A one-pot method synthesis of α-chloroketone dimethyl acetals

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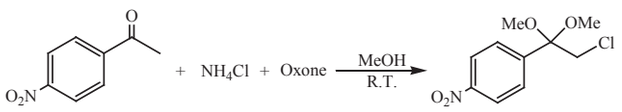
A new one-pot method has been developed for the direct preparation of α-chloroketone dimethyl acetals from ketones using ammonium chloride as the source of chlorine and potassium monoperoxysulfate as the oxidant in the presence of trimethyl orthoformate in methanol at room temperature. Ketones which have electron-withdrawing groups on the aryl rings gave the corresponding α-chloroketone dimethyl acetals in moderate to good yields.

Keywords: α-chloroketone dimethyl acetal, one-pot synthesis

α-Chloroketones are versatile intermediates in organic synthesis which react with large number of nucleophiles to provide a variety of useful compounds.[1] The synthesis of *α*-chloroketones from ketones has received considerable attention.[2–10] Recently, we have investigated the new procedure for direct α-chlorination of ketones with ammonium chloride (NH_4Cl) and potassium monoperoxysulfate (Oxone®), and found that this method was suitable for the aryl ketones which have electron-donating groups on the benzene ring. It gave the corresponding *α*-chloroketones in good yields. However, those having electron-withdrawing groups on the benzene ring, gave poor yields for the corresponding *α*-chloroketones and were usually accompanied by the *α*-chloroketone dimethyl acetals.[11] Narender's group has also reported similar results.[12] Although the *α*-chloroketone dimethyl acetals were by-products, the one-pot route interested us because methods for the preparation of *α*-chloroketone dimethyl acetals are rather limited and usually need chlorination and acetal formation in two steps using acid as catalysts.[13,14] Recently, Zou's group have reported a one-pot preparation of *α*-chloroketone dimethyl acetals using 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) as the chlorinating reagent.[15] Since *α*-haloketone dimethyl acetals are an interesting class of synthetic intermediates for the preparation of flavour material and other functional compounds,[16,17] the development of a novel, convenient method for their synthesis is desirable.

Table 1 Optimisation for preparation of α-chloro-4-nitroacetophenone dimethyl acetal from 4-nitroacetophenone



Entry	Additive/equiv.	NH_4Cl/equiv.	Time/h	Yield/%[a]
1	–	1.2	24	13
2	–	2.0	24	32
3	–	5.0	24	33
4	Silica gel (1.0 g)	2.0	24	26
5	4A molecular sieve (1.0 g)	2.0	24	28
6	$HC(OMe)_3$ (2.0)	2.0	24	61
7	$HC(OMe)_3$[b]	2.0	24	12
8	$HC(OMe)_3$ (2.0)	2.0	12	62
9	$HC(OMe)_3$ (2.0)	2.0	6	63
10	$HC(OMe)_3$ (2.0)	2.0	2	65
11	$HC(OMe)_3$ (2.0)	KCl (2.0)	2	54
12	$HC(OMe)_3$ (2.0)	NaCl (2.0)	2	40

[a]Isolated yield.

[b]2 mL $HC(OMe)_3$ was used as solvent.

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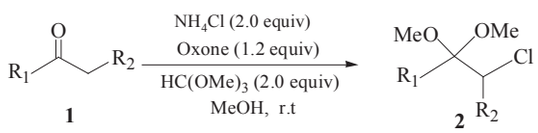
4-Nitroacetophenone (**1a**) was chosen as the model substrate to investigate the new method for preparation of *α*-chloroketone dimethyl acetals. When **1a** was treated with Oxone® and NH_4Cl in MeOH at room temperature, a mixture of *α*-chloro-4-nitroacetophenone and *α*-chloro-4-nitroacetophenone dimethyl acetal (2a) was formed. There is an equilibrium between the ketone and its ketal, in which we wished to favour the ketals. In order achieve this, a series of experiments were performed to determine suitable reaction conditions. The results are summarised in Table 1.

When 1.0 equiv. of **1a** was treated with 1.2 equiv. of Oxone® and NH_4Cl in MeOH at room temperature for 24 h, the reaction gave the desired product **2a**, but, the yields were rather low (Table 1, entries 1–3). When silica gel (1.0 g) was added and 2.0 equiv. of NH_4Cl were used in the reaction, the yield was only 26% after 24 h. A similar result was obtained when 1.0 g 4A molecular sieve was used to absorb the water (entries 4 and 5) which was produced. When 2.0 equiv. of trimethyl orthoformate ($HC(OMe)_3$) was added to the reaction, the yield rose significantly to 65% and the reaction time was shortened to 2 h. At that time, there was only a trace of *α*-chloro-4-nitroacetophenone in the reaction mixture (entries 6, 8–10). Under the same reaction conditions, KCl or NaCl was not effective as NH_4Cl (entries 11 and 12). However, when the reaction was carried out in just ($HC(OMe)_3$), only a 12% yield of **2a** was obtained (entry 7).

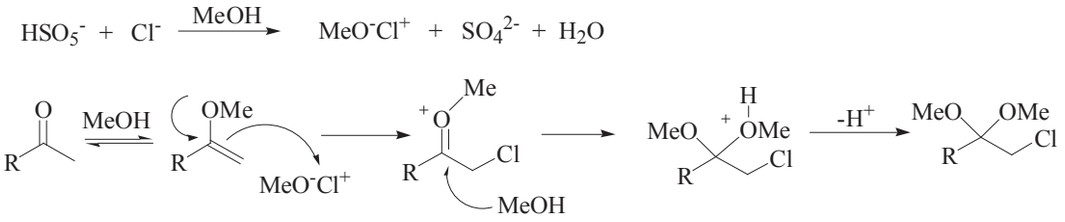
Having established the optimum conditions, the reaction of a series of ketones (1) with 1.2 equiv. of Oxone®, 2.0 equiv. of NH_4Cl and 2.0 equiv. of ($HC(OMe)_3$) in MeOH at room temperature was investigated. The corresponding *α*-chloroketone dimethyl acetals (2) were obtained (Scheme 1) and the results are summarised in Table 2. Ketones which have electron-withdrawing groups on the aryl rings usually afforded the corresponding *α*-chloroketone dimethyl acetals in moderate to good yields a short time, while other ketones gave poor yields.

The proposed mechanism for preparation of *α*-chloroketone dimethyl acetals from ketones is shown in Scheme 2.[11,12] The Cl^- from NH_4Cl is first efficiently oxidised into the MeOCl by Oxone®. The methoxy enol ether of the ketone then reacts with the MeOCl to afford the corresponding *α*-chloro compound,



1 **2**

Scheme 1



Scheme 2

Table 2 The result for preparation of α-chloroketone dimethyl acetals from ketones

Entry	Ketones (1)	α-Chloroketone dimethyl acetals (2)	Time/h	Yield/%[a]
1	$R^1 = p\text{-}NO_2C_6H_4$, $R^2 = H$ **1a**	2a	2	65
2	$R^1 = m\text{-}NO_2C_6H_4$, $R^2 = H$ **1b**	2b	2	68
3	$R^1 = p\text{-}CF_3C_6H_4$, $R^2 = H$ **1c**	2c	5	75
4	$R^1 = o\text{-}FC_6H_4$, $R^2 = H$ **1d**	2d	4	78
5	$R^1 = p\text{-}ClC_6H_4$, $R^2 = H$ **1e**	2e	8	74
6	$R^1 = o\text{-}BrC_6H_4$, $R^2 = H$ **1f**	2f	12	71
7	$R^1 = o\text{-}CO_2HC_6H_4$, $R^2 = H$ **1g**	2g	12	55
8	$R^1 = C_6H_5$, $R^2 = H$ **1h**	2h	24	35
9	$R^1 = p\text{-}MeC_6H_4$, $R^2 = H$ **1i**	2i	24	10
10	$R^1 = C_6H_5$, $R^2 = Me$ **1j**	2j	24	36
11	$R^1 = Me$, $R^2 = H$ **1k**	2k	24	21

[a]Isolated yield.

which is finally attacked by MeOH to provide the corresponding α-chloroketone dimethyl acetal.

In conclusion, we have achieved a novel one-pot procedure for the direct preparation of α-chloroketone dimethyl acetals from ketones which have electron-withdrawing groups on aryl rings. This method does not need acid catalyst and has some advantages such as mild reaction conditions, simple procedure and it affords moderate to good yields. Further investigation of the novel one-pot preparation of α-chloroketone diethyl acetals will be reported in due course.

Experimental

Melting points were measured with an XT-4 melting point apparatus and uncorrected. IR spectra were recorded on a Thermo Nicolet 6700 instrument. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker Avance III (500 MHz) spectrometer. Mass spectra were determined on a Thermo ITQ 1100 mass spectrometer. Ketones. NH_4Cl, Oxone®, $(HC(OMe)_3)$ and solvents were commercially available.

*Synthesis of α-chloroketone dimethyl acetal (**2**); typical procedure*

Ketone **1** (0.5 mmol), Oxone® (0.6 mmol), NH_4Cl (1.0 mmol) and $(HC(OMe)_3)$ (1.0 mmol) were added to MeOH (2 mL). The mixture was stirred at room temperature for 2 h and then the solvent was evaporated under reduced pressure. H_2O (10 mL) were added, the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified on a silica gel plate using (4:1 hexane-ethyl acetate) as eluant to give the α-chloroketone dimethyl acetal **2.**

α-Chloro-4-nitroacetophenone dimethyl acetal (**2a**): Light yellow solid, m.p. 48–50 °C (lit.[15] 48–49 °C); IR (KBr), ν/cm^{-1}: 1530, 1351, 1285, 1123, 1070, 1051; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (dd, 2H, J=7.0, 1.9 Hz), 7.72 (dd, 2H, J=7.0, 1.9 Hz), 3.75 (s, 2H), 3.27 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.1, 145.5, 128.6, 123.2, 101.5, 49.4, 45.9; ESI-MS, m/z: 247 ($Cl^{37}M^+$), 245 ($Cl^{35}M^+$).

α-Chloro-3-nitroacetophenone dimethyl acetal (**2b**): Light yellow solid, m.p. 49–51 °C (lit.[15] 51–52 °C); IR (KBr), ν/cm^{-1}: 1530, 1351, 1125, 1095, 1053; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40 (s, 1H), 8.22–8.25 (m, 1H), 7.86–7.88 (m, 1H), 7.58–7.60 (m, 1H), 3.76 (s, 2H), 3.27 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.3, 140.8, 133.4, 129.0, 123.5, 122.7, 101.3, 49.4, 45.9; ESI-MS, m/z: 247 ($Cl^{37}M^+$), 245 ($Cl^{35}M^+$).

α-Chloro-4-trifluoromethylacetophenone dimethyl acetal (**2c**):[15] Light yellow oil; IR (film), ν/cm^{-1}: 1389, 1123, 1071, 1000; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (s, 4H), 3.75 (s, 2H), 3.27 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.5, 130.5, 128.1. 125.1, 125.0, 101.5, 49.3, 46.2; ESI-MS, m/z: 270 ($Cl^{37}M^+$), 268 ($Cl^{35}M^+$).

α-Chloro-2-fluoroacetophenone dimethyl acetal (**2d**):[12] Light yellow oil; IR (film), ν/cm^{-1}: 1389, 1123, 1071, 1000; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24–7.19 (m, 2H), 7.01–6.92 (m, 2H), 3.77 (s, 2H), 3.24 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.1, 133.5, 129.6, 126.2, 121.7, 115.4, 98.5, 50.1, 47.1; ESI-MS, m/z: 220 ($Cl^{37}M^+$), 218 ($Cl^{35}M^+$).

α-Chloro-4-chloroacetophenone dimethyl acetal (**2e**):[14] Light yellow oil; IR (film), ν/cm^{-1}: 1384, 1285, 1123, 1079, 1051; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, 2H, J=8.4 Hz), 7.37 (d, 2H, J=8.4 Hz), 3.72 (s, 2H), 3.24 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.4, 133.5, 129.9, 126.2, 100.5, 50.3, 47.2; ESI-MS, m/z: 207 ($Cl^{37}M^+$–OMe), 205 ($Cl^{37}Cl^{35}M^+$–OMe), 203 ($Cl^{35}M^+$–OMe).

α-Chloro-4-bromoacetophenone dimethyl acetal (**2f**):[15] Light yellow oil; IR (film), ν/cm^{-1}: 1124, 1070, 1051, 1002; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (d, 2H, J=8.6 Hz), 7.39 (d, 2H, J=8.6 Hz), 3.72 (s, 2H), 3.23 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.1, 131.5, 128.6, 126.1, 101.2, 49.8, 45.9; ESI-MS, m/z: 249 ($Br^{81}Cl^{35}M^+$–OMe), 247 ($Br^{79}Cl^{35}M^+$–OMe).

2-(2-Chloro-1,1-dimethoxyethyl)benzoic acid (**2g**): White solid, m.p. 61–62 °C; IR (KBr), ν/cm^{-1}: 3530, 3051, 1185, 1123, 1058, 1043; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, 1H, J=7.5 Hz), 7.72–7.75 (m, 1H), 7.59–7.62 (m, 1H), 7.51 (d, 1H, J=7.6 Hz), 3.91 (s, 2H), 3.24 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.4, 135.5, 133.9, 130.2, 128.6, 127.4, 126.9, 103.2, 50.4, 47.1; ESI-MS, m/z: 246 ($Cl^{37}M^+$), 244 ($Cl^{35}M^+$); HR-MS, m/z: calcd for $C_{11}H_{13}O_4Cl$, 244.0502; found, 244.0484.

α-Chloroacetophenone dimethyl acetal (**2h**):[15] Light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51–7.53 (m, 2H), 7.38–7.41 (m, 3H), 3.76 (s, 2H), 3.26 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.4, 128.6, 128.7, 127.9, 127.5, 100.5, 49.4, 45.9; ESI-MS, m/z: 202 ($Cl^{37}M^+$), 200 ($Cl^{35}M^+$).

α-Chloro-4-methylacetophenone dimethyl acetal (**2i**):[15] Light yellow oil; IR (KBr), ν/cm^{-1}: 1135, 1063, 1009; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, 2H, J=8.4 Hz), 7.24 (d, 2H, J=8.4 Hz), 3.72 (s, 2H), 3.23 (s, 6H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.5, 135.5, 129.0, 125.2, 101.6, 49.7, 46.0, 24.1; ESI-MS, m/z: 216 ($Cl^{37}M^+$), 214 ($Cl^{35}M^+$).

α-Chloro-acetone dimethyl acetal (**2j**):[14] Light yellow oil; IR (KBr), ν/cm^{-1}: 1285, 1123, 1070, 1051; ^{1}H NMR (500 MHz, $CDCl_3$): 3.50 (s, 2H), 3.29 (s, 6H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 103.5, 51.6, 50.1, 20.9; ESI-MS, m/z: 140 ($Cl^{37}M^+$), 138 ($Cl^{35}M^+$).

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