Reduction of Enol Phosphates to Alkenes with Titanium Metal

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The reduction of selectively generated enol phosphates (and/or enol phosphorodiamidates) by lithium metal in ethylamine (or liquid ammonia) has been demonstrated to be an exceedingly useful synthetic method for the regioselective synthesis of alkenes from ketones.[1-3] Enolate anions of the type 2A, generated under thermodynamically controlled conditions,[4] afford enol phosphates 3A upon treatment with diethyl phosphorochloridate in the presence of tetramethylethylenediamine (TMEDA). Reduction of enol phosphates 3A then produces thermodynamically more stable alkenes 4A. Enolate anions of the type 2B,[5] generated under kinetically controlled conditions, upon the addition of diethyl phosphorochloridate in TMEDA give enol phosphates 3B. Reduction of enol phosphates 3B then affords thermodynamically less stable alkenes 4B. Thus either alkene 4A or 4B can be prepared with a high degree of regioselectivity depending on how the respective enolate anions are generated.[6] We wish to report herein a new method for reducing enol phosphates to alkenes in high yield under aprotic conditions utilizing freshly prepared titanium metal.[7]

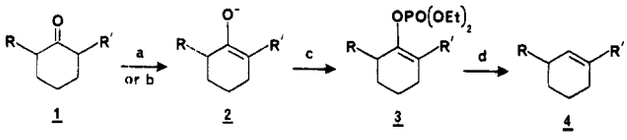
Highly activated titanium metal can be freshly prepared from anhydrous titanium(III) chloride by reduction with either magnesium[8] or potassium[9] metals in anhydrous tetrahydrofuran. The optimum stoichiometry for this reduction (eq 1) utilizes 6 to 6.6 equiv of potassium metal to prereduce 2 equiv of anhydrous titanium(III) chloride in refluxing dry tetrahydrofuran (0.75 to 1 h) followed by the addition of 3 equiv of enol phosphate and further reflux for 1 to 4 h. After cooling to 5 °C (ice bath) the reaction mixture is then quenched with 100% ethanol, filtered through silica gel, concentrated in vacuo, and either distilled or crystallized to afford the respective alkene in high yield.

$$6K + 2TiCl_3 \xrightarrow[THF]{\Delta} 2Ti \xrightarrow[\text{2. EtOH, 5 °C; 3. filter, } SiO_2\text{; 4. -THF}]{\text{1. } 3RC(OPO(OEt)_2)=CH_2,\ \Delta/THF} 3RCH=CH_2 \quad (1)$$

Table I lists the starting ketones, respective methods used to generate specific enolate anions, alkene products, yields of the enol phosphates, times for the reductions, and the respective yields for each reduction. This new reduction method is exceedingly simple and it appears to be quite general for ketones not conjugated with aromatic rings. No over reduction was observed in the case of diene products from ketones **14**, **15**, and **16**; however, the reduction of the enol phosphate derived from isobutyrophenone (**17**) proceeds very rapidly to give isobutylbenzene in 93% yield. Reduction of the enol phosphate derived from camphor (**6**) by this new method followed by quenching with deuterium oxide does not incorporate deuterium.[11]

In conclusion, this new reduction method appears to be quite general for the regioselective conversion of ketones (not conjugated to aromatic rings) to specific alkenes or dienes in excellent yields. The distinct advantages of this new reduction method over that of lithium in ethylamine are higher yields (81–100%) and utility in the regioselective synthesis of dienes. Further investigations and extentions of this reduction method are currently under investigation.

Scheme I[e]



1 2 3 4

[a] Ac_2O, $HClO_4$ (cat), CH_2Cl_2; 2 × CH_3Li, THF. [b] 1.1 × LDA, THF. [c] $ClPO(OEt)_2$, TMEDA. [d] Reduction. [e] A, R = H; R' = CH_2. B, R = CH_3; R' = H.

Experimental Section

Materials and Techniques. Melting points were determined on a Büchi melting-point apparatus. All melting points and boiling points are uncorrected and are reported in °C. Analytical gas-phase chromatography (GC) was performed on a Varian Aerograph Model 1400, equipped with a flame ionization detector with helium as the carrier gas using a 6 ft, stainless steel, 1/8 in. diameter column, packed with 3% SE-30 on Varaport 30, 100/120 mesh with a flow rate of 15 mL/min at ambient temperature. Silica gel PF 254 + 336 (E. Merck No. 7748) and silica gel "Baker Analyzed" reagent (60–200 mesh) were used for thin layer and column chromatography, respectively. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 237B grating infrared spectrophotometer. Spectra were taken as 10% solutions in spectroquality carbon tetrachloride or chloroform using balanced 0.1-mm sodium chloride cells or were taken as thin films between sodium chloride plates. Nuclear magnetic resonance (NMR) spectra were measured on a Varian Associates Model T-60 spectrometer in the solvent indicated. Ultraviolet (UV) spectra were recorded on a Beckman Model 26 spectrophotometer. Tetrahydrofuran (THF) and ether were freshly distilled from lithium aluminum hydride immediately before use in all reactions. Tetramethylethylenediamine (TMEDA) was freshly distilled from calcium hydride. Anhydrous titanium(III) chloride (Alfa No. 77116) was transferred under N_2 and utilized directly. All reactions were performed under an atmosphere of dry nitrogen utilizing an apparatus designed by Johnson and Schneider.[13] All equipment was dried in an oven at 120 °C for several hours prior to use then allowed to cool in a desiccator over Drierite. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. 48160.

General Method for Reduction of Enol Phosphate Esters. *cis*-Cyclopentadecene (11A).[14] Anhydrous titanium(III) chloride (0.105 g, 0.681 mmol) was stirred in THF (10 mL) and potassium metal (cut in small pieces, 0.117 g, 2.99 mg-atom) was added. This slurry was then stirred at reflux for 1 h until no trace of potassium metal was visible. The diethyl enol phosphate ester derived from cyclopentadecanone (**11**) (0.360 g, 1.00 mmol) was added and the mixture was stirred at reflux for 4 h. The reaction mixture was then cooled to 5 °C in an ice bath and quenched with absolute ethanol (1.0 mL), filtered through silica gel, and concentrated in vacuo. The pale yellow residual oil (0.223 g) was distilled to give 0.195 g (94%) of *cis*-cyclopentadecene (**11A**): bp 120 °C (0.6 mm) [lit.[14] bp 122–123 °C (1.2 mm)]; IR (thin film) 710 cm^{-1} (*cis*-CH=CH); NMR (CCl_4) δ 1.40 (s, 22 H, CH_2), 2.20 (m, 4 H, CH_2CH=CH), 5.30 (t, 2 H, CH=CH).

Method a. 1-Methylcyclohexene (4A).[10,15] 1-Acetoxy-2-methylcyclohexene (1.50 g, 9.74 mmol) was dissolved in THF (10 mL) and a trace of 2,2'-dipyridyl (0.007 g) was added. The mixture then cooled to −30 °C and methyllithium (12.5 mL, 1.6 M in ether, 20.0 mmol) was added dropwise at a rate maintaining the internal temperature of the reaction mixture below 0 °C. To the resulting red-orange solution was added diethyl phosphorochloridate (1.72 g, 10.0 mmol) and stirring was continued for 1 h. The reaction mixture was then poured into ice cold water (30 mL) and extracted with ether. The combined etheral extracts were then dried ($MgSO_4$) and concentrated in vacuo. The residual oil (2.461 g) was chromatographed on silica gel to give 1.956 g (81%) of the desired enol phosphate ester as an oil: IR (thin film) 1675 (C=C), 1250, 1035, and 970 cm^{-1} (trialkyl phosphate); NMR (CCl_4) δ 1.35 (t, 6 H, J = 7 Hz, CH_3CH_2O), 1.50 (s, 3 H, CH_3), 4.10 (m, 4 H, J = 7 Hz, CH_3CH_2O). This enol phosphate ester was then immediately reduced as in the above procedure for 2 h to afford 0.628 g (83%) of 1-methylcyclohexene (**4A**): bp 109–110 °C (760 mm) [lit.[15] bp 110 °C (760 mm)]; IR (thin film) 1670, 800 cm^{-1} (CH=C); NMR (CCl_4) δ 1.40 (s, 3 H, CH_3), 5.50 (m, 1 H, CH=C).

Method b. *cis*-Cyclooctene (8A).[16] To a cold (−30 °C) solution of lithium diisopropylamide (LDA) [prepared from diisopropylamine (0.505 g, 5.00 mmol) and *n*-butyllithium (4.0 mmol, 2.0 mL, 2.0 M in

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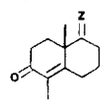
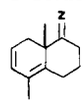
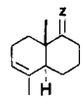
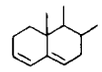
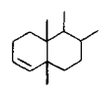
Table I

Ketone	Registry no.	Method	Alkene	Registry no.	% yield enol phosphate	Registry no.	Time (reduction),	% yield alkene	Ref
2-Methylcyclohexanone (**1**)	583-60-8	*a*	**4A**	591-49-1	81	30908-58-8	2	83	10
		b	**4B**	591-48-0	99	30908-59-5	2	90	10
4-*tert*-Butylcyclohexanone (**5**)	98-53-3	*b*	4-*tert*-Butylcyclohexene	2228-98-0	99	62845-83-4	1	100	20
Camphor (**6**)	76-22-2	*b*	2-Bornene	464-17-5	95	65898-11-5	1	81	11
Tetrahydroeucarvone (**7**)	4436-59-3	*b*	1,4,4-Trimethylcycloheptene	4755-36-6	97	65898-12-6	4	97	21
Cyclooctanone (**8**)	502-49-8	*b*	*cis*-Cyclooctene	931-87-3	97	65898-13-7	4	89	16
Cyclononanone (**9**)	3350-30-9	*b*	*cis*-Cyclononene	933-21-1	99	65898-14-8	4	92	22
Cyclodecanone (**10**)	1502-06-3	*b*	*cis*-Cyclodecene	935-31-9	97	65898-15-9	4	98	23
Cyclopentadecanone (**11**)	502-72-7	*b*	*cis*-Cyclopentadecene	34458-54-3	96	65898-16-0	4	94	14
2-Dodecanone (**12**)	6175-49-1	*b*	1-Dodecene	112-41-4	98	65898-17-1	4	95	24
2-Tridecanone (**13**)	593-08-8	*b*	1-Tridecene	2437-56-1	99	65898-18-2	4	96	24
 z = $OCH_2CH_2CH_2O$ (**14**)	33760-61-1	*b*		65898-10-4	98	65898-19-3	4	90	
		d		23931-36-4	56	23931-35-3	4	92	1
4-Cholesten-3-one (**15**)	601-57-0	*b*		4771-50-4	55	65898-20-6	1	99	12
		c		747-90-0	52	65898-21-7	1	92	12
		d		28338-69-4	48	65898-22-8	4	84	17
		e		23931-38-6	56	23931-37-5	4	84	1
Testosterone (**16**)	58-22-0	*f*		7244-00-0	48	65942-41-8	4	86	19
Isobutyrophenone (**17**)	611-70-1	*b*	Isobutylbenzene	538-93-2	100	10409-55-9	1	93	25

[a] Corresponding enol acetate, 2 to 2.2 × CH_3Li, THF, −78 to 0 °C. [b] 1.1 × LDA, THF, TMEDA (4:1), −78 to 0 °C. [c] 0.95 × LDA, THF, TMEDA (4:1), room temperature. [d] Li, NH_3, Et_2O. [e] $Li(CH_3)_2Cu$, Et_2O. [f] 2.0 × LDA, THF, −78 to 0 °C followed by 2 × $ClPO(OEt)_2$. All new compounds gave satisfactory combustion analyses.

hexane) in THF (5.0 mL)] was added cyclooctanone (0.504 g, 4.00 mmol) in TMEDA (1.25 mL) dropwise with vigorous stirring. After completion of the addition the cooling bath was removed and the mixture was allowed to warm to 0 °C. Diethyl phosphorochloridate (0.688 g, 4.00 mmol) was added and the stirring was continued for 1 h. The mixture was then poured into ice water (30 mL) and extracted with ether. The combined etheral extracts were then dried ($MgSO_4$) and concentrated in vacuo. The residual oil (1.295 g) was then chromatographed on silica gel to give 1.016 g (97%) of the enol phosphate ester: IR (thin film) 1675 (CH=C), 1260, 1035, and 975 cm^{-1} (trialkyl phosphate); NMR (CCl_4) δ 1.35 (t, 6 H, J = 7 Hz, $\mathbf{CH_3}CH_2O$), 1.50 (s, 8 H, CH_2), 2.20 (m, 4 H, $\mathbf{CH_2}C$=C), 4.10 (m, 4 H, J = 7 Hz, $CH_3\mathbf{CH_2}O$), 5.45 (m, 1 H, CH=C). This enol phosphate ester was then immediately reduced as in the above procedure for 4 h to afford 0.379 g (89%) of *cis*-cyclooctene (**8A**): bp 138–139 °C (760 mm) [lit.[16] bp 140 °C (760 mm)]; IR (thin film) 752 cm^{-1} (CH=CH); NMR (CCl_4) δ 1.50 (m, 8 H, CH_2), 2.20 (m, 4 H, $\mathbf{CH_2}$CH=CH), 5.65 (t, 2 H, CH=CH).

Method c. $\Delta^{3,5}$-Cholestadiene (15C).[12] To a solution of lithium diisopropylamide (0.048 g, 0.45 mmol) in THF (2.0 mL) at 0 °C was added slowly with stirring 4-chlosten-3-one (0.192 g, 0.499 mmol) dissolved in THF (2.0 mL) and TMEDA (1.0 mL). This mixture was then allowed to stir and equilibrate at room temperature for 3.5 h before quenching with diethyl phosphorochloridate (0.172 g, 1.00 mmol). After stirring for an additional hour at room temperature the reaction mixture was then poured into cold water (20 mL) and extracted with ether. The combined etheral extracts were then dried ($MgSO_4$) and concentrated in vacuo. The residual oil (0.296 g) was chromatographed on silica gel to give 0.135 g (52%) of the desired enol phosphate ester: IR ($CHCl_3$) 1670 (CH=C), 1250, 1025, and 960 cm^{-1} (trialkyl phosphate); NMR ($CDCl_3$) δ 1.33 (t, 6 H, J = 7 Hz, $\mathbf{CH_3}CH_2O$), 4.35 (m, 4 H, J = 7 Hz, $CH_3\mathbf{CH_2}O$), 5.40 (m, 1 H, CH=C), and 5.50 (s, 1 H, CH=C). This enol phosphate ester was then immediately reduced as in the above procedure for 1 h to afford 0.088 g (92%) of $\Delta^{3,5}$-cholestadiene (**15C**): mp 78.9–80.4 °C [lit.[12] mp 78.4–80.3 °C]; UV λ_{max} (EtOH) 228 (ϵ 18 300), 235 (ϵ 20 400), 243.5 nm (ϵ 13 200); IR ($CHCl_3$) 1655 (C=C), 840 cm^{-1} (CH=C); NMR ($CDCl_3$) δ 5.40 (m, 1 H, CH=C), 5.60 (m, 2 H, CH=C).

Method d. 5α-Cholest-3-ene (15D).[17] Anhydrous liquid ammonia (5 mL) was distilled through two KOH filled drying towers into a flask containing ether (2 mL). Lithium wire (0.007 g, 1.0 mg-atom) was added to the flask resulting in a dark blue solution. To this solution was added dropwise 4-cholesten-3-one (0.192 g, 0.500 mmol) dissolved in ether (1.0 mL). After the addition was completed, the ammonia was then allowed to evaporate and diethyl phosphorochloridate (0.172 g, 1.00 mmol) was added. The reaction mixture was allowed to stir for 1 h and then poured into cold water (20 mL) and extracted with ether. The combined etheral extracts were then dried ($MgSO_4$) and concentrated in vacuo to afford 0.207 g of a pale yellow oil. Chromatography on silica gel gave 0.125 g (48%) of the desired enol phosphate ester: IR ($CHCl_3$) 1680 (CH=CH), 1250, 1025, and 975 cm^{-1} (tri-

alkylphosphate); NMR ($CDCl_3$) δ 1.33 (t, 6 H, J = 7 Hz, $\mathbf{CH_3}CH_2O$), 4.10 (m, 4 H, J = 7 Hz, $CH_3\mathbf{CH_2}O$), 5.10 (m, 1 H, CH=C). This enol phosphate ester was then immediately reduced as in the above procedure for 4 h to afford 0.077 g (84%) of cholest-3-ene (**15D**): mp 71.5–72.5 °C [lit.[17] mp 72.0–7.25 °C]; IR ($CHCl_3$) 1660 cm^{-1} (CH=CH); NMR ($CDCl_3$) δ 5.28 (m, 1 H, CH=CH) and 5.60 (m, 1 H, CH=CH).

Method e. 5-Methyl-5β-cholest-3-ene (15E). To a solution of lithium dimethyl cuprate [prepared from purified CuI (0.190 g, 1.00 mmol) and methyllithium (1.25 mL, 2.00 mmol, 1.6 M in ether)] in ether (10 mL) at −40 °C was added 4-cholesten-3-one (0.192 g, 0.50 mmol) in ether (1.0 mL). This mixture was then allowed to warm to room temperature and diethyl phosphorochloridate (0.344 g, 2.00 mmol) was added. After stirring for 3 h at room temperature the reaction mixture was then poured into an ice-cold mixture of equal volumes of saturated aqueous NH_4Cl solution, saturated aqueous NH_4OH solution, and water. The mixture was then extracted with ether. The combined etheral extracts were then dried ($MgSO_4$) and concentrated in vacuo to give 0.185 g of a yellow oil. Chromatography on silica gel gave 0.149 g (56%) of the enol phosphate ester: IR ($CHCl_3$) 1675 (C=CH), 1250, 1025, and 975 cm^{-1} (trialkyl phosphate); NMR ($CDCl_3$) δ 1.33 (t, 6 H, J = 7 Hz, $\mathbf{CH_3}CH_2O$), 4.10 (m, 4 H, J = 7 Hz, $CH_3\mathbf{CH_2}O$), and 5.10 (m, 1 H, C=CH). This enol phosphate ester was then immediately reduced as in the above procedure for 4 h to afford 0.090 g (84%) of 5-methyl-5β-cholest-3-ene (**15E**): mp 78–80 °C [lit.[1,18] bp 150–180 °C (0.05 mm)]; IR ($CHCl_3$) 1660 cm^{-1} (CH=CH); NMR ($CDCl_3$) δ 5.27 (m, 1 H, CH=C) and 5.60 (m, 1 H, C=CH).

Method f. $\Delta^{2,4}$-Androstadiene-17β-ol (16F).[19] To a cold (−30 °C) solution of lithium diisopropylamide prepared from diisopropylamine (0.144 g, 1.42 mmol) and n-butyllithium (0.5 mL, 1.0 mmol, 1.0 M in hexane) in THF (5.0 mL) was added testosterone (0.144 g, 0.500 mmol) in THF (1.0 mL) dropwise with vigorous stirring. After the addition was completed the cooling bath was removed and the mixture was allowed to warm to 0 °C. Diethyl phosphorochloridate (0.344 g, 2.00 mmol) was added and the stirring was continued for an additional 30 min. The mixture was then poured into water (20 mL) and extracted with ether. The combined etheral extracts were then dried ($MgSO_4$) and concentrated in vacuo: The resulting oil, 0.203 g, was chromatographed on silica gel to give 0.102 g (48%) of the desired enol phosphate ester: IR (thin film) 3450 (OH), 1655 (C=C), 1250, 1025, and 960 cm^{-1} (trialkyl phosphate); NMR ($CDCl_3$) δ 1.35 (t, 6 H, J = 7 Hz, $\mathbf{CH_3}CH_2O$), 4.20 (m, 4 H, J = 7 Hz, $CH_3\mathbf{CH_2}O$), 5.10 (s, 1 H, C=CH), and 5.40 ppm (m, 1 H, CH=C). This enol phosphate ester was then immediately reduced as in the above procedure for 4 h to afford 0.056 g (86%) of $\Delta^{2,4}$-androstadien-17β-ol (**16F**): mp 170–171 °C [lit.[19] mp 171–173 °C]; UV (EtOH) λ_{max} 266 (ϵ 6030), 273 (ϵ 5720) nm; IR ($CHCl_3$) 3450 (OH), 1640, and 728 cm^{-1} (CH=CHCH=C); NMR ($CDCl_3$) δ 3.80 (m, 1 H, **CH**OH), and 5.55 (m, 3 H, CH=CHCH=C).

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Registry No.—$TiCl_3$, 7705-07-9; 1-acetoxy-2-methylcyclohexene, 1196-73-2; diethyl phosphorochloridate, 814-49-3.

References and Notes

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(4) Generation of the thermodynamic enolate anion can be accomplished either by treatment of the ketone with 0.95 equiv of lithium diisopropylamide in THF followed by an appropriate amount of time at room temperature for equilibration or treatment of the corresponding enol acetate with 2 to 2.2 equiv of methyllithium in THF: see ref 6.
(5) Generation of the kinetic enolate anion can be accomplished by treatment of the ketone with 1.1 equiv of lithium diisopropylamide in THF: see ref 6.
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Oxidation with Supported Oxidants. 2. Preparation of Sulfoxides by Alumina-Supported Sodium Metaperiodate

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Recent interest in utilizing reagents impregnated on inorganic solid supports has been proved to be successful for organic synthesis in a number of aspects, such as selectivity, reactivity, and manipulative convenience.[1-10] We have engaged in the study of selective oxidations of a variety of functional groups based on this concept. In this note we wish to report our results on a facile preparation of sulfoxides from sulfides by using sodium metaperiodate supported on acidic alumina.

The development of efficient reagents for selective oxidation of sulfides to sulfoxides has been a challenge for many years. The most commonly employed reagent for this purpose is sodium metaperiodate,[11,12] for which a careful control of reaction temperature and the quantity of oxidant is in general of necessity. The use of alumina-supported thallium(III) nitrate may circumvent such inconvenience but the reagent is toxic and is reactive toward many other functional groups, and the reaction is sensitive to steric hindrance.[10] None of these disadvantages exists, however, in the newly developed procedure using supported sodium metaperiodate.

The supported oxidant can readily be prepared by soaking the inorganic support with a hot 1.67 M solution of sodium metaperiodate and then evaporating to dryness. The oxidation is carried out simply by vigorous stirring of this solid oxidant with the solution of a sulfide at room temperature. The products were isolated by removal of the solid reagents by filtration and then evaporation of the solvent. Systematic study on some ten inorganic supports, including alumina, celite, charcoal, florisil, montmorillonite clays, and silica gel, indicated that the acidic alumina and the acidic clays, Girdler Catalyst K-10 and KO, are by far the most effective ones. The readily available chromatographic adsorbent, Merck acidic Aluminium oxide 90 for column chromatography, was then employed for the present purpose. Solvent also plays an im-

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