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# Synthesis and regioselective substitution of C-6 alkoxy derivatives of (*S*)-nicotine

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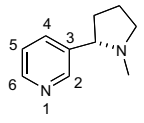
**Abstract**—Enantiopure (*S*)-6-alkoxynicotine derivatives have been synthesized in two steps from (*S*)-nicotine via (*S*)-6-iodonicotine. Deprotonation and substitution at the C-5 position of the pyridine ring of (*S*)-6-methoxynicotine were achieved using mesityllithium as the base at 0 °C. Conditions for the C-4 lithiation/substitution of (*S*)-6-isopropoxynicotine and (*S*)-5-chloro-6-methoxynicotine were also developed.


(*S*)-Nicotine (**1**, Fig. 1), a naturally occurring alkaloid found throughout the tobacco plant, *Nicotiana tabacum*, has drawn a lot of interest in the last few decades due to its potential role in therapeutics for the central nervous system (CNS) related disorders.[1] This is attributed to its activity as an agonist on the nicotinic acetylcholine receptors (nAChRs). Nicotine has been observed to show favorable effects on patients suffering from Alzheimer's disease (AD), Parkinson's disease (PD) and Tourette's syndrome along with other CNS related disorders. However, nicotine is non selective in its binding to acetylcholine (ACh) sites, which produces adverse side effects such as action on the cardiovascular and gastrointestinal systems, dependence, sleep disturbance, and at higher doses neuromuscular effects and seizures. These side effects are due to subtype selectivity, or a lack thereof, among the various nAChRs. Hence there has been a need to synthesize nicotine derivatives that are more selective in their binding to ACh sites to minimize side effects while retaining beneficial activity. In the past, reagents other than nicotine were usually used as starting materials for synthesis of (*S*)-nicotine derivatives.[2] Our group has been developing syntheses of enantioselective nicotine derivatives starting from commercially available (*S*)-nicotine. Previous work reported in the last couple of years includes synthesis of 4-substituted derivatives via an *N*-acylpyridinium salt of nicotine,[3] 5-alkylation via the reductive desilylation of nicotine,[4] 2- and 6-substitution of the pyridine ring of nicotine using regioselective deprotonations,[5] and regioselective 5-, 4- and 2-substitution of (*S*)-6-chloronicotine through directed lithiation of the pyridine ring.[5c] Since there was no precedence in the literature for the synthesis of alkoxy derivatives directly from natural (*S*)-nicotine, we initiated a study to develop a method for this conversion. Glennon and co-workers have reported racemic syntheses of 6- and 5-methoxynicotine starting from nonchiral reagents.[6]

Some of the most commonly used methods for preparation of alkyl aryl ethers complimentary to the Williamson ether synthesis include direct nucleophilic substitution and the copper(I)-catalyzed cross coupling of alkoxides with aryl halides.[7,8] Our initial attempts to synthesize (*S*)-6-methoxynicotine was by nucleophilic aromatic substitution of (*S*)-6-chloronicotine. (*S*)-6-Halonicotines were synthesized in one step from (*S*)-nicotine using directed lithiation as reported in our previous work.[5b] Refluxing (*S*)-6-chloronicotine and 3 equiv of



**1**

**Figure 1.** (*S*)-Nicotine.

*Keywords*: (*S*)-Nicotine; Alkoxynicotine; Lithiation; Regioselective deprotonation.
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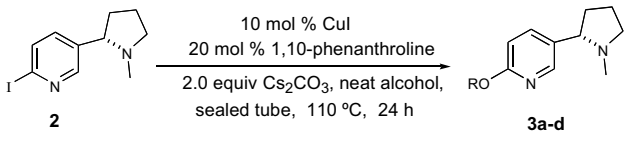
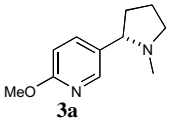
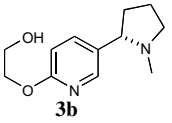
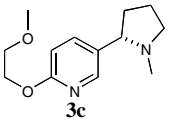
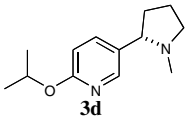
**Table 1.** Preparation of 6-alkoxynicotine derivatives from copper-catalyzed coupling of (*S*)-6-iodonicotine in neat alcohols




**2** **3a-d**

| Entry[a] | Alcohol | Product | Yield[b] (%) |
|---|---|---|---|
| 1[c] | MeOH |  **3a** | 95 |
| 2 | $HOCH_2CH_2OH$ |  **3b** | 90 |
| 3 | $HOCH_2CH_2OMe$ |  **3c** | 95 |
| 4[d] | $HOCH(CH_3)_2$ |  **3d** | 50 |

[a] Reactions were run at 0.1–1.0 mmol scale.
[b] Isolated yield after radial PLC.
[c] Reaction run on gram scale.
[d] Reaction temperature of 90 °C, time 48 h; at 110 °C, 34% isolated yield was obtained.

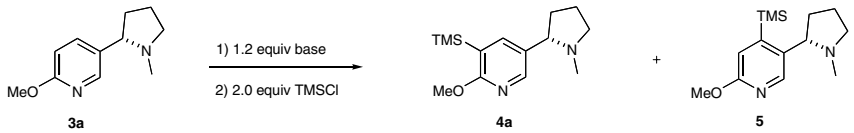
sodium methoxide in methanol for four days resulted in a mixture of starting material and product that proved difficult to separate by chromatography. Attempts to force the reaction to go to completion, by increasing the number of equivalents of sodium methoxide, unfortunately led to decomposition. Changing of the solvent to DMSO was also unsuccessful. Experiments with (*S*)-6-bromonicotine in classical copper-mediated displacement of the aryl halide with the alkoxide resulted in very low yields (15%) of the desired product.[8]

With the difficulties encountered, attention was turned to a method of ether formation reported by Buchwald et al.[9] This mild procedure involves a copper(I)-catalyzed coupling of aryl halides with aliphatic alcohols. A mixture of (*S*)-iodonicotine, an aliphatic alcohol as solvent, cesium carbonate, and 1,10-phenanthroline as the ligand, was heated to 110 °C in a sealed tube. Under these conditions, alkoxy nicotine derivatives were obtained in excellent yields when primary alcohols were used (entries 1–3) and in modest yield in the case of a secondary alcohol (Table 1).[10] The reaction with isopropanol was run at slightly lower temperature (90 °C) to obtain a better yield (entry 4). It was noted that the reactions occurred without racemization as confirmed via chiral column HPLC analysis, which showed enantiomeric purity greater than 99%.[11]

Having successfully established a method for the synthesis of (*S*)-6-alkoxynicotines (**3**), further investigations were carried out to establish what base(s) would be appropriate for regioselective deprotonation of the C-5 and C-4 positions of **3a**. The methoxy group at C-6 is an ortho-directing group and could direct metalation at C-5 while the C-4 proton should be the most acidic on the pyridine ring and may be easily deprotonated.[12] Lithiation of **3a** with different bases and trapping the anion with trimethylsilyl chloride gave some interesting results (Table 2). Regioselective deprotonation of (*S*)-6-methoxynicotine could not be effected with LiTMP even at 0 °C (entry 1). This contrasts greatly with deprotonation of (*S*)-6-chloronicotine which is achieved using LiTMP at −78 °C as reported in the previous work from our group.[5c] The electron donating effect of the methoxy group into the ring lowers the acidity of the proton at the C-5 position causing the need for a stronger base to effect the desired deprotonation.[13]

Treatment of **3a** with 1.2 equiv of *n*-BuLi at −78 °C even for up to 3 h yielded only 20% of C-4 substitution. Raising the temperature to −20 °C resulted in a 1:1 mixture of C-4 and C-5 substitution (entries 2 and 3). Use of the more sterically hindered but stronger base, *t*-BuLi, at −78 °C resulted in 15% of the C-5 substituted derivative. Change of solvent to diethyl ether and use of *s*-BuLi were not successful either as some decomposition occurred. The desired deprotonation was achieved with mesityllithium as the base[13d] in THF at 0 °C. Similarly, good results were obtained when phenyllithium was used. Both bases gave the desired product in good yields (entry 7).

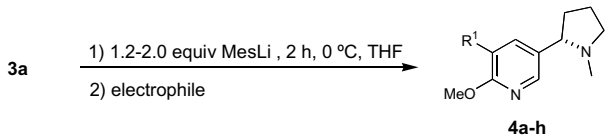
**Table 2.** Lithiation (*S*)-6-methoxynicotine using different bases

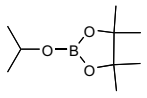
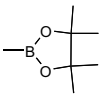



**3a** **4a** **5**

| Entry | Base/conditions | Results |
|---|---|---|
| 1 | LiTMP, −78 → 0 °C, THF, 1 h | sm |
| 2 | *n*-BuLi, −78 °C, THF, 1–3 h | ~20% of **5** |
| 3 | *n*-BuLi, −20 °C, THF, 1 h | **4a** and **5** in 1:1 ratio |
| 4 | *t*-BuLi, −78 °C, THF, 1 h | 15% of **4a** |
| 5 | *t*-BuLi, −78 °C, ether, 1 h | — |
| 6 | *s*-BuLi, −78 °C, THF, 1 h | — |
| 7 | PhLi or MesLi, 0 °C, THF, 2 h | **4a** in good yield |

**Table 3.** Substitution at the C-5 position of (*S*)-6-methoxynicotine using mesityllithium as base




| Entry[a] | Electrophile/conditions | Product, $R^1$ | Yield[b] (%) |
|---|---|---|---|
| 1 | TMSCl (3.0 equiv), −78 or 0 °C, 30 min | **4a**, TMS | 80 |
| 2 | $I_2$, (2.1 equiv), −78 °C, 5 min | **4b**, I | 87 |
| 3 | $C_2Br_2Cl_4$, (2.1 equiv) −78 °C, 10 min | **4c**, Br | 87 |
| 4 | $C_2Cl_6$ (2.1 equiv), −78 or 0 °C, 30 min | **4d**, Cl | 88 |
| 5 | DMF (3.0 equiv), 0 °C, 3 h | **4e,**CHO | 81 |
| 6 | MeI, (2.1 equiv), 0 °C, 5 min | **4f**, Me | 76 |
| 7 | Cl $SnBu_3$ (3.0 equiv), 0 °C, 3 h | **4g**, $SnBu_3$ | 60 |
| 8 | MeSSMe (3.0 equiv), 0 °C, 3 h | **4h**, SMe | 74 |
| 9 |  (3.0 equiv), - 78 → 0 ºC | **4i**,  | Decomposed on purification |

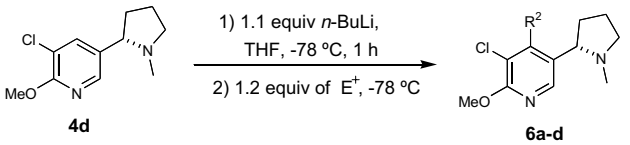
[a] Reactions were run on 0.10–3.0 mmol scale.
[b] Isolated yield after radial PLC.

Next, reaction of the anions with various representative electrophiles was examined (Table 3). While all other electrophiles were added at 0 °C, addition of the halogen electrophiles had to be done at −78 °C to avoid a C-4 substituted by-product, which could be attributed to a halogen dance reaction (entries 2 and 3).[14,15] Use of a boronate ester as an electrophile appeared successful by TLC and NMR analysis, but the product decomposed on purification (entry 9).

Further investigations were carried out on (*S*)-5-chloro-6-methoxynicotine (**4d**), which was treated with 1.2 equiv of *n*-BuLi in THF at −78 °C to effect a directed ortho metalation at the C-4 position. Upon addition of various electrophiles, 4-substituted 5-chloro-6-methoxynicotine derivatives **6a–d** were obtained in high yields (Table 4).

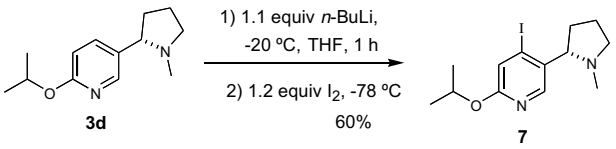
Finally, directed lithiation using *n*-BuLi was attempted on the more sterically hindered (*S*)-6-isopropoxynicotine (**3d**) (Scheme 1). Notably, only the C-4 substitution

**Table 4.** Substitution at C-4 of the pyridine ring of (*S*)-5-chloro-6-methoxynicotine (**4d**)




| Entry[a] | Electrophile, $E^+$ | Product, $R^2$ | Yield[b] (%) |
|---|---|---|---|
| 1 | $I_2$ | **6a**, I | 83 |
| 2 | $C_2Cl_6$ | **6b**, Cl | 88 |
| 3 | MeSSMe | **6c**, SMe | 81 |
| 4 | $C_2Br_2Cl_4$ | **6d**, Br | 80 |

[a] Reactions were run in 0.1–0.3 mmol scale.
[b] Isolated yields after radial PLC.




**Scheme 1.** Regioselective substitution at C-4 of the pyridine ring of (*S*)-6-isopropoxynicotine.

product was obtained on deprotonation with 1.1 equiv of base at −20 °C. A yield of 60% of **7** was obtained when the anion was quenched with iodine as the electrophile. This result differed markedly from the corresponding reaction of (*S*)-6-methoxynicotine, which gave a mixture of C-5 and C-4 regioisomers.

In conclusion, methodology to synthesize C-6 primary and secondary alkoxy derivatives of nicotine in two steps from (*S*)-nicotine has been developed. A variety of novel alkoxy derivatives as well as (*S*)-6-methoxynicotine have been synthesized in enantiopure form. New methods to substitute the C-5 and C-4 positions of the pyridine ring of (*S*)-6-alkoxynicotines have also been developed.

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