Selective α-Chlorination of Alkyl Aryl Ketones

Alain GUY, Marc LEMAIRE, Jean-Paul GUETTÉ

Laboratoire de Chimie Organique CNAM, 292 rue Saint-Martin, F-75141 Paris Cedex 03, France

α-Monohalogenation of ketones can be achieved using chlorine or bromine in the presence of a basic or acidic catalyst[1]. The low selectivity of this method with respect to other halogenizable functions and the high percentage of polyhalogenated products obtained with these methods has lead numerous authors to search for more effective methods or reagents. The use of enamines[2] as potential carbonyl substrates, silyl enol ethers[3] or enol acetates[4], as well as the use of reagents such as trimethylammonium perbromide[5], pyridinium perbromide[6], or Amberlyst A-26 perbromide form[7] are interesting results obtained in this field. Notwithstanding their great utility, the above-mentioned reagents resolve only one aspect of the problem: facile and sufficiently selective monobromination α to the carbonyl group. However, from an economic point of view α-bromination is less attractive than α-chlorination. The use of sulfuryl chloride allows for the α-chlorination of carbonyl compounds but this reagent may also chlorinate activated aromatic rings[8].

We have recently proposed two reagents for the regioselective chlorination of aromatic substrates[9] such as, for example, phenols[10] and naphthols[11]. The selectivity of these reagents is based on donor-acceptor and hydrogen-bonding interaction which leads to a well defined "recognition" between reagent and substrate. We report here that one of these reagents, *hexachloro-2,4-cyclohexadienone* **(1),** has a wider range of applicability and may be used, for example, for the convenient α-monochlorination of alkyl aryl ketones **(2).** The enolic form of these ketones[12] is capable of a donor-acceptor interaction with reagent **1.** The presence of an electron-rich aromatic ring is a necessary prerequisite for the mentioned complex formation and thereby for the α-chlorination. Purely aliphatic ketones form insufficiently stable complexes with reagent **1** so that α-chlorination does not proceed. However, with suitable alkyl aryl ketones **(1),** high yields of 1-chloroalkyl aryl ketones **(3)** are obtained, pentachlorophenol **(4)** being formed as by-product.

Acetylthiophenes **(2j, k)** and methyl 4-methoxystyryl ketone **(2l)** are also ω-chlorinated in high yields by reagent **1.**

Using two equivalents of reagent **1,** α,α-dihalogenation products may be formed. Thus, from the reaction of 3-hydroxyacetophenone **(2b)** with 2 equiv of reagent **1,** ω,ω-dichloro-3-hydroxyacetophenone **(5b)** is obtained in 34% yield.

0039-7881/82/1232-1018 $ 03.00

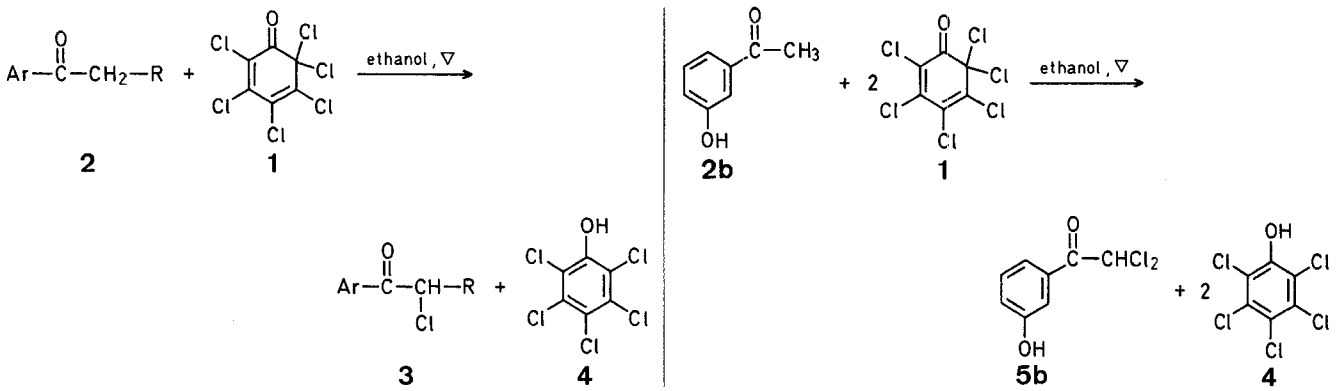
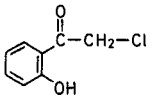
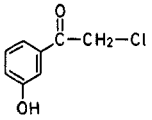
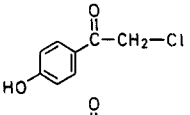
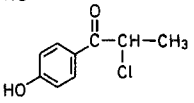
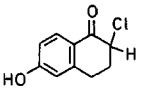
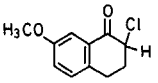
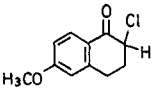
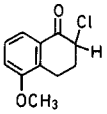
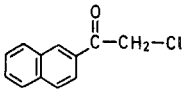
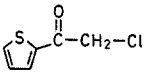
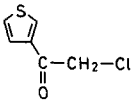
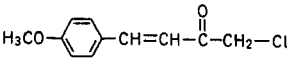


Table 1. 1-Chloroalkyl Ketones (**3**) prepared

3	Formula	Reaction time [h]	Yield [%]		m.p. [°C] (solvent)	Molecular formula[b] or m.p. [°C] reported
			Determined in crude product[a]	Isolated product		
a		7	66	66	73° (CH_2Cl_2/heptane 1/1)	73°[14]
b		5	79	50	93° (CCl_4/$CHCl_3$ 20/1)	$C_8H_7ClO_2$ (170.6)
c		5	86	77	142° (CCl_4/$CHCl_3$ 20/1)	148°[13]
d		6	85	81	79° (petroleum ether)	81°[18]
e		5	100	90	196° ($CHCl_3$)	$C_{10}H_9ClO_2$ (196.6)
f		4	100	76	58° (petroleum ether)	$C_{11}H_{11}ClO_2$ (210.65)
g		6	100	71	40°	40–42°[15]
h		6	100	~100	50° (extraction with NaOH)	$C_{11}H_{11}ClO_2$ (210.65)
i		5	83	64	65° ($CHCl_3$/petroleum ether)	67–68°[16]
j		6	85	66	46° (diisopropyl ether)	48°[17]
k		6	95	85	73° (diisopropyl ether)	C_6H_5ClOS (160.6)
l		5	83	64	98° (diisopropyl ether)	$C_{11}H_{11}ClO_2$ (210.65)

[a] H.P.L.C. Lichrosorb Si 60 5 μm; eluent: chloroform/methanol (99.5/0.5), flow rate 3 ml/min; detection by U.V. 280 nm.
[b] The microanalyses showed the following maximum deviations from the calculated values: C, ±0.38; H, ±0.26.

Table 2. Spectral Data of 1-Chloroalkyl Ketones (**3**)

3	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (90 MHz, $CDCl_3/TMS_{int}$) δ [ppm]
a	1635 (C=O); 1570 (C=C); 750 (C—Cl)	4.7 (s, —CO—CH_2Cl); 6.2 (s, OH); 7.6 (m, 4 H_{arom})
b	3400 (OH); 1685 (C=O); 1580 (C=C); 740 (C—Cl)	4.7 (s, —CO—CH_2Cl); 5.9 (s, OH); 7.4 (m, 4 H_{arom})
c	3330 (OH); 1670 (C=O); 1590 (C=C); 680-640 (C—Cl)	(acetone-d_6): 4.75 (s, —CO—CH_2Cl); 6.95 (d, 2 H_{arom}); 7.90 (d, 2 H_{arom})
d	3280 (OH); 1670 (C=O); 1590 (C=C); 780 (C—Cl)	1.76 (d, CH_3); 5.28 (q, 1 H, CHCl—CH_3); 6.98 (d, 2 H_{arom}); 7.98 (d, 2 H_{arom}); 7.2 (m, OH)
e	3380 (OH); 1665 (C=O); 1580 (C=C)	2.5 (m, CH_2); 3.2 (m, CH_2); 4.80 (dd, CH—Cl); 6.82 (s, 1 H_{arom}); 6.88 (dd, 1 H_{arom}); 7.95 (d, 1 H_{arom}); 7.29 (s, OH)
f	1680 (C=O); 1605 (C=C); 1040 (C—O—C); 690 (C—Cl)	2.5 (m, 2 H); 3.05 (m, 2 H); 3.8 (s, 3 H, OCH_3); 4.6 (dd, CH—Cl); 7.2 (m, 3 H_{arom})
g	1260 (OCH_3); 1675 (C=O); 1595 (C=C); 760 (C—Cl)	2.5 (m, 2 H); 3.1 (m, 2 H); 4.18 (s, OCH_3); 4.62 (dd, CH—Cl); 6.8 (s, 1 H_{arom}); 6.85 (dd, 1 H_{arom}); 7.9 (d, 1 H_{arom})
h	1695 (C=O); 1580 (C=C); 1260 (C—O—C); 745 (C—Cl)	2.5 (m, 2 H); 3 (m, 2 H); 3.8 (s, 3 H, OCH_3); 4.5 (dd, CH—Cl); 7.0 (dd, 1 H); 7.25 (t, 1 H); 7.6 (dd, 1 H)
i	1680 (C=O); 1620-1590 (C=C); 730 (C—Cl)	4.73 (s, —CO—CH_2Cl); 7.35 (m, 7 H_{arom})
j	1670 (C=O); 730 (C—Cl); 650 (C—S)	4.57 (s, —CO—CH_2Cl); 7.15 (s, 1 H_{arom}); 7.75 (m, 2 H_{arom})
k	1670 (C=O); 700 (C—Cl); 625 (C—S)	4.57 (s, —CO—CH_2Cl); 7.35 (m, 1 H_{arom}); 7.53 (m, 1 H_{arom}); 8.15 (m, 1 H_{arom})
l	1680 (C=O); 1590, 1560 (C=C); 1140 (OCH_3); 780 (C—Cl)	3.8 (s, OCH_3); 4.23 (s, —CO—CH_2Cl); 6.80 (d, C=CH); 6.88 (d, 2 H_{arom}); 7.5 (d, 2 H_{arom}); 7.63 (d, C=CH)

All chemicals were commercially available and were used without further purification. The analyses of the reaction products were run by H.P.L.C. with a Chromatem 38 (Lichrosorb Si 60 5 μm column, $CHCl_3/CH_3OH$ (99.5/0.5) elution, U.V. 280 nm detection. All microanalyses were performed on an Analyser CHN Carlo Erba 1106. I.R. spectra were recorded on a Perkin Elmer 457 spectrophotometer, with the samples either neat between KBr discs or pressed in tablets with KBr. The ^{1}H-N.M.R. spectra were obtained on a Perkin Elmer R 32 spectrometer.

Hexachloro-2,4-cyclohexadienone (1):
Sodium pentachlorophenoxide (57.2 g, 0.2 mol) is added to a well stirred solution of chlorine (0.3 mol) in tetrachloromethane (300 ml) at 0–5 °C and stirring is continued at 0–5 °C for 3 h. The precipitate is then filtered off and the filtrate concentrated in vacuo at <40 °C. The residue is stirred with petroleum ether (b.p. 40–60 °C; 200 ml) for 24 h at −10 °C. The solid product **1** is isolated by suction and washed with petroleum ether (2×20 ml) at −10 °C; yield: 34 g (56%); m.p. 50 °C (Ref.[19], m.p. 51 °C).

I.R. (KBr): ν = 1710, 1578, 1570 cm^{-1}.

1-Chloroalkyl Ketones (3); General Procedure:
Hexachloro-2,4-cyclohexadienone (**1**; 3.01 g, 10 mmol) is added to a solution of the ketone (**2**; 10 mmol) in freshly distilled ethanol (20 ml) under argon. The mixture is heated at reflux temperature for ~6 h and the solvent then evaporated [the residue is analyzed by ^{1}H-N.M.R. spectrometry or by H.P.L.C.]. The α-chloroketone **3** is crystallized from an appropriate solvent (see Table) in which pentachlorophenol (**4**) is soluble. In the case of products **3f–l** which do not contain a phenolic hydroxy group, pentachlorophenol (**4**) can be removed by washing the crude product with aqueous 10% sodium hydroxide and recrystallization.

ω,ω-Dichloro-3-hydroxyacetophenone (5b):
Hexachloro-2,4-cyclohexadienone (**1**; 6.02 g, 20 mmol) is added to a solution of 3-hydroxyacetophenone (**2b**; 1.362 g, 10 mmol) in freshly distilled ethanol (20 ml) under an inert atmosphere. The mixture is heated at reflux temperature for 8 h and the solvent then evaporated. [N.M.R. analysis indicates a 60% yield of **5b**]. Product **5b** is isolated from the residue by chromatography on silica gel (eluent: chloroform); yield: 0.7 g (34%); pale yellow oil.

$C_8H_6Cl_2O_2$	calc.	C 46.88	H 2.94
(205.0)	found	46.27	2.93

I.R. (KBr): ν = 3400 (OH); 1685 (C=O); 1585 (C=C_{arom}); 745 cm^{-1} (C—Cl).

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 6.6 (s, $CHCl_2$); 7.3 ppm (m, H_{arom}).

Received: January 18, 1982
(Revised form: May 13, 1982)

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