Novel Regioselective Chlorination of Aliphatic Ketones *via* Mono-organothallium(III) Derivatives

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Room temperature reaction of simple aliphatic ketones with an aqueous solution of $TlCl_3$ leads to mono-oxoalkylthallium(III) derivatives followed by formation of selectively α-monochlorinated ketones.

α-Halogenoketones are important intermediates in organic chemistry, particularly in heterocyclic synthesis. There is no simple method for regioselective chlorination of ketones and usually mixtures are obtained.[1a] Copper(II) chloride has been used for monochlorination of acetone;[1b] branched aliphatic ketones have been monochlorinated using morpholine enamines and halogenomethyl ketones could be obtained.[1c] Here, we report a new regioselective α-monochlorination of simple aliphatic ketones using aqueous $TlCl_3$. This reaction proceeds *via* a mono-organothallium(III) intermediate, only a few examples of which have been reported,[2] and usually in non-aqueous solvents. We have used ^{1}H, ^{13}C, and ^{205}Tl n.m.r. spectroscopy to follow the reaction and to characterize the compounds.

Aqueous solutions of $TlCl_3$ contain mainly the aquated $TlCl_3$, and also appreciable amounts of $TlCl_2^+$(aq.) and $TlCl_4^-$. Owing to fast exchange between the different species, only one singlet is observed in ^{205}Tl n.m.r. spectra.[3] The addition of any of the ketones investigated† to a ~2 M solution of $TlCl_3$ produces time-dependent changes in the spectra; the singlet is shifted towards higher frequencies characteristic for an increasing proportion of the $TlCl_4^-$ complex and a new 1 : 2 : 1 triplet appears at *ca.* 2700—3000 p.p.m. (*cf.* Figure 1).

A closer look at the triplet reveals its fine structure (*cf.* Figure 1b). Each of the triplet peaks comprises a 1 : 3 : 3 : 1 quartet for acetone and a 1 : 2 : 1 triplet for both butan-2-one and pentan-2-one, in all cases the additional splitting being ~70 Hz. We ascribe these findings to the intermediate (A)‡ (R = H, Me, or Et), where $^{2}J_{Tl\text{-}H}$ is ~1200 Hz and $^{4}J_{Tl\text{-}H}$ ~70 Hz. Thus, reaction (1) is occurring, if $TlCl_3$ is asumed to be the reacting thallium compound.

$$TlCl_3 + MeC(:O)CH_2R \rightarrow \underset{(A)}{Cl_2TlCH_2C(:O)CH_2R} + H^+ + Cl^- \quad (1)$$

The ^{205}Tl chemical shift values depend on the ketone to $TlCl_3$ molar ratio, as does the ratio of organic Tl to inorganic Tl and accordingly the rate of the reaction. The reaction is faster for higher ketone to Tl ratios and also in the sequence propan-2-one < butan-2-one < pentan-2-one ≪ pentane-2,4-dione. This is consistent with the thallation reaction proceeding *via* the enol form of the starting ketone. The enol form is generally assumed to be the reactive one in several reactions of ketones and particularly in direct halogenation.[4]

Since reaction (1) produces Cl^- ions, in the absence of other reactions, it would reach equilibrium for $[Cl^-]/[Tl]_{inorganic} > 4$, when the concentration of the reactive species, presumably $TlCl_2^+$ or $TlCl_3$, would be negligible.[3]

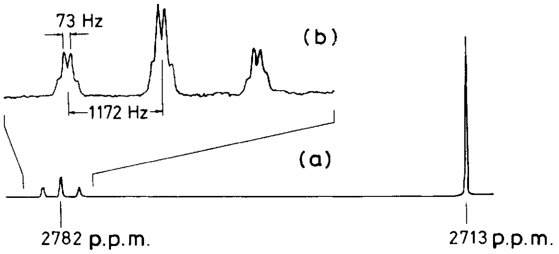

Figure 1. 51.9 MHz ^{205}Tl n.m.r. spectra at 27 °C of an aqueous solution containing Tl^{III} and Cl^- a few hours after addition of acetone (Tl : acetone ratio ~2 : 1), with the organothallium region expanded. Chemical shifts are in p.p.m. to high frequency of aqueous $TlClO_4$ at infinite dilution.

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† Replacement of H_2O by D_2O as solvent has no effect, but when $[^{2}H_6]$acetone is used a broad peak replaces the triplet. Hence, the triplet can be assigned to Tl–H spin–spin coupling in a Tl–acetone compound, with a coupling constant of ~1200 Hz, as can also be observed by ^{1}H n.m.r. spectroscopy. The literature values for both $^{2}J_{Tl\text{-}H}$ and $^{3}J_{Tl\text{-}H}$ for mono-organothallium(III) compounds vary in the range ~10^2—10^3 Hz.[2b,c]

‡ For pentane-2,4-dione also the Tl–H splitting pattern can only be explained assuming a structure $Cl_2TlCH_2C(:O)CH_2C(:O)Me$; *i.e.* thallium is bound to one of the outer methyl groups. The absence of ^{205}Tl–^{203}Tl spin–spin coupling excludes a polymeric structure.

During reaction (1), a second reaction takes place which can be followed by the precipitation of thallium in the form of $Tl_3[TlCl_6]$ (analyses[5] for Tl^I, Tl^{III}, and Cl, were satisfactory) and, accordingly, by the decrease in intensities of the Tl n.m.r. signals. After some time (hours to weeks, depending on the ketone and the ketone : Tl^{III} ratio) no Tl n.m.r. signal could be detected, Tl^{III} thus being partially reduced to Tl^I forming the precipitated $Tl_3[TlCl_6]$ and the ketone being oxidized. The organic component was distilled off, and the distillate dried (molecular sieve) and characterized by ^{13}C and ^1H n.m.r. spectroscopy§ (including selective $^{13}C\{^1H\}$, $^1H\{^1H\}$, and off-resonance $^{13}C\{^1H\}$ decoupling experiments; Bruker WP200 spectrometer). The major product appeared to be the selectively mono-α-chlorinated ketone (B) (R = H, Me, or Et), no other chlorinated products being detectable. Thus, we assume that the further reaction (2) takes place.

$$(A) + \tfrac{1}{3}\,TlCl_3 \rightarrow \underset{(B)}{MeC(:O)CHClR} + \tfrac{1}{3}\,Tl_3[TlCl_6] \qquad (2)$$

Reactions (1) and (2) occur simultaneously, the former being faster otherwise we would not have detected the intermediate (A).

At this stage we do not wish to speculate as to why the chlorination site of the final product is not the same as the thallation site of the intermediate. However, it has been observed previously[6] that de-thallation may involve re-arrangement of the product.

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§ *E.g.* ^{13}C n.m.r. data for MeC(:O)CHClEt: δ 13.62 (CH_2*Me*), 17.54 (*C*H_2Me), 29.34 (*Me*C:O), 45.43 (CHCl), and 207.49 (C:O).