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N-METHYL LITHIATION OF N-METHYLINDOLES DIRECTED BY α-AMINO ALKOXIDES

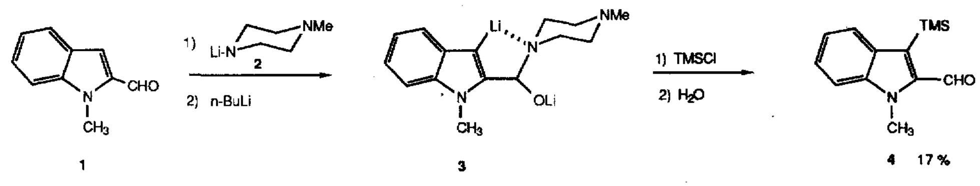
Daniel L. Comins*[1] and Michael O. Killpack

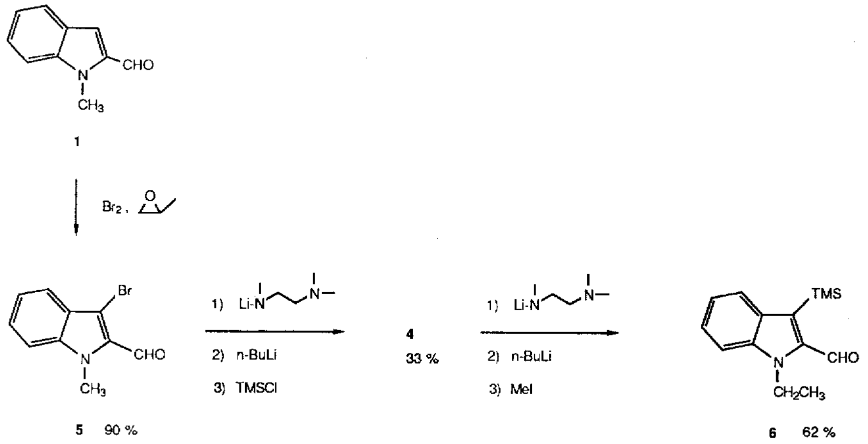
Department of Chemistry and Biochemistry
Utah State University, Logan, Utah 84322-0300

Summary: *A novel N-methyl lithiation-alkylation of an α-amino alkoxide derived from 3-chloro-N-methylindole-2-carboxaldehyde is described.*

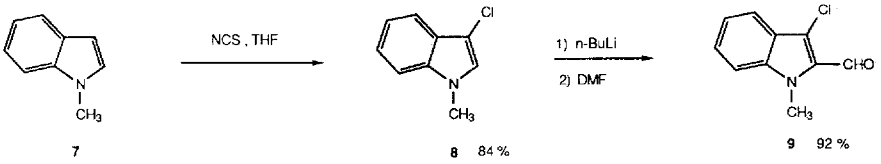
The reaction of aromatic aldehydes with certain lithium dialkylamides gives α-amino alkoxides in situ that can be ring lithiated with alkyllithiums. Alkylation and hydrolysis on workup provides ortho-substituted aryl aldehydes via a one-pot reaction.[2,3] This methodology works well for the one-pot substitution of heterocyclic aromatic aldehydes[3] as well as for benzaldehyde derivatives[2]. We previously reported that attempted C-3 lithiation of the α-amino alkoxide derived from N-methyl-2-pyrrolecarboxaldehyde and lithiated N,N,N′-trimethylethylenediamine gave metalation solely on the N-methyl group. When we tried to extend this novel directed lithiation to N-methylindole-2-carboxaldehyde, lithiation-methylation of the α-amino alkoxide prepared from N,N,N′-trimethylethylenediamine gave a mixture of 1-ethylindole-2-carboxaldehyde and 1,3-dimethylindole-2-carboxaldehyde in a ratio of 42/58. We were unable to find conditions to improve the ratio of products in favor of N-methyl substitution.[3] It appeared that a removable blocking group at C-3 was needed to effect a synthetically useful N-methyl substitution of N-methylindole-2-carboxaldehydes. We report herein our progress toward developing this potentially useful directed lithiation methodology.

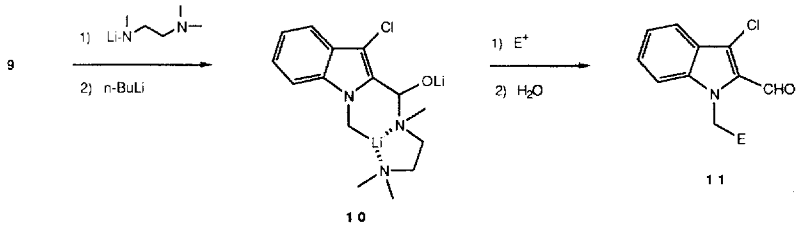
Initially we explored the use of a trimethylsilyl group to block the C-3 position. Treatment of N-methylindole-2-carboxaldehyde (**1**) with lithium N-methylpiperizide (**2**) followed by n-BuLi gave the dianion **3** in situ.[3] Addition of TMSCl and aqueous workup gave only a 17% yield of the desired aldehyde **4**. In an effort to find a more efficient method to prepare **4**, we brominated **1** to give 3-bromo-1-methylindole-2-carboxaldehyde **5** in 90% yield.[4] In situ protection as an α-amino alkoxide[5], followed by lithium-halogen exchange and silylation gave a disappointing 33% yield of **4**. Treatment of **4** with lithiated N,N,N′-trimethylethylenediamine, n-butyllithium, and methyl iodide provided a 62% yield of the N-methyl alkylated product **6**. This result demonstrated that the C-3 blocking group strategy is effective, but the low yield obtained for the preparation of **4** makes the use *of a C-3 TMS group unattractive.*[6]





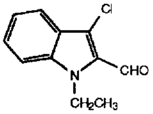
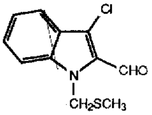
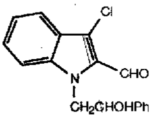
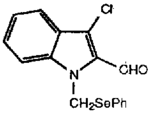
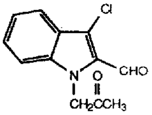
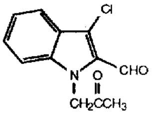
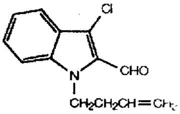
Since an aryl chloride is not prone to lithium-chloride exchange[7], we explored the possibility of using a chlorine as a C-3 blocking group. Chlorination of N-methylindole (**7**) with NCS in THF gave an 84% yield of 3-chloro-1-methylindole (**8**) (bp 92°C/0.5 mm). Lithiation of **8** with n-BuLi and addition of DMF provided the desired aldehyde **9** in 92% yield (mp 88-89°C). In situ α-amino alkoxide formation





and lithiation with n-BuLi (3 equiv, THF, 3h at -42°C, 15h at -20°C) gives dianion **10**, which on reaction with electrophiles and aqueous workup provides N-methyl substituted indoles **11** as shown in the Table.

Table. Reactions of Dianion **10** with Electrophiles

Entry [a]	Electrophile	Product [e]	yield,[f] %	mp,[g] °C
a	MeI		94	58-59.5
b	MeSSMe		85	95-97
c	PhCHO		84	130.5-132.5
d	PhSeSePh		73	119.5-120.5
e	EtOAc[b]		55	152.5-154
f	Ac_2O[c]		43	152.5-154
g	 [d]		75	30-31

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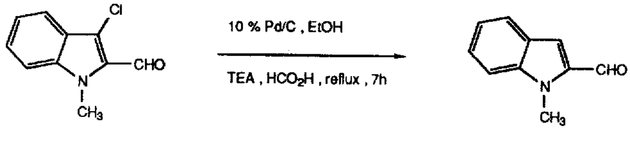
[a] Reactions were performed on a 1.5 mmol scale in 10 ml of THF. Unless indicated, electrophile (4-6 equiv) was added at -78°C and allowed to warm to room temperature. The workup consisted of pouring the reaction mixture into cold water followed by extraction with ether. [b] The dianion was added to EtOAc (50 mL). [c] Inverse addition and 30 mmol of Ac_2O were used. [d] A large excess of electrophile (18 mmol) was utilized. [e] All products gave the expected IR and NMR spectra and elemental analysis. [f] Yields are for isolated, pure material obtained from radial PLC (silica gel, EtOAc/hexanes). [g] Melting points are for material recrystallized from hexanes or EtOAc/hexanes.

To demonstrate that the C-3 chloro blocking group could be removed if required, we treated 3-chloro-1-methylindole-2-carboxaldehyde (**9**) with 10% Pd/C, EtOH, Et_3N, and formic acid to give an 81% yield of N-methylindole-2-carboxaldehyde (**1**).[8]



9

1 81 %

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1. Address correspondence to this author at Department of Chemistry, North Carolina State University, Raleigh, NC 27695-8204.

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