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Synthesis of five membered ring hetero cyclic compounds derived from methyl-6- methyl-2- oxo-4-substituted 1,2,3,4- tetrahydro pyrimidine-5-carboxylate

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الملخص

تم في هذا البحث تحضير6- مثيل-2- اوكسي-4- فنيل معوض4،3،2،1- رباعي هيدروبيريميدين -5-كاربوكسيلات المثيل (1-3) من تفاعل معوضات البنزالدهيد مع اليوريا واسيتوخلات المثيل . اعطى تفاعل البيريميدين المعوض (1-3) مع الهيدرازين المائي في البيوتانول،هيدرازيدالحامض (4-6) والتي تم تحويلها الى الهيدرازونات (7-12) من خلال التفاعل مع معوض البنزالدهيد . اعطى تحولق الهيدرازونات (7-12) باستعمال ثنائي اوكسيد الرصاص في حامض الخليك الثلجي 1، 4،3- اوكسادايازول معوض (13- 18) .تم مفاعلة الهيدرازيد (4-6) مع ثايوسيانات الامونيوم بوجود حامض الهيدروكلوريك المركز في الايثانول ليعطي ثايوسيميكاربازيد معوض (19-21) . اعطى تفاعل الثايوسيميكاربازيد المعوض(19-21) مع 4 % هيدروكسيد الصوديوم او حامض الكبريتيك المركز ليعطي معوض 1، 4،2- ترايازول (22- 24) و 4،3،1- ثايادايازول معوض (25- 27) على التوالي . تم تشخيص المركبات المحضرة باستخدام طيف IR و UV وبالطرق الفيزياوية.

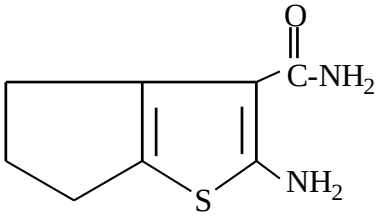
Abstract

In this paper the synthesis of methyl-6- methyl-2-oxo-4-substituted phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1-3) were synthesised from substituted benzaldehyde, urea and methyl acetoacetate, substituted pyrimidine (1-3) were treated with hydrazine hydrate in butanol to give acid hydrazide (4-6), which were converted to hydrazones (7-12) by their reaction with substituted benzaldehyde. Cyclizatian of hydrazones (7-12) with lead dioxide in glacial acetic acid gave substituted

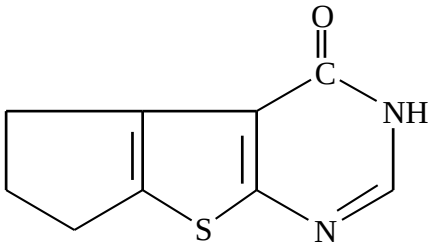
1,3,4- oxadiazole (13-18). Hydrazide (4-6) were treated with ammonium thiocyanate in ethanol and hydrochloric acid to give substituted thiosemicarbazides(19-21). Reaction of thiosemicarbazide (19-21) with 4% sodium hydroxide or with concentrated sulfuric acid gave substituted 1,2,4- (4H) - triazole (22-24) and 1,3,4- thiadiazole (25-27) respectively. The structure of the synthesized compounds, were confirmed by IR, UV and physical methods.

Introduction

It is well known that pyrimidine derivatives possess biological activities specially as antiviral , antimicrobial [1-4] and act as antitumour agent [5] , antibacterial [6 , 7] and anti-lukemic[8] . The synthesis and biological activity of thienopyrimidine derivatives from aromatic and hetroaromatic compounds and the preparation of various condensed pyrimidine was studied[9]. The synthesis of 5,6,7,8-tetrahydro [1] benzothieno[2,3-d] pyrimidine -4-(3H) - one (2) was achieved from 2-amino - 4,5- dihydro - 4H- cyclopenta [b] thiophene-3-carboxamide (1) by its reaction with formamide[10].

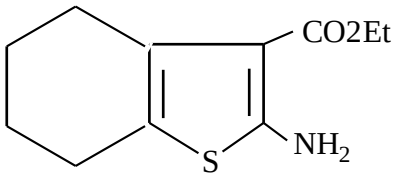


(1)

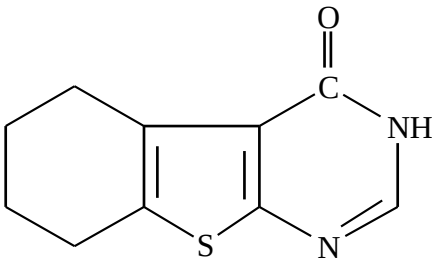


(2)

The pyrimidine derivative (4) was obtained from the reaction of ethyl - 2- amino- 4,5,6,7-tetra hydro- benzothiophene -3-carboxylate (3) with excess
formamide[11].



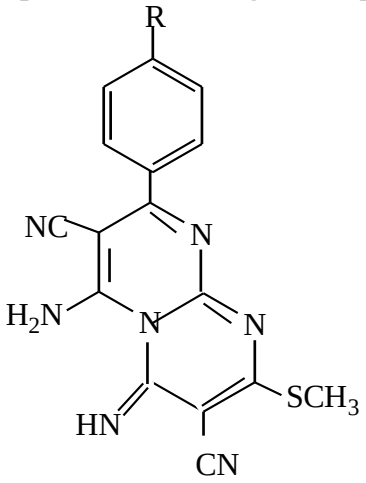
(3)



(4)

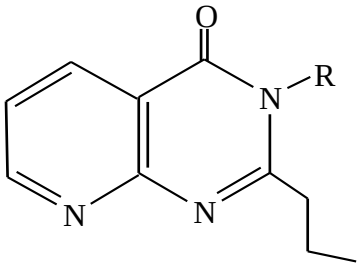
S-glycosyl pyrimdine and condensed pyrimidine derivatives were synthesized from isothiocyanate and acrylate [12]. Some heterocyclic compounds containing pyrimidino-pyrimidine moiety as

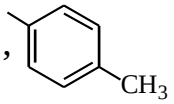
compound(5) have been synthesized, and these compounds showed antibacterial activity against gram – positive and negative species[13]



R =H , CH_3 , Cl , OMe ,NO_2 (5)

Pyrimidine derivatives as pyrido[2,3-d]pyrimidin -4-(3H) – one (6) was synthesized[14] where as condensation of chalcone with thiourea in presence of potassium hydroxide gave 1,6-Dihydropyrimidine-2-thiol which show antibacterial activity [15].



R = NH_2 ,H ,OH , 

(6)

3 – cyano -7- methyl – 4- oxo – 2 –(methyl thio)- 4H-pyrido[1,2-a] pyrimidine was synthesised from ethyl -2- cyano-3,3- bis (methyl thio) acrylate [16]. In this paper the synthesis of substituted tetrahydro-pyrimidines is reported.

Experimental

All chemicals were purchased from Flucka and BDH Chemical Ltd.The melting points were measured on an Electrothermal 9300 Engineering LTD and are uncorrected .IR spectra were recorded on

Infrared Spectrophotometer Model Tensor 27 ,Bruker Co.,Germany, using KBr discs . UV spectra were recorded on Shimadzu Double-Beam Spectrophotometer UV-210 A using ethanol as a solvent.

Methyl -6- methyl -2- oxo -4- substituted phenyl -1,2,3,4- tetra hydropyrimidine -5- carboxylate (1-3) [17]**:**

To a mixture of urea (0.75g , 0.0125mole), substituted aldelyde (0.0185 mole), methyl acetoacetate (2.2g, 0.0185 mole) in ethanol (20ml), dilute hydrochloric (4 drops) was added. The mixture was heated at 70ºC for 2h, ice cold water(100ml) was added and left for 24h. at room temperature, the solid was filtered and recrystallized from ethanol. Some of the physical data table (1)

6-methyl -2- oxo - 4-substituted phenyl -1,2,3,4-tetrahydropyrimidine -5- carbohydrazide (4-6) [18]**:**

A mixture of compound (1-3) (0.00125 mole) in ethanol (40 ml), hydrazine hydrate (5 ml) was added then the mixture refluxed for 5h, the solvent was evaporated under reduced pressure to give compounds 4,6 as solid and 5 as oil compounds, compounds were recrystallized from ethanol-water. Some of the physical data table (1)

Hydrazone (7-12) [18]**:**

To hydrazide (4-6)(0.011mole) in absolute ethanol (50 ml), substituted benzaldelyde (0.011 mole) in ethanol (25 ml) was added, the mixture refluxed for 5h, the precipitate was filtered and recrystallized from ethanol. Some of the physical data table (1)

2-(4-methyl -6- substituted -2- one tetrahydropyrimidin -5- yl) 5-substituted 1, 3, 4-oxadiazole . (13-18) [19]**:**

Hydrazone (7-12) (0.005 mole) was added to glacial acetic acid (16ml) with stirring, lead oxide (1.24g, 0.005mole) was added as portions at 25ºC the mixture was stirred for 1h. The reaction mixture was diluted with water (50 ml) and left for 24 h. the precipitate was filtered recrystallized from ethanol. Some of the physical data table (1)

N-(2-amino-2-thioxoethyl)-4-(substituted phenyl)-6- methyl -2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (19-21) [20]**:**

A mixture of hydrazide (4-6)(0.011 mole), ammonium thiocyanate (2.7 g, 0.034 mole) concentrated hydrochloric acid (6 ml) in absolute ethanol (50 ml) was refluxed for 22h. Solvent was evaporated under reduced pressure and the residue was added to crushed ice with stirring to give solid product filtered and recrystallizid from ethanol - water. Some of the physical data table (1)

4-(substituted phenyl) -5- (5-mercapto-4H-1,2,4-triazolo-3-yl)-6-methyl-3,4-dihydropyrimidin-2-(1H)-one (22-24) [21]**:**

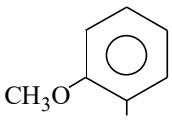
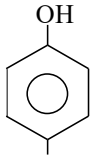
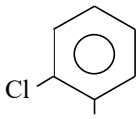
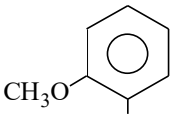
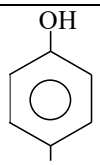
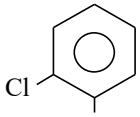
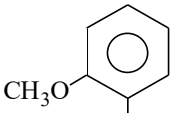
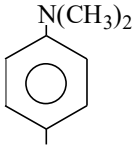
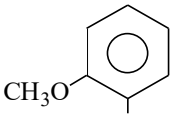
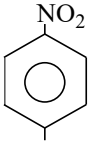
A mixture of thiosemicarbazide (19-21)(0.006 mole)in aqueous sodium hydroxide solution (4 % ,24ml) was refluxed for 3 h. The mixture then acidified with dilute hydrochloric acid to PH=6 with cooling , the

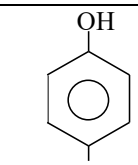
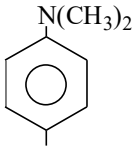
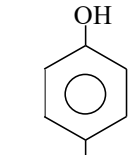
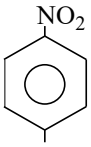
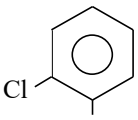
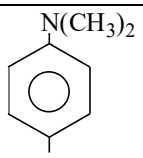
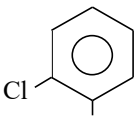
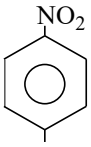
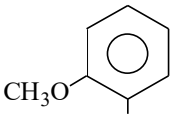
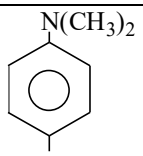
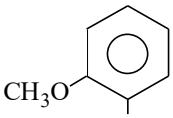
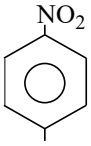
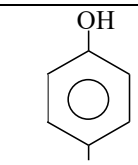
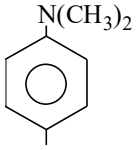
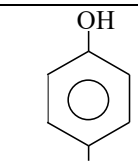
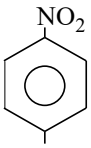
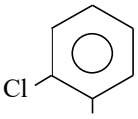
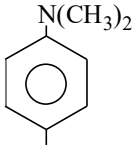
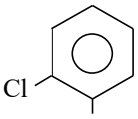
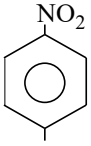
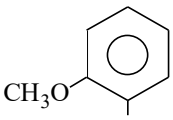
precipitate was filtered and recrystallized from ethanol. Some of the physical data table (1)

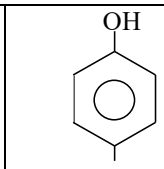
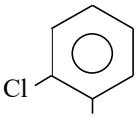
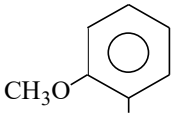
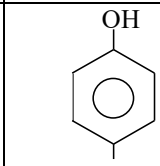
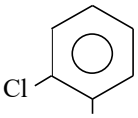
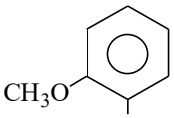
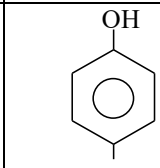
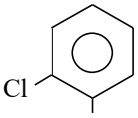
5-(5-amino-1,3,4-thiadiazol-2-yl)-4-(4- substitutedphenyl)-6-methyl-3,4-dihydropyrimidine-2-(1H)-one (25-27) [21]:

A mixture of substituted thiosemicarbazide (19-21)(0.06 mole) and concentrated sulfuric acid (12 ml) was stirred at room temperature for 1h. then heated on water path at 90 °C for 2 h. the mixture was poured on a beaker containing crushed ice and nutralized with concenterated ammonium hydroxide with cooling the solid was filtered , washed with cold water dried and recrystallized from ethanol . Some of the physical data table (1).

Table (1) : physical data of compounds (1-27)

Comp. No.	R	R\	m.p. °C	Molecular formula	Yield %	Color
1		–	280-282	$C_{14}H_{16}N_2O_4$	88	Yellow
2		–	223-225	$C_{13}H_{14}N_2O_4$	81	Orange
3		–	242-244	$C_{13}H_{13}ClN_2O_3$	83	Pale yellow
4		–	252-254	$C_{13}H_{16}N_4O_3$	85	Yellow
5		–	oily	$C_{12}H_{14}N_4O_3$	80	Redish-brown
6		–	208-210	$C_{12}H_{13}ClN_4O_2$	90	White
7			294	$C_{22}H_{25}N_5O_3$	76	Brown
8			264-266	$C_{20}H_{19}N_5O_5$	71	Pale yellow

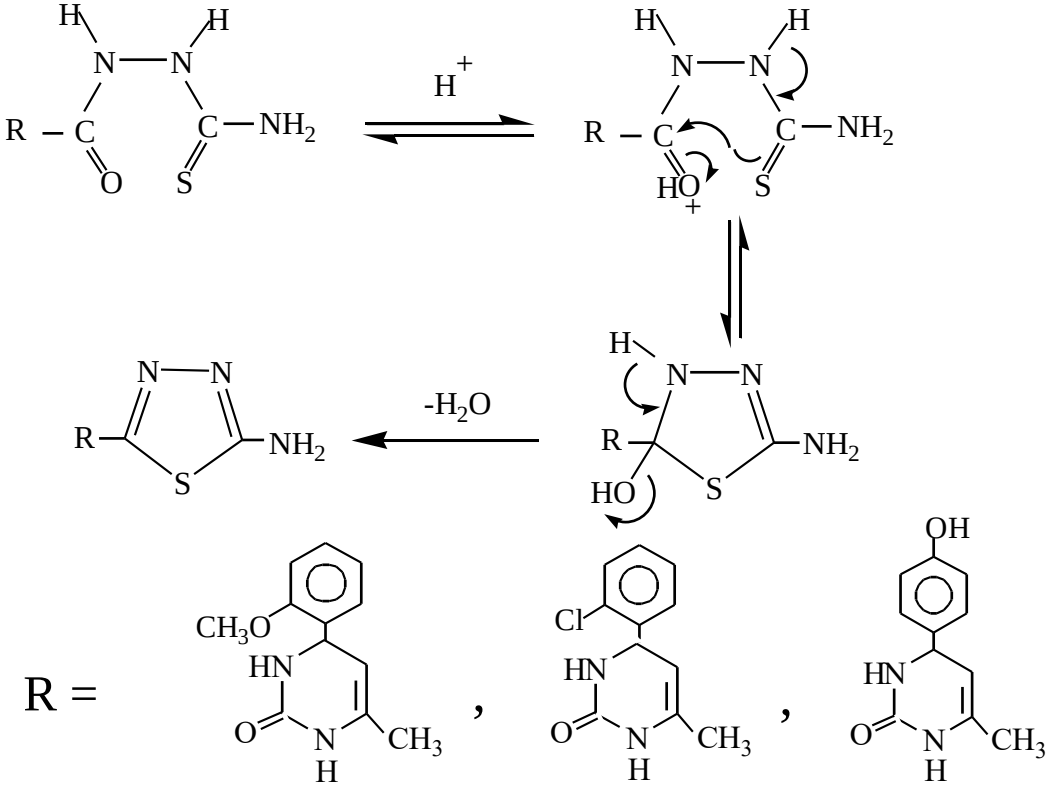
9			260-261	$C_{21}H_{23}N_5O_3$	77	Yellowish-brown
10			154-156	$C_{19}H_{17}N_5O_5$	69	Redish-brown
11			250	$C_{21}H_{22}ClN_5O_2$	75	Pale yellow
12			296-298	$C_{19}H_{16}ClN_5O_4$	79	Gray
13			310-312	$C_{22}H_{23}N_5O_3$	69	Pale brown
14			252-254	$C_{19}H_{17}N_5O_5$	73	Brown
15			239-241	$C_{21}H_{21}N_5O_3$	77	Brown
16			130-232	$C_{19}H_{15}N_5O_5$	71	Yellowish-brown
17			268-270	$C_{21}H_{20}ClN_5O_2$	76	Brown
18			275-277	$C_{19}H_{14}ClN_5O_4$	69	Dark brown
19		–	265-267	$C_{14}H_{17}N_5O_3S$	62	Pale brown

20		–	196-198	$C_{13}H_{15}N_5O_3S$	73	Dark brown
21		–	234-236	$C_{13}H_{14}ClN_5O_2S$	56	Yellowish brown
22		–	>350	$C_{14}H_{15}N_5O_2S$	81	White
23		–	244-246	$C_{13}H_{13}N_5O_2S$	57	Brown
24		–	259-261	$C_{13}H_{12}ClN_5OS$	77	White
25		–	>350 d.	$C_{14}H_{15}N_5O_2S$	39	Brown
26		–	Oily	$C_{13}H_{13}N_5O_2S$	41	Pale brown
27		–	277-279	$C_{13}H_{12}ClN_5OS$	51	Greenish-yellow

Results and discussion

Substituted tetrahydropyrimidine (1-3) were synthesized and converted to substituted 1,3,4- oxadiazoles, 1,3,4- thiadiazoles and 1,2,4- triazoles (Scheme -2). Substituted benzaldehyde, was treated with urea and methyl acetoacetate to give tetrahydropyrimidine 1-3. The IR spectra shows absorption peaks at 1644, 3444, 3104, 2955 and 1730 cm^{-1} for (CO-amide), N-H, (C-H aromatic), (C-H aliphatic) and (C=O ester) respectively. The esters (1-3) were treated with hydrazine hydrate in butanol to give acid hydrazide, (4-6), the IR spectra show absorption at 1643-1646 cm^{-1} for (C=O) with disappearance of C=O esters absorption band at 1713-1730 cm^{-1}. Acid hydrazide (4-6) were treated with substituted benzaldehyde to give hydrozone (7-12) which show absorption 1644-1681 cm^{-1} for(CO) 3257-3445-cm^{-1} for (N-H) compounds 8,10,12 show absorption at 1337-

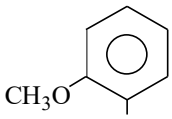
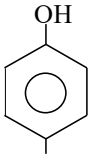
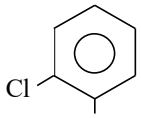
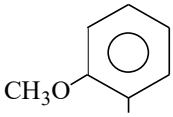
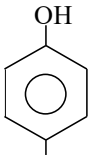
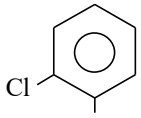
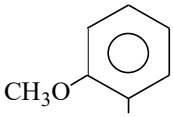
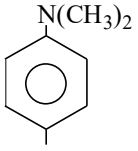
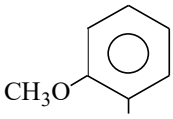
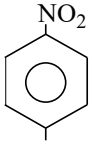
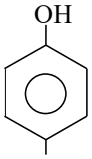
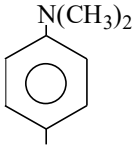
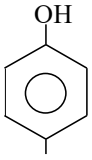
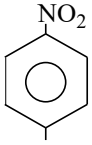
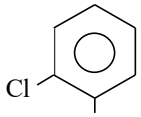
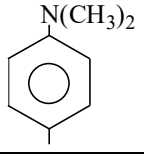
1346, 1487-1525 cm^{-1} sym, and asym. for NO_2. Substituted 1,3,4-oxadiazole (13-18) were synthesized from hydrazones(7-12) by their reaction with lead oxide in glacial acetic, the IR spectra show absorption עcm^{-1} at 1642-1700 (C=O), NO_2 group appears at 1337-1346 cm^{-1} and 1486-1519 cm^{-1} (sym. and asy.), the substituted thiosemicarbazides (19-21) were synthesized from hydrazide (4-6) by their reaction with ammonium thiocyanate -HCl in ethanol the IR spectra of compounds (19-21) show absorption at 1643-1649 cm^{-1} for (C=O amide) and 1180-1185 cm^{-1} for (C=S). The substituted thiosemicarbazides (19-21) were cyclized to substituted 1,2,4- triazoles (22-24) and to substituted 1,3,4- thiadiazole (25-27) by their reaction with 40% sodium hydroxide and with concentrated sulfuric acide respectively. The proposed mechanism of the cyclization of thiosemicarbazides (19-21) to thiadiazoles (25-27) as in scheme -1[22]

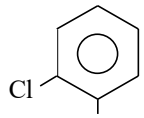
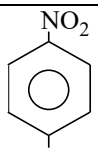
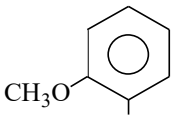
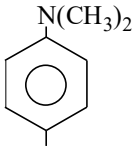
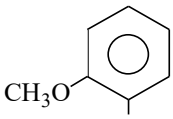
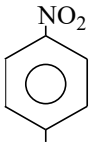
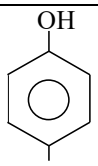
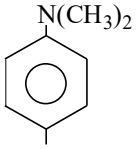
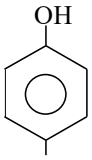
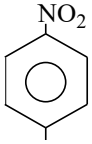
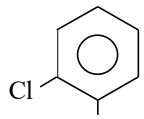
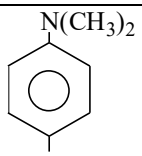
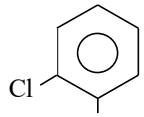
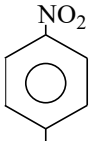
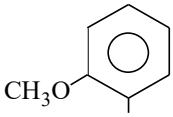
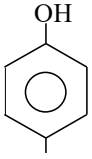
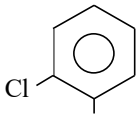
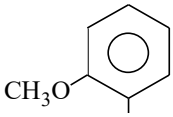


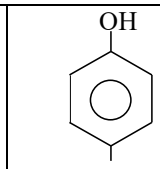
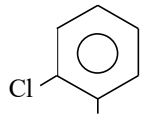
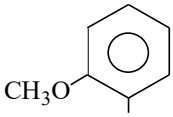
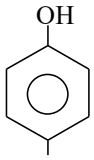
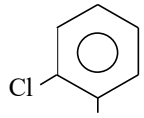
Scheme-1

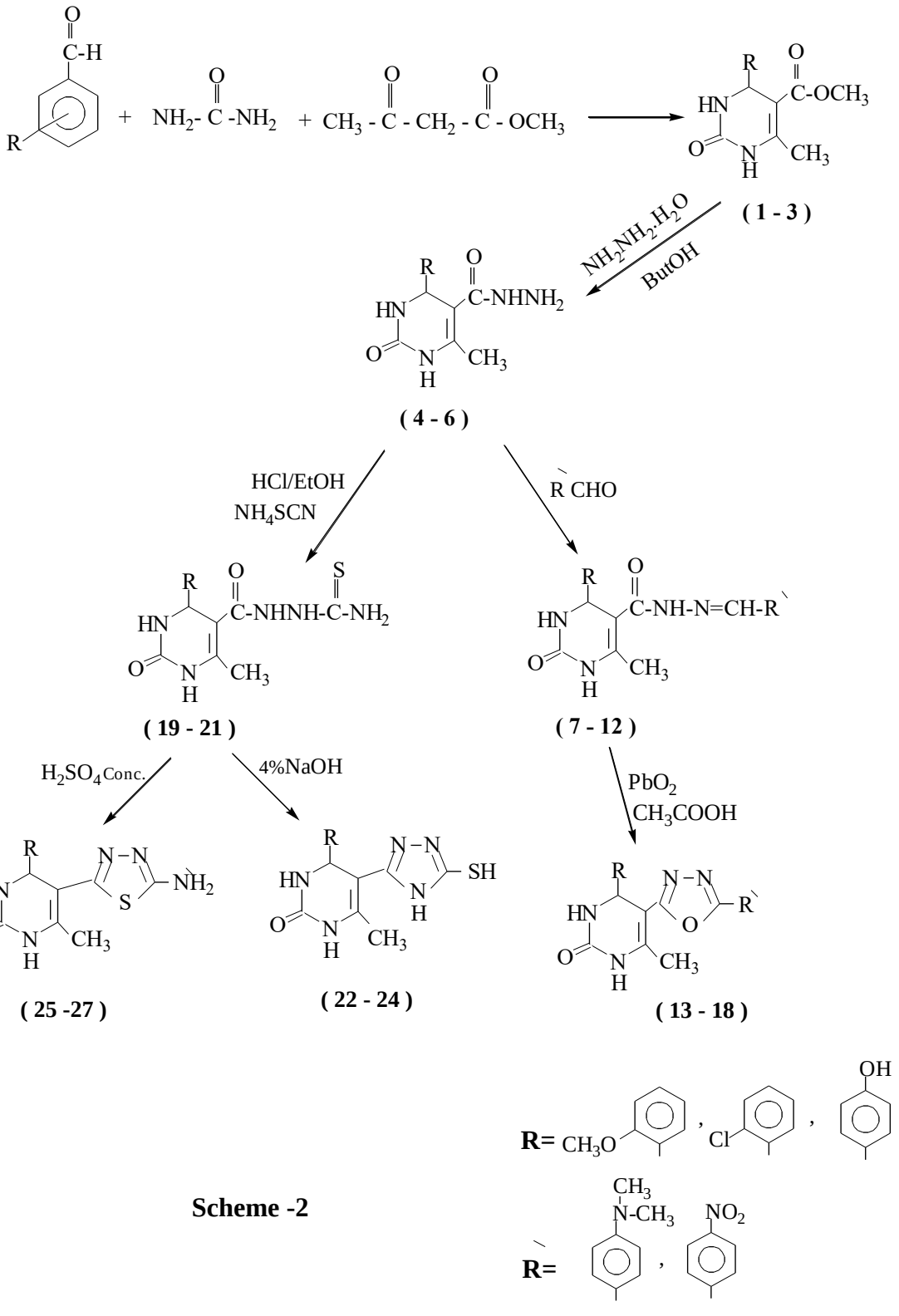
The IR of compounds (22-24) show absorption at 1638-1655 cm^{-1} for (C=N) and 1181-1218 cm^{-1} for (C=O). Compounds (25-27) showed absorption for (C=N) at 1631-1667 cm^{-1} and for (C=O at 1094-1129 cm^{-1}. The thiadiazoles (25-27) show in absorption bonds for (C=S) at 1180-1185 cm^{-1}which found in compounds (19-21) Table(2).

Table (2): spectral data of compounds (1-27)

Comp. No.	R	R\	U.V (EtOH) λ_{max} (nm)	IR υ cm^{-1} , (KBr)				
				C=O amide	N-H	ArC-H	aliphatic .C-H	others
1		–	383,362	1644	3444	3104	2955	C=Oester (1730)
2		–	393,362	1644	3403	3109	2955	C=Oester (1713)
3		–	342,269	1648	3426	3097	2926	C=Oester (1727)
4		–	364,203	1643	3260	3106	2951	-
5		–	400,389	1652	3270	3099	2946	-
6		–	289,240	1646	3226	3096	2955	-
7			415,410	1644	3257	3104	2953	N-CH_3 (2815)
8			394,359	1645	3263	3112	2935	NO_2 1346sym. 1525asy
9			423,412	1681	3443	3099	2920	N-CH_3 2820
10			395,361	1652	3445	3100	2900	NO_2 1345 sym. 1517asy
11			416,408	1648	3228	3096	2955	N-CH_3 2828

12			279,217	1644	3366	3023	2951	NO_2 1337 sym. 1487asy
13			351,347	1643	3261	3105	2951	N-CH_3 2830
14			360,210	1642	3447	3112	2950	NO_2 1346 sym. 1487asy. C-O-C (1027)
15			424,410	1700	3444	3091	2911	N-CH_3 (2802) C-O-C (1063)
16			360,346	1646	3443	3093	2959	NO_2 1346, 1519asy. C-O-C (1040)
17			383,259	1647	3227	3096	2955	N-CH_3 2890 C-O-C 1047
18			303,283	1643	3261	3105	2951	$NO_2$1337, 1486 C-O-C 1027
19		–	401,359	1643	3261	3023	2956	C=S 1183
20		–	403,343	1649	3440	3100	2948	C=S 1185
21		–	309,277	1646	3443	3103	2957	C=S 1180
22		–	317,267	1700	3449	3099	2961	C=N 1638 C=S 1218

23		–	391,344	1680	3443	3102	2951	C=N 1640 C=S 1181
24		–	340,300	1685	3444	3125	2925	C=N 1655 C=S 1198
25		–	339,315	1688	3423	3128	2925	C=N 1631 C-S 1098
26		–	388,359	1696	3333	3032	2950	C=N1667 C-S 1098
27		–	334,299	1684	3444	3095	2955	C=N 1655 C-S 1129



Scheme -2

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