***SHORT PAPER***

*J. Chem. Research (S),* 2000, 292–293

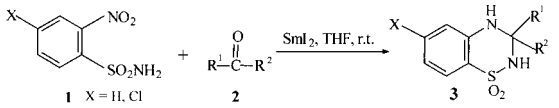
# Samarium diiodide induced reductive cyclization of nitro compounds with ketones: a novel synthesis of 3,4-dihydro-(2*H*)-1,2,4-benzothiadiazine-1,1-dioxides†

**Weihui Zhong[a], Xiaoyuan Chen[a,c] and Yongmin Zhang[a,b,*]**

[a]*Department of Chemistry, Zhejiang University (Campus Xixi), Hangzhou, 310028, P.R. China*
[b]*Laboratory of Organometallic Chemistry, Chinese Academy of Sciences, Shanghai, 200032, P.R. China*
[c]*Department of Chemistry, Hunan Jishou University, Jishou, 416000, P.R. China*

The intermolecular reductive cyclization of *o*-nitrobenzenesulfonamides with ketones induced by samarium diiodide has been studied and 3,3-disubstituted-3,4-dihydro-(2*H*)-1,2,4-benzothiadiazine-1,1-dioxides were obtained in satisfactory yields under mild and neutral condition.

Since the time Kagan[1] demonstrated a simple preparation of samarium diiodide from samarium metal and 1,2-diiodoethane, samarium diiodide has been developed as a mild, neutral, and versatile single electron transfer reductant. It has been widely used in synthetic reactions, especially in ring closure reactions, carbon–carbon bond formation reactions and stereocontrolled reactions.[2] The reactivity of $SmI_2$ towards various nitrogen compounds including nitro compounds,[3] azocompounds,[4] hydrazones,[3b,5] oximes,[3b] imines,[3b] azides[6] and hydroxylamines[7] has been examined. Recently we have reported a series of reductive coupling or cyclization reactions promoted by $SmI_2$ or samarium metal,[8] such as the reductive coupling of nitriles with nitro compounds;[8a,b] the reductive coupling reactions of ketones and nitriles;[8c] the reductive cyclization of substituted benzylidenecyanoacetates [8d] or substituted benzylidenemalonitriles.[8e, 8f] Chen[9] had reported the intramolecular ketone-nitro reductive cyclization induced by low-valent titanium to give Δ-pyrroline. Here, we have studied the intermolecular ketone-nitro reductive cyclization induced by samarium diiodide in anhydrous THF and the ring-closure products, 3,3-disubstituted-3,4-dihydro-(2*H*)-1,2,4-benzothiadiazine-1,1-dioxide derivatives, were obtained *via* reductive cyclization of *o*-nitrobenzenesulfonamides with ketones by $SmI_2$.



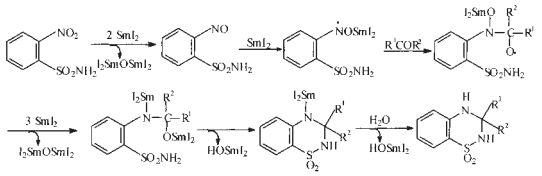

**Scheme 1**

The results are summarized in Table 1. When o-nitrobenzenesulfonamides **1** and ketones **2** were treated with six equivalents of $SmI_2$ in anhydrous THF at room temperature under a nitrogen atmosphere, the deep blue color of the mixture changed into yellow in a few minutes and the desired products **3** were formed. In this reaction, aliphatic ketones could react with compounds **1** to afford the desired products **3** in satisfactory yields. However, for aromatic ketones only *o*-aminobenzenesulfonamides were obtained and products **3** were not detected even for reaction at reflux temperature. If *o*-aminobenzenesulfonamides derived from compounds **1** were treated with ketones **2** under the same conditions, products **3** could not be detected. We consider therefore that treatment of nitro compounds and ketones with $SmI_2$ may not be a simple reductive procedure. Although the detailed mechanism of the above reaction has not been clarified, the formation of products **3** may be described by the possible mechanism presented in Scheme 2.[8a, 9]

**Table 1** Reaction of *o*-nitrobenzenesulfonamides with ketones promoted by $SmI_2$[a]

| Entry | X | $R^1$ | $R^2$ | T(h) | Yield(%)[b] |
|---|---|---|---|---|---|
| **3a** | H | Me | Et | 2 | 80 |
| **3b** | H | Me | *n*-Pr | 3 | 85 |
| **3c** | H | Me | *n*-Bu | 3 | 83 |
| **3d** | H | $-(CH_2)_4-$ | | 3 | 81 |
| **3e** | H | $-(CH_2)_5-$ | | 3 | 85 |
| **3f** | Cl | Et | Et | 4 | 68 |
| **3g** | Cl | Me | Et | 2 | 72 |
| **3h** | Cl | Me | *n*-Pr | 3 | 65 |
| **3i** | Cl | Me | *n*-Bu | 3 | 68 |
| **3j** | Cl | Me | $n\text{-}C_5H_{11}$ | 3 | 57 |
| **3k** | Cl | $-(CH_2)_4-$ | | 3 | 75 |
| **3l** | Cl | $-(CH_2)_5-$ | | 3 | 70 |
| **3m** | Cl | Me | Ph | 24 | 0[c] |
| **3n** | Cl | Ph | Ph | 24 | 0[c] |

[a]1 equiv. nitro compounds, 1.2 equiv. ketones and 6 equiv. $SmI_2$ were used. [b]Isolated yield based on nitro compounds. [c]The reaction was studied at 0°C,25°C and refluxing temperature.




**Scheme 2**

3,4-Dihydro-1,2,4-(2*H*)-benzothiadiazine-1,1-dioxide derivatives are very important and useful compounds in the pharmaceutical chemistry. Some derivatives of them are useful as diuretics,[10a] antihypertensive agents,[10b] a hair growth agents[10c] and non-peptidic angiotensin II receptor antagonists.[10d] A general procedure for the preparation of 3,4-dihydro-1,2,4-(2*H*)-benzothiadiazine-1,1-dioxide derivatives consists in condensing the appropriate *o*-aminobenzenesulfonamide with ketones or ketals under vigorous reaction conditions, such as high temperature and long reaction times, using acid or base catalysts.[10a,11] In contrast, our method for the preparation of these compounds circumvents these problems.

In summary, the intermolecular reductive cyclization reaction of nitro compounds and ketones was studied and a facile synthesis of 3,3-disubstituted-3,4-dihydro-(2H)-1,2,4-benzothiadiazine-1,1-dioxides was provided.

* To receive any correspondence.
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

## Experimental

Tetrahydrofuran (THF) was distilled from sodium-benzophenone immediately prior to use. All reactions were conducted under a nitrogen atmosphere. Melting points are uncorrected. Infrared spectra were recorded on an IR-408 spectrometer in KBr with absorption in $cm^{-1}$. $^1$HNMR spectra were recorded on a Bruker AC–80 spectrometer as $CDCl_3$ solutions. J values are in Hz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Mass spectra were recorded on a HP 5989B MS spectrometer. Microanalysis was carried out on a Carlo-Erba 1106 instrument.

*General procedure:* A solution of nitro compounds **1** (1 mmol) and ketones **2** (1 mmol) in anhydrous THF (3 ml) was added to $SmI_2$ (6 mmol) solution in THF (30 ml) at room temperature under a dry nitrogen atmosphere. The deep blue colour of samarium diiodide changed to a brownish yellow in a few minutes. After being stirred for a given time (Table 1, the reaction was monitored by TLC), the reaction was quenched with dilute HCl (0.1mol/l, 3 ml) and extracted with ether (3 × 30 ml). The crude product was isolated in the usual way and purified by preparative thin layer chromatography using ethyl acetate and cyclohexane (2 : 3) as eluant.

**2a**, *3-ethyl-3,4-dihydro-3-methyl-(2*H*)-1,2,4-benzothiadiazine-1,1-dioxide*: m.p. 178–180°C. $\nu_{max}/cm^{-1}$ 3350, 3210, 3010, 2980, 2930, 2865, 2845, 1610, 1575, 1500, 1470, 1385, 1375, 1160, 740. $\delta_H$ 7.66–6.44(4H, m), 5.10-5.00(2H, br s), 2.01–1.66(2H, m), 1.50(3H, s), 0.95(3H, t, *J*=7Hz). *m/z* (%): 226($M^+$, 3.5), 172(98.8), 155(97), 92(42.6), 91(100), 65(71). (Found: C, 53.23. H, 6.08. N, 12.15; $C_{10}H_{14}N_2O_2S$ requires C, 53.08. H, 6.24. N, 12.38%).

**2b**, *3,4-dihydro-3-methyl-3-propyl-(2*H*)-1,2,4-benzothiadiazine-1,1-dioxide*: m.p. 171–173°C. $\nu_{max}/cm^{-1}$ 3355, 3220,3010, 2980, 2930, 2870, 2830, 1600, 1580, 1501, 1465, 1380, 1360, 1148, 735. $\delta_H$ 7.76–6.46(4H, m), 6.04(1H, br s), 4.74(1H, br s), 2.44–1.40(4H, m), 1.44(3H, s), 0.85(3H, t, *J*=6Hz). *m/z*(%): 240($M^+$, 4.4), 173(29.3), 172(100), 156(28), 155(11.5), 65(18.5). (Found: C, 55.12. H, 6.58. N, 11.43; $C_{11}H_{16}N_2O_2S$ requires C, 54.98. H, 6.71. N, 11.66%).

**2c**, *3-butyl-3,4-dihydro-3-methyl-(2*H*)-1,2,4-benzothiadiazine-1,1-dioxide*: m.p. 158–160°C. $\nu_{max}/cm^{-1}$ 3340, 3200, 3010, 2980, 2930, 2870, 2850, 1605, 1575, 1500, 1475, 1385, 1340, 1160, 755, 720. $\delta_H$ 7.72–6.40(4H, m), 6.00(1H, br s), 4.78(1H, br s), 2.44-1.20(6H, m), 1.47(3H, s), 0.85(3H, t, *J*=6Hz). *m/z*(%): 254($M^+$, 1.6), 172(86.7), 155(87.8), 92(41.2), 91(100), 65(77.4). (Found: C, 56.52. H, 7.29. N, 10.83; $C_{12}H_{18}N_2O_2S$ requires C, 56.67. H, 7.13. N, 11.01%).

**2d**, *3,4-dihydro-3,3-tetramethylene-(2*H*)-1,2,4-benzothiadiazine-1,1-dioxide*: m.p. 165–167°C. $\nu_{max}/cm^{-1}$ 3345, 3170, 3015, 2925, 2845, 1610, 1575,1510, 1470, 1350, 1156, 740, 725. $\delta_H$ 7.62–6.55(4H, m), 4.01–3.85(2H, br s), 2.00–1.70(8H, m). *m/z*(%): 238($M^+$, 7.6), 237(M–1, 13.6), 172(100), 155(81.5), 92(41), 91(76.5), 84(68), 66(80), 65(56), 64(28). (Found: C, 55.58. H, 5.78. N, 11.55; $C_{11}H_{14}N_2O_2S$ requires C, 55.44. H, 5.92. N, 11.76%).

**2e**, *3,4-dihydro-3,3-pentamethylene-(2*H*)-1,2,4-benzothiadiazine-1,1-dioxide*: m.p. 166–168°C. $\nu_{max}/cm^{-1}$ 3352, 3220, 3012, 2950, 2830, 1610, 1580, 1500, 1465, 1365, 1150, 740, 725. $\delta_H$ 7.60–6.70(4H, m), 4.15–4.03(2H, br s), 2.28-1.50(10H, m). *m/z*(%): 253(M+1, 17.3), 252($M^+$, 57.2), 209(100), 172(26.5), 156(30.6), 92(51). (Found: C, 57.32. H, 6.13. N, 11.26; $C_{12}H_{16}N_2O_2S$ requires C, 57.12. H, 6.39. N, 11.10%).

**2f**, *6-chloro-3,3-diethyl-3,4-dihydro-(2*H*)-1,2,4-benzothiadiazine-1,1-dioxide*: m.p. 164–166°C. $\nu_{max}/cm^{-1}$ 3350, 3230, 3010, 2980, 2950, 2870, 2850, 1500, 1470, 1380, 1345, 1150, 865, 820, 705. $\delta_H$ 7.50-6.68(3H, m), 6.50(1H, br s), 6.20(1H, br s), 2.25(2H, q, *J*=6.5Hz), 1.72(2H, q, *J*=6.5Hz), 0.95(6H, t, *J*=6.5Hz). *m/z*(%): 276($^{37}$Cl-$M^+$, 1.4), 274($^{35}$Cl–$M^+$, 3.5), 208(5.7), 206(14.9), 191(4.7), 189(12), 84(86), 66(100) (Found: C, 47.92. H, 5.32. N, 10.35; $C_{11}H_{15}ClN_2O_2S$ requires C, 48.09. H, 5.50. N, 10.20%).

**2g**, *6-chloro-3-ethyl-3,4-dihydro-3-methyl-(2*H*)-1,2,4-benzothiadiazine-1,1-dioxide*: m.p. 154–156°C. $\nu_{max}/cm^{-1}$ 3343, 3225, 3010, 2980, 2925, 2860, 2845, 1608, 1580, 1500, 1470, 1378, 1360, 1145, 875, 790, 700. $\delta_H$ 7.52–6.60(3H, m), 5.09(1H, br s), 4.97(1H, br s), 2.10–1.44(2H, m), 1.50(3H, s), 0.96(3H, t, *J*=6Hz). *m/z*(%): 262($^{37}$Cl–$M^+$, 1.2), 260($^{35}$Cl-$M^+$, 4.3), 208(37.5), 206(99.6), 191(37.3), 189(100). (Found: C, 45.82. H, 5.18. N, 10.63; $C_{10}H_{13}ClN_2O_2S$ requires C, 46.07. H, 5.03. N, 10.47%).

**2h**, *6-chloro-3,4-dihydro-3-methyl-3-propyl-(2*H*)-1,2,4-benzothiadiazine-1,1-dioxide*: m.p. 145–147°C. $\nu_{max}/cm^{-1}$ 3345, 3216, 3010, 2980, 2930, 2870, 2845, 1610, 1588, 1500, 1465, 1380, 1356, 1150, 870, 784, 705. $\delta_H$ 7.67–6.50(3H, m), 6.01(1H, br s), 4.45(1H, br s), 2.35-1.35(4H, m), 1.50(3H, s), 0.85(3H, t, *J*=6Hz). *m/z*(%): 276($^{37}$Cl–$M^+$, 1.4), 274($^{35}$Cl-$M^+$, 4.3), 208(13), 206(35), 191(12.4), 189(31.2), 172(36.3), 84(92.6), 66(100). (Found: C, 47.82. H, 5.38. N, 10.38; $C_{11}H_{15}ClN_2O_2S$ requires C, 48.09. H, 5.50. N, 10.20%).

**2i,** *3-butyl-6-chloro-3,4-dihydro-3-methyl-(2*H*)-1,2,4-benzothiadiazine-1,1-dioxide*: m.p. 142–144°C. $\nu_{max}/cm^{-1}$ 3353, 3220, 3010, 2985, 2925, 2870, 2835, 1610, 1588, 1500, 1475, 1380, 1360, 1165, 880, 770, 700. $\delta_H$ 7.62–6.65(3H, m), 5.15(1H, br s), 4.78(1H, br s), 2.50–1.35(6H, m), 1.50(3H, s), 0.85(3H, t, *J*=6Hz). *m/z*(%): 290($^{37}$Cl-$M^+$, 1.2), 288($^{35}$Cl-$M^+$, 3.8), 208(37.6), 206(100), 191(36.2), 189(94.1), 172(17.5). (Found: C, 49.82. H, 6.08. N, 9.93; $C_{12}H_{17}ClN_2O_2S$ requires C, 49.91. H, 5.93. N, 9.70%).

**2j**, *6-chloro-3,4-dihydro-3-methyl-3-pentyl-(2*H*)-1,2,4-benzothiadiazine-1,1-dioxide*: m.p. 130–132°C. $\nu_{max}/cm^{-1}$ 3356, 3207, 3010, 2980, 2920, 2870, 2845, 1601, 1580, 1506, 1465, 1380, 1356, 1155, 870, 775, 702. $\delta_H$ 7.64–6.52(3H, m), 5.60(2H, br s), 2.52–1.36(8H, m), 1.50(3H, s), 0.85(3H, t, *J*=6Hz). *m/z*(%): 304($^{37}$Cl–$M^+$, 1.2), 302($^{35}$Cl–$M^+$, 3.6), 248(4.8), 246(12), 208(37), 206(100), 191(34), 189(90), 172(17.8), 127(19.3), 125(50.8). (Found: C, 51.39. H, 6.44. N, 9.37; $C_{13}H_{19}ClN_2O_2S$ requires C, 51.56. H, 6.32. N, 9.25%).

**2k**, *6-chloro-3,4-dihydro-3,3-tetramethylene-(2*H*)-1,2,4-benzothiadiazine-1,1-dioxide:* m.p. 176–178°C. $\nu_{max}/cm^{-1}$ 3360, 3218, 3010, 2985, 2935, 2870, 2850, 1610, 1588, 1500, 1475, 1365, 1148, 850, 760, 705. $\delta_H$ 7.66–6.55(3H, m), 6.50(1H, br s), 5.10(1H, br s), 2.56–1.75(8H, m). *m/z*(%): 274($^{37}$Cl–$M^+$, 1.3), 272($^{35}$Cl-$M^+$, 4), 208(4.4), 206(11.2), 191(2.3), 189(4.6), 86(38.9), 84(100), 66(96.6). (Found: C, 48.62. H, 4.93. N, 10.07; $C_{11}H_{13}ClN_2O_2S$ requires C, 48.44. H, 4.80. N, 10.27%).

**2l**, *6-chloro-3,4-dihydro-3,3-pentamethylene-(2*H*)-1,2,4-benzothiadiazine-1,1-di-oxide*: m.p. 190–192°C. $\nu_{max}/cm^{-1}$ 3370, 3275, 3010, 2985, 2930, 2870, 2840, 1608, 1580, 1500, 1475, 1360, 1150, 865, 785, 703. $\delta_H$ 7.42–6.40(3H, m), 5.25(1H, br s), 4.68(1H, br s), 2.50–1.58(10H, m). *m/z*(%): 288($^{37}$Cl–$M^+$, 6.9), 286($^{35}$Cl–$M^+$, 9.4), 208(6.3), 206(16.2), 191(1.8), 189(2.8), 99(20.6), 84(100), 66(71). (Found: C, 50.07. H, 5.38. N, 9.93; $C_{12}H_{15}ClN_2O_2S$ requires C, 50.26. H, 5.27. N, 9.77%).

We are grateful to the National Natural Science Foundation of China (Project No.29872010) for finance support.

*Received 15 February 2000; accepted 4 June 2000*
*Paper 99/164*

## References

1 Girard, P., Namy, J.L. and Kagan, H.B., *J. Am. Chem. Soc.*, 1980, **102**, 2693.
2 For reviews see: (a) Molander, G.A. and Harris, C.R., *Chem. Rev.*, 1996, **96**, 307; (b) Imamota, T., *Lanthanides in Organic Synthesis*, Academic Press, London, 1994. Chap. 4; (c) Molander, G.A., *Chem. Rev.*, 1992, **92**, 29; (d) Molander, G.A., *Comprehensive Organic Synthesis*, Trost, B.M. and Fleming, I., (eds) Pergamon, Oxford, Vol. 1, 1991, 251; (e) Kagan, H.B. and Namy, J.L., *Tetrahedron*, 1986, **42**, 1725.
3 (a) Zhang, Y.M. and Lin, R.H., *Synth. Commun.*, 1987, **17**, 329; (b) Souppe, J., Danon, L., Namy, J.L. and Kagan, H.B., *J. Organomet. Chem.*, 1983, **250**, 227; (c) Mukaiyama, T., Yoyozu, K., Kato, K. and Yamada, T., *Chem. Lett.*, 1992, 181.
4 Kende, A.S. and Mendoza, J.S., *Tetrahedron Lett.*, 1991, **32**, 1699.
5 Burk, M.J. and Feaster, J.E., *J. Am. Chem. Soc.*, 1992, **114**, 6266.
6 Benati, L., Monievecohi, P.C., Nanni, D., Spagnolo, P. and Volta, M., *Tetrahedron Lett.*, 1995, **36**, 7313.
7 Keck, G.E., McHardy, S.F., Wager, T.T., *Tetrahedron Lett.*, 1995, **36**, 7419.
8 (a) Zhou, L.H. and Zhang, Y.M., *J. Chem. Soc. Perkin Trans. I*, 1998, 2899; (b) Zhou, L.H. and Zhang, Y.M., *J. Chem. Res.(S)*, 1998, 596; (c) Zhou, L.H. and Zhang, Y.M., *Tetrahedron Lett.*, 1998, **39**, 8491; (d) Zhou, L.H. and Zhang, Y.M., *Tetrahedron Lett.*, 1997, **38**, 8063; (e) Wang, L. and Zhang, Y.M., *Tetrahedron Lett.*, 1998, **39**, 5257; (f) Wang, L. and Zhang, Y.M., *Tetrahedron*, 1998, **54**, 11129.
9 Jiang, J.P., Gao, J., Shen, W.B. and Chen, W.X., *Acta. Chimica Sinica*, 1992, **50**, 1134.
10 (a) Holdrege, C.T., Babel, R.B. and Cheney, L.C., *J. Am. Chem. Soc.*, 1959, **81**, 4807; (b) Werner, L.H., Halamandaris, A., Ricca, S., Jr., Dorfan, L., deStevens, G., *J. Am. Chem. Soc.*, 1960, **82**, 1161; (c) Tadahiro, C., Makato, U., Kiyoshi, M., Takashi, S., *Eur. Pat.*, 1988, EP 276,151; (d) Weller, H.N., U.S. Patent, 1992, U.S. 5,378,704.
11 (a) Novello, F.C., Bell, S.C., Abrams, L.A., Ziegler, C. and Sprague, J.M., *J. Org. Chem.*, 1960, **25**, 970; (b) Cragoe, J.E., Jr., Woltersdorf, O.W., Jr., Baer, J.E. and Sprague, J.M., *J. Med. Pharm. Chem.*, 1962, **5**, 896.