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ORTHO LITHIATION OF 2-, 3-, AND 4-METHOXYPYRIDINES

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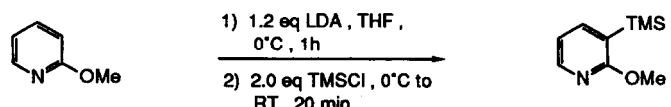
Summary: *The ortho lithiation of 2-, 3-, and 4-methoxypyridine was effected using mesityllithium as the metalating base.*

Alkoxypyridines are valuable precursors to pyridones and pyridinols,[1] as well as synthetically useful dihydropyridones.[2] Little attention has been given to the direct substitution of alkoxypyridines using directed metalation methodology. Quequiner[3] has reported a regioselective ortho lithiation at the C-2 position of 3-alkoxypyridines using n-butyllithium/TMEDA in tetrahydrofuran at -40°C. Reaction with electrophiles gave moderate to good yields of the 2,3-disubstituted pyridines. Metalation experiments with various 3-alkoxypyridines showed that the best yields were obtained with 3-ethoxypyridine. Ronald[4] showed that 3-(methoxymethoxy)pyridine lithiated at C-4 with tert-butyllithium in ether at -78°C, and Snieckus[5] has reported an efficient ortho lithiation of 2-, 3-, and 4-pyridyl diethylcarbamates. The 2- and 4-pyridyl diethylcarbamates lithiated at C-3 with sec-BuLi/TMEDA/THF at -78°C, whereas 3-pyridyl diethylcarbamate lithiated at the C-4 position.

Due to a need for substituted alkoxypyridines in our laboratories, we investigated the lithiation of 2-, 3-, and 4-methoxypyridines. To avoid competing side-reactions from nucleophilic addition of an alkyllithium base to the pyridine nucleus, our initial studies used lithium diisopropylamide (LDA) as the metalating agent.[6] Reaction of 2-methoxypyridine (1) with LDA followed by TMSCl gave an 83% yield of 2-methoxy-3-trimethylsilylpyridine (2). A similar reaction with 4-methoxypyridine (3) gave 4-methoxy-3-trimethylsilylpyridine (4) in 61% yield, along with 16% of the 3,5-disilylated derivative 5. The yield of 5 increased to 53% when the reaction was performed using 2.3 eq of LDA. Lithiation-trimethylsilylation of 3-methoxypyridine (6) at -42°C gave 3-methoxy-2-trimethylsilylpyridine (7), 3-methoxy-4-trimethylsilylpyridine (8), and the 2,4-disilylated derivative (9) in 42, 33 and 0.4% yields, respectively.



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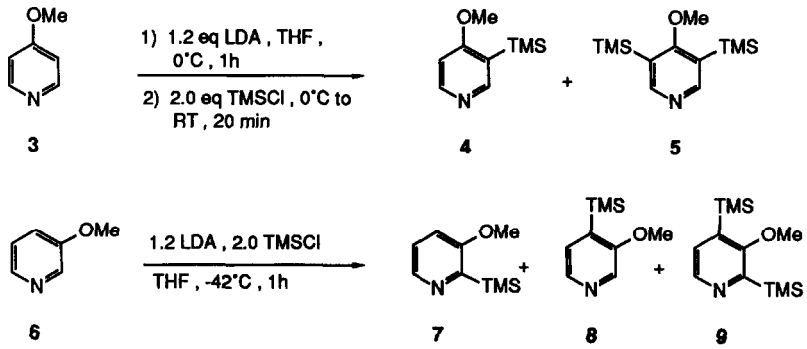
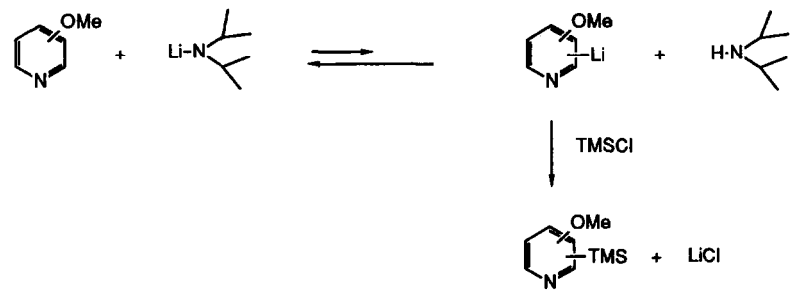


Other electrophiles (i.e., MeI, I_2, PhCHO) gave little or no substitution, and quenching with D_2O afforded recovered methoxypyridines with low amounts of deuterium incorporation (see Table I).

Table I.

Pyridine	Metalation conditions	% Deuterium Incorporation
2-MeO-	1.2 LDA, THF, 0°C, 1h	18.7 (C-3)
4-MeO-	1.2 LDA, THF, 0°C, 1h	11.4 (C-3)
3-MeO-	1.2 LDA, THF, -42°C, 1h	6.3 (C-2) 3.8 (C-4)

These data indicate that the reaction of methoxypyridines and LDA is reversible under the conditions studied, and the effectiveness of TMSCl as an electrophile is due to an in situ trapping[7] of the pyridyllithium as it is formed in equillibrium with LDA as shown below.



It was clear that a stronger metalation base was needed to effectively lithiate the methoxypyridines. After considerable study, mesityllithium was determined to be the base of choice,

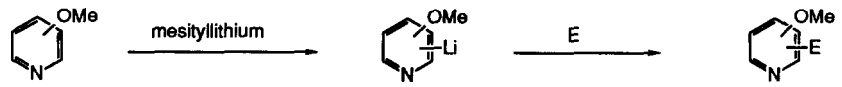
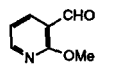
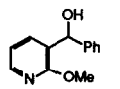
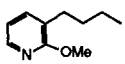
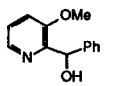
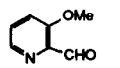
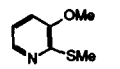
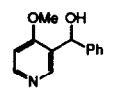
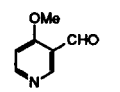
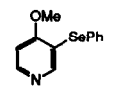
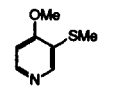


Table II. Ortho Substitution of Methoxypyridines Via Directed Lithiation

Pyridine	Metalation Conditions[a]	E	Product	% Yield[b]	mp, °C
2-MeO-	1.3 mesityllithium, 0°C, 1h; RT, 1h	DMF (1.5 equiv)		63	
2-MeO-	1.3 mesityllithium, 0°C, 1h; RT, 1h	PhCHO (1.4 equiv)		66	
2-MeO-	1.3 mesityllithium, 0°C, 1h; RT, 1h	n-BuI (3 equiv)		62	
3-MeO-	1.3 mesityllithium, -23°C, 3h	PhCHO (1.5 equiv)		73	119-120
3-MeO-	1.3 mesityllithium, -23°C, 3h	DMF (1.5 equiv)		85	67-68
3-MeO-	1.3 mesityllithium, -23°C, 3h	MeSSMe (3 equiv)		82	
4-MeO-	1.3 mesityllithium, -23°C, 3h	PhCHO		65	169.5-170.5
4-MeO-	1.3 mesityllithium, -23°C, 3h	DMF (1.5 equiv)		77	65.5-67.5
4-MeO-	1.3 mesityllithium, -23°C, 3h	PhSeSePh (1.5 equiv)		71	
4-MeO-	1.3 mesityllithium, -23°C, 3h	MeSSMe (3 equiv)		84	

[a]Reactions were performed on a 3-mmol scale. Mesityllithium was prepared from bromomesitylene and 2 equiv of tert-butyllithium (THF, -78°C, 1h). [b]Yields are for isolated, pure material obtained from radial preparative layer chromatography (silica gel, EtOAc/hexanes). All products gave the expected IR and ^{1}H NMR spectra and elemental analysis.

for it effectively lithiated the methoxypyridine ring without undergoing nucleophilic addition to the pyridine nucleus. Using mesityllithium, 2-, 3-, and 4-methoxypyridines were lithiated and treated with various electrophiles to give substituted methoxypyridines in good yields as shown in Table II.

The three isomeric methoxypyridines are readilly available from the corresponding halopyridines and sodium methoxide in DMSO, or from commerical sources.[8] The mesityllithium used in this study was prepared from bromomesitylene and 2 equiv of tert-butyllithium (THF, -78°C, 1h). For larger scale reactions, it may be more convenient to prepare mesityllithium from bromomesitylene and lithium metal.[9]

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8. We prepared 3-methoxypyridine from 3-chloropyridine and sodium methoxide (4 equiv) in DMSO (120°C, 4h; 70%). 2-Methoxypyridine was purchased from Aldrich Chemical Co., Inc. The 4-methoxypyridine was prepared from 4-methoxypyridine-N-oxide (Aldrich) by catalytic hydrogenation (5% Pd/C, H_2, MeOH).

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