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A one-pot assembly of 4-allyl-3-pyridinecarboxaldehyde. A new synthesis of 1-methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*f*]pyrindine, an annulated nicotine analogue

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Abstract—This paper describes a two-step synthesis of 1-methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*f*]pyrindine, a conformationally constrained nicotine analogue. The target molecule was effectively assembled by an intramolecular azomethine ylide-alkene [3+2] cycloaddition. The cyclization precursor, 4-allyl-3-pyridinecarboxaldehyde, was formed efficaciously in a single step from 3-pyridinecarboxaldehyde via sequential in situ protection, *ortho* lithiation, cuprate formation, allylation, and deprotection. The cuprate formation plays a vital role in minimizing/eliminating the extent of multiple alkylation.

1. Introduction

(−)-Nicotine (**1**, Fig. 1), an alkaloid present in tobacco at 0.2–5% levels, targets and activates nicotinic acetylcholine receptors (nAChRs).[1] The nAChRs provide ligand-gated ion channels in the human brain and participate in various biological processes related to numerous nervous system disorders.[2] Due to the therapeutic potential of (−)-nicotine for central nervous system (CNS) disorders such as Alzheimer's, Parkinson's, and Tourette's diseases, nicotine analogues have received much attention from both synthetic and medicinal chemists.[2] In particular, conformationally constrained nicotinoids have become attractive candidates for new selective nAChRs-targeting ligands.[2a,3,4] On one hand, this is because of the discovery of epibatidine, an alkaloid with a rigid structure, which displays strong activity despite of its toxicity.[5] On the other hand, molecular modeling studies have demonstrated that the two heterocyclic rings of nicotine are skewed and approximately perpendicular to one another to secure low energy conformations.[3,6]

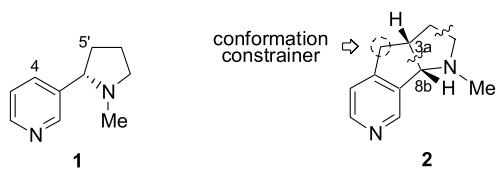

Figure 1.

Our laboratory has been fascinated in the chemistry of nicotine analogues aimed to develop new selective nAChRs-targeting ligands. A tricyclic nicotine analogue, 1-methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*f*]pyrindine (**2**, Fig. 1), was previously designed and synthesized in six steps from 3-bromopyridine.[4b] The conformational rigidity of **2** was achieved as a result of a methylene bridge erected between C-4 and C-5′ of nicotine (**1**).

2. Results and discussion

Herein we wish to report a new synthesis of **2** with high efficiency, featuring the construction of the hexahydropyrrolo[3,2-*f*]pyrindine tricyclic framework via intramolecular azomethine ylide-alkene [3+2] cycloaddition.[4b,7] The apparent precursor for the cycloaddition would be 4-allyl-3-pyridinecarboxaldehyde (**3**, Fig. 2), whose efficient synthesis itself represents one of the challenges for the current project. In principle, aldehyde **3** might be obtainable from 4-allyl-3-bromopyridine (**4**) by sequential treatment with BuLi and *N*,*N*-dimethylformamide (DMF). Alkene **4** was reportedly[8] synthesized from 3-bromopyridine in only

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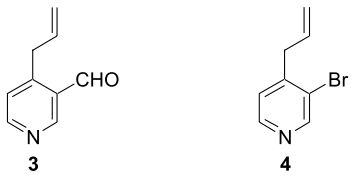
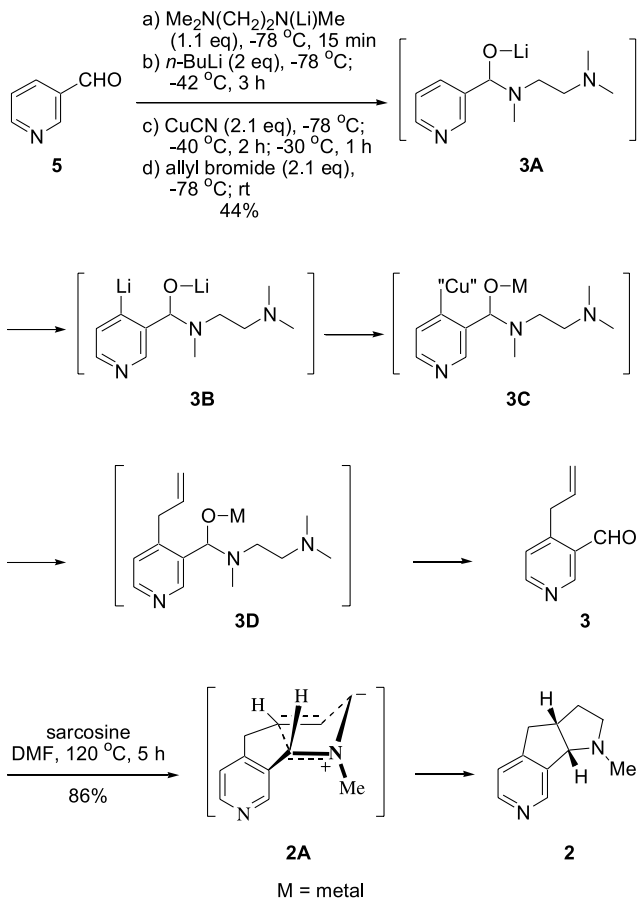


Figure 2.

40% yield. The unsatisfactory yield for this transformation resulted mainly from the further alkylatability because of the enhanced acidity of the benzylic hydrogens. By the same token, the conversion of **4** to **3** could not be a clean reaction.

Ortho lithiation of aromatic aldehydes with prior in situ aldehyde protection, first introduced by Comins and co-workers,[9] has proved to be a convenient and versatile technique having considerable potential in organic synthesis.[10] We envisaged that this protocol might be modified to synthesize enal **3** by a one-pot reaction from 3-pyridinecarboxaldehyde (**5**, Scheme 1). Indeed, the desired 4-allyl-3-pyridinecarboxaldehyde **3** was afforded when aldehyde **5** was protected in situ with LTMDA [$Me_2N(CH_2)_2N(Li)Me$, prepared by mixing *N*,*N*,*N*′-trimethylethylenediamine and *n*-BuLi], *ortho* lithiated with *n*-BuLi, converted to a high-order cuprate with CuCN, alkylated with allyl bromide, and finally hydrolyzed. The yield for this step was 44%, which amounted to an average yield of 85% for each of the five operations (**3A**–**3D** were the four plausible intermediates). We have not been able to further optimize this reaction so far. However, the current protocol should be acceptable considering the fact that such a useful intermediate as **3** can be assembled in a one-pot fashion. The absence of CuCN resulted simply in a complex reaction mixture because **3D** (an 4-allylpyridine derivative) was prone to further allylation due to the presence of the highly acidic benzylic/allylic hydrogens. Replacement of CuCN with CuBr led to less satisfactory results.



Scheme 1.

Having the enal in hand set the stage for intramolecular azomethine ylide-alkene [3+2] cycloaddition.[7] Treatment[4b] of **3** with sarcosine (120 mol%) in DMF at 120 °C for 5 h effected the desired cycloaddition (see the transition state **2A**) to produce in 86% yield the tricycle **2**, an annulated nicotine analogue. The spectroscopic data of the sample were in accord with those reported previously.[4b] Currently pharmacological studies of **2** are under way.

3. Conclusion

In summary, a two-step synthesis of 1-methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*f*]pyrindine (**2**), a conformationally constrained nicotine analogue, has been accomplished. The target molecule was effectively assembled by an intramolecular azomethine ylide-alkene [3+2] cycloaddition. The cyclization precursor, 4-allyl-3-pyridinecarboxaldehyde (**3**), was formed efficaciously in a single step from 3-pyridinecarboxaldehyde (**5**) via sequential in situ protection, *ortho* lithiation, cuprate formation, allylation, and deprotection. The cuprate formation plays a vital role in minimizing/eliminating the extent of multiple alkylation.

4. Experimental

4.1. General

NMR spectra were recorded in $CDCl_3$ (^1H at 300 MHz and ^{13}C at 75.47 MHz), using TMS as the internal standard when appropriate. Column chromatography was performed on silica gel. THF were distilled over sodium benzophenone ketyl under N_2 prior to use. DMF was distilled over calcium hydride under N_2 prior to use.

4.1.1. 4-Allyl-3-pyridinecarboxaldehyde (3). *n*-BuLi (2.08 M, 5.6 mL, 12 mmol) was added to a stirred solution of *N*,*N*,*N*′-trimethylethylenediamine (1.62 mL, 12.5 mmol) in THF (40 mL) at −78 °C. After 15 min, 3-pyridinecarboxaldehyde (1.0 mL, 10.6 mmol) was added at −78 °C, and the stirring was continued for 15 min. *n*-BuLi (2.08 M, 10 mL, 21 mmol) was added at −78 °C and the stirring was continued at −42 °C for 3 h. After cooling to −78 °C, CuCN (1.99 g, 22.2 mmol) was added as a solid and the temperature was maintained at −40 °C for 2 h and then at −30 °C for 1 h. After cooling to −78 °C, a solution of allyl bromide (1.9 mL, 22 mmol) in THF (10 mL) was added at −78 °C. The reaction mixture was allowed to warm to rt, diluted with saturated aqueous Na_2SO_3 and saturated aqueous $NaHCO_3$, and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column

chromatography to afford **3** (686 mg, 44%) as a colorless oil: FT-IR (KBr, cm^{-1}): 2861, 2754, 1702, 1639, 1592, 1556, 1489, 1400, 1222, 1058, 997, 923, 839, 735, 690, 658; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.73 (d, 2H, J=5.2 Hz), 4.97 (dd, 1H, J=17.2, 2.8 Hz), 5.06 (dd, 1H, J=10.5, 2.7 Hz), 5.81–5.96 (m, 1H), 7.18 (d, 1H, J=4.8 Hz), 8.58 (d, 1H, J=4.8 Hz), 8.87 (s, 1H), 10.17 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.9, 117.7, 125.2, 129.0, 134.3, 150.5, 153.6, 153.7, 191.2; MS (EI): 147 (M^+, 30), 146 (M−1, 100); HRMS (EI) calcd for C_9H_9NO, 147.0684, found 147.0687.

4.1.2. 1-Methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*f*]pyrindine (2). A mixture of aldehyde **3** (686 mg, 4.66 mmol) and sarcosine (495 mg, 5.56 mmol) in DMF (40 mL) was heated under N_2 at 120 °C for 5 h, cooled to rt, and concentrated in vacuo. The residue was diluted with saturated aqueous $NaHCO_3$ solution and extracted with isopropanol/$CHCl_3$ (1/3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (SiO_2, CH_2Cl_2–MeOH, 40/1) to give **2** (700 mg, 86%) as a pale yellow oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.62–1.74 (m, 1H), 2.15–2.25 (m, 1H), 2.44–2.55 (m, 1H), 2.55 (s, 3H), 2.77–2.86 (m, 1H), 2.99–3.21 (m, 3H), 3.80 (d, J=7.6 Hz, 1H), 7.13 (d, J=5.2 Hz, 1H), 8.42 (d, J=5.2 Hz, 1H), 8.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.23, 39.23, 40.50, 41.92, 57.59, 73.45, 120.34, 139.25, 145.78, 148.34, 152.95. MS (EI): 174 (M^+). Anal. calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.69; H, 7.84; N, 16.38.

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