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Acylphosphonamidates and α-Hydroxyiminophosphonamidates. Synthesis of N-Acylphosphordiamidates by Beckmann Rearrangement. Crystal Structure of (*E*)-α-Hydroxyiminobenzyl-1-pyrrolidinylphosphinate

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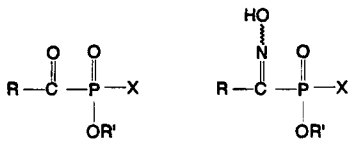
ABSTRACT

Reaction of methyl benzoylphosphonochloridate (3) with a secondary or primary series of amines yielded methyl benzoylphosphonamidates, **4a–e**. *The latter compounds reacted with hydroxylamine to yield α-hydroxyiminobenzylphosphonamidates (***5a–e***), largely as (E)-isomers. The structure of methyl (E)-α-hydroxyimino-benzyl-1-pyrrolidinylphosphinate (***5b***) was determined by single-crystal X-ray crystallography. Heating oximes* **5a–e** *in boiling toluene caused them to undergo Beckmann rearrangement to N-benzoylphosphordiamidates* **6a–e**. © *1996 John Wiley & Sons, Inc.*

INTRODUCTION

Acylphosphonates are versatile compounds, and their derivatives have recently been receiving increasing attention [1]. In previous publications, we described results from our work on acylphosphonates (1, X = OR') [2], acylphosphinates (1, X = Ph), and their oximes (2) [3].



1 2

Our interest in this area was stimulated by the assumption (subsequently confirmed) that the combination of the ketone or oxime with the phosphonic function may provide new types of bifunctional groups that may possess interesting metal binding properties [4]. Indeed, acylphosphonates and hydroxyiminophosphonates interact with calcium and influence hydroxyapatite formation and dissolution both in vitro and in vivo [5].

α-Hydroxyiminophosphonic and phosphinic acids are also of interest because they have been shown to act as phosphorylating or phosphonylating agents [6]. Their fragmentation proceeds by a dissociative mechanism involving the formation of three-coordinated metaphosphate or phosphonic anhydride intermediates (Scheme 1) [7].

In addition, hydroxyiminophosphonate and

Dedicated to Prof. Louis D. Quin on the occasion of his retirement from the University of Massachusetts at Amherst.

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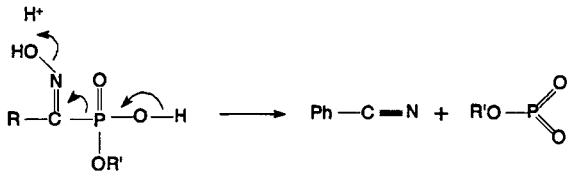
phosphinate esters exhibit stereoselective behavior when heated. While the (*E*) isomers undergo Beckmann rearrangement to phosphoramidates or phosphonamidates, (*Z*)-oximes fragment to nitrile and phosphate (Scheme 2) [3e].

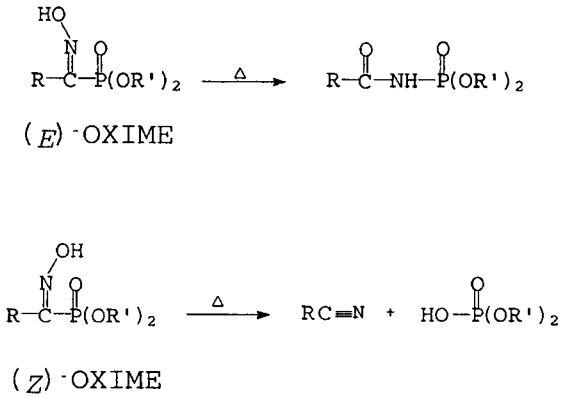
Following this, it was of interest to extend our studies to other derivatives, since the replacement of one of the methoxy groups of the phosphonate may result in molecules with properties modified in a number of ways: (1) alteration of the basicity of the phosphorus oxygens, (2) a change in the molecule's lipophilicity, and (3) altering the steric bulk at the vicinity of the phosphorus atom, all of which in turn might be reflected in the molecule's chemical properties. In addition, it was reasonable to expect that the variously substituted oxyiminophosphonic acids may be developed to a variety of phosphorylating agents, as well as conveniently accessible starting materials for the generation of metaphosphate analogs.

Recently, we reported on the behavior of 2,2,2-trihaloethyl phosphonates [3c,d]. We found that the replacement of the commonly used methoxy group by the electron-withdrawing trihaloethoxy group profoundly affects the chemical properties of acyl- and α-hydroxyiminophosphonates. Following this, it was of interest to study acylphosphonamidates and α-hydroxyiminophosphonamidates. The attachment of the amine group to the phosphorus is expected to exert the opposite, namely, an electron releasing, effect. The planned phosphonamidates would also serve as models for N-phosphonylated amino acids to be studied subsequently.

In this article, we describe the results of our studies concerning the preparation, characterization, and the reactivity of methyl benzoylphosphonamidates and α-hydroxyiminobenzylphosphonamidates derived from some primary and secondary amines, as representative compounds of this class.



SCHEME 1



SCHEME 2

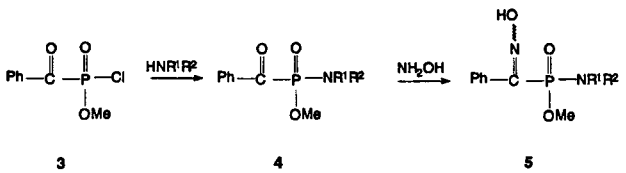
RESULTS AND DISCUSSION

Synthesis of Benzoylphosphonamidates and α-Hydroxyiminobenzylphosphonamidates

Alkyl acylphosphonamidates have previously been obtained in medium to fair yields by the Arbuzov reaction of acyl chlorides with dimethyl [8] or diethyl [9] N,N-diethylphosphoramidite, $(RO)_2PNEt_2$. Similarly, ethyl [8], or preferably trimethylsilyl N,N,N′,N′-tetraethylphosphordiamidite [10], reacted with acyl chlorides to give N,N,N′,N′-tetraethyl acylphosphonediamidates.

The syntheses of benzoylphosphonamidates, **4**, in the present work were based on the reactions of methyl benzoylphosphonochloridate (**3**) [3d] with a series of amines in dichloromethane in the presence of pyridine or excess amine to neutralize the HCl liberated in the reaction (Scheme 3). The advantage of this approach is that it allows the synthesis of a variety of phosphonamidates from a common starting material, without necessitating the preparation of many dialkyl phosphonamidites.

Special attention had to be paid to the molar ratio of the amine used. In case of excess amine, C–P bond cleavage was observed with the formation of the corresponding carboxamide and H-phosphonamidate. Methyl benzoylphosphonamidates, **4a–e**, obtained in these reactions were not isolated in pure



3 **4** **5**

a, $R^1 = R^2 = Et$; **b**, $R^1,R^2 = (CH_2)_4$; **c**, $R^1,R^2 = (CH_2)_5$;
d, $R^1 = H$, $R^2 = 2\text{-}Pr$; **e**, $R^1 = H$, $R^2 = t\text{-}Bu$.

SCHEME 3

form. Their formation could be monitored by ^{31}P NMR spectroscopy. Benzoylphosphonamidates **4** had chemical shifts in the ^{31}P NMR spectrum in the range of δ 5–8 in dichloromethane, compared to the starting **3** that resonates at δ 14. In the infrared spectrum, the crude benzoylphosphophosphonamidates **4** showed carbonyl absorptions in the range of 1640–1650 cm^{-1}, which are similar to those of dialkyl benzoylphosphonates [1,2]. The crude benzoylphosphonamidates **4** were converted to α-hydroxyiminobenzylphosphonamidates, **5a–e** (Scheme 3), by the addition of hydroxylamine to the reaction mixture. The formation of compounds **5** was often accompanied by some C–P bond cleavage, as evidenced by the appearance of absorptions characteristic of P–H bonds (coupling constants in the range of 700 Hz). Methyl α-hydroxyiminobenzylphosphonamidates **5** were obtained in isolated yields in the range of 25–40%. They were all crystalline solids and were characterized by elemental analysis, IR, ^{1}H, and ^{31}P NMR spectroscopy. The structure of the pyrrolidine derivative (*E*)-**5b** was determined by single-crystal X-ray crystallography (vide infra). In the ^{31}P NMR spectra, compounds **5** had resonances in the range of δ 13–17. The assignment of the stereochemistry of the other oximes **5** could be based on ^{31}P NMR spectroscopy. Similar to our earlier reports regarding the correlation of stereochemistry of α-hydroxyiminoalkylphosphonates [3] and -phosphinates, with their signals in ^{31}P NMR spectra, we assign in this series, too, the (*E*)-structure to the isomer that appears at lower field. Most methyl α-hydroxyiminobenzylphosphonamidates, **5**, were obtained as single isomers as indicated by their ^{31}P NMR signals. Only in oximes **5d** and **5e**, derived from the primary amines 2-propylamine and *t*-butylamine, was the formation of both (*E*) and (*Z*)-isomers noted when the reaction was monitored by ^{31}P NMR spectroscopy. The formation of oximes (*Z*)-**5d** and (*Z*)-**5e** in the syntheses is likely to result from kinetic control. This conclusion is supported by the fact that in these cases, too, during the isolation procedure, the product mixture was converted to pure (*E*)-isomers, which apparently are the more stable ones.

Hydroxyiminobenzylphosphonamidates **5a–e** were relatively unstable to hydrolysis, and, in the presence of water, they were converted by fission of the P–N bond to the corresponding amine salts of the methyl α-hydroxyiminobenzylphosphonate.

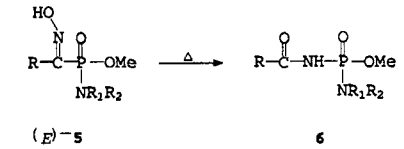
Benzoylphosphonamidates **4** and α-hydroxyiminobenzylphosphonamidates **5** were resistant to attempts at demethylation by nucleophilic reagents (e.g., LiBr in MeCN or NaI in acetone, or Bu_4NBr, or LiOH in MeOH, or Me_3SiBr in toluene), all of which were successfully used previously for the demethylation of acyl-[2] and α-hydroxyiminoalkylphosphonates [3] and -phosphinates [3]. This resistance of phosphonamidates **4** and **5** to undergo nucleophilic demethylation is likely to be a reflection of the poor leaving group properties of the phosphonamidate anion that would be formed in the dealkylations, due to the electron-releasing effect of the amino groups. Because of the lack of success in the demethylations, it was not possible to prepare α-hydroxyiminobenzylphosphonamidate anions that could be potential precursors for metaphosphoramidates.

Beckmann Rearrangement of Hydroxyiminobenzylphosphonamidates

Following our previous work on the thermal behavior of α-hydroxyiminobenzylphosphonates [3e], we examined the stability of α-hydroxyiminobenzylphosphonamidates **5** at elevated temperatures. We found that compounds **5** undergo facile rearrangement to phosphordiamidates **6** in refluxing toluene (Scheme 4). Reactions were complete in 45 minutes to 6 hours, far more rapidly than those of dimethyl α-hydroxyiminobenzylphosphonates or phosphinates studied previously [3e]. The Beckmann rearrangement products were all crystalline solids. They were isolated by preparative thin-layer chromatography or recrystallization, and identified by ^{1}H, ^{31}P NMR, and IR spectroscopy as well as by elemental analysis. Phosphordiamidates **6** had ^{31}P NMR signals in the range of δ 4–7.

The shorter reaction times (1–7 hours) required for the Beckmann rearrangement of hydroxyiminobenzylphosphonamidates as compared to those of the corresponding phosphonates (several days) and phosphinates (≈30 hours) [3e] reflect the increased migratory aptitude of the methoxyaminophosphinyl group as compared with those of the dimethoxyphosphinyl and methoxyphenylphosphinyl groups [11].

Following the discovery of this method for the



(*E*)-**5** **6**

a, $R^1 = R^2$ = Et; **b**, $R^1,R^2 = (CH_2)_4$; **c**, $R^1,R^2 = (CH_2)_5$;
d, R^1 = H, R^2 = 2-Pr; **e**, R^1 = H, R^2 = t-Bu.

SCHEME 4

preparation of phosphordiamidates, it occurred to us that subjecting hydroxyiminoalkylphosphonamidates derived from amino acids [12] to such Beckmann rearrangement could lead to new, modified peptide "transition-state analogs" [13] and thus to new biologically active compounds. We will continue exploring this methodology toward such a goal.

X-ray Crystallography

The molecular structure of **5b** is depicted in Figure 1, which clearly shows that the compound has (*E*) stereochemistry. The bond lengths and bond angles (see Tables S3 and S4 in the supplementary material) all fall into the range of values that might be expected for such compounds.

EXPERIMENTAL

General. Elemental analyses were performed by the Analytical Laboratories of the Hebrew University, Givat-Ram, Jerusalem. Infrared spectra were determined on an Analect FTIR spectrometer. NMR spectra were recorded on a Varian VXR-300S instrument. Chemical shifts are reported as δ values downfield from TMS or TSP as internal standards in ^{1}H spectra and from 85% H_3PO_4 as external standard in ^{31}P spectra. Positive chemical shifts are at low field with respect to the standard.

General Procedure for the Preparation of Methyl α-Hydroxyiminobenzylphosphonamidates (**5a–d**). Thionyl chloride (1.1 equiv.), freshly distilled, was added dropwise to a solution of methyl hydrogen benzoylphosphonate (1, X = OH, R′ = Me) in dry dichloromethane. After the reaction mixture had been stirred for 3 hours at ambient temperature, the solvent was evaporated to afford methyl benzoylphosphonochloridate (**3**) as an oil (^{31}P NMR δ = 14.4, *q*), which was used without further purification. To this phosphonochloridate dissolved in dichloromethane (30 cm^3) was added dropwise a solution of 1.8 equiv. of secondary amine (freshly distilled from potassium hydroxide) or a mixture of 0.9 equiv. of primary amine and 1.2 equiv. of pyridine, dissolved in freshly distilled dichloromethane. The mixture was allowed to stand at ambient temperature for 10 minutes and was evaporated to dryness. The residue containing the crude benzoylphosphonamidate was dissolved in dry isopropyl alcohol, 1.6 equiv. of pyridine and 1.6 equiv. of hydroxylamine hydrochloride were added, and the mixture was stirred overnight. After evaporation of the alcohol in vacuo, the residue was dissolved in water, the solution acidified to pH = 5–6, and the product extracted with three portions of ethyl acetate. The organic layer was dried with magnesium sulfate, and the solvent was evaporated. The residual product was purified either by chromatography or by direct crystallization.

Methyl (E)-α-Hydroxyiminobenzyl-N,N-diethylaminephosphinate (**5a**). Yield 33%, mp 115–116°C, from ethyl acetate. IR: 1218, 1200, 1044, 1021 cm^{-1}. NMR ($CDCl_3$): δ_H: 7.46 (2H, m), 7.29 (3H, m), 3.65 (3H, d, J = 11 Hz), 2.96 (4H, m), 0.90 (6H, t, J = 7.2 Hz); δ_P: 15.2 (appears as octet with apparent J = 10.9 Hz). Anal. calcd for $C_{12}H_{19}N_2O_3P$: C, 53.33; H, 7.03; N, 10.37. Found: C, 53.57; H, 7.30; N, 10.38.

Methyl (E)-α-Hydroxyiminobenzyl-1-pyrrolidinylphosphinate (**5b**). Yield 39%, mp 156–158°C, from water or ethyl acetate. IR: 1218, 1195, 1038, 1028 cm^{-1}. NMR ($CDCl_3$): δ_H, 7.48 (2H, m), 7.29 (3H, m),

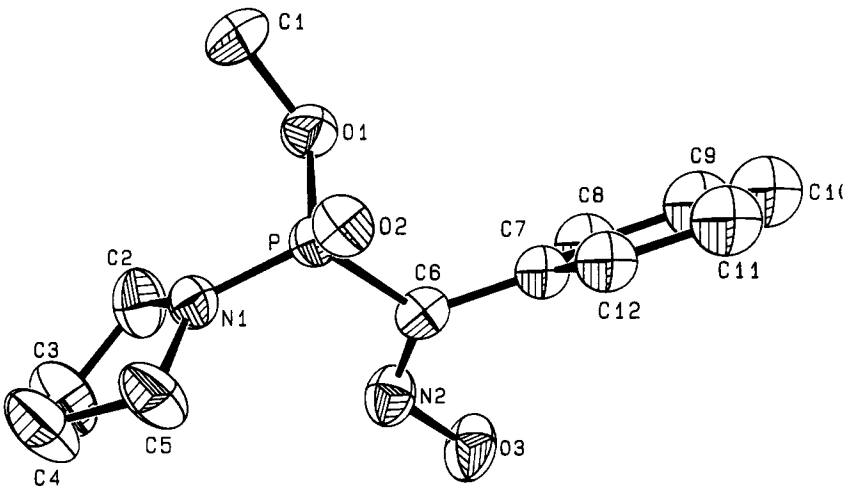


FIGURE 1

3.65 (3H, d, J = 12 Hz), 3.04 (4H, m), 1.64 (4H, m); δ_P, 13.2 (seen as octet). Anal. calcd for $C_{12}H_{17}N_2O_3P$: C, 53.73; H, 6.34; N, 10.45. Found: C, 53.45; H, 6.54; N, 10.42.

Methyl (E)-α-Hydroxyiminobenzyl-1-piperidinylphosphinate (**5c**). Yield 42%, mp 123°C, from $CHCl_3$/hexane. IR: 1205, 1080, 1041 cm^{-1}; NMR ($CDCl_3$): δ_H 7.52 (2H, m), 7.32 (3H, m), 3.65 (3H, d, J = 11 Hz), 2.93 (4H, m), 1.4 (6H, m); δ_P 13.3 (m). Anal. calcd for $C_{13}H_{19}N_2O_3P$: C, 55.32; H, 6.74; N, 9.92. Found: C, 55.18; H, 7.02; N, 9.91.

Methyl-α-hydroxyiminobenzyl-N-isopropylphosphonoamidate (**5d**). Yield, 40%, mp 105–106°C, from AcOEt/Et_2O. IR, 1653 cm^{-1}; NMR ($CDCl_3$): δ_H 7.58 (2H, m), 7.38 (3H, m), 3.67 (3H, d, J = 11 Hz), 3.42 (1H, m), 2.82 (1H, seen as triplet), 1.07 (6H, m); δ_P: 13.9 (seen as sextet, with apparent J = 10.8 Hz). Anal. calcd for $C_{11}H_{17}N_2O_3P$: C, 51.56; H, 6.64; N, 10.93. Found: C, 51.40; H, 6.91; N, 10.91.

Methyl-α-hydroxyiminobenzyl-N-t-butylphosphonoamidate (**5e**). Yield 34%, mp 127–129°C from AcOEt. IR 1651 cm^{-1}; NMR ($CDCl_3$) δ_H 7.55 (2H, m), 7.36 (3H, m), 3.62 (3H, m), 3.21 (1H, m), 1.27 (9H, s); δ_P 12.85 (seen as quintet). Anal. calcd for $C_{12}H_{19}N_2O_3P$: C, 53.33; H, 7.03; N, 10.37. Found: C, 53.48; H, 7.33; N, 10.43.

General Procedure for the Preparation of Phosphordiamidates **6** *by Beckmann Rearrangement of α-Hydroxyiminobenzylphosphonamidates* **5**. Toluene solutions of α-hydroxyiminoalkylphosphonamidates were boiled for the times specified. The progress of the reaction could be monitored by ^{31}P NMR spectroscopy. The products, which were obtained in yields of >90%, were isolated by evaporation of the solvent and purified by crystallization from water or by chromatography on silica.

Methyl N-benzoyl-N',N'-diethylphosphordiamidate (**6a**). The rearrangement was complete in 45 minutes. Mp 145–147°C. IR, 1735, 1665, 1270 cm^{-1}; NMR ($CDCl_3$) δ_H: 7.87 (2H), 7.48 (1H, m), 7.38 (2H, m), 3.67 (3H, d, J = 12 Hz), 3.19 (4H, m), 1.06 (6H, t, J = 7 Hz); δ_P, 5.5 (seen as octet). Anal. calcd for $C_{12}H_{19}N_2O_3P$: C, 53.33; H, 7.03; N, 10.37. Found: C, 52.90; H, 6.93; N, 10.12.

Methyl Benzamido Pyrrolidinylphosphinate (**6b**). Time required for completion of the rearrangement: 7 hours. Mp 118–119°C. Spectra, IR: 1738, 1669, 1273 cm^{-1}; NMR, ($CDCl_3$) δ_H 7.93 (m, 2H), 7.56 (m, 1H), 7.42 (m, 2H), 3.76 (d, 3H, J = 12 Hz), 3.18 (m, 4H), 1.81 (m, 4H). δ_P: 5.9. Anal. calcd for $C_{12}H_{17}N_2O_3P$: C, 53.73; H, 6.80; N, 10.01. Found: C, 54.02; H, 6.34; N, 10.45.

Methyl Benzamido Piperidinylphosphinate (**6c**). Time required for completion of the rearrangement: 6 hours. Mp 141–142°C, Spectra: NMR δ_H: 8.4 (m, 1H), 7.98 (m, 2H), 7.50 (m, 3H), 3.75 (3H, d, J = 12 Hz), 3.22 (m, 4H), 1.56 (m, 6H). δ_P: 6.5 (m). Anal. calcd for $C_{13}H_{19}N_2O_3P$: C, 55.32; H, 6.74; N, 9.92. Found: C, 55.27; H, 6.85; N, 9.97.

Methyl N-Benzoyl-N'-isopropylphosphordiamidate (**6d**). Time required for completion of the rearrangement: 5 hours. Mp 160–162°C. Spectra, IR: 3340, 1736, 1670, 1269 cm^{-1}; NMR ($CDCl_3$) δ_H 8.05 (m, 2H), 7.52 (m, 3H), 3.75 (3H, d, J = 12 Hz), 3.52 (1H, m), 1.22 (3H, d, J = 6 Hz), 1.14 (3H, d, J = 6 Hz); δ_P: 5.9 (m). Anal. calcd for $C_{11}H_{17}N_2O_3P$: C, 51.56; H, 6.64. Found: C, 51.23; H, 6.37.

Methyl N-Benzoyl-N'-t-butylphosphordiamidate (**6e**). Time required for completion of the rearrangement: 5 hours. Mp 140–142°C. Spectra: NMR (CDCl3) δ_H 8.1 (m, 1H), 7.55 (m, 3H), 3.73 (3H, d, 12 Hz), 2.18 (s, 1H), 1.39 (s, 9H); δ_P: 3.9 (m). Anal. calcd for $C_{12}H_{19}N_2O_3P$: C, 53.33; H, 7.04. Found: C, 52.95; H, 7.19.

X-ray Crystallography of Methyl (E)-α-Hydroxyiminobenzyl-1-Pyrrolidinylphosphinate

Data Collection and Processing. The crystal was mounted on a glass fiber using epoxy resin. The data were collected on a Philips PW 1100 four-circle com-

TABLE 1 Crystallographic Data for Compound (**5b**)

Elem. formula	$C_{12}H_{17}N_2O_3P$
Mol. weight	268.25
Space group	Cc
a (Å)	11.370 (2)
b (Å)	11.915 (2)
c (Å)	10.716 (1)
β (°)	104.96 (1)
V (Å^3)	1402 (1)
D (calc.) (g cm^{-3})	1.27
Z	4
μ (cm^{-1})	1.56
Range of 2Θ (°)	4 > 45
No. of unique data	1167
No. of data with $F_o2 > 3\sigma(F_o2)$	1125
R_1^a	0.0395
R_2^a	0.0392

$R_1 = |\Sigma|F_o| - |F_c||/\Sigma|F_o|$; $R_2 = [\Sigma w(|F_o| - |F_c|)^2/\Sigma|F_o|^2]^{1/2}$.

puter-controlled diffractometer. Mo-Kα (λ = 0.71069 A°) radiation with a graphite crystal monochromator in the incident beam was used. Unit cell parameters were obtained by a least-squares fit of 25 high-angle reflections ($13° < \Theta < 26°$). The data were collected in the Θ–2Θ scan mode. The scan width, ω, for each reflection was 1° with a scan time of 20 seconds. Background measurements were made at both limits of each scan. Lorenz and polarization corrections were applied. No absorption or intensity correction was applied. Other information pertinent to data collection and processing is given in Table 1.

Structure Analysis and Refinement. The coordinates of the phosphorus atom were obtained by the direct methods program SHELX-86. The positions of the remaining nonhydrogen atoms were obtained from subsequent refinements and difference Fourier maps. Anisotropic thermal parameters were used for all nonhydrogen atoms. The hydrogen atoms were placed in their calculated positions and were constrained to "ride" on the carbon atoms. The aromatic hydrogens were refined using a common thermal parameter.

Using SHELX-76 [14], full matrix, least-squares refinements were carried out on 137 variables. The refinement, using unit weights, converged to reasonable discrepancy factors that are listed in Table 1. The supplementary material, which may be obtained by written request to the senior author, contains the tables of atomic coordinates (S1) hydrogen atom parameters (S2), bond distances (S3), bond angles (S4), thermal parameters (S5), and observed and calculated structure factors (S6). Figure 1 depicts the geometry and atom labeling for compound **5b**.

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[11] One of the reviewers raised the alternative possibility that the present reaction proceeds through an "abnormal" Beckmann reaction pathway involving dissociation of molecules **5** to PhCN and the metaphosphoramidate species, $MeOP(=O)=N^+R_2$ (for **5a–c**) and $MeOP(=O)=NR$ (for **5d–e**), followed by recombination of these two species, in analogy to the Ritter reaction. We will investigate this possibility in the future. We thank this reviewer for his suggestion.

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