

Asymmetric Aza-Mannich Reactions of Sulfinimines: Scope and Application to the Total Synthesis of a Bromopyrrole Alkaloid

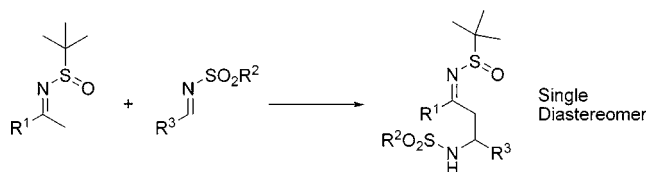
James C. Lanter,* Hongfeng Chen, Xuqing Zhang, and Zhihua Sui

Department of Medicinal Chemistry, Johnson & Johnson Pharmaceutical Research and Development, 1000 Route 202S, Raritan, New Jersey 08869

jlanter@prds.jnj.com

Received October 18, 2005

ABSTRACT



An asymmetric intermolecular aza variant of the Mannich reaction is reported utilizing chiral sulfinimine anions as the nucleophile and *N*-sulfonyl aldimines as the electrophilic component. A wide range of nucleophiles and electrophiles are tolerated by the reaction conditions, delivering the condensation products in good to excellent yield with a high degree of stereocontrol. Application of this methodology to the total synthesis of a natural product is reported.

Carl Mannich's methodology for the construction of β-amino carbonyls has been a fundamental tool of the synthetic organic chemist for decades. Originally limited to dialkyl-amino methylation, the Mannich reaction's scope¹ has expanded in recent years to include a wide variety of monosubstituted amines, ammonia equivalents and even acylated amines. In addition, a variety of tandem variants including the Aza-Cope Mannich² and Mannich–Michael³ methodologies have emerged. In parallel with these developments, significant strides have been made in the asymmetric versions of the reaction, particularly through the use of chiral catalysis.⁴

One area of this classical methodology that has received less attention is an aza variant⁵ wherein an enamide anion is

reacted with an imine to deliver a β-amino imine. Until recently, the general instability of the carbon–nitrogen double bond limited the utility of such imines. The development of sulfinimine methodology by Davis⁶ and Ellman⁷ has greatly expanded the scope of imine utility by not only providing a more synthetically versatile imine but also including an element of stereocontrol via the easily obtained

(1) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1045.

(2) (a) Brummond, K. M.; Hong, S. *J. Org. Chem.* **2005**, *70*, 907. (b) Cooke, A.; Bennett, J.; McDaid, E. *Tetrahedron Lett.* **2002**, *43*, 903.

(3) (a) Schneider, C.; Reese, O. *Angew. Chem., Int. Ed.* **2000**, *39*, 2948. (b) Kirschbaum, S.; Waldmann, H. *Tetrahedron Lett.* **1997**, *38*, 2829. (c) Waldmann, H.; Braun, M. *J. Org. Chem.* **1992**, *57*, 4444. (d) Waldmann, H.; Braun, M.; Weymann, M.; Gewehr, M. *Synlett* **1991**, *12*, 881. (e) Kunz, H.; Pfengle, W. *Angew. Chem.* **1989**, *101*, 1041.

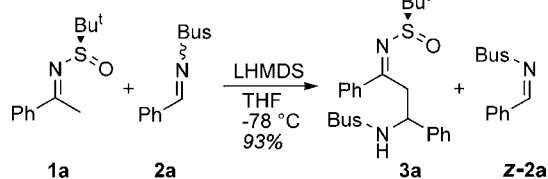
(4) (a) Josephsohn, N. S.; Carswell, E. L.; Snapper, M. L.; Hoveyda, Amir H. *Org. Lett.* **2005**, *7*, 2711. (b) Ibrahim, I.; Samec, J. S. M.; Baekvall, J. E.; Cordova, A. *Tetrahedron Lett.* **2005**, *46*, 3965. (c) Ibrahim, I.; Cordova, A. *Tetrahedron Lett.* **2005**, *46*, 2839. (d) Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1525. (e) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466. (f) Muench, A.; Wendt, B.; Christmann, M. *Synlett* **2004**, *15*, 2751. (g) Ibrahim, I.; Casas, J.; Cordova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6528. (h) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84. (i) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; S., M.; Hashizume, D.; Koshino, H. *Adv. Synth. Catal.* **2004**, *346*, 1435. (j) Notz, W.; Watanabe, S.; Chowdari, N. S.; Zhong, G.; Betancort, J. M.; Tanaka, F.; Barbas, C. F., III. *Adv. Synth. Catal.* **2004**, *346*, 1131. (k) Zhuang, W.; Saaby, S.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 476. (l) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580. (m) Cordova, A. *Acc. Chem. Res.* **2004**, *37*, 102.

(5) (a) Matsubara, R.; Nakamura, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1679. (b) Merla, B.; Risch, N. *Synthesis* **2002**, 1365.

sulfur chiral center. Of particular interest in the context of the aza-Mannich reaction was Ellman's recent^{7d} report on the self-condensation of sulfinimines for the construction of heterocycles. Both inter- and intramolecular variants were reported to proceed in good yield with reasonable diastereoselectivity. However, as with the analogous aldol condensation, the best results were observed when the sulfinimines were either self-condensed or were derived from a symmetrical dialdehyde.

Our goal was to develop a general methodology for the intermolecular cross coupling of enamides and imines. Taking our lead from the carbonyl condensation literature, we recognized that the use of coupling partners with very different reactivity would be a straightforward way to address the problem of complicated product distribution. Cognizant of Ellman's observations regarding the high reactivity of sulfinyl aldimines, we initiated our study utilizing the less reactive *N*-*tert*-butylsulfinimine of acetophenone (**1a**) as the nucleophile and a 2:1 *E/Z* mixture of the more reactive *N*-*tert*-butanesulfonyl (Bus⁸) benzaldehyde imine (**2a**⁹) as the electrophile (Scheme 1).

Scheme 1. Initial Condensation



Although we were pleased to see that the reaction of the lithium enamide with this sulfonyl imine mixture worked efficiently and with nearly complete stereocontrol at -78°C , we noted the reaction required a significant excess of the electrophile mixture to proceed to completion. Even more significantly, we recovered only the *Z* configuration *N*-Bus imine after workup and purification of the reaction mixture. Independent reaction of enamide **1a** with the *E* and *Z* isomers of **2a** revealed that while only a slight excess of *E*-**2a** was

required to deliver the product in the reported yield, **Z**-**2a** did not react at low temperature and decomposition of both starting materials occurred after the mixture was gradually warmed to room temperature. We were able to unambiguously establish the (*S*) absolute configuration of the newly formed stereocenter by converting **3a** to a diastereomeric pair of known amino alcohols¹¹ in two steps.^{7k,l}

Placing these observations in the context of Ellman's enamide–aldehyde condensations, it becomes apparent that the same mechanism must be in operation. Both the higher degree of stereocontrol and the lack of imine reactivity can be rationalized within this framework when one takes into account the steric bulk and orientation of the *tert*-butyl sulfonyl group.^{7l}

Armed with this information, we proceeded to explore the scope of the condensation reaction with a variety of sulfinimines and *E*-sulfonyl imines¹⁰ (Table 1). The reaction

Table 1. Reaction Scope

sulfinimine (R ₁)	sulfonyl imine (R ₂)	product (yield (%), dr)
1a (Ph)	2a (Ph)	3a (93, >99:1)
1b ((4-CN)Ph)	2a (Ph)	3b (81, >99:1)
1c ((4-OMe)Ph)	2a (Ph)	3c (84, >99:1)
1d (pyrid-3-yl)	2a (Ph)	3d (85, >99:1)
1e (pyrid-2-yl)	2a (Ph)	3e (80, >99:1)
1f ((2-OMe)Ph)	2a (Ph)	3f (50, >99:1)
1g (furan-2-yl)	2a (Ph)	3g (65, >99:1)
1h (Me)	2a (Ph)	3h (88, 4:1)
1i (Et)	2a (Ph)	3i (85, >99:1)
1j (BnOCH ₂)	2a (Ph)	3j (64, >99:1)
1a (Ph)	2b (Et)	3k (54, >99:1)
1a (Ph)	2c (^t Bu)	3l (80, >99:1)
1a (Ph)	2d ((4-NO ₂)Ph)	3m (91, >99:1)
1a (Ph)	2e ((4-OMe)Ph)	3n (85, >99:1)
1a (Ph)	2f (pyrid-2-yl)	3o (61, >99:1)
1a (Ph)	2g (cinnamyl)	3p (85, >99:1)

proceeded with a high degree of stereocontrol with both aryl and heteroaryl sulfinimine nucleophiles (**1a–g**). The reactions of alkyl substituted sulfinimines (**1h–j**) proceeded with similar efficiency and diastereoselectivity as their aryl counterparts with only the acetone-derived nucleophile (**1h**) showing diminished diastereoselectivity. An interesting feature of these alkyl enamide condensations was the tendency of the anion to react exclusively on the less substituted carbon (**1i** and **1j**).

(10) Ruano, J. L. G.; Aleman, J.; Cid, M. B.; Parra, A. *Org. Lett.* **2005**, 7, 179.

(11) Stuhmer, W.; Frey, H. H. *Arch. Pharm. (Weinheim, Ger.)* **1953**, 286, 26.

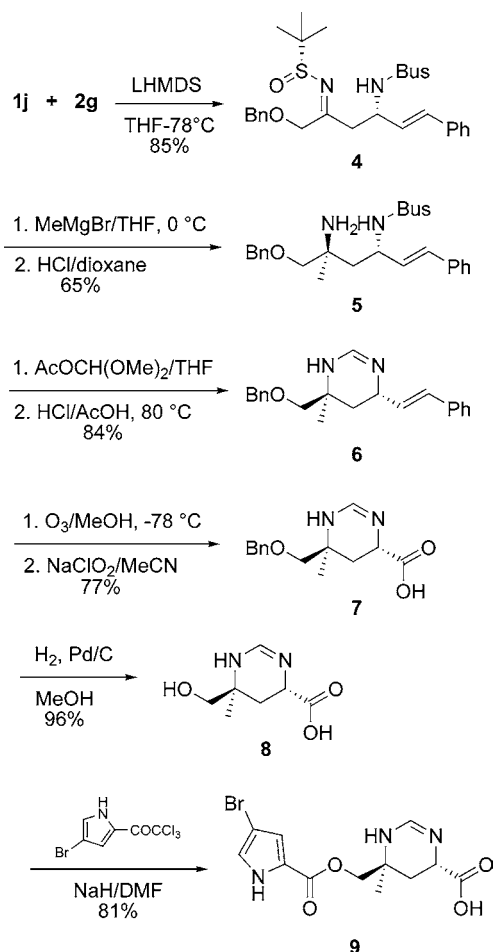
(6) (a) Zhou, P.; Chen, B.; Davis, F. A. *Tetrahedron* **2004**, 60, 8003. (b) Davis, F. A.; Yang, B. *J. Am. Chem. Soc.* **2005**, 127, 8398. (c) Davis, F.; Yang, B.; Deng, J.; Wu, Y.; Zhang, Y.; Rao, A.; Fang, T.; Goswami, R.; Prasad, K.; Nolt, M.; Anilkumar, G. *Phosphorus, Sulfur Silicon – Relat. Elem.* **2005**, 180, 1109. (d) Davis, F. A.; Nolt, M. B.; Wu, Y.; Prasad, K. R.; Li, D.; Yang, B.; Bowen, K.; Lee, S. H.; Eardley, J. H. *J. Org. Chem.* **2005**, 70, 2184. (e) Davis, F. A.; Deng, J. *Org. Lett.* **2005**, 7, 621.

(7) (a) Brinner, K. M.; Ellman, J. A. *Org. Biomol. Chem.* **2005**, 3, 2109. (b) Weix, D. J.; Shi, Y.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, 127, 1092. (c) Kochi, T.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, 126, 15652. (d) Schenkel, L. B.; Ellman, J. A. *Org. Lett.* **2004**, 6, 3621. (e) McMahon, J. P.; Ellman, J. A. *Org. Lett.* **2004**, 6, 1645. (f) Brinner, K. M.; Ellman, J. A. *Org. Biomol. Chem.* **2005**, 3, 2109. (g) Ellman, J. A. *Pure Appl. Chem.* **2003**, 75, 39. (h) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, 35, 984. (i) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, 64, 1278. (j) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2003**, 125, 11276. (k) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, 124, 6518. (l) See the Supporting Information for more details.

(8) Sun, P.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1997**, 62, 8604.

(9) Artman, G. D., III; Bartolozzi, A.; Franck, R. W.; Weinreb, S. M. *Synlett* **2001**, 232.

Scheme 2. Total Synthesis of Manzacidin C



High efficiency and stereocontrol were also observed in the condensation of a range of imine electrophiles (**2a–g**) with the enamide anion of **1a**. It is noteworthy that exclusive 1,2 addition in high yield was observed in the cinnamyl (**2g**) case.

Having completed our studies on the scope of the aza Mannich condensation, we looked for a suitable application to demonstrate the utility of this methodology. After survey-

ing the literature, we found that a key intermediate Ohfune had used in his manzacidin C¹² total synthesis¹³ could be made much more efficiently using our methodology (Scheme 2). Treating a mixture of **1j** and **2g** with LHMDS in dry THF at $-78\text{ }^{\circ}\text{C}$ smoothly effected their condensation. Although methyl Grignard addition to the resulting β -sulfonamido sulfinyl imine required an excess of the nucleophile, the reaction delivered a single diastereomer in good yield. Deprotection of the sulfinyl group was then achieved by treatment with HCl in dioxane to provide diamine **5**. Cyclization of **5** to the *N*-sulfonyl tetrahydropyrimidine followed by Bus deprotection in a mixture of HCl and acetic acid provided **6** in excellent yield without epimerization. Oxidative cleavage of the cinnamyl moiety was carried out by a two-step process, first cleaving the double bond to the aldehyde through ozonolysis followed by oxidation to tetrahydropyrimidinyl acid **7** in high yield. Hydrogenolysis of the benzyl protecting group followed by coupling of the alcohol to 2-(trichloroacetyl)-4-bromopyrrole using the literature reported conditions delivered the natural product in 28% overall yield, with a longest linear sequence of 10 steps. This compares favorably both to Ohfune's and Du Bois'¹⁴ reported asymmetric syntheses.

In conclusion, we have developed a general asymmetric synthesis of β -sulfonamido sulfinimines by the condensation of optically pure sulfinimines with sulfonyl imines. Application of this methodology to the total synthesis of the marine alkaloid manzacidin C has been demonstrated.

Acknowledgment. We thank Dr. Nareshkumar Jain and Dr. David C. Palmer for helpful discussions and Dr. Alexandra Shedlow for NMR technical assistance.

Supporting Information Available: Experimental procedures and compound characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL0525258

(12) Kobayashi, J.; Kanda, F.; Ishibashi, M.; Shigemori, H. *J. Org. Chem.* **1991**, *56*, 4574.

(13) (a) Namba, K.; Shinada, T.; Teramoto, T.; Ohfune, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10708. (b) Namba, K.; Teramoto, T.; Shinada, T.; Ohfune, Y. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1999**, 79.

(14) Wehn, P. M.; DuBois, J. *J. Am. Chem. Soc.* **2002**, *124*, 12950.