Notes

Reactions of 1,2-Oxaphospholenes. 9.[1] Attempted Deprotonation at C5

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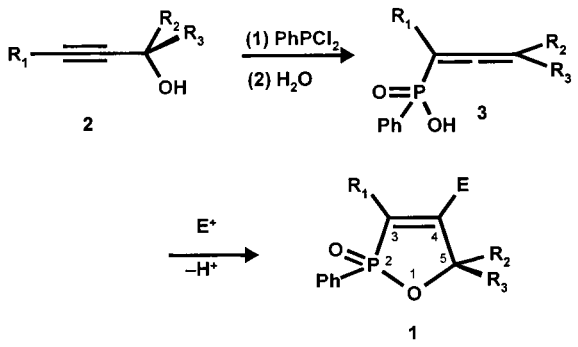
We[1] previously reported that C5 of 1,2-oxaphosphol-3-ene 2-oxides **1** (prepared from propargyl alcohols **2** via allenic phosphoryl derivatives **3**,[3] Scheme 1) can undergo facile allylic nucleophilic and free radical substitution reactions that leave the ring system intact.[1b,4] Judging from ^{1}H and ^{13}C NMR chemical shifts,[4] a C5 allylic hydrogen of **1** should exhibit increased acidity owing to the proximity of the phosphoryl group. In the present study, we wished to determine if the C5 position of such oxaphospholenes can be deprotonated to generate carbanion **4** (Scheme 2).[5] In selecting an appropriate base to deprotonate **1**, it is necessary to avoid strongly nucleophilic oxy bases because of their preferential attack at phosphorus.[6,7] We therefore selected sodium hexamethyldisilazide (NaHMDS) for our initial experiments.

The five substrates used in this study were prepared by previously published methods (Scheme 1). It should be noted that derivatives of **1** (as well as **3)** with $R_2 \neq R_3$ exist as two comparably stable chiral diastereomers. The diastereomers of **1a** and **1b** have been assigned by a combination of ^{1}H NMR spectroscopy and X-ray crystallography.[1b] Interestingly, although **1c** was first described in 1971,[8] no mention of the stereochemistry of the product(s) has heretofore been made. In our hands, **1c** is formed as a 60/40 mixture of two diastereomers; the major isomer has the *Z* configuration (with phenyl groups trans) by X-ray analysis (see Supporting Information).

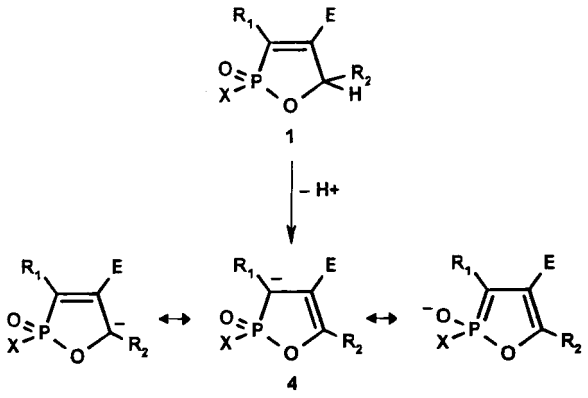
Addition of 2 equiv of NaHMDS to *Z*/*E*-**1a** at ambient temperature resulted in a transient burgundy color. The mixture was quenched with a slight excess of deuterated trifluoroacetic acid (TFA-*d*), under conditions to which all substrates and products are stable. The product mixture consisted quantitatively of allenic precursor **3a** (deuterated at oxygen). It seems likely that the steric bulk of the C5 *tert*-butyl group prevented proton abstraction from C5, directing the base instead to the vinyl hydrogen at C4, which occupies a perfect geometry for ring opening via an E2 process.

Scheme 1



Cmpd	R_1	R_2	R_3	E	Ref.
1a	t-Bu	t-Bu	H	H	1b
1b	t-Bu	t-Bu	H	Br	1b
1c	CH_3	Ph	H	H	8
1d	H	CH_3	CH_3	Br	6
1e	H	CH_3	CH_3	H	6

Scheme 2



To block the C4 position, we next examined the *Z* stereoisomer of 4-bromo derivative **1b**.[1b] Addition of up to 7 equiv of NaHMDS (at ambient temperature) gave a precipitate that, when quenched with TFA-*d*, afforded a quantitative yield of the starting material, without detectable epimerization to the *E* isomer nor incorporation of deuterium. We were not able to ascertain the composition of the precipitate, but lack of epimerization and deuterium exchange is strong evidence against C5 deprotonation.

With this additional evidence that the C5 *t*-Bu group blocks access to the C5 hydrogen, we next examined **1c** in which the C5 *t*-Bu group is replaced by an electronically facilitating and less sterically demanding phenyl group and the C3 *t*-Bu by a methyl. When stereoisomeri-

(1) Paper 8 in the series: Macomber, R. S.; Rardon, D. E.; Ho, D. M. *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *75*, 95. (b) A leading reference to earlier papers: Macomber, R. S.; Rardon, D. E.; Ho, D. M. *J. Org. Chem.* **1992**, *57*, 3874.

(2) Taken in part from the Ph.D. Dissertation of M.G., University of Cincinnati, 1999.

(3) Macomber, R. S. *J. Org. Chem.* **1971**, *36*, 2713.

(4) Rardon, D.; Macomber, R. S. *J. Org. Chem.* **1990**, *55*, 1493.

(5) Calculation on model structures predict that the 3-ene is more stable than the 4-ene by about 0.5 kcal/mol. When deprotonated, the 3-ene and 4-ene generate the same anion, which has the majority of charge on C3.

(6) Macomber, R. S.; Constantinides, I.; Garrett, G. *J. Org. Chem.* **1985**, *50*, 4711.

(7) Macomber, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 4386 and references therein.

(8) Campbell, I. G. M.; Raza, S. M. *J. Chem. Soc. C* **1971**, 1836.

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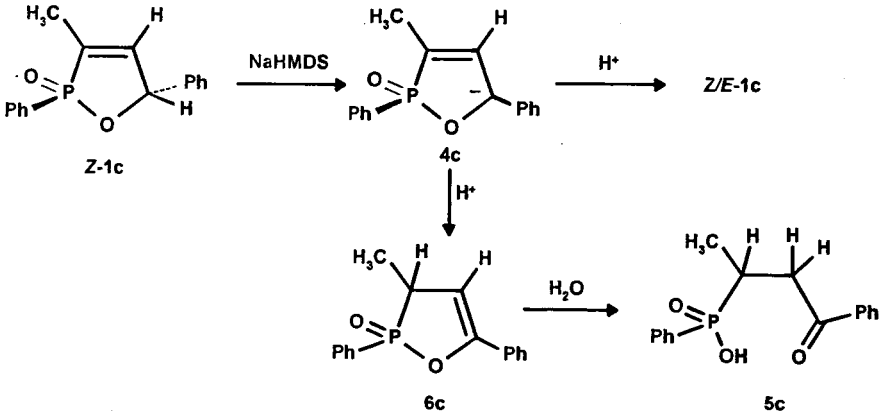
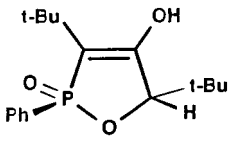
Scheme 3



cally pure *Z*-**1c** was treated with 10 equiv of NaHMDS at ambient temperature, a transient burgundy color appeared and faded immediately. Following a H_2O quench, an epimerized 75:25 *Z*/*E* mixture of **1c** was recovered in 30% yield. In addition, ring-opened keto-phospinate **5c**[9] was isolated in 70% yield (Scheme 3). Compound **5c** can be seen as arising from facile[10] hydrolysis of 1,2-oxaphosphole-4-ene **6c**, a slightly less stable isomer of the 3-ene.[5,11] Both the epimerization of **1c** and its isomerization to **5c** can be accommodated by a mechanism involving intermediate **4c**.

At this point, our attention shifted to potassium hydride (KH), a more powerful but less hindered base, which is able to deprotonate both hindered substrates[12] and the γ-position of α,β-unsaturated ketones.[13] When stereoisomerically pure *Z*-**1a** was allowed to react with 3.5 equiv of KH at ambient temperature, followed by a 2-propanol quench, allenic precursor **3a** was formed in 22% yield. Reisolated substrate **1a** (29% yield) proved to be partially epimerized (5:1 *Z*:*E*). The major product was ring-opened phosphinate **5a**, an analogue of the product formed from **1c**. Thus, KH seems able to promote deprotonation at C5 leading to formation of **6a**, rather than simply deprotonating at C4 as did NaHMDS. It is interesting to note that treatment of **3a** with KH, followed by quench with TFA-*d*, gives starting material with the allenic proton (as well as the hydroxyl proton) deuterated.

Though C4-brominated derivative *Z*-**1b** was inert to NaHMDS, it did react with KH to give a product mixture consisting of allene **3a** (20%) and unexpected enol **7** (80%). No debrominated **1a** was detected in the product



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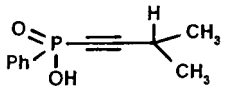
mixture. The formation of **3a** might suggest the intermediacy of **1a**, formed by an addition (of hydride)−elimination (of bromide) reaction at C4;[14] however, the formation of **7** rather than **5a** suggests that **1a** must *not* be involved as an intermediate in the formation of **7.** Alternatively, the formation of **3a** could be attributed to ring-opening elimination of bromide from **1b** by hydride.

Treatment of *Z*-**1c** with 4 equiv of KH at room temperature led to a dark red solution that was stable up to a week. TFA workup led to a mixture of epimerized **1c** (9%) and **5c** (53%), similar to the results with NaHMDS (Scheme 3). Attempts to trap presumed intermediate **4c** with other electrophiles (e.g., methyl iodide, TMSCl) were unsuccessful.

In an attempt to determine the mechanism of formation of **7** from **1b**, we next studied the reaction of **1d**, which lacks an extractable hydrogen at C4 and C5. While **1d** was inert toward NaHMDS, it reacted readily with KH (4 equiv) to yield allenic precursor **3d** and starting material **1d** in a 2:5 ratio. When **3d** itself was treated with 5 equiv of KH, propargyl phosphinate **8** was formed in 50% yield and 20% of the starting material **3d** could be recovered.



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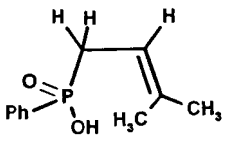
Compound **1e**, the debrominated analogue of **1d**, also was inert toward NaHMDS. However, when **1e** was allowed to react with 3 equiv of KH, the only product was phosphinic acid **9** (representing net reduction) plus



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unreacted starting material. Significantly, **9** was previously identified as the major product of the electron-transfer reactions of **1e** with sodium naphthalenide or lithium dimethylcuprate.[6] These results strongly suggests that, in the absence of an exchangeable hydrogen, KH also is reacting by an electron-transfer pathway.

(9) The structure of **5c** was established by comparison to a simulated spectrum generated by RACCOON Version 2.0 by P. F. Schatz, Department of Chemistry, University of Wisconsin-Madison, Madison, WI 53706 (see Supporting Information for calculated values).

(10) Bergesen, K. *Acta Chem. Scand.* **1965**, *19*, 1784; **1969**, *23*, 2556.

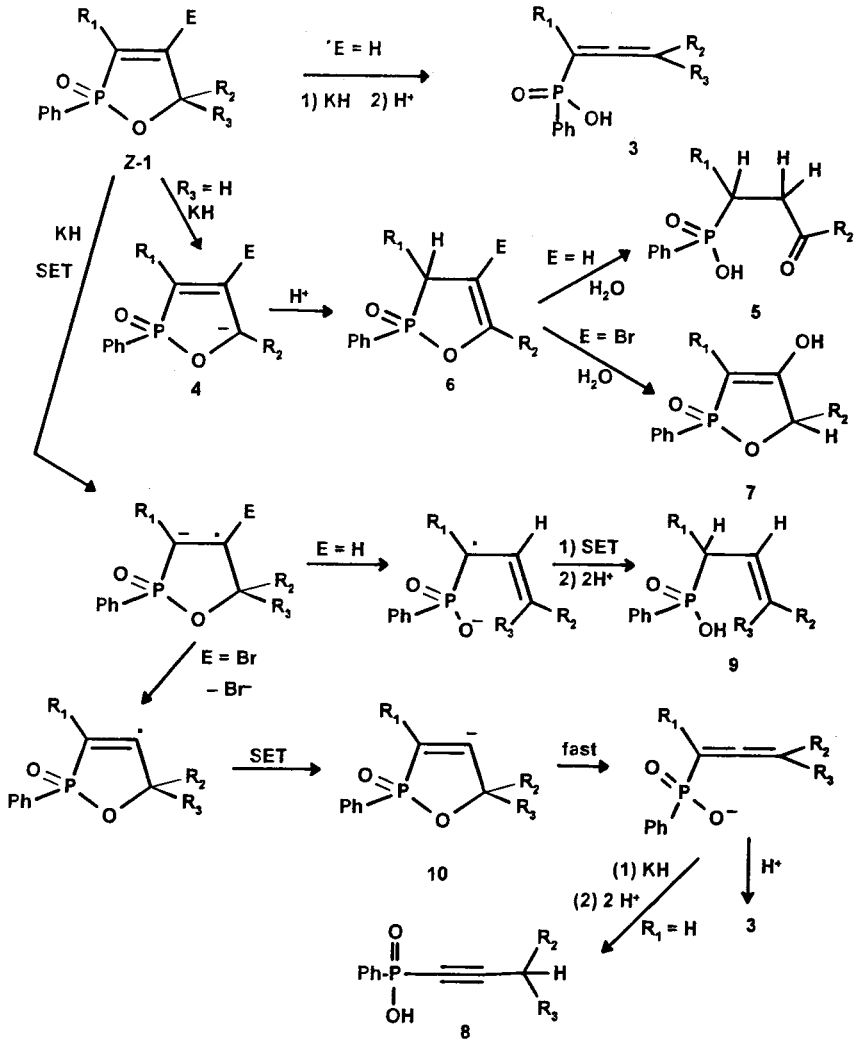
(11) Known compound **6d**[8] undergoes ready acid-catalyzed isomerization to **1d**.[2,8]

(12) Brown, C. A. *Synthesis* **1974**, 427.

(13) Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913.

(14) A similar addition−elimination has been noted in the reaction of the C4,C5-dibrominated derivative of **1b** with KH.[1b]

Scheme 4



It is our judgment that all our results can be rationalized most economically by a finely balanced competition between proton transfer and electron-transfer processes (Scheme 4). The ring opening of **1** (E = H) to allene **3** is an example of base-promoted E2 process, the reverse of the electrophilic cyclization of **3** to **1**. The formation of ring-opened ketone **5**, accompanied by epimerization of the starting material, we interpret as resulting from removal of a C5 proton by base, formation of intermediate carbanion **4**, protonation to give **6**, followed by subsequent hydrolysis to **5**. Since this pathway is followed when there is also a C4 hydrogen available (**1a** and **1c**), the C5 hydrogen must be at least comparably reactive (in the case of **1a**) or more reactive (in the case of **1c**). In the case of **1b** (E = Br), the hydrolysis of **6b** leads to enol **7** rather than ring opened ketone **5b**.

The ring opening of **1** (E = H) to allene **3**, as discussed above, can be regarded as a base-promoted E2 process. Because reaction of KH with C4-brominated oxaphospholenes **1b** and **1d** gave neither the corresponding debrominated oxaphospholenes (**1a** and **1e**, respectively) nor the products from **1a** or **1e**, we do not consider the addition (of hydride at C4)−elimination (of bromide from C4) mechanism to be a viable route for the reactions of **1b** and **1d**. Therefore, the corresponding reaction of **1** (E = Br) to allene **3** most likely proceeds by an electron-transfer process (i.e., halogen−metal exchange). Proposed carbanionic intermediate **10** must not survive long enough to protonate and regenerate **1** (E = H).

The rearrangement of **3** to **8** also is likely to be a simple base-promoted prototropy. However, the formation of **9** from allene **3** or from **1** (E = Br) must involve an electron-transfer process, as previously was shown using sodium naphthalenide.[6]

Experimental Section

Compounds **1a**−**e** were prepared by methods already reported in the literature. The reference numbers are given in Scheme 1. Spectral data for compounds **1** and **3** may be found in these references. All information about the X-ray structure of *Z*-**1c** may be found in the Supporting Information. Also in the Supporting Information are full experimental details for all reactions. Below are two typical procedures.

Reaction of *Z*-1c with NaHMDS. A solution of 19.9 mg (0.07 mmol) of *Z*-**1c** in 2.5 mL of THF was placed under argon and allowed to mix as 774 μL (0.774 mmol) of a 1.0 M solution of NaHMDS in THF was added dropwise over 2 min. Each drop produced a transient burgundy color, which faded immediately but persisted longer and longer with each drop, eventually leaving a bronze colored solution. Addition of 2.5 mL of D_2O caused the solution to fade to a pale yellow, from which the THF was removed in vacuo. This solution was extracted three times with CH_2Cl_2 and dried over $MgSO_4$, and the solvent was removed in vacuo to give 4.3 mg (0.02 mmol) of epimerized 75:25 *E*/*Z*-**1c**, identified by ^{1}H NMR spectroscopy. The remaining aqueous layer was hydrolyzed with TFA-d_1, diminishing the milky color of the solution. The aqueous solution was extracted two times

with CH_2Cl_2 and dried over $MgSO_4$, and the solvent was removed in vacuo to give 14.4 mg (0.05 mmol, 68.5% yield) of **5c**.

Reaction of *Z*-1c with Potassium Hydride. Glassware for this experiment was dried at 100 °C for 72 h. A suspension of 35% potassium hydride in mineral oil was dispersed initially with a screwdriver and then agitated for 4 h. Into a flask was added 1489.7 mg (13.0 mmol) of potassium hydride dispersion, which was washed three times with hexane under argon, and the remaining solvent as evaporated in an argon stream. The potassium hydride was suspended in 10 mL of THF into which a solution of 1000.1 mg (3.70 mmol) *Z*-**1c** in 15 mL of THF was added dropwise over 2 min, producing an dark red color after 1 h. The suspension was allowed to react for 48 h, producing a clear, deep red solution after the unreacted potassium hydride was allowed to settle. The supernatant was decanted from the reaction flask and acidified with TFA to pH 6 (pH paper), causing the solution to turn a clear, yellow. Analysis by TLC (50/50 CH_2Cl_2/ethyl acetate) indicated only very polar products. ^{1}H NMR spectroscopy of the product mixture showed epimerized *E*/*Z*-**1c** as the minor product and compound **5c** as the major product. The solvent was removed in vacuo to give an oil, which was dissolved in CH_2Cl_2, leaving potassium trifluoroacetate behind as a precipitate. The solution was extracted with aqueous sodium bicarbonate, and the bicarbonate layer was acidified with concentrated HCl to pH 3 (pH paper), producing a precipitate that was isolated by filtration and dissolved in acetone to remove inorganic salts. The solvent was removed in vacuo to give 636.4 mg of a tan solid with a melting point of 90−95 °C. The solvent was removed in vacuo from the CH_2Cl_2 layer from the extractions to yield 87.4 mg (0.32 mmol) *E*/*Z*-**1c**, which represents a recovery of 8.7% of epimerized starting material. The solid recovered from the bicarbonate layer was further dried at 0.025 mm pressure for 5 h to give 568.4 mg (1.97 mmol) of a pale yellow solid identified as **5c**, in a yield of 53.3%.

Acknowledgment. The authors would like to thank the reviewers for many very helpful suggestions.

Supporting Information Available: ^{1}H NMR spectra for new compounds **5a**, **5c**, **7**, and **9**, full experimental details for each reaction, results of the calculations mentioned in ref 5, and the chemical shifts for ref 11; ORTEP diagram and tables of crystal data, bond lengths, bond angles, atomic coordinates, and anisotropic thermal parameters for compond Z-**1c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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