referee of the preliminary communication[2] and to the referees of this paper for helpful comments, which were utilized herein. Thaks are also given to Drs. T. S. Osdene, E. B. Sanders, and R. B. Seligman for their encouragement and support.

Registry No. 1, 110-86-1; 2, 109-06-8; 3, 108-99-6; 4, 108-89-4; 5, 583-61-9; 6, 108-47-4; 7, 589-93-5; 8, 108-48-5; 9, 583-58-4; 10, 591-22-0; 11, 108-75-8; 12, 3748-84-3; 13, 3748-83-2; 14, 100-71-0; 15, 536-78-7; 16, 536-75-4; 17, 644-98-4; 18, 6304-18-3; 19, 696-30-0; 20, 5944-41-2; 21, 38031-78-6; 22, 3978-81-2; 23, 14159-59-2; 24, 104-90-5; 25, 80263-42-9; 26, 20194-71-2; 27, 80263-43-0; 28, 85735-96-2; 29, 56986-88-0; 30, 18113-81-0; 31, 1122-69-6; 32, 72693-04-0; 33, 6343-58-4; 34, 935-28-4; 35, 6832-21-9; 36, 533-37-9; 37, 10500-57-9; 38, 7197-96-8; 39, 504-29-0; 40, 504-24-5; 41, 1824-81-3; 42, 100-70-9; 43, 100-48-1; 44, 7295-76-3.

Organometallic Methylation of Nicotine and Nicotine *N*-Oxide. Reaction Pathways and Racemization Mechanisms[1]

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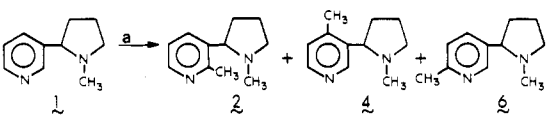
Received March 16, 1983

The reaction of nicotine with methyllithium leads to 2-methylnicotine as a major product in addition to the previously reported 4- and 6-methylnicotines. The reaction of nicotine *N*-oxide with methylmagnesium bromide furnishes both 2- and 6-methylnicotine. The product composition of these reactions is strongly dependent on the experimental conditions; the effects of solvent, temperature, and relative reagent concentration are presented. The methyllithium reactions lead to partially racemized methylnicotines, and the recovered nicotine is often nearly optically pure. Independently, (*S*)-(−)-6-methylnicotine was treated with methyllithium and was recovered with complete retention of optical activity. These results suggest that the loss of optical purity in the formation of methylnicotines in these methyllithium reactions occurs during the reaction itself and is not due either to racemization of the starting material or to subsequent racemization of the initially formed product.

Introduction

Investigations in the field of nicotine structure–activity remain a topic of considerable interest.[2] While almost all preparations of nicotine analogues involve lengthy synthesis from acyclic precursors,[3] some of these nicotinoids have been derived directly from nicotine itself.[4,5] This latter approach has appeal because optically pure (*S*)-nicotine is readily available as a starting material, and because this strategy can directly result in optically active analogues.

Some years ago, it was reported that reaction of nicotine (1) with methyllithium in a variety of solvents led to the isolation of 6-methylnicotine (6) with minor amounts of 4-methylnicotine (4) (eq 1).[6] In 1978, other workers reported repeating the original literature procedure and "obtaining essentially the same results" with the exception that the isolated 4 had a higher optical activity.[7,8]



(1)

(a) CH_3Li/toluene heat

Based on the well-documented propensity of alkyllithium reagents to attack in a regioselective manner at the 2-position of a 3-substituted pyridine in preference to the 6-position,[9] we were somewhat skeptical of the literature reports[6,7] which did not demonstrate the formation of 2-methylnicotine (2) as a reaction product. We were thus prompted to reexamine these methylations to confirm

(1) For the previous paper in this series, see: Kao, J.; Seeman, J. I. *J. Comput. Chem.*, in press.

(2) For leading references, see: (a) Aceto, M. D.; Martin, B. R. *Med. Res. Rev.* **1982**, *2*, 43–62. (b) Abood, L. G.; Reynolds, D. T.; Booth, H.; Bidlack, J. M. *Neurosci. Biobehav. Rev.* **1981**, *5*, 479–487. (c) Romano, C.; Goldstein, A. *Science* **1980**, *210*, 647–650. (d) Rondahl, L. *Acta Pharm. Suec.* **1980**, *17*, 347–351. (e) Sanders, E. B.; Secor, H. V.; Seeman, J. I. U.S. Patent 4 155 909, 1979; U.S. Patent 4 220 781, 1980.

(3) (a) Hu, M. W.; Bondinell, W. E.; Hoffmann, D. *J. Labelled Compds.* **1974**, *10*, 79–88. (b) Catka, T. E.; Leete, E. *J. Org. Chem.* **1978**, *43*, 2125–2127. (c) Seeman, J. I.; Secor, H. V.; Chavdarian, C. G.; Sanders, E. B.; Bassfield, R. L.; Whidby, J. F. *Ibid.* **1981**, *46*, 3040–3048. (d) Chavdarian, C. G.; Sanders, E. B.; Bassfield, R. L. *Ibid.* **1982**, *47*, 1069–1073. (e) Cushman, M.; Castagnoli, N., Jr. *Ibid.* **1972**, *37*, 1268–1271. (f) Hutchinson, C. R.; Nakane, M. *Ibid.* **1978**, *43*, 3922–3931. (g) Castonguay, A.; Van Vunakis, H. *Ibid.* **1979**, *44*, 4332–4337. (h) Sanders, E. B.; Secor, H. V.; Seeman, J. I. *Ibid.* **1978**, *43*, 324–330; **1976**, *41*, 2658–2659. (i) Seeman, J. I. *Synthesis* **1977**, 498–499.

(4) (a) For a preliminary communication of some of these results, see: Secor, H. V.; Chavdarian, C. G.; Seeman, J. I. *Tetrahedron Lett.* **1981**, *22*, 3151–3154. (b) Seeman, J. I.; Howe, C. R., unpublished results.

(5) Chavdarian, C. G.; Seeman, J. I. *Tetrahedron Lett.* **1982**, *23*, 2519–2522.

(6) (a) Haglid, F. *Acta Chem. Scand.* **1967**, *21*, 329–334. (b) Haglid, F. *Acta Pharm. Suec.* **1967**, *4*, 117–138. (c) Haglid indicates that a "third possible product",[6a] 2-methylnicotine, was present in "trace"[6d] quantities as judged by "the presence of trace amounts of 2-methylnicotinic acid methyl ester and quinolinic acid dimethyl ester"[6a] by packed column GC analysis of the permanganate oxidation mixture of the total methylation reaction product. (d) Haglid, F.; Norên, J. O. *Acta Chem. Scand.* **1967**, *21*, 335–340.

(7) Leete, E.; Leete, S. A. S. *J. Org. Chem.* **1978**, *43*, 2122–2125.

(8) The methylation of nicotine under homolytic radical conditions (t-BuOOH/$FeSO_4$·$7H_2O$/H_2SO_4) leads to 2-, 4-, and 6-methylnicotines of higher optical purity than obtained in the methyllithium alkylations. See: ref 4 and Itokawa, H.; Inaba, T.; Haruta, R.; Kameyama, S. *Chem. Pharm. Bull.* **1978**, *26*, 1295–1297.

(9) (a) Yale, H. L. in "Pyridine and Its Derivatives"; Abramovitch, R. A., Ed.; Wiley: New York, 1974; Vol. 14, Supplement, Part Two, Chapter VII. (b) Abramovitch, R. A.; Poulton, G. A. *J. Chem. Soc. B* **1969**, 901–903. (c) Hauck, A. E.; Giam, C.-S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2070–2076 and references cited in these papers.

0022-3263/83/1948-4899$01.50/0

Table II. Summary of Product Composition in the Methylation of Nicotine

entry	reaction conditions reagent:1/solvent	absolute yield,[a] % 2	4	6	1	recovered yield, %	conversion to product, %	product in mixture, %	ratio of 6/2
1	1:1 $CH_3Li/PhCH_3$[b]	6		7	75	96	13	15	1.2
2	2:1 $CH_3Li/PhCH_3$[b]	17		19	32	69	36	53	1.1
3	4:1 $CH_3Li/PhCH_3$[b]	19	0.8	21	15	55	40	73	1.1
4	5:1 $CH_3Li/PhCH_3$[b]	10	1.6	13	*d*	25	25	96	1.3
5	8:1 $CH_3Li/PhCH_3$[b]	10	1.0	6.6	*d*	17	18	99	0.7
6	4:1 $CH_3Li/PhCH_3$/ TMEDA[c]	5	0.6	>14	*d*	21	>20	>89	>2.8
7	4:1 CH_3Li/Et_2O/ TMEDA[e]	4.4		23	25	52	27	52	5.2
8	2:1 CH_3Li/THF[b]	3		3	52	58	6	10	1.0
9	4:1 CH_3Li/THF[b]	3		16	27	46	19	41	5.3
10	4:1 CH_3Li/THF/ TMEDA[e]	4		26	20	50	30	60	6.5
11	2:1 CH_3Li/decalin[b]	22	2	29	3	57	53	95	1.3
12	2:1 CH_3Li/decalin[b]	20	*d*	22	*d*	43	44	>99	1.1
13	*N*-oxide/MeMgBr/ THF/50 °C	6		9	6	20	15	71	1.5
14	*N*-oxide/MeMgBr/ THF/−70 °C[f]	25		26	14	65	51	78	1.0
15	6:1 *t*-BuO_2H[f,g]	7.5	11	32	34	84	51	60	4.3

[a] Absolute yields derived by multiplying relative yields times the total recovered yield following distillation. Relative yields determined by GC analysis of total mixture compared with independent measurements of detector response of pure nicotine and **2**, **4**, and **6**. [b] The ethyl ether which originated from the CH_3Li solution was removed by distillation from the reaction medium prior to reflux at the bp of the indicated cosolvent. [c] 80 °C/70 h. [d] <0.5%. [e] 0 °C to room temperature/17 h. [f] Minor products other than those listed were observed but not identified. [g] From ref 4b.

the apparent failure to produce 2-methylnicotine. Additionally, we wished to prepare these methylnicotines in optically active form, a task for which our previously published methods for the preparation of substituted nicotinoids were not well suited.[3c,3h,3i]

We describe herein the results of our investigations and report (a) the observation, in all cases, of an additional *major* product not previously reported; (b) an evaluation of the effects of reaction conditions on the methylation reaction regiochemistry; (c) the lack of configurational integrity in the methyllithium reactions; and (d) a novel mechanism for the observed racemizations based on experiments designed to distinguish between alternate reaction pathways.

Results and Discussion

Gas chromatographic (GC) analysis of the crude reaction product of nicotine and methyllithium under a number of experimental conditions with 8-ft SE-30 columns appeared to lead to the same conclusion reached previously in the literature, namely, that the major product was 6-methylnicotine (**6**) with minor amounts of 4-methylnicotine (**4**) and in some cases rather sizable recoveries of nicotine. However, ^{13}C NMR spectra[4a] of these product mixtures served as initial indication that 2-methylnicotine (**2**) was often a major product. The observation of fifteen resonances in the aromatic region of the ^{13}C NMR spectrum of a total distilled reaction mixture of a typical nicotine methylation with methyllithium was an early indication to us[4a] that *three* different nicotinoids were in fact present in significant quantities. The resonances in the total product mixture can be assigned based on the listings for all the carbon resonances for the pyridine substituted monomethyl nicotinoids in Table I (supplementary material). Based on the chemical shift identification, evidence for the presence of both 2-methylnicotine and 6-methylnicotine as major products is indicated.

To place these results on a more quantitative basis, we analyzed the total distilled reaction mixture with capillary gas chromatography; this allowed clear separation of nicotine, 2-, 4-, and 6-methylnicotine. The methyllithium–nicotine reactions were performed in a number of solvents [toluene, tetrahydrofuran (THF), and decalin, and in some cases with tetramethylethylenediamine (TMEDA) as cosolvent] and at various ratios of methyllithium:nicotine. The results, indicated in detail in Table II, lead to the following conclusions.

(1) Contrary to the literature findings,[6,7] 2-methylnicotine is a significant product under all the literature reaction conditions.

(2) Increasing the relative concentration of the methyllithium decreases the recovered yield of alkaloid, including nicotine. (Compare entries 1–5 in Table II, for example.) A tradeoff is observed between recovered, unreacted nicotine and lower overall isolation of methylnicotinoids. This may be due to the secondary reaction of excess methyllithium with **2**, **4** and **6**. Indeed, treatment of 6-methylnicotine with a large excess of methyllithium in decalin resulted in only a low recovery of distillables, thereby proving the instability of **6** and presumably also of **2** and **4** to the severe reaction conditions.

(3) The use of TMEDA appears to facilitate the reaction. For example, comparison of entries 9 and 10 indicates that a higher conversion to product can be obtained by the presence of TMEDA than with THF alone. The rate of addition of alkyllithium reagents to other substrates has previously been shown to be enhanced by the presence of TMEDA.[10] Presumably, TMEDA complexes with the lithium cation and renders the alkyllithium reagent a hotter nucleophile.

(4) A rather constant ratio of **6**/**2** $\simeq$ 1 is obtained for the methyllithium reactions with a lower ratio of reagent: substrate in the *absence* of TMEDA (see entries 1–4, 8, 11–12). However, at the highest relative concentration of methyllithium, **6**/**2** dips below 1 (entry 5). In the presence of TMEDA, **6**/**2** $\simeq$ 5. These observations are of value should one desire greater regioselectivity for preparative purposes.

(10) (a) Mulvaney, J. E.; Newton, D. J. *J. Org. Chem.* **1969**, *34*, 1936–1939. (b) Zieger, H. E.; Laski, E. M. *Tetrahedron Lett.* **1966**, 3801–3804. (c) Agami, C. *Bull. Soc. Chim. Fr.* **1970**, 1619–1624.

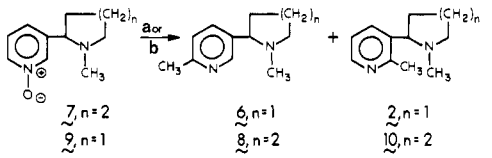
Table III. Optical Rotations for Methylation Reaction Products of (−)-Nicotine and (−)-Nicotine N-Oxide

entry[a]	reactions conditions reagent:1/solvent	specific rotation,[b-d,h] $[\alpha]^{20}_D$, deg: recovered Nic (1)	2-MeNic (2)	4-MeNic (4)	6-MeNic (6)	4,6-Me_2Nic[f]
4	5:1 $CH_3Li/PhCH_3$[e]	−160	−48	−155	−54	−64
6	4:1 $CH_3Li/PhCH_3$/TMEDA		−6		−8	
7	4:1 CH_3Li/Et_2O/TMEDA	−166	−93		−9	
9	4:1 CH_3Li/THF	−111			−33	
10	4:1 CH_3Li/THF/TMEDA	−166	−134	−73	−3	
11	2:1 CH_3Li/decalin		−202	−169	−73	−78
12	2:1 CH_3Li/decalin		−207		−79	−67
13	N-oxide/MeMgBr/THF		−167		−80	
15	6:1 t-BuO_2H[g]	−174	−216	−194	−172	−174

[a] Entry numbers and corresponding data refer to reactions listed under same entry number in Table II. [b] Samples were purified by HPLC and preparative GC. [c] In CH_2Cl_2. [d] All optical rotation measurements were performed at concentrations between 1.2–2.6 g/100 mL. See Table V for additional details. [e] Haglid reported optical rotations for nicotine, 4-methylnicotine, and 6-methylnicotine of $[\alpha]^{22}_D$ −56.3°, −103.5°, and −58.1° (in $CHCl_3$), respectively, for the reaction products from methyllithium:nicotine (2:1) in refluxing toluene (ref 6a). Leete and Leete report an optical rotation of $[\alpha]^{25}_D$ −170° for 4-methylnicotine (ref 7) following the Haglid procedure. The latter result is closer to our results than is the Haglid rotation. [f] The identity of this compound was established by comparison with an authentic sample (ref 3c). [g] Reference 4b. [h] Nic = nicotine.

(5) As indicated by the capillary GC results, no significant formation of 4-methylnicotine was observed in any of the methyllithium reactions.

As Grignard reagents are known to add to pyridine N-oxides,[11] we examined the reaction of methylmagnesium bromide with nicotine N-oxide in THF. Otroshchenko, et al. reported that the reaction of methylmagnesium iodide with N′-methylanabasine N-oxide (7) in "heated" benzene resulted in the formation of a single product, 6,1′-dimethylanabasine (8) in 33% yield (eq 2a).[12] In our



(2)

(a) n = 2, CH_3MgBr/benzene, heat; (b) n = 1, CH_3MgBr/THF

hands, the analogous reaction of nicotine N-oxide[13] (9) with methylmagnesium bromide in THF at 50 °C gave low yields of 2 and 6. At −70 °C, the distillable yield was more than three times greater (65%) than that found at 50 °C (20%). (See Table II, entries 13–14.) In both cases, nearly equal amounts of 2 and 6 were formed in the *absence* of 4. We speculate that thorough examination of the N′-methylanabasine N-oxide reaction mixture would most likely reveal the presence of 2,1′-dimethylanabasine (10) as a major product. However, since the preparation of nicotine N-oxide requires two steps from nicotine[12] and since no advantage was noted in this procedure over the more direct reaction of nicotine with methyllithium, we recommend use of the one-step procedures for large scale preparations of 2 and 6.

Racemization Studies

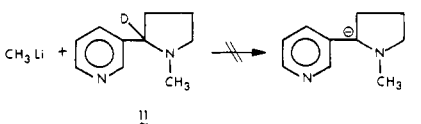
One of the objectives of this work was the preparation of pyridine-substituted methylnicotinoids of high optical purity. By using optically pure (−)-nicotine as the starting material in these reactions, we had hoped to discover at least one mode of preparation that would achieve this goal.

We have carefully purified the major and some of the minor products in nine of the alkylation reactions, and the rotations of these products are listed in Table III. The first column of Table III relates the reported optical activity data to the corresponding experimental conditions and product distributions/yields listed in the entries of Table II. The purification procedures included use of HPLC followed by preparative gas chromatography. In most cases, the final purified product used to determine the optical rotation was resubjected to capillary GC analysis to certify product purity. One reaction condition was replicated (entries 11 and 12) to determine the reproducibility of these results. The excellent replication of entries 11 and 12 in Tables II and III are noteworthy considering that the reactions are heterogeneous (see Experimental Section for additional details).

We have independently prepared 2-, 4-, and 6-methylnicotines in chemically pure form via homolytic radical methylation following a literature report[4,8] and have obtained higher specific rotations for these methyl nicotinoids than those obtained from the methyllithium reactions (cf. Table III, entry 15). We note that the rotation of 6-methylnicotine from the methyl radical reaction was, within experimental error, identical to that for optically pure nicotine, and one could speculate that the rotations observed in entry 15 for 2-, 4-, and 6-methylnicotine and for 4,6-dimethylnicotine represent those for optically pure materials. Table III clearly indicates that partially racemized products are formed in all the methyllithium reactions.

Three distinct types of mechanisms can be advanced to account for the reaction products and partial racemizations observed in the methyllithium reactions.

Hypothesis 1: The starting material could (partially) racemize under the reaction conditions, thereby leading to (partially) racemized products (e.g., eq 3). Strong bases,



(3)

11

including alkyllithium reagents, are known to deprotonate alkylpyridines at the picolyl position.[14,15] We can discount

(11) Abramovitch, R. A.; Smith, E. M. In "Pyridine and Its Derivatives"; Abramovitch, R. A., Ed.; Wiley: New York, 1974; Volume 14, Supplement, Part Two, Chapter IV.
(12) Otroshchenko, O. S.; Sadykov, A. S.; Utebaev, M. U.; Isametova, A. I. *Zh. Obshch. Khim.* **1963**, *33*, 1038–40; *Chem. Abstr.* **1963**, *59*, 10142d.
(13) Taylor, E. C.; Boyer, N. E. *J. Org. Chem.* **1959**, *24*, 275–277.
(14) Micetich, R. G. In "Pyridine and Its Derivatives"; Abramovitch, R. A., Ed.; Wiley: New York, 1974; Volume 14, Supplement, Part Two, Chapter V.

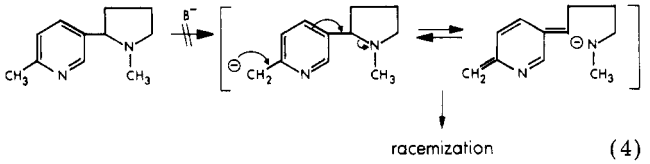
Table IV. Racemization Study of (−)-6-Methylnicotine (6)

entry	reaction conditions[a] solvent/temperature	observed rotations,[b] $[\alpha]^{20}_D$, deg: starting material (6)	recovered 6	% recovery
16[c]	$CH_3Li/PhCH_3$/reflux 3 h	−165	−167	50
17[c]	$CH_3Li/PhCH_3$/reflux 13 h	−165	−170	*e*
18[d]	LDA/THF/−70–25 °C	−172	−174	95

[a] One equivalent of base used to minimize destruction of starting material. [b] In CH_2Cl_2. [c] Reaction mixture turned black. [d] Reaction mixture turned yellow-orange. [e] Not determined.

this sequence because the recovered nicotine was nearly optically pure in all cases except for entry 9, and in this latter entry, the recovered nicotine was ca. 65% enantiomeric excess (e.e.) while the major product, 6-methylnicotine, was ca. 19% e.e. Further evidence against this proposal was our finding that the reaction of methyllithium with [2′-^{2}H]nicotine (**11**) under two different methylation conditions [(a) methyllithium/toluene, Table II, entry 4 conditions; (b) methyllithium/THF/TMEDA, Table II, entry 10 conditions] led to recovered [2′-^{2}H]nicotine having, within experimental error, unchanged deuterium incorporation. As an additional check for consistency, we noted that the product composition of these two methyllithium reactions with **11** was essentially the same as observed (Table II) with the methylation of the undeuterated (*S*)-(−)-nicotine.

Hypothesis 2: The optically pure (−)-nicotine could be transformed to optically pure methylnicotinoids which are subsequently (partially) racemized under the methyllithium reaction conditions (e.g., eq 4).[17] To examine this

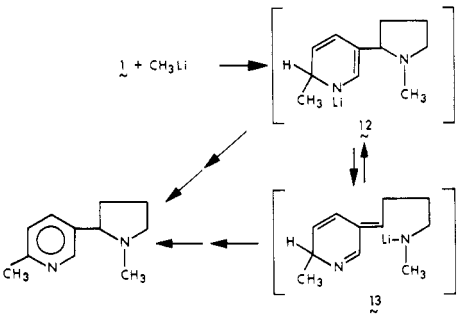


(4)

hypothesis, we have reacted 6-methylnicotine of high optical purity[8] with 1 equiv of methyllithium under conditions listed in Table IV. In each of these three experiments, the recovered and carefully purified 6-methylnicotine was obtained *without* loss of optical activity. It is interesting to note that in the methyllithium reactions cited in Table III, the 2-methyl- and 4-methylnicotines were obtained with higher optical rotation than the 6-methylnicotine. In that we have established that the 6-methylnicotine does *not* racemize under the reaction conditions, it is unlikely that either the 2-methyl- or 4-methylnicotines are racemized under the reaction conditions.

Hypothesis 3: After prereaction and postreaction racemization are ruled out, the third mechanism would incorporate racemization *during* the alkylation reaction itself. It is well-known that intermediates formed in the reaction of a variety of pyridines with alkyl- and aryllithium reagents,[18] can be alkylated,[19] carboxylated,[20] or

Scheme I

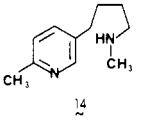


reacted with more complex reagents[21] to form 2,5-disubstituted pyridines.

Applying these precedents to nicotine alkylation, we postulate that intermediate **12** ring opens to **13** which recyclizes on either the *pro-R* or *pro-S* face of **13** and yields racemized product (Scheme I). Similar considerations can be applied to the intermediates resulting from methylation at C_2 or C_4. In these latter cases, destabilizing $A^{(1,2)}$ and $A^{(1,3)}$ strain[22] in the intermediate azacyclohexadienyl anion could render this ring opening reaction less favorable. Consistent with this proposed chemical reactivity of intermediates **12** and **13** is the recent report by Newcomb and Burchill[23] that an alkenyllithium amide will cyclize to an organolithium species (eq 5).

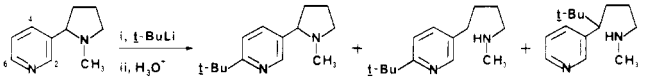
(5)

Additional substantiation of this ring-opening mechanism would follow from the isolation of a metanicotine derivative **14**. Unfortunately, careful examination of the



14

reaction products of nicotine and methyllithium for a number of Table II entries has not led to the observation of **14**. However, we have recently reported the isolation of the analogous 6-*tert*-butyldihydrometanicotine **15** in the reaction of *tert*-butyllithium with nicotine (eq 6).[5] On the



15

(6)

(15) For a study of the base-catalyzed racemization of (*S*)-nicotine involving deprotonation of the C_2–*H*, see: (a) Kisaki, T.; Matsubara, Y.; Tamaki, E. *Nippon Nogei Kagaku Kaishi* **1962**, *36*, 374–377; *Chem. Abstr.* **1964**, *61*, 12049c. (b) Tsujino, Y.; Shibata, S.; Katsuyama, A.; Kisaki, T.; Kaneko, H. *Heterocycles* **1982**, *19*, 2151–2154. (c) Bowman, E. R.; McKennis, H., Jr.; Martin, B. R. *Synth. Commun.* **1982**, *128*, 871–879.

(16) Duffield, A. M.; Budzikiewicz, H.; Djerassi, C. *J. Am. Chem. Soc.* **1965**, *87*, 2926–2932.

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basis of this wide variety of results, we conclude that the loss of optical purity in the methyllithium reactions is most likely due to the racemization processes illustrated in Scheme I.

Summary and Conclusions

Several conclusions can be drawn from the preceding experimental observations:

(1) The reaction of methyllithium with nicotine under a variety of reactions leads to 2-methylnicotine and 6-methylnicotine as major products, a result which expands upon a number of literature reports.[6-7] In addition, 2-methylnicotine is a major product in the reaction of methyl Grignard with nicotine N-oxide, contrary to expectation based on the literature report of methyl Grignard with anabasine N-oxide.[12]

(2) 4-Methylnicotine is only observed as a major product in the methyl radical alkylations.

(3) The formation of 2-methyl- and 6-methylnicotine in nearly equal amounts under many of the conditions in Table II indicates that the N-methylpyrrolidinyl group is not sufficient to prevent C-2 attack, be it from methyllithium or methylmagnesium bromide.

(4) For the methyllithium reactions, the retention of configuration in the recovered nicotine and the retention of deuterium in the alkylation of [2′-^{2}H]nicotine coupled with the retention of configuration of (−)-6-methylnicotine under the reaction conditions suggest that loss of optical purity in the products is due to a novel reversible ring-opening reaction (Scheme I) during the methylation.

Experimental Section

Methods and Materials. ^{1}H and ^{13}C NMR spectra were obtained on either a Varian XL-100 NMR spectrometer equipped with a Digilab NMR-3 FT accessory or a Bruker WP-80 spectrometer operated in the FT mode. Mass spectra were obtained on a Finnigan 3300 GC/MS/DS-6000. High-performance liquid chromatography (HPLC) was performed on a Waters isocratic system using a Whatman Partisil® M9 10/50 column with hexane–acetone–triethylamine (90:10:1.5) and refractive index detection. Optical rotations were determined on a Perkin-Elmer Model 241 MC polarimeter at 20 °C. The opticals rotations of three samples of authentic (S)-(−)-nicotine at two different concentrations each were determined in order to show that within these operating concentration limits, we can expect the rotations of nicotine and, by inference, the methylnicotines to be concentration independent (see Table V). The percent composition of products from methylation reactions was determined on either a Varian 1400 or a Varian 4600 gas chromatograph modified for capillary columns. The separations were accomplished with either a 60-m SP-1000 capillary column (0.25 mm ID) at 150 °C (relative retention times: nicotine, 1; 2-methylnicotine, 1.02; 4-methylnicotine, 1.71; 6-methylnicotine, 1.11) or a 30-m SE-54 capillary column (0.25 mm ID) at 175 °C (relative retention times: nicotine, 1; 2-methylnicotine, 1.12; 4-methylnicotine, 1.31; 6-methylnicotine, 1.14). Methyllithium in ether was obtained from Aldrich Chemical Company and was titrated before use.

Typical Procedure for the Alkylation Reactions. An ethereal solution (173 mL, 1.4 M) of methyllithium (0.242 mol) was slowly (15 min) added to nicotine (19.59 g, 0.121 mol) dissolved in ether (300 mL). The reaction mixture was heated, ether was allowed to distill off and was simultaneously replaced by decalin (560 mL) over a 1-h period while raising the temperature to 110 °C. After being stirred and heated at 110 °C for 7 h, the reaction mixture was cooled and carefully quenched with 200 mL of water. The aqueous phase was separated and the organic phase extracted with two 50-mL portions of 6 M hydrochloric acid. The aqueous fractions were combined, washed with ether, made alkaline, and extracted with methylene chloride. Concentration of the dried (Na_2SO_4) methylene chloride extracts followed by bulb-to-bulb distillation gave 9.1 g of an oil, bp 120 °C (oven)(0.1 torr). This fraction was then subjected to HPLC and preparative GC purification and capillary GC analysis of the individual purified components.

Table V. Effect of Concentration on Specific Rotation for (S)-Nicotine

specific rotation,[b] $[\alpha]^{20}_D$, deg	concentration,[b] g/100 mL
−173	2.534
−169	2.563
−170	2.556
−166	1.226
−170	1.327
−171	1.317

[a] Mean value −169.8 ± 2.3°. [b] In methylene chloride.

Racemization Studies. The Reaction of (S)-6-Methylnicotine and Methyllithium. An ethereal solution (0.37 mL, 1.55 M) of methyllithium (0.574 mmol) was added to (S)-6-methylnicotine (100 mg, 0.574 mmol, $[\alpha]_D$ −165°). The ether was removed by sweeping with nitrogen and was replaced with 3 mL of toluene. The mixture was heated under reflux at 110 °C for 13 h and the cooled reaction mixture was treated with dilute hydrochloric acid. The separated aqueous phase was washed with ether, basified (50% KOH), extracted with methylene chloride, and concentrated. Bulb-to-bulb distillation gave a colorless oil, bp 95 °C (oven) (0.05 torr). The major fraction corresponding to 6-methylnicotine was GC trapped: $[\alpha]^{20}_D$ −170° (c 0.1175, CH_2Cl_2). See Table IV for additional data.

(RS)-[2′-^{2}H]Nicotine and Methyllithium. (A) An ethereal solution (4.9 mL, 1.55 M) of methyllithium (7.6 mmol) was added to (RS)-[2′-^{2}H]nicotine (11) (250 mg, 1.53 mmol). The reaction mixture was heated, ether was allowed to distill off and was simultaneously replaced by toluene (8 mL) over a 30 min period. After being stirred and heated at 110 °C for 7 h, the reaction mixture was cooled and quenched with water (1 mL) and 6 N hydrochloric acid (2 mL). The aqueous phase was separated, washed with ether, basified (50% KOH), and extracted with ether. The ethereal extract was dried (Na_2SO_4) and distilled bulb-to-bulb to give 59 mg of colorless oil: bp 85 °C (oven) (0.025 torr). This material was subjected to GC/MS analysis. The relative percent composition of the m/z ions in the starting material, (RS)-[2′-^{2}H]nicotine (11), was: m/z (%) 161 (7.6%), 162 (19%), 163 (71%), 164 (3.2%). The relative percent composition in the recovered 11 was: m/z (%) 161 (9.5%), 162 (20%), 163 (67%), 164 (4%). We consider that these two sets of relative percentages are identical within experimental error.

(B) A cooled (0 °C) solution of tetrahydrofuran (4 mL) containing [2′-^{2}H]nicotine (0.238 g, 1.47 mmol) and tetramethylethylenediamine (1.3 mL) was treated over a 3 min period with an ether solution (3.8 mL, 1.55 M) of methyllithium (5.88 mmol). The reaction mixture was stirred at 0 °C for 25 min and at room temperature for 5 h and then quenched with water. The solution was treated with 10% NaOH (3 mL) and extracted with ether, and the ethereal solution was dried ($MgSO_4$). The ether was removed and the residue was distilled bulb-to-bulb to give 73 mg of a clear, colorless oil: bp 85 °C (oven) (0.3 torr). This material was subjected to GC/MS analysis. The relative percent composition of the m/z ions in the starting material, 11, are given in the above paragraph. The relative percent composition of the m/z ions in the recovered 11 was m/z (%) 161 (7.8%), 162 (21%), 163 (68%), 164 (2.9%). We consider that these two sets of relative percentages are identical within experimental error.

Reaction of (S)-Nicotine N-Oxide and Methylmagnesium Bromide. To a solution of (S)-nicotine N-oxide[12] (492 mg, 2.77 mmol) in tetrahydrofuran (10 mL) was added *via* syringe an ether solution (1.28 mL, 2.8 M) of methylmagnesium bromide (3.58 mmol). The resulting mixture was stirred at 50 °C for 30 min and then allowed to cool and stirring was continued overnight. Hydrochloric acid (10 mL of a 5% solution) was then added and the mixture was concentrated on a rotary evaporator. The residue was treated with 5% hydrochloric acid (5 mL), heated under reflux for 2.5 h, cooled, basified (50% NaOH), and extracted with methylene chloride. The combined methylene chloride extracts were dried (Na_2SO_4), concentrated, and distilled bulb-to-bulb to give 93 mg of a colorless oil: bp 80–100 °C (0.25 torr). This fraction was subjected to GC analysis and HPLC purification.

Acknowledgment. We thank Ronald L. Bassfield and John Naworal for invaluable technical assistance and Dr. E. B. Sanders for helpful discussions. We also acknowledge with gratitude Jim Day and Chuck Nilles for providing the graphic arts and Anne Donathan for continuing secretarial assistance.

Registry No. (*S*)-1, 54-11-5; (*S*)-9, 2820-55-5; (*S*)-2, 77698-47-6; (*S*)-4, 13270-57-0; (*S*)-6, 13270-56-9; (±)-11, 69980-22-9; methyllithium, 917-54-4; methylmagnesium bromide, 75-16-1.

Supplementary Material Available: Table I. ^{13}C NMR resonance of nicotine and nicotine analogues (1 page). Ordering information is given on any current masthead page.

New Method for the Preparation of Activated Nickel and Cobalt Powders and Their Application in Biaryl Synthesis

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Received March 24, 1983

An activated nickel powder has been prepared by the procedure of electrolysis of a $NiSO_4$ aqueous solution with Hg as the cathode to form a nickel amalgam followed by the removal of the mercury from the amalgam at 150 °C and 10^{-3} torr. The nickel powder, similar to Cu in Ullmann's biaryl synthesis, has been found to react with aryl iodide and aryl bromide at 140 °C to give biaryls in good yields and with dibromobenzene to yield a number of interesting products including triphenylene, tetraphenylene, and polyphenyls, depending on the relative position of the dibromo groups. In the presence of KI, the powder also induces, unprecedentedly, the homo coupling of an aryl chloride to a biaryl. The activity of the activated nickel powder was further demonstrated by the reaction with benzyl bromide to give 1,2-diphenylethane and with α,α-dichlorotoluene to afford mainly *trans*-stilbene.

Recently, one of us developed a new method for the preparation of uranium metal powder. The procedure involved electrolytic reduction of uranium ions on a mercury electrode to form a uranium amalgam followed by vacuum removal of the mercury from the amalgam.[1] We have successfully extended the amalgam method to the preparations of other highly active metal powders. In this paper we report the procedure for the preparation of nickel and cobalt powders and the results of the application of these powders in the syntheses of biaryls from aryl halides.

Prompted by the success of the application of nickel complexes in biaryl synthesis[2-6] and the great activities of the uranium powder activated by the amalgam method,[1] we have undertaken the present investigation. The results clearly demonstrated that the nickel powder not only reacts with aryl iodides and bromides at a temperature lower than that of the Ullmann's biaryl synthesis[9-11] but also couples, unprecedentedly, with aryl chloride in the presence of KI to give biaryls in good yields. The cobalt powder, briefly examined, shows a similar reactivity toward aryl halide. Two independent groups have reported results on the studies of the homo couplings of aryl halides with nickel powder. Rieke and his co-workers[7a,b] have shown that metallic nickel prepared by reduction of nickel halide with lithium metal in the presence of naphthalene is a convenient reagent for the dehalogenative coupling of aryl iodides and bromides. On the other hand, Klabunde[8] et al. have demonstrated that a Ni/THF slury from codeposition of nickel vapor and THF reacted with iodobenzene to give biphenyl in low yield.

Similar to the preparation of uranium powder, activated nickel powder used in the reactions was prepared by two separated steps. In the first, nickel amalgam was formed from electrolysis of an aqueous nickel sulfate solution by using mercury as a cathode, while in the second, the amalgam was placed in a flask (Figure 1), and the mercury was removed from the amalgam at 150 °C and 10^{-3} torr (see Experimental Section). The resulting black powder, which still contains 5–7% of mercury by weight, starts to burn on exposure to air. The coupling reactions of aryl halides were conducted in the same flask at 140 °C by using a 2.0–1.0:1 ratio of aryl halide to nickel metal. While complete removal of mercury from nickel seems unlikely, it is important to mention that the activity of nickel powder is affected by the amount of mercury remaining in the powder, with the activity decreasing as the relative amount of mercury in the nickel powder increases. In one experiment, nickel amalgam prepared from electrolysis was used directly to react with bromobenzene; no coupling product was detected at the end. The activity of nickel powder is further controlled by the ratio of nickel to mercury used in electrolysis with the most suitable value at ca. 1:6. The use of less mercury would lead to an incomplete dissolution of nickel in the amalgam and a decrement of activity due to the direct formation of metal particles from electrolysis, but the employment of more

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