Synthesis of Some New Schiff Bases and 1,3-Oxazepine Derivatives from 2-Aminoacetyl-5-thioacetic hydrazide-1,3,4-thiadiazole

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:Abstract
N-[5-(4-Chloro-benzylidene-hydrazinocarbonyl-methylsulfanyl)-[1,3,4]-thiadia zol-2-yl]-acetamide [5], N-[5-(4-Hydroxy-3-methoxy-benzylidene-hydrazinocarbonyl-methyl-sulfanyl)-[1,3,4]-thiadiazol-2-yl]-acetamide [6], N-(5-{[2-(4-Chloro-phenyl)-4,7-dioxo-4,7-dihydro-[1,3]-oxazepin-3-ylcarbamoyl]-me thylsulfanyl}-[1,3,4]-thiadiazol-2-yl)-acetamide [7], N-(5-{[2-(4-Hydroxy-3-methoxy-phenyl)-4,7-dioxo-4,7-dihydro-[1,3]-oxazepin-3-yl-a rbamoyl]methylsulfanyl} -[1,3,4]-thiadiazol-2-yl)-acetamide [8], N-(5-{[7-(4-Chloro-phenyl)-5,9-dioxo-5,9-dihydro-6-oxa-8-aza-benzocyclohepten-8-y lcarbamoyl]-methylsulfanyl }-[1,3,4]-thiadiazol-2-yl)-acetamide [9] and N-(5-{[7-(4-Hydroxy-3-methoxy-phenyl)-5,9-dioxo-5,9-dihydro-6-oxa-8-aza-benzocy clohepten-8-ylcarbamoyl]-methylsulfanyl}-[1,3,4]-thiadiazol-2-yl)-acetamide [10] .were prepared starting from 2-Aminoacetyl-5-thioacetic hydrazide-1,3,4-thiadiazole
Amino-5-mercapto-1,3,4-thiadiazole [1] obtaind from treatment of-2 thiosemicarbazide with carbon disulfide in presence of anhydrous sodium carbonate which was then converted into the 2-Aminoacetyl-5-mercapto-1,3,4-thiadiazole [2] by reaction with acetic anhydride in presence of glacial acetic acid. Thiol group in compound [2] was then converted into the thioethylacetate by reaction with Ethyl 1-chloroacetate to get 2-Aminoacetyl-5-thioethylacetate-1,3,4-thiadiazole [3] which was then treated with hydrazine monohydrate to get 2-Aminoacetyl-5-thioacetic hydrazide-1,3,4-thiadiazole [4]. Treatment of the resulting hydrazide derivative [4] with 4-Chlorobenzaldehyde and 4-Hydroxy-3-methoxybenzaldehyde in absolute ethanol resuted in the formation of new Schiff bases [5] and [6], respectively. Treatment of compounds [5] and [6] with maleic anhydride and phthalic anhydride under pericyclic reactions conditions resulted in the formation of new 1,3-oxazepine derivatives [7-10] respectively. The new compounds [5-10] may be used as .antibiotics
The structures of the new synthesized compounds were confirmed by melting .points, C.H.N. Elementary Analysis and FT-IR spectra

الخلاصة:
تم في هذا البحث تحضير 4)-5]-N-كلورو-بنزيليدين-هايدرازينوكاربونيل مثيل سلفانيل)-1،3،4-ثاياديازول-2-يل]- أسيتاميد [5], 4)-5]-N-هيدروكسي-3-ميثوكسي-بنزيليدين-هايدرازينوكاربونيل مثيل سلفانيل)- 1،3،4-ثاياديازول-2-يل]- أسيتاميد [6], 4)-2]}-5]-N-كلورو-فنيل)-4 ,7- دايوكسو-4 ,7- داي هايدرو-[3,1]-أوكسازبين-3-يل كارباميل]-مثيل سلفانيل}- 1،3،4-ثاياديازول-2-يل]- أسيتاميد [7], 4)-2]}-5)-N-هيدروكسي-3-ميثوكسي-فنيل) -4 ,7- دايوكسو-4 ,7- داي هايدرو-[3,1]-أوكسازبين-3-يل كارباميل]-مثيل سلفانيل}- 1،3،4-ثاياديازول-2-يل]- أسيتاميد [8], 4)-7]}-5)-N-كلورو-فنيل)-9,5-دايوكسو-9,5-داي هايدرو-6-أوكسا-8-آزا-بنزوسايكلوهبتين-8-يل كارباميل]-مثيل سلفانيل}- 1،3،4-ثاياديازول-2-يل]- أسيتاميد [9] و

4)-7]}-5)-N-هيدروكسي-3-ميثوكسي-فنيل)-9,5-دايوكسو-9,5-داي
هايدرو-6-أوكسا-8-آزا-بنزوسايكلوهبتين-8-يل كاربامويل]-مثيل سلفانيل}- 1،3،4-ثاياديازول-2-يل]-
أسيتاميد [10]. حضر 2-امينو-5-مركبتو-1،3،4-ثاياديازول [1] من تفاعل الثايوسميكاربزايد مع ثنائي كبريتيد الكاربون بوجود كاربونات الصوديوم اللامائية, الذي تم تحويله لاحقاً الى 2-
أمينوأسيتيل-5-مركبتو-1،3،4-ثاياديازول [2] عن طريق تفاعله مع انهدريد الخليك بوجود حامض الخليك الثلجي. بعد ذلك تم تحويل مجموعة الثايول في المركب [2] الى ثايوأثيل أسيتيت عن طريق تفاعلها مع أثيل 1-كلوروأسيتيت فتم الحصول على 2-أمينوأسيتيل-5-ثايوأثيل اسيتيت-1،3،4-ثاياديازول [3] الذي تمت معاملته لاحقاً مع الهايدرازين المائي فتم الحصول على 2-أمينوأسيتيل-5-ثايوأسيتيك هايدرازيد-1،3،4-ثاياديازول [4]. ان معاملة مشتق الهايدرازيد الناتج [4] مع كلٍ من 4-كلوروبنزالديهايد و 4-هيدروكسي-3-ميثوكسي بنزالديهايد في الايثانول المطلق أعطت قواعد شيف جديده [5] و[6]. ان معاملة قواعد شيف [5] و[6] مع كل من انهدريد الماليك وانهدريد الفثاليك تحت شروط تفاعلات الطوق الحلقي أعطت مشتقات 3,1-اوكسازبين جديده [7-10] وعلى التوالي.

شخصت كافة المركبات الجديده المحضرة بوساطة درجات الانصهار غير المصححة وتحليل نسب العناصر (C.H.N) واطياف الاشعة تحت الحمراء.

:Introduction

Since thiadiazole have a variety of potential biological activities and utilities as technologically useful materials, a number of methods for the preparation have been developed. Many synthesis of 1,3,4-thiadiazoles proceed from thiosemicarbazide or substituted thiosemicarbazide[1,2], for example thiosemicarbazide itself was shown to cyclize directly to 2-Amino-5-methyl-1,3,4-thiadiazole. A useful preparative method for 2-Amino-5-mercapto-1,3,4-thiadiazole was developed by Guha[3] which showed that when thiosemicarbazide is treated with carbon disulfide and potassium hydroxide, the potassium salt of thiosemicarbazide-4-dithiocarboxylic acid was formed, then heating to 140ºC causes cyclization to the salt of 2-Amino-5-mercapto-1,3,4-thiadiazole. Hiremarth et.al[4] synthesized a series of 2-Amino-5[4-(substituted)anilino]-methyl-1,3,4-thiadiazole through cyclocondensation of thiosemicarbazide derivatives with phosphoric acid. Mohan et.al[5] prepared 3-aryl-1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazole-6(5H)-thione by the reaction of 3-Aryl-4-amino-5-mercapto-1,2,4-triazoles with CS_2 in the presence of pyridine. Zamani et.al[6] synthesized new 1,3,4-thiadiazole derivative bearing pyridyl and 1-naphthyl rings, using 1,4-disubstituted thiosemicarbazide. Kuerzer and Secker[7] found that the use of reactants in corporating free hydrazine group have provided a versatile route to substituted 1,3,4-thiadiazoles. El-khawass et.al[8] synthesized a series of 6-substituted-3-[1-(1H-benzo triazole) methyl]-1,2,4-triazolo [3,4-b]-1,3,4-thiadiazoles from condensation of the 1-(4-amino-4H-1,2,4-triazole-3-thion-5-yl) methyl-1H-benzotriazole with carboxylic acids in the presence of phosphorus oxychloride. Shafiee et.al[9] found that the reaction of 1-methyl-4-nitropyrrol-2-carboxylic acid with phosphorus oxychloride and thiosemicarbazide afforded-2-amino-5-(1-methyl-4-nitro-2-pyrrole)-1,3,4-thiadiazole. Alho et.al[10] synthesized 1,3,4-thiadiazole derivatives from several diaryl ketones via the corresponding thiosemicarbazones. Onkol et.al[11] prepared a novel series of 1,3,4-thiadiazole derivatives by treatment of thiosemicarbazide derivatives with conc. H_2SO_4. Schiff bases (imines) were prepared via a condensation reaction of primary amines with aromatic aldehydes or ketones[12,13]. Mechanism of reaction was

well-known[14]. Many 1,3,4-thiadiazole derivatives containing imine group were prepared[15-17]. For a long time, the synthesis of 1,3- and 1,4-oxazepine rings was based on two limited classical types of reactions, the first reaction is called Valence-bond isomerization which is carried out via irradiation of polyarylpyridine N-oxides. This irradiation results in ring expansion to 1,3-oxazepine in high yield and some deoxygenation to the parent amines[18] . The second reaction is called Enamines condensation which is carried out by reaction of Erythro 1,2-diphenyl-2-phenylaminoethanol with dimethylacetylene dicarboxylate in methanol at room temperature to give a mixture of the Michael adduct and tetrahydro-1,4-oxazepin-7-one[19]. Recently, a pericyclic reactions are used to synthesis of 1,3-oxazepine ring[16,20-23]. This type of reactions is not limited and gives various 1,3-oxazepine ring derivatives. The type of cycloaddition reaction that used to synthesis of 1,3-oxazepine ring was classified as (2+5) → 7 cycloaddition reaction in which two atoms of imine group as two-membered component was added to five-membered component such as maleic or phthalic anhydrides to give a seven-membered heterocycle[16,20-23].

A large number of 1,3,4-thiadiazole derivatives were prepared and showed various biological activities[24-27], in eddition of another important uses[28-30], therefore we prepared some new derivatives of 1,3,4-thiadiazole ring might have some biological activity.

Experimental:

General

1) The solvents and liquid reagents were purified when it was necessary; the solid materials were also dried under reduced pressure when it was necessary.

2) TLC were performed on pre-coated sheets with 0.25 mm layer of Silica Gel GF254 of the Merck company, the detection was followed by coloring with iodine or H_2SO_4 in ethanol (60%) followed by heating.

3) Evaporating of solvents by using Buchi vacuum rotary evaporator type 160.

4) Melting points (M.P.) were determined by Stuart melting point apparatus.

5) Elemental analysis measured on E.A.300, Euro- Vector, Italy, 2003.

6) FT-IR spectra were recorded on FT-IR 8400_S, Schimadzu-Spectrophotometer and using KBr discs.

7) Compounds [1], [2] and [3] were prepared according to the literature [16].

Preparation Methods

[4] Synthesis of 2-Aminoacetyl-5-thioacetic hydrazide-1,3,4-thiadiazole

Hydrazine monohydrate (0.35g, 0.007mole) was dissolved in (10mL) absolute ethanol, then the mixture was stirred at room temperature for 30min., then 2-Aminoacetyl-5-thioethylacetate-1,3,4-thiadiazole [3] (1.827g, 0.007mole) was added. The reaction mixture was refluxed with stirring at 80ºC for 7hrs., T.L.C (ethanol:diethylether) (1:2), R_f=0.8. The mixture was then allowed to cool down to room temperature, a white precipitate developed, filtered under reduced pressure and recrystallized from distilled water, yield 77%, m.p=(254-255ºC), lit.[16], m.p.=(255-256ºC).

Synthesis of N-[5-(4-Chloro-benzylidene-hydrazinocarbonyl [methylsulfanyl)-[1,3,4]-thiadiazol-2-yl]-acetamide [5

Hydrazide derivative (0.988g, 0.004mole) was dissolved in (20mL) of absolute ethanol, then 4-Chlorobenzaldehyde (0.562g, 0.004mole) was added. The reaction mixture was refluxed with stirring at 80ºC for 4hrs., T.L.C (ethanol:diethylether) (2:1), R_f=0.65. Then the mixture was allowed to cool down to room temperature. The solvent was evaporated under reduced pressure, a red precipitate developed, filtered and recrystallized from ethanol, yield 70%, m.p=(165-167ºC).

Synthesis of N-[5-(4-Hydroxy-3-methoxy-benzylidene-hydrazinocarbonyl [methylsulfanyl)-[1,3,4]-thiadiazol-2-yl]-acetamide [6

Hydrazide derivative (0.988g, 0.004mole) was dissolved in (20mL) of absolute ethanol, then 4-Hydroxy-3-methoxybenzaldehyde (0.608g, 0.004mole) was added. The reaction mixture was refluxed with stirring at 80ºC for 3hrs., T.L.C (ethanol:diethylether) (1:1), R_f=0.71. Then the mixture was allowed to cool down to room temperature. The solvent was evaporated under reduced pressure, a red precipitate developed, filtered and recrystallized from ethanol, yield 73%, m.p=(185-187ºC).

Synthesis of N-(5-{[2-(4-Chloro-phenyl)-4,7-dioxo-4,7-dihydro-[1,3]-oxazepin-3-ylcarbamoyl]-[methylsulfanyl}-[1,3,4]-thiadiazol-2-yl)-acetamide [7

Schiff base derivative [5] (0.3695g, 0.001mole) and maleic anhydride (0.098g, 0.001mole) were dissolved in (20mL) of dioxan. The reaction mixture was refluxed with stirring at 90ºC for 4hrs., T.L.C (ethanol:diethylether) (1:1), R_f=0.70. The mixture was then allowed to cool down to room temperature, a red precipitate developed, filtered and recrystallized from ethanol, yield 69%, m.p=(150-152ºC).

Synthesis of N-(5-{[2-(4-Hydroxy-3-methoxy-phenyl)-4,7-dioxo-4,7-dihydro-[1,3]-oxazepin-3-yl [carbamoyl]methylsulfanyl}-[1,3,4]-thiadiazol-2-yl)-acetamide [8

Schiff base derivative [6] (0.381g, 0.001mole) and maleic anhydride (0.098g, 0.001mole) were dissolved in (20mL) of dioxan. The reaction mixture was refluxed with stirring at 90ºC for 4hrs., T .L.C (ethanol:diethylether) (1:2), R_f=0.78. The mixture was then allowed to cool down to room temperature, a orange precipitate developed, filtered and recrystallized from ethanol, yield 71%, m.p=(171-173ºC).

Synthesis of N-(5-{[7-(4-Chloro-phenyl)-5,9-dioxo-5,9-dihydro-6-oxa-8-aza-benzocyclohept en-8-ylcarbamoyl]-methylsulfanyl}-[1,3,4]-thiadiazol-2-yl)- acetamide [[9

Schiff base derivative [5] (0.3695g, 0.001mole) and phthalic anhydride (0.148g, 0.001mole) were dissolved in (20mL) of dioxan. The reaction mixture was refluxed with stirring at 90ºC for 4hrs., T .L.C (ethanol:diethylether) (1:1), R_f=0.74. The mixture was then allowed to cool down to room temperature, a pale yellow precipitate developed, filtered and recrystallized from ethanol, yield 66%, m.p=(155-157ºC).

Synthesis of N-(5-{[7-(4-Hydroxy-3-methoxy-phenyl)-5,9-dioxo-5,9-dihydro-6-oxa-8-aza-benzoc [ycloheptен-8-ylcarbamoyl]-methylsulfanyl}-[1,3,4]-thiadiazol-2-yl)-acetamide [10

Schiff base derivative [6] (0.381g, 0.001mole) and phthalic anhydride (0.148g, 0.001mole) were dissolved in (20mL) of dioxan. The reaction mixture was refluxed with stirring at 90ºC for 4hrs., T .L.C (ethanol:diethylether) (1:2), R_f=0.81. The mixture was then allowed to cool down to room temperature, a white precipitate developed, filtered and recrystallized from ethanol, yield 68%, m.p=(175-177ºC).

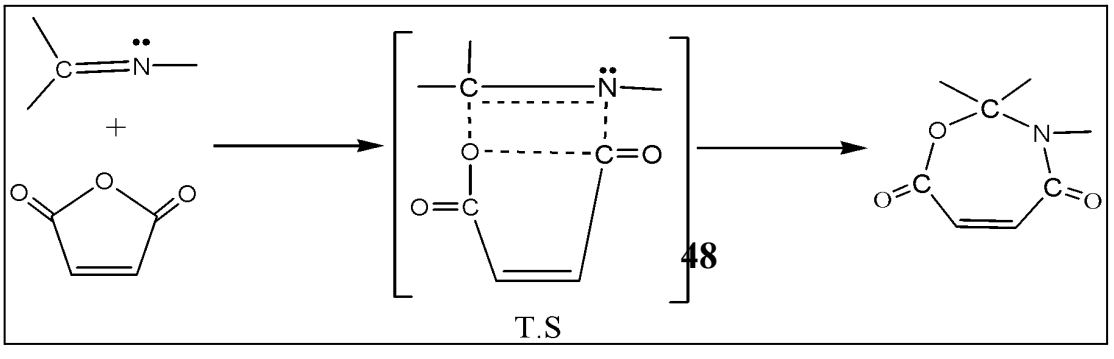
Table (1): Melting points, percent yields and (C.H.N.) analysis of the prepared (compounds (4-10

Comp. No.	M.F.	M.Wt.	(M.P.)ºC	Yield%	C.H.N. analysis					
					%Calculated			%Found		
					C	H	N	C	H	N
[4]	$C_6H_9N_5O_2S_2$	247	255-256	77	-	-	-	-	-	-
[5]	$C_{13}H_{12}N_5O_2S_2Cl$	369.5	165-167	70	42.21	3.24	18.94	42.69	3.53	18.61
[6]	$C_{14}H_{15}N_5O_4S_2$	381	185-187	73	44.09	3.93	18.37	44.51	3.82	18.56
[7]	$C_{17}H_{14}N_5O_5S_2Cl$	467.5	150-152	69	43.63	2.99	14.97	43.42	3.09	15.10
[8]	$C_{18}H_{17}N_5O_7S_2$	479	171-173	71	45.09	3.54	14.61	44.21	3.71	14.32
[9]	$C_{21}H_{16}N_5O_5S_2Cl$	517.5	155-157	66	48.69	3.09	13.52	48.52	2.98	14.08
[10]	$C_{22}H_{19}N_5O_7S_2$	529	175-177	68	49.90	3.59	13.23	50.41	3.63	13.03

Results and Discussion:

Compounds [1], [2], [3] and [4] were made as described in literature[16]. Amino group of hydrazide derivative [4] was reacted with aldehyde group of 4-chlorobenzaldehyde and 4-Hydroxy-5-methoxybenzaldehyde in absolute ethanol via a condensation reaction accompanied with releasing H_2O molecule to give Schiff bases derivatives [5] and [6], respectively[12-14].

A pericyclic reactions, between imine groups of Schiff bases derivatives [5] and [6], as two-membered components, and cyclic anhydrides (maleic anhydride and phthalic anhydride) as five-membered components in dry dioxan, were carried out to synthesis of 1,3-oxazepine derivatives [7-10][16,20-23]. A pericyclic reaction is a concerted process based on principle of conservation of molecular orbital symmetry between the reaction components during the reaction proceeding which is leading to a cyclic transition state corresponds with arrangement of participating orbitals[16,20]. Concerted reaction means that breaking and formation of bonds occur simultaneously via a single transition state and there is no intermediate in the process[31]. Mechanism of the pericyclic reaction for the synthesis 1,3-oxazepine ring shown in scheme (1)[16,20]:



Scheme(1): Approximate transition state geometry for addition of maleic anhydride to imine group

The structures of all synthesized compounds were shown in scheme (2) and scheme (3). Compounds [1-4] showed identical melting points with that published [16]. Compound [1] was also characterized with FT-IR spectrum which showed the following characteristic absorption bands: the two bands at 3392cm^{-1} and 3279cm^{-1} due to asymmetric and symmetric stretching vibrations of (-NH_2) group, an absorption band at 3095cm^{-1} was due to the (-NH) stretching vibration (tautomeric form). The absorption bands at 2912cm^{-1} and 2766cm^{-1} attributable to the intramolecularly hydrogen bonded of (-NH) group[31]. The (-SH) stretching band found as very weak shoulder at 2560cm^{-1}. The absorbtion bands at 1597cm^{-1}, 1533cm^{-1} and 1494cm^{-1} attributed to the streching vibrations of three different types of imine groups inside thiadiazole rings due to the tautomerism. Also, the absorption bands at (1350, 1280)cm^{-1} due to the presence of (=N-N-C-) cyclic grouping[32]. Moreover, the absorption band at 1180cm^{-1} for the (C=S) group stretching vibration gives evidence that compound [1] can exist in two tautomeric forms, thiol form [1a] and thione form [1b][33]. Beside this, the two strong absorption bands at 1058cm^{-1} and 738cm^{-1} due to (C-S) bond stretching exo and endo thiadiazole ring respectively are good evidence for the structure given to the product.

[1a] [1b]

FT-IR spectrum of compound [2], Amino acetyl derivative, showed appearance of single absorption band at 3150cm^{-1} due to the υ(N-H) and disappearance of the two absorption bands at 3392cm^{-1} and 3279cm^{-1} were due to the asymmetric and symmetric stretching vibrations of (-NH_2) group[16], respectively. The strong absorption band at 1650cm^{-1} was due to the υ(C=O) of amide group[16]. The weak bands at (3000-2800)cm^{-1} were due to the υ(C-H) aliphatic of methyl group. Moreover, FT-IR spectrum of compound [2] showed appearance of another important characteristic absorption bands as follow: The sharp strong absorption band at 1575cm^{-1} attributed to the υ(C=N) endocyclic of 1,3,4-thiadiazole ring. The sharp strong absorption band at 1185cm^{-1} attributed to the υ(C=S) of thione tautomer[32,33]. Also, the absorption band at 1250cm^{-1} was due to the presence of (=N-N-C-) cyclic grouping[32]. FT-IR spectrum of compound [3], thioester derivative, showed disappearance of the strong absorption band at 1185cm^{-1} due to the υ(C=S) and appearance of sharp strong absorption band at 1730cm^{-1} due to the υ(C=O) of ester group[16]. FT-IR spectrum of compound [4] showed disappearance of the sharp

strong absorption band at 1730cm^{-1} attributed to the υ(C=O) of ester group and appearance of two sharp absorption bands at 1690cm^{-1} and 1650cm^{-1} attributed to the υ(C=O) of amide and hydrazide groups, respectively[16]. FT-IR spectrum of compound [4] also showed appearance of two absorption bands at 3280cm^{-1} and 3150cm^{-1} due to the asymmetric and symmetric stretching vibrations of (-NH_2) group, respectively[16]. FT-IR spectrum of compound [4] also showed appearance of another important characteristic absorption bands shown in Table (2). FT-IR spectra of compounds [5] and [6], Schiff bases derivatives, showed disappearance of the two absorption bands at 3280cm^{-1} and 3150cm^{-1} due to the asymmetric and symmetric stretching vibrations of (-NH_2) group of hydrazide derivative [4], respectively, and appearance of sharp strong absorption band at 1690cm^{-1} and 1670cm^{-1}, respectively, attributed to the υ(C=N) exocyclic of thiadiazole ring. FT-IR spectra of compounds [5] and [6] also showed appearance of sharp strong absorption band at 1680cm^{-1} and 1670cm^{-1} interacted with υ(C=N) exocyclic, respectively, attributed to the υ(C=O) of amide groups. FT-IR spectrum of compound [5] showed appearance of absorption band at 3060cm^{-1} due to the υ(C-H) aromatic of benzene ring. Moreover, FT-IR spectrum of compound [5] showed appearance of two absorption bands at 1600cm^{-1} and 1490cm^{-1} attributed to the υ(C=C) aromatic of benzene ring. The strong absorption band at 800cm^{-1} due to the δ(C-H) aromatic out of plane. FT-IR spectrum of compound [6] showed appearance of absorption band at 3000cm^{-1} due to the υ(C-H) aromatic of benzene ring. Moreover, FT-IR spectrum of compound [6] showed appearance of two absorption bands at 1600cm^{-1} and 1510cm^{-1} attributed to the υ(C=C) aromatic of benzene ring. The strong absorption band at 830cm^{-1} due to the δ(C-H) aromatic out of plane. FT-IR spectra of compounds [5] and [6] also showed appearance of another important characteristic absorption bands shown in Table (2). FT-IR spectra of compounds [7] and [9], 1,3-oxazepine derivatives, showed disappearance of the strong absorption band at 1690cm^{-1} due to the υ(C=N) exocyclic and appearance of broad strong absorption band at 1670cm^{-1} and 1680cm^{-1}, respectively, attributed to the υ(C=O) of amide and lactone (interacted). FT-IR spectra of compounds [7] and [9] showed appearance of another important characteristic absorption bands shown in Table (2). FT-IR spectra of compounds [8] and [10], 1,3-oxazepine derivatives, showed appearance of sharp strong absorption band at 1730cm^{-1} and 1730cm^{-1}, respectively, attributed to the stretching vibration of cyclic ester carbonyl group (-CO-O-) of 1,3-oxazepine ring. FT-IR spectra of compounds [8] and [10] also showed appearance of sharp strong absorption band at 1680cm^{-1} and 1690cm^{-1}, respectively, attributed to the υ(C=O) of amide groups.

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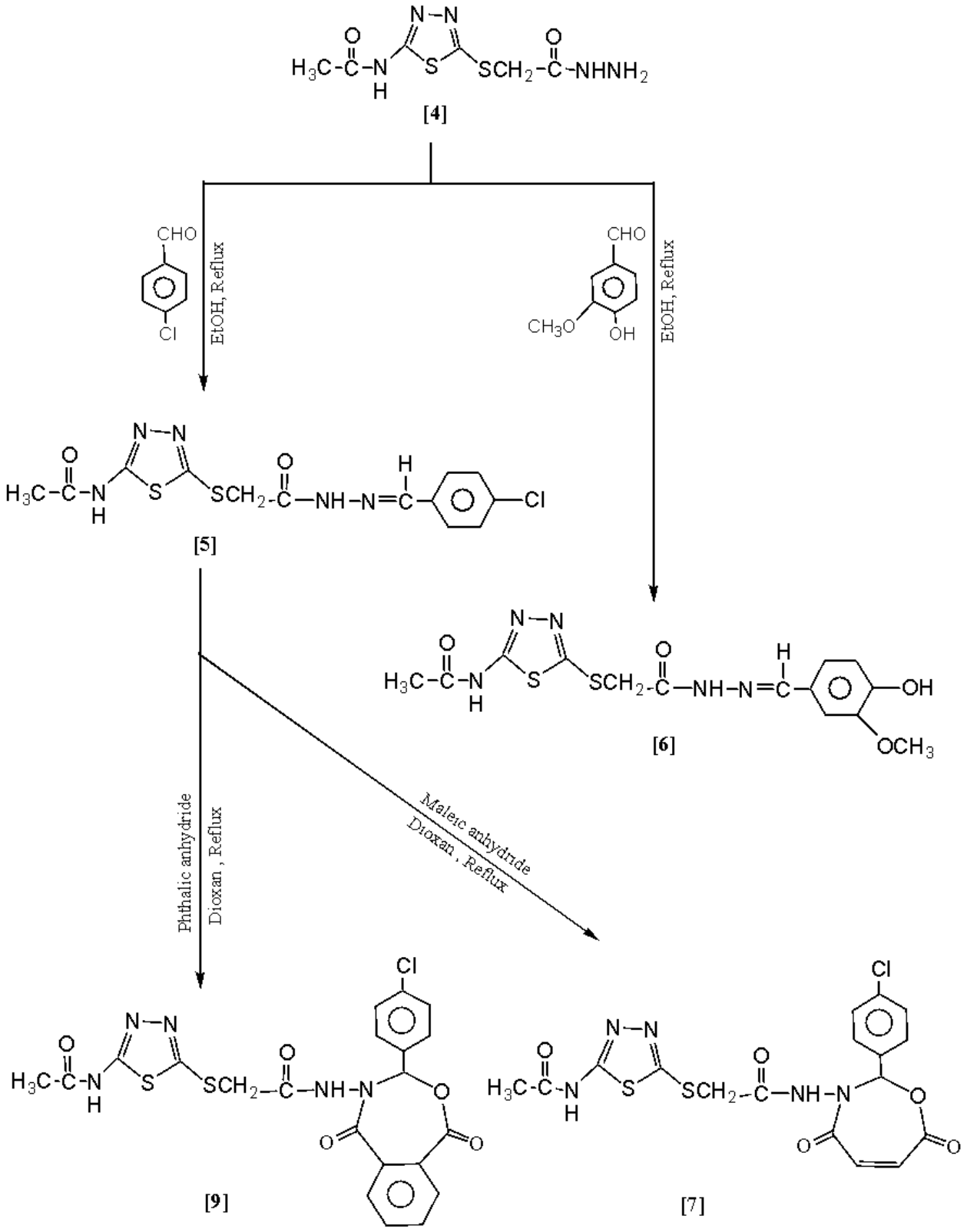
[Scheme (2): Reactions proceeding of synthesis of compounds [1-4



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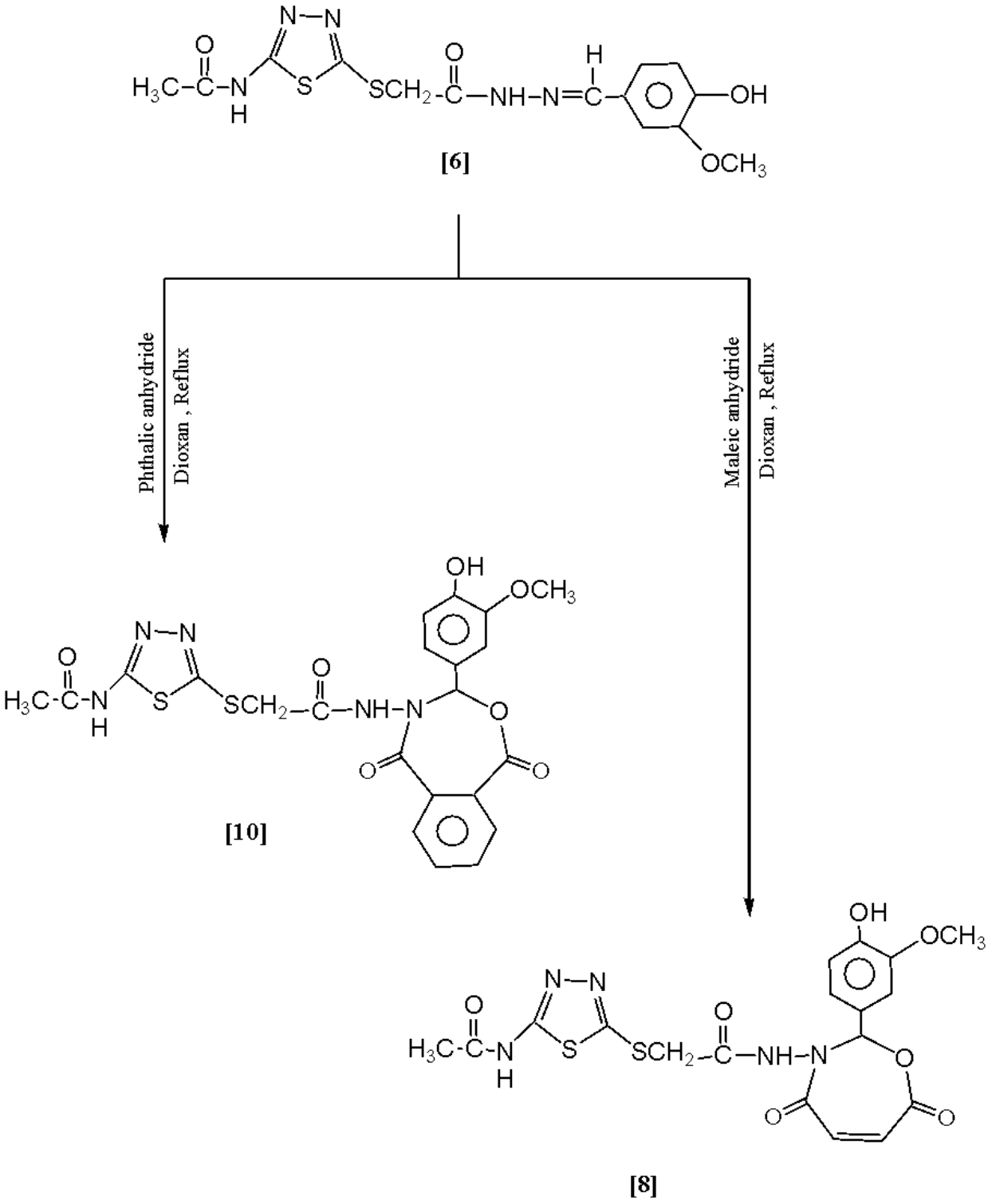

[Scheme (3): Reactions proceeding of synthesis of compounds [5-10