Synthesis of 2*H*-1,3-Benzothiazine Derivatives via Modified Ritter Reaction

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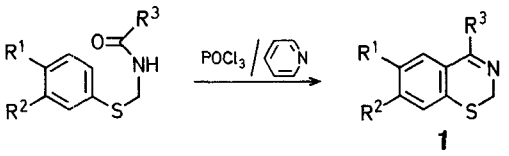
The pharmacological activities[1-9] (antiinflammatory, analgesic, psychotropic, antibacterial) of 1,2-, 1,3-, and 1,4-benzothiazine derivatives have arosed interest in the synthesis of 2*H*-1,3-benzothiazines (**1**). The known method[10,11,12] for their synthesis (Scheme **A**) cannot be applied to the products **1** where $R^1 = R^2 = H$. T.L.C. analysis of the reaction mixture revealed a number of spots, none of which, however, corresponded to the desired cyclized product. The only product identified was diphenyl disulfide along with some unreacted starting material.



$R^1, R^2 \neq H$ **1**

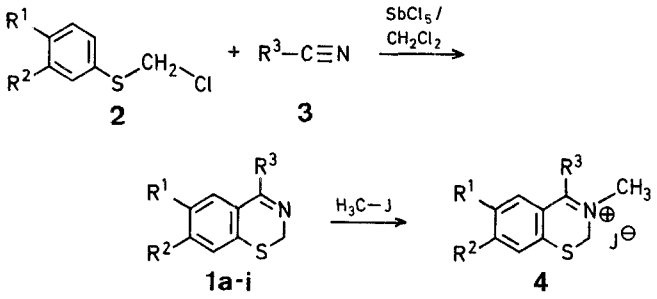
Scheme **A**

We have now developed a general method for the synthesis of compounds **1** where R^1, $R^2 = H$ or R^1, $R^2 \neq H$ using a modified Ritter reaction[13-16] (Scheme **B**). Thus, treatment of a chloromethyl aryl sulfide **2** with a nitrile **3** in the presence of a Lewis acid such as antimony pentachloride led to the formation of the desired products **1** in fair yields (Table).

Table. 2*H*-1,3-Benzothiazines **1a–i** prepared

Product No.	R^1	R^2	R^3	Reaction Conditions temperature/ time	Yield [%]	M.S. *m/e* (M^+)	I.R. $\nu_{C=N}$ [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	*N*-Methiodide **4** Yield [%]	m.p. [°C]	Molecular formula[a]
1a	H	H	CH_3	1. 0 °C/ 3 h 2. 30 °C/15 h	57	163	1600	2.26 (s, 3 H); 4.33 (s, 2 H); 7.1 (m, 4 H)	77	204–206°	$C_{10}H_{12}JNS$ (305.2)
1b	CH_3	H	CH_3	1. 0 °C/ 3 h 2. 30 °C/15 h	48	177	1635	2.33 (s, 6 H); 4.40 (s, 2 H); 7.1 (m, 3 H)	73	175–176°	$C_{11}H_{14}JNS$ (319.2)
1c	CH_3	H	4-H_3C—C_6H_4	0 °C/8 h	32	253	1590	2.25 (s, 3 H); 2.40 (s, 3 H); 4.55 (s, 2 H); 7.2 (m, 7 H)	70	228–230°	$C_{17}H_{18}JNS$ (395.3)
1d	CH_3	H	4-H_3CO—C_6H_4	0 °C/8 h	27	269	1610	2.20 (s, 3 H); 3.66 (s, 3 H); 4.43 (s, 2 H); 7.0 (m, 7 H)	70	192–193°	$C_{17}H_{18}JNOS$ (411.3)
1e	H	H	C_6H_5	0 °C/5 h	19	225	1610	4.50 (s, 2 H); 7.3 (m, 9 H)	63	194–196°	$C_{15}H_{14}JNS$ (367.3)
1f	CH_3	H	C_6H_5	0 °C/6 h	21	239	1600	2.16 (s, 3 H); 4.55 (s, 2 H); 7.3 (m, 8 H)	80	207–210°	$C_{16}H_{16}JNS$ (381.3)
1g	H	H	$C_6H_5CH_2$	1. 0 °C/ 3 h 2. 30 °C/ 3 h	19	239	1630	3.95 (s, 2 H); 4.60 (s, 2 H); 7.1 (m, 9 H)	75	180–181°	$C_{16}H_{16}JNS$ (381.3)
1h	CH_3	H	$C_6H_5CH_2$	1. 0 °C/ 3 h 2. 30 °C/ 2 h	20	253	1610	2.13 (s, 3 H); 3.84 (s, 2 H); 4.37 (s, 2 H); 7.0 (m, 8 H)	69	176–178°	$C_{17}H_{18}JNS$ (395.3)
1i	H	CH_3	CH_3	1. 0 °C/ 3 h 2. 30 °C/15 h	37	177	1635	2.33 (s, 6 H); 4.43 (s, 2 H); 7.1 (m, 3 H)	78	149–150°	$C_{11}H_{14}JNS$ (319.2)

[a] Satisfactory microanalyses obtained: C ±0.05, H ±0.07, N ±0.29, J ±0.35, S ±0.37.
The I.R. and ^{1}H-N.M.R. spectra were in accord with the proposed structures.



Scheme **B**

The order of mixing of the reactants plays an important role in the success of the synthesis. Thus, addition of an equimolar amount of antimony pentachloride to a nitrile **3** in dry dichloromethane followed by the addition of an equimolar amount of chloromethyl aryl sulfide **2** gave the best results (Table). On the other hand, addition of nitrile **3** to a mixture of antimony pentachloride and chloromethyl aryl sulfide **2** gave no or poor yields of the products.

The generally thick, oily products **1** were purified by column chromatography and characterized by spectral means and by conversion to the crystalline *N*-methiodide derivatives **4**.

2*H*-1,3-Benzothiazenes 1a–i; General Procedure:
To a stirred solution of nitrile **3** (0.01 mol) in dry dichloromethane (10 ml), a solution of antimony pentachloride (2.995 g, 1.4 ml, 0.01 mol) in dichloromethane (5 ml) is added dropwise during 10 min at 0 °C under a nitrogen atmosphere. After 3 h stirring, a solution of chloromethyl aryl sulfide **2** (0.01 mol) in dichloromethane (10 ml) is added dropwise during 30 min at 0 °C, stirring is continued for 3–8 h at 0 °C and in some cases (Table) stirring is additionally continued at 30 °C for 2–15 h. The reaction mixture is then poured into ice (20 g), neutralized with 20% aqueous sodium hydroxide solution (~10 ml) and extracted with benzene or ether (4 × 20 ml). The organic layer is then extracted with 20% aqueous hydrochloric acid (3 × 20 ml). The aqueous layer so obtained is thoroughly washed with benzene or ether (4 × 20 ml), cooled to 0 °C, neutralized with 20% aqueous sodium hydroxide (~40 ml), and extracted with benzene or ether (5 × 20 ml). The organic phase is separated, washed with water (3 × 15 ml) and brine (15 ml) and dried with anhydrous sodium sulfate. Removal of solvent under vacuum at low temperature gives a crude product which is purified by column chromatography over silica gel with benzene/ethyl acetate (90 : 10) as eluent to yield pure the 2*H*-1,3-benzothiazine **1** (Table).

***N*-Methiodides 4 of 2*H*-1,3-Benzothiazines 1; General Procedure:**
The 2*H*-1,3-benzothiazine **1** (500 mg) is stirred with an excess of methyl iodide (3 ml) for 18 h at room temperature during which time crystals of the *N*-methiodide derivative **4** separate out. The crystals are collected by filtration, washed with dry ether, and recrystallized from methanol/ether to give the pure *N*-methiodide **4** (Table).

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