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A Facile Synthesis of *cis*-1-Methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*f*]pyrindine, an Annulated Nicotine Analog

Hongbin Zhai,*,† Peng Liu,† Shengjun Luo,† Fang Fang,† and Mingyue Zhao‡

Laboratory of Modern Synthetic Organic Chemistry and State Key Laboratory of Bio-Organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, China 200032, and Zhengzhou Tobacco Research Institute, Zhengzhou, Henan, China 450000

zhaih@pub.sioc.ac.cn

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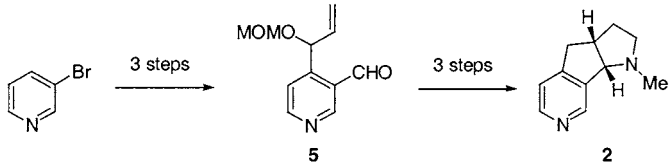
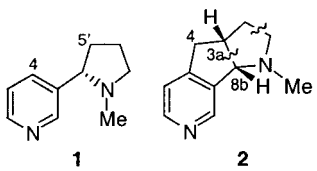
ABSTRACT



The title compound, 2, has been synthesized in 45% overall yield in six steps from 3-bromopyridine. The hexahydropyrrolo[3,2-*f*]pyrindine skeleton was constructed from key intermediate 5, via intramolecular azomethine ylide-alkene [3 + 2] cycloaddition. The present work constitutes a general method for rapid assembly of other related tricyclic nicotine analogues.

Nicotinic acetylcholine receptors (nAChRs) are a family of ligand-gated ion channels widely distributed in the human brain. These receptors participate in various biological processes related to numerous nervous system disorders.[1] Owing to its ability to target and activate nAChRs, (−)-nicotine (**1**, Scheme 1), a well-known alkaloid present in tobacco, has been observed to show favorable effects on patients with Alzheimer's, Parkinson's, and Tourette's disease.[2] Hence, design, synthesis, and biological evaluation of nicotine analogues has spurred considerable attention over the past decades. In particular, conformationally restricted nicotinoids have become attractive candidates for new selective nAChRs-targeting ligands.[2a,3,4] Instructively, epibatidine, an alkaloid discovered in 1992, has a rigid structure and displays strong activity despite of its toxicity.[5] Molecular modeling studies have demonstrated that the two heterocyclic

Scheme 1



† Shanghai Institute of Organic Chemistry.
‡ Zhengzhou Tobacco Research Institute.

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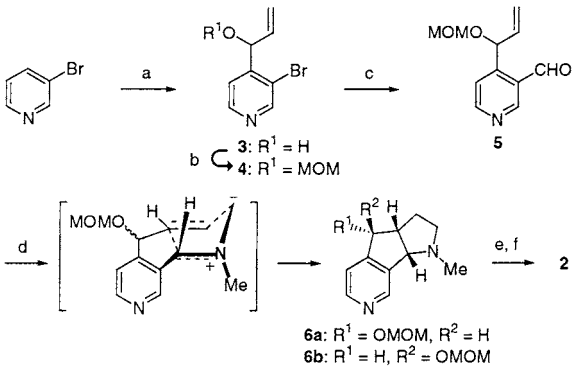
Scheme 2 [a]



[a] Conditions: (a) LDA (138 mol%), THF, −90 °C; acrolein (177 mol%), THF, −90 °C, 75%; (b) NaH (150 mol%), THF, 10−20 °C; MOMCl (130 mol %), THF, rt, 3 h, 92%; (c) BuLi (120 mol %), THF, −78 °C, 1 h; DMF (147 mol %), THF, −78 °C, 1 h, 92%; (d) sarcosine (105 mol %), DMF, 100−110 °C, 6 h, 84% (**6a**:**6b** = 1.37:1); (e) 4 M HCl (1400 mol %), 50−60 °C, 8 h; (f) Zn (740 mol %), HCO_2H, reflux, 25 h, 84% (two steps).

rings of nicotine are skewed and approximately perpendicular to one another to secure low-energy conformations.[3,6]

In connection with our efforts to develop new selective ligands targeting nAChRs, *cis*-1-methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,2-*f*]pyrindine (**2**, Scheme 1) has been designed and pursued as a novel nicotine analogue. The conformation of **2** is rigidified by a methylene bridge erected between C-4 and C-5′ of nicotine (**1**).

Herein we wish to report a concise synthesis of **2**, featuring highly efficient construction of the hexahydropyrrolo[3,2-*f*]-pyrindine tricyclic framework via intramolecular azomethine ylide-alkene [3 + 2] cycloaddition,[7] which required an appropriately functionalized enal. After preliminary exploration, we settled on a synthetic plan for **2**, as depicted in Scheme 2. Ortho lithiation[8] of 3-bromopyridine with LDA at −90 °C[9] followed by treatment with acrolein at the same temperature furnished alcohol **3** in good yield (75%). Alcohol **3** was protected as ether **4** by exposure to MOMCl in the presence of NaH.[10] Use of a slight excess of base, compared to MOMCl, was found to be effective in preventing the formation of the rearranged enol ether byproducts. Formylation[11] of **4** (BuLi, −78 °C; DMF, −78 °C) led conveniently to aldehyde **5**[12] in 92% yield, setting the stage for intramolecular azomethine ylide-alkene [3 + 2] cycloaddition.[7] After extensive experimentation, we found that treatment of **5** with sarcosine in DMF at 100−110 °C for 6 h effected the desired cycloaddition to give two isomers **6a**/**6b** in a combined yield of 84% and in a diastereomeric ratio of 1.37:1 (deduced from ^{1}H NMR integrals). The structures of **6a** and **6b** were assigned on the basis of the coupling constants for the hydrogen atoms at C-4 (J = 8.1 and 4.5 Hz, respectively). Finally, deprotection[13] of a **6a**/**6b** mixture (4 M HCl, 50−60 °C) followed by zinc-mediated reductive dehydroxylation[14] (Zn, formic acid, reflux) afforded **2**[15] in 84% overall yield for the two steps.

In conclusion, a highly efficient synthesis of **2**, an annulated nicotine analogue, has been accomplished in six steps starting from 3-bromopyridine. Intramolecular azomethine ylide-alkene [3 + 2] cycloaddition proved feasible in construction of the hexahydropyrrolo[3,2-*f*]pyrindine tricyclic framework. The present work constitutes a general method for rapid synthesis of a number of nicotine analogues with similar structures.

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Supporting Information Available: Experimental procedures and characterization data for new compounds as well as a copy of the ^{1}H NMR spectrum of aldehyde **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) **5**: Pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.34 (s, 3H), 4.63 (d, J = 6.6 Hz, 1H), 4.79 (d, J = 6.6 Hz, 1H), 5.22−5.42 (m, 2H), 5.86−5.98 (m, 2H), 7.64 (d, J = 5.2 Hz, 1H), 8.80 (d, J = 5.2 Hz, 1H), 9.01 (s, 1H), 10.31 (s, 1H). MS (EI) 207 (M^+).

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(15) **2**: Pale yellow oil. ^{1}H 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.