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Phosphorylation of Derivatives of β-Dialkyaminocrotonitriles with Phosphorus(III) Halides

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ABSTRACT: *The reaction of β-dialkylaminocrotontriles with phosphorus(III) halides has been investigated. The basicity of the dialkylamino group influences the phosphorylation markedly, with pyrrolidine being the amine of choice. It was found that a solvent and the ratio of triethylamine play a significant role in phosphorylation. Although chloro- and dichlorophosphine derivatives proved impossible to separate as individual compounds; their solutions can be successfully used for further transformations.* © 2009 Wiley Periodicals, Inc. Heteroatom Chem 20:194–201, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20532

INTRODUCTION

For over half a century, the interest in enamines has not been abated. Many reviews and books have appeared in this time. The most complete review on enamines persuasively shows them as C-nucleophiles that can be used in numerous reactions with various electrophiles [1]. At the same time, phosphorus halides, powerful electrophiles, are widely used in organophosphorus chemistry in electrophilic substitution reactions with many compounds embedding the double C=C bond bearing electron-releasing substituents, for example, alkylvinylether [2] and *N*,*N*-dialkylhydrazones [3]. In our previous works, we have shown that enamines can also be subjected to the reactions with phosphorus halides and the deactivated enamines were demonstrated to be readily phosphorylated with phosphorus(III) halides affording stable derivatives [4]. Contrary to that the linear enamines such as 2-morpholinoprop-1-ene are easily phosphorylated with phosphorus trichloride, affording dichlorophosphine derivatives that upon further treatment with triethylamine undergo C—P bond cleavage [5]. In addition, 2-methylpropenylidenebisdimethylamine behaves in the reaction with phosphorus trichloride analogously [6]. An analysis of the literature data showed that deactivated enamines are the most suitable substrates for these reactions. Two tendencies should be taken into account. Introducing electron-withdrawing groups into the conjugation chain or obstructing the conjugation between a dialkylamino group and a double bond makes these enamines less nucleophilic, so that a smaller set of phosphorus electrophiles would react with them. The advantage of the decreased activity of the enamine would be stronger C—P bond at halogen and dihalogenphosphine derivatives so that in the reactions with various nucleophiles C—P bond might remain intact. One of the ways to decrease enamine reactivity is the introduction

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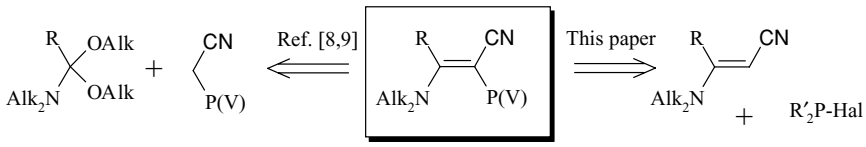


FIGURE 1

of an electron-withdrawing group at the β-position of enamines. Owing to the extended conjugation chain, these enamines are remarkably deactivated. Thus, derivatives of 3-dialkylaminocrotonic acid are the simplest stabilized push–pull enamines. Previously, these enamines were shown to react with diphenylchlorophosphine [7].

Phosphorylated derivatives of these enamines could be prepared by the condensation of activated methylene compounds with lactam acetals [8] or electrophilic thioiminium intermediates [9] (see Fig. 1).

As the starting enamines are widely used in heterocyclic synthesis, one can expect that their phosphorylated derivatives can also be used in similar types of transformation, affording phosphorylated heterocycles or phosphaheterocycles as it has been already demonstrated [10].

RESULTS AND DISCUSSION

Continuing our research on the phosphorylation of enamines with phosphorus(III) halides, we investigated reactions of push–pull enamines, namely **1** both pyrrolidine and morpholine derivatives with various phosphorus(III) halides.

We have started our research with the reaction of phosphorus trichloride with these enamines in the presence of triethylamine in various solvents (Scheme 1).

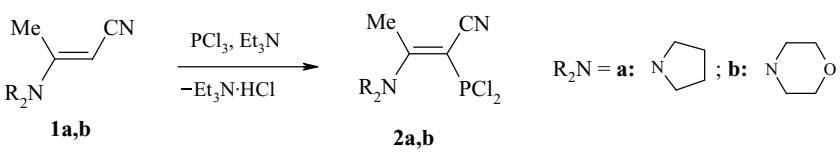
The phosphorylation of enamine **1a** with phosphorus trichloride was studied in dichloromethane at room temperature with 1:1 molar ratio of the reagents changing amount of triethylamine from 1 to 2 equiv. It should be noted that the amount of triethylamine has a remarkable effect on the reaction. One equivalent of triethylamine is not sufficient to convert all phosphorus trichloride into dichlorophosphine 2**a**. In this case, in 30 min in the reaction mixture the ratio of major isomer of dichlorophosphine to phosphorus trichloride was 1: 0.28, but in 6 days it changed to 1.78:1. Excess of triethylamine, 1.3–2 equiv, helps to consume the phosphorus trichloride completely, but on prolonged standing its traces reappear in the reaction mixture. We have found that it would be best to use 1.3 equivalents of triethylamine so that in 22 h all phosphorus trichloride is consumed and the isomers of dichlorophosphine **2** in 1:0.17 ratio formed. In almost every case, we registered a small admixture of an unidentified phosphorus product with $\delta_P = -8$.

It should be noted that almost an analogous pattern of phosphorylation was observed in benzene. In this case to convert all phosphorus trichloride, 1.3 equiv of triethylamine is also required. After 15–20 h, the reaction mixture contains two isomers of dichlorophosphine **2a** in 1:0.17 ratio as well as small amount of an unidentified phosphorus product with $\delta_P = -8$.

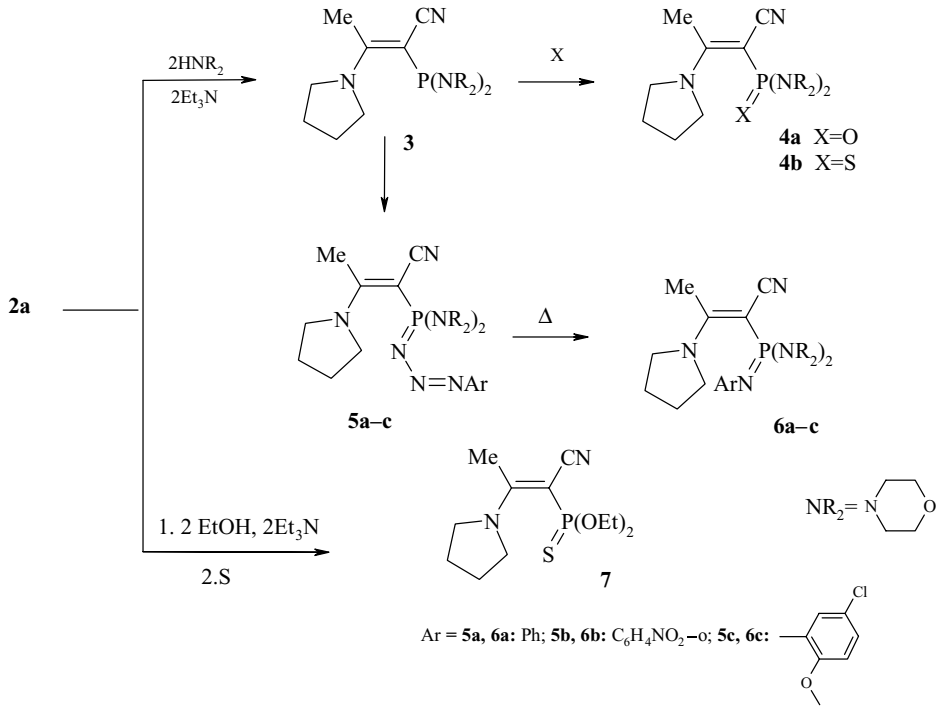
A decrease in the basicity of dialkylamine from pyrrolidine to morpholine considerably deteriorated the reaction, so that phosphorylation of enamine **1b** proceeded nonregioselectively, affording many by-products. In benzene, even the use of 1.5 equiv of triethylamine is not sufficient to convert all phosphorus trichloride.

Our attempt to separate dichlorophosphines **2** as individual compounds failed. After removing solvents, a set of unidentifiable products are present in the residue. Thus, we recommend further use of dichlorophosphine **2a** without separation and purification.

As pyrrolidine enamine **1a** reacted much better with phosphorus trichloride when compared with morpholine derivatives **1b**, the former was selected for further investigations. A solution of



SCHEME 1



SCHEME 2

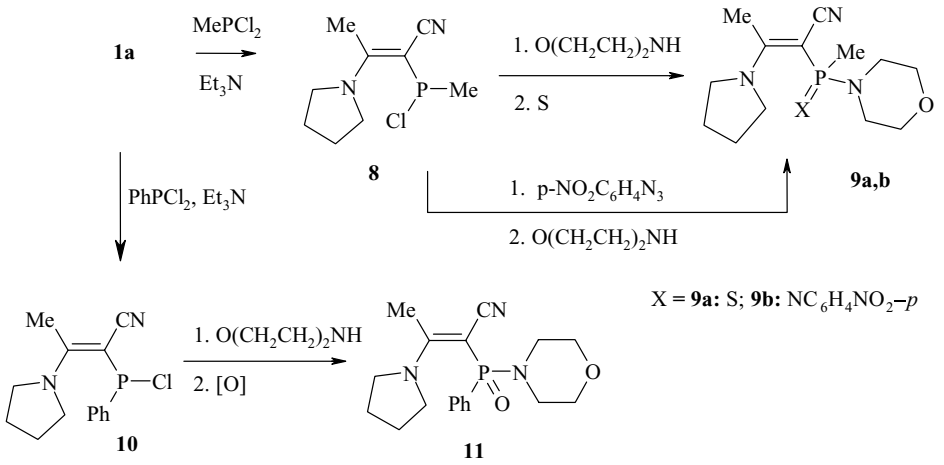
dichlorophosphine **2a** prepared by an optimized procedure in dichloromethane was used for further transformations with secondary amines and alcohols.

Compound **3** was prepared by the reaction of dichlorophosphine **2a** with 2 equiv of morpholine in the presence of 2 equiv of triethylamine. The behavior of phosphonite **3** in oxidation reactions is quite typical for this class of compounds. Thus, it was easily oxidized with hydrogen peroxide and sulfur into phosphonates **4a** and **4b**, respectively (see Scheme 2). It also reacted readily with a set of arylazides, affording phosphazides **5a–c** that were converted into the corresponding iminophosphonates **6a–c**. The constitution of compounds **5c** and **6c** was confirmed by the X-ray analysis. It should be noted that both the compounds are E-isomers, where pyrrolidine and nitrile groups are placed on the same side of the double bond. CCDC-675031 for **5c** and CCDC-675032 for **6c** contain all crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Thiophosphonate **7** was prepared without separating a trivalent phosphonite.

With the aim of substituting two and eventually three enamine residues at phosphorus, we have studied the phosphorylation of enamine **1a** with phosphorus trichloride in molar ratios 2:1 and 3:1 changing amount of triethylamine. Unfortunately in all cases, we failed to separate individual chlorophosphines or their derivatives. When phosphorylation was run in dichloromethane in the molar ratio enamine:phosphorus trichloride 2:1 with 2 equiv of triethylamine judging from ^{31}P NMR, it led to the formation of four products with $\delta_p = 168.1$, 163.3, 94.4, and −7.4 in the ratio 1:0.18:0.19:0.06. Signals $\delta_p = 168.1$, 163.3 can be attributed to isomers of dichlorophosphine **2a**; signal $\delta_p = 94.4$ may tentatively be assigned to the targeted chlorophosphine bearing two enamine residues. Unfortunately with time, the reaction mixture slowly decomposes leading to the appearance of phosphorus trichloride and decreasing intensities of other signals. The increase in the molar ratio of triethylamine from 2.5 to 3 equiv does not change the situation markedly. We also failed to introduce three enamine residues. With the molar ratio enamine:phosphorus trichloride 3:1 with 3 equiv of triethylamine, the reaction mixture contains low-intensity signals, which slowly degrade.

From phosphorus trichloride to dichlorophosphines, a pattern of phosphorylation remains analogous. The phosphorylation of enamine **1a** was studied in dichloromethane varying the amount of triethylamine from 1 to 2 equiv. In all cases, in 30 min all phenyldichlorophosphine was consumed, affording two isomers of chlorophosphine **10** in the



SCHEME 3

ratio 1:0.16 ($\delta_p = 94.1$ and 87.5). When 1 equiv of triethylamine is used in 8 h phenyldichlorophosphine reappears in the reaction mixture. When more than 1.3 equiv of triethylamine is used, an admixtures with signals −14.1 and −20.7 appear in the reaction mixture, and their intensities grow on standing. Thus the optimum amount of triethylamine is 1.1 equiv. In this case, the reaction runs cleanly, affording two isomers of chlorophosphine **10** in the ratio 1:0.16. Chlorophosphine **10** is a typical of its class, and as an example it was transformed into phosphinate **11** by reacting with morpholine followed by the oxidation with hydrogen peroxide (see Scheme 3).

Both in dichloromethane and benzene, the phosphorylation of enamine **1a** with methyldichlorophosphine also runs cleanly, but requires slight excess of triethylamine: 1.2–1.3 equiv. Chlorophosphine **8** readily reacts with morpholine and then with sulfur, affording thiophosphinate **9a**. It is also sufficiently nucleophilic to react with arylazides. Thus iminophosphinate **9b** was prepared by the oxidation of chlorophosphine **8** with *p*-nitrophenylazide followed by the reaction with morpholine.

CONCLUSION

Although the phosphorylation of β-dialkyaminocrotonitriles with phosphorus(III) halides requires fine-tuning of the reaction conditions, it can be used for synthesizing various phosphorus derivatives. It was shown that one enamine residue can be introduced at phosphorus halides that can be further transformed into stable three- and pentavalent derivatives. The basicity of the dialkylamine in the enamines and the amount of a base play a significant role.

EXPERIMENTAL

General

All procedures with compounds sensitive to hydrolysis and oxidation were carried out in an atmosphere of dry argon. All solvents were purified and dried by standard methods. NMR spectra were recorded on a Varian VXR-300 spectrometer: ^1H and ^{13}C NMR (300 and 75.4 MHz, respectively), C_6D_6 and $CDCl_3$ as solvents with TMS as an internal standard; ^{31}P (121 MHz) with 85% H_3PO_4 as an external standard, in $CHCl_3$. IR spectra were recorded on a Nexus-470 spectrometer for samples in KBr disks. Mass spectra were obtained on VG 70–70EQ, VG Analytical (FAB) for substances **5a–c** or a MX-1321 instrument (EI, 70 eV) by a direct inlet for other substances. Microanalyses were performed in the Microanalytical Laboratory of the Institute of Organic Chemistry, National Academy of Sciences of Ukraine. Melting points are uncorrected. Yields refer to pure isolated products. The starting enamines were prepared according to the literature [11].

2-Dichlorophosphanyl-3-pyrrolidin-1-yl-but-2-enenitrile **2a**

Solution in Dichloromethane. To a solution of phosphorus trichloride (1.01 g, 7.3 mmol) in dichloromethane (10 mL), a mixture of enamine **1a** (1 g, 7.3 mmol) and triethylamine (0.96 g, 9.5 mmol) in dichloromethane (10 mL) was added dropwise at temperature −20°C. The reaction mixture was allowed to warm to room temperature. After 20–22 h judging by ^{31}P NMR, the reaction mixture contains two isomers of dichlorophosphine **2a**, $\delta_p = 168$ and 163 in the ratio 1:0.17. The reaction mixture

contains an unidentified product with $\delta_P = -8$ ca. 4%–5%.

In benzene, the reaction was run analogously at 10°C. After 20 h, the reaction mixture can be used for further transformations.

2-(Dimorpholin-4-yl-phosphino)-3-pyrrolidin-1-yl-but-2-enenitrile **3**

To a stirred solution of PCl_3 (1.01 g, 7.3 mmol) in benzene (20 mL) under dry argon, a solution of enamine **1a** (1 g, 7.3 mmol) and Et_3N (0.96 g, 9.5 mmol) in benzene (20 mL) was added dropwise. After 20 h, a solution of morpholine (1.28 g, 14.6 mmol) and Et_3N (1.48 g, 14.6 mmol) in benzene (20 mL) was added dropwise. After 1 h, the reaction mixture was washed with water. The organic phase was separated, dried (Na_2SO_4), and evaporated in vacuo. The residue is brown oil (1.4 g, 57%). ^{31}P NMR: $\delta = 97.7$. ^1H NMR ($CDCl_3$): $\delta = 1.82$–1.92 (m, 4H, CH_2), 2.14 (s, 3H, CH_3), 2.91–3.06 (m, 8H, $PNCH_2$), 3.52–3.67 (m, 12H, OCH_2(8H), NCH_2). ^{13}C NMR ($CDCl_3$): $\delta = 19.8$ ($^3J_{CP} = 40$ Hz, C(4)), 25.3 (CH_2), 48.1 ($^2J_{CP} = 13.8$ Hz, $PNCH_2$), 50.9 (NCH_2), 67.9 ($^3J_{CP} = 7.5$ Hz, OCH_2), 70.3 ($^1J_{CP} = 18.9$ Hz, C(2)), 123.0 (CN), 163.8 ($^2J_{CP} = 36.5$ Hz, C(3)). MS, *m/z* (%): 338 (M^+,11), 252 (100), 203 (76), 165 (91), 136 (28), 118 (80), 88 (25), 68 (55), 42 (31). Anal. Calcd for $C_{16}H_{27}N_4O_2P$: C 56.79, H 8.04, N 16.56, P 9.15. Found: C 56.33, H 8.05, N 16.29, P 8.79.

2-(Dimorpholin-4-yl-phosphoryl)-3-pyrrolidin-1-yl-but-2-enenitrile **4a**

To a stirred solution of **3a** (0.5 g, 1.5 mmol) in benzene (30 mL), finely powdered $H_2O_2 \cdot H_2NC(O)NH_2$ was added. After 4 h, the reaction mixture was washed with water. The organic phase was separated, dried (Na_2SO_4), and evaporated in vacuo. The residue is light brown oil (0.32 g, 61%). ^{31}P NMR: $\delta = 28.3$. ^1H NMR ($CDCl_3$): $\delta = 1.93$–2.02 (m, 4H, CH_2), 2.42 (s, 3H, CH_3), 3.18–3.31 (m, 8H, $PNCH_2$), 3.44–3.62 (bm, 2H, NCH_2), 3.69 (t, $^3J_{HH} = 3.9$, 8H, OCH_2), 3.75–3.94 (bm, 2H, NCH_2). ^{13}C NMR ($CDCl_3$): $\delta = 20.9$ (C(4)), 24.8 (CH_2), 25.7 (CH_2), 44.9 ($PNCH_2$), 51.1 (NCH_2), 52.4 (NCH_2), 60.4 ($^1J_{CP} = 143$ Hz, C(2)), 67.2 ($^3J_{CP} = 5$ Hz, OCH_2), 121.3 ($^2J_{CP} = 11$ Hz, CN), 168.8 ($^2J_{CP} = 16.3$ Hz, C(3)). MS, *m/z* (%): 354 (M^+, 8), 269 (30), 184 (45), 183 (100), 136 (79), 108 (13), 88 (25), 86 (24), 68 (22), 42 (17). Anal. Calcd for $C_{16}H_{27}N_4O_3P$: C 54.23, H 7.68, N 15.81, P 8.74. Found: C 54.10, H 7.71, N 15.52, P 8.39.

2-(Dimorpholin-4-yl-phosphorothioyl)-3-pyrrolidin-1-yl-but-2-enenitrile **4b**

To a stirred solution of PCl_3 (1.01 g, 7.3 mmol) in benzene (20 mL) under dry argon, a solution of enamine **1a** (1 g, 7.3 mmol) and Et_3N (0.96 g, 9.5 mmol) in benzene (20 mL) was added dropwise. After 20 h, to the stirred solution obtained, a solution of morpholine (1.28 g, 14.6 mmol) and Et_3N (1.48 g, 14.6 mmol) in benzene (20 mL) was added dropwise. After 1 h, finely ground sulfur (0.119 g, 3.7 mmol) was added. The reaction mixture was stirred until complete dissolution of the sulfur in 4 h. The reaction mixture was washed with water. The organic phase was separated, dried (Na_2SO_4), and evaporated in vacuo. The residue was crystallized from *i*-PrOH. Brown solid (1.48 g, 56%). Mp 140–142°C. ^{31}P NMR: $\delta = 74.9$. ^1H NMR ($CDCl_3$): $\delta = 1.98$ (bs, 4H, CH_2), 2.48 (s, 3H, CH_3), 3.2 (m, 8H, $PNCH_2$), 3.71 (m, 12H, OCH_2 (8H), NCH_2). ^{13}C NMR ($CDCl_3$): $\delta = 22.3$ (C(4)), 24.8 (CH_2), 25.7 (CH_2), 45.5 ($PNCH_2$), 51.2 (NCH_2), 53.0 (NCH_2), 66.1 ($^1J_{CP} = 154$ Hz, C(2)), 66.9 ($^3J_{CP} = 7.5$ Hz, OCH_2), 121.1 ($^2J_{CP} = 8.8$ Hz, CN), 169.1 ($^2J_{CP} = 20.1$ Hz, C(3)). MS, *m/z* (%): 370 (M^+, 29), 285 (53), 252 (99), 199 (45), 197 (47), 165 (57), 136 (93), 86 (100), 70 (34), 56 (33), 43 (36). Anal. Calcd for $C_{16}H_{27}N_4O_2PS$: C 51.88, H 7.35, N 15.12, P 8.36, S 8.66. Found: C 51.57, H 7.14, N 14.95, P 8.01, S 8.16.

General Procedures for Phosphotriazenes **5**

To a stirred solution of PCl_3 (1.01 g, 7.3 mmol) in benzene (20 mL) under dry argon, a solution of enamine **1a** (1 g, 7.3 mmol) and Et_3N (0.96 g, 9.5 mmol) in benzene (20 mL) was added dropwise. After 20 h, a solution of morpholine (1.28 g, 14.6 mmol) and Et_3N (1.48 g, 14.6 mmol) in benzene (20 mL) was added dropwise. After 1 h, the reaction mixture was washed with water. The organic phase was separated and dried (Na_2SO_4). An appropriate arylazide was added, and the reaction mixture was left to stand at room temperature overnight. The precipitate formed was filtered, affording the targeted compound **5**.

(2-[Dimorpholin-4-yl(3-phenyltriaz-2-enylidene)-phosphoranyl]-3-pyrrolidin-1-yl-but-2-enenitrile **5a**. Yellow solid (2.17 g, 65%). Mp 182–186°C. ^{31}P NMR: $\delta = 44.7$. ^1H NMR ($CDCl_3$): $\delta = 1.94$–2.05 (bm, 4H, CH_2), 2.36 (s, 3H), 3.32–3.41 (m, 8H, $PNCH_2$), 3.45–3.55 (bm, 2H, NCH_2), 3.67–3.79 (bm, 8H, OCH_2), 3.86–3.97 (bm, 2H, NCH_2), 7.16 (t, $^3J_{HH} = 6.9$ Hz,

1H, 4-Ph), 7.32 (t, $^3J_{HH} = 6.9$ Hz, 2H, 3-Ph), 7.45 (d, $^3J_{HH} = 6.9$ Hz, 2H, 2-Ph). ^{13}C NMR ($CDCl_3$): $\delta = 23.1$ (C(4)), 24.6 (CH_2), 25.6 (CH_2), 45.3 ($PNCH_2$), 51.4 (NCH_2), 53.0 (NCH_2), 56.5 ($^1J_{CP} = 173$ Hz, C(2)), 66.8 ($^3J_{CP} = 5.2$ Hz, OCH_2), 120.5 (C(2′)), 125.5 (C(4′)), 128.6 (C(3′)), 151.6 (C(1′)), 169.6 ($^2J_{CP} = 16$ Hz, C(3)). MS FAB, *m/z* (%): 458 (M + 1, 78), 354 (53). 338 (32), 252 (100), 204 (17), 165 (27), 154 (46), 136 (33), 105 (21), 75 (26). Anal. Calcd for $C_{22}H_{32}N_7O_2P$: C 57.76, H 7.05, N 21.43, P 6.77. Found: C 57.42, H 6.93, N 21.12, P 6.41.

2-{Dimorpholin-4-yl[3-(2-nitrophenyl)triaz-2-enylidene]phosphoranyl}-3-pyrrolidin-1-yl-but-2-enenitrile **5b**. Yellow solid (1.65 g, 45%). Mp 160–164°C. ^{31}P NMR: $\delta = 44.3$. ^{1}H NMR ($CDCl_3$): $\delta = 1.95$–2.11 (m, 4H, CH_2), 2.28 (s, 3H), 3.22–3.41 (m, 8H, $PNCH_2$), 3.59 (t, $^3J_{HH} = 6.6$ Hz, 2H, NCH_2), 3.63–3.75 (m, 8H, OCH_2), 3.97 (t, $^3J_{HH} = 6.6$ Hz, 2H, NCH_2), 7.15 (t, $^3J_{HH} = 6.6$ Hz, 1H, 4-Ph), 7.43 (d, $^3J_{HH} = 6.6$ Hz, 1H, 6-Ph), 7.46–7.52 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$): $\delta = 22.8$ (C(4)), 24.7 (CH_2), 25.7 (CH_2), 45.2 ($PNCH_2$), 51.7 (NCH_2), 53.5 (NCH_2), 56.0 ($^1J_{CP} = 166$ Hz, C(2)), 66.8 ($^3J_{CP} = 5$ Hz, OCH_2), 120.6 ($^2J_{CP} = 8.8$ Hz, CN), 123.7, 124.4, 125.2, 131.6, 143.2 (C(1′)), 145.2 (C(2′)), 170.2 ($^2J_{CP} = 18.9$ Hz, C(3)). MS FAB, *m/z* (%): 503 (M + 1, 72), 354 (23), 338 (41), 252 (100), 204 (16), 165 (24), 154 (42), 136 (37). Anal. Calcd for $C_{22}H_{31}N_8O_4P$: C 52.58, H 6.22, N 22.30, P 6.16. Found: C 52.42, H 6.29, N 22.48, P 6.01.

2-[[3-(5-Chloro-2-methoxyphenyl)triaz-2-enylidene](dimorpholin-4-yl)phosphoranyl]-3-pyrrolidin-1-yl-but-2-enenitrile **5c**. Orange solid (1.4 g, 37%). Mp 145–147°C. ^{31}P NMR: $\delta = 44.3$. ^{1}H NMR: $\delta = 1.96$–2.14 (m, 4H, CH_2), 2.25 (s, 3H), 3.19–3.40 (m, 8H, $PNCH_2$), 3.54 (t, $^3J_{HH} = 6.9$ Hz, 2H, NCH_2), 3.65–3.75 (m, 8H, OCH_2), 3.86 (s, 1H, OCH_3), 3.94 (t, $^3J_{HH} = 6.9$ Hz, 2H, NCH_2), 6.85 (d, $^3J_{HH} = 8.7$ Hz, 1H, 3-Ph), 7.06 (dd, $^3J_{HH} = 8.7$ Hz, $^4J_{HH} = 3.0$ Hz, 1H, 4-Ph), 7.15 (d, $^4J_{HH} = 3.0$ Hz, 1H, 6-Ph). ^{13}C NMR ($CDCl_3$): $\delta = 23.5$ (C(4)), 24.7 (CH_2), 25.7 (CH_2), 45.2 ($PNCH_2$), 51.5 (NCH_2), 53.2 (NCH_2), 55.9 (OCH_3), 56.3 ($^1J_{CP} = 162$ Hz, C(2)), 66.9 ($^3J_{CP} = 4.3$ Hz, OCH_2), 113.0 (C(3′)), 116.4 (C(4′)), 120.6 ($^2J_{CP} = 8.8$ Hz, CN), 125.2 (C(6′)), 125.4 (C(5′)), 142.4 (C(1′)), 152.2 (C(2′)), 169.8 ($^2J_{CP} = 17.6$ Hz, C(3)). MS FAB, *m/z* (%): 522 (M + 1, 25), 494 (56), 354 (19), 338 (32), 252 (100), 204 (17), 169 (13), 165 (32), 154 (13), 136 (16). Anal. Calcd for $C_{23}H_{33}ClN_7O_3P$: C 52.92, H 6.37, N 18.78, P 5.93. Found: C 52.64, H 6.43, N 18.60, P 5.73.

General Procedure for Preparation of Iminophosphonates **6**

Phosphothriazene **5** (0.5 g) was heated in vacuo to 170°C for 30 min, affording iminophosphonate **6**.

(2-[Dimorpholin-4-yl(phenyl)phosphorimidoyl]-3-pyrrolidin-1-yl-but-2-enenitrile **6a**. Brown solid (0.45 g, 95%). Mp 87–92°C. ^{31}P NMR: $\delta = 17.1$. ^{1}H NMR ($CDCl_3$): $\delta = 1.89$–2.03 (bm, 4H, CH_2), 2.26 (s, 3H), 3.21–3.34 (m, 8H, $PNCH_2$), 3.46–3.94 (bm, 12H, OCH_2 (8H), NCH_2 (4H)), 6.68 (t, $^3J_{HH} = 7.2$ Hz, 1H, 4-Ph), 6.75 (d, $^3J_{HH} = 7.2$ Hz, 2H, 2-Ph), 7.08 (t, $^3J_{HH} = 7.2$ Hz, 2H, 3-Ph). ^{13}C NMR ($DMSO_{d6}$): $\delta = 20.4$ (C(4)), 24.4 (CH_2), 25.4 (CH_2), 45.0 ($PNCH_2$), 50.7 (NCH_2), 52.4 (NCH_2), 58.4 ($^1J_{CP} = 171$ Hz, C(2)), 66.5 ($^3J_{CP} = 6$ Hz, OCH_2), 116.2 (C(4′)), 121.5 ($^2J_{CP} = 9.9$ Hz, CN), 122.4 ($^3J_{CP} = 16.4$ Hz, C(2′)), 128.5 (C(3′)), 150.9 (C(1′)), 168.8 ($^2J_{CP} = 15.6$ Hz, C(3)). MS, *m/z* (%): 429 (M^+, 22), 259 (100), 252 (63), 183 (28), 167 (54), 122 (52), 93 (66), 86 (52), 70 (17), 56 (16), 42 (14). Anal. Calcd for $C_{22}H_{32}N_5O_2P$: C 61.52, H 7.51, N 16.31, P 7.21. Found: C 61.55, H 7.43, N 16.19, P 6.92.

2-[Dimorpholin-4-yl(2-nitrophenyl)phosphorimidoyl]-3-pyrrolidin-1-yl-but-2-enenitrile **6b**. Brown solid (0.47 g, 93%). Mp 98–103°C. ^{31}P NMR: $\delta = 18.5$. ^{1}H NMR ($CDCl_3$): $\delta = 1.90$–2.06 (bm, 4H, CH_2), 2.19 (s, 3H), 3.18–3.38 (m, 8H, $PNCH_2$), 3.41–3.56 (bm, 2H, NCH_2), 3.58–3.79 (m, 8H, OCH_2), 3.81–3.95 (bm, 2H, NCH_2), 6.62 (t, $^3J_{HH} = 7.2$ Hz, 1H, 4-Ph), 6.79 (d, $^3J_{HH} = 7.2$ Hz, 1H, 6-Ph), 7.18 (td, $^3J_{HH} = 7.2$ Hz, $^4J_{HH} = 1.5$ Hz, 1H, 5-Ph), 7.58 (ddd, $^3J_{HH} = 7.2$ Hz, $^4J_{HH} = 1.5$ Hz, $^5J_{PH} = 1.5$ Hz, 1H, 3-Ph). ^{13}C NMR ($CDCl_3$): $\delta = 20.8$ (C(4)), 24.7 (CH_2), 25.8 (CH_2), 45.2 ($PNCH_2$), 51.2 (NCH_2), 52.8 (NCH_2), 58.9 ($^1J_{CP} = 167$ Hz, C(2)), 67.1 ($^3J_{CP} = 7.5$ Hz, OCH_2), 115.6 (C(4′)), 121.4 ($^2J_{CP} = 11.3$ Hz, CN), 124.5 ($^3J_{CP} = 8.8$ Hz, C(6′)), 124.8 (C(5′)), 132.2 (C(3′)), 144.2 ($^2J_{CP} = 22.6$ Hz, C(1′)), 144.9 ($^3J_{CP} = 8.8$ Hz, C(2′)), 169.0 ($^2J_{CP} = 16.3$ Hz, C(3)). MS, *m/z* (%): 474 (M^+, 1), 457 (7), 287 (57), 199 (64), 183 (52), 136 (100), 86 (85), 70 (66), 56 (58), 42 (42). Anal. Calcd for $C_{22}H_{31}N_6O_4P$: C 55.69, H 6.59, N 17.71, P 6.53. Found: C 55.75, H 6.40, N 17.32, P 6.35.

2-[(5-Chloro-2-methoxyphenyl)(dimorpholin-4-yl)-phosphorimidoyl]-3-pyrrolidin-1-yl-but-2-enenitrile **6c**. Yellow solid (0.45 g, 95%). Mp 75–80°C. ^{31}P NMR: $\delta = 17.0$. ^{1}H NMR: $\delta = 1.93$–2.05 (bm, 4H, CH_2), 2.11 (s, 3H), 3.21–3.37 (m, 8H, $PNCH_2$),

3.40 (m, 15H, NCH_2 (4H), OCH_2 (8H), OCH_3 (3H)), 6.60 (s, 2H), 6.66 (s, 1H). ^{13}C NMR ($CDCl_3$): $\delta = 21.4$ (C(4)), 25.3 (b, CH_2), 45.5 ($PNCH_2$), 52.0 (b, NCH_2), 55.7 (OCH_3), 60.2 ($^1J_{CP} = 173$ Hz, C(2)), 67.1 ($^3J_{CP} = 5$ Hz, OCH_2), 111.5 (C(3′)), 117.2 (C(4′)), 121.6 ($^2J_{CP} = 10.1$ Hz, CN), 123.0 ($^3J_{CP} = 8.8$ Hz, C(6′)), 125.0 (C(5′)), 141.2 (C(1′)), 152.2 ($^3J_{CP} = 16.3$ Hz, C(2′)), 169.0 ($^2J_{CP} = 15.1$ Hz, C(3)). MS, *m/z* (%): 493 (M^+, 17), 323 (68), 252 (100), 203 (15), 183 (26), 167 (76), 165 (54), 157 (43), 118 (21), 86 (44), 70 (14), 56 (26), 42 (15). Anal. Calcd for $C_{23}H_{33}ClN_5O_3P$: C 55.92, H 6.73, N 14.18, P 6.27. Found: C 55.61, H 6.44, N 14.01, P 6.03.

O,O-Diethyl 1-cyano-2-pyrrolidin-1-yl-prop-1-enylphosphonothioate **7**

To a stirred solution of PCl_3 (1.01 g, 7.3 mmol) in benzene (20 mL) under dry argon, a solution of enamine **1a** (1 g, 7.3 mmol) and Et_3N (0.96 g, 9.5 mmol) in benzene (20 mL) was added dropwise. After 20 h, a solution of ethanol (0.67 g, 14.6 mmol) and Et_3N (1.48 g, 14.6 mmol) in benzene (20 mL) was added dropwise, and in 20 min finely ground sulfur (0.23 g, 7.3 mmol) was added. After 1 h, the reaction mixture was washed with water. The organic phase was separated, dried (Na_2SO_4), and evaporated in vacuo; the residue was recrystallized from cyclohexane. Yellow solid (0.53 g, 25%). Mp 89–92°C. ^{31}P NMR: $\delta = 84.6$. ^1H NMR (C_6D_6): $\delta = 0.87$–1.03 (bm, 4H, CH_2), 1.2 (t, $^3J_{HH} = 7$ Hz, 6H, $POCH_2\underline{CH_3}$), 2.03 (s, 3H, CH_3), 2.19–2.35 (bm, 2H, NCH_2), 3.39–3.61 (bm, 2H, NCH_2), 4.12–4.38 (m, 4H, $PO\underline{CH_2}CH_3$). ^{13}C NMR ($CDCl_3$): $\delta = 16.0$ ($^3J_{CP} = 7.5$ Hz, $\overline{POCH_2CH_3}$), 21.2 (C(4)), 24.7 (CH_2), 25.8 (CH_2), 51.3 ($N\overline{CH_2}$), 52.2 (NCH_2), 63.1 ($^2J_{CP} = 6.3$ Hz, $PO\underline{CH_2}CH_3$), 69.9 ($^1J_{CP} = 184$ Hz, C(2)), 120.2 ($^2J_{CP} = \overline{11.3}$ Hz, CN), 166.6 ($^2J_{CP} = 18.9$ Hz, C(3)). MS, *m/z* (%): 288 (M^+, 49), 244 (32), 215 (100), 199 (19), 183 (22), 167 (12), 135 (43), 108 (10), 93 (16), 70 (41), 42 (20). Anal. Calcd for $C_{12}H_{21}N_2O_2PS$: C 49.99, H 7.34, N 9.72, P 10.74, S 11.12. Found: C 49.78, H 7.37, N 9.51, P 10.47, S 10.91.

2-[Methyl(morpholin-4-ylthiophosphoroyl]-3-pyrrolidin-1-yl-but-2-enenitrile **9a**

To a solution of $MePCl_2$ (1.71 g, 14.7 mmol) in dichloromethane (20 mL), a solution of enamine **1a** (2 g, 14.7 mmol) and Et_3N (1.93 g, 19 mmol) in dichloromethane (30 mL) was added dropwise with stirring. In 2 h, a solution of morpholine (1.28 g, 14.6 mmol) and Et_3N (1.48 g, 14.6 mmol) in dichloromethane (20 mL) was added. After 1 h, finely ground sulfur (0.47 g, 14.7 mmol) was added and stirred until complete dissolution, ca.12 h. The reaction mixture was washed with water and was dried over Na_2SO_4, and the solvent was evaporated in vacuo. The residue was recrystallized from *i*-PrOH. Yellow crystals. (1.8 g, 41%). Mp 130–135°C. ^{31}P NMR: $\delta = 63.8$. ^1H NMR ($CDCl_3$): $\delta = 1.95$ (3H, d, $^2J_{PH} = 13.2$, PCH_3), 2.03 (4H, bm, CH_2), 2.46 (3H, s, CH_3), 3.09–3.31 (4H, m, $PNCH_2$), 3.54 (2H, bm, NCH_2), 3.66 (4H, t, $^3J_{HH} = 4.2$, OCH_2), 3.90 (2H, bm, NCH_2). ^{13}C NMR ($CDCl_3$): $\delta = 20.8$ (C(4)), 21.5 ($^1J_{CP} = 78.1$, PCH_3), 24.4 (b, CH_2), 25.4 (b, CH_2), 44.5 ($PNCH_2$), 51.0 (b, NCH_2), 51.9 (b, NCH_2), 65.0 ($^1J_{CP} = 124$, C(2)), 67.0 ($^3J_{CP} = 8.1$, OCH_2), 121.4 ($^2J_{CP} = 13.8$, CN), 167.3 ($^2J_{CP} = 12.8$, C(3)). MS, *m/z* (%): 299 (M^+, 50), 214 (99), 213 (48), 199 (100), 181 (81), 136 (61), 135 (64), 87 (53), 69 (73), 42 (45). Anal. Calcd for $C_{13}H_{22}N_3OPS$: C 52.16, H 7.41, N 14.04, P 10.35, S 10.71. Found: C 52.01, H 7.12, N 13.85, P 10.511, S 10.42.

2-[Methyl(morpholin-4-yl)(4-nitrophenyl)-phosphorimidoyl]-3-pyrrolidin-1-yl-but-2-enenitrile **9b**

To a solution of $MePCl_2$ (0.43 g, 3.7 mmol) in benzene (20 mL), a solution of **1a** (0.5 g, 3.7 mmol) and Et_3N (0.48 g, 4.8 mmol) in benzene (20 mL) was added dropwise with stirring. After 18 h, *p*-nitrophenylazide (0.61 g, 3.7 mmol) was added and after 30 min when the evolution of nitrogen stopped a solution of morpholine (0.32 g, 3.7 mmol) and Et_3N (0.37 g, 3.7 mmol) in benzene (20 mL) was added dropwise with stirring. After 1 h, the reaction mixture was washed with water. The organic layer was separated, dried over Na_2SO_4, and evaporated in vacuo. The residue was crystallized from *i*-PrOH. Orange amorphous crystals (0.3 g, 20%). ^{31}P NMR: $\delta = 24.4$. ^1H NMR ($CDCl_3$): $\delta = 1.82$ (d, $^2J_{PH} = 13.2$ Hz, 3H, PCH_3), 1.89–2.11 (bm, 4H, CH_2), 2.25 (s, 3H, CH_3), 3.18–3.34 (bm, 4H, $PNCH_2$), 3.40–3.58 (bm, 2H, NCH_2), 3.63–3.78 (bm, 4H, OCH_2), 3.84–4.07 (bm, 2H, NCH_2), 6.71 (d, $^3J_{HH} = 8.1$ Hz, 2H, 2-Ph), 8.00 (d, $^3J_{HH} = 8.1$ Hz, 2H, 3-Ph). ^{13}C NMR ($CDCl_3$): $\delta = 13.5$ ($^1J_{CP} = 90.5$ Hz, PCH_3) 20.4 (C(4)), 24.7 (CH_2), 25.8 (CH_2), 44.3 ($PNCH_2$), 51.4 (NCH_2), 52.5 (NCH_2), 60.6 ($^1J_{CP} = 126$ Hz, C(2)), 67.1 ($^3J_{CP} = 7.5$ Hz, OCH_2), 121.6 ($^2J_{CP} = 20.1$ Hz, CN), 125.8 ($^3J_{CP} = 2.5$ Hz, C(2′)), 128.3 (C(3′)), 137.9 (C(1′)), 159.3 (C(4′)), 167.5 ($^2J_{CP} = 13.8$ Hz, C(3)). MS, *m/z* (%): 403 (M^+, 5), 318 (40), 303 (79), 181 (100), 136 (16), 132 (36), 86 (23), 70 (19), 56 (10), 42 (13). Anal. Calcd for $C_{19}H_{26}N_5O_3P$: C 56.57, H 6.50, N 17.36, P 7.68. Found: C 56.61, H 6.37, N 17.11, P 7.52.

2-[Morpholin-4-yl(phenyl)phosphoryl]-3-pyrrolidin-1-yl-but-2-enenitrile **11**

To a stirred solution of $PhPCl_2$ (1.31 g, 7.3 mmol) in CH_2Cl_2 (20 mL) under dry argon, a solution of enamine **1a** (1 g, 7.3 mmol) and Et_3N (0.88 g, 8.8 mmol) in CH_2Cl_2 (20 mL) was added dropwise. After 1 h, to the stirred solution obtained, a solution of morpholine (0.64 g, 7.3 mmol) and Et_3N (0.74 g, 7.3 mmol) in CH_2Cl_2 (20 mL) was added dropwise. After 0.5 h, finely powered $H_2O_2 \cdot H_2NC(O)NH_2$ (0.69 g, 7.3 mmol) was added. After 2 h, the reaction mixture was washed with water. The organic phase was separated, dried (Na_2SO_4), and evaporated in vacuo. The residue is a light brown solid (1.98 g, 78%). Mp 103–105°C. ^{31}P NMR: $\delta = 30.0$. ^1H NMR ($CDCl_3$): $\delta = 1.90$–2.05 (bm, 4H, CH_2), 2.29 (s, 3H), 3.07–3.24 (m, 4H, $PNCH_2$), 3.39–3.56 (bm, 2H, NCH_2), 3.58–3.73 (bm, 4H, OCH_2), 3.75–3.98 (bm, 2H, NCH_2), 7.42–7.54 (m, 3H, Ph), 7.85–7.97 (m, 2H, *o*Ph). ^{13}C NMR ($DMSO_{d6}$): $\delta = 20.5$ ($^2J_{CP} = 11.3$ Hz, C(4)), 24.6 (CH_2), 25.5 (CH_2), 44.6 ($PNCH_2$), 50.8 (NCH_2), 52.4 (NCH_2), 63.7 ($^1J_{CP} = 153$ Hz, C(2)), 66.9 ($^3J_{CP} = 6.3$ Hz, OCH_2), 121.4 ($^2J_{CP} = 9.9$ Hz, CN), 128.3 (Ph), 131.5 (Ph), 131.7 ($^3J_{CP} = 10.1$ Hz, Ph), 132.5 ($^1J_{CP} = 133$ Hz, Ph), 168.9 ($^2J_{CP} = 16.3$ Hz, C(3)). Anal. Calcd for $C_{18}H_{24}N_3O_2P$: C 62.60, H 7.00, N 12.17, P 8.97. Found: C 62.71, H 6.85, N 11.94, P 8.61.

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