A convenient and general procedure for the synthesis of α-ureidophosphonates under catalyst-free conditions

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Dedicated to Prof. Paweł Kafarski to honor the achievements within his career

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Abstract

We report here a novel and convenient method for the synthesis of α-ureidophosphonates through a one-pot reaction of three component condensation of aldehyde with urea and diethylphosphite under catalyst-free conditions in toluene at reflux. Treatment of aldeyhde with a mixture of urea and diethylphosphite gives a α-ureidophosphonate in moderate yield. The α-ureidophosphonate product was easily separated and crystallized from the reaction mixture.

Keywords: Aminophosphonates, α-ureidophosphonates, urea, aldehyde, condensation reaction, catalyst-free

Introduction

The organic chemistry of phosphorus compounds have became increasingly useful and important in organic synthesis. Among the organophosphorus compounds, phosphonic acids are important class of compounds that exhibit a variety of interesting and useful properties.[1] The synthesis of α-substituted phosphoryl derivatives (phosphonic and phosphinic acids) has attracted significant attention due to their biological activities with broad application as enzyme inhibitors, antimetabolites and antibiotics.[2] Among α-functionalized phosphonic acids, α-aminoalkylphosphonic derivatives have biological activities such as anti-bacterial,[3] herbicidal[4] and fungicidal.[5] Aminoalkylphosphonic acids, the phosphonic acid analogues of 1-amino carboxylic acids, are important class of compounds that exhibit a variety of interesting and useful properties.[6] While the synthesis and properties of many types of aminophosphonic acid derivatives have been widely investigated,[7-9] studies of α-ureidophosphonates have received little

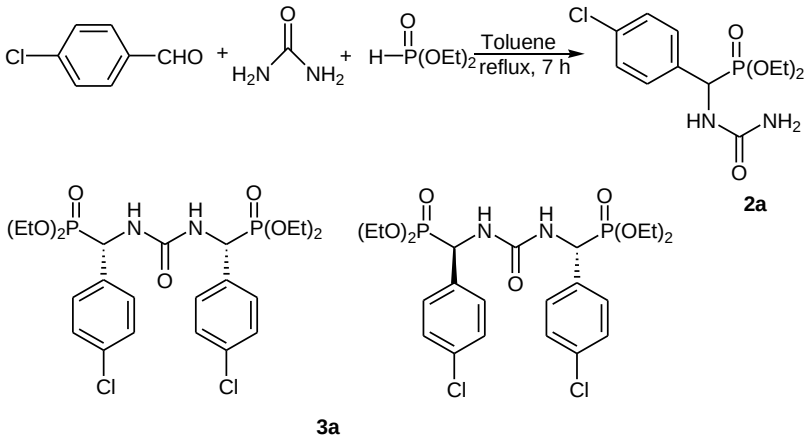
attention. α-Ureidophosphonates have been used as precursor for the synthesis of chiral 1-aminophosphonates.[10] α-Ureidophosphonates have shown moderate activity against number of fungal pathogens.[11] They also display powerful antiviral activities against TMV.[12] Besides their biological importance, α-ureidophosphonates are also known for their metal chelating ability.[13] In addition, these compounds used as active ingredients in pesticides especially insecticides and acaricides.[14]

In contrast to extensive studies on the synthesis of 1-aminophosphonic acid derivatives,[15] relatively few papers have been reported on the synthesis of α-ureidophosphonates. Synthetic routes to 1-ureidophosphonates involve prolonged heating of three component reaction of trialkylphosphite with urea and aldehydes at 50 °C in the presence of BF_3 as a catalyst under nitrogen described by Birum,[16] and the reaction of aminophosphonates with isocyanates in the presence of LDA at -30°C.[17] However there are some problems associated with these methods including harsh reaction conditions, long reaction times and side reactions. On the other hand, three component reaction of trialkylphosphite with urea and aldehydes at 50 °C in the presence of BF_3 as a catalyst under nitrogen, gave urylenediphosphonates as major product. In this method the formation of urea monophosphonates (α-ureidophosphonates) is accompanied by the formation of urylenediphosphonates, even when equimolar quantities of reactants was used and pure α-ureidophosphonates are difficult to isolate. As part of our efforts to explore the novel methods for the synthesis of organophosphorus compounds,[18] we report a new method for the synthesis of α-ureidophosphonates from the one-pot three component condensation of aldehyde with urea and diethylphosphite under catalyst-free conditions in toluene at reflux.

Results and Discussion

Treatment of *p*-chlorobenzaldehyde (**1a**), as a model compound, with a mixture of urea and diethylphosphite was studied in toluene, and the progress of the reaction was monitored by TLC. Treatment of **1a** with urea in the presence of diethylphosphite in dry toluene at room temperature failed after 24 h to form any product. When the reaction was carried out at reflux for 7 h, a mixture of products was obtained (Scheme 1). The ^{31}P-NMR spectrum of this mixture exhibited three peaks at δ 22.53, 22.82 and 23.11 ppm due to the mixture of two diastereoisomers **3a** (in a 63:37 ratio of diastereoisomers, Scheme 1) and diethyl α-ureido(4-chlorophenyl)-methylphosphonate **2a**.

When the reaction mixture was subjected to washing with water, and evaporation of the solvent, only **2a** crystallized from a mixture of diethyl ether and *n*-hexane. The structure of **2a** was confirmed by NMR data and X-ray analysis. In the ^{31}P-NMR spectrum, a singlet peak appeared at δ 22.50 ppm. The ^{1}H-NMR spectrum had a doublet of doublets peak at 5.40 ppm (J_{HP} 22 Hz and J_{HH} 10 Hz) which corresponds with the hydrogen -CH- in the product **2a** (simplified from doublet of doublets to doublet by addition of D_2O). The ^{13}C-NMR spectrum exhibited doublet peak at δ 50.2 (J_{CP} 152 Hz).



Scheme 1

The structure was supported by its X-ray analysis. We could obtain suitable crystals for **2a** for X-ray analysis. The crystal structure of **2a** is illustrated in Figure 1.

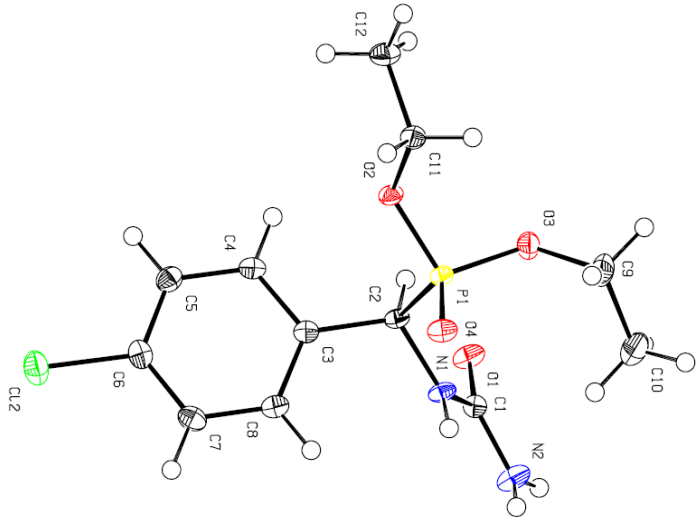
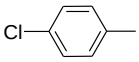
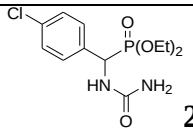
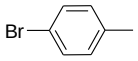
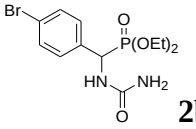
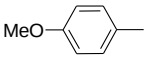
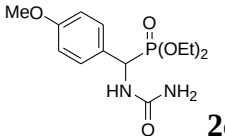
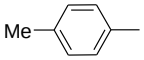
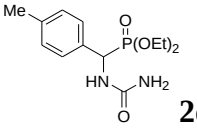
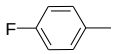
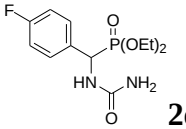
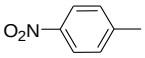
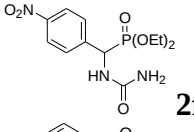
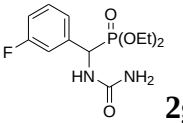
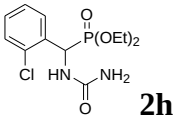
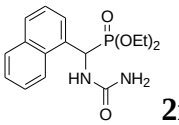
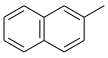
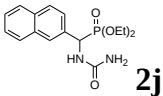
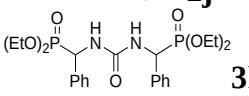
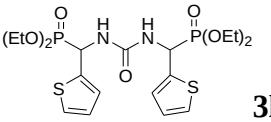


Figure 1. ORTEP drawing of **2a.**

This process was successfully applied to other aldehydes **1** as summarized in Table 1. As shown in Table 1, the reaction of different substituted (*ortho*, *meta* and *para*)- of benzaldehydes with a mixture of urea and diethylphosphite in dry toluene at reflux, afforded the corresponding α-ureidophosphonates derivatives **2** in 30-54 % isolated yields (entries 1-10). Treatment of benzaldehyde and thiophene-2-carbaldehyde with a mixture of urea and diethylphosphite in toluene at reflux, gave corresponding urylenediphosphonate **3k** and **3l** as major product (entries 11 and 12).

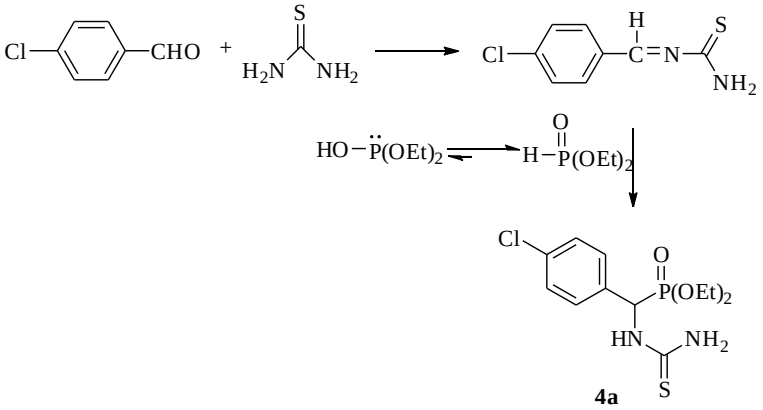
Table 1. Synthesis of α-ureidophosphonates *via* one-pot three component condensation of aldehyde, urea and diethylphosphite

Entry	R **1**	Product(s)	Reaction time (h)	Yield (%)[a]	^{31}P NMR δ (ppm) **2**
1		 **2a**	7	48	22.50
2		 **2b**	7	48	22.29
3		 **2c**	8	35	23.37
4		 **2d**	8	33	23.27
5		 **2e**	14	30	22.17
6		 **2f**	7	50	21.48
7		 **2g**	7	46	22.17
8		 **2h**	7	54	22.22
9		 **2i**	8	45	23.13
10		 **2j**	8	45	22.87
11		 **3k**	8	45 (60:40)	22.53 and 22.76
12		 **3l**	8	54 (58:42)	20.46 and 20.64
13	*n*-C_6H_{13}	-	-	-	-[b]

[a]Yields refer to the isolated pure products. [b]Unknown mixture.

When the reaction mixture of benzaldehyde and thiophene-2-carbaldehyde was subjected to washing with water followed by adding a mixture of solvents diethyl ether and *n*-hexane, corresponding α-ureidophosphonates (**2k** and **2l**) did not crystallize from the reaction mixture. The reaction of heptanal, as an aliphatic aldehyde, with a mixture of urea and diethylphosphite in toluene at reflux, afforded an unknown mixture (entry 13).

Birum reported three component reaction of trialkylphosphite with urea and aldehyde at 50 °C in the presence of BF_3 as a catalyst under nitrogen, but this method gave urylenediphosphonates as major product.[16a] In this catalytic method, three component reaction of trialkylphosphite with thiourea and aldehydes at 50 °C in the presence of BF_3 as a catalyst under nitrogen, failed to give the corresponding adduct.[16a] We were interested to examine the three component reaction of dialkylphosphite with thiourea and 4-chlorobenzaldehyde (**1a**) in toluene at reflux. Treatment of **1a** with thiourea in the presence of diethylphosphite in dry toluene at room temperature failed after 24 h to form any product. When the reaction was carried out at reflux for 7 h, gave corresponding α-thioureidophosphonate **4a** in 48 % isolated yield (Scheme 2).



Scheme 2

Conclusions

We have developed a simple and practical approach for the synthesis of α-ureidophosphonates. Through a three component reaction of aldehydes with a mixture of urea and diethylphosphite under catalyst-free conditions in toluene at reflux, α-ureidophosphonates can be synthesized cleanly in moderate yield. The structure of α-ureidophosphonates was determined by NMR data and X-ray analysis.[20] Treatment of aldehydes with thiourea in the presence of diethylphosphite in dry toluene at reflux for 7 h, gave corresponding α-thioureidophosphonate in moderate isolated yield. Some of the major advantages of this protocol are: simple procedure, easy work-up, and catalyst-free conditions.

Experimental Section

General. All chemicals were commercial products and distilled or recrystallized before use. NMR spectra were taken with a 400 MHz Brucker Avance instrument with the chemical shifts being reported as δ ppm and couplings expressed in Hertz. Silica gel column chromatography was carried out with Silica gel 100 (Merck No. 10184). Merck Silica-gel 60 F254 plates (No. 5744) were used for the preparative TLC. Mass spectra were measured on a LCMASS micromass LCT and Micromass Autospec. Melting points are uncorrected.
X-Ray crystal data of **2a** were collected by a diffractometer. The structure was solved by a direct method using SHLEXS-97 (Scheldrik, 1997) and refined with a full matrix laser-squares method. Molecular formula $C_{12}H_{18}ClN_2O_4P$, MW 320.07, Monoclinic, space group Pna21/c, a = 7.8880(11) Å, b = 25.221(3) Å, c = 9.1789(9) Å, V=1515.4(3) Å3, T=90 K, Z=4, Dx=1.406 Mg/m3, (Mo-Kα)=0.71073 Å, absolute structure parameter=0.12(10), R=0.0193 over independent reflections (3451). Crystallographic data (excluding structure factors) for the X-ray crystal structure analysis reported in this paper have been deposited with the Cambridge Crystallographic Data Center (CCDC) as supplementary publication No. CCDC 835018, copies of these data can be obtained, free of charge, upon application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax:+44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]**.**

Synthesis of α-ureidophosphonates (2). The aldehyde (10 mmol) was added to a stirred mixture of urea (1 g, 3.07 mmol) and diethylphosphite (10 mmol) in dry toluene (50 mL) at reflux and the solution was stirred for 7-14 h. Stirring was continued for 1 h at room temperature and then the reaction mixture was washed with water (3x50 mL) and the solvent was removed under vacuum. A mixture of 50:50 diethyl ether/*n*-hexane (50 mL) was added to the reaction mixture and pure product **2** was crystallized from the mixture. All products gave satisfactory spectral data in accord with the assigned structures.
Diethyl [α-ureido-(4-chlorophenyl)]methyl phosphonate (2a). White solid, mp 202-204 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 1.15 (t, *J* 7.2 Hz, 3H), 1.40 (t, *J* 7.2 Hz, 3H), 3.67-3.81 (m, 1H), 3.86-3.98 (m, 1H), 4.16-4.32 (m, 2H), 5.35 (br, NH_2, 2H), 5.39 (dd, *J* 22.0 Hz , *J* 10.0 Hz, 1H), 7.32 (d, *J* 8.0 Hz, 2H), 7.41 (dd, *J* 8.4 Hz, *J* 2.0 Hz, 2H), 7.65 (d, *J* 3.2 Hz, 1H, NH). ^{13}C NMR ($CDCl_3$-TMS, 100.6 MHz), δ: 16.2 (d, J_{PC} 6.0 Hz), 16.2 (d, J_{PC} 6.0 Hz), 50.1 (d, J_{PC} 155.0 Hz), 63.5 (d, J_{PC} 7.0 Hz), 63.9 (d, J_{PC} 7.0 Hz), 128.7 (d, J_{PC} 2.0 Hz Hz), 129.4 (d, J_{PC} 6.0 Hz), 133.9 (d, J_{PC} 3.0 Hz), 134.6, 158.4 (d, J_{PC} 10.0 Hz). ^{31}P NMR ($CDCl_3$/H_3PO_4), δ: 22.50. EI-MS: *m/z* 320 (M^+).
Diethyl [α-ureido-(4-bromophenyl)]methyl phosphonate (2b). White solid, mp197-199 °C. ^{1}H NMR (DMSO, 400 MHz), δ: 1.10 (t, *J* 7.2 Hz, 3H), 1.21 (t, *J* 7.2 Hz, 3H), 3.76-3.86 (m, 1H), 3.86-3.96 (m, 1H), 3.97-4.10 (m, 2H), 5.16 (dd, *J* 22.4 Hz, *J* 9.6 Hz, 1H), 7.10 (dd, *J* 9.6 Hz, *J* 4.0 Hz, 1H, NH), 7.31 (dd, *J* 8.2 Hz, *J* 2.0 Hz, 2H), 7.52 (d, *J* 8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz), δ: 16.5 (d, J_{PC} 6.0 Hz), 16.7 (d, J_{PC} 6.0 Hz), 50.1 (d, J_{PC} 152.0 Hz), 62.7 (d, J_{PC} 7.0 Hz), 63.1 (d, J_{PC} 7.0 Hz), 121.0 (d, J_{PC} 3.0 Hz Hz), 130.4 (d, J_{PC} 5.0 Hz), 131.5 (d, J_{PC} 2.0 Hz),

137.2, 157.9 (d, J_{PC} 10.0 Hz). ^{31}P NMR ($CDCl_3/H_3PO_4$), δ: 22.29. Anal. Calcd for $C_{12}H_{18}BrN_2O_4P$. C, 39.56; H, 4.94; N, 7.69. Found: C, 39.40; H, 4.91; N, 7.53.

Diethyl [α-ureido-(4-methoxyphenyl)]methyl phosphonate (2c). White solid, mp196-198 °C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 1.11 (t, *J* 6.4 Hz, 3H), 1.39 (t, *J* 6.4 Hz, 3H), 3.62-3.73 (m, 1H), 3.82 (s, 3H), 3.83-3.94 (m, 1H), 4.12-4.30 (m, 2H), 5.28 (br, NH_2, 2H), 5.34 (dd, *J* 21.2 Hz, *J* 8.4 Hz, 1H), 6.88 (d, *J* 7.6 Hz, 2H), 7.41 (d, *J* 7.6 Hz, 2H), 7.59 (br, NH, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz), δ: 16.2 (d, J_{PC} 7.0 Hz), 16.5 (d, J_{PC} 6.0 Hz), 49.9 (d, J_{PC} 155.0 Hz), 55.3, 63.3 (d, J_{PC} 8.0 Hz), 63.6 (d, J_{PC} 7.0 Hz), 113.9, 128.0, 129.3 (d, J_{PC} 7.0 Hz Hz), 158.8 (d, J_{PC} 10.0 Hz), 159.3. ^{31}P NMR ($CDCl_3/H_3PO_4$), δ: 23.37. Anal. Calcd for $C_{13}H_{21}N_2O_5P$. C, 49.35; H, 6.69; N, 8.86. Found: C, 47.20; H, 6.82; N, 9.10.

Diethyl [α-ureido-(4-methylphenyl)]methyl phosphonate (2d). White solid, mp188-190 °C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 1.11 (t, *J* 7.2 Hz, 3H), 1.39 (t, *J* 7.2 Hz, 3H), 2.35 (s, 3H), 3.62-3.74 (m, 1H), 3.83-3.95 (m, 1H), 4.17-4.32 (m, 2H), 5.30-5.40 (br, NH_2, 2H), 5.38 (dd, *J* 21.6 Hz, *J* 9.6 Hz, 1H), 7.16 (d, *J* 7.8 Hz, 2H), 7.38 (d, *J* 7.8 Hz, 2H), 7.65 (s, NH, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz), δ: 16.1 (d, J_{PC} 6.0 Hz), 16.5 (d, J_{PC} 6.0 Hz), 21.2, 50.4 (d, J_{PC} 156.0 Hz), 63.4 (d, J_{PC} 7.0 Hz), 63.6 (d, J_{PC} 7.0 Hz), 128.0 (d, J_{PC} 6.0 Hz Hz), 129.2 (d, J_{PC} 2.0 Hz), 132.8, 137.6 (d, J_{PC} 2.0 Hz), 158.6 (d, J_{PC} 10.0 Hz). ^{31}P NMR ($CDCl_3/H_3PO_4$), δ: 23.27. Anal. Calcd for $C_{13}H_{21}N_2O_4P$. C, 51.98; H, 7.05; N, 9.33. Found: C, 51.76; H, 7.0 ; N, 9.43.

Diethyl [α-ureido-(4-flourophenyl)]methyl phosphonate (2e). White solid, mp198-200 °C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 1.09 (t, *J* 7.2 Hz, 3H), 1.13 (t, *J* 7.2 Hz, 3H), 4.78-4.90 (m, 1H), 4.93-5.12 (m, 3H), 5.38 (dd, *J* 21.6 Hz , *J* 10.0 Hz, 1H), 6.97 (t, *J* 8.4 Hz, 2H), 7.33 (br, NH_2, 2H), 7.35-7.42 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz), δ: 16.1 (d, J_{PC} 6.0 Hz), 16.2 (d, J_{PC} 5.0 Hz), 50.0 (d, J_{PC} 155.0 Hz), 63.2 (d, J_{PC} 7.0 Hz), 63.4 (d, J_{PC} 7.0 Hz), 115.2 (d, J_{CF} 20.0 Hz), 129.6 (d, J_{PC} 6.0 Hz), 129.6-129.8 (m), 132.2 (d, J_{PC} 3.0 Hz), 156.7, 162.3 (d, J_{FC} 243 Hz). ^{31}P NMR ($CDCl_3/H_3PO_4$), δ: 22.17 (d, $J_{P\text{-}F}$ 3.2 Hz). Anal. Calcd for $C_{12}H_{18}FN_2O_4P$. C, 47.35; H, 5.96; N, 9.21. Found: C, 47.30; H, 5.73; N, 9.10.

Diethyl [α-ureido-(4-nitrophenyl)]methyl phosphonate (2f). Yellow solid, mp231-233 °C. ^{1}H NMR (CD_3SOCD_3, 400 MHz), δ: 1.12 (t, *J* 7.2 Hz, 3H), 1.22 (t, *J* 7.2 Hz, 3H), 3.82-3.91 (m, 1H), 3.91-3.99 (m, 1H), 4.00-4.11 (m, 2H), 5.35 (dd, *J* 23.2 Hz, *J* 9.6 Hz, 1H), 5.87 (s, NH_2, 2H), 7.24 (br, NH 1H), 7.64 (d, *J* 8.8 Hz, 2H), 8.23 (d, *J* 8.4 Hz, 2H). ^{13}C NMR (CD_3SOCD_3, 100.6 MHz), δ: 16.5 (d, J_{PC} 5.0 Hz), 16.7 (d, J_{PC} 5.0 Hz), 50.6 (d, J_{PC} 150.0 Hz), 63.0 (d, J_{PC} 7.0 Hz), 63.3 (d, J_{PC} 7.0 Hz), 123.8 (d, J_{PC} 2.0 Hz), 129.4 (d, J_{PC} 5.0 Hz), 145.7, 147.3 (d, J_{PC} 3.0 Hz), 157.9 (d, J_{PC} 10.0 Hz). ^{31}P NMR (CD_3SOCD_3/H_3PO_4), δ: 21.48. Anal. Calcd for $C_{12}H_{18}N_3O_6P$. C, 43.49; H, 5.48; N, 12.69. Found: C, 43.76; H, 5.53; N, 12.51.

Diethyl [α-ureido-(3-flourophenyl)]methyl phosphonate (2g). White solid, mp200-202 °C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 1.07 (t, *J* 6.8 Hz, 3H), 1.11 (t, *J* 6.8 Hz, 3H), 3.76-3.90 (m, 1H), 3.91-4.12 (m, 3H), 5.38 (dd, *J* 22.0 Hz , *J* 10.0 Hz, 1H), 6.95 (t, *J* 8.8 Hz, 2H), 7.35-7.45 (m, 2H and NH). ^{13}C NMR ($CDCl_3$, 100.6 MHz), δ: 16.0 (d, J_{PC} 6.0 Hz), 16.2 (d, J_{PC} 6.0 Hz), 49.9 (d, J_{PC} 156.0 Hz), 63.2 (d, J_{PC} 7.0 Hz), 63.5 (d, J_{PC} 7.0 Hz), 115.2 (dd, J_{CF} 24.0 Hz, J_{PC} 2.0 Hz), 129.6, 129.7 (d, J_{PC} 2.0 Hz), 129.8, 156.7 (d, J_{PC} 10.0 Hz), 162.3 (dd, J_{PC} 3.0 and J_{FC} 246 Hz).

^{31}P NMR ($CDCl_3$/H_3PO_4), δ: 22.17 (d, J_{PF} 3.2 Hz). Anal. Calcd for $C_{12}H_{18}FN_2O_4P$. C, 47.35; H, 5.96; N, 9.21. Found: C, 47.21; H, 5.68; N, 9.20.

Diethyl [α-ureido-(2-chlorophenyl)]methyl phosphonate (2h). Yellow solid, mp194-196 °C. ^{1}H NMR (CD_3SOCD_3, 400 MHz), δ: 1.02 (t, *J* 7.2 Hz, 3H), 1.25 (t, *J* 7.2 Hz, 3H), 3.63-3.74 (m, 1H), 3.78-3.90 (m, 1H), 4.02-4.13 (m, 2H), 5.69 (dd, *J* 22.0 Hz , *J* 10.0 Hz, 1H), 5.80 (s, NH_2, 2H), 7.28 (dd, *J* 10.0 Hz , *J* 4.0 Hz, 1H), 7.28-7.36 (m, 1H), 7.37-7.49 (m, 3H). ^{13}C NMR (CD_3SOCD_3-TMS, 100.6 MHz), δ: 16.4 (d, J_{P-C} 5.0 Hz), 16.7 (d, J_{P-C} 5.0 Hz), 47.2 (d, J_{P-C} 155.0 Hz), 62.8 (d, J_{P-C} 7.0 Hz), 63.1 (d, J_{P-C} 7.0 Hz), 127.7 (d, J_{P-C} 3.0 Hz Hz), 129.6, 129.8 (d, J_{P-C} 3.0 Hz), 133.2, 133.3, 133.8 (d, J_{P-C} 1.0 Hz), 157.8 (d, J_{P-C} 10.0 Hz). ^{31}P NMR (CD_3SOCD_3/H_3PO_4), δ: 22.12. Anal. Calcd for $C_{12}H_{18}ClN_2O_4P$. C, 44.99; H, 5.67; N, 8.75. Found: C, 45.11; H, 5.73; N, 8.68.

Diethyl [α-ureido-(1-naphthyl)]methyl phosphonate (2i). White solid, mp179-181 °C. ^{1}H NMR (CD_3SOCD_3, 400 MHz), δ: 0.82 (t, *J* 7.2 Hz, 3H), 1.26 (t, *J* 7.2 Hz, 3H), 3.47-3.64 (m, 1H), 3.72-3.83 (m, 1H), 4.02-4.16 (m, 2H), 5.8 (s, 2H, NH_2), 6.03 (dd, *J* 22.0 Hz, *J* 10.0 Hz, 1H), 7.24 (dd, *J* 9.6 Hz, *J* 3.6 Hz, 1H), 7.52-7.63 (m, 3H), 7.64-7.70 (m. 1H), 7.90 (d, *J* 8.4 Hz, 1H), 7.96 (d, *J* 8.4 Hz, 1H), 8.20 (d, *J* 8.4 Hz, 1H). ^{13}C NMR (CD_3SOCD_3, 100.6 MHz), δ: 16.3 (d, J_{PC} 5.0 Hz), 16.8 (d, J_{PC} 6.0 Hz), 46.1 (d, J_{PC} 152.0 Hz), 62.6 (d, J_{PC} 7.0 Hz), 63.0 (d, J_{PC} 7.0 Hz), 124.2, 125.4 (d, J_{PC} 3.0 Hz), 126.2 (d, J_{PC} 4.0 Hz), 126.7, 128.5 (d, J_{PC} 2.0 Hz), 129.0, 131.3, 131.4, 133.7, 134.2, 158.0 (d, J_{PC} 9.0 Hz). ^{31}P NMR (CD_3SOCD_3/H_3PO_4), δ: 23.13. Anal. Calcd for $C_{16}H_{21}N_2O_4P$. C, 57.12; H, 6.30; N, 8.33. Found: C, 57.11; H, 6.21; N, 8.30.

Diethyl [α-ureido-(2-naphthyl)]methylphosphonate (2j). White solid, mp178-179 °C. ^{1}H NMR (CD_3SOCD_3, 400 MHz), δ: 1.06 (t, *J* 7.2 Hz, 3H), 1.23 (t, *J* 7.2 Hz, 3H), 3.70-3.83 (m, 1H), 3.84-3.96 (m, 1H), 3.98-4.13 (m, 2H), 5.34 (dd, *J* 22.0 Hz, *J* 10.0 Hz, 1H), 5.82 (s, NH_2, 2H), 7.53 (dd, *J* 10.0 Hz, *J* 4.0 Hz, 1H), 7.49-7.58 (m, 3H), 7.86 (s, 1H), 7.88-7.96 (m, 3H). ^{13}C NMR (CD_3SOCD_3, 100.6 MHz), δ: 16.4 (d, J_{PC} 6.0 Hz), 16.7 (d, J_{PC} 5.0 Hz), 50.6 (d, J_{PC} 153.0 Hz), 63.0 (d, J_{PC} 7.0 Hz), 63.3 (d, J_{PC} 7.0 Hz), 126.3 (d, J_{PC} 4.0 Hz), 126.7, 126.8 (d, J_{PC} 6.0 Hz), 126.9, 128.0, 128.1, 128.2, 132.7, 133.0 (d, J_{PC} 2.0 Hz), 134.8, 158.2 (d, J_{PC} 10.0 Hz). ^{31}P NMR (CD_3SOCD_3/H_3PO_4), δ: 22.87. Anal. Calcd for $C_{16}H_{21}N_2O_4P$. C, 57.12; H, 6.30; N, 8.33. Found: C, 56.95; H, 6.20; N, 8.25.

Tetrakisethyl (α-urylene diphenylmethyl) diphosphonate (3k). White solid, ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 1.04-1.14 (m, 9H), 1.33 (t, *J* 7.2 Hz, 3H), 3.70-3.83 (m, 2H), 3.84-3.96 (m, 4H), 3.98-4.19 (m, 2H), 5.45 (dd, *J* 22.0 Hz, *J* 10.0 Hz, 2H, simplified from doublet of doublet to doublet by addition of D_2O), 7.24-7.33 (m, 6H), 7.35-7.50 (m, 4H and 2NH). ^{13}C NMR ($CDCl_3$, 100.6 MHz), δ: 15.9-16.4 (m), 50.6 (d, J_{PC} 155.9 Hz), 63.1-63.4 (m), 127.7-128.4 (m, Ar), 136.1 (d, J_{PC} 2.5 Hz), 158.2 (d, J_{PC} 10 Hz). ^{31}P NMR ($CDCl_3$/H_3PO_4), δ: 22.53 and 22.76. HRMS calcd for $C_{18}H_{34}O_7N_2P_2$ (MNa^+): 513.1706. Found 513.1916.

Tetrakisethyl (α-urylene dithiophenylmethyl) diphosphonate (3l). White solid. ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 1.08-1.17 (m, 9H), 1.24 (t, *J* 7.2 Hz, 3H), 3.80-4.15 (m, 8H), 5.45 (dd, *J* 22.0 Hz, *J* 10.0 Hz, 2H, simplified from doublet of doublet to doublet by addition of D_2O), 6.90-7.10 (m, 4H), 7.20-7.30 (m, 2NH), 7.40-7.55 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz), δ: 16.4-

16.6 (m), 46.4 (d, J_{PC} 160.0 Hz), 46.5 (d, J_{PC} 160.0 Hz) 63.4-63.7 (m), 126.3-127.6 (m, Ar), 139.2 (d, J_{PC} 4.0 Hz), 156.2 (d, J_{PC} 11 Hz). ^{31}P NMR ($CDCl_3/H_3PO_4$), δ: 20.46 and 20.64. Anal. Calcd for $C_{19}H_{30}N_2O_7PS_2$. C, 43.50; H, 5.77; N, 5.34. Found: C, 43.40; H, 5.38; N, 5.25.

Diethyl [α-thioureido-(4-chlorophenyl)]methyl phosphonate (4a). Yellow solid, mp180-182 °C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 1.15 (t, *J* 7.2 Hz, 3H), 1.41 (t, *J* 7.2 Hz, 3H), 3.71-3.83 (m, 1H), 3.87-3.99 (m, 1H), 4.17-4.35 (m, 2H), 6.25 (dd, *J* 21.2 Hz , *J* 9.6 Hz, 1H), 6.62 (br, NH_2, 2H), 7.33 (d, *J* 8.4 Hz, 2H), 7.44 (d, *J* 8.4 Hz, 1H), 8.93 (d, *J* 6.8 Hz, 1H, NH). ^{13}C NMR ($CDCl_3$, 100.6 MHz), δ: 16.1 (d, J_{PC} 6.0 Hz), 16.5 (d, J_{PC} 6.0 Hz), 54.6 (d, J_{PC} 154.0 Hz), 63.9 (d, J_{PC} 6.0 Hz), 64.4 (d, J_{PC} 7.0 Hz), 128.8 (d, J_{PC} 2.0 Hz Hz), 129.7 (d, J_{PC} 6.0 Hz), 133.4, 134.3 (d, J_{PC} 3.0 Hz), 184.5 (d, J_{PC} 12.0 Hz). ^{31}P NMR ($CDCl_3/H_3PO_4$), δ: 21.25. Anal. Calcd for $C_{12}H_{18}N_2ClO_3PS$. C, 42.85; H, 5.40; N, 8.33. Found: C, 42.91; H, 5.20; N, 8.21.

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