ORGANIC LETTERS

2007
Vol. 9, No. 2
355−357

A Convenient, NMR-Based Method for the Analysis of Diastereomeric Mixtures of Pseudoephedrine Amides

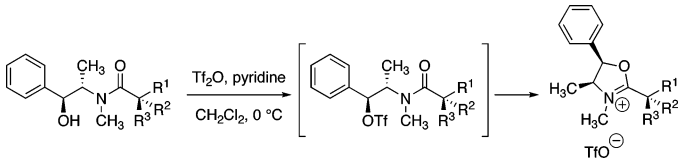
William J. Chain and Andrew G. Myers*

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

myers@chemistry.harvard.edu

Received November 27, 2006

ABSTRACT



Amides of pseudoephedrine and ephedrine are shown to undergo highly stereospecific, invertive cyclization to form 4,5-dihydro-3,4-dimethyl-5-phenyl-1,3-oxazolium triflate derivatives in the presence of triflic anhydride-pyridine. ^{1}H NMR spectra of the unpurified reaction products are remarkably clean, with sharp, well-defined peaks, and allow for rapid assessment of the diastereomeric purities of the starting amides.

Line-broadening greatly complicates the analysis of diastereomeric mixtures of pseudoephedrine amide alkylation products by NMR spectroscopy, necessitating the use of some more time-consuming analytical technique such as gas or liquid chromatography.[1] Here, we report that pseudoephedrine amides react stereospecifically with triflic anhydride and pyridine to form *cis*-4,5-dihydro-3,4-dimethyl-5-phenyl-1,3-oxazolium triflate derivatives (Scheme 1), providing the basis for a simple NMR-based technique for the analysis of diastereomeric mixtures of pseudoephedrine amides.

Scheme 1 illustrates four parallel transformations of (1*S*,2*S*)-pseudoephedrine and (1*R*,2*S*)-ephedrine amides of the enantiomeric α-methylbenzenepropanoic acids (I−IV). In each case the substrate (∼0.04 M) was treated with triflic anhydride (2 equiv) and pyridine (3 equiv) in dichloromethane at 0 °C;[2] after 2 min the cold product suspension was concentrated and the residue was held in vacuo at 23 °C (1 mmHg, 1 h); addition of $CDCl_3$, hand-mixing, and removal of the supernatant by pipet then provided a sample for ^{1}H NMR analysis. In Figure 1 are reproduced, in order, ^{1}H NMR spectra of the products of the four transformations I−IV (Scheme 1), obtained in the manner described. Analysis of the data makes it evident that the transformations are uniformly clean, that unlike the starting materials, the products give rise to ^{1}H NMR spectra with sharp, well-resolved signals, and that the diastereomeric products are readily differentiated spectroscopically.

Cyclization is stereospecific in each case, proceeding with inversion of the benzylic stereocenter, as established by NOE analysis (summarized in Scheme 1). Thus, pseudoephedrine amides give rise to *cis*-4,5-disubstituted oxazolium heterocycles (≥96% stereospecificity) and ephedrine amides produce the *trans*-4,5-disubstituted products (≥99% stereospecificity).[3] From this data we conclude that cyclization proceeds by triflation of the side chain hydroxyl group followed by invertive triflate displacement by the amide carbonyl oxygen (triflation of the carbonyl oxygen, for which there is precedent,[4] followed by cyclization would have led to retention of stereochemistry at the benzylic position).[5]

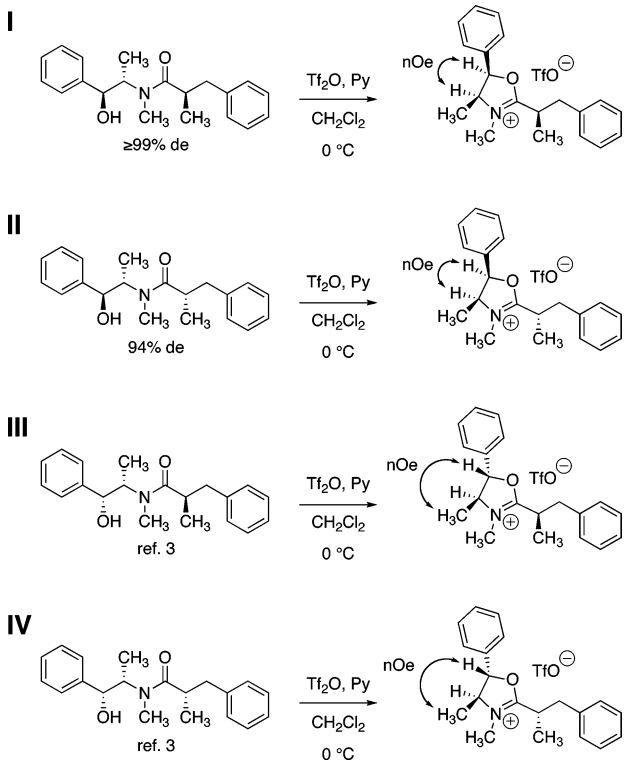
(1) Coalescence of ^{1}H NMR signals for the two rotameric forms of (2*R*)-*N*-[(1*S*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*,2-dimethylbenzenepropionamide requires temperatures in excess of 120 °C at 400 MHz (d_6-DMSO); see: Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496−6511.

(2) The transformation has also been successfully conducted with as little as 1.2 equiv of triflic anhydride (3.0 equiv of pyridine).

(3) The ephedrine amide substrate of transformation III was prepared by coupling (1*R*,2*S*)-ephedrine and (2*R*)-2-methyl-3-phenylpropionic acid (97% ee) in the presence of PyBOP. The ephedrine amide substrate of transformation IV was prepared by coupling (1*R*,2*S*)-ephedrine and (2*S*)-2-methyl-3-phenylpropionic acid (94% ee) in the presence of PyBOP.

10.1021/ol0628762 CCC: $37.00
Published on Web 12/19/2006

Scheme 1. Reaction of Pseudoephedrine (I and II) and Ephedrine (III and IV) Amides of (+)- and (−)-α-Methylbenzenepropanoic Acid with Triflic Anhydride−Pyridine To Form 4,5-Dihydro-3,4-dimethyl-5-phenyl-1,3-oxazolium Triflate Derivatives



Trace amounts (≤2%) of *trans*-4,5-disubstituted oxazolium heterocycles are formed during cyclization of the pseudoephedrine amide substrates (see peaks marked † in spectra I and II; these correspond exactly with product peaks in spectra III or IV, respectively) and are believed to result from a pathway involving ionization of the triflate intermediates, an apparently much slower process. These byproducts can be identified by a characteristic >0.5 ppm upfield shifting of resonances of protons bound to the oxazolium ring (protons labeled A and B in Figure 1).

The more consequential finding in the present context is that proton NMR spectra of pseudoephedrine amide-derived products epimeric at the exocyclic or "α" stereocenter are readily distinguished (see spectra I and II, Figure 1).[6] The methyl proton resonances labeled C in Figure 1 are especially well differentiated (both in pseudoephedrine- and ephedrine-derived products), allowing for visualization of even minor α-diastereomeric contaminants (marked as ◊ in Figure 1; compare spectrum I, obtained from a substrate of ≥99% de, with spectrum II, obtained from the α-diastereomeric substrate, of 94% de). Control experiments conducted by using contrived mixtures of α-diastereomeric pseudoephedrine amides have established that peak area ratios of diastereomeric oxazolium ion products accurately reflect the diaster-

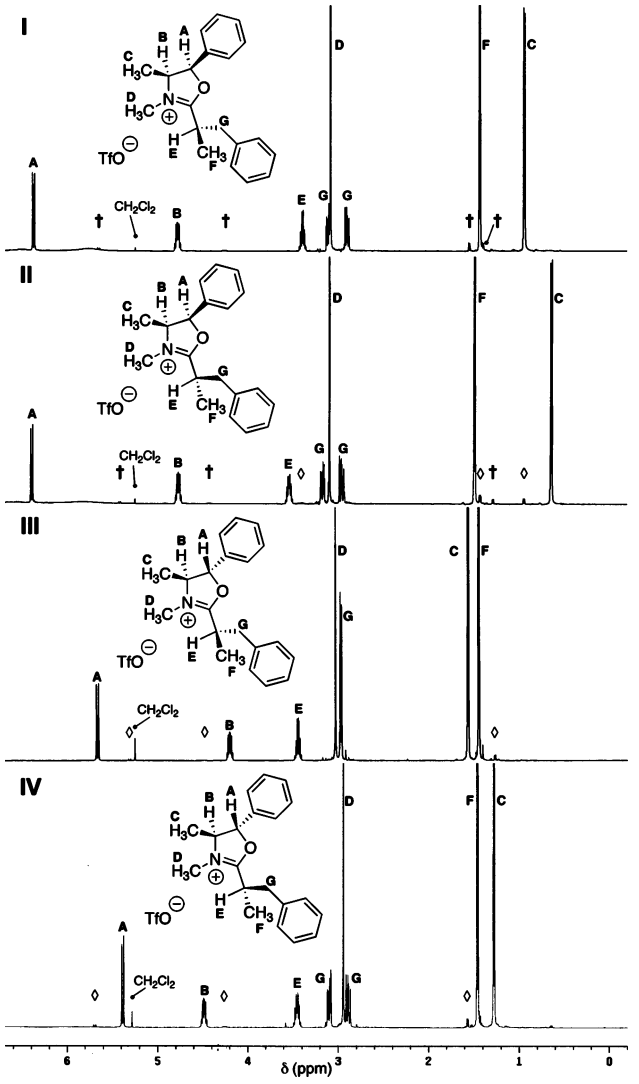


Figure 1. δ −0.2−6.7 ppm region of ^{1}H NMR spectra of the cyclization products of Scheme 1 ($CDCl_3$, 23 °C). Spectra are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.26).

(4) (a) Charette, A. B.; Chua, P. *Synlett* **1998**, 163−165. (b) Sforza, S.; Dossena, A.; Corradini, R.; Virgili, E.; Rosangela, M. *Tetrahedron Lett.* **1998**, *39*, 711−714. (c) Charette, A. B.; Chua, P. *J. Org. Chem.* **1998**, *63*, 908−909. (d) Charette, A. B.; Grenon, M. *Tetrahedron Lett.* **2000**, *41*, 1677−1680.

(5) The observed cyclization pathway is reminiscent of the cyclization of serine and threonine amides in the presence of Burgess reagent to form dihydrooxazoles: (a) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907−910. See also: (b) Ikuma, S. *J. Pharm. Soc. Jpn.* **1955**, *75*, 52−53. (c) Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Tetrahedron Lett.* **1987**, *28*, 6331−6334. (d) Poelert, M. A.; Hulshof, L. A.; Kellogg, R. M. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 355−364. (e) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297−2360.

(6) In the particular case of the substrates of Figure 1 a detailed analysis of chemical shift information provides not only internal consistency, but a means to correlate the stereochemistry of the α-position with the stereochemistry of the pseudoephedrine or ephedrine residues. In this analysis the products of Scheme 1 are assumed to adopt a conformation in which the α-C−H bond is co-planar with the *N*-methyl group (as indicated in the structural drawings of Figure 1); the α-benzyl group is found to shield the methyl protons C by ~0.3 ppm when these groups are cofacial. The analysis is found to extend to α-aryl pseudoephedrine amides (see the Supporting Information). These and other correlations from the compiled examples in the Supporting Information may provide a basis for the determination of the absolute configuration of many carboxylic acids.

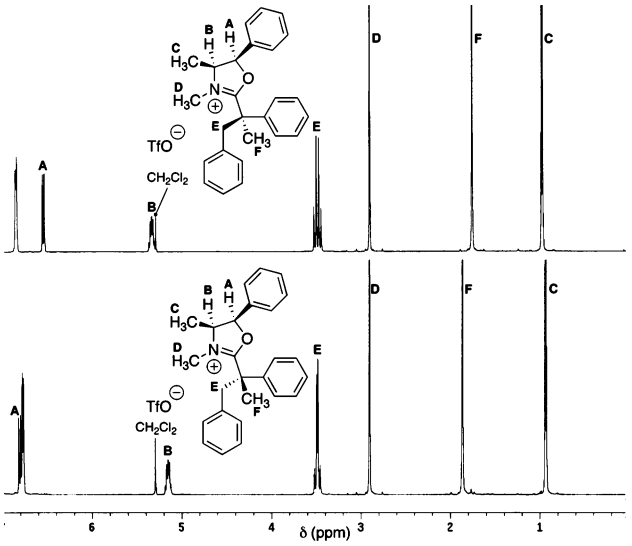


Figure 2. δ 0−7.0 ppm region of ^{1}H NMR spectra of the cyclization products ($CDCl_3$, 23 °C). Spectra are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.26).

eomeric composition of the starting materials; cyclization proceeds without detectable epimerization of the α-center.[7]

To date, we have used the analytical technique described to determine the diastereomeric ratios of 52 different pseudoephedrine amide alkylation reaction products of widely varying structures (structures and spectra are provided as Supporting Information). In no case have we been unable to identify distinguishing features in ^{1}H NMR spectra of diastereomeric products, although in some cases an NMR solvent other than $CDCl_3$ was necessary to resolve the diastereomers (C_6D_6, 4 cases; CD_2Cl_2, 1 case; d_6-acetone, 1 case). We have used the method primarily to distinguish alkylation reactions that are of practical synthetic value (≥90% de) from those that are impractical, and not for an exacting determination of diastereomeric ratios, although with care to identify the trace products of benzylic inversion (vide supra), this is also possible.[7] One area where the method described has been invaluable is in the analysis of pseudoephedrine amide alkylation products with an α-quaternary center, compounds whose ^{1}H NMR spectra are particularly subsceptible to line broadening. Shown in Figure 2 are ^{1}H NMR spectra of the α-diastereoisomeric oxazolium products of one such example (formed under conditions described above).[8]

In summary, we have found that amides of pseudoephedrine and ephedrine react stereospecifically with inversion in the presence of triflic anhydride and pyridine to form 4,5-dihydro-3,4-dimethyl-5-phenyl-1,3-oxazolium triflate derivatives. ^{1}H NMR analysis of these derivatives provides a simple means to establish the diastereomeric composition of the starting amides and may prove useful as a means to establish the absolute configuration of certain carboxylic acids.[6]

Acknowledgment. We are grateful to the National Science Foundation for funding. We gratefully acknowledge Christopher Coletta and David Kummer for the preparation of eight compounds appearing in the Supporting Information. This paper is dedicated with esteem to Professor Yoshito Kishi (Department of Chemistry and Chemical Biology, Harvard University) on the occasion of his 70th birthday.

Supporting Information Available: ^{1}H NMR spectra of 52 different oxazolium triflate derivatives formed by cyclization of pseudoephedrine amides with triflic anhydride-pyridine. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Reference samples of mixtures of α-diastereomeric pseudoephedrine amides can be obtained by epimerization of the α-center, where this is possible, under acidic or basic conditions, as previously described; see ref 1.

(8) Pseudoephedrine amides with an α-quaternary center cyclize with ≥99% stereospecificity, presumably reflecting an increased rate of cyclization of the triflate intermediates relative to ionization.