Synthesis and Antibacterial Evaluation of Some 1,2,3-Selenadiazole Derivatives

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الخلاصة

في هذا البحث تم تحضير عدد من مشتقات 3،2،1–سلينادايازول . حضرت مركبات التوسيل هيدرازون (1–3) من مفاعلة الاسيتوفينون (A) او الهكسانون الحلقي (B) والمنثون (C) مع هيدرازيد باراتولوين سلفونيل لتعطي هيدرازونات التوسيل (1–3) ، اعطى تحولق المركبات (1–3) باستعمال ثنائي اوكسيد السيلينيوم 3،2،1–سلينادايازول (4–6)، كما حضرت مشتقات السميكاربازون (7–9) من تفاعل المركبات (A–C) مع هيدروكلوريدسيمكاربازيد وأعطى معاملة السيميكاربازونات المحضرة مع ثنائي اوكسيد السيلينيوم تكون 3،2،1– سلينادايازول(4–6).

تم مفاعلة المركبات (A–C) مع اسيتات هيدرازينو الاثيل لتعطي استرات الاثيل (10–12) المقابلة، اعطى تحولق الاسترات باستعمال ثنائي اوكسيد السيلينيوم في الكلوروفورم مشتقات 1–أوكسو–سلينادايازول (13–15) ، بينما اعطى تفاعل (A–C) مع الفنيل هيدرازين الهيدرازونات (16–18) والتي تم تحولقها الى 2–فنيل –1–أوكسو – 3،2،1– سلينادايازول (19–20) باستعمال ثنائي اوكسيد السلينيوم ، تم دراسة الفعالية البايولوجية (ضد البكتريا) لبعض المركبات المحضرة ، شخصت المركبات المحضرة بالطرق الطيفية والفيزياوية .

Abstract

In this paper the synthesis of some 1,2,3-Selenadiazoles derivative is reported . Acetophenone (A) , Cyclohexanone (B) and menthone (C) each was treated with p-toluensulfoyl hydrazide in ethanol to give tosylhydrazones (1-3) , their cyclization with selenium dioxide gave 1,2,3-selenadiazoles (4-6) .

Semicarbazone derivatives (7-9) were obtained by from (A-C) by their reaction with semicarbazide hydrochloride , treatment of semicarbazone (7-9) with selenium dioxide gave 1,2,3-Selenadiazoles (4-6).

Compounds (A-C) were treatment with ethyl hydrazenoacetate to give the corresponding ethyl ester (10-12) .

* ***Presented at the second conference on Chemistry, University of Mosul, college of Education, 17-18 Novamber-2013.***

Cyclization of the esters with selenium dioxide in chloroforme gave 1-Oxo-selendiazole derivatives (13-15) , while the reaction of (A-C) with phenyl hydrazine gave hydrazones (16-18) , cyclization of the hydrazones with selenium dioxide in chloroforme gave 2-phenyl-1-oxo-1,2,3-selenadiazole derivatives (19-21). Scheme -1.
The antibacterial activity some of the synthesis compounds was studied .
The structures of synthesized compounds were confirmed by spectral and physical methods.

Introduction

The element selenium was first discovered in 1817 by the Swedish chemist Berzelius[(1)], and its deficiency in organism result in various diseases . selenium – containing heterocyclics are of considerable biological and pharmacological importance[(2-4)]. Some selenazole derivatives act as plasma phospholipids transfer protein inhibitors[(5)]. 1,2,3- selenadiazole and its derivatives have shown anti-bacterial activity against some gram-positive and gram-negative bacterias[(6-8)]. and as anti-inflamatory agent[(9)].

The synthesis of selenium heterocyclic compounds was achieved by the reaction of carbohydrazide with woollin's reagent in refluxing toluene[((10)]. 4-amino-1,3-seleazoles were prepared from dimethyl cyanodithioimidocarbonate by its reaction with amine in dimethyl formamide followed by the reaction with sodium selenide[(11)]. Substituted 2-amino -1,3- selenazoles were synthesis from seleourea and ketones in presence of iodine[(12)].

Experimental

All chemicals were purchased from Fluka and BDH Chemical Ltd. The melting points were measured on an Electrothermal 9300 Engineering LTD and were uncorrected . H^1NMR spectra were recorded on nucleic magnetic resonance model ultra shield 300MHz , Bruker Co ., Germany , using TMS as internal reference and DMSO-d6 as solvent . IR spectra were recorded on Infrared Spectrophotometer Model Tensor 27, Bruker Co., Germany, by using KBr discs. UV spectra were recorded on Shimadzu Double-Beam Spectrophotometer UV-210A by using ethanol as a solvent .

p-toludine sulfone hydrazine (I)

A mixture of p-toluene sulfonyl (0.01mole) and hydrazine hydrate 90% was stirred with cooling for 15 minute the mixture lift at room temperature for 2h . then was refluxed for 1h , cool , the mixture poured on a crashed – ice the product was separated , filtered and dried .

Ethyl aceto hydrazine (II)

Ethyl chloro acetate (0.01 mole) and 90% hydrazine hydrate (0.01 mole) was mixed with stirring and cooling , sodium acetate (4g) and few drops of acetic acid was added and the reaction mixture refluxed for 2h , cool

and neutralized with 20% sodium bicarbonate , the product was obtained by extraction with ether (2x25ml) ether layer was dried with calcium chloride and evaporated to give the product.

Tosylate hydrazone (1-3)

A mixture of p-toludine sulfone hydrazine (I) (9.3g,0.05 mole) and (acetophenone , cyclohexanone or menthone)(A-C) (0.01 mole) in absolute ethanol (35ml) was refluxed for 1.5h , the solvent was evaporated under reduced pressure , the solid product was recrystallized from ethanol. Tables (1,2)

5-Substituted -1,2,3- selenadiazole (4-6)

A) From hydrazone(1-3)

Amixtuer of tosylate compound (0.004 mole), selenium dioxide (0.444g,0.004 mole) and sodium sulfate (3g) in 1,4-dioxane (20ml) was heated at (35º-45ºC) for 1h, the reaction mixture was left at dark for 20h to complete the reaction , the 2/3 of the solvent was evaporated , water (15ml) was added and product was extracted with chloroform (3x20ml) , the organic layer dried with anhydrous calcium chloride, evaporated and the product recrystallized from chloroform-hexane . Table (1,2).

B) From semicarbazone (7-9)

A mixture of semicarbazone (7-9)(0.005 mole) , selenium dioxide (0.555g,0.005 mole) in acetic acid (10ml)was refluxed for 12h , filtered , washed with water , dried and recrystallized from chloroform. Table (1,2).

Substituted semicarbazone (7-9)

Compounds (A-C) (0.01 mole) was mixed with semicarbazone hydrochloride (1.679, 0.015 mole) sodium acetate (2g) and absolute ethanol (20ml) were added , the mixture was refluxed for 1h . The solvent was evaporated under reduced pressure filtered and recrystallized from ethanol . Table (1,2).

Ethyl substituted hydrazine crboxaylate (10-12)

A mixture of compounds (A-C)(0.001 mole) and ethyl acetate hydrazine (0.001) in chloroform (50ml) was refluxed for 24h , the solvent was evaporated under reduced pressure , cool , filtered and the precipitate was recrystallized from (ether – chloroform) . Table (1,2).

2-(ethoxycarbonylmethyl)-4-substituted-1-oxo-1,2,3-selenadiazole(13-15)

Compounds (10,11 or 12) (0.001 mole)was dissolved in glacial acetic acid (40ml) with stirring and heating (40-45ºC), selenium dioxide (0.166g, 0.0015 mole) was added then stirred for 5 minutes , the mixture left at room temperature for 24h , cold , water (20ml) was added , the product extracted with chloroform (3x40ml) , the chloroform was dried with calcium chloride and evaporated to give the product . Table (1,2).

Substituted phenyl hydrazine (16-18)

A mixture of (A,B or C) (0.001 mole) and phenyl hydrazine (0.108g, 0.001 mole) in chloroform (50ml) was refluxed for 24h , the solvent then evaporated under reduced pressure , the solid product was recrystallized from (ethanol-chloroform) . Table (1,2).

2-Phenyl -4- substituted -1-oxo-1,2,3-selenadiazole (19-21)

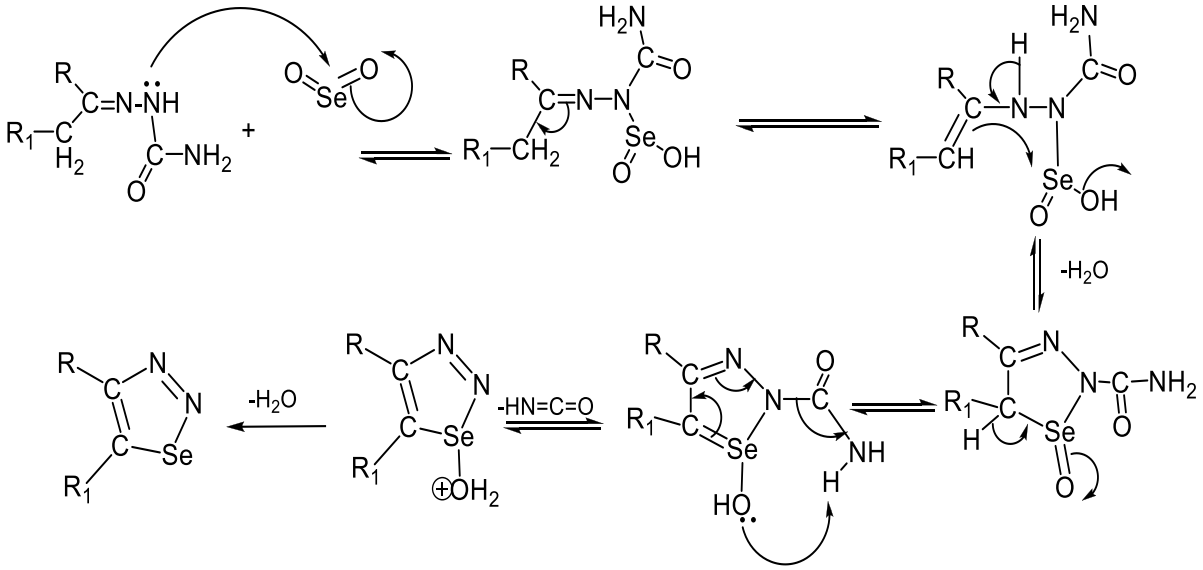
Substituted selenadiazoles (19-21) were synthesized following the procedure for the synthesis of compounds (13-15) , the starting compounds (16-18) (0.001 mole), was used . Table (1,2).

Table 1 : The Physical properties of compounds (1-21)

Comp.no.		m.p (°C)	Color	Yield %	λ Max (nm)	Molecule formula
1	Ph,CH_3	119-120	Metallic White	81	312	$C_{15}H_{16}N_2SO_2$
2		140-141	Brown	67	332	$C_{13}H_{18}N_2SO_2$
3		246-248	Green	88	346	$C_{17}H_{26}N_2SO_2$
4	Ph,CH_3	76-77	Dark Brown	71	386	$C_8H_6N_2Se$
5		188-189	Brown	69	371	$C_6H_8N_2Se$
6		190-193	Pale green	89	385	$C_{10}H_{16}N_2Se$
7	Ph,CH_3	201-203	Metallic White	81	327	$C_9H_{11}N_3O$
8		155-156	Brown	91	310	$C_7H_{13}N_3O$
9		234-236	Dark Green	77	319	$C_{11}H_{21}N_3O$
10	Ph,CH_3	131-132	Metallic White	76	331	$C_{11}H_{14}N_2O_2$
11		98-100	Metallic Brown	71	316	$C_9H_{16}N_2O_2$
12		138-139	Pale Green	81	328	$C_{13}H_{24}N_2O_2$
13	Ph,CH_3	87-88	Brown	66	422	$C_9H_{12}N_2SeO_3$
14		113-114	Red-Brown	69	416	$C_7H_{10}N_2SeO_3$
15		193-194	Red-Brown	73	396	$C_{11}H_{18}N_2SeO_3$
16	Ph,CH_3	61-63	Metallic Black	65	322	$C_{14}H_{14}N_2$
17		64-65	Dark Brown	68	316	$C_{12}H_{16}N_2$
18		130-133	Orange	79	334	$C_{16}H_{24}N_2$
19	Ph,CH_3	108-109	Pale Brown	69	437	$C_{14}H_{12}N_2SeO$
20		116-117	Brown	62	445	$C_{12}H_{14}N_2SeO$
21		122-123	Red-Brown	66	421	$C_{16}H_{22}N_2SeO$

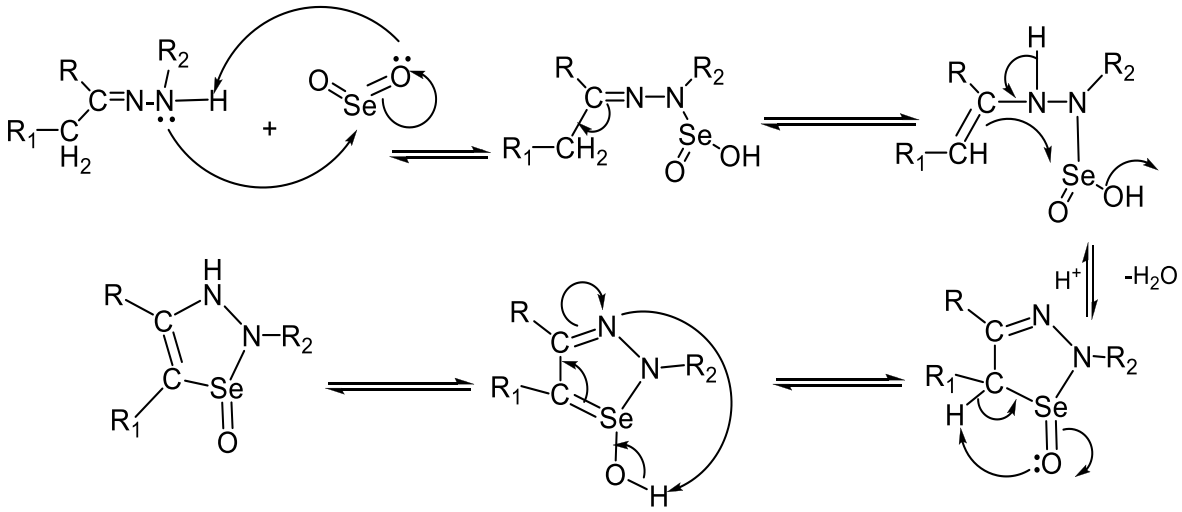
Result and Discussion

Acetophenone (A) , Cyclohexanone (B) or Menthone (C) was treated with p-toluenesulfonyl hydrazid to give tosylehydrazones (1-3) the IR spectra of the hydrazones (1-3) show absorption at ύ 1603 – 1624 cm^{-1}(C=N) , 1099-1192, 1416-1436 cm^{-1}(sym. and asym. SO_2) , cyclization of the hydrazones with selenium dioxide lead to the formation of the 1,2,3-selenadiazoles (4-6) the proposed mechanism reaction as follows



The IR spectra shows absorption at 742-765 cm^{-1} (C-Se-N) and 1429-1433 cm^{-1}(N=N) selenadiazole (4-6) were synthesized from (A-C) by their reaction with semicarbizade followed by cyclization with selenium dioxide.

Substituted 1,2,3-selenadiazole (13-15) were synthesis from (A-C) by their reaction with hydrazenoacetate to give the corresponding ethyl ester (10-12) which cyclized with selenium dioxide to give (13-15) the proposed mechanism of the reaction as follows



The IR spectra of compounds (13-15) show absorption at 1752-1753 cm^{-1}(C=O) ester and 1695-1696 cm^{-1}(Se=O) , 1,2,3-selenadiazole derivatives (19-21) were synthesis from (A-C) by their reaction with phenyl hydrazine to give hydrazone (16-18) which cyclized to 1,2,3-selenadiazole (19-21) with selenium dioxide in chloroform , the IR spectra showed absorption at 1670-1700 cm^{-1}(Se=O) and 735-767 , 648-702 cm^{-1} (C-Se-N) . The ^{1}HNMR for compounds 6,14,21 showed an expected peaks.

The structure of compound (6,14,21) were confirmed by ^{1}H-NMR (ppm) spectra :

Comp.6:(3.93 δ s , 1H , CH heterocyclic ring) ,(6.73-8.14 δ s , 5H , benzene ring) .

Comp.14: (1.11 δ t , 3H ester),(4.05 δ q , 2H ester) , (2.5 δ t , 4H cyclohexen $C_{3\&6)}$, (1.68 δ m , 4H cyclohexene $C_{4\&5}$) , (2.20 δ s , 2H between selenium ring and ester) , (8.94 δ s , 1H , NH selenium ring) .

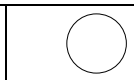
Comp.21: (1.17 δ d , 9H , 2 methyl group in isopropyl and methyl group at 6 position cyclohexane ring) , (1.9 δ m , 3H , 3 group CH in isopropyl and 3&6 position cyclohexane ring) ,(2.49 δ q , 4H cyclohexene $C_{4\&5}$), (7.24-8.33 δ m , 5H , benzene ring) , (10.17 δ s , 1H , selnium ring) .

s: single , d : doublet , t : triplet , q: quartet , m : multiplet.

Compounds (4-6,13-15,19-21) were tested against E.coli & Staphylococcua auro compounds 19,21 shows a good activity against E.coli with respect to standard controls used even at low concentration .

Compounds 14,21 shows high activity against Staphylococcus auro in various concentrations . Table 3 .

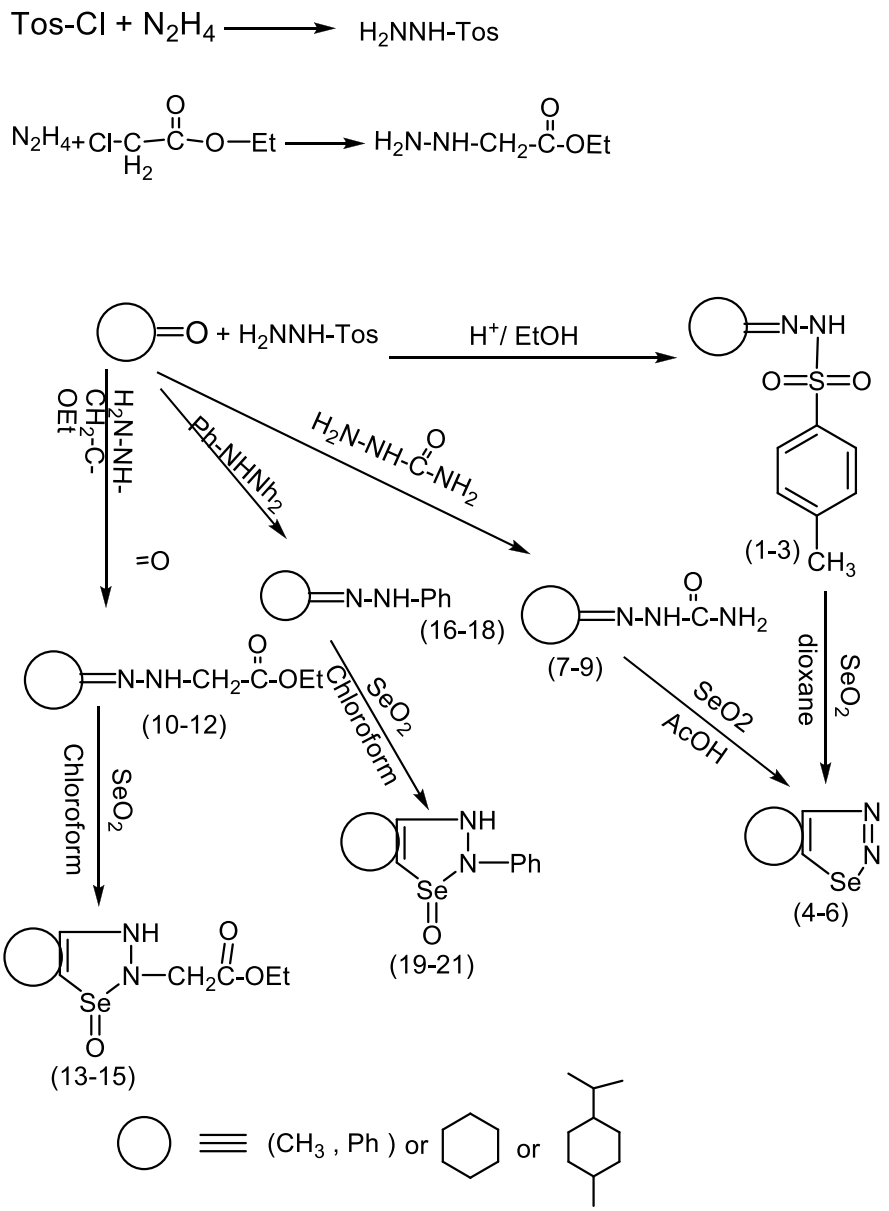
Table II: the IR spectra data of compounds (1-21)

Comp .no.		**IR ύ cm^{-1} , KBr**				
		N-H	C=N	C=O	C-Se-N	Other
1	Ph,CH_3	3424	1603	-	-	$SO_{2Assym,sym}$ 1436,1156
2		3442	1603	-	-	$SO_{2Assym,sym}$ 1416,1192
3		3423	1624	-	-	$SO_{2Assym,sym}$ 1430,1099
4	Ph,CH_3	-	-	-	758, 695	(N=N)1433
5		-	-	-	765, 614	(N=N)1429
6		-	-	-	742, 656	(N=N)1433
7	Ph,CH_3	3479	1638	1709	-	-
8		3441	1650	1696	-	-
9		3432	1660	1710	-	-
10	Ph,CH_3	3265	1645	1694	-	-

11		3244	1652	1697	-	-
12		3248	1650	1695	-	-
13	Ph,CH_3	3266	-	1752	732,698	(Se=O)1695
14		3245	-	1753	761,690	(Se=O)1696
15		3246	-	1753	744,690	(Se=O)1695
16	Ph,CH_3	3442	1615	-	-	-
17		3442	1623	-	-	-
18		3321	1604	-	-	-
19	Ph,CH_3	3352	-	-	753,674	(Se=O)1670
20		3301	-	-	735,648	(Se=O)1680
21		3385	-	-	767,702	(Se=O)1700

Table III: antibacterial activity of compounds (4-6 , 13-15 & 19-21)

Compounds no.		E.coli		Staphylococcua auro	
		10 mg/disk	0.1 mg/disk	10 mg/disk	0.1 mg/disk
4		-	-	9	-
5		10	-	10	-
6		-	-	12	15
13		-	-	13	-
14		8	8	28	15
15		-	-	12	15
19		15	12	-	-
20		-	9	-	-
21		20	-	30	25
Controls	Ciprofloxacin 5mg/disk	15		-	
	Chloramphenicol 30 mg/disk	14		17	



Scheme 1 : the synthetic route of the compounds (1-21)

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