A Facile Synthesis of Alkyl Iodides and Deuterated Alkyl Iodides by Hydroiodination and Deuterioiodination of Olefins

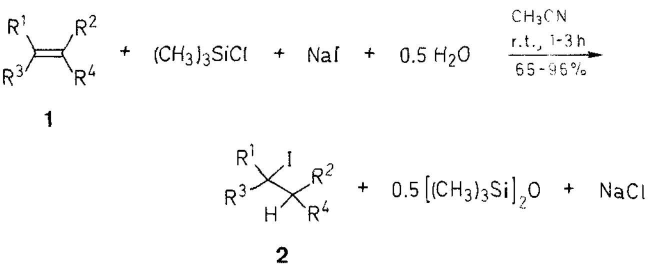
Shinji Irifune, Takao Kibayashi, Yasutaka Ishii,* Masaya Ogawa

Department of Applied Chemistry, Faculty of Engineering, Kansai University, Senriyama, Suita, Osaka 564, Japan

Chlorotrimethylsilane/sodium iodide in the presence of water has been found as facile method for the hydroiodination of olefins to alkyl iodides under mild conditions. This procedure has successfully been extended to the preparation of deuterated alkyl iodides by using deuterium oxide in place of water.

Alkyl iodides play an important role as the starting material in organic synthesis. Although the direct hydroiodination of olefins with hydriodic acid is straightforward in preparing alkyl iodides, this strategy is less often used because of the difficulty to accomplish the reaction in satisfactory yields. A solution of hydriodic acids tends to liberate iodine which causes side reactions. In general, hydrogen iodide is generated *in situ* by the action of potassium iodide and 95%-orthophosphoric acid,[1] and has frequently been used as the hydroiodination agent for olefins. This method, however, calls for the use of excess reagent (3–4 equiv) and a higher temperature (80 °C).[2] In recent years, alkyl iodides have been prepared from a variety of substrates (e.g., alcohols,[3] esters[3,4] and ethers[4,5] as well as lactones[3]) by the action of iodotrimethylsilane[6] or chlorotrimethylsilane/sodium iodide[3–5,7] reagent, but not from olefins which offer a wider range of substrate opportunities. Treatment of chlorotrimethylsilane/sodium iodide reagent with water is anticipated to provide a convenient alternative method for the *in situ* generaion of hydrogen iodide. In this paper, we wish to report a facile preparation of alkyl iodides and deuterated alkyl iodides by using chloromethylsilane/sodium iodide and water or deuterium oxide, respectively.

In order to establish an optimum condition for hydroiodination of olefins, cyclohexene (**1a**) was allowed to react with chlorotrimethylsilane/sodium iodide in the presence of water under several reaction conditions (Scheme A) (Table 1).



1, 2	R^1	R^2	R^3	R^4
a	$-(CH_2)_4-$		H	H
b	H	H	$(CH_2)_5CH_3$	H
c	CH_2CH_3	H	$(CH_2)_3CH_3$	H
d	H	CH_3	$(CH_2)_4CH_3$	H
e	H	H	H	CN
f	H	H	H	$COCH_3$

Scheme A

By the addition of 0.5 equivalent of water to chlorotrimethylsilane/sodium iodide reagent in acetonitrile, the addition of hydrogen iodide to **1a** proceeded smoothly to give iodocyclohexane (**2a**) in almost theoretical yield. No reaction took place under strictly anhydrous condition, but the reaction was not disturbed even in the presence of excess water in the reaction system. To complete the hydroiodination, a stoichiometric amount of chlorotrimethylsilane/sodium iodide reagent was needed. In a similar manner, trichloromethylsilane[8] was also found to be efficient for the hydroiodination of **1a**.

1-Octene (**1b**) was treated with a slight excess of reagent, chlorotrimethylsilane/sodium iodide/water (1.2:1.2:0.6), at room temperature, giving 2-iodooctane (**2b**)[9] in 64% yield. When the same reaction was carried out by using 1.0 equivalent of water, the hydroiodination was effected within 1 h to form **2b** in almost quantitative yield. 2-Ethyl-1-hexene (**1c**) reacted somewhat slowly with hydrogen iodide, affording 3-iodo-3-methylheptane (**2c**) in 86% yield. In these reactions, addition of hydrogen iodide to olefins occurred according to Markovnikov's rule affording a sole product. But 2-octene (**1d**) provided a 1:1 regioisomeric mixture of 2-iodooctane (**2b**) and 3-iodooctane (**2d**) whose ratio depended on the reaction conditions, especially temperature. For instance, at higher temperature (80 °C), thermodynamically more stable compound **2d** was formed in preference to **2b**.

Table 1. Reaction of a Variety of Substrates with $ClSiMe_3/NaI/H_2O$ Reagent[a]

Sub-strate	*Product*	*Time* (h)	*Yield*[b] (%)	*IR (Film)* ν (cm^{-1})	^{13}C-*NMR* ($CDCl_3/TMS$) δ	*MS* m/z
1a	**2a**	1	96	2950, 1460, 1260, 1180, 850, 660	23.3 (t); 25.3 (t); 30.5 (d); 37.7 (t)	210 (M^+)
1a[c]	**2a**	1	92			
1a[d]	**2a**	1	45			
1a[e]	**2a**	1	90			
1b	**2b**	1	65	2950, 1460, 1380, 1140, 850	13.9 (q); 22.5 (t); 28.4 (t); 28.9 (q); 29.6 (t); 30.4 (d); 31.6 (t); 42.9 (t)	113 ($M^+ - I$)
1b[f]	**2b**	1	98			
1c	**2c**	1.5	86	2900, 1460, 1380, 1130, 860	12.3 (q); 14.0 (q); 22.6 (t); 29.8 (t); 34.5 (q); 40.9 (t); 47.6 (t); 62.3 (s)	113 ($M^+ - I$)
1d[h]	**2b** + **2d**	1	82[g]	2950, 1460, 1380, 1150, 860	13.9 (q); 22.5 (t); 28.4 (t); 28.9 (q); 29.6 (t); 30.4 (d); 31.6 (t); 42.9 (t) 14.0 (q); 22.6 (t); 29.2 (t); 31.0 (d); 33.7 (t); 40.2 (t); 42.4 (t)	113 ($M^+ - I$)
1d	**2b** + **2d**	3	81[i]			
1e	**2e**	1	86	2950, 2250, 1420, 1250, 1180, 880	−7.5 (t); 20.6 (t); 116.3 (s)	181 (M^+)
1f	**2f**	3	66	2950, 1710, 1410, 1370, 1180	−4.5 (t); 14.2 (q); 46.9 (t); 205.5 (s)	–[j]
3	**4**	0.5	79	2900, 1710, 1460, 1380, 1140, 860	6.6 (t); 13.5 (q); 22.0 (t); 34.0 (d); 127.9 (d); 134.7 (d)	–[j]
3[k]	**4**	3	4			
5	**6**	0.5	36	3400, 2900, 1630, 1410, 1040, 910	70.7 (t); 110.2 (s); 124.2 (t)	–[j]
5[f]	**6**	1	57			

[a] Substrate (10 mmol) was allowed to react with $ClSiMe_3$ (12 mmol)/NaI (12 mmol)/H_2O (6 mmol) in MeCN (15 mL) at r.t.

[b] Determined by GC.

[c] H_2O (30 mmol) was used.

[d] $ClSiMe_3$ (5 mmol)/Na (10 mmol)/H_2O (10 mmol) was used.

[e] Cl_3SiMe (12 mmol) was used instead of $ClSiMe_3$.

[f] $ClSiMe_3$ (20 mmol)/NaI (20 mmol)/H_2O (10 mmol) was used.

[g] The ratio of **2b** to **2d** was about 1:1.

[h] Reaction was performed at 80 °C.

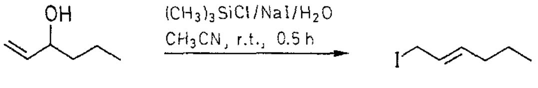
[i] The ratio of **2b** to **2d** was about 3:7.

[j] Because of decomposition of the product in the measurement, parent peak was not obtained.

[k] 95%-Orthophosphoric acid (20 mmol)/KI (20 mmol) was used.

The addition of hydrogen iodide to α, β-unsaturated olefins, such as acrylonitrile (**1e**) and methyl vinyl ketone (**1f**), could be achieved with ease, giving 1-cyano-2-iodo-ethane (**2e**)[11] and 3-iodo-2-propanone (**2f**),[12,13] respectively, in good yields.

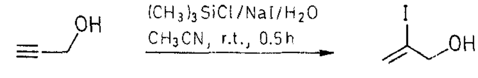
It is interesting to note that 3-hydroxy-1-hexene (**3**), involving a terminal double bond, when treated with the reagent in acetonitrile at room temperature induced S_N2' type reaction (allylic rearrangement) to give 1-iodo-2-hexene (**4**) (Scheme **B**). However, when the same reaction was carried out instead by the conventional method using phosphoric acid/potassium iodide as the hydroiodination reagent under similar condition, **4** was formed in poor yield (4%).



3 **4**

Scheme **B**

For propargyl alcohol (**5**), the addition of hydrogen iodide occurred with difficulty to form 3-hydroxy-2-iodo-1-propene (**6**)[10] in moderate yield (36%) (Scheme **C**). The yield of **6** was slightly improved when the reaction was conducted using 2 equivalent of the reagent. In these reactions, allene as a byproduct, which is expected from S_N2' type reaction, was not produced.



5 **6**

Scheme C

Table 2 summarizes the reaction of a series of bicyclo[2.2.1]heptenes **7** with the chlorotrimethylsilane/sodium iodide/ water reagent (Scheme **D**).

Table 2. Reaction of Bicyclo[2.2.1]heptenes with $ClSiMe_3/NaI/H_2O$ Reagent[a]

Substrate	Product	Yield[b] (%)	IR (Film) ν (cm^{-1})	^{13}C-NMR ($CDCl_3$/TMS) δ	MS *m/z*
7a	**8a**	90[a]	2920, 1440, 1300, 1210, 1170, 940, 750	28.4 (t); 28.7 (t); 30.0 (d); 36.3 (t); 37.9 (d); 45.2 (t); 47.9 (d)	222 (M^+)
7b	**8b**	91[c]	3040, 2940, 1450, 1610, 580	28.9 (d); 29.7 (t); 39.1 (d); 42.7 (d); 44.1 (t); 44.3 (t); 51.9 (d); 54.9 (d); 130.6 (d); 132.4 (d)[d] 32.0 (d); 37.6 (t); 39.4 (d); 41.3 (d); 42.4 (t); 43.1 (t); 50.6 (d); 53.6 (d); 131.6 (d); 131.9 (d)[e]	270 (M^+)

[a] Substrate (10 mmol) was allowed to react with $ClSiMe_3$ (12 mmol)/NaI (12 mmol)/H_2O (6 mmol) in MeCN (15 mL) at r.t. for 3 h.

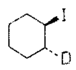
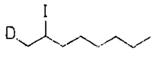
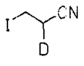
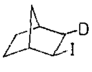
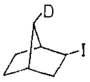
[b] Determined by GC.

[c] Isolated yield.

[d] *exo*-8-iodo isomer.

[e] *exo*-9-iodo isomer.

Table 3. Deuterioiodination of Olefins with $ClSiMe_3/NaI/D_2O$ Reagent[a]

Substrate	Product	Yield[b] (%)	IR (Film) ν (cm^{-1})	^{13}C-NMR ($CDCl_3$/TMS) δ[c]	MS *m/z*
1a	**9** 	92	2900, 2400, 1450, 1260, 1170, 980	23.4 (t); 25.4 (t); 25.5 (t); 30.4 (d); [36.5, 37.4, 38.3]; 37.7 (t)	211 (M^+)
1b	**10** 	65	2950, 2300, 1460, 1380, 950, 720	14.0 (q); 22.6 (t); 28.4 (t); [28.6, 28.9, 29.1]; 29.6 (t); 30.4 (d); 31.6 (t); 42.9 (t)	114 (M^+ – I)
1b	**10**[d]	96			
1e	**11** 	87	3050, 2950, 2250, 1430, 1260, 1200	–7.5 (t); [19.4, 20.3, 21.2]; 116.3 (s)	182 (M^+)
7a	**12** 	85[d]	2920, 2350, 1440, 1300, 1200, 940	28.4 (t); 28.7 (t); 30.0 (d); 36.2 (t); 37.8 (d); [43.8, 44.7, 45.6]; 47.9 (d)	223 (M^+)
	13 			28.4 (t); 28.7 (t); 30.0 (d); [35.0, 35.9, 36.8]; 37.8 (d); 45.1 (t); 47.9 (d)	

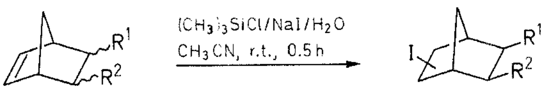
[a] Substrate (10 mmol) was allowed to react with $ClSiMe_3$ (12 mmol)/NaI (12 mmol)/D_2O (6 mmol) in MeCN (15 mL) at r.t. for 3 h.

[b] Determined by GC.

[c] The δ-values in square brackets refer to the carbon carrying the deutero atom.

[d] $ClSiMe_3$ (20 mmol)/NaI (20 mmol)/D_2O (10 mmol) was used.

[e] The ratio of **12** to **13** was about 1 : 1.



7 → 8

7, 8	R^1	R^2
a	H	H
b	–(CH=CHCH$_2$)–	

Scheme D

Treatment of bicyclo[2.2.1]hept-2-ene (**7a**) with chlorotrimethylsilane/sodium iodide/water in acetonitrile afforded *exo*-2-iodobicyclo[2.2.1]heptane (**8**)[9] in 90% yield. The NMR measurement of the product showed no formation of *endo*-isomer. The addition of hydrogen iodide to *endo*-tricyclo[5.2.1.0^{2,8}]deca-3,8-diene (**7b**) gave a 4:1 regioisomeric mixture of *exo*-8- and *exo*-9-iodo-*exo*-tricyclo[5.2.1.0^{2,6}]deca-3-enes (**8b**) in 91% isolated yield, although **8b** is reported to formed only in 44% yield in the literature procedure.[14] Even when the pure *endo*-**7b** was used as the starting compound, only *exo*-iodides (**8b**) were formed. Thus, the addition of hydrogen iodide to bicyclo[2.2.1]heptenes (**7**) took place always accompanying the Wagner-Meerwein rearrangement to form the adducts having *exo*-configuration.

The deuterioiodination of olefins could be easily accomplished when deuterium oxide was used in place of water in the above reaction (Table 3). This procedure offers a new and facile synthetic route to the deuterated compounds which are especially important as label compounds.

Cyclohexene (**1a**) was allowed to react with an approximately stoichiometric amount of the chlorotrimethylsilane/sodium iodide/deuterium oxide (ca. 1:1:0.5) reagent, giving 92% of 1-iodo-cyclohexane-1-*d* (**9**) in which the deuterium is incorporated better than 95%.[15] The reaction of 1-octene (**1b**) with a stoichiometric chlorotrimethylsilane/sodium iodide/deuterium oxide gave 2-iodooctane-1-*d* (**10**) in 65% yield, but the use of 2 equivalents of chlorotrimethylsilane/sodium iodide reagent provided **10** in satisfactory yield (96%). Acrylonitrile (**1e**) was also deuterated to 3-iodopropionitrile-2-*d* (**11**) in good yield. Bicyclo[2.2.1]heptene (**7a**) yielded a 1:1 mixture of *exo*-2-*d*-*exo*-3-iodobicyclo[2.2.1]heptane (**12**) and *syn*-7-*d*-*exo*-2-iodobicyclo[2.2.1]heptane (**13**).[16]

In conclusion, the hydroiodination of olefins is smoothly carried out by chlorotrimethylsilane/sodium iodide/water mixture under mild conditions, and the alkyl iodides are obtained in high yields without any troublesome work-up. In addition, the present method offers a novel synthesis of deuterated compounds from olefins by using deuterium oxide, inexpensive and easy to handle, as the deuterium source.

Hydroiodination of Olefins, Preparation of Iodides 2a–f, 6, 8a–e; General Procedure:

To an efficiently stirred solution of NaI (1.8 g, 12 mmol) in MeCN (15 mL) is slowly added ClSiMe$_3$ (1.5 mL, 12 mmol), water (108 mg, 6 mmol) and then the appropriate olefin (10 mmol). The reaction is allowed to react at room temperature for 1 h. The reaction is quenched with water (10 mL) and the product is extracted with ether (3 × 15 mL). The ether layer is washed with 10% Na$_2$S$_2$O$_3$ solution (20 mL) and dried (MgSO$_4$). Evaporation of the ether gives almost pure iodide. The iodides are further purified, if necessary, by column chromatography on silica gel by eluting successively with hexane (Table 1). The spectral data of the products were compared with those reported in the literature[1,9–12,14]

Conversion of 3-Hydroxy-1-hexene (3) to 1-Iodo-2-hexene (4):

To a vigorously stirred solution of NaI (1.8 g, 12 mmol) in MeCN (15 mL) is slowly added ClSiMe$_3$ (1.5 mL, 12 mmol) and then water (108 mg, 6 mmol). To the stirred mixture is added 3-hydroxy-1-hexene (**3**) 1.0 g (10 mmol) at a time, and the mixture is allowed to react at room temperature for 0.5 h. The reaction is quenched with water (10 mL) and extracted with ether (3 × 15 mL). The ether layer is washed with 10% Na$_2$S$_2$O$_3$ solution (20 mL) and dried (MgSO$_4$). Evaporation of the ether gives almost pure 1-iodo-2-hexene (**4**); yield: 1.7 g (79%).

Deuterioiodination of Olefins; General Procedure:

The reaction is carried out in a stream of nitrogen. To a well stirred solution of dry NaI (1.8 g, 12 mmol) in dry MeCN (15 mL) is added slowly ClSiMe$_3$ (1.5 mL, 12 mmol) and the D$_2$O (120 mg, 6 mmol), with continuous good stirring. To the mixture is added olefin (10 mmol) at a time, and the mixture is allowed to react at room temperature for 3 h. The reaction is quenched with water (10 mL, not D$_2$O) and extracted with ether (3 × 15 mL). The ether layer is washed with 10% Na$_2$S$_2$O$_3$ solution (20 mL) and dried (MgSO$_4$). After evaporation of ether, the product is subject to column chromatography on silica gel by eluting successively with hexane (Table 3). The product are identified by ^{13}C-NMR, GC-MS and IR.

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