The Stereochemistry of the 1,4-Elimination of Thiocyanic Acid from Hex-3-ene-2,5-diyl Dithiocyanates

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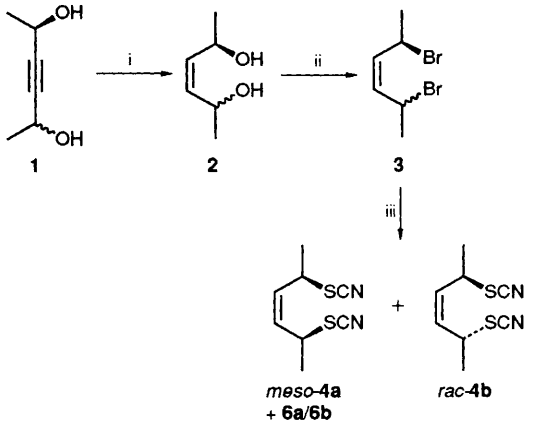
The elimination of thiocyanic acid from the stereoisomers of the hex-3-ene-2,5-diyl dithiocyanates, **4a**, **4b**, **6a** and **6b**, in the presence of a strong neutral base in an organic solvent, yields mixtures of the hex-2,4-dien-2-yl thiocyanates **9**, **10** and **11** *via* a preferentially *syn* process.

Nucleophilic-substitution processes, which are accompanied by an allylic rearrangement, so-called S_N' reactions, have been studied experimentally for almost 40 years.[1] The stereochemistry of the S_N' reaction has been investigated[2] and a series of theoretical analyses have been published,[3] predicting a *syn* preference. In contrast to the S_N' process the corresponding E′ is less well studied.[4]



Scheme 1 *Reagents and conditions*: i, H_2 100 bar (1 bar = 10^5 Pa), Lindlar catalyst, 2,2′-[ethane-1,2-diyl-bis(thio)]-bisethanol, methanol, room temp., 6 h, 90%; ii, PPh_3, Br_2, acetonitrile, 0 °C, then **2**, room temp., 60%; iii, KSCN, ethanol–water 10:2, 10 °C, 70 h, silica gel column **4b** 43%, mixture **4a**–**6a**–**6b** (79:19:9) 21%

The E′ elimination of thiocyanic acid to form substituted butadienes has been described in an earlier publication.[5] For the complete analysis of the stereochemistry of the elimination process the relative configuration of the four centres participating in the reaction has to be known. To analyse the stereochemistry of the E′ elimination of thiocyanic acid with a neutral base in an organic solvent we decided to synthesize the four diastereoisomers of the hex-3-ene-2,5-diyl dithiocyanates **4a**, **4b**, **6a** and **6b** and to study the relative configuration of the products formed.

To obtain the dithiocyanates **4a**, **4b**, **6a** and **6b** two synthetic pathways have been developed (Schemes 1 and 2), starting from the commercially available mixture of the hex-3-yne-2,5-diol **1**. Controlled hydrogenation of the diastereoisomeric mixture of diols **1** with Lindlar catalyst[6] gave, in good yield, a mixture of the *Z*-hexenediols **2**. Treatment of this mixture with dibromotriphenylphosphorane in acetonitrile[7] gave the dibromides **3**, which were treated with potassium thiocyanate

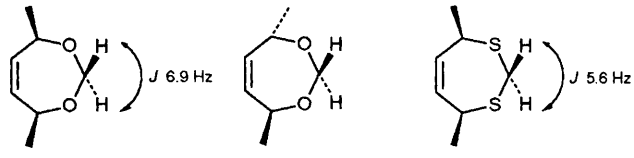
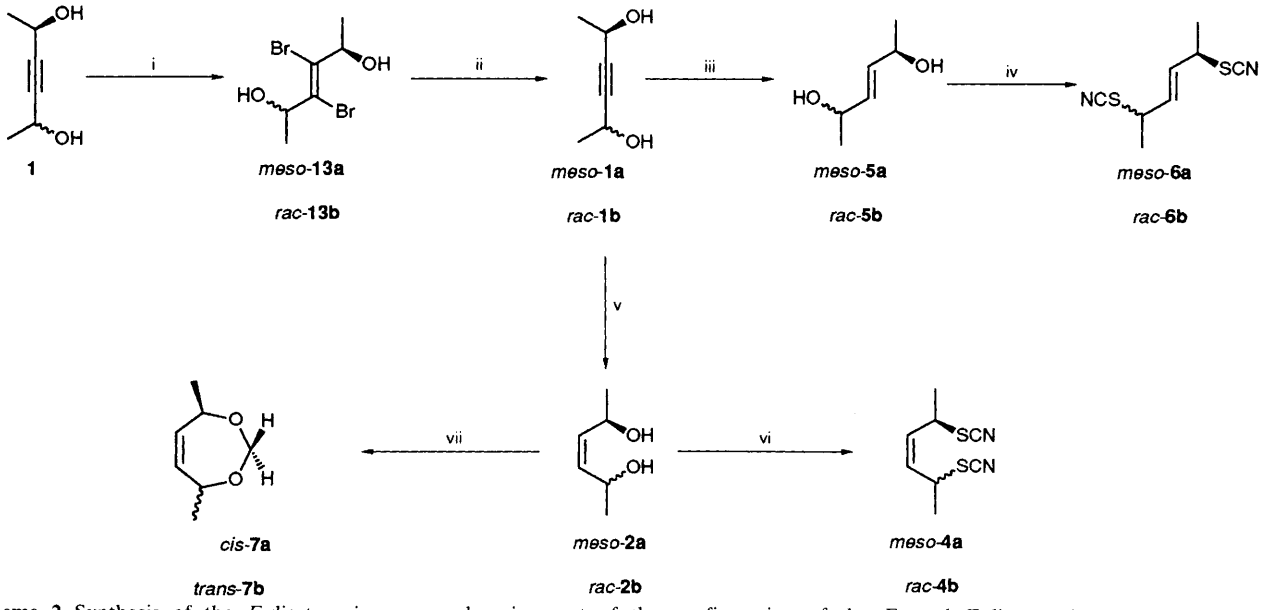
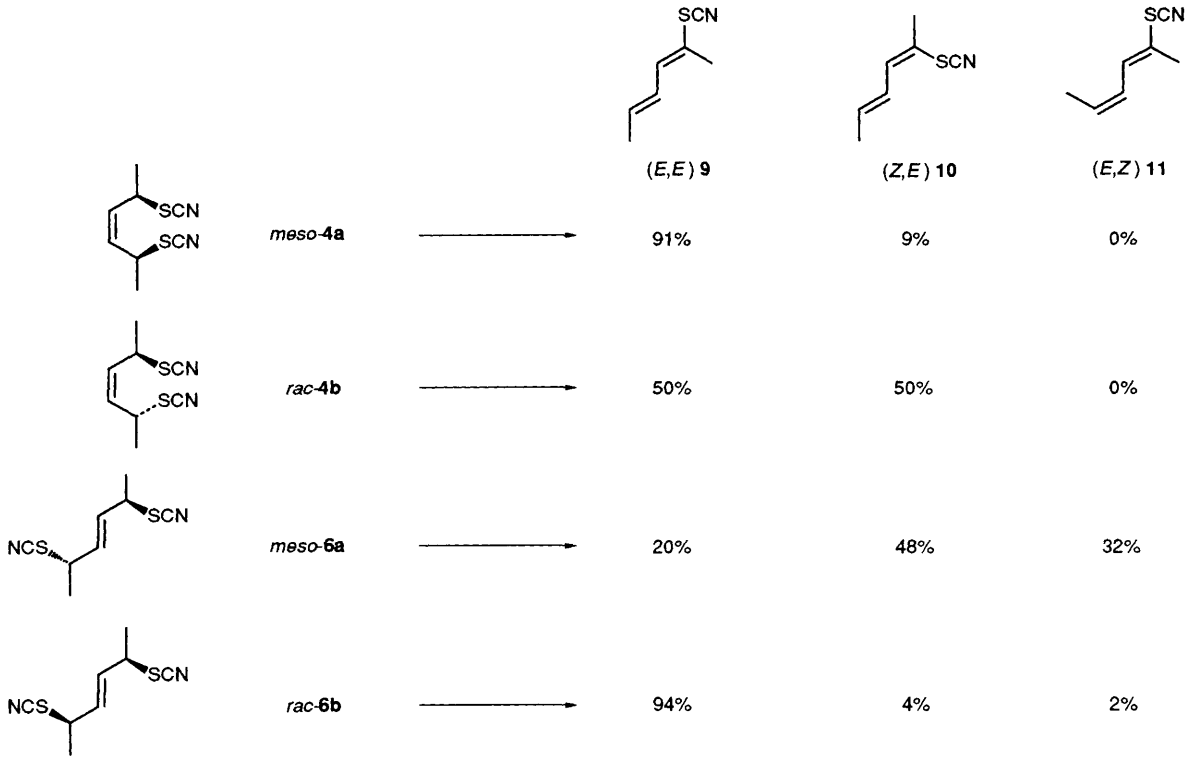


Fig. 1 Selected ^1H NMR data for **7a**, **7b** and **8**



Scheme 2 Synthesis of the *E*-diastereoisomers and assignment of the configuration of the *E*- and *Z*-diastereoisomers. *Reagents and conditions*: i, Br_2, $CHCl_3$, **13a** 48%, **13b** 38%; ii, Zn, AcOH, EtOH, reflux, 3 h, **1a** 83%, **1b** 86%; iii, $LiAlH_4$, diethyl ether, reflux, 4 h, **5a** 83%, **5b** 88%; iv, $Pb(SCN)_2$, Br_2, CH_2Cl_2, 0 °C, then PPh_3, −40 °C, then **5a** or **5b**, then room temp. **6a** 45%, **6b** 45%; v, H_2 100 bar, Lindlar catalyst, chinoline, methanol, room temp., 24 h, **1a** 78%, **1b** 77%; vi, *same conditions* as iv **4a** 29%, **4b** 32%; vii, $(H_2CO)_n$, TosOH, CH_2Cl_2, reflux, **7a** 70%, **7b** 70% (Tos = *p*-toluenesulfonyl)



Scheme 3 *Reagents and conditions*: *N'''*-butyl-*N*,*N*,*N'*,*N'*,*N''*,*N''*-hexamethylphosphorimidic triamide **12**, dry diethyl ether, −18 °C, 20 h, yields for **4a** (mixture) 90%, for **4b** 86%, **6a** 78%, **6b** 78%. For **4a** a mixture of **4a**–**6a**–**6b** was used and the eliminations results were corrected for the presence of **6a** and **6b**

in ethanol and water.[5] The two diastereoisomers *meso*-**4a** and *rac*-**4b** (*rac* = racemic) were separated by column chromatography on silica gel. *Rac*-**4b** was obtained pure, the fraction containing *meso*-**4a** was only enriched.

To synthesize the *E*-diastereoisomers *meso*-**6a** and *rac*-**6b**, we were forced to start with the pure diastereoisomers *meso*-**1a** and *rac*-**1b** obtained *via* a literature procedure.[8] These hex-3-yne diols **1a** and **1b** were in turn reduced separately with $LiAlH_4$ in diethyl ether.[9] The dithiocyanates **6a** and **6b** were obtained directly by treatment of the diols **5a** and **5b** with dithiocyanotriphenylphosphorane in dichloromethane,[10] to obtain pure *meso*-**6a** and pure *rac*-**6b**.

To prove the relative configuration of the diols **2a** and **2b** they were treated with paraformaldehyde to obtain the *cis*- and *trans*-4,7-dihydro-4,7-dimethyl-1,3-dioxepine **7a** and **7b**. The ^1H NMR spectrum of **7a** showed an AB system for the methylene group at C-2 whereas the spectrum of **7b** showed a singlet thereby proving the relative configuration of the products (Fig. 1).[11] To secure the stereochemical arrangement of *meso*-**4a** and *rac*-**4b** two independent determinations of the relative configuration were performed. Reduction of *meso*-**4a** with $LiAlH_4$ and directly treating the product with paraformaldehyde gave the *cis*-4,7-dihydro-4,7-dimethyl-1,3-dithiepine **8**, which showed an AB system for the methylene group at C-2. Finally *rac*-**4b** could be crystallised and the X-ray structure could be solved, confirming our assignment.[12]

For the stereochemical assignment of the *E*-diastereoisomers *meso*-**6a** and *rac*-**6b** the separated hexynediols *meso*-**1a** and *rac*-**1b** were chemically correlated with the dithiocyanates (Scheme 2). The hexynediols were independently transformed into the hexenediols **2a** and **2b**. With this correlation the relative configuration of the *E*-diastereoisomers could be assured.

The elimination proved to be difficult owing to the instability of the starting material in solution at room temperature. Finally, the use of the *N'''*-butyl-*N*,*N*,*N'*,*N'*,*N''*,*N''*-hexamethylphosphorimidic triamide **12**, a Schwesinger base,[13] allowed us to study the elimination process without side reactions (Scheme 3). The composition of the product mixture was analysed by ^1H NMR spectroscopy and gas chromatography (GC). The analysis of the distribution between the different products during the reaction showed that the products are not isomerized after the elimination. The configurations of the dienes **9**, **10** and **11** were determined observing the NOEs between the methyl groups and the adjacent olefinic protons.

The dithiocyanates *meso*-**4a** and *rac*-**6b** gave essentially **9** (Scheme 3), which indicates a *syn* elimination. For *meso*-**6a** the major products were **10** and **11**, which also corresponds to a *syn* elimination. In the case of *rac*-**4b** the elimination is essentially non-stereoselective. The elimination of thiocyanic acid from **4a**, **4b**, **6a** and **6b** in the presence of a strong neutral base proceeds mainly through a *syn* transition state.

The preference for a *syn* elimination could be attributed to stereoelectronic reasons similar to the arguments used to explain the stereochemistry of the S_N2' process.[3] To rationalize the non-stereospecificity of the elimination process starting from *rac*-**4b** we assume that the reaction follows a least motion pathway.[14] Therefore, the *Z*-diastereoisomers should form the products in s-*cis* conformation, with equilibration afterwards. Whereas the *E*-diastereoisomers would form directly the most stable s-*trans* conformation of the dienes. Following this argument for the *Z*-diastereoisomers the steric interactions present in the starting material and the corresponding steric repulsion in the products in their s-*cis* conformation should also be felt in the transition state. The non-stereoselective elimination starting with **4b** appears to indicate that a transition state in which SCN and H are buttressing, formation of **10**, is less favourable than that in which Me and H are butressing, formation of **9**.

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