A CONVENIENT ONE-POT SYNTHESIS OF α-ISOTHIOCYANATOETHERS AND UNUSUAL COURSE OF SOME OF ITS NUCLEOPHILIC DISPLACEMENT REACTIONS

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A simple new method has been devised for the preparation of α-isothiocyanatoethers **1a–1f** in good yields by reaction of $PO(NCS)_3$ or $(PhO)_2PONCS$ with an equimolar mixture of aldehydes and alcohols. The course of nucleophilic additions of methanol, amines and hydrazine to **1a–1f** is described.
Key words: Isothiocyanates; Thiocarbamates; Thioureas; Thiosemicarbazides.

The high chemical reactivity of the N=C=S group[1] made chemists look for various types of isothiocyanates as suitable reagents for organic synthesis. In this respect bifunctional isothiocyanates containing some additional reactive centre in the molecule such as halogenoisothiocyanates, acylisothiocyanates or vinylisothiocyanates[2] are interesting compounds. This group of isothiocyanates also includes α-isothiocyanatoethers, which can undergo addition as well as cyclization reactions. One of the best known methods of their preparation is the halogen displacement by an alkali thiocyanates in α-halogenoethers[3]. A recent approach to their synthesis showed that the reaction of trimethylsilyl isothiocyanate with acetals in the presence of $ZnCl_2$ gives the desired α-isothiocyanatoethers, whereas the reaction with aldehydes at similar conditions gives α,α′-diisothiocyanatoethers[4]. This paper deals with a new method for the preparation of isothiocyanatoethers and their application in nucleophilic addition reactions.

In contrast to the previous report[4], the method herein describes a one-pot process consisting of the reaction of an aldehyde with an equimolar amount of alcohol and the subsequent action of isothiocyanate agents $PO(NCS)_3$ and/or $(PhO)_2PONCS$ on the hemiacetal formed. Both the isothiocyanates give the same yields but $PO(NCS)_3$ has the

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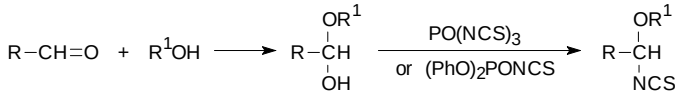
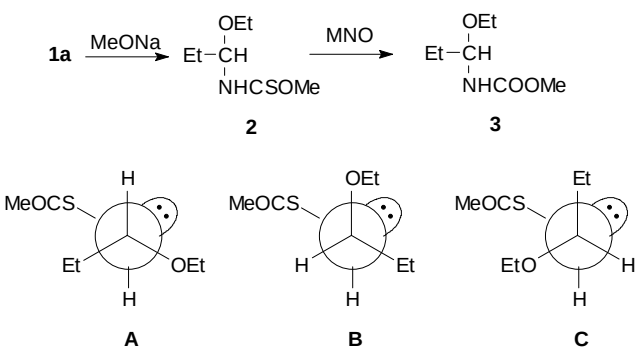
advantage of being prepared directly by a reaction of $POCl_3$ with KSCN. The advantage of this method – over the previous preparation from α-halogenoethers – is its broader application possibilities. Hemiacetals and the isothiocyanate reagents used are more reactive and are synthetically more accessible than many α-halogenoethers. The phosphorus-containing isothiocyanates were also employed in our previous work[5] concerning the synthesis of isothiocyanates from alcohols or carboxylic acids where a direct substitution of an –OH group by an –NCS group took place. The resulting α-isothiocyanatoethers **1a–1f** (Scheme 1) are pale yellow liquids sensitive to moisture. They decompose on prolonged standing, which can be prevented by keeping them in dry ether. Their structure was confirmed by ^{1}H NMR and ^{13}C NMR spectra and by the intensive IR spectral band ν_{asym}(NCS) at 2 050 cm^{-1}.



1	R	R^1	1	R	R^1
a	Et	Et	**d**	Me	Et
b	Et	Me	**e**	Pr	Et
c	Et	iPr	**f**	Ph	Et

SCHEME 1

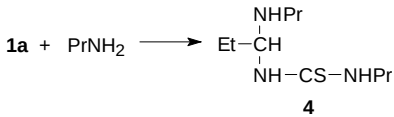
It is well known that isothiocyanates readily react with alcohols, amines and hydrazines[1,6] to give thiocarbamates, thioureas and thiosemicarbazides, respectively. These products have found applications as biologically active substances[1,7], analytical reagents[8] and synthons in heterocyclic chemistry[9–11]. It was interesting to investigate the reaction of α-isothiocyanatoethers with the previously mentioned nucleophiles (Schemes 2–4). The reaction of isothiocyanate **1a** with sodium methoxide gives methyl

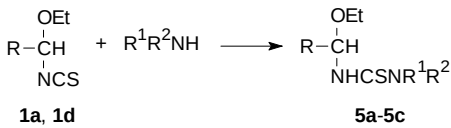


SCHEME 2

N-(1-ethoxypropyl)thiocarbamate **2** whose ^{1}H and ^{13}C NMR spectra showed double resonance signals in the ratio of 2.14 : 1, which are in accord with the structure **2**. Heating of thiocarbamate **2** to 130 °C in dideuterio-1,1,2,2-tetrachloroethane causes the resonance signals to coalesce, whereas the spectrum assumes the original form on cooling the sample. The largest differences in chemical shifts of pairs of signals (0.51 and 0.33 ppm) are exhibited by the CH and NH protons. One of possible interpretations is the presence of conformations **B** and **C** in the reaction mixture; their analogous gauche arrangement of hydrogens at CH–NH bond is indicated by the identical values of their coupling constants (*ca* 9.5 Hz) (Scheme 2). The reaction of thiocarbamate **2** with mesitylnitriloxide (MNO) gave methyl *N*-(1-ethoxypropyl)carbamate (**3**, Scheme 2) which, in contrast to its sulfur analogue **2**, shows no resonance doubling of signals in ^{1}H NMR spectra even after cooling to –100 °C.

α-Isothiocyanatoethers react with amines at 0 °C to give the corresponding thioureas. In the case of the reaction of propan-1-amine with 1-ethoxypropyl isothiocyanate (**1a**), the addition of the amine to the N=C=S group is accompanied by substitution of the ethoxy group, hence the final product is *N*-propyl-*N*′-[1-(propylamino)propyl]thiourea (**4**). Secondary amines react with α-isothiocyanatoethers **1a** and **1d** to give the corresponding *N*,*N*,*N*′-trisubstituted thioureas **5a–5c** (Scheme 3).

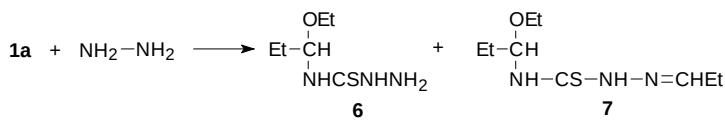




5	R	R^1R^2
a	Et	$(CH_2)_5$
b	Me	$(CH_2)_5$
c	Me	Et, Et

SCHEME 3

The reaction of isothiocyanate **1a** with hydrazine took place at –30 °C yielding the expected product 4-(1-ethoxypropyl)thiosemicarbazide (**6**) and a minor product 1-propylidene-4-(1-ethoxypropyl)thiosemicarbazide (**7**) which could be isolated from the reaction mixture. The course of this reaction was not studied. It is possible that it results from autocondensation of two molecules of compound **6** with elimination of ethanol and thiosemicarbazide (Scheme 4).



SCHEME 4

EXPERIMENTAL

Spectral Measurements

The ^{1}H NMR spectra were measured on a Tesla BS 587 spectrometer (80 MHz) and JEOL Alpha 400 instrument (399.65 MHz) in deuteriochloroform using tetramethylsilane as internal standard. To assign the conformational structures of thiocarbamate **2**, the homonuclear ^{1}H, ^{1}H COSY method was used. The ^{13}C NMR spectra were measured with a Tesla BS 567 spectrometer (25 MHz) in deuteriochloroform. The chemical shifts are given in ppm (δ-scale).The infrared spectra were recorded on a Specord 75 IR instrument (Zeiss, Jena) in chloroform. The elemental analyses were performed on a Perkin–Elmer CHN 2400 analyzer. $PO(NCS)_3$ and $(PhO)_2PONCS$ were obtained by refluxing $POCl_3$ and $(PhO)_2POCl$ with KSCN in benzene and acetonitrile, respectively[5]. The amines and hydrazine were commercial products (Aldrich). TLC was carried out on a Merck silica gel 60 (230–400 mesh).

General Procedure for Preparation of α-Isothiocyanatoethers (**1**)

To the respective aldehyde (0.1 mol), constantly stirred at 0 °C, the equivalent amount of alcohol (0.1 mol) was added. The reaction mixture was left to stand at room temperature for 1 h and then cooled again to 0 °C, whereupon a solution of $(PhO)_2PONCS$ (0.1 mol) or $PO(NCS)_3$ (0.037 mol) in hexane (20 ml) was added dropwise. The reaction mixture was left to stand for 15 h and distilled under reduced pressure. In the case of reaction with $PO(NCS)_3$, only the hexane layer was separated and distilled.

1-Ethoxypropyl isothiocyanate (**1a**): b.p. 59–62 °C/2.1 kPa; yield 65%. For $C_6H_{11}NOS$ (145.2) calculated: 49.62% C, 7.63% H, 9.65% N; found: 49.27% C, 7.51% H, 9.52% N. IR spectrum: 2 066 (NCS). ^{1}H NMR spectrum: 1.03 t, 3 H, J = 7.8 (CH_3, Pr); 1.26 t, 3 H, J = 7.1 (CH_3, EtO); 1.70–1.99 m, 2 H (CH_2, Pr); 3.53 dq and 3.89 dq, 2 H, J = 9.3, 7.1 (CH_2, EtO); 4.80 t, 1 H, J = 5.3 (CH, Pr). ^{13}C NMR spectrum: 8.6 (CH_3, Pr); 14.7 (CH_3, EtO); 30.2 (CH_2, Pr); 65.3 (CH_2, EtO); 89.8 (CH, Pr); 137.6 (NCS).

1-Methoxypropyl isothiocyanate (**1b**): b.p. 31–32 °C/2.1 kPa (reported[4] 72–73 °C/7.3 kPa); yield 44%. IR spectrum: 2 063 (NCS). ^{1}H NMR spectrum: 1.01 t, 3 H (CH_3); 1.62–2.05 m, 2 H (CH_2); 3.27 s, 3 H (CH_3O); 4.75 t, 1 H (CH).

1-Isopropoxypropyl isothiocyanate (**1c**): b.p. 41–43 °C/2.0 kPa; yield 35%. For $C_7H_{13}NOS$ (159.3) calculated: 52.79% C, 8.23% H, 8.79% N; found: 51.96% C, 8.05% H, 8.73% N. IR spectrum: 2 056 (NCS). ^{1}H NMR spectrum: 1.13 t, 3 H (CH_3, Pr); 1.19 d and 1.21 d, 6 H (2 × CH_3, iPr); 1.69–2.00 m, 2 H (CH_2, Pr); 3.83–4.28 m, 1 H (CH, iPr); 4.87 t, 1 H (CH, Pr). ^{13}C NMR spectrum: 8.7 (CH_3, Pr); 21.2 (CH_3, iPr); 22.9 (CH_3, iPr); 30.6 (CH_2, Pr); 71.3 (CH, iPr); 87.8 (CH, Pr).

1-Ethoxyethyl isothiocyanate (**1d**): b.p. 48–50 °C/2.4 kPa (reported[4] 84–85 °C/8.0 kPa); yield 57%. IR spectrum: 2 037 (NCS). ^{1}H NMR spectrum: 1.27 t, 3 H, J = 7.2 (CH_3, EtO); 1.57 d, 3 H, J = 6.0 (CH_3); 3.47–4.05 m, 2 H (CH_2, EtO); 5.07 q, 1 H, J = 6.0 (CH). ^{13}C NMR spectrum: 14.7 (CH_3, EtO); 23.2 (CH_3); 65.2 (CH_2, EtO); 85.1 (CH); 138.1 (NCS).

1-Ethoxybutyl isothiocyanate (**1e**): b.p. 55–56 °C/2.7 kPa; yield 64%. For $C_7N_{13}NOS$ (159.2) calculated: 52.79% C, 8.23% H, 8.79% N; found: 52.31% C, 8.16% H, 8.72% N. IR spectrum: 2 050 (NCS). ^{1}H NMR spectrum: 0.96 t, 3 H, J = 6.4 (CH_3, Bu); 1.25 t, 3 H, J = 7.2 (CH_3, EtO); 1.35–2.00 m, 4 H (CH_2CH_2, Bu); 3.40–4.05 m, 2 H (CH_2, EtO); 4.91 t, 1 H, J = 5.7 (CH, Bu). ^{13}C NMR spectrum: 13.5 (CH_3, Bu); 14.7 (CH_3, Et); 17.7 (CH_2, Bu); 38.9 (CH_2, Bu); 65.4 (CH_2, Et); 88.6 (CH, Bu); 137.5 (NCS).

1-Ethoxybenzyl isothiocyanate (**1f**): b.p. 59–61 °C/2.1 kPa; yield 45%. For $C_{10}H_{11}NOS$ (193.3) calculated: 62.15% C, 5.74% H, 7.25% N; found: 61.46% C, 5.69% H, 7.06% N. IR spectrum: 1 992 (NCS). ^{1}H NMR spectrum: 1.34 t, 3 H (CH_3); 3.60–4.00 m, 2 H (CH_2); 5.92 s, 1 H (CH); 7.40–7.75 m,

5 H (Ph). ^{13}C NMR spectrum: 14.7 (CH_3); 65.3 (CH_2); 88.8 (CH); 126.0 (2 CH-*ortho*); 128.7 (2 CH-*meta*); 129.4 (CH-*para*); 137.2 (C-*ipso*).

Methyl *N*-(1-Ethoxypropyl)thiocarbamate (**2**)

1-Ethoxypropyl isothiocyanate (**1a**, 1.45 g, 0.01 mol) was added dropwise to a suspension of sodium alkoxide (0.54 g, 0.01 mol) in dry ether under nitrogen at room temperature with constant stirring. The reaction mixture was left to stand overnight, then neutralized with dilute hydrochloric acid, the ether layer was separated and dried with sodium sulfate. Ether was evaporated and the residue was subjected to chromatography (silica gel; petroleum ether–ether 5 : 1). The product was recrystallized from hexane. M.p. 48–50 °C; yield 1.15 g (65%). For $C_7H_{15}NO_2S$ (177.3) calculated: 47.43% C, 8.53% H, 7.90% N; found: 47.02% C, 8.50% H, 7.88% N. IR spectrum: 3 400 (NH); 1 490 (NHCS). ^{1}H NMR spectrum for the major conformer: 0.97 t, 3 H, J = 7.3 (CH_3, Pr); 1.19 t, 3 H, J = 7.1 (CH_3, EtO); 1.70 m, 2 H (CH_2, Pr); 3.60 m, 1 H and 3.73 m, 1 H (CH_2, EtO); 3.98 s, 3 H (CH_3O); 5.49 dt, 1 H, J = 9.5; 6.1 (CH); 6.51 d, 1 H, J = 9.5 (NH); for the minor conformer: 0.94 t, 3 H, J = 6.7 (CH_3, Pr); 1.18 t, 3 H, J = 7.1 (CH_3, EtO); 1.62 m, 2 H (CH_2, Pr); 3.43 m, 1 H and 3.62 m, 1 H (CH_2, EtO); 4.08 s, 3 H (CH_3O); 4.98 dt, 1 H, J = 9.4; 6.1 (CH); 6.84 d, 1 H, J = 9.4 (NH). ^{13}C NMR spectrum for the major conformer: 9.0 (CH_3, Pr); 15.2 (CH_3, EtO); 28.6 (CH_2, Pr); 56.9 (CH_3O); 64.2 (CH_2, EtO); 86.9 (CH); 191.6 (CS); for the minor conformer: 9.0 (CH_3, Pr); 15.0 (CH_3, EtO); 28.6 (CH_2, Pr); 58.3 (CH_3O); 63.8 (CH_2, EtO); 84.0 (CH); 191.3 (C=S).

Methyl *N*-(1-Ethoxypropyl)carbamate (**3**)

A solution of mesitylnitriloxide (1.61 g, 0.01 mol) in acetonitrile (20 ml) was added dropwise to a solution of thiocarbamate **2** (1.77 g, 0.01 mol) in anhydrous acetonitrile (20 ml) at room temperature with constant stirring. The reaction mixture was stirred for 1 h, the solvent was evaporated, and the crude product was recrystallized from an acetone–hexane mixture. Oil; yield 1.34 g (83%). For ($C_7H_{15}NO_3$) (161.2) calculated: 52.16% C, 9.38% H, 8.69% N; found: 52.32% C, 9.27% H, 8.51% N. IR spectrum: 3 440 (NH); 1 725 (CO). ^{1}H NMR spectrum: 0.93 t, 3 H (CH_3, Pr); 1.16 t, 3 H (CH_3, EtO); 1.60 m, 2 H (CH_2, Pr); 3.53 m (CH_2, EtO); 3.68 s, 3 H (CH_3O); 4.88 m (CH, NH). ^{13}C NMR spectrum: 9.2 (CH_3, Pr); 15.2 (CH_3, EtO); 29.0 (CH_2, Pr); 52.1 (CH_3O); 63.3 (CH_2, EtO); 83.3 (CH, Pr); 156.7 (C=O).

General Procedure for Preparation of Thioureas **4** and **5a–5c**

A solution of the respective amine (0.1 mol) in ether (40 ml) was gradually added to a solution of α-isothiocyanatoether **1a–1d** (0.1 mol) in dry ether (40 ml) with stirring at 0 °C. After the isothiocyanate had reacted (TLC monitoring), ether was evaporated and hexane was added to the residue. The separated crystalline thiourea was collected by suction and dried in air.

N-Propyl-N′-[1-(propylamino)propyl]thiourea (**4**): m.p. 148–150 °C; yield 60%. For $C_{10}H_{23}N_3S$ (217.4) calculated: 55.25% C, 10.67% H, 19.33% N; found: 54.86% C, 10.41% H, 19.28% N. ^{1}H NMR spectrum: 0.98, 9 H (3 CH_3); 1.66 m, 6 H (3 CH_2); 3.53 m, 4 H (2 CH_2); 6.05 m, 1 H (CH); 7.34 s, 2 H (2 NH); 8.65 s, 1 H (NH). ^{13}C NMR spectrum: 9.6 (CH_3); 11.4 (2 CH_3); 22.2 (2 CH_2); 28.8 (CH_2); 47.3 (2 CH_2N); 64.6 (CH); 180.6 (C=S).

N-[N-(1-Ethoxypropyl)thiocarbamoyl]piperidine (**5a**): m.p. 76–78 °C; yield 72%. For $C_{11}H_{22}N_2OS$ (230.4) calculated: 57.35% C, 9.63% H, 12.16% N; found: 57.08% C, 9.56% H, 12.09% N. IR spectrum: 3 430 (NH); 1 510 (NHCS). ^{1}H NMR spectrum: 1.05 t, 3 H (CH_3, Pr); 1.25 m, 3 H (CH_3, EtO); 1.73 m, 8 H (CH_2, Pr; CH_2, skel.); 3.88 m, 6 H (CH_2NCH_2, CH_2O); 5.78 d, 1 H (NH); 6.08 m, 1 H (CHO).

N-[N-(1-Ethoxyethyl)thiocarbamoyl]piperidine (**5b**): m.p. 97–99 °C; yield 77%. For $C_{10}H_{20}N_2OS$ (216.4) calculated: 55.52% C, 9.32% H, 12.95% N; found: 55.36% C, 9.27% H, 12.79% N. IR spectrum: 3 430 (NH); 1 510 (NHCS). ^{1}H NMR spectrum: 1.25 t, 3 H (CH_3, EtO); 1.46 d, 3 H (CH_3); 1.73 m, 6 H (CH_2, skel.); 3.84 m, 6 H (CH_2NCH_2, CH_2O); 5.88 d, 1 H (NH); 6.25 m, 1 H (CHO). ^{13}C NMR spectrum: 15.3 (CH_3); 22.1 (CH_3); 24.3 (CH_2); 25.5 (2 CH_2); 48.9 (CH_2NCH_2); 63.7 (CH_2O); 83.2 (CHO); 180.6 (C=S).

N,N-Diethyl-N′-(1-ethoxyethyl)thiourea (**5c**): m.p. 35–38 °C; yield 45%. For $C_9H_{20}N_2OS$ (204.3) calculated: 52.90% C, 9.87% H, 13.71% N; found: 51.98% C, 9.79% H, 13.68% N. IR spectrum: 3 425 (NH); 1 500 (NHCS). ^{1}H NMR spectrum: 1.25 m, 12 H (CH_3); 3.68 m, 6 H (CH_2); 5.50 d, 1 H (NH); 6.05 dq, 1 H (CHO).

Preparation of 4-(1-Ethoxypropyl)thiosemicarbazide (**6**) and 1-Propylidene-4-(1-ethoxypropyl)thiosemicarbazide (**7**)

A solution of isothiocyanate **1a** (1 g, 7 mmol) in ether (10 ml) was added dropwise to a solution of 35% hydrazine (0.63 g, 7 mmol) in ethanol (10 ml) with constant stirring under nitrogen at –30 °C. The temperature of reaction mixture was allowed to increase to room temperature. The crude product obtained upon evaporation of the solvent was submitted to chromatography (silica gel; heptane–ether 1 : 1) to give compounds **6** and **7**.

4-(1-Ethoxypropyl)thiosemicarbazide (**6**): m.p. 67–70 °C (heptane); yield 38%. For $C_6H_{15}N_3OS$ (177.3) calculated: 40.65% C, 8.53% H, 23.70% N; found: 40.17% C, 8.47% H, 23.34% N. ^{1}H NMR spectrum: 0.98 t, 3 H (CH_3, Pr); 1.20 t, 3 H (CH_3, EtO); 1.68 m, 2 H (CH_2, Pr); 3.66 m, 2 H (CH_2, EtO); 3.84 s, 2 H (NH_2); 5.38 dt, 1 H (CH); 7.62 d, 1 H (NH); 8.13 s, 1 H (NH). ^{13}C NMR spectrum: 9.1 (CH_3); 15.3 (CH_3); 28.9 (CH_2); 63.8 (CH_2O); 85.3 (CH); 182.1 (C=S).

1-Propylidene-4-(1-ethoxypropyl)thiosemicarbazide (**7**): m.p. 187–188 °C; yield 23%. For $C_9H_{19}N_3OS$ (217.3) calculated: 49.74% C, 8.81% H, 19.23% N; found: 49.15% C, 8.69% H, 19.13% N. ^{1}H NMR spectrum: 0.99 t, 3 H (CH_3, Pr); 1.11 t, 3 H (CH_3, Pr); 1.21 t, 3 H (CH_3, EtO); 1.72 m, 2 H (CH_2, Pr); 2.30 m, 2 H (CH_2, Pr); 3.68 m, 2 H (CH_2, EtO); 5.69 dt, 1 H (CH); 7.30 t, 1 H (CH=N); 7.48 d, 1 H (NH); 9.85 s, 1 H (NH). ^{13}C NMR spectrum: 9.0 (CH_3); 10.5 (CH_3); 15.2 (CH_3); 25.7 (CH_2); 29.0 (CH_2); 64.0 (CH_2); 85.5 (CH); 148.4 (C=N); 177.4 (C=S).

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