Convenient Chlorination with Concentrated Hydrochloric Acid in the Presence of Iodosylbenzene

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Abstract: An efficient chlorination of β-keto esters, 1,3-diketones, and alkenes was performed conveniently with concentrated HCl in the presence of PhIO, selectively giving α-chloro-β-keto esters, 2-chloro-1,3-diketones, and 1,2-dichloroalkanes, respectively. It was suggested that the chlorination took place with (dichloroiodo)benzene generated in situ. A selective *anti*-addition was observed in the chlorination of indene.

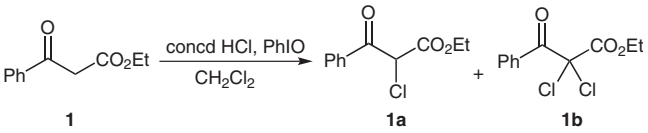
Key words: chlorination, hydrochloric acid, iodosylbenzene, iodine, halogenation

Chlorination is one of the fundamental reactions in organic chemistry and has been widely studied both in mechanistic and synthetic fields.[1] Although chlorine gas is mainly and conveniently used in chlorination reaction, it is highly toxic and not easy to handle. For laboratory use, the chlorine gas is generated by a conventional method and used for the chlorination. A special caution should be paid due to the high toxicity.

On the other hand, recently hypervalent iodine compounds have been extensively used in organic synthesis. (Dichloroiodo)benzene and its analogues have been reported as useful chlorinating reagents, which replace gaseous chlorine and can be applied to the chlorination of many substrates involving alkenes, alkynes, carbonyl compounds, and electron-rich aromatic compounds.[2]

Although most of the (dichloroiodo)arenes are stable crystals, they decompose gradually on standing at room temperature.[3] Therefore, it is recommended to use them immediately or within a short period after the preparation. Very recently, we found that $PhIF_2$ prepared in situ from aqueous HF and PhIO fluorinated the 1,3-dicarbonyl compounds efficiently.[4] Thus, we thought that the most convenient chlorination method might involve the in situ preparation of (dichloroiodo)arenes without isolation. For the choice of the reagents affording (dichloroiodo)arenes, the inertness toward the substrates must be considered. When the chlorination reaction using concentrated hydrochloric acid in the presence of iodosylbenzene (PhIO) as a mild oxidant was examined, it was found that several substrates such as alkenes, alkynes, and 1,3-dicarbonyl compounds underwent the chlorination efficiently. Here we report the convenient chlorination using concentrated hydrochloric acid and PhIO.

First, the reaction of ethyl benzoylacetate (**1**) as a substrate to optimize the reaction conditions was examined, as shown in Equation 1. After stirring a mixture of concentrated HCl (10 mmol) and PhIO (1.2 mmol) in CH_2Cl_2 or 1,2-dichloroethane (DCE) at room temperature for 15 minutes, **1** (1 mmol) was added. The reaction mixture was stirred at 40 °C for 24 hours. Column chromatography of the products on silica gel gave ethyl 2-chlorobenzoylacetate (**1a**) and ethyl 2,2-dichlorobenzoylacetate (**1b**) in 76 and 19% yield, respectively (Table 1, entry 1). The two-hour reaction also afforded the similar result, suggesting that the chlorination reaction proceeded readily within a short time (entry 2). Also, the use of half the amount of concentrated HCl (5 mmol) and a one-hour reaction resulted in the similar results (entries 3 and 4). Inversely, when the amounts of concentrated HCl and PhIO were increased to 10 and 3 mmol, respectively, the yield of **1a** was decreased to 50%, but that of **1b** was increased to 49% (entry 5).



1 **1a** **1b**

Equation 1

Table 1 Chlorination of Ethyl Benzoylacetate (**1**) with Concentrated HCl and PhIO[a]

Entry	HCl (mmol)	PhIO (mmol)	Time (h)	**1a** (%)[b]	**1b** (%)[b]
1	10	1.2	24	76	19
2	10	1.2	2	75	16
3	5	1.2	2	77	15
4	5	1.2	1	77	14
5[c]	10	3	2	50	49

[a] Conditions: **1** (1 mmol), concd HCl, PhIO, and CH_2Cl_2 (2 mL) at 40 °C.
[b] Isolated yield.
[c] DCE (2 mL) was used as solvent.

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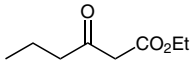
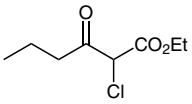
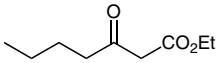
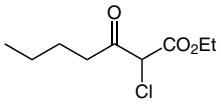
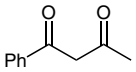
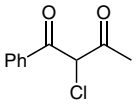
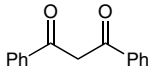
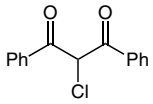
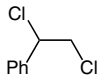
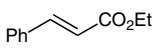
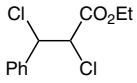
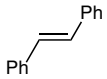
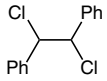
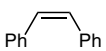
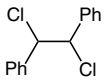
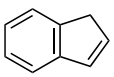
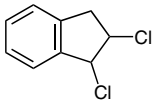
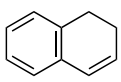
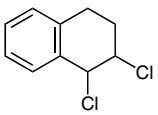
With the optimized conditions (Table 1, entries 3 or 4) in hand, the scope of this chlorination reaction for other substrates was examined. The results are given in Table 2. The chlorination of aliphatic β-keto esters, ethyl 3-oxohexanoate (**2**) and ethyl 3-oxoheptanoate (**3**), gave the chlorinated products **2a** and **3a** in 62 and 60% yield, respectively (entries 1 and 2). 1,3-Diketones, benzoylacetone (**4**) and dibenzoylmethane (**5**), afforded the corresponding chlorinated products **4a** and **5a** in 70 and 91% yield, respectively (entries 3 and 4). Next, several kinds of alkenes such as styrene (**6**), ethyl cinnamate (**7**), *trans*-stilbene (**8**), *cis*-stilbene (**9**), indene (**10**), and 1,2-dihydronaphthalene (**11**) were chlorinated under this condition. The chlorination of alkenes proceeded effectively to give the corresponding dichlorides **6a**–**11a** in good yields (entries 5–10).

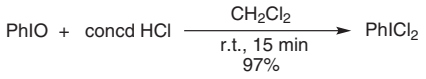
To clarify the chlorination mechanism, the real species for the chlorination reaction had to be identified. Since the chlorinating species was either a chlorine molecule or (dichloroiodo)benzene, we sought to determine whether (dichloroiodo)benzene was formed in the reaction. When a suspension of PhIO in CH_2Cl_2 was reacted with concentrated HCl at room temperature for 15 minutes, $PhICl_2$ was obtained in 97% yield as pale yellow crystals (Equation 2). This indicates that PhIO is readily converted into $PhICl_2$ with concentrated HCl, in analogy with the previously reported reaction of PhIO with chlorotrimethylsilane.[5]

Table 2 Chlorination with Concentrated HCl and PhIO[a]

Entry	Substrate	Time (h)	Product	Yield (%)[b]
1	**2** 	0.5	**2a** 	62
2	**3** 	0.5	**3a** 	60
3	**4** 	1	**4a** 	70
4	**5** 	0.5	**5a** 	91
5	**6** 	5	**6a** 	56
6	**7** 	5	**7a** 	73
7	**8** 	5	**8a** 	90
8	**9** 	2	**8a** 	93
9	**10** 	5	**10a** 	77
10	**11** 	5	**11a** 	88

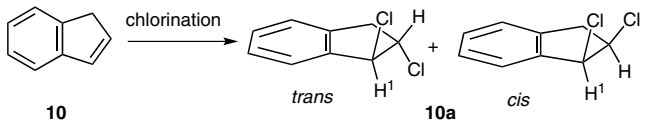
[a] Conditions: substrate **2**–**11** (1 mmol), concd HCl (5 mmol), PhIO (1.2 mmol), and CH_2Cl_2 (2 mL) at 40 °C.

[b] Isolated yield.



Equation 2

As reviewed before,[2] the mechanism of chlorination with $PhICl_2$ is complicated and depends on the reaction conditions. Then, the stereochemistry of the dichloride obtained by the chlorination of indene (Equation 3), which has been extensively discussed,[6] was checked. According to the literature,[6] the stereochemistry of the chlorinated products can be analyzed by ^1H NMR in benzene-d_6, where the characteristic proton at the 1-position of 1,2-dichloroindane appears at 5.07 ppm for the *trans*-adduct and 4.80 ppm for the *cis*-adduct. The chlorination of indene with chlorine gas under the present conditions (0.5 M) gave an isomeric mixture (55:45) of the *cis*- and *trans*-adducts (Table 3, entry 2). This is in accord with the result that the ratio of the *cis*-adduct increases at a high concentration.[6] However, the dichloride **10a** obtained in the present reaction (concd HCl/PhIO) showed that the ratio was 18:82 (entry 3), suggesting that the present chlorination proceeded predominantly via *anti*-addition. Furthermore, when indene was chlorinated with $PhICl_2$, it was found that the product was 100% the *trans*-adduct (entry 4), indicating a high stereoselective reaction. The previous studies report that the chlorination of cyclic alkenes with $PhICl_2$ gives *trans*-adduct of dichlorides.[7] Therefore, the present reaction exhibited almost the same result as the chlorination with $PhICl_2$, but was quite different from the chlorination reaction with molecular chlorine. The detail process of the *anti*-addition is still unclear, but the high stereoselectivity is of great value in organic synthesis.



Equation 3

Table 3 Stereochemistry of 1,2-Dichloride **10a** by Chlorination of Indene (**10**) Under Various Conditions

Entry	Conditions (concentration)	*trans*-adduct (%)[a]	*cis*-adduct (%)[a]
1[b]	Cl_2, DCE (0.16 M)	49.5	50.5
2[c]	Cl_2, DCE (0.5 M)	45	55
3[c]	concd HCl, PhIO, DCE (0.5 M)	82	18
4[c]	$PhICl_2$, DCE (0.5 M)	100	0

[a] The percentages were calculated based on ^1H NMR spectra in benzene-d_6.

[b] Reference 6.

[c] This work.

In conclusion, we have demonstrated that a simple mixed reagent of concentrated HCl and PhIO chlorinates a variety of organic substrates involving β-keto esters, 1,3-diketones, and alkenes. This reaction was suggested to proceed via the formation of $PhICl_2$. The high efficiency and high selectivity of the chlorination reaction will bring further advantages in organic synthesis as a convenient procedure without chlorine gas.

All solvents and starting materials were commercially available and used as received without further purification. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-AL 300 FT-NMR spectrometer ($SiMe_4$ as an internal standard). Melting points were measured with a YANACO micro melting point apparatus and are uncorrected. Column chromatographic separation was carried out using Silica Gel 60, spherical (Kanto Chemical Co.).

Chlorination with Concentrated HCl in the Presence of PhIO; General Procedure

In a test tube were placed PhIO (1.2 mmol), concd HCl (12 M, 5 mmol, 0.42 mL), and CH_2Cl_2 (2 mL) and the mixture was stirred for 15 min at r.t. To the resulting reagent mixture was added the appropriate substrate (1 mmol) and the mixture was stirred at 40 °C for the time given in Table 1. After the reaction, the mixture was neutralized with aq $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (15 mL) and dried (anhyd Na_2CO_3). After evaporation of the solvent, the product was isolated by column chromatography on silica gel or by distillation (Table 1).

Ethyl 2-Chloro-3-oxo-3-phenylpropanoate (1a)[8]

Yield: 174 mg (77%); colorless oil.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.2 Hz, 3 H, CH_3), 4.24 (q, *J* = 7.2 Hz, 2 H, CH_2), 5.61 (s, 1 H, CH), 7.46 (t, *J* = 7.5 Hz, 2 H, ArH), 7.59 (t, *J* = 7.5 Hz, 1 H, ArH), 7.96 (d, *J* = 7.5 Hz, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.70, 57.82, 63.01, 128.77, 129.08, 133.25, 134.21, 165.10, 188.14.

Ethyl 2,2-Dichloro-3-oxo-3-phenylpropanoate (1b)[9]

Yield: 39 mg (15%); colorless oil.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 7.2 Hz, 3 H, CH_3), 4.31 (q, *J* = 7.2 Hz, 2 H, CH_2), 7.47 (t, *J* = 7.5 Hz, 2 H, ArH), 7.61 (t, *J* = 7.5 Hz, 1 H, ArH), 8.04 (d, *J* = 7.5 Hz, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.48, 64.60, 81.88, 128.59, 129.99, 130.84, 134.14, 163.96, 183.16.

Ethyl 2-Chloro-3-oxohexanoate (2a)[10]

Yield: 119 mg (62%); colorless oil.

^1H NMR spectrum in $CDCl_3$ showed that **2a** contained 23% of the enol form.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.2 Hz, CH_3), 0.99 (t, *J* = 7.2 Hz, CH_3), 1.32 (t, *J* = 7.2 Hz, CH_3), 1.36 (t, *J* = 7.2 Hz, CH_3), 1.60–1.73 (m, CH_2), 2.50 (dt, *J* = 0.9, 7.2 Hz, CH_2), 2.67–2.73 (m, CH_2), 4.26–4.31 (m, CH_2), 4.81 (s, CH), 12.42 (t, *J* = 0.9 Hz, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.20, 13.52, 13.75, 13.94, 16.80, 19.12, 34.58, 40.60, 60.80, 61.77, 62.87, 96.42, 164.89, 169.40, 175.49, 198.65.

Ethyl 2-Chloro-3-oxoheptanoate (3a)[11]

Yield: 124 mg (60%); colorless oil.

^1H NMR spectrum in $CDCl_3$ showed that **3a** contained 19% of the enol form.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.2 Hz, CH_3), 0.94 (t, *J* = 7.2 Hz, CH_3), 1.29–1.36 (m, CH_2 and CH_3), 1.57–1.64 (m, CH_2), 2.52 (t, *J* = 7.2 Hz, CH_2), 2.68–2.74 (m, CH_2), 4.26–4.33 (m, CH_2), 4.79 (s, 1 H, CH), 12.42 (s, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.66, 13.67, 13.87, 14.07, 21.94, 22.26, 25.47, 27.81, 32.57, 38.55, 60.89, 61.87, 63.00, 96.39, 165.01, 169.50, 175.87, 198.96.

2-Chloro-1-phenylbutan-1,3-dione (4a)[12]
Yield: 138 mg (70%); colorless oil.

^{1}H NMR spectrum in $CDCl_3$ showed that **4a** contained 27% of the enol form.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, CH_3), 2.34 (s, CH_3), 5.51 (s, CH), 7.35–7.91 (m, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.50, 26.59, 64.14, 106.66, 127.92, 128.71, 128.91, 129.30, 131.27, 133.61, 134.41, 134.48, 180.42, 189.80, 195.08, 198.59.

2-Chloro-1,3-diphenylpropan-1,3-dione (5a)[12]
Yield: 235 mg (91%); white crystals; mp 86−87 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.30 (s, 1 H, CH), 7.11 (t, *J* = 7.2 Hz, 4 H, ArH), 7.33 (t, *J* = 7.2 Hz, 2 H, ArH), 7.71 (d, *J* = 7.2 Hz, 4 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 62.14, 128.79, 128.97, 133.64, 134.15, 189.28.

1,2-Dichloro-1-phenylethane (6a)[13]
Yield: 98 mg (56%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.88–4.01 (m, 2 H, CH_2), 4.96–5.01 (m, 1 H, CH), 7.35–7.42 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 48.32, 61.73, 127.37, 128.78, 129.13, 137.97.

Ethyl 2,3-Dichloro-3-phenylpropanoate (7a)[14]
Yield: 180 mg (73%); colorless oil; a 46:54 mixture of stereoisomers.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 7.2 Hz, CH_3), 1.36 (t, *J* = 7.2 Hz, CH_3), 4.04 (q, *J* = 7.2 Hz, CH_2), 4.34 (q, *J* = 7.2 Hz, CH_2), 4.60 (d, *J* = 10.7 Hz, CH), 4.65 (d, *J* = 8.4 Hz, CH), 5.18 (d, *J* = 10.7 Hz, CH), 5.28 (d, *J* = 8.4 Hz, CH), 7.30–7.44 (m, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.65, 13.91, 58.98, 61.04, 62.37, 62.58, 62.59, 63.63, 127.78, 128.05, 128.68, 128.75, 129.38, 136.41, 136.84, 166.53, 167.39.

1,2-Dichloro-1,2-diphenylethane (8a)[14]
Yield: 226 mg (90%) for entry 7, Table 2 and 234 mg (93%) for entry 8, Table 2; white crystals; mp 188–195 °C; a mixture of stereoisomers.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.21 (s, CH), 5.23 (s, CH), 7.13-7.21 (m, ArH), 7.34–7.44 (m, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 65.70, 67.66, 128.01, 128.07, 128.12, 128.49, 128.60, 128.94, 137.25, 138.29.

***trans*-1,2-Dichloroindane (*trans*-10a)[6]**
Yield: 144 mg (77%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.13–3.20 (m, 1 H, CH), 3.65–3.72 (m, 1 H, CH), 4.62–4.66 (m, 1 H, CH), 5.33 (d, *J* = 2.7 Hz, 1 H, CH), 7.23–7.45 (m, 4 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.74, 64.46, 67.62, 125.05, 125.45, 127.89, 129.65, 139.80, 139.83.

1,2-Dichloro-1,2,3,4-tetrahydronaphthalene (11a)[15]
Yield: 177 mg (88%); colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.09–2.14 (m, 1 H, CH), 2.59–2.70 (m, 1 H, CH), 2.80–2.88 (m, 1 H, CH), 3.08–3.19 (m, 1 H, CH), 4.61–4.65 (m, 1 H, CH), 5.22 (d, *J* = 3.0 Hz, 1 H, CH), 7.11–7.35 (m, 4 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.85, 25.03, 59.45, 59.76, 126.64, 128.75, 129.01, 131.00, 132.36, 134.84.

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