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NEW APPROACH TO THE SYNTHESIS OF 1,3-CHLOROISOTHIOCYANATOALKANES. SYNTHESIS OF TETRAHYDRO-1,3-THIAZINE-2-THIONES AND 2-ALKYLAMINO-5,6-DIHYDRO-1,3-THIAZINES

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A method was developed to prepare 1,3-chloroisothiocyanatoalkanes by reducing 1,3-isothiocyanato ketones using sodium borohydride at pH ~7 and subsequent treatment of the resultant 1,3-isothiocyanato alcohols with thionyl chloride. The reaction of 1,3-chloroisothiocyanatoalkanes with sodium hydrosulfide or amines gives substituted tetrahydro-1,3-thiazine-2-thiones or 2-amino-5,6-dihydro-1,3-thiazines.

Keywords: 2-amino-5,6-dihydro-1,3-thiazines, 1,3-isothiocyanato ketones, 1,3-isothiocyanato alcohols, tetrahydro-1,3-thiazine-2-thiones, 1,3-chloroisothiocyanatoalkanes, intramolecular cyclization.

Despite the common use of 1,3-haloisothiocyanates for the immobilization of natural compounds [1] and as synthones in heterocyclic chemistry [2-4], the methods for the synthesis of these compounds have not been developed sufficiently. The major method for the preparation of these compounds is the reaction of 1,3-halo amines with thiophosgene [5]. 1,3-Isothiocyanato alcohols, which may serve as precursors of 1,3-haloisothiocyanates, are also obtained by the reaction of thiophosgene [7] or carbon disulfide [7] with 1,3-amino alcohols. It has not been possible to synthesize 1,3-isothiocyanato alcohols by reduction of the carbonyl group of 1,3-isothiocyanato ketones since the reaction of these compounds with $NaBH_4$, $LiAlH_4$, and Grignard reagents leads to formation of tetrahydro-1,3-oxazine-2-thiones [8] or N-methyl-1,3-aminoalcohols [9].

We have developed a method for preparing 1,3-isothiocyanato alcohols [10] based on the reduction of available of 1,3-isothiocyanato ketones at controlled pH. Ketones **1a-d** react with $NaBH_4$ in aqueous ethanol at pH 7.0-7.5 and 0-10°C to give 1,3-isothiocyanato alcohols **2a-d** in 45-75% yield. Since sodium borohydride solutions are basic media, in which 1,3-isothiocyanato alcohols are converted to tetrahydro-1,3-oxazine-2-thiones, the required pH was maintained by adding phosphate buffer (NaH_2PO_4) or ion-exchange resin in H^+ form. 1,3-Isothiocyanato alcohols **2b-d** are oily liquids, which cyclize upon storage to give tetrahydrooxazine-2-thiones.

The reaction of **2b-d** with thionyl chloride gives 1,3-chloroisothiocyanatoalkanes **3b-d** in 34-72% yield. The reduction of the carbonyl group in isothiocyanato ketones **1b** and **1c** proceeds with low diastereoselectivity [11]. Alcohols **2b** and **2c** were also obtained as 55:45 and 60:40 diastereomer mixtures.

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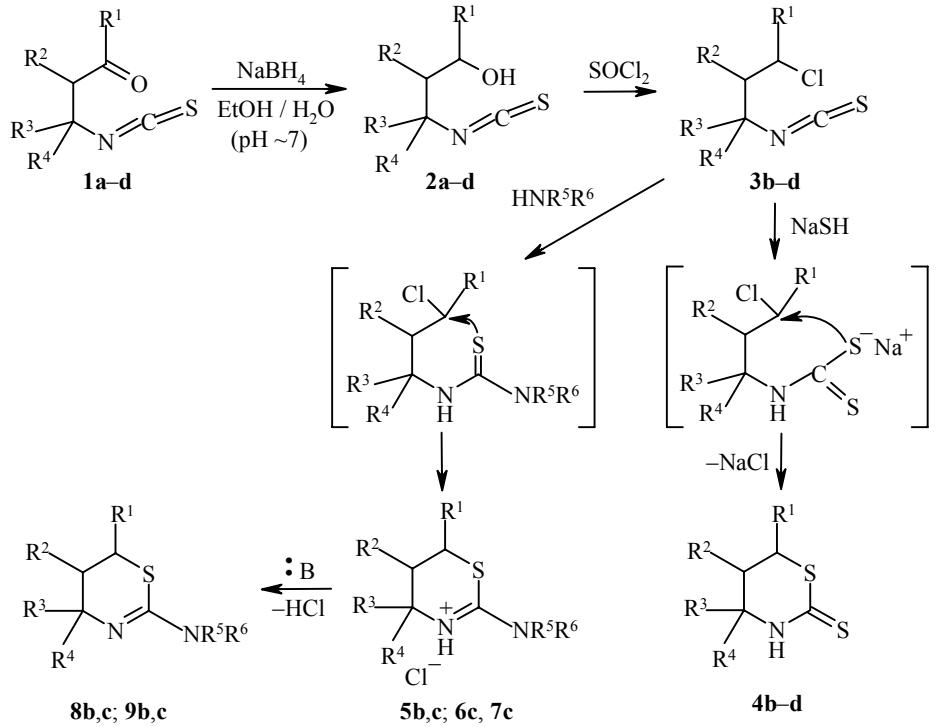
The IR spectra of **2** and **3** given in Table 1 show a strong band at 2100-2110 cm^{-1} corresponding to vibrations of the N=C=S group. The spectra of **2** taken neat show a strong broad band for the hydroxyl group in an intermolecular hydrogen bond at 3600-3100 cm^{-1}. The IR spectra of $5 \cdot 10^{-3}$ M chloroform solutions of **2** show a strong narrow band at 3650-3640 cm^{-1} for the nonassociated hydroxyl group.

We should note that the reaction with nucleophiles was mostly studied in the case of 1-halo-3-isothiocyanatopropanes. This circumstance necessitated a study of the analogous transformations for alkyl-substituted 1,3-chloroisothiocyanatoalkanes **3b-d**. We studied the reaction of **3b-d** with NaSH, which has been reported for 1,2-haloisothiocyanates [12]. This reaction gave substituted tetrahydro-1,3-thiazine-2-thiones **4b-d** in 65-94% yield.

1-Halo-3-isothiocyanatopropanes are used in the synthesis of 2-amino- and 2-alkylamino-5,6-dihydro-4H-1,3-thiazines, which hold interest as biologically active compounds [4, 13]. Some of these derivatives have been found to be analgetics. The Bayer firm produces N-(5,6-dihydro-4H-1,3-thiazin-2-yl)-N-(2,6-dimethylphenyl)amine as a veterinary drug.



1, 2 a $R^1 = R^2 = R^4 = H$, $R^3 = Me$; **1-5, 8 b** $R^1 = R^2 = Me$, $R^3 = R^4 = H$; **1-8 c** $R^1 = R^3 = R^4 = Me$, $R^2 = H$;
1-4 d $R^1 = R^2 = R^3 = R^4 = Me$; **5**, **8** $R^5 = R^6 = H$; **6** $R^5 = Bn$, $R^6 = H$; **7**, **9** $R^5 + R^6 = (CH_2CH_2)_2O$

The reaction of 1,3-chloroisothiocyanatoalkanes **3b** and **3c** with ammonia and amines gave hydrochloride salts of 2-amino-1,3-thiazines **5-7**, from which **8** and **9** were isolated upon treatment with base. Substituted 3-chloroisothiocyanatopropanes **3b-3d**, in contrast to 1,3-haloisothiocyanatopropanes [3], react with ammonia, primary amines, and secondary cyclic amines under mild conditions to give the corresponding products in 72-89% yield.

The structures of these products were supported by elemental analysis, IR, ^{1}H NMR and ^{13}C NMR spectra (Tables 1-3). The splitting of 5-H in the ^{1}H NMR spectra of *cis*-**4b** indicates the equatorial position of this proton ($^3J_{4\text{-He},5\text{-He}} = 3.5$, $^3J_{4\text{-He},5\text{-He}} = 6.2$, $^3J_{6\text{-Ha},5\text{-He}} = 6.5$), that is, axial orientation of the CH_3-5 group. The CH_3-6 group in **4c, 6c, 8c,** and **9c** is equatorial as indicated by the coupling constant of H-6, J_{aa} ~12.5-13.0 Hz.

TABLE 1. Characteristics of Compounds **2-4, 6, 8,** and **9**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (mm Hg)	n_D^{20}	mp, °C (solvent)*	IR spectrum, ν, cm^{-1}*[2]		Yield, %
		C	H (Cl)	S (N)				(NCS) NC=S; NC=N	OH (NH)	
2a	C_5H_9NOS	45.83 / 45.78	7.17 / 6.91	23.91 / 24.44	61-63 (0.2)	1.5290		(2100)	3100-3600	62.4
2b	$C_6H_{11}NOS$	49.65 / 49.63	7.60 / 7.63	21.93 / 22.08	87-90 (0.5)			(2100)	3100-3600	44.8
2c	$C_7H_{13}NOS$	52.67 / 52.80	8.14 / 8.23	20.23 / 20.13	55-56 (0.1)	1.5100		(2100)	3100-3600	75.2 (66.5)*[3]
2d	$C_8H_{15}NOS$	55.36 / 55.45	8.75 / 8.73	18.31 / 18.50	58-60 (0.09)			(2100)	3100-3600	50.8
3b	$C_6H_{10}ClNS$	44.06 / 44.03	6.00 / 6.16	—	61-63 (1.0)	1.5270		(2100)	—	72.0
3c	$C_7H_{12}ClNS$	—	(19.72) / (19.95)	18.04 / 18.04	60-61 (0.7)	1.5067		(2100)	—	76.1
3d	$C_8H_{14}ClNS$	—	—	17.80 / 17.72	62-65 (0.7)	1.5208		(2100)	—	34.3
4b	$C_6H_{11}NS_2$	44.61 / 44.68	6.80 / 6.87	40.03 / 39.76			140-144 (EtOH)	1545	(3100)	93.9
4c	$C_7H_{13}NS_2$	—	—	—			205-207 (EtOH)*[4]	1535	(3140)	90.3
4d	$C_8H_{15}NS_2$	50.64 / 50.75	8.01 / 7.99	—			165-168 (EtOH)	1545	(3100)	65.3
6c	$C_{14}H_{21}ClN_2S$	59.12 / 59.03	7.40 / 7.43	—			103-104 (AcOEt)	1605	(3150)	88.9
cis-**8b**	$C_6H_{12}N_2S$	49.90 / 49.96	8.42 / 8.39	(19.40) / (19.46)			82-83 (*n*-C_6H_{14})	1650	(3100)	39.9 (72.3)*[5]
8c	$C_7H_{14}N_2S$	53.52 / 53.13	8.90 / 8.92	(17.70) / (17.70)			109-112 (*n*-C_6H_{14}–$CHCl_3$)	1650	(3100) (1600)	74.9
9c	$C_{11}H_{20}N_2OS$	57.92 / 57.86	8.74 / 8.83	—			63-64 (MeOH–H_2O)	1605	—	82.0

* *trans:cis* isomer mixture: 55:45 for **4b**, 60:40 for **4d**.

*[2] Products **2a-d, 3c**, and **3d** taken in neat, **9c** taken in $CHCl_3$, **4b-d,** *cis*-**8b**, and **8c** taken in vaseline.

*[3] Using ion-exchange resin.

*[4] mp 205-207°C (ethanol) [14].

*[5] 50:50 *trans:cis* isomer mixture for **8b**.

TABLE 2. ^{1}H NMR Spectra of Compounds **3-9**

Compound	Chemical shifts ($CDCl_3$), δ, ppm (*J*, Hz)						
	H-6, m (^{3}J) C<u>H</u>–Cl	R^1, d (^{3}J)	R^2 ($^{2,3}J$)	CHR^2 ($^{2,3}J$)	R^3 ($^{2,3}J$)	R^4 ($^{2,3}J$)	NH, NRR^5 (^{3}J)
3b*	3.92 (7.0, 7.0)	1.44 (7.0)	1.03 d (7.0)	1.99 m	3.64 dd (14.0, 6.0)	3.60 dd (14.0, 5.0)	—
	4.20 (3.0, 7.0)	1.42 (7.0)	0.93 d (7.0)	1.55 m	3.54 dd (14.0,7.5)	3.44 dd (14.0, 7.5)	—
3c	4.17	1.52 (6.7)	2.04 dd (15.0, 7.5)	1.52 dd (15.0, 6.7)	1.45 s	1.41 s	—
3d*	4.54-3.88	1.53 (7.0)	1.08 d (7.0)	2.14-1.92 m	1.47 s	1.46 s	—
		1.51 (7.0)	1.14 d (7.0)		1.48 s	1.47 s	—
trans-**4b**	3.01 (9.0, 6.5)	1.25 (6.5)	1.05 d (6.5)	1.85 m	3.40 m (13.8, 3.5)	3.07 m (13.8, 9.2, 2.0)	8.93 br. s
cis-**4b**	3.37 (6.5, 3.5)	1.22 (6.5)	1.02 d (6.5)	2.28 m	3.42 m (13.8, 3.5)	3.24 m (13.8, 6.2, 4.0)	8.86 br. s
4c	3.35	1.22 (6.5)	1.92 dd (13.0, 4.0)	1.52 dd (13.0, 13.0)	1.34 s	1.24 s	8.84 br. s
trans-**4d**	3.10 (11.0, 6.5)	1.27 (6.5)	1.04 d (7.0)	1.58-1.80 m	1.37 s	1.21 s	8.28 br. s
cis-**4d**	3.80 (4.0, 6.5)	1.22 (6.5)	0.92 d (7.0)	1.58-1.80 m	1.36 s	1.26 s	8.28
6c	3.56	1.43 (6.6)	2.07 dd (14.0, 3.1)	1.63 dd (14.0, 12.5)	1.56 s	1.35 s	11.05 br. s, 10.25 br. s, 4.45 d (5.6), 7.33 m
trans-**8b**	3.05 (7.0, 9.0)	1.31 (7.0)	1.02 d (6.5)	1.50 m	3.58 dd (15.0, 3.5)	3.10 dd (15.0, 9.5)	3.98 br. s
8c	3.33	1.26 (7.0)	1.76 dd (13.8, 3.8)	1.10 dd (13.8, 13.0)	1.21 s	1.05 s	4.28 br. s
9c	3.40-3.21*[2]	1.29 (6.5)	1.80 dd (13.5, 3.4)	1.09 dd (13.5, 13.0)	1.23 s	1.07 s	3.69 m*[2] 3.33 m*[2]

* Mixture of *erythro* and *threo* isomers.

*[2] Signals overlap.

TABLE 3. ^{13}C NMR Spectra of Compounds **4**, **9**

Compound	Proton chemical shifts, δ, ppm			
	C–S	NC=S; (N=C–S)	C–N	Signals of other carbon nuclei
cis-**4b**	42.8	194.6	49.0	29.4, 16.5, 12.42
trans-**4b**	44.8	195.0	49.8	32.6, 19.02, 15.9
4c	35.8	193.1	55.3	29.4, 26.5, 19.7
cis-**4d**	39.1	193.3	57.8	41.0, 26.9, 17.9, 16.9, 7.6
trans-**4d**	40.2	194.3	58.7	42.8, 28.6, 21.2, 18.5, 12.3
9c	33.4	150.2	53.4	66.8, 66.8, 46.8, 46.8, 41.9, 32.8, 28.1, 22.4

Thus, we have found a new approach to the synthesis of substituted tetrahydro-1,3-thiazine-2-thiones and 2-amino-5,6-dihydro-4H-1,3-thiazines starting from 1,3-isothiocyanato carbonyl compounds.

EXPERIMENTAL

The ^1H NMR spectra were taken on a Bruker AC-200 spectrometer at 200 MHz and Bruker WM-250 spectrometer at 250 MHz in $CDCl_3$. The ^{13}C NMR spectra were taken on a Bruker WP80DS spectrometer at 20 MHz and Bruker AC-200 spectrometer at 50 MHz. TMS was used as the internal standard. The IR spectra were taken on a Specord IR-75 spectrometer. The reaction course and purity of the products were checked by thin-layer chromatography on Silufol UV-254 plates with development by iodine vapor and UV light.

3-Isothiocyanato-3-methyl-1-butanol (2a). A solution of (0.60 g, 16 mmol) $NaBH_4$ in water (6 ml) was added with vigorous stirring over 15 min to a suspension of 3-isothiocyanato-1-butanal (**1a**) (2.58 g, 20 mmol) and NaH_2PO_4 (5.00 g) in ethanol (20 ml) at 0°C. The reaction mixture was stirred for 15 min. Then, water (100 ml) and ether (100 ml) were added and the organic layer was separated. The aqueous layer was extracted with two 50-ml ether portions. The combined ethereal extract was washed with two 50-ml water portions and dried over Na_2SO_4. Ether was distilled off and the residue was distilled in vacuum to give 1.64 g of compound **2a**.

4-Isothiocyanato-3-methyl-2-butanol (2b) was obtained analogously to **2a** from 1,3-isothiocyanato ketone **1b** (10.60 g, 74 mmol) and NaH_2PO_4 (20.00 g) in ethanol (60 ml) and $NaBH_4$ (2.80 g, 74 mmol) in water (25 ml). The yield of **2b** 4.81 g.

4-Isothiocyanato-4-methyl-2-pentanol (2c). A. Pentanol **2c** was obtained analogously to **2a** from 1,3-isothiocyanato ketone **1c** (15.72 g, 100 mmol) and NaH_2PO_4 (45.50 g) in ethanol (100 ml) and $NaBH_4$ (3.78 g) in water (25 ml). The yield of **2c** 11.97 g.

B. A solution of $NaBH_4$ (0.76 g, 20 mmol) in water (7.5 ml) was added with vigorous stirring over 15 min to a suspension of 1,3-isothiocyanato ketone **1c** (3.30 g, 21 mmol) and moist Dowex 50×1 resin in the H^+ form (16.00 g) in ethanol (20 ml) at 10°C. After the addition was completed, the reaction mixture was stirred for an additional 15 min. The ion-exchange resin was filtered off and washed on the filter with two 7-ml ethanol portions. Then, water (150 ml) and ether (150 ml) were added to the combined filtrate. The organic layer was separated and the aqueous layer was extracted with two 60-ml ether portions. The combined ethereal extract was washed with two 60-ml water portions and dried over Na_2SO_4. Ether was distilled off. The residue was distilled in vacuum to give 2.22 g of compound **2c**.

4-Isothiocyanato-3,4-dimethyl-2-pentanol (2d) was obtained analogously to **2a** from 1,3-isothiocyanato ketone **1d** (10.05 g, 59 mmol) and NaH_2PO_4 (30.00 g) in ethanol (60 ml) and $NaBH_4$ (2.24 g, 59 mmol) in water (20 ml). The yield of **2d** 5.17 g.

3-Chloro-1-isothiocyanatoalkanes 3b-d. A sample of $SOCl_2$ (75 mmol) in benzene (10 ml) was added dropwise with stirring to isothiocyanatoalcohol **2** (25 mmol) in benzene (15 ml) at 10-15°C. Stirring was continued for 2-3 h at room temperature. Benzene and excess $SOCl_2$ were distilled off and the residue was distilled in vacuum.

Tetrahydro-1,3-thiazine-2-thiones 4b-d. A sample of NaSH (0.50 g, 9.0 mmol) in methanol (5 ml) was added dropwise with stirring to a solution of 3-chloro-1-isothiocyanatoalkane **3** (6.0 mmol) in methanol (5 ml). The reaction mixture was stirred for 210 min and then brought to pH ~5 by adding 10% hydrochloric acid. Methanol was distilled off. The residue was dissolved in $CHCl_3$ (40 ml) and washed with two 20-ml water portions and one 20-ml portion of saturated aqueous sodium chloride. The organic layer was separated and dried over $MgSO_4$. The solvent was removed.

2-Amino-4,4,6-trimethyl-5,6-dihydro-4H-1,3-thiazine (8c). A sample of **3c** (3.00 g, 16.9 mmol) was dissolved in methanol (100 ml) saturated with ammonia. After 96 h, methanol was distilled off. The residue was dissolved in water (15 ml) and extracted with two 15-ml ether portions. The organic layer was separated and NaOH (0.71 g, 17.5 mmol) in water (20 ml) was added to the aqueous layer, which was again extracted with three 50-ml chloroform portions. The combined chloroform extract was washed with saturated aqueous sodium chloride and dried over Na_2SO_4. The solvent was distilled off to give 2.04 g of compound **8c**.

***trans*-2-Amino-5,6-dimethyl-5,6-dihydro-4H-1,3-thiazine (8b).** A mixture of *cis* and *trans* isomers of **8b** (2.33 g) was obtained analogously to **8c** from isothiocyanate **3b** (0.351 g, 2.14 mmol) and ammonia-saturated methanol (13 ml). The reaction time was 48 h. Crystallization of the product from hexane gave 0.123 g of *trans*-**8b.**

2-Benzylamino-4,4,6-trimethyl-5,6-dihydro-4H-1,3-thiazine Hydrochloride (6c). A solution of isothiocyanate **3c** (1.78 g, 0.1 mmol) and benzylamine (0.107 g, 0.1 mmol) in $CHCl_3$ (2 ml) was heated at reflux for 2 h. The solvent was evaporated off. Recrystallization from ethyl acetate gave 0.253 g of compound **6c**.

4,4,6-Trimethyl-2-(4-morpholyl)-5,6-dihydro-4H-1,3-thiazine (9c). A solution of **3c** (0.178 g, 0.1 mmol) and morpholine (0.087 g, 0.1 mmol) in absolute methanol (2 ml) was maintained for 96 h at 20-25°C. The solvent was evaporated off and the residue was dissolved in water (2 ml). The aqueous solution was washed with two 2-ml ether portions and 1 ml saturated aqueous Na_2CO_3 was added. The mixture was extracted with three 2-ml chloroform portions. The organic layer was dried over Na_2SO_4 and the solvent was evaporated off. Crystallization of the residue from aqueous methanol gave 0.192 g of compound **9c**.

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REFERENCES

1. P. Gemeiner, K. Halak, and K. Polakova, *J. Solid-Phase Biochem.*, **5**, 197 (1980); *Chem. Abstr.*, **96**, 81882 (1982).
2. M. Tomura, O. Mori, H. Chikusa, K. Inazu, A. Ito, N. Matsumura, and H. Inoue, *Synthesis*, 457 (1991).
3. R. E. Hackler and T. W. Balbo, *Synth. Commun.*, **5**, 143 (1975).
4. V. L. Narayanan and R. D. Haugwitz, Ger. Offen. 2310015; *Chem. Abstr.*, **79**, 137122 (1973).
5. P. Friis, *Acta Chem. Scand.*, **19**, 766 (1965).
6. A. Kjaer and R. B. Jensen, *Acta Chem. Scand.*, **12**, 1746 (1958).
7. H. Tajima and K. Lee, Jpn. Pat. 09202768; *Chem. Abstr.*, **127**, 176196 (1997).
8. A. B. Khasirdzhev, N. F. Korolenok, and B. V. Unkovsky, USSR Inventor's Certificate No. 423796; *Byul. Izobr.*, No. 14, 82 (1974).
9. I. P. Boiko, Yu. F. Malina, A. V. Peretokin, B. V. Unkovsky, and A. B. Khasirdzhev, USSR Inventor's Certificate No. 643493; *Byul. Izobr.*, No. 3, 85 (1979).

10. A. B. Peretokin, T. D. Sokolova, A. S. Fisyuk, Yu. F. Malina, and B. V. Unkovsky, USSR Inventor's Certificate No. 1165678; *Byul. Izobr.*, No. 25, 91 (1985).
11. A. V. Peretokin, *Chemical Sciences Candidate's Dissertation*, Moscow (1984).
12. L. Kniezo, P. Kristian, M. Budesinsky, and K. Havrilova, *Coll. Czech. Chem. Commun.*, **46**, 717 (1981).
13. R. D. Haugwitz and V. L. Narayanan, US Patent 3767654; *Chem. Abstr.*, **80**, 27263 (1974).
14. M. Kahan, *Ber.*, **30**, 1318 (1897).