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A NEW SYNTHESIS OF 2-PHOSPHOLENE-1-OXIDES. REACTION OF sec-BENZYLPHOSPHINE OXIDES AND RELATED COMPOUNDS WITH α,β-UNSATURATED KETONES

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Abstract—The addition of sodium of sec-benzylphosphine oxide **1a** or **1b** as well as sodium O-ethyl benzylphosphonite **1c** to α,β-unsaturated ketones, followed by intramolecular aldol condensation has been described. The stereochemistry of the reaction and the structure of 2-phospholene-1-oxides **6a-h** thus formed is discussed.

INTRODUCTION

Although chemistry and biological properties of heterosteroids have been studied extensively, synthesis of phosphasteroids has received scant notice.[1-3]

In an effort to find a convenient route to 17-phosphasteroid system we have been interested in new synthetic approaches to five-membered heterocycles containing phosphorus. Recently we have demonstrated that phospholan-3-one-1-oxides can be readily obtained by the reaction of sec-benzylphosphine oxides with α,β-unsaturated esters.[2]

It is the purpose of the present paper to describe a simple method for preparation of 2-phospholene-1-oxides by the reaction of sec-benzylphosphine oxides and related compounds with α,β-unsaturated ketones.

Sodium salts of sec-benzylphosphine oxides and their analoques **1** are well known to react with α,β-unsaturated ketones to yield 1,4-adducts **3**.[4] However, in aprotic solvents these adducts could be expected to become transformed in carbanions **4**, which should further undergo intramolecular aldol condensation to afford 2-phenyl-2-phospholene-1-oxides **6** (Scheme 1). In order to receive representative data concerning synthetic utility as well as the steric course of cyclization the starting materials used in the reactions examined were diversified both in chemical properties and structure.

RESULTS

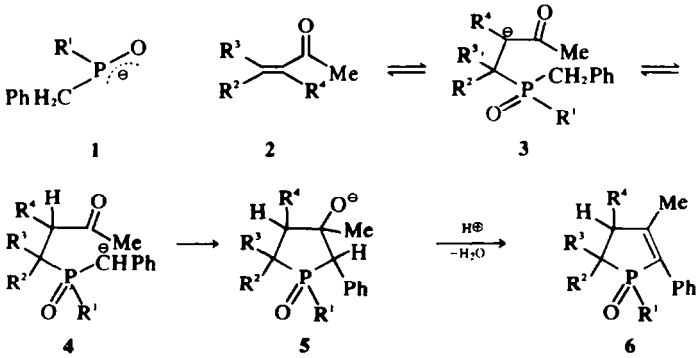
Heating of equimolar amounts of the reagents in THF, followed by neutralizing the reaction mixture with hydrochloric acid, leads to exclusive formation of the cyclic products **6a-6h** listed in Table 1.

The structure of the products is strongly supported by spectral evidence. IR spectra of 2-phospholene-1-oxides **6a-6h** exhibit absorptions attributable to the double bond and the phosphoryl group. Details are summarized in Table 2

^{1}H and ^{31}P NMR spectra provide substantial information on the geometry of a phospholene ring and establish the composition of those 2-phospholene-1-oxides which are mixtures of the corresponding stereoisomers. The most characteristic chemical shifts and coupling constants are listed in Table 1.

One of the typical features of proton resonance in 1-phenyl-2-phospholene-1-oxides is the shielding effect of phenyl on a vicinal substituent located on the same side of a ring.[5] This effect is well seen in the spectrum of **6b**. The signal due to the Me group *cis* to P–Ph is shifted upfield as compared with that due to the *trans* Me. With benzyl substituted for phenyl, as in the case of **6a**, the Me group has the same chemical shift, whether *cis* or *trans* to P–CH_2Ph.

A singlet in the ^{31}P spectrum of **6e** obtained upon

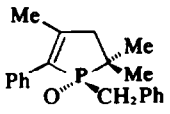
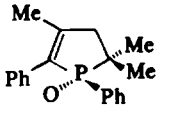
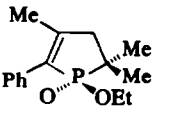
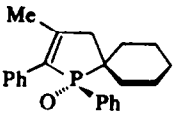
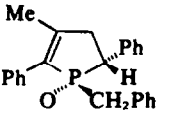
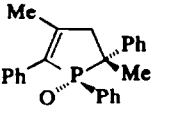
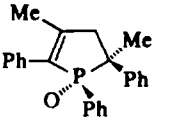
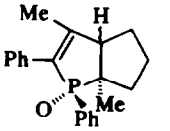
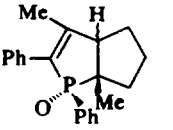
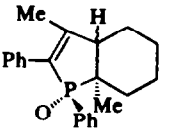
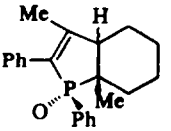


1a: $R^1 = PhCH_2$
1b: $R^1 = Ph$
1c: $R^1 = OEt$

2a: $R^2 = R^3 = Me$
2b: $R^2R^3 = -(CH_2)_5-$
2c: $R^2 = H$; $R^3 = Ph$
2d: $R^2 = Me$; $R^3 = Ph$
2e: $R^2 = Me$; $R^3R^4 = -(CH_2)_3-$
2f: $R^2 = Me$; $R^3R^4 = -(CH_2)_4-$

Scheme 1.

Table 1. Yields* and physical data for the 2-phospholene-1-oxides **6a–h**

No	Product		Starting materials	Yield [%]	M.p. or b.p./mmHg [°C]	Elemental analysis					
						Calculated			Found		
						%C	%H	%P	%C	%H	%P
6a			**1a, 2a**	48·5	117	77·3	7·4	9·9	77·1	7·5	10·1
6b			**1b, 2a**	58·0	140	77·0	7·1	10·2	77·0	7·0	10·2
6c			**1c, 2a**	41·0	112/0·4	68·5	7·9	11·8	68·1	7·5	11·9
6d			**1b, 2b**	67·5	151–3	78·5	7·5	9·2	78·5	7·4	9·2
6e		*trans*	**1a, 2c**	10·0	131	80·5	6·5	8·7	80·2	6·3	8·7
6f		*trans*	**1b, 2d**	37·2	191–2	80·4	6·5	8·6	80·4	6·7	8·6
		*cis*		24·8	162–3	80·4	6·5	8·6	80·6	6·6	8·5
6g		*trans*	**1b, 2e**	21	130–43	78·2	7·2	9·6	78·7	7·3	9·5
		*cis*		7							
6h		*trans*	**1b, 2f**	15	220–35	78·5	7·5	9·2	77·8	7·4	9·2
		*cis*		15							

*Percentage of stereoisomers were determined by integration of ^{1}H NMR and ^{31}P NMR spectra.

Table 2. Major IR absorption maxima of the 2-phospholene-1-oxides **6a-h**

Products	cm^{-1} C=C	cm^{-1} P=O
6a	1607	1180
6b	1612	1175
6c	1612	1205
6d	1640	1180
6e	1605	1195
6f-*trans*	1638	1195
6f-*cis*	1630	1175
6g	1630	1160; 1182
6h	1600	1187

Me group in the other oxide corresponds to the configuration *cis* (5-Me *trans* to P-Ph). The chemical shifts of the signals due to ^{31}P in the *cis* and *trans* stereoisomers are not identical. Integration of the ^{1}H and ^{31}P NMR spectra of **6f** shows the *trans*: *cis* ratio of the oxides to be 6:4.

Both **6g** and **6h** are mixtures of two out of the four possible stereoisomers. Although the mixtures were not separated into individual components the spectra of **6g** and **6h** exhibit signals due to two Me groups bonded with the tetrahedral carbons. On the basis of the criteria already mentioned, the upfield and the downfield signals of the Me groups can be attributed to the stereoisomers with the respective configurations *cis* (5-Me *cis* to P-Ph)

Table 3. ^{1}H NMR and ^{31}P NMR spectra of the 2-phospholene-1-oxides **6a-h**

	^{1}H NMR[a]						^{31}P NMR[b,c]
	3-CH_3[d]		5-CH_3[d]		CH_2Ph[d]		δ[ppm]
	δ[ppm]	J_{PCCCH}[Hz]	δ[ppm]	J_{PCCH}[Hz]	δ[ppm]	J_{PCH}[Hz]	
6a	1·88	2·0	1·31	13·8	3·18	13·8	−67·25
6b	2·02	1·8	1·26 0·95	13·2 15·8	—	—	−64·5
6c	1·87	1·9	1·34 1·29	14·8 14·0	—	—	−68·5
6d	2·05	2·4	—	—	—	—	−64·2
6e *trans*	1·92	2·0	—	—	3·24	16·5	−64·7
6f *trans*	2·16	2·1	1·27	16·0	—	—	−61·1
6f *cis*	2·16	2·1	1·85	13·5	—	—	−59·9
6g[e] *trans*	1·98	2·2	1·49	13·2	—	—	−64·0
6g[e] *cis*	1·98	2·2	0·9	15·8	—	—	−66·4
6h[e] *trans*	1·96	2·2	1·35	14·3	—	—	−59·7
6h[e] *cis*	1·96	2·2	0·9	16·0	—	—	−62·0

[a] Spectra taken in $CDCl_3$ solution with internal TMS.
[b] Spectra taken in $CDCl_3$ solution with external H_3PO_4.
[c] Spectra taken with ^{1}H decoupling; singlets.
[d] Deoublets due to ^{31}P coupling.
[e] Spectra obtained on a mixture of *cis* and *trans* oxides.

decoupling of protons indicates that **6e** is one of the two possible stereoisomers. The chemical shift of benzyl protons in **6e** corresponds to that in **6a**, in spite of **6e** having a phenyl substituent at the tetrahedral carbon C-5. It appears that, for steric reasons, interactions of phenyl with benzyl protons in **6e** should be closely related to those between phenyl and Me groups in **6b**. With no shielding effect due to phenyl on the chemical shift of benzyl protons in **6e**, one may suppose that in this compound phenyl is in the *trans*-position to the P-CH_2Ph bond.

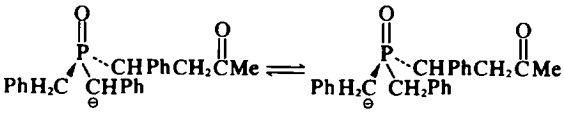
The product **6f** constitutes a mixture of the two possible stereoisomers. To receive accurate spectral data, each isomer was isolated by crystallization and analyzed individually. ^{1}H NMR spectra show that the chemical shift of the signal due to the Me group at C-5 is different for each isomer. Consideration of the shielding effect due to phenyl, leads to the conclusion that the oxide with an upfield signal of the Me group has the configuration *trans* (5-Me *cis* to P-Ph). The position of the signal due to the and *trans* (5-Me *trans* to P-Ph). Consequently each of the products **6g** and **6h** is believed to contain one oxide with the configuration *trans* and another with the configuration *cis*. This conclusion is borne out by the ^{31}P NMR spectral data. Upon decoupling of protons, spectra of **6g** and **6h** consist of two singlets. Integration of these singlets compared with integration of the Me groups in the ^{1}H NMR shows that the contributions of the *trans* and *cis* oxides are in **6g** identical, whereas in **6h** the *trans*-oxide: *cis*-oxide ratio is 7:3.

DISCUSSION

It is well known that the molecule of an α,β-unsaturated ketone may possess a plane of symmetry corresponding with the double-bond plane, and that nucleophilic addition to the C_β carbon of the ketone is likely to occur on either side of this plane. When the nucleophilic reagent contains a chiral atom and α,β-unsaturated ketone possesses a prochiral carbon in β position, two stereoisomers may be often expected to be

formed in nearly equimolecular proportion. If epimerization can occur in the reaction medium, the proportion is usually different. As already indicated, the reactions of the sodium salt of benzylphenyl-phosphine oxide **1b** with ketones **2d** and **2e** lead to mixtures composed of two stereoisomeric 1 - phenyl - 2 - phospholene - 1 - oxides, **6f** and **6g**. These reactions are selective and in either case one stereoisomer is the major product. Taking into account that epimerization of the oxides **6f** and **6g** involving exchange of substituents at the phosphorus or at the carbon C-5 is unlikely and considering that the cyclic oxides **6a-h** are the only isolable products of the corresponding reactions, we conclude that addition of the sodium derivative of sec-benzylphenylphosphine oxide **1b** to α,β-unsaturated ketones in THF is a reversible process $1+2\rightleftharpoons 3$. Formation of the chiral centre at C-5 in 1 - phenyl - 2 - phospholene - 1 - oxides appears to be, at least partially, controlled by thermodynamic factors.

The thermodynamic control of cyclization is particularly well pronounced in **6e**; however, in this case, the exclusive formation of the more stable stereoisomer can be associated not only with the reversible nature of the addition $1+2\rightleftharpoons 3$. It may be assumed that **6e** epimerizes by proton displacement at the carbon C-5 and also that each of the corresponding stereoisomeric carbanions **4** is capable of changing configuration via proton transfer (Scheme 2).



SCHEME 2.

We believe that thermodynamic factors play an important role in determining configuration at the carbon C-4 in **6g** and **6h**. Although the experimental data are still too scarce to postulate reversibility of a ring closure **4** → **5**, an equilibrium between the diastereoisomeric anions **3** and **4** seems to be very likely.

Studies on the relative configurations of all the chiral centres in **6g** and **6h** are in progress.

The Thorpe–Ingold effect[6] is of essential consequence for the course of cyclization. Only the phospholene oxides containing two substituents at the tetrahedral carbon C-5 are obtained in satisfactory yields. Other oxides, e.g. **6e**, are formed in low yields. It is also significant that attempts to prepare a cyclic oxide from the sodium salt of dibenzylphosphine oxide **1a** and methylpropenyl ketone failed.

EXPERIMENTAL

M.ps were taken on a Büchi SMP-20 apparatus and are uncorrected. IR spectra were recorded on a Jena–Zeiss UR-10 unit as KBr pellets. ^{1}H NMR and ^{31}P NMR spectra were run on a Jeol C–60HL spectrometer.

Starting materials. Dibenzylphosphine oxide,[4] benzylphenylphosphine oxide,[7] O-ethylbenzylphosphonite,[8] methylbenzylideneacetone,[9] cyclohexylideneacetone,[9] 1 - acetyl - 2 - methylcyclopentene[10] and 1 - acetyl - 2 - methylcyclohexene[11] were prepared by published routes. Mesityl oxide and benzylideneacetone were commercially available. THF was dried over NaH and distilled immediately before use.

Preparation of 2-phospholene-1-oxides **6**

General procedure. The appropriate sec-benzylphosphine oxide or O-ethyl benzylphosphonite (0·03 mole) in THF (50 ml) was added dropwise to a stirred suspension of NaH (0·72 g, 0·03 mole) in THF (30 ml) at room temp. The mixture was refluxed until the evolution of H_2 ceased. The corresponding α,β-unsaturated ketone (0·03 mole) in THF (50 ml) was then added and the resultant soln was refluxed for 5 hr. After evaporation of solvent the residue was neutralized with dil. HCl and extracted with chloroform (3 × 50 ml). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The crude products were recrystallized from benzene-cyclohexane or distilled *in vacuo* to afford analytically pure oxides **6**. The stereoisomeric compositions of **6e**, **6f**, **6g** and **6h** were evaluated from integration of the NMR spectra taken on unpurified materials. **6f-*trans*** and **6f-*cis*** were separated by fractional crystallization from cyclohexane.

Yields, analytical, IR and NMR data are summarized in Tables 1–3.

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