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HEXACHLOROACETONE: A NEW SOURCE OF POSITIVE HALOGEN AS A REGIOSELECTIVE CHLORINATING AGENT

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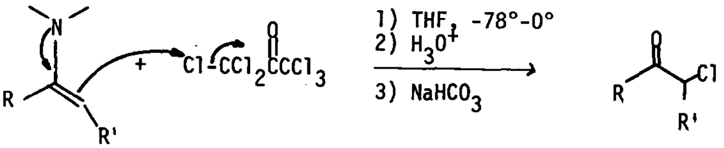
α-Chloroketones have been prepared by the interaction of the parent ketone with chlorine, N-chlorosuccinimide, sulfuryl chloride, copper (II) chloride, tert-butyl hypochlorite or selenium oxychloride.[1a,1b] Haloketones have also resulted from the reaction of halogens or N-halosuccinimide with silyl enol ethers,[2] and from the reaction of halogens,[3a-f] N-halosuccinimide[3g] or tert-butyl hypochlorite[3a] with enamines. We now wish to report the preparation of α-chloroketones by the reaction of enamines with hexachloroacetone (HCA). This new chlorination reaction involves a nucleophilic displacement on chlorine made possible by the nucleofugacity of the pentachloroacetonide ion.



Using this new chlorination procedure, α-chloroketones of cyclopentanone, cyclohexanone, cycloheptanone, 3-methylcyclohexanone and 2-methylcyclohexanone have been prepared in good yields from the morpholine or pyrrolidine enamines (Table I). The reaction of enamines with HCA gives, after acid hydrolysis, the α-chloroketone contaminated with pentachloroacetone. We have found that this pentachloroacetone can be destroyed, along with any excess hexachloroacetone, by simply stirring an ether solution of the crude product with a saturated sodium bicarbonate solution. Drying the ether solution over magnesium sulfate and rotory evaporation of the ether leaves an oil containing only monochloroketone contaminated with starting ketone, permitting pure chloroketone to be obtained by bulb to bulb distillation.

The reaction of the morpholine enamine of 3-methylcyclohexanone with HCA gave a mixture of four α-chloroketones.[4] These four chloroketones were separated by preparative glc and shown to be isomeric by mass spectral analysis. This mixture is shown to be 64% cis-6-chloro-3-methylcyclohexanone, 15% cis-2-chloro-3-methylcyclohexanone, 8% trans-2-chloro-3-methylcyclohexanone[4b] and 13% trans-6-chloro-3-methylcyclohexanone by their ir and pmr spectra

(Table II). The same proportions are found both after acid hydrolysis *and* after bicarbonate treatment showing that there is negligible epimerization during the removal of the polychlorinated acetones. Thus, the reaction is shown to be 77% regioselective.

Table I. α-Chloroketones[a] from the Reaction of Enamines with Hexachloroacetone.

Entry	Enamine	Temp.(°C)	Time(min)	yield(%)[b]
1	N-morpholino-1-cyclopentene	-78°	45	61
2	N-morpholino-1-1cyclohexene	0°	15	65
3	N-morpholino-1-cycloheptene	0°	15	62
4	morpholine enamines of 3-methylcyclohexanone	0°	15	75[c]
5	pyrrolidine enamines of 2-methylcyclohexanone	-78°	45	80[d]

a) All compounds have been fully characterized spectrally and have boiling points that agree with literature values. b) All yields for distilled chloroketones. c) Yield represents a mixture of chloroketones given in Table II. d) Yield represents a mixture made up of 91% 6-chloro-2-methylcyclohexanone and 9% 2-chloro-2-methylcyclohexanone.

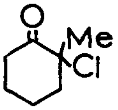
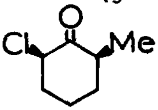
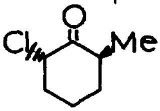
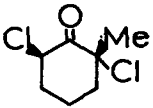
Table II. Spectral Data and Isomer Distribution of α-chloro-3-methylcyclohexanones.[5]

Chloroketone	% in mixture	$\nu_{C=0}$ in CCl_4	δH alpha to Cl
cis-6-chloro-3-methylcyclohexanone	64%	1726 cm^{-1}	(m)4.12 ppm($W_{\frac{1}{2}}$ = 8 Hz)
trans-6-chloro-3-methylcyclohexanone	13%	1737 cm^{-1}	(4-line mult.)4.28 ppm ($W_{\frac{1}{2}}$ = 17.5 Hz.)
cis-2-chloro-3-methylcyclohexanone	15%	1727 cm^{-1}	(m)4.04 ppm ($W_{\frac{1}{2}}$ = 8 Hz)
trans-2-chloro-3-methylcyclohexanone	8%	1729 cm^{-1}	(d)3.94 ppm (J = 8.5 Hz)

The reaction of the pyrrolidine enamine of 2-methylcyclohexanone with HCA gave three α-chloroketones: 2-chloro-2-methylcyclohexanone and the *cis* and *trans* isomers of 6-chloro-2-methylcyclohexanone in a 9:76:15 ratio, respectively. The structures of these isomers were proven by pmr, ^{13}C -NMR, and gc-mass spectral analysis. All of these isomers have been characterized previously.[6] Table III compares the isomeric distribution of chloroketones obtained by the reaction of HCA with the pyrrolidine enamine of 2-methylcyclohexanone with the distributions obtained in the chlorination of 2-methylcyclohexanone with chlorine or sulfuryl chloride. One can easily see that the regioselectivity has been completely reversed by using the HCA-enamine method: 91% 6-chloro-2-methylcyclohexanone versus 93% 2-chloro-2-methylcyclohexanone for the sulfuryl chloride method.

The advantages of this chlorination sequence are due to the ease of preparation of enamines [9a,b] and the availability of hexachloroacetone. Hexachloroacetone, being a stable high boiling liquid, can be used at the bench with no special precautions. Additional synthetic utility is envisioned in that HCA is completely inert toward enol ethers, alkenes and thioethers at room temperature.

Table III: Isomer Distribution Resulting from the Chlorination of 2-methylcyclohexanone.

Method	Isomers (given as % of product)				ref
					
SO_2Cl_2 in CCl_4	93%	1%	6%	0	6
Cl_2(gas),H_2O,$CaCO_3$	63%	3%	7%	27%	6
Cl_2 dissolved in CCl_4, $CaCO_3$	41%	10%	15%	28%	6
HCA + enamine	9%	75%	15%	0	This work

A typical preparation follows:

Chlorination of pyrrolidine enamine of 2-methylcyclohexanone: The pyrrolidine enamine of 2-methylcyclohexanone (5.2 g, 31 m moles) in 25 ml of dry THF was added dropwise with stirring to a dry THF solution (25 ml) of hexachloroacetone (8.4 g, 32 mmoles) [hexachloroacetone was freshly distilled from P_2O_5] under dry nitrogen at -78°C. After reacting for 45 min. at -78° the cold bath was removed, 20 ml of 14% HCl solution was added, and the resulting mixture stirred at 0°C for 45 min., then at room temperature for 15 min to effect hydrolysis of the enamine. The aqueous layer was separated and extracted three times with 15 ml of ethyl ether; the combined organic layers were washed with brine (2 x 25 ml) and dried over $MgSO_4$. Filtration and removal of the ethers at the water pump left an oil. The oil was taken up in 50 ml of ethyl ether and stirred for two hours at room temperature with 50 ml of saturated $NaHCO_3$ solution to convert the pentachloroacetone to chloroform and dichloroacetic acid. The aqueous layer was then removed and extracted with ethyl ether (3 x 15 ml). The extracts were combined with the original ether layer, washed with brine and dried over $MgSO_4$. Filtration and removal of the solvent at the water pump provided an oil which gave 3.63 g (85% yield) of α-chloroketone upon distillation at 102/110°C @ 16 mm Hg. This product consisted of 75% cis-6-chloro-2-methylcyclohexanone (1737 cm^{-1}; $\delta(CCl_4)$ 4.59 (m, overall spacing 19 Hz, 1H), 1.6 - 2.9 (m, 7H), 1.05 (d, 3H)),15% trans-6-chloro-2-methylcyclohexanone (1725 cm^{-1}; $\delta(CCl_4)$ 4.02 (m, 1H), 3.09 (sextet, 1H), 2.4 - 1.8 (m, 6H), 1.01 (d, 3H)) and 9% 2-chloro-2-methylcyclohexanone (1726 cm^{-1}, $\delta(CCl_4)$ 3.05 (m, 1H), 2.48 - 1.7 (m, 7H), 1.03 (s, 3H)).

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