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Enantioselective Synthesis of Nicotine via an Iodine-Mediated Hofmann–Löffler Reaction

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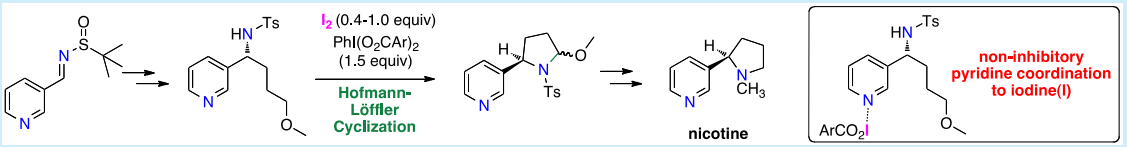
Supporting Information



ABSTRACT: An iodine-mediated Hofmann–Löffler reaction has been developed that enables the first enantioselective synthesis of nicotine based on this synthetic methodology. The effect of the free pyridine core on the involved electrophilic iodine reagents was explored in detail. The final synthesis proceeds under moderate reaction conditions that tolerate the free pyridine core. The same synthetic sequence is also applicable to a number of derivatives with higher substituted pyridine cores, including bipyridine derivatives.

Within the general quest to streamline amination chemistry, the direct conversion of C–H bonds into C–N bonds has encountered paramount interest from the synthetic community.[1,2] The Hofmann–Löffler reaction represents a unique radical-based methodology to form nitrogenated saturated heterocycles such as pyrrolidines from the corresponding acyclic N-halogenated precursors.[3−5] For the cases of nonsymmetrical heterocycles, retrosynthetic analysis of a given target compound provides two alternative C–N bond disconnections. Nicotine is a natural alkaloid occurring naturally in the leaves of the tobacco plant and, to a lesser extent, from other members of the nightshade plant family. Nicotine (**1**) has excitatory or debilitating effects on ganglia of the vegetative nervous system. Its pathophysiological importance is largely related to causes deriving from smoking excesses.[6]

Using the concept of C–H amination, the example of a nicotine synthesis in 1909 represents the early proof of principle in natural product synthesis for the venerable Hofmann–Löffler reaction.[7] Löffler and Kober disclosed their synthesis of nicotine within an intramolecular C–H amination reaction at the benzylic methylene group α to pyridine (Figure 1). Already in their pioneering report, the authors mentioned the alternative retrosynthetic approach of C–N bond formation at the primary C–H position. While this approach requires the C–H functionalization at a less favorable methyl position, it carries the advantage of an enantioselective approach since it departs from a precursor with an established stereogenic center. Apparently lacking the synthetic access to the required starting material,[7] this approach remained unrealized. We decided to explore such an enantioselective synthesis of nicotine[8] using iodine-based Hofmann–Löffler variants. This underlying concept is based

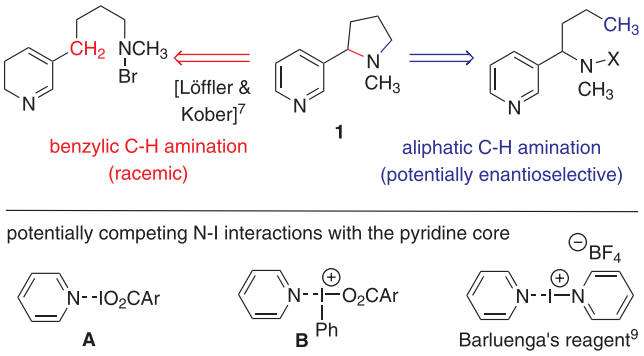


Figure 1. Retrosynthetic C–N bond disconnection for the pyrrolidine core of nicotine (X = Br, I) and iodine–pyridine interactions.

on the superior reactivity of N–I bonds at the outset of the C–H functionalization. Although of immediate synthetic logic at first sight, the anticipated C–H amination is of great challenge. Obviously, prior to NH iodination as the initial step of the transformation, the electrophilic iodine reagent should be prone to competitive pyridine coordination, which could be inhibitory. Such a behavior has been widely documented, and Barluenga's reagent $[Py_2I]BF_4$ provides major testimony to this end.[9,10] For iodine(III) reagents as terminal oxidants, the same coordination has been observed.[11]

Under the typical conditions of iodine-promoted Hofmann–Löffler reactions, the formation of N–I species such as **A** or **B** can be expected to inhibit the catalytic reaction or at least to slow it down significantly. Since the catalytic reaction variant

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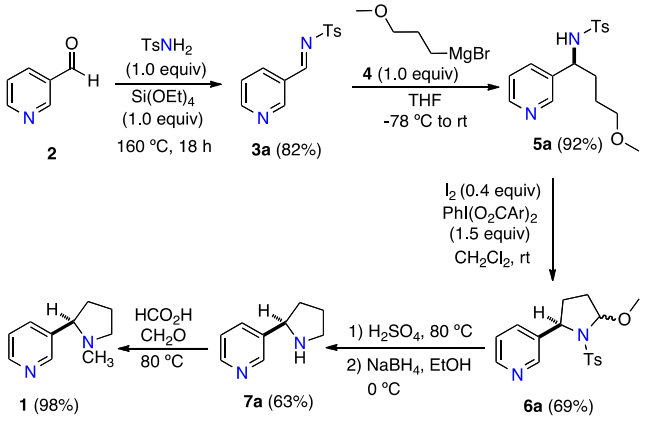
comprises a radical-chain reaction, in which an N-iodinated substrate participates, any loss in rate will affect the turnover and may ultimately shut down the reaction.

Initial exploratory attempts to realize a C−N bond formation at a nonactivated aliphatic position were indeed challenging.[12] These observations are considered to be the consequence of a reduced reactivity in the presence of the coordinative pyridine moiety.

To realize a synthesis without the requirement for masking the pyridine function, temporary introduction of a methoxy substitution was envisioned to facilitate a more favorable C−N bond formation due to the reduced C−H bond strength of the target methylene position. The resulting hemiaminal structure would then be susceptible to reductive removal of the methoxy group, providing the final pyrrolidine core. This strategy proved successful when explored in an initial racemic synthesis (Scheme 1).

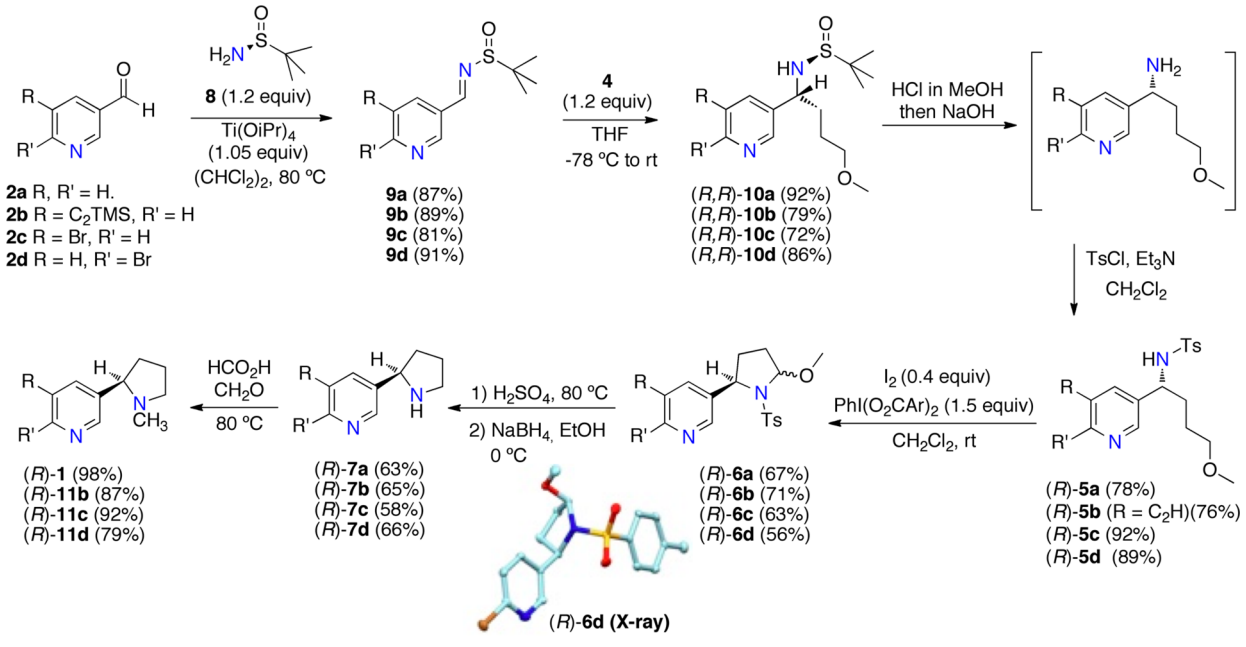
Scheme 1. Exploratory Synthesis of (±)-Nicotine via the Hofmann−Löffler Reaction



Formation of 3-pyridinyl *N*-tosylaldimine **3a** from pyridine-3-carboxaldehyde **2** was followed by 1,2-alkylation with the required Grignard reagent **4**. The resulting amide **5a** underwent clean C−H amination at the anticipated methylene position using a reagent combination of molecular iodine and iodine(III) compound $PhI(O_2CAr)_2$ [Ar = 3-Cl-C_6H_4],[5a] which forms electrophilic iodine(I) reagent I-O_2CAr.[13] The fact that 0.4 equiv of molecular iodine provide full conversion indicates that a certain turnover of iodine can be achieved despite the presence of the pyridine group. However, use of lower iodine concentrations led to drastically reduced yields of **6a**. The formed hemiaminal derivative **6a** was submitted to an acidic detosylation followed by imine reduction to provide the target pyrrolidine **7a**. *N*-Methylation by the Eschweiler−Clarke reaction yielded nicotine in 32% overall yield.

Based on the developed successful sequence, an enantioselective route could be devised subsequently (Scheme 2). This approach used Ellman's *tert*-butanesulfinylamide **8**[14] as the chiral nonracemic auxiliary. Thus, condensation of various pyridinyl carboxaldehydes **2a−d** with **8** provided the corresponding aldimines **9a−d** in very good yields.[15,16] Addition of the Grignard **4** provided the corresponding C−C bond formation in high yields and with very high diastereoselectivity. Since the incompatibility of the *tert*-butanesulfinyl handle with radical conditions had been reported,[17] this group was removed by acidic cleavage followed by tosylation of the intermediary primary amine. The desired enantiomerically pure tosylamides (*R*)-**5a−d** were obtained in 76−92% yield over the two steps. For acetylene derivative **5b**, deprotection of the TMS group was observed at this stage. Compounds **5a−d** then underwent clean Hofmann−Löffler cyclization to hemiaminal derivatives (*R*)-**6a−d** under the conditions from Scheme 1. At this stage, the anticipated configuration of the newly formed stereogenic center at the benzylic position was unambiguously assured by X-ray single-crystal analysis of derivative **6d** and determined to be (*R*).

Scheme 2. Enantioselective Synthesis of (−)-Nicotine 1 and Derivatives 11b−d via the Iodine-Mediated Hofmann−Löffler Reaction



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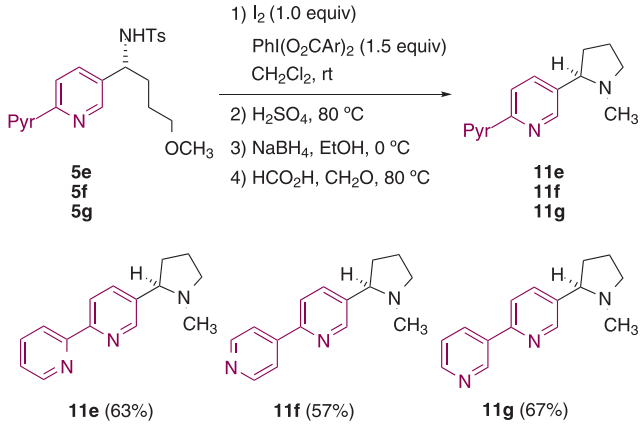
Final transformations of (*R*)-**6a−d** followed again the conditions explored in Scheme 1 and provided free pyrrolidines (*R*)-**7a−d** and, upon Eschweiler−Clarke methylation, the corresponding *N*-methylated target derivatives (*R*)-nicotine **1** and (*R*)-**11b−d**. The synthesis of (*R*)-**11b** constitutes a novel entry toward 5-acetylenyl-substituted nicotine, which had been explored previously under the name SIB-1508Y.[18] This compound could also be readily synthesized from product **11c** upon Sonogashira coupling. In general, the syntheses of enantiomerically pure bromo derivatives (*R*)-**11c,d** should enable additional diversification of nicotine derivatives through the corresponding pertinent cross-coupling procedures. Use of the other enantiomer of the Ellman auxiliary will provide access to the corresponding series of (*S*)-configured nicotine derivatives, and for compounds **11b−d** the racemic synthesis from Scheme 1 was also applied in order to provide the corresponding racemic material.[12] HPLC analyses for all products (*R*)-**1** and (*R*)-**11b−d** confirmed that all transformations from intermediates (*R,R*)-**10a−d** onward had proceeded without any racemization.

The apparent noteworthy compatibility of the pyridine functionality under the optimized cyclization conditions was further probed in the synthesis of three bipyridinyl derivatives (Scheme 3). This synthesis was of particular interest since it

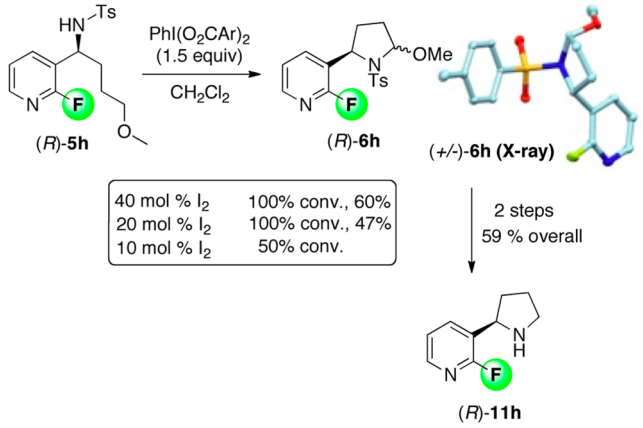
Scheme 3. Synthesis of Bipyridine Derivatives of Nicotine via the Hofmann−Löffler Reaction



again allows for an accurate investigation on the influence of the bipyridine core on the iodine reagents for the Hofmann−Löffler cyclization. To explore this context, three bipyridine derivatives **5e−g** were synthesized and employed in the pyrrolidine formation. In these cases, a full equivalent of molecular iodine was required in order to reach full conversions. Under this increased loading, the expected cyclization proceeded without detectable side-product formation. Following the final three transformations from Scheme 1, pyridinyl-containing nicotine derivatives **11e−g** were obtained in enantiomerically pure form. Compound **11e** contains the common 2,2′-bipyridine core, which should perform as a ligand for selective metal complexation. The 4- and 3-pyridinyl derivatives **11f,g** should be of general pharmaceutical interest, particularly **11g**,[19] which is the pyrrolidine derivative of naturally occurring anabasamine[20] containing an *N*-methylated piperidine unit.

The importance to consider an influence of the pyridine coordination on the iodine(I) performance was finally demonstrated by the synthesis of the corresponding 2-fluoro derivative (Scheme 4). Employing the established sequence from Scheme 2, precursor **5h** was obtained from 2-

Scheme 4. Enhanced Reactivity of the 2-Fluoropyridine Substituent in the Hofmann−Löffler Cyclization



fluoropyridine-3-carboxaldehyde **2h** in 61% overall yield. Cyclization of **5e** under stoichiometric conditions provided the expected C−H amination product. For the present case, the reduced coordination ability of the pyridine core due to the neighboring fluorine substituent provided the opportunity to explore lower iodine concentrations. In fact, a reduced 20 mol % of molecular iodine provided the same quantitative conversion as the standard 0.4 equiv. The reaction still proceeded to notable 50% conversion at 10 mol % iodine loading. These results demonstrate that pyridine coordination to the electrophilic iodine reagent may still result in an important decrease in overall rate for the cases of compounds **5a−d** but does not exercise an overall inhibitory effect.

We have developed an enantioselective total synthesis of nicotine using a direct C−H amination reaction within a Hofmann−Löffler cyclization as the key step. This synthesis stands out as it tolerates free pyridine units without inhibition of the electrophilic iodine reagent. This successful approach streamlines chemoselective C−H amination promoted by iodine(I) reagents and is expected to trigger further application of this methodology in the synthesis of heterocyclic alkaloids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03909.

Experimental procedures, analytical data for all compounds, NMR spectra, and X-ray data for compounds **6d** and **6h** (PDF)

Accession Codes

CCDC 1883567−1883568 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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