

# The Reaction of 4-Substituted Thiosemicarbazides with Phenyl Isocyanide. 1,3,4-Thiadiazoles and 1,2,4-Triazoles

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In connection with our investigations on the reactivity of isocyanides towards hydrazines<sup>1</sup> we were interested in the reaction between thiosemicarbazides and phenyl isocyanide. No  $\alpha$ -addition products or products from cleavage of the  $N^4-C$  bond as observed for reaction with thioureas<sup>2</sup> were isolated, instead we found cyclization by insertion of  $=CH-$  between N and S or between N and N. Similar insertion reactions of  $=CH-$  with isocyanides have been reported for reaction with bifunctional compounds such as diamines, aminoalcohols, and aminothiols.<sup>3</sup>

The reactions were carried out in refluxing benzene with copper(I) chloride as catalyst. Three thiosemicarbazides were examined, namely 4-methyl-, 4-phenyl- and unsubstituted thiosemicarbazide.

4-Methylthiosemicarbazide (*1a*) was the most slowly reacting thiosemicarbazide (1.75 h) giving almost exclusively 2,4-dihydro-4-methyl-3H-1,2,4-triazole-3-thione (*3a*). Thiosemicarbazide (*1b*) and 4-phenylthiosemicarbazide (*1c*) required both 0.75 h for consuming the isocyanide. Thiosemicarbazide (*1b*) gave only 2-amino-1,3,4-thiadiazole (*2b*), and 4-phenylthiosemicarbazide (*1c*) gave a mixture of 2-phenylamino-1,3,4-thiadiazole (*2c*) and 2,4-dihydro-4-phenyl-3H-1,2,4-triazole-3-thione (*3c*). In all three reaction mixtures we found an almost quantitative yield of aniline determined by GLC analysis.

By TLC analysis we determined that only 4-phenylthiosemicarbazide formed both the thiadiazole and the triazole in high yield. 2-Methylamino-1,3,4-thiadiazole (*2a*) and 2,4-dihydro-3H-1,2,4-triazole-3-thione (*3b*) could only be detected as traces (less than 1%) in the other two reaction mixtures.

It is known that thiosemicarbazides can be

cyclized to either thiadiazoles (*2*) or triazoles (*3*) or a mixture,<sup>4,5</sup> depending on the reaction conditions<sup>6</sup> and the cyclizing agent.<sup>7</sup> The substituent (alkyl or aryl) in the 4-position of the thiosemicarbazide has been reported important for the product distribution with triethyl orthoformate as cyclizing agent<sup>8</sup> as reported in this communication when phenyl isocyanide is used as cyclizing agent.

**Experimental.** Microanalyses were carried out in the Microanalysis Department of Chemical Laboratory II, The H. C. Ørsted Institute. <sup>1</sup>H NMR spectra were obtained on a JEOL JNM MH 60/II instrument. IR spectra were recorded on a Perkin-Elmer model 225 grating spectrograph or model 157 NaCl spectrophotometer. Mass spectra were taken on an AEI-902 instrument operating at 70 eV. GLC-analyses were carried out on a Perkin-Elmer F11 gas chromatograph equipped with a Chromosorb 103 column. Melting points are uncorrected.

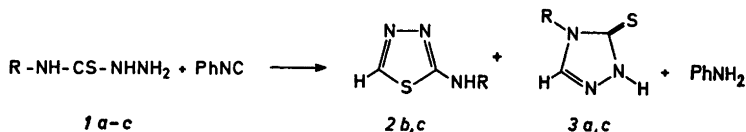
All the compounds mentioned have previously been described in the literature.<sup>9-13</sup> Their identities were established by IR, NMR and mass spectrometry. The IR spectra were compared with spectra of authentic samples.

**2,4-Dihydro-4-methyl-3H-1,2,4-triazole-3-thione (3a).**<sup>9</sup> A solution of phenyl isocyanide (0.05 mol) and copper(I) chloride (0.00075 mol) in 50 ml of benzene was refluxed with 4-methylthiosemicarbazide (*1a*) (0.05 mol) for 1.75 h. The reaction mixture was cooled in ice and the precipitate filtered off and washed with ether. Yield 81% of yellow crystals, m.p. 163–165 °C.

**2-Amino-1,3,4-thiadiazole (2b)**<sup>9</sup> was prepared from thiosemicarbazide (*1b*) as described above. Reflux for 0.75 h consumed the phenyl isocyanide and left a syrupy mass after decantation. Recrystallization from ethanol gave 30% of light yellow crystals, m.p. 188–190 °C.

When the reaction was carried out without copper(I) chloride the phenyl isocyanide was consumed after 2 h yielding 65% of 2-amino-1,3,4-thiadiazole (*2b*).

**2-Phenylamino-1,3,4-thiadiazole (2c)**<sup>11</sup> and **2,4-dihydro-4-phenyl-3H-1,2,4-triazole-3-thione (3c)**<sup>13</sup> A solution of phenyl isocyanide (0.10 mol) and copper(I) chloride (0.0015 mol) in 100 ml of benzene was refluxed with 4-phenylthiosemicarbazide (*1c*) (0.10 mol) for 0.75 h. The reaction mixture was cooled in ice and the precipitate was filtered off. The precipitate was extracted with 1 M NaOH solution, the



Scheme 1. a, R=CH<sub>3</sub>; b, R=H; c, R=Ph.

residue filtered off, washed with water yielding 32 % of light yellow crystals of 2-phenylamino-1,3,4-thiadiazole (2c), m.p. 171–172 °C.

2,4-Dihydro-4-phenyl-3*H*-1,2,4-triazole-3-thione (3c) was precipitated from the alkaline filtrate by acidification with glacial acetic acid. Yield 42 % of colourless crystals, m.p. 164–165 °C.

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## Conformational Analysis. XVI. The Enthalpy and Entropy Difference Between Twist and Chair Forms of the 1,3-Dithian Ring

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Conformational equilibria of substituted six-membered heterocycles have been widely investigated and the conformational energies obtained have led to at least a qualitative understanding of the different forces and interactions in these compounds. 1,3-Dithians are especially suitable for studies of conformational equilibria since  $-ΔG^{\circ}$ -values may be determined for a particular group at all three nonequivalent sites (2, 4/6 and 5) of the ring and moreover, acid-catalysed equilibration of epimeric derivatives normally occurs readily thus permitting the use of the reliable direct equilibrium method. For this purpose one must find models in which a given substituent biases one conformation for each isomer. In cyclohexanes the most commonly used models have a *t*-butyl group<sup>1</sup> ( $-ΔG^{\circ} \sim 24 \text{ kJ mol}^{-1}$ ) located in position 4 with respect to the group studied. In 1,3-dithians, however, *cis*-2,5-dialkyl substituted derivatives are seldom biased<sup>1,2</sup> and hence unsuitable as direct models of the twist-chair equilibrium. Consequently, it is preferable to employ, e.g., *r*-2-alkyl,*cis*-4,*cis*-6-dimethyl-(1) and *r*-2-alkyl,*trans*-4,*trans*-6-dimethyl-1,3-dithians (2) as model compounds<sup>1-3</sup> to determine the chair-twist enthalpy and entropy differences (Fig. 1). For this purpose epimeric 2-*t*-butyl-4,6-dimethyl-1,3-dithians were prepared in an acid-catalysed condensation reaction from *meso*-2,4-pentanedithiol and 2,2-dimethylpropanal.<sup>1</sup> Epimers were separated by preparative gas chromatography and then equilibrated at three temperatures using trifluoroacetic acid as catalyst. The samples were analysed by gas chromatography. The resulting equilibrium constants and thermodynamic parameters are shown in Table 1.

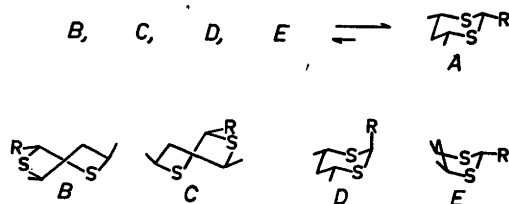


Fig. 1. The studied epimeric equilibria. 1 (A) is *r*-2-alkyl,*cis*-4,*cis*-6-dimethyl- and 2 (B–E) *r*-2-alkyl,*trans*-4,*trans*-6-dimethyl-1,3-dithian. a, R = *t*-Bu; b, R = *i*-Pr.