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OXAZOLINES AS ACTIVATING GROUPS IN AROMATIC SUBSTITUTION.[1]
REGIOSELECTIVE METALLATION OF THE 3-POSITION IN PYRIDINE.

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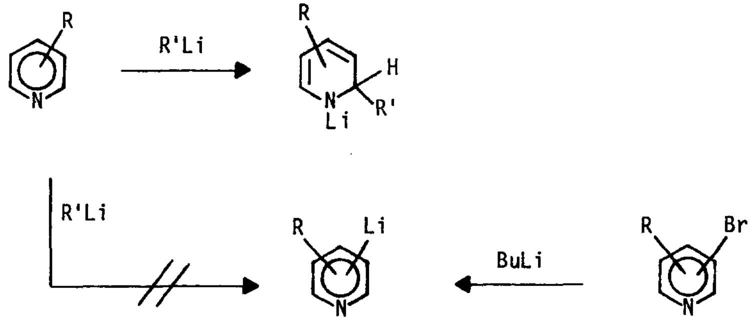
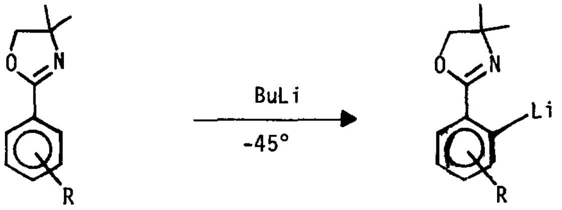
The direct metallation of pyridine, except in a few special cases,[2] is unknown mainly because organolithium reagents readily add across the C=N bond.[3] On the other hand, lithiated pyridines have been obtained by halogen metal exchange via the bromopyridines[4] (Scheme 1). In the course of a study designed to utilize the extraordinary activating effect of oxazolines toward ortho-metallation (1)[2,5] and ortho-substitution[1] (2) of aromatics, it was felt that

SCHEME 1





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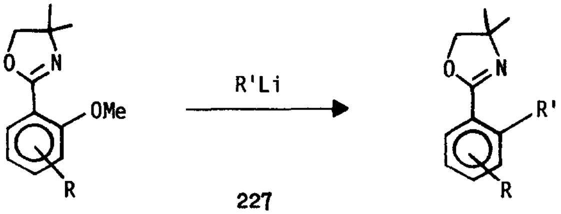
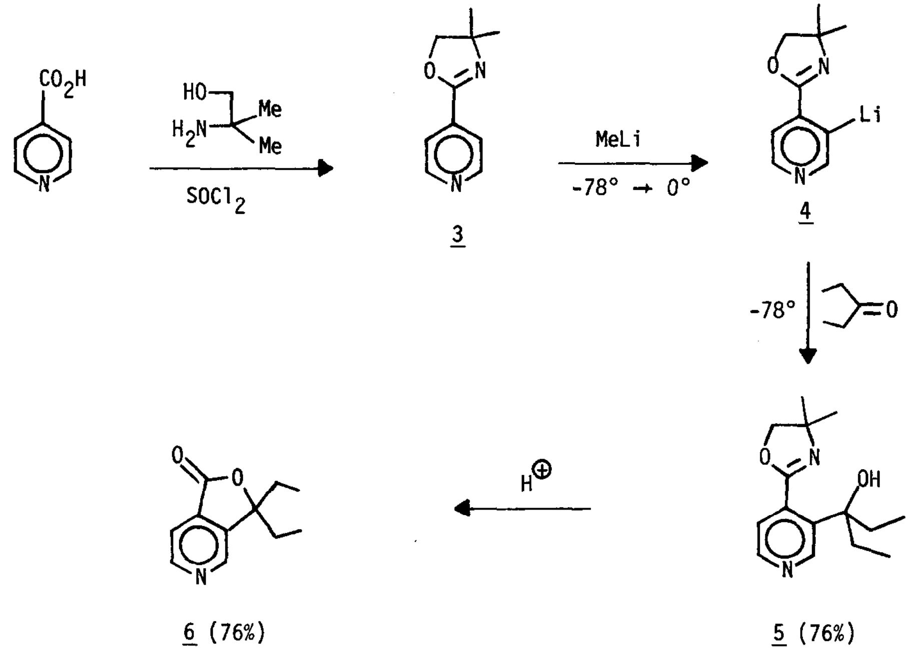


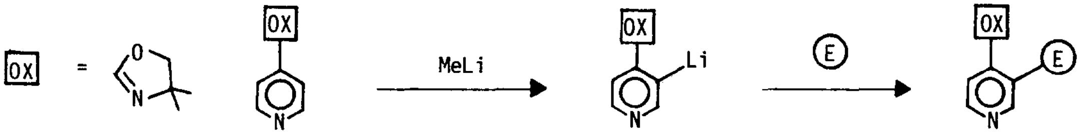
2

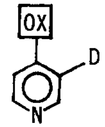
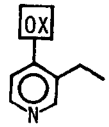
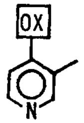
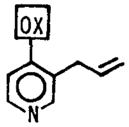
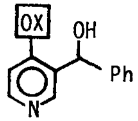
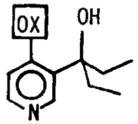
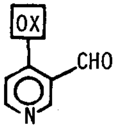
direct metallation of pyridines would be feasible. Thus, isonicotinic acid was transformed into the oxazoline 3 (80%, mp 51-52°) and subjected to various organolithium reagents. Use of *n*-butyllithium, *sec*-butyllithium, *tert*-butyllithium and



lithium diisopropyl amide gave mixtures of the 3-lithiopyridine 4 and addition to the pyridine ring as shown in Scheme 1. However, methyllithium, when added to a THF solution of the pyridyl oxazoline 3 at -78° (1 hr) and warmed to 0° (1 hr) gave on addition of diethyl ketone (-78°) essentially a quantitative yield of 5. Analytically pure material was recovered in 76% yield thus indicating the high efficiency of this process. No trace of addition product or lithiation at the 2-position was discernible from the nmr spectrum of the crude reaction product. Acid hydrolysis (4.5 N HCl, reflux) converted 5 to the lactone 6 (76%, mp 62°). The generality of the regiometallation and subsequent reaction with various electrophiles are presented in Table 1.

Table 1. Metallation of 2-(4-pyridyl)-4,4-dimethyl-2-oxazoline, 3



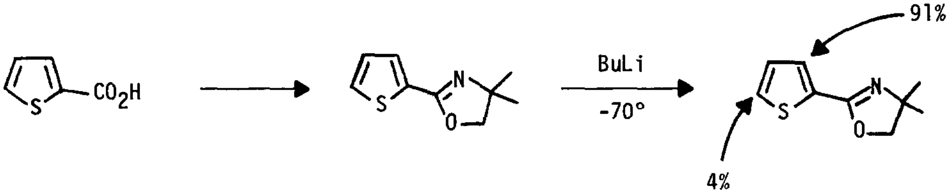
E	Product[a]	% Yield[b]	Rxn. Time	Bp (mp)°
D_2O		80	0.5 hr	(51-52)
EtI		56	4.5 hr	65 (0.1 torr)
MeI		63	2 hr	80 (0.05 torr)
		55	2 hr	88 (0.1 torr)
PhCHO		83	4 hr	125 (0.05 torr)
$Et_2C{=}O$		76	5 hr	(84.5-85.0)
 $HC(=O)NMe_2$		52	2 hr	c

a) All products gave satisfactory spectral and elementary analyses.

b) All yields represent isolated, pure material. Crude yields are 20-25% higher.

c) Unstable compound, decomposes in air.

A recent report[6] described a similar effect on the metallation of thiophenes in the presence of an oxazoline which directed metallation predominantly to the 3-position. The extent of metallation reached 91% at the 3-position while only 4% at the usually more reactive 2-position. This behavior in the thiophene series coupled with results described herein for pyridine seem to support the fact that the oxazoline moiety ranks among the most efficient of the so-called activating groups for ortho-metallation.[7] In fact, the coordination ability of the oxazoline is sufficiently strong to compete successfully with the well-known addition of organolithium reagents to the pyridine nucleus.



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REFERENCES

1. For previous papers in this series c.f. A. I. Meyers and E. D. Mihelich, J. Org. Chem., 40, 3158 (1975); A. I. Meyers and E. D. Mihelich, J. Am. Chem. Soc., 97, 7383 (1975); A. I. Meyers and R. Gabel, J. Org. Chem., 42, 2653 (1977).
2. J. D. Cook and B. Wakefield, J. Chem. Soc. (C), 1973 (1969) have reported metallation of the 4-position in 2,3,5,6-tetrachloropyridine and 2,3,6-trichloropyridine.
3. B. J. Wakefield, "The Chemistry of Organolithium Compounds", Pergamon Press, 1974, pp 112-116.
4. H. Gilman and S. M. Spatz, J. Org. Chem., 16, 1485 (1951); J. P. Wibaut et. al, Rec. Trav. Chim., 70, 1054 (1951); A. Murray, et. al, J. Am. Chem. Soc., 70, 1037 (1948); W. E. Parham and R. M. Piccirilli, J. Org. Chem., 42, 257 (1977).
5. A similar observation was reported by H. W. Geschwend and A. Hamdam, J. Org. Chem., 40, 2008 (1975).
6. L. DellaVecchia and I. Vlattas, J. Org. Chem., 42, 2649 (1977).
7. D. W. Slocum and D. I. Sugarman, Adv. Chem. Ser., No. 130, 222 (1974); D. W. Slocum and C. A. Jennings, J. Org. Chem., 41, 3653 (1976).