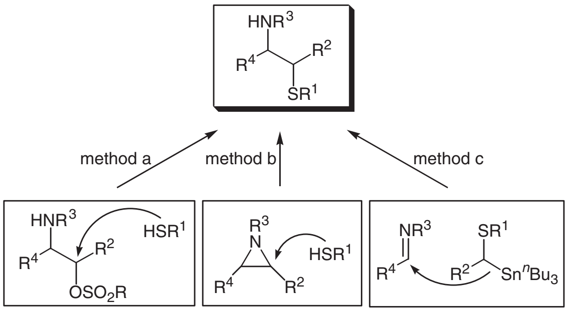
# Copper(II) Triflate-mediated Addition Reaction of α-Sulfurated Alkylstannanes to Imines: Facile Synthesis of Vicinal-amino Sulfides

Hirotaka Kagoshima* and Naoshi Takahashi
*Center for Instrumental Analysis, Ibaraki University, 2-1-1 Bunkyo, Ibaraki 310-8512*

(Received May 7, 2004; CL-040514)

In the presence of copper(II) triflate, the addition reaction of α-sulfurated alkylstannanes to imines proceeded smoothly to give the corresponding vicinal-amino sulfides in good yields.

Vicinal-amino sulfides are very important compounds in organic synthesis. Interest in useful intermediates and chiral ligands for application in asymmetric synthesis has prompted the development of a variety of methods for the synthesis of vicinal-amino sulfides.[1–3] Among the methods developed so far, representative synthetic routes to vicinal-amino sulfides include nucleophilic reactions of sulfur nucleophiles with nitrogen-containing electrophiles (Scheme 1); substitution reactions of vicinal-amino sulfonates[1] (method a) and ring-opening reactions of aziridines[2] (method b) with thiols or thiolates. In addition, another intriguing possibility is the synthesis of these vicinal-amino sulfides by addition reactions of nucleophilic α-sulfurated alkyl groups to imimes (method c).



**Scheme 1.**

As a part of our continuing interest in the development of synthetic methodology using imines,[4] we have reported the reaction of α-oxygenated alkylstannanes with imines leading to vicinal-amino alcohol derivatives.[4d] Here, we have anticipated that in place of α-oxygenated alkylstannanes, α-sulfurated alkylstannanes would react with imines to produce vicinal-amino sulfides in a similar fashion. In this paper, we would like to report a new facile synthesis of vicinal-amino sulfides. Although the photoinduced reaction of α-sulfurated alkylstannanes with α,β-unsaturated ketones has been reported,[5] this is the first example of the Lewis acid-mediated reaction of α-sulfurated alkylstannanes with imines for the synthesis of vicinal-amino sulfides.

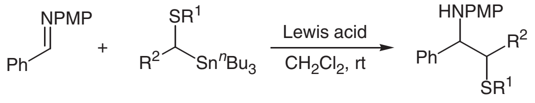
Initial optimization of the reaction of an imine **1a** with a stannane **2a**[6] focused on the effects of Lewis acids. The results are summarized in Table 1. When **1a** (1.0 equiv.) and **2a** (1.0 equiv.) were treated with $Cu(OTf)_2$ (1.0 equiv.) in $CH_2Cl_2$ at room temperature, the corresponding product **3a** was obtained in good yield (Entry 1). Use of AgOTf afforded **3a** in comparable yield albeit prolonged reaction time was required in order to complete the reaction (Entry 2). In contrast to the use of these Lewis acids, it was found that Lewis acids such as $Sc(OTf)_3$, $TiCl_4$, $BF_3{\cdot}OEt_2$, TMSOTf, $Sn(OTf)_2$, and $SnCl_4$ were not effective in this reaction; either none or a trace amount of **3a** was obtained. It is noted that the reaction did not take place without the Lewis acid, and no **3a** was detected in the reaction mixture. Even though both $Cu(OTf)_2$ and AgOTf effectively mediated the reaction, $Cu(OTf)_2$ was selected as the optimal Lewis acid because of the superior reaction rate and its cost, and was used for the subsequent reactions.[7]

Next, the effect of the substituents $R^1$ on the sulfur atom in the stannanes[6] was surveyed under the conditions optimized above (Table 1, Entries 1 and 3–5). As a result, it was found that yields highly depended on the nature of the substituents. Comparable yield was attained when a phenyl-substituted stannane **2b** was allowed to react with **1a** (Entry 3), while use of benzyl- or methoxymethyl-substituted stannanes **2c**, **2d** resulted in inferior yields (Entries 4 and 5). Furthermore, several stannanes[6] with different substituents $R^2$ on the α-carbon atom were prepared and employed in the addition reaction in order to clarify the scope and limitations of the present reaction (Table 1, Entries 1 and 6–8). Both isopropyl- and non-substituted stannanes **2e**, **2f** provided the corresponding products in lower yields (Entries 6 and 7). When a phenyl-substituted stannane **2g** was employed in the reaction, only a trace amount of the product was obtained (Entry 8). The low yields of **3c**–**3g** may be ascribed to the undesirable oxidation of **2** with $Cu(OTf)_2$ which competes with the addition reaction.[8]

We next examined the scope of the reaction of **2a** with various imines, and the results are shown in Table 2.[9] As can be seen from Table 2, a variety of aromatic imines were found to react smoothly under these conditions (Entries 1–8). Both electron-donating and electron-withdrawing substituents were tolerated in the *p*-position of the aromatic rings, and only modest dependence of the yields on the electronic property of the aromatic rings was observed. An imine prepared from a heteroaromatic aldehyde also reacted with **1a** (Entry 8). Not only aromatic imines but also an aliphatic imine **1i** can be used in the present reaction (Entry 9). An α-imino ester **1j** was found to be a good electrophile to afford the corresponding cysteine derivatives in 54% yield (Entry 10). In general, **2a** exhibited higher reactivity toward these imines than the corresponding α-oxygenated alkylstannanes and the reactions using **2a** were completed within a few hours.[4d]

In summary, we have developed a copper(II) triflate-mediated addition reaction of α-sulfurated alkylstannanes to imines. The present reaction provides a new, facile method for the synthesis of vicinal-amino sulfides. Development of new carbon-carbon bond-forming reactions of α-sulfurated alkylstannanes with other electrophiles is in progress.

**Table 1.** Effects of Lewis acids and substituents $R^1$ and $R^2$ in **2**[a]

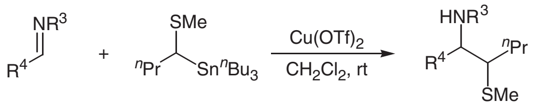


**1a** **2a–2g** **3a–3g**

| Entry | Lewis acid | Stannane **2** | | | Time (h) | Product **3** | | |
|---|---|---|---|---|---|---|---|---|
| | | | $R^1$ | $R^2$ | | | Yield/% | Diastereomer ratio[b] |
| 1 | $Cu(OTf)_2$ | **2a** | Me | $^n$Pr | 0.5 | **3a** | 56 | 49:51 |
| 2 | AgOTf | **2a** | Me | $^n$Pr | 24 | **3a** | 55 | 45:55 |
| 3 | $Cu(OTf)_2$ | **2b** | Ph | $^n$Pr | 3 | **3b** | 55 | 51:49 |
| 4 | $Cu(OTf)_2$ | **2c** | Bn | $^n$Pr | 4 | **3c** | 23 | 46:54 |
| 5 | $Cu(OTf)_2$ | **2d** | MOM | $^n$Pr | 3 | **3d** | 21 | 40:60 |
| 6 | $Cu(OTf)_2$ | **2e** | Me | $^i$Pr | 24 | **3e** | 30 | 23:77 |
| 7 | $Cu(OTf)_2$ | **2f** | Me | H | 24 | **3f** | 23 | — |
| 8 | $Cu(OTf)_2$ | **2g** | Me | Ph | 11 | **3g** | 9 | 47:53 |

[a]PMP = *p*-methoxyphenyl; MOM = methoxymethyl. [b]Determined by 400 MHz $^1$H NMR.

**Table 2.** $Cu(OTf)_2$-mediated addition reaction of **2a** to various imines



**1a–1j** **2a** **3a,3h–3p**

| Entry | Imine **1** | | | Time (h) | Product **3** | | |
|---|---|---|---|---|---|---|---|
| | | $R^3$ | $R^4$ | | | Yield/% | Diastereomer ratio[a] |
| 1 | **1a** | *p*-$MeOC_6H_4$ | Ph | 0.5 | **3a** | 56 | 49:51 |
| 2 | **1b** | *p*-$MeC_6H_4$ | Ph | 0.5 | **3h** | 59 | 50:50 |
| 3 | **1c** | *p*-$ClC_6H_4$ | Ph | 0.5 | **3i** | 63 | 50:50 |
| 4 | **1d** | Ph | Ph | 0.5 | **3j** | 56 | 49:51 |
| 5 | **1e** | Ph | *p*-$MeOC_6H_4$ | 0.5 | **3k** | 54 | 46:54 |
| 6 | **1f** | Ph | *p*-$MeC_6H_4$ | 0.5 | **3l** | 65 | 48:52 |
| 7 | **1g** | Ph | *p*-$ClC_6H_4$ | 0.5 | **3m** | 63 | 48:52 |
| 8 | **1h** | *p*-$MeOC_6H_4$ | 2-thienyl | 1 | **3n** | 55 | 45:55 |
| 9 | **1i** | *p*-$MeOC_6H_4$ | cyclohexyl | 2 | **3o** | 42 | 50:50 |
| 10 | **1j** | *p*-$MeOC_6H_4$ | $EtO_2C$ | 1 | **3p** | 54 | 47:53 |

[a]Determined by 400 MHz $^1$H NMR.

This work was partially supported by the Grant-in-Aid for Young Scientists (B) from Japan Society for the Promotion of Science, the Pfizer Pharmaceuticals Award in Synthetic Organic Chemistry, Japan, and the Mitsubishi Chemical Corporation Fund.

## References and Notes

1 a) F. Leyendecker and D. Laucher, *Tetrahedron Lett.*, **24**, 3517 (1983). b) I. W. Davies, T. Gallagher, R. B. Lamont, and D. I. C. Scopes, *J. Chem. Soc., Chem. Commun.*, **1992**, 335. c) B. G. Donner, *Tetrahedron Lett.*, **36**, 1223 (1995). d) G. A. Cran, C. L. Gibson, and S. Handa, *Tetrahedron: Asymmetry*, **6**, 1553 (1995).

2 a) H. M. I. Osborn and J. B. Sweeney, *Synlett*, **1994**, 145. b) M. Hayashi, K. Ono, H. Hosimi, and N. Oguni, *Tetrahedron*, **52**, 7817 (1996). c) J. H. Bae, S.-H. Shin, C. S. Park, and W. K. Lee, *Tetrahedron*, **55**, 10041 (1999). d) C. Xiong, W. Wang, C. Cai, and V. J. Hruby, *J. Org. Chem.*, **67**, 1399 (2002). e) Y. Furuta, T. Kumamoto, and T. Ishikawa, *Synlett*, **2004**, 362. f) X. E. Hu, *Tetrahedron*, **60**, 2701 (2004).

3 For other synthetic methods for vicinal-amino sulfides: a) R. K. Dieter and M. Tokles, *J. Am. Chem. Soc.*, **109**, 2040 (1987). b) G. S. Poindexter, D. A. Owens, P. L. Dolan, and E. Woo, *J. Org. Chem.*, **57**, 6257 (1992). c) B. S. Orlek, *Synlett*, **1996**, 477. d) R. Siedlecka and J. Skarzewski, *Synlett*, **1996**, 757. e) H. Ishibashi, M. Uegaki, and M. Sakai, *Synlett*, **1997**, 915.

4 a) H. Kagoshima and T. Akiyama, *J. Am. Chem. Soc.*, **122**, 11741 (2000). b) H. Kagoshima, T. Okamura, and T. Akiyama, *J. Am. Chem. Soc.*, **123**, 7182 (2001). c) H. Kagoshima, T. Uzawa, and T. Akiyama, *Chem. Lett.*, **2002**, 298. d) H. Kagoshima and K. Shimada, *Chem. Lett.*, **32**, 514 (2003).

5 T. Ikeno, M. Harada, N. Arai, and K. Narasaka, *Chem. Lett.*, **1997**, 169.

6 These stannanes were prepared by modifications of the literature procedures for analogous $\alpha$-sulfurated alkylstannanes: K. Narasaka, N. Arai, and T. Okauchi, *Bull. Chem. Soc. Jpn.*, **66**, 2995 (1993).

7 The yield of **3a** dropped to 22% when the amount of $Cu(OTf)_2$ was reduced to 0.5 equiv.

8 $\alpha$-Sulfurated alkylstannanes are easily oxidized with metallic oxidants. See, Ref. 6.

9 A typical experimental procedure (Table 2, Entry 1): To a mixture of **1a** (21 mg, 0.10 mmol) and $Cu(OTf)_2$ (36 mg, 0.10 mmol) in $CH_2Cl_2$ (1 mL) was added **2a** (39 mg, 0.10 mmol) in $CH_2Cl_2$ (0.5 mL) at room temperature. After being stirred for 0.5 h at this temperature, the reaction was quenched with saturated aqueous $NaHCO_3$. After a usual work up, the crude product was purified by TLC (AcOEt:hexane = 1:30) to give the corresponding product **3a** (18 mg, 56%, diastereomer ratio = 49:51).

Published on the web (Advance View) June 28, 2004; DOI 10.1246/cl.2004.962