Unprecedented 1,4-stannatropy: effective generation of azomethine ylides as nitrile ylide equivalents from *N*-(stannylmethyl)thioamides†

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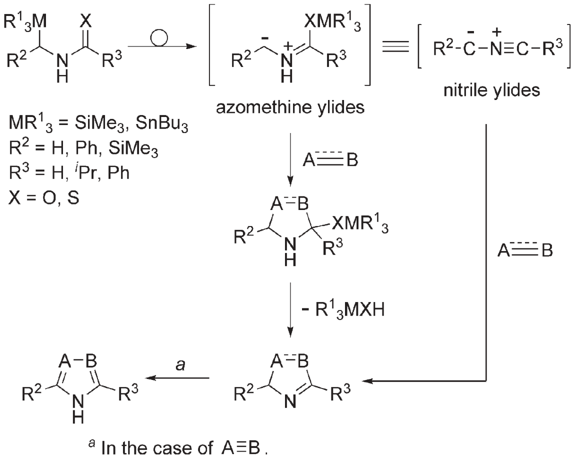
Generation and cycloaddition of less- or non-stabilized azomethine ylides, or nitrile ylide equivalents, *via* unprecedented 1,4-stannatropy of *N*-(tributylstannylmethyl)thioamides were achieved. The reactions with dipolarophiles, such as electron-deficient alkenes and alkynes, afforded corresponding pyrrolidine and pyrrole derivatives effectively.

1,3-Dipolar cycloaddition reactions are powerful tools for the construction of heterocyclic compounds because of their utility in forming a set of two bonds in a single operation.[1] Among such reactions, the cycloaddition of azomethine ylides is widely used in the synthesis of N-containing 5-membered heterocycles included in biologically active compounds and other functional materials.[2] While many methods for generating azomethine ylides have been reported,[3] we also found the cycloaddition of azomethine ylides generated from α-silylimines and α-silylamides by the intramolecular 1,2- and 1,4-migration of silyl groups, respectively.[4] In the reaction of α-silylamides, the strong affinity between silicon and oxygen causes a 1,4-silatropic shift onto the oxygen of the amide to afford the azomethine ylides (Scheme 1, X = O, MR^1_3 = $SiMe_3$, R^2 = Ph, $SiMe_3$).[4e]



MR^1_3 = $SiMe_3$, $SnBu_3$
R^2 = H, Ph, $SiMe_3$
R^3 = H, ^{i}Pr, Ph
X = O, S

[a] In the case of A≡B.

Scheme 1

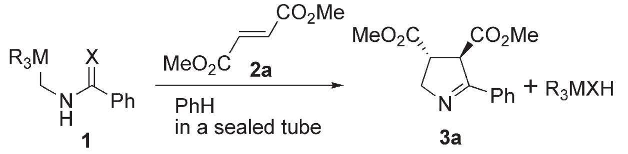
The azomethine ylides are regarded as nitrile ylide equivalents, because adducts of the corresponding nitrile ylides were obtained as the result of cycloaddition of the azomethine ylides followed by the elimination of silanol.

Stabilized azomethine ylides having aryl or electron-withdrawing groups at 1- or 3-positions are generated under moderate reaction temperature. However, when precursors of less- or non-stabilized azomethine ylides were employed, a high reaction temperature was required to generate the ylide intermediates. While generation of stabilized azomethine ylides under mild conditions is comparatively easy, generation of less- and non-stabilized azomethine ylides is a significant challenge in this field. Since it is well known that a sulfur atom stabilizes an adjacent ion and C=S bonds of thioamides are extensively polarized compared to C=O bonds of amides, α-metallothioamides would be expected to be better candidates for 1,4-sila- and/or stannatropy leading to less or non-stabilized azomethine ylides. Moreover, a tin atom has stronger affinity for a sulfur atom than a silicon atom, suggesting that *N*-(stannylmethyl)thioamides might be better starting materials.[5] Herein, we report on the highly effective cycloaddition of azomethine ylides generated by 1,4-stannatropy of *N*-(stannylmethyl)thioamides under neutral conditions. Although a number of studies of 1,2-[6] and 1,3-stannatropy[7] have been reported, there is just one example of an anionic reaction *via* 1,4-stannatropy,[8] and, hence, this type of migration under neutral conditions is unprecedented to the best of our knowledge.[9]

The cycloaddition of azomethine ylides generated from α-metalloamides with dimethyl fumarate (**2a**) is shown in Table 1.

The reaction of *N*-(silylmethyl)amide **1a** with the fumarate in benzene at 200 °C for 30 h afforded cycloadduct **3a** in very low yield. In clear contrast to the silylmethylamide, the reaction of

Table 1 Cycloaddition of azomethine ylides generated by 1,4-metallatropy



Substrate	MR_3	X	Time/h	Temp/°C	Yield[a] (%)
1a	$SiMe_3$	O	30	200	4
1b	$SiMe_3$	S	30	200	74
1c	$SnBu_3$	S	3	60	80

[a] Determined by ^1H NMR.

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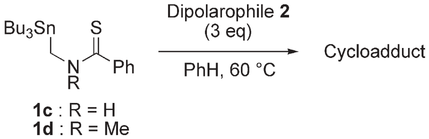
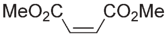
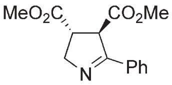
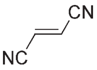
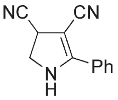
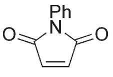
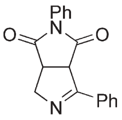
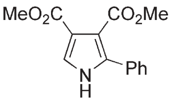
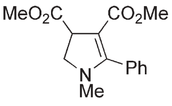
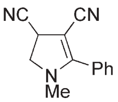
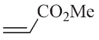
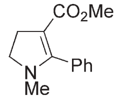
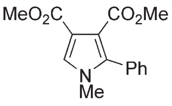
N-(silylmethyl)thioamide **1b** proceeded much more smoothly to give the same product. Surprisingly, the reaction of *N*-(stannylmethyl)thioamide **1c** was complete within 3 h even at 60 °C giving the cycloadduct **3a** in high yield. Thus *N*-(stannylmethyl)thioamide **1c** is the best precursor for the generation of the azomethine ylide. Since the reaction of amides **1** with alkenes and an alkyne gave the corresponding pyrrolines and pyrrole, the azomethine ylides generated from amides **1** are nitrile ylide equivalents most of which are difficult to be generated by conventional methods.[9c,10]

Table 2 Cycloaddition of azomethine ylides generated from *N*-(tributylstannylmethyl)thiobenzamides **1c,d** with dipolarophiles **2**



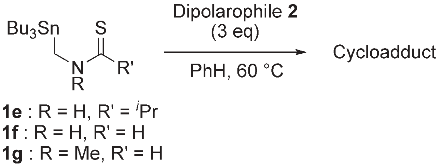
Entry	Thioamide	Dipolarophile	Time/h	Cycloadduct[a] (%)
1	**1c**	 **2b**	3	 51 (**3a**)
2	**1c**	 **2c**	0.5	 95 (**4a**)
3	**1c**	 **2d**	0.5	 90 (**3b**)
4	**1c**	 **2e**	40	 53 (**5a**)
5	**1d**	**2a**	40	 64[b] (**4b**)
6	**1d**	**2c**	6	 96 (**4c**)
7	**1d**	 **2f**	110	 43[b] (**4d**)
8	**1d**	**2e**	15	 81[b] (**5b**)

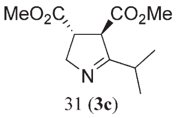
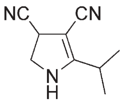
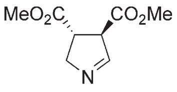
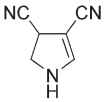
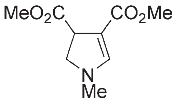
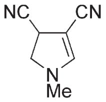
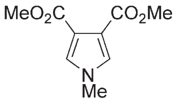
[a] Determined by ^1H NMR. [b] Isolated yields.

The reactions of *N*-(stannylmethyl)thioamide **1** with various dipolarophiles are shown in Table 2.

The reaction with dimethyl maleate (**2b**) gave cycloadduct **3a** which is the same product obtained in the reaction with dimethyl fumarate (**2a**) (entry 1). The result can be explained by isomerization at the 3-position of the initial 3,4-*cis* adduct because of the high acidity of the hydrogen at the 3-position and the stability of the 3,4-*trans* structure. When fumaronitrile (**2c**) was employed, 2-pyrroline derivative **4a** was obtained probably because of smaller steric repulsion between the substituents at the 3- and 4-positions in cycloadduct **4a** compared to cycloadduct **3a** (entry 2). The reaction with *N*-phenylmaleimide (**2d**), a cyclic dipolarophile, afforded cycloadduct **3b** in high yield (entry 3). In the case where dimethyl acetylenedicarboxylate (DMAD, **2e**), an

Table 3 Cycloaddition of azomethine ylides generated from *N*-(tributylstannylmethyl)thioamides **1e–g** with dipolarophiles **2**



Entry	Thioamide	Dipolarophile	Time/h	Cycloadduct[a] (%)
1[b]	**1e**	**2a**	35	 31 (**3c**)
2[b]	**1e**	**2c**	6	 80 (**4e**)
3	**1f**	**2a**	8	 50 (**3d**)
4	**1f**	**2c**	2	 74 (**4f**)
5	**1g**	**2a**	6	 80 (**4g**)
6	**1g**	**2c**	1	 80 (**4h**)
7[c]	**1g**	**2e**	<0.1	 89 (**5c**)

[a] Isolated yields. [b] Reaction temperature: 100 °C. [c] Reaction temperature: 20 °C

electron-deficient alkyne, was used, pyrrole derivative **5a** was obtained (entry 4).

Analogously, the reactions of *N*-methyl-*N*-(stannylmethyl)thioamide **1d** with dipolarophiles, electron-deficient alkenes and an alkyne, gave the corresponding cycloadducts in good yields under very mild conditions (entries 5–8). Among these, it is noteworthy that cycloadduct **4d** in the reaction with methyl acrylate (**2f**), an unsymmetrical dipolarophile, was produced with complete regioselectivity.

Surprisingly, the cycloaddition of azomethine ylides having *destabilizing substituents or no substituents* could also be carried out (Table 3). The introduction of an alkyl group to the 1- or 3-position of 1,3-dipoles causes extensive destabilization of the 1,3-dipoles. However, when *N*-(stannylmethyl)thioisobutyramide **1e** was employed in the reactions with dimethyl fumarate (**2a**) and fumaronitrile (**2c**), the corresponding cycloadducts **3c** and **4e** were readily obtained (entries 1 and 2). The reactions of *N*-(stannylmethyl)thioformamide **1f** and *N*-methyl-*N*-(stannylmethyl)thioformamide **1g** with these dipolarophiles afforded 2,5-unsubstituted pyrrolines **3d**, **4f**, **4g**, and **4h** in good yields respectively (entries 3–6). It is noteworthy that the azomethine ylide generated from thioamide **1f** is an ultimately non-substituted nitrile ylide equivalent, and thus, it is a very useful reactive species for the synthesis of less-substituted N-containing 5-membered heterocycles. When DMAD was employed, the reaction proceeded at ambient temperature to give pyrrole derivative **5c** in high yield (entry 7). The 2,5-unsubstituted pyrrolines and pyrroles are known, for example, to be precursors of polypyrroles which are mainly useful for conducting polymers.

In summary, we demonstrated an unprecedented method of effective generation of azomethine ylides on the basis of a new strategy using 1,4-stannatropy. Cycloaddition of the azomethine ylides, or nitrile ylide equivalents, proceeded under mild conditions to give pyrroline and pyrrole derivatives in good to excellent yields. The present strategy is also expected to be applicable to generation of other 1,3-dipoles and extension to 1,6-stannatropy for generation of 1,5-dipoles.

Notes and references

1 R. Huisgen, *1,3-Dipolar Cycloaddition Chemistry, Vol. 1*, ed. A. Padwa, John Wiley & Son, New York, 1984, 1.

2 G. W. Gribble, *Comprehensive Heterocyclic Chemistry II, Vol. 2*, ed. A. R. Katritzky, C. W. Rees, E. F. V. Scriven and C. W. Bird, Elsevier Science, Oxford, 1996, 207.

3 (*a*) J. W. Lown, *1,3-Dipolar Cycloaddition Chemistry, Vol. 1*, ed. A. Padwa, John Wiley & Son, New York, 1984, 653; (*b*) O. Tsuge and S. Kanemasa, *Advances in Heterocyclic Chemistry*, ed. A. R. Katritzky, Academic Press, 1989, 231; (*c*) W. H. Pearson and P. Stoy, *Synlett*, 2003, 903.

4 (*a*) Y. Oderaotoshi, W. Cheng, S. Fujitomi, Y. Kasano, S. Minakata and M. Komatsu, *Org. Lett.*, 2003, **5**, 5043; (*b*) M. Komatsu, H. Okada, H. Yokoi and S. Minakata, *Tetrahedron Lett.*, 2003, **44**, 1603; (*c*) H. Okada, T. Akaki, Y. Oderaotoshi, S. Minakata and M. Komatsu, *Tetrahedron*, 2003, **59**, 197; (*d*) M. Komatsu, H. Okada, T. Akaki, Y. Oderaotoshi and S. Minakata, *Org. Lett.*, 2002, **4**, 3505; (*e*) M. Ohno, M. Komatsu, H. Miyata and Y. Ohshiro, *Tetrahedron Lett.*, 1991, **32**, 5813; (*f*) M. Komatsu, M. Ohno, S. Tsuno and Y. Ohshiro, *Chem. Lett.*, 1990, **19**, 575; (*g*) M. Iyoda, F. Sultana, A. Kato, M. Yoshida, Y. Kuwatani, M. Komatsu and S. Nagase, *Chem. Lett.*, 1995, **24**, 1133.

5 (*a*) A. Tzschach and K. Jurkschat, *Pure Appl. Chem.*, 1986, **58**, 639; (*b*) K. Itoh, Y. Fukumoto and Y. Ishii, *Tetrahedron Lett.*, 1968, **9**, 3199; (*c*) W. T. Reiche, *Inorg. Chem.*, 1962, **1**, 650; (*d*) A. J. Bloodworth, A. G. Davis and S. C. Vasishtha, *J. Chem. Soc. C*, 1967, 1309.

6 (*a*) P. H. Dussault and U. R. Zope, *Tetrahedron Lett.*, 1995, **36**, 2187; (*b*) K. Iwamoto, N. Chatani and S. Murai, *J. Organomet. Chem.*, 1999, **574**, 171.

7 (*a*) M. Pereyre, B. Bellegarde, J. Mendelsohn and J. Valade, *J. Organomet. Chem.*, 1968, **11**, 97; (*b*) J. A. Marshall and W. Y. Gung, *Tetrahedron Lett.*, 1989, **30**, 2183; (*c*) A. Takuwa, T. Kanaue, K. Yamashita and Y. Nishigaichi, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1309.

8 H. Kumamoto, S. Shindoh, H. Tanaka, Y. Itoh, K. Haraguchi, E. Gen, A. Kittaka, T. Miyasaka, M. Kondo and K. T. Nakamura, *Tetrahedron*, 2000, **56**, 5363.

9 Generation and cycloaddition of azomethine ylides *via* demetallation of imminium salts have been reported. For examples see: (*a*) W. H. Pearson, P. Stoy and Y. Mi, *J. Org. Chem.*, 2004, **69**, 1919; (*b*) W. H. Pearson, A. Dietz and P. Stoy, *Org. Lett.*, 2004, **6**, 1005; (*c*) O. Tsuge, T. Hatta, M. Shinozuka and H. Tashiro, *Heterocycles*, 2001, **55**, 249; (*d*) O. Tsuge, T. Hatta, H. Tashiro, Y. Kakura, H. Maeda and A. Kakehi, *Tetrahedron*, 2000, **56**, 7723; (*e*) W. H. Pearson and R. B. Clark, *Tetrahedron Lett.*, 1999, **40**, 4467; (*f*) W. H. Pearson and Y. Mi, *Tetrahedron Lett.*, 1997, **38**, 5441; (*g*) E. Vedejs and F. G. West, *Chem. Rev.*, 1986, **86**, 941; (*h*) A. Padwa, G. Haffmanns and M. Tomas, *J. Org. Chem.*, 1984, **49**, 3314; (*i*) A. Padwa, G. Haffmanns and M. Tomas, *Tetrahedron Lett.*, 1983, **24**, 4303; (*j*) E. Vedejs and F. G. West, *J. Org. Chem.*, 1983, **48**, 4773.

10 References on nitrile ylides or their equivalents: (*a*) H.-J. Hansen and H. Heimgartner, *1,3-Dipolar Cycloaddition Chemistry, Vol. 1*, ed. A. Padwa, John Wiley & Son, New York, 1984, 177; (*b*) T. Ibata and K. Fukushima, *Nitrogen, Oxygen and Sulfur Ylide Chemistry*, ed. S. J. Clark, Oxford University Press, Oxford, 2002, 279.