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1,2-Asymmetric Induction in a New Tandem of (3,3)-Sigmatropic Rearrangement of Allylic Thiocyanates and Intramolecular Amine Addition to N=C=S Group

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Abstract: A new synthetic route to diastetereomerically pure 1,3-imidazolidin-2-thiones via a tandem of (3,3)-sigmatropic rearrangement of chiral thiocyanates followed by stereoselective intramolecular amine addition to arising isothiocyanates is reported. The semiempirical AMI calculations demonstrate that the observed diastereoselectivity is entirely consistent with the energy difference between diastereomeric transition states of heterocyclisation step. (© 1997, Published by Elsevier Science Ltd. All rights reserved.

The usefulness of chiral 1,2-diamines as auxiliaries and controller groups in asymmetric dihydroxylation¹, conjugate addition², olefination³, allylation⁴, epoxidation⁵ or aldol condensation⁶ is well documented. Although the 1,2-diamino unit is a constituent of natural products only an astonishingly small number of stereocontrolled syntheses have been developed for them⁷. Recently we have reported the excellent diastereoselectivity in 1,2-asymmetric

induction⁸ for the Paladium(II) catalyzed aza-Claisen rearrangement of allylic trichloroacetimidates 2 leading to anti-1,2diamines (Scheme 1).

This paper concerns a new and simple approach to highly stereoselective preparation of 1,3-imidazolidin-2-thiones, as



useful precursor for syn-1,2-diamines, by novel tandem of (3,3)-sigmatropic rearrangement of chiral allylic thiocyanates followed by stereoselective intramolecular amine addition to arising isothiocyanates.

The starting thiocyanates $4a-e^9$ were prepared by $S_N 2$ displacement of O-mesyl group in 3a-e, derived from allylic alcohols 1a-e,¹⁰ by thiocyanate group (KSCN/CH₃CN) in 85-90% overall yields (Scheme 2). The thermal rearrangement of thiocyanate 4a was carried out at 80°C in xylene under N₂ for 3h with high yield of isothiocyanates 5a and 6a (92%), but only poor diastereoselectivity (*anti-5a:syn-6a=60:40*)¹¹. The prolonged heating of reaction mixture (26h) unexpectedly led to the formation of 1-*t*-butoxycarbonyl-4(*S*)-vinyl-5(*S*)-methyl-1,3-imidazolidin-2-thione 7a as a single reaction product in 89% yield. To investigate the variability of this synthetic method, the different allylic thiocyanates 4b-e were examined. In all cases the heating of thiocyanates 4b-e in xylene at 80°C for 3h afforded the mixture of isothiocyanates 5b-e and 6b-e (*syn/anti*≈1:1). Further heating at the same temperature for 26-44h (Method A) led to intramolecular addition of amine to NCS group with stereoselective formation of imidazolidines 7b-e¹² (Table). In contrast with these results, the treatment of *anti-5a* and *syn-6a* (crude mixture 60:40, obtained by rearrangement of thiocyanate 4a) with sodium hydride (1 equiv.) in THF at 0°C for 1 h afforded the mixture of diastereoisomers 7a and 8a in essentially the same ratio.



Scheme 2

Table: 1-t-Butoxycarbonyl-4(S)-vinyl-5(S)-1,3-imidazolidin-2-thiones 7a-e.

		Ratio	Method A ^a		Method B ^b	
Compd.	R	7:8	Yield of 7 (%)	Period (hr)	Yield of 7 (%)	Period (hr)
4 a	Me	99.5 : 0.5	89	26	89	3
4b	Et	99.4 : 0.6	87	30	90	3
4c	i⊦Pr	99.5 :0.5	84	36	89	3
4d	Bn	99.5 : 0.5	80	29	85	3
4e	<i>i</i> ⊷Bu	99 : 1	84	44	88	з

*All reaction were carried out at 80°C in xylene. *All reaction were carried out at 80°C in

xylene in the presence of 0.20 mol% 2-hydroxypyridine

We have found that the presence of catalytic amount of 2-hydroxypyridine¹³ (0.20 mol%, Method B) significantly reduces the reaction time (from 26-44h to 3h) with the conservation of the high diastereoselectivity of the reaction.¹⁴

The reaction of imidazolidines 7a-e and 8a with TFA/H₂O (95:5, 15 min.) afforded the corresponding cyclic thioureas 9a-e and 10a (Scheme 3). The reaction stereochemistry was determined by NOE difference experiments of cyclic thioureas 9a and 10a. Irradiation of the methyl protons¹⁵ in 10a resulted in a 9% NOE on vinyl CH signal, indicating a *cis* relationship between these two substituents and thus 4R,5S configuration. Irradiation of the methyl protons in 9a resulted in almost 0% NOE on vinyl CH, indicating a *trans* relationship between these substituents and thus the 4S,5S configuration of 9a.¹⁶





The observed stereochemistry of these reactions can be rationalized by calculated transition states **A** and **B** in Scheme 2. Unfavorable interaction between the R group and vinyl group in the transition state **A** is in agreement with experimentally observed, very low yield of *cis*-isomer. Consequently, the preferred product is formed through transition state **B** in which the steric interactions between R and vinyl moiety is significantly reduced. The reversible rearrangement thiocyanate \leftrightarrow isothiocyanate¹⁷ is a reason for complete conversion of diastereoisomers **5a-e** to **6a-e** *via* the corresponding thiocyanates **4a-e** and preferred formation of **7a-e**.



Figure 1. The geometry of the disfavored transition state (5a->8a) according to AM1 calculation.



The calculated transition structures¹⁸ (AM1 method) for intramolecular cyclization **5a**->**8a** (transition state **A** with $\Delta H_{=}^{=}$ 22,63 kcal/mol, Figure 1) and **6a**->**7a** (transition state **B** with $\Delta H_{=}^{=}$ 20,03 kcal/mol, Figure 2) are in agreement with experimental observations. The calculated energy difference is 2.6 kcal/mol in favour of transition state **B** and predicts the exclusive formation of diastereomer **7a**.

In summary we have developed a novel tandem of (3,3)-sigmatropic rearrangement of chiral allylic thiocyanates, followed by stereocontrolled intramolecular addition of amine to NCS group, leading to diastereomerically pure 1,3imidazolidin-2-thiones. The scope and limitation of this methodology as well as modification of this reaction for the synthesis of chiral 1,3-oxazolidines will be reported in due course.

References and Notes

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- 9. All compounds showed ¹H, ¹³C, IR, HRMS spectra consistent with the reported structures.
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- 11. The ratio of the isothiocyanates 5 and 6 was determined by HPLC (Knauer, Nucleosil 5µC18/AcCN:H2O= 55:45).
- 12. The ¹H NMR data are supported by HPLC analysis (ref.11) of the reaction mixtures, which indicates the presence of a trace amounts (≥ 1%) of the second isomers 8a-e.
- 13. This indicates that the diastereoselectivity of the reaction may be explained by proton transfer in the transition state of the rate determining step. 2-Hydroxypyridine probably works as proton transfer catalysator. The protic nucleophilles react with isothiocyanates substantially slower as their anionic counterparts: Drobnica, L.; Kristian, P.; Augustin, J. in: The Chemistry of Cyanates and their Thio Derivatives (Patai S., Ed.), p. 1007. Wiley, New York 1977



- 14. A typical procedure for the preparation of 7: A solution of the thiocyanate 4a (0.1g, 0.0406mmol) and 2-hydroxypyridine (7.7mg, 0.0081mmol) in xylene (0.8ml) was heated at 80°C for 3h under N₂. The solvent was then removed under vacuum. The crude product was chromatographed (20% ethyl acetate in hexane) and afforded 0.089g (89%) of 7a as a white solid.
- 15. The ¹H and ¹³C NMR spectral data of 10a are identical with literature data (ref.8).
- 16. 9a: ¹H NMR (CDCI3, 300 MHz): 1.16 (d, 3H, J=8.3 Hz, CH3), 4.10 (m, H-C5) 4.41 (dd, 1H, J=6.8, 7.0 Hz, H-C4), 5.33 (m, 2H, CH2=), 5.80 (m, 1H, CH=), 6.20 (bs, 1H, NH), 6.10 (bs, 1H, NH).
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- 18. Theoretical calculations were carried out at the semiempirical RHF AM1 method, as implemented in the MOPAC 6.0 program (Stewart, J. P. P. J. Comput. Chem. 1989, 10, 209; Stewart, J. P. P. ibid. 1988, 44, 5597; Stewart, J. P. P. QCPE 1989, program 455). The transition states for intramolecular cyclization 5a->7a and 6a->8a were located using the SADDLE routine implemented in MOPAC. Further refinements of these approximate transition state geometries were carried out by minimizing the norm of energy (Baker, J. J. Comput. Chem. 1986, 7, 385) using the eigenvector-following (EF) method. The resulting geometries have a one negative vibration frequency (McIver, J. W.; Komornicky, A. J. Am. Chem. Soc. 1972, 94, 2625) and verification using intrinsic reaction coordinate calculations for modes 1 and -1 leads to the reactants and products of the reactions.

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