JOC*Note*

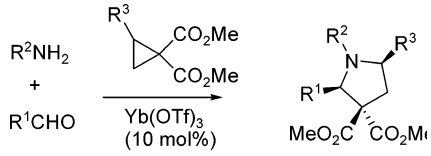
Diastereoselective Synthesis of Pyrrolidines via the $Yb(OTf)_3$ Catalyzed Three-Component Reaction of Aldehydes, Amines, and 1,1-Cyclopropanediesters

Cheryl A. Carson and Michael A. Kerr*

Department of Chemistry, The University of Western Ontario, London, Ontario, Canada, N6A 5B7

makerr@uwo.ca

Received June 15, 2005



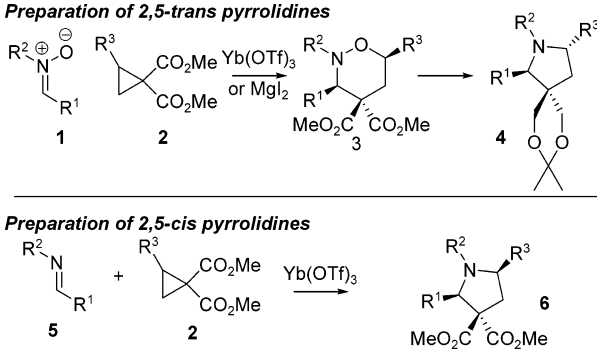
Aldimines, generated in situ by the reaction of primary amines or anilines with aldehydes, undergo smooth reaction with various 1,1-cyclopropanediesters in the presence of catalytic $Yb(OTf)_3$. The products are pyrrolidines in which the major diastereomer bears a cis relationship between substituents at the 2- and 5-positions. In most cases the diastereoselectivity is greater than 10:1.

The pyrrolidine ring represents one of the most ubiquitous heterocyclic motifs found in naturally occurring compounds.[1] The bioactivity of the indolizidine-, pyrrolizidine-, and proline-based compounds (to mention a few) has led to the investigation of the pyrrolidine as a central structural feature of many drug candidates. It stands to reason that simple methods for the formation of pyrrolidines from readily available materials would be most welcomed by the synthetic community.

Recently, we reported the synthesis of pyrrolidines **4** via the chemical manipulation of tetrahydrooxazines (Scheme 1).[2] The requisite oxazines **3** were prepared via cycloaddition of nitrones **1** with 1,1-cyclopropanediesters **2**.[3] An attractive feature of this method is the fact that, since the oxazines are prepared solely as the cis isomer, N−O bond cleavage and cyclization of the resulting 1,4-amino alcohol resulted in the formation of the 2,5-trans substituted pyrrolidines. In this note, we report a simple method for the formation of cis-2,5 disubstituted pyrrolidines **6** via the cycloaddition of imines **5** with 1,1-cyclopropanediesters catalyzed by ytterbium triflate.

The reaction of an imine with a cyclopropyl moiety to form a five-membered nitrogen heterocycle is not new. In the synthesis of spirotryprostatin and the related horsfiline, Carriera showed that 3-spirocyclopropyl-2-oxindoles undergo reaction with imines under the influence of magnesium iodide.[4] Lautens has shown that methylene cyclopropanes, when treated with imines in the presence of catalytic MgI_2, form pyrrolidines as a major product.[5] Cyclopropylmethyl ketone, under the influence of MgI_2 or Et_2AlI has undergone reactions with imines to form pyrrolidines.[6] In related work, Johnson has reported the reaction of aldehydes with 1,1-cyclopropanediesters in the presence of $Sn(OTf)_2$ to form tetrahydrofurans.[7] In light of previous work from our laboratory,[8] we felt that the use of lanthanide triflates (in particular $Yb(OTf)_3$) to activate various cyclopropanediesters would be ideal for the annulation of imines to form pyrrolidines.

SCHEME 1. Synthesis of 2,5-*trans*- and 2,5-*cis*-Pyrrolidines

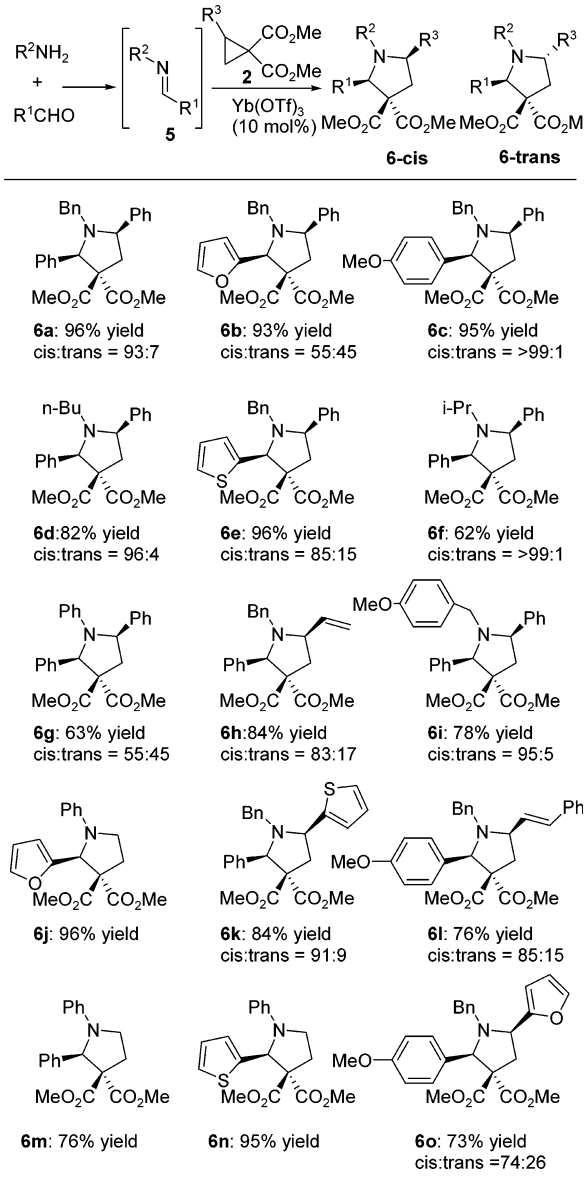


In our intial trials, the aldimines **5** were prepared and isolated in pure form prior to the reaction. Although this works reasonably well, it is far more preferable to generate them in situ since (a) many aldimines can be somewhat labile and (b) the reaction was found to be higher yielding and produced fewer unwanted byproducts. Scheme 2 shows a series of pyrrolidines prepared by the three-component coupling of an aldehyde, an amine, and a 1,1-cyclopropanediester. Using the substrates for entry **6m**, we screened a short series of Lewis acids including $Yb(OTf)_3$, $Y(OTf)_3$, $Dy(OTf)_3$, $Sm(OTf)_3$, and $Zn(OTf)_2$. Of these, $Yb(OTf)_3$ performed the best, giving generally higher yields and fewer byproducts.[9] The subsequent examples in Scheme 2 employed $Yb(OTf)_3$ as the catalyst. The reactions were performed by combining equimolar amounts of the aldehyde and amine (or aniline) and stirring to allow formation of the imine. The cyclopropane and catalyst were added to effect the cycloaddition. Allowing the preformation of the aldimine

(1) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435 and previous reports in this series.
(2) Young, I. S.; Williams, J. L.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 953.
(3) (a) Ganton, M. D.; Kerr, M. A. *J. Org. Chem.* **2004**, *69*, 8554. (b) Young, I. S.; Kerr, M. A. *Org. Lett.* **2004**, *6,* 139. (c) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023.
(4) (a) Meyers, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 694. (b) Lerchner, A.; Carreira, E. M. *J. Am. Chem. Soc.* **2002**, *124*, 14826. (c) Fischer, C.; Meyers, C.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 1175. (d) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3186.
(5) (a) Lautens, M.; Han, W.; Liu, J. H.-C. *J. Am. Chem. Soc.* **2003**, *125*, 4028. (b) Lautens, M.; Han, W *J. Am. Chem. Soc.* **2002**, *124*, 6312.
(6) Bertozzi, F.; Gustafsson, M.; Olsson, R. *Org. Lett.* **2002**, *4*, 3147.
(7) Pohlhaus, P. D.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 1057.
(8) (a) England, D. B.; Kuss, T. D. O.; Keddy, R. G.; Kerr, M. A. *J. Org. Chem.* **2001**, *66*, 4704. (b) Kerr, M. A.; Keddy, R. G. *Tetrahedron Lett.* **1999**, 5671. (c) Harrington, P.; Kerr, M. A. *Tetrahedron Lett.* **1997**, 5949.
(9) Athough we did not try the MgI_2 conditions employed by Carriera, it is quite possible that they would be satisfactory. The moisture- and air-tolerant nature of the lanthanide triflates was a strong factor in their selection as the catalysts of choice.

10.1021/jo0512251 CCC: $30.25
Published on Web 08/25/2005

SCHEME 2. Preparation of 2,5-*trans*-Pyrrolidines



prior to addition of the cyclopropane was necessary since both the aldehyde and amine are capable of undergoing reaction with the cyclopropane under the influence of Lewis acid catalysis.

Several observations from Scheme 2 are worthy of note. Both primary alkylamines and primary anilines seem to be well tolerated in the reaction; however, aryl (or heteroaryl) aldehydes produce far more satisfactory results than aliphatic aldehydes (which gave generally poor results). The presence of a strongly electron-withdrawing group on the aldehyde (i.e., *p*-nitrobenzaldehyde) produces some difficulties and did not yield the expected product. Interestingly, an 11% yield of the denitrated adduct was isolated, possibly via a retro electrophilic nitration reaction with overall transfer of the nitro group to the solvent toluene (although nitrotoluene was not isolated from the reaction mixture). In general, the diastereoselectivity was high, favoring the 2,5-cis disposition of substituents.[10] Stereochemical assignment was made in the case of **6a** by convergence with compounds made by us previously by cleavage of a

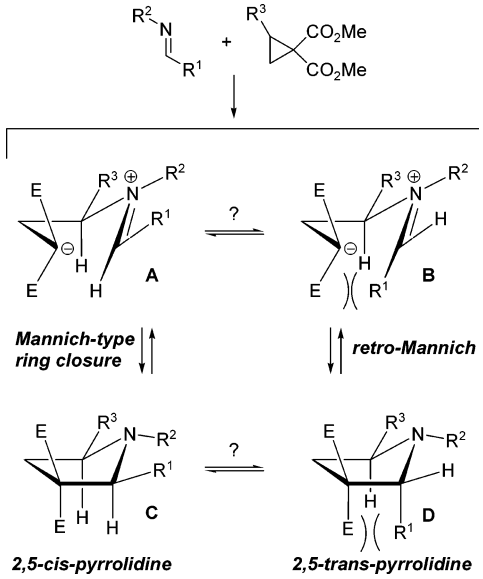


FIGURE 1. Proposed model for pyrrolidine formation.

tetrahydro-1,2-oxazine. In that case, X-ray data for both the cis and trans isomers were obtained. Since the chemical shifts of characteristic resonances of the two diastereomers are very distinct, stereochemical assignment of the compounds prepared here was made by analogy to the compounds for which conclusive X-ray data was available.

Aldimines derived from furfural and thiophene-2-carboxaldehyde produced adducts with diminished diastereoselectivity as did aldimines derived from aniline. The reasons for this are, at this time, unknown. The high yields and selectivities observed for aldimines derived from benzylamine are fortunate since we anticipate that cleavage by hydrogenolysis will allow access to pyrrolidines with a wide variety of subtitutents on the nitrogen atom.

A model, similar to Johnson's, which accounts for the cis selectivity as well as the diminished selectivity in the case of the aniline-derived aldimines, is shown in Figure 1. The fluxional *E*/*Z* geometry of imines should allow formation of both A and B, with the latter being higher energy as a consequence of a destabilizing pseudodiaxial interaction. Intermediate A would produce the 2,5-cis product C by a Mannich ring closure, whereas the minor trans isomer D would result from a similar Mannich closure from intermediate B. The disposition of the geminal diester should allow for a retro-Mannich process, and as a result the less stable trans isomer would have a reasonable pathway to the more stable cis isomer. This retro-Mannich process would be expected to be less facile with *N*-arylpyrrolidines. We have not been able to separate the cis and trans isomers to resubject them to the reaction conditions with the goal of probing this hypothesis.

In conclusion, we have reported an efficient and stereoselective three-component protocol for the reactions of aldimines with 1,1-cyclopropanediesters resulting in the

(10) Generally it was not possible to separate the diastereomers using flash chromatorgrapy. The products appeared as single spots when analyzed by thin layer chromatography.

production of *N*-alkyl- and *N*-arylpyrrolidines. The conditions employ the mild Lewis acid ytterbium triflate, and the substrate scope appears to be quite general. The cis stereoselectivity allows this to act as a complement to our previously reported synthesis of trans-2,5 substituted pyrrolidines. The application of this method to target oriented projects will be the subject of upcoming reports from our laboratory.

Experimental Section

General Procedure for Pyrrolidine Formation. Preparation of 6a. Benzaldehyde (233 mg, 2.20 mmol) and benzylamine (236 mg, 2.20 mmol) were dissolved in dry toluene (15 mL) and stirred over activated 4 Å molecular sieves under a balloon of argon for 30 min. $Yb(OTf)_3$ (124 mg, 0.20 mmol) and 2-phenyl-1,1-carbomethoxycyclopropane (469 mg, 2.00 mmol) were added, and the mixture was heated to 80 °C. The progress of the reaction was monitored by TLC. Upon disappearance of the cyclopropanediester, the reaction mixture was filtered, preabsorbed on silica gel, and purified by flash column chromatography (elution with EtOAc/hexane mixtures). Pyrrolidine **6a** (824 mg, 96% yield) was isolated as a 93:7 mixture of cis/trans isomers. R_f = 0.5 (40% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$, 93:7 mixture − major isomer only): δ 7.64 (d, J = 7.2 Hz, 2H), 7.54 (d, H = 7.2 Hz, 2 H), 7.43 (t, J = 7.2 Hz, 2 H), 7.33 (t, J = 8 Hz, 3H), 7.27−7.22 (m, 1 H), 7.20−7.15 (m, 3H), 6.90−6.88 (m, 2H), 4.75 (s, 1H), 3.74−3.69 (m, 1H), 3.69 (s, 3H), 3.61 (AB, 2H), 3.06 (s, 3H), 2.86 (dd, J = 13.5, 10.8 Hz, 1H), 2.40 (dd, J = 13.5, 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 93:7 mixture − major isomer only): δ 171.9, 169.7, 141.6, 139.2, 134.6, 130.2, 129.0, 128.6, 128.0, 127.8, 127.6, 127.5, 126.9, 66.3, 63.8, 63.7, 52.7, 52.0, 51.9, 42.1. IR (thin film) υ_{max} 3063, 3030, 2952, 1734, 1493, 1456, 1435, 1265, 1232, 1199, 1174, 1064, 916, 813, 754 cm^{-1}. HRMS (EI, 70 ev) calcd for $C_{27}H_{27}NO_4$ 429.1940, found 429.1937 amu.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada and Boehringer Ingelheim (Canada) for generous funding of this research. We are grateful to Mr. Doug Hairsine for performing MS analyses. C.A.C. is a recipient of an NSERC (CGSM) scholarship.

Supporting Information Available: Complete experimental procedures as well as ^{1}H NMR, ^{13}C NMR, IR, and MS analysis data for compounds **6a**−**o**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0512251