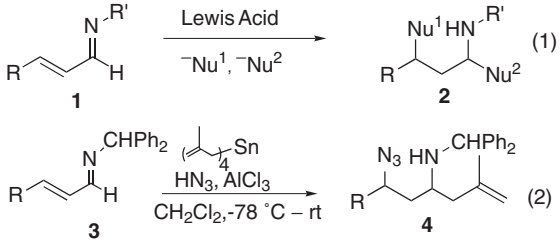
Double Nucleophilic Addition of Azide and Tetramethallyltin to α,β-Unsaturated Aldimines Promoted by Aluminum Chloride

Makoto Shimizu,* Chiaki Yamauchi, and Toshiki Ogawa
Department of Chemistry for Materials, Mie University, Tsu, Mie 514-8507

(Received February 27, 2004; CL-040224)

In the presence of $AlCl_3$, a mixture of hydrogen azide and tetramethallyltin underwent 1,4- and subsequently 1,2-addition, respectively, with α,β-unsaturated aldimines to give 1,3-amino azides in good yields. The 1,3-amino azides thus obtained were readily converted into 1,3-diamines by reduction with $LiAlH_4$.

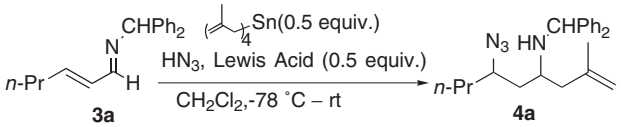
Although there are several reports on 1,3-amino alcohols and 1,3-diols, limited examples are available for their 1,3-diamine analogues.[1] This is due in part to lack of general synthetic methodologies for 1,3-diamines. However, recent interests in 1,3-diamine derivatives for use as catalysts in the asymmetric synthesis[2] and medicinal chemistry[3] involving HIV protease inhibitors have prompted us to explore simple approaches to them.



We have recently disclosed approaches to functionalized amines **2** using double nucleophilic addition to α,β-unsaturated imines **1** promoted by an appropriate Lewis acid,[4] where isomerization of an intermediary enamine to imino species was promoted by the use of the molecular sieves 4A containing a limited amount of water and/or thiols, and in such media hydrolysis of the relatively unstable imino species[5] was suppressed. We have now found that in the presence of $AlCl_3$ a mixture of hydrogen azide and tetramethallyltin undergoes a double nucleophilic addition with α,β-unsaturated aldimines to give 1,3-amino azides in good yields.

The initial reaction was carried out using $(allyl)_4Sn$ (0.5 equiv.), HN_3 (3.0 equiv.), and the imine **3a** (1.0 equiv.) in CH_2Cl_2 in the presence of $SnCl_4$(0.5 equiv.) at −78 °C to room temperature. In this case, however, only the 1,2-allylation product of the imine was obtained in 15% yield. We then focused our attention on the use of more reactive tetramethallyltin as a second nucleophile, and the results are summarized in Table 1. Among the Lewis acids examined, $SnCl_4$, $TiCl_4$, and $AlCl_3$ worked well, giving the double addition product **4a** in good yields (Entries 2, 6, and 9). The best yield was obtained, when the reaction was carried out with 5 equivalents of hydrogen azide in the presence of $AlCl_3$ (Entry 9). Hydrogen azide was prepared according to the reported procedure.[6] The reaction in the absence of a Lewis acid also proceeded to give the adduct but in low yield, where hydrogen azide worked as a promoter (Entry 10). Although we attempted to use NaN_3, $Zn(N_3)_2$, and $TMSN_3$ (without AcOH) besides the azide sources reported in Table 1, the product yields were not improved.

Table 1. Comparison of reaction conditions[a]



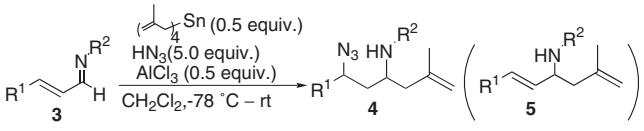
Entry	L. A.	HN_3/equiv.	Time/h	Yield/%[b]	*anti*:*syn*[c]
1	$SnCl_4$	1.0[d]	16.0	43	62:38
2	$SnCl_4$	3.0[d]	14.0	60	70:30
3	$SnCl_4$	5.0[d]	14.5	52	65:35
4	$SnCl_4$	3.0	14.5	46	53:47
5	$SnCl_4$	5.0	12.0	25	70:30
6	$TiCl_4$	3.0	15.0	62	68:32
7	$TiCl_4$	5.0	14.0	37	61:39
8	$AlCl_3$	3.0	16.0	33	68:32
9	$AlCl_3$	5.0	12.0	69	71:29
10	none	5.0	12.3	23	66:34

[a]Reaction was carried out according to the typical procedure (Ref. 7). [b]Isolated yield. [c]Isomer ratio determined by ^1H NMR. [d]Generated in situ from the reaction of $TMSN_3$ with AcOH.

Under the optimum conditions, a variety of α,β-unsaturated aldimines were subjected to the present double addition reaction, and Table 2 summarizes the results.

Regarding the substituent at the nitrogen atom, 4- or 2-methoxyphenyl group did not effect the conjugate addition, and only 1,2-addition of methallyl group was observed (Entries 1 and 2), whereas benzyl, cyclohexyl, and 9-fluorenyl derivatives

Table 2. Effects of the substituents[a]

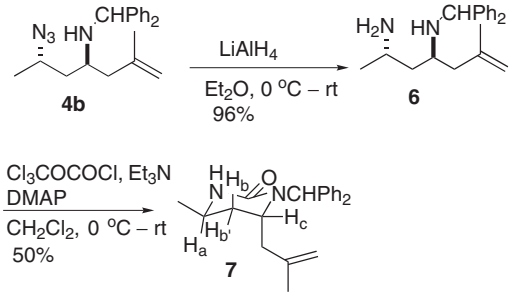


Entry	R^1	R^2	Time/h	**4**/%[b]	*anti*:*syn*[c]	**5**/%[b]
1	*n*-Pr	4-$MeOC_6H_4$	12.0	0	- : -	10
2	*n*-Pr	2-$MeOC_6H_4$	12.5	0	- : -	16
3	*n*-Pr	$PhCH_2$	12.5	29	67:33	0
4	*n*-Pr	Cy	14.0	50	63:37	0
5	*n*-Pr	9-Fluorenyl	15.0	20	60:40	0
6	Me	Ph_2CH	12.0	76	65:35	0
7	Et	Ph_2CH	12.5	63	64:36	0
8	TMS	Ph_2CH	14.3	45	70:30	27
9	TBDMS	Ph_2CH	13.5	0	- : -	50
10	Ph	Ph_2CH	12.0	0	- : -	22

[a]Reaction was carried out according to the typical procedure (Ref. 7). [b]Isolated yield. [c]Isomer ratio determined by ^1H NMR.

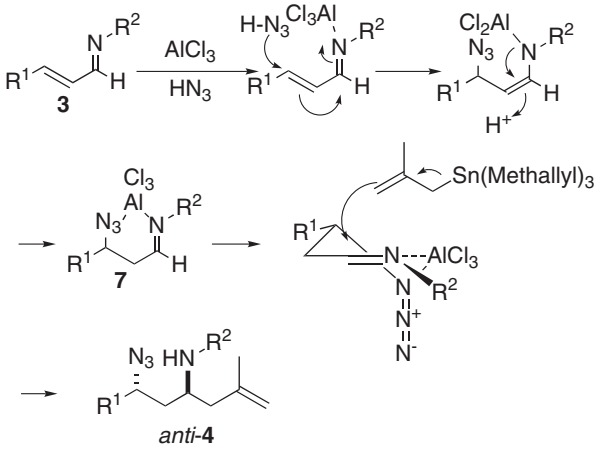
served as the double addition acceptors to give the adducts **4** in moderate yields (Entries 3–5). The reaction was sensitive to the substituents at the double bond. While the TMS derivative gave the double addition product **4** in moderate yield accompanied with 1,2-addtion product **5** (Entry 8), the TBDMS and Ph analogues did not afford the desired products **4** but only the 1,2-adducts **5** were obtained in moderate yields (Entries 9 and 10).

Reduction to 1,3-diamins was readily carried out using $LiAlH_4$ as a reducing agent. The following example shows the transformation and determination of the relative stereochemistry. First, each isomer was separated by silica gel chromatography. The major isomer **4b** was subjected to $LiAlH_4$ reduction to give the diamine **6** in 96% yield. The diamine **6** thus obtained was treated with diphosgene to give the tetrahydropyrimidinone **7**. Examination of the coupling constants of each proton unambiguously established the relative stereochemistry.



Scheme 1.

On the basis of the stereoselectivity observed in the present reaction, the following reaction mechanism was proposed (Scheme 2). First, the α,β-unsaturated imine **3** was activated with $AlCl_3$ followed by the conjugate addition of azide to give an intermediary enamine species. Protonation was effected with hydrogen azide to give the imine **7**, which was attacked via a six-membered metalla-cycle by tetramethallyltin from the stereoelectronically favored pseudo-axial side to afford *anti*-amino azide **4** as a major product.



Scheme 2.

In conclusion, the present double nucleophilic addition to α,β-unsaturated aldimines provides a rapid access to 1,3-amino azides, where relatively unstable imine intermediates were successfully utilized. Although the diastereoselectivity of the present reaction is not high, the ready transformation into 1,3-amines shows the utility of this approach.

References and Notes

1 a) J. Barluenga, M. Tomas, V. Kouznetsov, J. Jardon, and E. Rubio, *Synlett*, **1991**, 821. b) S. E. Denmark and J.-H. Kim, *Synthesis*, **1992**, 229. c) A. R. Katritzky and B. Rachwal, *J. Org. Chem.*, **58**, 812 (1993). d) M. T. Reetz, F. Kayser, and K. Haurmas, *Tetrahedron Lett.*, **35**, 8769 (1994). e) S. Hanessian, W. Wang, and Y. Gai, *Tetrahedron Lett.*, **37**, 7477 (1996). f) A. Kaiser and M. Balbi, *Tetrahedron: Asymmetry*, **10**, 1001 (1999). g) B. Merla, M. Arend, and N. Risch, *Synlett*, **1997**, 177. h) J. M. Conellon, H. Cuervo, and R. F.-Fano, *Tetrahedron*, **57**, 8983 (2001). i) X.-L. Hou, Y.-M. Luo, K. Yuan, and L.-X. Dai, *J. Chem. Soc., Perkin Trans. 1*, **2002**, 1487.

2 a) S. Ozaki, H. Miura, N. Yasuhara, M. Masui, Y. Yamagata, and K. Tomita, *J. Chem. Soc., Perkin Trans. 2*, **1990**, 353. b) S. G. Davies and A. A. Mortlock, *Tetrahedron*, **49**, 4419 (1993). c) D. Pini, A. Mastantuono, G. U.-Barratta, A. Iuliano, and P. Salvadori, *Tetrahedron*, **49**, 9613 (1993). d) M. Nakajima, K. Tomioka, and K. Koga, *Tetrahedron*, **49**, 9735 (1993). e) S. G. Davies, G. B. Evans, and A. A. Mortlock, *Tetrahedron: Asymmetry*, **5**, 585 (1994). f) A. Alexakis, J.-P. Tranchier, N. Lensen, and P. Mangeney, *J. Am. Chem. Soc.*, **117**, 10767 (1995). g) A. Alexakis, N. Lensen, J.-P. Tranchier, P. Mangeney, J. F.-Dupont, and J. P. Declercq, *Synthesis*, **1995**, 1038. h) T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya, and R. Noyori, *J. Am. Chem. Soc.*, **117**, 2675 (1995). i) A. Alexakis, P. Mangeney, R. R.-Munch, A. Perrotey, and E. Rose, *Tetrahedron: Asymmetry*, **6**, 2135 (1995). j) P. Gamez, F. Fache, and M. Lemaire, *Tetrahedron: Asymmetry*, **6**, 705 (1995). k) A. Alexakis, T. Kanger, A. Alexakis, F. R.-Munch, A. Perrotey, and E. Rose, *Tetrahedron: Asymmetry*, **6**, 47 (1995). l) K. Ogino, H. Tamiya, Y. Kimura, H. Azuma, and W. Takagi, *J. Chem. Soc., Perkin Trans. 2*, **1996**, 979. m) A. Alexakis, P. Mangeney, N. Lensen, J.-P. Tranchier, R. Gosmini, and S. Raussou, *Pure Appl. Chem.*, **68**, 531 (1996). n) A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya, and R. Noyori, *J. Am. Chem. Soc.*, **118**, 2521 (1996). o) T. Nishibayashi, Y. Arikawa, K. Ohe, and S. Uemura, *J. Org. Chem.*, **61**, 1172 (1996).

3 a) K. Vickery, A. M. Bonin, R. R. Fenton, S. O. Mara, P. J. Russeell, K. Webster, and T. W. Hambly, *J. Med. Chem.*, **36**, 3663 (1993). b) T. Kammermeier and W. Wiegrebe, *Arch. Pharm.* (*Weinheim*), **328**, 409 (1995). c) M. Cannarasa, *J. Chem. Ind.* (*London*), **1996**, 374.

4 M. Shimizu and T. Nishi, *Chem. Lett.*, **2002**, 46, and earlier references therein.

5 It was reported that several 1,4-addition products derived from α,β-unsaturated imines were readily hydrolyzed to the parent carbonyl compounds. See, M. D. Stadnichuk, A. V. Khramchikhin, Y. L. Piterskaya, and I. V. Suvorova, *Russ. J. Gen. Chem.*, **69**, 593 (1999).

6 H. Wolff, *Org. React.*, **3**, 307 (1946).

7 A typical procedure for the addition reaction: To a suspension of $AlCl_3$ (18.7 mg, 0.14 mmol) in CH_2Cl_2 (2.4 mL) was added a solution of *N*-diphenylmethylhexenylidenamine **3a** (73.9 mg, 0.28 mmol) in CH_2Cl_2 (3.0 mL) at $-78\,^{\circ}C$, and the mixture was stirred at $-78\,^{\circ}C$ for 15 min. A solution of hydrogen azide (0.80 mL, 1.4 mmol in 1.77 M benzene solution) was added at $-78\,^{\circ}C$, and the mixture was stirred at $-78\,^{\circ}C$ for 15 min. A solution of tetramethallyltin (47.4 mg, 0.14 mmol) in CH_2Cl_2 (3.0 mL) was added to the resulting mixture at $-78\,^{\circ}C$ and the mixture was gradually warmed to room temperature during 12.0 h. Normal work-up and purification on silica gel TLC (*n*-hexane:toluene:ethyl acetate = 120:30:1 as an eluent) gave *anti*-6-azido-4-(*N*-diphenylmethyl)amino-2-methyl-1-nonene **4a** (49.4 mg, 49%) and its *syn*-isomer **4a** (20.0 mg, 20%) as yellow oils.

Published on the web (Advance View) April 19, 2004; DOI 10.1246/cl.2004.606