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Regioselective C-2 and C-6 Substitution of (*S*)-Nicotine and Nicotine Derivatives

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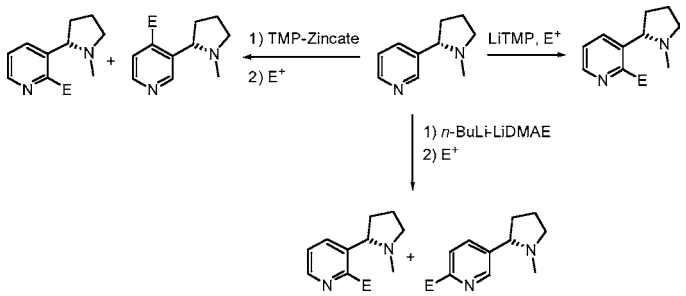
ABSTRACT



Regioselective deprotonations of (*S*)-nicotine and derivatives at the C-2 and C-6 positions of the pyridine ring were performed in good to excellent yields. These methodologies allow the direct introduction of a plethora of functional groups onto the pyridine ring of nicotine.

(*S*)-Nicotine (**1**), the most abundant alkaloid isolated from fresh *Nicotina tabacum*,[1] 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), Alzheimer's disease (AD), and Tourette's syndrome.[2] The neurotransmitter (NT) most consistently implicated in AD is acetylcholine (ACh). Many groups of compounds have been isolated from natural sources or synthesized as ligands for the nicotinic acetylcholine receptors, of which nicotine and its analogues represent an important class. However, nicotine is not suitable for therapeutical use due to its undesirable side effects including the potential for abuse and actions on the cardiovascular and gastrointestinal systems.[3] As a consequence, pharmaceutical reseachers are racing to synthesize a selective nAChR ligand for the development of neurodegenerative disorder drugs which possess the positive effects of nicotine without the compound's 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. In most previous studies, reagents other than nicotine were used as starting material for the synthesis of (*S*)-nicotine derivatives.[2d] Since nonchiral compounds have been used as starting material, a low-yielding resolution was often required to provide the desired enantiomer. In an attempt to avoid one or more resolution steps, our attention turned toward the synthesis of enantioselective nicotine derivatives using natural (*S*)-nicotine itself as an inexpensive starting material.

Lithiation of aromatic and heteroaromatic compounds has been widely used to introduce various functional groups.[4] This reaction is a very attractive functionalization method as electrophilic substitutions are often difficult on π-deficient

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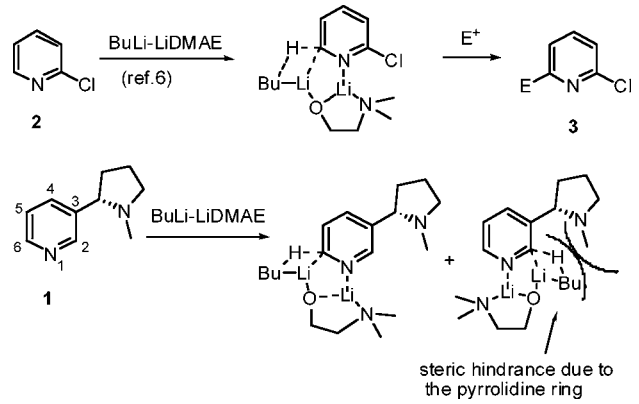
heterocycles. To investigate regioselectivity in the deprotonative metalation of nicotine, several metalating agents were screened. The choice of base was found to play a crucial role to access the desired lithiopyridine intermediates.

Recent efforts toward functionalization of pyridines have focused on the development of directed ortho-metalation methods (DoM effect).[5] The mechanism of this selective reaction was generally assumed to proceed via the well-known complex-induced proximity effect (CIPE) between the ortho-directing group and the lithiating agent promoting introduction of lithium at the ortho position. In 2000, Fort and co-workers reported a new base composed of *n*-BuLi and $Me_2N(CH_2)_2OLi$.[6] This unimetal superbase called *n*-BuLi−LiDMAE induced a regioselective lithiation of pyridine derivatives even when an ortho-directing group was present on the heterocyclic ring (Scheme 1). This selectivity strongly

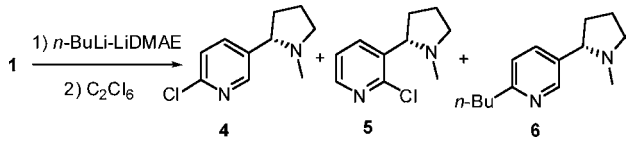
Scheme 1. Fort's Unimetal Superbase Complexation by the Pyridine Nitrogen Atom of **2** and Its Complexation with (*S*)-Nicotine (**1**)



contrasted with results observed with the well-known lithium diisopropylamine (LDA) and alkyllithium bases, which abstracted exclusively the hydrogen at C-3 in agreement with the DoM effect. The complete inhibition of the DoM effect of the C-2 chlorine of **2** with *n*-BuLi−LiDMAE was explained by the formation of aggregates between *n*-BuLi−LiDMAE and the substrate via lithium complexation by the pyridine nitrogen atom. The metalation had to be performed in apolar, noncoordinating solvents such as hexane. Aggregates were assumed first to deliver *n*-BuLi near the C-6 proton of 6-chloropyridine and second to ensure stabilization of the formed C-6 lithiated intermediate.[6]

The reaction of nicotine with *n*-BuLi−LiDMAE resulted in the selective deprotonation at the C-6 position of the pyridine ring (Scheme 1). The lack of lithiation at the C-2 position of the pyridine is probably due to steric hindrance resulting from the pyrrolidine ring at C-3. Initially, (*S*)-6-chloronicotine (**4**) was obtained in only 39% yield (Table 1). It is noteworthy to emphasize that this substitution of

Table 1. Formation of (*S*)-6-Chloronicotine



entry[a]	*n*-BuLi (equiv)	*T* (°C)	solvent system	**4** (%)
1	6.0	0	hexanes	39−60
2	6.0	0	hexanes/THF	36
3	6.0	−20	hexanes	70
4	5.4	0	hexanes	65
5	5.4	−20	hexanes/toluene	87

[a] Reactions were run on a 1.0 mmol scale.

(*S*)-nicotine happens without racemization.[7] The main side reaction was the substitution by a butyl group onto the pyridine ring at the C-6 position. Interested by the potential synthetic utility of compound **4**, solvent systems, number of equivalents of base, and temperature were varied. The reaction outcome was found to be highly sensitive to solvents. When THF was used as a cosolvent (needed to dissolve the electrophile) (entry 2), classical nucleophilic substitution by *n*-BuLi was observed due to aggregate disruption. Toluene (entry 5), a less polar solvent, did not disrupt the aggregate, thus providing a better cosolvent for this reaction. A lower temperature during the deprotonation (entries 3 and 5) limited the addition of the butyl group to the pyridine ring affording higher yields of 6-chloronicotine (**4**). The synthesis of **4** was successfully performed on a large scale (20 mmol) in excellent yield.

Next, the reaction of various representative electrophiles was examined (Table 2). The addition of electrophiles to the lithiated nicotine intermediate is very exothermic, which facilitates the formation of the undesired regioisomer **9**. The low yields of bromination and iodination (entries 2, 3, and 5, respectively) were due to decomposition of the starting material or butyl addition. The use of $C_2Br_2Cl_4$ (entry 4) afforded (*S*)-6-bromonicotine (**8b**) in good yield. Among other examples, (*S*)-6-(dimethylphenylsilyl)nicotine (**8d**) and (*S*)-6-(tributylstannyl)nicotine (**8f**) (entries 6 and 8) were obtained in high yield since these groups cannot be displaced by *n*-BuLi to form byproduct **6**. The chlorination of substituted analogues was performed as well and afforded the C-6 regioisomer preferably (entries 10−12).

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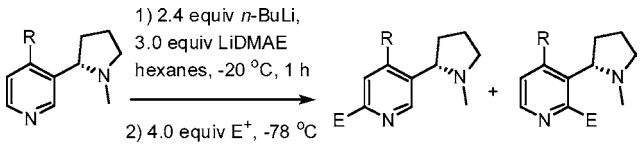
Table 2. Versatility of the Lithiation of Nicotine and Nicotine Derivatives via *n*-BuLi−LiDMAE



1 **8a-j** **9a-j**

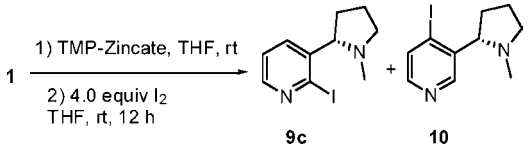
7a-c 55-92 % traces-21 %

entry[a]	nicotine, R	electrophile	**8**, %	**9**, %
1[b]	**1**, H	C_2Cl_6	**8a**, 87	**9a**, 4
2	**1**, H	NBS	**8b**, 27	*c*
3	**1**, H	Br_2	**8b**, 6	*c*
4[b]	**1**, H	$C_2Br_2Cl_4$	**8b**, 67	**9b**, 21
5[b]	**1**, H	I_2	**8c**, 55	**9c**, 4
6	**1**, H	$PhSi(Me)_2Cl$	**8d**, 92	*c*
7	**1**, H	MeSSMe	**8e**, 70	**9e**, 6
8	**1**, H	$ClSnBu_3$	**8f**, 55	*c*
9[b]	**1**, H	ethyl formate	**8g**, 26	*c*
10	**7a**,[d] $SiMe_3$	C_2Cl_6	**8h**, 53	*c*
11	**7b**,[d] $Si(allyl)Me_2$	C_2Cl_6	**8i**, 56	*c*
12	**7c**,[e] $SiMe_2Ph$	C_2Cl_6	**8j**, 43	*c*

[a] Reactions were run on a 1.0−2.0 mmol scale. [b] Spectral data matched the literature.[7,8] [c] Not observed. [d] Reference 11. [e] Reference 12.

Due to the bulky pyrrolidine ring at the C-3 position, functionalization of the C-2 position of the pyridine ring of nicotine appeared as the most challenging via lithiation. The selectivity of various bases was investigated. In 1999, Kondo and co-workers reported the chemoselective formation of arylzincates using lithium di-*tert*-butyltetramethylpiperidinozincate (TMP-zincate) prepared from the addition of di-*tert*-butylzinc to a solution of lithium tetramethylpiperidide (LiTMP).[9] Most interestingly, α-metalation of π-deficient aza-aromatics proceeds smoothly at room temperature to give the corresponding heteroarylzincates, which react with electrophiles. The α-metalation of pyridine followed by treatment with I_2 gave 2-iodopyridine in 76% yield. Based on this precedent, the α-metalation of nicotine (**1**) using TMP-zincate was therefore attempted (Table 3). When 1.0 equiv

Table 3. Regioselectivity in the Reaction of Nicotine with TMP−Zincate



1 **9c** **10**

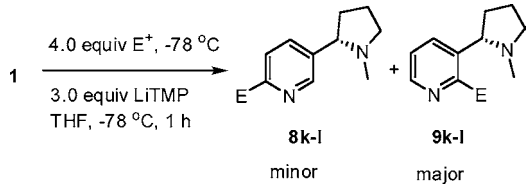
entry[a]	TMP−zincate (equiv)	**9c** (%)	**10** (%)
1	1.0	19	24
2	2.0	7	20

[a] Reactions were run on a 1.0−2.0 mmol scale.

of TMP-zincate was used as the base followed by addition of iodine, (*S*)-2-iodonicotine (**9c**) was obtained in only 19% yield, and (*S*)-4-iodonicotine (**10**) was formed in 24% yield. In all attempts, the reaction never went to completion and starting material was recovered.

Reactivity of LiTMP with nicotine (**1**) was then investigated (Table 4). When nicotine was added to a solution

Table 4. Electrophile-Dependent Regioselectivity in the Reaction of Nicotine with LiTMP



1 **8k-l** **9k-l**

minor major

entry[a]	electrophile	**8**, %	**9**, %
1	TMSCl	**8k**, 24	**9k**, 64
2	Cy_3SnCl	*b*	**9l**, 94
3	*N*-methyl-*N*-pyridin-2-yl-benzamide	decomposition of electrophile	

[a] Reactions were run on a 1.0−2.0 mmol scale. [b] Not observed.

containing both the base and chlorotrimethylsilane (TMSCl), the C-2-substituted nicotine **9k** was obtained as the major product in 64% yield and C-6 substituted **8k** in 24% yield. To rationalize these results, it is proposed that LiTMP can coordinate at the pyrrolidine nitrogen in the transition state (Figure 1). The C-2 position of the pyridine ring is selectively

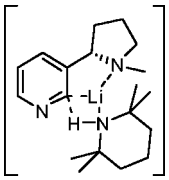


Figure 1. Possible complexation of LiTMP favoring the deprotonation at the C-2 position of the pyridine ring of nicotine.

deprotonated versus the C-6 position. Once the TMS group is attached, the coordination of another LiTMP to the pyridine nitrogen seems to be unlikely because of a steric effect. This may explain why a disubstituted nicotine was not obtained. Variation of the number of equivalents of base showed that the best yield of **9k** was achieved using 3.0 equivalents of LiTMP. Given this interesting regioselectivity, other electrophiles were tested. *N*-Methyl-*N*-pyridin-2-yl-benzamide, which would have allowed access to a phenyl ketone,[10] was not stable in the presence of LiTMP, and starting material was recovered. However, the installment

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of a versatile tin functionality was achieved with the synthesis of compound **9l** in an excellent yield of 94%. Future work will investigate the synthetic utillity of **9l** and related compounds.

In conclusion, a variety of novel, as well as known, C-2- and C-6-substituted nicotines have been synthesized directly from (*S*)-nicotine in moderate to high yield. To the best of our knowledge, this is the first regioselective deprotonation of (*S*)-nicotine. The new methodologies described herein provide opportunities for exploring new routes to interesting and potentially useful compounds based on nicotine. Ongoing studies in our laboratories are directed toward the regioselective substitution of all positions on the pyridine ring of nicotine, which would in therory provide an easy access to a plethora of nicotine derivatives.[11−13]

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Supporting Information Available: Experimental procedures and characterization and NMR data for **8c**−**f**,**h**−**l**, **9c**,**e**,**k**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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