Facile synthesis of 2*H*-1,2,4-benzothiadiazine 1,1-dioxides promoted by SmI_2

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2*H*-1,2,4-Benzothiadiazine 1,1-dioxides are prepared in good yields *via* reductive cyclisation of *N,N*-diethyl-*o*-nitrobenzenesulfonamides with appropriate nitriles promoted by SmI_2 under mild and neutral conditions.

Keywords: samarium diiodide, reductive cyclisation, 1,2,4-benzothiadiazine 1,1-dioxides

2*H*-1,2,4-Benzothiadiazine 1,1-dioxides are important and useful heterocyclic nitrogen compounds. Although 2*H*-1,2,4-Benzothiadiazine 1,1-dioxides are used as antihypertensive and antimicrobial agents, only a few synthetic methods for them have been reported.[1,2] A general procedure consists in condensing the appropriate *o*-aminobenzenesulfonamide with reactive carboxylic acid derivatives using polyphosphoric acid trimethylsilyl ester (PPSE) as catalyst under vigorous reaction conditions.[3,4]

The chemistry of samarium diiodide (SmI_2) is of current interest in organic synthesis because of its unique properties.[5-11] For example, the strong reducing ability of SmI_2 allows the easy reduction of many functional groups and provides a convenient method for reductive carbon-carbon bond formation. It is well known that various nitrogen compounds can be easily reduced by SmI_2.[13-15] Herein we report a facile synthesis of 2*H*-1,2,4-benzothiadiazine 1,1-dioxides (**3**) in one pot *via* the reductive cyclisation of *N,N*-diethyl-*o*-nitrobenzenesulfonamide (**1**) with appropriate nitriles promoted by SmI_2 under mild and neutral conditions (Scheme 1).The results are shown in Table 1.

From Table 1, it can be found that *N,N*-diethyl-*o*-nitrobenzenesulfonamide reacts with the given nitriles to afford the desired products in satisfactory yields. Unfortunately, for acetonitrile only *N,N*-diethyl-*o*-aminobenzenesulfonamide was obtained and product **3** (R = CH_3) was not detected even after a long time under reflux conditions. Further examination of the reaction conditions revealed the effect of the reaction temperature and the amount of SmI_2. We found that the results were satisfactory when substrates were treated with SmI_2 below –20°C at the start of the reaction. It was found that six equivalents of SmI_2 were enough to complete the reaction.

In summary, the intermolecular reductive cyclisation reaction of *N,N*-diethyl-*o*-nitrobenzenesulfonamide with nitriles was studied and a facile synthesis of 2*H*-1,2,4-Benzothiadiazine 1,1-dioxides was provided. Although the detailed mechanism of the above reaction has not clarified, the formation of products **3** may be described by the possible mechanism presented in Scheme 2.

Experimental

N,N-Diethyl-*o*-nitrobenzenesulfonamide was prepared from *o*-nitrobenzenesulfonyl chloride and diethylamine in tetrahydrofuran according to the literature.[16] Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. All reactions were carried out under a dry nitrogen atmosphere. ^{1}H NMR spectra were determined on a Bruker AC-80 instrument with DMSO-d_6 used as the solvent. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer 683 spectrometer in KBr with absorptions in cm^{-1}. Mass spectra were recorded on a Thermo Finnigan LCQ advantage (ESI). Microanalysis was carried out on a Carlo-Erba 1106 instrument.

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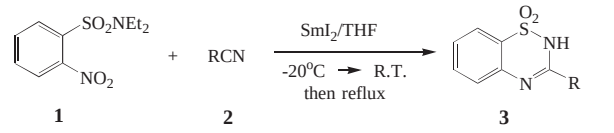
Table 1 Reductive cyclisation of *N,N*-diethyl-*o*-nitrobenzenesulfonamide with nitriles promoted by SmI_2 [a]

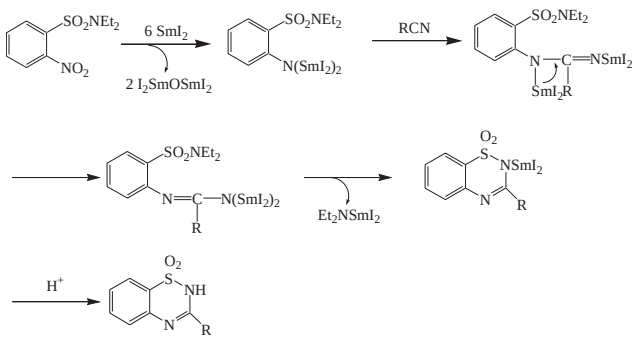
Entry	R	Time/h	Yield/%[b]
a	Ph	2	75
b	$PhCH_2$	2	85
c	*p*-ClC_6H_4	2	77
d	*p*-$CF_3C_6H_4$	2	75
e	*p*-MeC_6H_4	2	74
f	*m*-$MeOC_6H_4CH_2$	2	86
g	*p*-$MeOC_6H_4$	2	75
h	*m*-MeC_6H_4	2	79
j	CH_3	20	0

[a] *N,N*-diethyl-*o*-nitrobenzenesulfonamide 1 mmol, nitriles 1.5 mmol, SmI_2 6 mmol were used.
[b] Isolated yields based on *N,N*-diethyl-*o*-nitrobenzenesulfonamide.



1 **2** **3**

Scheme 1



Scheme 2

General procedure: A solution of *N,N*-diethyl-*o*-nitrobenzenesulfonamide (1 mmol) and a nitrile (1.5 mmol) in anhydrous THF (5 ml) was added dropwise to SmI_2 (6 mmol) at -20°C under a dry nitrogen atmosphere. The mixture was allowed to reach room temperature, then refluxed for the indicated time (see Table 1). The solvent was removed under reduced pressure. The residue was treated with dilute HCl (0.01 M, 20 ml) and extracted with ethyl acetate (3 × 20 ml). The organic layer was washed with satd. aq. $Na_2S_2O_3$ (15 ml) and brine (15 ml) successively, and then dried over anhydrous $MgSO_4$. After ethyl acetate was removed under reduced pressure the desired product was obtained by recrystallisation of the residue from anhydrous ethanol.

3-Phenyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (**3a**): m.p. 315–316°C (lit[4]. 317°C); ^{1}H NMR (DMSO-d_6) δ: 7.20-8.19 (9H, m, ArH), 4.80 (1H, br s, NH); IR (KBr) ν: 1290, 1150 cm^{-1}.

3-Benzyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (**3b**): m.p. 333–335°C; ^{1}H NMR (DMSO-d_6) δ: 7.20–8.19 (9H, m, ArH), 4.87 (1H, br s, NH), 4.0(2H, s); IR (KBr) ν: 1290, 1140 cm^{-1}; (ESI) MS *m/z* 273 $(M+H)^+$; Anal. calcd for $C_{14}H_{12}N_2O_2S$: C 61.76, H 4.41, N 10.29; found C 61.77, H 4.42, N 10.30%.

3-(4-Chlorophenyl)-2H-1,2,4-benzothiadiazine 1,1-dioxide (**3c**): m.p. 342–343°C (lit[4]. 343°C); ^{1}H NMR (DMSO-d_6) δ: 7.62–8.30 (8H, m, ArH), 4.92 (1H, br s, NH); IR (KBr) ν: 1260, 1150 cm^{-1}.

3-(4-Trifluoromethylphenyl)-2H-1,2,4-benzothiadiazine 1,1-dioxide (**3d**): m.p. 369–370°C; ^{1}H NMR (DMSO-d_6) δ: 7.60–8.19 (8H, m, ArH), 4.92 (1H, br s, NH); IR (KBr) ν: 1265, 1155 cm^{-1}; (ESI) MS *m/z* 327 $(M+H)^+$; Anal. calcd for $C_{14}H_9F_3N_2O_2S$: C 51.53, H 2.76, N, 8.59; found C 51.56, H 2.79, N 8.61%.

3-(4-Tolyl)-2H-1,2,4-benzothiadiazine 1,1-dioxide (**3e**): m.p. 354–356°C (lit[4]. 355°C); ^{1}H NMR (DMSO-d_6) δ: 7.43–8.19 (8H, m, ArH), 4.82 (1H, br s, NH); 2.30 (3H, s, CH_3); IR (KBr) ν: 1280, 1155 cm^{-1}.

3-(3-Methoxybenzyl)-2H-1,2,4-benzothiadiazine 1,1-dioxide (**3f**): m.p. 361–362°C; ^{1}H NMR (DMSO-d_6) δ: 7.20–8.19 (8H, m, ArH), 4.90 (1H, br s, NH), 4.0(2H, s), 3.84 (3H, s); IR (KBr) ν: 1290, 1140 cm^{-1}; (ESI) MS *m/z* 303.0 $(M+H)^+$; Anal. calcd for $C_{15}H_{14}N_2O_3S$: C 59.60, H 4.63, N, 9.27; found C 59.64, H 4.65, N 9.30%.

3-(4-Methoxyphenyl)-2H-1,2,4-benzothiadiazine 1,1-dioxide (**3g**): m.p. 322–323°C (lit[4]. 324°C); ^{1}H NMR (DMSO-d_6) δ: 7.10–8.19 (8H, m, ArH), 4.90 (1H, br s, NH); 3.85 (3H, s, OCH_3); IR (KBr) ν: 1280, 1160 cm^{-1}.

3-(3-Tolyl)-2H-1,2,4-benzothiadiazine 1,1-dioxide (**3h**): m.p. 271–273°C (lit[12]. 272°C); ^{1}H NMR (DMSO-d_6) δ: 7.40–8.19 (8H, m, ArH), 4.92 (1H, br s, NH); 2.33 (3H, s, CH_3); IR (KBr) ν: 1280, 1165 cm^{-1}.

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