New Uses of Amino Acids as Chiral Building Blocks in Organic Synthesis

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Received July 6, 2001

ABSTRACT

Amino acids have long been used as chiral building blocks in organic synthesis.1 Since naturally occurring α-amino acids contain a chiral center and at least two functional groups they can be transformed to a broad range of compounds through well-designed reactions.

One of the challenges in amino acid chemistry is to prepare an α-amino aldehyde from the corresponding α-amino acid and then to form a new C–C bond in a stereoselective manner to build more complicated structures. However, α-amino aldehydes are not configurationally stable, and a suitable amino protecting group is required.

N,N-Dibenzylamino aldehydes have emerged as a highly useful class of chiral building blocks in synthetic organic chemistry.2 We envisioned the transformation of the N,N-dibenzylamino aldehydes to the corresponding aldimines followed by diastereoselective methylene transfer with a sulfonium ylide to obtain α-amino aziridines in high yields.

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The versatile utilities of chiral aziridines as chiral building blocks for the synthesis of various nitrogen-containing compounds have drawn much attention in recent years.3 One of the most efficient methods to build the nitrogen-containing three-membered ring system is methylene group transfer to a suitable imine counterpart. There are some literature precedents for aziridine formations by methylene transfer using sulfonium ylides. However, the participating imines were mostly derived from aromatic aldehydes.4

Although the C==N bond is similar to the C==O bond, there are some differences between them especially in terms of reactivity toward nucleophiles. It is well-known that the low reactivity of imines toward nucleophiles has been the most difficult problem and that it can be improved by the presence

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10.1021/ol0164029 CCC: $20.00 © 2001 American Chemical Society

Published on Web 08/31/2001
was evaporated, and the residue was dissolved in 3 mL of THF. A 0.42 mmol, \( p \)-anisidine (57 mg, 0.47 mmol), and 1.0 g of 4ÅM Si gel were added. The reaction proceeded smoothly to give the corresponding aziridines in high yields. The \( N,N \)-dibenzyl \( \alpha \)-amino aldimines were subjected to the coupling reaction with dimethylsulfonium methyldide prepared from trimethylsulfonyl iodide and \( n \)-BuLi. The coupling reactions were in good agreement.

The sulfonium ylide addition reactions to the imines were in good agreement.

**Representative Procedure.** Preparation of \( N \)-PMP-azididine from \( N,N \)-dibenzylamino aldehydes 1 and expected this sulfonium ylide addition would show the same stereoselectivity where the nucleophiles approach from the \( re \) face of the imines by a Felkin-Ahn transition state. While we were preparing this manuscript we showed the same stereoselectivity where the nucleophiles attack the aldimines or ketimine carbon from the same side selectively to provide the major product that has opposite stereochemistry.

The above results show that the sulfonium ylide addition reactions to the \( \alpha,N \)-dibenzylamino aldehydes and hydride reduction of the \( \alpha,N \)-dibenzylaminoalkyl chloromethyl ketimines predominantly take place on the \( re \) face of the \( C=\!N \) double bonds and that the two methodologies can be complementary for the stereoselective synthesis of functionalyzed chiral aziridines.

**Acknowledgment.** M.T.R. and W.K.L. would like to thank the Alexander von Humboldt Foundation and Korea Research Foundation (KRF-99-013-000-348) for support.

**Supporting Information Available.** Experimental procedure from cyclohexanecarboxaldehyde and compound data shown in Scheme 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Representative Procedure. Preparation of \( N \)-PMP-azididine from \( N,N \)-dibenzylaminolinalenalinal. A mixture of the amino aldehyde (139 mg, 0.42 mmol), \( p \)-anisidine (57 mg, 0.47 mmol), and 1.0 g of 4ÅM Si gel in 3 mL of methylene chloride was stirred for 12 h at room temperature. The solvent was evaporated, and the residue was dissolved in 3 mL of THF. A suspension of MoSe (172 mg, 0.85 mmol) in 3 mL of THF was cooled to \(-30^\circ \text{C} \) and treated with \( n \)-BuLi (1.6 M, 0.48 mL, 0.77 mmol). The mixture was stirred for 1 h and cooled to \(-78^\circ \text{C} \). To the sulfonium ylide solution was added the cooled solution of the \( N \)-PMP-imine in 3 mL of THF slowly at \(-78^\circ \text{C} \). The mixture was slowly warmed to room temperature and stirred overnight. The reaction was quenched with water, and the aqueous layer was extracted with ether (5 mL × 5). The combined extract was dried over K₂CO₃, and the solvent was evaporated to give a crude product as brown oil, which was chromatographed on silica gel with 5% EtOAc/hexane to give 130 mg (69%) of the major product and 35 mg (19%) of the minor product. The purity of the products was determined by making the enantiomers of \( 3 \) and \( 3a \) starting from \( n \)-phenylalanine and analyzed them with chiral HPLC.

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