Synthesis of 2-substituted 6-bromo-4*H*-benzo[*d*]-1,3-thiazines by the reaction of 2-bromomethyl-4-bromophenyl isothiocyanate with *N*- and *O*-nucleophiles

P. KRISTIAN, J. GONDA, and M. BEITHE

Department of Organic Chemistry and Biochemistry, Faculty of Natural Sciences, P. J. Šafárik University, CS-041 67 Košice

Received 19 June 1986

Dedicated to Professor Ing. J. Kováč, DrSc., in honour of his 60th birthday

The reactions of 2-bromomethyl-4-bromophenyl isothiocyanate (prepared by radical bromination of 2-methyl-4-bromophenyl isothiocyanate with *N*-bromosuccinimide) with amines and sodium phenolate proceed on the NCS group under formation of unstable addition products which, at the reaction conditions, cyclize to the respective 4*H*-benzo[*d*]-1,3-thiazines. The structures of the synthesized compounds were proved by spectral methods.

Реакции 2-бромметил-4-бромфенилизотиоцианата (полученного путем радикального бромирования 2-метил-4-бромфенилизотиоцианата *N*-бромсукцинимидом) с аминами и фенолятом натрия проходят по NCS группе и ведут к образованию нестабильных продуктов присоединения, циклизующихся в условиях реакции в соответствующие 4*H*-бензо[*d*]-1,3-тиазины. Строение синтезированных соединений было доказано с помощью спектральных методов.

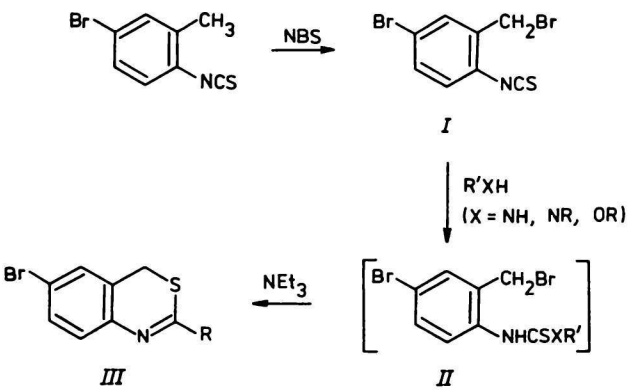
Synthetic utilization of isothiocyanates with reactive halogen is based on different reactivity of both centres against nucleophiles. In majority of cases nucleophilic reactions proceed on the NCS group much more rapidly than nucleophilic substitution, even in the case of a very reactive halogen. Intermediates of these reactions cyclize through the more nucleophilic atom of the formed ambident anion, which is most frequently sulfur. This principle was utilized in synthesis of 2-thiazolines [1, 2], 5,6-dihydro-4*H*-1,3-thiazines [3], thiazolidine-2-thiones [4], thiazoles [5], pyridothiazines [6], and pyridothiouracils [7].

In our previous work [8] we dealt with synthesis and study of reactions of 2-bromomethylphenyl isothiocyanate from the view-point of finding the selectivity of its both reaction centres (bromine and NCS group) against nucleophilic reagents.

In this work we have focused on the study of reactions of 2-bromo-4-bromophenyl isothiocyanate *I* with the possibility of obtaining 6-bromo-substituted 4*H*-benzo[*d*]-1,3-thiazines as potential psychopharmaceutics.

Of the mentioned type of compounds 2-ethylamino-4-methyl-4-phenyl-6--chloro-4*H*-benzo[*d*]-1,3-thiazine [9] showed neuroleptic activity, while 2--methylthio-4-phenyl-6-chloro-4*H*-benzo[*d*]-1,3-thiazine was characterized as tranquillizer [10].

2-Bromomethyl-4-bromophenyl isothiocyanate *I* was prepared in 52 % yield by radical bromination of 4-bromo-2-methylphenyl isothiocyanate with *N*-bromosuccinimide initiated by dibenzoyl peroxide (Scheme 1).



For R see Table 1.

Scheme 1

The presence of the absorption band ν_{as}(NCS) at $\tilde{\nu} = 2070\,cm^{-1}$ was characteristic of the IR spectrum of *I*. In the ^1H NMR spectrum a singlet of the methylene group appeared at $\delta = 4.42$ ppm. The signals of aromatic protons occurred in the region of $\delta = 6.95$—7.65 ppm. We accomplished series of reactions of *I* with aromatic and aliphatic primary and secondary amines. The reactions started by attack of amines on carbon of the NCS group and resulted in the corresponding thioureas, which we failed to isolate. These, in the presence of triethylamine, cyclized to 2-substituted 6-bromo-4*H*-benzo[*d*]-1,3-thiazines *III* (Scheme 1; Table 1). The IR spectra of these compounds showed absorption bands at $\tilde{\nu} = 3380$—$3440\,cm^{-1}$ and $\tilde{\nu} = 1560$—$1620\,cm^{-1}$ belonging to vibrations of NH groups and C=N bonds, respectively. In the ^1H NMR spectra a singlet of the methylene group was observed at $\delta = 3.76$—3.88 ppm. The signals of aromatic protons appeared in the region of $\delta = 6.52$—8.00 ppm (Table 2). The role of triethylamine lies in binding hydrogen bromide released during cyclization.

Table 1

Characteristic of 2-R-6-bromo-4*H*-benzo[*d*]-1,3-thiazines

Compound	R	Formula	M_r	w_i(calc.)/% w_i(found)/%			Yield	M.p.	Solvent
				C	H	N	%	°C	
IIIa		$C_{12}H_{13}BrN_2OS$	313.2	46.02 46.08	4.18 4.22	8.94 8.83	90	110—113	$CHCl_3$—hexane
IIIb	—$NHCH_2CH_3$	$C_{10}H_{11}BrN_2S$	271.2	44.29 44.33	4.09 4.16	10.33 10.38	82	81	Heptane—PE
IIIc	—$NHCH_2CH(CH_3)_2$	$C_{12}H_{15}BrN_2S$	299.2	48.17 48.21	5.05 5.02	9.36 9.27	80	51	Hexane
IIId	—$NHCH_2CH_2CH_2CH_3$	$C_{12}H_{15}BrN_2S$	299.2	48.17 48.31	5.05 5.12	9.36 9.27	69	66—68	Hexane
IIIe	—$NHCH_2C_6H_5$	$C_{15}H_{13}BrN_2S$	333.2	54.06 53.99	3.93 3.97	8.41 8.42	87	103—106	$CHCl_3$—PE
IIIf	—NHC_6H_4—4-CH_3	$C_{15}H_{13}BrN_2S$	333.2	54.06 54.02	3.93 3.98	8.41 8.54	74	188—191	$CHCl_3$—PE
IIIg	—NHC_6H_5	$C_{14}H_{11}BrN_2S$	319.2	52.68 52.72	3.47 3.54	8.78 8.63	85	219—221	$CHCl_3$—PE

Table 1 (Continued)

Compound	R	Formula	M_r	w_i(calc.)/% w_i(found)/%			Yield	M.p.	Solvent
				C	H	N	%	°C	
IIIh	—NHC_6H_4—4-OCH_3	$C_{15}H_{13}BrN_2OS$	349.2	51.59 51.63	3.75 3.71	8.02 8.01	77	201—202	$CHCl_3$—PE
IIIi	—NH—1-naphthyl	$C_{18}H_{13}BrN_2S$	369.3	58.55 58.68	3.55 3.62	7.59 7.49	64	158—161	$CHCl_3$—PE
IIIj	—NH—2-naphthyl	$C_{18}H_{13}BrN_2S$	369.3	58.55 58.59	3.55 3.67	7.59 7.52	67	187—190	$CHCl_3$—PE
IIIk	—O—C_6H_5	$C_{14}H_{10}BrNOS$	320.2	52.51 52.43	3.15 3.11	4.37 4.41	47	71—74	$CHCl_3$—PE

PE = petroleum ether.

Table 2

Spectral data for 2-substituted 6-bromo-4*H*-benzo[*d*]-1,3-thiazines

Compound	^{1}H NMR, δ_i/ppm				IR, $\tilde{\nu}_i$/cm^{-1}	
	NH	Ar—H	CH_2	Other protons	ν(N=C)	ν(N—H)
IIIa[a]	—	6.82—7.5	3.81	3.76 s (CH_2)	1595	—
IIIb[a]	4.44	6.85—7.3	3.79	3.52 q (CH_2) 1.2 t (CH_3)	1595	3415
IIIc[a]	4.28	6.8 —7.4	3.78	3.29 d (CH_2N) 1.85 m (CH)	1595	3420
IIId[a]	4.30	6.75—7.42	3.76	3.45 t (CH_2N) 1.45 m (CH_2—CH_2) 0.89 t (CH_3)	1590	3410
IIIe[d]	—	6.52—7.5	3.79	4.66 s (CH_2Ph)	1595	3440
IIIf[d]	—	6.75—7.75	3.84	2.28 s (CH_3)	1600	3420
IIIg[b]	—	6.78—8.0	3.88	—	1560	3400
IIIh[c]	—	6.68—7.62	3.84	3.75 s (CH_3O)	1595	3400
IIIi[d]	—	6.7 —8.18	3.76	—	1620	3380
IIIj[d]	8.38	6.82—7.95	3.89	—	1600	3420
IIIk[a]	—	6.68—7.5	4.00	—	1615	—

^{1}H NMR spectra measured: *a*) in $CDCl_3$; *b*) in $CDCl_3$—$(CD_3)_2SO$ (volume ratio = 3 : 1); *c*) in $CDCl_3$—$(CD_3)_2SO$ (volume ratio = 6 : 1); *d*) in $CDCl_3$—$(CD_3)_2SO$ (volume ratio = 5 : 1).
IR in $CHCl_3$.

Sterically hindered amines did not react with the NCS group. For example, 2,2,6,6-tetramethylpiperidine-4-one did not react even after several hours reflux in xylene (checked by TLC).

Phenols and thiols react with 4-bromo-2-bromomethylphenyl isothiocyanate only in the form of phenolates and thiolates, respectively. In the reaction of *I* with sodium phenolate 6-bromo-2-phenoxy-4*H*-benzo[*d*]-1,3-thiazine *IIIk* was formed, the ^{1}H NMR spectrum of which revealed a singlet of the methylene group of thiazine grouping at $\delta = 4.00$ ppm and a multiplet of signals of aromatic protons in the region of $\delta = 6.68$—7.5 ppm. The C=N bond manifested itself in the IR spectrum by the absorption band at $\tilde{\nu} = 1615\,\text{cm}^{-1}$. Due to increased reactivity of thiolates (*e.g.* sodium n-propyl and i-propyl thiolates), large amounts of by-products were formed and therefore, we failed to isolate the respective benzothiazines in pure state.

Experimental

IR spectra of the synthesized compounds were measured with a double-beam IR 75 (Zeiss, Jena) spectrophotometer in chloroform or KBr discs in the region of $\tilde{\nu} =$

= 800—4000 cm^{-1}. ^1H NMR spectra were measured with a Tesla BS 497 (80 MHz) and Tesla BS 567 (100 MHz) spectrometers.

4-Bromo-2-methylphenyl isothiocyanate was prepared by the reaction of 4-bromo-2-methylaniline with thiophosgene [11].

4-Bromo-2-bromomethylphenyl isothiocyanate (I)

4-Bromo-2-methylphenyl isothiocyanate (19.9 g; 0.087 mol), freshly prepared NBS (17 g; 0.096 mol), and dibenzoyl peroxide (2.1 g; 0.0087 mol) were added into a one-l reaction flask. The reaction mixture was heated under reflux for 1 h. After cooling, hexane (100 cm^3) was added and the precipitated succinimide was sucked off. The hexane solution was purified on a short column of silica gel, then hexane was distilled off. The residue was crystallized from petroleum ether or hexane (30—60 °C) to give white needles of m.p. = 55—56 °C in 52 % yield.

For $C_8H_5Br_2NS$ (M_r = 307.0) w_i(calc.): 31.30 % C, 1.64 % H, 4.56 % N; w_i(found): 31.33 % C, 1.69 % H, 4.52 % N. IR spectrum, $\tilde{\nu}(CHCl_3)/cm^{-1}$: 2070 (NCS). ^1H NMR spectrum, $\delta(CDCl_3)$/ppm: 4.42 (CH_2), 6.95—7.65 (H—Ar).

2-Amino-6-bromo-4H-benzo[d]-1,3-thiazines (IIIa—IIIj)

The equimolar mixture of amine, 4-bromo-2-bromomethylphenyl isothiocyanate, and triethylamine was heated under reflux in dry benzene for 1 h. The hot precipitate of triethylammonium bromide was separated and washed with benzene. Benzene was distilled off from the supernatant and the residue was crystallized.

6-Bromo-2-phenoxy-4H-benzo[d]-1,3-thiazine (IIIk)

Sodium (0.072 g) was dissolved in absolute ethanol and to the formed sodium ethanolate in ethanol phenol (0.294 g) was added. After evaporation of ethanol crystalline sodium phenolate was obtained and suspended in dry benzene. To this 4-bromo-2-bromomethylphenyl isothiocyanate (0.96 g) was added and heated under reflux. After cooling NaBr was filtered off and benzene was evaporated. The residue was crystallized (Table 1).

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Translated by A. Kardošová