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A facile construction of the 3,6-diamino-1,2,3,4-tetrahydropyridine-4-one scaffold: synthesis of N-3 to carbon replacement analog of TAN-1057A/B

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Abstract—A facile construction of the 3,6-diamino-1,2,3,4-tetrahydropyridine-4-one class of compounds is described. Compound **2**, a carbon analog at the N-3 position of TAN-1057A/B, was synthesized using this approach.

TAN-1057A/B (**1**) (Fig. 1), isolated from bacteria *Flexibacter* by Takeda Chemical Co. in 1993, is a dipeptide antibiotic with potent activity against methicillin-resistant *Staphylococcus aureus* (MRSA).[1] TAN-1057A/B consists of β-homoarginine and a distinctive heterocyclic amidinourea derivative of 2,3-diaminoproprionic acid. Its potent anti-infective activity and intriguing structural feature attracted attention from scientists around the world. Several total and/or core unit syntheses[2] and a few SAR studies have been published.[3] However, the unique 2,5-diamino-5,6-1*H*-dihydropyrimidine-4-one ring is rather sensitive toward hydrolysis, which occurs in both acidic and basic media. TAN-1057A/B gradually loses its antibacterial activity in basic aqueous solution due to the hydrolysis of the acetyl amidine and opening of the heterocyclic ring (Scheme 1).[1] It was envisioned that replacement of N-3 of the original hydrolytically labile 2,5-diamino-5,6-1*H*-dihydropyrimidine-4-one with a carbon, to produce a 3,6-diamino-1,2,3,4-tetrahydropyridine-4-one, would stabilize the ring system toward

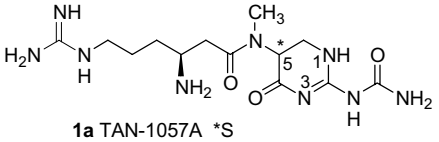
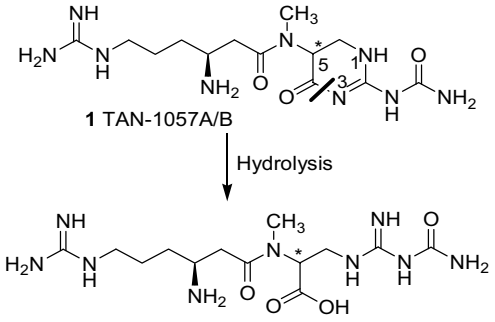


Figure 1. Structure of TAN-1057A/B.



Scheme 1.

hydrolysis and maintain minimal structural disturbance. Furthermore, we and others discovered that replacement of the 2-ureido moiety in TAN-1057A/B with 2-acetylamino provided a more potent analog.[4] Therefore compound **2**, the acetylamino N-3 to carbon replacement analog of TAN-1057A/B (Scheme 2), was targeted in our effort to discover novel antibacterial agents.

The synthesis of **2** can be realized through the coupling of diazoketone **3** and heterocycle core **4** (Scheme 2), utilizing a similar strategy used in the total synthesis of TAN-1057A/B and its analogs.[2b] Heterocycle core **4** is the key intermediate for synthesis of **2**. We envisaged that core **4**, 3,6-diamino-1,2,3,4-tetrahydropyridine-4-one, could be obtained from heterocycle **5** via decarboxylation. Through the extensive literature mining, we were very surprised to find that both tetrahydropyridone **4** and **5** are novel heterocycles: neither has been reported

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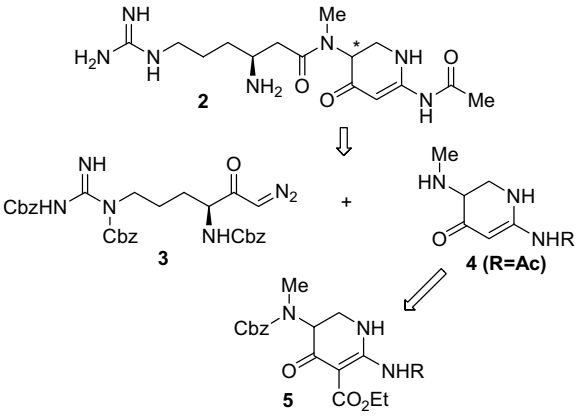
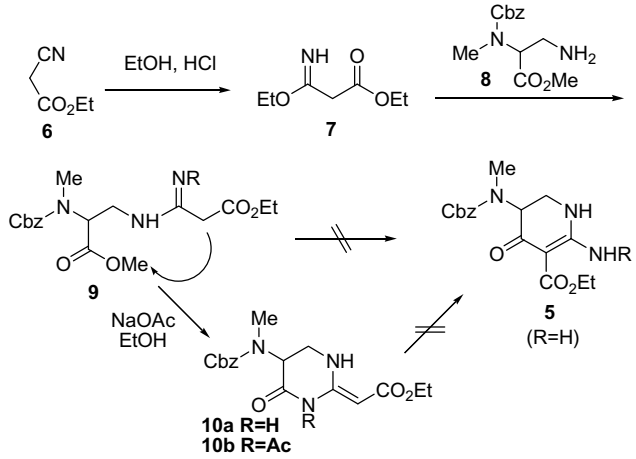


Scheme 2.

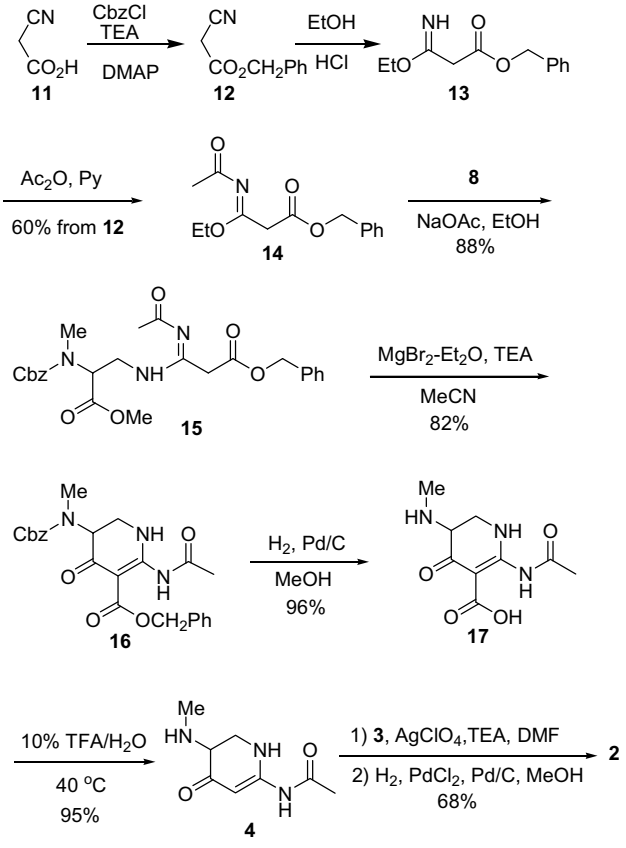
to date. In this Letter, we would like to report the new methodology we developed for an efficient construction of these types of heterocycles.

The most straightforward strategy for the construction of tetrahydropyridone **5** would be based on a Dieckmann-type cyclization of appropriately functionalized ester **9** (Scheme 3). Compound **9** was prepared through coupling of amino ester **8**[2b] with imidate **7**, which was obtained from cyanoacetate **6** by known procedures.[5] However, when amidine **9** was treated with sodium acetate in ethanol, cyclization only occurred via attack of amidine nitrogen to give compound **10a** (yield: ~30%). Effort to force the desired cyclization under various conditions was unsuccessful. Compound **10a** was subjected to a series of basic conditions in an effort to achieve a ring opening and closure sequence to generate the targeted heterocycle **5**. Unfortunately, all attempts toward this end were fruitless.

It is obvious that the undesired cyclization is due to the superior reactivity of amidine nitrogen over the α-carbon of the ester. To prevent this undesired cyclization, the reactivity of amidine nitrogen needs to be reduced. The amidine was deactivated with an acetyl group which is also present in target molecule **2**. To avoid generation of a mixture of regioisomers at amidine nitrogen by directly acetylating amidine **9**, the acetyl group was installed at the imidate stage regio-specifically. In addition, in order to obtain amine **4** in a more convergent manner under mild conditions, a benzyl ester was chosen instead of ethyl. As outlined in Scheme 4, to test our hypothesis, acetyl imidate **14** was prepared from cyanoacetic acid **11**. Acid **11** was converted to its benzyl ester **12**.[6] Acetyl imidate **14** was then prepared by conversion of nitrile **12** to imidate **13**, followed by acetylation. Coupling of imidate **14** with amine **8** proceeded smoothly to afford acetyl amidine **15**. As expected, when deactivated amidine **15** was treated with sodium acetate in ethanol, formation of pyrimidone **10b** was not observed. Unfortunately, under this condition, starting material **15** stayed untouched, the desired Dieckmann-type cyclization product carbocyclic **16** could not be detected. A variety of conditions, including basic (e.g., NaOEt, NaOAc, TEA) and acidic (e.g., AcOH) reaction media, failed to realize the desired cyclization to provide **16**. It has been shown that the combination of anhydrous magnesium chloride and triethylamine is a useful base system for chealating activation of malonate-type compounds,[7] and this condition was tested to direct the desired cyclization. When imidate **15** was treated with magnesium bromide diethyl etherate and triethylamine in acetonitrile at room temperature for 16 h, the desired cyclic product **16** was isolated in a good yield.[8] Concomitant removal of both benzyl and Cbz- groups by hydrogenation yielded amine **17**. Decarboxylation with 10% trifluoroacetic acid in water at room temperature proceeded uneventfully to give amine **4**. Compound



Scheme 3.



Scheme 4.

4 was coupled with side chain **3**,[3] then de-protected to provide target compound **2** following the known procedures.[9]

In summary, we developed a new methodology for the construction of 3,6-diamino-1,2,3,4-tetrahydropyridine-4-one, which is also suitable for the preparation of other amino tetrahydropyridine-4-ones. Compound **2**, a novel carbon analog at the N-3 position of TAN-1057A/B, was synthesized using this facile approach for the tetrahydropyridone scaffold. Studies indicated that the heterocycle core of **2** was stable to hydrolysis in both acidic and basic media, in which TAN-1057 A/B experienced decomposition. Its biological data will be reported in a future publication.

Acknowledgments

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8. *Experimental procedures for tetrahydropyridone* **16**: To a solution of **15** (1.3 g, 2.69 mmol) in acetonitrile (20 ml) was added $MgBr_2$–Et_2O (2.1 g, 8.1 mmol), followed by a slow addition of triethylamine (1.1 g, 10.9 mmol). The reaction mixture was stirred at room temperature for 16 h, and evaporated to a small volume. The residue was partitioned between ethyl acetate and 0.2 N HCl. The organic phase was washed with water and $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (eluted with 1:1 hexane/ethyl acetate) to give compound **16** as a colorless solid (0.7 g, 57.7%). ^{1}H NMR ($CDCl_3$) δ 12.95 (br s, 1H), 10.05 (br s, 1H), 7.3–7.6 (m, 10H), 5.1–5.5 (m, 4H), 5.0/4.75 (m, 1H), 3.8 (m, 2H), 3.0 (s, 3H), 2.3 (s, 3H). MS $(M+Na)^+$: 474.3.
9. *Spectra data for compound* **2** *(diastereomeric mixture ~1:2)*: ^{1}H NMR (DMSO-d_6) δ 10.87/10.76 (d, $J = 8$ Hz, 0.35H, s, 0.65H), 8.7/8.6 (s, 1H), 8.05 (br s, 2H), 7.9 (m, 1H), 7.3 (br s, 3H), 4.95/4.75 (m, 1H), 4.65/4.42 (s, 0.65H; m, 0.35H), 3.4–3.7 (m, 3H), 3.1 (m, 2H), 2.8/2.65 (s, 3H), 2.5–2.8 (m, 2H), 2.05 (s, 3H), 1.6 (m, 4H). MS $(M+1)^+$: 354.2.