ORGANIC LETTERS

2002
Vol. 4, No. 25
4381−4384

Synthesis of Enantiomerically Pure 2,2,3,4,5-Pentasubstituted Pyrrolidines by Phenylsulfanyl Migration†

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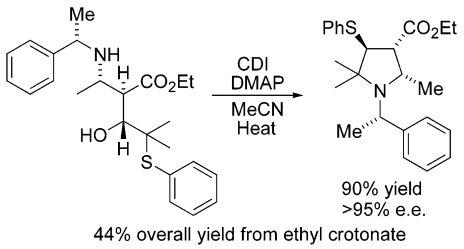
Received September 2, 2002

ABSTRACT

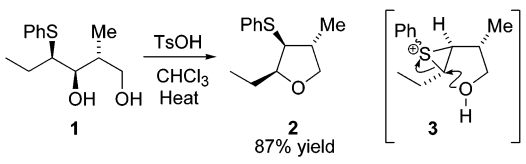


Enantiomerically pure 2,2,3,4,5-pentasubstituted pyrrolidines can be prepared, in high overall yield, from α,β-unsaturated esters. Asymmetry is introduced via a Michael addition, and additional stereogenic centers are introduced by an aldol reaction. A novel stereospecific ring-forming reaction, proceeding via a thiiranium (episulfonium) ion, yields pyrrolidines from β-hydroxy sulfides. In this manner, 2,2,3,4,5-pentasubstituted pyrrolidines, containing three contiguous stereogenic centers around the ring, can be prepared in 44% overall yield from ethyl crotonate.

We have shown that thiiranium (episulfonium) ions, generated by the treatment of β-hydroxy sulfides with acid, are useful intermediates in the synthesis of both oxygen- and nitrogen-containing heterocycles.[1] Thus, when the diol **1** is heated with *p*-toluenesulfonic acid (TsOH), an intermediate thiiranium ion **3** is formed; capture by the internal oxygen nucleophile gives the tetrahydrofuran (THF) **2**.[2] Both of the substitution steps in this mechanism proceed with clean inversion of stereochemistry (Scheme 1).[1]

However, the use of acidic methods for the synthesis of similar nitrogen-containing heterocycles is precluded by nitrogen protonation; removal of the internal nucleophile leads to the allylic sulfide **6** (with an unsubstituted amine). Specific protection is required to reduce the basicity of the nitrogen atom. Thus, the *N*-tosyl derivative **4** undergoes

Scheme 1



cyclization to give the pyrrolidine **5**, with only small quantities of the allylic sulfide **6** being produced. TMSOTf was a more efficient activating agent for this reaction than TsOH (Scheme 2).[3]

† This paper is dedicated to Dr. R. Bolton on the occasion of his retirement. He is an exceptional teacher of organic chemistry and an inspiration to many. We wish him a very long and enjoyable retirement.

‡ OSI Pharmaceuticals.

§ University Chemical Laboratory.

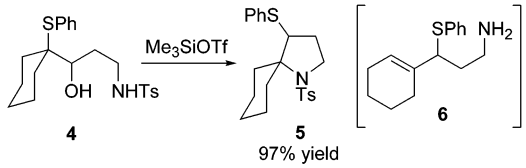
(1) Fox, D. J.; House, D.; Warren, S. *Angew Chem., Int. Ed.* **2002**, *41*, 2462 and references contained therein.

(2) Aggarwal, V. K.; Eames, J.; Villa, M.-J.: McIntre, S.; Sansbury, F. H.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 533.

(3) Coldham, I.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1637.

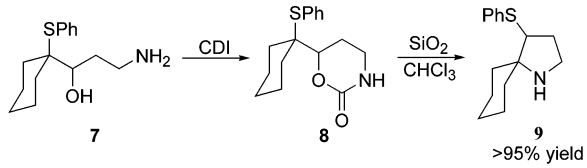
10.1021/ol0268384 CCC: $22.00
Published on Web 11/15/2002

Scheme 2



Recently, we have developed methods of forming thiiranium ions that avoid the need for strong Brønsted acids, turning instead to weak Lewis acids. Pyrrolidines can be formed in high yield from suitably substituted cyclic carbamates. Treatment of carbamate **8** with chromatography silica, in refluxing chloroform, results in complete conversion to the N-unsubstituted pyrrolidine **9** (Scheme 3).[4] We now

Scheme 3



report our attempts to apply this methodology to the synthesis of enantiomerically enriched pyrrolidines. This work has resulted in a novel method of generating thiiranium ions, unusually proceeding under basic conditions.

To prepare enantiomerically enriched pyrrolidines, optically active derivatives of the amino alcohol **7** were required. These can be easily prepared from α,β-unsaturated esters via a consecutive Michael addition−aldol reaction strategy (Figure 1). The stereochemical outcome of the Michael

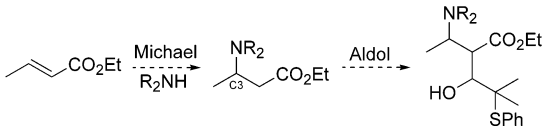


Figure 1. Strategy for the synthesis of enantiomerically enriched amino alcohols.

addition is controlled using methodology developed by Davies.[5] Addition of lithium α-methylbenzyl amide to an α,β-unsaturated ester produces the β-amino ester with excellent stereochemical control (Scheme 4); the (*S*)-α-methylbenzyl amide generates (*S*)-stereochemistry at the nitrogen-bearing center (C3) (Figure 1). This stereochemical information can then be used to control the absolute stereochemistry of the subsequent aldol reaction.

(4) Caggiano, L.; Fox, D. J.; Warren, S. *Chem. Commun.* **2002**, 2528.
(5) Davies, S.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183.

There are two approaches by which this type of strategy can be implemented, termed the tandem and stepwise procedures (Scheme 4). The tandem approach uses the (*Z*)-enolate **13**, selectively generated by the Michael addition,[6] directly in the aldol reaction; the β-amino ester is not isolated. In the stepwise procedure, deprotonation of the isolated β-amino ester **10**, selectively generates the (*E*)-enolate **11**,[6] this can be used in a boron-mediated aldol reaction (Scheme 4); this is based on a procedure employed by Davies in his formal synthesis of thienamycin, the sense of stereoinduction is the same.[7]

Thus, the amino alcohols **12** and **14** are produced in excellent overall yield, from ethyl crotonate, and in good diastereomeric excess; although a 4:1 mixture of two diastereoisomers is produced by the tandem procedure, three new stereogenic centers have been introduced in a one-pot reaction sequence. Aldehyde **15**, used in both aldol reactions, is easily prepared from the trimethylsilyl enol ether of isobutyraldehyde and phenylsulfenyl chloride. This procedure has been used in similar cases.[8]

The stereochemical outcomes of the aldol reactions are slightly counterintuitive; the boron-mediated aldol reaction, via an (*E*)-enolate, produces a *syn*-aldol product, and a (*Z*)-enolate yields an *anti*-aldol product. If a Zimmerman−Traxler chair transition state structure applies,[9] the R-group of the aldehyde may be forced into an axial position by the steric bulk of the benzylamine fragment of the molecule; however, a boatlike transition state cannot be discounted. Yamamoto noted identical stereochemical outcomes in similar work.[6]

The absolute stereochemistry of the *anti*-aldol amino alcohol **14** was determined by X-ray crystallography via reduction of the ester with $LiAlH_4$ to provide the crystalline diol **16** (Figure 2).

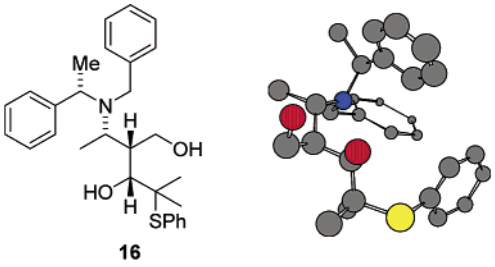
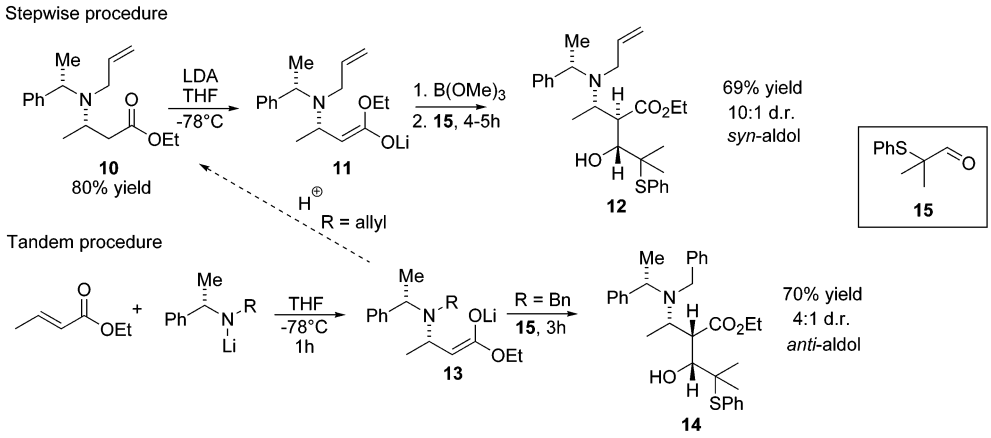


Figure 2. Chem3D representation of the crystal structure of diol **16**.[10a] Protons have been removed for clarity.

To apply our silica methodology (Scheme 3),[4] deprotection of the nitrogen atoms of the amino alcohols **12** and **14** was

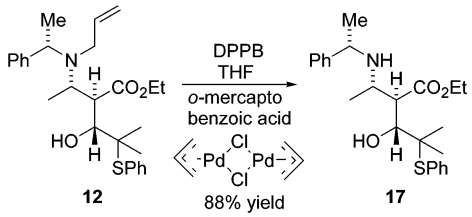
(6) Asao, N.; Uyehara, T.; Yamamoto, Y. *Tetrahedron* **1990**, *46*, 4563.
(7) Davies, S.; Fenwick, D. *J. Chem. Soc., Chem. Commun.* **1997**, 565.
(8) Aggarwal, V. K.; Coldham, I.; McIntyre, S.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1991**, 451.
(9) Zimmerman, H.; Traxler, M. *J. Am. Chem. Soc.* **1957**, *79*, 1920.
(10) (a) Crystal data or diol **16**: $C_{29}H_{37}NO_2S$, M = 463.66 gmol^{-1}, monoclinic, $P2_1$, a = 10.5006 Å, b = 10.1426 Å, c = 12.5752 Å, β = 104.610°. Absolute structure parameter −0.1(6). Structure was solved with *SHELXS*-97 and refined with *SHELXL*-97.[10b] (b) Sheldrick, G. M. *SHELXS*-97/*SHELXL*-97. University of Göttingen: Göttingen, Germany, 1997.

Scheme 4



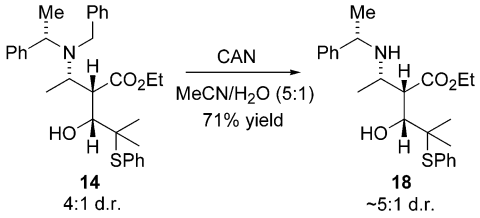
essential. Deallylation of alcohol **12** was easily achieved using a slightly modified palladium-catalyzed reaction developed by Genet.[11] The bidentate phosphine ligand [1,4-bis-(diphenylphosphino)butane, DPPB] stabilizes the metal center, preventing coordination by the sulfur atom present in the alcohol **12** (presumably the thiol of *o*-mercaptobenzoic acid also competes with the sulfide **12** for coordination to the metal center). The reaction produces high yields of the amino alcohol **17** (Scheme 5).

Scheme 5



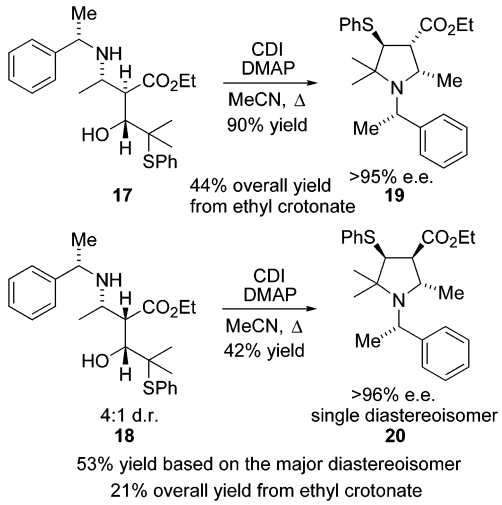
Debenzylation of the dibenzylamine **14** by palladium-catalyzed hydrogenolysis proved to be difficult, presumably due to deactivation of the metal center by sulfur ligation. Monodebenzylation could be achieved using an oxidative debenzylation procedure [mediated by ceric ammonium nitrate (CAN)],[12] to produce good yields of the desired amino alcohol **18** (Scheme 6).

Scheme 6



Previously, carbamates such as sulfide **8** could be prepared by treatment of the corresponding amino alcohol with 1,1′-carbonyldiimidazolide (CDI) at room temperature. When this procedure was carried out on amino alcohol **17**, no cyclic carbamate was observed and only starting material was recovered. However, heating the reaction mixture to reflux led directly to the desired pyrrolidine **19**, and no epimerization was observed (Scheme 7).[13]

Scheme 7



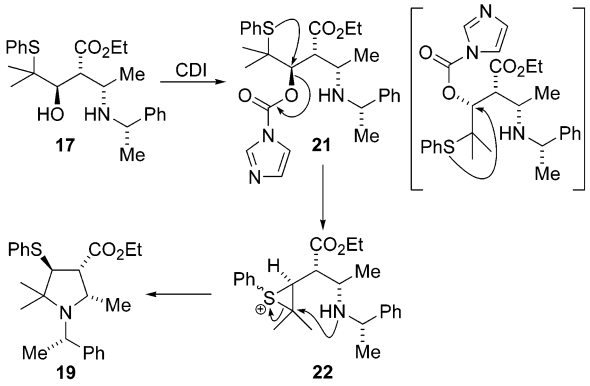
The reaction was also applicable to the other diastereomeric amino alcohol **18**. However, the yield of pyrrolidine **20** was lower in this case, due perhaps to the developing 3,4-syn relationship between the migrating sulfur atom and the ester substituent.[14] These cyclization reactions proceed

(11) Sandrine, L.; Savigac, M.; Genet, D. *Tetrahedron Lett.* **1995**, 1267.
(12) Bull, S. D.; Davies, S. G.; Fenton, G.; Mulvaney, A. W.; Prasad, R. S.; Smith, A. D. *Chem. Commun.* **2000**, 337.
(13) Typical procedure: to an acetonitrile (10 mL) solution of the amino alcohol (1 mmol) were added CDI (1.1 mmol) and DMAP (cat.). The reaction was heated at reflux until TLC analysis (4:1 hexane/EtOAc) indicated complete reaction. The solution was then concentrated onto silica and chromatographed, eluting 5−10% EtOAc in hexane, to yield the pyrrolidine as a clear colorless oil. NMR, HRMS, IR, and elemental analysis confirmed the structures of novel compounds.

stereospecifically via an intermediate thiiranium ion, with an overall [1,2]-PhS migration.

We propose that the alcohol rather than the amine (of sulfides **17** or **18**) reacts initially with CDI, to form the imidazolide **21**, and that the role of the amine is surprisingly that of a *general base catalyst* and not that of a nucleophile. The resulting imidazolide is then displaced by sulfur, liberating carbon dioxide and imidazole, to yield a thiiranium ion **22**; this is then captured by the internal nitrogen nucleophile (Scheme 8). This reaction is applicable to a

Scheme 8



variety of substitution patterns around the migration origin and terminus. This along with experiments on the mechanism of this reaction will be the subject of future publications.

The stereospecificity of the migration reaction has been confirmed by X-ray crystallography. Both pyrrolidines **19** and **20** can be debenzylated over Pearlman's catalyst [Pd(OH)$_2$] and reacted with 3,5-dinitrobenzoyl chloride to provide crystalline derivatives such as the amide **23** (Figure

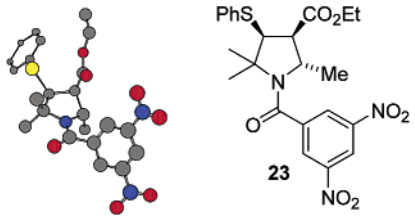


Figure 3. Chem3D representation of the crystal structure of amide **23**, derived from a tandem sequence.[15] Compared to diol **16**, inversion at the migration terminus is observed.

3). Enantiomeric excesses were measured via comparison of the ^{1}H NMR spectra of both pairs of the diastereomeric amides derived from of each of the pyrrolidines **19** and **20** and the two enantiomers of Mosher's acid.

Acknowledgment. M. D. E. thanks the BBSRC and British Biotech Pharmaceuticals Ltd. for funding. The assistance of Dr. J. E. Davies of the Cambridge University Crystallographic laboratory is gratefully acknowledged.

Supporting Information Available: Procedures for the preparation, and full characterization, of compounds **12**, **14**, **17**, **18**, **19**, and **20**. X-ray data for compounds **16** and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0268384

(14) Aggarwal, V. K.; Coldham, I.; McIntyre, S.; Sansbury, F. H.; Villa, M. J.; Warren, S. *Tetrahedron Lett.* **1988**, *29*, 4885.

(15) Selected X-ray data for the amide **23**: $C_{23}H_{25}N_3O_7S$, $M = 487.52$, orthorhombic, $P2_12_12_1$, $a = 7.92010(10)$ Å, $b = 14.8135(5)$ Å, $c = 20.5852(7)$ Å, $\beta = 104.610°$. Absolute structure parameter $-0.11(8)$. Structure was solved with *SHELXS*-97 and refined with *SHELXL*-97.[10b]