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Direct Conversion of Carbonyl Compounds into Organic Halides: Indium(III) Hydroxide-Catalyzed Deoxygenative Halogenation Using Chlorodimethylsilane

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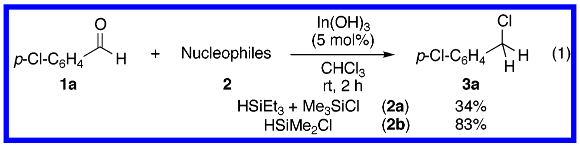
Transformation of carbonyls to other classes of compounds has been widely studied and utilized in organic synthesis.[1] However, a direct conversion of carbonyls to the corresponding alkyl halides (deoxygenative halogenation) still remains to be developed. In general, a multistep reaction under severe conditions is required on the basis of the reduction of carbonyls followed by chlorination.[2] In the present communication, we report the first example of a direct conversion of carbonyls into alkyl halides promoted by an indium catalyst with chlorodimethylsilane.

Because hydride and chloride sources both incorporate a carbonyl compound, three-component methodology could be appropriate to accomplish the deoxygenative chlorination. Silicon nucleophiles would be good candidates for the hydride and chloride sources from the selective synthetic point of view under mild conditions. Although a number of three-component reactions between a carbonyl compound and two silicon nucleophiles have been reported, one of the two nucleophiles is limited to be a heteroatom-substituted silane like *Si*-**ZR** (*Si*-OR, *Si*-SR, or *Si*-NR_2), because the heteroatom substituent predominantly attacks the carbonyl moiety to form acetal derivatives as shown in Scheme 1 (Path 1).[3] The formation of onium cationic species **A** considerably contributes to release of the siloxy group, in which representative Lewis acids such as $BF_3{\cdot}OEt_2$ and Me_3SiI also accelerate the releasing. To achieve the hydrochlorination in which no acetal type of intermediacy participates is not an extension of known methodology, and so the choice of silicon nucleophiles and Lewis acids is significantly important.

We have previously reported that $InCl_3$ peculiarly catalyzes the reaction, which includes formation of a carbocationic species such as **B** from silyl ethers (FG: ally, H).[4] In this context, we began to explore the “Path 2-type” deoxygenative halogenation using indium compounds as a catalyst.

Initially, we examined the reaction of aldehyde **1a** with $HSiEt_3$ and Me_3SiCl (**2a**) for the direct conversion to organic chloride. The desired product **3a** was obtained in the presence of $In(OH)_3$ catalyst, although the yield was not satisfactory (eq 1). Amazingly, the yield was dramatically improved to 83% by using $HSiMe_2Cl$ (**2b**), which bears both hydrogen and chlorine moieties.



Scheme 1. Three-Component Reaction on Using Carbonyl and Silicon Nucleophiles

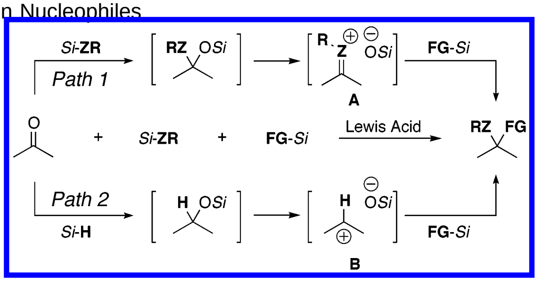
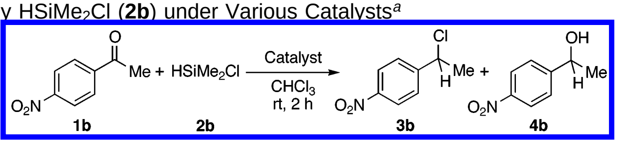


Table 1. Deoxygenative Chlorination of *p*-Nitroacetophenone (**1b**) by $HSiMe_2Cl$ (**2b**) under Various Catalysts[a]



entry	catalyst	yield/%	
		3b	**4b**
1	none	0	0
2	$In(OH)_3$	99	0
3	$Sc(OTf)_3$	69	0
4	$Yb(OTf)_3$	0	0
5	$AlCl_3$	0	0
6	$BF_3{\cdot}OEt_2$	0	0
7	$TiCl_4$	0	7
8	$B(C_6F_5)_3$	0	81

[a] All reactions were carried out in chloroform (4 mL) with catalyst (0.1 mmol), **1b** (2.0 mmol), and **2b** (2.4 mmol) at room temperature for 2 h.

The effect of the $In(OH)_3$ catalyst is essential for this reaction as shown in Table 1. *p*-Nitroacetophenone (**1b**) afforded the corresponding chloride **3b** exclusively catalyzed by $In(OH)_3$ (entry 2). The product **3b** was also obtained by $Sc(OTf)_3$ catalyst, although the yield was lower (entry 3). $Yb(OTf)_3$ or typical Lewis acids such as $AlCl_3$, $BF_3{\cdot}OEt_2$, or $TiCl_4$ exhibited no catalytic effect, and the starting ketone **1b** was quantitatively recovered (entries 4−7). When $B(C_6F_5)_3$, a well-known catalyst for hydrosilylation,[5] was used, only the alcohol **4b** was obtained (entry 8). The combination of $In(OH)_3$ and $HSiMe_2Cl$ in $CHCl_3$ solution is adjudged to be the best.

The deoxygenative chlorinations of various carbonyl compounds are summarized in Table 2. Aromatic aldehydes **1c** and **1d** afforded benzylic chlorides **3c** and **3d**, respectively, in high yields (entries 1 and 3). Because $InCl_3$, the most effective catalyst for our previous work,[4] had lower catalytic activity than $In(OH)_3$ (entries 1 and 2), we chose $In(OH)_3$ as a representative catalyst. Aromatic ketones **1e**−**j** were converted into the corresponding alkyl chlorides **3e**−**j** in which the cyano, ester, and carbohydroxy groups were not affected (entries 4−9). The desired chloride was not afforded in the cases of *p*-methoxyacetophenone (**1k**) and an aliphatic aldehyde (**1l**). The former gave a Clemmensen-type reduction product in 38%

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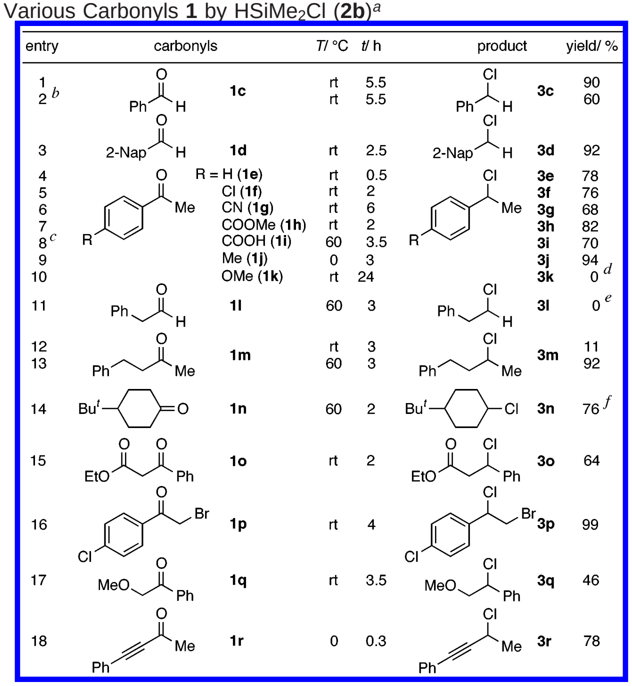
Table 2. In$(OH)_3$-Catalyzed Deoxygenative Chlorination of Various Carbonyls **1** by $HSiMe_2Cl$ (**2b**)[a]



entry	carbonyls		*T*/ °C	*t*/ h	product		yield/ %
1		**1c**	rt	5.5		**3c**	90
2[b]			rt	5.5			60
3		**1d**	rt	2.5		**3d**	92
4		R = H (**1e**)	rt	0.5		**3e**	78
5		Cl (**1f**)	rt	2		**3f**	76
6		CN (**1g**)	rt	6		**3g**	68
7		COOMe (**1h**)	rt	2		**3h**	82
8[c]		COOH (**1i**)	60	3.5		**3i**	70
9		Me (**1j**)	0	3		**3j**	94
10		OMe (**1k**)	rt	24		**3k**	0[d]
11		**1l**	60	3		**3l**	0[e]
12		**1m**	rt	3		**3m**	11
13			60	3			92
14		**1n**	60	2		**3n**	76[f]
15		**1o**	rt	2		**3o**	64
16		**1p**	rt	4		**3p**	99
17		**1q**	rt	3.5		**3q**	46
18		**1r**	0	0.3		**3r**	78

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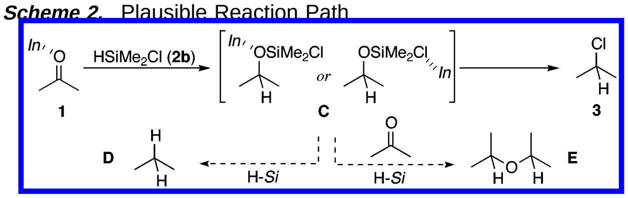
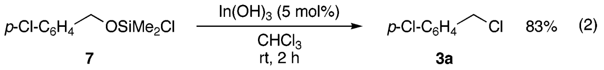
[a] All reactions were carried out with carbonyls **1** (2.0 mmol), chlorosilane **2b** (2.4 mmol), and $In(OH)_3$ (0.1 mmol) in chloroform (4 mL). [b] $InCl_3$ was used instead of $In(OH)_3$. [c] Chlorosilane **2b** (4.4 mmol) was used. [d] (4-Methoxyphenyl)ethane (**5**) was obtained in 38% yield. [e] The ether $(PhCH_2CH_2)_2O$ (**6**) was obtained in 70% yield. [f] Cis/trans = 12/88.

Scheme 2. Plausible Reaction Path



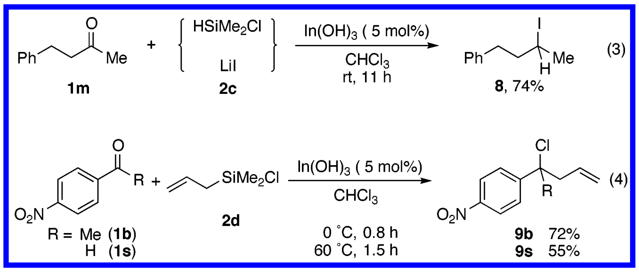
yield (entry 10), and the latter gave a dialkyl ether (entry 11). Aliphatic ketone afforded the *sec*-alkyl chlorides **3m** and **3n** at higher temperature (entries 13 and 14). Functionalized ketones **1o**−**r** selectively afforded the corresponding chlorides **2o**−**r**, respectively (entries 15−18).

A plausible reaction path is illustrated in Scheme 2. At first, hydrosilylation takes place to give silyl ether **C**, which then is activated by the indium catalyst to give chloride **3** with leaving of the siloxy group. This reaction path is confirmed by the fact that the silyl ether **7**, separately prepared by the conventional method, was facilely transformed to the corresponding chloride **3a** by $In(OH)_3$ catalyst (eq 2).[6] The formation of undesired products **D** and **E** (corresponding to the products **5** and **6** in entries 10 and 11 in Table 2) also supports the initial generation of **C**.[7]



Moderate Lewis acidity and oxophilicity are plausibly important for achievement of this catalytic cycle because strong Lewis acids seem to be trapped by oxygen during the reaction course, which would be the case of ineffective Lewis acids noted in Table 1. High desiloxylation ability of the indium catalyst[8] should accelerate the reaction from silyl ether to chloride **3**.

Deoxygenative iodination was succeeded by addition of LiI to give the iodide **8** (eq 3). Although details of the process are not clear, $HSiMe_2I$ generated in situ is expected to cause the iodination.[9]



To expand this methodology, the simultaneous induction of allyl and chlorine moieties was attempted (eq 4), where allylsilylation is required instead of hydrosilylation. The new C−C and C−Cl bonds could be formed on the carbonyl carbon of the ketone **1b** and the aldehyde **1s** with release of oxygen to afford **9b** and **9s**, respectively. It is noted that even the ketone successfully gave the product despite the difficulty in its catalytic allylation using allylsilane. The indium-catalyzed deoxygenation step might be a driving force for this process.

In summary, we have achieved novel deoxygenative halogenation catalyzed by $In(OH)_3$ using functionalized halosilanes. This method provides an unprecedented synthetic route to organic halides. Further extensions of this work are now in progress.

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Supporting Information Available: Reaction procedure and spectroscopic details of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) According to the advice of a referee, we examined the chlorination of chlorosilyl ether derived from (*R*)-1-phenylethanol, where complete racemization was observed (see the Supporting Information). Although this result indicates a S_N1 mechanism, the detail and generality of this stereochemistry are under investigation.

(7) We can rule out a reaction course that includes chlorosilylation of carbonyls because of the low nucleophilicity of chloride.

(8) Yasuda, M.; Onishi, Y.; Ueba, M.; Miyai, T.; Baba, A. *J. Org. Chem.* **2001**, *66*, 7741−7744.

(9) We confirmed that the product **8** was not obtained by the halogen-exchange from the corresponding chloride **3m** with LiI. Because the yield of deoxygenative iodination product **8** was considerably higher than that of deoxygenative chlorination (see Table 2, entry 12), the iodosilyl species is probably generated in situ.

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