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Preparation of 3-Aryl-2H-1,2,4-benzothiadiazine 1,1-Dioxides by the Reaction of *o*-Aminobenzenesulfonamide with Aromatic Carboxylic Acid Derivatives

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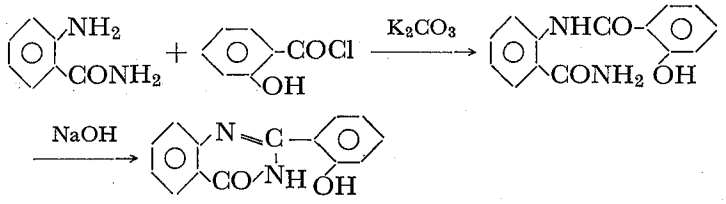
The reaction of *o*-aminobenzenesulfonamide with aromatic acyl chlorides in ether in the presence of K_2CO_3 afforded *o*-acylamidobenzamides (**1**), which were further cyclized by aqueous NaOH solution to 3-aryl-2H-1,2,4-benzothiadiazine 1,1-dioxides (**2**) in moderate to good yield. For the same purpose, the reaction of *o*-aminobenzenesulfonamide with aromatic carboxylic acids or their esters in polyphosphoric acid was also investigated.

KEY WORDS: Reaction of aromatic acyl chlorides/ Reaction of *o*-aminobenzenesulfonamide/ Synthesis of *o*-acylamidobenzenesulfonamides/ Reaction of benzoic acid/ Reaction of *p*-toluic acid/ Reaction of ethyl *p*-methylbenzoate/ Polyphosphoric acid/

The condensation reaction of *o*-aminobenzamide with aromatic acyl chlorides has been discussed in some detail.[1,2] When this reaction is carried out with an excess of K_2CO_3 in ether under reflux, *o*-acylamidobenzamide is obtained as a sole product. The compound is further cyclized by aqueous NaOH solution to 2-aryl-4(3H)-quinazolinone, which fluoresces strongly and exhibits good stability in u.v. light.[1]



To date, there has not been any information concerning the reaction of *o*-aminobenzenesulfonamide with aromatic acyl chlorides to give 3-aryl-2H-1,2,4-benzothiadiazine 1,1-dioxides (**2**) with the exception of 3-phenyl homologue (**2a**).[3,4] As *o*-aminobenzenesulfonamide bears a structural resemblance to *o*-aminobenzamide, it would be interesting to investigate the behavior of *o*-aminobenzenesulfonamide when similarly reacted with aromatic acyl chlorides.

First, the reaction of *o*-aminobenzenesulfonamide with benzoyl chloride in ether

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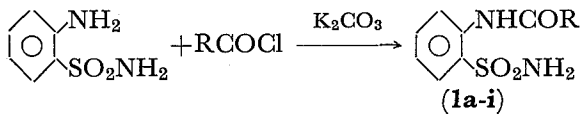
Table I. *o*-Acylamidobenzenesulfonamides (**1**)[a]

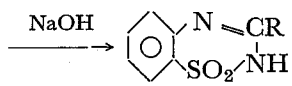
Abbreviation	Mp (°C) (lit.)	Yield[b] (%)	Formula	Found			Calcd.		
				C (%)	H (%)	N (%)	C (%)	H (%)	N (%)
1a	198–199 (198)[3]	74	$C_{13}H_{12}N_2O_3S$	56.80	4.36	10.17	56.51	4.38	10.14
1b	210–212	66	$C_{14}H_{14}N_2O_3S$	57.85	4.97	9.70	57.91	4.86	9.65
1c	162–164	63	$C_{14}H_{14}N_2O_3S$	57.70	4.90	9.66	57.91	4.86	9.65
1d	185–187	43	$C_{15}H_{14}N_2O_3S$	59.24	4.70	9.18	59.59	4.67	9.27
1e	199–201	58	$C_{17}H_{14}N_2O_3S$	62.29	4.36	8.32	62.56	4.32	8.58
1f	194–196	56	$C_{13}H_{11}N_3O_5S$	48.34	3.48	12.87	48.59	3.45	13.08
1g	191–192.5	63	$C_{13}H_{11}N_3O_5S$	48.82	3.49	12.97	48.59	3.45	13.08
1h[5]	203–204.5	64	$C_{13}H_{11}ClN_2O_3S$	49.99	3.61	8.96	50.25	3.57	9.02
1i[5]	172–174	70	$C_{13}H_{11}ClN_2O_3S$	50.23	3.66	8.90	50.25	3.57	9.02

a) All spectral data (nmr, ir, and mass spectral) of the isolated products were consistent with the assigned structures. b) Yield was based upon *o*-aminobenzenesulfonamide, and was of the isolated product.

in the presence of K_2CO_3 was investigated. But with K_2CO_3 no ring-closure was observed. A 74% yield of N-(2-sulfamoylphenyl)benzamide (**1a**) was obtained. The yield decreased to 45% in the absence of K_2CO_3 under the same conditions covering the same period of time. In addition to benzoyl chloride, eight aromatic acyl chlorides were chosen and submitted to the condensation reaction under the same conditions. The results are given in Table I.



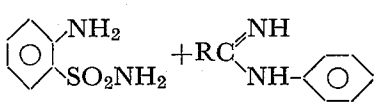
(**1a-i**)



(**2a-i**)

a: R=C_6H_5, **b**: R=*p*-$CH_3C_6H_4$, **c**: R=*m*-$CH_3C_6H_4$,
d: R=C_6H_5CH=CH, **e**: R=2-$C_{10}H_7$, **f**: R=*p*-$NO_2C_6H_4$,
g: R=*m*-$NO_2C_6H_4$, **h**: R=*p*-ClC_6H_4, **i**: R=*o*-ClC_6H_4

It has already been reported that in case where the ring closure of **1a** is desired the use of aqueous NaOH solution,[3,4] γ-picoline[4] or thionyl chloride[4] is efficient. However, these works are chiefly concerned with **1a**. Our experimental procedure was to reflux **1** in aqueous 5% NaOH solution for 3 hr with stirring. Thus, it was possible to prepare a series of high-melting **2** in moderate to good yield. The properties of the obtained products are given in Table II. Some of these compounds have also been prepared by treatment of *o*-aminobenzenesulfonamide with N-phenylamidines at 200–220°C.[6]



2a,**2b**, **2c**, or **2e**

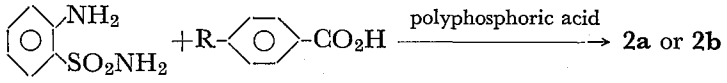
R=C_6H_5, *p*-$CH_3C_6H_4$, *m*-$CH_3C_6H_4$ or 2-$C_{10}H_7$

Table II. 3-Aryl-2H-1,2,4-benzothiadiazine 1,1-Dioxides (2)[a]

Abbreviation	Mp (°C) (lit.)	Yield[b] (%)	Formula	Found			Calcd.		
				C (%)	H (%)	N (%)	C (%)	H (%)	N (%)
2a	297–298.5 (302–303)[6]	77	$C_{13}H_{10}N_2O_2S$	60.36	3.81	10.88	60.45	3.90	10.85
2b	334–336.5 (340–342)[6]	90	$C_{14}H_{12}N_2O_2S$	61.65	4.45	10.34	61.74	4.44	10.29
2c	268–269.5 (272–274.5)[6]	86	$C_{14}H_{12}N_2O_2S$	61.75	4.27	10.28	61.74	4.44	10.29
2d	322–324.5	98	$C_{15}H_{12}N_2O_2S$	63.09	4.34	9.83	63.36	4.25	9.85
2e[c]	325–327.5 (331.5–333.5)[6]	89	$C_{17}H_{12}N_2O_2S$	66.04	3.95	9.16	66.21	3.92	9.09
2f[7]	376–377.5	74	$C_{13}H_9N_3O_4S$	51.25	3.15	13.74	51.48	2.99	13.86
2g	333–334.5	98	$C_{13}H_9N_3O_4S$	51.30	2.96	13.60	51.48	2.99	13.86
2h[8]	340–342.5	88	$C_{13}H_9ClN_2O_2S$	53.44	3.14	9.48	53.33	3.10	9.57
2i	208–209	74	$C_{13}H_9ClN_2O_2S$	53.52	3.12	9.52	53.33	3.10	9.57

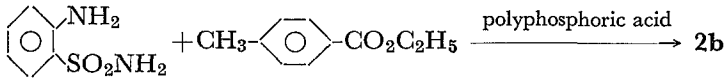
a) All spectral data (nmr, ir, and mass spectral) of the isolated products were consistent with the assigned structures. b) Represents isolated yield. c) Among the obtained products, 3-(2-naphthyl)-2H-1,2,4-benzothiadiazine 1,1-dioxide (**2e**) exhibits the strongest fluorescence.

Next, we found a new one-step process for the preparation of **2**, in which a mixture of *o*-aminobenzenesulfonamide and an aromatic carboxylic acid (or its ester) was heated in 105% polyphosphoric acid, *i.e.*, 3-phenyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (**2a**) was prepared (33% yield) by heating a mixture of *o*-aminobenzenesulfonamide and benzoic acid in 105% polyphosphoric acid at 90–100°C for 3 hr. In the similar manner 3-(*p*-tolyl)-2H-1,2,4-benzothiadiazine 1,1-dioxide (**2b**) was prepared (22% yield) from *p*-toluic acid. The reaction was also applied to the preparations of 3-(1-naphthyl)- and 3-(*p*-chlorophenyl)-2H-1,2,4-benzothiadiazine 1,1-dioxide (**2h**), but the yields were extremely low.



R=H, or CH_3

When was similarly reacted (90–100°C, 3 hr) ethyl *p*-methylbenzoate in place of the carboxylic acid in 105% polyphosphoric acid, **2b** was also obtained (24% yield), whereas the method failed in the reaction with ethyl *m*-nitrobenzoate.



EXPERIMENTAL

Illustrative examples of the reactions will be given below.

Reaction of o-Aminobenzenesulfonamide with Benzoyl Chloride. A solution of *o*-aminobenzenesulfonamide (3.44 g, 20 mmol) and benzoyl chloride (3.09

g, 22 mmol) in ether (80 ml) was placed in a 200 ml three-necked flask equipped with a reflux condenser, thermometer, and magnetic stirrer. Finely powdered K_2CO_3 (4.15 g, 30 mmol) was slowly added with efficient stirring at room temperature to the solution. The reaction mixture was refluxed for 2 hr and then chilled in an ice bath. The solid was collected, washed carefully with a small amount of ether then with three 50 ml portions of water, and dried. The crude product was recrystallized from the least possible amount of acetone. Yield 4.10 g (74%).

Ring Closure of 4-Methyl-N-(2-sulfamoylphenyl)benzamide (1b). **1b** (3.80 g, 13.1 mmol) was added to ca. 100 g of aqueous 5% NaOH solution, and the mixture was heated under reflux for 3 hr with stirring. The clear faintly colored solution was cooled to room temperature, and 10 ml of acetic acid was added dropwise with stirring. The resulting precipitate was filtered with suction, then washed successively with three 50 ml portions of water, a small amount of acetone, and ether. This product was further purified by recrystallization from ethanol. Yield 3.21 g (90%).

Reaction of o-Aminobenzenesulfonamide with Benzoic Acid in 105% Polyphosphoric Acid. *o*-aminobenzenesulfonamide (3.44 g, 20 mmol) and benzoic acid (2.56 g, 21 mmol) were added to 105% polyphosphoric acid (ca. 50 ml) in a 100 ml three-necked flask, fitted with a reflux condenser, a thermometer, and a stirrer. The mixture was heated at 90–100°C for 3 hr with stirring, then poured into 200 ml of water. The resulting precipitate was collected, then washed successively with water, a small amount of acetone, and ether. The product was recrystallized from ethanol. Yield 1.70 g (33%).

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