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One-Pot Preparation of Alkyl Iodides from Esters by Indium-Catalyzed Reductive Cleavage of a Carbon–Oxygen Bond

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Keywords: Indium / Iodine / Esters / Nucleophilic substitution / Reduction / Polymers

We describe the indium-catalyzed reductive iodination of aliphatic and aromatic esters with iodine and 1,1,3,3-tetramethyldisiloxane (TMDS). This reducing procedure accommodates a variety of esters, including esters containing alkyl groups, halogens, a hydroxy group, a thioether, and an alkene moiety. Also, this procedure was applied to the cleavage of carbon–oxygen bonds in acrylate polymers.

Introduction

The synthesis of alkyl halides has been widely investigated in organic chemistry, because they are important and central intermediates for a variety of further molecular transformations.[1] In particular, in the past two decades, the reductive halogenation of a carbonyl compound with an appropriate halide source in the presence of a relatively mild reducing reagent, a hydrosilane, has been one of the most straightforward approaches to the preparation of alkyl halides. As an example of a reductive halogenation of carbonyl compounds with superstoichiometric amounts of a catalyst in the presence of a hydrosilane, Palomo et al. reported the TMSCl-promoted (TMS = trimethylsilyl) reductive iodination of aldehydes with sodium iodide in the presence of TMDS (1,1,3,3-tetramethyldisiloxane).[2] Also, a reductive iodination of aldehydes and ketones with excess amounts of diiodosilane (SiH_2I_2) leading to the corresponding alkyl iodides has been disclosed by Keinan and coworkers.[3] Moreover, Das and coworkers reported a reductive bromination of aldehydes using a combination of PMHS (polymethylhydrosiloxane) and bromide sources, such as (bromodimethyl)sulfonium bromide or NBS (*N*-bromosuccinimide), without a metal catalyst.[4] In this context, Kabalka reported a reductive preparation of benzyl bromides from aldehydes and alkylboron dibromides, but this method was limited to aromatic aldehydes.[5] Periasamy et al. found that a BH_3/I_2/diethylaniline system produced a reductive iodination of carbonyl compounds, but this reducing system did not give any reaction with an ester.[6] In a breakthrough for catalytic conversion, Baba et al. achieved the catalytic reductive chlorination of ketones or aldehydes with Me_2SiHCl (chlorodimethylsilane) and a catalytic amount of $In(OH)_3$.[7] We also reported the indium-catalyzed reductive bromination and iodination of carboxylic acids with TMDS and halogen sources, such as trimethylsilyl bromide (TMSBr) or I_2, to give alkyl bromides or iodides.[8–10] However, reductive halogenation, and in particular the direct iodination of esters with a hydrosilane, has not been extensively examined before now.

Previously, we have shown that the desired reductive iodination of esters could be accomplished simply by the addition of iodine to a reducing catalytic system that converted esters into ethers.[8a] However, the substrates examined there were limited to only two examples. Because esters are commonly used as protecting groups for carboxylic acids in natural product synthesis, their synthetic utility is extremely high. Thus, we systematically investigated the indium-catalyzed reductive iodination of a variety of esters with TMDS and I_2. In this paper, we report the full details of this study, along with the results of the application of this reducing reagent system to an effective cleavage of ester moieties in a polymer chain.

Results and Discussion

On the basis of our previous work, we examined the optimal conditions for the direct iodination of methyl phenylacetate as a model substrate (Table 1). Initially, the effect of a hydrosilane was investigated. For instance, when an ester and molecular iodine were treated with 6 equiv. (Si–H) of TMDS in $CHCl_3$ at 60 °C, the reaction was complete within 1 h to give the corresponding alkyl iodide (i.e., **1a**) in quantitative yield (Table 1, Entry 1). When the amount of hydrosilane in the reaction was decreased to 4 equiv. (Si–H) per

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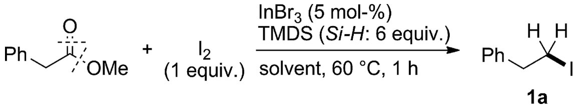
ester, a drastic decrease in the product yield was observed (Table 1, Entry 2). Ph_2MeSiH and $PhMe_2SiH$ both also showed a relatively high reductive effect (Table 1, Entries 3 and 4). When $PhSiH_3$ and PMHS were used, the yield of iodide **1a** decreased slightly (Table 1, Entries 5 and 6). However, the use of Et_3SiH, which was highly effective in the reductive conversion of esters into ethers in the presence of $InBr_3$, resulted in a drastic decrease in the yield to 37% (Table 1, Entry 7). In addition, when the reaction was carried out in THF, a solvent in which all the reaction components were highly soluble, the solvent effect drastically hindered the desired iodination (Table 1, Entry 8). Interestingly, when toluene was used instead of $CHCl_3$, the reaction proceeded cleanly at room temperature, although it required 3 d to complete. With a rise in the reaction temperature, both an improvement in the yield and a shortening of the reaction time were observed (Table 1, Entries 9 and 10). Neither *N*-iodosuccinimide (NIS) nor iodotrimethylsilane (TMSI) played the role of iodine source as well as I_2. The formation of by-products, such as methyl phenethyl ether or the alcohol derivative was not observed in any of the reactions. Thus, the optimal conditions were established as heating at 60 °C with $CHCl_3$ in the presence of TMDS (6 equiv. Si–H).

Table 1. Investigation of the optimal conditions for reductive iodination.

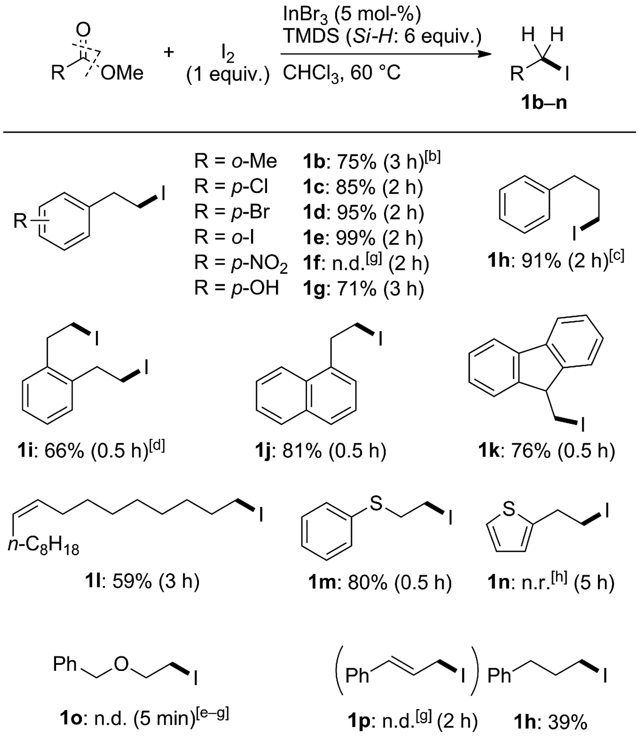


Entry	Hydrosilane	Solvent	Yield [%][a]
1	TMDS	$CHCl_3$	99 (91)
2[b]	TMDS	$CHCl_3$	43
3	Ph_2MeSiH	$CHCl_3$	95
4	$PhMe_2SiH$	$CHCl_3$	87
5	$PhSiH_3$	$CHCl_3$	74
6	PMHS	$CHCl_3$	62
7	Et_3SiH	$CHCl_3$	37
8[c]	TMDS	THF	n.d.[f]
9[d]	TMDS	PhMe	83
10[e]	TMDS	PhMe	80

[a] GC yield (isolated yield in parentheses). [b] 4 equiv. TMDS was used. [c] 60 °C, 2 h (NMR yield). [d] Room temp., 3 d (NMR yield). [e] 100 °C, 0.5 h (NMR yield). [f] Not determined.

The generality of deoxygenative iodination using a variety of aliphatic esters was then examined (Table 2). Methyl phenylacetate esters with an alkyl group and halogen substituents on the benzene ring were subjected to the optimal reductive iodination conditions, and in all cases, the corresponding alkyl iodides (i.e., **1b–e**) were obtained in good to excellent yields. In contrast, for the substrate with a nitro group, the reducing reagents seemed to affect to the nitro group rather than the ester moiety, which led to a complex mixture. The ester with a hydroxy group was effectively converted into the corresponding iodide (i.e., **1g**) in a satisfactory yield. Iodination of a diester was achieved smoothly using a double dose of the reagents to give the alkyl iodide (i.e., **1i**) in a practical yield. Moreover, when the reactions were carried out using esters with either a naphthyl or a fluorenyl group, the alkyl iodides (i.e., **1j** and **1k**, respectively) were obtained in good yields. Unlike the reductive iodination of a fatty acid,[8a] when the reaction was conducted with the corresponding ester derived from the *trans* fatty acid, the alkyl iodide (i.e., **1l**) was obtained with retention of its geometric structure in 59% yield. Although an ester with a thioether moiety was efficiently converted into the corresponding alkyl iodide (i.e., **1m**), a substrate with a thiophene ring did not undergo the desired iodination. When a substrate containing a benzyl ether moiety was treated under our optimal conditions, contrary to our expectations, the substitution by the iodine anion occurred at the benzylic position rather than at the reduced carbonyl carbon atom of the ester unit, and thus benzyl iodide was formed as a by-product. Methyl cinnamate gave the saturated alkyl iodide, 1-iodo-3-phenylpropane (**1h**), through overreduction of the conjugated alkene moiety.

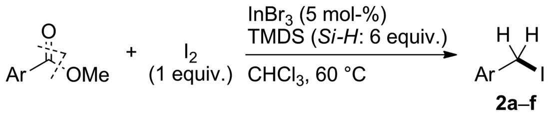
Table 2. Reductive iodination of a variety of aliphatic esters.[a]

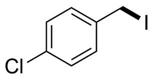
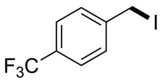
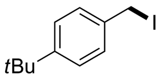
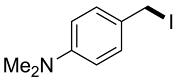
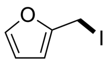
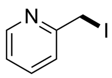


[a] Isolated yield. [b] Ph_2MeSiH was used. [c] The corresponding butyl ester was used. [d] Double doses of reagents were used. [e] Reaction temperature was 0 °C. [f] Benzyl iodide was formed in 88% yield. [g] Not determined. [h] No reaction.

Next, we attempted to extend the procedure to the reductive iodination of aromatic esters (Table 3). The deoxygenative etherification of an aromatic ester with an $InBr_3$/Et_3SiH system hardly proceeded, but the iodination did proceed with several substrates. For instance, when esters with an electron-withdrawing group, such as a trifluoromethyl or chloro group, were subjected to the optimal conditions, the corresponding benzyl iodide derivatives (i.e., **2a** and **2b**) were formed in relatively good yields. However, when the iodides were isolated, decomposition by substitution led to a drastic decrease in the product yield. In contrast, esters with an electron-donating group, such as a *tert*-butyl or a dimethylamino group, did not give even remotely satisfactory results. In particular, a dimethylamino group led to recovery of the starting ester. Unfortunately, esters with a heterocyclic ring did not undergo the desired iodination.

Table 3. Reductive iodination of a variety of aromatic esters.[a]



 **2a**: 80% (0.5 h)	 **2b**: 50% (10 min)	 **2c**: 39% (2 h)[b]
 **2d**: n.r.[c] (5 h)	 **2e**: n.r.[c] (5 h)	 **2f**: n.r.[c] (5 h)

[a] Isolated yield. [b] Reaction temperature was 40 °C. [c] No reaction.

To show the utility of this reductive iodination of esters, the reductive cleavage of an ester moiety in acrylate polymers was then carried out (Figure 1). The reaction of butyl acrylate polymers with I_2 (1 equiv.) was carried out in the presence of a catalytic amount of $InBr_3$ and Ph_2MeSiH (6 equiv. Si–H) in toluene at 100 °C, and the changes in the cleavage were monitored by ATR (attenuated total reflectance) IR spectroscopy. The peaks (C=O: 1733 cm^{-1}; C–O: 1246, 1164 cm^{-1}) due to the ester moiety of the polymers completely disappeared within 15 min. Instead, a broad peak (1200–1000 cm^{-1}) due to the Si–O–Si bond of a siloxane formed in situ appeared as the reaction proceeded. These results strongly imply that the reducing system effectively acts on the ester in the polymers to produce the corresponding iodinated moiety.

To clarify the reaction mechanism of the reductive iodination, several control experiments were then undertaken (Scheme 1). Initially, we assumed that the key intermediate would be either an ether or a silyl ether, but when the expected ether intermediate was treated with iodine either with no additional reagents or with the addition only of $InBr_3$, no substitution by iodide anion occured [Equations (1) and (2)]. When the same reaction was carried out with TMDS alone in the hope of generating both iodide anion and a Lewis acid in the form of a silyl iodide in situ, the corresponding alkyl iodide (i.e., **1a**) was detected in only 8% GC yield [Equation (3)].

However, when TMDS was used together with $InBr_3$, the iodination of the ether proceeded smoothly to produce iodide **1a** in an 80% yield [Equation (4)]. These results strongly imply that the indium catalyst plays a dual role: (i) activation of the ether moiety to facilitate substitution by the iodine anion; and (ii) promotion of the in situ generation of iodine anion from TMDS and molecular iodine. Also, when silyl ether **3**, which was prepared from phenethyl alcohol and $MePh_2SiCl$, was treated with $InBr_3$ (5 mol-%) and TMDS (2 equiv.) in the presence of I_2, iodination proceeded cleanly and effectively to produce iodide **1a** in 98%

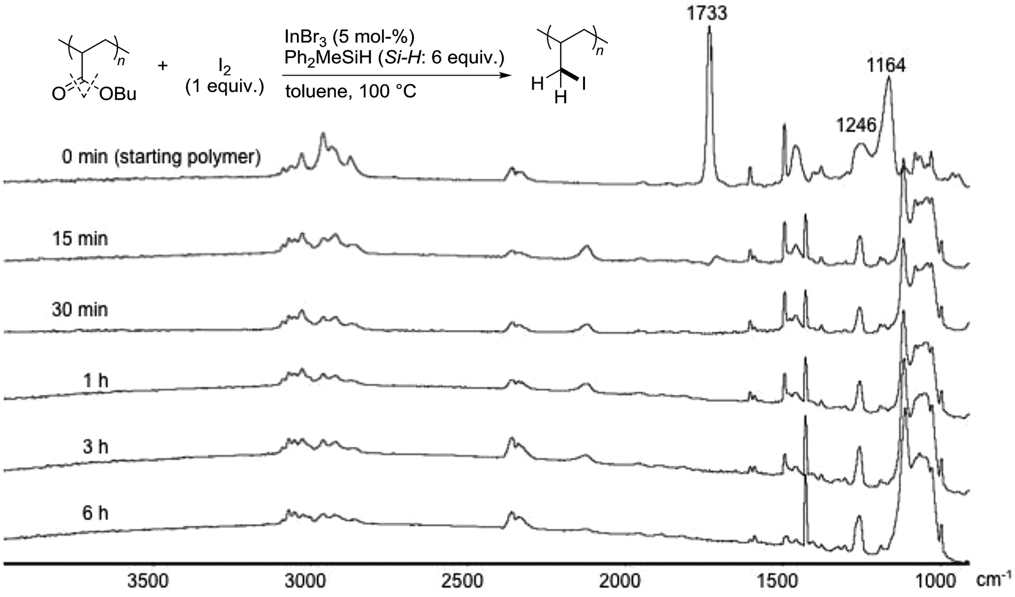
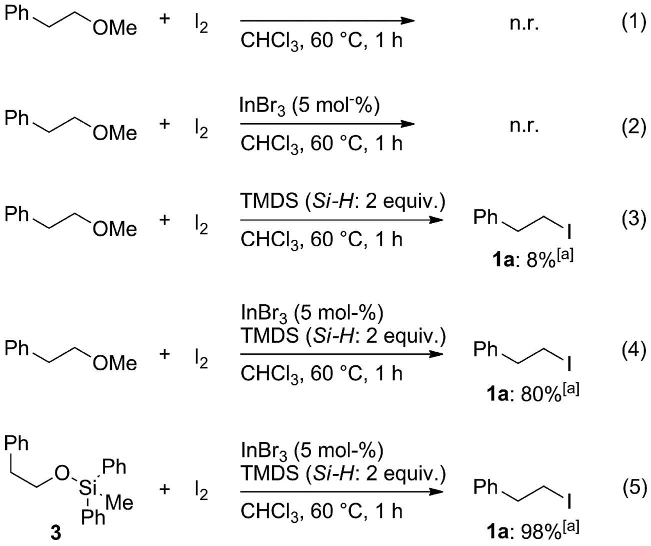


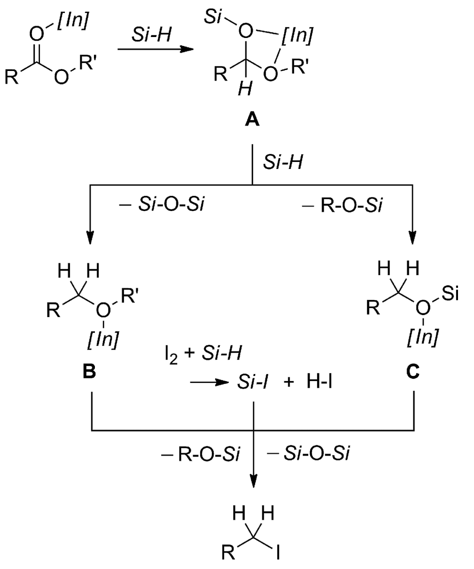
Figure 1. ATR-IR monitoring of the reductive cleavage of the ester moiety in acrylate polymers.



Scheme 1. Control experiments. [a] GC yield.

yield [Equation (5)]. These results strongly support the notion that a silyl ether could also function as an important intermediate in the iodination. Moreover, during the reductive iodination, the in situ formation of a siloxane was detected by ATR-IR.

Based on these results, we propose the reaction mechanism shown in Scheme 2. First, the ester, activated by the indium catalyst, is reduced to produce a silyl acetal **A**. This is followed by the substitution of an additional hydrosilane to form two intermediates: ether **B** and silyl ether **C**.[11,12] The two intermediates would then undergo nucleophilic substitution by iodine anion, generated in situ from molecular iodine and a hydrosilane,[13] to give the alkyl iodide. However, because TMSI did not function well as an iodine source during the search for optimal conditions, we suspect that another route exists for the final substitution step by iodine anion.



Scheme 2. Plausible reaction mechanism for the reductive iodination of esters.

Conclusions

We have demonstrated the indium-catalyzed reductive iodination of a variety of esters in the presence of molecular iodine leading to the preparation of alkyl iodides. This reductive iodination accommodated a variety of aliphatic esters as well as aromatic esters with an electron-withdrawing group. The procedure could also be applied to the reductive iodination of the ester moieties in acrylate polymers. Thus, this represents a facile method for the cleavage of polymer cross-links in materials chemistry.

Experimental Section

General Procedure for the Indium-Catalyzed Reductive Iodination of an Ester: Freshly distilled chloroform (0.6 mL) was placed into a screw-capped vial under N_2, and a magnetic stirrer bar, $InBr_3$ (0.0300 mmol, 10.6 mg), I_2 (0.600 mmol, 152 mg), ester **1** (0.6 mmol), and TMDS (1.8 mmol, 3.2×10^2 µL) were successively added. The vial was sealed with a cap that contained a PTFE septum. The reaction vial was heated in an oil bath, and the progress of the reaction was monitored by GC and TLC until the ester had been completely consumed. After the reaction was complete, the mixture was cooled to room temperature, and was quenched with H_2O (2 mL). The aqueous layer was extracted three times with dichloromethane (6 mL). The combined organic phases were dried with anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc, 99:1) to give the corresponding alkyl iodide. If necessary, further purification was performed by gel permeation chromatography (eluent: $CHCl_3$).

Procedure for the Reductive Iodination of Acrylate Polymers, Monitored by ATR-IR: Freshly distilled toluene (0.9 mL) was placed into a round-bottomed flask (10 mL) under N_2, and a magnetic stirrer bar, $InBr_3$ (0.0300 mmol, 10.6 mg), I_2 (0.600 mmol, 152 mg), butyl acrylate polymers (34% solution of the polymers in toluene; 0.600 mmol, 226 mg), and Ph_2MeSiH (3.60 mmol, 7.20×10^2 µL) were successively added. The reaction flask was heated in an oil bath at 100 °C. The reaction mixture was sampled at each reaction time shown in Figure 1, and the progress of the reaction was measured by ATR-IR.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and characterization data for the products.

Acknowledgments

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[11] Several groups have proposed that during the reductive halogenation of aldehydes in the presence of a hydrosilane, the corresponding silyl ether is formed as one of the reaction intermediates.[2a,4]

[12] In the indium-catalyzed reductive bromination or iodination of an aliphatic carboxylic acid with TMDS, the in situ formation of the corresponding silyl ether was observed by ^{1}H and ^{13}C NMR spectroscopy, and was detected with an HRMS spectrometer.[8a,8b]

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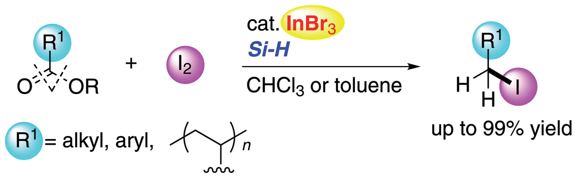
Reductive Iodination



Indium tribromide effectively catalyzed the reductive iodination of esters to produce the corresponding alkyl iodides. A range of aliphatic and aromatic esters underwent the reaction, as did ester moieties in polymers.

N. Sakai,* Y. Matsushita, T. Konakahara, Y. Ogiwara, K. Hirano 1–6

One-Pot Preparation of Alkyl Iodides from Esters by Indium-Catalyzed Reductive Cleavage of a Carbon–Oxygen Bond

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