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(15) We also note that, for all these aziridines, the protons which are cis with respect to the nitrogen lone pair and trans with respect to the OCH_3 group are always more shielded than the corresponding protons of the other invertomer. The same result is observed in the case of *N*-chloroaziridines[11b].
(16) The signals for these protons are masked by the signals of the ester groups.
(17) INDO calculations for these alkynes **8** show that the carbon atom bearing the hydrogen has the largest coefficients both in the HOMO and in the LUMO. A treatment similar to that described for the addition to monoactivated olefins[4a] allows the orientation to be correctly predicted in all cases.
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Mechanism of the Reaction of Hexachloroacetone with Enamines. A New, Convenient Synthesis of α-Chloro Ketones, β-Chloro Enamines, and Allylic Chloro Enamines[1]

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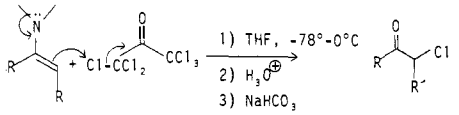
Abstract: A new, convenient preparation of α-chloro ketones by the reaction of hexachloroacetone with enamines is reported. The mechanism of this reaction has been examined and found to follow three pathways. The reaction with enamines that do not have axial α' substituents has been shown to generate solely allylic chloro enamines while the reaction with enamines containing axial α' substituents has been shown to generate β-chloroimmonium–pentachloroacetonide ion pairs. These ion pairs can be hydrolyzed directly or permitted to react at higher temperatures to generate β-chloro enamines. The regioselectivity and stereochemistry of this reaction are also discussed.

We have recently reported that hexachloroacetone (HCA) acts as a source of positive chlorine in its reactions with enamines giving, after acid hydrolysis, good yields of α-chloro ketones.[2] HCA reacts rapidly with enamines at temperatures between −78 and 0 °C while being inert toward enol ethers, alkenes, and thioethers at room temperature.[3] This mild



chlorination reaction results in regioselective α-chlorination of ketones owing to the availability of either α- or α'-enamines, thus making routes to 6-chloro-2-alkyl- or 6-chloro-3-alkylcyclohexanones quite feasible.

Enamines of cyclohexanone derivatives have been halogenated with halogens[4a,b] or *N*-halosuccinimide. While α-halo ketones do result from these procedures they are not always the methods of choice. The reaction of cyclhexanone enamines with *N*-chlorosuccinimide has been reported to give substantial amounts of dichlorinated product.[5] Published procedures for the preparation of 6-halo-2-methylcyclohexanones have, in general, not been satisfactory. Direct chlorination of 2-methylcyclohexanone with chlorine provides 2-chloro-2-methylcyclohexanone as the major isomer, *cis*- and *trans*-6-chloro-2-methylcyclohexanone, and substantial amounts of 2,6-dichloro-2-methylcyclohexanone.[6] The pyrrolidine enamines of 2-methylcyclohexanone (90% 6-methyl-1-pyrrolidino-1-cyclohexene[7]) react with bromine, sulfuryl chloride, *N*-bromosuccinimide, or *N*-chlorosuccinimide to give primarily the

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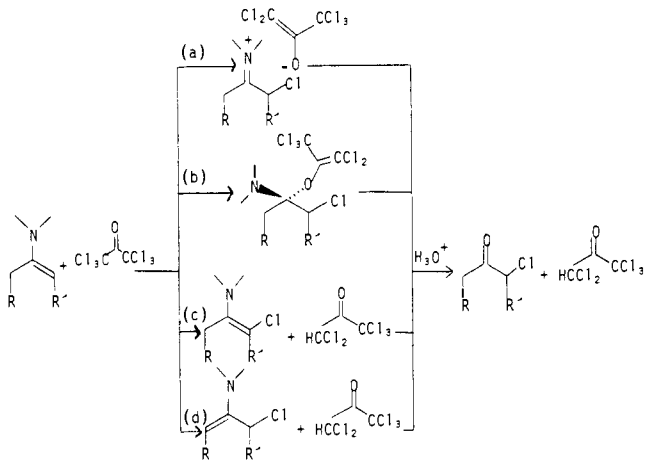
2-halo-2-methyl isomer. 6-Bromo-2-methylcyclohexanone has been prepared by the reaction of this enamine with bromine in an acetic acid–chloroform solvent mixture; however, this isomer was observed to rearrange completely to the 2-bromo-2-methyl isomer within 24 h.[4a]

The reaction of HCA with enamines of cyclic ketones can be envisioned to proceed by one of the four pathways shown in Scheme I. The pathways shown allow for the chlorination

Scheme I



reaction to occur with the intermediate formation of (a) a β-chloroimmonium ion–pentachloroacetonide anion pair, (b) a 1:1 covalent adduct, (c) a β-chloro enamine, or (d) an allylic chloro enamine. Our current investigations into the mechanism of the HCA–enamine reaction reveal that pathways a, c, and d can be selectively realized with a given enamine under appropriate experimental conditions, and that the respective intermediates along these pathways are available for further synthetic elaboration.

Experimental Section

General. ^{1}H NMR spectra were recorded at 90 MHz using a Perkin-Elmer R-32 spectrometer. ^{13}C NMR spectra were recorded at 20 MHz using a Varian CFT-20 spectrometer under conditions of proton noise decoupling. All chemical shifts for the NMR spectra were measured in parts per million relative to $(CH_3)_4Si$. Mass spectra were run on a Hitachi Perkin-Elmer RMU-6 spectrometer. Infrared spectra were taken on a Beckman Accu Lab 1 grating spectrophotometer. Gas chromatographic analyses were performed on a Hewlett-Packard 5711A dual column GC equipped with a Vidar 6300 digital integrator and using a 1/8 in. × 6 ft aluminum column packed with 10% Hi-Eff-1-BP on 80/100 mesh Chromosob P AW. Yields are averages of at least three GLC determinations and are corrected for relative flame responses. GLC collections were performed on a Varian Aerograph 2700 using a 1/4 in. × 10 ft aluminum column packed with 10% OV-17 on 60/80 mesh Chromosorb W.

The enamines used in this study were all prepared following the procedure of Stork et al.[8] Hexachloroacetone was obtained from Aldrich, distilled from P_2O_5, and stored under dry nitrogen. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride prior to use while ethyl ether was stored over sodium with benzophenone indicator and distilled prior to use. A stock solution of 7.23 M DCl was prepared from D_2O and benzoyl chloride according to the method of Brown and Groot[9] and diluted as needed.

Reaction of the Morpholine Enamines of 3-Methylcyclohexanone with HCA. The enamine (7.6 g, 42 mmol) was dissolved in 25 mL of dry THF and added dropwise with stirring to a solution of HCA (12 g, 45 mmol) in 25 mL of dry THF at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred at 0 °C for 45 min. At the end of this time the reaction was quenched by the addition of 30 mL of a 1.76 M HCl solution and stirred for 30 min at room temperature to effect hydrolysis of the chloro enamine. The organic layer was removed and the aqueous layer was extracted with ethyl ether (2 × 25 mL). The ether extracts were combined with the original organic layer, washed with brine (3 × 25 mL), and dried over $MgSO_4$. After filtration and concentration of the ether solution at reduced pressure, GLC revealed a 97% conversion of the enamine into α-chloro ketones. This product was found to consist of 64% *cis*-6-chloro-3-methylcyclohexanone, 15% *cis*-2-chloro-3-methylcyclohexanone, 8% *trans*-2-chloro-3-methylcyclohexanone, and 13% *trans*-6-chloro-3-methylcyclohexanone by GLC coalescence with authentic samples obtained by preparative GLC of a previous sample and identified spectroscopically. The spectral data for these chloro ketones are as follows. *cis*-6-Chloro-3-methylcyclohexanone: IR $\nu_{C=O}$ (CCl_4) 1730 cm^{-1}; ^{1}H NMR (CCl_4) δ 4.12 (m, $W_{1/2}$ = 8 Hz, 1 H, CHCl), 2.80–2.46 (m, 1 H, C*H*CH_3), 2.37–1.48 (m, 6 H), 1.09 (d, 3 H, J = 6.0 Hz, CH_3); MS P *m/e* 146, P + 2 33% P. *trans*-6-Chloro-3-methylcyclohexanone:[10b] IR $\nu_{C=O}$ (CCl_4) 1740 cm^{-1}; mp 55.5–56.5 °C (lit.[10a,b] 55–56 °C); ^{1}H NMR (CCl_4) δ 4.28 (4-line multiplet, 1 H, overall spacing 15.5 Hz, CHCl), 2.77–1.68 (m, 7 H), 1.05 (d, 3 H, J = 6.0 Hz, CH_3); MS P *m/e* 146, P + 2 33% P. *cis*-2-Chloro-3-methylcyclohexanone: IR $\nu_{C=O}$ (CCl_4) 1730 cm^{-1}; ^{1}H NMR (CCl_4) δ 4.04 (m, $W_{1/2}$ = 8 Hz, 1 H, CHCl), 2.32–1.36 (m, 7 H), 1.01 (d, 3 H, J = 5 Hz, CH_3); MS P *m/e* 146, P + 2 33% P. *trans*-2-Chloro-3-methylcyclohexanone: IR $\nu_{C=O}$ (CCl_4) 1730 cm^{-1}; ^{1}H NMR (CCl_4) δ 3.94 (d, 1 H, J = 8.5 Hz, CHCl), 2.87–1.36 (m, 7 H), 1.19 (d, 3 H, J = 6.5 Hz, CH_3); MS P *m/e* 146, P + 2 33% P.

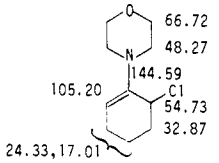
The crude oil was dissolved in 50 mL of ether and stirred with 50 mL of saturated sodium bicarbonate for 1 h at room temperature to effect a haloform reaction on the pentachloroacetone (PCA) and excess HCA. The ether layer was removed, washed with brine, and dried over $MgSO_4$. Filtration and removal of the ether provided an oil which was found to contain 66% *cis*-6-chloro-3-methyl-, 15% *cis*-2-chloro-3-methyl-, 8% *trans*-2-chloro-3-methyl-, and 11% *trans*-6-chloro-3-methylcyclohexanone.

When a similar sample was permitted to stand at −18 °C for 4 months the isomer ratio was found to be 35% *cis*-6-chloro-, 14% *cis*-2-chloro-, 11% *trans*-2-chloro-, and 40% *trans*-6-chloro-3-methylcyclohexanone.

Reactions of 1-Morpholino-1-cyclohexene with HCA. This enamine (0.982 g, 5.88 mmol) in 1 mL of $DCCl_3$ was added to a solution of HCA (1.0 mL, 6.58 mmol) in 5 mL of $DCCl_3$ cooled in a dry ice–methanol bath under an atmosphere of dry nitrogen. After the addition the mixture was warmed to 0 °C and examined by ^{1}H and ^{13}C NMR.

The ^{1}H NMR spectrum was obtained at −3 ± 2 °C and contained the resonances for PCA at δ 6.79 (s), *sym*-tetrachloroacetone at δ 6.53 (s), and 6-chloro-1-morpholino-1-cyclohexene:[5] ($DCCl_3$) δ 4.86 (t, 1 H, CHCl), 4.68 (t, 1 H, CH=C), 3.77 (t, 4 H, $-CH_2O-$), 2.86 (m, 4 H, $-CH_2N-$), 2.42–1.53 (m, 6 H). The sum of the integrated areas of PCA and *sym*-tetrachloroacetone was equal to 1 H. This ^{1}H NMR spectrum was unchanged after remaining for 11 h at room temperature under dry nitrogen.

The ^{13}C NMR spectrum was obtained at −9 °C and contained resonances for PCA, *sym*-tetrachloroacetone, and the following resonances corresponding to 6-chloro-1-morpholino-1-cyclohexene:



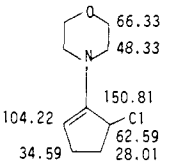
Deuterolysis of 1-Morpholino-1-cyclohexene–HCA Reaction Mixture. This enamine (2.25 g, 13.4 mmol) in 10 mL of dry THF was added dropwise to a solution of HCA (2 mL, 13.2 mmol) in 10 mL of dry THF at 0 °C under dry nitrogen. The mixture was permitted to react for 15 min after the addition, quenched with 10 mL of 1.38 M DCl solution, and stirred at room temperature for 30 min. The organic layer was removed and the aqueous layer was extracted with ether. The ether extracts were combined with the original organic layer, washed with brine, and dried over $MgSO_4$. Filtration and removal of the ether left an oil which was examined by ^{1}H NMR, ^{13}C NMR, GLC, and MS. ^{1}H NMR analysis of this oil revealed the presence of hydrogens in both PCA and on the carbon bearing the chlorine of 2-chlorocyclohexanone. GLC showed a 95% yield of PCA and 2-chlorocyclohexanone; these two products were then collected by preparative GLC. MS analysis of these pure compounds showed the parent of PCA at *m/e* 228 (no deuterium incorporation) and the

parent of 2-chlorocyclohexanone at *m/e* 133 (monodeuterium incorporation). The ^{13}C NMR showed, in addition to peaks corresponding to PCA and $DCCl_3$, the six resonances of 2-chlorocyclohexanone. The resonances at 203.5, 63.4, 37.7, 27.0, and 23.4 ppm showed no coupling while the resonance at 39.9 ppm showed a pair of ^2H triplets indicating unique incorporation of deuterium at C-6 of 2-chlorocyclohexanone.

Reaction of 1-Morpholino-1-cyclopentene with HCA. The enamine (0.80 g, 5.23 mmol) in 1.0 mL of $DCCl_3$ was added to a solution of HCA (1.0 mL, 6.58 mmol) in 4 mL of $DCCl_3$ at dry ice–methanol temperatures under an atmosphere of nitrogen. The resulting solution was examined by ^1H and ^{13}C NMR.

The ^1H NMR spectrum was obtained at −15 °C and contained the resonances for PCA at δ 6.83 (s) and 5-chloro-1-morpholino-1-cyclopentene:[5] ($DCCl_3$) δ 4.94 (m, 1 H, CHCl), 4.76 (m, 1 H, C=CH), 3.83 (t, 4 H, $-CH_2O-$), 3.00 (m, 4 H, $-CH_2N-$), 2.38 (m, 4 H).

The ^{13}C NMR spectrum was obtained at −3 °C and contained resonances for PCA and the following resonances for 5-chloro-1-morpholino-1-cyclopentene.



Reaction of the Pyrrolidine Enamine of 2-Methylcyclohexanone with HCA. The enamine (0.95 mL, 5.9 mmol) in 4 mL of THF was added to a solution of HCA (1.0 mL, 6.6 mmol) in 5 mL of THF at dry ice–methanol temperatures under a nitrogen atmosphere. The clear, bright red mixture was permitted to react at −78 °C for 15 min, then quenched with 10 mL of a 1.48 M HCl solution and stirred at room temperature for 90 min. After the usual workup an oil was obtained which was shown to be a 94% yield of a mixture of *cis*-6-chloro-2-methylcyclohexanone, *trans*-6-chloro-2-methylcyclohexanone, and 2-chloro-2-methylcyclohexanone in an 88:4:8 ratio as well as PCA.

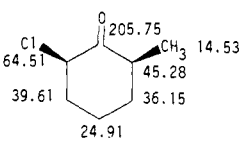
This oil was taken up in ether and stirred with saturated sodium bicarbonate for 70 min. Following a brine wash and magnesium sulfate drying the ratio of chloro ketones was found to be unchanged by GLC.

Rearrangement of α-Chloro-2-methylcyclohexanones in the Presence of Trace Amounts of Acid. In a similar experiment, the above procedure was repeated up to acid hydrolysis. After drying, filtration, and removal of the ether, GLC showed the oil to be the same as reported above. This oil, which contained PCA, THF, and a trace of HCl as well as the mixture of α-chlorocyclohexanones, was permitted to stand at room temperature for 72 h. After this time the ratio of α-chlorocyclohexanones was found to be 33:14:53 by GLC, i.e., most of the 6-chloro-2-methyl isomer had rearranged to the 2-chloro-2-methyl isomer.

Deuterolysis of 6-Methyl-1-pyrrolidino-1-cyclohexene–HCA Reaction Mixture at −78 °C. This enamine (0.95 mL, 5.9 mmol) in 5 mL of dry ether was added to a solution of HCA (1.0 mL, 6.6 mmol) in 6 mL of dry ether cooled to −78 °C under a dry nitrogen atmosphere. This clear, bright red mixture was permitted to react for 15 min, then quenched with 8 mL of a 1.26 M DCl solution at this low temperature. After stirring at room temperature for 60 min, the aqueous layer was removed and extracted with 5 mL of ether. The ether extract was combined with the original ether layer, washed with 5 mL of D_2O, and dried over $MgSO_4$. Filtration and removal of the ether left an oil which was examined by GLC, ^{13}C NMR, and MS.

GLC analysis revealed that there was a 96% conversion to α-chloromethylcyclohexanones with *cis*-6-chloro, *trans*-6-chloro, and 2-chloro isomer being formed in a 91:6:3 ratio. The other major product was PCA.

A ^{13}C NMR spectrum was obtained in $DCCl_3$ with a sweep width of 5000 Hz, pulse delay of 60.0 s, and pulse width of 37°. After 440 transients the seven lines of *cis*-6-chloro-2-methylcyclohexanone were clearly visible at the positions below. Peaks due to the carbonyl carbon



(166.08 ppm) and the trichloromethyl carbon (92.28 ppm) of PCA were also clearly visible. However, no peak, either singlet or triplet, was observed for the dichloromethyl carbon of PCA, indicating an extremely long T_1 for this carbon.

MS showed the parent peak of PCA at *m/e* 229 which was found to be ~87% deuterated when compared to the parent of normal PCA at *m/e* 228. The α-chloromethylcyclohexanones present were found to be ~13% monodeuterated by comparison of the intensity of the parent at *m/e* 146 with that of the parent at *m/e* 147 and taking into account the contribution to the intensity of the 147 peak from natural abundance ^{13}C and ^2H.

Deuterolysis of 6-Methyl-1-pyrrolidino-1-cyclohexene–HCA Reaction Mixture at −23 °C. This enamine (0.95 mL, 5.9 mmol) in 4 mL of dry ether was added to a solution of HCA (1.0 mL, 6.6 mmol) in 4 mL of dry ether at −78 °C under dry nitrogen. The red reaction mixture was stirred at this temperature for 20 min, then warmed to −23 °C with the aid of a CCl_4 slush bath. After 40 min at −23 °C the light orange solution was quenched with 10 mL of a 1.01 M DCl solution. After stirring with acid for 60 min the aqueous layer was removed and extracted with 10 mL of ether. The ether extract was combined with the original ether layer, washed with 4 mL of D_2O, and dried over $MgSO_4$. Filtration and removal of the ether provided an oil which was examined by GLC and ^1H NMR.

GLC showed a 95% conversion to α-chloromethylcyclohexanone with *cis*-6-chloro, *trans*-6-chloro, and 2-chloro isomers being formed in a 4:94:2 ratio.

^1H NMR revealed the presence of both the 6-chloro and 2-chloro positional isomers identified by their methyl resonances centered at 1.01 and 1.51 ppm, respectively. The spectrum also shows the methyl resonance of the 6-chloro-2-methylcyclohexanones to be a doublet while the resonances due to the proton α to chlorine at 4.20 ppm for the trans isomer and at 4.59 ppm for the cis isomer are missing.

The oil was then taken up in 10 mL of ether and stirred with 10 mL of saturated sodium bicarbonate for 60 min. At the end of this bicarbonate treatment and following the usual workup, the ratio of isomers was found to be 6:91:3 by GLC.

Table I. Isomer Distribution of α-Chloro-3-methylcyclohexanones Resulting from the Reaction of the Morpholine Enamines of 3-Methylcyclohexanone with HCA

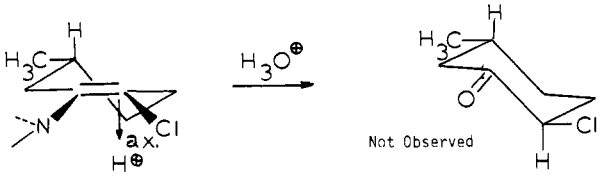
Chloro ketone	% in mixture after: Acid hydrolysis	Bicarbonate treatment	4 months at −18 °C
cis-6-Chloro-3-methylcyclohexanone	64	66	35
trans-6-Chloro-3-methylcyclohexanone	13	11	40
cis-2-Chloro-3-methylcyclohexanone	15	15	14
trans-2-Chloro-3-methylcyclohexanone	8	8	11

Results and Discussion

Reaction of the Morpholine Enamines of 3-Methylcyclohexanone with HCA. This reaction at 0 °C generates, after acid hydrolysis, a 97% yield of α-chloro ketone as a mixture of the four possible α-chloro-3-methylcyclohexanones. The isomer distribution resulting from this reaction is presented in Table I along with the isomer distribution obtained after treatment of the mixture with sodium bicarbonate (used to effect a haloform reaction on pentachloroacetone (PCA) and excess HCA) and the distribution obtained after keeping the mixture at −18 °C for 4 months. The data of Table I show clearly that the four α-chloro-3-methylcyclohexanones are not formed in equal amounts and are stable to workup conditions. The reaction exhibits regioselectivity in favoring the formation of the 6-chloro-3-methyl isomer over the 2-chloro-3-methyl isomer by a ratio of 77:23. This regioselectivity is a result of $A^{(1,2)}$ strain between the C-3 methyl group and the C-2 proton which destabilizes the Δ^1 isomer of the morpholine enamine of 3-methylcyclohexanone[11] and has been employed previously in

the reactions of enamines of 3-substituted cyclohexanones and cyclopentanones.[12]

The isomer distribution determined after acid hydrolysis and bicarbonate treatment corresponds to the kinetic distribution. Prolonged standing shows that the kinetic mixture does not correspond to the equilibrium mixture and that the cis isomer converts to the thermodynamically more stable trans isomer via epimerization of the α-chloro carbon by keto-enol tautomerism. The predominant kinetic isomer, *cis*-6-chloro-3-methylcyclohexanone, can be envisioned as resulting from HCA delivering chlorine axially to 1-morpholino-5-methyl-1-cyclohexene having its methyl substituent in the most stable equatorial position. The intermediacy of a β-chloro enamine in this reaction (pathway C, Scheme I) is unlikely since such an intermediate would suffer axial protonation during the hydrolysis step to minimize ring distortion yielding *trans*-6-chloro-3-methylcyclohexanone rather than the observed cis compound.

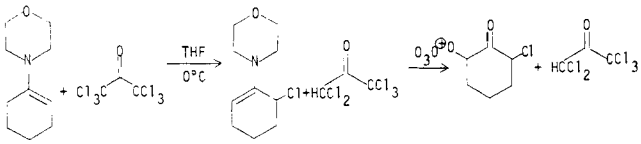


Reaction of 1-Morpholino-1-cyclohexene with HCA. HCA and 1-morpholino-1-cyclohexene react cleanly at 0 °C in $DCCl_3$. This reaction mixture was examined by ^1H and ^{13}C NMR prior to acid hydrolysis. The ^1H NMR spectrum is completely compatible with a mixture of PCA, *sym*-tetrachloroacetone, and 6-chloro-1-morpholino-1-cyclohexene which has previously been prepared by the reaction of an imidodialkylsulfonium salt with the enamine.[5]

The allylic chloro enamine structure is further supported by the ^{13}C NMR spectrum which shows resonances at 144.59, 105.20, and 54.73 ppm corresponding to the 1, 2, and 6 (chlorine bearing) carbons, respectively. The parent enamine shows the resonances of the 1 and 2 carbons at 145.26 and 100.34 ppm and has no resonances other than those due to the morpholine moiety between 50 and 100 ppm.

Deuterolysis of the mixture resulting from the reaction of HCA with 1-morpholino-1-cyclohexene yields solely 2-chlorocyclohexanone-*6-d* and undeuterated PCA. The ^{13}C NMR spectrum of this mixture demonstrates unique deuterium incorporation at the 6 carbon of 1-chlorocyclohexanone since only the resonance at 39.17 ppm shows substantial deuterium coupling. The PCA is unperturbed in both the ^{13}C and ^1H NMR.

Preparative GLC of the reaction mixture yielded pure samples of PCA and 2-chlorocyclohexanone-*6-d* for mass spectral analysis. PCA showed a parent peak of *m/e* 228, showing no deuterium incorporation, while the 2-chlorocyclohexanone was found to have its parent peak at *m/e* 133 indicating incorporation of a single deuterium.



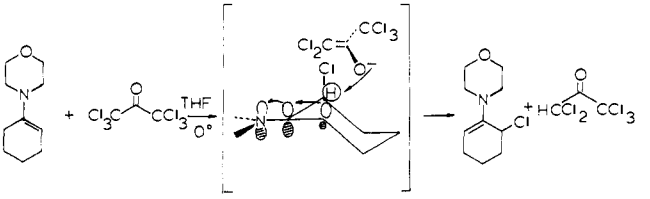
Reaction of 1-Morpholino-1-cyclopentene with HCA. HCA and 1-morpholino-1-cyclopentene react cleanly at dry ice-methanol temperatures in $DCCl_3$. Examination of this reaction mixture by ^1H and ^{13}C NMR again showed the presence of an allylic chloro enamine. The ^1H NMR spectrum is completely compatible with a mixture of PCA and 5-chloro-1-morpholino-1-cyclopentene.[5]

The ^{13}C NMR spectrum exhibits resonances at 150.81, 104.22, and 62.59 ppm corresponding to carbon 1, 2, and 5 (chlorine bearing) of the allylic chloro enamine. 1-Morpholino-1-cyclopentene exhibits resonances for the 1 and 2 carbons at 151.66 and 93.32 ppm and shows no resonances other than those due to the morpholine moiety between 50 and 100 ppm.

Conclusive proof that HCA reacts with enamines which do not have axial α' substituents to give allylic chloro enamines, as shown in path d of Scheme I, comes from the distribution of kinetic isomers obtained in the reaction of HCA with the morpholine enamine of 3-methylcyclohexanone; the ^1H and ^{13}C NMR spectral data obtained on the products of the reaction of HCA with the morpholine enamines of cyclohexanone and cyclopentanone; and the incorporation of deuterium into the α' position of the 2-chlorocyclohexanone resulting from deuterolysis of the 1-morpholino-1-cyclohexene–HCA reaction.

If an immonium ion–pentachloroacetonide ion pair were intermediate along the reaction coordinate, the pentachloroacetonide anion would be expected to abstract the most acidic proton in the immonium ion to form the chloro enamine product. Using this reasoning and knowing that the most acidic proton in these immonium ions is the hydrogen attached to the carbon bearing chlorine,[14] one would predict the formation of β-chloro enamines (path c, Scheme I). However, allylic chloro enamines rather than β-chloro enamines are produced. One could argue that allylic chloro enamines are just the thermodynamic products (for the removal of a proton in a β-chloroimmonium ion by a free base[15]) while the β-chloro enamines are kinetic products. Since we have no evidence for the formation of a β-chloro enamine and since one would not expect any β-chloro enamine–allylic chloro enamine equilibration under our reaction conditions, we are forced to conclude that β-chloro enamines are never formed in these systems. Thus the allylic chloro enamines are also the kinetic products in the reaction of HCA with these enamines.

The kinetic formation of allylic chloro enamines can be rationalized by the following arguments. The HCA delivers chlorine axially to the enamine generating a tight β-chloroimmonium–pentachloroacetonide ion pair. The α' hydrogen, located axially and on the same ring face as the newly placed chlorine, is then rapidly abstracted by the pentachloroacetonide anion to generate the allylic chloro enamine and the enol form of PCA. Abstraction of this α' hydrogen permits continuity of electron flow and minimal ring deformation owing to the favorable orbital overlap of this axial sp^3–s bond with the π system of the immonium ion, whereas abstraction of the more



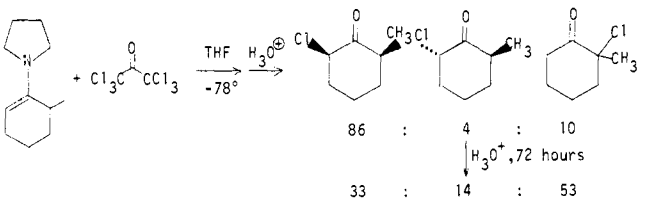
acidic equatorial hydrogen would be disfavored by orthogonality of the corresponding orbitals. This scheme is in accord with a recent mechanism proposed for the chlorination of ketones by molecular chlorine[16] and with the mechanism proposed for the reaction of 1-morpholino-1-cyclohexene with diethyl azodicarboxylate.[17]

As previously mentioned, the reaction of 1-morpholino-1-cyclohexene with *N*-chlorosuccinimide generates substantial amounts of dichloro product[5] whereas no dichlorination has been observed with HCA. The PCA produced is quite capable of chlorinating enamines[3] and we have shown that it is produced in equimolar quantities with the allylic chloro enamine. The NCS reaction undoubtedly proceeds through the same

allylic chloro enamine so we can say that HCA and PCA are more selective sources of positive chlorine than is NCS. The carbonyl groups in α-chloro ketones are known to be ~10^3 less basic than those of the parent ketone owing to the electronegativity of the α-chlorine atom.[18] This effect is apparently present in allylic chloro enamines and causes them to be much less reactive toward nucleophilic substitution,[19] thereby ensuring monochlorination with HCA whereas dichlorination pertains with better sources of positive halogen, e.g., NCS.

Reaction of 6-Methyl-1-pyrrolidino-1-cyclohexene with HCA. Abstraction of a proton from the immonium ion in this case is obviated by the absence of an axial proton with its concomitant favorable orbital overlap. The enamine is known to have the methyl substituent in the axial position because of the $A^{(1,2)}$ strain[20] between the methyl and the pyrrolidine ring. HCA can now deliver chlorine axially to the more sterically congested side of the ring to form a β-chloroimmonium pentachloroacetonide ion pair (pathway a of Scheme I) and give *cis*-6-chloro-2-methylcyclohexanone upon hydrolysis, or it can deliver chlorine equatorially to the less sterically congested side of the ring to form the same ion pair (since the α-methyl hydrogen is in an equatorial position and would require a ring twist for its abstraction) but give *trans*-6-chloro-2-methylcyclohexanone upon hydrolysis.

The reaction of this enamine at dry ice–methanol temperatures in THF gives, unlike all the other reported enamine–HCA reaction mixtures, a bright red solution which becomes colorless upon acid hydrolysis and provides a 97% yield of α-chloro-2-methylcyclohexanones. This yield represents a mixture of *cis*-6-chloro-, *trans*-6-chloro-, and 2-chloro-2-methylcyclohexanone in a 86:4:10 ratio as determined by GLC. This isomer distribution is stable to treatment with sodium bicarbonate and the predominant *cis*-6-chloro-2-methyl isomer can be isolated;[2] however, the distribution is sensitive to prolonged treatment with trace amounts of acid. When this mixture is permitted to stand with trace amounts of HCl for 72 h the isomer ratio becomes 33:14:53 showing that most of the *cis*-6-chloro-2-methylcyclohexanone rearranges to the 2-chloro-2-methyl isomer.

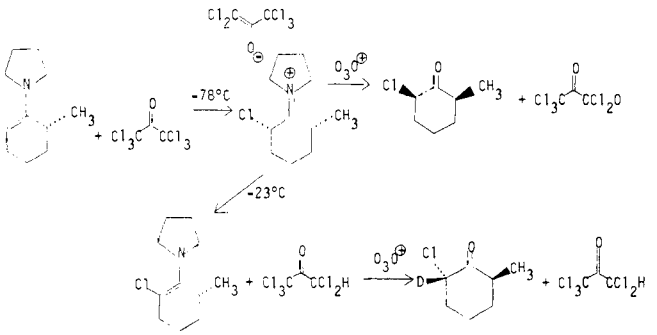


The bright red color of the reaction solution is consistent with the formation of a PCA enolate anion.[21] The intermediacy of the anion is confirmed by deuterium incorporation studies. Deuterolysis of the 6-methyl-1-pyrrolidino-1-cyclohexene–HCA reaction mixture at dry ice–methanol temperatures yields a 96% mixture of α-chloro-2-methylcyclohexanones as the *cis*-6-chloro, *trans*-6-chloro and 2-chloro isomers in a 91:6:3 ratio as well as PCA.

Deuterium incorporation into the PCA is demonstrated by both ^{13}C NMR and mass spectrometry. All seven carbons of the *cis*-6-chloro isomer were observed to be singlets whereas the *trans*-6-chloro and 2-chloro isomers were present in too low a concentration to be observed. The carbonyl carbon at 166.08 ppm and the trichloromethyl carbon at 92.28 ppm of PCA-*d* were quite evident while *no* resonance was observed for the deuteriodichloromethyl carbon. The total absence of dipole–dipole coupling would be expected to substantially lengthen the T_1 of deuterated carbon with respect to the protonated carbon. Under the experimental conditions used this T_1 would have to be >120 s.[22] A mass spectrum of the mixture shows the parent peak of PCA-*d* at *m/e* 229. Comparison of the PCA-*d* parent peak with the nondeuterated PCA parent revealed that the PCA was ~87% deuterated. Likewise, comparison of the α-chloro-2-methylcyclohexanone-d_1 parent at *m/e* 147 with its corresponding d_0 parent at *m/e* 146 showed that the mixture of α-chloro-2-methylcyclohexanones was ~13% monodeuterated.

The PCA anion, being a strong base, was found to abstract a proton from the β-chloroimmonium ion and form 2-chloro-6-methyl-1-pyrrolidino-1-cyclohexene when the reaction mixture containing the ion pair was permitted to warm from −78 to −23 °C (Scheme II). Abstraction of a proton by PCA anion was indicated by the color change from bright red to orange as the reaction mixture was warmed.

Scheme II



Deuterolysis of this reaction mixture at −23 °C, provided a 95% yield of α-chloro-2-methylcyclohexanones consisting of *cis*-6-chloro, *trans*-6-chloro, and 2-chloro isomers in a 4:94:2 ratio plus PCA.

^1H NMR analysis of this mixture showed that PCA contained no deuterium while the 6-chloro-2-methylcyclohexanones were deuterated in the 6 position. The 6-chloro-2-methylcyclohexanones had their methyl resonances at δ 1.01 split into a doublet while resonances of the protons α to chlorine in both the cis and trans isomers were missing.

These results show that HCA delivers chlorine axially to the more sterically congested side of the ring to form a β-chloroimmonium–pentachloroacetonide ion pair in its reaction with 1-pyrrolidino-6-methyl-1-cyclohexene at −78 °C. When this reaction mixture is permitted to warm to −23 °C, the PCA anion abstracts the proton from the chlorinated carbon to generate a β-chloro enamine (pathway c of Scheme I). This β-chloro enamine gives *trans*-6-chloro-2-methylcyclohexanone from axial attack of proton during acid hydrolysis (Scheme II).

Conclusion

This work demonstrates the availability of a new, mild, selective reagent for α-chlorination of ketones. The HCA–enamine reaction allows one to regioselectively halogenate ketones thus producing chloro ketones which are difficult to prepare by other methods. For instance, one can selectively prepare *cis*- or *trans*-6-chloro-2-methylcyclohexanone in high yield. Furthermore we have shown the intermediacy of allylic chloro enamines,[23] β-chloro enamines, and the pentachloroacetonide ion, all in solutions which can be used to good advantage in future synthetic elaboration.

Acknowledgments. We thank Dr. T. A. Bryson for the use of several of his instruments and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

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Spectroscopic Evidence for Electron Transfer Preceding or Accompanying Nucleophilic Aromatic Displacement Reactions on Nitrophthalic Systems with 4-Methylphenoxide Ion

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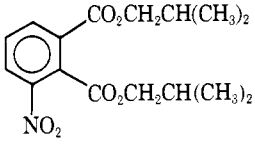
Received November 29, 1976

Abstract: The spectroscopically observed behavior of solutions containing the 4-methylphenoxide ion (**2**) and two different nitro aromatics, capable of undergoing nitro displacement, has been studied. In the case of **1**, the investigation mainly centered on the behavior under conditions where the nitro displacement did not proceed to any significant extent (although the behavior over an extended time interval during which very slow displacement occurred was also monitored). For **3**, where displacement is very much faster, spectral analyses were obtained during and subsequent to nitro displacement. The ^{13}C NMR, ^1H NMR, ESR, and UV evidence obtained strongly suggests that electron transfers occur prior to and in competition with the nitro displacement reactions.

The interaction of bases with nitro aromatics in solution has been reported to result in electron-transfer processes in which the radical anion of the nitro aromatic was formed.[1] These radical anions have been thoroughly characterized by electron spin resonance techniques in some cases[1] and proposed with good reason in others.[2]

During aromatic nucleophilic substitution (S_NAr) reactions involving, for example, methoxide and a nitro-activated aromatic containing an appropriately placed leaving group, both components needed to produce the radical anion of the nitro aromatic are present. However, only a few reports of the observation of radical anions in such systems have appeared,[3] presumably because of the dominant interest by most investigators in the structures of the Meisenheimer intermediates, the products, and the kinetics of their formation and decomposition.[4] In the few reported cases, the radical anions were identified[3a] or detected[3b-d] *only by ESR* and were produced in very low yields (e.g., <1%[3a]).

During our studies[5] of aromatic nitro displacement reactions on nitrophthalic esters, we found that an intense deep red color was produced by combining diisobutyl 3-nitrophthalate (**1**)



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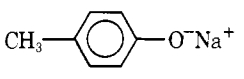

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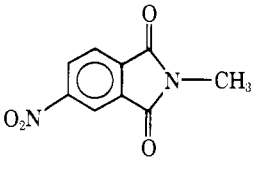

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with sodium 4-methylphenoxide (**2**) in *N,N*-dimethylformamide (DMF) at ca. 25 °C, but that, *at this temperature*, no detectable nitro displacement occurred for many hours. This report summarizes our attempt to spectroscopically determine the nature of the substance or substances responsible for this phenomenon and to compare these results with those obtained by allowing **2** to interact with 4-nitro-*N*-methylphthalimide (**3**) under nitro displacement conditions.