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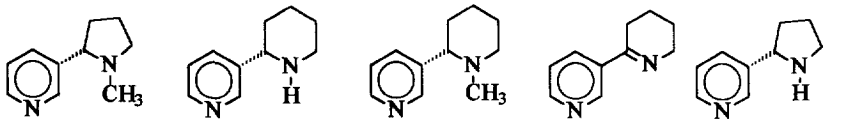
Regioselective Alkylation of N-(diphenylmethylidine)-3-(aminomethyl)pyridine: A Simple Route to Minor Tobacco Alkaloids and Related Compounds.

Niranjan M. Deo[1] and Peter A. Crooks*
College of Pharmacy
Division of Medicinal Chemistry
University of Kentucky
Lexington, KY 40536-0082

Abstract: A simple synthetic route to minor tobacco alkaloids and related compounds is described involving regioselective alkylation of N-(diphenylmethylidine)-3-(aminomethyl)pyridine with a suitable dielectrophile.

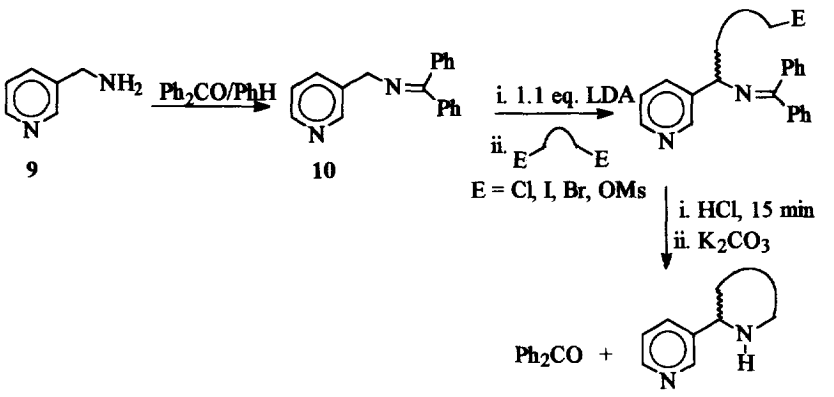
The principal tobacco alkaloid nicotine (**1**) activates nicotinic cholinergic receptors, and has been reported to elicit an increase in the number of such receptors upon acute administration to animals.[2] It has also been proposed that nicotine may have beneficial effects in suppressing the symptoms associated with certain cognitive disorders.[3] A recent study describing the effects of the minor tobacco alkaloids, S-(-)-anabasine (**2**), S-(-)-N-methylanabasine (**3**) and anabaseine (**4**), on [^{3}H]dopamine release from superfused rat striatal slices indicates that these alkaloids produce comparative and in some cases, greater effects than either S-(-)-nicotine,[4] or S-(-)-nornicotine (**5**); the latter compound is a minor tobacco alkaloid and a biotransformation product of nicotine found in the brain after nicotine administration.[5] These results suggest that, in addition to nicotine, minor tobacco constituents may also contribute to the neuropharmacological effects resulting from tobacco use.



1 **2** **3** **4** **5**

Fig. 1. Structures of Some of the Tobacco Alkaloids

Although there are several literature references[6] describing the synthesis of individual and specific tobacco alkaloids, the synthetic procedures described are usually multistep, resulting in a low overall yield of the alkaloid. Ohno and coworkers[7] have reported a general synthetic procedure leading to the formation of (±)-anatabine (**6**), (±)-anabasine (**7**), (±)-nornicotine (**8**), and their N-methylated analogs. However, the authors have neither reported the experimental details nor the yields of the reaction products.[8] We now report a very simple and convenient synthetic route to these minor tobacco alkaloids (Scheme 1), which also has utility in the synthesis of structural analogs of these pharmacologically active compounds.



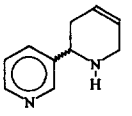
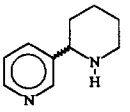
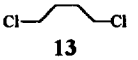
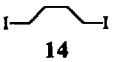
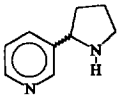
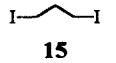
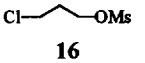
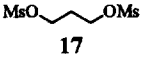
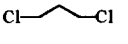
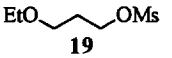
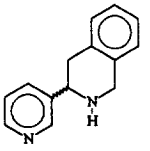
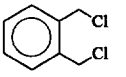
Scheme 1

Activation of the methylene protons of 3-(aminomethyl)pyridine **9** by formation of a suitable Schiff base, followed by carbanion formation and monoalkylation[9] with a dielectrophile was expected to yield the appropriate 3-pyridyl substituted nitrogen heterocycle as a result of subsequent intramolecular N-alkylation.[10] Accordingly, **9** was converted to Schiff base **10** by reaction with benzophenone in benzene. After completion of the reaction (monitored by TLC and NMR), the solvent benzene was replaced by THF. Treatment of **10** with LDA at -78°C followed by addition of dielectrophile resulted in α-alkylation of the imine. Hydrolysis of the alkylated imine was achieved in 15 - 20 minutes by treating the reaction mixture with 10% aq. HCl. Basification of the solution with K_2CO_3 resulted in intramolecular N-alkylation to yield the appropriate piperidine or pyrrolidine analog. This general strategy was applied successfully to the synthesis of **6**, **7**, **8** and a related tetrahydroisoquinoline analog **11**. The results obtained are provided in Table 1.

The anion of Schiff base **10** did not react with simple aliphatic dichloro or dibromo compounds. Nornicotine (**8**) was used as a model compound for optimizing the yields of the reaction. As indicated in Table 1, the yield of the reaction was low when the methanesulfonate of 3-chloropropanol (**16**) was used as a dielectrophile in place of diiodopropane. Similarly, the dimesylate **17** derived from 1,3-propanediol afforded nornicotine in very low yields. However, when the mesylate (**19**) derived from 3-ethoxypropanol was utilized, α[3-(ethoxy)propyl]-3-pyridinemethaneamine was isolated in 62% overall yield, which was then converted to nornicotine in almost quantitative yield, according to ref 6d.

In conclusion, this work provides a very convenient strategy for the synthesis of a variety of piperidine and pyrrolidine heterocycles which involves alkylation of the methylene carbon of 3-(aminomethyl)pyridine with a suitable dielectrophile followed by subsequent intramolecular N-alkylation.

Table 1. Results obtained after alkylation of Schiff base 10 with various dielectrophiles.[a]

Product	Dielectrophile	% Yield[b]
 6	 12	65 - 75
 7	 13	0
	 14	56
 8	 15	40
	 16	<20
	 17	<10
	 18	0
	 19	62[c]
 11	 20	82

[a]No alkylation at the benzylic site was observed. [b]Yields are based upon products isolated after column chromatography and/or distillation. [c]The ethoxyamine obtained in this case was treated with HBr as in ref 6d to obtain nornicotine in almost quantitative yield.

Experimental:

Schiff base 10 was synthesized by refluxing equimolar amounts of benzophenone and 3-(aminomethyl)pyridine (9) in benzene, under a nitrogen atmosphere with a Dean-Stark trap for 12 - 16 hours. A typical procedure is described for the synthesis of (±)-anatabine.

(±)-Anatabine (6): LDA (1.1 mmol, generated by adding *n*-BuLi (1.1 mmol, 0.46 mL, 2.4 M solution in hexane) to a solution of diisopropylamine (1.2 mmol, 0.17 mL) in dry THF (1.5 mL) under a nitrogen atmosphere at 0°C), was transferred to a flask containing Schiff base 10 (1.0 mmol, 272 mg) in THF (1.0 mL) at -78°C under a nitrogen atmosphere. The resulting dark purple mixture was stirred for an additional 30 minutes, during which time the temperature of the reaction mixture was allowed to warm to -45°C. *Cis*-1,4 dichlorobutene (1.5 mmol, 187.5 mg) was then added to the reaction mixture via a syringe. After an unchanged TLC-pattern was obtained indicating disappearance of all the starting Schiff base, the reaction mixture was poured into an Erlenmeyer flask containing 10% aq. HCl (15 mL). The resulting solution was stirred for 15 - 20 minutes at ambient temperature, and extracted with diethyl ether (3 x 10 mL). The aqueous portion of the reaction mixture was separated and basified first with solid K_2CO_3 and then with 40% aq. KOH to pH 10 - 12, and extracted with chloroform (3 x 15 mL). Evaporation of the combined and K_2CO_3-dried organic extracts afforded 288 mg of a yellow oil, which was purified by silica gel column chromatography using 10% MeOH in $CHCl_3$ as eluent to give (±)-anatabine (105 mg, 65%) as a pale yellow oil.

(±)-Nornicotine and (±)-anabasine were characterized by comparing their ^1H and ^{13}C NMR spectra with those of the commercially available samples while (±)-anatabine was characterized as in ref 6f. 2-(3-Pyridyl)-tetrahydroisoquinoline (11) was characterized as its diperchlorate salt (mp: 236 - 238°C). ^1H NMR (300 MHz, DMSO-d_6): δ 3.29 - 3.37 (m, 2H), 4.51 (s, 2H), 4.90 (br, 1H), 7.24 - 7.29 (m, 4H), 8.02 - 8.06 (m, 1H), 8.51 (d, 1H, J = 8.1 Hz), 8.89 - 8.91 (m, 1H), 9.80 (br, 3H); ^{13}C NMR δ 31.7, 45.1, 53.7, 126.4, 126.6, 127.0, 127.8, 127.9, 128.6, 131.2, 135.0, 142.1, 143.8, 145.0 ppm. Anal. Calcd. for $C_{14}H_{14}N_2.2HClO_4$; theory C 40.90%, H 3.91%, N 6.81%; found C 41.14%, H 3.92%, N 6.78%.

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