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Regioselective 5-, 4-, and 2-Substitution of (*S*)-6-Chloronicotine and 4-Substitution of (*S*)-5-Chloronicotine

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A variety of novel 2-, 4-, and 5-substituted 6-chloronicotine and 4-substituted 5-chloronicotine derivatives have been synthesized in a regioselective manner in moderate to high yield from (*S*)-6-chloronicotine and (*S*)-5-chloronicotine, respectively.

Introduction

(*S*)-Nicotine (**1**), the classical agonist of the nicotinic acetylcholine receptors (nAChR), has attracted much attention because of its important pharmacological effects on central nervous system (CNS) diseases. In particular, (*S*)-nicotine may have beneficial effects in the treatment of Parkinson's disease (PD) and Alzheimer's disease (AD).[1] Both neurodegenerative disorders have emerged as a major public health concern as a consequence of the post World War II baby boom and the changes in the global population age profile. Nicotine is not suitable for therapeutical use due to its undesirable side effects.[2] As a consequence, there is a considerable interest in synthesizing selective nAChR ligands for the development of neurodegenerative disorder drugs which possess the positive effect of nicotine without harmful side effects. The development of new pharmaceuticals based on the core nicotine structure has been limited by the lack of synthetic methods for preparing derivatives directly from natural nicotine. Our group has been developing syntheses of nicotine derivatives using natural (*S*)-nicotine itself as an inexpensive starting material. Previous work includes the synthesis of 4-substituted derivatives via an *N*-acylpyridinium salt of nicotine,[3] 5-alkylation by the reductive disilylation of nicotine,[4] and 2- and 6-substitution of the pyridine ring of nicotine using regioselective deprotonations.[5] Following in this vein, we report herein the regioselective substitution of (*S*)-6-chloronicotine (**2**) by directed lithiation of the pyridine ring (Figure 1).

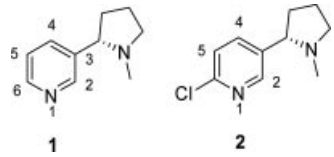

Figure 1. (*S*)-Nicotine (**1**) and (*S*)-6-chloronicotine (**2**).

Results and Discussion

The deprotonation at the 5-position of **2**, using the well-described *ortho*-directing effect of the chlorine atom,[6] was attempted first. Surprisingly, the lithiation of 6-chloronicotine (**2**) could not be effected by using up to 3 equiv. of LDA. Treatment of **2** with 1.1 equiv. of the stronger base LiTMP in THF at –78 °C, followed by addition of the appropriate electrophile, afforded the 5-substituted derivatives **3a**–**h** (Table 1). This facile reaction allows the regioselective introduction of various functional groups at the 5-position of **2**. The addition of iodomethane was problematic affording a complex mixture of 6-chloro-5-methyl-, and 6-chloro-5-ethylnicotine that could not be separated by chromatography (Entry 8).

Initially, we thought 6-chloro-4-iodonicotine (**4a**) would be easily accessible through an iodine dance reaction[7] on 6-chloro-5-iodonicotine (**3a**). However, multiple attempts using LDA or LiTMP in various amounts led to its formation in only very low yield, whereas diiodinated **6** and 2-iodinated **5a** were observed (Table 2). More interestingly, treatment of 6-chloronicotine (**2**) with 3.0 equiv. of LiTMP followed by the addition of only 1.0 equiv. of iodine resulted in the near quantitative formation of **5a** (Table 3). A related attempt using another electrophile, $C_2Br_2Cl_4$, under the same conditions failed and afforded (*S*)-5-bromo-6-chloronicotine (**3c**) and (*S*)-2,5-dibromo-6-chloronicotine.

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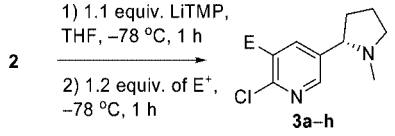
Table 1. Substitution at the 5-position of the pyridine ring of (*S*)-6-chloronicotine (**2**) using LiTMP.



Entry[a]	Electrophile E^+	Product, E	Yield[b] [%]
1	I_2	**3a**, I	74
2	C_2Cl_6	**3b**, Cl	87[c]
3	$C_2Br_2Cl_4$	**3c**, Br	37
4	$ClSiPhMe_2$	**3d**, $SiPhMe_2$	45
5	MeSSMe	**3e**, SMe	63
6	$ClSnBu_3$	**3f**, $SnBu_3$	66
7	ethyl formate	**3g**, CHO	58
8	MeI	**3h**, Me	–[d]

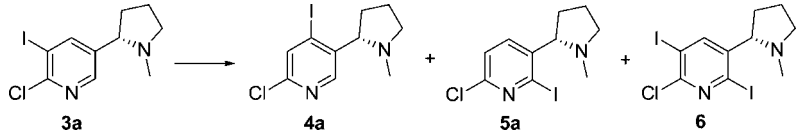
[a] Reactions were run on a 0.25–3.0 mmol scale. [b] Isolated yield after radial PLC. [c] **3b** was dehalogenated to afford nicotine using 10% Pd/C, H_2 in MeOH in >99% *ee*. [d] Reaction resulted in an inseparable mixture of **3h** and (*S*)-6-chloro-5-ethylnicotine.

The proposed halogen dance mechanism for the formation of **5a** is depicted in Scheme 1. The first lithiation occurs at the 5-position as discussed previously (Table 1) to give pyridyllithium compound **I** which on addition of iodine affords **3a**. A second equivalent of LiTMP deprotonates the 2-position of **3a**. This intermediate **II** might be stabilized by complexation to the pyrrolidine nitrogen atom. The 2-lithiated intermediate **II** reacts with another equivalent of **3a** by abstracting the iodine atom at the 5-position to form the diiodide **6** and the 5-lithiated 6-chloronicotine intermediate **I**. Intermediate **I** then attacks **6** and affords 5-lithiated 6-chloro-2-iodonicotine intermediate **III** and **3a** which reenters the reaction cycle. Quenching with a saturated aqueous solution of sodium hydrogencarbonate provides compound **5a** in very good yield. To provide evidence for this mechanism, 6-chloro-5-iodonicotine (**3a**) was added to a mixture of 1.0 equiv. of 2,2,6,6-tetramethylpiperidine with 2.0 equiv. of LiTMP at –78 °C for 1 h. After workup, 6-chloro-2-iodonicotine (**5a**) was the major product observed by crude ^{1}H NMR spectroscopy (purity >95%).

Although other 2-substituted 6-chloronicotines can likely be prepared from **5a** using lithium/halogen exchange or cross-coupling reactions, a direct route from **2** was developed. Treatment of 6-chloronicotine (**2**) with *n*BuLi/LiDMAE[8] in toluene at –78 °C, followed by addition of the electrophile, afforded the desired products **5b**–**f** in moderate to good yields (Table 4). It is noteworthy that the same reaction in hexanes, a common solvent for this base complex,[8] did not lead to product formation, and starting material was recovered. The use of the more polar solvent toluene is believed to break up aggregates and improve solubility allowing the deprotonation at the 2-position to occur.

Remarkably, regioselective formation of 4-substituted 6-chloronicotines **4a**–**i** was achieved by simple treatment of 6-chloronicotine (**2**) with 1.1 equiv. of *n*BuLi in THF at –78 °C (Table 5). In particular, 6-chloro-4-iodonicotine (**4a**) was prepared in 80% yield. This directed *ortho*-metalation (DoM)[6,9] is obviously effected by intramolecular coordina-

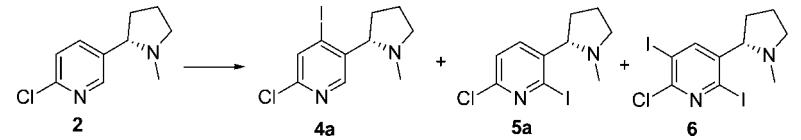
Table 2. Attempts at forming (*S*)-6-chloro-4-iodonicotine (**4a**) by an iodine dance reaction on (*S*)-6-chloro-5-iodonicotine (**3a**).



Entry[a]	Conditions	Product	Ratio[b]
1	1.0 equiv. LDA, THF, –78 °C, 2 h	**6**	–[c,d]
2	1.0 equiv. LDA, THF, –78 °C, 30 min	**3a**, **4a**	2:1
3	2.0 equiv. LDA, THF, –78 °C, 2 h	**3a**, **4a**, **6**	2:1:1
4	1.2 equiv. LiTMP, THF, –78 °C, 1 h	**3a**, **5a**, **6**	1:2:2

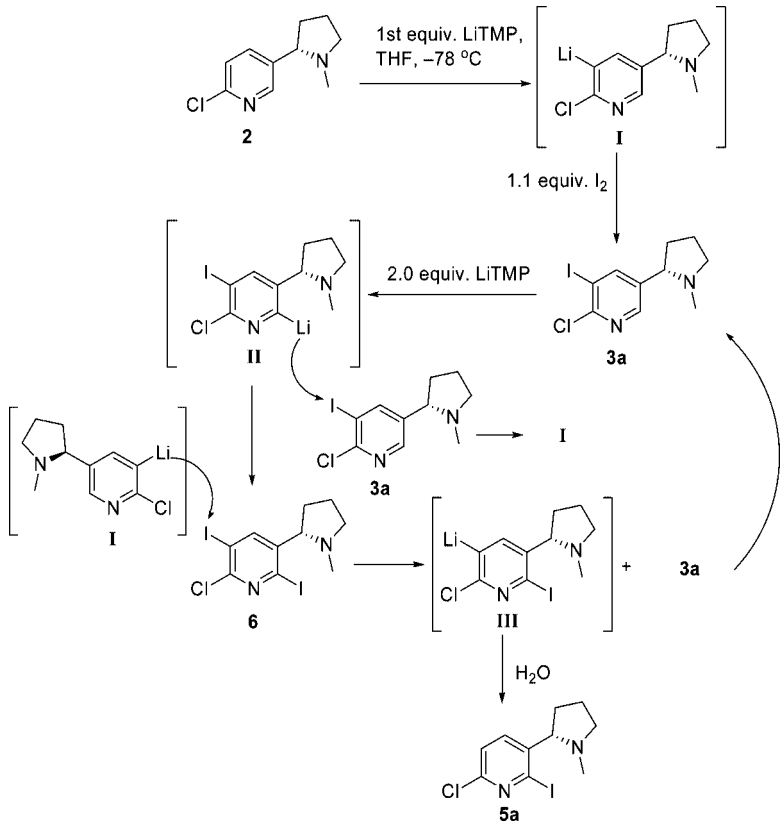
[a] Reactions were run on a 0.1–0.5 mmol scale. [b] Ratio determined by ^{1}H NMR spectroscopy. [c] 52% isolated yield after radial PLC. [d] Traces of **4a**.

Table 3. Iodine dance reactions starting from (*S*)-6-chloronicotine (**2**).



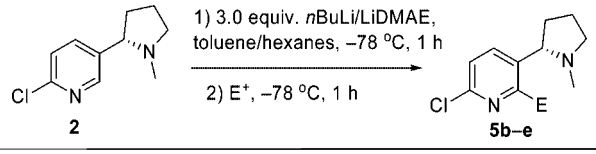
Entry[a]	Conditions	Product	Ratio[b]
1	2.0 equiv. LiTMP, THF, –78 °C, 1 h 1.0 equiv. of I_2, –78 °C, 1 h	**6**,**5a**	1:2
2	3.0 equiv. LiTMP, THF, –78 °C, 1 h 1.0 equiv. of I_2, –78 °C, 1 h	**5a**,**4a**, **6**	>95:5[c,d]

[a] Reactions were run on a 0.1–0.5 mmol scale. [b] Ratio determined by ^{1}H NMR spectroscopy. [c] 95% isolated yield of **5a** after radial PLC. [d] Crude product contained traces of **4a** and **6**.



Scheme 1. Proposed mechanism for the formation of **5a** by an iodine dance reaction.

Table 4. Substitution at the 2-position of the pyridine ring of (*S*)-6-chloronicotine (**2**) using *n*BuLi/LiDMAE.



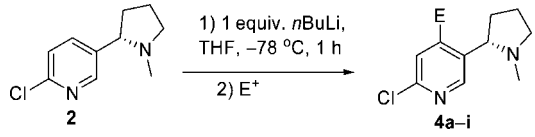
Entry[a]	Electrophile E^+	Product, E	Yield[b] [%]
1	C_2Cl_6	**5b**, Cl	72[c]
2	MeSSMe	**5c**, SMe	53
3	$ClSnBu_3$	**5d**, $SnBu_3$	42
4	ethyl formate	**5e**, CHO	57

[a] Reactions were run on a 1.0 mmol scale. [b] Isolated yield after radial PLC. [c] **5b** was dehalogenated to afford nicotine using 10% Pd/C, H_2 in MeOH in >99% *ee*.

tion of *n*BuLi to the pyrrolidine nitrogen atom during the deprotonation step. Finally, we developed a methodology for the synthesis of 4,5-disubstituted nicotines (Scheme 2). (*S*)-5,6-Dichloronicotine was treated with zinc powder in a 1.0 M solution of HCl in acetic acid at 60 °C for 2 h to afford (*S*)-5-chloronicotine (**7**) in 65% yield with only 12% of the over-reduced product, nicotine (**1**).

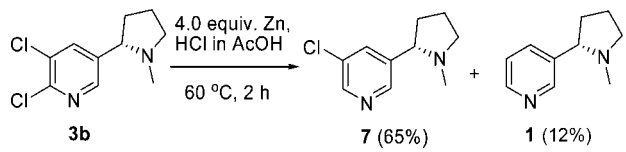
(*S*)-5-Chloronicotine (**7**) was treated with 1.1 equiv. of *n*BuLi in THF at –78 °C to effect a DoM reaction at the 4-position. Upon addition of electrophiles, 4-substituted 5-chloronicotine derivatives **8a**–**g** were obtained in moderate to good yield (Table 6).

Table 5. Regioselective substitution at the 4-position of the pyridine ring of (*S*)-6-chloronicotine (**2**).



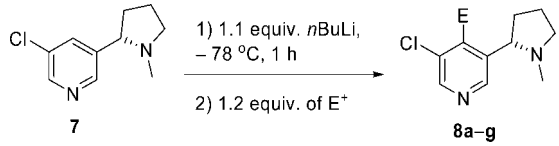
Entry[a]	Electrophile E^+	Product, E	Yield[b] [%]
1	I_2	**4a**, I	80
2	D_2O	**4b**, D	79
3	C_2Cl_6	**4c**, Cl	63[c]
4	$C_2Br_2Cl_4$	**4d**, Br	27
5	ethyl formate	**4e**, CHO	62
6	$ClSnBu_3$	**4f**, $SnBu_3$	51
7	MeSSMe	**4g**, SMe	34
8	PhCHO	**4h**–**i**, CH(OH)Ph	65[d]

[a] Reactions were run on a 0.5–3.0 mmol scale. [b] Isolated yield after radial PLC. [c] **4c** was dehalogenated to afford nicotine using 10% Pd/C, H_2 in MeOH in >99% *ee*. [d] 1:1 ratio of diastereomers.



Scheme 2. Regioselective dehalogenation.

Table 6. Regioselective substitution at the 4-position of the pyridine ring of (*S*)-5-chloronicotine (**6a**).



7 **8a–g**

Entry[a]	Electrophile E^+	Product, E	Yield[b] [%]
1	D_2O	**8a**, D	80
2	I_2	**8b**, I	65
3	MeSSMe	**8c**, SMe	68
4	ethyl formate	**8d**, CHO	55
5	$ClSnBu_3$	**8e**, $SnBu_3$	58
6	$ClSiMe_2Ph$	**8f**, $SiMe_2Ph$	39
7	TMSCl	**8g**, TMS	56

[a] Reactions were run on a 0.1–0.5 mmol scale. [b] Isolated yield after radial PLC.

Conclusions

In summary, a variety of novel 2-, 4-, and 5-substituted 6-chloronicotines have been synthesized in a regioselective manner from (*S*)-6-chloronicotine in moderate to high yield. Our previous studies[3–5] and the new methodologies described herein provide new routes to a plethora of interesting and potentially useful compounds based on nicotine. All positions on the pyridine ring of (*S*)-nicotine can now be regioselectively substituted. In particular, an iodine atom can be introduced at the 2-, 4-, or 5-positions of 6-chloronicotine and at the 4-position of 5-chloronicotine providing intermediates for sequential cross-coupling reactions.[10] Efforts are underway to expand the scope of these methods and to apply them to the preparation of potential pharmaceuticals, insecticides, synthetic intermediates, and novel ligands for catalytic asymmetric synthesis. Our goal is to transform commercially available (*S*)-nicotine from an underutilized natural product to a useful member of the chiral pool.[11]

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization, and NMR spectroscopic data for **3a**–**g**, **4a**–**i**, **5a**, **5b**–**f**, **6**, **7**, and **8b**–**g**.

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