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Low-valent Titanium Induced Simultaneous Reduction of Nitro Group and S-S Bond in Nitrodisulfides: A Novel Method For the Synthesis of Benzothiazoline, Benzothiazoles and 2,3-Dihydro- 1,5-benzothiazepines

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Abstract: The simultaneous reduction of nitro group and S-S bond in nitrodisulfides by $TiCl_4$/Sm system leds to the active intermediates **2**, which were "living" double-anions (nitride anions and sulfide anions) *in situ*. These new anion species reacted smoothly with aldehydes or ketones, acid chlorides or acid anhydrides and α,β-unsaturated ketones respectively to afford the desired benzothiazolines, benzothiazoles and 2,3-dihydro-1,5-benzothiazepines in good yields under mild and neutral conditions.

Benzothiazoline, benzothiazole and 1,5-benzothiazepine derivatives are very important and useful compounds in pharmaceutical chemistry. Krapcho and coworkers[1] reported that some derivatives have therapeutic activity as central nervous system depressants, ataractic agents and antipasedics. Furthermore, benzothiazoline derivatives can be used as addition agents for photographic

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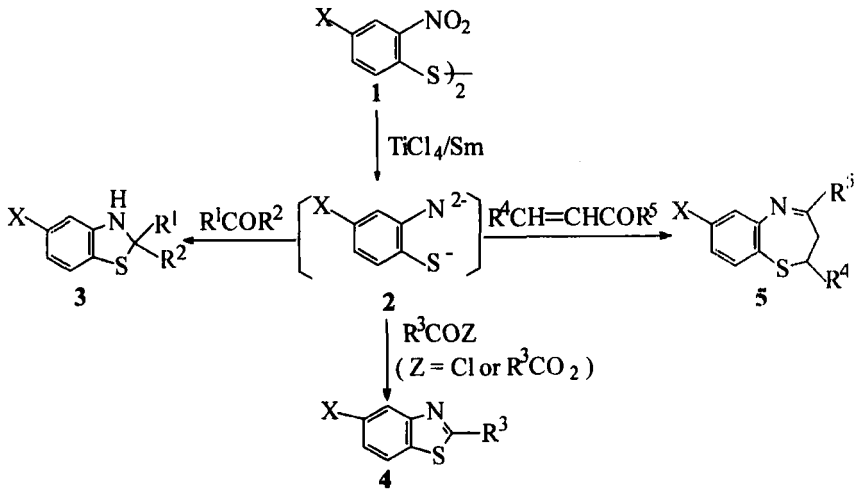
emulsions,[2a] effective acaricids,[2b] antituberculous agents,[2c] lubricating oil antioxidant[2d]. There are many methods for preparing benzothiazoline,[3] benzothiazole[4] and 1,5-benzothiazepine derivatives.[5] Some methods have been used successfully for the preparation of these kinds of compounds. However, most of these methods involve harsh conditions such as using acid or base catalysts, moderate to high thermal conditions as well as long reaction time.

Low-valent titanium reagent has an exceedingly high ability in promoting reduction of carbonyl compounds and is attracting increasing interest in organic synthesis.[6] A lot of other functional groups can also be coupled by this reagent.[7] Previous works have been concerned on using low-valent titanium to promote some reductive or coupling reactions, such as the reduction of nitro compounds and the reductive cleavage of S-S, Se-Se and Te-Te bonds.[8]



Scheme 1

However, to our knowledge, simultaneous reduction of more than one functional group with low-valent titanium has not been reported in the literature. Herein we wish to describe our preliminary results on simultaneous reduction of nitro group and S-S bond in nitrodisulfides by low-valent titanium reagent and its use in the synthesis of benzothiazolines, benzothiazoles and 2,3-dihydro-1,5-benzothiazepines (**Scheme 1**).

Table 1 Synthesis of benzothiazolines and benzothiazoles induced by $TiCl_4$/Sm system[a]

Entry	X	R^1	R^2	R^3	Z	T(h)	Yield(%)[b]
3a	H	n-Pr	H			2	80
3b	H	p-$NO_2C_6H_5$	H			2	75
3c	H	Me	n-Bu			2	74
3d	Cl	Me	Ph			4	72
3e	Cl	-$(CH_2)_5$-				3	78
3f	Cl	Ph	Ph			24	0[c]
4a	H			n-Pr	Cl	2	65
4a	H			n-Pr	n-$PrCO_2$	2	83
4b	Cl			Et	Cl	2	68
4b	Cl			Et	$EtCO_2$	2	86
4c	Cl			Ph	Cl	2	72

[a]Reaction conditions: 0.5mmol nitrodisulfides, 3mmol Sm powder, 0.33ml $TiCl_4$ and 1mmol aldehydes (ketones, acid chlorides or anhydrides); [b]isolated yields based on nitrodisulfides; [c]the reaction was studied at 0℃, 25℃ and refluxing temperature.

Table 2 Synthesis of 2,3-dihydro-1,5-benzothiazepins induced by $TiCl_4$/Sm system[d]

Entry	X	R^4	R^5	T(h)	Yield(%)[e]
5a	H	C_6H_5	Ph	4	86
5b	Cl	C_6H_5	Ph	4	83
5c	Cl	p-ClC_6H_4	Ph	3	78
5d	Cl	p-$CH_3C_6H_4$	Ph	4	80
5e	Cl	p-$CH_3OC_6H_4$	Ph	4	77
5f	Cl	3,4-$(OCH_2O)C_6H_3$	Ph	4	85
5g	Cl	C_6H_5	PhCH=CH	8	52

[d]Reaction conditions: 0.5mmol nitrodisulfides, 3mmol Sm powder, 0.33ml $TiCl_4$ and 1mmol α,β-unsaturated ketones were used; [e]isolated yields based on nitrodisulfides.

We 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 into brownish red within half an hour. The above appearance showed 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,[6a,8b,9] we consider that the intermediates **2** are "living" double-anion species(nitride anions and sulfide anions) *in situ*. These new anion species reacted smoothly with aldehydes or ketones at room temperature to afford the benzothiazolines **3** in good yields. Benzothiazoles **4** and 2,3-dihydro-1,5-benzothiazepines **5** were also obtained *via* reacting these new anion species with acid chlorides or acid anhydrides as well as α,β-unsaturated ketones respectively. The results are summarized in **Table 1** and **Table 2** respectively.

According to **Table 1**, we found that most of aldehydes or ketones except for benzophenone can give satisfactory yields; on the other hand, the yield using acid anhydrides is higher than using acid chlorides. It is apparent from **Table 2** that chalcones are more reactive towards the new anion species **2** than any other α,β-unsaturated ketones. Moreover, the substituted groups on the aromatic rings such as chloride and methoxyl groups can't be reduced under the same conditions.

In summary, a novel method for the preparation of benzothiazolines, benzothiazoles and 2,3-dihydro-1,5-benzothiazepines has been elucidated, the

advantages of which are accessible starting materials, simple and mild reaction conditions, convenient manipulation and good yields. Further studies to develop other new uses of the $TiCl_4$/Sm system are now in progress.

Experimental

Tetrahydrofuran(THF) was distilled from sodium-benzophenone immediately prior to use. All reactions were conduct under a nitrogen atmosphere. Melting points are uncorrected. Infrared spectra were recorded on IR-408 spectrometers in KBr or film with absorption in cm^{-1}. ^1H NMR spectra were determined in Bruker AC-80 spectrometers as $CDCl_3$ solutions. J values are in Hertz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Mass spectra were recorded on HP 5989A MS spectrometers. Microanalysis was carried out on a Perkin–Elmer 240C instrument.

General procedure for the preparation of benzothiazolines, benzothiazlocs, 2,3-dihydro-1,5-benzothiazepines $TiCl_4$ (0.33ml, 3mmol) was added dropwise using a syringe to a stirred suspension of Sm powder (0.45g, 3mmol) in freshly distilled dry THF (20ml) at room temperature under a nitrogen atmosphere. After the completion of addition, the mixture was refluxed for 2h. The suspension of the low-valent titanium reagent formed was cooled to room temperature and a solution of nitrodisulfides **1** (0.5mmol) in anhydrous THF (2ml) was added. The deep dark color of the solution changed to a brownish red within 30 minutes. Then 1mmol aldehydes (ketones, acid chlorides or anhydrides, α,β-unsaturated ketones) in anhydrous THF (2ml) were added slowly. After stirring for a given time (**Table 1**

and **Table 2**, the reaction was monitored by TLC), the reaction was quenched with dilute HCl (0.1mol/L, 3ml) and extracted with ether (3×30ml). The crude product was isolated with usual ways and purified by preparative thin layer chromatography using ethyl acetate and cyclohexane (1:7) as eluant.

3a, 2-n-propylbenzothiazoline oil[10]; ν_{max}/cm^{-1} 3350(NH); δ_H 7.15-6.20(4H, m), 4.92(1H, m), 3.07(1H, br s), 1.78-1.22(4H, m), 0.85(3H, t, J=6 Hz).

3b, 2-(4'-nitrophenyl)benzothiazoline yellow crystal, mp 116－118℃(lit.,[3d] 117 － 118℃); ν_{max}/cm^{-1} 3375(NH), 1520, 1350(NO_2); δ_H 8.21-7.48(4H,m), 7.09-6.47(4H, m), 6.29(1H, s), 4.10(1H, br s).

3c, 2-n-butyl-2-methylbenzothiazoline oil; ν_{max}/cm^{-1} 3340(NH); δ_H 6.90-6.30(4H, m), 3.65(1H, br s), 1.92-1.13(9H, m), 0.85(3H, t, J=6Hz, CH_3); *m/z* 207(M^+, 1.5), 136(25), 101(50), 43(100) (Found: C, 69.67; H, 8.13; N, 6.64. $C_{12}H_{17}NS$ requires C, 69.52; H, 8.26; N, 6.76%).

3d, 5-chloro-2-methyl-2-phenylbenzothiazoline yellow crystal, mp 68 － 70℃ (lit.,[3a] 71℃); ν_{max}/cm^{-1} 3345(NH); δ_H 7.85-6.48(8H, m), 5.65(1H, br s), 4.75(1H, m), 2.63(3H, s).

3e, 5-chloro-2,2-pentamethylenebenzothiazoline yellow crystal, mp 43 － 45℃ (lit.,[3a] 47℃); ν_{max}/cm^{-1} 3352(NH); δ_H 6.76-6.24(3H, m), 3.89(1H, br s), 2.02-1.20(10H, m).

4a, 2-propylbenzothiazole light yellow oil (lit.[4a]); ν_{max}/cm^{-1} 1620-1580(C=N), 760(C-S); δ_H 7.80-7.30(3H, m, ArH), 2.73(2H, t, J=6Hz), 2.10-1.35(2H, m), 0.95(3H, t, J=6.5Hz);.

4b, 5-chloro-2-ethylbenzothiazole pale yellow crystal, mp 54--56℃(lit.,[11] 56—57 ℃); ν_{max}/cm^{-1} 1618-1577(C=N), 763(C-S); δ_H 7.75-7.31(3H, m, ArH), 2.80(2H, q, J=6.5Hz), 1.18(3H, t, J=6.5Hz).

4c, 5-chloro-2-phenylbenzothiazole light yellow crystal, mp 136—138℃(lit.,[11] 139℃); ν_{max}/cm^{-1} 1625-1583(C=N), 1500, 1450(Ar), 762(C-S); δ_H 7.83-7.06(8H, m).

5a, 2,3-dihydro-2,4-diphenyl-1,5-benzothiazepine pale yellow crystal, mp 112 — 114 ℃ (lit.,[5a] 114 — 115 ℃); ν_{max}/cm^{-1} 1610-1590(C=N), 758(C-S); δ_H 8.06-6.76(14H, m), 4.90-4.45(1H, m), 3.10-2.45(2H, m).

5b, 7-chloro-2,3-dihydro-2,4-diphenyl-1,5-benzothiazepine light yellow crystal, mp 132—134℃; ν_{max}/cm^{-1} 1610-1580(C=N), 755(C-S); δ_H 8.07-6.57(13H, m), 4.87-4.57(1H, m), 3.47-2.77(2H, m); *m/z* 349(M^+, 2.0), 248(36), 246(100), 105(67), 77(36) (Found: C, 72.20; H, 4.53; N, 3.78. $C_{21}H_{16}ClNS$ requires C, 72.09; H, 4.61; N, 4.00%).

5c, 7-chloro-2-(4'-chlorophenyl)-2,3-dihydro-4-phenyl-1,5-benzothiazepine yellow crystal, mp 145—147℃; ν_{max}/cm^{-1} 1610-1580(C=N), 760(C-S); δ_H 8.00-6.40(12H, m), 5.90-5.67(1H, m), 2.62-2.34(2H, m); *m/z* 383(M^+, 1.6), 279(38), 248(36), 246(100); (Found: C, 65.39; H, 4.04; N, 3.78. $C_{21}H_{15}Cl_2NS$ requires C, 65.63; H, 3.93; N, 3.64%).

5d, 7-chloro-2,3-dihydro-2-(4'-methylphenyl)-4-phenyl-1,5-benzothiazepine light yellow crystal, mp 165-167℃; ν_{max}/cm^{-1} 1610-1578(C=N), 760(C-S); δ_H 8.04-6.92(8H, m, ArH), 4.90-4.62(1H, m), 3.14-2.74(2H, m), 2.24(3H, s); *m/z* 363(M^+,

1.9), 259(19), 245(14), 221(39), 207(100), 105(35), 77(37); (Found: C, 72.47; H, 5.10; N, 3.62. $C_{22}H_{18}ClNS$ requires C, 72.61; H, 4.99; N, 3.85%).

5e, 7-chloro-2,3-dihydro-2-(4'-methoxylphenyl)-4-phenyl-1,5-benzothiazepine light yellow crystal, mp 148－150℃; ν_{max}/cm^{-1} 1613-1585(C=N), 1250(=C-OMe), 755(C-S); δ_H 8.02-6.40(12H, m), 4.25-4.05(1H, m), 3.51(3H, s), 3.25-2.85(2H, m); *m/z* 379(M^+, 1.2), 248(19), 246(49), 134(100); (Found: C, 69.44; H, 4.52; N, 3.51. $C_{22}H_{18}ClNOS$ requires C, 69.56; H, 4.78; N, 3.69%).

5f, 7-chloro-2,3-dihydro-2-(3',4'-dioxomethylenephenyl)-4-phenyl-1,5-benzothiaze-pine light yellow crystal, mp 178－180℃; ν_{max}/cm^{-1} 2780, 925, 720(OCH_2O), 1615-1580(C=N), 760(C-S); δ_H 8.00-6.42(11H, m), 5.77(2H, s), 4.96-4.62(1H, m), 3.36-2.80(2H, m); *m/z* 393(M^+, 4.2), 289(23.3), 246(24.8), 149(100); (Found: C, 67.20; H, 3.92; N, 3.43. $C_{22}H_{16}ClNO_2S$ requires C, 67.09; H, 4.09; N, 3.56%).

5g, 7-chloro-2,3-dihydro-2-phenyl-4-styryl-1,5-benzothiazepine light yellow crystal, mp 102－104℃; ν_{max}/cm^{-1} 1650, 965(C=C), 1615-1582(C=N), 760(C-S); δ_H 8.10-6.70(13H, m), 6.23-5.76(2H, m), 4.53-4.23(1H, m), 3.10-2.53(2H, m); *m/z* 375(M^+, 1.2), 272(16), 270(33), 247(38.6), 245(100) (Found: C, 73.33; H, 4.76; N, 3.57. $C_{23}H_{18}ClNS$ requires C, 73.49; H, 4.83; N, 3.73%).

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