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THE REGIOSELECTIVE NUCLEOPHILIC ADDITION OF ORGANOLITHIUMS TO 3-(4,4-DIMETHYLOXAZOLIN-2-YL)PYRIDINE. SYNTHESIS OF 1,2-, 1,4- AND/OR 1,6-DIHYDROPYRIDINES

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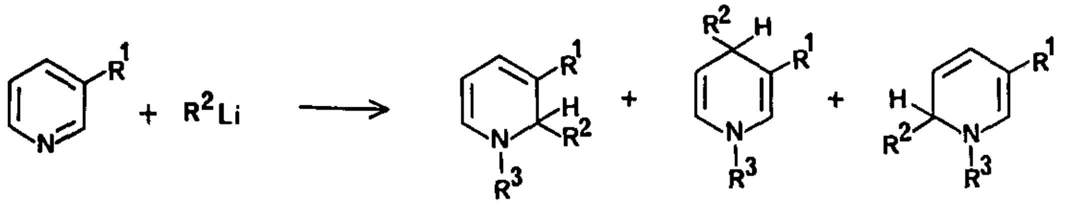
Abstract - The nucleophilic addition of organolithium reagents to 3-(4,4-dimethyloxazolin-2-yl)pyridine afforded stabilized N-unsubstituted 1,2-, 1,4- and/or 1,6-dihydropyridines. Solvent, temperature and nature of the organolithium reagent influence the regioselectivity of the reaction.

The nucleophilic addition of organolithium reagents to **1** is a useful synthetic procedure for the synthesis of 1,4-dihydropyridines. Thus reaction of **1** with methyl-, n-butyl- and phenyllithium in THF at -78°C[1] or in ether at 25°C[2] afforded 1,4-dihydropyridines in high isolated yields. We required stabilized N-unsubstituted dihydropyridines as medicinal synthons[3] for use in our drug design program. Micro tlc (silica gel, 5% MeOH in $CHCl_3$) examination of the product, obtained from the reaction of **1** with phenyllithium in ether at 25°C, showed two distinct spots. Purification on a short neutral alumina oxide column with ether as eluant afforded a stable yellow solid with mp 169-170°C (sub); ir (KBr) 3240, 1640 cm^{-1}; ^1H nmr (DMSO-d_6 + $CDCl_3$) δ: 7.16 - 7.66 (m,5H,Ph), 6.9 (d,$J_{4,5}$ = 6.5 Hz,1H,H-4), 6.48 (d,$J_{5,6}$ = 6Hz of d,$J_{NH,6}$ = 6Hz, 1H,H-6; collapses to a d,$J_{5,6}$ = 6Hz after D_2O exchange), 5.68 (d,$J_{NH,2}$ = 3Hz,1H,H-2), 4.85 (d,$J_{4,5}$ = 6.5 Hz of d,$J_{5,6}$ = 6Hz of d,$J_{NH,5}$ = 1.5 Hz, 1H,H-5; br s, 1H,NH, exchanges with D_2O), 3.9 (s,2H,-OCH_2), 1.3 and 1.18 (two s, 3H each, Me); Exact mass calcd. for $C_{16}H_{18}N_2O$: 254.1419; found (high resolution ms): 254.1414. This ^1H nmr spectral data are consistent with that expected for the 1,2-dihydro isomer **2c**[3]. The ^1H nmr spectrum of the reaction mixture indicated that the 1,2- and 1,4-dihydro isomers were present in a ratio of 4:1 as determined from integration of H-2 at 5.68 and H-6 at 6.2 δ for the respective isomers. The formation of the stable 1,2-dihydro isomer **2c** as the major product was unexpected since a similar reaction was reported to yield the 1,4-dihydro isomer **3c**.[2] This prompted us to investigate the effect of solvent, reaction temperature and organolithium reagent upon the ratio of dihydropyridines formed.

The reactions were allowed to procede at 25°, 0° and -78°C respectively for 1 h prior to addition of water. The reaction mixture was extracted with ether, the solvent dried (Na_2SO_4) and removed *in vacuo* at 25°C. The ^1H nmr spectrum of the reaction product(s) was determined immediately after addition of D_2O which simplified the spectrum[2]. The ratio of isomeric dihydropyridines formed was determined by integration of the H-6, H-2 and H-2 protons at 6.5, 6.82 and 7.1 δ for 2a, 3a and 4a respectively, and H-2 and H-6 at 5.68 and 6.2 δ for 2c and 3c respectively. The dihydropyridines 2a and 4a, which were difficult to obtain as pure products, were characterized as their N-methoxycarbonyl derivatives obtained by treatment of the N-lithio intermediates with methyl chloroformate[4]. Purification was effected on preparative silica gel G plates (0.5 mm) using ether:hexane (6:4) as development solvent[5].



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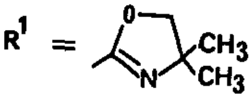

a, $R^2 = CH_3$, $R^3 = H$; b, $R^2 = CH_3$, $R^3 = CO_2CH_3$; c, $R^2 = Ph$, $R^3 = H$.

The results shown in the Table indicate that the reaction of 1 with methyl and phenyllithium with ether as solvent yields primarily (or only) 1,2- (2) and 1,4-dihydropyridines (3). On the other hand, in THF methyllithium attacks primarily at the C-4 and C-6 positions. In THF phenyllithium attacks primarily at C-4 to yield the 1,4-dihydro compound 3c, Lower temperatures favour attack at C-4 in both solvents. The ratio of dihydropyridines obtained using n-butyllithium was similar to those for methyllithium. These results indicate that the solvent, temperature and nature of the organolithium reagent influence the regioselective (and in some cases regiospecific) addition to 1.[6]

TABLE

Isomeric ratios (%) as determined from ^{1}H nmr integrals[a]

R^2-Li	Solvent	Temp., °C	1,2-Isomer(2)	1,4-Isomer(3)	1,6-Isomer(4)
MeLi(PhLi)	Et_2O	25°	67(80)	25(20)	8(-)
MeLi(PhLi)	Et_2O	0°	63(75)	32(25)	5(-)
MeLi(PhLi)	Et_2O	-78°	40(5)	54(95)	6(-)
MeLi(PhLi)	THF	25°	17(16)	50(84)	33(-)
MeLi(PhLi)	THF	0°	10(8)	60(92)	30(-)
MeLi(PhLi)	THF	-78°	-(-)	>95(100)	<5(-)

[a] The isomeric ratios (%) for phenyllithium are shown in brackets.

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