Tetrahedron Letters 52 (2011) 4713–4715

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of (±)-6-oxa-3-azabicyclo[3.1.1]heptan-2-thione: a potential synthon for the preparation of novel heteroaryl-annulated bicyclic morpholines

Donn G. Wishka, Daniel P. Walker *

Pfizer Worldwide Research & Development, Eastern Point Rd., Groton, CT 06340, USA

ARTICLE INFO

Article history:
Received 7 June 2011
Revised 1 July 2011
Accepted 5 July 2011
Available online 19 July 2011

Keywords:
Morpholine
Stereoselective synthesis
Heterocycles
Bicyclic compounds
Alkylation

ABSTRACT

The novel bridged bicyclic morpholinethione (±)-6-oxa-3-azabicyclo[3.1.1]heptan-2-thione (**9**) has been prepared in six steps. This conformationally restricted morpholinethione was prepared stereoselectively using straightforward chemistry and inexpensive starting materials. The key oxetane ring was formed via an intramolecular alkylation reaction.

Introduction

Morpholines are utilized extensively in drug discovery research. Numerous drugs possessing a directly linked morpholine have been approved by the FDA and other regulatory agencies, a snapshot of recently marketed drugs is shown in Figure 1, including linezolid (Zyvox®),[1] gifitinib (Iressa®),[2] and reboxetine (Vestra®).[3]

Analogs incorporating a fused morpholine ring have also shown potential for treating various human diseases; some recent preclinical and clinical candidates are shown in Figure 2, including BLI-489,[4] finafloxacin,[5] and AGN 193080.[6]

In addition, a number of reports detailing analogs incorporating a bridged bicyclic morpholine (e.g., **1**, **2**, and **3**, Fig. 3) have been reported in the medicinal chemistry literature.[7] In some instances, the bicyclic analog showed enhanced biological activity compared to the corresponding morpholine analog.[7c–e]

Given the promising biological profiles of analogs possessing a fused morpholine ring and the emerging potential of bridged bicyclic morpholine analogs, we became interested in preparing bridged bicyclic morpholines that were fused to an additional heteroaryl ring (e.g., **4**, **5**, and **6**, Fig. 4). The logical precursors to structures **4**, **5**, and **6** would be thiolactams **7**, **8**, and **9**, respectively. In general, thioamides and thiolactams are useful synthons for the preparation of a variety of fused heterocycles;[8] many of these heteroaryl-annulated analogs have shown interesting biological properties.[9] For instance, thiolactam **10** (Fig. 3) is the precursor to the imidazo[2,1-*c*][1,4]oxazine skeleton contained in BLI-489.[4a] In a prior study, we detailed the stereoselective synthesis of thiolactams **7** and **8**, both of which were derived from an appropriately substituted furan (Fig. 4).[10] Despite the structural similarities between thiolactams **7** and **9**, a new approach to the construction of thiolactam **9** was necessitated due to the incompatibility of the previous synthetic strategies with the 6-oxa-3-azabicyclo[3.1.1.]heptane framework contained in **9**. We detail below a stereoselective synthesis of the novel bridged bicyclic thiolactam **9.**

Results and discussion

Our synthesis of (±)-6-oxa-3-azabicyclo[3.1.1]heptan-2-thione (**9**) commenced from (±)-epichlorohydrin, an inexpensive, readily available starting material (Scheme 1). Using a modification of the Pharmacia & Upjohn procedure,[11] reaction of (2,4-dimethoxyphenyl)methanimine, generated in situ from 2,4-dimethoxybenzaldehyde and concentrated aqueous ammonia, with (±)-epichlorohydrin generated imine **11**. Sodium borohydride reduction of imine **11** gave rise (90%) to aminoalcohol **12**. While benzaldehyde and simple monosubstituted benzaldehydes have been used as starting materials in the above reaction, the choice of using 2,4-dimethoxybenzaldehyde as a starting material was to help facilitate its removal late in the synthesis (vide infra). Subjection of aminoalcohol **12** to chloroacetyl chloride under Schotten-Baumann conditions initially provided an α-chloroamide, which upon exposure to concentrated aqueous sodium hydroxide effected ring closure, furnishing a 79% yield of

* Corresponding author. Tel.: +1 860 715 6445; fax: +1 860 686 0013.
E-mail addresses: quassinoid@earthlink.net, daniel.p.walker.pfizer@gmail.com (D.P. Walker).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.07.017

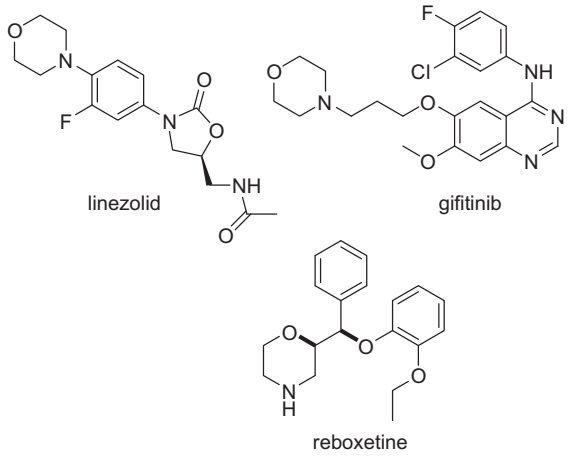


Figure 1. Drugs possessing a directly linked morpholine ring.

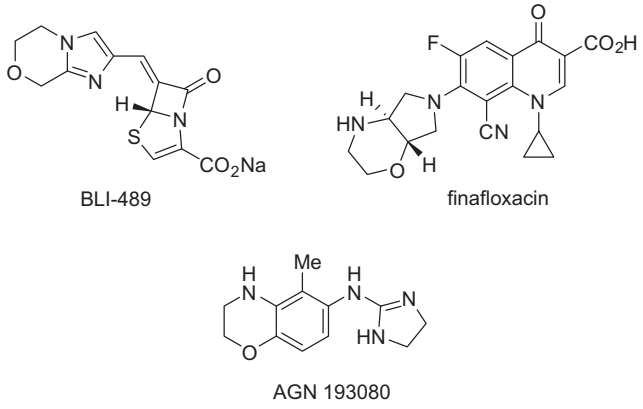


Figure 2. Clinical (BLI-489 and finafloxacin) and preclinical (AGN 193080) candidates possessing a fused morpholine ring.

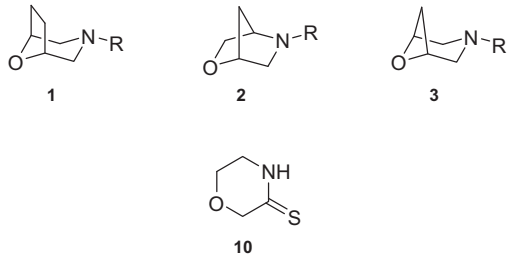


Figure 3. Row 1: Bicyclic morpholine templates utilized in medicinal chemistry research programs and structure of compound **10**.

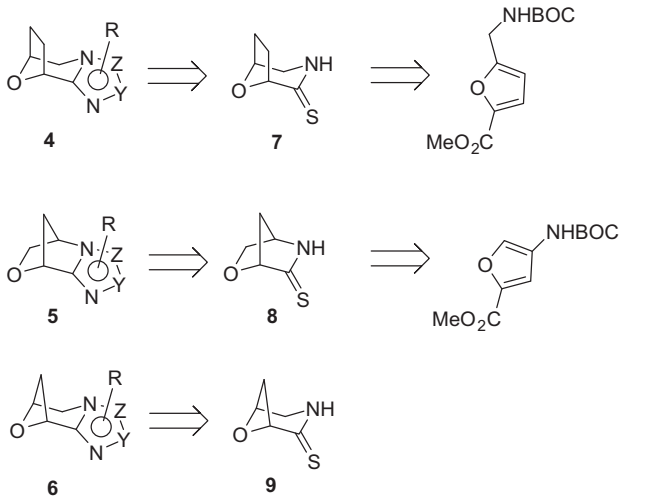
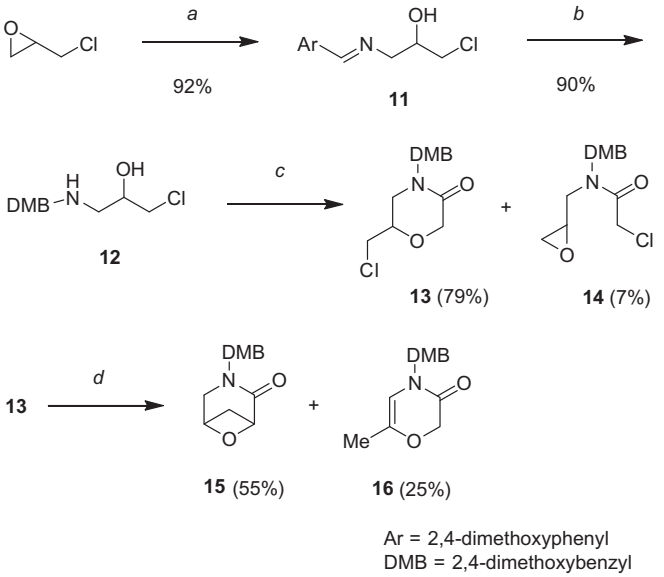


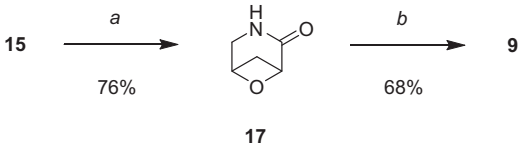
Figure 4. Retrosynthesis of novel heteroaryl-annulated bicyclic morpholine analogs **4**, **5**, and **6**; Y = CH, CR or N; Z = CH, CR, C(O) or N; R = H, alkyl, acyl, or aryl (see: Refs. 8,9). Prior synthetic targets **7** and **8**, and new synthetic target **9**.



Scheme 1. Reagents and conditions: (a) 2,4-dimethoxybenzaldehyde, 28% aq. ammonia, 0 °C to rt, 48 h; (b) $NaBH_4$, MeOH, 0 °C, 1 h; (c) $ClCH_2C(O)Cl$, CH_2Cl_2-aq NaOH, 0 °C, 1 h; 40% aq NaOH, rt, 4 h; (d) KHMDS (2.0 equiv), THF, 0 °C, 1.5 h.

morpholinone **13**. It is interesting to note that under these conditions less than 10% of epoxide **14** was formed. Similar results have been observed by others on a related system.[12] Bridged bicyclic morpholinone **15** was realized in 55% yield via an intramolecular cyclization reaction. Thus, treatment of a cold (0 °C) solution of morpholinone **13** with potassium bis(trimethylsilylamide) (KHMDS) generated the corresponding lactam enolate that underwent subsequent intramolecular alkylation by the primary alkyl chloride. The use of KHMDS to effect the intramolecular cyclization proved to be crucial as other strong bases, such as LDA, led to lower yields or no reaction.[13] The major side product formed in this reaction was oxazinone **16**. The formation of **16** presumably arises via an initial elimination reaction, followed by subsequent acid catalyzed migration of the exocyclic olefin to the thermodynamically more favorable endocyclic position.[14] The ^1H NMR spectrum (500 MHz) of the crude reaction mixture indicated that two compounds were present, morpholinone **15** and oxazinone **16**. Thus, the acid catalyzed migration likely occurred during workup where the initially formed exocyclic olefin was exposed to aqueous ammonium chloride. The formation of oxazinone **16** could be controlled to some extent based on the choice of solvent. For instance, a less polar solvent system, toluene-THF (1:1), led to a 60% yield of **16**.

Completion of the synthesis of thiolactam **9** necessitated removal of the dimethoxybenzyl (DMB) moiety and conversion of the lactam into a thiolactam. As it is known that many *N*-benzyl amides are inert toward hydrogenolysis, typically requiring strongly reducing conditions to facilitate their removal,[15] we chose



Scheme 2. Reagents and conditions: (a) TFA, Et_3SiH (3.0 equiv), 65 °C, 2.5 h; (b) Lawesson's reagent, tetrahydrofuran, rt, 24 h.

2,4-dimethoxybenzaldehyde as a starting material (vide supra) with the hope that the corresponding 2,4-dimethoxybenzyl group in **15** would be removed under mild conditions. Fortunately, treatment of lactam **15** with TFA[16] and triethylsilane as a scavenger[17] resulted in efficient removal of the DMB group (Scheme 2), giving rise to the previously unknown bicyclic lactam **17**. Subjection of **17** to Lawesson's reagent afforded the desired thiolactam **9**.

Conclusion

In summary, we have prepared in racemic form a conformationally restricted morpholinethione (**9**), which should serve as a useful synthon for the preparation of novel heteroaryl-annulated bicyclic morpholine analogs. The synthesis utilized inexpensive reagents, and the key step involved an oxetane ring formation via an intramolecular alkylation reaction.

Supplementary data

Supplementary data (experimental procedures and characterization data for all new compounds (**9, 11–17**) and copies of NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.017.

References and notes

1. Brickner, S. J.; Barbachyn, M. R.; Hutchinson, D. K.; Manninen, P. R. *J. Med. Chem.* **2008**, *51*, 1981.
2. Barker, A. J.; Gibson, K. H.; Grundy, W.; Godfrey, A. A.; Barlow, J. J.; Healy, M. P.; Woodburn, J. R.; Ashton, S. E.; Curry, B. J.; Scarlett, L.; Henthorn, L.; Richards, L. *Bioorg. Med. Chem. Lett.* **2001**, 1911.
3. Kasper, S.; El Giamal, N.; Hilger, E. *Exp. Opin. Pharmacother.* **2000**, *1*, 771.
4. (a) Abe, T.; Matsunaga, H.; Mihira, A.; Sato, C.; Ushirogochi, H.; Sato, K.; Takasaki, T.; Venkatesan, A. M.; Mansour, T. S. Patent Cooperation Treaty WO 2003/093277, November 13, 2003.; (b) Tabei, K.; Feng, X.; Venkatesan, A. M.; Abe, T.; Hideki, U.; Mansour, T. S.; Siegel, M. M. *J. Med. Chem.* **2004**, *47*, 3674; (c) Petersen, P. J.; Jones, C. H.; Venkatesan, A. M.; Bradford, P. A. *Antimicrob. Agents Chemother.* **2009**, *53*, 1698.
5. Vasiliou, S.; Vicente, M.; Castaner, R. *Drugs Future* **2009**, *34*, 451.
6. Munk, S. A.; Harcourt, D.; Ambrus, G.; Denys, L.; Gluchowski, C.; Burke, J. A.; Kharlamb, A. B.; Manlapaz, C. A.; Padillo, E. U.; Runde, E.; Williams, L.; Wheeler, L. A.; Garst, M. E. *J. Med. Chem.* **1996**, *39*, 3533.
7. (a) Griffin, R. J.; Fontana, G.; Golding, B. T.; Guiard, S.; Hardcastle, I. R.; Leahy, J. J. J.; Martin, N.; Richardson, C.; Rigoreau, L.; Stockley, M.; Smith, G. C. M. *J. Med. Chem.* **2005**, *48*, 569; (b) Blizzard, T. B.; DiNinno, F.; Morgan, J. D., II; Chen, H. Y.; Wu, J. Y.; Gude, C.; Kim, S.; Chan, W.; Birzin, E. T.; Yang, Y. T.; Pai, L.-Y.; Zhang, Z.; Hayes, E. C.; DaSilva, C. A.; Tang, W.; Rohrer, S. P.; Schaeffer, J. M.; Hammond, M. L. *Bioorg. Med. Chem. Lett.* **2004**, 3861; (c) Roecker, A. J.; Coleman, P. J.; Mercer, S. P.; Schreier, S. D.; Buser, C. A.; Walsh, E. S.; Hamilton, K.; Lobell, R. B.; Tao, W.; Diehl, R. E.; South, V. J.; Davide, J. P.; Kohl, N. E.; Yan, Y.; Kuo, L. C.; Li, C.; Fernandez-Metzler, C.; Mahan, E. A.; Prueksaritanont, T.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **2007**, 5677; (d) Venkatesan, A. M.; Chen, Z.; Santos, O. D.; Dehnhardt, C.; Santos, E. D.; Ayral-Kaloustian, S.; Mallon, R.; Hollander, I.; Feldberg, L.; Lucas, J.; Yu, K.; Chaudhary, I.; Mansour, T. S. *Bioorg. Med. Chem. Lett.* **2010**, 5869; (e) Zask, A.; Kaplan, J.; Verheijen, J. C.; Richard, D. J.; Curran, K.; Brooijmans, N.; Bennett, E. M.; Toral-Barza, L.; Hollander, I.; Ayral-Kaloustian, S.; Yu, K. *J. Med. Chem.* **2009**, *52*, 7942; (f) Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Müller, K. *J. Med. Chem.* **2010**, *53*, 3227.
8. Jagodzinski, T. S. *Chem. Rev.* **2003**, *103*, 197.
9. (a) Bromidge, S. M.; Arban, R.; Bertani, B.; Bison, S.; Borriello, M.; Cavanni, P.; Dal Forno, G.; Di-Fabio, R.; Donati, D.; Fontana, S.; Gianotti, M.; Gordon, L. J.; Granci, E.; Leslie, C. P.; Moccia, L.; Pasquarello, A.; Sortori, I.; Sava, A.; Watson, J. M.; Worby, A.; Zonzini, L.; Zucchelli, V. *J. Med. Chem.* **2010**, *53*, 5827; (b) Thurkauf, A.; Chen, X.; Zhang, S.; Gao, Y.; Kieltyka, A.; Wasley, J. W. F.; Brodbeck, R.; Greenlee, W.; Ganguly, A.; Zhao, H. *Bioorg. Med. Chem. Lett.* **2003**, 2921; (c) Weber, M.; Jager, W.; Erker, T. *J. Heterocyclic Chem.* **2003**, *40*, 851.
10. Walker, D. P.; Wishka, D. G.; Beagley, P.; Turner, G.; Solesbury, N. *Synthesis* **2011**, 1113.
11. (a) Paul, R.; Williams, R. P.; Cohen, E. *J. Org. Chem.* **1975**, *40*, 1653; (b) Pearlman, B. A. Patent Cooperation Treaty WO 1999/24393, 1999; Chem. Abstr. **1999**, *130*, 338099.; (c) Perrault, W. R.; Pearlman, B. A.; Godrej, D. B.; Jeganathan, A.; Yamagata, K.; Chen, J. J.; Lu, C. V.; Herrington, P. M.; Gadwood, R. C.; Chan, L.; Lyster, M. A.; Maloney, M. T.; Moeslein, J. A.; Greene, M. L.; Barbachyn, M. R. *Org. Process Res. Dev.* **2003**, *7*, 533.
12. Cf: Morie, T.; Kato, S.; Harada, H.; Matsumoto, J. *Heterocycles* **1994**, *38*, 1033.
13. The importance of forming a potassium enolate to effect efficient intramolecular cyclization on a related carbocyclic system has been previously observed, see: Nicolaou, K. C.; Magolda, R. L.; Claremon, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 1404.
14. Cf: Yadav, J. S.; Ather, H.; Gayathri, K. U.; Rao, N. V.; Prasad, A. R. *Synthesis* **2008**, 3945.
15. Cf: (a) Williams, R. M.; Lee, B. H.; Miller, M. M.; Anderson, O. P. *J. Am. Chem. Soc.* **1989**, *111*, 1073; (b) Julina, R.; Herzig, T.; Bernet, B.; Vasella, A. *Helv. Chem. Acta* **1986**, *69*, 368.
16. Schlessinger, R. H.; Bebernitz, G. R.; Lin, P.; Poss, A. Y. *J. Am. Chem. Soc.* **1985**, *107*, 1777.
17. (a) Sakya, S. M.; Van Den Berg, M.; Pouwer, K.; Humphrey, J. M.; Helal, C. J.; O'Donnell, C. J. *Tetrahedron Lett.* **2010**, 5859; (b) Pearson, D. A.; Blanchette, M.; Baker, M. L.; Guindon, C. A. *Tetrahedron Lett.* **1989**, 2739.