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Synthesis of Nicotine Derivatives via Reductive Disilylation of (*S*)-Nicotine

Emilie D. Smith, Florence C. Février, and Daniel L. Comins*

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695-8204

daniel_comins@ncsu.edu

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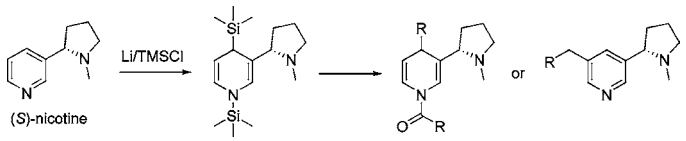
ABSTRACT



A variety of novel nicotine derivatives were prepared via reductive disilylation of (*S*)-nicotine. Treatment of nicotine with lithium powder and chlorotrimethylsilane afforded 1,4-bis(trimethylsilyl)-1,4-dihydronicotine in high yield. Addition of various carbonyl electrophiles and a catalytic amount of TBAF provided either C-5 substituted nicotines or 1,4-dihydronicotine derivatives.

(*S*)-Nicotine (**1**) is the most abundant alkaloid isolated from the genus *Nicotiana* plant.[1] Recent studies have shown beneficial effects following administration of nicotine to patients suffering from Parkinson's disease, anxiety, schizophrenia, Alzheimer's disease, uterative colitis, and other disorders.[2] Detrimental effects including actions on both the cardiovascular and gastrointestinal systems, sleep disturbance, and dependence limit the use of nicotine as a therapeutic reagent.[3] Considerable attention has been given to the synthesis of nicotine derivatives that would exhibit the beneficial biological properties at lower toxicity. Because of the reactivity of nicotine's pyrrolidine ring, few nicotine analogues with substituted pyridine rings have been synthesized from (*S*)-nicotine and subjected to physiological studies. In 1924, Tschitschibabin and Kirssanow reported that the reaction of (*S*)-nicotine with sodium or potassium amide gives a mixture of racemic 2- and 6-aminonicotine.[4] These compounds were shown to have nicotine-like properties but are less toxic than nicotine. In 1977, Rhondahl conducted an early study on the structure−activity relationship of nicotine analogues containing halogens at the C-5 position. He determined their order of potency to be F > Cl = I > Br, with 5-fluoronicotine having $^1/_{10}$ the activity of nicotine.[5] Seeman and co-workers reported in 1983 that the methylation of nicotine with methyllithium lacked regioselectivity and occurred with a loss of optical purity.[6] Since those early studies, a plethora of nicotine derivatives with modification at both the pyridine and the pyrrolidine ring have been synthesized.[2d] Among the more potent compounds are (*S*)-5-ethenyl-3-(1-methyl-2-pyrrolidinyl)pyridine (**2**, SIB-1508Y), which has undergone Phase II clinical trials for the treatment of Parkinson's disease,[7] and ABT-418 (**3**) (Figure 1). The latter analogue contains a 3-methylisoxazole isostere of pyridine and was found to have some beneficial effects in patients suffering from Alzheimer's disease.[8]

In most of the previous preparations of nicotine derivatives, nonchiral compounds were used as starting material, and a

(1) (a) Gorrod, J. W.; Jacob, P., III *Analytical Determination of Nicotine and Related Compounds and their Metabolites*; Elsevier: New York, 1999. (b) Pailer, M. In *Tobacco Alkaloids and Related Compounds*, US von Euler, Ed.; Pergamon Press: New York, 1965; p 15.

(2) (a) Levin, E. D. *J. Neurobiol.* **2002**, *53*, 633. (b) Newhouse, P. A.; Kelton, M. *Pharm. Acta Helv.* **2000**, *74*, 91. (c) Holladay, M. K.; Dart, M. J.; Lynch, J. K. *J. Med. Chem.* **1997**, *40*, 4169. (d) Breining, S. R. *Curr. Top. Med. Chem.* **2004**, *4*, 609−629. (e) Jensen, A. A.; Frølund, B.; Liljefors, T.; Krosgsgaard-Larsen, P. *J. Med. Chem.* **2005**, *48*, 4705.

(3) McDonald, I. A.; Vernier, J.-M.; Cosford, N.; Corey-Naeve, J. *Curr. Pharm. Des.* **1996**, *2*, 357. Cosford, N. D. P.; Bleiker, L.; Dawson, H.; Whitten, J. P.; Adams, P.; Chavez-Noriega, L.; Correa, L. D.; Crona, J. H.; Mahaffy, L. S.; Menzaghi, F. M.; Rao, T. S.; Reid, R.; Sacaan, A. I.; Santori, E.; Stauderman, K.; Whelan, K.; Lloyd, G. K.; McDonald, I. A. *J. Med. Chem.* **1996**, *39*, 3235.

(4) Tschitschibabin, A. E.; Kirssanow, A. W. *Chem. Ber.* **1924**, *57*, 1163.

(5) Rhondahl, L. *Acta Pharm. Suec.* **1997**, *14*, 113.

(6) (a) Seeman, J. I.; Secor, H. V.; Howe, C. R.; Chavdarian, C. G.; Morgan, L. W. *J. Org. Chem.* **1983**, *48*, 4899 and references therein. (b) Also see: Seeman, J. I.; Chavdarian, C. G.; Kornfeld, R. A.; Nworal, J. D. *Tetrahedron* **1985**, *41*, 595.

(7) Wang, D. X.; Booth, H.; Lerner-Marmarosh, N.; Osdene, T. S.; Abood, L. G. *Drug Dev. Res.* **1998**, *45*, 10.

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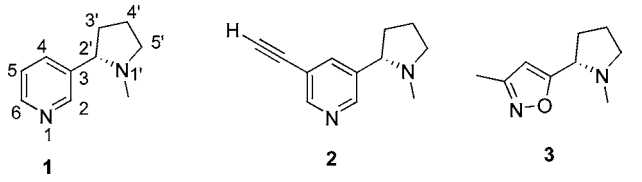
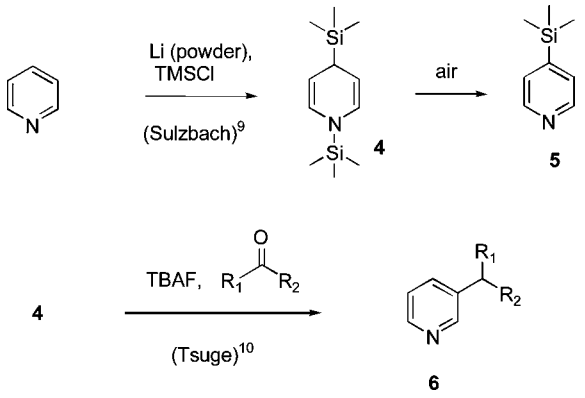


Figure 1. Nicotine (**1**), SIB-1508Y (**2**), and ABT-418 (**3**).

resolution was required to provide the desired enantiomer to the detriment of the overall yield. In an attempt to avoid a resolution step, we started a program to investigate regioselective syntheses of nicotine derivatives using natural (*S*)-nicotine as starting material. A reductive disilylation of nicotine seemed to be of particular interest because of its potential to allow the preparation of C-5-substituted derivatives in two steps from nicotine.

In 1970, Sulzbach reported the reductive disilylation of pyridine with alkali metals and trimethylsilyl chloride[9] (Scheme 1). The 1,4-bis(trimethylsilyl)-1,4-dihydropyridine

Scheme 1

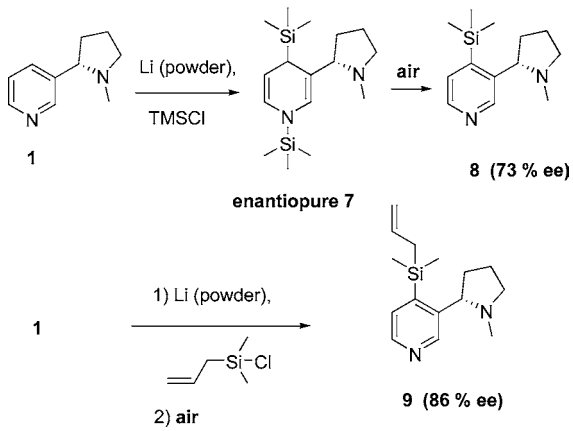


4 was isolated in 34% yield and was found to be extremely air sensitive; oxidation occurred on exposure to air to give 4-(trimethylsilyl)pyridine (**5**).

In 1984, Tsuge[10] reinvestigated this reaction and the reactivity of 1,4-dihydropyridine **4** with aldehydes and ketones in the presence of a catalytic amount of tetrabutylammonium fluoride (TBAF). A variety of 3-alkylpyridines **6** were prepared using this procedure (Scheme 1).

The reductive disilylation of nicotine was first conducted using the same conditions as those described by Tsuge, and only the oxidized product 4-(trimethylsilyl)nicotine (**8**) was isolated (Scheme 2). With a careful distillation under argon,

Scheme 2



the desired product **7** was isolated in 58% yield with a purity of 95% (determined by ^{1}H NMR). We discovered that the yield could be improved to 95% when the reaction was run at room temperature, and a high vacuum (0.1 mmHg) was used to distill the product.

Although no significant racemization occurs on formation of dihydronicotine **7**,[11] subsequent air oxidation provides nicotine **8** in 73% enantiomeric excess (ee). This partial racemization is presumably due to free radical intermediates generated during the oxidation step.

The analogous reaction using allylchlorodimethylsilane instead of chlorotrimethylsilane was investigated. After air oxidation, 4-(allyldimethylsilyl)nicotine (**9**) was obtained in 58% yield and 86% ee.

Several reactions of 1,4-bis(trimethylsilyl)-1,4-dihydronicotine (**7**) were investigated on the basis of the Tsuge reaction[10] (Scheme 3). First, the fluoride-catalyzed reaction of **7** with aldehydes was studied (reaction a). The reaction conditions described by Tsuge were applied using various aldehydes (Table 1). It was found that a temperature above room temperature was required to ensure reaction completion. Reaction of benzaldehyde gave a 56% yield of 5-benzylnicotine (**10**, entry 2). In a similar manner, 2-thiophenylcarboxaldehyde and 2-furaldehyde afforded the corresponding C-5-substituted nicotine derivatives **11** and **12** in 67% and 47% yields, respectively (entries 3 and 4). Reflux temperature was needed in the case of dodecyl aldehyde to provide 70% of 5-dodecylnicotine **13** (entry 5).

We next attempted the carbamylation of **7** at the nitrogen of the dihydropyridine ring (Scheme 3, reaction b). Reaction of **7** with dimethylcarbamyl chloride in methylene chloride yielded 59% of the desired dihydronicotine **14**. The reaction proceeded very slowly (1 day at room temperature is required), and increasing the temperature resulted in decomposition.

Removal of the TMS group located at C-4 of **14** was achieved using a stoichiometric amount of TBAF in THF to give a 75% yield of 1,4-dihydronicotine **15** (reaction c).

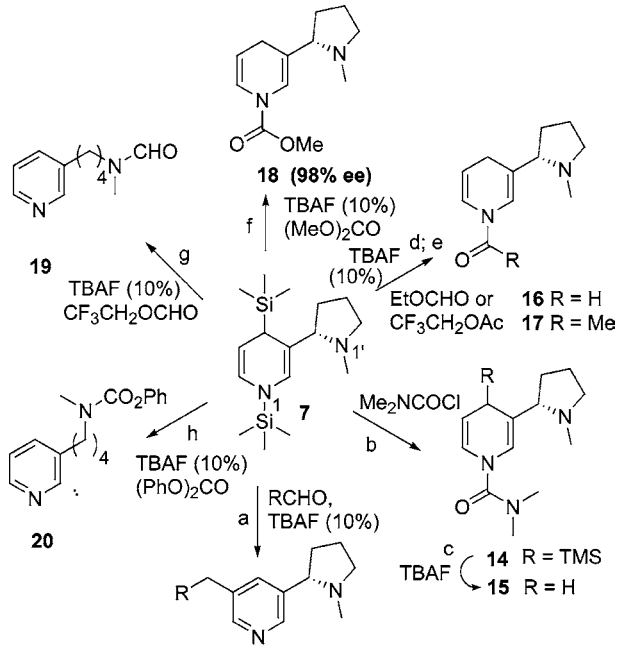
(8) Garvey, D. S.; Wasicak, J. T.; Elliot, R. L.; Lebold, S. A.; Hettinger, A.-M.; Carrera, G. M.; Lin, N.-H.; He, Y.; Holladay, M. W.; Anderson, D. J.; Cadman, E. D.; Raszkiewicz, J. L.; Sullivan, J. P.; Aneric, S. P. *J. Med. Chem.* **1994**, *37*, 4455.

(9) Sulzbach, R. A. *J. Organomet. Chem.* **1970**, *24*, 307.

(10) (a) Tsuge, O.; Kanemasa, S.; Naritomi, T.; Tanaka, J. *Chem. Lett.* **1984**, 1255. (b) Tsuge, O.; Kanemasa, S.; Naritomi, T.; Tanaka, J. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1497.

(11) This was determined by conversion of **7** to enantiopure **18** (98% ee by chiral column HPLC). See Scheme 3.

Scheme 3



Encouraged by these results, we decided to expand the versatility of the fluoride-catalyzed reaction of 1,4-dihydronicotine **7** by diversifying the carbonyl electrophiles.

When less-reactive reagents were used, such as ethyl formate, trifluoroethyl acetate, and methyl carbonate (reactions d−f), exclusive substitution at N-1 occurred to give 1,4-dihydronicotines **16**, **17**, and **18** in 60, 70, and 91% yields, respectively. The carbamate **18** was shown to be enantiopure (98% ee) by chiral column HPLC, indicating that the fluoride-catalyzed reactions proceed without significant racemization. To the best of our knowledge, this is the first example of a synthesis of 4-unsubstituted 1,4-dihydronicotines. No ring-opened products were detected.

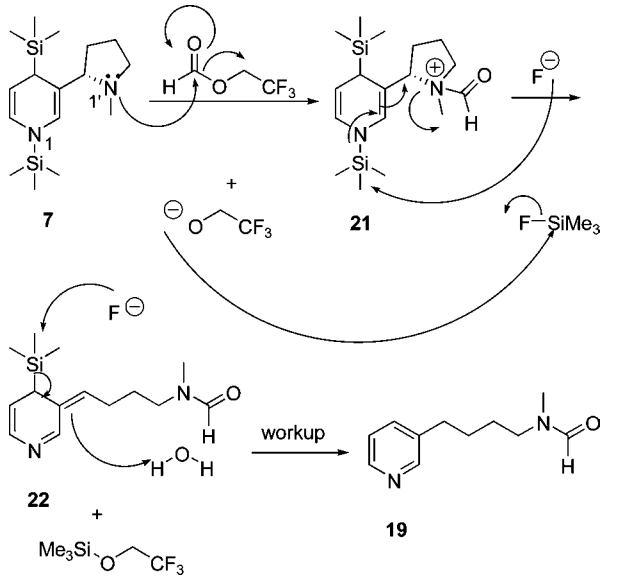
Trifluoroethyl formate leads to the pyrrolidine-opened product **19** in 45% yield (reaction g). A possible mechanism for this conversion is proposed in Scheme 4. Formylation at the nitrogen of the pyrrolidine, removal of the TMS group located on N-1 by fluoride, and opening of the pyrrolidine ring afford intermediate **22**. Removal of the second TMS group located at C-4 and protonation during the workup give the formamide **19**.

Table 1. Conditions for Fluoride-Catalyzed Reaction of **7** with Various Aldehydes

entry[a]	aldehyde	conditions[b]	product	yield (%)[c]
1	benzaldehyde	rt (1 day)	**10**	31
2	benzaldehyde	50 °C (1 day)	**10**	56
3	2-thiophenecarboxaldehyde	50 °C (1 day)	**11**	67
4	2-furaldehyde	50 °C (1 day)	**12**	47
5	dodecyl aldehyde	reflux (1 day)	**13**	70

[a] The reactions were generally performed on a 0.3−3.0 mmol scale in THF. [b] The aldehyde (1.1−2.0 equiv) and TBAF (0.1 equiv) were added at room temperature. [c] Yield of products obtained from radial preparative-layer chromatography.

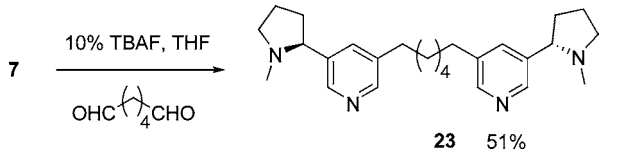
Scheme 4



We were surprised to discover that phenyl carbonate gave the pyrrolidine ring-opened product **20** (reaction h). Of the carbonyl compounds studied, only the more reactive reagents such as trifluoroethyl formate and phenyl carbonate react at N-1′ leading to ring-opened products.

The Tsuge reaction of dihydronicotine **7** has the potential to allow the preparation of unique nicotine analogues. For example, treatment of 1,4-hexanedial and **7** with TBAF afforded the tethered nicotine dimer **23** (Scheme 5).

Scheme 5



In conclusion, the reductive disilylation of (*S*)-nicotine was achieved in high yield. When 1,4-bis(trimethylsilyl)-1,4-dihydronicotine (**7**) was treated with aldehydes in the presence of a catalytic amount of TBAF, C-5-substituted nicotines were obtained in moderate to good yields. With methyl carbonate, ethyl formate, and trifluoroethyl acetate, N-1 substitution occurred leading to 4-unsubstituted 1,4-dihydronicotines in good to high yields. With phenyl carbonate and trifluoroethyl formate, we observed reactivity at N-1′ causing opening of the pyrrolidine ring. These novel nicotine derivatives and dihydronicotines are currently being

tested for CNS as well as insecticidal activities. The methods described above provide derivatives of nicotine with good to high enantiomeric purity in a regiospecific and inexpensive manner. Ongoing studies in our laboratories are directed at converting commercially available (*S*)-nicotine to useful compounds, such as potential pharmaceuticals, insecticides, synthetic intermediates, and ligands for asymmetric synthesis.[12,13]

(12) (a) Comins, D. L.; Despagnet, E. U.S. Patent Application 10/925,516. (b) King, L. S.; Smith, E.; Comins, D. L. U.S. Patent Application 10/715,147.

(13) For 2.2′-bipyridine ligands prepared from nicotine, see: Schmidt, B.; Neitemeier, V. *Synthesis* **1998**, 42.

Acknowledgment. NMR and mass spectra were obtained at NCSU instrumentation laboratories, which were established by grants from the North Carolina Biotechnology Center and the National Science Foundation (Grants CHE-0078253 and CHE-9509532).

Supporting Information Available: Experimental procedure for **7** and characterization data for compounds **8**−**20** and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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