Low-valent titanium induced reductive cyclization of nitro compounds and aliphatic ketones: facile synthesis of 3,4-dihydro-(2*H*)-1,2,4-benzothiadiazine-1,1-dioxides

ZHONG, Wei-Hui[a](钟为慧) CHEN, Xiao-Yuan[a,c](陈小原) ZHANG, Yong-Min*[,a,b](张永敏)

[a] *Department of Chemistry, Zhejiang University (Campus Xixi), Hangzhou, Zhejiang 310028, China*

[b] *Laboratory of Organometallic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*

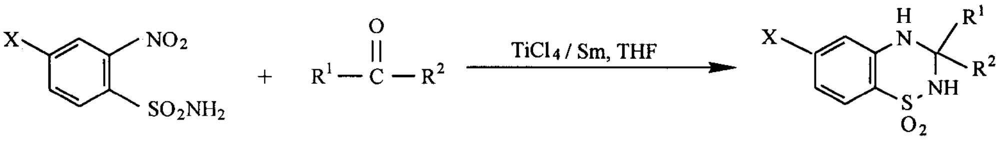
[c] *Department of Chemistry, Hunan Jishou University, Jishou, Hunan 416000, China*

The intermolecular reductive cyclization of *o*-nitrobenzenesulfonamides with aliphatic ketones induced by $TiCl_4$/Sm system was studied and a series of 3,3-disubstituted-3,4-dihydro-(2*H*)-1,2,4-benzothiadiazine-1,1-dioxides were synthesized in moderate to high yields under mild and neutral conditions.

Keywords Nitro compounds, ketones, reductive cyclization, samarium, titanium tetrachloride.

Low-valent titanium reagent has an exceedingly high ability in promoting reduction of carbonyl compounds and is attracting increasing interest in organic synthesis. A lot of other functional groups can also be coupled by this reagent.[1] Our previous work has been concerned on using $TiCl_4$/Sm system to promote some reductive coupling reactions, such as reductive coupling of nitriles with nitro compounds;[2a] the intermolecular and intramolecular ketone-nitrile reductive coupling reactions.[2b] Chen[3] has reported that the intramolecular reductive cyclization of 4-nitroketone with $TiCl_4$/Zn affords Δ-pyrroline, however, little attention has been concerned on the intermolecular reductive cyclization of nitro compounds with ketones because both nitro group and carbonyl group are reactive to this reagent. So if equal mole of nitro compounds and ketones are added simultaneously to a solution of low-valent titanium reagent, what will happen? In our work, the intermolecular reductive cyclization of nitro compounds with aliphatic ketones promoted by $TiCl_4$/Sm/THF system was studied and the products 3,3-disubstituted-3,4-dihydro-(2*H*)-1,2,4-benzothiadiazine-1,1-dioxides **3** were obtained in moderate to high yields (Scheme 1).

Scheme 1



1 X=H, Cl 2 3

The results are summarized in Table 1. When *o*-nitrobenzenesulfonamides **1** and aliphatic ketones **2** were treated with low-valent titanium prepared from samarium powder and titanium tetrachloride in anhydrous THF at room temperature under a nitrogen atmosphere, the deep black color of the mixture changed into brownish red

---

* Received March 30, 2000; accepted May 8, 2000.
Project supported by the National Natural Science Foundation of China (No. 29872010) and Natural Science Foundation of Zhejiang Province, China.

gradually and the products **3** were obtained. Aliphatic ketones could give the desired product **3** with satisfactory yields. Aromatic ketone such as acetophenone (Entry 14) has been tried in our experiment. However it brought the similar product with poor yield due to its self-coupling to form pinacol under the same conditions.

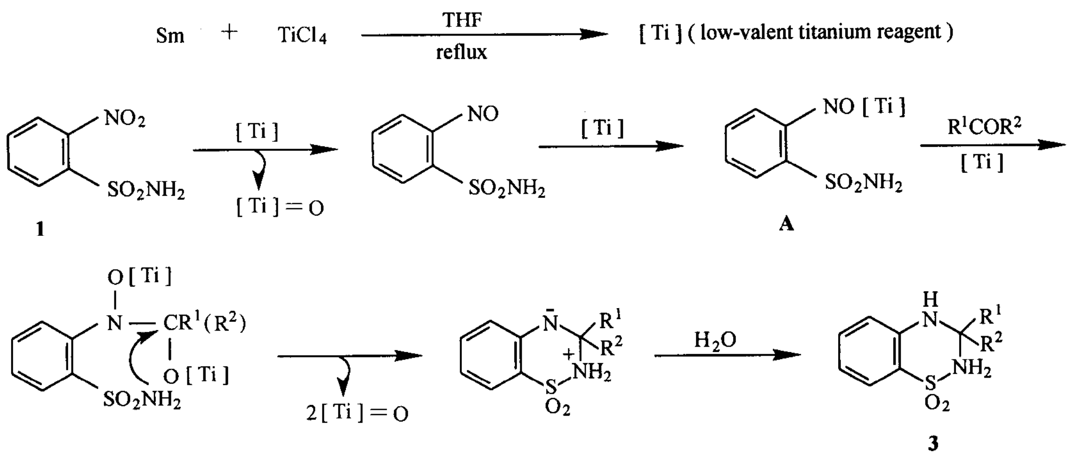
Although the detailed mechanism has not been clarified, according to the relative literature,[3] the product **3** formation may be described as shown in Scheme 2.

Table 1 Reductive cyclization of *o*-nitrobenzenesulfonamides with ketones induced by $TiCl_4$/Sm system

Entry	X	R^1	R^2	*T* (h)	Product	Yield (%)[a]
1	H	Me	Et	3	**3a**	70
2	H	Me	*n*-Pr	4	**3b**	68
3	H	Me	*n*-Bu	6	**3c**	73
4	H	Me	*n*-C_5H_{11}	6	**3d**	59
5	H	-$(CH_2)_4$-		4	**3e**	71
6	H	-$(CH_2)_5$-		4	**3f**	65
7	Cl	Me	Et	4	**3g**	72
8	Cl	Et	Et	6	**3h**	58
9	Cl	Me	*n*-Pr	4	**3i**	65
10	Cl	Me	*n*-Bu	4	**3j**	68
11	Cl	Me	*n*-C_5H_{11}	6	**3k**	54
12	Cl	-$(CH_2)_4$-		4	**3l**	75
13	Cl	-$(CH_2)_5$-		4	**3m**	70
14	Cl	Me	Ph	24	**3n**	26[b]

[a] Isolated yields based on nitro compounds. [b] The reaction was accomplished under refluxing temperature.

Scheme 2



2*H*-1, 2, 4-Benzothiadiazine-1, 1-dioxide derivatives are very important and useful compounds in pharmaceutical chemistry. They have been used for diuretics[4a] and antihypertensive agents[4b] for a long time. Many methods have been introduced for the preparation of these compounds. However, most of them invoved in harsh reaction conditions, such as high temperature and long reaction time, using acid or base catalysts.[4a, 5] In contrast, our method for the preparation of these compounds circumvents above problems.

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

Experimental

General

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

General procedure

$TiCl_4$ (0.33 mL, 3 mmol) was added dropwise using a syringe to a stirred suspension of Sm powder (0.45 g, 3 mmol) in freshly distilled dry 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 nitro compounds **1** (1 mmol) and aliphatic ketones **2** (1 mmol) in anhydrous THF (3 mL) was added. The deep black color of the mixture changed into a brownish red color gradually. After being stirred for a given time (Table 1, the reaction was monitored by TLC), the reaction was quenched with water and extracted with ether (3 × 30 mL). The crude product was isolated with usual way and purified by preparative thick layer chromatography using ethyl acetate and cyclohexane (2:3) as eluant.

The physical data of one typical new compound was listed below. Compound **3a**, light yellow crystal, mp 178—180℃. ν_{max}: 3350 (ArNH), 3210, 1375, 1160 (SO_2NH), 2980, 2860, 1475, 1380 (CH_3, CH_2) cm^{-1}. δ_H: 7.66—6.44 (m, 4H, ArH), 5.10—5.00 (m, 2H, $2 \times NH$), 2.01—1.66 (m, 2H, CH_2), 1.50 (s, 3H, CH_3), 0.95 (t, $J = 7Hz$, 3H, CH_3). m/z (%): 226 (M^+, 3.5), 172 (98.8), 155 (97), 91 (100). Anal. $C_{10}H_{14}N_2O_2S$. Calcd: C, 53.08; H, 6.24; N, 12.38. Found: C, 53.23; H, 6.08; N, 12.15.

References

1. For reviews see:
   a) McMurry, J.E., *Acc. Chem. Res.*, **7**, 281(1974).
   b) McMurry, J.E., *Acc. Chem. Res.*, **16**, 405(1983).
   c) McMurry, J.E., *Chem. Rev.*, **89**, 1513(1989).
   d) Lenoir, D., *Synthesis*, **883**(1989).
2. a) Zhou, L.H.; Zhang, Y.M., *Synth. Commun.*, **28**, 3249(1998).
   b) Zhou, L.H.; Zhang, Y.M., *Tetrahedron*, **56**, in press (2000).
3. Jiang, J.P.; Gao, J.; Shen, W.B.; Chen, W.X., *Acta Chim. Sin.*, **50**, 1134(1992);
4. a) Holdrege, C.T.; Babel, R.B.; Cheney, L.C., *J. Am. Chem. Soc.*, **81**, 4807(1959).
   b) Werner, L.H.; Halamandaris, A.; Ricca, S. Jr.; Dorfan, L.; deStevens, G., *J. Am. Chem. Soc.*, **82**, 1161(1960).
   c) Tadahiro, C.; Makato, U.; Kiyoshi, M.; Takashi, S., *EP 276, 151* (1988).
   d) Weller, H. N., *U.S. 5, 378, 704*(1992).
5. a) Novello, F.C.; Bell, S.C.; Abrams, L.A.; Ziegler, C.; Sprague, J.M., *J. Org. Chem.*, **25**, 970(1960).
   b) Cragoe, J.E. Jr.; Woltersdorf, O.W. Jr.; Baer, J.E.; Sprague, J.M., *J. Med. Pharm. Chem.*, **5**, 896 (1962).

(E200003065 JIANG, X.H.; DONG, L.J.)