PYRIDINE SYNTHESIS VIA ANODIC OXIDATION OF 1-ACYLDIHYDROPYRIDINES

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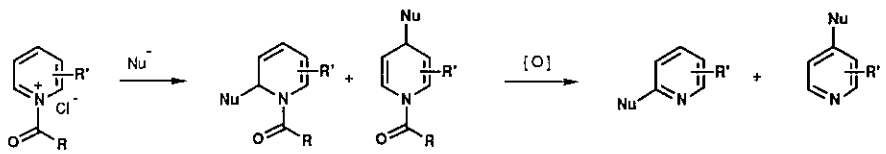
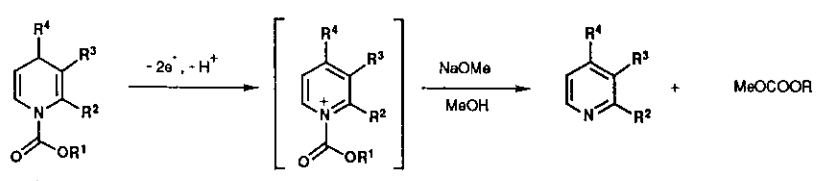
Abstract - The preparation of several substituted pyridines via anodic oxidation of 1-acyldihydropyridines is reported.

The addition of nucleophiles to 1-acylpyridinium salts (**1**) and subsequent aromatization of the intermediate dihydropyridines (**2** and **3**) is a very useful method for the synthesis of substituted pyridines (**4**) and (**5**).[2,3] Oxidizing agents used for the aromatization of 1-acyldihydropyridines include sulphur, *o*-chloranil, *p*-chloranil, DDQ, silver nitrate, and oxygen. The success of the oxidation is quite dependent on the oxidizing agent and the



structure of the 1-acyldihydropyridine. In our hands, aromatization using sulphur or the chloranils has proven to be quite useful and general.[2] However, reaction with sulphur requires a high boiling solvent (150-200°C), and oxidation using chloranil gives nonvolatile by-products which must be separated from the desired substituted pyridine. DDQ and silver nitrate are relatively expensive oxidizing agents, and oxygen is effective in only a limited number of cases. As a possible way to circumvent some of these problems, the electrochemical oxidation of 1-acyldihydropyridines was considered. The aromatization of 1,4-dihydropyridines using anodic oxidation has been studied and the mechanism of electrooxidation explored.[3b] However, we found only one example of a 1-acyl-1,4-dihydropyridine electrochemical oxidation. This involved the electrochemical dehydrogenation of 1-benzoyl-4-(3-indolyl)-1,4-dihydropyridine on a rotating platinum disk electrode with a ring in dimethylformamide on an analytical scale.[4] Since our goal was to oxidize dihydropyridines on a multi-gram scale, we decided to use the electrolysis cell described by Shono, which uses graphite-rod electrodes.[5]

Based on Shono's mechanism for the anodic oxidation of carbamates,[6] it was anticipated that the analogous electrochemical reaction of 1-acyldihydropyridines (**6**) would give aromatic 1-acylpyridinium salts (**7**) in situ as shown below. If sodium methoxide was present as an electrolyte and nucleophile, the 1-acylpyridinium salt intermediate would be deacylated and converted to the free base (**8**).



To test this approach, several 1-acyl-1,4-dihydropyridines (**6**) were prepared according to literature procedures[7,8] and subjected to anodic oxidation in methanol using sodium methoxide as the electrolyte. Shono's electrolysis cell was utilized and the reactions were performed on a 10-12 mmol scale. The results of our study are given in Table 1.

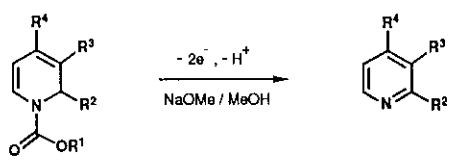
Table 1. Anodic Oxidation of 1-Acyl-1,4-dihydropyridines (**6**)

entry[a]	R^1	R^2	R^3	R^4	yield (%) of oxidation	overall yield(%)[b]	literature yield(%)
a.	Et	H	H	Ph	65	47	62[c]
b.	Et	H	H	*n*-Bu	79	52	62[c]
c.	Ph	H	H	*n*-Bu	60	59	62[c]
d.	Et	Me	H	Ph	60	49	--
e.	Et	H	Me	Ph	90	89	67[c]
f.	Ph	H	Cl	Ph	--	24	55[d]

[a] Reactions were run on a 10-12 mmol scale. The 1-acyl-1,4-dihydropyridines were prepared by literature procedure and were used without purification. Oxidation was achieved using 0.40 amps with a voltage reading between 18-22 V. Six F/Mol of electricity was passed through the solution. [b] The overall yield obtained for the two-step preparation. [c] See reference 7. [d] See reference 8.

As shown in entries a-c, the preparation and anodic oxidation of 1-acyl-1,4-dihydropyridines (**6**) gave yields of substituted pyridines comparable to those reported in the literature.[7,8] In one case, entry e, an excellent yield for the two-step process was obtained which was significantly higher than that reported for the literature procedure. Oxidation of 4-alkyl-3-halo-1,4-dihydropyridines has been carried out in moderate to good yield using *o*-chloranil. We had hoped that anodic oxidation of 3-halo-1,4-dihydropyridines would be competitive with the *o*-chloranil procedure; however, one attempt gave a yield too low to be synthetically useful (entry f).

The analogous anodic oxidation of 1-acyl-1,2-dihydropyridines (**9**) was examined. These electrochemical reactions turned dark brown, presumably due to polymerization, and were only moderately successful giving low yields of substituted pyridines (**10**) as can be seen in Table 2. Literature procedures were unavailable for comparison.



9 **10**

Table 2. Anodic Oxidation of 1-Acyl-1,2-dihydropyridines (**9**)

entry[a]	R^1	R^2	R^3	R^4	oxidation yield (%)	overall yield (%)[b]
a.	Et	Ph	H	Me	38	36
b.	Et	*n*-Bu	H	Me	31	30

[a] Reactions were run on a 10-12 mmol scale. The 1-acyl-1,2-dihydropyridines were prepared by literature procedure and were used without purification. Oxidation was achieved using 0.40 amps with a voltage reading between 18-22 V. Six F/Mol of electricity was passed through the solution. [b] The overall yield obtained for the two-step preparation.

EXPERIMENTAL SECTION

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nmr spectra were recorded on a Varian XL-300 spectrometer. Radial preparative-layer chromatography (radial plc) was carried out by using a Chromatotron (Harrison Associates, Palo Alto, CA). Infrared spectra were recorded on a Perkin-Elmer model 7500 spectrophotometer. The 1-acyldihydropyridines were prepared using literature procedures[7,8] and oxidized by electrolysis without prior purification.

4-*n*-Butylpyridine. General Procedure for the Aromatization of 1-Acyldihydropyridines by Anodic Oxidation. A solution of crude 4-*n*-butyl-1-(phenoxycarbonyl)-1,4-dihydropyridine (**6c**) (3.16 g, 12.3 mmol) in methanol (80 ml) was placed in an electrolysis cell[5] equipped with carbon electrodes and a magnetic stirrer. Sodium methoxide (4.35 M/MeOH) was added dropwise as an electrolyte until a constant current (0.4 A) could be maintained with a voltage reading between 18 V and 22 V. The cell was cooled with an external water bath (18°C) while 6 F/mol of electricity was passed through the solution with stirring. The solvent was removed under reduced pressure at room temperature and ether was added (40 ml). The solution was extracted with 10% HCl (3x20 ml) and the organic layer was discarded. To the aqueous layer was added CH_2Cl_2 (50 ml) and the mixture was cooled to 0°C. The mixture was made basic with 25% NaOH and extracted with CH_2Cl_2 (2x20 ml). The combined organic extracts were washed with brine (20 ml), dried (K_2CO_3), and concentrated. The crude product was purified by radial plc (30% EtOAc/hexane, 1% MeOH) to give 0.981 g (60%) of 4-*n*-butylpyridine as a clear yellow oil: Ir (neat) 2958, 2932, 2872, 1713, 1603, 1466, 1416, 1071 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 0.93 (t, J=7.4 Hz, 3H), 1.22-1.42 (m, 2 H), 1.55-1.71 (m, 2 H), 2.60 (t, J=7.8 Hz, 2 H), 7.10 (d, J=4.5 Hz, 2 H,), 8.48 (d, J=4.5 Hz, 2 H,); ^{13}C nmr (75 MHz, $CDCl_3$) δ 13.58, 21.99, 32.16, 34.66, 123.64, 149.32, 151.44. Picrate mp 112-113.5°C (lit.[7] picrate mp 112.8-113.8°C).

4-Phenylpyridine. Isolated as a white solid: 65% yield; ir (CH_2Cl_2) 3037, 2978, 1484, 1411, 831 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 7.40-7.55 (m, 5H), 7.65 (d, J=4.5 Hz, 2 H), 8.67 (d, J=4.5 Hz, 2 H); ^{13}C nmr (75 MHz, $CDCl_3$) δ 121.41, 126.78, 128.87, 128.92, 137.88, 148.08, 150.05; mp 73-74°C (hexanes) (lit.[7] mp 73-74°C)

3-Methyl-4-phenylpyridine. Isolated as a clear oil: 90% yield; ir (neat) 3028, 1708, 1591, 1479, 1444, 1405, 771, 703 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 2.29 (s, 3 H), 7.15 (d, J=5.0 Hz, 1 H), 7.25-7.50 (m, 5 H), 8.47 (d, J=5.0 Hz, 1 H), 8.51 (s, 1 H); ^{13}C nmr (75 MHz, $CDCl_3$) δ 17.09, 123.83, 127.81, 128.29, 128.39, 130.43, 138.91, 147.23, 148.98, 151.16. *Picrate mp 162-163°C (lit.[7] picrate mp 162-163°C).*

2-Methyl-4-phenylpyridine. Isolated as a clear oil: 60% yield; ir (neat) 3061, 3030, 1606, 1598, 1548, 1106, 1077, 763 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 2.63 (s, 3 H), 7.32 (d, J=5.4 Hz, 1 H). 7.35-7.52 (m, 4 H), 7.63 (d, J=7.5 Hz, 2 H), 8.54 (d, 5.4 Hz, 1 H); ^{13}C nmr (75 MHz, $CDCl_3$) δ 24.44 118.76, 121.09, 126.88, 128.79, 128.92, 138.29, 148.59, 149.43, 158.71. Picrate mp 218-220°C (lit.[7] picrate mp 219-220°C).

3-Chloro-4-phenylpyridine. Isolated as a white solid: 24% yield overall; ir (neat) 3056, 1581, 1489, 1397, 1106, 771 cm^{-1}; ^1H nmr (300 MHz $CDCl_3$) δ 7.24 (d, J=4.8 Hz, 1 H), 7.32-7.55 (m, 5 H), 8.49 (d, J=4.8 Hz, 1 H), 8.66 (s, 1 H); ^{13}C nmr (75 MHz, $CDCl_3$) δ 125.11, 128.21, 128.66, 128.70, 130.12, 136.25, 147.29, 147.63, 149.90. mp 35-37°C (lit.[8] mp 35-37°C). Picrate mp 160-161.5°C.

4-Methyl-2-phenylpyridine. Isolated as a clear oil: 38% yield; ir (neat) 3059, 1605, 1559, 1447, 776, 736 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 7.01 (d, J=5.1 Hz, 1 H), 7.33-7.48 (m, 3 H), 7.51 (s, 1 H), 7.97 (d, J=6.9 Hz, 2 H), 8.53 (d, J=5.1 Hz, 1 H); ^{13}C nmr (75 MHz, $CDCl_3$) δ 21.08, 121.36, 123.00, 126.79, 128.55, 128.67, 139.40, 147.57, 149.29, 157.20. Picrate mp 185-187°C (lit.[10] mp 186-187°C).

2-*n*-Butyl-4-methylpyridine. Isolated as a clear oil: 31% yield; ir (neat) 2958, 2931, 1606, 1563, 1456, 1378, 821 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 0.94 (t, J=7.5 Hz, 2 H), 1.33-1.42 (m, 2 H), 1.66-1.80 (m, 2 H), 2.28 (s, 3 H), 2.73 (t, J=7.8 Hz, 2 H), 6.88 (d, J=4.8 Hz, 1 H,), 6.94 (s, 1 H), 8.36 (d, J=4.8 Hz, 1 H); ^{13}C nmr (75 MHz, $CDCl_3$) δ 13.43, 20.35, 22.02, 31.59, 37.48, 121.30, 122.98, 146.53, 148.38, 161.66. Picrate mp 94-95°C (lit.[9] picrate mp 98.6-99.0°C).

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