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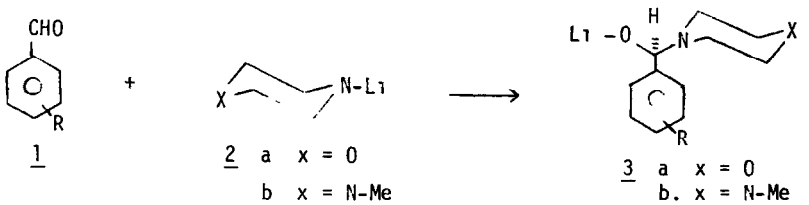
A ONE-POT ORTHO ALKYLATION OF AROMATIC ALDEHYDES

Daniel L. Comins*, Jack D. Brown, and Nathan B. Mantlo
Department of Chemistry and Biochemistry, Utah State University, Logan, Utah 84322.

Summary The addition of aromatic aldehydes to lithium N-methylpiperazide in benzene gave α-amino alkoxides which were ortho-lithiated with excess n-butyllithium. Subsequent alkylation and hydrolysis provided ortho-substituted aromatic aldehydes via a one-pot reaction.

Although a number of carboxylic acid-derived aromatic substituents have served as activating groups toward ortho metalation,[1] e.g. oxazolines[2] and N,N-diethylamides,[3] relatively few aldehyde derivatives have been utilized for this purpose [4] Since the transformation of aryloxazolines and N,N-diethylbenzamides to aldehydes requires subsequent chemical steps, a more direct route to ortho-substituted aromatic aldehydes is preferred. Harris[4b] points out this deficiency in a report of an alternative two-step synthesis utilizing the imidazolidine ring as the ortho-activating group. For example, 1,3-Dimethyl-2-phenylimidazolidine is prepared from benzaldehyde (77%), ortho-metalated and alkylated, and hydrolyzed to the ortho-substituted aldehydes with mild acid (21-95%) [4b] We report here a direct one-pot synthesis of ortho-substituted aromatic aldehydes via ortho lithiation utilizing an *in situ* formed α-amino alkoxide as the ortho-activating group.

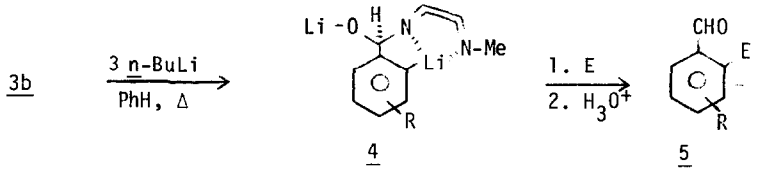
We recently described an *in situ* protection of aromatic and aliphatic aldehydes in high yield via the formation of α-amino alkoxides.[5] The α-amino alkoxides 3 are prepared *in situ* by the addition of an aromatic aldehyde (1) to the lithium amide of a secondary amine such as lithium morpholide[5] (2a) or lithium N-methypiperazide (2b)



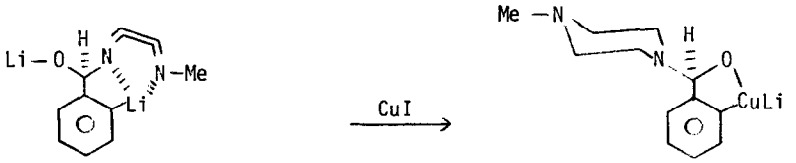
1

2 a x = O
b x = N-Me

3 a x = O
b. x = N-Me



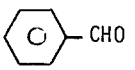
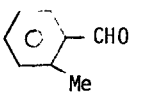
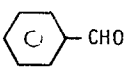
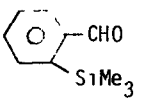
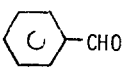
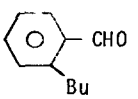
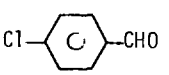
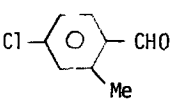
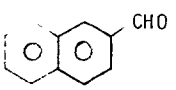
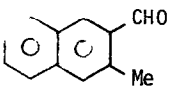
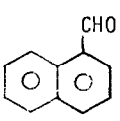
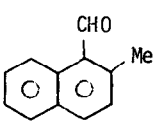
Ortho lithiation of α-amino alkoxides 3b using 3 equiv of n-butyllithium in refluxing benzene gave dianions 4 which were alkylated with various electrophiles (E).[6] Quenching the reactions with water or aqueous acid provided ortho-substituted aldehydes (5) in good yields as indicated in the table. Dianion 6 was readily alkylated by reactive electrophiles such as methyl iodide and chlorotrimethylsilane (entries 1 and 2). However, when n-butyl iodide was used little alkylation occurred[7] (~10% by NMR). The yield was significantly improved by the addition of cuprous iodide to the reaction mixture (entry 3). The organometallic intermediate is presumed to be the mixed cuprate 7.



The reactions of 1- and 2-napthaldehyde are particularly interesting. The α-amino alkoxide derived from 2-napthaldehyde (entry 5) is predominantly ortho-metalated at the 3-position.[8] In a related system, 2-dimethylaminomethylnaphthalene, lithiation occurs at the 1- and 3- positions in a ratio of about 45:55.[9] The analogous reaction with 1-napthaldehyde (entry 6) gave regioselective lithiation at the 2- position, whereas 1-dimethylaminomethylnaphthalene is lithiated with n-butyllithium in ether-hexane to form a mixture of the 8- and 2-lithioamines in a ratio of about 91:9.[9]

Further investigations of the synthetic utility of these organometallic intermediates (4, 6, and 7) are currently in progress.

Table.

Entry	Reactant	Reaction conditions[a]	Product[c]	% Yield[d]	mp, °C (Lit. mp, °C)
1		1. LNMP[a], PhH, RT 2. 3 n-BuLi, reflux 12 h 3. MeI, -42° to RT		67	2,4-DNP, 192-194 (191-194)[4b]
2		1 LNMP, PhH, RT 2 3 n-BuLi, reflux 12 h 3. Me_3SiCl, -42° to RT		64	p-nitrophenylhydrazone, 190-192 (192-193)[4b]
3		1. LNMP, PhH, RT 2. 3 n-BuLi, reflux 12 h 3 n-BuI, -42° 30 min 4 CuI (1 equiv), -42° to -20° (2 h), 0° (3 h)[b]		47	semicarbazone, 137-139 (137-139)[4b]
4		1. LNMP, PhH, RT 2. 3 n-BuLi, RT 1 h, reflux 1 h 3. MeI, -42° to RT		61	carboxylic acid, 166-167 (167-169)[10]
5		1. LNMP, PhH, RT 2 3 n-BuLi, reflux 12 h 3 MeI, -42° to RT		72[e]	123-124 (124-125)[11]
6		1. LNMP, PhH, RT 2. 3 n-BuLi, reflux 12 h 3. MeI, -42° to RT		76[f]	carboxylic acid, 124-125 (126-127)[12]

[a]Reactions were performed on a 3 mmol scale using 1 1 equiv of lithium N-methylpiperazide (LNMP) in benzene (8 ml) THF (8 ml) was added prior to cooling the reaction mixture to -42° and adding the halide (6 equiv). Unless indicated, the workup consisted of pouring the reaction mixture into cold 10% aqueous HCL followed by extraction with ether.

[b]The workup consisted of quenching with 20% NH_4Cl and washing the organic layer with 20% NH_4Cl: NH_4OH (50 50), 10% HCl, and brine.

[c]All products gave the expected IR and ^1H NMR spectra.

[d]Unless indicated, yields are for isolated, pure, material obtained from preparative layer chromatography (Silica gel, acetone-hexane).

[e]GC yield. The crude product contained the isomeric 1-methyl-2-napthaldehyde (14%) and 2-napthaldehyde (13%).

[f]GC yield. The crude product contained 1-napthaldehyde (14%) and unidentified minor components (10%)

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References and notes.

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   b. T. D. Harris and G. P. Roth, J. Org. Chem., 44, 2004 (1979).
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