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A NEW REAGENT FOR A "ONE-POT" CYCLOPENTENONE ANNELATION

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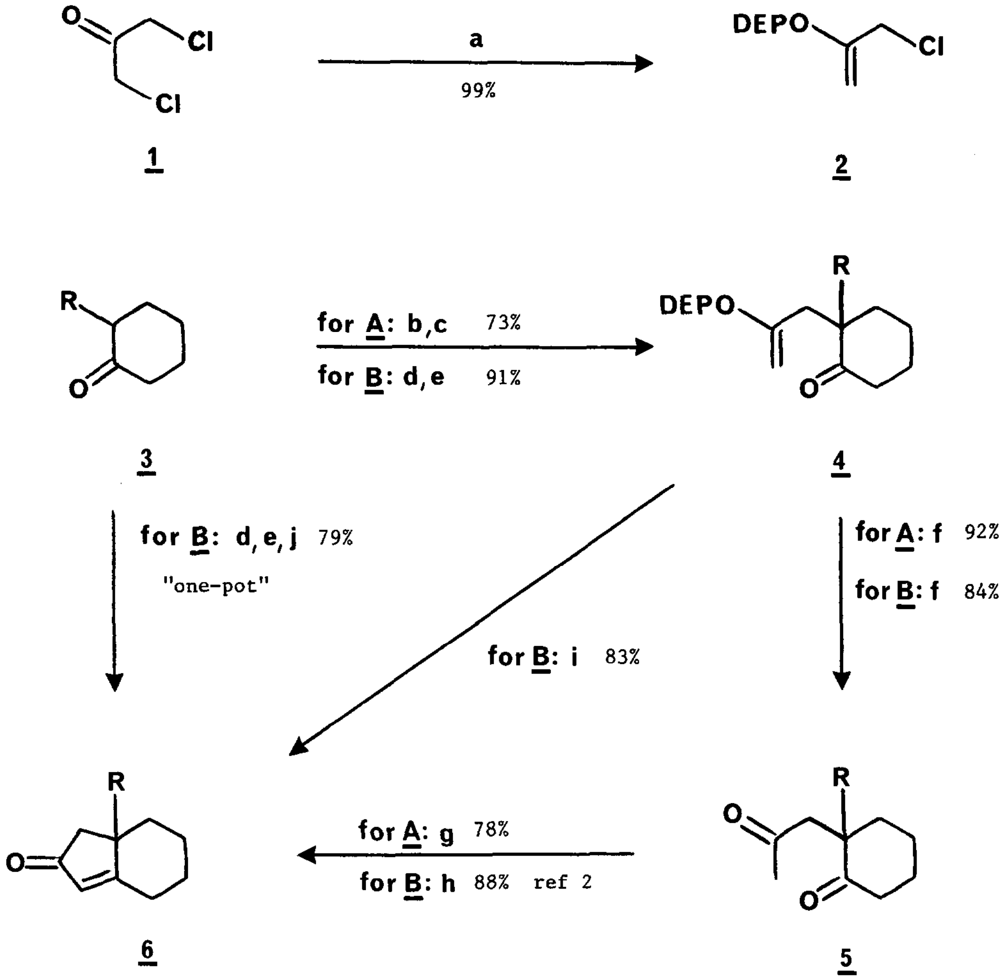
Abstract. A new reagent, 3-chloro-2-diethylphosphoryloxy-1-propene (2), for the preparation of cyclopentenones from ketone precursors via a "one-pot" synthesis is described.

The tremendous diversity and biological importance of cyclopentanoid natural products have made these compounds important synthetic goals and have stimulated the development of new methods and reagents for the preparation of cyclopentenone rings.[1] A well established strategy for the construction of cyclopentenones is the intramolecular aldol condensation of 1,4-diketones. The latter generally are available by carbon-carbon bond forming reactions between electrophilic C_3 synthons ($CH_3COCH_2^+$) and ketone enolate or imine anion or enamine precursors. Nearly all of these known C_3 synthons used in the preparation of cyclopentenones require three separate and distinct synthetic steps: 1) alkylation; 2) hydrolysis or oxidation; and 3) intramolecular aldol condensation.[2] The purpose of this Letter is to report a new reagent for a "one-pot" cyclopentenone annelation based upon enol phosphate chemistry.

The chemistry of enol phosphates has been reviewed.[3] Enol phosphates are hydrolyzed by C-O fission with dilute HCl in $EtOH/H_2O$ at reflux or with P-O fission with dilute KOH in H_2O at reflux with reasonably short half-lives. In the case of base cleavage the resulting diethylphosphate anion [$(EtO)_2PO_2^-$ = $DEPO^-$] is resistant to further hydrolysis or nucleophilic attack and the corresponding enolate anions are free to undergo aldol condensations.

The new reagent, 3-chloro-2-diethylphosphoryloxy-1-propene (2), is prepared in near quantitative yield from 1,3-dichloroacetone and triethylphosphite at 100°C via a Perkow



DEP = $(EtO)_2PO$

A,R = CO_2Me; B,R = H

a) $(EtO)_3P$, 100°C; b) KH, THF, HMPA; c) 2; d) 1.1 equiv. LDA, THF; e) 2, 5% $(Ph_3P)_4Pd$, THF; f) 10% HCl, acetone, reflux 3h; g) NaH, $PhCH_3$, reflux 19 h; h) 5% KOH, H_2O, reflux 6 h; i) 5% KOH, H_2O, reflux 8.5 h; j) 10% NaOH, H_2O, EtOH, reflux 24 h.

reaction.[4] The application of reagent 2 as a cyclopentenone annelating agent was explored with 2-carbomethoxycyclohexanone (3A, R = CO_2Me) and cyclohexanone (3B, R = H). Alkylation of β-ketoester 3A by generating the enolate anion with potassium hydride in THF/HMPA followed by the addition of 2 affords 4A in 73% yield. Generation of the enolate anion of ketone 3B with 1.1 equivalents of lithium diisopropylamide (LDA) in THF followed by the addition of 2 in THF containing 5 mole % of $(Ph_3P)_4Pd$ catalyst produces 4B in 91% yield.[5] The latter reaction proceeded in only 65% yield in the absence of the $(Ph_3P)_4Pd$ catalyst.[5]

Hydrolysis of enol phosphates 4A or 4B with 10% HCl in acetone/H_2O at reflux for 3 hours gives diketones 5A or 5B in 92% or 84% yields, respectively. Intramolecular aldol condensation of 5A with NaH in refluxing $PhCH_3$ for 19 hours affords 6A in 78% yield. Cyclization of diketone 5B with 5% KOH in H_2O at reflux for 6 hours produces 6B in 88%.[2] Concomitant hydrolysis and intramolecular aldol condensation of 4B to 6B in 88% yield was carried out with 5% KOH in H_2O at reflux for 8.5 hours. Finally, the "one-pot" cyclopentenone annelation process was conducted as follows: The kinetic enolate anion of cyclohexanone (3B) was generated with 1.1 equivalents of LDA in THF followed by the addition of 2 in THF containing 5 mole % of $(Ph_3P)_4Pd$, then quenching with 10% NaOH in EtOH/H_2O and heating at reflux for 24 hours affords 6B (R = H) in 79% overall yield from 3B (R = H).

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6. Satisfactory spectra and analyses were obtained on all new compounds.

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