



Synthesis of Chiral Tetrahydropyrrolo[2,1-b]thiazol-5(6H)-ones¹

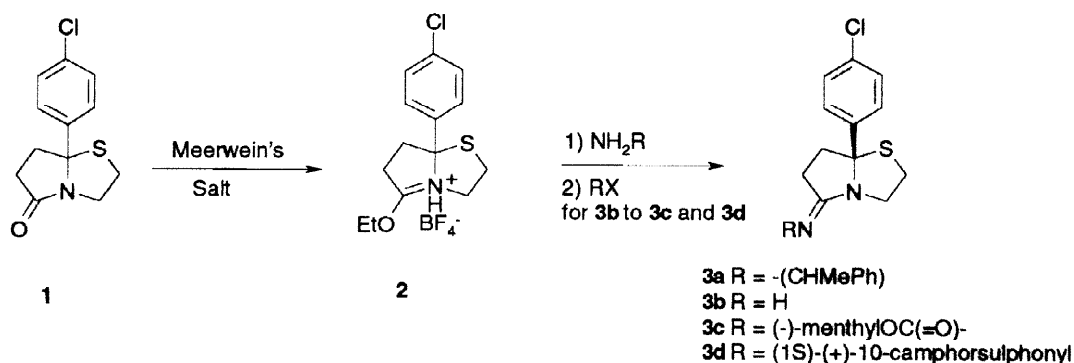
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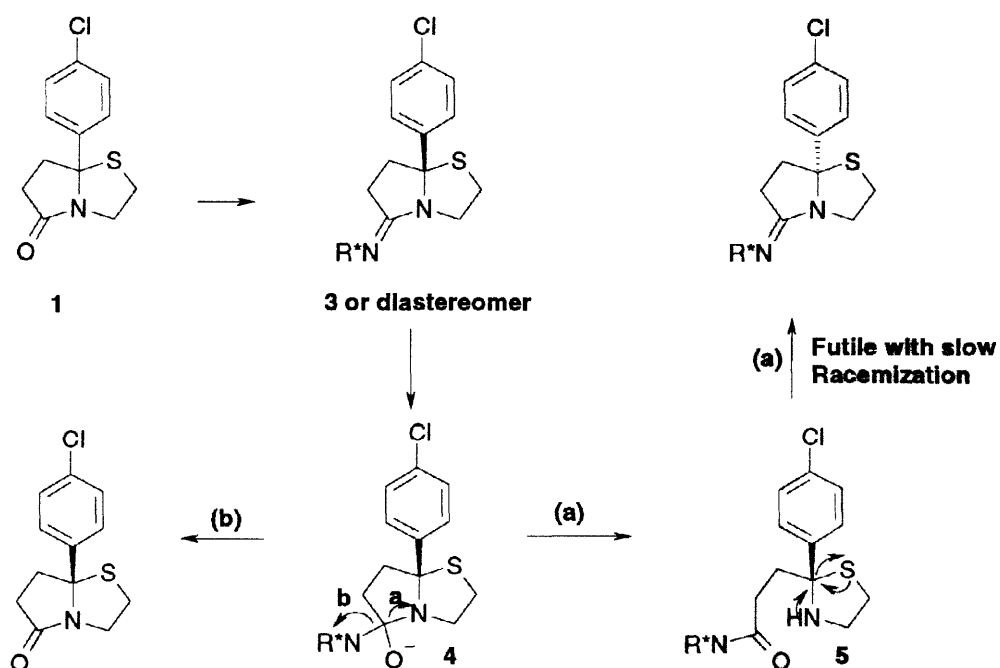
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Abstract: In our investigations of potential hypoglycemic agents,² it was desired to evaluate optically pure tetrahydropyrrolo[2,1- β]thiazol-5-ones. A novel, practical synthesis of each enantiomer of **1** via formation, separation, and hydrolysis of diastereomeric amidine derivatives is described.
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In our investigations of hypoglycemic agents, it was desired to evaluate optically pure tetrahydropyrrolo[2,1- β]thiazol-5(6H)-ones.² Members of this class of compounds have displayed a number of diverse pharmacological activities including anti-HIV and anti-inflammatory activity.³ The racemate of **1** was readily synthesized via a condensation of 3-(4-chlorobenzoyl)-propionic acid and cysteamine in near quantitative yield. This desirable brief synthesis employed two achiral components and there is no obvious way to induce enantioselectivity. Since **1** is a neutral compound, formation of a salt is not feasible. While a derivative of **5** could potentially be resolved, the propensity of the asymmetric center to racemize in the free amine may fatally flaw this approach. Separation of similar HIV-1 reverse transcriptase inhibitors using a chiral stationary phase has been demonstrated by Mertens *et al.*³ The chromatography group of Novartis successfully developed such a separation of **1** for analytical purposes.



We investigated whether formation, separation, and hydrolysis of diastereomeric amidines **3** would afford access to the chiral enantiomers of **1**. Although the two (E) amidines from (R)-(+)- α -methylbenzylamine were readily separable via chromatography, a problem arose upon the attempted basic hydrolysis of this amidine to **1**. From the transition state **4** of the hydrolysis, the reaction can proceed along



Optical Purity of the Hydrolysis of 3 is markedly improved where R = acyl, sulfonyl vs. alkyl since pathway (b) is favored over pathway (a).

two pathways. The desired pathway (b) leads to optically pure **1**. The alternative pathway (a) is futile, yielding **3** with significant racemization of the asymmetric center.

By changing *RN to a better leaving group via modification of **3b** (e.g. reaction with (1S)-(+)-10-camphorsulfonyl chloride, (-)-menthyl chloroformate, etc.), the diastereomeric amidines were still readily separable, and upon hydrolysis with dilute sodium hydroxide in methanol pathway (b) was favored. This allowed a practical synthesis of each enantiomer of **1** with high retention (> 99%) of optical purity.⁴

REFERENCES AND NOTES

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- Separation of the enantiomers of **1**: a) Et_3OBF_4 , CH_2Cl_2 , 20 °C b) sat. NH_3 , CH_2Cl_2 , 20 °C c) (-)-menthyl chloroformate, Et_3N , CH_2Cl_2 ; 60% (30 % of each diastereomer) for 3 steps d) aq. 2N NaOH, methanol, 81%.

Entry	Overall Chemical yield (1 to 3 *)	Purity of 3	Yield of 1 from 3	%ee of 1
3a	68	99	70	40
3c	60	99	81	99
3d	56	99	85	99