Tetrahedron Letters 56 (2015) 6056–6058

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of new heterocyclic analogs of linezolid

Son T. Nguyen, Bing Li, Norton P. Peet *

Department of Chemistry, Microbiotix Inc., One Innovation Drive, Worcester, MA 01605, USA

ARTICLE INFO

Article history:
Received 23 July 2015
Revised 12 September 2015
Accepted 16 September 2015
Available online 21 September 2015

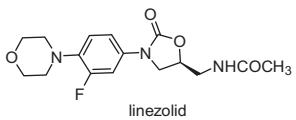
Keywords:
Linezolid
Oxazolidinones
50S ribosome
Thienyloxazolidinones

ABSTRACT

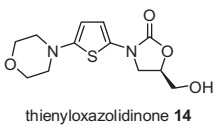
We have previously attempted to prepare 5-(4-morpholinyl)-2-aminothiophene (**3**) by reducing 5-(4-morpholinyl)-2-nitrothiophene (**2**), to prepare a precursor for the preparation of thienyloxazolidinones as potential linezolid-like antibiotics. This strategy failed, but allowed us to define an interesting reductive aromatization reaction. We have now succeeded in producing thienyloxazolidinones using an alternative strategy, initiating from 5-(4-morpholinyl)thiophene-2-carboxaldehyde (**8**). This Letter describes the synthesis of thienyloxazolidinone **14**, which is a key intermediate for the preparation of new oxazolidinone antibiotics with a thiophene core.

The oxazolidinones comprise an important class of Gram-positive antibiotics. The oxazolidinone class inhibits bacterial protein synthesis by a unique mechanism of action that involves binding to the 23S portion of the 50S ribosomal subunit and inhibition of the formation of *N*-formylmethionine, which is necessary for the translation process. Linezolid, the first oxazolidinone antibiotic, is a parental drug with excellent oral bioavailability and favorable pharmacokinetic properties.[1]

Linezolid was discovered by Barbachyn and colleagues at Pharmacia and Upjohn in the 1990s, and was identified for development through structure–activity, safety, tolerability, and pharmacokinetic studies.[2–6] Linezolid is the only agent in the oxazolidinone class that was marketed until 2014, when tedezolid[7] was approved for skin infections. Other oxazolidinones in later stages of development include radezolid,[8] posizolid,[9] sutezolid,[10] eperezolid,[11] and ranbezolid.[12]



linezolid



thienyloxazolidinone **14**

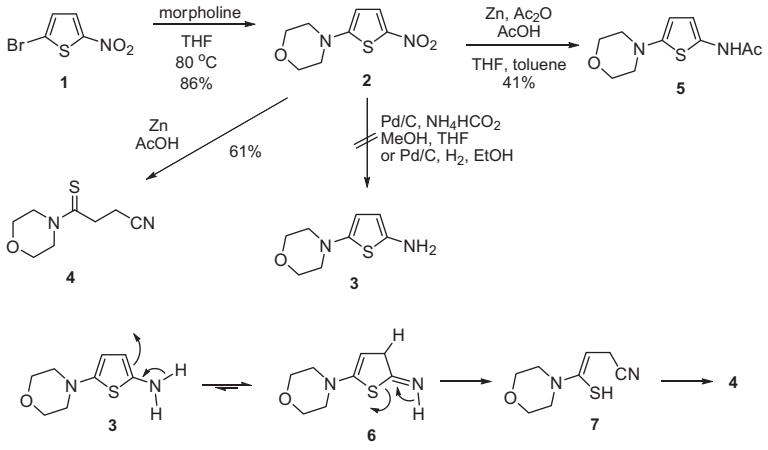
However, linezolid resistance has developed,[13–18] which in Gram-positive bacteria is usually driven by a point mutation of the genes encoding for the 23S ribosomal RNA.[19–23] New oxazolidinone structures that are less prone to resistance are therefore needed. With modeling studies, based on the known crystal structure of linezolid bound to the 50S ribosomal subunit,[24] we have shown that thienyl analogs of linezolid do indeed dock into the linezolid binding site, and the binding position suggests that a resistance profile for these new antibiotics might be improved with respect to linezolid. This report describes the synthesis of a key thienyloxazolidinone intermediate that allows access to thiophene analogs of linezolid. Challenges encountered in the synthesis of this key intermediate explain why these analogs have not previously been reported.

We previously described the attempted preparation of 2-amino-5-(4-morpholinyl)thiophene (**3**), as briefly summarized in Scheme 1.[25] It was straightforward to prepare the corresponding 2-nitro compound **2** from 2-bromo-5-nitrothiophene (**1**), by displacement of bromide using morpholine. We determined that the desired amino compound **3** was undoubtedly produced by reduction of the nitro group in **2** using catalytic hydrogenation conditions, since we could trap the amino compound **3** as the acetamide **5** when we performed the reduction of **3** using zinc in acetic acid with added acetic anhydride. The product isolated from the reduction of compound **2** was thioamide **4**, which is actually isomeric with compound **3**. We envision the mechanism of this remarkable dearomatization reaction, and the formation of the unexpected thioamide **4**, as shown in Scheme 1, where tautomerization of **3** to imine **6** allows fragmentation of the thiophene ring to cyano intermediate **7**. Tautomerization of intermediate **7** can then directly produce the observed thioamide **4**.

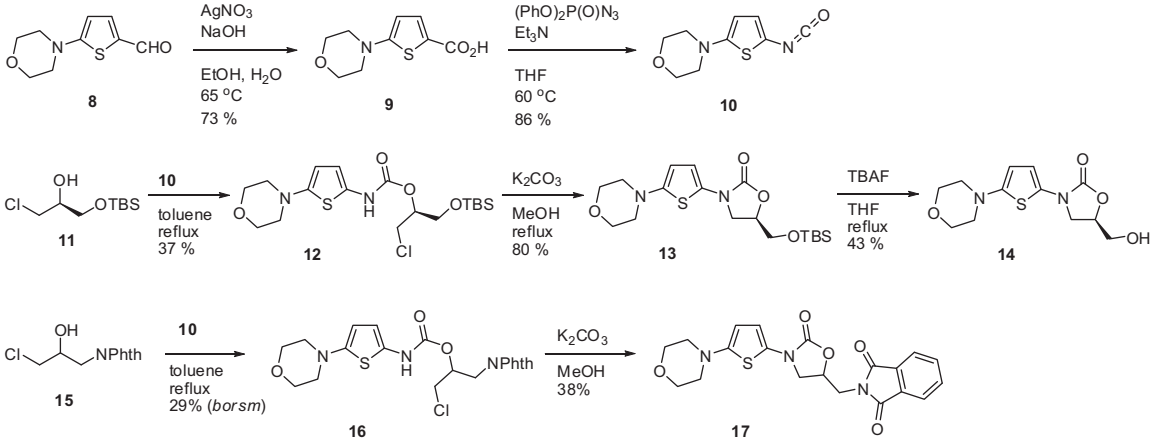
Our inability to isolate aminothiophene **3** was quite surprising, since the reduction of 4-(4-morpholinyl)nitrobenzene to 4-(4-morpholinyl)aniline is easily accomplished.[26–28] We attribute this difference to thiophenes possessing less aromatic character

* Corresponding author. Tel.: +1 616 298 8483; fax: +1 616 298 7337.
E-mail address: nppeet@gmail.com (N.P. Peet).

http://dx.doi.org/10.1016/j.tetlet.2015.09.065
0040-4039/



Scheme 1. Attempted synthesis of 2-amino-5-(4-morpholinyl)thiophene (**3**).



Scheme 2. Synthesis of key intermediates for the preparation of thienyloxazolidinones.

than benzenes, and having more diene character. 2-Aminothiophenes are well-known compounds, and scores of these compounds have been produced using the Gewald syntheses[29,30] and modified Gewald conditions.[31–36]

Since the desired aminothiophene **3** was not a stable, isolable compound, we sought a synthetic route in which the amino compound would not be produced as a discrete intermediate. The Curtius rearrangement[37] is one that allows the conversion of an aryl carboxylic acid, through the intermediacy of an acyl azide, to an arylisocyanate, which can be viewed as a protected arylamine. This route seemed attractive, since the required starting materials were accessible. 5-(4-Morpholinyl)thiophene-2-carboxaldehyde (**8**) was prepared as described[38,39] by treatment of 5-bromothiophene-2-carboxaldehyde with morpholine in water. Treatment of aldehyde **8** with silver nitrate produced the corresponding 5-(4-morpholinyl)thiophene-2-carboxylic acid (**9**) in 73% yield. Conversion of **9** to 2-isocyanato-5-(4-morpholinyl)thiophene (**10**) was then accomplished in 86% yield by treatment with diphenylphosphoryl azide, as shown in Scheme 2.

We next prepared (*R*)-(−)-1-(*tert*-butylmethylsilanyloxy)-3-chloropropan-2-ol (**11**) as described in the patent literature.[40] Treatment of chloropropanol **11** with isocyanate **10** gave carbamate **12** in 37% yield. Carbamate **12** underwent intramolecular alkylation when treated with potassium carbonate in methanol to produce oxazolidinone **13** in 80% yield. Removal of the silyl protecting group with *tert*-butylammonium fluoride then gave the key intermediate **14** in 43% yield. In a similar fashion, the phthalamido protected 3-chloro-2-hydroxypropylamine **15**[41] (racemic) was converted to carbamate **16** by treatment with isocyanate **10**, and intramolecular alkylation gave the second key intermediate **17**.

Syntheses of oxazolidinones **14** and **17** are highly significant, since they represent key intermediates for the preparation of thienyloxazolidinones that are new potential antibiotic agents. The chemistry described in this report also makes possible the preparation of other novel linezolid-like structures with electron-rich five-membered rings that replace the phenyl core, such as furanyloxazolidinones, as well as substituted versions of these compounds.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.065.

References and notes

1. Pandit, N.; Singla, R. K.; Shrivastava, B. *Int. J. Med. Chem.* **2012**, *2012*. 24 pages 158285.
2. Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, P. R.; Ulanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Tops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 673.
3. Ford, C. W.; Hamel, J. C.; Stapert, D.; Moerman, J. K.; Hutchinson, D. K.; Barbachyn, M. R.; Zurenko, G. E. *Trends Microbiol.* **1997**, *5*, 196.
4. Barbachyn, M. R.; Brickner, S. J.; Gadwood, R. C.; Garmon, S. A.; Grega, K. C.; Hutchinson, D. K. *Adv. Exp. Med. Biol.* **1998**, *456*, 219.

5. Barbachyn, M. R.; Ford, C. W. *Angew. Chem., Int. Ed.* **2010**, *2003*, 42.
6. Brickner, S. J.; Barbachyn, M. R.; Hutchinson, D. K.; Manninen, P. R. *J. Med. Chem.* **1981**, *2008*, 51.
7. Wong, E.; Rab, S. *Pharm. Ther.* **2014**, *39*, 555.
8. Zhou, J.; Bhattacharjee, A.; Chen, S.; Chen, Y.; Duffy, E.; Farmer, J.; Goldberg, J.; Hanselmann, R.; Ippolito, J. A.; Lou, R.; Orbin, A.; Oyelere, A.; Salvino, J.; Springer, D.; Tran, J.; Wang, D.; Wu, Y.; Johnson, G. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6175.
9. Wookey, A.; Turner, P. J.; Greenhalgh, J. M.; Eastwood, M.; Clarke, J.; Sefton, C. *Clin. Microbiol. Infect.* **2004**, *10*, 247.
10. Shaw, K. I.; Barbachyn, M. R. *Ann. N. Y. Acad. Sci.* **2011**, *1241*, 48.
11. (eperezolid) Rybak, M. J.; Cappelletty, D. M.; Moldovan, T.; Aeschlimann, J. R.; Kaatz, G. W. *Antimicrob. Agents Chemother.* **1998**, *42*, 721.
12. Naruganahalli, K. S.; Shirumalla, R. K.; Bansal, V.; Gupta, J. B.; Das, B.; Ray, A. *Eur. J. Pharmacol.* **2006**, *545*, 167.
13. Gu, B.; Lelesidis, T.; Tsiodras, S.; Hindler, J.; Humphries, R. M. *J. Antimicrob. Chemother.* **2013**, *68*, 4.
14. Long, K. S.; Vester, B. *Antimicrob. Agents Chemother.* **2012**, *56*, 603.
15. Billal, D. S.; Feng, J.; Leprohon, P.; Legare, D.; Quellette, M. *BMC Genomics* **2011**, *12*, 512.
16. Bonilla, H.; Huband, M. D.; Seidel, J.; Schmidt, H.; Lescoe, M.; McCurdy, S. P.; Lemmon, M. M.; Brennan, L. A.; Tait-Kamradt, A.; Puzniak, L.; Quinn, J. P. *Clin. Infect. Dis.* **2010**, *51*, 796.
17. Bourgeois-Nicolas, N.; Massias, L.; Couson, B.; Butel, M.; Andremont, A.; Doucet-Populaire, F. *J. Infect. Dis.* **2007**, *195*, 1480.
18. Bozdogan, B.; Appelbaum, P. C. *Antimicrob. Agents* **2004**, *23*, 113.
19. Gonzales, R. D.; Schreckenberger, P. C.; Graham, M. B.; Kelkar, S.; DenBesten, K.; Quinn, J. P. *Lancet* **2001**, *357*, 1179.
20. Swoboda, S.; Fritz, S.; Martignoni, M. E.; Feldhues, R. A.; Hoppy-Tichy, T.; Buchler, M. W.; Geiss, H. K. *J. Antimicrob. Chemother.* **2005**, *56*, 787.
21. Boo, T. H.; Hone, R.; Sheehan, G.; Walsh, M. *J. Hosp. Infect.* **2003**, *53*, 312.
22. Bersos, Z.; Maniati, M.; Kontos, F.; Petinaki, E.; Maniatis, A. N. *J. Antimicrob. Chemother.* **2004**, *53*, 685.
23. Auckland, C.; Teare, L.; Cooke, F.; Kaufmann, M. E.; Warner, M.; Jones, G.; Bamford, K.; Ayles, H.; Johnson, A. P. *J. Antimicrob. Chemother.* **2004**, *1010*, 39.
24. Ippolito, J. A.; Kanyo, Z. F.; Wang, D.; Franceschi, F. J.; Moore, P. B.; Steitz, T. A.; Duffy, E. M. *J. Med. Chem.* **2008**, *51*, 3353.
25. Nguyen, S. T.; Ding, X.; Peet, N. P. *Synthesis* **1904**, *2013*, 45.
26. Lee, R. L.; Lee, R. L.; Tangallapally, R. P.; Yendapally, R.; Lenaerts, A. J. M. *J. Med. Chem.* **2005**, *48*, 8261.
27. Jia, Z. J.; Wu, Y.; Huang, W.; Zhang, P.; Clizbe, L. A.; Goldman, E. A.; Sinha, U.; Arfsten, A. E.; Edwards, S. T.; Alphonso, M.; Hutchaleelaha, A.; Scarborough, R. M.; Zhu, B.-Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1221.
28. Nath, M.; Prasad, D.; Aggarwal, N.; Kumar, R. *Ind. J. Chem.* **2012**, *51B*, 731.
29. Gewald, K.; Shinke, E.; Bottcher, H. *Ber.* **1966**, *99*, 94.
30. Sabnis, R. W. *Sulfur Rep.* **1994**, *16*, 1.
31. Forero, J. S. B.; de Carvalho, E. M.; Junior, J. J.; da Silva, F. M. *Heterocycl. Lett.* **2011**, *1*, 6167.
32. Buchstaller, H.-P.; Siebert, C. D.; Lyssy, R. H.; Frank, I.; Duran, I.; Gottschlich, R.; Noe, C. R. *Monatsch. Chem.* **2001**, *132*, 279.
33. (Gewald var) Huang, X.-G.; Liu, J.; Ren, J.; Wang, T.; Chen, W.; Zeng, B.-B. *Tetrahedron* **2011**, *67*, 6202.
34. Sridhar, M.; Rao, R. M.; Baba, N. H. K.; Kumbhare, R. M. *Tetrahedron Lett.* **2007**, *48*, 3171.
35. Chavan, S. S.; Pedgaorkar, Y. Y.; Jadhav, A. J.; Degani, M. S. *Ind. J. Chem.* **2012**, *51B*, 653.
36. Mojtahedi, M. S.; Abaee, M. S.; Mahmoodi, P.; Adib, M. *Synth. Commun.* **2010**, *40*, 2067.
37. Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297.
38. Prim, D.; Kirsch, G.; Nicoud, J. F. *Synlett* **1998**, 383.
39. Kirsch, G.; Prim, D. *Tetrahedron* **1999**, *55*, 6511.
40. Goto, F.; Otani, T.; Takemura, N.; Hasegawa, T.; Utsumi, N.; Kuroda, H.; Sasaki, H.; Shitsuta, T.; Fujita, S.; Tsubouchi, H. European Patent 1,553,088 A1, July 13, 2005.
41. Pearlman, B. A. United States Patent 6,362,334 B1, March 26, 2002.