Facile Syntheses of 2*H*-1,2,4-Benzothiadiazine 1,1-Dioxides and 4-Oxo-3,4-dihydroquinazolines from 2-Aminobenzenesulfonamide or 2-Aminobenzamide and Aldehydes in the Presence of Sodium Hydrogen Sulfite

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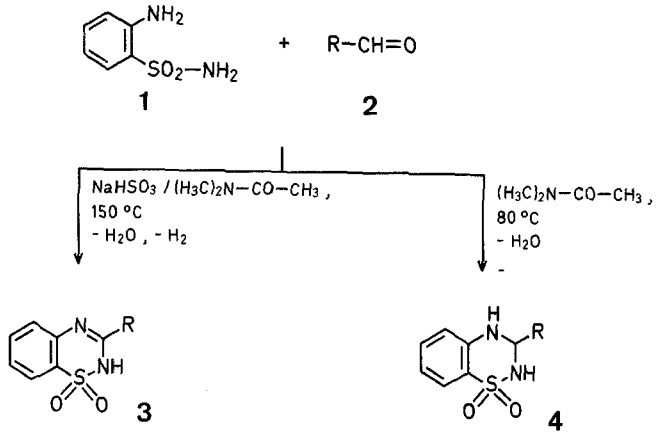
In previous papers[1,2], we reported on the chemistry and applications of 3-substituted 2*H*-1,2,4-benzothiadiazine 1,1-dioxides (**3**). Generally, such benzothiadiazine derivatives were synthesized either by the condensation of *o*-aminobenzenesulfonamide (**1**) with reactive carboxylic acid derivatives giving intermediate *o*-(*N*-acylamino)-benzenesulfonamides, followed by cyclodehydration[1,3], or by the direct cyclocondensation of **1** with amidines at an elevated temperature[4].

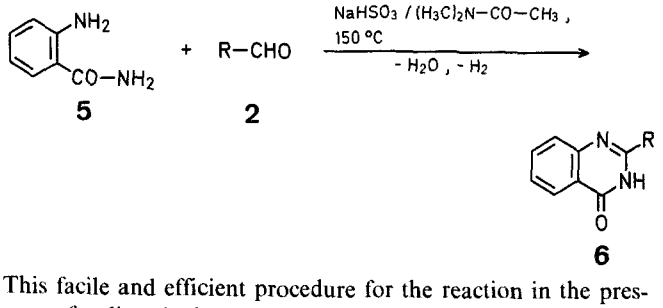
When aldehydes were employed as substrates in place of these carboxylic acid derivatives, the reaction products were not **3** but 3-substituted 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxides (**4**)[5,6]. Recently, it has been briefly shown that benzaldehyde-sodium hydrogen sulfite adduct condensed readily with *o*-phenylenediamine leading to 2-phenylbenzimidazole[7]. This information led us to the suggestion that use of aldehydes and sodium hydrogen sulfite would provide **3** by the reaction with **1**. We have now found a facile and efficient method for the synthesis of **3** by the reaction of **1** with various aldehydes (**2**) in the presence of sodium hydrogen sulfite.



The reaction leading to the formation of **3** was best carried out by heating a mixture of **1**, **2**, and sodium hydrogen sulfite (1.5 equivalent based on **2**) in dimethylacetamide at 150 °C for 2 h. The results of the reaction are summarized in Table 1. Various benzothiadiazine derivatives **3a–d** were obtained in high yields by the direct cyclodehydration-dehydrogenation of **1** with both aromatic and aliphatic aldehydes **2a–d**.

Further examination of the reaction conditions revealed effects of reaction temperature and amount of sodium hydrogen sulfite, as well as a solvent effect. The reaction at temperatures below 100 °C yielded a mixture of **3** and **4**, and the optimum reaction temperature was found to be 150 °C. Use of less than an equivalent of sodium hydrogen sulfite diminished the yield of **3** markedly. Therefore, a slight excess of sodium hydrogen sulfite might be necessary for the completion of the reaction. These observations suggest that sodium hydrogen sulfite plays an important role in the dehydrogenation of **4** to afford **3**. In fact, **4** was converted to **3** by treatment of **4** with sodium hydrogen sulfite at 150 °C. However, the mode of catalytic action of sodium hydrogen sulfite is not yet clearly known.

The reaction was then extended successfully to the synthesis of 2-substituted 4(3*H*)-quinazolinones (**6**). As shown in Table 2, a variety of quinazolinone derivatives **6a–e** was obtained readily in a similar manner to that described above from the direct cyclodehydration-dehydrogenation of *o*-aminobenzamide (**5**) with aldehydes **2** with the assistance of sodium hydrogen sulfite. Known methods for the preparation of **6** involve either the direct synthesis or the cyclodehydration of the isolated intermediate *o*-(*N*-acylamino)-benzamides, from *o*-aminobenzamides and various carboxylic acid derivatives[4,8,9,10].



This facile and efficient procedure for the reaction in the presence of sodium hydrogen sulfite should be applicable for a variety of aromatic and aliphatic aldehydes, leading to substituted 2*H*-1,2,4-benzothiadiazine 1,1-dioxides and 4(3*H*)-quinazolinones.

Table 1. 3-Substituted 2*H*-1,2,4-Benzothiadiazine 1,1-Dioxides **3a–d**

Product	R	Solvent[a]	Yield [%]	m.p. [°C]	Molecular formula[b]	I.R. (KBr) ν_{SO_2} [cm^{-1}]
3a	C_6H_5	DMAc	86	317°[c,d]	$C_{13}H_{10}N_2O_2S$ (258.3)	1290, 1150
		DMF	77			
		DMSO	59			
3b	4-H_3C—C_6H_4	DMAc	96	355°[c]	$C_{14}H_{12}N_2O_2S$ (272.3)	1280, 1155
3c	4-H_3CO—C_6H_4	DMAc	98	324°[c]	$C_{14}H_{12}N_2O_3S$ (288.3)	1280, 1160
		DMF	75			
		DMSO	57			
3d	*n*-C_6H_{13}	DMAc	80	144–145°[c]	$C_{13}H_{18}N_2O_2S$ (266.4)	1290, 1155

[a] DMAc = dimethylacetamide, DMF = dimethylformamide, DMSO = dimethyl sulfoxide.
[b] The microanalyses were in satisfactory agreement with the calculated values (C ±0.21, H ±0.26, N ±0.26).
[c] Determined by D.T.A. at a heating rate of 10 °C/min.
[d] Ref.[4], m.p. 302–303 °C.

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Table 2. 4(3*H*)-Quinazolinones **6a–e**

Product	R	Yield [%]	m.p. [°C] found	m.p. [°C] reported	Molecular formula[a]		I.R. (KBr) $\nu_{C=O}$ [cm^{-1}]
6a	C_6H_5	95	246°[b]	236°[10]	$C_{14}H_{10}N_2O$	(222.2)	1665
6b	4-H_3C—C_6H_4	67	252°[b]	241°[10]	$C_{15}H_{12}N_2O$	(236.3)	1660
6c	4-H_3CO—C_6H_4	95	253°[b]	247°[10]	$C_{15}H_{12}N_2O_2$	(252.3)	1660
6d	4-Cl—C_6H_4	94	318°[b]	306°[9]	$C_{14}H_9ClN_2O$	(256.7)	1670
6e	*n*-C_6H_{13}	97	149–151°	—	$C_{14}H_{18}N_2O$	(230.3)	1680

[a] The microanalyses were in satisfactory agreement with the calculated values (C ±0.21, H ±0.27, N ±0.26).
[b] Determined by D.T.A. at a heating rate of 10 °C/min.

3-(4-Tolyl)-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (3b); Typical Procedure:
Sodium hydrogen sulfite (0.390 g, 3.75 mmol) is added to a solution of *o*-aminobenzenesulfonamide (**1**; 0.430 g, 2.5 mmol) and *p*-tolualdehyde (**2b**; 0.300 g, 2.5 mmol) in dimethylacetamide (3 ml). The mixture is heated with stirring at 150 °C for 2 h and then poured into water (500 ml). A precipitate forms which is collected and dried; yield: 0.69 g (96%); m.p. 355 °C (recrystallized from ethanol).

$C_{14}H_{12}N_2O_2S$	calc.	C 61.75	H 4.44	N 10.29
(272.3)	found	61.7	4.7	10.2

M.S.: $m/e = 272$ (M^+).

I.R. (KBr): $\nu_{SO_2} = 1280, 1155$ cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): $\delta = 8.05–7.15$ (m, 8 H_{arom}); 2.48 ppm (s, 3 H, CH_3).

2-(4-Methoxyphenyl)-4(3*H*)-quinazolinone (6c); Typical Procedure:
A mixture of *o*-aminobenzamide (**5**; 0.340 g, 2.5 mmol), *p*-anisaldehyde (**2c**; 0.340 g, 2.5 mmol), and sodium hydrogen sulfite (0.390 g, 3.75 mmol) in dimethylacetamide (3 ml) is stirred at 150 °C for 2 h. The reaction mixture is worked up as described above to give **6c**; yield: 0.60 g (95%); m.p. 253 °C (recrystallized from benzene).

$C_{15}H_{12}N_2O_2$	calc.	C 71.43	H 4.79	N 11.10
(252.3)	found	71.4	5.0	10.9

M.S.: $m/e = 252$ (M^+).

I.R. (KBr): $\nu_{C=O} = 1660$ cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): $\delta = 8.30–6.75$ (m, 8 H_{arom}); 3.77 ppm (s, 3 H, CH_3).

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