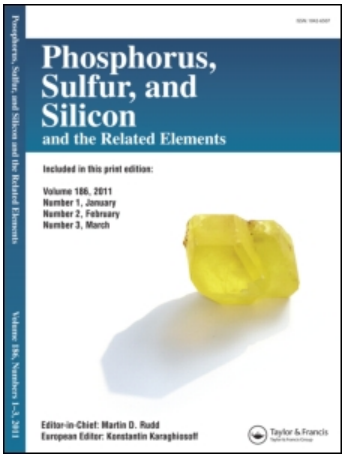

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BASE-CATALYZED CONDENSATION OF BIS(DIETHYLPHOSPHONOMETHYL)-PHOSPHINIC AMIDES WITH ALDEHYDES[1]

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BASE-CATALYZED CONDENSATION OF BIS(DIETHYLPHOSPHONOMETHYL)-PHOSPHINIC AMIDES WITH ALDEHYDES[1]

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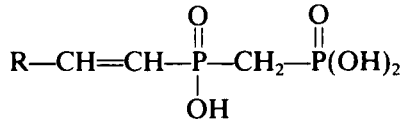
The reaction of the mono anion of bis(diethylphosphonomethyl)phosphinic amides (**3**) with aldehydes gives varying amounts of diethyl alkyl- or arylethenylphosphonates (**10**) and diethylphosphonomethyl-alkyl- or arylethenylphosphinic amides (**7**). When R in **3** is *N,N*-di-*n*-propylamino or *N*-cyclohexyl-*N*-methylamino, the predominate product is **7** and this condensation is a satisfactory synthesis of vinylphosphinic amides which are potential antimetabolites of organic pyrophosphates.

INTRODUCTION

As briefly discussed previously[1,2] the dihydrogen phosphonomethyl substituted ethenylphosphinic acids (**1**) should be antimetabolites of biologically active pyrophosphates (**2**) which are important in some biological processes such as the biosynthesis of cholesterol, dihydrofolic acid and thiamine.



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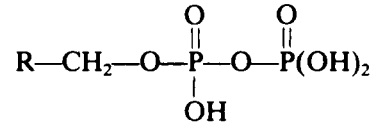

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In previous work[1,2] on methods of synthesis of **1** we have used carbonyl olefination of aldehydes with PO ylides from bis(diethylphosphonomethyl)-phosphinates. These reactions give low yields of **1** and are not satisfactory for the preparation of **1**.

Corey and Kwiatkowski[3] reported that the base-catalyzed condensation of phosphonic acid bisamides with carbonyl compounds afforded olefins only after converting the initial adducts to β-hydroxyphosphonic acid bisamides which undergo thermal elimination. Since the initial adducts did not undergo elimination under the usual basic conditions of the PO ylide olefination, we speculated that the phosphinic amides (**3**, R = alkylamino, arylamino or *N,N*-dialkylamino) would eliminate at the phosphonate phosphorus (Path B, Scheme 1) instead of at the phosphinic phosphorus (Path A, Scheme 1). However, we knew from previous work[2] that **3** (A, = morpholino) gave primarily elimination by Path A. Thus we knew it would be necessary to force **3** to follow Path B using steric

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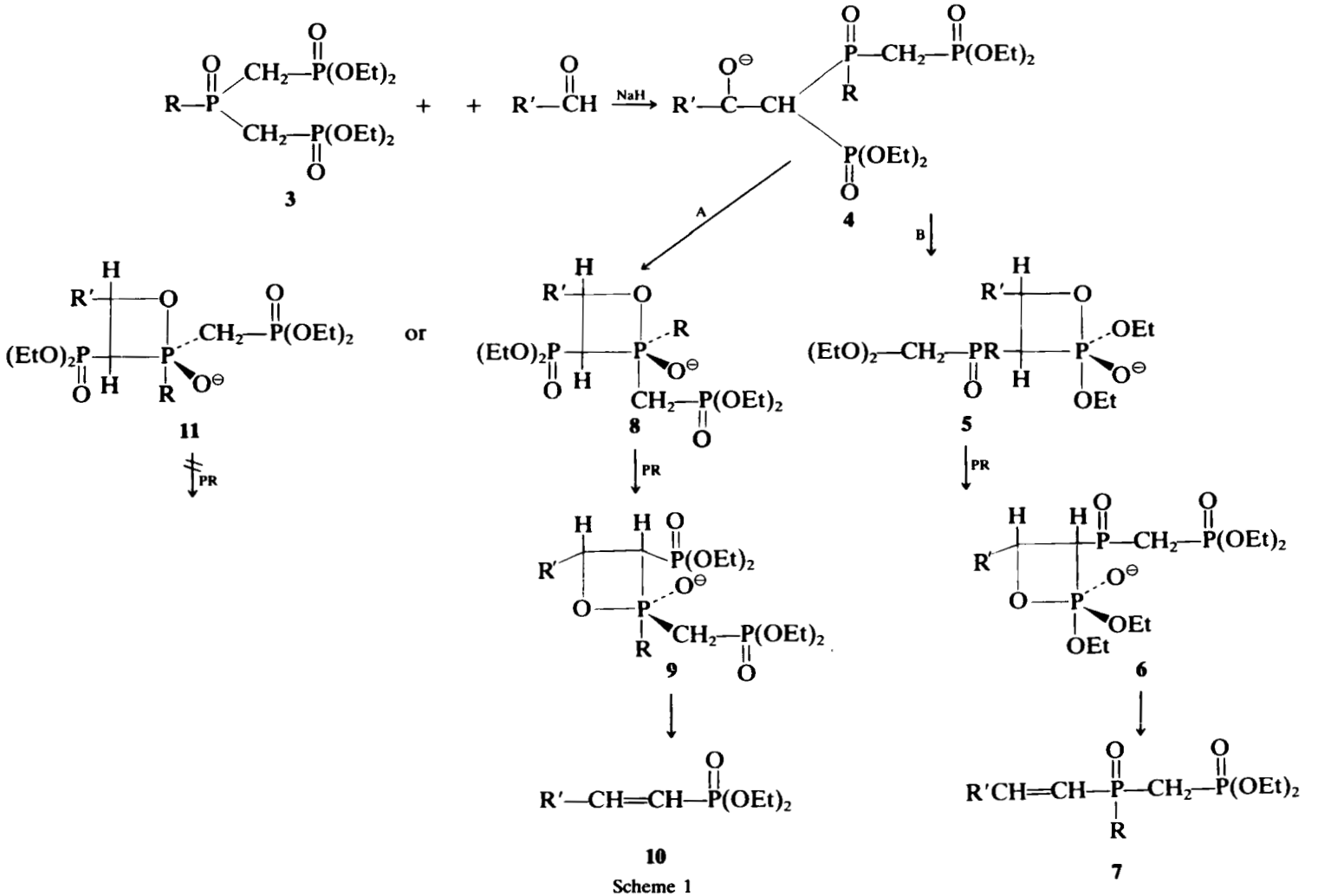


Scheme 1

control by making R a bulky group or using electronic control by making R strongly electron donating or by a combination of these effects. This report gives the results of our study of the base-catalyzed condensation of the phosphinic acid amides (**3**) with isobutyraldehyde and 4-tolualdehyde.

RESULTS AND DISCUSSION

The phosphinic acid amides (**3**) (Table I) were prepared by the Arbuzov reaction of bis(chloromethyl)phosphinic amides (**12**) with triethyl phosphite (Scheme 2).

The bis(chloromethyl)phosphinic amides (**12**) were prepared from bis(chloromethyl)phosphinic chloride[4] and two equivalents of the appropriate amine. The properties of these compounds are given in Table II.

Benzene solutions of the phosphinic amides (**3**) were added to a suspension of one equivalent of sodium hydride in benzene to generate the soluble mono anions. Complete evolution of the hydrogen required about four hours stirring at room temperature. Then a benzene solution of one equivalent of isobutyraldehyde or 4-tolualdehyde was added. Generally as the aldehyde was added a gummy precipitate separated on the walls of the flask. The results of these base-catalyzed condensation elimination reactions (Scheme 1) are shown in Table III.

The data in Table III suggest that the phosphinic amides behave differently than the phosphonic acid bisamides.[3] Unlike the phosphonic acid bisamides, the phosphinic amides give the usual carbonyl olefination without protonation of the initial adduct followed by thermal elemination. However, it is possible that the initial adduct **4** is protonated by transfer of a proton from the second methylene group as shown in Scheme 3.

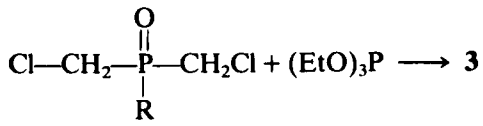
Another interesting question raised by the data presented in Table III is why some of the phosphinic amides follow primarily Path A while others follow primarily Path B in Scheme 1. When the amide group R, is relatively small, for example phenylamino in **3a**, attack of the anion of **4** from the side opposite the diethylphophonomethyl group at the amide phosphorus is favored and **8** is

TABLE I

Data for bis(diethylphosphonomethyl)phosphinic amides (**3**)[a]

Compd	R	Mass spectrum *m/e* 70 eV M^+	mp °C	Yield %	PCH_2P, nmr m, δ
3a	phenylamino	441	33–5	39	3.3–2.4
3b	α-methylbenzylamino	469	oil	25	3.3–2.0
3c	cyclohexylamino	447	oil	39	3.5–2.35
3d	*t*-butylamino	421	114–15	20	3.2–2.3
3e	morpholino	435	oil	30	2.8
3f	piperidino	433	35–8	39	3.9–2.4
3g	N,N-di-*n*-propylamino	449	oil	30	3.4–2.4
3h	N-cyclohexyl-N-methylamino	461	oil	39	3.15–2.4

[a] Satisfactory elemental analyses were obtained for all compounds for C, H, and P and for N for **3d** and **3g**.



12

Scheme 2

formed. Since the phenylamino group is more apicophilic than the diethylphosphonomethyl group, **8**, undergoes pseudo-rotation (PR) to form **9** which can undergo elimination to form **10**. In this process the rules for apical occupancy and for apical entry apical exit have been followed. When the amide group, R, is relatively large, for example dipropylamino in **3g**, attack of the anion of **4** from the side opposite the bulky dipropylamino group is favored and **11** is formed. In **11** the more apicophilic dipropylamino group rather than the diethylphosphonomethyl group is in the apical position and pseudo-rotation of **11** is not favorable. Without pseudo-rotation **11** cannot give elimination to an olefin without violation of the apical exit rule. Therefore when R in **4** is a bulky group such as dipropylamino, attack of the anion occurs at the phosphonate phosphorus atom with formation of **5**. Even if this is not the preferred process, formation of **11** does not lead to products and **11** equilibrates to **5**. Although pseudo-rotation is probably less favorable for **5** than for **8**, it can occur.

Thus, it appears the course of these condensation eliminations is controlled primarily by the magnitude of the steric resistance to nucleophilic attack at the two different types of phosphorus atoms and the ease of pseudo-rotation of the oxaphosphetane intermediates which are formed.

The base-catalyzed condensation elimination reaction of di-*n*-propyl bis(diethylphosphonomethyl)phosphinic amide (**3g**) with aldehydes furnishes a satisfactory yield of the vinyl phosphinic amides (**7**) which can be hydrolyzed to

TABLE II

Data for bis(chloromethyl)phosphinic amides (**12**).[a]

Compd	R	Mass spectrum m/e 70 eV M^+	mp °C	Yield %
12a	phenylamino	235	143–44	90
12b	α-methylbenzylamino[b]	265	156–57	90
12c	cyclohexylamino	243	163–64	86
12d	*t*-butylamino	217	67–8	80
12e	morpholino	231	135–37	80
12f	piperidino	229	123	70
12g	*N,N*-di-*n*-propylamino	245	37–9	89
12h	*N*-cyclohexyl-*N*-methylamino[b]	257	79–80	90

[a] Satisfactory elemental analyses were obtained for all compounds for C except as noted, and H, for P for **6b, 6c, 6e,** and **6h**, for N for **6f**, and for Cl for **6a** and **6d**.

[b] Compound 12b: C, Calcd, 45.13, Found, 46.11. Compound **12h**: C, Calcd. 41.87, Found, 41.23.

TABLE III

Reactions of aldehydes with bis(diethyl-phosphonomethyl)phosphinic amides (3)

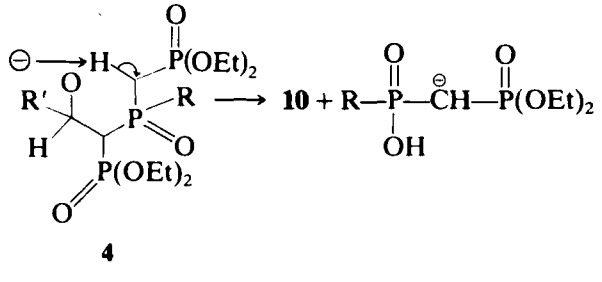
Compd.	R	Aldehyde	% Composition (% yield) by column chromatography 10[c]	7
3a	phenylamino	a	93(48)	7(2)[e]
3b	α-methylbenzylamino	a	88(57)	12(4)[e]
3c	cyclohexylamino	a	85(44)	14(4)[e]
3d	*t*-butylamino	a	60(54)	40(20)[d]
3e	morpholino	a	91(53)	9(3)[e]
3f	piperidino	a	67(38)	33(11)[e]
3g	*N,N*-di-*n*-propylamino	a	12(11)	88(46)[d]
3g	*N,N*-di-*n*-propylamino	b	9(12)	91(56)[d]
3h	*N*-cyclohexyl-*N*-methylamino	a	20(20)	80(46)[e]

[a] Isobutyraldehyde, R′ = isopropyl
[b] 4-Tolualdehyde, R′ = 4-methlyphenyl
[c] Identified by comparison to an authentic sample.
[d] Satisfactory elemental analyses were obtained for C, H, N and P.
[e] Identified by spectral data.

the vinyl phosphonomethylphosphinic acids (**1**). In addition to providing a satisfactory synthesis of **7** and **1**, this work clearly illustrates that the facility with which Wittig-type condensation eliminations occur depends on the ease with which the oxaphosphetane intermediate can undergo pseudo-rotation. Indeed, these results strongly suggest that by judicious selection of the groups attached to phosphorus Wittig-type reactions of PO ylides may be greatly enhanced or retarded.

EXPERIMENTAL SECTION

All melting points were taken on a Mel-Temp melting point apparatus and are corrected. Boiling points are uncorrected. Infrared spectra were recorded on either a Perkin–Elmer model 257 or a Beckman IR-33 spectrophotometer. Nmr spectra were taken on a Jeolco Model C–60–HL spectrometer using either tetramethylsilane (TMS) or sodium 2,2-dimethyl 2-silapentane-5-sulfonate (DDS) as internal standards. Mass spectra were taken on a Dupont Model 21–492 Mass Spectrometer. Gas Chromatographic analyses were carried out on a Perkin–Elmer Model 900 Gas Chromatograph with either 3% or 5% OV-17 columns. Elemental analyses were performed either by Galbraith Laboratories, Inc., Knoxville, Tennessee, Chemalytica, Inc., Tempe, Arizona or N-H-W Laboratories, Garden City, Michigan.



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Scheme 3

N,N-Di-n-propyl Bis(chloromethyl)phosphinic Amide (**12g**). To a cold stirred solution of 20.2 g (0.2 mol) of di-*n*-propylamine in 100 mL of anhy ether was added dropwise 18.1 g (0.1 mol) of bis(chloromethyl)phosphinyl chloride.[4] The mixture was warmed to room temp and stirring was continued for 3 hr. The suspension was filtered and the solid was washed with anhyd ether. The filtrate was washed with H_2O(3 × 100 mL), dried over $MgSO_4$ and concd *in vacuo* to afford 22 g (89%) of the crystalline amide **12g**, mp 37–39°C, nmr ($CDCl_3$) δ 3.9 (d, 4, $ClCH_2P$), 3.5–2.9 (m, 4, NCH_2), 2.1–1.8 (m, 4, NCH_2CH_2), and 1.2–0.8(t, 6, CH_3), mass spectrum (70 eV) m/e 245 (M^+), ir (KBr), 1200 (P→O) cm^{-1}.

Anal. Calcd. For $C_6H_{18}Cl_2NOP$: C, 39.04 H, 7.37 P12.59.
Found: C, 38.91 H, 7.30 P, 1259.

N,N-Di-n-propyl Bis(diethylphosphonomethyl)phosphinic Amide (**3g**). A mixture of 4.9 g (0.02 mol) of **12g** and 15 g (0.09 mol) of triethyl phosphite was heated at 140°C under a nitrogen atmosphere for 72 hr. The volatile material was removed *in vacuo* and the residue was chromatographed on a silica gel column using ether-ethanol (90:10) to afford 2.7 g (30%) of **3g** as an oil: nmr($CDCl_3$) δ3.4–2.4 (m, 8, PCH_2P and NCH_2), 1.9–1.4 (m, 16, OCH_2CH_3 and $NCH_2CH_2CH_3$), and 0.9 (t, 6, $NCH_2CH_2CH_3$), mass spectrum (70 eV) *m/e* 449 (M^+).

Anal. Calcd. for $C_{16}H_{38}NO_7P_3$: C, 42.76, H, 8.52, N, 3.13, P, 20.67. Found: C, 42.66, 8.41, N, 3.29, P, 20.47.

Base-Catalyzed Condensation and Elimination of Di-n-propyl Bis(diethylphosphonomethyl)phosphinic Amide (**3g**) *with Isobutyraldehyde*. To a suspension of 0.12 g (0.005 mol) of NaH in 30 mL of dry benzene was added dropwise over a period of 30 min 22.2 g (0.005 mol) of **3g** in 15 mL of benzene. The reaction mixture was stirred at room temperature for an additional 4 min. Most of the NaH was consumed. To the above reaction mixture was added 0.36 g (0.005 mol) of isobutyraldehyde in 30 mL of benzene. The reaction mixture was stirred at room temperature overnight and washed with H_2O (5 × 100 mL). The organic layer was dried over anhy Na_2SO_4 and concd *in vacuo* to give an oily substance. Separation on a silica gel column with ether-ethanol (90:10) as an eluant gave 420 mg (46%) of **7g** (R′ = isopropyl) and 60 mg (11%) of **10**(R′ = isopropyl). The following physical properties were obtained for **7g**(R′ = isopropyl): nmr ($CDCl_3$) δ 7.1–5.6 (m, 2, CH = CH), 4.15 (M, 4, OCH_2CH_3), 3.2–2.0 (m, 7, PCH_2P, NCH_2, and CH_3CHCH_3), and 1.9–0.7 (m, 22, $NCH_2CH_2CH_2CH_3$, and OCH_2CH_3), mass spectrum (70 eV) *m/e* 367 (M^+), ir (neat), 1385 (CH_3CHCH_3), 1250 (P═O), 1210 (P═O) cm^{-1}.

Anal. Calcd. for: $C_{16}H_{35}NO_5P_2$: C, 52.31, H, 9.60, N, 3.81, P, 16.96. Found: C, 52.08, H, 9.84, N, 3.64, P, 16.60.

Compound **10** (R′ = isopropyl) was identified by comparison to an authentic sample.[2]

The aqueous layer was concd *in vacuo* to give a glassy solid. The nmr spectrum of this material in D_2O did not show peaks for vinylic protons.

ACKNOWLEDGEMENT

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