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(CHLOROMETHYL)LITHIUM IN AN EFFICIENT CONVERSION OF CARBONYL COMPOUNDS TO CHLOROHYDRINS OR OXIRANES

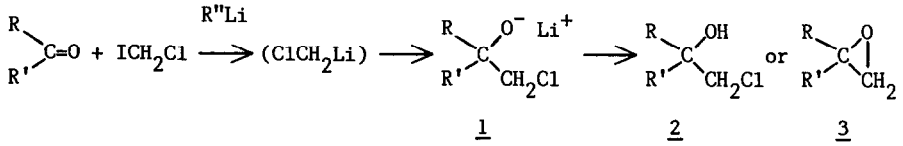
Kizhakethil Mathew Sadhu and Donald S. Matteson*

Department of Chemistry, Washington State University
Pullman, Washington 99164-4630 U.S.A.

Summary: (Chloromethyl)lithium has been generated and captured in nearly quantitative yields by addition of n-butyllithium or methyllithium to mixtures of chloroiodomethane with aldehydes or ketones in THF at -78 °C. Immediate acidification yields chlorohydrins, delayed workup yields epoxides.

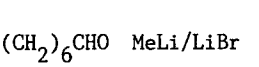
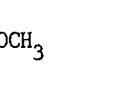
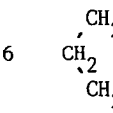
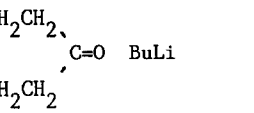
The extreme thermal instability of (chloromethyl)lithium,[1] $ClCH_2Li$, has severely limited its synthetic utility. Villieras and coworkers have reported a preparation of $ClCH_2Li$ and also $BrCH_2Li$ at -115 °C which on subsequent addition of aldehydes or ketones yielded 60-80% of chlorohydrins (2) or epoxides (3).[2] Cainelli and coworkers had earlier reported the in situ generation and capture of $BrCH_2Li$ from dibromomethane and lithium dispersion, yields 35-52% (with one exceptional steroid, 95%).[3]

We have recently reported the efficient generation and capture of $ClCH_2Li$ by addition of n-butyllithium to mixtures of chloroiodomethane with boronic esters in tetrahydrofuran at -78 °C.[4] Aldehydes and ketones appear to be slightly more reactive than boronic esters toward alkyllithium reagents,[5] and we therefore decided to test our new system with these substrates. As shown in Table I, very high yields of chlorohydrins (2) or oxiranes (3) can generally be obtained, the product depending on whether the lithium alkoxide intermediate (1) is protonated immediately or allowed time at 25 °C to undergo ring closure. Our yields of oxiranes generally exceed those achieved with the best previous reagent for this purpose, dimethylsulfonium methylide.[6] Usually the crude products are very clean by gc analysis. As indicated in Table I, there may be a few percent of unconverted aldehyde or ketone, and methyllithium attacked benzaldehyde directly to a small extent.



1 2 3

Table I. Conversion of Aldehydes and Ketones to Chlorohydrins and Oxiranes with $ClCH_2Li$ Generated *in situ* from ICH_2Cl and Alkyllithium

Run	RCOR'	R"Li	Product	% Yield	Remainder, %
1	PhCHO	MeLi/LiBr	$PhCHOHCH_2Cl$	95.5 gc	$PhCHOHCH_3$, 4.2
2	PhCHO	MeLi		(82 gc)	$PhCHOHCH_3$, 18
3	PhCHO	BuLi		88 isol	RCOR', 8.5
4	$CH_3(CH_2)_6CHO$	MeLi/LiBr		97 isol	RCOR', 0.3
5	$PhCOCH_3$	MeLi/LiBr		99 isol	--
6		BuLi		91 gc	RCOR', 3.6
7	PhCH=CHCHO	BuLi	$PhCH{=}CHCHOHCH_2Cl$	97 isol	--
8	$PhCH_2CHO$	BuLi	$PhCH_2CHOHCH_2Cl$	65 isol	Unidentified

Notes by run number: 1. Decane internal standard for gc anal. Product isolated (no yield data), ^1H NMR checked. 2. No gc standard; reagent clearly not optimum. 3. Yields marked "isol" always refer to products which appeared pure by 90 MHz ^1H NMR anal. This oxirane was distilled. 4. Purified by flash chromatography and dist. 5. Used 16.5 mmol MeLi, 16.5 mmol $ClCH_2I$, 15.0 mmol acetophenone. Purified by chromatography (3% ether/pentane) and bulb to bulb dist., 100 °C (12 torr); 90 MHz ^1H NMR ($CDCl_3$): δ 1.69 (s, 3, $\underline{CH}_3$), 2.77 + 2.92 (AB, $\underline{J}$ = 5.5 Hz, 2, $O\underline{CH}_2$), 7.32 (m, 5, $C_6\underline{H}_5$). In another run, BuLi led to BuI, inconvenient to remove. 6. Decane internal standard. 7. Purified by chromatography. In another run, overnight at 20 °C yielded mixture of chlorohydrin and oxirane. 8. Yield after chromatography and bulb to bulb dist., 110 °C (1.3 torr).

The success of this method depends on rate relationships between several fast reactions. Halogen/metal exchange between ICH_2Cl and R"Li must be faster than reaction of R"Li with RCOR', which is established for the first time in the present work. Also, reaction of $ClCH_2Li$ with RCOR' must be faster than decomposition of the $ClCH_2Li$, which was already known,[2,3] though our study shows much improved yields. We were unable to obtain any (halomethyl)boron compounds from preformed (halomethyl)lithium or (halomethyl)magnesium reagents,[4] as if the reagents decomposed during preparation or on mixing with the substrate. Our present work supports the claims of Villieras and coworkers,[2] but our procedure is much simpler and is easily duplicated.

Although n-butyllithium proved entirely satisfactory for generating $ClCH_2Li$, the byproduct iodobutane is inconvenient to separate by distillation from products of similar boiling range, and we therefore tested methyllithium. Salt free CH_3Li attacks benzaldehyde at a significant fraction of its rate of attack on ICH_2Cl (Table I), but the use of CH_3Li/LiBr reduced this side reaction to 4% without adjustment of reactant ratios. It appeared that the presence of LiBr increased the rate of ring closure of the intermediate chloro alkoxides (1) to oxiranes (3).

It was found by gc analysis that immediate acidification of the reaction mixtures within 0.5 h of removing the cooling bath (maximum temperature 0-15 °C) yielded chlorohydrins (2), and standing overnight at 20 °C usually sufficed to complete ring closure to the oxiranes (3). In two instances, conversion to oxirane was grossly incomplete. Cinnamaldehyde (run 7) reacted slowly, and conditions for achieving complete conversion to oxirane were not explored. Phenylacetaldehyde (run 8), which has an unusually acidic methylene group, gave side products of undetermined nature, and it appeared that closure to the oxirane stopped at about 35% conversion, perhaps because the alkoxide intermediate (1) abstracts an acidic hydrogen from the aldehyde. The yield of chlorohydrin (65%) is satisfactory considering the nature of the substrate. The carbonyl group of camphor proved too sterically hindered to react with $ClCH_2Li$, and gc analysis indicated a 96/4 ratio of recovered camphor to unidentified product.

Products were characterized by ^1H and ^{13}C NMR. The ^{13}C data matched reported values[2] for the products of runs 1 through 6 and the oxiranes from cinnamaldehyde and phenylacetaldehyde. A representative ^1H NMR is given in detail for run 5 (Table I, footnotes). The chlorohydrin from phenylacetaldehyde (run 8) is well known[7] but lacks NMR data (^1H, 90 MHz, $CDCl_3$): δ 2.3 (d, 1, O<u>H</u>), 2.87 (d, 2, Ph<u>CH</u>$_2$), 3.50 + 3.55 (m, 2, diastereotopic <u>CH</u>$_2$Cl), 4.0 (m, 1, <u>CH</u>OH), 7.25 (m, 5, C<u>H</u>$_5$); m/e 170.0490 (calcd 170.0495). Run 7 (cinnamaldehyde) is described on the next page, second paragraph.

In a typical experimental procedure, a solution of 15 mmol (2.35 mL) of redistilled octanal and 16.5 mmol (1.20 mL) of iodochloromethane in 40 mL of rigorously anhydrous tetrahydrofuran was cooled to -78 °C under argon and 15.75 mmol of 1.5 M methyllithium/lithium bromide in diethyl ether (Aldrich Chemical Company) was added dropwise over a period of 2 to 5 min. The mixture was allowed to warm to 20 °C and kept overnight, then treated with saturated ammonium chloride and extracted with ether. Analysis by gc indicated 98.5% oxirane and 0.3% unconverted octanal, with the remainder several unidentified minor contaminants. The ether solution was concentrated under vacuum and the residue was flash chromatographed on silica with 6% ether/pentane. Concentration followed by bulb to bulb distillation at 120 °C (35 torr) yielded 2.07 g (97%) of n-heptyloxirane. The ^{13}C NMR showed the characteristic oxirane RCH-O at δ 52.2 (lit.[2] 52.3) and CH_2-O at 46.9 (lit.[2] 47.1).

To prepare a chlorohydrin, the typical procedure was followed with cinnamaldehyde in place of octanal and butyllithium in place of methyllithium. The Dry Ice/acetone bath was removed and after 0.5 h the mixture was treated with saturated ammonium chloride. The iodobutane impurity was removed by flash chromatography on silica with 20% ether/hexane. Concentration under vacuum yielded 1-chloro-4-phenyl-3-buten-2-ol, 97%; 200 MHz ^1H NMR ($CDCl_3$): δ 2.55 (broad s, 1, OH), 3.60 + 3.65 (m, 2, diastereotopic CH_2Cl), 4.52 (m, 1, CHOH), 6.19 (dd, 1, C=CHCHOH), 6.71 (d, 1, PhCH=C), 7.33 (m, C_6H_5); 22.6 MHz ^{13}C NMR: δ 72.2 (CHOH), 49.6 (CH_2Cl); m/e 182.0440 (calcd 182.0495). When a similar reaction mixture was kept overnight before workup, a mixture of this chlorohydrin with the previously reported epoxide[2] was obtained.

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