Synthesis of 1,2,5,6-tetrathiocines from fused 1,2,3,4,5-pentathiepines*

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1,2,3,4,5-Pentathiepines fused with the pyrrole, thiophene, and indole systems react with sodium cyanide in acetonitrile to form the corresponding tri- and pentacyclic fused 1,2,5,6-tetrathiocines. In the case of unsymmetric pentathiepines annulated at the *b* side of thiophene or indole, mixtures of isomeric tetrathiocines (~1 : 1) are formed.

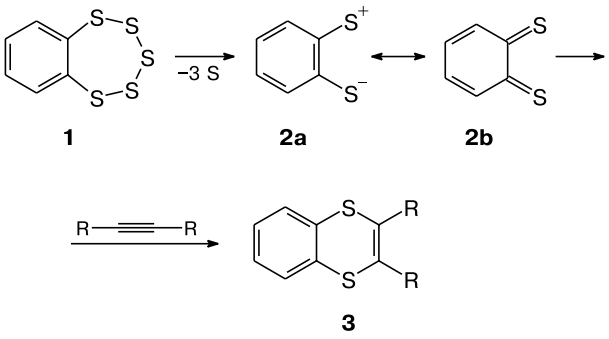
Key words: 1,2,5,6-tetrathiocines, 1,2,3,4,5-pentathiepines, sodium cyanide, pyrrole, thiophene, indole.

1,2,3,4,5-Pentathiepines evoke interest in recent years due to their high stability, abundance in the nature, and diverse biological activity and also because these compounds can serve as convenient starting substances in syntheses of a wide series of various polysulfur-containing derivatives, for instance, 1,4-dithiines, cyclic 1,3-dithioles, vicinal 1,2-dithiols, and many others.[1]

We have recently developed the methods for syntheses of 1,2,3,4,5-pentathiepines fused with such heterocycles as pyrrole, indole, thiophene, and furan.[2] These syntheses are based on the reaction of these nucleophilic heterocycles with sulfur monochloride and 1,4-diazabicyclo[2.2.2]octane (DABCO) or their complexes.[3] The chemistry of pentathiepines has previously been studied mainly for the benzofused analogs.[1] The most part of the reactions of these compounds involves the attack of nucleophilic or electrophilic agents at the sulfur atoms of the pentathiepine ring resulting in its opening as, for example, in benzopentathiepine **1** with the consecutive loss of one to five sulfur atoms.[4] Three sulfur atoms are eliminated most readily to form, evidently, intermediate species of the type **2a,b** (Scheme 1), which can add to alkynes giving 1,4-dithiines **3** (see Ref. 5).

We have shown[6] that the reaction of pentathiepines, which are fused with aromatic and heterocyclic rings, with alkynes containing electron-withdrawing groups in the presence of triphenylphosphine is characteristic of this class of compounds and affords the corresponding 1,4-dithiines in high yields. In the present work, we studied in detail the reaction of pentathiepines with sodium cyanide. This reagent similarly to triphenylphosphine can eliminate the sulfur atoms from a pentathiepine molecule.

Scheme 1



The interaction of pentathiepine **4** with three equivalents of NaCN in acetonitrile at ambient temperature affords sodium thiocyanate (NaSCN), which was isolated in practically quantitative yield (96%). Dimethyl acetylenedicarboxylate reacts readily with a mixture of pentathiepine **4** and NaCN to form dithiine **5** in 85% yield (Scheme 2).[6]

This reaction also gave a stable by-product different from 1,4-dithiine **5**. We assumed that this is the product of the reaction of pentathiepine **4** and NaCN. In fact, it was found that the interaction of compound **4** with three equivalents of NaCN in a large amount of acetonitrile for 1 h gives product **6** in high yield. The empirical formula of compound **6** was determined by the data of elemental analysis and mass spectrometry: $C_{10}H_6Cl_4N_2S_4$; the symmetric character of the structure formed was established using the NMR spectra. This suggests that the structure of product **6** corresponds to a tetrathiocine molecule

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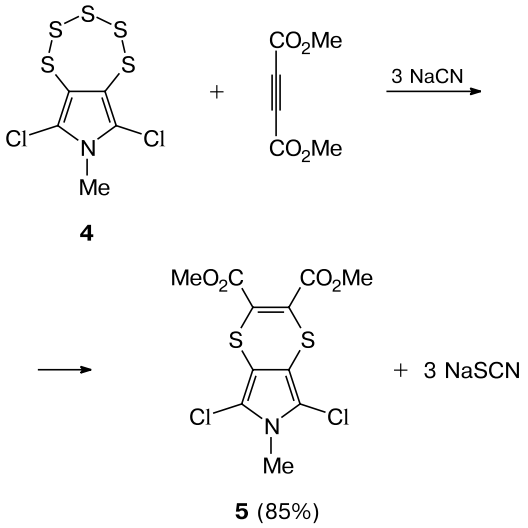
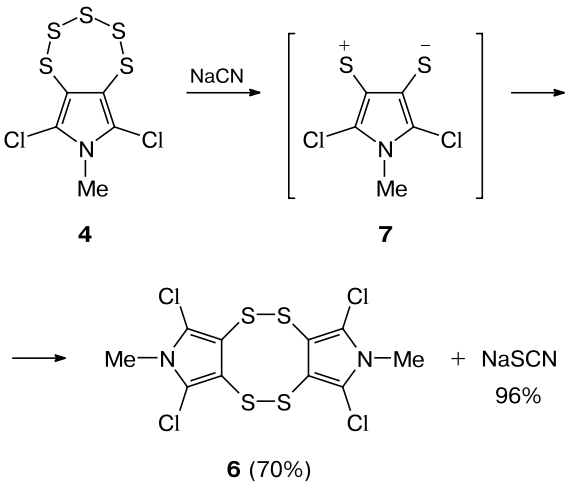
Scheme 2



Conditions: 1 h, 20 °C.

(Scheme 3). No similar conversion of pentathiepines have earlier been described.

Scheme 3

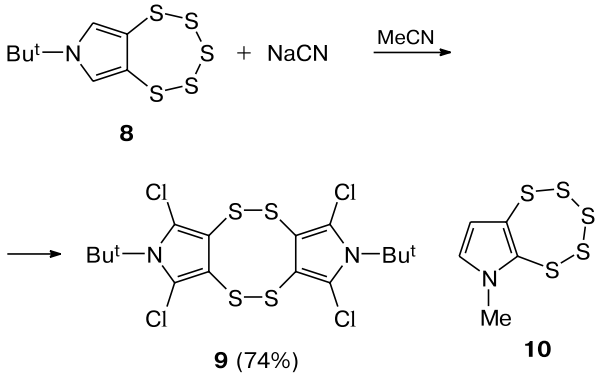


Conditions: 20 °C, 1 h.

The formation of tetrathiocine from pentathiepine **4** by the action of sodium cyanide can be due to the fact that after the elimination of three sulfur atoms dichloropentathiepine **4** is transformed into intermediate **7**, which is more stable in an aprotic dipolar solvent (acetonitrile) than dithioketone of the type **2b** due to the betaine structure and, finally, is dimerized to form tetrathiocine **6**.

The reaction with symmetric pentathiepinopyrrole **8** proceeds analogously, *i.e.*, with the formation of tetrathiocine **9** in high yield (Scheme 4).

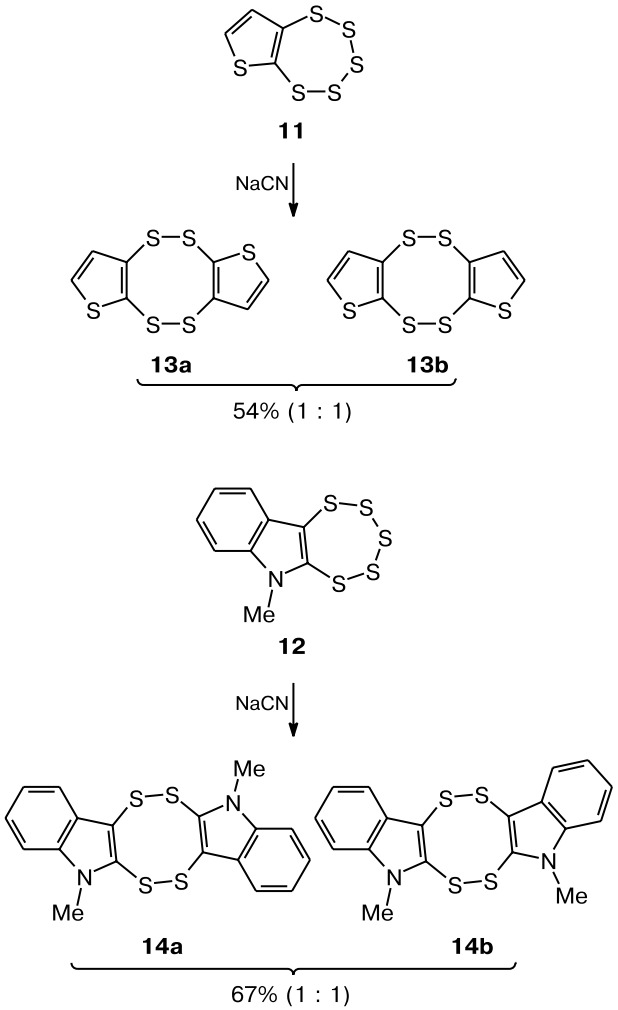
Scheme 4



Conditions: 20 °C, 1 h.

At the same time, 6-methyl-6*H*-[1,2,3,4,5]pentathiepino[6,7-*b*]pyrrole **10** decomposes upon the interac-

Scheme 5

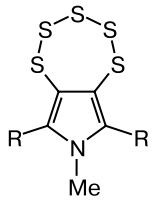


tion with sodium cyanide, most likely, because of instability of intermediates of the type **7**.

When other unsymmetric pentathiepines **11** and **12** react with sodium cyanide, mixtures of isomeric tetrathiocines **13a,b** and **14a,b**, respectively, in equal ratios are formed (according to the NMR spectral data) (Scheme 5).

Thus, the reaction of unsymmetric pentathiepines with sodium cyanide is not regiospecific. The structures of tetrathiocines **13** and **14** were proved using the data of elemental analysis, NMR spectroscopy, and mass spectrometry.

Some of pentathiepinopyrroles **15** containing alkyl and phenyl substituents in the pyrrole cycle are stable to the action of sodium cyanide and underwent no changes when keeping the reaction mixture for 48 h at ambient temperature.



15a,b

R = Me (**a**), Ph (**b**)

Tetrathiocines conjugated with the benzene ring manifest high antimicrobial activity toward *Candida albicans*[7] and fungicidal activity toward *Staphylococcus aureus*, *Escherichia coli*, and *Saccharomyces cerevisiae*.[8] 1,2,5,6-Tetrathiocines have earlier been synthesized from the poorly available starting compounds by the oxidation of vicinal 1,2-dithioles and their derivatives[9] and using the desulfurization of benzo-1,2.3-trithioles.[10] We proposed the method for synthesis of these potentially useful compounds from pentathiepines fused with heterocycles, which became easily accessible. Although the method is not general, it seems attractive due to simplicity.

Experimental

^{1}H NMR spectra (in $CDCl_3$) were obtained on Bruker WM-250 and Bruker AM-300 instruments with working frequencies of 250 and 300 MHz, respectively. Chemical shifts in the NMR spectra are given in the δ scale relative to Me_4Si. Melting points were determined on a Kofler heating stage and were not corrected. Mass spectra were recorded on a Finnigan MAT INCOS 50 instrument using electron impact. High-resolution mass spectra were measured on a VG Autospec Q instrument.

The starting pentathiepines were synthesized according to described procedures.[2,11]

Synthesis of tetrathiocines (general procedure). Sodium cyanide (0.15 g, 3 mmol) was added for 20 min to a solution of pentathiepine (1 mmol) in acetonitrile (400 mL) at room temperature with vigorous stirring. The reaction mixture was stirred for 1 h at room temperature. Then the solvent was distilled off under reduced pressure. The solid residue was washed with methylene chloride (3×100 mL). The joined mother liquor was washed with water (3×100 mL) and dried over $MgSO_4$. The solvent was distilled off under reduced pressure, and the resulting solid residue was dried *in vacuo* (at 5 Torr).

1,3,6,8-Tetrachloro-2,7-dimethyl[1,2,5,6]tetrathiocino[3,4-*c*;7,8-*c*´]dipyrrole (6), the yield was 0.3 g (70%), pale yellow crystals, m.p. 162—164 °C. Found (%): C, 28.45; H, 1.61; N, 6.41. $C_{10}H_6N_2S_4Cl_4$. Calculated (%): C, 28.31; H, 1.43; N, 6.60. ^{1}H NMR (Py-d_5), δ: 3.59 (s, 3 H, Me). MS (EI, 70 eV), m/z (I_{rel} (%)): 424 $[M]^+$ (10), 360 (10), 307 (10), 135 (20), 64 (100). Found, m/z: 421.8165 $[M]^+$. $C_{10}H_6N_2S_4Cl_4$. Calculated: 421.8168.

2,7-Bis(*tert*-butyl)[1,2,5,6]tetrathiocino[3,4-*c*:7,8-*c*´]dipyrrole (9), the yield was 0.27 g (74%), yellow crystals, m.p. 190—192 °C. Found (%): C, 51.98; H, 6.20; N, 7.90. $C_{16}H_{22}N_2S_4$. Calculated (%): C, 51.85; H, 5.98; N, 7.56. ^{1}H NMR ($CDCl_3$), δ: 1.51 (s, 18 H, Me); 7.06 (s, 4 H, CH). ^{13}C NMR ($CDCl_3$), δ: 30.27 (CH_3); 125.38 (CH); 56.16, 119.43 (two quaternary C atoms). MS (EI, 70 eV), m/z (I_{rel} (%)): 370 $[M]^+$ (90), 306 (90), 250 (65), 194 (100), 64 (90). Found, m/z: 370.0654 $[M]^+$. $C_{16}H_{22}N_2S_4$. Calculated: 370.0666.

Dithieno[2,3-*c*:2´,3´-*g*][1,2,5,6]tetrathiocine (13a) and dithieno[2,3-*c*;3´,2´-*g*][1,2,5,6]tetrathiocine (13b), the yield was 0.16 g (54%), yellow crystals, m.p. 153—154 °C. Found (%): C, 32.95; H, 1.64. $C_8H_4S_4$. Calculated (%): C, 32.85; H, 1.38. ^{1}H NMR (Py-d_5), δ: 6.80, 6.89, 7.06, 7.14 (all d, 2 H each, CH, J = 5.3 Hz). MS (EI, 70 eV), m/z (I_{rel} (%)): 292 $[M]^+$ (75), 228 (100), 146 (35), 70 (80). Found, m/z: 291.8638 $[M]^+$. $C_8H_4S_4$. Calculated: 291.8637.

1,8-Dimethyl[1,2,5,6]tetrathiocino[3,4-*b*;7,8-*b*´]diindole (14a) and 1,12-dimethyl[1,2,5,6]tetrathiocino[3,4-*b*;8,7-*b*´]diindole (14b), the yield was 0.26 g (67%), yellow crystals, m.p. 260—265 °C. Found (%): C, 56.10; H, 3.85; N, 7.90. $C_{18}H_{14}N_2S_4$. Calculated (%): C, 55.92; H, 3.65; N, 7.25. ^{1}H NMR (Py-d_5), δ: 3.93, 3.98 (both s, 3 H each, CH_3); 7.17 (m, 8 H, CH); 7.26, 7.36 (both m, 4 H each, CH). MS (EI, 70 eV), m/z (I_{rel} (%)): 386 $[M]^+$ (10), 322 (100), 275 (25), 225 (50), 192 (90), 178 (30). Found, m/z: 386.0024 $[M]^+$. $C_{18}H_{14}N_2S_4$. Calculated: 386.0024.

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