Available online at www.sciencedirect.com

ScienceDirect

Tetrahedron Letters 48 (2007) 9120–9123

Tetrahedron Letters

Carbonyl reduction with CaH_2 and R_3SiCl catalyzed by $ZnCl_2$

Akiko Tsuhako, Jing-Qian He, Mariko Mihara, Naoko Saino and Sentaro Okamoto*

Department of Material and Life Chemistry, Kanagawa University, 3-27-1 Rokkakubashi, Kanagawa-ku, Yokohama 221-8686, Japan

Received 8 September 2007; revised 20 October 2007; accepted 25 October 2007
Available online 30 October 2007

Abstract—Ketones and aldehydes were effectively reduced to the corresponding alcohols (or their silyl ethers) by the reaction with CaH_2 and R_3SiCl in the presence of a catalytic amount of $ZnCl_2$. In the absence of the carbonyl substrate, the reagent reduced R_3SiCl to the corresponding hydrosilane under mild reaction conditions.

Reduction of carbonyl compounds with metal hydride reagents is one of the most basic transformations in organic synthesis.[1] Recently, efforts have been devoted to utilize basically inert metal hydrides LiH and CaH_2 as a reductive hydride source because they are inexpensive, stable, easy to handle, and environmentally benign: with the use of LiH, reduction (formal hydrosilylation) of ketones by cat. $ZnX_2/LiH/Me_3SiCl$[2] and hydrozincation of dienes and alkynes by cat. (cyclopentadienyl)$_2TiCl_2/2LiH/ZnI_2$[3] have been reported by Noyori et al. and by Sato et al., respectively, where a zinc hydride species derived from LiH and ZnX_2 was proposed as an active hydride. Generation of dialkylzinc hydride ate complexes from LiH and ZnR_2 has also been documented.[4] Meanwhile, although there had been no report for the use of CaH_2 as a reductive hydride, except for reactions through the synthesis of boron[5] and aluminium[6] hydrides and the reductions of sulfates to sulfides,[7] we have recently reported the first example of a direct use of CaH_2 for the reduction of carbonyl compounds, where a mixture of CaH_2 and ZnX_2 reduced ketones and imines in the presence of a catalytic amount of a Lewis acid such as Ti(O-*i*-Pr)$_4$, B(O-*i*-Pr)$_3$, Al(O-*i*-Pr)$_3$ and ZnF_2.[8] Carbonyl reduction with these stable metal hydrides is promising as a practical process applicable to a large-scale synthesis. However, the reaction of aldehydes having α-hydrogen with the LiH-based reagent gave a complex mixture including aldol condensation products[2,9] and the CaH_2-based reagent also resulted in the formation of a complex mixture from aldehydes and no reaction with acyclic aliphatic ketones.[8] Herein, we report the development of a new CaH_2-based reagent, cat. $ZnX_2/CaH_2/R_3SiCl$, which effectively reduced (hydrosilylated) a variety of carbonyl compounds including aromatic, aliphatic ketones with a cyclic and acyclic form and aldehydes.

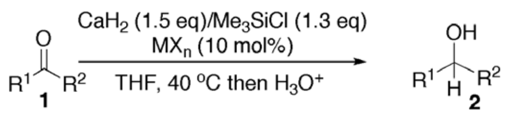
To overcome the aforementioned drawbacks to the reported LiH- and CaH_2-based reduction, we concentrated our effort to develop more general reagent system based on CaH_2. Inspired by the LiH-based reducing agent developed by Noyori et al., initial investigations were begun by reacting acetophenone (**1a**), 2-octanone (**1b**) and 3-phenylpropanal (**1c**) with a combination reagent cat. $ZnX_2/CaH_2/Me_3SiCl$. Thus, the reactions with CaH_2 (1.5 equiv) in the presence of Me_3SiCl (1.3 equiv) and a catalytic amount of ZnX_2 were carried out and the results are summarized in Table 1, where the yields were given for the corresponding alcohol obtained after acidic work-up. The possibility of the use of other metal salts instead of ZnX_2 was also examined.

As revealed from the results of the reaction of acetophenone (**1a**) (entries 1–8), in the absence of metal salt the reaction did not take place at all (entry 1), whereas, in the presence of ZnX_2 the reaction proceeded to afford the expected alcohol (entries 2–4). Though the reaction at room temperature sometimes faced the problem of reproducibility (entry 2), performing the reaction at 40 °C helped to overcome this matter (entries 3 and 4). Other metal salts such as $MgBr_2$, $CuCl_2$, Co(acac)$_3$ and $FeCl_3$ did not catalyze the reaction (entries 5–8). To our delight, acyclic aliphatic ketone **1b** and aldehyde **1c** having α-hydrogens were reduced to the corresponding alcohols in good yields (entries 9 and 10), although

* Corresponding author. Tel.: +81 45 481 5661; fax: +81 45 413 9770; e-mail: okamos10@kanagawa-u.ac.jp

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.10.123

Table 1. Reaction of carbonyl compounds with $CaH_2/Me_3SiCl/MX_n$



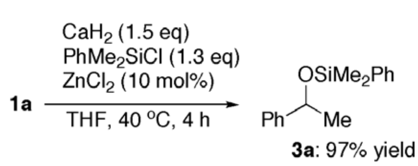
Entry		R^1	R^2	MX_n[a]	h	Yield[b] (%)
1	**1a**:	Ph	Me	—	24	~0
2[c]	**1a**:	Ph	Me	$ZnCl_2$	1	40–98
3	**1a**:	Ph	Me	$ZnCl_2$	0.5	96
4	**1a**:	Ph	Me	$ZnBr_2$	1.5	93
5	**1a**:	Ph	Me	$MgBr_2$	24	~0
6	**1a**:	Ph	Me	$CuCl_2$	24	~0
7	**1a**:	Ph	Me	$Co(acac)_3$	24	~0
8	**1a**:	Ph	Me	$FeCl_3$	24	~0
9	**1b**:	n-C_6H_{13}	Me	$ZnCl_2$	0.3	87
10	**1c**:	$Ph(CH_2)_2$	H	$ZnCl_2$[d]	24	74[e]

[a] Commercial anhydrous was used.
[b] Isolated yield.
[c] Performed at room temperature.
[d] 0.2 equiv of $ZnCl_2$ was used.
[e] 26% of **1c** was recovered.

the reduction of aldehyde needed longer reaction time even with the use of 0.2 equiv of $ZnCl_2$. Thus, the present method overcame the aforementioned limitation of the reported LiH- and CaH_2-based carbonyl reduction.[2,8]

Since the reaction with cat. $ZnX_2/CaH_2/Me_3SiCl$ system provided a mixture of the reduced alcohol and its silyl ether after neutral aqueous work-up or on TLC analysis of the reaction mixture, the reaction initially formed the corresponding Me_3Si ethers but they often were unstable to isolate. Therefore, an acidic aqueous work-up (or treatment with ammonium fluoride) was performed to isolate the products as the corresponding alcohol in the above-mentioned reactions. While the reaction used more bulky silyl chloride such as $PhMe_2SiCl$ rather than Me_3SiCl, the work-up under neutral conditions gave the corresponding silyl ether **3a** as an isolated product in good yield (Scheme 1).

Figure 1 shows the reduction (or hydrosilylation) of other representative carbonyl compounds **1** with a $CaH_2/R_3SiCl/ZnX_2$ (1.5/1.3/0.1 or 0.2 equiv) reagent, where the structure of the product alcohol **2** (with the use of Me_3SiCl) and silyl ether **3** or **4**, the reaction time and the yield are given. The reagent effectively reduced a variety of carbonyl compounds including aromatic, aliphatic, alkenyl ketones and aldehydes to alcohol **2** by using a $CaH_2/Me_3SiCl/ZnX_2$ reagent after an acidic work-up. 1,2-Dione **1k** was converted to 1,2-diol **2k** in a *meso*-selective fashion. The reactions with $PhMe_2SiCl$ or Et_3SiCl instead of Me_3SiCl, the corresponding silyl



Scheme 1. Reaction with $PhMe_2SiCl$.

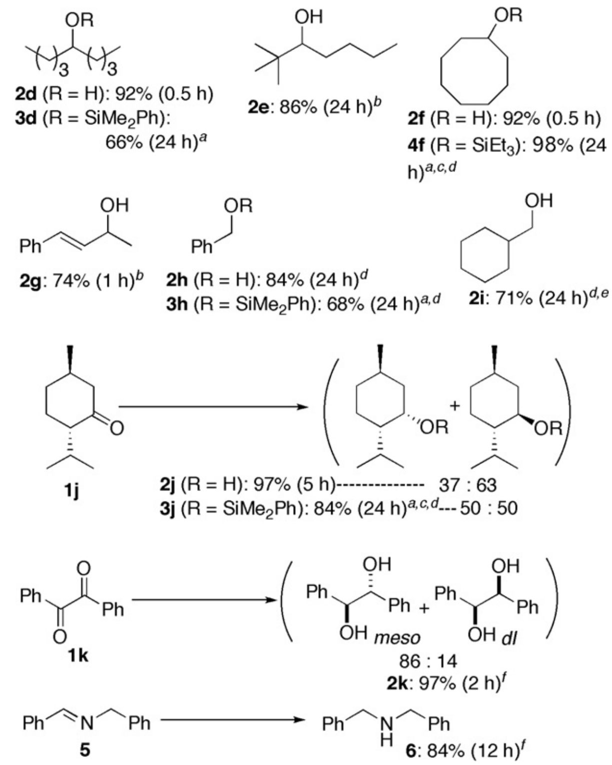


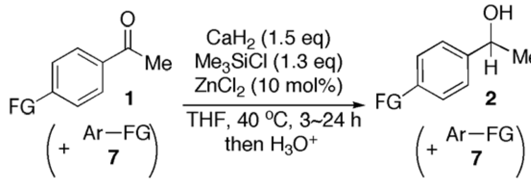
Figure 1. Reduction of carbonyl compounds with a $CaH_2/R_3SiCl/ZnCl_2$ catalyst system.[12] [a]For work-up, H_2O was used instead of 1 M HCl. [b]For work-up, n-Bu_4NF in THF was used instead of 1 M HCl. [c]1.8 equiv of R_3SiCl was used. [d]0.2 equiv of $ZnCl_2$ was used. [e]26 % of the substrate was recovered. [f]0.2, 6 and 2.6 equiv of $ZnCl_2$, CaH_2 and Me_3SiCl, respectively, were used.

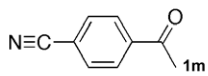
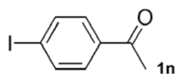
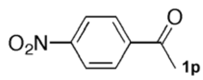
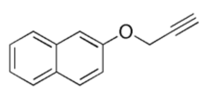
ethers **3d**, **4f**, **3h** and **3j** were obtained after a neutral work-up. In addition, imine **5** was also reduced effectively to give the corresponding amine **6**.

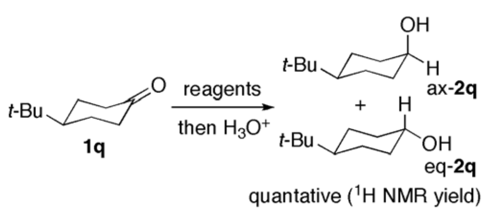
The results in Table 2 indicate a functional group compatibility of the present reaction. Thus, 4-substituted acetophenones **1m–p** were reduced to the corresponding aryl alcohols in good yields where cyano, iodo and nitro groups present in the substrates survived (entries 1–3). As shown in entries 4 and 5, acetophenone (**1a**) was reduced with the reagent in the presence of 1 equiv of substituted benzene (Ar-FG, **7**). The reduction of **1a** to **2a** proceeded with complete recovering of esters **7a** and **7b** having a propargyl ether with a terminal alkyne. It was noteworthy that the reaction in the presence of Ph–CO_2Et was somewhat slow and gave **2a** in 63% along with 35% of recovered **1a** (entry 2). Lewis basicity of an ester moiety may affect reaction, probably due to the coordination to the metal center of an active species.

Scheme 2 demonstrates the steric nature of the present reagent system and the reported systems for LiH- and CaH_2-based reduction. Thus, 4-t-butylcyclohexanone was subjected to the reduction with these reagents, providing a mixture of two diastereoisomers, that is, ax-**2q** and eq-**2q**. CaH_2-based reagents, cat. Ti(O-i-Pr)$_4$/$ZnCl_2/CaH_2$ and cat. $ZnCl_2/CaH_2/Me_3SiCl$ systems, exhibited the similar stereoselectivity and gave equatorial alcohol predominantly. The results suggest that

Table 2. Functional group compatibility



Entry	Substrate (s)	Isolated yield (%)
1		**2m**: 94%
2		**2n**: 98%
3		**2p**: 75%
4	**1a** + Ph–CO_2Et (**7a**, 1.0 equiv)	**2a**: 62% (**1a**: 35% recovered) **7a**: quantitatively recovered
5	 **1a** + (**7b**, 1.0 equiv)	**2a**: 80% **7b**: quantitatively recovered

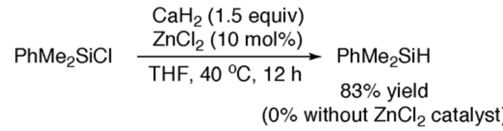


reagents and conditions		ax-**2q** : eq-**2q**
CaH_2/$ZnCl_2$/cat.Ti(O-*i*-Pr)$_4$ (1.4/1.3/0.05) THF, 40 °C, 24 h		16 : 84
CaH_2/Me_3SiCl/cat.$ZnCl_2$ (1.5/1.3/0.1) THF, 40 °C, 24 h		17 : 83
LiH/Me_3SiCl/cat.Zn(OSO_2Me)$_2$ (2.0/2.0/0.012) CH_2Cl_2, 40 °C, 50 h	[see ref. 2]	72 : 28[ref. 2]

Scheme 2. Reduction of 4-*t*-butylcyclohexanone with LiH- and CaH_2-based reagents.

the reaction may involve a small hydride source allowing an attack from the axial position and/or the reactions may proceed through the product-developing control process.[9] Meanwhile, interestingly, it has been reported that the reduction of **1q** with cat. Zn(OSO_2Me)$_2$/LiH/Me_3SiCl system gave the axial alcohol predominantly.[2]

The reduction with cat. ZnX_2/CaH_2/Me_3SiCl was heterogeneous throughout the reaction. After mixing the reagents, solid and liquid phases of the resulting heterogeneous mixture were separated by filtration and the reactivity of these phases was investigated. It was found that the filtrate from a mixture of CaH_2 (1.5 equiv),



Scheme 3. Reduction of $PhMe_2SiCl$ with cat. $ZnCl_2$/CaH_2.

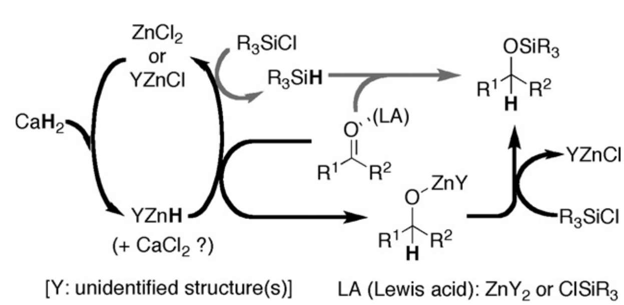
$ZnCl_2$ (0.1 equiv) and Me_3SiCl (1.3 equiv) reduced **1a** in 15% yield after 2 h at 40 °C but the precipitate was essentially inert even after the addition of Me_3SiCl (1.3 equiv) and $ZnCl_2$ (0.1 equiv). These suggest that a certain species soluble in THF was generated and it could reduce **1a**.

On the basis of the results, we thought about the possibility of the generation of a hydrosilane(s) from CaH_2 and silyl chloride. Thus, we carried out the reaction of $PhMe_2SiCl$ (1.0 equiv) and CaH_2 (1.5 equiv) in the presence or the absence of $ZnCl_2$ (0.10 equiv) in THF (for 2 h at 40 °C) (Scheme 3).

Though the reaction without the zinc salt did not provide the corresponding hydrosilane at all, 83% yield of $PhMe_2SiH$ was obtained by the reaction in the presence of $ZnCl_2$ after aqueous work-up. It has been reported that the reaction of CaH_2 and Me_3SiCl provided Me_3SiH in the presence of a catalytic amount of $AlCl_3$[10] but it needed a high reaction temperature (270 °C). Accordingly, it should be noted that the present hydrosilane formation proceeded under much milder conditions.

The results may suggest that the present carbonyl reduction would proceed via hydrosilylation by in situ generated R_3SiH.[11] However, **1a** did not react with Et_3SiH or $PhMe_2SiH$ (1.3 equiv) in the presence of a catalytic amount of $ZnCl_2$ (10 mol %) in THF at 40 °C (12 h).

Possible mechanism of the present reduction (or hydrosilylation) is illustrated in Scheme 4, which involves hydrozincation of carbonyl compounds with a zinc hydride species generated from CaH_2 and ZnX_2, where R_3SiCl may act as a Lewis acid to activate carbonyl compounds and as a silylation agent of the resulting zinc-alkoxides to give the corresponding silyl ether and zinc-chloride species. However, a hydrosilylation pathway (shown with gray arrows in Scheme 4) by in situ generated R_3SiH cannot be neglected even when the results in Scheme 3 could be considered because in the



Scheme 4. Possible reaction mechanism.

reaction mixture zinc salts may be no longer $ZnCl_2$. Further study to clarify the mechanism is underway.

In summary, we have demonstrated that CaH_2/silyl chloride reduced carbonyl compounds in the presence of a catalytic amount of zinc salt.[12] The cat. ZnX_2/CaH_2/R_3SiCl system developed here is more general for carbonyl reduction than the previously developed CaH_2- or LiH-based reagents. Although reaction mechanism is unclear at this time, the method may be useful because of its inexpensiveness and high functional group compatibility. In addition, it was found that hydrosilanes from chlorosilanes could be obtained under the mild reaction conditions by treatment with CaH_2 in the presence of a ZnX_2 catalyst.

Acknowledgement

This study was partially supported by the Scientific Frontier Research Project from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References and notes

1. Greeves, N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 9, p 1; Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; VHC, 1991.
2. Ohkuma, T.; Hashiguchi, S.; Noyori, R. *J. Org. Chem.* **1994**, *59*, 217.
3. Gao, Y.; Urabe, H.; Sato, F. *J. Org. Chem.* **1994**, *59*, 5521; Gao, Y.; Harada, K.; Hata, T.; Urabe, H.; Sato, F. *J. Org. Chem.* **1995**, *60*, 290.
4. Uchiyama, M.; Furumoto, S.; Saito, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1997**, *119*, 11425.
5. Gerhard, H.; Horst, J. *Chem. Ber.* **1959**, *92*, 2022; Mikheeva, V. I.; Fedneva, E. M.; Alpatova, V. I. *Dokl. Akad. Nauk. SSSR* **1959**, *131*, 318; Koester, R.; Huber, H. *Inorg. Synth.* **1977**, *17*, 17.
6. Schwarz, M.; Haidue, A.; Stil, H.; Paulus, P.; Greerlings, H. *J. Alloys Compd.* **2005**, *404-406*, 762.
7. Caldwell, W. E.; Krauskopf, F. C. *J. Am. Chem. Soc.* **1929**, *51*, 2936.
8. Aida, T.; Kuboki, N.; Kato, K.; Uchikawa, W.; Matsuno, C.; Okamoto, S. *Tetrahedron Lett.* **2005**, *46*, 1667.
9. It has been reported that Me_2ZnHLi reagent reduces aldehydes having a α-hydrogen effectively. See Ref. 4.
10. Calas, R.; Bourgeois, P. *Bull. Soc. Chim. Fr.* **1971**, 3263.
11. $ZnCl_2$-Catalyzed hydrosilylation has been reported: Lapkin, I. I.; Dvinskikh, V. V. *Zh. Obshch. Khim.* **1978**, *48*, 2509; Asymmetric reduction of ketones with polymethylhydrosiloxane in the presence of a chiral zinc catalyst has been reported: Mimoun, H.; de Saint Laumer, J. Y.; Giannini, L.; Scopelliti, R.; Floriani, C. *J. Am. Chem. Soc.* **1999**, *121*, 6158.
12. *General procedure for the reduction (or hydrosilylation) of carbonyl compounds*: A mixture of CaH_2 (3.0 mmol) and ZnX_2 (10–20 mol %) in THF (10 mL) was stirred for 1 h at 40 °C. To this were added the substrate **1** (2.0 mmol) and R_3SiCl (2.6 mmol) and the mixture was stirred at 40 °C. After checking the completion of the reaction by TLC analysis, the mixture was filtered through a pad of Celite with ether† and the filtrate was washed with aqueous 1 M HCl (for isolation of the alcohol) or saturated aqueous NH_4Cl (for isolation of the silyl ether) and extracted with ether. The combined organic layers were washed with saturated aqueous $NaHCO_3$. The following usual work-up gave the corresponding alcohol **2** or its silyl ether. †For work-up, other appropriate solvents such as hexane and pentane than ether can be used for filtration and extraction. After filtration, the resulting cake containing the remaining CaH_2 should be quenched by treatment with 2-propanol for safe. CaH_2 (powder), anhydrous $ZnCl_2$ and $ZnBr_2$ were purchased from Wako Pure Chemical Industries, Ltd.