Available online at www.sciencedirect.com
ScienceDirect
Chinese Chemical Letters 22 (2011) 801–803
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

# First total synthesis of two new heterocyclic compounds: Bretschneiderazines A and B

Qing Chao Liu [a,*], Tian Tian Guo [b], Zheng Fan [a], Dong Li [a], Wen Hong Li [a]

[a] *Department of Pharmaceutical Engineering, Northwest University, Xi'an 710069, China*
[b] *Department of Medical Science, Xi'an Creation College, Yanan University, Xi'an 710100, China*

Received 8 October 2010
Available online 17 April 2011

**Abstract**

Facile synthesis of the two new natural heterocyclic compounds bretschneiderazines A (**2**) and B (**3**), isolated from an extract of the stems of *Bretschneidera sinensis*, is reported. We employed the cyclization reaction of benzamide by directed lithiation and sequential treatment with sulfur and phosgene as key steps. All new compounds have been fully characterized by means of IR, $^{1}$H NMR, $^{13}$C NMR, and HRMS.


*Keywords:* Heterocyclic compounds; Bretschneiderazines; Directed lithiation; Synthesis

Natural compounds with the benzo[e][1,3]thiazine-2-thioxo-4-one ring system (**1**) exist rarely, and only some synthesized compounds with such structure were reported [1–3]. Bretschneiderazines A (**2**) and B (**3**) (Fig. 1), two new heterocyclic compounds with the benzo[e][1,3]thiazine-2-thioxo-4-one ring system, were first isolated from an extract of the stems of *Bretschneidera sinensis* [4]. *B. sinensis*, a well-known Chinese folk medicine, is distributed only on the southern bank of the Yangtse, China. Its bark has long been used to treat arthralgia and myalgia [5]. Besides, bretschneiderazines A (**2**) showed moderate activity against the NCI-H446 cell line *in vitro* [4].

Attracted by the particular structure and potent biological properties of bretschneiderazines A (**2**) and B (**3**), We report here the first total synthesis of bretschneiderazines A and B by a facile approach for thorough pharmacological research and further SAR investigation.

The synthetic route toward bretschneiderazines A (**2**) and B (**3**) is depicted in Scheme 1. Firstly, isovanillin **4** was converted to the intermediate **5** using *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of imidazole in anhydrous DMF with the yield of 95% [6]. Then, aldehyde **5** was oxidized by $H_2O_2$ and $NaClO_2$ to the corresponding carboxylic acid **6** in 63% yield [7], which was subjected to chlorination with thionyl chloride ($SOCl_2$) in dry $CH_2Cl_2$ affording acyl chloride **7** in 89% yield. Compound **8** was obtained from **7** using $CH_3NH_2$ in EtOAc with the yield of 86% [8]. Benzamide **8** was treated by directed lithiation with *n*-butyllithium in THF, after which sulfur powder and thiophosgene was added, affording the key intermediates **9** and **10** [3]. Because of the steric hindrance of TBS protecting group, the formation of heterocyclic ring mainly occurred at C-6 of benzamide **8**, which was supported by

* Corresponding author.
*E-mail address:* Liuqc21@nwu.edu.cn (Q.C. Liu).

1001-8417/$ – see front matter 
doi:10.1016/j.cclet.2010.11.036

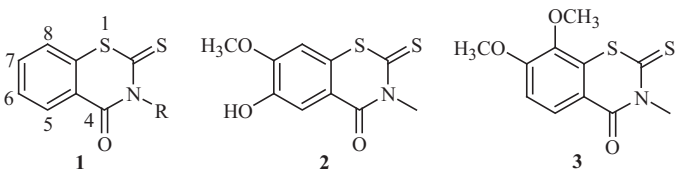
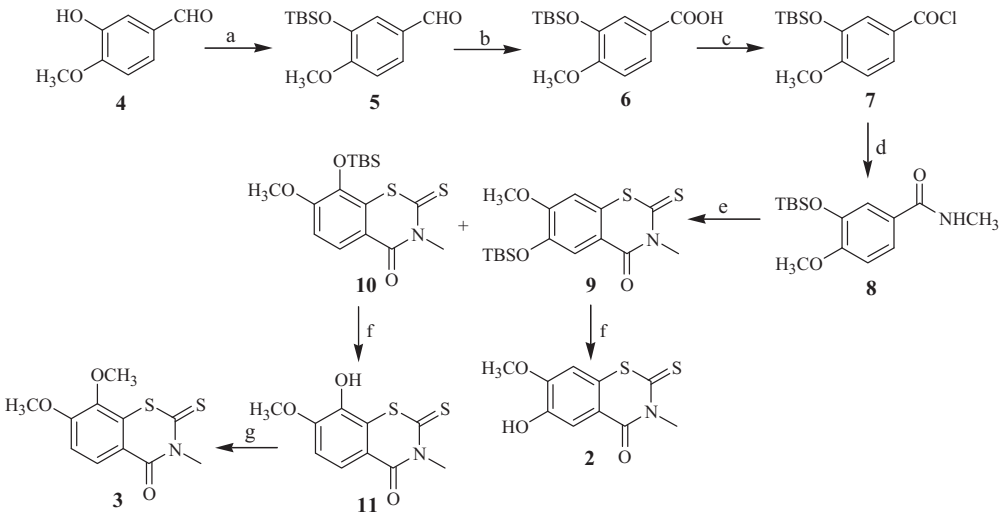


Fig. 1. The structures of bretschneiderazines A (**2**) and B (**3**).



Scheme 1. Reagents and conditions: (a) TBSCl, imidazole, DMF, 95%; (b) $NaH_2PO_4$, $H_2O_2$ (30%), $NaClO_2$, MeCN, $H_2O$, 10 °C, 63%; (c) $SOCl_2$, $CH_2Cl_2$, 89%; (d) $MeNH_2$, $Et_3N$, EtOAc, 86%; (e) *n*-BuLi, THF, −78 °C to 0 °C; S, 50 °C; $Cl_2C$ = S, 0 °C, 53% for **9**, 7% for **10**; (f) TBAF, THF, 89% for **2**, 81% for **11**; (g) $K_2CO_3$, MeI, $CH_3COCH_3$, 51%.

the ratio of **9** and **10** (53%:7%). Finally removal of TBS groups furnished bretschneiderazines A (**2**) and **11**. Compound **11** was subsequently methylated with MeI and $K_2CO_3$ to obtain bretschneiderazines B (**3**), whose analytical data are identical in all respects to those reported in the literature [5,9].

In conclusion, we have developed a practical, highly efficient method for the preparation of bretschneiderazines A (**2**) and B (**3**) employing the cyclization reaction of benzamide by directed lithiation and sequential treatment with sulfur and phosgene as key steps. Further study on preparation and biological evaluation of derivatives is in progress and will be reported in due course.

## Acknowledgment

This work was financially supported by the Scientific Research Foundation of Northwest University (No. PR10035).

## References

[1] A.A. Magid, L. Voutquenne, D. Harakat, et al. Pharmazie 22 (1967) 611.
[2] M. Ukiya, T. Akihisa, Heterocycles 78 (2009) 2559.
[3] S.W. Wright, J. Heterocycl. Chem. 38 (2001) 723.
[4] C.M. Liu, B. Li, Y.H. Shen, et al. J. Nat. Prod. 73 (2010) 1582.
[5] W.C. Wang, Flora of China, vol. 34, Science Press, Beijing, 1990, p. 8.
[6] R.P. Tanpure, A.R. Harkrider, T.E. Hamel, et al. Bioorg. Med. Chem. 17 (2009) 6993.
[7] T. Harayama, T. Sato, Y. Nakano, et al. Heterocycles 59 (2003) 293.
[8] K. Bailey, E.W. Tan, Bioorg. Med. Chem. Lett. 13 (2005) 5740.

[9] Selected spectra data. Compound **9**, IR (KBr) $\nu_{max}$ 2930, 2895, 1735, 1374 $cm^{-1}$; HRESIMS: *m/z* calcd. for $C_{16}H_{24}NO_3S_2Si$ $[M+H]^+$, 370.0961; found, 370.0989; $^1H$ NMR (500 MHz, acetone-$d_6$): $\delta$ 7.70 (s, 1H), 6.71 (s, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H); $^{13}C$ NMR (125 MHz, acetone-$d_6$): $\delta$ 191.0, 160.2, 151.3, 145.0, 129.1, 110.2, 113.8, 106.3, 54.3, 33.8, 25.7, 18.5, −4.7. Compound **10**, IR (KBr) $\nu_{max}$ 2927, 2897, 1741, 1374 $cm^{-1}$; HRESIMS: *m/z* calcd. for $C_{16}H_{24}NO_3S_2Si$ $[M+H]^+$, 370.0961; found, 370.0976; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 8.09 (d, 1H, $J$ = 8.1 Hz), 7.02 (d, 1H, $J$ = 8.0 Hz), 3.90 (s, 3H), 3.88 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 193.1, 160.1, 155.9, 135.6, 129.1, 128.0, 115.2, 111.2, 58.9, 34.3, 25.0, 18.5, −4.6. Compound **11**, IR (KBr) $\nu_{max}$ 3378, 2935, 2855, 1737, 1660, 1379 $cm^{-1}$; HRESIMS: *m/z* calcd. for $C_{10}H_8NO_3S_2$ $[M-H]^-$, 253.9942; found, 253.9927; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 8.11 (d, 1H, $J$ = 8.0 Hz), 7.02 (d, 1H, $J$ = 8.0 Hz), 3.95 (s, 3H), 3.91 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 193.2, 160.1, 155.8, 138.9, 131.2, 128.5, 115.5, 111.3, 60.4, 34.8. Compound **2**, IR (KBr) $\nu_{max}$ 3419, 2930, 2851, 1737, 1656, 1384 $cm^{-1}$; HRESIMS: *m/z* calcd. for $C_{10}H_8NO_3S_2$ $[M-H]^-$, 253.9942; found, 253.9951; $^1H$ NMR (500 MHz, acetone-$d_6$): $\delta$ 7.73 (s, 1H), 6.75 (s, 1H), 3.99 (s, 3H), 3.86 (s, 3H); $^{13}C$ NMR (125 MHz, acetone-$d_6$): $\delta$ 191.3, 159.0, 152.2, 129.1, 114,2, 106.7, 55.0, 33.8. Compound **3**, IR (KBr) $\nu_{max}$ 2945, 2917, 1737, 1638, 1601, 1532 $cm^{-1}$; HRESIMS: *m/z* calcd. for $C_{11}H_{12}NO_3S_2$ $[M+H]^+$, 270.0253; found, 270.0239; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 8.09 (d, 1H, $J$ = 8.1 Hz), 6.99 (d, 1H, $J$ = 8.1 Hz), 3.96 (s, 3H), 3.92 (s, 3H), 3.91 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 193.3, 160.3, 155.9, 139.3, 131.2, 128.6, 115.8, 111.6, 60.7, 56.3, 34.7.