GENERATION AND USE OF AZIRIDINYL ANIONS IN SYNTHETIC CHEMISTRY

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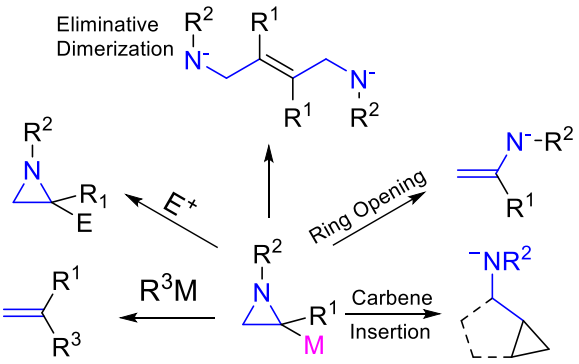
INTRODUCTION

Aziridines are present in many naturally occurring molecules, such as azinomycins, mitomycins, ficellomycin, miraziridine, and maduropeptin, structure-activity relationships have identified the aziridine ring as being essential for these molecules antitumor or antibacterial activites.[1] This nitrogen containing heterocycle is also well established as a versatile building block in organic synthesis and is most commonly known for electrophilic or nucleophilic ring opening reactions. Recently anionic aziridines, similar to the more studied oxiranyl anions, have gained considerable attention exhibiting nucleophilic, reductive alkylation, ring opening, eliminative dimerization, and carbenoid reactivity (Scheme 1).

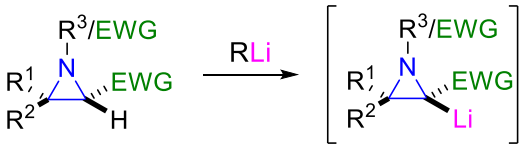
Scheme 1. Anionic Aziridine Chemistry



Traditionally the aziridinyl anions are classified on the basis of their structure into two broad categories, stabilized aziridinyl anions and nonstabilized aziridinyl anions.[2]

STABILIZED AZIRIDINYL ANIONS

In 1965, Turner first speculated on the existence of stabilized aziridinyl anions to explain the trans-cis isomerization of aziridinyl diketones.[3] Subsequently, Cromwell and Stevenson provided direct support for the presence of these negatively charged species using labeling studies.[4,5] Most stabilized aziridinyl anions are generated by deprotonation or desilylation. The acidic hydrogen next to the electron withdrawing group on the ring can be deprotonated using strong bases such as *t*-BuLi and LDA, producing lithiated aziridines (eq. 1). The carbon atom deprotonation is facilitated by inductive, conjugative, or complexation effects depending on the nature of electron withdrawing group on the aziridine. At cryogenic temperature, the lithiated carbon atom is configurationally stable thus allowing capture of electrophiles while retaining stereochemical integrity, although in rare cases the nature of N- or C-substituents can lead to ß-deprotonation or configurational unstability.[6]



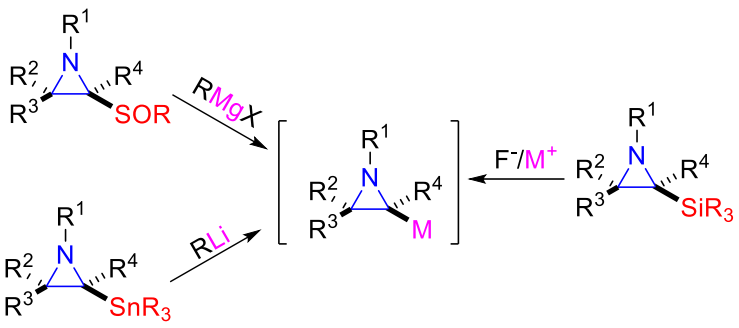
(1)

NONSTABILIZED AZIRIDINYL ANIONS

Nonstabilized aziridinyl anions, unlike their stabilized counterparts, have remained relatively underdeveloped due to difficulty in generating an anion alpha to an electronegative atom. It was not until

1988 that Yamakawa reported the desulfinylation of sulfinylaziridines using an excess of ethylmagnesium bromide. The reaction is postulated to proceed via an aziridinylmagnesium bromide intermediate that can be quenched with a proton source to generate the disubstituted aziridine while maintaining the configuration of the sulfinyl group.[7] Common methods for the generation of nonstablilized aziridinyl anions are desilylation, desulfinylation, and tin-lithium exchange reactions (Scheme 2). These exchange reactions are performed in the presence of alkylmagnesium or organolithium reagents at cryogenic temperatures to form configurationally stable anions which can be trapped with aldehydes, ketones, or halides. Since the generation of nonstablilized anions does not require a directing or stabilizing group it represents a more general method. However the chemistry to form them is dependent on the development of methods that form aziridines with groups that rapidly undergo exchange reactions to generate the nonstablilized anionic aziridines.

Scheme 2. Nonstabilized Aziridinyl Anions.



APPLICATIONS IN SYNTHESIS

Aziridinyl anions have been used in the generation of aziridinomitosene derivatives, potential anti-tumor drugs, and mitomycin C, an anticancer drug.[8,9] Site-selective cleavage of carbon-nitrogen bonds was used by Satoh for the generation of α-or ß-amino acids using enantiomerically pure sulfinyl aziridines.[10] These anions also exhibit non-nucleophilic behavior which is used in the generation of the azaspirocyclic core found in many naturally occurring compounds.[11] This reactive intermediate provides an excellent way to generate complexity and access structural motifs that are prevalent in naturally occurring compounds.

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