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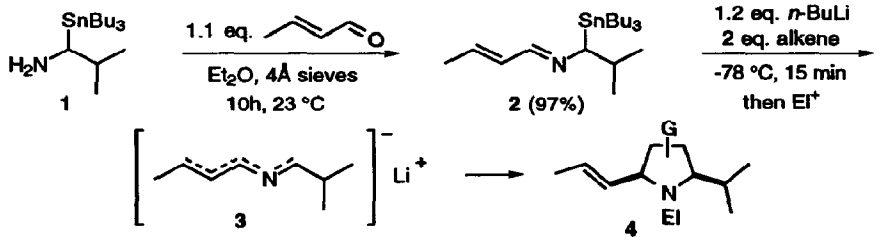
Generation of 2-Azapentadienyl Anions and Their Cycloaddition with Alkenes. Synthesis of 2-Alkenylpyrrolidines

William H. Pearson* and Valerie A. Jacobs

Department of Chemistry, The University of Michigan, Ann Arbor, MI 48109-1055

Abstract: α,β-Unsaturated imines **2** bearing an *N*-[1-(tri-*n*-butylstannyl)]alkyl group were transmetalated with *n*-BuLi to generate 2-azapentadienyl anions **3** which underwent [4πs+2πs] anionic cycloadditions with alkenes to afford 2-alkenylpyrrolidines **4** after workup with an electrophile. The alkenyl group could be oxidized to a diol, aldehyde, or ester. The imine **2** was found to undergo a [1,5]-sigmatropic rearrangement of the tri-*n*-butylstannyl group at 80 °C to provide the 2-azabutadiene **5**.

We have previously described the synthesis of pyrrolidines by the [4πs+2πs] cycloaddition of non-stabilized 2-azaallyl anions with electron-rich alkenes,[1,2] and we have recently extended the method to the synthesis of 1-pyrrolines and pyrroles.[3] The anions are prepared by tin-lithium exchange of 2-(azaallyl)stannanes. We now wish to describe the generation and cycloaddition chemistry of 2-azapentadienyl anions **3** which allow access to 2-alkenylpyrrolidines **4** (Scheme 1). In conjunction with oxidative transformations, these pyrrolidines are potentially valuable synthetic intermediates for the preparation of biologically important pyrrolidines bearing hydroxyalkyl, aldehyde, and carboxylic acid functionality at C(2). While similar pyrrolidines may be accessed using dipolar cycloaddition reactions of carboxyl-bearing azomethine ylides,[4,5] the two methods are complementary since azomethine ylide cycloadditions generally require electron-poor alkenes while non-stabilized 2-azaallyl anions are most efficient with electron-rich alkenes.

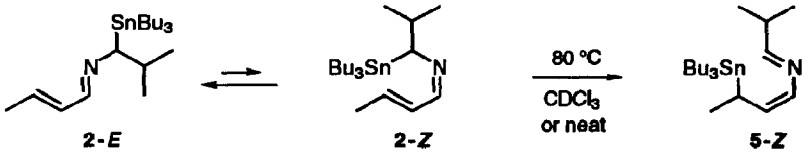


Scheme 1. Generation and Cycloaddition of 2-Azapentadienyl Anions

A number of studies on 2-azapentadienyl anions have appeared.[6-8] In every case, the anions were generated by deprotonation of imines, particularly those made by the condensation of allylic amines with aromatic aldehydes and ketones. As we have observed, this approach is limited to non-enolizable imines.[1] The tin-lithium exchange approach described below is not subject to this limitation. Spectroscopic and computational studies on 2-azapentadienyl anions have revealed that 1-phenyl-2-azapentadienyl anions prefer the all "W" conformation (i.e., all s-*trans*), whereas s-*cis* conformations are also present in 1-alkyl-2-azapentadienyl anions.[7] Regarding the chemistry of 2-azapentadienyl anions, 1,5-electrocyclization to 1-pyrrolines has been found to occur at temperatures above 0 °C.[6] Similar electrocyclizations have been observed for alkenyl azomethine ylides.[9,10] Other chemistry of 2-azapentadienyl anions includes alkylation, addition to aldehydes, conjugate addition, and in some cases cyclization with enones to give pyrrolidines.[7,8] The latter are thought to proceed by conjugate addition followed by cyclization rather than by a concerted cycloaddition. We have now found that simple alkyl-substituted 2-azapentadienyl anions may be prepared by

tin-lithium exchange. These anions undergo cycloadditions with electron-rich alkenes by what is presumed to be a concerted process.

Condensation of the α-amino stannane **1**[11,12] with crotonaldehyde afforded the stannyl imine **2** in excellent yield (Scheme 1). Purification was not only unnecessary, but is inadvisable since attempted distillation afforded the new imine **5** by a [1,5]-sigmatropic rearrangement of the tributylstannyl group (eq. 1). This rearrangement could also be observed by ^{1}H NMR spectroscopy at 80 °C in a sealed tube. First-order kinetics were observed ($k_1 = 3.5 \times 10^{-5}$ sec^{-1}; $t_{1/2} = 328$ min at 80 °C). The interconversion of the *E*- and *Z*-forms of **2** is presumed to be much faster than the sigmatropic rearrangement. Only one geometrical isomer of **2** (assumed to be the *E*-isomer) was observed by NMR. Similar [1,5]-tin shifts have been observed in 5-stannyl-1,3-pentadienes.[13] The greater thermodynamic stability of the 2-azabutadiene **5** versus the 1-azabutadiene **2** is expected.[6]



(1)

Cycloadditions were performed by mixing the stannane **2** with two equivalents of the anionophile in a small amount of THF, then adding this mixture to 1.2 equivalents of *n*-BuLi (a 2.1M solution in hexane) in THF at -78 °C (final anion concentration ca. 0.1M). After 15 min, the mixture was quenched with either water or two equivalents of MeI or MeO_2CCl. Normal aqueous workup provided the 2-alkenylpyrrolidines **6-14** (Table 1, entries 1-5). The pyrrolidines were formed as a mixture of regio- and stereoisomers in most cases, although the 1,3-*cis* relationship of the groups at C(2) and C(5) is consistently observed as would by expected from cycloaddition of the "W" form of the anion **3**. Such stereoselectivity is consistent with our prior work on the cycloaddition of 1,3-disubstituted 2-azaallyl anions.[1b] Also consistent is the failure of these anions to undergo cycloaddition with simple alkenes such as norbornene to provide adducts **15** (entry 6).[1] Stilbene and α-methyl styrene are successful anionophiles, providing aryl-substituted pyrrolidines **6-11** (entries 1-3). The *trans*-geometry of stilbene is translated into a 3,4-*trans* relationship in the pyrrolidines **6-9** (entries 1 and 2). In order to prepare pyrrolidines bearing no aryl groups, the use of phenyl vinyl sulfide as the anionophile is a useful solution since we have previously shown that the phenylthio group may be removed reductively or oxidatively.[1c] Entries 3 and 4 illustrate the formation of phenylthio-substituted pyrrolidines **12-14**.

Table 1. Generation and Cycloaddition of 2-Azaallylpentadienyl Anion **3**.

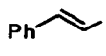
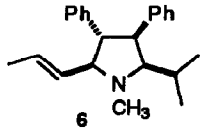
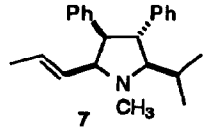
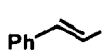
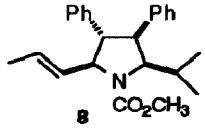
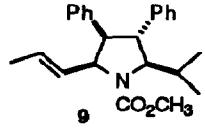
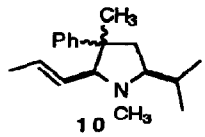
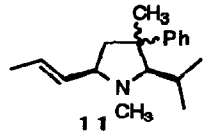
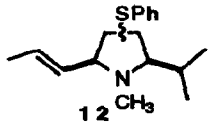
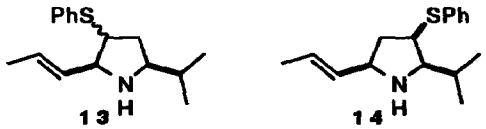
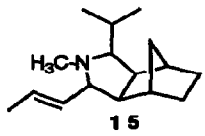
Entry	Anionophile	Electrophile	Product(s)		Yield,[a] Ratio
1		CH_3I	 **6**	 **7**	65% (2.7:1)[b]
2		$ClCO_2CH_3$	 **8**	 **9**	93% (2.7:1)[c]
3		CH_3I	 **10**	 **11**	43%[c,d,e]

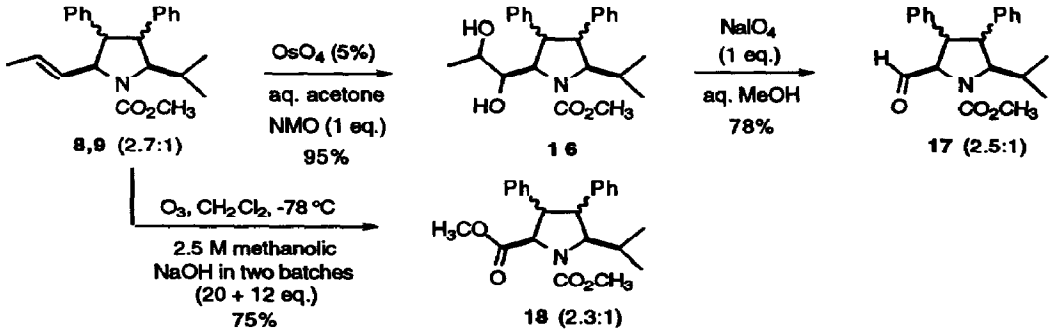
Table 1 (continued)

4	PhS	CH_3I	 **12**	47%[c,d]
5	PhS	H_2O	 **13** **14**	81% (2:1:2.1)[f]
6	norbornene	CH_3I	 **15**	trace

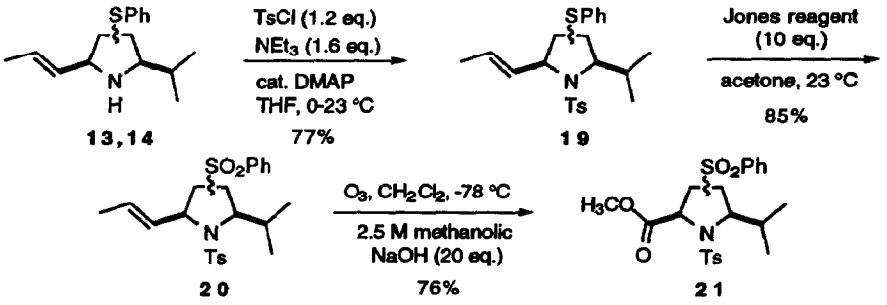
(a) Isolated, chromatographed yields. (b) Isomers separable. (c) Isomers not separable. (d) Assignment of regio- and stereochemistry was not possible. (e) ca. equal amounts of 3 isomers. (f) **13** separated from **14**, but stereoisomers of **14** could not be separated or assigned.

The rearranged imine **5** should also afford the 2-azapentadienyl anion **3** upon transmetalation. Thus, addition of **5** and *E*-stilbene to *n*-BuLi followed by MeI quench afforded a mixture of stereoisomers of **6/7** plus a new isomer isomer with a *Z*-propenyl substituent, but in only 22% yield.

Oxidative cleavage of the alkenyl group was explored, as shown in Schemes 2 and 3. Direct cleavage of the double bond of the diphenyl-substituted 2-propenylpyrrolidines **6/7** or their ammonium salts was not clean using ozonolysis or one-pot oxidations with $RuO_4/NaIO_4$, $OsO_4/NaIO_4$, or OsO_4/Jones reagent,[14] presumably because of the presence of the basic nitrogen. Dihydroxylation of **8/9** to the diol **16** followed by periodate cleavage gave the aldehyde **17** in good yield (Scheme 2). Direct conversion of **8/9** to the ester **18** was accomplished using Marshall's recent method.[15] Oxidative cleavage of the alkenyl group in the phenylthio-substituted 2-propenylpyrrolidines (Scheme 3) was not efficient unless the nitrogen was deactivated and the sulfide was first oxidized to the sulfone. Tosylation of **13/14** gave **19**, which was oxidized to the sulfone **20** with Jones' reagent. Marshall's ozonolysis conditions gave the ester **21**. Diols such as **16** are reminiscent of biologically active aza-sugars. The preparation of **17**, **18**, and **21** represents a new approach to the synthesis of novel proline analogues.



Scheme 2. Oxidative Transformations of 3,4-Diphenyl-2-propenylpyrrolidines



Scheme 3. Oxidative Transformations of Phenylthio-Substituted 2-Propenylpyrrolidines

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