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Lewis acid-catalysed isomerisation of thionolactones to thiolactones: inversion of configuration

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Abstract—Boron trifluoride and indium(III) trifluoromethanesulfonate were found to efficiently catalyse the isomerisation of thionolactones to thiolactones in good yields. When applied to an optically active γ-thionolactone, the isomerisation reaction proceeded with a complete inversion of configuration by using $BF_3{\cdot}Et_2O$.

Volatile organosulfur compounds are among the most powerful compounds in flavour and fragrance chemistry.[1] Owing to their strong organoleptic properties including low odour thresholds and remarkable olfactory notes, they have induced an intense research in analytical chemistry as well as in synthetic organic chemistry. In the last few years, some thiolactones have been shown to provide interesting tropical and fruity notes as compared to the corresponding lactones.[2] Moreover, thiolactones as well as other sulfur–lactone analogues were studied for their biological activities, including convulsive or anticonvulsive properties.[3]

Thiolactones are generally obtained from the corresponding lactones with sulfur nucleophiles (thiourea, benzyl mercaptan or potassium thioacetate), whose reactivity depends on the lactone substitution pattern.[4] Thiolactones have also been prepared from sulfur-containing heterocycles: for example, opening of episulfides,[5] carbon monoxide insertion into a thietane ring[6] or sulfuration of acyl chloride derivatives with a tetrathiomolybdate complex.[7]

In the frame of our interest in the chemistry of flavouring lactones and thionolactones,[4c,d] we report here on a novel thiono- to thiolactone transformation. We found that in the presence of Lewis acids, thionolactones were involved in an isomerisation reaction leading to the formation of the corresponding thiolactones.

We first considered the isomerisation of racemic γ-thionodecalactone **1a** to γ-thiodecalactone **2a** in the presence of several Lewis acids. The reactions were performed in refluxing anhydrous toluene with a 0.2–0.5 M thionolactone concentration and a 2–10% molar ratio of catalyst. Four Lewis acids were tested: aluminium(III) triflate, indium(III) triflate, bismuth(III) chloride and boron trifluoride etherate and the results are summarised in Table 1.

When γ-thionodecalactone **1a** was reacted with $Al(OTf)_3$ (Table 1, entry 1), the complete isomerisation to thiolactone **2a** occurred in 5 h. In addition to **2a**, obtained with 36% selectivity, both lactone **3a** and dithiolactone **4a** were obtained in 56% and 8% yields, respectively. The presence of **3a** and **4a** seemed to indicate the possibility of a bimolecular mechanism of isomerisation of **1a**. Moreover, the higher yield of lactone **3a** as compared to that of dithiolactone **4a** was attributed to the presence of some residual water in the commercially available $Al(OTf)_3$ catalyst, as it was further checked by IR. Similar results were obtained with $In(OTf)_3$ (entry 2). Since commercially available triflates were partially hydrated and their use generally led to the formation of important amounts of lactone by-product, we used indium triflate in only 2 mol % (entry 3). Indeed, the rate of the reaction was slowed down, but the selectivity in γ-thiodecalactone **2a** was increased to 73%. As compared with Al^{III} or In^{III} triflates, the use of $BiCl_3$ (entry 4) led to low conversion and low selectivity. With $BF_3{\cdot}Et_2O$ as the catalyst under anhydrous conditions, the isomerisation selectivity towards **2a** reached 82% (entry 5).

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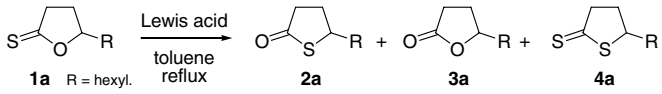
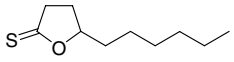
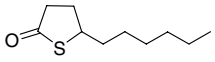
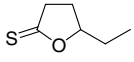
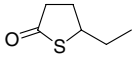
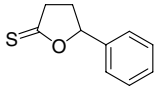
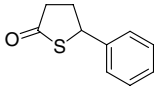
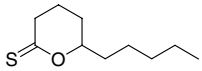
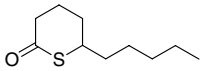
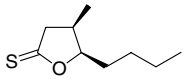
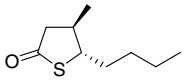
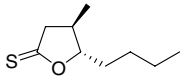
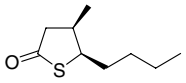
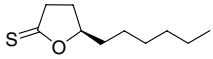
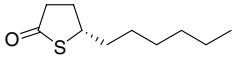
Table 1. Isomerisation of γ-thionodecalactone **1a** with different Lewis acids[a]



Entry	Lewis acid (mol %)	Conversion (%)	Time (h)	Selectivity (%)[b]		
				2a	**3a**	**4a**
1	$Al(OTf)_3$ (10)	100	5	36	56	8
2	$In(OTf)_3$ (10)	100	4	39	55	6
3	$In(OTf)_3$ (2)	98	18	73	22	5
4	$BiCl_3$ (10)	21	3	53	46	1
5	$BF_3{\cdot}Et_2O$ (10)	98	24	82	12	6

[a] All reactions were conducted in anhydrous toluene, under an inert atmosphere at 110 °C; the substrate consumption was followed by GC analysis.
[b] The selectivity was calculated by GC and/or by NMR analysis.

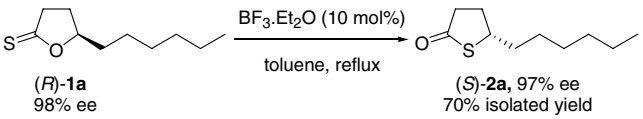
Table 2. Isomerisation of thionolactones with $BF_3{\cdot}Et_2O$ (10 mol %)[a]

Entry	Thionolactone substrates	Conversion (%)	Time (h)	Isomerised thiolactones	Selectivity of **2** (% isolated yield)
1	 **1a**	98	24	 **2a**	82 % (72)
2	 **1b**	88	48	 **2b**	76% (65)
3	 **1c**	100	2	 **2c**	93 % (88)
4	 **1d**	100	4	 **2d** [+ **3d** (63%)]	37 % (30)
5	 **1e** (*rac-cis*)	99	20	 **2e** (*rac-trans*)	93 % (68)
6	 **1f** (*rac-trans*)	32	48	 **2f** (*rac-cis*)	50 % (10)[b]
7	 (*R*)-**1a** (ee 98%)[c]	95	48	 (*S*)-**2a** (ee 97%)[c]	78 % (70)

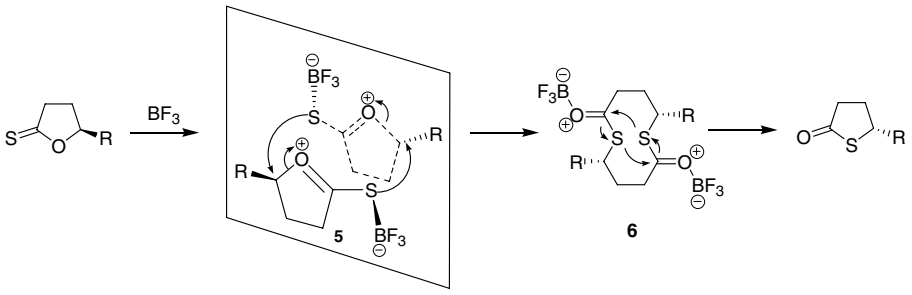
[a] For reaction conditions, see footnotes of Table 1. For experimental details on thiolactones, see Ref. 9.
[b] The yield was of 33% on the converted compound.
[c] Enantiomeric excess determined on a Hydrodex β-6tBDM capillary column (Macherey-Nagel, Germany) operated with a 2 °C/min rate starting from 80 °C (helium flow: 1.2 mL/min). The elution order of γ-thiolactone enantiomers has been previously described on the same chiral stationary phase.[2c]

$BF_3{\cdot}Et_2O$ was thus chosen as the best catalyst and this new thiono- to thiolactone transformation was extended to the isomerisation of a series of thionolactones, including five- and six-membered-ring compounds. The results are presented in Table 2.

The $BF_3{\cdot}Et_2O$-catalysed isomerisation reactions of 2-ethyl- and 2-phenyl-substituted thionolactones **1b** and **1c** led to the corresponding thiolactones **2b** and **2c** in excellent selectivities and in isolated yields of 65 and 88%, respectively (entries 2, 3). The isomerisation of the δ-thionolactone **1d** also afforded the expected δ-thiolactone **2d** though with moderate selectivity, due to the formation of lactone **3d** in 63% selectivity (entry 4).



Scheme 1. Enantioselective isomerisation of (*R*)-γ-thionodecalactone.



Scheme 2. Proposed mechanism for the isomerisation of γ-thionolactones.

When the *cis*-thionolactone derivative **1e** was submitted to isomerisation (entry 5), a clean reaction took place with the formation of *trans*-thiolactone **2e** in 93% selectivity. No *cis*-**2e** was observed. Interestingly, the isomeric *trans*-thionolactone **1f** (entry 6) underwent a slow isomerisation to *cis*-thiolactone **2f**, though with a selectivity of 50% (due to the presence of lactone **3f** in 41% selectivity). Compound **2f** was exclusively formed as the *cis* isomer. These results are in agreement with a previous study by Schmarr et al. dealing with P_4S_{10} sulfurisation of *cis*- and *trans*-whisky lactone diastereomers, in which an inversion of configuration was observed upon thiolactone formation.[2b]

This unexpected high isomerisation stereospecificity, with inversion of configuration at the α position to oxygen in starting **1** (and α to sulfur in compounds **2**) prompted us to further examine the possibility of an enantioselective isomerisation process.

When applied to the optically active (*R*)-γ-thionodecalactone, (*R*)-**1a** (98% ee, entry 7), the isomerisation reaction carried out with $BF_3{\cdot}Et_2O$ (10 mol %) led to the formation of (*S*)-γ-thiodecalactone **2a** with a total inversion of configuration at C-5 (97% ee) (Scheme 1). Chiral GC was used for ee analysis; the elution of (*R*) and (*S*)-2a have already been reported on the same column.[2c] Additionally, it was checked that no racemisation occurred once (*S*)-**2a** was formed, when running the reaction of (*R*)-**1a** with $BF_3{\cdot}Et_2O$ for more than four days.

The complete inversion of configuration observed for (*R*)-**1a** tends to exclude the possibility of a classical cationic-type mechanism to explain the results of the isomerisation.[8]

The results seem to indicate an SN_2-type mechanism involving at least two molecules of thionolactone. The possibility to consider the formation of several dimer intermediates can be considered. For example, an ylide intermediate of type **5**, followed by the formation of dimer **6**, as presented in Scheme 2, may explain the observed enantioselectivity.

In order to confirm the possibility of a bimolecular mechanism, the isomerisation of (*R*)-**1a** was performed at a 10-fold lower concentration (0.05 M). As expected, (*S*)-**2a** was obtained with a complete inversion of configuration (ee = 97%), but the kinetics of the process were highly slowed down and only 11% of the starting thionolactone was converted after 10 h of reaction.

When $In(OTf)_3$ was used to perform the reaction with (*R*)-**1a** (ee = 98%), (*S*)-**2a** was obtained in 66% yield after 24 h, with a 87% enantiomeric excess, indicating that a minor pathway of SN_1-type process could occur with this catalytic system during the isomerisation process. These results indicate that the nature of the Lewis acid strongly influences the isomerisation mechanism.

In conclusion, we describe here a novel boron trifluoride-catalysed thiono- to thiolactone isomerisation, which resulted to be highly regio- and stereoselective.

Acknowledgements

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9. *Experimental section*: Thionolactones were prepared using already described procedures from commercial lactones.[4b,c] All Lewis acids were purchased from Sigma-Aldrich and used as supplied. Enantioselective analyses were performed using an Agilent 6890 gas chromatograph coupled to a 5973A mass selective detector, stationary phase: Hydrodex β-6tBDM (heptakis-(2,3-*O*-dimethyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin) (Macherey-Nagel, Germany). Temperature program: 80–220 °C at 2 °C/min. The elution order of γ-thiolactone enantiomers has been previously reported on the same chiral stationary phase.[2c] In a typical procedure, a solution of γ-thionodecalactone **1** (5.0 mmol) and boron trifluoride etherate (0.5 mmol, 0.06 mL) in 10 mL of anhydrous toluene was refluxed under nitrogen atmosphere. Consumption of starting material **1** was followed by GC analysis. The final reaction mixture was washed with 0.1 M $NaHCO_3$, brine then dried over magnesium sulfate. Thiodecalactones **2** were purified by silica-gel column chromatography with petroleum ether/diethyl ether mixtures as the eluents. All compounds have been previously described: **1**,[4c,d] **2a**,**b**,**d**–**f**,[2a,b] **2c**,[4c,10] and **2e**.[2b,11]
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