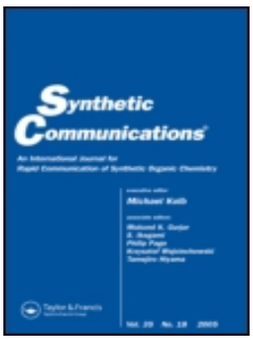

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Facile Synthesis of 2*H*-1,4-Benzothiazin-3(4*H*)-ketoximes and 2*H*-1,4-Benzoselenazin-3(4*H*)-ketoximes Promoted by SmI_2

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ABSTRACT

2*H*-1,4-Benzothiazin-3(4*H*)-ketoximes and 2*H*-1,4-benzoselenazin-3(4*H*)-ketoximes were synthesized by the reductive cyclization of *bis*(*o*-nitrophenyl) disulfides or diselenides with aromatic or aliphatic β-nitroethylenes using SmI_2 in moderate to good yields under mild conditions.

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The biological and pharmacological importance of 2*H*-1,4-benzothiazin-3(4*H*)-one derivatives, which can be used as efficient tranquilizers, angiotensin converting enzyme inhibitors, aldose reductase inhibitors and also showed antibacterial and antifugal activities, has led to important synthetic efforts in the past decades.[1] Among these compounds, the substituted 2*H*-1,4-benzothiazin-3(4*H*)-ones are well known in the literatures and several methods for their synthesis have been reported by many chemists including our group.[1a,2] However, upon checking the literature, only one example reported the synthesis of 2*H*-1,4-benzothiazin-3(4*H*)-ketoximes.[1e] The reason may be that 2*H*-1,4-benzothiazin-3(4*H*)-ones cannot react with hydroxyamine under usual conditions due to the low reactivity of their carbonyl groups. As far as 2*H*-1,4-benzoselenazin-3(4*H*)-ketoximes are concerned, no literature has ever been reported for their synthesis. Here we wish to describe a convenient method for the preparation of 2*H*-1,4-benzothiazin-3(4*H*)-ketoximes and 2*H*-1,4-benzoselenazin-3(4*H*)-ketoximes promoted by SmI_2.

Samarium diiodide[3] is an exceedingly reliable, mild, neutral, selective, and versatile single electron transfer reagent and its use in organic synthesis has been especially advantageous for ring closure reactions, carbon–carbon bond formation and stereoselective reactions. Its application in organic synthesis has been well documented in the past decades.[4] The reduction of nitro groups and reductive cleavage of S-S, Se-Se bonds by SmI_2 have been studied extensively.[5] Our group have reported the simultaneous reduction of two functional groups to form an active trivalent samarium species, which has been successfully applied in the synthesis of heterocyclic compounds.[2i,6] In order to extend the application of this active trivalent samarium species, we used SmI_2 to react with aromatic or aliphatic β-nitroethylenes and the corresponding products 2*H*-1,4-benzothiazin-3(4*H*)-ketoximes and 2*H*-1,4-benzoselenazin-3(4*H*)-ketoximes were readily obtained in moderate to good yields under mild conditions (Sch. 1).

When 0.5 equivalents of *bis*(*o*-nitrophenyl) disulfides or diselenides **1** were treated with 7 equivalents of SmI_2 in THF at room temperature, the deep blue color of SmI_2 vanished within 5 min and another substrate β-nitroethylenes **2** were added. The desired products 2*H*-1,4-benzothiazin-3(4*H*)-ketoximes or 2*H*-1,4-benzoselenazin-3(4*H*)-ketoximes **3** were obtained in moderate to good yields.[7]

Table 1 summarizes our results. All the reactions were completed at room temperature within 10–15 min. A wide range of structurally varied aryl-substituted β-nitroethylene underwent the cyclization reactions by using this procedure. Several functional groups such as NO_2, OMe, Br,

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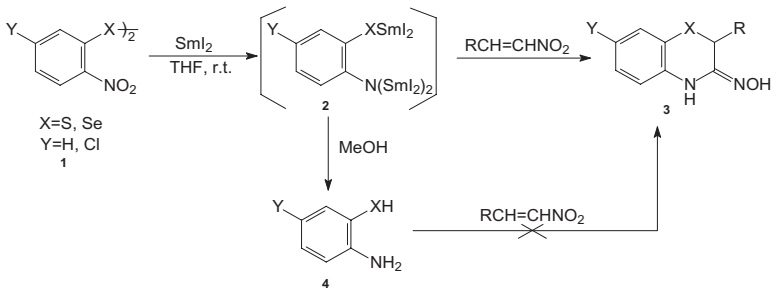

Scheme 1.

Table 1. Preparation of 2*H*-1,4-benzothiazin-3(4*H*)-ketoximes and 2*H*-1,4-benzoselenazin-3(4*H*)-ketoximes induced by SmI_2.

Entry	Y	X	R	Product	T (min)	Yield (%)[a]
1	H	S	C_6H_5	3a	10	83.0[b]
2	H	S	4-$CH_3OC_6H_4$	3b	10	87
3	H	S	4-$CH_3C_6H_4$	3c	10	75
4	H	S	3-BrC_6H_4	3d	10	68
5	H	S	2-$NO_2C_6H_4$	3e	10	65
6	H	S	2,6-$Cl_2C_6H_3$	3f	10	71
7	H	S	2-furanyl	3g	10	77
8	H	S	*iso*-butyl	3h	10	85
9	H	Se	4-$CH_3OC_6H_4$	3i	15	71.0[b]
10	H	Se	4-$CH_3C_6H_4$	3j	15	72
11	H	Se	*iso*-butyl	3k	15	82

[a]Isolated yields based on *bis*(*o*-nitrophenyl) disulfides or diselenides.
[b]MeOH (0.2 mL) was added after the formation of the intermediates **2** and *o*-aminothiophenols or *o*-aminoselenophenols were obtained. In this case, no products **3** could be detected.

Cl remained unaffected under the present reaction conditions. It should be noted that alkyl-substituted β-nitroethylenes (entries **8** and **12**) were also effective. However, if the intermediates **2** were protonated by adding MeOH, the corresponding products **4** (*o*-aminothiophenols or *o*-aminoselenophenols) could be obtained; if β-nitroethylene derivatives were added at this stage (entries **1** and **9**), no products of **3** could be detected.

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The structures of products **3** were confirmed by IR, ^{1}H NMR, MS and elemental analysis. The IR spectra of **1–14** exhibited a sharp band at ~3380 cm^{-1} (-NH stretching), a broad band at ~3270 cm^{-1}1 (=NOH stretching) and a medium absorption band at ~1660 cm^{-1} (C=N stretching). The ^{1}H NMR spectra (DMSO-d_6 solution) of products **1–14** showed two one-proton singlets at $\delta_H \sim 10.1$ and 9.5 ppm, which were attributed to the proton of the amine and hydroxy groups, respectively. The chemical shift of the product in methine groups was around 5.0 ppm and showed a one-proton singlet. On the other hand, in the mass spectra of the products **1–14**, the molecular ions were the base peak in most cases (Table 1).

In conclusion, the present procedure provides a novel, efficient, and general method for the synthesis of 2*H*-1,4-benzothiazin-3(4*H*)-ketoximes and 2*H*-1,4-benzoselenazin-3(4*H*)-ketoximes. The advantages of our method are the easily accessible starting materials, convenient manipulation and moderate to high yields of the process. Thus this procedure is endowed with considerable synthetic potential and may provide a practical method to synthesize the title compounds.

EXPERIMENTAL

Tetrahydrofuran was distilled from sodium-benzophenone immediately prior to use. All reactions were conducted under a nitrogen atomsphere. Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Bruker 400 MHz instrument as $CDCl_3$ or DMSO-d_6 solutions using TMS as internal standard. Chemical shifts (δ) are reported in ppm. Infrared spectra were recorded using KBr disks with a Bruker Vector-22 infrared spectrometer. Elemental analyses were performed on a EA-1110 instrument. Metallic samarium and all solvents were purchased from commercial sources, without further purification before use.

General procedure for the synthesis of 2*H*-1,4-benzothiazin-3(4*H*)-ketoximes and 2*H*-1,4-benzoselenazin-3(4*H*)-ketoximes. A solution of *bis*(*o*-nitrophenyl) disulfides or diselenides (0.5 mmol) in dry THF (5 mL) was added dropwise to the solution of SmI_2 (7 mmol) in THF (45 mL) at room temperature under a nitrogen atmosphere. The deep blue color of the solution changed to yellow (as for *bis*(*o*-nitrophenyl) disulfides) or brownish red (as for *bis*(*o*-nitrophenyl) diselenides) within 5 min. Then a solution of β-nitroethylene derivatives (1.1 mmol) in anhydrous THF (2 mL) was added. After being stirred for 5–10 min (Table 1, the reaction was monitored by TLC), the solvent was removed under reduced pressure. Then water (10 mL) was added and extracted

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with ethyl acetate (3×30 mL). The organic phase was successively washed with brine (25 mL), water (30 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude products, which were purified by preparative TLC using ethyl acetate and cyclohexane (1:3) as eluant.

Compound 3a. M.p. 164–166°C. ν_{max}: 3380, 3357, 3251, 1666, 1479, 942, 925, 752, 706 cm^{-1}. δ_H ($CDCl_3$): 7.71–7.42 (2H, brs), 7.38–7.36 (2H, d), 7.29–7.10 (5H, m), 6.87–6.82 (1H, t), 6.82–6.80 (1H, d), 4.75 (1H, s). *m*/*z* (%): 256 (M^+, 100), 257 (18.05), 237 (81.29), 77 (22.53), 51 (21.99), 89 (21.26), 109 (19.56). Anal. calcd. $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93. Found C, 65.69; H, 4.62; N, 10.88%.

Compound 3b. M.p. 162–164°C. ν_{max}: 3394, 1662, 1609, 1589, 1558, 1248, 754 cm^{-1}. δ_H ($CDCl_3$): 7.70–7.40 (2H, brs), 7.30–7.08 (4H, m), 6.89–6.79 (3H, m), 4.71 (1H, s), 3.75 (3H, s). *m*/*z* (%): 286 (M^+, 100), 267 (18.94), 253 (26.47), 121 (24.45), 51 (29.02), 77 (27.34), 63 (23.51), 65 (22.47), 45 (20.67). Anal. calcd. $C_{15}H_{14}N_2O_2S$: C, 62.92; H, 4.93; N, 9.78. Found C, 62.88; H, 4.79; N, 9.82%.

Compound 3c. M.p. 148–150°C. ν_{max}: 3363, 3185, 2919, 1647, 1481, 754 cm^{-1}. δ_H ($CDCl_3$): 7.71–7.39 (2H, brs), 7.26–7.18 (3H, m), 7.10–7.06 (3H, m), 6.88–6.79 (2H, m), 4.72 (1H, s), 2.28 (3H, s). *m*/*z* (%): 270 (M^+, 100.00), 251 (37.45), 237 (36.19), 91 (23.09), 77 (28.03), 65 (22.88), 63 (21.02), 51 (19.78). Anal. calcd. $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36. Found C, 66.54; H, 5.20; N, 10.27%.

Compound 3d. M.p. 115–117°C. ν_{max}: 3398, 3269, 3025, 1653, 1588, 1481 cm^{-1}. δ_H(DMSO-d_6): 10.11 (1H, s), 9.46 (1H, s), 7.47 (1H, s), 7.40–7.38 (1H, d), 7.28–7.20 (3H, m), 7.12–7.05 (2H, m), 6.79–6.75 (1H, t), 5.03 (1H, s). *m*/*z* (%): 334 (M^+, 98.38), 336 (M^++2, 100), 317 (57.11), 237 (74.20), 161 (38.50), 135 (41.32). Anal. calcd. $C_{11}H_{13}NOS$: C, 63.74; H, 6.32; N, 6.76. Found C, 63.89; H, 6.11; N, 6.53%.

Compound 3e. M.p. 131–133°C. ν_{max}: 3375, 1646, 1608, 1589, 1558, 1345, 722 cm^{-1}. δ_H (DMSO-d_6): 10.21 (1H, s), 9.68 (1H, s), 8.02-8.00 (1H, d), 7.60–7.57 (1H, t), 7.50–7.47 (1H, t), 7.33–7.31 (1H, d), 7.18–7.16 (1H, d), 7.13–7.09 (1H, t), 7.04–7.02 (1H, d), 6.78–6.74 (1H, t), 5.42 (1H, s). *m*/*z*(%): 301 (M^+, 22.42), 284 (17.80), 238 (47.77), 220 (40.19), 205 (100), 167 (49.93), 150 (51.78), 77 (43.87). Anal. calcd. $C_{14}H_{11}N_3O_3S$: C, 55.80; H, 3.68; N, 13.95. Found C, 55.87; H, 3.58; N, 13.98%.

Compound 3f. M.p. 184–185°C. ν_{max}: 3294, 1662, 1581, 1560, 1496, 1437, 1375, 727 cm^{-1}. δ_H (DMSO-d_6): 10.24 (1H, s), 9.30 (1H, s), 7.49–7.31 (4H, m), 7.20–7.12 (2H, m), 6.87–6.83 (1H, t), 5.57 (1H, s). *m*/*z* (%): 301 (M^+, 86.85), 325 (15.28), 326 (56.90), 289 (58.64), 271 (100), 237 (56.27), 136 (89.17), 109 (61.11). Anal. calcd. $C_{14}H_{10}Cl_2N_2OS$: C, 51.70; H, 3.10; N, 8.61. Found C, 51.62; H, 3.14; N, 8.82%.

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Compound 3g. M.p. 91–93°C. ν_{max}: 3379, 1647, 1589, 1482, 1375, 749 cm^{-1}. δ_H (DMSO-d_6): 10.04 (1H, s), 9.36 (1H, s), 7.51–7.50 (1H, t), 7.24–7.22 (1H, d), 7.10–7.05 (2H, m), 6.79–6.76 (1H, t), 6.26–5.93 (2H, m), 503 (1H, s). *m*/*z* (%): 246 (M^+, 100.00), 229 (27.91), 199 (13.52), 186 (22.96), 77 (11.78). Anal. calcd. $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37. Found calcd. C, 58.43; H, 4.11; N, 11.22%.

Compound 3h. Viscous oil. ν_{max}: 3385, 2956, 2868, 1648, 1482, 1387, 931, 748 cm^{-1}. δ_H ($CDCl_3$): 7.70 (1H, brs), 7.20–7.18 (1H, d), 7.12–7.08 (1H, t), 6.98 (1H, s), 6.90–6.87 (1H, t), 6.80–6.78 (1H, d), 3.58–3.54 (1H, t), 1.81–1.42 (3H, m), 0.98–0.85 (6H, m). *m*/*z* (%): 236 (M^+, 19.00), 205 (29.82), 180 (58.40), 163 (100.00), 162 (27.33), 136 (38.59), 41 (93.74), 43 (41.72), 57 (30.14). Anal. calcd. $C_{12}H_{16}N_2OS$: C, 60.98, H, 6.82; N, 11.85. Found C, 60.94; H, 6.79; N, 11.88%.

Compound 3i. M.p. 123–125°C. ν_{max}: 3384, 3275, 2835, 1644, 1608, 1510, 1248 cm^{-1}. δ_H(DMSO-d_6): 10.00 (1H, s, NH), 9.17 (1H, s, OH), 7.28–7.26 (1H, d), 7.19–7.15 (3H, m), 7.10–7.06 (1H, t), 6.77–6.71 (3H, m), 4.99 (1H, s), 3.66 (3H, s). *m*/*z* (%): 334 (^{80}Se-M^+, 100), 332 (^{78}Se-M^+, 42.09), 317 (80.89), 286 (46.51), 205 (72.95). Anal. calcd. $C_{15}H_{14}N_2O_2Se$: C, 54.06; H, 4.23; N, 8.41. Found C, 54.11; H, 4.31; N, 8.55%.

Compound 3j. M.p. 118–119°C. ν_{max}: 3424, 1631, 1585, 1511, 1478, 749 cm^{-1}. δ_H (DMSO-d_6): 10.05 (1H, s), 9.18 (1H, s), 7.27–6.99 (7H, m), 6.75–6.72 (1H, t), 4.99 (1H, s), 2.19 (3H, s). *m*/*z* (%): 318 (^{80}Se-M^+, 20.71), 318 (^{78}Se-M^+, 13.88), 302 (27.14), 285 (19.90), 273 (69.49), 119 (96.33), 91 (100). Anal. calcd. $C_{15}H_{14}N_2OSe$: C, 56.79; H, 4.45; N, 8.83. Found C, 56.82; H, 4.53; N, 8.92%.

Compound 3k. Viscous oil. ν_{max}: 3397, 2955, 2867, 1646, 1506, 1387, 748 cm^{-1}. δ_H ($CDCl_3$): 7.63 (1H, s), 7.32–7.30 (1H, d), 7.16–7.12 (1H, t), 6.98 (1H, s), 6.89–6.86 (1H, t), 6.82–6.80 (1H, d), 3.65–3.61 (1H, m), 1.78–1.58 (3H, m), 0.93–0.86 (6H, m). *m*/*z* (%): 284 (^{80}Se-M^+, 7.36), 282 (^{78}Se-M^+, 3.90), 267 (2.65), 228 (17.69), 220 (25.28), 205 (100.00), 177 (13.65) 91 (21.84), 77 (16.67). Anal. calcd. $C_{12}H_{16}N_2OSe$: C, 50.89; H, 5.69; N, 9.89. Found C, 50.79; H, 5.65; N, 9.92%.

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