ORGANIC LETTERS

2000
Vol. 2, No. 26
4201−4204

Total Synthesis of (±)-Cytisine

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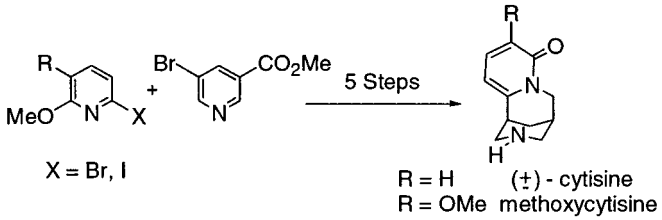
Received October 19, 2000

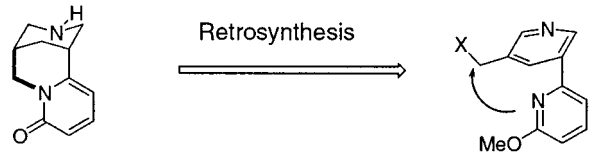
ABSTRACT



The nicotine partial agonist cytisine was prepared in five steps featuring an "in situ" Stille or Suzuki biaryl pyridine coupling. Differentiation of the pyridyl rings was accomplished via selective benzylation and then reduction of a pyridinium ring. The penultimate diazabicyclo[3.3.1]-nonane intermediate was obtained with high diastereoselectivity. A similar sequence has been employed for the synthesis of novel derivative 9-methoxycytisine.

Preclinical studies with acetylcholine receptor ligands such as nicotine, epibatidine, and ABT-594 have pointed toward new therapies in analgesia, cognition, and the treatment of addiction.[1] However, the nicotinic agent cytisine **1**, isolated from natural sources in 1894,[2] has not garnered nearly as much attention. Heinemann et al.[3] recently demonstrated that cytisine behaves as a partial agonist at neuronal nicotinic receptors with an $EC_{50} = 1\ \mu M$. Nicotine, a full agonist at neuronal nAcChR's, is known to possess reinforcing properties in vivo, and its use as a therapeutic agent has been limited. The partial agonist profile of cytisine may have therapeutic advantages in the treatment of addiction if efficacy measures can be improved. Few analogues of cytisine have been prepared thus far, and we report here a short total synthesis of this natural product as a prelude toward future investigation.

Van Tamelen and co-workers reported an elegant 11-step synthesis of (−)-cytisine in 1955 which incorporated an efficient resolution.[4] Building upon these results, we envisioned a shorter synthesis via a heterobiaryl pyridine coupling. Selective adjustment of oxidation levels and final ring closure would provide the natural product. In our retrosynthesis, the azabicyclic core of cytisine originates from selective reduction of unsymmetrically substituted biaryl pyridine **2**. The axial methylene bridge linking the piperidine



(-)-cytisine (1) 2

and pyridone rings (bold) in **1** was introduced as an ester, assuming that a simple transformation (as shown) would effect ring closure at the end of the synthesis. The pyridone was stored as a 2-methoxypyridine (**2**) to be released upon ring closure, thus avoiding a difficult oxidation.[4]

(1) Stolerman, I. P.; Mirza, N. R.; Shoaib, M. *Med. Res. Rev.* **1995**, *15* (1), 47−72. Holladay, M. W.; Dart, M. J.; Lynch, J. K. *J. Med. Chem.* **1997**, *40* (26), 4169−94. Brioni, J. D.; Decker, M. W.; Sullivan, J. P.; Arneric, S. P. *Adv. Pharmacol.* **1997**, *37*, 153−215. Ember, L. R. *Chem. Eng. News* **1994**, Nov. 28, 8−18.

(2) Partheil, A. *Arch. Pharm.* (*Weinheim, Ger.*) **1894**, *232*, 161. Ing, H. R. *J. Chem. Soc.* **1932**, 2778.

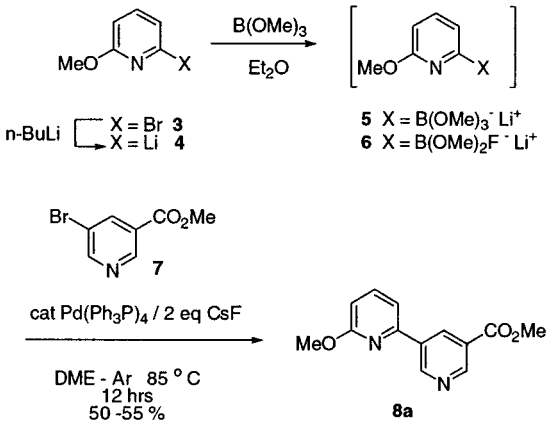
(3) Heinemann, S. F.; Papke, R. L. *Mol. Pharmacol.* **1994**, *45* (1), 142−9. Anderson, D. J.; Arneric, S. P. *Eur. J. Pharm.* **1994**, *253*, 261−7.

(4) Van Tamelen, E. E.; Baran, J. S. *J. Am. Chem. Soc.* **1955**, *77*, 4944−5. Van Tamelen, E. E.; Baran, J. S. *J. Am. Chem. Soc.* **1958**, *80*, 4659−70. See also: Bohlmann, F.; Englisch, A.; Ottawa, N.; Sander, H.; Weise, W. *Angew. Chem.* **1955**, *67*, 708. Govindachari, T. R.; Rajadurai, S.; Subramanian, M.; Thyagarajan, B. S. *J. Chem. Soc.* **1957**, 3839−44.

10.1021/ol0067538 CCC: $19.00
Published on Web 12/07/2000

We believed that either the Suzuki[5] or Stille[6] coupling procedures would provide the desired biaryl pyridine system. For instance, coupling of 3-pyridyldiethylborane and 2-bromo-6-methoxypyridine **3** has been reported by Terashima in 77% yield.[7] A related tin-mediated process was reported by Dehmlow in 81% yield.[8] We made few attempts to mirror either of these two processes as formation of the required organolithium (or magnesium) reagent from bromonicotinic ester **7** or the corresponding protected alcohol was problematic. The modified Suzuki approach, depicted in Scheme 1,

Scheme 1. Suzuki Coupling

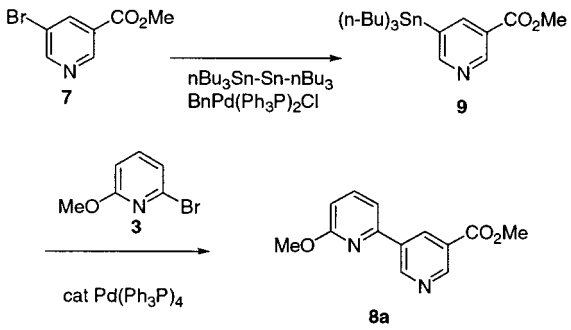


effected the desired coupling after conditions for handling the organoboranes were devised. Formation of organolithium **4** through halogen−metal exchange of **3** in ether at −40 °C was followed by addition of one of several boronic esters or alkyl boranes. Unfortunately, isolation of the requisite pyridine−2-borane adducts was always problematic.[9] For instance, reaction of **4** with triethylborane, followed by treatment with iodine, afforded low yields (20−30%) of the desired 6-methoxypyridyl-2-diethylborane. This alkylborane, once isolated, was a good substrate for Suzuki coupling. An 80% yield of purified **8a** was obtained after palladium-mediated reaction with methyl 5-bromonicotinate **7**. Attempted formation and isolation of a boronic acid from reaction of **4** with triisopropoxyborane was similarly problematic. Fortunately, it proved unnecessary to isolate the boronic acid. "In situ" treatment, by the method of Keay, of **4** with trimethylborate formed the presumed boron "ate" complex **5**.[10] Without isolation, the Suzuki coupling of **5** and **7** proceeded in moderate yield in the presence of palladium(0) and 2 equiv of cesium fluoride under the conditions of Wright et al.[11]

The cesium fluoride conditions were designed for substrates that are sensitive to base. The yield of **8a** was enhanced by 20% relative to the reaction without cesium fluoride. The role this salt plays in our reaction is not clear, although disproportionation of the preformed ate complex with substitution of methoxy by fluoride seems unlikely.[12] Formation of the ate complex from $B(OMe)_2F$ also afforded a satisfactory substrate for Suzuki coupling (**6**), but yields dropped without added cesium fluoride. Alternatively, rate enhancement may be due to the presence of cesium ion.[13]

An equally promising Stille coupling removed the need for highly nucleophilic organometallics (Scheme 2). Methyl

Scheme 2. Stille Coupling

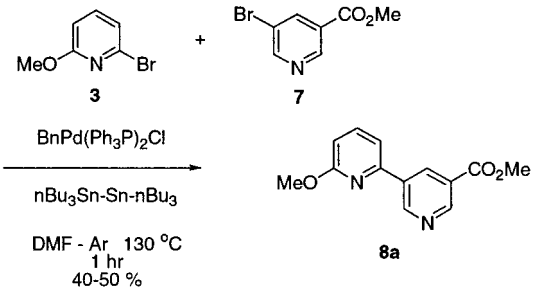


5-bromonicotinate **7** was incompatible with organolithium reagents, limiting the role of **7** to an acceptor in the Suzuki process (above). Formation of the organostannane **9** was readily accomplished through palladium-mediated reaction of **7** and hexabutylditin to afford **9** in 44−50% yield. The Stille coupling with bromide **3** provided the desired biaryl **8a** in 50% yield, demonstrating that either partner can serve as the donor.[14]

We then considered whether generation of the heteroaryl stannane **9** could be conducted "in situ" followed by heteroaryl coupling as a "one-pot" process. The prospects for this reaction were initially viewed as weak as we suspected coproduction of two undesired homodimeric heterobiaryl species. In the event (Scheme 3), the halides **3** and **7** were combined in degassed DMF followed by hexabutylditin and palladium catalyst. The reaction mixture was rapidly heated to 130 °C, and within 45 min palladium metal was deposited. The reaction was judged to be complete by TLC. Remarkably, the desired methoxybipyridinyl ester

(5) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.
(6) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524.
(7) Ishikura, M.; Kamada, M.; Terashima, M. *Synthesis* **1984**, 936−938.
(8) Dehmlow, E. V.; Sleegers, A. *Liebigs Ann. Chem.* **1992**, 953−959.
(9) See, however: Thompson, W. J.; Jones, J. H.; Lyle, P. A.; Thies, J. E. *J. Org. Chem.* **1988**, *53*, 2052−2055.
(10) Cristofoli, W. A.; Keay, B. A. *Tetrahedron Lett.* **1991**, *32*, 5881−5884. Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1994**, *59*, 6501−6503. Andersen, N. G.; Maddaford, S. W. P.; Keay, B. A. *J. Org. Chem.* **1996**, *61*, 9556−9559.
(11) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095−6097.
(12) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020−3027. Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028. No other salts were studied.
(13) Katz, H. E. *J. Org. Chem.* **1987**, *52*, 3932−3934. Zhang, H.; Kwong, F. Y.; Tian, Y.; Chan, K. S. *J. Org. Chem.* **1998**, *63*, 6886−6890. Bei, X.; Turner, H. W.; Weinberg, W. H.; Guram, A. S.; Petersen, J. L. *J. Org. Chem.* **1999**, *64*, 6797−6803.
(14) We have thus far been unable to use the conditions of Miyaura to directly prepare the "boron pinacolate" via a related palladium-catalyzed process. Ishiyama, T.; Myrata, M.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447. We have confirmed that the stannane derived from 2 methoxy-6-bromopyridine is also an excellent substrate for Stille coupling, affording **8a** in 40% yield.

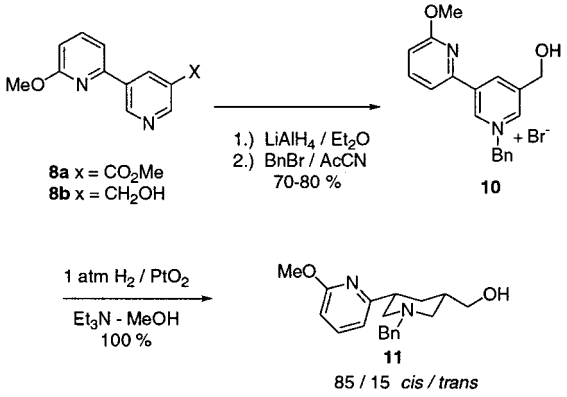
Scheme 3. In Situ Stille Coupling



8a was obtained in 40−50% yield together with a small amount of [3,3′]bipyridinyl-5,5′-dicarboxylate. None of the dimer originating from 2-bromo-6-methoxypyridine was observed. Isolation of the desired product was straightforward after a simple chromatography and was easily adaptable to production of large quantities of material.[15] While it was gratifying to obtain this result, its applicability may be limited (vide infra).

Formation of the diazabicyclo[3.3.1]nonane ring of cytisine was accomplished in two ways. In both, selective reduction of the more accessible 3,5-disubstituted pyridine (Schemes 4 and 5) was initiated through selective alkylation of the less hindered pyridine nitrogen.[16] Reduction selectivity was linked to the oxidation state of the side chain, either ester or alcohol, and to the oxidation state of the pyridine ring itself, either dihydropyridine or pyridinium salt. The first successful approach (Scheme 4) began with reduction of the ester **8a**

Scheme 4. Reduction

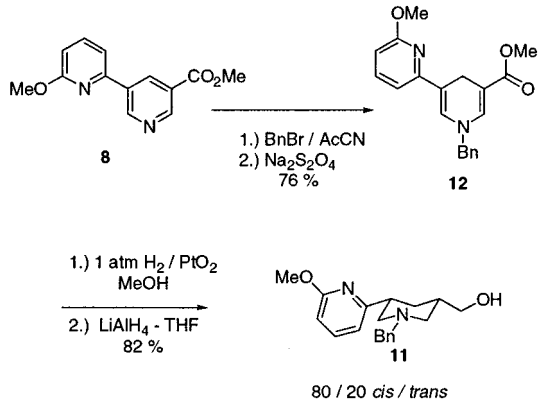


using lithium aluminum hydride followed by selective *N*-alkylation of **8b** with benzyl bromide to afford pyridinium salt **10** as a crystalline solid. Hydrogenation over platinum oxide afforded solely the product of pyridinium salt reduction, the 3,5-*cis*-piperidine **11** in quantitative yield as an 85:15 *cis*:*trans* mixture (by integration of the aromatic protons in the ^{1}H NMR of the crude product).

In these studies, we observed that platinum oxide catalyzed hydrogenation of the unactivated ester **8a** or its benzyl pyridinium salt provided lower selectivity for the 3,5-*cis* isomer. Hydrogenation of the unactivated alcohol **8b** prior to formation of the benzyl pyridinium salt **10** afforded only products of hydrogenolysis.

Alternatively, activation of the ester **8a** as the benzyl pyridinium salt followed by reduction with sodium dithionate afforded **12** in 76% yield (Scheme 5). Hydrogenation of **12**

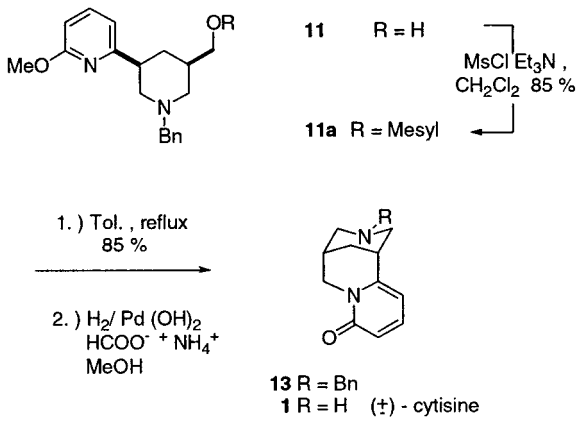
Scheme 5. Reduction



followed by ester reduction led to the cyclization precursor **11** in similar yield and diastereoselectivity as in Scheme 4. Intermediate **11** resembles the penultimate synthetic intermediate that was employed in Van Tamelen's cytisine synthesis with the notable addition of the oxygen necessary for formation of the pyridone.

Cyclization of **11** to form the cytisine diazabicyclo[3.3.1]-nonane framework (Scheme 6) was straightforward when conducted under standard mesylate activation conditions followed by heating under reflux to afford *N*-benzyl cytisine

Scheme 6. Cyclization



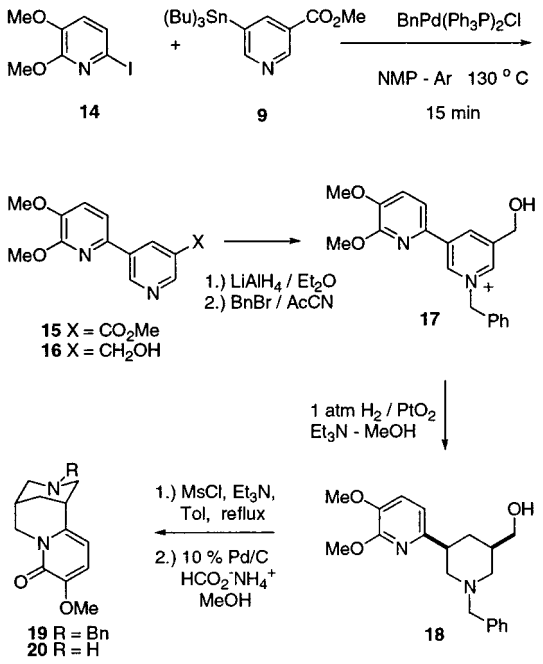
(15) Independent observations along similar lines have been reported with pyridyl triflates: Hitchcock, S. A.; Mayhugh, D. R.; Gregory, G. S. *Tetrahedron Lett.* **1995**, *36*, 9085−8. Modified Stille reaction of 6-methoxypyridyl-2-triflate and **7** afforded product **8a** in only 23% yield.

(16) For an alternative approach, see: Zoltewicz, J. A.; Cruskie, M. P., Jr. *J. Org. Chem.* **1995**, *60*, 3487−3493.

13 in 85% yield. The final palladium-catalyzed hydrogenolysis affords (±)-cytisine **1** identical in all respects to a sample of the natural product by ^{1}H and ^{13}C NMR. Presumably, intramolecular ring closure precedes cleavage of the *O*-methoxy group with exposure of the pyridone ring. This step also represents an advance in the original Van Tamelen synthesis in which ring closure afforded an unsubstituted pyridinium salt which was oxidized to cytisine in low yield.

The generality of the synthetic sequence was demonstrated through synthesis of (±)-9-methoxycytisine **20** (Scheme 7).

Scheme 7. (±)-9-Methoxycytisine



The palladium-mediated heterobiaryl fusion was more successful with the preformed stannane **9** and iodide **14**.[17] The desired **15** was obtained in 36−40% yield. The "in situ" Stille coupling (Scheme 3) was disappointing when applied to these substrates. Significant amounts of both homodimeric coupling products made isolation of **15** difficult and significantly lowered the yield. Reaction of the bromide corresponding to **14** afforded lower yields of biaryl **15**.

The remaining steps were unexceptional beginning with reduction of the ester **15** using lithium aluminum hydride followed by selective *N*-alkylation with benzyl bromide to afford pyridinium salt **17** as a crystalline solid in 67% overall yield. Hydrogenation over platinum oxide afforded solely the product of pyridinium salt hydrogenation, the 3,5-*cis* piperidine **18** in quantitative yield as an 85:15 *cis*:*trans* mixture (by NMR). Cyclization to form *N*-benzyl-protected **19** was straightforward when conducted under standard mesylate activation conditions followed by heating under reflux to afford *N*-benzyl-9-methoxycytisine **19** in 85% yield. The final palladium-catalyzed hydrogenolysis affords (±)-9-methoxycytisine **20**. The product demonstrated NMR and MS spectra in accord with the proposed structure and analogous to cytisine itself.

Cytisine **1** presents an unusually simple template and a unique partial agonist profile at neuronal nicotinic receptors. This facile construction of cytisine (and methoxycytisine) in 5 steps will make the natural product available for semisynthesis and serve as a template for the design of novel partial agonist templates. SAR results including a complete biological characterization of analogues will be reported in due course.

Acknowledgment. We thank Mr. Harry Howard Jr., Dr. Jotham Coe, and Prof. Steven Buchwald for helpful discussions during the course of this work. We also thank Dr. Martin Jefson for encouragement.

Supporting Information Available: Experimental procedures and full characterization including ^{1}H and ^{13}C NMR spectra for compounds **1**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) 2,3-Dimethoxy-6-iodopyridine **14** was prepared in three steps from commercially available 2-bromopyridin-3-ol (1. I_2, aqueous Na_2CO_3; 2. MeI K_2CO_3, DMF; 3. NaOMe, DMF; see Supporting Information).