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A NEW AND SIMPLE SYNTHESIS OF ALKOXY- AND ARYLOXYMETHYLLITHIUM REAGENTS ($ROCH_2Li$)

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Abstract: A series of halomethyl alkyl and aryl ethers can be converted to the corresponding organolithium reagents ($ROCH_2Li$) in a one-flask operation by sequential treatment (1) with stannous chloride-lithium bromide complex in tetrahydrofuran (THF) and (2) with n-butyllithium.

Over the past two decades one of the most important advances in synthetic organic chemistry has been the introduction of numerous and varied functional group-containing organolithium reagents. An especially interesting category of such reagents is that which an n-electron donor atom (nD) group is attached to the lithiated carbon. The class in which the nD group is ether oxygen, i.e., reagents of type $ROCH_2Li$, cannot be made from halides by the usual procedures involving reaction with metallic lithium or alkyllithiums. Nonetheless, such reagents can be prepared from organotin precursors as recently shown by Still[1] and Seebach.[2,3] This paper outlines another route to alkoxymethyllithium which is operationally simpler and considerably more convenient then previously described sequences.

Stannous chloride is a weak Lewis acid, insoluble in non-coordinating solvents (e.g., CH_2Cl_2) but very soluble in THF. Reaction of such solutions with α-chloro ethers leads to ether cleavage via a cationic mechanism. Thus, t-butyl chloromethyl ether is rapidly converted to t-butyl chloride and polyformaldehyde. However, the nucleophilic complex $Li^+ BrCl_2Sn^-$, generated in THF from equivalent quantities of $SnCl_2$ and LiBr, reacts cleanly with chloromethyl ethers in 30 min at 20° to form trihalostannylmethyl ethers, Hal_3SnCH_2OR. Treatment of these α-stannyl ethers with 4 equiv of n-BuLi at -78° for 1 hr results in formation of the alkoxymethyllithium reagent, the overall process being:

$$ROCH_2Cl + LiSnHal_3 \xrightarrow{THF} \underset{\underset{1}{\sim}}{ROCH_2SnHal_3} \xrightarrow{4\ BuLi} \underset{\underset{2}{\sim}}{ROCH_2Li} + Bu_4Sn$$

It is not necessary to isolate the intermediates 1, which are in any case quite unstable even in solution.[4]

The yield of alkoxymethyllithium reagent 2 was ascertained by addition of a slight excess of benzaldehyde and chromatographic isolation of reaction products. Along with the adduct from 2, $C_6H_5CHOHCH_2OR$ (3), small amounts of phenyl n-butyl carbinol (4) from addition of n-BuLi to benzaldehyde were isolated Data for the preparation of five alkoxymethyllithium reagents 2A - 2E are summarized in Table I.

Table I

$$ROCH_2Li\ (2) + C_6H_5CHO \longrightarrow ROCH_2\underset{\underset{OH}{|}}{CH}C_6H_5\ (3) + C_6H_5\underset{\underset{OH}{|}}{CH}Bu\ (4)$$

	R	% Yield of 3	% Yield of 4
2A	t-Bu	95	4
2B	$C_6H_5CH_2$	86	13
2C	$CH_3OCH_2CH_2$	82	13
2D	C_6H_5	78	15
2E	CH_3	65	34

The formation of by-product 4 is due to the fact that some n-BuLi remains as a consequence of a side reaction which consumes $ROCH_2Li$ with formation of products of type $(ROCH_2)_n SnBu_{4-n}$, which have been isolated by chromatography and identified by mass spectral and pmr measurements. The results in Table I show that this side reaction becomes significant for the case 2E, methoxymethyllithium. Curiously, neither the use of inverse addition with BuLi (i.e., of 1 to n-BuLi), nor the use of other organolithium reagents provide any improvement in efficiency of generation of the reagents 2. The following procedure is typical.

Preparation of 4B via 2B: A solution of stannous chloride (433.1 mg, 2.284 mmol) in THF was treated under argon with a 2M solution of lithium bromide (198.4 mg, 2.284 mmol) in THF followed by bromomethyl benzyl ether (459.3 mg, 316.8 μl, 2.284 mmol). After 30 min, the pale yellow solution was cooled to -78° and treated dropwise with a hexane solution of n-butyllithium (5.31 ml, 9.14 mmol) over 4 min. After 1 hr, the resulting yellow-orange solution was treated with benzaldehyde (242.5 mg, 2.284 mmol) in 5 ml of THF. The mixture was quenched with aqueous NH_4Cl at -78° and then subjected to standard extractive aqueous workup to afford 1.296 g of crude product which after chromatography (30 g of silica gel; elution with 5% ether in methylene chloride) afforded pure 4B, 450 mg (86%), as a colorless oil.[5]

References and Notes

1. W. C. Still, J. Am. Chem. Soc., 100, 1481 (1978) and refs. therein.
2. N. Meyer and D. Seebach, Chem. Ber., 113, 1290 (1980).
3. α-Lithio ethers have also been prepared by reaction of lithium napthalenides with α-phenylthio ethers: T. Cohen and J. R. Matz, J. Am. Chem. Soc., 102, 6900 (1980).
4. The decomposition of $ROCH_2SnHal_3$ leads to RHal, CH_2O and $SnHal_2$, probably by a cationic mechanism. The decomposition is retarded by added bromide ion (which doubtless coordinates with tin) and much slower with R = C_6H_5 than with R = t-Bu or $C_6H_5CH_2$, observations which are consistent with a cationic process.

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