Pergamon

Tetrahedron Letters 39 (1998) 2293–2294

TETRAHEDRON LETTERS

Efficient Regioselective Synthesis of Enantiomerically Pure 4-Hydroxymethyl-Δ^2-Thiazoline.

Fredrik Almqvist[a,b], Dom Guillaume[a,*], Scott J. Hultgren[b], Garland R. Marshall[a]

a) Center of Molecular Design, Department of Molecular Biology and Pharmacology,
b) Department of Molecular Microbiology
Washington University, 660 S. Euclid, Saint Louis, Missouri, 63110, USA

Received 23 December 1997; accepted 3 February 1998

Abstract : Optically pure 2-unsubstituted-4-hydroxymethyl-Δ^2-thiazoline was prepared by regioselective cyclization of (*R*)-3-hydroxy-2-aminopropanethiol.

4-Substituted-Δ^2-thiazolines are receiving considerable attention since natural[1] and synthetic[2] thiazoline-containing compounds have been shown to possess unique or interesting pharmacological and/or chelating properties. 2-Unsubstituted-4-substituted thiazolines are generally more difficult to prepare than their substituted counterparts, and because of the large variety of the chemistry that can subsequently be done on its side chain as well as on its 2-position,[3] the design of efficient synthetic pathways leading to a synthon such as optically pure **4** is challenging.

Complex catalysts have been proposed to furnish (non)[4a]racemic[4b] 2-unsubstituted-4-substituted thiazolines. However, inspired by the chemistry more recently developed in the oxazoline series,[5] the synthesis of these thiazolines is nowadays generally achieved in good yields by condensing, at 80°C or higher temperatures, 1,2-aminothiols with iminoether salts or orthoesters. Nevertheless, using this strategy, the preparation of **4** starting from L-cysteine methyl ester has been reported to proceed with total racemization.[3] Applying milder conditions, also designed in the oxazoline series,[6] the preparation of **3** in an optically active form has been briefly mentioned[7] and its regioselective reduction should lead to **4**. However, using such an approach, and in addition to the necessary unpleasent preparation of formimidate, the optical purity of **4** is governed by the optical purity of its ester precursor that is limited to 80% in the oxazoline series.[6] We herein report on an easy and efficient way to prepare optically pure (*R*)-4-hydroxymethyl-Δ^2-thiazoline **4**.

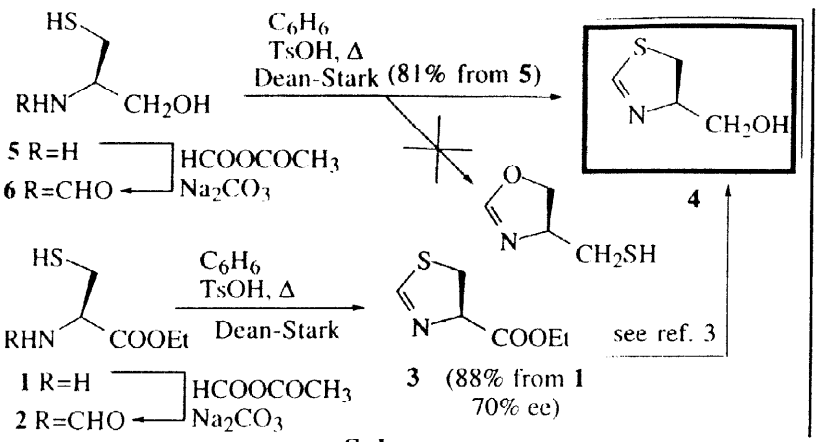
Whereas it is known that *N*-formyl-1,2-aminoalcohols do not lead to oxazolines but to degradative material only,[8] the use of *N*-formyl-1,2-aminothiols for the preparation of thiazoline has not been investigated. Since *N*-formyl derivatives should be easily available and amide derivatives have been shown to afford 2-substituted-thiazolines,[9] we decided to investigate the preparation of **4** from optically pure **5**[10] for which no racemization can occur during the synthetic process. *N*-Formylation of **5** could be easily achieved affording **6** in 96% yield (^{1}H-NMR of the crude reaction mixture) using the mixed anhydride of acetic and formic acids. No *S* or *O*-formyaltion was detected. We attempted cyclization of crude **6** by refluxing it, in the presence of traces of TsOH, in benzene and with continuous removal of water.[11] To our delight, compound **4**[12] ($[\alpha]^{21,D}$ +93 (c=1.7, $CHCl_3$) turned out to be the only product formed and could be isolated in 81% yield from **5** (Scheme).

Encouraged by these results we decided to prepare **3**, following the same strategy, from L-ethyl cysteinate **1**. As expected, cyclization of intermediate **2**, obtained under the conditions used to get **6**, afforded **3**[12] (88% yield from **1**) (Scheme). To determine its optical purity, we also prepared it in the racemic series and were able to show, by ^{1}H NMR in the presence of Eu(hfc)$_3$, that **3** was obtained in 70% ee (Figure).

In summary we have demonstrated that optically pure 2-unsubstitued-4-hydroxymethyl-Δ^2-thiazoline can be efficiently prepared from optically pure 2-substituted-1,2-aminothiol. Although both thiazolines and

PII: S0040-4039(98)00347-5

oxazolines can be prepared using the iminoether strategy, conversely thiazolines are selectively obtained using the *N*-formyl method.



Scheme

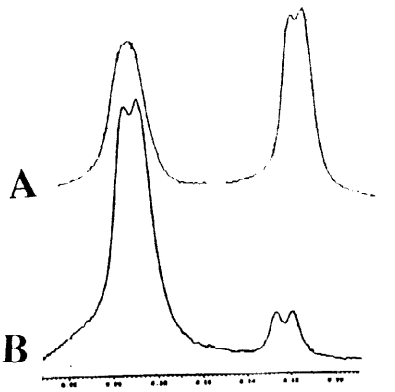


Figure: H-2 proton of (±)**3** (A) and **3** (B) in the presence of Eu(hcf)$_3$.

However, the nature of the substituent at the position 2 of the 1,2-aminothiol has to be carefully taken into account since electronwithdrawing groups can induce some racemization although to a much lesser extent than observed in the imino-ether strategy where total racemization occurs if high temperatures are used. Extension of our strategy to the preparation of optically pure 2-unsubstituted, 4-substituted 5,6-dihydro-4*H*-Δ^2-thiazines is under investigation and will be reported in due time.

Ackowledgments: We thank the Knut and Alice Wallenberg Foundation for financial support to F. A.

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10. Reduction was achieved using BH_3-THF. For other non racemizing methods see: Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835-875.
11. Standard procedure for the preparation of thiazoline derivatives: To a solution of 1,2-aminothiol and Na_2CO_3 in a minimum volume of water, a previously prepared solution of acetic anhydride (1.05 equiv.) and formic acid (1.2 equiv.) was added. The pH of the solution was kept alkaline by addition of solid Na_2CO_3 and the solution was stirred for 60 min. The remaining solids were removed by filtration and the cake washed three times with $CHCl_3$. The organic phase was neutralized (6N HCl) and concentrated. The residue was suspended in benzene, a catalytic amount of TsOH was added, and the solution was refluxed overnight using a Dean Stark apparatus. The organic phase was evaporated, the remaining oil dissolved in $CHCl_3$ and the organic phase washed by a saturated $NaHCO_3$ solution. After evaporation of the organic phase, the thiazoline was purified by chromatography if necessary.
12. **4**: ^{1}H NMR data of see ref 4b; ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 159.0, 78.2, 63.7, 32.2 . **3**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.03 (1H, d, *J*=2.4 Hz), 5.08 (1H, td, *J*=9.0, 2.4 Hz), 4.25 (2H, q, *J*=7.2 Hz), 3.54 (1H, dd, *J*=11.1, 9.5 Hz), 3.45 (1H, dd, *J*=11.1, 9.9 Hz), 1.32 (3H, t, *J*=7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 170.5, 159.5, 77.7, 61.7, 33.0, 13.8.