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Synthesis of 2*H*-1,4-benzothiazin-3(4*H*)-ones and 2*H*-1,4-benzoselenazin-3(4*H*)-ones with the aid of samarium(II) iodide

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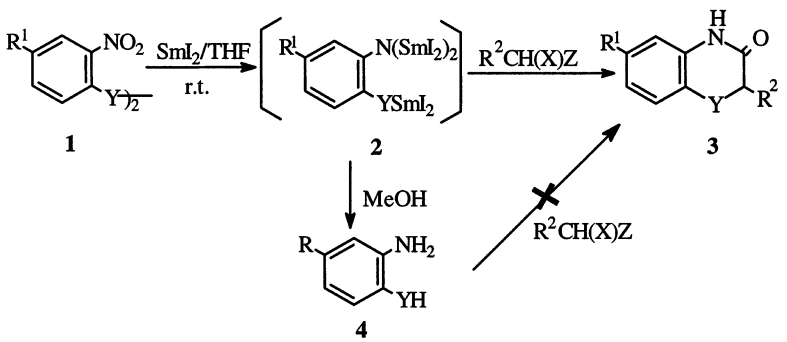
Abstract—Bis(*o*-nitrophenyl) disulfides or diselenides were easy to reduce by samarium(II) iodide to produce the active intermediates **2** in situ, which readily react with α-halocarboxylic derivatives to yield the corresponding products 2*H*-1,4-benzothiazin-3(4*H*)-ones and 2*H*-1,4-benzoselenazin-3(4*H*)-ones, respectively, in moderate to high yields under mild conditions.

2*H*-1,4-Benzothiazin-3(4*H*)-one derivatives have attracted strong interest due to their biological properties.[1] For example, they can be used as efficient tranquilizers,[1b] angiotensin converting enzyme inhibitors[1c] or aldose reductase inhibitors.[1d] The method for preparing this kind of compound using *o*-aminothiophenols or *o*-aminophenyldisulfides as starting materials requires harsh conditions such as acid or base as a catalyst, moderate to high thermal conditions and prolonged reaction times.[1a,2] These derivatives can also be obtained from other procedures such as cyclization of alkyl 2-haloacetamidophenyl sulfides[3a] or reductive cyclization of α-(*o*-nitrophenylthio)carboxylic acids with the aid of sodium borohydride and palladium on charcoal.[3b] Although many methods have been introduced for the preparation of 2*H*-1,4-benzothiazin-3(4*H*)-ones, to our knowledge very few reports on the synthesis of 2*H*-1,4-benzoselenazin-3(4*H*)-ones are known.[4] Here, we wish to describe a new method for the preparation of 2*H*-1,4-benzothiazin-3(4*H*)-ones and 2*H*-1,4-benzoselenazin-3(4*H*)-ones with the aid of samarium(II) iodide.

Kagan's reagent, samarium(II) iodide[5] (SmI_2) is an exceptional reagent for promoting reductive cyclization reactions, and the chemistry of this reagent has been well documented in several reviews.[6] Previous research demonstrated that nitro groups, sulfur–sulfur bonds or selenium–selenium bonds were easy to reduce and cleave with samarium(II) iodide.[7,8] These interesting



Scheme 1. R^1 = H, Cl; Y = S, Se; R^2 = H, alkyl, aryl; Z = CO_2H, CO_2Me, CO_2Et, CN.

Keywords: samarium(II) iodide; nitro group; disulfide; diselenide; reductive cyclization; 2*H*-1,4-benzothiazin-3(4*H*)-one; 2*H*-1,4-benzoselenazin-3(4*H*)-one.

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Table 1. Preparation of 2*H*-1,4-beznothiazin-3(4*H*)-ones and 2*H*-1,4-benzoselenazin-3(4*H*)-ones by SmI_2

Entry	R^1	Y	$R^2CH(X)Z$	Temp. (°C)	Time (h)	Yield (%)[a]
3a	H	S	$BrCH_2CO_2Et$	Rt	2	83, 0[b]
	H	S	$ClCH_2CO_2Et$	60	3	61
	H	S	$ClCH_2CO_2H$	60	4	60
	H	S	$ClCH_2CN$	60	24	0[c]
3b	H	S	$CH_3CH(Br)CO_2H$	40	3	73
3c	H	S	$(CH_3)_2CHCH(Br)CO_2H$	60	4	55, 0[b]
3d	H	S	$C_6H_5CH(Br)CO_2Me$	60	4	65
3e	Cl	S	$BrCH_2CO_2Et$	Rt	2	84
3f	Cl	S	$CH_3CH(Br)CO_2H$	40	3	71
3g	Cl	S	$(CH_3)_2CHCH(Br)CO_2H$	60	4	59
3h	H	Se	$BrCH_2CO_2Et$	Rt	2	88
3i	H	Se	$CH_3CH(Br)CO_2H$	40	3	79
3j	H	Se	$(CH_3)_2CHCH(Br)CO_2H$	60	4	71, 0[b]
3k	Cl	Se	$BrCH_2CO_2Et$	Rt	2	89
3l	Cl	Se	$CH_3CH(Br)CO_2H$	40	3	81
3m	Cl	Se	$(CH_3)_2CHCH(Br)CO_2H$	60	4	75

[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.
[c] The reaction was studied at 0°C, 25°C and at reflux.

results prompted us to investigate a new application of samarium(II) iodide, which is SmI_2-mediated simultaneous reduction of two functional groups to form an active trivalent samarium species and its application in the synthesis of heterocyclic compounds.[9] In order to extend the application of this reagent, we investigated the SmI_2-mediated simultaneous reduction of the nitro group and the sulfur–sulfur bond or the selenium–selenium bond in bis(*o*-nitrophenyl) disulfides and diselenides.

It was found in our experiment[10,11] that when 0.5 equivalents of bis(*o*-nitrophenyl) disulfides **1** (Y = S) were added dropwise to 7 equivalents of SmI_2 in anhydrous THF at room temperature under a nitrogen atmosphere, the deep blue color of the solution changed to a yellow color within several minutes; while under similar conditions, bis(*o*-nitrophenyl) diselenides **1** (Y = Se) led to a brown-red color. The above phenomena hinted that the nitro group was reduced and the sulfur–sulfur bond or selenium–selenium bond was reductively cleaved simultaneously by SmI_2 to form the intermediate **2** as a 'living' species in situ.[8c,9] When α-halocarboxylic derivatives were treated with intermediate **2**, the desired products 2*H*-1,4-benzothiazin-3(4*H*)-ones **3a**–**g** and 2*H*-1,4-benzoselenazin-3(4*H*)-ones **3h**–**m** were obtained in good yields (Scheme 1 and Table 1).

The results are summarized in Table 1. According to Table 1, we found that α-bromoesters are more reactive than other α-halocarboxylic derivatives (entry **3a**); chloroacetonitrile failed to react with the active species **2** to yield a similar product **3a**. However, if the intermediates **2** were protonated by adding MeOH, the corresponding products **4** (*o*-aminothiophenols or *o*-aminoselenophenols) were obtained; if this was followed by adding α-halocarboxylic derivatives under similar conditions (entries **3a**, **3c** and **3j**), no reaction took place and no products **3** could be detected.

In summary, a series of 2*H*-1,4-beznothiazin-3(4*H*)-ones and 2*H*-1,4-beznoselenazin-3(4*H*)-ones was synthesized via reductive cyclization of bis(*o*-nitrophenyl) disulfides or diselenides with α-halocarboxylic derivatives. The advantages of our method are the easily accessible starting materials, convenient manipulation and the moderate to high yields of the process.

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10. General procedure: A solution of bis(*o*-nitrophenyl) disulfides or diselenides (0.5 mmol) in dry THF (3 mL) was added dropwise to the solution of SmI_2 (7 mmol) in THF (30 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 5–10 minutes. Then a solution of α-halocarboxylic derivative (1.1 mmol) in anhydrous THF (2 mL) was added slowly. After being stirred for a given time (Table 1, the reaction was monitored by TLC), the reaction was quenched with dilute HCl (0.1 mol/L, 3 mL) and extracted with ether (3×30 mL). The organic phase was successively washed with a saturated solution of $Na_2S_2O_3$ (15 mL), saturated brine (15 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude product which was purified by preparative TLC using ethyl acetate and cyclohexane (1:3) as eluant.
11. Typical physical data of new compounds are listed. Compound **3c, 2-isopropyl-2*H*-1,4-benzothiazin-3(4*H*)-one** 115–117°C. ν_{max}: 3320 (NH), 2975, 2850, 1380 (CH_3, CH), 1665 (C=O) cm^{-1}. δ_H: 9.80 (1H, br s, NH), 7.32–6.96 (4H, m, ArH), 3.11 (1H, d, $J=7.8$ Hz, CH), 2.13–1.80 (1H, m, CH), 1.04 (6H, d, $J=6.5$ Hz, 2×CH_3). *m*/*z* (%): 208 (M+1, 17), 207 (M^+, 71), 165 (100), 164 (41), 136 (60), 132 (71). Anal. $C_{11}H_{13}NOS$. Calcd C, 63.74; H, 6.32; N, 6.76. Found C, 63.89; H, 6.11; N, 6.53%. Compound **3j, 2-isopropyl-2*H*-1,4-benzoselenazin-3(4*H*)-one** 123–125°C. ν_{max}: 3335 (NH), 2980, 2830, 1375 (CH_3, CH), 1655 (C=O) cm^{-1}. δ_H: 9.82 (1H, br s, NH), 7.46–6.95 (4H, m, ArH), 3.20 (1H, d, $J=8.0$ Hz, CH), 2.15–1.81 (1H, m, CH), 1.07 (6H, d, $J=6.5$ Hz, 2×CH_3). *m*/*z* (%): 255 ($^{80}Se-M^+$, 100), 253 ($^{78}Se-M^+$, 54.5), 213 (48), 211 (24.6), 184 (25), 132 (87), 83 (87). Anal. $C_{11}H_{13}NOSe$. Calcd C, 51.99; H, 5.16; N, 5.51. Found C, 52.12; H, 5.03; N, 5.65%. Compound **3l, 6-chloro-2-methyl-2*H*-1,4-benzoselenazin-3(4*H*)-one** 178–180°C. ν_{max}: 3325 (NH), 2960, 2830, 1380 (CH_3, CH), 1660 (C=O) cm^{-1}. δ_H: 10.23 (1H, br s, NH), 7.60–6.85 (3H, m, ArH), 3.56 (1H, q, $J=7.2$ Hz, CH), 1.53 (3H, d, $J=7.2$ Hz, CH_3). *m*/*z* (%): 261 ($^{80}Se-M^+$, 82), 180 (24), 156 (33), 154 (100), 55 (27). Anal. $C_9H_8ClNOSe$. Calcd C, 41.49; H, 3.10; N, 5.38. Found C, 41.56; H, 3.21; N, 5.14%.