

## Lithiation of Pyridones

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Lithiation of 1-methyl-4-pyridone with *n*-butyl-lithium at  $-78^{\circ}\text{C}$  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  $-78^{\circ}\text{C}$  with starting pyridone to give a dimer, (**3**).

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

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

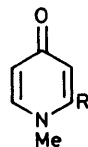
Treatment of 1-methyl-4-pyridone with *n*-butyl-lithium in tetrahydrofuran (THF) at  $-78 \rightarrow 0^{\circ}\text{C}$  (0.5 h) resulted in a yellow solution, shown to contain the 2-lithiated species (**1a**) by quenching with  $\text{D}_2\text{O}$  at  $-78^{\circ}\text{C}$  leading to recovery of

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

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

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

<sup>†</sup> Satisfactory elemental analyses were obtained for all new compounds.



(1) R

- a; Li  
 b; D  
 c; Me  
 d; CH<sub>2</sub>Ph  
 e; CH(OH)Ph  
 f; CPh  
 g; COC<sub>6</sub>H<sub>4</sub>-2-CH<sub>2</sub>OH  
 h; COC<sub>6</sub>H<sub>4</sub>-2-CO<sub>2</sub>H  
 i; Et  
 j; CH(Ph)CH<sub>2</sub>Ph

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<sup>3c</sup> in the alkylation of lithio-halogenopyridines.

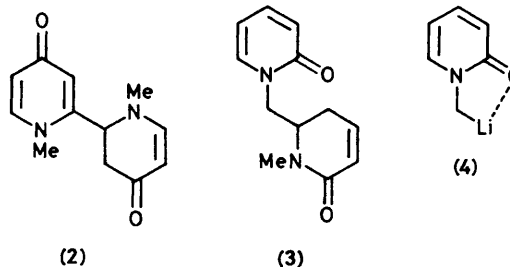
The phthalide condensation product (**1f**) was obtained as a mixture of ketoalcohol and cyclic hemiacetal forms, as evidenced by its <sup>1</sup>H n.m.r. spectrum, in a ratio of 1 : 2.

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%)<sup>†</sup> was shown to be the dimer (**2**) [ $\delta$ (<sup>1</sup>H) 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<sup>3c</sup> 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 D<sub>2</sub>O at –78 °C produced a mixture of starting pyridone (15%) and a dimer (m.p. 132–140 °C, 61%).<sup>†</sup> The recovered pyridone proved to be monodeuteriated and <sup>1</sup>H 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<sup>s</sup>Li 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 <sup>1</sup>H 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-



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 [ $\delta$  5.90 in (CD<sub>3</sub>)<sub>2</sub>CO], (ii) decoupling experiments established the sequence N·CH<sub>2</sub>CH(N)CH<sub>2</sub> [ $\delta$  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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