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Diastereoselective synthesis of multisubstituted thiacyclohexanes via cation–olefin cyclizations

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Abstract

Thiacyclohexane derivatives were synthesized in high yields with excellent diastereoselectivity via an indium trichloride-mediated cationic cyclization.

Tetrahydropyrans (THP) are the backbones of most carbohydrates and a common structural feature in many natural products. Thus, many methods have been developed for their formation.[1] In contrast, thiotetrahydropyrans (thiacyclohexanes) are less frequently encountered in nature. A fair number of thiacyclohexane derivatives are found in petroleum oil.[2] The thiacyclohexane ring also plays a key role in the biological activities of a number of pharmaceutical agents such as cephalosporins[3] and dithiathromboxane A_2.[4] Recently, there has been increased interest in developing new therapeutic agents based on thiacyclohexane structures.[5] In addition, thiacyclanes can be transformed to a variety of structures through simple reactions, such as hydrogenolysis, oxidation, and olefination.[6] Herein, we report a diastereoselective synthesis of thiacyclohexane derivatives via an indium chloride-mediated Prins-type cyclization between homoallyl mercaptans and aldehydes.[7]

The homoallyl mercaptans were readily synthesized by reacting the corresponding homoallyl alcohols with thioacetic acid via a modification of the Mitsunobu protocol[8] followed by lithium aluminum hydride (LAH) reduction. Attempts to synthesize the thiols by using the Lawesson's reagent[9] were not successful. The stirring of phenyl homoallyl mercaptan **1** with benzaldehyde and indium chloride in methylene chloride led to the smooth formation of 2,4,6-trisubstituted thiacyclohexanes **2a** and **2b** (97%) as a 8:1 mixture of diastereomers (Eq. (1)). However, reaction of this thiol with other substituted aromatic aldehydes gave rise to a mixture of several cyclization products (as was shown by GC/MS analysis of the reaction mixture), which apparently resulted from the scrambling of two different kinds of aryl rings on the thiocyclohexane ring. On the other hand, the reaction of an aliphatic homoallyl mercaptan **3** (when a *cis*-isomer was used) with aldehydes generated unsymmetrical 2,3,4-trisubstituted thiacyclohexanes

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4a and **4b** in high yield with good diastereoselectivity together with a trace amount of thiacyclohexene derivative **4c** (Eq. (2)). The diastereoselectivity remains nearly the same in all cases at ca. 7:1 favoring the *cis–trans–cis*-isomers (Table 1). The relative configurations of the diastereomers were assigned via the coupling constants of the two distinct pairs of peaks at ca. 4.0 ppm as shown in Fig. 1.

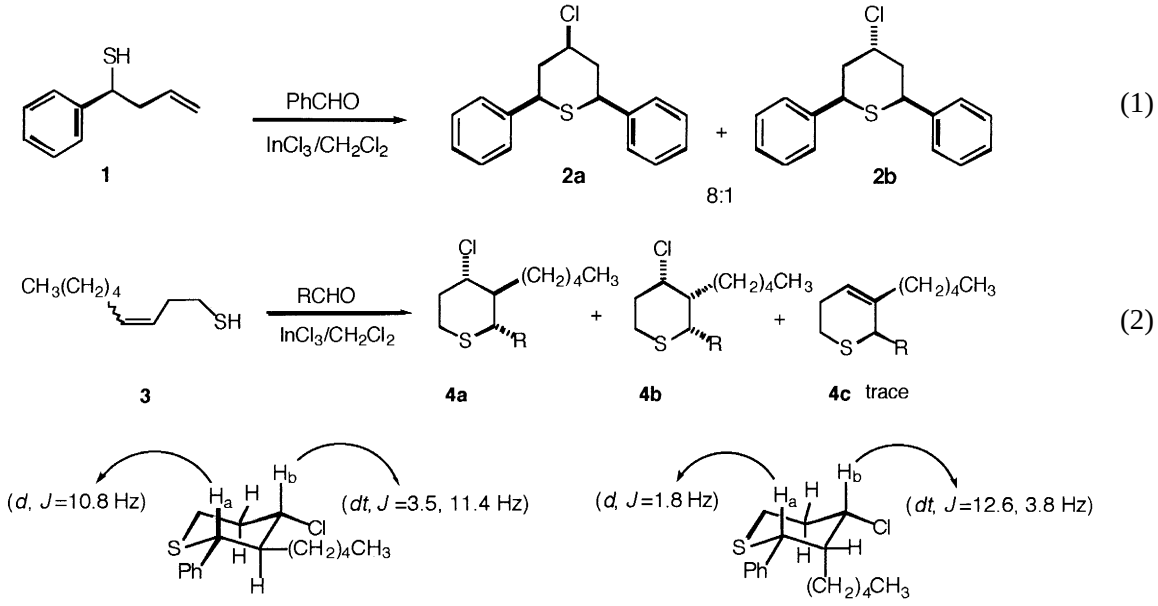


Fig. 1.

In order to investigate the effect of *cis–trans* conformations of the mercaptan on the diastereoselectivity of the cyclization, the corresponding *trans*-isomer of mercaptan **3** was also prepared by the previous method and was reacted with the aldehydes used earlier and indium trichloride under the same reaction conditions. Interestingly, reactions of both *cis*- and *trans*-mercaptans generated the cyclized product with the same major configuration but different selectivity. Whereas the use of the *cis*-mercaptan gave rise to a mixture of *cis–cis–cis* and *cis–trans–cis* thiacyclohexane derivatives with the latter as the predominant product, the reaction of the *trans*-mercaptan generated a *cis–trans–cis* thiacyclohexane derivative exclusively (Table 1). The results would suggest that, with the use of the *trans*-mercaptan, the stereospecificity associated with the product formation was most likely due to the formation of a chair-transition-state in the ring closure process; whereas, in the case of the *cis*-mercaptan, an isomerization of the less stable carbocation intermediate might have occurred (possibly via a decyclization–cyclization process) which led to the formation of the more stable *cis–trans–cis* product (Scheme 1).[10] The existence of such an isomerization might also explain the scrambling of products in the reaction between an aryl homoallyl mercaptan and an aryl aldehyde. Alternatively, a boat-transition-state might be involved in the cyclization of the *cis*-isomer, generating the same major product as in the case of the *trans*-isomer. The scope and mechanism of the reaction, as well as the biological activities of the thiacyclohexane derivatives are under investigation.

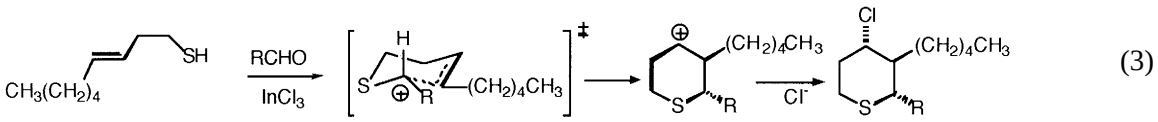
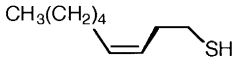
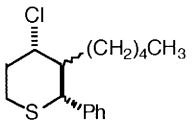
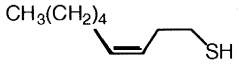
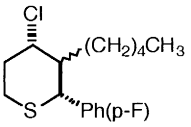
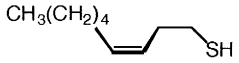
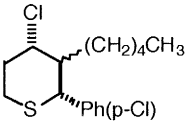
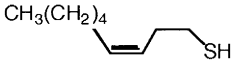
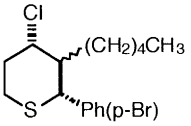
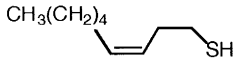
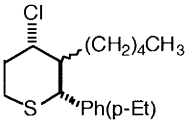
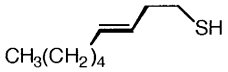
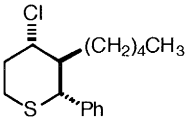
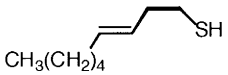
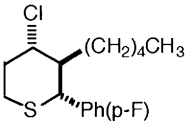
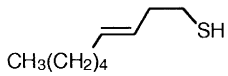
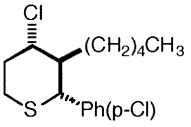
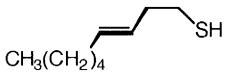
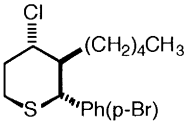
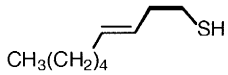
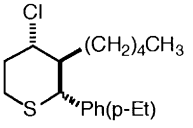
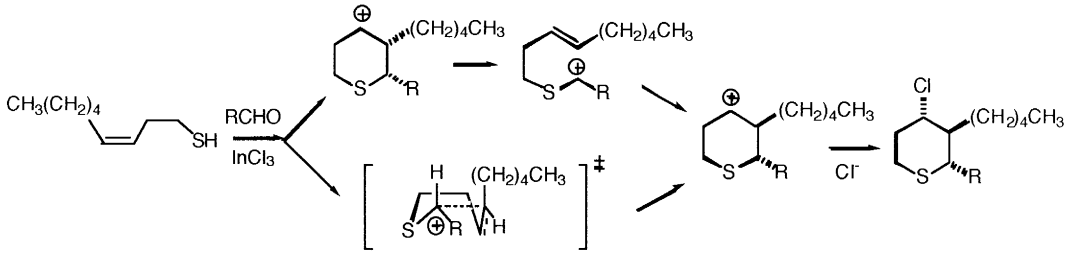


Table 1
Diastereoselective synthesis of thiacyclohexanes via cation–olefin cyclization

Entry	Thiol (**3**)	RCHO	**4a**/**4b**	Product (**4a**+**4b**) (Yield%)
1		PhCHO	7:1	 78
2		p-FPhCHO	8:1	 69
3		p-ClPhCHO	6:1	 82
4		p-BrPhCHO	6.5:1	 72
5		p-EtPhCHO	6:1	 79
6		PhCHO	> 99:1	 75
7		p-FPhCHO	> 99:1	 78
8		p-ClPhCHO	> 99:1	 73
9		p-BrPhCHO	> 99:1	 68
10		p-EtPhCHO	> 99:1	 70

Yields are (total) isolated ones (after column chromatography on silica gel) for both diastereomers. Ratios of diastereomers were measured with GC/MS or ^{1}HNMR on the crude reaction mixtures.



Scheme 1.

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10. A typical experimental procedure was as follows: Indium(III) chloride (265 mg, 1.2 mmol) was added to a mixture of benzaldehyde (212 mg, 2.0 mmol) and *cis*-3-nonen-1-thiol (158 mg, 1.0 mmol) in 25 mL methylene chloride which was pre-dried with 4 Å MS overnight. After being stirred at room temperature for 10 h, the mixture was concentrated. Column chromatography of the crude reaction mixture on silica gel (eluting with hexane) gave 220 mg (78%) of 4-chloro-3-pentyl-2-phenylthiacyclohexane (d.e.=7:1) as a colorless oil.