Pergamon

Tetrahedron Letters 41 (2000) 7289–7292

TETRAHEDRON LETTERS

# Synthesis of the first enantiomerically pure 3-thiazolines via Asinger reaction†

Imre Schlemminger, Hans-Hermann Janknecht, Wolfgang Maison, Wolfgang Saak and Jürgen Martens*

*Department of Chemistry, University of Oldenburg, D-26111 Oldenburg, Germany*

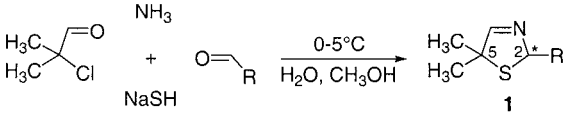
Received 2 June 2000; revised 17 July 2000; accepted 18 July 2000

**Abstract**

The first synthesis of an enantiomerically and diastereomerically pure 3-thiazoline via modified Asinger reaction using a galactose derived chiral auxiliary is described. The absolute configuration of this heterocyclic imine has been elucidated via X-ray analysis. In addition, the 3-thiazoline has been successfully derivatized under Ugi conditions. © 2000 Elsevier Science Ltd. All rights reserved.

*Keywords:* Asinger reaction; imines; thiazolines; enantioselection.

The Asinger reaction[1] has been known as a simple but powerful multicomponent reaction for the synthesis of 3-thiazolines for more than three decades. A variety of these sulphur-containing heterocyclic imines with different substitution patterns have been synthesized by the modified Asinger reaction.[2] Using an α-chloro-substituted aldehyde or ketone, aqueous ammonia, sodium hydrogensulfide and a second aldehyde or ketone, 3-thiazolines **1** were easily accessible in a one-pot procedure as outlined in Scheme 1. The imine bond of heterocycles **1** was subject to addition reactions with many different nucleophiles.[3] However, no enantiomerically pure, but only racemic, 3-thiazolines have been applied in the past since no practical approach[4] to stereochemically pure 3-thiazolines has previously been reported.




Scheme 1. Modified Asinger reaction

* Corresponding author. Fax: +49-441-798-3757; e-mail: juergen.martens@uni-oldenburg.de

† Dedicated to Peter Köll on the occasion of his 60th birthday.

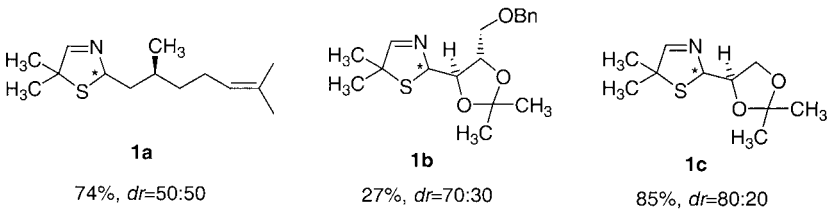

PII: S0040-4039(00)01266-1

Chiral 3-thiazolines of type **1** are attractive candidates for the enantioselective formation of compounds of pharmaceutical interest like amino acid derivatives,[3a,d] amino phosphonic acid derivatives[3b] and $\beta$-lactams[3d] by derivatization of the C=N function.

Herein, we report for the first time an access to enantiomerically pure 3-thiazolines of type **1** using chiral carbonyl compounds, obtained from the 'chiral pool', as stereochemical auxiliaries in the modified Asinger reaction.

In the course of our investigation we applied several different enantiomerically pure aldehydes and ketones to the synthesis of 3-thiazolines. While achiral ketones such as cyclohexanone or cyclopentanone lead to the corresponding 3-thiazolines in good yields within the Asinger reaction,[5] chiral ketones (such as camphor, carvone) do not participate in the reaction but cause self condensation of the $\alpha$-chloro aldehyde as a main reaction. Fortunately, chiral aldehydes lead to the desired 3-thiazolines **1** in high yields in most cases.

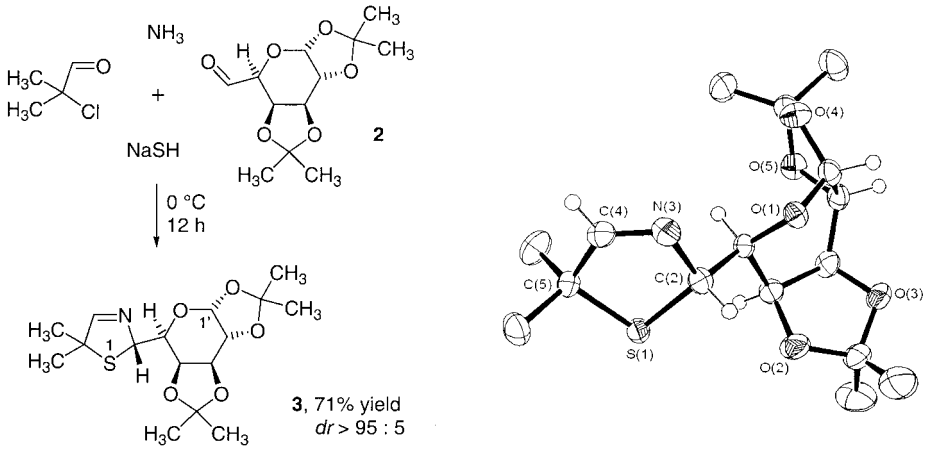
The 3-thiazolines depicted in Scheme 2 were obtained from the Asinger reaction as illustrated in Scheme 1 using *R*-citronellal in the case of **1a** and a tartaric acid derivative[6] in the case of **1b**. Compound **1c** was synthesized using a protected *R*-glyceraldehyde.[7] The 3-thiazolines **1b** and **1c** were prepared at –10°C and the aqueous ammonia was added slowly to avoid racemization of the chiral auxiliary in the alkaline reaction mixture. All heterocycles **1a–c** were formed as diastereomeric mixtures. Unfortunately, separation of the diastereomers via column chromatography was not possible.



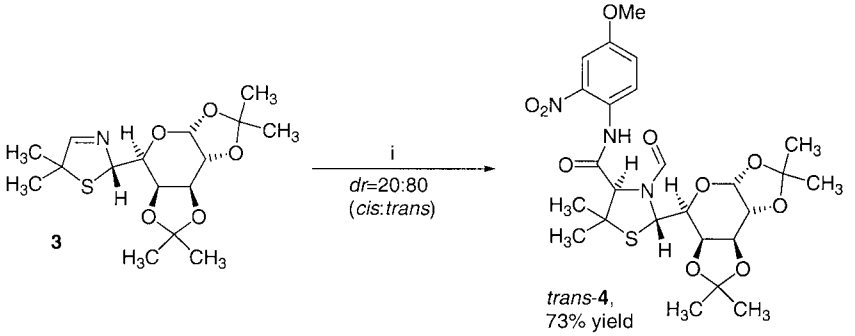

Scheme 2. First approach to enantiomeric pure 3-thiazolines

Compound **1c** showed a promising diastereoselectivity of the Asinger reaction with carbohydrate templates but poor stability under ambient conditions. Furthermore, even under mild basic conditions 3-thiazoline **1c** was in danger of racemization. In order to generate a 3-thiazoline with one single configuration, we decided to use a more bulky carbohydrate template **2**[8] as chiral auxiliary as outlined in Scheme 3. Application of the easy accessible galactose derivative **2** led to the enantiomerically pure 3-thiazoline **3** in good yield and in a highly diastereoselective way. The heterocyclic compound **3** exhibited good stability to ambient conditions and can be stored without special measurements for months. Reporting capacity for epimerization of the chiral auxiliary is provided by the presence of more than one stereogenic center in the aldehyde **2**. Although the Asinger reaction was carried out at 0°C and no care was taken about the basicity of the reaction mixture, epimerization was not observed. The carbohydrate system might be more resistant towards alkaline conditions due to the rigid tricyclic pyranoside system. The absolute *R*-configuration at C-2 was determined by X-ray analysis (Scheme 3).

Finally, we present the derivatization of the cyclic imine **3** under Ugi conditions[9] as outlined in Scheme 4. The major diastereomer of the bisamide **4** exhibits *trans*-configuration as identified from NMR spectra and can easily be separated by recrystallization from $CH_2Cl_2$. Formation of the adduct **4** might serve as an example for the conversion of the heterocyclic imine **3** to an enantiomerically pure $\alpha$-amino acid derivative.




Scheme 3. Synthesis of 3-thiazoline **3**[10] via Asinger reaction and crystal structure of 3-thiazoline **3**.[11] The *dr*-value was determined from the crude product by $^1$H NMR spectroscopy




Scheme 4. Formation of **4**[12] via Ugi reaction. **Reagents and Conditions**: (*i*) 4-methoxy-2-nitro-phenyl isocyanide, formic acid, dry methanol, 72 h. The *dr*-value was determined from the crude product by $^1$H NMR spectroscopy

In conclusion, we have presented a practical approach to enantiomerically pure 3-thiazolines using a galactose-derived carbohydrate as a chiral auxiliary. Absolute configuration of **3** has been elucidated by X-ray analysis. In addition, the cyclic imine **3** has been successfully derivatized under Ugi conditions.

## Acknowledgements

We are grateful to the Deutsche Forschungsgemeinschaft (DFG) for financial support of this project (Ma 1130/5-2). I. Schlemminger thanks the Heinz Neumüller Stiftung for a fellowship.

## References

1. (a) Asinger, F. *Angew. Chem.* **1956**, *68*, 377. (b) Asinger, F. *Angew. Chem.* **1956**, *68*, 413.
2. Martens, J.; Offermanns, H.; Scherberich, P. *Angew. Chem.* **1981**, *93*, 680–683; *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 668.

3. (a) Gröger, H.; Hatam, M.; Martens, J. *Synth. Commun.* **1996**, *26*, 3383–3394. (b) Gröger, H.; Wilken, J.; Martens, J.; Neda, I.; Pinchuk, V.; Thönnessen, H.; Jones, P. G.; Schmutzler, R. *Z. Naturforsch.* **1996**, *51b*, 1305–1312. (c) Westerhoff, O.; Martens, J.; Thöne, C. *Z. Anorg. Allg. Chem.* **1999**, *625*, 1823–1827. (d) Maison, W.; Kosten, M.; Charpy, A.; Kintscher-Langenhagen, J.; Schlemminger, I.; Lützen, A.; Westerhoff, O.; Martens, J. *Eur. J. Org. Chem.* **1999**, 2433–2441.
4. Very few enantiomeric pure 3-thiazolines have been obtained from the hydrolysis of some $\beta$-lactam antibiotics: (a) Baldwin, J. E.; Chan, R. Y.; Sutherland, J. D. *Tetrahedron Lett.* **1994**, *35*, 5519–5522. (b) Vilanova, B.; Donoso, J.; Muñoz, F.; García-Blanco, F. *Helv. Chim. Acta* **1996**, *79*, 1793–1802. (c) Visentin, G.; Perrone, E.; Borghi, D.; Rizzo, V.; Alpegiani, M.; Bedeschi, A.; Corigli, R.; Rivola, G.; Franceschi, G. *Heterocycles* **1992**, *33*, 859–891.
5. Drauz, K.; Koban, H. G.; Martens, J.; Schwarze, W. *Liebigs Ann. Chem.* **1985**, 448–452.
6. Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*,1373–1378.
7. Suzuki, T.; Sato, E.; Unno, K. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2263–2268.
8. Horton, D.; Nakadate, M. *Carbohyd. Res.* **1968**, *7*, 56–65.
9. For a review of the Ugi reaction, see: Ugi, I. *J. prakt. Chem.* **1997**, *339*, 499–516.
10. Data for **3**: mp 164°C; $[\alpha]_D^{20} = -31.9$ (*c* 1 in $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ (ppm) = 1.28, 1.31, 1.43, 1.44, 1.51, 1.52 [6 s, 18 H, $C(CH_3)_2$], 3.57 (dd, $^3J_{HH} = 9.4$ Hz, $^3J_{HaHe} = 1.7$ Hz, 1 H, 5′-H), 4.30 (dd, $^3J_{HaHa} = 5.0$ Hz, $^3J_{HaHe} = 2.8$ Hz, 1 H, 2′-H), 4.32 (dd, $^3J_{HaHa} = 7.7$ Hz, $^3J_{HaHe} = 1.7$ Hz, 1 H, 4′-H), 4.59 (dd, $^3J_{HaHa} = 7.7$ Hz, $^3J_{HaHe} = 2.8$ Hz, 1 H, 3′-H), 5.59 (d, $^3J_{HH} = 5.0$ Hz, 1 H, 1′-H), 5.78 (dd, $^3J_{HH} = 9.4$ Hz, $^4J_{HH} = 2.2$ Hz, 1 H, 2-H), 7.11 (d, $^4J_{HH} = 2.2$ Hz, 1 H, 4-H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ (ppm) = 25.1, 25.4, 26.4, 26.4, 29.3, 30.4, 64.6, 70.7, 71.5, 72.4, 74.0, 82.6, 97.1, 109.0, 110.1, 170.0; MS (CI, *i*Butan) 344 (base peak) [MH$^+$]; anal. calcd for $C_{16}H_{25}NO_5S$ (343.5): C, 55.96; H, 7.34; N, 4.08; S, 9.34. Found: C, 55.91; H, 7.30; N, 4.00; S, 9.26. $^1$H NMR peak assignments have been verified by HH–COSY–NMR experiments. Refer to Scheme 3 for numbering of atoms.
11. Single crystals of **3** were crystallized from MTBE, mounted in inert oil and transferred to the cold gas stream of the diffractometer. Crystal data: $C_{16}H_{25}NO_5S$, $M = 343.43$, monoclinic, $a = 8.7448(7)$, $b = 9.4567(8)$, $c = 11.7942(9)$ Å, $U = 919.38(13)$ Å$^3$, T = 193(2) K, space group *P*21, $Z = 2$, absorption coefficient = 0.199 mm$^{-1}$, 7126 reflections measured, 3534 unique ($R_{int} = 0.0543$) which were used in all calculations. The final $\omega R(F^2)$ was 0.0341 (all data). Crystallographic data (excluding structure factors) for **3** have been deposited with the Cambridge Crystallographic Data Centre, Cambridge, UK, as supplementary publication number CCDC 146345. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
12. Data for (2*S*,4*R*,5′*S*)-**4** (*trans*-**4**): mp 197°C; $[\alpha]_D^{20} = -159.2$ (*c* 1 in $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ (ppm) = 1.33, 1.35, 1.49, 1.72 [4 s, 18 H, $C(CH_3)_2$], 3.85 (s, 3 H, O-$CH_3$), 4.03 (dd, $^3J_{HH} = 9.4$ Hz, $^3J_{HaHe} = 1.7$ Hz, 1 H, 5′-H), 4.36 (dd, $^3J_{HaHa} = 5.0$ Hz, $^3J_{HaHe} = 2.7$ Hz, 1 H, 2′-H), 4.49 (dd, $^3J_{HaHa} = 7.7$ Hz, $^3J_{HaHe} = 1.7$ Hz, 1 H, 4′-H), 4.65 (s, 1 H, 4-H), 4.66 (dd, $^3J_{HaHa} = 7.7$ Hz, $^3J_{HaHe} = 2.7$ Hz, 1 H, 3′-H), 5.50 (d, $^3J_{HH} = 9.4$ Hz, 1 H, 2-H), 5.60 (d, $^3J_{HH} = 5.0$ Hz, 1 H, 1′-H), 7.22 (dd, $^3J_{HH} = 9.3$ Hz, $^5J_{HH} = 3.3$ Hz, 1 H, aryl 6-H), 7.68 (d, $^5J_{HH} = 3.3$ Hz, 1 H, aryl 3-H), 8.70 (s, 1 H, CHO), 8.71 (d, $^3J_{HH} = 9.3$ Hz, 1 H, aryl 5-H), 10.25 (s, 1 H, aryl-NH); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ (ppm) = 24.4, 24.7, 24.7, 25.9, 26.0, 34.7, 50.9, 55.9, 62.2, 70.1, 71.0, 71.8, 71.9, 74.1, 96.6, 108.6, 108.7, 109.8, 123.0, 123.5, 127.9, 136.9, 155.1, 163.9, 167.6; MS (CI, *i*Butan) 568 (26%) [MH$^+$], 400 (base peak) [MH$^+$–aryl-$NH_2$]; anal. calcd for $C_{25}H_{33}N_3O_{10}S$ (567.6): C, 52.90; H, 5.86; N, 7.40; S, 5.65. Found: C, 52.86; H, 5.80; N, 7.32; S, 5.58. $^1$H NMR peak assignments have been verified by HH–COSY–NMR experiments. Refer to Scheme 3 for numbering of atoms.