Ceric ammonium nitrate catalyzed mild and efficient α-chlorination of ketones by acetyl chloride

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Dedicated to Professor (Mrs.) A. Chatterjee on her 85th birthday
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Abstract
A mild and efficient method of α-chlorination of ketones has been developed using acetyl chloride as the chlorinating agent in the presence of a catalytic amount of ceric ammonium nitrate in good yield. The reaction is highly chemo and regio selective in nature.

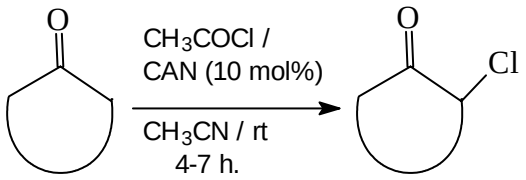
Keywords: Ceric ammonium nitrate, ketones, α-chlorination, acetyl chloride

Introduction

α-Chlorination of carbonyl compounds is one of the major investigated organic reactions and it has been discussed in a wealth of chemical literature. A wide variety of useful reagents and procedures are available for the synthesis of α-chloroketones[1] which are versatile intermediates in organic synthesis (such as Cornforth olefin synthesis, Favorskii rearrangement etc)[2] particularly for the synthesis of heterocyclic compounds. Direct side chain chlorination of ketones using chlorine or sulfuryl chloride[3] is a commonly accepted procedure. But this protocol is not reliable for activated aromatic substrates[4] such as hydroxy acetophenones or with electron rich heterocyclic systems where concurrent nuclear halogenation is facile.[5] Recent reports have been found to deal with the use of aqueous $TiCl_3$,[6] hexachloro-2,4-cyclohexadienone,[7] benzyl trimethylammonium dichloroiodate,[8] N-chlorosuccinimide,[9] α-chloroalkyllithium[10] etc for the α-chlorination of ketones.

Results and Discussion

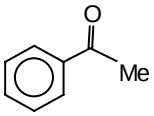
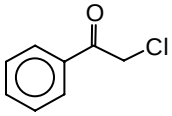
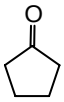
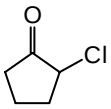
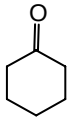
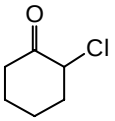
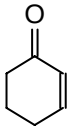
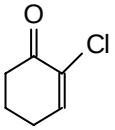
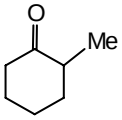
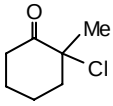
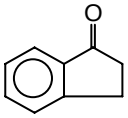
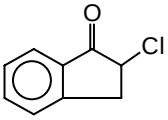
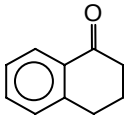
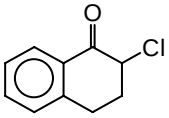
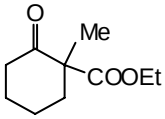
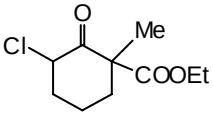
It has been observed that during direct α-halogenation, polychlorination, low yields and/or difficultly separable mixtures are common experimental outcomes. On the other hand there are certain disadvantages for the indirect procedures (enol derivatives, acetates, ethers etc) unless some thermodynamic, steric factors etc predominate.[11] Therefore, a new mild and efficient method for α-chlorination of ketones is still desirable. Recently, it has been reported[12] from this laboratory that acetyl chloride acted as an useful reagent for chlorination of aromatic nucleus in the presence of a catalytic quantity of ceric ammonium nitrate (CAN). We wish to report here that ketones have successfully been transformed to their corresponding α-chloro derivatives in good yields by acetyl chloride using CAN as the catalyst (Scheme 1).



Scheme 1

Various cyclic and acyclic ketones have been shown to undergo α-chlorination and the results are summarized in Table 1. In case of cyclohex-2-en-1-one, chlorination took place at the more electron-rich carbon (entry 4, Table 1). It has been found that chlorination preferred at the more substituted electron-rich α-carbon atom (entry 5, Table 1). It is noteworthy that acetophenone, indanone and α-tetralone (entry 1, 6 and 7, Table 1) afforded only the corresponding α-chloro substituted products without any trace of nuclear chlorination on aromatic rings. It is also interesting to note that in the presence of even large excess of acetyl chloride only mono-chlorination took place, no di-chlorinations were observed in any of the above reactions. When 2-hydroxy acetophenone was subjected to the reaction condition, instead of chlorination, acetylation on hydroxyl group occurred exclusively as expected.[12] Aldehydes gave an inseparable mixture of compounds under the reaction condition.

Table 1. CAN catalyzed α-chlorination of ketones by acetyl chloride

Entry	Substrate	Product [a]	Time (h)	Yield [b] (%)
1			5	87
2			4	69
3			4	72
4			4.5	70
5			6	75
6			7	84
7			6	87
8			6.5	73

[a]The spectral data of all the products were compared with those of authentic samples.
[b]Yields refer to pure isolated products.

Conclusions

In summary, we have successfully developed a mild and efficient regio and chemoselective method of α-chlorination of ketones by acetyl chloride in the presence of a catalytic amount of CAN in good yields without formation of any unwanted polychlorinated side products.

Experimental Section

General Procedures. Column chromatography was performed on silica gel (60–120 mesh). The progress of the reactions was monitored on aluminium backed TLC plates of silica gel 60 F254 (Merck, 0.2 mm). NMR spectra were recorded on a Bruker DPX 300 (300 MHz for ^{1}H, 75 MHz for ^{13}C) spectrometer. Chemical shifts (δ in ppm) are given from internal $CHCl_3$ (7.26) for ^{1}H NMR, $^{13}CDCl_3$ (77.0) for ^{13}C NMR. IR spectra were recorded in Shimadzu FT IR-8300. Spectral data of all the products obtained were compared with those of authentic samples.

2-Chlorocyclohexan-1-one. To a stirred mixture of cyclohexanone (490 mg, 5.0 mmol) and freshly distilled acetyl chloride (390 μL, 5.5 mmol) in acetonitrile (5 mL) was added a solution of ceric ammonium nitrate (274 mg, 0.5 mmol) in acetonirile (2 mL) during 2 h under nitrogen at ambient temperature. The reaction mixture was further allowed to stir for 2 h till the completion of the reaction (monitored by TLC). It was then diluted with diethyl ether (20 mL), washed thoroughly with saturated $NaHCO_3$ solution (2 × 10 mL), brine (2 × 10 mL) and dried (Na_2SO_4). Volatiles were removed under reduced pressure and the residue obtained was purified by a column chromatography over silica gel (15% ethyl acetate in light petroleum) to yield 2-chlorocyclohexan-1-one (477 mg, 72%). IR (neat): 2929, 2854, 1712, 1446, 1215 cm^{-1}.
^{1}H NMR: δ 1.51-2.01 (m, 5H), 2.24-2.33 (m, 2H), 2.67-2.75 (m, 1H), 4.30-4.35 (m, 1H). ^{13}C NMR: δ 23.1, 37.0, 42.3, 48.1, 63.1, 203.7.

2-Chlorocyclopentan-1-one. 2-Chlorocyclopentan-1-one was prepared from cyclopentanone by the same procedure as described for 2-chlorocyclohexan-1-one. IR (neat): 2929, 2858, 1732, 1703, 1450, 1407, 1215 cm^{-1}. ^{1}H NMR: δ 1.68-2.45 (m, 6H), 4.07 (t, J = 7.1 Hz, 1H). ^{13}C NMR: δ 19.6, 33.8, 35.4, 58.8, 211.4.

2-Chlorocyclohex-2-ene-1-one. 2-Chlorocyclohex-2-ene-1-one was prepared from cyclohex-2-ene-1-one by the same procedure as described for 2-chlorocyclohexan-1-one. IR (neat): 2950, 2871, 1693, 1606, 1502, 1454, 1330, 1226, 1197 cm^{-1}. ^{1}H NMR: δ 1.99-2.08 (m, 2H), 2.44-2.53 (m, 2H), 2.55-2.65 (m, 2H), 7.13 (t, J = 4.4 Hz, 1H). ^{13}C NMR: δ 22.9, 27.4, 38.8, 132.5, 147.2, 192.0.

2-Chloroindan-1-one. 2-Chloroindan-1-one was prepared from indan-1-one by the same procedure as described for 2-chlorocyclohexan-1-one. IR (neat): 2933, 1728, 1606, 1465, 1429, 1278, 1213 cm^{-1}. ^{1}H NMR: δ 3.28 (dd, J = 17.6, 3.99 Hz, 1H), 3.77 (dd, J = 17.6, 7.8 Hz, 1H), 4.55 (dd, J = 7.8, 4.0 Hz, 1H), 7.38-7.45 (m, 2H), 7.63-7.68 (m, 1H), 7.80 (d, J = 7.68 Hz, 1H). ^{13}C NMR:δ 37.9, 56.1, 125.4, 126.8, 128.7, 134.2, 136.5, 151.2, 199.7.

2-Chloro-1-tetralone. 2-Chloro-1-tetralone was prepared from 1-tetralone by the same procedure as described for 2-chlorocyclohexan-1-one. IR (neat): 2941, 1689, 1600, 1454, 1433, 1305, 1288, 1218 cm^{-1}. ^{1}H NMR: δ 2.41-2.62 (m, 2H), 2.92-3.01(m, 1H), 3.22-3.26 (m, 1H), 4.60 (dd, J =7 .7,3.9 Hz, 1H), 7.21-7.34 (m, 2H), 7.46-7.52 (m, 1H), 8.04 (d, J = 7.89 Hz, 1H). ^{13}C NMR: δ 26.2, 32.3, 59.8, 126.9, 128.3, 128.6, 133.3, 134.0, 143.0, 190.7.

2-Chloro-2-methylcyclohexan-1-one. 2-Chloro-2-methylcyclohexan-1-one was prepared from 2-methylcyclohexan-1-one by the same procedure as described for 2-chlorocyclohexan-1-one. IR

(neat): 2943, 2869, 1737, 1714, 1448, 1380, 1163 cm^{-1}. ^{1}H NMR: δ 1.61 (s, 3H), 1.64-1.90 (m, 4H), 2.02-2.09 (m, 2H), 2.28-2.34 (m, 2H). ^{13}C NMR: δ 21.3, 26.4, 26.9, 36.8, 42.9, 60.3, 205.6.

Chloromethyl phenyl ketone. Chloromethyl phenyl ketone was prepared from acetophenone by the same procedure as described for 2-chlorocyclohexan-1-one. IR (KBr): 2993, 2941, 1701, 1596, 1581, 1448, 1398, 1284, 1211 cm^{-1}. ^{1}H NMR: δ 4.71 (s, 2H), 7.47-7.52 (m, 2H), 7.59-7.64 (m, 1H), 7.95 (d, J = 7.26 Hz, 2H). ^{13}C NMR: δ 45.9, 128.2, 128.5, 128.8, 133.9, 190.9.

6-Chloro-2-ethoxycaronyl-2-methylcyclohexan-1-one. 6-Chloro-2-ethoxycarbonyl-2-methyl cyclohexan-1-one was prepared from 2-ethoxycarbonyl-2-methylcyclohexan-1-one by the same procedure as described for 2-chlorocyclohexan-1-one. IR (neat): 2981, 2938, 2869, 1727, 1714, 1454, 1376, 1301, 1259, 1212, 1157 cm^{-1}. ^{1}H NMR: δ 1.21-1.27 (m, 3H), 1.34 (s, 3H), 1.42-1.85 (m, 4H), 2.45-2.53 (m, 2H), 4.21 (dd, J = 6.8, 13.8 Hz, 2H), 4.69 (dd, J = 5.9, 12.6 Hz, 1H). ^{13}C NMR: δ 13.8, 21.5, 22.5, 37.9, 38.8, 57.9, 61.7, 63.2, 172.3, 199.2.

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