

Lithiation of Pyridones

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Lithiation of 1-methyl-4-pyridone with *n*-butyl-lithium at $-78\text{ }^{\circ}\text{C}$ proceeds smoothly at the C-2 position and 2-substituted-4-pyridones (**1c**–**j**) are obtained by subsequent reaction with electrophiles; lithiation of 1-methyl-2-pyridone takes place predominantly at the *N*-methyl, the lithio-derivative reacting rapidly, even at $-78\text{ }^{\circ}\text{C}$ with starting pyridone to give a dimer, (**3**).

The demonstrations of strong base-catalysed H-exchanges of pyridine at C-4^{1a} and of exchange in neutral^{1b} or acidic solutions^{1a} *via* an ylide at C-2 were followed later by preparative lithiations of oxazolino-,^{2a} ethoxycarbonyl-,^{2b} halogeno-,^{2c} and dialkylaminocarbonyl-^{2d} pyridines and recently pyridine itself.^{2e} C-2–H Exchange and lithiation of pyridine *N*-oxides^{2f} and C-2–H exchange of pyridinium salts^{1a,2g} have also been described and involve ylide species.

Acid-catalysed exchange^{3a} of 4-pyridone takes place at C-3/C-5. Hot aqueous sodium hydroxide brings about exchange^{3b} of 1-methyl-4-pyridone at C-2/C-6; however no preparative lithiations have been described hitherto.

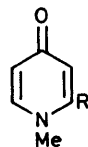
Treatment of 1-methyl-4-pyridone with *n*-butyl-lithium in tetrahydrofuran (THF) at $-78 \rightarrow 0\text{ }^{\circ}\text{C}$ (0.5 h) resulted in a yellow solution, shown to contain the 2-lithiated species (**1a**) by quenching with D_2O at $-78\text{ }^{\circ}\text{C}$ leading to recovery of

monodeuteriated (>98%) pyridone (**1b**) in 91% yield. The location of the label was easily established by ^1H n.m.r. analysis.

The 2-lithiopyridone (**1a**) was treated in THF at $-78 \rightarrow 0\text{ }^{\circ}\text{C}$ (2–3 h) with a range of alkylating and acylating agents to produce (**1c**) (m.p. $50\text{--}55\text{ }^{\circ}\text{C}$, 43%), (**1d**) (m.p. $86\text{--}92\text{ }^{\circ}\text{C}$, 34%), (**1e**) (m.p. $165\text{--}170\text{ }^{\circ}\text{C}$, 78%), (**1f**) (m.p. $126\text{--}132\text{ }^{\circ}\text{C}$, 48%), (**1g**) (m.p. $168\text{--}171\text{ }^{\circ}\text{C}$, 34%), and (**1h**) (m.p. $185\text{--}188\text{ }^{\circ}\text{C}$, 68%).†

A byproduct in the case of methylation was 2-ethyl-1-methyl-4-pyridone (**1i**) (amorphous, 6%) which must have been formed by deprotonation of product C-methyl by (**1a**) and then side chain methylation. This problem was worse in

† Satisfactory elemental analyses were obtained for all new compounds.



(1) R

- a; Li
b; D
c; Me
d; CH₂Ph
e; CH(OH)Ph
f; CPh
g; COC₆H₄-2-CH₂OH
h; COC₆H₄-2-CO₂H
i; Et
j; CH(Ph)CH₂Ph

the case of benzylation where the side chain alkylated material (**1j**) (m.p. 188–191 °C, 62%) was the major product. A comparable problem was noted^{3c} in the alkylation of lithio-halogenopyridines.

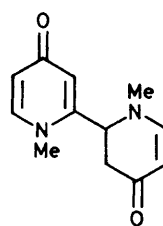
The phthalide condensation product (**1f**) was obtained as a mixture of ketoalcohol and cyclic hemiacetal forms, as evidenced by its ¹H n.m.r. spectrum, in a ratio of 1 : 2.

A trace impurity noted in the reaction forming (**1d**) and (**1e**) could be made the exclusive product by treating the pyridone with 0.5 mol equiv. of lithiating agent and allowing the mixture to come to room temperature. This material (m.p. 204–208 °C, 94%)[†] was shown to be the dimer (**2**) [δ (¹H) 2.52 (1H, dd, *J* 16, 6 Hz), 3.05 (1H, dd, *J* 16, 7 Hz), and 4.60 (1H, apparent t, *J* 6 Hz)] in which the lithiated pyridone had added to a second mol of starting material in a conjugate fashion at C-2.

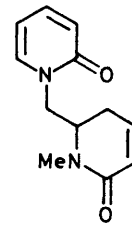
Hot aqueous sodium hydroxide was shown^{3c} to effect exchange of 1-methyl-2-pyridone at C-6 and at about one tenth the rate of exchange of the C-2/C-6 hydrogens in the 4-isomer. Again, no attempts to lithiate preparatively have been described.

Treatment of 1-methyl-2-pyridone with 1 mol equiv. of *n*-butyl-lithium in THF at –78 °C (1 h) resulted in a red solution; quenching with D₂O at –78 °C produced a mixture of starting pyridone (15%) and a dimer (m.p. 132–140 °C, 61%).[†] The recovered pyridone proved to be monodeuteriated and ¹H n.m.r. analysis demonstrated the location of label at C-6 and thus that ring lithiation had occurred at the anticipated position, but only to a minor extent. Attempts to improve the percentage of ring lithiation using lithium di-isopropylamide in THF, –78 °C, 1 h or Bu^sLi in THF, –100 °C, 2.5 h were unsuccessful, the dimer being produced in the same relative percentage yield in each case.

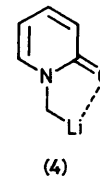
The dimer had only one ¹H n.m.r. *N*-methyl signal and was clearly formed as the result of addition of an *N*-methyl-lithiated species to the second pyridone molecule. A differen-



(2)



(3)



(4)

tiation between the two possible sites (C-4 and C-6) for conjugate addition to the 2-pyridone in favour of the latter and therefore of structure (**3**) for this dimer was made by n.m.r. analysis, thus (i) the dimer had signals for two olefinic hydrogens [δ 5.90 in (CD₃)₂CO], (ii) decoupling experiments established the sequence N·CH₂CH(N)CH₂ [δ 4.28 (2H, dd, *J* 5, 15 Hz), 4.46 (1H, m), and 2.67 (2H, dd, *J* 2, 18 Hz)], and (iii) there was a coupling between a ring methylene proton and an alkene proton.

Lithiation of 1-methyl-2-pyridone under these conditions must occur then most rapidly at the methyl group, presumably with assistance from oxygen (**4**). Even at –100 °C addition of this species to an unlithiated pyridone competes successfully with slower C-6-lithiation.

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