

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

By CHOO SEUG GIAM* and ALBERT E. HAUCK

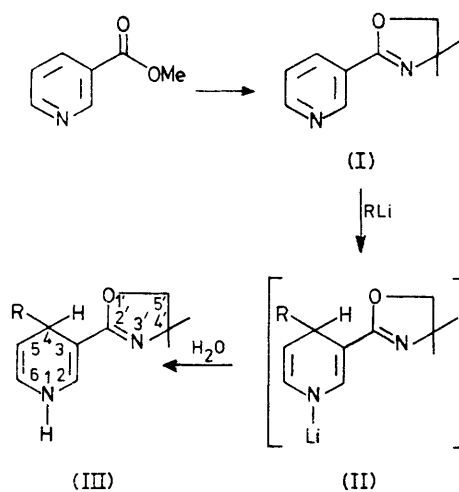
(Department of Chemistry, Texas A&M University, College Station, Texas 77843)

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

(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

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 pyridines² (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 ether⁵ 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 ¹H n.m.r. spectrum (THF) of the reaction mixture displayed a pattern [δ 7.29



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

SCHEME

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 unambiguously⁶ 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 ¹³C 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

TABLE

Chemical shifts (δ) of dihydropyridine-ring protons in CDCl₃ 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

oxidation with an acetone solution of potassium permanganate they are converted into the corresponding 3,4-disubstituted pyridines.

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.§

We thank the Robert A. Welch Foundation for financial support and Dr. R. A. Abramovitch for helpful comments.

(Received, 29th March 1978; Com. 337.)

† 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.

¹ (a) H. Gilman and H. A. McNinch, *J. Org. Chem.*, 1962, **27**, 1889; (b) R. A. Abramovitch and G. A. Poulton, *J. Chem. Soc. (B)*, 1969, 901; (c) T. Taguchi, M. Nishi, K. Watanabe, and T. Mukaiyama, *Chem. Letters*, 1973, 1307; (d) F. Haglid, *Acta. Chem. Scand.*, 1967, **21**, 329, 335.

² R. A. Abramovitch and J. G. Saha, in 'Advances in Heterocyclic Chemistry,' Vol. 6, eds. A. R. Katritzky and A. J. Boulton, Academic Press, New York, 1966, pp. 274–291, and references therein.

³ R. A. Abramovitch and G. A. Poulton, *J. Chem. Soc. (B)*, 1967, 267.

⁴ J. A. Frump, *Chem. Rev.*, 1971, **71**, 483; A. P. Phillips and R. Baltzly, *J. Amer. Chem. Soc.*, 1947, **69**, 200; D. Günther and K. H. König, *Chem. Ber.*, 1954, **87**, 1628 (*Chem. Abs.*, 1955, **49**, 14758e).

⁵ C. S. Giam and J. L. Stout, *Chem. Comm.*, 1969, 142.

⁶ J. W. Emsley, J. Feeney, and L. H. Sutcliffe, 'High Resolution Nuclear Magnetic Resonance Spectroscopy,' Pergamon Press, 1965, vols. 1 and 2.