A Convenient Synthesis of 2*H*-1,2,4-Benzothiadiazine 1,1-Dioxides from 2-Aminobenzenesulfonamide and Carboxylic Acids by using Polyphosphoric Acid Trimethylsilyl Ester as Condensing Agent

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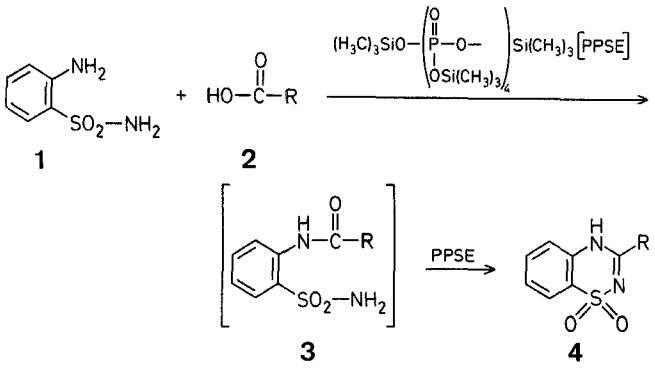
Although some attention has been focused on 2*H*-1,2,4-benzothiadiazine 1,1-dioxides **(4)** as antihypertensive and antimicrobial reagents[1,2], only a few synthetic methods for **4** have been developed. The cyclodehydration under basic conditions of isolated 2-(*N*-acylamino)-benzenesulfonamides **(3)**, which are synthesized by the reaction of 2-aminobenzenesulfonamides **(1)** with carboxylic acids **(2)**, has been commonly used for the synthesis of **4**[3,4]. In our previous paper, a facile one-pot synthesis of **4** from **1** and various aldehydes in the presence of sodium hydrogen sulfite was reported[5]. On the other hand, attempts to prepare **4** by the direct condensation of **1** with amidines at elevated temperature[6], and by the reaction of **1** and **2** by using polyphosphoric acid (PPA) as condensing agent[4] gave unsatisfactory results. In this communication we describe a high yield synthesis of the title compounds **4** by the direct condensation of **1** with **2** using polyphosphoric acid trimethylsilyl ester (PPSE).

Recently it has been reported that PPSE can be easily prepared from phosphorus pentoxide and hexamethyldisiloxane[7,8]. The unique properties of PPSE as a powerful but mild condensing agent compared to polyphosphoric acid or its ethyl ester were exemplified by the synthesis of heterocyclic compounds such as benzimidazoles[7]. The structure of PPSE was confirmed as a mixture of cyclotetraphosphate, isocyclotetraphosphate, and linear tetraphosphate[7]. For the sake of convenience only the linear structure is presented in the scheme.



Treatment of various carboxylic acids **2** with excess PPSE at 160°C gave a clear solution within several minutes. After the addition of compound **1**, the mixture was maintained at 160°C for 2 h. Work-up by pouring into ice/water afforded **4** as practically pure, yellow solids.

The reaction succeeds with a variety of carboxylic acids such as substituted benzoic acids as well as saturated and unsaturated aliphatic acids. It is significant that the low reactive *para*- and *meta*-nitrobenzoic acids and even the highly hindered pivalic acid can be used in this reaction (Table).

Although the mechanism of the present reaction is not clear in detail, amides **3** (or analogous forms like silylated **3**) can be assumed to be an intermediate for the ring closure reaction to **4**. For instance, when the reaction of **1** with benzoic acid **(2a)** was carried out in dichloroethane at 90°C for 2 h, the product was a mixture of **3a** and **4a**. In the case of the longer reaction time (5 h) under the same conditions, **3a** could not be isolated and **4a** was obtained in 74% yield.

This facile procedure should be applicable for other 2-aminobenzenesulfonamide derivatives leading to a variety of 2*H*-1,2,4-benzothiadiazine 1,1-dioxides.

3-Phenyl-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (4a); Typical Procedure:

Benzoic acid (305 mg, 2.5 mmol) is added at 160°C to PPSE which has been prepared just before use from phosphorus pentoxide (2.84 g, 20 mmol) and hexamethyldisiloxane (4.26 ml, 20 mmol)[7,8]. The mixture becomes clear within a few min. 2-Aminobenzenesulfonamide **1** (430 mg, 2.5 mmol) is added and the solution stirred for 2 h at 160°C. The cooled mixture is poured into ice/water (300 ml). The crude product is isolated as a pale yellow precipitate. Pure white needles are obtained by recrystallization from ethanol; yield: 541 mg (84%); m.p. 317°C (Lit.[5], m.p. 317°C).

I.R. (KBr): ν_{SO_2} = 1290, 1150 cm^{-1}.

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[1] A. Monzani, M. Di Bella, U. Fabio, G. Manicardi, *Farmaco, Ed. Sci.* **28**, 149 (1973); *C. A.* **78**, 111264 (1973).
[2] J. G. Topliss, M. D. Yudis, *J. Med. Chem.* **15**, 394 (1972).
[3] Y. Imai, H. Koga, *Nippon Kagaku Kaishi* **1973**, 1810; *C. A.* **79**, 126462 (1973).
[4] S. Tanimoto, N. Yoshida, T. Sugimoto, M. Okano, *Bull. Inst. Chem. Res., Kyoto Univ.* **57**, 381 (1979); *C. A.* **92**, 215403 (1980).
[5] Y. Imai, S. Sato, R. Takasawa, M. Ueda, *Synthesis* **1981**, 35.
[6] S. Tanimoto, S. Shimojo, R. Oda, *Yuki Gosei Kagaku Kyokaishi* **26**, 151 (1968); *C. A.* **69**, 36089 (1968).
[7] K. Yamanoto, H. Watamabe, *Chem. Lett.* **1982**, 1225.
[8] M. Yokoyama, S. Yoshida, T. Imamoto, *Synthesis* **1982**, 591. T. Imamoto, T. Matsumoto, T. Kusumoto, M. Yokoyama, *Synthesis* **1983**, 460.

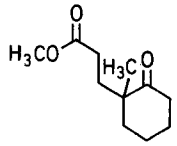
Table. 2*H*-1,2,4-Benzothiadiazine 1,1-Dioxides **(4)** prepared

Product No.	R	Yield [%]	m.p. [°C][b]	Lit. m.p. [°C] or Molecular formula[a]	I.R. (KBr) ν_{SO_2} [cm^{-1}]
4a	C_6H_5	84	317°	317°[5]	1290, 1150
4b	4-H_3C—C_6H_4	88	355°	355°[5]	1280, 1155
4c	4-H_3CO—C_6H_4	89	324°	324°[5]	1280, 1160
4d	4-Cl—C_6H_4	92	343°	340–342.5°[4]	1260, 1150
4e	4-O_2N—C_6H_4	93	389°	376–377.5°[4]	1280, 1160
4f	3-O_2N—C_6H_4	96	345°	333–334.5°[4]	1290, 1160
4g	H_3C—$(CH_2)_4$—	75	167–169°	142–144°[1]	1285, 1160
4h	C_6H_5—CH_2—CH_2—	89	236°	$C_{15}H_{14}N_2O_2S$ (286.3)	1280, 1150
4i	*c*-C_6H_{11}	87	285°	$C_{13}H_{16}N_2O_2S$ (264.3)	1280, 1150
4j	*t*-C_4H_9	52	258°	$C_{11}H_{14}N_2O_2S$ (238.3)	1280, 1135
4k	C_6H_5—CH=CH—	91	340°	322–324.5°	1260, 1155

[a] The microanalyses were in satisfactory agreement with the calculated values: C ±0.2, H ±0.35, N ±0.09.
[b] Determined by differential thermal analysis; except for **4g**.

J. K. Whitesell, M. A. Whitesell, *Synthesis* **1983** (7), 517–536:

Compound **14** (p. 521) should be named 3-methoxycarbonylmethyl-8a-methyl-5-methylene-2-oxo-6-(2,2-dimethylpropanoyloxy)-*trans*-decalin. The structure of compound **25** (p. 522) should be:



25

T. Kolasa, *Synthesis* **1983** (7), 539:

The heading for the 6th column in the Table should be (*Z*/*E*)-Ratio.

S. Kano, Y. Yuasa, T. Yokomatsu, S. Shibuya, *Synthesis* **1983** (7), 585–587:

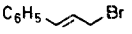
Compounds **5** should be named 3-oxo-2,3,4,5-tetrahydro-1*H*-azepino[4,3-*b*][1]benzothiophenes.

M. Sawada, Y. Furukawa, Y. Takai, T. Hanafusa, *Synthesis* **1983** (7), 593–595:

Compounds **4** and **5** should be named 2,4-dialkyl-1,3,6-trioxo-2,3,4,4a,5,6-hexahydro-1*H*-[1,3,5]triazino[1,2-*a*]quinolines and 1,3-dimethyl-2,4,8-trioxo-1,2,3,4,7,8-hexahydro-8a*H*-pyrido[1,2-*a*][1,3,5]triazine, respectively.

R. B. Cheikh, R. Chaabouni, A. Laurent, P. Mison, A. Nafti, *Synthesis* **1983** (9), 685–700:

The first substrate in Table 3 (p. 689) should be:



Y. Imai, A. Mochizuki, K. Kakimoto, *Synthesis* **1983** (10), 851:

The title compounds **4** should be named 4*H*-1,2,4-benzothiadiazine 1,1-dioxides.

R. Rastogi, S. Sharma, *Synthesis* **1983** (11); 861–882:

Compound **109** (p. 870) should be named: 7,12-dioxo-6,7-dihydro-12*H*-benzimidazo[1,2-*b*][2,4]benzodiazepine.

P. Kutschy, J. Imrich, J. Bernát, *Synthesis* **1983** (11), 929–931:

The title compounds **4** should be named 2-amino-4-oxo-4*H*-[1]benzothieno[2,3-*e*]-1,3-thiazines.

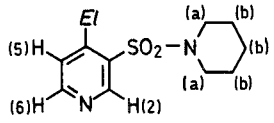
P. Breant, M. Marsais, G. Quéguiner, *Synthesis* **1983** (10), 822–824:

The following data should be added to the ^{1}H-N.M.R. spectra of compounds **3a–c** (p. 824):

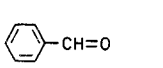
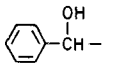
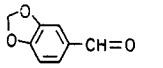
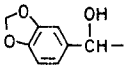
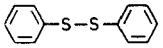
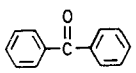
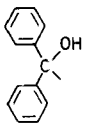
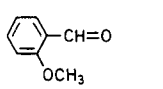
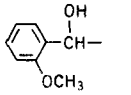
For compounds **3a–c**, $J_{H\text{-}4,H\text{-}5}$ = 8 Hz; $J_{H\text{-}5,H\text{-}6}$ = 5 Hz; $J_{H\text{-}4,H\text{-}6}$ = 2 Hz; $J_{H\text{-}4,H\text{-}2}$ = 2 Hz.

Tables 1 and 2 (p. 823) should be read as follows:

Table 1. 4-Substituted 3-Piperidinosulfonylpyridines prepared



5a, 7a-10a

Electrophile	*El*	Product	Yield [%]	m.p. [°C]	Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm][b]
		**5a**	80	127°	$C_{17}H_{18}N_2O_3S$ (330.4)	1.5 [m, 6 H(b)]; 3.1 [m, 4 H(a)]; 4.0 (m, OH); 5.3 (m, 1 H); 6.7 (m, 5 H); 7.53 (d, H-5); 8.63 (d, H-6); 8.93 (s, H-2)
		**7a**	60	80° (dec)	$C_{18}H_{18}N_2O_5S$ (374.4)	1.6 [m, 6 H(b)]; 3.2 [m, 4 H(a)]; 5.96 (s, 2 H); 6.63 (s, 1 H); 6.9 (m, 3 H); 7.50 (d, H-5); 8.86 (d, H-6); 8.93 (s, H-2)
$(H_3C)_3Si-Cl$	$(H_3C)_3Si-$	**8a**	42	<50°	$C_{13}H_{20}N_2O_2SSi$ (296.5)	0.50 (s, 9 H); 1.7 [m, 6 H(b)]; 3.2 [m, 4 H(a)]; 7.70 (d, H-5); 8.70 (d, H-6); 8.95 (s, H-2)
		**9a**	80	82°	$C_{16}H_{16}N_2O_2S_2$ (332.4)	1.7 [m, 6 H(b)]; 3.2 [m, 4 H(a)]; 6.70 (d, H-5); 7.56 (s, 5 H); 8.30 (d, H-6); 8.93 (s, H-2)
		**6a**	95	195°	$C_{23}H_{22}N_2O_3S$ (406.5)	1.5 [m, 6 H(b)]; 3.2 [m, 4 H(a)]; 6.70 (s, OH); 6.75 (d, H-5); 7.30 (s, 10 H); 8.51 (d, H-6); 9.06 (s, H-2)
		**10a**	53	164°	$C_{18}H_{20}N_2O_4S$ (360.4)	1.7 [m, 6 H(b)]; 3.2 [m, 4 H(a)]; 3.70 (s, 3 H); 4.2 (m, OH); 6.70 (s, 1 H); 7.15 (d, H-5); 7.5 (m, 4 H); 8.80 (d, H-6); 9.06 (s, H-2)
–	–	**12**	–	–	–[c]	1.7 [m, 6 H(b)]; 3.3 [m, 4 H(a)]; 4.6 (m, OH); 5.96 (d, 1 H, J = 3 Hz); 7.85 (d, H-5); 8.86 (d, H-6); 9.00 (s, H-2)
–	–	**13**	–	–	–[c]	1.7 [m, 6 H(b)]; 3.3 [m, 4 H(a)]; 5.83 (d, 1 H, J = 3 Hz); 7.60 (d, H-5); 8.83 (d, H-6); 9.13 (s, H-2)

[a] Satisfactory microanalyses obtained: C ±0.38, H ±0.32, N ±0.14; exception: **7**: C −0.70%.

[b] $J_{H\text{-}5,H\text{-}6}$ = 5 Hz for all products.

[c] See text.