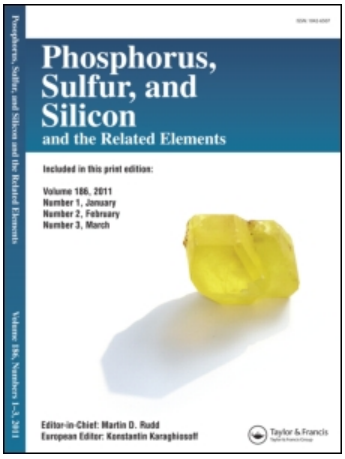

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Organic Selenium Compounds, Part IV: Synthesis and Applications of Some New Diaryl Selenides Containing Azomethine and Oxazole Moieties

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ORGANIC SELENIUM COMPOUNDS, PART IV: SYNTHESIS AND APPLICATIONS OF SOME NEW DIARYL SELENIDES CONTAINING AZOMETHINE AND OXAZOLE MOIETIES

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3,3′-Diacetyloxy (2), 3,3′-dihydroxy (3), 4,4′-diamino (4), and 4-amino (5) diphenylselenide derivatives were prepared as new precursors for the title studies. Compound 6 was obtained by condensation of 4 with an appropriate aromatic aldehyde. Unsymmetrical diphenylselenides 7 and 8 were obtained by condensation of 4 and/or 5 with an aromatic aldehyde. Compound 7 undergoes facile condensation with the same aldehyde present in its arylidene moiety to yield 6, while condensation with another different aromatic aldehyde yielded unsymmetrical 4-arylideneamino diphenylselenide derivative 9. Oxidation of 6, 8, and 9 using lead tetra acetate and/or N-bromosuccinimide yielded symmetrical bis-(2-aryl benzoxazol-6-yl) (10), unsymmetrical 3′-hydroxy, 2-aryl benzoxazol-6-yl selenides (11), and 2-aryl benzoxazol-6-yl, 2′-aryl′ benzoxazol-6′-yl selenide derivatives (12), respectively. Compound 10 was prepared in one-pot unequivocal synthesis by fusion of 4 with the appropriate aromatic aldehyde, while 12 was prepared by fusion of 4 with two different aromatic aldehydes. In certain cases, 6 and 9 were heated on a direct flame until complete homogeneity afforded the corresponding 10 and 12. The structures of the synthesized compounds are based on physical data, IR, ^{1}H NMR, ^{13}C NMR, chemical means, and mass spectral data. Some of the synthesized compounds were biologically tested.

Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.

Keywords Azomethines; diarylselenides; organic selenium compounds; oxazoles

INTRODUCTION

Organoselenium compounds have been found to function as antioxidants, enzyme inhibitors, and anti-tumor and anti-infective agents.[1] Moreover, introduction of selenium into organic compounds often permits modification of their chemical properties and biological activities.[2,3] On the other hand, oxazole moieties are widely used as solutes in liquid scintillators,[4–6] pharmaceuticals,[7–9] and photography.[10,11] In view of these reported applications and in continuation of our interest in the chemistry of diarylsulfides, -sulfones, -oxides,

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-selenides, and -selenones containing different heterocyclic and other organic moieties,[12–19] we report in this article a study on the synthesis of some new diarylselenides containing azomethine and oxazole moieties, and we also investigated their biological activities.

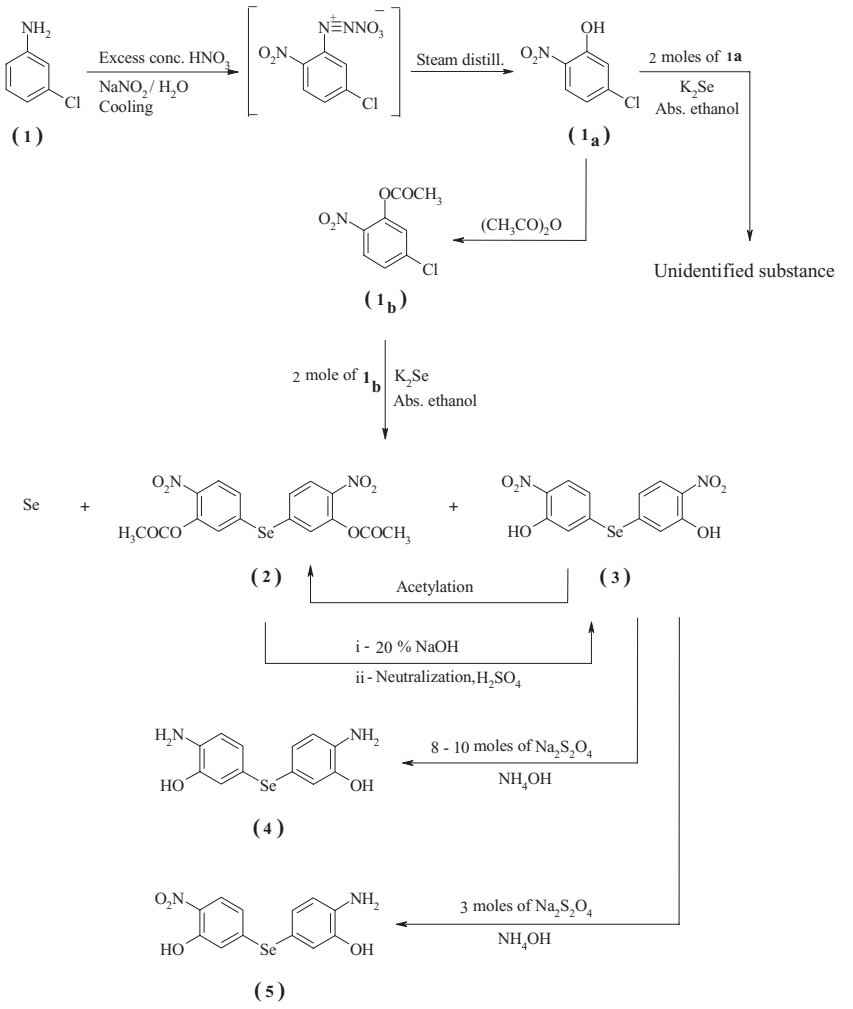
RESULTS AND DISCUSSION

In this article, we describe the synthetic studies of a series of hitherto unreported diarylselenides containing azomethine and oxazole moieties. The starting compound of the forthcoming synthesis and studies is the reported 4-chloro-2-hydroxy nitrobenzene (**1a**), which was prepared according to our modified procedure by diazotization of m-chloroaniline (**1**) in the presence of excess conc. HNO_3 (68%). The nitro diazonium salt formed in situ was steam distilled to produce **1a**. Attempt to condense 2 moles of **1a** with K_2Se in refluxing absolute ethanol via condensation using bimolecular nucleophilic aromatic substitution reaction (nucleophiles: KSe^- and/or $ArSe^-$) depending on the effect of NO_2 group to produce the expected 3,3′-dihydroxy-4,4′-dinitro diphenylselenide (**3**) has failed, whereby an unidentified resinous substance was formed. The formed resinous substance is probably due to the fact that two reactive sites are present in **1a** (−OH and −Cl) and are ready to react with K_2Se. We thought to protect the (−OH) group in **1a** by acetylation to produce 2-acetyloxy-4-chloro nitrobenzene **1b**. Two moles of **1b** were smoothly condensed with 1 mole of K_2Se in refluxing absolute ethanol. The condensation product was thoroughly investigated, and it was proven that it is a mixture of the following three substances: elemental selenium, 3,3′-diacetyloxy-4,4′-dinitro diphenylselenide (**2**), and 3,3′-dihydroxy-4,4′-dinitro diphenylselenide (**3**). The formed three substances were easily isolated separately by means of fractional crystallization and recrystallization to form pure, well-defined compounds. Compound **2** was also obtained by acetylation of **3** (Scheme 1).

3,3′-Diacetyloxy-4,4′-dinitro diphenylselenide (**2**) was treated with 20% NaOH followed by neutralization with H_2SO_4 to give 3,3′-dihydroxy-4,4′-dinitro diphenylselenide (**3**) in nearly quantitative yield. Reduction of **3** using sodium dithionite (8.0–10.0 mol) in the presence of ammonium hydroxide (33%) yielded 4,4′-diamino-3,3′-dihydroxy diphenylselenide (**4**), while its partial reduction using sodium dithionite (3.0 mol) in the presence of ammonium hydroxide (33%) furnished 4-amino-4′nitro-3,3′-dihydroxy diphenylselenide (**5**).

Compound (**4**) was condensed with 4 moles of aromatic aldehydes in absolute ethanol and in the presence of a catalytic amount of dry piperidine that gave symmetrical selenides in the form of a new bis-azomethines namely, 4,4′-di arylideneamino-3,3′-dihydroxy diphenylselenides (**6**). When **4** was condensed with 1 mole of aromatic aldehyde in absolute ethanol and in the presence of the same catalyst, mono-azomethines were obtained, namely 4′-amino-4-arylideneamino-3,3′-dihydroxy diphenylselenides (**7**). Compounds **6a–d** were obtained by another unequivocal synthetic route (stepwise); this was carried out by condensation of compound **7** with 1 mole of aromatic aldehyde (the same aromatic aldehyde present in arylidene moiety in **7**), using the same previously mentioned conditions to yield **6a–d**. The obtainable **6a–d** by two different routes are identical (mp, mixed mp, physical and spectral data).

Condensation of **7** with another different aromatic aldehyde (not present in arylidene moiety in **7**) using the same conditions and procedure gave unsymmetrical selenides

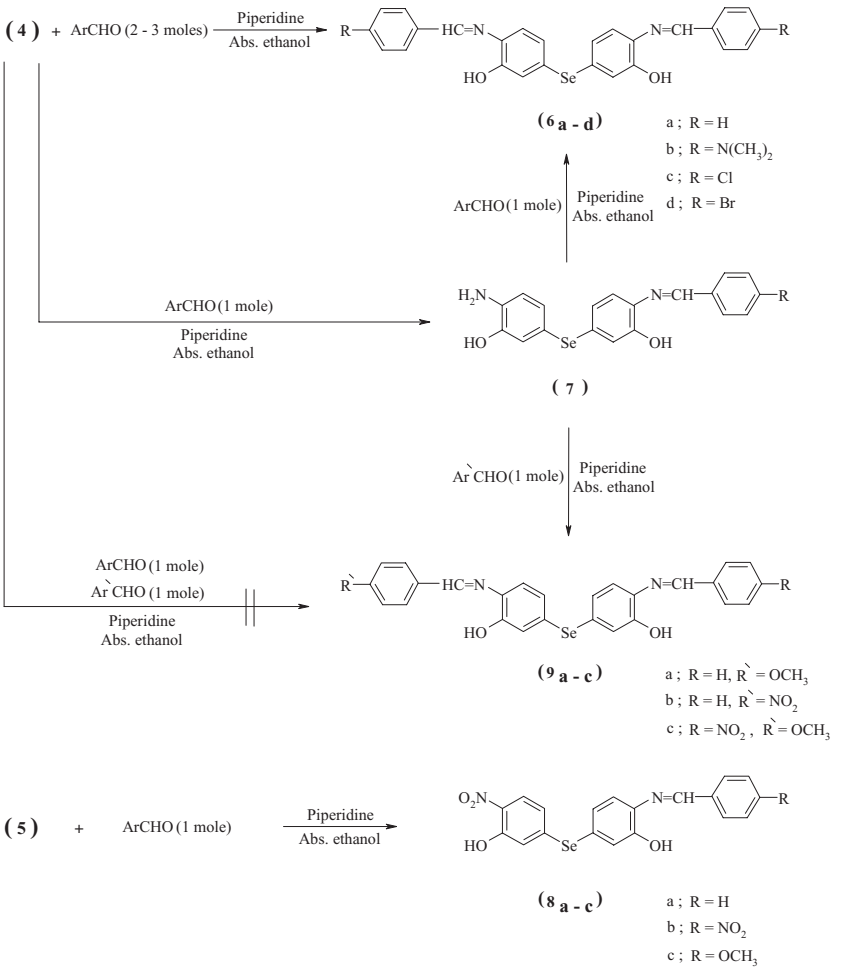


Scheme 1

namely, 4-arylideneamino-4′-arylidene′amino-3,3′-dihydroxy diphenylselenides (**9a–c**) (Scheme 2).

Attempts to obtain **9** by condensation of **4** with two different aromatic aldehydes spontaneously, using the solvent method as previously discussed, have failed and gave undefined substances. These results may be attributed to the variation of the reactivity of each reacted aldehyde toward the applied reactions, and this fact is under our further consideration. Condensation of **5** with aromatic aldehydes in the presence of piperidine and absolute ethanol furnished the expected aldimines, namely 4-arylideneamino-4′-nitro-3,3′-dihydroxy diphenylselenides (**8a–c**). The structures of the prepared compounds **1b–5** and **6–9** were established on the basis of elemental analyses, IR, NMR, chemical means, and mass spectral data (see the Experimental section).

Oxidation of bis-aldimines (**6**) using lead tetra acetate (LTA)[20] and/or N-bromo succinimide (NBS)[21] in refluxing dry benzene or glacial acetic acid for 20 min, as a



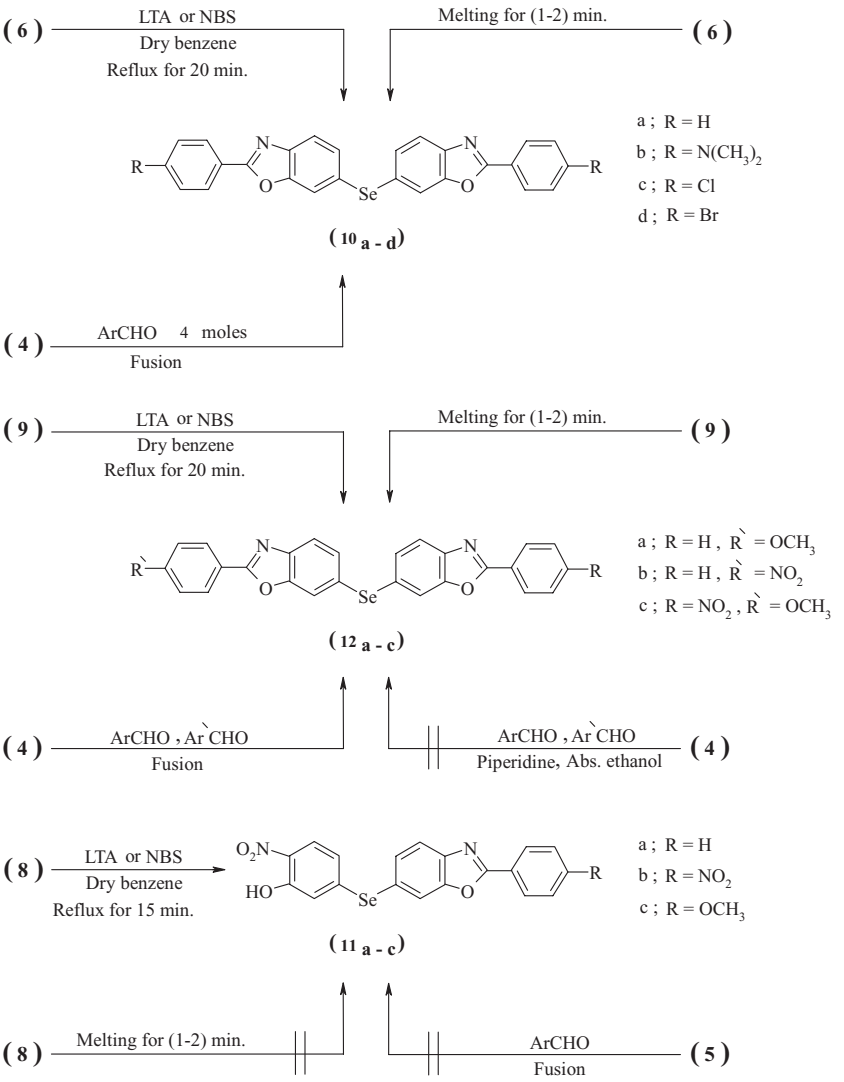
Scheme 2

result of dehydrogenation and ring closure, furnished the expected symmetrical bis-(2-aryl benzoxazol-6-yl) selenides (**10**).

Another route to synthesize **10** was accomplished by fusion of **4** with 4 moles of aromatic aldehydes and/or by melting **6** for 2 min. The oxazoles (**10**) obtained by three different routes (Scheme 3) are identical (mp, mixed mp, spectral data, and chemical means).

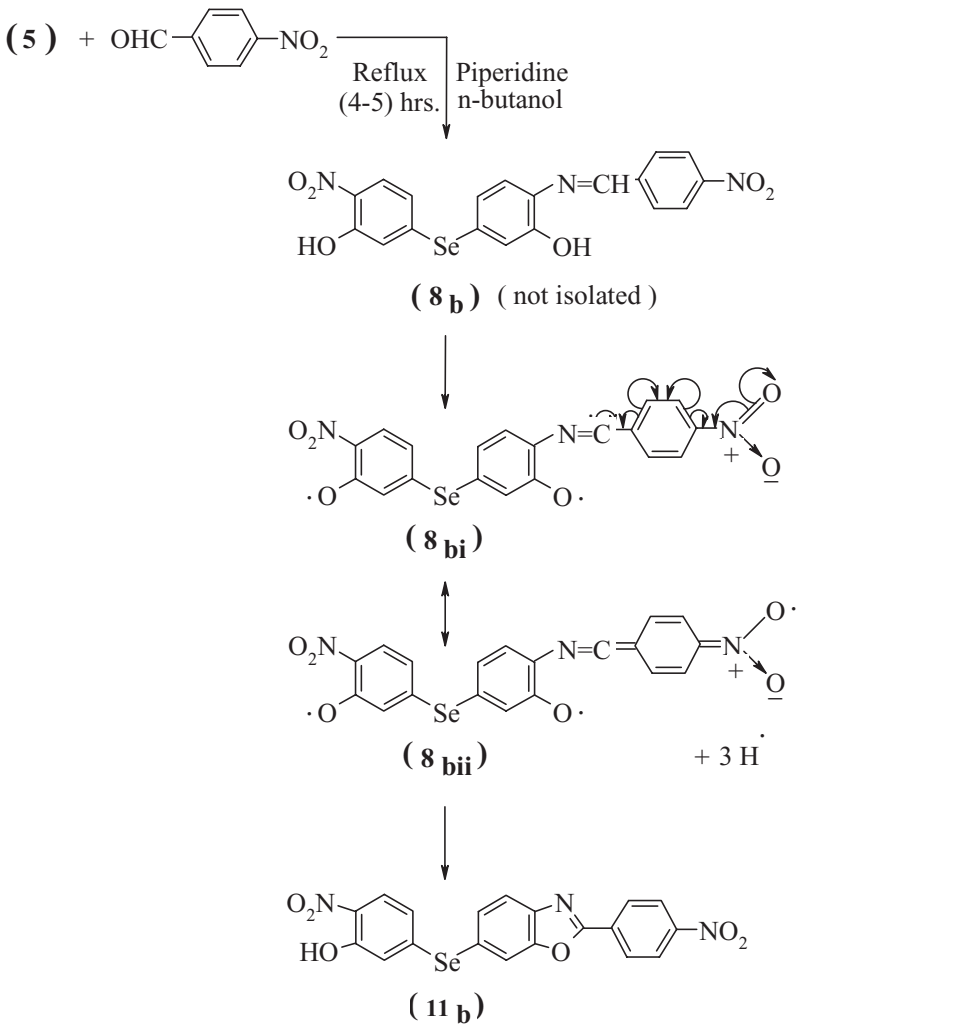
Unsymmetrical diarylselenides of type **11** were obtained by oxidation of **8** using LTA and/or NBS in refluxing dry benzene or glacial acetic acid and furnished the unsymmetrical diarylselenides namely, 3′-hydroxy-4′-nitrophenyl, 2-aryl benzoxazol-6-yl selenides (**11a–c**) in moderate yields.

Attempts to obtain **11** by direct fusion of **5** with the corresponding aromatic aldehyde and/or by melting **8** for 2 min were unsuccessful, and only unidentifiable substances were produced.



Scheme 3

It should be pointed out that 3′-hydroxy-4′-nitrophenyl, 2-(p-nitrophenyl) benzoxazol-6-yl selenide (**11b**) was obtained by interaction of **5** with p-nitro benzaldehyde in refluxing *n*-butanol, in the presence of dry piperidine as a basic catalyst for 5 h, then the reaction mixture was left overnight in an open container. Repeating this procedure using other aldehydes free from electron-withdrawing groups, such a nitro group, was unsuccessful. Here the nitro group exerts influence, depending on its catalyzation role of oxidation by removing the needed azomethine hydrogen to the ring closure of the formed in situ aldimine (**8b**) to the corresponding oxazole (**11b**) with access to air oxidation (oxygen atom behaves as a free biradical).[22] It is believed that, this reaction proceeds via a free radical mechanism. The presence of a nitro group considerably increases the probability of delocalization of the cloud of the odd electron of the free radical that is developed on the



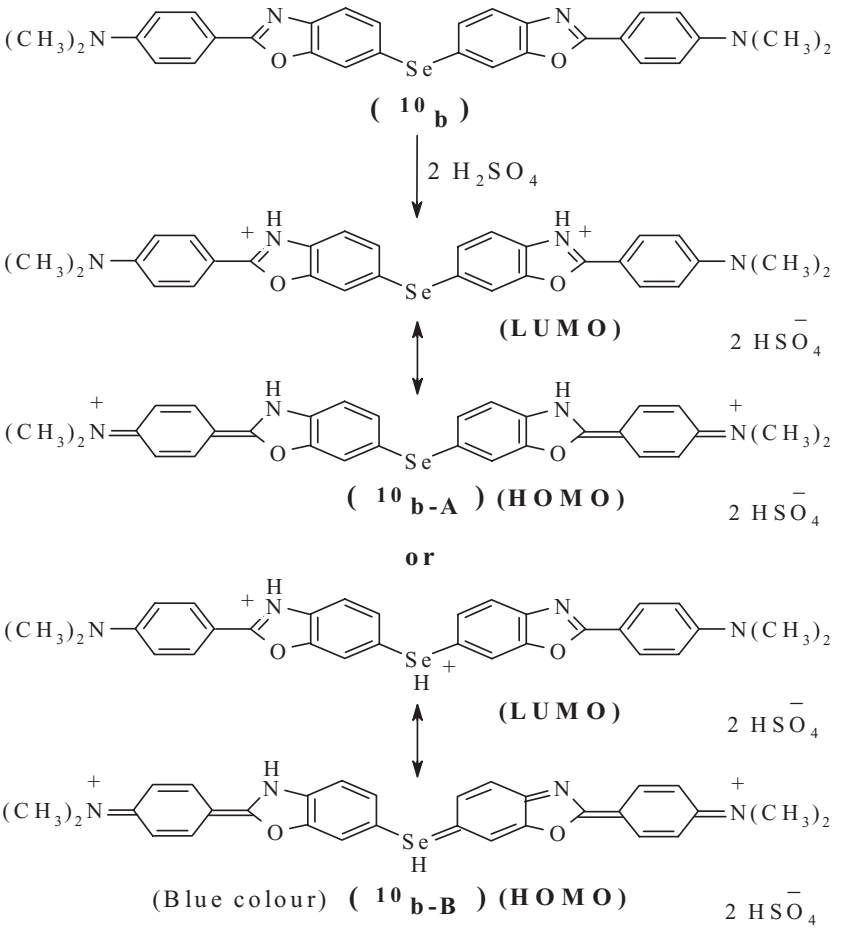
Scheme 4

azomethine linkage; the latter has become more stable through its contributing resonance structures **8bi** and **8bii** (Scheme 4).

Another type of unsymmetrical oxazole, namely 2-aryl benzoxazol-6-yl, 2′-aryl′ benzoxazol-6′-yl selenides (**12**), was obtained by oxidation of **9a–c** under refluxing dry benzene using LTA and/or NBS for 20 min. Moreover two additional different routes to synthesize **12** were carried out. The first one was accomplished by fusion of **4** with a mixture of two different aromatic aldehydes (1.5 mol of each) for 3 min. The second route was carried out by melting **9** for 3 min. The obtainable oxazoles (**12**) by the last three different routes (Scheme 3) are identical (mp, mixed mp, and spectral data). The prepared oxazoles **10**–**12** as expected are characterized by lower λmax. than that their corresponding aldimines; this

behavior is apparently attributed to the absence of an azomethine chromophore in **10–12** as a result of the previously mentioned oxidation, which must be described as a hypsochromic reaction under the given conditions (representative examples given below).

The formed oxazoles (**10–12**) are highly crystalline compounds with sharp melting points, and gave a pink-red colors in conc. H_2SO_4, while compound **10b** gave a blue color, which could be interpreted via inspection of the charged contributing resonance structure of **10b**),[23] as follows (Scheme 5).



Scheme 5

Structure **10b-B** has been suggested, depending on the capability of aromatic selenide linkage to form selenonium compounds, in the form of bisulfate salt.

It is worth noting that the oxidation of **6** and **9** to the corresponding **10** and **12** was achieved without any accompanying any side reactions or process (for example see Figure 1). In some cases, the previously used oxidation of **6**, **8**, and **9** to **10–12** proceeded near quantitatively; this was proven by using spectral means as follows.

A solution of 2×10^{-4} g/mol of **6d** in dry benzene was prepared, and the equivalent amount of NBS was added to this solution, which was refluxed for 20 min. The mixture was

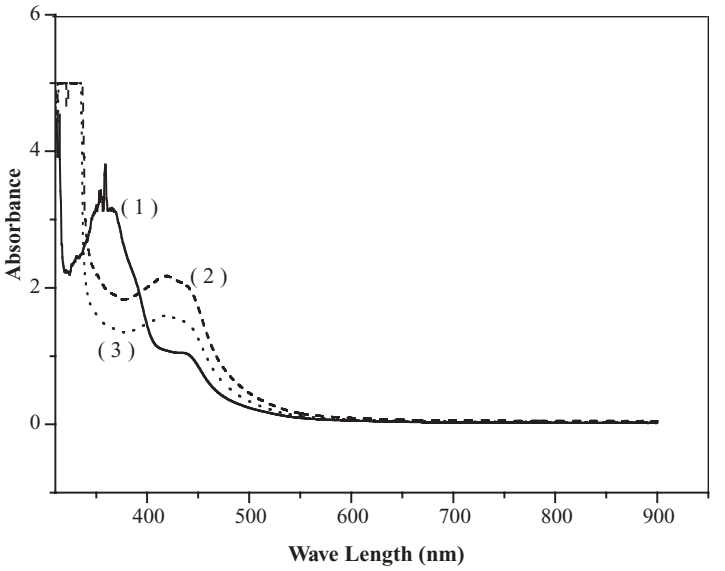


Figure 1 The UV-visible spectrum of compounds **6d** and **10d**. (1) Schiff's base **6d**; (2) the generated in situ oxazole **10d**; (3) separately prepared oxazole **10d**.

cooled, and then its UV-visible spectrum was measured. In fact, at the end of oxidation, this mixture represents a solution of 2×10^{-4} g/mol of the generated in situ oxazole (**10d**). Another solution of 2×10^{-4} g/mol of already synthesized oxazole (**10d**) by a separate procedure (see the Experimental section) was prepared in the same solvent, and its UV-visible spectrum was carried out. By comparison between the two spectra, we observed that both spectra coincided completely on each other. The obtainable result was chemical evidence to prove that the above oxidation in the given example proceeded nearly quantitatively.

The structures of the prepared compounds **10–12** were established by elemental analysis, IR, NMR, and mass spectral data (see the Experimental section).

Antimicrobial Activities

The results obtained from the antimicrobial screening of some newel synthesized compounds (**6b**, **6c**, **7a**, **8a**, **9a**, **10b**, **10c**, **11a**, **12a**, and **12b**) against representatives of bacteria and fungi are listed in Table S1 (Supplemental Materials, available online).

EXPERIMENTAL

Measurements

The times required for the completion of the reactions and the purity of the prepared compounds was monitored by thin layer chromatography (TLC). Melting points were determined on a Gallenkamp Melting Point apparatus with a digital thermometer type MFB-595–010M and are uncorrected. The elemental analyses were performed on a Perkin-Elmer 240 C elemental analyzer and a GmbH VAR IDEL V2.3 elemental Analysis System in CHNS Mode. IR Spectra were measured on an IR-470 spectrophotometer (Shimadzu)

using a KBr wafer technique. ^{1}H NMR spectra were recorded on INM-A (400 MHz) NMR spectrophotometer using the appropriate deuterated solvent and TMS as an internal standard (chemical shifts expressed in δ ppm). Mass spectra were recorded on a JEOL JMS-600 mass spectrometer.

4-Chloro-2-hydroxy Nitrobenzene (1a)

This compound was prepared according to the method given in the literature,[24] with some modification in which the mother-liquor of the desired compound was successively extracted by chloroform, and the collected extracts were evaporated under vacuum to small volume, cooled, filtered, and crystallized from commercial ethanol, mp 38°C, in literature 41°C; yield 26%. (This modified procedure leads an increase in the yield by 10%).

2-Acetyloxy-4-chloro Nitrobenzene (1b)

A solution of 4-chloro-2-hydroxy nitrobenzene (**1a**) (10 g, 0.057 mol) in acetic anhydride (35 mL, 0.370 mol) was refluxed for 45 min. The solution was poured in cold water (150 mL) with vigorous stirring, and was kept in the refrigerator overnight, in which the present oil solidifies. The product was filtered off and crystallized from petroleum ether (60–80°C), mp 44°C; yield 85%.

IR: 3100 cm^{-1} (Ar—C—H), 2950, 2850 cm^{-1} (CH_3), 1665 cm^{-1} (C=O), 1520, 1335 cm^{-1} (NO_2), 1178 cm^{-1} (Ar—O). ^{1}H NMR in $CDCl_3$: at δ 2.35 (s, 3H, —$OCOCH_3$), δ 7.30–8.25 (Ar—H). Anal. Calc. for $C_8H_6ClNO_4$ (215.59) (%): C, 44.57; H, 2.80; N, 6.49; Cl, 16.44; Found (%): C, 44.32; H, 3.02; N, 6.84; Cl, 16.08.

3,3′-Diacetyloxy-4,4′-dinitro Diphenylselenide (2)

To a solution of 2-acetyloxy-4-chloro nitrobenzene (**1b**) (12 g, 0.055 mol) in absolute ethanol (180 mL), potassium selenide (7.2 g, 0.045 mol) was added, which was prepared by fusion of a mixture of metallic selenium (3.65 g) and potassium hydroxide (5.19 g) in an oil bath for 2 h at 140°C. Then the mixture was boiled under reflux with stirring for 7 h. The precipitate which formed upon cooling (which also contains the unreacted selenium) was filtered off, dried, and dissolved by heating in aqueous ethanol. The solution was filtered, which separated about 2.42 g of metallic selenium, which was quite suitable for repeat preparations. After that the solvent was evaporated, and the dihydroxy compound (**3**) (3.50 g) was obtained. The mother-liquor of the reaction, which contained the desired diacetyloxy compound (**2**), was distilled off, and the formed crude product was crystallized from abs. ethanol, mp > 300°C decomp.; yield (83%).

IR: 3080 cm^{-1} (Ar. C—H), 2900 cm^{-1} (CH_3), 1690 cm^{-1} (C=O), 1540,1325 cm^{-1} (NO2), 1150 cm^{-1} (Ar—O), 738, 685 cm^{-1} (Ar—Se—Ar). ^{1}H NMR in DMSO: at δ 2.35 (s, 3H, —$OCOCH_3$), δ 6.60–8.20 (Ar—H). Anal. Calc. for $C_{16}H_{12}N_2O_8Se$ (439.24) (%): C, 43.75; H, 2.75; N, 6.37; Found (%): C, 43.98; H, 2.88; N, 6.24.

3,3′-Dihydroxy-4,4′-dinitro Diphenylselenide (3)

Diacetyloxy compound **2** (10 g, 0.022 mol) was boiled with a solution of sodium hydroxide (30 g) in distilled water (150 mL) for 1.5 h. Dilute sulfuric acid was added with stirring to the cold alkaline solution, until the solution was acidic to litmus paper. The crude product was filtered off and recrystallized from ethanol, mp (> 300)°C decomp; yield (68%).

IR: 3450 cm^{-1} (OH), 3080 cm^{-1} (Ar—H str.), 1530, 1320 cm^{-1} (NO_2), 1150 cm^{-1} (Ar—O), 738, 685 cm^{-1} (Ar—Se—Ar). ^1H NMR in DMSO: at δ 5.88–7.63 (the Ar. protons at the Ar—Se—Ar moiety), δ 8.67 (s, 2H, OH). MS: 355 (M^+, 4%), 172 (20%), 142 (19%), 62 (25%), 43 (100%). Anal. Calc. for $C_{12}H_8N_2O_6Se$ (355.16) (%): C, 40.58; H, 2.27; N, 7.88; Found C, 40.76; H, 2.45; N, 7.72.

4,4′-Diamino-3,3′-dihydroxy Diphenylselenide (4)

To a heated solution of 3,3′-dihydroxy-4,4′-dinitro diphenylselenide (**3**) (5 g, 0.014 mol) in distilled water (75 mL) and concentrated ammonium hydroxide solution (20 mL), a solution of sodium dithionite (24.5 g, 0.14 mol) in distilled water (about 300 mL) was added in three portions. The deep red color of the solution changed to a pale yellow. The whole reaction mixture (unfiltered) was extracted several times with ether. The extracts were collected, dried over anhydrous sodium sulfate, and evaporated, which furnished a brown product, which by crystallization from absolute ethanol yielded brown crystals, mp 150–152°C; yield (60%).

IR: 3450,3300 cm^{-1} (NH_2), 2550–3200 cm^{-1} (OH), 1140 cm^{-1} (Ar—O), 752, 700 cm^{-1} (Ar—Se—Ar). ^1H NMR in DMSO: δ 4.62 (s, 4H, $2NH_2$), δ 6.34–6.84 (the Ar. protons at the Ar—Se—Ar moiety), δ 9.47 (s, 2H, OH). MS: 296 (M+, 25%), 142 (89%), 79 (100%), 62 (52%). Anal. Calc. for $C_{12}H_{12}N_2O_2Se$ (295.20) (%): C, 48.82; H, 4.09; N, 9.49; Found (%): C, 49.12; H, 3.86; N, 9.68.

4-Amino-4′-nitro-3,3′dihydroxy Diphenylselenide (5)

To a heated solution of 3,3′-dihydroxy-4,4′-dinitro diphenylselenide (**3**) (2 g, 0.0056 mol) in distilled water (30 mL) and concentrated ammonium hydroxide solution (8 mL), a solution of sodium dithionite (2.940 g, 0.0168 mol) in distilled water (35 mL) was added in three portions. The deep red color of the solution changed to orange. The whole reaction mixture (unfiltered) was extracted several times with ether. The extracts were collected, dried over anhydrous sodium sulfate, and evaporated to small volume, whereby brown crystals were separated and recrystallized from absolute ethanol, mp 122°C, yield 40%.

IR: 3300, 3380 cm^{-1} (NH_2), 2550–3050 cm^{-1} (OH), 1500, 1330 cm^{-1} (NO_2) and 710 cm^{-1} (Ar—Se—Ar′). ^1H NMR in DMSO: δ 4.60 (s, 2H, NH_2), δ 6.0–7.40 (the Ar. protons at the Ar—Se—Ar′ moiety), δ 9.15 (s, 2H, OH). Anal. Calc. for $C_{12}H_{10}N_2O_4Se$ (325.18) (%): C, 44.32; H, 3.09; N, 8.61; Found (%): C, 44.71; H, 3.28; N, 8.92.

Symmetrical 4,4′-Diarylideneamino-3,3′-dihydroxy Diphenylselenides (6a–d)

Method A. A mixture of 4,4′-diamino-3,3′-dihydroxy diphenyl selenide (**4**) (1.0 g, 0.0033 mol), the appropriate aromatic aldehyde (0.0070 mol), and dry piperidine [2–3 drops in absolute ethanol (30 mL)] was heated under reflux for 5 h, evaporated to a small volume, and cooled, and the precipitate that formed was collected and washed with cold ethanol (10 mL). The crude product was crystallized from the proper solvent; the results are listed in Table I.

Table I Physical and spectral data for the synthesized compounds (**6–12**) derivatives

Compound No.	R	R′	M_p (°C) Solvent	Yield %	Molecular Formula (M. wt)	Elemental analysis Calc./Found C%	H%	N%	Cl%	Spectral data
*$\mathbf{6_a}$	H	H	132–134 abs. ethanol	88	$C_{26}H_{20}N_2O_2Se$ (471.41)	66.24 66.38	4.27 4.32	5.94 5.78	—	IR: 3350 cm^{-1} (OH), 2900 cm^{-1} (CH=N), 1600 cm^{-1} def. (C=N). ^{1}H-NMR CDCl3: δ 7.25–8.20 (m, 16H, Ar−H), δ 8.55 (s, 2H, −CH=N), δ 9.45 (s,2H,OH).
$\mathbf{6_b}$	$N(CH_3)_2$	$N(CH_3)_2$	116–118 abs. ethanol	93	$C_{30}H_{30}N_4O_2Se$ (557.55)	64.62 64.90	5.42 5.34	10.04 10.18	—	IR: 3300 cm^{-1} (OH), 2900 cm^{-1} (CH=N), 1590 cm^{-1} def. (C=N). ^{1}H-NMR DMSO: δ 3.02 (s, 12H, 2N $(CH_3)_2$), δ 6.50–7.80 (m, 14H, Ar−H), δ 8.44 (s, 2H, CH=N) δ 9.64 (s, 2H, OH).
$\mathbf{6_c}$	Cl	Cl	110–112 abs. ethanol	72	$C_{26}H_{18}Cl_2N_2O_2Se$ (540.30)	57.79 57.62	3.53 3.68	5.18 5.12	13.12 13.25	IR: 3380 cm^{-1} (OH), 2900 cm^{-1} (CH=N), 1600 cm^{-1} def. (C=N). ^{1}H-NMR DMSO: δ 7.41–8.06 (m, 14H, Ar−H), δ 9.98 (s, 2H, CH=N), δ 10.41 (s, 2H, OH).
$\mathbf{6_d}$	Br	Br	95–97 abs. ethanol	70	$C_{26}H_{18}Br_2N_2O_2Se$ (629.21)	49.63 49.75	2.88 2.79	4.45 4.56	—	IR: 3380 cm^{-1} (OH), 2900 cm^{-1} (CH=N), 1600 cm^{-1} def. (C=N). ^{1}H-NMR DMSO: δ 7.35–8.00 (m, 14H, Ar−H), δ 9.92 (s, 2H, CH=N), δ 10.35 (s, 2H, OH).
$\mathbf{7_a}$	H	—	100–102 abs. ethanol	94	$C_{19}H_{16}N_2O_2Se$ (383.30)	59.53 59.67	4.20 4.28	7.30 7.21	—	IR: 3380, 3300 cm^{-1} (NH_2), 2900 cm^{-1} (CH=N), (1620) cm^{-1} def. (NH_2), 1600 cm^{-1} def. (C=N). ^{1}H-NMR DMSO: δ 4.45 (s,2H,NH_2), δ 6.82–7.94 (m,11H, Ar−H), δ 8.65 (s,1H,CH=N), δ 9.32 (s,2H,OH).
$\mathbf{7_b}$	NO_2	—	228–230 abs. ethanol	78	$C_{19}H_{15}N_3O_4Se$ (428.30)	53.28 53.52	3.53 3.48	9.81 9.97	—	IR: 3375,3300 cm^{-1} (NH_2), 1550,1323 cm^{-1} (NO_2), 2930 cm^{-1} (CH=N), 1615 cm^{-1} def. (NH_2), 1590 cm^{-1} def. (C=N). ^{1}H-NMR in DMSO: δ 4.50 (s, 2H, NH_2), δ 7.12–8.25 (m, 10H, Ar−H), δ 8.70 (s, 1H, CH=N), δ 9.45 (s, 2H, OH).

8_a	H	—	132–134 benzene	82	$C_{19}H_{14}N_2O_4Se$ (413.29)	55.21 55.35	3.41 3.38	6.77 6.52	—	IR: 3300 cm^{-1} (OH), 2950 cm^{-1} (CH=N), 1600 cm^{-1} (C=N), 1550, 1318 cm^{-1} (NO_2). ^{1}H-NMR in DMSO: δ 7.35–8.20 (m, 11H, Ar—H), δ 8.40 (s, 1H, —CH=N), δ 9.50 (s, 2H, OH).
8_b	NO_2	—	168–170 abs. ethanol	70	$C_{19}H_{13}N_3O_6Se$ (458.28)	49.79 50.02	2.85 2.78	9.17 9.25	—	IR: 3250 cm^{-1} (OH), 2950 cm^{-1} (CH=N), 1600 cm^{-1} (C=N), 1555, 1325 cm^{-1} (NO_2). ^{1}H-NMR DMSO: δ 7.30–8.40 (m, 10H, Ar—H), δ 8.60 (s, 1H, —CH=N), δ 9.65 (s, 2H, OH).
8_c	OCH_3	—	112–114 abs. ethanol	79	$C_{20}H_{16}N_2O_5Se$ (443.31)	54.18 54.32	3.63 3.68	6.32 6.24	—	IR: 3250 cm^{-1} (OH), 2950 cm^{-1} (CH=N), 1610 cm^{-1} (C=N), 1550, 1320 cm^{-1} (NO_2), 1175, 1030 cm^{-1} (OCH_3). ^{1}H-NMR DMSO: δ 3.60 (s, 3H, OCH3), δ 7.20–8.20 (m, 10H, Ar—H), δ 8.80 (s, 1H, CH=N), δ 9.40 (s, 2H, OH).
9_a	H	OCH_3	88–90 abs. ethanol	94	$C_{27}H_{22}N_2O_3Se$ (501.44)	64.67 64.78	4.42 4.36	5.58 5.65	—	IR: 3350 cm^{-1} (OH), 2900 cm^{-1} (CH=N), 1610 cm^{-1} def. (C=N), 1160, 1020 cm^{-1} (OCH_3). ^{1}H-NMR DMSO: δ 3.70 (s, 3H, OCH_3), δ 7.40–8.25 (m, 15H, Ar—H), δ 8.50 (s, 1H, CH=N), δ 9.50 (s, 2H, OH).
9_b	H	NO_2	208–210 abs. ethanol	88	$C_{26}H_{19}N_3O_4Se$ (516.41)	60.47 60.62	3.70 3.78	8.13 7.79	—	IR: 3350 cm^{-1} (OH), 2900 cm^{-1} (CH=N), 1610 cm^{-1} def. (C=N), 1550, 1320 cm^{-1} (NO_2). ^{1}H-NMR DMSO: δ 7.40–8.25 (m, 15H, Ar—H), δ 8.50 (s, 1H, —CH=N), δ 9.50 (s, 2H, OH).
9_c	NO_2	OCH_3	198–200 abs. ethanol	68	$C_{27}H_{21}N_3O_5Se$ (546.44)	59.34 59.12	3.87 3.82	7.68 7.74	—	IR: 3350 cm^{-1} (OH), 2920 cm^{-1} (CH=N), 1610 cm^{-1} def. (C=N), 1550, 1335 cm^{-1} (NO_2), 1170, 1020 cm^{-1} (OCH_3). ^{1}H-NMR DMSO: δ 3.70 (s, 3H, OCH_3), δ 7.50–8.50 (m, 15H, Ar—H), δ 8.65 (s, 1H,CH=N), δ 9.60 (s,2H,OH).

(Continued on next page)

Table I Physical and spectral data for the synthesized compounds (**6–12**) derivatives *(Continued)*

Compound No.	R	R′	M_p (°C) Solvent	Yield %	Molecular Formula (M. wt)	Elemental analysis Calc./Found C%	H%	N%	Cl%	Spectral data
*$\mathbf{10_a}$	H	H	98–100 abs. ethanol	71	$C_{26}H_{16}N_2O_2Se$ (467.38)	66.81 67.02	3.45 3.48	5.99 5.86	—	IR: 3030 cm^{-1} (Ar. C—H str.), 1605 cm^{-1} (C=N), 1440, 1470, 1540 cm^{-1} (C=C). ^{1}H-NMR DMSO: δ 7.40–8.12 (m, 16H, Ar—H).M.S: 468 (M^+, 28%), 229 (90%),166 (34%), 77 (83%), 63 (100%).
$\mathbf{10_b}$	$N(CH_3)_2$	$N(CH_3)_2$	162–164 abs. ethanol	66	$C_{30}H_{26}N_4O_2Se$ (553.52)	65.09 65.38	4.73 4.52	10.12 9.88	—	IR: 2950 cm^{-1} (CH_3 str.), 1610 cm^{-1} (C=N). ^{1}H-NMR MSO: δ 3.01 (s, 12H, 2N $(CH_3)_2$), δ 6.82–7.96 (m, 14H, Ar—H).
$\mathbf{10_c}$	Cl	Cl	125–127 abs. ethanol	64	$C_{26}H_{14}Cl_2N_2O_2Se$ (536.27)	58.23 58.02	2.63 2.48	5.22 5.45	13.22 13.08	IR: 2950 cm^{-1} (CH_3 str.), 1610 cm^{-1} (C=N), 600 cm^{-1} (Ar—Cl). ^{1}H-NMR DMSO: δ 7.43–8.15 (m, 14H, Ar—H).M.S: 536 (M^+, 9%), 264 (89%), 163 (32%), 110(54%),62(100%).
$\mathbf{10_d}$	Br	Br	116–118 acetic acid	65	$C_{26}H_{14}Br_2N_2O_2Se$ (625.17)	49.95 50.18	2.25 2.12	4.48 4.70	—	IR: 2950 cm^{-1} (CH_3 str.), 1615 cm^{-1} (C=N), 590 cm^{-1} (Ar—Br). ^{1}H-NMR DMSO: δ 7.38–8.10 (m, 14H, Ar—H). M.S: 536 (M^+, 9%), 264 (89%), 163(32%), 110 (54%), 62 (100%)
$\mathbf{11_a}$	H	—	110–112 abs. ethanol	49	$C_{19}H_{12}N_2O_4Se$ (411.27)	55.48 55.72	2.94 3.02	6.81 6.74	—	IR: 3200 cm^{-1} (OH), 3030 cm^{-1} (Ar. C—H str.), 1605cm^{-1} (C=N), 1550, 1315 cm^{-1} (NO_2). ^{1}H-NMR DMSO: δ 6.95–8.10 (m, 11H, Ar—H), δ 9.10 (s, 1H, OH). M.S:408 (M^+,1%),229 (100%),166 (11%), 77 (20%), 63 (40%).
$\mathbf{11_b}$	NO_2	—	138–140 pet. ether (80–100°C)	62	$C_{19}H_{11}N_3O_6Se$ (456.27)	50.01 49.55	2.43 2.68	9.20 9.12	—	IR: 3250 cm^{-1} (OH), 3030 cm^{-1} (Ar. C—H str.), 1600cm^{-1} (C=N), 1555,1320 cm^{-1} (NO_2). ^{1}H-NMR in DMSO: δ 7.50–8.70 (m, 10H, Ar—H), δ 9.40 (s,1H,OH).
$\mathbf{11_c}$	OCH_3	—	178–180 benzene	72	$C_{20}H_{14}N_2O_5Se$ (441.30)	54.43 54.78	3.20 3.12	6.34 6.58	—	IR: 3200 cm^{-1} (OH), 3030 cm^{-1} (Ar. C—H str.), 1590 cm^{-1} (C=N), 1550,1320 cm^{-1} (NO_2), 1175,1030 cm^{-1} (OCH_3). ^{1}H-NMR DMSO: δ 3.60 (s, 3H, OCH_3), δ 6.50–8.20 (m, 10H,Ar—H) δ 9.30 (s,1H,OH).

12_a	H	OCH_3	116–118 abs. ethanol	72	$C_{27}H_{18}N_2O_3Se$ (497.41)	65.19 65.48	3.64 3.72	5.63 5.48	—	IR: 1600 cm^{-1} def. (C=N), 1160, 1025 cm^{-1} (OCH_3). ^{1}H-NMR in DMSO: δ 3.65 (s, 3H, OCH_3), δ 7.15–8.30 (m, 15H, Ar−H).
12_b	H	NO_2	182–184 acetic acid	65	$C_{26}H_{15}N_3O_4Se$ (512.38)	60.94 61.42	2.95 3.08	8.20 8.36	—	IR: 1600 cm^{-1} def. (C=N), 1550, 1320 cm^{-1} (NO_2). ^{1}H-NMR DMSO: δ 7.50–8.40 (m, 15H, Ar−H).
12_c	NO_2	OCH_3	232–234 abs. ethanol	68	$C_{27}H_{17}N_3O_5Se$ (542.41)	59.78 59.35	3.16 3.22	7.74 7.92	—	IR: 1600 cm^{-1} def. (C=N), 1545, 1318 cm^{-1} (NO_2), 1170, 1025 cm^{-1} (OCH_3). ^{1}H-NMR DMSO: δ 3.60 (s, 3H, OCH_3), δ 6.85–8.10 (m, 14H, Ar−H).

*^{13}C NMR (DMSO-d6, 50 MHz): the most important peaks at δ 165 (−N=CH), 152 (C−OH), 145 (C−N), 132.63, 131.36, 128.30, 125.46, 123, 122, 117 (Aryl),
^{13}C NMR (DMSO-d6, 50 MHz): the most important peaks at δ 155 (−N=CH), 150 (C−O), 140 (C−N), 132.63, 131.36, 128.30, 125.46, 123, 122, 111 (Aryl),

4′-Amino-4-arylideneamino-3,3′-dihydroxy Diphenylselenides (7)

A mixture of 4,4′-diamino-3,3′-dihydroxy diphenyl selenide (**4**) (1.0 g, 0.0033 mol), the appropriate aromatic aldehyde (0.0033 mol), and dry piperidine [2–3 drops in absolute ethanol (30 mL)] was heated under reflux for 5 h, evaporated to a small volume, and cooled, and the formed precipitate was collected and washed with cold ethanol (15 mL). The crude product was crystallized from the proper solvent; the results are listed in Table I.

Symmetrical 4,4′-diarylideneamino-3,3′-dihydroxy Diphenylselenides (6a–d)

Method B. A mixture of 4′-amino-4-arylideneamino-3,3′-dihydroxy diphenylselenide (**7**) (0.0026 mol), an aromatic aldehyde (the same aldehyde present in the arylidene moiety of **7**) (0.0026 mol), and dry piperidine [2–3 drops in absolute ethanol (30 mL)] was refluxed for 5 h, evaporated to a small volume, and cooled, and the formed precipitate was collected and washed with cold ethanol (10 mL). The crude product was crystallized from the proper solvent; the results are listed in Table I.

Unsymmetrical 4-Arylideneamino-4′-arylidene′amino-3,3′-dihydroxy Diphenyl Selenides (9a–c)

A mixture of 4′-amino-4-arylideneamino-3,3′-dihydroxy diphenylselenide (7) (0.0026 mol), different aromatic aldehydes (not present in the arylidene moiety in **7a–c**) (0.0026 mol), and dry piperidine [2–3 drops in absolute ethanol (30 mL)] was refluxed for 5 h, evaporated to a small volume, and cooled, and the formed precipitate was collected and washed with cold ethanol (15 mL). The crude product was crystallized from the proper solvent; the results are listed in Table I.

4-Arylideneamino-4′-nitro-3,3′-dihydroxy Diphenylselenides (8a–c)

A mixture of 4-amino-4′-nitro-3,3′-dihydroxy diphenylselenide (**5**) (1.0 g, 0.0030 mol), the appropriate aromatic aldehyde (0.0040 mol), and dry piperidine (2–3 drops) in absolute ethanol (30 mL) was heated under reflux for 5 h, evaporated to a small volume, and cooled, and the formed product was collected, washed with ethanol (20 mL), and crystallized from absolute ethanol. The results are given in Table I.

Symmetrical Bis-(2-aryl benzoxazol-6-yl) Selenides (10a–d)

Method A. A mixture of symmetrical Schiff's base 4,4′-di-arylideneamino-3,3′-dihydroxy diphenylselenides (**6a–d**) (0.0020 mol) and LTA (0.0070 mol) in dry benzene (40 mL) was refluxed for 15 min. The reaction mixture was allowed to stand for 1 h at room temperature, then the separated solid was filtered and washed with water, and the crude product was crystallized from the proper solvent. The results are listed in Table I.

Method B: Fusion method. A mixture of 4,4′-diamino-3,3′-dihydroxy diphenylselenide (**4**) (1.0 g, 0.0033 mol) and equimolar quantities of two identical aromatic aldehydes (0.0040 mol of each aldehyde) were mixed thoroughly and heated for 4 min on direct flame until complete homogeneity of the reaction mixture was achieved. The reaction was dried in a current of air, and the viscous residue was triturated with absolute

ethanol, then concentrated and cooled. The deposited crystalline product was collected and recrystallized from absolute ethanol. The results are listed in Table I.

Method C: Melting method. Symmetrical Schiff's base 4,4′-di-arylideneamino-3,3′-dihydroxy diphenylselenides (**6a–d**) (0.0020 mol) was melted in a dry porcelain crucible on a direct flame and in the presence of a current of air. The formed solid product was dissolved in absolute ethanol and evaporated to small volume and cooled Then the deposited crystalline product was collected and crystallized from the proper solvent (see Table I).

Unsymmetrical 3′-Hydroxy-4′-nitrophenyl, 2-Aryl Benzoxazol-6-yl Selenides (11a–c)

A mixture of Schiff's base 4-arylideneamino-4′-nitro-3,3′-dihydroxy diphenylselenides (**8a–c**) (0.0025 mol) and LTA (0.0040 mol) in dry benzene (40 mL) was refluxed for 15 min. The reaction mixture was allowed to stand for 1 h at room temperature, then the separated solid was filtered and washed with water, and the crude product was crystallized from the proper solvent. The results are listed in Table I.

Application of methods B and C for the preparation of **10a-d** to produce **11a–c** failed.

3′-Hydroxy-4′-nitrophenyl, 2-(p-Nitrophenyl) Benzoxazol-6-yl Selenide (11b)

A mixture of 4-amino-4′-nitro-3,3′-dihydroxy diphenylselenide (**5**) (1.0 g, 0.0030 mol), p-nitrobenzaldehyde (0.6 g, 0.0040 mol), and dry piperidine (2–3 drops) in n-butanol (30 mL) was refluxed for 5 h on an oil bath. Then the mixture was cooled, and the product was collected and washed thoroughly with water, and the crude product was crystallized from absolute ethanol. The results are given in Table I. When the same method was carried out with other aromatic aldehydes, e.g., C_6H_5CHO and p-C_6H_4-OCH_3, no product was formed.

Unsymmetrical 2-Aryl Benzoxazol-6-yl, 2′-Aryl′ Benzoxazol-6′-yl Selenides (12a–c)

Method A. Unsymmetrical Schiff's base 4-arylideneamino-4′-arylidene′amino-3,3′-dihydroxy diphenylselenides (**9a–c**) (0.0020 mol) and NBS (0.0070 mol) in dry benzene (40 mL) were refluxed for 15 min. The reaction mixture was allowed to stand for 1 h at room temperature. Then the deposited product was filtered and washed with water, crystallized, and recrystallized as usual. The results are given in Table I.

Method B: Fusion method. 4,4′-Diamino-3,3′-dihydroxy diphenylselenide (**4**) (1.0 g, 0.0033 mol) and equimolar quantities of two different aromatic aldehydes (0.0040 mol of each) where mixed thoroughly and heated for 4 min on direct flame until complete homogeneity of the reaction mixture was achieved. The reaction was dried in a current of air. The viscous residue was triturated with absolute ethanol, then concentrated and cooled. The deposited crystalline product was collected and recrystallized from absolute ethanol. The results are listed in Table I.

It must be noted that repeating this method using the solvent method was unsuccessful, apparently due to the difference of the reactivity of each aldehyde under the applied conditions.

Method C: Melting method. Unsymmetrical Schiff's base 4-arylideneamino-4′-arylidene amino-3,3′-dihydroxy diphenylselenides (**9a–c**) (0.0020 mol) were melted in a dry porcelain crucible on direct flame and in the presence of a current of air with stirring. The formed solid product was dissolved in absolute ethanol, evaporated to a small volume, and cooled. Then the deposited crystalline product was collected and crystallized from the proper solvent; see Table I.

Note: The o-amino compounds formed during this investigation should be used momentarily for the subsequent chemical reactions in order to avoid their partial oxidation by atmospheric oxygen.

Preparation of Solvents for Spectral Measurements

The solvent of an oxidation reaction of selected Schiff's bases to corresponding oxazoles must possesses a wide range of solubility to dissolve all the ingredients present and generated in the reaction mixture, without formation of any turbidity or precipitates during the whole reaction time. Factors, such as spectral purity, volume, and quantity of selected solvents, besides the concentrations of the solutes, must be taken in consideration.

Antibacterial and Antifungal Screening

Biological screening of some prepared compounds was carried out to evaluate their antibacterial properties. Preliminary screening of the tested compounds against different strains of both Gram-positive and Gram-negative bacteria and fungi were determined using the agar diffusion technique.[25] (See the Supplemental Materials.)

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