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Synthesis of 4-Aryl-2-imino-2*H*-selenazolines by a Reaction of α-(Selenocyanato)acetophenones With Anilines

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4-Aryl-2-imino-2H-selenazolines have been prepared by a reaction of α-(selenocyanato)acetophenones with anilines.

Keywords Cyclization; heterocycles; selenium

Selenium represents an essential element for higher organisms.[1] As selenium-containing enzymes—i.e., *Glutathioneperoxidase* and *5′-Deiodase type 1*—are very important for the organism, various diseases can result from selenium deficiency.[2,3] As a consequence, selenium-containing heterocycles are of considerable biochemical and pharmacological relevance. In this context, the antitumor and antiviral agent C-glycosyl selenazole selenazofurin represents a prominent example.[4] Selenium heterocycles are often less stable than the corresponding sulfur analogues. In addition, methods and conditions available for the synthesis of sulfur compounds often can not be applied to selenium. Therefore, the development of new methods for the synthesis of small selenium-containing building blocks is of considerable current interest.[5,6]

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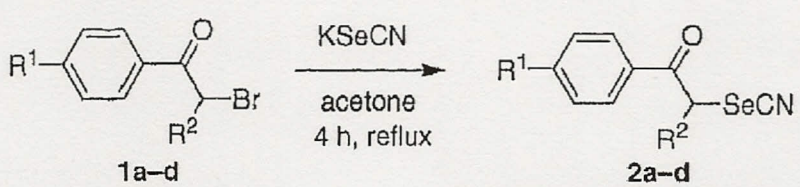
TABLE I The Synthesis of 2a–d

2	R^1	R^2	Yield (%)[a]
a	H	H	59
b	Cl	H	33
c	Br	H	41
d	H	Ph	46

[a]Yields of isolated products.

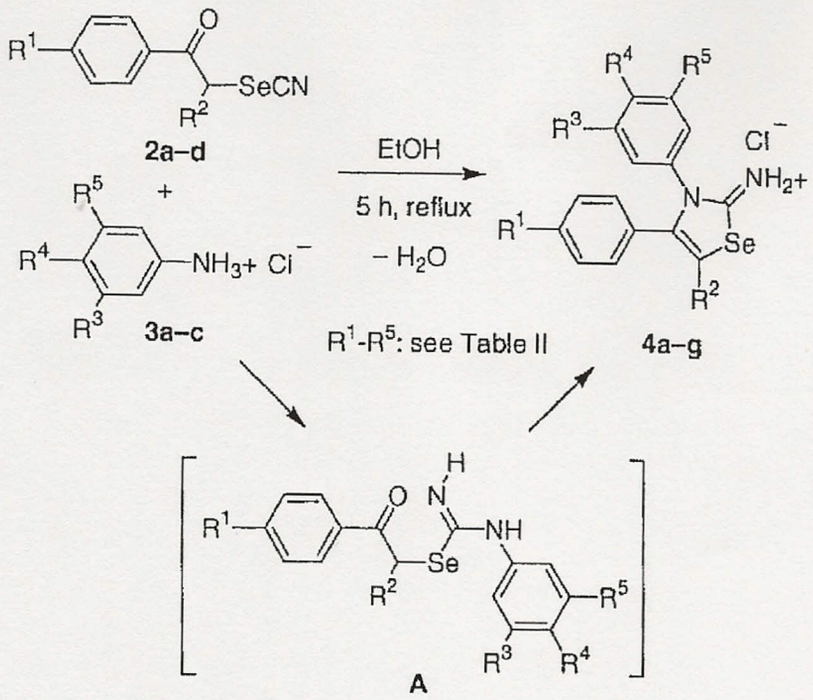
α-(selenocyanato)ketones represent useful synthetic building blocks for the synthesis of selenium heterocycles.[7] 1,3,4-selenadiazoles have been prepared by [3+2] cycloaddition of α-(selenocyanato)acetophenones with diazonium salts.[8] Aliphatic selenium heterocycles are available by [4+2] cycloaddition of α-(selenocyanato)ketones with 1,3-butadienes.[9] In addition, sodium-hydride mediated cyclizations of α-(selenocyanato)acetophenones that give five-membered selenium heterocycles have been reported.[10] Herein, we report the synthesis of 4-aryl-2-imino-2*H*-selenazolines that are, to the best of our knowledge, the first reactions of α-(selenocyanato)acetophenones with amines.[11] α-(selenocyanato)acetophenones are readily available by a reaction of phenacylbromides with potassium selenocyanate (KSeCN).[9b,10,12]

The known α-(selenocyanato)acetophenones **2a–d** were prepared by a reaction of phenacylbromides **1a–d** with KSeCN (Scheme 1, Table I). The acid-mediated cyclization of α-(selenocyanato)acetophenones **2a–d** with anilines **3a–c** afforded 4-aryl-2-imino-2*H*-selenazolines **4a–g** (Scheme 2, Table II). The formation of the latter can be explained by an acid-catalyzed attack of the amine onto the selenocyanato group, an attack of the imino group thus formed onto the carbonyl group, and the subsequent elimination of water. The reaction of α-(selenocyanato)acetophenone **2b** with hydroxylamine hydrochloride afforded the selenazoline **4h** (Scheme 3). During optimization of reaction conditions, employment of amines in the form of their hydrochlorides proved to be important. In addition, the reaction time and the solvent played an important role. The relatively low yields can be explained by the unstable nature of the products and decomposition during the reaction.



1a–d 2a–d

SCHEME 1 The cyclization of α-(selenocyanato)acetophenones.



SCHEME 2 The cyclization of α-(selenocyanato)acetophenones with phenacyl bromides.

In summary, 4-aryl-2-imino-2*H*-selenazolines have been prepared by a reaction of α-(selenocyanato)acetophenones with anilines.

EXPERIMENTAL

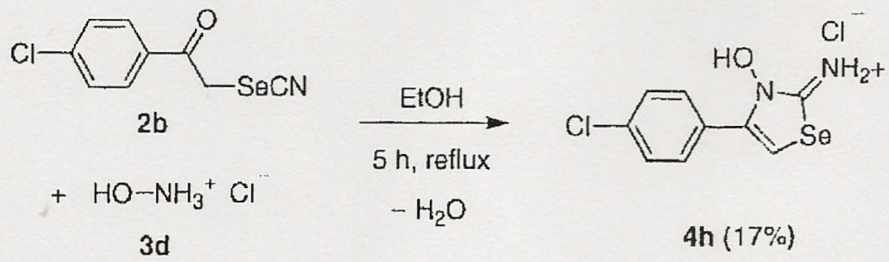
General Comments

All solvents were dried by standard methods, and all reactions were carried out under an inert atmosphere. For ^{1}H and ^{13}C NMR, the deuterated solvents indicated were used. Mass spectrometric data (MS) were

TABLE II The Synthesis of 4a–g

4	R^1	R^2	R^3	R^4	R^5	Yield (%)[a]
a	H	H	H	Cl	H	27
b	H	H	Cl	H	Cl	21
c	Cl	H	H	H	H	13
d	Cl	H	H	Cl	H	15
e	Br	H	Cl	H	Cl	2
f	Br	H	H	Cl	H	[b]
g	H	Ph	H	Cl	H	10

[a]Yields of isolated products.
[b]Product contains 4-chloroaniline hydrochloride.



SCHEME 3 The cyclization of α-(selenocyanato)acetophenones with phenacyl bromides.

obtained by electron ionization (70 eV), chemical ionization (CI, H_2O), or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60–200 mesh) was used. Melting points are uncorrected.

Synthesis of Phenacyl Selenocyanates 2a–d

The synthesis of **2a–d** by a reaction of potassium selenocyanate with phenacyl bromides has been previously reported.[7–12]

Phenacyl Selenocyanate (2a)

A mixture of potassium selenocyanate (2.88 g, 20.0 mmol) and phenacyl bromide (3.96 g, 20.0 mmol) in aceton (30 mL) was refluxed for 4 h. The hot mixture was filtrated, the solution concentrated in vacuo, and the resulting solid was isolated by filtration and recrystallization (EtOH). Yield: 2.63 g (59%), yellow prisms, m.p. 121°C (ethanol). IR (KBr): $\tilde{\nu} = 3002$, 2945 (w), 2155 (m), 1666 (s), 1594, 1578 (m), 1449, 1374 (s), 1324, 1310, 1287 (m), 1266, 1195, 996, 755, 688 (s) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 4.94$ (s, 2 H, CH_2), 7.51–7.71 (m, 3 H, Ar), 7.94–7.98 (m, 2 H, Ar). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 35.5$ (CH_2), 103.8 (C), 128.8, 128.9 (CH), 129.2, 134.1, 134.2, 194.6 (C). MS (EI, 70 eV): m/z (%) = 225 (3, $[M+H]^+$ (^{80}Se)), 139 (4), 105 (100, $[C_6H_5CO]^+$), 91 (8), 77 (35, $[C_6H_5]^+$), 51 (14). Anal. calcd. for C_9H_7NOSe (224.12): C, 48.23; H, 3.15; N, 6.25. Found: C, 48.42; H, 3.65; N, 6.41.

4-Chlorophenacyl Selenocyanate (2b)

Starting with potassium selenocyanate (2.88 g, 20.0 mmol) and 4-chlorophenacyl bromide (4.64 g, 20.0 mmol) in acetone (40 mL), product **2b** was isolated by filtration and recrystallization (EtOH). Yield: 1.72 g (33%), orange needles, m.p. 137°C (ethanol). IR (KBr): $\tilde{\nu} = 2989$, 2935 (w), 2154 (m), 1659, 1590 (s), 1571 (m), 1490, 1405, 1386 (w), 1313 (m),

1294, 1181, 1094 (s), 1015 (w), 999, 819 (s) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 4.88$ (s, 2 H, CH_2), 7.49–7.54 (m, 2 H, Ar), 7.88–7.92 (m, 2 H, Ar). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 35.0$ (CH_2), 103.8 (C), 129.0, 130.7 (CH), 132.9, 139.1, 193.9 (C). MS (EI, 70 eV): m/z (%) = 259 (4, $[M+H]^+$ (^{80}Se)), 139 (100), 110 (32). Anal. calcd. for $C_9H_6ClNOSe$ (258.56): C, 41.81; H, 2.34; N, 5.42. Found: C, 43.02; H, 2.54; N, 5.60.

4-Bromophenacyl Selenocyanate (2c)

Starting with potassium selenocyanate (2.88 g, 20.0 mmol) and 4-bromophenacyl bromide (5.52 g, 20.0 mmol) in acetone (40 mL), **2c** was isolated (2.46 g, 41%) by filtration and recrystallization (EtOH) as yellow prisms, m.p. 124°C (ethanol). IR (KBr): $\tilde{\nu} = 2988$, 2934 (w), 2154 (m), 1658, 1585 (s), 1567 (m), 1486 (s), 1402, 1313 (w), 1289, 1180, 1071, 997, 811 (m) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 4.88$ (s, 2 H, CH_2), 7.66–7.71 (m, 2 H, Ar), 7.80–7.84 (m, 2 H, Ar). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 35.0$ (CH_2), 103.8 (C), 128.3, 130.8 (CH), 132.0, 133.3, 194.5 (C). MS (EI, 70 eV): m/z (%) = 302 (5, $[M+H]^+$ (^{80}Se)), 234 (22), 183 (100), 155 (21), 77 (18). Anal. calcd. for $C_9H_6BrNOSe$ (303.02): C, 35.78; H, 2.00; N, 4.64. Found: C, 35.89; H, 2.26; N, 3.80.

Desyl Selenocyanate (2d)

Starting with potassium selenocyanate (2.88 g, 20.0 mmol) and desyl bromide (5.5 g, 20.0 mmol) in acetone (50 mL), **2d** was isolated (2.75 g, 46%) by filtration and recrystallization (EtOH) as red needles, m.p. 124°C (ethanol). IR (KBr): $\tilde{\nu} = 3051$, 2959 (w), 2150 (m), 1666 (s), 1595, 1450 (m), 1275 (s), 1143, 1004, 764 (m), 697, 620 (s) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 7.23$ (s, 1 H, CH), 7.29–7.51 (m, 7 H, Ar), 7.59–7.65 (m, 1 H, Ar), 7.96–7.98 (m, 2 H, Ar). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 58.1$ (CH), 104.0 (C), 128.6, 128.9, 129.3, 129.5, 129.6, 129.7 (CH), 133.0, 134.5, 136.6, 195.5 (C). MS (EI, 70 eV): m/z (%) = 301 (6, $[M+H]^+$ (^{80}Se)), 195 (74), 167 (88), 151 (63), 105 (100, $[C_6H_5CO]^+$), 90 (66), 77 (84, $[C_6H_5]^+$). Anal. calcd. for $C_{15}H_{11}NOSe$ (300.22): C, 60.01; H, 3.69; N, 4.67. Found: C, 60.03; H, 4.38; N, 4.37.

3-(4-Chlorophenyl)-4-phenyl-3*H*-(selenazol-2-ylidene)amine Hydrochloride (4a)

A mixture of **2a** (1.12 g, 5.0 mmol), and 4-chloroaniline hydrochloride (0.82 g, 5.0 mmol) in ethanol (50 mL) was refluxed for 5 h. The precipitated product was isolated by filtration, washed (ether), and dried

in vacuo. Yield: 0.50 g (27%), green to grey prisms, m.p. 245–252°C (decomp., EtOH). IR (KBr): $\tilde{\nu} = 3110$ (m), 3051, 3009, 1615, 1528, 1490 (s), 1087, 885, 744, 724, 696 (m) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 7.17–7.31$ (m, 6 H, 5-H, Ar-H), 7.48–7.57 (m, $J = 9.0$ Hz, 4 H, Ar-H), 8.98 (bs, 1 H, NH), 10.52 (bs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 108.1$ (C-5), 128.2, 129.2, 129.6, 130.3 (CH), 130.5 (C), 130.7 (CH), 133.5, 135.0, 140.4, 173.8 (C). MS (EI, 70 eV): m/z (%) = 336 (40), 335 (47), 334 (94, $[M–HCl]^+$ (^{35}Cl, ^{80}Se)), 333 (83), 332 (52), 331 (52), 330 (24), 214 (27), 102 (100). Anal. calcd. for $C_{15}H_{12}Cl_2N_2Se$ (370.14): C, 48.68; H, 3.27; N, 7.57. Found: C, 48.37; H, 3.70; N, 7.69.

3-(3,5-Dichlorophenyl)-4-phenyl-3*H*-(selenazol-2-ylidene)amine Hydrochloride (4b)

A mixture of **2a** (1.12 g, 5.0 mmol), 3,5-dichloroaniline (0.81 g, 5.0 mmol), and 3 drops of conc. hydrochloric acid in ethanol (30 mL) was refluxed for 10 h. The precipitated product was isolated by filtration, washed (ether), and dried in vacuo. Yield: 0.42 g (21%), grey prisms, m.p. 263–269°C (decomp., EtOH). IR (KBr): $\tilde{\nu} = 3121$, 3045, 2987 (m), 1627 (s), 1577, 1529, 1433 (m), 806, 744, 711, 696, 665 (w) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 7.20–7.32$ (m, 6 H, 5-H, Ar), 7.72–7.75 (m, 3 H, Ar), 9.23 (bs, 1 H, NH), 10.61 (bs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 108.3$ (C-5), 128.1, 128.2, 129.2, 129.5, 130.2 (CH), 134.9, 136.5, 139.7, 173.7 (C). MS (EI, 70 eV): m/z (%) = 372 (13), 371 (22), 370 (55), 369 (69), 368 (88, $[M–HCl]^+$ (^{35}Cl, ^{80}Se)), 367 (100), 366 (50), 365 (53), 364 (24), 363 (13), 261 (11), 260 (35), 252 (10), 250 (53), 248 (82), 182 (19), 146 (18), 145 (27), 102 (59). $C_{15}H_{11}Cl_3N_2Se$ (404.58).

3-Phenyl-4-(4-chlorophenyl)-3*H*-(selenazol-2-ylidene)amine Hydrochloride (4c)

A mixture of **2b** (1.30 g, 5.0 mmol) and aniline hydrochloride (0.65 g, 5.0 mmol) in ethanol (60 mL) was refluxed for 10 h. The precipitated product was isolated by filtration, washed (ether), and dried in vacuo. Yield: 0.24 g (13%), grey prisms, m.p. 268–271°C (decomp., EtOH). IR (KBr): $\tilde{\nu} = 3023$, 2961, 2937 (m), 1614 (m), 1527 (w), 1494 (s), 1090 (w), 744 (m) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 7.19–7.20$ (m, 2 H, Ar), 7.30–7.32 (m, 2 H, Ar), 7.34 (s, 1 H, 5-H), 7.41–7.50 (m, 5 H, Ar), 9.60 (bs, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 108.7$ (C-5), 127.7, 128.1 (CH), 129.2 (C), 129.8, 130.0, 130.8 (CH), 133.6, 134.1, 138.9, 173.4 (C). MS (EI, 70 eV): m/z (%) = 335 (14), 334 (36, $[M–HCl]^+$ (^{35}Cl, ^{80}Se)), 333 (51), 332 (20), 331 (27), 214 (62), 77 (100). $C_{15}H_{12}Cl_2N_2Se$ (370.14).

3-(4-Chlorophenyl)-4-(4-chlorophenyl)-3*H*-(selenazol-2-ylidene)amine Hydrochloride (4d)

A mixture of **2b** (1.30 g, 5.0 mmol) and of 4-chloroaniline hydrochloride (0.82 g, 5.0 mmol) in ethanol (20 mL) was refluxed for 5 h. The precipitated product was isolated by filtration, washed (ether), and dried in vacuo. Yield: 0.31 g (15%), brown prisms, m.p. 255–275°C (decomp., EtOH). IR (KBr): $\tilde{\nu} = 3111$, 2986, 1618, 1529, 1489 (s), 1093, 841 (m) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 7.19$–7.23 (m, 2 H, Ar-H), 7.33 (s+d, $^2J(^1H,^{77}Se) = 41.3$ Hz, 1 H, 5-H), 7.34–7.37 (m, 2 H, Ar), 7.49–7.59 (m, 4 H, Ar), 8.95 (bs, 1 H, NH), 10.38 (bs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 108.8$ (C-5), 128.3 (CH), 129.4 (C), 130.4, 130.7, 131.4 (CH), 133.4, 134.1, 135.1, 139.2, 173.7 (C). MS (EI, 70 eV): m/z (%) = 372 (2), 371 (3), 370 (11), 369 (11), 368 (20, $[M-HCl]^+$ (^{35}Cl, ^{80}Se)), 367 (16), 366 (10), 295 (17), 248 (23), 103 (100), 75 (57). $C_{15}H_{11}Cl_3N_2Se$ (404.58).

3-(3,5-Dichlorophenyl)-4-(4-bromophenyl)-3*H*-(selenazol-2-ylidene)amine Hydrochloride (4e)

A mixture of **2c** (1.51 g, 5.0 mmol), 3,5-dichloroaniline (0.81 g, 5.0 mmol), and 3 drops conc. hydrochloric acid in ethanol (30 mL) was refluxed for 10 h. The precipitated product was isolated by filtration, washed (ether), and dried in vacuo. Yield: 40 mg (2%), yellow prisms, m.p. 155–170°C (decomp., EtOH). IR (KBr): $\tilde{\nu} = 3073$, 3053 (w), 1604, 1577 (s), 1485, 1432, 1346, 1114, 1058, 831, 802, 748, 744 (m) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): $\delta = 6.64$ (s, 1 H, 5-H), 7.11–7.13 (m, 2 H, Ar), 7.25 (d, $J = 1.8$ Hz, 2 H, Ar), 7.45–7.48 (m, 3 H, Ar), 8.88 (bs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 100.1$ (C-5), 121.5 (C), 126.8, 128.1, 130.1, 131.3 (CH), 132.0, 133.5, 137.8, 140.7, 160.2 (C). MS (EI, 70 eV): m/z (%) = 450 (26), 449 (35), 448 (60), 447 (69, $[M-HCl]^+$ (^{79}Br, ^{35}Cl, ^{80}Se)), 446 (59), 445 (61), 444 (30), 443 (23), 340 (28), 338 (17), 330 (29), 328 (65), 326 (39), 146 (43), 145 (68), 102 (23). $C_{15}H_{10}BrCl_3N_2Se$ (483.48).

3-(4-Chlorophenyl)-4-(4-bromophenyl)-3*H*-(selenazol-2-ylidene)amine Hydrochloride (4f)

A mixture of **2c** (1.51 g, 5.0 mmol) and of 4-chloroaniline hydrochloride (0.82 g, 5.0 mmol) in ethanol (20 mL) was refluxed for 5 h. The precipitated product was isolated by filtration, washed (ether), and dried in vacuo. Yield: 0.25 g (4-chloroanilinium chloride could not be separated, **4f**/4-$ClC_6H_4NH_3Cl$ = 1.3:1). IR (KBr): $\tilde{\nu} = 3112$, 3000, 1615, 1527 (m), 1489 (s), 1094 (m), 840, 822 (w) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz):

$\delta = 7.11–7.15$ (m, 2 H, Ar), 7.32 (s, 1 H, 5-H), 7.43–7.58 (m, 6 H, Ar), 8.98 (bs, 1 H, NH), 10.81 (bs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 109.1$ (C-5), 122.9 (C), 123.4, 129.5 (CH), 129.8, 129.9 (C), 130.4, 130.8, 131.3, 131.7 (CH), 133.4, 134.2, 135.2, 139.1, 173.9 (C). MS (EI, 70 eV): m/z (%) = 417 (27), 416 (35), 415 (87), 414 (79), 413 (100, $[M–Cl]^+$ (^{79}Br, ^{35}Cl, ^{80}Se)), 411 (80), 410 (51), 409 (37), 408 (16), 296 (22), 294 (97), 292 (71). $C_{15}H_{11}BrCl_2N_2Se$ (449.04).

3-(4-Chlorophenyl)-4,5-diphenyl-3*H*-(selenazol-2-ylidene)amine Hydrochloride (4g)

A mixture of **2d** (1.50 g, 5.0 mmol) and 4-chloroaniline hydrochloride (0.82 g, 5.0 mmol) in ethanol (25 mL) was refluxed for 10 h. The precipitated product was isolated by filtration, washed (ether), and dried in vacuo. Yield: 0.22 g (10%), colourless prisms, m.p. 255–270°C (decomp., EtOH). IR (KBr): $\tilde{\nu} = 3191$ (m), 3023 (w), 1614, 1598, 1575, 1490, 1402, 1341 (m), 1090 (w), 732, 697 (m) cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.12–7.29$ (m, 10 H, Ar), 7.49–7.57 (m, 4 H, Ar), 9.18 (bs, 1 H, NH), 10.87 (bs, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 122.0$ (C-5), 128.3, 128.6, 128.7, 129.3, 129.7, 130.0, 130.8, 131.1 (Ar-H), 133.7, 134.9, 135.6, 170.8 (C). MS (EI, 70 eV): m/z (%) = 414 (12), 413 (43), 412 (45), 411 (100), 410 (70, $[M–HCl]^+$ (^{35}Cl, ^{80}Se)), 408 (55), 407 (42), 406 (25), 405 (10), 216 (33), 215 (14), 214 (100), 178 (38), 165 (19). Anal. calcd. for $C_{21}H_{16}Cl_2N_2Se$ (446.24): C, 56.52; H, 3.61; N, 6.28. Found: C, 56.25; H, 3.81; N, 6.07.

4-(4-Chlorophenyl)-2-iminoselenazol-3-ol Hydrochloride (4h)

A mixture of **2b** (1.30 g, 5.0 mmol) and hydroxyl amine hydrochloride (0.35 g, 5.0 mmol) in ethanol (50 mL) was refluxed for 10 h. The precipitated product was isolated by filtration, washed (ether), and dried in vacuo. Yield: 0.27 g (17%), colourless prisms, m.p. 215–223°C (decomp., EtOH). IR (KBr): $\tilde{\nu} = 3416$, 3284, 3244, 3176 (m), 3079 (s), 2679, 2622 (m), 1606 (s), 1545, 1485, 1092, 839, 740 (m) cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.25$ (s+d, $^2J(^1H,^{77}Se) = 40.7$ Hz, 1 H, 5-H), 7.54–7.58 (m, $J = 8.6$ Hz, 2 H, Ar), 7.68–7.72 (m, $J = 8.6$ Hz, 2 H, Ar), 9.88 (bs, 2 H, 2 NH), 12.81 (bs, 1 H, OH). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 104.6$ ($^1J(^{13}C,^{77}Se) = 108.6$ Hz, C-5), 128.0 (C), 128.4, 130.4 (Ar), 134.2, 137.4 (C), 167.1 ($^1J(^{13}C,^{77}Se) = 151.2$ Hz, CN). $C_9H_8Cl_2N_2OSe$ (310.04).

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