Tetrahedron Letters 50 (2009) 4703–4705

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A convenient synthesis of chiral amino acid derived 3,4-dihydro-2*H*-benzo[*b*][1,4]thiazines and antibiotic levofloxacin ☆

Maloy Kumar Parai, Gautam Panda *

Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow 226 001, UP, India

ARTICLE INFO

Article history:
Received 21 April 2009
Revised 15 May 2009
Accepted 27 May 2009
Available online 30 May 2009

ABSTRACT

A series of 3,4-dihydro-*2H*-benzo[*b*][1,4]thiazine derivatives **8a–g** were synthesized via- a copper-catalyzed intramolecular *N*-aryl amination reaction on substituted 2-(2-bromophenylthio)-ethanamines which were synthesized by the nucleophilic substitution reaction of 2-bromobenzenethiol with Boc-protected amino alcohol derivatives. This strategy provides a short and an efficient entry to (*S*)-3-methyl-1,4-benzoxazine **12**, an advanced synthetic intermediate for the synthesis of levofloxacin.

Benzothiazine derivatives represent one of the most important classes of organic molecules. Among several 1,2-, 1,4-, and 1,3-benzothiazine rings, 1,4-benzothiazines (1,4-BTs), in particular, are of significant interest and have been extensively studied because of their profound biological activities[1a–g] including *anti*-inflammatory, *anti*-hypertensive, *anti*-cancer, *anti*-fungal, *anti*-tumor, immunostimulating, *anti*-aldoso-reductase, *anti*-rheumatic, *anti*-allergic, vasorelaxant, *anti*-arrhythmic, neuroprotective, cytotoxic, K_{ATP}-channel openers, and *anti*-HIV activities. The diverse activities illustrate that 1,4-BT is a template potentially useful in medicinal chemistry research and therapeutic applications. Examples include *anti*-hypertensive drug[2] semotiadil (**1**), calcium antagonists (**2**),[3] *anti*-fungal agent (**3**)[4] (Fig. 1).

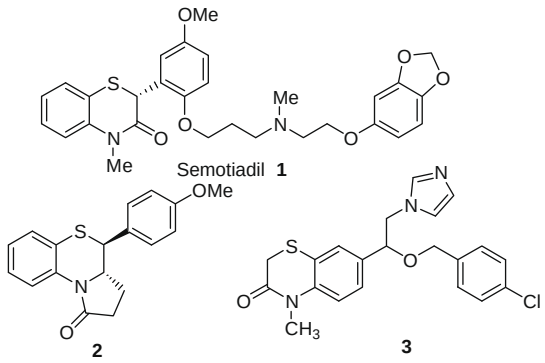


Figure 1. Structures of some biologically important 1,4-BTs.

The importance and utility of this family of compounds have led to the development of numerous synthetic routes.[5,6] Several approaches have been employed toward synthesis of benzothiazine derivatives, for example (i) by condensation of 2-aminobenzenethiol with α,β-unsaturated acids or esters,[7] electron-deficient alkynes,[8] (ii) by treatment of N-unsubstituted and *N,N*-dialkyldithiodianilines with an enolizable dicarbonyls or esters,[9] (iii) by reaction of 2-aminobenzenethiol with α-haloketones, α-haloacetic acids, acid chlorides, or esters,[10a,10b] and (iv) by condensation of benzil or *p*-methoxy benzil with an aromatic amine.[11] Ring enlargement of 2-chloromethylbenzothiazole[11] and ring contraction of benzothiazepinones[12] have also been reported to produce benzothiazinones. To the best of our knowledge, synthesis of amino acid based 1,4-benzothiazine derivatives by copper-catalyzed aryl amination reaction has not been reported so far.

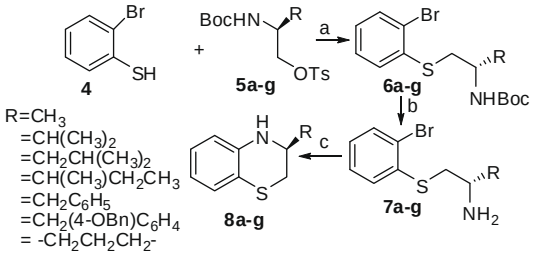
In our ongoing program we are engaged in the synthesis of *S*-amino acid based benzo-fused heterocyclic structures bearing nitrogen, oxygen, and sulfur atoms.[13] Interest in the use of easily accessible and versatile proteinogenic amino acids as a chiral pool for the synthesis of enantiomerically pure heterocycles has been growing because of their response to the enantiospecificity shown by most biological systems and the increased demand to market chiral drugs as single enantiomers. We recognized that the copper-catalyzed aryl amination approach for the formation of carbon-heteroatom bond offers a better and more convenient route to the synthesis of 3-substituted chiral 3,4-dihydro-2*H*-benzo[*b*][1,4]thiazines in optically pure form.

Toward this objective, 4-methylbenzenesulfonate derivatives **5a–g** were prepared from *N*-Boc amino alcohols which were obtained from *N*-Boc-amino acids. Intermolecular nucleophilic substitution reaction between commercially available 2-bromobenzenethiol **4** and **5a–g** under NaH/THF condition gave **6a–g** in 73–78% yields. Deprotection of Boc functionality in **6a–g** furnished **7a–g** which under copper iodide and anhy. K_2CO_3 catalyzed N-arylation reaction in *N,N*-dimethylacetamide afforded

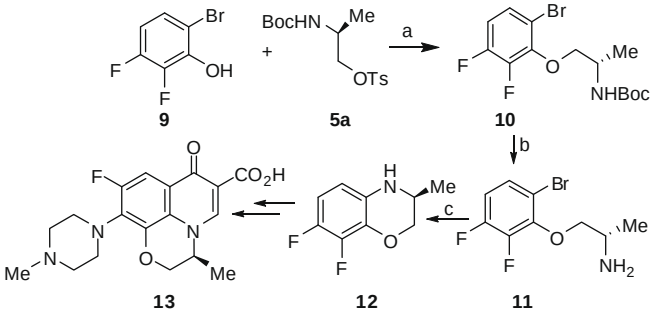
☆ CDRI communication number 7744.

* Corresponding author. Tel.: +91 522 2612411 18x4385, 4469, 4474; fax: +91 522 2623405.
E-mail address: gautam.panda@gmail.com (G. Panda).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.05.104

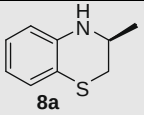
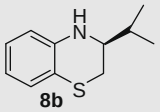
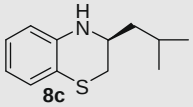
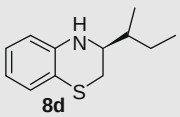
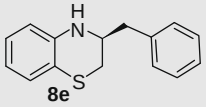
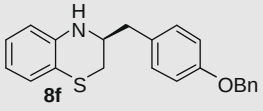
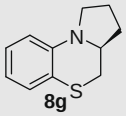


Scheme 1. Reagents and conditions: (a) NaH, THF, rt, 2–3 h; (b) 10% TFA in CH_2Cl_2, rt, 4–5 h; (c) 0.20 equiv CuI, K_2CO_3, DMA, 100–110 °C, 48 h.



Scheme 2. Reagents and conditions; (a) NaH, DMF, 100 °C, 5–6 h; (b) 10% TFA in CH_2Cl_2, rt, 4–5 h; (c) 0.20 equiv CuI, K_2CO_3, DMA, 100–110 °C, 36 h.

Table 1

Entry	Product	% ee	Yield (%)
1	 **8a**	>99	66
2	 **8b**	>99	64
3	 **8c**	>99	68
4	 **8d**	>99	63
5	 **8e**	>99	65
6	 **8f**	>99	72
7	 **8g**	>99	61

enantiomerically pure 3,4-dihydro-2*H*-benzo[*b*][1,4]thiazines **8a–g** (Scheme 1).

The scope of this methodology has been further extended toward the formal asymmetric synthesis of the potent antibiotic drug levofloxacin.[14] The major challenge associated with developing an asymmetric entry to levofloxacin lies in identifying efficient routes to the key chiral benzoxazine core **12**, and in this regard, several approaches have been reported.[15] We have achieved the synthesis of **12** from the reaction between L-alanine-derived 4-methylbenzenesulfonate derivative **5a** and 6-bromo-2,3-difluorophenol[16] **9** through the formation of **10** and **11** using the methodology described in this Letter (Scheme 2). This intermediate can easily be converted to levofloxacin by reported methods.[15a–d]

In conclusion, we have demonstrated an efficient synthesis of a new series of enantiomerically pure 3,4-dihydro-2*H*-benzo[*b*][1,4]thiazines **8a–g** and a formal synthesis of antibiotic levofloxacin **13** from naturally abundant chiral amino acids via copper-catalyzed intramolecular aryl amination reaction. Ease of the reaction sequence gave an access to enantiomerically pure chiral benzothiazines and benzoxazines, which could have interesting biological properties (Table 1).

Acknowledgments

This research project was partly supported by Department of Science and Technology (SR/S1/OC-23/2005) and ICMR, New Delhi, India. Maloy thanks CSIR for providing fellowships.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.104.

References and notes

1. 1,4-Benzothiazines (a) as *anti*-inflammatory agents: (i) Lombardino, J. G.; Wiseman, E. H. *Med. Res. Rev.* **1982**, *2*, 127; (ii) Turk, C. F. *J. Med. Chem.* **1973**, *16*, 776. (b) as *anti*-hypertensive agents: (i) Prasad, R. N. *J. Med. Chem.* **1969**, *12*, 290; (ii) Cecchetti, V.; Fravolini, A.; Schiaffella, F.; DeRegis, M.; Orzalesi, G.; Volpato, I. *Farmaco. Ed. Sci.* **1983**, *38*, 35. (c) As *anti*-cancer agents: (i) Gupta, R. R.; Dev, P. K.; Sharma, M. L.; Rajoria, C. M.; Gupta, A.; Nyati, M. *Anticancer Drugs* **1993**, *4*, 589; (ii) Todorov, D. K.; Ilarionova, M. V.; Gupta, R. R.; Molnar, J.; Motohashi, N. *Heterocycl. Commun.* **1995**, *1*, 153. (d) as *anti*-fungal agent: (i) Schiaffella, F.; Macchiarulo, A.; Milanese, L.; Vecchiarell, A.; Fringuell. R. *Bioorg. Med. Chem.* **2006**, *14*, 5196; (ii) Fringuelli , R .; Schiaffella, F.; Bistoni, F.; Pitzurra, L.; Vecchiarelli, A. *Bioorg. Med. Chem.* **1998**, *6*, 103. (e) as *anti*-tumour agent: (i) Coughlin, S. A.; Danz, D. W.; Robinson, R. G.; Klingbeil, K. M.; Wentland, M. P.; Corbett, T. H.; Waud, W. R.; Zwelling, L. A.; Altsschuler, E. *Biochem. Pharmacol.* **1995**, *50*, 111. (ii) Hasegawa, K.; Ito, S.; Inoue, S.; Wakamatsu, K.; Ozeki, H.; Ishiguro, I. *Biochem. Pharmacol.* **1997**, *53*, 1435. (iii) Inoue, S.; Hasegawa, K.; Wakamatsu, K.; Ito, S. *Melanoma Res.* **1998**, *8*, 105. (f) as K_{ATP}-Channel Openers (i) Cecchetti, V.; Calderone, V.; Tabarrini, O.; Sabatini, S.; Filipponi, E.; Testai, L.; Spogli, R.; Martinotti, E.; Fravolini, A. *J. Med. Chem.* **2003**, *46*, 3670. (g) as *anti*-HIV agent: (i) Grandolini. G;, Perioli.L;, Ambarogi. V. *Eur. J. Med. Chem.* **1999**, *34*, 701; h) as CETP inhibitors: (i) Kuo, G.; Wang, A.; Rano, T.; Prouty, C.; Demarest, K. T.; Pelton, P. US patent, **2007**, WO/134149.
2. Morino, T.; Yamamoto, T. *J. Chem. Eng. Jpn.* **1997**, *30*, 1005.
3. Corelli, F.; Manetti, F.; Tafi, A.; Campiani, G.; Nacci, V.; Botta, M. *J. Med. Chem.* **1997**, *40*, 125.
4. Macchiarulo, A.; Costantino, G.; Fringuelli, D.; Vecchiarelli, A.; chiaffella, F.; Fringuelli, R. *Bioorg. Med. Chem.* **2002**, *10*, 3415.
5. (a) Babudri, F.; DiNunno, L.; Florio, S. *Tetrahedron* **1982**, *38*, 3059; (b) Babudri, F.; DiNunno, L.; Florio, S. *Synthesis* **1983**, 230; (c) Huang, X.; Chan, C.-C. *Synthesis* **1984**, 851; (d) Marfat, A.; Carta, M. P. *Synthesis* **1987**, 515; (e) Trapani, G.; Latrofa, A.; Reho, A.; Liso, G. *J. Heterocycl. Chem.* **1989**, *26*, 721; (f) Singh, H.; Singh, D. J.; Kumar, S. *Indian J. Chem. Sect. B* **1992**, *31B*, 217; (g) Rai, D.; Gupta, V.; Gupta, R. R. *Heterocycl. Commun.* **1996**, *2*, 273.
6. (a) Lanoquist, J. K. Six membered Ring Systems. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Sammes, P. G., Eds.; Heterocyclic Compounds; Pergamon Press: Oxford, 1979; Vol. 4, p 1092; (b) Brown, C.; Davidson, R. M. *Adv. Heterocycl. Chem.* **1985**, *38*, 135; (c)*Phenothiazines and 1,4-Benzothiazines: Chemical and Biomedical Aspects*; Gupta, R. R., Ed.Bioactive Molecules; Elsevier: Amsterdam, Neth, 1988; Vol. 4, (d) Sainsbury, M. 1,4-Thiazines, 1,4-Benzothiazines, Phenothiazines and Related Compounds, 2nd

ed.. In *Rodd's Chemistry of Carbon Compounds*; Elsevier: Amsterdam, Neth, 1998; Vol. 4, pp 575–608 (Part G (partial)/Part H).
7. Kirchner, F. K.; Alexander, E. J. *J. Am. Chem. Soc.* **1959**, *81*, 1721.
8. Balasubramaniyan, V.; Balasubramaniyan, P.; Shaikh, A. S. *Tetrahedron* **1986**, *42*, 2731.
9. Florio, S.; Capriati, V.; Colli, G. *Tetrahedron* **1997**, *53*, 5839.
10. (a) Unger, O. *Chem. Ber.* **1897**, *30*, 607; (b) Unger, O.; Graff, G. *Chem. Ber.* **1897**, *30*, 2389.
11. Charrier, J. D.; Landreau, C.; Deniaud, D.; Reliquet, F.; Reliquet, A.; Meslin, J. C. *Tetrahedron* **2001**, *57*, 4195.
12. Erker, T.; Bartsch, H. *Liebigs Ann. Chem.* **1992**, 403.
13. (a) Mishra, J. K.; Panda, G. *J. Comb. Chem.* **2007**, *9*, 321; (b) Srivastava, A. K.; Panda, G. *Chem. Eur. J.* **2008**, *14*, 4675–4688; (c) Mishra, J. K.; Panda, G. *Synthesis* **2005**, 1881–1887; (d) Mishra, J. K.; Garg, P.; Dohare, P.; Kumar, A.; Siddiqi, M. I.; Ray, M.; Panda, G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1326–1331.
14. Ellsworth, E. L.; Tran, T. P.; Showalter, D. H.; Sanchez, J. P.; Watson, B. M.; Stier, M. A.; Domagala, J. M.; Gracheck, S. J.; Joannides, E. T.; Shapiro, M. A.; Dunham, S. A.; Hanna, D. L.; Huband, M. D.; Gage, J. W.; Bronstein, J. C.; Liu, J. Y.; Nguyen, D. Q.; Singh, R. *J. Med. Chem.* **2006**, *49*, 6435. and references cited therein.
15. (a) Hayakawa, I.; Atarashi, S.; Imamura, M.; Yokohama, S.; Higashihashi, N.; Sakano K.; Ohshima, M. US patent, 1986, 5, 53, 407.; (b) Atarashi, S.; Yokohama, S.; Yamazaki, K.; Sakano, K.; Imamura, M.; Hayakawa, I. *Chem. Pharm. Bull.* **1987**, *35*, 1896; (c) Sakano, K.; Yokohoma, S.; Hayakawa, I.; Atarashi, S.; Kadoya, S. *Agric. Biol. Chem.* **1987**, *51*, 1265; (d) Mitscher, L. A.; Sharma, P. N.; Chu, D. T. W.; Shen, L. L.; Pernet, A. G. *J. Med. Chem.* **1987**, *30*, 2283; (e) Atarashi, S.; Tsurumi, H.; Fujiwara, T.; Hayakawa, I. *J. Heterocycl. Chem.* **1991**, *28*, 329; (f) Kang, S. B.; Ahn, E. J.; Kim, Y.; Kim, Y. H. *Tetrahedron Lett.* **1996**, *37*, 9317; (g) Satoh, K.; Inenaga, M.; Kanai, K. *Tetrahedron: Asymmetry* **1998**, *9*, 2657; (h) Adrio, J.; Carretero, J. C.; Ruano, J. L. G.; Pallarés, A.; Vicioso, M. *Heterocycles* **1999**, *51*, 1563.
16. Bower, J. F.; Szeto, P.; Gallagher, T. *Org. Lett.* **2007**, *9*, 3283.