Bioorganic & Medicinal Chemistry Letters xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Asymmetric synthesis of 2-arylpiperazines

Satoshi Yokoshima [*,†], Kazutoshi Watanabe [*,‡], Fumiaki Uehara, Yoshihiro Usui [§], Hiroshi Tanaka

Research Division, Mitsubishi Tanabe Pharma Corporation, Kamoshida-cho, Aoba-ku, Yokohama 227-0033, Japan

ARTICLE INFO

Article history:
Received 22 September 2014
Revised 14 October 2014
Accepted 15 October 2014
Available online xxxx

Keywords:
Asymmetric synthesis
Heterocycles
Piperazines

ABSTRACT

An asymmetric synthesis of 2-arylpiperazines starting from phenacyl bromides, a variety of which are easily available, has been established. The synthesis features a CBS reduction of phenacyl bromide to provide optically enriched compounds, an S_N2 reaction of 1,2,3-oxathiazolidine 2-oxides with an azide anion with invert of configuration, and construction of the piperazine ring via reduction of piperazine-2,3-diones.

2-Arylpiperazines (Fig. 1) are fascinating moieties in the development of novel drugs because the aryl groups can be arranged on the molecules with restricted conformations, while the nitrogen atoms can be used to connect to other units.[1] A variety of synthetic methods for 2-arylpiperazines have been reported to date. While asymmetric preparations of 2-arylpiperazines, which include separation of diastereomers,[1c] resolution of racemic materials,[2,3] enantioselective addition of Grignard reagents to pyrazine *N*-oxides,[4] and diastereoselective reduction at the benzylic position,[5] have also been reported,[6] methods that can be used to synthesize a variety of derivatives are relatively limited.

During the optimization of lead compound in our GSK-3β inhibitor project,[7] we have been interested in introducing an optically active 2-phenylpiperazine moiety as the analog of promising compound possessing 2-phenylmorpholine substructure.[8] To supply optically active 2-arylpiperazines, we developed an asymmetric preparation method applicable to various derivatives.

Our first attempt was based on the reduction of diketopiperazine, which can be easily derived from amino acids. Condensation of (*S*)-phenylglycine methyl ester (**1**) with *N*-Boc-glycine yielded dipeptide **2** (Scheme 1). After cleaving the Boc group, the resulting amine was treated under basic conditions to provide diketopiperazine **3**. Subsequent reduction of **3** with lithium aluminum hydride

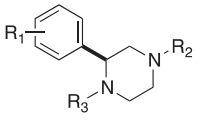
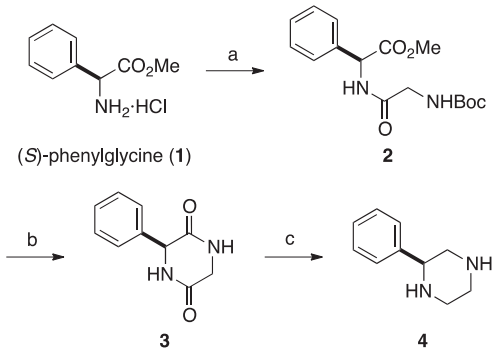


Figure 1. 2-Arylpiperazines.



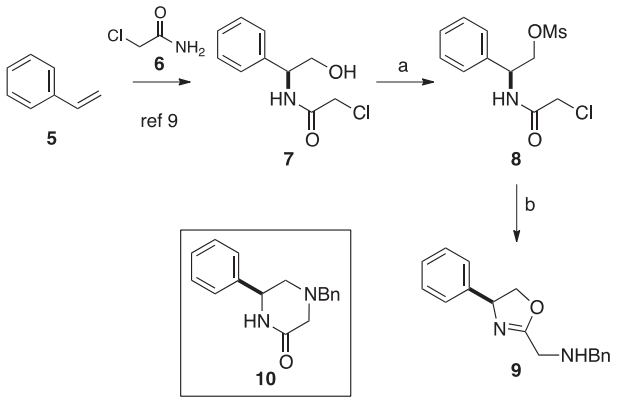
Scheme 1. Reagents and conditions: (a) *N*-Boc-glycine, EDCI, Et_3N, CH_2Cl_2, quant; (b) HCl in AcOEt; aq $NaHCO_3$, 36%; (c) $LiAlH_4$, THF, reflux, quant.

furnished phenylpiperazine **4**. Then the two nitrogen atoms were protected with Boc groups, and the optical purity was determined by HPLC, revealing that partial racemization occurred (73% ee). In addition to this result, the limited availability of phenylglycines derivatives made us turn our attention to development of other methods.

From the viewpoint of the availability, we decided to employ 1,2-aminoalcohols as substrates. Asymmetric aminohydroxylation

* Corresponding authors.
E-mail addresses: yokosima@ps.nagoya-u.ac.jp (S. Yokoshima), Watanabe.Kazutoshi@mb.mt-pharma.co.jp (K. Watanabe).
† Present address: Graduate School of Pharmaceutical Sciences, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, Aichi 464-8601, Japan.
‡ Present address: Research Division, Mitsubishi Tanabe Pharma Corporation, 2-2-50, Kawagishi, Toda-shi, Saitama 335-8505, Japan.
§ Present address: Synthetic Chemistry Department, Tanabe R&D Service Co., Ltd, 2-2-50, Kawagishi, Toda-shi, Saitama 335-8505, Japan.

http://dx.doi.org/10.1016/j.bmcl.2014.10.047
0960-894X/

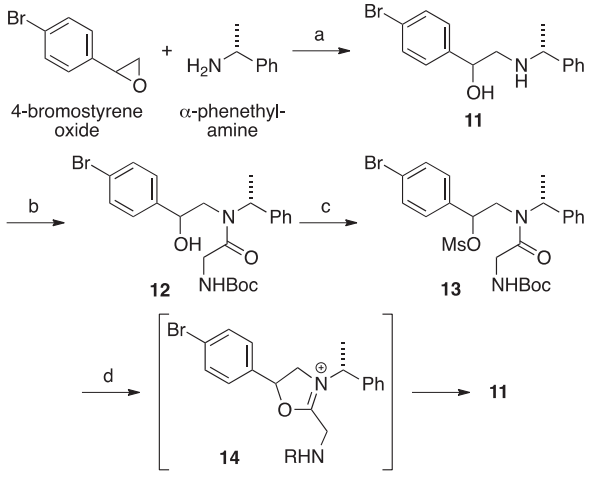


Scheme 2. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2; (b) $BnNH_2$, K_2CO_3, DMF, 11% (2 steps).

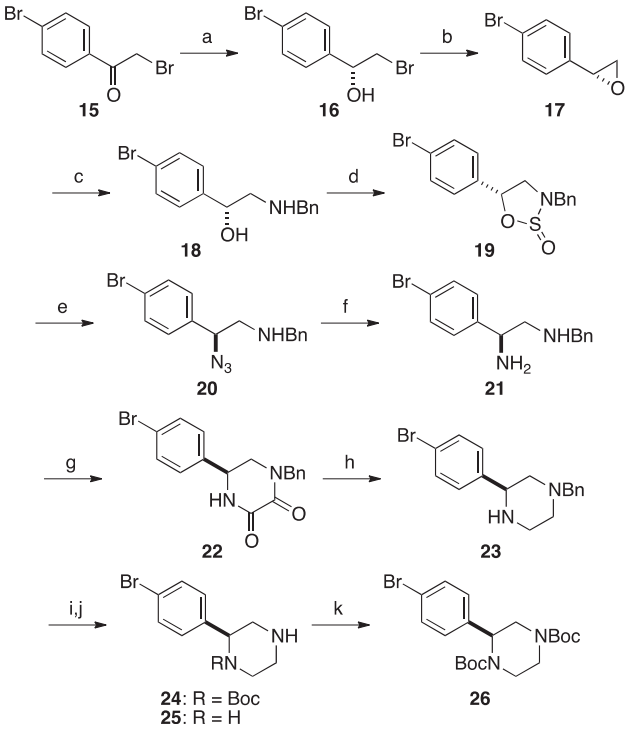
(AA) of styrenes may provide optically enriched 2-amino-2-phenylethanols. Fortunately, examples of AAs employing chloroacetamide (**6**) as a reagent have been reported.[9] Because resulting product **7** (Scheme 2) seems to possess suitable functional groups to synthesize 2-arylpiperazine, and we tried to convert **7**. After introducing a mesyl group onto the hydroxy group, resulting mesylate **8** was treated with benzylamine. However, desired piperazine **10** was not obtained. Instead, oxazoline **9** was isolated, indicating that the intramolecular S_N2 reaction of the mesylate with the carbonyl oxygen is faster than the intermolecular one with benzylamine.

We then attempted using a regioisomeric 1,2-aminoalcohol, 2-amino-1-arylethanol, which was prepared via epoxide cleavage of styrene oxide with amine (Scheme 3). Commercially available (±)-4-bromostyrene oxide was reacted with α-phenethylamine to furnish **11**, which was condensed with *N*-Boc-glycine to give **12**. After introducing a mesyl group onto the hydroxy group, the Boc group was cleaved with TFA. The resulting mixture was treated with aqueous sodium bicarbonate to liberate the amine for the intramolecular S_N2 reaction. However, the only detectable product was aminoalcohol **11** because the reaction likely proceeds via an undesired intramolecular reaction of the mesylate with the carbonyl oxygen and subsequent hydrolysis of resulting oxazolinium intermediate **14**.

As mentioned above, activation of the hydroxy group in 1,2-aminoalcohols, in which the amino group is substituted with an acyl



Scheme 3. Reagents and conditions: (a) 80 °C, 61%; (b) *N*-Boc-glycine, EDCI, CH_2Cl_2, 83%; (c) MsCl, Et_3N, CH_2Cl_2; (d) TFA, CH_2Cl_2; aq $NaHCO_3$.



Scheme 4. Reagents and conditions: (a) (*S*)-CBS catalyst, BH_3·THF, THF, −40 °C; (b) aq KOH, ether; (c) $BnNH_2$, 80 °C, 75% (3 steps); (d) $SOCl_2$, Et_3N, CH_2Cl_2, −78 °C, 88%; (e) NaN_3, DMF, 70 °C, 92%; (f) Ph_3P, THF–H_2O, 60 °C; (g) diethyl oxalate, 120 °C, 80% (2 steps); (h) BH_3·THF, THF, 96%; (i) Boc_2O, Et_3N, CH_2Cl_2, 80%; (j) $ClCO_2CHClCH_3$, $ClCH_2CH_2Cl$; MeOH, reflux; (k) Boc_2O, Et_3N, CH_2Cl_2; recrystallization from hexane, 65% (2 steps), 99.7% ee.

group resulted in undesired intramolecular reactions of the carbonyl oxygen. To avoid these undesired reactions, we attempted to employ a cyclic sulfamidite (1,2,3-oxathiazolidine 2-oxide)[10] as a substrate with the vision that activation of the hydroxy group and protection of the amino group would be realized simultaneously.

The synthesis began by preparing an optically active styrene oxide. CBS reduction[11,12] of 4-bromophenacyl bromide (**15**) gave bromohydrin **16** (Scheme 4). Treatment of **16** with aqueous potassium hydroxide afforded styrene oxide **17**, which was subsequently reacted with benzylamine to produce 2-amino-1-phenylethanol **18**. Treating **18** with thionyl chloride in the presence of triethylamine furnished 1,2,3-oxathiazolidine 2-oxide **19** as a mixture of diastereomers.[13] Upon heating **19** with sodium azide, the S_N2 reaction proceeded smoothly at the benzylic position with inversion of configuration to afford azide **20**, stereoselectively introducing the nitrogen atoms for the piperazine synthesis.

Next, we tried to form the piperazine ring. Reduction of azide **20** with triphenylphosphine, and subsequent condensation of resulting 1,2-diamine **21** with diethyl oxalate furnished lactam **22** as a highly crystalline solid.[14] Reducing the carbonyl groups with borane gave piperazine **23**. After protecting the secondary amine with a Boc group, the benzyl group was removed by treatment with ACE-Cl,[15] yielding a mixture of mono Boc-protected piperazine **24** and deprotected piperazine **25**. The mixture was treated

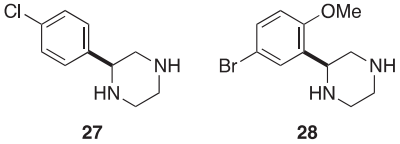


Figure 2. Other synthesized 2-arylpiperazines.

with Boc_2O to afford, after recrystallization from hexane, the product **26** as white crystals in 65% yield (2 steps) and 99.7% ee.

We have also used this procedure to synthesize other 2-arylpiperazines starting from the corresponding phenacyl bromides (Fig. 2).[16]

In conclusion, we have achieved the asymmetric syntheses of 2-arylpiperazines. CBS reduction of phenacyl bromides furnishes optically enriched substrates. The nitrogen atom at the benzylic position can be installed via an S_N2 reaction of an azide anion with 1,2,3-oxathiazolidine 2-oxide, giving optically active 1,2-diamines. The piperazine ring is constructed via the reduction of piperazine-2,3-diones. Currently, we are preparing other 2-arylpiperazines for potential applications in new drugs. The results will be reported in due course.

Acknowledgments

We gratefully thank Sanofi-Aventis R&D CNS Research Department (formerly Sanofi-Synthelabo R&D, Bagneux, France) for the fruitful collaboration.

References and notes

1. (a) Brockunier, L. L.; He, J.; Colwell, L. F.; Habulihaz, B.; He, H.; Leiting, B.; Lyons, K. A.; Marsilio, F.; Patel, R. A.; Teffera, Y.; Wu, J. K.; Thornberry, N. A.; Weber, A. E.; Parmee, E. R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4763; (b) Shao, Y.; Anilkumar, G. N.; Carroll, C. D.; Dong, G.; Hall, J. W.; Hobbs, D. W.; Jiang, Y.; Jenh, C.-H.; Kim, S. H.; Kozlowski, J. A.; McGuinness, B. F.; Rosenblum, S. B.; Schulman, I.; Shih, N.-Y.; Shu, Y.; Wong, M. K. C.; Yu, W.; Zawacki, L. G.; Zeng, Q. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1527; (c) Di Fabio, R.; Griffante, C.; Alvaro, G.; Pentassuglia, G.; Pizzi, D. A.; Donati, D.; Rossi, T.; Guercio, G.; Mattioli, M.; Cimarosti, Z.; Marchioro, C.; Provera, S.; Zonzini, L.; Montanari, D.; Melotto, S.; Gerrard, P. A.; Trist, D. G.; Ratti, E.; Corsi, M. *J. Med. Chem.* **2009**, *52*, 3238.
2. Guercio, G.; Bacchi, S.; Goodyear, M.; Carangio, A.; Tinazzi, F.; Curti, S. *Org. Proc. Res. Dev.* **2008**, *12*, 1188.
3. Binanzer, M.; Hsieh, S.-Y.; Bode, J. W. *J. Am. Chem. Soc.* **2011**, *133*, 19698.
4. Andersson, H.; Banchelin, T. S.-L.; Das, S.; Gustafsson, M.; Olsson, R.; Almqvist, F. *Org. Lett.* **2010**, *12*, 284.
5. Jida, M.; Laconde, G.; Soueidan, O.-M.; Lebegue, N.; Revelant, G.; Pelinski, L.; Agbossou-Niedercorn, F.; Deprez, B.; Deprez-Poulain, R. *Tetrahedron Lett.* **2012**, *53*, 5215.
6. Asymmetric syntheses of 2-alkylpiperazines have also been reported: (a) Crestey, F.; Witt, M.; Jaroszewski, J. W.; Franzyk, H. *J. Org. Chem.* **2009**, *74*, 5652; (b) O'Reilly, M. C.; Lindsley, C. W. *Org. Lett.* **2012**, *14*, 2910; (c) O'Reilly, M. C.; Lindsley, C. W. *Tetrahedron Lett.* **2012**, *53*, 1539.
7. (a) Fukunaga, K.; Uehara, F.; Aritomo, K.; Shoda, A.; Hiki, S.; Okuyama, M.; Usui, Y.; Watanabe, K.; Yamakoshi, K.; Kohara, T.; Hanano, T.; Tanaka, H.; Tsuchiya, S.; Sunada, S.; Saito, K.; Eguchi, J.; Yuki, S.; Asano, S.; Tanaka, S.; Mori, A.; Yamagami, K.; Baba, H.; Horikawa, T.; Fujimura, M. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6933; (b) Uehara, F.; Shoda, A.; Aritomo, K.; Fukunaga, K.; Watanabe, K.; Ando, R.; Shinoda, M.; Ueno, H.; Kubodera, H.; Sunada, S.; Saito, K.; Kaji, T.; Asano, S.; Eguchi, J.; Yuki, S.; Tanaka, S.; Yoneyama, Y.; Niwa, T. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6928.
8. Watanabe, K.; Uehara, F.; Hiki, S.; Yokoshima, S.; Usui, Y.; Okuyama, M.; Shoda, A.; Aritomo, K.; Kohara, T.; Fukunaga, K. WO 2004085408, 2004, March 26th, Mitsubishi Pharm Corp.
9. Demko, Z. P.; Bartsch, M.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 2221.
10. Gautun, H. S. H.; Carlsen, P. H. J. *Tetrahedron: Asymmetry* **1995**, *6*, 1667.
11. Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.
12. Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763.
13. Compound **19** has two stereogenic centers at the benzylic position and the sulfur atom.
14. (a) Beshore, D. C.; Dinsmore, C. J. *Tetrahedron Lett.* **2000**, *41*, 8735; (b) Yang, X.; Yudin, A. K. *Synlett* **2007**, 2912.
15. Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081.
16. The overall yield of **27** was 18% and the optical purity was confirmed to be 99% ee by HPLC after reaction with 2-chloro-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one. Compound **28** was obtained in 15% overall yield and 94% ee.