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Addition reaction of zinc acetylides to thioiminium salts leading to 3-amino-1-sulfenyl-1,4-enynes

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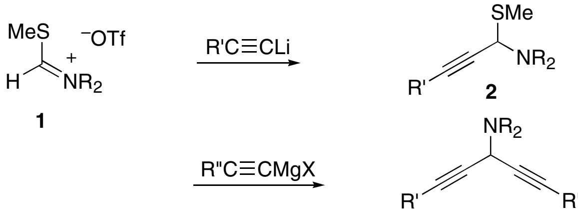
Abstract—The reaction of thioiminium salts with zinc acetylides took place at 60 °C to give 3-amino-1-sulfenyl-1,4-enynes in moderate to good yields. Two molecules of acetylides were incorporated into the products. Nucleophilic attack of zinc acetylides to thioiminium salts may initially occur to form alkynyl *S*,*N*-acetals, followed by their [1,3]-rearrangement to give 3-sulfenyl-1-aminoallenes.

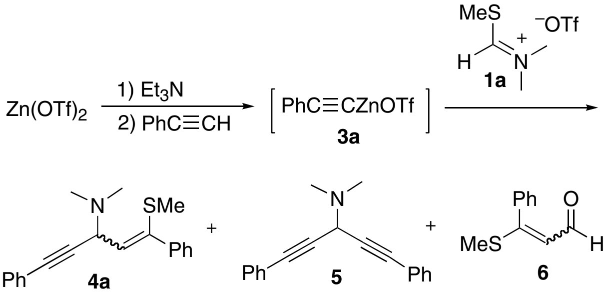
Addition of metal acetylides to imines[1] and iminium salts[2] is one of the most relevant methods for the syntheses of propargyl amines. In these reactions, one molecule of metal acetylides is efficiently introduced to iminium salts. In contrast, we have recently disclosed the synthesis of propargyl amines from thioiminium salts **1** (Eq. 1). Two different types of organometallic reagents, that is, lithium and magnesium acetylides, are introduced to salts **1** in one operation via alkynyl *S*,*N*-acetals **2**.[3]



(1)

The subtle difference of the reactivity of two organometallic reagents toward **1** and **2** has enabled the selective transformation in Eq. 1. The reactivity of **1** and **2** toward various organometallic reagents is of further interest. We report here the addition reaction of zinc acetylides to thioiminium salts leading to 3-amino-1-sulfenyl-1,4-enynes.

At the outset, to zinc acetylide **3a** in situ generated from $Zn(OTf)_2$, phenylacetylene, and Et_3N[4] was added thioiminium salt **1a**, and the mixture was stirred at room temperature for 5 h to give three types of products **4**–**6** at most in 44% combined yields. To obtain one of the three products more selectively, the reaction was examined under various reaction conditions. Consequently, the reaction of **1a** with 2 equiv of **3a** at 60 °C gave 3-amino-1-sulfenyl-1,4-enyne **4a** in 51% yield predominantly as the *Z*-isomer. Furthermore, 20 mol % of $Zn(OTf)_2$ was enough to run the reaction in Eq. 2, and the product **4a** was obtained in nearly equal yield.



(2)

A variety of thioiminium salts **1** and zinc acetylides **3** were subjected to the reaction. The results are summarized in Table 1.[5,6] In all cases, the products where

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Keywords: Thioamides; Thioiminium salts; Zinc acetylides; Alkynyl *S*,*N*-acetals; 3-Amino-1-sulfenyl-1,4-enynes; [1,3]-Rearrangement; 3-Sulfenyl-1-aminoallenes.

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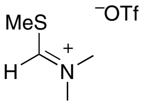
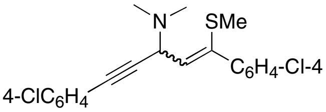
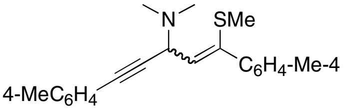
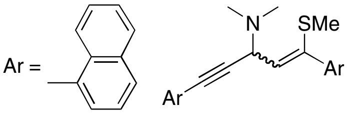
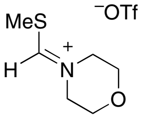
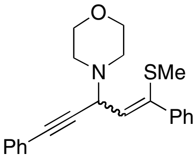
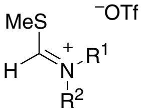
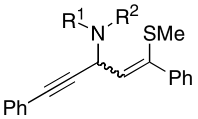
Table 1. Reaction of thioiminium salts **1** with zinc acetylides **3**[a]

Entry	Thioiminium salt **1**	Zinc acetylide **3**	Product **4**	Yield[b] (%)	Ratio[c] (*E*:*Z*)
1	 **1a**	$4\text{-ClC}_6\text{H}_4\text{C}{\equiv}\text{CZnOTf}$ **3b**	 **4b**	(34%)[d,e]	25:75
2	**1a**	$4\text{-MeC}_6\text{H}_4\text{C}{\equiv}\text{CZnOTf}$ **3c**	 **4c**	(66%)[d] 50%	33:67
3	**1a**	ArC≡CZnOTf **3d**	 **4d**	54%	0:100
4[f]	 **1b**	**3a**	 **4e**	(51%)[d,g]	36:64
					
5[e]	**1c** $R^1 = R^2 = \text{CH}_2\text{CH}{=}\text{CH}_2$	**3a**	**4f**	65%	37:63
6[e]	**1d** $R^1 = \text{CH}_2\text{CH}{=}\text{CH}_2$, $R^2 = \text{CH}_2\text{Ph}$	**3a**	**4g**	66%	33:67
7[e]	**1e** $R^1 = R^2 = \text{CH}_2\text{Ph}$	**3a**	**4h**	(78%)[d] 64%	36:64

[a] The reaction was carried out unless otherwise noted: thioiminium salts **1** (1 mmol) were added to zinc acetylides generated from Zn(OTf)_2 (0.2 mmol), acetylene (2.1 mmol), and Et_3N (2.1 mmol) in toluene (3.5 mL), and the mixture was stirred at 60 °C for 2 h.

[b] Isolated yields.

[c] The ratio was determined by ^{1}H NMR spectra.

[d] The yield was determined by ^{1}H NMR spectra.

[e] The product **4b** and 3-aryl-3-methylsulfenylpropenal were obtained in 52% combined yields.

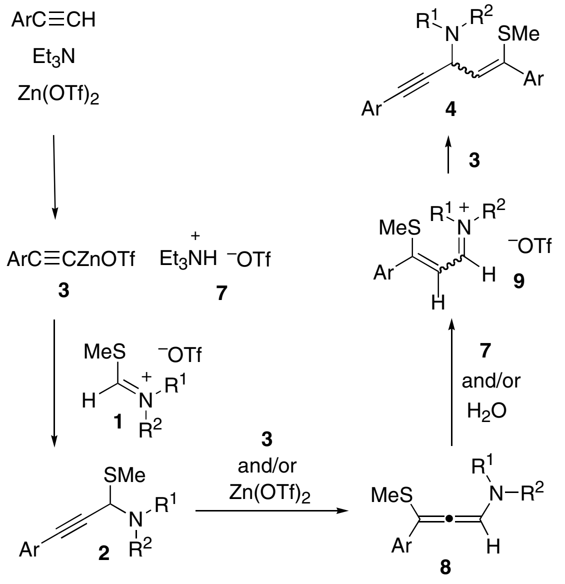
[f] Zn(OTf)_2 (2 mmol) was used.

[g] The product **4e** and 4-(1,5-diphenylpent-1,4-diynyl)morpholine were obtained in 75% combined yields.

two molecules of acetylides were incorporated to **1** were obtained. Zinc acetylides **3b–d** derived from 4-chloro-,4-methylphenylacetylenes, and 1-naphthylacetylene, 20 mol % of Zn(OTf)_2, and Et_3N reacted with thioiminium salt **1a** to give the corresponding 3-amino-1-sulfenyl-1,4-enynes **4b–d** in 34–66% yields (entries 1–3), although the use of aliphatic acetylenes gave complex mixtures. As for the reaction with **3d**, *Z*-isomer of **4d** was selectively obtained probably because of the steric reason. Thioiminium salts **1b–e**, where morpholino, diallylamino, allyl benzylamino, and dibenzylamino groups were attached to the carbon atom bearing MeS group, were also reacted with zinc acetylide **3a** (entries 4–7). The stoichiometric amounts of Zn(OTf)_2 were necessary to perform these reactions effectively.

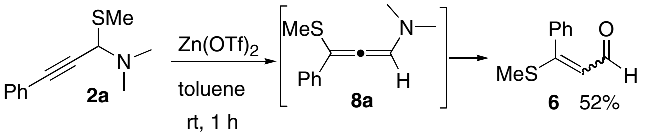
The reaction pathway of the present reaction is proposed in Scheme 1. The reaction of Zn(OTf)_2 and terminal acetylenes takes place in the presence of Et_3N to form zinc acetylides **3** and ammonium triflate **7**. Then, **3** attacks to thioiminium salts **1** to give alkynyl *S*,*N*-acetals **2**. Lewis acids such as Zn(OTf)_2 and/or **3** mediate [1,3]-rearrangement of alkynyl *S*,*N*-acetals **2** to form 3-sulfenyl-1-aminoallenes **8**,[7,9] followed by the protonation of **8** to give iminium salts **9**. Finally, the second molecule of zinc acetylides **3** adds to salts **9** to end up the formation of **4**.

The following two experiments have supported some steps of the proposed reaction pathway. Initially, the isolated alkynyl *S*,*N*-acetal **2a** was reacted with

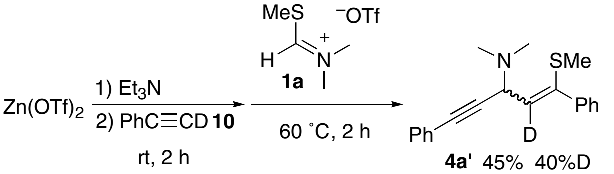


Scheme 1.

$Zn(OTf)_2$ to give α,β-unsaturated aldehyde **6**, which may be formed by the hydrolysis of 3-sulfenyl-1-aminoallene **8a** (Eq. 3). Secondly, deuterated phenylacetylene **10** was used in the present reaction (Eq. 4). As a result, acetylenic deuterium of **10** was partly transferred to the alkenyl carbon atom of **4a′**.[10]



(3)



(4)

In summary, we have demonstrated the addition reaction of zinc acetylides in situ generated from aromatic terminal acetylenes, $Zn(OTf)_2$, and Et_3N to thioiminium salts. Two molecules of acetylides were incorporated to the salts to give 3-amino-1-sulfenyl-1,4-enynes predominantly as *Z*-isomers. The reaction may involve [1,3]-rearrangement of alkynyl *S*,*N*-acetals leading to 3-sulfenyl-1-aminoallenes. Further studies on properties and reactivity of reactive species with organosulfur functionalities are underway.

Acknowledgements

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References and notes

1. For recent examples of the reaction of acyclic imines with metal acetylides, see: (a) Aubrecht, K. B.; Winemiller, M. D.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 11084; (b) Moroni, M.; Koksch, B.; Osipov, S. N.; Crucianelli, M.; Frigerio, M.; Bravo, P.; Burger, K. *J. Org. Chem.* **2001**, *66*, 130; (c) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638; (d) Meva'a, L. M.; Ndom, J. C.; Happi, E. N. *Bull. Chem. Soc. Ethiopia* **2002**, *16*, 169; (e) Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 3273; (f) Jiang, B. S. Y.-G. *Tetrahedron Lett.* **2003**, *44*, 6767; (g) Fischer, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1497; (h) Ji, J.-X.; Au-Yeung, T. T.-L.; Wu, J.; Yip, C. W.; Chan, A. S. C. *Adv. Synth. Catal.* **2004**, *346*, 42.
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4. Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373.
5. A typical experimental procedure for the reaction of in situ generated zinc acetylides with thioiminium salts: a 20 mL two necked flask was placed with $Zn(OTf)_2$ (73 mg, 0.2 mmol) and dried under high vacuum. To this were added toluene (1.5 mL) and triethylamine (0.3 mL, 2.1 mmol). The resulting mixture was vigorously stirred at 23 °C for 2 h, and to this was added phenylacetylene (0.24 mL, 2.1 mmol) via syringe in one portion. On the other hand, to a toluene (2 mL) solution of *N*,*N*-dimethyl thioformamide (0.085 mL, 1.0 mmol) was added methyl triflate (0.11 mL, 1.0 mmol) at room temperature, and the mixture was stirred at this temperature for 30 s. Then, this solution was added to the suspension of Zn acetylide via cannula, and this was stirred at 60 °C for 2 h. The resulting mixture was poured into a saturated aqueous solution of NH_4Cl and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane–EtOAc = 1:1) to give 3-amino-1-sulfenyl-1,4-enyne **4a** (0.157 g, 51%, *E*:*Z* = 22:78) as a dark red oil: *E*-isomer: ^1H NMR ($CDCl_3$): δ 2.16 (s, 3H, SMe), 2.23 (s, 6H, NMe_2), 3.91 (d, $J = 9.6$ Hz, 1H, CH), 5.54 (d, $J = 9.6$ Hz, 1H, *H*C=C), 7.22–7.24 (m, 6H, Ar), 7.25–7.33 (m, 4H, Ar). *Z*-Isomer: ^1H NMR ($CDCl_3$): δ 1.89 (s, 3H, SMe), 2.36 (s, 6H, NMe_2), 4.79 (d, $J = 8.8$ Hz, 1H, CH), 5.95 (d, $J = 8.8$ Hz, 1H, *H*C=C), 7.35–7.40 (m, 6H, Ar), 7.45–7.47 (m, 4H, Ar); HRMS calcd for $C_{20}H_{21}NS$: 307.1395, found: 307.1411.
6. The stereochemistry of product **4a** was determined by phase sensitive NOESY spectroscopy. The chemical shifts of **4** were calculated with substituents constants for chemical shifts of substituted ethylenes. Then, the stereochemistry of **4** was estimated by comparing these values with the observed values of **4**.
7. Although the thermal [1,3]-rearrangement of alkynyl *S*,*N*-acetal having cyclohexylsulfenyl group was reported,[8] Lewis acid mediated [1,3]-rearrangement of alkynyl *S*,*N*-acetals has not yet been reported.
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9. The reaction of isolated alkynyl *S*,*N*-acetals **2** with zinc acetylides gave **4** in lower yields. The results have implied the importance of the in situ generation of **2** in the present reaction.
10. This partial incorporation of deuterium has also suggested that the protonation of **8** takes place with small amounts of water contained in the reaction mixture.