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Formation and cycloaddition of nonstabilized *N*-unsubstituted azomethine ylides from (2-azaallyl)stannanes and (2-azaallyl)silanes

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Abstract

Protodestannylation or protodesilylation of (2-azaallyl)stannanes or (2-azaallyl)silanes led to the formation of nonstabilized *N*-unsubstituted azomethine ylides, which underwent cycloadditions with electron-poor alkenes to produce 2-alkyl- or 2,5-dialkylpyrrolidines. 1,3-Disubstituted ylides derived from the stannanes and silanes gave stereochemically complementary results; the stannanes led to *trans*-2,5-dialkylpyrrolidines with high stereoselectivity, whereas the silanes led to *cis*-2,5-dialkylpyrrolidines with moderate stereoselectivity.

The cycloaddition of azomethine ylides with dipolarophiles is an important method for the construction of five-membered-ring nitrogen heterocycles.[1] While several methods for the formation of nonstabilized[2] *N*-substituted azomethine ylides **2a** are known,[3,4] there appears to be only two methods for the generation of nonstabilized *N-unsubstituted* azomethine ylides **2b**, both of which lack either efficiency or generality.[3f,g,5] First, the decarboxylation of imines derived from the condensation of α-aminoacids with aldehydes produces 1,3-dialkyl azomethine ylides **2b**, which undergo inefficient cycloadditions to produce 2,5-dialkylpyrrolidines **3** with poor *trans*:*cis* stereoselectivity.[3f,g,5] Second, Tsuge and coworkers have reported the water-induced generation of certain *N*-unsubstituted azomethine ylides **2b** (R^1=Ph or *t*-Bu, R^2=H) from *N*-(silylmethyl)imines, which are available from the condensation of aldehydes with (aminomethyl)trimethylsilane.[6] Notably absent are ylides derived from enolizable *N*-(silylmethyl)imines or 1,3-disubstituted ylides derived ultimately from branched α-aminosilanes. We recently reported the generation of nonstabilized azomethine ylides **2a** by the intra- or intermolecular *N*-alkylation of (2-azaallyl)stannanes **1a** or (2-azaallyl)silanes **1b**.[4] We now wish to report our studies on the generation and cycloadditions of nonstabilized 1-alkyl and 1,3-dialkyl *N-unsubstituted* azomethine ylides **2b**, which may be generated by the protodestannylation or protodesilylation of **1a** or **1b** with protic acids. Surprisingly,

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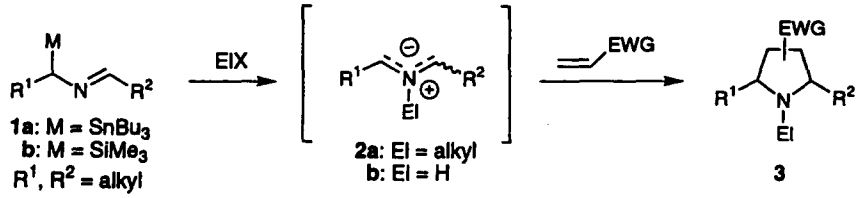
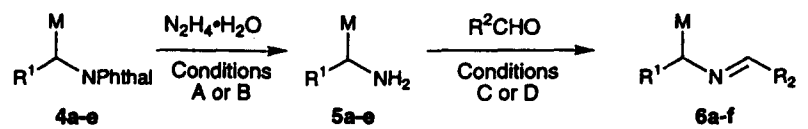
the *trans*:*cis* stereoselectivities observed in cycloadditions of the ylides **2b** with electron deficient alkenes was found to depend on whether the stannanes **1a** or the silanes **1b** were used.



The (2-azaallyl)stannanes **6a–d** and (2-azaallyl)silanes **6e,f** were prepared as outlined in Table 1. The tin- or silicon-bearing phthalimide derivatives **4a–e**[7–9] were deprotected by hydrazinolysis to afford the corresponding α-stannyl- or α-silylamines **5a–c** and **5d,e**, respectively.[7,8] The α-stannylamines **5a–c** were isolated after an aqueous workup and used without further purification, whereas the α-silylamines **5d,e** were isolated by distillation directly from the reaction mixture. Condensation of the appropriate amine with an aldehyde gave the imines **6a–f**. Imines **6a** and **6e** were isolated and purified by distillation. Silyl imine **6f** was prepared in situ without isolation or removal of water due to its high volatility. The stannyl imines **6b–d** were prepared in a similar fashion. Note that while α-aminostannanes (including branched versions) are readily prepared and easily handled,[7,8] branched α-aminosilanes are rare in the literature[10] and difficult to manipulate due to their volatility.

Table 1
Preparation of (2-azaallyl)stannanes and (2-azaallyl)silanes

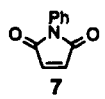
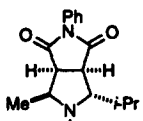
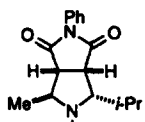
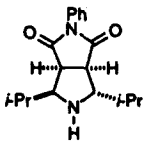
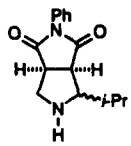
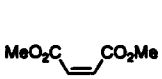
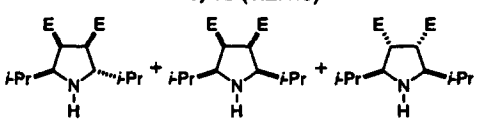
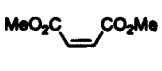
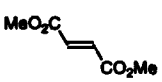
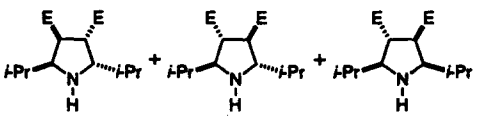
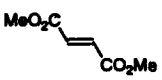
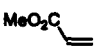
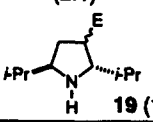


Phthalimide	M	R^1	Hydrazinolysis conditions[a]	Amine 5 (yield)[b]	R^2	Condensation conditions[c]	Imine 6 (yield)[b]
4a	$SnBu_3$	^{i}Pr	A	**5a** (--)	^{i}Pr	C	**6a** (92%)
4a	$SnBu_3$	^{i}Pr	A	**5a** (--)	Me	D	**6b** (--)
4b	$SnBu_3$	Me	A	**5b** (--)	^{i}Pr	D	**6c** (--)
4c	$SnBu_3$	H	A	**5c** (--)	^{i}Pr	D	**6d** (--)
4d	$SiMe_3$	^{i}Pr	B	**5d** (94%)	^{i}Pr	C	**6e** (51%)
4e	$SiMe_3$	H	B	**5e** (76%)	^{i}Pr	D	**6f** (--)

[a]Hydrazinolysis conditions: A) N_2H_4•H_2O, EtOH, reflux followed by aqueous workup. B) N_2H_4•H_2O, amine distilled from reaction mixture. [b]Isolated yield of purified material. (--) indicates that the material was used without purification. [c]Condensation conditions: C) Et_2O, 4Å molecular sieves, RT, 1hr, followed by concentration and distillation. D) THF or toluene, RT, 5 min, no isolation or removal of water.

Table 2 summarizes the cycloadditions of ylides derived from both (2-azaallyl)stannanes and -silanes.[11,12] Good to excellent yields (55–84%) of pyrrolidines were obtained, improving on the 10–30% yields observed in the decarboxylative route to azomethine ylides.[3f,g,5] While pyridinium *p*-toluenesulfonic acid (PPTS) was an efficient proton source for the reaction, HF–pyridine was found to be ideal due to shorter reaction times and the ease of removal of the Bu_3SnF by-product. Entries 2 and 3 show that the cycloaddition outcome is unaffected by the position of the stannyl moiety in the starting imines **6b** and **6c**, consistent with a common azomethine ylide intermediate. Monosubstituted azomethine ylides derived from the (2-azaallyl)stannanes and -silanes **6d** and **6f** produced pyrrolidines in similar

Table 2
Acid-promoted formation of azomethine ylides from (2-azaallyl)stannanes and -silanes and their cycloadditions

Entry	Imine	Alkene	Solvent (temp)	Acid	Products (ratio)[a]	Yield
1	6c	 7	Toluene (reflux)	PPTS	 8 (1.0) +  9 (1.0)	65%[b,e]
2	6c	7	THF (reflux)	PPTS	8, 9 (1.0:1.0)	56%[b,e]
3	6b	7	THF (50 °C)	HF-pyr	8, 9 (1.0:1.0)	55%[b,e]
4	6a	7	THF (50 °C)	HF-pyr	 10	69%[c]
5	6d	7	THF (50 °C)	HF-pyr	 11, 12 (1.3:1.0)	63%[b,e]
6	6f	7	THF (50 °C)	HF-pyr	11, 12 (1.2:1.0)	61%[d,e]
7	6a		THF (50 °C)	HF-pyr	 13 (18) + 14 (1.0) + 15 (0)	68%[c,e]
8	6e		THF (50 °C)	HF-pyr	13 (1.2) + 14 (1.3) + 15 (1.0)	68%[c,f]
9	6a		THF (50 °C)	HF-pyr	 16 (5.8) + 17 (11) + 18 (1.0)	84%[c,g]
10	6e		THF (50 °C)	HF-pyr	16 (1.0) + 17 (2.1) + 18 (6.1)	70%[c,h]
11	6a		THF (50 °C)	HF-pyr	 19 (1.5:1.0)	81%[c,i]

[a] Ratios of purified products. [b] Overall yield from the stannyl phthalimides 4. [c] Overall yield from the distilled amines 6. [d] Overall yield from the distilled amine 5e. [e] Isomers were not separated. [f] Isolated as three chromatographic fractions: 14% of 13, 30% of a 1.0:5.2 ratio of 13 and 14, and 19% of 15. [g] Isolated as three chromatographic fractions: 44% of 17, 13% of a 1.7:1.0 ratio of 17 and 18, and 27% of 16. [h] Isolated as two chromatographic fractions: 62% of a 1.0:2.6 ratio of 17 and 18, and 8% of 16. [i] Tentative assignment of configurations.

yields and product ratios (entries 5 and 6). Cycloadditions of the 1,3-disubstituted ylides derived from (2-azaallyl)stannanes **6a–c** were found to be highly selective for *trans*-2,5-dialkylpyrrolidines (entries 1–4, 7, and 9).[12] Wilson reported that the cycloadditions of 1,3-dialkyl substituted azomethine ylides derived from the decarboxylative route proceed with inconsistent and poor *trans*:*cis* ratios with the *cis* isomer predominating.[5b,c] Grigg reported examples of 2,5-*trans* selectivity as high as 10.1:1 for 1-phenyl-3-alkyl-substituted azomethine ylides generated by the decarboxylative route, but most examples gave 2,5-*trans* selectivities of about 3:1.[5e] Surprisingly, 1,3-disubstituted azomethine ylides derived from the (2-azaallyl)silane **6e** led to moderate selectivity for *cis*-2,5-dialkylpyrrolidines (entries 8 and 10, cf. entries 7 and 9), more closely reflecting the ratios observed for cycloadditions of 1,3-dialkyl azomethine ylides generated by the decarboxylative route. We are currently exploring the origin of this interesting stereochemical complementarity. Finally, entry 11 illustrates the use of a singly activated dipolarophile.

In conclusion, *N*-unsubstituted 2-alkyl- or 2,5-dialkylpyrrolidines may be prepared in an efficient manner by the cycloaddition of nonstabilized *N*-unsubstituted azomethine ylides with alkenes. Enolizable imines are tolerated. 1,3-Disubstituted ylides derived from the protodestannylation of (2-azaallyl)stannanes gave pyrrolidines with high 2,5-*trans* stereoselectivity, whereas protodesilylation of similar (2-azaallyl)silanes gave pyrrolidines with moderate 2,5-*cis* stereoselectivity. The generation of 1,3-disubstituted azomethine ylides from (2-azaallyl)stannanes is more practical than the silicon method, since it is easier to prepare and manipulate the requisite branched α-aminostannanes **5**. Both methods are more efficient than the few existing methods for the generation and cycloaddition of nonstabilized *N*-unsubstituted azomethine ylides.

Acknowledgements

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K.; Wada, E. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2866–2871. (g) Grigg, R.; Savic, V.; Thornton-Pett, M. *Tetrahedron* **1997**, *53*, 10633–10642.

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10. One general method is known for the synthesis of branched α-aminosilanes, which involves the reduction of enamines of acylsilanes, but involves the use of electrolysis conditions and large quantities of hexamethylphosphoramide (HMPA): Constantieux, T.; Picard, J.-P. *Organometallics* **1996**, *15*, 1604–1609.
11. Reactions with PPTS were carried out in standard glassware, while those with HF–Pyr were done in polypropylene centrifuge tubes. The following procedure is typical: the alkene (1.0–1.1 equiv.) was added to a solution of **6** (1.0 equiv., 0.2 M), prepared as described in Table 1. Upon heating to the desired temperature, a solution of the acid (1.0–1.5 equiv.) in 1 mL of solvent was added in a dropwise fashion over 5 minutes. The reaction was quenched with 2 M aqueous NaOH and diluted with ether. The organic layer was separated, washed once with saturated aqueous KF, dried over $MgSO_4$, and concentrated. The crude pyrrolidines were purified by silica gel chromatography.
12. Configurational assignments of pyrrolidines **8** and **9** were made based on NOESY experiments. The stereostructure of **10** was assigned assuming a *cis*-ring juncture and taking into account symmetry considerations; a stereoisomer with a *cis* relationship of the isopropyl groups would result in fewer resonances in the ^1H and ^{13}C NMR spectra than a stereoisomer with *trans*-isopropyl groups. The stereostructures of **13–18** were assigned based on NOESY experiments and similar symmetry issues.