Pergamon

Tetrahedron Letters, Vol. 38, No. 5, pp. 875-878, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02429-X

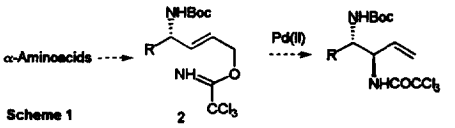
1,2-Asymmetric Induction in a New Tandem of (3,3)-Sigmatropic Rearrangement of Allylic Thiocyanates and Intramolecular Amine Addition to N=C=S Group

Miroslava Martinková and Jozef Gonda*

Department of Organic Chemistry, P.J.Šafárik University, Moyzesova 11, 04167 Košice, Slovak Republic

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 AM1 calculations demonstrate that the observed diastereoselectivity is entirely consistent with the energy difference between diastereomeric transition states of heterocyclisation step.

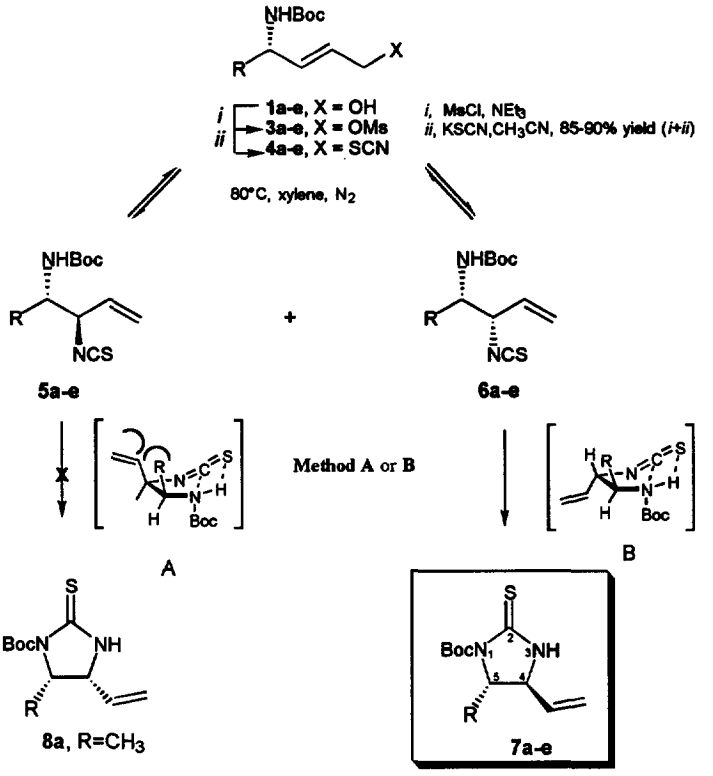
The usefulness of chiral 1,2-diamines as auxiliaries and controller groups in asymmetric dihydroxylation[1], conjugate addition[2], olefination[3], allylation[4], epoxidation[5] or aldol condensation[6] is well documented. Although the 1,2-diamino unit is a constituent of natural products only an astonishingly small number of stereocontrolled syntheses have been developed for them[7]. Recently we have reported the excellent diastereoselectivity in 1,2-asymmetric induction[8] for the Paladium(II) catalyzed aza-Claisen rearrangement of allylic trichloroacetimidates **2** leading to *anti*-1,2-diamines (Scheme 1).



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_N2 displacement of O-mesyl group in **3a-e**, derived from allylic alcohols **1a-e**,[10] by thiocyanate group ($KSCN/CH_3CN$) in 85-90% overall yields (Scheme 2). The thermal rearrangement of thiocyanate **4a** was carried out at 80°C in xylene under N_2 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-e**[12] (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

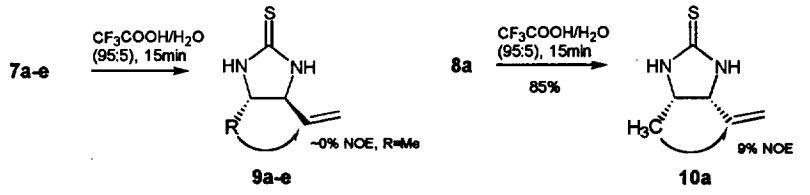
Table: 1-*t*-Butoxycarbonyl-4(*S*)-vinyl-5(*S*)-1,3-imidazolidin-2-thiones **7a-e**.

Compd.	R	Ratio 7:8	Method A[a]		Method B[b]	
			Yield of 7 (%)	Period (hr)	Yield of 7 (%)	Period (hr)
4a	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*-Bu	99 : 1	84	44	88	3

[a]All reaction were carried out at 80°C in xylene. [b]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-hydroxypyridine[13] (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]

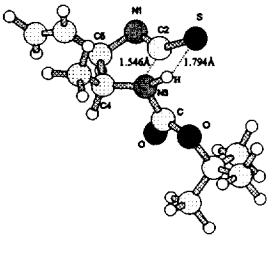
The reaction of imidazolidines **7a-e** and **8a** with TFA/H_2O (95:5, 15 min.) afforded the corresponding cyclic thioureas **9a-e** and **10a** (Scheme 3). The reaction stereochemistry was determined by NOE difference experiments of cyclic thioureas **9a** and **10a**. Irradiation of the methyl protons[15] in **10a** resulted in a 9% NOE on vinyl CH signal, indicating a *cis* relationship between these two substituents and thus 4*R*,5*S* 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 4*S*,5*S* configuration of **9a**.[16]



9a, R=CH_3 (92%); **9b**, R= Et (90%); **9c**, R=*i*-Pr (89%)
9d, R=Bn (93%); **9e**, R=*i*-But (89%)

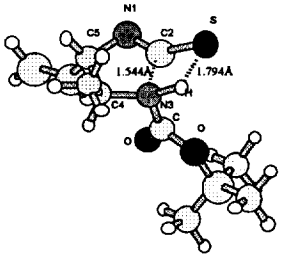
Scheme 3

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↔isothiocyanate[17] 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**.



A

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



B

Figure 2. The geometry of the favored transition state (**6a->7a**) according to AM1 calculation.

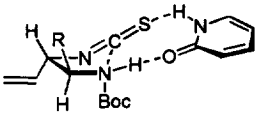
The calculated transition structures[18] (AM1 method) for intramolecular cyclization **5a->8a** (transition state **A** with ΔH_f= 22,63 kcal/mol, Figure 1) and **6a->7a** (transition state **B** with ΔH_f= 20,03 kcal/mol, Figure 2) are in agreement with experimental observations. The calculated energy 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 1,3-imidazolidin-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

1. Oishi, T.: Hirama, M. *J. Org. Chem.* **1989**, *54*, 5834. Tokles, M.; Snider, J. K. *Tetrahedron Lett.* **1986**, *27*, 3951. Corey, E. J.; DaSilva Jardine, P.; Virgil, S.; Yuen, P.-W.; Connel, R.D. *J. Am. Chem. Soc.* **1989**, *111*, 9243.
2. Alexakis, A..; Serdrani, R.; Mangeney, P.; Normant, J. F. *Tetrahedron Lett.* **1988**, *29*, 4411.

3. Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754.
4. Corey, E. J.; Yu,C.-M.;Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495.
5. Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801.
6. Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976.
7. Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S.; *Chem. Pharm. Bull.* **1988**, *57*, 6653. Nantz, M.H.; Lee, D. A.; Bender, D. M.; Roohi, A.H. *J. Org.Chem.* **1992**, *57*, 6653. Dieter, R.K.; Deo, N.; Lagu, B.; Dieter, J.W. *J. Org. Chem.* **1992**, *57*, 1663. Phammatter, E., Seebach, D. *Liebigs Ann. Chem.* **1991**, 1323. Yoda, H.; Shirai, T.; Kawasaki, T.;Katagiri, T.; Takabe, K.; Kimata, K.; Hosoya, K. *Cem. Lett.* **1991**, 793. Dunn, P.J.; Hänner, R.; Rappoport, H. *J. Org. Chem.* **1990**, *55*, 5017. Shigematsu, N.; Setoi, H.; Uchida, I.; Shibata, t.; Terano, H.; Hashimoto, M. *Tetrahedron Lett.* **1988**, *29*, 5147. Mangerey, P.; Tejero, T.; Alexakis, A.; Grosjean, F.; Normant, J. *Synthesis* **1988**, 255. Roskamp, E.J.; Pedersen, S.F. *J. Am. Chem. Soc.* **1987**, *109*, 3152. Arrowsmith, R.J.; Carter, K.; Dann, J.G.; Davies, D.E.; Harris, C.J.; Morton, J.A.; Lister, P.; Robinson, J.A.; Williams, D.J. *J. Chem. Soc., Chem. Commun.* **1986**, 755. Natsugari, H.; Whittle, R.R.; Weinreb, S.M. *J. Am. Chem. Soc.* **1984**, *106*, 7867.
8. Gonda, J.; Helland, A.-Ch.; Ernst, B.; Belluš, D. *Synthesis* **1993**, 729.
9. All compounds showed ^{1}H, ^{13}C, IR, HRMS spectra consistent with the reported structures.
10. Moriwake,T.; Hamano, S.; Miki, D.; Saito, S. *Chem. Lett.* **1986**, 815.
11. The ratio of the isothiocyanates **5** and **6** was determined by HPLC (Knauer, Nucleosil 5μC18/AcCN:H_2O= 55:45).
12. The ^{1}H 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 N_2. 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 ^{1}H and ^{13}C NMR spectral data of **10a** are identical with literature data (ref.8).
16. **9a:** ^{1}H NMR ($CDCl_3$, 300 MHz): 1.16 (d, 3H, J=8.3 Hz, CH_3), 4.10 (m, H-C5) 4.41 (dd, 1H, J=6.8, 7.0 Hz, H-C4), 5.33 (m, 2H, CH_2=), 5.80 (m, 1H, CH=), 6.20 (bs, 1H, NH), 6.10 (bs, 1H, NH).
17. DeWolfe, R.; Young, W. G. in: *The chemistry of alkenes* (Patai S., Ed.), p. 681. Wiley, Ney York 1964.
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.

(*Received in UK* 22 *October* 1996; *revised* 6 *December* 1996; *accepted* 13 *December* 1996)