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Pyridinium Chloride: a New Reagent for *N*-Demethylation of *N*-Methylazinium Derivatives.

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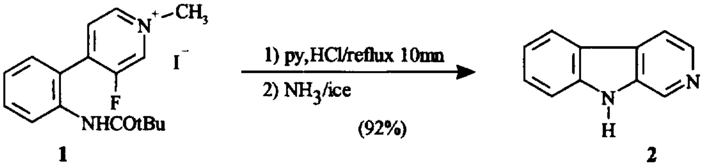
Abstract: A new *N*-demethylation reaction of *N*-methylazinium derivatives by using boiling pyridinium chloride is described. The reaction is quite clean, fast and yields are almost quantitatives.

Pyridinium chloride (py,HCl)[1] has been extensively used for ether cleavages[2], cyclization[3], dehydration reactions[4], and more recently for replacement of a bromine atom by chlorine in pyridine and quinoline series.[5] Several methods for *N*-demethylation of *N*-methylpyridinium derivatives have been described.[6] We can mention dry-heating,[6a] heating with various solvents (like *N*-methylimidazole,[6b] pyridine,[6c] dimethyl-formamide[6d] or ethyl benzyl ether[6e]) and treatment with various reagents such as PPh_3[6f] or $MeNH_2$[6g], but any mention of py,HCl. The major experimental drawback of the already described methods (except for the use of *N*-methylimidazole[6b]) is due to long reaction times (between several hours to several days) leading to degradation. We herein describe a new application of py,HCl as a convenient and rapid *N*-demethylation reagent of *N*-methylazinium derivatives. Working on a new route for the synthesis of substituted tetrahydro-beta-carbolines[7], we observed that cyclization of phenylpyridinium **1** in boiling pyridinium chloride (215°C) led to *N*-demethylated beta-carboline **2** in very good yields (scheme 1).



Scheme 1

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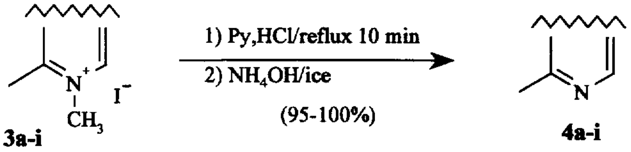
This observation prompted us to study this reaction as a new *N*-demethylation route of *N*-methylazinium structures. Some simple representative structures[8] (**3a-i**) were treated with boiling pyridinium chloride[9] and the corresponding *N*-demethylated nitrogen heterocyclic compounds (**4a-i**) were cleanly obtained in very good yields (scheme 2 and table).



Scheme 2

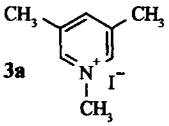
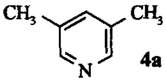
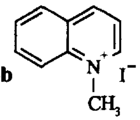
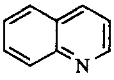
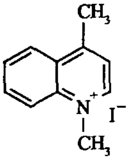
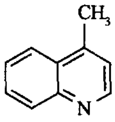
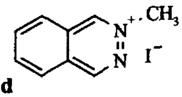
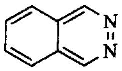
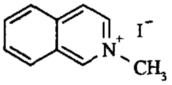
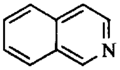
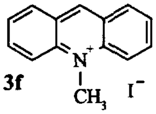
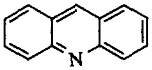
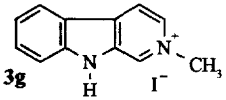
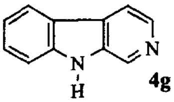
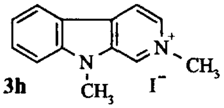
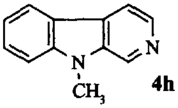
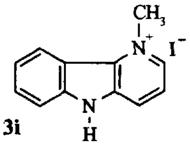
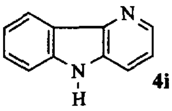
See **Table** on next page.

The two major experimental advantages of this new method are the very short time required to carry out the reaction and the fact that, after neutralization with ammonia, pyridine is an easy solvent to eliminate.

The reaction mechanism is certainly complex, but several observations can be made. First, when the reaction was carried out with compound **3h** (table, entry 8), *N*-demethylation on the indole ring did not occur. Second, when the reaction was carried out with the same compound in a non ionic solvent, like diphenyl ether or DMF, at 260 °C and 160 °C respectively, no *N*-demethylation was observed. Third, when compounds **3a,b,g** were treated during several days in boiling pyridine or quinoline, no *N*-demethylation has been observed, even with an excess (50eq) of lithium chloride or lithium iodide. Fourth, degradations took place with highly pi-deficient heterocycles such as *N*-methylated diazines.

A similar dealkylation reaction has been described by Katritzky and co-workers[10] for *N*-debenzylation of *N*-benzylpyridinium with various nucleophiles, including pyridine itself. However, they observed that *N*-methylpyridinium derivatives react very slowly (and with poor yield) compared to activated methylene such as a benzyl group towards nucleophiles. Deady and Finlayron[6b] had shown that the most general method for *N*-demethylation of *N*-methylazinium structures was to have a highly nucleophilic heterocycle, and use it as the reaction solvent. They have used 1-methylimidazole with reasonable success, but they have shown that its appreciable basic/nucleophilic properties caused side reactions to predominate for some sensitive compounds.

In conclusion, pyridine hydrochloride (py,HCl) is a powerful and rapid *N*-demethylation reagent of quaternised nitrogen heterocyclic compounds.[11] The reaction is quite clean (short reaction time and easy removal of the solvent) and yields are almost quantitatives. This reaction is currently being studied as the key step in the syntheses of polysubstituted carbolines.

Entry	Starting Material	Product	Yield (%)*
1	 **3a**	 **4a**	95
2	 **3b**	 **4b**	98
3	 **3c**	 **4c**	98
4	 **3d**	 **4d**	100
5	 **3e**	 **4e**	96
6	 **3f**	 **4f**	100
7	 **3g**	 **4g**	98
8	 **3h**	 **4h**	97
9	 **3i**	 **4i**	96

Table

*: isolated compound

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8. Compounds **3a-i** as well as compound **1**, were prepared according to a classical route by heating them in ethanol with a large excess (10 eq) of iodomethane during 3 days (Godard, A.; Lamour, P.; Ribéreau, P.; Quéguiner, G. *Tetrahedron Lett.* **1995**, *51*, 3247-3264).
9. Typical procedure: anhydrous boiling (215°C) pyridinium chloride (20g) is added to the required N-methylpyridinium compound (2 mmoles), and the resulting mixture is refluxed for 10 minutes. The resulting hot solution is poured onto a mixture of ice and concentrated ammonia. Extraction of the aqueous layer by ethyl acetate, drying over magnesium sulfate and solvent removal give the corresponding pyridine derivatives as pure material.
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11. All heterocycles (**4a-i**) are known. Here are the main characteristics of *N*-methylazinium derivatives: **1**: mp: 114 °C; ^{1}H NMR (DMSO) 1.0 (s, tBu) ; 4.4 (s, N^+-CH_3); 7.4 (m, 3H); 7.6 (m, NH); 8.1 (t, 1H); 9.0 (d, H_5); 9.5 (d, H_6); 9.55 (s, H_2); $J_{5\text{-}6}$= 6.1 Hz; IR (KBr) 3026, 2923, 1612. Anal. Calcd for $C_{17}H_{20}FIN_2O$ (414.3) C 49.3%; H 4.9%; N 6.8%. Found C 49.2%; H 4.8%; N 6.6%. **3a**: mp: 260 °C; ^{1}H NMR (DMSO) 2.4 (s, 2CH_3); 4.2 (s, N^+-CH_3); 8.25 (s, H_4); 8.65 (m, H_2+H_6); IR (KBr) 2997, 2939, 2519, 1907, 1866, 1819, 1624. Anal.Calcd for $C_8H_{12}NI$ (249.1) C 38.6%; H 4.9%; N 5.6%. Found: C 38.7%; H 4.8%; N 5.5%. **3b**: mp: 132°C; ^{1}H NMR (DMSO) 4.6 (s, CH_3); 8.2 (m, 3H); 8.5 (m, 2H); 9.25 (d, H_4); 9.45 (d, H_2); $J_{2\text{-}3}$= 5,7Hz, $J_{3\text{-}4}$= 8 Hz. IR (KBr): 3048, 3005, 1654, 1618. Anal. Calcd for $C_{10}H_{10}NI$ (271,1) C 44.3%; H 3.7%; N 5.2%. Found C 44.4%; H 3.9%; N 5.3%. **3c**: mp: 164 °C; ^{1}H NMR (DMSO) 3.0 (s, CH_3); 4.6 (s, N^+-CH_3); 8.2 (m, 5H); IR (KBr) 2695, 1598. Anal. Calcd for $C_{11}H_{12}NI$ (285.1) C 46.3%; H 4.2%; 4.9%. Found C 46.5%; H 4.4%; N 4.8%**3d**: mp: 110 °C; ^{1}H NMR (DMSO) 4.5 (s, N^+-CH_3); 8.3 (m, 4H); 8.6 (d, H_4); 8.7 (d, H_3); 10.0 (s, H_2); IR (KBr) 1967, 1648. Anal. Calcd for $C_{10}H_{10}NI$ (271.1) C 44.3%; H 3.7%; N 5.2%.Found C 44.1%; H 3.9%; N 5.5%. **3e**: mp: 220 °C; ^{1}H NMR (DMSO) 4.6 (s, N^+-CH_3); 8.5 (m, 4H); 10.0 (s, H_4); 10.6 (s, H_1); IR (KBr) 2980, 1654. Anal.Calcd for $C_9H_9N_2I$ (271.1) C 39.7%; H 3.3%; N 10.3%. Found C 39.8%; H 3.2%; N 10.2%. **3f**: mp: 144 °C; ^{1}H NMR (DMSO) 4.8 (s, N^+-CH_3); 8.4 (m, 4H); 8.6 (d, 2H, J= 6Hz); 8.8 (d, 2H, J= 5.9 Hz); 10.2 (s, H_6); IR (KBr) 2754, 1654. Anal. Calcd for $C_{14}H_{12}NI$ (321.2) C 52.4%; H 3.8%; N 4.4%.Found C 52.3%; H 3.75%; N 4.5%. **3g**: mp: 234 °C; ^{1}H NMR (DMSO) 4.5 (s, N^+-CH_3); 7.4 (comp, 1H); 7.8 (m, 2H); 8.5 (d, H_8); 8.6 (d, H_4); 8.8 (d, H_3); 9.3 (s, H_1); 10.2 (s, NH); J= 5 Hz; J= 8.1 Hz; IR (KBr) 3076, 3017, 1645, 1616, 1522, 1499. Anal. Calcd for $C_{12}H_{11}N_2I$ (310.1) C 46.5%; H 3.6%; N 9.0%. Found C 48.1%; H 3.9%; N 9.2%. **3h**: mp: >260 °C; ^{1}H NMR (DMSO) 4.0 (s, CH_3); 4.5 (s, N^+-CH_3); 7.5 (comp, 1H); 7.9 (s, 2H); 8.5 (d, 1H, J= 8.6Hz); 8.7 (d, H_4); 8.8 (d, H_3); 9.7 (s, H_1); $J_{3\text{-}4}$= 6 Hz; IR (KBr) 2931, 1637. Anal. Calcd for $C_{13}H_{13}N_2I$ (324.2) C 48.2%; H 4.0%; N 8.6%. Found C 48.1%; H 3.9%; N 8.5%. **3i**: mp: 256 °C; ^{1}H NMR (DMSO) 4.8 (s, N^+-CH_3); 7.5 (comp, 1H); 7.8 (m, 2H); 8.0 (comp, 1H); 8.5 (d, H_6); 8.7 (d, H_4); 8.9 (d, H_2); 10.1 (s, NH); J= 5.9Hz; J= 8.3 Hz; J= 8.1 Hz; IR (KBr) 3067, 1636, 1613. Anal. Calcd for $C_{12}H_{11}N_2I$ (310.1) C 46.5%; H 3.6%; N 9.0%. Found C 46.5%; H 3.5%; N 9.1%.

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