Pergamon

Tetrahedron Letters 43 (2002) 177–179

TETRAHEDRON LETTERS

Asymmetric synthesis of (+)- and (−)-7-(3-pyridyl)-1-azabicyclo[2.2.1]heptane as conformationally restricted analogues of nicotine

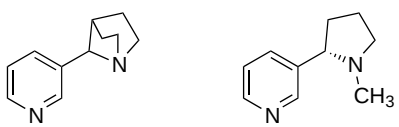
Thomas Ullrich,* Dieter Binder and Michael Pyerin

Laboratory of Medicinal Chemistry, Institute of Organic Chemistry, Vienna University of Technology, Getreidemarkt 9/154, A-1060 Vienna, Austria

Received 30 August 2001; accepted 22 October 2001

Abstract—Both enantiomers of the conformationally restricted nicotine analogue 7-(3-pyridyl)-1-azabicyclo[2.2.1]heptane were prepared in a convenient, asymmetric synthetic route.

Central nicotinic acetylcholine receptors (nAChRs) have been implicated in cognitive and learning processes, and their role in these processes allows them to be a potential target for the treatment of Alzheimer's and other neurodegenerative diseases.[1] Other findings suggest that activation of these receptors also plays a critical role in the antinociceptive effects of cholinergic channel modulators.[2] Recent reports[3,4] described the synthesis of racemic 7-(3-pyridyl)-1-azabicyclo[2.2.1]-heptane (**1**), a conformationally restricted analogue of nicotine (**2**), as a potential derivative for the prevention and treatment of CNS disorders. The structural resemblance between nicotine (**2**) and its derivative is evident in Fig. 1 (the ethylene bridge that connects the N-atom with the C3-atom of the pyrrolidine ring accounts for conformational restraint in **1**). While the relatively low enantioselectivity of nicotine has been an intriguing phenomenon for many years,[5] the premise that conformational restraint of nicotine should enhance enantioselectivity has been well established.[6] We were therefore interested in having both enantiomers of **1** available in large quantities for further biological studies.



1 **2**

Figure 1. Structures of 7-(3-pyridyl)-1-azabicyclo[2.2.1]-heptane and nicotine.

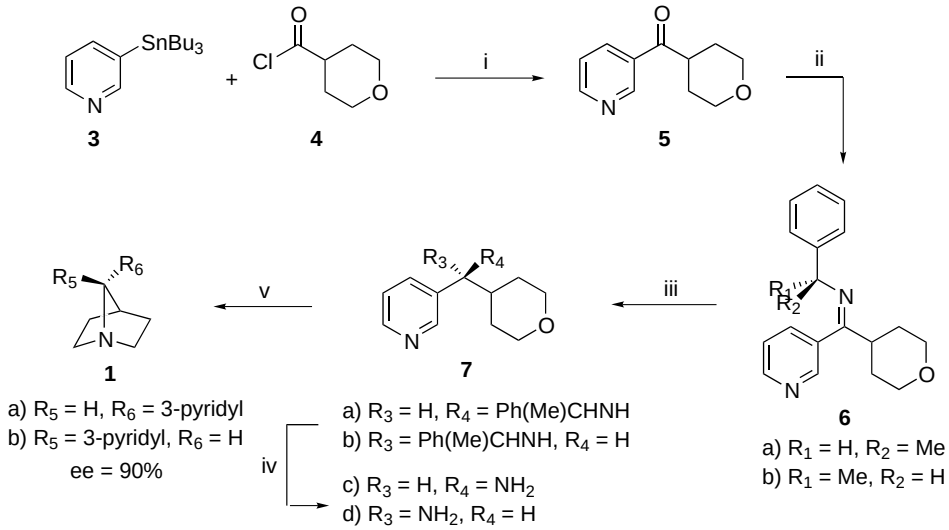
Caldwell et al.[4] suggested several possible pathways to generally achieve optical resolution of pyridine-substituted 1-azabicycloalkanes, including asymmetric synthesis. We pondered all methods proposed, especially those employing asymmetric addition across imine double bonds, affording optically resolved amines. Eventually we built our enantioselective key steps on a method described by Farkas et al.,[7] who synthesized *nor*-doxpicomine from 1,3-dioxan-5-yl 3-pyridyl ketone via imine formation with (*S*)-(−)-α-methylbenzylamine, diastereoselective reduction to the secondary amine with $NaBH_4$ and catalytic cleavage of the benzyl group. High asymmetry is attributed to distinct molecule properties which allow *E*,*Z*-stereoselectivity for imine formation and—provided careful control of reaction conditions—diastereoselectivity for reduction. By replacement of the dioxanyl moiety with a 4-tetrahydropyranyl residue we provided a synthon for one-pot cyclization to the azabicyclic compounds, depending on a practical and high-yielding synthesis of the ketone precursor **5** (Scheme 1).

Employment of Pd(II)-salts in benzene under Stille conditions[8,9] allows for conversions of a broad range of acyl halides to the corresponding pyridyl ketones. We were able to improve the suggested reaction conditions by using a catalytic amount of the Hermann–Beller

Keywords: nicotine; conformational restriction; Stille coupling; diastereoselective reduction.

* Corresponding author. Present Address: Laboratory of Medicinal Chemistry, NIDDK, National Institutes of Health, Bethesda, MD 20817, USA. Tel.: +1-301-435-1917; fax: +1-301-402-0589; e-mail: thomasu@intra.niddk.nih.gov

0040-4039/02/$ - see front matter
PII: S0040-4039(01)01985-2



Scheme 1. *Reagents and conditions*: (i) Pd catalyst, xylene, 120°C, 30 min, 65%; (ii) (*S*)- or (*R*)-α-methylbenzylamine, Et_3N, $TiCl_4$, CH_2Cl_2, 0–25°C, 12 h, 83–86%; (iii) $NaBH_4$, MeOH, –40°C, 86–89%; (iv) cyclohexene, 10% Pd–C, EtOH, HCl, 130°C, 6 h, 85–89%; (v) 62% HBr, 120°C (autoclave), 4 h; Na_2CO_3, H_2O, reflux, 2 h, 65%.

palladacycle *trans*-di(μ-acetato)bis[*o*-(di-*o*-tolylphosphino)phenylmethyl]dipalladium(II), prepared from palladium diacetate and tri(*o*-toluyl)phosphine.[10] This catalyst exhibits great temperature resistance, thus allowing for Stille chemistry to be carried out in high-boiling solvents rather than, for example, benzene. (Tributylstannyl)pyridine (**3**) was prepared from commercial tributyltin hydride and 3-bromopyridine, following a procedure described by Sandosham et al.,[11] and reacted with tetrahydropyran-4-carbonyl chloride (**4**) (prepared as reported by Radziszewskii et al.)[12] under catalysis of only 0.5–1 mol% of Pd catalyst. In order to establish a reasonable yield (65%), the coupling reaction was performed at sufficiently high temperatures, as the competing formation of symmetrically coupled 3,3′-bipyridine could then be repressed. Thus, yields decreased by more than 30% when the reaction was carried out in xylene at 90°C or in benzene at 70°C. Employment of the conventional catalyst $PdCl_2(PPh_3)$ at 70°C also afforded less than 30% of **5**.

Ketone **5** underwent stereoselective imine formation with (*R*)- and (*S*)-α-methylbenzylamine, respectively, providing single conformers **6** (anticipated *syn* geometry between the pyridyl and the α-methylbenzylamine moieties), as suggested in the literature.[7] Reduction was carried out on both imines, using $NaBH_4$ in MeOH. The highest degree of stereoselectivity was found at –40°C when 94% of the desired secondary amines **7a** and **7b** were obtained in 90% de, respectively, whereas at room temperature only 80% de resulted. Debenzylation to primary amines **7c** and **7d** was carried out in cyclohexene as a catalytic hydrogen transfer reagent[13] and 10% Pd–C in ethanol. No evidence of competing hydrogenolysis of the pyridyl–CH bond was found. The reaction time reported in the literature (20 h)[8] was reduced by 70% when using an autoclave, thus allowing for a higher reaction temperature (130°C) than that of boiling cyclohexene (70°C). Optical purity of **7c** and **7d** was determined by derivatization with (*S*)-phenylethylisocyanate and ^1H NMR interpretation. Both enantiomers were obtained in 90% ee, matching the result of the doxpicamine synthesis (88% ee).[7] In accordance with patent literature,[4] cyclization to the title compounds (+)-**1** and (–)-**1** was accomplished with ether cleavage in boiling 62% HBr and subsequent basification (pH 9). This step could be conducted under full retention of stereoconfiguration, and the optical resolutions of (+)-**1** and (–)-**1** were confirmed to be 90% ee, using (*R*)-(–)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate as an appropriate ^1H NMR shift reagent.[14] The absolute configurations of (+)-**1** and (–)-**1** were not determined in this study. (+)-**1** was obtained following the pathway with (*R*)-methylbenzylamine, and (–)-**1** resulted from the (*S*)-methylbenzylamine sequence.[15]

In summary, we prepared both enantiomers of 7-(3-pyridyl)-1-azabicyclo[2.2.1]heptane (**1**) in 29% overall yield, respectively, using a convenient route on a multigram scale that is based on a thoroughly optimized Stille acyl coupling reaction and diastereoselective reduction of ketimines. The reported methodology will be applied in the preparation of similar chiral analogues of nicotine, and pharmacological evaluation will be reported in due course.

References

1. Schmitt, J. D.; Bencherif, M. *Ann. Rep. Med. Chem.* **2000**, *35*, 41–51.
2. Meyer, M. D.; Decker, M. W.; Rueter, L. E.; Anderson, D. J.; Dart, M. J.; Kim, K. H.; Sullivan, J. P.; Williams, M. *Eur. J. Pharmacol.* **2000**, *393*, 171–177.
3. Piotrowski, D. W. PCT Int. Appl. WO 9,503,306, 1995.
4. Caldwell, W. S.; Bencherif, M.; Dull, G. M.; Crooks, P. A.; Lippiello, P. M.; Bhatti, B. S.; Deo, N. M.; Ravard, A. PCT Int. Appl. WO 9,900,385A1, 1999.

5. Martin, B. R. In *The Receptors*; Conn, P. M., Ed.; Academic Press: New York, 1986; pp. 393–415.
6. Damaj, M. I.; Glassco, W.; Marks, M. J.; Slobe, B.; James, J. R.; May, E. L.; Rosecrans, J. A.; Collins, A. C.; Martin, B. R. *J. Pharmacol. Exp. Ther.* **1997**, *282*, 1425–1434.
7. Farkas, E.; Sunman, C. J. *J. Org. Chem.* **1985**, *50*, 1110–1112.
8. Yamamoto, Y.; Yanagi, A. *Heterocycles* **1982**, *19*, 41–44.
9. Yamamoto, Y.; Yanagi, A. *Chem. Pharm. Bull.* **1982**, *30*, 2003–2010.
10. Beller, M.; Fischer, H.; Herrmann, W. H.; Öfele, K.; Brossmer, C. *Angew. Chem.* **1995**, *107*, 1992–1993.
11. Sandosham, J.; Undheim, K. *Tetrahedron* **1994**, *50*, 275–284.
12. Radziszewski, J. G.; Kaszinski, P.; Littmann, D.; Balaji, V.; Hess, B. A., Jr.; Michl, J. *J. Am. Chem. Soc.* **1993**, *115*, 8401–8408.
13. Jackson, A. E.; Johnstone, R. A. W. *Synthesis* **1976**, 685–688.
14. Ravard, A.; Crooks, P. A. *Chirality* **1996**, *8*, 295–299.
15. (+)-**1** and (−)-**1** were characterized as dihydrochloride salts. Melting points were not obtained due to the hygroscopicity of the crystals. Analytical data for (+)-**1**·2HCl: $[\alpha]_D^{20}=+13.3$ (*c* 1.0, MeOH); ^{1}H NMR (200 MHz, D_2O): δ 8.98 (t, $J=2$ Hz, 1H), 8.97–8.77 (m, 1H), 8.82–8.62 (m, 1H), 8.28–8.08 (m, 1H), 5.01 (s, 1H), 3.88–3.65 (m, 1H), 3.57 (t, $J=4$ Hz, 1H), 3.56–3.30 (m, 2H), 3.30–3.09 (m, 1H), 2.46–2.22 (m, 1H), 2.12–1.80 (m, 3H). Anal. calcd for $C_{11}H_{16}Cl_2N_2\cdot 0.25H_2O$: C, 52.49; H, 6.61; N, 11.13. Found: C, 52.39; H, 6.41; N, 10.96. Analytical data for (−)-**1**·2HCl: $[\alpha]_D^{20}=-13.1$ (*c* 1.0, MeOH); ^{1}H NMR (200 MHz, D_2O): identical with (+)-**1**. Anal. calcd for $C_{11}H_{16}Cl_2N_2$: C, 53.45; H, 6.52; N, 11.33. Found: C, 53.16; H, 6.23; N, 11.12.