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OXAZOLINES AS ACTIVATING GROUPS IN AROMATIC SUBSTITUTION. SELECTIVE METALATION OR ADDITION TO THE 4-POSITION OF PYRIDINE. A NEW SYNTHESIS OF 1,4-DIHYDROPYRIDINES*

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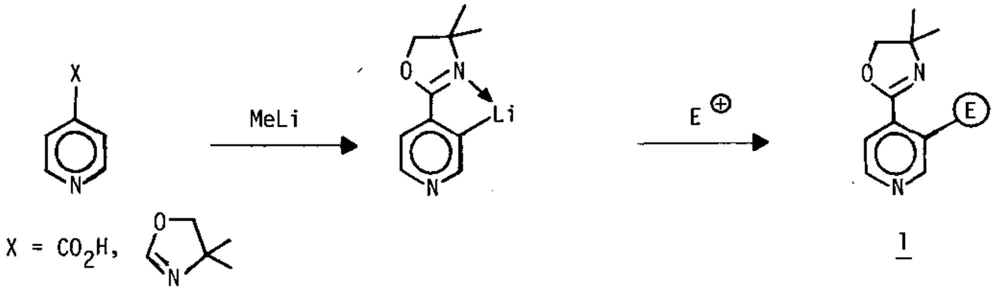
The use of the oxazoline moiety as an activating group on the 3-position of a pyridine ring has allowed formal electrophilic substitution via metalation-addition and nucleophilic substitution via oxidation of the intermediate 1,4-dihydropyridine.

The powerful activating ability of the oxazoline group in directing regiospecific alkylation or metalation on benzene derivatives has been recently described.[1] Our attention was also turned to the regiospecific metalation on the pyridine series whereby isonicotinic acid, in the form of



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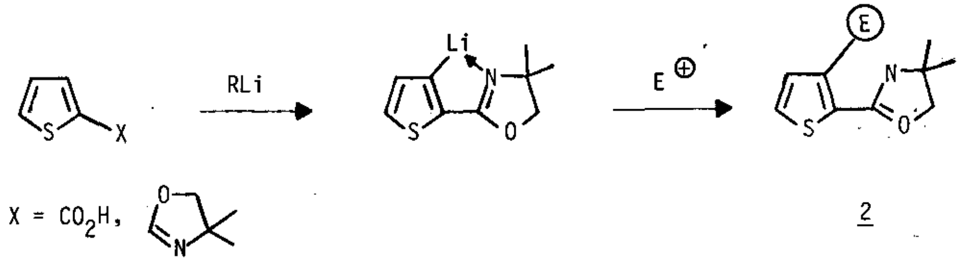

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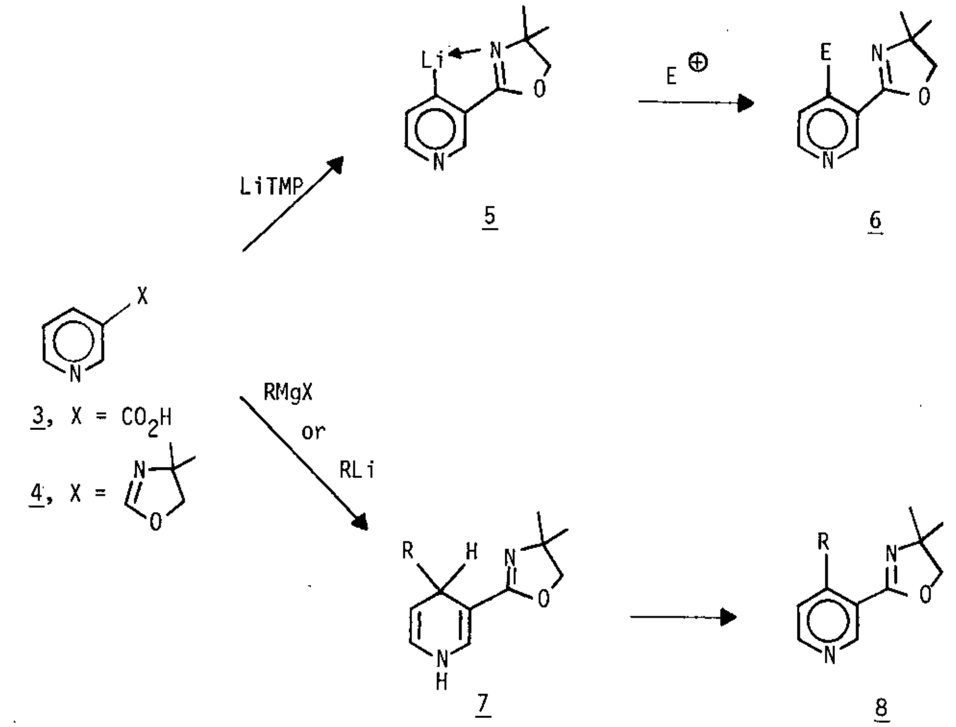
its oxazoline, was metalated in the 3-position to furnish 3-substituted pyridine derivatives, 1.[2] A similar metalation sequence was also observed by the Ciba-Geigy group[3] in the thiophene series, leading to 3-substituted thiophenes 2. In both of these examples, metalation occurred at a position rarely observed in the past and this was attributed to the strong complexation of the oxazoline to the lithium bases which readily overcomes the well known activation by the hetero-atom in pyridines and thiophenes.[4]

We now report two additional rare reactions, with considerable synthetic potential, observed in the nicotinic acid series which allows, in the presence of the oxazoline moiety, either metalation[4] or alkylation[5] to the 4-position of the pyridine nucleus.



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6

3, X = CO_2H

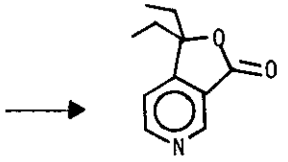
4, X =

7

8

Transformation of nicotinic acid 3 into the oxazoline 4 (mp 24°, 67%) was accomplished using thionyl chloride and 2-amino-2-methyl-1-propanol.[6] Addition of lithium 2,2,6,6-tetramethyl piperidide (LiTMP) to 4 (THF, 0°) gave the 4-lithio derivative 5 which, on treatment with electrophilic reagents, furnished the 4-substituted pyridines 6 (Table 1). These alkylated pyridines may be divested of the oxazoline group by hydrolysis. For example, treatment of 6c with 4.5 N HCl (95°, 2 h) gave the lactone 9 (72%, mp 78-79°). Attempts to metalate 4 with other bases (RLi, RMgX) gave very high yields of 1,4-addition products 7. Thus, in addition to metalation to introduce a 4-substituent in an electrophilic mode, it was also possible to introduce a variety of 4-substituents in a nucleophilic mode (Table 2). Except for t-butyllithium, which *gave 82% of 6-substituted derivative, all organolithium and Grignard reagents* provided the 4-substituted dihydropyridines. Oxidation, using either air bubbled through a THF solution of 7, or standard aromatization reagents, provided the aromatic derivatives 8. In two instances, the oxazoline was transformed to nicotinic esters, 10a, 10b using 4N HCl, evaporation to dryness, and treatment of diazomethane.[7]

6c



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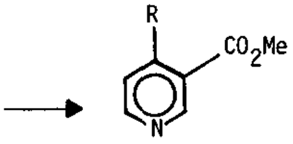
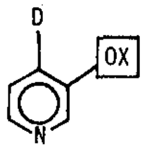
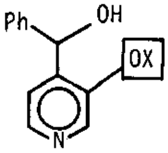
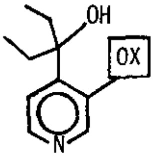


10a, R = Bu (88%)

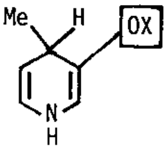
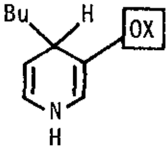
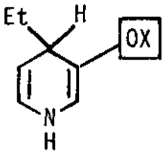
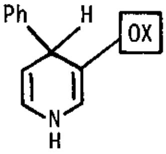
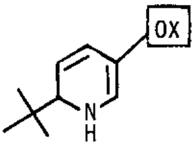
10b, R = Ph (60%)

Table 1 Metalation of 4 (LiTMP) and reaction with electrophiles

	Product 6	Electrophile[a,b]	% Yield[c]	B.P. (mm Hg)
6a		D_2O	70	60° (0.02)
6b		PhCHO	47	160° (0.35)
6c		$Et_2C=O$	52	85° (0.25)

a) Metalation performed using 1.0 equiv. of LiTMP at 0° in THF for 1 hr; b) Electrophiles added at 25° and stirred for 0.5-4 hr, quenched in saturated NH_4Cl, extracted with ether, dried, and concentrated; c) Yields are for pure isolated product which gave correct spectral and elemental analysis.

Table 2 Nucleophilic addition to 4 leading to 7 and 8

RM[a]	Product 7[b]	%	Mp°C	Oxidation Conditions	% 8[c]	Bp (Mp)
MeLi		100	125	air (6 hr)	45	60°/0.3 mm
n-BuLi		99	114	chloranil toluene 25°, (6 hr)	90	80°/0.25 mm
EtMgBr		99	112	air 25° (24 hr)	100	75°/0.4 mm
PhLi		100	183	chloranil toluene 25°, (2 hr)	60	(85-86°)
t-BuLi		82[d]		DDQ toluene 25°, (0.5 hr)	59[e]	(57-58°)

a) Organometallic added at -78° and allowed to warm to 0°. Workup as in Table 1; b) All dihydropyridines 7 were recrystallized from hexane and were stable for several months when kept refrigerated; c) Gave correct elemental analyses;

Table 2 - Footnotes (Continued)

d) Approximately 13% of 4-t-butyl pyridine was also observed; e) Accompanied by ∿30% of 4 which arose from loss of the tert-butyl group during the aromatization step.

REFERENCES

* Dedicated to Professor Tetsuo Nozoe on his 77th birthday.

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5. R. A. Abramovitch and J. G. Saha in "Advances in Heterocyclic Chemistry", A. R. Katritzky and A. J. Boulton, ed., Academic Press, 1966, pp 274-303; U. Eisner and J. Kuthan, Chem. Rev., 72, 1 (1972).
6. The authors would be pleased to supply complete experimental details of the preparation upon request.
7. We have just learned that a similar finding involving addition of organolithium reagents to 3-pyridyl oxazolines has been reported by Professor C. S. Giam (Texas A&M University) and has been submitted for publication.

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