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TRANSMETALLATION OF N-(TRIALKYLSTANNYL)METHYLIMINES. A NEW METHOD FOR THE GENERATION AND CYCLOADDITION OF 2-AZAALLYL ANIONS.

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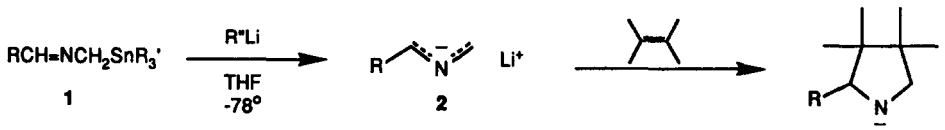
Summary: Transmetallation of imines **1** at -78° with RLi provided 2-azaallyl anions **2**, which readily undergo cycloaddition with olefinic anionophiles, providing pyrrolidines. Of particular note is the generation of unstabilized 2-azaallyl anions for the first time (Table 1, entries 1-3).

A potentially useful route to natural products having a pyrrolidine ring would be the [3+2] cycloaddition of 2-azaallyl anions onto olefins (eq. 1).[1,2] However, the scope of 2-azaallyl anion cycloadditions has been limited in the past by the methods available for anion generation.[3] All 2-azaallyl anions which have been generated and cycloadded to olefins bear two or more aryl groups, an obvious limitation for synthesis. We have recently presented studies on the preparation of bicyclic pyrrolidines based on the intramolecular cycloaddition of 2-azaallyl anions, but our examples were limited to anions bearing at least a single aryl ring.[4] Anions bearing more strongly electron-withdrawing groups have been generated, but these are generally too unreactive to be useful in cycloadditions.[5] We wish to report a new method for the generation and cycloaddition of 2-azaallyl anions which avoids these limitations, and for the first time allows access to completely *unstabilized* anions.

(1)

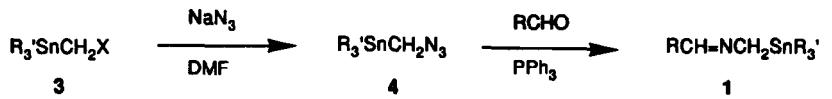
The most common method for the generation of 2-azaallyl anions has been the deprotonation of the N-alkyl group of imines with a strong base. When there is an anion stabilizing group present, there is no problem. However, based on an accumulation of data in our laboratories[6] and others,[7] it became apparent that 2-azaallyl anions lacking strong electron withdrawing groups must be generated in the absence of even weak proton sources (even iPr_2NH) due to their tendency

to isomerize to the more stable 1-azaallyl anions. We had also noticed that the yields of cycloadditions seemed to diminish when less substituted (and more basic) anions were used, presumably due to competitive isomerization to 1-azaallyl anions. Furthermore, deprotonative routes are undesireable due to their need for blocking or activating groups. In our search for rapid and essentially irreversible methods for anion generation, we were led to consider transmetallation reactions.[8] We now report that N-[(trialkylstannyl)methyl]-imines **1** (R'=Me or n-Bu) are readily transmetallated to lithium 2-azaallyl anions **2** through the agency of alkyllithium reagents (MeLi or n-BuLi) at low temperature.[10] These anions may then be trapped by olefinic anionophiles, providing N-lithiopyrrolidines in excellent yield (eq. 2).



(2)

The requisite stannyl imines **1** are prepared as shown in eq. 3 by a Staudinger reaction[11,12] between an aldehyde and (azidomethyl)trialkylstannane **4** (1.0 eq. of each, plus 1.0 eq. PPh_3, PhH, RT, 3-6h). Stannane **4** is simply prepared from **3** by sodium azide displacement (2 eq. NaN_3, DMF, 0.1M, RT, dark).[13]



(3)

a : R'=Me; X=I (ref. 14)

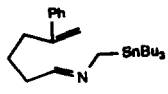
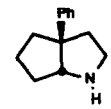
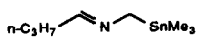
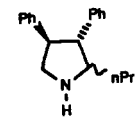
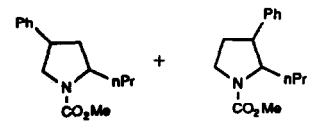
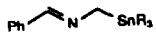
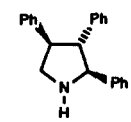
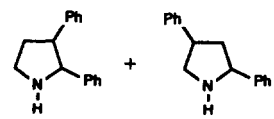
b : R'=nBu; X=OMs (ref. 15)

Treatment of a THF solution of the imine **1** with n-butyllithium or methyllithium at -78° leads to an orange to red solution of 2-azaallyl anion. These anions cycloadd with olefins intra- or intermolecularly at room temperature or lower (e.g., entry 5 proceeded rapidly at -78°) to provide pyrrolidines upon aqueous workup (Table 1).

Thus, for the first time, *2-azaallyl anions may be generated which bear no stabilizing groups* (such as aryl or carboxyl groups), and these anions undergo very efficient cycloaddition with olefinic anionophiles to provide pyrrolidines. Yields had only been moderate in the past, presumably due to alternate pathways available to the anions under the conditions of their generation (i.e., deprotonative methods). Application of this method to the synthesis of nitrogen containing natural products is underway in our laboratories.

Acknowledgement. We thank the Dreyfus Foundation (Award for Newly Appointed Faculty in Chemistry, 1984-89) and the National Institutes of Health for the generous support of this research.

Table 1. Generation and cyclization of 2-azaallyl anions.

Entry	Imine	RLi	Olefin	Products (ratio)	Yield, %[a]
1		nBuLi	---		83(94)
2		"	trans-stilbene	 (1:1)	62(93)
3	"	"	styrene	 (3:1)[b]	41
4	 R=nBu	"	trans-stilbene		80(97)
5	R=Me	"	"[c]	"	70[c]
6	R=Me	MeLi	"	"	83
7	R=Me	"	styrene	 (10:1)[d]	74

(a) Isolated yield of purified material. Satisfactory NMR, IR and Mass spectra were obtained. Parentheses indicate GC yields relative to internal decane standard after correction for relative reponse factors. (b) Quenched with $ClCO_2Me$. Four isomers were detected in a ratio of 6.5:4.2:2.7:1.0. (c) Quench after 5 min at -78°. (d) One stereoisomer of each regioisomer detected. Stereochemistry not yet determined.

References

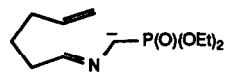
1. For a review on 2-azaallyl anions, see: Kauffmann, T. Angew. Chem., Int. Ed. Engl. **1974**, 13, 627.

2. A related approach to the synthesis of pyrrolidines involves 1,3-dipolar cycloadditions of azomethine ylides onto olefins. These dipoles use a 2-azaallylic anion set of orbitals. See: Lown, J. W. In 1,3-Dipolar Cycloaddition Chemistry; Padwa, A.; Ed.; Wiley-Interscience: New York, 1984; Vol. 1, Chapter 6..

3. The major methods for the generation of 2-azaallyl anions are deprotonation of imines,[1,4] electrocyclic ring opening of N-metalloaziridines,[1,6] and anionic cycloreversion of N-metalloimidazolidines.[4] To date, all of these methods suffer from the requirement of one or more anion stabilizing groups on the anion.

4. Pearson, W. H.; Walters, M. A.; Oswell, K. D. J. Am. Chem. Soc. **1986**, 108, 2769-2771.

5. For example, we have prepared the phosphonate anion **i** but cycloaddition fails to occur with normal olefins.



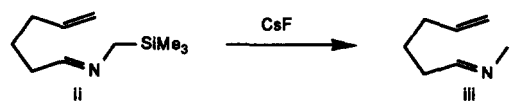
i

Dehnel has prepared similar phosphonate anions, and has observed cycloaddition with acrylates: (a) Dehnel, A.; Lavielle, G. *Tetrahedron Lett.* **1980**, *21*, 1315. (b) Rabilla, C.; Dehnel, A.; Lavielle, G. *Can. J. Chem.* **1982**, *60*, 926.

6. M. K. Rosen, W. G. Harter, unpublished results from these laboratories.

7. Smith, J.K.; Bergbreiter, D.E.; Newcomb, M. *J. Org. Chem.* **1985**, *50*, 4549.

8. Our early attempts at generation of 2-azaallyl anions by the desilylation of compound **ii** were unsuccessful. Even at 80° in DMF with anhydrous CsF, desilylation was slow (days), leading to low yields of the protodesilylated imine **iii** as the only identifiable product.



ii iii

Tsuge[9] has reported a similar desilylative approach to what are presumably 2-azaallyl anions. However, examples bearing no aryl groups have not been reported, which is consistent with our own findings.

9. (a) Tsuge, O.; Kanemasa, S.; Hatada, A.; Matsuda, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2537. (b) Tsuge, O.; Kanemasa, S.; Yamada, T.; Matsuda, K. *J. Org. Chem.* **1987**, *52*, 2523.

10. Pereyre, M.; Quintard, J.-P.; Rahm, A., "Tin in Organic Synthesis", Butterworths, London, 1987.

11. Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**,*2*, 635.

12. The yields for the preparation of the imines in Table 1 are as follows: entry 1: 90%; entry 2: 66%; entry 4: 92%; entry 5: 64%.

13. Azide **4b** is unstable toward light, heat, and moisture. It should be stored as a solution in benzene in the freezer, and should be flash chromatographed prior to use (SiO_2, hexane). Azide **4a** is more stable and easier to work with.

14. Seyferth, D.; Andrews, S. B. *J. Organomet. Chem.* **1971**, *30*, 151-166.

15. Seitz, D.; Carroll, J.; Claudia, P.; Cartaya, M.; Lee, S.; Zapata, A. *Syn. Commun.* **1983**, *13*, 129-134.

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