Synthesis of Some 1,4-Bis (Substituted 1,3,4-Oxadiazoles and 1,2,4-Triazoles) Benzene From Terephthalic Acid

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الملخص

تم في هذا البحث تحضير بعض مركبات ١,٤- بس (معوض ١,٣,٤-اوكسادايازول و ١,٢,٤-ترايازول) بنزين من حامض التيرفثاليك . تم استرة حامض التيرفثاليك بأستخدام الايثانول المطلق بوجود حامض الكبريتيك المركز الى تيرفثالات الاثيل (١) والذي تم تحويله الى هيدرازيد الحامض (٢) مع الهيدرازين المائي في الايثانول . تم مفاعلة هيدرازيد الحامض (٢) مع ايسوثايوسيانات الفنيل واعطى معوض ثايوسيمكاربازيد (٤) بينما اعطى تفاعله مع ثايوسيانات الامونيوم معوض ثايوسيمكاربازيد (٣). اعطت مفاعلة معوض ثايوسيمكاربازيد (٣) مع اوكسيد الزئبق في الميثان ول١-(٥-امينو ١,٣,٤-اوكسادايازول-٢- يل)-٤-(٢-امينو-١,٣,٤-اوكسادايازول-٥-يل) بنزين (٥). تم تحويل معوض ١,٣,٤-اوكسادايازول (٥) الى معوض ١,٢,٤-ترايازول (١١) و (٧) من خلال تفاعله مع الهيدرازين المائي في الايثانول وهيدروكسيد البوتاسيوم في الميثانول على التوالي . تم تحضير معوض ١,٢,٤-ترايازولون (٩) من معوض ١,٢,٤-ترايازول (٧) مع حامض الهيدروكلوريك كما تم تحضير معوض ١,٢,٤-ترايازولون (١٠) من معوض ثايوسيمكاربازيد (٤) ومن خلال ١,٣,٤-اوكسادايازول (٦) ومعوض ١,٢,٤-ترايازول (٨). بينما تم تحضير معوض ١,٢,٤-ترايازول (١٢) من مفاعلة معوض ١,٣,٤-اوكسادايازول مع الهيدرازين المائي في الايثانول . تم تشخيص المركبات المحضرة بأستخدام طيف IR والطرق الفيزياوية.

ABSTRACT

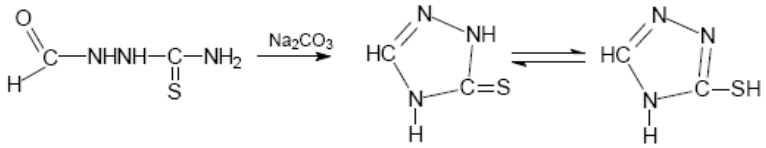
In this paper the synthesis of some 1,4-bis-(substituted1,3,4-oxadiazoles and 1,2,4-trizoles) benzene from terephthalic acid is reported. Terephthalic acid was esterified with absolute ethanol in presence of

concentrated sulfuric acid to give ethyl terephthalate (1) which was converted to acid hydrazide (2) with hydrazine hydrate in ethanol. The acid hydrazide (2) was treated with phenyl isothiocyanate to give substituted thiosemicarbazide(4), while it‘s reaction with ammonium thiocyanate gave substituted thiosemicarbazide (3). Treatment of substituted thiosemicarbazide (3) with mercury oxide in methanol gave 1-(5-amino-1,3,4-oxadiazol-2-yl)-4-(2-amino-1,3,4-oxadiazol-5-yl)benzene (5). Compound (5) was treated with hydrazine hydrate in ethanol and with potassium hydroxide in methanol to give substituted 1,2,4-trizole (11) and (7) respectively. 1,2,4-trizolone (9) was synthesized from substituted 1,2,4- triazole (7) with hydrochloric acid. Substituted 1,2,4-triazole (10) was obtained from substituted thiosemicarbazide (4) via 1,3,4-oxadiazole (6) and substituted triazole (8) substituted 1,2,4 triazole (12). The structures of synthesised compounds were confirmed by IR, UV and physical means.

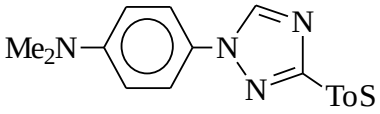
Introduction

1,2,4-Triazole derivatives are found to be associated with various biological activities such as anticonvulsant[(1)], antifungal[(2)], anticancer[(3)], anti-inflammatory[(4)] and antibacterial properties[(5)]. Several compounds containing 1,2,4-triazole rings are well known as drugs[(6)]. For example, fluconazole is used as an antimicrobial drug, while vorozole, letrozole and anastrozole are non-steroidal drugs used for the treatment of cancer and loreclezole is used as an anticonvulsant[(7)].

1,2,4-Triazoline-5-thione can be obtained by cyclization of 1-formylthiosemicar- bazide in a 2M sodium carbonate solution[(8)].

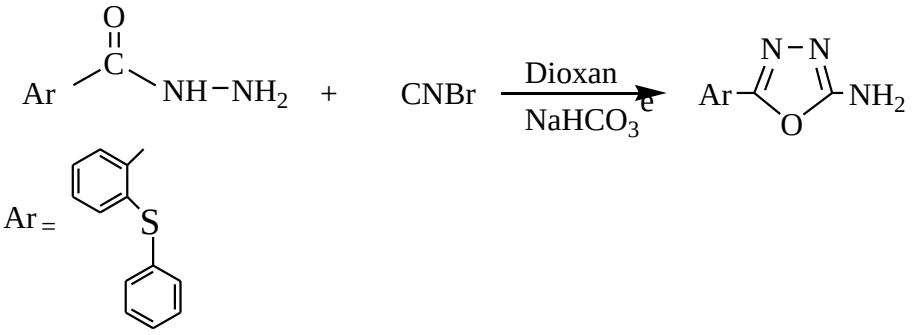


Substituted 1,2,4-triazole was synthesised form the reaction of diazonium salt with p-Toluene sulfonyl methyl isocyanide [(9)] as the following compound.

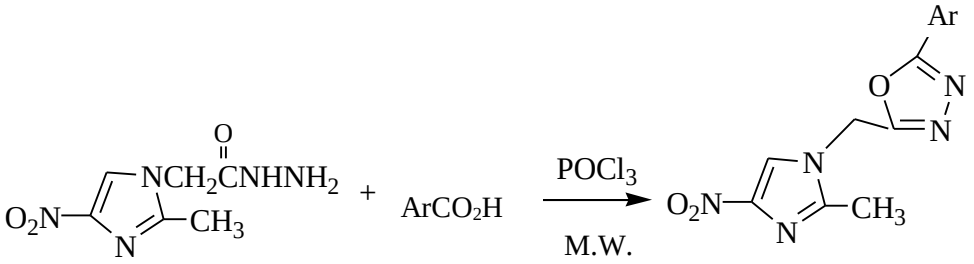


Substituted 1,3,4-oxadiazoles are of considerable pharmaceutical and biological interest[(10)]. They have been shown to possess muscle relaxant, antimitotic, analgesic, anti-inflammatory[(11)], anticonvulsive[(12)], diuretic

and anti-emetic properties[13]. They also possess tranquilizing, antitubercular, hypoglycemic, herbicidal, antiviral[14], amoebicidal, insecticidal, hypnotic and sedative activities. 2-Amino-5[2-(phenylthio) phenyl]-1,3,4-oxadiazole was synthesized from 2-(Phenylthio) benzoic acid hydrazide in dioxane sodium bicarbonate and cyanogene bromide[15].



5-Aryl-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazoles were prepared by microwave irradiation of 2-methyl-4-nitro-1-imidazoacethydrazide with appropriate carboxylic acids in the presence of phosphorousoxy chloride [16].



EXPERIMENTAL:

All chemicals were purchased from Fluka and BDH Chemical Ltd. The melting points were measured on an Electrothermal 9300 Engineering LTD and are uncorrected. IR spectrum were recorded on Infrared Spectrophotometer Model Tensor 27, Bruker Co., Germany, using KBr discs. The UV spectrum were recorded on UV-Visible Shimadzu 1601 Spectrophotometer using ethanol as a solvent .

Diethyl terephthalate [17](1)

To a mixture of (0.01mol, 1.66 g) of terephthalic acid, (50 ml) absolute ethanol, (5 ml) concentrated sulfuric acid was added with cooling. The mixture was refluxed for (8 hrs) the formed precipitate was treated with 20% NaHCO3 the white precipitate was filtered off and recrystallized from ethanol-water (1:1).

Terephthalic acid hydrazide[18] (2)

The mixture of (0.1 mol, 5 ml) of hydrazine hydrate was added to (0.01 mol, 2.22 g) of ester (1) in ethanol (30 ml) was refluxed for (12 hr)

the solvent was evaporated under vaccum. The brown precipitate was filtered off and recrystallized from ethanol.

1,4-Bis(1-carbonyl thiosemicarbazaide)benzene[١٩] (3)

A mixture of (0.01 mol,1.66 g) of compound (2) (0.02 mol, 1.52 g) of ammonium thiocyanate and (5 ml) of concentrated hydrochloric acid was refluxed for (8 hr) on cooling white solid crystals ,were formed filtered off, dried and recrystallized from ethanol-water.

1,4-Bis(4-phenyl-1-carbonyl thiosemicarbazaide)benzene[٢٠] (4)

Compound (2) (0.01 mol,1.66 g) was added to (0.02 mol, 2.7 g) phenyl isothiosyanate and (50 ml) ethanol. The mixture was refluxed for (10 hr) and cooled, filtered, recrystallized from ethanol-water.

1-(2-amino-1,3,4-oxadiazole-5-yl)4-(5-amino-1,3,4-oxadiazole-2-yl) benzene(5).

1-(2-phenylamino-1,3,4-oxadiazole-5-yl) 4-(5-phenylamino-1,3,4-oxadiazole-2-yl)benzene[٢١] (6)

A mixture of (0.02 mol) thiosimecarbazide (3,4) and (0.02 mol) HgO, in the (25 ml) methanol was refluxed for (6 hrs) and then mixture was filtered while hot. The solvent was evaporated and the product crystallized from ethanol. Tables (1,2)

1-(5-methoxy-1,2,4-triazol-3-yl)-4-(3-methoxy-1,2,4-triazole-5-yl) benzene(7).

1-(4-phenyl-5-methoxy-1,2,4-triazol-3-yl)-4-(3-methoxy-4-phenyle-1,2,4-triazole-5-yl)benzene[١٥](8).

To a suspension of compound (5,6) (0.75 mol) in methanol (20 ml) potassium hydroxide (0.35mol) was added. The solution was refluxed for (16 hrs). After cooling the reaction mixture was neutralized with acetic acid. The solvent was evaporated under reduced pressure and the residue was recrystallized from ethanol. Tables (1,2)

1-(5-1,2,4-triazolone-5-yl)-4-(3-1,2,4-triazolone-5-yl)benzene(9).

1-(4-phenyl-5-1,2,4-triazolone-3-yl)-4-(4-phenyl-3-1,2,4-triazolone-5-yl)benzene[١٥](10)

Compound (7,8) (0.14 mol) was suspended in concentrated hydrochloric acid (10 ml) then refluxed for (4 hrs). The mixture was cooled to room temperature and the precipitate was filtered off and crystallized from ethanol. Tables (1,2).

1-(4,5-diamino-1,2,4-triazol-3-yl)-4-(3,4-diamino-1,2,4-triazole-5-yl) benzene(11).

1-(4-amino-5-aminophenyl-1,2,4-triazole-3-yl)-4-(3-aminophenyl-4-amino-1,2,4-triazol-5-yl)benzene[١٥](12).

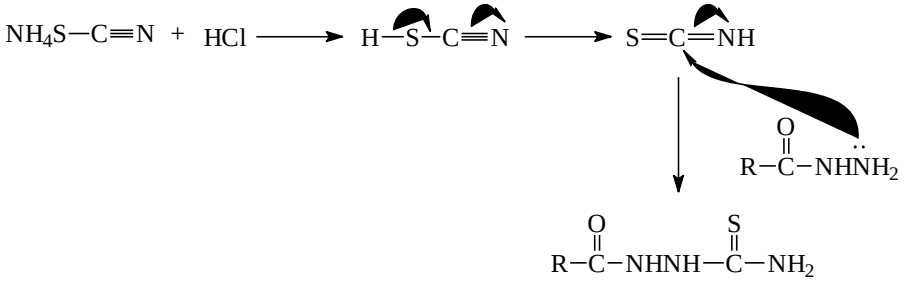
To a suspension of (5,6) (0.14 mol) in ethanol (2 ml), hydrazine hydrate (0.28 ml) was added. The reaction was heated under reflux for (20 hrs), cooled and acidified with cold aqueous 3N hydrochloric acid. The mixture was extracted with ether and the organic layer was washed with water and dried over sodium sulfate, filtered off, the solvent was evaporated under reduced pressure and the residue was recrystallized from ethanol. Table (1,2).

Table (1): Melting points, color, % yield and R_f for the synthesized compounds

Comp. No.	m.p. ^oC	Color	Yield %	$R_{f\ (Ethanol)}$
1	214-215	Brown	83	0.89
2	283	yellow	85	0.91
3	132-133	Dark brown	63	0.81
4	239-240	Pale yellow	82	0.76
5	201-202	Pink	82	0.78
6	195-196	Orange	87	0.74
7	132-133	Yellow	67	0.79
8	121-123	brown	79	-
9	278-280	Dark orange	76	0.85
10	262-264	Yellow	88	0.79
11	306-307	Brown	77	0.90
12	287-288	Pale brown	78	0.93

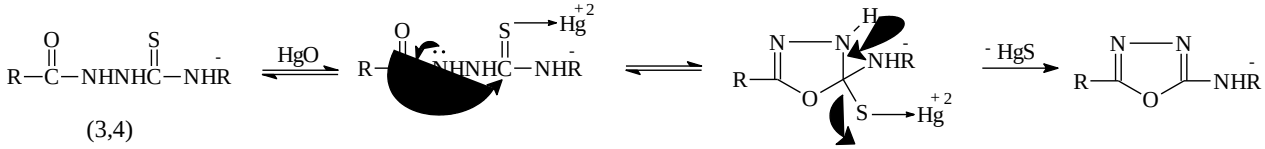
RESULTS AND DISCUSSION:

In this paper the synthesis of some substituted 1,3,4-oxadiazoles and 1,2,4-triazoles is reported Scheme (4). Terephthalic acid was esterified with absolute ethanol in presence of concentrated sulfuric acid to give ester (1). The IR spectrum shows absorption bands □cm^{-1} at 1741 (C=O), 3060 (CH-aromatic) 2950 (CH-aliphatic). Ester (1) was converted into acid hydrazide (2) by its reaction with hydrazine hydrate in ethanol. The IR spectrum shows absorption bands at 1696 (C=O), 3390 (NH), 3030 (CH-aromatic). Acid hydrazide (2) was treated with ammonium thiocyanate and phenyl isothiocyanate in absolute ethanol to give compounds (3 and 4) respectively. The proposed reaction mechanism of thiosemicarbazide formation is follows[٢٢]:



Scheme-1-

IR spectrum of compound (3) shows absorption bands at 1690 (C=O), 3320 (NH), 1125 (C=S) while compound (4) show absorption at 1692 (C=O), 3350, (NH), 1140 (C=S). The proposed mechanism of the conversion of thiosemicarbazides (3,4) to 1,3,4-oxadiazoles (5,6) as follows :



(3,4)

R=H,Ph

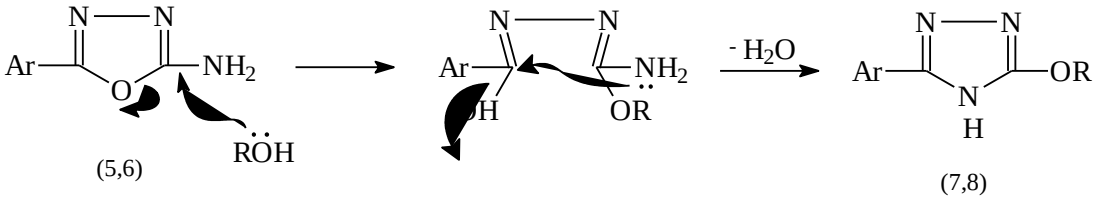
(5,6)

Scheme-2-

1,3,4-Oxdiazole (5) was obtained by cyclization of substituted thiosemicarbazide(3). The IR spectrum of compound (5) shows absorption bands at υcm^{-1}, 1622 (C=N), 3390, 3325, (NH_2), 3030 (CH-aromatic),1124 (C-O-C).

The1,3,4-oxadiazole (6) was synthesized from thiosemeicarbazied (4) by its reaction with mercuric oxide in methanol. The IR spectrum of 1,3,4-oxadiazole(6) shows absorption bands at υcm^{-1}, 1632 (C=N), 3410, 3356, (NH_2), 3050 (CH-aromatic), 1124, 1245 (C-O-C).1,3,4-Oxadiazoles (5,6) undergo rearrangement with methanol, potassium hydroxide to give1,2,4-triazoles (7,8).

The proposed mechanism of the conversion of 1,3,4-oxadiazoles (5,6) to 1,2,4-triazoles (7,8) as follows:



(5,6)

(7,8)

Scheme-3-

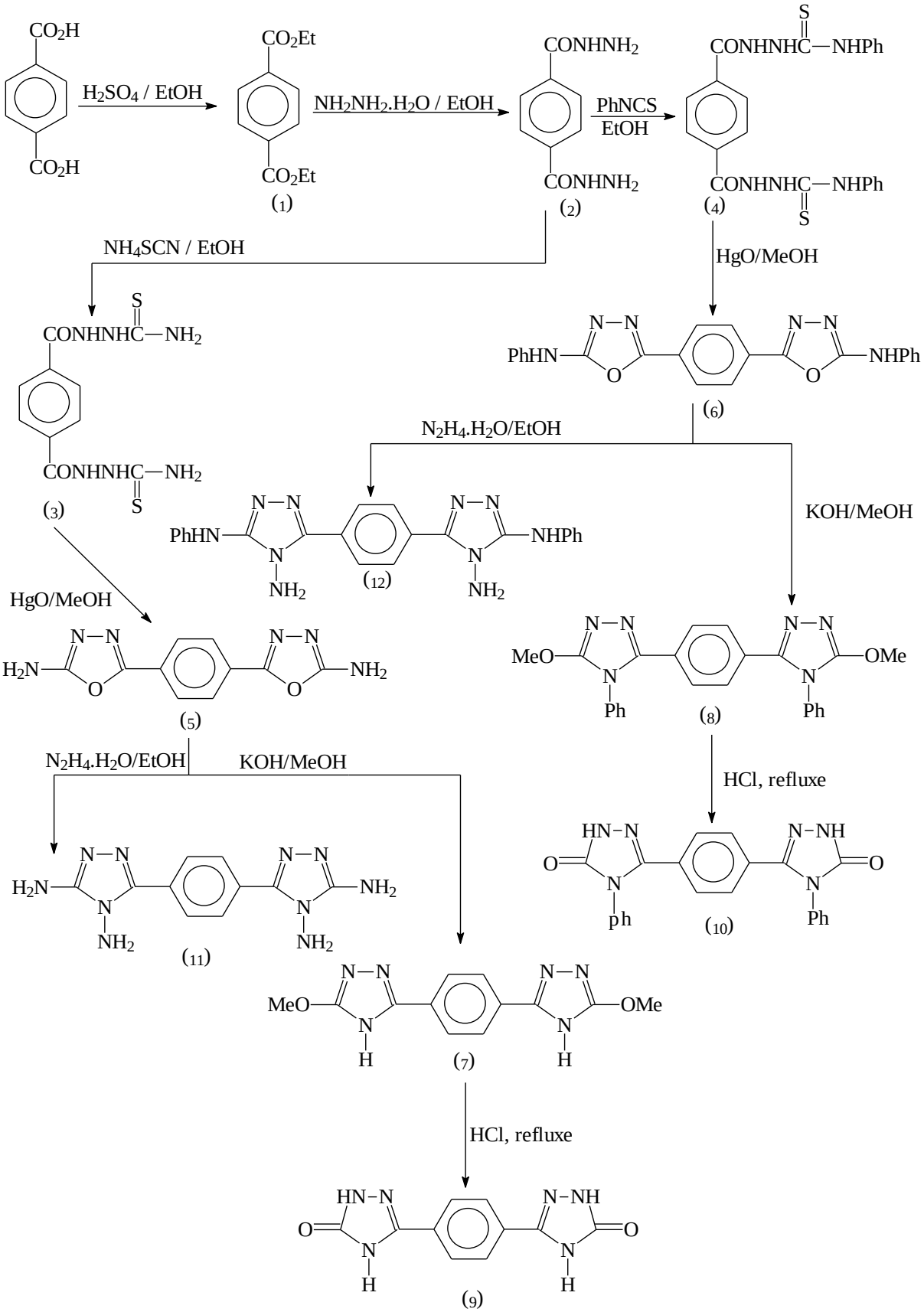
The IR spectrum of compound (7) shows absorption bands at υcm^{-1}, 1636 (C=N),3050(CH-aromatic), 2870, 2912 (CH-aliphatic), 1150, 1092 (C-O-C) while compound (8). shows absorption bands at υcm^{-1},1641 (C=N), 3060 (CH-aromatic), 2890, 2966 (CH-aliphatic), 1180,1052 (C-O-C).

Acid hydrolysis of compounds (7,8) provided triazolones (9,10) The IR spectrum of compound (9) shows absorption bands at υcm^{-1}, 1698 (C=O), 3050 (CH-aromatic), 1626 (C=N), 3185 (NH). The IR spectrum compound (10) shows absorption bands at υcm$^{-1,}$,1710 (C=O), 3030 (CH-aromatic) ,1636 (C=N), 3135 (NH).

The reaction of compounds (5,8) with hydrazine hydrate in ethanol gave substituted 1,2,4-triazoles (11,12) The IR spectrum of compound (11) shows absorption bands at υcm^{-1}, 3070 (CH-aromatic), 1632 (C=N), 3410, 3362 (NH_2) IR spectrum of compound (12) shows absorption bands at□cm^{-1} 3051 (CH-aromatic), 1628 (C=N),3390 (NH_2). The U.V. spectrum data where due to n-□* and □-□* transitions[23]. Table (2).

Table (2): IR and U.V spectrum data for the synthesised compounds

Comp. No.	□ cm^{-1} , KBr	**U.V.** □$_{max}$ nm EtOH
1	1741 (C=O),3060 (CH-aromatic),2950 (CH-aliphatic)	250,324
2	1696 (C=O),3390 (NH),3030 (CH-aromatic)	241,342
3	1690 (C=O),3320 (NH),1125 (C=S)	225,318
4	1692 (C=O),3350 (NH),1140 (C=S)	234,346
5	1622 (C=N),3390 (NH_2),3030(CH-aromatic),1124 (C-O-C)	242,358
6	1632 (C=N),3410 (NH_2),3050(CH-aromatic),1254 (C-O-C)	212,320
7	1636 (C=N),3050(CH-aromatic),2912 (CH-aliphatic),1150 (C-O-C)	219,298
8	1641 (C=N),3060(CH-aromatic),2960 (CH-aliphatic),1180 (C-O-C)	217,288
9	1698 (C=O)ring,3050(CH-aromatic),1626 (C=N),3185 (NH)	232,322
10	1710 (C=O),3030(CH-aromatic),1636 (C=N),3135 (NH)	256,313
11	3070 (CH-aromatic),1632 (C=N),3410 (NH_2)	207,250
12	3051 (CH-aromatic),1628 (C=N),3390 (NH_2)	233,282


CO2H
CO2H
H2SO4 / EtOH
CO2Et
CO2Et
(1)
NH2NH2.H2O / EtOH
CONHNH2
CONHNH2
(2)
PhNCS
EtOH
CONHNHC—NHPh
S
CONHNHC—NHPh
S
(4)
NH4SCN / EtOH
HgO/MeOH
CONHNHC—NH2
S
CONHNHC—NH2
S
(3)
PhHN
NHPh
O
(6)
N2H4.H2O/EtOH
KOH/MeOH
PhHN
NHPh
NH2
NH2
(12)
HgO/MeOH
H2N
NH2
(5)
MeO
OMe
Ph
Ph
(8)
N2H4.H2O/EtOH
KOH/MeOH
HCl, refluxe
H2N
NH2
NH2
NH2
(11)
O
O
ph
Ph
(10)
MeO
OMe
H
H
(7)
HCl, refluxe
O
O
H
H
(9)

Scheme -4-

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