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THE ELECTROPHILIC AMINATION OF ORGANOLITHIUMS WITH METHYLLITHIUM COMPLEXES OF N-SUBSTITUTED METHOXYAMINES

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Abstract: Three N-alkyl methoxyamine derivatives are shown to be effective as electrophilic reagents for the conversion of organolithiums to secondary amines.

Recently we reported that two equivalents of a methyllithium complex of methoxyamine, in a modification of the Sheverdina-Kocheshkov amination, provides an efficient reagent for the stoichiometric conversions of aliphatic and benzenoid aromatic organolithiums to primary amines.[1,2,3] Other methodology for effecting similar reactions in synthetically useful yields involves reactions of aromatic organometallics with azides[4] to give primary amines,[5] or with N,N-dialkyl-O-sulfonates[6] or copper salts of secondary amines to give tertiary amines.[7] Conversions of organometallics to secondary amines can be achieved by the latter oxidative coupling with copper salts of primary amines in 23-63% yields or with alkyl chloramines in lower yields.[8] In this communication we wish to report that methyllithium-N-alkyl-O-methylhydroxyamines provide useful reagents for the conversion of alkyl and phenyl lithiums to secondary amines in 30-77% yields. This amination can also be effected intramolecularly.

The reaction of methyllithium-N,O-dimethylhydroxyamine[9] with the butyl and phenyl lithiums provides the butyl and phenyl methyl amines which were converted to the benzamides as shown in Scheme I. The results, summarized in Table 1, show the complex is a convenient "CH_3NH^+" synthetic equivalent. Experimentally the reactions were carried out as previously described for methoxyamine.[2] Attempts to aminate 2-lithiothiophene[10] or 2-lithio-N,N-diisopropylbenzamide[11] were unsuccessful under these conditions. The substitution of another group on nitrogen is illustrated by the aminations of n-butyl and phenyl lithium with N-phenylethyl-O-methylhydroxyamine.[12] In these cases the free amines are isolated and increasing temperature significantly increases the extent of amination.

Scheme I

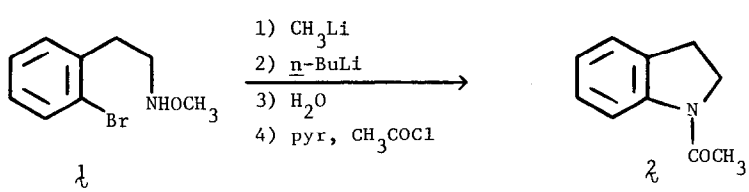
Table 1: Reactions of RLi with CH_3Li-R'NHOCH$_3$

RLi	R'	$C_6H_5CON(CH_3)R$[a,b]	$C_6H_5CON(CH_3)OCH_3$
n-BuLi	CH_3	63[c]	8
		72[d]	-
		45[e]	29
s-BuLi	CH_3	62[c]	-
t-BuLi	CH_3	30[c]	0
C_6H_5Li	CH_3	67[c]	7
		73[c,f,g]	1
		77[d]	-
		43[e]	22
		$RNHCHCH_3C_6H_5$[c]	$C_6H_5CHCH_3NHOCH_3$
n-BuLi	$C_6H_5CHCH_3$	0	75
		68[h]	11
C_6H_5Li	$C_6H_5CHCH_3$	10	63
		44[h]	10

a) % Yield based on RLi. b) Products were characterized by spectroscopic and combustion data. c) Reaction with 1 eq of the complex. d) Reaction with 2 eq of the complex. e) Reaction with CH_3NHOCH_3. f) Warmed to R.T. g) ca 16% amination of methyllithium is observed. h) Warmed to 40°C.

To test the possibility of achieving an intramolecular electrophilic amination of a carbanion[13], N-2-(2'-bromophenyl)ethyl-O-methylhydroxyamine (1) was prepared[14] and treated with methyllithium and n-butyllithium as shown in Scheme II. The cyclized product, N-acetylindoline (2), is obtained in 78% crude and 42% purified yield.

Scheme II



1 2

We examined the possibility of achieving amination to a tertiary amine by the reaction of N,N,O-trimethylhydroxyamine[15] with 1 equivalent phenyllithium under the conditions of Boche.[6a] No N,N-dimethylaniline could be isolated after the reaction was allowed to proceed for 3 days at ambient temperature. A 52% yield of N-methylbenzylamine was obtained, calculated on the basis of an elimination-addition sequence requiring 2 equivalents of phenyl lithium.

$$C_6H_5Li + (CH_3)_2NOCH_3 \longrightarrow C_6H_5CH_2NHCH_3$$

Synthetically the present results suggest that methyllithium-N-alkyl-O-methylhydroxyamines are convenient electrophilic aminating agents for organolithiums. Mechanistically the limiting choices are between displacement of alkoxide and addition to a nitrene intermediate. While the present results are by no means unambiguous, involvement of a free nitrene might have been expected to lead to products from 1,2-hydrogen migration from N,O-dimethylhydroxyamine or cyclization from N-phenylethyl-O-methylhydroxyamine[16]. Reduced yields with sterically more crowded systems also seems more consistent with a displacement process. Experiments are currently underway to distinguish nitrenoid and displacement possibilities, as well as to extend the synthetic utility of these aminations.

Preparation of N-acetylindoline (2):

A stirred 1.9 ml (.0022 mol) sample of a 1.17 M solution of methyllithium in ether was cooled to -78°C, under a nitrogen atmosphere, and a solution of .5 g (.0022 mol) 1 in 10 ml hexane was added dropwise, followed by 1.5 ml (.0022 mol) of a 1.51 M solution of n-butyllithium in hexane. The mixture was stirred for 15 min, and warmed to -15°C for 3 h, and quenched with .5 ml water. Then 10 ml ether, 1 ml pyridine, and .9 ml acetyl chloride were added, and the mixture was stirred overnight. Extractive workup with chloroform provided an oil which was chromatographed on a silica gel column using 70% ethyl acetate in hexane as eluant to provide .28 g of a white solid (mp = 85-95°C), which after recrystallization from hexane gave .15 g (42%) of 2 as white needles, mp 102-104°C (lit[17] mp 105°C). NMR (90 MHz; $CDCl_3$); 8.2 (doublet, 1H), 7.1 (multiplet, 3H), 4.0 (triplet, 2H), 3.1 (triplet, 2H), 2.2 (singlet, 3H).

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