Double Nucleophilic Addition of Thiols and Allylstannane to α, β-Unsaturated Aldimines Promoted by Titanium Tetrachloride

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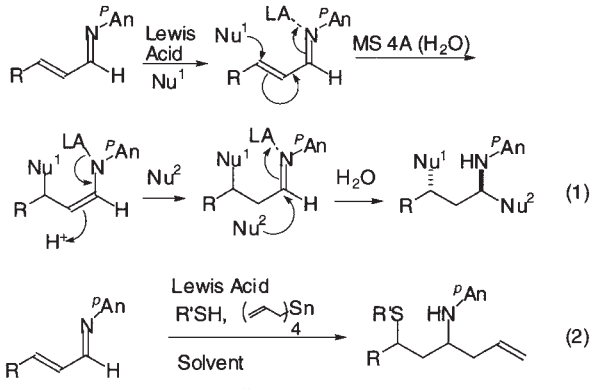
In the presence of $TiCl_4$, a mixture of thiol and tetraallyltin underwent 1,4- and 1,2-addition, respectively, with α, β-unsaturated imines to give 6-sulfenyl-4-amino-1-alkenes in good yields.

Conjugate addition of thiols to α, β-unsaturated carbonyl compounds constitutes one of the most popular modes of reactions in organic synthesis, since thiols are prone to add to electron deficient unsaturations.[1,2] In contrast, its imino versions have received little attention, since the addition products to α, β-unsaturated imines, β-sulfenyl imines and/or their enamine counterparts, are readily hydrolyzed to the parent β-sulfenyl carbonyl compounds.[3] We have recently introduced an efficient method for the introduction of two nucleophiles into α, β-unsaturated aldimines to furnish functionalized amines in a one-pot procedure, where the presence of a limited amount of water proved to be essential (eq 1).[4] In an effort to utilize the addition product of thiols to α, β-unsaturated aldimines, we carried out a similar double nucleophilic addition reaction using thiols and tetraallyltin which actually gave better results than trialkylallyltins or trialkylsilyl counterparts, and have now found that this procedure gives a convenient method for the utilization of intermediary imino functionality. This paper describes a double nucleophilic addition reaction of thiols and tetraallyltin to α, β-unsaturated aldimines, where the presence of water was not necessary due to the acidic hydrogen of the thiol (eq 2).

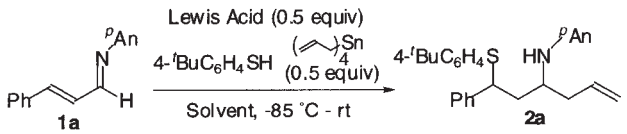


Scheme 1.

First, the best reaction conditions for the double nucleophilic addition to *N*-*p*-anisylcinnamylidenimine **1a** were investigated using 4-*t*-butylbenznethiol and tetraallyltin, and the results are summarized in Table 1.[5]

As shown in Table 1, the use of $AlCl_3$ which was the most effective Lewis acid found for the double nucleophilic addition of ketene silyl acetals also promoted the present reaction,[4b] whereas $SnCl_4$ did not induce the desired addition reaction efficiently

Table 1. Comparison of reaction conditions[a]



anti : syn

Entry	L. A.	RSH/eq	Time/h	Solvent	Yield/%[b]	Ratio[c]
1	$TiCl_4$	2.0	17.3	CH_2Cl_2	59	61 : 39
2	$AlCl_3$	2.0	17.3	CH_2Cl_2	74	58 : 42
3	$AlCl_3$	2.0	16.9	EtCN-CH_2Cl_2[d]	71	59 : 41
4	$SnCl_4$	2.0	16.8	EtCN-CH_2Cl_2[d]	22	57 : 43
5	$TiCl_4$	2.0	16.9	Toluene -CH_2Cl_2[e]	26	57 : 43
6	$TiCl_4$	2.0	17.0	EtCN-CH_2Cl_2[d]	80	56 : 44
7	$TiCl_4$	1.8	18.5	EtCN-CH_2Cl_2[d]	82	56 : 44
8	$TiCl_4$	1.5	15.7	EtCN-CH_2Cl_2[d]	79	56 : 44
9	$TiCl_4$	1.0	16.7	EtCN-CH_2Cl_2[d]	59	56 : 44
10	$TiCl_4(EtCN)_2$	2.0	15.0	CH_2Cl_2	65	62 : 38

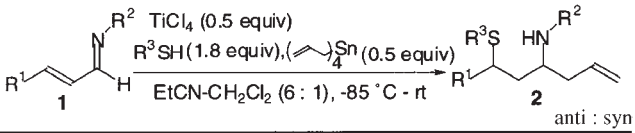
[a]Reaction was carried out according to the typical procedure.[5] [b]Isolated yield. [c]Isomer ratio determined by ^1H NMR. The relative stereochemistry was not determined. [d]EtCN : CH_2Cl_2 = 6 : 1. [e]Toluene : CH_2Cl_2 = 6 : 1..

(entries 2–4). When $TiCl_4$ was used, the effect of reaction solvent was noteworthy, and the reaction conducted in EtCN-CH_2Cl_2 (6:1) gave the desired double addition product **2a** in good yield (entries 1, 5 and 6). Due to the low solubility of the imine **1a** in EtCN, the present reaction was carried out in EtCN-CH_2Cl_2. The amount of the thiol was also important, and the best result was obtained using 1.8 equivalents of the thiol (entry 7). Precomplexed $TiCl_4(EtCN)_2$ species was not superior to $TiCl_4$ itself in EtCN-CH_2Cl_2 (entry 10). Under the optimum conditions a variety of thiols and imines participated in the present addition reaction, and the results are summarized in Table 2.

As shown in Table 2, in general, the reaction gave the double nucleophilic addition products **2** in good to excellent yields, although the diastereoselectivity was not always good. Better diastereoselectivity was obtained in the cases with imines derived from aliphatic aldehydes (entries 1–3). Regarding the substituents on the aromatic rings of the thiols examined here, pronounced effects were not observed, and in every case the double addition product was obtained in good yield (entries 1, 6, and 7). For further functional group manipulations, the thiols possessing removable substituents are preferable. For this purpose, thioacetic acid or thiobenzoic acid was subjected to the present reaction. These thiocarboxylic acids also participated in the double nucleophilic addition to give the desired products **2** in good yields (entries 9–14). In particular, when the reaction was carried out using *N*-*p*-anisylcinnamylidenimine and thioacetic acid, only *anti*-product was obtained in moderate yield (entry 9).

Removal of the acyl moiety was readily carried out using lithium aluminum hydride to give the free thiol **3** in good yield

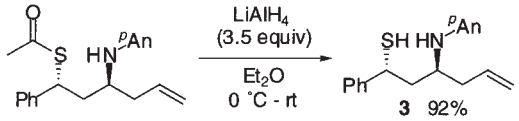
Table 2. Use of a variety of imines and thiols[a]



anti : syn

Entry	R^1	R^2	R^3	Time/h	Yield/%[b]	Ratio[c]
1	Ph	^{p}An	4-^{t}BuC$_6$H$_4$	18.5	82	56 : 44
2	Me	^{p}An	4-^{t}BuC$_6$H$_4$	16.3	68	81: 19
3	^{n}Pr	^{p}An	4-^{t}BuC$_6$H$_4$	16.7	77	73 : 27
4	Ph	Ph_2CH	4-^{t}BuC$_6$H$_4$	19.3	76	56 : 44
5	Ph	^{p}An	Ph	20.0	76	54 : 46
6	Ph	^{p}An	4-ClC$_6$H$_4$	17.0	74	52 : 48
7	Ph	^{p}An	2-ClC$_6$H$_4$	18.0	71	55 : 45
8	Ph	^{p}An	Bn	17.7	64	64 : 36
9	Ph	^{p}An	MeCO	17.0	40	100 : 0[d]
10	Ph	Ph_2CH	MeCO	18.3	82	60 : 40
11	Ph	^{p}An	PhCO	17.3	73	57 : 43[e]
12	Ph	Ph_2CH	PhCO	17.8	68	65 : 35
13	Me	^{p}An	PhCO	17.4	66	63 : 37
14	^{n}Pr	^{p}An	PhCO	17.0	54	59 : 41
15	Ph	^{p}An	MeO_2CCH_2	14.8	83	54 : 46

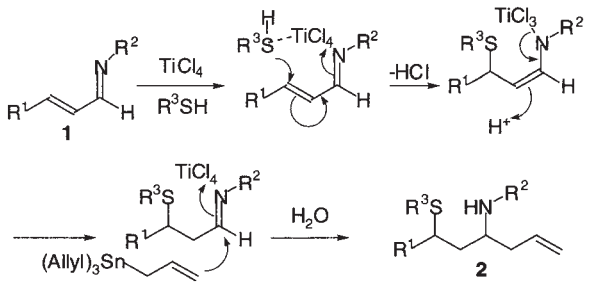
[a]Reaction was carried out according to the typical procedure.[5] [b]Isolated yield. [c]Isomer ratio determined by ^{1}H NMR. Unless otherwise noted, the relative stereochemistry was not determined. [d]*anti* : *syn* = 100 : 0.[6] [e]*anti* : *syn* = 57 : 43.[6]



Scheme 2.

(Scheme 2).

The present reaction most probably proceeds *via* the following mechanisms. First, the initial addition of the thiol is promoted by $TiCl_4$. The subsequent protonation is effected by the liberated HCl from $TiCl_4$ and the thiol to generate imino species, which in turn is attacked by the allyltin to give the double nucleophilic addition product **2** (Scheme 3).



Scheme 3.

In conclusion, the present double nucleophilic addition to α, β-unsaturated aldimines provides an easy use of intermediate, imino species, which are relatively difficult to be isolated and purified. Since thiols have relatively acidic hydrogens, this procedure does not need extra proton sources to reproduce imino functionalities, and thus provides a convenient method for the introduction of two different nucleophiles in a one-pot procedure.

This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 75th birthday.

References and Notes

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5 A typical procedure for the addition reaction: To a solution of $TiCl_4$ (1.0 M, 0.07 mL, 0.07 mmol) in EtCN (1.2 mL) was added a solution of *N*-*p*-anisylcinnamylidenimine **1a** (33.2 mg, 0.14 mmol) in CH_2Cl_2 (0.6 mL) and EtCN (0.4 mL) at −85 °C, and the mixture was stirred at −85 °C for 5 min. A mixture of 4-*t*-butylbenzenethiol (41.6 mg, 0.25 mmol) in EtCN (1.0 mL) was added to the resulting mixture during 10 min at −85 °C, and the mixture was stirred at −85 °C for 10 min. A solution of tetraallyltin (19.8 mg, 0.07 mmol) in EtCN (1.0 mL) was added to the resulting mixture during 10 min at −85 °C and the mixture was gradually warmed to room temperature during 18.5 h. Saturated aqueous $NaHCO_3$ (8.0 mL) was added to the mixture which was extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give a crude oil. Purification on silica gel TLC (toluene : *n*-hexane : ethyl acetate = 30 : 10 : 1 as an eluent) gave 1,4-1,2-adduct **2a** (50.9 mg, 82%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ = 1.25 (s, 3.96H), 1.27 (s, 5.04H), 1.96–2.28 (m, 4H), 3.13 (br, 1H), 3.21–3.22 (m, 0.44H), 3.56–3.61 (m, 0.56H), 3.72 (s, 1.32H), 3.73 (s, 1.68H), 4.32 (dd, J = 7.3 and 6.7 Hz, 0.56H), 4.41 (dd, J = 10.4 and 4.9 Hz, 0.44H), 4.96-5.07 (m, 2H), 5.62–5.78 (m, 1H), 6.37–6.40 (m, 0.88H), 6.46–6.48 (m, 1.12H), 6.69–6.73 (m, 2H), 7.12-7.28 (m, 9H).

6 Determination of the relative stereochemistry was carried out as follows: Each isomer was isolated on silica gel TLC, and it was treated with $LiAlH_4$ to give the free thiol, which was converted into the thiazolidine as in the following typical example. Examination of the coupling constants on ^{1}H NMR indicates the relative stereochemistry.