α-Chlorination of Ketones Using *p*-Toluenesulfonyl Chloride

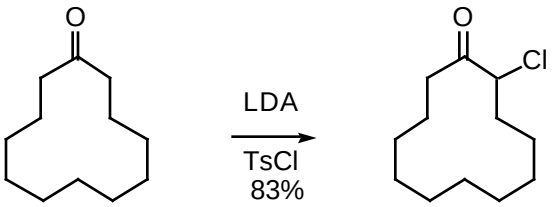
Kay M. Brummond* and Kirsten D. Gesenberg

Department of Chemistry, West Virginia University, Morgantown, WV 26506-6045

Abstract: Treatment of a variety of ketones with lithium diisopropylamide followed by *p*-toluenesulfonyl chloride gives α-chloroketones in good yields. In addition, a polymer bound tosyl chloride reagent has also been shown to effect this transformation.

Chlorination of ketones at the α-position has classically involved acid or light initiated addition of chlorine to ketones.[1] These conditions can be somewhat limited in scope for several reasons, for instance these are also the conditions used to halogenate olefins. Alternatively, the reaction of ketones with copper (II) chloride has been used to prepare α-chloroketones.[2] This provides a selective method for the chlorination of an unsymmetrical ketone at the more highly substituted α-carbon atom. To effect the α-chlorination of a ketone at the less substituted carbon, the reaction sequence involves the initial formation of an intermediate such as a silyl enol ether.[3] Other methods reported for the preparation of α-chloroketones use trichloroisocyanuric acid[4], *N*-chlorosuccinimide[5], sulfuryl chloride[6] and polymer-supported chlorine.[7] During our investigations probing the selective formation of alkynes[8a] and allenes[8b] via the elimination reactions of *O*-substituted enols we observed a process whereby chloroketones can be obtained efficiently from alkanones.

Sulfonyl chlorides have previously been recognized as a source of "Cl^+" as demonstrated when 2-lithio-1-(phenylsulfonyl)indole was converted to a 2-chloro-1-(phenylsulfonyl)indole using benzenesulfonyl chloride.[9] Additionally, one isolated example was reported whereby an enolate of a ketone was generated using LDA and α-chlorination was accomplished by the addition of trifluoromethanesulfonyl chloride.[10] Finally, a series of carbon acids were dichlorinated using a relatively weak base (NEt_3 or DBU) and trifluoromethanesulfonyl chloride.[11] We would now like to report a mild and inexpensive method for the preparation of α-chloroketones involving the initial formation of a kinetic enolate of a ketone and the addition of *p*-toluenesulfonyl chloride as a positive chlorine source.



eq. 1

In the first example, cyclododecanone was treated with one equivalent of lithium diisopropylamide and one equivalent of *p*-toluenesulfonyl chloride in THF at -78 °C and allowed to warm to room temperature (eq. 1). The product obtained by these reaction conditions was 2-chlorocyclododecanone in 83% yield.

In an effort to determine if this chlorination procedure is general for systems other than macrocyclic ketones, a variety of carbonyl compounds were subjected to the same conditions. The results from these studies are summarized in Table I. The chlorination of 2-methyl-cyclohexanone provides 2-chloro-6-methylcyclohexanone in an 85% yield as a (2:1) mixture of diastereomers with the *cis*-isomer predominating. Interestingly, none of the regioisomeric 2-chloro-2-methylcyclohexanone was observed and only minute amounts (<3%) of the 2-sulfonyl-6-methylcyclohexanone was formed. This impurity could be easily separated from the chloroketone via column chromatography. This method provides an attractive alternative to existing methods available for the chlorination of ketones since chlorination occurs at the less substituted α-carbon.[3]

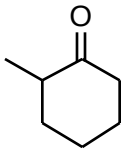
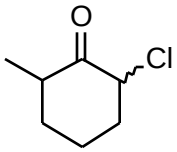
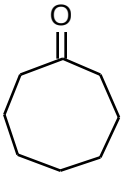
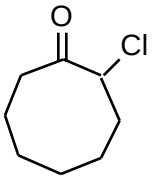
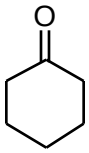
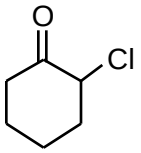
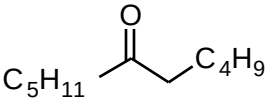
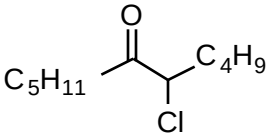
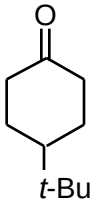
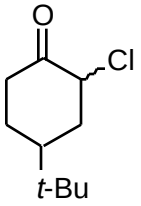
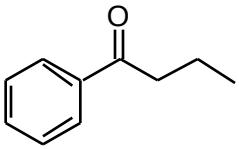
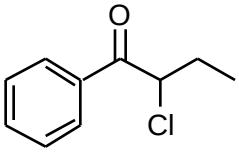
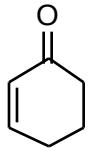
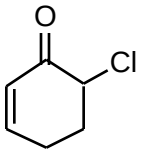
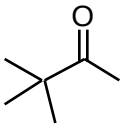
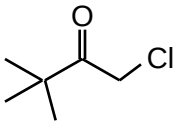
Attempts to effect the chlorination of cyclohexanone using *p*-toluenesulfonyl chloride resulted in low yields (entry 2, 49%) with small amounts of the α-sulfonyl ketone contaminant. Alternatively, cyclohexanone can be efficiently chlorinated at the α-position in good yields (74%) using an alternative positive chlorine source, trifluoromethanesulfonyl chloride.[10] Treatment of 4-*tert*-butylcyclohexanone (entry 3) to the LDA/*p*-toluenesulfonyl chloride conditions affords the monochlorinated compound in 77% yield. This compound was isolated as a (4:1) mixture of diastereomers with the *trans*-diastereomer predominating.

In entry 4 the compatibility of this method with an electron deficient olefin functionality was demonstrated by the successful chlorination of 2-cyclohexenone in 69% yield. Medium-sized rings are also efficiently chlorinated. Cyclooctanone was converted to 2-chlorocyclooctanone in 69% yield (entry 5). This process is also useful for the conversion of symmetrical and unsymmetrical acyclic ketones to chloroketones. 6-Undecanone can be selectively α-chlorinated to afford 5-chloro-6-undecanone in 66% yield under these reaction conditions (entry 6). Butyrophenone (entry 7), an acyclic unsymmetrical ketone, was chlorinated at the only position available in 61% yield. A limitation to this methodology was observed in the attempt to chlorinate methyl ketones. Submission of pinacolone (entry 8) to the standard chlorination conditions afforded the α-chloroketone in 65% yield. However, attempts to chlorinate other methyl ketones met with very little success; for instance both acetophenone and 6-methyl-5-hepten-2-one gave only decomposition of starting material. Evidence of this same problem has been previously observed where enolates of ketones have been substituted with a cyano moiety using *p*-toluenesulfonylcyanide as positive cyano source.[12]

Attempts to expand this methodology to other carbonyl containing functionality were unsuccessful. For example, the conditions described within do not appear to be amenable for the α-chlorination of esters (methyl decanoate), carboxylic acids (10-undecenoic acid) and aldehydes (decyl aldehyde).

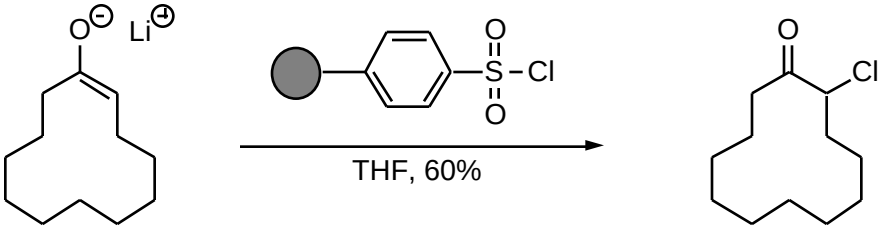
Representative procedure for α-chlorination of ketones:[13] A flame dried round bottom flask was charged with diisopropylamine (1.1 eq) and dry THF (1.0 M). The solution was cooled to 0 °C and *n*-BuLi (1.0 eq) was added dropwise. Upon completion of addition the solution was cooled to -78 °C and a 0.1 M solution of 2-methylcyclohexanone (1.0 eq) in THF was added followed by a 0.1 M solution of *p*-toluenesulfonyl chloride (1.0 eq) in THF. The mixture was allowed to warm to room temperature and the progress of the reaction was monitored by TLC. After 1 h the reaction mixture was filtered through silica gel eluting with ether and then concentrated *in vacuo* to give 2-chloro-6-methylcyclohexanone in 85% yield.

Table I

	ketone	chloroketone	yield		ketone	chloroketone	yield
1			85%	5			69%
2			49% 74%[a]	6			66%
3			77%	7			61%
4			69%	8			65%

[a] LDA, trifluoromethanesulfonyl chloride, THF, 0 °C.

An interesting application of this method is the attachment of the chlorosulfonyl moiety to an insoluble polymeric support, rendering the lithium sulfinate by-product insoluble and thus easily removed from the reaction mixture by simple filtration. In addition, side products resulting from α-sulfonylation would also be removed in this way. Toward this end, we have shown that cannulation of a solution of the lithium enolate of cyclododecanone at -78 °C (generated as described above) into a stirred suspension of THF-swelled chloro-*p*-toluenesulfonyl resin[14] (1.0 equivalents of resin, swelled for 2 h then cooled) at -78 °C then warming to room temperature affords 2-chlorocyclododecanone in 60% yield after filtration and concentration (eq. 2).



eq. 2

In conclusion, the α-chlorination of ketones has been demonstrated under non-equilibrating conditions using lithium diisopropylamide to effect the formation of an enolate and *p*-toluenesulfonyl chloride as a positive chlorine source. This method is effective with both cyclic and acyclic ketones; the only limitation observed being methyl ketones. Monochlorination of the ketone at the least substituted α-position predominates with no

contamination by the dichlorinated product. In addition, we have shown that this method can be effected with a polymer-bound reagent thus allowing the chloroketones to be simply washed from the reagent and isolated in good yield with minimal purification.

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13. All new compounds reported herein exhibit satisfactory spectral data (IR, ^{1}H NMR, ^{13}C NMR, GC/MS). Representative spectral data**: 2-Chlorocyclooctanone** ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.30 (dd, J = 9.6 and 3.9 Hz, 1H), 2.69 (m, 1H), 2.30 (m, 3H), 1.89 (m, 3H), 1.40 (m, 5H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 209.2, 63.7, 37.6, 32.9, 27.9, 25.8, 24.2, 24.1; IR (neat) 2934, 2859, 1718, 1466, 1448, 1327, 1085 cm^{-1}; MS (GC/MS) *m/z* 160 (M^+), 116, 98, 83, 67, 55, 41. **5-Chloro-6-undecanone** ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.16 (dd, J = 8.2 and 5.5 Hz, 1H), 2.62 (t, J = 7.3 Hz, 2H), 1.89 (m, 2H), 1.53 (m, 10H), 0.88 (m, 6H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 205.8, 63.9, 38.6, 33.6, 31.3, 28.3, 23.4, 22.5, 22.2, 14.0, 13.9; IR (neat) 2961, 2918, 2865, 1717, 1462, 1374, 1246, 1159 cm^{-1}; MS (GC/MS) *m/z* 204 (M^+), 99, 71, 43.

14. The polystyrene-TsCl resin is commercially available from Argonaut Technologies.