ORGANIC LETTERS

2004
Vol. 6, No. 20
3621−3624

Self-Condensation of *N-tert*-Butanesulfinyl Aldimines: Application to the Rapid Asymmetric Synthesis of Biologically Important Amine-Containing Compounds

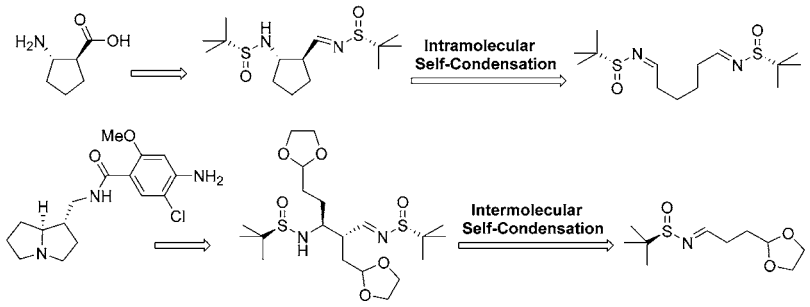
Laurie B. Schenkel and Jonathan A. Ellman*

Center for New Directions in Organic Synthesis, Department of Chemistry, University of California, Berkeley, California 94720

jellman@berkeley.edu

Received August 3, 2004

ABSTRACT



Highly diastereoselective intra- and intermolecular self-condensation reactions of *N-tert*-butanesulfinyl aldimines have been developed and applied to the rapid, asymmetric synthesis of *trans*-2-aminocyclopentanecarboxylic acid and the drug candidate SC-53116. Key to both syntheses is a novel microwave-assisted reaction in which *N*-sulfinyl aldimines are cleanly converted into nitriles in high-yielding concerted elimination processes.

Diastereoselective additions of nucleophiles to *N-tert*-butanesulfinyl imines have proven to be among the most effective methods for the asymmetric synthesis of amines.[1] The deprotonation of *N*-sulfinyl ketimines to provide metalloenamines, which then add with high diastereoselectivity to electrophiles, has significantly enhanced the utility of this chemistry. In particular, metalloenamines derived from *N-tert*-butanesulfinyl ketimines have been added to aldehydes to provide *β*-hydroxy *N*-sulfinyl imines. Stereoselective reduction then provides access to either *syn*- or *anti*-1,3-amino alcohols.[2]

Attempts to add metalloenamines derived from *tert*-butanesulfinyl aldimines to electrophiles have been unsuccessful as a result of competitive self-condensation during the deprotonation step.[3] However, it became apparent that a high-yielding, diastereoselective self-condensation reaction would enable the rapid construction of a variety of amine-containing compounds bearing two new contiguous stereocenters. Herein we report the development of highly diastereoselective intra- and intermolecular self-condensation

(1) (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (b) McMahon, J. P.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 1645 and references therein. (c) Higashibayashi, S.; Kohno, M.; Goto, T.; Suzuki, K.; Mori, T.; Hashimoto, K.; Nakata, M. *Tetrahedron Lett.* **2004**, *45*, 3707. (d) deSolms, S. J.; Ciccarone, T. M.; MacTough, S. C.; Shaw, A. W.; Buser, C. A.; Ellis-Hutchings, M. E.; Fernandes, C.; Hamilton, K. A.; Huber, H. E.; Kohl, N. E.; Lobell, R. B.; Robinson, R. G.; Tsou, N. N.; Walsh, E. S.; Graham, S. L.; Beese, L. S.; Taylor, J. S. *J. Med. Chem.* **2003**, *46*, 2973. (e) Kells, K. W.; Chong, J. M. *Org. Lett.* **2003**, *5*, 4215. (f) Cooper, I. R.; Grigg, R.; Hardie, M. J.; MacLachlan, W. S.; Sridharan, V.; Thomas, W. A. *Tetrahedron Lett.* **2003**, *44*, 2283. (g) Rech, J. R.; Floreancig, P. E. *Org. Lett.* **2003**, *5*, 1495. (h) Jung, P. M.; Beaudegnies, E.; DeMesmaeker, A.; Wendeborn, S. *Tetrahedron Lett.* **2003**, *44*, 293.

(2) (a) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 6518. (b) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 11276.

(3) Kochi, T. Unpublished results.

10.1021/ol048458j CCC: $27.50
Published on Web 09/04/2004

reactions of *N-tert*-butanesulfinyl aldimines, which, to our knowledge, represent the first examples of stereoselective imine self-condensation.[4] The utility of these self-condensation reactions is further demonstrated via the concise asymmetric syntheses of *trans*-2-aminocyclopentanecarboxylic acid **1** and SC-53116, a serotonin 5-HT_4 agonist (Figure 1).

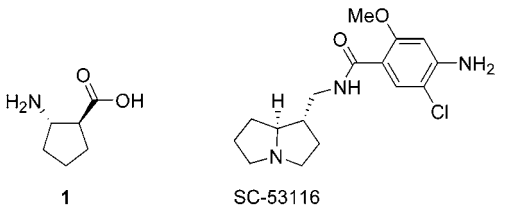
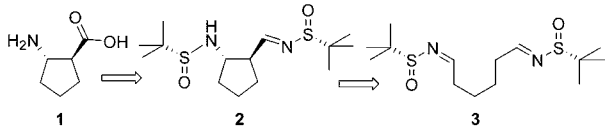


Figure 1. Biologically important compounds prepared utilizing self-condensation methodology.

The potential utility of an intramolecular *N*-sulfinyl aldimine self-condensation reaction was evident upon examination of the literature. There are several cyclic drug candidates[5] and biologically relevant compounds[6] that exhibit a core structure that could be accessed via aldimine self-condensation. One such compound, β-amino acid **1** (Scheme 1), is particularly useful because it has been incorporated

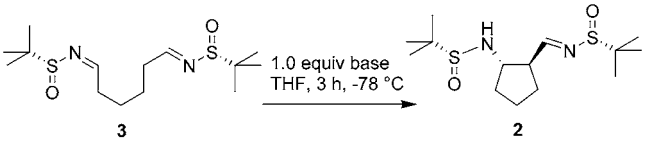
Scheme 1. Retrosynthesis for **1**



into unnatural homo- and heterogeneous foldamers that exhibit discrete folding properties.[7] Very recently, foldamers prepared from **1** were reported to display promising antimicrobial activity.[8]

We envisioned a rapid synthesis of **1** via intermediate **2**, which is the self-condensation product of bis-sulfinyl imine **3** (Scheme 1). Optimization of the intramolecular self-condensation reaction of imine **3** began with a survey of bases (Table 1). Previous observation of self-condensation

Table 1. Optimization of Intramolecular Self-Condensation



entry	base	yield (%)[a]	dr[b]
1	2-MePhMgBr	25	52:0:38:10
2	2-MeOPhMgBr	50	66:0:26:8
3	*t*-BuMgBr	80	50:0:37:13
4	LHMDS[d]	60	76:0:12:12
5	NaHMDS[d]	60	80:2:7:11
6[c]	NaHMDS[d]	81	78:3:8:11
7	KHMDS[d]	34	77:0:19:4

[a] Isolated yield after column chromatography. [b] Determined by ^{1}H NMR (see Supporting Information). Only the stereochemistry of the major diastereomer was determined. [c] Reaction run with 2.0 equiv of DMPU as additive. [d] 1.0 M in THF.

to provide oligomeric products as an undesired side reaction in the addition of Grignard reagents to sulfinyl aldimines[9] suggested that magnesium bases might effect the desired transformation. Imine **3**, which was prepared in 80% yield by condensation of (*R*)-*tert*-butanesulfinamide with hexanedial, was deprotonated with several sterically hindered Grignard reagents to provide the desired self-condensation product, albeit with poor diastereoselectivity (entries 1−3). Use of sodium and lithium hexamethyldisilazide (HMDS) improved both the yield and selectivity (entries 4−6). Optimization showed that NaHMDS with 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) as an additive significantly improved the reaction yield (entry 6). Notably, a single recrystallization of self-condensation product **2**, obtained according to the conditions listed in entry 6, provides the diastereomerically enriched product (≥95% dr) in 50% yield from **3**.[10] The absolute stereochemistry of **2** was determined by X-ray crystallography, establishing that the thermodynamically favored *trans* isomer was formed preferentially in the self-condensation reaction.

With the self-condensation product **2** in hand, conversion to β-amino acid **1** was rapidly completed in two high-yielding steps (Scheme 2). Previous work in these laboratories led to the observation that at temperatures above 130 °C, *tert*-butanesulfinyl aldimines undergo a concerted elimination of *tert*-butanesulfenic acid to provide nitriles.[11] Optimization of this novel reaction for the present work showed that the

(4) The self-condensation of 3,4,5,6-tetrahydropyridine is the only reported example of imine self-condensation. The stereochemical outcome of the reaction was not determined: Schöpf, C.; Braun, F.; Komzak, A. *Chem. Ber.* **1956**, *89*, 1821.

(5) (a) Babu, Y. S.; Chand, P.; Montgomery, J. A. U.S. Patent 6,562,-861, 2000. (b) Berge, J. M.; Brown, P.; Elder, J. S.; Forrest, A. K.; Hamprecht, D. W.; Jarvest, R. L.; McNair, D. J.; Sheppard, R. J. U.S. Patent 6,320,051, 2000. (c) McIver, J. M.; Degenhardt, C. R.; Eickhoff, D. J. U.S. Patent 6,307,049, 1999.

(6) (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (b) Strijowski, U.; Sewald, N. *Org. Biomol. Chem.* **2004**, *2*, 1105. (c) Yamazaki, T.; Zhu, Y.-F.; Probstl, A.; Chadha, R. K.; Goodman, M. *J. Org. Chem.* **1991**, *56*, 6644.

(7) (a) Appella, D. H.; Christianson, L. A.; Klein, D. A.; Richards, M. R.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 7574. (b) Hayen, A.; Schmitt, M. A.; Ngassa, F. N.; Thomasson, K. A.; Gellman, S. H. *Angew. Chem., Int. Ed.* **2004**, *43*, 505. (c) LePlae, P. R.; Fisk, J. D.; Porter, E. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2002**, *124*, 6820.

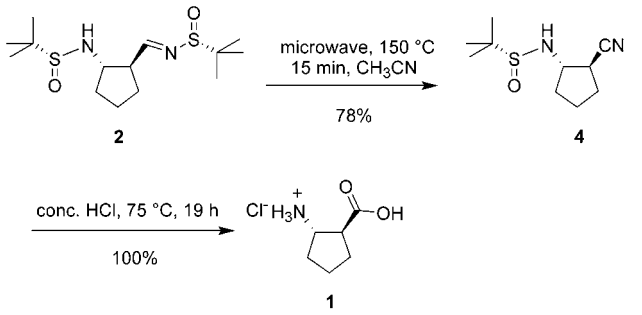
(8) Schmitt, M. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2004**, *126*, 6848.

(9) Barrow, J. C.; Ngo, P. L.; Pellicore, J. M.; Selnick, H. G.; Nantermet, P. G. *Tetrahedron Lett.* **2001**, *42*, 2051.

(10) A short survey of solvents revealed that THF is required for high yield and selectivity, as both Et_2O and toluene gave inferior results.

(11) (a) Mukade, T.; Dragoli, D. R.; Ellman, J. A. *J. Comb. Chem.* **2003**, *5*, 590. (b) Decomposition of a *p*-toluenesulfinyl imine has also been reported: Davis, F. A.; Friedman, A. J.; Kluger, E. W. *J. Am. Chem. Soc.* **1974**, *96*, 5000.

Scheme 2. Synthesis of **1**

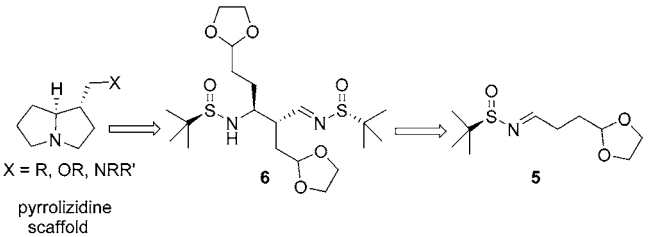


microwave-assisted transformation can be carried out in high yield in the presence of a sulfinamide moiety and other protected functionalities (vide infra).[12] The highest yields were obtained by heating at 150 °C for 15 min in acetonitrile in a microwave reactor. Incomplete conversion was observed at lower temperatures, and significant amounts of undesired decomposition products were obtained at temperatures higher than 150 °C.

Conversion of **4** to **1** was then carried out in quantitative yield via acid-catalyzed hydrolysis of the nitrile with concomitant removal of the sulfinyl protecting group (Scheme 2). Under these conditions, the stereochemical integrity of **1** was maintained as confirmed by preparation and GC analysis of the corresponding (*R*)- and (*S*)-Mosher amides. This synthesis of enantiomerically pure β-amino acid **1** was accomplished in four steps in 31% overall yield from hexanedial and represents one of the most efficient syntheses of **1** reported to date.[13]

The diastereoselective self-condensation of *tert*-butanesulfinyl aldimines was further applied to an intermolecular variant of the reaction. One powerful application of this method is the rapid construction of the pyrrolizidine scaffold (Scheme 3), an alkaloid motif that is present in multiple drug

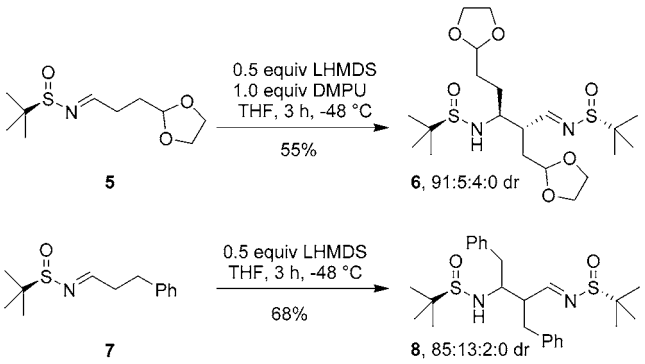
Scheme 3. Retrosynthesis for Preparation of Pyrrolizidines



candidates[14] and natural products.[15] It was envisioned that the pyrrolizidine framework could be prepared via functionalization of intermediate **6**, which is the product of intermolecular self-condensation of sulfinyl imine **5** (Scheme 3).

Investigation of the intermolecular variant thus focused on self-condensation of sulfinyl imine **5**, which was prepared in 89% yield via $CuSO_4$-catalyzed condensation of (*R*)-*tert*-butanesulfinamide and the corresponding aldehyde. As in the intramolecular case, hindered Grignard reagents were less effective bases for this transformation, and both KHMDS and NaHMDS failed to provide the desired product in synthetically useful yields or selectivities. Use of LHMDS proved to be critical, and we were pleased to find that, under optimized conditions, the desired intermolecular self-condensation product could be isolated in 55% yield and with an excellent 91:5:4:0 diastereomeric ratio (Scheme 4). Again,

Scheme 4. Intermolecular Self-Condensation



DMPU as an additive was beneficial, which in this case served to improve the diastereoselectivity from 87:7:6:0 in the case where LHMDS alone was employed. Notably, the intermolecular self-condensation reaction does not require a sulfinyl imine bearing a coordinating group for high selectivity, as self-condensation of imine **7** also provides a synthetically useful diastereoselectivity and yield (Scheme 4). In this case, however, additives did not improve either yield or selectivity.

The pyrrolizidine benzamide SC-53116[14a] seemed an ideal synthesis target for displaying the utility of the intermolecular aldimine self-condensation methodology (Scheme 5). SC-53116 is the first selective serotonin 5-HT_4 receptor agonist

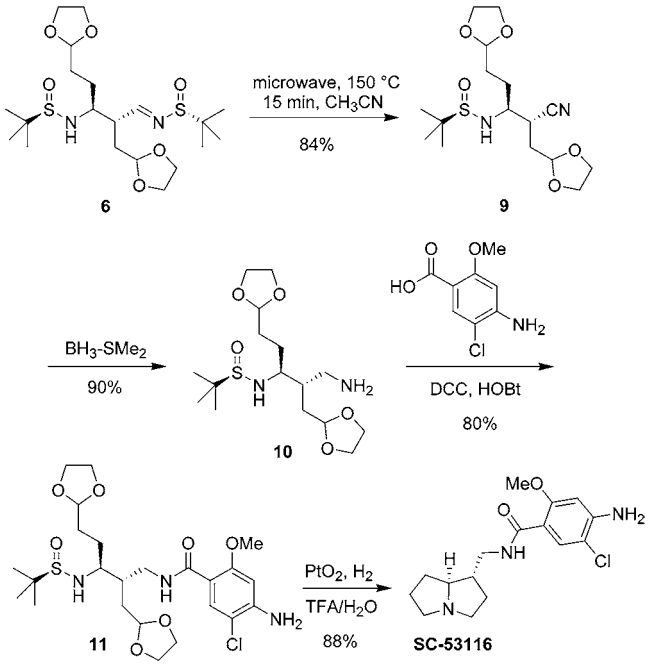
(12) *tert*-Butanesulfinamides also undergo concerted eliminations of *tert*-butanesulfenic acid to provide unsubstituted imines, but this transformation apparently has a higher activation barrier than for conversion of *N*-*tert*-butanesulfinyl imines to nitriles.

(13) For other asymmetric syntheses, see: (a) LePlae, P. R.; Umezawa, N.; Lee, H.-S.; Gellman, S. H. *J. Org. Chem.* **2001**, *66*, 5629. (b) Chippindale, A. M.; Davies, S. G.; Iwamoto, K.; Parkin, R. M.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Tetrahedron* **2003**, *59*, 3253. (c) Enders, D.; Weidemann, J. *Liebigs Ann./Recueil* **1997**, 699. (d) Davies, S. G.; Ichihara, O.; Lenoir, I.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1411. (e) Perlmutter, P.; Rose, M.; Vounatsos, F. *Eur. J. Org. Chem.* **2003**, 756.

(14) Representative examples include: (a) Flynn, D. L.; Zabrowski, D. L.; Becker, D. P.; Nosal, R.; Villamil, C. I.; Gullikson, G. W.; Moummi, C.; Yang, D.-C. *J. Med. Chem.* **1992**, *35*, 1489. (b) Becker, D. P.; Flynn, D. L.; Villamil, C. I. *Biorg. Med. Chem. Lett.* **2004**, *14*, 3073. (c) Zabrowski, D. L.; Flynn, D. L. U.S. Patent 4,992,461, 1989. (d) Becker, D. P.; Flynn, D. L.; Moormann, A. E.; Nosal, R.; Villamil, C. I. U.S. Patent 5,137,893, 1991.

(15) For representative natural product syntheses, see: (a) Ledoux, S.; Marchalant, E.; Célérier, J.-P.; Lhommet, G. *Tetrahedron Lett.* **2001**, *42*, 5397. (b) Bertrand, S.; Hoffman, N.; Pete, J.-P. *Eur. J. Org. Chem.* **2000**, 2227. (c) David, O.; Blot, J.; Bellec, C.; Fargeau-Bellassoued, M.-C.; Haviari, G.; Célérier, J.-P.; Lhommet, G.; Gramain, J.-C.; Gardette, D. *J. Org. Chem.* **1999**, *64*, 3122. (d) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Org. Chem.* **1990**, *55*, 1148.

Scheme 5. Synthesis of Pyrrolizidine Alkaloid SC-53116



to be identified[14b] and surpasses the potency and selectivity of other benzamides, such as metoclopramide, zacopride, renzapride, and cisapride.[14a] The reported synthesis of SC-53116 requires over 10 steps, with the key step being a highly diastereoselective alkylation of a cyclic acyl imine by a chiral tin enolate.[14a,15d]

The highly diastereoselective synthesis of self-condensation product **6** enables a significantly more efficient synthesis of SC-53116 (Scheme 5). Microwave-assisted sulfinyl imine decomposition was again key to the success of the sequence, as it allowed for selective functionalization of the self-condensation product in the presence of both the sulfinyl amine and cyclic acetal protecting groups. Microwave reaction of a 91:5:4:0 diastereomeric mixture of self-condensation product **6**, followed by chromatographic separation of the corresponding diastereomeric nitriles, provided the pure major diastereomer **9** in 84% yield. Absolute stereochemistry was established via X-ray crystallographic analysis of **9**. Mild reduction of the nitrile with borane−dimethyl sulfide complex was accomplished in 90% yield, followed by coupling of amine **10** with 4-amino-5-chloro-2-methoxybenzoic acid under standard amide bond forming conditions, to provide intermediate **11** in 80% yield. Under acidic reducing conditions, the sulfinyl and acetal protecting groups were removed, allowing for cyclization and reduction in a single step, which furnished SC-53116 in 88% isolated yield. This sequence is significantly more efficient than the prior synthesis, providing SC-53116 in 29% overall yield in only five steps from sulfinyl imine **5**.

The self-condensation reactions of *N*-*tert*-butanesulfinyl aldimines reported here are the first examples of stereoselective imine self-condensation processes and provide versatile, functionalized intermediates with multiple stereocenters. The diastereoselective intra- and intermolecular self-condensation reactions were applied to the rapid total syntheses of *trans*-2-aminocyclopentanecarboxylic acid **1** and serotonin 5-HT_4 agonist SC-53116, both of which featured a novel microwave-assisted thermal decomposition to cleanly convert *N*-sulfinyl imines to nitriles. The prevalence of structural motifs and scaffolds that are easily accessible via this strategy suggests that this self-condensation methodology may enjoy widespread use for a variety of applications.

Acknowledgment. This work was supported by the National Science Foundation (CHE0139468). L.B.S gratefully acknowledges Boehringer Ingelheim for a graduate fellowship. The authors thank Dr. Allen G. Oliver and Dr. Frederick J. Hollander for solving the X-ray crystal structures. The Center for New Directions in Organic Synthesis is supported by Bristol-Myers-Squibb as sponsoring member and Novartis as supporting member.

Supporting Information Available: Crystallographic data in CIF format, full experimental details, and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048458J