Strategy for the Preparation of Allenes From α,β-Unsaturated and Saturated Ketones via Enol Phosphates

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The versatility and synthetic utility of the allene moiety in organic synthesis have been extensively documented in the recent literature. For instance, allenes participate in a variety of cycloaddition and electrocyclic reactions affording products that are not easily accessible by other synthetic methods.[1,2] In addition, the allene moiety can be transformed into a variety of other functional groups such as olefins, α,β-unsaturated carbonyls and alkynes.[3] Moreover, allene axial chirality has been used to transfer asymmetry in cycloaddition reactions.[4] During the course of our synthetic studies directed toward the allenic Pauson-Khand reaction,[2] we required new, efficient protocols for the preparation of allenes. We subsequently initiated a program which focused on the conversion of ketones to allenes and in this paper report on this investigation.[5]

It is known that conversion of methyl ketones to the "kinetic" enol phosphates, followed by β-elimination affords terminal acetylenes.[6] We reasoned that conversion of a ketone to the more substituted enol phosphate (Scheme 1) followed by base induced elimination would form an allene instead of the internal alkyne if deprotonation of the least substituted carbon is kinetically preferred. Transformations of this type have been performed on vinyl halides where allylic deprotonation followed by elimination of HX affords an allene, but this reaction is reported to suffer from competing side reactions.[7] Similarly, allenes have been prepared by the elimination of enol triflates. However, this method has structural limitations.[5f] Wiemer has demonstrated that enol phosphates derived from five- and six-membered rings undergo a 1,3-phosphorous migration to afford β-keto phosphonates upon deprotonation with lithium diisopropylamide.[8]

SCHEME 1

In order to determine the feasibility of this method the enol phosphate of 3-octanone (Table 1, entry A) was readily prepared by an established procedure.[6] The ketone was added to a solution of lithium diisopropylamide (LDA) and THF at -78°C and allowed to stir at this temperature for 1 h. Then chlorodiethylphosphate was added and the solution was warmed to room temperature. Warming the enol phosphate reaction mixture to room temperature afforded a mixture of all possible regio- and stereoisomers by ^{1}H NMR (Eq.1). The enol phosphates were not isolated but taken on directly. Subjection of this mixture of isomers to elimination conditions (LDA, 2.2 equiv.) at -78°C gave a single allene, 2,3-octadiene in 43% yield. If the reaction mixture was allowed to warm slowly to 0°C during the elimination step, 2,3-octadiene (86%) was the major product but contamination with 2- and 3-octyne (11% and 3%, respectively, as determined by HPLC) was observed.[9] However, maintaining the reaction temperature at -78°C during the elimination step results in a higher allene to alkyne ratio (94.4% and 5.6% respectively).[10] Based upon this result, the *E/Z* configuration and the regiochemistry of the enol phosphate appear to have no effect on the allene to alkyne ratio. Fortunately, the allene can be easily separated from the isomeric alkynes by flash chromatography on silica gel using pentane as the eluent. The conversion of 3-octanone to 2,3-octadiene is a very clean reaction based upon the HPLC trace of the crude product, so the somewhat low yield is attributed to the volatility of 2,3-octadiene.

EQUATION 1

We next examined this protocol on higher molecular weight ketones, undecanone (entry B) and 1-phenyl-4-octanone (entry C). Formation of the enol phosphates of these ketones followed by LDA-induced elimination gave a 62% yield of 5,6-undecadiene and a

73% yield of 1-phenyl-3,4-octadiene. In both examples, the HPLC trace of the crude product showed allene accounting for greater than 96% of the material with the remainder being the alkyne. Alternative bases were studied for the elimination of the enol phosphate of 1-phenyl-4-octanone. The use of *n*-butyl lithium resulted in an identical allene to alkyne ratio as observed with LDA, but gave a lower yield (33%). No reaction was observed when lithium hexamethyldisilylazide was used as a base. Attempts to convert 1-phenyl-2-butanone (entry D) to the allene gave mixed results. Warming the elimination reaction of the enol phosphate to room temperature resulted in the conjugated alkyne as the major product (67% yield). Whereas maintaining the reaction temperature at -78°C during the elimination resulted in a mixture of allene to alkyne (3:2 as determined by HPLC) and the allene was isolated in 24% yield.

This method is also amenable to the preparation of macrocyclic allenes. This is demonstrated by the conversion of cyclododecanone and cyclopentadecanone to their corresponding allenes (entries E and F) in good yields. The allene to alkyne ratio for cyclododecanone and cyclopentadecanone are 92:8 and 84:16, respectively, as determined by HPLC. It is interesting to note that when the enol triflate of cyclododecanone was treated with LDA using the conditions described above, the product ratio changed to afford a 7:93 mixture of allene to alkyne. The cyclododecyne was isolated in a 95% yield (Eq. 2).

EQUATION 2

We have also demonstrated this method to be useful in the preparation of allenic ketones (entry G). The mildness of this procedure is confirmed by treatment of the enol phosphate of 3-*n*-amyl-2,4-pentanedione with LDA (3 equiv) to give the desired disubstituted allene in 38% yield. This new way to prepare this labile functionality will prove to be synthetically useful.

α,β-Unsaturated ketones can be readily converted to allenes. The enol phosphate derived from the cuprate addition of lithium dimethylcuprate[11] to β-ionone (entry G) gave excellent yields (81%) of the allene. The reaction was worked up in a manner analogous to that described for cuprate additions to enones.[11]

TABLE I

In conclusion, we have developed a new method for the conversion of ketones to allenes by way of their enol phosphates. The examples illustrated in Table 1 demonstrate that saturated, unsaturated, macrocyclic and acyclic ketones can be successfully converted to the corresponding allenes. Limitations were found with conjugated enol phosphates when the reaction using 1-phenyl-2-butanone lead to the internal, conjugated alkyne. Treatment of the enol triflate of cyclododecanone to the conditions described above gave a 7:93 mixture of allene of alkyne. Finally, isomerization of the allene to alkyne does take place when the elimination reaction is allowed to warm to room temperature. We are currently exploring the scope and limitations of this protocol. Investigations into the use of chiral lithium amide bases to form chiral allenes and the application of this methodology toward natural product synthesis are underway in our laboratories.

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Supporting Information Available: Experimental procedures and copies of ^{1}H NMR, ^{13}C NMR and IR spectra of allenes (entries A - H). ^{1}H NMR spectra of enol phosphates (entries A-H) (40 pages). See current masthead page for ordering information.

References and Notes:

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(9) The HPLC peak identity was determined by the co-injection of 2- and 3-octyne with the crude product mixture. The response factor of the RI detector to 2,3-octadiene and 2-octyne was determined to be 1.11.

(10) A control experiment was carried out where an allene was subjected to the reaction conditions employed for the elimination step and significant isomerization of the allene to acetylene occurred at room temperature.

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(12) Sample experimental details (Table I, Entry C): 1-phenyl-4-octanone (1.0 g, 4.9 mmol) dissolved in tetrahydrofuran (5 mL) was added dropwise via addition funnel over a

10 min under an atmosphere of argon, to a cooled (-78°C) solution of lithium diisopropylamide [freshly prepared by the addition of *n*-BuLi (3.4 mL of a 1.6 M solution in hexanes, 5.0 mmol) to diisopropylamine (0.82 mL, 5.9 mmol) in anhydrous tetrahydrofuran (5 mL) at 0°C]. Upon completion of addition, this solution was allowed to stir at -78°C for an additional hour, then chlorodiethylphosphate (0.78 mL, 5.4 mmol) was added. The resulting yellow solution was warmed slowly to 0°C (45 min) and then cooled back to -78°C and freshly prepared lithium diisopropylamide (10.3 mmol) was added. The resulting solution was stirred for 36 h while maintaining the temperature at -78°C, during which time a precipitate formed. Upon completion of the reaction (monitored by TLC) the mixture was then poured onto pentane (50 mL) and ice water (15 mL). The aqueous layer was extracted three times with pentane and the combined extracts were washed with cold 1N HCl, water, sat. $NaHCO_3$, water, brine and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to afford a yellow oil. (If this elimination reaction is stirred at -78°C for only 16 h, 1-phenyl-3,4-octadiene is afforded in 63% yield and the HPLC trace of the crude product shows a 97:3 ratio of allene to alkyne.) Purification by flash chromatography on silica gel (eluting with pentane) furnished a 73% yield 1-phenyl-3,4-octadiene and 7% combined yield of 1-phenyl-3-octyne and 1-phenyl-4-octyne as colorless oils. The HPLC trace of the crude product shows a 90:10 ratio of allene to alkyne. The selectivity was determined by the HPLC method using a silica column with hexanes as the eluent.