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# THE TERT-BUTYLATION OF NICOTINE: NOVEL REACTION PATHWAYS AND RACEMIZATION STUDIES

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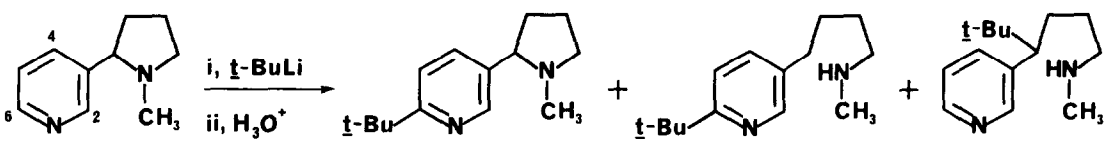
SUMMARY The reaction of nicotine with tert-butyllithium gives 6-tert-butylnicotine (2) and two novel pyrrolidine ring cleaved products, 3 and 4; mechanisms for the racemization of 1, 2, and 4 were elucidated by reacting tert-butyllithium with nicotine-2'-$d_1$.

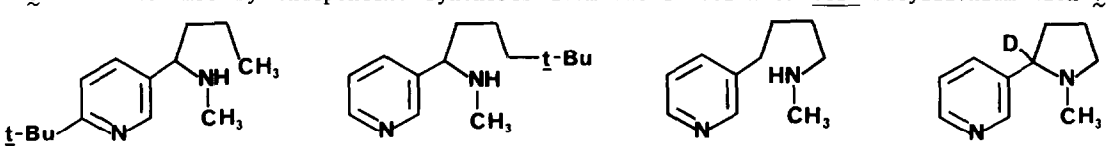
The reaction of organolithium reagents with the pyridine ring nucleus is an important route to substituted pyridine derivatives.[1-5] To exemplify the utility and simplicity of these procedures, we note that the pyridine-derived alkaloid nicotine (1) reacts with methyllithium to form high yields of 2-methylnicotine and 6-methylnicotine.[1a] Alternative preparations of these types of compounds require multistep syntheses, usually from acyclic precursors.[1b,3,6] Therefore, an understanding of the scope and limitations of these organolithium procedures is of value. We now report two unprecedented reaction pathways and two novel racemization mechanisms.

Treatment of nicotine with 1.2 equiv of tert-butyllithium in THF at 0° led to the three products 2-4 in addition to recovered starting material (Table I). 6-tert-Butylnicotine (2), the expected product based on the regioselectivity observed in the alkylation of 3-substituted pyridines by tert-butyllithium,[1,2a,2d] was indeed present as confirmed by spectral data.[7]




1 2 3 4

Amines 3 and 4 lack the pyrrolidine ring mass spectral fragmentations typical of nicotine[8-10]; the most abundant ion for both 3 and 4 is m/z 44, indicative of the presence of a $-CH_2NHCH_3$ moiety. Neither an m/z 121 nor an m/z 177 is present (<5%) in the mass spectrum of 3 or 4, ruling out the alternative products 5 and 6. The substitution pattern in the pyridine ring and the nature of the amino chain in 3 and 4 follows from their spectra.[8,9] The structure of 3 was confirmed by independent synthesis from the reaction of tert-butyllithium with 7[11].




5 6 7 8

TABLE I. Product Mixtures from Nicotine + tert-Butyllithium in THF

| Experiment | Reaction Conditions[a] | Deoxygenation | Product Distribution (%) 1 | 2 | 3 | 4 | Yield (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | 0°/$N_2$ | No | 12 | 23 | 9 | 56 | 83 |
| 2 | 0°/$N_2$ | No | 16 | 41 | 43 | <1 | 23 |
| 3 | 0°/$N_2$ | No | 12 | 42 | 18 | 28 | 37 |
| 4 | 0°/$N_2$ | No | 17 | 28 | 4 | 51 | 39 |
| 5 | 0°/Ar | Yes[c] | 22 | 46 | 25 | 7 | 40 |
| 6 | 0°/Ar | Yes[c] | 21 | 48 | 27 | 4 | 40 |
| 7 | -70°/$N_2$ | No | 25 | 62 | 13 | <1 | 50 |

[a]Temperature/atmosphere over reaction mixture. THF was distilled from LAH prior to use; tert-butyllithium was obtained from Alfa and used as received. [b]Distilled yield except for experiment #1 which lists crude yield. [c]Performed by bubbling argon through all solvents and reagents prior to reaction.

Table II indicates that substantial racemization occurs in both recovered nicotine and 2 during these tert-butylations. Scheme I details the possible interconversions which account for the products and optical purities observed. It is mechanistically significant that the degree of racemization is larger in 6-tert-butylnicotine (2) than in the recovered starting material, suggesting that the low optical purity for 2 results during its formation rather than by initial racemization of (-)-nicotine and subsequent product formation.

We have ruled out one mode of racemization, deprotonation-reprotonation of nicotine's $C_{2'}$-H, by examining the fate of the deuterium atom in the tert-butylation of nicotine-2'-$d_1$ (8).[10] As shown in Table II, nearly complete deuterium incorporation was maintained in both the recovered 1 and in 2, supporting the reversible formation of ring-cleaved intermediates 9-10 and/or the reduced pyridines 11-12; the latter two compounds could be formed during the quenching of the reaction with dilute HCl (Scheme I). The formation of racemized 1 via the dealkylative oxidation of 11-12 has precedent in terms of the loss of a tert-butyl group during the aromatization of an analogous dihydropyridine.[2a] We can only speculate regarding the nature of 9-10, given that radicals and radical anions have been implicated[12] in other reactions of tert-butyllithium with aromatic systems. A [1,5]-alkyl migration from 10 and/or 12 to 4 cannot be excluded. Metal salts of dihydropyridines have previously been postulated[13] as intermediates in the reaction of 1 with $CH_3Li$ and are known intermediates in numerous reactions of lithium reagents with pyridines.[2a,14] As shown in Table I, the yields of 1-4 were more reproducible when the reaction was performed with exclusion of oxygen, suggesting that competitive routes involving both anionic intermediates and radical anions[2b,12] are involved. The role of oxygen in product composition also favors the involvement of intermediates formed via electron transfer.[2b,12]

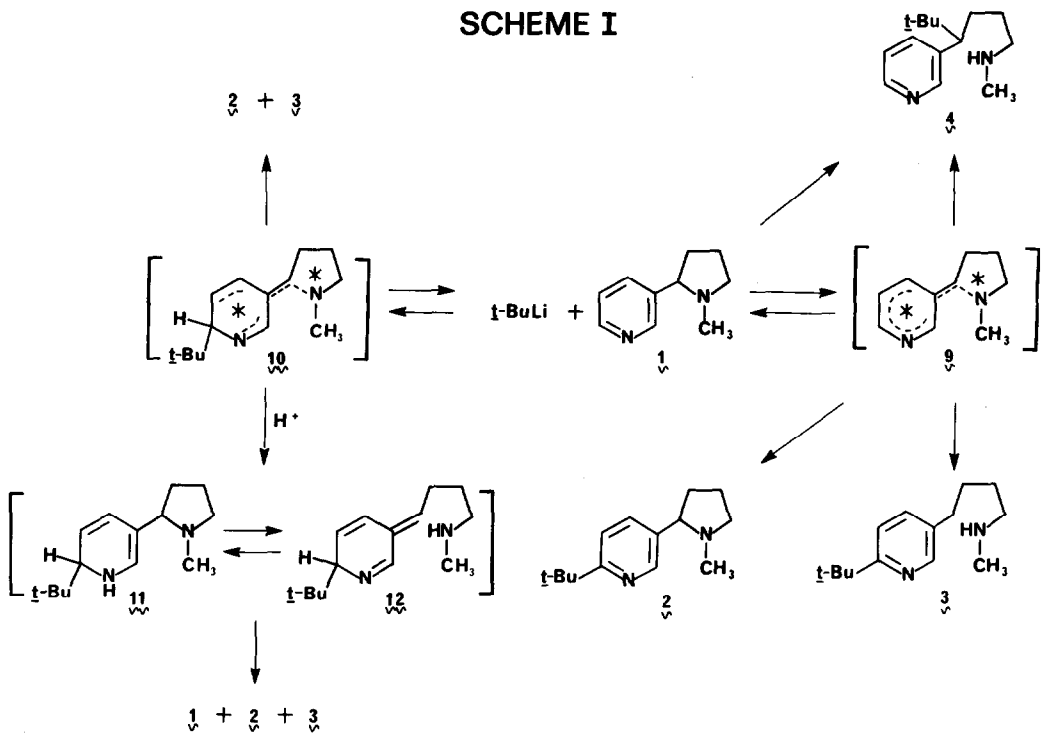
The formation of 3 and 4 is novel in that pyrrolidine ring cleavage must be incorporated in any proposed mechanism. We cannot specify the timing of the ring cleavage relative to C-C bond formation at nicotine's C-6 or C-2' positions, though information is at hand which suggests that these processes are closely linked. (1) We have been unable to identify 7 in these reaction mixtures, thereby suggesting a one-step addition-ring cleavage route to 3. (2) Only 1.2 equiv of tert-butyllithium was used; had one equiv of tert-butyllithium been needed for ring cleavage and one equiv for alkylation, a larger recovered yield of 1 would have resulted.

TABLE II. Racemization Analysis of Product Mixtures from the Reactions of (S)-(-)-Nicotine and d,l-Nicotine-2'-$d_1$ with tert-Butyllithium

| Experiment[a] | Optical Purity (%)[b,c] | | Residual $C_{2'}$-D Incorporation (%)[e] | |
|---|---|---|---|---|
| | Recovered 1 | 2[d] | 1 | 2 |
| 5 | 71 | 4.1 | >95 | >95 |
| 6 | 69 | 4.8 | -- | -- |
| 7 | 25 | 21 | >95 | >95 |

[a]See Table I. [b]All rotations performed with GC purified nicotinoids in $CH_2Cl_2$ solution. [c]For (S)-nicotine, $[\alpha]_D^{25}$ -169.8°±2.3°. [d]The maximum rotation observed for 2 obtained by an alternate procedure is $[\alpha]_D^{25}$ -146° (c 0.722) (ref. 5). [e]From the independent reactions of tert-butyllithium with d,l-nicotine-2'-$d_1$ under the conditions specified under the "Experiment" column of Table I. Quantitation obtains from mass spectral analysis taking into consideration the fragmentation pathways determined for nicotine by Djerassi (ref. 10).

**SCHEME I**




We attribute the regioselectivity of the tert-butylation of nicotine to the steric bulk of the reagent, given that nicotine's C-2 and C-4 positions are sterically hindered by its N-methylpyrrolidinyl moiety.[1a,15] We have carefully examined the reaction products of nicotine and methyllithium and have been unable to detect aberrant products analogous to 3 and 4. This latter result is consistent with the often observed unusual reactivity of tert-butyllithium[2b,12] and the likely intervention of radicals and/or radical anions.[16]

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(7) For 2: $^1$H NMR δ ($CDCl_3$) 8.51 (d, 1, J = 2 Hz, 2-H), 7.71 (dd, 1, J = 8, 2 Hz, 4-H), 7.36 (d, 1, J = 8 Hz with fine coupling, 5-H), 3.13-3.43 (m, 1, 5'-H), 3.08 (t, 1, J = 8 Hz, 2'-H), 1.63-2.55 (m, 5, 3'-,4'-, and 5'-H), 2.19 (s, 3, N'-Me), 1.39 (s, 9, t-Bu); mass spectrum, m/z (rel intensity) 218 (10), 217 (12), 189 (15), 133 (25), 84 (100); $[\alpha]_D^{20}$ -30° (c 0.209, $CH_2Cl_2$). Anal. ($C_{14}H_{22}N_2$) C, H, N.

(8) For 3: $^1$H NMR ($CDCl_3$) δ 8.45 (d, 1, J = 2 Hz, py 2-H), 7.5 (dd, 1, J = 8, 2 Hz, py 4-H), 7.28 (d, 1, J = 8 Hz, py 5-H), 2.48-2.75 (m, 4, 1- and 4-H), 2.44 (s, 3, N-Me), 1.38-1.75 (m, 4, 2- and 3-H), 1.46 (br s, 1, N-H) 1.39 (s, 9, t-Bu); mass spectrum, m/z (rel intensity) 220 (3), 219 (4), 205 (10), 176 (10), 163 (20), 162 (25), 149 (80), 134 (25), 44 (100). High resolution mass spectrum - Calcd for $C_{14}H_{24}N_2$: $M^+$ 220.1939. Found: $M^+$ 220.1909.

(9) For 4: $^1$H NMR ($CDCl_3$) δ 8.50 (dd, 1, J = 5, 2 Hz, py 6-H), 8.46 (m, 1, py 2-H), 7.56 (dt, 1, J = 8, 2 Hz, py 4-H), 7.26 (dd, 1, J = 8, 5 Hz, py 5-H), 2.56 (t, 2, J = 7 Hz, 1-H), 2.25-2.38 (m, 1, 4-H), 2.36 (s, 3, N-Me), 1.55-1.98 (m, 2, 2-H), 1.68 (br s, 1, N-H) 1.05-1.38 (m, 2, 3-H), 0.89 (s, 9, t-Bu); mass spectrum, m/z (rel intensity) 220 (2), 205 (5), 176 (6), 163 (10), 134 (38), 120 (40), 106 (38), 44 (100); $[\alpha]_D^{20}$ 0° (c 0.15, $CH_2Cl_2$). High resolution mass spectrum - Calcd for $C_{14}H_{24}N_2$: $M^+$ 220.1939. Found: $M^+$ 220.1935.

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