1,4-Benzothiazine Derivatives from 2-Aminobenzenethiol and Hydrazonoyl Halides

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2-Aminobenzenethiol was condensed with alkyl α-chlorophenylhydrazonoglyoxylates yielding alkyl 2-(2-aminophenylthio)-2-arylhydrazonoglyoxylates which were cyclized to the corresponding 2-arylhydrazono-2,3-dihydro-4*H*-1,4-benzothiazin-3-ones. Starting from α-chloro-α-arylhydrazonoacetones the corresponding 2-arylhydrazono-3-methylbenzo-1,4-benzothiazines were formed.

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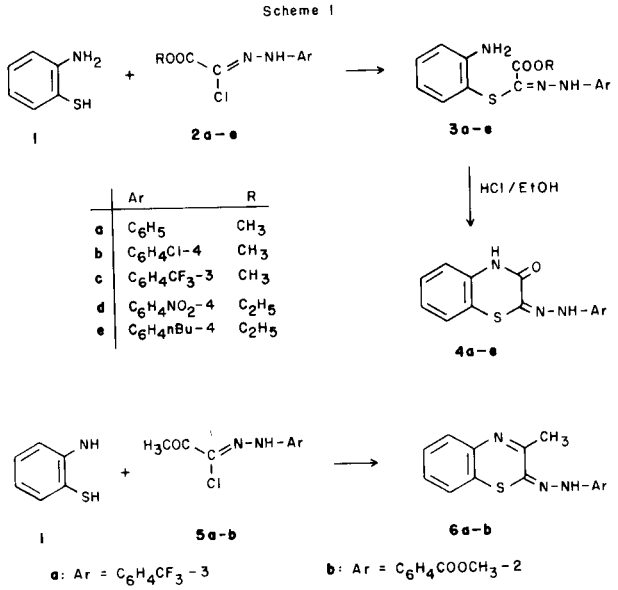
Hydrazonoyl halides have been largely employed as an exceedingly useful tool for the synthesis of heterocyclic compounds, both through condensation reactions and as precursors of nitrile imines, which can undergo cycloaddition with several dipolarophiles [1].

In this work we report a new synthesis of potentially herbicidal benzothiazine derivatives, which have been developed starting from *o*-aminobenzenethiol and readily accessible hydrazonoyl halides.

o-Aminobenzenethiol was easily condensed with compounds **2** and **5** in presence of a base as hydrogen chloride acceptor in a suitable solvent (Scheme 1). The following conditions were examined: (i) potassium hydroxide in ethanol, (ii) potassium carbonate in acetonitrile and (iii) triethyl amine in acetonitrile.

Scheme I



1 **2a-e** **3a-e**

	Ar	R
a	C_6H_5	CH_3
b	C_6H_4Cl-4	CH_3
c	$C_6H_4CF_3$-3	CH_3
d	$C_6H_4NO_2$-4	C_2H_5
e	C_6H_4nBu-4	C_2H_5

4a-e

1 **5a-b** **6a-b**

a: Ar = $C_6H_4CF_3$-3 b: Ar = $C_6H_4COOCH_3$-2

Starting with the glyoxylate derivatives **2a-e** and operating according to method (ii) or, preferably, (iii), the products of nucleophilic substitution were easily isolated by recrystallization of the crude reaction material.

The intermediates **3a-e** were readily identified through their ir spectra (NH stretching in the 3420-3280 region and CO stretching in the 1675-1720 region).

The cyclization of the intermediates **3a-e** was obtained by treating the substrates with (i) hydrogen chloride in ethanol solution, (ii) *p*-toluenesulfonic acid in ethanol solution, (iii) sodium methoxide in methanol.

Method (ii) yielded the best results. The cyclization products **4a-e** were identified as 2-(arylhydrazono)-2,3-dihydro-1,4-benzothiazin-3-ones on the basis of their analytical and spectroscopic data. In the ir spectrum the carbonyl group is associated with a band at 1650 cm^{-1} and in the ^1H-nmr spectrum the NH resonances are found in the 9.5-11.2 range.

Starting from the chloroacetone derivatives **5a,b**, no open-chain intermediates could be isolated. Instead, the 2-(arylhydrazono)-3-methyl-2*H*-1,4-benzothiazines **6a,b** were formed in excellent yield. Compounds **6a,b** are characterized by a 3151 cm^{-1} band (ν NH) in the ir spectrum. In the ^1H-nmr spectrum a singlet at δ 2.55-2.58 is associated with the 3-methyl substituent.

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded with a Beckman Acculab-4 spectrophotometer (nujol mull). The ^1H-nmr spectra were obtained on a Varian 360-A spectrometer. Values are expressed relative to TMS as internal standard. Column chromatography was run on silica gel and for tlc silica gel plates were used with ethyl acetate-benzene mixtures as eluent.

The hydrazonyl halides were prepared by a standard procedure [2] through coupling of diazotized arylamines and methyl 2-chloroacetate or 3-chloro-2,4-pentanedione respectively.

Methyl 2-(2-Aminophenylthio)-2-(arylhydrazono)glyoxylates (**3a-e**).

The hydrazonoyl halides **2a-e** (10 mmoles) were dissolved in the minimum amount of anhydrous acetonitrile. *o*-Aminobenzenethiol (10 mmoles) was then added, followed by anhydrous triethylamine (10 mmoles). The reaction mixture was stirred overnight at room temperature and then evaporated. The residue was partitioned between water and dichloromethane or chloroform. The organic layer was dried over sodium sulphate and evaporated. The residue was crystallized yielding pure products **3a-e**.

Table I

Compound	Mp (°C)	Recrystallization Solvent	Yield (%)	Formula	Required %/Found % C	H	N	IR (cm^{-1}) (NH)	(CO)	^{1}H-NMR [a,b] δ, NH
3a	121	Methanol	51	$C_{15}H_{15}N_3O_2S$	59.8	13.95	5.0	3400-3320	1705	4.55 (2H)
					59.75	14.0	5.15			9.45 (1H)
3b	143	Ethanol	43	$C_{15}H_{14}ClN_3O_2S$	53.65	4.15	12.5	3400-3300	1705	4.50 (2H)
					53.4	4.3	12.4			9.4 (1H)
3c	95	*iso*-Propyl ether	63	$C_{16}H_{14}F_3N_3O_2S$	52.0	11.45	3.85	3400-3300	1675	4.52 (2H)
					52.05	11.45	3.85			9.50 (1H)
3d	137	*iso*-Propyl ether	72	$C_{15}H_{14}N_4O_4S$	53.32	4.47	15.55	3400-3280	1720	4.52 (2H)
					53.15	4.67	15.45			8.58 (1H)
3e	64	*n*-Pentane	32	$C_{19}H_{23}N_3O_2S$	64.65	11.3	6.8	3420-3300	1680	4.85 (2H) [c]
					64.3	11.15	6.85			9.58 (1H)
4a	277	Methanol	73	$C_{14}H_{11}N_3OS$	62.45	15.05	4.1	—	1650	9.64 (1H) [d]
					62.4	15.3	4.3			10.8 (1H)
4b	261-262	Ethanol	28	$C_{14}H_{10}ClN_3OS$	55.35	3.3	13.85	—	1650	9.95 (1H)
					55.45	3.35	14.05			11.07 (1H)
4c	261	Ethanol	91	$C_{15}H_{10}F_3N_3OS$	53.45	12.45	3.0	—	1650	10.20 (1H)
					53.55	12.3	2.85			11.20 (1H)
4d	302-304	Ethanol	83	$C_{14}H_{10}N_4O_3S$	53.5	3.2	17.8	—	1650	10.4 (1H) [d]
					53.15	3.3	17.5			11.18 (1H)
4e	185	Methanol	62	$C_{18}H_{19}N_3OS$	66.45	5.9	12.9	—	1650	9.48 (1H) [d]
					66.05	5.8	12.7			10.75 (1H)
6a	138	Dichloromethane	97	$C_{16}H_{12}F_3N_3S$	57.3	12.55	3.6	3151	—	2.55 (3H) [e]
					57.25	12.5	3.55			10.25 (1H)
6b	183	2-Propanol	78	$C_{17}H_{15}N_3O_2S$	62.75	12.9	4.65	3151	1680	2.58 (3H) [e]
					62.6	12.8	4.8			10.78 (1H)

[a] Deuteriochloroform or other solvent indicated. [b] All NH signals slowly exchangeable. [c] Deuteriochloroform-DMSO-d_6. [d] DMSO-d_6. [e] Methyl singlet.

Methyl 2-(2-Aminophenylthio)-2-(4-chlorophenylhydrazono)glyoxylate (**3b**).

The method described above for the preparation of compounds **3a-e** was followed using potassium carbonate as hydrogen chloride acceptor. The product was isolated as described above.

2-(Arylhydrazono)-2,3-dihydro-4*H*-1,4-benzothiazinones **4a-e**.

The open-chain precursors **3a-e** were dissolved in the minimum amount of ethanol, which had been previously saturated with anhydrous hydrogen chloride. Alternatively an equimolecular amount of *p*-toluenesulfonic acid was added to the solution of the starting compound. The ethanol solution was refluxed until complete cyclization (tlc). Then the solvent was evaporated, the residue taken up with water and neutralized with sodium hydrogen carbonate solution. The product was extracted with diethyl ether and purified by recrystallization.

2-(4-Chlorophenylhydrazono)-2,3-dihydro-4*H*-1,4-benzothiazin-3-one (**4b**).

Method *a*.

Potassium hydroxide pellets (20 mmoles) were dissolved in ethanol (100 ml). To this solution 2-aminobenzenethiol (20 mmoles) and methyl 2-chloro-2-(4-chlorophenylhydrazono)glyoxylate (20 mmoles) dissolved in the minimum amount of ethanol were added and the reaction mixture was refluxed until disappearance of the starting compounds (tlc). The solvent was then evaporated and the residue was partitioned between water and ethyl acetate. The organic layer was recrystallized yielding pure **4b**.

Method *b*.

Methyl 2-(2-aminophenylthio)-2-(4-chlorophenylhydrazono)glyoxylate **3b** (0.6 mmole) was added to sodium methoxide (0.6 mmole) in methanol (10 ml). The reaction mixture was heated on a water bath until complete cyclization (tlc). The product was isolated through evaporation and partitioning between water and ethyl acetate as described for method *a*.

2-Arylhydrazono-3-methyl-2*H*-1,4-benzothiazines **6a,b**.

The α-arylhydrazono-α-chloroacetones **5a,b** (3.7 mmoles) were reacted with *o*-aminobenzenethiol (3.7 mmoles) in anhydrous acetonitrile (minimum amount), in the presence of triethylamine (3.7 mmoles). The reaction mixture was stirred for two hours and then evaporated. The residue was diluted with water and extracted with dichloromethane. The organic layer was dried over sodium sulphate and then evaporated, leaving practically pure products **6a,b**, which were purified further by recrystallization.

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