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Synthesis of β-prolinols via [3+2] cycloaddition and one-pot programmed reduction: Valuable building blocks for polyheterocycles

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ABSTRACT

A novel two-step synthesis of multisubstituted β-prolinols has been developed, featuring a [3+2] cycloaddition of azomethine ylides and a programmed reduction triggered by the combination of borane and lithium aluminum hydride (LAH). β-Prolinols are shown to be valuable building blocks for polyheterocycles.

Introduction

The α-prolinols have been widely used as heterocyclic building blocks,[1] organic catalysts[2] and ligands[3] for asymmetric catalysis. Various methods have been developed for the synthesis of α-prolinols.[4] Although their constitutional isomers, β-prolinol derivatives frequently occur as structural motifs in natural products[5] and bioactive molecules[6] (Fig. 1) and also serve as important building blocks in organic synthesis,[7] a convenient access to such small heterocycles remains elusive.[8]

In our recent study on the synthesis of pyrrolidine natural products,[9] we developed an efficient synthesis of a broad spectrum of 5-unsubstituted pyrrolidines through a two-step strategy, which involved a 1,3-dipolar cycloaddition of α-iminonitriles and a novel reductive decyanation reaction with borane and sodium borohydride (Scheme 1a). Notably, in the later transformation, we found that the borane played a dual role as Lewis acid activator and reducing agent while a catalytic amount of sodium borohydride functioned as a basic initiator for an anionic chain reaction. Inspired by these results, we envisioned that a similar two-step strategy might be feasible for accessing the multisubstituted β-prolinols (Scheme 1b), which could be elaborated into valuable polyheterocyclic compounds. Herein, we report a general approach to the synthesis of multifunctionalized β-prolinols via [3+2] cycloaddition followed by one-pot[10] programmed reduction.[11] Moreover, the resulting products were utilized for the facile synthesis of several polyheterocycles, including the core of martinellic acid.

By taking advantage of the technologies developed by Carretero[12] and us[9] for the synthesis of α-cyanopyrrolidines through the [3+2] cycloaddition of α-iminonitriles and electron-deficient olefins, the current proposal still poses a challenge in the second step (Scheme 1b). In this step, we designed a one-pot reduction including reductive removal of a cyano group next to an amino group[13] and a reduction of an ester group to primary alcohol. However, commonly-used powerful reductants (e.g., LAH or DIBAL-H) for the reduction of an ester group usually inevitably caused the direct reduction of the cyanide to a primary amine as a competitive reaction.[14] To date, this long-standing problem has yet to be solved. We envisioned that the desired chemoselectivity[15] could be achieved through a meticulous control of reaction pathway by the employment of Lewis acid activators. To our knowledge, such programmed reduction is unprecedented. Hence, the development of reductive system to realize a well-controlled reduction is pivotal for this two-step synthesis of β-prolinols.

Results and discussion

At the outset, α-cyanopyrrolidine **1a** was chosen as a model substrate for a survey of reductants and additives, and the results are outlined in Table 1. Not surprisingly, treatment of **1a** with LAH (2.0 equiv) at 0 °C afforded the desired β-prolinol **2a** in 48% ^{1}H NMR yield together with a significant amount of diamine **3**

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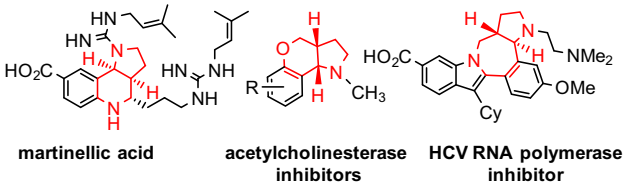
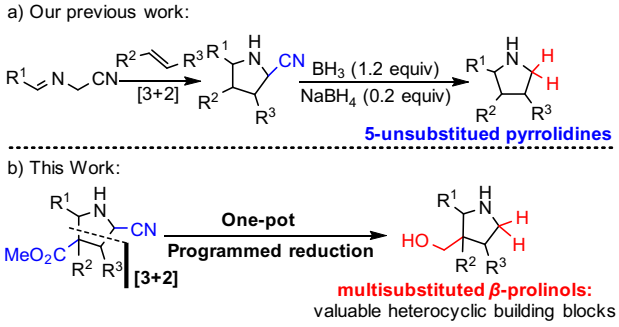


Fig. 1. Selected bioactive heterocycles containing masked β-prolinols.



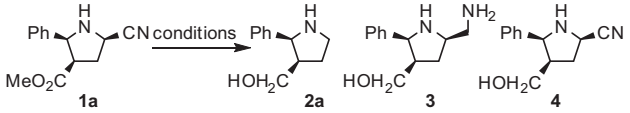
Scheme 1. Construction of Multisubstituted β-Prolinols via [3+2] Cycloaddition and Programmed Reduction.

(49% yield) (Table 1, entry 1). Interestingly, reaction of **1a** with 2.2 equiv of DIBAL-H at −78 °C produced prolinol **4** in 51% yield and a trace amount of **2a** (Table 1, entry 2). However, when **1a** was treated with 5.0 equiv of DIBAL-H at 0 °C then rt, diamine **3** was obtained as a major product (64% of **3** and 20% of **2a**; Table 1, entry 3). To our delight, sequentially running the reductive decyanation under our previously developed conditions[9a] (1.2 equiv of borane and 0.2 equiv of $NaBH_4$) and ester reduction (2.0 equiv of LAH) either in a two-pot or in a one-pot manner gave **2a** in high yields (Table 1, entries 4 and 5). Encouraged by the good performance of borane in reductive decyanation,[9a] we next explored the possibility to realize the two aforementioned reductions in single-step operation based on a concept of programmed reduction. Although the combination of borane and DIBAL-H did not improve the desired reaction (Table 1, entry 6), the cooperation of borane and LAH delivered the desired β-prolinol **2a** in high yield (Table 1, entry 7) and only a trace amount of diamine **3** was observed. In this programmed reduction, reductive decyanation and ester reduction proceeded harmoniously. Importantly, in contrast to the results of entry 1, *the introduction of borane significantly enhanced the chemoselectivity (the reductive decyanation v.s. direct reduction of cyano group) of powerful LAH.* To our knowledge, a combination of borane and LAH has not been employed previously in a reductive decyanation reaction.

With the optimal reaction conditions in hand, we next examined the scope of this two-step transformation. Cyanopyrrolidines **1a**–**1z** were conveniently prepared from corresponding α-iminonitriles and α,β-unsaturated esters via AgOAc catalyzed [3+2] cycloaddition in good yields.[23] As shown in Table 2, a variety of multisubstituted β-prolinols were efficiently prepared via the newly developed programmed reduction protocol. The cyanopyrrolidines bearing various substituted phenyl groups or heterocycles were well-tolerated substrates to deliver β-prolinols **2a**–**2n** in good to high yields. Interestingly, the styrenyl double bond of cyanopyrrolidine **1o** survived this double-site reduction with borane and LAH without the occurrence of evident hydroboration reaction. However, the cyanopyrrolidine with a terminal double bond (**1p**) failed to give pure desired β-prolinol **2p** because of excessive hydroboration in the presence of borane and hydrogenation in the workup operation with Pd/C.[16] A series of β-prolinols bearing aliphatic chains (**2q**–**2t**) or rings (**2u**–**2w**) were efficiently prepared through current protocol. Steric hindrance was proved to have little effect on the selective reduction and three multisubstituted β-prolinols (**2x**–**2z**) were synthesized in good yields. Notably, the current procedure could be also conducted on a gram scale with similar efficiency (**2a** and **2m**).

In our previous studies on the reductive decyanation of α-cyanopyrrolidines with borane and $NaBH_4$, the preliminary mechanistic study showed that borane acted not only as a Lewis acid activator but also as a major hydride source (Scheme 2a).[9a] In order to gain some mechanistic insight on the new programmed reduction, a reduction of **1a** with borane (1.3 equiv) and $LiAlD_4$ (2.0 equiv) was conducted (Scheme 2b). The results revealed that borane was still the major hydride source of the reductive decyanation on C5, albeit in a lower percentage of 62%. Notably,

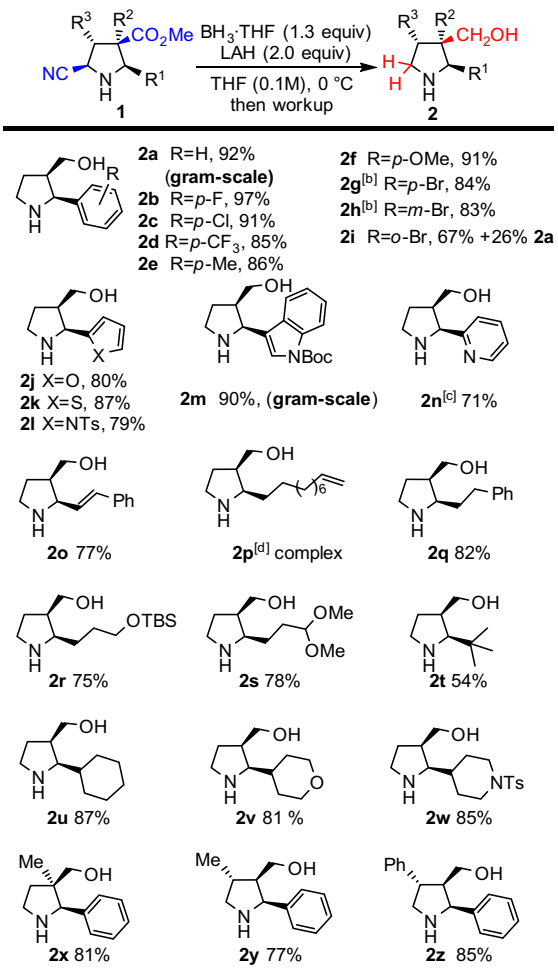
Table 1
Optimization of Reaction Conditions.[a]



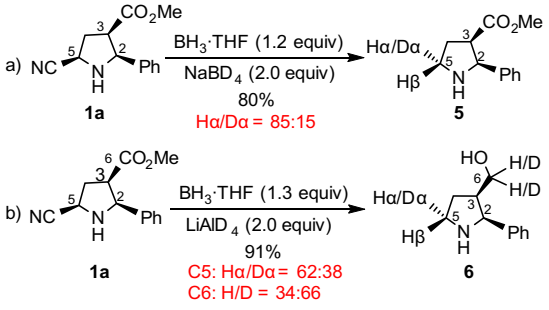
Entry	Reductants(equiv)	T(°C)	Yield%[b]	t(h)
1	LAH (2.0)	0	48% (**2a**), 49% (**3**)	1
2	DIBAL-H (2.2)	−78	51% (**4**)	6
3	DIBAL-H (5.0)	0 → 25	20% (**2a**), 64% (**3**)	3
4	BH_3 (1.2), $NaBH_4$ (0.2), workup; then LAH (2.0)[d]	0	86% (**2a**)[c]	–
5	BH_3 (1.2), $NaBH_4$ (0.2), then LAH (2.0)	25 → 0	93% (**2a**)[c]	3
6	BH_3 (1.3), DIBAL-H (5.0)	0 → 25	33% (**2a**), 31% (**3**)	5
7	BH_3 (1.3), LAH (2.0)	0	92% (**2a**)[c]	1

[a] Reactions were performed with 1.0 mmol of **1a** in 10 mL of THF (0.1 M). The reactions of entries 4–7 were quenched with aqueous NaOH (20%) and crude products was later treated with Pd/C (10 wt%) in methanol.
[b] NMR yield with triphenylmethane as an internal standard.
[c] Isolated yield.
[d] Through a stepwise manner. BH_3 refers to BH_3·THF. DIBAL-H = diisobutyl aluminum hydride, LAH = lithium aluminum hydride.

Table 2
Substrate Scope for Two-Step Synthesis of β-Prolinols.[a]



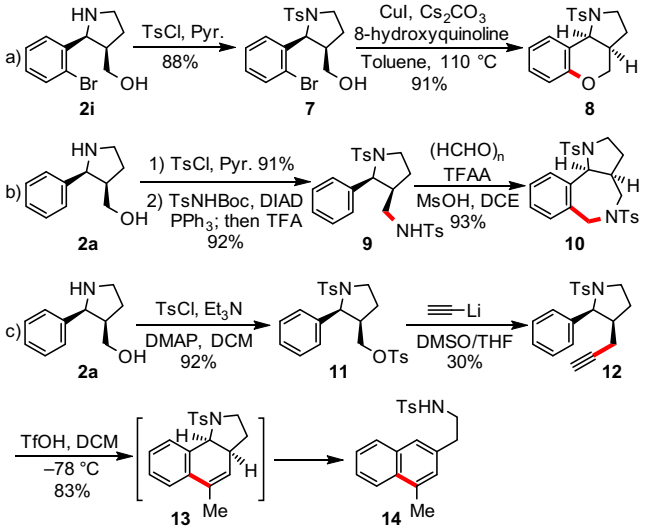
[a] Unless otherwise noted, all reactions were performed with the standard procedure; isolated yields are reported.
[b] A tiny amount (around 10%) of **2a** was also isolated.
[c] Column chromatography was necessary before the treatment with Pd/C in methanol.
[d] The amino-borane complex of **2p** could be obtained in 13% yield. Boc = *tert*-butoxycarbonyl, Ts = *p*-toluenesulfonyl, TBS = *tert*-butyldimethylsilyl.



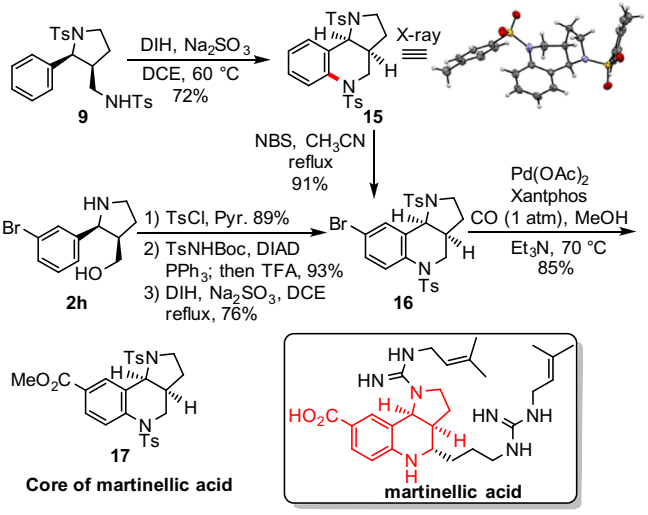
Scheme 2. Determination of the Hydride Source via Deuteration Experiments.

borane was also partially involved in the reduction of the ester group (C6).[23]

To further demonstrate the synthetic value of the β-prolinols obtained through this new two-step protocol, a couple of polyheterocycles were efficiently constructed (Scheme 3). As exemplified with **2i**, copper-catalyzed C—O bond formation[17] after a selective



Scheme 3. Synthesis of Heterotricycles from β-Prolinols.



Scheme 4. Synthesis of the Tricyclic Core of Martinellic Acid.

tosylation of secondary amine allowed the rapid access to the core skeleton (**8**) of a series of acetylcholinesterase inhibitors[6b] (Scheme 3a). Furthermore, Pictet-Spengler cyclization[18] over the tosylated β-prolinamine **9**, which was prepared from β-prolinol **2a** in two steps, afforded tetrahydrobenzazepine **10** in high yield (Scheme 3b). Although an attempt to construct tricyclic compound **13** failed,[19] interestingly, an otherwise difficult-to-make 2-(2-naphthyl)ethylamine derivative **14** was formed probably through a cyclization-elimination/aromatization cascade (Scheme 3c).

Finally, as a showcase of β-prolinols' application in natural product synthesis, the core of martinellic acid[20] was constructed in only four steps from **2h** (53% overall yield), featuring a direct aromatic C—H amination mediated by 1,3-diiodo-5,5-dimethylhydantoin (DIH)[18a,21] and palladium-catalyzed carbonylation[22] (Scheme 4). An alternative route starting from compound **9** was also viable.

Conclusions

In summary, a general two-step synthesis of multisubstituted β-prolinols through a [3+2] cycloaddition of azomethine ylides

and a programmed reduction triggered by the combination of borane and LAH has been developed. The resulting β-prolinols were utilized for the rapid construction of a couple of polyheterocycles, including the core of the martinellic acid. We expect this methodology will find more use in the synthesis of natural products and pharmaceuticals. Further studies on the asymmetric version of this strategy are ongoing in our laboratory.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.11.035.

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