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

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The elimination of thiocyanic acid from the stereoisomers of the hex-3-ene-2,5-diyli 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-yli thiocyanates \(9, 10\) and \(11\) via a preferentially syn process.

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

The \(E^1\) 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 \(E^1\) 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-diyli 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-ene-2,5-diyli \(1\). 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.

Scheme 1 Reagents and conditions: \(i\). \(\text{H}_2\) 100 bar (1 bar = \(10^5\) Pa), Lindlar catalyst, 2,2'-[ethylene-1,2-diyli-bis(thio)]-bisethanol, methanol, room temp., \(6\) h, 90%; \(ii\). \(\text{PPh}_3\), \(\text{Br}_2\), acetonitrile, \(0^\circ\)C, then \(2\), room temp., \(60\); \(iii\). \(\text{KSCN}\), ethanol–water \(10:2, 10^\circ\)C, \(70\) h, silica gel column \(4b\) 43%, mixture \(4a-6a-6b\) (79:19:9) 21%.

Scheme 2 Synthesis of the \(E\)-diastereoisomers and assignment of the configuration of the \(E\-) and \(Z\)-diastereoisomers. Reagents and conditions: \(i\). \(\text{Br}_2\), \(\text{CHCl}_3\), \(13\) \(48\), \(13b\) \(38\); \(ii\). \(\text{Zn}, \text{AcOH}, \text{EtOH}\), reflux, \(3\) h, \(11\) \(83\), \(1b\) \(86\); \(iii\). \(\text{LiAlH}_4\), diethyl ether, reflux, \(4\) h, \(5a\) \(83\), \(5b\) \(88\%\); \(iv\). \(\text{Pb(SCN)}_2\), \(\text{Br}_2\), \(\text{CH}_2\text{Cl}_2\), \(0^\circ\)C, then \(\text{PPh}_3\), \(-40^\circ\)C, then \(5a\) or \(5b\), then room temp. \(6a\) \(45\), \(6b\) \(45\); \(v\). \(\text{H}_2\) 100 bar, Lindlar catalyst, choline, methanol, room temp., 24 h, \(1a\) \(78\%), \(1b\) \(77\%; \(vi\). same conditions as \(iv\) \(29\), \(4b\) \(32\_; \(vii\). \((\text{H}_2\text{CO})_n\), \(\text{TosOH}\), \(\text{CH}_2\text{Cl}_2\), reflux, \(7a\) \(70\), \(7b\) \(70\) (\(\text{Tos} = \rho\)-toluenesulfonyl).
in ethanol and water. 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. These hex-3-yn diols 1a and 1b were in turn reduced separately with LiAlH₄ in diethyl ether. The diolocynates 6a and 6b were obtained directly by treatment of the diols 5a and 5b with diethoxytriphosphorylphosphate in dichloromethane, 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). 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 LiAlH₄ 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.

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 diolocynates (Scheme 2). The hexynediols were independently transformed into the hexynediols 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''-hexamethylphosphorimidic triamide 12, a Schesinger base, 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 isomerised 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 diolocynates meso-4a and rac-4b 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 stereoechemistry of the Sn2' process. To rationalize the non-stereospecificity of the elimination process starting from rac-4b we assume that the reaction follows a least motion pathway. Therefore, the E-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 butressing, formation of 10, is less favourable than that in which Me and H are butressing, formation of 9.
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References
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