A Stable Synthetic Equivalent of 2,3-Dihydropyridine

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Abstract: We introduce a synthetic procedure of 2,3-dihydropyridine derivative from its stable synthetic equivalent. The synthesis of a chiral 2,3-dihydropyridine derivative in a high yield and the unique mechanism of the unmasking step are described.

Key words: dihydropyridine, synthetic equivalent, enamine, imine, enone

2,3-Dihydropyridine has been implicated as a versatile intermediate in the proposed biosynthesis of alkaloids, highlighted by the biomimetic syntheses of a variety of natural products such as keramaphidin B and manzamine A,[1] as well as intermediates in the reactions of pyridines (Figure 1).[2]

Figure 1 Structures of 2,3-dihydropyridines

The stability of 2,3-dihydropyridine is assured so long as an alkyl or electron-withdrawing group (e.g., acyl) is attached to the nitrogen atom, effectively preventing facile oxidation for aromatization. While N-alkyl 2,3-dihydropyridinium salt is well documented, and even isolable,[1b,c,g] there is scant information on the synthesis and physical properties of an N-unprotected 2,3-dihydropyridine, other than that they are highly unstable.[3] This is surprising, given the potential number of chemical transformations that such an intermediate can provide.

The significance of a 2,3-dihydropyridine intermediate has been proposed in biosynthesis of the marine natural product symbioimine (Figure 2).[4] The intramolecular Diels–Alder reaction of a chiral 2,3-dihydropyridine intermediate followed by isomerization is proposed for construction of the tricyclic imine moiety as shown above. It is an alternative route to the originally proposed biosynthetic pathway via *exo*-Diels–Alder reaction from linear *trans*-enone precursor followed by cyclic imine formation.[5] In previously reported syntheses,[4c,d] the putative chiral 2,3-dihydropyridine was formed in situ from a precursor, followed immediately by an intramolecular Diels–Alder reaction. These Diels–Alder reactions suffered from low yield due to the instability of the intermediate under their respective reaction conditions.

Over the course of our own synthetic studies of symbioimine,[6] we developed a remarkably mild and high-yielding method to produce N-unprotected 2,3-dihydropyridines from a masked synthetic equivalent, for application in the total synthesis. Herein we report the synthesis of a stable synthetic equivalent of 2,3-dihydropyridine and the mechanism of its unique unmasking step.

Our initial approach to 2,3-dihydropyridine necessitated a preexisting *cis*-enone geometry to facilitate the intramolecular imine formation, directly generating the dihydropyridine. Unfortunately, under most N-deprotection conditions, the *cis*-enone is highly susceptible to isomerizing to the more thermodynamically stable *trans*-enone.[7] As a result, the imine formation by intramolecular cyclization was inhibited.

Due to its inherent instability and predisposition to isomerization and oxidation, a mild condition is required to generate 2-alkyl-2,3-dihydropyridine **A** from a precursor (Scheme 1). We designed masked compound **B** as the stable synthetic equivalent. The aza-1,3-diene moiety of **A** is masked by formal 1,4-addition of nucleophile X. The

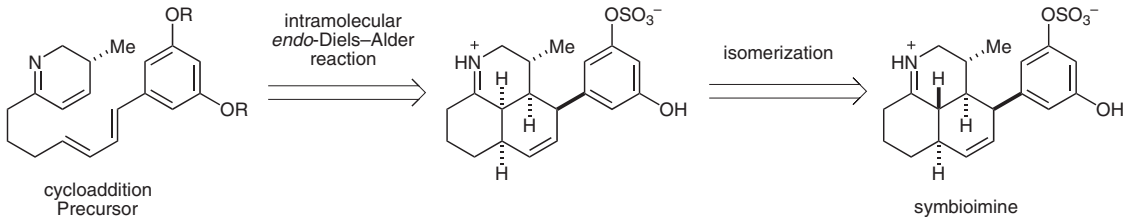

Figure 2 Proposed biosynthetic pathway of symbioimine

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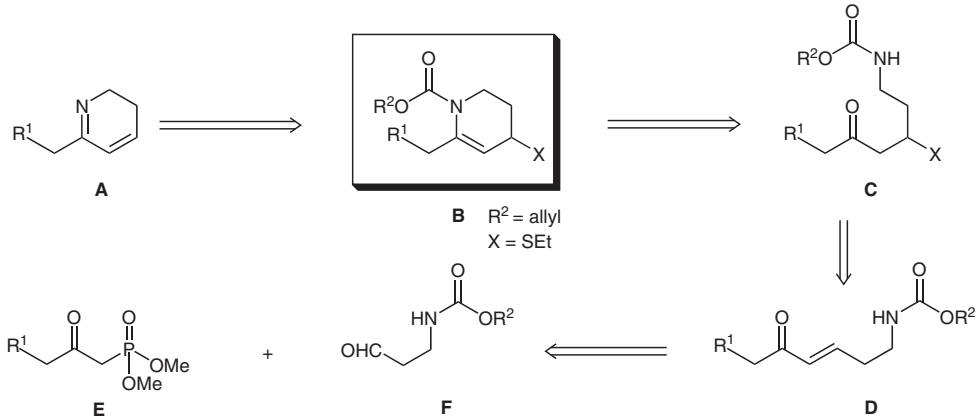


Scheme 1 Design of masked 2,3-dyhydropyridine

deprotection of carbamate **B** will induce a facile elimination of X^- to regenerate the aza-1,3-diene moiety. An appropriate scavenger must trap the resulting X^- immediately, otherwise **A** will react with X^- to form a 1,4-adduct.

We anticipated an alloc group (R^2 = allyl) could be the best candidate for the carbamate **B**, because the eliminated X^- will be scavenged by highly electrophilic Pd–π-allyl complex, concomitantly regenerating Pd(0) for the catalytic cycle. Compound **B** will be formed readily by dehydration of acyclic aminoketone **C**. Ketone **C** will be obtained by 1,4-addition of thiolate (X = SEt) to *trans*-enone **D**, which will be readily formed by condensation of phosphonate **E** and amino aldehyde **F**. It should be noted that a preparation of a chiral 2,3-dihydropyridine would be possible by using chiral aldehyde **F**. For the application to the synthesis of symbiomime, we planned a synthesis of masked compound **2** as a synthetic equivalent of 2,3-dihydropyridine **1** as shown in Figure 3.

The masked 2,3-dihydropyridine **2** was prepared in three steps in good yields as shown in Scheme 2. Beginning from commercially available β-ketophosphonate **3**, a Horner–Wadsworth–Emmons olefination with racemic aldehyde **4** yielded the exclusive *trans*-isomer **5** in very

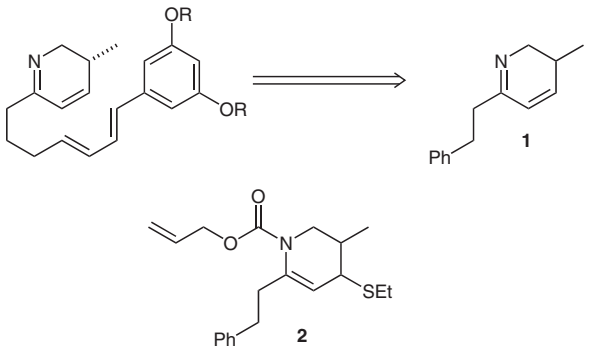
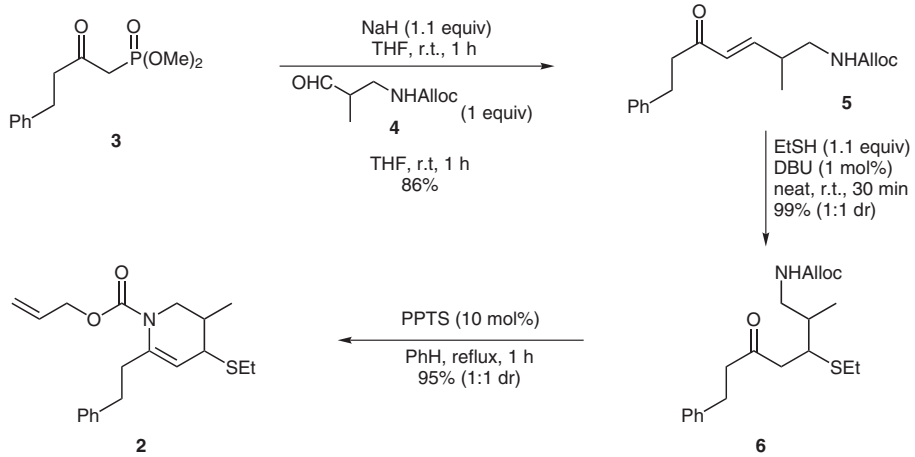


Figure 3 Design of model 2,3-dihydropyridine **1**

good yield. Next, treatment of enone **5** with ethanethiol in the presence of a catalytic amount of DBU under solvent-free conditions gave the conjugate adduct **6** as a 1:1 mixture of diastereomers. Taking the material directly on to the subsequent cyclodehydration step without purification, treatment with 10 mol% of PPTS under dilute refluxing benzene yielded the masked 2,3-dihydropyrdine **2** as a single regioisomer for an enanine moiety in excellent yield.[8]

The inherent reactivity of the 2,3-dihydropyridine suggests that of the many protecting groups for amine com-



Scheme 2 Synthesis of the masked 2,3-dihydropyridine **2**

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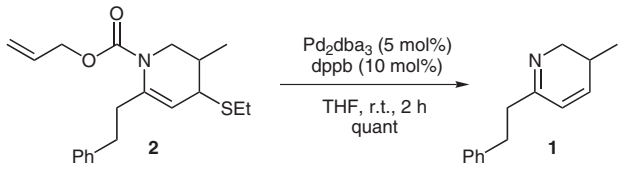
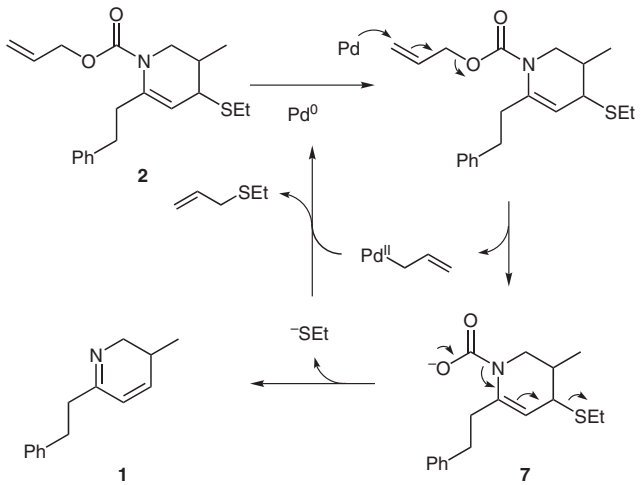
monly in use today, not all deprotection conditions are created equal. A brief survey of the more common protecting groups found that the deprotection conditions of allyloxy carbonyl (alloc) group of **2** were sufficiently mild to produce the desired product, and depending on the concentration (0.5 M), allowed the palladium loading to be dropped to an effective 2.5 mol% (Scheme 3) to yield the stable (>48 h at 25 °C in $CDCl_3$) 2,3-dihydropyrdine **1**.[9] It was found that dihydropyridine **1** decomposes upon purification with silica, but that catalyst removal via Celite filtration and subsequent high-vacuum drying to remove allyl ethyl sulfide yielded the desired product essentially free of impurities as shown in Scheme 2.



Scheme 3 Unmasking the 2,3-dihydropyridine equivalent **2**

The unmasking step of **2** to obtain **1** is quite unique, because of the reaction mechanism (Scheme 4). The alloc deprotection begins by the nucleophilic attack of Pd(0) on the allyl carbamate of the masked 2,3-dihydropyridine **2**, generating the Pd–π-allyl complex and carbamic acid **7**, which spontaneously undergoes decarboxylation. The resulting enamine induces an elimination of ethanethiolate to form **1**. There is no need for the addition of an external nucleophile (such as diethylamine, pyrrolidine, or dimedone) to intercept the Pd–π-allyl system and regenerate Pd(0) for the catalytic cycle. Instead, the extruded ethanethiolate can serve in this capacity as well as help avoiding an unwanted formation of conjugate adducts of **1**. Dihydropyridine **1** is a racemic mixture, but the enantiomerically pure form will be obtained by this procedure starting from a single enantiomer of **4**.



Scheme 4 Mechanism of Pd(0)-catalyzed unmasking step to generate 2,3-dihydropyridine

In this letter, we have shown that synthesis of a stable synthetic equivalent of 2,3-dihydropyridine and a unique mechanism in the unmasking step. The masked 2,3-dihydropyridine **2** was obtained via a high yielding three-step process from a *trans*-enone. In the unmasking step, the thiol served to regenerate the catalyst by intercepting the Pd-π-allyl intermediate. The 2,3-dihydropyridine **1** generated by this strategy has direct applications as a biomimetic intermediate in the synthesis of several classes of alkaloid natural products. Utilization of this methodology in the total synthesis of symbioimine will be reported in due course.

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(7) Under thermal (>100 °C), Brønsted/Lewis acid (TfOH, TFA, CSA–TsOH, BF_3·OEt, $MeAlCl_2$, Et_2AlCl, $EtAlCl_2$, etc.), basic (NaOEt, NaOH, LDA, etc.), or nucleophilic conditions (dimedone, piperidine, NaSEt, etc.).

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(8) **Experimental Procedure for Preparation of Compound 2**
To a 50 mL round-bottom flask at 25 °C was added **6** (1.23 g, 3.38 mmol) and benzene (34 mL). Pyridinium *p*-toluenesulfonate (PPTS, 85 mg, 0.34 mmol, 10 mol%) was then added and the solution allowed stirring under reflux while monitoring by TLC. After 1 h, the reaction was quenched by the addition of sat. $NaHCO_3$, and separated. The aqueous layer was extracted twice with EtOAc, the combined organics washed with brine, and dried over Na_2SO_4. Concentration in vacuo yielded crude material which was then purified on SiO_2 (hexane–EtOAc, 5:1) to yield compound **2** (1:1 mixture of diastereomers **2** and **2′**, 1.07 g, 95%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.20 (m, 2 H and 2 H′), 7.18–7.08 (m, 3 H and 3 H′), 6.00–5.90 (m, 1 H and 1 H′), 5.32 (d, *J* = 17.2 Hz, 1 H and 1 H′), 5.23 (d, *J* = 10.0 Hz, 1 H and 1 H′), 4.95 (d, *J* = 4.4 Hz, 1 H), 4.90 (d, *J* = 3.6 Hz, 1 H′), 4.63 (d, *J* = 5.6 Hz, 2 H and 2 H′), 3.73 (dd, *J* = 2.4, 12.8 Hz, 1 H), 3.67 (dd, *J* = 2.8, 12.8 Hz, 1 H′), 3.34 (dd, *J* = 7.2, 12.8 Hz, 1 H′), 3.31 (app. t, *J* = 4.8 Hz, 1 H′), 3.14 (dd, *J* = 9.2, 12.4 Hz, 1 H), 2.99 (m, 1 H), 2.89–2.65 (m, 4 H and 4 H′), 2.45 (q, *J* = 7.6 Hz, 2 H), 2.43 (q, *J* = 7.2 Hz, 2 H′), 2.14–2.10 (m, 1 H), 1.95–1.90 (m, 1 H′), 1.20 (t, *J* = 7.2 Hz, 3 H′), 1.18 (t, *J* = 7.2 Hz, 3 H), 1.06 (d, *J* = 6.8 Hz, 3 H), 0.99 (d, *J* = 6.8 Hz, 3 H′). ^{3}C NMR (100 MHz, $CDCl_3$): δ = 154.0 (C and C′), 141.5 (C′), 141.5, 139.9, 138.8 (C′), 132.5 (C and C′), 128.5 (2C′), 128.5 (2C), 128.2 (2 C and 2 C′), 125.8 (C and C′), 118.1 (C and C′), 112.7 (C and C′), 66.42 (C′), 66.38, 49.0, 48.5 (C′), 45.7, 45.1 (C′), 37.0 (C′), 36.8, 34.7 (C′), 34.4, 33.5 (C′), 26.5 (C′), 24.0, 16.9, 15.2 (C′), 14.89 (C′), 14.85. HRMS: *m/z* calcd for $C_{20}H_{27}NO_2S$: 345.1757; found: 345.1755.

(9) **Experimental Procedure for Preparation of Compound 1**
To a 10 mL round-bottom flask at 25 °C was added **2** (70 mg, 0.20 mmol) in THF (0.4 mL), and placed under a blanket of nitrogen. Then, $Pd_2dba_3{\cdot}CHCl_3$ (5.2 mg, 0.005 mmol, 5 mol%) and 1,4-bis(diphenylphosphino)butane (dppb, 8.6 mg, 0.020 mmol, 10 mol%) were added and the solution allowed stirring while monitoring by TLC. Upon completion after 2 h, the solution was diluted with THF, filtered over Celite, and concentrated in vacuo to yield compound **1** as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.23 (m, 2 H), 7.20–7.14 (m, 3 H), 6.21 (dd, *J* = 3.5, 9.5 Hz, 1 H), 5.86 (dd, *J* = 2.5, 10.0 Hz, 1 H), 3.66 (dd, *J* = 7.0, 15.5 Hz, 1 H), 3.16 (dd, *J* = 12.0, 16.0 Hz, 1 H), 2.86 (t, *J* = 7.5 Hz, 2 H), 2.56 (t, *J* = 8.5 Hz, 2 H), 2.27 (m, 1 H), 0.98 (d, *J* = 7.5 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 142.7, 141.5, 128.6 (2 C), 128.3 (2 C), 125.9, 121.7, 53.4, 35.7, 32.6, 30.4, 17.3. HRMS: *m/z* calcd for $C_{14}H_{19}N$: 199.1356; found: 199.1357.

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