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Reaction of 1-vinylpyrrole-2-carbaldehydes with phosphorus pentachloride: a stereoselective synthesis of *E*-2-(2-dichloromethylpyrrol-1-yl)vinylphosphonyl dichlorides

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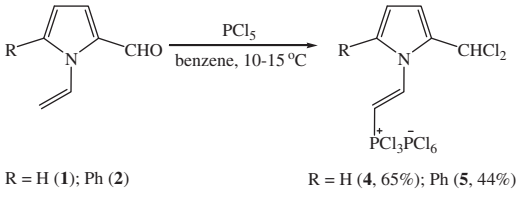
ABSTRACT

1-Vinylpyrrole-2-carbaldehydes react with phosphorus pentachloride (benzene, 10–15 °C) to afford *E*-2-(2-dichloromethylpyrrol-1-yl)vinylphosphonium hexachlorophosphates in up to 85% yield, which after treatment with SO_2 (benzene, rt) are converted into *E*-2-(2-dichloromethylpyrrol-1-yl)vinylphosphonyl dichlorides in 50–75% yields.

Pyrroles with diverse phosphorus functions, for example, pyrrolylphosphines, which act as hybrid ligands combining soft and hard donor sites, have attracted widespread attention in coordination and organometallic chemistry.[1] This is due, to a large extent, to the ability of these ligands to display hemilabile behavior toward platinum group metal centers.[2] As a result, new families of pyrrole-substituted phosphines have been synthesized.[3] Tertiary phosphines bearing pyrrolyl substituents have been successfully applied as ligands in a variety of transition metal catalyzed reactions (hydrogenation of alkenes and arenes,[4] allylic substitution,[5] isomerization of alkenes,[6] etc.). Tris(pyrrolyl)phosphine was shown to be suitable for development into a solid phase linker.[7] 5-(Diethoxyphosphorylmethyl)-5-methyl-4,5-dihydro-3*H*-pyrrole *N*-oxide was successfully employed as an efficient spin trap.[8] The combination of a pyrrole moiety with a phosphorus-containing function is expected to result in high and specific biological activity. An example of such a combination is the natural compound psilocybin (dimethyltryptamine-4-phosphate), which is the active principle of *Mexican mushrooms* with strong hallucinogenic activity.[9]



R = H (**1**); Ph (**2**) R = H (**4**, 65%); Ph (**5**, 44%)

Scheme 1.

The most general synthetic route to dihalogeno-, halogeno-, and tertiary pyrrolyl phosphines involves phosphorylation of N-substituted pyrroles with P(III) halides.[10]

For the synthesis of pyrrolylphosphonates, the Arbuzov rearrangement of trialkyl phosphites under the action of haloalkyl pyrroles was employed.[8] A conceptually new approach to the synthesis of phosphorus-containing pyrroles, which is developing rapidly, is based on available[11] 1-vinylpyrroles. Thus, secondary phosphines, under radical initiation, add readily to 1-vinylpyrroles to give the anti-Markovnikov adducts, diorganyl-2-(1-pyrrolyl)ethylphosphines, in 88–91% yields.[12] The 1-vinylpyrroles were also used for the synthesis of phosphorylated pyrroles via reaction with phosphorus pentachloride, the process affording various phosphorylation products, both on the pyrrole ring and vinyl group.[13] 1-Vinyl-2-trifluoroacetylpyrroles were phosphorylated with phosphorus

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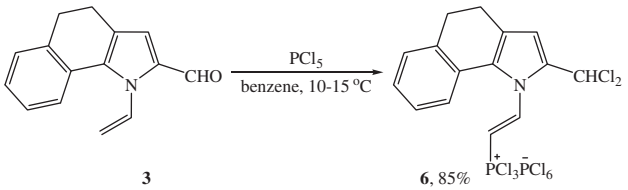
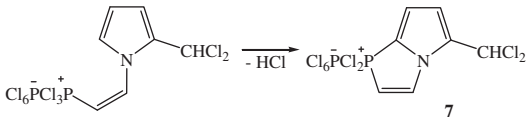
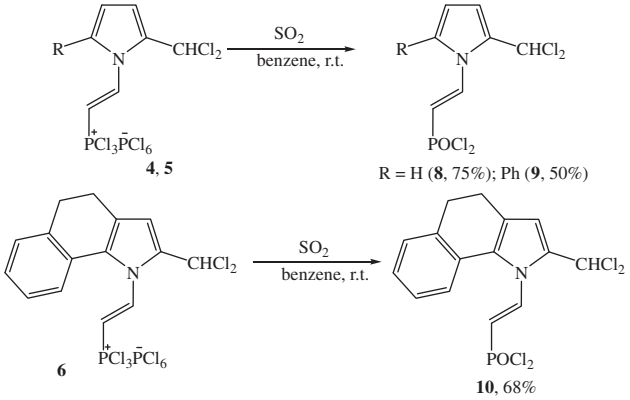


Scheme 2.



Scheme 3.



Scheme 4.

pentachloride selectively at the vinyl group to furnish 2-(2-trifluoroacetylpyrrol-1-yl)vinylphosphonium hexachlorophosphates in high yields,[14] which were further converted under the action of SO_2 into 2-(2-trifluoroacetylpyrrol-1-yl)vinylphosphonyl dichlorides in almost quantitative yields. Notably, in this case, the carbonyl group remained intact.

The purpose of the present work was to study the reaction of 1-vinylpyrrole-2-carbaldehydes **1–3** with phosphorus pentachloride and thereby synthesize new families of functionalized phosphorylated pyrroles. The starting pyrroles **1–3** were readily accessible via the recently developed efficient selective formylation of 1-vinylpyrroles.[15] Pyrroles **1–3** were found to react smoothly and stereoselectively with excess phosphorus pentachloride in benzene (10–15 °C)[16] involving both the formyl and vinyl groups to deliver *E*-2-(2-dichloromethylpyrrol-1-yl)vinylphosphonium hexachlorophosphates **4–6** (Schemes 1 and 2; Table 1).

The best yield of the phosphorylated product was obtained with the condensed pyrrole, 1-vinyl-4,5-dihydrobenz[*g*]indole-2-carbaldehyde (**3**) (Scheme 2).

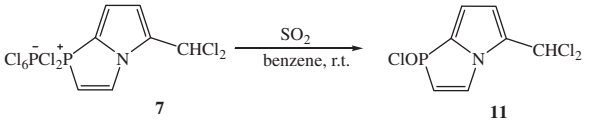
In the ^{31}P NMR spectra of salts **4–6**, signals in the regions −296.2 to −269.1 ppm and 89.7–93.9 ppm, assignable to PCl_6^- and PCl_3^+, were observed. The signals for the trichlorophosphonium cation (PCl_3^+) appeared as doublets of doublets ($^1J_{P-H}$–$2J_{P-H}$ = 13.2–33.8 Hz) indicating the *E*-configuration for the ethene moiety. For *E*-isomers of similar compounds, *J* values are 18–30 Hz, while for the corresponding *Z*-isomers, they can be up to 60 Hz.[17] The ^1H and ^{13}C NMR spectra, as well as 2D HMBC, were in full agreement with the assigned structures of salts **4–6**. In the ^{31}P NMR spectrum ($MeNO_2$) of salt **4**, a multiplet appeared at 66.6 ppm, where signals with $^1J_{P-H}$ = 25.7 and 7.9 Hz were present. The latter were attributable,[18] to 3,3-dichloro-6-(dichloromethyl)-1*H*-1λ^5-pyrrolo-[1,2-*a*]-1,3-azaphospholidinium hexachlorophosphate **7** (approx. 8–10%, ^{31}P NMR), which was probably formed via electrophilic cyclization of the *Z*-isomer of **4** (Scheme 3).

The phenyl substituent, being an acceptor toward the 1-vinylpyrrole moiety, decreases the nucleophilicity of the double bond, which probably results in the lower yield of the corresponding salt **5**. In the case of pyrrole **3**, the adverse effect of the phenyl substituent is compensated by the saturated fragment (the alkyl substituent at pyrrole position 4), which increases the yield of salt **6**.

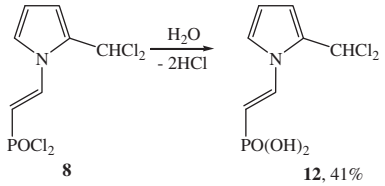
Table 1
Spectroscopic data for compounds **4–6**, **8–10** and **12**

Product[a]	Yield (%)	NMR (DMSO-d_6, δ, ppm); ^1H (400 MHz); ^{13}C (100 MHz); ^{31}P (161.98 MHz)		
		^1H	^{13}C	^{31}P
4	65	8.31 (m, 1H, N–CH=), 7.21 (m, 1H, H-5), 6.82 (s, 1H, $CHCl_2$), 6.45 (m, 1H, H-3), 6.23 (m, 1H, H-4), 6.16 (m, 1H, P–CH=)	148.7 (d, $^2J_{P-C}$ = 37.5 Hz, N–CH=), 130.9 (C-2), 121.4 (C-5), 114.2 (C-3), 112.6 (C-4), 95.8 (d, $^1J_{P-C}$ = 180.0 Hz, P–CH=), 62.0 ($CHCl_2$)	−296.1 (PCl_6^-) 92.1 (PCl_3^+)
5	44	9.11 (m, 1H, N–CH=), 8.41–8.33 (m, 5H, Ph) 7.54 (m, 1H, H-3), 7.22 (m, 1H, H-4), 7.10 (s, 1H, $CHCl_2$), 6.59 (m, 1H, P–CH=)	150.6 (d, $^2J_{P-C}$ = 38.0 Hz, N–CH=), 135.5 (C-2), 133.5 (C-5), 133.0, 132.8, 132.6, 131.9, 131.1, 130.9 (C_{Ph}), 119.5 (C-3), 118.4 (C-4), 102.3 (d, $^1J_{P-C}$ = 170.0 Hz, P–CH=), 62.5 ($CHCl_2$)	−296.2 (PCl_6^-) 89.7 (PCl_3^+)
6	85	8.89 (m, 1H, N–CH=), 8.20–8.01 (m, 4H, Ar) 7.49 (s, 1H, H-3), 6.96 (s, 1H, $CHCl_2$), 6.51 (m, 1H, P–CH=), 3.21 (m, 2H, CH_2), 2.88 (m, 2H, CH_2)	147.6 (d, $^2J_{P-C}$ = 37.9 Hz, N–CH=), 139.8, 136.6 (C_{Ar}), 132.2 (C-2), 132.0 (C-5), 128.8, 127.7, 126.7, 126.1 (C_{Ar}), 125.5 (C-9a), 121.0 (C-3a), 120.5 (C-3), 118.4 (C-4), 105.3 (d, $^1J_{P-C}$ = 171.3 Hz, P–CH=), 64.7 ($CHCl_2$)	−296.1 (PCl_6^-) 93.9 (PCl_3^+)
8	75	8.22 (m, 1H, N–CH=), 7.12 (m, 1H, H-5), 6.80 (s, 1H, $CHCl_2$), 6.39 (m, 1H, H-3), 6.20 (m, 1H, H-4), 6.07 (m, 1H, P–CH=)	141.3 (d, $^2J_{P-C}$ = 21.0 Hz, N–CH=), 131.5 (C-2), 128.7 (C-5), 114.0 (C-4), 112.3 (C-3), 106.5 (d, $^1J_{P-C}$ = 167.0 Hz, P–CH=), 61.8 ($CHCl_2$)	31.9 ($POCl_2$)
9	50	9.87 (m, 1H, N–CH=), 8.28–7.82 (m, 5H, Ph) 7.70 (m, 1H, H-3), 6.97 (s, 1H, $CHCl_2$), 6.81 (m, 1H, H-4), 5.73 (m, 1H, P–CH=)	142.9 (d, $^2J_{P-C}$ = 19.9 Hz, N–CH=), 137.0 (C-2), 134.0 (C-5), 131.5, 130.4, 129.8, 129.6, 129.1, 128.0 (C_{Ph}), 124.1 (C-3), 117.9 (C-4), 112.5 (d, $^1J_{P-C}$ = 193.8 Hz, P–CH=), 62.9 ($CHCl_2$)	33.7 ($POCl_2$)
10	68	8.81 (m, 1H, N–CH=), 8.29–7.98 (m, 4H, Ar) 7.50 (s, 1H, H-3), 6.99 (s, 1H, $CHCl_2$), 6.50 (m, 1H, P–CH=), 3.21 (m, 2H, CH_2), 2.80 (m, 2H, CH_2)	141.5 (d, $^2J_{P-C}$ = 27.8 Hz, N–CH=), 139.5, 136.0 (C_{Ar}), 132.2 (C-2), 131.8 (C-5), 128.8, 127.1, 126.6, 126.7 (C_{Ar}), 125.3 (C-9a), 120.8 (C-3a), 120.2 (C-3), 118.4 (C-4), 105.5 (d, $^1J_{P-C}$ = 191.3 Hz, P–CH=), 64.9 ($CHCl_2$)	34.4 ($POCl_2$)
12	41	8.26 (m, 1H, N–CH=), 7.13 (m, 1H, H-5), 6.77 (s, 1H, $CHCl_2$), 6.41 (m, 1H, H-3), 6.20 (m, 1H, H-4), 6.21 (m, 1H, P–CH=)	140.9 (d, $^2J_{P-C}$ = 25.8 Hz, N–CH=), 131.7 (C-2), 128.8 (C-5), 114.9 (C-4), 111.9 (C-3), 107.1 (d, $^1J_{P-C}$ = 208.8 Hz, P–CH=), 61.8 ($CHCl_2$)	12.4 ($PO(OH)_2$)

[a] Compounds **4–6** are deep-colored (from purple to dark-green) crystals, unstable in air. Compounds **8–10** and **12** are colored (from purple to brown) viscous oils. Elemental analyses of compounds **5**, **6**, **9**, **10** and **12** correspond well with calculated values.



Scheme 5.



Scheme 6.

When salts **4–6** were subjected to a reaction with SO_2 (benzene, rt),[19] *E*-2-(2-dichloromethyl-1-pyrrol-1-yl)vinylphosphonyl dichlorides **8–10** were formed in 50–75% yields (Scheme 4; Table 1).

In the ^{31}P NMR spectra of dichlorides **8–10**, signals in the region 31.9–34.4 ppm (dd, $^{1}J_{P-H}$ = 23.1–24.8 Hz) belonging to the $POCl_2$ moiety were present. The ^{31}P NMR spectrum of dichloride **8**, exhibited a low intensity signal at 20.7 ppm, which provided evidence for the presence of the corresponding cyclic phosphinyl chloride **11** (6%, ^{31}P NMR, Scheme 5).

Finally, phosphonyl chloride **8** is easily converted into the corresponding phosphonic acid (Scheme 6; Table 1).[20]

In summary, the stereoselective facile phosphorylation of 1-vinylpyrrole-2-carbaldehydes with phosphorus pentachloride has been elaborated. The first representatives of novel families of highly functionalized phosphorylated pyrroles, *E*-2-(2-dichloromethylpyrrol-1-yl)vinylphosphonyl dichlorides, *E*-2-(2-dichloromethylpyrrol-1-yl)vinylphosphonium hexachlorophosphates and *E*-2-(2-dichloromethyl-1-pyrrol-1-yl)vinylphosphonic acids have been synthesized. These compounds are promising intermediates and building blocks for a variety of phosphorus-containing pyrroles.

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16. PCl_5 (1.56 g, 7.5 mmol) in benzene (15 mL) was heated at reflux to give a homogeneous solution. This was cooled (10–15 °C) and a solution of 1-vinylpyrrole-2-carbaldehyde (2.5 mmol) in benzene (5 mL) was added dropwise under stirring. After 20 min, the resulting precipitate was removed by filtration and dried under vacuum to gave salts **4**–**6**.
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19. A mixture of salt **4**–**6** (1 mmol) and benzene (2–3 mL) was treated (rt) with dry SO_2. After complete dissolution of the salt, the benzene was distilled and the residue washed with hexane/Et_2O (10:1, 3 × 6 mL). After removal of the solvents, the dichlorides **8**–**10** were obtained.
20. A mixture of dichloride **8** (0.2 g, 0.7 mmol) and H_2O (5 mL) was stirred (rt) for 5 d. After removal of H_2O, the crude product was dried under vacuum to give 0.07 g of acid **12**.