Michael Addition of N-Heteroaromatics to Vinylphosphonates and Synthesis of Phosphoryl Pyrrolizones by Cyclization of Michael Adducts

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Abstract: Novel phosphonate compounds were synthesized via Michael addition of N-heteroaromatic compounds to aryl- and alkyl-substituted vinylphosphonates using scandium triflate as the catalyst. Intramolecular cyclization reaction of the Michael adducts obtained gives novel (dimethoxyphosphoryl)pyrrolizin-3-ones in high yields as a single diastereomer.

Key words: phosphonates, pyrrolizinones, Michael addition, metal triflates, heteroaromatic compounds

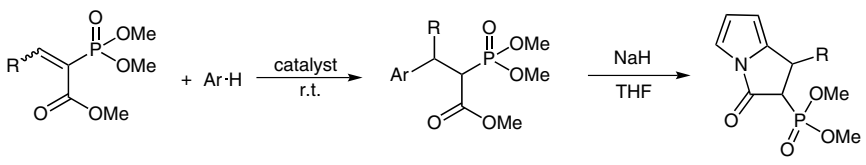
Phosphonates[1] and pyrrolizines[2] have attracted interest because of their biologically important properties. Derivatives of phosphonates are active as insecticides, herbicides, fungicides, plant growth regulators, and drugs and they are also effective transition-state-analogue inhibitors for a variety of enzymes.[3] Many synthetic methods for phosphonate analogues utilize C–C,[4] C–P,[5] and C–N[6] bond-formation processes. Among these, Michael addition appears to be more successful, since vinylphosphonates containing electron-withdrawing groups at the α-position are potential Michael acceptors.[4c] The Michael addition reactions of N-heteroaromatics, e.g. imidazole and pyridine to bis(phosphono)ethylenes,[4f] nitroalkanes to ethyl 2-(diethoxyphosphoryl)acrylate,[4g,h] indole to dicyclohexylammonium 2-(diethoxyphosphoryl)acrylate,[4i] vinylidene bisphosphonates and vinylphosphonates[4j] have been studied. However, to the best of our knowledge, direct addition of pyrrole to vinylphosphonates has not yet been reported.

Pyrrolizin-3-ones are mainly isolated from plants, insects, animals, marine organisms, and microbes.[7] The biological activity of pyrrolizines has been attributed to their unique bridgehead nitrogen skeleton.[8] They are used as anti-inflammatory and analgesic drugs and as aromatase and tumor inhibitors. Current methods for the construction of the pyrrolizine skeleton involve intramolecular cyclization of N-[2b,7b,8a,9] or C-substituted[10,11] pyrrole derivatives. Base-catalyzed condensation[11c] and intramolecular cyclization of *C*-alkylpyrrole derivatives in the presence of sodium carbonate[11d] and sodium hydride[10] are effective methods for the synthesis of pyrrolizine ring structures. Flash vacuum pyrolysis is also an applicable method for the cyclization of both *N*-alkyl-[9b] and *C*-alkyl-substituted[11a,b] pyrrole derivatives to pyrrolizine ring structures. The intramolecular Wittig reaction of N-substituted phosphorus ylides has been used for the synthesis of functionalized 1*H*-pyrrolizine derivatives.[2b,8a,9a] Aryl-substituted pyrrolizine derivatives have been synthesized by the intramolecular cyclization of *N*-alkylpyrrole derivatives in the presence of boron tribromide.[7b]

In our previous studies we reported that the metal triflates are suitable catalysts for the addition reactions of pyrrole to α,β-unsaturated systems.[12] We obtained ester- and cyano-functionalized pyrrole addition products in high yields with metal triflates. Among the obtained products, the ester-functionalized dimethyl 2-[phenyl(1*H*-pyrrolyl)methyl]malonate, methyl 2-cyano-3-phenyl-3-(1*H*-pyrrol-2-yl)propanoate and their substituted derivatives gave pyrrolizin-3-one structures via intramolecular cyclization reactions.[10,12b]

These results and the above-mentioned importance of phosphonate analogues encouraged us to search the catalytic addition reaction of N-heteroaromatics to vinylphosphonates with metal triflates. The obtained products were used in intramolecular cyclization reactions (Scheme 1).

The Knoevenagel condensation was used for the synthesis of vinylphosphonates **3a**–**p** from the corresponding aldehydes **1a**–**p** and trimethyl phosphonoacetate (**2**) in toluene in the presence of acetic acid and piperidine.[13] The condensation products **3a**–**p** were obtained in 10–86% yields (Table 1). The configurational assignment for the compounds **3a**–**p** were based on the values of the vicinal cou-



Scheme 1

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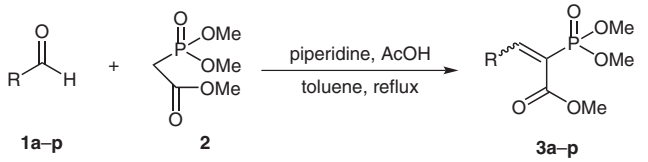
pling constant $^3J_{H,P}$ of the olefinic proton and the phosphorus atom. Nickson reported $^3J_{H,P}$ values of diethyl *E*- and *Z*-(3,3,3-trifluoroprop-1-enyl)phosphonate as 21 Hz for $^3J_{cis,H,P}$ and 43 Hz for $^3J_{trans,H,P}$.[14] In our case, $^3J_{H,P}$ values of the major isomers are in the range of 22.6–26.8 Hz, except in the case of **3l** where $^3J_{H,P}$ for the major isomer is 44.0 Hz. According to these values, the configurations of **3a**–**k**,**m**–**p** are assigned as mainly *E*, and of **3l** as mainly *Z*.

Table 1 Knoevenagel Reactions of Trimethyl Phosphonoacetate with Aldehydes



1a–p **2** **3a–p**

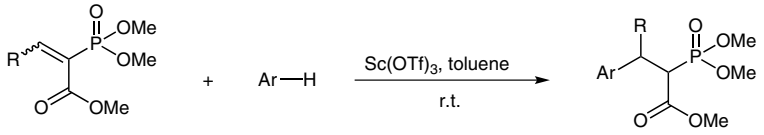
Entry	R	Product	Yield[a] (%)	Ratio *E*/*Z*
1	Ph	**3a**	55	95:5
2	4-$F_3CC_6H_4$	**3b**	40	89:11
3	4-MeC_6H_4	**3c**	65	95:5
4	4-$MeOC_6H_4$	**3d**	35	88:12
5	4-FC_6H_4	**3e**	50	87:13
6	4-ClC_6H_4	**3f**	45	92:8
7	4-BrC_6H_4	**3g**	50	93:7
8	4-HOC_6H_4	**3h**	86	86:14
9	4-NCC_6H_4	**3i**	36	89:11
10	4-$O_2NC_6H_4$	**3j**	30	87:13
11	2,4,6-$Me_3C_6H_2$	**3k**	20	75:25
12	pyrrol-2-yl	**3l**	77	31:69
13	2-furyl	**3m**	70	93:7
14	2-thienyl	**3n**	50	91:9
15	Cy	**3o**	15	93:7
16	*i*-Bu	**3p**	10	83:17

[a] Isolated yields after column chromatography.

After obtaining the Michael acceptors **3a**–**p**, we next investigated the optimum conditions using different metal triflates in different solvents in a model system; the reaction of pyrrole with the mixture of (*E*)- and (*Z*)-**3a** (Supporting Information, Table S1). The best result (98% yield) was obtained with 10 mol% scandium triflate in toluene at room temperature with 55:45 diastereomeric ratio. The same diastereomeric ratios were obtained when additions of pyrrole to (*E*)- and (*Z*)-**3a** were performed separately, indicating that *E*- and *Z*-isomers have no impact on the diastereoselectivity. With the optimized conditions in hand, we performed the addition reaction of pyrrole to vinylphosphonates **3b**–**p** and the addition reactions of different N-heteroaromatics to **3a**. The results are summarized in Table 2. The addition of pyrrole to substituted vinylphosphonates **3b**–**j** gave the addition products **4b**–**j** in 40–98% yields (entries 2–10). The electron-withdrawing 4-trifluoromethyl substituent did not affect the performance of the reaction and **4b** was obtained in 98% yield (entry 2). On the other hand, electron-donating 4-methoxy and 4-hydroxy substituents lowered the yield and gave the addition products **4d** and **4h** in 84% and 85% yields, respectively (entries 4 and 8); 4-methyl, 4-fluoro, 4-chloro, 4-bromo, and 4-cyano substituents gave the products **4c**,**e**,**f**,**g**,**i** in 62–92% yields (entries 3, 5–7, and 9). The 4-nitro-substituted addition product **4j** was obtained with the lowest yield of 40% (entry 10). Sterically hindered 2,4,6-trimethyl-substituted vinylphosphonate **3k** did not give the addition product **4k** (entry 11). Next, we performed the addition reaction of pyrrole to pyrrol-2-yl-, 2-furyl-, and 2-thienyl-substituted vinylphosphonates **3l**–**n**. Attempts at the addition of pyrrole to these vinylphosphonates were disappointing under the optimized conditions. We recovered the starting material in all cases and no addition product was observed. Hereafter to obtain the addition products **4l**–**n**, the catalytic activities of the hydrochloric acid, trifluoroacetic acid, Montmorillonite K-10, and Montmorillonite KSF were investigated. Only trifluoroacetic acid catalyzed the addition reaction of pyrrole to **3l** and the addition product **4l** was obtained in 45% yield (entry 12). The addition reactions of pyrrole to 2-furyl- and 2-thienyl-substituted vinylphosphonates **3m**,**n** were catalyzed by Montmorillonite K-10 in 25% and 30% yields (entries 13 and 14). However, the addition products **4m** and **4n** could not be obtained as pure compounds as they have the same R_f values as the starting materials **3m**,**n**. To test the applicability of this reaction for alkyl-substituted vinylphosphonates, cyclohexyl- and isobutyl-substituted vinylphosphonates were selected as α,β-unsaturated systems. The addition of pyrrole to **3o** and **3p** yielded the corresponding products **4o** and **4p** with 69% and 77% yields, respectively (entries 15 and 16). N-Substituted pyrroles and indole were examined to determine whether these molecules are viable on the Michael additions to **3a**. When 1-methyl-1*H*-pyrrole was employed, a sharp decrease was observed in the yield of the addition product **4q** (entry 17). With 1-phenyl-1*H*-pyrrole, no addition product was observed even after 96 hours (entry 18). These results showed that substituents on the pyrrole nitrogen complicated the reaction. On the indole side, the addition product **4s** was obtained with 99% yield (entry 19). The addition products **4a**–**j**,**m**–**s** were obtained as a mixture of diastereomers. The ratio of diastereomers was identified by NMR spectroscopy.

We then carried out several experiments to determine whether the diastereoselectivity is kinetically or thermodynamically controlled. The effect of temperature on the ratio of diastereomers was investigated by performing the addition reaction of pyrrole to **3g** at different temperatures. The products were obtained with 40:60, 48:52, and 49:51 ratios at –70 °C, room temperature, and 100 °C, re-

Table 2 Addition Reaction of N-Heteroaromatics to Vinylphosphonates



3a–p **4a–s**

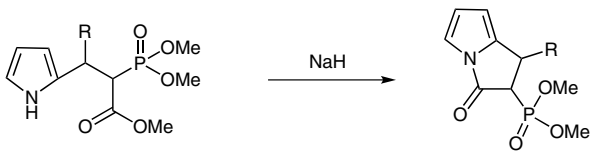
Entry	R	Ar	Product	Yield[a] (%)	dr
1	Ph	pyrrol-2-yl	**4a**	98	55:45
2	4-$F_3CC_6H_4$	pyrrol-2-yl	**4b**	98	61:39
3	4-MeC_6H_4	pyrrol-2-yl	**4c**	92	51:49
4	4-$MeOC_6H_4$	pyrrol-2-yl	**4d**	84	55:45
5	4-FC_6H_4	pyrrol-2-yl	**4e**	62	65:35
6	4-ClC_6H_4	pyrrol-2-yl	**4f**	78	53:47
7	4-BrC_6H_4	pyrrol-2-yl	**4g**	86	51:49
8	4-HOC_6H_4	pyrrol-2-yl	**4h**	85	56:44
9	4-NCC_6H_4	pyrrol-2-yl	**4i**	72	54:46
10	4-$O_2NC_6H_4$	pyrrol-2-yl	**4j**	40	52:48
11	2,4,6-$Me_3C_6H_2$	pyrrol-2-yl	**4k**	-	-
12	pyrrol-2-yl	pyrrol-2-yl	**4l**[b]	45	-
13	2-furyl	pyrrol-2-yl	**4m**[c]	25	81:19
14	2-thienyl	pyrrol-2-yl	**4n**[c]	30	66:34
15	Cy	pyrrol-2-yl	**4o**	69	61:39
16	*i*-Bu	pyrrol-2-yl	**4p**	77	67:33
17	Ph	1-methylpyrrol-2-yl	**4q**	58	57:43
18	Ph	1-phenylpyrrol-2-yl	**4r**	–	–
19	Ph	indol-3-yl	**4s**	99	60:40

[a] Isolated yields after column chromatography.
[b] Reaction was performed with 10% TFA in excess pyrrole.
[c] Reactions were performed with 0.093 g Montmorillonite K-10 in excess pyrrole and the products could not be purified for further reactions.

spectively. These results indicated that temperature change has no clear effect on diastereoselectivity and formation of the addition product is thermodynamically controlled.

The obtained addition products **4a–j,l–p** appear to be suitable compounds for the synthesis of dimethoxyphosphoryl-substituted pyrrolizin-3-ones through intramolecular cyclization of the pyrrole nitrogen. We next turned our attention to the intramolecular cyclization of the addition products **4a–j,l–p** with sodium hydride. The intramolecular cyclization reaction of **4a** was performed as a model reaction with 1.5 equivalents of sodium hydride in tetrahydrofuran at room temperature. The cyclization product **5a** was obtained as single diastereomer with 81% yield (Table 3, entry 1). Performing the reaction in different solvents, at different temperatures and with various amounts of sodium hydride lowered the yield of the cyclization product **5a** (entries 2–7). When the intramolecular cyclization reactions of **4b–j,l–p** were performed under optimum conditions [NaH (1.5 equiv), THF, r.t.], the 4-(trifluoromethyl)-, 4-methyl-, 4-methoxy-, 4-fluoro-, 4-chloro-, 4-bromo-, and 4-cyanophenyl-, pyrrol-2-yl-, 2-furyl-, 2-thienyl-, cyclohexyl-, and isobutyl-substituted cyclization products **5b–g,i,l–p** were obtained in high yields (74–99%) and as single diastereomers (entries 8–13, 15, 17–21). 4-Hydroxy and 4-nitro substituents on the phenyl ring lowered the yield of the cyclization products **5h** and **5j** to 44% and 45%, respectively (entries 14 and 16). The configuration of the phosphorylpyrrolizones **5a–j,l–p** could be assigned from their $^3J_{H,H}$ values. In our previous study, we demonstrated that 3-oxo-1-phenyl-2,3-dihydro-1*H*-pyrrolizine-2-carbonitrile derivatives had *trans*

Table 3 Intramolecular Cyclization Reaction of **4a–j,l–p**

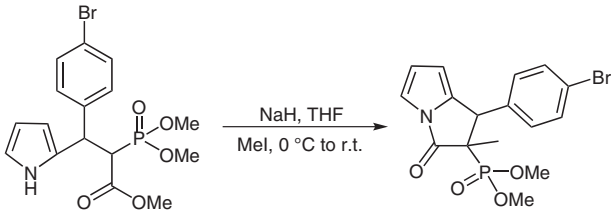


4a–j,l–p **5a–j,l–p**

Entry	R	Product	Solvent	Temp (°C)	Ratio **4a–j,l–p**/NaH	Yield[a] (%)
1	Ph	**5a**	THF	r.t.	1:1.5	81
2	Ph	**5a**	toluene	r.t.	1:1.5	57
3	Ph	**5a**	CH_2Cl_2	r.t.	1:1.5	49
4	Ph	**5a**	THF	0	1:1.5	55
5	Ph	**5a**	THF	50	1:1.5	33
6	Ph	**5a**	THF	r.t.	1:2	78
7	Ph	**5a**	THF	r.t.	1:1	39
8	4-$F_3CC_6H_4$	**5b**	THF	r.t.	1:1.5	99
9	4-MeC_6H_4	**5c**	THF	r.t.	1:1.5	98
10	4-$MeOC_6H_4$	**5d**	THF	r.t.	1:1.5	98
11	4-FC_6H_4	**5e**	THF	r.t.	1:1.5	74
12	4-ClC_6H_4	**5f**	THF	r.t.	1:1.5	88
13	4-BrC_6H_4	**5g**	THF	r.t.	1:1.5	99
14	4-HOC_6H_4	**5h**	THF	r.t.	1:1.5	44
15	4-NCC_6H_4	**5i**	THF	r.t.	1:1.5	87
16	4-$O_2NC_6H_4$	**5j**	THF	r.t.	1:1.5	45
17	pyrrol-2-yl	**5l**	THF	r.t.	1:1.5	99
18	2-furyl	**5m**	THF	r.t.	1:1.5	92
19	2-thienyl	**5n**	THF	r.t.	1:1.5	96
20	Cy	**5o**	THF	r.t.	1:1.5	99
21	*i*-Bu	**5p**	THF	r.t.	1:1.5	65

[a] Isolated yields after column chromatography.

configuration if the vicinal coupling constant of the hydrogens was in the range 4.8–6.4 Hz and *cis* configuration if the vicinal coupling constant was in the range of 8.2–8.8 Hz.[10] In this work, the vicinal coupling constants of the hydrogens of **5a–j,l–p** are between 4.0–4.4 Hz. As the vicinal coupling constants of **5a–j,l–p** are in good agreement with the coupling constants previously correlated with *trans* configurations, the novel phosphorylpyrrolizones **5a–j,l–p** are also assigned as *trans*. An experiment was designed to understand why only the *trans* diastereoisomer is formed in all cases. In this experiment, the reaction of **4g** with sodium hydride in the presence of iodomethane in tetrahydrofuran was investigated (Scheme 2). The methyl group at C2 in dimethyl 1-(4-bromophenyl)-2-methyl-3-oxo-2,3-dihydro-1*H*-pyrrolizin-2-ylphosphonate (**6**) indicated that epimerization took place under the applied reaction conditions. Consequently, after epimerization the thermodynamically more stable *trans* products **5a–j,l–p** are formed. The structures and diastereomeric ratios of both the addition and the cyclization products were identified by ^1H, ^{13}C, and ^{31}P NMR spectroscopic techniques.



4g **6**

Scheme 2

Commercially available reagents and solvents were used without further purification. ^1H NMR (400 MHz), ^{13}C NMR (100 MHz), and ^{31}P NMR (162 MHz) spectra were recorded using TMS or H_3PO_4 as an internal reference with a Bruker 400 FT NMR spectrometer. Peaks that represent both the major and minor diastereomers are indicated by *. Square brackets indicate peaks arising from the minor diastereomer, where applicable. Infrared spectra were recorded by ATR (Nicolet İS10). HRMS were recorded on a Agilent (1200/6210) TOF LC/MS spectrometer. Melting points were recorded on Gallenkamp melting-point apparatus. Reactions were monitored by TLC using precoated silica plates (Kieselgel 60, F254, E. Merck), visualized with UV light. Flash column chromatography was performed by using silica gel (0.05–0.63 mm, 230–400 mesh ASTM, E. Merck).

In this experimental section procedures are given for the formation of **3a–p**, **4a–j,l–q,s**, **5a–j,l–p**, and **6**, however, physical and spectroscopic data are only given for one example. Physical and spectroscopic data for compounds **3a**[15] and **3f**[16] correspond to those given in the literature. Compounds **3b–e,g–p**, **4a–j,l–q,s**, **5a–j,l–p**, and **6** are novel and their physical and spectroscopic data are given in the Supporting Information.

Methyl 3-Aryl-2-(dimethoxyphosphoryl)acrylates 3a–p; General Procedure

Triethyl phosphonoacetate (**2**, 2.08 mmol) and aldehyde **1a–p** (2.35 mmol) were dissolved in toluene (10 mL) and piperidine (0.062 mmol) and AcOH (0.033 mmol) were added to this soln. The resulting mixture was refluxed under a Dean–Stark trap for 8 h (TLC monitoring). After the completion of the reaction, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, EtOAc–hexane, 1:1).

Methyl (*E*/*Z*)-2-(Dimethoxyphosphoryl)-3-phenylacrylate (3a)[15]

Colorless viscous oil; yield: 309 mg (55%); ratio *E*/*Z* 95:5; R_f = 0.20 (EtOAc–hexane, 1:1).

IR (ATR): 3007, 2956, 2854, 1743, 1613, 1566, 1436, 1255, 1211, 1006, 861, 746 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.60 (s, 3 H, OCH_3, *Z*), 3.63 (s, 3 H, OCH_3, *Z*), 3.82 (s, 3 H, OCH_3, *E*), 3.84 (s, 3 H, OCH_3, *E*), 3.87 (s, 3 H, OCH_3, *E*), 3.91 (s, 3 H, OCH_3, *Z*), 7.37–7.45 (m, 8 H, ArH, *E* and *Z*), 7.61–7.65 (m, 2 H, ArH, *Z*), 7.70 (d, $^3J_{P,H}$ = 24.2 Hz, 1 H, CH=C, *E*), 8.28 (d, $^3J_{P,H}$ = 44.1 Hz, 1 H, CH=C, *Z*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.4 (*E* and *Z*), 52.9 (*E* and *Z*), 53.0 (*E* and *Z*), 122.6 (d, $^1J_{P,C}$ = 180.0 Hz, *E* and *Z*), 128.5 (*E* and *Z*), 128.9 (*E* and *Z*), 130.4 (*E* and *Z*), 133.2 (d, $^3J_{P,C}$ = 19.8 Hz, *E* and *Z*), 149.0 (d, $^2J_{P,C}$ = 6.2 Hz, *E* and *Z*), 166.5 (d, $^2J_{P,C}$ = 12.6 Hz, *E* and *Z*).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 14.7 (*Z*), 17.1 (*E*).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{16}O_5P$: 271.0735; found: 271.0705.

Methyl 2-(Dimethoxyphosphoryl)-3-phenyl-3-(1*H*-pyrrol-2-yl)propanoate (4a); Typical Procedure

To a soln of methyl (*E*/*Z*)-2-(dimethoxyphosphoryl)-3-phenylacrylate (**3a**, 0.093 mmol) in toluene (2 mL) at r.t. was added $Sc(OTf)_3$ (0.0093 mmol, 10 mol%) and the mixture was stirred for 0.5 h. Pyrrole (0.93 mmol) was added to the mixture instantly via syringe pump. The resulting mixture was stirred at r.t. for 48 h (TLC monitoring). Metal triflate was removed from the reaction medium by subjecting the mixture to a short flash column chromatography (silica gel, EtOAc). The eluent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, EtOAc–hexane, 1:1 or 4:1) to give a light brown powder; yield: 31 mg (98%); dr 55:45; mp 173.8–174.8 °C; R_f = 0.13 (EtOAc–hexane, 1:1).

IR (ATR): 3260, 3007, 2948, 2849, 1731, 1570, 1495, 1439, 1264, 1234, 1209, 1030, 805, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.33–3.42 (m, 12 H, 4 OCH_3)*, 3.56 (s, 3 H, OCH_3), [3.65 (d, $^3J_{P,H}$ = 11.1 Hz, 3 H, OCH_3)], 3.75 (dd, $^3J_{H,H}$ = 6.2 Hz, $^2J_{P,H}$ = 21.3 Hz, 1 H, CH), [3.77 (dd, $^3J_{H,H}$ = 5.2 Hz, $^2J_{P,H}$ = 21.7 Hz, 1 H, CH)], 4.57–4.73 (m, 2 H, 2 CH)*, [5.80 (br s, 1 H, $H_{pyrrole}$)], 5.97–6.08 (m, 3 H, 3 $H_{pyrrole}$)*, 6.60 (br s, 2 H, 2 $H_{pyrrole}$)*, 7.12–7.25 (m, 10 H, ArH)*, 8.66 (br s, 1 H, NH), [9.17 (br s, 1 H, NH)].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.2 (d, $^2J_{P,C}$ = 2.6 Hz), [43.8 (d, $^2J_{P,C}$ = 3.0 Hz)], 51.2 (d, $^1J_{P,C}$ = 131.5 Hz), [52.2 (d, $^1J_{P,C}$ = 132.3 Hz)], 52.4, [52.8], 53.0 (d, $^2J_{P,C}$ = 6.6 Hz), [53.2], 53.3, [53.6 (d, $^2J_{P,C}$ = 7.1 Hz)], 106.7, [107.5], 108.1, [108.4], [117.3], 117.7, [127.1], 127.2, 127.9*, 128.3*, 128.5*, 130.1, [130.7 (d, $^3J_{P,C}$ = 8.3 Hz)], 140.3 (d, $^3J_{P,C}$ = 4.0 Hz), [140.5], [168.0 (d, $^2J_{P,C}$ = 4.8 Hz)], 169.3 (d, $^2J_{P,C}$ = 4.4 Hz).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 23.5, [25.5].

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{21}NO_5P$: 338.1152; found: 338.1127.

Methyl 2-(Dimethoxyphosphoryl)-3-(1*H*-pyrrol-2-yl)propanoates 4l–n; General Procedure

Vinylphosphonate **3l–n** (0.093 mmol) was dissolved in excess pyrrole (3.72 mmol) and catalyst [TFA (0.0093 mmol) or Montmorillonite K-10 (0.093 g)] was added to the mixture at r.t.. The resulting mixture was stirred at r.t. for 48 h (TLC monitoring). The catalyst was removed from the reaction medium by subjecting the mixture to short flash column chromatography (silica gel, EtOAc). The eluent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, EtOAc–hexane, 4:1).

Methyl 2-(Dimethoxyphosphoryl)-3,3-di(1*H*-pyrrol-2-yl)propanoate (4l)

Light yellow powder; yield: 14 mg (45%); mp 168.5–169.7 °C; R_f = 0.44 (EtOAc).

IR (ATR): 3255, 2968, 2836, 1737, 1638, 1520, 1443, 1358, 1226, 1120, 1025 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.21 (d, $^3J_{P,H}$ = 10.8 Hz, 3 H, OCH_3), 3.43 (s, 3 H, OCH_3), 3.47 (d, $^3J_{P,H}$ = 10.8 Hz, 3 H, OCH_3), 4.03 (dd, $^3J_{H,H}$ = 12.4 Hz, $^2J_{P,H}$ = 19.6, 1 H, CH), 4.63 (dd, $^3J_{H,H}$ = 10.0 Hz, $^3J_{P,H}$ = 12.0, 1 H, CH), 5.80 (br s, 1 H, $H_{pyrrole}$), 5.84 (br s, 1 H, $H_{pyrrole}$), 5.89 (br s, 1 H, $H_{pyrrole}$), 5.96 (br s, 1 H, $H_{pyrrole}$), 6.50 (br s, 1 H, $H_{pyrrole}$), 6.60 (br s, 1 H, $H_{pyrrole}$), 10.49 (br s, 1 H, NH), 10.55 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 37.1, 50.7 (d, $^1J_{P,C}$ = 129.2 Hz), 52.5, 52.9 (d, $^2J_{P,C}$ = 6.7 Hz), 53.2 (d, $^2J_{P,C}$ = 6.4 Hz), 104.7, 106.4, 107.3, 107.4, 116.9, 117.5, 132.0, 132.2, 168.5 (d, $^2J_{P,C}$ = 4.3 Hz).

^{31}P NMR (162 MHz, DMSO-d_6): δ = 24.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{20}N_2O_5P$: 327.1109; found: 327.1116.

Dimethyl 3-Oxo-1-phenyl-2,3-dihydro-1*H*-pyrrolizin-2-ylphosphonate (5a); Typical Procedure

Methyl 2-(dimethoxyphosphoryl)-3-phenyl-3-(1*H*-pyrrol-2-yl)propanoate (**4a**, 0.074 mmol) was dissolved in THF (2 mL) and NaH (0.111 mmol) was added to the soln at 0 °C. The resultant mixture was stirred at r.t. for 2 h (TLC monitoring). After completion of the reaction pH 7 phosphate buffer (5 mL) was added to the mixture and the product was extracted with EtOAc (3 × 10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, EtOAc–hexane, 1:1) to give a light yellow powder; yield: 18 mg (81%); mp 71.2–72.1 °C; R_f = 0.27 (EtOAc–hexane, 1:1).

IR (ATR): 2952, 2925, 2893, 2838, 1751, 1593, 1558, 1499, 1479, 1389, 1286, 1251, 1192, 1026, 888, 829, 810, 687, 601 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.45 (dd, $^3J_{H,H}$ = 4.0 Hz, $^2J_{P,H}$ = 24.8 Hz, 1 H, CH), 3.75 (d, $^3J_{P,H}$ = 10.5 Hz, 3 H, OCH_3), 3.78 (d, $^3J_{P,H}$ = 10.4 Hz, 3 H, OCH_3), 4.79 (dd, $^3J_{H,H}$ = 4.0 Hz, $^3J_{P,H}$ = 16.8 Hz, 1 H, CH), 5.90–5.91 (m, 1 H, $H_{pyrrole}$), 6.46 (t, $^3J_{H,H}$ = 3.2 Hz, 1 H, $H_{pyrrole}$), 7.05 (d, $^3J_{H,H}$ = 3.2 Hz, 1 H, $H_{pyrrole}$), 7.15–7.28 (m, 5 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.1 (d, $^2J_{P,C}$ = 1.4 Hz), 52.3 (d, $^2J_{P,C}$ = 6.7 Hz), 53.1 (d, $^2J_{P,C}$ = 6.5 Hz), 54.6 (d, $^1J_{P,C}$ = 137.5 Hz), 105.3, 110.8, 118.9, 126.2, 126.8, 128.0, 139.5 (d, $^3J_{P,C}$ = 7.0 Hz), 140.0 (d, $^3J_{P,C}$ = 4.0 Hz), 164.5 (d, $^2J_{P,C}$ = 3.7 Hz).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 22.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{17}NO_4P$: 306.0890; found: 306.0885.

Dimethyl 1-(4-Bromophenyl)-2-methyl-3-oxo-2,3-dihydro-1*H*-pyrrolizin-2-ylphosphonate (6)

Methyl 3-(4-bromophenyl)-2-(dimethoxyphosphoryl)-3-(1*H*-pyrrol-2-yl)propanoate (**4g**, 0.074 mmol) was dissolved in THF (2 mL) and MeI (0.081 mmol) was added. Then NaH (0.111 mmol) was added to this soln at 0 °C. The resultant mixture was stirred at r.t. for 1 h (TLC monitoring). After completion of the reaction, pH 7 phosphate buffer (5 mL) was added to the mixture and the product was extracted with EtOAc (3 × 10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, EtOAc–hexane, 1:1) to give a light yellow viscous oil; yield: 14 mg (60%); R_f = 0.57 (EtOAc–hexane, 2:1).

IR (ATR): 2954, 2923, 2890, 1752, 1595, 1557, 1493, 1477, 1387, 1285, 1190, 1023, 889, 687, cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.81 (d, $^3J_{P,H}$ = 15.6 Hz, 3 H, CH_3), 3.25 (d, $^3J_{P,H}$ = 11.1 Hz, 3 H, OCH_3), 3.63 (d, $^3J_{P,H}$ = 9.0 Hz, 3 H, OCH_3), 4.37 (d, $^3J_{P,H}$ = 17.1 Hz, 1 H, CH), 5.97 (br s, 1 H, $H_{pyrrole}$), 6.55 (t, $^3J_{H,H}$ = 3.1 Hz, 1 H, $H_{pyrrole}$), 7.14 (d, $^3J_{H,H}$ = 3.1 Hz, 1 H, $H_{pyrrole}$), 7.33 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, ArH), 7.45 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.2 (d, $^3J_{P,C}$ = 4.9 Hz), 50.7, 52.5 (d, $^2J_{P,C}$ = 7.2 Hz), 54.1 (d, $^2J_{P,C}$ = 7.0 Hz), 58.6 (d, $^1J_{P,C}$ = 137.7 Hz), 106.0, 112.2, 119.5, 122.0, 129.6, 131.8, 135.4 (d, $^3J_{P,C}$ = 5.4 Hz), 138.5 (d, $^3J_{P,C}$ = 2.0 Hz), 169.5 (d, $^2J_{P,C}$ = 3.1 Hz).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 22.6.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{16}H_{18}BrNO_4P$: 398.0151; found: 398.0154.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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