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SYNTHESIS OF SOME NEW HETEROCYCLIC COMPOUNDS FROM 2-AMINOBENZHYDRAZIDE

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Abstract

2-Aminobenzhydrazide (1) was used as a precursor for preparation of some new heterocyclic compounds and Schiff bases (2-9). Also, derivatives containing thiadiazole, oxadiazole and triazole rings were prepared by treating compound (1) with phenyl isothiocyanate (10-13). The structure of these compounds were characterized from there melting point, FTIR spectroscopy and elemental analysis.

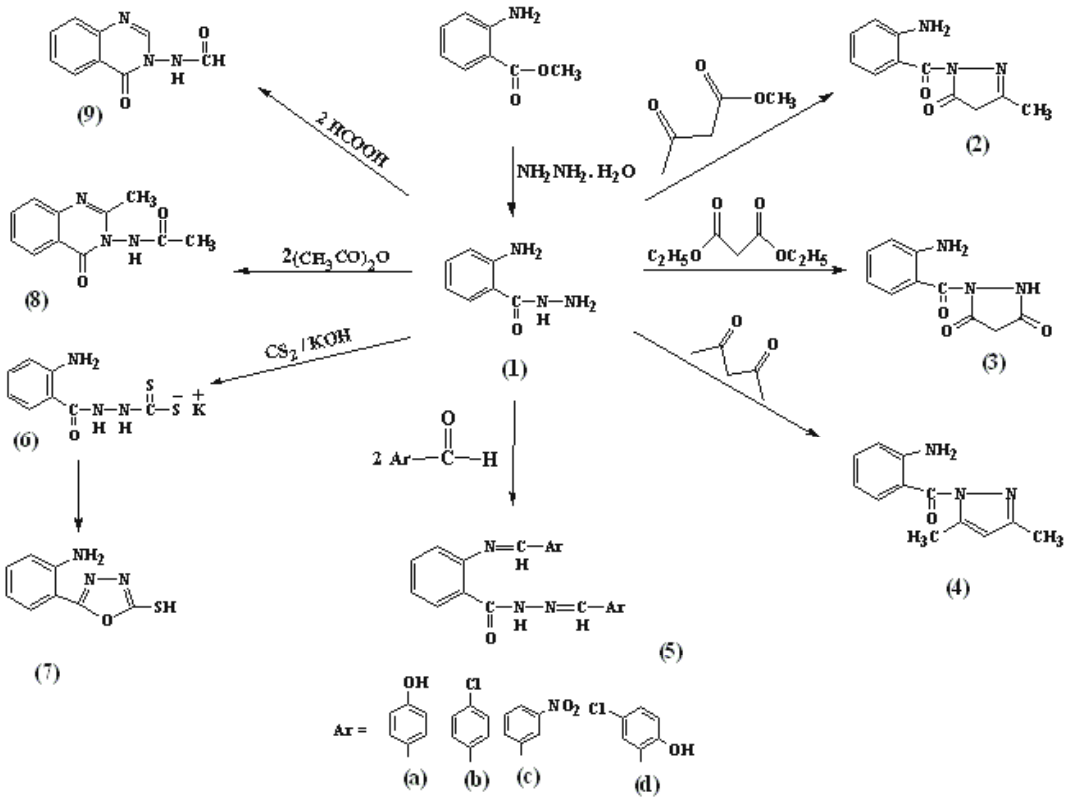
Keywords: 2-Aminobenzhydrazide, pyrazole, Schiff bases, quinazoline.

Introduction

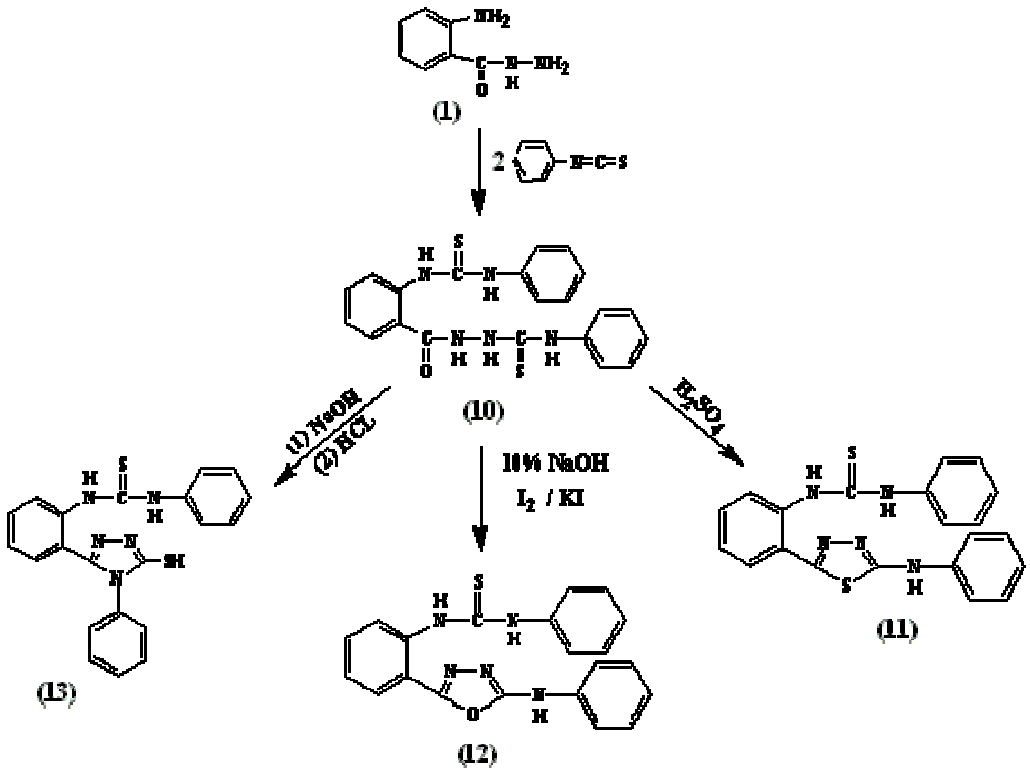
Heterocyclics bearing nitrogen, sulphur and oxygen atoms constitute the core structure of a number of pharmacologically and biologically active interesting compounds. The efficiency of azoles as chemotherapeutic agents is well studied. For example pyrazole and pyrazolone derivatives exhibit antibacterial, antifungal [1,2] and Cox inhibition activity [3] while oxadiazole, thiadiazole and triazole derivatives are widely used for medicinal [4-7] and industrial purposes [8] like azoles, quinazoline derivatives showed therapeutic effects because of their antihistaminic [9], analgesic and anti-inflammatory activities [10]

Recently, quinazoles and quinazolines were tested as a good immune modulators [11]. Schiff bases have also been widely reported biologically active due to the toxophoric C=N linkage in them [12].

Prompted by these observations, it was decided to use 2-aminobenzhydrazide as a starting material for the preparation of new heterocyclic compounds and Schiff bases.



Scheme (1).



Scheme (2).

Experimental

Materials:

All chemical used were supplied from Merk Chemical, Fluka AG, BDH Chemicals**.** Melting points were recorded using Electrothermal melting point apparatus. Infrared spectra were recorded with Pye – Unicam SP3-100 or Shimadzu FTIR – 8400. Elemental analysis (C.H.N) were carried out in Euro EA elemental analyzer.

Preparation of 2- amino benzhydrazide. (1):

A mixture of methyl anthranilate (0.01 mole) and hydrazine hydrate 40% (10ml) in ethanol (30ml) was heated under reflux for 4hr.

The reaction mixture was concentrated and cooled. The solid was filtered, washed with water and recrystallized from ethanol [13].

General procedure for preparation of (2-amino benzoyl)-3-methyl-1H-pyrazole-5-(4H)-one.(2) ,(2-aminobenzoyl) pyrazolidine-3,5-dione. (3) and (2-aminophenyl) (3,5-dimethyl-1H-pyrazole-1-yl) methanone. (4):

To (0.01 mole) of compound (1) methyl acetoacetate, diethyl malonate and acetylacetone (0.01 mole) was added and reaction mixture was heated under reflux for half an hour then (10ml) of ethanol absolute was added and the mixture was refluxed for an additional 1hr, respectively. The products, which separated on cooling, were collected by filtration and recrystallized from ethanol [14].

General procedure for preparation of Schiff bases. (5 a, b, c, d):

A mixture of compound (1) (0.01 mole) and substituted aromatic aldehydes (0.02 mole) in absolute ethanol (25ml) was heated under reflux for 1hr. this mixture allowed to cool and the solid product was collected and recrystallized from ethanol.

Preparation of potassium 2-(2- amino benzoyl) hydrazine carbo dithioate. (6):

Compound (1) (0.01 mole) was dissolved in absolute ethanol (25ml) and (0.01 mole) of potassium hydroxide was added to the stirred solution. Then CS_2 was added gradually with cooling. After 1hr of stirring, the salt was collected without further purification.

Preparation of 5-(2-aminophenyl)-1,3,4-oxadiazole-2-thiol. (7):

Compound (6) was dissolved in ethanol and heated under reflux for 4hr. The reaction mixture was cooled, filtrated and the filtrate was acidified with dilute hydrochloric acid. The solid product was collected and recrystallized from ethanol.

Preparation of N-(2-methyl-4-oxoquin azoline-3-(4H)-yl) acetamide. (8):

To (0.01 mole) of compound (1) (10ml) of acetic anhydride was added and the mixture was heated under reflux for 4hr. Then allowed to cool and poured over crushed ice and extracted with chloroform. The solvent was removed from the organic layer to give an oily residue [14].

Preparation of N-(4-oxoquinazoline-3-(4H)-yl) fromamide. (9):

(0.01 mole) of compound (1) was dissolved in (10ml) of formic acid and heated under reflux for 4hr. The mixture allowed to cool and poured into cold water. The solid product was collected and recrystallized from ethanol [14].

Preparation of N-phenyl-2-(2-(3-phenyl thioureido)benzoyl) hydrazine carbothioamide. (10):

A mixture of compound (1) (0.01 mole) and (0.02 mole) of phenyl isothiocyanate in ethanol absolute was heated under reflux. After 1hr the reaction mixture was cooled and the solid product was collected and recrystallized from ethanol [6, 7].

Preparation of 1-phenyl -3-(2-(5-(phenyl amino)-1, 3, 4-thiadiazole-2-yl) phenyl) thiourea. (11):

(0.01 mole) of compound (10) was dissolved in (10ml) of conc. H_2SO_4 and stirred for 1hr then poured onto crushed ice. The resulting solid was recrystallized from ethanol [6, 7].

Preparation of 1-phenyl -3-(2-(5-(phenyl amino)-1, 3, 4-oxadiazole-2-yl) phenyl) thiourea. (12):

To alcoholic solution of compound (10) (0.01 mole), (10ml) of 10% NaOH was added with cooling and stirring then iodine solution in 10% KI was added gradually, and the

stirring continued until the iodine color persisted. Heating was continued for 5hr with reflux and the mixture was cooled and poured onto ice-cold water. The resulting solid was washed with water and recrystallized from ethanol [6, 7].

Preparation of 1-(2-(5-mercapto-4-phenyl-4H-1,2,4-triazole-3-yl) phenyl thiourea.(13):

An aqueous solution of NaOH (10%, 10ml) was added to (0.01 mole) of compound (10) and reaction mixture was refluxed for 4hr. The resulting solution was cooled and acidified with 10% HCL adjusted PH to 6. The precipitate was collected, washed with cold water and recrystallized from ethanol [6, 7].

All physical constant for these compounds were reported in Table (1). Infrared data were reported in Table (2).

Table (1)
Physical constants for compounds.

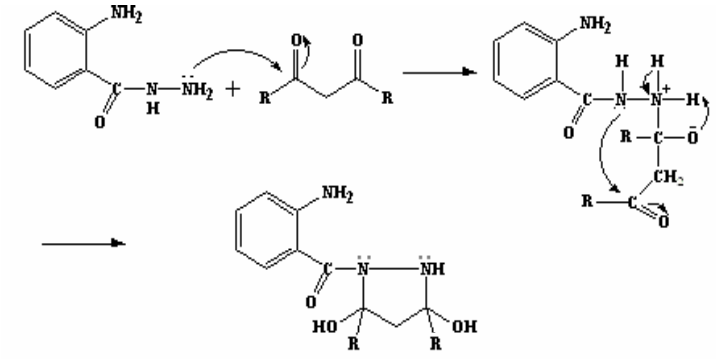
Comp. No.	*Formula*	*Melting point ℃*	*Elemental analysis calc. (found)%*			*Yield %*
			C %	*H %*	*N %*	
1	$C_7H_9N_3O$	121 - 123	55.62 (55.11)	5.96 (5.63)	27.81 (27.69)	71
2	$C_{11}H_{11}N_3O_2$	250 dec.	60.83 (60.47)	5.07 (4.91)	19.53 (19.36)	65
3	$C_{10}H_9N_3O_3$	230 dec.	54.79 (53.98)	9.11 (8.89)	19.18 (18.66)	67
4	$C_{12}H_{13}N_3O$	156 - 158	66.98 (66.01)	6.05 (5.83)	19.53 (18.97)	63
5a	$C_{21}H_{17}N_3O_3$	206 - 208	70.19 (69.96)	4.74 (4.52)	11.70 (11.54)	86
5b	$C_{21}H_{15}N_3OCl_2$	172 – 174	63.64 (62.98)	3.79 (3.11)	10.61 (10.43)	80
5c	$C_{21}H_{15}N_5O_5$	118 – 120	60.43 (59.98)	3.60 (3.21)	16.79 (16.33)	79
5d	$C_{21}H_{15}N_3O_3$	226 – 228	58.88 (58.43)	3.50 (3.21)	9.81 (9.37)	91
7	$C_8H_7N_3OS$	184 – 186	49.74 (47.11)	3.63 (3.43)	21.76 (20.92)	69
8	$C_{10}H_9N_3O_2$	oily	59.11 (58.83)	4.43 4.12	20.69 20.30	60
9	$C_9H_7N_3O_2$	218 – 220	57.14 (55.38)	3.70 (3.11)	22.22 (21.43)	66
10	$C_{21}H_{19}N_5OS_2$	148 – 150	59.90 (51.84)	4.51 (3.13)	16.63 (15.16)	66
11	$C_{21}H_{17}N_5S_2$	240 dec.	62.53 (62.12)	4.22 (3.95)	17.37 (16.97)	61
12	$C_{21}H_{17}N_5OS$	210 dec.	65.12 (64.69)	4.39 (3.98)	18.09 (17.78)	58
13	$C_{21}H_{17}N_5S_2$	194 – 196	62.53 (62.31)	4.22 (3.92)	17.37 (17.09)	52

Table (2)
Characteristic IR absorption bands.

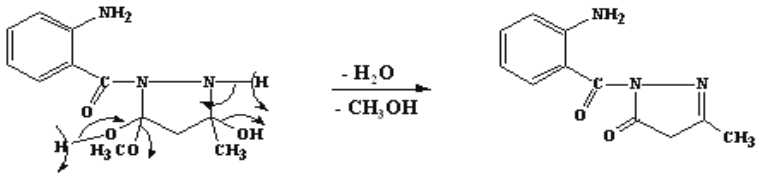
Comp. No.	*Infrared data (υ_{max} cm^{-1}) (KBr disc)*
1	(NH, $2NH_2$) 3450 – 3200; (CO amide) 1620.
2	(NH_2) 3280 – 3200; (C-H methyl) 2985; (CO amide) 1689, 1643; (C=N) 1580; (CH_3 bend.) 1370.
3	(NH, NH_2) 3440 – 3325; (C-H arm.) 3186; (CO amide) 1620, 1600.
4	(NH_2) 3400 – 3280; (C-H methyl) 2990; (CO amide) 1660; (C=N) 1580; (C=C) 1525; (CH_3 bend.) 1460.
5a	(OH), (NH) 3400 – 3300; (CO amide) 1620; (C=N) 1510.
5b	(NH) 3325; (CO amide) 1635; (C=N) 1488; (C-CI) 825.
5c	(NH) 3350; (CO amide) 1650; (C=N) 1590; (NO_2) 1520 asym. and 1340 sym.
5d	(OH), (NH) 3400 – 3250; (CO amide) 1630; (C=N) 1475; (C-CI) 820.
7	(NH2) 3471 – 3371; (S-H weak) 2761; (C=N) 1627; (C=S) 1272; (C-O-C oxadiazole ring) 1188.
8	(NH amide) 3142;(C-H arm.) 3016; (C-H methyl) 2929; (CO amide) 1697, 1610; (C=N) 1525; (CH3 bend.) 1367.
9	(NH amide) 3433; (CH arm.) 3062; (CO- H) 2923 (CO amide) 1697,1604; (C=N) 1566.
10	(NH) 3355 – 3200; (C-H arm.) 3116, 3031; (CO amide) 1674; (C=S) 1334, 1195.
11	(NH) 3247- 3217; (C-H arm.) 3132; (C=N) 1658; (C-S-C thiadiazole ring) 1640.
12	(NH) 3300 – 3100; (C=N) 1670; (C=S) 1230 (C-O-C oxadiazole ring) 1190.
13	(NH) 3278; (C-H arm.) 3132; (-S-H) 278; (C=N triazole ring) 1650; (C=S) 1240.

Results and Discussion

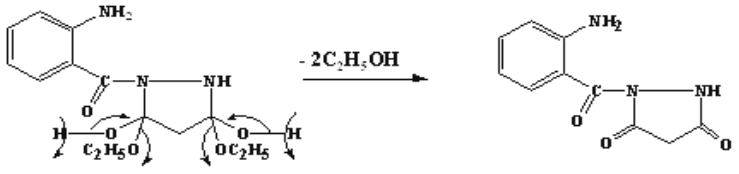
Acid hydrazides can be considered as useful intermediates leading to the formation of some heterocyclic compounds. So compound (1) has been chosen as a starting material for synthesis of new heterocyclic compounds and Schiff bases. In the first part of this work compound (1) was treated with different carbonyl compounds such as methyl acetoacetate, diethylmalonate and acetyl-acetone to give the corresponding pyrazole derivatives (2-4), respectively[14] (Scheme 1). The IR spectra of compounds (2), (3) and (4) showed the stretching bands of (NH_2) group at 3200-3440 cm^{-1} and appearance of (C =N) stretching band at 1580 cm^{-1} for compound (2) and (4) while it appears at 1525 cm^{-1} for compound (3). The stretching band of (CO amide) appears at 1689 cm^{-1} for compound (2), 1600 cm^{-1} for compound (3) and 1660 cm^{-1} for compound (4). Moreover, the IR spectra for compound (2) and (4) showed stretching bands for (C – H of CH_3) at 2985 cm^{-1} for compound (2) and at 2990 cm^{-1} for compound (4) in addition to the bands at 1370 cm^{-1} for compound (2) and 1460 cm^{-1} for compound (4) due to (C – H bending in CH_3). The mechanism for the formation of pyrazole ring includes nucleophilic attack of NH - NH_2 electrons of compound (1) at the carbonyl carbons of methyl acetoacetate, diethyl-malonate and acetylacetone with ring closing and elimination of two molecules consists of H_2O and CH_3OH for compound (2), two C_2H_5OH for compound (3) or two molecule of H_2O for compound (4) (Scheme 3).



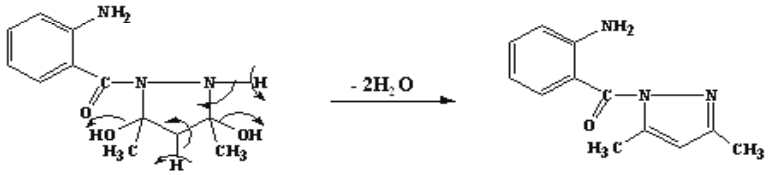
If R= OCH_3, CH_3 the mechanism will be



If R= OC_2H_5, OC_2H_5 the mechanism will be



If R=CH_3, CH_3 the mechanism will be

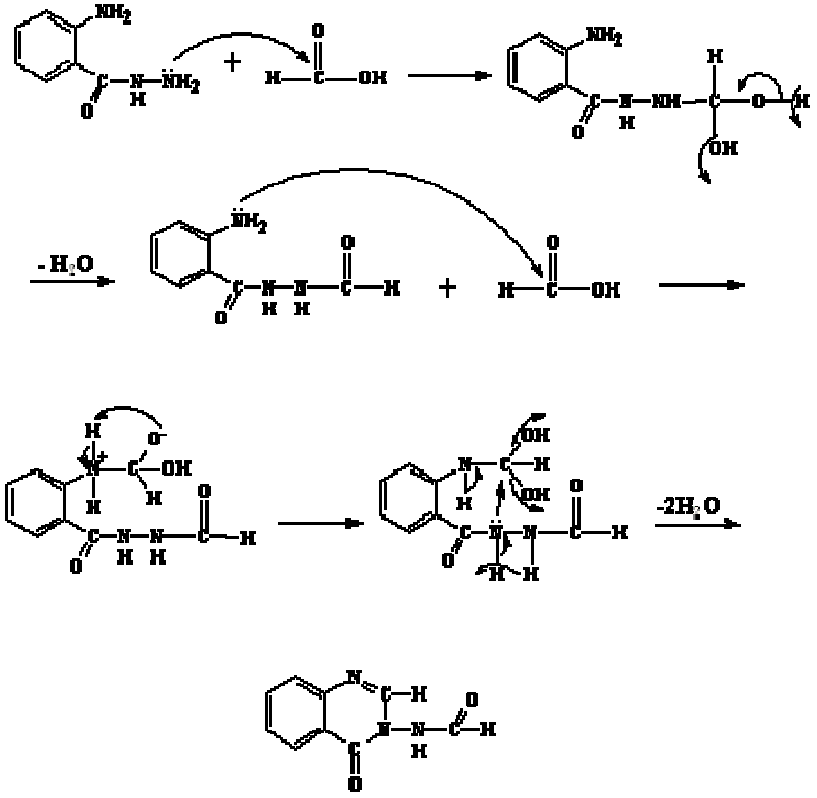


Scheme (3).

And the appearance of stretching. The Schiff bases (5 a, b, c, d) were synthesized from the reaction of compound (1) with two moles of deferent substituted benzaldehydes. The IR spectra of Schiff bases showed the stretching bands of (NH) groups of the derivatives at 3250 – 3400 cm^{-1} bands at 1470 -1590 cm^{-1} for two (C = N) groups.

The treatment of compound (1) with CS_2 in presence of alcoholic KOH give xanthate salt 6 which was heated for 4hr. to produce the oxadiazole derivative (7). The IR spectrum of this compound displayed two stretching bands of NH and NH_2 at 3471 cm^{-1} and at 3371 cm^{-1}. The other observed bands were at 2761 cm^{-1} for (S-H weak), 1627 cm^{-1} for (C = N), 1272 cm^{-1} for (C = S) and 1188 cm^{-1} which was characteristic for (C–O–C) of oxadiazole ring. See Table (2).

One the other hand, the reaction of compound (1) with other carbonyl compounds such as formic acid and acetic anhydride resulted in the formation of quinazoline derivatives (8) and (9) respectively[14]. By nucleophilic attack of the electros of two (NH_2) groups of compound (1) on the carbonyl group of two molecules of formic acid or acetic anhydride with elimination two H_2O molecules in the first step followed by another nucleophilic attack of NH electrons on the inner carbonyl group resulting intermolecular cyclization with elimination of another H_2O molecule (Scheme4).



Scheme (4).

The IR spectra of these compounds revealed the absence of the stretching bands of (NH_2) groups and appearance of stretching bands of (N–H amide) at 3142 cm^{-1} for compound (8) and at 3433 cm^{-1} for compound (9). The IR showed also the appearance of two stretching bands at 1697 cm^{-1} and 1610 cm^{-1} for compound (8) and at 1697 cm^{-1} and 1604 cm^{-1} for compound (9) due to the two carbonyl amide groups of the quinazoline ring in addition to the appearance of (C = N) stretching band at 1525 cm^{-1} for compound (8) and at 1566 cm^{-1} for compound (9).

The second part of this work involves reacting compound (1) with two moles of phenyl isothiocyanate to give thiosemicarbazide derivative (10) [7,8] which showed IR stretching bands at 3355 – 3200 cm^{-1} of (N – H) groups, 3116 cm^{-1}, 3031 cm^{-1} of (C – H aromatic) of the benzene rings,1674 cm^{-1} of (C = O amide) and two bands at 1334 $cm^{-1}$and at 1195 cm^{-1} of the two groups of (C = S).

The cyclization of compound (10) with H_2SO_4, I_2 in KI in presence of 10% NaOH or 10% NaOH produce thiadiazole (11), oxadiazole (12) and triazole (13) derivatives respectively [6,7] (Scheme 2). Thiadiazole derivatives (11) gave diagnostic IR stretching bands at 3247 cm^{-1}, 3217 cm^{-1} for (N – H) groups, 1658 cm^{-1} for (C = N) and at 640 cm^{-1} (C – S – C) of thiadiazole ring, while oxadiazole derivative (12). IR spectrum displayed the following stretching bands at 3300 – 3100 cm^{-1} for (N –H) groups, 1670 cm^{-1} for (C = N), 1230 cm^{-1} for (C = S) and 1190 cm^{-1} for (C – O – C) of oxadiazole ring. Also triazole derivative (13) showed characteristic IR stretching bands at 3278 cm^{-1} for (N-H) group, 2785 cm^{-1} weak for (S – H) group, 1650 cm^{-1} for (C = N) of triazole ring and 1240 cm^{-1} for (C = S).

These products included Scheme 1 and 2 are useful intermediate heterocyclic compounds for further investigations such as the physiological effects, good chelating reagents for organometallic cyclo compounds using deferent central ions, this work may be continued for investigating the NMR – spectra for those heterocyclic compounds.

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الخلاصة

تم في هذا البحث استخدام 2-امينو بنزهيدرازايد (1) كمادة اولية لتحضير بعض المركبات الحلقية غير المتجانسة الجديدة وقواعد شف (2 – 9). كما تم تحضير مشتقات تحوي حلقات الثايادايزول والاوكسادايازو والترايازول بمفاعلة مركب (1) مع فنيل ايزوثايوسيانات (10 – 13) . شخصت هذه المركبات من خلال درجات الانصهار وتقنية FTIR وتحليل العناصر.