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Indium-Catalyzed Reductive Bromination of Carboxylic Acids Leading to Alkyl Bromides

**Toshimitsu Moriya, Shinichiro Yoneda, Keita Kawana, Reiko Ikeda,
Takeo Konakahara, and Norio Sakai***

*Department of Pure and Applied Chemistry, Faculty of Science and Technology, Tokyo
University of Science (RIKADAI), Noda, Chiba 278-8510, Japan*

sakachem@rs.noda.tus.ac.jp

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ABSTRACT

The combination of 1,1,3,3-tetramethyldisiloxane (TMDS) and trimethylbromosilane (Me$_3$SiBr) with a catalytic amount of indium bromide (InBr$_3$) undertook direct bromination of carboxylic acids, which produced the corresponding alkyl bromides in good to excellent yields. The reducing system was tolerant to several functional groups.

Alkyl bromides are useful building blocks that can be converted to various compounds such as amines, ethers, and nitriles.[1,2] Although a number of methods have been developed for the synthesis of alkyl bromides, a single-step bromination from other functional groups has not been studied extensively.[3] Achievement of the method is quite valuable to the aspects of decreasing the synthetic steps and the environmental load of organic synthesis. Thus far, several groups have established direct bromination with alcohols,[4] aldehydes,[5] and ketones.[6] However, a direct conversion from carboxylic acids has not been studied to date. Generally, the conventional method for the bromination of carboxylic acids requires a multistep procedure involving the initial reduction of a carboxylic acid with lithium aluminum hydride (LAH) and a subsequent nucleophilic substitution using a hydrogen halide or a phosphorus halide.[7] In addition, a poor chemoselectivity to other functional groups and the moisture sensitivity of LAH lower the synthetic utility.

The reductive conversion of various functional groups by a combination of indium(III) salt and a hydrosilane has been developed by several groups. For example, Baba's group has reported the reductive transformation of alcohols,[8] aryl/alkyl ketones/aldehydes,[9] and acid chlorides.[10]

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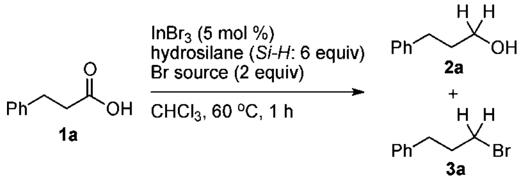
Miura and Hosomi's group has reported the dehalogenation of organic halides[11] and the 1,4-reduction of enones.[12] We also developed the selective reduction of the carbonyl group of esters and amides by indium tribromide ($InBr_3$) and triethylsilane (Et_3SiH).[13] Then, we applied the reducing system to the chemoselective reduction of carboxylic acids.[14] Herein we report the unprecedented direct preparation of alkyl bromides via the indium-catalyzed reduction of carboxylic acids with a siloxane and a bromine source. A particular feature of this reaction is that the carbon number is maintained from the substrate to the product throughout the reductive halogenation series.[15]

When 3-phenylpropionic acid (**1a**) was initially treated with $InBr_3$ (5 mol %) and $PhSiH_3$ (*Si–H*: 6 equiv) in $CHCl_3$ at 60 °C, an unexpected alkyl bromide **3a** was obtained in a 10% yield with 43% of the primary alcohol **2a** (Table 1, entry 1). Interestingly this result showed that a counterion of the indium catalyst functioned as a bromine source. Also this type of direct preparation of an alkyl bromide is quite an unusual example. Thus, improvement of the bromination yield was attempted with several bromine sources. For example, use of a common bromine source (2 equiv for a carboxylic acid), such as Br_2, PBr_3, and *N*-bromosuccinimide (NBS), resulted in the formation of a complex mixture (entries 2–4). In the case with lithium bromide (LiBr) or tetrabutylammonium bromide (Bu_4NBr), the reduction did not proceed (entries 5 and 6). When the counterion of a copper salt was used as a bromine source, the yield of the alkyl bromide **3a** was increased to 32% (entry 7). It was noted that when the reaction was carried

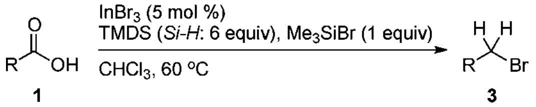
Table 1. Reaction Conditions of $InBr_3$-Catalyzed Reductive Bromination of Carboxylic Acid **1a**[a]

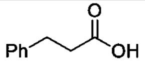
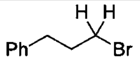
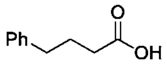
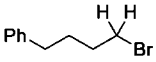
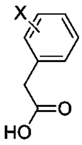
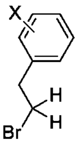
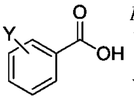
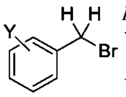
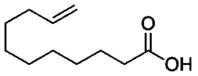
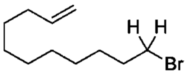
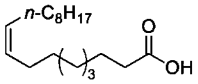
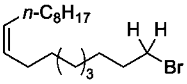
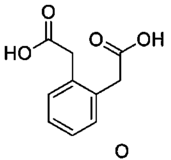
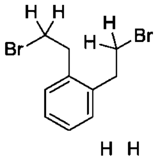
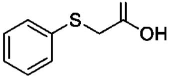
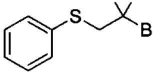


entry	hydrosilane	Br source	yield (%)[b]	
			2a	**3a**
1	$PhSiH_3$	none	43	10
2	$PhSiH_3$	Br_2	complex mixture	
3	$PhSiH_3$	PBr_3	complex mixture	
4	$PhSiH_3$	NBS	complex mixture	
5	$PhSiH_3$	LiBr	no reaction	
6	$PhSiH_3$	Bu_4NBr	no reaction	
7	$PhSiH_3$	$CuBr_2$	ND[d]	32
8	$PhSiH_3$	Me_3SiBr	ND[d]	89
9	$PhSiH_3$	Et_3SiBr	ND[d]	69
10	TMDS	Me_3SiBr	ND[d]	(96)
11[c]	TMDS	Me_3SiBr	ND[d]	99

[a] The reaction was carried out with 3-phenylpropionic acid (**1a**) (0.6 mmol), $InBr_3$ (5 mol %), hydrosilane (2 equiv), and a Br source (2 equiv) in chloroform at 60 °C for 1 h. [b] NMR (Isolated) yield. [c] Me_3SiBr (1 equiv) was used. [d] ND: not detected.

Table 2. $InBr_3$-Catalyzed Reductive Bromination of Carboxylic Acid[a]



entry	carboxylic acid		product		time (h)	yield (%)[b]
1		**1a**		**3a**	1	96
2		**1b**		**3b**	4	97
3	 X=*o*-Me	**1c**	 X=*o*-Me	**3c**	1	91
4	X=*p*-Cl	**1d**	X=*p*-Cl	**3d**	2	95
5	X=*p*-Br	**1e**	X=*p*-Br	**3e**	1	95
6	X=*o*-I	**1f**	X=*o*-I	**3f**	1	92
7	X=*p*-OH	**1g**	X=*p*-OH	**3g**	1	89
8	X=*p*-NO_2	**1h**	X=*p*-NO_2	**3h**	1	0[c]
9	 Y= *p*-OMe	**1i**	 Y= *p*-OMe	**3i**	5	NR[d]
10	Y= *p*-Cl	**1j**	Y= *p*-Cl	**3j**	1	87
11	Y= *p*-CF_3	**1k**	Y= *p*-CF_3	**3k**	2	85
12		**1l**		**3l**	0.5	80
13		**1m**		**3m**	0.5	82
14		**1n**		**3n**	1	89[e]
15		**1o**		**3o**	1	93

[a] The reaction was carried out with carboxylic acid **1** (0.6 mmol), $InBr_3$ (5 mol %), TMDS (*Si–H*: 6 equiv), and Me_3SiBr (1 equiv) in chloroform at 60 °C. [b] Isolated yield. [c] 3-(4-Nitrophenyl)propanol was obtained in a 49% yield. [d] NR: no reaction. [e] $InBr_3$ (10 mol %), TMDS (*Si–H*: 12 equiv) and Me_3SiBr (2 equiv) were employed.

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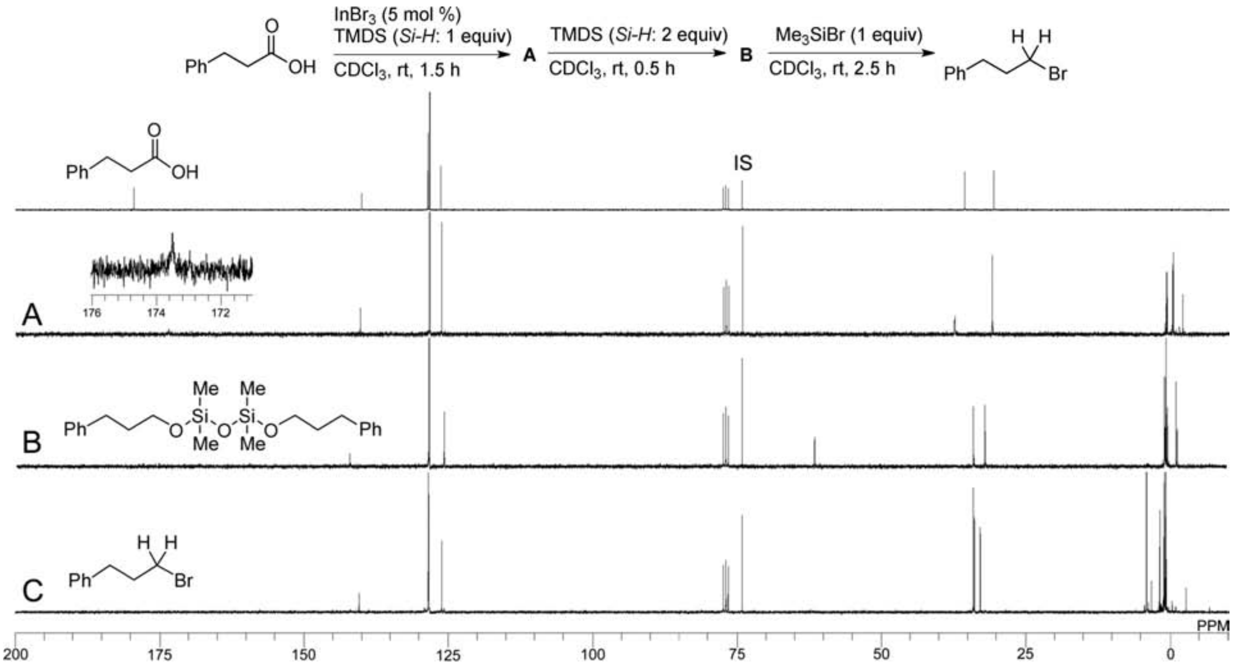

Figure 1. Monitoring of InBr$_3$-catalyzed reductive bromination of carboxylic acid **1a** by ^{13}C NMR.

out with a typical silyl halide, trimethylbromosilane (Me$_3$SiBr), the bromination proceeded cleanly, and the yield of the corresponding alkyl bromide **3a** was remarkably improved to 89% (entry 8). The use of triethylbromosilane (Et$_3$SiBr) also showed a moderate effect (entry 9). With respect to a silane, 1,1,3,3-tetramethyldisiloxane (TMDS) was the best silane to produce the desired alkyl bromide **3a** in a quantitative yield (entry 10). The use of 1 equiv of Me$_3$SiBr was sufficient to give the quantitative brominated product (entry 11).

To generalize this reaction, the direct bromination of various carboxylic acids was carried out under optimized conditions (Table 2). The direct bromination of aliphatic carboxylic acids **1a** and **1b**, with different lengths of the alkyl chain, was completed in a short time and produced the corresponding bromides **3a** and **3b** in excellent yields (entries 1 and 2). Functional groups such as a methyl, halogens, and a hydroxy group were tolerated under the reducing conditions (entries 3−7). The substrate **1h** with a nitro group gave only 3-(4-nitrophenyl)propanol in a 49% yield without the desired bromide **3h** (entry 8). Also, a remarkable substituent effect was observed for an aromatic carboxylic acid. For example, the use of benzoic acid **1i** with an electron-donating group, a methoxy group, did not produce the expected bromide **3i** (entry 9). Although there was no clear explanation for this result, the indium catalyst preferentially coordinated the methoxy group on the benzene ring to retard the activation of the carbonyl group.[16] In contrast, when the reaction was conducted with benzoic acids **1j** and **1k**, which have an electron-withdrawing group, a chloride or a trifluoromethyl group, the corresponding bromides **3j** and **3k** were obtained in good yields (entries 10 and 11). These results suggested that the electrophilicity of the carbonyl group was reduced by the electron-donating effect of the methoxy group to retard the subsequent reduction. The carboxylic acids bearing a terminal or internal alkene gave the corresponding bromides **3l** and **3m** in good yields (entries 12 and 13). The bromination of dicarboxylic acid **1n** was effectively achieved by double doses of the reagent (entry 14). This reductive bromination system was applicable to phenylthioacetic acid (**1o**), giving the corresponding sulfide **3o** in an excellent yield (entry 15). On the other hand, the bromination of the substrate containing a heterocyclic compound, such as furan, thiophene, and pyridine, did not proceed at all.

To investigate the reaction mechanism, the reaction system comprising 3-phenylpropionic acid (**1a**), InBr$_3$ (5 mol %), TMDS (*Si*−*H*: 1 equiv), and d_1-chloroform was monitored by ^{13}C NMR (Figure 1).[17] Initially, when the starting carboxylic acid **1a** was treated with TMDS (*Si*−*H*: 1 equiv) in the presence of InBr$_3$ (5 mol %), both the clear disappearance of the carbonyl peak (179.4 ppm)

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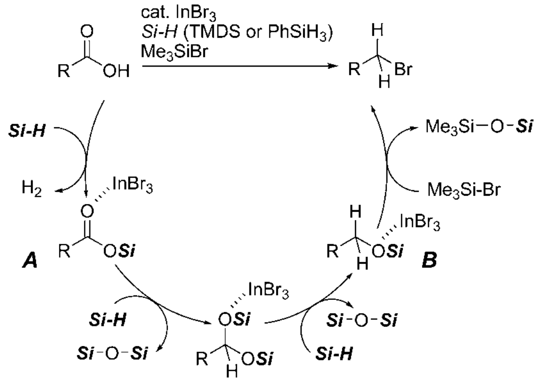
(16) When the reductive bromination of **1a** was conducted in the presence of methoxybenzene (1 equiv), a decrease in the yield (60%) of the alkyl bromide **2a** was observed. This result implied that the bromination was retarded by a methoxy substituent.

(17) Neither the silyl ester nor the silyl ether prepared from TMDS could be isolated due to their instability.

(18) Characterization of the silyl ester could not be well established due to the lack of detection of the mass peak (see ref 17). However, both synthesis of a silyl ester and in situ generation of hydrogen gas from a carboxylic acid and a hydrosilane with an indium catalyst were already reported; see: Nishimoto, Y.; Okita, A.; Yasuda, M.; Baba, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8623.

Scheme 1. Plausible Reaction Pathway of Reductive Bromination of Carboxylic Acids



of **1a** and the appearance of a new peak (173.5 ppm), which was derived from the corresponding silyl ester A, were observed (Figure 1A).[18] Then, when 2 more equivalents (*Si–H*) of TMDS were added to the resultant mixture, both the disappearance of the peak of the silyl ester A and the formation of the new peak (61.5 ppm), which was derived from the silyl ether B, were observed (Figure 1B). Finally, when 1 equiv of Me_3SiBr as a bromine source was added to the NMR tube, the quantitative formation of 1-bromo-3-phenylpropane (**3a**) was observed (C in Figure 1). To support the reaction mechanism from a different aspect, mass analysis of the solution was also conducted. A high resolution-mass spectral peak of the compound in solution B was observed at m/z 425.1947 $[M + Na]^+$. This was in good agreement with the exact mass of the corresponding silyl ester (calculated for $C_{22}H_{34}NaO_3Si_2$: 425.1944). Thus, the results proved that the silyl ether was one of the intermediates through the reductive bromination series.

On the basis of these results, the reaction pathway for reductive bromination of carboxylic acids is shown in Scheme 1. First, the dehydrogenative silylation of a carboxylic acid with a silane occurred to produce a silyl ester. Then, a second reduction led to deoxygenation of the silyl ester to produce the corresponding silyl ether. Finally, nucleophilic substitution with Me_3SiBr produced the brominated product.[19]

In summary, we have demonstrated the indium-catalyzed reductive bromination of a carboxylic acid with 1,1,3,3-tetramethyldisiloxane (TMDS) and trimethylbromosilane (Me_3SiBr). This reducing system tolerated several functional groups, such as halogens, a hydroxy group, a thioether moiety, and an alkene. Also, we have clarified a reaction pathway for a reductive bromination series by monitoring the time course with ^{13}C NMR.

CAUTION: *When we added bromine* (Br_2) *to a chloroform solution containing* $InBr_3$, $PhSiH_3$, *and a reducible substrate (entry 2 in Table 1)* under atmosphere, *we encountered a small explosion with combustion. Very careful attention is required for handling a hydrosilane and Lewis acids under atmosphere. Do not use a bromine source that functions as a strong oxidizing agent. See a related incident report.*[20]

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Supporting Information Available. Experimental details, characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[19] When 3-phenypropyltriethylsilyl ether was treated with $InBr_3$ (5 mol %) and Me_3SiBr (1 equiv), the corresponding 1-bromo-3-phenylpropane was obtained in a 32% yield. However, when the same reaction was conducted without $InBr_3$, the corresponding bromide was not formed at all. Thus, these results strongly supported the fact that $InBr_3$ promoted nucleophilic substitution of a silyl ether with TMSBr.

[20] Wells, A. S. *Org. Process Res. Dev.* **2010**, *14*, 484 and references cited therein.

The authors declare no competing financial interest.