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Diphenylsilane Reduction of C=O and C=N Bearing Electron-Withdrawing Group in the Presence of Aluminum(III) Chloride

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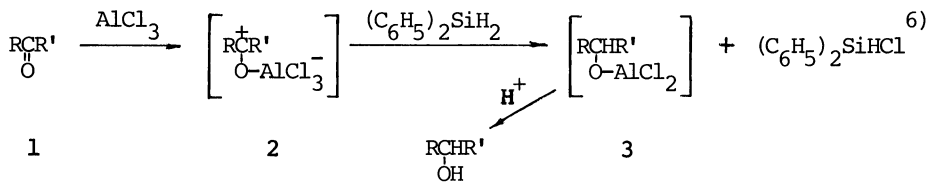
Several α-keto esters and methyl *N*-*p*-tolylsulfonyl-2-aryl-2-iminoacetates were reduced to the corresponding α-hydroxy esters and methyl *N*-*p*-tolylsulfonyl-2-arylglycinates in high yields by a combination of aluminum(III) chloride and diphenylsilane under operating conditions in which diphenylsilane was added to the pre-formed substrate-aluminum(III) chloride complex in dichloromethane and the mixture stirred. The case of an exactly equivalent amount of aluminum(III) chloride as the substrate resulted in good results.

The usefulness of silicon hydrides as a hydrogen source in reduction, including asymmetric reduction, of an unsaturated functional group, such as C=O, is well-known.[1] For example, the reduction of the C=O group of aldehydes and ketones by silicon hydride in the presence of KF or CsF has been reported in the literature.[2] It is likely that the silicon hydrides reacted with fluoride ions generated from KF or CsF to form complex ions from which a hydride migrated to aldehyde or ketone, leading to the formation of the corresponding alcohols. On the other hand, the reduction of the C=O group of aromatic aldehydes and ketones to the methylene group by triethylsilane in trifluoroacetic acid has been proposed.[3] The coordination of a proton from trifluoroacetic acid to the oxygen of the C=O group facilitates a subsequent hydride transfer from triethylsilane to the carbon of the C=O group. Reactions of the aldehydes or ketones with a combination of triethylsilane and concentrated hydrochloric acid (or aqueous sulfuric acid) providing the corresponding alcohols can also be accounted for by the almost same mechanism.[4] Regarding a combination of silicon hydride and Lewis acid, only that of triethylsilane and gaseous boron trifluoride has been used for the reduction of aldehydes or ketones, where the corresponding alcohols or hydrocarbon products have been obtained.[5] These studies concerning the silicon hydride reduction of aldehydes or ketones suggest that, for the occurrence of such a reduction, an effective activation of either silicon hydride or aldehyde (or ketone) is necessary before a hydride transfer. Reduction using silicon hydride and KF (or CsF) illustrates the activation of silicon hydride and that using triethylsilane and trifluoroacetic acid, concentrated hydrochloric acid, aqueous sulfuric acid, or gaseous boron trifluoride illustrates the activation of aldehyde or ketone. The catalytic hydrogenation[1] of aldehydes or ketones by silicon hydride over a noble metal catalyst, such as nickel(II) chloride or ruthenium(II) chloride, providing the corresponding alcohols or alkyl silyl ethers, seems to be another example which illustrates the activation of silicon hydride. It is clear from the above-mentioned survey that only the combination of triethylsilane and gaseous boron trifluoride has been utilized to accomplish silicon hydride reduction, and that the capability of many such combinations of silicon hydrides and Lewis acids which effect silicon hydride reduction, have not been examined.

Thus, an acetophenone-alminum(III) chloride complex in dichloromethane was allowed to react with a slight excess of triethylsilane or diphenylsilane at room temperature over a period of 24 h. Acetophenone, however, failed to undergo reduction and was recovered unaltered. A complex of nonenolizable benzophenone with aluminum(III) chloride in dichloromethane was similarly treated with a slight excess of triethylsilane or diphenylsilane. In this case, the starting benzophenone was also recovered unaltered. However, we have found that such a combination of silicon hydrides and Lewis acids is well fitted to a silicon hydride reduction of the C=O group bearing an electron-withdrawing group. Among the easily available silicon hydrides and Lewis acids, diphenylsilane and aluminum(III) chloride promoted the reduction most easily and efficiently.

Results and Discussion

When a complex of α-keto ester (**1a**, **1b**, **1c**, or **1d**) with aluminum(III) chloride [prepared by allowing both components (1:1 molar ratio) to react in dichloromethane] in dichloromethane was treated with a slight excess of diphenylsilane, reduction occurred smoothly, while providing the corresponding α-hydroxy ester in excellent yield. By almost the same procedure, benzil(**1e**) and 2,2,2-trifluoroacetophenone (**1f**) were reduced to benzoin(**4e**) and α-(trifluoromethyl)benzyl alcohol(**4f**), respectively, in moderate yields (Table 1). If aluminum(III) chloride and diphenylsilane were used in excess in the above reactions, hydrogenation proceeded further, providing compound RCH_2R' by which the desired **4** was appreciably contaminated. If exactly equivalent amounts of aluminum(III) chloride and the substrate (**1**) were used, however, the obtained product was the



Scheme 1.

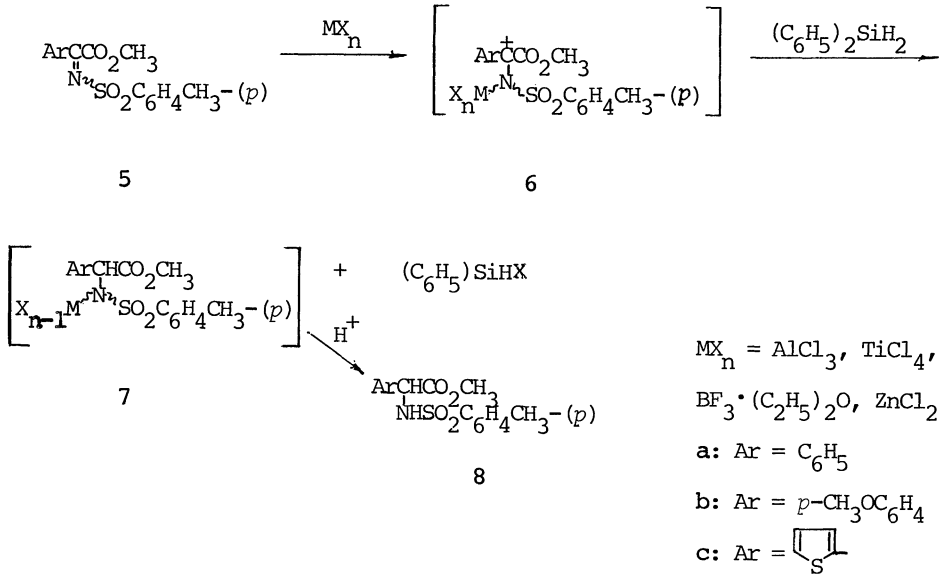
Table 1. Diphenylsilane Reduction of C=O Group Bearing Electron-Withdrawing Group in the Presence of Aluminum(III) Chloride

Substrate (1)	Reaction conditions	Product (4)	Yield[a]/%
1a	CH_2Cl_2, 20 °C, 20 h	**4a**[b]	90
1b	CH_2Cl_2, 20 °C, 18 h; 40 °C, 4 h	**4b**	78
1c	CH_2Cl_2, 20 °C, 18 h; 40 °C, 11 h	**4c**	64
1d	CH_2Cl_2, 20 °C, 19 h	**4d**	90
1e	CH_2Cl_2, 20 °C, 24 h	**4e**	77
1f	CH_2Cl_2, 20 °C, 22 h	**4f**[c]	30

a) Isolated yield by column chromatography on silica gel. b) Identified by direct comparison with commercially available methyl mandelate. c) Identified by direct comparison with commercially available α-(trifluoromethyl)benzyl alcohol.

desired **4** alone. This is the principal advantage of the present reaction, although it is applicable only for the nonenolizable α-keto esters and related compounds. When the reduction of **1b** was carried out by adding 1 equivalent of alminum(III) chloride to the **1b**-diphenylsilane mixture in dichloromethane followed by stirring under the conditions described in Table 1, the yield of **4b** was greatly decreased. The electron-donating effect of CH_3O group of intermediate **2b** probably served to slow down the rate of hydride transfer from diphenylsilane, so that a side-reaction between aluminum(III) chloride and diphenylsilane forming an ate-like complex[7] occurred competitively. With other starting substrates than **1b**, however, the yields of **4** were not decreased, even if the above procedure was adopted, meaning that, in these cases, the conversion of **1** to **2** occurred more rapidly than that of diphenylsilane to the ate-like complex with aluminum(III) chloride. The employment of triethylsilane instead of diphenylsilane under the same conditions decreased the yields of **4** to one half or less.

In the course of searching for substrates which are capable of undergoing such a diphenylsilane reduction in the presence of aluminum(III) chloride, we found that methyl *N*-*p*-tolylsulfonyl-2-aryl-2-iminoacetates (**5**) are suitable for producing the required result.[8] To again make sure that aluminum(III) chloride promotes the reduction of **5** most efficiently, a complex of methyl *N*-*p*-tolylsulfonyl-2-imino-2-phenylacetate(**5a**) with a Lewis acid [prepared by allowing both components (1:1 molar ratio) to react in dichloromethane] was allowed to react with a slight excess of diphenylsilane under the conditions described in Table 2. Among the aluminum(III) chloride, titanium(IV) chloride, boron trifluoride–diethyl ether-(1/1) and zinc(II) chloride which were examined, the former two were most efficient. In the case of zinc(II) chloride, only a 48% yield of methyl *N*-*p*-tolylsulfonyl-2-phenylglycinate(**8a**) was obtained; the starting **5a** was recovered, suggesting the poor coordinating ability of zinc(II) chloride to **5a**. Thus, the complex of methyl *N*-*p*-tolylsulfonyl-2-imino-2-(*p*-methoxyphenyl)-acetate(**5b**) with aluminum(III) chloride as well as that of methyl *N*-*p*-tolylsulfonyl-2-imino-2-(2-thienyl)acetate(**5c**) with aluminum(III) chloride, both of which were similarly prepared, as mentioned above, were allowed to react with a slight excess of diphenylsilane in dichloromethane under the conditions described in Table 2. The corresponding hydrogenated compounds, **8b** and **8c**, were obtained as the sole products. Also in these cases, exactly 1 equivalent of aluminum(III) chloride must be used to the substrate. If aluminum-(III) chloride was used in excess, the yields of **8a—c** decreased as the final result, due to a further reduction



Scheme 2.

Table 2. Silicon Hydride Reduction of C=N Group of Methyl *N*-*p*-Tolylsulfonyl-2-aryl-2-iminoacetates (**5**) in the Presence of Lewis Acid

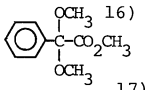
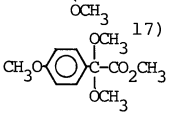
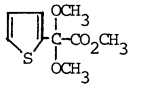
Substrate (**5**)	Lewis acid	Silicon hydride	Reaction conditions	Product (**8**)	Yield[a]/%
5a	$AlCl_3$	$(C_6H_5)_2SiH_2$	CH_2Cl_2, 20 °C, 11 h	**8a**	90
5a	$TiCl_4$	$(C_6H_5)_2SiH_2$	CH_2Cl_2, 20 °C, 19 h	**8a**	90
5a	$BF_3{\cdot}(C_2H_5)_2O$	$(C_6H_5)_2SiH_2$	CH_2Cl_2, 20 °C, 21 h	**8a**	63
5a	$ZnCl_2$	$(C_6H_5)_2SiH_2$	CH_2Cl_2, 40 °C, 36 h	**8a**	48
5b	$AlCl_3$	$(C_6H_5)_2SiH_2$	CH_2Cl_2, 20 °C, 20 h; 40 °C, 6 h	**8b**	78
5c	$AlCl_3$	$(C_6H_5)_2SiH_2$	CH_2Cl_2, 20 °C, 15 h	**8c**	86
5c	$AlCl_3$	$(C_2H_5)_3SiH$	CH_2Cl_2, 20 °C, 15 h	**8c**	85

a) Isolated yield by column chromatography on silica gel.

of an intermediate **7a—c** leading to an unfavorable elimination of the *p*-toluenesulfonamide moiety from the substrates. When the reduction of **5b** was started by adding **5b** to a homogeneous solution of aluminum(III) chloride and diphenylsilane (1 : 1.2 molar ratio) in dichloromethane, **8b** was not obtained but the starting **5b** was recovered unaltered. This is probably due to an ate-like complex formation between aluminum(III) chloride and diphenylsilane, as pointed out before.[7] When the reduction of **5b** was carried out by adding 1 equivalent of aluminum(III) chloride to the **5b**-diphenylsilane mixture in dichloromethane, followed by stirring under the conditions described in Table 2, **8b** (31%) and methyl (*p*-methoxyphenyl)acetate (20%) were obtained. The latter product seemed to be formed by a further reduction of intermediate **7b** by diphenylsilane and aluminum(III) chloride remaining in the reaction system. With **5a** and **5c** as the starting substrate, however, the yields of **8a** and **8c** were not altered by changing the operating conditions, as mentioned above. Also, the formation of methyl phenylacetate from **5a** and that of methyl (2-thienyl)-acetate from **5c** were not recognized. This means that, in these cases where **5a** and **5c** were used, the conversion of **5** to **6** prevails to that of diphenylsilane, forming an ate-like complex with aluminum(III) chloride. When the above-mentioned reactions were carried out by using triethylsilane instead of diphenylsilane as the hydride source, such a restriction of the operating conditions described above was unnecessary, since there was no interaction between aluminum(III) chloride and triethylsilane.[7] The result of a reduction of **5c** with a combination of aluminum(III) chloride and triethylsilane in dichloromethane is recorded in Table 2. However, when **5a** or **5b** was reduced by this combination in dichloromethane at room temperature over a period of 48 h, the yield of **8a** or **8b** never exceed 30%. This was the same with a combination of titanium(IV) chloride and triethylsilane. On the contraty, a combination of aluminum(III) chloride and diphenylsilane worked best for a reduction of all of **5**, while providing **8**.

We failed in the reduction of **1** or **5** by diphenylsilane in trifluoroacetic acid under the conditions

Table 3. ^1H NMR Spectral Data of the Main Compounds

Compound	^1H NMR (δ, in $CDCl_3$)
1b[10]	1.41 (t, 3H, J=7.4 Hz), 3.89 (s, 3H), 4.42 (q, 2H, J=7.4 Hz), 7.0—8.0 (m, 4H)
1c[9]	1.42 (t, 3H, J=7.4 Hz), 4.43 (q, 2H, J=7.2 Hz), 7.2—7.3 (m, 1H), 7.81 (d, 1H, J=4.8 Hz), 8.13 (d, 1H, J=4.8 Hz)
1d	1.40 (t, 3H, J=7.2 Hz), 1.67 (s, 6H), 4.42 (q, 2H, J=7.2 Hz)
4b[11]	1.22 (t, 3H, J=7.0 Hz), 3.41 (d, 1H, J=5.8 Hz), 3.80 (s, 3H), 4.16 (dq, 1H, J=26.5, 7.0 Hz), 4.25 (dq, 1H, J=26.5, 7.0 Hz), 5.09 (d, 1H, J=5.8 Hz), 6.9—7.3 (m, 4H)
4c[12]	1.28 (t, 3H, J=7.4 Hz), 3.30 (bs, 1H), 4.24 (dq, 1H, J=19.0, 7.2 Hz), 4.33 (dq, 1H, J=19.0, 7.2 Hz), 5.39 (s, 1H), 6.98 (dd, 1H, J=5.2, 5.0 Hz), 7.1 (m, 1H), 7.27 (d, 1H, J=5.0 Hz)
4d	1.36 (t, 3H, J=7.2 Hz), 1.37 (s, 3H), 1.45 (s, 3H), 3.23 (d, 1H, J=6.6 Hz), 4.07 (d, 1H, J=6.6 Hz), 4.32 (dq, 1H, J=10.8, 7.2 Hz), 4.39 (dq, 1H, J=10.8, 7.2 Hz)
5a[13]	2.42 (s, 3H), 4.08 (s, 3H), 7.3—7.9 (m, 9H)
5b	2.42 (s, 3H), 3.85 (s, 3H), 4.07 (s, 3H), 6.9—7.0 (m, 8H)
5c	2.42 (s, 3H), 4.07 (s, 3H), 7.14 (dd,1H, J=5.0, 3.9 Hz), 7.33 (d, 2H, J=8.4 Hz), 7.58 (d, 1H, J=3.9 Hz), 7.74 (d, 1H, J=5.0 Hz), 7.89 (d, 2H, J=8.4 Hz),
8a[14]	2.38 (s, 3H), 3.56 (s, 3H), 5.05 (d, 1H, J=8.0 Hz), 5.65 (d, 1H, J=8.0 Hz), 7.2—7.6 (m, 9H)
8b[15]	2.38 (s, 3H), 3.56 (s, 3H), 3.76 (s, 3H), 4.99 (d, 1H, J=7.8 Hz), 5.56 (d, 1H, J=7.8 Hz), 6.8—7.6 (m, 8H)
8c	2.40 (s, 3H), 3.62 (s, 3H), 5.31 (d, 1H, J=8.4 Hz), 5.60 (d, 1H, J=8.4 Hz), 6.8—7.0 (m, 3H), 7.2—7.3 (m, 2H), 7.67 (d, 2H, J=8.4 Hz)
 16)	3.26 (s, 6H), 3.72 (s, 3H), 7.3—7.6 (m, 5H)
 17)	3.25 (s, 6H), 3.72 (s, 3H), 3.80 (s, 3H), 6.9—7.5 (m, 4H)
	3.30 (s, 6H), 3.77 (s, 3H), 7.00 (dd, 1H, J=5.0, 3.6 Hz), 7.16 (d, 1H, J=3.6 Hz), 7.33 (d, 1H, J=5.0 Hz)

reported earlier.[3] With a combination of diphenylsilane and concentrated hydrochloric acid (or aqueous sulfuric acid), only some of the compounds among **1** and **5**, which were used in this research, provided the desired hydrogenated compounds in moderate yields under the conditions reported earlier,[4] suggesting that this combination lacks general applicability for the reduction of **1** and **5**.

Experimental

General. The ^1H NMR spectra were obtained on a Varian VXR-200 spectrometer in $CDCl_3$ with $Si(CH_3)_4$ as an internal standard. Microanalyses were performed with a Yanaco MT-3 elemental analyzer. The dichloromethane used for reduction was distilled before use. Aluminum(III) chloride and titanium(IV) chloride were purified by sublimation and distillation, respectively. Other chemicals, except for the starting substrates, were purchased and used without further purification.

Preparation of Starting Substrates. Compounds **1a**, **1e** and **1f** were purchased and purified before use. The α-keto esters, **1b** and **1c**, were prepared according to an established method.[9] The α-keto ester **1d** was synthesized by allowing lithium diisobutyramide, prepared in situ from diisobutylamine and butyllithium in tetrahydrofuran, to react with isobutyronitrile at low temperature, followed by a treatment with diethyl oxalate in ether, also at low temperature. Compounds **5a**, **5b** and **5c** could be derived easily from methyl benzoylformate(**1a**), methyl (*p*-methoxybenzoyl)formate (**9b**) and methyl 2-(2-thienyl)-2-oxoacetate (**9c**), respectively. The latter two compounds, **9b** and **9c**, were prepared according to an established method[9] with a slight modification, and identified by comparing their ^1H NMR spectra with those of **1b** and **1c**, respectively. Thus, **1a** was allowed to react with trimethyl orthoformate in methanol under the catalytic action of concentrated sulfuric acid. The obtained methyl 2,2-dimethoxy-2-phenylacetate was allowed to react with *p*-toluenesulfonamide at high temperature, affording **5a**. The compound **9b** and **9c** also underwent the same type of alteration consisting of such the acetalization with trimethyl orthoformate and condensation with *p*-toluenesulfonamide affording **5b** and **5c**, respectively.

Reduction of 1 with the Combination of Aluminum(III) Chloride and Diphenylsilane Providing 4 (General Procedure). In this case **1** (0.50 mmol) was mixed with aluminum(III) chloride (66.7 mg, 0.50 mmol) in dichloromethane (2 ml) under argon. After completely dissolving the aluminum(III) chloride, diphenylsilane (111 mg, 0.60 mmol) was added by syringe to the above-mentioned homogeneous solution. This was followed by stirring at 20 or 40 °C, as shown in Table 1, whereupon the reaction mixture was quenched with methanol (2 ml) and water (4 ml). It was extracted with dichloromethane (3×4 ml). The combined extracts were washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a residue, which was subjected to column chromatography on silica gel using 20% ethyl acetate–80% hexane as eluent.

Reduction of 5 with Some Combinations of Lewis Acids and Silicon Hydrides Providing 8 (General Procedure). One of **5** (0.50 mmol) was mixed with a Lewis acid

(0.50 mmol) in dichloromethane (4 ml) under argon. The mixture was stirred for 30 min or more for the purpose of allowing the Lewis acid to coordinate to the substrate. Then, diphenylsilane (111 mg, 0.60 mmol) or triethylsilane (70 mg, 0.60 mmol) was added by syringe to the mixture. This was followed by stirring at 20 or 40 °C, as shown in Table 2, whereupon the reaction mixture was quenched with methanol (2 ml) and water (5 ml). It was extracted with ethyl acetae (3×10 ml). The combined extracts were washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a residue, which was subjected to column chromatography on silica gel using 40% ethyl acetate–60% hexane as eluent. If necessary, the product obtained was recrystallized from ethanol.

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6) Before quenching the reaction mixture with methanol, it was submitted to GLC analysis, where the presence of diphenylsilane and dichlorodiphenylsilane was recognized and the amount of chlorodiphenylsilane seemed to be negligible. This means that chlorodiphenylsilane release a hydride more easily than diphenylsilane in the reaction; K. Yamamoto, T. Hayashi, and M. Kumada, *J. Organomet. Chem.*, **46**, C65 (1972).

7) When aluminum(III) chloride is mixed with diphenylsilane in dichloromethane, aluminum(III) chloride is dissolved in dichloromethane. This appears to be due to the formation of a complex such as ate compound. When aluminum(III) chloride is mixed with triethylsilane in dichloromethane, however, aluminum(III) chloride remains unaltered. Probably, there is no interaction between aluminum(III) chloride and triethylsilane.

8) When a few Schiff bases were submitted to the diphenylsilane reduction in the presence of aluminum(III) chloride in dichloromethane at room temperature, the yields of hydrogenated compounds were low.

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