

Halomethylithium Carbenoids: Versatile Reagents for the Homologation of Electrophilic Carbon Units

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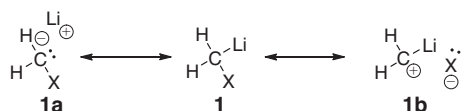
Background

Organometallic compounds presenting a lithium atom and at least one electronegative atom (e.g. halogen) are referred as carbenoids.^[1] In this sense, it is indicative of the choice of the term ‘carbenoid’ by Closs and Moss to define such species, which show a reactivity ‘qualitatively analogous to those of carbenes without necessarily being free divalent carbon species’.^[2] Their chemistry is characterized by the intrinsic dichotomy (ambiphilicity) between nucleophilic and electrophilic behaviour.^[3] Depending on the experimental conditions, they can selectively exhibit one of these properties: usually, at low temperatures they act as nucleophiles, whereas at higher temperatures their electrophilic reactivity comes into play. This fact can be rationalized by the resonance structures depicted in Scheme 1, in which the extreme ionization of the polar bonds could lead, in principle, to the carbanionic (**1a**) or carbocationic (**1b**) species (Scheme 1). In-depth spectroscopic investigations support such a behaviour based on the high s character of the C–Li bond and on the high p character of the C–X bond.^[4] In this scenario, monohalomethylithium reagents (i.e. LiCH₂X, X = Cl, Br, I) have received particular attention, and since their introduction by Köbrich as nucleophilic agents in the 1960s (Scheme 2),^[5] have become a versatile tool to perform homologation reactions as an alternative to diazomethane-based procedures^[6] or sulfur ylides (e.g. Corey–Chaykovski-type chemistry).^[7] Significantly, fluoromethylithium has been reported to be chemically too unstable, and thus its application in organic processes has been very limited.^[8]

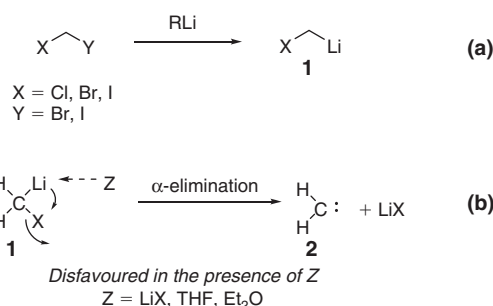
Key features of the Li carbenoids chemical reactivity can be summarized as follows: (i) they are immediately formed on treatment of a dihalomethane (ICH₂Cl, ICH₂Br, CH₂Br₂, CH₂I₂) with an alkylolithium base, as a consequence of the faster rate of halogen–Li exchange compared with the possible attack of the organolithium on a given electrophilic substrate (Scheme 2a)^[9]; (ii) to ensure complete formation of the

carbenoids and thus, minimize competing attack of the organolithium on the electrophile, it is wise to use a slight excess (~0.2–0.4 equiv.) of dihalomethane respect to RLi^[10]; (iii) their pronounced thermal instability requires negative temperatures (<–78°C) to accomplish the reactions^[4a] (for a remarkable exception, see below); (iv) because of the facile decomposition via α-elimination they undergo, reactions are performed in the presence of the electrophile^[11]; (v) the stability of this species is enhanced by both Lewis bases (e.g. THF or diethyl ether) and LiX salts, which, through the coordination to the lithium atom of the carbenoid, disrupt the internal Li–X interaction responsible for α-elimination with consequent decomposition of the carbenoid to the carbene **2** (Scheme 2b).^[12]

The effective thermal stability of LiCH₂Cl has been a topic of intense debate in the literature. In this sense, Köbrich considered it the most unstable of the three monohalocarbenoids (except LiCH₂F), because of decomposition at temperatures above –110°C.^[5] This behaviour was also confirmed by Villieras in the 1980s.^[12] However, studies published in the late 1980s^[9] and in the 1990s^[13] point out its stability at temperatures up to –78°C, and thus it is now well recognized that working at this non-prohibitive temperature does not compromise the efficiency of the reactions in which such species are involved. Though various alkylolithium bases have been employed for generating the carbenoids, MeLi–LiBr seems to provide the best results because of the aforementioned stabilization of the carbenoid with LiBr^[9,10] and of its lower basicity compared with other organolithiums (e.g. *n*-BuLi) that can further react with the so-formed carbenoids.^[11]



Scheme 1. Ambiphilicity of lithium carbenoids.



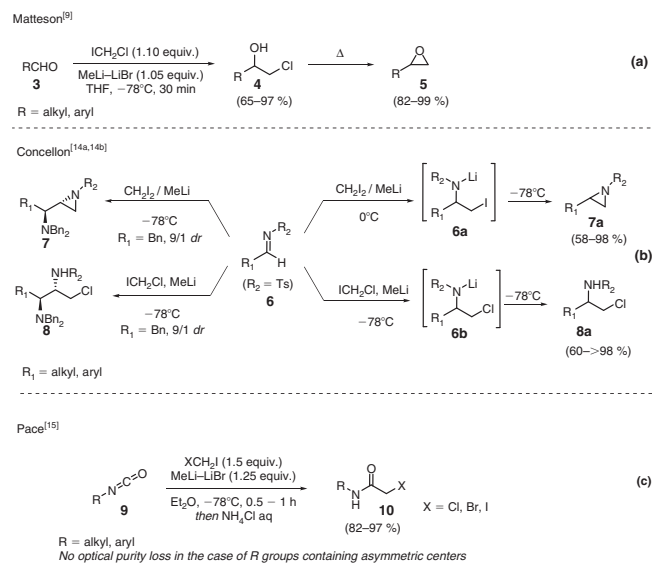
Scheme 2. Formation and degradation of lithium carbenoids.

Application of Halomethylithiums in Organic Synthesis

Homologation of Carbonyl-type Derivatives

Owing to their inherent electrophilicity, carbonyl-type compounds have been extensively homologated with lithium carbenoids. The addition of LiCH₂X to an aldehyde or a ketone (**3**) after mild acidic treatment provides the corresponding halohydrin (**4**) in high yields (Scheme 3a).^[9] Interestingly, when the reaction is allowed to reach room temperature before quenching, an intramolecular nucleophilic displacement takes place, thus directly affording the epoxide (**5**). Concellón and coworkers conveniently exploited such a strategy for the (diastereoselective) preparation of aziridines (**7–7a**)

and β-chloroamines (**8–8a**) starting from activated *N*-arylsulfonamido imines **6** (Scheme 3b).^[14] Remarkably, iodomethylithium used for these aziridination reactions could be efficiently prepared at 0°C, thus representing the highest temperature known for reaction involving such species. According to the authors, the reaction proceeds through the addition of the carbenoids to the *N*-tosyl-protected imine **6** to provide the intermediate lithiated haloamides (**6a–6b**), which then can undergo a spontaneous heterocyclization to **7a** (i.e. expulsion of the good leaving group iodine), or rather, stop at the β-chloroamine **8a** because of the non-optimal leaving ability of the chlorine. Very recently, Pace and coworkers reported the treatment of isocyanates **9** with LiCH₂X to access versatile *N*-haloacetamides **10** (Scheme 3c).^[15]

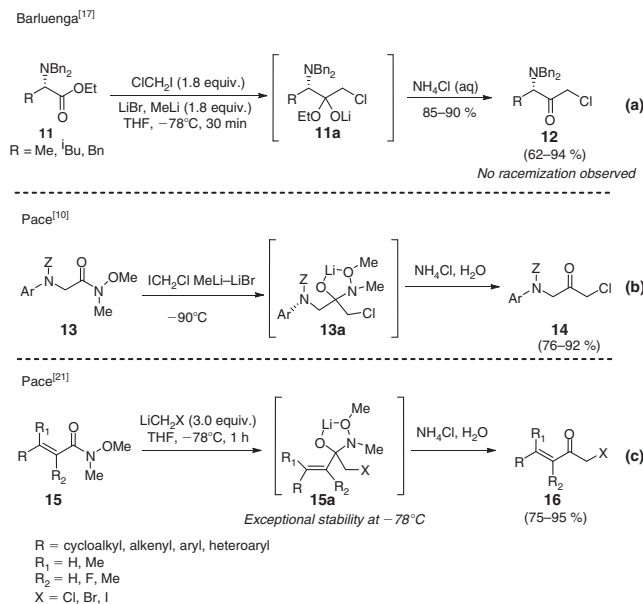


Scheme 3. Reactivity of lithium carbenoids with carbonyl-type compounds. dr, diastereomeric ratio.

Homologation of Carboxylic Acid Derivatives

Most of the success of these species have in the organic community is due to their use in the preparation of α -amino- α' -haloketones starting from α -amino esters, which represent valuable scaffolds for the synthesis of HIV-inhibitors.^[16] In this sense, Barluenga and coworkers reported the chloromethylation of *N*-protected amino esters **11** to the corresponding α -haloketones **12** without loss of optical purity during the transformation (Scheme 4a).^[17] However, the feasibility of the procedure is conditioned by the electronic behaviour of the nitrogen protecting group.^[18] In this sense, a general

method has been developed by Pace et al. who employed Weinreb amides^[19] **13** as the electrophilic starting materials (Scheme 4b, c).^[10,20] Remarkably, the use of such amides could be successfully extended to the synthesis of α' -halo- α,β -unsaturated ketones **16**, for which the use of esters provided exclusively the double-addition products (i.e. carbinols).^[21] In this regard, the high stability under the reaction conditions of the tetrahedral intermediate **15a** arising from the addition of the carbenoids to a Weinreb amide, which prevents a deleterious double addition of the carbenoid, should be stressed.



Scheme 4. Reactivity of lithium carbenoids with carboxylic-type compounds.

Conclusions and Outlook

Monohalomethyl lithium carbenoids are clearly synthetically useful methylene transfer agents commonly employed in synthetic operations both at academic and industrial levels. Remarkably, they allow the direct incorporation of a (reactive) halomethylene fragment into an electrophile, thus overcoming additional steps needed for the transformation of intermediate diazoketones or β -oxo dimethylsulfoxonium ylides into the

desired adducts. The good nucleophilicity of these lithium species accounts for the exclusive 1,2-addition to α,β -unsaturated systems (e.g. esters), thus complementing the 1,4-addition observed with sulfur ylides.^[22] Though the preparation of these reagents requires cryogenic temperatures and the use of pyrophoric reagents, the hazardous risks can be considered less problematic than those involving the use of the carcinogenic and explosive diazomethane.

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