

One-Step Hydroamidation of a Schiff Base with Trichlorosilane

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We have found that the treatment of a Schiff base (**2**) with trichlorosilane and chloroacetyl chloride results in a highly active chloroacetamide herbicide (**1**) in an excellent yield. This one-step hydroamidation reaction of a Schiff base is a useful synthetic method.

Recently, we have reported on a highly active chloroacetamide herbicide (**1**) for paddy field rice.¹⁾ The compound (**1**) has previously been synthesized in two steps (a reducing step and a chloroacetylating step) from a Schiff base (**2**) as shown in Scheme 1.

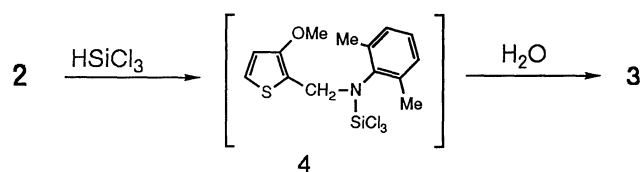
During the course of our studies, we found that treatment of a Schiff base (**2**) with trichlorosilane and chloroacetyl chloride produces the chloroacetamide (**1**) in one step with an excellent yield. Further studies have revealed this method to be quite general and versatile for the synthesis of amides from Schiff bases.

Results and Discussion

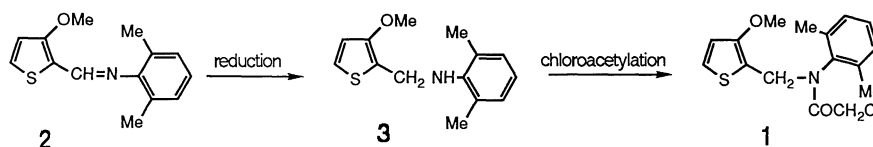
One-Step Hydroamidation of a Schiff Base (2). The reduction of a Schiff base (**2**) has previously been accomplished by two steps as shown in Scheme 2. The *N*-trichlorosilyl adduct (**4**) can be converted to the amide without hydrolysis by treatment with chloroacetyl chloride. These results are summarized in Table 1. As we expected, the trichlorosilylation of **2** in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, followed by the chloroacetylation of the

intermediary silyl adduct, resulted in the chloroacetamide (**1**) (Entry 2). Further work established that the amide could be obtained without the $\text{BF}_3 \cdot \text{Et}_2\text{O}$ catalyst (Entry 3).

We have examined the chloroacetamidation of **2** in the presence of trichlorosilane. Chloroacetyl chloride (1.1 equiv) and trichlorosilane (1.6 equiv) in benzene were added to **2** in benzene at room temperature and the mixture was heated at 40 °C for 3 h to give **1** in 97% yield. Consequently, by reacting **2** with chloroacetyl chloride in the presence of trichlorosilane in benzene, we could prepare **1** easily in an almost quantitative yield (Scheme 3).

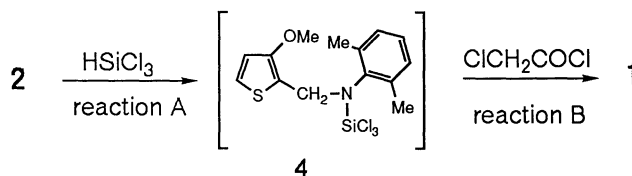


Scheme 2.



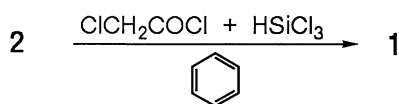
Scheme 1.

Table 1. Hydroamidation of a Schiff Base (**2**)



Entry	Reaction A ^{a)}			Reaction B ^{b)}		Yield of 1 ^{c)}
	$\text{HSiCl}_3/\mathbf{2}$	Cat.	Time/h	Temp/°C	Time/h	
1	1.5	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	6	50	1	23
2	3.0	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	6	r.t.	12	69
3 ^{d)}	1.5	None	10	50	1	74

a) Reaction was carried out at 70 °C. b) The ratio of chloroacetyl chloride to **2** was 1.1:1. c) The yield was determined by ^1H NMR. d) Reaction was carried out in an autoclave.



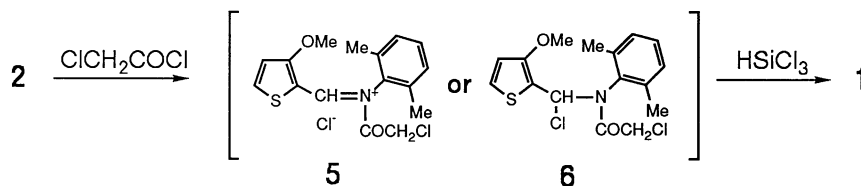
Scheme 3.

Reaction Mechanism. In order to study the mechanism of this reaction, we have measured the ^1H NMR spectra of the reactants in C_6D_6 . When the Schiff base (2) was treated with trichlorosilane in C_6D_6 at room temperature, the spectral pattern of the Schiff base did not change; it showed only an additional signal originating from trichlorosilane (at 5.59 ppm). No interaction between 2 and trichlorosilane could be observed in the benzene solution. When 2 was treated with chloroacetyl chloride in C_6D_6 at room temperature, the signal at 8.40 ppm ($\text{CH}=\text{N}$) disappeared and a signal at 3.49 ppm, attributable to the NCOCH_2Cl group ($\delta=3.72$ in 1), was observed. This indicates that chloroacetyl chloride reacts or interacts with 2. When trichlorosilane was added to this mixture, a new signal at 4.89 ppm (CH_2-N) appeared. The spectrum of this product was the same as that of 1. From these observations, it has been concluded that 2 and chloroacetyl chloride react to form an iminium salt-type compound (5) or its chlorine adduct (6) as an intermediate which

further reacts with trichlorosilane to form the desired amide compound 1 as shown in Scheme 4.

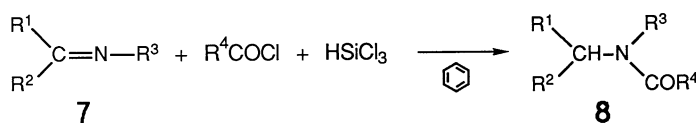
Generalization of the One-Step Hydroamidation of Schiff Bases. We have extensively studied a new preparative method of an amide from a Schiff base. The results are summarized in Table 2. A Schiff base prepared by the reaction of an aldehyde or a ketone with an amine was treated with an acyl chloride and trichlorosilane in benzene. The amide was obtained in a good yield. According to the ^1H NMR spectra, the products formed were highly pure before purification. When an acyl chloride was treated with a Schiff base at room temperature, a slight exothermic reaction occurred with the formation of either an iminium salt or its chlorine adduct. This was demonstrated by ^1H NMR studies of compound 8a. The signal from the methine proton ($\text{CH}=\text{N}$) at 8.33 ppm disappeared and a new signal at 7.88 ppm appeared after the addition of chloroacetyl chloride in CDCl_3 . In the case of 8i, no exothermic reaction took place. When the reaction was carried out in acetonitrile instead of benzene, 8a was obtained in 53% yield accompanied by some decomposed products, such as chloroacetanilide. When trifluoroacetic anhydride was employed as an acid derivative, trifluoroacetamide (8j) was produced in 76% yield.

Previously, several reports have been published on the



Scheme 4.

Table 2. One-Step Hydroamidation of a General Schiff Base (7)



Reaction	R^1	R^2	R^3	R^4	Conditions		Yield ^{a)} %
					Temp/ $^{\circ}\text{C}$	Time/h	
a	C_6H_5	H	C_6H_5	CH_2Cl	30	0.5	97
b	C_6H_5	H	$\text{CH}_2\text{CH}_2\text{OC}_2\text{H}_5$	CH_2Cl	40	1	80
c	2-MeOC $_6\text{H}_4$	H	2,6-Me $_2\text{C}_6\text{H}_3$	CH_2Cl	35	1	83
d	2-Thienyl	H	C_4H_9	CH_2Cl	30	1	91
e	2-Furyl	H	C_2H_5	CH_2Cl	40	2	72
f	C_4H_9	H	$\text{C}_{10}\text{H}_{21}$	CH_2Cl	30	1	77
g	C_6H_5	H	C_6H_5	CH_3	r.t.	3	78
h	3-MeO-2-thienyl	H	2,6-Me $_2\text{C}_6\text{H}_3$	CH_3	r.t.	5	92
i	C_6H_5	H	C_6H_5	C_6H_5	50	6	91
j ^{b)}	C_6H_5	H	C_6H_5	CF_3	45	3	76
k	C_6H_5	Me	C_6H_5	CH_2Cl	50	6	92
l	C_6H_5	Me	C_6H_5	CH_3	60	2	82

a) The yield was determined by ^1H NMR after the product was dried. b) Trifluoroacetic anhydride was used as an acyl derivative.

Table 1. ^1H NMR Data of Amides

Compound	^1H NMR (CDCl_3 , δ)
8a	3.80 (2H, s, COCH_2), 4.85 (2H, s, CH_2N), 6.85—7.40 (10H, m, aromatic H)
8b	1.11 (3H, t, $J=8$ Hz, CH_3), 3.15—3.60 (6H, m, $\text{NCH}_2\text{CH}_2\text{OCH}_2$), 4.05 and 4.28 (2H, COCH_2), 4.61 (2H, s, CH_2N), 7.18 (5H, s, aromatic H)
8c	1.90 (6H, s, $\text{CH}_3\times 2$), 3.42 (3H, s, OCH_3), 3.61 (2H, s, COCH_2), 4.86 (2H, s, CH_2N), 6.55—7.42 (7H, m, aromatic H)
8d	0.75—1.75 (7H, br, $\text{CH}_2\text{CH}_2\text{CH}_3$), 3.05—3.50 (2H, br, NCH_2), 4.06 (2H, s, COCH_2), 4.63 (2H, s, CH_2N), 6.75—7.25 (3H, m, aromatic H)
8e	1.05 and 1.16 (3H, t, $J=7$ Hz, CH_3), 3.39 (2H, q, $J=7$ Hz, NCH_2), 4.10 and 4.22 (2H, COCH_2), 4.51 (2H, s, CH_2N), 6.25 (2H, s, aromatic H), 7.31 (1H, s, aromatic H)
8f	0.70—1.90 (26H, br, $\text{CH}_2\times 10$ and $\text{CH}_3\times 2$), 3.10—3.50 (4H, br, CH_2NCH_2), 4.06 (2H, s, COCH_2)
8g	1.83 (3H, s, CH_3), 4.81 (2H, s, CH_2N), 6.60—7.40 (10H, m, aromatic H)
8h	1.17 (3H, s, CH_3), 2.01 (6H, s, $\text{CH}_3\times 2$), 3.46 (3H, s, OCH_3), 4.80 (2H, s, CH_2N), 6.65 (1H, d, $J=6$ Hz, thienyl H), 7.07 (1H, d, $J=6$ Hz, thienyl H), 7.06 (3H, s, aromatic H)
8i	5.10 (2H, s, CH_2N), 6.70—7.40 (15H, m, aromatic H)
8j	4.88 (2H, s, CH_2N), 6.80—7.40 (10H, m, aromatic H)
8k	1.42 (3H, d, $J=7$ Hz, CH_3), 3.68 (2H, s, COCH_2), 6.20 (1H, q, $J=7$ Hz, CHN), 7.16 (10H, br, aromatic H)
8l	1.41 (3H, d, $J=7$ Hz, CH_3), 1.77 (3H, s, CH_3), 6.30 (1H, q, $J=7$ Hz, CHN), 7.18 (10H, br, aromatic H)

preparation of amides from Schiff bases using hydrosilanes.^{2,3)} However, these reactions required a catalyst, such as a rhodium compound, and required several steps.

This one-step reaction is applicable to the reaction of a wide range of Schiff bases with a variety of carboxylic acid derivatives.

Experimental

The IR spectra were measured with a Hitachi I-2000 spectrometer. The ^1H NMR spectra were measured in a CDCl_3 solution with a Hitachi R-1500 spectrometer using tetramethylsilane as an internal standard. The mass spectra were obtained on a Hitachi M-80 spectrometer.

Synthesis of the Schiff Base (2). 3-Methoxy-2-thiophene-carbaldehyde (18.4 g, 0.13 mol), 2,6-dimethylaniline (15.6 g, 0.13 mol), benzene (30 ml), and a catalytic amount of $\text{BF}_3\cdot\text{Et}_2\text{O}$ were added to a flask equipped with a Dean-Stark trap. The mixture was refluxed in an oil bath until the water had distilled out. The resulting yellow liquid (31.1 g, 99% yield) was composed of *N*[(3-methoxy-2-thienyl)methylene]-2,6-dimethylaniline which boiled at $144^\circ\text{C}/0.1\text{ mmHg}$ (1 mmHg = 133.322 Pa). ^1H NMR (CDCl_3) δ =2.13 (6H, s, CH_3), 3.78 (3H, s, OCH_3), 6.77—7.31 (5H, aromatic H), and 8.29 (1H, s, $\text{CH}=\text{N}$); IR (KBr) 1640 cm^{-1} ($\text{CH}=\text{N}$); MS m/z 245 (M^+). Other Schiff bases were prepared from aldehydes or ketones by reaction with amines according to an established method similar to that described above.

Reduction of 2 with Trichlorosilane Followed by Chloroacetamidation. To a flask were added **2** (2.48 g, 10 mmol), trichlorosilane (4.00 g, 30 mmol), benzene (20 ml), and a catalytic amount of $\text{BF}_3\cdot\text{Et}_2\text{O}$. The mixture was stirred for 1 h at room temperature and then heated in an oil bath (70°C) for 6 h. A solution of chloroacetyl chloride (1.19 g, 11 mmol) in benzene (10 ml) was then gradually added dropwise with stirring at room temperature. This mixture was stirred overnight at room temperature. The low-boiling components were evaporated, and the resulting viscous liquid was dissolved in benzene, cooled to 5°C , and neutralized with aqueous potassium carbonate. The organic layer was extracted with benzene and dried over sodium sulfate. The benzene was then

distilled out and the resulting viscous liquid was dried under reduced pressure to give a brown solid (2.29 g, 69% yield) composed of **1**.

One-Step Hydroamidation of 2. Compound **2** (3.80 g, 15 mmol) and benzene (25 ml) were combined in a flask. A solution of trichlorosilane (3.58 g, 26 mmol) and chloroacetyl chloride (1.90 g, 17 mmol) in benzene (10 ml) was gradually added dropwise while stirring at 5°C . The mixture was heated in an oil bath (40°C) for 3 h, then stirred for 1 h at room temperature. The low-boiling components were evaporated and the resulting liquid was dried under reduced pressure to give a brown solid (5.03 g, 97% yield) composed of **1**. ^1H NMR (CDCl_3) δ =1.95 (6H, s, CH_3), 3.50 (3H, s, OCH_3), 3.72 (2H, s, COCH_2Cl), 4.75 (2H, s, CH_2N), 6.55 (2H, q, thienyl H), and 7.00—7.45 (3H, m, aromatic H); IR (KBr) 1670 cm^{-1} ($\text{C}=\text{O}$); MS m/z 323 (M^+), 288 (M^+-Cl), and 246 ($\text{M}^+-\text{COCH}_2\text{Cl}$).

One-Step Hydroamidation of a Schiff Base. The general procedure is as follows. A Schiff base (10 mmol) and benzene (15 ml) were combined in a flask. A solution of trichlorosilane (15—20 mmol) in benzene and a carboxylic acid derivative (11—12 mmol) in benzene were gradually added dropwise while stirring at 5 — 10°C . The mixture was heated in an oil bath for several hours, and then stirred for 1 h at room temperature. The low-boiling components were evaporated, and the resulting viscous liquid was dissolved in benzene, cooled to 5°C , and neutralized with aqueous potassium carbonate. The organic layer was extracted with benzene and dried over sodium sulfate. The benzene was then distilled out and the resulting viscous liquid was dried under reduced pressure to give the desired amide. The ^1H NMR data of the amides obtained by this procedure are summarized in Table 3.

References

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