Tetrahedron Letters, Vol. 34, No. 35, pp. 5537-5540, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Resolution of Hydroxyureas

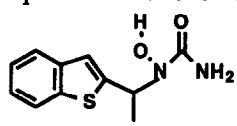
Ravi S. Garigipati*, Margaret E. Sorenson, Karl F. Erhard and Jerry L. Adams

Department of Medicinal Chemistry,
SmithKline Beecham Pharmaceuticals,
P.O.Box 1539, King of Prussia, PA 19046

Abstract: Racemic hydroxyureas can be efficiently resolved on a preparative scale using (4S)-4-benzyl-2-oxazolidinone-3-carbonyl chloride **3**. The resulting carbamates can be separated by chromatography and hydrolysis of these diastereomers yields enantiomerically pure hydroxyureas.

The leukotrienes are a family of bioactive fatty acids generated from the ubiquitous membrane constituent, arachidonic acid. These molecules have a plethora of pharmacologic effects on respiratory, cardiovascular and gastrointestinal systems. In view of the biological actions of leukotrienes, the control of leukotriene biosynthesis represents a potential method of treating diseases such as asthma, psoriasis and inflammatory bowel disease (IBD)[1]. As the first dedicated enzyme in the biosynthetic cascade leading to leukotrienes, 5-lipoxygenase (5-LO) is an actively investigated therapeutic target.[2]

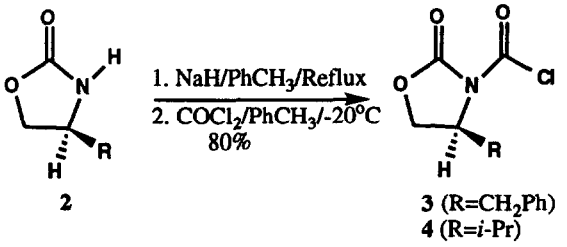
Hydroxamic acids and hydroxyureas are potent inhibitors of 5-LO.[3] While the enzyme shows little or no enantiomeric preference for most of the hydroxamic acid and hydroxyurea inhibitors reported to date[4] (zileuton (**1**), the first generation hydroxy urea in the clinic is racemic), to facilitate the evaluation of *in vivo* pharmacology and drug metabolism of individual hydroxyurea enantiomers, there is a need for both enantiomers. However, currently there are no general methods for either resolution or enantioselective synthesis of hydroxyureas.[5,7] In this communication we will describe an efficient and general technique for the chemical resolution of hydroxyureas.



1

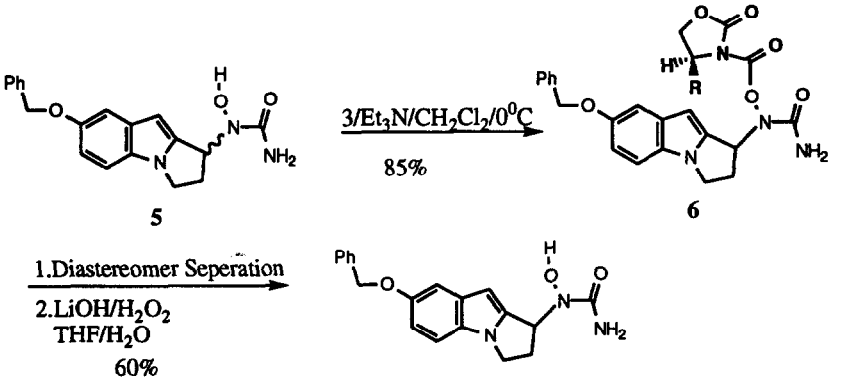
Ideally for resolution one would selectively derivatize the hydroxyurea with an appropriate chiral auxiliary, separate the diastereomers and regenerate the hydroxy urea. In practice, however one is confronted with the low reactivity of the hydroxy ureas and the hydrolytic instability of O-acylhydroxyureas. Initially, we attempted the resolution with several acyl auxiliaries, but none were found suitable. For instance (R)-2-phenylpropionic acid can be used to derivatize hydroxyureas, but the chiral auxiliary

suffered epimerization and the O-acyl hydroxyurea was hydrolytically unstable. We reasoned that O-acyl hydroxyureas derived from reagent 3 might overcome these shortcomings.



Scheme I

Carbamyl chlorides 3 and 4 can be easily prepared[9] from the corresponding commercially available (S)-oxazolidinones[8](Scheme I). These carbamyl chlorides can be indefinitely stored desiccated at 0°C. A variety of hydroxyureas react efficiently with the (S)-carbamyl chloride 3 ($R=CH_2Ph$) to yield diastereomeric carbamates in high yield, which can be separated either by flash chromatography or HPLC (Scheme II). The homochiral diastereomers can be readily converted to the enantiomerically pure hydroxyureas[10,11] (Scheme II). As the examples in the table illustrate, the method is general and very efficient. The carbamyl chloride derived from phenylalanine ($R=CH_2Ph$) is superior to the one derived from valine (R=*i*-Pr) because of the ease of diastereomer separation (entries 5 and 6). This might suggest a possible π stacking

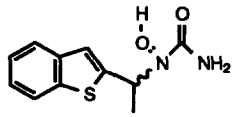
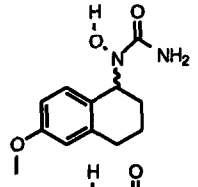
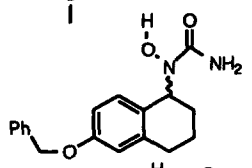
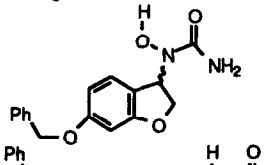
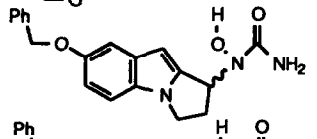
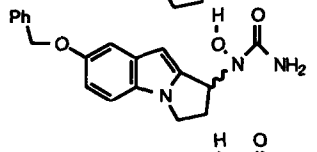
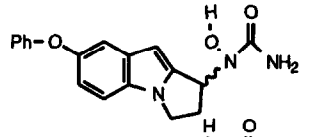
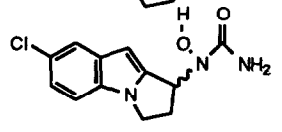


Scheme II

interaction between the phenyl group of the auxiliary and the aromatic portion of the hydroxyurea.

In a typical experiment, to a solution of the hydroxyurea 5[12](0.210g, 0.63mmol) in CH_2Cl_2 (6ml) was added Et_3N (0.16ml, 1.18mmol), followed by the carbamyl chloride at 0°C and the resulting solution was stirred at 0°C for 2 hrs. The reaction mixture was poured into water, extracted with CH_2Cl_2 and dried. Evaporation of the solvent yielded

Table. Resolution of Hydroxy Ureas with Carbamyl Chloride 3 (except entry 6)

Entry	Hydroxyurea	Acylation (%)[1]	Hydrolysis (%)[3]	α–Value
1.		40/40	69	1.13
2.		45/40	78	1.14
3.		45/43	63	1.44
4.		44/33	94	1.15
5.		46/42	70	0.49/0.44[4]
6.		30/30 [2]	30	1.47
7.		40/36	40	0.36/0.31[4]
8.		45/45	62	1.45

1. The diastereomeric oxazolidinones were separated by flash chromatography or HPLC.
2. Carbamyl Chloride 4 (R= *i*-Pr).
3. Combined yield of the enantiomers. All the enantiomers were >97%ee by HPLC.
4. R_f Values.

the crude oxazolidinones that were separated by flash chromatography on silica gel (88%, combined yield of the diastereomers).

LiOH (0.045g 1.8 mmol) was added to aq. hydrogen peroxide (30%, 1.8 mmol) at 0°C followed by the oxazolidinone **6** (0.21g 0.4mmol) in THF/H_2O (3:1/15ml) and the mixture was stirred for 20 min. The reaction mixture was quenched with satd. $NaHSO_3$ and the solution was concentrated and filtered. The crude reaction product was purified by flash chromatography on silica gel (5% MeOH in CH_2Cl_2) to afford a single enantiomer of **7** (70%, 97% ee).

In conclusion, the above described method is an efficient and preparatively useful one that should facilitate the speedy pharmacological evaluation of hydroxy urea enantiomers[12].

Notes and References

1. (a) Samuelsson, B., *Science*, **1983**, *220*, 568. (b) Masamune, H., Melvin Jr., L.S. *Ann. Rep. in Med .Chem.*, **1989**, *24*, 71.

2. (a) Gleason, J.G., Perchnock, C.D., Torphy, T.J., *Ann. Rep in Med Chem*, **1986**, *21*, 73. (b) Shaw, A., *ibid.*, **1990**, *25*, 61.

3. Summers, J.B., Gunn, B.P., Martin, J.G., Martin, M.B., Mazdiyasni, H., Stewart, A.O., Young, P.R., Bouska, J.B., Goetze, A.M., Dyer, R.D., Brooks,D.W., Carter, G.W., *J.Med Chem.*,**1988**, *31*, 1960.

4. Garland, L.G., Salmon, J.A., *Drugs of the Future*, **1991**, *16(6)*, 547.

5. There has been a report of enantioselective synthesis[6] of zileuton (**1**).

6. Hsiao, C.N., Kolasa, T., *Tetrahedron Lett.*, **1992**, *33 (19)*, 2629.

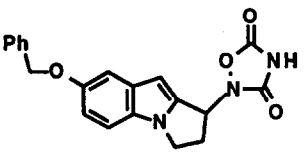
7. Thomas, S.B., Surber, B.W., Fitzgerald M., *J. Chromatography*, **1992**, *623*, 390.

8. Evans D.A., Ennis, M.D., Mathre, M.D., *J. Am. Chem. Soc.* **1982**, *104*, 1737.

9. A typical procedure would involve addition of the corresponding oxazolidinone (5.0 mmol) to a suspension of NaH (5.6 mmol) in toluene (18ml) and refluxing the mixture for 15 hrs. The resulting solution was cooled and added to a 20% phosgene solution (**CAUTION!**) at -25°C. (We did not attempt this reaction with any other phosgene equivalents.) Filtration and evaporation afforded the crude carbamyl chloride which upon triturating with ether yielded an amorphous solid.

10. Evans, D.A., Britton, T.C., Ellman, J.A., *Tetrahedron Lett.*, **1987**, *28*, 6141.

11. When LiOH was used for hydrolysis, oxadiazolidinedione **7** was obtained in 75% yield.



7

12. The biological properties of these hydroxyurea enantiomers will be described elsewhere.[13]

13. Manuscript in preparation.

(Received in USA 26 May 1993; accepted 9 July 1993)