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2-Phosphaindolizines via 1,5-Electrocyclization

Raj K. Bansal*, Anushka Surana and Neelima Gupta

Department of Chemistry, University of Rajasthan, Jaipur - 302 004, India.

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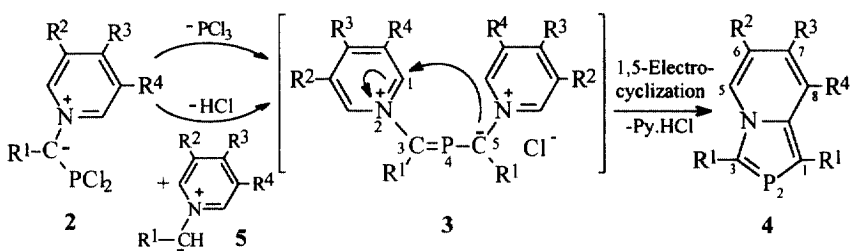
Abstract: *N-Pyridinium dichlorophosphinomethylides disproportionate to generate bis(N-pyridinium ylidyl)phosphenium chloride which undergoes 1,5-electrocyclization to give 2-phosphaindolizines. In one-pot synthesis N-(alkoxycarbonylmethyl)pyridinium bromide reacts with PCl_3 in presence of Et_3N to form 2-phosphaindolizine.*

The chemistry of azaphospholes having σ^2,λ^3-phosphorus has aroused much interest during the last two decades.[1-6] The phosphaindolizines which incorporate 1,3-azaphosphole structural system have been prepared through [4+1]cyclocondensation,[7-9] O/P exchange in oxazolopyridinium salts with tris(trimethylsilyl)phosphine[10] and [3+2]cycloaddition of N-pyridinium ylides to phosphaalkynes.[11] 1-Aza-2-phosphaindolizines can be obtained from [3+2]cyclocondensation of 2-aminopyridines with chloromethyldichlorophosphine.[12]

2-Phosphaindolizines prepared from [4+1]cyclocondensation of 1,2-dialkylpyridinium bromide with PCl_3 possess an electron-withdrawing group at the 3-position.[7-9] Electrophilic substitution[13] and coordination complexes[14] of these compounds have been reported recently. A new class of 2-phosphaindolizines having electron-withdrawing groups at both the 1- and 3-positions, which are expected to show remarkably distinct properties as indicated by semiempirical PM3 calculations,[15] has now become accessible through the 1,5-electrocyclization described here.

Triphenylphosphonium dichlorophosphinomethylides are reported to generate ionic bis(triphenylphosphonium ylidyl)phosphenium chlorides.[16] N-Pyridinium dichlorophosphinomethylides **2** recently prepared from the reaction of N-alkylpyridinium bromides **1** with PCl_3[17] behave analogously and the resulting bis(N-pyridinium ylidyl)phosphenium chlorides **3** by virtue of incorporating a 1,5-dipolar structure undergo 1,5-electrocyclization[18] (Scheme 1).



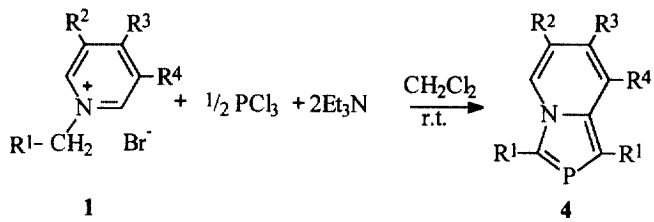
Scheme 1

PII: S0040-4039(98)02645-8

N-Pyridinium dichlorophosphinomethylide **2e** on standing in methylene chloride solution at r.t. slowly changes into 2-phosphaindolizine **4e.**[19] The ^{31}P NMR signal for **2e** (δ 149.6) disappears completely in 4 days accompanied by the appearance of an intense signal at δ 220 for PCl_3 and a signal at δ 179.0 for the 2-phosphaindolizine.

In an alternative approach, to the benzene solution of **2a,** generated *in situ*, is added a methylene chloride solution of **5a**, again generated *in situ*. This leads to the formation of **4a**[20] (Scheme 1).

In a one-pot synthesis, **4** can be prepared from the reaction of **1** with PCl_3(0.5 equiv.) in the presence of Et_3N (2 equiv.) in a polar solvent like methylene chloride[21] (Scheme 2).

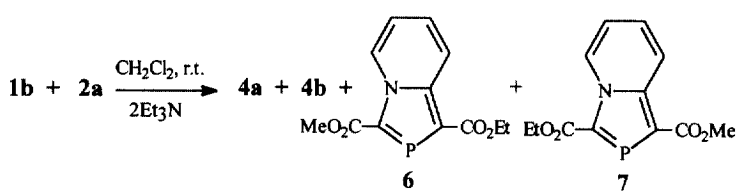


1 **4**

1 - 5	a	b	c	d	e	f	g
R^1	CO_2Me	CO_2Et	CO_2Me	CO_2Et	CO_2Et	CO_2Me	CO_2Et
R^2	H	H	Me	Me	H	Me	Me
R^3	H	H	H	H	Me	H	H
R^4	H	H	H	H	H	Me	Me

Scheme 2

A crossed reaction between **1b** and **2a** leads to the formation of a mixture of four 2-phosphaindolizines **4a, 4b, 6** and **7** (Scheme 3); formation of the latter two isomers confirms the intermediacy of **3**.



6 **7**

Scheme 3

The products **4** are yellow to orange solids or viscous mass, soluble in common organic solvents like benzene, acetonitrile and methylene chloride. They have been characterized by ^{31}P and ^{1}H NMR (Table 1). The ^{31}P NMR chemical shift in the range δ 174-180 is characteristic for a two-coordinate tervalent (σ^2, λ^3) phosphorus in 2-phosphaindolizines.[4, 22]

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Table 1. Physical and Spectral Data of 2-Phosphaindolizines **4**.

Compd.*	m.p. [°C]	Yield [%]	^{31}P NMR [C_6D_6, δ ppm]	^{1}H NMR[a] [C_6D_6, δ ppm] *J*(Hz)
4a	202-204	57	178.2	[3.90(s, 3H), 3.91(s, 3H), 1- and 3-$CO_2\underline{CH_3}$]; 7.02(t, 1H, $^3J_{HH}$ = 6.8, H-6); 7.36(t, 1H, $^3J_{HH}$ = 6.9, H-7); 8.66(d, 1H, $^3J_{HH}$ = 8.0, H-8); 9.88(d, 1H, $^3J_{HH}$ = 7.1, H-5).
4b	156-158	74	179.4	[1.07(t, 3H), 1.11(t, 3H), $^3J_{HH}$ = 7.1, 1- and 3-$CO_2CH_2\underline{CH_3}$]; [4.14(q, 2H), 4.23(q, 2H), $^3J_{HH}$ = 7.1, 1- and 3-$CO_2\underline{CH_2}$]; 6.16(t, 1H, $^3J_{HH}$ = 6.8, H-6); 6.59(t, 1H, $^3J_{HH}$ = 6.7, H-7); 8.86(d, 1H, $^3J_{HH}$ = 6.6, H-8); 9.85(d, 1H, $^3J_{HH}$ = 7.1, H-5).
4c	160-164	67	176.4	1.65(s, 3H, 6-CH_3); [3.48(s, 3H), 3.57(s, 3H), 1- and 3-$CO_2\underline{CH_3}$]; 6.30(d, 1H, $^3J_{HH}$ = 9.4, H-7); 8.60(d, 1H, $^3J_{HH}$ = 9.4, H-8); 9.64(s, 1H, H-5).
4d	185-187	81	176.6	[0.83(t, 3H), 0.87(t, 3H), $^3J_{HH}$ = 7.1, 1- and 3-$CO_2CH_2\underline{CH_3}$]; 1.45(s, 3H, 6-CH_3); [3.89(q, 2H), 3.97(q, 2H), $^3J_{HH}$ = 7.1, 1- and 3-$CO_2\underline{CH_2}$]; 6.24(d, 1H, $^3J_{HH}$ = 9.3, H-7); 8.46(d, 1H, $^3J_{HH}$ = 9.3, H-8); 9.39(s, 1H, H-5).
4e	170-172	18	178.9	[0.81(t, 3H), 0.85(t, 3H), $^3J_{HH}$ = 7.1, 1- and 3-$CO_2CH_2\underline{CH_3}$]; 1.99(s, 3H, 7-CH_3); 4.30(q, 4H, $^3J_{HH}$ = 7.1, 1- and 3-$CO_2\underline{CH_2}$); 6.09(d, 1H, $^3J_{HH}$ = 8.0, H-6); 8.62(s, 1H, H-8); 9.66 (d, 1H, $^3J_{HH}$ = 6.7, H-5).
4f	Syrupy	51	175.5	1.51(s, 3H, 6-CH_3); 2.30(s, 3H, 8-CH_3); [3.35(s, 3H), 3.43(s, 3H), 1- and 3-$CO_2\underline{CH_3}$]; 6.16(s, 1H, H-7); 9.73 (s, 1H, H-5).
4g	Syrupy	25	175.5	[0.79(t, 3H), 0.84(t, 3H), $^3J_{HH}$ = 7.1, 1- and 3-$CO_2CH_2\underline{CH_3}$]; 1.45(s, 3H, 6-CH_3); 2.24(s, 3H, 8-CH_3); [3.87(q, 2H), 3.93(q, 2H), $^3J_{HH}$ = 7.1, 1- and 3-$CO_2\underline{CH_2}$]; 6.41(s, 1H, H-7); 9.46(s, 1H, H-5).
4a + 4b + 6 + 7	-	-	180.7, 180.4, 180.3, 180.1[b]	-

* The compounds **4a-e** give satisfactory C, H, N analysis.

a In ^{1}H NMR in $CDCl_3$ signals for 1- and 3-alkoxycarbonyl groups are not resolved.

b Of mixture in $CDCl_3$.

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19. A solution of **2e** (585mg, 2.25mmol) in CH_2Cl_2 (30ml) was stirred at r.t. under nitrogen atmosphere for 4 days. The solvent was thereafter removed under reduced pressure and the residue left was extracted with diethyl ether (2 x 10ml). 2-Phosphaindolizine **4e** separated on keeping the concentrated extract in refrigerator.
20. A solution of **2a** was generated from the reaction of **1a** (2.24g, 9.6mmol) with PCl_3 (1.32g, 9.6mmol) and Et_3N (1.95g, 19.2mmol) in benzene (40ml) at r.t. To this was added a solution of **1a** (2.24g, 9.6mmol) in CH_2Cl_2 (25ml) containing Et_3N (1.95g, 19.2mmol) slowly at r.t. with stirring. After 5 hours the solvent was evaporated and the residue extracted with diethyl ether (2 x 50ml). Orange crystals of **4a** separated on leaving the combined and concentrated ether extract in the refrigerator.
21. To a solution of **1** (20mmol) in CH_2Cl_2 (40ml) was added Et_3N (4.04g, 40mmol) followed by a solution of PCl_3 (1.36g, 10mmol) in CH_2Cl_2 (15ml) at r.t. After 5 hours the solvent was evaporated and the residue was worked up as in 20.
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