Unexpected Regioselective Nucleophilic Addition to 3-(4,4-Dimethyloxazolin-2-yl)-pyridine: Formation of Stable 1,4-Dihydropyridines

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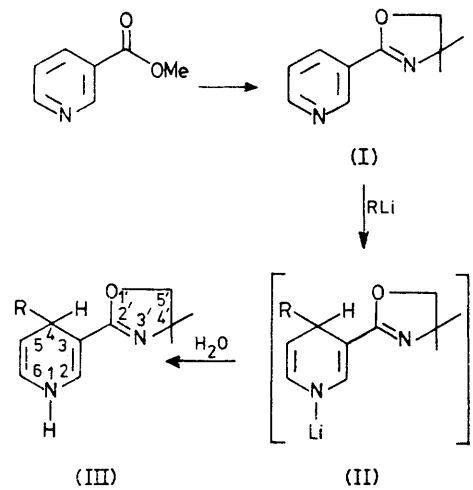
Summary The regioselective addition of organolithium reagents to 3-(4,4-dimethyloxazolin-2-yl)pyridine leads to stable 1,4-dihydropyridines.

EXCEPT for a few isolated reports in which benzyl-lithium [1a,b] and 2-alkyl-2-lithio-1,3-dithian[1c] reacts with pyridine or 3-picoline[1b] to give the corresponding 4-substituted pyridines, organolithium compounds preferentially attack the pyridine nucleus at the 2- or 6- but not the 4-position.[1d] This was particularly true when phenyl-lithium was used. For example, the reaction of phenyl-lithium under various conditions with a variety of 3-substituted pyridines[2] (alkyl-,[3] amino-, methoxy-, or *NN*-diethylsulphamido-pyridine) exclusively resulted in phenylation of the pyridine ring at positions 2 and 6, with the former predominating. In spite of careful analysis, no 4-phenylated pyridines were detected. We now report the unexpected phenylation at the 4-position of 3-(4,4-dimethyloxazolin-2-yl)pyridine (I) by phenyl-lithium, and also the preparation of a novel class of stable 1,4-dihydropyridines.

Compound (I) was obtained by heating methyl nicotinate at reflux with 2-amino-2-methylpropan-1-ol.[4] When (I) was carefully added to a solution of phenyl-lithium in ether[5] at room temperature, a dark precipitate formed. When tetrahydrofuran (THF) was used as the solvent no precipitate was formed, but the product was the same as that obtained in the ethereal solutions. The ^{1}H n.m.r. spectrum (THF) of the reaction mixture displayed a pattern [δ 7·29 (s, H-2), 6·46 (d, H-6), 4·87 (d, H-4), and 4·66 (dd, H-5)] consistent with that of the *N*-lithio dihydropyridine (IIa) (Scheme). Hydrolysis of the reaction mixture gave a



a; R = Ph
b; R = Me
c; R = Bu^n
d; R = Bu^t

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yellow precipitate which showed 18 protons in its n.m.r. spectrum [δ 7·91 (m, 5H, Ph), 4·32 (ABq, 2H, H-5′), 1·76 (s, 3H, Me), and 1·62 (s, 3H, Me); the chemical shifts of the dihydropyridine-ring protons are reported in the Table]. The intensities, positions, and multiplicities of the spectral lines were unambiguously[6] assigned to the stable dihydropyridine (IIIa). The addition of deuterium oxide to the sample eliminated coupling between the N–H and pyridine-ring protons at positions 2, 5, and 6. The ^{13}C n.m.r., i.r., and u.v. spectra and elemental† analyses of (IIIa) (m.p. 169—172 °C; 62·5% by g.l.c.‡) were also consistent with the proposed structure.

Similarly, treatment of (I) with other organolithium compounds followed by hydrolysis led to the formation of the corresponding 1,4-dihydropyridine adducts (IIIb—d) (Table). G.l.c. analyses of the hydrolysed reaction mixtures leading to compounds (IIIa—d) indicate that the 1,4-dihydropyridine derivatives are the major products. Dihydropyridines are generally unstable and not isolable; these 1,4-dihydropyridines, however, are stable in air and may be recrystallized from organic solvents. Upon oxidation with an acetone solution of potassium permanganate they are converted into the corresponding 3,4-disubstituted pyridines.

Table

Chemical shifts (δ) of dihydropyridine-ring protons in $CDCl_3$ at 100 MHz

Compound (III)	H-1	H-2	H-4	H-5	H-6
a	6·19	7·58	5·18	5·39	6·62
b	7·09	7·37	3·90	5·16	6·46
c	7·16	7·45	3·93	5·15	6·53
d	6·03	7·46	4·08	5·14	6·54

The above reaction thus provides a regioselective addition to the 4-position of a 3-substituted pyridine by organolithium compounds and the preparation of a new class of stable 1,4-dihydropyridines.§

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† Analytically pure samples were obtained by sublimation and/or recrystallization.

‡ 90·5% G.l.c. yield based upon recovered (I).

§ While this work was in progress, A. I. Meyers and R. Gabel reported (*Tetrahedron Letters*, 1978, 227) the lithiation of 4-pyridyloxazoline by methyl-lithium.

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