ACS Combinatorial Science

Letter

pubs.acs.org/acscombsci

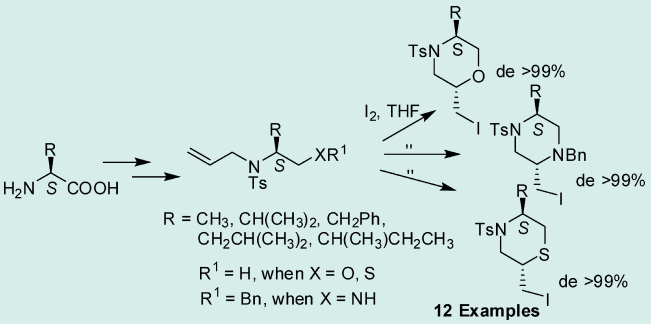
I_2-Mediated Diversity Oriented Diastereoselective Synthesis of Amino Acid Derived *trans*-2,5-Disubstituted Morpholines, Piperazines, and Thiomorpholines

Saurav Bera and Gautam Panda*

Medicinal and Process Chemistry Division, CSIR, Central Drug Research Institute, Lucknow-226001, UP, India

Supporting Information

ABSTRACT: Diastereoselective *trans*-2,5-disubstituted amino acids derived diverse morpholines, piperazines and thiomorpholines were prepared in 30 min-1 h with high yields through iodine-mediated 6-*exotrig* type cyclization from a single common synthetic intermediate. The displacement of iodine with hydride ion gave a methyl substituent at the 2-position of morpholines which provides an additional opportunity for diversity oriented nucleophilic substitution on the rings as well as incorporation of substituents at the 5-position from amino acids constituents.



KEYWORDS: *amino acids, morpholines, piperazines, thiomorpholines, diastereoselective reaction*

Nitrogen-, oxygen-, and sulfur-containing heterocyclic frameworks are ubiquitous subunits in biologically active molecules.[1−3] For example, 2,5-disubstituted morpholine derivatives are used as chiral auxiliaries in asymmetric synthesis,[4] and in a variety of biologically active structures such as the antidepressant drug reboxetine[5] and the antifungal compound fenpropimorph.[6] Similarly, the piperazine moiety is present in various biologically active compounds including the antimicrobial[7] pefloxacin and related quinolones, dopaminergic D3 agents,[8] HIV-protease inhibitors,[9] and the antidepressant clozapine.[10]

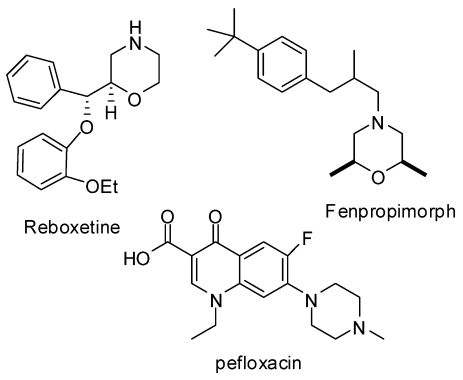


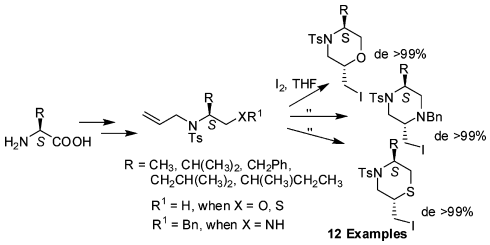
Figure 1. Some bioactive disubstituted morpholines and piperazine derivatives.

One major constraint of using morpholines, piperazines and thiomorpholines as building blocks is the difficulty of introducing functional groups on the carbon backbone, and so SAR studies have been dominated by changes in the N-substituents. Many of the existing protocols for accessing these types of 2,5-disubstituted heterocycles give diastereomeric mixtures of products.[11] For example, morpholines can be prepared by the epoxide ring-opening with amino alcohols, with cyclization of the resulting amino diol to give the desired product. De Kimpe and co-workers[12] have shown that disubstituted morpholines can also be prepared by ring enlargement of 2-(allyloxymethyl)aziridine via an electrophile−induced ring closure reaction, but isolated yields are low in many cases. Although C-functionalized disubstituted chiral morpholines have been synthesized,[13] only two enantioselective synthesis of *trans*-2,5-disubstituted morpholines have been reported so far.[14] Substituted piperazines have been mostly prepared by dimerization of amino acids to afford diketopiperazines, which were subsequently reduced.[15]

We have been working on the synthesis and biology of S-amino acid-derived chiral heterocycles and natural-product-like molecules.[16] Recently, we have published a new series of amino acids derived benzoxazepines as antitumor agents in breast cancer[16b] and a novel methodology for the synthesis of substituted piperazine.[16d] In continuation of our work, herein we describe the asymmetric synthesis of *trans*-2,5-disubstituted morpholines, piperazines and thiomorpholines through a straightforward and modular pathway involving (iodine mediated 6-exotrig cyclization of precursors) bearing four different groups at N1, C2, N4 and C5 (Scheme 1).[17]

Received: August 10, 2011
Revised: November 14, 2011
Published: November 29, 2011

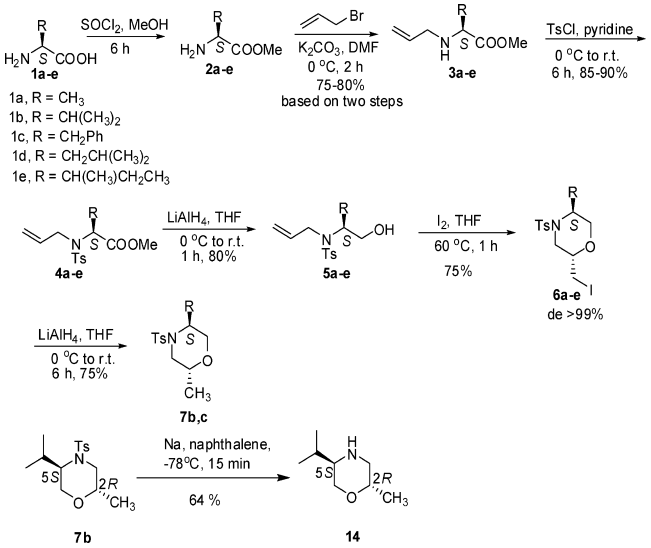
Scheme 1. Synthesis of Amino Acid Derived *trans*-2,5-Disubstituted Morpholines, Piperazines, and Thiomorpholines



RESULT AND DISCUSSION

The synthesis of the required substrates for iodocyclization began with *S*-amino acids **1a−e** which were converted to their methyl-esters **2a−e** followed by allylation to give **3a−e** (Scheme 2).

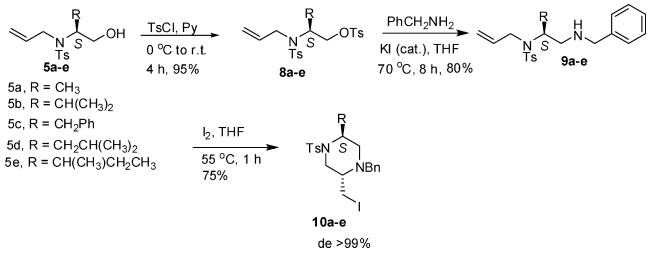
Scheme 2. Synthesis of Disubstituted Morpholines



Tosylation to **4a−e** proceeded smoothly, followed by ester reduction to give primary alcohols **5a−e**. All of these steps were accomplished in excellent yields and are amenable to easy scale-up. The carbinols were used as common intermediates for diversification. Thus, direct iodine mediated cyclization of, **5a−e** furnished **6a−e** in 1 h with diastereoselectivity up to >99%. The replacement of iodine by hydride through nucleophilic displacement furnished compounds **7b,c** in 75% yield. Of course, other nucleophiles than hydride can be easily introduced at this step give diverse *trans*-2,5-disubstituted morpholines. In addition, the tosyl group can be removed as shown for **7b** using sodium naphthalenide.[16d] Derivatization of the resulting secondary amine provides additional opportunity for diversity oriented synthesis.

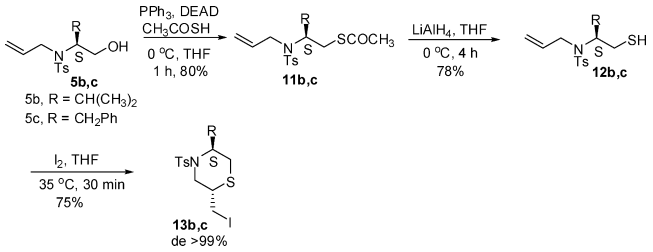
With intermediate carbinols **5a−e** in hand, synthesis of 2,5 disubstituted piperazines was attempted (Scheme 3). The derived tosylates **8a−e** reacted smoothly with benzyl amine and KI as catalyst to give **9a−e**. As above, iodine-mediated cyclization at 55 °C gave 2,5-disubstituted piperazines **10a−e** in diastereoselective fashion and good yield. Only one isomer each was detected by chiral HPLC analysis of the products derived from *R*- and *S*-leucine, showing complete retention of absolute stereochemistry as well as completely diastereoselectivity in the iodocyclization step.

Scheme 3. Synthesis of Disubstituted Piperazines



A similar pathway was adopted for the synthesis of chiral thiomorpholines from the common carbinol precursor (Scheme 4).

Scheme 4. Synthesis of Disubstituted Thiomorpholines



Compounds **5b,c** were thioesterified with thioacetic acid under Mitsunobu conditions and then reduced to the corresponding thiol compounds **12b,c** in good yield. Under similar iodocyclization condition, **12b,c** provided thiomorpholines **13b,c** with excellent diastereoselectivity. In this case, the starting materials were fully consumed within 30 min as monitored by TLC even at 30 °C, representing considerably faster reactions than the other two substrates. This is presumably because of the high nucleophilicity of sulfur in **12b,c** compared to nitrogen and oxygen in **5a−e** and **9a−e**.

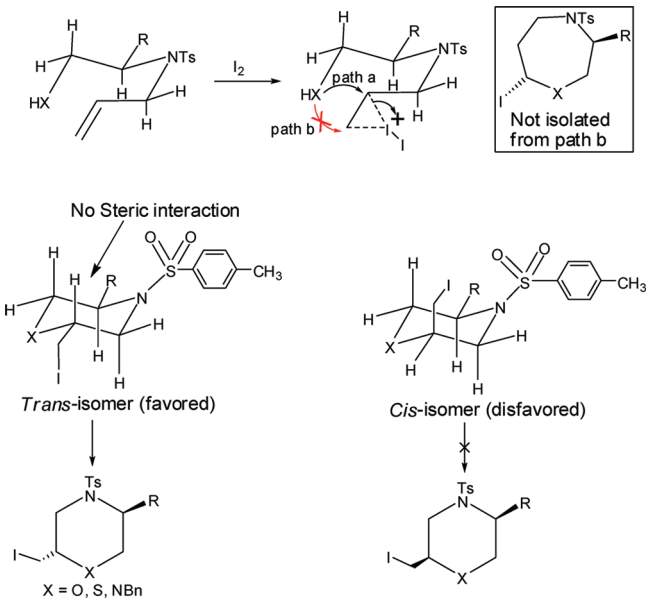


Figure 2. Possible iodocyclization transition states.

All the final molecules were characterized by 1D NMR, mass, IR, and elemental analysis. The stereochemistries of final molecules were confirmed by NOESY spectroscopy and chiral

dx.doi.org/10.1021/co200129t | ACS Comb. Sci. 2012, 14, 1−4

HPLC analysis (see Supporting Information). The stereochemistry at 5-position of six membered ring was also confirmed by NMR and NOESY spectroscopic analysis (see Supporting Information). In compound **10d**, (Figure 3) the location of all protons were

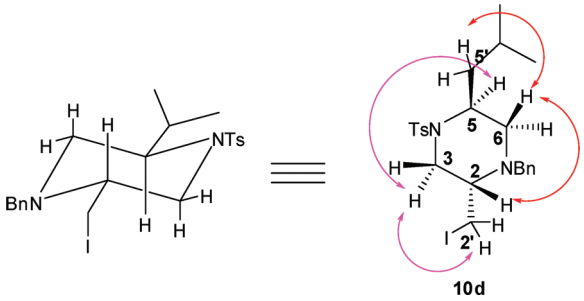


Figure 3. Confirmation of stereochemistry of **10d** by NOESY (400 MHz, $CDCl_3$).

confirmed on the basis of the DEPT, HSQC and COSY spectra. The H-5 showed NOESY correlation with H-3, which is syn to H-2′, whereas H-2 showed NOESY correlation with H-6, which is syn to H-5′.

The trans-stereoselectivity of the iodocyclization reactions of heterosubstituted amino acids derived allylamines **5a−e**, **9a−e**, and **12b**,**c** can be explained on the basis of the expected conformational preferences in the proposed transition state of the reaction (Figure 2). The reaction does not follow "path b" giving rise to seven-membered rings, and selects the trans isomer of the 6-membered ring. A chairlike transition state exposes the iodomethyl group to 1,3-diaxial interactions for the cis isomer but not for the trans isomer, giving rise to considerably more steric crowding in the former case.

In summary, we have described a simple and powerful synthetic route that provides access to diastereoselective 2,5-disubstituted diverse morpholines, piperazines and thiomorpholine starting from commercially available S-amino acids derived synthetic intermediates. The key step involves iodine mediated cyclization under mild reaction condition, giving heterocycles that can be further elaborated in several ways, such as by nucleophilic substitution on the rings as well as incorporation of substituent at 5-position from amino acids constituents.

EXPERIMENTAL PROCEDURES

General Experimental Procedure for the Synthesis of 6a−e. To a stirred solution of compound **5a−e** (1 equiv) in anhydrous THF (10 mL), I_2 (1 equiv) was added at 60 °C. Then it was continuously stirred for 1 h. The reaction mixture was quenched by addition of sodium thiosulfite and diluted with water (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the organic layer was dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was chromatographed on silica gel with as eluent (hexane/ethyl acetate, 9.5/0.5) to furnish the disubstituted morpholine **6a−e** (75−80% yield) as a colorless oil.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and compound characterization data for products. This information is available free of charge via the Internet at http://pubs.acs.org/.

AUTHOR INFORMATION

Corresponding Author

* Tel: 91-522-2612411-18, Ext. 4385, 4603. Fax: 91-522-2623405. E-mail: gautam.panda@gmail.com; gautam_panda@cdri.res.in.

ACKNOWLEDGMENTS

This research project was supported by Department of Science and Technology, New Delhi, India. Saurav thanks CSIR for providing fellowship (NET-SRF) and Mr. Purushottam for HPLC analysis. For Instrumental facilities from SAIF, CDRI (communication no 8167), Lucknow is acknowledged.

REFERENCES

(1) Bates, R.; Sa-Ei, K. Syntheses of the sedum and related alkaloids. *Tetrahedron* **2002**, *58*, 5957.

(2) (a) Bailey, P. D.; Millwood, P. A.; Smith, P. D. Asymmetric routes to substituted piperidines. *Chem. Commun.* **1998**, 633. (b) Laschat, S.; Dickner, T. Stereoselective synthesis of piperidines. *Synthesis* **2000**, 1781.

(3) (a) Clarke, P. A.; Santos, S. Strategies for the formation of tetrahydropyran rings in the synthesis of natural products. *Eur. J. Org. Chem.* **2006**, 2045−2053. (b) Larrosa, I.; Romea, P.; Urpi, F. Synthesis of six-membered oxygenated heterocycles through carbon-oxygen bond-forming reactions. *Tetrahedron* **2008**, *64*, 2683.

(4) (a) Enders, D.; Meyer, O.; Raabe, G.; Runsink, J. (*S*,*S*)-3,5-dimethylmorpholine, a novel C_2-symmetric auxiliary. First application in [4 + 2]-cycloadditions leading to 4-oxohexahydropyridazine derivatives. *Synthesis* **1994**, 66−72. (b) Dave, R.; Sasaki, N. A. Facile route to 3,5-disubstituted morpholines: enantioselective synthesis of O-protected *trans*-3,5-bis(hydroxymethyl)morpholines. *Org. Lett.* **2004**, *6*, 15−18.

(5) Hajos, M.; Fleishaker, J. C.; Filipiak-Reisner, J. K.; Brown, M. T.; Wong, E. H. F. The selective norepinephrine reuptake inhibitor antidepressant reboxetine: pharmacological and clinical profile. *CNS Drug Rev.* **2004**, *10*, 23−44.

(6) Dieckmann, H.; Stockmaier, M.; Kreuzig, R.; Bahadir, M. Simultaneous determination of fenpropimorph and the corresponding metabolite fenpropimorphic acid in soil. *Fresenius' J. Anal. Chem.* **1993**, *345*, 784.

(7) Lu, S.; Zhang, Y.; Liu, J.; Zhao, C.; Liu, W.; Xi, R. Preparation of anti-pefloxacin antibody and development of an indirect competitive enzyme-linked immunosorbent assay for detection of pefloxacin residue in chicken liver. *J. Agric. Food. Chem.* **2006**, *54*, 6995−7000.

(8) Leopoldo, M.; Lacitiva, E.; Colabufo, N. A.; Contino, M.; Berardi, F.; Perrone, R. First structure−activity relationship study on dopamine D3 receptor agents with *N*-[4-(4-arylpiperazin-1-yl)butyl]carboxamide structure. *J. Med. Chem.* **2005**, *48*, 7919−7922.

(9) Askin, D.; Eng, K. K.; Rossen, K.; Purick, R. M.; Welss, K. M.; Volante, R. P.; Reider, P. J. Highly diastereoselective reaction of a chiral, non-racemic amide enolate with (*S*)-glycidyl tosylate. Synthesis of the orally active HIV-1 protease inhibitor L-735,524. *Tetrahedron Lett.* **1994**, *35*, 673−676.

(10) Su, J.; Tang, H.; McKittrick, B. A.; Burnett, D. A.; Zang, H.; Smith-Torhan, A.; Fawzi, A.; Lachowicz, J. Modification of the clozapine structure by parallel synthesis. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4548−4553.

(11) (a) Sun, G.; Savle, P. S.; Gandour, R. D.; Bhaird, N. N. a; Ramsay, R. R.; Fronczek, F. R. Syntheses, structures, and enzymic evaluations of conformationally constrained, analog inhibitors of carnitine acetyltransferase: (2*R*,6*R*)-, (2*S*,6*S*)-, (2*R*,6*S*)-, and (2*S*,6*R*)-6-(carboxylatomethyl)-2-(hydroxymethyl)-2,4,4-trimethylmorpholinium. *J. Org. Chem.* **1995**, *60*, 6688−6695. (b) Take, K.; Konishi, N.; Shigenaga, S.; Kayakiri, N.; Azami, H.; Eikyu, Y.; Nakai, K.; Ishida, J.; Morita, M. Preparation of piperazines for treating or preventing tachykinin-mediated diseases. PCT Int. Appl. WO 00035915, Jun 22, 2000.

(12) D'hooghe, M.; Vanlangendonck, T.; T€ornroos, K. W.; De Kimpe, N. Novel Synthesis of *cis*-3,5-disubstituted morpholine derivatives. *J. Org. Chem.* **2006**, *71*, 4678−4681.
(13) (a) Wijtmans, R.; Vink, M.K. S.; Schoemaker, H. E.; van Delft, F. L.; Blaauw, R. H.; Rutjes, F. P. J. T. Biological relevance and synthesis of c-substituted morpholine derivatives. *Synthesis* **2004**, *5*, 641−662. (b) D'hooghe, M.; Vanlangendonck, T.; T€ornroos, K. W.; De Kimpe, N. Novel synthesis of *cis*-3,5-disubstituted morpholine derivatives. *J. Org. Chem.* **2006**, *71*, 4678−4681. (c) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. An annulation reaction for the synthesis of morpholines, thiomorpholines, and piperazines from *β*-heteroatom amino compounds and vinyl sulphonium salts. *Angew. Chem., Int. Ed.* **2008**, *47*, 3784−3786. (d) Lupi, V.; Albanese, D.; Landini, D.; Scaletti, D.; Penso, M. Synthesis of 2,6-disubstituted morpholines through regioselective oxirane ring opening by tosylamide under PTC conditions. *Tetrahedron* **2004**, *60*, 11709−11718.
(14) (a) Lanman, B. A.; Myers, A. G. Efficient, stereoselective synthesis of *trans*-2,5-disubstituted morpholines. *Org. Lett.* **2004**, *6*, 1045−1047. (b) Leathen, M. L.; Rosen, B. R.; Wolfe, J. P. New strategy for the synthesis of substituted morpholine. *J. Org. Chem.* **2009**, *74*, 5107−5110.
(15) Dinsmore, C. J.; Beshore, D. C. Recent advances in the synthesis of diketopiperazins. *Tetrahedron* **2002**, *58*, 3297−3312.
(16) (a) Mishra, J. K.; Panda, G. Diversity-oriented synthetic approach to naturally abundant s-amino acids based benzannulated enantiomerically pure medium ring heterocyclic scaffolds employing inter- and intramolecular mitsunobu reactions. *J. Comb. Chem.* **2007**, *9*, 321. (b) Samanta, K.; Chakravarti, B.; Mishra, J. K.; Dwivedi, S. K. D.; Nayak, L. V.; Choudhry, P.; Bid, H. K.; Konwar, R.; Chattopadhyay, N.; Panda, G. Anti-tumor activity of a new series of benzoxazepine derivatives in breast cancer. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 283. (c) Mishra, J. K.; Samanta, K.; Jain, M.; Dikshit, M.; Panda, G. Amino acid based enantiomerically pure 3-substituted benzofused heterocycles: a new class of antithrombotic agents. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 244. (d) Samanta, K.; Panda, G. Regioselective ring-opening of amino acid-derived chiral aziridines: an easy access to *cis*-2,5-disubstituted chiral piperazines. *Chem.—Asian J.* **2011**, 189−197.
(17) For selected recent approaches, see: (a) Mercer, G. J.; Sigman, M. S. Diastereoselective synthesis of piperazines by Manganese-mediated reductive cyclization. *Org. Lett.* **2003**, *5*, 1591. (b) Ferber, B.; Prestat, G.; Vogel, S.; Madec, D.; Poli, G. Synthesis of 3,5-disubstituted piperazinones via palladium(II)-catalyzed amination. *Synlett* **2006**, 2133−2135. (c) Viso, A.; Fernandez de la Pradilla, R.; Flores, A.; Garcia, A.; Tortosa, M.; Lopez-Rodriguez, M. L. Synthesis of highly substituted enantiopure piperazines and ketopiperazines from vicinal N-sulfinyl diamines. *J. Org. Chem.* **2006**, *71*, 1442 and references cited therein.