SOME NUCLEOPHILIC REACTIONS OF 2-ISOTHIOCYANATOBENZYL BROMIDE. A NEW SIMPLE SYNTHESIS OF 2-SUBSTITUTED 4*H*-BENZO[*d*][1,3]-THIAZINES

Jozef GONDA and Pavol KRISTIAN

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

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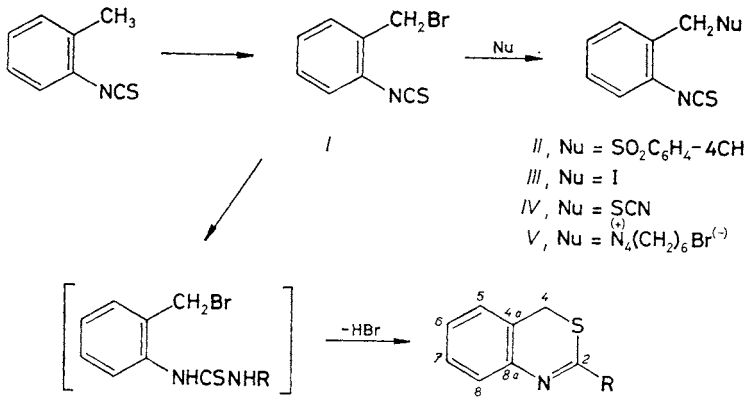
N-Bromosuccinimide reacts with *o*-tolyl isothiocyanate to afford 2-isothiocyanatobenzyl bromide, a new type of bifunctional synthon. Nucleophiles I^-, SCN^-, $4\text{-}CH_3C_6H_4SO_2^-$ and hexamethylenetetramine yield substitution products of bromine. Amines and phenols react exclusively with the NCS grouping under formation of unstable thioureas, which in turn cyclize to the corresponding 4*H*-benzo[*d*][1,3]thiazines. Structure of these compounds was corroborated by IR, ^1H, ^{13}C NMR and mass spectral data and backed by elemental analysis.

Several papers report the suitably functionalized isothiocyanates to be starting material for the synthesis of heterocycles. Utilization of halogen isothiocyanates for the preparation of heterocyclic compounds is based upon a considerable reactivity of both reaction centres (*i.e.* the halogen and NCS group) towards nucleophiles. Nucleophilic additions to NCS group proceed in most cases much quicker than the nucleophilic substitution of halogen. Intermediates of these reactions (thioureas, thioamides *etc.*) cyclize through the more nucleophilic atom of sulfur to furnish heterocycles with the 1,3-thiazine grouping. This principle was utilized when synthesizing thiazolidine derivatives by reaction of 2-bromoethyl isothiocyanate with C, N, O, and S nucleophiles[1-4], whereas 3-halogenpropyl isothiocyanates afford derivatives of 1,3-thiazine under similar conditions[5-6]. Also nitrogen containing heterocycles can enter the reaction with halogen isothiocyanates in form of their salts. Thus, *e.g.* sodium indolate and 2-bromoethyl isothiocyanate afford 1-(2-thiazolyl)indole[7]. Trisubstituted thioureas with 1,2-dichloroethyl isothiocyanate yielded tetrahydro-1,3,5-thiadiazine[8]. γ-Isothiocyanatoallyl chlorides were successfuly employed for the synthesis of 2-substituted 6*H*-1,3-thiazines[9]. ω,4-Dichloro-2-isothiocyanatophenylpropenylaldehyde, prepared from 4,7-dichloroquinoline and thiophosgene, reacts with some N-nucleophiles to give 4*H*-benzo[*d*][1,3]thiazines[10].

4*H*-Benzo[*d*][1,3]thiazines have been reported to be antipyretics[11], anthelmintics[12], bactericides[13], and tranquilizers[14]. These compounds were synthesized from *o*-benzylalkohols and isothiocyanates and cyclization of the corresponding thioureas by concentrated hydrobromic acid[15,16].

This paper is directed towards the synthesis of 2-substituted 4*H*-benzo[*d*][1,3]-thiazines utilizing the selectivity of the reaction centres of the bifunctional 2-isothiocyanatobenzyl bromide. This isothiocyanate is a new type of synthon having both a highly reactive halogen of the benzyl type, selective towards S_N reactions and an NCS group easily undergoing Ad_N reactions.

2-Isocyanatobenzyl bromide (*I*) was prepared by a dibenzoyl peroxide initiated radical bromination of *o*-tolyl isothiocyanate with N-bromosuccinimide (Scheme 1);



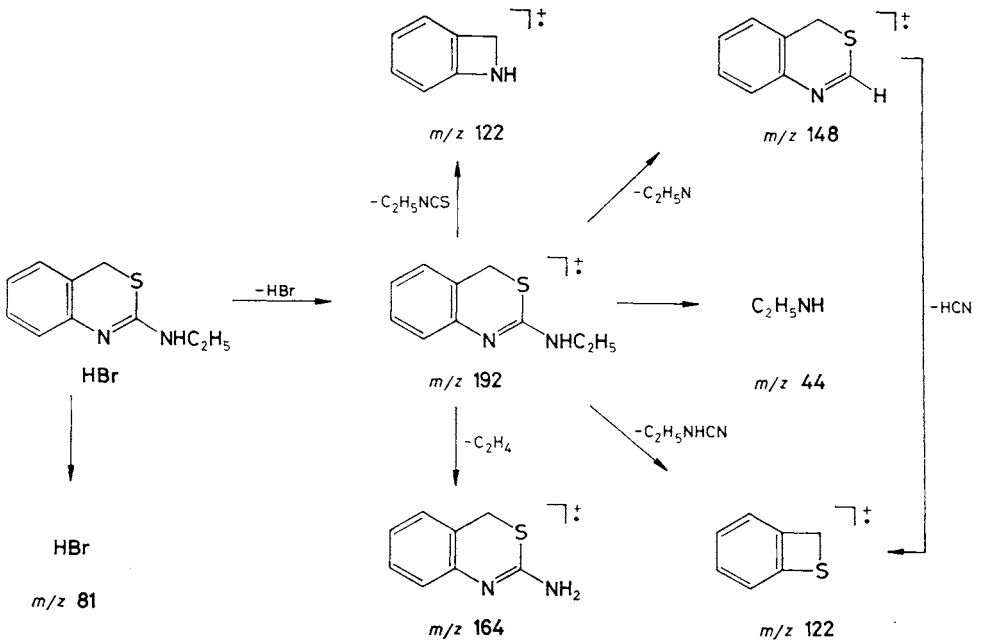
SCHEME 1

yield of this reaction varies within 48 and 56% depending on the purity of the starting material and amount of the iniciator. Bromination with N-bromosuccinimide is general, nevertheless it should be mentioned that the benzyl radical formed did not attack the NCS group even at an advantageous steric arrangement. This fact accords with the statement that radicals do not add to polar bonds in most cases[17].

The IR spectrum of 2-isothiocyanatobenzyl bromide is characteristic of the presence of ν_{as}(NCS) at 2 050 cm^{-1}. The ^1H NMR spectrum revealed, in addition to signals of protons at aromatic ring, a singlet of the methylene group (δ = 4·48 ppm). The

chemical shifts of NCS carbon and CH_2 group appeared in the ^{13}C NMR spectrum at δ = 137·7 and 28·6 ppm, respectively.

Reactions with some nucleophiles as *e.g.* I^-, SCN^-, 4-$CH_3C_6H_4SO_2^-$, and hexamethylenetetramine afforded substitution products of bromine in the CH_2Br group (Scheme 1). Structure of these isothiocyanates was evidenced by spectral methods and elemental analysis. The above-mentioned nucleophiles did not form stable addition compounds with the NCS group, *i.e.* the reaction equilibrium is strongly shifted to the side of starting compounds. The situation was dramatically changed when using primary and secondary amines or phenolates as nucleophiles. They reacted with 2-isothiocyanatobenzyl bromide to form 4*H*-benzo[*d*][1,3]thiazines *VIa*–*VIh*, *VIIa*,*b* in good yields (Scheme 1, Table I). This reaction was carried out by heating the starting compounds in benzene in the presence of triethylamine. The absence of triethylamine or other base was manifested by formation of the corresponding hydrogen bromides in 44–61% yields. Formation of thiazines is an evidence



SCHEME 2

that the reaction starts with an addition of amines to NCS grouping under formation of thioureas, which, under the given reaction conditions underwent an intramolecular alkylation through the more nucleophilic sulfur atom.

The IR spectra of 2-amino-4*H*-benzo[*d*][1,3]thiazines contained a diagnostic

absorption band at 3 443 to 3 380 cm^{-1}, belonging to stretching vibrations of the N—H bond, and a strong band at 1 632 to 1 602 cm^{-1} associated with vibrations of C=N bond. The ^1H NMR spectra revealed signals of a methylene group of the thiazine ring at δ = 4·22—3·82 ppm (Table II). The $C_{(2)}$ chemical shifts of some selected derivatives (Table III) appearing at δ = 150·1 to 150·2 ppm proved the presence of a thiazine grouping. The chemical shift of carbon-2 towards lower field for 2-ethylamino-4*H*-benzo[*d*][1,3]thiazine hydrogen bromide (*VIb* . HBr) $C_{(2)}$ = 168·40 ppm is due to protonation of the —N=C—NH system. The mass spectra of further derivatives also backed the proposed structure (Table II).

TABLE I

2-N-Substituted 2-amino-4*H*-benzo[*d*][1,3]thiazines *VIa*—*VIh* and 2-aryloxy-4*H*-benzo[*d*][1,3]-thiazines *VIIa,b*

Compound R	Formula (M_r)	M.p., °C Solvent	Yield %	Calculated/found		
				% C	% H	% N
VIa NH_2	$C_8H_8N_2S$ (164·2)	137—138 $CHCl_3$–ether	87	58·50 58·48	4·91 4·93	17·05 17·11
VIb NHC_2H_5[a]	$C_{10}H_{12}N_2S$ (192·3)	100—101 hexane	95	62·46 62·42	6·24 6·30	14·56 14·51
VIc $NHCH_2CH(CH_3)_2$	$C_{12}H_{16}N_2S$ (220·3)	61—62 hexane	90	65·41 65·37	7·32 7·35	12·71 12·67
VId $NHCH_2C_6H_5$	$C_{15}H_{14}N_2S$ (254·4)	121—122 $CHCl_3$–hexane	93	70·83 70·85	5·54 5·46	11·01 11·00
VIe $NHCH_2CH_2C_6H_5$	$C_{16}H_{16}N_2S$ (268·4)	95—97 $CHCl_3$–hexane	91	71·60 71·52	6·01 6·08	10·43 10·39
VIf NHC_6H_4(2-CH_3O)	$C_{15}H_{14}N_2OS$ (270·4)	116—117 $CHCl_3$–LP[b]	51	66·64 66·70	5·22 5·20	10·36 10·33
VIg NHC_6H_4(3-CH_3O)	$C_{15}H_{14}N_2OS$ (270·4)	168—170 $CHCl_3$–hexane	68	66·64 66·58	5·22 5·19	10·36 10·31
VIh NHC_6H_4(2-CH_3)	$C_{15}H_{14}N_2S$ (254·4)	169—170 $CHCl_3$–hexane	56	70·83 70·75	5·54 5·47	11·01 11·09
VIIa OC_6H_4(3-Cl)	$C_{14}H_{10}ClNOS$ (275·8)	61—63 hexane	63	60·98 60·85	3·65 3·58	5·08 5·11
VIIb OC_6H_4(4-Cl)	$C_{14}H_{10}NOS$ (275·8)	87—88 hexane	74	60·98 60·91	3·65 3·62	5·08 5·03

[a] Hydrogen bromide: m.p. 161—162°C ($CHCl_3$–ether), yield 61%; [b] light petroleum.

EXPERIMENTAL

The IR spectra were measured with a double-beam spectrophotometer IR-75 (Zeiss, Jena) either in chloroform or in KBr discs in the 800—4 000 cm^{-1} range, the UV spectra were run with a Perkin–Elmer, model 402, in 1 cm-cells, the ^1H and ^{13}C NMR spectra of C^2HCl_3, C^2HCl_3–$(C^2H_3)_2SO$ (5 : 1), or $(C^2H_3)_2SO$ solutions containing tetramethylsilane as internal reference were recorded with Tesla BS 497 (80 MHz) and Tesla BS 567 (25·04 MHz) apparatuses, respectively. Signals of the ^{13}C NMR spectra were ascribed by the method of selective decoupling of protons. The mass spectra were measured with an MS 902 S (AEI, Manchester) and LKB 9000 instruments at 70 eV ion source energy.

2-Isothiocyanatobenzyl Bromide (*I*)

A mixture consisting of *o*-tolyl isothiocyanate (29·88 g, 0·2 mol), N-bromosuccinimide (35·6 g, 0·2 mol) and dibenzoyl peroxide (2·42 g, 20 mmol) in carbon tetrachloride (20 ml) was refluxed for 1·5 h and cooled. The separated succinimide was filtered off, washed with carbon tetra-

TABLE II

Spectral data of benzothiazines *VIa*—*VIh* and *VIIa,b*

Compound	IR, (cm^{-1})[a]		^1H NMR (δ, ppm)[b]			
	ν(NH)	ν(C=N)	CH_2	H_{Ar}	NH	Further protons
VIa	3 430, 3 380	1 602	3·85	6·87—7·32	6·20	
VIb[c]	3 385	1 609	3·82	7·05—7·25	4·30	1·2 (t, CH_3); 3·55 (q, CH_2)
VIc	3 380	1 607	3·82	7·05—7·25	4·50	0·94 (d, CH_3); 3·32 (d, CH_2); 1·86 (m, CH)
VId	3 400	1 610	3·83	7·05—7·33	4·08	4·52 (s, CH_2)
VIe	3 385	1 018	3·82	7·05—7·32	4·6	2·9 (t, CH_2Ph); 3·75 (t, CH_2N)
VIf	3 423, 3 383	1 605	3·83	6·83—7·20	—	2·2 (s, CH_3)
VIg	3 420, 3 380	1 607	4·15	7·08—7·40	9·42	3·97 (s, CH_3)
VIh	3 430	1 630	4·20	7·15—7·45	9·75	3·92 (s, CH_3)
VIIa	—	1 611	4·03	6·95—7·25	—	
VIIb	—	1 614	4·00	6·83—7·38	—	

[a] Compounds *VIa*—*VIh* in $CHCl_3$; *VIIa,b* in KBr; [b] compounds *VIa*—*VIf*, *VIIa,b* in C^2HCl_3; *VIa*—*VIh* in C^2HCl_3–$(C^2H_3)_2SO$; [c] mass spectrum, *m/z* (relat. intens., %): 192 (100), 178 (8·6), 164 (11·5), 149 (17·2), 148 (14·3), 138 (28·6), 137 (14·9), 132 (20), 122 (15), 105 (18), 104 (16·5), 77 (15·5), 44 (20·3); mass spectrum *VIb* + HBr is identical with that of free base *VIb*.

chloride and the filtrate was evaporated. The residue dissolved in hexane was purified through a silica gel column with hexane as eluent. The eluate was concentrated and left to crystallize overnight at −18°C. The separated 2-isothiocyanatobenzyl bromide was filtered off and recrystallized from the same solvent; m.p. 39–41°C; yield 48–56%. For C_8H_6BrNS (228·1) calculated: 34·00% C, 2·65% H, 6·14% N; found: 34·18% C, 2·50% H, 6·21% N. IR spectrum ($CHCl_3$), cm^{-1}): 2 050 ν (NCS). ^1H NMR spectrum (C^2HCl_3), δ, ppm: 4·48 (s, CH_2), 7·2 to 7·38 (m, H_{Ar}). ^{13}C NMR spectrum (C^2HCl_3), δ, ppm: 137·7 (NCS), 133·63 (C_6), 130·57, 129·82, 127·51, 127·06 ($C_{(2)}$, $C_{(3)}$, $C_{(4)}$, $C_{(5)}$), 130·7 (C_1), 28·593 (CH_2).

2-N-Substitutued 1-Amino-4*H*-benzo[*d*][1,3]thiazines (*VIa–VIh*)

To a solution of 2-bromomethyl phenylisothiocyanate (2·28 g, 10 mmol) in benzene (70 ml) the respective amine (10 mmol) and triethylamine (10 mmol) were added. The mixture was refluxed for 1·5 h, triethylamine hydrogen bromide was hot-filtered and the solvent was evaporated. The residue was crystallized from an appropriate solvent.

2-N-*Substituted 2-amino-4H-benzo*[*d*][1,3]*thiazine hydrogen bromides*: isothiocyanate *I* (10 mmol) and amine (10 mmol) in benzene (100 ml) were refluxed for 3 h, the little amount of salts was filtered off, the solvent was distilled off and the residue was crystallized from chloroform–hexane.

2-Aryloxy-4*H*-benzo[*d*][1,3]thiazines (*VIIa,b*)

Isothiocyanate *I* (10 mmol) in benzene (20 ml) was refluxed with the suspension of the respective sodium phenolate (10 mmol) in benzene (30 ml) for 1 h. The separated NaBr was removed, the solvent was evaporated and the residue was crystallized.

TABLE III

^{13}C NMR spectral data for 2-amino-4*H*-benzo[*d*][1,3]thiazines

C-atom	*VIb*	*VIb* . HBr	*VIc*	*VIe*	*VIh*
2	153·49	168·49	154·01	153·71	151·18
4	29·93	28·59	30·01	29·94	29·78
4a	119·89	117·80	119·80	119·89	119·97
5–8	128·18	121·4	128·18		128·18
	126·46	127·43	120·39	[a]	126·61
	124·37	129·61	124·39		123·61
	123·105	129·68	123·03		122·65
8a	146·02	134·45	146·02	145·80	143·86[b]
1′	37·40	40·91	50·02	43·75	—
2′	14·93	14·40	28·51	35·09	—
3′	—	—	20·15	138·93	143·71[b]
4′–6′	—	—	—	[a]	[c]

[a] $C_{(5)}$–$C_{(8)}$, $C_{(6')}$ 128·33, 128·78, 128·63, 126·46, 124·45, 123·33, 126·46; [b] values are interchangeable; [c] $C_{(4')}$ 105·1, $C_{(5')}$ 159·11, $C_{(6')}$ 112·95, $C_{(7')}$ 129·23, $C_{(8')}$ 108·69, $C_{(9')}$ 55·09.

2-(*p*-Tolylsulfonylmethyl)phenyl Isothiocyanate (*II*)

Sodium *p*-toluene sulfinate (0·80 g, 5 mmol) in dimethylformamide (50 ml) was added to 2-bromomethylphenyl isothiocyanate (1·14 g, 5 mmol) in dimethylformamide (10 ml). The mixture was stirred for 10 min, poured into cold water (200 ml), the product was filtered off and crystallized from ethanol; yield 89%. m.p. 130—131°C. For $C_{15}H_{13}NO_2S_2$ (303·4) calculated: 59·38% C, 4·32% H, 4·61% N; found: 59·26% C, 4·35% H, 4·58% N. IR spectrum ($CHCl_3$), cm^{-1}: 2 093 *v* (NCS). ^1H NMR spectrum (C^2HCl_3), δ, ppm: 2·4 (s, CH_3), 4·38 (s, CH_2), 7·08—7·58 (m, H_{Ar}).

2-(Iodomethyl)phenyl Isothiocyanate (*III*)

2-Bromomethylphenyl isothiocyanate (2·28 g, 10 mmol) in acetone (20 ml) was added at 0°C to a stirred solution of sodium iodide (1·5 g, 10 mmol) in acetone (35 ml). The mixture was poured into ice-cold water (200 ml) after 5 min and extracted with ether (3 × 50 ml). The ethereal extracts were combined, washed with water, dried with sodium sulfate and the solvent was evaporated. The residue was crystallized from hexane; m.p. 48°C, yield 72%. For C_8H_6INS (275·1) calculated: 34·92% C, 2·19% H, 5·09% N; found: 34·80% C, 2·22% H, 5·18% N. IR spectrum ($CHCl_3$), cm^{-1}: 2 085 *v* (NCS). ^1H NMR spectrum (C^2HCl_3), δ, ppm: 4·68 (s, CH_2), 7·2—7·33 (m, H_{Ar}).

2-(Thiocyanatomethyl)phenyl Isothiocyanate (*IV*)

2-Isothiocyanatobenzyl bromide (2·28 g, 10 mmol) in acetone (20 ml) was added to a stirred solution of sodium thiocyanate (0·81 g, 10 mmol) in acetone (20 ml). The mixture was poured into ice-cold water (100 ml) and extracted with ether (3 × 30 ml). The ethereal extracts were combined, washed with water, dried with magnesium sulfate, the solvent was removed and the residue was crystallized from hexane; m.p. 38°C, yield 93%. For $C_9H_6N_2O_2$ (206·3) calculated: 52·40% C, 2·93% H, 13·58% N; found: 52·51% C, 2·99% H, 13·67% N. IR: spectrum ($CHCl_3$), cm^{-1}: 2 150 *v* (NCS), 2 150 *v* (SCN). ^1H NMR spectrum (C^2HCl_3), δ, ppm 4·16 (s, CH_2), 7·34 (s, H_{Ar}).

2-(Hexamethylenetetramethylammoniummethyl)phenyl Isothiocyanate (*V*)

A solution of hexamethylenetetramine (0·7 g, 5 mmol) in chloroform (10 ml) was added to 2-bromomethylphenyl isothiocyanate (1·14 g, 5 mmol) in chloroform (5 ml) and left to stand overnight. The separated crystals were filtered off, washed with ether and dried; m.p. 115—125°C (decomposition), yield 55%. For $C_{14}H_{18}BrN_5S$ (368·3) calculated: 45·66% C, 4·92% H, 19·02% N; found: 45·71% C, 4·78% H, 18·89% N. IR spectrum ($CHCl_3$), cm^{-1}: 2 050 ν_{as}(NCS).

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