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MONOHALOMETHYLLITHIUM XCH_2Li : STABILIZATION OF A POTENTIAL SYNTHETIC REAGENT

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SUMMARY : The preparation of monohalomethyllithium XCH_2Li is achieved by Bromine-lithium exchange from the corresponding Bromohalomethane in the presence of one equivalent of lithium bromide at -110° in THF-Ether-Pentane solutions. This reagent, on coupling with various carbonyl compounds leads to halohydrins, epoxides and α-halomethyl ketones with high yields.

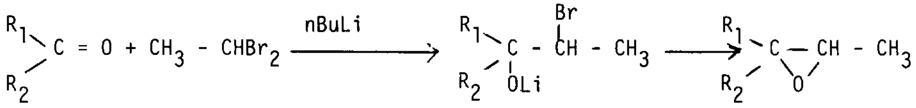
α-haloalkyllithium compounds are useful synthetic tools for the synthesis of regiospecific halogeno compounds. The preparation of trihalo- and dihaloalkyllithium has been fully described (1) and α-functionalized α-haloalkyllithium reagents have also been successfully prepared (2). The synthesis of non-functional α-monohaloalkyllithium compounds however remained unpublished until we showed that they could be prepared and used at very low temperatures (-115°, -120°C) (3).

$$\text{R-CHXBr} + \text{nBuLi} \xrightarrow[\text{THF, Et}_2\text{O, pentane}]{\text{T} < -115°\text{C}} \text{R-CHXLi} + \text{nBu-Br}$$

Attempts to prepare bromo- and chloromethyllithium by this method have been unsuccessful since immediate decomposition of the reaction medium occurred even at -130°C. This observation was in agreement with the results published by KOBRICH (4), who obtained only a 4% yield of monochloroacetic acid after carbonation of the probable intermediate, $ClCH_2Li$, formed by bromine-lithium exchange.

$$CH_2ClBr \xrightarrow[-110°C]{nBuLi} [ClCH_2Li] \xrightarrow[2)\ H_3O^+]{1)\ CO_2} ClCH_2COOH \quad 4\%$$

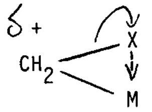
CAINELLI et Al (5) overcame the problem of instability by trapping the α-monobromolithioalkanes formed with a carbonyl compound which had been previously introduced.



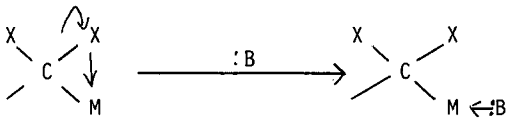
However this method also involves the formation of a number of side products, and therefore cannot be undertaken on a large scale.

Thus it would seem that α-monohalomethyllithium is particularly unstable as compared to α-halomethyl magnesium chloride (6) which have both been prepared and used as good synthetic reagents.

It is well known that the instability of carbenoïds can be correlated to the electrophilic behaviour of these reagents. A recent NMR study of carbenoïds by SEEBACH and coworkers (7), suggests that the functional carbon atom exhibits an electronic deficiency since its chemical shift is greater the more polarisable the halogen I > Br > Cl. This observation is in agreement with the structure of carbenoïds proposed earlier by CASTRO (8)and VILLIERAS (7) in which an intramolecular coordination between the halogen (or alkoxy group) and the metal was suggested to account for the apparition of electrophilicity and decomposition.

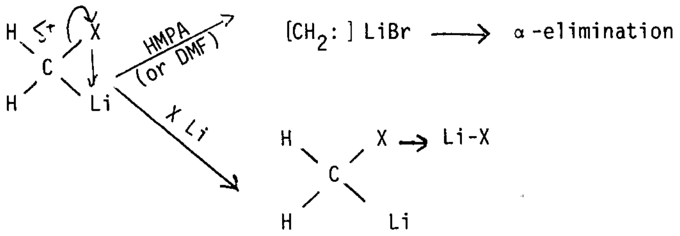


Removing or decreasing this coordination should therefore stabilize the carbenoïds. This is seen in the caseof dihalo and trihalocarbenoïds where the addition of basic solvents, such as THF (1a) or HMPA (1b,6), contributes to their stabilization and enhances their nucleophilic properties.



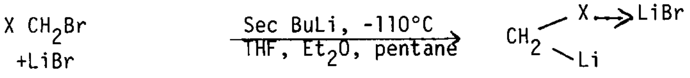
(coordination of the metal by a Lewis base)

With α-monohaloalkyllithium reagents, the reverse is observed when HMPA, which seems to favour α-elimination, is added. In this case, stabilization of the α-monohaloalkyllithium is achieved by adding an electron-acceptor such as a lithium salt.



(coordination of the halogen by a Lewis acid)

The presence of one equivalent of LiBr is sufficient to stabilize the carbenoïd **BrCH$_2$Li - LiBr** affording an almost quantitative yield. Commercially available n-Butyl lithium solutions in hexane or pentane do not provide the needed salt which explains the failure encountered by KOBRICH and coworkers. n-Butyllithium in ether which solubizes LiBr is preferable, however best results are obtained by adding secondary butyllithium in pentane to a solution of BrCH$_2$X (X = Cl, Br), THF, Et$_2$O, pentane and LiBr at -110°C.



$$\text{X CH}_2\text{Br} + \text{LiBr} \xrightarrow[\text{THF, Et}_2\text{O, pentane}]{\text{Sec BuLi, -110°C}} \text{CH}_2\begin{matrix}\text{X} \rightarrow \text{LiBr} \\ \text{Li}\end{matrix}$$

α- halomethyllithium compounds are excellent synthetic reagents for the preparation

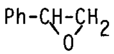
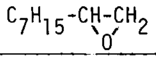
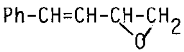
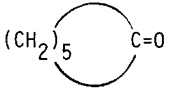
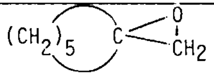
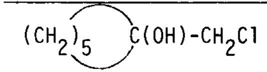
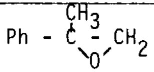
X	Carbonyl compounds	Products	Yield %	b.p./torr or * F °C	^{13}C-NMR ($CDCl_3$). δ ppm
Br	PhCHO		74	70/15 (53/4)^a	51,69 [>CH-O-] ; 50.58 [-CH_2O-]
Cl		Ph-CHOH-CH_2Cl	60	70/0,4 (105/5)^a	74.15 [>CH-OH] ; 50.64 [-CH_2Cl]
Br	C_7H_{15}-CHO		80	50/0,15	52.3 [>CH-O-] ; 47.1 [-CH_2-O-]
Br	Ph-CH=CH-CHO		65	83/0,15	52.56 [>CH-O-] ; 49.12 [-CH_2-O-]
Br			79	60/40 (62/37)^b	59.28 [>C-O-] ; 54.38 [-CH_2-O-]
Cl			76	* 61 (54/4) ^{b}	70.69 [>C-OH] ; 55.23 [-CH_2Cl]
Br	Ph-CO-CH_3		78	45/0,15 (84/15)^c	56,65 [CH_2-O-] ; 56.33 [>C-O-]; 21.63 [CH_3-]
Cl		Ph-C(CH3)(OH)-CH_2Cl	58	73/0,4 (124/13)^d	73.81 [>C-OH] ; 51,5 [-CH_2Cl]
Cl	C_6H_{13}-COOEt	C_6H_{13}-CO-CH_2Cl	62	65/4 (104/20)^e	202.52 [>C=O] ; 48.27 [-CH_2Cl]
Cl	Ph-COOEt	Ph-CO-CH_2Cl	61	80/0,4 (139/14)^e	191,02 [>C=O] ; 46.13 [-CH_2Cl]
Cl	Ph-CH_2-COOEt	Ph-CH_2-CO-CH_2Cl	55	70/0,4 (134/14)^f	195.2 [>C=O] ; 51.2 [Ph-CH_2-] ; 45.31 [-CH_2Cl]

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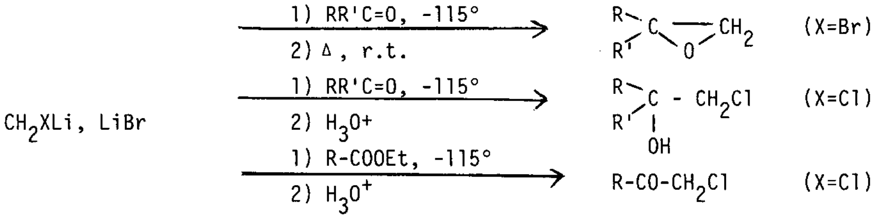
TABLE 1 - COUPLING OF XCH_2Li WITH CARBONYL COMPOUNDS

of halohydrins, epoxides (coupling to carbonyl compounds) and α-halomethylketones (coupling with esters) (see table).



A typical procedure for the synthesis of oxiranes : THF (75 ml), Ether (15 ml), pentane (10 ml), lithium bromide (1.66 g, 20 mmol) and methylene bromide (3.48 g, 20 mmol) are mixed and cooled to -115°C under nitrogen atmosphere and a 1.5 pentane solution of sec-butyl lithium (13.3 ml, 20 mmol) is added dropwise at -115°C. After stirring for 30 mn a solution of benzaldehyde (1.9 g, 18 mmol) in THF (10 ml) is then added at the same temperature. After 90 mn the reaction mixture is allowed to warm to room temperature for 60 mn before being hydrolised with saturated ammonium chloride solution. After classical work-up 1-phenyl ethylene-oxide is obtained by simple distillation (yield 1.6 g, 74 %).

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