Published in final edited form as:

Tetrahedron Lett. 2011 May 25; 52(21): 2667–2669. doi:10.1016/j.tetlet.2011.03.065.

Expeditious synthesis of *cis*-1-methyl-2, 3,3*a*,4,5,9*b*-hexahydro-1*H*-pyrrolo-[3,2*h*]isoquinoline / [2,3-*f*]quinoline via azomethine ylide-alkene [3+2] cycloaddition

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Abstract

Expeditious syntheses of *cis*-1-methyl-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-pyrrolo-[3,2*h*]isoquinoline / [2,3-*f*]quinoline have been developed. The syntheses started with commercially available material and afforded excellent overall yields in straightforward steps. Intramolecular azomethine ylide-alkene [3+2] cycloaddition is the key step in the construction of these pyrroloisoquinoline and pyrroloquinoline scaffolds. This route is much more atom-economic than those reported in the literature and appropriate for scale-up synthesis.

Keywords

Azomethine ylide; [3+2] cycloaddition; Nicotine analog synthesis

Structural modification of the nicotine molecule provided many novel potent and drugable nicotinic acetylcholine receptor (nAChR) ligands in CNS drug discovery.¹ In light of this strategy, conformationally restrained analogs of nicotine have attracted much attention among medicinal chemists.² In this regard, compounds based on two scaffolds: *cis*-1-methyl-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-pyrrolo [3,2-*h*] isoquinoline (**1**, figure 1) and *cis*-1-methyl-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-pyrrolo [2,3-*f*]quinoline (**3**),³ which were designed to mimic the two isoenergetic conformers of nicotine that are believed to be present in aqueous solution,⁴ demonstrated considerable potential. Compound **1** may represent a new class of analgesic because of its unique pharmacological profile⁵ and, **SIB-1663** (**2**) has been established to have distinctive nAChR subtype selectivity.⁶ Additionally, haptens **4** and **5** (figure 1), which have the scaffold of **1** and **3** respectively, yielded enhanced immune response as demonstrated in a new strategy for the development of nicotine vaccines.⁷ Thus, an expeditious synthetic pathway to the scaffolds **1** and **3** would have important value in the CNS drug discovery area. Herein we report a new approach for the efficient construction of **1** and **3**, which will be much more viable for scale-up synthesis.

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Supplementary Material

Experimental procedures and spectroscopic data for all intermediates and final products are included in the supplementary material.

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For the synthesis of compound **1**, the original route has been followed for two decades,⁸ which resorts to the key intermediate 6,7-dihydro-8(5*H*)-isoquinolinone (**6**, Scheme 1). However, the approaches related to the preparation of **6** involved either harsh conditions, tedious isolation or/and rare precursors that are laborious to prepare, and additionally, all these approaches afforded relatively poor overall yields of the desired intermediate **6** and eventually product **1**. The same strategy has also been employed for the synthesis of **3** starting from the corresponding isomer **8** with similar overall yield.

An alternative route to the synthesis of compound **1** has been reported recently utilizing Diels-Alder chemistry for the construction of the central 6-membered ring system.⁹ Unfortunately, the key step proceeds only when multiple functional groups are present on specific positions of the precursor molecule **7** (scheme 1). Obviously these particular requirements, as well as the reported low yields, substantially limit the scope and utilization of this synthetic approach.

As a valuable strategy, azomethine ylide-alkene [3+2] cycloaddition constitutes an efficient method for the construction of a pyrrolidine ring. This synthetic approach has been widely employed for the synthesis of many biologically active molecules.¹⁰ Utilizing this strategy, we have synthesized **1** in our earlier research (scheme 2).¹¹ We envisaged that this approach may serve as a good starting point for the development of new efficient synthetic route to **1** and **3**.

Upon close analysis of the route in scheme 2, it is realized that the stepwise introduction of the ene-containing side chain to the 4-position of 3-bromopyridine (**9**) left a hydroxyl group in the resulting molecule **11**. This hydroxyl group has to be protected (as **12**) for the next step, i.e. Li-bromo exchange, to proceed smoothly.¹² And eventually, the protecting MOM group has to be removed (as **15**) and the exposed hydroxyl group reduced to furnish the final product **1**. Obviously the introduction of the hydroxyl group in **11** necessitated a few manipulations on the functional group that is not present in the final molecule, which largely depreciated the atom-economy for the whole process. Thus we developed a new synthetic route to **1** as illustrated in Scheme 3.

Taking advantage of the acidity of the methyl proton in commercially available compound 3-bromo-4-methylpyridine (**16**), we chose this as our starting material. Thus, **16** was treated with LDA and allylbromide at -78 °C to afford 3-bromo-4-(but-3-en-1-yl)pyridine (**17**) in excellent yield (92 %). The resulting **17** was subjected to bromine-lithium exchange with *n*-BuLi at -78 °C followed by formylation to furnish the corresponding aldehyde **18** (87 % yield). The key intermediate **18** sets the stage for intramolecular azomethine ylide-alkene [3+2] cycloaddition. Accordingly, when the mixture of **18** and sarcosine in DMF was heated at 110 °C for 4 h, the cycloadduct **1** was obtained in excellent yield (86 %). The ¹H and ¹³C NMR spectrum of **1** were identical to that of an authentic sample prepared in this group previously following the route depicted in scheme 2¹¹ or the route of Glassco et al,^{3, 13} who had established the *cis*-geometry of **1** through X-ray analysis. Only the *cis*-isomer was detected as the product of the intramolecular ylide-alkene [3+2] cycloaddition. This result is consistent with the observations of other groups.¹⁴

Obviously, this route for the synthesis of **1** is much more expeditious than those reported in the literature as illustrated in Scheme 1 and Scheme 2. It starts from commercially available material and affords an excellent overall yield of 69 % in 3 straightforward steps. From an atom-economy point of view, this is a very efficient process for the synthesis of **1**, and affords a more appropriate process for scale-up synthesis.

Furthermore, we discovered that this route can be easily adapted for the synthesis of compound **3** (Scheme 4). Following the same process as that illustrated in Scheme 3 for the synthesis of **1**, the desired product **3** was very conveniently prepared in 3 steps from 3-bromo-2-picoline (**19**¹⁵). The ¹H and ¹³C NMR spectrum of the resulting **3** were also identical to that of an authentic sample prepared previously following the synthetic route of Glassco et al.¹³ Apparently, the current route is also significantly more efficient than the reported method for the synthesis of compound **3**.⁸

In conclusion, expeditious syntheses of *cis*-1-methyl-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-pyrrolo[3,2-*h*]iso-quinoline (**1**) and *cis*-1-methyl-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-pyrrolo-[2,3-*f*]quinoline (**3**) have been established utilizing intramolecular azomethine ylide-alkene [3+2] cycloaddition. For the synthesis of **1** and **3**, this route is considerably more efficient than previously reported routes. It provides a viable route for large scale production of such molecules, which is important for subsequent preclinical development as therapeutic agents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by a grant from the National Institutes of Health (U19DA017548, 2002–2007). We thank the University of Kentucky Mass Spectrometry Facility for providing high resolution mass spectral data for the compounds in this study.

References and notes

- (a) Taylor P, Talley TT, Radic Z, Hansen SB, Hibbs RE, Shi J. *Biochem Pharmacol*. 2007; 74:1164–1171. [PubMed: 17826748] (b) Soudijn W, van Wijngaarden I, Ijzerman AP. *Med Res Rev*. 2007; 27:417–433. [PubMed: 17238156] (c) Bunnelle WH, Dart MJ, Schrimpf MR. *Curr Topics Med Chem (Sharjah, United Arab Emirates)*. 2004; 4:299–334. (d) Astles PC, Baker SR, Boot JR, Broad LM, Dell CP, Keenan M. *Curr Drug Targets: CNS & Neurol Disorders*. 2002; 1:337–348.
- (a) Ullrich T, Krich S, Binder D, Mereiter K, Anderson DJ, Meyer MD, Pyerin M. *J Med Chem*. 2002; 45:4047–4054. [PubMed: 12190326] (b) Ji J, Schrimpf MR, Sippy KB, Bunnelle WH, Li T, Anderson DJ, Faltynek C, Surowy CS, Dyhring T, Ahring PK, Meyer MD. *J Med Chem*. 2007; 50:5493–5508. [PubMed: 17929796] (c) Bunnelle WH, Daanen JF, Ryther KB, Schrimpf MR, Dart MJ, Gelain A, Meyer MD, Frost JM, Anderson DJ, Buckley M, Curzon P, Cao Y, Puttfarcken P, Searle X, Ji J, Putman CB, Surowy C, Toma L, Barlocco D. *J Med Chem*. 2007; 50:3627–3644. [PubMed: 17585748] (d) Lennox JR, Turner SC, Rapoport H. *J Org Chem*. 2001; 66:7078–7083. [PubMed: 11597233]
- Glassco W, Suchocki J, George C, Martin BR, May EL. *J Med Chem*. 1993; 36:3381–3385. [PubMed: 8230128]
- Elmore DE, Dougherty DA. *J Org Chem*. 2000; 65:742–747. [PubMed: 10814006]
- Damaj MI, Glassco W, Marks MJ, Slobe B, James JR, May EL, Rosecrans JA, Collins AC, Martin BR. *J Pharmacol Exp Ther*. 1997; 282:1425–1434. [PubMed: 9316856]
- Rao TS, Sacca AI, Menzaghi FM, Reid RT, Adams PB, Correa LD, Whelan KT, Vernier JM. *Brain Res*. 2004; 1003:42–53. [PubMed: 15019562]
- (a) Cerny EH, Cerny T. *Expert Opin Invest Drugs*. 2008; 17(5):691–696. (b) Meijer MM, Matsushita M, Altobelli LJ, Wirsching P, Janda KD. *J Am Chem Soc*. 2003; 125:7164–7165. [PubMed: 12797775]
- (a) Chavdarian CG, Seeman JJ, Wooten JB. *J Org Chem*. 1983; 48:492–494. (b) Glassco W, Suchocki J, George C, Martin BR, May EL. *J Med Chem*. 1993; 36:3381–3390. [PubMed: 8230128] (c) Dickerson, Tobin J.; Lovell, T.; Meijler, MM.; Noodleman, L.; Janda, KD. *J Org Chem*. 2004; 69:6603–6609. [PubMed: 15387581]

9. (a) Sarkar TK, Basak S, Wainer I, Moaddel R, Yamaguchi R, Jozwiak K, Chen HT, Lin CC. *J Med Chem.* 2004; 47:6691. [PubMed: 15615518] (b) Sarkar TK, Basak S, Ghosh SK. *Tetrahedron Lett.* 2000; 41:759–762. (c) Sarkar TK, Basak S, Slanina Z, Chow TJ. *J Org Chem.* 2003; 68:4206–4214. [PubMed: 12762719]
10. (a) Padwa, A.; Pearson, WH., editors. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Towards Heterocycles and Natural Products.* Wiley; New York: 2003. (b) Zhai H, Liu P, Luo S, Fang F, Zhao M. *Org Lett.* 2002; 4:4385–4386. [PubMed: 12465893]
11. (a). The route in scheme 2 depicts the reagents and conditions we used for the synthesis of **1** in the initial discovery phase without publication. This route turned out to be essentially the same as the later published route by Yang et al. (ref. 11b) with only slight difference in reagents and conditions. Our detailed procedures are now provided in the supplementary material along with the original characterization data for references. Yang X, Luo S, Liu F, Fang P, Lu Y, He M, Zhai H. *Tetrahedron.* 2006; 62:2240–2246.
12. Furukawa N, Shibutani T, Fujihara H. *Tetrahedron Lett.* 1989; 30:7091–7094.
13. (a) Xu R, Dwoskin LP, Grinevich V, Sumithran SP, Crooks PA. *Drug Dev Res.* 2002; 55:173–186. (b) Papke RL, Zheng G, Horenstein NA, Dwoskin LP, Crooks PA. *Bioorg & Med Chem Lett.* 2005; 15:3874–3880. [PubMed: 16005216]
14. Pandey G, Banerjee P, Gadre SR. *Chem Rev.* 2006; 106:4484–4517. [PubMed: 17091927]
15. Guthikonda RN, Cama LD, Quesada M, Woods MF, Salzmann TN, Christensen BG. *J Med Chem.* 1987; 30:871–880. [PubMed: 3572975]
16. Procedure for the preparation of **17** and **20**: For **17**: Compound **16** (4.2 g, 24.4 mmol) was dissolved in anhydrous THF (100 mL) and LDA (2 M, 15 mL, 30 mmol) was added at -78°C over 5 min. The mixture was stirred at -78°C for an additional 45 min, a solution of allyl bromide (2.0 mL, 30 mmol) in THF (10 mL) was added drop-wise over 15 min. After stirring at -78°C for another 2 h, aqueous NaHCO_3 was added to quench the reaction and the mixture was warmed up to RT. Most of the solvent was removed *in vacuo* and the resulting residue was partitioned into ethyl acetate (50 mL) and brine (50 mL). The aqueous layer was further extracted with ethyl acetate (3×50 mL) and the combined organic layers were dried over MgSO_4 , concentrated under reduced pressure. The residue was purified by chromatography (SiO_2 , hexane:ethyl acetate, 10:1) to afford **17** (4.8 g, 92 % yield) as a pale yellow oil. ^1H NMR (300 MHz, CDCl_3), δ 8.62 (s, 1 H), 8.38 (d, $J = 8.8$ Hz, 1H), 7.18 (d, $J = 8.8$ Hz, 1H), 5.76–5.84 (m, 1H), 4.96–5.02 (m, 2H), 2.80 (t, $J = 7.2$ Hz, 2H), 2.38–2.40 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3), 151.9, 150.0, 148.2, 136.7, 125.4, 123.3, 116.2, 35.1, 33.0. HRMS m/e 210.9993, 212.0860 (Calcd. for $\text{C}_9\text{H}_{10}\text{BrN}$, 210.9997; $\text{C}_9\text{H}_{10}^{81}\text{BrN}$, 212.0864). Following the same procedure, compound **20** was prepared from 3-bromo-2-picoline (**19**) in 88% yield as pale yellow oil. ^1H NMR (300 MHz, CDCl_3), δ 8.47 (dd, $J = 4.8, 1.5$ Hz, 1H), 7.82 (dd, $J = 8.4, 1.5$ Hz, 1H), 7.00 (dd, $J = 8.4, 4.8$ Hz, 1H), 5.85–5.99 (m, 1H), 4.96–5.11 (m, 2H), 3.06 (t, $J = 8.4$ Hz, 2H), 2.46–2.54 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3), δ 159.8, 147.8, 140.4, 137.7, 122.7, 121.6, 115.4, 37.2, 32.7. HRMS m/e 210.9993 (Calcd for $\text{C}_9\text{H}_{10}\text{NBr}$, 210.9997).
17. Procedure for the preparation of **18** and **21**. For **18**: $n\text{-BuLi}$ (2 M in hexane, 7 mL, 14 mmol), was added drop-wise to a solution of **17** (2.56 g, 12.1 mmol) in anhydrous THF (30 mL) under N_2 at -78°C over 10 min. After stirring an additional 20 min at -78°C , anhydrous methyl formate (1.5 mL, 25 mmol) was added over 10 min and the mixture stirred at -78°C for 1 h. The reaction was quenched with saturated aqueous NaHCO_3 and warmed up to RT. The reaction mixture was concentrated under reduced pressure and the resulting residue was partitioned into ethyl acetate (50 mL) and water (50 mL). The aqueous layer was further extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried over MgSO_4 and concentrated *in vacuo*, the residue was purified by chromatography (SiO_2 , hexane:ethyl acetate, 5:1) to give **18** (1.70 g, 87 %) as a pale yellow oil. ^1H NMR (300 MHz, CDCl_3), δ 10.26 (s, 1H), 8.94 (s, 1H), 8.65 (d, $J = 4.8$ Hz, 1H), 7.22 (d, $J = 4.8$ Hz, 1H), 5.76–5.87 (m, 1H), 4.98–5.04 (m, 2H), 3.14 (t, $J = 5.7$ Hz, 2H), 2.34–2.40 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3), δ 191.6, 154.5, 153.6, 153.0, 136.7, 125.8, 116.3, 34.7, 32.0. HRMS m/e 161.0843 (Calcd for $\text{C}_{10}\text{H}_{11}\text{NO}$, 161.0841). Following the same procedure, compound **21** was prepared from **20** in 87 % yield as brownish oil. ^1H NMR (300 MHz, CDCl_3), δ 10.25 (s, 1H), 8.72 (dd, $J = 4.5, 1.5$ Hz, 1H), 8.12 (dd, $J = 7.5, 1.8$ Hz, 1H), 7.32 (dd, $J = 7.8, 4.8$ Hz, 1H), 5.81–5.94 (m, 1 H), 4.96–5.07 (m, 2H), 2.98 (t, $J = 7.8$

Hz, 2H), 2.46–2.55 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3), δ 191.1, 163.51, 153.6, 138.1, 137.2, 129.5, 122.0, 116.0, 34.5, 34.4. HRMS m/e 161.0842 (Calcd for $\text{C}_{10}\text{H}_{11}\text{NO}$, 161.0841).

18. Procedure for the preparation of **1** and **3**. For **1**. A mixture of **18** (1.6 g, 10 mmol) and sarcosine (1.2 g, 13.5 mmol) in DMF (30 mL) was heated under N_2 at 110 °C for 4 h, cooled to RT and the DMF then removed *in vacuo*. The resulting residue was partitioned into CHCl_3 (50 mL) and water (20 mL) and the aqueous layer was further extracted with chloroform (5×50 mL). The combined organic layers were washed with brine and dried over MgSO_4 . The solvent was removed *in vacuo* and the residue was purified by chromatography (SiO_2 , CH_2Cl_2 :methanol, 10:1) to give **1** (1.6 g, 86 % yield). ^1H NMR (300 MHz, CDCl_3), δ 8.36 (d, $J = 4.8$ Hz, 1H), 8.30 (s, 1H), 7.05 (d, $J = 4.8$ Hz, 1H), 3.03–3.07 (m, 2H), 2.75–2.83 (m, 1H), 2.48–2.59 (m, 2H), 2.29 (s, 3H), 2.21–2.27 (m, 1H), 2.04–2.09 (m, 1H), 1.64–1.80 (m, 2H), 1.49–1.58 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3), δ 150.5, 149.7, 148.4, 132.2, 123.7, 64.8, 56.1, 40.7, 36.4, 30.2, 29.3, 26.6. HRMS m/e 188.1308 (Calcd for $\text{C}_{12}\text{H}_{16}\text{N}_2$, 188.1314). Following the same procedure, compound **3** was prepared from 2-(but-3-en-1-yl)nicotinaldehyde in 82 % yield as light brown oil. ^1H NMR (300 MHz, CDCl_3), δ 8.41 (dd, $J = 5.1, 1.6$ Hz, 1H), 7.42 (d, $J = 6.6$ Hz, 1H), 7.10 (dd, $J = 5.1, 7.5$ Hz, 1H), 3.03–3.12 (m, 2H), 2.94–3.01 (m, 1H), 2.73–2.82 (m, 1H), 2.52–2.62 (m, 1H), 2.23–2.36 (m, 4H), 2.03–2.12 (m, 1H), 1.82–1.92 (m, 1H), 1.66–1.78 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3), δ 160.3, 147.8, 137.5, 131.0, 121.0, 67.3, 56.0, 40.9, 36.6, 30.4, 29.9, 29.4. HRMS m/e 188.1311 (Calcd for $\text{C}_{12}\text{H}_{16}\text{N}_2$, 188.1314).

Figure 1.

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.