Hypervalent Iodine in Synthesis 50: A Novel Method of Synthesis of Selenazoles by Cyclocondensation of Selenoamides and Alkynyl(Phenyl)Iodonium Salts

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A novel method for the synthesis of selenazoles by cyclocondensation of primary selenoamides and alkynyl(phenyl)iodomium salts and the reaction mechanism are reported. The synthetic method is simple, mild and the yields are high.

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Introduction.

Although the first reported preparations of selenazoles go back to the year 1889, for decades after this no further details were found in the literature. Only after 1940 was a somewhat more intensive study of the selenazoles begun. Selenazole derivatives possess antitumor activity, antibacterial activity and other notable activities [1].

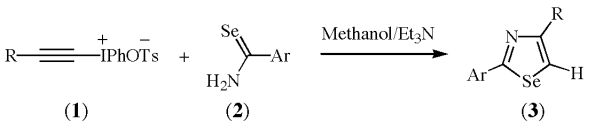
There are probably two reasons for the small number of investigations be found in the area of selenazole chemistry. One of these is that there is practically only one useful method for preparing selenazoles, in contrast to the many methods available for oxazoles and thiazoles. Corresponding to the Hantzsch thiazole synthesis, this consists of the condensation of α-haloketones with selenoamides [2]. Also, the essential selenium containing starting materials are not as readily available as those of the sulfur analogue intermediates.

In our earlier reports dealing with hypervalent iodine in organic synthesis, it has been observed that alkynyl(phenyl)iodonium salts are highly reactive toward many nucleophilic heteroatoms [3]. In addition, we have recently developed a simple method for the synthesis of selenoamides [4]. These facts prompted us to examine the reaction of alkynyl(phenyl)iodonium salts with selenoamides, Such a reaction would provide a new route to selenazoles.

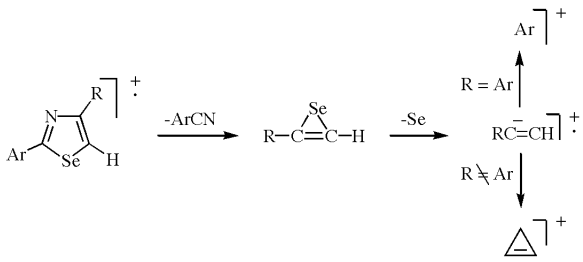
Herein we report our result, a new effective method for the synthesis of selenazoles by cyclocondensation of alkynyl(phenyl)iodonium salts with selenoamides. Under reflux condition, simple stirring of the mixture of alkynyl(phenyl)iodonium salts (**1**) with selenoamides (**2**) in methanol under an atmosphere of dry nitrogen in the presence of triethyl amine (Et_3N) gave, after workup and isolation, the desired products, selenazoles (**3**) in good yields as shown in Table I.

The products are characterized by microanalyses, ^1H NMR, IR and Mass-spectral data. The microanalyses and proton NMR spectra are consistent with the proposed structures. In the infrared there are two characteristic intense absorptions centered around 1530-1460 cm^{-1} and 1410-1380 cm^{-1} due to the selenazole ring. All mass spectra show the correct molecular ions peaks, ion clusters and fragmentation patterns shown in Scheme 2.

Scheme 1



Scheme 2

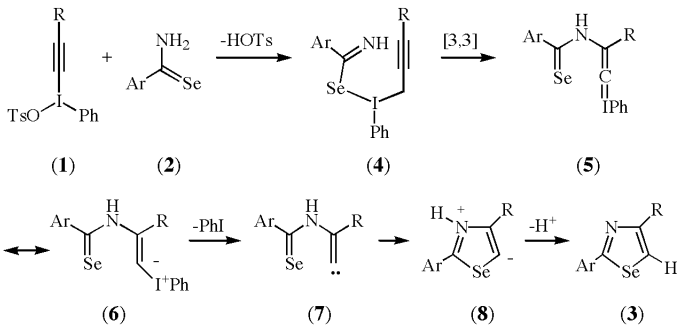


The reaction was found to be general and applicable to alkylethynyl(phenyl)iodonium salts or phenylethnyl-(phenyl)iodonium salt. Several arylselenoamides containing various substituents, such as chloro, methyl, methoxy and dimethylamino groups, were successfully reacted.

A plausible mechanism for the formation of selenazoles (**3**) is analogous to the synthesis of thiazoles from alkynyliodonium salts and thioamides [5] and is shown in Scheme 3. It involves the selenophilic attack of the iodonium atom of alkynyl(phenyl)iodonium salts (**1**) on the selenoamides (**2**) to form primary addition products (**4**) followed by an unusual room temperature polyhetero-Claisen rearrangement [6] and 1,1-elimination of iodobenzene to generate carbene (**7**), final cycloaromatization of the resulting carbene to give selenazoles (**3**).

In summary, a novel method for the synthesis of selenazoles based on the cyclocondensation of alkynyl-(phenyl)iodnium salts and selenoamides has been developed. The synthetic method is simple, mild and the yields are high. Furthermore, the method now described

Scheme 3



(**1**) (**2**) (**4**) (**5**)

(**6**) (**7**) (**8**) (**3**)

can give a contribution to the growing applications of selenazoles.

EXPERIMENTAL

General Procedures.

All experiments were carried out under dry nitrogen using standard Schlenk techniques. selenoamides were prepared according to the literature [4a]. Methanol was distilled from sodium metal (Na) prior to use. Melting points were determined on a X_4-Data microscopic melting point apparatus and are uncorrected. Microanalyses were obtained using Carlo-Erba 1106. ^{1}H Nmr spectra were obtained at 500MHz or 60MHz (AVANCE DMX500 or JEOL PMX60$_{SI}$) in dimethyl-d_6 sulfoxide (DMSO-d_6) or deuteriochloroform ($CDCl_3$) using TMS as an interal standard. Ir spectra were recorded on a Perkin Elmer 683 spectrometer at room temperature. Mass spectra were acquired under electron impact conditions with 70 eV ionizing potential (HP5989B).

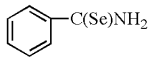
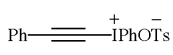
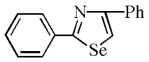
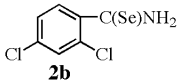
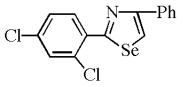
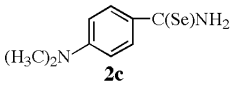
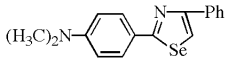
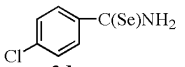
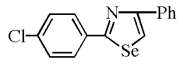
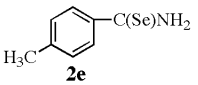
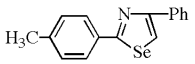
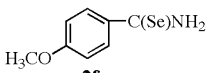
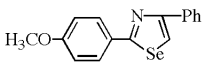
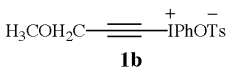
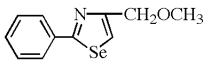
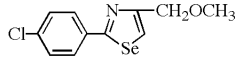
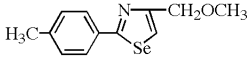
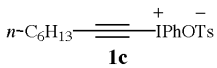
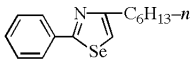
2,4-Diphenylselenazole (**3a**).

To a solution of Selenobenzamide (0.28 g, 2 mmol) in dry methanol (5 ml) was added a solution of phenylethynyliodonium salt (0.95 g, 2 mmol) and 1 ml Et_3N in dry methanol (5 ml) under a nitrogen atmosphere. The mixture was refluxed for 30 minutes and then concentrated under reduced pressure. The residue was recrystallized with ethanol (EtOH) to give pure **3a**, 0.47 g (82% yield); white lamelae crystals, mp 97-99 (lit. [2d] 99 °C); ^{1}H NMR (DMSO-d_6): δ 8.69(s, 1H), 8.06-8.01(m, 5H), 7.53-7.35(m, 5H); ^{13}C NMR (DMSO-d_6): δ 120.02, 125.60, 125.97, 127.16, 128.04, 128.55, 129.78, 134.12, 134.96, 154.84, 172.51; IR (KBr): ν 3100 (m) 1500 (s) and 1380 (s) cm^{-1}; MS: 288(M$^+$, 5), 286(17), 284(9), 185(18), 183(100), 181(52), 103(70), 77(5), 76(27), 51(10). Compounds **3b-3j** were prepared following the same procedure as **3a.**

2-(2,4-Dichlorophenyl)-4-phenylselenazole (**3b**).

Compound **3b** has mp. 103-105 °C; IR (KBr): ν 3120 (m), 1515 (s), 1385 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.42 (s, 1H), 7.79-7.90

Table 1
Selenazoles (**3**) by Cyclocondensation of (**1**) and (2)

Selenoamides	Alkynyl(Phenyl)Iodinium Salts	Selenazoles	Yield (%)
 **2a**	 **1a**		82
 **2b**	**1a**		74
 **2c**	**1a**		77
 **2d**	**1a**		56
 **2e**	**1a**		83
 **2f**	**1a**		84
2a	 **1b**		54
2d	**1b**		59
2e	**1b**		70
2a	 **1c**		20

(m, 3H), 7.30-7.50 (m, 5H); MS: 355(M^+,15), 353(25), 351(12), 184(6), 182(19), 180(9), 102(18), 77(31), 76(26), 51(14).

Anal. Calcd for $C_{15}H_9Cl_2NSe$: C, 51.01; H, 2.57; N, 3.92. Found: C, 51.37; H, 2.89; N, 4.31.

2-(*p*-*N*,*N*-Dimethylaminophenyl)-4-phenylselenazole (**3c**).

Compound **3c** has mp. 94-96 °C; IR (KBr): ν 3100 (m), 2960 (s), 1460 (s), 1360 (s), 860 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.71(s,1H), 7.72-7.86 (m, 4H), 7.25-7.48 (m, 5H), 2.93 (s, 6H); MS: 330(M^+,32), 328(100), 326(48), 184(28), 182(83), 180(41), 102(88), 77(32), 76(13).

Anal. Calcd for $C_{17}H_{16}N_2Se$: C, 62.39; H, 4.93; N, 8.56. Found: C, 62.78; H, 4.53; N, 8.92.

2-(4-Chlorophenyl)-4-phenylselenazole (**3d**).

Compound **3d** has mp. 106-108 °C (lit. [2d] 108 °C); IR (KBr): ν 3090 (m), 1465 (s), 1375 (s), 870 (vs) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.75 (s, 1H), 8.10-8.20 (m, 4H), 7.45-7.60 (m, 5H).

2-(4-Methylphenyl)-4-phenylselenazole (**3e**).

Compound **3e** has mp 134-136 °C (lit. [2d] 136 °C); IR (KBr): ν 3105 (m), 2990, 2940 (s), 1505 (s), 1400 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.60 (s, 1H), 7.91-8.00 (m, 4H), 7.21-7.39 (m, 5H), 2.35 (s, 3H).

2-(4-Methoxyphenyl)-4-phenylselenazole (**3f**).

Compound **3f** has mp 103-105 °C (lit. [2d] 105 °C); IR (KBr): ν 3092 (m), 2980 (s), 1505 (s), 1365 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.48 (s, 1H), 7.83-7.92 (m, 2H), 7.00-7.42 (m, 2H), 6.96-7.03 (m, 5H), 3.80 (s, 3H).

4-Methoxymethyl-2-phenylselenazole (**3g**).

Compound **3g** has mp 59-60 °C; IR (KBr): ν 3100 (m), 1585 (s), 1460 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.39 (s, 1H), 7.30-7.52 (m, 5H), 4.83 (s, 2H), 3.70 (s, 3H); MS: 255(M^+,11), 253(33), 251(17), 152(30), 150(100), 148(51), 70(41).

Anal. Calcd for $C_{11}H_{11}NOSe$: C, 52.39; H, 4.40; N, 5.55. Found: C, 52.71; H, 4.69; N, 5.02.

2-(4-Chlorophenyl)-4-methoxymethylselenazole (**3h**).

Compound **3h** has mp 79-80 °C; IR (KBr): ν 3100 (m), 1580 (s), 1450 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.30 (s, 1H), 7.70-7.90 (m, 2H), 7.33-7.55 (m, 2H), 4.96 (s, 2H), 3.78 (s, 3H); MS: 289(M^+,8), 287(26), 285(13), 152(30), 150(100), 148(49), 70(48).

Anal. Calcd for $C_{11}H_{10}ClNOSe$: C, 46.09; H, 3.52; N, 4.89. Found: C, 46.43 H, 3.82; N, 4.53.

4-Methoxymethyl-2-(4-methylphenyl)selenazole (**3i**).

Compound **3i** has mp 116-117 °C; IR (KBr): ν 3105 (m), 1570 (s), 1460 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.03 (s, 1H), 7.60-7.90 (m, 2H), 7.20-7.40 (m, 2H), 4.25 (s, 2H), 3.40 (s, 3H), 2.40 (s, 3H); MS: 269(M^+,15), 267(42), 265(22), 166(29), 164(100), 162(49), 84(43).

Anal. Calcd for $C_{12}H_{13}NOSe$: C, 54.14; H, 4.92; N, 5.26. Found: C, 54.51; H, 4.55; N, 4.61.

4-(*n*-Hexyl)-2-phenylselenazole (**3j**).

Compound **3j** was obtained as a yellow Oil; IR: ν 3090 (m), 1565 (s), 1405 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.05 (s, 1H), 7.05-7.50 (m, 5H), 3.64 (t, 2H, J = 7.6 Hz), 2.44 (m, 2H), 1.10-1.32 (m, 6H), 0.90 (t, 3H, J = 8.0Hz); MS: 295(M^+,4), 293(13), 291(6), 192(33), 190(100), 188(52), 110(17), 39(41).

Anal. Calcd for $C_{15}H_{19}NSe$: C, 61.64; H, 6.55; N, 4.79. Found: C, 62.02; H, 6.23; N, 4.43.

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