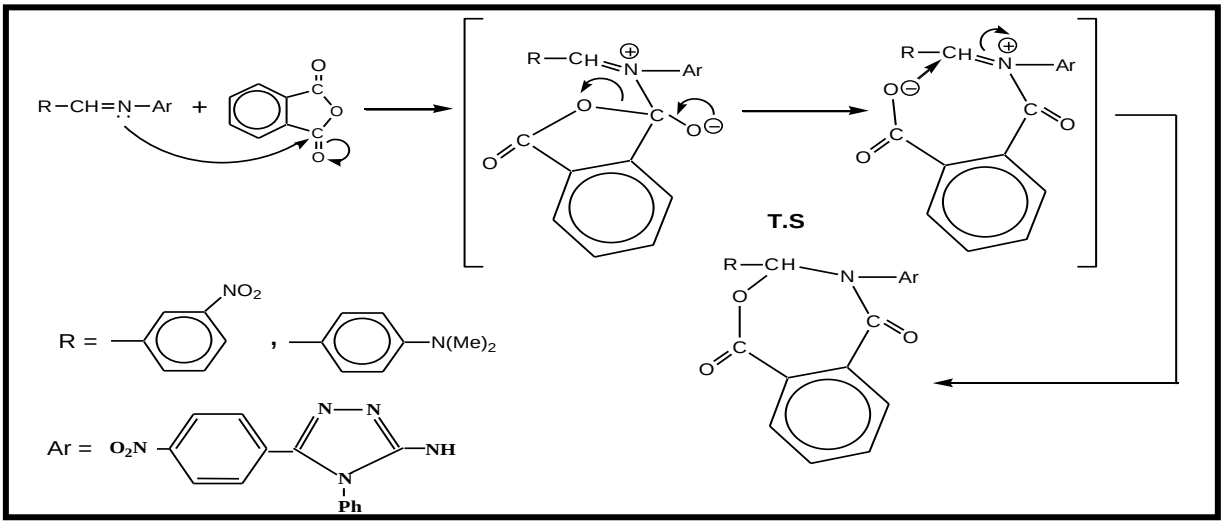
Table (2): FT-IR spectral data of compounds [7,8].

Comp. No.	***υ(N-H) cm^{-1}***	***υ(C-H) Aliphatic. cm^{-1}***	***υ(C=O) cm^{-1}***	***υ(C=N) cm^{-1}exo***	***υ(C-H)ar cm^{-1}***	***Others***
7	***3320***	***2970***	***1675***	***1612***	***3089***	υ(NO_2) 1415
8	***3440***	***2920***	***1662***	***1660***	***3082***	***$N(CH_3)_2$*** υ(N-Me) 1373

The compounds [1,3]oxazepine-4,7-dione [9-12] were synthesized from the reaction of compounds [7]or[8] with maleic or phthalic anhydride in dry benzene[17,18].

These compounds were characterized by their melting points, colours, FT-IR table (3), and they checked by T.L.C .

The suggested mechanism[19] of the reaction is shown in scheme(below):



Scheme , Mechanism steps for the prepared compounds [9-12].

The FT-IR spectrum of compound [11] as example was confirmed from the appearance of carbonyl group band at (1720 cm^{-1}) and (C-H) aliphatic band at (2924-2854 cm^{-1}), besides the (C=N) band of thiadiazole ring at (1610cm^{-1}) and bands at (1239 and 1118 cm^{-1}) belong to the asymmetric and symmetric (C-O-C) band,]. All the spectral data for other compounds are listed in table (3).

Table (3): FT-IR spectral data for (9,10,11,12) compounds.

Comp. No.	***υ(N-H) cm^{-1}***	***υ(C-H) Aliphatic. cm^{-1}***	***υ(C=O)cm^{-1} Lactone***	***υ(C=N) cm^{-1} triazole***	***υ(C=C) cm^{-1} Ar***	***Others***
9	***3320***	***2950***	***1675***	***1650***	***1600***	***NO_2***1315- 1438 υ(C-N) 1192 υ(C-O) 1222
10	***3440***	***2989***	***1660***	***1620.09***	***1510***	***$N(CH_3)_2$***1327 υ(C-N) 1168 υ(C-O) 1239-
11	***3420***	2924,2854	***1720,1633***	***1612***	1563,1433	-
12	***3320***	***2920,2858***	1720,1630	***1620***	1560,1450	-

Thiazolidinones play a vital role due to their wide range of biological activity and industrial importance as stabilizer for polymeric material[20].

Table (4): FT-IR spectral data for (15,16) compounds

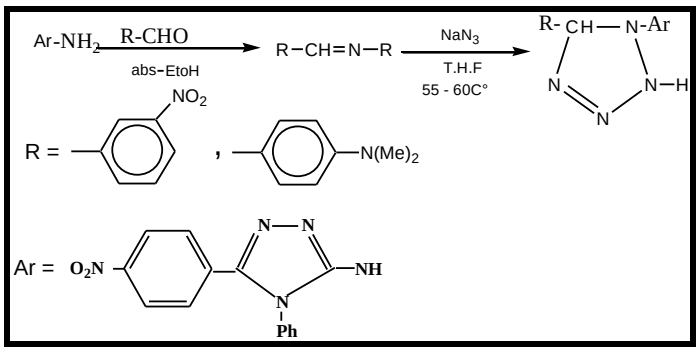
Comp. No.	*υ(N-H) cm^{-1}*	*υ(C-H) Aliphatic. cm^{-1}*	*υ(C=O) cm^{-1}*	*υ(C=N) cm^{-1}*	*υ(C=C) cm^{-1}*	*Others*
15	***3320***	***2950***	***1675***	***1650***	***1600***	***$NO_2$1330-1415***
16	***3440***	***2989.46***	***1660***	***1620.09***	***1510***	***$N(CH_3)_2$ 1317***

Table (5): Physical properties of the synthesized compounds.

Comp. No.	*Molecular formula*	*Molecular Weight*	*Yield (%)*	*M.P (^oC)*	*Colour*
1	$C_8H_8O_2$	136.15	-	77-78	White
2	$C_9H_9NO_4$	159	75	229	Pale yellow
3	$C_7H_7N_3O_3$	181	73	222-224	Pale yellow
4	$C_{14}H_{12}N_4O_3S$	316	70	160-163	Yellow
5	$C_{14}H_{10}N_4O_2S$	298	77	212-215	orange
6	$C_{14}H_{12}N_6O_2$	296	72	203-205	Red
7	$C_{21}H_{15}N_7O_4$	429	60	164-166	orange
8	$C_{23}H_{21}N_7O_2$	427	78	213-215	=
9	$C_{25}H_{17}N_7O_7$	517	70	210	=
10	$C_{27}H_{23}N_7O_5$	525	70	251	=
11	$C_{29}H_{19}N_7O_7$	567	80	120	Yellow
12	$C_{31}H_{25}N_7O_5$	575	80	140	White
13	$C_{21}H_{16}N_{10}O_4$	346	65	130	Yellow
14	$C_{23}H_{22}N_{10}O_2$	470	65	150	Orange
15	$C_{23}H_{17}N_7O_5S$	503	75	120	Pale yellow
16	$C_{25}H_{23}N_7O_3S$	501	75	148	Orange
17	$C_{23}H_{19}N_8O_5$	487	75	219	Yellow
18	$C_{25}H_{24}N_8O_3$	484	75	156	Orange

The synthesis and interesting pharmacological properties of tetrazole compounds were recently described[21]. For synthesis of the target tetrazoles, the reaction sequence outlined in the scheme below. The compound [7,8] Schiff base were heated in water bath at (55 - 60°C) with sodium azide, to give the desired product. The titled

compounds were characterized by their melting points, FT-IR table (6), or Uv/vis. spectra and checked by T.L.C.



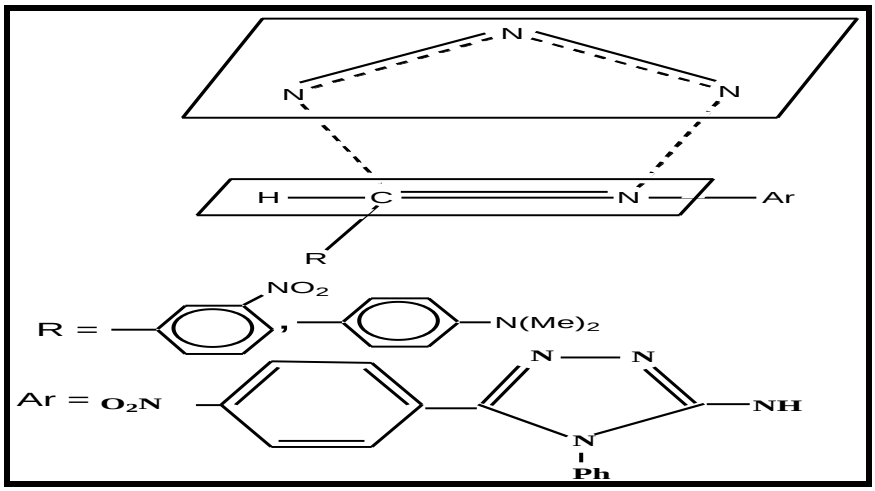
Scheme : Regents and conditions of the preparation of tetrazole.[13,14]

The mechanism of the reaction systematically investigated as [3+2] cyclo additions which christened as a 1,3-dipolar cycloadditions[22]. It involved the addition of unsaturated systems, dipolarphiles, to 1,3-dipoles, a molecule possessing resonance

cycloadditions. They are of great synthetic value and have been studied mechanistically in great detail[23].

The common features of this type of reactions is best accommodated by a T.S. contributors in which a positive and negative charge are located in 1,3-position relative to each other. The addition results in a five-member ring. Azides are a prominent class of 1,3-dipoles and azide 1,3-dipolar

geometry in which the dipolarphile and its ligands lies in one plane, and the azide lies in a parallel plane above or below, so that the orbitals perpendicular to the planes interact to form bonds, scheme below.



Scheme: Approximate transition state geometry for azide addition[13,14].

The FT-IR absorption bonds, was utilized to characterize the specific structure of the synthesized compounds. The disappearance of band at (1605-1635 cm^{-1}), attributed to (C=N) (imine group) stretching frequency is good evidence for the success of this step of reaction. It also, the IR spectra for these compounds were devoid of a strong band at (2120–2160)cm^{-1} attributed stretching frequency of a zide group. A band at (1531 cm^{-1}) was due to the cyclic (N=N) stretching of tetrazole ring[14].and a band at (3390 cm^{-1}) was due to (N-H) group. The characteristic data are reported in Table (6).

Table (6): Uv/vis and FT-IR spectral data of compounds [13,14].

Comp. No.	UV,λmax (nm),DMSO	υ(C-H) aliphatic cm^{-1}	υ(C-H) aromatic cm^{-1}	υ(C=C) cm^{-1}	υ(N=N) cm^{-1}	υ(C=N) cm^{-1}	Others Bands cm^{-1}
13	260	2920	3086	1573, 1415	1531	1605	υ(NO_2) 1354,1460 υ(N-H) 3390 υ(C-N) 1192
14	270,350	2839, 2962	3093	1597, 1465	1512	1635	4-(N-me) 1354 υ(N-H) 3390, 3278 υ(C-N) 1168

Imidazolidine derivatives prepared by the heating of Schiff bases derivatives with glycine (α-amino acetic acid) in THF the product were identified by the FT-IR spectrum which show the appearance of NH vibration in(3230-3390 cm^{-1}) and the disappearance of C=N band in 1612,or1662 cm^{-1} the product was also identified by 1H-NMR ,the duplet (7.8) ppm for aromatic protons , singlet at 2.5 ppm for cyclic proton and singlet at 6.7,6.1 ppm for NH proton of triazole and imidazole ring respectively, compound(17) .

Table (7): FT-IR spectral data for (17,18) compounds.

Comp.No.	CH_2	ν N-H imidazole	ν C= O	C=C Aromatic
17	2930-2847	3230	1710	1590-1442
18	2936-2846	3390	1709	1589-1430

Table (8) :Antimicrobial activity for some prepared compounds .

Comp. No.	***Staph. aureus***	***E. coli***	***Sal. typhi***	***Ps. aerugenosa***
5	-	±	±	-
6	-	±	±	-
7	-	+	-	±
8	+	+	+	±
9	-	±	-	-
10	+	++	-	±
11	+	+	-	+
12	+	++	±	++

13	+	+	-	++
14	+	±	-	++
15	++	±	±	++
17	-	±	-	±
18	-	+	-	+

Key the symbols :(-) = No inhibition , (±) = 6-9 mm, (++) = 15-22 mm.

Microbiological tests

In this work, the antibacterial test was performed according to the disc diffusion method. Compounds (10,12) were assayed for their antimicrobial activity in vitro against Gram-negative bacteria (*Escherichia coli*) and Gram-positive bacteria (*staphylococcus aurous*). Prepared agar and Petri dishes were sterilized by autoclaving for 15min at 121C°. DMSO was used as a solvent. These plates were incubated at 37C° for 24h for both bacteria. The inhibition zones caused by the various compounds were examined. The results of the preliminary screening tests are listed in table (8).

The biological activity test showed that compounds with free (-SH) groups and free ($-NH_2$) groups having a biological effect on each of *E.Coli* and *Staph.aureus*, these compounds are also considered biologically active on *bacteria* while when free ($-NH_2$) and (-SH) groups disappeared the existence of Pyridine lead to increase of the biological activity.

Conclusion

1. Compounds [6] showed slightly activity on Escherichia coli and sale typhi.
2. Compound [15] showed moderate activity on *Staphylococcus aureus* and ps.aerugenosa while compound [8] showed slight activity on this bacteria . Compounds [5] showed no effect on ps.aerugenosa and *Staphylococcus aureus* .
3. Compounds [6] showed slightly activity on Escherichia coli and sale typhi.
4. Compound [15] showed moderate activity on *Staphylococcus aureus* and ps.aerugenosa while compound [8] showed slight activity on this bacteria . Compounds [5] showed no effect on ps.aerugenosa and *Staphylococcus aureus*
5. Compounds [6] showed slightly activity on Escherichia coli and sale typhi.
6. Compound [15] showed moderate activity on *Staphylococcus aureus* and ps.aerugenosa while compound [8] showed slight activity on this bacteria .

Compounds [5] showed no effect on ps.aerugenosa and *Staphylococcus aureus* .

7. Compounds [6] showed slightly activity on Escherichia coli and sale typhi.
8. Compound [15] showed moderate activity on *Staphylococcus aureus* and ps.aerugenosa while compound [8] showed slight activity on this bacteria .
Compounds [5] showed no effect on ps.aerugenosa and *Staphylococcus aureus* .

9. Compounds [6] showed slightly activity on Escherichia coli and sale typhi.
10. Compound [15] showed moderate activity on *Staphylococcus aureus* and ps.aerugenosa while compound [8] showed slight activity on this bacteria .
11. Compounds [5] showed no effect on ps.a Compounds [6] showed slightly activity on Escherichia coli and sale typhi.
12. Compound [15] showed moderate activity on *Staphylococcus aureus* and ps.aerugenosa while compound [8] showed slight activity on this bacteria .
Compounds [5] showed no effect on ps.aerugenosa and *Staphylococcus aureus* .

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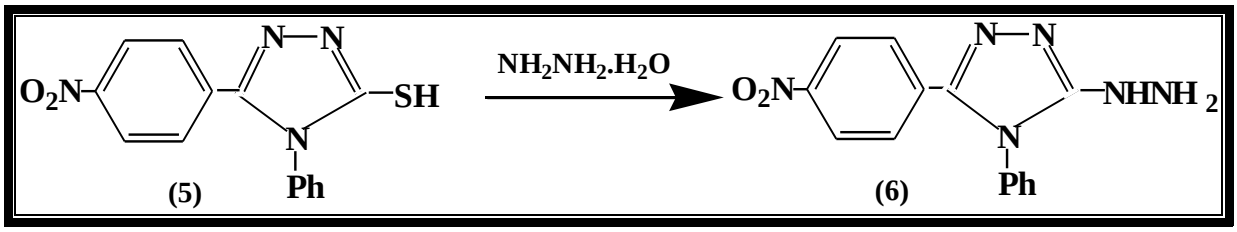
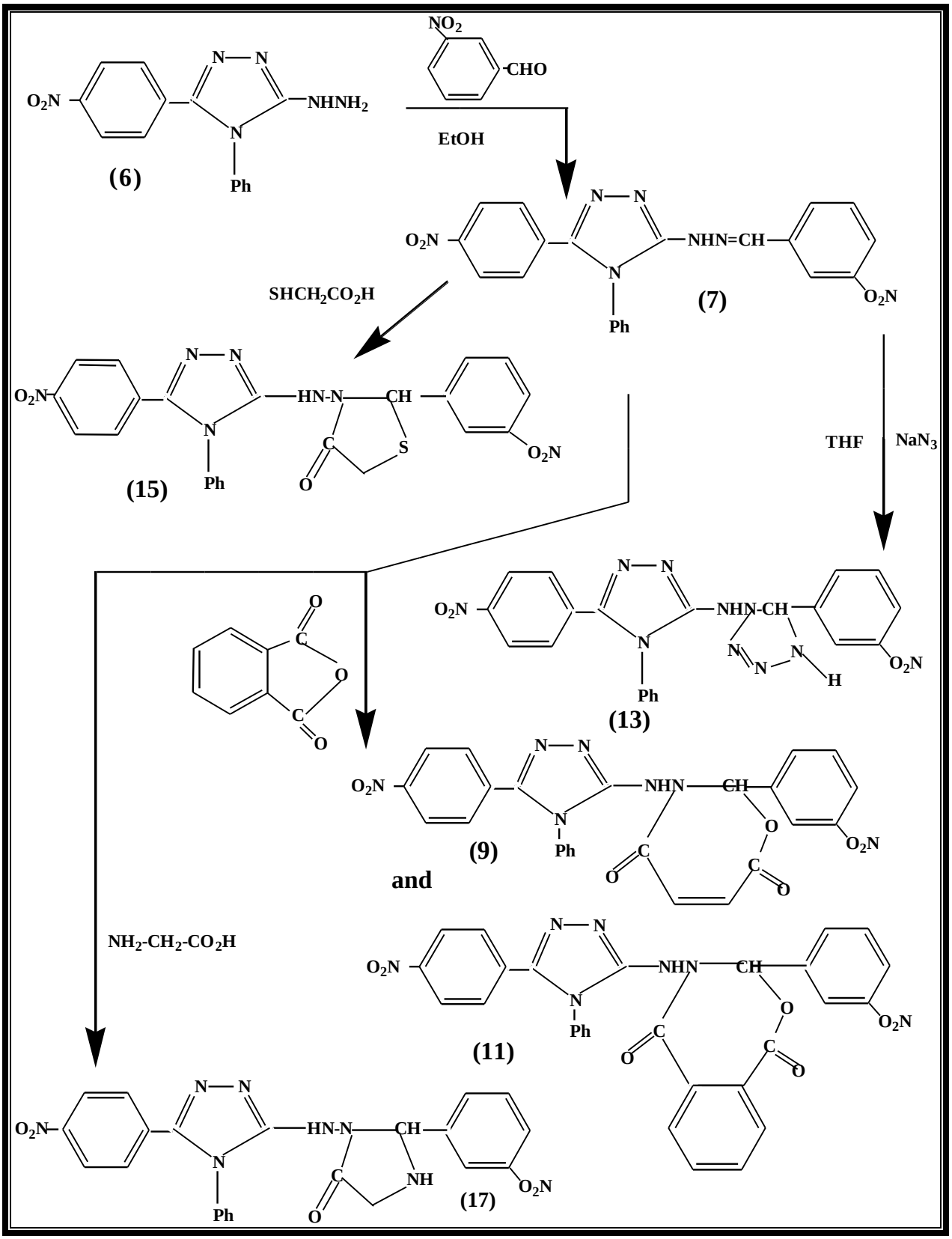
Compounds [5] showed no effect on ps.aerugenosa and *Staphylococcus aureus* .

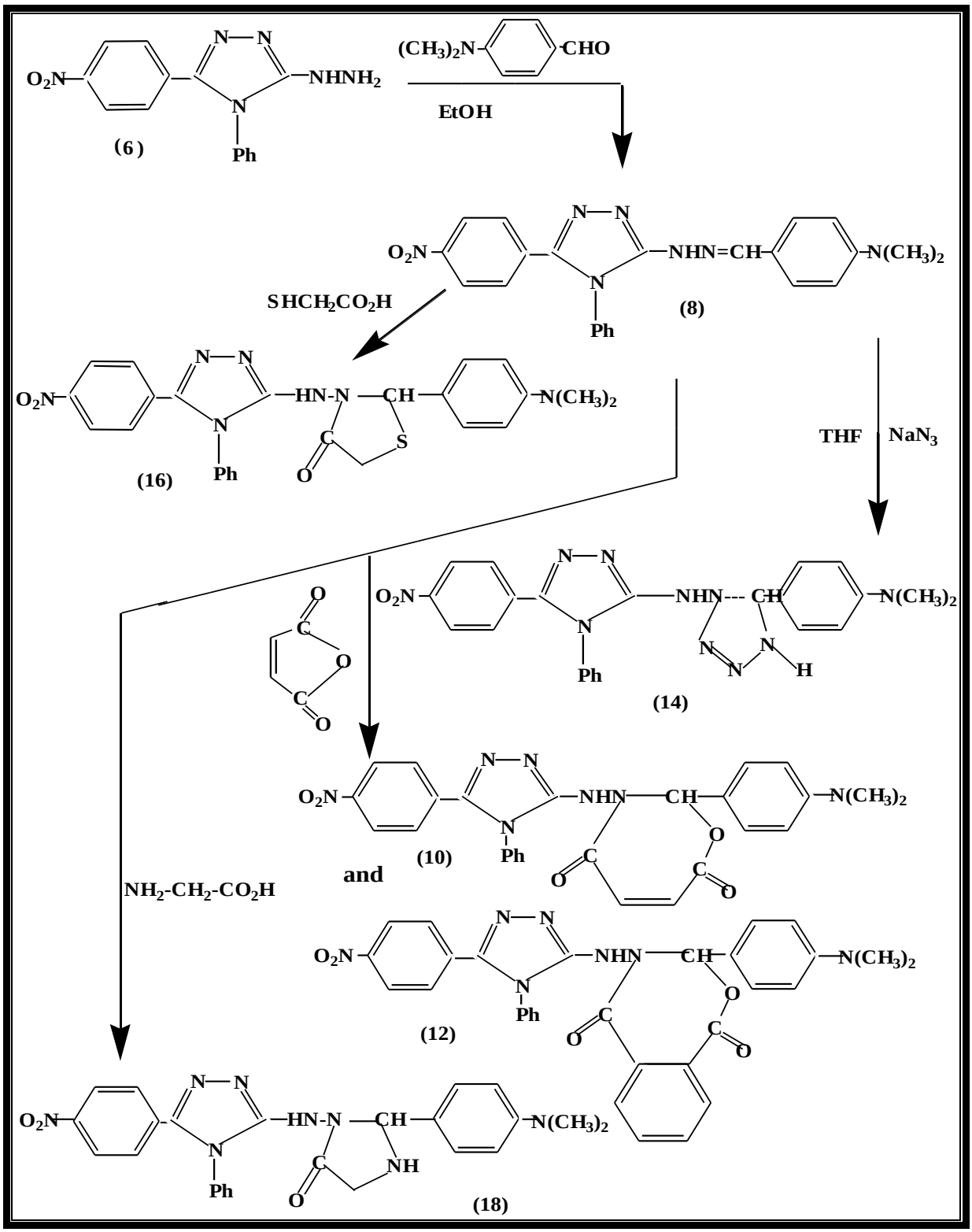
15. Compounds [6] showed slightly activity on Escherichia coli and sale typhi.
16. Compound [15] showed moderate activity on *Staphylococcus aureus* and ps.aerugenosa while compound [8] showed slight activity on this bacteria .
17. Compounds [5] showed no effect on ps.aerugenosa and *Staphylococcus aureus* .



Scheme 1.


NO2
CHO
EtOH
O2N
NHNH2
(6)
Ph
NHN=CH
(7)
SHCH2CO2H
HN-N
CH
S
O
(15)
THF
NaN3
NHN-CH
H
(13)
NHN
(9)
and
NH2-CH2-CO2H
(11)
NH
(17)

Scheme 2



Scheme 3

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