ORGANIC LETTERS

2005
Vol. 7, No. 22
5059−5062

Synthesis of C-4 Substituted Nicotine Derivatives via an *N*-Acylpyridinium Salt of (*S*)-Nicotine

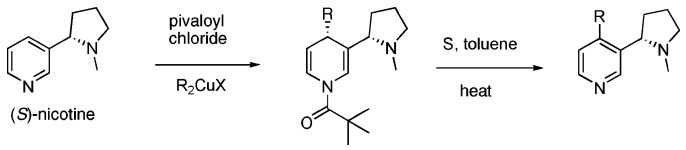
Daniel L. Comins,* Laura S. King, Emilie D. Smith, and Florence C. Février

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

daniel_comins@ncsu.edu

Received August 24, 2005

ABSTRACT



A variety of novel nicotine derivatives were prepared from (*S*)-nicotine via a two-step sequence. Addition of a cuprate reagent to an *N*-acylpyridinium salt of nicotine, followed by aromatization with elemental sulfur, afforded C-4 substituted nicotines in moderate to high yield. Using this method, 4-(dimethylphenylsilyl)nicotine was prepared and oxidized to afford (*S*)-4-hydroxynicotine.

(*S*)-Nicotine (**1**) is the most abundant alkaloid isolated from the tobacco plant. Of the minor alkaloids studied only nornicotine (**2**), metanicotine (**3**), and anabasine (**4**) (Figure 1) have been shown to have significant pharmacological activity; their actions are similar to those of nicotine but are less potent.[1]

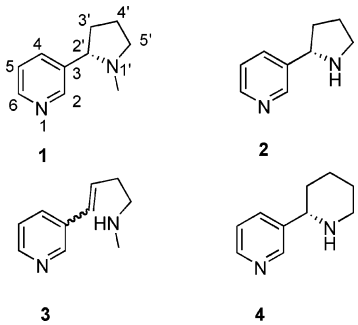


Figure 1. Structures of (*S*)-nicotine (**1**), nornicotine (**2**), metanicotine (**3**), and anabasine (**4**).

Recently, nicotine was found to have some beneficial effects on patients suffering from Parkinson's disease, anxiety, schizophrenia, Alzheimer's disease, ulcerative colitis, and other CNS disorders.[2] Various nuisances associated with the use of nicotine, which include cardiovascular and gastrointestinal systems disturbance, sleep disorder, and addiction, limit the use of nicotine as a therapeutic agent. One of the contemporary challenges is to synthesize nonaddictive nicotine derivatives that display the same beneficial effects of nicotine at lower toxicity.

Numerous nicotine analogues with substituted pyridine and pyrrolidine rings have been synthesized and subjected to physiological studies. As a result of the difficulty in substituting nicotine directly and/or regioselectively, analogue synthesis is often lengthy and low-yielding because of the necessity to start with non-nicotine starting materials. We initiated an investigation into the regioselective synthesis of nicotine derivatives starting from natural (*S*)-nicotine. This approach avoids the use of a resolution to obtain enantiopure material and reduces both the length and the cost of the synthesis of certain nicotine analogues.

Nicotine's two nitrogen atoms are both nucleophilic and can compete for electrophiles. When treating nicotine with

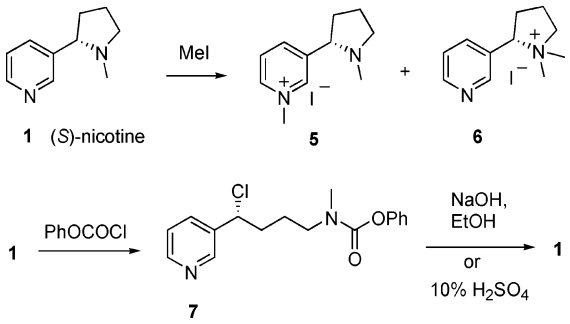
(1) Pailer, M. *Tobacco alkaloids and Related Compounds*; von Euler, U. S., Ed.; Pergamon Press: New York, 1965; p 15.

(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.

10.1021/ol0520469 CCC: $30.25
Published on Web 09/28/2005

iodomethane, Seeman[3] observed a 2.5:1 ratio of monoalkylated products **6** and **5**, indicating that the pyrrolidine nitrogen is about three times more nucleophilic than the pyridine nitrogen. In nicotine, the pK_a of N-1 is 3.04 and the pK_a of N-1′ is 7.84.[1]

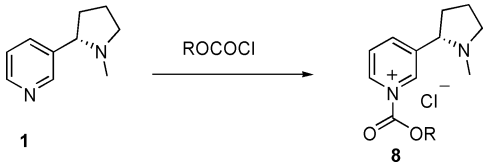
Scheme 1. Reactions of Nicotine with Electrophiles



Cosford and Bleicher demonstrated that the pyrrolidine ring of nicotine can be opened by phenyl chloroformate with inversion of configuration at C-2′ and subsequently reclosed with net retention of configuration.[4] This conversion is unfortunate in the sense that *N*-acylpyridinium salts are valuable intermediates for pyridine substitution reactions,[5] but in this case the pyrrolidine nitrogen wins the acylation competition, preventing this pathway to substituted nicotines.

Years ago, we reported the copper-mediated addition of Grignard reagents to *N*-acylpyridinium salts to access various C-4 substituted pyridines.[5a] Since the corresponding reaction with nicotine would be valuable for preparing analogues, we initiated a screening of various chloroformates in an attempt to form the desired pyridinium salt intermediate **8** (Scheme 2).

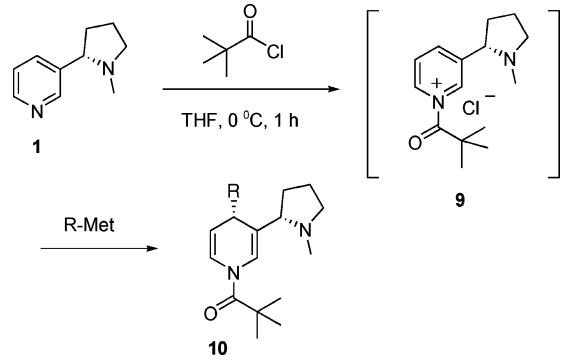
Scheme 2. Acylation at N-1 of Nicotine



We first investigated the reaction of phenyl chloroformate, nicotine, and a Lewis acid. The addition of a Lewis acid additive, such as boron trifluoride etherate, was intended to block acylation at N-1′, but the combination failed to produce the desired pyridinium salt, the ring-opened product **7** described by Cosford and Bleicher[4] being isolated instead. The use of a bulky chloroformate, such as *trans*-2-(cumyl)-cyclohexyl chloroformate[6] (to inhibit acylation at the more hindered pyrrolidine ring nitrogen) led to no reaction with phenyl Grignard reagent.

Since the use of chloroformates failed to provide the desired pyridinium salt intermediate, we turned our attention to the use of hindered and less reactive acyl chlorides. It was discovered that pivaloyl chloride reacted selectively at N-1 to form the desired pyridinium salt of nicotine. We then investigated the reaction of that salt with cuprate reagents to give *N*-pivaloyl-1,4-dihydronicotines **10** (Scheme 3).

Scheme 3. Addition of Cuprate Reagents to C-4 of *N*-Acylpyridinium Salt **9**



Initially, the reactivity of the *N*-pivaloylpyridinium salt of nicotine with simple alkyl and aryl cuprates was examined. The cuprates were easily prepared by the transmetalation of their corresponding Grignard reagent with CuBr·SMe$_2$. The results of the addition reactions are presented in Table 1

Table 1. Addition of Organocopper Reagents to **9**

entry[a]	R-Met[b]	conditions	product	yield,[c] %
1	MeMgBr, CuBr	−78 °C, 3 h	**10a**	71
2	PhMgBr, CuBr	−78 °C, 3 h	**10b**	79
3	*n*-BuMgBr, CuBr	−78 °C, 3 h	**10c**	40
4	BnMgBr, CuBr	−78 °C, 3 h	**10d**	64
5	**11**	−78 °C, 3 h −30 °C, 10 h	**10e**	77
6	**12**	−78 °C, 3 h	**10f**	76 (52% dr)[d]
7	**13**	−78 °C, 3 h −30 °C 10 h	**10g**	58
8	**14**	−78 °C, 3 h −30 °C 10 h	**10h**	81 (68% dr)[d]

[a] The reactions were generally performed on a 1−3.0 mmol scale in THF. [b] The organometallics were prepared in a separate flask (1−2 equiv) and added to **9** at −78 °C. [c] Unless indicated, the products were isolated as one diastereomer. [d] The ratio of diastereomers (dr) was determined by ^{1}H NMR.

(entries 1−4). The yields range from 40% to 79%, and all of the 1,4-dihydronicotine products were isolated as a single diastereomer. The stereochemistry at C-4 was confirmed by

(3) Seeman, J. I.; *Heterocycles* **1984**, *22*, 165.
(4) Bleicher, L. S.; Cosford, N. D. P. *J. Org. Chem.* **1999**, *64*, 5299.
(5) (a) Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1982**, *47*, 4315. For reviews, see: (b) Comins, D. L.; O'Connor, S. *Adv. Heterocycl. Chem.* **1998**, *44*, 199. (c) Comins, D. L.; Joseph, S. P. In *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI Press: Greenwich, CT, 1996; Vol. 2, pp 251−294. (d) Comins, D. L.; Joseph, S. P. Chemistry of Pyridines at Ring Positions, in Comprehensive Heterocyclic Chemistry, 2nd ed.; McKillop, A., Ed.; Pergamon Press: Oxford, England, 1996; Vol. 5.

(6) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719.

X-ray crystallography of product **10b**. The diastereofacial selectivity observed in these transformations must be caused by the pyrrolidine ring acting as a chiral inductor through complexation of its nitrogen to the organometallic during the addition step.[7]

Encouraged by these results, we decided to expand the scope of this transformation by using some heterocyclic and functionalized cuprate reagents (Figure 2).

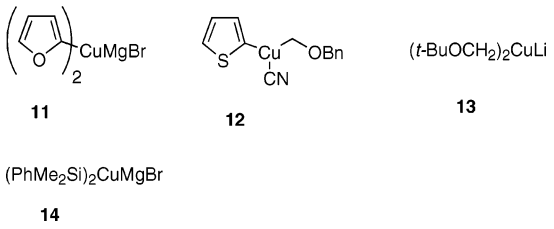


Figure 2. Organocopper nucleophiles used in the preparation of **10e**−**h**.

Synthesis of 4-furanyldihydronicotine **10e** was achieved in 77% yield by addition of cuprate **11** to **9** (entry 5). This cuprate was prepared from lithiation of furan, followed by addition of freshly made $MgBr_2$ and transmetalation with $CuBr{\cdot}SMe_2$. A benzyloxymethyl group was introduced in 76% yield using higher order cuprate **12**, formed from the transmetalation of the corresponding stannane[8] with *n*-BuLi and addition of the Lipshutz reagent. Although the yield was good, the addition resulted in the formation of a mixture of diastereomers (**10f**) with a 52% de (entry 6).

Addition of cuprate **13**, formed from deprotonation of *tert*-butylmethyl ether with *s*-butyllithium and potassium *tert*-butoxide followed by transmetalation with $CuBr{\cdot}SMe$,[9] to **9** yielded 58% of product **10g** as a single diastereomer along with 40% of recovered starting material (entry 7).

Finally, addition of (dimethylphenylsilyl)cuprate **14**, prepared from (dimethylphenylsilyl)magnesium bromide and $CuBr{\cdot}SMe_2$, gave a surprisingly high yield (81%) of **10h**;[10] however, the stereoselectivity was moderate, as two diastereomers were isolated with a 68% dr (entry 8).

Once a regioselective method had been developed to synthesize *N*-acyl-1,4-dihydronicotines, the next step was to find a mild oxidation to afford 4-substituted nicotines **15**. Early attempts using *p*-chloranil, *o*-chloranil, or palladium on carbon in toluene at reflux proved to be fruitless, as no reaction occurred after 6 h in each case. The use of a stoichiometric amount of sulfur in refluxing toluene[5a,11] was successful after 1−3 days of heating and provided good yields (59−93%) of 4-substituted nicotines **15** (Scheme 4, Table 2).

Scheme 4. Aromatization of Dihydropyridines **10** with Sulfur

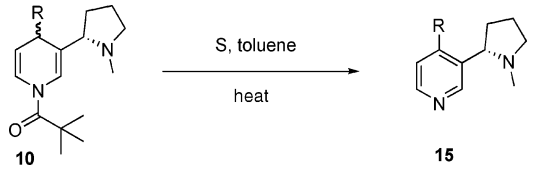


Table 2. Aromatization of Dihydropyridines **10** with Sulfur

entry[a]	**10**	conditions[b]	**15**	R	yield,[c] %
1	**10a**	reflux (32 h)	**15a**	Me	79
2	**10b**	reflux (32 h)	**15b**	Ph	59
3	**10c**	reflux (32 h)	**15c**	*n*-Bu	93
4	**10d**	reflux (32 h)	**15d**	Bn	64
5	**10e**	reflux (3 d)	**15e**	2-furanyl	74
6	**10f**	reflux (3 d)	**15f**	$BnOCH_2$	60
7	**10g**	act. C, reflux (2 d)	**15g**	*t*-$BuOCH_2$	68
8	**10h**	90 °C (1 d)	**15h**	$PhMe_2Si$	80

[a] The reactions were generally performed on a 1−3.0 mmol scale in toluene. [b] Sublimed sulfur (1.0 equiv) was used. [c] Yield of products obtained from radial preparative-layer chromatography.

Aromatization of 4-*n*-butyl-1,4-dihydronicotine **10c** was achieved in an excellent yield of 93% (entry 3). A temperature of only 90 °C was needed for 4-(dimethylphenylsilyl)-dihydronicotine **10h** (entry 8) to afford an 80% yield of **15h**. In the case of substrate **10g**, addition of activated charcoal was required to provide a 68% yield of the corresponding nicotine derivative.

To verify that no racemization occurred during the oxidation step, a method was developed to separate racemic nicotine by chiral HPLC. All new 4-substituted nicotines showed >99% ee using this method.

The analogue 4-(hydroxymethyl)nicotine (**15i**, R = $HOCH_2$) was previously synthesized by Seeman[12] as a byproduct (5% yield) in the development of a ligand for radioimmunoassay for tobacco alkaloids. Deprotection of the hydroxymethyl group in compounds **15f** and **15g** would afford 4-(hydroxymethyl)nicotine. Various hydrogenation conditions were attempted to cleave the benzyl group of **15f**. Hydrogenation using a catalytic amount of Pd/C in ethanol did not yield any product, whereas use of Pearlman's catalyst as well as phase transfer catalysis[13] resulted in opening of the pyrrolidine ring.

(7) For related reactions using chiral auxiliaries, see: (a) Meyers, A. I.; Oppenlaender, T. *J. Am. Chem. Soc.* **1986**, *108*, 1989. (b) Mangeney, P.; Gosmini, R.; Raussou, S.; Commercon, M.; Alexakis, A. *J. Org. Chem.* **1994**, *59*, 1877. (c) Yamada, S.; Ichikawa, M. *Tetrahedron Lett.* **1999**, *40*, 4231. (d) Yamada, S.; Morita, C. *J. Am. Chem. Soc.* **2002**, *124*, 8184 and references therein.

(8) Kaufman, T. S. *Synlett* **1997**, 1378.

(9) Corey, E. J.; Eckrich, T. *Tetrahedron Lett.* **1983**, *24*, 3165.

(10) For related reactions, see: (a) Comins, D. L.; Killpack, M. O.; Despagnet, E.; Zeller, E. *Heterocycles* **2002**, *58*, 505. (b) Comins, D. L.; Killpack, M. O. *J. Am. Chem. Soc.* **1992**, *114*, 10, 972. (c) Hösl, C. E.; Wanner, K. T. *Heterocycles* **1998**, *48*, 2653

(11) Comins, D. L.; Stroud, E. D.; Herrick, J. J. *Heterocycles* **1984**, *22*, 151.

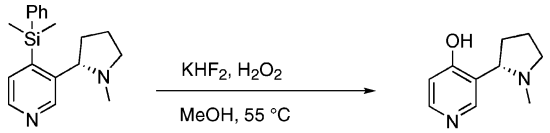
(12) Seeman, J. I.; Chavdarian, C. G.; Secor, H. V.; Osdene, T. S. *J. Org. Chem.* **1986**, *51*, 1548.

(13) Hanesina, S.; Liak, T. J.; Vanasse, B. *Synthesis* **1981**, *397*.

Cleavage of the *tert*-butyl ether of **15g** using TFA/CH_2Cl_2 followed by an anhydrous workup afforded 98% of 4-(hydroxymethyl)nicotine (**15i**). This synthesis of (*S*)-4-(hydroxymethyl)nicotine was achieved with an overall yield of 39%.

We next turned our attention to the oxidation of 4-(dimethylphenylsilyl)nicotine **15h** (Scheme 5). A dimethylphenylsilyl group has been widely used as a masked hydroxy group.[14] It can easily be oxidized and converted to an hydroxy group by using Tamao's procedure (TFA; KHF_2, H_2O_2).[15] Tamao's conditions resulted in the conversion of **15h** to **16** in 30% yield. In this case, formation of nicotine *N*-1′-oxide was of concern so milder conditions were investigated. In a report by Dunogues,[16] an aromatic alkoxysilane was converted to the corresponding phenol using potassium fluoride and hydrogen peroxide in ethanol. Similar conditions proved to be more suitable for the oxidation of **15h**. The use of KHF_2 and H_2O_2 in methanol at 55 °C and modifying the workup afforded 82% of novel 4-hydroxynicotine (**16**).[17]

Scheme 5. Conversion 4-(dimethylphenylsilyl)nicotine to 4-hydroxynicotine



15h **16** 82%

The presence of a hydroxyl group on the pyridine ring of nicotine opens up new pathways to regioselective introduction of substituents via aromatic electrophilic substitution and directed lithiation. These potential substitution reactions of 4-hydroxynicotine are currently under investigation. The novel nicotine derivatives and *N*-acyldihydronicotines prepared in this study are currently being tested for CNS as well as insecticidal activities.

In conclusion, a variety of novel 1,4-dihydronicotines and C-4 substituted nicotines have been synthesized from (*S*)-nicotine in moderate to high yield. To the best of our knowledge, this is the first synthesis of 4-substituted 1,4-dihydronicotines. We also report the formation and reactivity of the first *N*-acylpyridinium salt of nicotine. The two-step procedure developed for the preparation of 4-substituted nicotine derivatives is cost-efficient, regioselective, and resolution-free. The new methodologies described in this paper provide rich opportunities for exploring new routes to interesting and potentially useful compounds based on nicotine.[18]

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-9121380 and CHE-9509532).

Supporting Information Available: Experimental procedures for **10** and **15**; characterization data and NMR spectra for compounds **10a**−**h, 15a**−**h**, and **16**; ORTEP plot and X-ray crystal data for **10b** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0520469

(14) For a review, see: Fleming, I. *Chemtracts Org. Chem*. **1996**, *9*, 1.
(15) Tamao, K.; Ishida, N. *J. Organomet. Chem*. **1984**, *269*, C37.
(16) Prouilhac-Cros, S.; Babin, P.; Bennetau, B.; Dunogues, J. *Bull. Soc. Chim. Fr*. **1995**, *132*, 513.
(17) Isolated **16** exists in the 4-hydroxypyridine tautomeric form presumably as a result of hydrogen bonding with the pyrrolidine nitrogen.
(18) King, L. S.; Smith, E.; Comins, D. L. U.S. Patent Application 10/715, 147, Nov 17, 2003.