Pergamon

Tetrahedron Letters, Vol. 38, No. 31, pp. 5441-5444, 1997
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0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01217-3

The Generation and Cycloaddition of 2-Azaallyl Anions and Azomethine Ylides from a Common Precursor. A Novel Synthesis of Indolizidines and Other Heterocycles

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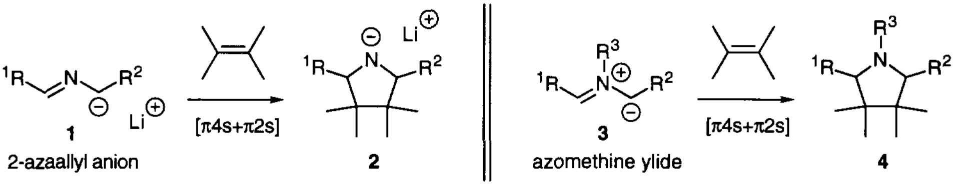
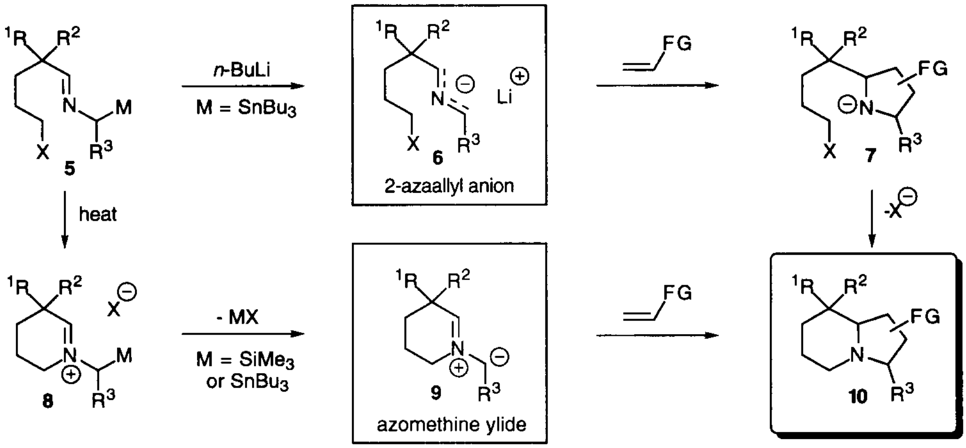
Abstract: Nonstabilized azomethine ylides may be generated by the intra- or intermolecular *N*-alkylation of 2-(azaallyl)stannanes or 2-(azaallyl)silanes. The cycloaddition of these ylides with electron poor or electron rich dipolarophiles provides indolizidines or simple monocyclic pyrrolidines (e.g., **5** → **8** → **9** → **10**). The same 2-(azaallyl)stannanes may be subjected to tin-lithium exchange to afford 2-azaallyl anions, which may also enter into cycloadditions (e.g., **11** → **12** or **13**). An *in situ* method for the generation and cycloaddition of azomethine ylides from an ω-halocarbonyl compound, an α-stannyl amine, and a dipolarophile is also described (Table 2).

Our work on the [π4s+π2s] cycloaddition of nonstabilized 2-azaallyl anions (**1**) with alkenes to provide *N*-lithiopyrrolidines (**2**)[1] has proven to be an effective complement to the related cycloaddition of azomethine ylides (**3**) with alkenes, which produces neutral pyrrolidines **4**.[2] Nonstabilized 2-azaallyl anions, generated by tin-lithium exchange, undergo cycloadditions with electron-rich alkenes at low temperature. Azomethine ylides generally cycloadd best with electron-poor alkenes and alkynes. We wish to report that 2-(azaaallyl)stannanes, the precursors to 2-azaallyl anions, may also be used for the generation of azomethine ylides. Application of both the anion and ylide methods to the synthesis of indolizidines and other heterocycles is also reported.

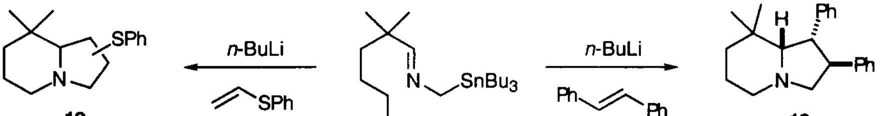


In our work on 2-azaallyl anion cycloadditions to produce pyrrolidines, we considered that a second ring might be formed if a pendant electrophile were present which might capture the *N*-lithiopyrrolidine cycloadduct. For example, tin-lithium exchange on the stannyl imine **5** would produce the anion **6**, which upon cycloaddition with an alkene would produce the *N*-lithiopyrrolidine **7** and thus the indolizidine **10** after intramolecular *N*-alkylation (Scheme 1). The leaving group X would have to be compatible with the 2-azaallyl anion.[3] This idea led us to consider that an alternative strategy using the same starting material **5** but proceeding through an azomethine ylide would be possible. Thus, heating **5** would generate the iminium ion **8**,[4] which might be destannylated (or desilylated if M=SiMe$_3$) to give the ylide **9**, and thus the target indolizidine[5] **10** after dipolar cycloaddition. Desilylative methods are commonly used to generate azomethine ylides from *N*-(trimethylsilyl)methyl iminium ions, themselves derived by *N*-alkylation or *N*-acylation of imines, imidates, or thioimidates.[2,6,7] Most closely related to the present work is the observation by Achiwa, *et. al*, that PhCH=NCH$_2$SiMe$_3$ undergoes *N*-alkylation/desilylation upon heating with alkyl halides or tosylates to produce azomethine ylides.[7,8] Destannylation has not been used to generate azomethine ylides.



Scheme 1. Synthesis of indolizidines (**10**) from **5** using either 2-azaallyl anions (**6**) or azomethine ylides (**9**).

Transmetalation of the stannyl imine **11**[9] in the presence of phenyl vinyl sulfide or *E*-stilbene provided the indolizidines **12** and **13**, respectively, in modest yield (eq. 1), thus demonstrating that the sequence **5** → **6** → **7** → **10** in Scheme 1 is viable. The yield of this tandem process prompted us to examine the azomethine ylide route.



12
(41%, 1:1.1 mixture)

11

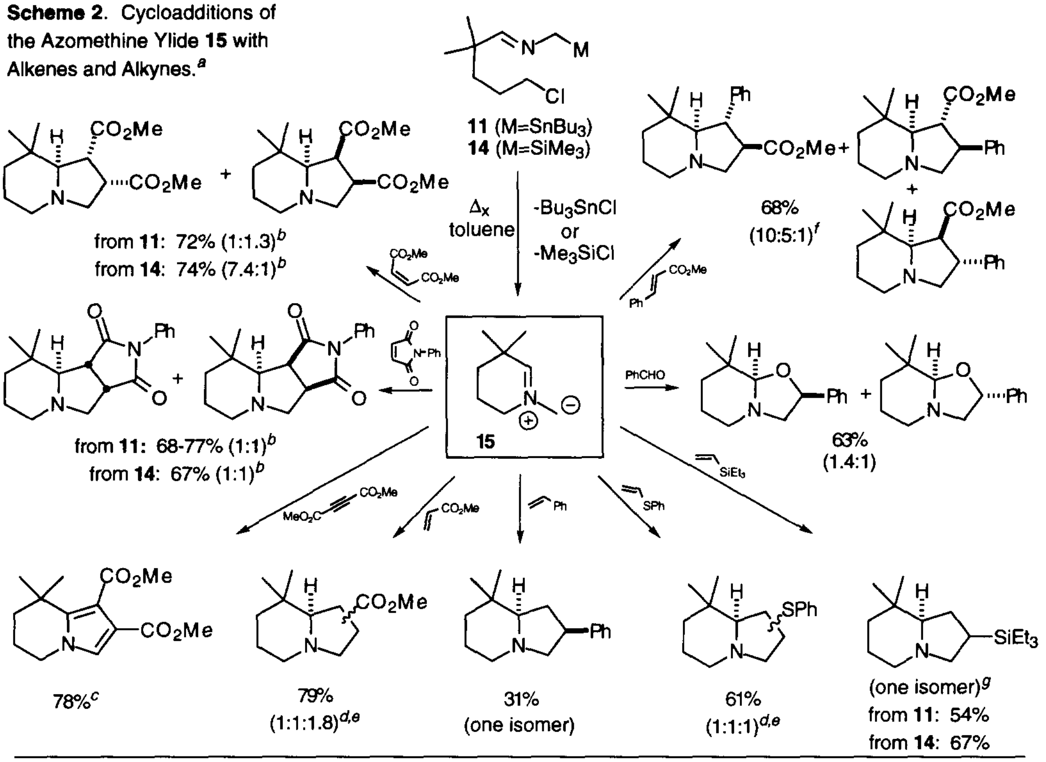
13
(31%, one isomer)

(eq. 1)

Heating the stannyl imine **11** or the silyl imine **14** in refluxing toluene in the presence of a variety of dipolarophiles produced the indolizidines shown in Scheme 2, presumably via the azomethine ylide **15**. The dipolarophiles used ranged from typical electron poor alkenes such as dimethyl maleate and dimethyl acetylenedicarboxylate to relatively atypical alkenes such as styrene, phenyl vinyl sulfide, and triethylvinylsilane. Benzaldehyde was also an effective dipolarophile. The tandem process failed with the following dipolarophiles: *E*-stilbene, ethyl vinyl ether, 1-vinyl-2-pyrrolidinone, 1-hexene, norbornene, diphenylacetylene, dihydrofuran, and phenylacetylene.

Table 1 shows additional examples of the tandem *N*-alkylation/cycloaddition involving different azomethine ylides. Table 2 shows that the formation and use of the 2-(azaallyl)stannane or 2-(azaallyl)silane may be accomplished in one pot by mixing the carbonyl compound, the α-amino stannane or α-amino silane, and the dipolarophile at reflux in toluene. The stannane **18**[9] demonstrates that branching next to the tin group is viable, producing even more densely functionalized indolizidines **19** and bicyclic oxazolidines **20**. The branched α-amino stannanes such as that required to make **18** are readily available.[1c,10] The use of **21**[1c] and **23**[1c] show that intermolecular *N*-alkylation is also viable. The formation of quaternary centers is also possible, as illustrated by the formation of **24** . Imines with enolizeable hydrogens are tolerated, as demonstrated by the formation of **22**, **24**, **25**.[11]

Scheme 2. Cycloadditions of the Azomethine Ylide **15** with Alkenes and Alkynes.[a]



Notes: [a]Unless noted, the stannyl imine **11** was used as the starting material. [b]Isomers separated. [c]After DDQ oxidation of intermediate 3-pyrroline. [d]Diastereomers not separated. [e]Regio- and stereochemical assignment(s) not made. [f]Regio- and stereochemical assignments made by COSY experiments on alcohols derived from $LiAlH_4$ reduction. [g]Stereochemistry not determined.

Acknowledgement. We thank the National Institutes of Health (GM-52491) for support of this research.

NOTES AND REFERENCES

(1) (a) Pearson, W. H.; Szura, D. P.; Harter, W. G. *Tetrahedron Lett* **1988**, *29*, 761-764. (b) Pearson, W. H.; Szura, D. P.; Postich, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1329-1345. (c) Pearson, W. H.; Postich, M. J. *J. Org. Chem.* **1992**, *57*, 6354-6357. (d) Pearson, W. H.; Stevens, E. P. *Tetrahedron Lett.* **1994**, *35*, 2641-2644. (e) Pearson, W. H.; Postich, M. J. *J. Org. Chem* **1994**, *59*, 5662-5671. (f) Pearson, W. H.; Jacobs, V. A. *Tetrahedron Lett.* **1994**, *35*, 7001-7004. (g) Pearson, W. H.; Lovering, F. E. *Tetrahedron Lett.* **1994**, *35*, 9173-9176. (h) Pearson, W. H.; Lovering, F. E. *J. Am. Chem. Soc.* **1995**, *117*, 12336-12337.

(2) (a) Lown, W. J. In *1,3-Dipolar Cycloaddition Chemistry*; A. Padwa, Ed.; Wiley: New York, 1984; Vol. 1; pp 663-732. (b) Pearson, W. H. In *Studies in Natural Products Chemistry*; A. Rahman, Ed.; Elsevier: Amsterdam, 1988; Vol. 1; pp 323-358. (c) Vedejs, E. In *Advances in Cycloaddition*; D. P. Curran, Ed.; JAI Press: Greenwich, CT, 1988; Vol. 1; pp 33-51. (d) Tsuge, O.; Kanemasa, S. *Adv. Het. Chem.* **1989**, *45*, 231-349. (e) Padwa, A. In *Comprehensive Organic Synthesis*; B. M. Trost and I. Fleming, Ed.; Pergamon: Oxford, 1991; Vol. 4; pp 1069-1109. (e) Wade, P. A. In *Comprehensive Organic Synthesis*; B. M. Trost and I. Fleming, Ed.; Pergamon: Oxford, 1991; Vol. 4; pp 1111-1168.

(3) Tin-lithium exchange is extremely fast, thus the *n*-butyllithium should not react at the leaving group X. The cyclization of **6** by displacement of X by a carbanionic site was of some concern, but since the C-

Table 1. Other cycloadditions.

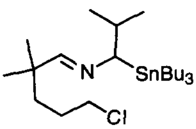
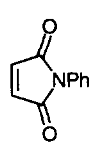
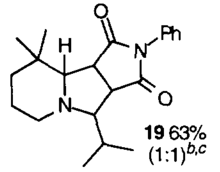
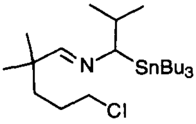
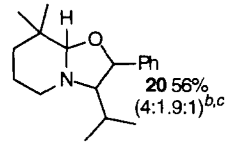
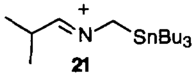
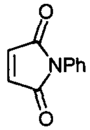
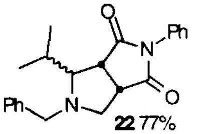
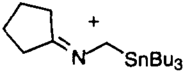
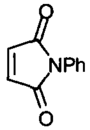
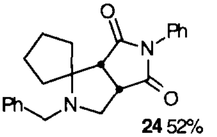
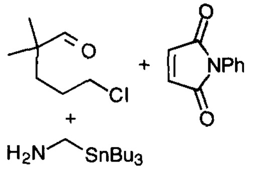
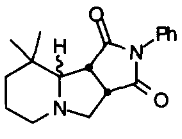
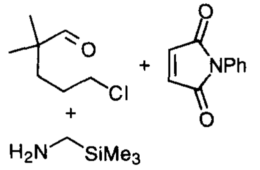
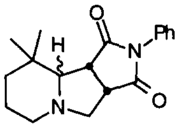
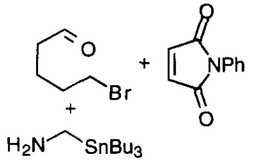
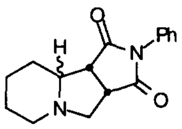
Stannane	Dipolarophile	Product(s)[a]
 **18**		 **19** 63% (1:1)[b,c]
 **18**	PhCHO	 **20** 56% (4:1.9:1)[b,c]
BnBr +  **21**		 **22** 77% (1:1.5 α iPr:β iPr)[d]
BnBr +  **23**		 **24** 52%

Table 2. *In situ* method.

Reactants	Product(s)[a]
	 67% (3:2 αH:βH)[d]
	 58% (1:1)[d]
	 **25** 77% (1:1)[d]

[a] Isolated yields. [b] Diastereomers not separated. [c] Stereochemistry not determined. [d] Diastereomers separated.

alkylation of organolithiums by organic halides is not an efficient reaction, we felt that cycloaddition might compete effectively, especially if a good anionophile were already present.

(4) The intramolecular *N*-alkylation of imines is a popular method for the formation of nitrogen heterocycles. For example, see: (a) Evans, D. A. *J. Am. Chem. Soc.* **1970**, *92*, 7593-7595. (b) Pearson, W. H.; Lin, K.-C. *Tetrahedron Lett.* **1990**, *31*, 7571-7574. (c) Stevens, C.; De Kimpe, N. *SYNLETT* **1991**, 351-352.

(5) Azomethine ylide cycloadditions have been used to prepare pyrrolizidines and indolizidines. See references 2c-2e, 7, and Pandey, G.; Lakshmaiah, G. *Tetrahedron Lett.* **1993**, *34*, 4861-4864.

(6) (a) Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1979**, *101*, 6452-6454. (b) Vedejs, E.; West, F. G. *J. Org. Chem.* **1983**, *48*, 4773-4774.

(7) Terao, Y.; Aono, M.; Achiwa, K. *Heterocycles* **1988**, *27*, 981-1008.

(8) (a) Achiwa, K.; Imai, N.; T.Inaoka; Sekiya, M. *Chem. Pharm. Bull.* **1984**, *32*, 2878-2881. (b) Imai, N.; Achiwa, K. *Chem. Pharm. Bull.* **1987**, *35*, 593-601.

(9) Prepared from $Me_2CHCH{=}N(c\text{-}C_6H_{11})$ by the sequence: i) LDA; ii) $Br(CH_2)_3Cl$; iii) aq. HOAc/NaOAc to produce $Cl(CH_2)_3C(CH_3)_2CHO$, which was condensed with the appropriate amino stannane $RCH(NH_2)SnBu_3$[1c,10] or amino silane $NH_2CH_2SiMe_3$ (Letellier, M.; McPhee, D. J.; Griller, D. *Synth. Commun.* **1988**, *18*, 1975-1978.). This technique for making such ω-haloimines was reported by Kuehne; see: Kuehne, M. E.; Matsko, T. H.; Bohnert, J. C.; Motyka, L.; Oliver-Smith, D. *J. Org. Chem* **1981**, *46*, 2002-2009. For closely related work, see also De Kimpe in reference 4c above. Similar strategies were used to make imines **14** and **18**.

(10) Chong, J. M.; Park, S. B. *J. Org. Chem* **1992**, *57*, 2220-2222.

(11) Preparation of 5-bromopentanal: Kulkarni, S. U.; Patil, V. D. *Heterocycles* **1982**, *18*, 163-167.

(*Received in USA* 2 *May* 1997; *accepted* 12 *June* 1997)