A Safe, Convenient and Efficient One-Pot Synthesis of α-Chloroketone Acetals Directly from Ketones Using Iodobenzene Dichloride

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Abstract: Various ketones, including aliphatic and aromatic ketones, can be directly converted into their corresponding α-chloroketone acetals in high to excellent yields using iodobenzene dichloride in ethylene glycol in the presence of 4 Å molecular sieves at room temperature.

Key words: ketones, iodobenzene, dichloride, halogenation, hypervalent iodine, acetals

α-Chloroketone acetals are valuable synthetic intermediates in organic synthesis.[1] For example, nucleophilic substitution reaction of α-chlorocyclohexanone acetal with nucleophiles such as allyltrimethylsilane, in the presence of a Lewis acid, has been reported.[1a] Furthermore, dehydrochlorination of α-chloroketone acetals provides a reliable way to produce α,β-unsaturated ketones.[1c–e] Usually, α-chloroketone acetals are prepared from ketones via two separate steps, that is, the α-chlorination of ketones[2] followed by the acetalization of the resulting α-chloroketones.[3] The use of molecular chlorine for the direct conversion of acetone into the cyclic ketal of chloroacetone in ethylene glycol has been repoted,[4] however, since chlorine is a toxic gas and difficult to handle safely, this method has not gained widespread use in organic synthesis. Therefore, it is highly desirable to develop a safe, simple, easy to handle, and efficient protocol with which to transform various ketones directly into their corresponding α-chloroketone acetals.

Iodobenzene dichloride ($PhICl_2$), the first reported hypervalent iodine reagent, was synthesized by C. Willgerodt in 1886.[5] Because of its low toxicity and ease of handling, it has been mainly used to replace molecular chlorine as a chlorinating reagent in organic synthesis.[6] For example, Garvey et al. first observed that the reaction of iodobenzene dichloride with unsaturated hydrocarbons in refluxing ethylene dichloride gave the same products as chlorine addition.[7] One example was given for an aromatic substitution reaction in which iodobenzene dichloride was successfully applied to chlorinate *p*-aminoacetophenone on a large scale.[8] Moreover, Breslow et al. have shown beautiful examples of template-directed chlorination of an inactivated C–H bond in steroids using iodobenzene dichloride.[9] Numerous applications of iodobenzene dichloride for the introduction of elemental chlorine into a range of metal complexes have also been described.[10] Iodobenzene dichloride has also been employed to facilitate the α-chlorination of ketones in various organic solvents, including acetic acid, acetonitrile, and toluene, to afford the corresponding α-chlorocarbonyl compounds.[11] Herein, as part of our ongoing program on the exploration of new reactivity of iodobenzene dichloride,[12] we present a safe, convenient and highly efficient one-pot procedure for the synthesis of α-chloroketone acetals directly from various ketones using iodobenzene dichloride in ethylene glycol in the presence of 4 Å molecular sieves at room temperature.

When cyclohexanone was subjected to treatment with 1.1 equivalents of iodobenzene dichloride in methanol at room temperature, it was interesting to find that 2-chloro-1,1-dimethoxycyclohexane was formed in 96% yield after 30 minutes. Similarly, treatment of cyclopentanone under the same reaction conditions resulted in the formation of 2-chloro-1,1-dimethoxycyclopentane in a yield of 96%, again after 30 minutes. However, other ketones such as cycloheptanone, indan-1-one and α-tetralone gave only the corresponding α-chlorination products, 2-chlorocycloheptanone, 2-chloro-2,3-dihydroinden-1-one and 2-chloro-3,4-dihydronaphthalen-1(2*H*)-one, in 80%, 94% and 94% yield, respectively; in order to obtain their corresponding α-chloroketone acetals directly, two changes were made to the initial procedure. These adjustments were based on an understanding of working mechanism involved in the formation of 2-chloro-1,1-dimethoxycyclohexane directly from cyclohexanone (Scheme 1).

Firstly, electrophilic addition of iodobenzene dichloride to the enol form of cyclohexanone gave the intermediate **1**, which lost hydrochloric acid to yield intermediate **2**. Nucleophilic attack of a chloride anion on the α-carbon bearing the iodine(III) structural unit in **2**, yields the α-chloroketone with concomitant reductive elimination of iodobenzene and the formation of hydrochloric acid. The generated hydrochloric acid not only promotes the formation of the enol form of cyclohexanone but also catalyzes the formation of acetals in alcohols such as methanol. During acetalization of the 2-chlorocyclohexanone, one equivalent of water is produced. Since it is known that acetal functionality can be removed in the presence of water under acidic conditions, we therefore added 4 Å molecular sieves to the reaction mixture in order to remove the generated water. Furthermore, in order to produce more

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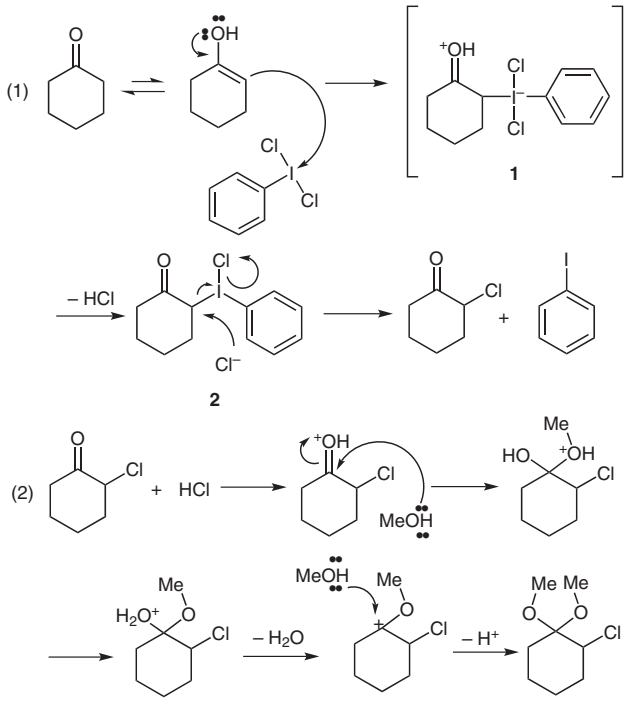
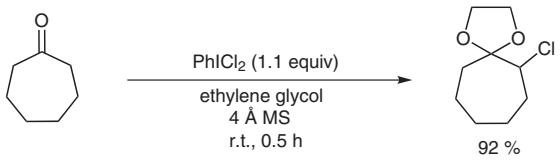


Scheme 1 Working mechanism

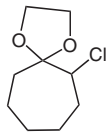
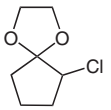
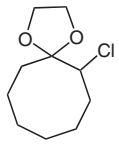
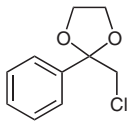
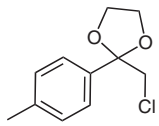
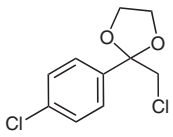
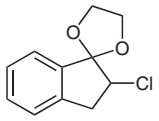
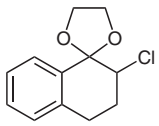
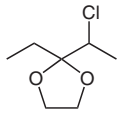
stable cyclic acetals, ethylene glycol was employed in place of methanol. Both changes were assumed to guarantee the formation of α-chloroketone acetal. Gratifyingly, after these two changes were made, we found that the reaction system $PhICl_2$/ethylene glycol/4 Å molecular sieves could directly convert cycloheptanone into its corresponding α-chloroketone acetal, 6-chloro-1,4-dioxaspiro[4.6]undecane, in an excellent yield within 30 minutes (Scheme 2).



Scheme 2 One representative example for the syntheses of α-chloroketone cyclic acetals from ketones

Other cyclic ketones such as cyclopentanone and cyclooctanone were also tested; their corresponding α-chloroketone acetals were obtained in high yields in 30 minutes (Table 1, entries 2 and 3). Aromatic ketones were good substrates under the present reaction conditions. In the case of acetophenone, the reaction gave the corresponding α-chloroacetophenone acetal in 82% yield within 30 minutes (entry 4). Similar results were obtained for 4′-methylacetophenone and 4′-chloroacetophenone (entries 5 and 6). Cyclic aromatic ketones such as indan-1-one and α-tetralone, gave the corresponding α-chloroketone acetals in 70% and 74% yield, respectively, in 30 minutes (entries 7 and 8). When the reaction of an aliphatic ketone, pentan-3-one, was examined under these reaction conditions, it was found that although the reaction afforded a good yield of the corresponding α-chloroketone acetal, a much longer reaction time was required (2 h) owing to the difficulty of generating the enol form of pentan-3-one compared with other tested ketones (entry 9).

Table 1 Substrate Scope[a]

Entry	Products	Time (min)	Yield (%)[b]
1		30	92
2		30	86[c]
3[d]		30	80
4		30	82
5		30	95
6		30	85
7[e]		30	70[c]
8[f]		30	74[c]
9		2 h	72[c]

[a] Reactions were conducted with 1 mmol of the ketone and 5 mL of solvent, under the conditions shown in Scheme 2.
[b] Isolated yield.
[c] GC yield.
[d] The yield of the minor product 2-chlorocyclooctanone was 10%.
[e] The yield of the minor product 2-chloro-2,3-dihydroinden-1-one was 18%.
[f] The yield of the minor product 2-chloro-3,4-dihydronaphthalen-1(2*H*)-one was 25%.

Though it has been reported that chlorination of acetone by molecular chlorine in ethylene glycol gave the cyclic

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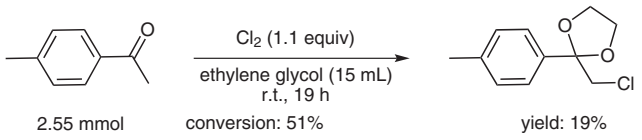
ketal of chloroacetone as the only product,[4] 4′-methylacetophenone, which was an excellent substrate under our conditions (Table 1, entry 5), performed poorly under the reported conditions,[4] with very low yields of the desired cyclic ketal of the chloroketone (Scheme 3).[13] This result indicated that, in some cases,[8,14] including the case described here, iodobenzene dichloride showed superior reactivity to that of molecular chlorine in terms of both chemical yield and selectivity.



Scheme 3 Treatment of 4′-methylacetophenone with chlorine gas

In conclusion, the reported hypervalent iodine reagent – iodobenzene dichloride – was found to effect the direct conversion of various ketones into their corresponding α-chloroketone acetals in high to excellent yields. Iodobenzene dichloride can be prepared in quantitative yield in five minutes by reacting iodobenzene with sodium hypochlorite in a dilute hydrochloric acid solution at room temperature.[12a] The readily availability of iodobenzene dichloride, as well as its low toxicity and ease of handling compared with those of molecular chlorine, make the present $PhICl_2$/ethylene glycol system an attractive alternative method for the effective synthesis of α-chloroketone acetals.

Iodobenzene dichloride was prepared according to the method developed in our lab.[12a] Ethylene glycol was dried over anhydrous $MgSO_4$, then distilled under reduced pressure and stored over 4 Å molecular sieves. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz, using a Bruker AV300 instrument; $CDCl_3$ was used as solvent. IR spectra were recorded on an FT-IR spectrometer (Bruker Equinox55) using KBr pellets. GC analyses were carried out on a Shimadzu 2014 series GC system equipped with an Rtx-5 column (30 m, ID 0.25 mm) and an FID; injector temperature = 250 °C, detector temperature = 300 °C. N_2 was used as the carrier gas, flow rate 3.0 mL/min. Temperature program: initial isothermal period of 3.0 min at 100 °C, then an increase at 10.0 °C/min to 250 °C with an isothermal period of 1 min at 250 °C. High-resolution mass spectral analyses (HRMS) were performed on a high-resolution APCI–FTICR mass spectrometer (Varian 7.0 T). Elementary Analyses were carried out on an Elemental Vario EL analyzer. Petroleum ether (PE), where used, had a boiling range 60–90 °C.

Synthesis of α-Chloroketone Acetals; Typical Procedure

To a solution of acetophenone (120 mg, 1 mmol) in anhydrous ethylene glycol (5 mL) in a 10 mL round-bottom flask, was added 4 Å MS and iodobenzene dichloride (302 mg, 1.1 mmol). The reaction was stirred at r.t. and monitored by TLC. After 30 min, the resulting mixture was diluted with EtOAc (50 mL) and washed with sat. aq $NaHCO_3$ (5 mL) and sat. aq $Na_2S_2O_3$ (5 mL). The combined aqueous phase was extracted with EtOAc (20 mL) and the combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford the crude product, which was purified by flash column chromatography (PE–EtOAc, 9:1) to give 2-chloromethyl-2-phenyl[1,3]dioxolane.

Yield: 162 mg (82%); colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.76 (s, 2 H), 3.89–3.94 (m, 2 H), 4.17–4.21 (m, 2 H), 7.35–7.41 (m, 3 H), 7.50–7.54 (m, 2 H).

^{13}C NMR (75 MHz): δ = 49.36, 65.77, 107.86, 125.96, 128.23, 128.72, 139.70.

2-Chloro-1,1-dimethoxycyclohexane[1a]

Colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30–1.37 (m, 1 H), 1.45–1.50 (m, 1 H), 1.60–1.62 (m, 1 H), 1.65–1.72 (m, 1 H), 1.74–1.79 (m, 2 H), 1.88–1.94 (1 H), 1.96–2.08 (m, 1 H), 3.20 (s, 3 H), 3.24 (s, 3 H), 4.21 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.34, 21.85, 26.79, 31.26, 47.07, 48.08, 59.24, 100.29.

2-Chloro-1,1-dimethoxycyclopentane

Colorless oil.

IR (KBr): 2960, 2832, 1468, 1437, 1333, 1174, 1122, 1082, 1049, 962, 823, 721, 553 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.61–1.69 (m, 1 H), 1.87–1.98 (m, 4 H), 2.26–2.32 (m, 1 H), 3.24 (s, 3 H), 3.31 (s, 3 H), 4.13 (d, *J* = 4.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.89, 28.98, 33.57, 48.98, 50.42, 62.13, 111.12.

Anal. Calcd for $C_7H_{13}ClO_2$: C, 51.07; H, 7.96. Found: C, 50.82; H, 7.78.

2-Chlorocycloheptanone[15]

Colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (s, 1 H), 1.42–1.65 (m, 3 H), 1.80–1.95 (m, 3 H), 2.12–2.22 (m, 1 H), 2.42–2.51(m, 1 H), 2.66–2.75 (m, 1 H), 4.36 (q, *J* = 4.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.03, 25.85, 28.87, 34.24, 40.13, 63.98, 206.21.

2-Chloroindan-1-one[16]

Pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.31 (dd, *J* = 3.9, 17.4 Hz, 1 H), 3.79 (dd, *J* = 7.8, 17.4 Hz, 1 H), 4.57 (dd, *J* = 3.9, 7.8 Hz, 1 H), 7.45 (t, *J* = 8.1 Hz, 2 H), 7.65–7.70 (m, 1 H), 7.85 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.40, 55.62, 124.80, 126.32, 128.19, 133.67, 135.95, 150.64, 199.05.

2-Chloro-1-tetralone[17]

White Solid; mp 103–105 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.41–2.52 (m, 1 H), 2.54–2.64 (m, 1 H), 2.95–3.05 (m, 1 H), 3.25–3.35 (m, 1 H), 4.64 (dd, *J* = 3.9, 7.5 Hz, 1 H), 7.29–7.38 (m, 2 H), 7.50–7.55 (m, 1 H), 8.09 (d, *J* = 7.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.22, 32.35, 59.75, 127.02, 128.42, 128.66, 130.39, 134.05, 143.05, 190.72.

6-Chloro-1,4-dioxaspiro[4.6]undecane (Table 1, Entry 1)[1c]

Colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.58–2.07 (m, 10 H), 3.93–4.10 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.37, 23.33, 26.03, 31.95, 34.76, 65.02, 65.45, 66.74, 111.14.

6-Chloro-1,4-dioxaspiro[4.4]nonane (Table 1, Entry 2)[1d]

Colorless oil.

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^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.67–1.77 (m, 1 H), 1.80–2.00 (m, 3 H), 2.06–2.14 (m, 1 H), 2.21–2.28 (m, 1 H), 3.96–4.10 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.73, 32.11, 33.02, 62.81, 64.98, 65.47, 116.18.

α-Chlorocyclooctanone Acetal (Table 1, Entry 3)
Colorless oil.

IR (KBr): 2926, 2684, 1726, 1642, 1447, 1332, 1158, 1084, 1032, 953, 853, 784, 716, 658, 505 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.52–1.73 (m, 8 H), 1.78–1.86 (m, 1 H), 1.95–2.03 (m, 1 H), 2.08–2.23 (m, 2 H), 3.94–4.01 (m, 2 H), 4.10–4.14 (m, 2 H), 4.40 (dd, *J* = 3.0, 8.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.04, 25.10, 25.64, 27.41, 33.37, 34.03, 65.30, 65.63, 66.12, 111.17.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{17}ClO_2$: 205.0990; found: 205.0997.

2-Chloromethyl-2-phenyl[1,3]dioxolane (Table 1, Entry 4)[3b]
Colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.76 (s, 2 H), 3.89–3.94 (m, 2 H), 4.17–4.21 (m, 2 H), 7.35–7.41 (m, 3 H), 7.50–7.54 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 49.36, 65.77, 107.86, 125.96, 128.23, 128.72, 139.70.

2-Chloromethyl-2-*p*-tolyl-1,3-dioxolane (Table 1, Entry 5)[18]
Colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 3.75 (s, 2 H), 3.87–3.95 (m, 2 H), 4.13–4.23 (m, 2 H), 7.18 (d, *J* = 5.7 Hz, 2 H), 7.40 (d, *J* = 5.7 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.13, 49.38, 65.72, 107.89, 125.91, 128.95, 136.70, 138.60.

2-Chloromethyl-2-(4-chlorophenyl)-1,3-dioxolane (Table 1, Entry 6)
White solid; mp 59–60 °C.

IR (KBr): 2958, 2895, 2853, 2284, 2053, 1916, 1874, 1800, 1642, 1600, 1479, 1437, 1389, 1295, 1221, 1174, 1079, 1026, 953, 826, 758, 689, 637, 511, 474 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.72 (s, 2 H), 3.88–3.92 (m, 2 H), 4.16–4.20 (m, 2 H), 7.34 (d, *J* = 6.3 Hz, 2 H), 7.46 (d, *J* = 6.3 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 49.16, 65.86, 107.59, 127.57, 128.48, 134.81, 138.27.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{10}Cl_2O_2$: 233.0131; found: 233.0129.

2′-Chloro-2′,3′-dihydrospiro([1,3]dioxolane-2,1′-indene) (Table 1, Entry 7)
White solid; mp 44–46 °C.

IR (KBr): 2929, 1729, 1602, 1466, 1430, 1313, 1269, 1226, 1133, 1076, 1035, 1016, 942, 872, 815, 759, 685, 641, 581, 485 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.15 (dd, *J* = 7.2, 15.6 Hz, 1 H), 3.40 (dd, *J* = 7.2, 15.6 Hz, 1 H), 4.21–4.34 (m, 4 H), 4.47 (t, *J* = 7.2 Hz, 1 H), 7.22–7.39 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.83, 63.23, 66.08, 66.36, 114.24, 123.36, 124.81, 127.64, 130.18, 139.29, 139.42.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{11}ClO_2$: 211.0520; found: 211.0517.

2′-Chloro-3′,4′-dihydro-2′*H*-spiro([1,3]dioxolane-2,1′-naphthalene) (Table 1, entry 8)
Pale-yellow oil.

IR (KBr): 2968, 2895, 2674, 2295, 1958, 1932, 1832, 1700, 1605, 1484, 1442, 1342, 1311, 1232, 1158, 1026, 942, 868, 758, 663, 611, 568, 511, 458 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30–2.42 (m, 1 H), 2.45–2.55 (m, 1 H), 2.81–2.91 (m, 1 H), 3.06–3.17 (m, 1 H), 4.22–4.33 (m, 4 H), 4.37 (dd, *J* = 3.0, 7.8 Hz, 1 H), 7.11–7.14 (m, 1 H), 7.21–7.30 (m, 2 H), 7.49–7.52 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.86, 29.11, 61.39, 66.23, 66.38, 106.69, 126.11, 126.36, 128.42, 128.80, 135.53, 136.22.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}ClO_2$: 225.0677; found: 225.0682.

2-(1-Chloroethyl)-2-ethyl-1,3-dioxolane (Table 1, Entry 9)
Colorless oil.

IR (KBr): 2981, 2939, 2885, 1454, 1377, 1196, 1157, 1066, 930, 783, 696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.5 Hz, 3 H), 1.50 (d, *J* = 6.9 Hz, 3 H), 1.68–1.81 (m, 1 H), 1.88–2.00 (m, 1 H), 4.00–4.11 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.18, 19.68, 26.87, 60.18, 66.22, 66.38, 111.73.

Anal. Calcd for $C_7H_{13}ClO_2$: C, 51.07; H, 7.96. Found: C, 50.88; H, 8.22.

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