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Synthesis of New Phosphonoamide and Phosphonocaprolactam Derivatives via the Diethyl Chlorophosphate-Promoted Beckmann Rearrangement of γ-Phosphonyloximes

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ABSTRACT: *Herein, we report an efficient and straightforward synthesis of new phosphonoamide and phosphonocaprolactam derivatives, via the Beckmann rearrangement of γ-phosphonyloximes. The reaction proceeded smoothly in the presence of diethyl chlorophosphate as a promoter, to afford the title compounds in satisfactory yields. A mechanistic rationalization for this reaction is provided allowing for the prediction of its regiochemistry.* © 2015 Wiley Periodicals, Inc. Heteroatom Chem. 26:397–404, 2015; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21273

INTRODUCTION

An increasing interest has been paid for several years to the synthesis of oximes. Such interest has been stimulated by their promising applications as antimicrobial [1], anticancer [2], antioxidant [3], and vasodilator [4] agents. Certain oxime derivatives have also found applications in coordination chemistry especially as uranium extractants [5]. On the other hand, oximes and their derivatives are recognized as key intermediates for the synthesis of amines [6], amides [7], nitriles [8], nitro compounds [9], and azaheterocycles [10].

The introduction of a phosphoryl group on oximes may be very interesting for the enhancement of the biological and complexing properties of these molecules, and for synthetic transformations leading to phosphonylated amines, amides, and azaheterocycles, which are known to exhibit a variety of pharmacological properties [11, 12].

In view of the above, and in the continuation of our studies on the synthetic applications of phosphonyl ketones [13–16], we report here for the first time the synthesis of γ-phosphonyloximes from the base-catalyzed reaction of hydroxylamine hydrochloride with γ-ketophosphine oxides.

Furthermore, and to explore the synthetic utility of these oximes, we have investigated their behavior in the Beckmann rearrangement, which could represent an easy and direct access to novel types of phosphonoamide and phosphonocaprolactam derivatives with potential biological or technological importance. Indeed, phosphonoamides are well known for their promising applications as antibacterial, insecticidal, or acaricidal agents [17–19]. Some of them are also useful as antiwear and friction-reducing additives for lubricants and liquid hydrocarbon fuels [20] and as plasticizer agents [21]. On the other hand, phosphonocaprolactams have found uses as modifying additives in the synthesis of phosphorus-containing polyamide-6, which

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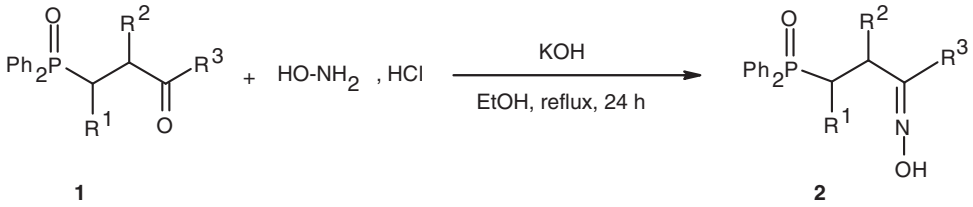


1 2

SCHEME 1 Synthesis of γ-phosphonyloximes **2**.

TABLE 1 Substrate Scope for the Synthesis of Compounds **2**

Entry	R^1	R^2	R^3	*Product*	*Yield (%)*[a]	$\delta^{31}P$ *(Z)*[b,c]	$\delta^{31}P$ *(E)*	*% Z*[d]	*% E*[d]
1	Ph	H	Me	**2a**	84	34.3	34.2	44	56
2	Ph	H	Ph	**2b**	71	35.7	34.3	17	83
3		H	Me	**2c**	69	33.4	33.0	43	57
4		H	Me	**2d**	73	33.2	33.6	42	58
5	Ph	$(CH_2)_4$		**2e**	68	30.6	32.9	38	62
6	*	H	*	**2f**	81	34.6	34.2	47	53

*R^1 and R^3: $(CH_2)_3$.
[a]Isolated yield.
[b]121.5 MHz, $CDCl_3$.
[c]δ in ppm.
[d]Determined from the ^{31}P NMR spectra.

possesses improved flame retardancy as well as improved thermo- and thermooxidative resistance [22].

RESULTS AND DISCUSSION

The starting γ-ketophosphine oxides **1** were easily prepared from the reaction of *P*-chlorodiphenylphosphine with α,β-unsaturated ketones in refluxing acetic acid, according to the reported procedure [23]. It was found that the reaction of compounds **1** with hydroxylamine hydrochloride, performed in refluxing ethanol, for 24 h, in the presence of an equimolar amount of potassium hydroxide, led to γ-phosphonyloximes **2** (Scheme 1). The isolated yield of the reaction ranges from 68 to 81% (Table 1).

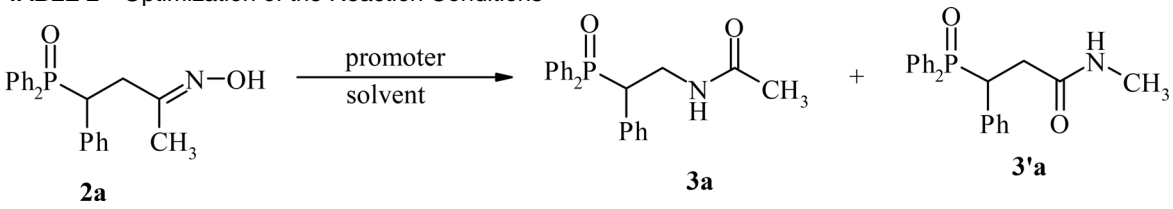
Compounds **2** were characterized on the basis of their IR, NMR (^1H, ^{31}P, ^{13}C), and mass spectral data, which indicate that they are obtained as a mixture of *Z* and *E* isomers. Their relative proportions were estimated from the ^{31}P NMR spectra where a singlet for each isomer is present (Table 1). The *Z* and *E* configurations were assigned on the basis of the ^{13}C chemical shifts of carbons in α position with respect to the C=N double bond. Indeed, according to some literature data [24–28] concerning the stereochemistry of imines, hydrazones, and oximes, the carbon adjacent to the C=N double bond resonates at higher field when it is in the syn position to the group on the nitrogen atom (OH in our case).

In all cases, *E* isomers were the predominant forms probably due to the steric hindrance between the phosphonoethyl and hydroxyl groups, which destabilizes the *Z* isomers.

With these oxime derivatives in hand, we next focused our efforts to investigate their behavior in the Beckmann rearrangement to obtain new phosphonoamide and phosphonocaprolactam derivatives, which could have promising applications as precursors of new phosphorus-containing polymers.

To optimize the reaction conditions for the formation of the target compounds, we used γ-phosphonyloxime **2a** as a model substrate. The reaction was studied with various promoters. The results of these comparative experiments are summarized in Table 2. It was found that performing the model reaction using protonic and Lewis acids as promoters did not yield the desired products but this left the starting materials intact even after prolonged heating under reflux (Table 2, entries 1–6). Also tested was the use of sulfonyl- and acyl chlorides such as chlorosulfonic acid, tosyl-, and acetyl

TABLE 2 Optimization of the Reaction Conditions



2a **3a** **3'a**

Entry	Promoter (1 equiv)	Solvent	Temperature	Time (h)[a]	Yield (%)[b]
1	H_2SO_4	H_2O	Reflux	24	0
2	H_2SO_4	Toluene	Reflux	24	0
3	TsOH	Toluene	Reflux	24	0
4	H_3NSO_3	MeCN	Reflux	24	0
5	TsOH/$ZnCl_2$	MeCN	Reflux	24	0
6	TsOH/$ZnCl_2$	1,4-Dioxane	Reflux	24	0
7	TsCl/$ZnCl_2$	MeCN	Reflux	24	5
8	$ClSO_3H$	Toluene	Reflux	24	10
9	AcCl	Toluene	Reflux	24	14
10	$(EtO)_2P(O)Cl$	Toluene	Reflux	2	52

[a]The progress of the reactions was monitored by TLC.
[b]Overall yield.

chloride, but lower than 14% overall yield was obtained after refluxing the mixture for long periods of time (Table 2, entries 7–9). A net improvement in the yield was observed when using diethyl chlorophosphate as a promoter, in refluxing toluene, for 2 h. The reaction furnished a mixture of two regioisomers **3a** and **3′a** in 52% overall yield (Table 2, entry 10).

With optimized reaction conditions in hand, we next studied the scope of this methodology. A variety of structurally diverse γ-phosphonyloximes were investigated, and a series of new phosphonoamide (**3a-d** and **3′a-d**) and phosphonocaprolactam (**3e,f** and **3′e,f**) derivatives were afforded in satisfactory yields. In all cases, the reaction furnished a mixture of two regioisomers **3** and **3'** in an approximate 3:1 ratio (Table 3).

A mechanistic rationalization for this reaction is provided in Scheme 2. In this proposed mechanism, the role of diethyl chlorophosphate is the conversion of the oxime OH into a good leaving group via a substitution reaction on the phosphorus atom. The departure of this leaving group and the migration of the organyl substituent on the C=N double bond to the nitrogen atom then take place during a concerted process; it is thus the organyl substituent anti to the leaving group that migrates, resulting in a nitrilium ion, which is converted into the final amide product, during the basic hydrolysis.

This *anti* [1,2]-shift allows for the prediction of the regiochemistry of this reaction and explains the obtention of a mixture of two regioisomers **3** and **3′** with the major isomer **3** arising from the predominant *E*-stereoisomer of the starting γ-phosphonyloxime. It is important to note here that the product ratio (**3**:**3′**) did not reflect exactly the equilibrium distribution of the starting isomers (*E*-**2**:*Z*-**2**). This can be explained taking into account the Curtin–Hammett principle. The *Z*-**2**/*E*-**2** equilibrium, required for this principle, was easily confirmed by performing ^{31}P NMR experiments of oximes **2** at higher temperature and observing changes in the *Z*/*E* ratio.

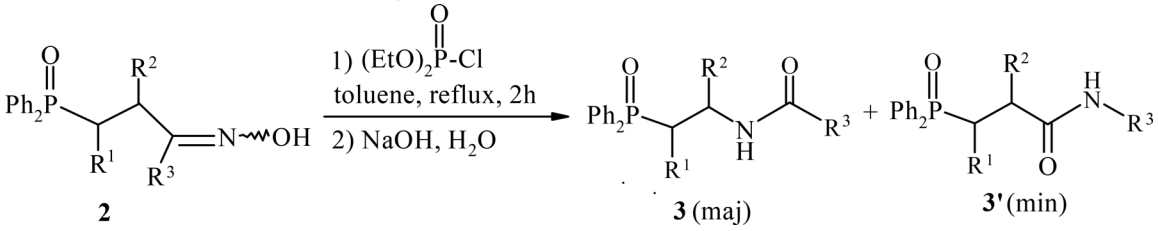
The proposed reaction mechanism was corroborated by collecting an IR spectrum on the reaction mixture (relative to oxime **2a**) prior to the basic hydrolysis. The obtained spectrum revealed the presence of an absorption band at 2296 cm^{-1} corresponding to the proposed nitrilium intermediate.

In summary, we have successfully developed an efficient and straightforward synthesis of new phosphonoamide and phosphonocaprolactam derivatives via the diethyl chlorophosphate-promoted Beckmann rearrangement of γ-phosphonyloximes. The synthesized compounds could have promising applications as precursors of new phosphorus-containing polymers, which are known for their improved flame retardancy as well as improved thermo- and thermooxidative resistance. These studies are ongoing in our laboratory and will be reported in due course.

EXPERIMENTAL

^1H, ^{31}P, and ^{13}C NMR spectra were recorded with $CDCl_3$ as the solvent, on a Bruker AC-300 spectrometer operating at 300.1 MHz for ^1H, 121.5 MHz for ^{31}P, and 75.5 MHz for ^{13}C. The chemical shifts are reported in ppm relative to TMS (internal reference)

TABLE 3 Substrate Scope for the Synthesis of Compounds **3** and **3'**



Entry	*R^1*	*R^2*	*R^3*	*Product*	*Yield (%)[a]*	*$\delta^{31}P$(**3**)[b,c]*	*$\delta^{31}P$(**3'**)*	*% (**3/3'**)[d]*
1	Ph	H	Me	**3a + 3′a**	52	33.0	32.8	63/37
2	Ph	H	Ph	**3b + 3′b**	51	33.3	35.1	73/27
3		H	Me	**3c + 3′c**	61	32.3	33.6	78/22
4		H	Me	**3d + 3′d**	68	32.2	32.2	74/26
5	Ph	$(CH_2)_4$		**3e + 3′e**	67	30.3	32.4	90/10
6	*	H	*	**3f + 3′f**	71	36.6	34.1	69/31

*R^1 and R^3: $(CH_2)_3$.
[a]Isolated overall yield.
[b]121.5 MHz, CDCl3.
[c]δ in ppm.
[d]Determined from the ^{31}P NMR spectra of the crude product.

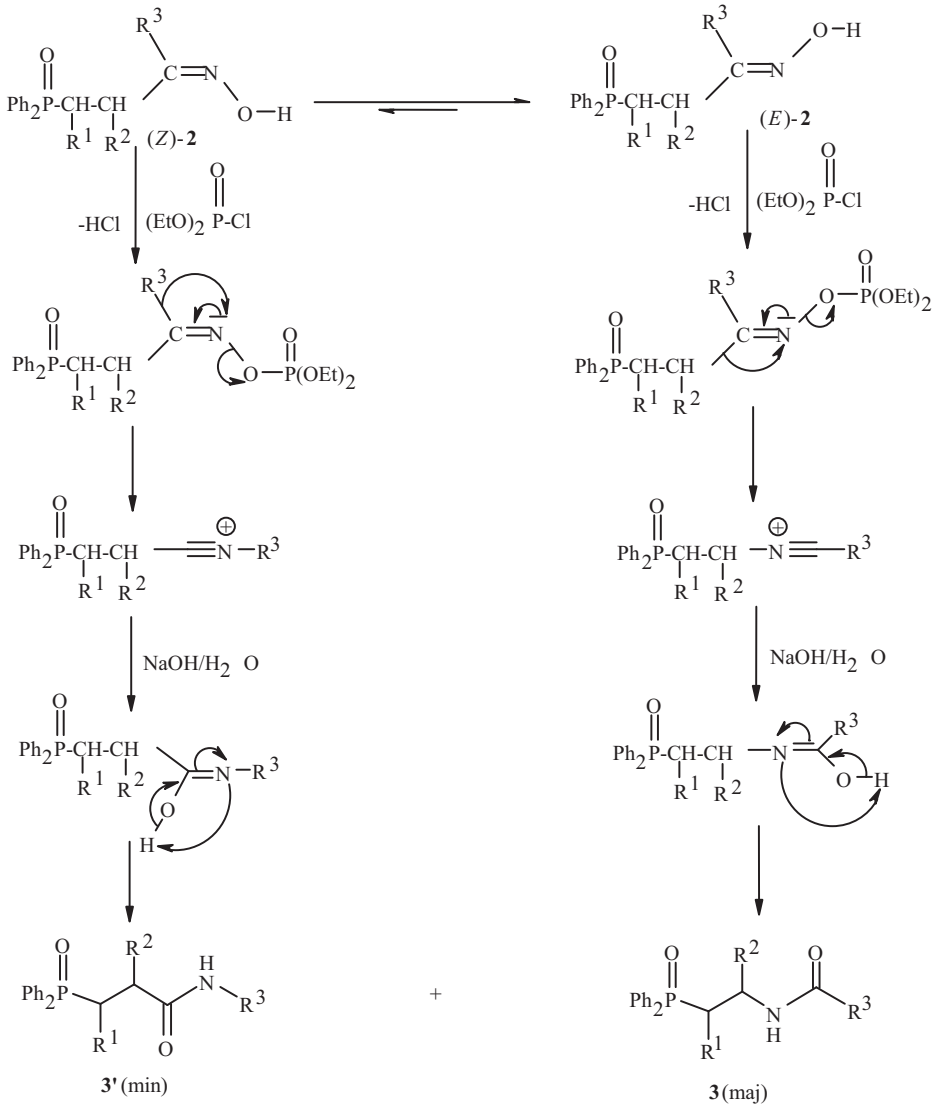
for ^1H and ^{13}C NMR and relative to 85% H_3PO_4 (external reference) for ^{31}P NMR. The coupling constants are reported in hertz. The multiplicities of signals are indicated by the following abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet. For the ^{13}C NMR data of aromatic carbons, the signals are listed as they appear on the spectrum. Mass spectra were determined on a Voyager DE STR spectrometer under MALDI ionization conditions. Elemental analyses (C, H, N) were performed on a CE440 elemental analyzer. IR spectra were recorded on a Nicolet IR200 spectrometer. The progress of the reactions was monitored by TLC. Purification of products was performed by column chromatography using silica gel 60 (Fluka).

General Procedure for the Synthesis of γ-Phosphonyloximes **2**

To a mixture of hydroxylamine hydrochloride (0.01 mol, 0.695 g), potassium hydroxide (0.01 mol, 0.561 g), and dry ethanol (30 mL), a solution of γ-ketophosphine oxide **1** [23] (0.01 mol, e.g., **1a**: 3.484 g) was added dropwise with stirring, at 25°C, in dry ethanol (20 mL). The reaction mixture was then heated under reflux for 24 h. After cooling, the solvent was removed under reduced pressure. The residue obtained was diluted with $CHCl_3$ (40 mL) and washed with water (2×20 mL). The organic phase was dried over Na_2SO_4 and concentrated under vacuum. The product obtained was washed with petroleum ether.

2a: White solid; mp = 96–98°C; ^1H NMR: δ = 1.27 (s, 3H, CH_3–C=N, *Z*); 1.52 (s, 3H, CH_3–C=N, *E*); 2.71–3.09 (m, 2H, CH_2–C=N); 3.84–3.92 (m, 1H, CH-P, *E*); 4.13–4.21 (m, 1H, CH-P, *Z*); 6.88–8.01 (m, 15H, arom-H); 9.39 (br s, 1H, OH, *E*); 9.77 (br s, 1H, OH, *Z*); ^{13}C NMR: δ = 14.3 (s, $\underline{C}H_3$–C=N, *E*); 21.8 (s, $\underline{C}H_3$–C=N, *Z*); 30.3 (s, $\underline{C}H_2$–C=N, *Z*); 35.5 (s, $\underline{C}H_2$–C=N, *E*); 42.0 (d, $^1J_{CP}$ = 67.2, CH-P, *Z*); 44.0 (d, $^1J_{CP}$ = 67.2, CH-P, *E*); 154.8 (d, $^3J_{CP}$ = 14.3, C=N, *Z*); 155.6 (d, $^3J_{CP}$ = 14.3, C=N, *E*); aryl carbons: 125.1, 125.4, 125.6, 125.7, 125.9, 126.1, 126.3, 126.5, 126.7, 126.8, 127.1, 127.3, 128.1, 128.9, 129.3, 129.9, 130.7, 130.9, 131.0, 131.2, 131.3, 131.5, 131.8, 131.9, 132.0, 132.6, 134.9, 135.1, 135.2, 135.7, 136.0, 136.6, 136.9, 138.0, 138.7, 139.5, 141.0, 141.1, 141.5, 141.7; IR (neat): $\upsilon_{P=O}$ = 1270 cm^{-1}; $\upsilon_{C=N}$ = 1662 cm^{-1}; υ_{OH} = 3241 cm^{-1}; MALDI-MS: *m/z* = 364.060 ($[M + H]^+$).

2b: White solid; mp = 96–99°C; ^1H NMR: δ = 3.21–3.65 (m, 2H, CH_2–C=N); 4.15–4.23 (m, 1H, CH-P, *E*); 4.38–4.45 (m, 1H, CH-P, *Z*); 6.86–8.01 (m, 20H, arom-H); 10.26 (br s, 1H, OH); ^{13}C NMR: δ = 38.9 (s, $\underline{C}H_2$–C=N, *E*); 41.1 (d, $^1J_{CP}$ = 54.3, CH-P, *Z*); 42.6 (d, $^1J_{CP}$ = 59.6, CH-P, *E*); 44.0 (s, $\underline{C}H_2$–C=N, *Z*); 155.7 (d, $^3J_{CP}$ = 12.8, C=N, *Z*); 155.8 (d, $^3J_{CP}$ = 12.8, C=N, *E*); aryl carbons: 126.5, 127.0, 127.1, 127.9, 128.1, 128.4, 128.6, 128.7, 128.9, 129.0, 129.1, 129.4, 129.5, 129.6, 129.7, 129.8, 129.9, 130.0, 130.1, 130.2, 130.4, 130.5, 130.7, 130.8, 130.9, 131.0, 131.2, 131.5, 131.6, 131.7,



SCHEME 2 Proposed mechanism for the synthesis of compounds **3** and **3′**.

131.9, 132.1, 132.5, 133.1, 133.3, 133.5, 133.7, 133.8, 133.9, 134.0, 134.2, 134.8, 134.9, 136.2; IR (neat): $\upsilon_{P=O}$ = 1276 cm^{-1}; $\upsilon_{C=N}$ = 1650 cm^{-1}; υ_{OH} = 3211 cm^{-1}; MALDI-MS: *m/z* = 426.087 ($[M + H]^+$).

2c: Brown solid; mp = 92–94°C; ^1H NMR: δ = 1.41 (s, 3H, CH_3–C=N, *Z*); 1.65 (s, 3H, CH_3–C=N, *E*); 2.67–3.19 (m, 2H, CH_2–C=N); 4.31–4.44 (m, 1H, CH-P, *E*); 4.53–4.61 (m, 1H, CH-P, *Z*); 6.70–8.14 (m, 13H, arom-H); 9.83 (br s, 1H, OH, *E*); 10.07 (br s, 1H, OH, *Z*); ^{13}C NMR: δ = 14.3 (s, $\underline{C}H_3$–C=N, *E*); 21.8 (s, $\underline{C}H_3$–C=N, *Z*); 31.6 (s, $\underline{C}H_2$–C=N, *Z*); 36.6 (s, $\underline{C}H_2$–C=N, *E*); 37.4 (d, $^1J_{CP}$ = 69.4, CH-P, *Z*); 39.2 (d, $^1J_{CP}$ = 68.7, CH-P, *E*); 154.0 (d, $^3J_{CP}$ = 14.3, C=N, *E*); 155.5 (d, $^3J_{CP}$ = 12.8, C=N, *Z*); aryl carbons: 124.6, 124.9, 125.0, 126.7, 126.8, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.6, 128.7, 128.9, 130.0, 130.1, 130.2, 130.3, 130.9, 131.0, 131.1, 131.3, 131.4, 131.5, 131.6, 131.7, 131.8, 132.0, 132.1, 132.2, 136.5, 136.6, 136.8, 136.9; IR (neat): $\upsilon_{P=O}$ = 1283 cm^{-1}; $\upsilon_{C=N}$ = 1674 cm^{-1}; υ_{OH} = 3230 cm^{-1}; MALDI-MS: *m/z* = 370.035 ($[M + H]^+$).

2d: Brown solid; mp = 90–92°C; ^1H NMR: δ = 1.40 (s, 3H, CH_3–C=N, *Z*); 1.61 (s, 3H, CH_3–C=N, *E*); 2.63–3.02 (m, 2H, CH_2–C=N); 4.12–4.29 (m, 1H, CH-P, *E*); 4.33–4.45 (m, 1H, CH-P, *Z*); 6.00–7.92 (m, 13H, arom-H); 9.93 (br s, 1H, OH, *E*); 10.02 (br s, 1H, OH, *Z*); ^{13}C NMR: δ = 13.9 (s, $\underline{C}H_3$–C=N, *E*); 21.0 (s, $\underline{C}H_3$–C=N, *Z*); 28.4 (s, $\underline{C}H_2$–C=N, *Z*); 33.6 (s, $\underline{C}H_2$–C=N, *E*); 36.8 (d, $^1J_{CP}$ = 68.7, CH-P, *Z*); 38.4 (d, $^1J_{CP}$ = 69.4, CH-P, *E*); 155.2 (d, $^3J_{CP}$ = 12.1, C=N, *Z*); 154.0 (d, $^3J_{CP}$ = 13.6, C=N, *E*); aryl carbons: 108.9, 109.4, 109.5, 109.6, 110.7, 110.8, 110.9, 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 128.7, 129.7, 130.2, 130.8, 130.9, 131.0, 131.2, 131.3, 131.4, 131.6, 131.8, 132.0,

132.1, 132.7, 132.9, 133.0, 141.5, 141.6, 141.8, 141.9; IR (neat): $\upsilon_{P=O}$ = 1279 cm^{-1}; $\upsilon_{C=N}$ = 1658 cm^{-1}; υ_{OH} = 3255 cm^{-1}; MALDI-MS: *m/z* = 354.028 ($[M + H]^+$).

2e: Yellow solid; mp = 100–102°C; ^1H NMR: δ = 1.14–3.85 (m, 10H, cyclic-H and CH-P); 6.96–8.12 (m, 15H, arom-H); 9.95 (br s, 1H, OH, *Z*); 10.18 (br s, 1H, OH, *E*); ^{13}C NMR: δ = 20.3 (s, $(CH_2)_2$–CH_2–CH_2–C=N, *Z*); 21.7 (s, $(CH_2)_2$–CH_2–CH_2–C=N, *E*); 22.7 (s, $(CH_2)_3$–CH_2–C=N, *E*); 23.3 (s, $(CH_2)_3$–CH_2–C=N, *Z*); 24.9 (s, CH_2–CH_2–$(CH_2)_2$–C=N, *E*); 25.9 (s, CH_2–CH_2– $(CH_2)_2$–C=N, *Z*); 30.8 (d, $^1J_{CP}$ = 82.3, CH-P, *E*); 41.2 (s, CH–C=N, *E*); 42.2 (d, $^1J_{CP}$ = 70.2, CH-P, *Z*); 43.2 (s, CH–C=N, *Z*); 43.6 (s, CH_2–$(CH_2)_3$–C=N); 156.9 (d, $^3J_{CP}$ = 12.1, C=N, *Z*); 157.9 (d, $^3J_{CP}$ = 12.1, C=N, *E*); aryl carbons: 125.9, 126.2, 126.6, 127.1, 127.3, 127.5, 127.6, 127.7, 127.9, 128.0, 128.2, 128.3, 130.1, 130.2, 130.3, 130.4, 130.5, 130.6, 130.7, 130.9, 131.1, 131.2, 131.3, 132.3, 132.7, 133.5, 133.9, 135.0, 136.6; IR (neat): $\upsilon_{P=O}$ = 1281 cm^{-1}; $\upsilon_{C=N}$ = 1654 cm^{-1}; υ_{OH} = 3270 cm^{-1}; MALDI-MS: *m/z* = 404.081 ($[M + H]^+$).

2f: Yellow solid; mp = 99–101°C; ^1H NMR: δ = 1.61–3.45 (m, 9H, cyclic-H); 7.40–8.81 (m, 10H, arom-H); 10.13 (br s, 1H, OH, *Z*); 10.28 (br s, 1H, OH, *E*); ^{13}C NMR: δ = 22.5 (s, CH_2–CH_2–CH_2–C=N); 23.8 (s, $(CH_2)_2$–CH_2–C=N, *Z*); 24.1 (s, $(CH_2)_2$–CH_2–C=N, *E*); 25.2 (s, CH_2–$(CH_2)_2$–C=N, *E*); 26.7 (s, CH_2–$(CH_2)_2$–C=N, *Z*); 30.2 (s, CH–CH_2–C=N, *Z*); 31.5 (s, CH–CH_2–C=N, *E*); 36.1 (d, $^1J_{CP}$ = 72.5, CH-P, *Z*); 37.4 (d, $^1J_{CP}$ = 72.5, CH-P, *E*); 157.2 (d, $^3J_{CP}$ = 12.8, C=N, *E*); 157.5 (d, $^3J_{CP}$ = 14.3, C=N, *Z*); aryl carbons: 128.6, 128.8, 129.0, 129.1, 130.1, 130.2, 130.5, 130.7, 130.8, 130.9, 131.0, 131.1, 131.4, 131.7, 131.8, 131.9, 132.0, 132.1; IR (neat): $\upsilon_{P=O}$ = 1177 cm^{-1}; $\upsilon_{C=N}$ = 1660 cm^{-1}; υ_{OH} = 3188 cm^{-1}; MALDI-MS: *m/z* = 314.017 ($[M + H]^+$).

General Procedure for the Synthesis of Phosphonoamides and Phosphonocaprolactams **3** *and* **3′**

The γ-phosphonyloxime **2** (5 mmol, e.g. **2a**: 1.817 g) and toluene (1 mL) were charged into a 50-mL two-necked round-bottomed flask equipped with a magnetic stirrer, under nitrogen atmosphere. The reaction was heated to reflux with stirring, and diethyl chlorophosphate (5 mmol, 0.863 g) was added dropwise to the mixture. Stirring was continued for 2 h under reflux. After cooling to room temperature, a 5% aqueous NaOH solution (10 mL) was added and the mixture was extracted with $CHCl_3$ (10 mL). The organic phase was dried over Na_2SO_4 and concentrated under vacuum. The crude obtained was chromatographed on silica gel column using a mixture of ether and hexane 1:1 as an eluent.

3a: Yellow solid; mp = 161–163°C; ^1H NMR: δ = 1.66 (s, 3H, CH_3–C=O); 3.80–3.98 (m, 2H, CH_2–NH); 4.06–4.12 (m, 1H, CH-P); 7.05–7.88 (m, 15H, arom-H); 7.95 (br s, 1H, NH); ^{13}C NMR: δ = 21.5 (s, CH_3–C=O); 35.4 (s, CH_2–NH); 43.4 (d, $^1J_{CP}$ = 67.2, CH-P); 170.9 (s, NH–C=O); aryl carbons: 127.2, 127.6, 128.1, 128.3, 128.7, 128.9, 129.7, 129.9, 130.8, 131.0, 131.2, 131.4, 131.6, 131.8, 132.1, 132.5, 132.8, 133.2, 133.4, 134.5; IR (neat): $\upsilon_{P=O}$ = 1276 cm^{-1}; $\upsilon_{C=O}$ = 1670 cm^{-1}; υ_{NH} = 3447 cm^{-1}; MALDI-MS: *m/z* = 364.026 ($[M + H]^+$); elemental analysis calcd (%) for $C_{22}H_{22}NO_2P$: C 72.71, H 6.10, N 3.85; found: C 72.80, H 6.17, N 3.79.

3b: White solid; mp = 208–210°C; ^1H NMR: δ = 3.93–4.26 (m, 2H, CH_2–NH); 4.40–4.45 (m, 1H, CH-P); 7.14–8.01 (m, 20H, arom-H); 10.28 (br s, 1H, NH); ^{13}C NMR: δ = 41.4 (s, CH_2–NH); 45.0 (d, $^1J_{CP}$ = 67.2, CH-P); 167.7 (s, NH–C=O); aryl carbons: 123.4, 126.9, 127.4, 128.0, 128.2, 128.6, 128.9, 129.1, 129.7, 130.4, 130.9, 131.1, 131.3, 131.5, 131.9, 132.1, 132.5, 132.9, 133.7, 134.0, 135.0, 135.8, 136.4, 139.0; IR (neat): $\upsilon_{P=O}$ = 1266 cm^{-1}; $\upsilon_{C=O}$ = 1667 cm^{-1}; υ_{NH} = 3309 cm^{-1}; MALDI-MS: *m/z* = 426.051 ($[M + H]^+$); elemental analysis calcd (%) for $C_{27}H_{24}NO_2P$: C 76.22, H 5.69, N 3.29; found: C 76.36, H 5.81, N 3.16.

3c: Brown solid; mp = 177–178°C; ^1H NMR: δ = 1.70 (s, 3H, CH_3–C=O); 3.80–3.99 (m, 2H, CH_2–NH); 4.50–4.64 (m, 1H, CH-P); 6.70–8.04 (m, 13H, arom-H); 5.50 (br s, 1H, NH); ^{13}C NMR: δ = 22.8 (s, CH_3–C=O); 41.6 (s, CH_2–NH); 40.3 (d, $^1J_{CP}$ = 67.9, CH-P); 171.1 (s, NH–C=O); aryl carbons: 124.9, 126.6, 126.8, 127.5, 127.7, 128.1, 128.3, 128.9, 130.5, 130.7, 130.9, 131.2, 131.5, 131.9, 132.3, 132.7, 133.7, 134.5, 135.8, 137.0; IR (neat): $\upsilon_{P=O}$ = 1269 cm^{-1}; $\upsilon_{C=O}$ = 1687 cm^{-1}; υ_{NH} = 3297 cm^{-1}; MALDI-MS: *m/z* = 369.987 ($[M + H]^+$); elemental analysis calcd (%) for $C_{20}H_{20}NO_2PS$: C 65.02, H 5.46, N 3.79; found: C 65.19, H 5.55, N 3.60.

3d: Brown solid; mp = 195–197°C; ^1H NMR: δ = 2.24 (s, 3H, CH_3–C=O); 3.87–4.09 (m, 2H, CH_2–NH); 4.27–4.44 (m, 1H, CH-P); 5.80 (br s, 1H, NH); 6.08–7.86 (m, 13H, arom-H); ^{13}C NMR: δ = 21.5 (s, CH_3–C=O); 35.9 (d, $^1J_{CP}$ = 70.2, CH-P); 40.8 (s, CH_2–NH); 172.9 (s, NH–C=O); aryl carbons: 108.7, 109.3, 110.8, 117.8, 126.6, 128.1, 128.3, 128.5, 128.8, 129.0, 129.4, 129.8, 130.4, 131.1, 131.4, 131.6, 131.9, 132.7, 137.8, 140.4; IR (neat): $\upsilon_{P=O}$ = 1290 cm^{-1}; $\upsilon_{C=O}$ = 1670 cm^{-1}; υ_{NH} = 3419 cm^{-1}; MALDI-MS: *m/z* = 354.003 ($[M + H]^+$); elemental analysis calcd (%) for $C_{20}H_{20}NO_3P$: C 67.98, H 5.70, N 3.96; found: C 68.17, H 5.83, N 3.78.

3e: Yellow solid; mp = 221–223°C; ^{1}H NMR: δ = 1.16–3.15 (m, 8H, cyclic-H); 3.52–3.57 (m, 1H, CH-P); 3.85 (br s, 1H, NH); 3.95–4.02 (m, 1H, CH–NH); 7.03-7.84 (m, 15H, arom-H); ^{13}C NMR: δ = 21.8 (s, CH_2–CH_2–$(CH_2)_2$–C=O); 28.1 (s, $(CH_2)_2$–CH_2– CH_2–C=O); 32.3 (s, CH_2– $(CH_2)_3$–C=O); 35.5 (s, $(CH_2)_3$–CH_2–C=O); 49.5 (d, $^1J_{CP}$ = 67.2, CH-P); 53.8 (s, CH–NH); 175.8 (s, NH–C=O); aryl carbons: 124.4, 124.8, 125.4, 125.8, 126.0, 126.9, 127.1, 127.5, 127.8, 128.9, 129.8, 130.0, 130.3, 130.5, 131.5, 133.0, 133.7, 134.0, 135.7, 136.7; IR (neat): $\upsilon_{P=O}$ = 1266 cm^{-1}; $\upsilon_{C=O}$ = 1668 cm^{-1}; υ_{NH} = 3406 cm^{-1}; MALDI-MS: *m/z* = 404.065 ([M + H]$^+$); elemental analysis calcd (%) for $C_{25}H_{26}NO_2P$: C 74.42, H 6.50, N 3.47; found: C 74.48, H 6.59, N 3.36.

3f: Yellow solid; mp = 148–149°C; ^{1}H NMR: δ = 1.19–2.15 (m, 6H, cyclic-H); 3.02–3.17 (m, 1H, CH-P); 4.30–4.62 (m, 2H, CH_2–NH); 6.60 (br s, 1H, NH); 7.00–7.84 (m, 10H, arom-H); ^{13}C NMR: δ = 22.9 (s, CH_2–CH_2–CH_2–C=O); 28.4 (s, CH_2– $(CH_2)_2$–C=O); 33.2 (d, $^1J_{CP}$ = 70.2, CH-P); 35.3 (s, $(CH_2)_3$–CH_2–C=O); 42.1 (s, CH_2–NH); 178.2 (s, NH–C=O); aryl carbons: 128.6, 128.9, 129.1, 129.3, 129.6, 129.9, 130.2, 130.4, 130.8, 131.0, 131.3, 131.6, 131.9, 132.1; IR (neat): $\upsilon_{P=O}$ = 1268 cm^{-1}; $\upsilon_{C=O}$ = 1661 cm^{-1}; υ_{NH} = 3392 cm^{-1}; MALDI-MS: *m/z* = 314.009 ([M + H]$^+$); elemental analysis calcd (%) for $C_{18}H_{20}NO_2P$: C 69.00, H 6.43, N 4.47; found: C 69.11, H 6.49, N 4.33.

3′a: Yellow solid; mp = 188–190°C; ^{1}H NMR: δ = 1.82 (s, 3H, CH_3–NH); 2.75–2.99 (m, 2H, CH_2–C=O); 3.06–3.13 (m, 1H, CH-P); 7.05–7.88 (m, 15H, arom-H); 7.97 (br s, 1H, NH); ^{13}C NMR: δ = 31.4 (s, CH_3–NH); 31.5 (s, CH_2–C=O); 42.8 (d, $^1J_{CP}$ = 67.2, CH-P); 166.3 (d, $^3J_{CP}$ = 13.8, O=C–NH); aryl carbons: 127.5, 128.0, 128.2, 128.4, 128.8, 129.1, 129.8, 130.4, 130.9, 131.1, 131.3, 131.5, 131.7, 132.0, 132.2, 132.6, 133.1, 133.3, 133.7, 134.6; IR (neat): $\upsilon_{P=O}$ = 1276 cm^{-1}; $\upsilon_{C=O}$ = 1669 cm^{-1}; υ_{NH} = 3284 cm^{-1}; MALDI-MS: *m/z* = 364.029 ([M + H]$^+$); elemental analysis calcd (%) for $C_{22}H_{22}NO_2P$: C 72.71, H 6.10, N 3.85; found: C 72.82, H 6.23, N 3.73.

3′b: White solid; mp = 248–250°C; ^{1}H NMR: δ = 3.02–3.09 (m, 2H, CH_2–C=O); 3.71–3.75 (m, 1H, CH-P); 7.14–8.01 (m, 20H, arom-H); 10.28 (br s, 1H, NH); ^{13}C NMR: δ = 36.9 (s, CH_2–C=O); 42.5 (d, $^1J_{CP}$ = 69.4, CH-P); 168.7 (d, $^3J_{CP}$ = 15.8, O=C–NH); aryl carbons: 119.6, 126.3, 127.1, 127.5, 128.1, 128.3, 128.8, 129.0, 129.2, 129.8, 130.8, 131.0, 131.2, 131.4, 131.7, 132.0, 132.4, 132.6, 133.4, 133.9, 134.9, 135.8, 135.9, 138.8; IR (neat): $\upsilon_{P=O}$ = 1266 cm^{-1}; $\upsilon_{C=O}$ = 1687 cm^{-1}; υ_{NH} = 3271 cm^{-1}; MALDI-MS: *m/z* = 426.057 ([M + H]$^+$); elemental analysis calcd (%) for $C_{27}H_{24}NO_2P$: C 76.22, H 5.69, N 3.29; found: C 76.30, H 5.86, N 3.18.

3′c: Brown solid; mp = 258–260°C; ^{1}H NMR: δ = 1.97 (s, 3H, CH_3–NH); 2.48–3.00 (m, 2H, CH_2–C=O); 3.42–3.63 (m, 1H, CH-P); 7.05–7.88 (m, 13H, arom-H); 9.80 (br s, 1H, NH); ^{13}C NMR: δ = 26.1 (s, CH_3–NH); 35.5 (d, $^1J_{CP}$ = 70.9, CH-P); 38.5 (s, CH_2–C=O); 170.3 (d, $^3J_{CP}$ = 14.3, O=C–NH); aryl carbons: 124.7, 125.1, 126.6, 127.3, 127.6, 128.0, 128.2, 128.8, 130.1, 130.6, 130.8, 131.1, 131.3, 131.8, 132.1, 132.6, 132.9, 133.9, 135.7, 136.9; IR (neat): $\upsilon_{P=O}$ = 1269 cm^{-1}; $\upsilon_{C=O}$ = 1671 cm^{-1}; υ_{NH} = 3222 cm^{-1}; MALDI-MS: *m/z* = 369.990 ([M + H]$^+$); elemental analysis calcd (%) for $C_{20}H_{20}NO_2PS$: C 65.02, H 5.46, N 3.79; found: C 65.14, H 5.58, N 3.64.

3′d: Brown solid; mp = 285–287°C; ^{1}H NMR: δ = 2.31 (s, 3H, CH_3–NH); 2.76–2.90 (m, 2H, CH_2–C=O); 3.22–3.43 (m, 1H, CH-P); 3.80 (br s, 1H, NH); 6.08–7.86 (m, 13H, arom-H); ^{13}C NMR: δ = 30.2 (s, CH_3–NH); 34.4 (d, $^1J_{CP}$ = 70.2, CH-P); 40.8 (s, CH_2–C=O); 170.9 (d, $^3J_{CP}$ = 13.8, O=C–NH); aryl carbons: 107.7, 108.8, 110.7, 117.6, 125.3, 126.8, 128.2, 128.4, 128.7, 128.9, 129.1, 129.6, 130.1, 130.9, 131.2, 131.5, 131.7, 132.2, 134.1, 138.0; IR (neat): $\upsilon_{P=O}$ = 1290 cm^{-1}; $\upsilon_{C=O}$ = 1670 cm^{-1}; υ_{NH} = 3400 cm^{-1}; MALDI-MS: *m/z* = 354.006 ([M + H]$^+$); elemental analysis calcd (%) for $C_{20}H_{20}NO_3P$: C 67.98, H 5.70, N 3.96; found: C 68.15, H 5.88, N 3.70.

3′e: Yellow solid; mp = 264–265°C; ^{1}H NMR: δ = 1.16–3.29 (m, 9H, cyclic-H); 3.66–3.69 (m, 1H, CH-P); 3.86 (br s, 1H, NH); 7.03–7.84 (m, 15H, arom-H); ^{13}C NMR: δ = 21.4 (s, CH_2–CH_2–$(CH_2)_2$–NH); 27.8 (s, CH_2– $(CH_2)_3$–NH); 31.0 (s, $(CH_2)_2$–CH_2–CH_2–NH); 35.5 (d, $^1J_{CP}$ = 67.1, CH-P); 41.8 (s, $(CH_2)_3$–CH_2–NH); 53.7 (s, CH–C=O); 175.5 (d, $^3J_{CP}$ = 16.4, O=C–NH); aryl carbons: 124.2, 124.6, 124.9, 125.6, 125.9, 126.7, 127.0, 127.4, 127.7, 127.9, 129.5, 129.9, 130.1, 130.4, 131.0, 132.2, 133.4, 133.9, 135.4, 135.8; IR (neat): $\upsilon_{P=O}$ = 1266 cm^{-1}; $\upsilon_{C=O}$ = 1660 cm^{-1}; υ_{NH} = 3300 cm^{-1}; MALDI-MS: *m/z* = 404.069 ([M + H]$^+$); elemental analysis calcd (%) for $C_{25}H_{26}NO_2P$: C 74.42, H 6.50, N 3.47; found: C 74.55, H 6.64, N 3.41.

3′f: Yellow solid; mp = 271–273°C; ^{1}H NMR: δ = 1.19–3.30 (m, 8H, cyclic-H); 3.82–4.17 (m, 1H, CH-P); 6.50 (br s, 1H, NH); 7.00–7.84 (m, 10H, arom-H); ^{13}C NMR: δ = 22.7 (s, CH_2–CH_2–CH_2–NH); 29.4 (s, CH_2–$(CH_2)_2$–NH); 35.8 (s, $(CH_2)_3$–CH_2–NH); 39.9 (d, $^1J_{CP}$ = 67.2, CH-P); 41.9 (s, CH_2–C=O); 176.4 (d, $^3J_{CP}$ = 18.9, O=C–NH); aryl carbons: 128.4, 128.7, 129.0, 129.2, 129.4, 129.8, 130.0, 130.3, 130.7, 130.9, 131.1, 131.5, 131.8, 132.0; IR (neat): $\upsilon_{P=O}$ = 1268 cm^{-1}; $\upsilon_{C=O}$ = 1655 cm^{-1}; υ_{NH} = 3300 cm^{-1}; MALDI-MS:

$m/z = 314.011$ ($[M + H]^+$); elemental analysis calcd (%) for $C_{18}H_{20}NO_2P$: C 69.00, H 6.43, N 4.47; found: C 69.07, H 6.54, N 4.35.

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