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Rapid and one-pot synthesis of tri- to tetradeca-deutero nicotines

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ABSTRACT

A very rapid one-pot synthesis of (±)-nicotine and tri- to tetradeca-deuterated nicotines is described where the synthetic sequence requires less than 4 h.

Synthesis of bioactives engaging stereo-flexible strategies has been in the forefront, which enables access to analogues with ease for SAR and drug discovery. Recently, the replacement of hydrogen 'H' with deuterium 'D' has triggered newer interest in pharmaceutical industry [1]. The deuterated version gives prolonged metabolic stability [2]. Several patents have been filed specially in the domain of pharmaceuticals which highlight the incorporation of deuteration at key sites of the chosen molecules [3]. The 'D' incorporation is expected to provide better stability and pKa. To provide access to deuterated compounds, researchers have developed several methods [4]. Major procedure for deuterium incorporated molecules can be classified into (i) substrate driven where substrate already possess deuterium incorporation. (ii) The second procedure is to react substrates with deuterated reagents *viz.* $LiAlD_4$, $NaBD_4$ etc. (iii) The third procedure may involve transition metal catalyzed hydrogenation using D_2 gas on olefins or alkynes, (iv) exchange of H with D with catalysts and (v) other base catalysis in presence of D_2O is also used for deuteration [5–15].

These methodologies of deuteration enabled researchers to synthesize deuterated FDA approved drugs and one such example is deutetrarobenazine useful in Huntigton's disease [16]. The FDA approval was given for metabolic stability the deuterated version offered. Our group has been engaged in total synthesis of alkaloids of medicinal relevance and also deuterated chemicals as building blocks in drug discovery [17].

Genus Nicotiana is one of the largest members of Solanaceae family. (*S*)-Nicotine **1** is the major constituent alkaloid of tobacco (*N. rustica, N. tabacum, A. syriaca*) along with anatabine, anabasine, nornicotine and (*R*)-nicotine (Fig. 1) [18]. While nicotine is described in the literature as a health hazard, it is also documented as as a pharmaceutical product for the treatment of Parkinson's (PD) and Alzheimer's diseases (AD), schizophrenia, attention deficiency/hyperactivity and Tourette's syndrome [19,20]. in addition to its insecticidal properties [21]. Nicotine has the ability to cross 'Blood Brain Barrier' and is extensively metabolized by the liver to a number of compounds [22]. There is no epidemiological evidence that nicotine acts as a carcinogen, but several experiments have proved it to stimulate cancer cells [23].

The observation that nicotine undergoes a rapid metabolism in liver provided a thought to explore if deuterated analog will have better stability in living systems. Thus, access to deuterium incorporation at various sites of nicotine becomes an essential requirement for biological studies. The initial attempts to follow some of the known synthetic methods for nicotine with a few alterations to access deuterated analogues were only partially successful due to multiple steps involved in the synthesis.

We reasoned, that a short synthesis with flexibility in access to raw materials is essential towards achieving various deuterated nicotines. To our satisfaction, we were able to synthesize (±)-nicotine in a single pot in 4 h of operation.

We envisioned that the coupling of 3-bromo pyridine with *N*-methyl succinimide could give the desired product. The advantage of this methodology was that all the carbons bearing hydrogen could be converted selectively or totally into 'D' bearing carbons which include even the *N*-CH_3 group. Thus, the reaction of 3-bromo

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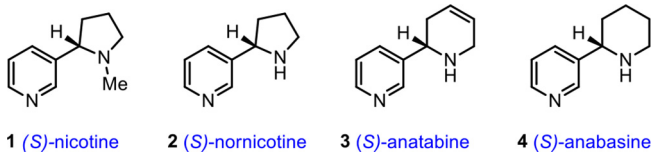


Fig. 1. Various constituents of Tobacco.

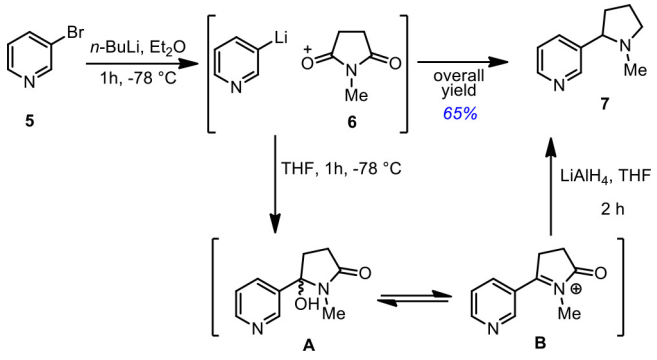
pyridine with *N*-methyl succinimide mediated by *n*-BuLi at −78 °C for 1 h generated the adduct **A** which is in equilibrium with imine **B** [24]. Addition of THF followed by $LiAlH_4$ provided (±)-nicotine in less than 3 h with 65% yield involving minimal purification steps (Scheme 1). After optimization of this one-pot process for nicotine synthesis, we looked at various sources of deuteration to synthesize deuterated nicotine with varying degrees of D incorporation.

The deuterated *N*-methyl succinimide was prepared following the procedures described in Scheme 2. *N*-methyl succinimide **8** was *N*-alkylated with either CH_3I or CD_3I to get **6** or **6-*d*$_3$** in 92% yield by treating with K_2CO_3, acetone and CH_3I or CD_3I [12].

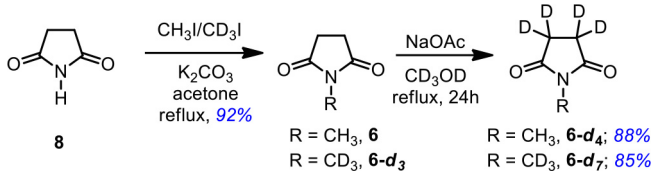
Thus obtained **6/6-*d*$_3$** was convened to **6-*d*$_4$/*d*$_7$** in CD_3OD in presence of NaOAc in good yields (Scheme 2). This sequence allowed us access to *N*-methyl succinimide (**6**, **6-*d*$_3$**, **6-*d*$_4$** and **6-*d*$_7$**) with various levels of deuteration. With this in hand, the lithiated pyridine (generated by adding *n*-BuLi to 3-bromo pyridine **5**) was added to **6-*d*$_4$** to obtain the pyridine-pyrrolidine adduct (Scheme 3a). To the same flask was added either $LiAlH_4$ or $LiAlD_4$ to generate (±)-nicotine (**7-*d*$_4$** or **7-*d*$_7$**) in over 65% yield (Scheme 3a). To synthesize (±)-nicotine (**7-*d*$_3$**), the lithiated pyridine reaction of *n*-Buli and 3-bromo pyridine **5** was added to **6** followed by reduction with $LiAlD_4$ (Scheme 3b).

Similarly, the lithiated deuteropyridine (generated by reaction between *n*-BuLi and tetradeutero 3-bromopyridine 5-d_4) was allowed to react with 6-d_4 or 6-d_7 followed by reduction with $LiAlD_4$ to synthesize (±)-nicotine 7-d_{11} or 7-d_{14} respectively, in over 60% yield (Scheme 4).

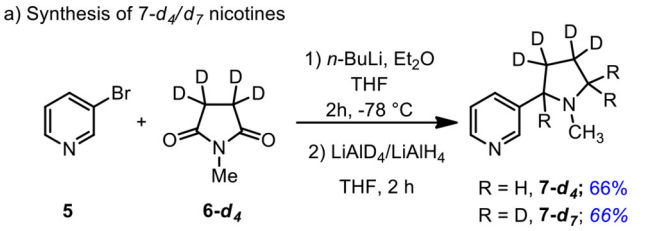
In conclusion, the shortest synthesis of nicotine is described with building blocks amenable to deuteration.

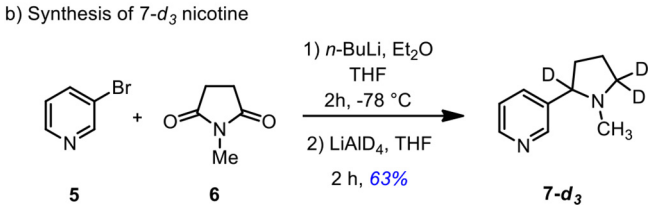


Scheme 1. One-pot synthesis of (±)-nicotine.

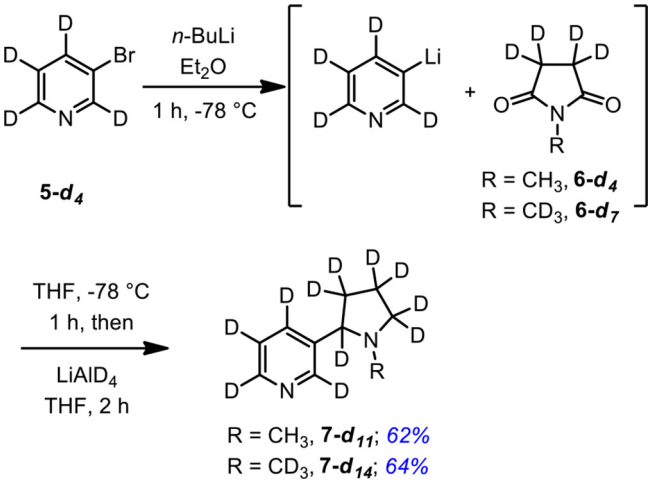


Scheme 2. Synthesis of ***d*$_4$/*d*$_7$**-Succinimides.





Scheme 3. Synthesis of **7-d$_3$/*d*$_4$/*d*$_7$**.



Scheme 4. Synthesis of **7-d$_{11}$/*d*$_{14}$** nicotines.

Justification

1. A very fast one-pot synthesis of (±)-nicotine and tri- to tetradeca-deuterated nicotines is described where the synthetic sequence requires less than 4 h.
2. The scheme has the flexibility to allow insertion of deuterium on any carbon of choice and total substitution of hydrogen with deuterium.
3. The work will be of interest to synthetic organic chemists and medicinal chemists as alkaloid analogues with selective or total deuteration can be synthesized with ease.
4. The manuscript will also interest biologists and pharmacologists to understand the mechanism of molecules crossing blood–brain barrier (BBB) and stability of deuterated molecules in the living systems.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151680.

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