Low-Valent Titanium Induced Simultaneous Reduction of Nitro Group and S—S Bond in Nitrodisulfides: A Facile Synthesis of 2*H*-1,4-Benzothiazines

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The simultaneous reduction of nitro group and S—S bond in nitrodisulfides by $TiCl_4$/Sm system led to the active intermediates 2, which were "living" double-anions *in situ* and reacted smoothly with ω-bromoketones to afford the desired 2*H*-1,4-benzothiazines in good yields under mild and neutral conditions.

Keywords Titanium tetrachloride, samarium, reduction, nitro group, disulfide, 2*H*-1,4-benzothiazine.

2*H*-1,4-Benzothiazine derivatives are compounds of pharmacological interest.[1] Krapcho[2a] reported some derivatives of them had therapeutic activity as central nervous system depressants, ataractic agents and antispasmodics. Recently it was shown that pharmaceutical compounds containing benzothiazine derivatives were useful as ciliary relaxants for pseudomyopia and eye fatigue.[2b] These compounds were early prepared from *o*-aminothiophenols and ω-bromoacetophenones in a basic medium.[3] 1,4-Benzothiazine derivatives can also be obtained by other procedures such as by ring expansion of benzothiazoles or benzothiazolines;[4] by reaction of *o*-nitrobenzenesulfenyl chlorides with ketones in the presence of HCl;[5] by treatment of aminothioalkenols with TsOH or H_3PO_4;[6] by using 3*H*-1,2,3-benzodithiazole-2-oxides as synthons[7] or by reaction of bis(*o*-aminophenyl)-disulfide with ketones.[8] However, most of above methods involve harsh conditions such as using acid or base catalysts, moderate to high thermal conditions as well as long reaction time.

The application of low-valent titanium reagent in organic synthesis has received more and more attention in the last two decades.[9] A lot of functional groups including carbonyl group can be coupled by this reagent.[10] Many methods have been introduced to prepare low-valent titanium reagents, such as $TiCl_3$-$LiAlH_4$, $TiCl_4$-Mg (Hg), $TiCl_4$-Zn and $CpTiCl_3$-$LiAlH_4$ system.[9e] Our groups have found that low-valent titanium reagent could be derived from Cp_2TiCl_2-Sm or $TiCl_4$-Sm system and nitro groups, Se—Se and Te—Te bonds could be easily reduced or cleaved by this reagent, which might be due to the synergistic action of divalent samarium with low-valent titanium.[11] However, to our knowledge, little has been concerned on simultaneous reduction of more than one functional group with low-valent titanium reagent.[12] Herein we wish to describe a facile synthesis of 2*H*-1,4-benzothiazines *via* simultaneous reduction of nitro group and S—S bond in nitrodisulfides induced by low-valent titanium reagent. Treatment of nitrodisulfides **1** with low-valent titanium reagent led to the "living" intermediates **2** which reacted consequently with ω-bromoketones to form 2*H*-1,4-benzothiazines (**3**) under mild and neutral conditions (Scheme 1).

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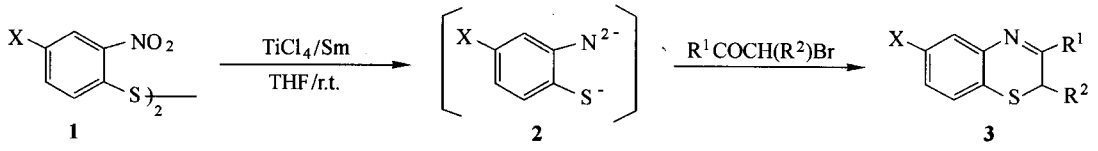
Scheme 1



1 2 3

The results are summarized in Table 1. It was found that when nitrodisulfides **1** were treated at room temperature with low-valent titanium reagent prepared from titanium tetrachloride and samarium powder in anhydrous THF, the deep dark color of the solution gradually turned brownish red within half an hour. The above appearance showed that the nitro group had been reduced and the S—S bond had been reductively cleaved simultaneously by low-valent titanium reagent; the active intermediates **2** were formed at the same time. Although the detail mechanism of this reaction has not been clarified, according to the relative literature,[9,10] we considered that the intermediates **2** were "living" double-anion species *in situ*. These new anion species reacted smoothly with ω-bromoketones at room temperature to afford the desired products **3** in good yields.

Table 1 Synthesis of 2*H*-1,4-benzothiazines induced by low-valent titanium

Entry	X	R^1	R^2	*T* (h)	Yield (%)*
3a	H	C_6H_5	H	2	82
3b	H	*p*-MeC_6H_4	H	2	88
3c	H	*p*-ClC_6H_4	H	4	77
3d	H	*p*-BrC_6H_4	H	4	73
3e	H	2-benzofuryl	H	4	79
3f	H	C_6H_5	Me	2	68
3g	Cl	CH_3	H	24	50
3h	Cl	C_6H_5	H	2	82
3i	Cl	2-benzofuryl	H	4	75
3j	Cl	*p*-BrC_6H_4	H	4	75
3k	Cl	*p*-MeC_6H_4	H	2	87
3l	Cl	*p*-$MeOC_6H_4$	H	4	84
3m	Cl	*p*-ClC_6H_5	H	4	85

* Isolated yields based on nitrodisulfides.

Compounds **3** were confirmed by IR, ^{1}H NMR, MS and elemental analysis. The IR spectrum of products **3** exhibited a middle strong absorption band at ~1670 cm^{-1} (C = N) and a characteristic C—S stretching absorption band at ~760 cm^{-1}. The ^{1}H NMR spectra of all the products **3** (except for entry **3f**) showed a two-proton singlet due to SCH_2 protons at δ_H ~ 3.60 apart from the usual peaks in the aromatic region. Mass spectra of all the products **3** showed that the cyclic benzothiazole ions derived from the fragmentation and skeletal rearrangement of the molecular ions were the main spectral features.

In summary, The present study provides a new and simple synthesis of **3** *via* simultaneous reduction of nitro group and cleavage of S—S bond in nitrodisulfides induced by low-valent titanium reagent.

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 or film with absorption in cm^{-1}. ^{1}H NMR spectra were recorded on a Bruker AC-80 spectrometer as $CDCl_3$ solutions. *J* values are in Hz. Chemical shifts are expressed in δ downfield from internal tetramethylsilane. Mass spectra were recorded on an HP 5989B MS spectrometer. Microanalysis was carried out on an EA1110 instrument.

General procedure for the synthesis of 2H-1,4-benzothiazines

$TiCl_4$ (0.27 mL, 2.5 mmol) was added dropwise using a syringe to a stirred suspension of Sm powder (0.375 g, 2.5 mmol) in THF (20 mL) at room temperature under a nitrogen atmosphere. After the completion of addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to room temperature and a solution of nitrodisulfides **1** (0.5 mmol) in anhydrous THF (2 mL) was added. The deep dark color of the solution changed into a brownish red within 30 min. Then 1 mmol ω-bromoketones in anhydrous THF (2 mL) was added slowly. After stirring for a given time (Table 1, the reaction was mon-

itored by TLC), the reaction was quenched with dilute HCl (0.1 mol/L, 3 mL) and extracted with ether (3 × 30 mL). The crude product was isolated with usual way and purified by preparative thin layer chromatography using ethyl acetate and cyclohexane (1:7) as eluant.

3-*Phenyl*-2*H*-1,4-*benzothiazine* (**3a**)

Light yellow crystal, m.p. 46—48℃ (Lit.[3a] 47—48℃); ^{1}H NMR δ: 3.63 (s, 2H), 6.87—7.42 (m, 9H); IR ν: 2930, 1475 (CH_2), 1650 (C = N), 765 (C—S) cm^{-1}.

3-(4′-*Methylphenyl*)-2*H*-1,4-*benzothiazine* (**3b**)

Light yellow crystal, m.p. 52—54℃ (Lit.[3b] 53—55℃); ^{1}H NMR δ: 2.32 (s, 3H, CH_3), 3.48 (s, 2H), 6.60—8.00 (m, 8H); IR ν: 2980, 2930, 1475, 1380 (CH_3, CH_2), 1660 (C = N), 760 (C—S) cm^{-1}.

3-(4′-*Chlorophenyl*)-2*H*-1,4-*benzothiazine* (**3c**)

Light yellow crystal, m.p. 56—58℃ (Lit.[3c]); ^{1}H NMR δ: 3.48 (s, 2H), 6.60—8.00 (m, 8H); IR ν: 2930, 1475 (CH_2), 1630 (C = N), 752 (C—S), 740 (C—Cl) cm^{-1}.

3-(4′-*Bromophenyl*)-2*H*-1,4-*benzothiazine* (**3d**)

Light yellow crystal, m.p. 60—62℃ (Lit.[3b] 59—61℃); ^{1}H NMR δ: 3.74 (s, 2H), 6.72—8.04 (m, 8H); IR ν: 2940, 1475 (CH_2), 1685 (C = N), 760 (C—S) cm^{-1}.

3-(2′-*Benzofuryl*)-2*H*-1,4-*benzothiazine* (**3e**)

Light yellow crystal, m.p. 86—88℃; ^{1}H NMR δ: 3.62 (s, 2H), 6.85—8.06 (m, 9H); IR ν: 2930, 1475 (CH_2), 1675 (C = N), 1250 (C—O—C), 760 (C—S) cm^{-1}; MS(70 eV) *m/z*(%): 265 (M^+, 15), 251 (100); Anal. Calcd. for $C_{16}H_{11}NOS$: C 72.43, H 4.18, N 5.28; Found: C 72.28, H 4.23, N 5.36.

2-*Methyl*-3-*phenyl*-2*H*-1,4-*benzothiazine* (**3f**)

Light yellow crystal, m.p. 75—77℃ (Lit.[3c]); ^{1}H NMR δ: 1.20 (d, *J* = 5 Hz, 3H), 3.83 (q, *J* = 5 Hz, 1H), 6.71—7.62 (m, 9H); IR ν: 2980, 2840, 1380 (CH_3), 1660 (C = N), 763 (C—S) cm^{-1}.

6-*Chloro*-3-*methyl*-2*H*-1,4-*benzothiazine* (**3g**)

Oil; ^{1}H NMR δ: 2.13 (s, 3H), 2.75 (s, 2H), 6.92—7.58 (m, 3H); IR ν: 2980, 2930, 1475, 1380 (CH_3, CH_2), 1650 (C = N), 760 (C—S), 742 (C—Cl) cm^{-1}. MS(70 eV) *m/z*(%): 199 (M + 2, 3.2), 197 (M^+, 8.7), 184 (32.7), 182 (100); Anal. Calcd. for C_9H_8ClNS: C 54.68, H 4.08, N 7.09; Found: C 54.77, H 3.89, N 6.83.

6-*Chloro*-3-*phenyl*-2*H*-1,4-*benzothiazine* (**3h**)

Light yellow crystal, m.p. 62—64℃ (Lit.[3a] 64℃); ^{1}H NMR δ: 3.60 (s, 2H), 6.85—7.51 (m, 8H); IR ν: 2930, 1475 (CH_2), 1660 (C = N), 760 (C—S), 740 (C—Cl) cm^{-1}.

6-*Chloro*-3-(2′-*benzofuryl*)-2*H*-1,4-*benzothiazine* (**3i**)

Light yellow crystal, m.p. 125—127℃; ^{1}H NMR δ: 3.53 (s, 2H), 6.83—7.63 (m, 8H); IR ν: 2940, 1465 (CH_2), 1645 (C = N), 1250 (C—O—C), 763 (C—S), 740 (C—Cl) cm^{-1}; MS(70 eV) *m/z*(%): 301 (M + 2, 1.2), 299 (M^+, 3.5), 286 (32.4), 284 (100); Anal. Calcd. for $C_{16}H_{10}ClNOS$: C 64.11, H 3.36, N 4.67; Found: C 64.27, H 3.29, N 4.49.

6-*Chloro*-3-(4′-*bromophenyl*)-2*H*-1,4-*benzothiazine* (**3j**)

Light yellow crystal, m.p. 155—158℃; ^{1}H NMR δ: 3.64 (s, 2H), 6.90—7.98 (m, 7H); IR ν: 2930, 1475 (CH_2), 1670 (C = N), 760 (C—S), 740 (C—Cl) cm^{-1}; MS(70 eV) *m/z*(%): 337 (M^+, 12.8), 322(100); Anal. Calcd. for C_{14}-$H_9BrClNS$: C 49.65, H 2.68, N 4.14; Found: C 49.47, H 2.89, N 4.03.

6-*Chloro*-3-(4′-*methylphenyl*)-2*H*-1,4-*benzothiazine* (**3k**)

Light yellow crystal, m.p. 122—124℃; ^{1}H NMR δ: 2.26 (s, 3H), 3.45 (s, 2H), 6.95—7.81 (m,

7H); IR ν: 2980, 2930, 1475, 1380 (CH_3, CH_2), 1667 (C=N), 760 (C—S), 742 (C—Cl) cm^{-1}; MS (70 eV) *m/z*(%): 275 (M+2, 4.5), 273 (M^+, 12.8), 261 (34.2), 258 (100); Anal. Calcd. for $C_{15}H_{12}ClNS$: C 65.81, H 4.42, N 5.12; Found: C 65.73, H 4.25, N, 5.18.

6-*Chloro*-3-(4′-*methoxyphenyl*)-2*H*-1,4-*benzothiazine* (**3l**)

Light yellow crystal, m.p. 117—119℃; ^1H NMR δ: 3.68 (s, 2H), 3.86 (s, 3H), 6.70—7.85 (m, 7H); IR ν: 2980, 2925, 1475, 1380 (CH_3, CH_2), 1650 (C=N), 1250 (C—O—C), 760 (C—S), 740 (C—Cl) cm^{-1}; MS(70 eV) *m/z*(%): 291 (M+2, 4.8), 289 (M^+, 14.9), 276 (31.7), 274 (100); Anal. Calcd. for $C_{15}H_{12}ClNOS$: C 62.17, H 4.17, N 4.83; Found: C 62.02, H 4.22, N 4.09.

6-*Chloro*-3-(4′-*chlorophenyl*)-2*H*-1,4-*benzothia-zine* (**3m**)

Light yellow crystal, m.p. 119—121℃; ^1H NMR δ: 3.82 (2H, s, CH_2), 7.05—8.01 (m, 7H); IR ν: 2935, 1470 (CH_2), 1660 (C=N), 760 (C—S), 742 (C—Cl) cm^{-1}; MS(70 eV) *m/z*(%): 294 (M^+, 12.7), 279 (100); Anal. Calcd. for C_{14}-H_9Cl_2NS: C 57.16, H 3.08, N 4.76; Found: C 56.97 H, 3.14, N, 4.56.

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