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Efficient synthesis of phosphorylated *ortho*-fused azaheterocycles

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ABSTRACT

A simple and efficient two-step synthesis of various *ortho*-fused azaheterocycles, containing phosphorylated pyrimidinones as a parent component, was accomplished by the reaction of 2-diethoxyphosphoryl-3-methoxyacrylate with heteroaromatic amines followed by intramolecular N-acylation of the obtained substitution products. Optimization studies performed for the N-acylation reaction revealed that heating the addition products in Dowtherm A at 250 °C gave the best results. The same conditions applied in the intramolecular cyclization of ethyl 2-diethoxyphosphoryl-3-aminophenylacrylate gave expected product of the electrophilic aromatic substitution, but in low yield.

1. Introduction

Phosphorylated, nitrogen-containing heterocycles are a very important class of organic compounds, which are widely used in industrial, agrochemical, or medicinal chemistry.[1] For example, 2-pyridylthionophosphonate **1** is an important constituent of various preparations of pesticides,[2] 2-pyridylphosphonate **2** is an agonist of cyclic adenosine monophosphate-dependent protein kinase (i.e., it is potential blood platelet aggregation inhibitor, smooth muscle relaxant, and inflammation inhibitor[3]), and 6,7-dichloro-2-oxoquinoline-3-phosphonic acid **3** is a potent and selective AMPA/kainate antagonist with neuroprotective properties[4] (Fig. 1). It is also well documented that phosphonate moiety can regulate important biological functions by mimicking carboxylic acid functionality.[1a,5] Therefore, phosphorus analogs of the biologically active carboxy-substituted azaheterocycles, such as derivatives of nalidixic acid **4** (well-known antibacterial agents[6]) or 4-oxopyrimidobenzimidazole-3-carboxylic acids **5** (central nervous system depressants and anti-inflammatory agents[7]) are attractive synthetic targets. Furthermore, phosphorylated azaheterocycles are very important intermediates often employed in organic synthesis.[1a,b] Not surprisingly, many approaches to the synthesis of this class of compounds have been elaborated. These approaches were summarized in 2004 by Stevens and co-workers in excellent review.[1b] More recent reports on this topic include aza-Diels–Alder reaction of 3-phosphinyl-1-aza-1,3-butadienes[8] and 1,2-diaza-1,3-butadienes[9] or addition of β-phosphorylated enamines to dimethyl acetylenedicarboxylate followed by intramolecular cyclization of the adduct.[10] Direct phosphonylation of aromatic azaheterocycles was the topic of 2009 review published by Van der Jeught and Stevens.[1a] Very recently direct, tandem 1,4/1,2 addition of phosphites to quinolines has been described.[11] Also, in our laboratory we developed the synthesis of 3-diethoxyphosphorylpyrrolidin-2-ones **6**,[12] 4-diethoxyphosphorylisoxazolidin-5-ones **7**,[13] as well as 4-diethoxyphosphoryl-4,5-dihydropyridazin-3(2*H*)-ones **8**,[14] which were next used as effective Horner–Wadsworth–Emmons reagents.

Herein, we report on a new methodology, which can be applied to the synthesis of diverse phosphorylated *ortho*-fused azaheterocycles **13**–**22** starting from easily available 2-diethoxyphosphoryl-3-methoxyacrylate **9**. Reagent **9** was very recently applied in our laboratory in the synthesis of various vinylphosphonates[15] as well as 3-diethoxyphosphorylchromen-3-ones and 3-diethoxyphosphorylbenzochromen-3-ones.[16] Now we would like to show that the substitution of methoxy group in **9** by a variety of aromatic amines **10** gives ethyl 2-diethoxyphosphoryl-3-aminoacrylates **12**, which in turn undergo intramolecular cyclizations under thermal conditions with the formation of phosphorylated azaheterocycles **13**–**22**.

2. Results and discussion

Ethyl 2-diethoxyphosphoryl-3-aminoacrylates **12a**–**h** were obtained by heating 2-diethoxyphosphoryl-3-methoxyacrylate **9** with heteroaromatic amines **10a**–**h** in xylene (Scheme 1). Crude substitution products were purified by column chromatography to give pure 2-diethoxyphosphoryl-3-aminoacrylates **12a**–**h** in good to

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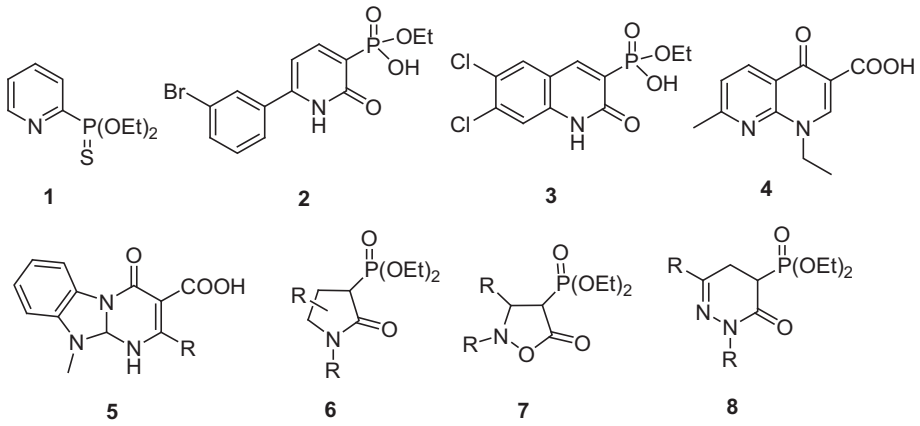
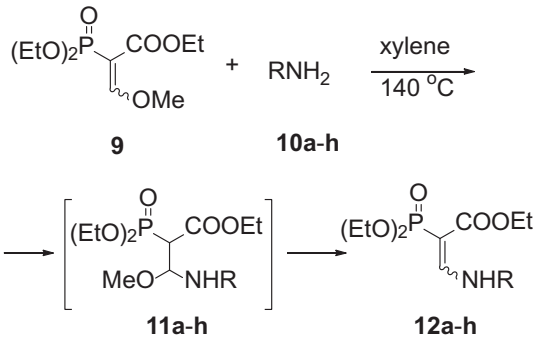


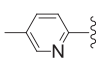
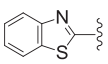
Fig. 1. Azaheterocycles containing phosphoryl or carboxy group.



Scheme 1. Preparation of 2-diethoxyphosphoryl-3-aminoacrylates **12a**–**h**.

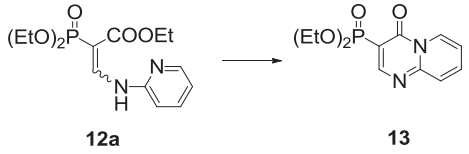
excellent yields, as mixtures of *E* and *Z* isomers in a close to 30:70 ratio. Pleasingly, a small sample of acrylate **12f** was easily separated into individual (*E*)-**12f** and (*Z*)-**12f** isomers for the analytical purposes. Reaction times and yields are given in Table 1. For the determination of *E*/*Z* ratios, diagnostic were the $^{3}J_{PH}$ coupling constants, which fall in the range of 13.0–14.8 or 38.7–39.6 for *E* or *Z* isomers, respectively.[17] The reaction clearly proceeds by a two-step addition/elimination sequence, via adducts **11a**–**h**.

Table 1
Ethyl 2-diethoxyphosphoryl-3-aminoacrylates **12a**–**h** obtained

Compound	R	Reaction time (h)	**12** Yield (%)	*E*/*Z* ratio
a		16	86	35:65
b		16	84	30:70
c		16	90	30:70
d		16	83	30:70
e		16	81	30:70
f		8	72	35:65
g		8	89	30:70
h		8	91	30:70

Acrylates **12a**–**h** were next subjected to intramolecular cyclization. To optimize conditions for this reaction a small sample of acrylate **12a** (0.1 mmol), which was chosen as a model compound, was heated neat, in polyphosphoric acid (PPA) or in Dowtherm A (a mixture of diphenyl ether and biphenyl) at different temperatures and for different periods of time, and progress of the reaction was monitored by ^{31}P NMR. Experiments performed neat or in Dowtherm A were carried out directly in the NMR tube, whereas those in polyphosphoric acid were carried out in a small reaction vessel and after a standard aqueous work-up ^{31}P NMR spectra of the crude reaction mixtures were registered. To evaluate the effectiveness of the reaction, integration of the signals of the substrate and product was compared with the integration of all the remaining signals in a ^{31}P NMR spectrum. Selected results of these experiments are shown in Table 2. Heating **12a** neat at 300 °C gave 32% of the cyclization product in the best experiment (entry 5). A slightly better result was obtained when **12a** was heated in PPA (46% of the cyclization product, 100 °C, 120 min, entry 7). Increasing the reaction time or temperature (entries 8 and 9, respectively) resulted in significantly lower yields. However, we were pleased to observe that when **12a** was heated in Dowtherm A at 250 °C for 40 min, about 80% of the cyclization product was present in the reaction

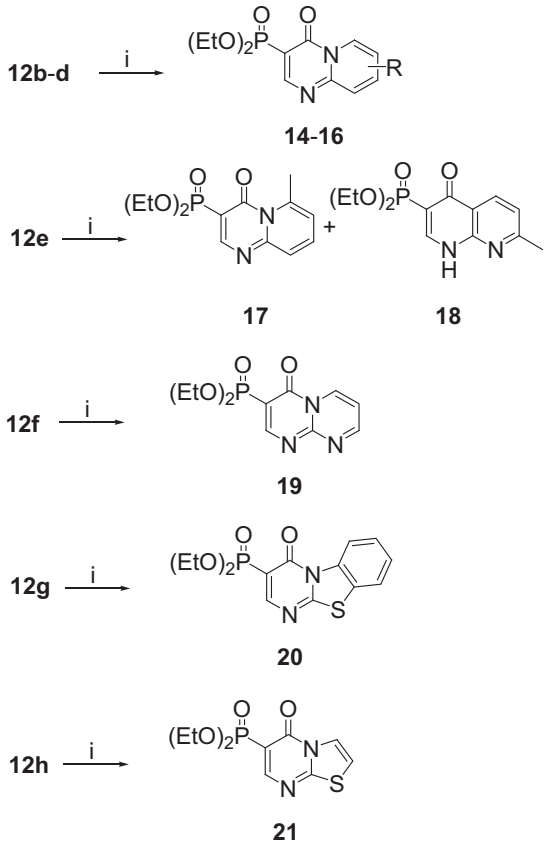
Table 2
Optimalization of the intramolecular cyclization of acrylate **12a**



Entry	Solvent, catalyst	Temp (°C)	Reaction time (min)	**12a** (%)	**13** (%)
1	Neat	200	5	81	8
2	Neat	200	10	20	14
3	Neat	200	20	6	10
4	Neat	300	0.5	77	13
5	Neat	300	1.0	9	32
6	PPA	85	240	50	31
7	PPA	100	120	25	46
8	PPA	100	240	0	11
9	PPA	120	150	0	33
10	Dowtherm A	200	10	98	0
11	Dowtherm A	225	20	79	9
12	Dowtherm A	250	10	45	42
13	Dowtherm A	250	20	25	61
14	Dowtherm A	250	30	5	77
15	Dowtherm A	250	40	0	80

mixture and all substrate was consumed (entry 15). These conditions appear to be optimal because heating the substrate at 225 °C for 20 min gave only a 9% yield of the desired product (entry 11). Having established optimal reaction conditions for the cyclization of **12a**, this reaction was performed on a larger, 5 mmol scale. After heating the substrates at 250 °C for 40 min, the reaction mixture was applied to a silica gel column and the column was washed in turn with hexane (elution of Dowtherm A), ethyl acetate (elution of the less polar by-products), and ethanol (elution of the product and some by-products). The crude product obtained after the evaporation of the ethanol fraction was finally purified by column chromatography to give 3-diethoxyphosphorylpiridopyrimi-dinone **13** in a 75% yield.

Next, we extended this optimized protocol to the cyclization of the remaining acrylates **12b**–**h** (Scheme 2). In this respect, mixtures of *E* and *Z* acrylates **12b**–**h** were heated in Dowtherm A at 250 °C for the time given in Table 3. The reaction time was determined in the additional time-optimization studies, carried out in NMR tubes, as described before. The work-up of the reaction mixtures and purification of the crude products by column chromatography furnished phosphorylated azaheterocycles **14**–**21** in good to excellent yields (Table 3). Acrylates **12a**–**d**,**f**–**h** underwent fully regioselective intramolecular N-acylation followed by deprotonation to give pyridopyrimidinones **13**–**16**, pyrimidopyrimidinone **19**, benzothiazolopyrimidinone **20**, or thiazolopyrimidinone **21**. On the other hand, cyclization of acrylate **12e** gave a mixture of N- and C-cyclization products, i.e., pyridopyrimidinone **17** and naphthyridinone **18** in a 1:2 ratio, respectively. This mixture was purified and separated by column chromatography on silica gel to give pure pyridopyrimidinone **17** (14% yield) and naphthyridinone **18** (27% yield). We believe that the observed competition between N-acylation and electrophilic aromatic substitution can be attributed to the steric



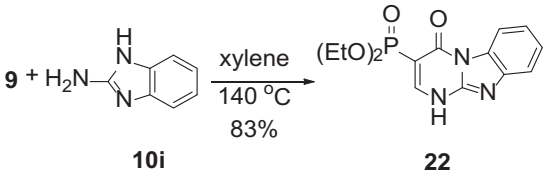
Scheme 2. Cyclization of acrylates **12b**–**h**. Reaction conditions: (i) Dowtherm A, 250 °C.

Table 3
Phosphorylated azaheterocycles **14**–**21** obtained

Substrate	Product	Reaction time (min)	Yield (%)
12b	**14**	40	84
12c	**15**	40	67
12d	**16**	40	68
12e	**17**	60	14
	18		27
12f	**19**	60	73
12g	**20**	20	89
12h	**21**	30	88

effect of the methyl group in position 6 of the pyridine ring, which hinders the N-acylation process.

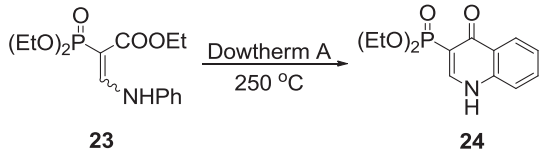
We also performed the reaction between acrylate **9** and 2-aminobenzimidazole **10i** (Scheme 3). Heating these substrates in xylene at 140 °C for 30 h produced directly final benzoimidazopyrimidinone **22**. No intermediate substitution product was detected in the reaction mixture. Relatively mild conditions in which pyrimidinone **22** is formed, when compared to those necessary for other cyclization reactions, clearly reflects the greater nucleophilicity of the benzoimidazole nitrogen atom, which facilitates intramolecular N-acylation. Purification of the crude product by column chromatography gave benzoimidazopyrimidinone **22** in an 83% yield.



Scheme 3. Synthesis of benzoimidazopyrimidinone **22**.

Finally, to test whether our methodology can also be applied in the synthesis of 3-diethoxyphosphoryl-4-quinolones, ethyl 2-diethoxyphosphoryl-3-aminophenylacrylate **23**[15] was heated in Dowtherm A at 250 °C and time-optimization studies were carried out in NMR tubes (Table 4). The best result, 30% of the expected 3-diethoxyphosphoryl-4-quinolone **24** in the reaction mixture was obtained when **23** was heated for 15 min. Disappointingly, further heating resulted in the formation of substantial amounts of difficult to identify side-products and a lower yield of **24**. Apparently, the electrophilic aromatic substitution reaction requires more drastic conditions in which the substrate and/or product is not stable. When this experiment was repeated on a 5 mmol scale, pure 3-diethoxyphosphoryl-4-quinolone **24** was obtained in a 29% yield.

Table 4
Optimalization of the intramolecular cyclization of acrylate **23**



Entry	Temperature (°C)	Reaction time (min)	**23** (%)	**24** (%)
1	250	10	66	17
2	250	15	50	30
3	250	20	46	18
4	250	40	7	3

The structures of all the final products **13**–**22** and **24** were in agreement with their IR, ^{1}H, ^{13}C, and ^{31}P NMR spectra as well as elemental analyses.

3. Conclusion

We have described a new, simple, and efficient, two-step synthesis of phosphorylated *ortho*-fused azaheterocycles **13**–**22**, starting from easily available 2-diethoxyphosphoryl-3-methoxyacrylate **9** and heteroaromatic amines **10a**–**i**. Intramolecular cyclizations of the intermediate 3-aminoacrylates **12a**–**I** proceeded effectively and usually with full *N*-regioselectivity to give a variety of azaheterocyles containing a common 6-diethoxyphosphorylpyrimidin-4-one moiety. It is worth noting that when the N-cyclization process is hampered by the steric effect (acrylate **12e**), electrophilic aromatic substitution competes effectively with N-acylation. Disappointingly, intramolecular electrophilic aromatic substitution in acrylate **23** was not effective and gave the expected 3-diethoxyphosphoryl-4-quinolone **24** only in low yield (29%).

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker DPX 250 instrument at 250.13 MHz for ^{1}H, 62.9 MHz for ^{13}C, and 101.3 MHz for ^{31}P NMR using tetramethylsilane as internal and 85% H_3PO_4 as external standard. ^{31}P NMR spectra were recorded using broadband proton decoupling. IR spectra were recorded on a Bruker Alpha ATR spectrophotometer. Melting points were determined in open capillaries and are uncorrected. Column chromatography was performed on Sigma–Aldrich silica gel 60 (230–400 mesh). All solvents, other reagents, and starting materials were purchased from commercial vendors and used without further purification.

4.2. General procedure for the preparation of acrylates 12a–h

To a solution of amine **10a**–**h** (10.0 mmol) in xylene (50 mL) 2-diethoxyphosphoryl-3-methoxyacrylate **9** (2.66 g, 10.0 mmol) was added and the mixture was heated at 140 °C for the time given in Table 1. Next, the reaction mixture was cooled and the solvent was evaporated. The crude product was purified by column chromatography (eluent: $CHCl_3$–acetone, 98:2).

*4.2.1. (E,Z)-Ethyl 2-(diethoxyphosphoryl)-3-(pyridin-2-ylamino)acrylate (**12a**).* (2.82 g, 86%, *E*/*Z*=35/65); oil; [found: C, 51.16; H, 6.52; N, 8.37. $C_{14}H_{21}N_2O_5P$ requires C, 51.22; H, 6.45; N, 8.53%]; R_f ($CHCl_3$–acetone, 98:2) 0.35; ν_{max} (film): 2904, 1563, 1217, 1020, 775 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.27–1.35 (m, 9H, C(O)OCH$_2$C*H*$_3$, P(O)(OCH$_2$C*H*$_3$)$_2$), 4.02–4.32 (m, 6H, P(O)(OC*H*$_2$CH$_3$)$_2$, C(O)OC*H*$_2$CH$_3$), 6.79–6.87 (m, 1H, C^{Ar}–*H*), 6.94–7.03 (m, 1H, C^{Ar}–*H*), 7.57–7.67 (m, 1H, C^{Ar}–*H*), 8.29–8.32 (m, 1H, C^{Ar}–*H*), 8.86 (dd, *J* 12.9, 14.2 Hz, 0.35H, =C*H*–NH (*E*)-isomer), 8.36 (dd, *J* 13.0, 39.5 Hz, 0.65H, =C*H*–NH (*Z*)-isomer), 10.98–11.09 (m, 1H, N*H*); δ_C (62.9 MHz, $CDCl_3$) 14.1 (s, C(O)CH$_2$C*H*$_3$ (*E*)-isomer), 14.3 (s, C(O)CH$_2$C*H*$_3$ (*Z*)-isomer), 16.1 (d, *J* 6.2 Hz, P(O)(OCH$_2$C*H*$_3$)$_2$ (*Z*)-isomer), 16.2 (d, *J* 5.8 Hz, P(O)(OCH$_2$C*H*$_3$)$_2$ (*E*)-isomer), 59.9 (s, C(O)OC*H*$_2$CH$_3$, (*E*)-isomer), 60.2 (s, C(O)OC*H*$_2$CH$_3$, (*Z*)-isomer), 61.7 (d, *J* 5.2 Hz, P(O)(OC*H*$_2$CH$_3$)$_2$ (*E*)-isomer), 62.2 (d, *J* 5.1 Hz, P(O)(OC*H*$_2$CH$_3$)$_2$ (*Z*)-isomer), 87.3 (d, *J* 188.9 Hz, P(O)*C*= (*Z*)-isomer), 88.5 (d, *J* 204.9 Hz, P(O)*C*= (*E*)-isomer), 111.0 (s, C^{Ar} (*E*)-isomer), 111.9 (s, C^{Ar} (*Z*)-isomer), 119.0 (s, C^{Ar} (*Z*)-isomer), 119.4 (s, C^{Ar} (*E*)-isomer), 138.3 (s, C^{Ar} (*Z*)-isomer), 138.4 (s, C^{Ar} (*E*)-isomer), 148.3 (s, C^{Ar} (*Z*)-isomer), 148.5 (s, C^{Ar} (*E*)-isomer), 150.4 (s, C^{Ar} (*E*)-isomer), 150.5 (s, C^{Ar} (*Z*)-isomer), 152.4 (d, *J* 18.8 Hz, =*C*H–N (*E*)-isomer), 152.8 (d, *J* 5.8 Hz, =*C*H–N (*Z*)-isomer), 166.3 (d, *J* 12.3 Hz, *C*(O) (*Z*)-isomer), 168.3 (d, *J* 10.9 Hz, *C*(O) (*E*)-isomer); δ_P (101.3 MHz, $CDCl_3$) 20.10 (*E*)-isomer, 21.26 (*Z*)-isomer.

*4.2.2. (E,Z)-Ethyl 2-(diethoxyphosphoryl)-3-((3-methylpyridin-2-yl) amino)acrylate (**12b**).* (2.88 g, 84%, *E*/*Z*=30/70); oil; [found: C, 52.53; H, 6.89; N, 8.20. $C_{15}H_{23}N_2O_5P$ requires C, 52.63; H, 6.77; N, 8.18%]; R_f ($CHCl_3$–acetone, 98:2) 0.30; ν_{max} (film): 2981, 1619, 1222, 1021, 785 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.28–1.36 (m, 9H, C(O)OCH$_2$C*H*$_3$, P(O)(OCH$_2$C*H*$_3$)$_2$), 2.31 (s, 3H, C*H*$_3$), 4.02–4.33 (m, 6H, P(O)(OC*H*$_2$CH$_3$)$_2$, C(O)OC*H*$_2$CH$_3$), 6.89–6.95 (m, 1H, C^{Ar}–*H*), 7.42–7.47 (m, 1H, C^{Ar}–*H*), 8.15–8.18 (m, 1H, C^{Ar}–*H*), 9.06 (dd, *J* 12.4, 14.0 Hz, 0.3H, =C*H*–NH (*E*)-isomer), 9.45 (dd, *J* 12.6, 39.6 Hz, 0.7H, =C*H*–NH (*Z*)-isomer), 11.19–11.33 (m, 1H, N*H*); δ_C (62.9 MHz, $CDCl_3$) 14.2 (s, C(O)CH$_2$C*H*$_3$ (*E*)-isomer), 14.4 (s, C(O)CH$_2$C*H*$_3$ (*Z*)-isomer), 16.1 (d, *J* 11.0 Hz, P(O)(OCH$_2$C*H*$_3$)$_2$ (*Z*)-isomer), 16.2 (s, CH$_3$), 16.3 (d, *J* 8.9 Hz, P(O)(OCH$_2$C*H*$_3$)$_2$ (*E*)-isomer), 59.9 (s, C(O)OC*H*$_2$CH$_3$, (*Z*)-isomer), 60.2 (s, C(O)OC*H*$_2$CH$_3$, (*E*)-isomer), 61.7 (d, *J* 5.3 Hz, P(O)(OC*H*$_2$CH$_3$)$_2$ (*E*)-isomer), 62.3 (d, *J* 5.4 Hz, P(O)(OC*H*$_2$CH$_3$)$_2$ (*Z*)-isomer), 87.5 (d, *J* 189.1 Hz, P(O)*C*= (*Z*)-isomer), 88.7 (d, *J* 205.3 Hz, P(O)*C*= (*E*)-isomer), 118.8 (s, C^{Ar} (*Z*)-isomer), 119.2 (s, C^{Ar} (*E*)-isomer), 119.4 (s, C^{Ar} (*E*)-isomer), 120.1 (s, C^{Ar} (*Z*)-isomer), 138.9 (s, C^{Ar} (*E*)-isomer), 139.0 (s, C^{Ar} (*Z*)-isomer), 145.6 (s, C^{Ar} (*Z*)-isomer), 145.9 (s, C^{Ar} (*E*)-isomer), 148.8 (s, C^{Ar} (*E*)-isomer), 149.2 (s, C^{Ar} (*Z*)-isomer), 152.6 (d, *J* 18.7 Hz, =*C*H–N (*E*)-isomer), 153.1 (d, *J* 5.7 Hz, =*C*H–N (*Z*)-isomer), 166.3 (d, *J* 12.4 Hz, *C*(O) (*Z*)-isomer), 168.9 (d, *J* 11.0 Hz, *C*(O) (*E*)-isomer); δ_P (101.3 MHz, $CDCl_3$) 19.97 (*E*)-isomer, 21.54 (*Z*)-isomer.

*4.2.3. (E,Z)-Ethyl 2-(diethoxyphosphoryl)-3-((4-methylpyridin-2-yl) amino)acrylate (**12c**).* (3.08 g, 90%, *E*/*Z*=30/70); oil; [found: C, 52.55; H, 6.87; N, 8.13. $C_{15}H_{23}N_2O_5P$ requires C, 52.63; H, 6.77; N, 8.18%]; R_f ($CHCl_3$–acetone, 98:2) 0.30; ν_{max} (film): 2981, 1609, 1223, 1057, 794 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.27–1.36 (m, 9H, C(O)OCH$_2$C*H*$_3$, P(O)(OCH$_2$C*H*$_3$)$_2$), 2.30 (s, 0.90H, C*H*$_3$ (*E*)-isomer), 2.33 (s, 2.10H, C*H*$_3$ (*Z*)-isomer), 4.01–4.32 (m, 6H, P(O)(OC*H*$_2$CH$_3$)$_2$, C(O)OC*H*$_2$CH$_3$), 6.63–6.66 (m, 0.30H, C^{Ar}–*H* (*Z*)-isomer), 6.71–6.73 (m, 0.70H, C^{Ar}–*H* (*E*)-isomer), 6.79–6.86 (m, 1H, C^{Ar}–*H*), 8.14–8.18 (m, 1H, C^{Ar}–*H*), 8.80 (dd, *J* 13.0, 14.2 Hz, 0.30H, =C*H*–NH (*E*)-isomer), 9.34 (dd, *J* 13.0, 39.5 Hz, 0.70H, =C*H*–NH (*Z*)-isomer), 10.94–11.10 (m, 1H, N*H*); δ_C (62.9 MHz, $CDCl_3$) 14.1 (s, C(O)CH$_2$C*H*$_3$ (*E*)-isomer), 14.3 (s, C(O)CH$_2$C*H*$_3$ (*Z*)-isomer), 16.1 (d, *J* 6.2 Hz, P(O)(OCH$_2$C*H*$_3$)$_2$ (*Z*)-isomer), 16.2 (d, *J* 5.7 Hz, P(O)(OCH$_2$C*H*$_3$)$_2$ (*E*)-isomer), 20.8 (s, CH$_3$ (*Z*)-isomer), 20.9 (s, CH$_3$ (*E*)-isomer), 59.9 (s, C(O)OC*H*$_2$CH$_3$, (*Z*)-isomer), 60.1 (s, C(O)OC*H*$_2$CH$_3$, (*E*)-isomer), 61.7 (d, *J* 5.2 Hz, P(O)(OC*H*$_2$CH$_3$)$_2$ (*E*)-isomer), 62.2 (d, *J* 5.1 Hz, P(O)(OC*H*$_2$CH$_3$)$_2$ (*Z*)-isomer), 87.0 (d, *J* 188.9 Hz, P(O)*C*= (*Z*)-isomer), 88.1 (d, *J* 204.8 Hz, P(O)*C*= (*E*)-isomer), 111.4 (s, C^{Ar} (*E*)-isomer), 112.4 (s, C^{Ar} (*Z*)-isomer), 120.3 (s, C^{Ar} (*Z*)-isomer), 120.7 (s, C^{Ar} (*E*)-isomer), 147.9 (s, C^{Ar} (*Z*)-isomer), 148.0 (s, C^{Ar} (*E*)-isomer), 149.7 (s, C^{Ar} (*Z*)-isomer), 149.9 (s, C^{Ar} (*E*)-isomer), 150.7 (s, C^{Ar}), 152.6 (d, *J* 18.8 Hz, =*C*H–N (*E*)-isomer), 153.0 (d, *J* 5.8 Hz, =*C*H–N (*Z*)-isomer), 166.3 (d, *J* 12.4 Hz, *C*(O) (*Z*)-isomer), 168.3 (d, *J* 10.8 Hz, *C*(O) (*E*)-isomer); δ_P (101.3 MHz, $CDCl_3$) 20.21 (*E*)-isomer, 21.54 (*Z*)-isomer.

*4.2.4. (E,Z)-Ethyl 2-(diethoxyphosphoryl)-3-((5-methylpyridin-2-yl) amino)acrylate (**12d**).* (2.84 g, 83%, *E*/*Z*=30/70); oil; [found: C, 52.59; H, 6.85; N, 8.24. $C_{15}H_{23}N_2O_5P$ requires C, 52.63; H, 6.77; N, 8.18%]; R_f ($CHCl_3$–acetone, 98:2) 0.30; ν_{max} (film): 2981, 1598, 1204, 1090, 1019; δ_H (250 MHz, $CDCl_3$) 1.27–1.34 (m, 9H, C(O)OCH$_2$C*H*$_3$, P(O)(OCH$_2$C*H*$_3$)$_2$), 2.26 (s, 3H C*H*$_3$), 4.01–4.30 (m, 6H, P(O)(OC*H*$_2$CH$_3$)$_2$, C(O)OC*H*$_2$CH$_3$), 6.75 (d, *J* 8.2 Hz, 0.3H, C^{Ar}–*H* (*Z*)-isomer), 6.82 (d, *J* 8.3 Hz, 0.7H, C^{Ar}–*H* (*E*)-isomer), 7.39–7.46 (m, 1H, C^{Ar}–*H*), 8.10–8.12 (m, 1H, C^{Ar}–*H*), 8.80 (dd, *J* 13.1, 14.1 Hz, 0.3H, =C*H*–NH (*E*)-isomer), 9.31 (dd, *J* 13.1, 39.5 Hz, 0.7H, =C*H*–NH (*Z*)-isomer), 10.90–10.98 (m, 1H, N*H*); δ_C (62.9 MHz, $CDCl_3$) 14.3 (s, C(O)CH$_2$C*H*$_3$ (*E*)-isomer), 14.4 (s, C(O)CH$_2$C*H*$_3$ (*Z*)-isomer), 16.2 (d, *J* 6.4 Hz, P(O)(OCH$_2$C*H*$_3$)$_2$), 17.6 (s, CH$_3$), 60.0 (s, C(O)OC*H*$_2$CH$_3$, (*Z*)-isomer), 60.2 (s, C(O)OC*H*$_2$CH$_3$, (*E*)-isomer), 62.0 (d, *J* 5.2 Hz, P(O)(OC*H*$_2$CH$_3$)$_2$ (*E*)-isomer), 62.4 (d, *J* 5.1 Hz, P(O)(OC*H*$_2$CH$_3$)$_2$ (*Z*)-isomer), 86.3 (d, *J* 190.2 Hz, P(O)*C*= (*Z*)-isomer), 87.2 (d, *J* 207.5 Hz, P(O)*C*= (*E*)-isomer), 110.5 (s, C^{Ar} (*E*)-isomer), 111.6 (s, C^{Ar} (*Z*)-

isomer), 128.6 (s, C^{Ar} (*Z*)-isomer), 129.0 (s, C^{Ar} (*E*)-isomer), 139.0 (s, C^{Ar} (*Z*)-isomer), 139.2 (s, C^{Ar} (*E*)-isomer), 148.3 (s, C^{Ar} (*Z*)-isomer), 148.5 (s, C^{Ar} (*E*)-isomer), 148.6 (s, C^{Ar}), 152.9 (d, *J* 19.3 Hz, =*C*H–N (*E*)-isomer), 153.2 (d, *J* 6.1 Hz, =*C*H–N (*Z*)-isomer), 166.6 (d, *J* 12.5 Hz, *C*(O) (*Z*)-isomer), 168.4 (d, *J* 11.0 Hz, *C*(O) (*E*)-isomer); δ_P (101.3 MHz, $CDCl_3$) 19.86 (*E*)-isomer, 21.33 (*Z*)-isomer.

*4.2.5. (E,Z)-Ethyl 2-(diethoxyphosphoryl)-3-((6-methylpyridin-2-yl) amino)acrylate (**12e**).* (2.77 g, 81%, *E*/*Z*=30/70); oil; [found: C, 52.60; H, 6.84; N, 8.10. $C_{15}H_{23}N_2O_5P$ requires C, 52.63; H, 6.77; N, 8.18%]; R_f ($CHCl_3$–acetone, 98:2) 0.30; ν_{max} (film): 2981, 1564, 1212, 1018, 786 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.10–1.17 (m, 9H, C(O)OCH_2CH_3, P(O)$(OCH_2CH_3)_2$), 2.27 (s, 3H, CH_3), 3.84–4.13 (m, 6H, P(O)$(OCH_2CH_3)_2$, C(O)OCH_2CH_3), 6.42–6.50 (m, 1H, C^{Ar}–*H*), 6.63–6.69 (m, 1H, C^{Ar}–*H*), 7.27–7.37 (m, 1H, C^{Ar}–*H*), 8.74 (dd, *J* 12.9, 13.0 Hz, 0.3H, =*C*H–NH (*E*)-isomer), 9.21 (dd, *J* 13.1, 39.5 Hz, 0.7H, =*C*H–NH (*Z*)-isomer), 10.76–10.85 (m, 1H, N*H*); δ_C (62.9 MHz, $CDCl_3$) 14.2 (s, C(O)CH_2CH_3 (*E*)-isomer), 14.3 (s, C(O)CH_2CH_3 (*Z*)-isomer), 16.1 (d, *J* 6.7 Hz, P(O)$(OCH_2CH_3)_2$ (*Z*)-isomer), 16.2 (d, *J* 6.6 Hz, P(O)$(OCH_2CH_3)_2$ (*E*)-isomer), 24.0 (s, CH_3 (*E*)-isomer), 24.1 (s, CH_3 (*Z*)-isomer), 59.9 (s, C(O)OCH_2CH_3, (*Z*)-isomer), 60.1 (s, C(O)OCH_2CH_3, (*E*)-isomer), 61.7 (d, *J* 5.2 Hz, P(O)$(OCH_2CH_3)_2$ (*E*)-isomer), 62.1 (d, *J* 5.1 Hz, P(O)$(OCH_2CH_3)_2$ (*Z*)-isomer), 86.5 (d, *J* 188.7 Hz, P(O)*C*= (*Z*)-isomer), 87.9 (d, *J* 204.9 Hz, P(O)*C*= (*E*)-isomer), 107.9 (s, C^{Ar} (*E*)-isomer), 108.6 (s, C^{Ar} (*Z*)-isomer), 118.5 (s, C^{Ar} (*Z*)-isomer), 118.9 (s, C^{Ar} (*E*)-isomer), 138.4 (s, C^{Ar} (*Z*)-isomer), 138.6 (s, C^{Ar} (*E*)-isomer), 149.7 (s, C^{Ar} (*E*)-isomer), 149.8 (s, C^{Ar} (*Z*)-isomer), 152.5 (s, C^{Ar} (*E*)-isomer), 152.8 (s, C^{Ar} (*Z*)-isomer), 153.2 (d, *J* 6.0 Hz, =*C*H–N (*E*)-isomer), 157.8 (d, *J* 10.3 Hz, =*C*H–N (*Z*)-isomer), 166.6 (d, *J* 12.0 Hz, *C*(O) (*Z*)-isomer), 168.4 (d, *J* 10.9 Hz, *C*(O) (*E*)-isomer); δ_P (101.3 MHz, $CDCl_3$) 20.04 (*E*)-isomer, 21.49 (*Z*)-isomer.

*4.2.6. (E)-Ethyl 2-(diethoxyphosphoryl)-3-(pyrimidin-2-ylamino)acrylate (E)-(**12f**).* (0.95 g, 29%); oil; [found: C, 47.30; H, 6.21; N, 12.59. $C_{13}H_{20}N_3O_5P$ requires C, 47.42; H, 6.12; N, 12.76%]; R_f ($CHCl_3$–acetone, 98:2) 0.25; ν_{max} (film): 2981, 1612, 1562, 1391, 1202, 1018 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.31 (t, *J* 7.2 Hz, 9H, $CH_3CH_2OC(O)$, $(CH_3CH_2O)_2P(O)$), 4.01–4.18 (m, 4H, $(CH_3CH_2O)_2P(O)$), 4.27 (q, *J* 7.2 Hz, 2H, $CH_3CH_2OC(O)$), 6.96 (t, *J* 4.8 Hz, 1H, C^{Ar}–*H*), 8.50 (d, *J* 4.8 Hz, 2H, C^{Ar}–*H*), 8.88 (dd, *J* 12.9, 14.8 Hz, 1H, =*C*H–NH), 10.96 (d, *J* 12.9 Hz, 1H, N*H*); δ_C (62.9 MHz, $CDCl_3$) 14.0 (s, $CH_3CH_2OC(O)$), 16.1 (d, *J* 6.6 Hz, $(CH_3CH_2O)_2P(O)$), 60.3 (s, $CH_3CH_2OC(O)$), 61.8 (d, *J* 5.3 Hz, $CH_3CH_2OP(O)$), 91.1 (d, *J* 203.6 Hz, P(O)*C*=), 116.5 (s, C^{Ar}), 152.1 (d, *J* 19.0 Hz, =*C*H–N), 156.7 (s, C^{Ar}), 158.3 (s, C^{Ar}), 167.3 (d, *J* 10.7 Hz, *C*(O)); δ_P (101.3 MHz, $CDCl_3$) 18.86.

*4.2.7. (Z)-Ethyl 2-(diethoxyphosphoryl)-3-(pyrimidin-2-ylamino)acrylate (Z)-(**12f**).* (1.42 g, 43%); oil; [found: C, 47.27; H, 6.23; N, 12.61. $C_{13}H_{20}N_3O_5P$ requires C, 47.42; H, 6.12; N, 12.76%]; R_f ($CHCl_3$–acetone, 98:2) 0.35; ν_{max} (film): 2981, 1612, 1562, 1391, 1202, 1018 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.30 (t, *J* 7.1 Hz, 3H, $CH_3CH_2OC(O)$), 1.32 (t, *J* 7.0 Hz, 6H, $(CH_3CH_2O)_2P(O)$), 4.03–4.19 (m, 4H, $(CH_3CH_2O)_2P(O)$), 4.25 (q, *J* 7.1 Hz, 2H, $CH_3CH_2OC(O)$), 6.95 (t, *J* 4.8 Hz, 1H, C^{Ar}–*H*), 8.51 (d, *J* 4.8 Hz, 2H, C^{Ar}–*H*), 9.29 (dd, *J* 13.1, 39.3 Hz, 1H, =*C*H–NH), 11.15 (d, *J* 13.1 Hz, 1H, N*H*); δ_C (62.9 MHz, $CDCl_3$) 14.2 (s, $CH_3CH_2OC(O)$), 16.1 (d, *J* 6.6 Hz, $(CH_3CH_2O)_2P(O)$), 60.2 (s, $CH_3CH_2OC(O)$), 62.2 (d, *J* 5.1 Hz, $CH_3CH_2OP(O)$), 90.5 (d, *J* 187.6 Hz, P(O)*C*=), 116.1 (s, C^{Ar}), 152.8 (d, *J* 5.0 Hz, =*C*H–N), 156.8 (s, C^{Ar}), 158.2 (s, C^{Ar}), 165.9 (d, *J* 11.7 Hz, *C*(O)); δ_P (101.3 MHz, $CDCl_3$) 19.34.

*4.2.8. (E,Z)-Ethyl 3-(benzo[d]thiazol-2-ylamino)-2-(diethoxyphosphoryl)acrylate **12g**.* (3.42 g, 89%, *E*/*Z*=30/70); oil; [found: C, 49.80; H, 5.67; N, 7.14. $C_{16}H_{21}N_2O_5PS$ requires C, 49.99; H, 5.51; N, 7.29%]; R_f ($CHCl_3$–acetone, 98:2) 0.35; ν_{max} (film): 2980, 1606, 1525, 1209, 1016 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.29–1.36 (m, 9H, C(O)OCH_2CH_3, P(O)$(OCH_2CH_3)_2$), 4.00–4.33 (m, 6H, P(O)$(OCH_2CH_3)_2$, C(O)OCH_2CH_3), 7.22–7.29 (m, 1H, C^{Ar}–*H*), 7.36–7.43 (m, 1H, C^{Ar}–*H*), 7.68–7.78 (m, 2H, C^{Ar}–*H*), 8.52 (dd, *J* 12.2, 14.2 Hz, 0.3H, =*C*H–NH (*E*)-isomer), 9.02 (dd, *J* 12.3, 38.8 Hz, 0.7H, =*C*H–NH (*Z*)-isomer), 11.36 (d, *J* 12.2 Hz, 0.3H, N*H* (*E*)-isomer), 11.52 (d, *J* 12.3 Hz, 0.7H, N*H* (*Z*)-isomer); δ_C (62.9 MHz, $CDCl_3$) 14.0 (s, C(O)CH_2CH_3 (*E*)-isomer), 14.3 (s, C(O)CH_2CH_3 (*Z*)-isomer), 16.0 (d, *J* 6.7 Hz, P(O)$(OCH_2CH_3)_2$ (*Z*)-isomer), 16.2 (d, *J* 6.7 Hz, P(O)$(OCH_2CH_3)_2$ (*E*)-isomer), 60.5 (s, C(O)OCH_2CH_3, (*Z*)-isomer), 60.8 (s, C(O)OCH_2CH_3, (*E*)-isomer), 62.0 (d, *J* 5.4 Hz, P(O)$(OCH_2CH_3)_2$ (*E*)-isomer), 62.7 (d, *J* 5.4 Hz, P(O)$(OCH_2CH_3)_2$ (*Z*)-isomer), 91.9 (d, *J* 186.2 Hz, P(O)*C*= (*Z*)-isomer), 92.7 (d, *J* 202.1 Hz, P(O)*C*= (*E*)-isomer), 121.1 (s, C^{Ar}), 121.2 (s, C^{Ar} (*Z*)-isomer), 121.5 (s, C^{Ar} (*E*)-isomer), 123.9 (s, C^{Ar} (*E*)-isomer), 124.1 (s, C^{Ar} (*Z*)-isomer), 126.4 (s, C^{Ar} (*Z*)-isomer), 126.5 (s, C^{Ar} (*E*)-isomer), 131.4 (s, C^{Ar} (*E*)-isomer), 131.6 (s, C^{Ar} (*Z*)-isomer), 150.8 (s, C^{Ar} (*E*)-isomer), 150.9 (s, C^{Ar} (*Z*)-isomer), 152.5 (d, *J* 18.4 Hz, =*C*H–N (*E*)-isomer), 152.8 (d, *J* 5.2 Hz, =*C*H–N (*Z*)-isomer), 159.5 (s, C^{Ar} (*E*)-isomer), 159.7 (s, C^{Ar} (*Z*)-isomer), 165.3 (d, *J* 11.3 Hz, *C*(O) (*E*)-isomer), 167.7 (d, *J* 10.0 Hz, *C*(O) (*E*)-isomer); δ_P (101.3 MHz, $CDCl_3$) 17.28 (*E*)-isomer, 19.00 (*Z*)-isomer.

*4.2.9. (E,Z)-Ethyl 2-(diethoxyphosphoryl)-3-(thiazol-2-ylamino)acrylate (**12h**).* (3.04 g, 91%, *E*/*Z*=30/70); oil; [found: C, 43.08; H, 5.79; N, 8.24. $C_{12}H_{19}N_2O_5PS$ requires C, 43.11; H, 5.73; N, 8.38%]; R_f ($CHCl_3$–acetone, 98:2) 0.40; ν_{max} (film): 2980, 1606, 1525, 1209, 1016 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.32 (t, *J* 7.2 Hz, 9H, $CH_3CH_2OC(O)$, $(CH_3CH_2O)_2P(O)$), 4.00–4.33 (m, 6H, P(O)$(OCH_2CH_3)_2$, C(O)OCH_2CH_3), 6.86 (d, *J* 3.5 Hz, 0.7H, C^{Ar}–*H* (*Z*)-isomer), 6.89 (d, *J*=3.5 Hz, 0.3H, C^{Ar}–*H* (*E*)-isomer), 7.36 (d, *J* 3.5 Hz, 0.7H, C^{Ar}–*H* (*Z*)-isomer), 7.37 (d, *J* 3.5 Hz, 0.3H, C^{Ar}–*H* (*E*)-isomer), 8.38 (dd, *J* 12.5, 14.0 Hz, 0.3H, =*C*H–NH (*E*)-isomer), 8.92 (dd, *J* 12.3, 38.7 Hz, 0.7H, =*C*H–NH (*Z*)-isomer), 11.35 (d, *J* 12.5 Hz, 0.3H, N*H* (*E*)-isomer), 11.45 (d, *J* 12.3 Hz, 0.7H, N*H* (*Z*)-isomer); δ_C (62.9 MHz, $CDCl_3$) 14.1 (s, C(O)CH_2CH_3 (*E*)-isomer), 14.3 (s, C(O)CH_2CH_3 (*Z*)-isomer), 16.0 (d, *J* 6.4 Hz, P(O)$(OCH_2CH_3)_2$ (*Z*)-isomer), 16.2 (d, *J* 6.4 Hz, P(O)$(OCH_2CH_3)_2$ (*E*)-isomer), 60.3 (s, C(O)OCH_2CH_3, (*Z*)-isomer), 60.6 (s, C(O)OCH_2CH_3, (*E*)-isomer), 61.9 (d, *J* 5.4 Hz, P(O)$(OCH_2CH_3)_2$ (*E*)-isomer), 62.5 (d, *J* 5.3 Hz, P(O)$(OCH_2CH_3)_2$ (*Z*)-isomer), 89.8 (d, *J* 187.4 Hz, P(O)*C*= (*Z*)-isomer), 90.9 (d, *J* 203.5 Hz, P(O)*C*= (*E*)-isomer), 112.5 (s, C^{Ar} (*Z*)-isomer), 112.7 (s, C^{Ar} (*E*)-isomer), 139.7 (s, C^{Ar} (*Z*)-isomer), 140.0 (s, C^{Ar} (*E*)-isomer), 152.9 (d, *J* 18.3 Hz, =*C*H–N (*E*)-isomer), 153.2 (d, *J* 5.7 Hz, =*C*H–N (*Z*)-isomer), 161.4 (s, C^{Ar}), 165.5 (d, *J* 11.4 Hz, *C*(O) (*E*)-isomer), 167.9 (d, *J* 10.1 Hz, *C*(O) (*E*)-isomer); δ_P (101.3 MHz, $CDCl_3$) 17.79 (*E*)-isomer, 19.63 (*Z*)-isomer.

4.3. General procedure for the preparation of phosphonates 13–21 and 23

A solution of acrylate **12a**–**h** or **24** (5 mmol) in Dowtherm A (50 mL) was heated for the time given in Tables 3 or 4. After cooling, the reaction mixture was applied to a silica gel column. The column was washed in turn with hexane (150 mL), ethyl acetate (150 mL), and ethanol (150 mL). The ethanol fraction was evaporated and the residue purified by column chromatography (eluent: EtOAc–MeOH, 10:1).

*4.3.1. Diethyl (4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl)phosphonate (**13**).* (1.06 g, 75%); white solid; mp 148–150 °C; [found: C, 51.01; H, 5.48; N, 9.84. $C_{12}H_{15}N_2O_4P$ requires C, 51.07; H, 5.36; N, 9.93%]; R_f (EtOAc–MeOH, 10:1) 0.20; ν_{max} (film): 2981, 1693, 1481, 1015, 801 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.21 (t, *J* 7.1 Hz, 6H, P(O)$(OCH_2CH_3)_2$), 4.00–4.22 (m, 4H, P(O)$(OCH_2CH_3)_2$), 7.29–7.35 (m, 1H, C^{Ar}–*H*), 7.62–7.67 (m, 1H, C^{Ar}–*H*), 7.91–7.99 (m, 1H, C^{Ar}–*H*), 8.62 (d, *J* 8.8 Hz, PC=C*H*), 9.00–9.04 (m, 1H, C^{Ar}–*H*); δ_C (62.9 MHz, $CDCl_3$) 16.2 (d, *J* 6.5 Hz, P(O)$(OCH_2CH_3)_2$), 62.6 (d, *J* 5.7 Hz, P(O)$(OCH_2CH_3)_2$), 102.6 (d, *J* 199.1 Hz, P(O)*C*=), 117.1 (s, C^{Ar}), 126.7

(s, C^{Ar}), 127.9 (s, C^{Ar}), 139.0 (s, C^{Ar}), 153.4 (s, C^{Ar}), 156.2 (d, *J* 13.4 Hz, *C*(O)), 160.7 (d, *J* 10.0 Hz, PC=*C*H–N); δ_P (101.3 MHz, $CDCl_3$) 14.84.

*4.3.2. Diethyl (9-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl)phosphonate (**14**).* (0.99 g, 67%); orange solid; mp 80–82 °C; [found: C, 52.61; H, 5.88; N, 9.40. $C_{13}H_{17}N_2O_4P$ requires C, 52.70; H, 5.78; N, 9.46%]; R_f (EtOAc–MeOH, 10:1) 0.25; ν_{max} (film): 2982, 1693, 1479, 1012, 773 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.35 (t, *J* 7.1 Hz, 6H, P(O)(OCH_2CH_3)$_2$), 2.64 (s, 3H, CH_3), 4.16–4.33 (m, 4H, P(O)(OCH_2CH_3)$_2$), 7.22 (t, *J* 7.0 Hz, 1H, C^{Ar}–*H*), 7.79 (d, *J* 7.0 Hz, 1H, C^{Ar}–*H*), 8.81 (d, *J* 8.6 Hz, 1H, PC=C*H*), 9.09 (d, *J* 7.0 Hz, 1H, C^{Ar}–*H*); δ_C (62.9 MHz, $CDCl_3$) 16.2 (d, *J* 6.6, P(O)(OCH_2CH_3)$_2$), 17.9 (s, CH_3), 63.0 (d, *J* 5.5 Hz, P(O)(OCH_2CH_3)$_2$), 101.4 (d, *J* 200.4 Hz, P(O)*C*=), 117.2 (s, C^{Ar}), 126.3 (s, C^{Ar}), 135.6 (s, C^{Ar}), 138.5 (s, C^{Ar}), 152.6 (s, C^{Ar}), 157.7 (d, *J* 14.5 Hz, *C*(O)), 159.5 (d, *J* 9.5 Hz, PC=*C*H–N); δ_P (101.3 MHz, $CDCl_3$) 15.59.

*4.3.3. Diethyl (8-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl)phosphonate (**15**).* (1.27 g, 86%); orange solid; mp 85–87 °C; [found: C, 52.57; H, 5.90; N, 9.38. $C_{13}H_{17}N_2O_4P$ requires C, 52.70; H, 5.78; N, 9.46%]; R_f (EtOAc–MeOH, 10:1) 0.25; ν_{max} (film): 2978, 1681, 1388, 1016, 799 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.26 (t, *J* 7.1 Hz, 6H, P(O)(OCH_2CH_3)$_2$), 2.48 (s, 3H, CH_3), 4.02–4.26 (m, 4H, P(O)(OCH_2CH_3)$_2$), 7.12 (dd, *J* 1.8, 7.3 Hz, 1H, C^{Ar}–*H*), 7.46 (d, *J* 1.8 Hz, 1H, C^{Ar}–*H*), 8.64 (d, *J* 8.7 Hz, 1H, PC=C*H*), 8.98 (d, *J* 7.3 Hz, 1H, C^{Ar}–*H*); δ_C (62.9 MHz, $CDCl_3$) 16.2 (d, *J* 6.6 Hz, P(O)(OCH_2CH_3)$_2$), 21.55 (s, CH_3), 62.7 (d, *J* 5.6 Hz, P(O)(OCH_2CH_3)$_2$), 101.0 (d, *J* 200.6 Hz, P(O)*C*=), 119.9 (s, C^{Ar}), 124.9 (s, C^{Ar}), 127.3 (s, C^{Ar}), 152.2 (s, C^{Ar}), 153.1 (s, C^{Ar}), 156.6 (d, *J* 13.8 Hz, *C*(O)), 160.8 (d, *J* 9.9 Hz, PC=*C*H–N); δ_P (101.3 MHz, $CDCl_3$) 15.51.

*4.3.4. Diethyl (7-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl)phosphonate (**16**).* (1.01 g, 68%); orange solid; mp 81–82 °C; [found: C, 52.54; H, 5.97; N, 9.35. $C_{13}H_{17}N_2O_4P$ requires C, 52.70; H, 5.78; N, 9.46%]; R_f (EtOAc–MeOH, 10:1) 0.25; ν_{max} (film): 2983, 1681, 1484, 1230, 1014, 957 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.32 (t, *J* 7.3 Hz, 6H, P(O)(OCH_2CH_3)$_2$), 2.44 (s, 3H, CH_3), 4.11–4.28 (m, 4H, P(O)(OCH_2CH_3)$_2$), 7.66 (d, *J* 9.0 Hz, 1H, C^{Ar}–*H*), 7.78 (dd, *J* 2.1, 9.0 Hz, 1H, C^{Ar}–*H*), 8.73 (d, *J* 8.7 Hz, 1H, PC=C*H*), 8.93 (d, *J* 2.1 Hz, 1H, C^{Ar}–*H*); δ_C (62.9 MHz, $CDCl_3$) 16.1 (d, *J* 6.6 Hz, P(O)(OCH_2CH_3)$_2$), 18.2 (s, CH_3), 62.6 (d, *J* 5.6 Hz, P(O)(OCH_2CH_3)$_2$), 101.6 (d, *J* 199.3 Hz, P(O)*C*=), 125.4 (s, C^{Ar}), 126.0 (s, C^{Ar}), 127.9 (s, C^{Ar}), 141.8 (s, C^{Ar}), 152.0 (s, C^{Ar}), 156.2 (d, *J* 13.7 Hz, *C*(O)), 160.0 (d, *J* 9.9 Hz, PC=*C*H–N); δ_P (101.3 MHz, $CDCl_3$) 15.47.

*4.3.5. Diethyl (6-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl)phosphonate (**17**).* (0.21 g, 14%); orange solid; mp 81–83 °C; [found: C, 52.58; H, 5.96; N, 9.40. $C_{13}H_{17}N_2O_4P$ requires C, 52.70; H, 5.78; N, 9.46%]; R_f (EtOAc–MeOH, 10:1) 0.25; ν_{max} (film): 2908, 1632, 1477, 1234, 1015, 797 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.31 (t, *J* 7.1 Hz, 6H, P(O)(OCH_2CH_3)$_2$), 3.04 (s, 3H, CH_3), 4.07–4.29 (m, 4H, P(O)(OCH_2CH_3)$_2$), 6.81 (d, *J* 6.9 Hz, 1H, C^{Ar}–*H*), 7.45 (d, *J* 8.8 Hz, 1H, C^{Ar}–*H*), 7.60 (dd, *J* 6.9, 8.8 Hz, 1H, C^{Ar}–*H*), 8.55 (d, *J* 8.6 Hz, 1H, PC=C*H*); δ_C (62.9 MHz, $CDCl_3$) 16.3 (d, *J* 6.5 Hz, P(O)(OCH_2CH_3)$_2$), 24.8 (s, CH_3), 62.4 (d, *J* 5.6 Hz, P(O)(OCH_2CH_3)$_2$), 104.5 (d, *J* 199.6 Hz, P(O)*C*=), 120.1 (s, C^{Ar}), 125.3 (s, C^{Ar}), 137.9 (s, C^{Ar}), 145.4 (s, C^{Ar}), 156.1 (s, C^{Ar}), 159.7 (d, *J* 9.8 Hz, PC=*C*H–N), 160.1 (d, *J* 13.8 Hz, *C*(O)); δ_P (101.3 MHz, $CDCl_3$) 15.92.

*4.3.6. Diethyl (7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridin-3-yl)phosphonate (**18**).* (0.40 g, 27%), white solid; mp 100–102 °C; [found: C, 52.63; H, 5.83; N, 9.38. $C_{13}H_{17}N_2O_4P$ requires C, 52.70; H, 5.78; N, 9.46%]; R_f (EtOAc–MeOH, 10:1) 0.40; ν_{max} (film): 2983, 1709, 1477, 1016, 797 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.32 (t, *J* 7.1 Hz, 6H, P(O)(OCH_2CH_3)$_2$), 2.56 (s, 3H, CH_3), 4.14–4.36 (m, 4H, P(O)(OCH_2CH_3)$_2$), 7.16 (d, *J* 8.1 Hz, 1H, C^{Ar}–*H*), 8.51 (d, *J* 8.1 Hz, 1H, C^{Ar}–*H*), 8.52 (d, *J* 12.8 Hz, 1H, PC=C*H*), 12.19 (br s, 1H, N*H*); δ_C (62.9 MHz, $CDCl_3$) 16.3 (d, *J* 6.5 Hz, P(O)(OCH_2CH_3)$_2$), 24.7 (s, CH_3), 62.6 (d, *J* 5.7 Hz, P(O)(OCH_2CH_3)$_2$), 107.9 (d, *J* 196.7 Hz, P(O)*C*=), 119.0 (d, *J* 11.3 Hz, C^{Ar}), 121.1 (s, C^{Ar}), 135.7 (s, C^{Ar}), 147.9 (d, *J* 17.1 Hz, PC=*C*H–N), 150.3 (s, C^{Ar}), 163.6 (s, C^{Ar}), 177.4 (d, *J* 4.9 Hz, *C*(O)); δ_P (101.3 MHz, $CDCl_3$) 17.92.

*4.3.7. Diethyl (4-oxo-4H-pyrimido[1,2-a]pyrimidin-3-yl)phosphonate (**19**).* (1.03 g, 73%); brown oil; [found: C, 46.54; H, 5.07; N, 14.67. $C_{13}H_{17}N_2O_4P$ requires C, 46.65; H, 4.98; N, 14.84%]; R_f (EtOAc–MeOH, 10:1) 0.30; ν_{max} (film): 2981, 1679, 1521, 1216, 1013, 960 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.30 (t, *J* 7.1 Hz, 6H, P(O)(OCH_2CH_3)$_2$), 4.07–4.29 (m, 4H, P(O)(OCH_2CH_3)$_2$), 7.38 (dd, *J* 7.0, 4.0 Hz, 1H, C^{Ar}–*H*), 8.89 (d, *J* 9.1 Hz, 1H, PC=C*H*), 9.16 (dd, *J* 4.0, 2.3 Hz, 1H, C^{Ar}–*H*), 9.34 (dd, *J* 7.0, 2.3 Hz, 1H, C^{Ar}–*H*); δ_C (62.9 MHz, $CDCl_3$) 16.9 (d, *J* 6.4 Hz, P(O)(OCH_2CH_3)$_2$), 62.8 (d, *J* 5.7 Hz, P(O)(OCH_2CH_3)$_2$), 104.3 (d, *J* 199.9 Hz, P(O)*C*=), 113.6 (s, C^{Ar}), 136.9 (s, C^{Ar}), 154.0 (s, C^{Ar}), 156.3 (d, *J* 14.2 Hz, *C*(O)), 163.1 (d, *J* 10.5 Hz, PC=*C*H–N), 164.3 (s, C^{Ar}); δ_P (101.3 MHz, $CDCl_3$) 13.81.

*4.3.8. Diethyl (4-oxo-4H-benzo[4,5]thiazolo[3,2-a]pyrimidin-3-yl)phosphonate (**20**).* (1.51 g, 89%); yellow solid; mp 70–73 °C; [found: C, 49.59; H, 4.57; N, 8.14. $C_{14}H_{15}N_2O_4PS$ requires C, 49.70; H, 4.47; N, 8.28%]; R_f (EtOAc–MeOH, 10:1) 0.35; ν_{max} (film): 2977, 1691, 1485, 1348, 1235, 1012 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.43 (t, *J* 7.1 Hz, 6H, P(O)(OCH_2CH_3)$_2$), 4.23–4.40 (m, 4H, P(O)(OCH_2CH_3)$_2$), 7.55–7.66 (m, 2H, C^{Ar}–*H*), 7.76–7.81 (m, 1H, C^{Ar}–*H*), 8.60 (d, *J* 9.6 Hz, 1H, PC=C*H*), 9.14–9.18 (m, 1H, C^{Ar}–*H*); δ_C (62.9 MHz, $CDCl_3$) 16.2 (d, *J* 6.4 Hz, P(O)(OCH_2CH_3)$_2$), 62.7 (d, *J* 5.8 Hz, P(O)(OCH_2CH_3)$_2$), 108.6 (d, *J* 197.7 Hz, P(O)*C*=), 120.3 (s, C^{Ar}), 121.8 (s, C^{Ar}), 123.9 (s, C^{Ar}), 127.3 (s, C^{Ar}), 127.5 (s, C^{Ar}), 135.5 (s, C^{Ar}), 158.8 (d, *J* 12.8 Hz, *C*(O)), 159.1 (d, *J* 11.1 Hz, PC=*C*H–N), 166.3 (s, C^{Ar}); δ_P (101.3 MHz, $CDCl_3$) 14.41.

*4.3.9. Diethyl (5-oxo-5H-thiazolo[3,2-a]pyrimidin-6-yl)phosphonate (**21**).* (1.25 g, 87%); yellow oil; [found: C, 41.60; H, 4.61; N, 9.70. $C_{10}H_{13}N_2O_4PS$ requires C, 41.67; H, 4.55; N, 9.72%]; R_f (EtOAc–MeOH, 10:1) 0.30; ν_{max} (film): 2981, 1679, 1475, 1350, 1223, 1016 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.36 (t, *J* 7.1 Hz, 6H, P(O)(OCH_2CH_3)$_2$), 4.14–4.31 (m, 4H, P(O)(OCH_2CH_3)$_2$), 7.16 (d, *J* 4.9 Hz, 1H, SC*H*=CHN), 8.10 (d, *J* 4.9 Hz, 1H, SCH=C*H*N), 9.47 (d, *J* 9.5 Hz, 1H, PC=C*H*); δ_C (62.9 MHz, $CDCl_3$) 16.1 (d, *J* 6.5 Hz, P(O)(OCH_2CH_3)$_2$), 62.5 (d, *J* 5.8 Hz, P(O)(OCH_2CH_3)$_2$), 104.6 (d, *J* 197.9 Hz, P(O)*C*=), 113.2 (s, SCH=CHN), 122.2 (s, SCH=*C*HN), 156.3 (d, *J* 12.9 Hz, *C*(O)), 159.7 (d, *J* 11.6 Hz, PC=*C*H–N), 166.8 (s, CN=*C*S); δ_P (101.3 MHz, $CDCl_3$) 14.77.

*4.3.10. Diethyl (4-oxo-1,4-dihydroquinolin-3-yl)phosphonate (**24**).* (0.41 g, 29%); white solid; mp 68–70 °C; [found: C, 55.43; H, 5.89; N, 4.87. $C_{13}H_{16}NO_4P$ requires C, 55.52; H, 5.73; N, 4.98%]; R_f (EtOAc–MeOH, 10:1) 0.40; ν_{max} (film): 3081, 2905, 1474, 1195, 1018, 790 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.32 (t, *J* 7.0 Hz, 6H, P(O)(OCH_2CH_3)$_2$), 4.14–4.28 (m, 4H, P(O)(OCH_2CH_3)$_2$), 7.36 (dd, *J* 6.9, 8.1 Hz, 1H, C^{Ar}–*H*), 7.61 (dd, *J* 6.9, 8.1 Hz, 1H, C^{Ar}–*H*), 7.77 (d, *J* 8.1 Hz, 1H, C^{Ar}–*H*), 8.32 (d, *J* 8.1 Hz, 1H, C^{Ar}–*H*), 8.45 (dd, *J* 6.4, 12.1 Hz, 1H, PC=C*H*), 12.19 (br s, 1H, N*H*); δ_C (62.9 MHz, $CDCl_3$) 16.2 (d, *J* 6.6 Hz, P(O)(OCH_2CH_3)$_2$), 62.3 (d, *J* 5.4 Hz, P(O)(OCH_2CH_3)$_2$), 105.8 (d, *J* 196.6 Hz, P(O)*C*=), 119.4 (s, C^{Ar}), 124.9 (s, C^{Ar}), 125.4 (s, C^{Ar}), 126.2 (d, *J* 10.4 Hz, C^{Ar}), 132.6 (s, C^{Ar}), 140.3 (s, C^{Ar}), 147.0 (d, *J* 16.2 Hz, PC=*C*H–N), 177.8 (d, *J* 4.9 Hz, *C*(O)); δ_P (101.3 MHz, $CDCl_3$) 18.82.

4.4. Preparation of diethyl (4-oxo-4,10-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-3-yl)phosphonate (22)

To a solution of 2-aminobenzimidazole **10i** (10.0 mmol) in xylene (50 mL), 2-diethoxyphosphoryl-3-methoxyacrylate **9** (2.66 g, 10.0 mmol) was added. The mixture was heated at 140 °C for 30 h.

Next, the mixture was cooled and the solvent was evaporated. The crude product was purified by column chromatography (eluent: $CHCl_3$–acetone 98:2) to give **22** (2.18 g, 68%) as a white solid; mp 171–173 °C; [found: C, 52.30; H, 5.14; N, 13.01. $C_{14}H_{16}N_3O_4P$ requires C, 52.34; H, 5.02; N, 13.08%]; R_f ($CHCl_3$–acetone, 98:2) 0.20; ν_{max} (film): 2981, 1677, 1597, 1208, 1018; δ_H (250 MHz, $CDCl_3$) 1.38 (t, J 7.0 Hz, 6H, P(O)(OCH_2CH_3)$_2$), 4.10–4.40 (m, 4H, P(O)(OCH_2CH_3)$_2$), 7.37 (t, J 7.9 Hz, 1H, C^{Ar}–H), 7.48 (t, J 7.9 Hz, 1H, C^{Ar}–H), 7.61 (d, J 7.9 Hz, 1H, C^{Ar}–H), 8.59 (d, J 7.9 Hz, 1H, C^{Ar}–H), 8.70 (d, J 10.0 Hz, 1H, PC=CH), 10.68 (br s, 1H, NH); δ_C (62.9 MHz, $CDCl_3$) 16.2 (d, J 6.6 Hz, P(O)(OCH_2CH_3)$_2$), 62.7 (d, J 5.7 Hz, P(O)(OCH_2CH_3)$_2$), 99.8 (d, J 203.9 Hz, P(O)C=), 112.3 (s, C^{Ar}), 116.6 (s, C^{Ar}), 123.1 (s, C^{Ar}), 126.0 (s, C^{Ar}), 126.5 (s, C^{Ar}), 130.7 (s, C^{Ar}), 150.6 (s, C^{Ar}), 158.3 (d, J 13.4 Hz, C(O)), 160.1 (d, J 12.9 Hz, PC=CH–N); δ_P (101.3 MHz, $CDCl_3$) 17.39.

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