Hypervalent Iodine in Synthesis 53: Synthesis of 2,4-Disubstituted and 2,4,5-Trisubstituted 1,3-Selenazoles

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Abstract: α-Tosyloxylation of ketones with [hydroxy(tosyloxy)iodo]benzene, followed by treatment with primary selenoamides provides a convenient method of synthesis of selenazoles without the use of lachrymatory and toxic α-haloketones. The synthetic method is simple, mild and the yields are higher.

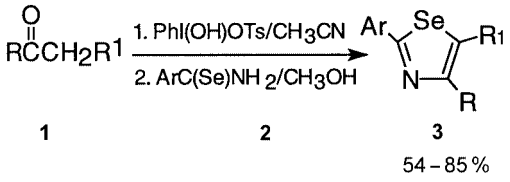
Key words: α-tosyloxylation, selenium, primary selenoamides, [hydroxy(tosyloxy)iodo]benzene (HTIB), cyclization, 2,4-disubstituted and 2,4,5-trisubstituted 1,3-selenazoles, heterocycles

The selenazole derivatives are of marked interest because of their antitumor, antibacterial and other notable activities.[1] However, since the first preparation of selenazoles appeared in 1889,[2a] for decades after this no further details were found in the literature. Only after 1940 was a somewhat more intensive study of the selenazoles began.

The number of the selenazole derivatives hithero is few. There are probably two reasons for the small number of selenazole derivatives to be found in the literature. 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 Hantzch thiazole synthesis, this consists of the condensation of α-haloketones with selenoamides.[2] On the other hand, the essential selenium containing starting materials are less readily available than the sulfur analog intermediates.

There is considerable current interest and research activity in hypervalent iodine compounds.[3] It has been demonstrated that the [hydroxy(tosyloxy)iodo]benzene (HTIB) is a versatile reagent in organic synthesis and especially useful is the reaction of HTIB with ketones leading to α-tosyloxylketones. This reaction followed by treatment with the appropriate nucleophilies in situ offers a variety of valuable synthetic methods. In addition, we have recently developed a simple method for synthesis of selenoamides.[4] On the basis of these facts, we were prompted to examine the α-tosyloxylation of ketones with HTIB followed by treatment with selenoamides. Such reaction would provide a new route to selenazoles without use of lachrymatory and toxic α-haloketones.[5]

Herein we report our result, a new effective method for the synthesis of selenazoles by cyclocondensation of α-tosyloxylketones with selenoamides. We have found that the α-tosyloxylation of ketones with HTIB, followed by treatment with selenoamides gave selenazoles in one-pot (Scheme). The results are summarized in the Table.



Scheme

The products are characterized by microanalyses, ^{1}H NMR, IR and mass spectral data. The microanalyses and ^{1}H NMR spectra are consistent with the proposed structures. In the infrared there are two characteristic intense absorption centered in ν = 1530−1460cm^{-1} and 1410−1360 cm^{-1} regions due to the selenazole ring. All mass spectra show the correct molecular ions peaks and ion clusters. The reaction is found to be general and applicable to aliphatic ketones or aromatic ketones with electron-donating or electron-withdrawing groups. Additionally, the reaction can be carried out readily with several selenoamides containing various substitutes, such as *N*,*N*-dimethylamino, methoxy, methyl, chloro and nitro groups.

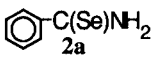
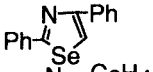
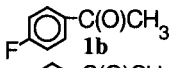
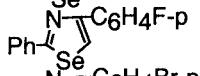
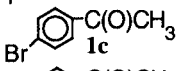
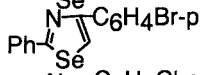
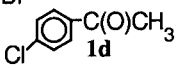
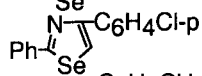
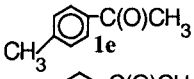
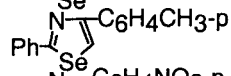
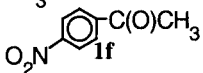
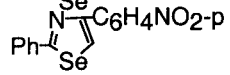
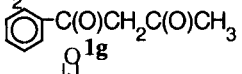
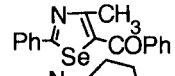
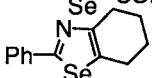
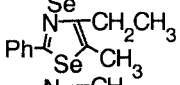
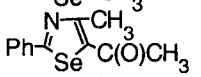
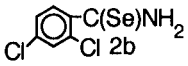
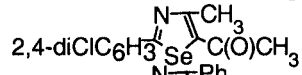
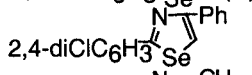
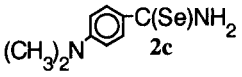
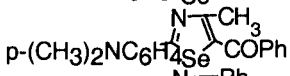
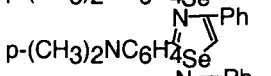
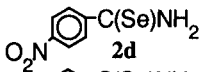
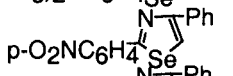
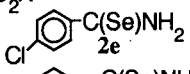
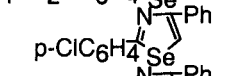
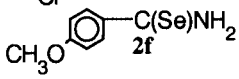
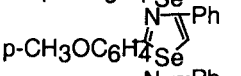
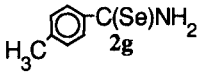
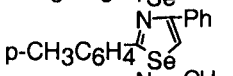
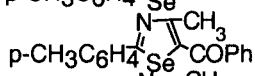
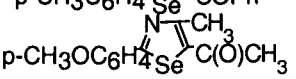
In conclusion, the present study provides a one-pot procedure for the synthesis of selenazoles which has some advantages, such as avoiding the use of lachrymatory and toxic α-haloketones, simplicity of the procedure and higher yields.

Selenoamides were prepared according to the literature.[4a] MeOH was distilled from Na prior to use. Melting points were determined on a X_4-Data microscopic melting point apparatus and were 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 DMSO-d_6 or $CDCl_3$ using TMS as an interal standard. IR spectra were recorded on a Perkin Elmer 683 spectrometer at r.t. Mass spectra were obtained by electron impact at 70ev (HP5989B).

2,4-Diphenylselenazole (3a); Typical Procedure

To a solution of acetophenone (0.24 g, 2 mmol) in MeCN (15 mL) was added HTIB (0.79 g, 2 mmol) and the mixture was refluxed for 45 min, and then the solvent was evaporated in vacuo. Then MeOH (10 mL) and a solution of selenobenzamide (0.14 g, 1 mmol) in MeOH (10 mL) was added under N_2. After the addition was complete, refluxing was continued for 30 min. The mixture was then concentrated under reduced pressure and the residue was chromatographed on a silica gel plate using mixtures of cyclohexane/EtOAc (8:2) as eluent to afford **3a**; yield: 0.22 g (78%); mp 97−99 °C (Lit.[2d] mp 99 °C).

Table Synthesis of Selenazoles **3a–3t**

Entry	Ketones	Selenoamides	Products		Yield(%)[a]
1	 **1a**	 **2a**		3a	78
2	 **1b**	**2a**		3b	83
3	 **1c**	**2a**		3c	85
4	 **1d**	**2a**		3d	83
5	 **1e**	**2a**		3e	73
6	 **1f**	**2a**		3f	85
7	 **1g**	**2a**		3g	65
8	 **1h**	**2a**		3h	81
9	$CH_3CH_2C(O)CH_2CH_3$ **1i**	**2a**		3i	56
10	$CH_3C(O)CH_2C(O)CH_3$ **1j**	**2a**		3j	76
11	**1j**	 **2b**		3k	75
12	**1a**	**2b**		3l	71
13	**1g**	 **2c**		3m	66
14	**1a**	**2c**		3n	77
15	**1a**	 **2d**		3o	85
16	**1a**	 **2e**		3p	58
17	**1a**	 **2f**		3q	83
18	**1a**	 **2g**		3r	72
19	**1g**	**2g**		3s	60
20	**1j**	**2f**		3t	54

[a] The yields based on selenoamides as limiting reagents

IR (KBr): ν = 3100(m), 1500(s), 1380(s) cm^{-1}.

^1H NMR (DMSO-d_6): δ = 8.687 (s 1 H), 8.008−8.064 (m, 5 H), 7.352−7.528 (m, 5 H).

^{13}C NMR (DMSO-d_6): δ = 120.024, 125.602, 125.965, 127.155, 128.038, 128.545, 129.775, 134.123, 134.959, 154.844, 172.511.

MS: *m/z* = 288 (M^+, 5), 286 (M^+, 17), 284 (M^+, 9), 185 (18), 183 (100), 181 (52), 103 (10), 77 (5), 76 (27), 51 (10).

4-(4 -Flurophenyl)-2-phenylselenazole (3b)
Mp 112−114 °C.

IR (KBr): ν = 3125(m), 1480(s), 1390 (s) cm^{-1}.

^1H NMR (DMSO-d_6): δ = 8.828 (s,1 H), 7.802−8.005 (m, 5 H), 7.127−7.553 (m, 4 H).

MS: *m/z* = 305 (M^+, 28), 303 (M^+, 100), 301 (M^+, 49), 202 (24), 200 (84), 198 (40), 120 (92).

Anal. calcd for $C_{15}H_{10}FNSe$: C, 59.62; H, 3.34; N, 4.63. Found: C, 59.67; H, 3.29; N, 4.65.

4-(4-Bromophenyl)-2-phenylselenazole (3c)
Mp 76−77 °C.

IR (KBr): ν = 3090(m), 1495(s), 1370(s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.70 (s, 1 H), 7.73−8.03 (m, 5 H), 7.10−7.31 (m, 4 H).

MS: *m*/*z* = 365 (M^+, 99), 363 (M^+, 100), 361 (M^+, 48), 262 (70), 260 (71), 258 (35), 182 (80), 180 (84).

Anal. calcd for $C_{15}H_{10}BrNSe$: C, 49.62; H, 2.78; N, 3.86. Found: C, 49.93; H, 2.54; N, 3.99.

4-(4-Chlorophenyl)-2-phenylselenazole (3d)
Mp 136−138 °C.

IR (KBr): ν = 3110(m), 1490(s), 1385(s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.75 (s, 1 H), 7.70−8.05 (m, 5 H), 7.11−7.52 (m, 4 H).

MS: *m*/*z* = 321 (M^+, 17), 319 (M^+, 35), 317 (M^+, 17), 218 (45), 216 (100), 214 (32), 138 (25), 136 (75), 101 (9).

Anal. calcd for $C_{15}H_{10}ClNSe$: C, 56.53; H, 3.16; N, 4.39. Found: C, 56.65; H, 3.09; N, 4.51.

4-(4-Methylphenyl)-2-phenylselenazole (3e)
Mp 117−119 °C.

IR (KBr): ν = 3120(m), 2940(s), 1495(s), 1320 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.46 (s,1 H), 7.73−8.01 (m, 5 H), 7.02−7.55 (m, 4 H), 2.35 (s, 3 H).

MS: *m*/*z* = 301 (M^+, 31), 299 (M^+, 100), 297 (M^+, 48), 198 (25), 196 (77), 194 (39), 116 (84), 101 (11).

Anal. calcd for $C_{16}H_{13}NSe$: C, 64.43; H, 4.39; N, 4.70. Found: C, 64.52; H, 4.31; N, 4.76.

4-(3-Nitrophenyl)-2-phenylselenazole (3f)
Mp 67−69 °C.

IR (KBr): ν = 3080(m), 1460(s), 1380(s), 1360 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.93 (s,1 H), 7.91−8.03 (m, 5 H), 7.33−7.61 (m, 4 H).

MS: *m*/*z* = 332 (M^+, 34), 330 (M^+, 100), 328 (M^+, 49), 229 (23), 227 (68), 225 (33), 147 (81), 122 (7).

Anal. calcd for $C_{15}H_{10}N_2O_2Se$: C, 54.72; H, 3.06; N, 8.51. Found: C, 54.83; H, 2.98; N, 8.89.

5-Benzoyl-4-methyl-2-phenylselenazole (3g)
Mp 88−90 °C.

IR (KBr): ν = 2950(m), 1638(s), 1500(s), 1410(s) cm^{-1}.

^{1}H NMR($CDCl_3$): δ = 7.65−8.05 (m, 5 H), 7.25−7.50 (m, 5 H), 2.50 (s, 3 H).

MS: *m*/*z* = 329 (M^+, 22), 327 (M^+, 67), 325 (M^+, 33), 226 (1), 224 (3), 222 (2), 182 (9), 144 (10), 119 (9), 105 (100), 77 (64).

Anal. calcd for $C_{17}H_{13}NOSe$: C, 62.58; H, 4.02; N, 4.29. Found: C, 62.61; H, 3.99; N, 4.26.

2-Phenyl-4,5,6,7-tetrahydrobenzoselenazole (3h)
Bp 67−69 °C/5 Torr.

IR (neat): ν = 2880−2860(m), 1480(s), 1285(s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.10−7.90 (m, 5 H), 2.75 (t, 4 H, *J* = 2 Hz), 1.75 (m, 4 H).

MS: *m*/*z* = 265 (M^+, 31), 263 (M^+, 100), 261 (M^+, 49), 162 (27), 160 (82), 158 (40), 80 (11).

Anal. calcd for $C_{13}H_{13}NSe$: C, 59.57; H, 4.99; N, 5.34. Found: C, 59.61; H, 4.96; N, 5.22.

4-Ethyl-5-methyl-2-phenylselenazole (3i)
Bp 96−98 °C/5 Torr.

IR (neat): ν = 2960, 2930(s), 1510(s), 1295(s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.60−7.80 (m, 2 H), 7.20−7.30 (m, 3 H), 2.36−2.75 (q, 2 H), 2.35 (s, 1 H), 1.05−1.30 (t, 3 H).

MS: *m*/*z* = 253 (M^+, 33), 251 (M^+, 100), 249 (M^+, 49), 150 (19), 148 (58), 146 (30), 68 (29), 53 (33).

Anal. calcd for $C_{12}H_{13}NSe$: C, 57.60; H, 5.24; N, 5.60. Found: C, 57.81; H, 5.16; N, 5.63.

5-Acetyl-4-methyl-2-phenylselenazole (3j)
Mp 71−73 °C.

IR (KBr): ν = 2920(m), 1650(s), 1485(s), 1350(s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.20−7.90 (m, 5 H), 2.60 (s, 3 H), 2.40 (s, 3 H).

MS: *m*/*z* = 267 (M^+, 31), 265 (M^+, 100), 263 (M^+, 49), 164 (20), 162 (60), 160 (29), 119 (34), 104 (33).

Anal. calcd for $C_{12}H_{11}NOSe$: C, 54.56; H, 4.20; N, 5.30. Found: C, 54.62; H, 3.97; N, 5.26.

5-Acetyl-2-(2,4-dichlorophenyl)-4-methylselenazole (3k)
Mp 91−93 °C.

IR (KBr): n = 2980, 2960(s), 1645(s), 1470(s), 1375(s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.30−7.50 (m, 3 H), 2.71 (s, 3 H), 2.50 (s, 3 H).

MS: *m*/*z* = 335 (M^+, 17), 333 (M^+, 36), 331 (M^+, 19), 164 (17), 162 (52), 160 (25), 119 (31), 82 (3), 76 (9), 43 (100).

Anal. calcd for $C_{12}H_9Cl_2NOSe$: C, 43.26; H, 2.27; N, 4.20. Found: C, 43.23; H, 2.96; N, 4.25.

2-(2,4-Dichlorophenyl)-4-phenylselenazole (3l)
Mp 103−105 °C.

IR (KBr): ν = 3120(m), 1515(s), 1385(s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.42 (s, 1 H), 7.79−7.90 (m, 3 H), 7.30−7.50 (m, 5 H).

MS: *m*/*z* = 355 (M^+, 15), 353 (M^+, 25), 351 (M^+, 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, 51.61; H, 2.52; N, 4.01.

5-Benzoyl-2-(4-*N*,*N*-dimethylaminophenyl)-4-methylselenazole (3m)
Mp 64−66 °C.

IR (KBr): ν = 2940(s), 1650(s), 1495(s), 1400(s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.70−7.90 (m, 2 H), 7.21−7.35 (m, 5 H), 6.62−6.79 (m, 2 H), 2.95 (s, 6 H), 2.40 (s, 3 H).

MS: *m*/*z* = 372 (M^+, 19), 370 (M^+, 60), 368 (M^+, 29), 226 (3), 224 (10), 222 (5), 144 (9), 105 (100), 77 (63).

Anal. calcd for $C_{19}H_{18}N_2OSe$: C, 61.79; H, 4.91; N, 7.59. Found: C, 61.83; H, 4.89; N, 7.61.

2-(4-*N*,*N*-Dimethylaminophenyl)-4-phenylselenazole (3n)
Mp 94−96 °C.

IR (KBr): ν = 3100(m), 2960(s), 1460(s), 1360(s), 860(s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.71 (s, 1 H), 7.72-7.86 (m, 4 H), 7.25-7.48 (m, 5 H), 2.93 (s, 6 H).

MS: *m*/*z* = 330 (M^+, 32), 328 (M^+, 100), 326 (M^+, 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, 62.53; H, 4.66; N, 8.61.

2-(4-Nitrophenyl)-4-phenylselenazole (3o)
Mp 69−71 °C.

IR (KBr): ν = 3100(m), 1505(s), 1455(s) cm^{-1}.

^{1}H NMR($CDCl_3$): δ = 8.82 (s, 1 H), 7.60−7.85 (m, 2 H), 7.45−7.54(m, 5 H), 7.20−7.30 (m, 2 H).

MS: *m*/*z* = 332 (M^+, 7), 330 (M^+, 21), 328 (M^+, 10), 184 (30), 182 (100), 180 (49), 102 (68), 77 (23), 76 (11).

Anal. calcd for $C_{15}H_{10}N_2O_2Se$: C, 54.73; H, 3.06; N, 8.51. Found: C, 55.03; H, 2.99; N, 8.60.

2-(4-Chlorophenyl)-4-phenylselenazole (3p)
Mp 106−108 °C (Lit.[2d] mp108 °C).

IR (KBr): ν = 3090(m), 1465(s), 1375(s), 870 (vs) cm^{-1}.

^1H NMR($CDCl_3$): δ = 8.75 (s, 1 H), 8.10−8.20 (m, 4 H), 7.45−7.60 (m, 5 H).

2-(4-Methoxyphenyl)-4-phenylselenazole (3q)
Mp 103−105 °C (Lit.[2d] mp 105 °C).

IR (KBr): ν = 3092(m), 2980(s), 1505(s), 1365(s) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.48 (s,1 H), 7.83−7.92 (m, 2 H), 7.00−7.42 (m, 2 H), 6.96−7.03 (m, 5 H), 3.80 (s, 3 H).

2-(4-Methylphenyl)-4-phenylselenazole (3r)
Mp 134−136 °C (Lit.[2d] mp 136 °C).

IR (KBr): ν = 3105(m), 2990, 2940(s), 1505(s), 1400(s) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.60 (s, 1 H), 7.91−8.00 (m, 4 H), 7.21−7.39 (m, 5 H), 2.35 (s, 3 H).

5-Benzoyl-2-(4-methylphenyl)-4-methylselenazole (3s)
Mp 89−91 °C.

IR (KBr): ν = 2970, 2940(s), 1635(s), 1500(s), 1405(s) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.68−8.00 (m, 4 H), 7.10-7.60 (m, 5 H), 2.44 (s, 3 H), 2.38 (s, 3 H).

MS: *m*/*z* = 343 (M^+, 20), 341 (M^+, 60), 339 (M^+, 30), 226 (2), 224 (5), 222 (3), 181 (18), 144 (2), 105 (100).

Anal. calcd for $C_{18}H_{15}NOSe$: C, 63.54; H, 4.44; N, 4.12. Found: C, 63.71; H, 4.39; N, 4.27.

5-Acetyl-2-(4-methoxyphenyl)-4-methylselenazole (3t)
Mp 68-70 °C.

IR (KBr): ν = 2995-2920(s), 1665(s), 1490(s), 1390(s) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.85−7.96 (m, 2 H), 7.31−7.50 (m, 2 H), 3.84 (s, 3 H), 2.55 (s, 3 H), 2.38 (s, 3 H).

MS: *m*/*z* = 297 (M^+, 19), 295 (M^+, 57), 293 (M^+, 28), 164 (17), 162 (53), 160 (26), 119 (35), 104 (30), 82 (7), 43 (100).

Anal. calcd for $C_{13}H_{13}NO_2Se$: C, 53.07; H, 4.45; N, 4.76. Found: C, 53.61; H, 4.38; N, 4.79.

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