Chloromethylithium

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Introduction

Chloromethylithium (LiCH\textsubscript{2}Cl) is a synthetically useful reagent belonging to the category of carbenoids, which are known to exhibit an ambiphilic behavior ranging from nucleophilic (at low temperatures) to electrophilic (at higher temperatures). This fact can be deduced by the resonance structures represented in Scheme 1, in which the extreme ionization of the polar bonds could lead, in principle, to the carbanionic (1a) or carbocationic (1b) species.\textsuperscript{1} Chloromethylithium can be prepared via a halogen–lithium exchange reaction on a given dihalomethane. Iodo- and bromo-chloromethane (ICH\textsubscript{2}Cl and BrCH\textsubscript{2}Cl) are the ideal precursors jointly with methyl-lithium–lithium bromide complex or \textit{n}-butyllithium.\textsuperscript{2} It is highly unstable except at very low temperatures (\textasciitilde78 °C or below); however, performing the reaction in the presence of the electrophile (i.e. Barbier-type conditions) allows to realize efficient processes. The presence of lithium halides and the use of ethereal-type solvents (THF or diethyl ether) had beneficial effects on its stability.\textsuperscript{3}

Scheme 1 Ambiphilicity of chloromethylithium

Interestingly, Le Floch and co-workers showed that by replacing the two hydrogens with electron-withdrawing groups, it is possible to dramatically improve the stability of the corresponding carbenoid.\textsuperscript{4}

Abstracts

\textbf{(A)} Carbonyl-type compounds have been homologated with lithium carbenoids. The addition of LiCH\textsubscript{2}Cl to an aldehyde or a ketone (2) after mild acidic treatment provides the corresponding halohydrin (3) in high yields. Interestingly, when the reaction is allowed to reach room temperature, an intramolecular nucleophilic displacement takes place, thus affording directly the epoxide 4.\textsuperscript{5} The strategy has very recently been applied to cyclic α,β-unsaturated enones to access chloromethyl allylic alcohols in high yield.\textsuperscript{6}

\textbf{(B)} Concellón and co-workers conveniently used a strategy for the preparation of β-chloro amines (7,7\texttextsubscript{a}) starting from activated N-aryl-sulfonamido imines 5.\textsuperscript{7}

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(C) Very recently Pace and co-workers reported the treatment of isocyanates 8 with LiCH₂Cl to access versatile N-chloro acetamides 9 in high yields even in the presence of optically active starting materials which did not racemize during the process.5

(D) A general method for the synthesis of α-arylamino-α′-chloro ketones in the presence of various substituents on the nitrogen atom has been developed by Pace et al. who employed Weinreb amides 9 as electrophilic starting materials for the chloromethylation.6 Remarkably, the chloromethylation of the complex ketone intermediate 10 resulted in exceptionally stable under the reaction conditions for which the use of esters provided exclusively the double addition products (i.e. carbonyl intermediates),10 resulting in the high stability under the reaction conditions for which the use of esters provided exclusively the double addition products (i.e. carbonyl intermediates),10 in this regard, the high stability under the reaction conditions for which the use of esters provided exclusively the double addition products (i.e. carbonyl intermediates),10 for which the use of esters provided exclusively the double addition products (i.e. carbonyl intermediates),10

(E) Simpkins and co-workers realized an efficient synthesis of the key intermediate 15 needed for the total synthesis of fumagilol 16. Interestingly, the chloromethylation of the complex ketone 14 proceeded in good yield and dr.11

(F) Matteson pioneered the chemistry of monohalolithium carbenoids with boronic esters.12 Recently, Aggarwal reported the homologation of tertiary boronic esters 17 with chloromethyllithium followed by oxidation to produce the corresponding enantiopure alcohols 18. In addition, they rationalized that the formation of 18 or 19 depends on the intermediate complex formed from 17 and chloromethyllithium, which can undergo O-migration (giving 19) or C-migration.12a By switching to LiCH₂Br the undesired O-migration can be minimized.

References


