Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 2601–2604

TETRAHEDRON LETTERS

A new and convergent synthesis for 2,5-diamino-tetrahydropyrimidones

Lianhong Xu,* Lijun Zhang, Clifford M. Bryant and Choung U. Kim

Department of Medicinal Chemistry, Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404, USA

Received 18 December 2002; revised 21 January 2003; accepted 21 January 2003

Abstract—AN1057A/B has shown potent activity against MRSA. A novel and concise route to the synthesis of its heterocycle core 2,5-diamino-5,6-dihydro-1*H*-pyrimidine-4-one is described. This methodology allows the synthesis of an array of analogs with different amine substitutions at the 2-position.

TAN-1057A/B, isolated a few years ago from *Flexibacter* in Japan, exists as a mixture of tautomers **1a** and **1b** (Fig. 1). This unique dipeptide antibiotic has exhibited potent in vitro and in vivo activity against Gram-positive bacteria, especially against methicillin resistant *Staphylococcus aureus* (MRSA).[1] During the course of our investigation of the structure–activity relationship (SAR) of TAN-1057A/B analogs, we were interested in modification of the urieo-substitutions at the 2-position.

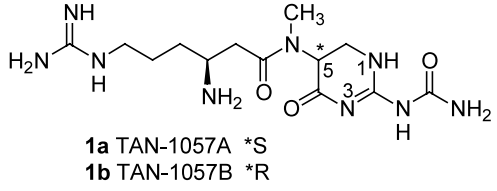
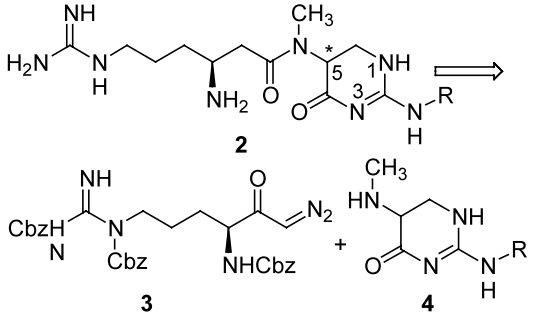


Figure 1.

Two independent total syntheses of TAN-1057A/B have been reported to date.[2] Some preliminary investigation at the 2-position was published by the Williams group.[3] Recently, an approach to TAN-1057A/B heterocycle was also disclosed.[4] Unfortunately, these existing approaches of building the heterocyclic core preclude an extensive investigation at the 2-position. In this communication we report a new strategy that allows for the convenient synthesis of novel TAN-1057A/B analogs with a variety of alterations at 2-position.

In order to introduce a variety of amine substitutions at 2-position, it was necessary to develop a new and efficient pathway for the synthesis of 2,5-diamino-5,6-dihydro-1*H*-pyrimidine-4-one (**4**). As shown in Scheme 1, we envisioned that once the heterocyclic core was built, the desired analogs **2** could be constructed by coupling of diazoketone **3** and dihydropyrimidone **4** with the known strategy disclosed by the de Meijere group.[2b]

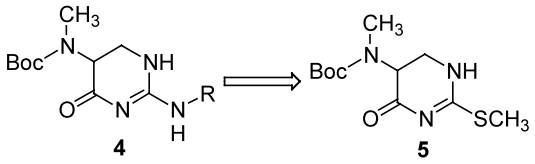


Scheme 1.

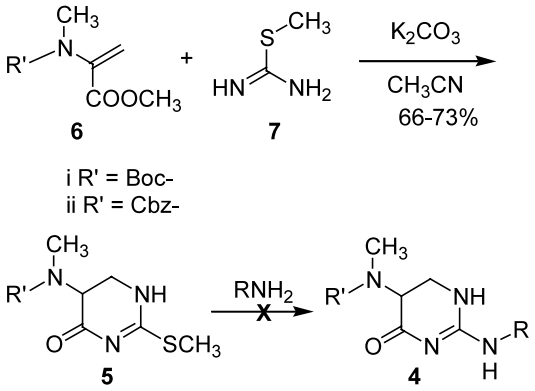
Based on the knowledge that guanidine are generated via reaction of amines with acyl-*S*-methylisothioureas,[5] we reasoned if acyl-*S*-methylisothiourea **5** could be obtained, treatment of **5** with requisite primary and secondary amines should provide an efficient and convergent way to access a variety of structurally diverse acyl guanidines **4** (Scheme 2).

* Corresponding author. E-mail: lianhong_xu@gilead.com

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00226-0



Scheme 2.



Scheme 3.

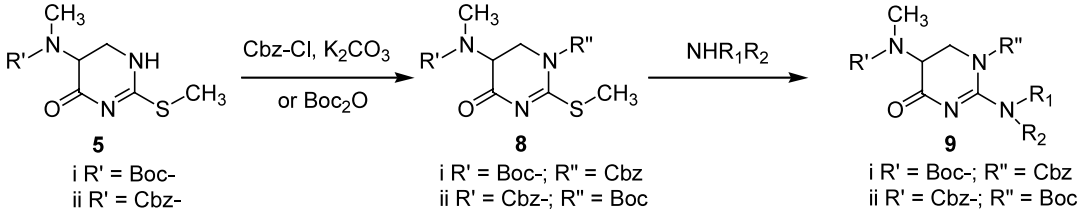
It was envisioned that **5** could be formed from *N*-protected *N*-methyldehydroalanine methyl ester **6**[6] and *S*-methylisothiourea **7** by Michael addition and subsequent cyclization analogous to the known method for the preparation of 2-*S*-methylthio-5,6-dihydro-1*H*-pyrimidine-4-one.[7] As illustrated in Scheme 3, reaction of dehydroalanine **6** with isothiourea **7** in the presence of base (K_2CO_3) afforded heterocyclic compound **5** as a white solid in 70% yield. The reaction proceeded under mild condition and was amenable to a large scale preparation. During the process of preparing dihydropyrimidone **4**, we came to realize that **4** decomposed readily in the presence of strong nucleophiles or under strongly basic conditions, especially at elevated temperatures. The sensitivity of heterocycle **4** required the identification of mild reaction conditions for any follow up transformations. Unfortunately, treatment of monoacyl isothiourea **5i** with amines under mild conditions failed to provide any desired dihydro-pyrimidone product **4** (Scheme 3). In order to facilitate the smooth conversion, the isothioureas **5** were activated with either a Cbz- or a Boc- function to provide **8** as shown in Scheme 4. Upon treatment with amines, the diacyl isothiourea **8** was smoothly converted to the desired cyclic guanidine **9** in fair to excellent yields.[8] Examples that demonstrate this transformation with a variety of amines are listed in Table 1.

As depicted in Table 1, both primary and secondary amines gave good yield (entries a, d and g). Hydroxyamine and morpholine (entries b and c) also provided product with good yield. When the amine salt was used for the reaction, organic base (iPr_2NEt) was added. However, neither pre-generated amide salt nor its silylated imidate reacted with **8** (entry h).

With 2-amino heterocyclic compound **9** in hand, it was further converted to TAN-1057A/B analog. TAN-1057 analogs with 2-alkylamines **2b–e** were thus obtained following the procedures displayed in Scheme 5, represented by **2e**. The Cbz-group was removed by hydrogenolysis, and the resulting amine **10e** was coupled with diazoketone **3** in the presence of $AgClO_4$ to afford compound **11e**. We found that $AgClO_4$ was a better catalyst than PhCOOAg used by the de Meijere group for the coupling reaction. $AgClO_4$ had much wider tolerance of substrates and provided more consistent yield. In addition, purification of the final product is easier. Final deprotections of coupled product **11e**, removal of Boc with acid followed by hydrogenolysis of Cbz-groups afforded the desired **2e**.

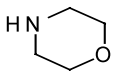
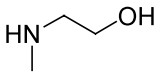
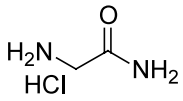
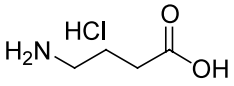
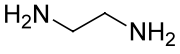
Syntheses of TAN-1057 analogs with 2-carboxy amines **2f–g** are outlined in Scheme 6. It was observed[9] that the triacylated guanidines were highly reactive toward nucleophiles. In order to introduce an acylamino at 2-position, Boc-group of **9f** and **9g** was first removed to afford **12f** and **12g**, respectively. Compound **12f** was converted to 2-acylaminoguanidine **13f** by treating with EDC and HOBt. Treatment of **12g** with CDI in the presence of triethylamine yielded 2-urieo **13g**. Following the established procedure, deprotection of the Cbz-group, coupling the resulting amine with diazoketone **3**, followed by removal of the Cbz-group on the side chain provided TAN-1057A/B analogs **2f–g**.

In summary, we have demonstrated an efficient and convergent route to construct the heterocyclic core of TAN-1057A/B by first forming 2-thio-tetrahydropyrimidone through Michael addition and subsequent cyclization, followed by elaboration at the 2-position

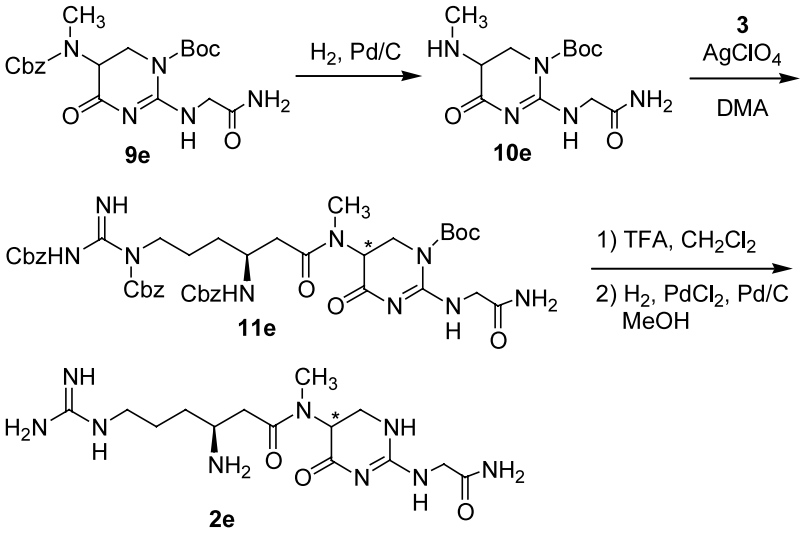


Scheme 4.

Table 1. Conversion of isothiourea **8** to guanidine **9**

Compound **9**	R'-, R"-	Amine	base	yield[i]
a	Boc-, Cbz-	NH_2Me	-	74%
b	Boc-, Cbz-	NH_2OBn	-	93%
c	Boc-, Cbz-		-	42%
d	Cbz-, Boc-		-	96%
e	Cbz-, Boc-		iPr_2EtNH	48%
f	Cbz-, Boc-		iPr_2EtNH	75%
g	Cbz-, Boc-		-	100%
h[ii]	Cbz-, Boc-		NaH	-

i. Yields refers to isolated products. *ii.* Amide anion was generated first, and added to the reaction mixture, no desired product was isolated. Some starting material was recovered.

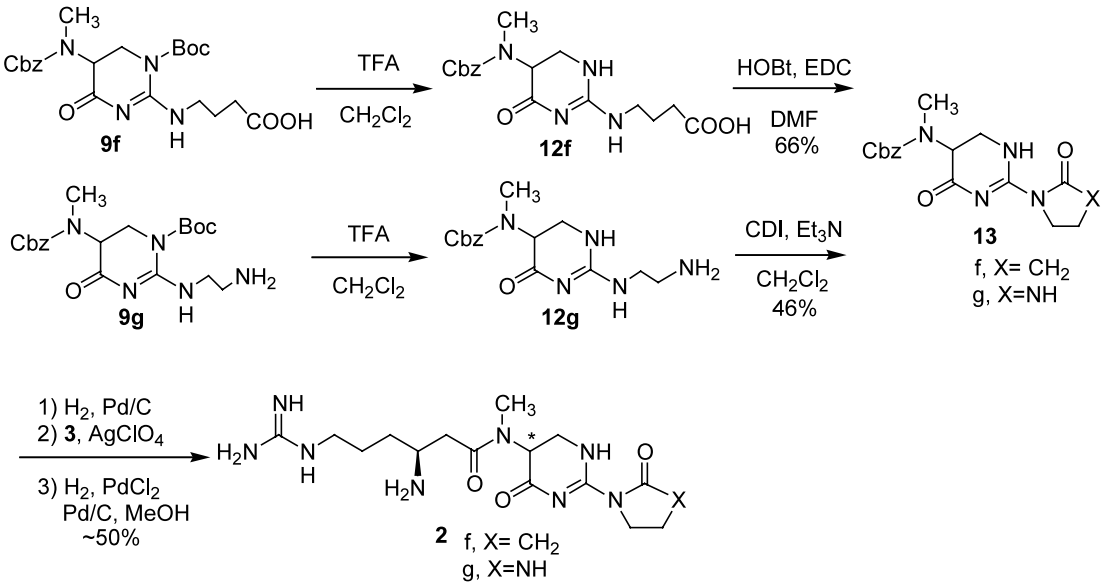


Scheme 5.

with various amines. A variety of TAN analogs were thus prepared. This route enables us to quickly evaluate analogs and establish SAR in this region. The biological activity of these series of analogs will be reported soon.

Acknowledgements

We thank Dr. Ke-Yu Wang for performing NMR studies on the key intermediates and compound, and Dr. Dean Boojamra for his assistance in manuscript preparation.



Scheme 6.

References

1. (a) Katayama, N.; Fukusumi, S.; Funabashi, Y.; Iwahi, T.; Ono, H. *J. Antibiot*. **1993**, *46*, 606; (b) Funabashi, Y.; Tsubotani, S.; Koyama, K.; Katayama, N.; Harada, S. *Tetrahedron* **1993**, *49*, 13.
2. (a) Williams, R. M.; Yuan, C. *J. Am. Chem. Soc*. **1997**, *119*, 11777; (b) Sokolov, V. V.; Kozhushkov, S. I.; Nikolskaya, S.; Belov, V. N.; Es-Sayed, M.; de Meijere, A. *Eur. J. Org. Chem*. **1998**, *63*, 777.
3. Williams, R. M.; Yuan, C.; Lee, V.; Chamberland, S. *J. Antibiot*. **1998**, *51*, 189.
4. Lin, P.; Ganesan, A. *Synthesis* **2000**, 2127.
5. (a) Bergeron, R. J.; Mcmanis, J. S. *J. Org. Chem*. **1987**, *52*, 1700; (b) Dodd, D. S.; Wallace, O. B. *Tetrahedron Lett*. **1998**, *39*, 5701 and references cited therein.
6. Wendelin, W.; Riedl, R. *Monatsh. Chem*. **1985**, *116*, 237.
7. Torisawa, Y.; Nakagawa, M.; Hosaka, T.; Tanabe, K.; Lai, Z.; Ogata, K.; Nakata, T.; Oishi, T.; Hino, T. *J. Org. Chem*. **1992**, *57*, 5741.
8. Typical experimental procedures: A solution of **6** (R′= Boc, 2.15 g, 10 mmol) in CH_3CN (25 mL) was treated with K_2CO_3 (1.52 g, 11 mmol) followed by isothiourea **7** (1.46 g, 10.5 mmol). After stirring at room temperature for 30 h, the mixture was diluted with EtOAc, and filtered. The filtrate was evaporated and the resulting crude product was purified by flash chromatography to give **5** (1.86 g, 68%) as a white solid. A solution of **5** (274 mg, 1 mmol) in CH_3CN (8 mL) was added K_2CO_3 (277 mg, 2.0 mmol), followed by CbzCl (255 mg, 1.5 mmol). The resulting mixture was stirred at room temperature for 2 h before $MeNH_2/CH_3OH$ (2.0 M, 1.5 mL, 3 mmol) was added. After stirring at room temperature for 1.5 h, the mixture was filtered, and evaporated to dryness. The crude product was purified on silica gel to afford **9a** (290 mg, 74%) as a white foam.
9. In our effort trying to synthesize compound **14**, we observed that **14** was slowly converted to the methyl ester **15** in the presence of methanol.