SYNLETT Spotlight

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research.

Chloromethyllithium

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Introduction

Chloromethyllithium (\( \text{LiCH}_2\text{Cl} \)) 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} Chloromethyllithium can be prepared via a halogen–lithium exchange reaction on a given dihalomethane. Iodo- and bromo-chloromethane (\( \text{ICH}_2\text{Cl} \) and \( \text{BrCH}_2\text{Cl} \)) are the ideal precursors jointly with methyllithium–lithium bromide complex or \( n \)-butyllithium.\textsuperscript{2} It is highly unstable except at very low temperatures (\( \sim -78^\circ\text{C} \) 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}

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\textbf{Scheme 1} Ambiphilicity of chloromethyllithium
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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

(A) Carbonyl-type compounds have been homologated with lithium carbenoids. The addition of \( \text{LiCH}_2\text{Cl} \) 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 \( \alpha,\beta \)-unsaturated enones to access chloromethyl allylic alcohols in high yield.\textsuperscript{6}

(B) Concellón and co-workers conveniently used a strategy for the preparation of \( \beta \)-chloro amines (7,7a) 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 \( \alpha \)-arylamino-\( \alpha' \)-chloro ketones in the presence of various substituents on the nitrogen atom has been developed by Pace et al. who employed Weinreb amides 10 as electrophilic starting materials for the chloromethylation.3 Remarkably, the use of such amides could be successfully extended to the synthesis of \( \alpha' \)-halo-\( \alpha, \beta \)-unsaturated ketones 13 for which the use of esters provided exclusively the double addition products (i.e. carbinols).10 In this regard, the high stability under the reaction conditions of tetrahydro intermediate 12a, formed upon the addition of chloromethylithium to Weinreb amide 12, prevents the deleterious double addition of the reagent.

(E) Simpkins and co-workers realized an efficient synthesis of the key intermediate 15 needed for the total synthesis of fumagillin 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.6 Recently, Aggarwal reported the homologation of tertiary boronic esters 17 with chloromethylithium 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 chloromethylithium, which can undergo O-migration (giving 19) or C-migration.12 By switching to LiCH2Br the undesired O-migration can be minimized.

References


